

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GUARDANT HEALTH, INC.,
Petitioner,

v.

UNIVERSITY OF WASHINGTON,
Patent Owner.

IPR2022-01159
Patent 10,752,951 B2

Before JOHN G. NEW, ZHENYU YANG, and TINA E. HULSE,
Administrative Patent Judges.

YANG, *Administrative Patent Judge.*

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Guardant Health, Inc. (“Petitioner”) filed a Petition (Paper 3, “Pet.”), seeking an *inter partes* review of claims 1, 6, 7, and 9–26 of U.S. Patent No. 10,752,951 B2 (Ex. 1001, “the ’951 patent”). University of Washington (“Patent Owner”) filed a Patent Owner Preliminary Response. Paper 10 (“Prelim. Resp.”). With our authorization (Ex. 1054), Petitioner filed a Reply (Paper 11), and Patent Owner filed a Sur-reply (Paper 13).

We have authority under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted “unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a).

For the reasons provided below, we determine Petitioner has not demonstrated a reasonable likelihood that it would prevail with respect to at least one claim challenged in the Petition. Accordingly, we deny institution of an *inter partes* review.

A. Related Matters

According to the parties, the ’951 patent is asserted against Petitioner in *TwinStrand Biosciences, Inc. et al. v. Guardant Health, Inc.*, 1-21-cv-01126 (D. Del.). Pet. 13–14; Paper 6, 1.

Petitioner also filed a petition in IPR2022-01158, challenging claims 1–28 of the ’951 patent. In a concurrently issued decision, we institute review in that case.

The parties further identify IPR2022-00449, IPR2022-00450, IPR2022-00816, IPR2022-00817, and IPR2022-00935 as related proceedings. Pet. 14; Paper 6, 1–2. In those cases, Petitioner challenged claims of patents related to the ’951 patent. Pet. 14. We instituted review in

IPR2022-00817 but denied the other petitions. Petitioner has requested Precedential Opinion Panel review of our decisions denying institution in IPR2022-00449, IPR2022-00450, and IPR2022-00816.¹ Those requests are currently pending.

B. The '951 Patent and Related Background

The '951 patent relates to methods of lowering the error rate of massively parallel DNA sequencing using duplex consensus sequencing (“DCS”). Ex. 1001, code (54), 17:17–19.

The '951 patent states massively parallel DNA sequencing “offer[ed] the unique ability to detect minor variants within heterogeneous mixtures.” *Id.* at 1:33–42. It notes the rapid development of clinical applications of deep sequencing in “prenatal screening for fetal aneuploidy, early detection of cancer and monitoring its response to therapy with nucleic acid-based serum biomarkers.” *Id.* at 1:43–50 (internal citations omitted). Deep sequencing, however, according to the '951 patent, had limitations, including “a practical limit of detection . . . imposed by errors introduced during sample preparation and sequencing,” resulting in “approximately 1% of bases [being] incorrectly identified.” *Id.* at 1:61–2:8. The '951 patent states “[t]his background level of artifactual heterogeneity establishes a limit below which the presence of true rare variants is obscured.” *Id.* at 2:9–11.

The '951 patent acknowledges several attempts aimed at improving the accuracy and sensitivity of sequencing. *Id.* at 2:12–33. But, according to the '951 patent, “significant technical artifacts” still result in error rates far higher than the “true mutation frequency.” *Id.* at 2:33–39.

¹ Petitioner did not seek rehearing of our decision denying institution in IPR2022-00935. That case, thus, has concluded.

The '951 patent states “[i]t would be desirable to develop an approach for tag-based error correction.” *Id.* at 2:64–65. According to the '951 patent, its approach, termed duplex consensus sequencing (“DCS”), “greatly reduces errors by independently tagging and sequencing each of the two strands of a DNA duplex.” *Id.*, Abstract. It explains that, because the two strands are complementary, true mutations are found at the same position in both strands. *Id.*

In one embodiment, the DCS method of the '951 patent involves tagging both strands of duplex DNA with a random, yet complementary double-stranded nucleotide sequence, known as a single molecule identifier (SMI) sequence. *Id.* at 21:41–45. After PCR amplifying the individually tagged strands, “a family of molecules is obtained that arose from a single DNA molecule.” *Id.* at 21:51–67. According to the '951 patent, “members of the same PCR ‘family’ are then grouped together by virtue of having a common (i.e., the same) SMI tag sequence. The sequences of uniquely tagged PCR duplicates are subsequently compared in order to create a PCR consensus sequence,” called single strand consensus sequence (SSCS). *Id.* at 21:67–22:13.

The '951 patent further discloses that SSCSs from two complementary strands of duplex DNA can be identified by virtue of the complementary SMIs to identify the “partner SMI.” *Id.* at 22:14–17. “Following partnering of two strands by virtue of their complementary SMIs, the sequences of the strands are compared. Sequence reads at a given position are kept only if the read data from each of the two paired strands is in agreement.” *Id.* at 22:21–25.

C. Illustrative Claim

Independent claim 1 is illustrative of the claimed subject matter and is reproduced below.

1. A method, comprising:

- (a) providing a sample comprising a set of double-stranded polynucleotide molecules, each double-stranded polynucleotide molecule including first and second complementary strands;
- (b) tagging said double-stranded polynucleotide molecules with a set of duplex tags;
- (c) sequencing at least some of said tagged strands to produce a set of sequence reads;
- (d) sorting sequence reads into paired sequence reads and unpaired sequence reads, wherein (i) each paired read corresponds to sequence reads generated from a first tagged strand and a second differently tagged complementary strand derived from an original parent polynucleotide molecule in said set, and (ii) each unpaired read represents a first tagged strand having no second differently tagged complementary strand derived from an original parent polynucleotide molecule represented among said sequence reads in said set of sequence reads; and
- (e) quantifying at least two of (i) said paired sequence reads, (ii) said unpaired sequence reads, (iii) read depth of said paired sequence reads and (iv) read depth of said unpaired sequence reads.

Id. at 37:36–59.

D. Asserted Challenge to Patentability

Petitioner asserts the following challenges to patentability:

Claim(s) Challenged	35 U.S.C. §	References
1, 6, 7, 9–26	103	Kinde ² , Craig ³

Petitioner relies on the declaration of John Quackenbush, Ph.D., as support for its Petition. Ex. 1002.

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, we construe a claim term “using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. [§] 282(b).” 37 C.F.R. § 42.100(b) (2020). Under that standard, the words of a claim “are generally given their ordinary and customary meaning,” which is “the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc).

The parties agree that, for purposes of this Decision, no claim term needs specific construction beyond its plain and ordinary meaning. Pet. 15;

² Kinde et al., *Detection and quantification of rare mutations with massively parallel sequencing*, 108 PNAS 9530–35 (2011) (Ex. 1006, “Kinde”). Petitioner also submits, as part of Exhibit 1006, Supporting Information for Kinde. See Ex. 1006, S1–S10.

³ Craig et al., *Identification of genetic variants using bar-coded multiplexed sequencing*, 5 NATURE METHODS 887–93 (2008) (Ex. 1007, “Craig”). Petitioner also submits, as part of Exhibit 1007, supplementary figures and text associated with Craig. See Ex. 1007, 10–19.

Prelim. Resp. 7. The parties nevertheless seek to provide context, or reiterate the plain meaning, of certain claim terms. Pet. 15–17; Prelim. Resp. 7–8.

Claim terms need only be construed to the extent necessary to resolve the controversy. *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011). On this record and for purposes of this Decision, we see no need to construe any claim term.

B. Prior Art Disclosures

1. Kinde

Kinde describes a method for increasing the sensitivity of massively parallel sequencing instruments to identify rare mutations in DNA. Ex. 1006, Abstract. According to Kinde, massively parallel sequencing can be used to analyze multiple bases “sequentially and easily” in an automated fashion but “cannot generally be used to detect rare variants because of the high error rate associated with the sequencing process.” *Id.* at 9530.

Kinde refers to its improved method as the “Safe-Sequencing System” or “Safe-SeqS.” *Id.* at Abstract. Kinde describes “how templates can be prepared and the sequencing data obtained from them [can be] more reliably interpreted, so that relatively rare mutations can be identified with commercially available instruments.” *Id.* at 9530. The Safe-SeqS involves the following two basic steps: (1) assignment of a unique identifier (UID) to each DNA template molecule to be analyzed; and (2) amplification of each uniquely tagged template, so that many daughter molecules with the identical sequence are generated (defined as a UID family). *Id.*

Kinde explains that “[a] UID family in which at least 95% of family members have the identical mutation is called a ‘supermutant.’” *Id.* According to Kinde, “[m]utations not occurring in the original templates,

such as those occurring during the amplification steps or through errors in base calling, should not give rise to supermutants.” *Id.*

Kinde states that “UIDs, sometimes called barcodes or indexes, can be assigned to nucleic acid fragments using a variety of methods.” *Id.* at 9531. Specifically, Kinde describes using endogenous and exogenous UIDs. *Id.* at 9531–32, S1. Kinde states that “randomly sheared genomic DNA inherently contains [endogenous] UIDs consisting of the sequences of the two ends of each sheared fragment.” *Id.* at 9531.

Kinde also teaches an inverse PCR method, in which, like the endogenous method, the ends of the random sheared genomic DNA serve as UIDs. *Id.* at S4. The DNA fragments are ligated with adapters, which do not contain exogenous UIDs, and are amplified. *Id.* at S1, S4. The adapter-DNA molecules are circularized and inverse PCR amplified with gene specific primers. *Id.* at S1, S4. The forward primer used in the PCR reaction “contain[s] one of 12 index sequences at its 5’ end.” *Id.* at S1, S4.

Kinde further teaches using PCR with a forward primer that contains “a stretch of 12–14 random nucleotides” to introduce exogenous UIDs. *Id.* at 9532. In discussing the exogenous UIDs, Kinde states that “[i]t is important that the number of distinct UIDs greatly exceeds the number of original template molecules to minimize the probability that two different original templates acquire the same UID.” *Id.* at S1.

Kinde states that its Safe-SeqS approach “can be implemented through either endogenous or exogenously introduced UIDs and can be applied to virtually any sample preparation workflow or sequencing platform.” *Id.* at 9533.

2. Craig

Craig describes “a generalized framework for multiplexed resequencing of targeted human genome regions on the Illumina Genome Analyzer using degenerate indexed DNA bar codes ligated to fragmented DNA before sequencing.” Ex. 1007, 3. It teaches (1) amplifying genomic DNA regions by PCR; (2) modifying the amplicons, including digestion, blunt end repair, and adding adenosine overhang; (3) ligating indexed adapters to the modified amplicons; (4) amplifying the adapter-ligated amplicons; and (5) sequencing the amplification products of step (4). *Id.*; *see also id.* at 18 (describing the methods in detail).

C. *Alleged Obviousness over Kinde and Craig*

Petitioner explains that it has challenged the priority date of the claims of the '951 patent in the companion case IPR2022-01158. Pet. 1–3. Petitioner contends that, if we adopt Patent Owner’s position and reject the priority challenge, then the challenged claims would have been obvious over Kinde and Craig. *Id.* at 3, 17–44. Based on this record, and for at least the following reasons, we determine Petitioner has not established a reasonable likelihood that it would prevail in this assertion. We focus our analysis on claim 1.

Petitioner asserts that Kinde teaches each limitation of claim 1, and Craig teaches steps (a)–(c) of claim 1. Pet. 17–30. Petitioner also argues that “[a] POSA would have had motivation and reasonable expectation of success in achieving what is claimed.” *Id.* at 19, 22–23.

Patent Owner contends that Petitioner fails to establish Kinde teaches steps (d) and (e) of claim 1. Prelim. Resp. 26–38. We do not need to address these arguments because we agree with Patent Owner that Petitioner has not

met its burden in showing that an ordinarily skilled artisan would have had a reason to combine the teachings of Kinde and Craig. *See id.* at 20–26.

Petitioner discusses the combination of Kinde and Craig in addressing step (b) “tagging said double-stranded polynucleotide molecules with a set of duplex tags.” Pet. 21–23. Petitioner argues that Kinde teaches assigning endogenous and/or exogenous UIDs to double-stranded nucleic acids. *Id.* at 21 (citing Ex. 1006, 9530, 9531, Fig. 2). Petitioner points out that Kinde (1) teaches ligating Y-shaped adapters (e.g., standard Illumina adapters) to DNA molecules; and (2) “cites Craig, which discloses barcoded-adapters and ligating exogenous barcodes to the template DNA.” *Id.* at 22 (citing Ex. 1006, 9531, 9535, Fig. 2). Craig, Petitioner continues, discloses ligating Illumina Y-shaped adapters comprising a barcode to double-stranded DNA. *Id.* (citing Ex. 1007, 887, 888, Fig. 1, Supplementary Tables 3 and 4, Supplementary Methods).

According to Petitioner, “skilled artisans had good reason to use [Craig’s] Y-shaped Illumina adapters comprising barcodes to arrive at the challenged claims in view of Kinde’s Safe-SeqS approach.” *Id.* As explained below, we are not persuaded by Petitioner’s arguments.⁴

As an initial matter, we agree with Petitioner that “[b]oth Kinde and Craig describe use of Y-shaped (e.g., Illumina) adapters to produce

⁴ As Patent Owner points out, we previously rejected Petitioner’s arguments regarding the reason to combine Kinde and Craig in IPR2022-00816. *See* Prelim. Resp. 1–2, 21–22 (citing IPR2022-00816, Paper 16, 13–16). Later, we reiterated our determination when denying the petition in IPR2022-00935. *See* IPR2022-00935, Paper 11 (“935 DDI”), 32–36. Because Petitioner’s reason-to-combine arguments in the instant case are substantially the same as those in IPR2022-00816 and IPR2022-00935, we see no reason to deviate from our previous decisions.

adapter-DNA molecules.” *Id.* at 19. But, the Y-shaped adapters in Kinde are different from those in Craig: the former do not contain barcodes, whereas the latter do. *Compare* Ex. 1006, S9 (showing the adapters used in the endogenous method do not contain barcodes), *with* Ex. 1007, Supplementary Table 3 (showing adapters with barcodes).

To the extent Petitioner argues that an ordinarily skilled artisan *could have* swapped Kinde’s Y-shaped adapters with Craig’s, that is insufficient for our analysis. *See Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015) (“[O]bviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention”).

To answer the question why the artisan would have used Craig’s adapters with barcodes in Kinde’s Safe-SeqS approach, Petitioner contends that “Kinde cites Craig in discussing exogenous barcodes with DNA molecules.” Pet. 19; *see also id.* at 22–23 (“[C]iting to Craig, Kinde discusses methods including assigning exogenous barcodes to nucleic acid fragments.”). But, as Patent Owner points out, Kinde does not use Craig’s approach. Prelim. Resp. 1. Instead, immediately after citing Craig as teaching attaching exogenous UIDs through ligation, Kinde introduces its endogenous method as an “[e]ven more simpl[e]” approach. Ex. 1006, 9531. Thus, Kinde appears to teach Craig as an alternative, not an additional, method to assign UIDs.

Petitioner points to Shiroguchi as reflective of the state of the art. *Id.* (citing Ex. 1010, Figure 1, Figure S5). Shiroguchi is directed to a “method for bias and noise reduction in [RNA sequencing] that allows the use of PCR to amplify a cDNA library before sequencing” to provide accurate digital

quantification of the transcriptome. Ex. 1010, 1347. In this method, “each cDNA molecule is attached to a unique barcode sequence from a large pool of barcodes before amplification (Fig. 1A). Deep sequencing then allows quantification of the number of cDNA molecules in the original sample by counting the number of unique barcode sequences associated with a given cDNA sequence.” *Id.* (internal references omitted). According to Shiroguchi, to avoid complication caused by the fact “a substantial fraction of reads contained misidentified barcodes,” it “designed optimized barcodes that can be ligated and amplified with minimal bias and distinguished from one another despite the accumulation of PCR mutations and sequencing errors.” *Id.*

Petitioner refers to Shiroguchi to buttress its argument that “Kinde and Craig describe use of Y-shaped (*e.g.*, Illumina) adapters to produce adapter-DNA molecules that have a region of non-complementarity that provides a strand-distinguishing sequence.” Pet. 19. We previously considered and rejected substantially the same argument. *See* 935 DDI, 24–30.

In that decision, we stated:

With respect to Shiroguchi, Petitioner relies primarily upon the fact that the reference teaches the use of conventional Y-shaped Illumina adapters to each barcoded end of the phosphorylated cDNA fragments (*see* Ex. 1010, Fig. 1B) and Shiroguchi’s single statement, in the caption to Figure S5, that “we are able to distinguish the different strands of an original cDNA molecule because of the design of the paired-end sequencing adapters.” *See, e.g.*, Pet. 7–8. However, we are not persuaded by Petitioner’s argument that this sentence teaches that it is the Y-shaped Illumina adapter itself that provides the strand-distinguishing nucleotide sequence.

Id. at 27. After analyzing Shiroguchi, specifically Figure S5, we found

Shiroguchi teaches that the barcodes and adapter sequences identify, for this limited purpose of identifying errors introduced into the barcode, the different strands of barcoded cDNA from the non-barcoded DNA of the *E. coli* genome. What Figure S5 does *not* purport to show is that the design of the adapters, let alone the region of non-complementarity, is such that it can be used to distinguish the two strands of barcoded cDNA from each other.

Id. at 29.

We adopt the same analysis in 935 DDI and reach the same conclusion here. As such, we are not persuaded that Shiroguchi supports Petitioner's argument that it is the non-complementary region of the Y-shaped adapters that provides a strand-distinguishing sequence.

See Pet. 19.

Citing the legend to Figure 2, Petitioner further argues that “Kinde even explains that ‘[o]ne uniquely identifiable fragment is produced from each strand of the double-stranded template.’” Pet. 19 (citing Ex. 1006, Fig. 2). Kinde's Figure 2 illustrates the endogenous method, in which “[t]he sequences of the ends of each fragment produced by random shearing . . . serve as the unique identifiers (UIDs).” Ex. 1006, 9531, Fig. 2; *see also id.* at S1 (“The ends of each template molecule provide endogenous UIDs corresponding to their chromosomal positions.”).

Thus, Kinde's “uniquely identifiable fragment” is identified by the ends of the nucleic acid molecules generated by random shearing, and not, as Petitioner asserts, due to the Y-shaped Illumina adapters. Petitioner does not explain sufficiently why an ordinarily skilled artisan would have introduced Craig's adapters, which comprises exogenous barcodes, to Kinde's endogenous method.

In sum, Petitioner has not met its burden to sufficiently explain the reason to combine the teachings of Kinde and Craig. Thus, Petitioner has not demonstrated a reasonable likelihood that it would prevail in showing that claim 1, as well as claims 6, 7, and 9–26, which depend from claim 1, would have been obvious over the combination of Kinde and Craig.

III. CONCLUSION

Based on the current record, and for the reasons explained above, we find Petitioner has not demonstrated a reasonable likelihood that it would prevail with respect to at least one claim challenged in the Petition.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is denied, and we do not institute *inter partes* review of any claim of the '951 patent based on the grounds asserted in the Petition.

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