

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INTEGRATED DNA TECHNOLOGIES, INC.,
Petitioner,

v.

TECAN GENOMICS, INC.,
Patent Owner.

IPR2025-00015
U.S. Patent 10,036,012

PETITIONER'S REPLY

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EXHIBIT LIST

Exhibit	Short Name	Document
Ex. 1001	'012 patent	U.S Patent No. 10,036,012
Ex. 1002	'108 patent	U.S. Patent No. 10,876,108
Ex. 1003		Reserved
Ex. 1004		Reserved
Ex. 1005		Reserved
Ex. 1006	Meyer	Meyer et al., <i>Sequencing and de novo analysis of a coral larval transcriptome using 454 GSFix</i> , BMC GENOMICS 10:219 (2009)
Ex. 1007	Siebert	Siebert et al., <i>An improved PCR method for walking in uncloned genomic DNA</i> , NUCLEIC ACIDS RES. 23(6) 1087–1088 (1995)
Ex. 1008	Caruccio	Caruccio, <i>Preparation of Next-Generation Sequencing Libraries using Nextera™ Technology: Simultaneous DNA Fragmentation and Adaptor Tagging by In Vitro Transposition</i> , HIGH-THROUGHPUT NEXT GENERATION SEQUENCING: METHODS AND APPLICATIONS, METHODS IN MOLECULAR BIOLOGY, Ch. 17 (2011)
Ex. 1009	Bronner	Bronner et al., <i>Improved Protocols for Illumina Sequencing</i> , CURR PROTOC HUM GENET. (2009)
Ex. 1010	Kelley	Kelley and Dobler, <i>Comparative analysis of microbial diversity in Longitarsus flea beetles (Coleoptera: Chrysomelidae)</i> , GENETICA 139:541–550 (2011)

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Ex. 1011	Iafrate	U.S. Patent Application Publication No. 2013/0303461
Ex. 1012		Reserved
Ex. 1013		Reserved
Ex. 1014	Masoudi-Nejad	Masoudi-Nejad et al., <i>Next Generation Sequencing and Sequence Assembly Methodologies and Algorithms</i> (2013)
Ex. 1015	Zheng	Zheng et al., <i>Anchored multiplex PCR for targeted next-generation sequencing</i> , NATURE MEDICINE (2014)
Ex. 1016		File History for U.S. Patent No. 10,036,012
Ex. 1017		File History for U.S. Patent No. 10,876,108
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Ex. 1019		Reserved
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Ex. 1031		Reserved
Ex. 1032		Reserved
Ex. 1033		Reserved
Ex. 1034		SMART™ PCR cDNA Synthesis Kit User Manual (May 15, 2007)
Ex. 1035		Non-Final Rejection, U.S. Patent Application 13/750,768 (July 15, 2015)
Ex. 1036	Rabinowitz 2011	U.S. Patent Application Publication No. 2011/0288780
Ex. 1037	Rabinowitz 2012	U.S. Patent Application Publication No. 2012/0270212
Ex. 1038	Borodina	Borodina et al., <i>A Strand-Specific Library Preparation Protocol for RNA Sequencing</i> , METHODS IN ENZYMOLOGY, Ch.5 79–98 (2011)
Ex. 1039	Jones 2003	U.S. Patent Application Publication No. 2003/0232348
Ex. 1040	Jones 2005	U.S. Patent Application Publication No. 2005/0142577
Ex. 1041	Kurn	U.S. Patent Application Publication No. 2011/0224105
Ex. 1042		Non-Final Rejection, U.S. Patent Application 13/750,768 (Feb. 5, 2014)

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Ex. 1043		Final Rejection, U.S. Patent Application 13/750,768 (Sept. 25, 2014)
Ex. 1044		Final Rejection, U.S. Patent Application 13/750,768 (Oct. 30, 2015)
Ex. 1045		Non-Final Rejection, U.S. Patent Application 13/750,768 (June 2, 2016)
Ex. 1046		Non-Final Rejection, U.S. Patent Application 15/471,785 (Aug. 18, 2017)
Ex. 1047		Non-Final Rejection, U.S. Patent Application 16/017,340 (Apr. 30, 2020)
Ex. 1048		U.S. Provisional Patent Application 61/645,364
Ex. 1049		U.S. Provisional Patent Application 61/679,302
Ex. 1050	Moorthie	Moorthie et al., <i>Review of massively parallel DNA sequencing technologies</i> , HUGO JOURNAL 5:1–12 (2011)
Ex. 1051	Tonooka	Tonooka and Fujishima, <i>Comparison and critical evaluation of PCR-mediated methods to walk along the sequence of genomic DNA</i> , APPL. MICROBIOL. BIOTECHNOL. 85:37–43 (2009)
Ex. 1052	Leoni	Leoni et al., <i>Genome walking in eukaryotes</i> , FEBS JOURNAL 3953–3977 (2011)
Ex. 1053		Reserved
Ex. 1054		Reserved

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Ex. 1055	Kircher	Kircher et al., <i>Double indexing overcomes inaccuracies in multiplex sequencing on the Illumina platform</i> , NUCLEIC ACIDS RESEARCH 40:1 (2012)
Ex. 1056		Reserved
Ex. 1057		Reserved
Ex. 1058	Troutt	Troutt et al., <i>Ligation-anchored PCR: A simple amplification technique with single-sided specificity</i> , PNAS, USA 9823–9825 (1992)
Ex. 1059		Reserved
Ex. 1060	Meyer & Kircher	Meyer and Kircher, <i>Illumina Sequencing Library Preparation for Highly Multiplexed Target Capture and Sequencing</i> , COLD SPRING HARBOR PROTOCOLS (2010)
Ex. 1061	Kircher Thesis	Kircher Thesis, <i>Understanding and improving high-throughput sequencing data production and analysis</i> , LEIPZIG UNIVERSITY, Germany (2011)
Ex. 1062	Smith Thesis	Smith Thesis, <i>Low-Level Variant Detection in Human Mitochondrial DNA Using The Illumina® MiSeq™ Next-Generation Sequencing (NGS) Platform</i> , WESTERN CAROLINA UNIVERSITY (2013)
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Ex. 1065	Pray	Pray, <i>Major Molecular Events of DNA Replication</i> , NATURE EDUCATION (2008)

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Ex. 1066	Mackenzie	Mackenzie, <i>DNA vs. RNA – 5 Key Differences and Comparison</i> , TECHNOLOGY NETWORKS (2020)
Ex. 1067	Clancy	Clancy and Brown, <i>Translation: DNA to mRNA to Protein</i> , NATURE EDUCATION (2008)
Ex. 1068	Gauthier Thesis	Gauthier Thesis, <i>Simulation of polymer translocation through small channels</i> , UNIVERSITY OF OTTAWA, Canada (2008)
Ex. 1069	Lohman	Lohman et al., <i>DNA Ligases</i> , CURRENT PROTOCOLS IN MOLECULAR BIOLOGY 3.14.1-3.14.7 (2011)
Ex. 1070	Margulies	Margulies et al., <i>Genome sequencing in microfabricated high-density picolitre reactors</i> , NATURE 376–380 (2005)
Ex. 1071		DNA Sequencing Costs: Data, https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data
Ex. 1072	Craig	Craig et al., <i>Identification of Genetic Variants Using Barcoded Multiplexed Sequencing</i> , NAT. METHODS 5(10) 887–893 (2008)
Ex. 1073	Parameswaran	Parameswaran et al., <i>A pyrosequencing-tailored nucleotide barcode design unveils opportunities for large-scale sample multiplexing</i> , NUCLEIC ACIDS RESEARCH 35:19 (2007)
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Ex. 1076		Reserved
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Ex. 1079		Reserved
Ex. 1080	Colgan	Colgan and Manley, <i>Mechanism and regulation of mRNA polyadenylation</i> , GENES & DEVELOPMENT 2755-2766 (1997)
Ex. 1081	Bentley	Bentley et al., <i>Accurate whole human genome sequencing using reversible terminator chemistry</i> , NATURE 456:6 (2008)
Ex. 1082	Rothberg	Rothberg et al., <i>An integrated semiconductor device enabling non-optical genome sequencing</i> , NATURE 348-352 (2011)
Ex. 1083	Myers	Myers and Rothberg, <i>Semiconductor Sequencing for Life</i> , JOURNAL OF BIOMOLECULAR TECHNIQUES 22: Supplement (2011)
Ex. 1084	Faircloth	Faircloth and Glen, <i>Not All Sequence Tags Are Created Equal: Designing and Validating Sequence Identification Tags Robust to Indels</i> , PLOS ONE 7(8) (2012)
Ex. 1085	Sims Declaration	Declaration of Peter A. Sims – '012 and '108
Ex. 1086		Anna Searle declaration in support of motion for pro hac vice admission
Ex. 1087		Patrick Hynds declaration in support of motion for pro hac vice admission

Exhibit	Short Name	Document
Ex. 1088		Kevin Hoagland-Hanson declaration in support of notice of intent to designate
Ex. 1089		Email thread between Dr. Matz and Petitioner's counsel
Ex. 1090		Executed consulting agreement between Dr. Matz and Petitioner's counsel
Ex. 1091		Email thread between Dr. Matz and Petitioner's counsel
Ex. 1092		Meeting invite from Petitioner's counsel to Dr. Matz
Ex. 1093		Petitioner's counsel's notes of videoconference between Dr. Matz and Petitioner's counsel
Ex. 1094		Petitioner's counsel's notes of videoconference between Dr. Matz and Petitioner's counsel
Ex. 1095		Email thread between Dr. Matz and Petitioner's counsel
Ex. 1096		Email from Dr. Matz to Petitioner's counsel
Ex. 1097		Email from Dr. Matz to Petitioner's counsel
Ex. 1098		Email from Dr. Matz to Petitioner's counsel
Ex. 1099		Email thread between Dr. Matz and Petitioner's counsel and Dr. Matz's attached invoice
Ex. 1100		Petitioner's counsel's remittance for Dr. Matz's invoice

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Ex. 1101		Email thread between Dr. Matz and Petitioner's counsel
Ex. 1102		Petitioner's initial invalidity contentions filed in <i>Tecan Genomics, Inc. v. Integrated DNA Technologies, Inc.</i> , C.A. No. 23-1114-GBW (D. Del.)
Ex. 1103		Email thread between Dr. Matz and Petitioner's counsel
Ex. 1104		Meeting invite from Petitioner's counsel to Dr. Matz
Ex. 1105		Petitioner's counsel's notes of videoconference between Dr. Matz and Petitioner's counsel
Ex. 1106		Email thread between Dr. Matz and Petitioner's counsel
Ex. 1107		Email thread between Dr. Matz and Petitioner's counsel
Ex. 1108		Email thread between Petitioner's counsel and Patent Owner's counsel
Ex. 1109		Petitioner's timeline of communications with Dr. Mikhail Matz
Ex. 1110		Email thread between Petitioner's counsel and Patent Owner's counsel
Ex. 1111		2025.05.23 Tecan – Expert Engagement Letter – Matz signed_Redacted
Ex. 1112		Curriculum Vitae of Dr. Eli Meyer
Ex. 1113		Reserved

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Ex. 1114		Reserved
Ex. 1115		Reserved
Ex. 1116		Reserved
Ex. 1117		Reserved
Ex. 1118		Reserved
Ex. 1119		Reserved
Ex. 1120		Reserved
Ex. 1121		Reserved
Ex. 1122		Reserved
Ex. 1123		Library Preparation Method
Ex. 1124		Bustamante Deposition Transcript—Part I
Ex. 1125		Bustamante Deposition Transcript—Part II
Ex. 1126		Meyer Deposition Transcript

The Challenged Claims recite a series of chemical reactions that must be performed on a single nucleic acid fragment—1(a) ligation, 1(b) annealing, 1(c) extension, 1(d) amplification, 1(e) surface annealing, and 1(f) sequencing. EX1001.35:20-57; EX1085.¶125; EX1125.275:3-21. Tecan now concedes the 3' end fragments in Meyer undergo every claimed chemical manipulation 1(a) to 1(f). Paper 41 (“POR”) 27-45; EX1124.178:3-179:14, 188:23-194:18.

Having conceded this, Tecan attempts to re-write its claims, imposing new limitations on the term “enrich” in step 1(d) that the parties and the Board all previously agreed has a plain and ordinary meaning. POR 21-25. In short, Tecan and its expert argue that “to enrich” in step 1(d) requires amplification relative to other fragments, and that amplification is solely responsible for enrichment. POR 1, 23, 34. The claims impose no such limitations. As the Board recognized, the claims simply require that more fragments containing the sequence of interest are created, which undisputedly happens to Meyer’s 3' end fragments. *Infra* §I.A. Tecan’s new construction appears nowhere in the claims or specification, and is also inconsistent with Tecan’s allegations in district court litigation against Petitioner, where it is trying to stretch the claims to ensnare Petitioner’s technology that is not taught anywhere in the patent. *Infra* §I.B; EX1125.295:20-298:11.

Next, Tecan argues Meyer does not anticipate because Meyer did not intend to enrich for the 3' end fragments. POR 27. Meyer’s intent is irrelevant because the

claim is anticipated if the prior art teaches a method with all the claimed steps, regardless of whether the authors intended to enrich for the 3' end fragments or considered that a desirable outcome. *Infra* §I.C.1. But even if intent were relevant, Meyer expressly wanted to enrich for 3' end fragments in order to “ensure that all sequences in the sample were adequately represented,” POR 2, as the authors feared—and sought to specifically address—*underrepresentation* of the 3' end fragments, EX1006.0009.

Finally, Tecan argues Meyer did not show enough enrichment. POR 41-45. But while Tecan quibbles with the quantum of enrichment reported by Meyer, Tecan's expert conceded that the POSA's expectation for the number of 3' end fragments would be “13 or 14%,” EX1125.417:20-21, while the undisputed frequency of sequenced 3' end fragments was 16%, EX1006.0009. Even under Tecan's expert's interpretation of Meyer, there was enrichment—an increase in the proportion—of 3' end fragments. *Infra* §I.C.2.

For the reasons in the Petition and herein, the Board should cancel all Challenged Claims because Meyer anticipates or renders them obvious.

I. ANTICIPATION BY MEYER

A. Meyer Enriches The 3' End Fragments Under The Board's Correct Construction.

The Board should not depart from the plain and ordinary meaning of “enrich”: “to process so as to add or increase the proportion of a desirable ingredient.” Paper 9 at 15. Tecan and Dr. Bustamante concede that this construction is correct. POR 19; EX2038.¶149. Dr. Bustamante opined the proper “baseline” against which to measure enrichment is the number of fragments expected if the method were not performed: “without practicing the claimed invention, what you would get without the process of targeting the nucleic acid sequence of interest, extending and then amplifying the extension product and its complement.” EX1125.283:9-14, 283:15-284:17.

Under the Board's construction and using Dr. Bustamante's baseline, Meyer enriches for the 3' end fragments. Paper 1 (“Petition”) 33; EX1085.¶¶143-144. Dr. Bustamante admitted that Meyer “adds” to the absolute number of 3' end fragments. EX1125.392:16-20. And Meyer also “increases the proportion” of 3' end fragments compared to the proportion of those fragments that would be present in the sequencing library without the claimed method steps. EX1085.¶¶143-144; EX1125.283:9-14.

Meyer accomplishes this through “special chemistry”: the “Meyer 3’ End Method” to “selectively target and amplify—and thereby enrich”—the 3’ end fragments. EX1085.¶¶143-144. Indeed, Meyer reports that its method increased the proportion of 3’ end fragments compared to other fragments, including internal fragments, relative to the expectation from unbiased amplification. EX1006.0009.

The amplification step in Meyer is necessary for “enriching” the 3’ end fragments—without the PCR reaction, no additional copies of the 3’ end fragments would be added at all. EX1126.26:19-27:10; EX2037.193:17-22; POR 30-31. And without the annealing and extension steps, which introduce a PCR adaptor through the tail of a target-specific primer, many 3’ end fragments would not be able to participate in the amplification reaction. EX1126.26:14-27:10; POR 30-31. As Dr. Bustamante agreed, the 3’ end fragments in Meyer are capped and cannot ligate, and only a minority of those fragments—in which fragmentation occurs within the cap sequence—will be ligated with adaptors at both ends. EX1125.249:6-250:12; *infra* §I.E. Therefore, if the Meyer method were performed **without** the claimed steps, the majority of 3’ end fragments would not have the adaptors from the annealing and extending steps that are required for amplification. EX1125.249:6-250:12, 391:2-7; EX1085.¶¶157-161, ¶¶190-196. Thus, Meyer’s method undisputedly resulted in an “increased proportion of” the 3’ end fragments relative to the proportion of those fragments without the claimed method. *See* EX1125.283:9-14.

The Meyer method also enriches by “increas[ing] the proportion of” 3’ end fragments relative to (1) Meyer’s 10% expected prevalence of 3’ end fragments, EX1006.0009, (2) Tecan’s expert’s *ipse dixit* “13 or 14%” expected prevalence of 3’ end fragments, EX1125.417:20-21, and (3) “other types of RNA and other nucleic acids present in the original sample,” which are absent from the final sequencing data, EX1085.¶143; POR 29; EX1125.382:4-16.

B. Tecan’s Revised Construction Of Step 1(d) Should Be Rejected.

Despite purporting to “not dispute” the Board’s construction of enrich, POR 19, Tecan says that “context” requires rewriting step 1(d), and now argues that “[t]he phrase ‘amplify the one or more oligonucleotide extension products ... to enrich for the nucleic acid sequence of interest’” actually means “increase the proportion of the nucleic acid sequence of interest relative to the nucleic acid fragments in the solution not containing the sequence of interest by amplifying the oligonucleotide extension product and its complement,” POR 21; EX1125.267:17-268:12. In other words, Tecan contends that (1) the amplification step must amplify fragments with the sequence of interest relative to other unrecited fragments (instead of relative to the sequence of interest absent the claimed amplification), and (2) the amplification step must be solely responsible for enrichment. Tellingly, no part of Tecan’s construction appears anywhere in the patent—it was concocted by Tecan for the first time in its POR. The Board should reject it because it is inconsistent with the plain language

of the claim, the specification, all three experts' testimony, and Tecan's infringement contentions in parallel litigation.

1. Step 1(d) Does Not Require Amplification Relative To Other Fragments.

Nothing in the claims or the intrinsic record requires that amplification of the sequence of interest be assessed relative to other fragments, and Tecan's effort to require this is inconsistent with Tecan's expert's testimony.

The phrase "to enrich" in step 1(d) does not add this limitation. Steps (a), (b), and (c) cause nucleic acid fragments containing the sequence of interest to be flanked by adaptors, so the PCR reaction described in step (d) using corresponding primers necessarily "enrich[es] for the nucleic acid sequence of interest." EX1001.35:27-49. The infinitive clause "to enrich" in 1(d) "merely states the result of the limitations in the claim," *Tex. Instr. v. ITC*, 988 F.2d 1165, 1172 (Fed. Cir. 1993), it does not create the new limitation Tecan tries to import. Such a clause "in a method claim is not given weight when it simply expresses the intended result of a process step positively recited." *Minton v. Nat'l Ass'n of Secs. Dealers*, 336 F.3d 1373, 1381 (Fed. Cir. 2003); *see also Bristol-Myers Squibb v. Ben Venue*, 246 F.3d 1368, 1376 (Fed. Cir. 2001) ("statement of purpose and intended result" not limiting).

Dr. Bustamante conceded the proper "baseline" is not a comparison to other fragments but rather the number of fragments with the sequence of interest expected

if the method were not performed. EX1125.283:9-14, 286:2-287:6. Tecan's other expert, Dr. Meyer, confirmed that amplification of the sequence of interest necessarily results in "enrichment," consistent with the Board's construction: "any PCR could be described as enrichment if you wanted to use it in that way because you've amplified a product, you've amplified a target, such that it—it's more—its relative frequency is higher in the product than it was in the initial template." EX1126.170:18-171:1.

Nothing in the claim—which recites steps performed on "a nucleic acid fragment"—or the intrinsic record supports Tecan's assertion that "the claims require [1] that the sample include fragments in the solution that do not contain the sequence of interest and [2] that those fragments are not amplified" at the same time as the "amplifying" recited in step (d). POR 16. This is also contrary to Tecan's own proposed construction, which does not include these limitations. POR 21. The claim simply does not speak to whether there are other fragments present, or what is happening to those fragments. EX1125.254:24-255:5, 275:3-21. It would be improper to construct such limitations from whole cloth.

Tecan alleges that "Dr. Sims admitted at deposition" that step (d) of the claim "provides that only the oligonucleotide extension products from step (c) undergo the claimed amplification." POR 16. In fact, Dr. Sims's testimony (which Tecan cites but does not quote) was that "The amplification process in step D amplifies

oligonucleotide extension products described in 1C.” EX2037.186:15-19. But Dr. Sims never testified that the claim requires that **only** those products are amplified.

Tecan’s position also conflicts with Dr. Bustamante’s concession that the claim would still be practiced if the amplified fragments containing the sequence of interest were “shotgun sequenced” in a single sequencing run alongside amplified fragments that do not contain the sequence of interest. EX1125.406:12-408:2 (“if somebody wanted to create a system where you were doing targeting and another step and pooled those libraries [for sequencing], there’s nothing [in the claim] that prohibits that from happening”). There, fragments with and without the sequence of interest are both amplified in separate reactions and then pooled together for sequencing. The sequence of interest is not the only thing that is amplified, but Dr. Bustamante admits that this scenario is still covered by the claims and is thus “enrichment.”

The Board’s plain and ordinary meaning construction also makes sense because nothing in the specification requires a special or narrowed definition. *Phillips v. AWH*, 415 F.3d 1303, 1323 (Fed. Cir. 2005). The patent does not require more for “enrichment” than an increase in the sequence of interest over the baseline that Dr. Bustamante offered: sequencing without the claimed steps. EX1125.283:9-14. The patent does not define the terms “enrich” or “enrichment,” does not report any sequencing results from the method or data quantifying enrichment, and does

not explain that the enrichment should be measured in any particular way, let alone how Tecan now argues. EX1085.¶¶125-127, ¶¶182-184; EX1125.281:20-22, 307:22-309:21.

Tecan argues Meyer does not enrich because the entire transcriptome is sequenced simultaneously. POR 27. But the patent discloses doing exactly that: “the plurality of target sequences may comprise ... *a whole transcriptome* or fraction (e.g., substantial fraction) thereof,” EX1001.22:27-30 (emphasis added), or “all known coding regions” or “the entire exome,” EX1001.6:12-19; *see* EX1126.118:1-9; EX1124.206:14-207:21.

Nor is the “sequence of interest” limited to a known gene. POR 6; EX1124.195:14-196:16. Dr. Bustamante agreed the sequence of interest can be anything—a portion of a gene, a noncoding region, an artificial sequence, or *even a random sequence*. EX1124.202:5-206:8. In this regard, the broken chain T or CAP primer sequences targeted by Meyer fall squarely within the “sequence of interest” defined in the patent—they are sequences for which enrichment is desired. EX1001.21:1-3; EX1126.32:15-34:3. Indeed, those sequences, which demarcated the 3’ end of Meyer’s mRNA transcripts, a region with biological importance, EX1126.32:2-22; EX1085.¶144; EX1124.228:21-234:22, are more “of interest” than the random sequences discussed in the patent’s Example 3 that Dr. Bustamante agreed were “sequences of interest,” EX1124.228:13-19.

Finally, despite admitting Figure 1 is an “illustration of a preferred embodiment of claim 1,” POR 12, Tecan repeatedly conflates the claims with this embodiment and Tecan’s SPET products, POR 11-17, 65; EX1125.292:14-293:13. Tecan relies on Figure 1 in support of its argument (again contrary to Tecan’s proposed construction, POR 21) that step (d) requires “that only the oligonucleotide extension products from step (c) undergo the claimed amplification” and not other fragments, POR 16.

But there is no basis to limit the claim to the preferred embodiment in Figure 1, *Phillips*, 415 F.3d at 1323, or to Tecan’s SPET “commercial embodiments,” *SmithKline Beecham v. Apotex*, 403 F.3d 1331, 1339 (Fed. Cir. 2005). “The fact that the inventor may have anticipated that the invention would be used in a particular way does not mean that the scope of the patent is limited to that context.” *Northrop Grumman v. Intel*, 325 F.3d 1346, 1355 (Fed. Cir. 2003). To the contrary, the claims were drafted more broadly in multiple respects, including by use of the “comprising” transition and that the claims address only a single nucleic acid fragment. *Supra* §I.B.1-2; EX1001.35:16-57; EX1085.¶125; EX1125.275:3-21, 313:2-314:2; EX1124.223:6-228:19. Moreover, as discussed *infra* §I.B.2, Tecan has asserted the claims cover Petitioner’s product that undisputedly does not use SPET; Tecan may not invoke its commercial embodiment to import limitations to avoid

invalidity where it has elsewhere asserted a construction not limited to those products. EX1085.¶¶112-120; EX1125.296:2-298:11.

2. Enrichment Need Not Be Solely The Result Of Amplification.

Tecan also argues—without legal citation—that “to meet the limitations of the challenged claims” enrichment cannot occur “prior to the claimed method.” POR 29. But the claims are “comprising” claims, which are open-ended and not closed to additional steps. *Exergen v. Wal-Mart*, 575 F.3d 1312, 1319 (Fed. Cir. 2009); *Invitrogen v. Biocrest Mfg.*, 327 F.3d 1364, 1368 (Fed. Cir. 2003). To construe the claims narrowly to exclude enrichment via other steps would require “words or expressions of manifest exclusion or restriction” that are not present in the claims or intrinsic record. *Unwired Planet v. Apple*, 829 F.3d 1353, 1358 (Fed. Cir. 2016).

Tecan cites the prosecution history but it does not require that enrichment occur *exclusively* during “amplifying.” POR 23-24 (citing EX1016.0190-93). There is no dispute that the claim contemplates “enrichment of nucleic acid sequences occur[ing] during amplification,” POR 23; EX2037.188:7-193:10, but this does not amount to a clear statement limiting the claim to enrichment *only* through amplification. *See Purdue v. Endo*, 438 F.3d 1123, 1136 (Fed. Cir. 2006).

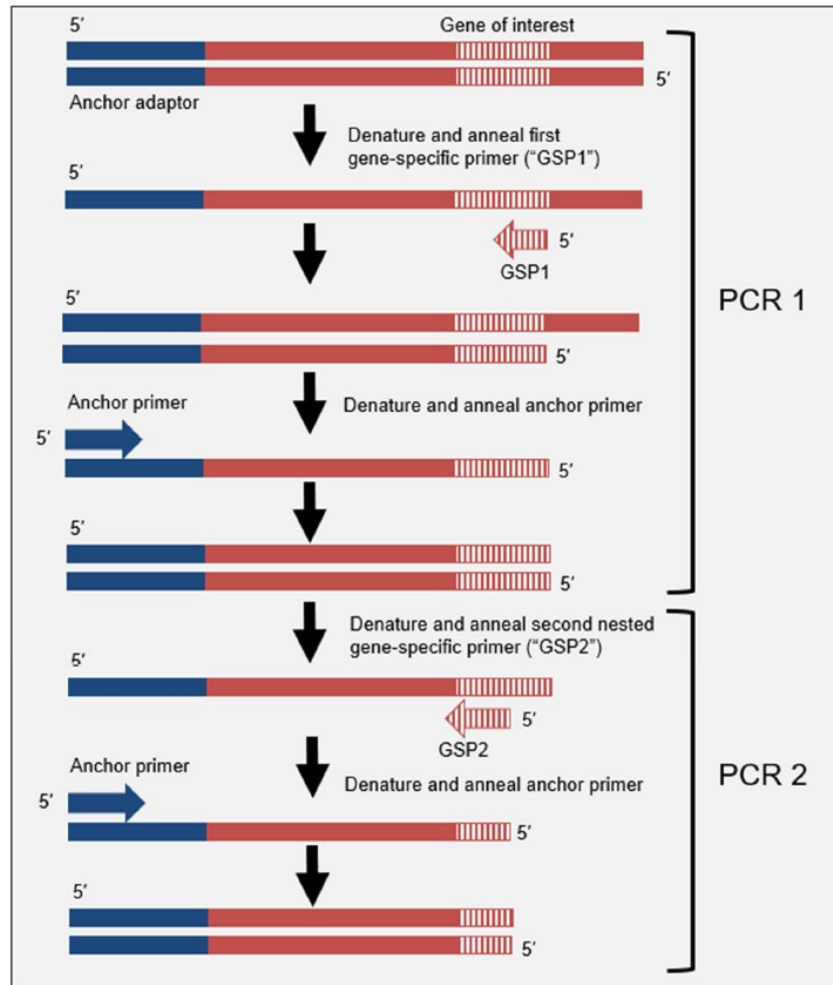
Tecan’s insistence that limitation (d) must be solely responsible for enrichment of the sequence of interest, POR 22, 29, also conflicts with the testimony

of both sides' experts. Dr. Sims and Dr. Bustamante agreed the claim allows for "a pre-enrichment step that enriches for [the] target of interest" if the "pre-enrichment proportion [of the sequence of interest] is now enriched through practicing the claimed invention." EX1125.281:14-283:6; EX2037.190:17-192:15.

Tecan's contention that Dr. Sims "confirmed" "enrichment must occur as part of the *claimed method*, and not prior to the claimed method" overreads his testimony. POR 29. As Dr. Sims explained, the amplification step will necessarily contribute to enrichment by making more copies of fragments with the sequence of interest, EX2037.187:3-195:9, and "overrepresentation of a nucleic acid sequence of interest at the beginning of the process doesn't satisfy the claim," EX2037.194:9-16. He was simply acknowledging that at least *some* of the enrichment must result from the recited steps. But that is not the same thing as saying other events cannot contribute to, or even start, the enrichment. Indeed, Dr. Sims explained "it's possible for some of those nucleic acid fragments to be overrepresented at the end of this process ... if an earlier process caused overrepresentation of a sequence of interest," EX2037.190:19-191:3, and amplification is "not the only thing that contributes to enrichment, necessarily," EX2037.192:13-15, 191:22-192:5. Dr. Bustamante agreed. EX1125.281:14-283:6.

Tecan's position that the claim excludes enrichment "by an earlier step" prior to the "amplifying" step, POR 29-30, is diametrically opposed to its district court

infringement contentions against Petitioner's MGH method, Petition 1-2, 16-18. The MGH method is a "nested PCR" method in which the sequences of interest *have already been enriched* in an earlier unclaimed step, PCR1, before the PCR2 step that Tecan accuses of infringement. EX1085.¶¶114-120.



While Tecan argues that Meyer does not anticipate because some enrichment results from the SMART kit, POR 29-30, in both the MGH method and Meyer, the amplifying step only contributes further to "enrichment" that has already begun in an earlier, unclaimed targeted enrichment step, EX1085.¶¶116-120; EX2037.187:3-

195:9, 214:20-215:8. Tecan can argue that the claim covers both the MGH and Meyer methods—or neither—but “cannot have it both ways.” *See Bristol-Meyers*, 246 F.3d at 1376.

C. Meyer Discloses Enrichment Of The 3’ Ends Under Tecan’s Construction.

Even under Tecan’s (incorrect) construction, Meyer anticipates because Meyer’s method “increase[s] the proportion of the nucleic acid sequence of interest relative to the nucleic acid fragments in the solution not containing the sequence of interest by amplifying the oligonucleotide extension product and its complement.” *See* POR 21. Meyer wanted to increase the 3’ end fragments to overcome underrepresentation, and after the library preparation method, including amplification, Meyer sequenced proportionally more 3’ end fragments than other fragments. EX1006.0009; EX1125.412:20-25.

1. Meyer Wanted To Enrich The 3’ End Fragments To Overcome Underrepresentation.

Tecan repeatedly refers to the “purpose” of the Meyer reference. *E.g.*, POR 2, 27-28; EX1125.269:5-270:25. Meyer’s “purpose” is irrelevant because “[t]he anticipation analysis asks solely whether the prior art reference ... discloses the claimed invention, and not how the prior art characterizes that disclosure.” *Hewlett-Packard v. Mustek Sys.*, 340 F.3d 1314, 1324 n.6 (Fed. Cir. 2003). Likewise, Meyer’s failure to mention enrichment “as a goal is ... irrelevant” if Meyer

“achieves” enrichment. *MEHL/Biophile Int’l v. Milgraum*, 192 F.3d 1362, 1366 (Fed. Cir. 1999); *see also Homeland Housewares v. Whirlpool*, 865 F.3d 1372, 1378-79 (Fed. Cir. 2017); *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997). If Meyer discloses the chemistry steps arranged as in the claim and states that they lead to enrichment, the claim is anticipated even if Meyer did not consider enrichment of 3’ end fragments a desirable outcome. *See Rasmusson v. SmithKline Beecham*, 413 F.3d 1318, 1325-26 (Fed. Cir. 2005); *Celeritas Techs. v. Rockwell Int’l*, 150 F.3d 1354, 1361 (Fed. Cir. 1998).

But even if Meyer’s “intent” were relevant to anticipation, Tecan’s assertion that “[t]he purpose of Meyer was not to target and enrich for 3’ end fragments over other fragments,” POR 27, is factually incorrect. Meyer expressly states that it sought to overcome “under-representation of the 3’ ends of transcripts.” EX1006.0009. Tecan’s repeated refrain that “Meyer sought to ensure that all sequences in the sample were adequately represented,” POR 2, proves the opposite of Tecan’s point. In order to achieve the goal of even representation, Meyer needed to specifically enrich for the 3’ ends, as the expectation without Meyer’s method would be ***underrepresentation*** of those fragments. EX1006.0009.

Tecan claims that Meyer was only interested in avoiding the “homopolymer” issue with 3’ end fragments caused by the 454 sequencer, and that there is a “lack of a mechanistic explanation to support an expectation of enrichment.” POR 38-39.

But that is wrong. To achieve their goal of avoiding underrepresentation and “to selectively enrich for sequences falling near the 3’ end,” Dr. Sims explains, “Meyer applied special chemistry to these sequences ... to selectively target and amplify—and thereby enrich” those sequences. EX1085.¶144; EX1006.0003, .0020. Neither Dr. Bustamante nor Dr. Meyer disputed that Meyer taught the use of an additional primer to target and amplify 3’ end fragments, or that the amplification step in Meyer created exponentially more 3’ end fragments.

Tecan’s experts contend Meyer was actually concerned about purported “overrepresentation” of 3’ end fragments. EX2287.¶25; EX2038.¶170. But Dr. Bustamante and Dr. Meyer could not identify any discussion in Meyer of *over*representation of 3’ end fragments, while both conceded Meyer expressly discusses *under*representation. EX1125.367:10-368:2, 374:7-379:13; EX1126.123:20-135:10. Moreover, Dr. Meyer conceded the POSA would understand the SMART kit alone resolved any concern about overrepresentation. EX1126.135:12-19.

2. Meyer’s Data Demonstrates Enrichment.

a. Meyer Observed More 3’ End Fragments Than Expected.

Even under Tecan’s incorrect interpretation, Meyer anticipates the claim because proportionally more 3’ end fragments were sequenced than expected. The

Meyer authors expected 3' end fragments to make up 10% of sequence reads, based on dividing the “average read length (232 bp)” by the assumed “average transcript size of 2,200 bp.” EX1006.0009. But 3' end fragments were found in 16% of sequencing reads, which was “slightly more” than the expectation of 10%. EX1006.0009. That Meyer did not use the word “enrichment” to describe this result is irrelevant—“[t]he invention is not the language of the claim but the subject matter thereby defined,” *Teva v. AstraZeneca*, 661 F.3d 1378, 1385 (Fed. Cir. 2011)—and this express disclosure of enrichment cannot be overcome by the unsupported testimony of Dr. Bustamante, *see Ericsson v. Intellectual Ventures*, 890 F.3d 1336, 1346 (Fed. Cir. 2018).

b. The Data In Meyer Is Representative Of Both Methods.

Meyer discloses two methods—Figure 1, and an “improved protocol,” EX1006.0014, in additional file 4. “Meyer touts the method in Additional File 4 as an improvement over the one in Figure 1,” Paper 9 at 28, and Dr. Meyer agreed that the POSA would be motivated to use the additional file 4 method, EX1126.50:10-53:6. And there is no dispute that Figure 1 recites nearly identical chemistry steps, including the same ligated adaptors, and a primer specific to the 3' end fragments. EX1006.0003, .0014, .0020; EX2037.225:11-228:1.

Tecan argues the POSA would not understand the sequencing results and conclusions reported in the paper to apply to both methods. POR 36. But nothing in Meyer suggests that Meyer's findings would not apply to both methods. To the contrary, Meyer explains that additional file 4 contains only "minor modifications" "to reduce the number of manipulations required, improve reproducibility, and to further reduce adaptor concatenation." EX1006.0014; EX2037.225:11-228:1. Indeed, Dr. Meyer confirmed "it's reasonable to believe that if you repeated it exactly with the modified protocol, you would get very similar and comparable results." EX1126.53:2-5. While Dr. Bustamante flatly contradicted his co-expert, he could provide no explanation for why the POSA would have expected the method in additional file 4 to perform differently from the method it was designed to refine. EX1125.393:4-397:16.

c. Tecan Identifies No Reason The POSA Would Have Second-Guessed Meyers' Result.

Tecan does not challenge the Meyer authors' report that the 3' end fragments were found in 16% of reads, or the use of that number as an appropriate signifier for the results of the method. POR 36-45; EX2038.¶¶242-273. Instead, Tecan argues that the POSA "would have understood" that the numerator and denominator "used to form Meyer's [10%] estimate were not accurate." POR 41. But Tecan's own expert, Dr. Meyer, contradicted this, testifying he "obviously thought [the 10%

calculation] was reasonable, and my co-authors agreed because we included it,” and he “stand[s] by the statement as written.” EX1126.44:3-7.¹

1) The POSA Would Not Have Questioned Meyer’s 232 bp Numerator.

Tecan argues “the data shows that the average sequence read length was actually longer than 232 bp” because the sequencing reads are not normally distributed. POR 41; EX2038.¶¶260-65. Tecan’s expert may not unilaterally re-write the reference, *see Homeland Housewares*, 865 F.3d at 1378-79, but even if that were appropriate, neither Tecan nor Dr. Bustamante take a position on what the numerator should have been, only that it should have “been higher,” POR 41-42; EX2038.¶¶254-259. Dr. Meyer testified that the numerator “is not an assumption,” and he does not “have any reason ... to think that [he] should have used a different number.” EX1126.46:16-19.

Alternatively, Tecan suggests that the POSA would disregard the number the authors reported and instead base the numerator on Meyer’s disclosure that “sonication ‘produced fragments in the appropriate size range (ca. 300-400 bp).”

¹ Dr. Bustamante refused to agree or disagree with Dr. Meyer’s testimony that the calculation was based on reasonable assumptions. *Compare* EX1125.411:23-412:19 *with* EX1126.42:11-44:7, 46:6-19, 49:9-16.

POR 44 (quoting EX1006.0013); EX2038.¶269. Dr. Meyer again disagreed and testified the “appropriate size range” following sonication does *not* “mean that this is the fragment size that [they] obtained from this particular run of the experiment,” and that “measurements that we made of fragment size ... would be quite imprecise.” EX1126.155:17-157:15.

2) The POSA Would Not Have Questioned Meyer’s 2200 bp Denominator.

Tecan asserts that “the value used for the average transcript length [i.e., the denominator] was wrong.” POR 42. But again Dr. Meyer testified that 2200 bp was “a reasonable number for us to choose.” EX1126.49:13-14.

Dr. Sims opined the POSA would understand the denominator was empirically derived, EX1085.¶184, which Dr. Bustamante agreed was “not unreasonable,” EX2038.¶267. While Dr. Bustamante argued that the denominator “would be less,” he again stopped short of offering an opinion on what the number should have been. EX2038.¶¶261-265

Tecan further attempts to discredit the denominator based on a single sentence in Dr. Meyer’s declaration: “I believe this number was based on the average mRNA length in mammals, which had been reported to be 2,200 nucleotides.” POR 42; EX2038.¶260; EX2287.¶58. That sentence was not written by Dr. Meyer—it was written by the disqualified Dr. Matz, who identified a textbook (EX2080) as the

source. EX1126.56:11-57:5. But Dr. Meyer recanted any reliance on this textbook, and testified that 2200 bp was *not* based on “sitting down with textbooks,” EX1126.58:7-59:1, 56:8-65:20, but rather “based on our general knowledge of biology.” EX1126.58:7-14, 49:13-16.

Dr. Meyer also rejected any notion the POSA would have interpreted the 2200 bp number as somehow relating to mammals. When asked whether the POSA reading Meyer would “understand ... that an average transcript size of 2200 base pairs is based on the average length of a mammalian transcript,” Dr. Meyer objected that the “introduction of the term ‘mammalian transcript’ into that sentence is not necessarily something that we were relying on or that the reader would assume,” and “the reasonable interpretation ... of that sentence is that this is a general average overall transcript length.” EX1126.64:22-65:20.²

**d. Even Under Tecan’s Expert’s Revised Expectations,
Meyer Enriched For 3’ End Fragments.**

Even under his proposed construction, Dr. Bustamante admitted there is “no threshold [of enrichment] specifically laid out in the patent.” EX1125.275:23-277:3,

² Dr. Bustamante disagreed with Dr. Meyer and maintained his reliance on the recanted declaration testimony. EX1125.413:7–22, 348:12-349:2, 413:23-416:2.

307:22-309:21. And Dr. Meyer agreed creating just “one more copy” enriches for a sequence of interest. EX1126.166:5-10.

Critically, even if Dr. Bustamante’s criticisms of the Meyer calculation were credited (they should not be), when asked what a “more appropriate” expectation of the prevalence of 3’ end fragments should have been, Dr. Bustamante testified “my sense is it is perhaps closer to 13 or 14 percent.” EX1125.417:12-418:5. Thus, even if the express teaching of the reference were replaced with Tecan’s expert’s say-so, Meyer still demonstrated enrichment. Dr. Bustamante testified absent the method the expected proportion of 3’ end fragments sequenced by Meyer would have been “13 or 14 percent,” and it is undisputed that by practicing the method Meyer sequenced more than that expected proportion—16%. That is enrichment under any proposed construction.

D. Claim 21 Is Anticipated.

Tecan re-writes “RNA fragment” in claim 21 to require “purposeful” “fragmentation of an RNA ... before its reverse transcription into cDNA.” POR 25-26; EX1124.238:17-239:16. That limitation appears nowhere in the patent, and is contrary to the plain and ordinary meaning of “RNA fragment,” which is simply any RNA polynucleotide. EX2037.170:8-171:1; EX1085.¶146, ¶253.

Tecan’s construction also excludes the specification’s embodiments wherein RNA is transcribed to cDNA prior to fragmentation. EX1001.16:9-25, 34:1-27; *see*

In re Katz, 639 F.3d 1303, 1324 (Fed. Cir. 2011). Dr. Bustamante ignores these examples, relying instead on extrinsic evidence. *See* EX2038.¶¶157-160.

E. Claim 22 Is Anticipated.

While Tecan criticizes Petitioner's argument that Meyer's data shows fragmentation in the CAP sequence and resulting ligation on both ends of the fragment as required by claim 22, POR 47, Dr. Bustamante conceded that fragmentation in the CAP sequence "did, in fact, happen" in "about 1 percent" of reads, EX1125.250:7-12; EX2038.¶303. Tecan did not ask Dr. Meyer to opine on this issue, EX1126.93:22-96:22; EX1125.265:12-266:20, but he agreed such fragmentation happened, EX1126.144:5-146:11.

Tecan is left arguing that Meyer did not intend such fragmentation and that an "accidental" result cannot anticipate. POR 47-48; EX1125.253:7-254:2. But this is not the law. As explained in the very case Tecan cites for this proposition, in those cases "dealing with 'accidental, unwitting, and unappreciated' anticipation," the record "did not show that the prior art produced the claimed subject matter." *Schering v. Geneva Pharms.*, 339 F.3d 1373, 1378 (Fed. Cir. 2003). Here, Dr. Bustamante agrees that Meyer reveals *thousands* of instances of adaptors ligating to both ends of 3' end fragments. EX1125.250:7-12, 251:10-14; EX1085.¶¶255-264.

Incorrectly inverting the standard, Dr. Bustamante contends fragmentation "is not inevitable in every instance of the method." EX2038.¶303. That is irrelevant

because it actually happened—in the data generated by the authors, which Dr. Meyer contends was representative, EX1126.53:2-5, there was fragmentation, EX1125.250:7-12, 251:10-14; EX1085.¶¶255-264. Petitioner does not need to prove that *every theoretical* instance of the Meyer method would anticipate if the method can *and did* anticipate. See *SmithKline Beecham v. Apotex*, 403 F.3d 1331, 1343 (Fed. Cir. 2005). Indeed, Tecan has no evidence that practicing the Meyer method could ever *not* result in fragmentation in the CAP sequences.

F. The Remaining Claims Are Anticipated.

Tecan concedes claims 3, 5-8, 10-14, 16, and 20 are anticipated if Claim 1 is. POR 48.

II. OBVIOUSNESS OVER MEYER

A. Claim 2 Is Obvious.

Tecan argues “the purposes of Meyer and Siebert are incompatible,” and thus the POSA would not be motivated to use Meyer’s cDNA method on genomic DNA. POR 50-51. But the chemical steps of the Meyer method can be performed on genomic DNA just as well as on cDNA, Petition 69-72; EX1085.¶¶318-25; EX1125.388:14-390:16, and chemistry like that used in Meyer had been previously used on genomic DNA, Petition 8-12; EX1085.¶¶73-79, ¶182; EX2038.¶¶62-66. The POSA would understand Meyer’s 3’ end method could selectively target any “known, fixed sequence” “to ensure sequencing coverage for an unknown and/or

variable sequence directly adjacent to the known, fixed sequence,” regardless of the type of DNA. EX1085.¶¶322-325.

Meyer was a proof of concept that anchored PCR—well-known pre-NGS chemistry described in Siebert for “genome walking”—could be successfully applied to NGS. EX1085.¶¶320-325, ¶¶73-79; EX1126.102:20-103:17; EX1016.190-92. The POSA would be motivated to apply Meyer to the types of applications previously recognized in Siebert because “merging [genome walking] strategies to next generation sequencing will undoubtedly extend the future application of this by now basic technique of molecular biology.” EX1052.016.

While Dr. Bustamante contends the POSA would not have adapted Meyer to genomic DNA because “the use of a single target-specific primer without additional safeguards would not work,” EX2038.¶¶317-318, he does not explain what these “additional safeguards” are. Meyer discloses *every* chemistry step recited in claim 1, *supra* 1, and the patent provides no other “safeguards,” *supra* 8-9. The *only* limitation of claim 2 not present in Meyer is the application to genomic DNA, and the POSA would have been motivated to extend Meyer from cDNA to genomic DNA with a reasonable expectation of success. Petition 69-72; EX1085.¶¶318-325.

Tecan’s argument that Dr. Sims testified “a POSA would not have looked to older, pre-NGS methods” mischaracterizes his testimony, which was simply that pre-NGS library preparation techniques could not be used with NGS platforms that

required specific adaptors. POR 53 (citing EX2037.152:14-153:2). As Dr. Sims explained, the POSA would look to Siebert for its teachings regarding genome-walking, not library preparation—Meyer teaches all of the claimed chemistry, and Siebert teaches the application of analogous chemistry to genomic DNA, EX1085.¶324, ¶¶320-321, ¶¶73-79, ¶182.

B. Claims 17-19 Are Obvious.

Claims 17-19 recite limitations required for the use of Illumina and Ion Torrent sequencers. EX1085.¶¶326-338. Tecan concedes that the POSA would have been motivated to use library preparation methods compatible with Illumina and Ion Torrent instead of 454 by the priority date. POR 5, EX2038.¶92. Tecan argues the POSA would not have wanted to convert the Meyer method to the more popular platforms because Meyer was “specific to fixing issues with the 454 sequencer,” POR 56, and Bronner and Caruccio teach different library preparation methods, POR 57-58. But the POSA would recognize the chemistry Meyer discloses for targeted enrichment of 3’ ends is a broadly-applicable “method for generating a selectively enriched library for NGS,” EX1085.¶322, and the concept of targeting a known sequence to enrich an unknown or variable adjacent sequence is not specific to a particular platform, EX1085.¶322, ¶327, ¶¶334-35. If so motivated, Tecan does not dispute the POSA could easily swap out the 454 adaptor sequences used in

Meyer for those used by Illumina and Ion Torrent with a reasonable expectation of success. EX1085.¶¶334-335, ¶¶337-338.

C. The Remaining Claims Are Obvious.

Tecan makes no separate arguments for claims 9 and 15, and thus these claims fall with the others. POR 55-59.

D. There Is No Nexus To Tecan’s Secondary Considerations.

Tecan’s secondary considerations apply only to claims 2 and 17-19, POR 59-67, but there is no evidence of nexus between the SPET embodiment and the claims. While Dr. Bustamante opined that the claims are “coextensive” with the SPET embodiment, his opinion was based on legal error because he did not consider whether there were other embodiments within the scope of the claims, EX1125.317:4-13, 318:11-321:17, 309:12-21, 315:22-319:7, 321:19-324:3, 359:10-360:23, and nexus requires the patentee “provide[] an adequate basis to support the conclusion that other embodiments falling within the claim will behave in the same manner.” *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). The claims here are far broader than the SPET embodiment. *Supra* §I.B.

Dated: November 7, 2025

Respectfully submitted,

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

I hereby certify that the foregoing complies with the type-volume limitations of 37 C.F.R. § 42.24(d) and contains 5,597 words, excluding those portions exempted under 37 C.F.R. § 42.24(a)(1).

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e) and 37 C.F.R. § 42.105, I hereby certify that on November 7, 2025, I caused the foregoing Petitioner's Reply Brief, Exhibit List, and the accompanying exhibits to be served on Patent Owner by electronic mail to Linnea P. Cipriano, Scott T. Weingaertner, John P. Padro, and Timothy J. Beavers, at DG-GoodwinTecan@goodwinlaw.com, counsel for Plaintiffs in *Tecan Genomics, Inc. v. Invitae Corp. et al.*, C.A. No. 23-cv-1114-GBW (D. Del.).

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