

**UNITED STATES PATENT AND TRADEMARK OFFICE**

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**BEFORE THE PATENT TRIAL AND APPEAL BOARD**

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NEOGENOMICS LABORATORIES, INC.  
Petitioner,

v.

NATERA, INC.  
Patent Owner.

Patent No. 11,319,596

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*Inter Partes* Review No. IPR2025-00455

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**PETITION FOR *INTER PARTES* REVIEW  
UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. § 42.100 *et seq.***

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| Exhibit Description                                                                                                                                                                                                                                                              | Exhibit |
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| <i>Natera, Inc. v. NeoGenomics Laboratories, Inc.</i> , No. 1:23-cv-626, Dkt No. 354, Plaintiff Najera, Inc.’ Opposition to Defendant NeoGenomics’ Motion for Issuance of Letters of Requests to Examine Persons Pursuant to Hague Evidence Convention, (M.D.N.C. Dec. 17, 2024) | 1103    |
| Mardis, <i>Next-Generation DNA Sequencing Methods</i> , 9 Ann. Rev. Genomics Hum. Genet. 387 (2008)                                                                                                                                                                              | 1104    |
| Meyerson, et al., <i>Advances in understanding cancer genomes through second-generation sequencing</i> , 11 Nature Genetics 685 (2010)                                                                                                                                           | 1105    |
| Labrousse, et al., <i>Evaluation of a tumor informed MRD assay with contrived breast cancer samples</i> , AACR General Meeting (2003)                                                                                                                                            | 1106    |

NeoGenomics Laboratories, Inc. (“Petitioner”) petitions for *inter partes* review of claims 1, 2, 5, and 10–18 of U.S. Patent No. 11,319,596 (the “’596 patent” (Ex.1001)) pursuant to 35 U.S.C. §§ 311–319 and 37 C.F.R. § 42.100 *et seq.*

## **I. INTRODUCTION**

The ’596 patent claims a method for preparing biological samples for monitoring the progression of cancer in a subject. First, a tumor biopsy sample of the subject is sequenced and one or more single nucleotide variant (“SNV”) mutations are identified. Second, the sequence results are evaluated to determine target loci spanning the identified SNVs. Finally, cell-free DNA (“cfDNA”) obtained from the subject at multiple time points is assayed based on the target loci, with the target loci being amplified through targeted multiplex PCR amplification and sequenced via high-throughput sequencing.

The Examiner recognized that none of these steps was new, either individually or in combination. But the Examiner nonetheless allowed the claims after they were amended to require “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” (the “0.015% limitation”). The Examiner noted that the “closest” prior art reference only taught a “detection limit of 0.1% for SNV mutations in cell-free DNA by sequencing.” After allowance, the Examiner cited a

reference that taught “detection of mutations with frequencies around  $10^{-6}$ ” but that method was incompatible with targeted multiplex amplification according to the reference.

The Examiner’s conclusion was error, because the Examiner did not have the benefit of references such as Diaz, Kinde 2013, and Bettegowda, all of which describe the same underlying technology of PCR/multiplex PCR and high-throughput sequencing. Diaz teaches cfDNA assays for tumor-specific mutations using PCR and high-throughput sequencing and discusses the problem of distinguishing mutations from errors, which imposes a technical limit on sensitivity. Addressing that problem, Kinde 2013 and Bettegowda disclose error-corrected sequencing methods that detect rare “somatic mutations” at detection levels below the 0.015% limitation and are compatible with multiplex amplification.

Patent Owner has no right to a monopoly on the use of pre-existing methods to achieve known results. The Board should institute *inter partes* review and then cancel every challenged claim.

## II. BACKGROUND

### A. State Of The Art By 2014<sup>1</sup>

Scientists have long known that the plasma of cancer patients contains circulating cell-free DNA from both normal cells and cancer cells. (Ex.1004, ¶72.) By 2008, scientists knew that cancers could be diagnosed and monitored based on the presence of cell-free circulating tumor DNA (“ctDNA”) and developed assays to leverage their findings. (*Id.*, ¶¶73–75.) These assays—called “tumor-informed assays”—first identified mutations in a tumor biopsy, *e.g.*, via whole exome sequencing, and then tracked those mutations in ctDNA over time. (*Id.*, ¶¶74–76.)

The success of these assays drove interest in tracking rarer and rarer SNV mutations. (*Id.*, ¶¶84–90.) But that interest faced a technical challenge: sequencing error rates could overwhelm the true signals for rare SNVs. (*Id.*, ¶87.) By 2014, scientists had developed molecular barcoding and error correction

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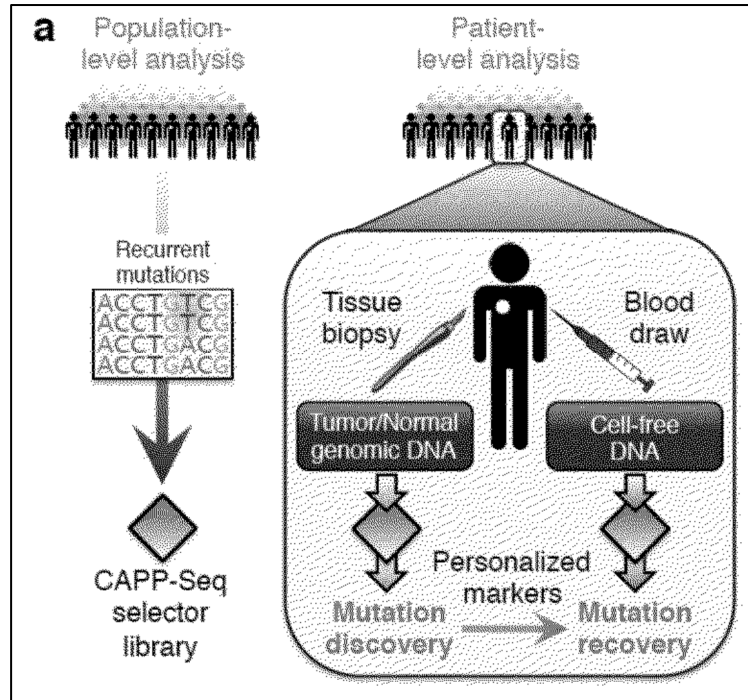
<sup>1</sup> As discussed *infra*, the critical date (or priority date) of the ’596 patent is no earlier than April 21, 2015. Petitioner sets out the state of the art by 2014, however, because Patent Owner has apparently asserted in the co-pending litigation that the critical date is no later than April 21, 2015 and because the ’596 patent’s earliest provisional application is dated April 21, 2014. (Ex.1001, 1; Ex. 1012.)

approaches that allowed SNVs to be detected at levels well below 0.015% of the DNA having the SNV locus. (*Id.*, ¶¶87–89.) These included methods that were compatible with multiplex PCR amplification. (*Id.*, ¶88.) By 2014, such error correction methods had already been performed to detect ctDNA mutations. (*Id.*, ¶90.)

### **B. The '596 Patent**

The '596 patent was filed on February 28, 2019. Original claim 1 recited only two steps: “performing whole exome sequencing on a tumor biopsy sample of the subject to identify a plurality of tumor-specific mutations” and “assaying cell-free DNA isolated from a plurality of biological samples obtained from the subject at different time points for the presence or absence of the tumor-specific mutations, thereby monitoring the progression of the cancer.” (Ex.1003, 1597.)

As discussed above, tumor-informed assays were well known, and the Examiner rejected claim 1 as anticipated by Diehn et al. (“Diehn”; Ex.1030) based in part on Fig. 1a below:



(Ex.1003, 682.) The Examiner also rejected dependent claims 14–16—directed to targeted multiplex PCR amplification, 10–50 target loci, and high-throughput sequencing—as obvious based on Diehn in view of Mertes et al., Nguyen-Dumont et al. and Wang et al. (Exs. 1032, 1033, 1034). (Ex.1003, 684–85.) For example, she cited Mertes for the benefits of PCR-based enrichment over Diehn’s hybridization capture. (*Id.*, 685.)

On October 16, 2020, Patent Owner conducted an interview with the Examiner, where it argued that “the invention lies in the determination of mutations in a tumor obtained from a subject and following up the mutations in cell-free DNA obtained from the subject” unlike Diehn that “tests for mutations in

a pre-selected set of genes.” (*Id.*, 647.) But the Examiner did not find the argument persuasive.

In response, Patent Owner amended claim 1 to recite a new step of “evaluating results of the sequencing on the tumor biopsy sample to determine a plurality of target loci specific to the subject . . .” (*Id.*, 622.) For the assaying step, Patent Owner added that the step comprises “amplifying the isolated cell-free DNA using primers specific to the plurality of target loci for the individual subject” and “sequencing the amplified DNA comprising the plurality of target loci.” (*Id.*) It then argued that Diehn and the other references did not meet the new recitations directed to target loci specific to the subject. (*Id.*, 618–19.) But, once again, the Examiner was not convinced and rejected the claims, this time citing another Diehn et al. publication with additional details regarding tumor-informed assays (Ex.1031). (Ex.1003, 561–66.)

Based on dependent claims 14 and 16, Patent Owner further amended the assaying step of claim 1 to recite performing “targeted multiplex PCR amplification” of target loci “together in a same reaction volume,” and performing “high-throughput” sequencing. (*Id.*, 469.) In addition, Patent Owner added the 0.015% limitation. (*Id.*) It argued that none of the cited references disclosed performing targeted multiplex PCR on cfDNA (as opposed to cellular DNA).

(*Id.*, 474–75.) And it argued that none of the references taught high-throughput sequencing and the 0.015% limitation. (*Id.*)

The Examiner was aware of a reference, Talasaz (Ex.1035), that taught utilizing multiplex PCR and high-throughput sequencing with ctDNA, but did not disclose the 0.015% limitation. Based on that limitation, she allowed the claims:

4. Applicant's claim amendments overcame all of the previously presented rejections. 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 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).

(Ex.1003, 334.)

After allowance, Patent Owner submitted hundreds of references. In a follow-on Notice of Allowance, the Examiner noted that one reference (Kennedy *et al.*; Ex.1036) taught “detection of mutations with frequencies around  $10^{-6}$ ” but that the method was incompatible with target-specific multiplex amplification according to Kennedy. (Ex.1003, 62–63.) As discussed *infra*, the Examiner was not aware of art, such as Diaz, Kinde 2013, and Bettegowda, that disclose tumor-informed assays compatible with targeted multiplex amplification and high-throughput sequencing and that meet the 0.015% limitation.

### **C. Level Of Ordinary Skill In The Art**

A person of ordinary skill in the art (“POSA”) would have had, by the critical date,<sup>2</sup> at least (1) a Master’s degree and/or Ph.D. in biochemistry, molecular genetics, pharmacology, or an equivalent discipline with applications in genomics and (2) at least five years of academic or industrial laboratory experience.

(Ex.1004, ¶64.)

A POSA would have had a deep understanding of genomics, including nucleic acid detection, quantification, and genotyping and would understand the underlying scientific principles to such. (*Id.*, ¶65.) A POSA also would have been apprised of then-current literature on genomic assays, such as multiplex PCR, NGS techniques, methods for detecting SNVs, and the use of cfDNA in genotyping. (*Id.*, ¶66.) A POSA would also have generally understood the processes behind the development of DNA mutation-based illnesses, such as cancers, and would have been apprised of the recent literature in those fields. (*Id.*)

### **III. CLAIM CONSTRUCTION**

Claim construction for the ’596 patent has just begun in the co-pending litigation. On January 13, 2025, the parties submitted a Joint Claim Construction

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<sup>2</sup> A POSA’s qualifications would have been, for the purposes of this proceeding, roughly the same in 2014 as in 2015. (Ex.1004, ¶67.)

Statement (Ex.1073) along with accompanying Exhibit A (Ex.1074). Patent Owner's statements in Exhibit A reflect how Patent Owner currently understands the scope of certain terms.

First, for “performing high-throughput sequencing of the amplified DNA” (in the last step of claim 1), Patent Owner contends that there may be “intermediate steps after multiplex amplification but before sequencing.” (Ex.1074, 9.)

Second, Patent Owner contends that “the isolated cell-free DNA” (in the penultimate step of claim 1) “includes cell-free DNA isolated from any of the plurality of biological samples obtained from the subject at different time points.” (*Id.*, 1.)

Petitioner disagrees with Patent Owner's understanding above but adopts them for the purposes of this proceeding.<sup>3</sup> *See Gen. Elec. Co. v. Vestas Wind Sys. A/S*, No. IPR2018-00928, Paper 9, 16 (P.T.A.B. Nov. 5, 2018) (petitioner can argue “more than one construction, including one that it believes is incorrect, such as patent owner's”). The Board therefore need not construe either term. *See*

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<sup>3</sup> Petitioner reserves the right to challenge Patent Owner's understanding of these terms in the district court proceeding and to provide its understanding of the terms for that proceeding.

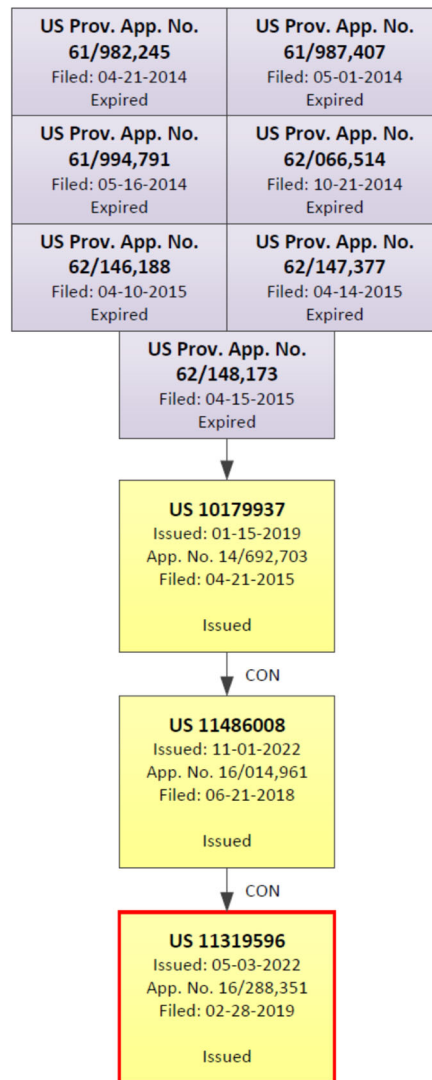
*Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1375 (Fed. Cir. 2019) (claim construction only required if “necessary to resolve the controversy”) (cleaned up).

#### **IV. PRECISE REASONS FOR RELIEF REQUESTED**

Pursuant to 37 C.F.R. § 42.104(b), Petitioner requests cancellation of claims 1, 2, 5, and 10–18 of the ’596 patent based on five references in four grounds and the accompanying declaration of Dr. Niall Lennon (Ex.1004):

| <b>Ground</b> | <b>35 U.S.C. §</b> | <b>Claims</b>             | <b>Prior Art</b>                            |
|---------------|--------------------|---------------------------|---------------------------------------------|
| 1             | 103                | 1, 2, 5, 10, 12–14, 16–18 | Diaz (Ex.1006) & Kinde 2013 (Ex.1007)       |
| 2             | 103                | 1, 2, 5, 10–14, 16–18     | Diaz, Kinde 2013, & Rabinowitz (Ex.1009)    |
| 3             | 103                | 15                        | Diaz, Kinde 2013, & Fleischhacker (Ex.1010) |
| 4             | 103                | 1, 2, 10–13, 15–18        | Rabinowitz & Bettegowda (Ex.1008)           |

The ’596 patent is an AIA patent that claims priority to a number of applications going back to April 21, 2014 as shown below (Ex.1002):



Petitioner submits the challenged claims are entitled to a priority date no earlier than April 21, 2015—the filing date of the grandparent application (Ex.1019) that matured into the ’937 patent. (Ex.1004, ¶¶58–62.) The disclosures of “0.015%” as a threshold for SNV detection first appeared on April 21, 2015 in the priority chain. Based on that priority date, all five references qualify as prior art under 35 U.S.C. § 102(a)(1). Diaz, Kinde 2013, Rabinowitz, Fleischhacker,

and Bettegowda were published at least by February 20, 2014, January 9, 2013, October 25, 2012, October 7, 2006, and February 19, 2014, respectively—all of which predate the '596 patent's April 21, 2015 priority date. (Ex.1006, 1; Ex.1007, 1; Ex.1009 (code 43); Ex.1010, 1; Ex.1008, 1; *see also* Ex.1004, ¶¶92–97; Ex.1011.)<sup>4</sup>

In the co-pending litigation, Patent Owner appears to agree, stating that the priority date is no later than April 21, 2015. If Patent Owner attempts to assert an earlier priority date, Petitioner notes that the first mention of detecting a SNV present at any level was in U.S. Provisional Application No. 62/066,514, filed on October 21, 2014 (Ex.1015). Petitioner does not consider this mention as establishing entitlement to an October 2014 priority date. (Ex.1004, ¶¶61–62.) In any event, whether Patent Owner relies on this October 2014 date or even the earliest priority date of April 21, 2014, all five of the references are still prior art under § 102(a)(1) based on their respective publication dates as discussed above.

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<sup>4</sup> A citation to an exhibit page number is to the stamped page number, except for patents, patent publications and declaration exhibits.

## **V. GROUND 1: DIAZ & KINDE 2013**

### **A. Summary Of Diaz**

Diaz discloses various methods for performing “liquid biopsies” involving genotyping circulating tumor DNA at multiple time points. (Ex.1006, 1.) For example, it describes tumor-informed assays comprising “identifying a specific mutation or mutations in the tumor tissue” and then targeting and quantifying the level of ctDNA at a particular time point. (*Id.*, 4.) According to Diaz, such tumor-informed assays have particular advantages for monitoring ctDNA over time via liquid biopsies. Specifically, identification of “personalized markers based on the unique mutational profiles of resected tumors” is advantageous because it allows for “exquisitely high specificity” to evaluate postoperative levels of ctDNA. (*Id.*)

Diaz also teaches that “PCR-based digital approaches have been updated with techniques that use next-generation sequencing (NGS) to identify rare variants in complex mixtures of DNA,” and that these techniques have allowed “multiple genes of interest” to be investigated “in one sample.” (*Id.*, 2.) A POSA would have understood that Diaz’s references to “next-generation sequencing” or “NGS” meant high-throughput sequencing. (Ex.1004, ¶102.)

In the context of identifying rare variants, Diaz discusses the problem of distinguishing mutations from errors. (*Id.*, 3.) Polymerase errors, according to Diaz, impose a technical limit on sensitivity for detecting a true mutation. (*Id.*) To

address this challenge, Diaz points to Safe-SeqS (discussed below) as a solution “aimed at increasing overall sensitivity” for detecting mutations in ctDNA in the context of next-generation sequencing. (*Id.*, 3 (citing Ex.1049).)

## **B. Summary Of Kinde 2013**

Kinde 2013<sup>5</sup> discloses application of an error-corrected sequencing method to detect rare tumor-specific “somatic mutations.” (Ex.1007, 1, 4.) Kinde 2013 discloses an improved version of the Safe-SeqS method referenced in Diaz, as Diaz cited to a Kinde 2011 article (Ex.1049). (Ex.1004, ¶¶104–108, 111.) Safe-SeqS became a widely-cited error-correction method and, by 2014, Safe-SeqS had been applied to cfDNA samples. (Ex.1004, ¶¶89–90.)

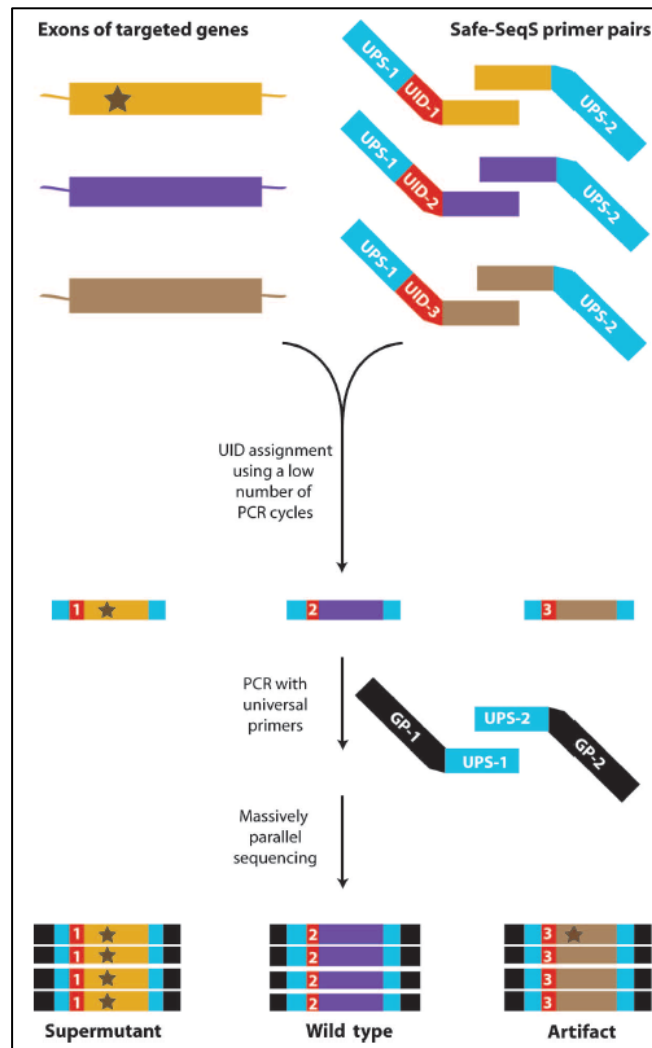
The improved Safe-SeqS method (below) comprises amplifying template nucleic acids using primers comprising binding sites for universal primers (“UPS,” blue), a unique identifier (“UID,” red) and target-specific sequences (colors matching the target in Fig. 2). (Ex.1007, 5.) Kinde 2013 discloses that the templates and primers are then “combined into a single PCR compartment and a UID is assigned to each targeted template, along with UPS binding sites, after a low number of PCR cycles (“UID assignment”).” (*Id.*) Next, the “Safe-SeqS

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<sup>5</sup> Kinde 2013 includes supplementary materials and provides a link to them. (Ex.1007, 11.)

primers are removed, and subsequent PCR is performed with primers containing UPS sites, as well as sequences for attachment to the sequencing instrument (“GP,” black) to prepare the templates for massively parallel sequencing.” (*Id.*)

The “multiplexed assays” using multiplex PCR are “performed in a similar fashion.” (*Id.*, 8, 18.)



(Ex.1007, Fig. 2.)

Kinde 2013 discloses that the UID assignment, which can be performed as a multiplex PCR, allows true SNVs to be distinguished from errors. Kinde 2013 explains that a true SNV present in template DNA before sample preparation will be present in the majority “of the sequenced daughter molecules sharing the same UID[.]” (*Id.*, 5.) According to Kinde 2013, “[in] contrast, artifactual mutations caused by sample preparation or sequencing are unlikely to be observed in most other daughter molecules sharing the same UID (‘Artifact’).” (*Id.*) Based on this principle, Kinde 2013 distinguished true SNVs from artifactual mutations “by requiring that >50% of reads sharing the same UID contained the identical mutation.” (*Id.*, 19.) Kinde 2013 disclosed that its improved Safe-SeqS approach is capable of detecting 1 mutant template among as many as 1,000,000 wild-type templates, including a specific example of detecting a mutation present at 0.01% of the DNA having the locus. (*Id.*, 4, 6.)

### **C. Combination Of Diaz And Kinde 2013**

For starters, Diaz and Kinde 2013 are analogous art because they are in the same field as the '596 patent. *Wyers v. Master Lock Co.* 616 F.3d 1231, 1238–39; Ex.1001, 1:28–31; Ex.1004, ¶¶43, 110. Both references relate to detection of tumor-specific SNVs. (*See, e.g.*, Ex.1006, 2–6; Ex.1007, 309–10 (table S3) (showing detection of single nucleotide variants).)

A POSA reading Diaz would have been motivated to develop tumor-informed cfDNA assays with improved sensitivity for detecting rare tumor-specific mutations as taught by Kinde 2013. Diaz discusses the problem of distinguishing mutations from errors. (*See* Ex.1006, 3.) To address this challenge, Diaz points to Safe-SeqS (citing Kinde 2011) as a solution “aimed at increasing overall sensitivity” for detecting mutations in ctDNA in the context of next-generation sequencing. (Ex.1006, 3 (citing Ex.1049).) Kinde 2013 discloses an improved version of Safe-SeqS that is both compatible with multiplex PCR and capable of detecting SNVs present at levels well below 0.015% of the DNA having the SNV locus, thereby teaching what the Examiner believed was missing from the prior art. (Ex.1007, 4–5; Ex.1004, ¶¶109–20.)

**D. Diaz And Kinde 2013 Render Obvious Claims 1, 2, 5, 10, 12–14, And 16–18**

**1. Claim 1**

**a. Preamble<sup>6</sup>**

*A method for preparing biological samples useful for monitoring the progression of cancer in a subject, the method comprising:*

Diaz discloses applications of liquid biopsies including monitoring tumor dynamics, monitoring minimal residual disease, and evaluation of early treatment response:

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<sup>6</sup> For this Petition only, Petitioner assumes the preamble is limiting for all grounds.

| Table 1. Applications of Liquid Biopsy                      |  |
|-------------------------------------------------------------|--|
| Application                                                 |  |
| Early detection                                             |  |
| Assessment of molecular heterogeneity of overall disease    |  |
| Monitoring of tumor dynamics                                |  |
| Identification of genetic determinants for targeted therapy |  |
| Evaluation of early treatment response                      |  |
| Monitoring of minimal residual disease                      |  |
| Assessment of evolution of resistance in real time          |  |

(Ex.1006, 2; Ex.1004, ¶¶121–23.)

**b. Limitation 1[A]**

*(a) 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;*

Diaz describes methods wherein “[a] mutation profile was determined from each patient’s resected tumor, and this personal and unique molecular signature was then used” to track the particular tumor-specific mutations for each patient in a personalized cfDNA assay. (Ex.1006, 4; Ex.1004, ¶¶124, 127.) A POSA would understand that this approach involves sequencing a tumor biopsy. (*Id.*, ¶125.)

Kinde 2013 also teaches this limitation. (*Id.*, ¶126.)

**c. Limitation 1[B]**

*(b) 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; and*

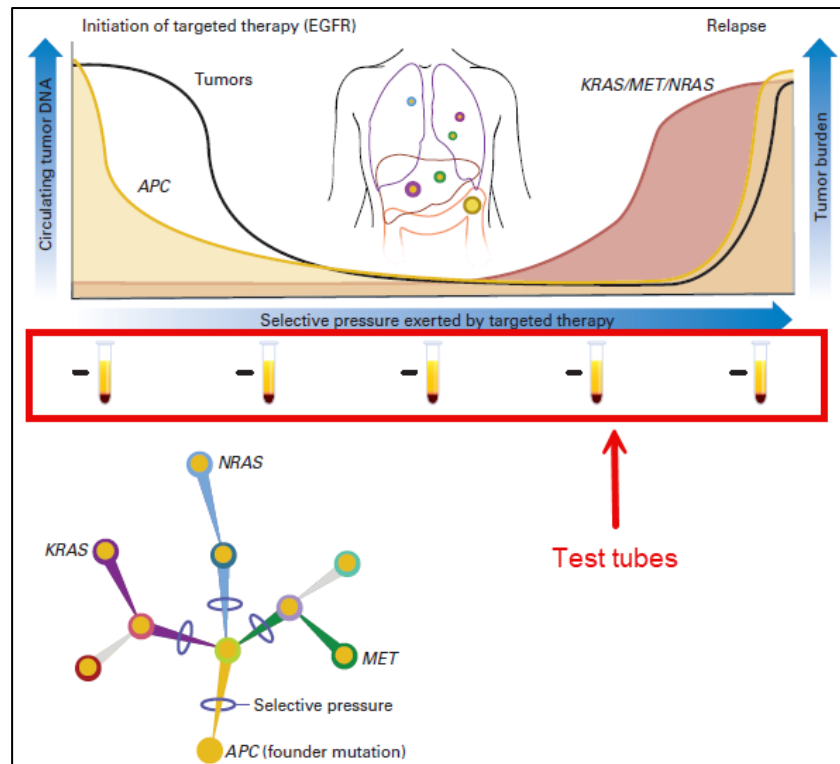
Diaz teaches that the mutations identified in the tumor tissue are used to “target and quantify the level of ctDNA.” (Ex.1006, 4.) A POSA would understand that targeting in this context involves identifying and targeting loci comprising the tumor-specific mutations taught by Diaz. (Ex.1004, ¶128.)

Kinde also discloses this limitation. (*See* Ex.1007, 3 (“12,795 somatic mutations were identified in the 22 sequenced cancers”); *see also id.*, 16 (describing evaluating the results of the sequencing a tumor sample to identify mutations).) Kinde also discloses designing primers to detect mutations identified in the sequenced cancers. (*Id.*, 17.) A POSA would understand that such primers amplify target loci wherein each target locus spans a tumor-specific mutation. (Ex.1004, ¶129.)

**d. Limitation 1[C][i]**

*(c) assaying cell-free DNA isolated from a plurality of biological samples obtained from the subject at different time points, wherein the assaying comprises:*

Diaz discloses “[c]ontinuous monitoring of plasma DNA” to detect mutations in tumor DNA. (Ex.1006, 5.) In Diaz’s Fig. 3, for example, “[t]est tubes represent samples of plasma from which circulating free DNA is extracted and used to monitor the presence of cancer-specific aberrations.” (*Id.*; Ex.1004, ¶¶130–31.)



(Ex.1006, Fig. 3 (cropped and annotated).)

**e. Limitation 1[C][ii]**

*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; and*

Diaz discloses that “PCR-based [] approaches” have been updated to use “next-generation sequencing (NGS) to identify rare mutant variants in complex mixtures of DNA” wherein “multiple genes of interest can be investigated in one sample.” (*Id.*, 2.) 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. (Ex.1004, ¶¶133, 83.) Multiplex PCR also has the advantage of requiring only a single reaction to analyze multiple genes or loci of interest in one sample. (*Id.*, ¶133.) Indeed, multiplex PCR is faster, less expensive, and less cumbersome compared to performing PCR for each target DNA sequence in a separate reaction or container. (*Id.*, ¶79.)

Furthermore, Kinde 2013 discloses multiplex PCR using primers comprising unique identifier sequences. (Ex.1007, 5, 8; Ex.1004, ¶¶118–119.) And by 2014, multiplex PCR of isolated cfDNA followed by NGS of the amplified DNA was within the knowledge of a POSA. (*Id.*, ¶¶138, 80, 83.) Use of molecular barcodes—synonymous with unique identifier sequences—in primers for multiplex amplification of cfDNA had also been described. (*Id.*, ¶120.) Therefore, a POSA would reasonably expect to succeed in using Kinde’s unique identifiers in primers for multiplex amplification from cfDNA. (*Id.*)

**f. Limitation 1[C][iii]**

*performing high-throughput sequencing of the amplified DNA comprising the plurality of target loci to obtain sequence reads,*

Diaz teaches that “PCR-based [] approaches” have been updated to use “next-generation sequencing (NGS) to identify rare mutant variants in complex mixtures of DNA” wherein “multiple genes of interest can be investigated in one sample.” (Ex.1006, 2; *see also* Ex.1004, ¶¶136–38.)

**g. Limitation 1[C][iv]**

*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.*

For ctDNA assays, Diaz discusses the problem of distinguishing mutations from errors. (See Ex.1006, 3.) Polymerase errors, according to Diaz, impose a technical limit on sensitivity for detecting a true mutation. (*Id.*) A POSA would have been motivated to accurately detect mutations at or below 0.015%, because “the fraction of circulating DNA contributed from the tumor varies greatly, between 0.01% and more than 90%” and the ctDNA fraction can even be lower than 0.01%. (*Id.*, 2; see also *id.*, 3; Ex.1004, ¶113.) To address this challenge, Diaz points to Safe-SeqS (citing Kinde 2011) as a solution “aimed at increasing overall sensitivity” for detecting mutations in ctDNA in the context of next-generation sequencing. (Ex.1006, 3 (citing Ex.1049).)

Kinde 2013 discloses an improved version of the Safe-SeqS solution for increased sensitivity. (Ex.1007, 4–5; see also Ex.1004, ¶¶105–108.) Kinde 2013 uses modified target-specific primers comprising “unique identifier” sequences for single-plex or multiplex amplification of target loci. (Ex.1007, 4–5.) The unique identifiers are used to identify families of sequencing reads originating from the same template DNA molecule, allowing true mutations to be distinguished from errors. (*Supra* § V.B.) According to Kinde 2013, this solution is designed to “reliably identify a rare population of mutant alleles among a great excess of wild-

type alleles.” (Ex.1007, 4.) Kinde teaches that its improved Safe-SeqS approach is capable of detecting mutant templates present at levels even below 0.01% (down to 1 mutant template in 1,000,000 wild-type templates, or 0.0001%). (*Id.*, 4; Ex.1004, ¶¶139–41.) Kinde further discloses using its improved Safe-SeqS for multiplex amplification. (*See, e.g., id.*, 5; *see also* Ex.1004, ¶142.)

The problem of distinguishing SNVs from artifactual errors and the Safe-SeqS error correction solution were also widely discussed in the art by the earliest possible priority date, including application of Safe-SeqS to cfDNA. (*See, e.g.,* Ex.1048, 7 (for cfDNA analysis, explaining that “[t]argeted assays have the promise of reduced cost and can, in principle, be combined with molecular bar-coding strategies that may reduce sequencing and PCR error rates”) (citing Ex.1049); Ex.1004, ¶114.)

A POSA would reasonably have expected to detect an SNV mutation that is present in less than or equal to 0.015% of the cfDNA having the SNV locus. (*Id.*, ¶143.) Kinde 2013 teaches that its improved Safe-SeqS is capable of detecting mutations present at levels as low as one mutant template among 1,000,000 wild-type templates (Ex.1007, 4), and Kinde 2013 demonstrates detection of an SNV present at less than 0.015% for PAP 026. (*Id.*, 6 (Fig. 3), 309 (table s3); *see also* Ex.1004, ¶¶144–45 (explaining that a POSA would reasonably expect to succeed in performing Safe-SeqS on reasonable input amounts of cfDNA of at least around

7,000 templates per reaction)). Kinde 2013 also discloses a higher limit of detection (0.1%) using more stringent SNV detection parameters for a mutation “agnostic” screening assay. A POSA would understand, however, such stringent detection parameters are not required when the mutations to be detected are known *a priori*, as is the case in a tumor-informed assay. (*Id.*, ¶¶119, 145.)

A POSA would also have reasonably expected to succeed in applying Safe-SeqS barcodes and error-correction methods to cfDNA. (*Id.*, ¶¶116–17.) Before the earliest possible priority date for the ’596 patent, Safe-SeqS had already been applied in a tumor-informed assay to analyze tumor-specific mutations in serial plasma samples. (*See, e.g.*, Ex.1050 (“[the] same mutation” assayed in tumor tissue was “queried and quantified in plasma using a [massively parallel sequencing] platform (Safe SeqS)”; Ex.1008, 2, 16 (disclosing that Safe-SeqS amplification and sequencing was able to detect one mutant template in the DNA purified from up to 5 ml of plasma); Ex.1004, ¶¶116–17.)

Kinde 2013 teaches that its improved Safe-SeqS approach described “is capable of detecting 1 mutant template among 5000 to 1,000,000 wild-type templates, depending on the amplicon and the position within the amplicon that is queried.” (Ex.1007, 4.) This is because mutations that preexist in template DNA before sample preparation (*e.g.*, true SNVs) can be distinguished from artifactual mutations caused by sample preparation or sequencing. (Ex.1004, ¶139; Ex.1007,

4–5, 19.) Only base changes that represent true SNVs will be present in the majority of sequence reads sharing the same UID. (*Id.*)

Although Kinde 2013 discloses detecting an SNV present at 0.01% for a liquid Pap smear (not for cfDNA), a POSA would reasonably expect to achieve detection of an SNV present in less than or equal to 0.015% of the cfDNA having the SNV locus in the context of a cfDNA assay. (Ex.1004, ¶¶116–117.) As discussed *supra*, Safe-SeqS had also been applied to cfDNA by 2014. (*Id.*)

Kinde 2013 also teaches that its improved Safe-SeqS assay is compatible with multiplex PCR, and demonstrates multiplex PCR followed by high-throughput sequencing. (See Ex.1007, 5; Ex.1004, ¶¶142, 145.) As an example, Kinde 2013 demonstrates application of its improved Safe-SeqS assay with multiplex PCR as a screening test to target regions from commonly mutated cancer genes. (*Id.*)

## **2. Claim 2**

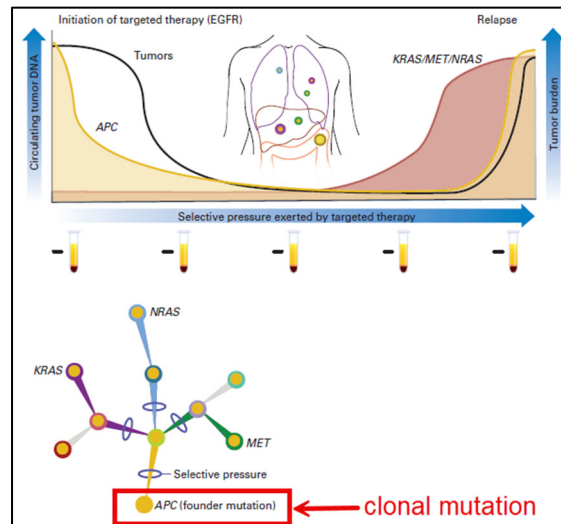
*The method of claim 1, wherein the cell-free DNA comprises circulating tumor DNA.*

Diaz discloses that cfDNA comprises “[c]irculating tumor DNA,” also referred to as “ctDNA.” (Ex.1006, 3–4; Ex.1004, ¶146.)

## **3. Claim 5**

*The method of claim 1, wherein the tumor-specific mutations comprise one or more clonal SNV mutations.*

Diaz teaches using DNA from a primary tumor to identify a “founder mutation,” which a POSA would understand is a clonal mutation. (Ex.1004, ¶¶147–48.)



(Ex.1006, Fig. 3 (cropped and annotated).)

#### 4. Claim 10

*The method of claim 1, wherein the method further comprises designing targeted PCR assays for the tumor-specific mutations identified in the cancer sample.*

As discussed above, Kinde 2013 discloses identifying tumor-specific mutations in the cancer sample. (Ex.1007, 3, 16.) Kinde 2013 also discloses designing primers for targeted PCR assays to detect the tumor-specific mutations identified in the sequenced cancers. (*Id.*, 17.) Kinde 2013 teaches that the primers were designed using Primer3 software (*id.*), one of the same primer design methods disclosed in the '596 patent (Ex.1001, 106:35–39). Kinde 2013 also discloses designing Safe-SeqS primers and its improved Safe-SeqS method for

multiplex amplification in a single reaction volume. (Ex.1007, 5–8.) Therefore, a POSA would have found it obvious to design targeted PCR assays for the tumor-specific mutations identified in the cancer sample in view of Diaz and Kinde 2013. (Ex.1004, ¶149.)

## **5. Claim 12**

*The method of claim 1, wherein the method further comprises detecting recurrence and/or metastases of the cancer from the tumor-specific mutations detected in the cell-free DNA.*

Diaz teaches in an example that “[a]ll patients with detectable postoperative levels of ctDNA experienced recurrence, whereas all patients with undetectable postoperative levels of ctDNA remained disease free.” (Ex.1006, 4.) Furthermore, a POSA would understand that applications of the cfDNA assay such as minimal residual disease monitoring described by Diaz include detecting recurrence. (Ex.1004, ¶150.)

## **6. Claims 13, 14 and 16**

*Claim 13: The method of claim 1, wherein the cancer is colorectal cancer.*

*Claim 14: The method of claim 1, wherein the cancer is lung cancer.*

*Claim 16: The method of claim 1, wherein the cancer is breast cancer.*

Diaz discloses that detection of tumor-specific mutations in cfDNA has been demonstrated for multiple types of cancer, including colorectal cancer (Ex.1006, 4, 5), breast cancer (*id.*) and lung cancer (*id.*, 5). (Ex.1004, ¶¶151–53.)

**7. Claim 17**

*The method of claim 1, wherein the biological sample is a blood, serum, plasma, or urine sample.*

Diaz discloses plasma samples. (Ex.1006, 5; Ex.1004, ¶154.)

**8. Claim 18**

*The method of claim 1, wherein step (a) comprises performing whole exome sequencing on a tumor biopsy sample of the subject to identify the plurality of tumor-specific mutations.*

Kinde 2013 teaches whole exome sequencing of a tumor biopsy to identify mutations that are then tracked in liquid biopsies. (Ex.1007, 3 (“somatic mutations in [] tumors were identified through whole exome sequencing . . . In each of the 46 cases, we identified at least one somatic mutation (table S3) that was confirmed by an independent assay”), 5 (describing identifying the tumor-specific mutations in Pap specimens from the corresponding patients); Ex.1004, ¶¶155–59.)

**VI. GROUND 2: DIAZ, KINDE 2013, & RABINOWITZ**

**A. Summary Of Rabinowitz**

In Rabinowitz, the inventors of the ’596 patent admit that “the prior art includes disclosures of successful multiplexed PCR reactions involving pools of up to about 50 or 100 primers. . . .” (Ex.1009, [0217]; Ex.1004, ¶162.) Rabinowitz states that it provides methods that include “highly efficient highly multiplexed targeted PCR to amplify DNA followed by high throughput sequencing to determine the allele frequencies at each target locus.” (Ex.1009, [0064].)

According to Rabinowitz, the provided methods include “the ability to multiplex more than about 50 or 100 PCR primers in one reaction in a way that most of the resulting sequence reads map to targeted loci.” (*Id.*)

Rabinowitz also teaches that the multiplex assays can be applied to isolated cfDNA from maternal plasma or cancer patient plasma. For example, Rabinowitz teaches that “[a]ssays may be combined in a single reaction with the entirety of a cfDNA sample isolated from maternal plasma, a fraction thereof, or a further processed derivative of the cfDNA sample.” (*Id.*, [0267].) Rabinowitz further states that the same assays can be applied to determine the genetic state of a cancer from measurements on host blood. (*Id.*, [0209] (“Any claim in the instant disclosure that reads on determining the ploidy state or genetic state of a fetus from the measurements made on maternal blood can equally well read on determining the ploidy state or genetic state of a cancer from the measurements on host blood.”).) Rabinowitz discloses that “[in] some embodiments, the target DNA may originate from. . . cancer patient plasma.” (*Id.* at [0284]; Ex.1004, ¶163.)

Rabinowitz also demonstrates that the multiplex PCR methods described in the ’596 patent were already within the prior art. (*Id.*, ¶164.) For example, *compare* Ex.1001, 97:32–98:17 (incorporating Rabinowitz by reference for description of mini-PCR and its combination with multiplexed PCR) *with* Ex.1009, [0302]–[0322] (describing methods of multiplexed mini-PCR); *compare* Ex.1001,

105:50–110:21 (describing primer design methods that are characterized as “essential” for high levels of multiplexing) *with* Ex.1009, [0291]–[0298] (same).

**B. Combination Of Diaz, Kinde 2013, And Rabinowitz**

Diaz, Kinde 2013, and Rabinowitz are analogous art because they are in the same field as the ’596 patent, related to detecting mutations including single base changes. (Ex.1004, ¶¶100, 104, 110, 161.) As set forth below, a POSA reading Diaz, Kinde 2013, and Rabinowitz would have found it obvious to design targeted PCR assays and to perform targeted multiplex amplification of 10 to 50 of the target loci spanning tumor-specific mutations. (*Id.*, ¶¶165–73.)

Teachings from Rabinowitz would have motivated a POSA to combine its primer design and multiplex PCR methods with Diaz and Kinde 2013.

Specifically, Rabinowitz describes its “highly multiplexed targeted PCR” as “highly efficient.” (Ex.1009, [0064]; Ex.1004, ¶167.) According to Rabinowitz, “[g]reater multiplexing allows more alleles to be targeted, giving more accurate results.” (Ex.1009, [0239].) Rabinowitz discloses that there are “a number of ways to choose primers for a library where the amount of non-mapping primer-dimer or other primer mischief products are minimized.” (*Id.*, [0292].)

Rabinowitz further discloses that its multiplex PCR methods result in a high percentage of sequencing reads that map to targeted loci (*e.g.*, greater than 99% DNA molecules that map to targeted loci). (*Id.*, [0064]; *see also id.*, [0515].)

A POSA would also have been motivated to combine Diaz, Kinde 2013, and Rabinowitz because all three references discuss advantages of PCR-based molecular barcoding methods. (Ex.1004, ¶168.) Diaz specifically suggests barcoding strategies to increase sensitivity in the context of NGS, citing an earlier Kinde 2011 version of the Safe-SeqS method. (Ex.1006, 3.) Kinde 2013, in turn, discloses that its improved Safe-SeqS approach is capable of enhanced mutation detection for mutant templates present at levels even below 0.01%. (*See, e.g.*, Ex.1007, 4.) Rabinowitz teaches designing multiplex PCR assays wherein any of the primers may comprise molecular barcodes. (*See, e.g.*, Ex.1009, [0496], [0277], [0020].)

A POSA would reasonably expect to succeed in amplifying target loci spanning tumor-specific mutations including one or more SNVs in view of the combined teachings of Diaz, Kinde 2013, and Rabinowitz. (Ex.1004, ¶¶169–73.) Rabinowitz discloses primer designs to amplify target regions encompassing polymorphic positions. (*See e.g.*, Ex.1009, [0015], [0031], [0277].) According to Rabinowitz, the disclosed primer design methods are suitable for multiplex amplification of short DNA fragments such as cfDNA, while avoiding allelic amplification bias for different single nucleotide polymorphisms (SNPs). (*See, e.g., id.*, [0271]–[0275]; *see also id.* at [0333].) Because SNVs are also

single base changes in DNA, a POSA would expect to similarly be able to amplify target loci spanning SNVs.

A POSA would also reasonably expect the combination to succeed because Rabinowitz discloses that “[the] targeted PCR may be massively multiplexed” and “[the] selective [] amplification may involve tagging each individual molecule with different tags, molecular barcodes, tags for amplification, and/or tags for sequencing.” (Ex.1009, [0201]; Ex.1004, ¶169.) A POSA would understand that Kinde’s Safe-SeqS barcode sequences are a type of molecular barcode. (*Id.*, ¶¶170–71.) Because Rabinowitz discloses that the amplification can involve adding molecular barcodes, a POSA would expect that Kinde’s Safe-SeqS barcode sequences could be included in primers designed as described in Rabinowitz. (*Id.*, Ex.1009, [0277], [0020] (“In some embodiments, at least some of the primers additionally contain a molecular barcode.”); *see also id.*, [0120].)

**C. Diaz, Kinde 2013, And Rabinowitz Render Obvious 1, 2, 5, 10–14, And 16–18**

**1. Claim 1**

**a. Preamble**

*A method for preparing biological samples useful for monitoring the progression of cancer in a subject, the method comprising:*

Diaz teaches a method for preparing biological samples useful for monitoring the progression of cancer in a subject. (*Supra* § V.D.1.a; Ex.1004, ¶174.)

**b. Limitation 1[A]**

*(a) 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;*

This limitation is obvious in view of Diaz and Kinde 2013, which teach tumor-informed assays for cancer mutations. (*Supra* § V.D.1.b; Ex.1004, ¶175.)

**c. Limitation 1[B]**

*(b) 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; and*

This limitation is also obvious in view of Diaz and Kinde 2013, which teach tumor-informed assays for cancer mutations. (*Supra* § V.D.1.c; Ex.1004, ¶176.)

**d. Limitation 1[C][i]**

*(c) assaying cell-free DNA isolated from a plurality of biological samples obtained from the subject at different time points, wherein the assaying comprises:*

Assaying cell-free DNA isolated from a plurality of biological samples obtained from the subject at different time points is obvious in view of Diaz and Kinde 2013 as discussed in Ground 1 for this limitation. (*Supra* § V.D.1.d; Ex.1004, ¶177.)

**e. Limitation 1[C][ii]**

*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; and*

This limitation is obvious in view of Diaz and Kinde 2013 alone, as discussed above. (*Supra* § V.D.1.e; Ex.1004, ¶¶178–79.) A POSA also would have a reasonable expectation of success for achieving the claimed method in view of Rabinowitz, which discloses methods for multiplex PCR amplification to amplify a plurality of target loci together in the same reaction volume from the isolated cfDNA using target-specific primers. For example, Rabinowitz teaches that “[w]hereas traditional multiplex PCRs evaluate up to fifty loci simultaneously” the disclosed multiplex PCR assays can involve many more than 50 target loci, and “[a]ssays may be combined in a single reaction with the entirety of a cfDNA sample isolated from maternal plasma, a fraction thereof, or a further processed derivative of the cfDNA sample.” (Ex.1009, [0267]; Ex.1004, ¶¶180, 162–163.)

Rabinowitz also generally states that the same assays can be applied to determine the genetic state of a cancer from measurements on host blood. (Ex.1009, [0209]; Ex.1004, ¶¶178–83.) Rabinowitz further discloses that “[in] some embodiments, the target DNA may originate from . . . cancer patient plasma.” (Ex.1009, [0284].) As discussed above, by 2014 a POSA would have

been aware that multiplex PCR reactions followed by NGS had successfully been applied to detect circulating tumor DNA in cancer patient plasma. (Ex.1039, 1–3; Ex.1004, ¶¶80, 83.)

A POSA would also have a reasonable expectation of success in using Safe-SeqS molecular barcodes in primers for multiplex amplification from isolated cfDNA because Rabinowitz discloses that a “molecular barcode” can be included in “any of the primers” disclosed in Rabinowitz. (Ex.1009, [0277].) Rabinowitz further discloses that “[the] targeted PCR may be massively multiplexed” and “[the] selective [] amplification may involve tagging each individual molecule with different tags, molecular barcodes, tags for amplification, and/or tags for sequencing.” (*Id.*, [0201].) A POSA would understand that the Safe-SeqS barcode sequences used in Kinde 2013 are molecular barcodes. Because Rabinowitz discloses that the amplification can involve adding molecular barcodes, a POSA would expect that Kinde 2013’s Safe-SeqS barcode sequences could be included in primers designed as described in Rabinowitz. (*Id.*, [0277], [0020] (“In some embodiments, at least some of the primers additionally contain a molecular barcode.”); *see also id.*, [0120]; Ex.1004, ¶¶168–171.)

**f. Limitation 1[C][iii]**

*performing high-throughput sequencing of the amplified DNA comprising the plurality of target loci to obtain sequence reads*

*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;*

*and* This limitation is obvious in view of Diaz and Kinde 2013 alone, as discussed above. (*Supra* § V.D.1.f; Ex.1004, ¶184.) Rabinowitz also states that the provided methods include “highly efficient highly multiplexed targeted PCR to amplify DNA followed by high throughput sequencing to determine the allele frequencies at each target locus.” (Ex.1009, [0064].) According to Rabinowitz, the provided methods include “the ability to multiplex more than about 50 or 100 PCR primers in one reaction in a way that most of the resulting sequence reads map to targeted loci.” (*Id.*; Ex.1004, ¶¶185–86.)

**g. Limitation 1[C][iv]**

*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.*

This limitation is obvious in view of Diaz, Kinde 2013, and Rabinowitz for the same reasons discussed above for Diaz and Kinde 2013. (*Supra* § V.D.1.g; Ex.1004, ¶187.)

**2. Claim 2**

Diaz discloses ctDNA. (*Supra* § V.D.2.; Ex.1004, ¶188.)

**3. Claim 5**

Diaz discloses that the tumor-specific mutations comprise one or more clonal SNV mutations. (*Supra* § V.D.3.; Ex.1004, ¶189.)

**4. Claim 10**

Kinde 2013 discloses designing primers for target loci spanning tumor-specific mutations. And Rabinowitz discloses designing primers for multiplexed PCR of target loci followed by NGS, with a particular focus on cfDNA assays. A POSA would reasonably expect to succeed in designing targeted PCR assays including Safe-SeqS molecular barcodes in the primers, because Rabinowitz describes methods by which “the design and generation of molecular barcoding primers may be reduced to practice.” (Ex.1009, [0496]; Ex.1004, ¶¶190–91, 168–71.)

**5. Claim 11**

Rabinowitz teaches that “the prior art includes disclosures of successful multiplexed PCR reactions involving pools of up to about 50 or 100 primers.” (*See, e.g.*, Ex.1009, [0217].) Rabinowitz discloses primer design methods for much higher levels of multiplexing, including for cfDNA. (Ex.1004, ¶¶172, 182–83, 192–193.)

A POSA would have reasonably expected to succeed with targeted multiplex PCR amplification of 10 to 50 of the target loci based on the combined teachings of Diaz, Kinde and Rabinowitz. (*Id.*, ¶194.) Kinde 2013 disclosed multiplex reactions of up to nine different target loci in a single reaction using Safe-SeqS primers. (Ex.1007, 312 (table S5).) Even if Safe-SeqS barcodes were incorporated into 10 or more pairs of primers, a POSA would reasonably expect to succeed because the modification would only require one additional primer pair. (Ex.1004, ¶194.) A POSA would also expect to succeed because Rabinowitz discloses that molecular barcodes and/or random sequences can be incorporated into Rabinowitz's primer designs. (*Id.*; *see also id.* ¶¶168–71.)

**6. Claim 12**

Diaz discloses detecting cancer recurrence and/or metastases from the tumor-specific mutations detected in the cfDNA. (*Supra* § V.D.5.; Ex.1004, ¶195.)

**7. Claims 13, 14 and 16**

Diaz discloses detection of tumor-specific mutations in cfDNA for colorectal cancer (Ex.1006, 4, 5), breast cancer (*id.*) and lung cancer (*id.*, 5). (*See also* Ex.1004, ¶196.)

**8. Claim 17**

Diaz discloses plasma samples. (Ex.1006, 5; Ex.1004, ¶197.)

**9. Claim 18**

Kinde 2013 discloses whole exome sequencing of a tumor biopsy to identify mutations that are then tracked in liquid biopsies (*Supra* § V.D.8.; Ex.1004, ¶198.)

**VII. GROUND 3: DIAZ, KINDE 2013, & FLEISCHHACKER**

**A. Summary Of Fleischhacker**

Fleischhacker describes detection of tumor-associated mutations including SNVs in bladder cancer circulating tumor nucleic acids. (*See, e.g.*, Ex.1010, 9–13 (Table 2); *see also* Ex.1004, ¶¶199–201.)

**B. Combination Of Diaz, Kinde 2013, And Fleischhacker**

A POSA would have found it obvious to combine Diaz, Kinde 2013, and Fleischhacker. Like Diaz and Kinde 2013, Fleischhacker is analogous art because it is in the same field as the '596 patent, that is, related to detection of tumor-specific SNVs. *Wyers*, 616 F.3d at 1238–39; Ex.1004, ¶202. A POSA reading Diaz would reasonably look to articles such as Fleischhacker for examples of types of cancers and associated tumor mutations that have been detected in cfDNA. Both references disclose detection of the same types of mutations in cfDNA. (*Id.*, ¶203.)

**C. Diaz, Kinde 2013, And Fleischhacker Render Obvious Claim 15**

*Claim 15: The method of claim 1, wherein the cancer is bladder cancer.*

Fleischhacker discloses detection of point mutations (SNVs) in bladder cancer patients. (Ex.1010, 12.) The '596 patent itself admits that detection of

mutations in cfDNA for bladder cancer patients was in the prior art, citing Fleischhacker as an example. (*See, e.g.*, Ex.1001, 133:15–20, 133:26–32.)

A POSA would reasonably have expected to be able to perform the method wherein the cancer is bladder cancer based on the combined teachings of Diaz, Kinde 2013, and Fleischhacker. Doing so would be a simple matter of applying a tumor-informed ctDNA assay based on the combined teachings of Diaz and Kinde 2013 to a bladder cancer patient as taught by Fleischhacker. (Ex.1004, ¶¶204–07.)

## **VIII. GROUND 4: RABINOWITZ & BETTEGOWDA**

### **A. Summary Of Bettegowda**

Bettegowda is directed to tumor-informed assays for ctDNA. For example, it explains that results were “obtained by first identifying a mutation in a tumor and then determining whether that same mutation was detectable in the plasma.” (Ex.1008, 4; *see also* Ex.1004, ¶¶209–10.) To that end, Bettegowda compared multiple different methods to evaluate ctDNA levels. (Ex.1008, 2, 16.) It compared the results obtainable using BEAMing with results from Safe-SeqS and found that the sensitivity of the two different methods were comparable. (*Id.*, 16 (citing Ex.1049).) Bettegowda teaches that the results from both methods were able to detect “one mutant template in the DNA from 5 ml plasma, as determined by spiking known amounts of mutant KRAS DNA in plasma DNA from normal individuals.” (*Id.*)

**B. Combination Of Rabinowitz And Bettgowda**

A POSA would have found it obvious to combine the teachings of Rabinowitz and Bettgowda to arrive at the presently claimed method. (Ex.1004, ¶¶211–13.) Both references are analogous art because they relate to detection of single nucleotide variants and other genetic mutations, which is the same field as the '596 patent. *Wyers*, 616 F.3d at 1238–39; Ex.1004, ¶211. And Rabinowitz suggests applying its multiplex PCR and next-generation sequencing assays to determine the genetic state of a cancer from measurements on host blood. (Ex.1009, [0209]; Ex.1004, ¶212.) Rabinowitz further discloses that “[in] some embodiments, the target DNA may originate from . . . cancer patient plasma.” (Ex.1009, [0284].) Rabinowitz also suggests using “tumor DNA [that] may be present in many different body fluids [] of tumor patients” for “detection of tumor recurrence.” (*See id.*, [0289].) A POSA seeking to configure Rabinowitz’s cfDNA assays for detecting cancer recurrence would reasonably turn to references in the field of ctDNA analysis and detection, including references like Bettgowda. (Ex.1004, ¶212.)

A POSA reading Bettgowda would also understand that Safe-SeqS provides advantages for detecting mutations such as SNVs in cfDNA, because it achieves detection of rare SNVs while being compatible with multiplex PCR, as discussed in more detail below. (*Id.*, ¶213.) Bettgowda teaches that Safe-SeqS

achieved sensitivities comparable to BEAMing, which detects mutations in ctDNA at levels as low as 0.005% (Ex.1072, 1). (Ex.1008, 15.) While achieving the similarly high sensitivity as the older BEAMing technology, Safe-SeqS allows profiling of more target loci simultaneously. (*See, e.g.*, Ex.1062, 4 (explaining that Safe-SeqS provides a variant of “digital” technology by tagging individual template molecules with unique identifiers which enables researchers to analyze “many more loci—up to 30 or more—than BEAMing can reasonably handle”).)

**C. Rabinowitz And Bettgowda Render Obvious Claims 1, 2, 10–13, and 15–18**

**1. Claim 1**

**a. Preamble**

*A method for preparing biological samples useful for monitoring the progression of cancer in a subject, the method comprising:*

Rabinowitz generally suggests applying its multiplex PCR and next-generation sequencing assays to determine the genetic state of a cancer from measurements on host blood. (Ex.1009, [0209], [0284], [0289]; Ex.1004, ¶222.)

Bettgowda discloses methods for preparing samples comprising ctDNA useful for “monitoring patients with advanced cancers” which Bettgowda teaches may at least have “psychological benefits” for patients who are “anxious to know, as soon as possible, whether disease has progressed.” (*See* Ex.1008, 7; Ex.1004, ¶223.)

**b. Limitation 1[A]**

*(a) 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;*

Bettegowda discloses performing sequencing on a tumor biopsy sample of the subject to identify a plurality of tumor-specific mutations that are then assayed in cfDNA. (See Ex.1008, 2 (“Targeted sequencing, exomic sequencing, or whole-genome sequencing was used to identify mutations in the tumors”); *id.*, 6 (explaining that in this study “[the] specific mutations [assayed in ctDNA] are defined by evaluation of the primary tumor” which “may be less of an obstacle in the future because more cancer patients will have their tumors genetically analyzed to guide therapeutic decisions”); Ex.1004, ¶226.) Bettegowda teaches that by sequencing the tumor sample to identify mutations, the “genetic alterations used to guide therapies can also be used for ctDNA analysis.” (*Id.*, 6–7.) Additionally, Bettegowda teaches identifying a plurality of tumor-specific mutations comprising one or more SNVs. (See, e.g., *id.*, 3 (“tumor-specific rearrangements as well as tumor-specific point mutations were identified in 19 patients (table S2)”); see also *id.*, 24 (table S2) (showing point mutations and rearrangement mutations identified for the same specimens).) (Ex.1004, ¶226.)

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. (*Id.*, ¶¶214–16.)

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* Ex.1072, 5, 1; Ex.1004, ¶215.) Additionally, Bettegowda teaches that some cancer patients have their tumors sequenced to guide therapeutic decisions, and the “genetic alterations used to guide therapies can also be used for ctDNA analysis.” (Ex.1008, 6–7.)

A POSA would also have a reasonable expectation of success for 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 which could then be assayed in cfDNA. Bettegowda actually achieved this. (*See, e.g., id.*, 3; Ex.1004, ¶216.) Additionally, Bettegowda teaches that sequencing a tumor sample to identify mutations is already performed in some cases to guide therapeutic decisions. (Ex.1008, 7.) Tumor-informed assays and their advantages were also well-known to a POSA by 2014. Therefore, this modification would involve simply combining prior art elements according to known methods to yield predictable results.

**c. Limitation 1[B]**

*(b) 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; and*

Bettegowda discloses 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. (*See, e.g.*, Ex.1008, 15; Ex.1004, ¶227.)

**d. Limitation 1[C][i]**

*(c) assaying cell-free DNA isolated from a plurality of biological samples obtained from the subject at different time points, wherein the assaying comprises:*

Bettegowda discloses assaying cfDNA isolated from a plurality of biological samples obtained from the subject at different time points. (*See* Ex.1008, 14 (“two plasma draws were obtained: one prior to initiating EGFR blockade and one sample when the tumors had recurred after a clinical response”); *see also id.*, 15 (explaining that Safe-SeqS was used to perform the cfDNA assays); Ex.1004, ¶¶228–30.) Bettegowda also discloses the advantages of assaying cfDNA at multiple timepoints because it is “noninvasive” compared to other types of repeated assays. (*See* Ex.1008, 7 (explaining that unlike assaying cfDNA to monitor cancer progression, “[r]epeated imaging also subjects patients to radiation”).)

A POSA would have been motivated to assay cfDNA isolated from a plurality of biological samples obtained from the subject at different time points in

order to monitor cancer progression over time. (Ex.1004, ¶230.) Additionally, tumor-informed assays and serial monitoring of ctDNA in plasma were well-known to a POSA by 2014. (*Id.*, ¶¶73–75.)

**e. Limitation 1[C][ii]**

*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; and*

Rabinowitz discloses methods for multiplex PCR amplification to amplify a plurality of target loci together in the same reaction volume from the isolated cfDNA using target-specific primers. For example, Rabinowitz teaches that “[w]hereas traditional multiplex PCRs evaluate up to fifty loci simultaneously” the disclosed multiplex PCR assays can involve many more than 50 target loci, and “[a]ssays may be combined in a single reaction with the entirety of a cfDNA sample isolated from maternal plasma, a fraction thereof, or a further processed derivative of the cfDNA sample.” (Ex.1009, [0267]; Ex.1004, ¶¶231–32.)

Rabinowitz also generally states that the same assays can be applied to determine the genetic state of a cancer from measurements on host blood. (Ex.1009, [0209].) Rabinowitz further discloses that “[in] some embodiments, the target DNA may originate from... cancer patient plasma.” (*Id.*, [0284].) As discussed above, by 2014 a POSA would have been aware that multiplex PCR

reactions followed by NGS had successfully been applied to detect circulating tumor DNA in cancer patient plasma. (Ex.1039, 1–3; Ex.1004, ¶233.)

Bettegowda discloses tracking mutations in ctDNA at 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. (*See, e.g.*, Ex.1008, 15; Ex.1004, ¶213.) A POSA would have been motivated to apply multiplex PCR of cfDNA 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. (*Id.*, ¶234 *see also id.*, ¶¶227, 214–16.)

A POSA would also have a reasonable expectation of success in using Safe-SeqS molecular barcodes in primers for multiplex amplification from isolated cfDNA because Rabinowitz discloses that a “molecular barcode” can be included in “any of the primers” disclosed in Rabinowitz. (Ex.1009, [0277]; Ex.1004, ¶235.) Rabinowitz further discloses that “[the] targeted PCR may be massively multiplexed” and “[the] selective [] amplification may involve tagging each individual molecule with different tags, molecular barcodes, tags for amplification, and/or tags for sequencing.” (Ex.1009, [0201].) A POSA would understand that the Safe-SeqS barcode sequences used in Bettegowda are molecular barcodes. Because Rabinowitz discloses that the amplification can involve adding molecular

barcodes, a POSA would expect that Bettegowda's Safe-SeqS barcode sequences could be included in primers designed as described in Rabinowitz. (*Id.*, [0277], [0020] ("In some embodiments, at least some of the primers additionally contain a molecular barcode."); *see also id.*, [0120]; Ex.1004, ¶¶219–20.) A POSA would also expect to succeed because Bettegowda teaches use of SafeSeqS in a "multiplexed, sequencing-based assay to query known mutated hotspots of several genes in the EGFR pathway." (Ex.1008, 4, 15–16; Ex.1004, ¶236.)

**f. Limitation 1[C][iii]**

*performing high-throughput sequencing of the amplified DNA comprising the plurality of target loci to obtain sequence reads,*

Rabinowitz states that the provided methods include "highly efficient highly multiplexed targeted PCR to amplify DNA followed by high throughput sequencing to determine the allele frequencies at each target locus."

(Ex.1009, [0064].) According to Rabinowitz, the provided methods include "the ability to multiplex more than about 50 or 100 PCR primers in one reaction in a way that most of the resulting sequence reads map to targeted loci." (*Id.*)

Bettegowda also discloses detecting tumor-specific mutations in cfDNA using Safe-SeqS (Ex.1008, 16 (citing Ex.1049)), which a POSA would understand involves performing next-generation (high-throughput) sequencing of the amplified DNA. (Ex.1004, ¶¶237–38.)

**g. Limitation 1[C][iv]**

*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.*

Based on the combined teachings of Rabinowitz and Bettegowda, it would have been obvious to perform the claimed method wherein an SNV mutation that is present in less than or equal to 0.015% of the cfDNA having the SNV locus is detected from the sequence reads. (Ex.1004, ¶¶239–42; *see also id.*, ¶¶217–20.) A POSA would have been motivated to detect an SNV that is present in less than or equal to 0.015% of the cfDNA having the SNV locus because a POSA was aware that “circulating mutant DNA represents only a tiny fraction of the total circulating DNA, sometimes less than 0.01%.” (Ex.1072, 1; Ex.1004, ¶239.) A POSA would look to references such as Bettegowda to achieve this, because Bettegowda applies the well-known Safe-SeqS error correction method to cfDNA for detection of rare SNVs.

Bettegowda teaches that Safe-SeqS can be applied to cfDNA to detect SNVs and can achieve results comparable to BEAMing in that context. (Ex.1008, 4, 16.) BEAMing was able to detect mutations in ctDNA at levels as low as 0.005% (Ex.1072, 1). A POSA would understand, however, that BEAMing does not readily allow multiplex analysis of different target loci in the same reaction. (Ex.1004, ¶¶213, 218.) Additionally, BEAMing requires generation of fluorescently labeled probes for each mutation and wild-type allele analyzed

(Ex.1072, 2), which is costly. (Ex.1004, ¶218.) Therefore, a POSA would be motivated to use the newer Safe-SeqS method that allows multiplexing and does not require fluorescent probes.

A POSA would have reasonably expected to achieve the 0.015% limitation using Safe-SeqS barcodes and error correction because Bettegowda teaches that Safe-SeqS was able to detect one mutant template in the DNA purified from up to 5 ml of plasma. (Ex.1008, 2, 16.) Although Bettegowda uses alternative units (mutant templates per cfDNA purified from up to 5 ml of plasma) to describe the mutant allele fraction, a POSA would have understood that the isolated cfDNA purified from 5 ml of plasma contained sufficient template copies such that a single mutant template would be present in less than or equal to 0.015% of the cfDNA having the SNV locus. (*See, e.g.*, Ex.1051, 4 (for the cfDNA purification kit used by Bettegowda, explaining that circulating cfDNA yields per 5 mL sample varied from about 8,000 to more than 80,000 genome equivalents).) A POSA would understand 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, which is less than 0.015%. (Ex.1004, ¶240.)

According to Bettegowda, the sensitive methods used in their study (which included Safe-SeqS) did not allow detection of point mutations at “levels less than

1 in 100,000 cells,” (0.001%, 15-fold below the 0.015% level required by the ’596 patent claims). (Ex.1008, 7 (citing Ex.1049).) Because Bettegowda describes 0.001% as the level below which point mutations could not be detected, a POSA would understand that the limit of detection for SNVs was on the order of 0.001%, and well below 0.015%. Therefore, a POSA would reasonably expect to detect an SNV mutation present in less than or equal to 0.015% of the cfDNA having the SNV locus by using the Safe-SeqS barcodes and error correction method in a multiplex PCR reaction with a sufficient number of cfDNA templates in the reaction. (Ex.1004, ¶242.)

A POSA in 2014 would reasonably expect to be able to perform the multiplex assay in a single reaction containing a sufficient number of templates of a cfDNA locus such that a mutant template would be present in less than or equal to 0.015% of the cfDNA having the SNV locus. (*Id.*, ¶¶241–42.) As discussed above, Bettegowda teaches that Safe-SeqS was able to detect one mutant template in the DNA purified from up to 5 ml of plasma. (Ex.1008, 2, 16.) A POSA 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. (*See, e.g.*, Ex.1051, 4; Ex.1004, ¶¶240–41). One mutant template out of 8,000 templates is 0.0125%, which is less than 0.015%. Obtaining such quantities of cfDNA was also

routine to a POSA. For example, as early as 2008, cfDNA assays were performed that involved PCR amplification with 8,000 or more copies of a cfDNA template in the reaction. (*See* Ex.1072 at 6, 1 (describing cfDNA assays performed using a median of 8,000 fragments per reaction); Ex.1004, ¶242).

Additionally, a POSA would reasonably expect the combination to succeed because Rabinowitz discloses that primers comprising molecular barcodes can be used to identify “tagged molecules” that originate from the same “original” DNA molecule. (Ex.1009, [0488]; Ex.1004, ¶220.) Specifically, Rabinowitz discloses a molecular barcoding approach that “entails targeting one or more specific loci and generating a tagged copy of the original molecules such manner [*sic*] that most or all of the tagged molecules from each targeted locus will have a unique tag and can be distinguished from one another upon sequencing of this barcode using clonal or single molecule sequencing.” (Ex.1009, [0488].) Thus, Rabinowitz suggests that molecular barcodes can be used to identify sequences that originate from the same original DNA template. A similar principle underlies the Safe-SeqS error correction method of Bettegowda. (*See* Ex.1008, 16 (citing Ex.1049 for details of Safe-SeqS method).)

## **2. Claim 2**

Bettegowda teaches that the cfDNA comprises circulating tumor DNA. (Ex.1008, 3; Ex.1004, ¶¶243–44.)

**3. Claim 10**

Rabinowitz discloses designing primers for multiplexed PCR of target loci followed by NGS, with a particular focus on cfDNA assays. A POSA would reasonably expect to succeed in designing targeted PCR assays including Safe-SeqS molecular barcodes in the primers, because Rabinowitz describes methods by which “the design and generation of molecular barcoding primers may be reduced to practice.” (Ex.1009, [0496]; Ex.1004, ¶¶245–47.)

**4. Claim 11**

As discussed *supra*, Rabinowitz teaches multiplex PCR amplification of 10 to 50 target loci. (See Ex.1004, ¶¶234, 163–80.) A POSA would also be motivated to perform targeted multiplex amplification of 10 to 50 of the target loci, because this would allow tracking of more tumor-specific mutations in cfDNA without requiring additional reactions. (*Id.*, ¶235.) A POSA would reasonably expect to identify at least 10–50 target loci spanning tumor-specific mutations in a solid tumor biopsy. (*Id.*) A POSA would also have a reasonable expectation of success because Rabinowitz discloses primer design methods for much higher multiplexing, including primers comprising molecular barcodes. (*Id.*, ¶¶248–50.)

**5. Claim 12**

Bettegowda discloses detecting tumor recurrence by detecting ctDNA mutations. (Ex.1008, 4 (“Liquid biopsies can also be used to monitor patients

being treated with targeted agents, providing an early warning of recurrence and information about the genetic basis of resistance.”); Ex.1004, ¶¶251–53.)

**6. Claims 13, 15 and 16**

Bettegowda discloses detection of ctDNA in colorectal, bladder, and breast cancers. (Ex.1008, 6 (Fig. 3), 5 (Fig. 2) (showing detection of ctDNA for bladder, colorectal, and breast cancers), 1, 2.) Therefore, it would have been obvious to apply the method of claim 1 to colorectal, bladder, and breast cancers. (Ex.1004, ¶¶254–55.)

**7. Claim 17**

Bettegowda discloses that the cfDNA is isolated from plasma samples. (*See, e.g.*, Ex.1008, 2, 4; Ex.1004, ¶¶256–58.)

**8. Claim 18**

Bettegowda teaches identifying a plurality of tumor-specific mutations in a tumor biopsy by “exomic sequencing” according to previously described methods. (Ex.1008, 2.)

A POSA would have been motivated to use exomic sequencing because it avoids the expense of whole genome sequencing while still covering ~85% of known disease-causing variants. (Ex.1038, 5; Ex.1004, ¶76.). A POSA would also have a reasonable expectation of success because kits for performing whole exome sequencing were commercially available. (Ex.1008, 14–15; Ex.1004, ¶¶76, 259–61.)

## **IX. THE BOARD SHOULD REACH THE MERITS**

### **A. 35 U.S.C. § 325(d) Does Not Support Discretionary Denial**

The Board may discretionarily deny review under Section 325(d) if (1) the same or substantially the same art or arguments were presented to the patent office and (2) the examiner did not materially err in evaluating those art or arguments.

*Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, 2020 WL 740292, at \*3 (P.T.A.B. Feb. 13, 2020) (precedential). Neither condition is met here, and Section 325(d) denial therefore is improper.

#### **1. The Examiner considered different art and arguments**

When assessing the “same or substantially the same” *Advanced Bionics* prong, the Board considers three factors<sup>7</sup> from *Becton, Dickinson and Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (P.T.A.B. Dec. 15, 2017).

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<sup>7</sup> The factors are: “(a) the similarities and material differences between the asserted art and the prior art involved during examination; (b) the cumulative nature of the asserted art and the prior art evaluated during examination; . . . and (d) the extent of the overlap between the arguments made during examination and the manner in which petitioner relies on the prior art.” 2020 WL 740292, at \*4, n.10.

*Advanced Bionics*, 2020 WL 740292, at \*4. These factors confirm the art and arguments here are different.

Factor (a): Different Art. The Examiner never considered four of the five references—Diaz, Kinde 2013, Bettgowda and Fleischhacker<sup>8</sup>—in this Petition, and every ground includes at least one of these references. The remaining reference—Rabinowitz—appears on the '596 patent's face (Ex.1001, 4, 17),<sup>9</sup> but, as Patent Owner buried it among 800 others in a 91-page IDS, the Examiner never discussed or applied it. (Ex.1003, 1255, 1237–1328.) As no asserted art was at issue during prosecution, discretionary denial is improper. *Amazon Inc. v. M2M Sols. LLC*, IPR2019-01204, Paper 14, 16 (P.T.A.B. Jan. 23, 2020).

Factors (b) & (d): Non-cumulative Art & Non-overlapping Arguments. The asserted art is not cumulative because it fills a gap identified by the Examiner during prosecution. The Examiner granted allowance because she did not identify art that disclosed a method of detecting mutations at the claimed 0.015% frequency or lower that was compatible with targeted multiplex amplification. (Ex.1003, 62–

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<sup>8</sup> The specification mentions Fleischhacker but does not identify it as a “Reference[] Cited.” (Ex.1001, 133:15–20, 133:26–32.)

<sup>9</sup> The '596 patent specification also refers to Rabinowitz. (Ex.1001, 4:21–26, 97:32–35, 98:4–16, 125:54–126:11.)

63, 334.) The Petition, however, relies on Kinde 2013 and Bettegowda, which teach methods for detecting the claimed frequency mutations compatible with targeted multiplex amplification. (*Supra* §§ V-VIII.)

As a corollary, the Petition’s arguments also differ from the Examiner’s. The disputes in this proceeding are likely to revolve around whether combinations of Kinde 2013 and Bettegowda with other references were obvious, rather than whether the 0.015% limitation itself was novel and non-obvious.

## **2. The Examiner committed material error**

The Board considers the remaining *Becton, Dickinson* factors<sup>10</sup> when assessing the “material error” *Advanced Bionics* prong. 2020 WL 740292, at \*4. The Board should not reach the “material error” prong because different art and arguments are at issue, but if the Board does so, it should find the Examiner erred.

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<sup>10</sup> The factors are: “(c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection; ... (e) whether petitioner has pointed out sufficiently how the examiner erred in its evaluation of the asserted prior art; and (f) the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments” 2020 WL 740292, at \*4, n.10.

Factor (c): Extent that Examiner Evaluated Asserted Art. The Examiner did not evaluate any of the asserted art.

Factor (e): Whether Petitioner Identified Examiner Error in the Examiner's Evaluation of the Asserted Prior Art. This factor favors institution because, again, the Examiner never evaluated the asserted art. Nonetheless, if the Board considers this factor, the Examiner's conclusion that targeted, multiplex amplification of low-frequency mutations was novel and non-obvious was a material error. (Ex.1003, 62–63, 334.) That Kinde 2013 and Bettegowda disclose or render that limitation obvious is not an issue about which reasonable minds could disagree—the Examiner simply did not locate and apply these references. (*Supra* §§ V.B (summarizing disclosures), VIII.A (same).) There is no doubt that this error was material: it is why the claims issued. (Ex.1003, 62–63, 334.)

Patent Owner may argue the Board's denial of *inter partes* review for related U.S. Patent No. 11,530,454 (Ex.1028) shows the Examiner did not materially err during prosecution of the '596 patent. (Ex.1025 (institution denial).) That argument would be incorrect. The Board based its Section 325(d) denial on grounds not present in the Petition, and it never reached whether allowing claims with the 0.015% limitation was error. (*Id.*, 4–6, 17.) The prior denial is irrelevant.

Factor (f): Import of Additional Evidence and Facts in Petition. Kinde 2013's and Bettegowda's disclosures warrant reconsideration of the Examiner's

conclusions. But the Petition also presents new, exhaustive testimony by Dr. Niall Lennon, the director for genomics at the Harvard/MIT Broad Institute, which confirms unpatentability. (Ex.1004.) If the Examiner had had access to the Petition and this evidence, the challenged claims would not have issued.

**B. *Fintiv* Does Not Support Discretionary Denial**

Patent Owner first asserted the '596 patent against Petitioner in a parallel district court action last month. The Board therefore must assess whether to discretionarily deny institution under six factors enumerated in *Apple Inc. v. Fintiv, Inc.* IPR2020-00019, Paper 11 at 6 (P.T.A.B. Mar. 20, 2020) (precedential). Because the *Fintiv* factors favor institution, discretionary denial is unwarranted.

**1. Factor 1: likelihood of a stay**

This factor favors institution or is neutral. The Middle District of North Carolina tends to stay proceedings if the Board institutes *inter partes* review. Compare *CAO Lighting, Inc. v. Cree, Inc.*, No. 21-cv-00634, Dkt.32 (M.D.N.C. Nov. 30, 2022) (granted) and *Advanced Mktg. Sys., LLC v. Delhaize Amer., Inc.*, No. 15-cv-00635, Dkt.52 (M.D.N.C. June 20, 2016) (granted) with *Altria Client Serv. LLC v. RJ Reynolds Vapor Co.*, No. 20-cv-00472, Dkt.171 (M.D.N.C. Oct. 13, 2021) (denied where Board declined to institute seven of nine petitions). Any decision granting review is due in July of this year, which predates

the earliest possible trial date set by the district court. 35 U.S.C. § 314(b).

Moreover, as noted below, the trial date may slip due to Patent Owner’s conduct.

A partial stay of district court proceedings for the challenged patent thus is possible.

## **2. Factor 2: proximity of trial date to FWD**

This factor favors institution. Because “scheduled trial dates are unreliable and often change,” the Director instructs the Board to compare the statutory deadline for any FWD against the “median time-to-trial for civil actions. . . in which the parallel litigation resides.” (Ex.1020, 8–9.) Here, the statutory deadline for any FWD is roughly July 2026. For the 12-month period ending June 30, 2024, the median time to trial for civil actions in the Middle District of North Carolina was 30.5 months. (Ex.1021, 22.) Because Patent Owner first asserted the ’596 patent on December 10, 2024,<sup>11</sup> these data indicate a median time-to-trial date in June 2027—nearly a year after the FWD deadline.

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<sup>11</sup> Patent Owner sued Petitioner in 2023 alleging that Petitioner’s Radar™ 1.0 assay infringed patents other than the ’596 patent. Last month, Patent Owner amended to allege that Petitioner’s new product, RaDaR™ 1.1, infringed the ’596 patent.

The North Carolina action’s current schedule is not to the contrary. At the parties’ request, the district court recently delayed trial until October 13–17, 2025. But Patent Owner has already suggested that it believes this date may require further delay. In particular, Patent Owner opposed Petitioner’s request for foreign discovery under the Hague convention by arguing that such discovery will likely be barred by the current discovery deadline or “will necessitate modification of the scheduling order.” (Ex.1103, 5.) Although Petitioner disagrees with Patent Owner’s suggestion, the Court has granted Petitioner’s motion for foreign discovery, and the parties’ dispute about scheduling illustrates that there is no guarantee of trial before the Board issues any final written decision. The trial date also is “subject to the Court’s availability and subject to adjustment based on the Court’s criminal court schedule.” (Ex.1022, 8; Ex.1023, 3.)

### **3. Factor 3: investment in parallel proceeding**

This factor favors institution. The Board considers investment in the parallel proceeding as “of the institution decision.” *Fintiv*, IPR2020-00019, Paper 11 at 9. The parties are in the early stages of claim construction briefing. (Ex.1023, 2; Ex.1073.) Petitioner submitted its preliminary infringement contentions only recently on December 18, 2024. And although the current schedule would close fact and expert discovery by the institution deadline, that schedule is—again, per Patent Owner—subject to change. (Ex.1103, 5.) Also, “the most burdensome parts

of the case—filing and responding to pretrial motions, preparing for trial, going through the trial process, and engaging in post-trial motions practice—all [will] lie in the future.” *CyWee Grp. Ltd. v. Samsung Elecs. Co.*, No. 2:17-CV-00140-WCB-RSP, 2019 WL 11023976, at \*6 (E.D. Tex. Feb. 14, 2019) (Bryson, J.). In short, much remains to be done for the newly asserted ’596 patent and the newly accused RaDaR™ 1.1 assay.

#### **4. Factor 4: overlapping issues**

This factor favors institution. In the North Carolina action, Petitioner contests validity of claims 1, 11, 12, and 18 under the clear and convincing evidentiary standard. Here, Petitioner challenges claims 1, 2, 4, 5 and 10–18 under the lower, preponderance of the evidence standard. Regardless of the outcome in North Carolina, that action will not resolve patentability of every challenged claim. Furthermore, Petitioner hereby submits that, should the Board institute this proceeding on the grounds presented in this Petition, Petitioner will not pursue these same grounds in the North Carolina action. *Sand Revolution II, LLC v. Cont’l Intermodal Gr.—Trucking LLC*, IPR2019-01393, Paper 24, at 11–12 (P.T.A.B. June 16, 2020) (informative) (“Petitioner’s stipulation, however, mitigates to some degree the concerns of duplicative efforts between the district court and the Board, as well as concerns of potentially conflicting decisions”).

**5. Factor 5: same parties**

As is the norm, the parties here also are parties to the parallel proceeding.

**6. Factor 6: the merits and other circumstances**

If the Board finds *Fintiv* factors 1–5 favor denial, it must then consider whether the Petition presents “compelling merits” such that it still must institute. *Commscope Techs. LLC v. Dali Wireless, Inc.*, IPR2022-01242, Paper 23 at 4–5 (Dec. Dir. Pat. Feb. 27, 2023). “Compelling, meritorious challenges are those in which the evidence, if unrebutted in trial, would plainly lead to a conclusion that one or more claims are unpatentable by a preponderance of the evidence.” *Id.*, \*4. A challenge meets this test “if it is highly likely that the petitioner would prevail with respect to at least one challenged claim.” *OpenSky Indus., LLC et al. v. VLSI Tech., LLC*, IPR2021-1064, Paper 102 at 41 (P.T.A.B. Oct. 4, 2022) (precedential).

The Petition clears that bar. It presents multiple grounds addressing every limitation of the challenged claims. It advances art (Kinde 2013, Bettegowda) teaching the 0.015% limitation compatible with targeted multiplex amplification which—again—was the basis for allowance. (Ex.1003, 62–63, 334.) And it offers testimony by Dr. Lennon and documentary evidence showing why each challenged claim would have been obvious. The Petition and supporting evidence are “highly likely” to lead to cancellation.

*Fintiv* factor 6 also allows the Board to consider “other circumstances.”

Here, the public interest favors institution. Both Petitioner and Patent Owner have commercialized assays that use cell-free tumor DNA to detect and monitor cancer. In 2023, however, a district court enjoined Petitioner’s RaDaR™ 1.0 assay, an FDA-designated “breakthrough device,” over another of Patent Owner’s patents. (Ex.1024.) That enjoined assay was more sensitive than competing assays and could find cancers that other assays could not. (*See, e.g.*, Ex.1106 (Petitioner’s assay: 0.0001% VAF limit of detection); Ex.1046, 1 (Patent Owner’s assay: 0.01% VAF limit of detection).) Petitioner has since developed a new, similarly sensitive assay, RaDaR™ 1.1, but its availability in the United States is at risk. Cancelling the ’596 patent would defend public access to that assay and, thus, this proceeding has import far beyond whether Patent Owner must pay Petitioner royalties.

## **X. MANDATORY NOTICES**

### **A. Real Party-in-Interest**

Pursuant to 37 C.F.R. § 42.8(b)(1), NeoGenomics Laboratories, Inc. is the real party-in-interest. Only Petitioner has funded this Petition and has full and exclusive control over this proceeding.

### **B. Related Matters**

Pursuant to 37 C.F.R. § 42.8(b)(2), Petitioner identifies the following related matter: *Natera, Inc. v. NeoGenomics Laboratories, Inc.*, No. 23-cv-00629

(M.D.N.C.) in which Patent Owner asserts the '596 patent against Petitioner. In this case, Patent Owner has asserted another patent, the '454 patent (Ex.1028). Petitioner sought review of the '454 patent in IPR2024-00346 (institution denied) (Ex.1025). Patent Owner also previously asserted U.S. Patent No. 11,519,035 (the "'035 patent") (Ex.1029) against Petitioner in the district court case. Petitioner sought review of the '035 patent in IPR2024-00812 (terminated via settlement) (Ex.1026).

Pursuant to 37 C.F.R. § 42.104(a), Petitioner certifies that the '596 patent is available for *inter partes* review and that Petitioner is not barred or estopped from requesting an *inter partes* review challenging the patent claims on the grounds identified in this Petition.

### **C. Lead And Back-Up Counsel And Service Information**

Pursuant to 37 C.F.R. § 42.8(b)(3), Petitioner identifies the following counsel (and a power of attorney accompanies this Petition).

| <b>Lead Counsel</b>                                                                                                                                                                                                                                                            | <b>Backup Counsel</b>                                                                                                                                                                                                                                                                                                                                                |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
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|--|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Pursuant to 37 C.F.R. § 42.8(b)(4), service information for lead and back-up counsel is provided above. Petitioner consents to electronic service by email to [NeoGenomics-Natera-IPR@mofo.com](mailto:NeoGenomics-Natera-IPR@mofo.com).

The USPTO is authorized to charge any required fees, including the fee as set forth in 37 C.F.R. § 42.15(a) and any excess claim fees, to Deposit Account No. **03-1952** referencing Docket No. **31789-00000.06**.

## **XI. CONCLUSION**

For the foregoing reasons, the Board should find all challenged claims unpatentable.

Dated: January 14, 2025

Respectfully submitted,

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**Certification of Word Count (37 C.F.R. § 42.24)**

I hereby certify that this Petition for *Inter Partes* Review has 12,550 words (as counted by the “Word Count” feature of the Microsoft Word™ word-processing system), exclusive of “a table of contents, a table of authorities, mandatory notices under § 42.8, a certificate of service or word count, or appendix of exhibits or claim listing.”

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Dated: January 14, 2025

By: /Mehran Arjomand/  
Mehran Arjomand

**Certificate of Service (37 C.F.R. § 42.6(e)(4) and 42.105(a))**

I hereby certify that the attached Petition for *Inter Partes* Review and supporting materials were served on January 15, 2025 by UPS, which is a means at least as fast and reliable as U.S. Express Mail, on the Patent Owner at Natera, Inc., 201 Industrial Road, Suite 401, San Carlos, California 94070 (the correspondence address indicated for U.S. Patent No. 11,319,596) and were served on January 14, 2025 (PST) via email to Patent Owner's counsel in the co-pending litigation at the following email addresses:

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