

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TEMPUS AI, INC.,
Petitioner,

v.

GUARDANT HEALTH INC.,
Patent Owner.

IPR2025-01434
Patent 11,149,306

**PATENT OWNER'S
PRELIMINARY RESPONSE**

TABLE OF CONTENTS

	<u>Pages</u>
I. INTRODUCTION	1
II. BACKGROUND	3
A. The '306 Patent.....	3
B. Prosecution History and Prior Adjudication in IPR2022-01400	4
C. The Cited Prior Art.....	6
1. The Proposed Amplification Generates Indistinguishable Progeny Duplexes	7
2. Bielas	10
3. Vogelstein.....	11
III. CLAIM CONSTRUCTION	11
IV. GROUND 1 FAILS	13
A. Bielas is Undisputedly Blind to Whether Reads are Paired or Unpaired	14
B. Vogelstein Does Not Cure the Deficiency of Bielas.....	18
C. Petitioner Does not Assert the Z Limitation is Taught in the Prior Art.....	20
V. GROUND 2 FAILS	24
VI. GROUND 3 FAILS	24
VII. GROUND 4 FAILS	25
VIII. CONCLUSION.....	25
IX. APPENDIX.....	27

I. INTRODUCTION

The validity of all claims of the '306 patent was adjudicated in IPR2022-01400 (“the 1400IPR”) where the Board heard from at least five different expert witnesses in the field and considered nearly 80 different prior art references. Yet, the Board upheld all claims at Final Written Decision. The present petition asks the Board to reconsider the claims in view of much less relevant art and arrive at a different outcome. Worse yet, the prior art references now asserted were recycled from the face of the '306 patent but were already considered by the Examiner during prosecution at least 3 different times.

Lacking a compelling obviousness theory, Petitioner engages in claim construction gamesmanship. Where Petitioner has no answers for claim terms, they simply ignore them. For example, the claims recite “paired” and “unpaired” sequence reads, which are expressly defined in the claim and were a point of distinction from the prior art in the previous 1400IPR. The petition flatly ignores the claim language in attempting to shoehorn in the prior art already distinguished from the challenged claims. Petitioner also advances incompatible positions between the district court and the Board. At district court, Petitioner asserts that multiple elements of claims 1-29 are indefinite. *See, e.g.*, EX2015. Yet in the petition, claim terms allegedly indeterminable according to Petitioner’s district court arguments are simply ignored. Remarkably, without explanation or

acknowledgement of its district court positions, Petitioner inconsistently tells the Board here that no claim construction is necessary. Pet. 13-14. This alone is reason to deny the petition. *Revvo Technologies, Inc. v. Cerebrum Sensor Technologies, Inc.*, IPR2025-00632, Paper 20 at 5 (precedential) (requiring a reason for advancing different claim construction positions); *Tesla, Inc. v. Intellectual Ventures II LLC*, IPR2025-00340, Paper 18 at 4 (informative) (“Allowing a petitioner to advance a claim construction before the Board when that petitioner has made inconsistent indefiniteness arguments in district court fails to further, but instead detracts from, the Office’s goal of ‘providing greater predictability and certainty in the patent system.’”).

To the extent the merits are reached, there is good reason why the claims were allowed over the asserted prior art. As explained herein, multiple elements are missing from the prior art. For example, independent claims 1 and 17 require identifying and processing “paired” and “unpaired” reads. But the petition relies on a reference (Bielas) that does not discuss paired or unpaired reads and is, in fact, widely recognized in the scientific literature as blind to whether such reads exist. This is readily apparent from the reference itself and confirmed by the testimony of Petitioner’s own expert.

In some instances, the petition does not even bother to meaningfully address certain limitations in the claims. For example, claim 1 recites tagging cfDNA

molecules “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.” Here, Petitioner simply ignores z —presumably in service of its indefiniteness positions at district court where it is arguing the same claim limitation is hopelessly indeterminable. Without addressing the entirety of the claims, Petitioner cannot establish obviousness.

Accordingly, for the reasons detailed below, the Board should deny institution of the petition.

II. BACKGROUND

A. The '306 Patent

The '306 patent discloses and claims an innovative technique for preparing and measuring cfDNA, including a new technique for tagging physical DNA strands and estimating the number of unseen molecules using a specific number of molecular barcode combinations and a mean of an expected number of duplicate molecules.

The '306 patent states that although known methods for detecting cfDNA are able to reduce the errors introduced by the sample preparation and sequencing processes for the molecules that are converted and sequenced, these methods suffer from insensitivity due to molecules being lost to the sequencing process. EX1001,

1:59–63. The '306 patent states this inability to count unsequenced molecules “can dramatically and adversely affect the sensitivity that can be achieved.” EX1001, 1:63–67. Accordingly, the '306 patent relates to a method of tagging and counting both halves of double-stranded DNA and estimating the number of unseen

molecules based on the number of Pairs

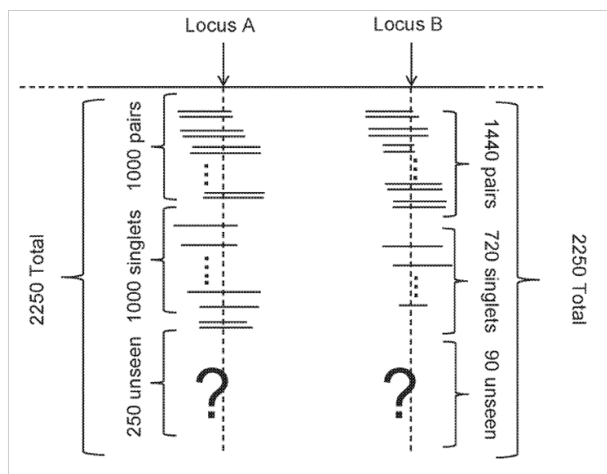
(i.e., molecules where both strands were

identified) and Singlets (i.e., molecules

where only one strand was identified)

detected in a particular region. EX1001,

2:1-18; *see also id.*, 35:25-61



(“Referring to FIG. 2, as an example, counts for a particular genomic locus, Locus A, are recorded, where 1000 molecules are paired and 1000 molecules are unpaired.”), Fig. 2 (reproduced herein); EX1027, 3-4.

B. Prosecution History and Prior Adjudication in IPR2022-01400

The validity of the '306 patent was adjudicated previously where the Board confirmed the patentability of the '306 patent claims at Final Written Decision.

The Board upheld the claims of the '306 patent in the 1400IPR because the closest prior art (Schmitt) does not teach: (1) tagging with a small number of molecular barcodes relative to a number of sample molecules; and (2) distinguishing paired and unpaired reads as claimed. EX1027, 21-22, 30. The Board’s analysis in the

1400IPR was no cursory review. There, the '306 patent was heavily litigated, and the Board heard from at least five different technical experts in the field.¹ At least 78 different prior art references were considered by both the various experts and the Board, including many of the same references now asserted here.

The present IPR presents nothing new. It merely recycles prior art already considered by the Office. Petitioner's main reference—Bielas—was submitted to the Office no fewer than three times during prosecution. In particular, Bielas was considered as US2021/0222243 in an IDS on August 19, 2021. EX1002, 774. In this IDS, Bielas was the *only reference* and was submitted along with a search report for a European counterpart of the '306 patent—EP Application No. 20183626.9 (“EP626”). EX1002, 725; *see also* EX2002, 5-7. Petitioner's file history exhibit omits the EP626 search report even though it was submitted to the Office in its entirety. *See* EX2001, 1191-1202. The EP626 search report includes Bielas as WO2013123442 where even the EPO characterized the reference as “A”

¹ Testifying experts in the 1400IPR included Dr. John Quackenbush from Harvard, Dr. Ian Hagemann from Washington University, Dr. Paul Spellman from Oregon Health & Science University, Dr. Rahul Satija from New York University, and Dr. Aleksandar Rajkovic from University of California at San Francisco.

—i.e., not a reference that is relevant to the claims but one that provides “technological background.” EX2001, 1192. WO2013123442 was additionally submitted in an IDS amongst 50 other foreign patent documents on July 31, 2020. EX1002, 346. Bielas was submitted yet another time as US2015/0024950 in an IDS on July 31, 2020. EX1002, 338.

Petitioner’s other ground references (i.e., Vogelstein, Forshew, Hendricks, Diehn, and Hicks) are listed on the face of the patent and have been fully considered by the Office including during examination and by the Board in the 1400IPR.²

C. The Cited Prior Art

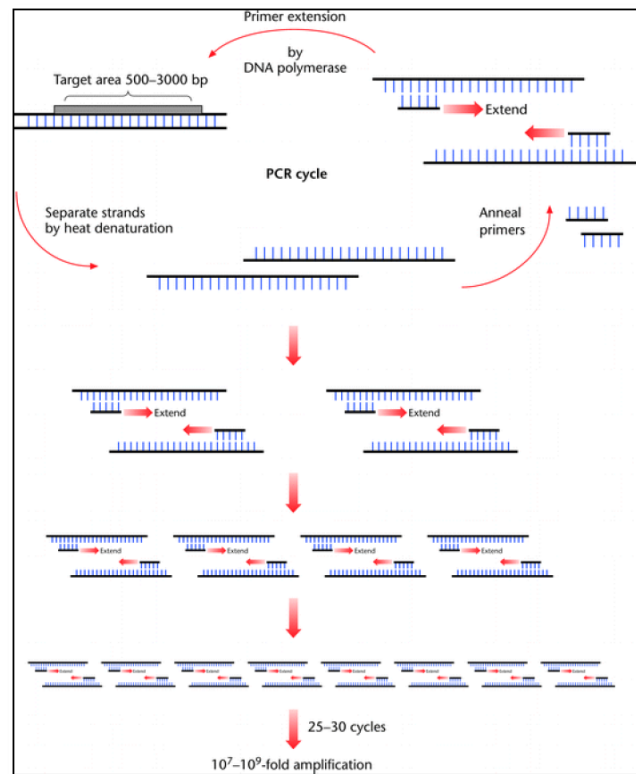
Independent claims 1 and 17 are challenged as obvious in view of second-tier art recycled from the face of the ’306 patent. Specifically, the petition argues that the tagging (barcoding), amplifying (PCR amplification) and sequencing of Bielas satisfies the challenged claims, particularly in view of Vogelstein. Grounds 2-4 relate only to dependent claims; thus, it is unnecessary to address the additional art asserted in these grounds to deny the petition.

² Forshew and Diehn were of record in the 1400IPR as was the Kinde reference which, like Vogelstein, discusses the SafeSeqS method.

1. The Proposed Amplification Generates Indistinguishable Progeny Duplexes

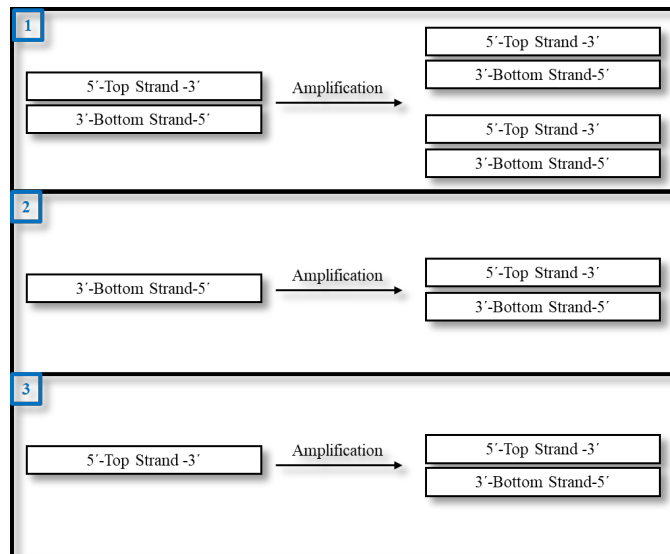
The petition relies on tagging DNA target molecules as specifically described by the Bielas reference. *See, e.g.*, Pet. 24-27 (citing only Bielas for Element [1b1]). According to the petition, such tagged molecules are then amplified or copied using PCR and the amplified progeny molecules sequenced to generate sequence reads. As Petitioner’s own expert confirms, the proposed amplification renders the process blind as to whether the original sample molecule is single-stranded (e.g., a singlet) or double-stranded—in either instance, identical duplex progeny is generated.

As Dr. Metzker explains, PCR amplification is used to make copies of the original DNA molecules. EX1003, ¶61; *see also id.*, ¶62 (“generating thousands to millions of copies of the target nucleic acid”). Copies (e.g., amplicons) are generated using an iterative process involving denaturation and replication of complementary DNA strands. EX1003, ¶63. The replication step is performed by DNA polymerase



which synthesizes a complementary strand from each single-stranded template. *Id.* DNA polymerase initiates synthesis of the complementary strand from a primer that hybridizes to the template in a 5'-to-3' direction to create double-stranded DNA progeny. *Id.* Because two primers are used—one that hybridizes to the top strand and one that hybridizes to the bottom strand³—complementary strands for both the top and bottom strand are generated. *Id.* This process is depicted in the schematic accompanying paragraph 63 (reproduced above) of Dr. Metzker's declaration.

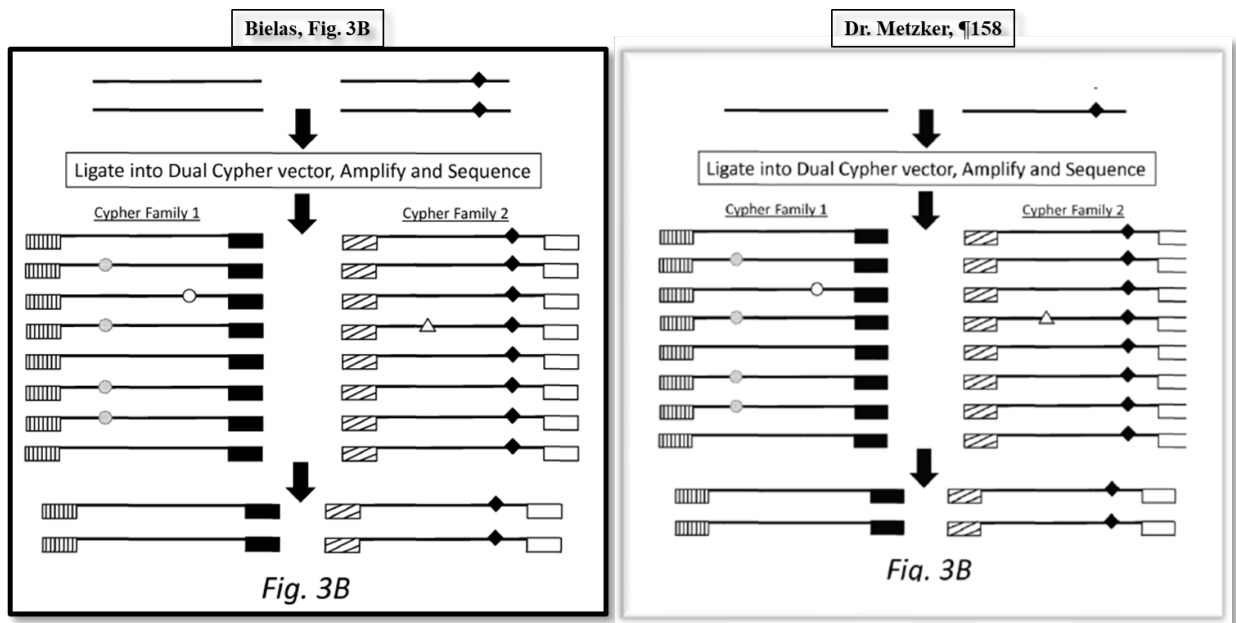
As illustrated in the below schematic, amplification generates the same duplex progeny as copies. If both strands of an original template are amplified (box 1), duplex progeny is produced. If only one strand of the original template is amplified (boxes 2 or 3), the same duplex progeny is produced. The



³ The use of “top” and “bottom” strand labels is arbitrary—the top strand is the complement of the bottom strand and *vice versa*. See EX1003, ¶¶41-43.

amplification products of 1, 2, and 3 are indistinguishable. Sequencing a duplex progeny molecule generates a sequence read for one strand (e.g., top) and a read for its complement (e.g., bottom) with no indication of original strand origin.

As Dr. Metzker’s testimony illustrates, Bielas is oblivious to whether one strand or both strands of a target molecule are amplified since the same duplex progeny is produced in either scenario. Figure 3B of Bielas illustrates duplex progeny produced for two different double-stranded molecules and corresponding sequence reads that are grouped by identical cyphers (barcodes) into a family. At ¶158, Dr. Metzker illustrates how the same duplex progeny is produced even where only a single-strand is amplified. In either instance, the cypher families are identical, rendering the two different scenarios indistinguishable.



2. Bielas

Bielas discloses “Cypher Seq” which is described as a method for reducing errors associated with preparation and sequencing of DNA molecules. EX1005, 4:8 (“Cypher Seq eliminates errors introduced during library preparation and sequencing”), 5:8-24 (“The compositions and methods of this disclosure allow a person of ordinary skill in the art to more accurately distinguish true mutations (*i.e.*, naturally arising *in vivo* mutations) of a nucleic acid molecule from artifact ‘mutations’ ...”).

Bielas’s method generally includes assigning cyphers (e.g., barcodes) to opposing ends of target DNA molecules using a circular dual cypher vector followed by amplifying the cypher-tagged molecules using PCR, and sequencing the amplification progeny. *E.g.*, EX1005, Figs. 1-2, 3B, 3:29-4:17, 6:10-27. The resulting sequence reads are then grouped into families that share the same pair of cyphers (*i.e.*, all strands of duplex progeny). *Id.*, Fig. 3B, 4:4-17, 5:30-6:9, 7:8-16, 25:7-12, 29:26-30:2. Following grouping, a consensus sequence is built from the grouped sequence reads and mutations are distinguished from sequencing errors. *Id.*, Fig. 3B, 4:4-17, 29:26-30:2.

As plainly illustrated in Bielas, the same cyphers are present on each strand of a duplex DNA molecule, which are copied (amplified), sequenced and indiscriminately grouped into the same family based on having the same cypher.

Bielas does not describe distinguishing sequence reads in any capacity (e.g., as either paired or unpaired) and, in fact, cannot do so. *See* §IV.A.

3. Vogelstein

Vogelstein discloses “SafeSeqS” which is described as a method for producing error-corrected sequence reads. EX1006, Abstract. Vogelstein discloses several embodiments. In one embodiment, no UID is introduced at all, rather native sequence at the target molecule end is used as a UID. *E.g.*, EX1006, [13] (discussing endogenous UIDs). In other embodiments, UID’s are introduced in progeny molecules through a PCR amplification process. [14] (discussing assigning exogenous UIDs with PCR), [16] (discussing inverse PCR method). The petition makes no distinction between the various embodiments. *See, e.g.*, Pet. 3, 34-35 (“After sequencing, ‘reads [are] grouped into families based on their *endogenous or exogenous UIDs.*’”), 36, 42, 51, 53.

No embodiment of Vogelstein involves use of a circular vector such as described by Bielas.

III. CLAIM CONSTRUCTION

In an *inter partes* review, a claim is given its ordinary and customary meaning in light of the specification. 37 C.F.R. §42.100(b); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc). No specific construction is believed necessary to deny the petition. *Nidec Motor Corp. v. Zhongshan Broad*

Ocean Motor Co., 868 F.3d 1013, 1017 (Fed. Cir. 2017).

While no construction is necessary, the plain language of claims 1 and 17 set forth what is meant by “paired read” and “unpaired read.” Specifically, a paired read “correspond[s] 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.” On the other hand, an unpaired read “correspond[s] 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.” That is, whether a read is paired or unpaired depends on whether there are sequence reads representing both strands or only one of the two strands of the original cfDNA molecule.

Petitioner never addresses the plain language of the claims. Instead, it erroneously points to the sequencing of a duplex progeny producing a sequence read for one strand and another read for the other strand (e.g., complement). *E.g.*, Pet. 33, 45. But, as discussed above, double-stranded DNA molecules (e.g., duplex progeny from PCR amplification) comprise complementary strands. *See* §II.C.1; EX1003, ¶¶41-43. But obtaining sequence reads from both strands of an amplicon, for example, does not satisfy the plain language of the claims.

Additionally, as discussed herein, Petitioner’s assertion here that no claim construction is necessary is inconsistent with its arguments at district court. There,

Petitioner asserts that the scope of claims 1-29 of the '306 is indeterminable and unpatentably indefinite based on multiple recited terms. *See* EX2015, 2-3. For other terms, Petitioner has argued at district court narrow interpretations to avoid infringement. *Id.* None of these district court claim construction arguments or positions are discussed in the petition materials, let alone accounted for in the prior art mapping allegations of the petition. Petitioner's claim construction gamesmanship and, in some instances, flatly ignoring claim language provides ample reason to deny the petition. *See Revvo Technologies, Inc. v. Cerebrum Sensor Technologies, Inc.*, IPR2025-00632, Paper 20 at 5 (precedential); *Tesla, Inc. v. Intellectual Ventures II LLC*, IPR2025-00340, Paper 18 at 4 (informative).

IV. GROUND 1 FAILS

Petitioner alleges that independent claims 1 and 17 along with dependent claims 2, 7-8, 12-13, 18, 20-21, 24-26, and 29, would have been obvious over Bielas in view of Vogelstein. *See* Pet., 20-53. As explained below, the combination of Bielas and Vogelstein does not teach or suggest identifying “paired” or “unpaired” reads as required by claims 1-29. Furthermore, the petition materials fail to identify any prior art teaching of tagging cfDNA molecules with “n different combinations of molecular barcodes, wherein n is at least 2 and no more than 100,000*z” as required by claim 1-16 and 29.

Accordingly, the petition is fatally flawed for failure to establish that each

and every claim element was known in the prior art.

A. Bielas is Undisputedly Blind to Whether Reads are Paired or Unpaired

The petition materials fail to establish that cited art teach or suggest identifying “paired” and “unpaired” as specifically recited in claims 1 and 17.

Claim 1
(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
(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 petition relies on Bielas for tagging DNA target molecules—there is no modification proposed for the circular cypher plasmid of Bielas. *See, e.g.*, Pet. 24-27, 43. (citing only Bielas for Element [1b1]). Regarding “paired” and “unpaired”

reads, this aspect of claims 1 and 17 is addressed at pages 32-35 and 44-47 of the petition, where Petitioner relies on Bielas and Vogelstein. Specifically, for both claims, Petitioner asserts Bielas alone teaches determining cfDNA molecules based on “paired reads” and Vogelstein alone teaches determining cfDNA molecules based on “unpaired reads.”

Petitioner relies solely on a phrase from the caption of Fig. 3B as meeting the requirement for paired reads. Pet. 33 (citing EX1005, 4:10-12), 44-45 (citing EX1005, 4:10-12). Bielas describes Fig. 3B at 4:10-12 as depicting “[a]ll sequencing reads having identical cypher

pairs, along with their reverse complements, were grouped into families.” But the petition never addresses “paired” reads as specifically recited in the challenged claims. The natural structure of double-stranded DNA is a double-helix comprising complementary

strands. EX1003, ¶¶41-43. Duplex progeny produced from the PCR amplification process (amplicons) indeed comprise two complementary strands. As discussed above, the petition provides no explanation how the mere sequencing of duplex progeny distinguishes between amplification of a single-strand molecule versus a double-stranded molecule when either scenario produces the same PCR

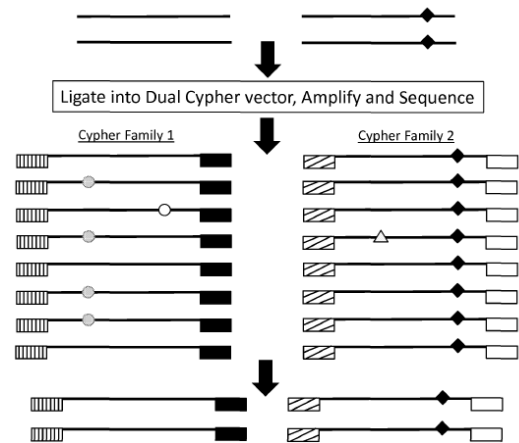


Fig. 3B

amplification product. Nor does the petition identify any distinct sequence or characteristic that would distinguish an amplification product of one target strand versus an amplification product of the other strand. There is none in Bielas. As disclosed in Bielas and confirmed in the petition materials, all sequence reads generated from duplex progeny (e.g., sequence read of one strand and a read of its complement) contain the same cypher pair. Identification of a generic read and its reverse complement is not disclosure of a “paired read” or “a first tagged strand and a second tagged complementary strand derived from cfDNA molecules,” as specifically recited in the challenged claims. Nothing in the petition materials demonstrates otherwise.

Indeed, as acknowledged in the petition (p. 44), Bielas relies on the same cypher being present on both reads and their reverse complements and must specifically group them together—there is no basis of distinction by Bielas’s own design. As expressly shown in Fig. 3B, all grouped reads are identical (other than sporadic errors).

The petition’s (pp. 15, 34, 45) annotations to Fig. 3B placing boxes around “paired reads” is unsupported attorney argument that should be given no weight. Bielas itself does not include the same attorney-generated annotations. Moreover, no such annotated version of Bielas Fig. 3B is found in Dr. Metzker’s declaration. Petitioner’s own expert was either unwilling or unable to support this argument.

Nothing in Bielas indicates it distinguishes the strand origin of different sequence reads or otherwise distinguishes whether the sequenced PCR progeny was generated from a single-strand molecule or a DNA duplex molecule. Nothing in the petition establishes otherwise.

In contrast, it is well documented in the scientific literature that Bielas's Cypher Seq method cannot determine if one or both strands of an original DNA molecule are represented in the sequence reads. For example, Salk in 2018 explained:

A more recent variant upon this method, known as CypherSeq, incorporates rolling-circle amplification from primers targeting both strands after ligation into a circularized adapter sequence to achieve a degree of target enrichment before PCR amplification (FIG. 2e). With both methods, PCR products derived from each strand of individual molecules can be used to form a consensus sequence; however, as the *amplicons of the two strands are indistinguishable, it is impossible to tell whether the resulting consensus is based on single-strand or double-strand data.*

EX2024, 275; *see also id.*, Fig. 2, 272 (“Although information from both strands may contribute to consensus making, lack of asymmetry between the two strands makes it *impossible to discern* whether one or both strands is successfully amplified.”).

Bae confirmed the same in a 2021 publication:

CypherSeq generates a circularized duplex followed by rolling circle amplification, but the lack of asymmetry between the two strands *obscures whether both strands were actually sequenced.*

EX2023, 1.

Because Bielas cannot determine if one or both strands of the original DNA are sequenced, it does not—and cannot—identify sequence reads as either paired or unpaired reads as claimed. This fatal flaw cannot be overcome by combination with Vogelstein or any other reference.

B. Vogelstein Does Not Cure the Deficiency of Bielas

As an initial matter, the petition mischaracterizes the disclosure of Vogelstein. Petitioner relies on Vogelstein alone for alleged identification of “unpaired reads.” The petition argues “A POSA would understand that [Vogelstein’s] UID families are unpaired reads.” Pet. 34-35, 45-46. But Petitioner fails to substantiate this argument. The petition only points to Vogelstein’s off-hand remark acknowledging the imperfect nature of amplification reactions. *See* EX1006, ¶[66] (“various amplifications are not perfect, so every strand of every original template molecule is not recovered as a UID family”). But a mere acknowledgement that amplification is not always perfect does not establish that Vogelstein’s UID families are necessarily “unpaired reads” as claimed, or that Vogelstein makes any distinction between reads that are “paired” or “unpaired.” The petition admits as much, retreating to the watered-down assertion that “a

POSA would understand that at least some families of Vogelstein are families of unpaired reads....” Pet. 46. But the petition identifies no disclosure of such in Vogelstein because there is none. Only *ipse dixit* is cited, which points back to the same comment in Vogelstein that “various amplifications are not perfect.”

Vogelstein does not discuss identifying, sorting or separately processing unpaired reads. No such disclosure is found in Vogelstein and the petition does not establish otherwise.

Regardless of the disclosure in Vogelstein, that reference cannot cure the deficiencies of Bielas at least because the petition proposes no modification of Bielas amenable to cure. As discussed above, the petition relies only on Bielas for tagging DNA target molecules—there is no modification proposed for the circular cypher plasmid of Bielas. *See, e.g.*, Pet. 24-27, 43 (citing only Bielas for Element [1b1]). The proposed amplification and sequencing in the petition stems from this same cypher plasmid product of Bielas. Bielas is also relied upon for downstream amplification and sequencing, with a comment that Vogelstein “also discloses” PCR amplification and sequencing using a “commercially available” sequencing platform.” *See, e.g.*, Pet. 31-32. There is no modification proposed for the cypher plasmid product of Bielas and certainly none that would cure Bielas’s inability to distinguish between any reads that are “paired” versus “unpaired.”

No modification is proposed, let alone any explanation as to how a

combination of the fundamentally different methods of Bielas and Vogelstein would be accomplished. *Personal Web Technologies, LLC v. Apple, Inc.*, 848 F.3d 987, 993–94 (Fed. Cir. 2017) (explaining that “a clear, evidence-supported account of the contemplated workings of the combination is a prerequisite to adequately explaining and supporting a conclusion that a relevant skilled artisan would have been motivated to make the combination and reasonably expect success in doing so.”). Petitioner offers only the conclusory assertion that a “POSA would have understood that the methods disclosed in Vogelstein could be used with those disclosed in Bielas.” Pet. 22. Nothing is discussed in the petition beyond conventional PCR amplification and use of a commercial sequencing platform, teachings which Petitioner asserts do not require modification of Bielas.

Accordingly, Vogelstein fails to cure the deficiencies of Bielas nor is there any modification proposed that would change this fact.

C. Petitioner Does not Assert the Z Limitation is Taught in the Prior Art

The petition fails to establish the cited prior art discloses tagging according to the number of duplicate molecules in a sample as required by claims 1-16 and 29:

(b) tagging a plurality of the cfDNA molecules in the population with duplex tags ... 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;

Petitioner purports to address this limitation at pages 27-30 where it relies on Bielas and Vogelstein.

Petitioner maintains in the co-pending district court case that this limitation is indefinite. *See also* EX2015, 2; Pet. 27 (“Without taking a position on whether a POSA would have understood the ‘ z ’ term...”). In service of its indefiniteness position, Petitioner identifies no prior art disclosure of tagging with a number of molecular barcodes based on the number of expected duplicate molecules. Instead of addressing the claim language, Petitioner takes the value of z from claim 7 (“wherein z is between 2 and 8”) and only maps disclosure of values of n calculated based on the range of z claimed in the ’306 patent. *E.g.*, Pet. 28 (“Bielas alone or in view of Vogelstein discloses the use of a number of different molecular barcode combinations within the claimed range.”); *see also id.*, 37-38 (mapping number of barcodes onto “ z is between 2 and 8”). Having ignored part of the claim language, Petitioner cannot show the asserted obviousness combination teaches tagging as claimed.

While it is not Patent Owner’s burden to show nonobviousness, it is readily apparent why Petitioner opted not to map prior art disclosure. Neither Bielas nor Vogelstein describe tagging cfDNA molecules with far fewer molecular barcode

combinations than sample molecules as claimed. In fact, these references teach just the opposite.

Petitioner assumes that z is between 2 and 8 for purposes of its analysis, but ignores the corresponding sample population as implicated by the language specifying “a mean of an expected number of duplicate molecules in the population.” The ’306 patent explains that a sample comprising “10,000 haploid human genome equivalents of fragmented genomic DNA, e.g., cfDNA, z is expected to be between 2 and 8.” EX1001, 20:47-50. The ’306 patent further describes such a sample as comprising “about 200 billion (2×10^{11}) individual polynucleotide molecules.” *Id.*, 16:60-64. Thus, when z is between 2 and 8, the claim specifies using between 2 and 800,000 different combinations of molecular barcodes to tag 200 billion cfDNA molecules. Even if the maximum number of molecular barcode combinations is used, there are 250,000 times as many cfDNA molecules as combinations of molecular barcodes.

Bielas and Vogelstein however instruct unique tagging in which an *excess* of different combinations of molecular barcodes are used relative to the number of DNA molecules in the sample. While ignored in the petition’s discussion of claim 1, there seems to be agreement that Vogelstein teaches using an excess of barcodes relative to the number of target molecules. *See* Pet. 60 (citing EX1006, [08]) (“Vogelstein teaches that the barcodes should be in excess of the target DNA

molecules.”). Indeed, Vogelstein repeatedly emphasizes using more barcodes than target molecules in the sample. EX1006, [08] (“The UIDs are in excess of the analyte DNA fragments during amplification.”), [27] (“Because the diversity of UIDs is greatly in excess of the diversity of the fragments, ...”), [57] (“It is important that the number of distinct UIDs greatly exceed the number of original template molecules to minimize the probability that two different original templates acquired the same UID.”).

Bielas similarly instructs that each target molecule receives a unique combination of cyphers. *E.g.*, EX1005, 5:24-26 (“the two cyphers on each target molecule have sequences that are distinct from each other and, therefore, provide a unique pair of identifiers”), 15:29-16:2 (“each target nucleic acid molecule of a library will have a unique pair of cyphers that differ from each of the other pairs of cyphers found associated with each other target nucleic acid molecule of the library”), 16:11-24 (“provided that the double-stranded cypher for each target nucleic acid molecule is different... target nucleic acid molecules of the nucleic acid molecule library will each have a unique pair of X^a - X^b cyphers wherein none of the X^a or X^b cyphers have the same sequence”).

For Petitioner’s assumed sample size of 200 billion cfDNA molecules, Bielas and Vogelstein teach at least 200 billion different combinations of molecular barcodes are required. Yet, Petitioner proposes using 16,384 (Bielas) or

256 (Vogelstein) different combinations of molecular barcode. Such small numbers of molecular barcodes are inconsistent with the teachings of both references.

V. GROUND 2 FAILS

Petitioner alleges that claims 3 and 9-11, which depend from claim 1, and claims 19 and 22-23, which depend from claim 17, would have been obvious over Bielas in view of Vogelstein and Forshew. *See* Pet., 54-59. As explained above, the combination of Bielas and Vogelstein does not teach or suggest each and every limitation of claims 1 or 17. Petitioner does not allege that Forshew teaches or suggests any of the limitations of claims 1 or 17. Accordingly, Ground 2 may be rejected for the same reasons as discussed above with respect to claims 1 and 17.

VI. GROUND 3 FAILS

Petitioner alleges that claims 4-6 which depend from claim 1, would have been obvious over Bielas in view of Vogelstein, Hendricks and/or Diehn. *See* Pet., 60-62. As explained above, the combination of Bielas and Vogelstein does not teach or suggest each and every limitation of claim 1. Petitioner does not allege that Hendricks or Diehn teaches or suggests any of the limitations of claim 1. Accordingly, Ground 3 may be rejected for the same reasons as discussed above with respect to claim 1.

VII. GROUND 4 FAILS

Petitioner alleges that claims 14-16, which depend from claim 1, and claims 27-28, which depend from claim 17, would have been obvious over Bielas in view of Vogelstein and Hicks. *See* Pet., 64-69. As explained above, the combination of Bielas and Vogelstein does not teach or suggest each and every limitation of claims 1 or 17. Petitioner does not allege that Hicks teaches or suggests any of the limitations of claims 1 or 17. Accordingly, Ground 4 may be rejected for the same reasons as discussed above with respect to claims 1 and 17.

VIII. CONCLUSION

Petitioner has failed to make a facial case of unpatentability for any challenged claim, so institution is unwarranted and should be denied.

Respectfully submitted,

Date: November 20, 2025

/ Michael T. Rosato /
Michael T. Rosato, Lead Counsel
Reg. No. 52,182

CERTIFICATION UNDER 37 C.F.R. §42.24(d)

Pursuant to §42.24(d), the undersigned certifies that this paper contains no more than 14,000 words, not including the portions of the paper exempted by §42.24(b). According to the word-processing system used to prepare this paper, the paper contains 5,166 words.

Respectfully submitted,

Date: November 20, 2025

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IX. APPENDIX

Exhibit No.	Description
2001	Excerpts from File History of U.S. Patent Application No. 16/945,124 (issued as U.S. Patent No.11,149,306)
2002	Excerpts from File History of EP Application No. 20183626.9
2003	Information Disclosure Statement App. No. 17/179,279 which issued as U.S. Patent No. 11,221,144
2004	U.S. Patent No. 11,211,144 to Zhu
2005-2014	Intentionally left blank
2015	Tempus Proposed Claim Constructions, <i>Guardant Health, Inc., v. Tempus AI, Inc.</i> , Case 1:24-cv-00687
2016	Guardant Health Introduces Major Smart Liquid Biopsy Upgrade to Market – Leading Guardant 360 Test, Further Extending its Best-In-Class Performance. https://investors.guardanthealth.com/press-releases/press-releases/2024/Guardant-Health-Introduces-Major-Smart-Liquid-Biopsy-Upgrade-to-Market-Leading-Guardant360-Test-Further-Extending-Its-Best-in-Class-Performance/default.aspx (last viewed on October 20, 2024)
2017	Guardant Health to Showcase New Data at ESMO 2022 Demonstrating Utility of its Portfolio of Blood Tests for Advanced – Stage Cancer Patients. https://investors.guardanthealth.com/press-releases/press-releases/2022/Guardant-Health-to-showcase-new-data-at-ESMO-2022-demonstrating-utility-of-its-portfolio-of-blood-tests-for-advanced-stage-cancer-patients/default.aspx (last viewed on October 20, 2024)
2018	FDA Approves First Liquid Biopsy Next-Generation Sequencing Companion Diagnostic Test. News Provided by U.S. Food and Drug Administration https://www.prnewswire.com/news-releases/fda-approves-first-

	liquid-biopsy-next-generation-sequencing-companion-diagnostic-test-301108536.html (last viewed October 20, 2024)
2019	GOZILA Study Published in Nature Medicine Shows Patients with Advanced Cancer Who Receive Liquid Biopsy – Guided Treatment Using Guardant360 CDX Survive Twice as Long. https://investors.guardanthealth.com/press-releases/press-releases/2024/GOZILA-Study-Published-in-Nature-Medicine-Shows-Patients-With-Advanced-Cancer-Who-Receive-Liquid-Biopsy-Guided-Treatment-Using-Guardant360-CDX-Survive-Twice-as-Long/default.aspx (last viewed October 20, 2024)
2020	Guardant Health Named to TIME100 Most Influential Companies. https://investors.guardanthealth.com/press-releases/press-releases/2024/Guardant-Health-Named-to-TIME100-Most-Influential-Companies/default.aspx (last viewed October 20, 2024)
2021	Guardant Health and Foundation Medicine Reach Settlement in Digital Sequencing Technology Litigation. https://investors.guardanthealth.com/press-releases/press-releases/2022/Guardant-Health-and-Foundation-Medicine-Reach-Settlement-in-Digital-Sequencing-Technology-Litigation/default.aspx (last viewed October 20, 2024)
2022	Guardant Health, Inc.’s First Amended Complaint, <i>Guardant Health, Inc., v. Tempus AI, Inc.</i> , Case 1:24-cv-00687
2023	Jin H. Bae, et al., “CODEC enables ‘single duplex’ sequencing”
2024	Jesse J. Salk, Michael W. Schmitt, and Lawrence A. Loeb, “Enhancing the accuracy of next-generation sequencing for detecting rare and subclonal mutations”

CERTIFICATE OF SERVICE

The undersigned certifies that the foregoing Patent Owner's Preliminary Response and accompanying Exhibits 2023-2024 were served on November 20, 2025, on the Petitioner at the electronic correspondence address of the Petitioner as follows:

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