

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NEOGENOMICS LABORATORIES, INC.
Petitioner,

v.

NATERA, INC.
Patent Owner.

Patent No. 11,519,035

Inter Partes Review No. IPR2024-00812

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

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NeoGenomics Laboratories, Inc. (“Petitioner”) petitions for *inter partes* review of claims 1-5 and 10-15 of U.S. Patent No. 11,519,035 (“the ’035 patent” (Ex.1001)) pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42.100 *et seq.*

I. INTRODUCTION

Scientists have long known that human cells can release DNA into the bloodstream. This “cell-free DNA” can be analyzed, including for mutations originating in fetal cells in a pregnant woman (which may indicate genetic anomalies in the fetus) and from tumor cells (which may indicate cancer).

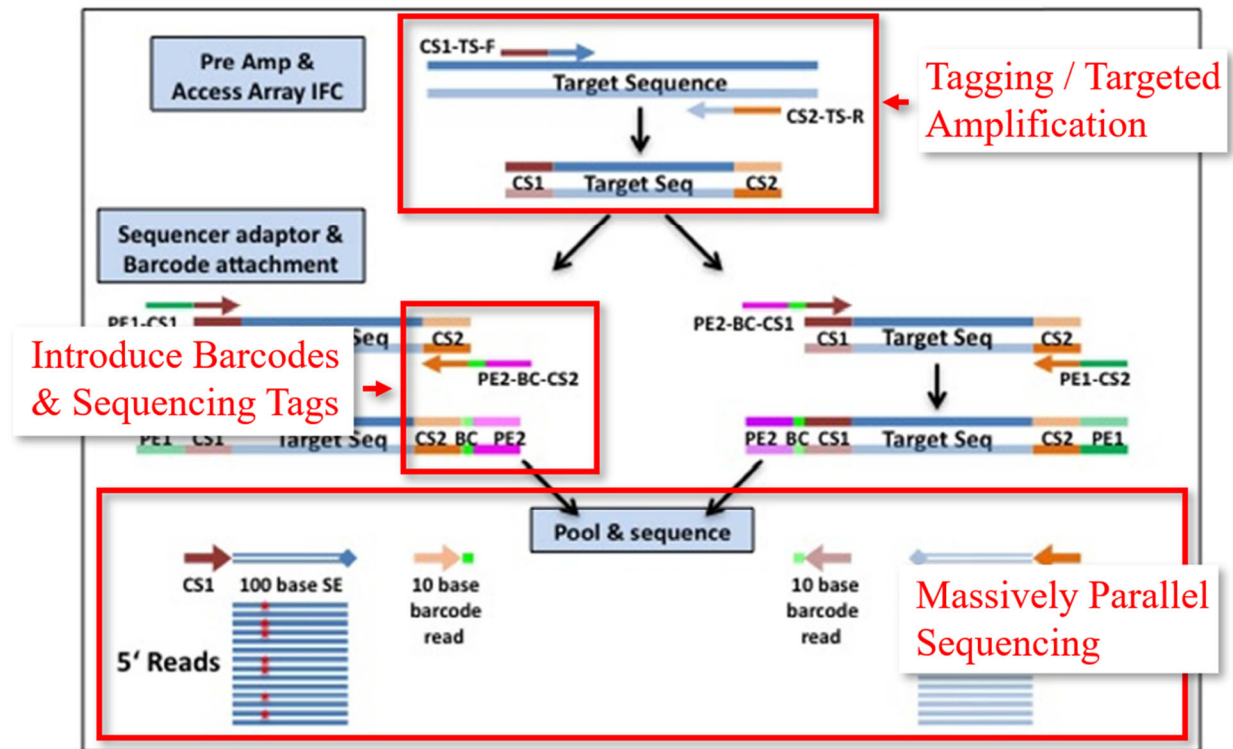
The ’035 patent claims a method of analyzing mutations in cell-free DNA. Claim 1 requires the steps of: (1) tagging cell-free DNA with one or more adaptors, (2) performing targeted amplification of a plurality of tagged products in a single reaction volume, including introducing barcodes and sequencing tags via amplification, and (3) sequencing the amplified DNA with massively parallel sequencing. The Examiner recognized that none of these steps was new, either individually or in combination. But the Examiner nonetheless allowed the claims after they were amended to require that the cell-free DNA be not “from a pregnant female” and be evaluated for particular differences “associated with cancer.”

Patent Owner has asserted in co-pending litigation against Petitioner that the claims are novel insofar as they cover methods for analyzing point mutations in cell-free tumor DNA. About a month before the ’035 patent was filed, however,

Patent Owner itself asserted that techniques for detecting “tumor cfDNA in a cancer patient’s blood” were “routinely used before November 2009.” Consistent with that statement, the ’035 patent does not treat such techniques as unique, acknowledging that methods for detecting mutations for non-cancer applications were equally suited for detecting mutations associated with cancer.

In fact, the entire claimed method, including its application to cell-free tumor DNA, was well-known long before the ’035 patent’s priority date. Patent publications to Pieprzyk and May dating to 2010 and asserted in this Petition teach tagging, multiplex targeted amplification, introducing barcodes and sequencing tags via amplification, and massively parallel sequencing of cell-free tumor DNA from a non-pregnant person—just as Patent Owner contends its claims require. So do Porreca, Hoyal, and Wessler, which date from 2002 to 2010.

Patent Owner’s own arguments in the co-pending litigation also establish unpatentability. Patent Owner alleges that a 2012 article by Forshaw *et al.* shows how Petitioner’s commercialized assay for detecting cell-free DNA works and, in doing so, establishes infringement. But Patent Owner did not provide sufficient written description support for the claimed invention until 2015, three years after Forshaw published. Forshaw therefore is prior art, and Patent Owner’s own arguments establish anticipation. The steps of Forshaw’s method, annotated according to Patent Owner’s infringement theory, are shown below:



Patent Owner has no right to a monopoly on these well-worn methods. The Board should institute *inter partes* review and then cancel every challenged claim.

II. BACKGROUND

A. State Of The Art By 2010¹

Since 1947, scientists have known that dying and dead cells release DNA into the blood stream. (Ex.1004, ¶63; *see also id.* ¶¶58-71.) Cell-free DNA from

¹ As discussed *infra*, the critical date (or priority date) of the '035 patent is no earlier than October 20, 2015. Petitioner sets out the state of the art by 2010, however, because Patent Owner has asserted in the co-pending litigation that the

cancer cells often includes mutations relative to healthy cells and, since the 1970s, scientists have correlated such mutations in cell-free DNA to cancer. (*Id.*) Cell-free DNA thus has long been known as a potent diagnostic tool. (*Id.*, ¶89.)

As Patent Owner acknowledges, methods for studying “tumor [cell-free] DNA in a cancer patient’s blood” were “routinely used before November 2009.” (Ex.1039, 3.) In 2005, Cantor *et al.* described detecting “circulating tumor-specific nucleic acids in a blood, urine, or stool sample.” (Ex.1046, Abstract, ¶35.) In 2008, Ehrich *et al.* described a “method for the detection of specific polymorphic alleles in a mixed DNA population,” where the cell-free DNA could come from a blood sample from an individual with cancer. (Ex.1047, 3:20-29, 4:24-29.) And in 2009, Lo *et al.* disclosed that a “sequencing technique on plasma cell-free DNA may be used to detect the chromosomal aberrations in the plasma DNA for the detection of a specific cancer.” (Ex.1048, ¶248.) The Federal Circuit also observed that, by 2009, extracting, amplifying, and next-generation sequencing cell-free DNA was “merely...the conventional use of existing techniques.” *CareDx, Inc. v. Natera, Inc.*, 40 F.4th 1371, 1379 (Fed. Cir. 2022). The prior art asserted in this Petition further shows that the use of tagging, amplifying, and

critical date is “by May 18, 2011” and because the ’035 patent’s earliest provisional application is dated May 18, 2010. (Ex.1001, 2; Ex.1034, 6-7.)

massively parallel sequencing to monitor cell-free tumor DNA was known. (*E.g.*, Exs.1006-1009.)

The same goes for the exact mechanics of each of the claimed tagging, amplifying, and massively parallel sequencing steps. (Ex.1004, ¶¶72-92.) Take tagging with universal tail adapters. In another lawsuit, Patent Owner’s expert testified that, by January 2010, adding universal “adaptor sequences” was known. (Ex.1040, ¶63.) He similarly called methods of “employ[ing] PCR amplification and utilize[ing] primers with sample specific barcodes and sequences to which the sequencing primer could anneal” “well-known” and “widely used.” (Ex.1040, ¶54.) The prior art in this Petition—much of it dating to 2010 or earlier—also discloses tagging cell-free DNA with universal tail adapters as claimed. (*See, e.g.*, Ex.1007, ¶¶11, 115, Ex.1008, 8:13-15, 8:28-31, 43:29-33; Ex.1009, 27-28, Fig.3.)

Targeted multiplex PCR amplification, in which multiple distinct primer pairs are used to exponentially replicate multiple DNA locations in a single amplification, also was known by 2010. (Ex.1004, ¶¶72-78.) The ’035 patent states that “multiplexing PCR for sequencing” of up to “100 assays in the same well” was not new. (Ex.1001, 48:25-27, 85:14-20, 87:32-33.) Likewise, the asserted prior art discloses performing “10000 or more amplification reactions” in one reaction volume. (*E.g.*, Ex.1007, ¶210; *see also* Ex.1008, 29:10-18.) Even

Patent Owner's own experts have stated that, by 2010, "selectively amplifying at least 1,000 SNPs" was "routine." (Ex.1041, ¶¶202; Ex.1040, ¶¶69, 98, 114.)

Massively parallel sequencing also was known by 2010. (Ex.1004, ¶¶87-92.) The '035 patent describes using commercially available HiSeq and MiSeq devices to perform massively parallel sequencing. (Ex.1001, 90:60-64.) The asserted prior art also confirms this sequencing method was known. (*E.g.*, Ex.1007, ¶161; Ex.1008, 21:8-32, 23:4-13.) So does Patent Owner's own expert, who admitted that, by 2007, "next-generation sequencing was in widespread use," including for cell-free DNA.² (Ex.1040, ¶115.)

B. The '035 Patent

The '035 patent was filed on July 21, 2020 as a fast-track continuation. (Ex.1003, 1276; *see also* Ex.1004, ¶¶38-49.) Original claim 1 recited "tagging isolated cell free DNA with one or more universal tail adaptors," "amplifying the tagged products" and "sequencing a plurality of loci on the cell free DNA...wherein the plurality of loci comprises 25-2,000 loci." (*Id.*, 1635.)

The Examiner first rejected the claims as anticipated by Fan (Ex.1022), which the Examiner found taught the three recited steps. (Ex.1003, 957-58.) Patent Owner overcame that rejection by adding a recitation directed to "targeted

² Massively parallel sequencing is next-generation sequencing. (Ex.1004, ¶91.)

amplification” and “SNP” loci: “wherein one of the amplification steps comprises targeted amplification of a plurality of single nucleotide polymorphism (SNP) loci.” (*Id.*, 853, 858-59.)

The Examiner next rejected the amended claims as anticipated by Chuu (Ex.1023). (Ex.1003, 635-36.) In response, Patent Owner amended its claims to require that the cell-free DNA be isolated from a subject “who is not a pregnant women [*sic*],” that the targeted amplification is “in a single reaction volume,” and that SNP loci are “associated with cancer.” (*Id.*, 626.)

Patent Owner then distinguished Chuu based on its amendment. It first argued that Chuu is directed to the analysis of “maternal plasma samples for detection of fetal aneuploidy,” unlike claim 1 as amended. (Ex.1003, 629.) Patent Owner did not, however, acknowledge its own specification’s statements that methods for tracking cell-free DNA unrelated to cancer “equally well read on determining the ploidy state or genetic state of a cancer from the measurements on host blood.” (Ex.1001, 204:11-12.) Patent Owner also argued that Chuu did not disclose targeted amplification of 25-2,000 target loci “associated with cancer” in a single reaction volume. (Ex.1003, 629.) But again, it did not tell the Examiner that, roughly a month before filing the ’035 patent’s application, it had represented to a court that methods for studying “tumor [cell-free] DNA in a cancer patient’s blood” were “routinely used before November 2009.” (Ex.1039, 3.)

The Examiner allowed the '035 patent on April 9, 2021—less than one year from filing—on the basis that detecting SNP loci associated with cancer in non-pregnant people's DNA was not disclosed or suggested in the prior art. (Ex.1003, 573.) She found that the prior art taught “multiplex amplification and sequencing of 25 to 2000 SNP targets in a sample,” but not SNP loci “associated with cancer” and excluding “samples of cell free nucleic acid obtained from a pregnant female.” (*Id.*, 578-79.) Patent Owner then submitted hundreds of references in information disclosure statements. (*Id.*, 2, 16, 50, 56, 144, 151, 171, 230, 301, 379, 492, 547, 555.) Buried in those post-allowance disclosures were several references at issue here, such as May and Hoyal, that teach or render obvious detecting SNP loci associated with cancer in non-maternal DNA. (*Id.*, 237, 239.)

C. Level Of Ordinary Skill In The Art

A person of ordinary skill in the art (“POSA”) would have had, by the critical date,³ at least (1) a Master's Degree and/or Ph.D. in biochemistry, molecular genetics, pharmacology, or an equivalent discipline with applications in genomics and (2) at least five years of academic or industrial laboratory experience. (Ex.1004, ¶¶53-54, 57.)

³ A POSA's qualifications would have been, for the purposes of this proceeding, roughly the same in 2010 and 2011 as in 2015. (Ex.1004, ¶57.)

A POSA would have had a deep understanding of genomics, including nucleic acid detection, quantification, and genotyping and would understand the underlying scientific principles to such. (*Id.*, 55.) A POSA also would have been apprised of then current literature on genomic assays, such as multiplex PCR, NGS techniques, and the use of cfDNA in genotyping. (*Id.*, 56.) A POSA would also have generally understood the processes behind the development of DNA mutation-based illnesses, such as cancers, and would have been apprised of the recent literature in those fields. (*Id.*)

III. CLAIM CONSTRUCTION

In co-pending litigation, two terms are in dispute: (1) “amplifying the tagged products...wherein one of the amplification steps comprises targeted amplification”; and (2) “SNP loci...associated with cancer.” (Ex.1035, 3, 7.) For the first term, Patent Owner contends that “amplifying the tagged products” can occur in the same PCR reaction as tagging: in Patent Owner’s view, the first amplification cycle can satisfy the tagging requirement and the next amplification cycle can satisfy the amplifying requirement. (*Id.*, 5.) For the second term, Patent Owner contends that “SNP loci...associated with cancer” encompasses mutations specific to cancer cells. (*Id.*, 8.)

Petitioner disagrees with Patent Owner’s constructions but adopts them for the purposes of this proceeding. *See Gen. Elec. Co. v. Vestas Wind Sys. A/S*, No.

IPR2018-00928, Paper 9, 16 (P.T.A.B. Nov. 5, 2018) (petitioner can argue “more than one construction, including one that it believes is incorrect, such as patent owner’s”). The Board therefore need not construe either term. *See Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1375 (Fed. Cir. 2019) (claim construction only required if “necessary to resolve the controversy”) (cleaned up).

IV. PRECISE REASONS FOR RELIEF REQUESTED

Pursuant to 37 C.F.R. § 42.104(b), Petitioner requests cancellation of claims 1-5 and 10-15 of the '035 patent based on six references in four Grounds and the accompanying declaration of Dr. Niall Lennon (Ex.1004):

Ground	35 U.S.C. §	Claims	Prior Art
1	102/103	1, 12, 13	Forsheew (Ex.1005)
2	103	1, 10-15	Pieprzyk (Ex.1006) & May (Ex.1007)
3	103	1-3, 10-13	Porreca (Ex.1008) & Hoyal (Ex.1009)
4	103	1-5, 10-15	Porreca & Wessler (Ex.1010)

How these six references qualify as prior art turns on the priority date of the challenged claims. (Ex.1004, ¶¶157-160.) That date is in dispute. In the co-pending litigation, Patent Owner has asserted a priority date “by May 18, 2011,” placing the '035 patent within the pre-AIA’s first to invent provisions. (Ex.1034, 6-7.) As discussed below, however, the challenged claims are entitled to a priority date no earlier than October 20, 2015, which would place the '035 patent within the AIA’s first inventor to file provisions. Determining priority thus is a threshold step before the asserted references are applied against the challenged claims. *See*,

e.g., *3M Company v. Bay Materials, LLC*, IPR2022-01215, Paper 41 at 8-17 (P.T.A.B. Jan. 16, 2024) (rejecting Patent Owner’s proposed effective filing date and then cancelling all challenged claims over intervening art).

A. The Priority Date Is No Earlier Than October 20, 2015

The ’035 patent’s priority date is no earlier than October 20, 2015, because that is when Patent Owner *might* have first provided support for certain elements of independent claim 1. (Ex.1004, ¶¶50-52, 93-156.) In seeking to overcome Chuu during prosecution, Patent Owner amended claim 1 to recite: “isolated cell free DNA...*collected from a subject who is not a pregnant women* [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*.”⁴ (Ex.1003, 853; Ex.1001 (claim 1).)

To show support for these added elements (collectively, the “cancer limitation”), Patent Owner cited certain paragraphs and examples 26-29 in the ’035 specification. Only three of those citations—Examples 27-29—might plausibly support the cancer limitation. (Ex.1004, ¶¶98-122 (testifying to how a POSA would have understood each cited disclosure).) They describe multiplex amplification and sequencing of 3,168 SNPs, some potentially associated with cell-

⁴ All emphases are added unless otherwise noted.

free tumor DNA. (*Id.*) The examples were introduced in a parent CIP application (14/918,544) (“’544 CIP”) on October 20, 2015.⁵ (Ex.1021, Examples 27-29; *see also* Ex.1001, 239:6-245:26.) As a result, challenged claim 1 and its dependents have an effective filing date of October 20, 2015. *See, e.g.*, M.P.E.P. 2133.01.

The prosecution of a parent application, U.S. Application No. 14/877,925 (“’925 application”), confirms that the cancer limitation was not supported until the disclosures of the ’544 CIP (at the earliest). In that prosecution, an Examiner rejected for lack of written description a limitation having similar scope to what Patent Owner now contends the ’035 patent’s cancer limitation covers:

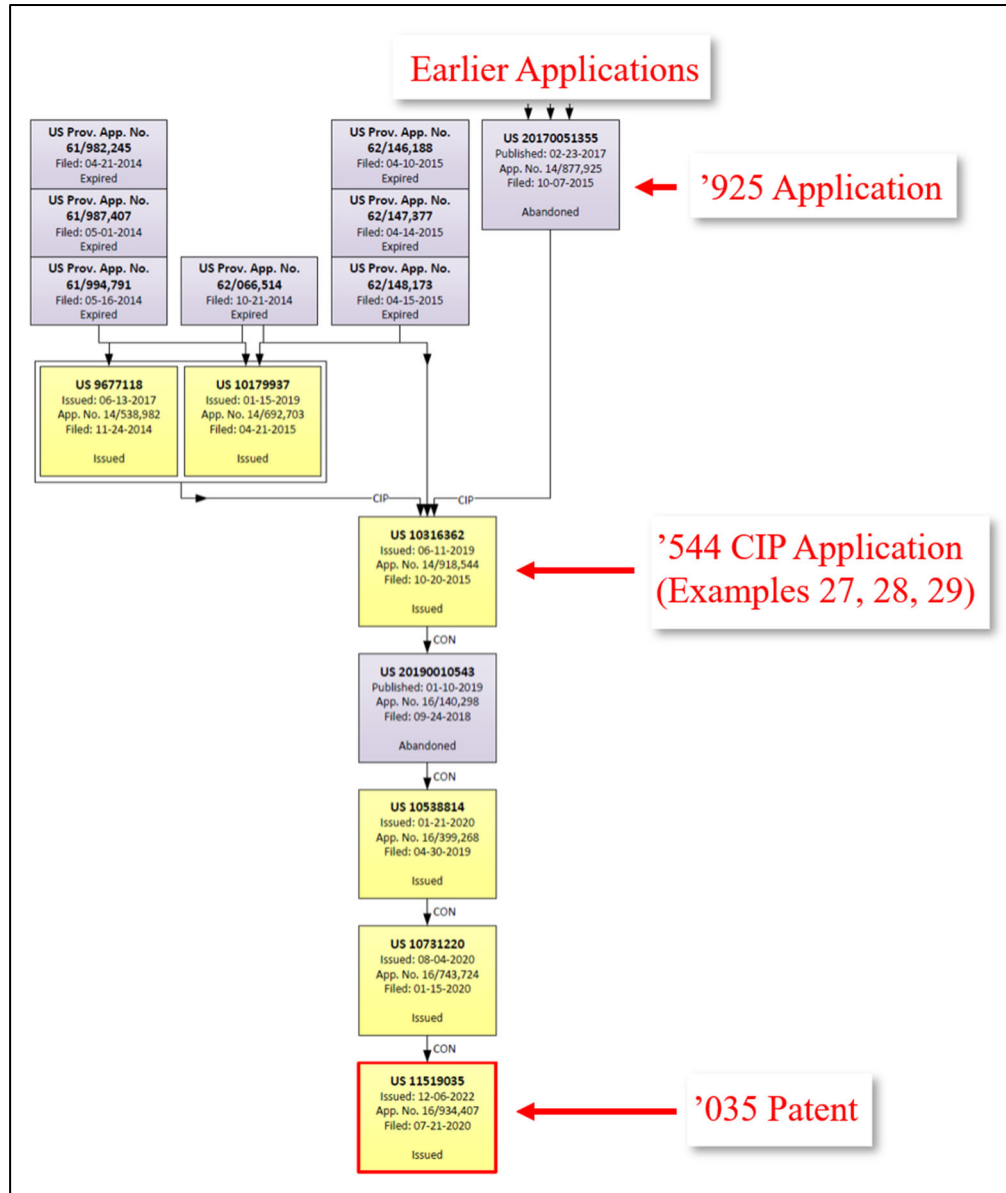
’925 Application (Claim 1)	’035 Patent Cancer Limitation
“measuring free-floating DNA in a plasma sample of the host that comprises both DNA from normal cells and DNA from cancer” and “by simultaneously amplifying the at least 1000 polymorphic loci to obtain amplicons and sequencing the amplicons”	“isolated cell free DNA...collected from a subject who is not a pregnant women [and]...targeted amplification of a plurality of single nucleotide polymorphism (SNP) loci...wherein the plurality SNP loci comprises 25-2,000 loci associated with cancer”

⁵ Versions of these examples also appear in other 2014 and 2015 patent filings to which the ’035 patent claims priority, such as U.S. Provisional Application Nos. 62/066,514 and 62/148,173 and U.S. Patent No. 10,179,937. (*E.g.*, Exs.1105-07.) The disclosures in these filings differ from the ’544 CIP’s. (Ex.1004 ¶¶123-126.)

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(Ex.1024, 10, 40; Ex.1001 (claim 1); Ex.1004, ¶¶127-133.)

In remarks accompanying that amendment, Patent Owner identified alleged support for the additions. It cited paragraphs from the '925 application's specification, including a paragraph identical to the '035 patent's statement that monitoring cell-free DNA unrelated to cancer would "equally well read on determining the ploidy state or genetic state of a cancer from the measurements on host blood." (Ex.1024, 48 (citing paragraph 569), 804-805 (paragraph 569); Ex.1001, 204:2-12.) But what Patent Owner did not—and could not—cite were Examples 27-29, which were later added in the '544 CIP. (*See* Ex.1021.)



(Ex.1002 (cropped and annotated).)

As a result, Patent Owner's attempt to identify support failed. The Examiner wrote, "[w]hile the specification supports free floating fetal DNA in blood or plasma the cited [*sic*] sections for fetal DNA and review of the specification did not reveal support for, 'measuring free-floating DNA in a plasma sample of the host that comprises both DNA from normal cells and DNA from cancer.'"

(Ex.1024, 10.) And indeed, the cited paragraphs did not provide any of the technical details that would show possession of the cancer limitation—they contained only a vague assertion of equivalence between non-cancer and cancer methods. (Ex.1004, ¶¶134-144.)

Rather than challenge the Examiner’s rejection, Patent Owner then *abandoned* the ’925 application. (Ex.1024, 2.) The Examiner’s rejection—and Patent Owner’s abandonment—confirms that, without the disclosures added to the specification in October 2015, the cancer limitation lacked written description support. That abandonment makes sense in view of Patent Owner’s later insistence that Chuu’s cell-free fetal DNA methods did not render methods directed to cell-free tumor DNA obvious (thus its effort to carve pregnant women out of the challenged claims). (Ex.1003, 629.) Moreover, having failed to disclose the claimed invention before October 2015, Patent Owner cannot fill that gap with the earlier knowledge and motivations of a POSA. *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) (“[a] description which renders obvious the invention for which an earlier filing date is sought is not sufficient”). The challenged claims are entitled to a priority date no earlier than October 20, 2015.

Because this priority date is after the 2013 pre-AIA cut-off date, the Board should cancel challenged claims 1-5 and 10-15 under the first inventor to file provisions of AIA, *i.e.*, AIA § 103. Cancellation is proper because each reference

qualifies as prior art against the '035 patent under AIA § 102(a)(1). Forshew, Pieprzyk, May, Porreca, Hoyal, and Wessler were published or issued on May 30, 2012, November 17, 2011, October 7, 2010, November 4, 2010, December 6, 2007, and July 16, 2002, respectively—all of which predate the '035 patent's 2015 priority date. (Exs.1005-1010.)

B. The References Are Prior Art Based On A Priority Date Of May 18, 2011 Or Even Earlier

If the Board disagrees and finds the '035 patent's priority date to be May 18, 2011, as Patent Owner asserts in the co-pending litigation, the Board should still cancel the challenged claims according to Grounds 2-4 of this Petition. Those grounds would then be based on pre-AIA § 103 and their references would qualify under pre-AIA § 102. Wessler, which issued July 16, 2002, and Hoyal, which published December 6, 2007, are both prior art under § 102(b). Porreca, Pieprzyk and May were PCT applications filed on April 30, 2010, May 16, 2011 and April 2, 2010, respectively, that designated the United States and were published in English. (Exs.1006-1008.) They qualify under at least § 102(e) based on their PCT filing dates. *See* M.P.E.P. 2136.03(II)(A).

Moreover, if Patent Owner asserts an even earlier priority date, such as the May 18, 2010 U.S. provisional date on the face of the '035 patent, Pieprzyk, May, Porreca, Hoyal, and Wessler of Grounds 2-4 are still prior art. Wessler and Hoyal still would qualify as prior art under at least pre-AIA § 102(b), and the other

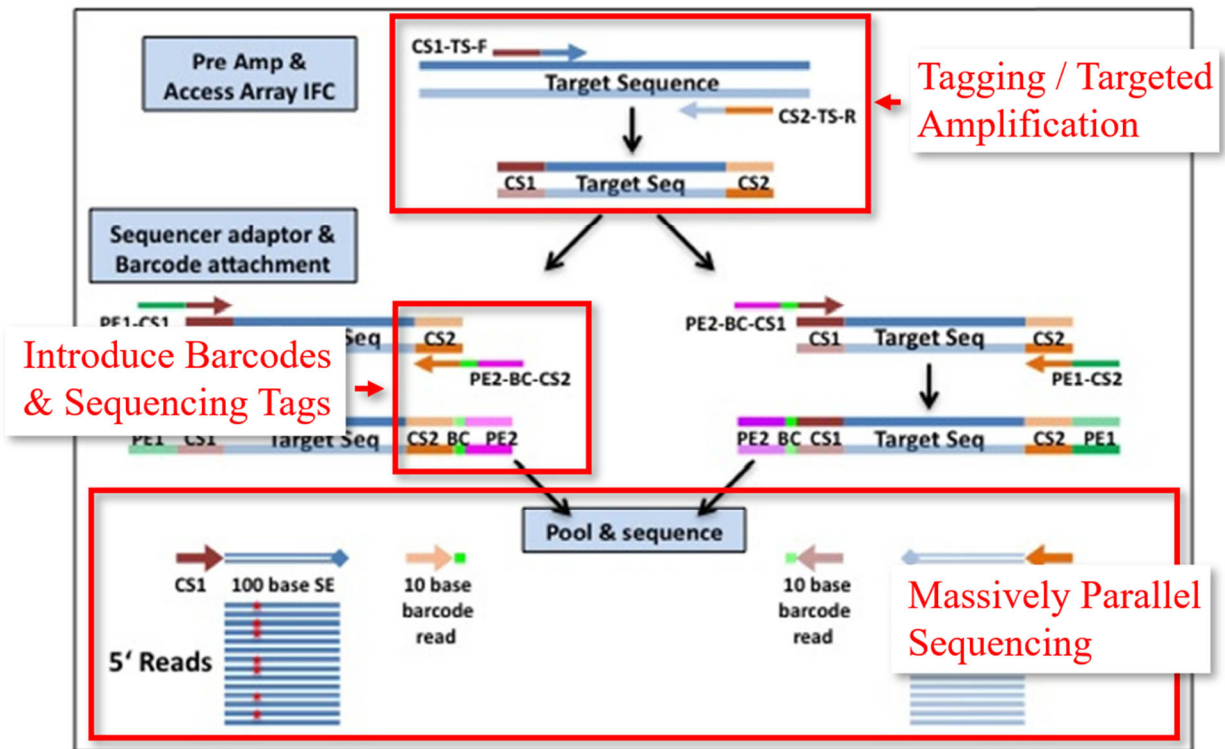
references also still would qualify as prior art under § 102(e) based on *their* U.S. provisional filing dates, as detailed below. (*Infra* §§ VI.E, VI.F, VII.E.)

V. GROUND 1: FORSHEW

A. Summary Of Forshew

Forshew is a 2012 scientific paper and accompanying supplementary materials.⁶ (Ex.1005, 1; Ex.1004, ¶¶162-164.) Forshew discloses a method called “TAm-Seq” for identifying point mutations in a tumor sample and then tracking them by monitoring cell-free tumor DNA. (Ex.1005, 2-10.) In Forshew’s method (as applied by Patent Owner in its infringement contentions), target-specific primers CS1-TS-F and CS2-TS-R amplify a plurality of target sequences in a pre-amplification step. (*Id.*, 3-4, 19.)

⁶ Forshew indicates it was “Downloaded from stm.sciencemag.org on June 6, 2012” and that “the online version of this article” included the supplementary material. (Ex.1005, 1.) Alternatively, the “Research Article” portion of Forshew incorporates the supplementary materials by reference by calling them “supplementary materials” and repeatedly citing them. (*Id.*, 1, 4, 6, 8, 11.)



(*Id.*, Fig.S1, 19.) Those target-specific primers include common adapter sequences (CS1 and CS2) at their ends. (*Id.*, 19.) Then, in later amplifications, Forsheh's method adds sequencing adapters and barcodes with barcoding primers PE1-CS1 and PE2-BC-CS1. (*Id.*) Finally, Forsheh's method sequences the resulting amplicons via massively parallel Illumina sequencing. (*Id.*, 4, 19)

B. Forsheh Anticipates Or Renders Obvious Claims 1, 12, 13

In district court, Patent Owner uses Forsheh to show how Petitioner's product allegedly practices claims 1, 12, and 13.⁷ But because the '035 patent's

⁷ Patent Owner's infringement contentions cite pages from a highlighted copy of Forsheh produced in the co-pending litigation. (Ex.1038; Ex.1118; Ex.1005.)

priority date is 2015, Forshew is prior art and Patent Owner's infringement contentions instead show unpatentability. The following analysis assumes, without conceding, that Patent Owner's infringement theory is correct.

1. Claim 1

a. Preamble

A method for amplifying and sequencing DNA, comprising:

Forshew discloses a "TAm-Seq" method of amplifying and sequencing DNA. (*Supra* § V.A.; Ex.1004, ¶166.)

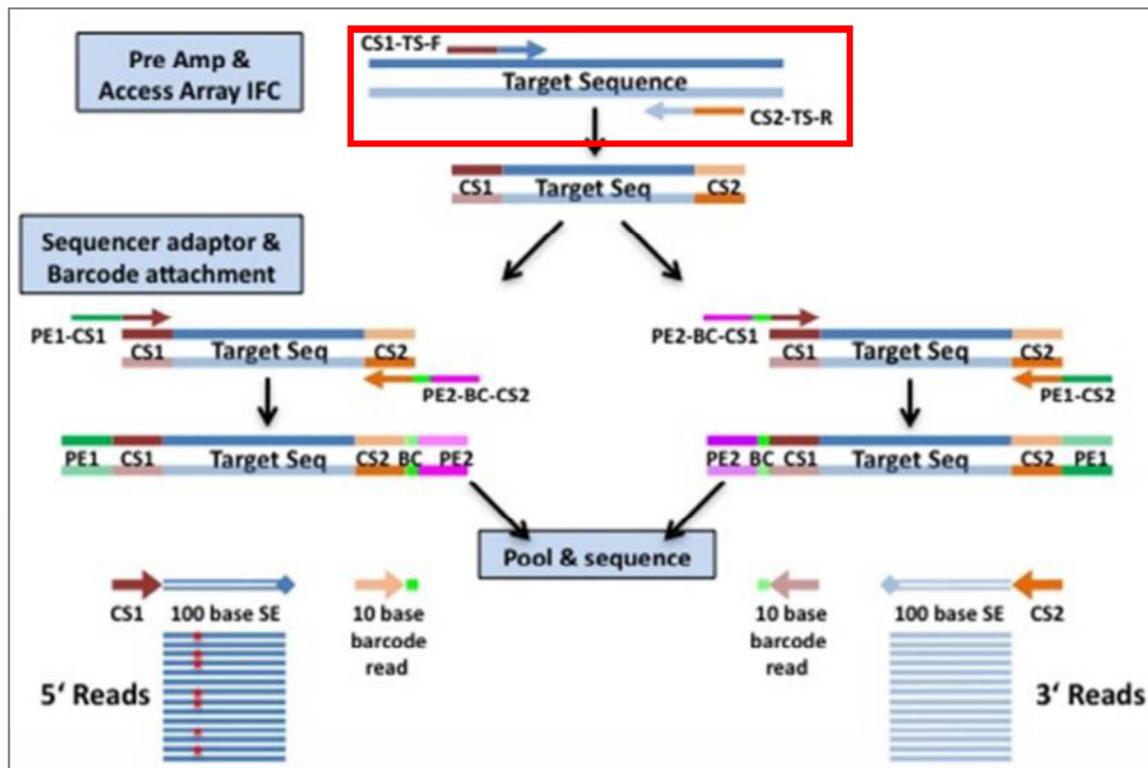
b. Limitation 1[A]

tagging isolated cell free DNA with one or more universal tail adaptors to generate tagged products,

Forshew discloses applying TAm-Seq to isolated cell-free tumor DNA. (*E.g.*, Ex.1005, 5 ("[w]e applied TAm-Seq to directly identify mutations in plasma of cancer patients"), 11 ("[c]irculating DNA was extracted from between 0.85 and 2.2 ml of plasma"); *see also id.*, 2, 10; Ex.1004, ¶167.) According to Patent Owner, Forshew also discloses the other elements of this limitation:

Forshew discloses that common tail sequences (i.e., CS1 and CS2) are added to each end of a target sequence in a pre-amplification step via PCR to generate a tagged product, as reproduced in the figure below. One of ordinary skill in the art would have understood that an adaptor with a common tail sequence is a universal tail adaptor.

(Ex.1038, 8.) The foregoing excerpt refers to Forshew's Figure S1 below, as annotated by Patent Owner:



(Ex.1038, 9 (reproducing Ex.1005, Fig.S1).)

c. Limitation 1[B]

wherein the isolated cell-free DNA is isolated from a blood sample collected from a subject who is not a pregnant women;

Under Patent Owner's infringement theory, Forshew teaches applying TAM-Seq to cell-free DNA isolated from cancer patients' blood. (Ex.1005, 2-3, 5, 10-11.) It also discloses collecting samples from subjects in their late 60's and 70's with ovarian cancer, *i.e.*, non-pregnant women, and then applying TAM-Seq to those samples. (*Id.*, 2-3, 5, Table S6; Ex.1004, ¶168.) *Almiral, LLC v. Amneal*

Pharms. LLC, 28 F.4th 265, 273 (Fed. Cir. 2022) (“a reference need not state a feature’s absence in order to disclose a negative limitation”) (cleaned up).

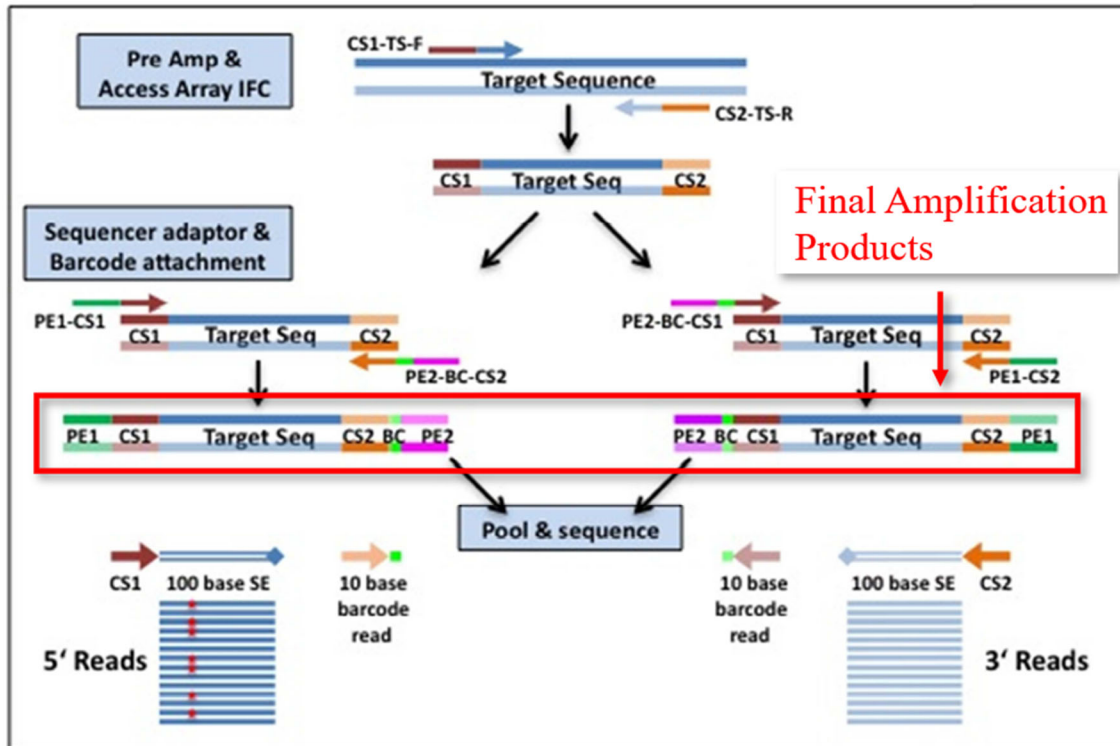
Alternatively, it would have been obvious to use TAm-Seq on subjects who are not pregnant women. A POSA would have been motivated to apply Forshew’s methods to humans who are not pregnant women because many humans with cancer are not pregnant. (Ex.1004, ¶169.) And they would have reasonably expected success in doing so: after all, Forshew discloses that its method is suitable for monitoring for breast and ovarian cancers, and many non-pregnant people have breasts and ovaries. (Ex.1005, 5-11; Ex.1004, ¶169.)

d. Limitation 1[C]

amplifying the tagged products one or more times to generate final amplification products,

Under Patent Owner’s infringement theory, TAm-Seq’s preamplification step amplifies tagged products because “[a]t the end of each of the remaining amplification cycles in the PCR process, one of ordinary skill would have understood that the output (amplified tagged products) is used as the input for the following amplification cycle, thus thereby performing targeted amplification of already tagged products.” (Ex.1038, 21; Ex.1004, ¶¶170-171.) In other words, Patent Owner asserts that claim 1’s separate tagging and amplifying steps can be different cycles in one PCR reaction. (Ex.1035, 5; Ex.1038, 22.)

Patent Owner also contends that Forshew teaches “an additional round of PCR,” *i.e.*, a second amplification, to generate “final amplification products.” (*Id.* at 23.) Those alleged final amplification products are shown below:



(Ex.1005, Fig.S1 (annotated).)

e. Limitation 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,

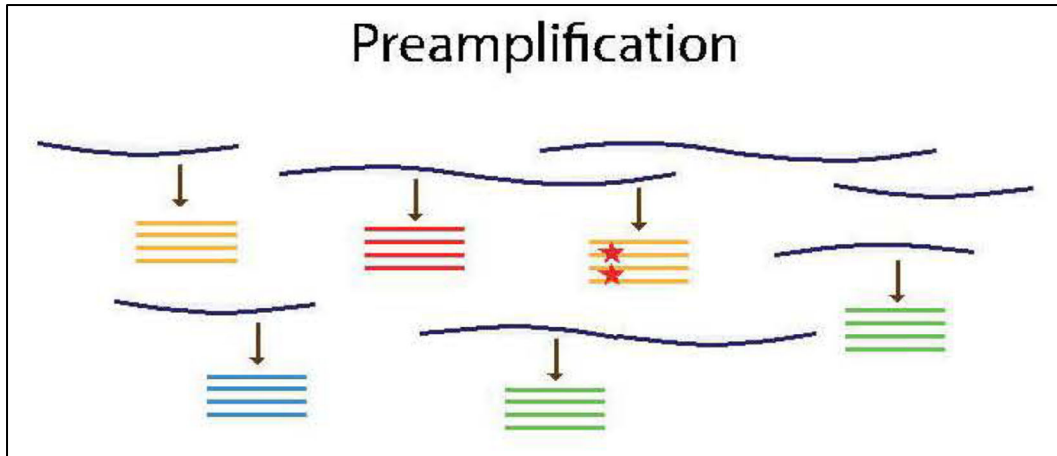
According to Patent Owner, Forshew’s preamplification is a “targeted amplification of already tagged products.” (Ex.1038, 21; *see* Ex.1004, ¶172.)

Patent Owner explains that, in Forshew’s “preamplification...involve[ing] ...targeted multiplex amplification,” the products of the first amplification cycle

are “the input for the subsequent PCR cycle wherein the tagged products are amplified.” (*Id.*; *see also* Ex.1005, 4, Figs.1A-B, S1.)

Those tagged products include a plurality of SNP loci. TAm-Seq’s preamplification uses “48 primer pairs to amplify 5995 bases of genomic sequence covering coding regions...of *TP53* and *PTEN*, and selected regions in *EGFR*, *BRAF*, *KRAS*, and *PIK3CA*...by overlapping short amplicons.” (Ex.1005, 4-5.) Those regions were known to contain locations of common point mutations associated with cancer, which Patent Owner contends are SNP loci.⁸ (*Id.*, 4 (target regions “cover mutations that account for 38% of all point mutations in the COSMIC database”); Ex.1004, ¶173.) Forshew depicts preamplifying one such point mutation (starred red) in its Figure 1:

⁸ As noted above, Patent Owner interprets “SNP[] loci” as any single-point mutation, somatic or germ-line. (Ex.1035, 7-11.) Although Petitioner does not agree with this reading of claim 1, the challenged claims are unpatentable under it and Petitioner applies it herein. *Gen. Elec.*, No. IPR2018-00928, Paper 9, 14.



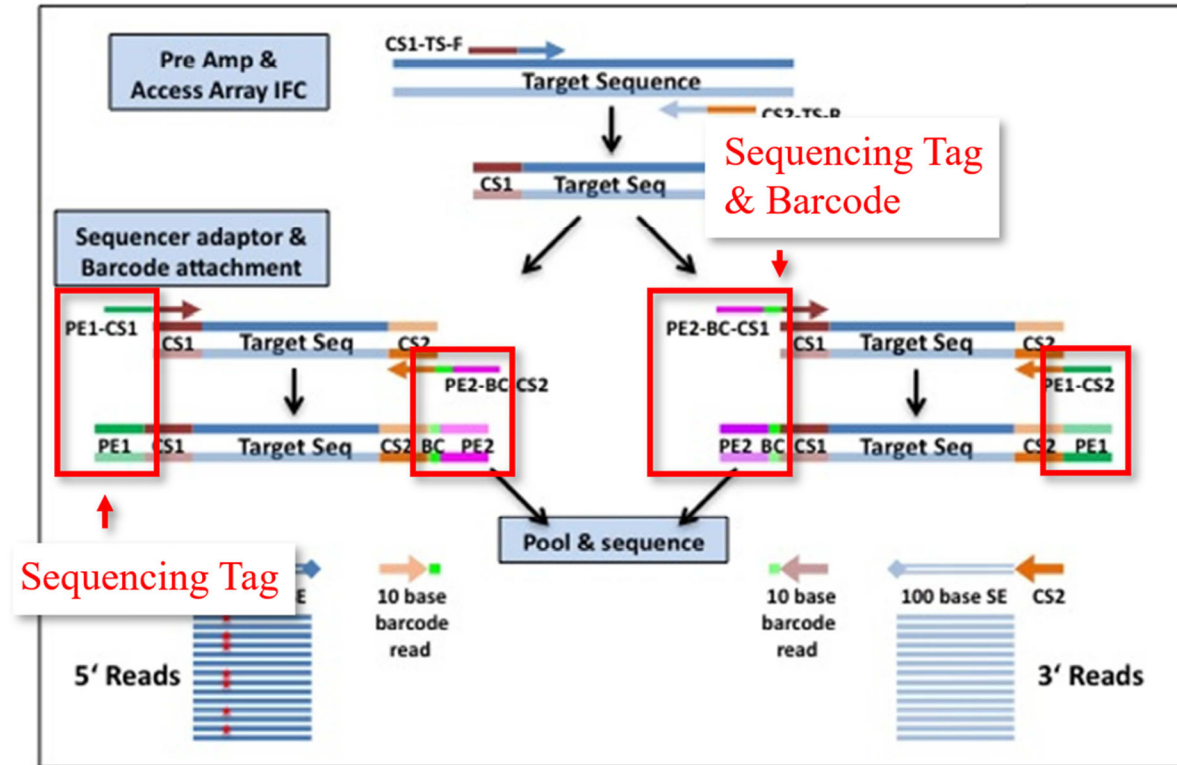
(Ex.1005, Fig.1 (cropped).)

TAm-Seq’s preamplification occurs in a single reaction volume: “a limited-cycle preamplification step *where all primer sets were used together.*” (*Id.*, 4, 16, Figs.1A-B, S1; Ex.1004, ¶174.)

f. Limitation 1[E]

wherein one of the amplifying steps introduces a barcode and one or more sequencing tags; and

According to Patent Owner, “Forsheew discloses[,] in an additional round of PCR[,] introducing a barcode and one or more sequencing tags.” (Ex.1038, 21-22 (quoting Ex.1005, 19 (“Sequencing platform specific adaptors and unique sample barcodes were attached during an additional round of PCR.”))); *see also* Ex.1005, 4 (“barcode sequencing primer”); Fig.S1 (“sequencing adaptor and barcode attachment”) (cleaned up); Ex.1004, ¶175.) Patent Owner identifies Illumina sequencing adapters (PE1 and PE2) and a 10-base barcode as the claimed barcode and sequencing tags. (Ex.1038, 10, 21.)

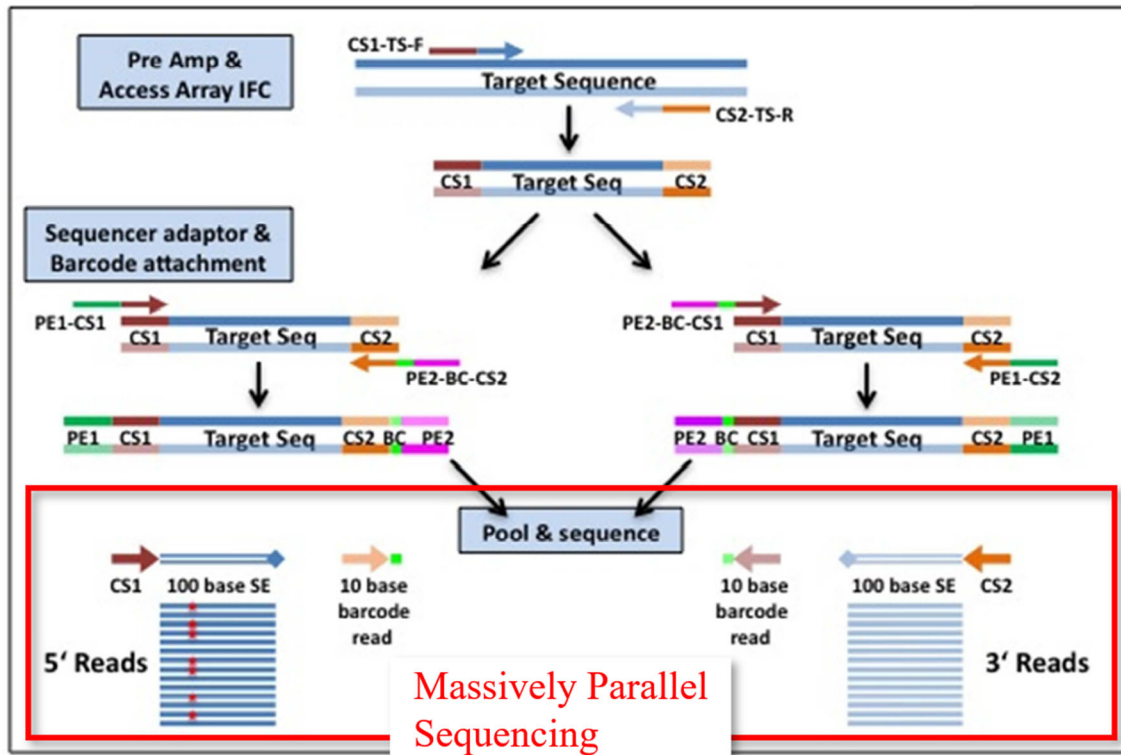


(Ex.1005, Fig.S1 (annotated).)

g. Limitation 1[F]

sequencing the plurality of SNP loci on the cell free DNA by conducting massively parallel sequencing on the final amplification products,

Under Patent Owner's theory, Forsheo depicts sequencing its final amplification products in its Figure S1's "Pool & sequence step":



(Ex.1005, Fig.S1 (annotated); *see also id.*, 3, 19, Fig.1; Ex.1004, ¶176) Forshew discloses TAM-Seq performs massively parallel sequencing of those products.

(*Id.*, 4 (“100-base single-end sequencing (GAIIx sequencer, Illumina)...generating ~30 million reads per lane”); *see also id.*, 5 (“the mutation was also identified by TAM-Seq”); Ex.1004, ¶176.)

h. Limitation 1[G]

wherein the plurality of SNP loci comprises 25-2,000 loci associated with cancer.

As explained above, TAM-Seq uses 48 primer pairs to amplify and then sequence 48 genomic regions containing point mutations associated with cancer, which Patent Owner contends are SNP loci. (*Supra* § V.B.1.e.; Ex.1005, 4.)

Forsheew thus discloses 48 SNP loci associated with cancer under Patent Owner's construction. (Ex.1038, 24 (asserting "primer panel of up to 48 primer pairs capturing at least one somatic variant" practices the limitation); Ex.1004, ¶177.)

2. Claim 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.

According to Patent Owner, Forsheew's "common tail sequences (i.e., CS1 and CS2)" are "universal tail adaptors." (Ex.1038, 8.) Under that view, Forsheew's CS1 is a "first" universal tail adapter and "CS2" is a second universal tail adapter. (Ex.1004, ¶178.)

3. Claim 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.

Forsheew's CS1 and CS2 sequences are part of its "[t]arget-specific primers." (Ex.1005, 19.) According to Patent Owner, Forsheew teaches tagging target cell-free DNA via amplification with those primers. (Ex.1038, 8; *see also* Ex.1005, 3-5, 11, Fig.S1; Ex.1004, ¶179.)

VI. GROUND 2: PIEPRZYK & MAY

Like Forsheew, Pieprzyk and May disclose aspects of commercially available technology. But unlike Forsheew, both references predate the alleged 2011 priority

date. Thus, even if the Board concludes Forshew is not prior art, it still should cancel claims 1 and 10-15 according to this combination.

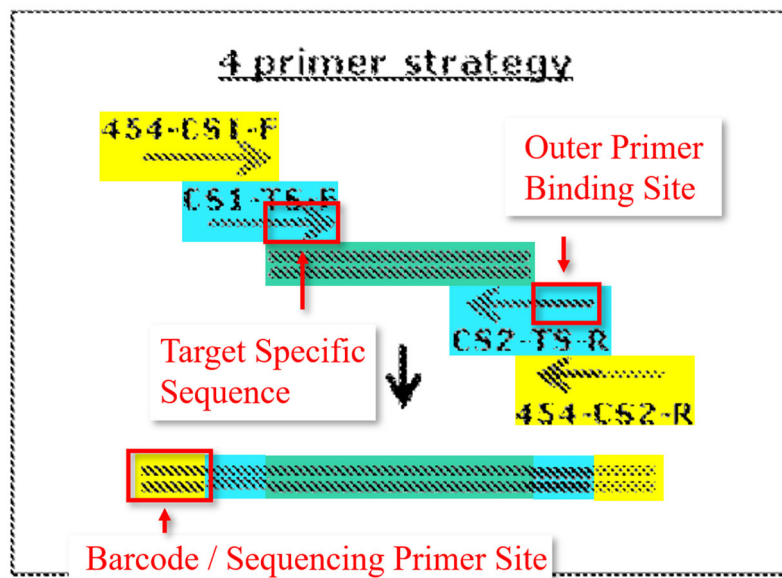
A. Summary Of Pieprzyk

Pieprzyk is a PCT application originally assigned to Fluidigm Corporation. (Ex.1006; Ex.1004, ¶¶181-182.) Pieprzyk teaches methods for analyzing “cell-free DNA in the bodily fluid (*e.g.*, plasma) of subjects with cancer.” (Ex.1006, ¶111; *see also id.*, ¶¶3, 116, 138.) Its methods can be applied to 50 to 1,000 “or more amplification reactions...carried out in each individual reaction chamber.” (*Id.*, ¶218.) They can “identify[] the presence of particular polymorphisms (such as SNPs).” (*Id.*, ¶221.) And they can “facilitate the detection and or quantification of target sequences in...tumor DNA in plasma from cancer patients.” (*Id.*, ¶116.)

In one of Pieprzyk’s methods, cell-free DNA is tagged and amplified in a four-primer PCR reaction. (*Id.*, ¶10.) Two of the four primers are “inner forward” and “inner reverse” primers, which include “target specific portion[s]” and universal “nucleotide tags.” (*Id.*; *see also id.*, ¶¶57, 113-14.) The other two primers, “outer forward” and “outer reverse” primers, anneal to the first two primers’ nucleotide tags and can “include one or more additional nucleotide sequences to be added to the target nucleic acid.” (*Id.*, ¶10.) Pieprzyk teaches sequencing the amplified DNA via “high throughput sequencing.” (*Id.*, ¶187.)

B. Summary Of May

May also is a Fluidigm Corporation PCT application. (Ex.1007; Ex.1004, ¶¶183-184.) May teaches the same four-primer strategy as Pieprzyk. Like Pieprzyk, it teaches inner primers with universal “nucleotide tag[s]” and outer primers including additional sequences. (Ex.1007, ¶11.) What May adds is that the outer “barcode” primers can contain both a “barcode nucleotide sequence” and “additional primer binding sites...capable of being bound by DNA sequencing primers.” (*Id.*, ¶115.) May illustrates its approach by depicting outer primers (yellow), inner target-specific primers (blue), a target sequence (green), and an amplification product (multicolor) in its Figure 18:



(*Id.*, Fig.18 (cropped and annotated).)

May discloses using its four-primer strategy for similar applications as Pieprzyk. May teaches using its method for “identifying the presence of particular

polymorphisms (such as SNPs).” (*Id.*, ¶235.) And it teaches analyzing “[n]ucleic acids [] extracted or amplified from...blood [or] a blood fraction,” including via “multiplex detection...[in an] individual amplification mixture.” (*Id.*, ¶¶132, 210.) Like Pieprzyk, May also teaches sequencing the amplified DNA via massively parallel sequencing. (*E.g., id.*, ¶121.)

C. Combination Of Pieprzyk And May

A POSA would have found it obvious to use May’s four primers, with their barcodes and sequencing tags in the outer primers, in place of Pieprzyk’s four primers. (Ex.1004, ¶185.) Both Pieprzyk and May are analogous art because they are in the same field as the ’035 patent or, at the very least, are reasonably pertinent to the problem the ’035 patent sought to solve. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1238-39 (Fed. Cir. 2010). (*See also* Ex.1004, ¶185.) Like the ’035 patent, Pieprzyk is directed to “the area of detecting genotype and/or aneuploidy.” (Ex.1006, ¶2.) Similarly, May is directed to the “detection and/ or sequencing of particular target nucleic acids” and its “methods can be performed in determining genotypes.” (Ex.1007, ¶¶2, 28.)

A POSA would have been motivated to make this combination. Doing so would have been a simple substitution of one known element (May’s primers) for another (Pieprzyk’s primers) between two references describing the same, underlying Fluidigm technology. (Ex.1004, ¶186.) Indeed, a POSA would have

viewed May as disclosing just one more way to configure Pieprzyk's outer primers. (*Id.*) Moreover, May's configuration had benefits. Placing barcodes and sequencing tags on outer primers rather than on inner primers would shorten and thereby simplify the design of the inner, target-specific primers. (*Id.*, ¶187.) Short primers also are less prone to dimerization than long ones. (*Id.*) Moreover, May's configuration is economical: separating barcodes from targeting primers reduces the number of unique primers needed by orders of magnitude. (*Id.*, ¶¶188-190; Ex.1049, ¶96 (explaining 200-plex reaction targeting 30 amplicons would require 6030 primers if one barcode were included in each target-specific primer pair).)

A POSA would have reasonably expected the combination to succeed. Both references relate to the same Fluidigm technology. Both already teach using four primers to tag and amplify DNA. (*Supra* §§ VI.D.1.b., VI.D.1.d.) And May even discloses that its 4-primers works for multiplex reactions like those in Pieprzyk. (Ex.1007, ¶¶210, 276, Fig.18; Ex.1006, ¶¶201, 218.) This combination would have been trivial. (Ex.1004, ¶191.)

D. Claims 1, 10-15 Are Obvious Over Pieprzyk And May

1. Claim 1

a. Preamble

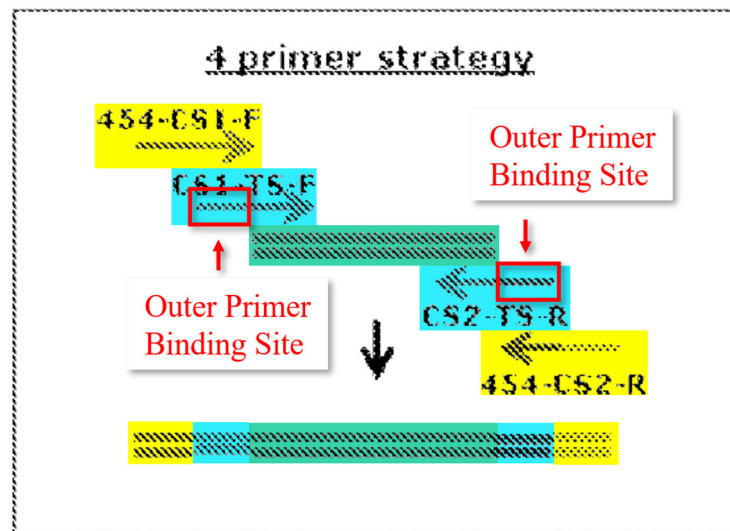
A method for amplifying and sequencing DNA, comprising:

Pieprzyk and May disclose methods for amplifying and/or sequencing DNA. (*Supra* §§ VI.A, VI.B; Ex.1004, ¶192.)

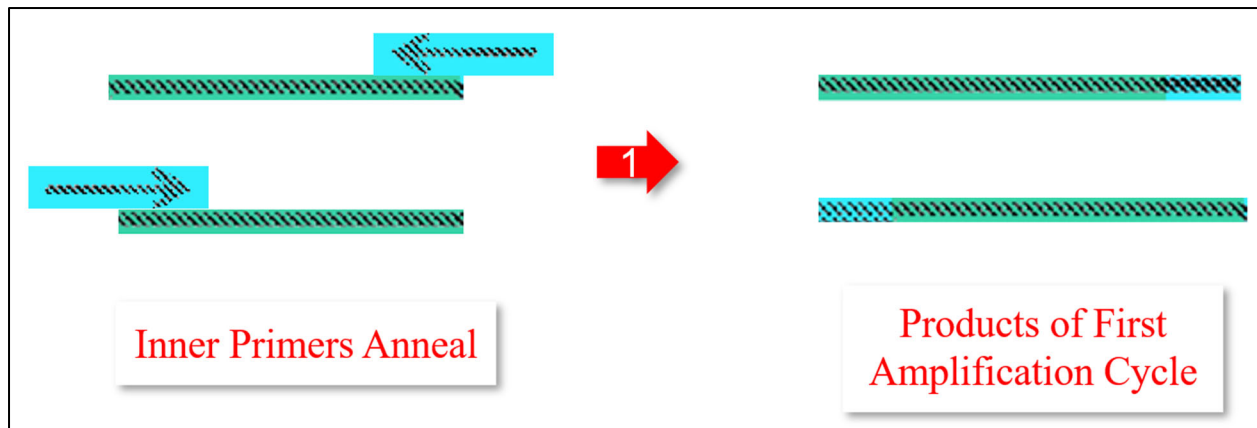
b. Limitation 1[A]

tagging isolated cell free DNA with one or more universal tail adaptors to generate tagged products,

In the combined method, the inner primers (blue) comprise universal tail adapters because they contain nucleotide tags, which are not target specific and to which the outer primers anneal. (Ex.1007, ¶¶11, 115; Ex.1004, ¶193.)



(Ex.1007, Fig.18 (cropped and annotated).) Under Patent Owner's view of the claims, the inner primers would tag target DNA in the first amplification cycle of a PCR reaction and thereby yield tagged products:



(Ex.1004, ¶194; Ex.1038, 7.)

In the combined method, the inner primers would tag isolated, cell-free DNA. (Ex.1004, ¶195.) Pieprzyk discloses performing “the amplification steps” on “[n]ucleic acids of interest...isolated using methods well known in the art.” (Ex.1006, ¶149.) And it further discloses applying its methods to “cell-free DNA in the bodily fluid (e.g., plasma) of subjects with cancer.” (*Id.*, ¶111; *see also id.*, ¶¶3, 116, 138, 147, 149.)

c. Limitation 1[B]

wherein the isolated cell-free DNA is isolated from a blood sample collected from a subject who is not a pregnant women;

Pieprzyk discloses tagging cell-free DNA isolated from plasma, which is part of blood. (*Supra* § VI.D.1.b; Ex.1006, ¶¶3, 111, 116, 138, 147, 149.) It also discloses collecting those samples from a subject who is not a pregnant woman. When referring to pregnant women, it uses the adjective “maternal.” (*E.g.*, Ex.1006, ¶138 (“[i]n various embodiments the nucleic acid [sic] are derived from a

maternal biological sample (e.g. . . . from a pregnant mammal (e.g., human))”).) But when discussing monitoring cancer, it does not. (*Id.* (“derived from *a biological sample* . . . having, suspected of having, or at risk for a cancer”); *see also, e.g., id.*, ¶¶111, 116.) Pieprzyk’s omission of the limiting adjective “maternal” in that second phrase teaches that its method extends to non-pregnant women. (Ex.1004, ¶196.) *Almiral*, 28 F.4th at 273 (“a reference need not state a feature’s absence in order to disclose a negative limitation”) (cleaned up).

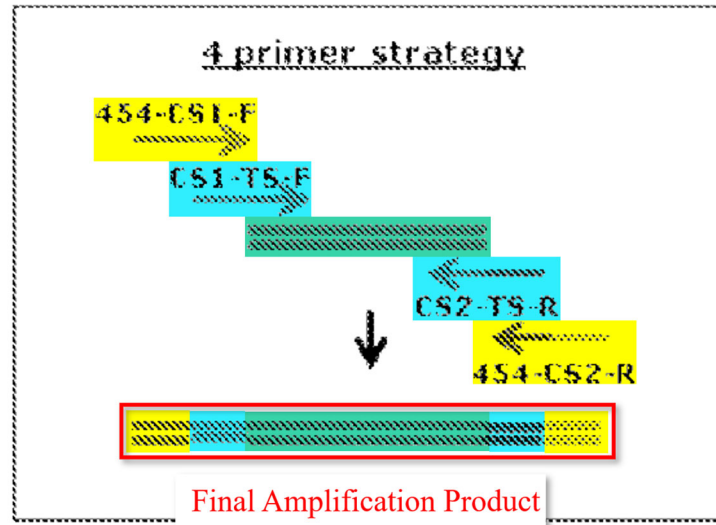
Alternatively, it would have been obvious to isolate the cell-free DNA from non-pregnant women. A POSA would have been motivated to apply the combined method to non-pregnant females because many humans with cancer are not pregnant. (Ex.1004, ¶197.) A POSA would have reasonably expected success in doing so because Pieprzyk’s method, which is nearly identical to the combined method, would work equally on blood samples from pregnant women and non-pregnant persons alike. (Ex.1006, ¶138; *see also id.*, ¶221; Ex.1004, ¶197.)

d. Limitation 1[C]

amplifying the tagged products one or more times to generate final amplification products,

As discussed above, the combined method tags cell-free DNA via amplification. (*Supra* § VI.D.1.b; Ex.1007, ¶¶11, 115.) In a single PCR reaction, the inner primers generate tagged products by amplifying DNA and the outer primers then amplify those tagged products. (Ex.1007, ¶¶11, 115; Ex.1004, ¶198.)

The products of those later amplification cycles are the final amplification products. (Ex.1004, ¶198; *see also* Ex.1006, ¶¶187, 210; Ex.1007, ¶¶121, 164.)

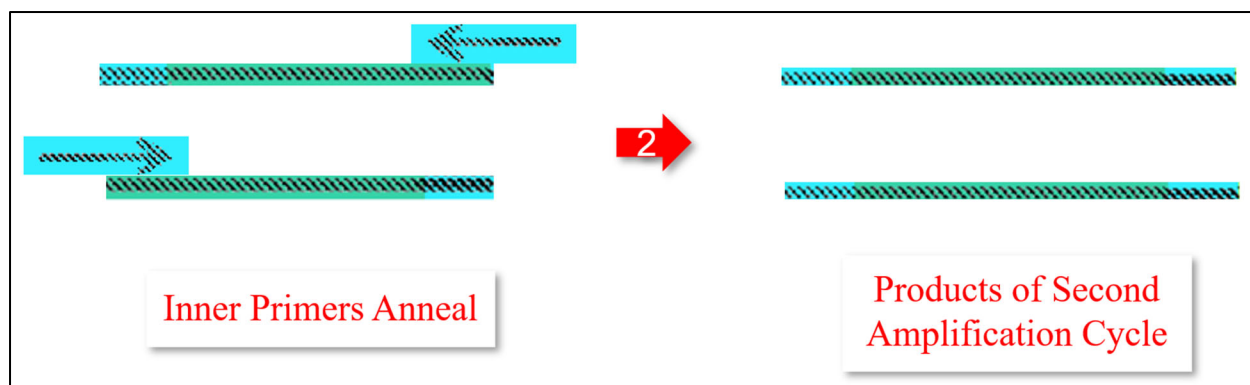


(Ex.1007, Fig.18 (cropped and annotated).)

e. Limitation 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,

In the combined method, the inner primers perform target-specific amplification in the second amplification cycle of the PCR reaction with the inner target-specific primers. (Ex.1007, ¶11.) That second cycle is illustrated below:



(Ex.1004, ¶199.)

In the combined method, the inner primers amplify the plurality of SNP loci disclosed in Pieprzyk in a single reaction chamber. (Ex.1004, ¶200.) Pieprzyk discloses targeting “genomic DNA, which can be analyzed for specific polymorphisms (such as SNPs).” (Ex.1006, ¶151; *see also id.*, ¶221 (similar).) It further discloses targeting “genomic DNAs that are altered (e.g., amplified, deleted, and/or mutated) in genetic diseases or other pathologies.” (*Id.*) And it 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. (*Id.*, ¶218.) May also contains similar disclosure, confirming that its primers also are suitable for multiplexing. (Ex.1007, ¶210.)

If Pieprzyk had not disclosed targeted amplification of a plurality of SNP loci in a single reaction volume, that step would have been obvious. (Ex.1004, ¶201.) Disclosures in Pieprzyk would have motivated a POSA to conduct multiplex amplification in a single reaction volume on cell-free tumor DNA. In

the context of detecting fetal cell-free DNA, Pieprzyk teaches that “[p]lasma contains a limited concentration of target nucleic acids (...SNPS...etc.).” (Ex.1006, ¶379.) There, “[m]ultiplexing will be necessary” because the alternative, “[d]ividing the sample[,] will reduce the number of target[s] per assay and increase sampling error.” (*Id.*) Pieprzyk also teaches that “[s]imilar challenges exist for mutation detection by mutation dosage in...cancer, and therefore this approach can be used in these contexts.” (*Id.*, ¶387; *see also* Ex.1025, 5.) Finally, Pieprzyk proposes analyzing between “30” and “1000 or more target and/or internal control sequences,” which falls within the claimed bounds of 25-2,000 SNP loci under Patent Owner’s construction. (Ex.1006, ¶110.)

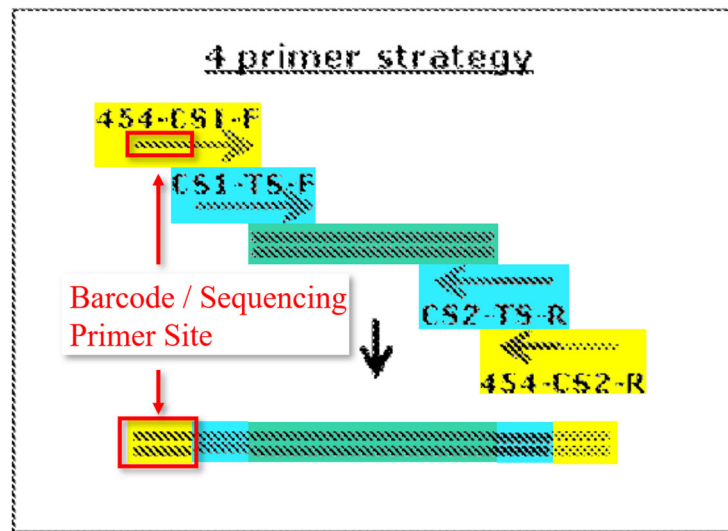
A POSA also would have reasonably expected success in performing multiplex amplification. (Ex.1004, ¶202-203.) By the early 2000s, multiplex amplification was routine. (*Id.*) In 1995, Shuber *et al.* disclosed a 15-plex reaction with primers having universal tail adapters. (Ex.1026, 1, 3.) In 2004, Inagaki *et al.* disclosed a 39-plex reaction. (Ex.1027, 2-3.) Also by 2004, software called “AutoDimer” could screen sets of up to 1,000 primers for simultaneous use in multiplex reactions. (Ex.1028, 1; *see also* Ex.1006, ¶¶484-86.) And, as Patent Owner’s own expert once admitted, even 9,216-plex amplifications were known by 2010. (*See* Ex.1040, ¶¶91, 98.) Finally, the ’035 patent itself confirms that “multiplexing PCR for sequencing” of up to “100 assays in the same well” was

known, showing a POSA would have had no difficulty multiplexing at least that many sequences. (Ex.1001, 48:25-27; 85:14-20, 87:32-33; *see also supra* § II.A.)

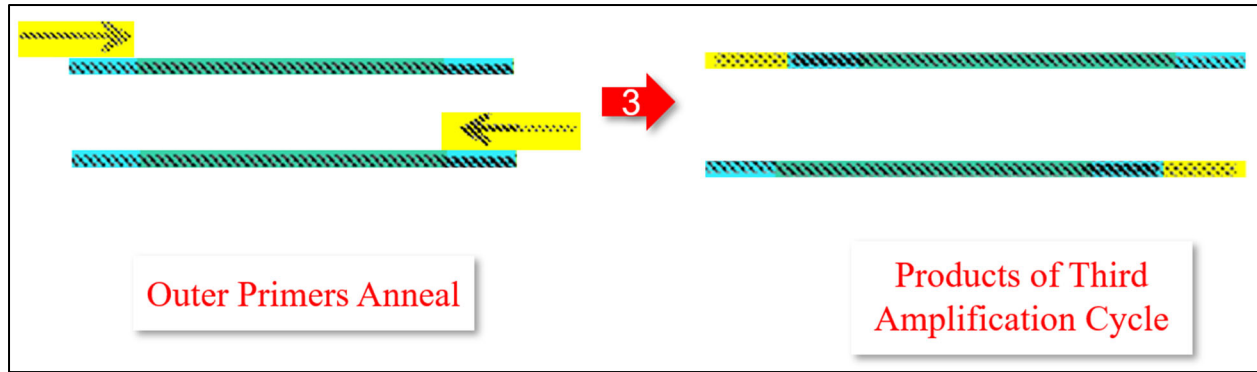
f. Limitation 1[E]

wherein one of the amplifying steps introduces a barcode and one or more sequencing tags; and

In the combined method, the outer primers introduce barcodes and sequencing tags beginning in the third amplification cycle of the PCR reaction because they include barcode sequences and sequencing tags and, thus, so do their amplification products. (Ex.1007, ¶¶11, 115; Ex.1004, ¶204.)



(Ex.1007, Fig.18 (cropped and annotated).) The below graphic illustrates some of the amplifications that occur in the third amplification cycle:



(Ex.1004, ¶204.)

g. Limitation 1[F]

sequencing the plurality of SNP loci on the cell free DNA by conducting massively parallel sequencing on the final amplification products,

Pieprzyk’s methods “can include subjecting at least one target amplicon to DNA sequencing using any available DNA sequencing,” including “high throughput sequencing.” (Ex.1006, ¶187; *see also id.*, ¶207; Ex.1004, ¶205 (high throughput sequencing is massively parallel sequencing).) Pieprzyk also discloses or renders obvious that the target amplicons (*i.e.*, the final amplification products) can include a plurality of SNP loci on cell-free DNA. (*Supra* § VI.D.1.e.)

h. Limitation 1[G]

wherein the plurality of SNP loci comprises 25-2,000 loci associated with cancer.

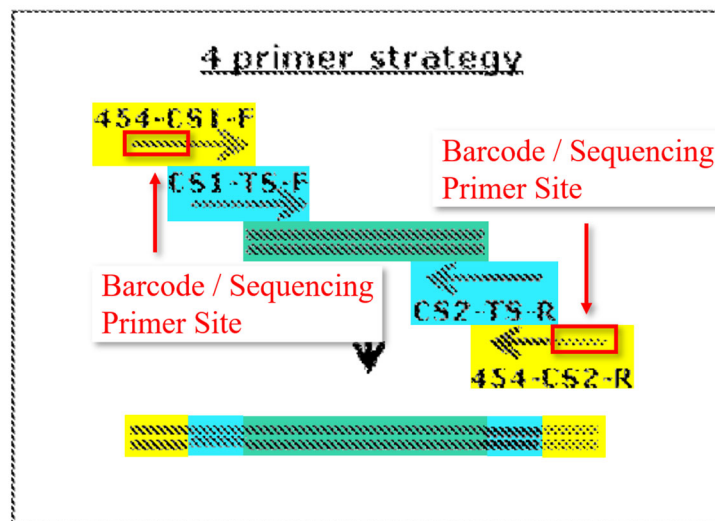
As explained above, Pieprzyk discloses or renders obvious applying the combined method in multiplex to between 30 and 1000 or more cell-free tumor DNA sequences. (*Supra* § VI.D.1.e.) Those sequences would contain SNP loci associated with cancer under Patent Owner’s construction. (Ex.1004, ¶206.)

2. Claims 10 & 11

Claim 10: The method of claim 1, wherein the one or more universal tail adaptors comprise a second barcode.

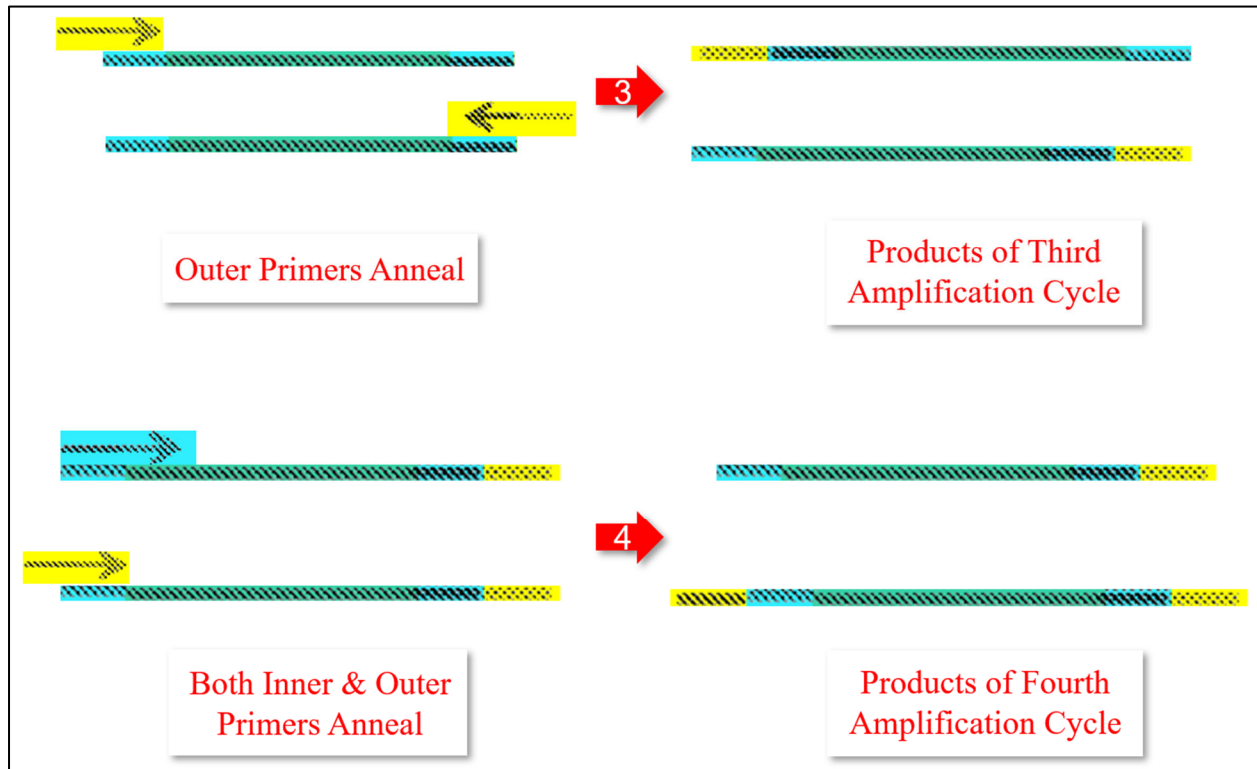
Claim 11: The method of claim 1, wherein the one or more universal tail adaptors comprise a second sequencing tag.

These claims are obvious over Pieprzyk and May. May's 4-primer strategy uses two outer primers that include barcodes and sequencing tags. (Ex.1007, ¶¶118 (“each of the outer primers contains a unique barcode”), 115 (“first additional primer binding site” and “second additional primer binding site”).) The outer primers comprise universal tail adapters because their “additional primer binding sites” for “DNA sequencing primers” allow for universal amplification with sequencing primers. (Ex.1007, ¶¶115, 129; Ex.1004, ¶¶207-208.)



(Ex.1007, Fig.18 (cropped and annotated).)

Moreover, under Patent Owner's view of the claims, the outer primers generate tagged products beginning in the third amplification cycle of a PCR reaction, which then would be amplified in a targeted amplification with inner primers in a fourth amplification cycle:

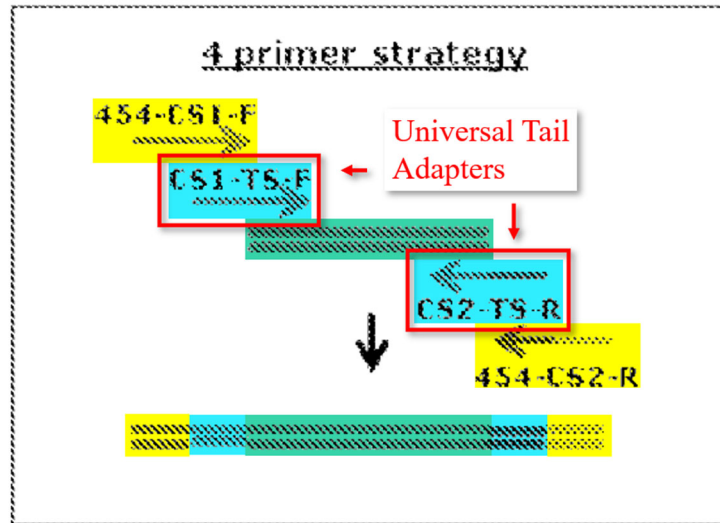


(Ex.1004, ¶¶209-210.)

3. Claim 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.

Claim 12 is obvious over Pieprzyk and May. May discloses using two inner primers, which comprise universal tail adapters. (*Supra* § VI.D.1.b.)

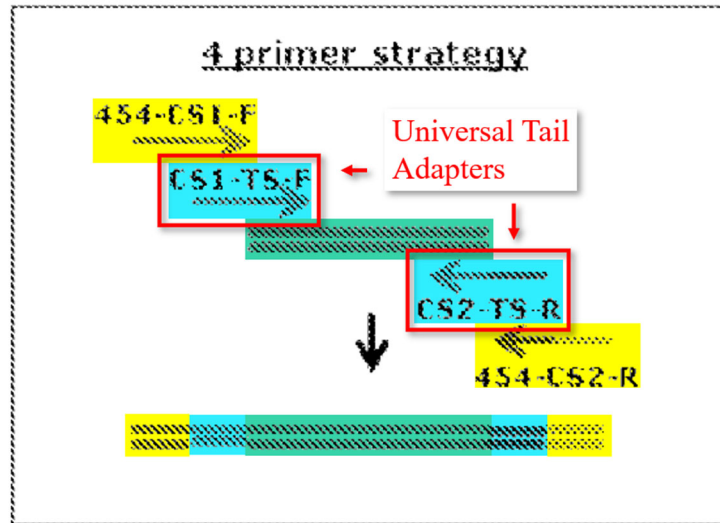


(Ex.1007, Fig.18 (cropped and annotated).)

4. Claim 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.

Claim 13 is obvious over Pieprzyk and May. In the combined method, cell-free DNA is tagged by amplifying it with the inner primers, which comprise universal tail adapters. (*Supra* §§ VI.D.1.b, VI.D.1.d; Ex.1004, ¶212.)



(Ex.1007, Fig.18 (cropped and annotated).)

5. Claim 14

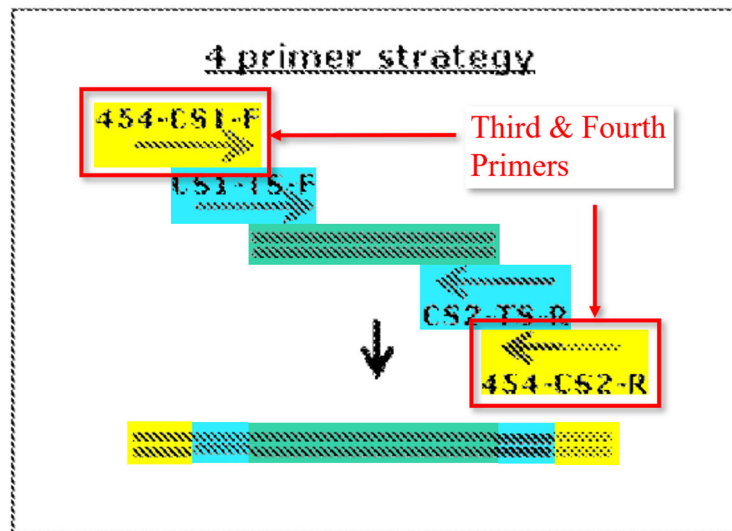
The method of claim 12, wherein amplifying the tagged products comprises a single amplifying step.

Claim 14 also is obvious over Pieprzyk and May. (Ex.1004, ¶213.) Both references teach using four primers in one PCR reaction. (Ex.1007, ¶11 (“an amplification mixture”); Ex.1006, ¶10 (same).) Alternatively, if “a single amplifying step” is a single PCR cycle, both references teach amplifying the tagged products in one or more PCR cycles, which is all this comprising claim requires. (*Supra* § VI.D.1.d.)

6. Claim 15

The method of claim 14, wherein amplifying the tagged products comprises using a third primer and a fourth primer, wherein the third primer comprises a first sequencing tag and wherein the fourth primer comprises a second sequencing tag.

Claim 15 is obvious over Pieprzyk and May. May's 4-primer strategy amplifies the tagged products with all four primers. (Ex.1007, ¶¶11, 115; Ex.1004, ¶214.) And, again, the outer primers can include "additional primer binding sites [that] are capable of being bound by DNA sequencing primers," *i.e.*, sequencing tags. (Ex.1007, ¶115.) Those outer primers, which are May's third and fourth primers, therefore comprise first and second sequencing tags.



(Ex.1007, Fig.18 (cropped and annotated).)

E. Pieprzyk's Provisional Application

If Patent Owner asserts that the claims challenged in Ground 2 are entitled to an earlier priority date than 2011, such as the '035 patent's May 18, 2010 provisional date, Pieprzyk still is prior art under at least pre-AIA § 102(e) by May 14, 2010, the filing date of *Pieprzyk's* provisional Application No. 61/395,551 ("551 application"). (Ex.1017.) See *Dynamic Drinkware, LLC v. Nat'l Graphics*,

Inc., 800 F.3d 1375, 1381-82 (Fed. Cir. 2015); M.P.E.P. 2136.03(II)(A). First, the '551 application discloses, essentially verbatim, at least Pieprzyk's claim 1.

(*Compare* Ex.1006 (claim 1) *with* Ex.1017, ¶49.) Second, it also includes substantively the same disclosure from Pieprzyk cited in Ground 2. (*Compare* Ex.1006, ¶¶2-3, 10, 57, 110-11, 113-14, 116, 138, 147, 149, 151, 187, 201, 207, 218, 221, 379, 387 *with* Ex.1017, ¶¶1-2, 25, 55, 78-79, 81-82, 84, 106, 115, 117, 119, 155, 169, 190, 240, 246, Example 6; Ex.1004, ¶215.)

F. May's Provisional Applications

If Patent Owner asserts an earlier priority date to May's April 2, 2010 PCT filing date for the claims challenged under Ground 2, May still is prior art under pre-AIA § 102(e) based on, at the latest, the February 18, 2010 filing date of *May's* provisional Application No. 61/305,907 ("907 Application"). (Ex.1016.) *See Dynamic Drinkware*, 800 F.3d at 1382-83; M.P.E.P. 2136.03(II)(A). First, the '907 Application discloses essentially verbatim, at least May's claim 1. (*Compare* Ex.1007 (claim 1) *with* Ex.1016 (claims 1, 2).) Second, May's provisional applications also include substantively the same disclosures from May cited in Ground 2. (*Compare* Ex.1007, ¶¶2, 11, 28, 115, 118, 121, 129, 132, 164, 210, 235, 276, and Fig.18 *with* Ex.1016, ¶¶2, 71-73, 83, 86, 89, 97, 100, 132, 178, 203, 245, Fig.18, and claim 39; Ex.1004, ¶216.)

VII. GROUND 3: PORRECA & HOYAL

Like Pieprzyk and May, Porreca and Hoyal render obvious all of claims 1 and 10-15. But because the Porreca and Hoyal combined method also includes a ligation step, it also renders claims 2-3 unpatentable. Summaries of these references, the combination, and the unpatentability ground are set forth below.

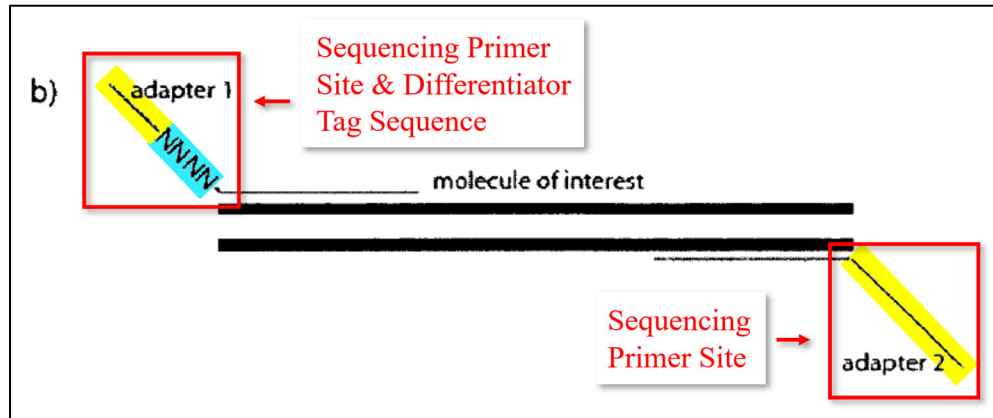
A. Summary Of Porreca

Porreca is a PCT application that discloses a method of analyzing “multiple genetic loci...from a patient sample, such as...blood.” (Ex.1008, 4:3-5; Ex.1001, 1-2.) According to Porreca, “10-25, 25-50, 50-75, 75-100 or more loci may be evaluated for each subject.” (Ex.1008, 29:15-16.) “The genetic loci may be analyzed by sequencing to obtain a genotype at one or more polymorphisms (e.g., SNPs)[,]” including “any locus associated with a disease or condition of interest.” (*Id.*, 4:21-22, 45:11-12; *see also id.*, 10:22-23.) Porreca also describes “monitoring tumor progression/regression,” and detecting “mutations” in some cell-free DNA. (*Id.*, 4:23-33, 7:5-10, 29:5.)

Porreca’s method includes two steps. (*See also* Ex.1004, ¶¶219-220.) First, “a polymerase chain reaction...selectively amplifies each locus using one or more oligonucleotide primers.” (*Id.*, 8:5-8.) An early step in that amplification, annealing target-specific primers having sequencing primer sites (yellow) and

differentiator tag sequences (blue) to a target sequence, is shown below in

Porreca's Figure 4b:



(*Id.*, Fig.4b (annotated), 8:13-15, 8:28-31, 43:29-33.) Porreca's amplification can be a "multiplex amplification (amplification of multiple target nucleic acids in parallel)." (*Id.*, 8:15-17, 22:11-13.)

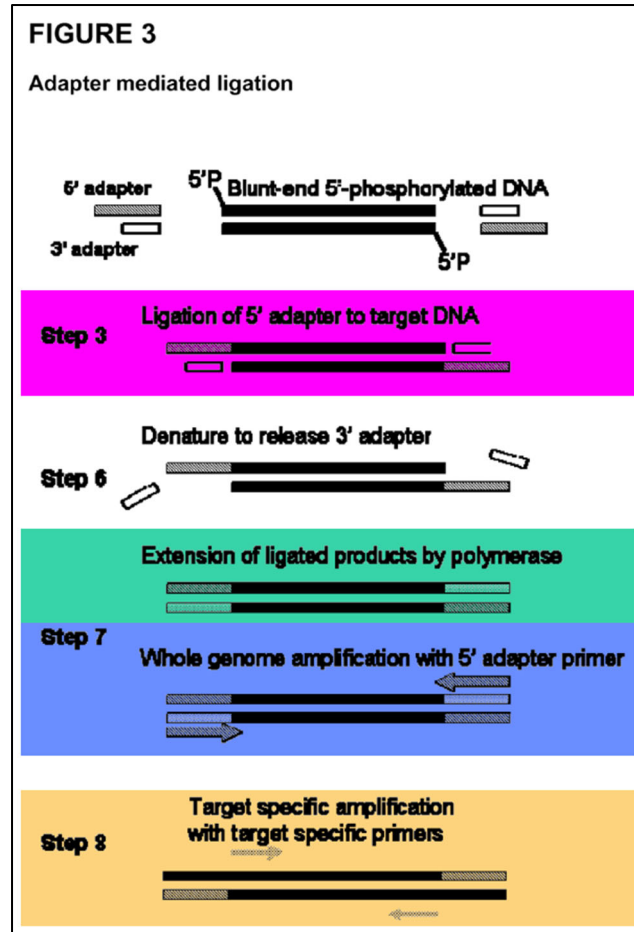
Second, Porreca's method sequences the amplified products. (Ex.1004, ¶221.) Porreca teaches "[n]ext-generation sequencing may be used to quantitatively measure the abundance of each isolated target nucleic acid obtained from a certain preparative method[,]" including from its "amplification technique." (*Id.*, 23:4-13, 34:10-13.) Up to "100 or more loci may be evaluated for each subject out of any number of subject samples that may be processed in parallel." (*Id.*, 29:15-18.)

B. Summary Of Hoyal

Like Porreca, Hoyal discloses methods for isolating and amplifying DNA from human blood and plasma. (Ex.1009, 1 (Title), 4; Ex.1004, ¶222.)

Specifically, it teaches “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,” *i.e.*, detecting cell-free tumor DNA. (*Id.*, 20.)

What Hoyal adds is a preamplification step involving “[a]dapter-mediated ligation.” (*Id.*, 27; Ex.1004, ¶223.) Adapter-mediated ligation ligates “a non-genome specific adapter to the blunt ends” of DNA in a sample, extends the ligated adapter, performs “whole genome amplification” with primers specific to the ligated adapter, and performs “specific amplification of a nucleic acid region of interest for further analysis.” (*Id.*, 27-28.) Hoyal depicts ligation (lavender), primer extension (green), universal whole-genome amplification (navy), and target-specific amplification (gold) in Figure 3:



(*Id.*, Fig.3 (annotated).)

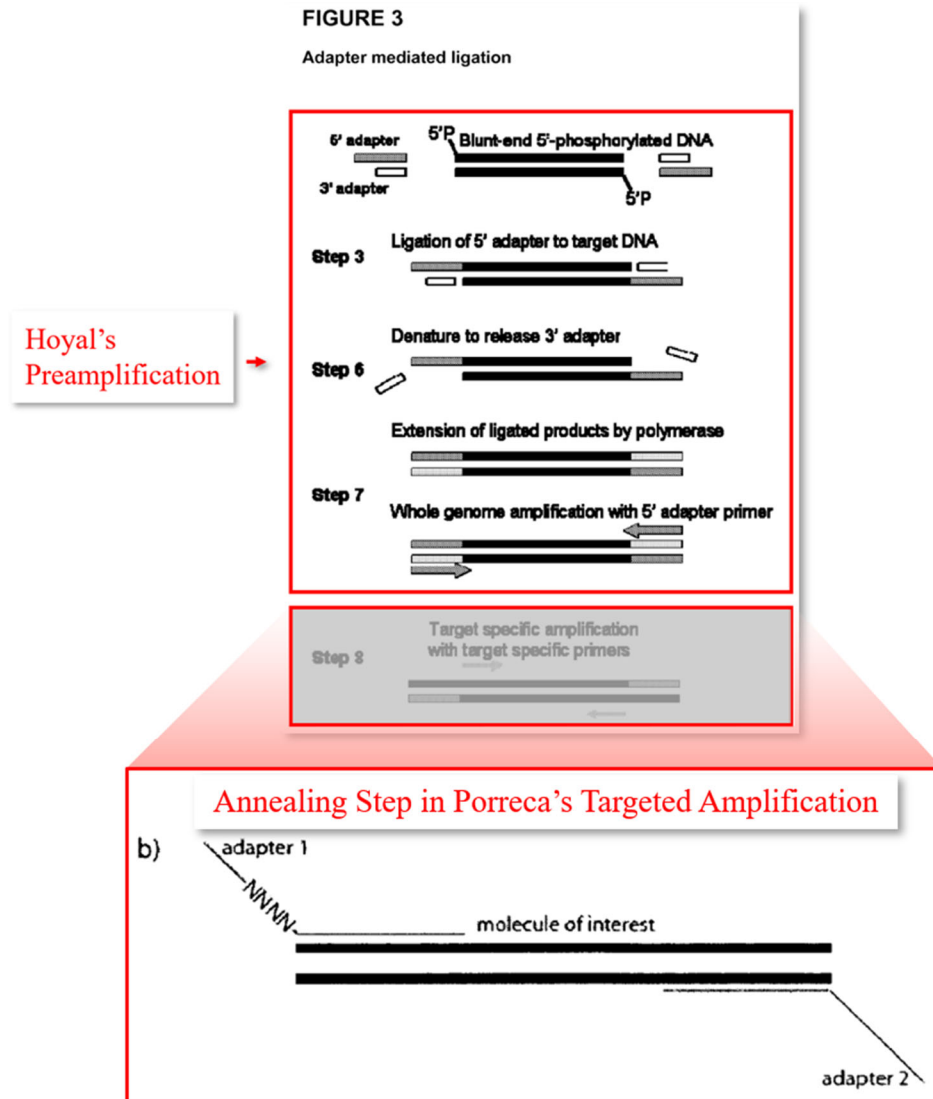
C. Combination Of Porreca And Hoyal

Porreca and Hoyal are analogous art because both are in the same field as the '035 patent or, at the very least, are reasonably pertinent to the problem the '035 patent sought to solve. *Wyers*, 616 F.3d at 1238-39. (Ex.1004, ¶224.) Like the '035 patent, both references teach analyzing cell-free DNA derived from blood. (*E.g.*, Ex.1008, 4:3-5 (“methods for analyzing multiple genetic loci...from a patient sample, such as a blood”); Ex.1009, 10, 20 (“monitoring...tumor-associated DNA found in the plasma or serum fraction of blood by using DNA extraction

with enrichment for mutant DNA,”); Ex.1001 (Example 27).) As set forth below, it would have been obvious to combine two aspects of Hoyal with Porreca.

1. Modification 1: Universal Preamplification

A POSA would have found it obvious to modify Porreca’s method by adding Hoyal’s isolation and adapter-mediated ligation preamplification steps to Porreca’s method before Porreca’s targeted amplification step. (Ex.1004, ¶225.) The following graphic showing Hoyal’s Figure 3 (top) and Porreca’s Figure 4b (bottom) illustrates how the combined method’s amplifications would flow together by depicting Hoyal’s steps 3, 6 and 7 before Porreca’s targeted amplification step:



(Ex.1008, Fig.4b; Ex.1009, Fig.3 (combined & annotated).)

Teachings from both Porreca and Hoyal would have motivated a POSA to combine these methods. (Ex.1004, ¶226.) Porreca states that some methods, like its targeted amplification, can produce a skewed pool of amplicons that “does not adequately represent the input abundance distribution.” (Ex.1008, 67:27-28.) This flaw “reduce[s] the sensitivity of the sequencing method” by increasing the risk

that “potentially the ‘mutant’ allele was not the one observed.” (*Id.*, 67:33-68:2.)

Porreca calls this flaw “acute” in the context of monitoring cancer. (*Id.*, 68:2-7.)

Hoyal’s teachings provided a solution. (Ex.1004, ¶227.) Like Porreca, Hoyal acknowledges that there was “a need for improved extraction methods capable of capturing small nucleic acid molecules”—cell-free DNA—because “the ability to successfully analyze short, fragmented DNA in the presence of more abundant, longer DNA ha[d] remained elusive.” (Ex.1009, 1-2, 20.) Hoyal solved that problem with isolation followed by universal preamplification. By isolating and then pre-amplifying the cell-free tumor DNA, Hoyal’s method increased the initial number of copies of all target sequences and thereby improved the odds that a later, targeted amplification and sequencing could detect sequences with low prevalence. (*Id.*, 7; Ex.1004, ¶227.) A POSA thus would have been motivated to add a pre-amplification step to Porreca’s method to achieve that benefit.

A POSA would have had a reasonable expectation of success in adding Hoyal’s preamplification steps to Porreca’s method. Porreca already discloses applying its method to nucleic acids from blood. (Ex.1008, 8:5-8, 18:31-32, 19:3-4, 22:1-4, 67:20-21.) It already discloses ligating adapters to cell-free DNA to provide primer sites for non-targeted amplification. (*Id.*, 8:5-17, 43:17, 43:23-29; *see also id.*, 8:28-31.) And it already discloses using primers for targeted amplification. (*Id.*, 8:5-7, 43:29-33, Fig.4b; *see also id.*, 8:28-31.) A POSA would

reasonably have expected success in sequentially performing these routine steps, as in the combined method. (Ex.1004, ¶228.)

2. Modification 2: SNP Loci Associated With Cancer In Isolated Cell-Free DNA

A POSA would have been motivated to apply the combined method to SNP loci associated with cancer in cell-free DNA (according to Patent Owner's construction) in view of disclosures from Porreca and Hoyal. As Patent Owner admits, techniques for studying "tumor [cell-free] DNA in a cancer patient's blood" were "routinely used before November 2009." (Ex.1039, 9.) Porreca discloses one such technique for studying cell-free DNA. It teaches that its method is suitable for the "detection of mutations in maternally-circulating fetal DNA," meaning cell-free fetal DNA. (Ex.1008, 7:5-8.) It teaches its method is useful for detecting cancer. (*See, e.g.*, Ex.1008, 18:32-33 ("[i]n some embodiments, the biological sample is a...tumor sample, circulating tumor cells"), 29:5-6 ("monitoring tumor progression/regression [or] analyzing circulating tumor cells"), 25:3-7 ("detection of cancer mutations"), 4:23-33, 7:5-10.) And it teaches that its method is "useful for any application where sensitivity is important." (*Id.*, 25:3-7; *see also id.*, 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.) These disclosures would have motivated a POSA to apply the combined method to SNP loci associated with cancer in cell-free DNA. (Ex.1004, ¶229.)

To the extent Patent Owner argues that Porreca does not suggest applying its method to cell-free *tumor* DNA, Hoyal does so. Hoyal states its method is 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.” (Ex.1009, 20.) A POSA thus would have been motivated to extend the combination to detecting mutations in cell-free tumor DNA isolated from blood. (Ex.1004, ¶230.)

A POSA would have had a reasonable expectation of success in applying the combined method to cell-free DNA containing SNP loci associated with cancer, including cell-free tumor DNA. For one thing, Hoyal already teaches that its preamplification steps, plus a targeted amplification step, can enrich cell-free tumor DNA. (Ex.1009, 20.) For another, as Patent Owner told the USPTO when seeking other claims, the “same lab techniques including extraction of cell-free DNA, amplification of targeted loci, and sequencing of the amplicons can be used in both [the] fetal DNA context and [the] cancer DNA context.” (Ex.1025, 5). As explained above, designing primers suitable for multiplex PCR was well within a POSA’s skill. (*Supra* § II.A.) And as for sequencing, cell-free tumor DNA, or other cell-free DNA containing SNP loci associated with cancer, is no more difficult to sequence than cell-free fetal DNA. (Ex.1004, ¶231.)

D. Claims 1-3, 10-15 Are Obvious Over Porreca And Hoyal

1. Claim 1⁹

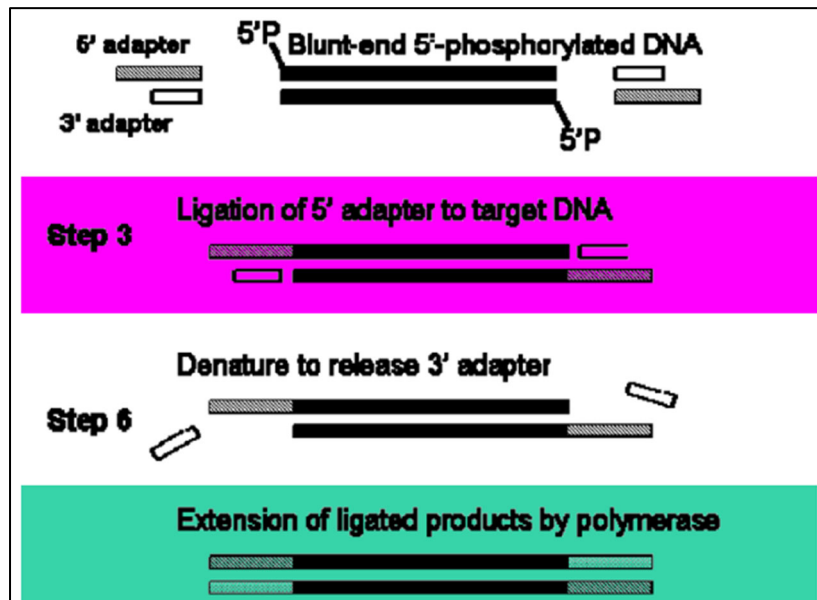
a. Preamble

Porreca and Hoyal teach methods of amplifying and/or sequencing DNA.

(*Supra* §§ VII.A-VII.B; Ex.1004, ¶232.)

b. Limitation 1[A]

The combined method satisfies Limitation 1[A] in Hoyal's preamplification step. In that step, DNA is tagged by ligating adapter complexes made up of a 5' adapter and a 3' adapter (lavender) and then extending the ligated products (green):



(Ex.1009, Fig.3 (cropped and annotated), 16, 27-28; Ex.1004, ¶233.)

⁹ Element labels for Claim 1 in Grounds 3 and 4 correspond to those used above.

The adapter complexes comprise universal tail adapters because their constituent adapters contain sequences used for non-targeted “whole genome amplification.” (*Id.*, 16, 27-28.) As Dr. Lennon explains, “whole genome amplification” refers to a universal, non-specific amplification of all DNA in solution. (Ex.1004, ¶234.) Alternatively, the 5’ adapters themselves comprise universal tail adapters. In either scenario, the green highlighted DNA is a tagged product. Finally, as discussed above, a POSA would have found it obvious to apply the combined method to isolated cell-free DNA. (*Supra* § VII.C.)

c. Limitation 1[B]

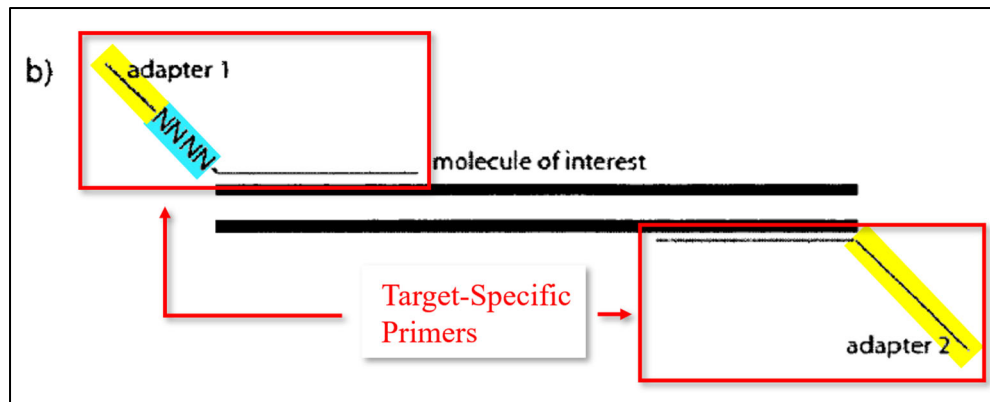
The combined method satisfies this limitation. (Ex.1004, ¶236.) Porreca teaches collecting target “nucleic acid from a biological sample obtained from a subject,” such “blood.” (Ex.1008, 18:30-32.) And it further teaches that the “subject or patient may be male,” *i.e.*, not a pregnant woman. (*Id.*, 31:29-30.)

d. Limitation 1[C]

The combined method has two amplification steps. First, the tagged products from Hoyal’s ligation steps undergo “[w]hole genome amplification”:



(Ex.1009, Fig.3 (cropped and annotated), 27-28.) Second, the products of that first amplification undergo targeted amplification with Porreca’s primers:



(Ex.1008, Fig.4b (annotated), 8:5-8, 8:15-17, 8:28-31, 43:29-33.) The products of both amplification steps—target sequences tagged with Porreca’s target-specific primers—are final amplification products. (Ex.1004, ¶236.)

e. Limitation 1[D]

The combined method discloses or renders obvious every element of Limitation 1[D]. First, the combined method’s second amplification step is a “targeted amplification” because it selectively amplifies the cell-free DNA with target-specific primers. (Ex.1008, 8:5-8, 43:29-33, Fig.4b; Ex.1004, ¶237.)

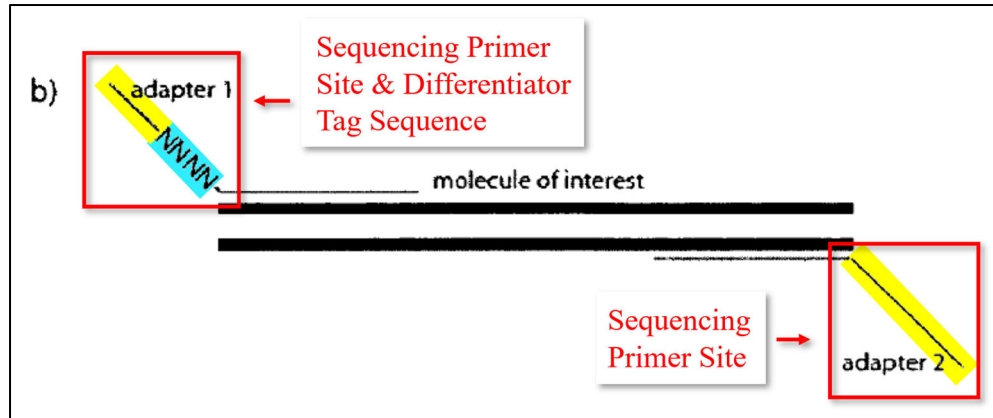
Second, that targeted amplification amplifies a plurality of SNP loci in a single reaction volume. Porreca discloses that its “PCR based methods may include...multiplex amplification (amplification of multiple target nucleic acids in parallel).” (Ex.1008, 22:11-13.) It discloses its invention is “particularly useful for analyzing multiple loci in a multiplex assay” and for the “detection of cancer mutations,” which Patent Owner contends are SNPs. (*Id.*, 10:22-23; 25:3-7.) And it discloses that its “[m]ultiplex amplification strategies disclosed herein may be

used analytically, as in detection of SNPs.” (*Id.*, 37:24-26; *see also id.*, 13:9-10, 28:7-10, 29:15-18, 45:11-12.) A POSA would have known that “multiplex amplification” meant amplifying multiple sequences in a single reaction volume. (Ex.1004, ¶238; *see also, e.g.*, Ex.1008, 8:15-17; 29:23-25.)

Alternatively, if Porreca had not disclosed this limitation, Porreca renders it obvious. A POSA would have been motivated by the foregoing disclosures to selectively amplify sequences containing SNP loci associated with cancer in a single reaction volume because doing so is more efficient than amplifying them separately. (Ex.1004, ¶239; Ex.1008, 29:15-18.) A POSA would have reasonably expected the combined amplification to succeed because, as the ’035 patent confirms, multiplexing up to “100 assays in the same well” was known. (Ex.1001, 48:25-27; 85:14-20, 87:32-33; Ex.1040, ¶98; Ex.1041, ¶202; Ex.1004, ¶239.)

f. Limitation 1[E]

The combined method’s targeted amplification step introduces a sequencing adapter and differentiator tag, which correspond to the claimed sequencing tag and barcode, respectively. (Ex.1008, 8:5-8, 43:29-33; Ex.1004, ¶240.) Porreca’s Figure 4b, below, depicts its target-specific primers having two sequencing primer sites (yellow) and one differentiator tag (blue):



(Ex.1008, Fig.4b (annotated).) Through amplification, the barcode and sequencing tags are incorporated into final amplification products. (Ex.1004, ¶240.)

g. Limitation 1[F]

Porreca teaches “sequencing to obtain a genotype at one or more polymorphisms (e.g., SNPs).” (Ex.1008, 45:9-15; *see also id.*, 21:8-32.) It also discloses using “[n]ext-generation sequencing” to analyze “each isolated target nucleic acid,” including those isolated via its “amplification technique[s]” (discussed *supra*). (*Id.*, 23:4-13; *see also id.*, 21:8-32.) Thus, Porreca discloses sequencing the plurality of SNP loci on the cell-free DNA in its final amplification products via massively parallel sequencing (Ex.1004, ¶241).

Alternatively, had Porreca not disclosed the foregoing method, it would have been obvious to use Porreca’s massively parallel sequencing to sequence the final amplification products. A POSA would have been motivated to use massively parallel sequencing because, as Patent Owner’s own expert has admitted, before 2010, “next generation sequencing was in widespread use,” including for cell-free

DNA. (Ex.1040, ¶115.) Unlike prior Sanger sequencing, such massively parallel sequencing was accessible and easy-to-use. (Ex.1004, ¶242.) And as the '035 patent itself indicates, Illumina's HiSeq and MiSeq massively parallel sequencers were widely available before its drafting. (Ex.1001, 90:60-64; Ex.1004, ¶242.) Given the method's widespread use and ready availability, a POSA would also have found it trivial to perform massively parallel sequencing on the final amplification products by the critical date. (Ex.1004, ¶242.)

h. Limitation 1[G]

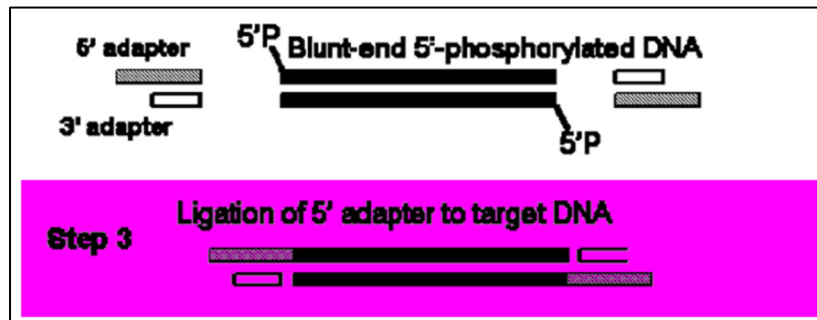
Porreca discloses analyzing (including sequencing) “10-25, 25-50, 50-75, 75-100 or more loci...for each subject.” (Ex.1008, 29:10-18; *see also id.*, 12:25-26, 25:28-31, 31:15-19.) It discloses that “[e]mbodiments of [its] invention may be used for any of a number of different settings,” including “identifying subjects having cancer.” (*Id.*, 30:9-18.) It even recites that its “multiplex diagnostic methods comprise capturing a plurality of genetic loci in parallel,” and gives specific examples of genes containing SNP loci associated with cancer. (*Id.*, 31:15-21, 45:16-49:33 (ATRX/RAD54, FANCC); Ex.1004, ¶242 (confirming foregoing genomic variants are associated with cancer).) Finally, it would have been obvious to apply the combined method to cell-free DNA that contains SNP loci associated with cancer (under Patent Owner's construction). (*Supra* § VII.C.2.)

2. Claims 2 & 3

Claim 2: The method of claim 1, wherein tagging the cell free DNA comprises ligating the one or more universal tail adaptors to the cell free DNA.

Claim 3: The method of claim 2, wherein the one or more universal tail adaptors each comprise a first strand and a second strand, wherein a first end of each of the universal tail adaptors comprises a double-stranded section comprising the 5' portion of the first strand and the 3' portion of the second strand, wherein the first end is ligated to the cell free DNA.

The combined method tags cell-free DNA by ligating universal tail adapters to it. (*Supra* § V.B.1.b; Ex.1009, 16, 27-28, Fig.3.) Those adapter complexes are double-stranded:



(Ex.1009, Fig.3 (cropped and annotated), 27-28.) Each adapter complex has two ends, and each end includes a 5' portion of one strand and a 3' portion of a second strand (that is how double-stranded DNA is structured). (Ex.1004, ¶244.) The first blunt ends of the adapter complexes are ligated to the cell-free DNA via a covalent link between the 5' adapters and the target DNA. (Ex.1009, 16, 27-28, Fig.3.)

Alternatively, it would have been obvious to use (and ligate) a double-stranded adapter with two strands of equal length in place of Hoyal's single-

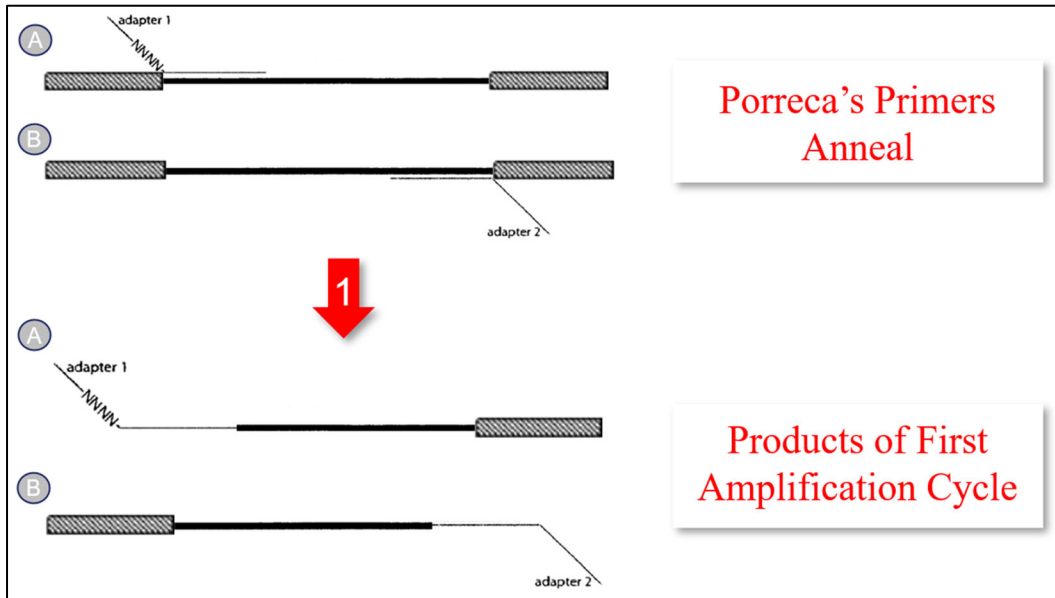
stranded 5' adapter. (Ex.1004, ¶¶245-248.) DNA either is double-stranded or single-stranded and where, as here, an “ordinary artisan would...be left with two design choices...[e]ach of these two design choices is an obvious combination of prior-art elements.” *ACCO Brands Corp. v. Fellowes, Inc.*, 813 F.3d 1361, 1367 (Fed. Cir. 2016). A POSA also would have been motivated to do so because this configuration would simplify the combined method by obviating the extension reaction. (Ex.1004, ¶248.) A POSA would have reasonably expected success in ligating double-stranded DNA sequences because doing so would have required nothing more than including a 5' phosphate group on the '3 adapter strand's 5' prime end, which was well-known and trivial by the critical date. (*Id.*, ¶247.)

3. Claims 10 & 11

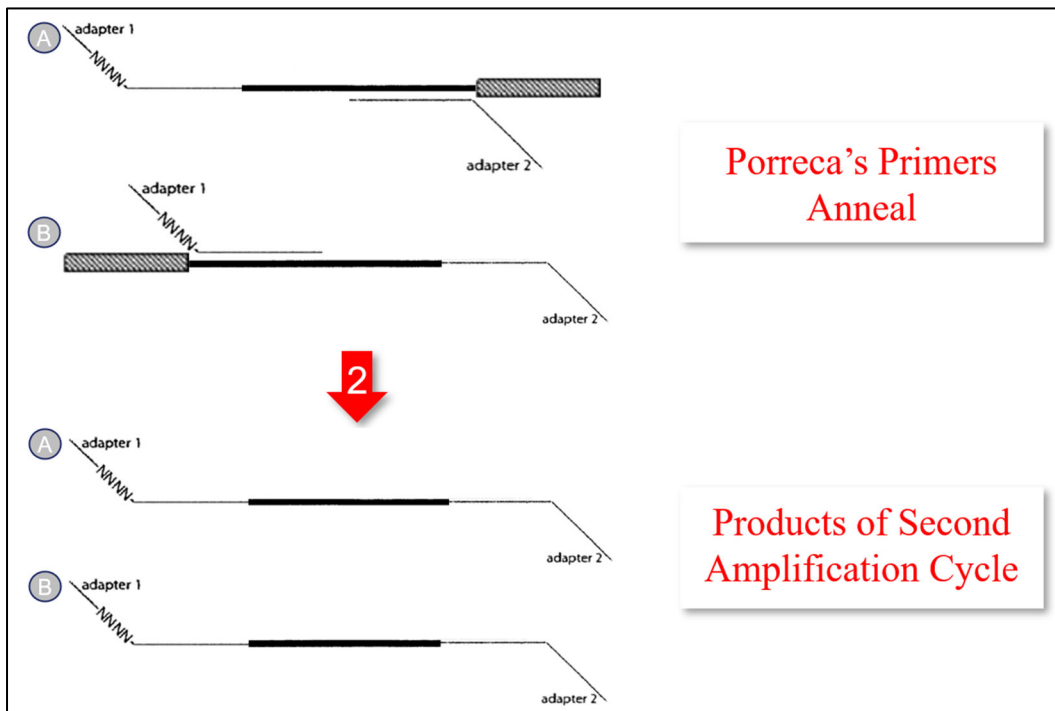
These claims are obvious over Porreca and Hoyal. (Ex.1004, ¶249.) Porreca's target-specific primers comprise universal tail adapters because they include “common adapter sequence[s].” (Ex.1008, 43:29-33.) The common adapter portions comprise sequencing tags because they “contain the sequencing primer site.” (Ex.1008, 43:29-33.) The primers can contain multiple differentiator tags, which are barcodes. (*Id.*, 6:29-30, 22:9-11, 43:29-33, 63:16, 71:21.)

Under Patent Owner's construction, the target-specific primers would generate tagged products in the first amplification cycle in which they anneal to the

products of Hoyal's whole genome amplification step. (Ex.1008, 8:5-8, 43:29-33; Ex.1004, ¶250.) A graphic illustrating that amplification is shown below:



(Ex.1004, ¶250.) Then, in later cycles, the tagged products undergo targeted amplification:



(*Id.*)

4. Claim 12

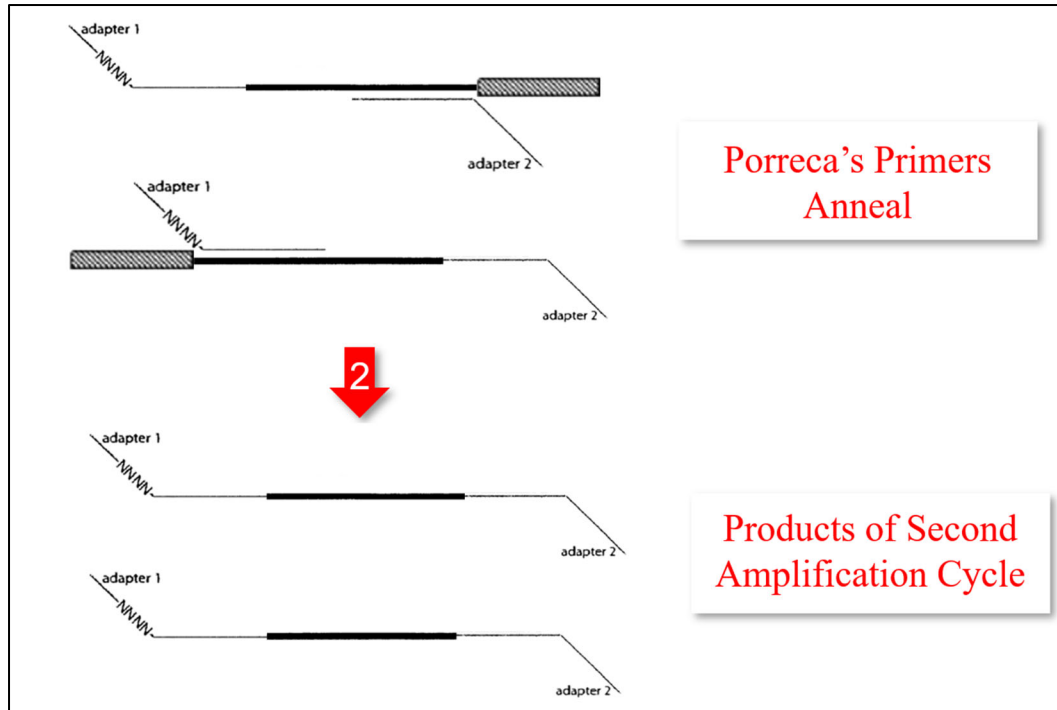
The combined method tags with two universal tail adapters in both the ligation and, alternatively, the targeted amplification steps. (*Supra* § V.B.1.b.; VII.D.3; Ex.1004, ¶251.)

5. Claim 13

The combined method satisfies claim 13’s additional limitation. (Ex.1004, ¶252.) In the first amplification cycle of the targeted amplification, the combined method tags the cell-free DNA with two, target specific-primers, which comprise universal tail adapters. (*Supra* § VII.D.3.)

6. Claim 14

The combined method amplifies tagged products in one or more single amplification steps, which is all this “comprises” claim requires. (*Supra* § VII.D.1.d.) Alternatively, if required, the targeted amplification also performs all of targeted multiplex amplification and introducing barcodes and sequencing tags to tagged DNA strands in the second amplification cycle of its reaction:



(Ex.1004, ¶253; Ex.1008, 43:29-33.)

7. Claim 15

The combined method amplifies the tagged products using four primers: first and second, Hoyal's forward and reverse 5' adapter primers; and third and fourth, Porreca's forward and reverse target-specific primers. (*Supra* § VII.D.1.d; Ex.1008, 8:5-8, 8:15-17, 8:28-31, 43:29-33; Ex.1009, 27-28, Fig.3.) As explained above, Porreca's forward and reverse target-specific primers contain sequencing tags. (*Supra* § VII.D.1.f; Ex.1008, 8:5-8, 43:29-33; Ex.1004, ¶254.)

E. Porreca's Provisional Applications

Finally, Patent Owner may assert that the challenged claims in Grounds 3 and 4 have an earlier priority date than the April 30, 2010 PCT filing date of Porreca. (Ex.1001, 2.) Even with that assertion Porreca still is prior art under pre-

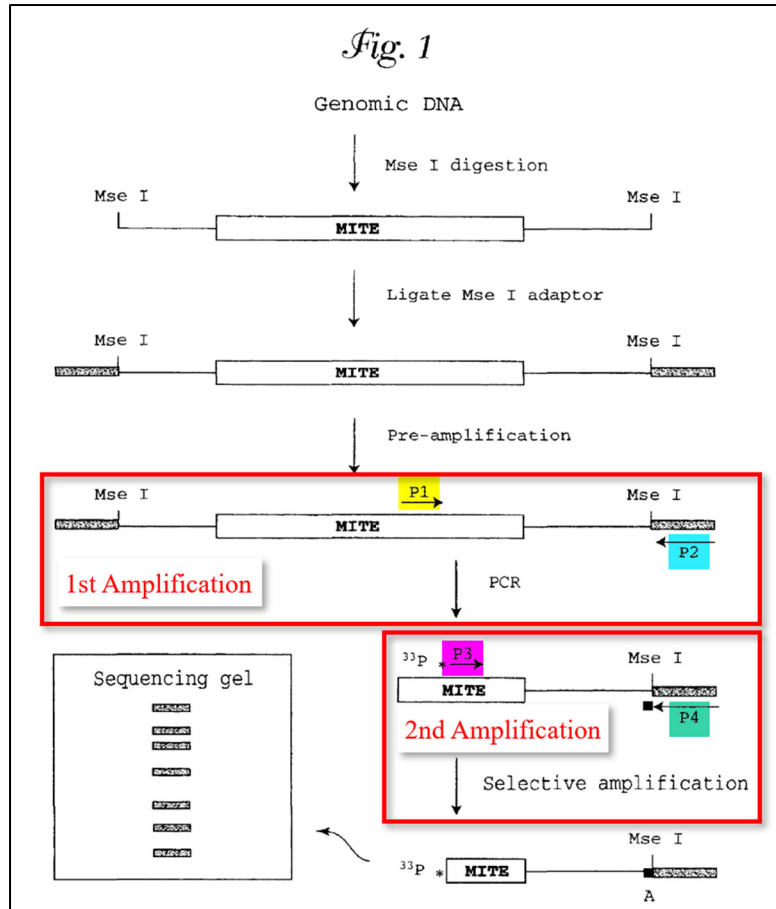
AIA § 102(e) based on, at the latest, the May 28, 2009 filing date of *Porreca*'s U.S. provisional Application No. 61/182,089 ("089 Application"). (Ex.1014.) *See Dynamic Drinkware*, 800 F.3d at 1381-82; M.P.E.P. 2136.03(II)(A). First, *Porreca*'s '089 Application discloses, essentially verbatim, at least *Porreca*'s claim 20. (*Compare* Ex.1008 (claim 20) *with* Ex.1014, 4:26-30.) Second, *Porreca*'s provisional applications include substantively the same disclosure from *Porreca* cited in Grounds 3 and 4. (*Compare* Ex.1008, 4:4-5, 4:21-33, 5:1-3, 6:29-30, 7:5-10, 8:5-17, 8:28-31, 10:22-23, 12:25-26, 13:9-10, 18:31-33, 19:3-4, 20:16-17, 21:8-32, 22:1-4, 22:9-13, 23:4-13, 25:3-7, 25:28-31, 26:18-25, 28:7-10, 29:5, 29:10-18, 29:23-25, 30:9-18, 31:15-21, 31:29-30, 34:10-13, 37:24-26, 43:17, 43:23-33, 45:9-49:33, 63:16, 67:20-21, 67:27-68:7, 71:21, 87:31-88:4, Fig.4b *with* Ex.1011, 6:18-21, 9:11-13; Ex.1012, 2:27-3:16, 4:15-27, 5:31-34; 7:32-33, 8:5-13; Ex.1013, 3:6-10, 4:4-7, 4:11-15, 7:6-9, 7:21-32, 8:2-3, 10:28-29, 11:1-11, 12:18-24, 13:25-19:10, 28:23-33:4, Fig.1b; *and* Ex.1014, 2:5-6, 4:3-4, 4:17-21, 7:15-17, 7:18-19, 7:27-28, 9:14-24, 10:22-24; *see also* Ex.1004, ¶255)

VIII. GROUND 4: PORRECA & WESSLER

Like Hoyal, Wessler teaches tagging target DNA via ligation followed by two amplification steps. But unlike Hoyal's, Wessler's amplifications use one target-specific and one universal primer each. As a result, the combination of *Porreca* and Wessler renders obvious all of claims 1-5 and 10-15.

A. Summary Of Wessler

Wessler discloses methods of “detecting at least one polymorphism between the nucleic acid fragments of two individuals.” (Ex.1010, Abstract; Ex.1004, ¶257.) First, Wessler teaches ligating double-stranded adapters onto target DNA. (Ex.1010, 10:53-62, Fig.1.) It then describes a targeted amplification involving selectively amplifying part of a target sequence (“MITE”) via a first primer that anneals to MITE and a second primer complementary to part of a ligated sequencing adapter. (*Id.*, 10:63-11:7, 11:45-60, 12:5-15; *see also id.*, 3:36-42.) Then, in a second, optional targeted amplification, Wessler uses third and fourth primers to amplify part of the earlier amplification product. (*Id.*, 10:63-11:7, 11:45-60, 12:16-37; *see also id.*, 3:36-42.) Like the first primer, the third primer anneals to part of MITE and, like the second primer, the fourth primer contains a nucleotide sequence identical to a portion of the adapter’s first strand. (*Id.*, 11:45-60, 12:16-37.) Wessler depicts these amplifications and its first, second, third, and fourth primers (yellow, blue, lavender, and green, respectively), in its Figure 1:



(*Id.*, Fig.1 (annotated).)

B. Combination Of Porreca And Wessler

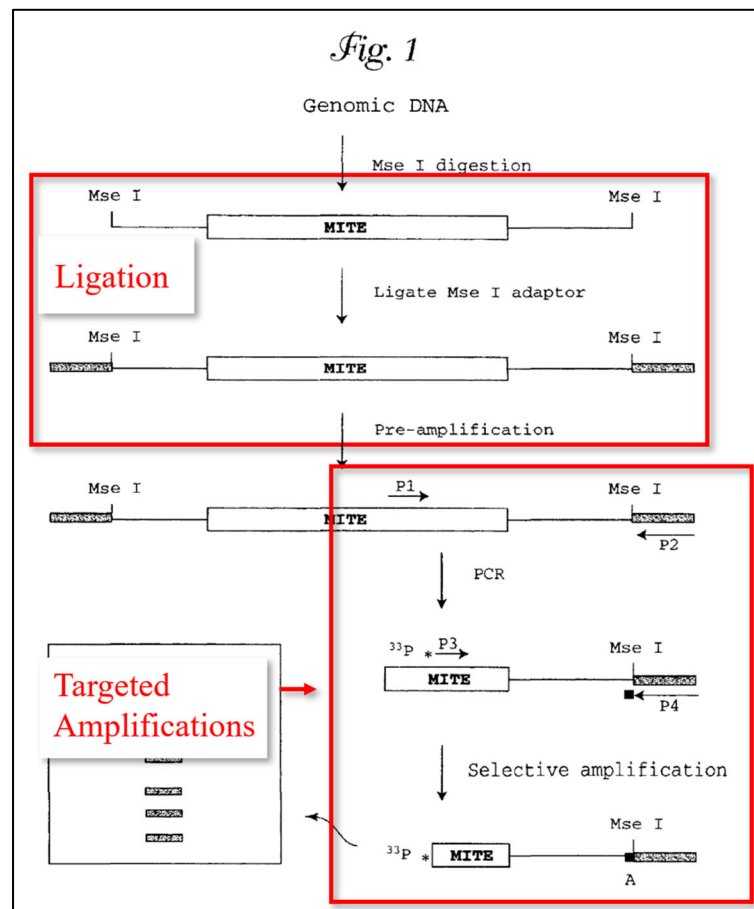
Wessler is analogous art because it is in the same field as the '035 patent or, at the very least, is reasonably pertinent to the problem the '035 patent sought to solve. *Wyers*, 616 F.3d at 1238-39. (Ex.1004, ¶¶258-260.) Like the '035 patent, Wessler teaches methods for detecting polymorphisms in DNA. (Ex.1010, 3:6-4:41; Ex.1001, 1:1-2.) Although Wessler applies its methods to plant genomes, similar polymorphisms exist in humans and Wessler's methods are not limited to plants. (Ex.1010, 2:1-4, 3:6-4:41, 29:22-30:4.) And even if otherwise, by the

critical date a POSA would have considered methods developed in the plant genomic context when devising methods of characterizing human genomes.

(Ex.1004, ¶260.) Thus, as set forth below, it would have been obvious to combine Porreca and Wessler and then extend that combination to cell-free tumor DNA.

1. Modification 1: Targeted Amplifications

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. (*Id.*, ¶261.) The following graphic from Wessler shows its ligation and targeted amplification steps:



(Ex.1010, Fig.1 (annotated).)

Teachings from Porreca and Wessler would have motivated a POSA to combine these methods. (Ex.1004, ¶¶262-266.) First, using two targeted amplifications would improve performance. Porreca's single targeted amplification can sometimes produce a skewed pool of amplicons that limits the method's accuracy. (Ex.1008, 67:27-68:7.) Wessler's ligation followed by preamplification provides a solution. (Ex.1004, ¶262; Ex.1010, Fig. 1.) By preamplifying isolated, cell-free DNA, the combined method would increase the initial numbers of copies of all target sequences and thereby improve the odds that a later targeted amplification and sequencing could detect sequences with low initial prevalence. (*Id.*)

Second, a POSA also would have recognized that Wessler's second, optional amplification offered improved specificity over Porreca's method. Amplifying a first sequence and then amplifying a second sequence within the first sequence was a well-known method of reducing the abundance of non-specific or off-target amplification products compared to a single PCR reaction. (*Id.*, ¶¶263-264.)

Third, Wessler's two targeted amplifications would significantly reduce the number of possible off-target interactions between primers. (*Id.*, ¶265.) Each targeted amplification uses half as many target-specific primers as in Porreca's amplifications. (*Id.*) A reaction with 100 pairs of unique forward and reverse

primers involves 10,000 possible interactions between forward and reverse primers. (*Id.*) A reaction with 100 unique forward primers and one reverse primer, however, involves only 100 such interactions. (*Id.*)

A POSA also would have reasonably expected the combination to succeed. By the critical date, adapting Porreca's method according to Wessler was within a POSA's skill. (*Id.*, ¶267.) Porreca teaches its methods can "be implemented as described herein using alternative techniques and/or protocols that are available to one o[f] ordinary skill in the art." (Ex.1008, 87:31-33, 88:1-2.) And the modification would have required nothing more than applying known ligation and amplification methods to isolated, cell-free DNA. (Ex.1004, ¶267.)

2. Modification 2: SNP Loci Associated With Cancer In Isolated Cell-Free DNA

As explained above, Porreca's disclosures would have motivated a POSA to target SNP loci associated with cancer in cell-free DNA (according to Patent Owner's construction). (*Supra* § VII.C.2; Ex.1004, ¶268.) A POSA would have had a reasonable expectation of success in extending Porreca's method to isolated cell-free DNA in the cancer context because, again, applying such methods to such DNA was no more difficult than applying them to cell-free fetal DNA, which Porreca already discloses. (*Id.*) As Patent Owner has conceded, methods for studying "tumor [cell-free] DNA in a cancer patient's blood" were "routinely used before November 2009." (Ex.1039, 9.) The Federal Circuit also has confirmed

that, by 2009, identifying mutations, sequencing, and quantifying cell-free DNA was “the conventional use of existing techniques.” *CareDx*, 40 F.4th 1371 at 1379.

C. Claims 1-5, 10-15 Are Obvious Over Porreca And Wessler

1. Claim 1

a. Preamble

Porreca and Wessler teach methods of amplifying and/or sequencing DNA. (*Supra* §§ VII.A, VIII.A; Ex.1004, ¶269.)

b. Limitation 1[A]

The combined method performs Limitation 1[A]’s step on isolated, cell-free tumor DNA during Wessler’s ligation step. (Ex.1010, 10:53-62, Fig.1; *Supra* VIII.B.2.) The ligated adapters comprise universal tail adapters because they contain sequences used for non-target specific amplification. (Ex.1010, 12:5-36, Fig.1.) Ligating the adapters generates amplicons tagged with the adapters. (Ex.1004, ¶270; Ex.1010, Fig.1.)

c. Limitation 1[B]

As explained above, it would have been obvious to apply the combined method to isolated cell-free DNA. (*Supra* § VIII.B.2; Ex.1004, ¶271.) Porreca teaches collecting “nucleic acid from a biological sample obtained from a subject,” such as “a blood sample.” (Ex.1008, 18:30-32.) And it further teaches that the “subject or patient may be male,” *i.e.*, not a pregnant woman. (*Id.*, 31:29-30.)

d. Limitation 1[C]

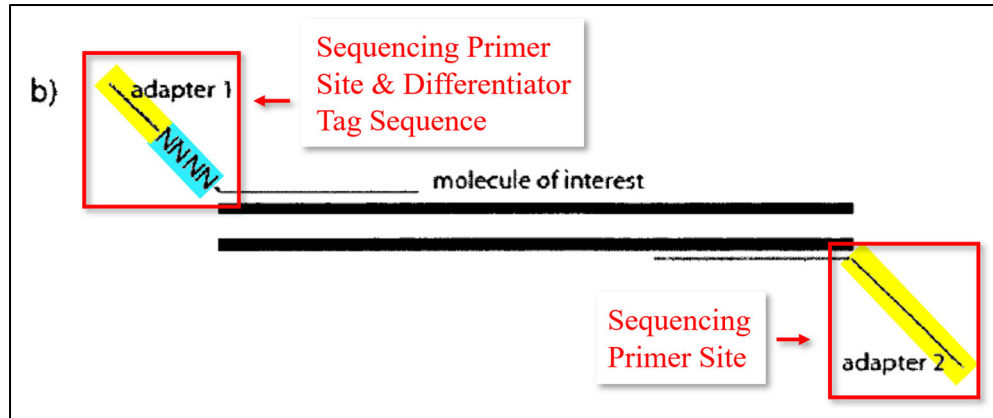
The combined method has two targeted amplification steps. First, the tagged products from Wessler's ligation undergo targeted amplification using one of Porreca's target-specific primers and one of Wessler's adapter primers. (*Supra* § VIII.B.1.) Second (and optionally), the process repeats. (*Id.*) The products of these amplification steps are final amplification products. (Ex.1004, ¶272.)

e. Limitation 1[D]

The combined method discloses or renders obvious every element of Limitation 1[D]. First, the combined method's targeted amplifications are "targeted" because they selectively amplify the cell-free DNA with target-specific primers. (*E.g.*, Ex.1008, 8:5-8, 43:29-33, Fig.4b; Ex.1004, ¶273.) Second, those amplifications would amplify a plurality of SNP loci in a single reaction volume because, as explained above, Porreca teaches those elements or renders them obvious. (*Supra* § VII.D.1.e.)

f. Limitation 1[E]

The combined method's first and optional second amplification steps introduce sequencing adapter and differentiator tags, which correspond to the claimed sequencing tag and barcode, respectively. (Ex.1008, 8:5-8, 43:29-33; Ex.1004, ¶274.) The left-hand portion of Porreca's Figure 4b depicts a sequencing adapter (yellow) and a barcode (blue):



(Ex.1008, Fig.4b (annotated).) Through amplification, the barcode and sequencing tags are incorporated into final amplification products. (Ex.1004, ¶274.)

g. Limitation 1[F]

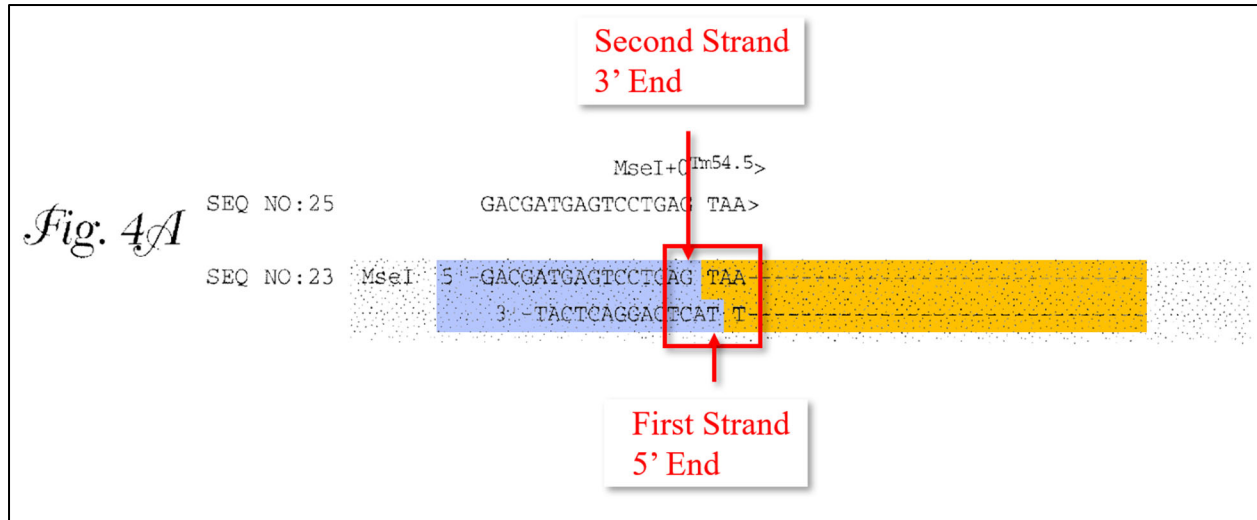
Porreca discloses or renders obvious this limitation. (*Supra* § VII.D.1.g.)

h. Limitation 1[G]

Porreca discloses or renders obvious this limitation. (*Supra* § VII.D.1.h.)

2. Claims 2 & 3

As explained above, the combined method tags cell-free DNA by ligating universal tail adapters to it. (*Supra* § VIII.C.1.b.) Wessler teaches that its adapters may comprise a double-stranded “SEQ ID No:23.” (Ex.1010, 6:28-34; 10:59-62, 13:9-14.) Those adapters include a first strand and a second strand, wherein a first end of each adapter includes a 5’ portion of the first strand and a 3’ portion of the second strand that are ligated to the target, cell-free DNA. (*Id.*, Fig.4A, Ex.1004, ¶277.) Wessler depicts one of these adapters (navy) ligated to one end of target DNA (gold) with a first end in Figure 4A:

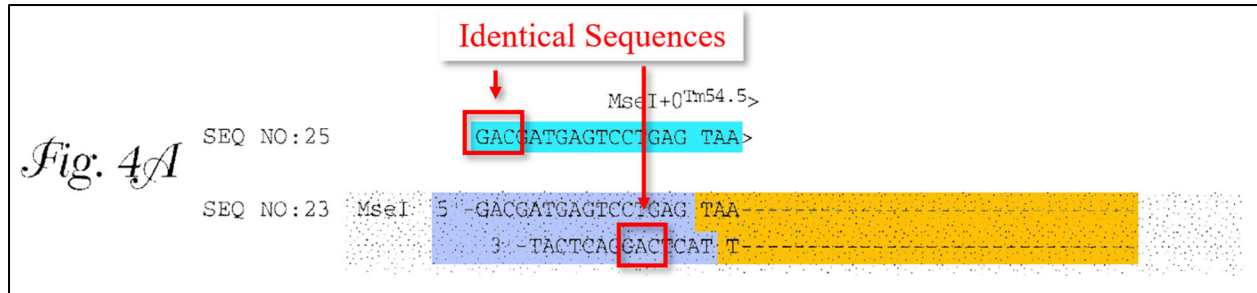


(*Id.*, Fig.4A (annotated); *Supra* § VIII.B.2.)

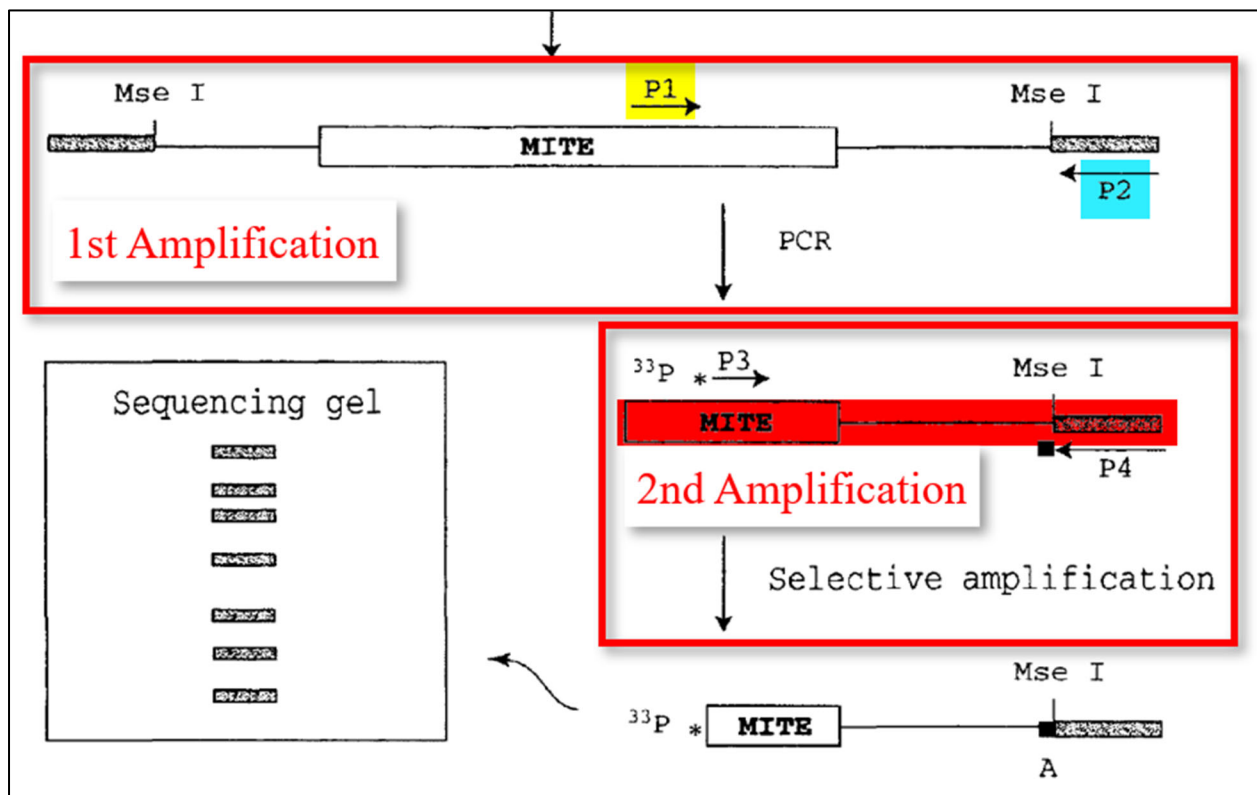
3. Claim 4

The method of claim 3, wherein amplifying the tagged products comprises a first amplifying step and a second amplifying step, wherein the first amplifying step comprises using a first target-specific primer that specifically anneals to a target sequence and a first adaptor primer having a nucleotide sequence identical to a first portion of the first strand to generate a first amplification product.

Claim 4 is obvious over Porreca and Wessler. (Ex.1004, ¶278.) The combined method includes a first amplification step where Porreca's first target-specific primer specifically anneals to a target sequence. (*Supra* § VIII.B.1.) That amplification step also uses one of Wessler's adapter primers, such as "SEQ ID NO:25," to anneal to the portion of the target sequence tagged with an adapter. (Ex.1010, 13:9-19, Figs.1, 4A.) SEQ ID NO:25 (blue) has a sequence identical to a first portion of the first strand of Wessler's adapter SEQ ID NO:23 (navy):



(*Id.*, Fig.4A (annotated).) In combination with Porreca's target-specific primer, it then generates a first amplification product. (Ex.1004, ¶278.) Wessler's Figure 1, which is illustrative, shows using a first target-specific primer ("P1," (yellow)) and a first adapter primer ("P2," (blue)) to generate a first amplification product (red):



(Ex.1010, Fig.1 (cropped and annotated).) The combined method also includes a second, optional amplifying step. (*Supra* § VIII.B.1.)

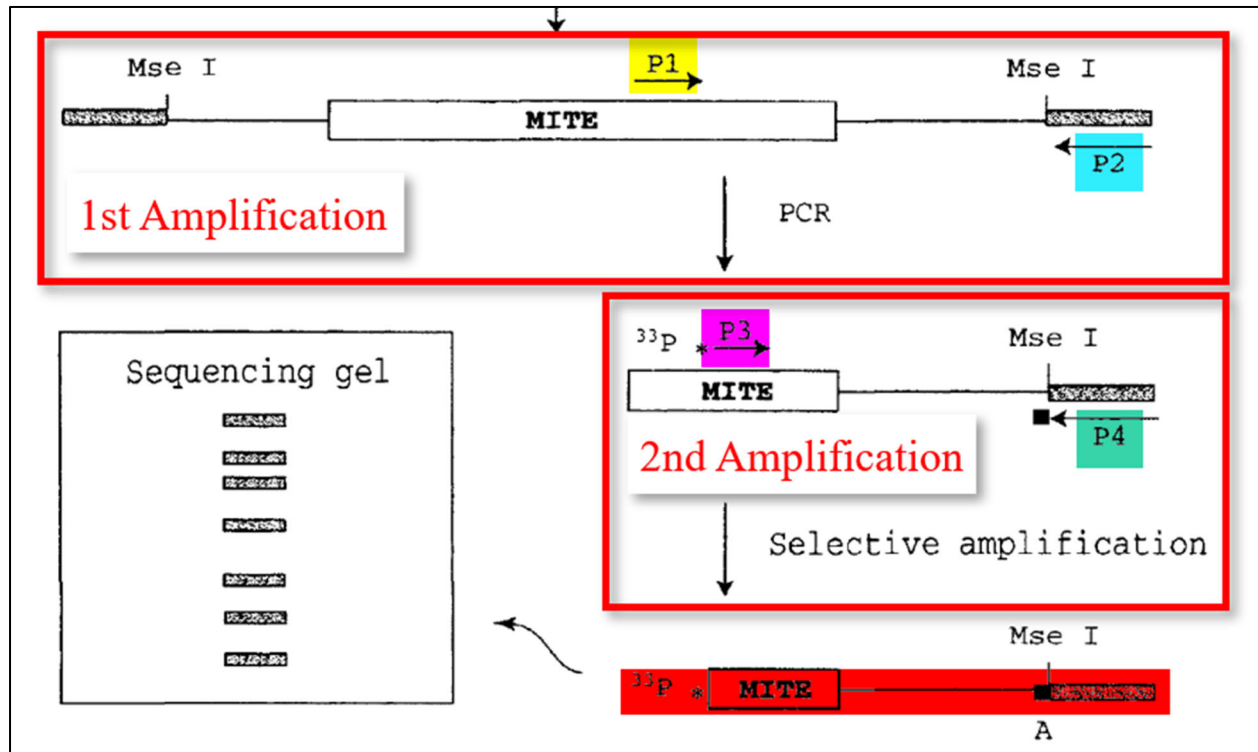
4. Claim 5

The method of claim 4, wherein the second amplifying step comprises using a second target-specific primer that specifically anneals to the first amplification product and a second adaptor primer having a nucleotide sequence identical to a second portion of the first strand to generate the final amplification product.

Claim 5 is obvious over Porreca and Wessler. (Ex.1004, ¶279.) In the combined method's second, optional amplification step, it would use a second target-specific primer and a second 5' adapter primer. The second target-specific primer would specifically anneal to the first amplification product. (Ex.1008, 43:29-32, Fig.4b.) And the 5' adapter primer would have, again, a sequence identical to a portion of a first strand of a 5' adapter introduced via ligation. (Ex.1010, 10:53-62, Fig.1.) Wessler discloses, for example, a second adapter primer "SEQ ID NO: 3 1", which it calls a "fourth primer[]," composed of the following bases: "5' GACGATGAGTCCTGAGTAAN." (*Id.*, 13:9-22.) Wessler's SEQ ID NO: 3 1 has a nucleotide sequence identical to a second portion of the first strand of SEQ ID NO: 23 because both strands include the sequence "AC." (*See id.*, 13:9-22 (SEQ ID NO: 3 1), Fig.4A (SEQ ID NO:23).)

This amplification would generate a final amplification product. (Ex.1004, ¶280.) Wessler's Figure 1, which is illustrative, shows using third (lavender) and

fourth (green) primers to generate a final amplification product (red):



(*Id.*, Fig.1 (cropped and annotated).)

5. Claims 10 & 11

These claims are obvious over Porreca and Wessler. Porreca's target-specific primers comprise universal tail adaptors comprising barcodes and sequencing tags. (*Supra* § VII.D.3.) Under Patent Owner's construction, the first amplification cycle in the combined method's second PCR reaction would generate products tagged with a second target-specific primer and thus also a second barcode and sequencing tag. (Ex.1010, Fig.1; Ex.1004, ¶281.) Then, under Patent Owner's construction, targeted amplification of the tagged products is performed in later cycles. (*Supra* § VII.D.3)

6. Claim 12

The combined method tags isolated cell-free DNA with multiple universal tail adapters across the ligation and targeted amplification steps. (*Supra* §§ VIII.C.1.b, VIII.C.5; Ex.1004, ¶282.)

7. Claim 13

The combined method's amplification steps satisfy this limitation. As explained above, the first and second target-specific primers comprise universal tail adapters. (*Supra* § VIII.C.5; Ex.1004, ¶283.)

8. Claim 14

The combined method amplifies tagged products in one or more single amplification steps, which is all this “comprises” claim requires. (*Supra* § VII.D.1.d; Ex.1004, ¶284.)

9. Claim 15

The combined method amplifies the tagged products using four primers: Wessler's adapter primers and Porreca's target-specific primers. (*Supra* § VIII.B.1.) The target-specific primers contain sequencing tags and are third and fourth primers. (*Supra* § VIII.C.1.f; Ex.1008, 8:5-8, 43:29-33, Ex.1004, ¶285.)

IX. THE BOARD SHOULD REACH THE MERITS

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

Section 325(d) is inapplicable here. To begin with, the Petition does not raise substantially the same art or arguments in the same way as the examination of

the '035 patent. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6, at 7-11 (P.T.A.B. Feb. 13, 2020) (precedential). Of the references in Grounds 1-4, only Forshew, May, Hoyal, and a 2014 version of Pieprzyk were cited on '035 patent's face. (Ex.1001, 4, 6, 10.) Their disclosures were not, however, substantively discussed or applied against the claims. (*Id.*) See *Amazon Inc. v. M2M Sols. LLC*, IPR2019-01204, Paper 14 at 16 (P.T.A.B. Jan. 23, 2020) ("reference that 'was neither applied against the claims nor discussed by the Examiner'" weighs against section 325(d) denial). Moreover, Forshew and the 2014 version of Pieprzyk both were dated after the '035 patent's purported 2010 priority date and, at first blush, may not have seemed to be prior art. (Ex.1003, 1288.) As for May and Hoyal, Patent Owner buried them amongst hundreds of references that it disclosed only *after* the Examiner already had resolved to allow the claims. (*Id.*, 237, 239, 573.)

The '035 Patent's specification also mentions a prior art 48-reaction "FLUIDIGM ACCESS ARRAY." (Ex.1001, 85:21-33.) Pieprzyk and May do refer to 48-reaction Fluidigm arrays, and some of the art considered by the Examiner contains passing references to Fluidigm-brand technologies. (*E.g.*, Ex.1006, ¶203; Ex.1007, 143; Ex.1022, ¶¶85, 87; Ex.1023, 5:3-4, 17:53-67, 18:38-46, Fig.8.) But no evidence shows that the Examiner assessed whether the pending

claims were patentable over Pieprzyk and May's methods *as detailed in the PCT applications*. See *Amazon*, IPR2019-01204, Paper 14 at 16.

Finally, even had the art and arguments in this Petition mirrored the '035 patent's prosecution—and they do not—the Examiner plainly erred. The Examiner allowed the challenged claims because she believed the “associated with cancer” and “non-pregnant women” limitations rendered the claims novel and non-obvious. (Ex.1003, 578-79.) They do not. As explained in the body of this Petition, nothing about the claimed method was new.

B. *Fintiv* Does Not Support Discretionary Denial

Because Patent Owner has asserted the '035 patent in a parallel proceeding in the Middle District of North Carolina, the Board must assess whether to discretionarily deny institution under six factors enumerated in *Apple Inc. v. Fintiv, Inc.* IPR2020-00019, Paper 11 at 6 (P.T.A.B. Mar. 20, 2020) (precedential). Here, the *Fintiv* factors favor institution and discretionary denial is unwarranted.

1. Factor 1: likelihood of a stay

This factor favors institution. The Middle District of North Carolina has granted stays pending IPR in four of five cases in which it considered that issue. Compare *Sade v. North Star Solar LLC*, No. 22-cv-01109, Text Order (M.D.N.C. Aug. 23, 2023) (granted), *Watson Guide IP, LLC v. Absolute Dental Serv., Inc.*, No. 22-cv-00558, Dkt.19 (M.D.N.C. Dec. 14, 2022) (granted), *CAO Lighting, Inc.*

v. Cree, Inc., No. 21-cv-00634, Dkt.32 (M.D.N.C. Nov. 30, 2022) (granted), *and JIG IP Holdings, LLC v. Machinex Indus. Inc.*, No. 19-cv-00437, Dkt.40 (M.D.N.C. May 8, 2020) (granted) *with Altria Client Serv. LLC v. RJ Reynolds Vapor Co.*, No. 20-cv-00472, Dkt.171 (M.D.N.C. Oct. 13, 2021) (denied where Board declined to institute seven of nine petitions). If the Board also institutes co-pending IPR2024-00346, which challenges the only other patent at issue in the North Carolina action, the likelihood of a stay will further increase.

2. Factor 2: proximity of trial date to FWD

This factor favors institution. Because “scheduled trial dates are unreliable and often change,” Director Vidal has instructed the Board to compare the statutory deadline for any FWD against the “median time-to-trial for civil actions...in which the parallel litigation resides.” (Ex.1030, 8-9.) Here, the statutory deadline for any FWD is roughly October 2025 and, for the 12-month period ending June 30, 2023, the median time to trial for civil actions in the Middle District of North Carolina was 42.4 months. (Ex.1031, 22.) With a filing date of July 28, 2023, that indicates a projected trial date in February 2027.

The North Carolina action’s current schedule is not to the contrary. Although the district court scheduled trial for March 10, 2025, at the parties’ request, its scheduling order states that date is “subject to adjustment based on the Court’s criminal trial schedule and as needed for resolution of dispositive

motions.” (Ex.1032, 3.) The district court already has continued the preliminary injunction hearing. (Ex.1043.) And its orders setting hearings on claim construction and dispositive motions indicate that even more delays are possible: those hearing dates are “subject to adjustment” based on the district court’s “availability,” “criminal schedule,” and “trial schedule.” (Exs.1044-1045.) There is no guarantee of trial before the Board issues any FWD.

3. Factor 3: investment in parallel proceeding

This factor favors institution or is neutral. The Board considers investment in the parallel proceeding as “of the institution decision.” *Fintiv*, IPR2020-00019, Paper 11 at 9. To date, the parties have conducted some discovery and are in the early stages of claim construction briefing. The district court also has issued a preliminary injunction over preliminary invalidity arguments by Petitioner, but that decision is on appeal. And, in any event, the court did not consider obviousness based on any of the references presented here in Grounds 1-4.¹⁰ By the statutory deadline for institution, fact and expert discovery may have closed, but the district court will not have ruled on summary judgment. (Ex.1032, 2.) Also, “the most

¹⁰ The district court found the lead reference in the preliminary injunction proceeding did not expressly refer to cell-free DNA. (*Compare* Ex.1042, 9-10 (referring to Ex.1029) *with* Ex.1006, ¶111, Ex.1008, 7:5-8.)

burdensome parts of the case—filing and responding to pretrial motions, preparing for trial, going through the trial process, and engaging in post-trial motions practice—all [will] lie in the future.” *CyWee Grp. Ltd. v. Samsung Elecs. Co.*, No. 2:17-CV-00140-WCB-RSP, 2019 WL 11023976, at *6 (E.D. Tex. Feb. 14, 2019) (Bryson, J.).

4. Factor 4: overlapping issues

This factor favors institution. In the North Carolina action, Petitioner contests validity of claims 1, 2, 12, and 13 under the clear and convincing evidentiary standard. Here, Petitioner challenges claims 1-5 and 10-15 under the lower, preponderance of the evidence standard. Regardless of the outcome in North Carolina, that action will not resolve patentability of every challenged claim.

5. Factor 5: same parties

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

6. Factor 6: the merits and other circumstances

If the Board finds *Fintiv* factors 1-5 favor denial of institution, it must then consider whether the Petition presents “compelling merits” such that it nonetheless must institute review. *Commscope Techs. LLC v. Dali Wireless, Inc.*, IPR2022-01242, Paper 23 at 4-5 (Dec. Dir. Pat. Feb. 27, 2023). A Petition presents compelling merits if “it is highly likely that the petitioner would prevail with respect to at least one challenged claim. *Id.*, *4. This Petition more than clears

that bar: each of the Forshew, Pieprzyk, and Porreca grounds independently discloses or renders obvious every limitation of at least challenged claim 1.

Fintiv factor 6 also allows the Board to consider “other circumstances.” Here, the public interest favors institution. Both Petitioner and Patent Owner have commercialized assays that use cell-free tumor DNA to detect and monitor cancer. Earlier this year, a district court preliminarily enjoined Petitioner’s RaDaR™ assay, an FDA-designated “breakthrough device,” over the ’035 patent. (Ex.1033.) RaDaR™ was more sensitive than other assays, and it could find cancers that competing products could not. (*See, e.g.*, Ex.1036 (Petitioner’s assay: 0.0001% VAF limit of detection); Ex.1037, 1 (Patent Owner’s assay: 0.01% VAF limit of detection).) But its availability in the United States now is severely limited. Cancelling the ’035 patent would restore public access to that assay and, thus, this proceeding has import far beyond whether Patent Owner must pay Petitioner royalties. The Board should reach its merits.

X. MANDATORY NOTICES

A. Real Party-in-Interest

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

B. Related Matters

Pursuant to 37 C.F.R. § 42.8(b)(2), Petitioner identifies the following related matters: *Natera, Inc. v. NeoGenomics Laboratories, Inc.*, No. 23-cv-00629 (M.D.N.C.); and *Natera, Inc. v. NeoGenomics Laboratories, Inc.*, Nos. 24-1324, 24-1409 (Fed. Cir.). Patent Owner asserts the '035 patent against Petitioner in the district court case. In that case, Patent Owner has asserted another patent, U.S. Patent No. 11,540,454 (“the '454 patent”). Petitioner has sought review of the '454 patent in IPR2024-00346.

Pursuant to 37 C.F.R. § 42.104(a), Petitioner certifies that the '035 patent is available for *inter partes* review and that Petitioner is not barred or estopped from requesting an *inter partes* review challenging the patent claims on the grounds identified in this Petition.

C. Lead And Back-Up Counsel And Service Information

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

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

The USPTO is authorized to charge any required fees, including the fee as set forth in 37 C.F.R. § 42.15(a) and any excess claim fees, to Deposit Account

No. **03-1952** referencing Docket No. **31789-00000.04**.

XI. CONCLUSION

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

Dated: April 17, 2024

Respectfully submitted,

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

I hereby certify that this Petition for *Inter Partes* Review has 13,864 words (as counted by the “Word Count” feature of the Microsoft Word™ word-processing system), exclusive of “a table of contents, a table of authorities, mandatory notices under § 42.8, a certificate of service or word count, or appendix of exhibits or claim listing.”

Dated: April 17, 2024

By: /Mehran Arjomand/
Mehran Arjomand

Certificate of Service (37 C.F.R. § 42.6(e)(4) and 42.205(a))

I hereby certify that the attached Petition for *Inter Partes* Review and supporting materials were served as of the below date by UPS, which is a means at least as fast and reliable as U.S. Express Mail, on the Patent Owner at the correspondence address indicated for U.S. Patent No. 11,519,035.

Natera, Inc.
201 Industrial Road
Suite 410
San Carlos, California 94070

Dated: April 17, 2024

/Mehran Arjomand/
Mehran Arjomand