

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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TEMPUS AI, INC.,  
Petitioner,

v.

GUARDANT HEALTH INC.,  
Patent Owner.

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IPR2025-01435  
Patent 10,793,916

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**PATENT OWNER'S  
PRELIMINARY RESPONSE**

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## I. INTRODUCTION

The Board has considered the Schmitt reference—the primary reference here—nine times in relation to Guardant’s claimed inventions.<sup>1</sup> In no instance have Guardant’s claims been invalidated or canceled in view of Schmitt. Petitioner asks the Board to consider Schmitt for a tenth time as it relates to the patentability of claims 13-30 of the ’916 patent but provides no good reason to do so.<sup>2</sup>

In fact, the Board recently addressed claims with similar language in IPR2022-01400 (“the 1400IPR”) and determined that claims reciting “attaching” molecular barcodes to cfDNA molecules—just like the currently challenged

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<sup>1</sup> IPR2019-00652 (vacated in *Guardant Health, Inc. v. Vidal*, No. 2021-1104, 2023 U.S. App. LEXIS 11037 (Fed. Cir. 2023)), IPR2019-00636, IPR2019-00637, IPR2022-00746, IPR2022-00747, IPR2022-01115, IPR2022-01116, IPR2022-01152, IPR2022-01400.

<sup>2</sup> This petition does not even challenge all claims of the ’916 patent or all claims that Guardant is contending are infringed at district court. Specifically, claims 1-12 are unchallenged here but asserted at district court. This is yet another illustration that the present challenge is a waste of judicial resources generally and a poor use of Board resources specifically.

claims—do not encompass Schmitt’s hybrid embodiment relied on here. Petitioner never grapples with this decision and fails to provide any reason for a different outcome here.

Lacking a compelling obviousness theory, Petitioner engages in claim construction gamesmanship. Specifically, Petitioner advances incompatible claim construction positions between the district court and the Board. At district court, Petitioner asserts that multiple elements of claims 13-30 are indefinite. *See, e.g.*, EX2015. Yet the petition, without explanation or acknowledgement of its district court positions, inconsistently argues 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, 5 (precedential); *Tesla, Inc. v. Intellectual Ventures II LLC*, IPR2025-00340, Paper 18, 4 (informative).

To the extent the merits are reached, there is good reason why the Examiner allowed the claims over the asserted prior art. None of the asserted references teach a method for determining rare somatic alterations (e.g., microsatellite changes) in cfDNA obtained from patients. Petitioner’s argument boils down to arguing a POSA could have used Schmitt to do so. But this argument fails to address any of the countervailing evidence including: the Board’s prior findings regarding Schmitt, Petitioner’s own conflicting arguments to the Office, and the teachings of the asserted references. Instead of addressing this evidence, Petitioner clings to a

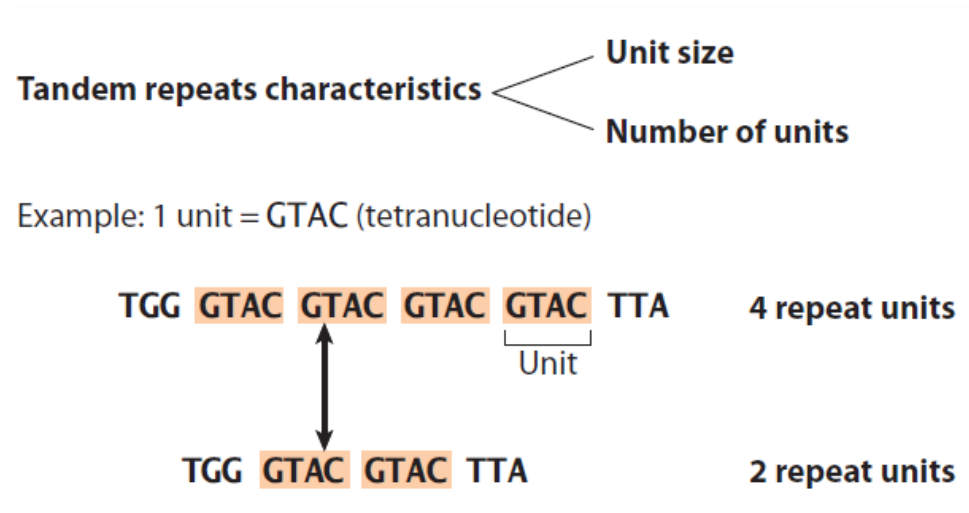
vacated Board decision concerning different art and claims of materially different scope.

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

## II. BACKGROUND

### A. Detection of Instability in Microsatellite Regions

Microsatellite regions are “short tandem repeats with units less than ten nucleotides long.” EX1033, 446; *see also id.*, Fig. 1 (reproduced in part below).



Certain diseases (e.g., cancer) are associated with microsatellite instability (“MSI”) which results in an accumulation of insertions and deletions (e.g., changes) within microsatellite regions across the genome. EX1035, Abstract. Tests for MSI typically involve determining change in several microsatellite regions. EX1035, Abstract (“no single marker is accurate enough for MSI testing”); *see also* EX1001, claims 13 & 30 (“comprising microsatellite changes in the one or

more microsatellite regions”); EX2014, 1 (“>19 unstable MS [microsatellite] sites”). As discussed, in detail below, in pursuing its own patents Petitioner itself has argued that detecting MSI is significantly more challenging than detecting other types of rare somatic mutation—particularly when the detecting is performed in cfDNA. *See* §IV.C.

The ’916 patent is directed to laboratory techniques for DNA sequencing-based methods for detecting rare somatic mutations (e.g., < 1%) including changes in microsatellite regions, in cfDNA samples derived from cancer patients. *E.g.*, EX1001, Abstract, 30:15-31, 61:8-65; *see also* EX2014, 1 (reporting limits of detection of < 1%). Specifically, the ’916 patent solves prior art challenges by providing innovative techniques for ligating adapters comprising barcodes to cfDNA using a specific number of molecular barcodes and performing innovative techniques for, among other things, amplifying, enriching, sequencing, and aligning cfDNA strands. The sequencing-based methods described and claimed allow sensitive detection of changes in microsatellite regions even in samples containing minute amounts of cfDNA. *E.g.*, EX1001, 4:9-22, 9:13-24, claims 13, 25 (“the sample of cell-free nucleic acid molecules comprises 1 nanogram (ng) to 100 ng of cell-free nucleic acid molecules”), 30.

## **B. The Board Previously Rejected a Similar Challenge**

Petitioner cites an old and vacated Board decision but never discusses the recent and more pertinent decision in the 1400IPR distinguishing the same relied-upon prior art from the claims of U.S Pat. No. 11,149,306 (“the ’306 patent”). Various un rebutted findings in the 1400IPR undermine the current petition challenge but are ignored here.

For example, the Board in the 1400IPR determined that claims reciting “attaching” molecular barcodes to cfDNA molecules—just like the currently challenged claims—do not encompass Schmitt’s hybrid embodiment relied on here. Specifically, the Board found that the plain language of claim 1 of the ’306 patent “distinguishes the duplex tags [comprising molecular barcodes] from the ends of the cfDNA molecule to which they are attached.” EX1027, 21. “That is, the duplex tag is not part of the cfDNA molecule itself, but rather is ‘attached to both the ends’ of that molecule by ‘tagging’ it as recited in element 1(b).” *Id.* The Board further found that such claims “do[] not encompass Schmitt’s hybrid embodiment” because the SMI (molecular barcode) includes sequences within the DNA molecule itself (“end of the target DNA”). *Id.*, 21-22. That is, Schmitt’s hybrid molecular barcode includes part of the DNA molecule itself rather than being “attached” to the DNA molecule.

Claims 13 and 30 of the '916 patent similarly recite “ligating” or “attached” molecular barcodes that are distinguished from the cfDNA molecule itself. The plain language of claim 13 specifies the “molecular barcodes” are ligated to the “cell-free nucleic acid molecules.” Claim 30 specifies the “molecular barcodes” are attached to the “cfDNA molecules.” That is, unlike the relied-upon Schmitt method, the claimed molecular barcode is not part of the original cfDNA molecule.

Despite this distinction confirmed previously, Petitioner here relies on the same Schmitt hybrid embodiment rejected by the Board in the 1400IPR. With respect to step **a** of claim 13, Petitioner points to the hybrid method as satisfying the claim limitation. *See* Pet. 36 (citing EX1005, 9:9-13) (“Schmitt also discloses a DCS ‘hybrid method’ ...”). Petitioner relies on this same disclosure for step **a** of claim 30. Pet. 56 (“see 13[a]”), 62 (pointing to Ground 1). Petitioner’s assertion of Schmitt’s hybrid embodiment for the “ligating”/“attached” step of independent claims 13 and 30 fails for the same reason as it did in the 1400IPR. *SynQor, Inc. v. Vicor Corp.*, 988 F.3d 1341, 1351 (Fed. Cir. 2021) (“Factual determinations made by the expert agency entrusted by Congress to make those determinations—and to make them finally—need not be endlessly reexamined.”).

Furthermore, there does not seem to be any dispute that sensitive methods are needed for determining microsatellite changes in cfDNA samples. *E.g.*, Pet. 28 (quoting EX1010, 1) (“[s]ensitive methods”), 28 (“high accuracy and sensitivity”).

Yet, despite acknowledging this need, the petition materials never address evidence and findings from the 1400IPR demonstrating that Schmitt is anything but sensitive.

Guardant established in the 1400IPR, without rebuttal from Schmitt's owner/petitioner, that Schmitt analyzes only a tiny fraction of the DNA molecules within a sample. Specifically, Schmitt's preferred embodiment (e.g., Example 1 of EX1005) produces duplex consensus sequences for about 2 out of every billion DNA molecules. EX2006, 28-29; *see also* EX2007, 29:20-30:9 ("No, Your Honor, Petitioner did not dispute Dr. Quackenbush's calculations"). The massive loss in sample and data is described in Schmitt itself as well as the scientific literature. EX2006, 24, 27-32, 58-60. Schmitt's loss of sample molecules and data is relevant in assessing sensitivity because mutations cannot be determined in sample molecules that are never analyzed. *See also* EX2007, 30:12-24 (Schmitt's owner explaining the distinction between "accuracy" and "sensitivity" and agreeing that Schmitt's error correction is about accuracy).

The Board credited Guardant's evidence and the admissions of Schmitt's owner regarding sample and data loss in the 1400IPR FWD. EX1027, 29 ("Patent Owner cites evidence, as well as Petitioner's own argument, to show that 'this problem was widely recognized in the scientific literature...'", 33 (crediting

evidence of “sequencing errors” and “data loss”). Given the extreme amount of sample/data loss, the Board questioned Schmitt’s application to cfDNA.

Okay. Now I understand your argument that Schmitt’s method is designed to filter out data, sort of by design, in order to increase accuracy through error checking. But isn’t there a point where one filters out too much data such that Schmitt’s DCS method might not be the best choice of sequencing methods in a scenario where you have a more limited supply of input DNA, such as might be the case with cfDNA?

EX2007, 30:25-31:4. Schmitt’s owner had no answer other than to propose modifications to Schmitt to provide more input DNA. EX2007, 31:5-14 (“boost up the input DNA”). Petitioner here proposes no such modification and ignores the countervailing evidence and findings by the Board.

Guardant further identified in the 1400IPR that a follow-up publication by the same Schmitt inventors reported that the Schmitt method was essentially inoperable where the SMI tag (e.g., alleged molecular barcode) was less than 12 nucleotides in length. EX2006, 32-34 (citing Kennedy, EX2023, 2591) (“a tag length of <12 is incompatible with the Illumina sequencer...and should be avoided.”). Remarkably, the present petition ignores Kennedy and proposes using 4-mer tag embodiments that Schmitt inventors themselves instructed should be “avoided” as non-functional. Pet. 36 (“4-mer tags”), 7-9, 48 (discussing Illumina

sequencing). Not only is Kennedy unaddressed but no modifications to Schmitt are proposed.

### **C. The Vacated 652IPR Decision Does not Control**

Instead of addressing the 1400IPR FWD, Petitioner puts its reliance on the vacated Board decision in IPR2019-00652 (“the 652IPR”) concerning U.S. Pat. No. 9,834,822 (“the ’822 patent”). Petitioner’s reliance is misplaced.

The 652IPR decision does not control here at least because it was vacated by the Federal Circuit. *Guardant Health, Inc. v. Vidal*, No. 2021-1104, 2023 U.S. App. LEXIS 11037 (Fed. Cir. 2023). A “judgment’s vacatur on appeal renders it a legal nullity.” *Statewide Reapportionment Advisory Comm. v. Beasley*, 99 F.3d 134, 136 (4th Cir. 1996) (quoting *S-1 by & Through P-1 v. State Bd. of Educ.*, 6 F.3d 160, 171 (4th Cir. 1993)); *see also Durning v. Citibank, N.A.*, 950 F.2d 1419, 1424 n.2 (9th Cir. 1991) (“[A] decision that has been vacated has no precedential authority whatsoever.” (citing *O’Connor v. Donaldson*, 422 U.S. 563, 578 n.12 (1975))). Contrary to Petitioner’s argument (pp. 2, 63), the ’822 claims have not been invalidated nor have they been partially canceled.

Furthermore, the ’822 patent claims are materially different than those of the ’916 patent. For example, claim 1 of the ’916 patent is directed to detecting “genetic variation in one or more microsatellite regions” and further recites determining “a quantitative measure of polymorphic forms comprising

microsatellite changes in one or more microsatellite regions.” Such language is not recited in the ’822 patent claims, which do not mention “microsatellite” changes or regions. In fact, claim 1 of the ’822 patent does not require detection of somatic variants in cfDNA nor do they mention cancer patients; the petition does not assert otherwise. The 652IPR had nothing to do with the issue of detecting “microsatellite changes” as recited in the current claims. Nor did the 652IPR address the currently relied upon references to Porreca or Sacko.

In addition, the ’822 patent claims recite “converting the population of cfDNA molecules into a population of non-uniquely tagged parent polynucleotides”—language not found in the ’916 patent claims. In contrast, the ’916 patent claims recite “ligating molecular barcodes” (claim 13) and specify “molecular barcodes [] attached to both ends” of the cfDNA molecule (claim 30). As discussed further below, the Board in the 1400IPR already determined the more specific “ligating”/“attached” language as recited in the ’916 claims distinguishes from the Schmitt’s hybrid method now relied upon in the present petition.

#### **D. Asserted Prior Art**

None of the asserted prior art teaches sequencing-based methods for detecting microsatellite changes in cfDNA obtained from patients or any other sample type.

## 1. Schmitt

Schmitt does not describe detecting mutations in cfDNA at all and certainly does not discuss analyzing mutations in cfDNA obtained from cancer patients. Nor does Schmitt discuss microsatellite regions or detection of changes (e.g., insertions, deletions) in such regions. Rather, Schmitt discloses Duplex Consensus Sequencing or “DCS” which is described as a method for reducing the error rate in sequence data obtained from massively parallel DNA sequencing. *E.g.*, EX1005, (56) (“Methods Of Lowering The Error Rate Of Massively Parallel DNA Sequencing Using Duplex Consensus Sequencing”), Abstract (“This approach greatly reduces errors...”), 2:56-57 (“It would be desirable to develop an approach for tag-based error correction...”), 3:21-23 (“generating an error-corrected double-stranded consensus sequence”), 4:4-5 (“FIG. 3 illustrates error correction...”) Fig. 3.

Schmitt emphasizes the benefits of using SMI (Single Molecule Identifier) sequences (identified in the petition as the claimed “molecular barcodes”) which provide a high degree of diversity. EX1005, 6:46-7:5, 17:61-18:2, 18:36-43, 23:34-41, 26:65-27:8; *see also* Pet. 38-38 (grouping and collapsing based on “SMI sequences”), 45 (“SMI sequence (i.e., barcode)”). Consistent with this teaching, Schmitt’s preferred embodiment involves ligating adapters comprising random 12-mer SMIs to both ends of sample DNA molecules. EX1005, 3:47-53, 20:58-61.

Schmitt explains that use of 12-mer SMIs in this manner produces “up to  $4^{24}$  (i.e.,  $2.8 \times 10^{14}$ ) distinct tag sequences.” EX1005, 7:2-5. Schmitt provides a single comment about a hypothetical “hybrid” approach, where the SMI is partially defined by sequence in the target molecule itself—rather than what is separately attached. Schmitt offers no working examples or explanation of how it might be implemented, nor is there any evidence such an approach has ever been reduced to practice. EX1005, 9:9-13.<sup>3</sup> The present petition relies on the latter embodiment, which the Board already distinguished in the 1400IPR. *See also* EX1027, 10-12 (discussing Schmitt).

To the extent Schmitt discusses detecting mutations, it is in the context of discussing correction of sequence errors that might otherwise be indistinguishable from point mutations. *E.g.*, EX1005, 16:43-47 (“This error corrected double-stranded consensus sequence may be used in a method for confirming the presence of a true mutation ...”). As for mutations in the context of Schmitt’s method, only single nucleotide mutations are discussed and exemplified. EX1005, 5:28-36

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<sup>3</sup> As discussed above, the same Schmitt inventors later published Kennedy et al (EX2023) explaining its DCS method is essentially inoperable when attempting use of exogenous SMI sequences less than 12 nucleotides in length.

(discussing G→T mutations caused by DNA damage), 5:37-41 (“known single-nucleotide substitution”), 27:22-27 (“a single nucleotide change”), 27:46-49 (“one spontaneous base substitution error”).

## **2. Forshew**

Forshew does not mention microsatellite regions or describe methods for determining insertions and deletions, and the petition does not assert otherwise. Forshew describes a targeted deep sequencing method for identifying single nucleotide mutations in cell-free tumor DNA obtained from patients. *E.g.*, EX1010, Abstract, Tables 1 & 3, Fig. 4. The petition relies specifically on Forshew for disclosure of a cfDNA sample. Pet. 34, 52 (asserting Forshew discloses a sample of “0.9 to 19.7 ng” of cfDNA).

## **3. Porreca**

The petition relies on Porreca (Ground 1 only) as disclosing “methods for detecting nucleic acid deletions or insertions...” Pet. 34. In contrast to the claimed sequence-based methods, Porreca describes approaches to assaying repetitive DNA regions (e.g., microsatellite regions) that avoid sequencing. *E.g.*, EX1075, [0040] (“According to aspects of the invention, evaluating the capture efficiency as opposed to determining the sequence of the entire repeat region reduces errors associated with sequencing through repeat regions.”), [0044] (“This does not require sequencing the captured repeat region itself.”).

#### **4. Sacko**

The petition (Ground 2 only) relies on Sacko as “provid[ing] the rationale and methodology for interpreting microsatellite variations in cfDNA.” Pet. 59, 60. In contrast to the claimed sequencing-based methods, Sacko is directed to methods for fluorescence-based nucleic acid concentration determination. EX1076, Abstract.

### **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).

Petitioner acknowledges its burden to explain “[h]ow the challenged claim is to be construed” and, under its proffered constructions, explain “[h]ow the construed claim is unpatentable.” Pet. 17. Petitioner then argues it “does not believe any terms require construction.” Indeed, its expert purports to apply the plain and ordinary meaning to the claim terms. EX1003, ¶37 (“claim terms are presumed to take on the ordinary and customary meaning”).

At district court, however, Petitioner asserts that the scope of the claims of the ’916 is indeterminable and unpatentably indefinite based on multiple recited

terms. For other terms, Petitioner has argued at district court narrow interpretations to avoid infringement. 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 district court positions regarding claim terms recited in independent claims 13 and 30 are illustrated below. *See* EX2015, 2-3. Petitioner also alleges at district court that the term “unique sequence read” recited in claim 30 is indefinite. Again, none of these inconsistent positions are accounted for in the present petition.

“the amplified progeny polynucleotides” (’306 claims 1 and 17) / “the amplified tagged progeny polynucleotides” (’916 claims 1, 13, 30)	the polynucleotides generated by amplification of the tagged parent polynucleotides
“sequence information of the molecular barcodes” (’916 claims 1, 13, 30)	Indefinite
“a quantitative measure of polymorphic forms comprising microsatellite changes” (’916 claim 13)	Indefinite
“amplifying the tagged parent polynucleotides” (’916 claim 30)	amplifying every one of the tagged parent polynucleotides

Where Petitioner has proposed constructions at district court, those constructions are not presented in the petition materials and, in some instances, are irreconcilable with the claim mapping presented in the petition. For example, at district court Petitioner argues the “amplifying” step of claim 30 requires

amplifying “every one” of the tagged polynucleotides. Yet, the petition here maps this claim element to an amplification step that produces only “a set” of amplified molecules (i.e., less than “every one”). Pet. 56 (“See 13[b] (Section IX.C.1.c.)”), 37 (citing EX1005, 3:10–20); EX1003, ¶¶158-160, 227. Petitioner makes similar arguments (but inconsistent with its district court argument) in the concurrently filed IPR2025-01434 against a different Guardant patent. In that 1434IPR petition, Petitioner argues that prior art amplification is “not perfect” such that it is typical that not “every one” of the tagged parent polynucleotides gets amplified. 1434IPR Pet. 35 (“amplifications are not perfect, so every strand of every original template molecule is not recovered”). The present petition does not explain this inconsistency—or address Petitioner’s different district court constructions and arguments at all—burdening Patent Owner and the Board with resolving the conflicting argument.

Petitioner’s claim construction gamesmanship alone is reason to deny the petition. *Revvo Technologies, Inc. v. Cerebrum Sensor Technologies, Inc.*, IPR2025-00632, Paper 20, 5 (precedential) (requiring a reason for advancing different claim construction positions); *Tesla, Inc. v. Intellectual Ventures II LLC*, IPR2025-00340, Paper 18, 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.’”).

**IV. NONE OF THE ASSERTED REFERENCES DISCUSS DETECTING MICROSATELLITE CHANGES FROM SEQUENCE READS**

The petition alleges the cited prior art taught determining microsatellite changes from sequence reads at pages 37-41 (Ground 1) and page 60 (Ground 2). No such teaching is found in any of the cited references.

The petition materials fail to establish the cited prior art discloses or teaches detecting microsatellite changes in sequence reads as required by all challenged claims. Independent claims 13 and 30<sup>4</sup> of the ’916 patent recite:

<b>Claim 13</b>
(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;
<b>Claim 30</b>
(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, thereby detecting the genetic variation in the one or more microsatellite regions.

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<sup>4</sup> The petition makes no distinction between claims 13 and 30. *See* Pet. 55-56,

62.

Petitioner asserts that Schmitt *explicitly* taught a POSA to look for mutations in microsatellite regions. This allegation is unsupported and demonstrably false, the petition fails to identify any such teachings because there are none. Perhaps aware of Schmitt's deficiency in this regard, Petitioner alternatively argues Porreca (Ground 1), or Sacko (Ground 2) teaches determining microsatellite changes from sequence reads. But this too is unsupported and false. While microsatellite changes are discussed, neither of these references describes sequence-based methods to determine microsatellite changes.

#### **A. Ground 1 Fails**

The petition argues (p. 40) "Schmitt explicitly taught a POSA to look for mutations in microsatellite regions" but no such teaching is identified in Schmitt. Instead, Petitioner bootstraps its way to an alleged teaching by pointing to discussion of correcting sequencing error so that it is not confused with a "true mutation" and then arguing "microsatellite changes are just another type of 'mutation.'" Petitioner also points to discussion of "sites of DNA damage" and leaps to the conclusion this disclosure could include "observation of increased insertions/deletions in microsatellite regions."

Disclosure regarding microsatellite changes is simply absent from Schmitt and is not cured by Petitioner's unsubstantiated reliance on terms taken out of context in an attempt to make them generic. "It is well established that disclosure

of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus.” *Wasica Fin. GmbH v. Cont’l Auto. Sys.*, 853 F.3d 1272, 1285 (Fed. Cir. 2017); *see also Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367 (Fed. Cir. 2004) (“A prior art reference that discloses a genus still does not inherently disclose all species within that broad category.”). Here, cherry-picking the word “mutation” out of context is not disclosure of changes in microsatellite regions specifically—disclosure simply absent from Schmitt.

Reading the reference in context, Schmitt solely describes distinguishing between true point mutations and artifactual sequencing errors. EX1005, 4:63-64 (“eliminates sequencing artifacts and reveals the true distribution of mitochondrial mutations”), 5:41-45 (“because artifactual mutations occurring at every position obscure the presence of less abundant true mutations”), 16:43-47 (“presence of a true mutation (as opposed to a PCR error or other artifactual mutation) in a target nucleic acid sequence.”). Schmitt does not mention application of its method to insertions or deletions, nor does it discuss microsatellite regions. The petition makes the conclusory assertion that “Schmitt does not preclude using the DCS method for evaluating DNA fragments from microsatellite regions.” Pet. 40. Not only is such an assertion plainly insufficient, but it is flatly inconsistent with Petitioner’s assertions to the Office during the prosecution of its own patents

(discussed below). *See* §IV.C.

Petitioner alternatively argues (p. 41) that quantifying mutations in microsatellite regions would have been obvious. But no reference in Ground 1 addresses the deficiency of Schmitt. Forshew does not discuss microsatellite regions and the petition materials do not demonstrate otherwise. Instead, the petition points to Forshew’s mention of “regions of interest” and argues microsatellite regions are of interest, improperly attempting to cure nonexistent prior art disclosure with attorney argument. Furthermore, like Schmitt, Forshew is limited to detection of point mutations. *E.g.*, EX1010, 3 (“The sequenced regions cover mutations that account for 38% of all point mutations ... we called point mutations ... different known point mutation in TP53 ...we identified all 33 expected point mutations”), 8 (“Of 40 point mutations detected... Eleven additional point mutations detected”), Tables 1 & 3, Fig. 4.

Petitioner asserts (p. 41) Porreca describes a quantitative method for “detecting MSI.” But Porreca mentions MSI once when discussing diseases associated with genetic instability. EX1075, [0160] (“Other examples include cancer, which has been associated with microsatellite instability (MSI) ...”). To the extent Porreca discusses methods applicable to changes in microsatellite regions, these are described as relying on determining the size of a region rather than its sequence. *E.g.*, EX1075, [0040] (“evaluating the capture efficiency as opposed to

determining the sequence of the entire repeat region”), [0044] (“This does not require sequencing the captured repeat region itself.”), [0046], [0162], [0163].

Porreca’s mere mention of MSI does not cure the deficiency of Schmitt or otherwise elevate Schmitt’s single nucleotide error correction to a different method for determining microsatellite changes.

In fact, rather than providing explanation as to how or why Schmitt would be modified for MSI detection, Porreca counsels against using sequencing-based methods for this purpose. For example, in the paragraph that mentions MSI, [0160], Porreca explains that prior art sequencing-based methods do not sequence the “entire length” of an affected region and are “not useful” for detecting insertions and deletions. Porreca further explains that “the presence of sequence repeats often complicates the analysis of a genetic locus and increases the risk of errors when using sequencing techniques to determine the precise sequence and number of repeats at that locus.” EX1075, [0161]. Given the deficiencies of sequencing-based methods, Porreca proposes using methods that assess the length of repetitive sequences rather than their sequence. EX1075, [0161], [0044] (“This does not require sequencing the captured repeat region itself.”).

Accordingly, none of Schmitt, Forshew, and Porreca describes methods for detecting microsatellite changes in sequence reads.

## **B. Ground 2 Fails**

The petition materials assert (p. 60) that Schmitt alone or with Forshew and Sacko teaches determining microsatellite changes in sequence reads. As discussed above, neither Schmitt nor Forshew describe such methods. Neither does Sacko.

Petitioner argues, based on Sacko, “a POSA knew that cancer mutations of particular interest include MSIs found in ctDNA.” Pet. 60 (citing EX1076, [0005]). Petitioner does not assert that Sacko teaches methods for determining MSI and, indeed, it does not. Sacko is directed to “determining the amount of nucleic acid present in a sample” using fluorescence. EX1076, Abstract. Sacko never discusses sequencing methods and the only mention of MSI is in paragraph [0005] which suggests MSI may be a biomarker for cancer.

Accordingly, none of Schmitt, Forshew, and Sacko describes methods for detecting microsatellite changes in sequence reads.

## **C. Petitioner Ignores its Own Conflicting Arguments to the Office**

The present petition can also be rejected for failure to account for or explain Petitioner’s own conflicting argument before the Office. For example, the petition materials take the position that as of 2012, detection of microsatellite changes in cfDNA using sequencing would have been a routine and predictable endeavor not requiring specialized techniques. *E.g.*, Pet. 11 (“Petitioner assumes the claimed priority date of September 4, 2012”), 30 (“predictable use of known techniques...

routine molecular biology and sequencing methods”), 58 (similar). Not only is this argument inconsistent with the asserted prior art—which does not teach sequence-based methods for MSI detection—but it is incompatible with Petitioner’s statements in its own later-filed applications concerning similar subject matter.

Petitioner has filed several patent families directed to detection of rare somatic mutations (e.g., microsatellite changes associated with MSI) in cfDNA with filing dates in the 2019-2020 timeframe. For example, U.S. Pat. Appl. No. 2021/0098078 (“the ’078 application”) is assigned to Tempus (Petitioner) and is directed to methods for detecting MSI in cfDNA samples derived from cancer patients. *E.g.*, EX2012, [0023]. The ’078 application describes MSI detection as conventionally performed on tissue samples (“solid biopsy”) *not* cfDNA samples (“liquid biopsy”). EX2012, [0024]. The ’078 application further explains the difficulty associated with the analysis of genomic alterations associated with cancer including microsatellite instability.

The identification of actionable genomic alterations in a patient’s cancer genome is a ***difficult and computationally demanding problem***. For instance, the determination of various prognostic metrics useful for precision oncology, such as variant allelic ratio, copy number variation, tumor mutational burden, microsatellite instability status, etc., requires analysis of hundreds of millions to billions, of sequenced nucleic acid bases.  
EX2012, [0072].

It further notes that these difficulties are increased when attempting the analysis on liquid biopsy samples.

This is particularly true when performed in the context of a liquid biopsy assay, because liquid biological samples contain a ***complex mixture of short DNA fragments*** originating from many different germline (e.g., healthy) and diseased (e.g., cancerous) tissues. Thus, the cellular origins of the sequence reads are unknown, and the sequence signals originating from cancerous cells, which may constitute multiple sub-clonal populations, must be computationally deconvoluted from signals originating from germline and hematopoietic origins, in order to provide relevant information about the subject's cancer. Thus, in addition to the computationally taxing processes required to align sequence reads to a human genome, there is a computation problem of determining whether a particular abnormal signal, e.g., one or more sequence reads corresponding to a genomic alteration, (i) is not an artifact, and (ii) originated from a cancerous source in the subject. This is ***increasingly difficult*** during the early stages of cancer—when treatment is presumably most effective—when only ***small amounts of ctDNA*** are diluted by germline and hematopoietic DNA.

EX2012, [0074].

During prosecution, the applicant doubled-down on the “unconventional” nature of determining MSI status in liquid biopsy samples. EX2013, 50; *see also id.*, 147 (“detecting and/or validating cancer-specific genomic alterations of a liquid biopsy sample is significantly challenging and problematic”).

Petitioner’s statements in its patent application and to the Office regarding the state of the art in 2019 are wholly *inconsistent* with arguments in the petition. This includes Petitioner’s assertion that sequence-based methods are found in the prior art (as discussed above, they are not) as well as the assertion that sequence-based MSI detection was simply “predictable use of known techniques to address a recognized problem using conventional tools.” Pet. 30.

#### **V. SCHMITT IS EXCLUDED FROM THE CHALLENGED CLAIMS**

Petitioner addresses the “ligating” limitation of claim 13 at pages 35-36 where it relies solely on Schmitt and proposes ligation of random 4-mer tags according to the hybrid embodiment. Petitioner addresses the “attaching” limitation of claim 30 at pages 55-56 where it refers back to its discussion of claim 13.

The petition materials fail to establish the cited prior art discloses or teaches the “ligating”/“attaching” steps of claims 13 and 30 of the ’916 patent which recite:

<b>Claim 13</b>
(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; <sup>5</sup>

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<sup>5</sup> Claim 17 recites “wherein the molecular barcodes from the set of molecular barcodes have 2 to 1,000 different molecular barcode sequences.”

### Claim 30

(a) tagging a plurality of the cfDNA molecules from the sample with molecular barcodes from a set of molecular barcodes to produce tagged parent polynucleotides, wherein a molecular barcode from the set of molecular barcodes is attached to both ends of a molecule of the plurality of the cfDNA molecules, and wherein a plurality of the tagged parent polynucleotides has identical molecular barcode sequences;

As discussed above, the Board in the 1400IPR determined that claims reciting “attaching” molecular barcodes to cfDNA molecules—just like claims 13 and 30—do not encompass Schmitt’s hybrid embodiment. *See* §II.B. Claims 13 and 30 of the ’916 patent similarly recite “ligating” or “attached” molecular barcodes that are distinguished from the cfDNA molecule itself. The plain language of claim 13 specifies the “molecular barcodes” are ligated to the “cell-free nucleic acid molecules.” Claim 30 specifies the “molecular barcodes” are attached to the “cfDNA molecules.” That is, unlike the relied-upon Schmitt method, the claimed molecular barcode is not part of the original cfDNA molecule. Accordingly, Schmitt’s hybrid embodiment is excluded from the challenged claims.

The same “hybrid” embodiment of Schmitt is relied upon here but distinguished from the challenged claims at least for the same reasoning the Board applied in the 1400IPR. In the 1400IPR, the Board found that the SMI in Schmitt’s hybrid method is *the combination* of the short n-mer tag and the end of the target DNA. EX1027, 21; *see also* EX1005, 9:9-13 (“a combination of sheared ends and

a shorter n-mer tag”). Schmitt teaches that this combination of sequences is what is used to group reads for DCS processing. EX1027, 26; *see also* EX1005, 18:39-41 (“true PCR duplicates may be unambiguously identified by virtue of having a common (i.e., the same or identical) SMI sequence”). That is, to the extent Schmitt’s hybrid SMI is a molecular barcode, it is *not* within the adapter that is attached to the target DNA. *Id.*, 22. Rather, the SMI includes sequences within the molecule itself. *Id.*

Despite this distinction, Petitioner relies on the hybrid embodiment just like the previous petitioner in the failed 1400IPR. The petition repeatedly points to Schmitt’s hybrid embodiment in mapping the claim elements. For example, Petitioner argues the hybrid embodiment meets the “ligating”/“attaching” requirement of claims 13 and 30. Pet. 36, 55-56. Petitioner also points to the hybrid embodiment for dependent claim 17 (p. 45) and claim 22 (p. 49).

But Schmitt’s hybrid embodiment is not encompassed by claims 13-30, consistent with the Board’s prior determination in the 1400IPR. The claims require “ligating”/“attaching” molecular barcodes to cfDNA and further require use of the molecular barcodes in the “determining” step of the challenged claims. The petition points to Schmitt’s SMI as meeting these requirements. *See* Pet. 35-36 (“SMI tags”), 38 (“grouped together by virtue of having a common (i.e., the same) SMI tag sequence”). But, as the Board explained in the 1400IPR, the SMI of the

hybrid embodiment includes sequences at the end of the target DNA molecule. EX1027, 21. These sequences are neither ligated nor attached as required by claims 13-30 of the '916 patent. Thus, the hybrid method is excluded from the currently challenged claims.

To the extent Petitioner attempts to abandon Schmitt's hypothetical "hybrid" embodiment in favor of Schmitt's preferred embodiment<sup>6</sup>, that too fails. As discussed below, the challenged claims require using fewer barcodes than cfDNA sample molecules. In contrast, Schmitt's preferred embodiment does the opposite—it involves flooding the sample with an excess of SMI tags ("n-mers") to ensure every DNA fragment in the sample is uniquely labeled. *E.g.*, EX1005, 3:44-53, 6:59-63 ("The first and/or second degenerate or semi-degenerate nucleotide *n-mer sequences may be any suitable length to produce a sufficiently*

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<sup>6</sup> The petition, at times, appears to confuse and conflate Schmitt's discussion of its preferred embodiment with different discussion of the alternative and hypothetical hybrid embodiment. However, Petitioner's confusion and lack of understanding of the cited reference should not be credited as lucid argument. As discussed herein, the petition clearly relies on Schmitt's hybrid embodiment as the basis of the petition challenge.

*large number of unique tags* to label a set of sheared DNA fragments from a segment of DNA.”) (emphasis added), 18:36-41. Even the vacated 652IPR decision that Petitioner here cites confirms the same. EX1083, 34 (“There is no dispute that this embodiment of Schmitt is directed to a *unique* tagging method because the number of SMI tags exceeds the number of parent polynucleotides in the sample”).

The ’916 patent claims, however, require using fewer barcodes than cfDNA molecules. *See* EX1001, claim 13 (“2 to 1,000,000 different molecular barcode sequences”), claim 17 (“2 to 1,000 different molecular barcode sequences”), claim 25 (“1 nanogram (ng) to 100 ng of cell-free nucleic acid molecules”), claim 30 (“wherein a plurality of the tagged parent polynucleotides has identical molecular barcode sequences”). To meet these requirements, Petitioner proposes use of a 4-mer that results in 256 distinct barcode sequences.

While the petition proposes tagging 0.9 to 19.7 nanogram of cfDNA, it never acknowledges the indisputably enormous number (billions+) of cfDNA molecules in such a sample. *See* Pet. 52 (discussing claim 25). This is expressly addressed in the ’916 patent itself. *See* EX1001, 40:27-34 (“A sample of about 30 ng DNA can contain about 10,000 haploid human genome equivalents. ... A sample containing about 10,000 ( $10^4$ ) haploid genome equivalents of such DNA can have about 200 billion ( $2 \times 10^{11}$ ) individual polynucleotide molecules.”). Applying this relationship

(i.e., molecules per nanogram) to the proposed amount of cfDNA establishes that there are, at minimum, 6 billion cfDNA molecules to be tagged.<sup>7</sup> As discussed above, however, Schmitt instructs that its preferred embodiment would require at least as many SMI tags as the 6 billion+ molecules in such a proposed sample. Yet, the petition proposes using only 256 barcodes. Pet. 36 (“256”). Using only 256 barcodes for billions+ of molecules is incompatible with Schmitt’s preferred embodiment and in direct conflict with Schmitt’s instruction to use more barcodes than sample molecules with such an approach. This confirms that the petition here did not—and could not—rely on Schmitt’s preferred embodiment in challenging the ’916 patent. Instead, the petition asserts Schmitt’s hybrid embodiment for the same misguided reasons rejected by the Board in the 1400IPR. The present challenge should similarly be rejected as rehashing the same failed argument is a waste of Board resources with no reasonable likelihood this Petitioner will prevail.

Accordingly, Schmitt is excluded from claims 13-30 of the ’916 patent.

## **VI. CONCLUSION**

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

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<sup>7</sup> (200 billion molecules/30 ng)\*0.9 ng = 6 billion molecules

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 6,184 words.

Respectfully submitted,

Date: November 20, 2025

/ Michael T. Rosato /  
Michael T. Rosato, Lead Counsel  
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## VII. APPENDIX

Exhibit No.	Description
2001	FMI Invalidity Chart Exhibit B-1
2002	FMI Invalidity Chart Exhibit D-1
2003	Excerpts from File History of U.S. Patent Application No. 15/669,779
2004	Excerpts from File History of U.S. Patent Application No. 16/601,168
2005	Excerpts from File History of U.S. Patent Application No. 16/672,267
2006	IPR2019-01400 - Patent Owner's Response
2007	IPR2022-01400 - Hearing Transcript
2008	IPR2022-01400 - Patent Owner's Surreply
2009	Excerpts from File History of U.S. Patent Application No. 15/828,099
2010	Excerpts from File History of U.S. Patent Application No. 16/593,633
2011	Excerpts from File History of U.S. Patent Application No. 16/277,724
2012	Patent Application Publication No. US20210098078A1
2013	Excerpts from File History of U.S. Patent Application No. 16/945,588
2014	Guardant360-Liquid-Specification-Sheet
2015	Tempus Proposed Claim Constructions, <i>Guardant Health, Inc., v. Tempus AI, Inc.</i> , Case 1:24-cv-00687

2016	<p>Guardant Health Introduces Major Smart Liquid Biopsy Upgrade to Market – Leading Guardant 360 Test, Further Extending its Best-In-Class Performance.</p> <p><a href="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">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</a> (last viewed on October 20, 2024)</p>
2017	<p>Guardant Health to Showcase New Data at ESMO 2022 Demonstrating Utility of its Portfolio of Blood Tests for Advanced – Stage Cancer Patients.</p> <p><a href="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">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</a> (last viewed on October 20, 2024)</p>
2018	<p>FDA Approves First Liquid Biopsy Next-Generation Sequencing Companion Diagnostic Test. News Provided by U.S. Food and Drug Administration</p> <p><a href="https://www.prnewswire.com/news-releases/fda-approves-first-liquid-biopsy-next-generation-sequencing-companion-diagnostic-test-301108536.html">https://www.prnewswire.com/news-releases/fda-approves-first-liquid-biopsy-next-generation-sequencing-companion-diagnostic-test-301108536.html</a> (last viewed October 20, 2024)</p>
2019	<p>GOZILA Study Published in Nature Medicine Shows Patients with Advanced Cancer Who Receive Liquid Biopsy – Guided Treatment Using Guardant360 CDX Survive Twice as Long.</p> <p><a href="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">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</a> (last viewed October 20, 2024)</p>
2020	<p>Guardant Health Named to TIME100 Most Influential Companies. <a href="https://investors.guardanthealth.com/press-releases/press-releases/2024/Guardant-Health-Named-to-TIME100-Most-Influential-Companies/default.aspx">https://investors.guardanthealth.com/press-releases/press-releases/2024/Guardant-Health-Named-to-TIME100-Most-Influential-Companies/default.aspx</a> (last viewed October 20, 2024)</p>

2021	Guardant Health and Foundation Medicine Reach Settlement in Digital Sequencing Technology Litigation. <a href="https://investors.guardanthealth.com/press-releases/press-releases/2022/Guardant-Health-and-Foundation-Medicine-Reach-Settlement-in-Digital-Sequencing-Technology-Litigation/default.aspx">https://investors.guardanthealth.com/press-releases/press-releases/2022/Guardant-Health-and-Foundation-Medicine-Reach-Settlement-in-Digital-Sequencing-Technology-Litigation/default.aspx</a> (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	Scott R. Kennedy, et al. “Detecting ultralow-frequency mutations by Duplex Sequencing

**CERTIFICATE OF SERVICE**

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

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Respectfully submitted,

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