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Paper 13
Entered: August 1, 2022

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GUARDANT HEALTH, INC.,
Petitioner,

v.
UNIVERSITY OF WASHINGTON,
Patent Owner.

IPR2022-00450
Patent 10,689,699 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 1–27 of U.S. Patent No. 10,689,699 B2 (Ex. 1001, “the ’699 Patent”). University of Washington (“Patent Owner”) filed a Preliminary Response. Paper 9 (“Prelim. Resp.”). With our authorization (Ex. 3001), Petitioner filed a Reply (Paper 11), and Patent Owner filed a Sur-reply (Paper 12).

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 ’699 patent is asserted against Petitioner in *TwinStrand Biosciences, Inc. et al. v. Guardant Health, Inc.*, 1-21-cv-01126 (D. Del.). Pet. 13; Paper 5, 1.

Petitioner also filed a petition in IPR2022-00449, challenging the same claims of the ’699 patent. In a concurrently issued decision, we deny that petition. IPR2022-00449, Paper 13.

B. The ’699 Patent and Related Background

The ’699 patent relates to methods of lowering the error rate of massively parallel DNA sequencing using duplex consensus sequencing. Ex. 1001, code (54), 17:57–59.

The ’699 patent states massively parallel DNA sequencing “offer[ed] the unique ability to detect minor variants within heterogeneous mixtures.” *Id.* at 1:31–40. 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 1:41–48 (internal citations omitted). Deep sequencing, however, according to the ’699 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 1:59–2:6. The ’699 patent states “[t]his background level of artifactual heterogeneity establishes a limit below which the presence of true rare variants is obscured.” *Id.* at 2:7–9.

The ’699 patent acknowledges several attempts aimed at improving the accuracy and sensitivity of sequencing:

> For example[,] techniques whereby DNA fragments to be sequenced are each uniquely tagged prior to amplification have been reported. Because all amplicons derived from a particular starting molecule will bear its specific tag, any variation in the sequence or copy number of identically tagged sequencing reads can be discounted as technical error. This approach has been used to improve counting accuracy of DNA and RNA templates and to correct base errors arising during PCR or

> sequencing. Kinde et. al.[1] reported a reduction in error frequency of approximately 20-fold with a tagging method that is based on labeling single-stranded DNA fragments with a primer containing a 14 bp degenerate sequence. This allowed for an observed mutation frequency of ~0.001% mutations/bp in normal human genomic DNA.

Id. at 2:10–31 (footnote added, internal citations omitted). But, because "true mutation frequency in normal cells is likely to be far lower," the '699 patent reasons that "the mutations seen in normal human genomic DNA by Kinde et al. [still] are likely the result of significant technical artifacts." *Id.* at 2:32–38.

Thus, the '699 patent states "[i]t would be desirable to develop an approach for tag-based error correction, which 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 which capitalizes on the redundant information stored in complexed double-stranded DNA." *Id.* at 2:63–3:2.

C. Illustrative Claims

Among the challenged claims, claims 1 and 20 are independent. They are illustrative of the claimed subject matter and are reproduced below.

> 1. A method, comprising:
>
> a) providing a population of circulating DNA molecules obtained from a bodily sample from a subject;

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[1] Kinde et al., *Detection and Quantification of Rare Mutations with Massively Parallel Sequencing*, 108 Proc. Natl. Acad. Sci. 9530–35 (2011) (Ex. 1039, "Kinde"). Kinde is one of the prior-art references asserted in this proceeding.

b) converting the population of circulating DNA molecules into a population of non-uniquely tagged parent polynucleotides, wherein each of the non-uniquely tagged parent polynucleotides comprises (i) a sequence from a circulating DNA molecule of the population of circulating DNA molecules, and (ii) an identifier sequence comprising one or more polynucleotide barcodes, such that each non-uniquely tagged parent polynucleotide is substantially unique with respect to other non-uniquely tagged parent polynucleotides in the population;

c) amplifying the population of non-uniquely tagged parent polynucleotides to produce a corresponding population of amplified progeny polynucleotides;

d) sequencing at least a portion of the population of amplified progeny polynucleotides to produce a set of sequence reads;

e) grouping the sequence reads into families, each of the families comprising sequence reads comprising the same identifier sequence and having the same start and stop positions, whereby each of the families comprises sequence reads amplified from the same non-uniquely tagged parent polynucleotide; and

f) collapsing sequence reads in each family to yield a base call for each family corresponding to one or more genetic loci.

Ex. 1001, 37:46–38:51.

20. A method, comprising:

a) attaching a set of molecular tags to a population of circulating DNA molecules obtained from a bodily sample of a subject to produce a population of tagged original DNA molecules, wherein a plurality of the tagged original DNA molecules has identical molecular tags, and wherein each tagged original DNA molecule is substantially unique with respect to other tagged original DNA molecules in the population;

b) amplifying the population of tagged original DNA molecules to produce a corresponding population of DNA molecule amplicons;

> c) sequencing at least a portion of the population of DNA molecule amplicons to produce a set of sequence reads;
>
> d) grouping the sequence reads into families based on i) the molecular tag and ii) sequence information derived from the circulating DNA molecule, whereby each of the families comprises sequence reads amplified from the same tagged original DNA molecule; and
>
> e) collapsing sequence reads in each family to provide an error-corrected consensus sequence read for each family corresponding to one or more genetic loci.[2]

Id. at 40:12–32.

D. Asserted Challenges to Patentability

Petitioner asserts the following challenges to patentability:

Claims Challenged	35 U.S.C. §[3]	References
1–27	103(a)	Kinde, Miner[4]
1–27	103(a)	Kinde, Miner, Fan[5]

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

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[2] We incorporate the Certificate of Correction (Ex. 3002) to correct certain typographic errors in claim 20.

[3] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. § 103, effective March 16, 2013. On its face, the '699 patent has an effective filing date before March 16, 2013, which Petitioner does not dispute in this proceeding. Thus, for purposes of this Decision, we apply the pre-AIA version of § 103.

[4] Miner et al., *Molecular Barcodes Detect Redundancy and Contamination in Hairpin-Bisulfite PCR*, 32 Nucleic Acids Res. E135 (2004) (Ex. 1037, "Miner").

[5] Fan et al., *Noninvasive Diagnosis of Fetal Aneuploidy by Shotgun Sequencing DNA from Maternal Blood*, 105 Proc. Natl. Acad. Sci. 16266–71 (2008) (Ex. 1021, "Fan").

II. ANALYSIS

A. Claim Construction

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

Petitioner states that no claim term needs to be construed for this proceeding. Pet. 14. It nevertheless discusses the term "circulating DNA molecules" to "provide[] context for understanding the scope of the term." *Id.* at 15. Petitioner observes that the term is not used in the specification of the '699 patent. *Id.* Citing "[s]tatements made by Patent Owner during prosecution of a related case" (*i.e.*, Ex. 1005, 183–84), Petitioner argues that "[cfDNA] cell-free DNA obtained from blood is included within the meaning of the term 'circulating DNA molecules.'" *Id.* Petitioner contends "circulating DNA molecules" include cfDNA "found in blood plasma and serum after removal of the cells," but not DNA "extracted *ex vivo* from intact circulating cells (*e.g.*, blood cells, tumor cells)." *Id.* at 16 (citing Ex. 1002 ¶¶ 48–49; Ex. 1020, 1–2, 8–9; Ex. 1023, 10515–16).

Patent Owner does not dispute Petitioner's arguments. *See* Prelim. Resp. 5. Based on the arguments and evidence presented, we determine "circulating DNA molecules" include cfDNA circulating in plasma and

serum, and do not include cellular DNA molecules. This determination as to the scope of "circulating DNA molecules" is sufficient for purposes of this Decision, and we need not further address the term at this time.

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 expressly construe any other claim term.

B. Alleged Obviousness over Kinde and Miner

Petitioner asserts that claims 1–27 of the '699 patent would have been obvious over the combination of Kinde and Miner. Pet. 16–60. 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. 1039, 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. According to Kinde, however, "the number of different molecules that can be examined using endogenous UIDs is limited." *Id.* at 9532. Thus, Kinde teaches using PCR with a forward primer that contains "a stretch of 12–14 random nucleotides" to introduce exogenous UIDs. *Id.* 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. Nonetheless, according to Kinde, the endogenous approach has limitations and is not ideally suited for many clinical applications. *Id.* at 9532, 9534.

b. Miner

Miner teaches using "molecular barcoding to label each genomic DNA template with an individual sequence tag prior to PCR amplification." Ex. 1037, 1. Specifically, it teaches "[l]igation of the hairpin linker . . . to DraIII-cleaved genomic DNA." *Id.*

According to Miner, the hairpin linker can be used to "encode each ligated genomic fragment with information that distinguishes it from other sequences within a sample, allowing . . . evaluat[ion of] cloned sequences for redundancy and contamination." *Id.* at 2. Miner states "[w]ith a random 7 nt barcode, the number of possible codes is 2187; in selecting 15 cloned PCR products from one DNA sample, the probability that two of these will be different genomic fragments labeled with identical 7 nt barcodes is 0.047." *Id.*

2. Previous Representations Made by Petitioner

In defending several of its own patents before this Board and the European Patent Office ("EPO"), Petitioner made statements, characterizing

the teachings of Kinde. *See, e.g.*, Ex. 2001,[6] 23;[7] Ex. 2002,[8] 27; Ex. 2003,[9] 7. Petitioner emphasizes that the prior proceedings "involved different records and different legal theories," and in the case of EPO Opposition, "non-US law and procedure." Reply 6. We agree. But, despite the differences in law, procedure, or legal theories, Kinde's teachings, from an ordinarily skilled artisan point of view remain the same.

Explanation of Kinde's teachings made to this Board by Petitioner constitute admissions that we must consider. *See Cook Grp. Inc. v. Bos. Sci. Scimed*, Inc., 809 F. App'x 990, 1000 (Fed. Cir. 2020) (stating that "an admission in a preliminary patent owner response, just like an admission in any other context, is evidence appropriately considered by a factfinder"). In addition, Petitioner's representations to the EPO are relevant to determine how an ordinarily skilled artisan would understand Kinde. *See Tanabe Seiyaku Co. v. U.S. Int'l Trade Comm'n*, 109 F.3d 726, 733 (Fed. Cir. 1997) (stating that "representations made to foreign patent offices are relevant to determine whether a person skilled in the art would consider butanone or other ketones to be interchangeable with acetone"); *Cf. Gillette Co. v. Energizer Holdings, Inc.*, 405 F.3d 1367, 1374 (Fed. Cir. 2005) (considering admission before the EPO as support for claim construction).

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[6] *Foundation Medicine, Inc. v. Guardant Health, Inc.*, IPR2019-00130 ("Guardant I"), Paper 6 (Ex. 2001, Guarduant's Preliminary Response).
[7] For Exhibits 2001 and 2002, we cite the original page number, not the number provided by Patent Owner.
[8] *Foundation Medicine, Inc. v. Guardant Health, Inc.*, IPR2019-00653 ("Guardant II"), Paper 6 (Ex. 2002, Guarduant's Preliminary Response).
[9] Opposition Proceedings for EP 2893040 B1 ("EPO Opposition"), Guarduant's Response to Notices of Opposition (Ex. 2003).

Thus, we consider Petitioner's representations made in Guardant I, Guardant II, and EPO Opposition when weighing the evidence supporting each side's understanding of Kinde.

a. Guardant I

In Guardant I, Petitioner argued that "[i]t was well-known that cell-free DNA presented unique technical difficulties compared to analysis of cellular DNA." Ex. 2001, 24. There, Petitioner asserted Kinde "only discuss[es] analysis of cellular DNA, there is no discussion . . . about application of the methods to cell-free DNA." *Id.* at 23–24 (citing Kinde for teaching "determining . . . mutations in the nuclear and mitochondrial genomes of ***normal cells***"). Citing another reference that discussed Kinde, Petitioner argued that "one of the recognized problems with the Kinde approach is that the method actually introduces significant error into the process." *Id.* at 23. According to Petitioner, "[t]he introduction of significant error with Kinde's tagging method is inconsistent with an intended reduction of errors as an alleged basis for employing cell-free DNA in the Kinde method." *Id.*

b. Guardant II

In Guardant II, Petitioner again argued that "Kinde does not disclose applying the endogenous UID embodiment (or any embodiment) to cell-free DNA." Ex. 2002, 27. According to Petitioner, "[t]his is not a trivial point and cannot simply be glossed over." *Id.*

c. EPO Opposition

In EPO Opposition, Petitioner explained that Kinde[10] teaches three distinct embodiments: (1) the exogenous UID embodiment, which incorporates UID through PCR with a primer that comprises the UID; (2) the endogenous UID embodiment, which involves ligation of adaptors (without exogenous UIDs) onto polynucleotides after random shearing; and (3) the inverse PCR embodiment, which involves, after the random shearing and adapter ligation (without exogenous UIDs), "circularisation and inverse PCR with gene specific primers." Ex. 2003, 14–15.

Petitioner argued that Kinde "had not applied [its] techniques to cfDNA," and had not "appreciated the challenges which are presented when working with this analyte." *Id.* at 7. According to Petitioner, Kinde "typically aimed to obtain randomly-sheared DNA fragments which are quite different from cfDNA molecules that arise naturally *in vivo*." *Id.* (arguing "cfDNA molecules and randomly-sheared DNA fragments are not analogous").

Petitioner also cited Kinde for "discuss[ing] the suitability of each of the three embodiments for the analysis of clinical samples with relatively few template molecules, outlining that the ligation-based methods (i.e. the 'endogenous UID' and 'inverse PCR' embodiments) are not suited to such samples." *Id.* at 15 (citing Ex. 1039, 9534). According to Petitioner, "[t]his point had also been acknowledged in prior art which had considered [Kinde]." *Id.*

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[10] D11 in EPO Opposition is Kinde. *See* Ex. 2006, 4.

Petitioner argued in EPO Opposition:

> Accordingly, in pursuit of a method for error correction in the analysis of clinical samples with low input amounts (e.g. cfDNA), the most realistic starting point would be the 'exogenous UID' embodiment because [Kinde] specifically teaches that this is the method which is most suitable for this purpose. Put differently, [Kinde] teaches away from using ligation-based methods when there are "*relatively few template molecules in the initial sample*."

Id.

Petitioner acknowledged that, in Kinde, "the inverse PCR embodiment is based on endogenous UIDs (created by acoustic shearing) but also introduces 12 different index sequences using the forwards PCR primer." *Id.* at 17. According to Petitioner, "the exogenous UID is not used when generating a consensus sequence, but rather is used to permit multiplexing of several different samples in a single sequencing experiment." *Id.* at 18. In addition, Petitioner contends that

> [E]ven if the skilled person would consider using the index sequence for collapsing sequences into sets (or 'UID families" with [Kinde]'s nomenclature), it remains the case that the inverse PCR embodiment (i) is reported in [Kinde] itself to be "not ideally suited" to situations where "there are relatively few template molecules in the initial sample" . . . , (ii) relies on random shearing of the fragments . . . , and (iii) does not involve tagging with exogenous UIDs by ligation (the index sequences are introduced through primers . . .).

Id.

3. Analysis

Independent claim 1 recites, in part, "converting the population of circulating DNA molecules into a population of non-uniquely tagged parent polynucleotides." Ex. 1001, 37:49–51. Independent claim 20 recites, among

others, "attaching a set of molecular tags to a population of circulating DNA molecules obtained from a bodily sample of a subject to produce a population of tagged original DNA molecules." *Id.* at 40:12–15.

Petitioner relies on Kinde for teaching (1) tagging the original parent polynucleotides;[11] and (2) applying its method to cfDNA obtained from blood plasma, which is circulating DNA molecules. In the analyses below, we address each argument in turn.

a. Tagging Parent Polynucleotides/Original DNA Molecules

Petitioner previously explained to the EPO that Kinde teaches three distinct embodiments for tagging: the PCR-based exogenous UID embodiment, the ligation-based endogenous UID embodiment, and the inverse PCR embodiment, which involves ligation and inverse PCR with gene specific primers. *See supra* Section II.B.2.c; Ex. 2003, 14–15.

In this proceeding, Petitioner contends that its challenges do not rely on the PCR based tagging. Reply 6 (citing Pet. 10, 19, 23, 24, 26). As such, we understand that the Petition does not rely on Kinde's exogenous UID embodiment. *See* Ex. 1039, 9532 (teaching the exogenous UID embodiment employs PCR).

Next, Petitioner faults Patent Owner for "attack[ing] Kinde's endogenous and inverse PCR embodiments, rather than Kinde's

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[11] Petitioner appears to treat the terms "parent polynucleotides" and "original DNA molecules" interchangeably. *See, e.g.*, Pet. 11, 17, 18, 25 (describing using UIDs to identify the amplification progeny of "original parent molecules" or "original parent DNA molecules"). For purposes of this Decision, we do the same.

ligation-based approach." Reply 5.[12] As an initial matter, before the EPO, Petitioner equated the endogenous and inverse PCR embodiments with the ligation-based methods. Ex. 2003, 15 (arguing "the ligation-based methods (*i.e.* the 'endogenous UID' and 'inverse PCR' embodiments)" are not suited for clinical samples). Thus, Petitioner's argument of "Kinde's ligation-based approach," separate and different from the endogenous and inverse PCR embodiments, appears inconsistent with its representations to the EPO. More problematically, if, as Petitioner argued, Kinde teaches three distinct embodiments, yet the Petition does not rely on any of them, then it is unclear which Kinde approach the Petition actually relies on.

Of course, it is not lost on us that Kinde, in a single sentence, mentions "introduction of exogenous sequences through PCR (40, 41) or ligation (42, 43)." Ex. 1039, 9531.[13] Petitioner emphasizes the ligation aspect of this sentence. *See* Pet. 20, 23, 24, 26 (citing Ex. 1039, 9531). Kinde, however, does not teach ligating exogenous UIDs to tag the original parent polynucleotides in its Safe-SeqS approach. Instead, as Petitioner acknowledges, "Kinde uses PCR to add exogenous UIDs prior to library amplification and sequencing." *Id.* at 25. Where Kinde teaches ligating exogenous sequences, those sequences are adapters for sequencing, and not

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[12] Petitioner cites page 26 of the Preliminary Response as support. Reply 5. That page, however, does not appear to discuss any specific embodiment of Kinde. *See* Prelim. Resp. 26.

[13] Petitioner contends that Kinde cites two references for examples of how to use ligation to attach exogenous UIDs. Pet. 26. As explained below, those two references discuss genomic DNA, not cfDNA, which is the circulating DNA molecules in Kinde that Petitioner relies on. *See infra* Section II.B.3.b.

UIDs to tag the original parent polynucleotides. *See* Ex. 1039, 9531, 9535, S1.

Petitioner points to the Supporting Information in Kinde. Pet. 22, 24, 29 (citing Ex. 1039, S1). There, in exemplifying the inverse PCR embodiment, Kinde states:

> For the inverse PCR experiments (Fig. S1), we ligated custom adapters (IDT) (Table S4) instead of standard Y-shaped Illumina adapters to sheared cellular DNA. These adapters retained the region complementary to the universal sequencing primer but lacked the grafting sequences required for hybridization to the Illumina GA IIx flow cell. The ligated DNA was diluted into 96 wells and the DNA in each column of 8 wells was amplified with a unique forward primer containing one of 12 index sequences at its 5' end plus a standard reverse primer (Table S4). . . . The resulting DNA fragments contained UIDs composed of three sequences: 2 endogenous ones, represented by the two ends of the original sheared fragments, plus the exogenous sequence *introduced during the indexing amplification*. As 12 exogenous sequences were used, this increased the number of distinct UIDs by 12-fold over that obtained without exogenous UIDs.

Ex. 1039, S1 (emphasis added). As this passage makes clear, the "12 exogenous sequences" Petitioner points to are introduced through PCR, the tagging method Petitioner explicitly disclaimed. *See* Reply 6; *see also* Ex. 2003, 18 ("[T]he exogenous UID is not used when generating a consensus sequence, but rather is used to permit multiplexing of several different samples in a single sequencing experiment.").

Moreover, as Petitioner previously acknowledged, Kinde discusses the "12 exogenous sequences" in the inverse PCR embodiment. Ex. 2003, 17; Ex. 1039, S1. In this proceeding, Petitioner argues that the Petition does not rely on the inverse PCR embodiment. Reply 5. Petitioner has not

adequately explained why it is proper to combine the teaching of this disclaimed embodiment with other embodiments, especially given its previous argument that "it is not allowable to create an artificial starting point by mixing & matching features from distinct embodiments to create an undisclosed hybrid." Ex. 2003, 14.

In sum, based on the current record, we find the Petition has not sufficiently shown that the combination of Kinde and Miner teaches the limitation of tagging original parental DNA molecules, as required in independent claims 1 and 20.

b. Applying Kinde's Approach to cfDNA

Petitioner argues that Kinde teaches applying Safe-SeqS to cfDNA in plasma, which is circulating DNA. Pet. 19–20, 24, 26–28. After considering the current record as a whole, including Petitioner's previous representations to this Board and EPO, we are not persuaded.

Petitioner acknowledges that "Kinde exemplifies its tagging methodology exclusively with cellular DNA," but asserts "Kinde references clinical applications which use circulating DNA." Pet. 19 (citing Ex. 1039, 9531). Specifically, Petitioner refers to Kinde for citing references, including Fan, which, according to Petitioner, "describe providing a population of circulating DNA molecules obtained from a bodily sample in the form of DNA in maternal plasma." *Id.* at 26–27 (citing Ex. 1039, 9530), *id.* at 26 ("Kinde references clinical applications of massively parallel sequencing as including prenatal screening."). Petitioner also contends that Kinde teaches "massively parallel sequencing technology was useful for detecting rare mutants in blood plasma of individuals with malignant neoplastic disease

(i.e., cancer).” *Id.* at 27 (citing Ex. 1039, 9530), *id.* at 24 (quoting Kinde with the emphasis that the evaluation is assessed in plasma).

We find Petitioner’s argument here is inconsistent with its previous representations of Kinde’s teachings to this Board and the EPO. *See supra* Section II.B.2. Indeed, in Guardant II, Petitioner asserted, in no uncertain terms, that “Kinde does not disclose applying the endogenous UID embodiment (*or any embodiment*) to cell-free DNA.” Ex. 2002, 27 (emphasis added). Similarly, in Guardant I, Petitioner argued Kinde “only discuss[es] analysis of cellular DNA, there is no discussion in th[]e reference[] about application of the methods to cell-free DNA.” Ex. 2001, 23–24; *see also id.* at 23 (arguing “there is nothing” in Kinde that shows its methods apply to cell-free DNA). According to Petitioner, Kinde’s tagging method was known to introduce “significant error,” which “is inconsistent with an intended reduction of errors as an alleged basis for employing cell-free DNA in the Kinde method.” *Id.* at 23. These statements, made by Petitioner before this Board, provide strong evidence that, contrary to Petitioner’s contentions here, an ordinarily skilled artisan would not have applied Kinde’s methods to cfDNA.

To the extent Petitioner relies on Kinde’s citations to references 42[14] and 43[15] for teaching using ligation to attach exogenous UIDs (Pet. 26), those references, like Kinde, only discuss analysis of cellular DNA, and not

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[14] Craig et al., *Identification of Genetic Variants Using Bar-Coded Multiplexed Sequencing*, 5 Nature Methods 887–93 (2008) (Ex. 1036, “Craig”).
[15] Reference 43 is Miner.

cfDNA. *See* Ex. 1036, 887 (describing "a generalized framework for multiplexed resequencing of targeted human genome regions"); Ex. 1037, 1 (describing using "molecular barcoding to label each genomic DNA template").

Petitioner previously argued before this Board that "[i]t was well-known that cell free DNA presented unique technical difficulties compared to analysis of cellular DNA." Ex. 2001, 24. It also represented to the EPO that randomly-sheared DNA fragments are "quite different from cfDNA molecules that arise naturally *in vivo*." Ex. 2003, 7 (arguing "cfDNA molecules and randomly-sheared DNA fragments are not analogous.").

In Craig and Miner, genomic DNA was enzyme digested. *See* Ex. 1036, 887 (describing method of digesting the amplicons of the genomic regions, followed by several other steps, before ligating the modified amplicons to one of the indexed adapters); Ex. 1037, 1 (describing ligating the hairpin linker to "DraIII-cleaved genomic DNA"). Petitioner has not pointed to any evidence, or otherwise argued, that enzyme-digested genomic DNA fragments are analogous or similar to cfDNA. Indeed, it appears that, just like Kinde, Craig and Miner "had not applied these techniques to cfDNA," and had not "appreciated the challenges which are presented when working with this analyte." *See* Ex. 2003, 7.

Thus, based on the current record, we find the Petition has not sufficiently shown that the combination of Kinde and Miner teaches applying their tagging methods to circulating DNA, specifically, plasma cfDNA.

c. Summary

In sum, we determine that Petitioner has not demonstrated a reasonable likelihood that it would prevail in showing that claims 1 and 20 would have been obvious over Kinde and Miner.

Each of claims 2–19 depends from claim 1, and each of claims 21–27 depends from claim 20. Petitioner's arguments and evidence for dependent claims 2–19 and 21–27 do not remedy the deficiencies discussed with respect to claims 1 and 20. *See* Pet. 40–60. Thus, we determine that Petitioner has not demonstrated a reasonable likelihood that it would prevail in showing that claims 2–19 and 21–27 would have been obvious over Kinde and Miner either.

C. Alleged Obviousness over Kinde, Miner, and Fan

Petitioner asserts that claims 1–27 of the '699 patent would have been obvious over the combination of Kinde and Miner. Pet. 61–62. Petitioner relies on Fan for "details on techniques for providing circulating DNA from maternal plasma." *Id.* at 62. It is undisputed that circulating DNA exists in plasma. That fact, however, does not resolve the issue that the asserted references do not teach applying their tagging methods to circulating cfDNA. *See supra* Section II.B.3.b. In other words, Petitioner's arguments and evidence under this ground do not remedy the deficiencies discussed above. Thus, for the same reasons explained above (*see supra* Section II.B.3), we determine Petitioner has not established a reasonable likelihood that it would prevail in this assertion.

III. CONCLUSION

For the reasons explained above, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing that at least one of the challenged claims is unpatentable.[16]

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

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[16] Patent Owner also argues that we should deny *inter partes* review for other reasons. *See, e.g.*, Prelim. Resp. 51–62 (arguing we should exercise our discretion to deny the Petition under § 325(d)). We do not address those contentions because we deny the Petition for reasons explained above.

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