

Petitioner's Opposition To Patent Owner's
Request For Discretionary Denial Of Institution
U.S. Patent No. 11,149,306

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TEMPUS AI, INC.,

Petitioner,

v.

GUARDANT HEALTH, INC.,

Patent Owner.

Case IPR2025-01434

U.S. Patent 11,149,306

**PETITIONER'S OPPOSITION TO PATENT OWNER'S
DISCRETIONARY DENIAL REQUEST**

TABLE OF CONTENTS

	<u>Page</u>
I. INTRODUCTION	1
II. DISCRETIONARY DENIAL IS NOT WARRANTED.....	3
A. Patent Owner’s Background Discussion Is Unsupported and Misleading	3
B. The Petition Relies On Art That Was Not Addressed In Any Prior Proceedings	5
1. The Examiner Erred During Original Prosecution	6
2. The Petition Relies On Art That Expressly Teaches Elements Found Lacking From Schmitt During The Prior IPR Proceeding	10
C. Petitioner Has Not Advanced “Inconsistent” Claim Constructions.....	13
III. CONCLUSION.....	16

TABLE OF AUTHORITIES

Page

Cases

Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH,
IPR2019-01469, Paper 6 (P.T.A.B. Feb. 13, 2020).....6, 9

Activision Blizzard, Inc. v. Milestone Entertainment, LLC,
IPR2025-00708, Paper 13 (Director Aug. 14, 2025).....6

Anthony Inc. v. ControlTec, LLC,
IPR2025-00559, Paper 12 (Director July 16, 2025).....7

Cambridge Industries USA, Inc. v. Applied Optoelectronics, Inc.,
IPR2025-00433, Paper 11 (Director June 27, 2025)4

Ecto World, LLC v. Rai Strategic Holdings, Inc.,
IPR2024-01280, Paper 13 (Director May 19, 2025)5, 7, 9

Geotab USA, Inc. v. Omega Patents, LLC,
IPR2023- 00504, Paper 11 (P.T.A.B. July 25, 2023)3

Med-El Elektromedizinische Geräte Ges.m.b.H. v. Advanced Bionics AG,
No. IPR2020-00190, 2020 WL 3033320 (P.T.A.B. June 3, 2020)14

Mylan Pharm. Inc. v. Merck Sharp & Dohme Corp.,
IPR2020-00040, Paper 21 (P.T.A.B. May 12, 2020)7

Samsung Elecs. Am., Inc. v. Prisia Eng'g Corp.,
948 F.3d 1342 (Fed. Cir. 2020)14

Sun Pharms. Indust., Inc. v. Nivagen Pharms., Inc.,
IPR2025-00893, Paper 18 (Director Sept. 19, 2025)15

Petitioner’s Opposition To Patent Owner’s
Request For Discretionary Denial Of Institution
U.S. Patent No. 11,149,306

Other Authorities

37 C.F.R. §§ 42.6(e), 42.105(a)17
37 C.F.R. § 42.20(c).....3

Petitioner's Opposition To Patent Owner's
Request For Discretionary Denial Of Institution
U.S. Patent No. 11,149,306

EXHIBIT LIST

Exhibit	Description
1001	U.S. Patent No. 11,149,306 (“the ’306 patent”)
1002	Prosecution history for the ’306 patent
1003	Declaration of Michael Metzker, Ph.D.
1004	Curriculum Vitae of Michael Metzker, Ph.D.
1005	PCT Publication No. WO 2013/123442 A1 (“Bielas”)
1006	PCT Publication No. WO 2012/142213 A2 (“Vogelstein”)
1007	U.S. Patent Application Publication No. 2011/0160078 (“Fodor”)
1008	PCT Publication No. WO 2012/099832 A2 (“Hendricks”)
1009	U.S. Patent Publication No. 2014/0296081 (“Diehn”)
1010	T. Forshew et al., <i>Noninvasive Identification and Monitoring of Cancer Mutations by Targeted Deep Sequencing of Plasma DNA</i> , Cancer Genomics, Vol. 4 Issue 136 (May 30, 2012) (“Forshew”)
1011	U.S. Patent No. 9,404,156 (“Hicks”)
1012	K. Shiroguchi et al., <i>Digital RNA Sequencing Minimizes Sequence-Dependent Bias And Amplification Noise With Optimized Single-Molecule Barcodes</i> , PNAS Vol. 109, No. 4 (Jan. 24, 2012) (“Shiroguchi”)
1013	U.S. Patent Publication No. 2012/0316074 A1 (“Saxonov”)
1014	Schwarzenbach et al., <i>Cell-free nucleic acids as biomarkers in cancer patients</i> , NATURE REVIEWS CANCER 11:426–437 (2011) (“Schwarzenbach”).

Petitioner’s Opposition To Patent Owner’s
Request For Discretionary Denial Of Institution
U.S. Patent No. 11,149,306

1015	Human genome variation, fact sheet, National Human Genome Research Institute (NHGRI)
1016	<i>Guardant Health, Inc. v. Foundation Medicine</i> , IPR2017-01448, Paper 2 – Petition for Inter Partes Review of U.S. Patent No. 9,340,830
1017	Metzker, <i>Sequencing technologies — the next generation</i> , NATURE REVIEWS GENETICS 11:31 –46 (2010) (“Metzker2010”)
1018	<i>Guardant Health, Inc. v. University of Washington</i> , IPR2022-00816, Paper 3 – Petition for Inter Partes Review of U.S. Patent No. 10,760,127
1019	Metzker & Caskey, <i>Polymerase Chain Reaction</i> , In ENCYCLOPEDIA OF MEDICAL DEVICES AND INSTRUMENTATION, Second Edition, Volume 5 (2006) (“Metzker2006”).
1020	Mamanova <i>et al.</i> , <i>Target-enrichment strategies for next-generation sequencing</i> , NATURE METHODS 7:111–118 (2010) (“Mamanova”)
1021	<i>Guardant Health, Inc. v. University of Washington</i> , IPR2022-00450, Paper 3 – Petition for Inter Partes Review of U.S. Patent No. 10,689,699
1022	<i>Guardant Health, Inc. v. University of Washington</i> , IPR2022-01388, Paper 2 – Petition for Inter Partes Review of U.S. Patent No. 10,689,699
1023	Declaration of Sylvia D. Hall-Ellis, Ph.D
1024	<i>Guardant Health, Inc. v. University of Washington</i> , IPR2022-00935, Paper 2 – Petition for Inter Partes Review of U.S. Patent No. 10,287,631
1025	U.S. Provisional Patent Application No. 61/600535 (“Diehn Provisional”)

Petitioner's Opposition To Patent Owner's
Request For Discretionary Denial Of Institution
U.S. Patent No. 11,149,306

1026	<i>Twinstrand Biosciences, Inc. v. Guardant Health, Inc.</i> , IPR2022-01400, Paper 2 – Petition for Inter Partes Review of U.S. Patent No. 11,149,306
1027	<i>Twinstrand Biosciences, Inc. v. Guardant Health, Inc.</i> , IPR2022-01400, Paper 41 – Final Written Decision
1028	<i>Twinstrand Biosciences, Inc. v. Guardant Health, Inc.</i> , IPR2022-01400, Paper 9 – Institution Decision
1029	Li et al., <i>Structure-independent and quantitative ligation of single-stranded DNA</i> , Analytical Biochemistry (2005)
1030	U.S. Patent No. 9,085,798 (“Chee”)
1031	Thomas et al., <i>Sensitive mutation detection in heterogeneous cancer specimens by massively parallel picoliter reactor sequencing</i> , NATURE MEDICINE 12:852–855 (2006)
1032	Buckingham, <i>Chromosomal structure and chromosomal mutations</i> , In MOLECULAR DIAGNOSTIC FUNDAMENTAL, METHODS, & CLINICAL APPLICATIONS, Eds. Buckingham & Flaws, F.A. Davis Company, Chapter 8, pp. 155–172 (2007)
1033	Gemayel et al., <i>Variable tandem repeats accelerate evolution of coding and regulatory sequences</i> , ANNUALS REVIEW OF GENETICS 44:445–477 (2010)
1034	Tóth et al., <i>Microsatellites in different eukaryotic genomes: Survey and analysis</i> , GENOME RESEARCH 10:967–981 (2000)
1035	Laghi et al., <i>Differences and evolution of the methods for the assessment of microsatellite instability</i> , ONCOGENE 27:6313– 6321 (2008)
1036	Richard & Pâques, <i>Mini- and microsatellite expansions: the recombination connection</i> , EMBO REPORTS 1:122–126 (2000)
1037	Hastings et al., <i>Mechanisms of change in gene copy number</i> , NATURE REVIEWS GENETICS 10:551–564 (2009)

Petitioner's Opposition To Patent Owner's
Request For Discretionary Denial Of Institution
U.S. Patent No. 11,149,306

1038	Hiatt <i>et al.</i> , <i>Single molecule molecular inversion probes for targeted, high-accuracy detection of low-frequency variation</i> , GENOME RESEARCH 23:843–854 (2013)
1039	Somatic & germline mutations, https://my.clevelandclinic.org/health/body/23067-somatic--germline-mutations (last visited July 30, 2025)
1040	Gene changes and cancer, https://www.cancer.org/cancer/understanding-cancer/genes-and-cancer/gene-changes.html (last visited July 30, 2025)
1041	International Human Genome Sequencing Consortium, <i>Initial sequencing and analysis of the human genome</i> , NATURE 409:860–921 (2001)
1042	International Human Genome Sequencing Consortium, <i>Finishing the euchromatic sequence of the human genome</i> , NATURE 431:931–945 (2004)
1043	Forbes, et al., <i>COSMIC: mining complete cancer genomes in the Catalogue of Somatic Mutations in Cancer</i> , NUCLEIC ACIDS RESEARCH 39:D945–D950 (2011)
1044	<i>Genomic Data Commons Data Portal</i> , https://portal.gdc.cancer.gov/ ((last visited July 30, 2025)
1045	Metzker, <i>Emerging technologies in DNA sequencing</i> , GENOME RESEARCH 15:1767–1776 (2005)
1046	Rothberg <i>et al.</i> , <i>An integrated semiconductor device enabling non-optical genome sequencing</i> , NATURE 475:348-352 (2011)
1047	Jain <i>et al.</i> , <i>Improved data analysis for the MinION nanopore sequencer</i> , NATURE METHODS 12:351-356 (2015)
1048	Kinde et al., <i>Detection and quantification of rare mutations with massively parallel sequencing</i> , PNAS (June 7, 2011) (“Kinde”)

Petitioner's Opposition To Patent Owner's
Request For Discretionary Denial Of Institution
U.S. Patent No. 11,149,306

1049	Turner <i>et al.</i> , <i>Methods for genomic partitioning</i> , ANNUAL REVIEW OF GENOMICS AND HUMAN GENETICS 10:263-284 (2009)
1050	Edwards & Gibbs, <i>Multiplex PCR: Advantages, development, and applications</i> , GENOME RESEARCH 3:S65-S75 (1994)
1051	Sharma <i>et al.</i> , <i>(TG/CA)_n repeats in human gene families: abundance and selective patterns of distribution according to function and gene length</i> , BMC GENOMICS 6:83 pp. 1–12 (2005) (“Sharma (2005)”)
1052	Gnirke <i>et al.</i> , <i>Solution hybrid selection with ultra-long oligonucleotides for massively parallel targeted sequencing</i> , NATURE BIOTECHNOLOGY 27:182–189 (2009) (“Gnirke (2009)”).
1053	Meyerson <i>et al.</i> , <i>Advances in understanding cancer genomes through second-generation sequencing</i> , NATURE REVIEWS GENETICS 11:685–696 (2010) (“Meyerson (2010)”)
1054	Preston <i>et al.</i> , <i>Innovation at Illumina: The road to the \$600 human genome</i> , NATURE PORTFOLIO (2023) at https://www.nature.com/articles/d42473-021-00030-9 (“Preston (2023)”).
1055	Bentley <i>et al.</i> , <i>Accurate whole human genome sequencing using reversible terminator chemistry</i> , NATURE 456:53–59 (2008) (“Bentley (2008)”)
1056	Kircher <i>et al.</i> , <i>Double indexing overcomes inaccuracies in multiplex sequencing on the Illumina platform</i> , NUCLEIC ACIDS RESEARCH 40:e3 pp. 1–8 (2012) (“Kircher 2012”)
1057	Pierce <i>et al.</i> , <i>A unique and universal molecular barcode array</i> , NATURE METHODS 3:601–603 (2006) (“Pierce (2006)”)
1058	Schmitt <i>et al.</i> , <i>Detection of ultra-rare mutations by next-generation sequencing</i> , PROCEEDINGS OF THE NATIONAL

Petitioner's Opposition To Patent Owner's
Request For Discretionary Denial Of Institution
U.S. Patent No. 11,149,306

	ACADEMY OF SCIENCES OF THE UNITED STATES 109: 14508-14513 (2012) (“Schmitt (2012)”)
1059	Glenn, <i>Field guide to next-generation DNA sequencers</i> , MOLECULAR ECOLOGY RESOURCES 11:759-769 (2011) (“Glenn (2011)”)
1060	Cock <i>et al.</i> , <i>The Sanger FASTQ file format for sequences with quality scores, and the Solexa/Illumina FASTQ variants</i> , NUCLEIC ACIDS RESEARCH 38:1767–1771 (2010) (“Cock (2010)”)
1061	CASAVA 1.8: enhanced variant calling in whole-genome resequencing data (2011) (“CASAVA User Guide”)
1062	Li <i>et al.</i> , Mapping short DNA sequencing reads and calling variants using mapping quality scores, <i>Genome Research</i> 18:1851–1858 (2008) (“Li (2008)”)
1063	Li & Durbin, Fast and accurate short read alignment with Burrows–Wheeler transform, <i>Bioinformatics</i> 25:1754–1760 (2009) (“Li & Durbin (2009)”)
1064	Li & Durbin, Fast and accurate long-read alignment with Burrows–Wheeler transform, <i>Bioinformatics</i> 26: 589–595 (2010) (“Li & Durbin 2010”)
1065	Langmead <i>et al.</i> , Ultrafast and memory-efficient alignment of short DNA sequences to the human genome, <i>Genome Biology</i> 10:R25.1–R25.10 (2009) (“Langmead (2009)”)
1066	Li <i>et al.</i> , <i>The sequence alignment/map format and SAMtools</i> , BIOINFORMATICS 25:2078–2079 (2009) (“Li (2009)”)
1067	DePristo <i>et al.</i> , <i>A framework for variation discovery and genotyping using next-generation DNA sequencing data</i> , NATURE GENETICS 43:491–498 (2011) and Online Methods (collectively, “DePristo (2011)”)
1068	McKenna <i>et al.</i> , <i>The Genome Analysis Toolkit: A MapReduce framework for analyzing next-generation DNA sequencing</i>

Petitioner's Opposition To Patent Owner's
Request For Discretionary Denial Of Institution
U.S. Patent No. 11,149,306

	<i>data</i> , GENOME RESEARCH 20:1297-1303 (2010) (“McKenna (2010)”)
1069	https://github.com/broadinstitute/gatk/releases (last visited Aug 11, 2025) (“GATK Updates”)
1070	Koboldt <i>et al.</i> , <i>VarScan: variant detection in massively parallel sequencing of individual and pooled samples</i> , BIOINFORMATICS 25:2283–2285 (2009) (“Koboldt (2009)”)
1071	Koboldt <i>et al.</i> , <i>VarScan 2: Somatic mutation and copy number alteration discovery in cancer by exome sequencing</i> , GENOME RESEARCH 22:568–576 (2012) (“Koboldt (2012)”)
1072	Cibulskis <i>et al.</i> , <i>Sensitive detection of somatic point mutations in impure and heterogeneous cancer samples</i> , NATURE BIOTECHNOLOGY 31:213–219 (2013) (“Cibulskis (2013)”)
1073	Schmitt <i>et al.</i> <i>Methods of lowering the error rate of massively parallel DNA sequencing using duplex consensus sequencing</i> , PCT International Publication No. WO 2013/142389 (2013) (the “’389 PCT Appl. (Schmitt)”)
1074-1085	Intentionally omitted
1086	Xi <i>et al.</i> , <i>Copy number variation detection in whole-genome sequencing data using the Bayesian information criterion</i> , PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES 108: E1128–E1136 (2011) (“Xi (2011)”)
1087	Quail <i>et al.</i> , <i>Improved protocols for the Illumina Genome Analyzer sequencing system</i> , CURRENT PROTOCOLS IN HUMAN GENETICS 18.2.1-18.2.27 (2009) (“Quail (2009)”)
1088	Fernández-Suárez & Galperin, <i>The 2013 Nucleic Acids Research Database Issue and the online Molecular Biology Database Collection</i> , Nucleic Acids Research 41:D1-D7 (2013) (“Fernández-Suárez (2013)”)
1089	Danecek <i>et al.</i> , <i>The variant call format and VCFtools</i> , BIOINFORMATICS 27:2156–2158 (2011) (“Danecek (2011)”)

Petitioner's Opposition To Patent Owner's
Request For Discretionary Denial Of Institution
U.S. Patent No. 11,149,306

1090	Schatz <i>et al.</i> , <i>Assembly of large genomes using second-generation sequencing</i> , GENOME RESEARCH 20:1165–1173 (2010) (“Schatz (2010)”)
1091	Cooper <i>et al.</i> , <i>Mutational and selective effects on copy-number variants in the human genome</i> , NATURE GENETICS 39:S22–S29 (2007) (“Cooper (2007)”)
1092	Complaint in <i>Guardant Health, Inc. v. Tempus AI, Inc.</i> , C.A. No. 24-cv-687 (D. Del.)
1093	Complaint in <i>Guardant Health, Inc. v. Foundation Medicine, Inc.</i> , C.A. No. 17-cv-1616 (D. Del.)
1094	Complaint in <i>Illumina, Inc. v. Guardant Health, Inc.</i> , C.A. No. 22-cv-334 (D. Del.)
1095	Stipulation of Dismissal in <i>Twinstrand Biosciences, Inc. v. Guardant Health, Inc.</i> , C.A. No. 21-cv-1126 (D. Del.)
1096	Scheduling Order in <i>Guardant Health, Inc. v. Tempus AI, Inc.</i> , C.A. No. 24-cv-687 (D. Del.)

I. INTRODUCTION

The Director should deny Patent Owner's Request for Discretionary Denial (Paper 8) ("DD Request") and refer the Petition to the panel. Discretionary denial is not appropriate here, at least because there are no "settled expectations" of validity (the challenged patent issued in 2021), and *Fintiv* is not an issue, as trial will not occur until 2028.

Tempus's Petition challenges all of the claims of U.S. Patent No. 11,149,306 ("'306 patent") that Patent Owner has asserted against Tempus in the pending district court litigation. That litigation is in its earliest stages, with a trial date that is scheduled to take place more than two years from now – in February **2028** – long after this *inter partes* review proceeding will reach a final written decision.¹ See EX1096. This is precisely the scenario where a focused and efficient *inter partes* review process makes the most sense. By adjudicating the invalidity of the '306 patent now in these streamlined proceedings, a finding by the Board that the asserted claims are unpatentable would avoid the need for a trial on this patent in the district court, along with more than a year of burdensome litigation. If, on the other hand, the Board affirms the patentability of any of the claims, Petitioner will be estopped

¹ For this reason, it is unsurprising that Patent Owner does not advance any argument for discretionary denial based on *Fintiv*.

Petitioner's Opposition To Patent Owner's
Request For Discretionary Denial Of Institution
U.S. Patent No. 11,149,306

pursuant to Section 315(e).² And, contrary to Patent Owner's assertions, Petitioner has not taken inconsistent claim construction positions at the district court. In fact, the previously exchanged claim construction proposals on which Patent Owner relies are no longer operative and the parties are not due to identify claim terms in need of construction and proposed constructions until March 27, 2026.

Moreover, although Guardant has asserted infringement in the district court against a Tempus diagnostic test that was released in 2018 – several years before the October 2021 issuance of the '306 patent – Guardant waited nearly three years before filing suit against Tempus in June 2024, right around the time Tempus made its initial public offering. EX1092 at ¶25. Accordingly, if anyone had settled expectations with respect to the '306 patent it was Tempus, not Guardant.

Finally, Guardant misleadingly argues that the Office “already considered the same art multiple times during prosecution and the prior IPR challenge” and “previously considered the same art now presented and it was rejected as deficient.” DD Request at 1, 6. To be clear, none of the art relied on by Petitioner in the grounds was considered as part of any ground in IPR2022-01400, and none of the art was the basis for any rejection during the original prosecution. Thus, it is simply incorrect

² Because estoppel will apply in the district court more than a year before the scheduled trial, a *Sotera* stipulation is unnecessary. Nevertheless, Petitioner has filed a stipulation in order to avoid any doubts about potential duplication of effort.

that the Office considered this art during the prior IPR challenge, or that the art was ever rejected by the Office as deficient. Furthermore, the Petition demonstrates that it was error to have overlooked the teachings of these references during the original prosecution as they disclose all of the elements of the challenged claims, including those that were deemed to be absent from the prior art during the original prosecution and during the prior IPR proceeding. Petition at 1-3, 11-12, 24-30, 44-48.

In short, all of the relevant factors weigh heavily in favor of the Director denying Patent Owner's request for discretionary denial.

II. DISCRETIONARY DENIAL IS NOT WARRANTED

Patent Owner bears the burden of proof with respect to the request for exercising discretionary denial. *Geotab USA, Inc. v. Omega Patents, LLC*, IPR2023-00504, Paper 11, at *16 (P.T.A.B. July 25, 2023) (citing 37 C.F.R. § 42.20(c)).

A. Patent Owner's Background Discussion Is Unsupported and Misleading

Patent Owner argues that it has filed a series of lawsuits against competitors who allegedly "copied Guardant's technology" – citing prior cases against Foundation Medicine, TwinStrand and Illumina. Yet the '306 patent was not asserted by Guardant in the Foundation Medicine case (EX1093) or in the Illumina

Petitioner's Opposition To Patent Owner's
Request For Discretionary Denial Of Institution
U.S. Patent No. 11,149,306

case (EX1094),³ and although the '306 patent was asserted by Guardant in the TwinStrand case, Guardant voluntarily dismissed the patent from that case with prejudice before trial. EX1095. The TwinStrand case is still pending and, because of Guardant's voluntary dismissal, has not resulted in any judgment or license involving the '306 patent.

Similarly, Guardant's claim that "the '306 patent [] embodies Guardant's highly successful Guardant360® tests" is completely unsupported. Guardant does not provide any evidence at all that its Guardant360 tests practice any claim of the '306 patent and, thus, the alleged "commercialization" of the patent cannot support settled expectations. To the contrary, the fact that the '306 patent issued in 2021 supports a finding that Patent Owner does not have any settled expectations. *Cambridge Industries USA, Inc. v. Applied Optoelectronics, Inc.*, IPR2025-00433, Paper 11 at 2 (Director June 27, 2025) ("[M]ost of the challenged patents have not been in force for a significant period of time (issued in 2020, 2019, and 2019), and, accordingly, Patent Owner has not developed strong settled expectations that favor discretionary denial as to at least those patents."). Indeed, despite the fact that Tempus' accused xF diagnostic test was released in 2018 – several years before the October 2021 issuance of the '306 patent – Guardant waited nearly three years before

³ The Illumina case involved allegations of patent infringement *against* Guardant, along with claims that Guardant had stolen Illumina technology.

filing suit against Tempus in June 2024. EX1092 at ¶25. This timing coincided exactly with Tempus' IPO. Accordingly, if anyone had settled expectations with respect to the '306 patent it was Tempus, not Guardant.

B. The Petition Relies On Art That Was Not Addressed In Any Prior Proceedings

As set forth in the Petition, the original prosecution of the '306 patent and the proceedings before the Board in IPR2022-01400 both focused on the Schmitt reference.⁴ Petition at 12. The Petition does not rely on the Schmitt reference in any of the grounds – instead relying on prior art that the Examiner and Board previously overlooked. As set forth in the Petition, and discussed further below, the art relied on in the Petition expressly discloses each of the elements of the challenged claims, including the elements that were previously found to be lacking in the prior art.

Although the references relied on in the grounds in the Petition were cited in information disclosure statements during prosecution, those references were not a basis for rejection during examination; they were not presented in the grounds of the

⁴ The two decisions cited by Patent Owner in support of its argument that discretionary denial is appropriate where there was a prior finding that the challenged claims are not unpatentable are both distinguishable. In both *Samsung Electronic Co. Ltd. v. VB Assets, LLC* and *Advanced Micro Devices, Inc. v. Advanced Cluster Sys., Inc.*, the district court trials were scheduled to take place right around the time of the final written decisions, and the challenged patents had been in force for six to ten years. IPR2025-00869, Paper 13 at 2; IPR2025-00862, Paper 14 at 2. Neither of those factors is present here.

prior IPR proceeding; they are not substantially the same as the Schmitt reference applied during prosecution and in the prior IPR; and the grounds in the Petition identify specific teachings that “impact patentability of the challenged claims.” *Ecto World, LLC v. Rai Strategic Holdings, Inc.*, IPR2024-01280, Paper 13 at 5-6 (Director May 19, 2025). Accordingly, all of the facts that the Director identified in *Ecto World* as supporting a finding of Examiner error in overlooking the prior art, under part two of *Advanced Bionics*, are present here. Thus, *Becton, Dickinson* factors (c), (e), and (f) demonstrate that the Office erred in a manner material to the patentability of challenged claims such that discretionary denial is not appropriate.⁵

1. The Examiner Erred During Original Prosecution

As explained in the Petition, during the original prosecution the references relied on in the Petition were cited along with approximately 750 other references in multiple IDSs filed on the same day. Petition at 19; EX1002 at pp. 27-128. The Examiner did not cite or discuss any of the references as a basis for rejection of the claims. Instead, the Examiner relied solely on the Schmitt reference.

⁵ Those factors are: (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection; (e) whether petitioner has pointed out sufficiently how the examiner erred in its evaluation of the asserted prior art; and (f) the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 9, n.10 (P.T.A.B. Feb. 13, 2020) (designated precedential Mar. 24, 2020).

Petitioner's Opposition To Patent Owner's
Request For Discretionary Denial Of Institution
U.S. Patent No. 11,149,306

The Petition presents evidence, however, that the limitation added to claim 1 in order to obtain allowance of the claims is disclosed in both the Bielas and Vogelstein references.⁶ Petition at 1-2, 27-30. Specifically, to obtain allowance of the claims applicants added a requirement to claim 1 that “the plurality of the cfDNA molecules are tagged with n different combinations of molecular barcodes, wherein n is at least 2 and no more than $100,000 * z$, wherein z is a mean of an expected number of duplicate molecules in the population of cfDNA molecules that map to identical start and stop positions on a reference sequence.” EX1002 at pp. 684-689. As set forth in the Petition, Bielas and Vogelstein both expressly disclose using combinations of barcodes within this claimed range. See Petition at 1-2, 27-30. These facts are sufficient to establish that the Examiner erred in overlooking the teachings of these references. *Mylan Pharm. Inc. v. Merck Sharp & Dohme Corp.*, IPR2020-00040, Paper 21, at *18 (P.T.A.B. May 12, 2020); *Ecto World*, IPR2024-01280, Paper 13 at 5-7; *Anthony Inc. v. ControlTec, LLC*, IPR2025-00559, Paper 12

⁶ Although both independent claims were rejected by the Examiner over Schmitt, applicant only amended independent claim 1 in order to secure allowance, suggesting that the Examiner also erred in overlooking that the limitation added to independent claim 1 to obtain allowance was not included in independent claim 17. See generally *Activision Blizzard, Inc. v. Milestone Entertainment, LLC*, IPR2025-00708, Paper 13 at 2-3 (Director Aug. 14, 2025) (“Petitioner, however, presents evidence that the challenged claims omit limitations added during prosecution of the parent patent that appear to have been the patent examiner’s reason for allowing the parent patent’s claims.”).

Petitioner's Opposition To Patent Owner's
Request For Discretionary Denial Of Institution
U.S. Patent No. 11,149,306

at 2 (Director July 16, 2025) (“Petitioner persuasively explains that the patent examiner erred by overlooking the teachings of Carter. . . . [I]t is an appropriate use of Office resources to review the potential error.”).⁷

Patent Owner argues that in addition to citing Bielas along with 750 other references, Patent Owner also submitted related Bielas references in other IDSs and complains that “Petitioner’s file history exhibit omits the EP626 search report,” which cited Bielas.⁸ DD Request at 7-8. As is common practice, Petitioner used the version of the ’306 file history that it downloaded directly from the PTO website, which did not include copies of non-patent literature. Notably, although Patent Owner was required to produce a complete copy of the ’306 patent file history in the co-pending district court litigation, the version it produced likewise did not include a copy of the EPO search report it now complains of. Patent Owner should not fault Petitioner for relying on the publicly available file history when Patent Owner did the same thing in the district court.

⁷ Institution is further supported by the fact that the Examiner was not presented with the specific combinations of references set forth in the Petition and did not have the benefit of the arguments in the Petition or the evidence cited in the Petition, including admissions by Patent Owner from other IPR proceedings and declaration testimony from expert Dr. Michael Metzker. Petition at 3-8; EX1003.

⁸ Patent Owner does not dispute that the other references cited in the grounds in combination with Bielas were buried in a single IDS amongst over 750 references during prosecution.

Petitioner's Opposition To Patent Owner's
Request For Discretionary Denial Of Institution
U.S. Patent No. 11,149,306

In any event, the EP626 search report does not change the fact that the Examiner never discussed or based a rejection on Bielas, or any of the other references relied on in the proposed grounds. The EPO search report listed Bielas only as “technological background” rather than as a relevant primary reference, and further concerned different claims in a different application where the EPO Examiner apparently held a different view concerning the relevance of the prior art.⁹ Moreover, even if Bielas was cited in multiple IDSs, that does not demonstrate that “Patent Owner specifically called attention to Bielas.” DD Request at 8. Simply citing a reference in an IDS without explanation does not constitute specifically calling attention to the reference, particularly where that reference is presented with many others. Nor does it demonstrate that Bielas was substantively considered.

Patent Owner conflates “awareness” with “substantive consideration.” *Advanced Bionics*, Step 2 requires showing that “the Office erred in a manner material to patentability.” *Advanced Bionics*, Paper 6 at 8. Here, the material error is not that the Examiner was unaware of these references—it is that the Examiner

⁹ Notably, the EPO Examiner indicated that the Schmitt reference disclosed all of the elements of the pending claims in that EP application with the exception of the reference to cell-free DNA (EX2001 at 1200), which differs from the findings of the Office with respect to the '306 patent claims in both the original protection and IPR2022-01400. The difference in the treatment of the prior art by the EPO may have misled the USPTO Examiner to overlook the relevance of Bielas to the '306 patent claims.

failed to recognize how these references, in the specific combinations presented in the Petition, teach all claim limitations.

In view of the fact that the Petition demonstrates that the references relied on in the grounds disclose each and every element of the challenged claims, yet the Examiner did not discuss or rely on any of the references during prosecution, Petitioner has demonstrated that the Examiner erred in a manner material to the patentability of challenged claims by overlooking the teachings of those references. *Ecto World*, IPR2024-01280, Paper 13 at 5 (“[A] petitioner may argue that it satisfies the second part of *Advanced Bionics* because the asserted prior art was not a basis for rejection during examination, is not substantially the same as prior art the Examiner applied, and includes specific teachings that ‘impact patentability of the challenged claims.’”).

2. The Petition Relies On Art That Expressly Teaches Elements Found Lacking From Schmitt During The Prior IPR Proceeding

Although patentability of the '306 patent claims was affirmed in IPR2022-01400, that decision was based on grounds that are entirely distinct from those raised in the present proceeding. Importantly, the Petition demonstrates that the specific elements founding lacking in the Schmitt reference relied on in that prior proceeding are taught by the combination of references relied on here. Petition at 2-3, 12, 24-27, 44-48.

Petitioner's Opposition To Patent Owner's
Request For Discretionary Denial Of Institution
U.S. Patent No. 11,149,306

In an effort to avoid the fact that the grounds in the Petition expressly teach what the Board found absent from Schmitt, Patent Owner mischaracterizes the Board's prior findings by falsely claiming that the Board found that Schmitt did not teach "tagging with a small number of molecular barcodes relative to a number of duplicate molecules." DD Request at 5. The Board made no such finding. To the contrary, the Board expressly found that the claims of the '306 patent do not even include such a limitation: "claim 1 does not require a particular 'relationship' between the number of tags and the expected number of duplicate molecules Rather, element 1(b) recites a range for 'n' the number of 'different combinations of molecular bar codes, wherein n is at least 2 and no more than 100,000*z.'" EX1028, p.23. The Petition explains precisely where this range is disclosed by both Bielas and Vogelstein. Petition at 1-2, 27-30, 37-38.

Contrary to Patent Owner's argument, the Board also did not find that this element of the claim – which recites that "n is at least 2 and no more than 100,000*z" – was lacking from Schmitt. Rather, the Board found that the petitioner in IPR2022-01400 had failed to show that Schmitt disclosed duplex tags that are "attached to both ends of a molecule." EX1027 at 20-23. Here, Petitioner has demonstrated that Bielas expressly discloses attaching duplex tags to both ends of the target molecules, the only element of claim 1 that the Board found missing from Schmitt. Petition at 2, 24, 27. Of significance, Patent Owner does not dispute in its brief that Bielas

teaches attaching duplex tags to both ends of a molecule, or that all of the other elements of claim 1 are likewise taught or rendered obvious by the grounds in the Petition. This alone is sufficient reason to institute the IPR.

Petitioner has also demonstrated that the one element of independent claim 17 the Board found was not disclosed by Schmitt – sorting sequence reads into families of paired and unpaired reads – would have been obvious in view of Bielas and Vogelstein. Petition at 2-3, 44-48. With respect to this limitation, Patent Owner makes the unsupported and non-sensical argument that Bielas does not teach sorting sequence reads into paired reads. But that is exactly how the process of minimizing errors in the identification of sequencing reads works in Bielas. Bielas explains that:

target nucleic acid molecules include dual cyphers (i.e., barcodes or origin identifier tags), one on each end (same or different), so that sequencing each complementary strand can be connected or linked back to the original molecule. The unique cypher on each strand links each strand with its original complementary strand (e.g., before any amplification), so that *each paired sequence* serves as its own internal control. In other words, by uniquely tagging double-stranded nucleic acid molecules, *sequence data obtained from one strand of a single nucleic acid molecule can be specifically linked to sequence data obtained from the complementary strand of that same double-stranded nucleic acid molecule.*

EX1005 at 4:25-28 (emphasis added). As disclosed in Bielas, after each strand is sequenced, “[a]ll sequencing reads having *identical cypher pairs, along with their reverse complements*, were grouped into families.” *Id.* at 4:11-12 (emphasis added).

In other words, all of the identical copies of a strand are grouped together with their

complementary strands into families of paired reads. This grouping is not agnostic as to whether the reads are paired or unpaired, as Patent Owner argues. DD Request at 10-11. Rather, Bielas expressly requires the reads to be grouped in a family with their complements, meaning that paired reads are specifically identified and grouped together.

The Petition further explains why it would have been obvious, and why a person of ordinary skill in the art would have been motivated, to combine Bielas with Vogelstein to separately sort any reads that do not have pairs into families of unpaired reads. Petition at 46-48. Patent Owner does not address these arguments, or dispute that they provide a combination of teachings that has never before been considered by the Office. Accordingly, the ground of Bielas in combination with Vogelstein relied on in the Petition teaches the sorting element of claim 17 that the Board previously found lacking in the Schmitt reference.

C. Petitioner Has Not Advanced “Inconsistent” Claim Constructions

Patent Owner argues for discretionary denial based on the incorrect assertion that Petitioner has taken different claim construction positions in this proceeding and the parallel district court proceeding. Because Petitioner has not taken inconsistent positions, this is not a basis on which to discretionarily deny institution.

The claim construction process in the district court is barely in its infancy. The parties have exchanged preliminary lists of terms and constructions but have not

Petitioner's Opposition To Patent Owner's
Request For Discretionary Denial Of Institution
U.S. Patent No. 11,149,306

met and conferred to narrow disputes, no briefing has taken place, and nothing has been filed with the district court. In fact, on November 5, 2025, the district court issued a new scheduling order whereby the parties are not due to identify claim terms in need of construction and proposed constructions until March 27, 2026. EX1096. In other words, the previously exchanged claim construction proposals are no longer operative. Further, the claim construction hearing is not scheduled to take place until August **2026**, meaning that an order will not issue prior to the PTAB's institution decision. *See Med-El Elektromedizinische Geräte Ges.m.b.H. v. Advanced Bionics AG*, No. IPR2020-00190, 2020 WL 3033320, at *5 (P.T.A.B. June 3, 2020) (finding that the fact that "a claim construction order will not have issued" at the time of the institution decision weighs in favor of institution).

Patent Owner complains that Petitioner identified certain terms as potentially indefinite in its preliminary district court disclosures while simultaneously challenging validity in this IPR. There is no inconsistency. With respect to the preliminary indefiniteness issues that Petitioner has identified to Patent Owner in the district court case, Petitioner was required to identify those in its preliminary identification of claim constructions or risk waiving them. As noted above, operative preliminary identifications in the district court are not due until March 2026. At this stage, however, Petitioner has not presented any indefiniteness arguments to the district court and it may never do so. Moreover, as Patent Owner

Petitioner's Opposition To Patent Owner's
Request For Discretionary Denial Of Institution
U.S. Patent No. 11,149,306

well knows, indefiniteness is not an issue that can be raised in an IPR, and there is no rule that prohibits the pursuit of an IPR in instances where claims may contain terms that are indefinite. *Samsung Elecs. Am., Inc. v. Prisia Eng'g Corp.*, 948 F.3d 1342, 1350 (Fed. Cir. 2020). In any event, whether any of those indefiniteness issues are actually presented to the district court will not be determined for close to a year.

Patent Owner's assertion that "Petitioner does not even bother to map allegedly indefinite terms to the prior art" (DD Request at 16) is plainly incorrect. The Petition clearly explains where the proposed grounds disclose the use of a number of different combinations of molecular barcodes within the range of "at least 2 and no more than 100,000*z" recited in claim 1 (Petition at 28-30), and also how the grounds disclose grouping or sorting sequence reads based at least in part on "sequence information at the start and stop positions" as recited in claims 13 and 24 (Petition at 41-43, 50-51).

Finally, Patent Owner's assertion that Petitioner's preliminary constructions in the district court are "irreconcilable with the claim mapping presented in the petition" is totally unsupported. In fact, Patent Owner's argument that there is any inconsistency in how Petitioner has mapped step 1.e of claim 1 is plainly wrong. That claim element requires that "distinct cfDNA molecules are determined based on (i) paired reads . . . *or*, (ii) unpaired reads." As noted in the Petition, the Board previously determined that the plain language of this claim element requires use of

paired *or* unpaired reads, but not both.” Petition at 32, n. 14. The Petition explains that “[b]ecause reads in Bielas are grouped into families ‘along with their reverse complements,’ they are families of paired reads.” *Id.* at 33. Thus, Bielas is not “agnostic” to whether reads are paired or unpaired; rather, Bielas expressly teaches that the reads in its families are identified as paired reads. Thus, there is no inconsistency nor any “conflict” for the Board to resolve.

Even if there were any arguable inconsistency (there is not), Patent Owner cites no authority supporting discretionary denial on this basis where claim constructions have not even been briefed, let alone decided. The case Patent Owner relies on, *Sun Pharms. Indust., Inc. v. Nivagen Pharms., Inc.*, IPR2025-00893, Paper 18 at 2-3 (Director Sept. 19, 2025), involved actual claim construction positions that had already been advanced in the district court—a far cry from preliminary, unbriefed position statements here. Denying institution based on speculative future inconsistencies that may never materialize would be premature and improper.

III. CONCLUSION

For the reasons above, Petitioner respectfully requests that Patent Owner's request for discretionary denial should be rejected and inter partes review should be instituted.

Petitioner's Opposition To Patent Owner's
Request For Discretionary Denial Of Institution
U.S. Patent No. 11,149,306

Date: November 20, 2025

Respectfully submitted,

/s/ James M. Glass

James M. Glass
Registration No. 46,729

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6, I hereby certify that on November 20, 2025 the foregoing document and accompanying exhibits was served via email on the following counsel of record:

Jordan R. Jaffe
Wendy L. Devine
WILSON SONSINI GOODRICH & ROSATI
One Market Plaza,
Spear Tower, Suite 3300
San Francisco, CA 94105
jjaffe@wsgr.com
wdevine@wsgr.com

Michael T. Rosato
Jad A. Mills
Sonja R. Gerrard
Patrick M. Medley
Eric P. Tuttle
WILSON SONSINI GOODRICH & ROSATI
701 Fifth Avenue, Suite 5100
Seattle, WA 98104
mrosato@wsgr.com
jmills@wsgr.com
sgerrard@wsgr.com
pmedley@wsgr.com
eric.tuttle@wsgr.com

David E. Moore
Bindu A. Palapura
POTTER ANDERSON & CORROON LLP
Hercules Plaza, 6th Floor
1313 N. Market Street
Wilmington, DE 19801
dmoore@potteranderson.com
bpalapura@potteranderson.com

Petitioner's Opposition To Patent Owner's
Request For Discretionary Denial Of Institution
U.S. Patent No. 11,149,306

Jennifer L. Keller
Chase Scolnick
Gregory M. Sergi
Akhil Sheth
KELLER ANDERLE SCOLNICK LLP
18300 Von Karman, Ave., Suite 930
jkeller@kelleranderle.com
cscolnick@kelleranderle.com
gsergi@kelleranderle.com
asheth@kelleranderle.com

/s/ James M. Glass

James M. Glass
Registration No. 46,729