

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

GUARDANT HEALTH, INC.,)	
)	
Plaintiff,)	
)	C.A. No. 24-687-RGA
v.)	
)	JURY TRIAL DEMANDED
TEMPUS AI, INC.,)	
)	
Defendant.)	

PLAINTIFF’S FIRST AMENDED COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff Guardant Health, Inc. (“Guardant”) files this First Amended Complaint for Patent Infringement against Defendant Tempus AI, Inc. (“Tempus”) and alleges as follows:

OVERVIEW OF THE ACTION

1. This action is necessitated by Tempus’s unauthorized use of Guardant’s groundbreaking, patented innovations in the field of cancer diagnostics. Specifically, this is an action against Tempus for infringement of Guardant’s U.S. Patent Nos. 11,149,306 (the “306 Patent”), 9,902,992 (the “992 Patent”), 10,501,810 (the “810 Patent”), 10,793,916 (the “916 Patent”), and 11,643,693 (the “693 Patent”) (collectively, the “Patents-in-Suit”). Tempus’s infringement of the Patents-in-Suit has caused and is causing ongoing harm to Guardant. Guardant brings this suit to stop Tempus’s infringement and enjoin Tempus from practicing Guardant’s patented inventions. And Tempus must compensate Guardant for the infringement and injury that has already occurred.

2. Guardant is a leading precision oncology company dedicated to helping conquer cancer with data obtained through its proprietary blood tests. Guardant was founded over a decade ago by Helmy Eltoukhy, Ph.D., and AmirAli Talasaz, Ph.D., pioneers in DNA sequencing and cancer diagnostics. Since its inception, Guardant has focused its expertise on the development of

groundbreaking liquid biopsy cancer tests, including Guardant360[®] CDx, the first FDA-approved liquid biopsy test. To date, over 500,000 patient samples have been analyzed using Guardant's tests.

3. A liquid biopsy is the sampling and analysis of non-solid biological tissues, such as a patient's blood. It is distinct from a conventional biopsy, which involves the removal of tissue for examination and is often conducted surgically. All cells in the human body contain DNA. When a person's organ or tissues suffer from disease such as cancer, the DNA in the cells making up the organ or tissue may contain biomarkers that indicate the presence of the disease. Traditionally, a biopsy would need to extract cells from a particular organ or tissues of interest. The DNA from those cells would then be analyzed for biomarkers.

4. But pieces of DNA originating from cells in many different organs and tissues also circulate freely in the human bloodstream. These DNA fragments circulating in the bloodstream are known as "cell-free DNA" or "cfDNA." A simple, non-invasive blood draw can capture cell-free DNA originating from cells in many different organs and tissues all at once. That DNA can then be analyzed for relevant biomarkers indicating the presence of disease. But using cell-free DNA in the bloodstream to look for biomarkers raises substantial complexity and problems. A traditional biopsy provides a very large sample of DNA from a particular type of cell. With cell-free DNA, very small numbers of DNA fragments originating from the cells of interest may be present, mixed in with very large numbers of DNA fragments from many other cells.

5. Guardant is a pioneer in the field and solved many of the problems critical to unlocking the use of cell-free DNA to detect cancer and other disease in the blood. For example, Guardant was one of the first companies to commercialize a comprehensive liquid biopsy test to identify genomic biomarkers. Guardant's liquid biopsy technology enables patients, including

those who are ineligible for traditional tissue biopsies, to obtain detailed genomic information about their cancer. Guardant's technology also allows patients to be screened for a large number of potential cancers or diseases that may be present in different parts of the body, all with a simple blood draw.

6. For example, the Guardant360[®] CDx test is a liquid biopsy test that provides clinically actionable information from a routine blood draw taken from cancer patients. From the extracted cell-free DNA, the test sequences a panel of genes commonly mutated in cancer and detects genetic aberrations such as single nucleotide variants, indels (insertions or deletions of nucleotides), gene fusions, and copy number variants.

7. In addition to the FDA-approved Guardant360[®] CDx test, Guardant currently offers six other tests: the Guardant360[®] laboratory developed test (LDT), the Guardant360 Response[™], Guardant360 TissueNext[™], Guardant Infinity[™], Guardant Reveal[™], and Shield[™] tests. These tests span the cancer care continuum, including early cancer screening, treatment selection, and residual disease and recurrence monitoring.

8. Guardant's liquid biopsy technology has several additional advantages when compared to traditional tissue biopsies. Traditional tumor-based genotyping tests are limited in the number of genes interrogated, require invasive biopsies, and often take upwards of 15 days before results are generated. Guardant's liquid biopsies are less painful and do not require hospital services. This technology is also less expensive and generates results in a shorter period of time, often in less than a week. Further, cfDNA samples allow for the detection of mutations that may be missed by a tissue biopsy sample.

9. Guardant's technology is built on a series of cutting-edge innovations that Guardant's scientists developed over many years and at great cost through an extensive research

and development program. Those innovations are protected by over 95 patents issued by the United States Patent and Trademark Office, including the Patents-in-Suit. These patents were issued in recognition of the novelty and usefulness of Guardant's patents.

10. Tempus was founded in 2015. Since its inception, Tempus has capitalized on Guardant's pioneering efforts to develop copy-cat cell-free DNA liquid biopsy tests. Tempus was formerly known as Tempus Labs, Inc.

11. Tempus makes, markets, and uses liquid biopsy panels in ways that practice Guardant's Patents-In-Suit. One such category of liquid biopsy panels includes products known as Tempus xF, Tempus xF+, and Tempus xM Monitor. These panels, and others that may function in relevantly similar ways, will be referred to as the "Accused xF Tests." More recently, Tempus has developed a second generation of liquid tests known as Tempus xM MRD. The Tempus xM MRD will be referred to as the "Accused xM Tests." Together, the Accused xF Tests and the Accused xM Tests will be referred to collectively as the "Accused Tests."

12. On information and belief, Tempus has been monitoring Guardant's intellectual property portfolio while making the Accused Tests. For example, in Tempus's S-1 filing dated May 20, 2024,¹ Tempus stated the following:

The intellectual property landscape in the next generation sequencing, generative AI, and other fields in which we operate continues to evolve in ways that may impact our business. For example, we are aware of patent litigation involving certain disciplines in which we operate, such as liquid biopsy sequencing methods and minimal residual disease testing methods. While we are not a party to these suits, many of our competitors are or have been, including Guardant Health, Inc., Haystack Oncology, Inc., Invitae Corp., Illumina, Inc., Natera, Inc., NeoGenomics Laboratories, Inc., Personalis, Inc., TwinStrand Biosciences, Inc., and others, and, as a result, we have monitored and continue to

¹ Available at <https://www.sec.gov/Archives/edgar/data/1717115/000119312524142956/d221145ds1.htm>

monitor their developments and their potential impact on the Company. Given the uncertainty of outcomes of patent litigation disputes, we have not determined whether our products and services could be subject to potential claims of patent infringement based on the patents at issue in these or other cases, whether we may need to modify or change any existing or planned sequencing procedures, or whether any of the patents at issue are valid or enforceable against us. However, it is possible that we will be subject to claims of patent infringement and that we may need to either modify our existing or future sequencing methods or license intellectual property from third parties, both of which could be time consuming and expensive.

13. As shown above, Tempus “monitored and continue[s] to monitor” patent litigation involving Guardant and the potential impact of Guardant’s patents on Tempus. Tempus also understands that because of Guardant’s intellectual property, Tempus may need to “modify [its] existing or future sequencing methods.”

14. Tempus has achieved market success with its Accused Tests. But, as described below, that success derives from Tempus’s unauthorized use of Guardant’s pioneering inventions.

THE PARTIES

15. Guardant is a corporation organized and existing under the laws of the state of Delaware, having its principal place of business at 3100 Hanover Street, Palo Alto, CA 94034.

16. Tempus is a corporation organized and existing under the laws of the state of Delaware. Its principal place of business is 600 West Chicago Avenue, Suite 510, Chicago, Illinois 60654.

JURISDICTION AND VENUE

17. This civil action arises under the patent laws of the United States, 35 U.S.C. § 1 *et seq.*, including without limitation 35 U.S.C. §§ 271, 281, 283, 284, and 285. Accordingly, this Court has subject matter jurisdiction under, *inter alia*, 28 U.S.C. §§ 1331, 1338(a), 2201 and 2202. This Court has personal jurisdiction over Tempus because Tempus is subject to general and

specific jurisdiction in the state of Delaware. Tempus is subject to personal jurisdiction at least because Tempus is a Delaware corporation and resides in this District. Tempus has made certain minimum contacts with Delaware such that the maintenance of this suit does not offend traditional notions of fair play and substantial justice.

18. The exercise of personal jurisdiction comports with Tempus's right to due process because, as described above, Tempus has purposefully availed itself of the privilege of Delaware corporate laws such that it should reasonably anticipate being haled into court here.

19. Venue is proper in this District pursuant to 28 U.S.C. §§ 1391 and 1400(b) because, among other things, Tempus is incorporated in Delaware.

THE GUARDANT PATENTS-IN-SUIT

20. On October 19, 2021, the United States Patent and Trademark Office lawfully issued U.S. Patent No. 11,149,306, entitled "Methods and systems for detecting genetic variants." A true and correct copy of the patent is attached hereto as Exhibit A. Guardant is the owner and assignee of all right, title, and interest in and to the '306 Patent, including the right to assert all causes of action arising under the '306 Patent and the right to sue and obtain any remedies for past, present, or future infringement.

21. On February 27, 2018, the United States Patent and Trademark Office lawfully issued U.S. Patent No. 9,902,992, entitled "Systems and methods to detect rare mutations and copy number variation." A true and correct copy of the patent is attached hereto as Exhibit B. Guardant is the owner and assignee of all right, title, and interest in and to the '992 Patent, including the right to assert all causes of action arising under the '992 Patent and the right to sue and obtain any remedies for past, present, or future infringement.

22. On December 10, 2019, the United States Patent and Trademark Office lawfully issued U.S. Patent No. 10,501,810, entitled “Systems and methods to detect rare mutations and copy number variation.” A true and correct copy of the patent is attached hereto as Exhibit C. Guardant is the owner and assignee of all right, title, and interest in and to the ’810 Patent, including the right to assert all causes of action arising under the ’810 Patent and the right to sue and obtain any remedies for past, present, or future infringement.

23. On October 6, 2020, the United States Patent and Trademark Office lawfully issued U.S. Patent No. 10,793,916, entitled “Methods and systems for detecting genetic variants.” A true and correct copy of the patent is attached hereto as Exhibit D. Guardant is the owner and assignee of all right, title, and interest in and to the ’916 Patent, including the right to assert all causes of action arising under the ’916 Patent and the right to sue and obtain any remedies for past, present, or future infringement.

24. On May 9, 2023, the United States Patent and Trademark Office lawfully issued U.S. Patent No. 11,643,693, entitled “Compositions and methods for isolating cell-free DNA.” A true and correct copy of the patent is attached hereto as Exhibit E. Guardant is the owner and assignee of all right, title, and interest in and to the ’693 Patent, including the right to assert all causes of action arising under the ’693 Patent and the right to sue and obtain any remedies for past, present, or future infringement.

TEMPUS’S INFRINGEMENT OF GUARDANT’S PATENTS-IN-SUIT

25. In or around September 14, 2018, Tempus announced the release of its Tempus xF liquid biopsy test, describing it as “a non-invasive genomic sequencing panel” that “analyzes 77 genes.” Press Release titled “Tempus Adds Tempus xF, a Liquid Biopsy Assay, to Sequencing Capabilities press release,” <https://www.tempus.com/news/pr/tempus-adds-tempus-xf-a-liquid->

biopsy-assay-to-sequencing-capabilities/ (last visited October 25, 2024). On or around July 12, 2021, Tempus published a press release announcing the results of a validation study purporting to demonstrate “the reliable analytical performance of the Tempus xF liquid biopsy.” Press release titled “Tempus xF Liquid Biopsy Assay Demonstrates Extensive Analytical and Clinical Validity in npj Precision Oncology Study,” <https://www.tempus.com/news/pr/tempus-xf-liquid-biopsy-assay-demonstrates-extensive-analytical-and-clinical-validity-in-npj-precision-oncology-study/> (last visited October 25, 2024).

26. The validation study for Tempus xF was authored by scientists affiliated with Tempus, including J. Finkle, and is titled “Validation of a liquid biopsy assay with molecular and clinical profiling of circulating tumor DNA.” It was published in the Journal of Precision Oncology on July 2, 2021. On information and belief, this paper describes the methodology that Tempus uses in its Tempus xF liquid biopsy test. This paper will be referred to as “Finkle” and attached as Exhibit F.

27. On or around June 3, 2022, Tempus published a press release announcing the launch of Tempus xF+, which it described as “a new non-invasive, liquid biopsy panel of 523 genes, focused on pathogenic mutations in cell-free DNA (cfDNA).” Press release titled “Tempus to Launch Largest Clinically Available Liquid Biopsy Panel, xF+,” <https://www.tempus.com/news/pr/tempus-to-launch-largest-clinically-available-liquid-biopsy-panel-xf/> (last visited October 25, 2024). In this same press release, Tempus stated that it “expects that the xF+ panel will be the largest clinically available liquid biopsy panel on the market, covering more genes with single nucleotide variants and indels reported in all genes, plus expanded coverage of translocations/gene rearrangements, and copy number variants.” On information and

belief, Tempus xF+ and Tempus xF operate in a substantially similar manner, with the largest difference being the number of genes targeted by each product.

28. Tempus's xF liquid biopsy test detects cell-free DNA in blood specimens of patients with advanced solid tumors. The test is capable of detecting mutations in 105 genes, including Single Nucleotide Variants (SNVs) and insertions and deletions (INDELs), as well as Copy Number Gains (CNGs) in 6 genes, and gene rearrangements in 7 genes. The test covers recurrent hotspot mutations in 70 genes. Microsatellite Instability High (MSI-H) status is also reported when detected. Blood Tumor Mutational Burden (bTMB) status is also reported when detected. *See, e.g.,* Tempus xF Validation specifications document, available at https://www.tempus.com/wp-content/uploads/2024/03/Tempus-xF_Validation.pdf.

29. Tempus's xF+ test covers clinically relevant exons and select non-coding regions in 523 genes and is capable of detecting mutations in four variant classes: single nucleotide variants (SNVs) and insertion-deletions (INDELs) in 523 genes; copy number gains (CNGs) in 7 genes; and gene rearrangements in 10 genes. Blood Tumor Mutational Burden (bTMB) as well as detected Microsatellite Instability High (MSI-H) will be reported by the test. *See, e.g.,* Tempus xF+ Validation specifications document, available at https://www.tempus.com/wp-content/uploads/2024/02/Tempus-xFPlus_Validation.pdf.

30. On or around November 3, 2023, Tempus published a press release announcing the launch of Tempus xM Monitor (formerly xF Monitor), which it described as “detect[ing] and monitor[ing] changes in circulating tumor fraction to determine early response to immunotherapy for patients with advanced cancers.” Press release titled “Tempus Announces New ctDNA Assay, xM Monitor,” <https://www.tempus.com/news/tempus-announces-new-ctdna-assay-xm-monitor/> (last visited October 25, 2024). In this same press release, Tempus stated that “xM Monitor is now

available for research use only for both Tempus' 105-gene liquid test, xF, and Tempus' 523-gene liquid assay, xF+." The Tempus xM Monitor uses the Tempus xF+ and Tempus xF Tests as inputs.

31. On information and belief, Tempus performs the xF and xF+ tests at facilities in the United States on a regular basis. *See, e.g.*, Tempus xF Validation specifications document, available at https://www.tempus.com/wp-content/uploads/2024/03/Tempus-xF_Validation.pdf. When using the Accused xF Tests, Tempus obtains samples of cell-free DNA from subjects. The cell-free DNA is ligated to adapters, including ligating unique molecular identifiers (UMIs) to the ends of each cell-free DNA fragment, with these UMIs including 96 different pairs of barcodes. On information and belief, Tempus uses a quantity of adapters having a number of moles more than ten times the number of moles of cell-free DNA in the sample, and these adapters are ligated to the cell-free DNA with an efficiency of 20 percent or more.

32. Subsequent to ligating the adapters to a cell-free DNA sample, Tempus amplifies and sequences the ligated cell-free DNA to generate sequence reads. Tempus maps the sequence reads to a reference sequence. Tempus groups these reads into families based on the barcodes (UMIs) as well as the alignment of the sequence reads to the reference sequence. Families are then collapsed into consensus sequences, each representing a unique sequence read corresponding to the sequence of an original cell-free DNA fragment. Reads failing to meet a set accuracy, quality score, or mapping score threshold are filtered out.

33. The consensus sequence reads are then used to determine the presence of genetic variants including copy number variations (CNVs), rearrangements, insertions, deletions, microsatellite instabilities (MSIs), single nucleotide variations (SNV), and gene fusions.

34. On or around January 18, 2024, Tempus published a press release announcing the launch of Tempus xM MRD, which it described as a process to "Assess Minimal Residual

Disease.” Press release titled “Tempus Introduces xM MRD to Assess Minimal Residual Disease (MRD) in Patients with Colorectal Cancer (CRC) for Research Use Only,” <https://www.tempus.com/news/tempus-introduces-xm-to-assess-minimal-residual-disease-mrd-in-patients-with-colorectal-cancer-crc-for-research-use-only/> (last visited October 25, 2024). In this same press release, Tempus stated that the xM MRD “assay delivers a binary MRD assessment based on both methylation and genomic variant MRD classifiers+.” On information and belief, Tempus performs the xM MRD tests at facilities in the United States on a regular basis. On information and belief, when using the xM MRD Test, Tempus performs steps substantially similar to the steps performed with the tests used in the Tempus xF+ and Tempus xF Tests, and Tempus also analyses consensus sequences generated from the test to detect methylation profiles including at least the detection of methylation.

FIRST COUNT
(Infringement of '306 Patent) (All Accused Tests)

35. Guardant repeats and re-alleges the foregoing paragraphs as if set forth specifically herein.

36. The claims of the '306 Patent are valid and enforceable.

37. The claims of the '306 Patent are directed to patentable subject matter. The '306 Patent is directed to new techniques for detecting genetic variants such as copy number variations associated with a particular disease in cell free DNA for early disease detection. '306 Patent at Abstract.

38. Disorders that are caused by rare genetic mutations (e.g., sequence variations) or changes in epigenetic markers, such as cancer and partial or complete aneuploidy, may be detected or more accurately characterized with DNA sequence information. *Id.* at 1:26-30. Early detection and monitoring of genetic diseases are useful and needed to successfully treat or manage a disease.

In the prior art, methods were developed to estimate copy number variations, but those methods involve preparing a sample by converting the original nucleic acids into a sequenceable library, followed by massively parallel sequencing, and then conducting a bioinformatic analysis to estimate the copy number variation at one or more loci. *Id.* at 1:51–55. The '306 patent states that although known methods for detecting cfDNA could reduce the errors introduced by the sample preparation and sequencing processes for the molecules that are converted and sequenced, these methods are not able to infer the counts of molecules that were converted, but not sequenced. *Id.* at 1:59–63. The '306 patent states this inability to count converted but unsequenced molecules “can dramatically and adversely affect the sensitivity that can be achieved.” *Id.* at 1:63–67.

39. The '306 Patent claims solve these deficiencies in the prior art by describing an innovative technique for sequencing and analyzing cell free DNA samples, including a new technique for tagging physical DNA strands and estimating the number of unseen molecules using a specific number of different combinations of molecular barcodes for tagging and using a mean of an expected number of duplicate molecules in a sample population.

40. The '306 patent thus provides a new and unconventional way of sequencing and analyzing DNA samples not found in the prior art. For example, the '306 patent describes tagging and counting both halves of double-stranded DNA and estimating the number of unseen molecules based on the number of pairs (i.e., molecules where both strands were identified) and singlets (i.e., molecules where only one strand was identified) detected in a particular region. *See id.* at 2:1-18.

41. The asserted claims describe innovations for reducing or tracking redundancy of sequence reads for genetic testing by, *inter alia*, an unconventional method involving non-unique duplex tagging to infer information about DNA. *See, e.g.*, '306 Patent at cls. 1-29.

42. Independent Claim 1 of the '306 Patent, for example, recites:

1. A method, comprising:

(a) providing a population of cell-free deoxyribonucleic acid (cfDNA) molecules having first and second complementary strands;

(b) tagging a plurality of the cfDNA molecules in the population with duplex tags comprising molecular barcodes to produce tagged parent polynucleotides, wherein the duplex tags are attached to both ends of a molecule of the plurality of the cfDNA molecules, wherein the plurality of the cfDNA molecules are tagged with n different combinations of molecular barcodes, wherein n is at least 2 and no more than $100,000 \cdot z$, wherein z is a mean of an expected number of duplicate molecules in the population of cfDNA molecules that map to identical start and stop positions on a reference sequence;

(c) amplifying a plurality of the tagged parent polynucleotides to produce amplified progeny polynucleotides;

(d) sequencing at least a subset of the amplified progeny polynucleotides to produce a set of sequence reads; and

(e) reducing or tracking redundancy of a plurality of sequence reads from the set of sequence reads using at least sequencing information from the molecular barcodes of the duplex tags to determine distinct cfDNA molecules from among the tagged parent polynucleotides, wherein the distinct cfDNA molecules are determined based on (i) paired reads corresponding to sequence reads generated from a first tagged strand and a second tagged complementary strand derived from cfDNA molecules from among the tagged parent polynucleotides, or (ii) unpaired reads corresponding to sequence reads generated from a first tagged strand having no second tagged complementary strand derived from cfDNA molecules from among the tagged parent polynucleotides, wherein reducing or tracking the redundancy of the plurality of sequence reads comprises mapping at least a subset of the plurality of sequence reads to the reference sequence.

43. The innovations in the '306 Patent claims were not conventional, well-understood, or routine. Indeed, the U.S. Patent and Trademark Office ("USPTO" or "Patent Office") found the '306 Patent claims patentable over certain prior art. Ex. L. As one example, the USPTO found the '306 Patent's innovations include the claim element found in claim 1 and its dependent claims 2-16, 29:

tagging a plurality of cfDNA molecules with duplex tags comprising molecular barcodes to produce tagged parent polynucleotides, wherein the duplex tags are attached to both ends of a molecule of the cfDNA molecules.

44. According to the USPTO, this claim element, in combination with other elements recited in the claims, was not present in the cited prior art. *See id.* at 15-16. It is thus unconventional, not routine, and not well-understood, including as shown by the USPTO's decision.

45. Furthermore, independent claim 1 and its dependent claims 2-16, 29 recite:

wherein the plurality of the cfDNA molecules are tagged with n different combinations of molecular barcodes, wherein n is at least 2 and no more than $100,000 * z$, wherein z is a mean of an expected number of duplicate molecules in the population of cfDNA molecules that map to identical start and stop positions on a reference sequence.

This element, in combination with the other elements of the claims, was not present in the prior art. The USPTO found this innovation is directed to solving a problem of ensuring enough tags to differentiate "cognates" (i.e., original cfDNA fragments with identical start and stop mappings) while still allowing use of non-unique tags. The technique of applying between 2 and $100,000 * z$ different combinations of molecular barcodes for tagging and tracking cfDNA molecules was not taught in the prior art and improves the functionality of tagging for DNA fragments. *See Ex. M* (finding claim reciting similar limitation non-obvious in final written decision), *vacated in part on other grounds sub nom. Guardant Health, Inc. v. Vidal*, No. 2021-1104, 2023 U.S. App. LEXIS 11037 (Fed. Cir. May 5, 2023) (vacating finding of obviousness for other claims). It is thus unconventional, not routine, and not well-understood, including as shown by the USPTO's decision.

46. Even further, the innovations of the '306 Patent claims involve determining paired and unpaired molecules. For example, independent claim 1 and its dependent claims 2-16 and 29 involve:

determin[ing] distinct cfDNA molecules from among the tagged parent polynucleotides, wherein the distinct cfDNA molecules are ***determined based on (i) paired reads*** corresponding to sequence reads generated from a first tagged strand and a second tagged complementary strand derived from cfDNA molecules from among the tagged parent polynucleotides, ***or (ii) unpaired reads*** corresponding to sequence reads generated from a first tagged strand having no second tagged complementary strand derived from cfDNA molecules from among the tagged parent polynucleotides.

'306 Patent at cl. 1 (emphasis added). The claimed determining of paired and unpaired molecules is unconventional, not routine, and not well-understood in the art, including as shown by the prosecution history of the '306 patent.

47. As another example, independent claim 17 of the '306 Patent recites:

17. A method, comprising:

(a) tagging a population of double-stranded cell-free deoxyribonucleic acid (cfDNA) molecules obtained or derived from a sample of a subject with a set of tags comprising molecular barcodes to produce tagged parent polynucleotides;

(b) amplifying a plurality of the tagged parent polynucleotides to produce amplified progeny polynucleotides;

(c) sequencing at least a subset of the amplified progeny polynucleotides to produce a set of sequence reads; and

(d) sorting a plurality of sequence reads from the set of sequence reads into (i) families comprising ***paired reads*** corresponding to sequence reads generated from a first tagged strand and a second tagged complementary strand derived from double-stranded cfDNA molecules from among the tagged parent polynucleotides, and (ii) families comprising ***unpaired reads*** corresponding to sequence reads generated from a first tagged strand having no second tagged complementary strand derived from double-stranded cfDNA molecules from among the tagged parent polynucleotides.

Id. at cl. 17 (emphasis added). The claimed determining of paired and unpaired molecules is unconventional, not routine, and not well-understood in the art, including as shown by the prosecution history of the '306 patent.

48. Similarly, Claim 17 and its dependent claims 18-28 include the element:

sorting a plurality of sequence reads from the set of sequence reads into (i) families comprising paired reads . . . and (ii) families comprising unpaired reads.

Id. at 16.

49. The Patent Office confirmed that detecting paired and unpaired molecules was a non-obvious technical improvement over the cited prior art. *See* Ex. L at 15-16, 27. Thus, determining paired and unpaired molecules was not well-understood, routine, or conventional, as it is directed to improvements in error reduction and counting of cfDNA molecules, including improvements in assessing cfDNA fragments that were present in a sample but not sequenced.

50. As another example, dependent claims 4 and 6 recite:

4. The method of claim 1, wherein the molecular barcodes are ligated to the plurality of the cfDNA molecules using more than a 10× excess of duplex tags as compared to the population of cfDNA molecules, wherein at least 20% of the cfDNA molecules from the population are tagged with the duplex tags.

6. The method of claim 5, wherein at least 40% of the cfDNA molecules from the population are tagged with the duplex tags.

51. The USPTO found the specific percentages “at least 20%” and “at least 40%” of the cfDNA molecules that must be tagged with duplex tags using more than a 10× molar excess of adapters to be novel and nonobvious over the prior art. Ex. L at 37-43. These steps were thus not conventional, routine, or well-understood.

52. Additionally, not only are the elements identified above unconventional and innovative, the ordered combination of the elements of each of the '306 Patent claims recites an

invention that is not routine or conventional, including as shown by the prosecution history of the '306 patent and the IPR decisions cited herein.

53. In sum, the '306 Patent claim elements, individually and as an ordered combination, present an innovative technique for sequencing cell free DNA that was neither conventional nor routine nor well-understood.

54. Each of the Accused Tests, and Tempus's use of each of the Accused Tests, practices steps that are identical or equivalent to each claimed element of the patented invention pointed out by at least claim 1 of the '306 Patent.

55. Tempus is not licensed or otherwise authorized to practice the claims of the '306 Patent.

56. On information and belief, Tempus has infringed and continues to infringe one or more claims of the '306 patent pursuant to 35 U.S.C. § 271(a), including at least claim 1, literally or under the doctrine of equivalents, by its use of the Accused Tests within the United States, without authority. As an example, attached as Exhibit G is a preliminary and exemplary claim chart illustrating one way in which Tempus infringes claim 1 of the '306 patent.

57. Thus, by its acts, Tempus has injured Guardant and is liable to Guardant for directly infringing one or more claims of the '306 Patent, whether literally or under the doctrine of equivalents.

58. As a result of Tempus's infringement of the '306 Patent, Guardant has suffered monetary damages, and seeks recovery, in an amount to be proven at trial, adequate to compensate for Tempus's infringement, but in no event less than a reasonable royalty with interest and costs.

59. On information and belief, Tempus will continue to infringe the '306 Patent unless enjoined by this Court. Tempus's infringement of Guardant's rights under the '306 Patent will

continue to damage Guardant, causing irreparable harm for which there is no adequate remedy at law, unless enjoined by this Court.

SECOND COUNT
(Infringement of '992 Patent) (All Accused Tests)

60. Guardant repeats and re-alleges the foregoing paragraphs as if set forth specifically herein.

61. The claims of the '992 Patent are valid and enforceable.

62. The claims of the '992 Patent are directed to patentable subject matter. The '992 Patent is directed to new techniques to detect genetic aberrations in cell-free DNA. '992 Patent at 1:61-2:40, claim 1.

63. Disorders that are caused by rare genetic mutations (e.g., sequence variations) or changes in epigenetic markers, such as cancer and partial or complete aneuploidy, may be detected or more accurately characterized with DNA sequence information. *Id.* at 1:36-40. Early detection and monitoring of genetic diseases are often useful and needed in the successful treatment or management of a disease. *Id.* at 1:41-43. According to the '992 patent, one approach may include monitoring a sample derived from cell-free nucleic acids, which are polynucleotides that can be found in different types of bodily fluids. *Id.* at 1:43-46.

64. Detecting and analyzing cell-free DNA was known to be challenging for several reasons, including that it is highly fragmented and present in minute quantities in clinical samples. The '992 patent solved challenges in the prior art and filled the “need in the art for improved methods and systems for using cell-free DNA to detect and monitor disease” by disclosing novel technological solutions to this particularly technological problem.

65. The '992 Patent claims a specific technological solution that creates a high efficiency conversion of cell-free DNA into nonuniquely tagged parent polynucleotides. Among

other things, the claims disclose methods for high efficiency conversion of cell-free DNA into nonuniquely tagged parent polynucleotides in an unconventional manner. *E.g., id.*, 1:55-57.

66. Claim 1 of the '992 Patent, for example, recites:

A method for detecting genetic aberrations in cell-free DNA ("cfDNA") molecules from a subject, comprising:

providing cfDNA molecules obtained from a bodily sample of the subject;

b) attaching tags comprising barcodes having a plurality of different barcode sequences to the cfDNA molecules to tag at least 20% of the cfDNA molecules, which attaching comprises ligating adaptors comprising the barcodes to both ends of the cfDNA molecules, wherein ligating comprises using more than 10× molar excess of the adaptors as compared to the cfDNA molecules, thereby generating tagged parent polynucleotides;

c) amplifying the tagged parent polynucleotides to produce amplified tagged progeny polynucleotides;

d) sequencing the amplified tagged progeny polynucleotides to produce a plurality of sequence reads from each of the tagged parent polynucleotides, wherein each sequence read of the plurality of sequence reads comprises a barcode sequence and a sequence derived from a cfDNA molecule of the cfDNA molecules;

e) mapping sequence reads of the plurality of sequence reads to one or more reference sequences from a human genome;

f) grouping the sequence reads mapped in e) into families based at least on barcode sequences of the sequence reads, each of the families comprising sequence reads comprising the same barcode sequence, whereby each of the families comprises sequence reads amplified from the same tagged parent polynucleotide;

g) at each of a plurality of genetic loci in the one or more reference sequences, collapsing sequence reads in each family to yield a base call for each family at the genetic locus; and

h) detecting, at one or more genetic loci, a plurality of genetic aberrations, wherein the plurality of genetic aberrations comprises two or more different members selected from the group of members consisting of a single base substitution, a copy number variation (CNV), an insertion or deletion (indel), and a gene fusion.

67. For example, the invention claimed in independent claims 1 and its dependent claims 2-33 improved on prior art genetic testing by, *inter alia*:

attaching tags comprising barcodes having a plurality of different barcode sequences to the cfDNA molecules to tag at least 20% of the cfDNA molecules, which attaching comprises ligating adaptors comprising the barcodes to both ends of the cfDNA molecules, wherein ligating comprises using more than 10× molar excess of the adaptors as compared to the cfDNA molecules, thereby generating tagged parent polynucleotides.

'992 Patent at cl. 1.

68. This, alone and in combination with other claimed elements, was not well-understood, routine, or conventional. Indeed, the USPTO has repeatedly found that this innovation involving tagging at least 20% of the cfDNA molecules using more than a 10× molar excess of adaptors and combinations with other elements were nonobvious over various proposed combinations of prior art asserted against the '992 patent. *See* Ex. N at 11-15 (denying institution for failure to render this limitation obvious), Ex. O at 3-5 (confirming non-obviousness in denial of rehearing); Ex. P at 11-15 (denying institution for failure to render this limitation obvious), Ex. Q at 3-5 (confirming non-obviousness in denial of rehearing).

69. The PTAB also found parallel limitations in the '306 patent described above and other Guardant patents related to the '306 patent non-obvious. Ex. L (confirming non-obviousness of limitations in the '306 patent reciting a minimum percentage of cfDNA molecules from population); *see also* Ex. R; Ex. S; Ex. T; Ex. U (each denying institution based on non-obviousness of parallel limitations in U.S. Patent Nos. 10,801,063 and 10,889,858).

70. Additionally, not only are the elements identified above unconventional and innovative, the ordered combination of the elements of each of the '992 Patent claims recites an invention that is not routine or conventional.

71. In sum, the '992 Patent claim elements, individually and as an ordered combination, present an innovative technique for non-unique tagging that was neither conventional nor routine nor well-understood.

72. Each of the Accused Tests, and Tempus's use of each of the Accused Tests, practices steps that are identical or equivalent to each claimed element of the patented invention pointed out by at least claim 1 of the '992 Patent.

73. Tempus is not licensed or otherwise authorized to practice the claims of the '992 Patent.

74. On information and belief, Tempus has infringed and continues to infringe at least claim 1 of the '992 patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by its use of the Accused Tests within the United States, without authority. As an example, attached as Exhibit H is a preliminary and exemplary claim chart illustrating one way in which Tempus infringes claim 1 of the '992 patent.

75. Thus, by its acts, Tempus has injured Guardant and is liable to Guardant for directly infringing one or more claims of the '992 Patent, whether literally or under the doctrine of equivalents.

76. On information and belief, Tempus will continue to infringe the '992 Patent unless enjoined by this Court. Tempus's infringement of Guardant's rights under the '992 Patent will continue to damage Guardant, causing irreparable harm for which there is no adequate remedy at law, unless enjoined by this Court.

THIRD COUNT
(Infringement of '810 Patent) (All Accused Tests)

77. Guardant repeats and re-alleges the foregoing paragraphs as if set forth specifically herein.

78. The claims of the '810 Patent are valid and enforceable.

79. The claims of the '810 Patent are directed to patentable subject matter. The '810 Patent is directed to new techniques to detect somatic genetic variants in cell-free DNA. '810 Patent at 1:56-2:35, 60:49-61:25, claim 1.

80. Disorders that are caused by rare genetic alterations (e.g., sequence variations) or changes in epigenetic markers, such as cancer and partial or complete aneuploidy, may be detected or more accurately characterized with DNA sequence information. *Id.* at 1:31-35. Early detection and monitoring of genetic diseases are often useful and needed in the successful treatment or management of a disease. *Id.* at 1:36-38. According to the '810 patent, one approach may include monitoring a sample derived from cell-free nucleic acids, which are polynucleotides that can be found in different types of bodily fluids. *Id.* at 1:38-41.

81. Detecting and analyzing cell-free DNA was known to be challenging for several reasons, including that it is highly fragmented and present in minute quantities in clinical samples. The '810 Patent claims solve challenges in the prior art by providing innovative techniques for ligating adapters comprising barcodes to cfDNA using a specific number of molecular barcodes with specific nucleotide lengths and performing innovative techniques for, among other things, amplifying, enriching, sequencing, and aligning cfDNA strands. The '810 Patent claims are directed to an innovative technique for ligating adapters comprising barcodes to cfDNA using a specific number of molecular barcodes with specific nucleotide lengths and performing innovative techniques for, among other things, amplifying, enriching, sequencing, and aligning cfDNA strands.

82. The '810 patent discloses methods for detecting genetic variation in a sample of cfDNA with high sensitivity, including the use of tools such as the following:

First, the efficient conversion of individual polynucleotides in a sample of initial genetic material into sequence-ready tagged parent polynucleotides, so as to increase the probability that individual polynucleotides in a sample of initial genetic material will be represented in a sequence-ready sample. This can produce sequence information about more polynucleotides in the initial sample. Second, high yield generation of consensus sequences for tagged parent polynucleotides by high rate sampling of progeny polynucleotides amplified from the tagged parent polynucleotides, and collapsing of generated sequence reads into consensus sequences representing sequences of parent tagged polynucleotides.

Id. at 32:42-54.

83. Parent polynucleotides as described above are tagged with barcodes that may be unique or non-unique. *Id.* at 37:50-55. For example, the '810 patent describes an example of non-unique tagging of cfDNA polynucleotides as follows:

A set of polynucleotides in the composition that map to a mappable base position in a genome can be non-uniquely tagged, that is, the number of different identifiers can be at least at least 2 and fewer than the number of polynucleotides that map to the mappable base position. A composition of between about 10 ng to about 10 µg (e.g., any of about 10 ng-1 µg about 10 ng-100 ng, about 100 ng-10 about 100 ng-1 µg, about 1 µg-10 µg) can bear between any of 2, 5, 10, 50 or 100 to any of 100, 1000, 10,000 or 100,000 different identifiers. For example, between 5 and 100 different identifiers can be used to tag the polynucleotides in such a composition.

Id. at 41:60-42:4.

84. The '810 patent further discloses methods for high efficiency conversion of cell-free DNA into nonuniquely tagged parent polynucleotides in an unconventional manner. The invention of the '810 Patent improved on prior art systems and methods to detect rare mutations and copy number variation, including by, *inter alia*, obtaining specific amounts of double-stranded cell-free DNA (10 to 100 nanograms) from a blood sample and ligating adapters comprising molecular barcodes to ends of a plurality of molecules of the double-stranded cfDNA to produce

tagged parent polynucleotides, wherein the molecular barcodes together constitute a specific set of molecular barcodes with a specific range of nucleotides (5-100) in length.

85. These innovations are specifically claimed in the '810 patent. Claim 1 of the '810 Patent, for example, recites:

1. A method for detecting somatic genetic variants of cell-free deoxyribonucleic acid (DNA) in a human subject, the method comprising:

a) obtaining 10 to 100 nanograms (ng) of double-stranded cell-free DNA from a blood sample from the human subject;

b) ligating adapters comprising molecular barcodes to ends of a plurality of molecules of the double-stranded cell-free DNA to produce tagged parent polynucleotides, wherein the molecular barcodes together constitute a set of 5-100 molecular barcodes from 5-20 nucleotides in length;

c) amplifying a plurality of the tagged parent polynucleotides to produce progeny polynucleotides with associated molecular barcodes;

d) selectively enriching the progeny polynucleotides for target regions associated with cancer, whereby enriched progeny polynucleotides are generated;

e) sequencing a portion of the enriched progeny polynucleotides to produce sequencing reads of the progeny polynucleotides with associated molecular barcodes;

f) aligning mappable portions of the sequencing reads to a human reference genome;

g) grouping a plurality of the sequencing reads into families based on the sequence information of the molecular barcodes and the beginning and end base positions of the mapped portion of the progeny polynucleotides; and

h) detecting, from among a plurality of the families, the presence or absence of one or more somatic genetic variants comprising a single nucleotide variant (SNV), a copy number variation (CNV), an insertion or deletion (indel), a gene fusion, or any combination thereof.

86. The following claim elements in claim 1 and its dependent claims 2-28 are directed to non-unique tagging, since the number of molecular barcodes (5 to 100) is far smaller than the number of cfDNA molecules in the sample:

- a) obtaining 10 to 100 nanograms (ng) of double-stranded cell-free DNA from a blood sample from the human subject;
- b) ligating adapters comprising molecular barcodes to ends of a plurality of molecules of the double-stranded cell-free DNA to produce tagged parent polynucleotides, wherein the molecular barcodes together constitute a set of 5-100 molecular barcodes from 5-20 nucleotides in length;

'810 Patent at cl. 1. The specification explains that:

For example, cfDNA has a peak of fragments at about 160 nucleotides, and most of the fragments in this peak range from about 140 nucleotides to 180 nucleotides. Accordingly, cfDNA from a genome of about 3 billion bases (e.g., the human genome) may be comprised of almost 20 million (2×10^7) polynucleotide fragments. A sample of about 30 ng DNA can contain about 10,000 haploid human genome equivalents.

'810 Patent at 40:23-30.

87. Moreover, the claimed invention involved grouping sequencing reads into families based on sequence information of the molecular barcodes and beginning and end base positions of the mapped portion of progeny polynucleotides. '810 Patent at cls. 1-28. This grouping was not routine, well-understood, or conventional, as it leverages a combination of barcode sequence and mapping location of the tagged fragment to provide unique grouping to families using non-unique tagging. These aspects, alone and in combination with other claimed elements, were not conventional, well-understood, or routine.

88. As another example, claim 5 depends from claim 1 and recites:

wherein at least 20% of the double-stranded cell-free DNA are ligated with adapters.

The specific percentages “at least 20%” of the double-stranded cfDNA molecules that must be ligated with adapters was not conventional, routine, or well-understood.

89. Additionally, not only are the elements identified above unconventional and innovative, the ordered combination of the elements of each of the '810 Patent claims recites an invention that is not routine or conventional.

90. In sum, the '810 Patent claim elements, individually and as an ordered combination, present an innovative technique for non-unique tagging that was neither conventional nor routine nor well-understood.

91. Each of the Accused Tests, and Tempus's use of each of the Accused Tests, practices steps that are identical or equivalent to each claimed element of the patented invention pointed out by at least claim 1 of the '810 Patent.

92. Tempus is not licensed or otherwise authorized to practice the claims of the '810 Patent.

93. On information and belief, Tempus has infringed and continues to infringe at least claim 1 of the '810 patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by its use of the Accused Tests within the United States, without authority. As an example, attached as Exhibit I is a preliminary and exemplary claim chart illustrating one way in which Tempus infringes claim 1 of the '810 patent.

94. Thus, by its acts, Tempus has injured Guardant and is liable to Guardant for directly infringing one or more claims of the '810 Patent, whether literally or under the doctrine of equivalents.

95. On information and belief, Tempus will continue to infringe the '810 Patent unless enjoined by this Court. Tempus's infringement of Guardant's rights under the '810 Patent will

continue to damage Guardant, causing irreparable harm for which there is no adequate remedy at law, unless enjoined by this Court.

FOURTH COUNT
(Infringement of '916 Patent) (At Least the Accused xF Tests)

96. Guardant repeats and re-alleges the foregoing paragraphs as if set forth specifically herein.

97. The claims of the '916 Patent are valid and enforceable.

98. The claims of the '916 Patent are directed to patentable subject matter. The '916 Patent shares a common specification with the '810 Patent. The '916 Patent is directed to new techniques for detecting polymorphic forms arising in cell-free DNA, and in particular to microsatellite changes. '916 Patent at 1:59-2:39, 60:30-61:6, claim 1.

99. Disorders that are caused by rare genetic alterations (e.g., sequence variations) or changes in epigenetic markers, such as cancer and partial or complete aneuploidy, may be detected or more accurately characterized with DNA sequence information. *Id.* at 1:34-38. Early detection and monitoring of genetic diseases are often useful and needed in the successful treatment or management of a disease. *Id.* at 1:39-41. According to the '916 patent, one approach may include monitoring a sample derived from cell-free nucleic acids, which are polynucleotides that can be found in different types of bodily fluids. *Id.* at 1:41-44.

100. Detecting and analyzing cell-free DNA was known to be challenging for several reasons, including that it is highly fragmented and present in minute quantities in clinical samples. The '916 patent discloses methods for detecting genetic variation in a sample of cfDNA with high sensitivity, including the use of tools such as the following:

First, the efficient conversion of individual polynucleotides in a sample of initial genetic material into sequence-ready tagged parent polynucleotides, so as to increase the probability that individual

polynucleotides in a sample of initial genetic material will be represented in a sequence-ready sample. This can produce sequence information about more polynucleotides in the initial sample. Second, high yield generation of consensus sequences for tagged parent polynucleotides by high rate sampling of progeny polynucleotides amplified from the tagged parent polynucleotides, and collapsing of generated sequence reads into consensus sequences representing sequences of parent tagged polynucleotides.

Id. at 32:47-59.

101. Parent polynucleotides as described above are tagged with barcodes that may be unique or non-unique. *Id.* at 37:50-55. For example, the '916 patent describes an example of non-unique tagging of cfDNA polynucleotides as follows:

A set of polynucleotides in the composition that map to a mappable base position in a genome can be non-uniquely tagged, that is, the number of different identifiers can be at least at least 2 and fewer than the number of polynucleotides that map to the mappable base position. A composition of between about 10 ng to about 10 µg (e.g., any of about 10 ng-1 µg about 10 ng-100 ng, about 100 ng-10 about 100 ng-1 µg, about 1 µg-10 µg) can bear between any of 2, 5, 10, 50 or 100 to any of 100, 1000, 10,000 or 100,000 different identifiers. For example, between 5 and 100 different identifiers can be used to tag the polynucleotides in such a composition.

Id. at 41:51-62.

102. The '916 Patent claims are directed to an innovative technique for ligating adapters comprising barcodes to cfDNA using a specific number of molecular barcodes sequences and performing innovative techniques for, among other things, amplifying, enriching, sequencing, and aligning cfDNA strands.

103. Claim 1 of the '916 Patent, for example, recites:

1. A method for inferring a quantitative measure of microsatellite changes in a sample of cell-free nucleic acid molecules from a subject having a cancer, the method comprising:

(a) tagging a plurality of the cell-free nucleic acid molecules from the sample with molecular barcodes from a set of molecular barcodes to produce tagged parent polynucleotides;

- (b) amplifying a plurality of the tagged parent polynucleotides to produce amplified tagged progeny polynucleotides;
- (c) sequencing a plurality of the amplified tagged progeny polynucleotides to produce a set of sequencing reads;
- (d) grouping a plurality of sequencing reads from the set of sequencing reads into families based at least on sequence information of the molecular barcodes, each family having sequencing reads amplified from a same tagged parent polynucleotide from among the tagged parent polynucleotides;
- (e) determining a quantitative measure of sequencing reads in a plurality of the families and a quantitative measure of unique families from among a plurality of the families;
- (f) inferring a number of the tagged parent polynucleotides based on the quantitative measure of the sequencing reads in the plurality of the families and the quantitative measure of unique families from among the plurality of the families;
- (g) determining a quantitative measure of microsatellite changes from among a plurality of the families; and
- (h) based on the determined quantitative measure of microsatellite changes from among the plurality of the families, inferring a quantitative measure of microsatellite changes in the inferred number of the tagged parent polynucleotides.

104. Claim 13 of the '916 Patent, for example, recites:

13. A method for detecting a genetic variation in one or more microsatellite regions in a sample of cell-free nucleic acid molecules from a subject having a cancer, the method comprising:

- (a) ligating molecular barcodes from a set of molecular barcodes having 2 to 1,000,000 different molecular barcode sequences to a plurality of the cell-free nucleic acid molecules from the sample to produce tagged parent polynucleotides;
- (b) amplifying a plurality of the tagged parent polynucleotides to produce amplified tagged progeny polynucleotides;
- (c) sequencing a plurality of the amplified tagged progeny polynucleotides to produce a set of sequencing reads; and
- (d) determining, from among a plurality of sequencing reads in the set of sequencing reads, a quantitative measure of polymorphic

forms comprising microsatellite changes in the one or more microsatellite regions based at least on sequence information of the molecular barcodes, thereby detecting the genetic variation in the one or more microsatellite regions.

105. Claims 1 and 13 and their dependent claims 2-12 and 14-29, respectively, are directed to new ways to detect microsatellite genetic variation in cell-free DNA.

106. The innovations claimed in claim 1 and 13 and their dependent claims 2-12 and 14-29 improve on prior art genetic testing by, *inter alia*, tagging of parent cfDNA molecules with molecular barcodes. For example, claim 1 recites in part “tagging a plurality of the cell-free nucleic acid molecules from the sample with molecular barcodes from a set of molecular barcodes to produce tagged parent polynucleotides,” and claim 13 recites in part “ligating molecular barcodes . . . to a plurality of the cell-free nucleic acid molecules from the sample to produce tagged parent polynucleotides.” This innovation alone and in combination with other claimed elements, was not well-understood, routine, or conventional, as it is directed to tagging of parent polynucleotides from a sample of cfDNA with barcodes.

107. The innovations claimed in claim 13 and its dependent claims 14-29 further improve on prior art genetic testing by, *inter alia*, tagging of cfDNA molecules with molecular barcodes, and further:

ligating molecular barcodes from a set of molecular barcodes having 2 to 1,000,000 different molecular barcode sequences to a plurality of the cell-free nucleic acid molecules from the sample to produce tagged parent polynucleotides.

108. This innovation alone and in combination with other claimed elements, was not well-understood, routine, or conventional, as it is directed to non-unique tagging, since the number of molecular barcodes (up to 1 million) is far smaller than the number of cfDNA molecules in a sample.

109. Furthermore, dependent claim 9, which depends from claim 8 and claim 1, recites:

Grouping is based at least on a combination of the sequence information of the molecular barcodes and a beginning base position and an end base position of the sequencing reads that map to the reference sequence.

Claim 22, which depends from claims 13 and 21, recites:

grouping a subset of sequencing reads into families based on sequence information of the molecular barcodes and (1) a start base position of a given sequencing read from among the subset of sequencing reads at which the given sequencing read is determined to start mapping to the reference sequence or (2) a stop base position of the given sequencing read at which the given sequencing read is determined to stop mapping to the reference sequence.

110. These limitations claim the innovation of grouping based on a combination of molecular barcodes and beginning and end base positions as mapped to a reference sequence, which is also directed to non-unique tagging and was not well-understood, routine, or conventional.

111. Additionally, not only are the elements identified above unconventional and innovative, the ordered combination of the elements of each of the '916 Patent claims recites an invention that is not routine or conventional.

112. In sum, the '916 Patent claim elements, individually and as an ordered combination, present an innovative technique for non-unique tagging that was neither conventional nor routine nor well-understood.

113. At least each of the Accused xF Tests, and Tempus's use of each of the Accused xF Tests, practices steps that are identical or equivalent to each claimed element of the patented invention pointed out by at least claim 13 of the '916 Patent.

114. Tempus is not licensed or otherwise authorized to practice the claims of the '916 Patent.

115. On information and belief, Tempus has infringed and continues to infringe at least claim 13 of the '916 patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by its use of at least the Accused xF Tests within the United States, without authority. As an example, attached as Exhibit J is a preliminary and exemplary claim chart illustrating one way in which Tempus infringes claims 13 of the '916 patent.

116. Thus, by its acts, Tempus has injured Guardant and is liable to Guardant for directly infringing one or more claims of the '916 Patent, whether literally or under the doctrine of equivalents.

117. As a result of Tempus's infringement of the '916 Patent, Guardant has suffered monetary damages, and seeks recovery, in an amount to be proven at trial, adequate to compensate for Tempus's infringement, but in no event less than a reasonable royalty with interest and costs.

118. On information and belief, Tempus will continue to infringe the '916 Patent unless enjoined by this Court. Tempus's infringement of Guardant's rights under the '916 Patent will continue to damage Guardant, causing irreparable harm for which there is no adequate remedy at law, unless enjoined by this Court.

FIFTH COUNT
(Infringement of '693 Patent) (At Least the Accused xM Tests)

119. Guardant repeats and re-alleges the foregoing paragraphs as if set forth specifically herein.

120. The claims of the '693 Patent are valid and enforceable.

121. The claims of the '693 Patent are directed to patentable subject matter. The '693 Patent is directed to new techniques to determine a likelihood that a subject has cancer by improving the isolation of cell free DNA for use in liquid biopsies.

122. The '693 Patent explains that “[e]arly detection of cancer may result in improved outcomes because early-stage cancer tends to be more susceptible to treatment.” ’693 Patent at 1:15-18. “Improperly controlled cell growth is a hallmark of cancer that generally results from an accumulation of genetic and epigenetic changes, such as copy number variations (CNVs), single nucleotide variations (SNVs), gene fusions, insertions and/or deletions (indels), epigenetic variations include 5-methylation of cytosine (5-methylcytosine) and association of DNA with chromatin proteins and transcription factors.” *Id.* at 1:18-26.

123. The prior art made use of biopsies for “detecting or diagnosing cancer in which cells or tissue are extracted from a possible site of cancer and analyzed for relevant phenotypic and/or genotypic features.” *Id.* at 1:27-30. Biopsies, however, have the drawback of being invasive. *Id.* at 1:30-31. Liquid biopsies are a non-invasive alternative based on the observation that DNA from cancer cells is released into body fluids. *Id.* at 1:32-35. However, the prior art liquid biopsies presented challenges: developing accurate and sensitive methods for analyzing liquid biopsy material given the low concentration and heterogeneity of cell-free DNA. *Id.* at 1:36-41. “Isolating the fractions of cell-free DNA useful for further analysis in liquid biopsy procedures is an important part of this process. Accordingly, there is a need for improved methods and compositions for isolating cell-free DNA, e.g., for use in liquid biopsies.” *Id.* at 1:41-43.

124. The '693 Patent provided an improvement over the prior art to “isolate cell-free DNA so as to capture two sets of target regions—a sequence-variable target region set and an epigenetic target region set—wherein the capture yield of the sequence-variable target region set is greater than the capture yield of the epigenetic target region set.” *Id.* at 1:49-54. The '693 Patent claims are directed to an innovative technique for capturing two sets of cfDNA target

regions—i.e., a sequence-variable target region set and an epigenetic target region set—with different relative yields of the two sets.

125. Claim 1, for example, recites:

1. A method of determining a likelihood that a subject has cancer, comprising:

a) collecting cfDNA from a test subject;

b) partitioning the cfDNA from the test subject into at least two fractions on the basis of methylation level;

c) contacting the cfDNA of the at least two fractions with a set of target-specific probes, wherein the set of target-specific probes comprises target-binding probes specific for a sequence-variable target region set and target-binding probes specific for an epigenetic target region set, and the set of target-specific probes is configured to capture cfDNA corresponding to the sequence-variable target region set with a greater capture yield than cfDNA corresponding to the epigenetic target region set, whereby complexes of target-specific probes and cfDNA are formed; and

separating the complexes from cfDNA not bound to target-specific probes, thereby providing a set of captured cfDNA molecules;

d) sequencing the captured cfDNA molecules, wherein the captured cfDNA molecules of the sequence-variable target region set are sequenced to a greater depth of sequencing than the captured cfDNA molecules of the epigenetic target region set;

e) obtaining a plurality of sequence reads generated by a nucleic acid sequencer from sequencing the captured cfDNA molecules;

f) mapping the plurality of sequence reads to one or more reference sequences to generate mapped sequence reads; and

g) processing the mapped sequence reads corresponding to the sequence-variable target region set and to the epigenetic target region set to determine the likelihood that the subject has cancer.

126. Claim 14 recites:

14. A method of determining a likelihood that a subject has cancer, comprising:

a) collecting cfDNA from a test subject;

b) contacting the cfDNA with a set of target-specific probes, wherein the set of target-specific probes comprises target-binding probes specific for a sequence-variable target region set and target-binding probes specific for an epigenetic target region set, and the set of target-specific probes is configured to capture cfDNA corresponding to the sequence-variable target region set with a greater capture yield than cfDNA corresponding to the epigenetic target region set, whereby complexes of target-specific probes and cfDNA are formed; and

separating the complexes from cfDNA not bound to target-specific probes, thereby providing a set of captured cfDNA molecules;

c) sequencing the captured cfDNA molecules, wherein the captured cfDNA molecules of the sequence-variable target region set are sequenced to a greater depth of sequencing than the captured cfDNA molecules of the epigenetic target region set;

d) obtaining a plurality of sequence reads generated by a nucleic acid sequencer from sequencing the captured cfDNA molecules;

e) mapping the plurality of sequence reads to one or more reference sequences to generate mapped sequence reads; and

f) processing the mapped sequence reads corresponding to the sequence-variable target region set and to the epigenetic target region set to determine the likelihood that the subject has cancer.

127. The patented invention improved on prior art genetic testing by, *inter alia*, using target-specific probes as recited in independent claims 1 and 14:

contacting the cfDNA [of the at least two fractions] with a set of target-specific probes, wherein the set of target-specific probes comprises target-binding probes specific for a sequence-variable target region set and target-binding probes specific for an epigenetic target region set.

Id. at cls. 1, 14.

128. Further, claims 1 and 14, along with their respective dependent claims 2-13 and 15-18 recite that the target specific probes are configured to capture cfDNA with a greater capture yield:

the set of target-specific probes is configured to capture cfDNA corresponding to the sequence-variable target region set with a greater capture yield than cfDNA corresponding to the epigenetic target region set, whereby complexes of target-specific probes and cfDNA are formed.

Id. This innovation was not well-understood, routine, or conventional, as it involves specific methods of using probes with capture yields adapted to provide greater capture yields for sequence-variable target regions relative to epigenetic target regions, thereby improving methods for detecting combinations of sequence-based and epigenetic-based indications of cancer.

129. Independent claims 1 and 14, along with their respective dependent claims, also recite the following innovation:

sequencing the captured cfDNA molecules, wherein the captured cfDNA molecules of the sequence-variable target region set are sequenced to a greater depth of sequencing than the captured cfDNA molecules of the epigenetic target region set.

This innovation was not well-understood, routine, or conventional, as it recites specific methods of sequencing with depths adapted to provide sequencing depth for sequence-variable target regions relative to epigenetic target regions, thereby improving methods for detecting combinations of sequence-based and epigenetic-based indications of cancer. These aspects, alone and in combination with other claimed elements, were not conventional, well-understood, or routine.

130. Additionally, not only are the elements identified above unconventional and innovative, the ordered combination of the elements of each of the '693 Patent claims recites an invention that is not routine or conventional.

131. In sum, the '693 Patent claim elements, individually and as an ordered combination, present an innovative technique for capture and sequencing of cfDNA that was neither conventional nor routine nor well-understood.

132. At least each of the Accused xM Tests, and Tempus's use of each of the Accused xM Tests, practices steps that are identical or equivalent to each claimed element of the patented invention pointed out by at least claim 14 of the '693 Patent.

133. Tempus is not licensed or otherwise authorized to practice the claims of the '693 Patent.

134. On information and belief, Tempus has infringed and continues to infringe at least claim 14 of the '693 patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, at least by its use of the Accused xM Tests within the United States, without authority. As an example, attached as Exhibit K is a preliminary and exemplary claim chart illustrating one way in which Tempus infringes claim 14 of the '693 patent.

135. As a result of Tempus's infringement of the '693 Patent, Guardant has suffered monetary damages, and seeks recovery, in an amount to be proven at trial, adequate to compensate for Tempus's infringement, but in no event less than a reasonable royalty with interest and costs.

136. On information and belief, Tempus will continue to infringe the '693 Patent unless enjoined by this Court. Tempus's infringement of Guardant's rights under the '693 Patent will continue to damage Guardant, causing irreparable harm for which there is no adequate remedy at law, unless enjoined by this Court.

PRAYER FOR RELIEF

WHEREFORE, Guardant prays for judgment and seeks relief from Tempus as follows:

a. For judgment that Tempus has infringed and continues to infringe the claims of the Patents-in-Suit;

b. For an injunction against Tempus and its respective officers, directors, agents, servants, affiliates, employees, divisions, branches, subsidiaries, parents, and all other acting in active concert therewith from infringement of the Patents-in-Suit;

c. For an accounting of all damages sustained by Guardant as a result of Tempus's acts of infringement;

d. For a judgment that Guardant be awarded all damages adequate to compensate it for Tempus's infringement of the Patents-In-Suit, such damages to be determined by a jury and an accounting, if necessary, to compensate adequately Guardant for the infringement;

e. For a mandatory future royalty payable by Tempus for each use of an Accused Test that is found to infringe one or more of the Patents-in-Suit and all future products which are not colorably different from products found to infringe, to the extent not enjoined;

f. For a judgment and order requiring Tempus to pay Guardant's damages, costs, expenses, and pre- and post-judgment interest for its infringement of the Patents-in-Suit as provided under 35 U.S.C. § 284;

g. For a judgment and order finding that this is an exceptional case within the meaning of 35 U.S.C. § 285 and awarding to Guardant its reasonable attorneys' fees; and

h. For such other and further relief in law and in equity as the Court may deem just and proper.

DEMAND FOR JURY TRIAL

Pursuant to Rule 38(b) of the Federal Rules of Civil Procedure, Guardant demands a trial by jury in this action for all issues triable by a jury.

Respectfully submitted,

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