United States Court of Appeals for the Federal Circuit

ROCHE MOLECULAR SYSTEMS, INC.,
Plaintiff-Appellant

v.

CEPHEID,
Defendant-Appellee

2017-1690

Appeal from the United States District Court for the Northern District of California in No. 3:14-cv-03228-EDL, Magistrate Judge Elizabeth D. Laporte.

Decided: October 9, 2018

STEPHEN S. RABINOWITZ, Hughes Hubbard & Reed LLP, New York, NY, argued for plaintiff-appellant. Also represented by JAMES W. DABNEY, MITCHELL EPNER, PATRICE POLYXENE JEAN, DAVID E. LANSKY, LYNN M. RUSSO.

ERIK R. PUKNYS, Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, Palo Alto, CA, argued for defendant-appellee. Also represented by MICHAEL PAUL BARKER; GRANT L. KIM, WESLEY ELLSWORTH OVERSON, Morrison & Foerster LLP, San Francisco, CA.

Before O'MALLEY, REYNA, and HUGHES, *Circuit Judges.*

Opinion for the court filed by *Circuit Judge* REYNA.

Concurring opinion filed by *Circuit Judge* O'MALLEY.

REYNA, *Circuit Judge.*

Appellant Roche Molecular Systems, Inc. ("Roche") owns U.S. Patent No. 5,643,723 ("the '723 patent"), titled "Detection of a Genetic Locus Encoding Resistance to Rifampin in Microbacterial Cultures and in Clinical Specimens." The United States District Court for the Northern District of California found that the asserted claims of the '723 patent are directed to patent-ineligible subject matter and are therefore invalid under 35 U.S.C. § 101. Roche appeals from a grant of summary judgment of invalidity. We *affirm*.

I. THE '723 PATENT

The '723 patent is directed to methods for detecting the pathogenic bacterium Mycobacterium tuberculosis ("M. tuberculosis" or "MTB"). '723 patent col. 2 ll. 50–54. MTB infection is a major cause of tuberculosis. *Id*. col. 1 ll. 13–30. In 1994, before the priority date of the '723 patent, the general method of MTB detection in a tuberculosis patient was known as sputum examination by the acid-fast bacilli smear. For this test, a biological sample taken from a patient is subjected to cell culture in a process that can take three to eight weeks. *Id*. col. 2 ll. 9–11. This test has limitations: it can identify the presence of bacterial cells in a biological sample, but cannot identify the cells as MTB. There is a need to know whether the MTB from a patient is resistant to antibiotics. The standard of care for MTB treatment at the time involved a regimen of antibiotics, with rifampin being a first-line anti-tuberculosis drug. *Id.* col. 1 ll. 31–33. Tuberculosis outbreaks, however, still resulted because of delays in diagnosis and reporting of rifampin-resistant tuberculosis

due to the inability to rapidly identify MTB strains that are resistant to rifampin and put a patient on an appropriate alternative therapy. *Id.* col. 1 ll. 61–65.

Prior to the '723 patent, scientists in the field had been working on diagnostic tests for faster detection of MTB, particularly rifampin-resistant MTB strains. *Id.* col. 2 ll. 18–46. It was speculated that "[g]enotypic detection of multi-drug resistant MTB [strains] directly from clinical specimens is theoretically the fastest and most direct step toward determining effective therapy for patients." *Id.* col. 2 ll. 39–42. It was known in the art that rifampin has a unique site of action on a particular gene that encodes the ß subunit of bacterial RNA polymerase ("the *rpoB* gene"). *Id.* col. 1 ll. 31–42. The *rpoB* gene is present in MTB and other bacterial species, and its deoxyribonucleic acid ("DNA") sequences were known to be highly conserved, with little variation from one bacterial species to another. In 1994, single site mutations in the *rpoB* gene that confer rifampin resistance in some bacteria, such as Escherichia coli ("E. coli"), were well characterized, making *rpoB* a prime candidate for studying rifampin resistance in MTB. *Id.* col. 1 ll. 42–52.

The inventors of the '723 patent—scientists from Roche and the Mayo Foundation for Medical Education and Research ("Mayo")—sequenced the *rpoB* gene from various bacteria species, including MTB, obtained from a commercial vendor.[1] *Id.* col. 8 ll. 1–3 and col. 8 l. 15–col. 9 l. 20. After comparing *rpoB* DNA sequences across different species, the inventors discovered that the *rpoB* gene in MTB contains eleven "position-specific 'signature nucleotides'" (i.e., naturally occurring single nucleotide

[1] Mayo later assigned its rights in the '723 patent to Roche. *See Roche Molecular Sys., Inc. v. Cepheid*, No. 14-CV-03228-EDL, 2017 WL 6311568, at *1 (N.D. Cal. Jan. 17, 2017).

mutations) that are only present in MTB but not in other bacteria. *Id.* col. 2 l. 60–col. 3 l. 2. In other words, these naturally occurring signature nucleotides are like fingerprints of MTB: if an investigator detects one of the eleven signature nucleotides from a biological sample, she knows the sample contains MTB, and vice versa. These signature nucleotides, therefore, could be used to identify MTB using genetic testing, which is both faster and more accurate than the traditional MTB detection methods. *Id.* col. 2 ll. 9–31.

Based on these eleven MTB-specific signature nucleotides, the Roche inventors devised a diagnostic test that could (1) identify whether or not a biological sample contains MTB, and (2) if MTB is present, predict whether that MTB is a strain that is resistant to rifampin treatment. The diagnostic test of the '723 patent involves subjecting DNA extracted from a biological sample taken from a patient (e.g., a tissue or fluid sample) to amplification by polymerase chain reaction ("PCR") using a short, single-stranded nucleotide sequence (a "primer") that can hybridize (i.e., bind) to at least one of the eleven position-specific signature nucleotides in the MTB *rpoB* gene.

PCR is a method of amplifying DNA exponentially. *See Roche*, 2017 WL 6311568, at *2. In PCR, a pair of primers effectively "flanks," or marks the start and finish of, the DNA segment—e.g., the *rpoB* gene or a portion of it—to be copied. Strands of DNA are then replicated between the primer pair by a DNA polymerase. This process is repeated until a sufficient number of copies of the desired DNA segment are generated. These copies, known as "amplification product," make it possible to detect whether a specific type of DNA is present. *Id.* It is undisputed that by the time of the invention in 1994, PCR had become a well-understood, routine, and conventional technique. *Id.*

After PCR is performed, the presence of DNA amplification product in sufficient copies from the reaction indicates that MTB is present in the biological sample. The absence of DNA amplification product (i.e., below the detection limit using standard assays) indicates that MTB is absent from the biological sample. The amplified *rpoB* DNA segment from the PCR can, in turn, be tested for the presence of known genetic mutations associated with rifampin resistance. Thus, the '723 patent represents an improvement over the traditional sputum examination method for detecting MTB, as its genetics-based diagnostic method is faster and more accurate.

The '723 patent provides two types of claims: (1) composition-of-matter claims for the primers used in the PCR, which could hybridize to the *rpoB* gene of MTB at a site that includes at least one of the eleven signature nucleotides ("the primer claims"); and (2) process claims for methods for detecting MTB that include amplifying target sequences by PCR and detecting amplification products, which, if present, indicate the presence of MTB ("the method claims").

Claims 1–13 are the method claims. Claim 1, the sole independent method claim, recites:

> 1. A method for detecting Mycobacterium tuberculosis in a biological sample suspected of containing M. tuberculosis comprising:
>
> > (a) subjecting DNA from the biological sample to polymerase chain reaction [PCR] using a plurality of primers under reaction conditions sufficient to simplify a portion of a M. tuberculosis rpoB [gene] to produce an amplification product, wherein the plurality of primers comprises at least one primer that hybridizes under hybridizing conditions to the amplified portion of the [gene] at a site comprising at least

> one position-specific M. tuberculosis signature nucleotide selected, with reference to FIG. 3 (SEQ ID NO: 1), from the group consisting
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> a G at nucleotide position 2312,
>
> a T at nucleotide position 2313,
>
> an A at nucleotide position 2373,
>
> a G at nucleotide position 2374,
>
> an A at nucleotide position 2378,
>
> a G at nucleotide position 2408,
>
> a T at nucleotide position 2409,
>
> an A at nucleotide position 2426,
>
> a G at nucleotide position 2441,
>
> an A at nucleotide position 2456, and
>
> a T at nucleotide position 2465; and
>
> (b) detecting the presence or absence of an amplification product, wherein the presence of an amplification product is indicative of the presence of M. tuberculosis in the biological sample and wherein the absence of the amplification product is indicative of the absence of M. tuberculosis in the biological sample.

'723 patent col. 25 l. 57–col. 27 l. 6.[2] Dependent claims 2–13 add various limitations to claim 1 concerning PCR, PCR analysis, and primer preparation details.

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[2] Adenine ("A"), Thymine ("T"), and Guanine ("G"), together with Cytosine ("C"), constitute the four nucleo-

Claims 17–20 are the primer claims. Independent claim 17 is representative and recites:

> 17. A primer having 14–50 nucleotides that hybridizes under hybridizing conditions to an M. tuberculosis rpoB [gene] at a site comprising at least one position-specific M. tuberculosis signature nucleotide selected, with reference to FIG. 3 (SEQ ID NO: 1), from the group consisting of [the same 11 nucleotides at the positions disclosed in claim 1].

Id. col. 28 ll. 14–31. Dependent claims 18–20 each add further limitations.[3] *Id.* col. 28 ll. 32–46. Dependent claim 20, for example, discloses full DNA sequences of certain primers. *Id.* col. 28 ll. 44–46.

II. DISTRICT COURT PROCEEDING

Appellee Cepheid makes and sells "Xpert® MTB/RIF Assay," an assay that can detect MTB in a biological sample and can identify rifampin-resistant MTB. Roche brought a patent infringement case against Cepheid asserting that Cepheid's product infringed the '723 patent. *Roche*, 2017 WL 6311568, at *1. Cepheid filed a motion for summary judgment, arguing that all of the asserted claims claim patent-ineligible subject matter under 35 U.S.C. § 101. *Id.* at *9.

The district court granted Cepheid's motion. *Id.* at *19. The district court found that the primer claims of the '723 patent, "which have genetic sequences identical to those found in nature, are indistinguishable from those held to be directed to nonpatentable subject matter" and

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tide building blocks of DNA. *See Roche*, 2017 WL 6311568, at *2.

[3] The remaining claims of the '723 patent, claims 14–16 and 21–23, are also primer claims, but they are not asserted in this litigation.

are thus invalid. *Id*. at *14. The district court also found that the method claims are invalid because they are directed to "nonpatentable laws of nature or natural phenomena" and "the use of newly developed, non-patentable primers to bind to newly identified naturally occurring signature nucleotides . . . using the well-known, routine process of PCR in a conventional way does not transform the claimed methods into" patent-eligible subject matter. *Id*. at *16–17.

Roche timely appealed. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

III. DISCUSSION

We review the grant of summary judgment under the law of the regional circuit, in this case the Ninth Circuit. *Charles Mach. Works, Inc. v. Vermeer Mfg. Co.*, 723 F.3d 1376, 1378 (Fed. Cir. 2013). The Ninth Circuit reviews the grant or denial of summary judgment de novo. *Leever v. Carson City*, 360 F.3d 1014, 1017 (9th Cir. 2004). We also review de novo the question of whether a claim is invalid under 35 U.S.C. § 101. *Voter Verified, Inc. v. Election Sys. & Software LLC*, 887 F.3d 1376, 1384 (Fed. Cir. 2018).

The only issues on appeal are whether the aforementioned primer claims and the method claims of the '723 patent are patent-ineligible within the meaning of § 101. Section 101 provides that "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. § 101. There are certain exceptions to this provision: laws of nature, natural phenomena, and abstract ideas are not patent-eligible subject matter. *Alice Corp. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2354 (2014) (collecting cases).

The Supreme Court has established a two-step framework for distinguishing patents that claim laws of nature, natural phenomena, and abstract ideas from those that claim patent-eligible applications of those concepts. *Id.* at 2355 (citing *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 77–79 (2012)). Under the *Alice/Mayo* two-step framework, we first "determine whether the claims at issue are *directed to* one of those patent-ineligible concepts." *Id.* (emphasis added); *see also Enfish, LLC v. Microsoft Corp.*, 822 F.3d 1327, 1335 (Fed. Cir. 2016). "[T]he 'directed to' inquiry applies a stage-one filter to claims, considered in light of the specification, based on whether 'their character as a whole is directed to excluded subject matter.'" *Enfish*, 822 F.3d at 1335 (quoting *Internet Patents Corp. v. Active Network, Inc.*, 790 F.3d 1343, 1346 (Fed. Cir. 2015)). At step one, "it is not enough to merely identify a patent-ineligible concept underlying the claim; we must determine whether that patent-ineligible concept is what the claim is 'directed to.'" *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1050 (Fed. Cir. 2016).

If a claim is directed to one of those patent-ineligible concepts, we move to step two of the *Alice/Mayo* inquiry to "examine the elements of the claim to determine whether it contains an 'inventive concept' sufficient to 'transform' the claimed abstract idea into a patent-eligible application." *Alice*, 134 S. Ct. at 2357 (quoting *Mayo*, 566 U.S. at 72–73, 78). At step two, there must be a further inventive concept to take the claim into the realm of patent-eligibility. *Id.* For claims that encompass natural phenomena, the method steps are the "additional features that must be new and useful." *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1377 (Fed. Cir. 2015); *see also Genetic Techs. Ltd. v. Merial L.L.C.*, 818 F.3d 1369, 1376 (Fed. Cir. 2016), *cert. denied*, 137 S. Ct. 242 (2016). Following the *Alice/Mayo* framework, we address the primer claims and the method claims in turn.

A. The Primer Claims

Roche argues that at *Alice/Mayo* step one, the primer claims (claims 17–20) are patent-eligible because they are directed to artificial, man-made primers that are different from naturally occurring DNA. *Roche*, 2017 WL 6311568, at *10. Specifically, Roche argues that the claimed primers have both a 3-prime end and a 3-prime hydroxyl group, while the naturally occurring bacterial MTB DNA contains neither of these. *Id.* at *11. The district court rejected Roche's arguments and found that "the primer claims in this case, which have genetic sequences identical to those found in nature, are indistinguishable from those held to be directed to nonpatentable subject matter in *In Re BRCA1*." *Id.* at *14 (citing *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d 755, 760 (Fed. Cir. 2014) ("*BRCA1*")). We agree.

BRCA1 forecloses Roche's arguments. There, this court examined the subject matter eligibility of similar primer claims and held that those primers "are not distinguishable from the isolated DNA found patent-ineligible in *Myriad*" and thus are not patent-eligible. *BRCA1*, 774 F.3d at 760 (citing *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 591 (2013)). It is well established that primers are short, single-stranded nucleic acid molecules that bind to their complementary nucleotide sequence.[4] *Id.* at 761; *see Roche*, 2017 WL 6311568, at *10. As this court found in *BRCA1*, "[p]rimers necessarily contain the identical sequence of

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[4] Complementarity refers to the inherent property of nucleotides that causes them to pair with each other: Adenine pairs with Thymine, and Cytosine pairs with Guanine. J.A. 1129–30. This property allows investigators who know the sequence of a single strand of DNA to accurately predict the sequence of the opposite DNA strand. *Id.*

the [nucleotide] sequence directly opposite to the [DNA] strand to which they are designed to bind. They are structurally identical to the ends of DNA strands found in nature." 774 F.3d at 760. The court further held:

> A DNA structure with a function similar to that found in nature can only be patent eligible as a composition of matter if it has a unique structure, different from anything found in nature. *Myriad*, 133 S. Ct. at 2116–17. Primers do not have such a different structure and are patent ineligible.

Id. at 761 (citation omitted).

It is undisputed that the primers before us have the identical nucleotide sequences as naturally occurring DNA, just like the primers found subject matter ineligible in *BRCA1*. Appellant Br. 23 (admitting that "the claimed primers include DNAs with the same nucleotide sequence as portions of the MTB *rpoB* gene"). Nothing in the '723 patent suggests that the Roche inventors introduced any mutations that would have made the primers' nucleotide sequences different from those found in nature. Thus, Roche's primers are indistinguishable from their corresponding nucleotide sequences on the naturally occurring MTB *rpoB* gene.

Roche argues that the claimed primers are nonetheless patent-eligible because they "are chemically and structurally distinct from any nucleic acid that occurs in nature or that can be isolated from naturally occurring DNA." Appellant Br. 23. According to Roche, its claimed primers have a 3-prime end and a 3-prime hydroxyl group, which are absent in naturally occurring DNA. This distinction is unavailing. The same argument was raised in the opening brief in *BRCA1*. *Roche*, 2017 WL 6311568, at *14 (citing Appellant Br. at 11–12, 65–66, *BRCA1* 774 F.3d 775 (Nos. 14–1361, –1366), 2014 WL 1668324). This court rejected this argument, holding that the primers at issue were patent-ineligible subject matter.

BRCA1, 774 F.3d at 761. As we held in *BRCA1*, "it makes no difference that the identified gene sequences are synthetically replicated." *Id.* at 760. It was undisputed that the primers in *BRCA1* contain 3-prime ends and 3-prime hydroxyl groups, exactly as Roche's primers in this case. *Roche*, 2017 WL 6311568, at *14. Thus, except for the nucleotide sequences, the primers before us are not chemically or structurally different from the primers that we held patent-ineligible in *BRCA1*.

Roche also contends that *BRCA1* is distinguishable because, as a bacterium, MTB has "a circular chromosome, which has neither a 3-prime end nor a 3-prime hydroxyl [group]," while "[t]he primers at issue in *BRCA1* were derived from human DNA, in which each chromosome occurs as a linear molecule." Appellant Br. 23, 31. Roche's emphasis on the chromosome is misplaced. The shape of MTB's chromosomes is not relevant to the inquiry on the subject matter eligibility of the claimed primers. As this court determined in *BRCA1*, the subject matter eligibility inquiry of primer claims hinges on comparing a claimed primer to its corresponding DNA *segment* on the chromosome—not the whole chromosome. 774 F.3d at 760–61 (emphasizing the appropriate comparison being between the primers and "the relevant *portion* of the naturally occurring sequence" (emphasis added)). Neither the claims nor the written description of the '723 patent contain any reference to the circular nature of MTB chromosomes. Indeed, Roche's expert admitted that "whether a chromosome is linear or circular makes no difference in designing a primer." *Roche*, 2017 WL 6311568, at *12. Therefore, at *Alice/Mayo* step one, we find that the asserted primers are indistinguishable from naturally occurring DNA and that the primer claims are directed to a natural phenomenon.

Roche next argues that its primers can be distinguished from the patent-ineligible primers of *BRCA1* because they can hybridize to only one of eleven position-

specific signature nucleotides on the MTB *rpoB* gene. Appellant Br. 24. This is an *Alice/Mayo* step two argument: Roche is arguing that the specificity of its primers to the eleven signature nucleotides would "transform" the claimed naturally occurring phenomenon into patent-eligible subject matter. But Roche's emphasis on hybridizing to particular DNA sequences is unavailing. A primer that is otherwise patent-ineligible does not gain subject matter eligibility simply because it can selectively hybridize to a certain position of naturally occurring DNA, because a primer having an identical nucleotide sequence to naturally occurring DNA without further chemical modification is a natural phenomenon. *See BRCA1*, 774 F.3d at 760. Here, the primers before us have no further chemical modification.[5]

The eleven position-specific signature nucleotides on the MTB *rpoB* gene that Roche's primers are designed to hybridize to are naturally occurring; the Roche inventors identified these eleven positions after sequencing MTB DNA. '723 patent col. 12 ll. 1–23. In other words, Roche identified these pre-existing position-specific signature nucleotides; it did not create them. There is no doubt that Roche's discovery of these signature nucleotides on the MTB *rpoB* gene and the designing of corresponding primers are valuable contributions to science and medicine,

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[5] We do not address the subject matter eligibility of primers that have been altered—e.g., investigator-induced mutation(s) such that their nucleotide sequences are not found in nature, or primers which are chemically modified or labeled by investigators such that they cannot be isolated directly from naturally occurring DNA. *See Myriad*, 569 U.S. at 596 ("Scientific alteration of the genetic code presents a different inquiry, and we express no opinion about the application of § 101 to such endeavors.").

allowing for faster detection of MTB in a biological sample and testing for rifampin resistance. However, "[g]roundbreaking, innovative, or even brilliant discovery does not by itself satisfy the § 101 inquiry." *Myriad*, 569 U.S. at 591; *Ariosa*, 788 F.3d at 1379. The primers are not patent-eligible because they can be found in nature, not because they are not valuable scientific discoveries.

We hold that the primers before us are indistinguishable from their corresponding nucleotide sequences on the naturally occurring DNA, and that the primer claims, therefore, are patent-ineligible within the meaning of § 101. We next address the asserted method claims.

B. The Method Claims

At *Alice/Mayo* step one, the plain language of the asserted method claims, viewed in light of the written description, demonstrates that they are directed to naturally occurring phenomena. The method claims disclose a diagnostic test based on the observation that the presence of the eleven position-specific signature nucleotides of the naturally occurring MTB *rpoB* gene indicates the presence of MTB in a biological sample. Claim 1, the sole independent method claim, provides "[a] method for detecting Mycobacterium tuberculosis in a biological sample" and contains two steps: (1) PCR amplification of DNA ("the amplification step"), and (2) determination of the presence of MTB based on the presence or absence of PCR amplification product ("the detecting step"). '723 patent col. 25 l. 57–col. 27 l. 6. The amplification step subjects DNA from a biological sample—naturally occurring matter—to amplification by PCR using primers that are designed to hybridize to at least one of the eleven naturally occurring position-specific signature nucleotides on the MTB *rpoB* gene. *Id.* at col. 25 l. 60–col. 26 l. 67. The primers, as discussed above, are indistinguishable from their corresponding naturally occurring segments on DNA. The detecting step of claim 1 is a mental determi-

nation step: if a PCR amplification product is detected, MTB is present in the biological sample, and vice versa. *Id*. at col. 27 ll. 1–6.

Claim 1 establishes that the method claims are *directed to* a relationship between the eleven naturally occurring position-specific signature nucleotides and the presence of MTB in a sample. In other words, the method claims assert that if an investigator detects a signature nucleotide from a sample, she knows the sample contains MTB. This relationship between the signature nucleotides and MTB is a phenomenon that exists in nature apart from any human action, meaning the method claims are directed to a natural phenomenon, which itself is ineligible for patenting.

The written description supports the conclusion that the method claims of the '723 patent are directed to a patent-ineligible natural phenomenon. In the Summary of the Invention, the patent states:

> This invention involves a comparative analysis of the rpoB sequences in MTB, other mycobacteria and related . . . bacteria . . . demonstrating the heretofore *undiscovered presence* of a set of MTB-specific position-specific "signature nucleotides" that permits unequivocal identification of MTB . . . .

'723 patent col. 2 ll. 60–65 (emphasis added). The language makes clear what the inventors' discovery entails: the revelation of a previously undiscovered natural phenomenon. *Id*. The patent further states that "[i]t was found upon inspection of the sequence alignment that there were eleven sites . . . at which the nucleotide observed for Mycobacterium tuberculosis (MTB) differed from all or most related organisms." *Id*. col. 12 ll. 18–23. Because these signature nucleotides are naturally occurring, we conclude that the method claims, as informed by

the written description, are directed to a patent-ineligible natural phenomenon. We turn to *Alice/Mayo* step two.

We hold that the method claims do not contain an inventive concept that transforms the eleven position-specific signature nucleotides of the MTB *rpoB* gene into patent-eligible subject matter. PCR amplification of DNA is the main action step of the method claims. '723 patent col. 25 l. 60–col. 26 l. 67. The district court found, and Roche does not challenge, that "the background techniques of PCR amplification and detection were '*routine*' when the patent application was filed in 1994." *Roche*, 2017 WL 6311568, at *16 (emphasis added); Appellant Br. 45 ("In the case at bar, the technique of PCR was well known in the prior art."). Indeed, the '723 patent itself makes clear that "[t]he methods of the present invention use *standard PCR techniques*." '723 patent col. 3 ll. 65–66 (emphasis added). Neither the claims nor the written description of the '723 patent disclose any "new and useful" improvement to PCR protocols or DNA amplification techniques in general. The detecting step of claim 1 is similarly devoid of an inventive concept because it involves a simple mental determination of the presence of MTB based on the presence or absence of a PCR amplification product.

Roche asserts that the method claims constitute more than a patent-ineligible natural phenomenon. Roche argues that at the time of the invention, it was "not routine or conventional to use PCR (or any other genetic test) to detect the presence of MTB in a biological sample" and "unprecedented to perform PCR using the type of primer specified in claims 1 through 13." *Roche*, 2017 WL 6311568, at *15; Appellant Br. 42.

While it may be true that Roche inventors were the first to use PCR to detect MTB in a biological sample, being the first to discover a previously unknown naturally occurring phenomenon or a law of nature alone is not

enough to confer patent eligibility. Many groundbreaking, innovative, and brilliant discoveries have been held patent-ineligible. *See e.g., Mayo*, 566 U.S. at 73–77 (discovery of natural correlation between level of certain metabolites and drug dosage, resulting in claimed method of optimizing treatment using standard techniques to administer the drug and then check if the metabolite level indicated the need for a dosage change); *Genetic Techs.*, 818 F.3d at 1374 (discovery of natural correlation between non-coding regions of DNA and the presence of an allele in the coding region, resulting in claimed method of detecting alleles using standard PCR to amplify and detect); *Ariosa*, 788 F.3d at 1373 (discovery of natural phenomenon that pregnant women's blood contains cffDNA, resulting in claimed methods using standard techniques to amplify and detect cffDNA in maternal blood). The Supreme Court in "*Mayo* made clear that transformation into a patent-eligible application requires more than simply stat[ing] the law of nature while adding the words 'apply it.'" *Ariosa*, 788 F.3d at 1377 (internal quotation marks omitted) (quoting *Mayo*, 566 U.S. at 72). *Alice/Mayo* step two's requirement of "additional features that must be new and useful" is simply not met in this case because the asserted method claims recite standard PCR methods applied to a naturally occurring phenomenon; there is no additional innovation. *See id*.

Roche argues that to use its primers to detect MTB "is no less an inventive act than to make a specific artificial drug that is effective to treat an MTB infection." Appellant Br. 26 (emphasis omitted). We disagree. It is a well-established law of nature that "complementary nucleotide sequences bind to each other." *BRCA1*, 774 F.3d at 761. Roche's method claims exploit the same law of nature—the primer binds to its complementary nucleotide sequence on the MTB *rpoB* gene. This court's holding in *BRCA1* applies to this case with equal force: the primers "do not perform a significantly new function. Rather,

[they are] used to form the first step in a [PCR] chain reaction—a function that is performed because the primer maintains the exact same nucleotide sequence as the relevant portion of the naturally occurring sequence." *Id.* Thus, unlike a method of treating a disease with a new drug, Roche's method claims do not involve "a significantly new function" for the primers.[6] *Id.*

This case is distinguishable from *CellzDirect*, where this court vacated a district court's decision that the method claims at issue were ineligible for patenting. 827 F.3d at 1052. This court held that while the claims were based on the discovery of a natural phenomenon (the ability of certain liver cells, or hepatocytes, to survive multiple freeze cycles), they were "directed to a new and useful *laboratory technique* for preserving hepatocytes"—namely, freezing and thawing hepatocytes twice even though the prior art taught away from this process. *Id.* at 1046–51 (emphasis added) (distinguishing cases that did not invent a new and useful method based on the discovery of a natural phenomenon). This court held that "[t]his type of constructive process, carried out by an artisan to achieve 'a new and useful end,' is precisely the type of

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[6] DNA or RNA can sometimes be used as a drug. For example, technologies such as RNA interference ("RNAi") and small inhibitory RNAs ("siRNAs") use RNA to silence the expression of individual genes. *See*, *e.g.*, *Univ. of Utah v. Max-Planck-Gesellschaft Zur Forderung Der Wissenschaften E.V.*, 734 F.3d 1315, 1318 (Fed. Cir. 2013) (an attorneys' fees case not involving subject matter eligibility of the claims); *Ex parte Reich*, No. 2013-004817, 2016 WL 750325, at *1 (P.T.A.B. Feb. 24, 2016); *Ex parte Khvorova*, No. 2012-010359, 2015 WL 4267897, at *1 (P.T.A.B. July 10, 2015). We express no opinion on subject matter eligibility of method claims that exploit DNA or RNA for drug-like new applications.

claim that is eligible for patenting. . . . [The inventors] employed their natural discovery to create *a new and improved way of preserving hepatocyte cells* for later use." *Id.* at 1048 (emphasis added) (quoting *Alice*, 134 S.Ct. at 2354). Unlike the method claims of the '723 patent, the invention in *CellzDirect* went beyond applying a known laboratory technique to a newly discovered natural phenomenon, and instead created an entirely new laboratory technique that "is not simply an observation or *detection*" based on the natural phenomenon. *Id.* (emphasis added). In contrast, the '723 patent claims a method of *detection* based on a natural phenomenon and employs only conventional, well-known laboratory techniques, which are the opposite of those at issue in *CellzDirect*.[7]

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[7] Similarly, this case is also distinguishable from *Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals International Ltd.*, where this court found that the claimed methods of treatment are subject matter eligible because they claim "'a new way of using an existing drug' that is safer for patients" with schizophrenia at *Alice/Mayo* step one. 887 F.3d 1117, 1135 (Fed. Cir. 2018) (quoting *Mayo*, 566 U.S. at 87). *But see id.* at 1142 (Prost, C.J., dissenting) (stating that the treatment claims are "no more than an optimization of an existing treatment of schizophrenia, just as the claims in *Mayo*"). *Vanda* "underscore[s] the distinction between method of treatment claims and those in *Mayo*," i.e., claims "directed to a diagnostic method." *Id.* at 1134–35 (majority opinion). In contrast, Roche's method claims, consisting of a standard PCR amplification step and a mental determination step, are not directed to a method of treatment. Every time an investigator practices Roche's claimed invention—detecting the presence or absence of the eleven signature nucleotides of MTB *rpoB* gene in a sample—she is simply rediscovering a preexisting natural phenomenon. Unlike

Roche attempts to distinguish its invention from the patent-ineligible method claims in *BRCA1*. In *BRCA1*, this court invalidated claims 7 and 8, which were directed to methods of diagnosing genetic mutations of the BRCA1 gene in patients, as subject matter ineligible.[8] 774 F.3d at 763–65. Relevant here, *BRCA1* distinguished the subject matter ineligible method claims 7 and 8 from the potential subject matter eligibility of a different method claim, claim 21, which was not asserted and was thus not at issue; in dicta, the court pointed out that claim 21

> claims a method of detecting alterations in which the alterations being detected are expressly identified in the specification by tables 11 and 12. These tables expressly identify ten predisposing mutations of the BRCA1 gene sequence discovered by the patentees. Thus, the detection in claim 21 is limited to the particular mutations the inventors discovered: detecting ten specific mutations from the wild-type, identified as "[p]redisposing [m]utations," for the specific purpose of identifying increased susceptibility to specific cancers. Claims 7 and 8 are significantly broader and more abstract, as they claim all comparisons between the patient's BRCA genes and the wild-type BRCA genes.

Id. at 765 (footnote and citations omitted).

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in *Vanda*, Roche does not claim a method of treatment based on an underlying natural phenomenon, but the natural phenomenon itself. *Id.* at 1135.

[8] Briefly, claim 7 requires "1) hybridizing a BRCA gene probe and 2) detecting the presence of a hybridization product. Similarly, claim 8 requires 1) amplification of the BRCA1 gene and 2) sequencing of the amplified nucleic acids." *BRCA1*, 774 F.3d at 764.

Roche argues that its method claims are analogous to claim 21, and distinguishable from claims 7 and 8 in *BRCA1*, because they require primers hybridizing to one of eleven signature nucleotides expressly identified in the claims, and thus would not preempt or limit use of other DNAs for detecting MTB. Appellant Br. 34, 50; *see* '723 patent col. 26 ll. 58–68. To be clear, *BRCA1* did not find claim 21 subject matter eligible; in response to the parties' arguments, this court emphasized that "we express no view" on whether claim 21 is subject matter eligible, and simply noted that "claim 21 is qualitatively different from" claims 7 and 8. 774 F.3d at 765. Roche is mistaken that limiting the scope of an otherwise ineligible method claim would necessarily confer subject matter eligibility. Roche's attempt to limit the breadth of the method claims by showing alternative uses of MTB DNA outside of the scope of the claims "does not change the conclusion that the claims are directed to patent ineligible subject matter." *See Ariosa*, 788 F.3d at 1379. "While preemption may signal patent ineligible subject matter, the absence of complete preemption does not demonstrate patent eligibility." *Id*. Thus, the method claims before us cannot gain subject matter eligibility solely because they are limited to specific signature nucleotides.

Therefore, we hold that the asserted method claims of the '723 patent are patent-ineligible because they are directed to a natural phenomenon and lack any inventive concept that transforms them into patent-eligible subject matter.

IV. CONCLUSION

For the foregoing reasons, we affirm the district court's summary judgment ruling.

AFFIRMED

COSTS

No costs.

United States Court of Appeals for the Federal Circuit

ROCHE MOLECULAR SYSTEMS, INC.,
Plaintiff-Appellant

v.

CEPHEID,
Defendant-Appellee

2017-1690

Appeal from the United States District Court for the Northern District of California in No. 3:14-cv-03228-EDL, Magistrate Judge Elizabeth D. Laporte.

O'MALLEY, *Circuit Judge*, concurring.

I agree with the majority that our decision in *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litigation*, 774 F.3d 755, 758 (Fed. Cir. 2014) ("*BRCA1*") compels the conclusion that the primer and method claims of U.S. Patent No. 5,643,723 ("the '723 patent") are not eligible for patent protection.

I write separately to express my belief that we should revisit our holding in *BRCA1* at least with respect to the primer claims. Specifically, I believe that our holding there was unduly broad for two reasons: (1) the question raised in *BRCA1* was narrower than our holding in that case; and, (2) our interpretation of the nature and func-

tion of DNA primers lacked the benefit of certain arguments and evidence that the patent owner presents in this case.

First, the question before us in *BRCA1* was not whether the primer claims were patent-ineligible, but, rather, whether the district court abused its discretion when it denied the patent owner's motion for a preliminary injunction. 774 F.3d at 757. After filing an infringement suit in district court, the patent owner in *BRCA1* moved for a preliminary injunction arguing that it was likely to succeed on the merits of its infringement claim. *In re BRCA1-, BRCA2-Based Hereditary Cancer Test Patent Litig.*, 3 F. Supp. 3d 1213, 1256 (D. Utah 2014). The district court denied the motion, in part, because it found that the accused infringer had "raised a substantial question concerning whether [the patent owner]'s [p]rimer [c]laims are drawn to patent ineligible subject matter." *Id.* at 1263. The district court made no findings regarding whether the primer claims were indeed patent ineligible. *Id.* It correctly acknowledged that, "[a]t this early stage, . . . the court 'does not resolve the validity question,' but instead assesses 'the persuasiveness of the challenger's evidence, recognizing that it is doing so without all the evidence that may come out at trial.'" *Id.* at 1257 (quoting *Titan Tire Corp. v. Case New Holland, Inc.*, 566 F.3d 1372, 1377 (Fed. Cir. 2009)).

The patent owner appealed. We affirmed by expressly concluding that the primer claims were directed to patent-ineligible subject matter. 774 F.3d at 757 ("Because we hold that these claims are directed to ineligible subject matter under 35 U.S.C. § 101, we affirm and remand."); *id.* at 761 ("Primers . . . are patent ineligible"). But that was not the question before us; it was only whether the district court abused its discretion when it found that the accused infringer raised a substantial question regarding invalidity under § 101. Appellants' Br., *BRCA1*, 2014 WL 1668324, Nos. 14-1361, -1366 (Fed. Cir. Apr. 18, 2014), at

*2 (listing in its "Statement of Issues" the question of "[w]hether the district court erred in finding that Ambry raised a substantial question that Myriad's pair of primer claims are not directed to patent eligible subject matter . . . .").

This procedural context in *BRCA1* is important. We have routinely recognized that the question of whether an accused infringer has raised a substantial question of invalidity in the context of a motion for a preliminary injunction—such as the question before the district court in *BRCA1*—presents a different type of inquiry than the question of whether an asserted claim is invalid—such as the question that was before the district court on summary judgment in this case. Indeed, "[w]hile the evidentiary burdens at the preliminary injunction stage track the burdens at trial, importantly the ultimate question before the trial court is different" because "[i]nstead of the alleged infringer having to persuade the trial court that the patent is invalid, at [the preliminary injunction] stage[,] it is the patentee, the movant, who must persuade the court that, despite the challenge presented to validity, the patentee nevertheless is likely to succeed at trial on the validity issue." *Titan Tire*, 566 F.3d at 1377. Significantly, "the trial court 'does not resolve the validity question, but rather must . . . make an assessment of the persuasiveness of the challenger's evidence, recognizing that it is doing so *without all of the evidence* that may come out at trial." *Id.* (emphasis added) (citations omitted).

This brings me to my second point. Because of the procedural posture in *BRCA1*, it is hardly surprising that we did not have the benefit of certain arguments and evidence that the patent owner presents in this case when we decided *BRCA1*. As noted, in *BRCA1*, we considered whether claims directed to the following were patent-eligible under § 101:

> A pair of single-stranded DNA primers for determination of a nucleotide sequence of a BRCA1 gene by a polymerase chain reaction, the sequence of said primers being derived from human chromosome 17q, wherein the use of said primers in a polymerase chain reaction results in the synthesis of DNA having all or part of the sequence of the BRCA1 gene.

774 F.3d at 759 (quoting U.S. Patent No. 5,747,282 col. 155, ll. 23–29). In concluding that these claims were not eligible for patent protection, we relied primarily on the Supreme Court's decision in *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576 (2013), which involved other claims related to the BRCA1 gene. *See BRCA1*, 774 F.3d at 759–61.

In *Myriad*, the Supreme Court separately considered the eligibility of claims directed to "isolated DNA" having a specific genetic sequence, on the one hand, and those directed to complementary DNA ("cDNA")—synthetically created DNA "which contains the same protein-coding information found in a segment of natural DNA but omits portions within the DNA segment that do not code for proteins"—on the other. 569 U.S. at 580. The Court began its analysis by observing that the patent owner in *Myriad* "did not create or alter any of the genetic information encoded in the BRCA1 and BRCA2 genes," nor did it "create or alter the genetic structure of DNA." 569 U.S. at 590. "Instead, [the patent owner]'s principal contribution was uncovering the precise location and genetic sequence of the BRCA1 and BRCA2 genes within chromosomes 17 and 13." *Id.* The Court concluded that, in light of this "principal contribution," the isolated DNA claims were not eligible for patent protection, while the cDNA claims, which do not occur in nature, were. *Id.* at 593–94.

The Court distinguished the isolated DNA claims from the "modified bacterium" claims held patent-eligible

in *Diamond v. Chakrabarty*, 447 U.S. 303 (1980). *Id.* at 590–91. In the Court's view, Chakrabarty's claims were eligible because his bacterium was "new 'with markedly different characteristics from any found in nature.'" *Id.* (quoting *Chakrabarty*, 447 U.S. at 310). The patent owner in *Myriad*, in contrast, "did not create anything" when it isolated DNA having a particular sequence—though "it found an important and useful gene, . . . separating that gene from its surrounding genetic material is not an act of invention." *Id.* at 591. Critically, the Court recognized that claims are not "saved by the fact that isolating DNA from the human genome severs chemical bonds and thereby creates a nonnaturally occurring molecule": the "claims are simply not expressed in terms of chemical composition, nor do they rely in any way on the chemical changes that result from the isolation of a particular section of DNA." *Id.* at 593. It went on to explain that "[i]f the patents depended upon the creation of a unique molecule, then a would-be infringer could arguably avoid at least Myriad's patent claims on entire genes . . . by isolating a DNA sequence that included both the BRCA1 or BRCA2 gene and one additional nucleotide pair." *Id.*

The Court reached a different conclusion with respect to the patent owner's cDNA claims. The Court began by stating that the "creation of a cDNA sequence from mRNA results in an exons-only molecule that is not naturally occurring." *Id.* at 594. It noted that, although viruses can incorporate cDNA into the human genome in rare instances, "[t]he possibility that an unusual and rare phenomenon might randomly create a molecule similar to one created synthetically through human ingenuity does not render a composition of matter nonpatentable." *Id.* at 594 n.8 (emphasis omitted). The Court rejected the accused infringers' argument that cDNA is not patent eligible because "[t]he nucleotide sequence of cDNA is dictated by nature, not by the lab technician," writing

that "the lab technician unquestionably creates something new when cDNA is made." *Id.* at 595. This is because, while "cDNA retains the naturally occurring exons of DNA, . . . it is distinct from the DNA from which it was derived" because the intron sequences are removed. *Id.* Thus, the Court concluded that "cDNA is not a 'product of nature' and is patent eligible under § 101, except insofar as very short series of DNA may have no intervening introns to remove when creating cDNA." *Id.* "In that situation, a short strand of cDNA may be indistinguishable from natural DNA." *Id.*

In *BRCA1*, we discussed *Myriad*'s teachings, culminating in a summary of that case by citing the Supreme Court's observation that, "[t]o the extent that the exon-only sequence does not exist in nature, the lab technician 'unquestionably creates something new when cDNA is made.'" 774 F.3d at 760 (quoting *Myriad*, 569 U.S. at 595). But, in the very next sentence, we concluded that "[t]he primers before us are not distinguishable from the isolated DNA found patent-ineligible in *Myriad* and are not similar to the cDNA found to be patent-eligible." *Id.* We arrived at this conclusion based on two facts that we perceived as entirely resolving the question of whether primers are structurally identical to that which exists in nature. We found that "[p]rimers necessarily contain the identical sequence of the BRCA sequence directly opposite to the strand to which they are designed to bind," and that "[t]hey are structurally identical to the ends of DNA strands found in nature." *Id.*

But it is not clear from the *BRCA1* opinion or record why we reached this conclusion. The lack of record evidence underlying *BRCA1*'s conclusion on this point is important in light of the record in this case. Specifically, *BRCA1* concludes that primers have "identical sequences" to the natural DNA strands directly opposite the strands to which they bind, but, as the record in this case reveals, a finding that the two have identical *sequences* does

entirely resolve the question of whether they are *structurally* identical because structure is not defined solely by nucleotide sequence.[1] Nor is it clear how primers "are structurally identical to the ends of DNA strands found in nature." *Id.* As I explain below, the additional facts in this record, viewed in the light most favorable to Roche, give rise to genuine issues of material fact[2] regarding whether the claimed primers have a "unique structure, different from anything found in nature," and therefore, challenge the conclusion that this entire class of molecules is ineligible under § 101.

Roche developed a record in this case demonstrating the ways in which the claimed primers differ structurally from anything that occurs in nature. Roche first submitted evidence supporting a finding that the claimed primers differ from primers that naturally occur in the bacteria of the M. tuberculosis complex ("MTB"). Roche's expert explained that, unlike the claimed primers, the naturally occurring MTB primers are never single-stranded. J.A. 1892 at ¶ 88. Roche's expert also explained that the naturally occurring MTB primers are comprised of RNA whereas the claimed primers are comprised of DNA. J.A. 1892 at ¶ 89. This means that

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[1] Notably, there can be no dispute that primers, though complementary, are structurally different in sequence from the strands to which they hybridize. Indeed, a primer comprising a nucleotide sequence of ATCG is complementary to, but unquestionably different from, a natural DNA strand comprising a sequence of TAGC.

[2] *See Berkheimer v. HP Inc.*, 890 F.3d 1369, 1370 (Fed. Cir. 2018) (Moore, J., concurring in the denial of rehearing en banc) ("While the ultimate question of patent eligibility is one of law, it is not surprising that it may contain underlying issues of fact.").

naturally occurring MTB primers differ chemically from the claimed primers "both (i) in the type of sugar they contain (ribose [in MTB primers] v. deoxyribose [in the claimed primers]) and (ii) the sets of bases that they use (A, C, G, U [in the MTB primers] v. A, C, G, T [in the claimed primers])." J.A. 1892 at ¶ 89. Finally, Roche's expert explained that "[n]aturally occurring MTB primers are 3–10 nucleotides long, and thus differ structurally from the claimed primers, which are at least 14 nucleotides long." J.A. 1892 at ¶ 90. This record evidence supports a finding that the claimed primers differ from naturally occurring MTB primers.

Roche also explained that the claimed primers differ structurally from the native MTB *rpoB* gene. Roche explained that because "the DNA of MTB occurs in the form a circular chromosome," the native MTB *rpoB* gene lacks a 3-prime end with a 3-prime hydroxyl (-OH) group. J.A. 1891 at ¶ 85. In contrast, the parties agree that the claimed primers *necessarily* have hydroxyl groups at their 3-prime end, and that skilled artisans would recognize as much. Roche's expert explained that "[a] free hydroxyl group at the 3' end of the primer or extension product is *essential* for DNA replication, because it provides a free end to which the next nucleotide can be attached." J.A. 1881 ¶ 40 (emphasis added). Indeed, "[a] DNA that lacks a free hydroxyl group at the 3' end cannot support replication and thus cannot serve as a primer." J.A. 1881 ¶ 40; *see also* J.A. 1884–85 ¶ 48 ("If a DNA does not have a free hydroxyl at the 3'-end, it cannot be a primer.").

Moreover, because the DNA of MTB found in nature occurs in the form of a circular chromosome, and therefore lacks any sort of end, J.A. 1876 at ¶ 26 ("If the DNA is in the form of a closed circle, there are no . . . 3-prime ends, nor a 3-prime hydroxyl group."), the claimed primers cannot be "structurally identical to the ends of DNA strands found in nature," as we concluded in *BRCA1*, 774 F.3d at 760. And, even if the DNA in MTB occurred in

linear strands, Roche's expert testified that, in linear strands of native DNA, only the last nucleotide *in the entire strand* typically has a hydroxyl group at its 3-prime end. Thus, based on the above evidence, Roche's expert concluded that, while a portion of the native MTB *rpoB* gene has the same nucleotide sequence as the claimed primers, the two differ chemically vis-à-vis the presence of a 3-prime end with a 3-prime hydroxyl group at a nonnaturally occurring location. *See* J.A. 1892 at ¶ 86 ("Thus, there is a chemical difference between the primer and the longer DNA strand of which the primer has, in part, the same sequence.").

Said another way, although it is undisputed that all the claimed primers here have nucleotide *sequences* that are identical to segments of the naturally occurring *rpoB* gene found in MTB, a genuine factual dispute exists as to whether they have a *materially different structure* than any DNA molecules typically found in nature. *Cf. Myriad*, 569 U.S. at 595 (deeming relevant whether short strands of cDNA are "indistinguishable from natural DNA"); *Chakrabarty*, 447 U.S. at 310 (holding claims patent-eligible where "the patentee has produced a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility").

Not only does the record demonstrate that the claimed primers could be structurally different from that which exists in nature, but the claims here also appear to be distinguishable from the molecule that would result from isolating the sequence of the strand directly opposite the strand to which the claimed primers hybridize. This is critical because, in *Myriad*, the Court explained that claims directed to isolated DNA sequences "are not saved by the fact that isolating DNA from the human genome severs the chemical bonds that bind gene molecules together." 569 U.S. at 592. But, unlike the claims in *Myriad*, which were neither "expressed in terms of chemi-

cal composition, nor" reliant "in any way on the chemical changes that result from the isolation of a particular section of DNA," 569 U.S. at 592, the primer claims here, by virtue of being directed to the well-known, structural term "primer" and by virtue of including "14-50 nucleotides that hybridize[] under hybridizing conditions" to at least one signature nucleotide, '723 patent, col. 28, ll. 14–31, *are* expressed in terms of chemical composition and *are* reliant on the presence of a 3-prime end and a 3-prime hydroxyl group at a nonnaturally occurring location. Therefore, Roche's evidence regarding the presence of a 3-prime end with a 3-prime hydroxyl group, coupled with the claim language, support a finding that the claims here are distinguishable from the DNA claims in *Myriad*.

These structural differences between the claimed primers and that which exists in nature are not my only concerns with our conclusion in *BRCA1*, however: we also held that primers "do not perform a significantly new function" than does naturally occurring DNA. 774 F.3d at 761. In reaching this conclusion, we rejected the patentee's contention that DNA, when part of the naturally occurring genetic sequence, "stores the biological information used in the development and functioning of all known living organisms," but when isolated as a primer, the DNA fragment "prime[s], i.e., . . . serve[s] as a starting material for a DNA polymerization process." *Id.* We disagreed, writing that:

> [i]n fact, the naturally occurring genetic sequences at issue here *do not perform a significantly new function*. Rather, the naturally occurring material is used to form the first step in a chain reaction—a function that is performed because the primer maintains the exact same nucleotide sequence as the relevant portion of the naturally occurring sequence. One of the primary functions of DNA's structure in nature is that complementary nucleotide sequences bind to each other. It is this same

> function that is exploited here—the primer binds to its complementary nucleotide sequence. Thus, just as in nature, primers utilize the innate ability of DNA to bind to itself.

Id. at 760–61 (emphasis added). We then concluded that *Myriad* does not "confer[] patent eligibility on composition of matter claims directed to naturally occurring DNA strands under such circumstances." *Id.* at 761. Thus, "[a] DNA structure with a function similar to that found in nature can only be patent eligible as a composition of matter if it has a unique structure, different from anything found in nature." *Id.* (citations omitted). We, therefore, held that "[p]rimers do not have such a different structure and are patent ineligible." *Id.*

Here, not only is there at least a genuine issue of material fact as to whether the claimed primers have a different *structure* from anything found in nature, the record also suggests that the claimed primers may have a different *function* from that of native DNA. Particularly, record evidence shows that, unlike native DNA, which merely stores genetic information and serves as a template for replication, the claimed primers can *selectively* hybridize, or bind, to specific nucleotides of a target gene—here, the "signature nucleotides" of the MTB *rpoB* gene. This function is reliant on the presence of the free 3-prime hydroxyl group at a nonnaturally occurring location and allows scientists, among other things, to amplify and detect the MTB *rpoB* gene using techniques such as polymerase chain reaction ("PCR"). The fact that claimed primers, once synthesized, "utilize the innate ability of DNA to bind to itself," *id.* at 761, to achieve this selective hybridization should not render them wholesale patent-ineligible. In *Myriad*, the Supreme Court explained that, although "[t]he nucleotide sequence of cDNA is dictated by nature, not by the lab technician," this is irrelevant for § 101 purposes because "the lab technician unquestionably creates something new when cDNA is

made." 569 U.S. at 595. Similarly, this record contains evidence that the lab technician creates something new when the claimed primers are made, even though, once made, the primers "utilize the innate ability of DNA to bind to itself." *BRCA1*, 774 F.3d at 760–61.

Cepheid argues on appeal that the patent owner in *BRCA1* pointed to the same differences that Roche points to here. Specifically, Cepheid contends that the patent owner in *BRCA1* raised the same 3-prime hydroxyl group argument that Roche makes here, and that we squarely rejected that argument. But, that is not an accurate characterization of the record in *BRCA1*. There, the patent owner merely alluded to the structural distinction between primers and native DNA when explaining the functional differences between the two. Appellants' Br., *In re BRCA1*, 2014 WL 1668324, at *50. The only reference the patent owner made to the free 3-prime hydroxyl group was in its statement of facts in its opening brief where it stated that, "[t]here are no short, single strands of DNA with a free 3'-OH group in nature that can serve as primers." *Id.* at *8. Notably, when attempting to establish the existence of structural differences between native DNA and primers, the patent owner in *BRCA1* did not reference the presence of a hydroxyl group at a nonnaturally occurring location and focused instead on the fact that primers are designed and synthetically created in a lab. *Id.* at *48–50. Therefore, perhaps because of the procedural posture in which the issue was developed, the patent owner in *BRCA1* did not develop a record demonstrating that primers differ structurally from native DNA based on the presence of a hydroxyl group at a nonnaturally occurring location. Nor did we expressly address this hydroxyl group "argument" in *BRCA1* or include language indicating that we had considered, but rejected, any such argument.

The patent owner in *BRCA1* also never argued that its claimed primers were structurally distinct from natu-

rally occurring primers. While the patent owner in *BRCA1* pointed out that "[t]here are no short, single strands of DNA with a free 3'-OH group in nature that can serve as primers" and that "[i]n natural DNA replication, RNA primers are used as the starting material," it never used these facts to demonstrate that the primers at issue were structurally distinct from anything that exists in nature. Appellants' Br., *BRCA1*, 2014 WL 1668324, at *8. Simply, the patent owner in *BRCA1* did not make the specific arguments Roche makes here.

These points were also not raised or addressed in *Myriad*. While the patent owner there argued that native DNA differs from isolated DNA because "[n]ative DNA cannot be used as a molecular tool, such as a probe or a primer," it did not explain that isolated DNA differs structurally from native DNA vis-à-vis a 3-prime end and a 3-prime hydroxyl group at a nonnaturally occurring location. Myriad's Mem. of Law in Support of Mot. for Summary J. and in Opp. to Pl's Mot. for Summary J., *Myriad Genetics v. Assoc. for Molecular Pathology*, No. 1:09-cv-04515-RWS (S.D.N.Y. Dec. 23, 2009), ECF No. 153, 8–9. Significantly, and as explained above, the claims at issue in *Myriad* were not reliant on the presence of this 3-prime hydroxyl group at a nonnaturally occurring location. Accordingly, Myriad could not have properly raised, and the Supreme Court could not have considered, the particular points that Roche now raises. *See Myriad*, 569 U.S. at 593 ("Myriad's claims are simply not expressed in terms of chemical composition, nor do they rely in any way on the chemical changes that result from the isolation of a particular section of DNA.").

Therefore, unlike the appellants in *Myriad* and in *BRCA1*, here, Roche submitted evidence of record that, at the very least, raises genuine issues of material fact as to whether there exists anything in nature that both has the structure and performs the function of the claimed primers. For these reasons, while I agree with the majority

that the broad language of our holding in *BRCA1* compels the conclusion that the primer claims in this case are ineligible under 35 U.S.C. § 101, I believe that holding exceeded the confines of the issue raised on appeal and was the result of an underdeveloped record in that case. I believe, accordingly, that we should revisit our conclusion in *BRCA1* en banc.