Gene Probes As Unpatentable Printed Matter

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Introduction

So-called gene patent claims are often actually directed to *gene probes*.[1] A gene probe is a short nucleic acid molecule (also known as an "oligonucleotide") that can be used to detect the presence of complementary sequences in a genetic sample.[2] For example, two of the claims challenged by the American Civil Liberties Union and numerous public health organizations in the recent *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office* ("Myriad")[3] case cover any "isolated DNA having at least [fifteen] nucleotides" of the DNA sequence encoding BRCA1, a protein associated with breast cancer,[4] based on its utility as a gene probe in various diagnostic procedures.[5]

Like the patenting of genetic material more generally,[6] the patenting of gene probes has been controversial. Appealing to the intimate connections

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The author wishes to dedicate this article to Prof. Keith Aoki of the University of California at Davis School of Law, who passed away as this article was going to press. The author will treasure the memory of Prof. Aoki's encouragement of this project, his steadfast support as a role model and mentor, and his engaged, inspiring scholarship in intellectual property and critical race theory.

[1] *See* Christopher M. Holman, *The Impact of Human Gene Patents on Innovation and Access: A Survey of Human Gene Patent Litigation*, 76 UMKC L. Rev. 295, 313–14 (2007).

[2] *See* Jeffrey C. Pommerville, Alcamo's Fundamentals of Microbiology 282 (9th ed. 2011).

[3] 702 F. Supp. 2d 181 (S.D.N.Y. 2010), *appeal docketed*, No. 2010-1406 (Fed. Cir. June 16, 2010). Co-defendants Myriad Genetics and the University of Utah Research Foundation are the owners of the patents in suit. *Id.* at 184.

[4] U.S. Patent No. 5,747,282, col.153 l.65–col.154 l.55 (filed June 7, 1995).

[5] *Id.* at cols.11–17.

[6] *See generally* Andrew Chin, *Research in the Shadow of DNA Patents*, 87 J. Pat. & Trademark Off. Soc'y 846, 854–78 (2005) (surveying the controversy over gene patenting).

between the human genome and the life, identity, and shared heritage of the human species, some commentators have expressed ethical concerns over the commodification and propertization of parts of the human genome, concerns that extend to both full-length genes and gene probes.[7] Other scholars have argued that the disclosures supporting gene probe patents provide the public with only preliminary characterizations of genetic sequences, while precluding a broad range of downstream research on diagnostic and therapeutic techniques,[8] as well as parallel research directed toward identifying other patentable gene probes.[9] Concerns over the development of a research anticommons[10] have led to some notable defensive publication efforts, including the Merck Gene

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[7] *See, e.g.*, Baruch A. Brody, *Protecting Human Dignity and the Patenting of Human Genes*, *in* Perspectives on Gene Patenting 111, 118 (Audrey R. Chapman ed., 1999) ("[I]t is wrong to commercialize something with which individuality and personhood are intertwined."); Mark J. Hanson, *Biotechnology and Commodification Within Health Care*, 24 J. Med. & Phil. 267 (1999). Hanson opined:

> If the rhetoric regarding our genes becomes increasingly commodified at a time when media reports continue to strengthen the link between genes and human traits that centrally define us both as a species and as individuals, a subtle but not insignificant offense to notions of personhood and concomitant self-perception may occur.

Id. at 277; Richard D. Land & C. Ben Mitchell, *Patenting Life: No*, 63 First Things, May 1996, at 20, 21 (condemning the patenting of genes as an illegitimate effort to claim that which can only be owned by God); *U.S. Coalition Counters Breast Gene Patents*, 381 Nature 265, 265 (1996) (reporting criticisms from women's organizations that breast cancer gene probe patents deny women "control over the most intimate aspect of their being, their bodies' genetic blueprint").

[8] *See, e.g.*, Thomas D. Kiley, *Patents on Random Complementary DNA Fragments?*, 257 Science 915, 915 (1992) ("These patents cluster around the earliest imaginable observations on the long road toward practical benefit, while seeking to control what lies at the end of it."); Cynthia D. Lopez-Beverage, *Should Congress Do Something About Upstream Clogging Caused By the Deficient Utility of Expressed Sequence Tag Patents?*, 10 J. Tech. L. & Pol'y 35, 76 (2005) (describing the poor quality and preclusive effects of gene fragment patents); Jon F. Merz et al., Commentary, *Diagnostic Testing Fails the Test*, 415 Nature 577, 577 (2002); Cara Koss, Note, *Oysters & Oligonucleotides: Concerns and Proposals for Patenting Research Tools*, 25 Cardozo Arts & Ent. L.J. 747, 754–58, 756 n.67 (2007) (describing the granting of oligonucleotide patents of dubious utility); *Position Statement on Gene Patents and Accessibility of Gene Testing*, American College of Medical Genetics (Aug. 2, 1999), http://www.acmg.net/StaticContent/StaticPages/Gene_Patents.pdf ("[R]estricting the availability of gene testing . . . retards the usually very rapid improvement of a test that occurs through the addition of new mutations or the use of new techniques by numerous laboratories that have accumulated samples from affected individuals over many years.").

[9] Chin, *supra* note 6, at 895 ("[E]xisting patents on oligonucleotides might impair the future search for patentable DNA molecules, including other oligonucleotides.").

[10] Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 Science 698, 698–99 (1998).

Index and the SNP Consortium.[11] More recently, critics of gene patents have taken aim at the doctrinal distinction between patented isolated and purified nucleic acids and unpatentable genetic materials occurring in nature,[12] finding a sympathetic ear in the district court in *Myriad*.[13] None of these arguments, however, has yet persuaded the Federal Circuit or the U.S. Patent and Trademark Office.[14]

Patent claims directed to short DNA molecules raise particular concerns about overbreadth, because they typically cover all possible longer sequences that include the claimed subsequence.[15] In principle, such claims should also be the most vulnerable to anticipation. General methods of synthesizing oligonucleotides have been widely known and used since at least the 1980s.[16] As demonstrated in a previous article,[17] and the Federal Circuit confirmed in *In re Gleave*,[18] any prior art reference describing these methods and listing any of the claimed oligonucleotide sequences would anticipate and invalidate these claims under 35 U.S.C. § 102(b).[19] It is trivial to computer-generate and publish a list of all oligonucleotide sequences of a given length, provided that

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[11] *See* Andrew Chin, *Artful Prior Art and the Quality of DNA Patents*, 57 Ala. L. Rev. 975, 1016–18 (2006).

[12] *See, e.g.*, John M. Conley, *Gene Patents and the Product of Nature Doctrine*, 84 Chi.-Kent L. Rev. 109, 119 (2009); John M. Conley & Roberte Makowski, *Back to the Future: Rethinking the Product of Nature Doctrine as a Barrier to Biotechnology Patents*, 85 J. Pat. & Trademark Off. Soc'y 301, 303–04, 308 (2003); Linda J. Demaine & Aaron Xavier Fellmeth, *Reinventing the Double Helix: A Novel and Nonobvious Reconceptualization of the Biotechnology Patent*, 55 Stan. L. Rev. 303, 406, 409–10 (2002) (arguing that patents for isolation and purification of DNA molecules would not pass the authors' proposed "substantial transformation" test).

[13] Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office (*Myriad*), 702 F. Supp. 2d 181, 185 & n.1 (S.D.N.Y. 2010) (citing Conley & Makowski, *supra* note 12, at 305), *appeal docketed*, No. 2010-1406 (Fed. Cir. June 16, 2010). The *Myriad* court concluded "the claimed isolated DNA [was] not markedly different from native DNA as it exists in nature" and was therefore unpatentable. Id. at 232.

[14] *See* Chin, *supra* note 6, at 868–69, 874–76 (discussing the Federal Circuit's and Patent Office's responses to criticisms of gene patenting).

[15] *See* Jasemine C. Chambers, *Update on USPTO Practice—Tips for Biotech Patent Prosecution*, *in* 2005 Biotechnology Law 7, 23–24 (Practising Law Institute ed.) (explaining that a claim to an oligonucleotide "comprising at least a portion" of a recited nucleotide sequence "contemplates additional nucleotides"); Holman, supra note 1, at 314 ("In a practical sense, these claims to probes and sequence fragments can provide more expansive patent coverage than claims directed to the full-length gene sequence.").

[16] *See infra* note 87.

[17] *See* Chin, *supra* note 11.

[18] 560 F.3d 1331 (Fed. Cir. 2009).

[19] 35 U.S.C. § 102(b) (2006); *Id.* at 1336.

such a list can be stored feasibly on a medium that can be made accessible to the public.[20] Thus, the novelty of DNA oligonucleotide claims hinges largely on whether structural definitions of the claimed sequences have previously been typed out as As, Cs, Gs, and Ts in such a computer-generated list and published. Such a consideration has more to do with the norms of the scientific community regarding scholarly communication and with the availability of low-cost, high-capacity information storage media, than with the state of the art in biotechnology.[21]

This Article argues that the patentability analysis of DNA oligonucleotide claims should not reach these irrelevant considerations, because DNA oligonucleotides capable of being synthesized by known general methods should be held ineligible for patenting under patent law's printed matter doctrine. The printed matter doctrine serves to preempt inapposite analyses of differences between the claimed invention and the prior art—e.g., analyses focused on the management of stored information, rather than on the field of invention—that would otherwise be applied under the novelty doctrine of 35 U.S.C. § 102 or the nonobviousness doctrine of 35 U.S.C § 103.[22]

As this Article will argue, the printed matter doctrine is applicable to DNA oligonucleotide molecules because they are disposed to store nucleotide sequence information in a manner analogous in all relevant respects to other substrates that may be more intuitively recognizable as information storage media, such as laser-printed text on paper. Moreover, to the extent that a hybridization reaction involving a claimed oligonucleotide is recognized as having specific and substantial utility, it is by virtue of semantic properties that scientists have attached to the complementary DNA sequence, not an inventive functional relationship between the sequence information and its molecular substrate. While hybridization reactions involving the claimed oligonucleotide probes may impart new and unobvious information regarding cancer, such information is useful and intelligible only to the human mind and cannot confer patentability.

This Article opens a new front in the gene patenting debate. Until the *Myriad* amicus brief on which this Article is based was filed in the Federal Circuit,[23] no one had ever challenged the validity of a gene patent on the

[20] *See* Chin, *supra* note 11, at 1009–10.

[21] *See id.* at 1021–23.

[22] 35 U.S.C. §§ 102, 103 (2006); *see In re* Gulack, 703 F.2d 1381, 1385 (Fed. Cir. 1983).

[23] Corrected Brief for Professor Andrew Chin as Amici Curiae Supporting Appellees, Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office, No. 2010-1406 (Fed. Cir. Dec. 28, 2010), 2010 WL 5650477.

ground that it was directed to printed matter.[24] While it is widely recognized that "DNA is information embedded in a substrate of . . . molecule[s]" and that "it is the informational content of a DNA molecule that differentiates it from the prior art of other DNA molecules,"[25] opponents of gene patents have appealed to these characterizations only for the purpose of arguing that genetic information is a phenomenon of nature.[26] Such arguments have tended to conflate claimed DNA molecules with the sequence information they contain, an approach the patent system has vigorously rejected.[27] This Article will argue that DNA's informational content is significant for patentability, but it is an insight more properly addressed to the printed matter doctrine than to the product of nature exclusion.

I. Description and Purpose of the Printed Matter Doctrine

A. The Doctrine's Broad Applicability

The printed matter doctrine states that "'[m]ere printed matter can not impart a patentable feature to a claim.'"[28] The doctrine does not apply, however,

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[24] *See* Kevin Emerson Collins, *Semiotics 101: Taking the Printed Matter Doctrine Seriously*, 85 Ind. L.J. 1379, 1389 n.40 (2010).

[25] *Id.* at 1389.

[26] *See, e.g.*, Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office (*Myriad*), 702 F. Supp. 2d 181, 194 (2010) (finding that "[g]enes and the information represented by human gene sequences are products of nature universally present in each individual."), *appeal docketed*, No. 2010-1406 (Fed. Cir. June 16, 2010); U.S. Patent & Trademark Office, Utility Examination Guidelines, 66 Fed. Reg. 1092–93 (Jan. 5, 2001) [hereinafter *Utility Guidelines*] (summarizing public comments to the effect that "the sequence of the human genome is at the core of what it means to be human and no person should be able to own/control something so basic" or obtain patents "for discoveries in nature"); Bita Amani, *Patents, the Charter, & A Healthy Dose of Rights in Wrongs: The Poison is the Elixir for Life, Liberty & Security of the Person*, 57 U. New Brunswick L.J. 162, 173 (2007) (arguing that "genes are information" and are "our endowment from nature; they are *not* 'invented'") (Can.); Debra Greenfield, *Intangible or Embodied Information: The Non-Statutory Nature of Human Genetic Material*, 25 Santa Clara Computer & High Tech. L.J. 467, 536 (2009) (arguing that the law of nature exclusion should preclude the granting of patents "on the exclusive use of genetic information").

[27] *See Utility Guidelines*, *supra* note 26, at 1093 (acknowledging that "descriptive sequence information alone is not patentable subject matter" but explaining that a patent claim may be directed to "a new and useful purified and isolated DNA compound described by the sequence").

[28] *In re* Gulack, 703 F.2d 1381, 1384 (Fed. Cir. 1983) (citing examiner's § 103 rejection pursuant to the holding of *In re* Miller, 418 F.2d 1392 (C.C.P.A. 1969)).

when there is a "new and unobvious functional relationship between the printed matter and the substrate."[29]

As Judge Linn explained in *In re Nuijten*,[30] the printed matter doctrine precludes patentability where the differences between the claimed invention and the prior art subsist merely in stored information:

> Under the "printed matter" doctrine, if the only distinction between a prior art storage medium and a claimed storage medium is the information stored thereon—rather than a different "functional relationship between the printed matter and the substrate"—then the claimed storage medium (with associated information) is unpatentably obvious over the prior art because the information lacks "patentable weight."[31]

The printed matter doctrine has survived the progression of printing technologies, from typewriters and treadle presses to laser printers and nanolithography, without having been limited to any particular kind of storage medium.[32] Instead, it extends to any physical substrate capable of holding information, subject to the "functional relationship" limitation noted above. Accordingly, courts over the years have proceeded to apply the doctrine and its accompanying limitation in cases involving a wide range of substrates.[33]

B. The Doctrine's Structural Role

The printed matter doctrine has traditionally been viewed as an elaboration of the § 101 patentable subject matter requirement.[34] The doctrine's reliance on "patentable weight" considerations, however, is more akin to a *Graham v. John Deere Co.*[35] analysis of the nonobviousness of the "differences between

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[29] *Id.* at 1386.

[30] 500 F.3d 1346 (Fed. Cir. 2007).

[31] *Id.* at 1365 (Linn, J., concurring in part and dissenting in part).

[32] *See id.*

[33] *See, e.g.*, *In re* Bryan, 323 F. App'x 898, 901 (Fed. Cir. 2009) (per curiam) (game boards); *In re* Gulack, 703 F.2d at 1384 (paper, fabric, or plastic bands); Cincinnati Traction Co. v. Pope, 210 F. 443, 447 (6th Cir. 1913) (trolley transfer tickets); *In re* Miller, 418 F.2d 1392, 1396 (C.C.P.A. 1969) (measuring cups and spoons); *In re* Kothny, 96 F.2d 289, 291 (C.C.P.A. 1938) (scales for measuring cylindrical records); *In re* McKee, 75 F.2d 991, 992 (C.C.P.A. 1935) (meat products); *In re* Johns, 70 F.2d 913, 915 (C.C.P.A. 1934) (animal carcasses); *In re* Sterling, 70 F.2d 910, 911–12 (C.C.P.A. 1934) (checkbooks) *superseded by statute*, Revision of Title 35, United States Code, Pub. L. No. 82-593, 66 Stat. 792 (1952), *as recognized in In re* Gulack, 703 F.2d at 1385 n.8 *Ex parte* Gwinn, 112 U.S.P.Q. 439, 447 (B.P.A.I. Sept. 11, 1955) (dice in a "parlor golf game").

[34] 35 U.S.C. § 101 (2006)*; see* Donald S. Chisum, 1 Chisum on Patents § 1.02[4], at 1-24 (2010) ("'[P]rinted matter' by itself did not constitute a 'manufacture'"); *see also* Examination Guidelines for Computer-Related Inventions, 61 Fed. Reg. 7478, 7481 (Feb. 28, 1996) (instructing examiners to reject non-functional descriptive material under § 101).

[35] 383 U.S. 1 (1966).

the prior art and the claims at issue,"[36] than the "claim as a whole" approach that pervades modern patentable subject matter doctrine.[37] Accordingly, the printed matter doctrine has also sometimes been applied as part of a § 102 or § 103 analysis.[38] Despite the ambiguous location of its statutory basis, the printed matter doctrine has survived to the present day.[39]

As the Federal Circuit recently explained in *King Pharmaceuticals, Inc. v. Eon Labs*,[40] the rationale behind the printed matter cases is "preventing the indefinite patenting of known products by the simple inclusion of novel, yet functionally unrelated limitations."[41] The printed matter doctrine guards against the diversion of patentability analysis into assessments of the novelty and nonobviousness of information fixed in, but not conferring new and nonobvious functionality upon, the underlying substrate.[42]

In so doing, the printed matter doctrine serves alongside the judicially created exceptions to patentable subject matter to preempt inapposite analyses of differences between the claimed invention and the prior art that would otherwise be applied under the novelty doctrine of § 102 and/or the nonobviousness doctrine of § 103.[43] Courts do not inquire into the nonobviousness of newly discovered natural principles, because "the discovery of some of the handiwork of nature . . . is not patentable . . . . however ingenious the discovery of that natural principle may have been."[44] Similarly, where "the only distinction between a prior art storage medium and a claimed storage medium is the information stored thereon,"[45] a *Graham* analysis of the nonobviousness of the "differences between the prior art and the claims at issue" would entail inquiries into the nonobviousness of the stored information relative to prior art stored information and the level of ordinary skill in information recombination, regardless of the field of the underlying invention.[46]

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[36] *Id.* at 17–18.

[37] *See* Diamond v. Diehr, 450 U.S. 175, 189–91 (1981).

[38] *See, e.g.*, *In re* Ngai, 367 F.3d 1336, 1338 (Fed. Cir. 2004) (per curiam); *In re* Gulack, 703 F.2d at 1384; *see also In re* Nuijten, 500 F.3d 1346, 1365 (Fed. Cir. 2007) (Linn, J., concurring in part and dissenting in part) (characterizing the doctrine as supporting a conclusion of obviousness).

[39] *See infra* Part I.C.

[40] 616 F.3d 1267 (Fed. Cir. 2010).

[41] *Id.* at 1279.

[42] *See In re* Gulack, 703 F.2d at 1385.

[43] *Cf.* Collins, *supra* note 24, at 1387 (explaining that the doctrine in effect "excludes certain useful and nonobvious products of human ingenuity from the patent regime").

[44] Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 131 (1948).

[45] *In re* Nuijten, 500 F.3d 1346, 1365 (Fed. Cir. 2007).

[46] *See* Graham v. John Deere Co., 383 U.S. 1, 17 (1966).

Courts have consistently regarded such information-management considerations as inapposite to the assessment of inventive contributions in the relevant field of endeavor. For example, *In re Russell*[47] dealt with a directory in which surnames were arranged phonetically.[48] The applicant argued that his invention comprised "finished tangible subject matter bearing specifically arranged data or means, combined to produce a novel result."[49] The court affirmed the Patent Office's rejection, holding: "[t]he mere arrangement of printed matter on a sheet or sheets of paper, in book form or otherwise, does not constitute 'any new and useful art, machine, manufacture, or composition of matter.'"[50] This expression of the printed matter doctrine served to obviate an irrelevant inquiry into the novelty and nonobviousness of the applicant's "finished tangible" directory as an information source, relative to prior art directory and phonetic information sources.[51]

Similarly, in *Guthrie v. Curlett*,[52] the patentee asserted a claim to a "consolidated tariff index" that compiled the shipping rates set by numerous transportation companies, using a system of symbols to facilitate a compact presentation.[53] The court credited the patentee with showing "how to compress into small space a lot of information about freight tariffs," but explained that the proper subject of the patentability inquiry was the "*means* . . . for making a *consolidated index*."[54] Finding the disclosed means to consist solely of the non-novel "employment of symbols," the court concluded that the claim was directed to unpatentable subject matter.[55] The court thereby refrained from an inapposite inquiry into the ability of one skilled in the art to combine and compress the information from prior art individual tariff schedules into a single compact document.

In *In re Ngai*,[56] the applicant invented a new procedure for normalizing and amplifying RNA using a known reagent.[57] The Patent Office allowed his method claims, but rejected a claim directed to a kit combining the reagent with instructions for performing the new procedure.[58] The Federal Circuit affirmed the rejection under the printed matter doctrine, finding that the

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47 48 F.2d 668 (C.C.P.A. 1931).
48 *Id.* at 668.
49 *Id.* at 668.
50 *Id.* at 669.
51 *See id.* at 668.
52 10 F.2d 725 (2d Cir. 1926).
53 *Id.* at 725.
54 *Id.* at 726.
55 *Id.*
56 367 F.3d 1336 (Fed. Cir. 2004) (per curiam).
57 *Id.* at 1337.
58 *Id.* at 1337–38.

claimed invention amounted to "the addition of new printed matter to a known product" with no functional relationship between the two:

> Here, the printed matter in no way depends on the kit, and the kit does not depend on the printed matter. All that the printed matter does is teach a new use for an existing product . . . . If we were to adopt [applicant's] position, anyone could continue patenting a product indefinitely provided that they add a new instruction sheet to the product.[59]

The court's application of the printed matter doctrine thereby avoided a *Graham* inquiry as to whether one of ordinary skill would have been able to assemble the claimed kit from the prior art—a task that would entail producing and storing instructions for a new and nonobvious procedure.[60]

Patent law's novelty and nonobviousness doctrines are particularly ill-suited to fact-specific assessments of the inventiveness embodied in stored information, because these doctrines artificially construct the knowledge of the person having ordinary skill in the art as including all publicly accessible information resources, no matter how obscure.[61] By obviating an analysis focused on stylized facts and inapposite information-management considerations, the printed matter doctrine preserves the integrity of the novelty and nonobviousness doctrines as promoters of progress in the useful arts.

C. The Doctrine's Continuing Operation

The printed matter doctrine is a long-established principle of patent law that survived the enactment of the 1952 Patent Act.[62] While there is some ambiguity today as to which section of the 1952 Act supplies its statutory basis,[63] the doctrine has never been repudiated in over a century.[64]

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[59] *Id.* at 1338–39.

[60] *See id.* at 1338 (noting applicant's attempt to distinguish the kit claim by "argu[ing] that . . . prior art does not teach a limitation of 'instructions describing the method of [the method claim],' combined with an amplification kit").

[61] *See, e.g.*, *In re* Hall, 781 F.2d 897, 899–900 (Fed. Cir. 1986) (finding that "a single cataloged thesis in one university library" was sufficiently accessible to one exercising reasonable diligence to constitute a § 102(b) "printed publication").

[62] Revision of Title 35, United States Code, Pub. L. No. 82-593, 66 Stat. 792 (1952); *see, e.g.*, U.S. Credit Sys. Co. v. Am. Credit Indem. Co., 59 F. 139, 142–43 (2d Cir. 1893); *In re* Miller, 418 F.2d 1392, 1396 (C.C.P.A. 1969); *In re* Russell, 48 F.2d 668, 669 (C.C.P.A. 1931). *See generally* Harold C. Wegner, *The Disclosure Requirements of the 1952 Patent Act: Looking Back and a New Statute for the Next Fifty Years*, 37 Akron L. Rev. 243, 243 (2004) ("The great bulk [of the 1952 Act] was a mere codification of principles, going back in some cases to the earliest patent laws of the eighteenth century . . . .").

[63] *See supra* Part I.B.

[64] *See, e.g.*, *In re* Ngai, 367 F.3d at 1339.

In particular, the Supreme Court's recent decision in *Bilski v. Kappos*[65] did not disturb the printed matter doctrine, not least because the doctrine does not arise solely in connection with claims to § 101 "process[es]."[66] Moreover, none of the Court's reasoning in *Bilski* affects the operation of the printed matter doctrine.

As discussed in Part I.B *supra*, the printed matter doctrine's functional role in preempting inapposite analyses of differences between the claimed invention and the prior art is essentially complementary to the judicially created exceptions to patentable subject matter affirmed in *Bilski* and *Diamond v. Diehr*.[67] Thus, even though the Supreme Court required an "invention as a whole" approach to § 101 patent-eligible subject matter analysis in these decisions,[68] that requirement has not affected the printed matter doctrine's reliance on "patentable weight" considerations, as shown by the post-*Diehr* decisions of the Federal Circuit.[69] Since *Bilski*, the court has continued to treat the printed matter doctrine as operative and relevant to patentability analysis.[70]

The *Bilski* Court clarified that the only exceptions to patentable subject matter supported by the Court's precedents are for "laws of nature, physical phenomena, and abstract ideas,"[71] definitively retiring the concept of a categorical exclusion for business methods.[72] The printed matter doctrine's precedential support, however, is in no way undermined by the Court's repudiation of the supposed "business method" exception. While it may be observed that the printed matter doctrine originated in part from cases involving printed business forms,[73] its applicability has never been limited to business methods.[74] Moreover, since the early business form cases, the role of the printed matter doctrine has developed independently of any putative justification for excluding the category of business methods from patentability.[75]

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[65] 130 S. Ct. 3218 (2010).

[66] *See* Chisum, *supra* note 34, § 1.02[4] ("'[P]rinted matter' by itself did not constitute a 'manufacture'").

[67] 450 U.S. 175 (1981).

[68] *See Bilski*, 130 S. Ct. at 3230 (citing Diamond v. Diehr, 450 U.S. 175, 188 (1981)).

[69] *See, e.g.*, *In re* Ngai, 367 F.3d at 1339.

[70] *See* King Pharm., Inc. v. Eon Labs, Inc., 616 F.3d 1267, 1278–79 (Fed. Cir. 2010) (citing printed matter cases as persuasive authority for point-of-novelty analysis of method claims).

[71] *Bilski*, 130 S. Ct. at 3226.

[72] *Id.* at 3228.

[73] *See, e.g.*, Hotel Sec. Checking Co. v. Lorraine, 160 F. 467, 467 (2d Cir. 1908); U.S. Credit Sys. Co. v. Am. Credit Indem. Co., 59 F. 139, 141 (2d Cir. 1893).

[74] *See, e.g.*, *In re* Ngai, 367 F.3d at 1337.

[75] *See, e.g.*, *In re* Nuijten, 500 F.3d 1346, 1365 (Fed. Cir. 2007) (Linn, J., concurring in part and dissenting in part) (describing the printed matter doctrine as "potentially more apposite as a consequence of the 'useful' requirement of § 101"); Boggs v. Robertson, 13

In summary, the printed matter doctrine continues to serve alongside other judicial exclusions, fulfilling an important role in maintaining the integrity of patentability doctrine where novelty and nonobviousness inquiries would improperly be directed at the content, form, and management of stored information, rather than the functionality it confers upon the underlying substrate.

II. Oligonucleotides Under the Printed Matter Doctrine

A. Locus of the Inventive Contribution

The synthesis and use of isolated DNA oligonucleotides as hybridization probes has been known in the published literature since at least 1975.[76] Oligonucleotides as gene probes differ from the oligonucleotides used in prior art hybridization probe procedures only with respect to the nucleotide sequences carried thereon.[77] Thus, the inventive contributions of the claimed oligonucleotide compositions subsist merely in the nucleotide sequence information stored in the claimed molecules.[78]

By structure and function, DNA oligonucleotides are disposed to store nucleotide sequence information in a manner analogous in all relevant respects to other substrates that may be more intuitively recognizable as information storage media.[79] Structurally, characters comprising textual information are

U.S.P.Q. 214, 214 (D.C. 1931) (applying the doctrine as an extension of the abstract ideas exception); *see also supra* Part I.B (describing the doctrine's complementary role to the exceptions for laws of nature, physical phenomena, and abstract ideas); Collins, *supra* note 24, at 1402 (arguing that the abstract ideas exception "comes the closest to a source of support for the doctrine").

[76] *See* Edwin Mellor Southern, *Detection of Specific Sequences Among DNA Fragments Separated by Gel Electrophoresis*, 98 J. Molecular Biology 503 (1975).

[77] *See, e.g.*, U.S. Patent No. 5,198,338 cols.3–4 (filed May 31, 1989) (describing the use of Southern hybridization with isolated DNA olignoucleotide probes "of a suitable hybridizable length (generally longer than 15 nucleotides)" for the detection of T-cell malignancy).

[78] *See* Collins, *supra* note 24, at 1389 ("The difference between a newly isolated and purified strand of DNA and prior art DNA molecules resides in the content of the DNA-as-information . . . .").

[79] Admittedly, all chemical structures carry structural information. *See* Dan L. Burk, *The Problem of Process in Biotechnology*, 43 Hous. L. Rev. 561, 583–84 (2006) ("Due to its size, DNA can carry a very large amount of structural information, but this structural encoding is similarly the case for all biological macromolecules and indeed is at some greater or lesser degree true of all chemical structures."); Collins, *supra* note 24, at 1389 n.44 (noting that it would be "a conceptual error to frame DNA as unique in raising the question of whether molecules are information with content"). Significantly, however, gene probes are the subjects of such routine methods of synthesis and use that any inventive contributions necessarily reside in the sequence information itself.

physically represented on a laser-printed page by defined patterns of toner powder fused to a paper surface.[80] Similarly, nucleotide sequence information is physically represented in the DNA molecule by four defined types of submolecular units, called "bases," wherein each base is bonded to a 5-carbon sugar that has a phosphate group attached to form a sequential unit called a "nucleotide."[81] The resulting structure in each case physically manifests the specific information stored in the substrate, thereby enabling that information to be retrieved.

Functionally, laser printing stores textual information on a paper substrate through a computer-automated procedure that sequences and controls the process of placing and fusing the toner powder onto the page.[82] Analogously, automated oligonucleotide synthesis stores nucleotide sequence information in a DNA molecule through a computer-automated procedure that sequences and controls the process of placing and binding nucleotides onto the molecule, which is covalently bonded to a solid support.[83] The user of an oligonucleotide synthesizer merely has to type in the sequence and "press[] a few buttons."[84] Nucleotide sequence information can subsequently be retrieved from a DNA oligonucleotide using modern sequencing procedures.[85]

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[80] Edwin D. Reilly, Milestones in Computer Science and Information Technology 152 (2003).

[81] *See In re* O'Farrell, 853 F.2d 894, 896 (Fed. Cir. 1988).

[82] Erik Arctander & John Free, *Quiet—High-Tech Printers at Work*, Popular Science, Feb. 1984, at 72.

[83] Oligonucleotide synthesis dates back to the early 1950s, soon after the discovery of the structure of DNA. *See* Daniel M. Brown, *A Brief History of Oligonucleotide Synthesis*, *in* 20 Methods in Molecular Biology: Protocols for Oligonucleotides and Analogs 1, 2 (Sudhir Agrawal ed.,1993). Phosphotriester technology for oligonucleotide synthesis was primarily developed in the 1960s and 1970s and refined and popularized in the 1980s. *See id.* at 7–9; *see also* Keiichi Itakura et al., *Synthesis and Use of Synthetic Oligonucleotides*, *in* 53 Ann. Rev. Biochemistry 323, 353 (1984) ("[T]he chemical synthesis of oligodeoxyribonucleotides has become a routine laboratory procedure."). In phosphotriester synthesis, the most widely used methodology, there are four steps in each nucleotide addition, and at each step appropriate compounds are added and washed out as the reaction proceeds. The four steps are: (1) de-blocking of the DMT group on the last nucleotide added, (2) coupling to the next nucleotide, (3) capping against any unreacted nucleotides, and (4) oxidation of the linkage to render it stable. *See Oligonucleotide Synthesis*, BGI, http://www.genomics.cn/en/platform.php?*id*=195 (last visited April 14, 2011).

[84] Richard Pon, *Solid-Phase Supports for Oligonucleotide Synthesis*, *in* 20 Methods in Molecular Biology: Protocols for Oligonucleotides and Analogs 465, 465 (Sudhir Agrawal ed., 1993).

[85] *See* Enzo Biochem, Inc. v. Gen-Probe, Inc., 323 F.3d 956, 965–66 (Fed. Cir. 2002) (finding that one of ordinary skill can use known sequencing techniques to obtain nucleotide sequences from deposited DNA molecules).

While the fixation of nucleotide sequence information in the DNA molecule occurs at an intramolecular level, the microscopic scale of this phenomenon does not belie the fact that DNA oligonucleotides are analogous in structure and function to other physical substrates that store and manifest information as printed matter, such as laser-printed paper. Any structural differences between the claimed oligonucleotide compositions and prior art DNA oligonucleotides are simply the physical manifestation of differences in nucleotide sequence information as it is stored in the respective molecular substrates. Under the printed matter doctrine, therefore, any inventive contributions of the claimed oligonucleotide contributions should be found to subsist merely in stored information.

B. Inapposite Patentability Inquiries

As explained in Part I.B *supra*, the printed matter doctrine serves to preempt the diversion of patent law's novelty and nonobviousness analyses into information-management considerations unrelated to progress in the field of the underlying invention. The patentability analysis of oligonucleotide probes is uniquely susceptible to such diversion, because of two interrelated facts. First, as the Federal Circuit has recently explicitly recognized, general methods of making isolated DNA oligonucleotides of arbitrary sequence have long been well known.[86] Second, large databases providing nucleotide sequence information, but not listing all oligonucleotide subsequences thereof, have been available to the public since the early 1980s.[87]

Until recently, the Federal Circuit has characterized both of these facts as largely irrelevant to the novelty and nonobviousness analyses of claims to particular isolated DNA oligonucleotides. In *In re Deuel*,[88] the court held that the availability of general methods of making isolated DNA molecules "is essentially irrelevant to the question whether the specific [claimed] molecules themselves would have been obvious" to one of ordinary skill.[89] Databases

[86] *See In re* Gleave, 560 F.3d 1331, 1336 (Fed. Cir. 2009) (finding prior art to be enabling based on applicant's admission that "it is well within the skill of an ordinary person in the art to make any oligodeoxynucleotide sequence"); Brown, *supra* note 83, at 14.

[87] *See GenBank Celebrates 25 Years of Service with Two-Day Conference; Leading Scientists Will Discuss the DNA Database at April 7-8 Meeting*, National Institutes of Health (April 3, 2008), http://www.nih.gov/news/health/apr2008/nlm-03.htm; David S. Roos, *Bioinformatics: Trying to Swim in a Sea of Data*, 291 Science 1260, 1260 (1992) (noting GenBank "continues to more than double in size every year").

[88] 51 F.3d 1552 (Fed. Cir. 1995).

[89] *Id.* at 1559. *But see In re* Kubin, 561 F.3d 1351, 1358–59 (Fed. Cir. 2009) (noting the Supreme Court's repudiation of *Deuel* to the extent that *Deuel* foreclosed arguments that a combination of elements was "obvious to try").

of nucleotide sequences, without more, typically do not anticipate claims to isolated oligonucleotides comprising specific subsequences thereof, because such databases usually do not teach all limitations of an isolated oligonucleotide claim (e.g., by listing the sequence of every such oligonucleotide).[90]

Gleave implies that the patentability analysis of claimed DNA oligonucleotides would be very different if scientists were in the practice of publishing lists of oligonucleotide subsequences in addition to the full-length sequences from which they were derived. In *Gleave*, the Federal Circuit reviewed the Patent Office's rejection of a claim to an antisense DNA oligonucleotide substantially complementary to genes encoding two types of insulin-dependent growth factor binding protein.[91] The examiner imposed, and the Board approved, a § 102(b) rejection over a reference that first listed each of the more than 1,400 fifteen-base-long sense oligonucleotides contained in one of the genes and then suggested making antisense oligonucleotides capable of interacting with the listed sense oligonucleotides.[92] Noting "a person of ordinary skill in the art equipped with an IGFBP sequence is admittedly capable of envisioning how to make any antisense sequence," the court found the reference to anticipate all of the listed sense oligonucleotides and their antisense counterparts.[93]

That the proliferation of nucleotide sequences in public databases has not been accompanied by equally extensive and particularized documentation of oligonucleotide sequences does not reflect limitations in the state of the art in biotechnology, but norms in scholarly communication. Given any long nucleotide sequence, it is a trivial matter to identify all of the oligonucleotides of a given length contained therein; to list them all would contribute nothing to the advancement of science and be a frivolous waste of space. It is not surprising that the lengthy oligonucleotide listing cited as prior art in *Gleave* was from a patent application, rather than a professional scientific publication.[94]

It is an equally trivial (though scientifically uninteresting) matter to list all oligonucleotide sequences of a given length that can be made with known synthesis techniques, thereby generating a defensive publication that anticipates a broad class of oligonucleotide compositions. As demonstrated in a previous

[90] *See generally In re Gleave*, 560 F.3d at 1336–38 (discussing different treatment of lists and genera under anticipation case law).

[91] *Id.* at 1333.

[92] *Id.* at 1333–34.

[93] *Id.* at 1338.

[94] *Id.* at 1333.

article,[95] the potential impact of such defensive publications on the patentability of oligonucleotides is limited only by the capacity of digital storage media.[96]

In March 2002, a text document entitled *On the Preparation and Utilization of Isolated and Purified Oligonucleotides*, was created by the author, containing (1) a technical explanation of how to make and use isolated and purified oligonucleotides of arbitrary sequence (derived from the presumably enabling specifications of previously issued patents), and (2) a computer-generated list of 11 million nucleotide sequences eight to twelve bases in length that could be made and used by the disclosed methods.[97] This document was recorded on CD-ROM and deposited in the University of North Carolina School of Law's library, where it was indexed, cataloged, and shelved under the Library of Congress subject heading for oligonucleotides on March 14, 2002.[98] This "shotgun reference" has been effective § 102(b) prior art against oligonucleotide composition claims filed on or after March 15, 2003.[99]

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[95] *See* Chin, *supra* note 11.

[96] *See id.* at 1021–23.

[97] Andrew Chin, *On the Preparation and Utilization of Isolated and Purified Oligonucleotides* (Mar. 9, 2002) (CD-ROM on file with The Katherine R. Everett Law Library, University of North Carolina at Chapel Hill) *see also* Chin, *supra* note 11, at 1036 & n.410, 1037–38.

[98] Chin, *supra* note 11, at 1010.

[99] *See* 35 U.S.C. § 102(b) (2006). As of October 15, 2010, the CD-ROM has been cited in the prosecution history of thirty-nine issued patents, including thirty-five whose applications originally contained oligonucleotide composition claims. *See* U.S. Patents Nos. 6,946,267, at [56] (filed Mar. 13, 2002); 6,953,669, at [56] (filed Mar. 20, 2002); 7,049,067, at [56] (filed Oct. 30, 2001); 7,087,733, at [56] (filed Sept. 2, 2003); 7,090,980, at [56] (filed Dec. 18, 2003); 7,098,192, at [56] (filed Feb 6, 2004); 7,105,319, at [56] (filed July 24, 2002); 7,108,973, at [56] (filed Mar. 20, 2002); 7,132,233, at [56] (filed Dec. 5, 2003); 7,166,430, at [56] (filed May 21, 2002); 7,176,181, at [56] (filed May 21, 2002); 7,186,537, at [56] (filed Aug. 22, 2005); 7,198,898, at [56] (filed Apr. 7, 2003); 7,229,976, at [56] (filed Sept. 25, 2003); 7,291,725, at [56] (filed June 25, 2003); 7,339,041, at [56] (filed May 20, 2003); 7,342,109, at [56] (filed May 9, 2005); 7,345,161, at [56] (filed Feb. 3, 2005); 7,393,641, at [56] (filed May 6, 2004); 7,393,950, at [56] (filed Aug. 29, 2002); 7,407,943, at [56] (filed May 15, 2002); 7,414,033, at [56] (filed Mar. 18, 2004); 7,416,725, at [56] (filed Dec. 19, 2006); 7,468,431, at [56] (filed Jan. 24, 2005); 7,495,094, at [56] (filed Aug. 30, 2004); 7,514,241, at [56] (filed Sept. 23, 2005); 7,553,618, at [56] (filed July 1, 2003); 7,589,190, at [56] (filed Nov. 9, 2005); 7,618,947, at [56] (filed Aug. 25, 2005); 7,622,455, at [56] (filed Sept. 21, 2006); 7,678,895, at [56] (filed June 7, 2006); 7,700,574, at [56] (filed Sept. 17, 2004); 7,709,628, at [56] (filed Nov. 3, 2006); 7,718,628, at [56] (filed Dec. 29, 2006); 7,732,590, at [56] (filed Feb. 24, 2005); 7,737,264, at [56] (filed Apr. 4, 2003); 7,759,318, at [56] (filed May 27, 2005); and 7,759,479, at [56] (filed Sept. 30, 2005). In all thirty-five cases, the oligonucleotide composition claims were either canceled or narrowed by amendment to exclude sequences of eight to twelve bases in length. In one case, the patent

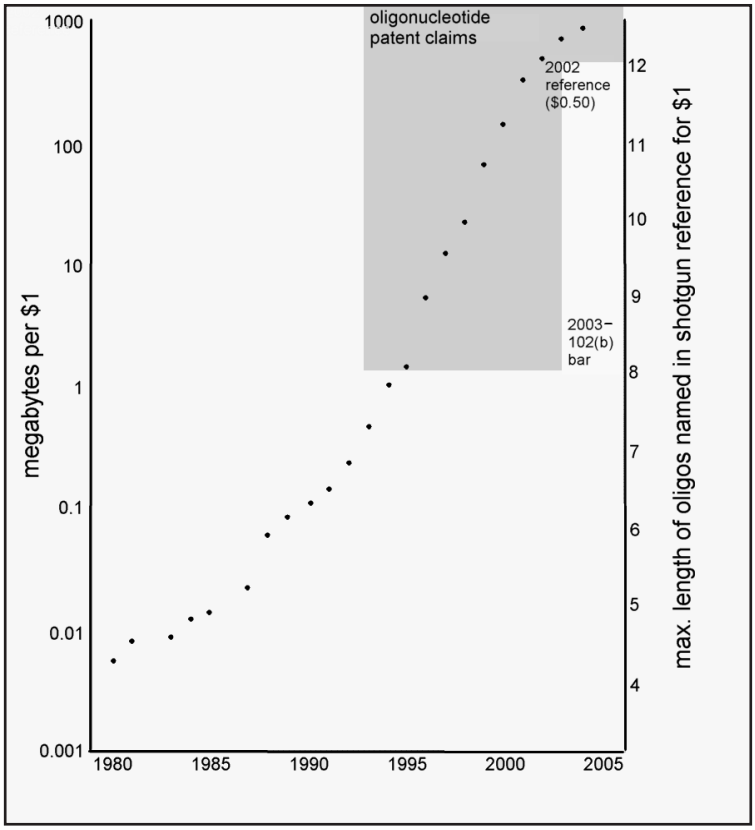

Fig. 1. Impact of the CD-ROM reference on patentability of oligonucleotides.[100]

The "shotgun reference" was limited to 11 million sequences only by the capacity of a CD-ROM in 2002. As Fig. 1 illustrates, at any given time, the feasibility of producing a shotgun reference as effective prior art against oligonucleotides of a given length is dependent on the availability of high-capacity, low-cost digital media. In Fig. 1, the impact of the CD-ROM reference is represented by the white segment that has been carved out of the shaded rectangle; the right scale indicates that, as of 2003, broad claims to oligonucleotides of eight to twelve bases were no longer patentable. As the data points plotted against the left scale illustrate, continuing advances in information storage technology may be expected to make it feasible to generate and publish shotgun references covering oligonucleotides of ever-increasing lengths.

There is a deep incongruity in these results. Known methods of synthesizing arbitrary isolated DNA oligonucleotides represent a significant portion of the

examiner also cited the reference in a § 103 rejection of several method claims. *See* Oct. 14, 2005 Final Rejection at 4–5, U.S. Patent No. 7,090,980 (filed Dec. 18, 2003).

[100] Chin, *supra* note 11, at 1022.

state of the art in biotechnology.[101] In contrast, the existence (or nonexistence) of shotgun references listing the sequences of arbitrary isolated oligonucleotides is of no significance to the state of the art in biotechnology. The feasibility of generating and publishing a shotgun reference of a given scope is determined solely by the state of information storage technology. Yet patent doctrine holds that such a sequence listing anticipates an oligonucleotide composition claim,[102] while oligonucleotide synthesizers do not even render such a claim obvious.[103]

The CD-ROM reference (and the patent system's response thereto) concretely demonstrates that the novelty and nonobviousness analyses of oligonucleotide composition claims are deeply and inextricably contingent on information-management considerations irrelevant to the state of the art in biotechnology. The printed matter doctrine can serve its functional role by obviating such analyses.[104]

C. The Information-Substrate Relationship

"Additional advantageous activity" may distinguish a claimed species as nonobvious over a known genus.[105] While the specific utility of oligonucleotides in testing for longer, clinically significant genetic sequences may represent "additional advantageous activity" in which nonobviousness subsists, this utility is not the result of a "new and unobvious functional relationship between the printed matter and the substrate."[106] Accordingly, the printed matter doctrine should be applied to invalidate gene probe claims.

In *Gulack*, the claimed invention was an endless band on which had been printed the first P-1 significant digits in the repeating decimal expansion of $1/P$, where P is a prime number.[107] This number has the property that cyclic shifts of the digits produce integer multiples of the original number.[108] The inventor claimed the band as "an educational and recreational mathematical device" that would display cyclic shifts of the original number, whose multiplicative properties might be used, *inter alia*, "to perform magic tricks or to display

[101] *See* Brown, *supra* note 83, at 7–9.

[102] *See In re* Gleave, 560 F.3d 1331, 1336–38 (Fed. Cir. 2009).

[103] *See In re* Deuel, 51 F.3d 1552, 1559 (Fed. Cir. 1995).

[104] *See supra* Part I.B.

[105] *See In re* Albrecht, 514 F.2d 1389, 1396 (C.C.P.A. 1975).

[106] *In re* Gulack, 703 F.2d 1381, 1386 (Fed. Cir. 1983).

[107] *Id.* at 1383–84.

[108] *Id.* at 1383. For example, the decimal expansion of 1/7 is .142857142857. A cyclic shift of the number 142,857 has the property that 428,571 = 3*142,857.

various aspects of number theory."[109] The specification and claims included such embodiments as a belt, hatband, necklace, or ring.[110]

The examiner rejected several claims under the printed matter doctrine, and the Board affirmed, finding "no functional relationship of the printed material to the substrate."[111] The court reversed, finding that "the digits of Gulack's invention are functionally related to the band."[112] The court reasoned:

> The appealed claims, on the other hand, require a particular sequence of digits to be displayed on the outside surface of a band. These digits are related to the band in two ways: (1) the band supports the digits; and (2) there is an endless sequence of digits—each digit residing in a unique position with respect to every other digit in an endless loop. Thus, the digits exploit the endless nature of the band.[113]

Crucial to the court's analysis was its finding that "there is an endless sequence of digits" that could not have been stored on anything other than a distinctive kind of substrate (i.e., one with an "endless nature").[114] Gulack's specification, however, teaches that "the sequence of digits imprinted on the band" is the finite sequence of *P*-1 digits described above.[115] The *Gulack* court thus appears to have construed "the digits of Gulack's invention" as intrinsically incorporating a special mathematical property that could be manifested only by also including all cyclic shifts of those digits.

In contrast, the nucleotide sequences of the claimed oligonucleotide compositions do not possess any intrinsic property that necessitates a distinctive kind of substrate. An oligonucleotide synthesizer fixes the sequence information of the claimed oligonucleotides into the substructures of a DNA molecule in the same way as it processes any other sequence information.[116]

It may be argued that oligonucleotides manifest higher-order structures that dispose them to hybridize specifically with clinically significant complementary DNA sequences. From a functional standpoint, however, the causal disposition of oligonucleotides to hybridize with complementary DNA sequences—the *only* causal disposition that the oligonucleotides of a typical gene probe claim have in common[117]—is common to *all* oligonucleotides, and is neither new nor

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[109] *Id.*

[110] *Id.*

[111] *Id.* at 1384.

[112] *Id.* at 1385.

[113] *Id.* at 1386–87.

[114] *See id.* at 1386–87.

[115] *See id.* at 1383.

[116] *See supra* note 83.

[117] The universe of oligonucleotides is structurally diverse. *See* M.A. Viswamitra, *Structural Diversity in DNA: From Monomer Structures to Oligonucleotides*, 47 Cold Spring Harbor Symp. Quantitative Biology 25, 25 (1983). Typical gene probe claims are broad enough to cover a diverse group of oligonucleotides (i.e., by using the open transitional term

unobvious.[118] The sequence information of a group of claimed oligonucleotides possesses no intrinsic property that distinguishes the functional properties of their underlying substrates from those of other oligonucleotides.

To the extent that a hybridization reaction involving a claimed oligonucleotide is recognized as having specific utility, it is by virtue of the semantic properties that scientists have attached to the complementary DNA sequence, not a new and unobvious functional relationship between the sequence information and the molecular substrate.[119] While hybridization reactions involving the claimed oligonucleotide probes may impart new and unobvious information regarding cancer, such information is "useful and intelligible only to the human mind" and cannot confer patentability.[120]

Conclusion

This is admittedly an unusual argument. The courts have not previously applied the printed matter doctrine to preclude the patenting of DNA molecules.[121] It has only been relatively recently, however, that unrelated but

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"comprising" and covering all sufficiently long subsequences of a recited longer sequence). *See* Chambers, *supra* note 15, at 23–24. Because of this diversity, such claims can ensure a common causal property only by picking out precisely those oligonucleotides that hybridize with a specified DNA sequence.

In contrast to oligonucleotides, longer DNA molecules that encode proteins with metabolic functions may have both meaning that is semantic and information content that is non-semantic, *see* Peter Godfrey-Smith, *Genes Do Not Encode Information for Phenotypic Traits, in* Contemp. Debates Phil. Sci. 275, 281–84 (Christopher Hitchcock ed., 2004), and therefore might not be covered by the printed matter doctrine. *Cf. In re* Fisher, 421 F.3d 1365, 1373 (Fed. Cir. 2005) (finding expressed sequence tags that were "unable to provide any information about the overall structure let alone the function of the underlying [protein-encoding] gene" to lack patentable utility as research tools).

[118] *See In re* Deuel, 51 F.3d 1552, 1554–55 (Fed. Cir. 1995) (explaining that DNA probes "exploit the fact that the bases in DNA always hybridize in complementary pairs").

[119] *See* U.S. Patent No. 5,747,282, col.7 (filed June 7, 1995) (describing the observation of "large extended families . . . with multiple cases of breast cancer" to support scientists' inferences regarding the locus of the BRCA1 gene); *see also* Godfrey-Smith, *supra* note 117, at 283 (arguing that, apart from protein synthesis, causal claims linking genes and phenotypic traits are grounded in semantic description).

[120] *See In re* Lowry, 32 F.3d 1579, 1583 (Fed. Cir. 1994) (quoting *In re* Bernhart, 417 F.2d 1395, 1399 (C.C.P.A. 1969)) ("The printed matter cases 'dealt with claims defining as the invention certain novel arrangements of printed lines or characters, useful and intelligible only to the human mind.'"); *see also* Collins, *supra* note 24, at 1383 ("Standing alone, newly invented semiotic meanings are not eligible for patent protection. Similarly, attaching new semiotic meanings to old worldly things does not make the worldly things patentable.").

[121] *See* Collins, *supra* note 24, at 1389 n.40 (noting that "printed matter challenges have not been brought against gene patents").

contemporaneous developments in biotechnology and information technology have thrown the doctrinal incongruity described above into high relief. It is only a matter of time until information technology supports the publication of shotgun references that foreclose the patenting of oligonucleotides of any given length. The courts can declare an end to this irrelevant waiting game by holding that the printed matter doctrine precludes the patenting of oligonucleotides capable of being synthesized by known general methods.