

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GUARDANT HEALTH, INC.,
Petitioner,

v.

UNIVERSITY OF WASHINGTON,
Patent Owner.

IPR2022-01388
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 2 (“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 6 (“Prelim. Resp.”).

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). The Board, however, has discretion to deny a petition even when a petitioner meets that threshold. *Id.*; see also *Cuozzo Speed Techs., LLC v. Lee*, 579 U.S. 261, 272 (2016) (“[T]he agency’s decision to deny a petition is a matter committed to the Patent Office’s discretion.”); *General Plastic Indus. Co. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19 (PTAB Sept. 6, 2017) (precedential) (recognizing the same) (“*General Plastic*”); Patent Trial and Appeal Board Consolidated Trial Practice Guide (Nov. 2019) (“CTPG”) 55–63, available at <https://www.uspto.gov/TrialPracticeGuideConsolidated> (identifying considerations that may warrant exercise of this discretion).

For the reasons discussed below, after considering the parties’ submissions and the evidence of record, we determine it is appropriate to exercise our discretion and decline to institute *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. 16–17; Paper 4, 1.

Petitioner previously filed two petitions in IPR2022-00449 (“’449 IPR”) and IPR2022-00450 (“’450 IPR”), challenging the same claims of the ’699 patent. We denied those petitions. Petitioner has requested Precedential Opinion Panel review of our decisions. Those requests are currently pending.

The parties further identify IPR2022-00816, IPR2022-00817, IPR2022-00935, IPR2022-01158, and IPR2022-01159, as related proceedings. Pet. 17; Paper 4, 1–2. In those cases, Petitioner challenged claims of patents related to the ’699 patent. Pet. 17. We instituted review in IPR2022-00817 and IPR2022-01158, but denied the other petitions. Petitioner requested Precedential Opinion Panel review of our decision denying institution in IPR2022-00816.¹ That request has been denied.

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,

¹ Petitioner did not seek rehearing of our decision denying institution in IPR2022-00935. That case has therefore concluded. The period for Petitioner to seek rehearing of our decision in IPR2022-01159 remains open.

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.² 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

² 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.

et al. [still] are likely the result of significant technical artifacts.” *Id.* at 2:32–38.

Consequently, 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.

According to the ’699 patent, its approach, termed duplex consensus sequencing (“DCS”), “greatly reduces errors by independently tagging and sequencing each of the two strands of a DNA duplex.” *Id.*, Abstract. It explains that, because the two strands are complementary, true mutations are found at the same position in both strands. *Id.*

Figure 1 of the ’699 patent, illustrative of the DCS method, is reproduced below:

Figure 1

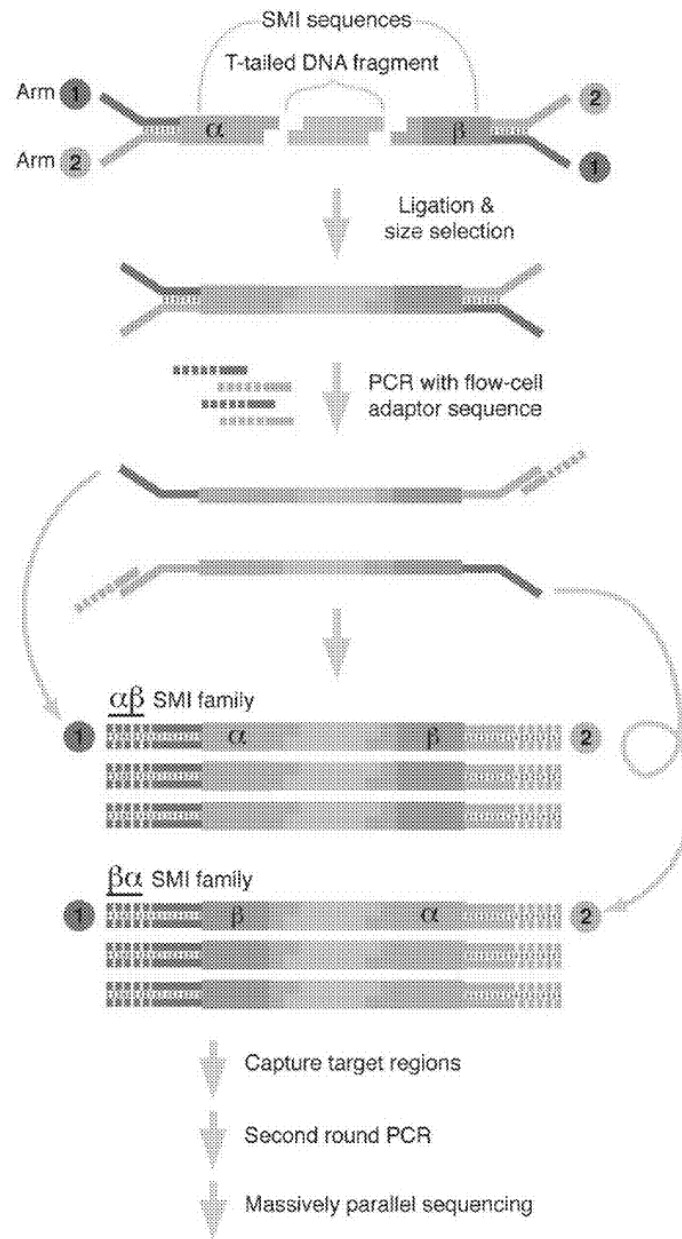


Figure 1 of the '699 patent, reproduced above, depicts an overview of the DCS method. Ex. 1001, 3:52–53. It shows sheared double-stranded DNA, that has been end-repaired and T-tailed, is combined with the A-tailed single molecule identifier (“SMI”) adaptors and ligated. *Id.* at 3:53–55. The '699 patent explains that, because every adaptor contains a unique,

double-stranded, complementary n-mer random tag on each end, 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 3:55–60.

According to the '699 patent, 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 3:61–64. 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 3:64–4:1. Thus, “PCR products originating from the complementary strand are labeled reciprocally.” *Id.* at 4:2–3.

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;
- 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.³

Id. at 40:12–32.

D. Asserted Challenge to Patentability

Petitioner asserts the following challenges to patentability:

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

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

II. ANALYSIS

Patent Owner asks us to exercise our discretion under 35 U.S.C. § 314(a) and deny this Petition. Prelim. Resp. 29–48. Patent Owner argues that “[a] weighing of the *General Plastic* factors here presents a compelling case for denying institution of [Petitioner] Guardant’s *third* Petition, with six of the seven factors weighing in favor of denying institution and the seventh factor being neutral.” *Id.* at 48. We find Patent Owner’s arguments persuasive.

³ We incorporate the Certificate of Correction to correct certain typographic errors in claim 20.

⁴ 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.

⁵ Miner et al., *Molecular Barcodes Detect Redundancy and Contamination in Hairpin-Bisulfite PCR*, 32 Nucleic Acids Res. E135 (2004) (Ex. 1037, “Miner”).

Under *General Plastic*, the Board considers the following non-exclusive factors (“*GP* factors”) in determining whether to exercise discretion under § 314(a) to deny a petition:

1. whether the same petitioner previously filed a petition directed to the same claims of the same patent;
2. whether at the time of filing of the first petition the petitioner knew of the prior art asserted in the second petition or should have known of it;
3. whether at the time of filing of the second petition the petitioner already received the patent owner’s preliminary response to the first petition or received the Board’s decision on whether to institute review in the first petition;
4. the length of time that elapsed between the time the petitioner learned of the prior art asserted in the second petition and the filing of the second petition;
5. whether the petitioner provides adequate explanation for the time elapsed between the filings of multiple petitions directed to the same claims of the same patent;
6. the finite resources of the Board; and
7. the requirement under 35 U.S.C. § 316(a)(11) to issue a final determination not later than 1 year after the date on which the Director notices institution of review.

General Plastic, Paper 19 at 16. The *General Plastic* factors “are not dispositive, but part of a balanced assessment of all relevant circumstances in the case, including the merits.” CTPG 58.

As explained below, we determine that, in view of the policy goals articulated in *General Plastic*, under the circumstances of this case, it is appropriate for us to exercise our discretion under 35 U.S.C. § 314(a) to deny the Petition.

A. Petitioner Previously Filed Two Petitions Directed to the Same Claims of the Same Patent

Petitioner previously filed petitions in the '449 and '450 IPRs, challenging the same claims of the same patent.

The Director recently stated:

General Plastic factor 1 must be read in conjunction with factors 2 and 3. Where the first-filed petition under factor 1 was discretionarily denied or otherwise was not evaluated on the merits, factors 1–3 only weigh in favor of discretionary denial when there are ‘road-mapping’ concerns under factor 3 or other concerns under factor 2.

Code200, UAB v. Bright Data Ltd., IPR2022-00861, Paper 18 at 5 (PTAB Aug. 23, 2022) (precedential).

As explained below, in our decision denying institution, we evaluated the '450 IPR petition on its merits. *See infra* Section II.C.2. Also as explained below, this third Petition is “refined based on lessons learned from later developments,” i.e., receiving Patent Owner’s preliminary responses in the '449 and '450 IPRs and our decision denying institution in the '450 IPR. *See Code200*, Paper 18 at 5; *see also infra* Section II.C.3. Thus, the first *GP* factor weighs in favor of denying institution.

B. At the Time of Filing the Petitions in the '449 and '450 IPRs, Petitioner Knew of the Prior Art Asserted in This Third Petition

In this proceeding, Petitioner asserts that the challenged claims would have been obvious over the combination of Kinde and Miner. Pet. 18.

Petitioner also argues that the general knowledge in the prior art, as shown in Craig⁶ and Shiroguchi,⁷ informs the obviousness analysis. *Id.* at 11–15.

Petitioner knew of all these references at the time of filing the petitions in the '449 and '450 IPRs. In fact, in the '450 IPR, Petitioner asserted the same prior art (Kinde and Miner) and discussed Craig and Shiroguchi in the petition. *See, e.g.*, '450 IPR, Paper 3, 7, 8, 21–23, 26. Thus, the second *GP* factor weighs in favor of denying institution.

C. At the Time of Filing of This Third Petition, Petitioner Already Received Patent Owner's Preliminary Responses and the Board's Decisions Denying the Petitions in the '449 and '450 IPRs

The third *GP* factor addresses whether a petitioner had the opportunity to study a patent owner's preliminary response to, or the Board's institution decision on, a prior petition, such that the petitioner would have been in a position to gain a benefit from having that information before filing another petition. *General Plastic*, Paper 19 at 17. Under this analysis, we disfavor a follow-on petition that "us[es] our decisions as a roadmap." *Id.*

Petitioner filed this third Petition on August 10, 2022, after Patent Owner filed its Preliminary Responses in the '449 and '450 IPRs on May 6, 2022, and after we issued our decisions denying the petitions in those cases on August 1, 2022.

⁶ Craig et al., *Identification of Genetic Variants Using Bar-Coded Multiplexed Sequencing*, 5 NATURE METHODS 887–93 (2008) (Ex. 1036, "Craig").

⁷ Shiroguchi et al., *Digital RNA Sequencing Minimizes Sequence Dependent Bias and Amplification Noise with Optimized Single-Molecule Barcodes*, 109 PROC. NATL. ACAD. SCI. 1347–52 (2012) (Ex. 1010, "Shiroguchi").

Petitioner nevertheless argues that we should institute review of this third Petition because “the Board never reached the merits of patentability under the prior petition[s],” and Petitioner “derived few if any benefits” from seeing Patent Owner’s preliminary responses and our decisions denying institution in those cases. Pet. 62. We disagree. Below, to explain that this third Petition indeed uses our prior decisions as a roadmap, we: (1) summarize Kinde’s teachings; (2) summarize the parties’ arguments and our decision denying institution in the ’450 IPR; and (3) discuss Petitioner’s arguments in this third Petition.

1. 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.

Kinde also teaches an inverse PCR method, which involves, after the random shearing and adapter ligation (without exogenous UIDs), performing inverse PCR with gene specific primers. *Id.* at 9531, 9535, S1.

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.

2. The ’450 IPR

In the petition for the ’450 IPR, Petitioner asserted that the challenged claims would have been obvious over the combination of Kinde and Miner. ’450 IPR, Paper 3, 16–60.

In that petition, Petitioner stated that no claim term needs to be construed but discussed the term “circulating DNA molecules” to “provide[] context for understanding the scope of the term.” *Id.* at 14–15. Petitioner contended “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. Based on this understanding, Petitioner argued that Kinde teaches applying Safe-SeqS to cfDNA in plasma, which is circulating DNA. *Id.* at 19–20, 24, 26–28.

Petitioner argued that Kinde teaches introducing exogenous sequences through ligation, and thus, meets claim 20’s limitation “attaching a set of molecular tags” to a population of original DNA molecules. *Id.* at 24–26. As support, Petitioner pointed out Kinde specifically cites Craig and Miner for examples of how to do so. *Id.* at 26.

Petitioner relied on the same teachings in Kinde for satisfying claim 1’s limitation of “converting” parent polynucleotides into tagged parent polynucleotides. *Id.* at 36–37.

Observing that Petitioner’s obviousness challenge “is based on alleged embodiments using cfDNA,” Patent Owner did not dispute Petitioner’s explanation of “circulating DNA molecules,” that is, the term encompasses circulating cfDNA and not cellular DNA. ’450 IPR, Paper 8, 5. According to Patent Owner, Petitioner has repeatedly argued to this Board and the European Patent Office (“EPO”) that an ordinarily skilled artisan would not have applied Kinde’s methods to cfDNA with a reasonable expectation of success. *Id.* at 35–46.

Patent Owner also contended that Petitioner failed to establish the combination of Kinde and Miner teaches non-uniquely tagging parent/original polynucleotides. *Id.* at 26–34.

In our decision denying institution, we stated

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.

450 IPR, Paper 13, 7–8.

After considering the ’450 IPR record as a whole, we found Petitioner’s arguments in the ’450 IPR petition regarding applying Kinde’s teachings to cfDNA to be inconsistent with its previous representations to this Board and the EPO. *Id.* at 18–20.

We also found Petitioner did not sufficiently show the combination of Kinde and Miner teaches the limitation of tagging original parental DNA molecules as required in the challenged claims. *Id.* at 15–18. We explained that, because Petitioner did not rely on any PCR based tagging, we did not

consider Kinde’s exogenous method. *Id.* at 15. We also noted Petitioner’s contention that it did not rely on Kinde’s endogenous and inverse PCR methods. *Id.* Pointing out that Kinde teaches only three distinct embodiments (endogenous UID, inverse PCR, and exogenous UID) for its Safe-SeqS method, which Petitioner agreed, we found it problematic that the ’450 IPR petition did not rely on any of them. *Id.* at 16.

Recognizing that Kinde, in a single sentence, cites Craig and Miner as examples of introducing exogenous UIDs through ligation, we stated

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.” Where Kinde teaches ligating exogenous sequences, those sequences are adapters for sequencing, and not UIDs to tag the original parent polynucleotides.

Id. at 16–17 (citations omitted).

Contrary to Petitioner’s assertion that we did not reach the merits of patentability in the ’450 IPR (Pet. 62), we found Petitioner did not sufficiently show: (1) the combination of Kinde and Miner teaches the limitation of tagging original parental DNA molecules as required in the challenged claims; and (2) an ordinarily skilled artisan would have applied Kinde’s methods to cfDNA, the only “circulating DNA” Petitioner relied on in the ’450 IPR petition. Thus, we determined Petitioner did not demonstrate a reasonable likelihood that it would prevail in showing the challenged claims would have been obvious over Kinde and Miner, and on that basis, denied that petition. ’450 IPR, Paper 13, 21–22.

3. The Current Third Petition

In the current, third Petition, Petitioner argues that the term “circulating DNA molecules” includes “circulating cellular DNA, as Patent Owner has argued to the Board and at [the] district court, and is unopposed by Petitioner.” Pet. 21. This construction is in direct response to our ’450 IPR decision, finding, in view of the record as a whole, Petitioner did not sufficiently show an ordinarily skilled artisan would have applied Kinde’s teachings to cfDNA.

Petitioner faults Patent Owner for engaging in “claim construction gamesmanship.” Pet. 68. According to Petitioner, in the ’449 and ’450 IPRs, Patent Owner argued two different interpretations for the same term in the same patent. In IPR2022-00449, Patent Owner argued that the term “circulating DNA molecule” broadly encompasses both circulating cfDNA molecules and circulating cellular DNA . . . In IPR2022-00450, Patent Owner ignored cellular DNA entirely and only argued Kinde’s applicability to cfDNA.

Id. at 63–64 (citations omitted). We are not persuaded by Petitioner’s arguments.

First, Patent Owner did not propose any construction for the term “circulating DNA molecule” in the ’450 IPR. Instead, it merely applied Petitioner’s proposed construction that the term encompasses circulating cfDNA. ’450 IPR, Paper 8, 5. In our view, there is nothing unwholesome in this approach, given that Petitioner’s obviousness challenge in the ’450 IPR petition rests solely on application of Kinde’s method to cfDNA. *Id.* Patent Owner did not, and does not, have the obligation to propose a claim construction to help Petitioner.

Second, even if Patent Owner proposed to construe the term “circulating DNA molecule,” as it did in the ’449 IPR, to include both circulating cfDNA molecules and circulating cellular DNA, it would not have changed our decision. In fact, after seeing Patent Owner’s proposed claim construction of “circulating DNA molecule” in the ’449 IPR, Petitioner argued—for the first time in its ’450 IPR reply—that “Kinde plainly discusses application of its method to blood cells.” ’450 IPR, Paper 11, 1. This argument, relying on cellular DNA as the circulating DNA, changed the obviousness theory articulated in the ’450 IPR petition, which relied solely on cfDNA as the circulating DNA. Because an IPR petitioner may not raise in its reply “an entirely new rationale” for why a claim would have been obvious, we did not address this argument in our ’450 IPR decision. *See Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369 (Fed. Cir. 2016) (“Unlike district court litigation—where parties have greater freedom to revise and develop their arguments over time and in response to newly discovered material—the expedited nature of IPRs bring with it an obligation for petitioners to make their case in their petition to institute.”).

Third, as Patent Owner correctly points out, Petitioner “could have proposed that ‘circulating DNA molecules’ included DNA from cells in the circulatory system, but chose not to.” Prelim. Resp. 8; *see also id.* at 38 (Patent Owner arguing Petitioner “chose to proceed with an interpretation of ‘circulating DNA molecules’ that did not encompass cellular DNA and obviousness theories that depended solely on cfDNA”). We do not speculate

whether that was an oversight⁸ or a deliberate strategy, given the parties' many challenges to each other's patents before the Board and the district court. Whatever the reason may be, we see no "gamesmanship" when Patent Owner only addressed cfDNA as circulating DNA in the '450 IPR in response to Petitioner's arguments.

As Petitioner puts it, this third Petition is warranted "because Patent Owner's post-petition claim construction fundamentally altered the patentability landscape." Pet. 62–63. In our view, this amounts to an admission that Petitioner benefits from having Patent Owner's preliminary responses in the '449 and '450 IPRs before filing this third Petition.

Petitioner also uses our decision denying institution in the '450 IPR as a roadmap to guide its arguments in this third Petition. Indeed, Petitioner changes its construction of "circulating DNA molecules" to include circulating cellular DNA only after we rejected its earlier argument applying Kinde's method to cfDNA. *See, e.g.*, Pet. 19 ("Consistent with discussion provided in recently filed IPR2022-00449 and -00450, the term 'circulating DNA molecules' was initially understood as intended to encompass circulating cfDNA."); 1 ("Prior IPR2022-00449 and -00450 were denied stating that the claims of the '699 patent excluded circulating cellular DNA and Kinde lacks of disclosure of cell-free DNA."); 21 ("[T]he term 'circulating DNA molecules' is construed herein as including circulating

⁸ Patent Owner points out that "a simple review" of a related patent would have revealed "circulating DNA molecules" can include cellular DNA. Prelim. Resp. 8 n.3.

cellular DNA, as Patent Owner has argued to the Board and at district court, and is unopposed by Petitioner.”).

Petitioner also changes its argument related to the limitation “converting” parent polynucleotides to “tagged parent polynucleotides,” as recited in claim 1. After we rejected Petitioner’s argument that Kinde teaches this limitation because it teaches ligating exogenous UIDs in the Safe-SeqS approach (’450 IPR, Paper 13, 16–17), Petitioner now argues the tag in “tagged parent polynucleotide” also includes the endogenous sequences, i.e., randomly sheared ends. Pet. 21–24. Petitioner’s inclusion of the endogenous sequences as tags is an attempt to address a deficiency we identified in its ’450 IPR petition. It further demonstrates that Petitioner formulates the arguments in this third Petition using our previous decision denying institution in the ’450 IPR.

Because this third Petition “is refined based on lessons learned” from Patent Owner’s preliminary responses in the ’449 and ’450 IPRs, as well as our decision denying institution in the ’450 IPR, the third *GP* factor weighs in favor of denying institution. *See Code200*, Paper 18 at 5.

D. Petitioner Filed This Third Petition More Than Six Months After Learning of the Asserted Prior Art

Again, in this proceeding, Petitioner asserts Kinde and Miner against the challenged claims. Pet. 18. The ’699 patent itself cites both Kinde and Miner. Ex. 1001, 2:16–19 (citing Kinde (reference 36) and Miner (reference 34) as teaching uniquely tagging DNA fragments prior to amplification), 2:26–38 (discussing Kinde’s method as reducing the error frequency in identifying mutations), 27:32–43 (comparing the results of the ’699 patent method and those of Kinde’s method). It is, thus, not unreasonable under the

circumstances of this proceeding, to presume that Petitioner learned of the asserted prior art at or shortly after the time the '699 patent issued on June 23, 2020.

The evidence of record confirms that Petitioner, in fact, learned of the prior art (at least Kinde) before the issuance of the '699 patent.⁹ Indeed, Kinde was cited against Petitioner's own patent in an opposition proceeding before the European Patent Office. Ex. 2004, 4 (identifying reference D11 as Kinde). That opposition was filed on October 2, 2019. *Id.* at 6. In its response filed in May 2020, Petitioner discussed Kinde in detail. *See generally* Ex. 2003.

In any event, Petitioner filed the '450 IPR petition, asserting the same prior art (Kinde and Miner), more than six months before filing this third Petition. Thus, the fourth *GP* factor weighs in favor of denying institution.

E. Petitioner Has Not Provided Adequate Explanation for the Time Elapsed Between the Filings of Multiple Petitions Directed to the Same Claims of the Same Patent

Petitioner argues that “[s]everal days” before the Board’s decisions in the '449 and '450 IPRs, “Patent Owner offered its Opening Claim-Construction Brief in the co-pending district court case acknowledging the claims of the '699 patent encompass circulating cellular DNA.” Pet. 2 (citing Ex. 1040, 15–16). According to Petitioner, this amounts to “[a] material change in circumstances [that] warrants review of the present challenge.” *Id.* We are not persuaded.

⁹ Patent Owner also points out that Kinde was asserted against one of Petitioner's U.S. patents in IPR2019-00130. Prelim. Resp. 24. That petition was filed on November 7, 2018. IPR2019-00130, Paper 1.

Although Patent Owner’s opening Markman brief was filed shortly before we issued our decisions denying institution in the ’449 and ’450 IPRs, its argument that “circulating DNA molecules” include circulating cellular DNA was not new. Indeed, in its pre-institution reply in the ’450 IPR, Petitioner already complained about Patent Owner’s “expansive interpretation” of the term in the preliminary response in the ’449 IPR. ’450 IPR, Paper 11, 1. Thus, the filing of Patent Owner’s Markman brief in the district court is not a persuasive explanation for filing this third Petition more than six months after filing the first two.

Petitioner argues that “Patent Owner’s post-petition claim construction fundamentally altered the patentability landscape, affording [P]etitioner with a patentability argument that even Patent Owner argued could not have been raised in the prior petitions.” Pet. 62–63. As Patent Owner persuasively argues, however, Petitioner “*was in control* of the theories it put forth in its two previous petitions,” but “made the strategic choice to *exclude* cellular, genomic DNA from its interpretation of ‘circulating DNA molecules.’” Prelim. Resp. 38. Thus, we agree that the fact that Petitioner could not have raised the patentability argument based on applying Kinde’s teaching to cellular DNA is “purely a problem of its own making.” *Id.*

We also note that, presumably, Petitioner became aware of Patent Owner’s proposed construction of “circulating DNA molecules” on May 6, 2022, when Patent Owner filed its preliminary responses in the ’449 and ’450 IPRs. Yet, it waited for more than three months later, until after we denied institution in those IPRs, and until, according to Patent Owner, “the

eve of the expiration of the § 315(b) statutory bar.” Prelim. Resp. 1. Even if we were to accept that Patent Owner’s proposed claim construction of “circulating DNA molecules” could be a reason to file a third petition, Petitioner has not sufficiently accounted for the additional three-month lapse between receiving Patent Owner’s preliminary responses in the first two IPRs and filing this third Petition.

Thus, this fifth *GP* factor weighs in favor of denying institution.

F. The Board Has Finite Resources

In this third Petition, Petitioner asserts the same prior art and same ground of unpatentability to challenge the same claims as it did in ’450 IPR petition. As explained above, we reached the merits in the ’450 IPR, and based on Petitioner’s arguments therein, determined that Petitioner did not establish a reasonable likelihood of prevailing in showing obviousness of at least one claim over Kinde and Miner. *See supra* Section II.C.2. Petitioner has requested panel rehearing and Precedential Opinion Panel review of that decision. Petitioner raises substantially the same arguments in those requests as in this third Petition. *See* ’450 IPR, Papers 17, 19. Thus, we agree with Patent Owner that instituting review of this Petition in view of those previously filed requests would be a needlessly repetitive and inefficient use of the Board’s finite resources.

In sum, this sixth *GP* factor weighs in favor of denying institution.

G. Timeline for Issuing a Final Decision

Petitioner argues that this *GP* factor favors institution because “there is no instituted trial against the ’699 patent and no reason the Board cannot issue a decision within the statutory deadline.” Pet. 67. Patent Owner contends this factor is neutral. Prelim. Resp. 48. Even if we agree with

Petitioner that this factor favors institution, it would not outweigh considerations under the other six factors, all of which favor denying institution. This is so especially in view of the weak merits, as discussed below.

H. The Merits of This Third Petition Are Weak

In this third Petition, Petitioner relies on an alleged “Craig Variation” of Kinde’s method. *See, e.g.*, Pet. 10, 26, 35–36. According to Petitioner, “all claims encompass the obvious variation of Kinde’s method utilizing barcoded adapters (i.e., the Craig Variation).” *Id.* at 26. Patent Owner contends the so-called Craig Variation is “imaginary.” Prelim. Resp. 7. Putting aside that issue, we found in at least three related IPR proceedings that Petitioner did not explain sufficiently why an ordinarily skilled artisan would have introduced Craig’s adapters, which comprises exogenous barcodes, to Kinde’s endogenous method. *See* IPR2022-00816, Paper 16, 13–15; IPR2022-00935, Paper 11, 32–35; IPR2022-01159, Paper 17, 10–14. In the current Petition, Petitioner relies on substantially the same arguments regarding modifying Kinde’s endogenous UIDs with Craig’s adaptors. In other words, the merits of this third Petition are weak.

In sum, the weakness in the merits of this third Petition further favors denying institution.

III. CONCLUSION

After a holistic review of the *General Plastic* factors and the arguments presented for and against the exercise of discretionary denial, we conclude that the factors weigh in favor of denying institution of this proceeding. Thus, on balance and in view of the policy goals articulated in

General Plastic, we exercise our discretion under 35 U.S.C. § 314(a) to deny the Petition.¹⁰

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that pursuant to 35 U.S.C. § 314(a), the Petition is denied.

¹⁰ Patent Owner also argues that we should deny *inter partes* review for other reasons. *See, e.g.*, Prelim. Resp. 49–55 (arguing we should exercise our discretion to deny the Petition under 35 U.S.C. § 325(d)). We do not address those contentions because we deny the Petition for reasons explained above.

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