

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NEOGENOMICS LABORATORIES, INC.,
Petitioner

v.

NATERA, INC.,
Patent Owner

Case IPR2025-00455
Patent 11,319,596

**PATENT OWNER'S PRELIMINARY RESPONSE
UNDER 37 C.F.R. § 42.107**

LIST OF EXHIBITS

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I. Introduction

As with Patent Owner Natera, Inc.'s ("PO" or "Natera") April 14 brief concerning Discretionary Denial (Pap.10), this §42.107 Preliminary Response confirms the Board should deny the above-captioned Petition ("Petition"/"Pet."). The Petition fails to show claims 1, 2, 5, and 10-18 (the "Challenged Claims") of U.S. Patent No. 11,319,596 (the "'596 patent") are unpatentable.¹ While the Petition offers four Grounds resting on two base references and a handful of additional documents, *Petitioner fails to identify even one prior art teaching that it contends detects a single-nucleotide variant ("SNV") at the claimed 0.015% sensitivity following single-volume multiplex PCR amplification of cell-free DNA ("cfDNA")*. Thus, the same prior art failure that the Examiner relied on to allow the claims during original prosecution remains a gap in the Petition's evidence today.

Instead of pointing to any actual prior art disclosure, Petitioner attempts to suggest this key set of claimed features would have been obvious based on conclusory assertions and assumptions. In particular, the Petition repeatedly combines disclosures of *multiplex* PCR (having *low* or *unspecified* sensitivities) with descriptions of Safe-SeqS *single-plex* PCR that Petitioner contends achieve the

¹ Unless stated, statutory and regulatory citations are to 35 U.S.C. or 37 C.F.R., as context indicates, internal citations omitted, and emphases/annotations are added.

higher claimed sensitivity. Petitioner then *assumes* that the single-volume *multiplex* PCR amplification (using Safe-SeqS) in its prior art will achieve the same sensitivity as *single-plex*. But this critical leap is contradicted by Petitioner's own art in this proceeding: Petitioner's Kinde 2013 reference (explicitly a part of Grounds 1-3) confirms that when its authors shifted from a Safe-SeqS assay using single-plex PCR amplification (as in the Kinde 2011 paper cited by Petitioner's Ground 4 Bettegowda reference) to a Safe-SeqS assay using single-volume multiplex PCR amplification, the *sensitivity dropped substantially* and was much worse than claimed. This failing is more than sufficient for denial of institution.

Further, with respect to Grounds 1-3, Petitioner ignores the District Court's and Federal Circuit's findings *against Petitioner* in related litigation regarding the well-known *barriers* to successfully amplifying and sequencing *cfDNA*, as opposed to pap smear samples containing "cells or cell fragments" used by Kinde 2013 (which Petitioner simply assumes are equivalent). And Petitioner does not acknowledge (let alone address) the physical incompatibility between the claimed cfDNA and Kinde 2013's PCR primers, which are relied on by Petitioner and used to amplify longer (non-cfDNA) sequences in Kinde 2013's multiplex Safe-SeqS assay.

And with respect to Ground 4, the Petition fails to show the required sensitivity in Bettegowda even with a *single-plex assay*, making various

unsupported and erroneous assumptions and logical leaps in an attempt to divine the claimed sensitivity.

Finally, the Petition repeatedly obscures its failures by providing poorly-articulated, unarticulated, or internally-contradictory obviousness mappings of its prior art. For example, Petitioner (1) improperly changes its mapping of references mid-stream, initially identifying Rabinowitz as its base reference but then switching to Bettegowda, (2) improperly mixes and matches multiple disparate embodiments within the asserted references for the same claim limitations, (3) improperly maps multiple references for the same limitations within a ground, and (4) fails to identify the differences between the claims and the prior art. All of these failures additionally require denial under the Board's clear precedent.

Because the Petition fails to show a reasonable likelihood of prevailing as to any claim of any Ground, it should be denied.

II. Background

A. Cancer and its Detection

Cancer is caused by mutations in DNA and one of the leading causes of preventable death worldwide. EX1001, 2:7–11. Successful treatment and increased chances of survival often depend on close monitoring to prevent or detect relapse. *See* EX1001, 2:7-20, 44:26-34.

DNA consists of two intertwined strands of nucleotides (adenine (“A”), thymine (“T”), cytosine (“C”), or guanine (“G”)) arranged in complementary base pairs. EX1004, ¶¶69-70. DNA is generally found in the nucleus of most living cells, including cancer cells. EX1004, ¶71. Free-floating DNA (*e.g.*, DNA released from a cell when it dies and ruptures) is known as cell-free DNA (“**cfDNA**”) and is found within the bloodstream. EX1004, ¶¶71-72. The cfDNA from a tumor cell is known as circulating *tumor* DNA (“ctDNA”). EX1004, ¶72. And while a human cell’s complete “genomic” DNA contains approximately **3 billion nucleotide base pairs** separated across 23 pairs of chromosomes, circulating cfDNA (including ctDNA) is comparatively tiny, measuring an average of just **180–200 base pairs** in length. EX1006, 2.

Single-nucleotide variations (“SNVs”) are one of the various possible types of genetic mutations that can occur in cancerous cells, and can be important in understanding a patient’s cancer development and detecting possible recurrence. *See* EX1001, 4:55-62, 130:15-20. An SNV, as used in the ’596 patent, is a single-nucleotide alteration in a tumor cell’s genome sequence that differs from the nucleotide at the same position in the patient’s healthy cells. *See* EX1004, ¶84. Cancerous cells with mutations accumulate over time, and the full set of DNA (or “genome”) of a patient’s tumor cells differs from the genome of the patient’s healthy somatic cells (*i.e.*, any cell other than reproductive cells). *See* EX1001, 130:15-41.

Patients' tumors often develop their own unique set of mutations, including SNVs, providing a signature of patient- and tumor-specific markers for detection of the tumor, and thus allowing, for example, early detection of tumor re-growth (*i.e.*, relapse) after treatment. *See* EX1001, 43:52-44:65; *see also, e.g.*, EX1072, 5 & Fig.1; EX2075, 2, 5.

Detection of mutations such as SNVs can be accomplished in various ways. DNA sequencing identifies the order of nucleotides in DNA in a sample. EX1004, ¶81.² DNA fragments may be sequenced using a commercial machine, which generates “sequence read” data. EX1004, ¶¶81, 85. Current “next-generation” DNA sequencing technology permits a “high-throughput” approach that allows sequencing of many DNA molecules simultaneously. EX004, ¶81. However, this technology requires a large amount of input DNA—significantly more than the amount of cfDNA that can typically be isolated from a patient's blood sample. *E.g.*, EX1001, 157:39-46; *see also* EX1004, ¶77.

² PO relies, solely for purposes of this preliminary response, on various points conceded by Petitioner and its expert, Dr. Lennon, and accordingly cites various passages of EX1004 without waiver of its ability to challenge Dr. Lennon's testimony.

To address this need for a large amount of input DNA, cfDNA can be copied or “amplified” using polymerase chain reaction amplification (“PCR” or “PCR amplification”). EX1004, ¶77. PCR often involves a series of heating and cooling cycles that causes the two strands of the template (original) DNA to first separate and then form new (duplicate) molecules of DNA by binding new complementary bases to each of the original single-stranded templates. EX1004, ¶78. This results in exponential creation of copies of the original template DNA. This is achieved by using pairs of DNA primers, which are short, single-stranded DNA sequences (one forward primer and one reverse primer) made in the lab. EX1004, ¶¶78-79. The DNA primer pairs are used to target specific segments of DNA that contain SNVs of interest—known as “target loci”—for amplification. EX1004, ¶¶78-80.

Standard PCR amplifies one target locus at a time using a single set of primers: one primer that binds on one side of the target locus, and a second primer that binds on the other side, to essentially “frame” the locus of interest for copying. This process, which employs a single pair of PCR primers targeting a single locus individually, is referred to in this Response as “**single-plex PCR.**” *See also* Pet.22.

Another PCR method involves amplifying multiple target loci at the same time, using multiple pairs of PCR primers in a single reaction volume. This is required by the Challenged Claims (“performing targeted multiplex PCR amplification to amplify the plurality of target loci together in the same reaction

volume”) and is referred to in this Response as “**multiplex PCR**” or “**single-volume multiplex PCR**.” EX1004, ¶79; EX1001, 103:18–27; EX1067, 1.

Multiplex PCR has some significant attendant challenges compared with single-plex PCR. The use of multiple primer pairs at once can yield copies of off-target junk—rather than just copies of the intended target loci—because the primers may bind to one another or to unintended or unexpected areas of the sample DNA, such as nearby or adjacent target loci, instead of to their respective targets. EX1001, 105:65-106:10, 108:14-49. For example, errors can also be introduced by differences in nucleotide sequences or length differences at the sites on the template DNA where the primers bind, causing unequal or biased amplification of certain targets over others (EX1001, 105:50-63), by the degrading or displacement of primers (EX1001, 103:65-104:5), by variability in primer binding efficiency for certain alleles (*e.g.*, heterozygous alleles having an SNP) (EX1001, 105:24-36), and by the effects of unproductive side reactions such as the formation of primer dimers (EX1001, 105:65-106:28). The enzyme that performs DNA replication, DNA polymerase, may also introduce errors by inserting the wrong nucleotide into a DNA sequence during replication. EX2076, 3.

B. The '596 Patent's Claimed Invention

PO Natera's innovative methods claimed in the '596 patent permit detection of SNVs present at very low concentrations and that are specific to an individual

patient's tumor using cfDNA obtained from a minimally invasive blood test. *See* EX1001, 5:32-34, 6:16-21, 44:11-17, 44:26-36. The '596 patent discloses a personalized assay for each cancer patient by using DNA from the patient's own tumor biopsy to identify a set of mutations specific to that patient's tumor using sequencing. *See* EX1001, 63:50-63, 67:30-53; EX1004, ¶84. A subset of those identified tumor-specific SNVs are then selected to create a multiplex PCR assay that can be used to identify ctDNA from that patient's cancer signature in cfDNA in subsequent repeated non-invasive testing. *See* EX1001, 44:36-42. The claimed methods can be used to monitor recurrence for relatively low cost with high throughput and fast turnaround time. EX1001, 44:26-42. Natera's groundbreaking, efficient, and highly sensitive methods, which are capable of detecting low-frequency SNVs, (EX1001, 44:17-21), including Natera's SignateraTM test, can detect one mutation in about 7,000 copies. *See* EX2077, 16-20; *see also* EX2020, 2.

C. The Examination of the '596 Patent

The Patent Office thoroughly examined the application that led to the '596 patent, issuing multiple prior-art-based rejections (among other rejections). To overcome prior art rejections, Natera amended then-pending claim 1 to require “performing targeted multiplex PCR amplification” to amplify “the plurality of target loci together in the same reaction volume” and “obtain[ing] sequence reads,

wherein an SNV mutation that is present in less than or equal to 0.015% of the cell-free DNA having the SNV locus is detected from the sequence reads.” EX1003, 469. In a September 15, 2021 Notice of Allowance, the Examiner confirmed that the ’596 patent claims were patentable, noting that

No new references were found teaching or suggesting claim 1 which now requires detection of SNV mutation that is present in less than or equal to 0.015% of the cell free DNA having the SNV locus. The closes [*sic*] prior art reference, Talasaz et al. (US 2014/0066317 A1; published March 2014), teaches detection limit of 0.1% for SNV mutations in cell-free DNA by sequencing (Example 4, Fig. 6B.).

EX1003, 334. After reviewing still more references in a further IDS, the Examiner again confirmed the patentability of the ’596 claims, and, in particular, distinguished a reference by Kennedy *et al.*:

The reference of Kennedy et al. (Nature Protocols, vol. 9, pp. 2586-2606, 2014; cited in the IDS) teaches detection of mutations with frequencies around 10^{-6} , however, the protocol relies on sequencing both strands of DNA fragments which are amplified using barcode-specific primers and the libraries are enriched by hybridization, whereas the instant claims provide enrichment via target-specific multiplex amplification, therefore the claimed method cannot be used for double-strand sequencing of Kennedy et al.

EX1003, 62-63. In a final March 22, 2022 Notice of Allowance, the Examiner noted that “[t]he IDS does not contain references teaching or suggesting the previously allowed claims, therefore they remain allowed.” EX1003, 5.

III. Asserted Art

A. Diaz (EX1006)

Diaz is a review article entitled “Liquid Biopsies: Genotyping Circulating Tumor DNA.” EX1006, 1. Diaz generally discusses how the “analysis of circulating tumor DNA is a promising area of investigation that allows for interrogation of tumor-specific molecular alterations in the circulation,” and, pertinent to this proceeding, how “[i]n scenarios where only low levels of ctDNA are present (*e.g.*, early-stage disease and minimal residual disease), novel genomic methodologies, *based on digital PCR*, have made such applications possible.” *Id.* at 6.

In a seven-paragraph discussion captioned “Tissue Versus Liquid Biopsy,” Diaz discusses (over the first four of those paragraphs) the concern that, “[a]lthough tumor tissue is the gold standard for clinical and investigational sequencing, major barriers exist in terms of acquisition and utility.” EX1006, 3. Diaz next posits that “less invasive techniques” such as ctDNA analysis may “*in principle*” “overcome the limitations of tissue biopsies,” but acknowledges that “much of the current data for ctDNA are *investigational*,” and that, “[d]espite the promising results in *advanced* disease, the sensitivity of measuring ctDNA is reliant on biologic and

technical factors.” *Id.* As Diaz notes at the outset, “detection of cfDNA derived from tumors... has been challenging for three primary reasons: discrimination of ctDNA from normal cfDNA; presence of sometimes extremely low levels of ctDNA; and the accurate quantification of the number of mutant fragments in a sample.” EX1006, 1. And in this introduction Diaz further concedes that, “[u]nfortunately, detection of cfDNA derived from tumors *carries substantial challenges*, largely because ctDNA often represents a small fraction (< 1.0%) of total cfDNA.” *Id.* Diaz also explains that “most cfDNA fragments measure between 180 and 200 base pairs.” EX1006, 2.

Although Diaz notes that “[n]ewer approaches... using barcoding strategies in the context of [next-generation sequencing] *are being investigated*,” it cites for this possibility *not* to the Kinde 2013 reference (EX1007) that Petitioner relies on here (despite Kinde 2013 being published before Diaz, and Luis Diaz himself being one of its co-authors), but instead to an earlier Kinde 2011 article (EX1049) that is not part of Petitioner’s combinations. *Id.* at 3 & n.40; *see also* EX1006, 1; EX1007, 1; Pet.11-12.

Diaz discloses at least five separate embodiments, each describing disparate investigational methods and experiments related to different aspects of detecting ctDNA: (1) “Monitoring Tumor Burden”; (2) “Minimal Residual Disease”; (3) “Monitoring of Molecular Resistance and Heterogeneity”; (4) “Chromosomal

Alterations: Amplification, Rearrangements, and Aneuploidy”; and (5) “Epigenetic Changes.” EX1006, 3-4, 6.

B. Kinde 2013 (EX1007)

Kinde 2013, “Evaluation of DNA from the Papanicolaou Test to Detect Ovarian and Endometrial Cancers,” discusses two separate experiments using modified (and, according to the Petition, “improved” (Pet.14)) versions of a “Safe-Sequencing System” (“Safe-SeqS”) earlier described in Kinde 2011. EX1007, 1-2. Kinde 2011 described its single-plex Safe-SeqS as involving “two basic steps”: (1) the assignment of a unique identifier (“UID”) to each DNA template molecule to be analyzed (“tagging”), and (2) PCR amplification of each uniquely-tagged template to generate a collection of molecules having the same, identical sequence (“UID family”). EX1049, 1, 5 (discussing analysis of a “single amplicon”). Kinde 2013 asserts that using UIDs allows researchers to determine whether a sequence, after amplification, reflects “mutations [that] preexist[ed] in template DNA” (*i.e.*, **before** amplification), which Kinde 2013 calls “supermutants,” or whether, instead, a mutation was “caused by sample preparation or sequencing” (*i.e.*, introduced by error **during** amplification, for example, due to nucleotide misincorporation, or **after** amplification). EX1007, 4, 5; *see also* EX1049, 1, 5.

Kinde 2013 reports on the results of two separate “experiments”: One used (as in the earlier Kinde 2011 paper cited by Bettegowda (*e.g.*, EX1008, 15 & n.40))

a **single-plex** PCR assay (EX1007, 3-4), and the other used a **multiplex** PCR assay (EX1007, 5-7). *See also* EX1007, 2. None of Kinde 2013's experiments ever used cfDNA; instead, they all used samples from "liquid-based Pap smears," which contained "cells or cell fragments." EX1007, 2, 6; *see also id.*, 1 (Title: "Evaluation of *DNA from the Papanicolaou Test* to Detect Ovarian and Endometrial Cancers").

Using Kinde 2013's reported **single-plex** assay experiments, the authors attempted to identify ctDNA corresponding to mutations in "tumors from 46 cancer patients for whom Pap specimens were available," including "24 patients with endometrial cancers and 22 with ovarian cancers." EX1007, 3, 11. This single-plex experiment looked for individual mutations identified by sequencing a patient's tumor. EX1007, 5. Kinde 2013's single-plex experiment showed that, "[i]n the 24 Pap specimens from patients with endometrial cancers, a mutation present in the tumor was identified in every case," but that "only 41% of ovarian cancers could be detected in Pap specimens." EX1007, 4, 6. Thus, despite the single-plex format "appear[ing] to be promising as a *screening tool* for endometrial cancer," it missed 59% of ovarian cancers "even when the mutations in their tumors were known." EX1007, 6. As to sensitivity, in one pap smear sample ("Pap 026") in the

endometrial cancer category in the single-plex experiment the “fraction of mutant alleles” was 0.01%.³ EX1007, Fig.3.

In Kinde 2013’s *multiplex PCR* assay experiment, the authors designed a “prototype test based on Safe-SeqS that could assess several genes and could be used in a screening setting.” EX1007, 5. The authors dubbed this “prototype test” the “PapGene test.” EX1007, 5, 6. Unlike the above-described single-plex assay, the PapGene test “simultaneously” “assess[es] 12 genes in Pap specimens with the multiplexed Safe-SeqS strategy,” with “six independent amplifications—each containing 66 ng of DNA (that is, ~400 ng total)—per sample.” (EX1007, 11, 18, Table S5).

Kinde 2013’s multiplex PCR PapGene test is not a personalized assay informed by a biopsy of a patient’s actual tumor (as in the Challenged Claims); instead, it is a “screening” test for “early detection of gynecologic malignancies” (EX1007, 1) where “the presence and genotype of tumors would... not be known before evaluation.” EX1007, 5. The multiplex PCR PapGene test utilizes a

³ For ovarian cancer, Kinde 2013 reported a lower sensitivity: “Pap specimen DNA from ovarian cancer patients revealed detectable mutations in 9 of the 22 patients (41%),” with the lowest detectable fraction of mutant alleles at “0.021%” in this single-plex experiment. EX1007, 5.

“multiplexed approach [that] included 50 primer pairs that amplified segments of 241 to 296 base pairs (bp) containing *frequently mutated regions* of DNA” that were “chosen from the *most commonly mutated genes* in endometrial and ovarian cancers” (EX1007, 5)—not (as in the challenged claims of the ’596 patent) the actual mutations in a particular patient’s known cancer.

The 241 to 269 bp segments Kinde 2013’s multiplex PCR PapGene test amplifies are from pap specimen DNA, not cfDNA, and are significantly longer than typical cfDNA fragments, as recognized by co-author Diaz in his separate 2014 paper (discussed above). EX1006, 2 (“most cfDNA fragments measure between 180 and 200 base pairs”). The multiplex PCR PapGene test was evaluated using “14 samples selected from the positive cases” that were also tested using Kinde 2013’s single-plex approach. EX1007, 1.

Of particular pertinence to this proceeding, Kinde 2013 *admits that the theoretical detection limit of its multiplex PCR PapGene test is only 0.1%*, explaining that “[t]he 14 cancer cases were arbitrarily chosen from those which had *mutant allele fractions $\geq 0.1\%$ (table S3) and therefore above the detection limit of the multiplexed assay.*” EX1007, 6. Kinde 2013 further explains that, “[i]n eight of the nine Pap specimens from ovarian cancer patients that contained detectable mutations, the mutant allele fractions were *$>0.1\%$ and therefore within the range currently detectable by [Kinde 2013’s multiplex PCR] PapGene testing*” (EX1007,

6-7), and thus Kinde 2013 concedes that only a “fraction of ovarian cancers” can be detected by PapGene. EX1007, 1.

Consistent with this express acknowledgement of lowered sensitivity with Kinde 2013’s multiplex PCR test as compared to its single-plex results, but as the Petition conspicuously fails to mention, the smallest mutation fraction *actually detected* using the multiplex PCR PapGene test was 0.31%, which is much less sensitive than the 0.015% sensitivity recited in the claims of the ’596 patent at issue here. EX1007, 314 (PAP 071). The Petition (correctly) does not assert that Kinde 2013’s multiplex PCR PapGene test discloses the claimed 0.015% sensitivity. Instead, it merely asserts that Kinde 2013’s more sensitive *single-plex* methods are “compatible” with Kinde 2013’s *multiplex* PCR PapGene test, although Kinde 2013 (which discusses *both*) never stated that its Safe-SeqS assay with a multiplex PCR amplification step is able to achieve this sensitivity. Pet.2 (“Kinde 2013... disclose[s] error-corrected sequencing methods that detect rare ‘somatic mutations’ at detection levels below the 0.015% limitation *and are compatible with multiplex amplification.*”).

C. Rabinowitz (EX1009)

Rabinowitz is a patent publication naming PO Natera’s Executive Chairman and co-founder as an inventor. EX1009, 1. Rabinowitz is cited on the face of the ’596 patent, and—contrary to the Petition’s assertion that Rabinowitz was “buried”

in an IDS (Pet.56)— is expressly identified and discussed multiple times in, and explicitly *incorporated by reference into*, the '596 patent specification. EX1001, 49:21-26, 97:32-39, 98:4-17, 125:60-126:15. In one of its several discussions of Rabinowitz, the '596 patent states that, “[i]n some embodiments, amplification is performed using direct multiplexed PCR,” and acknowledges that multiplex PCR is “described in” (among other references) Rabinowitz. EX1001, 98:4-17. Rabinowitz is also extensively discussed in a written opinion of the International Searching Authority that was issued in connection with the '596 patent’s parent PCT application, and this opinion is included as part of the '596 patent’s prosecution history. EX1003, 932, 1115; EX1001, 13 (“References Cited” include “PCT/US2014/51926, ‘International Search Report and Written Opinion’”). Petitioner never contends that Rabinowitz discloses the claimed detection of SNV mutations present in $\leq 0.015\%$ of the cfDNA having the SNV locus. Pet.28-30; EX1001, cl.1[C][iv].

D. Bettegowda (EX1008)

Petitioner asserts that Bettegowda, “Detection of Circulating Tumor DNA in Early- and Late-Stage Human Malignancies” (EX1008, 1), was “published at least by... February 19, 2014.” Pet.11-12. While the experiments in Bettegowda were performed in the same laboratory as Kinde 2011 and Kinde 2013 (EX1008, 1; EX1007, 1; EX1049, 1), and although Petitioner asserts Bettegowda was published

more than a year *after* Kinde 2013 (Pet.11-12), Bettgowda does not cite or rely on Kinde 2013 or Kinde 2013's "improved" Safe-SeqS assay (either the single-plex or multiplex PCR version).⁴ EX1008, 2, n.1 (Ludwig Center for Cancer Genetics and Therapeutics); Pet.14. Instead, Bettgowda cites Kinde 2011's years-earlier discussion of a single-plex version of Safe-SeqS. *E.g.*, EX1008, 7 & n.40 (Bettgowda's reference 40 is Kinde 2011), 15-16.

Bettgowda discloses multiple separate embodiments on which Petitioner relies to piece together various aspects of the challenged claims. Pet.43 (citing EX1008, 2, evaluation of "Patients with metastatic cancers" to "identify mutations in the tumors"), 45 (citing EX1008, 14, analysis of plasma draws taken, respectively, "prior to initiating EGFR blockade" and "when the tumors had recurred after a clinical response").

While Petitioner contends that Bettgowda *discloses* the claimed 0.015% sensitivity in a single-plex assay, the Petition never identifies any such explicit disclosure in Bettgowda using either single-plex or single-volume multiplex PCR amplification. Instead, Petitioner argues that Bettgowda's assay "*can* achieve results comparable to" a very different technology known as BEAMing (which it

⁴ Nor does Bettgowda refer to Kinde 2013's multiplex PCR PapGene test, instead only referring to "SafeSeqS" and citing Kinde 2011. *E.g.*, EX1008, 14, 15.

does not map to any limitations). Pet.49-50. Petitioner acknowledges BEAMing differs from the Challenged Claims since (in Petitioner’s own words) it “does *not* readily allow multiplex analysis of different target loci in the same reaction.” *Id.* Petitioner also offers its own calculations—based on numerous unfounded assumptions, such as the amount of ctDNA in Bettegowda’s samples (*see infra*, §VII.A.2.b)—in an attempt to show that Bettegowda’s assay had the claimed 0.015% sensitivity. Pet.50. But tellingly, Petitioner never contends that Bettegowda discloses the claimed 0.015% sensitivity in a single-volume *multiplex Safe-SeqS* assay (for which Bettegowda cites to Kinde 2011, EX1008, 10 (reference (40) is Kinde 2011), 16 (“Safe-SeqS (40)”). Instead, Petitioner merely argues that Bettegowda’s assay is “*compatible*” with *multiplex* PCR amplification. Pet.57; *see also* Pet.41, 47, 49-52.

E. Fleischhacker (EX1010)

Petitioner relies on Fleischhacker—“Circulating nucleic acids (CNAs) and cancer—A survey,” which is named and discussed in the specification of the ’596 patent (EX1001, 133:15-20, 25-32)—only for dependent claim 15, and only for its purported teaching of “detection of tumor-associated mutations including SNVs in bladder cancer circulating tumor nucleic acids.” Pet.39.

IV. Ground 1: Diaz in View of Kinde 2013 (Claims 1, 2, 5, 10, 12-14, and 16-18)

A. The Petition Fails to Show That Achieving the Required Sensitivity Following Single-Volume Multiplex PCR Amplification, as Required by Limitations 1[C][ii] and 1[C][iv], Is Obvious

Claim 1 requires amplifying target loci of *cell-free DNA* using *single-volume multiplex PCR* and detecting SNV mutations present in *less than or equal to 0.015%* of the cell-free DNA having the SNV locus. In particular, limitation 1[C][ii] requires, in part, “performing targeted *multiplex PCR amplification* to amplify the plurality of target loci *together in the same reaction volume* from the *isolated cell-free DNA*...[,]” and limitation 1[C][iv] requires, in part, detecting an SNV mutation that is present “*in less than or equal to 0.015% of the cell-free DNA* having the SNV locus....” Indeed, as detailed above (*supra*, §II.C), in allowing the ’596 patent’s claims, the Examiner explicitly called out that *the prior art (including Talasaz and Kennedy) failed to teach or suggest these three features in combination*: detection (1) at a level of “*less than or equal to 0.015%*” (2) in *cfDNA* (3) *amplified by single-volume multiplex PCR*. EX1003, 334, 62, 5.

Just as in the original prosecution, *this critical combination of features remains entirely absent from the Petition here*: across all four of its Grounds the Petition presents *not even one prior art reference that it claims actually achieves the required 0.015% sensitivity using single-volume multiplex PCR amplification*,

let alone in *cfDNA*. Nor does the Petition show this would have been obvious. This failure for Ground 1 is clear from Petitioner's own characterizations of Kinde 2013 and the reference itself.

1. The Petition Identifies No Disclosure in Kinde 2013 of Achieving the Required Sensitivity in Any Assay with Multiplex PCR Amplification

Petitioner never argues (let alone shows) that Kinde 2013's *multiplex PCR* PapGene test achieved the "0.015%" sensitivity claimed in 1[C][iv]. Pet.25. Instead, notwithstanding the Examiner's analysis and the fact that this had never been achieved in *any* of Petitioner's references, the Petition argues that it would have been obvious to achieve the same sensitivity in Kinde 2013's *multiplex PCR* assay (and with cfDNA, *see infra*, §IV.B) as Kinde 2013 achieved in a *single-plex* assay (with a non-cfDNA sample derived from a pap smear) because, Petitioner claims, Kinde 2013's single-plex assay "is *compatible with* multiplex PCR." Pet.25.⁵

⁵ As with limitation 1[C][ii], *infra*, Petitioner and its expert also cite Bettegowda's use of a prior, single-plex version of Safe-SeqS. Pet.24 (arguing that Bettegowda disclosed "that Safe-SeqS amplification and sequencing was able to detect one mutant template in the DNA purified from up to 5 ml of plasma"); *see also* Pet.14 (citing EX1004, ¶¶89-90). Dr. Lennon, in turn, also cites to this earlier, single-plex-only version of Safe-SeqS used in Bettegowda (EX1008). EX1004, ¶90. But

Petitioner’s assumption about achieving the same sensitivity in multiplex PCR as single-plex ignores the significant attendant challenges of multiplex PCR as compared to single-plex PCR, including the potential creation of copies of off-target junk, unequal or biased amplification of certain targets over others, or introduction of errors caused by insertion of the wrong nucleotide into a DNA sequence during replication. *Supra*, §II.A. It also ignores Kinde 2013’s own explicit disclosures about its assays. Kinde 2013’s ***single-plex*** assay (from a non-cfDNA pap smear sample (*see infra*, §IV.B)) purportedly detected an SNV present at 0.01% in one out of 46 tested pap smear samples. Pet.23; EX1007, Fig.3, 309. But Kinde 2013 expressly admits—twice—that its ***multiplex*** PCR PapGene test (which also did not

Bettegowda is not part of this Ground, and in any event used a prior, single-plex version of Safe-SeqS discussed in Kinde 2011. *See, e.g.*, EX1008, 15 & 10 n.40 (Bettegowda citing Kinde 2011, not Kinde 2013); Pet.45. Bettegowda never cites or refers to Kinde 2013—which Petitioner argues discloses the “improved version” of the single-plex Safe-SeqS assay (Pet.14) that Petitioner relies for Ground 1—and thus never suggests that Kinde 2013’s method had ***ever*** been used with multiplex PCR amplification (or with cfDNA (*see infra*, §VII.A.1)). And, as discussed with respect to Ground 4, Bettegowda’s single-plex version of Safe-SeqS does not disclose the claimed sensitivity. *See infra*, §VII.A.2.b.

use cfDNA) is only able to detect mutations present in DNA at a *theoretical* sensitivity of **>0.1%** in pap samples (whereas the lowest observed sensitivity in *actual practice* was only 0.31%):

The 14 cancer cases were arbitrarily chosen from those which had *mutant allele fractions >0.1%* (table S3) *and therefore above the detection limit of the multiplexed [PapGene] assay.*

and

In eight of the nine Pap specimens from ovarian cancer patients that contained detectable mutations, the mutant allele fractions were **>0.1%** *and therefore within the range currently detectable by PapGene testing* (table s3).

EX1007, 6-7. Kinde 2013 thus tells the skilled artisan that the Pap 026 mutation detected in its *single-plex* assay (and its 0.01% sensitivity, on which Petitioner relies (Pet.23)) was expressly **not** “within the range currently detectable by [*multiplex PCR*] PapGene testing.” EX1007, 7. Indeed, Kinde 2013’s results show that the best sensitivity achieved using Kinde 2013’s multiplex PapGene test was 0.31%. EX1007, 314 (Table S6, PAP 071). Kinde 2013’s multiplex Safe-SeqS results had a limit of detection that was **over 20 times less sensitive** than required by the claims. In other words, far from suggesting that a *multiplex Safe-SeqS* assay would be expected to achieve the same sensitivity as a *single-plex* assay (see Pet.25), Kinde 2013 disclosed a much lower sensitivity for the multiplex version of Safe-SeqS

(EX1007, 6, 7, 314). Despite recognizing and indicating that higher sensitivity was desirable (*e.g.*, EX1007, 1, 3-4), Kinde 2013 described a ***multiplex assay*** with sensitivity that was ***far worse than its single-plex*** sensitivity.

Petitioner and its expert do not contend otherwise, but instead argue that Kinde 2013's multiplex PCR PapGene test used "more stringent SNV detection parameters for a mutation 'agnostic' screening assay." Pet.24 (citing EX1004, ¶¶119, 145). But neither Petitioner nor its expert explain how these "detection parameters" could be altered to achieve the claimed sensitivity or why a skilled artisan would have altered these "detection parameters" or expected to be successful (let alone with cfDNA (*see infra*, §IV.B)). Petitioner's expert, Dr. Lennon, merely asserts that based on the use of some unspecified different metric than what is actually used in Kinde 2013, "a POSA would expect Kinde 2013's ***general teachings*** regarding the mutation detection capabilities of improved Safe-SeqS to apply in a tumor-informed method." EX1004, ¶145 (*e.g.*, generally referencing "other threshold requirements"). But Dr. Lennon never explains how these "general teachings" would be expected to result in Kinde 2013's multiplex PCR PapGene test achieving the claimed sensitivity (let alone with cfDNA). EX1004, ¶145. Petitioner's bare assertion here, without any explanation as to how Kinde 2013 would need to be modified to achieve the claimed sensitivity (or why), fails to show obviousness. *Axon Enter., Inc. v. Digital Ally, Inc.*, IPR2017-00515, Pap.10, 18-19

(July 6, 2017) (denying institution, stating neither petitioner nor its expert “explains in sufficient detail the nature of Petitioner’s proposed modification.... Petitioner does not explain in sufficient detail how the proposed modification is supposed to work”).

2. The Petition Identifies No Disclosure in Kinde 2013 of Achieving the Required Sensitivity in Any Assay with Multiplex PCR Amplification of *cfDNA*

Similarly, Petitioner never argues (let alone shows) that *any* Kinde 2013 assay ever achieved the “0.015%” sensitivity claimed in 1[C][iv] *with cfDNA*. Pet.25. Again, the Petitioner offers the conclusory assumption that it would somehow have been obvious to achieve, in a multiplex PCR assay *with cfDNA*, the same, far-higher sensitivity that Kinde 2013 achieved (according to Petitioner) in a single-plex assay of a *non-cfDNA* pap smear sample, based on a conclusory assertion that that Kinde 2013’s single-plex assay “is *compatible with* multiplex PCR.” Pet.25.⁶ But this

⁶ As discussed above (n.5), while Petitioner and its expert also attempt to rely on Bettegowda and its use of a prior, single-plex version of Safe-SeqS (Pet.24; *see also* Pet.14 (citing EX1004, ¶¶89-90)), Bettegowda is not part of this Ground, and in any event used a prior, single-plex version of Safe-SeqS discussed in Kinde 2011. EX1008, 15 & n.40 (citing Kinde 2011); Pet.45. Bettegowda thus never suggests that Kinde 2013’s “improved version” of the Safe-SeqS assay (the version on which

ignores, as discussed below, the District Court’s and Federal Circuit’s explicit findings *against Petitioner* that there were “well-known barriers to successfully amplifying and sequencing *cfDNA*” (EX2032, 10; *infra*, §IV.B), and also ignores the physical incompatibilities between the length of template targeted by the primers used in Kinde 2013’s multiplex PCR PapGene test (241 to 296 base pairs), on the one hand, and most cfDNA (180 to 200 base pairs), on the other. *Infra*, §IV.B. And as above, this argument also suffers the same failings as Petitioner’s unsupported assertions about the sensitivity of multiplex PCR assays more generally—assumptions contradicted by Kinde 2013 itself (*see supra*, §IV.A.1). Again, Dr. Lennon never explains how any “general teachings” of Kinde 2013—which undisputedly *do not concern cfDNA*—would result in Kinde 2013’s multiplex PCR PapGene test achieving the claimed sensitivity *with cfDNA*. EX1004, ¶145. Petitioner’s conclusory assertions again fail to fill this substantive hole in the art—the same failure that the Examiner found was present during original examination, and that Kinde 2013 itself underscores.

Petitioner relies for Ground 1) had *ever* been used with single-volume multiplex PCR amplification, let alone *with cfDNA*.

B. Petitioner Fails to Show That Diaz or Kinde 2013, Alone or Combined, Disclose or Render Obviousness Limitation 1[C][ii]’s Requirements About Performing Targeted Multiplex PCR Amplification of cfDNA Together in the Same Reaction Volume

Even apart from the Petition’s improper unexplained double-mapping of *both* Diaz and Kinde 2013 to this limitation (discussed *infra*, §IV.D), the Petition fails to show it to be disclosed or obvious based on *either* Diaz or Kinde 2013, or their combination.

First, while the Petition does not appear to assert that Diaz discloses multiplex PCR amplification as required by limitation 1[C][ii], it does appear to argue obviousness of this limitation based on Diaz alone. Pet.20-21. The limitation requires “performing targeted multiplex PCR amplification to amplify the plurality of target loci together in the same reaction volume from the isolated cell-free DNA using primers specific to the plurality of target loci for the individual subject[.]” But while the Petition asserts that “[a] POSA would have been motivated to perform multiplex PCR followed by next-generation sequencing,” it provides *no explanation for why such a combination of single-volume multiplex PCR with sequencing would be compatible with or otherwise reasonably expected to succeed* with the disclosures of Diaz the Petition relies upon. Pet.20-21 (citing EX1006, 2; EX1004, ¶¶79, 83, 133). Thus, it fails to show obviousness.

Second, Kinde 2013 fares no better: it neither discloses limitation 1[C][ii] nor renders it obvious. The Petition relies on Kinde 2013’s testing of *pap smear samples*—which undisputedly are *not comprised of cfDNA*—and asserts that a skilled artisan “would reasonably expect to succeed in using Kinde’s unique identifiers in primers for multiplex amplification from cfDNA” because “multiplex PCR of isolated cfDNA followed by [next-generation sequencing] of the amplified DNA was within the knowledge of a POSA” and the use of molecular barcodes “in primers for multiplex amplification of cfDNA had also been described.” Pet.21. But absent from Petitioner’s assertions regarding cfDNA is any mention of the Federal Circuit’s *explicit findings against Petitioner* made in its affirmance of the Preliminary Injunction regarding the related ’035 patent (EX1029) asserted in the parties’ parallel District Court litigation. There, the Federal Circuit explained that, “[b]ased on evidence of *well-known barriers to successfully amplifying and sequencing cfDNA*, the district court found it was *unlikely a skilled artisan would have been motivated to use cfDNA with the [prior-art non-cfDNA assay]* for the claimed cancer detection *and unlikely a skilled artisan would have anticipated success* in doing so.” EX2032, 10. The Federal Circuit (rejecting Petitioner’s contrary arguments) also credited PO’s “*significant evidence of obstacles to using cfDNA* in the present setting [*i.e.*, cancer detection] that would have been known to

a skilled artisan.” EX2032, 11 (citing EX2079, 4-12).⁷ The Petition never even attempts to contend with this contradictory evidence of which Petitioner was clearly aware. *See, e.g., Luitpold Pharms., Inc. v. Apicore US LLC*, IPR2018-01640, Pap.19, 24 (Mar. 6, 2019) (denying institution where petitioner “fail[ed] to explain adequately for institution why the ordinarily skilled artisan would have reasonably expected success under the particular facts of this case, especially where, as the Federal Circuit noted” in a prior decision involving the challenged patent that “the path to arrive at [the claim limitation at issue] was not known before the relevant date of the [challenged patent]”).

Not only does the Petition fail to address this highly-relevant contrary evidence from parallel litigation (comprising findings *against Petitioner*), but it also fails to address the significant issues raised *by Petitioner’s own Diaz and Kinde 2013 references, which form the basis of this Ground*. The “primers comprising unique identifier sequences” argued by the Petition (Pet.21) and used in Kinde

⁷ EX2079 contains a portion of a redacted declaration submitted by an expert for PO in related litigation and cited at EX2032, 11. The full redacted declaration (without exhibits) is available is available at *Natera, Inc. v. NeoGenomics Laboratories, Inc.*, No. 24-1324, Dkt. 42-3, Non-Confidential Joint Appendix Vol. III of IV, Appx18741-18912 (Mar. 18, 2024).

2013’s multiplex PCR “PapGene” test (targeting specific genomic DNA regions deemed to be hot spots for cancer (EX1007, 5)) would not have worked to analyze *cfDNA*—most of which is far shorter in length—for the claimed patient-specific targets.⁸ Kinde 2013 states that its multiplex PCR PapGene test used “50 primer pairs that amplified segments of **241 to 296 base pairs** (bp) containing frequently mutated regions of DNA.” EX1007, 5. But Petitioner’s Diaz reference explains that “most cfDNA fragments measure between **180 and 200 base pairs**.” EX1006, 2. Petitioner never acknowledges, let alone attempts to explain, how Kinde 2013’s primers would need to be modified to amplify “most cfDNA fragments” and whether any modification of the primers would necessitate modifications of other aspects of

⁸ Petitioner elsewhere asserts that “by 2014, Safe-SeqS **had been applied** to cfDNA samples,” citing the declaration of Dr. Lennon. Pet.14 (citing EX1004, ¶¶89-90). Dr. Lennon, in turn, also cites a single-plex version of Safe-SeqS used in Bettegowda (EX1008). But, as above (*see* n.5), Bettegowda is not part of this Ground, and in any event references a different, prior version of Safe-SeqS discussed in Kinde 2011. EX1008, 15 & n.40 (citing Kinde 2011); Pet.45. Bettegowda thus never suggests that Kinde 2013’s “improved version” of the Safe-SeqS assay (the version on which the Petition relies) had **ever** been used with cfDNA. Pet.14, 20-21.

Kinde 2013's assay.⁹ Additionally, Petitioner fails to explain how Diaz (as the base reference for this Ground 1 combination) would need to be modified to add and incorporate any Kinde 2013 teachings that Petitioner points to for this limitation, and fails to explain any motivation for such changes. Pet.20-21.

Third, to the extent the Petition was attempting to combine Diaz and Kinde 2013 for this limitation, any reliance on Kinde 2013 would have required an explanation of the specific proposed combination with particular teachings from Diaz. *Quest Diagnostics Inc. v. Ravgen, Inc.*, IPR2021-00790, Pap.21, 34 (Oct. 19, 2021) (denying institution, explaining that Petitioner failed to “provide a sufficient evidence-backed theory on how [the asserted art] would be combined.... Doing so might be straightforward. Or there may have been known or unknown complexities still to be explored.”). Petitioner cannot rely on a mere generalized and unspecified invocation of “obviousness” to fill the gaps in Diaz and Kinde 2013, and the Petition does not mention obviousness using a combination of Diaz and Kinde when

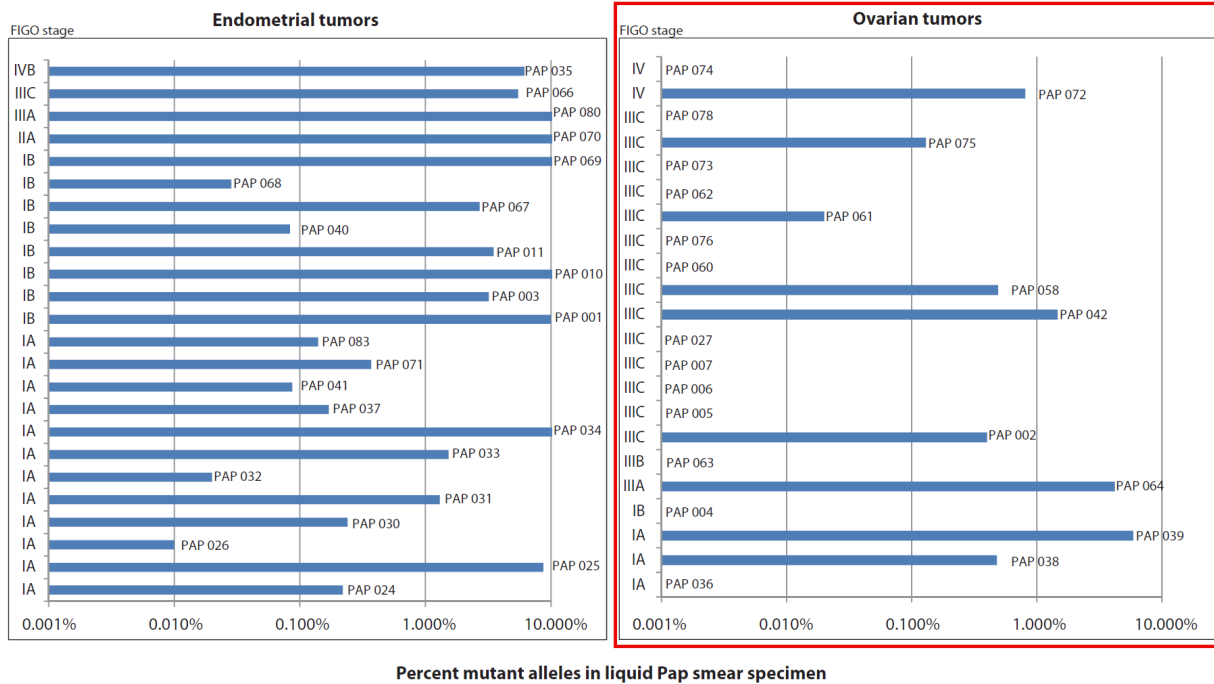
⁹ Petitioner makes the conclusory assertion that “Diaz points to [Kinde 2011's version of] Safe-SeqS... as a solution ‘aimed at increasing overall sensitivity’ for detecting mutations in ctDNA in the context of next-generation sequencing” (Pet.14), but in fact *Kinde 2011 (like Kinde 2013) does not utilize or test ctDNA*. EX1049, 1; Pet.21.

analyzing this limitation; nor does it clearly identify which particular aspects of which reference(s) it relies on for any potential combination. Pet.20-21.¹⁰

¹⁰ In contrast to what is presented in the Petition, Petitioner’s expert, Dr. Lennon, asserts that the references are to be combined to cover this claim element. EX1004, ¶132. But this paragraph from Dr. Lennon is *never cited* in the Petition, and any attempted reliance on it would amount to improper incorporation by reference (Patent Trial and Appeal Board, *Consolidated Trial Practice Guide*, 35-36 (Nov. 2019))—and would only add to the confusion of what aspects of which reference might purportedly be relied on for which aspects of the claim. *E.g.*, *Dongguan Juxing Power Co. v. Noco Co.*, IPR2018-00503, Pap.9, 17 (July 11, 2018) (denying institution, noting that “[t]he only discussion in either the Petition or Dr. Schalkwijk’s Declaration that is apparently directed to the issue is ¶84 of the Declaration. The Petition itself, however, does not cite or otherwise reference that paragraph of the Declaration.”); *Palo Alto Networks, Inc. v. Centripetal Networks, Inc.*, IPR2021-01154, Pap.11, 18-19 (Jan. 24, 2022) (denying institution, explaining that “the Declaration was not cited in the Petition but rather is referred to indirectly in a portion of the Declaration which is cited in the Petition” and “the Petition improperly incorporates this section of the Declaration by reference because the basis of the... argument is not explained sufficiently in the Petition”).

Moreover, Petitioner fails to explain any motivation to modify Diaz in view of Kinde 2013 to utilize single-volume multiplex PCR, which is perhaps unsurprising considering the clear drawbacks of Kinde 2013's multiplex PCR SafeSeqS methods that *Kinde 2013 itself acknowledges*. For example, Kinde 2013 explains that, while higher sensitivity is desirable (EX1007, 1, 3-4), its *multiplex* PCR PapGene test has a significantly *lower sensitivity* than Kinde 2013's *single-plex* assay. EX1007, 7.

Further, Kinde 2013's purportedly more sensitive single-plex assay also *failed to detect any mutations in 13 out of 24 patients with ovarian cancer*: "only 41% of ovarian cancers could be detected in Pap specimens, *even when the mutations in their tumors were known*." EX1007, 6; *see also* EX1007, Fig. 3. Petitioner and its expert ignore these teachings in Kinde 2013, including by selectively excerpting Kinde 2013's Figure 3 to include only results for endometrial tumors while omitting the much less favorable results for ovarian tumors (in red, on the right, below):



EX1004, ¶140 (red box on the right showing the portion of Figure 3 omitted from Dr. Lennon’s declaration). These far less favorable results even in Kinde 2013’s *single-plex* assay contradict Petitioner’s assertion that using less “stringent detection parameters” (as Petitioner contends were used in Kinde 2013’s “tumor-informed” *single-plex* Safe-SeqS assay, Pet.24) in the *multiplex* PCR PapGene test would have resulted in better sensitivity. Pet.24. And Petitioner’s conspicuous failure to address this known contradictory evidence is another independent reason for rejecting the Petition. *Luitpold*, Pap.19, 24.

C. Petitioner Improperly Shifts its Reliance, Without Explanation, Among Three Different Diaz Embodiments for Overlapping Elements in Limitations 1[A], 1[B], 1[C][i]

Petitioner improperly relies on disparate Diaz embodiments for different limitations without providing any arguments about their combination. Pet.18-20.

The Challenged Claims require, in part, assaying cfDNA isolated from a plurality of biological samples obtained from a patient having a tumor. EX1001, cl.1[A], [B], [C][i]. In particular, following the preamble, the claim introduces three interconnected limitations. Limitation 1[A] requires “performing sequencing on a tumor biopsy sample of the subject to identify a plurality of tumor-specific mutations, wherein the tumor-specific mutations comprise one or more single nucleotide variant (SNV) mutations.” EX1001, cl.1[A]. Limitation 1[B] requires “evaluating results of the sequencing on the tumor biopsy sample to determine a plurality of target loci specific to the subject, wherein each target locus spans a tumor-specific mutation of the identified plurality of tumor-specific mutations.” EX1001, cl.1[B]. And limitation 1[C] requires, in part, “assaying cell-free DNA isolated from a plurality of biological samples” using elements resulting from 1[A] and 1[B]. EX1001, cl.1[C][i].

The Petition improperly relies, for these three interconnected limitations, on *three different, separate Diaz embodiments* with no acknowledgment or explanation for why a skilled artisan would have combined them. For limitation 1[A], the Petition relies on Diaz’s “Minimal Residual Disease” embodiment (*Diaz’s second embodiment*, see §III.A, *supra*), which the Petition asserts “involves sequencing a tumor biopsy.” Pet.18; EX1006, 4 (“*Another* potential application of ctDNA is the detection of minimal residual disease....”). But for limitation 1[B],

the Petition relies on Diaz’s “Monitoring Tumor Burden” embodiment (*Diaz’s first embodiment*, see §III.A, *supra*), which Petitioner asserts discloses “target[ing] and quantify[ing] the level of ctDNA” and “identifying and targeting loci comprising the tumor-specific mutations taught by Diaz.” Pet.19. And for limitation 1[C][i], Petitioner relies on yet another Diaz embodiment, “Monitoring of Molecular Resistance and Heterogeneity” (*Diaz’s third embodiment*, see §III.A, *supra*), Pet.19-20, which Petitioner asserts discloses “[c]ontinuous monitoring of plasma DNA’ to detect mutations in tumor DNA.” Pet.19. Notably, for each of these three limitations (1[A], 1[B], and 1[C][i]) the Petition relies *only* on the isolated embodiment it has snipped from Diaz for that limitation (*e.g.*, Petitioner relies *only* on Diaz’s second embodiment for limitation 1[A], etc.) (Pet.18-20), and offers no motivation to combine these isolated embodiments.

In violation of clear Board precedent, the Petition never even *acknowledges* that it relies on three separate Diaz embodiments for these three limitations, let alone *explains* why a skilled artisan would have been motivated to combine features of these different embodiments from across Diaz with one another or had a reasonable expectation of success in doing so. Pet.18-20. Instead, the Petition *impermissibly* “*treats the various features of [Diaz’s] different embodiments as if they are interchangeable with one another.*” *Abiomed, Inc. v. Maquet Cardiovascular, LLC*, IPR2017-01204, Pap.9, 8-11 (Oct. 23, 2017) (denying institution, explaining

“Petitioner... fails to provide a sufficient rationale to combine the teachings of [the asserted reference’s] different embodiments. Petitioner simply *fails to explain sufficiently why one skilled in the art would have found it obvious to combine those teachings.*”). Petitioner’s failure to address and explain its reliance on these three different, separate embodiments is fatal and requires denial of institution here. *Id.*; *First Alert, Inc. v. Walter Kidde Portable Equip., Inc.*, IPR2023-00896, Pap.14, 20-21 (Dec. 13, 2023) (denying institution, concluding petitioner failed to provide sufficient reasoning to combine various embodiments of a reference to meet two separate claim limitations); *Hewlett Packard Enter. Co. v. Intell. Ventures II LLC*, IPR2022-00115, Pap.9, 12-16 (Mar. 29, 2022) (denying institution, concluding “Petitioner does not explain sufficiently, let alone with particularity, how or why the skilled artisan would have combined such distinct embodiments [of the asserted reference] or had an expectation of success in doing so.”).

D. The Petition Improperly Maps Both Diaz and Kinde 2013 for Multiple Limitations Without Explaining What Teachings of Either Are Relied Upon in Any Proposed Combination

In addition to the above-discussed deficiencies, Ground 1 lacks the particularity required by §312(a)(3) because Petitioner appears to assert that both Diaz and Kinde 2013 disclose multiple limitations without explaining which

teachings of which of these two references the Petition applies to each claim element. Pet.20-21.¹¹

For example, the Petition’s single paragraph purporting to analyze limitation 1[A] (which does not even mention SNV mutations, as required by this limitation) first appears to argue that Diaz discloses that limitation, but concludes by asserting that “Kinde 2013 also teaches this limitation.” Pet.18. And as to limitation 1[B], the Petition’s two-paragraph analysis again begins by appearing to assert that Diaz discloses limitation 1[B], but then again states that “Kinde also discloses this limitation.” Pet.19.

Finally, as to limitation 1[C][ii], the Petition’s two-paragraph analysis begins by arguing that “***Diaz discloses***... ‘multiple genes of interest can be investigated in one sample. A POSA would have been motivated to perform multiplex PCR followed by next-generation sequencing to investigate ‘multiple genes’ or loci of interest ‘in one sample’ as taught by Diaz because multiplex PCR of cfDNA followed by next-generation sequencing was well known by 2014.” Pet.20-21. The

¹¹ In contrast to what is actually in the Petition, Petitioner’s expert appears to suggest that Diaz and Kinde 2013 should be combined for these limitations. *E.g.*, EX1004, ¶¶124, 126, 128, 129. Again, this only adds to the confusion of what aspects of which references are relied on for these limitations. Pet.18-19. *See supra*, n.10.

second paragraph of the Petition’s analysis of limitation focuses only on Kinde 2013, stating: “[f]urthermore, *Kinde 2013 discloses* multiplex PCR using primers comprising unique identifier sequences” and concludes that “a POSA would reasonably expect to succeed in using Kinde [2013’s] unique identifiers in primers for multiplex amplification of DNA.” Pet.21.

Nowhere in the Petition’s five total paragraphs discussing these three claim limitations (or the introductory section discussing the combination more generally, Pet.16-17) is an explanation of *whether and how Diaz and Kinde 2013 are to be combined* as to those limitations, how any such combination would render those limitations obvious, what aspects of each reference are to be combined (if any), and why a skilled artisan would have been motivated to do so and had a reasonable expectation of success.¹² This does not permit the Board and PO to understand, assess, and respond to Petitioner’s arguments because “it is not clear which teachings of each reference [petitioner] combines to account for all the limitations.” *ADT LLC v. Vivint, Inc.*, IPR2022-00634, Pap.7, 13-15 (Oct. 14, 2022) (denying institution where petitioner “maps each limitation of the challenged claims to [two different

¹² In arguing Ground 2, Petitioner cites back to the Ground 1 sections of these limitations and refers to them as obviousness arguments, again without explanation. See Pet.33, 36.

references independently]).” Again, this is yet another independent reason that the Petition’s Ground 1 arguments should be rejected.

V. Ground 2: Diaz in View of Kinde 2013 and Rabinowitz (Claims 1, 2, 5, 10-14 and 16-18)

Ground 2 again combines Diaz and Kinde 2013, and largely retreads the Petition’s deficient Ground 1 (*see supra*, §IV). Thus, it fails for at least the same reasons. The Petition adds Rabinowitz to Ground 1’s Diaz and Kinde 2013 for limitations 1[C][ii], 1[C][iii], and 1[C][iv], but does not rely on Rabinowitz to cure Ground 1’s defects as to these limitations. In fact, the entirety of Petitioner’s analysis for limitation 1[C][iv] is “[t]his limitation is obvious in view of Diaz, Kinde 2013, and Rabinowitz for the same reasons discussed above for Diaz Kinde 2013. (*Supra* §V.D.1.g; EX1004, ¶187.).” Pet.36.

VI. Ground 3: Diaz in View of Kinde 2013 and Fleischhacker (Claim 15)

Ground 3 relies on Fleischhacker—which is discussed twice and incorporated by reference in the specification of the ’596 patent—EX1001, 133:15-20, 25-32, for the additional limitations of claim 15, which depends from claim 1. Ground 3 relies on the same defective claim 1 analysis in Ground 1, and thus fails for at least the reasons discussed above. *See supra*, §IV.

VII. Ground 4: Rabinowitz in View of Bettgowda (Claims 1, 2, 10-13, and 15-18)

Petitioner's Ground 4 fails for many reasons. While numerous details of Petitioner's Ground 4 theory are unexplained, as discussed below, its failures are clear. As with Grounds 1-3, the Petition still *does not argue that anyone in the art had ever achieved the claimed SNV detection sensitivity in cfDNA using single-volume multiplex PCR amplification*. Instead, the Petition again argues that the sensitivity would be assumed to be the *same* for both single-plex amplification (as described in Bettgowda) and single-volume multiplex amplification. But its own art confirmed that shifting from single-plex to multiplex PCR in the Safe-SeqS framework—even in the far simpler context of non-cfDNA pap samples, instead of cfDNA—actually led to *reduced* sensitivity. Thus, Petitioner fails to show obviousness of the claimed sensitivity in the context of single-volume multiplex PCR.

Petitioner further errs in asserting that Bettgowda suggests achieving the claimed sensitivity even in a single-plex assay. Petitioner's arguments attempting to turn Bettgowda's reference to BEAMing and "comparable" results into the claimed sensitivity in the context of Safe-SeqS are not supported by the record. Further, Petitioner's assumptions about how many genome equivalents were in Bettgowda are undermined by explicit disclosures in Petitioner's own art of record.

The Petition also scrambles its reliance on Rabinowitz (relied on primarily for its disclosure relating to multiplex PCR assays¹³) and Bettegowda for limitation 1[C][ii]’s “same reaction volume” requirement (*see infra*, §VII.A.3). The Petition further repeatedly and improperly changes its mapping of references and claim elements mid-stream, initially identifying Rabinowitz as its base reference modified by Bettegowda, but then shifting to Bettegowda as its base reference modified by Rabinowitz. *See infra*, §VII.B. Petitioner also fails to explain how Rabinowitz’s method would supposedly be improved by Petitioner’s suggested modifications (*see infra*, §VII.C), improperly mixes and matches separate Bettegowda embodiments without explanation (*see infra*, §VII.D.1), improperly maps both Bettegowda and Rabinowitz for the preamble (*see infra*, §VII.D.2), and fails to identify the differences between the claims and the prior art as required in any obviousness analysis (*see infra*, §VII.D.3).

¹³ E.g., Pet.46 (“***Rabinowitz discloses methods for multiplex PCR amplification***”), 47 (“A POSA would have been motivated to apply ***multiplex PCR of cfDNA as taught by Rabinowitz...***”).

A. The Petition Fails to Show That the Sensitivity Required by Limitations 1[C][ii] and 1[C][iv] Is Obvious

As discussed with respect to Ground 1, above (§IV.B), claim 1 requires amplifying target loci of cell-free DNA using *multiplex PCR in the “same reaction volume”* and detecting SNV mutations present in *less than or equal to 0.015%* of the cell-free DNA having the SNV locus. *See* EX1001, cl.1. But just as in Ground 1, Bettgowda never achieves the required 0.015% sensitivity using single-volume multiplex PCR amplification—indeed, Bettgowda fails to achieve this even in *single-plex* amplification. Petitioner’s conclusory and inconsistent obviousness arguments do not fill this gap.

1. Achieving the Claimed Sensitivity in a Single-Volume Multiplex PCR Reaction Is Not Obvious

The Petition never contends that Bettgowda actually discloses an assay with *single-volume multiplex PCR amplification* that achieves the claimed *sensitivity*. Pet.49-50, 51-52. And this is, apparently, because the parties agree it *couldn’t*: for the method relied on by Petitioner, *Bettgowda* states that it used the *single-plex* Safe-SeqS assay “as described” in Kinde 2011 (EX1008, 15 (citing EX1049)),¹⁴ which in turn confirms it examined only a single amplicon, and thus did not employ single-volume multiplex PCR amplification. EX1049, 5 (“[W]e have demonstrated

¹⁴ *See, e.g.*, EX1008, 10 (reference (40) is Kinde 2011), 16 (“Safe-SeqS (40)”).

that the exogenous UIDs strategy can be used to analyze a *single amplicon* in depth. This technology may not be applicable to situations wherein multiple amplicons must be analyzed from a sample containing a limited number of templates.”). Instead, the Petition’s obviousness combination squarely identifies *Rabinowitz* as the source of its argued multiplex PCR disclosure (e.g., Pet.46 (“*Rabinowitz discloses methods for multiplex PCR amplification*”), 47 (“A POSA would have been motivated to apply *multiplex PCR of cfDNA as taught by Rabinowitz...*”)),¹⁵

¹⁵ Petitioner later argues that an expectation of success in combining Rabinowitz’s multiplex PCR with Bettgowda’s sensitivity from a single-plex Safe-SeqS assay is supported by a statement in Bettgowda about a *different* Bettgowda embodiment, “Monitoring patients for resistance-conferring mutations,” regarding a “*multiplexed, sequencing-based* assay to query known mutated hotspots of several genes in the EGFR pathway.” EX1008, 4; Pet.48 (“A POSA would also expect to succeed”; citing EX1004, ¶236); EX1004, ¶236 (“a POSA would understand that Safe-SeqS *can be used in the context of a multiplexed assay*, as well as for individual assays”)); EX1008, 4, 15-16. But neither Petitioner nor its expert ever contend that Bettgowda’s so-called “*multiplex, sequencing-based* assay” actually involves “*multiplex PCR amplification*” (much less *single-volume* multiplex PCR

and Petitioner relies on *Bettegowda* for the claimed *sensitivity* in the context of a *single-plex* Safe-SeqS assay (Pet.50) (although even in this context Bettegowda does

amplification as the '596 claims require). Nor could they, as *Bettegowda does not refer to or disclose any use of single-volume multiplex PCR*. Indeed, in describing the disclosure Petitioner relied on for this limitation, Bettegowda states that it identified “a mutation” and determined “whether that same mutation was detectable in [] plasma” for each of the various loci tested. EX1008, 4. Moreover, even Petitioner is unwilling to suggest that combining volumes *after amplification* for sequencing (“the [amplified] DNA from all wells was pooled and subjected to *massively parallel sequencing* and analysis as described [in Kinde 2011]”) would satisfy the claim. See EX1008, 15 (citing *Kinde 2011’s single-plex*-amplified SafeSeqS disclosure). Instead of claiming disclosure by Bettegowda, Petitioner relies for this limitation on arguing obviousness based on *Rabinowitz’s multiplex PCR amplification* and a purported *sensitivity* calculation based on *Bettegowda*. And even here Petitioner’s expert merely claims that “Safe-SeqS *can* be used in the context of a multiplexed assay.” EX1004, ¶236. However, “[t]he obviousness inquiry does not merely ask whether a skilled artisan *could* combine the references, but instead asks whether ‘they *would* have been motivated to do so.’” *Adidas AG v. Nike, Inc.*, 963 F.3d 1355, 1359 (Fed. Cir. 2020).

not actually disclose the claimed sensitivity, as discussed below (§VII.A.2.b)). Petitioner asserts that it would have been obvious to achieve the same purported sensitivity in a single-volume ***multiplex*** assay because Bettegowda’s single-plex assay is “***compatible*** with multiplex PCR” (Pet.41), because “the ***newer Safe-SeqS method***¹⁶ allows multiplexing” (Pet.50), and because a skilled artisan would have been motivated to “analyze target loci spanning a plurality of tumor-specific mutations... without requiring separate reactions.” Pet.47.

Setting aside the fact that these motivations turn Petitioner’s asserted combination on its head by using ***Bettegowda*** as the primary reference here, rather than Rabinowitz (*see infra*, §VII.B), Petitioner nowhere explains how or why changing Bettegowda’s ***single-plex*** Safe-SeqS assay (for which Bettegowda points to Kinde 2011 (*see, e.g.*, EX1008, 10 n.40, 15-16)) to a single-volume ***multiplex*** PCR assay would result in the same purported sensitivity as a single-plex assay, particularly given the significant attendant challenges of multiplex PCR, discussed above (*supra*, §II.A), and given that ***Petitioner’s own art shows that making this change with Safe-SeqS*** (from Kinde 2011 to “improved” Kinde 2013 (Pet.14))

¹⁶ The newer “Kinde 2013” article is introduced by the Petition as “disclos[ing] an improved version of the Safe-SeqS method [from the] Kinde 2011 article (Ex.1049).” Pet.14.

yielded a multiplex PCR assay having a sensitivity that is lower than its single-plex sensitivity. See *supra*, §IV.A.1; EX1006, 6, 7; see *bioeq IP AG v. Genentech, Inc.*, IPR2016-01608, Pap.11, 12 (Feb. 22, 2017) (denying institution where petitioner failed to address issues that could affect prior art’s ability to successfully perform the claimed method).

Indeed, the best sensitivity observed in Kinde 2013’s multiplex PapGene test was only 0.31%—far worse than the 0.015% required by the claims. EX1007, 314 (PAP 071). Petitioner fails to explain why, given this significant **drop** in sensitivity for multiplex PCR Safe-SeqS compared to what Petitioner asserts Bettegowda’s single-plex Safe-SeqS from Kinde 2011 was able to achieve, a skilled artisan would have been motivated to use multiplex amplification with Bettegowda’s single-plex version of Safe-SeqS. Notably, this **reduction** in sensitivity for single-volume multiplex PCR Safe-SeqS conflicts with Petitioner’s rationale that a skilled artisan would have been motivated to arrive at the claimed invention because “circulating mutant DNA represents only a tiny fraction of the total circulating DNA, sometimes less than 0.01%.” Pet.49 (citing EX1072, 1). The Petition’s failure even to address this **decrease** in sensitivity between the single-plex and multiplex Safe-SeqS assays in its own asserted art is even more glaring because neither Kinde 2011’s nor Kinde 2013’s disclosed sensitivities are in the context of **cfDNA**. Again, Petitioner simply ignores this, along with the “many well-known barriers to using cfDNA” that

“presented obstacles to successfully amplifying and sequencing ctDNA with precision.” EX2020, 9-10.

2. Even with Respect to Single-Plex PCR, Bettegowda’s Disclosures Do Not Support the Claimed Sensitivity

a. Petitioner’s BEAMing Arguments Do Not Support Petitioner’s Assertions About the Claimed Sensitivity in the Context of Safe-SeqS

In attempting to show the required sensitivity in Bettegowda even with a *single-plex* assay (rather than with single-volume multiplex amplification, as required), Petitioner relies, first, *not* on any evidence in Bettegowda about achieving that sensitivity with Safe-SeqS, but instead on Bettegowda’s statement that Safe-SeqS can achieve results “comparable” to BEAMing. Pet.49 (citing EX1008, 4, 16). But this is not a disclosure of the claimed sensitivity using Safe-SeqS, for at least two reasons. First, “comparable” does not mean “the same” or “identical,” and Petitioner does not argue otherwise. Pet.41-42. Second, the text accompanying Fig.S1 of Bettegowda explains that the results from both Safe-SeqS and BEAMing were *combined* into the plotted “Quantification Method #2” results, and Bettegowda provides no way to discern whether BEAMing or Safe-SeqS yielded any particular data point displayed in the graph. EX.1008, 18. The legend to Fig.S1 also describes a separate experiment in which “Quantification Method #1” (PCR-ligation) is compared with Quantification Method #2 (Safe-SeqS and BEAMing combined) to

evaluate “10 other duplicate samples containing *low amounts of mutant DNA*,” and Bettgowda reports that in half (five) of those (ten) cases, “neither of the aliquots tested by the two methods revealed *any* mutations,” and “[i]n five other cases, one method revealed a single mutant template molecule while the other method revealed zero.” EX1008, 18. Petitioner does not acknowledge this distinction or offer any other explanation as to how Safe-SeqS and BEAMing are similar *when there are low amounts of mutant DNA*—a condition clearly present at the claimed sensitivity.¹⁷

¹⁷ Indeed, Bettgowda explicitly acknowledged that its methods produced *false-negative results* at lower ctDNA levels—*i.e.*, that *Bettgowda was missing mutations at lower concentrations* (the very point addressed by the challenged claims’ sensitivity threshold). For example, Bettgowda explained that the “factors associated with a false-negative ctDNA result” included “low CEA level” (CEA may be used as a biomarker for identifying cancer in some patients, EX1008, 1), and that this was “consistent with the idea that lower tumor burdens (reflected by normal CEA levels) are associated with lower ctDNA levels.” EX1008, 4 (“we identified 10 cases (of 206) in which *mutations were present in the primary tumors but not in the plasma*, yielding a sensitivity of 87.2%”). This further calls into question

b. Petitioner's Calculations and Assumptions Regarding Bettegowda's Single-Plex Sensitivity Are Wrong

Petitioner's suggestions that the required sensitivity can be found in Bettegowda's discussion of single-plex Safe-SeqS based on assumptions about the number of "genome equivalents" in Bettegowda's 5 mL sample are also flawed. Petitioner contends that Bettegowda's 5 mL sample contains 8,000–80,000 "genome equivalents" based on an assay in a separate reference (EX1051 ("Horlitz")) that used 66-bp amplicons to determine the number of copies of that 66-bp sequence in a sample following amplification. Pet.50 (citing EX1051); *see* EX1051, 3-4. But Horlitz confirms that the number of genome equivalents it found *depended on the length of the amplicon*: Horlitz found many *fewer* genome equivalents in the same sample using 500-bp amplicons. EX1051, 3-4. And this length is an unknown variable in Bettegowda. Bettegowda does not disclose a 66 base pair amplicon or specify the lengths of the amplicons it used to attempt to detect mutations in cfDNA with Safe-SeqS, and Petitioner does not explain why it would be reasonable to rely on Horlitz's 66-bp amplicon calculation to determine how many copies of amplicons of the (unspecified) length targeted by Bettegowda existed in the sample.

Petitioner's assumptions about Bettegowda's ability to detect "*rare*" mutations. Pet.49-50.

Petitioner's assertion that Horlitz and Bettegowda used the same *purification method* (the "QIAamp Circulating Nucleic Acid Kit") to purify cfDNA from plasma (Pet.50) does not mean that Horlitz and Bettegowda were the same in *other* respects, such as their respective amplifications of target sequences: both references are clear that this QIAamp purification of cfDNA precedes and is separate from the subsequent PCR amplification of target sequences. EX1051, 4, Fig.35.1; EX1008, 14.

Lastly, Petitioner's sensitivity arguments (and its arguments about combining Rabinowitz and Bettegowda for single-volume multiplex PCR amplification and achieving the claimed sensitivity) are premised on its assertion that Bettegowda's "Safe-SeqS was able to detect *one mutant template* in the DNA purified from *up to 5 ml* of plasma," and that the DNA templates from that 5 mL sample were "in a *single reaction*." Pet.50 (citing EX1008, 2, 16 (Bettegowda relying on Kinde 2011 (reference "40") for Safe-SeqS). In particular, Petitioner argues that a 5 mL volume of plasma would contain enough total genome equivalents such that detecting a single mutation in that overall 5 mL sample would purportedly satisfy the 0.015% sensitivity and disclose the single reaction required by the claim. Pet.50-51. But the Petition fails to mention the fact that Bettegowda initially uses only 25% of the total up to 5 mL sample and then—but only if no mutations are detected with the first 25%—Bettegowda retests the sample using another 65% of the up to 5 mL

sample. EX1008, 15.¹⁸ Petitioner thus *failed to show that the entire 5 mL sample is used “in a single reaction”* as the Petition argues. Pet.50. And beyond the broad 8,000–80,000 genome equivalent range argued by the Petition, Petitioner never addresses exactly how many genome equivalents were contained in the 5 mL samples in which only one mutant was detected. If the sample contained 8,000 genome equivalents (as Petitioner’s argument admits may be the case), a reaction would contain only 5,200 genome equivalents even assuming 65% (rather than 25%) of the sample were used in a single reaction. And if there were only one mutant template present in those 5,200 genome equivalents, detecting that mutant template would yield a sensitivity of only 0.019% and thus would not meet the claimed sensitivity. Petitioner’s failure even to address this further undermines Petitioner’s conclusions regarding Bettgowda’s sensitivity.

3. Petitioner’s Analysis of Limitations 1[C][ii] and 1[C][iv] Improperly Shifts Its Mapping of the DNA Comprising Target Loci Amplified in the “Same Reaction Volume”

Petitioner fails to clearly and consistently identify the art and disclosures it relies on for the claimed “same reaction volume” in its argued combination because

¹⁸ Bettgowda reserves the remaining 10% of the sample “to determine DNA concentration and to confirm that the plasma and tumor were derived from the same patient....” EX1008, 15.

Petitioner's mapping of the prior art *changes* between claim elements 1[C][ii] and 1[C][iv]. In discussing 1[C]*iii* Petitioner relies on *Rabinowitz* as disclosing amplifying a plurality of target loci "*together in the same reaction volume.*" Pet.46. But in discussing limitation 1[C]*iv*, Petitioner switches references, and alleges *Bettegowda* discloses a single volume that was amplified to yield the input for sequencing: Petitioner asserts that "*Bettegowda* teaches that Safe-SeqS was able to detect one mutant template... from *up to 5 ml of plasma*" (Petitioner's new single volume) and that "detecting one mutant template among 8,000–80,000 genome equivalents (1/8,000–1/80,000) *in a single reaction* would be equivalent to detecting an SNV that is present in 0.0125%-0.00125% of the cfDNA having the SNV locus. Pet.50. Petitioner then concludes that, starting with *Bettegowda* (not Rabinowitz) and its 5 mL of plasma, one of skill therefore "would expect to be able to prepare *a single reaction* containing sufficient cfDNA templates because the cfDNA purification method used by Bettegowda yields about 8,000 to more than 80,000 genome equivalents per 5 mL sample." Pet.51.

Because the Petition identifies multiple different references as the source of Petitioner's argued prior-art disclosure of the amplified "same reaction volume" whose output is then sequenced, it is unclear exactly what the Petition's proposed combination is and whether the "single reaction volume" is meant to come from Rabinowitz or Bettegowda, or how Rabinowitz is purportedly modified to achieve

the single reaction volume and related claim requirements. These failures are further reasons that Petitioner failed to carry its burden, and institution should be denied. *Mediatek, Inc. v. Mosaid Techs. Inc.*, IPR2024-00718, Pap.10, 24 (Oct. 9, 2024) (denying institution, finding that Petitioner’s analysis failed to “stat[e] which reference’s teaching is used in the combination and [did] not clearly identify[] the proposed combination”); *Personal Web Techs., LLC v. Apple, Inc.*, 848 F.3d 987, 994 (Fed. Cir. 2017) (reversing obviousness determination where there was no “clear, evidence-supported account of the contemplated workings of the combination,” which “is a prerequisite to adequately explaining and supporting a conclusion” of obviousness); *Axon*, Pap.10, 18-19 (denying institution, stating neither petitioner nor its expert “explains in sufficient detail the nature of Petitioner’s proposed modification... Petitioner does not explain in sufficient detail how the proposed modification is supposed to work”).

B. Petitioner’s Ground 4 Analysis Does Not Consistently Treat Rabinowitz as the Base Reference

The Petition initially presents Rabinowitz as the primary reference in its Ground 4 combination, describing the combination as “Rabinowitz and Bettegowda,” in that order (Pet.40-44), asserting that “*a POSA seeking to configure Rabinowitz’s cfDNA assays for detecting cancer recurrence would reasonably turn to... references like **Bettegowda***” (Pet.41), and arguing that a “POSA would have

been *motivated to modify the Rabinowitz method by sequencing a tumor...as taught by Bettegowda.*” Pet.43-44. The Petition relies on Rabinowitz for its disclosure of the underlying single-volume multiplex assays, and it is apparent that Petitioner argues Rabinowitz’s multiplexing method can be modified using Bettegowda to arrive at the claimed invention. Pet.41, 43-44, 46-48.

Certain of the Petition’s arguments, however, *improperly change this base combination in mid-claim* by turning the combination on its head, from Rabinowitz in light of Bettegowda to Bettegowda in light of Rabinowitz. For example, in the discussion of limitation 1[C][ii], instead of applying Bettegowda’s teachings to modify the single-volume multiplex PCR assays taught by *Rabinowitz*, the Petition argues POSA would use Rabinowitz’s teachings to modify the assays taught in *Bettegowda*, asserting a “POSA would have been *motivated to apply multiplex PCR of cfDNA as taught by Rabinowitz in a tumor-informed assay.... as taught by Bettegowda.*” Pet.47.

Petitioner’s expert likewise improperly changes this base combination mid-claim. For example, Dr. Lennon initially argues that “[a] POSA would have been motivated to *modify the Rabinowitz method* by sequencing a tumor biopsy to identify a plurality of tumor-specific mutations comprising one or more SNV mutations and then assaying those mutations in cfDNA, *as taught by Bettegowda,*” but, in later analyzing the same claim element, swaps Rabinowitz and Bettegowda

and asserts that “[a] POSA would have been motivated to *apply multiplex PCR as taught by Rabinowitz in a tumor-informed assay* in order to analyze target loci spanning a plurality of tumor-specific mutations *as taught by Bettegowda* without requiring separate reactions.” EX1004, ¶¶ 214, 234. Petitioner cannot establish obviousness by switching base references (and thus its argued §103 combination) mid-stream within the same ground. *See Hirsch Glass Corp. v. Cambria Co.*, IPR2022-00583, Pap.7, 23-24 (Aug. 8, 2022) (denying institution where it was “unclear whether Petitioner is proposing that a [POSITA] would select [the first reference] and modify some aspect of that reference in view of [the second reference] or the other way around”). Ground 4 thus also fails for this independent reason.

C. Petitioner’s Limitation 1[A] Arguments Fail Because Petitioner Never Explains How Rabinowitz’s Method Would Supposedly Be Improved

Petitioner argues a skilled artisan would have been motivated to modify Rabinowitz’s disclosed assay by sequencing a tumor biopsy to identify “highly specific biomarkers in cfDNA” and allow their use to guide therapeutic decisions and for ctDNA analysis. Pet.43-44 (citing EX1004, ¶215). But Petitioner insufficiently explains this conclusory assertion, and Petitioner’s expert fails to support—and instead merely parrots—it, stating that “[a] POSA would have been motivated to make this modification because of the well-known advantages of sequencing a tumor biopsy to identify mutations that serve as highly specific

biomarkers in cfDNA.” *See id.*; EX1004, ¶215 (citing EX1072, 5, 1); *see also, e.g., Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Pap.9, 15 (Aug. 24, 2022) (precedential) (denying institution and according petitioner’s expert “little weight” where the expert’s declaration was conclusory and failed to “cite to any additional supporting evidence or provide any technical reasoning to support his statement”); *Motorola Mobility LLC v. Maxell, Ltd.*, IPR2023-00110, Pap.7, 34-35 (June 15, 2023) (finding cited declaration testimony was “conclusory, unsupported, and entitled to little or no weight” where it did not provide “any additional supporting evidence or technical reasoning”).

For example, Rabinowitz’s approach *already* scans for and sequences well-known target loci to identify any mutations and therefore does not need a prior invasive procedure such as a biopsy to identify its targets. EX1009, [0228] (“methods that specifically target and/or preferentially enrich segments of DNA in the sample that are more likely to be polymorphic in the genome”), [0335] (discussing DNA probes “designed to target loci where the loci have maximal minor allele frequencies,” “designed to target where the loci have the maximum likelihood of the fetus having a highly informative SNP at those loci,” and “designed to target loci where the probes are optimized for a given population subgroup” or a “mix of population subgroups”), [0276] (“designed to amplify potentially heterozygous SNP loci on chromosomes X, Y, 13, 18, and 21 and 1 or 2”); *see also* EX1004, ¶74

(acknowledging prior art “screening assays... targeting commonly mutated regions of DNA called ‘hotspots’”). Petitioner never explains *how* Rabinowitz’s method would supposedly be improved—or *why* a skilled artisan would think it improved—by sequencing a tumor biopsy in advance of performing Rabinowitz’s multiplex cfDNA assay, given these Rabinowitz disclosures.

Petitioner fails to address these aspects of Rabinowitz, and instead ignores them in arguing a skilled artisan would have been motivated to change Rabinowitz to address an issue (identifying assay targets) that *Rabinowitz already addresses*. EX1009, [0267]; *Life Spine, Inc. v. Globus Med., Inc.*, IPR2022-01603, Pap.8, 40 (June 12, 2023) (denying institution where petitioner “has not articulated sufficient reasoning to explain why a POSITA would modify [its base reference] to address a concern [it] already addresses via a different mechanism”); *Google LLC v. Jawbone Innovations, LLC*, IPR2022-00889, Pap.12, 20 (Nov. 14, 2022) (denying institution where petitioner failed to explain “motivat[ion] to solve a problem [the reference] already solves”).

D. Petitioner’s Ground 4 Arguments Are Unclear and Incomplete

1. The Petition Improperly Mixes and Matches Separate Embodiments Without Explanation

Further, as with Ground 1 (*see* §IV.C), the Petition’s Ground 4 mapping snips and pastes together separate disclosures from across multiple different embodiments

in Bettegowda without explaining why it would have been obvious to combine those disparate embodiments—a mandatory component of any obviousness analysis. *Hewlett Packard*, Pap.9, 14-16. For example, for limitation 1[A], the Petition relies on a Bettegowda embodiment involving 136 patients with metastatic tumors (EX1008, 2-3), whereas for limitation 1[B] and 1[C][i] the Petition relies on a different and wholly separate Bettegowda embodiment relating to monitoring following EGFR blockade (EX1008, 4-6). Pet.43-45. Petitioner never even acknowledges its mixing and matching of different prior-art embodiments, and certainly does not provide the mandatory evidentiary basis required for combining them. *First Alert*, Pap.14, 20-21; *Abiomed*, Pap.9, 8-11; *Hewlett Packard*, Pap.9, 12-16. Again, Ground 4 thus also fails for this independent reason.

2. The Petition Improperly Maps Both Bettegowda and Rabinowitz for the Preamble in Violation of Clear Board Precedent

A petition must make clear “which teachings of each reference [petitioner] combines to account for all the limitations” (*ADT*, Pap.7, 13-15), and the failure to do so provides an independent basis for denying institution. Here, Petitioner violates this rule by mapping both Bettegowda and Rabinowitz as disclosing the preamble to claim 1, without explaining which (or which parts) of these references the Petition actually applies for this claim element in Petitioner’s Ground 4 mapping. Pet.42. Indeed, to the extent Petitioner seeks to *combine* Rabinowitz and Bettegowda’s

disclosures that the Petition recites as purportedly applicable to the preamble, Petitioner never explains in the Petition whether and how those references are to be combined, or why a skilled artisan would have been motivated to do so with a reasonable expectation of success. Pet.42.¹⁹ This does not permit the Board and PO to understand, assess, and respond to Petitioner's arguments because "it is not clear which teachings of each reference [petitioner] combines to account for all the limitations." *ADT*, Pap.7, 13-15. As a result, Ground 4 lacks the particularity required by §312(a)(3), and institution should be denied for this additional reason.

3. The Petition Fails to Identify the Differences Between the Claims and the Prior Art

Obviousness under §103 requires a showing that the claimed invention "as a whole would have been obvious." A key (and mandatory) component of this

¹⁹ In contrast to what is presented in the Petition, Petitioner's expert asserts that the references are to be combined to cover this claim element. EX1004, ¶221. Crediting this expert assertion that does not appear in the Petition would amount to improper incorporation by reference (*see, e.g., Cisco Sys., Inc. v. C-Cation Techs., LLC*, IPR2014-00454, Pap. 12, 9-10 (Aug. 29, 2014) (informative)), and this conflict only adds to the confusion of what aspects of which reference the Petition relies on for which aspects of the claim.

analysis is identifying the differences between the prior art and the claimed invention. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17 (1966). But the Petition fails to identify the differences between the subject matter claimed in the '596 patent, on the one hand, and Bettgowda and Rabinowitz, on the other, effectively “plac[ing] the burden on [the Board] to sift through the information presented by Petitioners, determine where each element of [the claims] is found in [the prior art], and identify any differences between the claimed subject matter and the [prior art].” *Google Inc. v. EveryMD.com LLC*, IPR2014-00347, Pap. 9, 25, 27 (May 22, 2014). Indeed, to make the §314(a) threshold, Petitioner was required to “identify sufficiently or precisely the difference between the prior art and the claims.” *John Crane, Inc. v. Finalrod IP, LLC*, IPR2016-01827, Pap.6, 11 (Jan. 31, 2017). Yet, in almost 17 pages of text devoted to obviousness based on Ground 4, the Petition never once identifies or explains any difference between the claimed invention and the disclosures of either Rabinowitz or Bettgowda. Having failed to “set out what [Petitioner] regards to be any precise difference” between the Challenged Claims, on the one hand, and Bettgowda and Rabinowitz, on the other, Petitioner falls short of even the most basic requirements of obviousness. *Johns Manville Corp. v. Knauf Insulation, Inc.*, IPR2015-01402, Pap.18, 12-14 (Oct. 21, 2015). Petitioner’s failure to perform that essential analysis is fatal to its argument that the Challenged Claims as a whole are obvious, and is another freestanding

reason to deny institution. *E.g., Whole Space Indus. Ltd. v. Zipshade Indus. (B.V.I.) Corp.*, IPR2015-00488, Pap.14, 15-16, 18 (July 24, 2015) (denying institution in part for failure to “identify the differences between the prior art and the claims at issue” and explaining that “Petitioner has not provided a persuasive, fact-based analysis of whether the claimed invention as a whole would have been obvious”).

VIII. Institution Should Also Be Denied Under §314(a)

Although the Petition has clearly failed to do so, even if the Petition had satisfied its burden as to one or more of the arguments it presents, the Board should still exercise its discretion here to deny institution because the overwhelming bulk of its arguments are meritless. United States Patent and Trademark Office, *FAQs for Interim Processes for PTAB Workload Management*, <https://www.uspto.gov/patents/ptab/faqs/interim-processes-workload-management> (last visited May 3, 2025), FAQ No. 9 (merits panel “will not address discretionary considerations, *except where the petition presents an insufficient number of challenges that meet the reasonable likelihood standard indicating that institution is an inefficient use of resources*”). “[E]ven when a petitioner demonstrates a reasonable likelihood of prevailing with respect to one or more claims,” “institution of review remains discretionary.” *Deeper, UAB v. Vexilar, Inc.*, IPR2018-01310, Pap.7, 41-43 (Jan. 24, 2019) (informative) (denying institution where “Petitioner demonstrate[d] a reasonable likelihood of prevailing with respect to only two claims

on one asserted ground”). The Board thus has discretion to “consider the number of claims and grounds that meet the reasonable likelihood standard when deciding whether to institute inter partes review under” §314(a). *Chevron Oronite Co. v. Infineum USA L.P.*, IPR2018-00923, Pap.9, 10-11 (Nov. 7, 2018) (informative). Institution should be denied here given the above-discussed substantive infirmities with each of the Grounds herein.

IX. Conclusion

For the foregoing reasons, the Board should deny institution.

Respectfully submitted,

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CERTIFICATE OF WORD COUNT

The undersigned certifies that the foregoing Patent Owner's Preliminary Response Under 37 C.F.R. § 42.107 complies with the type-volume limitation in 37 C.F.R. §42.24(c)(1). According to the word-processing system's word count, the brief contains 13,510 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a)(1).

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of Patent Owner's Preliminary Response Under 37 C.F.R. § 42.107 and the accompanying exhibits have been served in their entirety on May 14, 2025, by causing the aforementioned documents to be electronically mailed to the following attorneys of record for the Petitioner listed below.

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