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Federal Circuit Friday

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In *Roche Molecular Systems v. Cepheid* (October 9) the Federal Circuit affirmed summary judgment that claims to PCR primers for identifying Mycobacterium tuberculosis ("MTB") strains were not patent-eligible.[1]

Roche argued that its claimed primers differed from naturally-occurring DNA in three ways:

- They have 3' termini, unlike their counterpart sequences in the circular MTB chromosome.
- They have 3' hydroxyl groups, unlike their counterpart sequences in the circular MTB chromosome.
- They can each hybridize to only one of 11 position-specific "signature" nucleotides in the MTB *rpoB* gene (which is implicated in antibiotic resistance).

The Federal Circuit found the first two distinctions unpersuasive at *Alice* Step One per *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litigation*[2] because the claimed primers "have the identical nucleotide sequences as naturally occurring DNA, just like the primers found subject matter ineligible in *BRCA1,*" the arguments regarding the presence of 3' termini and 3' hydroxyls were made and rejected in the *BRCA1* case, and the circularity of the MTB chromosome was not relevant because subject matter eligibility for primer claims "hinges on comparing a claimed primer to its corresponding DNA segment on the chromosome—not the whole chromosome." The essential point is that the claimed primers are not materially distinguishable from naturally occurring DNA and are therefore directed to a natural phenomenon.

The court interpreted the third distinction as an *Alice* Step Two argument and found that the specificity of the primers did not impart patent eligibility because such primers are still identical to a naturally-occurring sequences and as such are "a natural phenomenon." The court explained that "Roche identified these pre-existing position-specific signature nucleotides; it did not create them," and although the discovery of the signature nucleotides and design of the primers were "valuable contributions to science and medicine[,] . . . [g]roundbreaking, innovative, or even brilliant discovery does not by itself satisfy the § 101 inquiry."

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The majority opinion is a straightforward application of Federal Circuit precedent. What's more interesting about this case is Judge O'Malley's concurrence, where she argues that the precedent should be revisited *en banc*.

Judge O'Malley makes both a procedural argument (to help open the door to reconsideration of the *BRCA1* decision) and a substantive argument (to show how the *BRCA1* decision might come out differently in the context of the *Roche v. Cepheid* facts). Below is an outline-form summary of her essential points:

Procedure

1. The Federal Circuit did not need to decide the primer eligibility issue in the *BRCA1* case.
    a. The procedural posture was appeal of a denial of preliminary injunction.

[1] The patent at issue is US 5,643,723.

[2] 774 F.3d 755, 760 (Fed. Cir. 2014).

b. At the preliminary injunction stage, the issue is whether there is a substantial question of invalidity (on grounds of ineligibility, in the *BRCA1* case), ***not*** whether the claims are actually invalid.

c. The issue on appeal therefore was solely whether the district court abused its discretion in denying the preliminary injunction on the grounds that the alleged infringer had raised a substantial question of patent-ineligibility.

2. The Federal Circuit nevertheless determined, as a matter of law, that the primer claims were patent-ineligible.

3. The Federal Circuit decision was not only unnecessary, it was premature having been made without the benefit of evidence that is typically adduced and arguments identified, developed, and refined in the phases of district court action occurring after the preliminary injunction phase.[3]

Substance

1. In *Myriad*, the Supreme Court explained that isolated DNA fragments were not patent eligible where (i) the fragments corresponded to naturally-occurring gene sequences; (ii) the "principal contribution was uncovering the precise location and genetic sequence of the" genes at issue; and (iii) the claims were "not expressed in terms of chemical composition, nor [did] they rely in any way on the chemical changes that result from the isolation of a particular section of DNA."

2. In *BRCA1*, the Federal Circuit concluded that the primers at issue were not legally distinguishable from the patent-ineligible DNA fragments in *Myriad* because (i) the primers "necessarily contain the identical sequence of the BRCA sequence directly opposite to the strand to which they are designed to bind," and (ii) the termini of the primers "are structurally identical to the ends of DNA strands found in nature." But the bases for these conclusions are not clear.

   a. First, that claimed and naturally-occurring DNA fragments share "identical sequence" does not "entirely resolve the question of whether they are structurally identical because structure is not defined solely by nucleotide sequence."

   b. Second, it is not clear that primer termini "are structurally identical to the ends of DNA strands found in nature."

3. The facts in this case (*Roche v. Cepheid*) demonstrate that there *could* be differences between the claimed primers and naturally-occurring DNA that render the primers patent-eligible, including:

   a. Naturally-occurring primers (*i.e.,* replication primers) never exist single-stranded, are made of RNA rather than DNA, and are shorter than the claimed primers;

   b. The native MTB *rpoB* gene lacks a 3' termini or a 3' hydroxyl (unlike the claimed primers, which must have 3' termini and 3' hydroxyls to function);

   c. Because the bacterial chromosome is circular, there are no 3' termini or 3' hydroxyls in nature, so the claimed primers do not mimic the ends of the naturally-occurring DNA in which the sequence at issue resides.

4. Thus, "a genuine factual dispute exists as whether [the primers] have a materially different structure than any DNA molecules typically found in nature."

5. There may also be a *functional* difference – "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."

[3] Implicit here is that the facts adduced in *Roche v. Cepheid* could lead to a result different than *BRCA1*, and therefore to a reversal or limitation of that precedent.

Although these are all good points, and suggest that the holding in *BRCA1* could properly be revisited using *Roche v. Cepheid* as a vehicle, it is not clear that ultimately any change in the law would or should occur because the facts likely do not materially distinguish Roche's claimed primers from naturally-occurring DNA either structurally or functionally. For example:

- The claimed primers at issue in *BRCA1* and *Roche v. Cepheid* comprise naturally-occurring sequences and naturally-occurring nucleotides,[4] and "separating [a fragment of DNA] from its surrounding genetic material is not an act of invention."[5]
- Per *Myriad*, the naturally-occurring RNA replication primers are a less relevant comparator than are the fragments of the bacterial DNA genome that correspond to the claimed primer sequences.
- The naturally-occurring DNA fragments corresponding to the primers *do have* 3' termini and 3' hydroxyls transiently during replication.[6] But even if they did not, claims cannot be "saved by the fact that isolating DNA from the human genome severs chemical bonds and thereby creates a nonnaturally occurring molecule."[7]
- Whether there is a functional distinction depends on how the function is defined.
    - If the function of a primer is defined as allowing the addition of one or more nucleotides in a 5' to 3' direction (by providing a free 3' hydroxyl) at a particular place on a single stranded DNA molecule, then the claimed primers and the naturally-occurring replicated DNA strand that aligns with the primer sequence during the replication process are functionally equivalent.
    - However, if the function is defined as selective binding in a manner that permits determination of the presence of a particular sequence, then the functions would be different, and probably materially so. But the claims at issue in *Roche v. Cepheid* are directed to "primers," with no other language indicating function, and determining of the presence of a particular sequence is likely too much function to read into the composition-of-matter claims via the word "primer."[8]
- In sum, the claimed primers are naturally-occurring DNA molecules isolated from their natural environment, with no material modification or chemical change resulting from the isolation.[9]

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[4] The primers in *Roche v. Cepheid* are claimed in terms of capability of hybridizing under hybridizing conditions, and so the claims embrace both the naturally-occurring sequences and non-naturally-occurring sequences sufficiently homologous to hybridize.

[5] *Association for Molecular Pathology v. Myriad Genetics*, 569 US 576, 591 (2013).

[6] Replication of both leading strand (continuous) and lagging strand (serial synthesis of Okazaki fragments) utilize DNA Polymerase III and proceeds step-wise (via nucleophilic attack by the 3' hydroxyls) to add each nucleotide. At discrete points during replication after the initiating RNA primers are extended the newly-generated double-stranded portion should directly align with primer sequences and have a 3' terminus and a 3' hydroxy available for incorporation of the next nucleotide – *appearing, from the polymerase's perspective, identical to the claimed primers*. Regarding the lagging strand, it may be theoretically possible that no portion of an Okazaki fragment ever directly aligns with a primer sequence (*i.e.,* a ligation gap always happens to occur within primer sequences), but that seems unlikely.

[7] *Myriad*, 569 US at 593. Moreover, generating 3' termini and 3' hydroxyls by "separating [a fragment of DNA] from its surrounding genetic material is not an act of invention." *Id.* at 591.

[8] However, the word "primer" is used in the '723 specification solely in connection with PCR processes, and the characteristics of "primers" are discussed solely in terms of their properties in the context of PCR. So, the function might be defined as "allowing the addition of one or more nucleotides in a 5' to 3' direction at a pre-determined place on a single stranded DNA molecule *in a polymerase chain reaction process.*" That distinguishes the function from natural processes, but only via a human-developed process that was likely routine and conventional as of the filing date (May 1994).

[9] In contrast, primers having non-naturally-occurring structures should be patent-eligible (e.g., base modifications, labels, 5' tails, etc.). Of course, there will be an obviousness issue, but at least you get past the threshold 101 eligibility issue.