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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NEOGENOMICS LABORATORIES, INC.,
Petitioner,

v.

NATERA, INC.,
Patent Owner.

Case No. IPR2024-00346
U.S. Patent No. 11,530,454

PATENT OWNER'S PRELIMINARY RESPONSE

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2008	Inivata, Inc. Summons In A Civil Action, <i>Natera, Inc. v. Inivata, Inc. and Inivata, Ltd.</i> , Case No. 1:22-cv-01609, Dkt. 8 (D. Del. Jan. 13, 2023) (docket entries filed in lead Case No. 1:21-cv-0056)
2009	Inivata, Ltd. Summons In A Civil Action, <i>Natera, Inc. v. Inivata, Inc. and Inivata, Ltd.</i> , Case No. 1:22-cv-01609, Dkt. 9 (D. Del. Jan. 13, 2023) (docket entries filed in lead Case No. 1:21-cv-0056)
2010	Inivata’s Preliminary Invalidity Contentions Claim Chart, <i>Natera, Inc. v. Inivata, Inc. and Inivata, Ltd.</i> , Case No. 1:22-cv-01609, (D. Del. Served March 1, 2024) (Forshaw Chart)

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2012	Complaint For Patent Infringement, <i>Natera, Inc. v. NeoGenomics Labs., Inc.</i> , Case No. 1:23-cv-00629, Dkt. 1 (M.D.N.C. July 28, 2023)
2013	Plaintiff Natera’s Memorandum Of Law In Support Of Its Motion For A Preliminary Injunction, <i>Natera, Inc. v. NeoGenomics Labs., Inc.</i> , Case No. 1:23-cv-00629, Dkt. 6 (M.D.N.C. July 31, 2023)
2014	Defendant’s Opening Brief In Support Of Motion To Dismiss, <i>Natera, Inc. v. NeoGenomics Labs., Inc.</i> , Case No. 1:23-cv-00629, Dkt. 52 (M.D.N.C. Sept. 5, 2023)
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2017	Preliminary Injunction, <i>Natera, Inc. v. NeoGenomics Labs., Inc.</i> , Case No. 1:23-cv-00629, Dkt. 171 (M.D.N.C. Dec. 27, 2023)
2018	Order Denying NeoGenomics’ Motion to Dismiss, <i>Natera, Inc. v. NeoGenomics Labs., Inc.</i> , Case No. 1:23-cv-00629, Dkt. 172 (M.D.N.C. Dec. 27, 2023)
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2024	NeoGenomics’ Preliminary Invalidity Contentions Claim Chart, <i>Natera, Inc. v. NeoGenomics Labs., Inc.</i> , Case No. 1:23-cv-00629 (M.D.N.C. served Feb. 23, 2024) (Forsheew Chart)
2025	Joint Claim Construction Statement and Ex. A, <i>Natera, Inc. v. NeoGenomics Labs., Inc.</i> , Case No. 1:23-cv-00629, Dkt. 249, 249-1 (M.D.N.C. March 15, 2024)
2026	<i>Foresight Diagnostics Inc. v. Personalis, Inc.</i> , IPR2023-00545, Petitioner’s Reply to Patent Owner Response
2027	March 27, 2024 email from NeoGenomics re substitution of counsel

I. INTRODUCTION

Natera is a pioneer in cell-free DNA (cfDNA) technologies. Its breakthrough tests have globally revolutionized cancer screening and life-saving medical treatments. With hundreds of millions of dollars invested in research and development, Natera's innovations are widely acclaimed as a scientific feat and Natera has been awarded hundreds of patents worldwide.

Natera's U.S. Patent No. 11,530,454 embodies its revolutionary Signatera™ test: the first personalized “tumor-informed” molecular residual disease (MRD) test on the market. MRD references a tiny number of cancer cells remaining in the body. Signatera™ is custom-built for each patient. After identifying a patient tumor-specific set of genetic changes, Signatera™ detects trace amounts of tumor DNA from a simple blood draw, months or years earlier than a conventional x-ray, scan, or biopsy. This allows patients in remission to be closely monitored for recurrence, and has revolutionized MRD testing since its launch in 2017.

Following the entry of NeoGenomics' infringing RaDaR test in the tumor-informed MRD market, Natera filed suit in Delaware and North Carolina. Days after RaDaR was approved for Medicare coverage, the North Carolina court enjoined NeoGenomics' further infringement of Natera's intellectual property. The district court declined to stay the injunction, and fast-tracked the case for a jury trial in March 2025. NeoGenomics is already contesting validity of the '454 Patent in the

North Carolina, and the court denied NeoGenomics' request to dismiss the case based on Section 101 grounds.

On nearly the last possible day before the one-year window elapsed in Delaware, NeoGenomics came to the Board. This Petition presents a classic *Fintiv* scenario: NeoGenomics is already litigating these same defenses in district court and offers no *Sotera* stipulation to avoid duplication here. NeoGenomics agreed to an expedited trial in North Carolina, and the most efficient path forward for everyone is to let that case take precedence.

This Petition also may be disposed of under *Advanced Bionics*: its lead reference Forshaw was already extensively considered by the Office. NeoGenomics makes a very serious allegation that Natera purportedly misled the patent Examiner about Forshaw's disclosure. But Natera was unequivocally forthright with the Office and the file history confirms it. The Examiner thoroughly vetted the claims, and insisted Natera amend its claims to overcome Forshaw. NeoGenomics shows no material error by the Examiner, and indeed knows its allegations have no merit, having already dropped its parallel inequitable conduct defenses in North Carolina.

More troubling are NeoGenomics' own statements about Forshaw in the Petition. NeoGenomics' lead IPR counsel is lead IPR counsel in *Foresight Diagnostics v. Personalis*, IPR2023-00545, also involving Forshaw grounds and pending before the Office. In *Personalis*, counsel fluently exposed Forshaw's flaws

but takes directly contradictory positions here. Counsel has been notified of his conflicting factual representations in *Personalis*, EX2026 at 6, 18, 25-27, 31-35, 39, and he asked to withdraw from this IPR on the same day this brief was filed, EX2027. The Petition provides no good faith showing for counsel's divergent factual statements about Forshew in this proceeding and *Personalis*. See 37 C.F.R. § 42.11.

Even if considered on the merits, NeoGenomics' Petition is not reasonably likely to prevail.

First, Grounds 1-2 of the Petition assert that Forshew's breast cancer embodiment "discloses" most of independent Claims 1 and 14 and relies on Forshew's Figure 1B for "targeted multiplex amplification" without mentioning or addressing the fact that Figure 1B is a separate ovarian cancer testing embodiment. This sleight-of-hand does not sustain NeoGenomics' burden.

Second, for the "sequencing" limitations, the Petition fails to show obviousness of all claims by mixing-and-matching from Forshew's different embodiments without addressing the required motivation to combine them. Counsel agreed in *Personalis* that "Forshew describes a series of experiments," including a single-patient metastatic breast cancer experiment distinct from the other tests. EX2001 at 15-18. Yet here he conflates Forshew's different embodiments without comment, let alone supplying the required motivation to combine them.

Third, NeoGenomics does not show Forshew’s assay teaches or suggests a “depth of read of at least 50,000 per target locus” required by Claim 1, its dependents, and Claim 15. NeoGenomics again cherry-picks numbers from different Forshew embodiments to assert obviousness. But even the highest read depth it identifies—7,700 from Forshew’s Table 1—is nowhere near 50,000.

Fourth, NeoGenomics has not shown that Forshew is sensitive enough to detect “an SNV mutation that is present in less than or equal to 0.015%” required by Claims 14-28. Counsel argues that Forshew’s Figure S3 “shows frequencies that could be detected” including mutation “frequencies of 0.015% and below,” Pet. at 43, yet in *Personalis* he said the opposite—that Forshew was limited to detecting “mutations occurring at a frequency higher than 2%,” EX2001 at 17; *see also* EX1003 at 2.¹ NeoGenomics’ position is indefensible.

Finally, NeoGenomics’ Ground 3 does not show unpatentability of Claims 14-28. Even if combined, Forshew, Bentley and Narayan do not satisfy the claims as a whole, including the requirement of an increased sensitivity of 0.015% while satisfying the 10 to 500 target loci limitation.

¹ All citations are to the page numbers added to the IPR exhibits by the parties.

All emphasis in this brief is added unless otherwise noted.

The Board should deny institution.

II. BACKGROUND

A. Natera’s Pioneering Signatera™ MRD Test

Natera was founded in 2004 after its founder lost his nephew, born with Down syndrome, at just six days of age. That personal tragedy was the catalyst for transforming medical care for millions. In the twenty years since, Natera has analyzed more than four million patient samples, and its tests are validated by over 180 peer-reviewed studies. Consistent with its mission, Natera invests more than \$50 million per year in research and development and has been awarded more than 330 patents for its inventions worldwide.

Cancer is the second leading cause of preventable death. After initial treatment, early detection of cancer recurrence can lead to quicker interventions and an increased likelihood of survival. *See* EX1001 at 44:26-34. The standard tests for identifying cancer relapse include X-rays, CT scans, biopsy, or detection of certain antibodies, but these tests are either invasive or not sensitive enough to detect relapse at its early stages. *E.g.*, EX2007 at 1 (“MRD... can detect cancer recurrence up to two years before conventional imaging.”).

In 2017, Natera launched its personalized Signatera™ MRD test, the first of its kind on the market. It was a medical breakthrough—based on a novel technique of hunting down remnants of cancer that may be indicative of relapse in a person’s bloodstream months before the cancer is detectable using standard X-rays or CT scans. EX2007 at 1. This bespoke approach first used DNA from a patient’s own tumor biopsy to identify a signature of specific mutations, and then looked for these DNA mutations to monitor for cancer recurrence from a simple blood draw. Natera’s pioneering innovations in “Tracking Tumours” was the cover story in *Nature* that same year. EX2004.



That was just the beginning of the industry acclaim for Signatera™. In clinical studies and peer-reviewed publications, Signatera™ is proven to identify cancer significantly earlier than conventional imaging or biopsies. This test has received *three* “Breakthrough Device” designations from the Food and Drug Administration, fast-tracking Natera’s market approval because its tests “provide for

more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases.” EX2005 at 2; EX2012 ¶20. Signatera™ also won acclaim from the medical community, EX2006 at 5; EX2012 ¶24, and Natera has made its tests widely available, including through Medicare, EX2007 at 1; EX2012 ¶21.

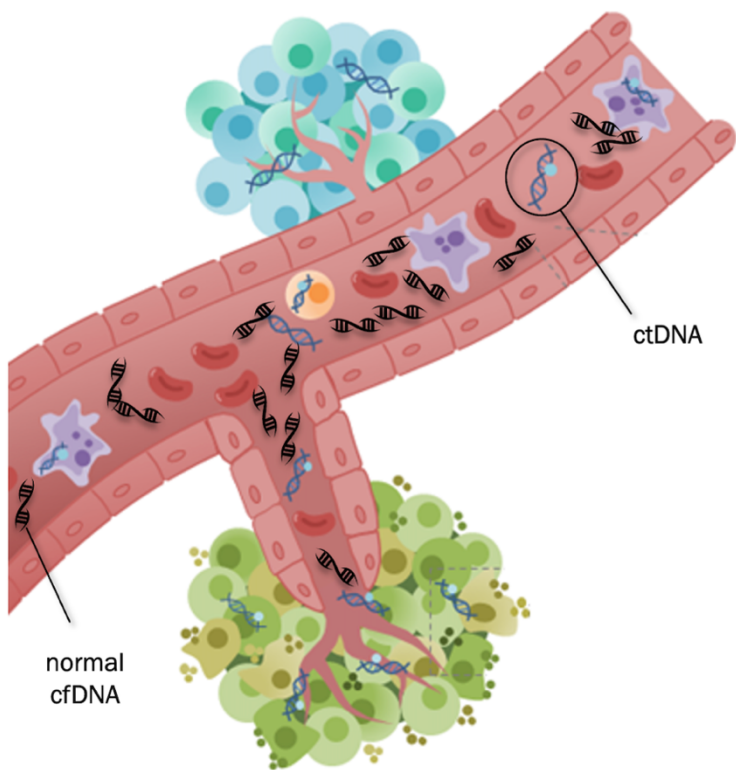
B. Cell-Free DNA, Tumors, PCR, And The Invention Of The '454 Patent

DNA is a double-helix made up of nucleotides (the complimentary A, T, C, and G bases) and found in the nucleus of most living cells, including cancer cells.

When a cell dies, its DNA fragments and the cell ruptures, spilling its contents into the bloodstream including its fragmented DNA called cell-free DNA or “cfDNA.”

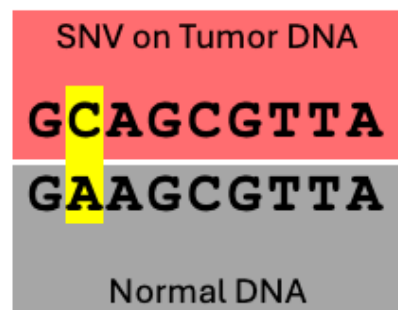
Like healthy cells, cancer cells die and undergo the same process, releasing their fragmented tumor DNA

into the bloodstream. These DNA fragments are called circulating tumor DNA or “ctDNA.” Tumor cell genomes differ from those of healthy cells because they



accumulate mutations, including single nucleotide variants (“SNVs”), in their nucleotide sequence.

An SNV is a change of a single nucleotide in a DNA sequence, as shown in the example highlighted in yellow. Most cancers are caused by SNVs. SNVs unique to a cancer can provide specific markers for cancer detection.



SNVs specific to a patient’s tumor can be identified by sequencing all or part of the patient’s tumor genome and comparing it to the genome from healthy tissue. This results in a bespoke panel of tumor-specific SNVs that can be used in further testing. The next step is searching for these tumor signatures in a patient’s blood sample.

SNVs can be identified by DNA sequencing. Next-generation DNA sequencing is a “high-throughput” approach meaning that it can sequence many DNA molecules at the same time, but it requires significantly more input DNA than the cfDNA that is typically isolated from a blood sample. Increasing the amount of cfDNA covering the specific SNV locations (or “target loci”) is typically achieved through polymerase chain reaction (“PCR”), which is a method for creating copies (amplifying) of one or more target loci *in vitro*. The DNA is heated to separate (denature) the DNA double helix. Then the mixture is cooled, and small, lab-made

DNA sequences called primers, will anneal (bind) to their complementary bases on the single strand of DNA. An enzyme (DNA polymerase) attaches to the primer and extends it, creating a complementary strand from the original single-strand template, thereby copying it. This completes one PCR cycle.

The number of times a specific base in the DNA is “read” (identified) during the sequencing process is referred to as “read depth.” Depth of read thus refers to the number of amplification products containing that specific base that is sequenced.

Each PCR cycle generally doubles the number of DNA molecules containing the target loci, creating an exponential increase in the number of copies as additional cycles are run. This is known as the exponential phase. When multiple targets are amplified together (known as “multiplex amplification”) using multiple primer pairs, the primers may bind to one another instead of their respective targets, creating off-target junk rather than copies of the target regions. Differences in nucleotide sequences at the primer binding sites can also cause unequal or biased amplification of certain targets over others. In addition, the DNA polymerase itself is not perfect and may also introduce errors.

Whole genome sequencing (“WGS”) or whole exome sequencing (“WES”) provides a comprehensive view of a patient’s tumor genome. *See, e.g.*, EX1001 at 168:9-19. WGS determines the entire DNA sequence of both the tumor and healthy

cells, then compares them to identify the ctDNA SNVs. WES can also be used to sequence only exonic DNA in order to identify potential SNVs. EX1081 ¶238.

Finding the ctDNA among all of the other DNA fragments naturally occurring in the bloodstream presents a classic needle-in-the-haystack problem. The test has to find the ctDNA “needles” and replicate them, without also replicating a lot of undesired DNA fragments in the biochemical reagents themselves. Otherwise, the amplification results in large amounts of unwanted byproducts, and just creates more noise by enlarging the haystack along with the “needles,” creating false needles and drowning out the faint signal. Natera solved this problem by adjusting the PCR reaction conditions in a manner that makes more ctDNA needles while minimizing the haystack.

Signatera™ is a commercial embodiment of Natera’s ’454 Patent claims challenged here. The ’454 Patent describes a cfDNA sample preparation method capable of detecting SNVs in concentrations as low as 0.1% compared to the relative number of copies of unmutated SNV loci. EX1001 at 44:6-17. With its patented technology, Natera developed a way to find the veritable needle in the haystack.

C. Examination Of The ’454 Patent

The Patent Office thoroughly examined the ’454 Patent application with Forshew “front and center during examination.” Pet. at 59.

The Examiner rejected then-pending claims 1, 3-15 (but not claim 2) as obvious over Forshew and required four additional references (Benesova, Marusyk, Anderson or Diehl) to fill in Forshew's gaps. EX1020 at 5-9. Natera amended independent Claim 1 to incorporate Claim 2's limitation, observing that "[n]one of the cited references teaches or suggests sequencing each of the target loci with a depth of read of at least 50,000 per target locus." EX1022 at 3. It also rewrote pending claim 15 (issued Claim 14) into independent form, adding a requirement that the method be "capable of detecting an SNV mutation that is present in less than or equal to 0.015%" which was not disclosed in Forshew because it "was only able to achieve a detection limit of 2%." EX1022 at 3. Natera also added new claims 16-29, which depended from claim 15. EX1021 at 3-4 (claims).

Natera explained that Forshew's method "was rationally and deliberately designed to rely on single-plex" amplification, meaning that multiple different regions of DNA being targeted for amplification were split up and amplified separately in single reaction volumes. EX1022 at 4. Natera further explained that Forshew "had considered but dismissed multiplex targeted amplification," which refers to amplifying the multiple different regions of DNA all together in the same reaction volume. EX1022 at 4 (quoting EX1003 at 4). "There was no reason or motivation for one of ordinary skill in the art to alter Forshew's TAm-Seq process" in this way. *Id.*

In an interview summary not submitted by NeoGenomics, *see* EX1018-1024, the Examiner and Natera discussed the “depth of read of at least 50,000 per target locus in independent claim 1 and detection of an SNV at 0.015%” in Claim 15. EX2003 at 431. The Examiner stated these limitations “require further search to determine obviousness of the claims.” *Id.* After further searching and consideration of submitted references, EX2003 at 666-1095 (also not submitted by NeoGenomics), the Examiner withdrew the Forshew rejections and allowed all pending claims. EX1024 at 7. He explained that “[t]he prior art does not show the limitation in independent claim 1 of a sequencing read depth of at least 50,000 per target locus” or the “detecting a single nucleotide variant mutation that is present in less than or equal to 0.015% of the cell-free DNA” in Claim 15. EX1024 at 9.

D. Forshew

Forshew is a research article disclosing a series of different experiments on ctDNA detection from cancer patients’ plasma samples. EX1003 at 2-3. For ovarian cancer patients, Forshew designed primers to target known mutations in the *PIK3C*, *EGFR*, *PTEN*, *KRAS*, and *TP53* genes that were to be used in all samples from ovarian cancer patients. EX1003 at 3, 23-24 (Table S1). It shows “a two-step amplification process,” EX1003 at 3-4, Fig. 1B, because performing multiplex amplification of multiple targets in a single reaction volume would create “nonspecific amplification products and biased coverage,” and single-plex alone

would “considerably increas[e] the probability of sampling errors and allelic loss.”
EX1003 at 4.

For the ovarian cancer patients, Forshew used a short, targeted multiplex “preamplification” PCR process of 15 cycles, where the amplification remained in the exponential phase “to capture the starting molecules.” EX1003 at 3-4, Fig. 1B. The second amplification involved single-plex PCR using a Fluidigm microfluidic system “to purify and select for intended targets.” *Id.* Forshew teaches barcoding and attaching sequencing adaptors, and then sequencing the amplified products to determine whether the known ovarian cancer mutations were present in each patient. EX1003 at 3-4.

Forshew ran several distinct experiments on preserved tumor and plasma samples from different subjects:

First, on the **ovarian cancer patients**, Forshew tested primers by sequencing DNA extracted from formalin-fixed, paraffin-embedded (“FFPE”) tumor specimens, which are whole tumor cells (not cfDNA). EX1003 at 4. Forshew compared its results to non-high-throughput Sanger sequencing results from the same specimens. *Id.* Data from the ovarian cancer patient FFPE experiments are illustrated in Figures 1A-D, 2A-D, S2, and Table S3. EX1003 at 3, 5, 20, 27-28.

Second, Forshaw tested primers from the FFPE experiment on plasma containing cfDNA from **healthy subjects**, EX1003 at 4, and provided data from this experiment in Figures 3A-B and Tables S4-S5, EX1003 at 6, 29-30.

Third, Forshaw tested plasma from **another ovarian cancer patient group** to identify SNVs in cancer patients, EX1003 at 5, and provided experimental data in Figures 3C-D, 4A-C, E, S4, Tables 1-3 and S6, EX1003 at 6-9, 22, 31-32. Whole genome sequencing was *not* performed. *See* EX1003 at 3 (Fig. 1A-B), 5 (“We applied TAm-Seq to directly identify mutations in plasma from individuals with HGSOC.”). The highest read-depth value reported in this experiment was 7,700 and reported sensitivity “at allele frequencies as low as 2%.” EX1003 at Abstract, 6-7, 31-32 (Tables 1-2, S6).

Fourth, Forshaw performed a retrospective analysis on a **patient with primary bowel and ovarian cancer**. EX1003 at 10. It sequenced the patient’s FFPE tumor specimens and ctDNA from plasma samples collected after tumor removal and provided data in Figure 4E. EX1003 at 8.

Fifth, Forshaw used whole genome sequencing on a tumor from **one breast cancer patient** to identify SNVs and tested plasma to monitor these mutations over time to evaluate disease progression. EX1003 at 10. Forshaw looked at 10 SNVs. EX1003 at 8, Fig. 4D. Forshaw reported no read depth values or detection sensitivity

for the breast cancer experiment. *See* EX1003 at 8 (Fig. 4D), 33 (Table S7). Data from this experiment is shown in Figure 4D and Table S7. EX1003 at 8, 33.

E. The District Court Litigation

NeoGenomics began selling RaDaR in March 2023. EX2012 ¶42. Days after RaDaR was approved by Medicare, Natera filed suit against NeoGenomics in North Carolina for infringing the '454 Patent and U.S. Patent No. 11,519,035 and moved for a preliminary injunction. EX2012 ¶¶34-74.

The North Carolina court preliminarily enjoined NeoGenomics from infringing the '035 Patent. EX2017 at 1-2. As part of that proceeding, the parties briefed NeoGenomics' invalidity challenge to the '454 Patent based on *Forsheew*. *See, e.g.* EX1053 at 9-10; EX1054 at 6-7; EX1006 ¶¶119-54; EX1081 ¶¶81-124. Days before the injunction issued on December 27, 2023, NeoGenomics filed this IPR Petition. The North Carolina case set an expedited trial date for March 10, 2025. EX2021 at 3. In parallel, NeoGenomics appealed the preliminary injunction decision, and the North Carolina court denied NeoGenomics' motion to stay the injunction pending the appeal, EX2022 at 7, which will be heard on March 29, 2024.

III. LEVEL OF ORDINARY SKILL IN THE ART

One of skill in the art for the '454 Patent would have “at least a bachelor’s degree (with several additional years of laboratory experience) in a life or physical sciences discipline with applications in genomics” and specific knowledge. EX1025

¶32. NeoGenomics’ Dr. Lennon provides a different set of qualifications for the person having ordinary skill. *See* Pet. at 15-16; EX1002 ¶¶48-52. Dr. Lennon acknowledges that his opinion “would remain unchanged” regardless of how the person of ordinary skill in the art is defined. EX1002 ¶54.

For purposes of denying institution and finding that NeoGenomics has not met its burden to show a reasonable likelihood of prevailing, Natera submits that the Board need not determine the level of ordinary skill in the art. *Johnson & Johnson Surgical Vision v. Alcon*, IPR2021-01003, 2021 WL 6338373, at *4 (P.T.A.B. Nov. 23, 2021) (denying institution: “For our analysis on whether to institute, we need not determine the level of ordinary skill in the art...”). Natera reserves the right to address the level of ordinary skill in the event the Board institutes trial.

IV. CLAIM CONSTRUCTION

The Petition proposed constructions for the terms “targeted multiplex amplification” and “sequencing the amplicons.” Pet. at 19-20. The parties have already proposed claim constructions in the North Carolina case and dispute the meaning of “sequencing the amplicons.” EX2025 at 18.

For purposes of denying institution and finding that NeoGenomics has not met its burden to show a reasonable likelihood of prevailing, Natera submits that the Board need not construe any terms of the Challenged Claims. *Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1375 (Fed. Cir. 2019) (“The Board is required to construe

‘only those terms... that are in controversy, and only to the extent necessary to resolve the controversy.’” (quoting *Vivid Techs. v. Am. Sci. & Eng’g*, 200 F.3d 795, 803 (Fed. Cir. 1999)). Natera reserves the right to assert claim construction positions if trial is ordered.

V. THE BOARD SHOULD EXERCISE ITS DISCRETION TO DENY INSTITUTION

Because Forshew was already considered in detail by the Examiner and will again be considered in the North Carolina case before any Final Written Decision here, the Board may deny institution under either *Advanced Bionics* or *Fintiv*.

A. The Petition Should Be Denied Under *Advanced Bionics* Because The Patent Office Already Analyzed Forshew

NeoGenomics’ duplicative Petition should be denied under *Advanced Bionics*. NeoGenomics admits that Forshew “was front and center during examination” by the Patent Office, Pet. at 59, yet it premised all four of the Petition’s grounds on Forshew, Pet. at 18-19. Indeed, Forshew was already thoroughly vetted, and overcome, during the original prosecution. NeoGenomics has not identified any actual errors by the Examiner in allowing the claims, let alone a material error, meriting another go-around.

In determining whether it should decline institution under Section 325(d), the Board applies a two-part framework: (1) “whether the same or substantially the same art previously was presented to the Office,” and (2) “whether the petitioner has

demonstrated that the Office erred in a manner material to the patentability of challenged claims.” *Advanced Bionics v. MED-EL Elektromedizinische Geräte*, IPR2019-01469, 2020 WL 740292, at *3 (P.T.A.B. Feb. 13, 2020) (precedential).

1. NeoGenomics Relies On The Same Forshaw Reference Previously Presented To The Office

There is no dispute that the Petition exclusively relies on the same art previously presented to the Office. Pet. at 57-61. NeoGenomics admits that Forshaw was “of record and considered during examination,” and was the basis of a rejection. Pet. at 57; *see also id.* at 59 (“Forshaw... was front and center during examination”). NeoGenomics also concedes that all of its secondary references were either “of record,” or related to a reference that was of record. Pet. at 60-61; *BlephEx, LLC v. Myco Indus., Inc.*, 24 F.4th 1391, 1402 (Fed. Cir. 2022) (“When prior art is listed on the face of a patent, the examiner is presumed to have considered it.”) (cleaned up).

Part one of the *Advanced Bionics* test is satisfied. *Parse Bioscis. v. 10x Genomics*, IPR2023-01033, 2023 WL 8789872, at *6, *9 (P.T.A.B. Dec. 19, 2023) (denying institution based on art overcome by patent owner during prosecution).

2. NeoGenomics Shows No Material Error By The Office

Under part two of *Advanced Bionics*, NeoGenomics has the burden “to make a showing of material error” in the Petition; otherwise, “the Director generally will exercise discretion not to institute *inter partes* review.” 2020 WL 740292, at *3.

Advanced Bionics considered *Becton Dickinson* factors (c), (e), and (f) in determining whether a petitioner has shown material error. *Id.* at *4. Each of these factors weighs in favor of discretionary denial in this case.

a. *Becton* Factor (c): “the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection”

Factor (c) supports denying institution because the Examiner rejected the claims over Forsheew, and Natera overcame the rejection during prosecution. *See* EX1020 at 5-9; EX1024 at 7-9; *Flex Logix Techs. v. Konda*, IPR2020-00262, 2020 WL 4462127, at *4 (P.T.A.B. Aug. 3, 2020) (denying institution: factor (c) favored denial because IPR reference “was applied by the Examiner as a basis for a rejection that was overcome by the Patent Owner”); *Xilinx v. Analog Devices*, IPR2021-00294, 2021 WL 2385526, at *10 (P.T.A.B. June 10, 2021) (similar); *Parse*, 2023 WL 8789872, at *7, *9 (similar).

b. *Becton* Factor (e): “whether petitioner has pointed out sufficiently how the examiner erred in its evaluation of the asserted prior art”

NeoGenomics does not meet its burden to show that the Examiner erred, again supporting a denial of institution under Factor (e). Where the examiner specifically relied on the reference at issue and yet the petitioner disagrees “with a specific finding of record by the Office, then ordinarily the petitioner’s required showing of

material error must overcome persuasively that specific finding of record.”

Advanced Bionics, 2020 WL 740292, at *4.

Here NeoGenomics asserts two alleged Examiner errors, specifically that the Examiner “fail[ed] to appreciate that:

- (1) Forshew’s pre-amplification step is multiplex amplification; and
- (2) a greater depth of sequencing and the resulting increased sensitivity would have been obvious because sequencing depth was a known result effective variable for increased sensitivity.”

Pet. at 57. Neither is supported.

First, because the Examiner already articulated NeoGenomics’ first theory, NeoGenomics cannot reasonably assert the Examiner misapprehended it. NeoGenomics’ second theory that the Examiner failed to evaluate the “depth of read of at least 50,000 per target locus” limitation, fares even worse because the Examiner expressly cited that limitation as a reason for allowance. As explained below, neither theory has any merit.

NeoGenomics has already made and abandoned this argument. In the North Carolina litigation, NeoGenomics asserted allegations that Natera misled the patent Examiner about Forshew as part of an inequitable conduct defense. EX2015 at 22-24, 29-30 (Tenth and Eleventh Defenses & Fifth Counterclaim). Only months later, NeoGenomics voluntarily dropped the defenses. EX2023.

NeoGenomics’ remaining arguments also have no merit. NeoGenomics completely ignores the mutation detection sensitivity limitation of independent Claim 14, which was cited as a reason for allowance. NeoGenomics instead asserts that the Examiner should have transformed Forshew’s generic teaching that increasing depth of read could increase sensitivity into obviousness of “depth of read of at least 50,000 per target locus” in the context of Claim 1’s other requirements, even though NeoGenomics offers no evidence or argument that Forshew disclosed a depth of read that high.

NeoGenomics claims that the Examiner’s “[f]ailure to reject claims over” Bai, Bashashati, Narayan, and Bentley “was also material error,” yet NeoGenomics provides no analysis beyond that simple assertion. *See* Pet. at 60-61. Such conclusory statements fall far short of NeoGenomics’ burden to show a material error.

1) No Material Error About Multiplex Amplification (All Claims)

The Examiner did not miss that “Forshew’s pre-amplification step is multiplex amplification.” Pet. at 57. He asserted that Forshew disclosed “targeted multiplex amplification” and never withdrew that assertion, stating:

Forshew et al. shows in the abstract and throughout analysis of cell-free DNA of individuals with tumors for mutation analysis by ***multiplex amplification using a pool of primer pairs*** followed by sequencing of

amplicons. Forshew et al. outlines the process in Figure 1, which shows *a preamplification step that uses a single multiplex amplification of regions of interest followed by a second amplification followed by barcoded amplification* and sequencing.

EX1020 at 6. The Examiner stood by his position during prosecution, and never withdrew or contradicted it. NeoGenomics’ claim of material error is thus contradicted by the plain record. *Advanced Bionics*, 2020 WL 740292, at *4 (petitioner may show error by showing that the Office “overlook[ed] something persuasive” or “must overcome persuasively [a] specific finding of record”).

NeoGenomics next claims that Natera falsely asserted that “Forshew had considered but dismissed multiplex targeted amplification,” because Natera’s expert confirmed that Forshew disclosed “multiplex PCR.” Pet. at 57-58. NeoGenomics again alleges that “the Examiner materially erred by accepting Patent Owner’s false statement and not maintaining the rejection of claims over Forshew.” Pet. at 58. Not so.

First, Natera did not mislead the Examiner. Forshew plainly did consider and reject use of multiplex amplification alone: “Multiplex amplification using a large set of primers could result in nonspecific amplification products and biased coverage. We therefore applied a two-step amplification process....” EX1003 at 4. In *Personalis*, NeoGenomics’ own counsel told the Board all about Forshew’s

teaching of “a two-step amplification process” with “limited cycle multiplex pre-amplification”:

Forsheew describes a “two-step amplification process,” wherein *limited cycle multiplex preamplification* is used to capture starting molecules, followed by “individual amplification to purify and select for intended targets.” Then, additional sequencing adaptors and a barcode are added via additional PCR steps.

EX2001 at 16. He noted criticism that “Forsheew’s assay already suffered from ‘technical limitations related to multiplexing of PCR assays....’” EX2002 at 52.

Second, NeoGenomics cites nothing showing the Examiner’s alleged “accept[ance of] Patent Owner’s false statement.” Pet. at 58. Even if this statement were somehow false (it was not), without showing that the Examiner relied on this statement, NeoGenomics cannot show error because (1) the Examiner did not overlook this asserted teaching of Forsheew, and (2) there is no “finding of record” about which NeoGenomics is now complaining. *Advanced Bionics*, 2020 WL 740292, at *4; *Parse*, 2023 WL 8789872, at *9 (no examiner error allowing claims after patent owner highlighted differences between prior art and claims).

NeoGenomics’ first alleged material error is baseless.

2) No Material Error About “sequencing ... depth of read of at least 50,000 per target locus” (Claims 1-13, 15)

NeoGenomics next claims that the Examiner materially erred by not issuing “a rejection of then-pending claim 2, which recited the use of a ‘sequencing depth’ of at least 50,000,” and speculates the Examiner must have “neglected” the limitation. Pet. at 58. Yet again the record shows the Examiner plainly, and expressly, considered this limitation and exercised his reasoned judgment to determine that it was not disclosed or obvious over the prior art, finding:

The prior art does not show the limitation in independent claim 1 of a sequencing depth of at least 50,000 per target locus in the context of the claimed subject matter.

EX1024 at 9. And this finding occurred after the Examiner told Natera that adding the 50,000 depth-of-read limitation to claim 1 “would require further search to determine obviousness of the claims.” EX2003 at 431.

NeoGenomics asserts that the Examiner made two mistakes about the “50,000 per target locus” limitation. First, it claims that the Examiner “utterly failed to recognize” that Forshew “teaches that increasing sequencing depth was obvious and natural, explaining that ‘[h]igher read depth’ can be used to achieve ‘enhanced mutation detection without change to protocols.’” Pet. at 59 (quoting EX1003 at 11). But vaguely mentioning “[h]igher read depth” is not the same as disclosing a “depth of read of at least 50,000 per target locus” as required by Claims 1-13 and

15. The 50,000 read depth is almost an order of magnitude higher than the 7,700 depth disclosed by Forshew. EX1003 at 6 (Table 1 showing maximum depth of read of “7700”); *see infra* § VI.C.2.a. NeoGenomics offers no support for its claim that the Examiner “utterly failed to recognize” that Forshew taught an order of magnitude increase in depth of read—because there is none. Forshew plainly did not. *Risen (Suzhou) Pharma Tech. v. Alzheon*, IPR2022-01200, 2023 WL 130471, at *14 (P.T.A.B. Jan. 9, 2023) (denying institution: no material error because reference did not disclose or suggest the claim limitation).

Additionally, Claim 1’s “depth of read of at least 50,000 per target locus” is required in the context of all the claim requirements, including using “10 to 500 target loci” to “obtain amplicons having a length of 50-150 bases,” which are also not disclosed by Forshew in a single embodiment. ’454 Patent at 171:32-33, 36-37; *see also infra* § VI.A-B. The Examiner again recognized this deficiency: “The prior art does not show the limitation in independent claim 1 of a sequencing depth of at least 50,000 per target locus ***in the context of the claimed subject matter.***” EX1024 at 9. NeoGenomics offers no explanation for why the Examiner reading Forshew should have recognized a motivation to achieve a depth of read of at least 50,000 per target locus at all, much less in the context of the claim’s other requirements.

NeoGenomics’ only cited case is inapposite. *See* Pet. at 58-59. In *Halliburton*, the previously considered art disclosed the same limitations that the

Examiner found missing. *Halliburton Energy Servs., Inc. v. U.S. Well Servs. LLC*, IPR2021-01316, Paper 9 at 15 (P.T.A.B. Feb. 22, 2022). Here, however, NeoGenomics does not assert that the sequencing depth “of at least 50,000 per target locus” limitation is even disclosed in Forshew. *See* Pet. at 26; *see infra* § VI.C.2.a .

NeoGenomics’ second alleged Examiner error regarding the “depth of read of at least 50,000 per target locus” limitation was that “Patent Owner failed to provide the Examiner with any evidence documenting its extensive prior statements confirming the obviousness of increasing sequencing ‘depth.’” *Id.* at 60. But all of these statements allegedly “confirming the obviousness of increasing sequencing ‘depth’” are cumulative of Forshew’s own disclosure according to NeoGenomics. *See id.* at 59-60 (providing quotations). In fact, none of them are even in the context of Forshew’s procedure, *see id.*, and thus are not even as relevant as Forshew’s own comment that “[h]igher read depth... could allow for enhanced mutation detection...” EX1003 at 11. Moreover, fatal to NeoGenomics’ alleged material error by the Examiner, none of these statements assert that a “depth of read of at least 50,000 per target locus” would have been obvious, much less in the context of the claimed invention as a whole. *See id.*

NeoGenomics may disagree with the Examiner’s assessment, but that alone does not “rise[] to the level of a clear and material error about which reasonable minds could not disagree.” *Boragen v. Syngenta Participations*, IPR2020-00124,

2020 WL 2206972, at *13 (P.T.A.B. May 5, 2020); *Advanced Bionics*, 2020 WL 740292, at *3 (“If reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability. At bottom, this framework reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown.”); *see also Janssen Biotech v. United States*, IPR2021-01484, 2022 WL 683199, at 14 (P.T.A.B. Mar. 2, 2022); *Weatherford U.S. v. Enventure Global Tech.*, IPR2020-01661, 2021 WL 1432974, at *11 (P.T.A.B. Apr. 15, 2021).

Indeed, NeoGenomics provides no evidence that the “Examiner utterly failed to recognize [Forshew’s] teaching” as opposed to exercising his judgment to find the claims nonobvious over the cited art. *Risen (Suzhou) Pharma Tech. v. Alzheon*, PGR2022-00051, 2023 WL 181339, at *26 (P.T.A.B. Jan. 13, 2023) (“[W]e find that Petitioner has not sufficiently shown the Examiner’s actions were error rather than an exercise of judgment on which reasonable minds can disagree.”).

Accordingly, NeoGenomics fails to meet its burden to show that the Examiner materially erred in allowing Claims 1-13 and 15 over Forshew.

3) NeoGenomics Does Not Argue Material Error Based On A “0.015%” Detection Sensitivity (Claims 14-28)

Challenged Claim 14 and its dependent claims 15-28 recite a method “capable of detecting an SNV mutation that is present in less than or equal to 0.015% of the

cell-free DNA comprising the SNV locus.” EX1001 at 172:27-30. The Examiner cited this limitation as a reason for allowing then-claim 15 (issued Claim 14) and its dependents, explaining:

The prior art does not show the limitation in independent claim 15 of detecting a single nucleotide variant mutation that is present in less than or equal to 0.015% of the cell-free DNA comprising the single nucleotide variant locus in the context of the claimed subject matter.

EX1024 at 9.

NeoGenomics does not argue that the Examiner materially erred in this determination. Pet. at 57-61. Nor could it. As explained below, Forshew does not disclose or render obvious a sensitivity of 0.015%. *See infra* § VI.D. NeoGenomics’ counsel apparently agrees, having told the Board multiple times in *Personalis* that Forshew was not particularly sensitive because its TAm-Seq assay is only “able to identify 95% of digital-PCR-detected mutations occurring at a frequency higher than 2%.” EX2001 at 17; EX2002 at 53, 63.

NeoGenomics also fails to meet its burden to show that the Examiner erred in allowing Claims 14-28 over Forshew.

4) Secondary References

Finally, NeoGenomics asserts that the Examiner materially erred by not rejecting the claims over Bai, Bashashati, Narayan, and Bentley. Pet. at 60-61. However, NeoGenomics does not argue that these references disclosed or rendered

obvious the limitations found missing in the art, *id.*, and the mere lack of a rejection by itself is not sufficient to show material error, *Microsoft v. ThroughPuter*, IPR2022-00757, 2022 WL 16625414, at *8 (P.T.A.B. Nov. 1, 2022); *Ivantis v. Sight Scis.*, IPR2022-01540, 2023 WL 2604378, at *6 (P.T.A.B. Mar. 22, 2023).

Because NeoGenomics musters no actual material error by the Examiner during his prior evaluation of Forsheew, *Becton Dickinson* factor (e) also supports denying institution here.

c. *Becton* Factor (f): “the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments”

Factor (f) weighs in favor of denying institution. NeoGenomics does not expressly argue that the Petition contains additional evidence or facts that warrant reconsideration of Forsheew. Nor could it. Natera’s prior statements do not say anything that was not already in Forsheew according to NeoGenomics—that sequencing depth can be a factor in sensitivity. *Fortinet v. British Telecommc’ns*, IPR2019-01326, 2020 WL 95869, at *6-7 (P.T.A.B. Jan. 7, 2020) (finding alleged additional evidence “cumulative” of art before the examiner). Further, the Examiner found that Forsheew disclosed “targeted multiplex amplification” and never withdrew that finding, rendering Dr. Metzker’s subsequent testimony on this point irrelevant. EX1020 at 6.

In sum, NeoGenomics’ attempt to re-evaluate Forsheew, a reference that was “front and center” during prosecution, Pet. at 59, should be rejected under *Advanced Bionics* and 35 U.S.C. § 325(d).

B. Because The North Carolina Litigation Is Far Ahead With A Preliminary Injunction Entered, The Board Should Discretionarily Deny Institution Under *Fintiv*

This case also presents a quintessential *Fintiv* situation. By the time the Board has the opportunity to issue a final written decision here, validity over Forsheew will already have been decided either on summary judgment, or at the March 2025 jury trial, in the expedited North Carolina litigation. If NeoGenomics really wanted to have the Patent Office reconsider validity of the ’454 Patent, it would have filed its Petition long ago. The Board should exercise its discretion to decline institution under 35 U.S.C. § 314(a). *See Apple v. Fintiv*, IPR2020-00019, 2020 WL 2126495, at *2-3 (P.T.A.B. Mar. 20, 2020) (precedential). Adding another go-around at the Patent Office will only result in inefficiency, introduce uncertainty, and delay final resolution of this long-running dispute.

1. Factor 1: “whether the court granted a stay or evidence exists that one may be granted if a proceeding is instituted”

Factor 1 weighs in favor of denial. The North Carolina district court’s entry of a preliminary injunction, and refusal to stay it pending appeal, shows a stay is highly unlikely. EX2017; EX2022 at 7. Indeed, the Federal Circuit instructs that

“the district court ordinarily should not grant both a preliminary injunction and a stay.” *Procter & Gamble v. Kraft Foods*, 549 F.3d 842, 849 (Fed. Cir. 2008).

With a preliminary injunction in effect, parties and courts typically try to accelerate a final resolution, not delay it. *See e.g., Garvey Corp. v. Barry-Wehmiller Design Grp., Inc.*, 365 F. Supp. 2d 893, 901 (N.D. Ill. 2005) (“Having entered a preliminary injunction, this Court intends to reach the merits of this case as quickly as possible.”). This is exactly what happened here. After filing its Petition, NeoGenomics stipulated to an expedited schedule with a jury trial set for March 2025. EX2019 at 7; EX2020-EX2021. Then the parties and Delaware court agreed to a stipulated stay of that case involving additional patents and parties, acknowledging “the resolution of the M.D.N.C. Action against... NeoGenomics is likely to simplify issues and preserve judicial economy.” EX2011 at 2.

The Petition vaguely argues that stays generally can be granted, including in the North Carolina district court. *See* Pet. at 62-63. The Board should not speculate whether a district court will grant a stay, especially in the current circumstances where the North Carolina court issued a preliminary injunction, refused to stay it, and NeoGenomics agreed to an expedited trial. EX2022 at 1; EX2020-EX2021; *Apple v. Fintiv*, IPR2020-00019, 2020 WL 2486683, at *5 (P.T.A.B. May 13, 2020) (informative) (“We decline to infer, based on actions taken in different cases with

different facts, how the District Court would rule should a stay be requested by the parties in the parallel case here.”).

The most efficient path forward is for all concerned to yield to the North Carolina’s fast-track resolution of the dispute. That is what the parties and District of Delaware have done, and it makes sense for the Board to do likewise.

2. Factor 2: “proximity of the court’s trial date to the Board’s projected statutory deadline for a final written decision”

Factor 2 weighs heavily in favor of discretionary denial. The projected deadline for any Final Written Decision here is late June 2025. 35 U.S.C. § 316(a)(11). The North Carolina jury trial is set for March 10, 2025, EX2021 at 3, more than three months before the Final Written Decision deadline.

NeoGenomics’ reliance on an alleged median time to trial in the North Carolina case projecting a February 2027 trial, Pet. at 64, fails to acknowledge that NeoGenomics sought an accelerated trial date because of the preliminary injunction currently in force, EX2019 at 6-7. Under these circumstances, NeoGenomics’ hypothetical trial date should not override the reality of the March 2025 North Carolina trial date. EX2021; *10x Genomics v. President and Fellows of Harvard Coll.*, IPR2023-01299, 2024 WL 993828, at *7 (P.T.A.B. Mar. 7, 2024) (discretionary denial: district court trial date set approximately five months before FWD deadline); *Samsung Elecs. v. Mojo Mobility*, IPR2023-01098, 2024 WL

517450, at *3-4 (P.T.A.B. Feb. 9, 2024) (discretionary denial: jury trial scheduled about six months before FWD deadline).

3. Factor 3: “investment in the parallel proceeding by the court and the parties”

The parties’ investment in parallel litigation strongly weighs in favor of denying institution here. The parties already provided evidence, expert testimony, and briefing on Forshev in connection with the North Carolina preliminary injunction motion. EX2013; EX1053; EX1054; *Fintiv*, 2020 WL 2486683, at *5 (“preliminary injunction” probative of Factor 3).

The North Carolina case is fast-tracked for the March 10, 2025 jury trial. EX2021 at 3; EX2011 at 2. Claim construction is set for completion before the Board’s institution decision deadline here. EX2021 at 2 (setting the Markman hearing for May 14, 2024). Also, contrary to NeoGenomics’ contentions, Pet. at 65-66, final invalidity and infringement contentions will be done by the institution deadline here, with fact discovery scheduled to close only a few weeks later in July 2024, EX2021 at 2.

The parties’ substantial investment in the North Carolina litigation strongly favors discretionary denial. *See, e.g., 10x Genomics*, 2024 WL 993828, at *8 (discretionary denial due to substantial resources invested in the parallel district court proceeding including completed claim construction); *Samsung*, 2024 WL

517450, at *4 (discretionary denial: fact discovery well underway and claim construction would be complete before institution decision); *Vector Flow v. HID Global*, IPR2023-00353, 2023 WL 5167491, at *7-8 (P.T.A.B. July 17, 2023) (discretionary denial: claim construction complete and fact discovery substantially complete showed a “significant investment” in the parallel litigation).

4. Factor 4: “overlap between issues raised in the petition and in the parallel proceeding”

Because NeoGenomics’ Petition is a reenactment of its invalidity defense in North Carolina, Factor 4 also supports a discretionary denial.

NeoGenomics acknowledges that it is asserting Forshew, “the same reference relied upon here,” in North Carolina. Pet. at 1. NeoGenomics’ invalidity contentions mirror the allegations in the Petition. Compare Pet. at 20-47 with EX2024. NeoGenomics weakly offers that its Petition challenges more claims than are currently asserted in the litigation, Pet. at 67, but its reliance on Claim 1 to argue unpatentability for the bulk of independent Claim 14 shows this argument has little practical meaning, see Pet. at 42-43.

NeoGenomics never offered a *Sotera* stipulation to reduce the overlap between the North Carolina case and any IPR, nor could it at this point since NeoGenomics has already submitted to the district court an invalidity defense based on Forshew. See Pet. at 67; *10x Genomics*, 2024 WL 993828, at *8-9 (discretionary

denial because petitioner did not offer a *Sotera* stipulation and was “silent as to the overlapping issues” with the district court litigation); *Vector Flow*, 2023 WL 5167491, at *8.

5. Factor 5: “whether the petitioner and the defendant in the parallel proceeding are the same party”

The parties in the North Carolina litigation, NeoGenomics and Natera, are the same parties here. Factor 5 thus weighs heavily in favor of discretionary denial. *See, e.g., Fintiv*, 2020 WL 2486683, at *6 (“Because the petitioner and the defendant in the parallel proceeding are the same party, this factor weighs in favor of discretionary denial.”); *10x Genomics*, 2024 WL 993828, at *9 (discretionary denial: because petitioner and defendant in the parallel proceeding were the same); *Vector Flow*, 2023 WL 5167491, at *8 (same).

6. Factor 6: “other circumstances that impact the Board’s exercise of discretion, including the merits”

Factor 6 also strongly favors discretionary denial. Where “the Board’s analysis of *Fintiv* factors 1-5 favors denial of institution, the Board shall then assess compelling merits.” *Commscope Techs. v. Dali Wireless*, No. IPR2022-01242, 2023 WL 2237986, at *2 (P.T.A.B. Feb. 27, 2023); *see also* Director’s Interim Procedure for Discretionary Denials in AIA Post-Grant Proceedings with Parallel District Court Litigation (June 21, 2022), at 4-5. The merits of NeoGenomics’ arguments are certainly not “compelling,” and fail to even establish a reasonable likelihood of

prevailing. *See infra* § VI. The Examiner already allowed these claims over ForsheW during prosecution. *See* EX1024 at 7; *see supra* § V.A. The Petition is simply a retread of this same art overcome during prosecution and NeoGenomics points to nothing new here. NeoGenomics’ conclusory assertion that its Petition presents a “compelling, meritorious challenge” is belied by its grounds. *See* Pet. at 68.

7. None Of The *Fintiv* Factors Supports Institution

Every factor supports discretionary denial of the Petition. Accordingly, Natera requests that the Board deny institution to conserve resources and avoid repetitive challenges to the same patent based on the same prior art.

VI. NEOGENOMICS HAS NOT SHOWN ITS CHALLENGES ARE REASONABLY LIKELY TO PREVAIL

The Board should decline to institute trial because the Petition fails to show a reasonable likelihood of prevailing on any ground. The Petition first attempts to mislead the Board that ForsheW’s metastatic breast cancer embodiment includes the Figure 1B embodiment to satisfy the “targeted multiplex amplification” claim requirement. Then it covertly mixes-and-matches features from the distinct testing embodiments in ForsheW without providing a required motivation to combine. It does the same thing to try to establish a read depth of 50,000, and still comes up short. NeoGenomics knows that ForsheW has limited sensitivity and can only detect mutations occurring at frequencies higher than 2%, but still tries to convince the

Board it would be obvious to improve that by several orders of magnitude to reach the sensitivity of “of less than or equal to 0.015%” required by the claims. Its resort to Bentley and Narayan in Ground 3 does not make up for Forshe’s lack of sensitivity. None of this meets NeoGenomics’ burden to show unpatentability.

A. Forshe Does Not Disclose Limitations [1.b] and [14.b] (All Claims)

Limitation [1.b] requires:

performing targeted multiplex amplification to amplify 10 to 500 target loci each encompassing a different tumor-specific SNV mutation from cell-free DNA isolated from a plasma sample of the subject or DNA derived therefrom to obtain amplicons having a length of 50-150 bases, wherein the target loci are amplified together in the same reaction volume;

EX1001 at 171:32-38. Limitation [14.b] is similar but omits that the “amplicons hav[e] a length of 50-150 bases.” *Id.* at 172:18-23.

Forshe discloses a breast cancer example where “[t]en mutations were selected, and short amplicons (<120 bp) were designed to cover the mutation loci (table S7).” EX1003 at 10. For limitations [1.b] and [14.b], the Petition relies on this breast cancer embodiment: “Forshe discloses amplifying ten SNV mutations from a tumor sample that were identified based on WGS data, which are listed in Table S7.” Pet. at 22; *see also id.* at 42 (limitation [14.b] relying on [1.b] argument). For the “amplicons having a length of 50-150 bases” requirement of Claim 1,

NeoGenomics again asserts amplicons with lengths of greater than 50 and less than 120 bases based on Table S7, which is the breast cancer embodiment. *Id.* at 24.

However, in describing how Forshew allegedly satisfies the targeted multiplex amplification step in the breast cancer embodiment, NeoGenomics incorrectly asserts that Forshew discloses “that the ten mutations [from the breast cancer embodiment] were amplified by a targeted multiplex amplification wherein all of the targets were amplified in the same reaction: ‘An initial preamplification step was performed for 15 cycles using a *pool of the target-specific primer pairs*’ which included ‘*each* forward and reverse target-specific primer.’” Pet. at 23 (quoting EX1003 at 3 (Fig. 1B Legend)) (emphases original). However, the passage NeoGenomics quotes from Forshew’s Figure 1B plainly describes the ovarian cancer embodiment.

The series of Figures 1A-D describe a specific example involving ovarian cancer patients in Forshew. For Figure 1A, for example, Forshew states, “[p]rimers were designed to amplify regions of interest in overlapping short amplicons (table S1).” EX1003 at 3, Fig. 1. Table S1 describes a different set of amplicons than those used in Table S7, referenced above for the breast cancer embodiment. *Compare* EX1003 at 23-24 (Table S1) *with id.* at 33 (Table S7: “one breast cancer patient”). Figure 1B then describes how the experiment was performed, “Workflow overview. Multiple regions were amplified in parallel.” *Id.* at 3, Fig. 1. Figure 1C

next describes the “[d]istribution of observed nonreference read frequencies, averaged over 47 FFPE samples, across all loci and all nonreference bases.” *Id.* And Figure 1D also depicts the “[d]istribution of the observed background nonreference read frequencies averaged over 47 FFPE samples....” *Id.* Thus, Figures 1A-D describe a single experiment involving testing for the specific regions of interest shown in Table S1, including the procedure (Figure 1B) and the results (Figures 1C-D).

NeoGenomics asserts that the Figure 1B embodiment is the breast cancer embodiment, Pet. at 23 (asserting that the ten mutations of the breast cancer embodiment were amplified as described in Figure 1B), which is plainly contradicted by Forshew itself. Figure 1B was the procedure used to “amplify regions of interest in overlapping short amplicons (*table S1*).” EX1003 at 3, Fig. 1.

Because Forshew’s Figure 1B embodiment is not the breast cancer testing embodiment, NeoGenomics’ assertion that Forshew *discloses* limitations [1.b] and [14.b] fails. *See, e.g.*, Pet. at 42 (stating for limitation [14.b] simply “Disclosed”). Forshew does not disclose a single embodiment that has all of the features of limitations [1.b] and [14.b], and NeoGenomics never argues that it would have been obvious to combine Forshew’s embodiments to achieve these limitations.

This is not an inadvertent error. Counsel told the Board in *Personalis* that “Forshew describes a series of experiments....” EX2001 at 15. There is no basis for it argue otherwise here.

Grounds 2 and 4 do not state the basis for obviousness of Claims 1 and 14 and thus for any Challenged Claim. *See, e.g.*, Pet. at 47-53 (Ground 2), 56 (Ground 4). The Board could deny those grounds on that basis alone. Ground 3 expressly relies on Ground 1. *Id.* at 54-56. To the extent the Board implies an assertion that Grounds 2 and 4 rely on Forshew’s disclosure of limitations [1.b] and [14.b] as described in Ground 1, even though the Petition does not say that, those grounds and Ground 3 fail for the same reason as Ground 1. NeoGenomics cannot prevail on any ground for any claim. Institution should be denied on this basis alone.

B. NeoGenomics Gathers Features Of Multiple Different Embodiments Of Forshew For The “Sequencing” Limitations Without Any Argument Or Evidence As To Why They Would Be Combined (All Claims)

Because Forshew does not disclose a use of its method that meets the requirements of independent Claim 1 or 14, NeoGenomics resorts to picking and choosing features of various embodiments using hindsight. NeoGenomics knows that “Forshew describes a series of experiments,” EX2001 at 15, yet combined them anyway without providing the required motivation. Counsel knows that tinkering with Forshew’s method was a bad idea, warning in the *Personalis* IPR that one of

skill would “avoid attempting to redesign the TAm-Seq assay” in Forsheew because the “risks associated with modifying Forsheew’s already-working assay could very well cause the assay to lose sensitivity or even worse, not work at all.” EX2002 at 60-61.

NeoGenomics cannot carry its burden without showing why one of skill would have selected the various features of Forsheew’s different embodiments and combined them into a single operative method or system. *In re Stepan Co.*, 868 F.3d 1342, 1346 n.1 (Fed. Cir. 2017) (when “combining multiple embodiments from a single reference... there must be a motivation to make the combination and a reasonable expectation that such a combination would be successful, otherwise a skilled artisan would not arrive at the claimed combination”); *Markforged v. Continuous Composites*, IPR2022-00679, 2023 WL 6534357, at *6-7 (P.T.A.B. Sept. 26, 2023) (rejecting “Petitioner’s reliance on multiple embodiments”); *Enfish v. Microsoft*, 822 F.3d 1327, 1343 (Fed. Cir. 2016).

1. Limitations [1.a] And [14.a] – Breast Cancer Embodiment

Independent Claims 1 and 14 start by requiring “performing whole exome sequencing or whole genome sequencing on a tumor sample of the subject to identify a plurality of tumor-specific SNV mutations.” EX1001 at 171:29-31, 172:15-17. NeoGenomics relies solely on Forsheew’s “identif[ication of] tumor mutations in a patient with metastatic breast cancer” for this limitation. Pet. at 22 (citing EX1003

at 10, Table S7); *see also id.* at 42 (citing argument for Claim 1 for Claim 14). To assert that the identified mutations were SNVs, NeoGenomics cites Tables S3 and S6-S7 without explanation. Pet. at 22. Although Table S7 relates to the breast cancer embodiment, EX1003 at 33 (“Table S7: Mutations and amplicons studied in one breast cancer patient.”), Tables S3 and S6 do not, EX1003 at 27 (“Table S3: Mutations identified in FFPE samples.”); *see also* EX1003 at 31 (“Table S6: Additional data for Table 2 for mutations identified in plasma samples.”); EX1003 at 7 (“Table 2. Mutations identified by TAm-Seq in a set of 62 plasma samples from ovarian cancer patients.”).

NeoGenomics’ lead counsel knows that each of these are separate experiments. EX2001 at 15-18 (“Forsheew describes a series of experiments” including ones involving “a patient with metastatic breast cancer,” “FFPE samples,” “ovarian tumor mutants,” “mutants in the plasma of cancer patients”). The Petition is entirely silent on why it cited Tables S3 and S6 or how they might satisfy the “sequencing” limitations.

NeoGenomics’ expert, however, goes a step further and asserts that “[a] POSA would have also understood that such tumor-specific SNVs [in Table S3] *could be identified* in the same manner by performing whole exome sequencing or whole genome sequencing.” EX1002 ¶144. This statement confirms that neither the Petition nor NeoGenomics’ expert argue that Forsheew discloses using whole

exome sequencing or whole genome sequencing to generate the SNVs in Table S3 or even that it would have been obvious to do so. *See, e.g., Pers. Web Techs. v. Apple*, 848 F.3d 987, 993–94 (Fed. Cir. 2017) (motivation to combine is proven by showing what one of skill would have been motivated to do, not could have done if motivated).

Nor can NeoGenomics take this position which it knows is factually inaccurate. EX2001 at 15-18 (NeoGenomics lead counsel: Forshe’s experiments involving “a patient with metastatic breast cancer,” is different from the “FFPE samples” and “ovarian tumor mutants” experiments shown in Tables S3 or S6); 37 C.F.R. § 42.11. Thus, for limitation [1.a], NeoGenomics relies solely on the breast cancer embodiment.

2. Limitations [1.b] And [14.b] – Breast Cancer Embodiment

As noted above in Section VI.A., NeoGenomics relies on the breast cancer embodiment for limitations [1.b] and [14.b] even though it improperly relies on the preamplification step from the Figure 1 ovarian cancer embodiment for “targeted multiplex amplification.” *See* Pet. at 22-24, 42.

3. Limitations [1.c] And [14.c] – Figure 1 Embodiment

Limitation [1.c] requires “sequencing the amplicons to obtain sequence reads, and detecting one or more of the tumor-specific SNV mutations present in the cell-

free DNA from the sequence reads, wherein the sequencing has a depth of read of at least 50,000 per target locus.” EX1001 at 171:39-43.

Limitation [14.c] recites the same limitation except that the wherein clause is replaced with “wherein the method is capable of detecting an SNV mutation that is present in less than or equal to 0.015% of the cell-free DNA comprising the SNV locus.” *Id.* at 172:24-30.

For the “sequencing” requirement, the Petition again pivots away from the breast cancer embodiment to the distinct Figure 1 embodiment of Forshew. The Petition asserts that “Forshew teaches the key components of this claim element, including sequencing followed by detecting mutations in the sequence data.” Pet. at 24. The Petition then asserts disclosure of “sequencing” based on Figure 1B and the following passage from Forshew: “We performed 100-base single-end sequencing (GAIIx sequencer, Illumina), with an additional 10 cycles using the barcode sequencing primer, generating ~30 million reads per lane.” Pet. at 25 (quoting EX1003 at 4).

As discussed above in Section VI.A, Figure 1B is not the breast cancer embodiment. EX1003 at 3-4, Fig. 1 (describing the series of steps in generating Figures 1A-D). As noted above, Figure 1 itself refers to “Primers ... designed to amplify regions of interest in overlapping short amplicons (table S1).” EX1003 at 3. Thus, the amplicons for Figure 1 are shown in Table S1, not Table S7, which

reflects the breast cancer embodiment. *See* EX1003 at 10 (“Whole genome sequencing of tumor material was used to identify tumor mutations in a patient with metastatic breast cancer Ten mutations were selected, and short amplicons (<120 bp) were designed to cover the mutation loci (*table S7*).”).

NeoGenomics’ quotation referencing “perform[ing] 100-base single-end sequencing,” Pet. at 25, also comes from the Figure 1 embodiment, EX1003 at 4 (quotation appearing in the same paragraph as the discussion of Figures 1A and 1B). Thus, NeoGenomics’ single quotation from Forshew for “sequencing” also does not pertain to the breast cancer embodiment.

Given that all of NeoGenomics’ evidence for “sequencing” pertains to the Figure 1 ovarian cancer embodiment, NeoGenomics has no evidence that the breast cancer embodiment it relied on for most of Claims 1 and 14 discloses the “sequencing” required by those claims. NeoGenomics’ expert offers nothing more than the Petition. EX1002 ¶¶158-59. NeoGenomics does not argue that it would have been obvious to combine the “sequencing” of the Figure 1 embodiment with the breast cancer embodiment. *See* Pet. at 24 (“Forshew *teaches* the key components of this claim element, *including sequencing* followed by detecting mutations in the sequence data.”), 43 (“For the reasons stated above, the ‘sequencing’ and ‘detecting’ limitations in this element are taught in Forshew.”). NeoGenomics cannot combine features of various embodiments without explaining why it would have been obvious

to do so. *Stepan*, 868 F.3d at 1346 n.1 (when “combining multiple embodiments from a single reference ... there must be a motivation to make the combination and a reasonable expectation that such a combination would be successful, otherwise a skilled artisan would not arrive at the claimed combination”).

NeoGenomics thus cannot prevail on its assertion of invalidity for Claims 1 and 14 or any of their dependent claims. Moreover, this deficiency also infects Grounds 2 and 4, to the extent the Board implies a reliance on Ground 1 in these grounds, which it should not do as explained above in Section VI.A. Ground 3 expressly relies on Ground 1 for Claim 14, Pet. at 54-56, and thus fails for the same reason as Ground 1. The Board can deny institution on all grounds on this basis alone.

C. NeoGenomics Never Shows That Forsheo Renders Obvious “sequencing ... wherein the sequencing has a depth of read of at least 50,000 per target locus” (Claims 1-13, 15)

Claims 1-13 and 15 require a series of steps including the following:

- “performing targeted multiplex amplification to amplify 10 to 500 target loci ... to obtain amplicons having a length of 50-150 bases”; and
- “sequencing the amplicons to obtain sequence reads... wherein the sequencing has a depth of read of at least 50,000 per target locus.”

EX1001 at 171:32-43, 172:24, 172:31-32. NeoGenomics does not argue or attempt to show that Forsheo discloses “a depth of read of at least 50,000 per target locus”

for any embodiment. *See* Pet. at 26-32. Instead, it asserts that a “POSA would have been motivated to increase sensitivity by modifying Forshew so as to sequence more molecules and reach a depth of at least 50,000 and would have expected success.” *Id.* at 26.

NeoGenomics never argues or attempts to show that the Claims 1 and 15 *as a whole* would have been obvious, which was its burden. *Univ. of Strathclyde v. Clear-Vu Lighting*, 17 F.4th 155, 162 (Fed. Cir. 2021) (“We decline Clear-Vu’s invitation to read the inactivation limitation in isolation, divorced from the claim as a whole.”). Even if it had, NeoGenomics’ argument that a read depth of 50,000 would be obvious in the context of Forshew is baseless.

1. NeoGenomics Failed To Show Claims 1 And 15 As A Whole Would Have Been Obvious

NeoGenomics claims that “Forshew’s Table 1 discloses examples of sequencing depth of up to 15,400.” Pet. at 27. It plainly does not. *See* EX1003 at 6 (Table 1 showing “7700”). NeoGenomics then posits that “Forshew thus discloses sequencing depths on the order of tens of thousands, such that increasing to at least 50,000 would have been an obvious change.” Pet. at 27; *see also id.* at 45 (relying on “claim 1” for Claim 15). NeoGenomics’ logic that 15,400 renders 50,000 obvious is faulty at best, and NeoGenomics cites no authority to support it.

More importantly, NeoGenomics’ Table 1 example involved data from “seven ovarian cancer patients.” EX1003 at 6. NeoGenomics does not assert, nor could it, that Table 1 pertains in any way to the “ten SNV mutations from a tumor sample that were identified based on WGS [whole genome sequencing] data, which are listed in Table S7” from the breast cancer embodiment it relies on for limitations [1.a], [1.b], [14.a], and [14.b]. *See* Pet. at 22-25, 42; EX2002 at 50 (NeoGenomics’ lead counsel: Forshew’s experiment involving “a breast cancer patient” is different from the “ovarian cancer” experiment); EX2001 at 15-18.

Forshew never discloses a depth of read for the breast cancer embodiment, *see* EX1003 at 10, yet also teaches that read depth varies significantly across its embodiments. *E.g.*, EX1003 at 4 (“average read depth of 3250 for each of 96 barcoded samples”); EX1003 at 5 (“average sequencing depth of 650 for 62 plasma samples”). NeoGenomics presents no argument or evidence why it would have been obvious to use Table 1’s read depths with the breast cancer embodiment. *See* Pet. at 26-32 (starting with alleged read depth of 15,400 for Forshew without explanation).

NeoGenomics simply cannot meet its burden to show obviousness of Claims 1 and 15 without providing a motivation to combine the features of the breast cancer embodiment with Table 1’s read depths. *Stepan*, 868 F.3d at 1346 n.1 (when “combining multiple embodiments from a single reference ... there must be a motivation to make the combination and a reasonable expectation that such a

combination would be successful, otherwise a skilled artisan would not arrive at the claimed combination”). Absent establishing the required motivation, NeoGenomics’ obviousness contention fails. *Markforged*, 2023 WL 6534357, at *6-7 (rejecting “Petitioner’s reliance on multiple embodiments”); *see Enfish*, 822 F.3d at 1343.

2. NeoGenomics Fails To Show 50,000 Read Depth Would Have Been Obvious

Even if Forshew had disclosed a single embodiment combining the claimed features with a read depth of 7,700 (it does not), NeoGenomics still fails to show that one of skill would be motivated to modify Forshew’s methodology to achieve a read depth of 50,000 while meeting all the remaining claim limitations (*i.e.*, the claims as a whole), either through one of skill’s own knowledge or by using Dr. Lennon’s shopping list of references. *See* Pet. at 27-28, 32; EX1002 ¶¶168-70, 179-88. NeoGenomics’ misrepresentation of Natera’s previous statements and expert testimony also fail to bolster NeoGenomics’ obviousness claim.

“In an *inter partes* review, the burden of persuasion is on the petitioner to prove unpatentability by a preponderance of the evidence, 35 U.S.C. § 316(e), and that burden never shifts to the patentee.” *In re Magnum Oil Tools*, 829 F.3d 1364, 1375 (Fed. Cir. 2016) (internal quotations omitted). NeoGenomics cannot carry its burden.

a. Forshew Does Not Disclose Or Render Obvious A Read Depth Of 50,000 Per Target Locus

Despite never asserting that Forshew discloses this limitation, NeoGenomics cryptically asserts “to the extent Forshew is deemed to not disclose this element, a POSA would have found it obvious to modify Forshew to achieve the claimed invention.” *See* Pet. at 26; EX1002 ¶160. It is, of course, difficult to conceive how Forshew could be “deemed” to disclose a 50,000 read depth when NeoGenomics does not argue, much less prove, that it does. *Magnum Oil*, 829 F.3d at 1375 (burden is always on petitioner).

NeoGenomics focuses only on the 7,700 mean read depth listed for Patient ID 27 in Table 1, ignoring the other 50 or so lower read-depth values in Tables 1-2, and argues that “Forshew thus discloses sequencing depths on the order of tens of thousands, such that increasing to at least 50,000 would have been an obvious change.” Pet. at 27 (citing EX1002 ¶164). To get there, NeoGenomics relies on Dr. Lennon’s math that doubles the 7,700 mean read depth to 15,400 based on his claim that “[a] POSA would have understood that the mean sequencing depth of 7,700 for duplicate samples is a total sequencing depth of 15,400.” EX1002 ¶163. Even if Dr. Lennon’s unsupported assertion were correct, Dr. Lennon never explains how he knows that Table 1 did not already double the read depths to account for one of skill’s alleged understanding. *See id.* Forshew certainly does not say one way or

the other. *See* EX1003 at 6 (Table 1). NeoGenomics presents no evidence that it is even correctly characterizing Forshew.

Dr. Lennon is not done. Next he converts 15,400 into 50,000, asserting that a “sequencing depth of 50,000 is nothing more than an obvious variation on 15,400 because 50,000 is also on the order of tens of thousands.” EX1002 ¶164. That is pure conjecture. Wishful thinking is not a basis for obviousness—it requires explanation and evidence. *Elbit Sys. v. Thales Visionix*, 881 F.3d 1354, 1358 (Fed. Cir. 2018) (affirming the Board’s final written decision of nonobvious leaving undisturbed the Board’s determination that petitioner’s expert’s opinion was “‘unsupported’ and entitled to ‘little weight’”); *Arendi S.A.R.L. v. Apple*, 832 F.3d 1355, 1366 (Fed. Cir. 2016) (reversing the Board’s obviousness determination finding that it did not rely on “a reasoned explanation” but only an expert’s “conclusory generalizations”). Dr. Lennon’s *ipse dixit* fails.

NeoGenomics cites Forshew’s teaching of “higher read depth” as motivating a read depth of at least 50,000 per target locus. Pet. at 27 (citing EX1002 ¶¶165-67). It takes this statement out of context. Forshew criticizes alternative approaches requiring “custom-designed probes” or that use “whole-genome sequencing,” such as the Challenged Claims here, because they “are difficult to implement on a routine basis.” EX1003 at 11. Forshew explains “TAm-Seq is a flexible and cost-effective platform” that “strikes a balance between sensitivity and ease of use and could

facilitate study and application of circulating DNA.” EX1003 at 11. Forshew does not recommend sacrificing its “cost-effective[ness]” for increased sensitivity. *See id.* There is simply nothing in Forshew showing it would be obvious to increase sequencing depth by at least an order of magnitude to achieve a sensitivity goal that Forshew did not endorse, especially not in the context of the claims as a whole.

Even if Forshew had recommended higher read depth, it did not recommend 50,000 per target locus, and thus does not render such a limitation obvious. *TQ Delta v. CISCO Sys.*, 942 F.3d 1352, 1362 (Fed. Cir. 2019) (reversing obviousness finding based on expert testimony “untethered to any supporting evidence” and rooted in hindsight).

b. NeoGenomics’ Backup References Do Not Cure The Deficiencies Of Forshew

NeoGenomics relies on a list of “numerous prior art references” allegedly teaching increased sensitivity but ignores the remaining limitations of the claims. Pet. at 27-28 (citing EX1086, EX1090-1091, EX1057, EX1101-1102, EX1105, EX1108, EX1132). NeoGenomics never asserts that these references provide a motivation to increase sensitivity in Forshew’s system specifically or override Forshew’s express desire for a balance between “sensitivity and ease of use” and a “cost-effective” system. *See id.*; EX1003 at 11. Neither NeoGenomics nor Dr. Lennon explains how these alleged systems could be combined with Forshew’s

TAm-Seq in a manner that meets all the limitations of the Challenged Claims, including “10 to 500 target loci... to obtain amplicons having a length of 50-150 bases” with “a depth of read of at least 50,000 per target locus.” *Strathclyde*, 17 F.4th at 162.

Forsheew does not disclose such a feature set, and NeoGenomics never explains how combining any of its reference list with Forsheew would result in a process that includes all claim features. *See Arendi*, 832 F.3d at 1366. Moreover, neither NeoGenomics nor its expert even attempts to square these proposed modifications with Forsheew’s warning that other methods might “have better analytical sensitivity than currently achieved by TAm-Seq, but are difficult to implement on a routine basis.” EX1003 at 11; *see also* Pet. at 27-28; EX1002 ¶¶168-69.

For example, even if combined with Forsheew, Bentley would not teach the 50,000 read depth limitation

required by the Challenged Claims. Bentley’s Table 2 (EX1057 at 14) discloses high depths of read within the 50,000 range only for targeting 1-2 loci, EX1057 ¶88, not “10-500 target

TABLE 2

SNP Classes	Number of Reads	Minimum frequency of SNP in population detectable with 95% confidence	Minimum frequency of SNP in population detectable with 99% confidence
1	200000	0.002%	0.003%
2	100000	0.005%	0.007%
5	40000	0.014%	0.018%
10	20000	0.028%	0.037%
50	4000	0.14%	0.18%
100	2000	0.28%	0.37%
200	1000	0.55%	0.74%
500	400	1.39%	1.85%
1000	200	2.76%	3.64%

loci” as required by all the claims, EX1001 at 171:32-33, 172:18-19. Instead, Table 2 shows the read depths for 10 or more target loci fall far short of the 50,000 read depth limitation, and read depth only decreases as the number of target loci increases. EX1057 ¶88, Table 2. Bentley does not help NeoGenomics.

Similarly for Narayan, NeoGenomics and Dr. Lennon fail to explain why one of skill using Forshew’s method would look to Narayan, or how the resulting combination would satisfy the remaining claim limitations. Pet. at 27-28; EX1002 ¶169. Narayan does not satisfy the “10-500 target loci” required by all claims, EX1001 at 171:32-33, 172:18-19, because Narayan used only four target loci:

we restricted the analysis to frequently mutated codons within 3 oncogenes that commonly develop somatic mutations in various malignancies: codons 12 and 13 of *KRAS*, codon 600 of *BRAF*, and codon 858 of *EGFR*.

EX1086 at 3. Thus, even if combined with Forshew, NeoGenomics offers no explanation for how the resulting combination would satisfy any challenged claim as a whole. *Strathclyde*, 17 F.4th at 162.

c. Natera’s And Its Experts’ Prior Statements Do Not Render Obvious A Read Depth Of 50,000 Per Target Locus

NeoGenomics next distorts Natera’s and its experts’ statements to assert they agree with NeoGenomics’ position that it would be routine to increase read depth to increase sensitivity. Pet. 28-32. This tactic also does not support NeoGenomics’

assertions that it would have been obvious to increase read depth to at least 50,000 per target locus in a system based on Forshaw that meets the claims as a whole.

First, NeoGenomics and Dr. Lennon inaccurately assert that Dr. Metzker effectively opined that increasing depth of read would yield higher sensitivity when he stated that to “increase the accuracy of the Illumina GA sequencer, it would have been obvious in my opinion to target regions of a genome with high sequence coverage.” Pet. at 29, 30 n.5; EX1002 ¶174 (quoting EX1082 ¶214). Dr. Metzker’s statement offers nothing more than the general observation that regions of the genome with higher sequence coverage would be more accurate in the specific context about which he was opining, which NeoGenomics does not identify. His opinion says nothing about a read depth of 50,000, much less in the context of the claims as a whole at issue here. His statement in no way supports NeoGenomics’ argument.

NeoGenomics then incorrectly uses Natera’s statements as somehow endorsing modification of Forshaw to meet the Challenged Claims. For example, NeoGenomics asserts that the following statement shows obviousness of the 50,000 read depth limitation: “It was well-known by 2009 that the number of molecules analyzed is one component of sensitivity, and that higher sensitivity could be achieved by sequencing more molecules.” EX1088 at 32. But this statement says that the number of molecules analyzed is “*one component of sensitivity*” not the

only component. *See id.* Natera did not say anything about a read depth of 50,000 per target locus, much less in a system meeting all the other requirements of the Challenged Claims.

NeoGenomics’ other quotations offer no more. It quotes a general statement by Dr. Quackenbush that points out that there are other considerations in sensitivity, including error rate:

Dr. John Quackenbush, likewise testified that “POSAs prior to November 6, 2009 were *well aware* that sequencing more molecules, or increasing sequencing depth, improves sensitivity” and that “the detection limit is determined by sequencing error rate and sequencing read depth (i.e., how many molecules are sequenced), reflecting the fact that there was a *well-known* correlation between the number of molecules sequenced and sensitivity.”

Pet. at 29 (quoting EX1094 ¶119) (emphases by NeoGenomics). This passage also does not establish that a read depth of 50,000 per target locus would have been obvious in a system meeting all the other requirements of the Challenged Claims.

NeoGenomics next relies on Dr. Metzker’s testimony that “as of 2009 the literature taught that at ‘high sequence coverage *all* [*sic*] NGS platforms have *excellent variant calling accuracy* (>95%) as assessed by the detection of known SNP variants.” Pet. at 31 (quoting EX1082 ¶213 (quoting EX1042 at 9) (emphasis changed and provided by NeoGenomics)). There is no definition of “high sequence

coverage” here, rendering this quotation useless to show obviousness of read depth of at least 50,000 per target locus, much less in the context of the remaining claim limitations.

What NeoGenomics failed to show, despite its mountain of exhibits, is “a motivation and likelihood of success to use a read depth of at least 50,000 per target locus with amplification of 10 to 500 target loci” and in the context of Claims 1-13, with amplicons having a length of 50-150 bases. In other words, NeoGenomics has no evidence of obviousness of any challenged claim “as a whole.” *See Strathclyde*, 17 F.4th at 162.

Because NeoGenomics cannot show that the entirety of Claim 1 would have been obvious, including a read depth of at least 50,000 per target locus, it cannot prevail on its Ground 1 challenge to Claims 1-13 or 15. To the extent the Board implies that Grounds 2 and 4 similarly rely on Ground 1 for these limitations, which it should not do as explained above in Section VI.A, they fail for the same reasons. Thus, the Board should deny institution on Grounds 1, 2, and 4 for Claims 1-13 and 15.

D. NeoGenomics Fails To Demonstrate That Forshew Discloses Or Renders Obvious A “method [] capable of detecting an SNV mutation that is present in less than or equal to 0.015%” (Claims 14-28)

NeoGenomics fails to show obviousness of Claims 14-28 based on Forshew (all grounds). *Magnum Oil*, 829 F.3d at 1375. Claims 14-28 require “detecting one or more of the tumor-specific SNV mutations present in the cell-free DNA ... wherein the method is capable of detecting an SNV mutation that is present in less than or equal to 0.015% of the cell-free DNA comprising the SNV locus.” EX1001 at 172:25-30. It is unclear if NeoGenomics contends that Forshew discloses the 0.015% mutation detection sensitivity limitation, because the Petition includes only a single sentence regarding Figure S3 that does not clearly state that Forshew discloses this limitation. *See* Pet. at 43. NeoGenomics also does not offer any evidentiary support for why one of skill would have a reasonable expectation of successfully modifying Forshew’s method to have increased sensitivity of 0.015% especially in the context of the remaining limitations of Claim 14. *See* Pet. at 44-45.

1. Forshew Does Not Disclose A Mutation Sensitivity “of less than or equal to 0.015%”

Forshew states, “we identified cancer mutations present in circulating DNA at allele frequencies as low as 2%, with sensitivity and specificity of >97%.” EX1003 at 2. NeoGenomics’ lead counsel told the Board in *Personalis* that Forshew

could only detect “mutations occurring at a frequency higher than 2%.” EX2001 at 17 (NeoGenomics lead IPR counsel).

Despite this disclosure, NeoGenomics asserts that “Figure S3 of Forsheew shows frequencies that could be detected with different confidence levels above the background read rate, including frequencies of 0.015% and below (*i.e.*, frequencies of 0.00015 and below).” Pet. at 43. NeoGenomics overlooks the fact that this particular figure was “generated from the set of 62 plasma samples (cumulative distribution shown in black), and the standard deviation.” EX1003 at 21. Simply put, Figure S3 represents calculated theoretical values based simply on standard deviation, not actual data (other than the background read rate on which NeoGenomics does not rely).

Further, the 62 plasma samples did not come from the breast cancer embodiment on which NeoGenomics relies for the rest of Claim 14. *See* § VI.B. NeoGenomics makes no effort to argue or show how any sensitivity for these 62 plasma samples might be obvious to combine with the remaining features of the breast cancer embodiment, rendering this data irrelevant. *Stepan*, 868 F.3d at 1346 n.1 (when “combining multiple embodiments from a single reference ... there must be a motivation to make the combination and a reasonable expectation that such a combination would be successful, otherwise a skilled artisan would not arrive at the

claimed combination”); *Markforged*, 2023 WL 6534357, at *6-7 (rejecting “Petitioner’s reliance on multiple embodiments”); *see Enfish*, 822 F.3d at 1343.

2. NeoGenomics’ Numerous Backup References Do Not Cure The Deficiencies In Forshew

NeoGenomics next pivots to asserting that sensitivity of less than or equal to 0.015% would have been obvious in view of Forshew. Pet. at 43-45. It again relies on generic statements by Forshew that (1) “[h]igher read depth,” (2) “fidelity,” (3) “additional replicates, or” (4) “improved algorithms,” *see* EX1003 at 11, would somehow provide one of skill a specific motivation to increase the sensitivity 133-fold from 2% to 0.015%. Pet. at 43-44 (citing EX1003 at 11, EX1002 ¶250). This assertion is nothing more than classic hindsight. *See TQ Delta*, 942 F.3d at 1362. Moreover, it ignores Forshew’s express teaching that other methods with “better analytical sensitivity than currently achieved by TAm-Seq ... are difficult to implement on a routine basis.” EX1003 at 11.

NeoGenomics does not explain how Forshew’s teachings would motivate one of skill to attempt to increase the sensitivity of TAm-Seq 133-fold. Nor could it. NeoGenomics’ counsel acknowledged that Forshew could only detect “mutations occurring at a frequency higher than 2%,” EX2001 at 17, and that Forshew had been criticized for “need[ing] to achieve a more sensitive detection limit (<2% allele frequency) to identify mutations in the plasma of patients with less advanced

cancers.” EX2002 at 53 (quoting EX1003 at 1). In *Personalis*, counsel criticized Forshew as “several orders of magnitude less sensitive than” modern ctDNA testing. *Id.* at 63-64 (citing EX1003 at 1). Counsel’s effort to conjure different facts in this IPR is unsupported and not credible.

NeoGenomics also dumps a laundry list of references that purportedly prove that “achieving a sensitivity of 0.015%... had already been accomplished long before the priority date.” Pet. at 44. But disclosure of a limitation alone does not show that it would have been obvious to use that particular feature in Forshew’s system, much less in a modified version of Forshew’s system that met all of the remaining requirements of Claim 14:

An invention is not obvious simply because all of the claimed limitations were known in the prior art at the time of the invention. Instead, we ask whether there is a reason, suggestion, or motivation in the prior art that would lead one of ordinary skill in the art to combine the references, and that would also suggest a reasonable likelihood of success.

Forest Labs. v. Sigmapharm Labs., 918 F.3d 928, 934-35 (Fed. Cir. 2019) (citation and internal quotations omitted) (“generic need for more antipsychotic treatment options did not provide a motivation to combine” prior art treatment options); *Arendi*, 832 F.3d at 1366. Indeed, counsel admitted in *Personalis* that Forshew was

“several orders of magnitude less sensitive than” modern techniques, and therefore didn’t render modern DNA testing obvious. EX2002 at 63-64.

Forsheew taught that “TAm-Seq strikes a balance between *sensitivity and ease of use* and could facilitate study and application of circulating DNA.” EX1003 at 11. And that “TAm-Seq is a flexible and *cost-effective* platform for applications in noninvasive cancer genomics and diagnostics.” *Id.* Other than hindsight, NeoGenomics provides no explanation why one of skill would be motivated to depart from Forsheew’s careful balance between sensitivity and ease of use to drastically modify Forsheew’s TAm-Seq to accomplish a 133-fold increase in sensitivity. *See* Pet. at 43-45. Nor does NeoGenomics explain how that modification would satisfy the remaining limitations of Claim 14 or any of its dependent claims.

NeoGenomics cannot prevail on its Ground 1 assertion that Claims 14-28 would have been obvious based on Forsheew. Grounds 2 and 4, to the extent the Board implies that they rely on Ground 1, which it should not as explained in Section VI.A, fail for the same reason.

E. NeoGenomics Never Demonstrates That Ground 3 Cures The Deficiencies In Ground 1 For Claims 14-28

For Ground 3, NeoGenomics pivots to arguing that “Bentley and Narayan teach detection with this degree of sensitivity.” Pet. at 54. It asserts that Narayan “teaches that a detection limit of 0.014% for mutations in circulating tumor DNA

can be reached using DNA sequencing methods like TAm-Seq with high read depths.” *Id.* What NeoGenomics omits is that Narayan did so with only four target loci. EX1086 at 3 (analysis restricted to “codons 12 and 13 of *KRAS*, codon 600 of *BRAF*, and codon 858 of *EGFR*”). Thus, even if one of skill were motivated to use Narayan’s method in Forshew, NeoGenomics’ proposed combination is irrelevant because it still would not satisfy Claim 14’s requirement of 10 to 500 target loci.

NeoGenomics next asserts

that Bentley teaches that “SNPs with a frequency between 0.014% and 0.018% can be detected with 95-99% confidence with a sequencing depth of 40,000, and at a

TABLE 2

SNP Classes	Number of Reads	Minimum frequency of SNP in population detectable with 95% confidence	Minimum frequency of SNP in population detectable with 99% confidence
1	200000	0.002%	0.003%
2	100000	0.005%	0.007%
5	40000	0.014%	0.018%
10	20000	0.028%	0.037%
50	4000	0.14%	0.18%
100	2000	0.28%	0.37%
200	1000	0.55%	0.74%
500	400	1.39%	1.85%
1000	200	2.76%	3.64%

frequency between 0.005% and 0.007% with 95-99% confidence with a sequencing depth of 100,000.” Pet. at 54-55. These data, of course, come from the second and fifth lines of Table 2, but again fall outside Claim 14’s requirements because they only achieve these sensitivities with 5 or fewer target loci. EX1057 ¶88 (“Table 2 displays the number of SNPs [i.e., “SNP Classes”] that can be screened simultaneously on a single PicoTiterPlate Array...”). Thus, even if combined with

Forsheew, NeoGenomics does not explain how the combination would render Claim 14 “as a whole” obvious. *See Strathclyde*, 17 F.4th at 162.

Because NeoGenomics cannot prevail on its assertion that Claim 14 would have been obvious in Ground 3, NeoGenomics also cannot prevail on its assertion that dependent Claims 15-28 would have been obvious for at least the same reason. The Board should deny institution of Ground 3 as well.

VII. CONCLUSION

For any of these reasons, the Board should deny institution.

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that foregoing **PATENT OWNER’S PRELIMINARY RESPONSE** exclusive of the parts exempted as provided in 37 C.F.R. § 42.24, contains 13, 939 words and therefore complies with the type-volume limitations of 37 C.F.R. § 42.24.

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CERTIFICATE OF SERVICE

The undersigned certifies that pursuant to 37 C.F.R. § 42.6(e), a true copy of the foregoing **PATENT OWNER'S PRELIMINARY RESPONSE** and **EXHIBITS 2001-2027** are being served electronically on March 27, 2024 to the following lead and backup counsel for Petitioner to the following email addresses:

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