

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GUARDANT HEALTH, INC.,
Petitioner,

v.

UNIVERSITY OF WASHINGTON THROUGH ITS CENTER FOR
COMMERCIALIZATION,
Patent Owner.

IPR2022-00935
Patent 10,287,631 B2

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

NEW, *Administrative Patent Judge.*

DECISION

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

I. INTRODUCTION

Petitioner Guardant Health, Inc. has filed a Petition (Paper 2, “Pet.”) seeking *inter partes* review of claims 1–23 of US Patent 10,287,631 B2 (Ex. 1001, the “’631 patent”). Patent Owner University of Washington Through Its Center for Commercialization (“Patent Owner”) timely filed a Preliminary Response. Paper 10 (“Prelim. Resp.”).

Under 35 U.S.C. § 314, the Board “may not authorize an *inter partes* review to be instituted unless ... the information presented in the petition ... and any response ... shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” Upon consideration of the Petition and Preliminary Response, and the evidence of record, we determine that the evidence presented does not demonstrate a reasonable likelihood that Petitioner would prevail in establishing the unpatentability of the challenged claims of the ’631 patent.

II. BACKGROUND

A. *Real Parties in Interest*

Petitioner identifies itself, Guardant Health, Inc. as its real party-in-interest. Pet. 15. Patent Owner identifies the University of Washington and TwinStrand Biosciences, Inc. as its real parties-in-interest. Paper 3, 1.

B. *Related Matters*

Petitioner and Patent Owner point to the following related matters:

TwinStrand Biosciences, Inc. et al. v. Guardant Health, Inc.,
No. 1-21-cv01126 (D. Del.);

*Guardant Health, Inc. v. University of Washington Through Its
Center for Commercialization*, IPR2022-01158 (PTAB);

Guardant Health, Inc. v. University of Washington Through Its Center for Commercialization, IPR2022-01159 (PTAB);

Guardant Health, Inc. v. University of Washington Through Its Center for Commercialization, IPR2022-001388 (PTAB);

Guardant Health, Inc. v. University of Washington Through Its Center for Commercialization, IPR2022-00450 (PTAB);

Guardant Health, Inc. v. University of Washington Through Its Center for Commercialization, IPR2022-00816 (PTAB);

Guardant Health, Inc. v. University of Washington Through Its Center for Commercialization, IPR2022-00817 (PTAB);

Twinstrand Biosciences, Inc. v. Guardant Health, Inc., IPR2022-00746 (PTAB);

Twinstrand Biosciences, Inc. v. Guardant Health, Inc., IPR2022-00747 (PTAB);

Twinstrand Biosciences, Inc. v. Guardant Health, Inc., IPR2022-01115 (PTAB);

Twinstrand Biosciences, Inc. v. Guardant Health, Inc., IPR2022-01116 (PTAB); and

Twinstrand Biosciences, Inc. v. Guardant Health, Inc., IPR2022-01152 (PTAB).

Paper 9, 1; Paper 5, 1; Paper 7, 1.

C. *The Asserted Grounds of Unpatentability*

Petitioner contends that claims 1–23 of the ’631 patent are unpatentable, based upon the following grounds:

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1	16–21	103	Kinde ¹

¹ I. Kinde et al., *Detection and Quantification of Rare Mutations with Massively Parallel Sequencing*, 108(23) PNAS 9530–35 (2011) (“Kinde”) Ex. 1006.

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
2	1–15, 22, 23	103	Kinde, Craig ²
3	1–23	103	Kinde, Craig, Travers Publications ³

Petitioner also relies upon the Declaration of Dr. John Quackenbush (the “Quackenbush Declaration,” Ex. 1002).

D. The ’631 patent

The ’631 patent is entitled “Methods Of Lowering the Error Rate of Massively Parallel DNA Sequencing using Duplex Consensus Sequencing” Ex. 1001, code (54). The ’631 patent issued from US Ser. No. 15/660,785 (the “’785 application”). *Id.* at code (21).

The ’631 patent is directed to a method of duplex consensus sequencing (“DCS”) that reduces errors by independently tagging and sequencing each of the two strands of a DNA duplex. Ex. 1001, Abstr. The ’631 patent explains that, because the two strands are complementary, true mutations are found at the same position in both strands. *Id.*

Specifically, the ’631 patent discloses that, in one embodiment:

² D.W. Craig et al., *Identification of Genetic Variants using Bar-Coded Multiplexed Sequencing*, 5(1) NATURE METHODS 887–93 (2008) (“Craig”) Ex. 1007.

³ Travers et al., (US 2009/0298075 A1, December 3, 2009) (“Travers ’075”) Ex. 1018; and

K.J. Travers et al., *A Flexible and Efficient Template Format for Circular Consensus Sequencing and SNP Detection*, 38(15) NUCLEIC ACIDS RES. e159 1–8 (2010) (“Travers”) Ex. 1021.

[A] single molecule identifier (“SMI”)⁴ adaptor molecule for use in sequencing a double-stranded target nucleic acid molecule is provided. Said SMI adaptor molecule includes a single molecule identifier (SMI) sequence which comprises a degenerate or semi-degenerate DNA sequence; and an SMI ligation adaptor that allows the SMI adaptor molecule to be ligated to the double-stranded target nucleic acid sequence. The SMI sequence may be single-stranded or double-stranded. In some embodiments, the double-stranded target nucleic acid molecule is a double stranded DNA or RNA molecule.

Ex. 1001 cols. 2–3, ll. 66–9.

The ’631 patent points to its Figure 1 as being illustrative of the DCS method. Ex. 1001 col. 3, ll. 44–45. Figure 1 of the ’631 patent is reproduced below:

⁴ For the purposes of this Decision, the terms “SMI,” “unique identifier (‘UID’)” and “barcode” used by the ’631 patent and various references are considered synonymous.

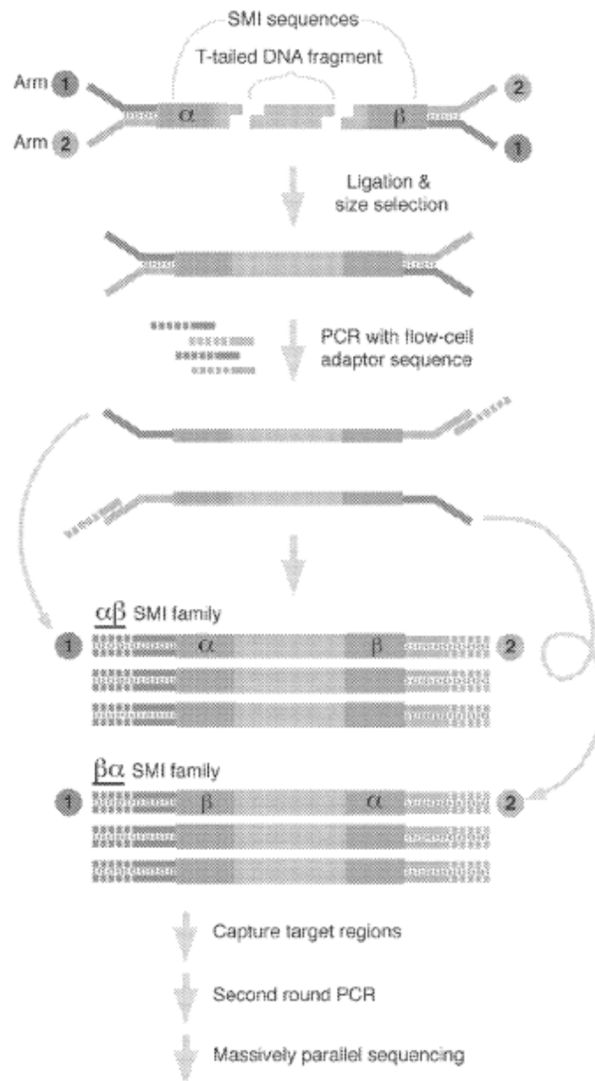


Figure 1 of the '631 patent depicts an overview of duplex consensus shearing

Briefly, the '631 patent discloses a double-stranded SMI adaptor molecule, which may include an SMI nucleotide sequence, and an SMI ligation adaptor, and may optionally further include at least two PCR primer binding sites, at least two sequencing primer binding sites, or both. Ex. 1001 col. 5, ll. 55–62. The '631 patent discloses that the SMI adaptor molecule may form a “Y-shape” or a “hairpin shape”: a “Y-shape” allows both strands to be independently amplified by PCR prior to sequencing because both the top and bottom strands have binding sites for PCR primers FC1 and FC2.

Id. at cols. 5–6, ll. 63–1. Alternatively, a “hairpin-shaped” (or “U-shaped”) adaptor SMI adaptor molecule may be employed. *Id.* at col. 6, ll. 23–26. As the ’631 patent explains, a hairpin-shaped DNA product can be used for error correction, because the end product contains both of the two DNA strands. *Id.* at col. 6, ll. 24–31. This allows for reduction of a given sequencing error rate N to a lower rate of $N*N*(1/3)$, because independent sequencing errors would need to occur on both strands, and the same error among all three possible base substitutions would need to occur on both strands. *Id.*

As depicted in Figure 1 of the ’631 patent, sheared double-stranded DNA, that has been end-repaired and T-tailed, is combined with the A-tailed SMI adaptors and ligated. *Id.* at col. 3, ll. 45–47. The ’631 patent explains that, because every adaptor contains a unique, double-stranded, complementary n -mer random tag on each end (an n -mer=12 base pairs in length, according to one embodiment), every DNA fragment becomes labeled with two distinct SMI sequences (arbitrarily designated α and β in the single capture event shown in Figure 1). *Id.* at col. 3, ll. 47–53.

The ’631 patent discloses that, after size-selecting for appropriate length fragments, PCR amplification with primers containing Illumina flow-cell-compatible tails is carried out to generate families of PCR duplicates. *Id.* at col. 3, ll. 47–55. By virtue of the asymmetric nature of adapted fragments, two types of PCR products are produced from each capture event: those derived from one strand will have the α SMI sequence adjacent to flow-cell sequence 1 and the β SMI sequence adjacent to flow cell sequence 2. *Id.* at col. 3, ll. 56–60. The ’631 patent discloses that PCR products originating from the complementary strand are therefore labeled reciprocally. *Id.* at col. 3, ll. 61–62.

E. The Challenged Claims

Claims 1–24 are the challenged claims in this proceeding. *See* Section II.C. above. Independent claims 16 and 1⁵ are representative of the challenged claims. Claim 16 recites:

16. A method of generating high accuracy sequence reads of a population of double-stranded target nucleic acid molecules, wherein each individual double-stranded target nucleic acid molecule comprises one or more fragment features that distinguish the individual double-stranded target nucleic acid molecules from other double-stranded target nucleic acid molecules in the population, the method comprising:

ligating each of the double-stranded target nucleic acid molecules to at least one double-stranded adapter molecule, to form an adapter-target nucleic acid complex, wherein—

the at least one double-stranded adapter molecule comprises a region of non-complementarity between a first adapter strand of the double-stranded adapter molecule and a second adapter strand of the double-stranded adapter molecule, and

following the ligation step, the region of noncomplementarity provides a strand-distinguishing nucleotide sequence such that a first strand of the adapter-target nucleic acid complex has a distinctly identifiable nucleotide sequence relative to its complementary second strand;

for each of the adapter-target nucleic acid complexes—

⁵ We recite the claims in this order because that is the order in which they are addressed by the sequential Grounds in the Petition, and because, during prosecution of the '631 patent, the Examiner noted that “claim [1] is a species of claim [16].” Ex. 1004, 140.

amplifying each strand of the adapter-target nucleic acid complex to produce a plurality of first strand adapter-target nucleic acid complex amplicons and a plurality of second strand adapter-target nucleic acid complex amplicons;

sequencing the adapter-target nucleic acid complex amplicons to produce a plurality of first strand sequence reads and plurality of second strand sequence reads;

grouping the first and second strand sequence reads into a family of sequence reads by identifying the one or more distinguishing fragment features shared by each strand of the double-stranded target nucleic acid molecule;

separating the first and second sequence reads from each family into a set of first strand sequence reads and a set of second strand sequence reads based on the strand-distinguishing nucleotide sequence;

confirming the presence of at least one first strand sequence read and at least one second strand sequence read;

comparing the at least one first strand sequence read with the at least one second strand sequence read; and

generating a high accuracy consensus sequence read for each of the double-stranded target nucleic acid molecules in the population that includes only the nucleotide positions where the compared first and second strand sequence reads are complementary.

Ex. 1001 cols. 39–40, ll. 41–31. Claim 1 recites:

1. A method of generating high accuracy sequence reads of a population of double-stranded target nucleic acid molecules, comprising:

ligating each of the double-stranded target nucleic acid molecules to at least one adapter molecule, to form a population of adapter-target nucleic acid complexes, wherein each of the adapter molecules comprises—

- (a) a degenerate or semi-degenerate single molecule identifier (SMI) sequence that alone or in combination with the target nucleic acid fragment ends uniquely labels each ligated double-stranded target nucleic acid molecule such that each ligated double-stranded target nucleic acid molecule is distinguishable from other ligated double-stranded target nucleic acid molecules in the population, and
- (b) a strand-distinguishing nucleotide sequence that, following the ligation step, provides a region of non-complementarity between a first strand of each adapter-target nucleic acid complex and a second strand of the same adapter-target nucleic acid complex;

for each of the adapter-target nucleic acid complexes—

amplifying each strand of the adapter-target nucleic acid complex to produce a plurality of first strand adapter-target nucleic acid complex amplicons and a plurality of second strand adapter-target nucleic acid complex amplicons;

sequencing the adapter-target nucleic acid complex amplicons to produce a plurality of first strand sequence reads and plurality of second strand sequence reads;

grouping the first strand sequence reads and the second strand sequence reads into a family of first and second strand sequence reads based on the degenerate or semi-degenerate SMI sequence alone or in combination with the target nucleic acid fragment ends;

separating the first and second strand sequence reads into a set of first strand sequence reads and a set of second strand sequence reads based on the region of non-complementarity between the first strand and the second strand of the adapter-target nucleic acid complex;

- confirming the presence of at least one first strand sequence read and at least one second strand sequence read;
- comparing the at least one first strand sequence read with the at least one second strand sequence read;
- identifying nucleotide positions where the compared first and second strand sequence reads are non-complementary; and
- identifying nucleotide positions where the compared first and second strand sequence reads are complementary; and generating a high accuracy consensus sequence read for each of the double-stranded target nucleic acid molecules in the population that includes only the nucleotide positions where the compared first and second strand sequence reads are complementary.

Id. at cols. 37–38, ll. 27–41.

F. Prosecution History of the '631 patent

The '631 patent matured from the '785 application which was filed on July 26, 2017, with original claims 1–36. Ex. 1001, codes (21), (22); Ex. 1024, 0060–0064. On December 10, 2018, Patent Owner canceled original claims 1–36 and substituted new claims 37–66. *Id.* at 215–221.

On February 19, 2018, Patent Owner entered a preliminary amendment, canceling claims 1–36 of the '785 application and adding new claims 37–57. Ex. 1004, 0117–0122. On April 10, 2018, the Examiner entered a Non-Final Rejection of claims 37–57 as unpatentable under 35 U.S.C. § 102 as being anticipated by Steemers et al. (WO2012/061832 A1, May 10, 2012) (“Steemers”). *Id.* at 0140–0149. The Examiner also rejected the claims as unpatentable under 35 U.S.C. § 112(b) as being

indefinite and rejected claim 44 as unpatentable under 35 U.S.C. § 101 and 112(a). *Id.* at 0137–0140.

In response, Patent Owner amended claims 37, 40–49, and 51–53, and canceled claim 38. Ex. 1004, 279–0285. Patent Owner also added new claims 58–60. *Id.* at 285. The Examiner subsequently issued a Notice of Allowance on July 10, 2018. The ’631 patent issued on May 14, 2019 after post-allowance amendment of the Specification on March 27, 2019. *See* Ex. 1004, 0439

III. Analysis

A. *Claim Construction*

The Board applies the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b). *See* 37 C.F.R. § 100(b) (2020). Under that standard, claim terms “are generally given their ordinary and customary meaning” as understood by a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc). “In determining the meaning of the disputed claim limitation, we look principally to the intrinsic evidence of record, examining the claim language itself, the written description, and the prosecution history, if in evidence.” *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005, 1014 (Fed. Cir. 2006) (citing *Phillips*, 415 F.3d at 1312–17). Extrinsic evidence may also be considered, but is “less significant than the intrinsic record in determining ‘the legally operative meaning of claim language.’” *Phillips*, 415 F.3d at 1317 (quoting *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 862 (Fed. Cir. 2004)).

Neither Petitioner nor Patent Owner proposes a construction for any claim terms apart from their plain and customary meaning. Pet. 17–18; Prelim. Resp. 5. Nor do we perceive, at this stage of the proceeding, a need to construe any claim term of the '631 patent for purposes of determining whether to institute trial. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (holding that “only those terms need to be construed that are in controversy, and only to the extent necessary to resolve the controversy”); *see also Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (applying *Vivid Techs* in the context of an *inter partes* review).

B. Person of Ordinary Skill in the Art

Petitioner asserts that a person of ordinary skill in the art at the time of filing would typically have had an advanced degree, such as a Ph.D., with research experience in genomics, molecular biology, bioinformatics, or a related field. Pet. 15 (citing Ex. 1002, ¶¶ 53–54). Alternatively, Petitioner proposes, a skilled artisan could have less education but significant professional experience in one or more of these fields. *Id.*

Patent Owner does not contest Petitioner's proposed definition of a person of ordinary skill in the art. *See generally* Prelim. Resp. At this stage of the proceeding and for purposes of our analysis in this Decision, we therefore adopt Petitioner's proposed definition. We find that this definition is consistent with the level of skill in the art as reflected by the prior art. *See, e.g.*, Exs. 1003, 1006, 1007, 1010, 1021; *see also Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required “where the prior art itself reflects an appropriate level and a need for testimony is not shown” (quoting

Litton Indus. Prods., Inc. v. Solid State Sys. Corp., 755 F.2d 158, 163 (Fed. Cir. 1985))).

C. Ground 1: Obviousness of claims 16–21 over Kinde

1. Overview of Kinde (Ex. 1006)

Kinde teaches a method for increasing the sensitivity of massively parallel sequencing instruments to identify rare mutations in DNA. Ex. 1006, Abstract. Kinde states that 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,’” and notes that “[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 teaches that “UIDs, sometimes called barcodes or indexes, can be assigned to nucleic acid fragments using a variety of methods.” Ex. 1006, 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. Ex. 1006, 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.” Ex. 1006, 9533.

2. Claim 16

a. Petitioner's contentions

- i. **[Preamble]:** A method of generating high accuracy sequence reads of a population of double-stranded target nucleic acid molecules, wherein each individual double-stranded target nucleic acid molecule comprises one or more fragment features that distinguish the individual double-stranded target nucleic acid molecules from other double-stranded target nucleic acid molecules in the population, the method comprising

Petitioner argues that, to the extent that the preamble is limiting, Kinde teaches generating high-accuracy sequence reads, in which double-stranded nucleic acids are distinguished from other double-stranded nucleic acids in the population. Pet. 24. According to Petitioner, Kinde discloses a method for reducing errors in sequencing reads using substantially the same steps as DCS (e.g., assigning a UID, amplifying, sequencing, consensus formation). *Id.* Petitioner contends that Kinde further describes generating high-accuracy sequence reads for populations of double-stranded target nucleic acid molecules. *Id.* (citing Ex. 1006, 9533, 9531, Fig. 2; also citing Ex. 1001 col. 26, ll. 56–62).

Petitioner notes that Kinde explains that its methods “substantially improve the accuracy of massively parallel sequencing” such that “rare mutants” may be identified in “population[s] of DNA templates.” Pet. 24 (quoting Ex. 1006, 9533, 9530). Petitioner also points to Kinde’s further teaching that increasing the specificity of the method for detecting rare mutations “by requiring that each strand of the original double-stranded template contain the mutation.” *Id.* at 24–25 (citing Ex. 1006, SI3).

Petitioner contends that Kinde also discloses distinguishing double-stranded nucleic acids within a population based on UIDs, in a manner that

addresses the claimed “fragment features,” which Petitioner asserts are characterized in claim 18 of the ’935 patent as “includ[ing] a shear point or other fragment region.” Pet. 26 (citing Ex. 1001 col. 40, ll. 35–37).

Petitioner further states that Kinde’s “UIDs” are comparable to the ’631 patent’s discussion of SMIs. Pet. 25. By way of example, Petitioner points to Kinde’s teaching of assigning “unique identifier (UID)” sequences to the double-stranded nucleic acids in the population. *Id.* (citing Ex. 1006, 9530, Fig. 1, Fig. 2; also citing Ex. 1001 col. 2, ll. 11–15). According to Petitioner, Kinde explains that UIDs may comprise endogenous and/or exogenous sequences. *Id.* at 25–26 (citing Ex. 1006, 9531).

- ii. **[16.1]:** ligating each of the double-stranded target nucleic acid molecules to at least one double-stranded adapter molecule, to form an adapter-target nucleic acid complex, wherein—the at least one double-stranded adapter molecule comprises a region of non-complementarity between a first adapter strand of the double-stranded adapter molecule and a second adapter strand of the double-stranded adapter molecule, and

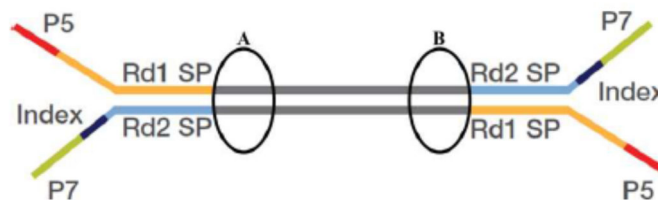
Petitioner contends that Kinde teaches ligating Y-shaped adapters (e.g., standard Illumina adapters) to double-stranded DNA molecules to form adapter-DNA complexes. Pet. 26 (citing Ex. 1006, 9531, Fig. 2). Petitioner asserts that prior art Y-shaped adapters have a region of non-complementarity (i.e., the arms of the Y) between the first and second strands of the double-stranded adapter molecule. *Id.* at 27 (citing Ex. 1012, Fig. 4; Ex. 1002 ¶¶ 73–75).

- iii. **[16.2]:** following the ligation step, the region of non-complementarity provides a strand-distinguishing nucleotide sequence such that a first strand of the adapter-target nucleic acid complex has a distinctly identifiable nucleotide sequence relative to its complementary second strand

Petitioner contends that this limitation merely recites well-known and art-recognized properties of prior art: asymmetric, sequencing adapters (e.g., standard Y-shaped Illumina adapters) that would have been recognized by a skilled artisan and that are documented in the literature. Pet. 27.

According to Petitioner, Kinde discloses ligating Y-shaped “standard Illumina sequencing adapters” to double-stranded DNA fragments “according to standard Illumina protocols.” Pet. 27 (citing Ex. 1006, 9531, Fig. 2, SI1). Petitioner states that Kinde discloses that, ultimately, “[o]ne uniquely identifiable fragment is produced from each strand of the double-stranded template.” *Id.* (citing Ex. 1006, Fig. 2; see also Ex. 1002 ¶¶ 76-77).

Petitioner contends that standard Illumina adapters ligated to sample DNA produce partially-complementary, asymmetrical double-stranded adapter-DNA molecules. Pet. 28. Petitioner points to Figure 4 of the Illumina Data Sheet, which is reproduced, with Petitioner’s annotations, below:



Petitioner’s annotated Figure 4 of the Illumina Data Sheet depicts Illumina Y-shaped adapters ligated to a target nucleic acid sequence

By virtue of the non-complementary region of the adapted fragments, argues Petitioner, two types of PCR products are produced from each

capture event: those derived from one strand will have the A sequence adjacent to flow-cell sequence P5 and the B sequence adjacent to flow cell sequence P7. *Id.* PCR products originating from the complementary strand are labeled reciprocally (i.e., P7 adjacent to A and P5 adjacent to B). Pet. 28. Petitioner contends that the “asymmetry” discussed in the ’631 patent is no different. *Id.* (citing Ex. 1001 col. 3, ll. 56–62, Fig. 1).

Petitioner contends that the region of non-complementarity provides a strand-distinguishing nucleotide sequence such that a first strand of the adapter-target nucleic acid complex has a distinctly identifiable nucleotide sequence relative to its complementary second strand. Pet. 28. Petitioner points to both Shiroguchi⁶ and the ’631 patent. *Id.* (citing Ex. 1010, Fig. 1, Fig. S5).

Petitioner argues that it was therefore well known that, following ligation, prior art Y-shaped adapters (e.g., Illumina adapters) provide an adapter-DNA complex where the top strand of the duplex is distinguishable from the bottom strand based on a nucleotide sequence in the region of non-complementarity. *Id.* (citing Ex. 1013⁷, Fig. 1; Ex. 1012, Figure 4; also citing Ex. 1001 col 18, ll. 50–59, col. 22, ll. 22–27; Ex. 1002 ¶¶ 76–82).

⁶ K. Shiroguchi et al., *Digital RNA Sequencing Minimizes Sequence-Dependent Bias and Amplification Noise with Optimized Single-Molecule Barcodes*, 109(4) PNAS 1347–52 (2012) (“Shiroguchi”) Ex. 1010.

⁷ D.R. Bentley et al., *Accurate Whole Human Genome Sequencing Using Reversible Terminator Chemistry*, 456 NATURE 53–59 (2008) (“Bentley”) Ex. 2013.

- iv. **[16.3]:** for each of the adapter-target nucleic acid complexes amplifying each strand of the adapter-target nucleic acid complex to produce a plurality of first strand adapter-target nucleic acid complex amplicons and a plurality of second strand adapter-target nucleic acid complex amplicons

Petitioner argues that Kinde discloses “amplification” of each strand of adapter-target nucleic acid complexes. Pet. 29 (citing Ex. 1006, Abstr., Fig. 2, SI1). According to Petitioner, Kinde specifically discloses that amplification produces copies of both the first and second strands. *Id.* at 30 (citing e.g., Ex. 1006, Fig. 2, SI3). Petitioner reasons that, by this method, Kinde therefore produced a plurality of first strand adapter-target nucleic acid complex amplicons and a plurality of second strand adapter-target nucleic acid complex amplicons. *Id.* (citing, e.g., Ex. 1006, 9530, 9531; also citing Ex. 1002 ¶¶ 83–85).

b. Analysis

We begin our analysis at this point. Kinde teaches two basic methods by which UIDs, or “barcodes,” can be used to identify nucleic acid fragments, either via the introduction of exogenous sequences or the identification of endogenous identifiers:

Endogenous UIDs. UIDs, sometimes called barcodes or indexes, can be assigned to nucleic acid fragments using a variety of methods. These methods include the introduction of exogenous sequences through PCR or ligation. Even more simply, randomly sheared genomic DNA inherently contains UIDs consisting of the sequences of the two ends of each sheared fragment (Fig. 2 and Fig. S1). Paired-end sequencing of these fragments yields UID families that can be analyzed as described above.

Ex. 1006, 9531 (internal references omitted). Figure 2 of Kinde, which depicts the Saf-SeqS with endogenous method taught by Kinde is reproduced below:

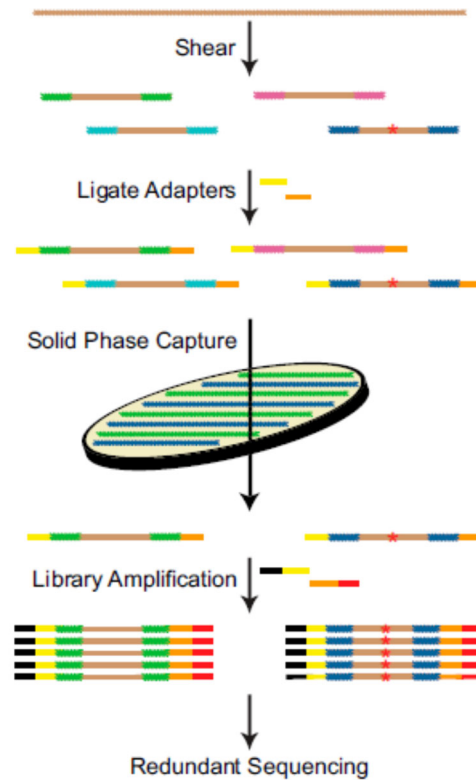


Figure 2 of Kinde depicts a schematic version of the SafSeqS method

As Kinde explains of Figure 2:

The sequences of the ends of each fragment produced by random shearing (variously colored bars) serve as the unique identifiers (UIDs). These fragments are ligated to adapters (yellow and orange bars) so they can subsequently be amplified by PCR. One uniquely identifiable fragment is produced from each strand of the double-stranded template; only one strand is shown. Fragments of interest are captured on a solid phase containing oligonucleotides complementary to the sequences of interest. Following PCR amplification to produce UID families with primers containing 5' "grafting" sequences (black and red bars), sequencing is performed and supermutants are defined as in Fig. 1.

Ex. 1006, Fig. 2. Kinde thus indeed teaches that “[o]ne uniquely identifiable fragment is produced from each strand of the double-stranded template,” however, these are depicted in Kinde Figure 2 as the variously colored bars at the ends of the target sequences that serve as the endogenous UIDs, as shown in the detail of Figure 2 depicted below:



Detail of Figure 2 depicting individual strands of target nucleic acid with identified endogenous UIDs. The asterisk identifies a mutant sequence

Adapters, depicted as short yellow and red bars are then ligated to the terminal 5' and 3' ends of target sequences with their endogenous UIDs, with different adapters ligated at the 5' and 3' termini of the target sequence:



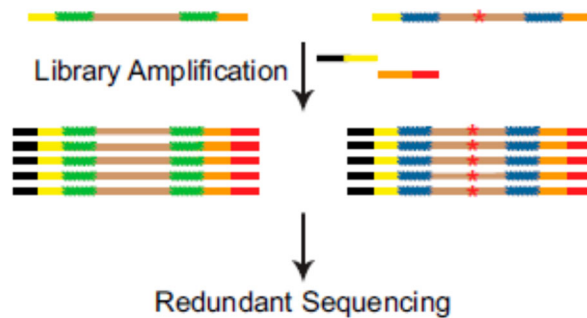
Detail of Figure 2 depicting individual strands of target nucleic acid with identified endogenous UIDs and adapters attached. The asterisk identifies a mutant sequence

Kinde teaches that the strands are then amplified by PCR, and that fragments of interest are “captured on a solid phase containing oligonucleotides complementary to the sequences of interest.” Ex. 1006, Fig. 2, *see also id.* at 9531 (“For the evaluation of multiple genes, we ligated standard Illumina sequencing adapters to the ends of sheared DNA fragments to produce a standard sequencing library and then captured genes of interest on a solid phase”) (internal reference omitted). Kinde elaborates that:

DNA was fragmented to an average size of ~200 bp by acoustic shearing (Covaris) and then end-repaired, A-tailed, and ligated to Y-shaped adapters according to standard Illumina protocols. *The ends of each template molecule provide endogenous UIDs corresponding to their chromosomal positions.* After PCR-mediated amplification of the libraries with primer sequences within the adapters, DNA was captured with a filter containing 2,594 nt corresponding to six cancer genes.

Id. at SI1 (emphasis added, internal citation omitted).

Subsequent to this step, Kinde teaches, “primers containing 5’ “grafting” sequences (black and red bars), sequencing is performed and supermutants are defined,” as depicted schematically below:



Detail of Figure 2 depicting individual strands of target nucleic acid with identified endogenous UIDs, ligated adapters and 5’ “grafting” sequences (black and red bars) attached and amplified prior to redundant sequencing.

We find no direct teaching or suggestion in this endogenous UID method taught by Kinde that its method employs a “a strand-distinguishing nucleotide sequence that, following the ligation step, provides a region of non-complementarity between a first strand of each adapter-target nucleic acid complex and a second strand of the same adapter-target nucleic acid complex,” as recited in claim 16. Rather, the strand specificity of this method of Kinde relates to the UID-adapter sequence rather than relying upon adapter-UID sequence at the 5’ and 3’ termini of the target nucleic acid

sequence, rather than relying on the region of “non-complementarity,” i.e., the individual “Y-arms” of the Illumina adapters.

Nor is the less-favored exogenous UID method of Kinde availing for Petitioner. Kinde teaches that, in this method:

DNA was quantified with digital PCR using primers that amplified single-copy genes from human cells, with qPCR or by optical absorbance. Each strand of each template molecule was encoded with a 12- or 14-base UID using two cycles of amplicon-specific PCR, as described in the text and Fig. 3. The amplicon-specific primers both contained universal tag sequences at their 5' ends for a later amplification step. The UIDs constituted 12 or 14 random nucleotide sequences appended to the 5' end of the forward amplicon- specific primers.

....

To ensure complete removal of the first-round primers, each well was digested with 60 units of a single-strand DNA-specific nuclease (Exonuclease-I; Enzymatics) at 37°C for 1 h. After a 5-min heat inactivation at 98°C, primers complementary to the introduced universal tags (Table S4) were added to a final concentration of 0.5 µM each. These primers contained two terminal phosphorothioates to make them resistant to any residual Exonuclease-I activity. They also contained 5'-grafting sequences necessary for hybridization to the Illumina GA IIx flow cell. Finally, they contained an index sequence between the grafting sequence and the universal tag sequence. This index sequence enables the PCR products from multiple different individuals to be simultaneously analyzed in the same flow cell compartment of the sequencer.

Ex. 1006, SI1. Thus, the exogenous UID method taught Kinde is similarly silent with respect to employment of a non-complementary sequence of the adapter molecule acting as a strand-specific identifier.

Petitioner seeks to buttress its arguments with respect to this limitation by pointing to Shiroguchi as reflective of the state of the art, arguing that Shiroguchi teaches adapters “designed in the same Y-shaped construct as the

conventional Illumina paired-end adapter with a 22- to 25-bp extension that contained the barcode and a T-overhang.” Pet. 7 (quoting Ex. 1010, SI3). Shiroguchi, Petitioner asserts, “confirms its strand-specific labeling enabled distinction of different strands of the DNA molecule. *Id.* at 8 (citing Ex.1010, Fig. S5 (“We are able to distinguish the different strands of an original cDNA molecule because of the design of the paired-end sequencing adapters (Fig. 1B)”).

Shiroguchi teaches “a system-wide method for bias and noise reduction in RNA-Seq that allows the use of PCR to amplify a cDNA library before sequencing, providing accurate digital quantification of the transcriptome.” Ex. 1010, 1347. Shiroguchi teaches that:

Following reverse transcription, a large set of barcode sequences is added in excess, and nearly every cDNA molecule is uniquely labeled by random attachment of barcode sequences to both ends. After PCR, we applied paired-end deep sequencing to read the two barcodes and cDNA sequences. Rather than counting the number of reads, RNA abundance is measured based on the number of unique barcode sequences observed for a given cDNA sequence.

Id. Fig. 1B of Shiroguchi depicts a schematic version of the relevant portion of this method:

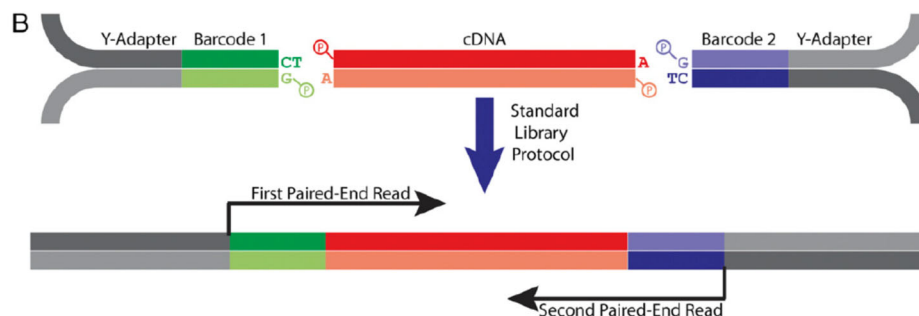


Figure 1B of Shiroguchi depicts the portion of the method in which barcoded cDNA molecules are amplified by PCR.

We agree with Petitioner that Shiroguchi depicts the use of Y-shaped adapters of a type that are well known in the art (e.g., Illumina adapters). However, we are not persuaded that Shiroguchi teaches that it is the non-complementary, Y-arm portion of the adapters that provides a “strand-distinguishing nucleotide sequence that, following the ligation step, provides a region of non-complementarity between a first strand of each adapter-target nucleic acid complex and a second strand of the same adapter-target nucleic acid complex,” as required by claim 16.

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:

[E]ach cDNA molecule is attached to a unique barcode sequence from a large pool of barcodes before amplification. 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). Shiroguchi reports that a substantial fraction of reads contained misidentified barcodes, and that, to avoid this complication, “we 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.* internal references omitted). Specifically, Shiroguchi teaches that: “[w]e generated 2,358 random 20-base barcode candidates using a computer, such that even if a barcode accumulated nine mutations, it would not take the sequence of any other generated barcode sequences [unlike the random barcode case]. *Id.*

Shiroguchi teaches that, as shown in Figure 1, reproduced above, “[t]he cDNA library of *E. coli* [K-12 MG1655 strain (U00096.2)] was generated by a standard method” and that “the cDNA library was ligated to the barcode adapter mixture, and the sequencing sample was prepared by the standard Illumina protocol with some modifications along with an internal standard.” Ex. 1010, 1351. Shiroguchi emphasizes that it is the design of the barcode sequences that is essential to the reduction of read errors.

Specifically:

Each of the 2,358 barcodes was analyzed for sequence characteristics that would contribute to either amplification or sequencing errors.... All barcodes with less than 40% or greater than 60% GC-content or containing homopolymers greater than length four were deleted. All barcode sequences were compared with the PE 1.0 and 2.0 Illumina PCR primer sequences and discarded if there were more than 10 total base matches or more than five consecutive base matches in any possible alignment with either primer sequence (sense and antisense).

Id. at SI2.

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.

Figure S5 of Shiroguchi is reproduced below:

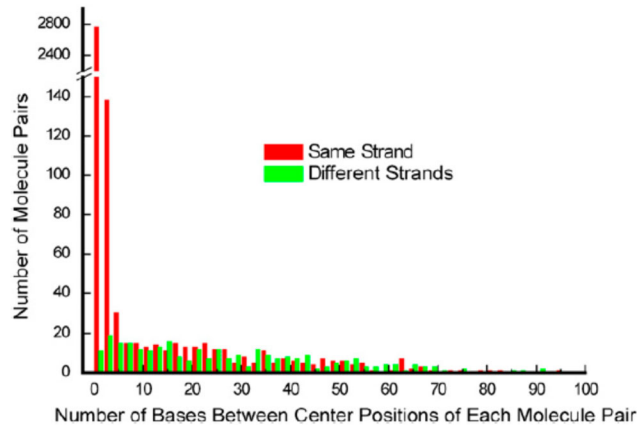


Figure 5 depicts a histogram of the number of bases between the center positions of all pairs of molecules mapped to the same transcription unit that contain the same barcode

The caption to Figure S5 states that it illustrates a histogram of the number of bases between the center positions of all pairs of molecules mapped to the same transcription unit that contain the same barcode for pairs of molecules both mapped to the sense or antisense strand of the *E. coli* genome (red), and also for pairs of molecules mapping to different strands of the *E. coli* genome (green). We are able to distinguish the different strands of an original cDNA molecule because of the design of the paired-end sequencing adapters (Fig. 1B). The distribution for molecule pairs mapping to different strands is more uniform than the distribution for molecule pairs mapping to the same strand, which confirms that molecule pairs mapping to different strands on the *E. coli* genome are on average far apart from each other. From the distribution of molecule pairs mapping to the same strand, we determined that molecule pairs with fewer than four bases between center positions are identical molecules. This analysis allows us to keep 98% of all molecules but reduces the counting error rate.

Ex. 1010, S7.

Of Figure 5S, Shiroguchi teaches:

We determined that more than one sequence with the same unique tag were identical if the distance between their center positions was less than 4 bp and if the difference in length was less than 9 bp (Figs. S5 and S6). Thus, the read counts for sequences deemed identical were summed and the sequence with more read counts was deemed as the actual correct sequence.

Ex. 1010, 1351. In short, Shiroguchi thus teaches that it used the barcode-adaptor sequence to distinguish a strand of its barcoded cDNA from DNA containing the same transcription unit that contain the same barcode, or to different strands of the *E. coli* genome. In other words, in Figure S5, Shiroguchi teaches a method for verifying error by measuring the number of bases between the center positions of all pairs of molecules, whether mapped to the original transcription unit or to other portions of *E. coli* DNA. We consequently find that 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. To the contrary, the green and red bars in the histogram of Figure S5 illustrate the number of bases between the center positions of barcoded cDNA bound to the original transcription unit DNA (red) or to DNA from other regions of the *E. coli* genome (green).

Claim 16 requires that “following the ligation step, the region of non-complementarity provides a strand-distinguishing nucleotide sequence such that a first strand of the adapter-target nucleic acid complex has a distinctly identifiable nucleotide sequence relative to its complementary second strand.” Ex. 1001 cols. 39–40, ll. 58–2. We are not persuaded that

Petitioner has sufficiently demonstrated that Shiroguchi teaches that it was well known in the art to use the region of non-complementarity of the adapter to provide a strand-distinguishing nucleotide sequence, as required by claim 16. We are consequently not persuaded by Petitioner's argument that it has shown a reasonable likelihood of prevailing in demonstrating that claim 16 is obvious over Kinde. Furthermore, because claims 17–21 depend from claim 16, we find Petitioner's arguments with respect to these claims to be similarly not persuasive.

D. Ground 2: Obviousness of claims 1–15, 22, and 23 over Kinde and Craig

1. Overview of Craig

Craig was published in the journal *Nature Methods* in October 2008 and is prior art to the '631 patent. Ex. 1007, 1.

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. Petitioner's contentions

Petitioner notes that, during prosecution of the '785 application, the Examiner determined that “claim [1] is a species of claim [16].” Pet. 43

(quoting Ex. 1004, 140). Petitioner argues that claim 1 is similar in scope to claim 16, but additionally requires “a degenerate or semi-degenerate single molecule identifier (SMI) sequence” on the adapter molecule that “uniquely labels each ligated double-stranded target nucleic acid molecule.” *Id.*

Petitioner repeats its arguments with respect to Kinde presented above. Pet. 43; *see* Section III.C.2.a. Petitioner also notes that Kinde also cites Craig, which discloses barcoded-adapters and ligating exogenous barcodes to the template DNA. *Id.* at 43–44 (citing Ex. 1006, 9531 (reference 42); also citing Ex. 1022 ¶¶ 22, 23). Petitioner argues that Kinde discloses that random nucleotide sequences generate large numbers of barcodes, which may be used to uniquely label sample molecules. *Id.* at 44 (citing Ex. 1006, SI1).

Petitioner contends that a skilled artisan would have had good reason to arrive at the claimed invention in view of Kinde and Craig. Pet. 44. First, Petitioner argues, Kinde identifies Craig regarding adding exogenous barcodes to DNA molecules, citing Kinde’s statement that “exogenous sequences [introduced] through ... ligation (42 [Craig], 43).” *Id.* (citing Ex. 1006, 9531; also citing Ex. 1022 ¶¶ 22, 23). Petitioner asserts that Craig discloses Illumina Y-shaped adapters that include a barcode in the double-stranded portion. *Id.* (citing Ex. 1007, 888, Supplementary Tables 3 and 4, Supplementary Methods). Petitioner also contends that Craig describes ligating the barcoded adapters to target DNA. *Id.* (citing Ex. 1007, 888; Ex. 1002 ¶¶ 121–124. Petitioner points out that an express suggestion in the prior art, although not required to demonstrate obviousness, supports a conclusion of obviousness. *Id.* (citing *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007)).

Furthermore, argues Petitioner, both Kinde and Craig disclose using Illumina Y-shaped adapters. Pet. 44 (citing Ex. 1007, 888, Supplementary Tables 3 and 4, Supplementary Methods). Petitioner points to a recent filing in the related IPR2022-00746, in which Patent Owner argued that Craig's barcoded Y-shaped adapters are amenable to use in the DCS method of the '631 patent. *Id.* (citing *Twinstrand Biosciences, Inc. v. Guardant Health, Inc.*, IPR2022-00746, Paper 2, 67). According to Petitioner, a skilled artisan would therefore have had good reason, and with a reasonable expectation of success, to use Y-shaped Illumina adapters with random barcodes, as taught by Kinde in view of Craig, to determine whether sequence variations could be detected in both strands. *Id.* at 44–45 (citing Ex. 1002 ¶ 125).

Additionally, Petitioner points to the Declaration of Dr. Quackenbush, who opines that the scientific literature at the time further corroborates that a skilled artisan would have had a reasonable expectation of success in arriving at Patent Owner's claimed invention. Pet. 45. Patent Owner points to Shiroguchi, which illustrates that barcoded Y-shaped adapters were well known at the time, and further confirms such adapters individually labeled each strand of a target DNA molecule. *Id.* (see Ex. 1002 ¶¶ 43–45). Patent Owner further argues that Shiroguchi also discusses the use of such adapter molecules in consensus sequencing approaches, as described by Kinde and others. *Id.* (citing Ex. 1010, 1347).

3. Analysis

We have considered the combination of Kinde and Craig in our Decision denying institution of *inter partes* review in the related *Guardant Health, Inc. v. University of Washington*, IPR2022-00816, Paper 16 at 13–16 (the '816 IPR). In that Decision, we found that Petitioner had not met its

burden to sufficiently explain the reason why a person of ordinary skill in the art would have been motivated to combine the teachings of Kinde and Craig. We repeat that reasoning here. IPR2022-00816, Paper 16 at 15–16.

Specifically, we agree with Petitioner that “Kinde and Craig both use Illumina Y-shaped adapters attached to each end of DNA molecules.”

IPR2022-00816, Paper 16 at 13 (citing Paper 3 at 22). Petitioner makes essentially the same argument in the present proceeding *See* Pet. 43. But, we found, 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. *Id.* (*comparing* Ex. 1006, S9 (showing the adapters used in the endogenous method do not contain barcodes) *with* Ex. 1007, 15 (showing adapters with barcodes)).

We further found in the ’816 IPR that Petitioner’s argument that an ordinarily skilled artisan could have swapped Kinde’s Y-shaped adapters with Craig was insufficient for our analysis. IPR2022-00816, Paper 16 at 14 (citing *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015) (holding that “obviousness 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”))).

In the ’816 IPR, we further observed that, 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.” IPR2022-00816, Paper 16 at 14 (citing Paper 3 at 22, 30). Again, Petitioner repeats the same argument in the present Petition. *See* Pet. 44; *see also* Ex. 1002 ¶ 42. But, as we observed in the ’816 proceeding, Kinde does not use Craig’s approach. IPR2022-00816, Paper 16 at 14. Instead, we found that

immediately after citing Craig as teaching attaching exogenous UIDs through ligation, Kinde introduces its endogenous method as an “[e]ven more simpl[e]” approach. *Id.* (quoting Ex. 1006, 9531). We therefore found that Kinde appears to teach Craig as an alternative, not an additional, method to assign UIDs. *Id.* The same reasoning applies equally here.

In the ’816 IPR, we further observed that Petitioner contended that “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.” IPR2022-00816, Paper 16 at 14 (citing Paper 3 at 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).

In its present Petition, Petitioner contends that:

Kinde identifies Craig regarding adding exogenous barcodes to DNA molecules. Specifically, Kinde discloses that methods include “exogenous sequences [introduced] through ... ligation (42, 43).” Craig discloses Illumina Y-shaped adapters that include a barcode in the double-stranded portion. Craig describes ligating the barcoded adapters to target DNA.

Pet. 44 (references omitted). Furthermore, argues Petitioner: “[B]oth Kinde and Craig disclose using Illumina Y-shaped adapters.” *Id.* (references omitted). Petitioner concludes that “a skilled artisan would have had good reason with a reasonable expectation of success to use Y-shaped Illumina adapters with random barcodes, as taught by Kinde in view of Craig, to determine whether sequence variations could be detected in both strands.” *Id.* at 45 (reference omitted).

But, as we explained in the ’816 IPR:

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.”

IPR2022-00816, Paper 16 at 15 (citing Paper 3 at 22). And, as we further explained:

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.

Id.

We apply the same reasoning here and, therefore, arrive at the same conclusion with respect to Petitioner’s Ground 2: that Petitioner has not explained sufficiently why a person of ordinary skill in the art would have been motivated to combine the teachings of Kinde and Craig to arrive at the invention recited in claims 1–15, 22, and 23 of the ’631 patent. We

therefore conclude, as we have previously in the '816 IPR, that Petitioner has not demonstrated a reasonable likelihood that it would prevail in showing that the claims would have been obvious over the combination of Kinde and Craig.

E. Ground 3: Obviousness of claims 1–23 over Kinde, Craig, and the Travers Publications

1. Overview of Travers '075

Travers '075 relates to compositions and methods for nucleic acid sequencing, which include “template constructs that comprise double stranded portions in a partially or completely contiguous constructs, to provide for redundant sequence determination through one or both of sequencing sense and antisense strands, and iteratively sequencing the entire construct multiple times.” Ex. 1018, Abstract.

Specifically, Travers '075 teaches Single Molecule Real Time (SMRT) sequencing, which is schematically illustrated in Figure 1A, reproduced below:

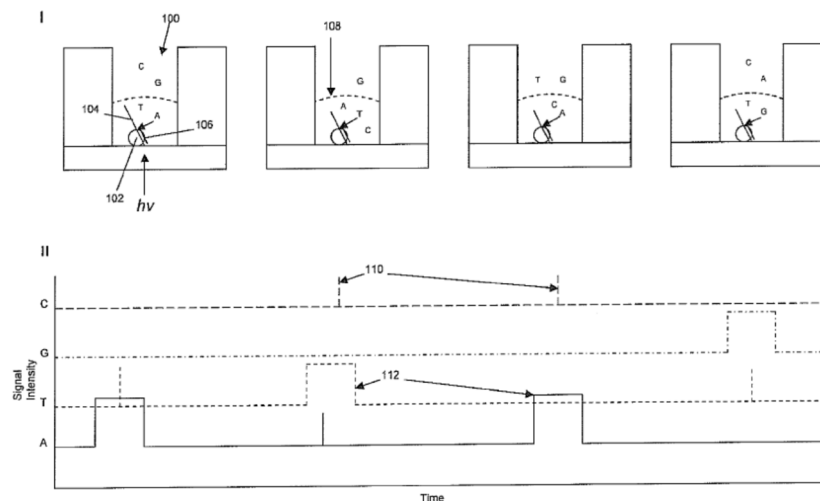


Figure 1A of Travers '075 depicts the SMRT sequencing scheme

Figure 1A of Travers '075 shows the SMRT sequencing process. Ex. 1018 ¶ 21. In Panel I, “a nucleic acid synthesis complex comprising a polymerase enzyme 102, a template sequence 104 and a primer sequence 106 complementary to a portion of the template sequence 104, is provided immobilized within a confined illumination volume (indicated by the dashed line 108).” *Id.* ¶ 43.

Travers '075 teaches that “[t]he reaction mixture surrounding the complex contains the four different nucleotides (A, G, T and C) each labeled with a spectrally distinguishable fluorescent label attached through its terminal phosphate group.” Ex. 1018 ¶ 44. Travers '075 explains the fluorescent label of free nucleotide provides a very short signal, whereas a nucleotide incorporated by the polymerase in a primer extension reaction provides a longer signal. *Id.* According to Travers '075, “[b]y identifying longer pulses of different spectral characteristics, one can detect, in real time, the identity of each incorporated base as it is being incorporated.” *Id.* ¶ 45.

In one embodiment, as shown in Figure 2B, Travers '075 teaches a circular template comprising a double-stranded portion linked by two single-stranded portions. *Id.* ¶ 50. Figure 2B is reproduced below:

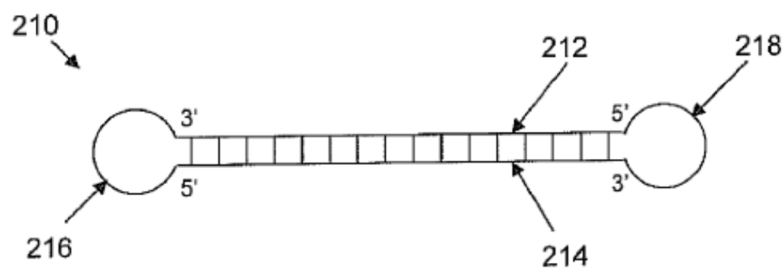


Figure 2B of Travers '075 illustrates an exemplary embodiment of a template construct

Travers '075 teaches, with respect to Figure 2b, that “[s]equence 210 includes a double stranded portion again comprised of two complementary segments 212 and 214.” *Id.* ¶ 50. “[T]he 3’ end of segment 212 is joined to the 5’ end of segment 214 via oligonucleotide 216 in a first single stranded portion,” and “the 5’ end of segment 212 is joined to the 3’ end of segment 214 via linking oligonucleotide 218, providing a second single stranded portion.” *Id.* This construct yields “a completely contiguous or circular template sequence.” *Id.*

In Figure 3B, Travers '075 teaches applying the SMRT sequencing process to the circular template of Figure 2B. Figure 3B is reproduced below:

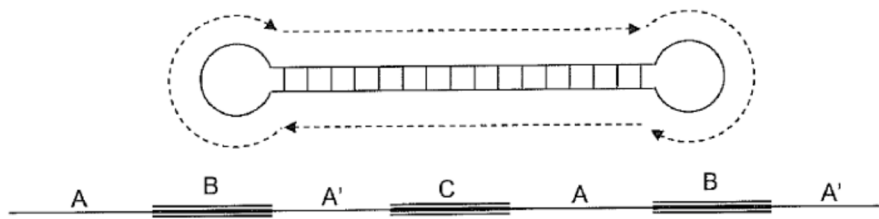


Figure 3B illustrates redundant sequencing using the construct shown in Figure 2B, above

With respect to Figure 3B, Travers '075 teaches:

As shown, a sequencing process that is primed at one end, e.g., primed within one linking oligonucleotide sequence, e.g., linking oligonucleotide 218 of FIG. 2, proceeds along the first or sense strand 214, again providing the nucleotide sequence A of that strand. The sequence process then proceeds around the first linking oligonucleotide, e.g., linking oligonucleotide 216 from FIG. 2, to provide the nucleotide sequence B of that segment of the template. Proceeding along the antisense strand, e.g., segment 212 of FIG. 2B, provides the nucleotide sequence A', which is again, complementary to sequence A. The sequencing process then continues around the template providing the nucleotide sequence for the other linking oligonucleotide, e.g.,

linking oligonucleotide 218 of FIG. 2B, where the illustrated sequencing process began, providing nucleotide sequence C.

Id. ¶ 55.

Travers '075 further states that although the constructs of its invention, such as the circular template shown in Figure 2B, are “primarily, and preferably, for use directly as templates for, e.g., sequencing applications,” they “may also serve as intermediate structures in the preparation of templates that provide for sequence redundancy.” *Id.* ¶ 122. Specifically, it describes using the circular template “in a rolling circle replication process to produce concatamer molecules that include repeating copies of both the sense and antisense strands of the originating double stranded segment included within the circular nucleic acid.” *Id.* “These replicated products,” Travers '075 continues, “may then be employed directly as template molecules in a template dependent sequencing process.” *Id.*

2. Overview of Travers

Travers describes a template design for single-molecule sequencing referred to as a SMRTbell template. Ex. 1021, Abstr. Figure 1 of Travers, reproduced below, shows a SMRTbell template:

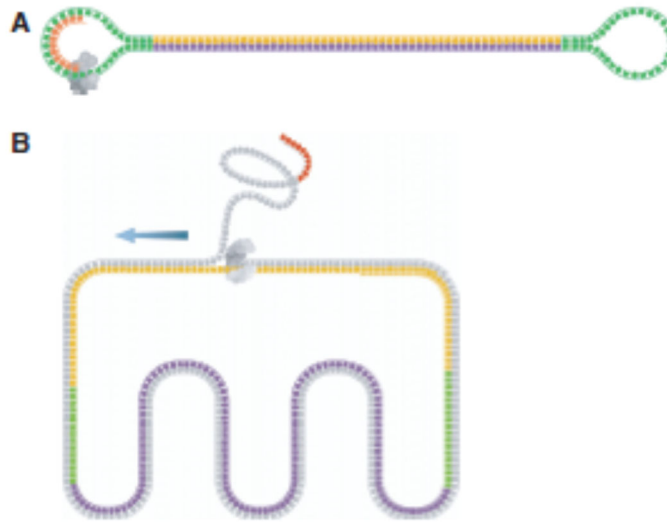


Figure 1 is a schematic of a SMRTbell template

As depicted in Travers' Figure 1A, the structure "consists of a double-stranded region (the insert) flanked by two hairpin loops. The hairpin loops present a single-stranded region to which a sequencing primer can bind (orange)." *Id.* Travers teaches that "[s]tructurally, this format resembles a linear double-stranded molecule, and yet it is topologically circular." *Id.*, Abstract. Travers teaches applying the circular molecule to SMRT sequencing. *Id.* at 4. Figure 1B of Travers shows that as a strand-displacing polymerase (gray) extends a primer from one of the hairpin loops, it uses one strand as the template strand and displaces the other. When the polymerase returns to the 5'-end of the primer, it begins strand displacement of the primer and continues to synthesize DNA (moving in the direction of the blue arrow). *Id.* at 3. As a result, the sequence is derived from both sense and anti-sense strands. *Id.*

3. Petitioner's contentions

Petitioner incorporates its arguments presented above with respect to Kinde, as applied to claims 16–21 in Ground 1, and Kinde and Craig, as applied to claims 1–15, 22 and 23 in Ground 2. Pet. 63.

Petitioner contends that Travers and Travers '075 (collectively, the “Travers Publications”) describe methods including attaching adapters, amplifying, and sequencing from both strands of an original double-stranded nucleic acid molecule to generate what they describe as “high-quality consensus” or “high-accuracy consensus” sequence. Pet. 63 (citing Ex. 1021, Abstr., 1). Petitioner argues that the Travers Publications disclose consensus sequencing following the same essential workflow of the '631 patent. *Id.* Petitioner points out that the '631 patent borrows the same terminology found in the Travers Publications (e.g., “high accuracy consensus”) and expressly indicates its method is meant to capture Travers' U-shaped (“hairpin”) adapters. *Id.* at 63–64 (citing, e.g., Ex. 1001 col. 10, ll. 58–64, claim 10, 20). As such, argues Petitioner, the Travers Publications further corroborate that any aspects of amplification, redundant sequencing, adapter use, and consensus analysis of sequence reads recited in the '631 patent claims were well-known in the art at the time. *Id.* at 64. Petitioner asserts that the Travers Publications, particularly viewed in combination with other relevant art at the time, like Kinde and Craig, confirm the obviousness of claims 1–23. *Id.* (citing Ex. 1002 ¶¶ 189–190).

According to Petitioner, the Travers Publications disclose a method for generating “high-accuracy” consensus sequences from both strands of an original DNA duplex molecule. Pet. 64. Referring to Figure 1B, Petitioner contends that the Travers Publications teach that adapters (green) are attached to both ends of double-stranded DNA to produce adapter-target

nucleic acid complexes (“SMRTbell™ templates”) comprising a region of non-complementary that provides a strand-distinguishing nucleotide sequence. *Id.* (citing Ex. 1021, Fig. 1, e159; Ex. 1018, Figs. 2, 3, 7, ¶¶ 16, 51–55, 100–102).

Petitioner argues that the Travers Publications teach that the SMRTbell™ templates are amplified by primer extension with a strand-displacing polymerase to produce a concatemer comprising repeating copies of the sense and antisense strands separated by a copy of the adapter. Pet. 65 (citing, e.g., Ex. 1018 ¶ 122; Ex. 1021, Figs. 1, 4). According to Petitioner, use of the SMRTbell allows for generation of a consensus sequence based on redundant reads of the sense and antisense strands of the original molecule. *Id.* (citing Ex. 1021, Abstr., 1, Fig. 4; Ex. 1018 ¶¶ 53, 54, 122; Ex. 1002 ¶¶ 190–192). Petitioner points out that Patent Owner, during *ex parte* prosecution of a related case, acknowledged that virtually every aspect of the claimed subject matter is disclosed by Travers ’075. *Id.* (citing Ex. 1024, 0551⁸; also citing Ex. 1001 col. 10–11, ll. 58–12, col. 15, ll. 33–43).

Petitioner contends that, given the breadth of the claims and the teachings in the combined cited references, a person of ordinary skill in the art would have good reason to look to the combined teachings of the cited references with a reasonable expectation of successfully arriving at the claimed subject matter. Pet. 65 (citing *In re Keller*, 642 F.2d 413, 425 (C.C.P.A. 1981)).

Petitioner contends that both Kinde and the Travers Publications

⁸ Exhibit 1024 is the prosecution history of related US Appl. Ser. No. 16/118,306 (the “’306 application”).

disclose methods of determining sequencing consensus based on amplification, redundant sequencing, and analysis of sequence reads of both strands of a DNA duplex. Pet. 66. Furthermore, asserts Petitioner, both references utilized commercially available sequencing adapters that enable distinguishing of different duplex strands: Kinde discloses using prior art Y-shaped adapters, including those commercially available from Illumina at the time. *Id.* Petitioner again argues that Kinde also cites to Craig, which further illustrates prior art Y-shaped adapters. *Id.* Petitioner contends that the Travers publications discuss consensus sequencing using U-shaped (“hairpin”) adapters that were commercially available from PacBio at the time. *Id.* According to Petitioner, a skilled artisan, contemplating consensus sequence analysis would look to prior art descriptions of consensus sequencing utilizing well-known and commercially available sequencing technologies. *Id.* (citing Ex. 1002 ¶¶ 192–196).

Petitioner also points out that the Specification of the ’631 patent specification mirrors the disclosure of Kinde, borrows graphics and terminology from the prior art literature, and expressly describes its methods of encompassing prior art and commercially available Y- and U-shaped adapters, including Illumina Y-shaped adapters and PacBio U-shape (“hairpin”) adapters. *Id.* (citing Ex. 1001 col. 3, ll. 56–62, col. 26, ll. 9–22, claims 10, 20). Petitioner also asserts that the Travers Publications also discuss inclusion of barcodes with the adapter molecules. *Id.* at 66 (citing Ex. 1002, ¶¶ 197–240).

4. Analysis

We have explained, in Sections III.C and III.D above, why we are not sufficiently persuaded by Petitioner’s arguments that it is likely to prevail

with respect to Grounds 1 and 2, and we incorporate our analyses with respect to those Grounds here. We are not persuaded that the Travers Publications cure the deficiencies of Petitioner's arguments with respect to Grounds 1 and 2.

Petitioner argues that, during prosecution of the related '306 application, "Patent Owner ... acknowledged that virtually every aspect of the claimed subject matter is disclosed by Travers '075." *See* Pet. 65 (citing Ex. 1024, 0551). This is not quite accurate; in that same proceeding, Patent Owner expressly argued that:

Nowhere does Travers disclose or suggest separating the sense strand from the antisense strand of a double-stranded DNA fragment in a manner that such original strand amplification products are distinct yet relatable. Moreover, one of ordinary skill in the art would understand from a reading of Travers that separating the sense and antisense strands before, during or after amplification of the template molecules would thwart the entire purpose of Travers (e.g., to generate a consensus sequence of the double stranded molecule by redundant sequencing of the entire single template).

Ex. 1024, 0551. We agree, noting that Petitioner does not point to any specific teaching in either of the Travers Publications that expressly teaches, or suggests, using the adapter, with its non-complementary sequences, as a strand-distinguishing nucleotide sequence to distinguish one separate nucleic acid strand from another. Nor can we discern any such teaching.

Consequently, and in view of our analyses of Kinde and Craig with respect to Grounds 1 and 2 in Sections III.C and III.D above, we conclude that Petitioner has not demonstrated a reasonable likelihood of prevailing at trial with respect to Ground 3. We consequently decline to institute *inter partes* review.

F. Conclusion

For the reasons we have explained, because we have determined that Petitioner has failed to establish a reasonable likelihood of prevailing at trial upon Grounds 1–3, we do not institute *inter partes* review of challenged claims 1–23 of the ’631 patent. *See SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1359–60 (2018); *PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018).

IV. CONCLUSION

For the forgoing reasons, we conclude that Petitioner has failed to demonstrate a reasonable likelihood that at least one challenged claim of the ’631 patent would have been obvious over the prior art of record. Accordingly, we do not institute *inter partes* review of challenged claims 1–23 of the ’631 patent, based on the grounds identified in the Petition.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED, pursuant to 35 U.S.C. § 314(a), that the Petition for *inter partes* review of claim 1–23 of the ’631 patent is DENIED with respect to all grounds in the Petition; and

FURTHER ORDERED that no *inter partes* review is instituted.

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FOR PETITIONER:

Michael T. Rosato

Jad A. Mills

Sonja R. Gerrard

Wilson Sonsini Goodrich & Rosati

mrosato@wsgr.com

jmills@wsgr.com

sgerrard@wsgr.com

FOR PATENT OWNER:

Ralph Wilson Powers III, Ph.D.

David H. Holman, Ph.D.

Kristina C. Kelly, Esq.

Christopher M. Gallo, Ph.D.

Sterne, Kessler, Goldstein & Fox P.L.L.C.

tpowers-PTAB@sternekessler.com

dholman-PTAB@sternekessler.com

kckelly-PTAB@sternekessler.com

cgallo-PTAB@sternekessler.com