United States Court of Appeals for the Federal Circuit

GENETIC TECHNOLOGIES LIMITED,
Plaintiff-Appellant

v.

MERIAL L.L.C., BRISTOL-MYERS SQUIBB COMPANY,
Defendants-Appellees

2015-1202, 2015-1203

Appeals from the United States District Court for the District of Delaware in Nos. 1:12-cv-00396-LPS, 1:12-cv-00394-LPS Chief Judge Leonard P. Stark.

Decided: April 8, 2016

BENJAMIN B. LIEB, Sheridan Ross, PC, Denver, CO, argued for plaintiff-appellant. Also represented by ROBERT R. BRUNELLI, HIWOT M. COVELL.

GREGORY A. CASTANIAS, Jones Day, Washington, DC, argued for defendant-appellee Merial L.L.C. Also represented by JOHN PATRICK ELSEVIER, PHILIP SHENG, San Diego, CA; JUDY CATHERINE JARECKI-BLACK, Merial Limited, Atlanta, GA.

AMY K. WIGMORE, Wilmer Cutler Pickering Hale and Dorr LLP, Washington, DC, argued for defendant-appellee Bristol-Myers Squibb Company. Also represented by THOMAS SAUNDERS, TRACEY COTE ALLEN; WILLIAM F. LEE, ALLISON TRZOP, Boston, MA.

Before PROST, *Chief Judge,* DYK, and TARANTO, *Circuit Judges.*

DYK, *Circuit Judge.*

Genetic Technologies Limited ("GTG") brought suit against Merial L.L.C. ("Merial") and Bristol-Myers Squibb ("BMS") (together, "appellees"). GTG alleged that appellees had infringed U.S. Patent No. 5,612,179 ("the '179 patent"), which relates to methods of detecting genetic variations. The district court granted appellees' motions to dismiss for failure to state a claim and entered final judgment that claims 1–25 and 33–36 of the '179 patent are ineligible for patenting under 35 U.S.C. § 101. For purposes of this appeal, the parties have stipulated that claim 1 is representative of all of the invalidated claims. Because we agree that claim 1 is directed to unpatentable subject matter, we affirm.

BACKGROUND

The '179 patent claims methods of analyzing sequences of genomic deoxyribonucleic acid ("DNA"). Genetic information is encoded in DNA, which carries instructions for the development and function of all life. DNA sequences spell out instructions for synthesis of shorter sequences of ribonucleic acid ("RNA"), which in turn provide templates for synthesis of proteins. An individual's complete set of DNA is known as his genome, and a particular sequence of DNA within the genome that codes for a given protein (or functional RNA molecule) is referred to as a gene. Genes are the individual units defin-

ing heredity, and a person's overall collection of genes is known as his genotype. The site on a chromosome occupied by a particular gene is the genetic locus. Genes typically contain both coding regions, called exons, and non-coding regions, called introns. Exons are regions of the DNA sequence of the gene that are expressed, i.e., ultimately "decoded" and translated into the protein sequence. Introns are regions that are not expressed; these regions do not code for protein.

Each individual has his own unique genotype, inherited from his two parents. Variation of the precise genetic sequence within a particular gene among different people is known as genetic polymorphism, and the various alternative forms (mutations) of the gene are referred to as individual alleles. Detection of specific alleles can be useful for a variety of purposes, including diagnosis and treatment of genetic disorders and diseases correlated with those alleles, e.g., sickle-cell anemia, hemophilia, and cystic fibrosis.

In the 1980s, Dr. Malcolm J. Simons, the named inventor of the '179 patent, working with GTG,[1] discovered an interesting feature of genomic DNA. Dr. Simons discovered that certain DNA sequences in coding regions (exons) of certain genes are correlated with non-coding regions (introns) within the same gene, non-coding regions in different genes, or non-coding regions of the genome that are not part of any gene. Non-coding DNA regions between genes are referred to by the '179 patent as "intergenic spacing sequences" and have been referred to colloquially as "junk DNA," because, at least historical-

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[1] Dr. Simons's work was done for a predecessor company, GeneType, AG. For simplicity we refer to both GTG and GeneType as "GTG."

ly, they appeared to serve no function. '179 patent col. 5 ll. 42–46.

Dr. Simons found that the correlated coding and non-coding regions tend to be inherited together, with only rare shuffling. In other words, the regions are in "linkage disequilibrium," meaning that the coding and non-coding regions appear "linked" together in individuals' genomes more often than probability would dictate. '179 patent col. 5 ll. 20–32; *see also, e.g.*, *Henderson's Dictionary of Biology* 366 (14th ed. 2008) ("[L]inkage disequilibrium [is a] condition in which certain alleles at two linked loci are non-randomly associated with each other."). The correlated coding and non-coding regions may be linked even though the two sequences are located far apart from one another on the chromosome.

Dr. Simons concluded that alleles of a particular gene may be detected, using well-established laboratory techniques, not by looking for the coding region of the gene itself but instead by amplifying and analyzing non-coding regions known to be linked to the coding region. Between 1989 and 1992, Dr. Simons and GTG filed several patent applications related to the discovery. One of these applications ultimately became the '179 patent. Claim 1 of the '179 patent recites:

> 1. A method for detection of at least one coding region allele of a multi-allelic genetic locus comprising:
>
> a) amplifying genomic DNA with a primer pair that spans a non-coding region sequence, said primer pair defining a DNA sequence which is in genetic linkage with said genetic locus and contains a sufficient number of non-coding region sequence nucleotides to produce an amplified DNA sequence characteristic of said allele; and

> b) analyzing the amplified DNA sequence to detect the allele.

'179 patent col. 59 ll. 57–67. Claim 1 is thus broad in scope; it encompasses methods of detecting a coding region allele by amplifying and analyzing any linked non-coding region, which could be found within the same gene as the coding region, within a different gene, or within an intergenic region.

According to GTG, the methods of the '179 patent have various advantages over prior art methods involving direct analysis of a coding region. For example, GTG stated that "analysis of relatively short regions of non-coding sequences, of a size which can be amplified, can provide more information than prior art analyses such as cDNA RFLP analyses which involve the use of significantly larger DNA sequences . . . ." '179 Patent Prosecution History, Applicant's Amendment and Remarks of Jan. 14, 1993, at 6.

In 2011, GTG sued several pharmaceutical and biotechnology companies, including Merial and BMS, in the United States District Court for the District of Colorado for infringement of the '179 patent. GTG's claims against Merial and BMS were severed and transferred to the District of Delaware. GTG alleged infringement of at least one claim of the '179 patent and, in BMS's case, infringement of a second patent not at issue in this appeal. Merial and BMS subsequently moved to dismiss under Federal Rule of Civil Procedure 12(b)(6) ("Rule 12(b)(6)") for failure to state a claim, arguing that the claims of GTG's patents covered ineligible subject matter under 35 U.S.C. § 101.

After briefing and oral argument, the district court granted defendants' motions, holding that claim 1 of the '179 patent is invalid for claiming a law of nature, which is patent-ineligible subject matter. "A claim is unpatent-

able if it merely informs a relevant audience about certain laws of nature, even newly-discovered ones, and any additional steps collectively consist only of well-understood, routine, conventional activity already engaged in by the scientific community. The claim involved here, claim 1 of the '179 patent, does just that and no more." *Genetic Techs. Ltd. v. Bristol-Myers Squibb Co.*, 72 F. Supp. 3d 521, 527 (D. Del. 2014) (citing *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1298 (2012)). The district court did not evaluate the validity of other claims of the '179 patent under § 101, noting that GTG had not specified which of those claims it was asserting against Merial and BMS.

GTG, Merial, and BMS subsequently stipulated that, for purposes of appeal, claim 1 is representative of claims 2–25 and 33–36 of the '179 patent with respect to eligibility under § 101. GTG also covenanted not to assert the remaining claims, 26–32, of the '179 patent. Upon the parties' request, the district court dismissed GTG's infringement claims against Merial and BMS and entered judgment that claims 1–25 and 33–36 of the '179 patent are invalid for claiming unpatentable subject matter. GTG appeals. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

I

We review de novo the dismissal for failure to state a claim under Rule 12(b)(6). *Content Extraction & Transmission LLC v. Wells Fargo Bank, Nat'l Ass'n*, 776 F.3d 1343, 1346 (Fed. Cir. 2014); *Sands v. McCormick*, 502 F.3d 263, 267 (3d Cir. 2007). Patent eligibility under 35 U.S.C. § 101 is a question of law that we review de novo. *OIP Techs., Inc. v. Amazon.com, Inc.*, 788 F.3d 1359, 1362 (Fed. Cir. 2015); *Content Extraction*, 776 F.3d at 1346.

We have repeatedly recognized that in many cases it is possible and proper to determine patent eligibility under 35 U.S.C. § 101 on a Rule 12(b)(6) motion. *See, e.g.*, *OIP Techs.*, 788 F.3d at 1362; *Content Extraction*, 776 F.3d at 1351; *buySAFE, Inc. v. Google, Inc.*, 765 F.3d 1350, 1355 (Fed. Cir. 2014). In many cases, too, evaluation of a patent claim's subject matter eligibility under § 101 can proceed even before a formal claim construction. "[C]laim construction is not an inviolable prerequisite to a validity determination under § 101." *Bancorp Servs., L.L.C. v. Sun Life Assurance Co. of Canada (U.S.)*, 687 F.3d 1266, 1273 (Fed. Cir. 2012); *see also Content Extraction*, 776 F.3d at 1349. Here, there is no claim construction dispute relevant to the eligibility issue.

II

Section 101 establishes that "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof" may be eligible for a patent, subject to the conditions and requirements of the Patent Act. 35 U.S.C. § 101. But the Supreme Court has "long held that this provision contains an important implicit exception: Laws of nature, natural phenomena, and abstract ideas are not patentable." *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2116 (2013) (quoting *Mayo*, 132 S. Ct. at 1293). "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." *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972). "Groundbreaking, innovative, or even brilliant discovery does not by itself satisfy the § 101 inquiry." *Myriad*, 133 S. Ct. at 2117.

In the past several years, most notably in its *Mayo* and *Alice* decisions, the Supreme Court has articulated a now well-established two-step test for patent eligibility

under § 101. The test "distinguish[es] patents that claim laws of nature, natural phenomena, and abstract ideas from those that claim patent-eligible applications of those concepts." *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014) (citing *Mayo*, 132 S. Ct. at 1296–97). As set forth in *Alice*:

> First, we determine whether the claims at issue are directed to one of those patent-ineligible concepts. If so, we then ask, what else is there in the claims before us? . . . We have described step two of this analysis as a search for an inventive concept—i.e., an element or combination of elements that is sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the ineligible concept itself.

Id. (alterations, citations, and quotation marks omitted).

As noted above, claim 1 of the '179 patent is the only claim before us. We begin at step one of the *Mayo*/*Alice* test and ask first whether claim 1 is directed to a patent-ineligible concept—e.g., a law of nature, natural phenomenon, or abstract idea. *Alice*, 134 S. Ct. at 2355. We find that it is. Claim 1 is directed to the relationship between non-coding and coding sequences in linkage disequilibrium and the tendency of such non-coding DNA sequences to be representative of the linked coding sequences—a law of nature.

Claim 1 recites a method of detecting an allele of interest at a multi-allelic locus (i.e., a location on the chromosome where multiple variations of a particular gene are known) by amplifying a sequence of non-coding region DNA known to be linked with the allele and then analyzing the non-coding region to detect the allele. In somewhat plainer terms, claim 1 covers a method of detecting a coding region of a person's genome by amplifying and

analyzing a linked non-coding region of that person's genome.

Claim 1 covers any comparison, for any purpose, of any non-coding region sequence known to be linked with a coding region allele at a multi-allelic locus. The '179 patent states that "[t]he method can be used to detect alleles of genetic loci for any eukaryotic organism," '179 patent col. 4 ll. 12–13, and "is generally applicable to detection of any type of genetic trait," *id.* at col. 46 ll. 8–9. The '179 patent does not limit its scope to methods of detecting any particular alleles linked to any particular non-coding sequences, although the specification does provide some examples of linked alleles known to be diagnostic of inherited diseases such as cystic fibrosis and muscular dystrophy. *See generally*, '179 patent col. 43 l. 43–col. 46 l. 6. Claim 1 broadly covers essentially all applications, via standard experimental techniques, of the law of linkage disequilibrium to the problem of detecting coding sequences of DNA.

The product of the method of claim 1 is information about a patient's natural genetic makeup—at least one coding region allele. The claim relies on the existence of linkage disequilibrium between the non-coding and coding regions—i.e., the tendency of these regions to be linked. Linkage disequilibrium is indisputably a universal, inherent feature of human DNA, and the '179 patent itself notes that the claims are based on this fact. "The present invention is based on the discovery that amplification of intron sequences that exhibit linkage disequilibrium with adjacent and remote loci can be used to detect alleles of those loci." '179 patent col. 4 ll. 28–31.

Claim 1 of the '179 patent is in this respect quite similar to the claims invalidated in *Mayo* itself. In *Mayo*, the Supreme Court considered method claims that likewise required analysis of a biological sample (the blood of a

patient being treated with a thiopurine drug) and in which the focus of the claimed advance over the prior art was allegedly newly discovered information about human biology: the likelihood that a patient could suffer toxic side effects from particular doses of the drug. *Mayo*, 132 S. Ct. at 1296–97. "Claim 1, for example, states that *if* the levels of 6-TG in the blood (of a patient who has taken a dose of a thiopurine drug) exceed about 400 pmol per 8 x 10^8 red blood cells, *then* the administered dose is likely to produce toxic side effects." *Id.* The Court concluded that the claims were necessarily directed to an underlying law of nature or natural phenomenon, even if implementation of the method involves substantial human labor and ingenuity:

> While it takes a human action (the administration of a thiopurine drug) to trigger a manifestation of this relation in a particular person, the relation itself exists in principle apart from any human action. The relation is a consequence of the ways in which thiopurine compounds are metabolized by the body—entirely natural processes. And so a patent that simply describes that relation sets forth a natural law.

Id. at 1297. We agree with the district court that "just as the relationship at issue in *Mayo* was entirely a consequence of the body's natural processes for metabolizing thiopurine, so too is the correlation here (between variations in the non-coding regions and allele presence in the coding regions) a consequence of the naturally occurring linkages in the DNA sequence." *Genetic Techs.*, 72 F. Supp. 3d at 530.

In our court's recent *Ariosa v. Sequenom* decision, we considered genetic testing method claims remarkably similar to the claim here and found, at step one of the *Mayo*/*Alice* test, that they too were directed to unpatenta-

ble subject matter. *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1373–74, 1376 (Fed. Cir. 2015). The claims in *Ariosa* covered a method of detecting fetal DNA by amplifying and analyzing cell-free fetal DNA ("cffDNA") sampled from a pregnant woman's blood. *Id.* at 1373–74. The court found that "the claims are directed to matter that is naturally occurring" and that the inventors there did not purport to "create[] or alter[] any of the genetic information encoded in the cffDNA." *Id.* at 1376. The focus of the claimed advance over the prior art was allegedly newly discovered information about human biology: paternally inherited cffDNA is to be found in maternal blood (using established detection techniques). So too in the present case: the patent claim focuses on a newly discovered fact about human biology (the linkage of coding and non-coding regions of DNA), involves no creation or alteration of DNA sequences, and does not purport to identify novel detection techniques.

The similarity of claim 1 to the claims evaluated in *Mayo* and *Ariosa* requires the conclusion that claim 1 is directed to a law of nature. The sole function of the "primer pair defining a DNA sequence which is in genetic linkage with [a multi-allelic] genetic locus" is to amplify a sequence of non-coding DNA in linkage disequilibrium with a sequence of coding DNA of interest. '179 patent col. 59 ll. 60–62. "The method comprises amplifying genomic DNA with a primer pair that spans an intron sequence and defines a DNA sequence in genetic linkage with an allele to be detected." *Id.* at col. 4 ll. 37–39. The claim is directed to a natural law—the principle that certain non-coding and coding sequences are in linkage disequilibrium with one another.[2] We hold that claim 1 is

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[2] At various points in its briefs, GTG appears to concede that claim 1 is directed to a law of nature. *See,*

directed to unpatentable subject matter at the first step of the *Mayo*/*Alice* test.

III

We thus proceed to step two of the *Mayo*/*Alice* analysis. At step two, after identifying a claim directed to unpatentable subject matter, "we must examine the elements of the claim to determine whether it contains an inventive concept sufficient to transform the claimed abstract idea [or law of nature] into a patent-eligible application." *Alice*, 134 S. Ct. at 2357 (internal quotation marks omitted) (citing *Mayo*, 132 S. Ct. at 1294, 1298). "The question . . . is whether the claims do significantly more than simply describe [a] natural relation[]." *Mayo*, 132 S. Ct. at 1297. The inventive concept necessary at step two of the *Mayo*/*Alice* analysis cannot be furnished by the unpatentable law of nature (or natural phenomenon or abstract idea) itself. That is, under the *Mayo*/*Alice* framework, a claim directed to a newly discovered law of nature (or natural phenomenon or abstract idea) cannot rely on the novelty of that discovery for the inventive concept necessary for patent eligibility; instead, the application must provide something inventive, beyond mere "well-understood, routine, conventional activity." *Mayo*, 132 S. Ct. at 1294; *see also Myriad*, 133 S. Ct. at 2117; *Ariosa*, 788 F.3d at 1379. "[S]imply appending

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e.g., Appellant's Br. at 8 ("The District Court found that the Discovery was a natural phenomenon: 'The correlations between variations in non-coding regions of DNA—formerly known as "junk DNA"—and variations in coding regions of DNA—specifically, alleles—are natural phenomena. . . .' [T]his finding is correct . . . ."); *id.* at 17 ("[T]he natural phenomenon underlying Claim 1 is the Discovery [of linkage disequilibrium between coding and non-coding regions] . . . .").

conventional steps, specified at a high level of generality, to laws of nature, natural phenomena, and abstract ideas cannot make those laws, phenomena, and ideas patentable." *Mayo*, 132 S. Ct. at 1300. Claims directed to laws of nature are ineligible for patent protection when, "(apart from the natural laws themselves) [they] involve well-understood, routine, conventional activity previously engaged in by researchers in the field." *Mayo*, 132 S. Ct. at 1294.

We conclude that the additional elements of claim 1 are insufficient to provide the inventive concept necessary to render the claim patent-eligible.

A

We look first at the physical steps by which claim 1 implements the natural law of linkage disequilibrium between coding and non-coding regions to determine whether they provide more than "well-understood, routine, conventional activity" already engaged in by those in the field. *Id.* Claim 1 contains two implementation steps, "amplifying genomic DNA with a primer pair" and "analyzing the amplified DNA sequence to detect the allele." '179 patent col. 59 ll. 57–67.

The first claimed step of "amplifying" genomic DNA with a primer pair was indisputably well known, routine, and conventional in the field of molecular biology as of 1989, when the first precursor application to the '179 patent was filed. GTG concedes that "[t]he general laboratory technique of primer pair amplification of DNA, admittedly, was known as of the Filing Date." Appellant's Br. at 4. The '179 patent repeatedly characterizes primer pair amplification as prior art. "The method is commonly referred to as the polymerase chain reaction sequence amplification method or PCR." '179 patent col. 2 ll. 53–55; *see also id.* at col. 3 ll. 5–8 and ll. 39–45 (listing specific primer pair amplification techniques known in the art);

col. 12 ll. 47–64 (same). To overcome an examiner's claim rejection for lack of enablement under 35 U.S.C. § 112, GTG expressly argued during prosecution of the '179 patent that "amplification . . . [was a] technique[] . . . readily practiced by those in skill at the time the application was filed." '179 Patent Prosecution History, Applicant's Amendment and Remarks of Jan. 14, 1993, at 7–8.

The second physical implementation step, "analyzing" amplified DNA to provide a user with information about the amplified DNA, including its sequence, was also clearly well known, routine, and conventional at the time the '179 patent was filed. GTG concedes that "[t]echniques to analyze amplified DNA were . . . admittedly known." Appellant's Br. at 4. Moreover, the Background section of the '179 patent acknowledges as prior art the claimed two-step combination of amplification of DNA and subsequent analysis of its sequence. "A number of techniques have been employed to detect allelic variants of genetic loci including analysis of restriction fragment length polymorphic (RFLP) patterns, use of oligonucleotide probes, and DNA amplification methods." '179 patent col. 1 ll. 50–53; *see also* col. 10 ll. 6–34 (discussing methods of analyzing amplified DNA, including "sequencing the amplified DNA sequence"). GTG granted during prosecution of the '179 patent that it did not invent any new physical techniques. "Applicant has not invented a new way to analyze genetic loci. Rather Applicant has found that when prior art techniques are applied to the non-coding sequences, the result can be more informative than analysis of the coding regions." '179 Patent Prosecution History, Applicant's Amendment and Remarks of Jan. 14, 1993, at 6.

Thus the physical steps of DNA amplification and analysis of the amplified DNA to provide a user with the sequence of the non-coding region do not, individually or

in combination, provide sufficient inventive concept to render claim 1 patent eligible.[3] In this regard, claim 1 of the '179 patent is directly comparable to the claims invalidated in *Ariosa*. *Ariosa*, 788 F.3d at 1377 ("Using methods like PCR to amplify and detect cffDNA was well-understood, routine, and conventional activity in 1997.").

B

GTG argues that claim 1 provides more: once the non-coding DNA has been amplified and sequenced, an instruction to users to "analyz[e] the amplified DNA sequence *to detect the [coding region] allele*." '179 patent col. 59 ll. 66–67 (emphasis added). "[T]he analysis limitation of Claim 1 requires that analysis to be performed upon the amplified, i.e., man-made, non-coding DNA to detect the coding region allele. [This and other] limitations do not recite the Discovery [of linkage disequilibrium between coding and non-coding regions] or the Observation [of using a non-coding polymorphism to learn about a coding region allele] . . . ." Appellant's Reply Br. at 15. GTG argues that, at the time the '179 patent was

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[3] We are not persuaded by GTG's arguments that claim 1 is inventive because it involves analysis of *man-made* amplified DNA. While the man-made amplified non-coding DNA may have an "altered methylation status," Appellant's Br. at 22, its sequence is identical to that of naturally occurring DNA, unlike the cDNA held to be patent-eligible in *Myriad*, 133 S. Ct. at 2119. As with the claims to genomic DNA invalidated in *Myriad*, claim 1 "is concerned primarily with the information contained in the genetic *sequence*, not with the specific chemical composition of a particular molecule," and any minor chemical differences are irrelevant. *Id.* at 2118; *see also In re Roslin Inst. (Edinburgh)*, 750 F.3d 1333, 1337 (Fed. Cir. 2014).

filed, "no one had before analyzed man-made non-coding DNA in order to detect a coding region allele," and that this additional feature, at least, provides sufficient inventive concept to pass step two of the *Mayo*/*Alice* test. Appellant's Br. at 4.

We disagree. The term "to detect the allele" (in the sense of examining the non-coding region to detect an allele in the coding region) is a mental process step, one that provides claim 1 with a purpose but does not create the requisite inventive concept, because it merely sets forth a routine comparison that can be performed by the human mind. As we held in *Cybersource*, "[m]ethods which can be performed entirely in the human mind are unpatentable not because there is anything wrong with claiming mental method steps as part of a process containing non-mental steps, but rather because computational methods which can be performed *entirely* in the human mind are the types of methods that embody the 'basic tools of scientific and technological work' that are free to all men and reserved exclusively to none." *CyberSource Corp. v. Retail Decisions, Inc.*, 654 F.3d 1366, 1373 (Fed. Cir. 2011) (citing *Benson*, 409 U.S. at 67); *see also Diamond v. Diehr*, 450 U.S. 175, 187 (1981); *SmartGene, Inc. v. Advanced Biological Labs., SA*, 555 F. App'x 950, 955 (Fed. Cir. 2014).

Mayo itself considered and rejected diagnostic and therapeutic method claims that combined routine and conventional physical implementation of a law of nature with a simple mental process step. An exemplary claim evaluated in *Mayo* recited "[a] method of optimizing therapeutic efficacy for treatment of [a] gastrointestinal disorder, comprising: (a) administering a [thiopurine] drug . . . and (b) determining the level of [a metabolite] . . . wherein" a certain low metabolite level indicated a need to increase drug dosage and a certain high metabolite level indicated a need to decrease drug dosage. *Mayo*,

132 S. Ct. at 1295. *Mayo* held that the "'wherein' clauses simply tell a doctor about the relevant natural laws, at most adding a suggestion that he should take those laws into account when treating his patient." *Id.* at 1297. That is, "these clauses tell the relevant audience about the laws while trusting them to use those laws appropriately where they are relevant to their decisionmaking (rather like Einstein telling linear accelerator operators about his basic law and then trusting them to use it where relevant)." *Id.*

Here, the phrase "to detect the allele" in claim 1 of the '179 patent also merely informs the relevant audience—e.g., doctors or others seeking to make a genetic diagnosis—to apply a law of nature for a purpose—detecting a polymorphism within a coding region of an allele of interest. The limitation "to detect the allele" merely asks the user to compare the non-coding sequence he has amplified and analyzed with a library of non-coding sequences known to be in linkage disequilibrium with certain coding region alleles. This instruction to undertake a simple comparison step does not represent an unconventional, inventive application sufficient to make the claim patent-eligible. "[T]o transform an unpatentable law of nature into a patent-eligible *application* of such a law, one must do more than simply state the law of nature while adding the words 'apply it.'" *Mayo*, 132 S. Ct. at 1294 (citing *Benson*, 409 U.S. at 71–72).

Ariosa is again relevant. The claims challenged and invalidated in *Ariosa* included claims 21 and 25 of U.S. Patent No. 6,258,540, methods of "performing a prenatal diagnosis." *Ariosa*, 788 F.3d at 1374. To various routine and conventional steps of physical implementation (amplifying DNA in a blood sample and then performing analysis of that DNA to detect DNA of a particular origin), these claims also added a mental process step (performing a prenatal diagnosis based on the DNA

detected). The mental process of "performing a prenatal diagnosis" based on the DNA detected is directly comparable to claim 1's mental process of detecting the allele. The addition of this mental process step to the routine and conventional physical activity of amplification and analysis of DNA did not distinguish claims 21 and 25, which were invalidated with the other claims of the '540 patent. *Ariosa*, 788 F.3d at 1378.

Our decision in *In re BRCA1- & BRCA2-Based Hereditary Cancer Test*, 774 F.3d 755 (Fed. Cir. 2014), is also instructive. Claim 8 of U.S. Patent No. 5,753,441 evaluated in that case recited a method of screening for alterations of the BRCA1 gene that included the steps of "amplifying all or part of a BRCA1 gene from [a] sample using a set of primers to produce amplified nucleic acids and sequencing the amplified nucleic acids" and "comparing" the sequence with wild-type BRCA1. *Id.* at 761–62. We held that claim to be invalid because it was directed to an abstract idea and did not add enough to distinguish it from a claim to the abstract idea. *Id.* at 762–65. An aspect of our analysis there supports our analysis of the law-of-nature issue here. We noted that "[t]he non-patent-ineligible elements of claim[] . . . 8 do not add 'enough' to make the claim[] as a whole patent-eligible. . . . The [physical implementation steps] of claim[] . . . 8 do nothing more than spell out what practitioners already knew—how to compare gene sequences using routine, ordinary techniques." *Id.* at 764. Claim 8, which combined conventional physical implementation of a law of genetics with a simple mental process step of "comparing," was held to be patent-ineligible. *Id.* at 765.

To be sure, it seems to be true, as GTG alleges, that at the time the '179 patent was filed, no one was "using the non-coding sequence as a surrogate marker for the coding region allele." Appellant's Reply Br. at 7. Claim 1 was found by the patent examiner to be novel over the prior

art and survived multiple rounds of reexamination. But the novelty of looking to non-coding DNA to detect a coding region allele of interest resides in the novelty of the newly discovered natural law of linkage disequilibrium between coding and non-coding regions and adds little more than a restatement of the natural law itself. We thus hold that the simple mental process step of "detect[ing] the allele" in claim 1, either alone or in combination with the physical steps described above, does not supply sufficient inventive concept to make the claim patent-eligible under § 101.

As a final matter, we note that GTG's attempts to distinguish this case on the ground that the method of claim 1 is useful have no basis in case law or in logic. Claim 1 stands rejected under § 101 as ineligible for claiming unpatentable subject matter, not for lack of utility. The method claims of *Mayo* and *Ariosa* were apparently also useful, and also invalid. *Mayo*, 132 S. Ct. at 1294 ("[This case] concerns patent claims covering processes that help doctors who use thiopurine drugs to treat patients with autoimmune diseases determine whether a given dosage level is too low or too high."); *Ariosa*, 788 F.3d at 1380 ("We do not disagree that detecting cffDNA in maternal plasma or serum that before was discarded as waste material is a positive and valuable contribution to science. But even such valuable contributions can fall short of statutory patentable subject matter, as it does here.") Utility is not the test for patent-eligible subject matter. *See Bilski*, 561 U.S. at 659 (Breyer, J., concurring).

CONCLUSION

For the foregoing reasons, we hold that claim 1 of the '179 is invalid under 35 U.S.C. § 101 as directed to patent-ineligible subject matter. We therefore affirm the district court's grant of appellees' motions to dismiss under Rule 12(b)(6).

AFFIRMED

COSTS

Costs to appellees.