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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. IPR2024-00812
U.S. Patent No. 11,519,035

PATENT OWNER'S PRELIMINARY RESPONSE

TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	BACKGROUND.....	3
A.	Natera’s Pioneering Signatera™ MRD Test	3
B.	Cell-Free DNA, Tumors, PCR, And The Invention Of The ’035 Patent.....	5
C.	Examination Of The ’035 Patent	7
D.	The Asserted Art	8
1.	Forsheew Article (EX1005).....	8
2.	Pieprzyk Application (EX1006)	8
3.	Porreca Application (EX1008)	8
E.	The District Court Litigation	9
III.	LEVEL OF ORDINARY SKILL IN THE ART.....	10
IV.	CLAIM CONSTRUCTION	11
V.	THE BOARD SHOULD EXERCISE ITS DISCRETION TO DENY INSTITUTION.....	12
A.	NeoGenomics’ Belated And Empty Stipulation	12
B.	NeoGenomics Did Not Meet Its Burden To Show That The Examiner Erred Regarding Its Grounds 1-2 References.....	13
1.	<i>Advanced Bionics</i> Part 1: Grounds 1-2 References Were Previously Presented To The Office	14
2.	<i>Advanced Bionics</i> Part 2: NeoGenomics Failed To Meet Its Burden To Show Material Error	15

VI. THE PETITION’S CHALLENGES ARE NOT REASONABLY LIKELY TO PREVAIL	17
A. Ground 1: Forshew Is Not Prior Art	17
1. Legal Standards For Priority Claims	18
2. The ’035 Patent Properly Claims Priority To The ’235 Application Filed In 2011	19
3. The ’235 Application Provides Support For Applying Its Methods To Cancer.....	22
a. Support For “not a pregnant women”.....	24
b. Support For “targeted amplification of ... 25-2,000 loci associated with cancer”	26
4. The ’235 Application Provides Section 112 Support For All Challenged Claims.....	28
5. NeoGenomics’ Arguments About The ’925 Application Do Not Demonstrate A Lack Of Written Description Support.....	34
a. The ’035 Patent Prosecution History Has No Bearing On The Priority Claim	34
b. The ’925 Application Prosecution History Offers Nothing On Natera’s Priority Claim To A Different Application	35
6. Dr. Lennon Does Not Show The ’035 Patent Is Not Entitled To The November 18, 2011 Priority Date.....	37
B. Ground 2: NeoGenomics Does Not Demonstrate Obviousness Over Pieprzyk And May	42
1. The Combination Does Not Disclose Or Suggest Targeted Amplification Of A Plurality Of SNP Loci In A Single Reaction Volume.....	42

2.	NeoGenomics Fails To Allege That Pieprzyk, May, Or The Combination Would Have Motivated A Skilled Artisan To Use Multiplex Amplification With May’s Four-Primer Set	45
C.	Ground 3: NeoGenomics Fails To Demonstrate That One Of Skill Would Have Been Motivated To Make The Asserted Combination Of Porreca And Hoyal.....	48
1.	NeoGenomics Does Not Demonstrate That One Of Skill Would Have Been Motivated To Add Hoyal’s Preamplification To Porreca	49
2.	NeoGenomics Does Not Establish A Motivation To Apply The Combined Method To SNP Loci Associated With Cancer In Cell-Free DNA.....	57
D.	Ground 4: NeoGenomics’ Porreca And Wessler Ground Does Not Demonstrate A Reasonable Likelihood Of Success.....	61
1.	NeoGenomics Fails To Show That It Would Have Been Obvious To Apply Its Porreca-Wessler Combination To SNPs From Cell-Free DNA Associated With Cancer.....	61
2.	Ground 4’s Combined Method Is Internally Inconsistent And Contradicts Its Asserted Motivation To Combine.....	63
VII.	CONCLUSION	66

TABLE OF AUTHORITIES

	Page No(s).
<i>ABS Global v. Cytonome/ST</i> , IPR2021-00306, 2021 WL 2350052 (P.T.A.B. June 7, 2021).....	15
<i>Advanced Bionics v. MED-EL Elektromedizinische Geräte</i> , IPR2019-01469, 2020 WL 740292 (P.T.A.B. Feb. 13, 2020)	14, 15, 16
<i>In re Anova Hearing Labs</i> , 809 F. App’x 840 (Fed. Cir. 2020)	55
<i>Becton, Dickinson v. B. Braun</i> , IPR2017-01586, 2017 WL 6405100 (P.T.A.B. Dec. 15, 2017).....	15, 16, 17
<i>Boragen v. Syngenta Participations</i> , IPR2020-00124, 2020 WL 2206972 (P.T.A.B. May 5, 2020)	16
<i>Cisco Sys. v. C-Cation Techs.</i> , IPR2014-00454, 2014 WL 4352301 (P.T.A.B. Aug. 29, 2014)	37
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<i>DynaEnergetics Europe v. QinetiQ</i> , PGR2023-00003, 2024 WL 1579442 (P.T.A.B. Apr. 11, 2024).....	48
<i>Dynamic Drinkware v. Nat’l Graphics</i> , 800 F.3d 1375 (Fed. Cir. 2015)	18
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<i>Google v. Valtrus Innovations</i> , IPR2022-01197, Paper 18 (P.T.A.B. June 13, 2023).....	13, 14, 16
<i>In re Gordon</i> , 733 F.2d 900 (Fed. Cir. 1984)	49
<i>Huawei Techs v. Samsung Elecs.</i> , IPR2017-01980, 2018 WL 1124380 (P.T.A.B. Feb. 27, 2018)	19, 21

NeoGenomics Laboratories v. Natera
Patent No. 11,519,035 – IPR2024-00812

<i>Hugel v. Medytox</i> , IPR2023-00604, 2023 WL 5979990 (P.T.A.B. Aug. 28, 2023)	13
<i>Inphi v. Netlist</i> , 805 F.3d 1350 (Fed. Cir. 2015)	24, 25
<i>Intelligent Bio-Sys. v. Illumina Cambridge</i> , 821 F.3d 1359 (Fed. Cir. 2016)	56, 58
<i>Johnson & Johnson Surgical Vision v. Alcon</i> , IPR2021-01003, 2021 WL 6338373 (P.T.A.B. Nov. 23, 2021)	10
<i>Kinetic Concepts v. Smith & Nephew</i> , 688 F.3d 1342 (Fed. Cir. 2012)	55
<i>In re Koller</i> , 613 F.2d 819 (C.C.P.A. 1980)	36
<i>KSR Int’l Co. v. Teleflex</i> , 550 U.S. 398 (2007)	46, 57, 59
<i>In re Magnum Oil Tools Int’l</i> , 829 F.3d 1364 (Fed. Cir. 2016)	56
<i>Maplebear v. Consumeron</i> , IPR2022-01357, 2023 WL 2602373 (P.T.A.B. Mar. 3, 2023)	12
<i>Markforged v. Continuous Composites</i> , IPR2022-00679, 2023 WL 6534357 (P.T.A.B. Sept. 26, 2023)	60
<i>Medtronic CoreValve v. Speyside Medical</i> , IPR2021-00241, 2021 WL 3137302 (P.T.A.B. July 23, 2021)	17
<i>Nalox-1 Pharms. v. Opiant Pharms.</i> , IPR2019-00694, 2020 WL 4920200 (P.T.A.B. Aug. 21, 2020)	47, 48
<i>Natera, Inc. v. NeoGenomics Labs., Inc.</i> , No. 2024-1324, 2024 WL 3381916 (Fed. Cir. July 12, 2024)	10, 13, 46
<i>Novartis Pharms. v. Accord Healthcare</i> , 38 F.4th 1013 (Fed. Cir. 2022)	24

<i>In re NTP</i> , 54 F.3d 1268 (Fed. Cir. 2011)	18, 20
<i>NXP USA v. Impinj</i> , IPR2020-00519, 2020 WL 4805424 (P.T.A.B. Aug. 17, 2020)	15
<i>One World Techs. v. Chevron (HK)</i> , PGR2020-00059, 2020 WL 7222691 (P.T.A.B. Dec. 7, 2020)	60, 66
<i>Panduit v. Corning Optical Commc'ns</i> , IPR2021-01562, 2022 WL 1094029 (P.T.A.B. Apr. 6, 2022)	17
<i>Par Pharm. v. Jazz Pharm.</i> , IPR2016-00002, Paper 12 (P.T.A.B. Apr. 12, 2016)	48
<i>Plas-Pak Indus., Inc. v. Sulzer Mixpac AG</i> , 600 F. App'x 755 (Fed. Cir. 2015)	53, 62
<i>Purdue Pharma v. Faulding</i> , 230 F.3d 1320 (Fed. Cir. 2000)	18
<i>Realtime Data v. Iancu</i> , 912 F.3d 1368 (Fed. Cir. 2019)	11
<i>Sanofi-Synthelabo v. Apotex</i> , 550 F.3d 1075 (Fed. Cir. 2008)	45, 47
<i>Trend Micro v. Open Text</i> , IPR2023-00655, 2023 WL 6847114 (P.T.A.B. Oct. 11, 2023)	37
<i>TQ Delta v. CISCO Sys.</i> , 942 F.3d 1352 (Fed. Cir. 2019)	59, 61
<i>Virtek Vision Int'l v. Assembly Guidance Sys.</i> , 97 F.4th 882 (Fed. Cir. 2024)	57
<i>Vital Connect v. Bardy Diagnostics</i> , IPR2023-00381, 2023 WL 5059771 (P.T.A.B. July 11, 2023)	15, 16
<i>Volkswagen Grp. of Am. v. StratosAudio</i> , IPR2021-00717, 2021 WL 6340178 (P.T.A.B. Nov. 12, 2021)	13

Xerox v. Bytemark,
IPR2022-00624, 2022 WL 3648989 (P.T.A.B. Aug. 24, 2022) 40, 61, 66

OTHER AUTHORITIES

37 C.F.R. § 42.65	40, 61, 66
37 C.F.R. § 42.100	12
35 U.S.C. § 120	18, 19, 20
35 U.S.C. § 325	13, 14
MPEP § 2143.01	49
MPEP § 2173.05	24

TABLE OF EXHIBITS

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2001	RESERVED
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2004	Abbosh et al., <i>Phylogenetic ctDNA Analysis Depicts Early-stage Lung Cancer Evolution</i> , Nature, Vol. 545 (2017)
2005	Press Release, FDA Grants Two Breakthrough Device Designations for Natera’s Signatera™ MRD Test, (March 24, 2021), https://www.natera.com/company/news/fda-grants-two-new-breakthrough-device-designations-for-nateras-signatera-mrd-test/
2006	2021 MedTech Breakthrough Award Winners, https://medtechbreakthrough.com/2021-winners/ (annotated)
2007	Press Release, Natera Awarded Advanced Diagnostic Laboratory Test (ADLT) Status for its Signatera® MRD Test From CMS (June 18, 2021), https://www.natera.com/company/news/natera-awarded-advanced-diagnostic-laboratory-test-adlt-status-for-its-signatera-mrd-test-from-cms-2/
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2010	RESERVED
2011	Stipulation To Stay Consolidated Action, <i>Natera, Inc. v. Inivata, Inc. and Inivata, Ltd.</i> , Case No. 1:21-cv-0056 (D. Del. March 6, 2024)
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	RESERVED

Exhibit No.	Description
2015	RESERVED
2016	Order Granting Preliminary Injunction, <i>Natera, Inc. v. NeoGenomics Labs., Inc.</i> , Case No. 1:23-cv-00629, Dkt. 169 (M.D.N.C. Dec. 27, 2023)
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	RESERVED
2019	Order Setting Preliminary Injunction Bond, <i>Natera, Inc. v. NeoGenomics Labs., Inc.</i> , Case No. 1:23-cv-00629, Dkt. 193 (M.D.N.C. Jan. 10, 2024)
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2025	RESERVED
2026	RESERVED
2027	RESERVED
2028	Claim Construction Order, <i>Natera, Inc. v. NeoGenomics Labs., Inc.</i> , Case No. 1:23-cv-00629, Dkt. 280 (M.D.N.C. May 17, 2024)
2029	Plaintiff Natera, Inc.’s Opening Claim Construction Brief, <i>Natera, Inc. v. NeoGenomics Labs., Inc.</i> , Case No. 1:23-cv-00629, Dkt. 262 (M.D.N.C. Apr. 8, 2024)

NeoGenomics Laboratories v. Natera
Patent No. 11,519,035 – IPR2024-00812

Exhibit No.	Description
2030	Defendant NeoGenomics, Inc.’s Opening Claim Construction Brief, <i>Natera, Inc. v. NeoGenomics Labs., Inc.</i> , Case No. 1:23-cv-00629, Dkt. 264 (M.D.N.C. Apr. 8, 2024)
2031	Plaintiff Natera, Inc.’s Responsive Claim Construction Brief, <i>Natera, Inc. v. NeoGenomics Labs., Inc.</i> , Case No. 1:23-cv-00629, Dkt. 272 (M.D.N.C. Apr. 22, 2024)
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2034	Order On Joint Motion To Modify Scheduling Order, <i>Natera, Inc. v. NeoGenomics Labs., Inc.</i> , Case No. 1:23-cv-00629, Dkt. 256 (M.D.N.C. Apr. 2, 2024)
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2036	U.S. Patent Application No. 16/743,724 Specification
2037	U.S. Patent Application No. 16/399,268 Specification
2038	U.S. Patent Application No. 16/140,298 Specification
2039	U.S. Patent Application No. 14/918,544 Specification
2040	U.S. Patent Application No. 14/877,925 Specification
2041	U.S. Patent Application No. 13/780,022 Specification
2042	U.S. Patent Application No. 13/335,043 Specification
2043	U.S. Patent Application No. 13/683,604 Specification
2044	U.S. Patent Application No. 13/300,235 (excerpted)
2045	Defendant NeoGenomics Laboratories, Inc.’s Opposition to Plaintiff Natera Inc.’s Motion For a Preliminary Injunction, Public Redacted Version, <i>Natera, Inc. v. NeoGenomics Labs., Inc.</i> , Case No. 1:23-cv-00629, Dkt. 89 (M.D.N.C. Oct. 19, 2023)

NeoGenomics Laboratories v. Natera
Patent No. 11,519,035 – IPR2024-00812

Exhibit No.	Description
2046	Plaintiff Natera’s Reply in Support of Its Motion For a Preliminary Injunction, Public Redacted Version, <i>Natera, Inc. v. NeoGenomics Labs., Inc.</i> , Case No. 1:23-cv-00629, Dkt. 139 (M.D.N.C. Nov. 6, 2023)
2047	Patent Owner Natera’s annotated version of Petitioner NeoGenomics’ Exhibit 1002 in IPR2024-00812
2048	NeoGenomics’ Final Invalidity Contentions (Redacted), <i>Natera, Inc. v. NeoGenomics Labs., Inc.</i> , Case No. 1:23-cv-00629 (M.D.N.C. served July 11, 2024)

I. INTRODUCTION

This is the second IPR stemming from litigation between the parties in the United States District Court for the Middle District of North Carolina on the technology underlying Natera's revolutionary Signatera™ tumor-tracking test. Petitioner NeoGenomics already contested (and lost) its validity challenge to Natera's U.S. Patent No. 11,519,035 in the district court, and the Federal Circuit affirmed the preliminary injunction decision upholding the validity of the patent.

Natera is a pioneer in cell-free DNA (cfDNA) technologies, fielding a range of breakthrough tests which have globally revolutionized patient care, including monitoring cancer for recurrence, prenatal testing, and organ transplant assessment. With hundreds of millions of dollars invested in research and development, Natera's innovations are widely acclaimed by the industry, the medical community, and patients as a scientific feat, and it has been awarded hundreds of patents worldwide.

Natera filed suit in Delaware and North Carolina federal district courts alleging infringement of the '035 Patent, among other patents, based on NeoGenomics' RaDaR test. The North Carolina litigation is far along; the court construed the claims and denied NeoGenomics' Section 101 challenge. Shortly after RaDaR was approved for Medicare coverage, Natera moved for a preliminary injunction, and the North Carolina district court found the '035 Patent both likely

valid and infringed and preliminarily enjoined NeoGenomics' further infringement. The district court declined to stay the injunction and set a jury trial in March 2025.

NeoGenomics now comes to the PTAB to re-litigate validity of the '035 Patent, even though it will already get a second chance via the March 2025 North Carolina trial. Undoubtedly, NeoGenomics offered its best validity challenge at the preliminary injunction stage in North Carolina (and lost), and its offer to drop certain validity claims in the district court if this IPR is instituted offers no efficiency.

NeoGenomics' current challenge is unlikely to succeed. Grounds 1-2 exclusively rely on art that Natera already presented to the Examiner, and NeoGenomics fails to satisfy its burden to show the Examiner materially erred.

Even if Ground 1 were considered, the Forshew challenge fails because Forshew is not prior art. NeoGenomics knew from the North Carolina case that Natera asserted a May 18, 2011 priority date for the '035 Patent claims but does not address that assertion. Instead, it attacks a straw man—that the prosecution of another abandoned application shows a later priority date.

Ground 2 fares no better. Even if combined, Pieprzyk and May are still missing the “targeted amplification” limitation, and NeoGenomics' backup argument that the limitation would have been obvious is a non-starter because Pieprzyk teaches away.

Grounds 3-4, among other infirmities, fail to meet their burden of proving motivation to combine, rely on improper overhauling of Porreca, and fail to disclose the material fact that Porreca only analyzed cancer cells, not ctDNA. Ground 4 is internally inconsistent: invoking Porreca's targeted amplification to satisfy certain limitations even though its proposed combination eliminates Porreca's targeted amplification.

II. BACKGROUND

A. Natera's Pioneering Signatera™ MRD Test

Natera was founded in 2004. In the twenty years since, Natera has spent considerable time and resources producing cutting edge medical technology including generating over 180 peer-reviewed studies and being 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. 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.”).¹

In 2017, Natera launched its personalized Signatera™ MRD test for research use only, 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 years before the cancer is detectable using standard X-rays or CT scans. EX2007 at 1. This bespoke approach used DNA from a patient’s tumor biopsy to identify tumor



specific mutations, and then utilized multiplex PCR (“mPCR”) to track a subset of the identified mutations in the plasma of patients, *i.e.*, to monitor for cancer recurrence. Natera’s pioneering innovations were the cover story in *Nature* that same year. EX2004.

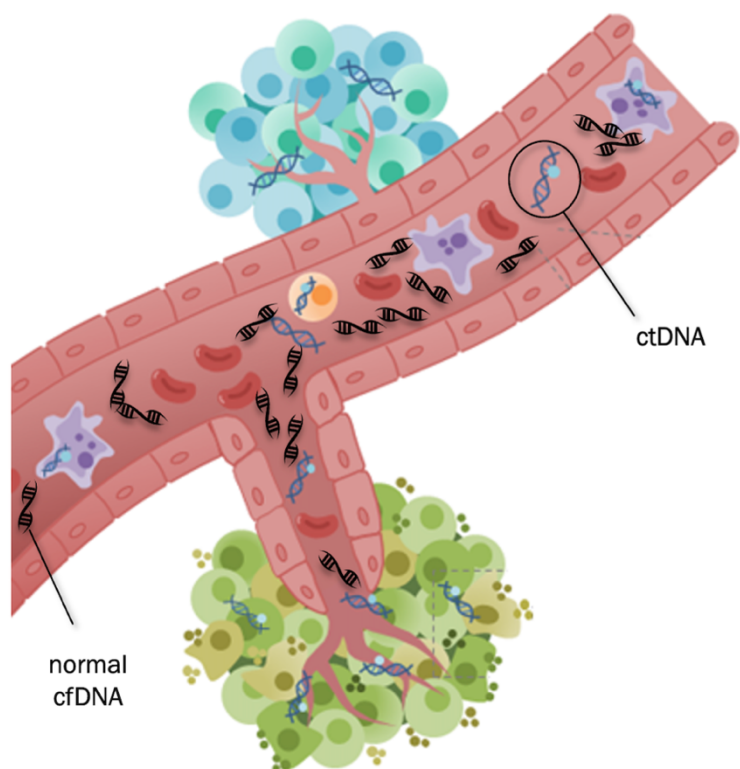
¹ All emphasis in this brief is added unless otherwise noted.

That was just the beginning of the industry acclaim for Signatera™. 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 human 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 ’035 Patent

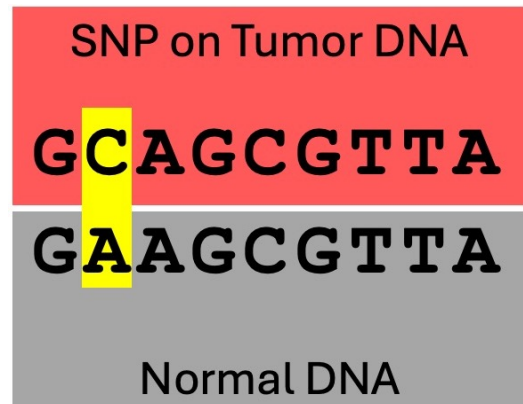
DNA is a double-helix made up of nucleotides (the complementary A, T, C, and G bases) and found in living cells, including cancer cells. When a cell dies, its DNA fragments, and the cell ruptures, spilling its contents into the bloodstream—including its fragmented DNA, called cell-free DNA or “cfDNA.”

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.” Both normal cfDNA and ctDNA are types of free-floating DNA found in the portion of blood known as plasma.

Tumor cell genomes differ from those of healthy cells because they contain mutations, including single nucleotide polymorphisms (“SNPs”), in their nucleotide sequence. A SNP is a change of a single nucleotide in a DNA sequence, as shown in the example highlighted in yellow. SNPs unique to a particular cancer can provide specific markers for cancer detection.



SNPs can be identified by DNA sequencing. Next-generation DNA sequencing is a “high-throughput” approach that can sequence many DNA molecules at the same time, but it requires significantly more input DNA than is typically present as cfDNA in a blood sample. Increasing the amount of cfDNA including the specific SNP locations (or “loci”) is typically achieved using polymerase chain reaction (“PCR”), which is a method for creating copies of (amplifying) 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 an inverse complementary strand from the original single-strand template, thereby copying it.

The claims recite methods for amplifying and sequencing DNA, including “targeted amplification of a plurality of” SNP “loci in a single reaction volume,” introducing barcodes, sequencing tags, and “massively parallel sequencing on the final amplification products” where the “SNP loci comprise[] 25-2,000 loci associated with cancer.” EX1001 at 249:45-62 (Claim 1).

C. Examination Of The '035 Patent

The application that resulted in the '035 Patent was filed on July 21, 2020. EX1001 at cover page. The application claims priority through a tree of applications, all of which are fully incorporated by reference. *Id.* at 2:46-47. The application overcame two office actions, rejecting the claims on a variety of grounds. EX1003 at 953-62, 853-55, 857-60, 634-41, 626-31. Ultimately, the Examiner allowed the claims, explaining that the “prior art which is focused on combined amplification and sequencing of cell-free or circulating nucleic acid targets neither teach or suggest each of the claimed features of the method.” *Id.* at 20-23.

D. The Asserted Art

1. Forshew Article (EX1005)

Forshew is a research article purportedly published on May 30, 2012. EX1005. The district court found “[t]he priority date for the claims of the ‘035 patent is May 18, 2011.” EX2016 at 9.

2. Pieprzyk Application (EX1006)

Pieprzyk describes different methods for analyzing DNA. NeoGenomics relies on its “fourth method,” which uses four primers to add “nucleotide sequences to one or more target nucleic acids by amplification.” EX1006 ¶10. This method involves two “inner” primers “including a target-specific sequence” and a “nucleotide tag,” as well as two “outer” primers which also include a “nucleotide tag.” *Id.* The outer primers “optionally[] include one or more additional nucleotide sequences to be added to the target nucleic acid.” *Id.* Pieprzyk teaches this method is only useful in certain embodiments, EX1006 ¶218, because “[t]his protocol may cause uneven incorporation of the sequencing tag between PCR assays,” which becomes worse “when one tries to multiplex the PCR reactions for tagging (in the access array),” EX1006 ¶306.

3. Porreca Application (EX1008)

Porreca is an international patent publication titled “Methods And Compositions For Evaluating Genetic Markers.” EX1008 at cover page. Porreca’s

aim was to detect and thereby “reduce bias and increase the reproducibility of multiplex analysis of genetic loci.” *Id.* at Abstract. Porreca taught that various preparative methods, including single-plex or multiplex PCR “can result in a pool of isolated product that does not adequately represent the input abundance distribution.” *Id.* at 67:20-28. For example, a given input sample could start with a 50:50 ratio of two alleles and be skewed during amplification to a 10:90 ratio, which could “decrease[] the sensitivity of detecting mutations present in a heterogeneous tumor tissue.” *Id.* at 67:28-68:4. Porreca’s solution was to add a unique molecular barcode (“differentiator tag”) to each individual nucleic acid molecule originally present in the sample to allow for bias detection and correction in subsequent preparative steps. *Id.* at 41:3-9.

E. The District Court Litigation

Days after NeoGenomics’ RaDaR diagnostic test was approved by Medicare, Natera filed suit against NeoGenomics in the United States District Court for the Middle District of North Carolina for infringing the ’035 Patent and U.S. Patent No. 11,530,454 and moved for a preliminary injunction. EX2012 ¶¶34-74.

The North Carolina district court found that Natera had established the ’035 Patent was likely valid and infringed, and preliminarily enjoined NeoGenomics from further infringement. EX2017 at 1-2. NeoGenomics challenged the ’035 Patent’s validity, and the district court rejected NeoGenomics’ arguments. EX2016 at 8-10.

The court set an expedited trial date for March 10-14, 2025. EX2034 at 3. In parallel, NeoGenomics appealed the preliminary injunction decision, and the district court denied NeoGenomics’ motion to stay the injunction pending the appeal. EX2022 at 7. On July 12, 2024, the Federal Circuit affirmed the district court’s preliminary injunction grant. *Natera, Inc. v. NeoGenomics Labs., Inc.*, No. 2024-1324, 2024 WL 3381916 (Fed. Cir. July 12, 2024).

In the meantime, the district court construed the claims. EX2028. By the deadline for an institution decision here, the parties will have completed fact and expert discovery and filed dispositive and *Daubert* motions. EX2034 at 2.

III. LEVEL OF ORDINARY SKILL IN THE ART

NeoGenomics’ Dr. Lennon provides a set of qualifications for the person having ordinary skill yet opines that all claims of the ’035 Patent would have been obvious under any “reasonable definition” of a skilled artisan. Pet. at 8-9; EX1004 ¶¶53-57.

For purposes of denying institution, 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 if the Board institutes trial.

IV. CLAIM CONSTRUCTION

The North Carolina district court construed the following terms in the litigation:

'035 Claim Term	District Court Claim Construction
“amplifying the tagged products...wherein one of the amplification steps comprises targeted amplification.”	Plain and ordinary meaning
“SNP loci...associated with cancer.”	“A single nucleotide that may differ between the genomes of two members of the same species and is associated with cancer. The usage of the term ‘SNP’ should not imply any limit on the frequency with which each variant occurs.”

EX2028 at 15. The court agreed with Natera that for the “amplifying the tagged products” limitation, “tagging and amplifying can occur in the same PCR process.” *Id.* at 4. The court also recognized the parties’ dispute on whether “SNP loci...associated with cancer” included “both acquired and inherited mutations,” but left this issue for later briefing. *Id.* at 14.

For purposes of denying institution, the Board need not construe any terms of the Challenged Claims. *Realtime Data 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))).

To the extent the Board construes the “amplifying the tagged products” or “SNP loci... associated with cancer” limitations, it should adopt the constructions from the North Carolina litigation. 37 C.F.R. § 42.100(b); *Maplebear v. Consumeron*, IPR2022-01357, 2023 WL 2602373, at *2 (P.T.A.B. Mar. 3, 2023) (adopting district court construction because “we see no reason to depart from the district court’s careful and comprehensive analysis of this term”). In fact, NeoGenomics contends that its grounds are based on Natera’s interpretation of “amplifying the tagged products,” Pet. at 9, which was adopted by the court, EX2028 at 4. Natera reserves the right to assert additional claim construction positions if trial is ordered.

V. THE BOARD SHOULD EXERCISE ITS DISCRETION TO DENY INSTITUTION

A. NeoGenomics’ Belated And Empty Stipulation

More than two months after filing this Petition and following an adverse claim construction order, NeoGenomics suddenly stipulated it would not raise parallel anticipation or obviousness challenges in the district court litigation. EX1119. But the least efficient course here is an IPR trial.

The district court case was filed a year ago and is racing toward its fast-tracked March 2025 trial date. EX2034 at 3. NeoGenomics already presented, and lost, its strongest invalidity arguments for the ’035 Patent at the preliminary injunction hearing, which were subsequently affirmed by the Federal Circuit. EX2045 at 10-

11; *Natera*, 2024 WL 3381916, at *4-6. By the time of the institution decision here, the parties will have completed expert discovery and thus will have done everything except conduct the actual trial on NeoGenomics’ invalidity contentions, which raise the same art asserted here. EX2048 at 26-27. NeoGenomics’ belated stipulation prejudices Natera because Natera has already litigated almost to trial the very issues NeoGenomics promises to forgo if given a *Fintiv* pass to litigate them anew in an IPR.

B. NeoGenomics Did Not Meet Its Burden To Show That The Examiner Erred Regarding Its Grounds 1-2 References

The Board should discretionarily deny trial under 35 U.S.C. § 325(d) because NeoGenomics fails to meet its burden to demonstrate material error by the Examiner with respect to Grounds 1-2. NeoGenomics admits that all the art in Grounds 1-2 was presented during prosecution. Pet. at 80. The Board may deny institution in part for certain grounds under Section 325(d). *See, e.g., Google v. Valtrus Innovations*, IPR2022-01197, Paper 18 at 2, 11, 28-29 (P.T.A.B. June 13, 2023) (Board “denied Grounds 1-5 on the merits and denied Grounds 6-8 under 35 U.S.C. § 325(d).”); *Hugel v. Medytox*, IPR2023-00604, 2023 WL 5979990, at *13 (P.T.A.B. Aug. 28, 2023); *Volkswagen Grp. of Am. v. StratosAudio*, IPR2021-00717, 2021 WL 6340178, at *17 (P.T.A.B. Nov. 12, 2021).

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. *Advanced Bionics* Part 1: Grounds 1-2 References Were Previously Presented To The Office

Part one of the *Advanced Bionics* test is satisfied because Grounds 1 and 2 rely on Forshew, Pieprzyk, and May, which were already presented to the Office. There is no dispute that Forshew, May, and a national stage entry of Pieprzyk appear on the face of the '035 Patent and were listed in Information Disclosure Statements (“IDS”) considered by the Examiner. EX1003 at 29, 92, 706; Pet. at 79-80; EX1001 at 4, 6, 10.

References submitted in an IDS are considered “previously presented” for the purposes of Section 325(d). *Advanced Bionics*, 2020 WL 740292, at *3 (IDS art is “previously presented” to the Office.); *see also Google*, IPR2022-01197, Paper 18 at 15-16 (“Our precedent holds that providing a document to the Office in an Information Disclosure Statement is sufficient to satisfy prong one of the *Advanced*

Bionics analysis....”); *NXP USA v. Impinj*, IPR2020-00519, 2020 WL 4805424, at *3 (P.T.A.B. Aug. 17, 2020) (similar).

2. *Advanced Bionics* Part 2: NeoGenomics Failed To Meet Its Burden To Show Material Error

Part two also supports discretionary denial because NeoGenomics failed to meet its burden to show the Examiner materially erred in considering the Grounds 1-2 references.

Under part two of *Advanced Bionics*, NeoGenomics has the burden “to make a showing of material error”; otherwise, “the Director generally will exercise discretion not to institute *inter partes* review.” 2020 WL 740292, at *3. The Board considers *Becton* factors (e) and (f) under part two. *Id.* at *4 (citing *Becton, Dickinson v. B. Braun*, IPR2017-01586, 2017 WL 6405100, at *6 (P.T.A.B. Dec. 15, 2017)).

NeoGenomics argues that the references were not applied against the claims. Pet. at 80. But that alone cannot satisfy NeoGenomics’ burden to show material error. *See, e.g., ABS Global v. Cytonome/ST*, IPR2021-00306, 2021 WL 2350052, at *6 (P.T.A.B. June 7, 2021) (Argument that “the Examiner did not apply the Weigl reference” was insufficient because petitioner “has not pointed out any specific disclosure from Weigl that was overlooked by the Office.”); *Vital Connect v. Bardy Diagnostics*, IPR2023-00381, 2023 WL 5059771, at *7 (P.T.A.B. July 11, 2023)

(Argument that grounds were “not previously considered and/or applied by the Examiner..., without any further analysis, cannot persuade us of material error.”).

Becton factors (e) and (f) favor discretionary denial in this case. *Advanced Bionics*, 2020 WL 740292, at *4.

Becton Factor (e). NeoGenomics argues that the Examiner erred in allowing the claims after an amendment adding the “‘associated with cancer’ and ‘non-pregnant women’ [sic] limitations,” Pet. at 81, but provides no analysis showing any “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). NeoGenomics generically references the Petition to argue that “nothing about the claimed method was new.” Pet. at 81. But NeoGenomics’ “alleged grounds of unpatentability cannot establish material error per se under our binding precedent.... Otherwise, the reasonable likelihood standard of § 314(a) and the second part of the *Advanced Bionics* framework (‘material error’) would collapse into one.” *Vital Connect*, 2023 WL 5059771, at *7; *see also Google*, IPR2022-01197, Paper 18 at 21-22 (collecting cases rejecting argument that petition grounds alone can show material error).

NeoGenomics also speculates, without evidence, that the Examiner ignored Forshew and Pieprzyk due to their priority dates and had already “resolved to allow the claims” before reviewing May. Pet. at 80. Such unsupported theories cannot

demonstrate material error. *See, e.g., Panduit v. Corning Optical Commc'ns*, IPR2021-01562, 2022 WL 1094029, at *7 (P.T.A.B. Apr. 6, 2022) (no material error because “Petitioner’s assertion of Examiner error... is unsupported”).

Becton Factor (f) also favors denying institution because NeoGenomics does not expressly argue that the Petition contains any additional evidence or facts that warrant reconsideration of Forshew, Pieprzyk, or May. *See* Pet. at 79-80; *Medtronic CoreValve v. Speyside Medical*, IPR2021-00241, 2021 WL 3137302, at *13 (P.T.A.B. July 23, 2021).

VI. THE PETITION’S CHALLENGES ARE NOT REASONABLY LIKELY TO PREVAIL

A. Ground 1: Forshew Is Not Prior Art

Ground 1 is based exclusively on Forshew. Pet. at 10, 17-27. But Forshew is not prior art. The Petition admits that Forshew was published “on May 30, 2012,” Pet. at 16; EX1005 at 2, after the ’035 Patent’s May 18, 2011 priority date, EX1001, 1:7-2:45 (Related U.S. Application Data). NeoGenomics contends that the earliest written description support in the ’035 Patent priority chain for claim 1 is in 2015, Pet. at 11-15, after Forshew’s purported publication date, *id.* at 16, but NeoGenomics is incorrect.

The district court found “[t]he priority date for the claims of the ’035 patent is May 18, 2011.” EX2016 at 9. The Challenged Claims are fully supported by U.S. Application No. 13/110,685 (“the ’685 Application,” EX2033) and properly claim

the benefit of its May 18, 2011 filing date. However, Forshew is not prior art if the Challenged Claims are entitled to priority to any application that antedates Forshew. *Dynamic Drinkware v. Nat’l Graphics*, 800 F.3d 1375, 1380 (Fed. Cir. 2015) (holding patentee bore burden of production to show “the asserted claims... are entitled to the benefit of a filing date (constructive or otherwise) prior to the filing date of Raymond”). Because the Petition offers no argument that Forshew qualifies as prior art under the May 18, 2011 priority date or even the later November 18, 2011 priority date of U.S. Application No. 13/300,235 (“’235 Application”), which still antedates Forshew, *see* Pet. at 16-17, it does not demonstrate a reasonable likelihood of success for Ground 1.

1. Legal Standards For Priority Claims

A claim is entitled to the filing date of an earlier application if the earlier application: (1) provides written description support for the claim, (2) has at least one common inventor with the later application, (3) is co-pending with the later application, and (4) is referenced by the later application. *In re NTP*, 654 F.3d 1268, 1277 (Fed. Cir. 2011); *see also* 35 U.S.C. § 120.

“In order to satisfy the written description requirement, the disclosure as originally filed does not have to provide *in haec verba* support for the claimed subject matter at issue.” *Purdue Pharma v. Faulding*, 230 F.3d 1320, 1323 (Fed. Cir. 2000). “[T]he test for sufficiency is whether the specification ‘reasonably conveys

to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.” *In re Glob. IP Holdings*, 927 F.3d 1373, 1377 (Fed. Cir. 2019) (quoting *Ariad Pharms. v. Eli Lilly*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc)). The “level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology.” *Id.*

In an IPR, a petitioner challenging a claim to an earlier filing date under Section 120 “first must raise the issue... by ‘identifying, *specifically*, the features, claims, and ancestral applications allegedly lacking written description support for the claims based on the identified features.” *Huawei Techs. v. Samsung Elecs.*, IPR2017-01980, 2018 WL 1124380, at *4 (P.T.A.B. Feb. 27, 2018) (emphasis in original) (citation omitted). Once the issue is raised, a patent owner need only “make a sufficient showing of entitlement to earlier filing date(s), in a manner that is commensurate in scope with the specific points and contentions raised by petitioner.” *Id.*

2. The '035 Patent Properly Claims Priority To The '235 Application Filed In 2011

The '035 Patent claims priority to the '235 Application through an unbroken chain of applications. *See* EX1001 at 1:7-2:45 (Related U.S. Application Data identifying “Ser. No. 13/300,235, filed Nov. 18, 2011, now U.S. Pat. No.

10,017,812”); EX2047 (Natera’s annotated version of EX1002). The ’235 Application was filed on November 18, 2011 and thus antedates Forshew. *See* Pet. at 16 (asserting Forshew was published on May 30, 2012).

NeoGenomics’ sole challenge to the ’035 Patent’s priority claim is that the priority applications prior to 2015 lack written description support. *See* Pet. at 11-16. There is no dispute that Natera satisfied the other requirements of 35 U.S.C. § 120, including enablement—the applications:

- have overlapping inventorship, *compare* EX1001 at [72], *with* EX2044 at 4-7;
- were co-pending throughout the pertinent priority chain, *see* EX2047; and
- specifically reference the ’235 Application, *see* EX1001 at 1:7-2:45; EX2036-EX2044.

See NTP, 654 F.3d at 1276-77; Pet. at 11-16.

NeoGenomics’ only substantive challenge is its underdeveloped written description argument. *See* Pet. at 11-16. NeoGenomics was aware that both Natera asserted, and the North Carolina district court found, that “[t]he priority date of each of the asserted claims is by May 18, 2011,” EX1034 at 7, which plainly is the date of the ’685 Application, EX1001, 2:4-6 (“U.S. Utility application Ser. No. 13/110,685... filed May 18, 2011”). Despite being aware of Natera’s successful priority claim, NeoGenomics only addresses the intervening ’925 Application. *See*

Pet. at 11-16; *see also* EX1024 at 1091:16-17. As a threshold matter, NeoGenomics failed to carry its burden of identifying specifically what is lacking in Natera’s priority claim to the ’685 Application or any other pre-Forsheiw priority application, including the ’235 Application, which is a basis to reject its priority claim challenge at the outset. *Huawei Techs.*, 2018 WL 1124380, at *4.

Should the Board decide to consider NeoGenomics’ arguments, they do not withstand scrutiny. NeoGenomics only disputes written description support for the following two limitations in Claims 1 and 12-13, which are collectively referred to as “the cancer limitation” in the Petition:

- “isolated cell free DNA... *collected from a subject who is not a pregnant women [sic],*” and
- “targeted amplification of a plurality of single nucleotide polymorphism (SNP) loci... wherein the plurality of SNP loci comprises 25-2,000 loci *associated with cancer.*”

Pet. at 11 (citing EX1003 at 853; EX1001 (Claim 1)).

But the “cancer limitation” is fully supported by the ’235 Application and is entitled to its November 18, 2011 priority date. Although the Challenged Claims are also entitled to the May 18, 2011 filing date of the ’685 Application, priority to the ’235 Application is sufficient to antedate Forsheiw.

3. The '235 Application Provides Support For Applying Its Methods To Cancer

The Petition asserts that the '925 Application “contained only a vague assertion of equivalence between non-cancer and cancer methods.” Pet. at 15. But that is contradicted by the text of the '235 Application, which in this respect is similar to the '925 Application. The '235 Application expressly states that the same methods disclosed for prenatal testing can also be used for cancer testing:

Note that it has been demonstrated that *DNA that originated from cancer that is living in a host can be found in the blood of the host*. In the same way that genetic diagnoses can be made from the measurement of mixed DNA found in maternal blood, *genetic diagnoses can equally well be made from the measurement of mixed DNA found in host blood*. The genetic diagnoses may include aneuploidy states, or gene mutations. Any claim in the instant disclosure that reads on determining the ploidy state or genetic state of a fetus from the measurements made on maternal blood can equally well read on determining the ploidy state or *genetic state of a cancer* from the measurements on host blood.

In some embodiments, a method of the present disclosure *allows one to determine the ploidy status of a cancer*, the method including *obtaining a mixed sample* that contains genetic material from the host, and genetic material from the cancer; *measuring* the DNA in the mixed sample; *calculating* the fraction of DNA that is of cancer origin in the mixed sample; and *determining* the ploidy status of the cancer using the measurements made on the mixed sample and the calculated

fraction. In some embodiments, the *method may further include administering a cancer therapeutic* based on the determination of the ploidy state of the cancer.

EX2044 at 68:30-69:12; *see also* EX2040 ('925 Application) at 198:27-199:9. Importantly, the '235 Application disclosed that ploidy status was determined by analyzing SNPs as required by Claim 1. EX2044 at 17:6-13 (describing determining ploidy status by measuring DNA “at a plurality of polymorphic loci”), 21:3-4 (describing embodiments in which “the plurality of polymorphic loci are SNPs”).

This passage provides a clear instruction to check host blood samples for cancer “[i]n the same way that” maternal blood samples are checked for prenatal defects. EX2044 at 68:30-69:12. The steps of the method are spelled out: “obtaining... measuring... calculating... determining...,” and finally, “administering a cancer therapeutic....” *Id.* It was immediately apparent that the very same methods already used for prenatal testing should also be used to test for cancer.

The Petition’s focus on the absence of the '035 Patent’s Examples 27-29 from the '925 Application, Pet. at 11-12, is a red herring where other disclosures provide written description support for the cancer limitations.

a. Support For “not a pregnant women”

Despite listing “isolated cell free DNA... *collected from a subject who is not a pregnant women*” as the first limitation allegedly lacking support, NeoGenomics barely mentions it in its priority date argument, Pet. at 11-16. This is not surprising because the “not a pregnant women” limitation is supported by the ’235 Application’s discussion of “*maternal* blood” used for prenatal testing and “*host* blood” used for cancer testing, as alternative sample sources. EX2044 at 68:30-69:1. A “host” is characterized as someone in whom “cancer ... is living,” *id.* at 68:30-31, distinct from a pregnant woman with a fetus.

NeoGenomics appears to assert that the “not a pregnant women” limitation is a negative claim limitation. Pet. at 20-21, 34 (citing caselaw regarding “negative limitation[s]”). If so, it is well-established that disclosure of “alternative features [is] sufficient to satisfy the written description standard of § 112, paragraph 1 for negative claim limitations.” *Inphi v. Netlist*, 805 F.3d 1350, 1357 (Fed. Cir. 2015); *see also Novartis Pharms. v. Accord Healthcare*, 38 F.4th 1013, 1017, 1020 (Fed. Cir. 2022) (noting “discussion of... alternatives” as providing support for negative limitations); MPEP § 2173.05(i).

The ’235 Application makes a bright-line distinction between “maternal blood” used to check a “fetus” and “host blood” used to check a “cancer.” Specifically, the application teaches that methods that can be used in “determining

the ploidy state or genetic state of a fetus from the measurements made on **maternal blood**” can also be used in “determining the ploidy state or genetic state of a cancer from the measurements on **host blood**.” EX2044 at 69:2-5; *see also id.* at 68:31-69:1 (“In the same way that genetic diagnoses can be made from the measurement of mixed DNA found in **maternal blood**, genetic diagnoses [of cancer] can equally well be made from the measurement of mixed DNA found in **host blood**.”). By distinguishing between “maternal blood” containing DNA from a “fetus” and “host blood” containing DNA from a “cancer,” one of skill would understand that the inventors contemplated using blood samples from (1) a subject who is a pregnant woman, **and** (2) a subject with cancer (*i.e.*, not a pregnant woman). *Inphi*, 805 F.3d at 1357.

The '235 Application further confirms that its methods are not limited to “maternal blood,” which it describes as just one “example” of the “blood” from which cell-free DNA can be isolated. EX2044 at 39:29-31 (“[T]his [maternal blood] example is not meant to limit to [sic] possible contexts that this method may be applied to.”). Confirming this, NeoGenomics argues that Pieprzyk met the “not a pregnant women” claim limitation simply because of its separate teachings of “**a biological sample... at risk for a cancer**” and of “**a maternal biological sample**.” Pet. at 33-34. Dr. Lennon agrees. EX1004 ¶196 (asserting “Pieprzyk’s omission of

the limiting adjective ‘maternal’... teaches to a POSA that its method extends to non-pregnant women”).

The ’235 Application’s disclosure is more compelling than Pieprzyk and provides ample written description support for the “not a pregnant women” limitation.

b. Support For “targeted amplification of ... 25-2,000 loci associated with cancer”

Finally, the ’235 Application teaches “targeted amplification of a plurality of single nucleotide polymorphism (SNP) loci in a single reaction volume... wherein the plurality of SNP loci comprises 25-2,000 loci.” *See, e.g.*, EX2044 at 68:30-69:5, 74:17-28, 72:18-22, 91:5-92:13, 121:5-12; *infra* §VI.A.4 (claim chart). NeoGenomics does not seriously dispute that these limitations are supported by the ’235 Application and instead focuses on “*associated with cancer.*” Pet. at 11 (emphasis in original) (challenging “these added elements”). But as discussed above, the ’235 Application teaches that its “methods would be particularly advantageous... [in] **cancer testing** where... genetic measurements... could be made on any sample comprising DNA or RNA... [such as] **plasma**,” which, for example, “involve[] calculating... allele ratios at [a] plurality of polymorphic loci....” EX2044 at 36:15-32. It also carries an instruction to apply its prenatal-testing methods, including its SNP-detection methods, to “genetic diagnoses

[associated with cancer, that] may include ***aneuploidy*** states, or ***gene mutations***.”

EX2044 at 69:1-2. As noted above, ploidy determinations in the ’235 Application are made by analyzing SNPs. *Id.* at 17:6-20, 21:3-4. One of skill would thus understand that the targeted amplification of 25-2,000 SNP loci disclosed in the ’235 Application would, in the case of cancer diagnosis, include “SNP loci... associated with cancer.” *Infra* §VI.A.4 (claim chart).

In fact, the ’235 Application confirms this understanding:

In an embodiment, a multiplex pool of about 10,000 PCR assays (10,000-plex) are designed to amplify potentially heterozygous ***SNP loci*** ... and these assays are used ***in a single reaction*** to amplify cfDNA obtained from a material [sic] plasma sample, ..., ***cancers***, or other genetic matter.

EX2044 at 96:10-14; *see also id.* at 98:31-99:9 (“The methods described herein may be used for a number of purposes where there is a ***target*** set of DNA that is mixed with an amount of ***contaminating*** DNA.... For example, genetic abnormalities in a fetus (target) may be detected from maternal plasma which contains fetal (target) DNA and also maternal (contaminating) DNA; the abnormalities include... ***single nucleotide polymorphisms***.... [T]he target and contaminating DNA may be from the same individual, but where ***the target and contaminating DNA are different by one or more mutations, for example in the case of cancer***.”).

The '235 Application thus provides ample support for the “associated with cancer” claim limitation.

4. The '235 Application Provides Section 112 Support For All Challenged Claims

Even if NeoGenomics had properly challenged Natera’s priority claim, the '235 Application provides written description support for each of Claims 1, 12, and 13 challenged in Ground 1 as demonstrated in the chart below:

'035 Patent Claim	'235 Application Support
1[Preamble] A method for amplifying and sequencing DNA, comprising:	The workflow may entail: (1) extracting plasma DNA, ... (2) preparing..., (3) amplifying..., ... (5) performing multiplex (e.g. about 100-plex, 1,000, or 10,000-plex ...) amplifications..., ... (9) sequencing the sample. EX2044 at 91:27-92:1.

'035 Patent Claim	'235 Application Support
1[A] tagging isolated cell free DNA with one or more universal tail adaptors to generate tagged products,	The workflow may entail: (1) extracting plasma DNA, (2) preparing fragment library with universal adaptors on both ends of fragments, ... EX2044 at 91:27-29. [A] method ... can be used for preferentially enriching a DNA mixture at a plurality of loci, the method comprising ... : generating and amplifying a library from a mixture of DNA where the molecules in the library <i>have adaptor sequences ligated on both ends of the DNA fragments</i>, ... performing a first round of multiplex amplification of selected targets using one target specific “forward” primer per target and one or a plurality of adaptor specific <i>universal “reverse” primers</i>. <i>Id.</i> at 91:8-14.
1[B] wherein the isolated cell-free DNA is isolated from a blood sample collected from a subject who is not a pregnant women;	[I]t has been demonstrated that <i>DNA that originated from cancer that is living in a host can be found in the blood of the host</i>. In the same way that genetic diagnoses can be made from the measurement of mixed DNA found in <i>maternal blood</i>, genetic diagnoses can equally well be made from the measurement of mixed DNA found in <i>host blood</i>. The genetic diagnoses may include aneuploidy states, or gene mutations. EX2044 at 68:30-69:2. [T]he mixture of DNA molecules could be derived from DNA isolated <i>from biological material that has already liberated from cells such as blood plasma, which is known to contain cell free DNA</i>. <i>Id.</i> at 79:18-20.

'035 Patent Claim	'235 Application Support
1[C] amplifying the tagged products one or more times to generate final amplification products,	The workflow may entail: ... (3) <i>amplifying the library using universal primers specific to the adaptors</i>, ... (5) <i>performing multiplex</i> (e.g. about 100-plex, 1,000, or 10,000-plex with one target specific primer per target and a tag-specific primer) <i>amplifications</i> on aliquots, EX2044 at 91:27-31. Described herein are methods to <i>first globally amplify the plasma DNA of a sample</i> and then divide the sample up into multiple multiplexed target enrichment reactions with more moderate numbers of target sequences per reaction. In an embodiment,... the method comprising one or more of the following steps: generating and <i>amplifying a library from a mixture of DNA where the molecules in the library have adaptor sequences ligated on both ends of the DNA fragments</i>,... <i>performing a first round of multiplex amplification of selected targets</i>.... In an embodiment, a method of the present disclosure further includes <i>performing a second amplification</i>.... <i>Id.</i> at 91:5-17.
1[D] wherein one of the amplification steps comprises targeted amplification of a plurality of single nucleotide polymorphism (SNP) loci in a single reaction volume,	<i>See</i> 1[C] above. [A] multiplex pool of about 10,000 PCR assays (10,000-plex) are designed to amplify potentially heterozygous <i>SNP loci</i> on chromosomes X, Y, 13, 18, and 21 and 1 or 2 and these assays are used <i>in a single reaction</i> to amplify cfDNA obtained from a material [sic] plasma sample,... <i>cancers</i>, or other genetic matter. EX2044 at 96:10-14.

'035 Patent Claim	'235 Application Support
	[A] method of the present disclosure can be used for preferentially enriching a DNA mixture at a plurality of loci.... <i>Id.</i> at 91:7-8, 91:19-20. In some embodiments, the plurality of polymorphic loci are SNPs. <i>Id.</i> at 21:3-4; <i>see also id.</i> at 74:17-18 (similar), 90:22-24 (“Disclosed herein are methods that permit the targeted amplification of over a hundred to tens of thousands of target sequences (e.g. SNP loci) from genomic DNA obtained from plasma.”).
1[E] wherein one of the amplifying steps introduces a barcode and one or more sequencing tags; and	The workflow may entail: ... (7) barcoding the sample, ... EX2044 at 91:27-32. <i>See also id.</i> at 91:25-26 (“In an embodiment, the primers carry partial or full length sequencing compatible tags.”), 92:4-5 (“Steps of the workflow may be combined, divided up or performed in different order (e.g. bar coding and pooling of samples).”). <i>PCR assays can have the tags, for example sequencing tags</i>, (usually a truncated form of 15-25 bases). After multiplexing, PCR multiplexes of a sample are pooled and then <i>the tags are completed (including bar coding) by a tag-specific PCR</i> (could also be done by ligation). Also, the <i>full sequencing tags can be added in the same reaction as the multiplexing.</i> <i>Id.</i> at 92:9-13.

'035 Patent Claim	'235 Application Support
1[F] sequencing the plurality of SNP loci on the cell free DNA by conducting massively parallel sequencing on the final amplification products,	The workflow may entail: ... (9) sequencing the sample. EX2044 at 91:27-92:1. The genetic data ... can be transformed from a molecular state to an electronic state by ... <i>high throughput sequencing</i>. Some <i>high throughput sequencing methods include Sanger DNA sequencing, pyrosequencing, the ILLUMINA SOLEXA platform, ILLUMINA's GENOME ANALYZER, or APPLIED BIOSYSTEM'S 454 sequencing platform, HELICOS's TRUE SINGLE MOLECULE SEQUENCING platform, HALCYON MOLECULAR's electron microscope sequencing method, or any other sequencing method</i>[]. <i>Id.</i> at 60:27-61:3.
1[G] wherein the plurality of SNP loci comprises 25-2,000 loci associated with cancer.	<u>[Plurality of SNP loci comprises 25-2,000 loci]</u> In an embodiment of the present disclosure, <i>it is possible to use a targeting method that focuses on SNPs ...</i>, for example <i>between 1 and 100 SNPs, or a larger number, for example, between 100 and 1,000, between 1,000 and 10,000, between 10,000 and 100,000 or more than 100,000 SNPs.</i> EX2044 at 74:17-21. In some embodiments, <i>the plurality of polymorphic loci comprises at least 10 loci, at least 20 loci, ..., at least 2,000 loci,....</i> <i>Id.</i> at 121:9-12.

'035 Patent Claim	'235 Application Support
	<u>[Associated with cancer]</u> Note that it has been demonstrated that <i>DNA that originated from cancer that is living in a host can be found in the blood of the host.</i> In the same way that genetic diagnoses can be made from the measurement of mixed DNA found in maternal blood, <i>genetic diagnoses can equally well be made from the measurement of mixed DNA found in host blood.</i> The genetic diagnoses may include aneuploidy states, or gene mutations. Any claim in the instant disclosure that reads on determining the ploidy state or genetic state of a fetus from the measurements made on maternal blood can equally well read on determining the ploidy state or <i>genetic state of a cancer</i> from the measurements on host blood. <i>Id.</i> at 68:30-69:5; <i>see also id.</i> at 69:6-11 (describing determining ploidy status of cancer using blood of host), 96:10-14 (describing analyzing about 10,000 SNP loci in a single reaction volume to amplify cfDNA obtained from cancers); <i>see also id.</i> at 99:2-9 (describing analyzing SNPs “where <i>the target and contaminating DNA are different by one or more mutations, for example in the case of cancer</i>”).
12. The method of claim 1, wherein the one or more universal tail adaptors comprise a first universal tail adaptor and a second universal tail adaptor. -and-	The workflow may entail: (1) extracting plasma DNA, (2) preparing fragment library <i>with universal adaptors on both ends of fragments,</i> (3) <i>amplifying the library using universal primers specific to the adaptors....</i> EX2044 at 91:27-29.

'035 Patent Claim	'235 Application Support
13. The method of claim 12, wherein tagging the cell free DNA comprises amplifying the cell free DNA with a first primer comprising the first universal tail adaptor and a second primer comprising the second universal tail adaptor.	[T]he method comprising... generating and amplifying a library from a mixture of DNA where the molecules in the library <i>have adaptor sequences ligated on both ends of the DNA fragments,... performing a first round of multiplex amplification of selected targets using</i> one target specific “forward” primer per target and one or a plurality of <i>adaptor specific universal “reverse” primers</i> [A] method... further includes <i>performing a second amplification using</i> “reverse” target specific primers and one or a plurality of <i>primers specific to a universal tag that was introduced as part of the target specific forward primers</i> in the first round. <i>Id.</i> at 91:7-17.

5. NeoGenomics’ Arguments About The ’925 Application Do Not Demonstrate A Lack Of Written Description Support

The Petition addresses only the straw man of the ’925 Application, asserting the “cancer limitation” cannot claim priority before October 20, 2015 based on the ’035 Patent’s and ’925 Application’s prosecution histories. Pet. at 11-15. Even if the Board considers this tangent, NeoGenomics’ arguments are unsupported.

a. The ’035 Patent Prosecution History Has No Bearing On The Priority Claim

Citing the ’035 Patent prosecution history, NeoGenomics argues that Natera’s mere citation to Examples 27-29 in the ’035 specification as support for claim amendments directed to the “not a pregnant women” and “associated with cancer” limitations limits the Challenged Claims to an effective filing date of October 20,

2015 because these Examples were introduced in a parent CIP application filed on that date. *Id.* at 11-12. This aspect of the '035 prosecution history is irrelevant to determining Claim 1's priority date—it only addressed support in the then-current specification for proposed claim amendments, not any priority date. *See* EX1003 at 628 (“Support for the amendments to claim 1 can be found in the published application at paragraphs 0041, 0082, 0388, 0397, 0450, 0956, and Examples 26-29.”).

b. The '925 Application Prosecution History Offers Nothing On Natera's Priority Claim To A Different Application

NeoGenomics next pivots to the '925 Application prosecution history, arguing it shows that “the cancer limitation lacked written description support.” Pet. at 15. The '925 prosecution history does not help NeoGenomics. Natera never substantively addressed the priority claim for the cancer limitations in this application. EX1024 at 48-49. The written description rejections in the '925 prosecution history reflect a simple oversight or, according to the Examiner, could have been resolved with a simple clarification. *See* EX1024 at 11.

In a second office action, the Examiner asserted that Claim 1's amended limitation, “measuring free-floating DNA in a plasma sample of the host that comprises both DNA from normal cells and DNA from cancer,” was not supported by “paragraphs 0010 0233, 0298, and 0569,” EX1024 at 8, but never addressed

original claim 2 cited in the amendment, *id.* at 10, which provided almost *in haec verba* support for the amended limitation, *id.* at 1323 (lines 6-8, 19). The Examiner’s rejection of the cited support for this limitation in the ’925 Application can only be deemed an oversight. *In re Koller*, 613 F.2d 819, 823–24 (C.C.P.A. 1980) (“[O]riginal claims constitute their own description.”).

In the same office action, the Examiner asserted that the amended limitation requiring “simultaneously amplifying the at least 1000 polymorphic loci to obtain amplicons and sequencing the amplicons” “encompasses ***simultaneously amplifying and sequencing*** at least 1000 polymorphic loci.” EX1024 at 10. He proposed that “[t]his rejection can easily be overcome by amending the claims to... require that amplifying is done sequentially prior to sequencing.” *Id.* at 11. In other words, the Examiner’s rejection was based on his misunderstanding that “simultaneously” modified amplifying and sequencing rather than simply “simultaneously amplifying the at least 1000 polymorphic loci” followed by sequencing as written. As the Examiner expressly stated, a simple clarification would have overcome this rejection. *See id.*

These written descriptions could have easily been overcome. Additionally, NeoGenomics ignores that the second office action, which the examiner made final, EX1024 at 4, contained additional rejections based on Sections 101, 103, and 112, *id.* at 9-27. And NeoGenomics ignores Natera’s child application claiming priority

through the '925 Application and filed only thirteen days after the '925 Application. EX2047 (App. No. 14/918,544). Natera's decision to pursue the child application instead, which promptly issued as U.S. Patent No. 10,316,362, in no way supports NeoGenomics' claim that "the cancer limitation lacked written description support." Pet. at 15.

6. Dr. Lennon Does Not Show The '035 Patent Is Not Entitled To The November 18, 2011 Priority Date

Dr. Lennon does not show a different priority date. His testimony includes twelve paragraphs about the '035 Patent's pre-2015 parent applications, EX1004 ¶¶145-56, but this testimony is neither discussed nor substantively cited in NeoGenomics' Petition aside from a single bulk cite to over 60 paragraphs of his testimony. See Pet. at 11 (citing EX1004 ¶¶50-52, 93-156). This is insufficient. Under Board rules, "[a]rguments and information that are not presented and developed in the Petition, but instead are incorporated by reference, are not entitled to consideration." *Trend Micro v. Open Text*, IPR2023-00655, 2023 WL 6847114, at *5 (P.T.A.B. Oct. 11, 2023) (citing 37 C.F.R. § 42.6(a)(3)); *Cisco Sys. v. C-Cation Techs.*, IPR2014-00454, 2014 WL 4352301, at *5-6 (P.T.A.B. Aug. 29, 2014) (informative).

Even if considered, Dr. Lennon's testimony cannot be credited because it relies on selective excerpts and omits important facts. EX1004 ¶145 (Dr. Lennon:

“**certain** paragraphs from patents and patent applications in the ’035 priority chain”). For example, Dr. Lennon addresses only three paragraphs from the ’235 Application. See EX1004 ¶¶151-56. His carefully selected disputes taken out of the context of the ’235 Application are not credible.

Dr. Lennon first addresses the passage at EX2044 at 96:4-24 (EX1076 ¶276) relied upon above in Section VI.A.3.b. Despite disclosing analyzing SNP loci “in a single reaction to amplify cfDNA obtained from... cancers,” Dr. Lennon opines that the “passage does not refer to collecting cfDNA from each listed sample type.” EX1004 ¶152. His explanation that cfDNA could not refer to “chorion villus samples” or “a small number of cells” does not explain why it could not refer to cfDNA from cancer. See *id.* ¶106. His further explanation that “[c]ancer is a group of diseases; it is not a biological material like the other listed samples,” *id.*, is even less convincing because he elsewhere opines that cfDNA may be **obtained from** cancers: “cfDNA in blood plasma may originate from both normal cells and cancer cells....” *Id.* ¶63. His final comment that “SNP loci on the majority of the recited chromosomes are traditionally amplified to diagnose aneuploidy in prenatal testing, not to diagnose cancer,” *id.* ¶106, ignores the ’235 Application’s reference to determining the ploidy status of cancer. EX2044 at 69:6-11 (“[A] method of the present disclosure allows one to determine the ploidy status of a cancer...”). Dr. Lennon’s attempt to discredit this disclosure fails.

Dr. Lennon next attacks the passage at EX2044 at 98:31-99:15 (EX1076 ¶283) describing analyzing SNPs in a cancer, for example. EX1004 ¶154. This passage describes analyzing “single nucleotide polymorphisms” followed by “[i]n some embodiments, the target and contaminating DNA may be from the same individual, ... for example in the case of cancer.” EX2044 at 98:32-99:9. Dr. Lennon offers a single sentence that “the paragraph does not disclose amplification of SNPs associated with cancer.” EX1004 ¶154. But he does not explain how he reached that conclusion in view of this disclosure. But even if the disclosure were not clear, the ’235 Application describes analyzing SNPs *obtained from* cancer in the paragraph Dr. Lennon just addressed above. *See* EX1004 ¶151 (quoting EX2044 at 96:4-24 (EX1076 ¶276)). Notably Dr. Lennon does not opine that that passage does not disclose amplification of SNPs associated with cancer nor could he. His piecemeal isolated arguments are disingenuous and not credible.

Additionally, Dr. Lennon offers two reasons why paragraph 400 of the ’685 Application (aka “the published application that became U.S. Patent No. 8,825,412,” EX1004 ¶147), could not show possession of the cancer limitation. *See* EX1004 ¶¶147-48. Paragraph 400 is one of the paragraphs relied upon by Natera above as support for the cancer limitation in the ’235 Application. *Compare* EX2044 at 68:30-69:5, *with* EX1110 ¶400. Dr. Lennon argues that paragraph 400 “provides the same disclosure as paragraph [00569] of the ’925 application, which Patent Owner

unsuccessfully cited as disclosure supporting ‘measuring free-floating DNA in a plasma sample of the host that comprises both DNA from normal cells and DNA from cancer.’” EX1004 ¶147. But he offers only a conclusory single sentence explanation of his opinion, claiming that it lacked “the technical features necessary to achieve the method.” *Id.* ¶143. He provides no explanation of what technical features would be necessary or any description of why the provided written description is insufficient. His testimony is entitled to no weight. *Xerox v. Bytemark*, IPR2022-00624, 2022 WL 3648989, at *6 (P.T.A.B. Aug. 24, 2022) (precedential); 37 C.F.R. § 42.65(a).VI.A.5.b

Dr. Lennon next opines that there is some inconsistency in Natera’s reliance on paragraph 400 of the ’685 Application for priority and Natera’s argument regarding ’035 Claim 1 during prosecution that Chuu “fails to teach or suggest anything about amplifying and sequencing cell-free DNA isolated from a blood sample collected from a subject who is not a pregnant women [sic].” EX1004 ¶148 (quoting EX1003 at 629). He first asserts that this passage regarding Chuu shows Natera “argued that the remaining scope of the claim, i.e., amplifying and sequencing cfDNA isolated from a blood sample of a non-pregnant woman, was inventive and non-obvious.” *Id.* Dr. Lennon then asserts that if the limitation argued regarding Chuu were a patentable distinction over the asserted art, then Natera needed to say as much in the specification: “[T]hat assertion [regarding Chuu not

disclosing a limitation] is inconsistent with the statement in paragraph [0400], ***which provides no indication that anything is inventive about monitoring cfDNA in non-maternal applications.***” *Id.* Dr. Lennon’s imagined inconsistency is wrong both because (1) the specification need not identify future distinctions over cited art as “inventive,” and (2) even if there were such a requirement, the specification here did it. Paragraph 400 explains:

Note that it has been demonstrated that ***DNA that originated from cancer that is living in a host can be found in the blood of the host.*** In the same way that genetic diagnoses can be made from the measurement of mixed DNA found in maternal blood, ***genetic diagnoses can equally well be made from the measurement of mixed DNA found in host blood.***

EX1110 ¶400. Even if considered, Dr. Lennon’s baseless testimony shows no lack of written description support for the cancer limitation in the ’235 Application.



For these reasons, the ’035 Patent properly claims the benefit of the ’235 Application’s November 18, 2011 filing date, antedating Forshew and defeating Ground 1. *See* Pet. at 16 (asserting Forshew published on May 30, 2012).

B. Ground 2: NeoGenomics Does Not Demonstrate Obviousness Over Pieprzyk And May

Ground 2 is based entirely on modifying one of Pieprzyk’s disclosed methods to “use May’s four primers... in place of Pieprzyk’s four primers.” Pet. at 30. But NeoGenomics fails to show that its proposed combination would include “targeted amplification of a plurality of single nucleotide polymorphism (SNP) loci in a single reaction volume” in conjunction with amplification using a four-primer set. Although NeoGenomics includes a backup argument that performing this type of multiplexing would have been obvious, it fails to mention or address Pieprzyk’s teaching away due to problems associated with multiplexing with the four-primer process. NeoGenomics thus cannot succeed on Ground 2.

In addition, the Petition improperly mixes and matches different and unrelated methods and incorrectly asserts that Pieprzyk’s so-called fourth method (“Method 4” herein) teaches or suggests *all* elements of Claim 1 except for barcodes and sequencing tags.

1. The Combination Does Not Disclose Or Suggest Targeted Amplification Of A Plurality Of SNP Loci In A Single Reaction Volume

Claim 1 includes a step of amplifying a plurality of SNP loci in a single reaction volume (the “multiplex” requirement herein). EX1001 at 249:53-55. Pieprzyk’s Method 4 fails to disclose this limitation.

The Petition relies on Pieprzyk’s Method 4, which it asserts is a “four-primer PCR reaction.” Pet. at 28 (citing EX1006 ¶10). Then, the Petition proposes using May’s four primers (EX1007 ¶11) “in place of Pieprzyk’s four primers.” *Id.* at 29-30. But the Petition does not mention that Pieprzyk’s Method 4 prepares “an amplification mixture for *each* target,” after which “[*e*]ach amplification mixture is subjected to amplification.” EX1006 ¶10. May’s teaching is identical. EX1007 ¶11. Pieprzyk and May thus taught that each genetic site of interest (“target”) must be assayed in its own, separate amplification mixture—*i.e.*, in a single-plex assay with a single set of primers. Pieprzyk and May do not teach multiplex amplification in a single reaction volume as required by Claim 1.

Other parts of Pieprzyk reinforced that each target is amplified in its own separate well. As Petitioner emphasized, Pieprzyk was a Fluidigm application. Pet. at 28. Its amplification methods, including Method 4, were designed to “be carried out using a microfluidic device”—namely, Fluidigm’s proprietary microfluidic arrays such as the “Dynamic Array™,” “Digital Array™,” or “Access Array™.” EX1006 ¶¶201, 202, 204, 507. These arrays amplify many target sequences separately in many parallel single-plex reactions. They “allow the simultaneous pair-wise combination of a plurality of different amplification primers and samples” such that “each reaction is a unique combination of a particular sample and a particular primer.” *Id.* ¶¶201, 208. Various configurations of the arrays

included tens of thousands of chambers, allowing for a large panel of primer assays to be individually tested against a biological sample. *Id.* ¶201.

NeoGenomics alleges that Pieprzyk “discloses performing 50, 100, 500, and 1000 ‘multiplex detection’ reactions ‘in each individual reaction chamber’ of a device, *i.e.*, in a single reaction volume,” Pet. at 36 (quoting EX1006 ¶218), and that “May also contains similar disclosure, confirming that its primers also are suitable for multiplexing,” *id.* (citing EX1007 ¶210). But this disclosure in both references is in a generic section on “Microfluidic Devices,” which described the multiplexing capability of the *devices*, not Method 4: “In ***certain embodiments***, multiplex detection is carried out in individual amplification mixture[s], *e.g.*, ***in individual reaction chambers of a microfluidic device....***” EX1006 ¶218; EX1007 ¶210.

Pieprzyk did not suggest this disclosure applied to Method 4. Instead, Pieprzyk expressly taught that attempting to multiplex with a four-primer method is particularly problematic. Pieprzyk explained that a four-primer protocol, such as that used in Method 4, “may cause uneven incorporation of the sequencing tag between PCR assays” and that “[t]his problem is increased when one tries to multiplex the PCR reactions for tagging (in the access array).” EX1006 ¶306.

May’s paragraph 210 does not remedy the problem because it contained verbatim Pieprzyk’s paragraph 218 and is also limited to “certain embodiments.”

Compare EX1007 ¶210, *with* EX1006 ¶218. NeoGenomics provides no argument or explanation as to why these “certain embodiments” would have included the four-primer format of Method 4, from either May or Pieprzyk, especially in light of Pieprzyk’s express teaching away. *See* Pet. at 36; EX1006 ¶308 (providing a “Solution” to this problem).

Thus, NeoGenomics’ assertion that the combination of Pieprzyk and May discloses Limitation 1[D] in the context of Claim 1 *as a whole* is baseless.

2. NeoGenomics Fails To Allege That Pieprzyk, May, Or The Combination Would Have Motivated A Skilled Artisan To Use Multiplex Amplification With May’s Four-Primer Set

NeoGenomics asserts that even if “Pieprzyk had not disclosed targeted amplification of a plurality of SNP loci in a single reaction volume, that step would have been obvious.” Pet. at 36. NeoGenomics alleges that “[d]isclosures in Pieprzyk would have motivated a POSA to conduct multiplex amplification in a single reaction volume on cell-free tumor DNA,” *id.*, but NeoGenomics fails to even allege, much less show, that Pieprzyk, May, or the combination would have motivated a skilled artisan to use multiplex amplification with May’s four-primer set as proposed in its own combination, *see id.* at 36-38. NeoGenomics overlooked that showing obviousness requires showing that the claim *as a whole* would have been obvious, not each limitation in isolation. *Sanofi-Synthelabo v. Apotex*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is made with

respect to the subject matter as a whole, not separate pieces of the claim.”); *see also* *Natera*, 2024 WL 3381916, at *5 (“It is not sufficient to merely allege that the individual elements of the claimed invention were each known in the prior art.”); *KSR Int’l Co. v. Teleflex*, 550 U.S. 398, 418 (2007) (A “patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.”).

NeoGenomics selectively quotes a portion of a paragraph of Pieprzyk that is completely silent on the primers used in the method being disclosed and instead simply states:

Fetal aneuploidy detection from plasma: Plasma contains a limited concentration of target nucleic acids (DNA, methylation markers, SNPs, RNA etc).... Dividing the sample will reduce the number of target [sic] per assay and increase sampling error. Multiplexing will be necessary, which is traditionally viewed as being in direct conflict with the requirement for highly precise quantitative analysis.

EX1006 ¶379. Because this paragraph says nothing about accomplishing the method with a four-primer set as proposed by NeoGenomics in its combination, it does not provide the motivation NeoGenomics needed for the missing Limitation 1[D]. Nor does it explain or address Pieprzyk’s teaching that multiplexing with four primers should not be done. EX1006 ¶306.

Finally, NeoGenomics asserts that “Pieprzyk proposes analyzing between ‘30’ and ‘1000 or more target and/or internal control sequences,’ which falls within the claimed bounds of 25-2000 SNP loci under Patent Owner’s construction.” Pet. at 37 (quoting EX1006 ¶110). NeoGenomics fails to explain how or why this disclosed example regarding an aneuploidy determination discloses amplification of a plurality of SNP loci as required by Limitation 1[D], much less in the context of the use of its proposed four-primer set from May.

Moreover, NeoGenomics’ assertions of a likelihood of success fly in the face of Pieprzyk’s own teachings. NeoGenomics asserts that “[b]y the early 2000s, multiplex amplification was routine,” Pet. at 37, but it never specifically addresses expectation of success for use of Pieprzyk’s and May’s four-primer format, which it had to do to carry its burden to show obviousness of the claim *as a whole*. *Sanofi-Synthelabo*, 550 F.3d at 1086 (“The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim.”). Indeed, NeoGenomics does not mention or address Pieprzyk’s express teaching on why its four-primer set will not work with multiplexing and its proposed solution of eliminating the inner primers. *See* EX1006 ¶¶306, 308. This express teaching in Pieprzyk would have convinced one of skill that NeoGenomics’ proposed combination would not succeed. *Nalox-1 Pharms. v. Opiant Pharms.*, IPR2019-

00694, 2020 WL 4920200, at *9 (P.T.A.B. Aug. 21, 2020) (reference taught away when it “explicitly and unambiguously discourage[d]” asserted combination).

NeoGenomics never acknowledges Pieprzyk’s criticisms, much less explains why one of skill would have made the combination in spite of them. Pet. at 27-31, 35-38; *Par Pharm. v. Jazz Pharm.*, IPR2016-00002, Paper 12 at 12 (P.T.A.B. Apr. 12, 2016) (denying institution where “Petitioner does not account for the prior art’s teaching away”); *DynaEnergetics Europe v. QinetiQ*, PGR2023-00003, 2024 WL 1579442, at *25 (P.T.A.B. Apr. 11, 2024) (rejecting asserted combination where petitioner provided “no analysis” on the reference’s teaching away).

The Petition thus does not demonstrate a reasonable likelihood of success to show any of the claims are obvious over Pieprzyk in view of May.

C. Ground 3: NeoGenomics Fails To Demonstrate That One Of Skill Would Have Been Motivated To Make The Asserted Combination Of Porreca And Hoyal

NeoGenomics’ Ground 3 is based on two modifications to Porreca:

- Adding Hoyal’s “preamplification steps... before Porreca’s targeted amplification step,” Pet. at 50, and
- Applying the “combined method to SNP loci associated with cancer in cell-free DNA,” Pet. at 53.

NeoGenomics does not establish that one of skill would be motivated to make either modification.

1. NeoGenomics Does Not Demonstrate That One Of Skill Would Have Been Motivated To Add Hoyal's Preamplification To Porreca

NeoGenomics' first modification proposes adding the "preamplification" steps from Hoyal's Figure 3 method (steps 3, 6, and 7) before Porecca's Figure 4b "targeted amplification." Pet. at 50-51; *see also id.* at 56-59 (relying on combined method for limitations 1[C]-1[E]). NeoGenomics argues that one of skill would have been motivated to add Hoyal's "preamplification" to solve the problem of Porreca's "targeted amplification... produc[ing] a skewed pool of amplicons that 'does not adequately represent the input abundance distribution.'" Pet. at 51-52 (quoting EX1008 at 67:27-28). But NeoGenomics does not demonstrate how "Hoyal's teachings provided a solution" to this problem. Pet. at 52.

If a proposed modification would render the prior art invention being modified "inoperable for its intended purpose," then there is no motivation to make it. *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984); MPEP § 2143.01(V). The combination of Porreca with either Hoyal (Ground 3) or Wessler (Ground 4) in the manner suggested in the Petition vitiated the utility of Porreca's methods entirely.

Porreca sought to detect and "reduce bias and increase the reproducibility of multiplex analysis of genetic loci." EX1008 at Abstract. Porreca recognized a long-standing problem of "systematic and random errors (bias) in genome capture, amplification and sequencing methods, namely high variability in the capture and

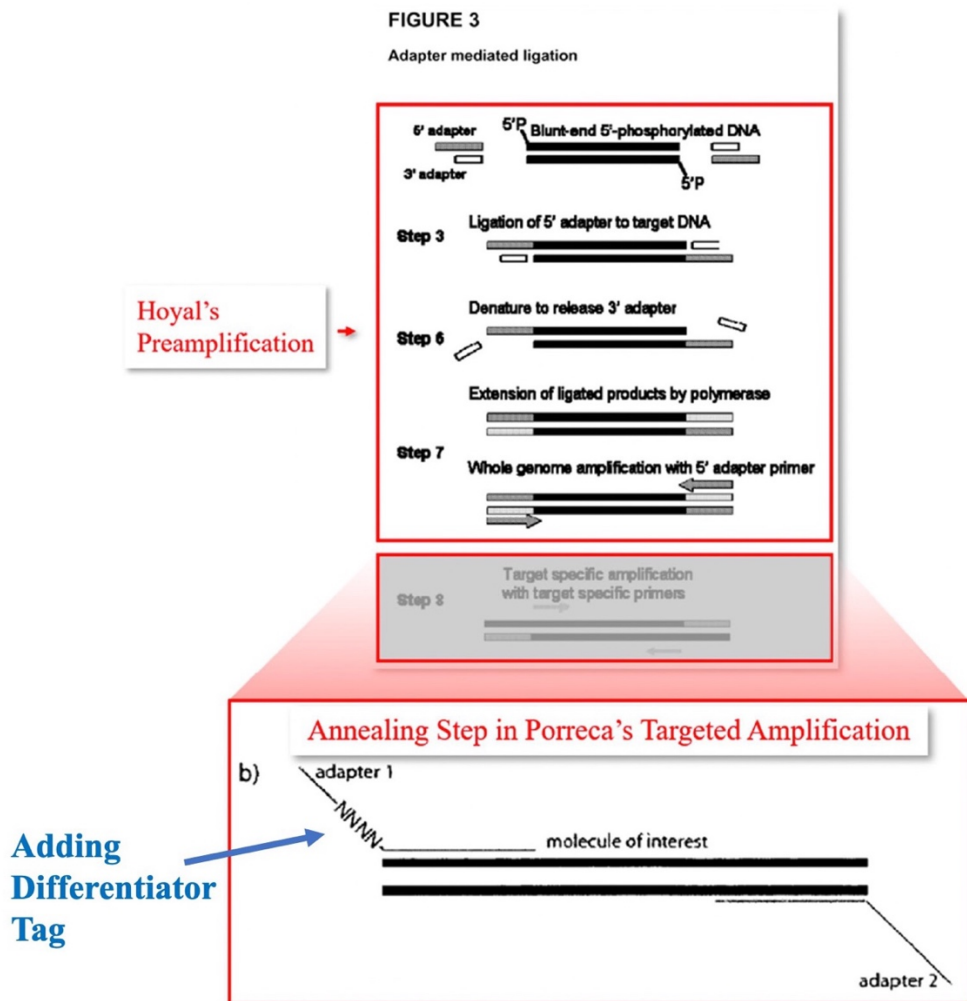
amplification of nucleic acids and disproportionate representation of heterozygous alleles in sequencing libraries.” EX1008 at 6:13-17. Any target sequence could be “under-represented or over-represented in a genetic analysis due to a combination of stochastic variation and systematic bias in any of the preparative stages (e.g., capture, amplification, etc.)....” *Id.* at 2:12-15. Correcting these errors provides “sequence information that is reliable and can be used to make a genotype conclusion (e.g., call) with a desired degree of confidence.” *Id.* at 6:33-7:3.

Porreca’s solution was to add “differentiator tag sequences to uniquely tag individual nucleic acid molecules.” *Id.* at 6:20-23. These differentiator tags “are useful to determine whether target nucleic acid sequences identified in an assay are from independently isolated target nucleic acids or from multiple copies of the same target nucleic acid molecule (e.g., due to bias in a preparative step, for example, amplification).” *Id.* at 6:29-33. In other words, in situations where “multiple [sequence] reads [were] collected for a given locus,” Porreca’s differentiator tags could reveal if the plurality of sequence “reads [we]re derived from a single originating [DNA] molecule” or truly reflected the presence of multiple different DNA molecules in the original sample. *Id.* at 44:29-31. If there was any “bias in any part of the [subsequent preparative] protocol [this bias] would change the uniformity of th[e] distribution [of differentiator tags in the original sample], which can be observed after sequencing.” *Id.* at 44:8-11.

Porreca emphasized time and again that *amplification* was a source of bias. Porreca recognized a long-standing problem of “systematic and random errors (bias) in genome capture, *amplification* and sequencing methods, namely high variability in the capture and *amplification* of nucleic acids and disproportionate representation of heterozygous alleles in sequencing libraries.” EX1008 at 6:13-17. Porreca taught that bias was, for example, “caused by PCR amplification steps,” *id.* at 44:29-31, that “overrepresentation” of a sequence “is indicative of bias in the preparative process (e.g., bias in the *amplification* process),” *id.* at 41:28-30, that “changes in the occurrence of differentiator tag sequences after *amplification* and sequencing may be indicative of bias,” *id.* at 42:8-10, and that it was important to “detect[] bias in the *amplification* of” nucleic acids, *id.* at 9:28-10:6.

In contrast, Hoyal and Wessler did not recognize the issue of bias at all. As a result, their workflows, either alone or combined with Porreca, involved bias-prone amplifications without any corresponding method to detect potential bias. *See, e.g.*, Pet. at 51 (showing proposed combination using Hoyal Figure 3 and Porreca Figure 4b). Porreca taught that the proposed combination would increase bias without any corresponding remedy. NeoGenomics provides no reasoning as to why a skilled artisan would turn to the error-prone methods of Hoyal or Wessler.

More concerning, NeoGenomics proposes making Porreca's first tagging step employing differentiator tags the next-to-last step in the combination with Hoyal. *See, e.g.,* Pet. at 51 (annotated figure reproduced below with blue annotation added).



As shown, in the Porreca-Hoyal combination, differentiator tags would be added only after all other preparative steps were complete, rendering them useless to detect bias. In the Porreca-Wessler combination, the use of differentiator tags is eliminated. Pet. at 69 (proposing modifying “the Porreca method by performing Wessler’s

ligation and one or two targeted amplifications *in lieu of Porreca’s targeted amplification*”).

The Porreca-Hoyal combination’s use of differentiator tags only after all other preparative steps deprives Porreca’s “differentiator tags” of their intended purpose. *DePuy Spine v. Medtronic Sofamor Danek*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (combination not obvious “if the prior art indicated that the invention would not have worked for its intended purpose”); *Plas-Pak Indus., Inc. v. Sulzer Mixpac*, 600 F. App’x 755, 760 (Fed. Cir. 2015) (finding no motivation to combine when modification “would render [the reference] ‘inoperable for its intended purpose’”). Porreca’s tagging strategy rested on one fundamental premise: that the “distribution of differentiator tag sequences can be assumed to be uniform” at the time of their attachment to target molecules (the “incorporation step”). EX1008 at 44:8-9. As Porreca explained: “incorporation of... a differentiator tag sequence at a particular step [only] allows the detection and correction of biases in *subsequent* steps of the protocol.” *Id.* at 41:7-9. Conversely, differentiator tags could not reveal any biases in manipulations that preceded the tagging.

As a result, Porreca explained its solution to bias required targeting molecules “*prior to amplification* or other process that may introduce bias.” *Id.* at 39:21-24; *see also id.* at 41:7-9 (“The incorporation... a differentiator tag sequence... allows the detection and correction of biases in *subsequent steps* of the protocol.”). That is

because “target:differentiator tag sequence combinations that are statistically overrepresented are indicative of bias in the protocol at one or more steps *between the incorporation of the differentiator tag sequences into MIPs [molecular inversion probes] and the actual sequencing* of the MIP capture products.” *Id.* at 41:30-42:2.

In contrast, NeoGenomics’ proposed combination with Hoyal defers the tagging step until *after* all other preparative steps, too late to be of any use in detecting bias. *See* Pet. at 59 (Limitation 1[E]: “barcode and sequencing tags are incorporated into *final amplification products*” and Limitation 1[F]: “Porreca discloses sequencing the plurality of SNP loci on the cell-free DNA in its *final amplification products*”). The combination deprives Porreca’s differentiator tags of their intended purpose, rendering them useless in the proposed combination, and eliminates Porreca’s solution to bias.

The Petition asserts that Hoyal “provided a solution” to Porreca’s bias problem. Pet. at 52. But the explanation shows that Hoyal was directed to a different problem—“a need for improved extraction methods capable of capturing small nucleic acid molecules.” *Id.* (quoting EX1009 at 1-2). Porreca taught that biases arose from “uneven synthesis error rates and representational biases” and lack of “uniformity of amplification efficiency when multiple molecules are amplified in parallel,” rather than from the size of the nucleic acid molecules. EX1008 at 37:1-

8, 37:19-21. In fact, Porreca noted that many different types of amplification—including inversion-probe methods essentially like Hoyal’s adaptor-primed amplification—all suffered from bias. *See id.* at 67:20-28. Rather than providing a “solution,” Hoyal’s methods suffer the same bias that Porreca attempted to eliminate.

Moreover, NeoGenomics’ proposed combination overlooks Porreca’s own solution to this problem (differentiator tags), which destroys its motivation to combine Porreca with Hoyal. *Kinetic Concepts v. Smith & Nephew*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (“Because each device independently operates effectively, a person having ordinary skill in the art, who was merely seeking to create a better device to drain fluids from a wound, would have no reason to combine the features of both devices into a single device.”); *In re Anova Hearing Labs*, 809 F. App’x 840, 843 (Fed. Cir. 2020) (“The Board also does not explain why a person of ordinary skill in the art would be motivated to modify Brown, which already includes vents, to address occlusion effect.”).

Dr. Lennon contends that Hoyal’s “universal preamplification” would increase the initial number of copies of the sequences in the sample, which would “facilitate[] subsequent targeted amplification by ensuring that target sequences will be present in high enough abundance to serve as templates for targeted PCR.” EX1004 ¶227. But neither NeoGenomics nor its expert explain how increasing the initial amount of all sequences would prevent skewing the “abundance distribution”

of amplicons in the sample, rather than causing it as Porreca taught. *See* Pet. at 51-52; EX1004 ¶227.

Porreca does not cite initial sample size as causing its sensitivity problem and instead points to “a skewed ratio” resulting from any of its sample preparation techniques as “decreas[ing] the sensitivity of detecting mutations.” EX1008 at 67:27-68:7. For example, Porreca explains that if two alleles are present in the initial sample at a 50:50 ratio and sample preparation skews the ratio of those two alleles to 10:90, then there is a “high probability that one of the two alleles would not be observed” during sequencing. *Id.* NeoGenomics does not explain how Hoyal’s preamplification would prevent the ratio of two alleles in the initial sample from being skewed. *See* Pet. at 52.

In fact, the Petition fails to explain how Hoyal’s preamplification step—being an amplification reaction—could avoid **exacerbating** bias. As Porreca explained, all amplification—both Porreca’s and Hoyal’s—is a source of bias. Hoyal’s preamplification itself was the problem Porreca identified, not a solution.

NeoGenomics bore the burden to demonstrate “that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention.” *Intelligent Bio-Sys. v. Illumina Cambridge*, 821 F.3d 1359, 1367-68 (Fed. Cir. 2016); *In re Magnum Oil Tools Int’l*, 829 F.3d 1364, 1381 (Fed. Cir. 2016). It did not do so. Because NeoGenomics does not demonstrate why one

of skill would modify Porreca to include Hoyal’s “preamplification” steps, it fails to demonstrate that the combination would have been obvious. The Board can reject Ground 3 for this reason alone.

2. NeoGenomics Does Not Establish A Motivation To Apply The Combined Method To SNP Loci Associated With Cancer In Cell-Free DNA

NeoGenomics’ second predicate modification is applying the combined method of Porreca and Hoyal already discussed “to SNP loci associated with cancer in cell-free DNA.” Pet. at 53; *see also id.* at 55-56, 60 (relying on same for limitations 1[A]-[B] and 1[G]). Again, NeoGenomics does not prove that a skilled artisan would have been motivated to make this modification or had a reasonable expectation of success. NeoGenomics first points to Natera’s arguments in unrelated litigation that techniques to study “tumor cfDNA in a cancer patient’s blood” were known. EX1039 at 3; Pet at 53 (citing same); *see also* EX1004 ¶229 (Dr. Lennon arguing that it was “known” to study cancer via “ctDNA”). Even if true, NeoGenomics’ assertion that “techniques for studying ‘tumor [cell-free] DNA in a cancer patient’s blood’ were ‘routinely used before November 2009,’” Pet. at 53 (citation omitted), does not itself provide a motivation to combine. *KSR*, 550 U.S. at 401 (“A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art.”); *Virtek Vision Int’l v. Assembly Guidance Sys.*, 97 F.4th 882, 888 (Fed. Cir. 2024) (“[T]he

fact that the claim elements are known in the prior art.... alone does not show a motivation to combine.”). Nor would it make it obvious to apply a different technique—the proposed combined method of Porreca and Hoyal—to SNP loci associated with cancer in cell-free DNA.

The Petition next cobbles together various portions of Porreca in an attempt to show a motivation “to apply the combined method to SNP loci associated with cancer in cell-free DNA.” Pet. at 53. But NeoGenomics, conceding that Porreca does not disclose Limitation 1[A], argues instead that the combination of three teachings would provide the motivation. NeoGenomics asserts that Porreca’s method is: (1) “suitable for the ‘detection of mutations in maternally-circulating fetal DNA,’” (2) “useful for detecting cancer,” and (3) “useful for any application where sensitivity is important.” *Id.* (quoting EX1008 at 7:5-8, 25:3-7). NeoGenomics does not explain how a skilled artisan aware of these three teachings would make the leap to analyzing ctDNA to detect cancer, and it is not apparent from these alleged teachings. *Intelligent Bio-Sys.*, 821 F.3d at 1367-68 (“It was [Petitioner’s] burden to demonstrate both ‘that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.’” (citation omitted)).

Additionally, NeoGenomics does not mention that its references to detecting cancer in Porreca describe analyzing cancer *cells*, not ctDNA. EX1008 at 4:23-33 (“tumor or circulating tumor cells”), 7:5-10 (“heterogeneous tissue sample”), 18:32-33 (“tissue sample,... tumor sample, circulating tumor cells”), 25:3-7 (“detection of cancer mutations in a heterogeneous tissue sample”), 29:4-6 (“analyzing circulating tumor cells”). NeoGenomics offers no explanation for how the skilled artisan would have jumped from analyzing cancer cells to ctDNA.

Dr. Lennon goes a step further and adds that “it has been known since the 1990s that cancers may be diagnosed and monitored by detecting and analyzing the presence of ctDNA, as well as any changes in the ctDNA.” EX1004 ¶229. But neither the Petition nor Dr. Lennon provides a reasoned explanation why a skilled artisan would have been motivated to apply the teachings of Porreca and Hoyal to the diagnosis and monitoring of cancer using ctDNA. *TQ Delta v. CISCO Sys.*, 942 F.3d 1352, 1359 (Fed. Cir. 2019) (“[A] conclusory assertion with no explanation is inadequate to support a finding that there would have been a motivation to combine because this type of finding, without more, tracks the *ex post* reasoning *KSR* warned of and fails to identify any actual *reason* why a skilled artisan would have combined the elements in the manner claimed.” (cleaned up) (italics in original) (citation omitted)).

NeoGenomics’ citations to Porreca’s generic statements that its methods can be used in “any” application and are not limited by the disclosed embodiments do not fill this gap either. EX1008 at 25:3-7, 5:1-3, 20:16-17, 25:3-7, 25:28-29, 26:18-25, 28:7-10, 30:9-10, 87:31-88:4; Pet. at 53 (citing same). None of these broad generic disclosures provide a specific reason to apply one of Porreca’s methods (as modified by Hoyal) to SNP loci associated with cancer in cell-free DNA. *Cf. Markforged v. Continuous Composites*, No. IPR2022-00679, 2023 WL 6534357, at *6 (P.T.A.B. Sept. 26, 2023) (finding “generic passage regarding ‘various features’ that ‘may’ be provided in a single embodiment lacks specificity and precision” and “falls short of describing why a person of ordinary skill in the art would have been motivated to combine such features”).

As a backup, NeoGenomics argues Hoyal’s methods are useful for “detecting and monitoring extracellular mutant oncogenes or tumor-associated DNA found in the plasma or serum fraction of blood by using DNA extraction with enrichment for mutant DNA as provided herein.” Pet. at 54 (quoting EX1009 at 20). The Petition then concludes, “[a] POSA thus would have been motivated to extend the combination to detecting mutations in cell-free tumor DNA isolated from blood” and cites Dr. Lennon who provides an almost verbatim conclusory assertion. Pet. at 54 (citing EX1004 ¶230); *One World Techs. v. Chevron (HK)*, PGR2020-00059, 2020 WL 7222691, at *16 (P.T.A.B. Dec. 7, 2020) (Expert testimony that “merely parrots

the words in the Petition.... is entitled to little or no weight.”); *Xerox*, 2022 WL 3648989, at *6; 37 C.F.R. § 42.65(a). But this conclusory assertion is no better than the first one and still provides no explanation for why a skilled artisan would have been motivated to use one of *Porreca*’s alleged methods (modified by Hoyal) to “detect[] mutations in cell-free tumor DNA isolated from blood.” Pet. at 54; *TQ Delta*, 942 F.3d at 1359 (“[A] conclusory assertion with no explanation is inadequate to support a finding that there would have been a motivation to combine.” (citation omitted)).

As NeoGenomics again fails to meet its burden to show that one of skill would be motivated to make these asserted modifications much less with any reasonable expectation of success, it fails to demonstrate that the asserted combination renders the claims obvious. For this additional reason, the Board can reject Ground 3 in its entirety.

D. Ground 4: NeoGenomics’ Porreca And Wessler Ground Does Not Demonstrate A Reasonable Likelihood Of Success

1. NeoGenomics Fails To Show That It Would Have Been Obvious To Apply Its Porreca-Wessler Combination To SNPs From Cell-Free DNA Associated With Cancer

Ground 4 is based on modifying Porreca in view of Wessler and then applying the modified method to SNP loci associated with cancer in cell-free DNA. Pet. at 69-72. In particular, NeoGenomics first proposes modifying Porreca “by performing Wessler’s ligation and one or two targeted amplifications *in lieu of Porreca*’s

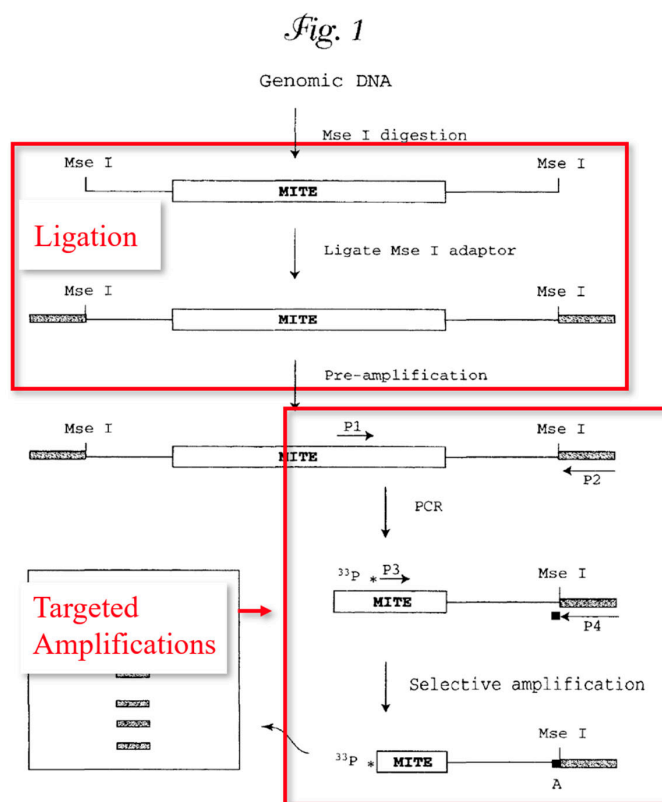
targeted amplification,” Pet. at 69, and then using the combined method “to target SNP loci associated with cancer in cell-free DNA,” *id.* at 71. But NeoGenomics’ removal of Porreca’s targeted amplification eliminates Porreca’s use of differentiator tags to solve the problem of bias in amplification as explained above regarding Ground 3. *See supra* § VI.C.1. Rendering Porreca inoperable for its intended purpose precludes any motivation to combine for the reasons explained above. *DePuy Spine*, 567 F.3d at 1326 (combination not obvious “if the prior art indicated that the invention would not have worked for its intended purpose”); *Plas-Pak Indus.*, 600 F. App’x at 760 (finding no motivation to combine when modification “would render [the reference] ‘inoperable for its intended purpose’”).

Additionally, NeoGenomics does not demonstrate a motivation for targeting SNP loci associated with cancer in cell-free DNA, let alone a reasonable expectation of success.. Instead of providing a specific motivation for Ground 4, the Petition simply relies on one of the flawed motivation arguments from Ground 3 based on Porreca’s alleged disclosures. Pet. at 71 (“Porreca’s disclosures would have motivated a POSA to target SNP loci associated with cancer in cell-free DNA....”). This argument fails for the same reasons explained in Ground 3 above. *See supra* § VI.C.2. As NeoGenomics does not demonstrate a motivation to apply its Porreca-Wessler combination to SNP loci associated with cancer in cell-free DNA, it cannot show that the combination would have been obvious.

For these reasons, the Board should reject Ground 4 in its entirety.

2. Ground 4’s Combined Method Is Internally Inconsistent And Contradicts Its Asserted Motivation To Combine

NeoGenomics asserts that a “POSA would have been motivated to modify the Porreca method by performing Wessler’s ligation and one or two targeted amplifications *in lieu of Porreca’s targeted amplification.*” Pet. at 69. Then, NeoGenomics includes the following annotated figure showing Wessler’s “ligation and targeted amplification steps”:



Id. NeoGenomics argues that “*Wessler’s* ligation followed by preamplification provides a solution” to “Porreca’s single targeted amplification.” *Id.* at 70.

NeoGenomics then contends that “*Wessler’s* second, optional amplification offered improved specificity over Porreca’s method” and that “*Wessler’s* two targeted amplifications would significantly reduce the number of possible off-target interactions between primers.” *Id.* NeoGenomics thus proposed supplanting Porreca’s alleged targeted amplification step with Wessler’s ligation and two targeted amplifications.

However, when NeoGenomics applies Claim 1 to its combined method, it forgets that it has replaced Porreca’s alleged targeted amplification with Wessler’s. The Challenged Claims require:

- 1[C] “amplifying the tagged products one or more times to generate final amplification products,”
- 1[D] “wherein one of the amplification steps comprises targeted amplification of a plurality of single nucleotide polymorphism (SNP) loci in a single reaction volume,” and
- 1[E] “wherein one of the amplifying steps introduces a barcode and one or more sequencing tags.”

EX1001 at 249:51-57. NeoGenomics’ application of each of these limitations relies at least in part on Porreca’s alleged targeted amplification. Pet. at 73-74.

For example, NeoGenomics relies solely on Porreca’s alleged targeted amplification step for Limitation 1[E]. Pet. at 73 (citing EX1008 at 8:5-8, 43:29-33,

Fig. 4(b)); *see also id.* at 58-59 (citing same as describing Porreca’s “targeted amplification step”). NeoGenomics does not argue that either of Wessler’s targeted amplification steps introduces barcodes and one or more sequencing tags. *See* Pet. at 73-74. Nor does NeoGenomics argue it would be obvious to modify Wessler’s steps to include barcodes and sequencing tags. *Id.* Because Porreca’s Figure 4b would not be part of NeoGenomics’ proposed “combined method,” Pet. at 69, its assertion that the combined method satisfies Limitation 1[E] based solely on Porreca’s Figure 4b must fail, *id.* at 73.

The Petition similarly cites Porreca’s alleged targeted amplification for Limitations 1[C] and 1[D]. Pet. at 73 (pointing to “Porreca’s target-specific primers” for 1[C]); *id.* (citing Porreca (EX1008) at 8:5-8, 43:29-33, Fig.4b for limitation 1[D]). For Limitation 1[C], for example, NeoGenomics asserts that the combined method involves “amplification using one of Porreca’s target-specific primers and one of Wessler’s adapter primers” without explaining how the skilled artisan knew to select this specific feature of Porreca’s alleged targeted amplification to use in Wessler’s targeted amplifications. *See* Pet. at 73. NeoGenomics cites its motivation discussion, but it does not discuss use of Porreca’s target-specific primers in that discussion. *See id.* at 69-71. For Limitation 1[D], NeoGenomics relies solely on Porreca without any explanation of why Wessler’s targeted amplification steps should be multiplexed based on Porreca. *See id.* at 73 (citing *id.* at 57-58 (asserting

that Porreca’s targeted amplification step satisfies Limitation 1[D])). Again, NeoGenomics makes no effort to explain how its asserted combination, using Wessler “*in lieu of* Porreca’s targeted amplification,” Pet. at 69, satisfies these limitations, *id.* at 73.

Dr. Lennon’s testimony is no help here as he merely repeats the Petition’s argument without further explanation or support. *See* EX1004 ¶¶272-74; *One World*, 2020 WL 7222691, at *16; *Xerox*, 2022 WL 3648989, at *6; 37 C.F.R. § 42.65(a).

NeoGenomics thus fails to even argue much less demonstrate that its “combined method” meets these limitations.

VII. CONCLUSION

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

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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 13,970 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 2004-2007, 2011-2013, 2016-17, 2019-2022, 2028-2048** are being served electronically on July 29, 2024 to the following counsel for Petitioner to the following email addresses:

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