

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

GUARDANT HEALTH, INC.,

Plaintiff,

v.

TEMPUS AI, INC.,

Defendant.

C.A. No. 24-687-GBW

TEMPUS AI, INC.'S PRELIMINARY INVALIDITY CONTENTIONS

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(iii) “unique sequencing read” (claim 30)

Claim 30 of the '916 patent recites “(d) identifying, from among a plurality of sequencing reads in the set of sequencing reads, a plurality of unique sequencing reads based at least on sequence information of the molecular barcodes, wherein a unique sequencing, read corresponds to a nucleic acid sequence of a cfDNA molecule from among the tagged parent polynucleotides.” For the same reasons explained above with respect to enablement, claim 30 also lacks written description. The '916 does not provide any disclosure of using “unique sequencing reads” to determine “a quantitative measure of polymorphic forms comprising microsatellite changes in the one or more microsatellite regions.”

(c) **Indefiniteness**

For at least the reasons below, the '916 Asserted Claims are indefinite and are thus invalid.

- (i) (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 (claim 1); (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 barcode (claim 13); (d) identifying, from among a plurality of sequencing reads in the set of sequencing reads, a plurality of unique sequencing reads based at least on sequence information of the molecular barcodes (claim 30)

Claim 1 of the '916 patent recites “(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.” Claim 13 of the '916 patent recites “(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.” Claim 30 of the ’916 patent recites “(d) identifying, from among a plurality of sequencing reads in the set of sequencing reads, a plurality of unique sequencing reads based at least on sequence information of the molecular barcodes.” Claims 1, 13, and 30 of the ’916 patent fail to provide objective boundaries for POSA because the term “sequence information of the molecular barcodes” is open to multiple plausible interpretations.

The ’916 patent does not define the term “sequence information of the molecular barcode.” Moreover, a POSA would have understood that “sequence information of the molecular barcode” could refer to multiple different things, including, but not limited to, the (1) the sequence of the barcode; (2) the sequence length of the barcode; or (3) some portion of the barcode. The ambiguity of this term is confirmed by Guardant’s other patents. For example, claim 1 of the ’992 patent recites grouping sequence reads “based at least on barcode sequences of the sequence reads.” Thus, a POSA would have understood that “sequence information of the molecular barcodes” must mean something other than simply the barcode sequence.

- (ii) “(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” (claim 1)

Claim 1 of the ’916 patent recites “(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.” Claim 1 fails to provide objective boundaries for POSA because the term “determining a quantitative measure of sequencing reads in a plurality of the families” is open to multiple plausible interpretations. A POSA would have understood that this term could mean (1) determining a quantitative measure of sequence reads in each family of multiple

families; or (2) determining a quantitative measure of reads in total for a plurality of families. Neither the rest of claim 1, nor the specification provides any clarity. For example, claim 1 also recites “(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.” The ’916 patent, however, does not provide any explanation of how to infer “a number of the tagged parent polynucleotides based on the quantitative measure of the sequencing reads in the plurality of the families” and thus does not provide any insight into the meaning of “determining a quantitative measure of sequencing reads in a plurality of the families.”

(iii) “inferring” (claim 1)

Claim 1 of the ’916 patent recites “(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.” Claim 1 also recites “(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.” Claim 1 is indefinite because a POSA would not have understood the scope of the claim with reasonable certainty.

Claim 1 of the ’916 patent requires “inferring” two different values (1) the number of tagged parent polynucleotides; and (2) a quantitative measure of microsatellite changes in the tagged parent polynucleotides. As explained above, the ’916 patent fails to teach or explain to a POSA what it means to “infer” either value, much less how to do so. In addition, a POSA would not have understood what it means to infer “a quantitative measure of microsatellite changes in the inferred number of the tagged parent polynucleotides,” including whether this means

determining the total number of microsatellite changes that existed in the original sample or something else.

- (iv) “(d) determining, from among a plurality of sequencing reads in the set of sequencing reads, a quantitative measure of polymorphic forms comprising microsatellite changes” (claim 13) / “(e) determining, from among the plurality of unique sequencing reads, a quantitative measure of polymorphic forms comprising microsatellite changes in the one or more microsatellite regions” (claim 30)

Claim 13 of the '916 patents recite “(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.” Claim 30 of the '916 patent recites “(e) determining, from among the plurality of unique sequencing reads, a quantitative measure of polymorphic forms comprising microsatellite changes in the one or more microsatellite regions.” Claims 13 and 30 fail to provide objective boundaries for POSA because they fail to teach what constitutes a “a quantitative measure of polymorphic form comprising microsatellite changes.”

The scope of the term “a quantitative measure of polymorphic form comprising microsatellite changes” is unclear from the claims and specification of the '916 patent and is open to multiple plausible interpretations. For example, the '916 patent discloses that: “In another embodiment wherein polymorphic forms include but are not limited to: substitutions, insertions, deletions, inversions, *microsatellite changes*, transversions, translocations, fusions, methylation, hypermethylation, hydroxymethylation [sic], acetylation, epigenetic variants, regulatory-associated variants or protein binding sites.” '916 patent at 9:18-24 (emphasis added); *see also id.* at 23:32-39. The '916 patent, however, does not disclose whether determining a quantitative measure of polymorphic forms requires (1) counting the number of microsatellite changes in each read; (2) counting the number of reads that contain at least one

microsatellite change; (3) counting the number of different versions of the microsatellite region (*i.e.*, number of different read lengths), or (4) something else. This ambiguity renders claims 13 and 30 indefinite.

(v) “unique sequencing read”

Claim 30 of the '916 patent recites “(d) identifying, from among a plurality of sequencing reads in the set of sequencing reads, a plurality of unique sequencing reads based at least on sequence information of the molecular barcodes, wherein a unique sequencing, read corresponds to a nucleic acid sequence of a cfDNA molecule from among the tagged parent polynucleotides.” Claim 30 fails to provide objective boundaries for POSA because it fails to indicate what constitutes a “unique sequencing read.”

By its plain terms, a “unique sequencing read” would seem to be one that does not match any other sequencing read, *i.e.*, is unique. Claim 30, however, recites that “a unique sequencing read corresponds to a nucleic acid sequence of a cfDNA molecule from among the tagged parent polynucleotides.” But this definition not only fails to identify what constitutes a “unique sequencing read,” but encompasses every sequencing read. Indeed, every sequencing read that results from a sample “corresponds to a nucleic acid sequence of a cfDNA molecule from among the tagged parent polynucleotides.” Thus, the claims fail to provide reasonable certainty of the scope of claim 30.

In addition, the term “unique sequence reads” only appears once in the specification of the '916 patent, in the context of detecting copy number variations, not microsatellite changes:

The disclosure provides for a method for detecting copy number variation comprising: a) sequencing extracellular polynucleotides from a bodily sample from a subject, wherein each of the extracellular polynucleotide generate a plurality of sequencing reads; b) filtering out reads that fail to meet a set threshold; c) mapping the sequence reads obtained from step (a), after reads are filtered out, to a reference sequence; d) quantifying or enumerating

mapped reads in two or more predefined regions of the reference sequence; and e) determining copy number variation in one or more of the predefined regions by: (ii) normalizing number of reads in the predefined regions to each other and/or the number of unique sequence reads in the predefined regions to one another; (ii) comparing the normalized numbers obtained in step (i) to normalized numbers obtained from a control sample.

'916 patent at 14:8-24. This use provides no additional information about the meaning of the term, particularly in the context of identifying microsatellite changes. Accordingly, claim 30 is indefinite.

C. The '306 Patent

1. Patent Description

The '306 patent acknowledges that “many methods have been developed for accurate copy number variation estimation, especially for heterogeneous genomic samples, such as tumor-derived gDNA or for cfDNA for many applications” and “these methods include sample preparation whereby the original nucleic acids are converted into a sequenceable library, followed by massively parallel sequencing, and finally bioinformatics to estimate copy number variation at one or more loci.” '306 Patent, 1:46-55. According to the '306 patent, “[a]lthough many of these methods are able to reduce or combat the errors introduced by the sample preparation and sequencing processes for all molecules that are converted and sequenced, these methods are not able to infer the counts of molecules that were converted but not sequenced.” *Id.*, 1:59-63. Thus, the '306 patent indicates that it is directed to providing a method by which “[t]he number of unseen molecules can be estimated based on the number of Pairs and Singlets detected.” *Id.*, 2:17-18.

Although it professes to address this purported need in the art for a way to estimate “the number of unseen molecules,” the claims of the '306 patent are not directed to such a method. Instead, the claims cover sequencing methods that were well-known to a person of ordinary skill

Claims 1 and 17 lack written description support because the specification does not describe “unpaired reads” that meet the requirements of claims 1 and 17. At most, the specification describes “unpaired read[s]” that “represent[] a first tagged strand having no second differently tag complementary strand derived from a double-stranded polynucleotide molecule *represented among the sequence reads in the set of sequence reads.*” ’306 at 9:12-25. The language of claims 1 and 17, however, require the unpaired reads to be from a first strand that has no second complementary strand, not a first strand with no second complementary strand represented in the sequence reads. Thus, claims 1 and 17 lack written description.

(c) **Indefiniteness**

For at least the reasons below, the ’306 Asserted Claims are indefinite and are thus invalid.

- (i) “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” (claim 1)

Claim 1 of the ’306 patent recites “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.” Claim 1 fails to provide objective boundaries for POSA because a POSA would not have understood how to calculate “z.”

Calculating “z” in claim 1 requires (1) determining an expected number of duplicate molecules in the population of cfDNA molecules that map to identical start and stop positions on a reference sequence; and (2) determining the mean (*i.e.*, average) of the expected number. A POSA would not have understood how to do this calculation.

First, a POSA would have understood that an “expected number” is a single value. Indeed, the claim does not recite determining an expected range. And a POSA would have understood that it is impossible to determine the mean of a single value. For this reason alone, claim 1 is indefinite.

Second, the specification does not explain how to determine (1) an expected number of duplicate molecules in the population of cfDNA molecules that map to identical start and stop positions on a reference sequence or (2) the mean of the expected number. The quantity of the population of cfDNA molecules is not described by claim 1 and the patent is not limited to any particular “population of cfDNA molecules,” which could come from any source and could range in fragment size making the calculation complicated. Moreover, the specification does not disclose how to calculate z for any population of cfDNA molecules mapped against any particular reference sequence. Given the lack of supporting disclosure, POSAs would not be reasonably certain about the scope of the claims, and in particular about how to ascertain an expected number of the “duplicate molecules” that match to identical start and stop positions on a reference genome. For this additional reason, claim 1 is indefinite.

(ii) “wherein n is at least 2 and no more than $100,000 * z$,”
(claim 1)

Claim 1 of the '306 patent recites “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.” Claim 1 fails to provide objective boundaries for POSA because the term “ n is at least 2 and no more than $100,000 * z$ ” is open to at least two plausible interpretations: (1) n is at least $2 * z$ and no more than $100,000 * z$; or (2) n is at least 2 and no more than $100,000 * z$.

While the plain language seems to suggest the lower limit is 2, the '306 specification discloses a lower limit of 2*z. '306 Patent at 20:30-36 (“In certain embodiments, n is at least any of 2*z, 3*z, 4*z, 5*z, 6*z, 7*z, 8*z, 9*z, 10*z, 11*z, 12*z, 13*z, 14*z, 15*z, 16*z, 17*z, 18*z, 19*z, or 20*z (e.g., lower limit). In other embodiments, n is no greater than 100,000*z, 10,000*z, 1000*z or 100*z (e.g., upper limit). Thus, n can range between any combination of these lower and upper limits.”). Since, based on the specification, a POSA would not have understood with reasonable certainty whether the lower limit is 2 or 2*z, claim 1 is indefinite.

- (iii) “(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” (claim 1) / “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” (claim 17)

Claim 1 of the '306 patent recites “(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.” Claim 17 of the '306 patent recites “(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.” The patent specification does not enable a POSA to make and use the full scope of the claimed invention.

Claims 1 and 17 each recite using “unpaired reads” which the claims define as “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.” In its PICs, Guardant fails to explain how the Accused Products meet this limitation. To the extent that Guardant argues that “unpaired reads” are any reads without a corresponding read, this term is indefinite because it is open to at least two plausible interpretations.

As explained above, according to the claim language, the strand from which the unpaired read is generated (the first strand) must have “no second tagged complementary *strand* derived from cfDNA molecules from among the tagged parent polynucleotides.” Thus, a POSA could interpret the claim to require “unpaired reads” to be only those which result from strands that never had a complementary strand, not just those that ultimately did not have a complementary sequencing read in the set of sequencing reads.

D. The '693 Patent

1. Patent Description

The '693 patent is directed to methods of “determining the likelihood that a subject has cancer” using both methylation testing and sequence variant testing. According to the patent, “[i]t can be beneficial 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

B. The '992 and '306 patents are invalid based on “infectious unenforceability”

The '992 and '306 patents are also unenforceable against Tempus because the inequitable conduct described above bears “an immediate and necessary relation” to enforcement of the '992 and '306 patents.

1. There is a close relationship between the content of the '992 and '306 patents and the inequitable conduct

The '916, '992, and '306 patents are closely related in substance. First, the '916 patent and the '992 patents both claim priority to four of the same provisional applications: provisional application No. 61/845,987, provisional application No. 61/793,997, provisional application No. 61/7044,400, and provisional application No. 61/696,734. Second, the specifications of the three patents are nearly identical. The abstracts are word-for-word identical, and each of the patents contains the exact same figures.

In addition, the claims are all closely related. In particular, the claims of the three patents all relate to a “communication theory[,]” which allows for reduced errors in the amplification and sequencing of cfDNA when conducting a “liquid biopsy.” And the claims of the three patents implement this “communication theory” solution by invoking the same general steps, including tagging of sequence reads, the grouping of sequence reads with the same tags into families and the collapsing the sequence reads to create “consensus sequences.”

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