

Exhibit 1

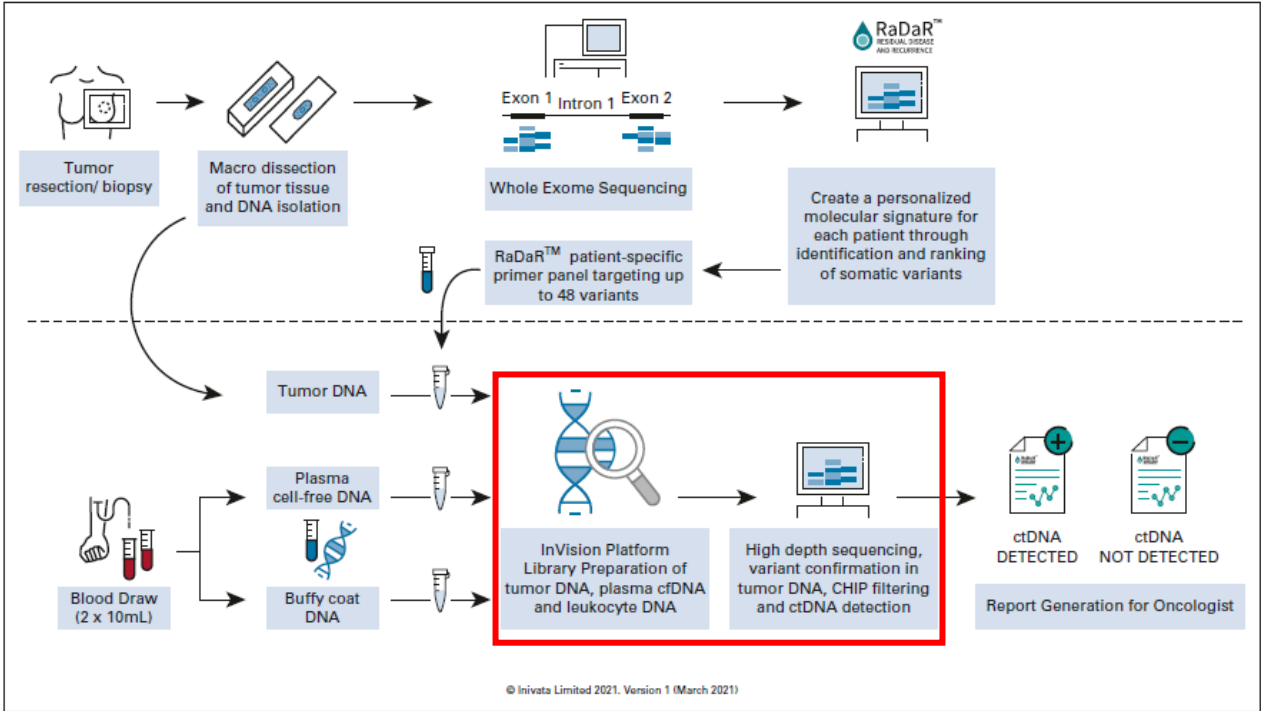
EXHIBIT 1

NATERA’S PRELIMINARY CLAIM CHART FOR U.S. PATENT NO. 11,519,035 (“the ’035 Patent”)

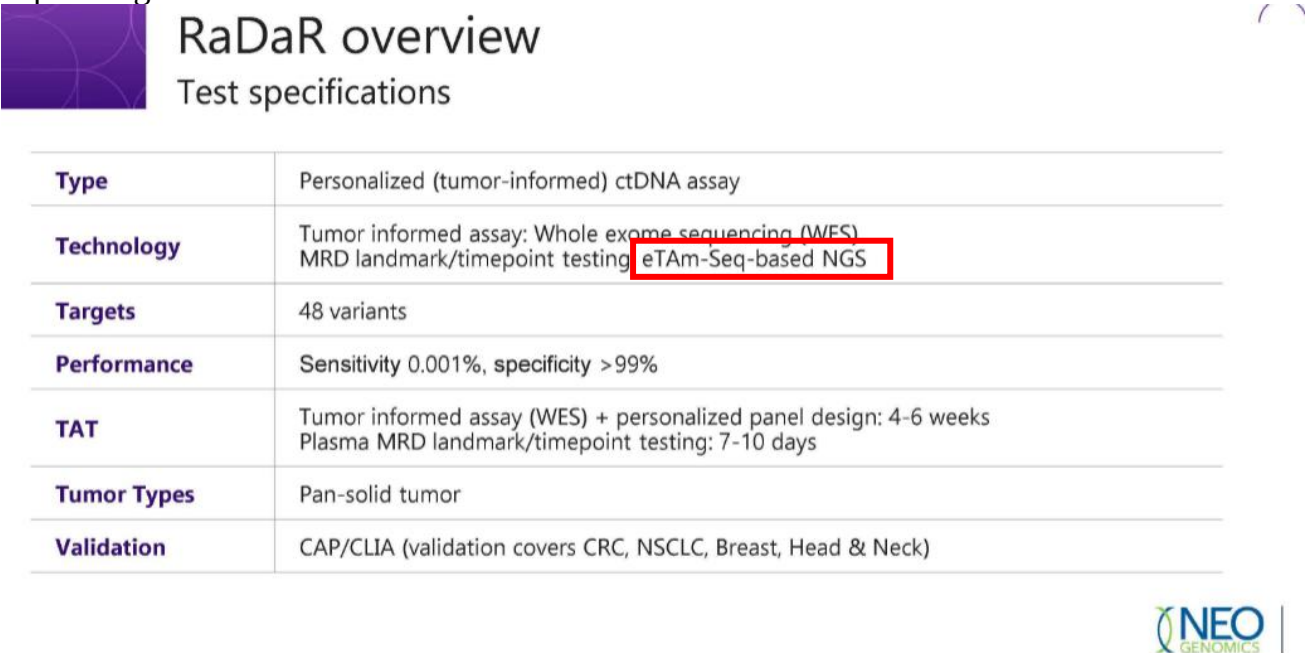
’035 Patent Claim Language	NeoGenomics’ Accused Products
1[preamble]. A method for amplifying and sequencing DNA, comprising:	To the extent the preamble is considered a claim limitation, this limitation is met by Inivata’s Accused Products including RaDaR™. For example, Inivata’s RaDaR assay comprises methods for amplifying and sequencing DNA. For example, Inivata’s website (https://www.inivata.com/radar-residual-disease-and-recurrence/, (Doc. 1-5)¹) states “The RaDaR™ assay is built on Inivata’s proven InVision® liquid biopsy platform technology. This next-generation sequencing platform incorporates built-in controls and error-correction for highly sensitive and specific variant detection. RaDaR™ is a personalized assay that tracks a set of up to 48 tumor-specific variants in a patient using a liquid biopsy with exceptional sensitivity, allowing both detection of residual disease following curative intent or definitive treatment and early detection of relapse.” For example, Inivata’s website (https://www.inivata.com/radar-residual-disease-and-recurrence/, (Doc. 1-5)) includes a page titled “Publications and Posters,” which includes a poster presentation presented at an AACR conference by Heider at al. titled, “Sensitive detection of ctDNA in early-stage non-small cell lung cancer patients with a personalized sequencing assay” (herein after “Heider”), which states “RaDaR™ is a highly sensitive personalised sequencing ctDNA assay. Tumor-specific variants are first identified by exome sequencing of tumor tissue, followed by multiplex PCR and high-depth next generation sequencing to track low levels of ctDNA in patient plasma.”

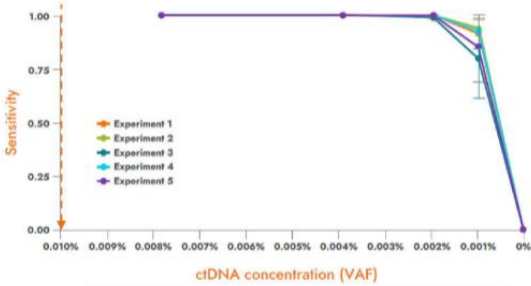
¹ Attached to Complaint (Doc. 1).

'035 Patent Claim Language	NeoGenomics’ Accused Products
	For example Heider (Doc. 1-6) contains the following figure showing that RaDaR includes amplifying and sequencing DNA: Step 1: Creation of a patient-specific list of tumor mutations Biopsy or surgical resection → Macrodissection of tumor tissue → Exome sequencing of tumor and buffy coat → Identification of tumor somatic variants → Prioritization of variants for patient-specific panel design Step 2: Creation of a RaDaR™ patient-specific ctDNA panel Prioritized set of somatic variants (median 48 variants) → Automated design of patient-specific primers → Patient-specific primers → Patient-specific primer-pool covering 48 variants Step 3: NGS testing of patient samples and analysis Blood draw → Plasma cell-free DNA Tumor tissue → Tumor DNA Plasma cell-free DNA → Buffy coat DNA Patient-specific primer panel → Replicate PCRs performed to increase signal to noise ratio to detect low frequency variants → Pool reactions for high-depth sequencing Doc. 1-6 (annotated).

'035 Patent Claim Language	NeoGenomics’ Accused Products
	According to NeoGenomics, RaDaR includes a method for amplifying and sequencing DNA as shown below.  The diagram illustrates the RaDaR assay workflow. It begins with 'Tumor resection/ biopsy', leading to 'Macro dissection of tumor tissue and DNA isolation'. This is followed by 'Whole Exome Sequencing' (showing Exon 1, Intron 1, and Exon 2) and 'Create a personalized molecular signature for each patient through identification and ranking of somatic variants' (RaDaR™). This step leads to a 'RaDaR™ patient-specific primer panel targeting up to 48 variants'. The workflow then branches into two paths: 'Tumor DNA' and 'Blood Draw (2 x 10mL)'. The 'Blood Draw' path leads to 'Plasma cell-free DNA' and 'Buffy coat DNA'. Both paths lead to 'InVision Platform Library Preparation of tumor DNA, plasma cfDNA and leukocyte DNA' (highlighted in a red box). This is followed by 'High depth sequencing, variant confirmation in tumor DNA, CHIP filtering and ctDNA detection'. The final step is 'Report Generation for Oncologist', which shows 'ctDNA DETECTED' and 'ctDNA NOT DETECTED' results. © Inivata Limited 2021. Version 1 (March 2021) FIG A1. RaDaR assay workflow. Used with permission from Inivata, Inc.³⁸ cfDNA, cell-free DNA; CHIP, clonal hematopoiesis of indeterminate potential; ctDNA, circulating tumor DNA. NEOGEN00000002 (annotated).

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	For example, as shown below, RaDaR includes an “eTAm-Seq-based NGS” method for amplifying and sequencing DNA.  The slide titled "RaDaR overview Test specifications" features a purple graphic on the left and a table of specifications on the right. The table lists: Type (Personalized (tumor-informed) ctDNA assay), Technology (Tumor informed assay: Whole exome sequencing (WES), MRD landmark/timepoint testing, and eTAm-Seq-based NGS), Targets (48 variants), Performance (Sensitivity 0.001%, specificity >99%), TAT (Tumor informed assay (WES) + personalized panel design: 4-6 weeks, Plasma MRD landmark/timepoint testing: 7-10 days), Tumor Types (Pan-solid tumor), and Validation (CAP/CLIA (validation covers CRC, NSCLC, Breast, Head & Neck)). The NeoGenomics logo is in the bottom right corner. NEOGEN00008248 (annotated).
1[a]: tagging isolated cell free DNA with one or more universal tail adaptors to generate tagged	Inivata’s Accused Products meet this limitation. For example, Inivata’s RaDaR assay includes tagging isolated cell free DNA with one or more universal tail adaptors to generate tagged products. For example, RaDaR is built on the InVision platform with enhanced TAm-Seq technology as shown below.

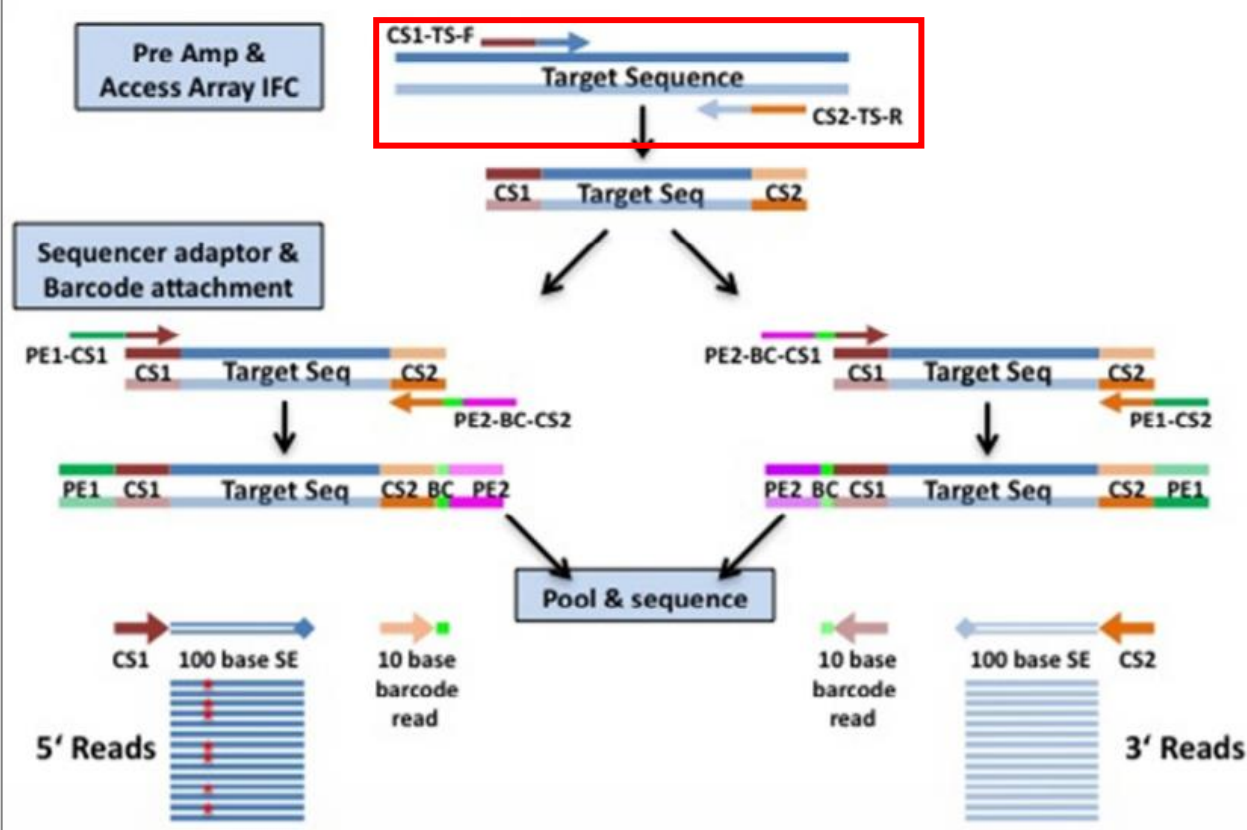
'035 Patent Claim Language	NeoGenomics’ Accused Products				
products, wherein the isolated cell-free DNA is isolated from a blood sample collected from a subject who is not a pregnant woman; ...	 Best in class ctDNA detection with RaDaR • RaDaR is built on the InVision platform with enhanced Tam-Seq technology • RaDaR designs personalized panels of up to 48 genomic loci, optimizing sensitivity • RaDaR utilizes an algorithmic approach to determine MRD status, ensuring high sensitivity and specificity • RaDaR rules out biological artifacts like CHIP mutations other technologies may miss, reducing false positive results  Analytical validation studies showed RaDaR could detect down to 0.001% VAF with 100% specificity  High confidence MRD detection NEOGEN00001055 (annotated). For example, according to NeoGenomics, the method of library preparation in RaDaR involves “direct multiplex PCR amplification.” <table border="1"> <thead> <tr> <th>Feature</th><th>RaDaR</th></tr> </thead> <tbody> <tr> <td>Library prep method</td><td>Direct multiplex PCR Amplification</td></tr> </tbody> </table> NEOGEN00010754	Feature	RaDaR	Library prep method	Direct multiplex PCR Amplification
Feature	RaDaR				
Library prep method	Direct multiplex PCR Amplification				

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'035 Patent Claim Language	NeoGenomics’ Accused Products
	Inivata’s website (https://www.inivata.com/our-publications/, (Doc. 1-13) at p. 4) includes a page titled “Our Publications,” which lists a publication by Gale, <i>et al.</i>, PLoS One (2018) 13(3):e0194630 (“Gale”) that describes the InVision liquid biopsy platform technology (used in the RaDaR assay). Gale (Doc. 1-9) discloses, “The development of next generation sequencing (NGS) has allowed for a broader application of ctDNA analysis. In 2012, Forshew et al. developed TAm-Seq technology, or tagged amplicon deep sequencing which, for the first time, enabled interrogation of 6 genes across a large genomic region spanning 5995 bases to detect low frequency mutations in cell-free DNA...Since this time, other NGS technologies have been implemented for analysis of ctDNA, including the use of hybrid capture and the introduction of panel assays that use molecular barcodes to enable error suppression...<u>Here we describe the development of the InVision liquid biopsy platform which utilizes enhanced TAm-Seq (eTAm-SeqTM) technology for the identification of low frequency mutations in ctDNA. The assay has been expanded to target hotspots and entire coding regions from 35 cancer-related genes, utilizing a primer design strategy that allows for amplification of highly fragmented DNA, typical of ctDNA. The calling algorithm has been revised, and in addition to improved detection of single nucleotide variants (SNVs) and short insertions/deletions (indels), it also identifies copy number variants (CNVs).</u>” Gale at 3 (emphasis added). Gale (Doc. 1-9) also discloses, “Library preparation using eTAm-Seq technology. eTAm-Seq technology is based on methods previously described . . . with an optimized assay workflow utilizing multiplex PCR to enable high-throughput library preparation without the use of microfluidics. Next generation sequencing libraries were prepared using a <u>two-step multiplex PCR amplification process</u> incorporating replicate and patient-specific barcodes and Illumina sequencing adaptors.” Gale at 4 (emphasis added).

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	According to Gale, eTAm-Seq is a version of TAm-Seq, which is described by Forshew et al., <i>Noninvasive identification and monitoring of cancer mutations by targeted deep sequencing of plasma DNA</i>, SCIENCE TRANSLATIONAL MEDICINE 4:136ra68 (2012) (“Forshew”, NEOGEN00017098). Gale at 4. 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. See Doc. 17 (Metzker Opening Decl.) at ¶88. For example, eTAm-Seq is an enhanced version of TAm-Seq, which is depicted below. Gale at 4. The limited 15-cycle preamplification of TAm-Seq involves performing targeted multiplex amplification to amplify a plurality of SNV target loci each encompassing a different tumor-specific SNV mutation from cell-free DNA isolated from plasma sample, wherein the target loci are amplified together in the same reaction volume. NEOGEN00017099-17100. The first PCR cycle of preamplification tags cell-free DNA with universal tail adaptors CS1 and CS2. See NEOGEN00017082; NEOGEN00017099-17100; see also Doc. 145 (Metzker Reply Decl.) at ¶¶295-300. Accordingly, a person of ordinary skill in the art would recognize that in the first PCR cycle of preamplification, RaDaR involves tagging isolated cell free DNA with one or more universal tail adaptors to generate tagged products.

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	 The diagram illustrates the process of NeoGenomics' Accused Products, starting with a 'Pre Amp & Access Array IFC' step. A 'Target Sequence' is shown with primers 'CS1-TS-F' and 'CS2-TS-R'. This is followed by 'Sequencer adaptor & Barcode attachment', where the target sequence is flanked by 'CS1' and 'CS2' sequences. The process then branches into two paths: one involving 'PE1-CS1' and 'PE2-BC-CS2', and another involving 'PE2-BC-CS1' and 'PE1-CS2'. Both paths lead to a 'Pool & sequence' step. Finally, the process results in '5' Reads' (CS1, 100 base SE, 10 base barcode read) and '3' Reads' (10 base barcode read, 100 base SE, CS2). NEOGEN00017082 (annotated). For example, Forshew discloses that in TAm-Seq that “[t]arget-specific primers were synthesised with common adaptor sequences at their 5’ ends (CS1 and CS2). These were used during the preamplification and single-plex stages to amplify the selected regions. Sequencing platform-specific

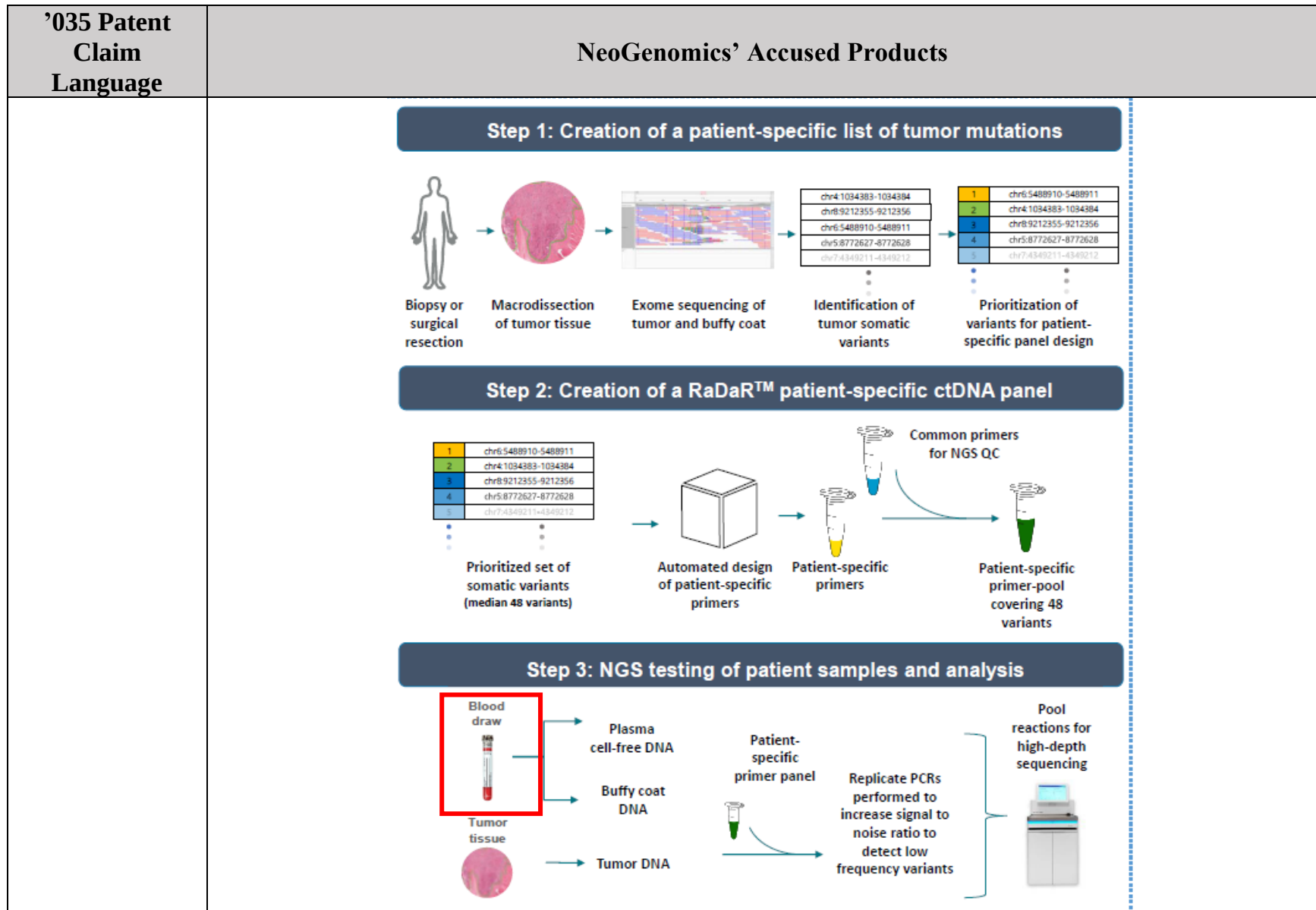
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'035 Patent Claim Language	NeoGenomics’ Accused Products
	adaptors and unique sample barcodes were attached during an additional round of PCR. The barcoding primers consist of Illumina sequencer adaptors (PE1 and PE2) at their 3’ end, a unique 10 base barcode, and the common CS1 and CS2. Permutations of the universal tags and the sequencing adaptors enabled construction of bidirectional barcoded sequencing libraries. Using custom sequencing primers directed to the two tag sequences, sequence reads representing both strands of the amplicon pool were obtained from a single-end run. Both combinations were used in order to barcode and read amplicons in both directions. All samples were then pooled, cleaned, and then sequenced.” NEOGEN00017082 (emphasis added). RaDaR also includes tagging isolated cell free DNA with one or more universal tail adaptors to generate tagged products, wherein the isolated cell-free DNA is isolated from a blood sample. For example, Lipsyc-Sharf (Doc. 1-8) states, “Blood samples were collected prospectively, spun, and stored at –80°C as plasma and buffy coat. Four milliliter of plasma and 2 mL of buffy coat samples were sent in batches to Inivata Inc. DNA was extracted from buffy coat, and circulating cell-free DNA was extracted from plasma as previously described. . . RaDaR assays were applied retrospectively in a research setting to identify plasma ctDNA (Appendix 1 and Appendix Figs A1 and A2, online only).” Lipsyc-Sharf at 2410. For example, NeoGenomics discloses that RaDaR includes a blood draw, thereby isolating cell-free DNA from a blood sample as shown below.

'035 Patent Claim Language	NeoGenomics’ Accused Products
	The diagram illustrates the RaDaR assay workflow. It begins with 'Tumor resection/ biopsy', leading to 'Macro dissection of tumor tissue and DNA isolation'. This is followed by 'Whole Exome Sequencing' (showing Exon 1, Intron 1, and Exon 2) and 'Create a personalized molecular signature for each patient through identification and ranking of somatic variants'. A 'RaDaR™ patient-specific primer panel targeting up to 48 variants' is then used. The workflow branches into two paths: one for 'Tumor DNA' and another for 'Blood Draw (2 x 10mL)'. The blood draw path involves 'Plasma cell-free DNA' and 'Buffy coat DNA', which are processed through the 'InVision Platform Library Preparation of tumor DNA, plasma cfDNA and leukocyte DNA'. This is followed by 'High depth sequencing, variant confirmation in tumor DNA, CHIP filtering and ctDNA detection'. The final step is 'Report Generation for Oncologist', showing 'ctDNA DETECTED' and 'ctDNA NOT DETECTED' results. A red box highlights the 'Blood Draw (2 x 10mL)' step. © Inivata Limited 2021. Version 1 (March 2021) FIG A1. RaDaR assay workflow. Used with permission from Inivata, Inc.³⁸ cfDNA, cell-free DNA; CHIP, clonal hematopoiesis of indeterminate potential; ctDNA, circulating tumor DNA. NEOGEN00000002 (annotated). For example, Heider (Doc. 1-6) states, “RaDaR™ is a highly sensitive personalised sequencing ctDNA assay.

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	Tumor-specific variants are first identified by exome sequencing of tumor tissue, followed by multiplex PCR and high-depth next generation sequencing to track low levels of ctDNA in patient plasma.” Heider at 1. For example, Heider (Doc. 1-6) contains the following figure showing that RaDaR includes a blood draw, thereby isolating cell-free DNA from a blood sample:



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	Doc. 1-6 (annotated). RaDaR also includes cell-free DNA isolated from a blood sample collected from a subject who is not a pregnant woman. For example, a publication by Flach et al., <i>Liquid BIOPsy for MiNimal RESidual DiSease Detection in Head and Neck Squamous Cell Carcinoma (LIONESS)—a personalised circulating tumour DNA analysis in head and neck squamous cell carcinoma</i>, BRITISH J. CANCER (2022) (https://doi.org/10.1038/s41416-022-01716-7) (hereinafter “Flach”) states, “Seventeen patients with resectable disease at the time of diagnosis were recruited into the LIONESS study and underwent longitudinal blood sampling. 103 serial plasma samples were assessed for evidence of ctDNA (Supplementary Table 3). <u>All 17 patients had blood samples taken before surgery. The median age of the study participants was 63 years (range 48–78 years), and the majority (76.5%) were male</u>, as is typical of HNSCC patients. In our cohort, all patients had either Stage III or IVa-b disease. 2/17 patients had recurrent disease and/or a second primary cancer of the head and neck at diagnosis/enrolment. . . The RaDaR™ assay demonstrated 95% sensitivity at 0.001% median VAF and 100% specificity in analytical validation studies (Supplementary Methods) and was used to analyse serial pre- and post-operative plasma samples for evidence of minimal residual disease and recurrence (Fig. 1). Personalised panels were designed with between 34 and 52 somatic variants (median 48). Tumour specific variants were detected as ctDNA pre-operatively in 100% of patients.” Flach (Doc. 1-10) at 1188 (emphasis added).
1[b]: amplifying the tagged products one or more times to	Inivata’s Accused Products meet this limitation.

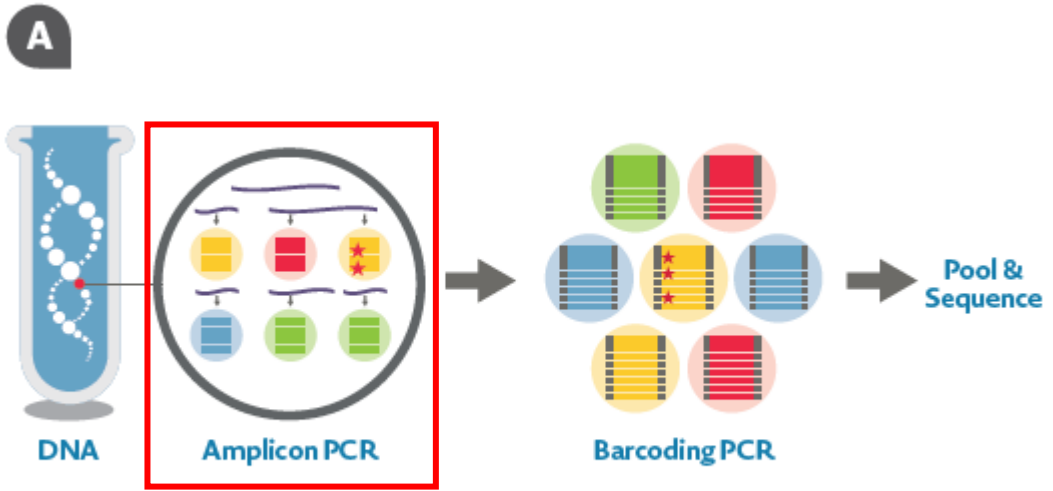
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’035 Patent Claim Language	NeoGenomics’ Accused Products
generate final amplification products, wherein one of the amplification steps comprises targeted amplification of a plurality of single nucleotide polymorphism (SNP) loci in a single reaction volume, wherein one of the amplifying steps introduces a barcode and one or more sequencing tags; and ...	For example, Inivata’s RaDaR assay includes amplifying the tagged products one or more times to generate final amplification products, wherein one of the amplification steps comprises targeted amplification of a plurality of single nucleotide polymorphism (SNP) loci in a single reaction volume. For example, Lipsyc-Sharf (Doc. 1-8) states that RaDaR’s workflow has a “Multiplex PCR and Sequencing” step. Specifically, “[a]fter primer panel qualification and DNA extraction, RaDaR multiplex PCR was performed on cfDNA from plasma alongside a buffy coat DNA control sample[.]” Lipsyc-Sharf at Appx. 1. For example, Inivata’s website (https://www.inivata.com/radar-residual-disease-and-recurrence/, (Doc. 1-5)) also states that RaDar “tracks a set of up to 48 tumor-specific variants.”

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	The RaDaR™ assay is built on Inivata’s proven InVision® liquid biopsy platform technology. This next-generation sequencing platform incorporates built-in controls and error-correction for highly sensitive and specific variant detection. RaDaR™ is a personalized assay that tracks a set of up to 48 tumor-specific variants in a patient using a liquid biopsy with exceptional sensitivity, allowing both detection of residual disease following curative intent or definitive treatment and early detection of relapse. Doc. 1-5 at 2. Gale (Doc. 1-9) discloses, for example, that the InVision “panel was designed optimizing primers for amplification of fragmented DNA with amplicon sizes ranging from 72bp-154bp.” Gale at 4. For example, Flach (Doc. 1-10) states “RaDaR™ is a personalised ctDNA assay built on the InVision® platform [43], which utilises multiplex PCR and targeted NGS. Somatic variants identified in the tumour tissue by WES were prioritised using proprietary algorithms to build a patient-specific primer panel of up to 48 primer pairs capturing at least one somatic variant (Supplementary Table 2). The personalised primer panel was manufactured (IDT, Coralville, IA) and combined with a fixed

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'035 Patent Claim Language	NeoGenomics’ Accused Products
	primer panel of 21 common population-specific SNPs for quality control purposes during the NGS testing.” Flach at 1187. For example, Flach (Doc. 1-10) states, “Following primer panel qualification, RaDaR™ assays were performed on cfDNA from plasma aliquots alongside a buffy coat DNA control sample, which was used for identification and removal of germline variants, the removal of variants due to clonal haematopoiesis of indeterminate potential (CHIP) from the analysis, and as a positive amplification control. Multiplex PCR was performed with input concentrations ranging from 1452 to 20,000 amplifiable copies per sample, as measured by droplet digital PCR, with a median value of 14,550 copies.” Flach at 1187. Inivata’s website includes a page titled “Publications and Posters,” which includes a poster presentation presented at an AACR conference by Gale et al. titled, “Analytical performance and validation of an enhanced TAm-Seq™ circulating tumor DNA sequencing assay” (herein after “Gale (2016)”, (Doc. 1-15)), showing that the RaDaR™ assay uses multiplex PCR, which amplifies multiple targets in a single reaction volume.

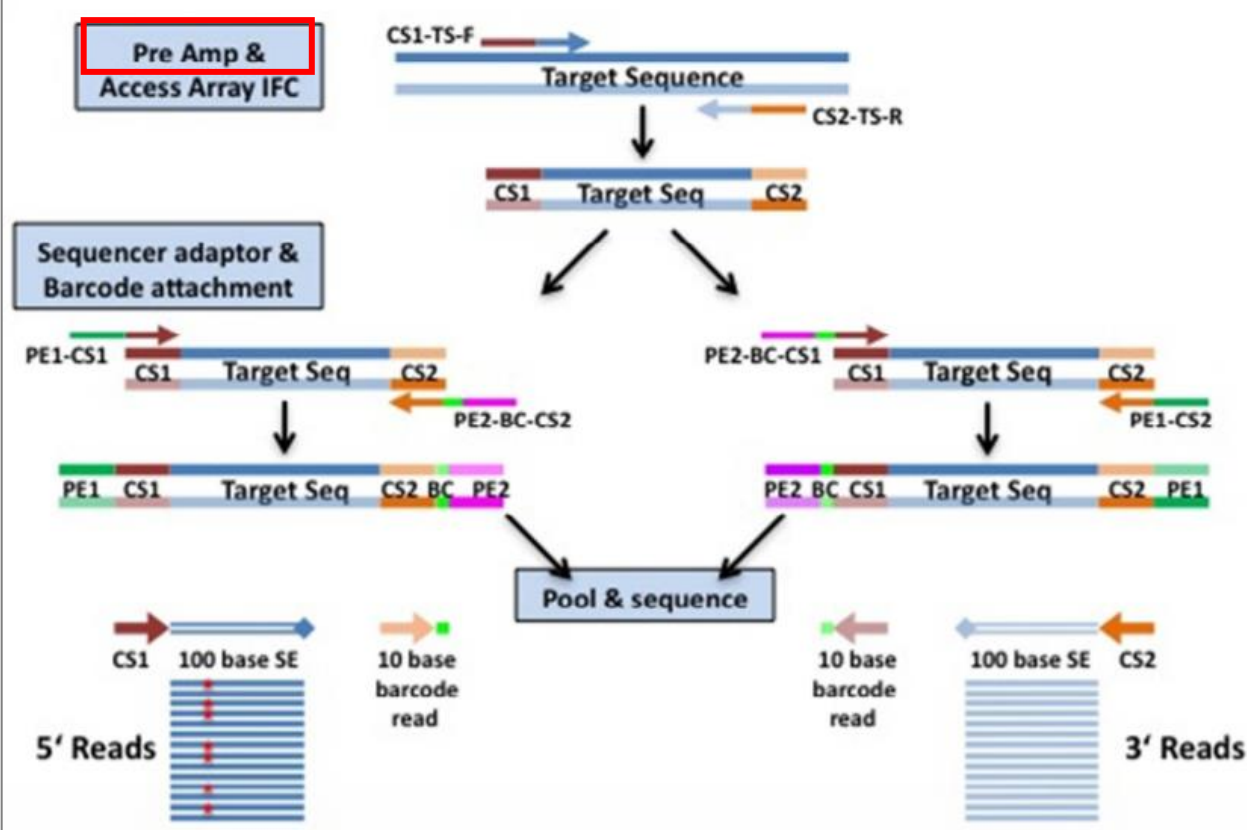
'035 Patent Claim Language	NeoGenomics’ Accused Products
	 Fig. 2A. Overview of the eTAm-Seq assay. Adapted from Forsheew et al.; Sci Trans Med; 2012;4(136):136ra68. Doc. 1-15 (annotated) In addition, for example, Inivata’s website (https://www.inivata.com/our-publications/, (Doc. 1-7) at p. 3) includes a page titled “Our Publications,” which lists a poster presentation presented at the AACR 2020 conference by Marsico et. al., entitled “Analytical development of the RaDaR™ assay, a highly sensitive and specific assay for the monitoring of minimal residual disease” (hereinafter “Marsico”). Marsico (Doc. 1-11) discloses RaDaR includes amplifying the tagged products one or more times to generate final amplification products, wherein one of the amplification steps comprises targeted amplification of a plurality of single nucleotide polymorphism (SNP) loci in a single reaction volume.

'035 Patent Claim Language	NeoGenomics’ Accused Products												
	Marsico includes a figure showing that targeted multiplex amplification occurs in the same reaction volume using a patient-specific primer-pool covering 48 variants: RaDaR™ ASSAY The workflow consists of the following steps: Biopsy or surgical resection → Macro dissection of tumor tissue → Exome sequencing → Identify tumor-specific somatic variants Step 1: Creation of a patient specific list of mutations Rank and prioritize somatic variants for patient specific panel design Step 2: Prioritization of variants Automated design of patient-specific primers → Patient-specific primer-pool covering 48 variants Step 3: Creation of a RaDaR™ patient-specific panel The diagram also includes a table of variant coordinates: <table border="1"> <tbody> <tr><td>1</td><td>chr6:5488910-5488911</td></tr> <tr><td>2</td><td>chr4:1814383-1814384</td></tr> <tr><td>3</td><td>chr4:7758851-7758852</td></tr> <tr><td>4</td><td>chr8:1821295-1821296</td></tr> <tr><td>5</td><td>chr5:8772627-8772628</td></tr> <tr><td>6</td><td>chr7:14349211-14349212</td></tr> </tbody> </table>	1	chr6:5488910-5488911	2	chr4:1814383-1814384	3	chr4:7758851-7758852	4	chr8:1821295-1821296	5	chr5:8772627-8772628	6	chr7:14349211-14349212
1	chr6:5488910-5488911												
2	chr4:1814383-1814384												
3	chr4:7758851-7758852												
4	chr8:1821295-1821296												
5	chr5:8772627-8772628												
6	chr7:14349211-14349212												

'035 Patent Claim Language	NeoGenomics’ Accused Products
	Qualified primer panel Predicted panel performance Blood draw Plasma cell-free DNA Buffy coat DNA Patient-specific primer panel Modified InVision® platform High-depth sequencing Confirm variant are present in tumor DNA. Subtract leukocyte signal (germline/CHIP) Step 4 Panel QC Step 5 NGS testing of patient samples Step 6 Sequencing analysis, QC, calling Doc. 1-11 (annotated). For example, Gale (Doc. 1-9) describes the eTAm-Seq technology used in the RaDaR assay. Gale discloses, “The development of next generation sequencing (NGS) has allowed for a broader application of ctDNA analysis. In 2012, Forshew et al. developed TAM-Seq technology, or tagged amplicon deep sequencing which, for the first time, enabled interrogation of 6 genes across a large genomic region spanning 5995 bases to detect low frequency mutations in cell-free DNA...Since this time, other NGS technologies have been implemented for analysis of ctDNA, including the use of

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	hybrid capture and the introduction of panel assays that use molecular barcodes to enable error suppression...Here we describe the development of the InVision liquid biopsy platform which utilizes enhanced TAm-Seq (eTAm-Seq™) technology for the identification of low frequency mutations in ctDNA. The assay has been expanded to target hotspots and entire coding regions from 35 cancer-related genes, utilizing a primer design strategy that allows for amplification of highly fragmented DNA, typical of ctDNA. The calling algorithm has been revised, and in addition to improved detection of single nucleotide variants (SNVs) and short insertions/deletions (indels), it also identifies copy number variants (CNVs).” Gale at 3. For example, eTAm-Seq is an enhanced version of TAm-Seq, which is depicted below. Gale at 4. The limited 15-cycle preamplification of TAm-Seq involves performing targeted multiplex amplification to amplify a plurality of SNV target loci each encompassing a different tumor-specific SNV mutation from cell-free DNA isolated from plasma sample, wherein the target loci are amplified together in the same reaction volume. NEOGEN00017099-17100. The first PCR cycle of preamplification tags cell-free DNA with universal tail adaptors CS1 and CS2. <i>See</i> NEOGEN00017082; NEOGEN00017099-17100; <i>see also</i> Doc. 145 (Metzker Reply Decl.) at ¶¶295-300. Accordingly, a person of ordinary skill in the art would recognize that these tagged products are the input for the subsequent PCR cycle wherein the tagged products are amplified. Doc. 145 (Metzker Reply Decl.) at ¶¶72, 295-300. At 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. <i>Id.</i> Moreover, as shown in “sequence adaptor & barcode attachment” stage of the same figure below, Forsheew discloses in an additional round of PCR introducing a barcode and one or more sequencing tags.

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	 The diagram illustrates the sequencing process for NeoGenomics' Accused Products. It begins with a 'Target Sequence' flanked by 'CS1' and 'CS2' sequences. This is followed by 'Pre Amp & Access Array IFC' and 'Sequencer adaptor & Barcode attachment' steps. The process then branches into two paths: one leading to '5' Reads' and another to '3' Reads'. Both paths involve 'Pool & sequence' and '10 base barcode read' steps. The final output shows '5' Reads' and '3' Reads' with '100 base SE' and '10 base barcode read' components. NEOGEN00017082 (annotated). For example, Forshew discloses that in TAm-Seq that “[t]arget-specific primers were synthesised with common adaptor sequences at their 5’ ends (CS1 and CS2). These were used during the preamplification and single-plex stages to amplify the selected regions. <u>Sequencing platform-specific</u>

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	<u>adaptors and unique sample barcodes were attached during an additional round of PCR. The barcoding primers consist of Illumina sequencer adaptors (PE1 and PE2) at their 3’ end, a unique 10 base barcode, and the common CS1 and CS2.</u> Permutations of the universal tags and the sequencing adaptors enabled construction of bidirectional barcoded sequencing libraries. Using custom sequencing primers directed to the two tag sequences, sequence reads representing both strands of the amplicon pool were obtained from a single-end run. Both combinations were used in order to barcode and read amplicons in both directions. All samples were then pooled, cleaned, and then sequenced” (emphasis added). NEOGEN00017082. To the extent NeoGenomics contends this element is not literally found in the Accused Products, the Accused Products practice this limitation under the doctrine of equivalents because the differences, if any, between the claimed inventions and the Accused Products are insubstantial and the Accused Products perform the same or substantially the same functions, in the same or substantially the same ways, to achieve the same or substantially the same results as such elements. Doc. 145 (Metzker Reply Decl.) at ¶¶301-304.
1[c]: sequencing the plurality of SNP loci on the cell free DNA by conducting massively parallel sequencing on the final amplification products,	Inivata’s Accused Products meet this limitation. For example, Inivata’s RaDaR assay includes sequencing the plurality of SNP loci on the cell free DNA by conducting massively parallel sequencing on the final amplification products, wherein the plurality of SNP loci comprises 25-2,000 loci associated with cancer. Inivata’s website (https://www.inivata.com/radar-residual-disease-and-recurrence/, (Doc. 1-5)) states that “[t]he RaDaR assay . . . tracks a set of up to 48 tumor-specific variants in a patient using a liquid biopsy with exceptional sensitivity[.]”

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wherein the plurality of SNP loci comprises 25-2,000 loci associated with cancer.	The RaDaR™ assay is built on Inivata’s proven InVision® liquid biopsy platform technology. This next-generation sequencing platform incorporates built-in controls and error-correction for highly sensitive and specific variant detection. RaDaR™ is a personalized assay that tracks a set of up to 48 tumor-specific variants in a patient using a liquid biopsy with exceptional sensitivity, allowing both detection of residual disease following curative intent or definitive treatment and early detection of relapse. Doc. 1-5 at 2. For example, Flach (Doc. 1-10) states, “RaDaR™ is a personalised ctDNA assay built on the InVision® platform [43], which utilises multiplex PCR and targeted NGS. Somatic variants identified in the tumour tissue by WES were prioritised using proprietary algorithms to build a patient-specific primer panel of up to 48 primer pairs capturing at least one somatic variant (Supplementary Table 2). The personalised primer panel was manufactured (IDT, Coralville, IA) and combined with a fixed primer panel of 21 common population-specific SNPs for quality control purposes during the NGS testing.” Flach at 1187.

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	For example, Flach (Doc. 1-10) states, “Following primer panel qualification, RaDaR™ assays were performed on cfDNA from plasma aliquots alongside a buffy coat DNA control sample, which was used for identification and removal of germline variants, the removal of variants due to clonal haematopoiesis of indeterminate potential (CHIP) from the analysis, and as a positive amplification control. Multiplex PCR was performed with input concentrations ranging from 1452 to 20,000 amplifiable copies per sample, as measured by droplet digital PCR, with a median value of 14,550 copies.” Flach at 1187. For example, Flach (Doc. 1-10) states, “RaDaR™ libraries were sequenced using the Nova-Seq 6000 system (Illumina Inc., San Diego, USA) and sequencing data analysed in a multistep process: fastq files were demultiplexed using bcl2fastq, reads were then aligned using the <i>bwa mem</i> alignment software and processed using proprietary software to identify primer pairs and count mutant and reference bases.” Flach at 1187. According to NeoGenomics, RaDaR includes sequencing the plurality of SNP loci on the cell free DNA by conducting massively parallel sequencing on the final amplification products, wherein the plurality of SNP loci comprises 25-2,000 loci associated with cancer as shown below.

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	The diagram illustrates the RaDaR assay workflow. It begins with 'Tumor resection/ biopsy', leading to 'Macro dissection of tumor tissue and DNA isolation'. This is followed by 'Whole Exome Sequencing' (showing Exon 1, Intron 1, and Exon 2) and 'Create a personalized molecular signature for each patient through identification and ranking of somatic variants'. A 'RaDaR™ patient-specific primer panel targeting up to 48 variants' is then used. The workflow branches into two paths: 'Tumor DNA' and 'Blood Draw (2 x 10mL)'. The 'Blood Draw' path involves 'Plasma cell-free DNA' and 'Buffy coat DNA', both leading to 'InVision Platform Library Preparation of tumor DNA, plasma cfDNA and leukocyte DNA'. The 'Tumor DNA' path also leads to this platform. The next step is 'High depth sequencing, variant confirmation in tumor DNA, CHIP filtering and ctDNA detection', which is highlighted with a red box. This leads to 'ctDNA DETECTED' or 'ctDNA NOT DETECTED' results, and finally 'Report Generation for Oncologist'. A copyright notice at the bottom reads: '© Inivata Limited 2021. Version 1 (March 2021)'. FIG A1. RaDaR assay workflow. Used with permission from Inivata, Inc.³⁸ cfDNA, cell-free DNA; CHIP, clonal hematopoiesis of indeterminate potential; ctDNA, circulating tumor DNA. NEOGEN00000002 (annotated). For example, Lipsyc-Sharf, Exhibit 8, states that “RaDaR is a personalized next generation sequencing (NGS) assay[,]” “[m]ultiplex polymerase chain reaction (PCR) and NGS were used to assess tumor variants in cfDNA[,]” and “[a]fter multiplex PCR, reaction-specific index barcode sequences were . . . sequences using the NovaSeq 6000 system (Illumina Inc.).” Lipsyc-Sharf at Appx. 1.

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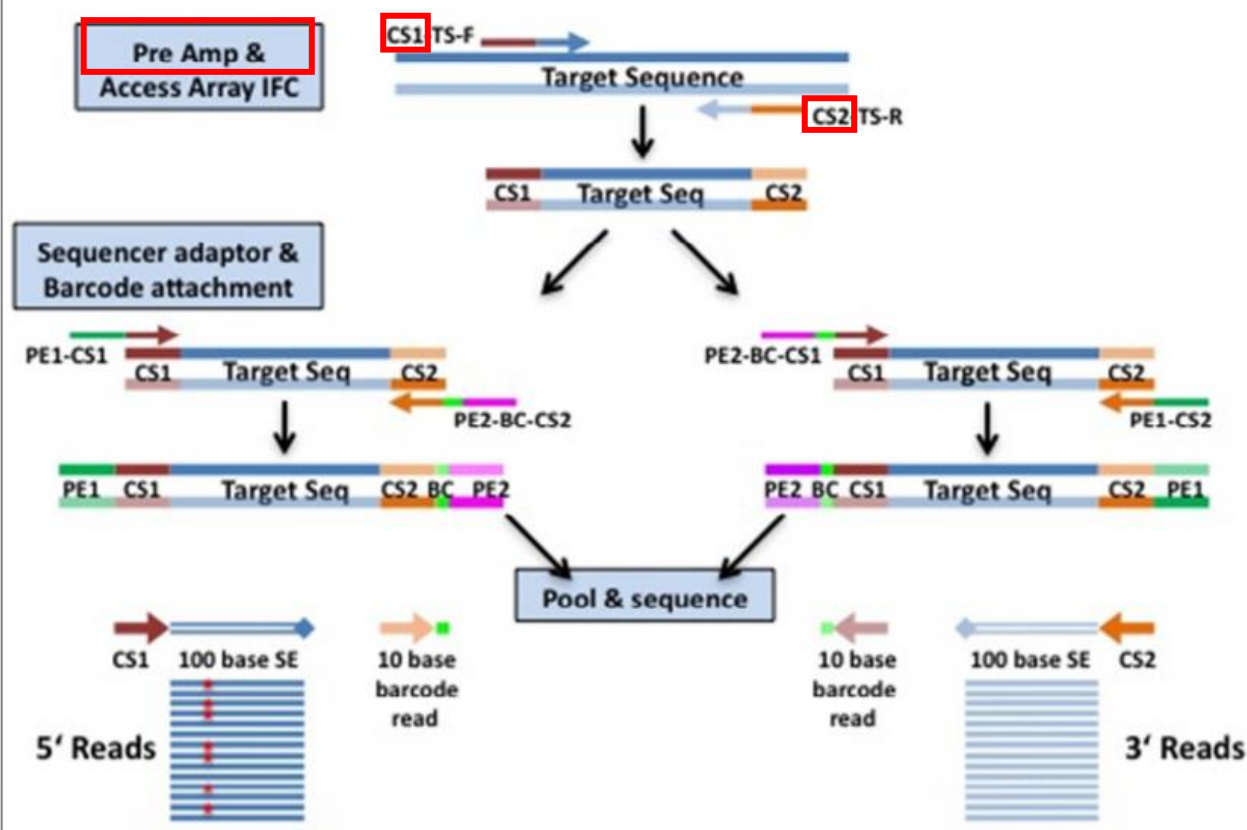
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	For example, Gale (Doc. 1-9) describes the InVision liquid biopsy platform technology used in the RaDaR assay, which includes eTAm-Seq technology to sequence a plurality of SNP loci on the cell free DNA by conducting massively parallel sequencing. Gale discloses, “Library preparation using eTAm-Seq technology. eTAm-Seq technology is based on methods previously described [22, 25,26], with an optimized assay workflow utilizing <u>multiplex PCR to enable high-throughput library preparation</u> without the use of microfluidics. <u>Next generation sequencing libraries were prepared using a two-step multiplex PCR amplification</u> process incorporating replicate and patient-specific barcodes and Illumina sequencing adaptors.” Gale at 4 (emphasis added). For example, Inivata’s website (https://www.inivata.com/our-publications/, (Doc. 1-14) at p. 2) includes a page titled “Our Publications,” which lists a poster presented at the AACR 2021 Conference by Cutts et. al, entitled “Molecular Residual Disease detection in early stage breast cancer with a personalized sequencing approach” (hereinafter “Cutts”). Cutts (Doc. 1-12) provides that, as part of RaDaR assay workflow, “cell free DNA was extracted from 147 plasma samples (median volume 4ml, range 0.5-5ml) and sequenced with RaDaR assays, with 10-61 variants (median 41) per panel, to 100,000x per locus.” - Cell free DNA was extracted from 147 plasma samples (median volume 4ml, range 0.5-5ml) and sequenced with RaDaR™ assays, with 10-61 variants (median 41) per panel, to 100,000x per locus. A matched single timepoint buffy coat was sequenced to verify removal of germline SNPs and any potential clonal hematopoiesis (CHIP). A proprietary algorithm was used to identify ctDNA. Droplet digital PCR (ddPCR) was performed as previously described^{1,2}.

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	Doc. 1-12.
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.	The Accused Products satisfy this claim limitation. According to NeoGenomics, “RaDaR differs from traditional cancer liquid-biopsy NGS tests in that it does not focus on detecting oncogenic driver or hotspot mutations. Instead, the test uses a tumor-specific information identified from exome patient’s sequencing and tracks the mutations. Inivata’s enrichment technology does not <u>involve ligation of molecular adapters to cfDNA</u>, an approach enables us to prevent molecular loss during library preparation. Additionally, the RaDaR tracks more variants than most assays and uses a bioinformatic analysis for MRD calling” (emphasis added). NEOGEN00014377. To the extent that the Accused Products do not literally satisfy this claim limitation, the Accused Products infringe under the Doctrine of Equivalents. For example, RaDaR includes tagging the cell free DNA by amplification. Under the Doctrine of Equivalents, a person of ordinary skill in the art would recognize that tagging may be performed by different methods. <i>See</i> Sept. 26, 203 Metzker Tr. at 114: 8-115:12; <i>see also</i> Oct. 25, 2023 Van Ness Depo Tr. at 215:5-10. Tagging by amplification is substantially similar to tagging by ligating the one or more universal tail adaptors to the cell free DNA because both methods of tagging perform substantially the same function of adding adaptor sequences to DNA in substantially the same way to achieve substantially the same result as the claimed method. <i>See</i> Sept. 26, 203 Metzker Tr. at 114: 8-115:12; <i>see also</i> Oct. 25, 2023 Van Ness Depo Tr. at 215:5-218:13.
12. The method of claim 1, wherein the one or more	The Accused Products satisfy this claim limitation.

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universal tail adaptors comprise a first universal tail adaptor and a second universal tail adaptor.	RaDaR involves tagging isolated cell free DNA with one or more universal tail adaptors to generate tagged products wherein the one or more universal tail adaptors comprise a first universal tail adaptor and a second universal tail adaptor. For example, Gale (Doc. 1-9) describes the InVision liquid biopsy platform technology used in the RaDaR assay, which includes eTAm-Seq technology to sequence a plurality of SNP loci on the cell free DNA by conducting massively parallel sequencing. Gale discloses, “Library preparation using eTAm-Seq technology. eTAm-Seq technology is based on methods previously described [22, 25,26], with an optimized assay workflow utilizing <u>multiplex PCR to enable high-throughput library preparation</u> without the use of microfluidics. Next generation sequencing libraries were prepared using a two-step multiplex PCR amplification process incorporating replicate and patient-specific barcodes and Illumina sequencing adaptors.” Gale at 4 (emphasis added). For example, eTAm-Seq is an enhanced version of TAm-Seq, which is depicted below. Gale at 4. The limited 15-cycle preamplification of TAm-Seq involves performing targeted multiplex amplification to amplify a plurality of SNV target loci each encompassing a different tumor-specific SNV mutation from cell-free DNA isolated from plasma sample, wherein the target loci are amplified together in the same reaction volume. NEOGEN00017099-17100. The first PCR cycle of preamplification tags cell-free DNA with universal tail adaptors CS1 and CS2. <i>See</i> NEOGEN00017082; NEOGEN00017099-17100; <i>see also</i> Doc. 145 (Metzker Reply Decl.) at ¶¶295-300. Accordingly, a person of ordinary skill in the art would recognize that in the first PCR cycle of preamplification, RaDaR involves tagging isolated cell free DNA with one or more universal tail adaptors to generate tagged products wherein the one or more universal tail adaptors comprise a first universal tail adaptor and a second universal tail adaptor.

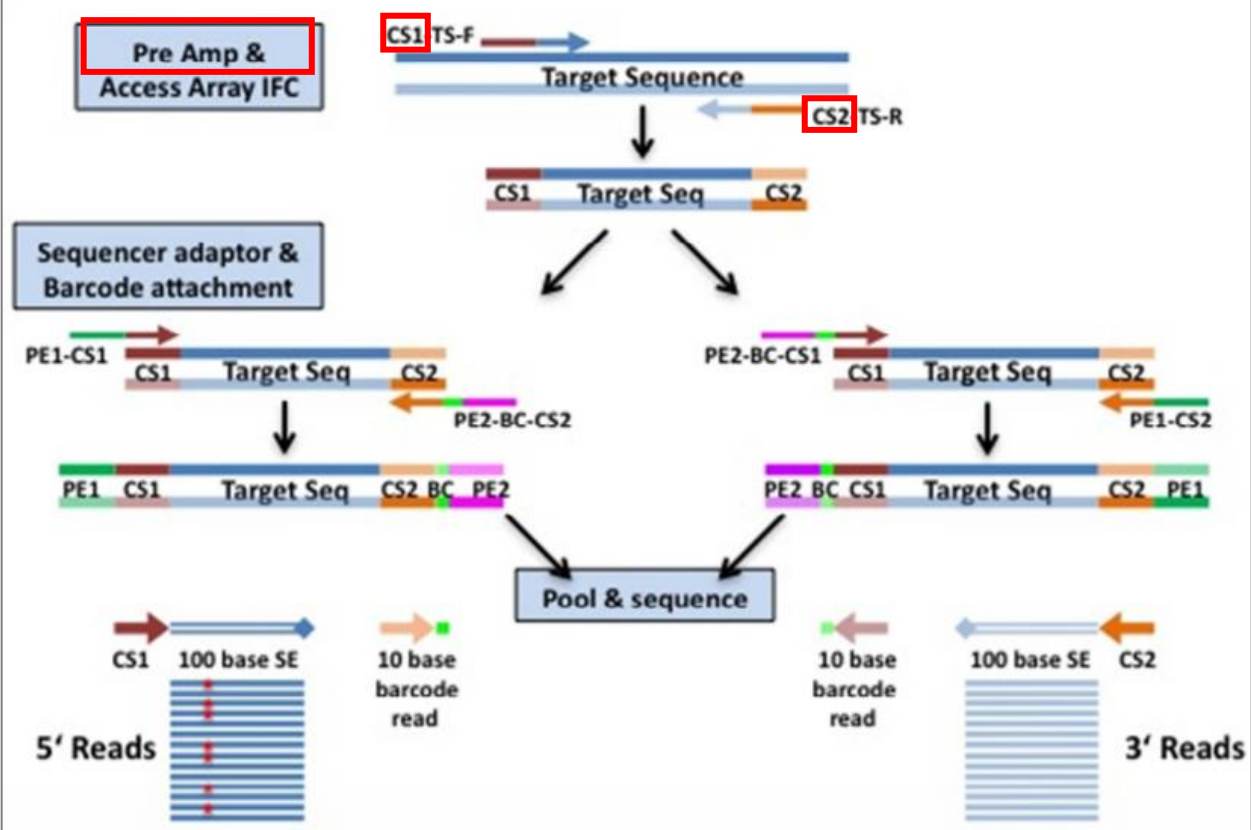
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	 The diagram illustrates the sequencing process for NeoGenomics' accused products. It begins with a 'Target Sequence' flanked by common adaptor sequences 'CS1' and 'CS2'. The process involves 'Pre Amp & Access Array IFC' and 'Sequencer adaptor & Barcode attachment'. The resulting fragments are then 'Pool & sequence'. The final output consists of '5' Reads' (100 base SE) and '3' Reads' (100 base SE), with a '10 base barcode read' in between. The diagram also shows the specific primers used: 'CS1 TS-F' and 'CS2 TS-R' for the initial amplification, and 'PE1-CS1', 'PE2-BC-CS1', 'PE2-BC-CS2', and 'PE1-CS2' for the subsequent sequencing steps. NEOGEN00017082 (annotated). According to Forshew, “Target-specific primers were synthesised with common adaptor sequences at their 5’ ends (CS1 and CS2). These were used during the preamplification and single-plex stages to amplify the selected regions. Sequencing platform-specific adaptors and unique sample barcodes were

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	<u>attached during an additional round of PCR.</u> The barcoding primers consist of Illumina sequencer adaptors (PE1 and PE2) at their 3’ end, a unique 10 base barcode, and the common CS1 and CS2. Permutations of the universal tags and the sequencing adaptors enabled construction of bidirectional barcoded sequencing libraries. Using custom sequencing primers directed to the two tag sequences, sequence reads representing both strands of the amplicon pool were obtained from a single-end run. Both combinations were used in order to barcode and read amplicons in both directions. All samples were then pooled, cleaned, and then sequenced” (emphasis added). NEOGEN00017082.
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.	The Accused Products satisfy this claim limitation. RaDaR involves tagging isolated cell free DNA with one or more universal tail adaptors to generate tagged products 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. For example, Gale (Doc. 1-9) describes the InVision liquid biopsy platform technology used in the RaDaR assay, which includes eTAm-Seq technology to sequence a plurality of SNP loci on the cell free DNA by conducting massively parallel sequencing. Gale discloses, “Library preparation using eTAm-Seq technology. eTAm-Seq technology is based on methods previously described [22, 25,26], with an optimized assay workflow utilizing <u>multiplex PCR to enable high-throughput library preparation</u> without the use of microfluidics. Next generation sequencing libraries were prepared using a two-step multiplex PCR amplification process incorporating replicate and patient-specific barcodes and Illumina sequencing adaptors.” Gale at 4 (emphasis added). For example, eTAm-Seq is an enhanced version of TAm-Seq, which is depicted below. Gale at 4. The limited 15-cycle preamplification of TAm-Seq involves performing targeted multiplex amplification to amplify a plurality of SNV target loci each encompassing a different tumor-specific SNV mutation

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	from cell-free DNA isolated from plasma sample, wherein the target loci are amplified together in the same reaction volume. NEOGEN00017099-17100. The first PCR cycle of preamplification tags cell-free DNA with universal tail adaptors CS1 and CS2. <i>See</i> NEOGEN00017082; NEOGEN00017099-17100; <i>see also</i> Doc. 145 (Metzker Reply Decl.) at ¶¶295-300. Accordingly, a person of ordinary skill in the art would recognize that in the first PCR cycle of preamplification, RaDaR involves tagging isolated cell free DNA with one or more universal tail adaptors to generate tagged products 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.

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	<u>attached during an additional round of PCR.</u> The barcoding primers consist of Illumina sequencer adaptors (PE1 and PE2) at their 3’ end, a unique 10 base barcode, and the common CS1 and CS2. Permutations of the universal tags and the sequencing adaptors enabled construction of bidirectional barcoded sequencing libraries. Using custom sequencing primers directed to the two tag sequences, sequence reads representing both strands of the amplicon pool were obtained from a single-end run. Both combinations were used in order to barcode and read amplicons in both directions. All samples were then pooled, cleaned, and then sequenced” (emphasis added). NEOGEN00017082.