

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 No. 10,036,012

PATENT OWNER'S SUR-REPLY

TABLE OF CONTENTS

I.	TECAN APPLIES THE CORRECT CONSTRUCTION.....	2
A.	Enrichment Is a Change in Proportion, Not Just Raw Number	2
B.	Petitioner’s Other Arguments Have No Bearing on the Present Claim Construction Dispute	7
II.	MEYER FAILS TO ANTICIPATE THE CHALLENGED CLAIMS	10
A.	<i>Meyer</i> Fails to Disclose Steps 1(d) and 1(f).....	10
B.	A POSA Would Have Understood that <i>Meyer</i> Did Not Enrich for the 3' Fragments.....	14
C.	<i>Meyer</i> ’s Data Cannot and Does Not Demonstrate Enrichment	15
D.	A POSA Cannot Infer Enrichment From <i>Meyer</i>	16
E.	Claim 21 Is Not Anticipated: <i>Meyer</i> Fails to Disclose the Reverse Transcription of an RNA Fragment	21
F.	Claim 22 Is Not Anticipated: <i>Meyer</i> Discloses a Method that Blocks Ligation on One End of Petitioner’s Target Fragments.....	22
III.	PETITIONER’S OBVIOUSNESS CHALLENGES FAIL.....	23
A.	Claim 2 Is Not Obvious.....	23
B.	Claims 17-19 Are Not Obvious.....	25
C.	Petitioner Fails to Rebut Tecan’s Secondary Considerations	25

TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>Allergan Sales, LLC v. Sandoz, Inc.</i> , 935 F.3d 1370 (Fed. Cir. 2019)	6
<i>Aspex Eyewear, Inc. v. Marchon Eyewear, Inc.</i> , 672 F.3d 1335 (Fed. Cir. 2012)	7
<i>AstraZeneca LP v. Apotex, Inc.</i> , 633 F.3d 1042 (Fed. Cir. 2010)	17
<i>DDR Holdings, LLC v. Priceline.com LLC</i> , 122 F.4th 911 (Fed. Cir. 2024)	5
<i>Dippin' Dots, Inc. v. Mosey</i> , 476 F.3d 1337 (Fed. Cir. 2007)	8
<i>Hytera Commc'ns Co. Ltd. v. Motorola Sols., Inc.</i> , 841 F. App'x 210 (Fed. Cir. 2021)	6, 7
<i>In re Chudik</i> , 851 F.3d 1365 (Fed. Cir. 2017)	13, 14
<i>In re Katz</i> , 639 F.3d 1303 (Fed. Cir. 2011)	21
<i>In re Huai-Hung Kao</i> , 639 F.3d 1057 (Fed. Cir. 2011)	25, 26
<i>Janssen Pharms., Inc. v. Teva Pharms. USA, Inc.</i> , 760 F. Supp. 3d 184 (D.N.J. 2024)	26
<i>Kyocera Senco Indus. Tools Inc. v. ITC</i> , 22 F.4th 1369 (Fed. Cir. 2022)	7
<i>Microsoft Corp. v. Multi-Tech Sys., Inc.</i> , 357 F.3d 1340 (Fed. Cir. 2004)	6

<i>Neville v. Foundation Constructors, Inc.</i> , 972 F.3d 1350 (Fed. Cir. 2020)	4
<i>Pacing Techs., LLC v. Garmin Int’l, Inc.</i> , 778 F.3d 1021 (Fed. Cir. 2015)	21
<i>Samsung Elecs. Co., Ltd. v. Elm 3DS Innovations, LLC</i> , 925 F.3d 1373 (Fed. Cir. 2019)	6
<i>Schering Corp. v. Geneva Pharms., Inc.</i> , 339 F.3d 1373 (Fed. Cir. 2003)	22
<i>SmithKline Beecham Corp. v. Apotex Corp.</i> , 403 F.3d 1331 (Fed. Cir. 2005)	22, 23
<i>Tec Air, Inc. v. Denso Mfg. Michigan Inc.</i> , 192 F.3d 1353 (Fed. Cir. 1999)	25

EXHIBIT LIST

Ex.	Short Name	Description
2001	Evans 2009	Mark F. Evans, <i>The Polymerase Chain Reaction and Pathology Practice</i> , 15 DIAGN. HISTOPATHOL. 344 (2009)
2002	N/A	<i>The Cost of Sequencing a Human Genome</i> , NAT'L INST. OF HEALTH NAT'L HUMAN GENOME RESEARCH INST., https://www.genome.gov/about-genomics/fact-sheets/Sequencing-Human-Genome-cost (last visited July 18, 2025)
2003	Goodwin 2016	Sara Goodwin et al., <i>Coming of Age: Ten Years of Next-Generation Sequencing Technologies</i> , 17 NAT. REV. 333 (2016).
2004	Mardis 2017	Elaine R. Mardis, <i>DNA Sequencing Technologies: 2006-2016</i> , 12 NAT. PROTOC., 213 (2017).
2005	Fuller 2009	Carl W. Fuller et al., <i>The Challenges of Sequencing by Synthesis</i> , 27 NAT. BIOTECHNOL. 1013 (2009).
2006	Marguiles 2005	Marcel Margulies et al., <i>Genome Sequencing in Open Microfabricated High Density Picoliter Reactors</i> , 437 NATURE 376 (2005).
2007	Luo 2012	Chengwei Luo et al., <i>Direct Comparisons of Illumina vs. Roche 454 Sequencing Technologies on the Same Microbial Community DNA Sample</i> , 7 PLOS ONE 1 (2012).
2008	Hert 2008	Daniel G. Hert et al., <i>Advantages and Limitations of Next-Generation Sequencing Technologies: A Comparison of Electrophoresis and Non-Electrophoresis Methods</i> , 29 ELECTROPHORESIS 4618 (2008).
2009	N/A	<i>Six Years After Acquisition, Roche Quietly Shuttters 454</i> , BioIT World (Oct. 16, 2013),

Ex.	Short Name	Description
		https://www.bio-itworld.com/news/2013/10/16/six-years-after-acquisition-roche-quietly-shutters-454 .
2010	Mamanova 2010	Lira Mamanova et al., <i>Target-Enrichment Strategies for Next-Generation Sequencing</i> , 7 NAT. METHODS 111 (2010).
2011	Treangen 2011	Todd J. Treangen et al., <i>Repetitive DNA and Next-Generation Sequencing: Computational Challenges and Solutions</i> , 29 NAT. REV. GENET. 36 (2012).
2012	Brownie 1997	Jannine Brownie et al., <i>The Elimination of Primer-dimer Accumulation in PCR</i> , 25 NUCLEIC ACIDS RES. 3235 (1997).
2013	Tewhey 2009	Ryan Tewhey et al., <i>Microdroplet-based PCR Enrichment for Large-scale Targeted Sequencing</i> , 27 NAT. BIOTECHNOL. 1025 (2009).
2014	Link 2012	U.S. Patent Application No. 2012/0309002 (published Dec. 6, 2012).
2015	Franck 1998	Sophia M. Franck et al., <i>Multiplex PCR for Enterotoxigenic, Attaching and Effacing, and Shiga Toxin-Producing Escherichia coli Strains from Calves</i> , 36 J. CLIN. MICROBIOL. 1795 (1998).
2016	AmpliTaq Gold	Applied Biosystems, <i>AmpliTaq Gold, with GeneAmp® 10X PCR Buffer or GeneAmp 10X PCR Buffer II & MgCl₂ Solution or GeneAmp 10X PCR Gold Buffer & MgCl₂ Solution</i> (2000).
2017	Fool 2002	University of Hawaii, <i>The Simple Fool's Guide to PCR</i> (2002).
2018	Ying 2019	Hua Ying et al., <i>The Whole-Genome Sequence of the Coral Acropora Millepora</i> , 1 GENOME BIOL. Genome Biology 1374 (2019).

Ex.	Short Name	Description
2019		Office Action Summary, Application No. 13/750,768 (U.S. Patent & Trademark Office July 15, 2015).
2020	Singleton 2011	A. Singleton, <i>Exome sequencing: a transformative technology</i> , 10 Lancet Neurol. 942-46 (2011).
2021	Former Bustamante Declaration	Declaration of Carlos D. Bustamante, Ph.D. for Patent Owner's Preliminary Response
2022-2035		<i>Reserved</i>
2036	Sims Deposition 1	Transcript for the June 26, 2025 Deposition of Dr. Peter A. Sims
2037	Sims Deposition 2	Transcript for the June 27, 2025 Deposition of Dr. Peter A. Sims
2038	Bustamante Declaration	Declaration of Carlos D. Bustamante, Ph.D. (<i>amended on October 14, 2025</i>)
2039	Matz Declaration	Declaration of Mikhail V. Matz, Ph.D.
2040	Mullis 1986	K. Mullis et al., <i>Specific Enzymatic Amplification of DNA In Vitro: The Polymerase Chain Reaction</i> , 51 COLDSRING HARBOR SYMPOSIA QUANTITATIVE BIOL. 1 (1986)
2041	Kanagawa 2003	Takahiro Kanagawa, <i>Bias and Artifacts in Multitemplate Polymerase Chain Reactions (PCR)</i> , 96 J. BIOSCI. & BIOENG 4 (2003)
2042	Aird 2011	Daniel Aird et al., <i>Analyzing and minimizing PCR amplifications bias in Illumina sequencing libraries</i> , 12 GENOME BIOL. (2011)
2043	Chenchik 1996	A. Chenchik et al., <i>Full-Length cDNA Cloning and Determination of mRNA 5' and 3' Ends by</i>

Ex.	Short Name	Description
		<i>Amplification of Adaptor-Ligated cDNA</i> , 21 BIOTECHNIQUES 3 (1996)
2044	Devon 1995	Rebecca S. Devon et al., <i>Splinkerettes—improved vectorettes for greater efficiency in PCR walking</i> , 23 NUCLEIC ACIDS RES. 9 (1995)
2045	Padegimas 1998	Linus S. Padegimas & Nancy A. Reichert, <i>Adaptor Ligation-Based Polymerase Chain Reaction-Mediated Walking</i> , 260 ANALYTICAL BIOCHEMISTRY (1998)
2046	Arnold 1991	C. Arnold & I.J. Hodgson, <i>Vectorette PCR: A Novel Approach to Genomic Walking</i> , PCR METHODS & APPLICATIONS (1991)
2047	Miura 2005	Fumihito Miura et al., <i>A novel strategy to design highly specific PCR primers based on stability and uniqueness of 3'-end subsequences</i> , 21 BIOINFORMATICS 24 (2005)
2048	Tsoktouridis 2005	Georgios Tsoktouridis et al., <i>Adaptor Long-Range PCR Procedure for Clone-Specific Characterization and Chromosomal Localization</i> , 38 BIOTECHNIQUES 6 (2005)
2049	Bower 2010	Neil I. Bower & Ian A. Johnston, <i>Targeted rapid amplification of cDNA ends (T-RACE)—an improved RACE reaction through degradation of non-target sequences</i> , 38 NUCLEIC ACIDS RES. 21 (2010)
2050	Sohn 2011	Jung-Hoon Sohn, <i>A Novel Genome Walking Method for Cloning of Unknown DNA Sequences Adjacent to Known Sequence</i> , Application No. WO 2011/004994
2051	Almomani 2011	Rowida Almomani et al., <i>Experiences with array-based sequence capture; toward clinical applications</i> , 19 EURO. J. HUMAN GENETICS (2011)
2052	Myllykangas 2011	Samuel Myllykangas et al., <i>Targeted sequencing library preparation by genomic</i>

Ex.	Short Name	Description
		<i>DNA circularization</i> , 11 MCB BIOTECH. 122 (2011)
2053	Quail 2008	Michael A. Quail et al., <i>A large genome center's improvements to the Illumina sequencing system</i> , 5 NAT. METHODS 12 (2008)
2054	Kozarewa 2009	Iwanka Kozarewa et al., <i>Amplification-free Illumina sequencing-library preparation facilitates improved mapping and assembly of (G+C)-biased genomes</i> , 6 NAT. METHODS 4 (2009)
2055	Syvänen 2001	Ann-Christine Syvänen, <i>Accessing Genetic Variation: Genotyping Single Nucleotide Polymorphisms</i> , 2 NAT. REV. (2001)
2056	Grunenwald 2010	Haiying Gruenwald et al., <i>Rapid, high-throughput library preparation for next-generation sequencing</i> , NAT. METHODS (2010)
2057	Glenn 2011	Travis C. Glenn, <i>Field guide to next-generation DNA sequencers</i> , MOLECULAR ECOLOGY RES. (2011)
2058	Zhang 2021	Lu Zhang, <i>Advances in Metagenomics and Its Application in Environmental Microorganisms</i> , 12 FRONTIERS IN MICROBIOL. (2021)
2059	2008 GS-Flx Operating Manual	<i>Genome Sequencer FLX Operator's Manual</i> , ROCHE (2008)
2060	Niedringhaus 2011	Thomas P. Niedringhaus, <i>Landscape of Next-Generation Sequencing Technologies</i> , 83 ANALYTICAL CHEMISTRY (2011)
2061	Thoma 2011	Generation of Stable mRNA Fragments and Translation of N-Truncated Proteins Induced by Antisense Oligodeoxynucleotides
2062	Ernani 2009	Fred Ernani et al., <i>Bringing Cost and Process Efficiency to Next Generation Sequencing</i> , DDW (2009)

Ex.	Short Name	Description
2063	Irwin 2011	Jodi Irwin et al., <i>Assessing the potential of next generation sequencing technologies for missing persons identification efforts</i> , 3 FORENSIC SCI. J. (2011)
2064	Lange 2010	Julia Lange, <i>Targeted resequencing for large-scale genomic studies: accelerating NGS throughput using molecular barcodes</i> , NAT. METHODS (2010)
2065	Barchi 2019	Lorenzo Barchi, <i>Single Primer Enrichment Technology (SPET) for High-Throughput Genotyping in Tomato and Eggplant Germplasm</i> , 10 FRONTIERS IN PLANT SCI. (2019)
2066	Gnirke 2009	Andreas Gnirke et al., <i>Solution Hybrid Selection with Ultra-Long Oligonucleotides for Massively Parallel Targeted Sequencing</i> , 27 NAT. BIOTECH. 182 (2009)
2067	Smith 2021	Caitlin Smith, <i>Growing Options for Enriching Target DNA</i> , FUTURELABS, June 17, 2021, https://www.biocompare.com/Editorial-Articles/576645-Growing-Options-for-Enriching-Target-DNA/ .
2068	Scaglione 2019	Davide Scaglione et al., <i>Single primer enrichment technology as a tool for massive genotyping: a benchmark on black poplar and maize</i> , 124 ANNALS OF BOTANY (2019)
2069	Benjamino 2021	Jacquelynn Benjamino et al., <i>Genome-Based Targeted Sequencing as a Reproducible Microbial Community Profiling Assay</i> , 6 MSPHERE 2 (2021)
2070	Knierim 2011	Ellen Knierim, <i>Systematic comparison of three methods for fragmentation of long-range PCR products for next generation sequencing</i> , 6 PLoS ONE 11 (2011)
2071	Quail 2011	Michael A. Quail et al., <i>Optimal enzymes for amplifying sequencing libraries</i> , 9 NAT. METHODS 1 (2012)

Ex.	Short Name	Description
2072	Whiley 2005	David M. Whiley et al., <i>Sequence variation in primer targets affects the accuracy of viral quantitative PCR</i> , 34 J. CLINICAL VIROLOGY (2005)
2073	Ghedira 2009	Rim Ghedira et al., <i>Assessment of Primer/Template Mismatch Effects on Real-Time PCR Amplification of Target Taxa for GMO Quantification</i> , 57 J. AGRICULTURAL & FOOD CHEMISTRY (2009)
2074	Matz 2002	Mikhail V. Matz, <i>Amplification of Representative cDNA Samples from Microscopic Amounts of Invertebrate Tissue to Search for New Genes</i> , in GREEN FLUORESCENT PROTEIN: APPLICATIONS AND PROTOCOLS 3 (Barry W. Hicks ed., 2002)
2075	Bielas 2013	International Publication No. WO 2013/123442 A1
2076	JPMorgan Report	Tycho W. Peterson et al., <i>Next Gen Sequencing Survey</i> , J.P. MORGAN (2010)
2077	Ambion 2008	<i>Ambion® RNA Fragmentation Reagents</i> , APPLIED BIOSYSTEMS (2008)
2078	Illumina 2008	<i>Preparing Samples for Sequencing of mRNA</i> , ILLUMINA (2008)
2079	Additional File 3	Additional File 3 to EX1006
2080	Lewin 1994	Benjamin Lewin, <i>The eukaryotic gene: conserved exons and unique introns</i> , in GENES V 677 (1994)
2081	Evrogen Trimmer Kit Manual	<i>Trimmer-Direct cDNA Normalization Kit User Manual</i> , EVROGEN (2012)
2082	NuGEN Nature	<i>Accelerating Genomics with Advanced Sample Preparation Solutions</i> , NATURE RESEARCH CUSTOM MEDIA

Ex.	Short Name	Description
2083	Scolnick 2015	Jonathan A. Scolnick et al., <i>An Efficient Method for Identifying Gene Fusions by Targeted RNA Sequencing from Fresh Frozen and FFPE Samples</i> , PLOS ONE (2015)
2084	NuGEN BioSpace	Priya Balachandran, <i>NuGEN Announces Issuance of U.S. Patent For Its Single Primer Target Enrichment Technology (SPET) For Next Generation Sequencing Applications</i> , BIOSPACE, https://www.biospace.com/nugen-announces-issuance-of-u-s-patent-for-its-single-primer-target-enrichment-technology-spet-for-next-generation-sequencing-applications (last visited July 18, 2025)
2085	Allegro V2	<i>Allegro® Targeted Genotyping V2 Product Sheet</i> , TECAN GENOMICS, INC. (2019)
2086	Feng 2016	Weixing Feng et al., <i>Improving Alignment Accuracy on Homopolymer Regions for Semiconductor-Based Sequencing Technologies</i> , 17 BMC GENOMICS 521 (2016)
2087	Nakamura 2011	Kensuke Nakamura et al., <i>Sequence-Specific Error Profile of Illumina Sequencers</i> , 39 NUCLEIC ACIDS RES. 90 (2011)
2088	Sambrook 2006	Joseph Sambrook et al., <i>Fragmentation of DNA by Nebulization</i> , COLD SPRING HARB. PROTOC. (2006)
2089	QIAGEN 2010	<i>QIAGEN® Multiplex PCR Handbook</i> , QIAGEN (2010).
2090	Han 2006	Sangjo Han et al., <i>AtRTPrimer: Database for Arabidopsis Genome-Wide Homogeneous and Specific RT-PCR Primer-Pairs</i> , 7 BMC BIOINFORMATICS 179 (2006).
2091	Matz 1999	Mikhail V. Matz et al., <i>Amplification of cDNA Ends Based on Template-Switching Effect and Step-out PCR</i> , 27 NUCLEIC ACIDS RES. 1558 (1999).
2092	Bru 2008	D. Bru et al., <i>Quantification of the Detrimental Effect of a Single Primer-</i>

Ex.	Short Name	Description
		<i>Template Mismatch by Real-Time PCR Using the 16S rRNA Gene as an Example</i> , 74 APPL. ENVIRON. MICROBIOL. 1660 (2008).
2093	Bustin 2005	Stephen A. Bustin et al., <i>Quantitative Real-time RT-PCR – A Perspective</i> , 34 J. MOL. ENDOCRINOL. 597 (2005).
2094	Duncavage 2011	Eric J. Duncavage et al., <i>Hybrid Capture and Next-Generation Sequencing Identify Viral Integration Sites from Formalin-Fixed, Paraffin-Embedded Tissue</i> , 13 J. MOL. DIAGNOSTICS. 325 (2011).
2095	Mertes 2011	Florian Mertes et al., <i>Targeted Enrichment of Genomic DNA Regions for Next-Generation Sequencing</i> , 10 BRIEF. FUNCT. GENOM. 374 (2011).
2096	Shen 2010	Zhiyong Shen et al., <i>MPrimer: A Program for Reliable Multiplex PCR Primer Design</i> , 11 BMC BIOINFORMATICS FUNCT. GENOM. 143 (2010).
2097	Deutsche 2011	Ulla Deutsch et al., <i>Streamlining Multiplex PCR Analysis</i> , GENETIC ENGINEERING & BIOTECHNOLOGY, Dec. 1, 2011, https://www.genengnews.com/insights/streamlining-multiplex-pcr-analysis/ .
2098	Bragg 2013	Lauren M. Bragg et al., <i>Shining a Light on Dark Sequencing: Characterising Errors in Ion Torrent PGM Data</i> , 9 PLOS COMPUT. BIOL. 1 (2013)
2099	Stapleton 2002	Mark Stapleton et al., <i>The Drosophila Gene Collection: Identification of Putative Full-Length cDNAs for 70% of D. melanogaster Genes</i> , 12 COLD SPRING HARB. LAB. 1294 (2002)
2100	Infinitives	Evin de Leon Sanchez, <i>Infinitives</i> , SAN JOSE STATE UNIVERSITY WRITING CENTER, https://www.sjsu.edu/writingcenter/docs/handouts/Infinitives.pdf (last visited July 18, 2025)

Ex.	Short Name	Description
2101	Meyer Comparison	Redline document comparing Exhibits 2103 and 2039
2102	Matz Email 1	Email thread between counsel and Petitioner's counsel
2103	Meyer Declaration	Declaration of Eli Meyer, Ph.D.
2104	Matz Email 2	Email thread between counsel and Petitioner's counsel
2105	Matz Email 3	Email thread between counsel and Petitioner's counsel
2106	Matz Email 4	Email thread between counsel and Petitioner's counsel
2107-2199		<i>Reserved</i>
2200-2284		Privileged & Confidential Correspondence (submitted <i>in camera</i>)
2285		Privileged & Confidential Declaration and Timeline Submitted Under Seal for <i>In Camera</i> Review
2286	Beavers Decl.	Declaration of Timothy J. Beavers
2287	Meyer Decl.	Declaration of Eli Meyer, Ph.D.
2288	Meyer Errata	Errata Sheet for the Deposition Transcript of Eli Meyer, Ph.D. (signed and served on November 6, 2025)
2289	Bustamante Errata	Errata Sheet for the Deposition Transcript of Carlos D. Bustamante, Ph.D., Volumes I and II (signed and served on November 1, 2025)

Meyer describes a method that is different from the claimed invention and that addresses a different problem. *Meyer* breaks a homopolymer chain to remedy sequencing errors and non-selectively amplifies the entire transcriptome. *Meyer* does not disclose the claimed amplification to enrich for target sequences (step 1(d)) and the sequencing of the enriched target sequences (step 1(f)). As Dr. Meyer explained (without rebuttal from Petitioner), not only is there no enrichment of a target sequence, but the method is not designed to do so: “our method did not target a specific gene or region, but rather, the entire class of transcripts.” EX1126.0118:18-119:1. Not only did *Meyer* not seek to enrich, there is no evidence that any of the fragments were enriched through *Meyer*’s amplification process.

Unable to dispute these facts, Petitioner improperly advocates for rewriting the claims. First, Petitioner incorrectly conflates “enrichment” with amplification. That is directly at odds with the plain meaning of the term and the intrinsic record. The Board initially found that the plain meaning of “to enrich” was “to process so as to add or increase the *proportion* of a desirable ingredient.” Paper 9, 15 (emphasis added). Petitioner offers no justification for departing from the plain meaning. Second, Petitioner’s proposed construction reads the explicit language that the amplification is “to enrich for the nucleic acid sequence of interest” out of the claim entirely. This is at odds with the law and intrinsic record. The claims describe a specific amplification method that results in enrichment of the target sequence.

Petitioner's strained positions are its attempt to salvage its reliance on *Meyer*. Petitioner mistakenly maps *Meyer*'s general amplification step onto the target-specific amplification claimed in step 1(d) of the '012 patent. Importantly, *Meyer* introduces the "second adaptor sequence" to *every* fragment—not just fragments with a sequence of interest. *Meyer* then amplifies all fragments, without enriching for any sequences over others. Petitioner ignores this point as well as Dr. Bustamante's extensive testimony that a POSA would not have been able to reasonably infer enrichment based on *Meyer*'s data. The record, therefore, supports only one conclusion: *Meyer* does not disclose the selective enrichment methods recited in the '012 patent and thus cannot anticipate the challenged claims.

I. TECAN APPLIES THE CORRECT CONSTRUCTION

Petitioner's arguments are predicated on an erroneous rewriting of the claims. Petitioner not only applies a construction for enrichment contrary to the plain meaning identified by the Board but also seeks to entirely remove the limitation that requires that the "amplifying" limitation is used "to enrich for the nucleic acid sequence of interest." Petitioner's construction, therefore, cannot be correct, and the Board should apply Tecan's proposed construction.

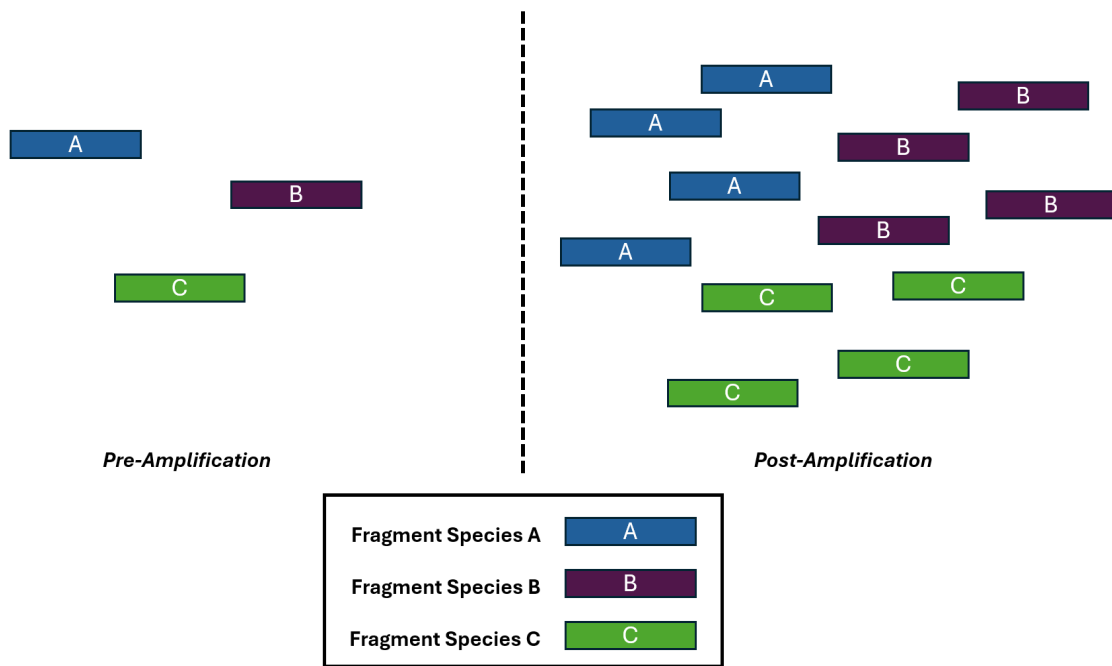
A. Enrichment Is a Change in Proportion, Not Just Raw Number

To support its position that *Meyer* does not disclose enrichment, Petitioner argues that step 1(d) "simply require[s] that more fragments containing the sequence

of interest are created.” Paper 47, 1. However, that is not “enrichment” as it is ordinarily understood and as all three experts in this case used the term.

As the Board acknowledged, the plain meaning of “to enrich” is “to process so as to add or increase the *proportion* of a desirable ingredient.” Paper 9, 15 (emphasis added). The specification confirms that enrichment, as used in the claims, relates to the proportionality of the target sequence in the library. *See infra* p. 7. Proportionality is, by definition, relative. The proportion of an ingredient in a mixture is not synonymous with the absolute amount of the ingredient. For example, an ingredient can be enriched if other ingredients are preferentially removed from the mixture, leaving the same absolute amount of the enriched ingredient, but less of the other ingredients. Alternatively, an ingredient can be enriched when it is preferentially amplified over other ingredients, as described in the challenged claims. In either case, the end result has a different proportion of ingredients than before enrichment.

Under Petitioner’s construction, however, “enrichment” and “amplification” are equivalent. The illustration below exposes Petitioner’s fallacy. Under Petitioner’s construction, fragment A would be considered “enriched” because it is increased from one fragment to four fragments—even though the proportion of fragment A in solution (1/3) stayed the same after amplification.



Ordinary understanding of the terms, however, necessitates a conclusion that each fragment was amplified but none were enriched. Based on Petitioner’s understanding, any method that increases the number of a desired fragment necessarily enriches for that fragment. This conflation of “amplification” and “enrichment” is unsupported by the record and contrary to black letter law. *See Neville v. Foundation Constructors, Inc.*, 972 F.3d 1350, 1357 (Fed. Cir. 2020) (“two terms in a claim require[] that they connote different meanings”).

Here, all three declarants agree with Tecan’s proposed construction. Dr. Bustamante testified that “the term ‘enrichment’ means to selectively increase the proportion of one part of a sample or reaction mixture over other portions of the sample or reaction mixture.” EX2038.¶95; EX1125.0283:1-6, 286:22-287:14.

Contrary to Petitioner’s claims, Dr. Bustamante used the term “baseline” to refer to a comparison of percentages, not raw numbers. *See* Paper 47, 3. Dr. Sims testified that in the context of the claims, “enriched” refers to “an enrichment process [that] results in overrepresentation of certain nucleic acid sequences *relative* to others in a sample.” EX2037.0173:15-17 (emphasis added); EX2037.0150:18-22. As Dr. Sims explained, “[t]o assess enrichment, one would compare the abundance of sequences of interest to that of other sequences in the sample.” EX2037.0217:15-17. Dr. Meyer likewise testified that a fragment is enriched when “its *relative frequency* is higher in the product than it was in the initial template.” EX1126.0170:18-171:1 (emphasis added). Petitioner’s construction, therefore, is not supported by any expert testimony.

Petitioner’s critique that enrichment cannot be an increase in proportion because the claims do not reference other fragments is misplaced. Paper 47, 7. Claims are construed based on “how a skilled artisan would read the claim term in the context of the entire patent.” *DDR Holdings, LLC v. Priceline.com LLC*, 122 F.4th 911, 916 (Fed. Cir. 2024) (cleaned up). As Dr. Bustamante testified, a POSA would have understood the claim to mean “[a] fragment in the milieu of nucleic acids that are being put through the protocol for enrichment.” EX1125.0275:7-10. This is common sense. *See* EX2038.¶128. Further, all three Examples describe the claimed amplification process as the “[s]election for [target] fragments” in solution.

EX1001.0031-33 (31:35-35:16). This is also consistent with the language of the related '108 patent, which states that “the reaction mixture comprises a plurality of nucleic acid fragments.” EX1002.0033 (35:22-24). *See Microsoft Corp. v. Multi-Tech Sys., Inc.*, 357 F.3d 1340, 1349 (Fed. Cir. 2004) (the intrinsic record of “one patent is relevant to an understanding of the scope of a common term in a second patent stemming from the same parent application”); *Samsung Elecs. Co., Ltd. v. Elm 3DS Innovations, LLC*, 925 F.3d 1373, 1378 (Fed. Cir. 2019) (patents derived from the same parent application should be construed consistently).

Arguing that the claims do not require enrichment, Petitioner relies exclusively on a subset of cases concerning the construction of “whereby” clauses that have no bearing here. Paper 47, 6-7. In those cases, the “whereby” clauses were not material to patentability. However, as is the case here, the Federal Circuit has repeatedly held that “when a ‘whereby’ or [similar] clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention.” *Allergan Sales, LLC v. Sandoz, Inc.*, 935 F.3d 1370, 1376 (Fed. Cir. 2019) (cleaned up).

Enrichment of the target sequence resulting from the amplification step is critical to the invention. This language in step 1(d) is the antecedent basis for “the enriched nucleic acid sequence of interest” in step 1(f), which Petitioner’s construction improperly ignores. *See Hytera Commc’ns. Co. Ltd. v. Motorola Sols.*,

Inc., 841 Fed. App'x 210, 218 (Fed. Cir. 2021). The specification reinforces the critical nature of enrichment in the claimed invention. *See, e.g.*, EX1001.0001 (“The present invention provides methods ... for targeted nucleic acid sequence enrichment in a nucleic acid sample”), 16 (2:25-28) (“There is a need for improved methods for selective target enrichment”), 18 (6:12-16) (“methods of the invention can be used for the *selective enrichment of a plurality of defined target sequences* from complex DNA” (emphasis added)), 31 (31:41-32:42) (Example 1 determining enrichment “by calculating the number of rRNA reads as a percent of total mapped reads in the control and test samples.”).

Petitioner’s request that the Board interpret the claim contrary to its plain meaning and entirely read out the “to enrich” limitation is improper. *See Kyocera Senco Indus. Tools Inc. v. I.T.C.*, 22 F.4th 1369, 1378 (Fed. Cir. 2022) (terms should be given their plain and ordinary meaning absent lexicography or disavowal); *Aspex Eyewear, Inc. v. Marchon Eyewear, Inc.*, 672 F.3d 1335, 1348 (Fed. Cir. 2012) (reversing construction that read out a claim limitation).

B. Petitioner’s Other Arguments Have No Bearing on the Present Claim Construction Dispute

Failing to provide any intrinsic support, Petitioner presents a series of irrelevant arguments, none of which are grounds to rewrite the claims.

First, the claim's use of "comprising" does not permit reading out an explicit limitation that requires enrichment to occur in at least the amplification step. *See* Paper 47, 10-11. As the Federal Circuit stated, "comprising" is "not a weasel word with which to abrogate claim limitations." *Dippin' Dots, Inc. v. Mosey*, 476 F.3d 1337, 1343 (Fed. Cir. 2007). Step 1(d) requires that amplification enrich the sequence of interest. That other steps in the method may further enrich genetic material is irrelevant. As both parties' experts agree, if the *proportion* of fragments containing the sequence of interest remains the same before and after the amplification of step 1(d), the claimed limitation is not met. EX2037.0188:22-189:1 (Dr. Sims "agree[d] that at the conclusion of this amplification process, enrichment must occur"); EX1125.0271:10-15 (Dr. Bustamante testified that "[f]or you to practice the claim, you need to enrich through the process laid out here where you are amplifying the extension products that arise as a result of the targeting process"); *see also* EX2037.0183:14-22 (Dr. Sims could not "definitively answer" whether the claimed inventions would still work under Petitioner's interpretation of the claims).

Second, Dr. Bustamante's testimony concerning shotgun sequencing is immaterial. *See* Paper 47, 8. Shotgun sequencing has no bearing on step 1(d) since it concerns fragments that are "amplified in separate reactions" and then pooled for sequencing. *Id.* Rather, as Dr. Bustamante explained, the claims do not restrict the

sequencing of other fragments along with the enriched sequence so long as the claimed amplification enriches for the target sequence. EX1125.0407:12-21.

Third, Petitioner's critiques of Tecan's reliance on Figure 1 are misplaced. Petitioner incorrectly alleges that Tecan seeks to import the limitation that "only the oligonucleotide extension products from step (c) undergo the claimed amplification" from Figure 1. Paper 47, 10-11. As Tecan has explained, the claimed inventions enrich a target sequence through amplification because of the claimed combination of a target-specific primer and a set of universal primers. Paper 41, 14-16. This is not an added limitation but simply how the invention functions. There is no need for the Board to decide whether other amplification can occur in addition to the enrichment step because Petitioner only cites prior art where all fragments undergo amplification, which does not meet limitation 1(d).

Further, Petitioner's attempts to minimize the importance of Figure 1's disclosures because it depicts a "commercial embodiment" (Paper 47, 10-11) are misleading. As Petitioner recognized, the patent expressly identifies Figure 1 as a "preferred embodiment of the methods described herein for enriching for target sequences of interest." EX1001.0023 (15:57-59).

Fourth, Tecan's infringement contentions are consistent with its positions here. Paper 47, 12-13. Petitioner's cropped figure (Paper 47, 13) omits a second round of amplification during PCR 2 that enriches for the target sequence by using

universal primers. *See, e.g.*, EX1085.¶117. Tecan relies on this second round of selective amplification for infringement of the limitation at issue. As explained above, the claims do not preclude earlier enrichment; however, to practice the claimed invention, some enrichment must result from step 1(d). PCR 2 does this, which Petitioner attempts to conceal from the Board.

II. MEYER FAILS TO ANTICIPATE THE CHALLENGED CLAIMS

Meyer fails to disclose the claimed amplification process of step 1(d). Paper 41, 28-35. Because the sequence of interest is not enriched, step 1(f) is also not met (“sequencing the enriched nucleic acid sequence of interest”). *See id.* Petitioner has no substantive response beyond its effort to rewrite the claims to exclude these limitations and to misapply the limited data *Meyer* discloses.

A. Meyer Fails to Disclose Steps 1(d) and 1(f)

Petitioner fails to identify any disclosure in *Meyer* “amplifying the one or more oligonucleotide extension products ... to enrich for the nucleic acid sequence of interest.” As Dr. Meyer testified, they were “not enriching for any particular sequence in terms of particular gene or families of genes.” EX1126.0030:9-11. They “were interested in sequencing all of the regions of the transcript. That was [their] goal, [] to try to capture all the transcripts and all the parts of the transcript.” EX1126.0161:15-18; EX1125.0378:1-379:1. In fact, Dr. Meyer explains that they actively sought to avoid enrichment. As he explained, one of the biggest challenges

for transcriptome sequencing is “avoid[ing] the preferential sequencing of certain genes or transcript regions.” EX1126.0119:13-123:19. *Meyer* discloses a method that amplifies cDNA fragments *spanning the entire length of the transcriptome*. That is not disputed.

Petitioner points to two sequences in *Meyer* for disclosure of the claimed “sequence of interest”: the broken T chain and cap primer. Paper 1, 47, 56. *Meyer*, however, amplifies these fragments as well as fragments not containing Petitioner’s alleged sequences of interest (e.g., the internal fragments). Paper 41, 30-35. This indiscriminate amplification occurs because *Meyer* introduces the “second adaptor sequence” in one of the two adaptors that are ligated *to every fragment in solution*. *Id.*, 33-35. Because all fragments are amplified, *Meyer*’s amplification process does not enrich for target sequences. *Id.* Unlike *Meyer*, the challenged claims introduce the “second adaptor sequence” through the target-specific oligonucleotide (rather than the partial duplex adaptor as in *Meyer*), which allows for selective amplification and enrichment of the target sequences over other sequences, which do not have the second adaptor sequence appended. *Id.*

Petitioner is incorrect that “Dr. Meyer agreed [that] creating just ‘one more copy’ enriches for a sequence of interest.” Paper 47, 22. Dr. Meyer instead testified that the hypothetical presented during deposition was an artificial example that is not reflective of the *Meyer* method. EX1126.0166:10-15. There is no evidence in

Meyer that it increased the number of 3' fragments over the other fragments by even “one copy number.” EX1126.0178:10-20. Dr. Meyer further rejected Petitioner’s speculation by explaining that the internal fragments may have been amplified at a higher rate than the 3' ends. EX1126.0171:20-174:1.

Petitioner raises three new, unsupported arguments in reply. First, Petitioner argues that because there are more 3' fragments after amplification than before, *Meyer* must necessarily enrich for the 3' fragments regardless of whether the proportion changes. Paper 47, 3-4. That argument conflates amplification with enrichment and misapplies the proper construction of “to enrich.” *See supra* Section I. Under the proper construction, *Meyer* fails to disclose the method of the challenged claims. Paper 41, 30-35.

Second, Petitioner incorrectly suggests that the removal of other nucleic acids present in the original sample from the final sequencing data satisfies the claimed enrichment. Paper 47, 5. Setting aside that *Meyer* does not disclose a method where the amplification step results in enrichment of a target sequence, the record also does not support an assumption that other nucleic acids would have been present at the amplification step. Dr. Meyer testified that the sample was purified to remove nucleic acids other than RNA from the solution before reverse transcription. EX2287.¶34. Then, *Meyer* reverse transcribed mRNA into cDNA. By the start of the process that Petitioner attempts to map to the claims, Dr. Sims testified that he

did not “expect there to be any actual RNA molecules present,” just the cDNA. EX2037.0215:9-21. As such, Petitioner’s argument that there were nucleic acids other than cDNA in the solution is pure speculation.

Third, Petitioner misapplies the patent’s disclosure that a “plurality of target sequences may comprise ... a whole transcriptome.” Paper 47, 9. The specification’s description of the “oligonucleotides of the invention” does not negate the other limitations of the claims—namely the requirement for an oligonucleotide designed to bind to each target sequence. EX1001.0026 (21:10-22:36). *Meyer* does not disclose this embodiment because *Meyer* fails to disclose target-specific oligonucleotides corresponding to each of the amplified fragments. See EX2038.¶¶182-183, 188-190. If anything, this passage bolsters Tecan’s construction: “In some embodiments, multiple sequence-specific oligonucleotides or primers are employed to hybridize to a multiplicity of genomic regions of interest, allowing for *selective enrichment* of the regions of interest.” EX1001.0026 (22:8-12) (emphasis added).

Notably, Petitioner has never asserted in this proceeding that a POSA would have been motivated to modify the amplification step of *Meyer* to arrive at the challenged claims. Yet at his deposition, Petitioner asked Dr. Meyer how his methods might work if modified. EX1126.0137:8-141:15. A reference cannot anticipate if it must be modified beyond its disclosure. *In re Chudik*, 851 F.3d 1365,

1372 (Fed. Cir. 2017) (“a prior art reference that must be distorted from its obvious design does not anticipate a patent claim”) (cleaned up).

B. A POSA Would Have Understood that *Meyer* Did Not Enrich for the 3' Fragments

Meyer expected that a 454 optical sequencing error caused by homopolymer regions would “result in under-representation of the 3' ends of transcripts.” EX1006.0009. There is no dispute that *Meyer* resolved this homopolymer issue by “simply interrupting” the polyT chain during cDNA synthesis. But Petitioner twists this disclosure, essentially arguing that it must reflect enrichment. Paper 47, 15. To the contrary, all three witnesses confirmed that *Meyer* resolved the expected 3' underrepresentation by breaking the polyT chain. EX1085.¶¶144-145; EX2038.¶¶238-249; EX2287.¶¶28-31.

Petitioner misconstrues two quotes from *Meyer* to argue that it addressed this underrepresentation through amplification. Neither supports Petitioner. First, Petitioner incorrectly relies on *Meyer*'s disclosure of “the use of an additional primer to target and amplify 3' end fragments.” Paper 47, 16. As Drs. Bustamante and Meyer testified (which Petitioner does not dispute), the authors proposed using the “A+Trsac” primer as a means of *conserving sequencing read space by shortening the 3' amplicons*. EX2038.¶235; EX2287.¶¶49-50. The use of this custom primer cannot show enrichment where the other fragments are also being amplified in

parallel. Paper 41, 30-34. Second, that “the amplification step in Meyer created exponentially more 3' end fragments” is of no moment. Paper 47, 16. Exponential amplification is the purpose of PCR amplification and does not necessarily lead to enrichment. In *Meyer*, the 5', internal, and 3' fragments were all exponentially amplified during PCR amplification. EX2038.¶216; EX2287.¶¶44-45. *Meyer* does not disclose any enrichment since *Meyer* amplified cDNA fragments running the full length of the transcriptome in an unbiased manner. Paper 41, 27-28.

The lack of enrichment of the 3' end is further evidenced by *Meyer*'s use of the SMART cDNA synthesis kit. EX2038.¶¶229-232; EX2287.¶¶25, 66. It was a known problem that reverse transcription can terminate prematurely. EX2038.¶60; EX2287.¶25. Because reverse transcription begins at the 3' end, early termination leads to an overrepresentation of 3' ends in the sample as compared to sequences closer to the 5' end. EX2287.¶25 (citing EX1034.0004). As all three experts explained, the SMART protocol was a known method for favoring full mRNA over 3' end fragments. EX2038.¶170; EX1085.¶¶147-148; EX1126.0134:19-135:19. Thus, a POSA would have understood the use of this method as antithetical to methods seeking to enrich for 3' ends. EX2038.¶170.

C. *Meyer*'s Data Cannot and Does Not Demonstrate Enrichment

Petitioner has not, and indeed cannot, identify any disclosure in *Meyer* of the proportions of any of the fragments before amplification or the proportions of the

other fragments sequenced. Paper 47, 4-5, 14. Rather, as Dr. Meyer testified, they did not “have the data at hand to evaluate whether the frequency of [the 3' fragments] in the final pool was more or less than it started at or more or less than the other fragments.” EX1126.0180:3-10. Dr. Meyer explained that “you would really need to have replicates to evaluate whether the relative frequency of the target that you obtained in this experiment is statistically more than you started with,” and that they did not “have replicates in this experiment.” EX1126.0178:10-179:2. Petitioner fails to rebut this explanation. As Dr. Bustamante confirmed, this explanation is consistent with how a POSA would have interpreted *Meyer*. EX2038.¶¶246-251.

D. A POSA Cannot Infer Enrichment From *Meyer*

Given the lack of any data, Petitioner incorrectly attempts to reframe the question as whether the POSA would have “second-guessed Meyer’s result.” Paper 47, 18. This is not the standard for anticipation. It ignores Petitioner’s burden of establishing that a POSA would have understood that *Meyer* disclosed all limitations of the challenged claims. Dr. Bustamante testified that a POSA would not have reasonably inferred enrichment from *Meyer*. EX2038.¶270. Dr. Sims never rebutted that point. *See* EX1085.¶¶145, 183-184. Petitioner instead raises extraneous arguments, attempting to obfuscate the record.

As an initial point, Petitioner concedes that the data reported in *Meyer is not based on the method on which the Petition relies*. Paper 47, 17-18. Any argument

that the POSA would “understand the sequencing results and conclusions reported in the paper to apply to both methods” is speculative and based on impermissible hindsight. *Id.* As Drs. Meyer and Bustamante testified, the data was “generated using the method that is outlined in the main body of the text.” EX1126.0052:15-53:1; EX1125.0393:12-25. And both witnesses testified that they could not speak to the results of the modified method “with any certainty” given the lack of data. EX1126.0053:2-7; EX1125.0394:7-395:16. Petitioner fails to identify any data generated by its relied-upon method (Supplemental File 4), instead relying on data generated *by a different method* (Figure 1).

There is also no dispute that *Meyer* does not describe its data as evidencing enrichment. Paper 47, 17. As Dr. Bustamante explains, a POSA would not have reasonably understood or inferred enrichment from that data. *See* EX2038.¶¶251-265. Petitioner counters by claiming that Dr. Bustamante is “unilaterally rewrit[ing] the reference,” (Paper 47, 19) but Dr. Bustamante is not rewriting anything. “[T]he dispositive question regarding anticipation is whether one skilled in the art would reasonably understand or infer from a prior art reference that every claim element is disclosed in that reference.” *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1055 (Fed. Cir. 2010) (cleaned up). Dr. Bustamante offers the *only* testimony as to whether a POSA would have reasonably inferred enrichment from that data and he confirms they would not.

Moreover, Petitioner still has no answer for the undisputed facts that underpin Dr. Bustamante's opinion that the skewed distributions in Figure 2 are "why a POSA would have inferred from the calculation that the expected 10% was meant to be directional and could not be used to measure exact changes in proportion." *See* EX2038.¶259. Dr. Bustamante provided testimony regarding how a POSA would have understood the average read length and average transcript length based on Figure 2 in *Meyer*. EX2038.¶¶254-265. Dr. Bustamante explained that the POSA's understanding of these Figures would have led the POSA to also understand that *Meyer's* 10% estimate could not be used as a reasonable baseline for assessing enrichment. EX2038.¶¶251-265, 270.

Petitioner fails to rebut any of this testimony and instead raises non-responsive arguments.

Petitioner makes contradictory, irrelevant arguments concerning Dr. Bustamante's testimony. Petitioner faults Dr. Bustamante for "stopp[ing] short of offering an opinion on what the number should have been." Paper 47, 19-20. As a threshold matter, it is not Tecan's burden to disprove Petitioner's claims. Petitioner must set forth how the cited reference discloses the claims. Further, as Dr. Bustamante explains, "it is hard to calculate without the full data set." EX2038.¶263. Even Dr. Meyer could not use the data reported in the publication to assess whether enrichment occurred. EX1126.0178:10-179:2.

Petitioner's position is even more absurd as it then also tries to argue that Dr. Bustamante "conceded that the POSA's expectation for the number of 3' end fragments would be '13 or 14%.'" Paper 47, 2, 22. Dr. Bustamante testified that he could not provide an estimate because he did not "have the actual data." EX1125.0417:12-22. Dr. Bustamante offered a "guesstimate" based on only the published distributions in *Meyer's* Figure 2. *Id.* Petitioner ignores that Dr. Bustamante also testified that a POSA could not reasonably infer enrichment based on the 10% expectation and available data. EX1125.0415:1-416:2, 417:22-418:5.

Petitioner misconstrues testimony to incorrectly assert that Dr. Meyer disagrees with Tecan's positions. Petitioner claims that Dr. Meyer contradicted Tecan by saying that he "obviously thought [the 10% calculation] was reasonable, and my co-authors agreed because we included it," and that he "stand[s] by the statement as written." Paper 47, 18-19. Petitioner never asked whether those numbers are reasonable for assessing enrichment. EX1126.0043:6-44:7. When Petitioner did ask Dr. Meyer whether he had enriched for the 3' fragments, Dr. Meyer explained that they did not have the data to make that assessment. EX1126.0178:10-179:2, 183:9-190:13. Dr. Meyer repeatedly explained that the estimate could not be used to assess enrichment. *Id.*

Nor did Dr. Meyer recant his testimony (Paper 47, 20-21) that the average transcript length is based off a mammalian transcript, which is ***not even the same***

phylum as the coral sequenced in *Meyer*. EX1126.0045:12-19, 60:18-61:5. Rather the question was whether Drs. Matz and Meyer first encountered this number in a well-known textbook or from their general knowledge. EX1126.0061:6-62:1. This is of no consequence, let alone the “admission” Petitioner claims it to be. Either way, it confirms what Dr. Bustamante repeatedly testified: a POSA would not have reasonably inferred enrichment based on a general assumption. EX2038.¶¶260-265, 270; EX1125.0413:1-416:2.

Petitioner presents disjointed, contradictory arguments concerning what a POSA could infer from *Meyer*’s gel reads. Petitioner argues that a POSA would have understood *Meyer*’s average transcript length as being empirically derived from a gel and thus acceptable for assessing enrichment. Paper 47, 19-20. Yet Petitioner then argues that the gel reads would be too “imprecise” to estimate the average fragment length. *Id.* Petitioner contradicts itself, exposing the flaws in its arguments. Either Dr. Sims is incorrect and the gel reads are too imprecise for calculating a baseline value, underscoring *Meyer*’s lack of data. EX2038.¶251. Or the gel reads are acceptable, in which case a POSA would have understood the expected baseline to be approximately 16% since *Meyer* reported the average fragment length as between 300-400 bp. EX2038.¶¶266-269.

E. Claim 21 Is Not Anticipated: *Meyer* Fails to Disclose the Reverse Transcription of an RNA Fragment

Petitioner claims that the plain meaning of “RNA fragment” is simply “any RNA polynucleotide.” Paper 47, 22. This argument reads out the distinction the patent makes between “nucleic acids” like “DNA” or “RNA” and “fragments” thereof. The proper construction of “RNA fragment” is “an RNA polynucleotide product generated through fragmentation.” This construction is supported by unrefuted intrinsic and extrinsic evidence. *See* Paper 41, 25-26.

Petitioner argues that Tecan’s construction “excludes the specification’s embodiments wherein RNA is transcribed to cDNA prior to fragmentation.” Paper 47, 22. But Petitioner relies on embodiments that are silent as to whether the RNA is fragmented prior to reverse transcription (*see* EX1124.0236-238) and fails to explain how these embodiments would necessarily be excluded from claim 21. Petitioner’s reliance on *In re Katz* is also misplaced since it concerns independent claims while claim 21 is a narrower, dependent claim. 639 F.3d 1303, 1324 (Fed. Cir. 2011). Even if claim 21 excludes certain embodiments described in the specification, Tecan’s construction remains proper: “[I]n a case such as this, where the patent describes multiple embodiments, every claim does not need to cover every embodiment.” *Pacing Techs., LLC v. Garmin Int’l, Inc.*, 778 F.3d 1021, 1026 (Fed. Cir. 2015).

F. Claim 22 Is Not Anticipated: *Meyer* Discloses a Method that Blocks Ligation on One End of Petitioner’s Target Fragments

Petitioner argues that “Tecan has no evidence that practicing the *Meyer* method could ever **not** result in fragmentation in the CAP sequences.” Paper 47, 24. Petitioner incorrectly inverts its burden and misconstrues the record. Petitioner argues that *Meyer* anticipates the claim despite *Meyer* expressly disclosing that the cap sequences blocked ligation. EX1125.0257; EX2037.0205:3-18; EX1006.0019. Nowhere in the publication does *Meyer* disclose the ligation of a partial duplex adaptor to each end of Petitioner’s target fragments. Petitioner claims that *Meyer* discloses the claimed method because of its published data. Paper 47, 23-24. But Dr. Sims admitted that Petitioner’s relied-upon sequences “**are not** the fragments that actually underwent all the steps of the method,” EX1085.¶263 (emphasis in original). Petitioner fails to identify a single fragment that underwent all steps of the method.

Instead, Petitioner relies on other fragments that are the unintended results of fragmentation. For those unintended results to anticipate, Petitioner must show that the results are inherent to the disclosed method. Paper 41, 47-48. To be inherent, Petitioner must prove that these results are the necessary consequence and inevitable result each and every time the method is performed. *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1378 (Fed. Cir. 2003); *SmithKline Beecham Corp. v.*

Apotex Corp., 403 F.3d 1331, 1343 (Fed. Cir. 2005). That is not the case here. Petitioner's relied-upon results are "a by-product and not in any way, shape[,] or form part of the design." EX1125.0260:4-6. Dr. Bustamante's unrebutted testimony explains that it is not the inevitable result of the *Meyer* method that a practitioner will obtain fragments containing Petitioner's sequence of interest where partial duplex adaptors are ligated to both ends. EX1125.0260:17-261:7; EX2038.¶¶294-307.

III. PETITIONER'S OBVIOUSNESS CHALLENGES FAIL

A. Claim 2 Is Not Obvious

Petitioner argues that "the chemical steps of the Meyer method can be performed on genomic DNA just as well as on cDNA" and "chemistry like that used in *Meyer* had been previously used on genomic DNA" (gDNA). Paper 47, 24. But Dr. Bustamante testified that because of differences in cDNA and gDNA, a POSA would have to redesign the *Meyer* method for use with gDNA. EX2038.¶¶313-315. Petitioner does not address the necessary adjustments or how Siebert teaches the missing limitations of *Meyer*. See EX2036.0053:6-69:4; Paper 41, 54.

Petitioner also has no response to Dr. Bustamante's testimony as to why a POSA would not have been motivated to modify *Meyer* for use with gDNA. Dr. Bustamante testified to fundamental gaps in Petitioner's arguments, including: (1) *Meyer* relies on reverse transcription to install cap primers but that process cannot

be used with gDNA; (2) cDNA only contains sequences for coding regions whereas gDNA contains sequences for both coding and non-coding regions; and (3) *Meyer* sought to address a specific issue with the 454 sequencing of mRNA polyA tails whereas gDNA has no direct comparison. EX2038.¶¶313-315; Paper 41, 50-53.

Petitioner chooses to respond only to prior art genome walking publications that taught away from the combination. *See* EX2038.¶¶66-67, 316-320; Paper 47, 25. However, Petitioner's arguments are based on a single reference, Leoni, that does not actually support Petitioner's conclusion. Leoni never discusses coupling the specific methods disclosed in *Meyer* with Siebert. Rather, Leoni generally chronicles the evolution of genome walking and identifies 53 different genome walking methods, of which, Siebert is just one method. EX1052.0003. In any case, as Dr. Bustamante explained, Siebert would have discouraged "amplification with single target-specific primers where no other safeguards are available." *See* EX2038.¶¶316-320. Yet Petitioner dismisses Siebert's disclosures because the "patent provides no other 'safeguards.'" Paper 47, 25. That argument rests entirely on hindsight and fails to address Siebert's teach-aways. And it undermines their entire Petition: that the inventors of the '012 patent forged a path contrary to the weight of the prior art is evidence of the nonobviousness of the claims. Paper 41, 59-62.

B. Claims 17-19 Are Not Obvious

Contrary to Petitioner's arguments, Bronner and Caruccio teach away from the claimed methods. *See* Paper 41, 57-58. As the Federal Circuit has explained, "[t]here is no suggestion to combine [] if a reference teaches away from its combination with another source." *Tec Air, Inc. v. Denso Mfg. Michigan Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999). That is the case here.

Petitioner relies on the broad assertion 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." Paper 47, 26. Petitioner fails to address why a POSA would be motivated to look back at methods specifically designed to solve issues with 454 sequencing when Illumina was the dominant sequencing technology by 2012. Paper 41, 56.

C. Petitioner Fails to Rebut Tecan's Secondary Considerations

Petitioner raises a single argument in response to Tecan's secondary considerations: that Tecan failed to demonstrate nexus. However, Petitioner misstates the law and holding of *In re Huai-Hung Kao*. Petitioner mistakes *Kao*'s discussion of nexus for unexpected results as a broad rule for all other secondary considerations. *See* 639 F.3d 1057, 1068 (Fed. Cir. 2011). But in discussing commercial success, *Kao* explains that a patentee does not need to consider "every conceivable embodiment ... so long as what was sold was within the scope of the

claims.” *Id.* at 1069. Thus, for secondary considerations, Tecan only needed to show that the considerations “aimed directly at novel aspects” of the claimed invention. *See e.g., Janssen Pharms., Inc. v. Teva Pharms. USA, Inc.*, 760 F. Supp. 3d 184, 217, 222 (D.N.J. 2024) (summarizing Federal Circuit precedent). Tecan did that. Paper 41, 59-67. And notably, Petitioner does not dispute any of Tecan’s evidence.

Date: December 23, 2025

/Linnea P. Cipriano/
Linnea P. Cipriano (Reg. No. 67,729)
GOODWIN PROCTER LLP
620 Eighth Avenue
New York, NY 10018
Tel: (212) 813-8800
Fax: (212) 937-2204
lcipriano@goodwinlaw.com

*Lead Counsel for Patent Owner Tecan
Genomics, Inc.*

CERTIFICATE OF WORD COUNT

The undersigned hereby certifies that the foregoing **Patent Owner's Sur-Reply** complies with the type-volume limitation of 37 C.F.R. § 42.24(c)(4). The Sur-Reply contains 5,594 words, excluding the parts exempted by 37 C.F.R. § 42.24(a)(1), as measured by the word-processing system used to prepare the Sur-Reply.

Dated: December 23, 2025

/Linnea P. Cipriano/
Linnea P. Cipriano (Reg. No. 67,729)
GOODWIN PROCTER LLP
620 Eighth Avenue
New York, NY 10018
Tel: (212) 813-8800
Fax: (212) 937-2204
lcipriano@goodwinlaw.com

*Counsel for Patent Owner Tecan
Genomics, Inc.*

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing **PATENT OWNER'S SUR-REPLY** was served on December 23, 2025 via email to Petitioner by serving the correspondence addresses of record as follows:

<p>Lead Counsel: Thomas S. Fletcher (Reg. No. 72,383) IDT-Tecan-IPRs@wc.com WILLIAMS & CONNOLLY LLP 680 Maine Avenue SW Washington, DC 20024 Phone: (202) 434-5497 Fax: (202) 434-5029</p>	<p>Backup Counsel: Jessamyn S. Berniker (Reg. No. 72,328) IDT-Tecan-IPRs@wc.com WILLIAMS & CONNOLLY LLP 680 Maine Avenue SW Washington, DC 20024 Phone: (202) 434-5497 Fax: (202) 434-5029</p>
<p>Backup Counsel: Kevin Hoagland-Hanson (Pro Hac Vice) IDT-Tecan-IPRs@wc.com WILLIAMS & CONNOLLY LLP 680 Maine Avenue SW Washington, DC 20024 Phone: (202) 434-5497 Fax: (202) 434-5029</p>	<p>Backup Counsel: Patrick Hynds (Pro Hac Vice) IDT-Tecan-IPRs@wc.com WILLIAMS & CONNOLLY LLP 680 Maine Avenue SW Washington, DC 20024 Phone: (202) 434-5497 Fax: (202) 434-5029</p>
<p>Backup Counsel: Nicholas G. Vincent (Reg. No. 79,788) IDT-Tecan-IPRs@wc.com WILLIAMS & CONNOLLY LLP 680 Maine Avenue SW Washington, DC 20024 Phone: (202) 434-5497 Fax: (202) 434-5029</p>	<p>Backup Counsel: Anna Searle (Pro Hac Vice) IDT-Tecan-IPRs@wc.com WILLIAMS & CONNOLLY LLP 680 Maine Avenue SW Washington, DC 20024 Phone: (202) 434-5497 Fax: (202) 434-5029</p>

December 23, 2025

/Linnea P. Cipriano/

Linnea P. Cipriano

(Reg. No. 67,729)

GOODWIN PROCTER LLP

620 Eighth Avenue

New York, NY 10018

Tel: (212) 813-8800

Fax: (212) 937-2204

lcipriano@goodwinlaw.com

*Counsel for Patent Owner Tecan
Genomics, Inc.*