

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GUARDANT HEALTH, INC.,
Petitioner,

v.
UNIVERSITY OF WASHINGTON,
Patent Owner.

IPR2022-00816
Patent 10,760,127 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 1–30 of U.S. Patent No. 10,760,127 B2 (Ex. 1001, “the ’127 patent”). University of Washington (“Patent Owner”) filed a Patent Owner Preliminary Response. Paper 10 (“Prelim. Resp.”). With our authorization (Ex. 3001), Petitioner filed a Reply (Paper 13), and Patent Owner filed a Sur-reply (Paper 15).

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 ’127 patent is asserted against Petitioner in *TwinStrand Biosciences, Inc. et al. v. Guardant Health, Inc.*, 1-21-cv-01126 (D. Del.). Pet. 15; Paper 6, 1.

Petitioner also filed a petition in IPR2022-00817, challenging the same claims of the ’127 patent. In a concurrently issued decision, we institute review in that case.

Patent Owner further identifies IPR2022-00449 and IPR2022-00450 as related proceedings. Paper 6, 1. In those two cases, Petitioner challenged the claims of Patent No. 10,689,699, which is in the same family as the ’127 patent challenged here. We denied those petitions. IPR2022-00449,

Paper 13; IPR2022-00450, Paper 13. Petitioner has requested review of each of those decisions by the Precedential Opinion Panel. *See* IPR2022-00449, Paper 19; IPR2022-00450, Paper 19. Those requests are currently pending.

B. The '127 Patent and Related Background

The '127 patent relates to methods of lowering the error rate of massively parallel DNA sequencing using duplex consensus sequencing (“DCS”). Ex. 1001, code (54), 17:8–10.

The '127 patent states massively parallel DNA sequencing “offer[ed] the unique ability to detect minor variants within heterogeneous mixtures.” *Id.* at 1:32–41. 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 1:42–49 (internal citations omitted). Deep sequencing, however, according to the '127 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 1:60–2:7. The '127 patent states “[t]his background level of artifactual heterogeneity establishes a limit below which the presence of true rare variants is obscured.” *Id.* at 2:8–10.

The '127 patent acknowledges several attempts aimed at improving the accuracy and sensitivity of sequencing. *Id.* at 2:11–32. But, according to the '127 patent, “significant technical artifacts” still result in error rates far higher than the “true mutation frequency.” *Id.* at 2:32–38.

The '127 patent states “[i]t would be desirable to develop an approach for tag-based error correction.” *Id.* at 2:63–64. According to the '127 patent, its approach “reduces or eliminates artifactual mutations arising from DNA

damage, PCR errors, and sequencing errors; allows rare variants in heterogeneous populations to be detected with unprecedented sensitivity; and . . . capitalizes on the redundant information stored in complexed double-stranded DNA.” *Id.* at 2:64–3:2.

C. Illustrative Claims

Among the challenged claims, claims 1 and 22 are independent. They are illustrative of the claimed subject matter and, with the Certificate of Correction incorporated,¹ are reproduced below.

1. A method of sequencing DNA comprising:

a) attaching adapters to double-stranded DNA fragments to generate a plurality of partially-complementary, asymmetrical double-stranded adapter-DNA molecules, wherein the adapters comprise barcodes selected from a plurality of distinct barcode sequences;

b) amplifying original strands of at least a portion of the double-stranded adapter-DNA molecules to produce first and second strand copies;

c) sequencing a plurality of first and second strand copies to obtain first and second strand sequence reads for at least a portion of the adapter-DNA molecules; and

d) for at least some of the adapter-DNA molecules comprising barcodes—

confirming the presence of at least one sequence read derived from each of the original first and second strands of the adapter-DNA molecules;

comparing at least one of the confirmed first and second strand sequence reads to a reference sequence; and

analyzing one or more correspondences between the at least one of the confirmed first and second strand

¹ The Certificate of Correction was issued on March 9, 2021, before the filing of the Petition.

sequence reads and the reference sequence to identify a sequence variation.

Ex. 1001, 37:31–52.

22. A method of sequencing DNA comprising:

a) attaching partially single-stranded adapters comprising barcodes selected from a plurality of distinct barcode sequences to double-stranded DNA fragments obtained from a bodily sample, wherein attachment of the adapters to double-stranded DNA fragments generates a library of tagged double-stranded adapter-DNA molecules;

b) amplifying strands from a plurality of the double-stranded adapter-DNA molecules in the library to produce strand copies;

c) sequencing a plurality of the strand copies to obtain strand sequence reads comprising one or more barcode sequences and DNA fragment-specific information; and

d) for at least some of the double-stranded adapter-DNA molecules in the library—

grouping the strand sequence reads into families based on i) the barcode sequence, and ii) DNA fragment-specific information;

collapsing a plurality of strand sequence reads within the families to provide a consensus sequence for each of the at least some of the double-stranded DNA molecules in the library;

comparing the consensus sequence to a reference sequence; and

analyzing one or more correspondences between the consensus sequence and the reference sequence to identify a sequence variation.

Id. at 39:56–40:25.

D. Asserted Challenges to Patentability

Petitioner asserts the following challenges to patentability:

Claim(s) Challenged	35 U.S.C. §	References
1–10, 12–30	103	Kinde ² , Craig ³
11	103	Kinde, Craig, NEB Expressions ⁴

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,

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. The parties cite to the page numbers of the Exhibit provided by Petitioner. For consistency, we do the same.

⁴ Evans et al., *DNA Damage the major cause of missing pieces from the DNA puzzle*, NEW ENGLAND BIOLABS (2007) (Ex. 1014, “NEB Expressions”).

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).

Petitioner argues that, for purposes of this Decision, no claim term needs specific construction beyond its plain and ordinary meaning. Pet. 16. Petitioner, however, seeks to clarify the scope of the challenged claims as related to the recited adapters. *Id.* at 16–17. Patent Owner does not address the adapter issue; instead, Patent Owner contends that the double-stranded DNA fragments recited in the challenged claims must be the original DNA from the bodily sample being analyzed. Prelim. Resp. 3–6. We address the parties’ positions below.

1. Adapters

Petitioner argues the claims encompass “adapter-DNA molecules generated by attachment of Y-shaped or U-shaped adapters comprising barcodes to each end of double-stranded DNA molecules.” Pet. 17.

According to Petitioner,

Y-shaped adapters are partially single-stranded (the arms of the Y) and also are partially-complementary (the trunk of the Y). When the adapters are ligated to a double-stranded DNA molecule, the resulting adapter-DNA molecule is partially-complementary and asymmetric . . . The same is true when using U-shaped hairpin adapters, which also are partially single-stranded and partially-complementary adapters.

Id. (citing Ex. 1002 ¶¶ 58–62). Patent Owner does not dispute these assertions.

Based on the current record, we agree with Petitioner that the claims encompass Y-shaped adapters and hairpin adapters, as long as they comprise “barcodes selected from a plurality of distinct barcode sequences,” which is also required by the claims.

2. Double-Stranded DNA Fragments

Claim 1 recites “attaching adapters to double-stranded DNA fragments.” Claim 22 recites attaching adapters “to double-stranded DNA fragments obtained from a bodily sample.” Patent Owner contends that from their “plain language,” the claims require attaching adapters “to the *original* double-stranded DNA fragments found in the bodily sample being analyzed.” Prelim. Resp. 5. In other words, Patent Owner continues, these DNA fragments “have not been subjected to any amplification steps.” *Id.*

We agree with Patent Owner that claim 22 explicitly requires the double-stranded DNA fragments of interest be “obtained from a bodily sample.” Claim 22 demonstrates that when Patent Owner wants to limit the source of the DNA fragments, it knows the precise language to do so.

Claim 1, however, plainly lacks such language. Indeed, claim 1 puts no limitation on the origin of the DNA fragments of interest. Patent Owner points to step (b) of claim 1, which recites “amplifying original strands of . . . the double-stranded adapter-DNA molecules.” Prelim. Resp. 5. According to Patent Owner, this language shows “the claimed amplification step does not occur on previously generated copies. It occurs on the original strands.” Prelim. Resp. 5. We are not persuaded.

Patent Owner conflates the original DNA fragments from a bodily sample, as claim 22 requires, with the original strands of the adapter-DNA molecules, as step (b) of claim 1 recites. For claim 1, step (a) recites attaching adapters to the DNA fragments of interest, regardless of the source of the DNA fragments—they may be from a bodily sample, or they may be the products of a PCR reaction. Step (b) only requires amplification of the

original adapter-DNA hybrid molecules; it does not speak to the source of the DNA fragments of interest.

Patent Owner also conflates adding adapters by PCR with generating double-stranded DNA fragments by PCR. According to Patent Owner, “adding adapters by PCR would involve using primers containing adapter sequences. And the primers would anneal to single-stranded DNA molecules, not double-stranded DNA molecules. Then, amplification steps would be needed to incorporate the adapter containing primers into *the amplified copies of the* nucleic acid molecules.” Prelim. Resp. 5.

Based on the current record, we agree with Patent Owner that attaching adapters, as recited in the challenged claims, does not encompass adding adapters by PCR. That, however, is unrelated to, and thus, does not exclude, generating double-stranded DNA fragments of interest by PCR. *See, e.g.*, Ex. 1017, 3, 18 (teaching amplifying genomic DNA regions by PCR and ligating indexed-adapters to the double-stranded amplicons).

In sum, we determine that, unlike claim 22, claim 1 does not require the double-stranded DNA fragments of interest be from a bodily sample.

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 address any other claim term.

B. Alleged Obviousness over Kinde and Craig

Petitioner asserts that claims 1–10, and 12–30 of the ’127 patent would have been obvious over Kinde and Craig. Pet. 18–64. 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.

1. Prior Art Disclosures

a. 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 were ligated with adapters, which do not contain exogenous UIDs, and 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.

b. 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).

2. Analysis

a. Claims 1–10 and 12–21

We focus our analysis on claim 1. Petitioner contends that the combination of Kinde and Craig teaches each limitation of claim 1. Pet. 25–35. In Kinde, Petitioner relies on its teaching of endogenous UIDs. *See id.* at 26 (citing Ex. 1006, 9531 (“Endogenous UIDs”), Fig. 2 (showing “Safe-SeqS with endogenous UIDs”)). This is not surprising, as the other two embodiments, i.e., the inverse PCR method and the exogenous method, introduce UIDs through PCR primers.⁵ *See* Ex. 1006, 9532, 9535, S1, Fig. 3. As explained above, attaching adapters, as recited in the challenged claims, does not encompass adding adapters by PCR. *See supra* Section II.A.2; *see also* Prelim. Resp. 5 (“[A]dding adapters by PCR would involve using primers containing adapter sequences. And the primers would anneal to single-stranded DNA molecules, not double-stranded DNA molecules.”). In Craig, Petitioner relies on its teaching of adapters comprising barcodes. Pet. 29 (citing Ex. 1007, 4, 15, 16, 18). Petitioner also argues that Kinde and Craig teach the other limitations of claim 1. *Id.* at 30–35.

Patent Owner only challenges that Petitioner fails to show Kinde and Craig teach attaching adapters comprising barcodes to double-stranded DNA fragments “originally found in the sample.” Prelim. Resp. 19–25. As

⁵ Our reading of Kinde is consistent with Petitioner’s previous representation of Kinde’s teachings to the European Patent Office when defending one of its own patents there. *See* Ex. 2002, 14–15.

explained above, we determine that claim 1 does not require the double-stranded DNA fragments be from a bodily sample. *See supra* Section II.B.2. Craig teaches ligating indexed adapters to amplicons of genomic DNA regions. Ex. 1007, 3, 18. Thus, based on the current record, we find Petitioner has shown sufficiently that the combination of Kinde and Craig teaches each limitation of claim 1. We adopt Petitioner’s detailed accounting of each limitation as our own findings. *See* Pet. 25–35.

That, however, does not end our obviousness inquiry. An invention is not obvious just because all of the elements that comprise the invention were known in the prior art. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.”). Rather, “it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.” *Id.*

Petitioner argues that an ordinarily skilled artisan “would have had good reason to combine Kinde and Craig to use Y-shaped adapters comprising barcode sequences, as disclosed in Craig, in order to arrive at the ’127 patent claims.” Pet. 21. As explained below, we are not persuaded by Petitioner’s arguments.

As an initial matter, we agree with Petitioner that “Kinde and Craig both use Illumina Y-shaped adapters attached to each end of DNA molecules.” *See* Pet. 22. But, the Y-shaped adapters in Kinde are different from those in Craig: the former do not contain barcodes, a limitation recited in the challenged claims; whereas the latter do. *Compare* Ex. 1006, S9 (showing the adapters used in the endogenous method do not contain

barcodes), *with* Ex. 1007, 15 (showing adapters with barcodes); *see also* Prelim. Resp. 22–23 (showing Kinde’s adapters do not include 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 identifies Craig in expressly discussing exogenous barcodes with DNA molecules.” Pet. 21; *see also id.* at 30 (“[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. 10. 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.

According to Petitioner, “Kinde describes sequencing and comparing the sequence of amplification progeny for each strand of the original DNA duplex to confirm the presence of apparent mutations in the original DNA duplex.” Pet. 21. Petitioner observes that “Kinde explains that the specificity of sequencing may be increased ‘by requiring that each strand of the original double-stranded template contain the mutation.’” *Id.* at 22 (quoting Ex. 1006, S3).

We agree with Petitioner on these representations of Kinde's teachings; but, we find Petitioner has not explained sufficiently its logic to link these teachings with its conclusion that "[a]ccordingly, a skilled artisan would have had good cause to utilize Y-shaped Illumina adapters and exogenous barcodes, as taught by Kinde in view of Craig, to determine whether apparent mutations were confirmed in both strands." *See id.* at 22.

Kinde teaches that, in its endogenous method, each strand of the double-stranded template includes "[o]ne uniquely identifiable fragment" as the UID. Ex. 1006, 9531. Kinde explains that, when illustrating "Safe-SeqS with endogenous UIDs" in Figure 2, "only one strand is shown." *Id.* Kinde, however, does not limit its sequence analysis to only one strand in its endogenous method. Indeed, Kinde states that, when identifying mutations, the specificity can be increased by "requiring more than one supermutant to identify a position as mutant, as described above for endogenous UIDs. When requiring multiple supermutants, the specificity can be further increased by requiring that each strand of the original double-stranded template contain the mutation." *Id.* at S3.

Thus, Kinde teaches analyzing multiple supermutants and analyzing both strands of a template to more accurately identify mutations. Read in context, these analyses can be applied in the endogenous method, and do not depend on the introduction of exogenous UIDs. 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.

To be sure, we do not hold there is no reason to combine the teachings of Kinde and Craig; we merely find Petitioner has not met its burden to

sufficiently explain the reason. Thus, Petitioner has not demonstrated a reasonable likelihood that it would prevail in showing that claim 1, as well as claims 2–10 and 12–21, which depend from claim 1, would have been obvious over the combination of Kinde and Craig.

b. Claims 22–30

Similar to claim 1, step (a) of claim 22 recites “attaching partially single-stranded adapters comprising barcodes.” Relying on the same arguments as presented in its obviousness analysis of claim 1, Petitioner argues that Kinde and Craig teach this step. Pet. 36. For the same reason as explained above, we find Petitioner has not shown sufficiently the reason to combine the teachings of Kinde and Craig. *See supra* Section II.B.2.a. Thus, Petitioner has not demonstrated a reasonable likelihood that it would prevail in showing that claim 22, as well as claims 23–30, which depend from claim 22, would have been obvious over the combination of Kinde and Craig.

C. Alleged Obviousness over Kinde, Craig, and NEB Expressions

Petitioner asserts that claim 11 would have been obvious over the combination of Kinde, Craig, and NEB Expressions. Pet. 64–65. Claim 11 depends from claim 1. Petitioner relies on NEB Expressions for teaching the additional limitation of claim 11. Based on the current record, we agree with Patent Owner that NEB Expressions does not cure the deficiencies in Petitioner’s argument regarding the combination of Kinde and Craig. *See* Prelim. Resp. 31. For the same reason as explained above, we find Petitioner has not shown sufficiently the reason to combine the teachings of Kinde and Craig. *See supra* Section II.B.2.a. Thus, Petitioner has not demonstrated a reasonable likelihood that it would prevail in showing that claim 11 would

have been obvious over the combination of Kinde, Craig, and NEB Expressions.

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 '127 patent based on the grounds asserted in the Petition.

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