

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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TWINSTRAND BIOSCIENCES, INC.,  
Petitioner,

v.

GUARDANT HEALTH, INC.,  
Patent Owner.

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Case No. IPR2022-01400  
Patent No. 11,149,306

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**PATENT OWNER SURREPLY**

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## I. INTRODUCTION

The Reply argues for new interpretations of the claim scope, relies on new argument and citations, abandons the obviousness rationale of the petition, and attempts to improperly backfill deficiencies identified at the institution stage. “Shifting arguments in this fashion is foreclosed by statute, [Federal Circuit] precedent, and Board guidelines.” *Wasica Fin. GmbH v. Cont’l Auto. Sys.*, 853 F.3d 1272, 1286 (Fed. Cir. 2017). Petitioner’s untimely and improper arguments in reply should be given no weight (if not stricken). To the extent the merits of the new Reply arguments are reached, the Reply is non-responsive to dispositive issues and instead relies on legal error, sham testimony, and misleading or outright false statements regarding record evidence. As such, the Reply provides no basis for concluding obviousness.

Dispositive of Petitioner’s challenge, the ’306 patent claims exclude the Schmitt hybrid method relied upon in the petition and the Reply fails to demonstrate otherwise. This is no surprise considering Schmitt, including the same hybrid method, was cited and overcome during prosecution where the claims were drafted to exclude it. Here, the Patent Owner Response (“POR” or “Response”) established that the plain language of claim 1 (and claim 17) excludes Schmitt’s hybrid method where the “SMI” (molecular barcode) is not contained in the exogenously attached duplex tag, but instead made up of endogenous sequence

(e.g., sheared ends) of the sample DNA molecule itself. *See also infra* §VI. Claim 1, in contrast, explicitly states: 1) the duplex tags include the molecular barcodes and 2) those duplex tags are attached to and distinguished from the “cfDNA molecules.” POR, 8; EX2015, ¶¶38, 39. There is no dispute to any of this—nor could there be—as it is consistent with the plain language of the claims, Schmitt, and testimony of all witnesses. EX1002, ¶300 & n.18; EX2015, ¶42; POR, 11-18.

The Response (pp. 21-24) also demonstrated how the petition’s cursory discussion failed to adequately address the “mapping” limitation of step (e) of claim 1. The Reply dodges the three inadequate citations from the petition and attempts to salvage its defective showing with new citations and by newly arguing a special definition for the term “sequence reads.” This new argument conflicts with both the plain language of the claims and Dr. Spellman’s testimony where he specifically distinguished “sequence reads” from “consensus sequences.”

Regarding the motivation stated in the petition, Dr. Spellman already conceded during cross-examination there was no substantiated basis for replacing Narayan’s method with the hybrid method as proposed. POR, 25-27. Moreover, publications by the Schmitt inventors themselves, which were ignored in the petition, undermine the proposed modification to the cited hybrid method. POR, 32-35. The Reply offers no meaningful response to any of this. Poor sensitivity of Schmitt’s method is now conceded. Reply, 17 (“Of course there is a reduction in

sequenced molecules by the end of the process—this is expected and intentionally part of Schmitt’s error-correction process.”). The Reply abandons the “improved sensitivity” clinical diagnostic/cancer screening theory of the petition and now retreats to newly arguing for “useful data” and “developmental research testing.” Having abandoned its stated motivation, Petitioner cannot meet its burden.

The patentability of claims 1-29 should be affirmed.

## **II. THE PLAIN LANGUAGE OF THE CLAIMS EXCLUDES THE HYBRID EMBODIMENT**

The Response established that the plain language of claim 1 (and claim 17) excludes Schmitt’s hybrid method. *See also infra* §VI. Claim 1 explicitly states that 1) the duplex tags include the molecular barcodes and 2) those duplex tags are attached to and distinguished from the “cfDNA molecules.” POR, 11-21. The Reply (pp. 8-10), just like the petition, never addresses the plain language of the claims because it has no legitimate answer. This un rebutted issue alone is dispositive of the petition challenge.

Instead of addressing the claim language, the Reply newly (and incorrectly) argues the term “duplex tags” is expressly defined at 17:9-13 of the ’306 specification. *E.g.*, Reply, 8 (“the 306 patent’s definition of *duplex* tags”), 9 (“the 306 patent’s definition of tagging”); EX1098, ¶¶38 (“definition of ‘duplex tag’ in the ’306 patent”), 40 (same), 43 (same); *see also* EX1097, 96:10-12 (no construction from Dr. Spellman confirmed). As an initial matter, this new argument

should be given no weight as the petition never argued an express definition of “duplex tags” in the ’306 specification. *Intelligent Bio-Systems, Inc. v. Illumina Cambridge, Ltd.*, 821 F.3d 1359, 1369 (Fed. Cir. 2016); CTPG, 73; DI, 13-15 (no construction argued or necessary).

Even if considered, Petitioner’s new express definition argument is legally erroneous and factually wrong. First, the Reply invites legal error in abandoning claim language in favor of cherry-picking from the specification. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (“It is a ‘bedrock principle’ of patent law that ‘the claims of the patent define the invention to which the patentee’... [t]hat principle has been recognized since at least 1836...”). It is the claims that “delimit the right to exclude” not the written description. *Id*; *see also Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 980 (Fed. Cir. 1995) (*aff’d* 517 U.S. 370 (1996)) (“The written description part of the specification itself does not delimit the right to exclude. That is the function and purpose of claims.”). The Reply provides no justification, and none exists, for ignoring claim language in favor of a select citation from the ’306 specification.

Second, the Reply is wrong in arguing the ’306 patent “indisputably defines” duplex tags at 17:9-13. Reply, 8 (quoting EX1001, 17:9-13). The cited provision from the ’306 patent begins “*for example*,” which is conspicuously omitted from the Reply argument and inconsistent with an intent to expressly define. *See*

EX1001, 17:9-15. Furthermore, even where duplex tags are described functionally in the specification as differentially labeling complementary strands of cfDNA, that in no way negates claim language placing structural limitations on duplex tags such as those recited in claim 1. The Reply offers no argument or evidence to the contrary.

Besides inviting legal and factual error, the Reply offers false allegations and misrepresentations of the record. For example, the Reply (p. 2) falsely claims Guardant's expert admitted the claims encompass Schmitt's hybrid embodiment. *See also* Reply, 9 (citing Dr. Quackenbush's deposition transcript EX1097, 73:9-74:4). There is no such admission—just the opposite. Dr. Quackenbush testified at 73:9-74:4 and throughout his deposition (and direct testimony) that the claims ***exclude*** Schmitt's hybrid embodiment.

The SMI barcode in the hybrid method of Schmitt includes both an exogenous and endogenous piece, right, but they're required together to make that SMI tag the molecular barcode. That is distinct from the claim — the molecular barcode appearing in Claim 1, which is distinguished from the cell-free DNA molecule because it is part of the attached duplex tags which comprise the molecular barcodes. Hence the molecular barcodes in the '306 patent are purely exogenous. They're purely from an external source. They do not include sequence from the cell-free DNA.

EX1097, 73:12-74:4; *see also id.*, 68:17-69:5 (“That is materially distinct from the molecular barcodes claimed in the '306 patent which do not include endogenous

sequences.”), 70:7-22, 72:6-73:7, 73:12-82:7, 93:15-94:17; EX2015, ¶¶58-65. The Reply materials offer no meaningful rebuttal.

The Reply also misquotes and mischaracterizes the '306 specification, falsely arguing “[t]he 306 patent admits that ‘tagging’ can be achieved using ‘the combination of a DNA barcode and one or more endogenous sequences of the polynucleotide.’” Reply, 9 (citing EX1001, 21:23-25, 21:39-42, 22:44-47, 22:47-51, 34:55-58). None of the identified provisions of the '306 patent even includes the word “tagging”—despite the Reply’s misleading use of quotation marks. Moreover, the cited provisions describe molecular barcodes as exogenous sequences just like the claims. *E.g.*, EX1001, 17:16-17 (describing tags as “molecules attached to a polynucleotide”); 18:26-27 (“the tags herein comprise molecule barcodes”); 22:44-47 (“barcodes may be attached (e.g., by ligation) to individual molecules”). Petitioner’s frivolous allegations regarding “admissions” are not supported by its own citations.

Finally, the Reply argues (pp. 9-10) Schmitt meets claim 1’s requirement for “n different combinations of molecular barcodes, wherein n is at least 2 and no more than 100,000\*z” by repeating the same flawed argument from the petition addressing only the 3-nucleotide n-mer sub-portion. *See also* EX1098, ¶¶44. Petitioner’s own experts have already conceded: (1) Schmitt’s  $\alpha$  and  $\beta$  SMIs (not a sub-portion thereof) are the molecular barcodes; and (2) Schmitt’s hybrid  $\alpha$  and  $\beta$

SIMs are the combination of endogenous sequences and the exogenous n-mer. POR, 11-18; EX1002, ¶300 & n.18; EX1098, ¶40; *see also* EX1097, 77:5-16 (“So Dr. Spellman is attempting to have it both ways. ...”). As explained in the Response (p. 21), neither Petitioner (the moving party) nor Dr. Spellman ever calculated the number of different SIMs in the incomplete 3-mer hybrid hypothetical.

The patentability of the challenged claims may be confirmed for this reason alone.

### **III. THE REPLY’S CONSTRUCTION OF “SEQUENCE READS” IS UNTIMELY AND WRONG**

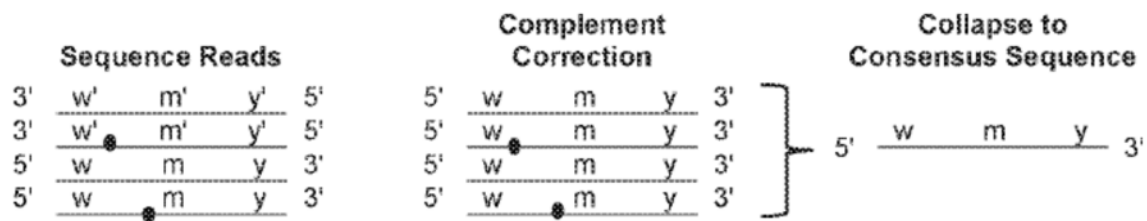
The petition (pp. 31-32) exclusively relied on disclosure at ¶¶60, 66, and 68 of Schmitt’s ’623 provisional application (EX1083) and argued these paragraphs “disclose” mapping sequence reads to a reference sequence as recited in step e of claim 1. The Response (pp. 21-24) demonstrated that none of ¶¶60, 66, and 68 describe Schmitt’s DCS as including mapping sequence reads as claimed. The Reply offers no meaningful rebuttal, but instead pivots to improperly new and erroneous argument.

Petitioner newly (and incorrectly) argues the claim term “sequence reads” generically includes both sequence reads and consensus sequences. *E.g.*, Reply, 5 (“the term ‘sequence reads’ is generic and encompasses *both* raw sequence reads and consensus sequence reads.”). This new argument is both untimely and conflicts

with Dr. Spellman’s declaration testimony where he specifically distinguishes between “sequence reads” and “consensus sequences.” *E.g.*, EX1002, ¶¶114 (“the ’306 patent discloses that after grouping the sequence reads, a consensus sequence is generated by comparing multiple sequence reads from a single original DNA fragment.”), 233 (describing consensus sequences as “built from sequence reads”); *see also* EX1097, 62:14-63:5 (“...mapping duplex consensus sequences is not the same as mapping sequence reads...”). In his mapping of Schmitt to element 1(d), which defines sequence reads in the claims, Dr. Spellman cites only two paragraphs from Schmitt, neither of which mention consensus sequences. *See* EX1002, ¶¶171 (citing EX1009, ¶¶74, 95), 229 (citing EX1009, ¶74). The Reply materials also introduce new terminology like “raw sequence reads,” which are repeated *ad nauseum* to further seed confusion. *E.g.*, Reply, 1, 3-7, 10, 12, 27; EX1098, ¶¶24, 27, 28, 31, 32, 34, 35. The term “raw sequence reads” appears nowhere in the ’306 patent.

The Reply (pp. 3-8) cannot avoid the consequences of its defective petition by contradicting and ignoring Dr. Spellman’s prior testimony. *See Cleveland v. Policy Mgmt. Sys. Corp.*, 526 U.S. 795, 806 (1999) (explaining that “a party cannot create a genuine issue of fact” by contradicting earlier sworn testimony without explanation); *SPTS Technologies LTD., v. Plasma-Therm LLC*, IPR2018-00618, Paper 24, 16-27 (concluding expert testimony was “sham” and would be “given

very little weight”). Dr. Spellman understood the ’306 patent to distinguish sequence reads from consensus sequences. *E.g.*, EX1002, ¶114 (citing 31:59-33:61, Figs. 1, 4C). The Reply (pp. 4-5) now inconsistently argues that there is no distinction. *See also* EX1098, ¶¶28-31. Neither the Reply nor Dr. Satija even acknowledge Dr. Spellman’s earlier testimony much less explain the inconsistency. The Reply materials cherry-pick and mischaracterize disclosure from the ’306 patent but never address what Dr. Spellman identified as supporting his understanding of the claims—for good reason, it plainly does not support Petitioner’s new interpretation. *See* EX1001, Fig. 4C (reproduced in part below).



The Reply’s argument for a special definition of “sequence reads” and Dr. Satija’s sham testimony should be given no weight.

The Reply (pp. 5-6) argues Guardant mischaracterizes and “ignores” ¶66 of the ’623 provisional (EX1083) and Example 4 of Schmitt (EX1009). This is false. Dr. Quackenbush addressed ¶66 in detail and explained that it does not discuss DCS but rather discusses a prior art method deemed inferior by the inventors to consensus sequencing. EX2015, ¶¶71-72. Petitioner offers no rebuttal but points to discussion in ¶66 of scoring mutation “without consideration of the SMI

sequences.” To the extent this passage relates to mapping, it explicitly describes a different method that does not use SMI sequences, whereas DCS does. *Id.* As for Example 4, the Reply falsely accuses Guardant of ignoring this disclosure, improperly attempting to pivot to new content not previously relied upon in the petition materials for “mapping” as claimed. Reply, 6; EX1098, ¶34. The petition provides one conclusory paragraph regarding “mapping” where it relies exclusively on three paragraphs of the ’623 provisional, but “ignores” Example 4. *See* Pet. 31-32. As the non-moving party, Guardant responded to the unpatentability allegations brought by Petitioner. *See* DI, 16 n. 13 (“The Petition cites to the disclosure in Schmitt-623, rather than Schmitt itself, as support for the asserted grounds.”), 31 n. 21; *Dell Inc. v. Acceleron, LLC*, 818 F.3d 1293, 1301 (Fed. Cir. 2016).

The Reply (p. 6) argues that even if “Schmitt did not expressly disclose mapping raw sequence reads, it indisputably suggests doing so.” Reply, 6 (emphasis added) (citing *Beckson Marine, Inc. v. Nfm, Inc.*, 292 F.3d 718, 727 (Fed. Cir. 2002)). But the petition did not argue Schmitt suggests step e—it argued Schmitt “discloses” the limitation. *See* Pet. 31-32, 34; DI, 21. It is simply too late in reply to change theories with respect to mapping sequence reads as claimed. *See In re Leithem*, 661 F.3d 1316, 1320 (Fed. Cir. 2011) (explaining that patent owner “would certainly have responded differently had the [] original rejection been

premised upon” the prior art teaching the limitation rather than the prior art disclosing the limitation).

Finally, the Reply (p. 7) argues the word “comprising” is found elsewhere in the claim and leaps to the conclusion this somehow justifies ignoring actual language in the claim regarding “mapping” to reimagine the challenged claims to better fit Petitioner’s litigation objectives. Claim 1 defines sequence reads at step (d) and, at step (e), recites “mapping at least a subset of the plurality of sequence reads to the reference sequence.” The petition failed to identify such “mapping” in its paltry discussion of Schmitt, and this deficiency is not cured by new citations and argument, or illogical new claim constructions that contradict both the plain language of the claims and testimony of Dr. Spellman.

The patentability of claims 1-16 and 29 may be confirmed for this additional reason.

#### **IV. PETITIONER FAILS TO ESTABLISH MOTIVATION**

##### **A. The Reply Abandons the Motivation of the Petition**

Petitioner’s stated motivation for replacing Narayan with Schmitt’s 3-mer hybrid was to improve on Narayan’s sensitivity for clinical diagnostics or screening for cancer using cfDNA. *E.g.*, Pet., 34-35 (“analyzing cfDNA from cancer patients”, “for diagnostic or screening applications”, “improve the sensitivity”, “motivated to use it in clinical settings”); EX1002, ¶¶188 (“to guide

clinical decisions”), 189 (“to improve the sensitivity of sequence detection in clinical settings”); EX2017, 15:10-16:24, 44:9-45:15; DI, 22.

As the Response demonstrated, the petition’s asserted motivation is unsubstantiated and illogical. POR, 25-27. Despite specifically alleging improved sensitivity in clinical settings as reason to replace Narayan’s “ultrasensitive” clinical assay, the petition materials provide no meaningful discussion of sensitivity of Schmitt’s hybrid DCS method. Dr. Spellman never identifies or offers any explanation regarding sensitivity of Schmitt’s 3-mer hybrid tag embodiment or addresses any actual application in clinical settings. *See* EX1002, ¶¶188, 189. Schmitt contains no working example of its hypothetical hybrid method and the record lacks any evidence such a hybrid DCS method has ever been used to detect cancer or anything else. Regarding the assertion of “improved sensitivity,” Dr. Spellman conceded he did not provide any information or calculation regarding sensitivity of the relied upon hybrid method. EX2017, 45:4-15. The record is simply devoid of evidence supporting cancer diagnostics or sensitivity, despite those being critical components of the stated motivation to turn to the relied upon hybrid method. The Reply offers no meaningful response.

The Reply materials now argue the petition’s motivation is not expressly recited in the challenged claims in an improper attempt to retreat from and re-write the stated motivation. *E.g.*, Reply, 2 (“The challenged claims do not require

performing the methods in a ‘clinical setting,’ nor do the Petition’s rationales.”), 17 (same), 18 (same), 19 (same), 20 (“developmental research testing”); EX1098, ¶¶62-65; EX1099, ¶¶17-24. The petition never argued a lack relevance to a clinical setting. Just the opposite—the petition cites Narayan’s clinical cfDNA sample and specifically argues, repeatedly, *clinical* diagnostics/screening as the motivation to turn to the Schmitt-PCT hybrid. *Teva Pharms. USA, Inc. v. Corcept Therapeutics, Inc.*, PGR2019-00048 (PTAB Nov. 18, 2020), *aff’d* 18 F.4d 1377 (Fed. Cir. 2021) (holding inappropriate new argument that claims do not require safety—it contradicted argument in petition “because Petitioner’s obviousness rationale incorporates an expectation of safety.”). The Reply (pp. 18, 19) attempts to disguise the new argument by falsely rebranding its own stated motivation as “Guardant’s ‘clinical setting’ theory.” Guardant, as the non-moving party, simply responded to what the petition expressly argued. *See, e.g.*, Pet., 35 (“...in clinical settings...”); EX1002, ¶¶188 (“...to guide clinical decisions.”), 189 (“...in clinical settings.”); *see also* DI, 22.

The Reply materials newly argue motivation for “developmental research testing.” The Reply (p. 20) attempts to shoehorn one mention of the term “research” from the background section of Dr. Spellman’s declaration—the same witness (now abandoned) who confirmed a different motivation theory at cross. *See, e.g.*, EX2017, 15:10-17:15, 44:9-45:15. The Reply identifies no stated

“developmental research testing” motivation in the petition because none exists.

*See also* EX1096, 35:17-36:24.

The Reply materials appears to have conceded a lack of sensitivity and abandoned the “improved sensitivity” argument entirely. Reply 17 (“of course there is a reduction...”); EX1098, ¶¶56 (conceding that “[Schmitt’s] stringent criteria is expected to result in data loss...”), 57 (“Schmitt’s DCS method is designed to offer higher accuracy rather than high yield.”); *see also* Pet., 35; EX1002, ¶189; EX1097, 90:3-15, 91:14-22, 95:14-23; EX2017, 44:9-45:15. In place of improved sensitivity, the Reply (pp. 17-18) presents an undeveloped new argument regarding “accuracy” of the irrelevant 12-mer embodiment described in the Schmitt 2012 PNAS paper (EX1064). *See also* EX1098, ¶¶54-61. Improved accuracy is not argued in the motivation discussion in the petition. *See* Pet., 34-37. Moreover, Kirsch does not support new argument regarding accuracy of the relied upon hybrid method of the Schmitt PCT. EX1098, ¶59 (citing EX1103, 1). Kirsch does not address the relied upon hybrid method or the Schmitt PCT, Kirsch discusses the 12-mer tag method of the Schmitt 2012 paper. *See* EX1103, 2. As Dr. Spellman confirmed, Schmitt 2012 is not relevant to the obviousness theory of the petition. *See* POR, 38-40; EX1002, ¶121; EX2017, 37:3-38-25.

## **B. Kukita Undermines Petitioner's Obviousness Theory**

The Response (pp. 38-40) demonstrated that Kukita does not support the petition theory of obviousness. Kukita does not discuss the 2012 Schmitt PCT or the relied upon hybrid method. Kukita instead cites to Narayan and a Schmitt 2012 PNAS paper (EX1064), and Dr. Spellman admitted the latter as being irrelevant to the petition's obviousness theory.

First, the Reply offers no rebuttal to the Response (p. 40) argument that Kukita's citation to Narayan (ignored in the petition materials) undermines the petition's illogical argument of replacing Narayan with a hypothetical 3-mer hybrid. Kukita does cite to Narayan but does *not* cite to or discuss the Schmitt PCT or the relied upon hybrid method.

Second, regarding Schmitt 2012 cited in Kukita, Dr. Spellman testified that the disclosures of Schmitt PCT and Schmitt 2012 are materially different. According to Dr. Spellman, Schmitt 2012 critically lacks discussion of the relied upon hybrid method or 3-nucleotide n-mers. EX1002, ¶122; EX2017, 38:12-39:3. On this basis, Dr. Spellman dismissed literature (e.g., Perakis) discussing Schmitt 2012 as irrelevant to his obviousness theory. EX1002, ¶121. The Reply seeks to sidestep Dr. Spellman's unhelpful admissions regarding Kukita by agreeing with them. Reply, 23 ("Schmitt 2012 contains *less disclosure* than Schmitt PCT") (original emphasis). Such acknowledgement confirms that Kukita offers no support

to the petition theory of obviousness. If Kukita's brief mention of Schmitt 2012 is considered, it should be weighed alongside the body of literature critical of the Schmitt 2012 as terribly inefficient and poorly designed. *E.g.*, EX1067, 102 (“Prospects of success are limited since the method is relatively inefficient when limited amounts of input DNA—as is most likely the case for cfDNA—are used.”); EX2006, 2 (“However, poor ligation efficiency resulted in sample loss ...”); EX2007, 10 (“inefficient processes leading to critical losses of template DNA molecules”).

### **C. No Motivation for Selection of the 3-mer Hybrid Approach**

The Reply (p. 20) alleges “three criticisms” of the proposed hybrid DCS theory but ignores the critical threshold deficiency identified in the Response. That is, the petition materials provided zero evidence regarding Schmitt's 3-mer hybrid DCS being used for anything, let alone detecting cancer with “improved sensitivity” as proposed. POR, 24-27. As the Response established, the hypothetical 3-mer hybrid embodiment is not used in any working example in Schmitt. Its sensitivity in any setting, clinical or otherwise, is unknown and not addressed in the petition materials, including by Dr. Spellman. EX2015, ¶76; EX2016, ¶¶27, 28. This critical deficiency of the petition materials is unaddressed in Reply.

Separately, the petition's generic comments about why shorter n-mers might be preferable to longer n-mers do not justify motivation to select the 3-mer hybrid specifically for use with cfDNA as proposed. *See* Pet. 35-36; EX1002, ¶¶193-196; POR, 36-38. The Response identified disclosure in Schmitt and a publication by the same inventors indicating that the proposed 3-mer hybrid would be more error-prone and suffer from disadvantages that were not addressed in the petition materials. POR, 32-36; *see, e.g.*, EX1083, ¶60 (“error prone” sheared ends); EX2003, 2591 (“a tag length of <12 is incompatible with the Illumina sequencer”).

The Reply departs from the petition argument and the disclosure of Schmitt to newly propose additional modifications. For example, the Reply now argues the “error-prone” sheared ends, which the hybrid method describes as forming part of the SMI sequence, could be removed. Reply, 21 (citing EX1083, ¶60); *see also* EX1083, ¶30 (“A hybrid method using a combination of sheared ends and a shorter n-mer tag...”). This proposed modification, however, lacks support in either the petition or in Schmitt. The only description of using sheared ends as SMI sequences is in the context of Example 3. In this embodiment, Schmitt explicitly describes using the “first 10 nucleotides” of sequence and does not mention any trimming. EX1083, ¶71 (“*Data analysis*. The first 10 nucleotides of each sequencing read pair, corresponding to the randomly sheared DNA ends, were combined, such that the first 10 nucleotides of read 1, referred to as A, was

combined with the first 10 nucleotides of read 2, referred to as B, to yield an SMI tag of form AB.”). Petitioner’s modification of the hybrid embodiment should be rejected as both untimely and unsupported.

Regarding the identified phasing issues, the Reply (pp. 21-22) inconsistently argues that phasing issues with shorter tags were both “imagined” by Guardant **and** known problems for which the art provided solutions. To be clear, it is the Schmitt inventors themselves, not Guardant, who instructed that shorter tags (e.g., 3-mers) render its DCS method incompatible with the sequencing platform.

Twelve random nucleotides per adapter...significantly exceed the degeneracy needed to ensure unique labeling of every molecule in a library. However, ***a tag length of <12 is incompatible*** with the Illumina sequencer because of technical limitations of the platform’s ‘phasing’ requirement and should be avoided.

EX2003, 2591.

Petitioner’s new argument that phasing issues could be “mitigated” runs headlong into Kennedy’s (EX2003) conclusion that tag lengths less than 12 were “incompatible” with sequencing. The allegedly mitigating modifications argued by Petitioner were known prior to publication of the Kennedy reference as evidenced by the cited exhibits predating the Kennedy paper. *Compare* EX2020 (published 2011) and EX2021 (published 2013), *with* EX2003 (published 2014). The Reply offers no explanation why the Kennedy authors, the same inventors as in Schmitt, would have been unaware of these “routine” techniques when they concluded

shorter tags were “incompatible.” *See* EX2018, 153:21-154:8 (Dr. Satija confirming the inventors of Schmitt were credible scientists and would have been considered POSAs). The Reply lacks reasonable basis why the Board should credit Petitioner’s new illogical and conclusory arguments over the contrary assessment of the inventors found in a peer-reviewed publication.

The Reply (p. 21) argues “the fragment ends would have provided enough sequence diversity to avoid phasing issues.” This is new and unsupported attorney argument. *See* EX1098, ¶¶70-74 (not addressing shear sequences). As Dr. Quackenbush explained and as corroborated in the literature, calibration of the sequencing instrument depends on having an equal representation of all four bases across the library in the first 12 cycles. POR 33-35; EX2015, ¶¶91-92; EX2020, 11; EX2021, 1. With the 3-mer hybrid SMI, the first 12 cycles include a 5-nucleotide fixed sequence (i.e., “CAGTA”). EX1083, ¶60; EX2015, ¶¶91-93. The shear sequences are after the fixed sequence and could not be used to avoid the phasing issues. EX2015, ¶93.

The Reply (pp. 22-23) further argues that both the 3-mer and 12-mer embodiments “were obvious choices in view of Schmitt’s teachings.” This argument misses the point. The Reply never sufficiently grapples with its own argument *in the petition* regarding what exactly the 3-mer was chosen for and the stated reasons *why*. *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1379 (Fed.

Cir. 2016) (burden is on petitioner to establish “motivation to combine the specific teachings of [the asserted prior art] to achieve the claimed invention”). Petitioner specifically proposed use of Schmitt’s 3-mer hybrid—not the 12-mer—for detecting cancer using cfDNA with improved sensitivity in the clinical setting. Pet., 34-35; DI, 22. This motivation carried with it the burden to explain and substantiate what the petition chose to argue as the basis for asserting obviousness—which Petitioner has not done. Now retreating in Reply to vague and generic statements about “obvious choices” does not absolve Petitioner of its burden.

**D. Petitioner Never Identified Reason to Abandon Narayan in Favor of a Method that Requires So Much More Blood**

The petition states that Narayan’s method could be performed with only about 0.6 mL of blood but estimates that Schmitt’s method would require 21-36 mL. The petition materials argued that such larger amounts “could” be obtained from routine blood draws. Pet. 37; EX1002, ¶211; *see also id.*, 39.

As the Response (pp. 40-44) explained, independent of other identified defects in the petition case, the petition materials never grappled with known clinical downsides of the proposal or explained why a POSA would want to abandon the small volumes of Narayan in favor of the far greater volumes proposed and the corresponding comorbidities and complexities. Neither the petition nor Dr. Spellman (a laboratory scientist, not a clinician) ever weighed

these drawbacks of the proposed modification to determine whether there would be a motivation to combine as proposed. *See* POR, 41.

The Reply (pp. 24-26) does not dispute the undesirable downsides and added complexity of their proposed combination as explained in the Response and by Dr. Hagemann. Indeed, Petitioner’s new reply witness, Dr. Rajkovic, even agrees. EX1099, ¶27 (“Dr. Hagemann is correct that, in general, physicians prefer to draw as little blood as possible to minimize patient discomfort or any potential side effects”).

The Reply (p. 24) argues that “ample volumes of blood could be drawn...” and that the larger proposed volumes are “within the medically acceptable range for research studies...” EX1099, ¶27. But whether such amounts “could be drawn” from patients misses the point—Patent Owner never argued impossibility. Petitioner and its new witness still do not identify a reason why a POSA would have wanted to draw so much blood for a single assay and even agree with Dr. Hagemann regarding the downsides of such a proposal. And, as discussed above, the new “research studies” argument is an improper shift from what was argued in the petition.

At bottom, Petitioner’s arguments still amount to the non-dispositive assertion about what “could” be done; it never explains why a POSA would want to pursue the proposed combination or grapples with factors weighing against the

combination. Here, known drawbacks and added complexity of the proposed combination weigh against motivation. The Reply materials fail to demonstrate otherwise.

## **V. DEPENDENT CLAIMS**

Dependent claims 1-16 and 29 are not obvious for the same reasons identified above with respect to claim 1. Claims 3, 5, 7, 8, and 14-16 are not obvious for the additional reasons below. The Reply fails to rebut the arguments in the Response.

### **A. Claim 3**

Patent Owner established that when applying DCS to the amount of cfDNA asserted in the petition (16.7 to 27.8 ng), a POSA would expect to generate duplex consensus sequences for very few molecules. POR, 45-46. The Reply concedes this point thus abandoning the increased sensitivity motivation of the petition. Reply, 13 (“a POSA would expect to have fewer molecules after performing Schmitt’s methods”).

### **B. Claim 5**

Patent Owner established that the molar excess calculations of the petition were based on DNA lengths of 200 to 500 bp, however Petitioner acknowledges that cfDNA is 140 to 170 bp. Applying Petitioner’s calculations to the actual size range of cfDNA would result in a molar excess of adapters between 29 $\times$  and

35×—that is, much less than the claimed 80×. The Reply (pp. 13-14) offers no argument or evidence to the contrary.

### **C. Claim 7**

Patent Owner established that claim 7 is directed to a cfDNA sample having a *z* value between 2 and 8. *See also* Pet. 19 (explaining that *z* is a property of the sample). The petition materials relied exclusively on Schmitt, which does not describe (1) cfDNA samples; or (2) samples of any type having a *z* value between 2 and 8. The Reply (p. 15) points only to discussion of Schmitt's 3-mer hybrid tag embodiment which is not a sample.

### **D. Claim 8**

Patent Owner established that the motivation to swap Schmitt's 3-nucleotide *n*-mers with Craig's barcoded adapters to mitigate barcode sequencing errors was nonsensical at least because it fails to grapple with disclosure in Schmitt indicating that the shear sequences used in the hybrid approach are error prone and increase sequencing errors. The Reply (p. 26) newly argues that errors in the endogenous portion of the hybrid SMI sequence could be mitigated but as explained above, this argument is both new and unsubstantiated. *See supra* §IV.C.

### **E. Claims 14-16**

Patent Owner established that claims 14-16 require quantifying paired or unpaired sequence reads that map to a genomic locus of a reference sequence,

however the petition materials fail to identify such disclosure in Schmitt (because there is none). POR, 51-52, 54-55. The Reply (pp. 15-16, 26-27) argues that sequence reads should be understood to encompass consensus sequences but this argument is both new and lacks merit for all the same reasons discussed above. *See supra* §III.

## **VI. GROUNDS CORRECTLY DEEMED DEFICIENT**

The Board's Institution Decision found the petition materials failed to demonstrate a reasonable likelihood to prevail regarding claims 4, 6, and 17-29. Paper 9, 30-41; *see also* IPR2022-01152, Paper 11, 12-23; IPR2022-00746, Paper 14 at 14-16; IPR2022-00747, Paper 14 at 14-16; IPR2022-01115, Paper 14, 12-19; Paper 9, 39-40. The Response (pp. 55-61) agreed with the Board's conclusions made at institution and in multiple other proceedings and provided additional reasons to affirm patentability. Specifically, claims 4, 6, and 29 depend from claim 1 and are patentable for the same reasons. *See* POR, 10-44; *see also supra* §§II-IV. As discussed above with respect to claim 1, the plain language of claim 17 excludes the hybrid method. *See* EX2015, ¶¶141; EX1097, 65:15-66:1; *supra* §§II & IV.

The Reply materials attempt to belatedly backfill petition deficiencies where Petitioner had no reasonable likelihood of prevailing at the institution stage. Dr. Satija's declaration addresses claim 17's requirement for sorting sequence reads

into families of paired reads and unpaired reads. EX1098, ¶¶46-53; *see also* DI, 30 (“Petitioner has not sufficiently explained how the cited references teach or suggest the sorting of reads into families of unpaired reads as recited in element 17(d) or determining distinct cfDNA molecules based on unpaired reads as recited in claim 29.”). Dr. Satija’s declaration also addresses the tagging efficiency limitations of claims 4 and 6. EX1098, ¶¶96-98; *see also* DI, 40 (“Petitioner has not sufficiently explained why a person of ordinary skill in the art would have expected Meyer’s tagging efficiency to apply to Schmitt’s DCS method when used with Narayan’s sequencing of cfDNA.”). These arguments based on the improper new testimony of Dr. Satijia should be accorded no weight.

Even if considered, the Reply fails to rectify deficiencies identified at institution. The Board determined with respect to the sorting limitation of claims 17-29 that the petition materials did not account for the impact of sequencing errors in its analysis. DI, 35-36. As for claims 4 and 6, the Board found that the petition “does not address the differences between Meyer’s adapters and Schmitt’s adapters and how those differences affect the tagging efficiency.” DI, 40. The Reply addresses neither of these deficiencies. *See* Reply, 10-12, 25-26. Accordingly, the patentability of claims 4, 6, and 17-29 should be affirmed.

## VII. CONCLUSION

For at least the reasons set forth above, petitioner has failed to meet its burden and the challenged claims should be found *not unpatentable*.

Respectfully submitted,

Date: October 10, 2023

/Michael T. Rosato/

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

**CERTIFICATE OF COMPLIANCE**

Pursuant to §42.24(d), the undersigned certifies that this paper contains no more than 5,600 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 5,545 words.

Respectfully submitted,

Date: October 10, 2023

/Michael T. Rosato/  
\_\_\_\_\_  
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**CERTIFICATE OF SERVICE**

The undersigned certifies that the foregoing Patent Owner Surreply was served on this 10th day of October 2023, on the Petitioner at the following electronic service addresses:

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