

Petitioner's Opposition To Patent Owner's
Request For Discretionary Denial Of Institution
U.S. Patent No. 10,793,916

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TEMPUS AI, INC.,

Petitioner,

v.

GUARDANT HEALTH, INC.,

Patent Owner.

Case IPR2025-01435

U.S. Patent 10,793,916

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

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EXHIBIT LIST

Exhibit	Description
1001	U.S. Patent No. 10,793,916 (“the ’916 patent”)
1002	Prosecution history for the ’916 patent
1003	Declaration of Michael Metzker, Ph.D.
1004	Curriculum Vitae of Michael Metzker, Ph.D.
1005	U.S. Patent No. 9,752,188 (“Schmitt”)
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 Application 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> , SCIENCE TRANSLATIONAL MEDICINE, 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”).
1015	Human genome variation, fact sheet, National Human Genome Research Institute (NHGRI)

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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	Intentionally Left Blank
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”)
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

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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)
1038	Hiatt et al., <i>Single molecule molecular inversion probes for targeted, high-accuracy detection of low-frequency variation</i> , GENOME RESEARCH 23:843–854 (2013)

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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 <i>et al.</i> , <i>Detection and quantification of rare mutations with massively parallel sequencing</i> , PNAS (June 7, 2011) (“Kinde”)
1049	Turner <i>et al.</i> , <i>Methods for genomic partitioning</i> , ANNUAL REVIEW OF GENOMICS AND HUMAN GENETICS 10:263-284 (2009)

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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 ACADEMY OF SCIENCES OF THE UNITED STATES 109: 14508-14513 (2012) (“Schmitt (2012)”)

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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, Genome Research 18:1851–1858 (2008) (“Li (2008)”)
1063	Li & Durbin, Fast and accurate short read alignment with Burrows–Wheeler transform, Bioinformatics 25:1754–1760 (2009) (“Li & Durbin (2009)”)
1064	Li & Durbin, Fast and accurate long-read alignment with Burrows–Wheeler transform, Bioinformatics 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, Genome Biology 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 data</i> , GENOME RESEARCH 20:1297-1303 (2010) (“McKenna (2010)”)

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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> , <i>BIOINFORMATICS</i> 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> , <i>GENOME RESEARCH</i> 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> , <i>NATURE BIOTECHNOLOGY</i> 31:213–219 (2013) (“Cibulskis (2013)”)
1073	U.S. Patent No. 9,840,743
1074	U.S. Patent No. 9,834,822
1075	U.S. Patent Application Publication No. 2012/0165202 A1 (“Porreca”)
1076	U.S. Patent Application Publication No. 2010/0264331 (“Sacko”)
1077	M. van Lier, et al., <i>A review on the molecular diagnostics of Lynch syndrome: a central role for the pathology laboratory</i> , <i>J. CELL. MOL. MED.</i> Vol. 13, No. 1-2 (2010) (“van Lier”)
1078	C. Boland and A. Goel, <i>Microsatellite Instability in Colorectal Cancer</i> , <i>GASTROENTEROLOGY</i> , 138(6) (June 2010) (“Boland 2010”)
1079	C. Boland, et al., <i>A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer</i> , <i>CANCER RES</i> , 58(22) (Nov. 15, 1998) (“Boland 1998”)

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1080	F. Sinicrope and D. Sargent, <i>Clinical implications of microsatellite instability in sporadic colon cancers - PMC</i> , CURR OPIN ONCOL., 21(4) (July 2009) (“Sinicrope”)
1081	G. Li, <i>Mechanisms and functions of DNA mismatch repair</i> , CELL RESEARCH 18 (2008)
1082	U.S. Provisional Application 61/613,413 (“Schmitt '413 provisional”)
1083	Foundation Medicine, Inc. v. Guardant Health, Inc., IPR2019-00652, Paper 47 – Final Written Decision (“822FWD”)
1084	Foundation Medicine, Inc. v. Guardant Health, Inc., IPR2019-00652, Paper 54 – Termination
1085	Foundation Medicine, Inc. v. Guardant Health, Inc., IPR2019-00652, Paper 12 – Decision Granting Institution of <i>Inter Partes Review</i>
1086	Declaration of Sylvia D. Hall-Ellis, Ph.D.
1087	<i>Guardant Health, Inc. v. Tempus AI, Inc.</i> , No. 1:24-cv-00687-GBW (D. Del. June 11, 2024), D.I. 1
1088	Excerpt of prosecution history of U.S. Application No. 15/669,779
1089	Excerpt of prosecution history of U.S. Application No. 16/601,168
1090	Excerpt of prosecution history of U.S. Application No. 16/672,267
1091	<i>Guardant Health, Inc. v. Tempus AI, Inc.</i> , No. 1:24-cv-00687-GBW (D. Del. Nov. 5, 2025), D.I. 99

I. INTRODUCTION

The Director should deny Patent Owner's Request for Discretionary Denial (Paper 8) ("DD Request") and refer the Petition to the panel. Patent Owner's request for discretionary denial rests entirely on the false premise that U.S. Patent No. 10,793,916's ("916 Patent) claims are substantially similar to claims of an unrelated patent—U.S. Patent No. 11,149,306 ("306 Patent")—that was previously reviewed in IPR2022-01400 ("1400IPR"). They are not. Importantly, the '916 Patent has *no* settled expectations: it issued five years ago and its validity has never before been challenged. Thus, Petitioner is not "[a]sking the Board to take yet another look at the same failed prior art," as Patent Owner incorrectly asserts. DD Request at 1. To the contrary, the specific claim limitations of the '916 Patent—particularly its microsatellite detection and its simpler molecular barcode structure—have never been tested against the prior art in any IPR or district court proceeding.

With respect to the original prosecution, the references relied upon in the grounds in the Petition were cited in an IDS on the same day as *750* other references. The relied-upon references—Schmitt, Forshew, Porreca, and Sacko—were not used as the basis for a rejection, nor did the applicant in any way indicate their relevance. Accordingly, the Examiner erred in overlooking the fact that these references teach all of the elements of the challenged claims, as set forth in the Petition.

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With respect to the co-pending litigation, it is in its earliest stages, with a trial date scheduled to take place *over two years from now* – in February 2028 – long after this inter partes review proceeding will reach a final written decision.¹ This is precisely the scenario where the focused and efficient *inter partes* review process makes sense. By adjudicating the invalidity of the '916 Patent now in streamlined proceedings, a finding by the Board that the asserted claims are unpatentable would avoid the need for a trial on the challenged claims. If, on the other hand, the Board affirms the patentability of any of the claims, Petitioner will be estopped 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. Moreover, 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 2020 issuance of the '916 Patent – Guardant waited nearly four years before

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

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.

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filing suit against Tempus in June 2024. EX1087 at ¶25. Within that same time period, the Board invalidated a patent related to the '916 Patent (U.S. Patent No. 9,834,822 (“’822 Patent”)) in IPR2019-00652 (“652IPR”) on the basis of one of the references relied on here—Schmitt—and then the Federal Circuit rejected Guardant’s appeal on all but one narrow issue (nexus) and remanded to the Board for consideration in 2023. The case settled before the Board could make any further determination. Accordingly, if either party had settled expectations as to the '916 Patent it was Tempus, not Guardant.

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 (PTAB July 25, 2023) (citing 37 C.F.R. § 42.20(c)).

A. The '916 Patent Validity Has Never Been Adjudicated And Patent Owner Has No Settled Expectations

Patent Owner asserts 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. DD Request at 2-3. Yet the '916

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Patent was not asserted by Guardant in any of those prior cases. Accordingly, the validity of the '916 Patent has never been tested in district court or by the Board.

Likewise, Guardant's claim that "the '916 patent [] embodies Guardant's highly successful Guardant360® tests" (DD Request at 2) is completely unsupported. Guardant does not provide any evidence that Guardant360 practices any claim of the '916 Patent and, thus, the alleged "commercialization" of the patent cannot support settled expectations. To the contrary, the fact that the '916 Patent issued in 2020 supports a finding that Patent Owner does not have any settled expectations. *Cambridge Industries USA, Inc. v. Applied Optoelectronics, Inc.*, IPR2025-00433, Paper 12 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 – years before the October 2020 issuance of the '916 Patent – Guardant waited nearly four years before filing suit against Tempus in June 2024. EX1087 at ¶25. To the extent settled expectations exist with respect to the '916 Patent, they are Tempus's, not Guardant's.

B. The Prior Adjudication of An Unrelated Patent Involving Entirely Different Claim Limitations Does Not Support Denial

Patent Owner's primary argument is that the Board previously conducted an IPR proceeding for the '306 Patent (1400IPR) – a patent unrelated to the '916 Patent that contains substantially different claim language – and concluded that the Schmitt reference did not render unpatentable the '306 Patent claims. EX1027. The claim language that formed the basis for the Board's decision in the 1400IPR is not found in the claims of the '916 Patent, and Patent Owner's brief mischaracterizes those proceedings and their purported relevance here. In fact, the Board's findings in the 1400IPR turned on specific claim language that does not appear in the '916 Patent.

In the 1400IPR, the petitioner contended that Schmitt's teaching of a hybrid embodiment, which used 3-mer barcodes, satisfied the '306 Patent's requirement of attaching "duplex tags . . . to both ends of a molecule." EX1027.16-17. The petitioner relied on that specific embodiment alone because, in addition to requiring the use of duplex tags that comprise molecular barcodes, the '306 Patent claims require tagging molecules with "n different combinations of molecular barcodes, wherein n is at least 2 and no more than 100,000*z." Neither the attachment of duplex tags to both ends of a molecule nor the "n different combinations" limitations are found in the challenged '916 Patent claims.

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Importantly, the petitioner in the 1400IPR argued that in Schmitt's hybrid embodiment, the 3-mer barcode *in combination with end portions of the DNA fragments* comprised the "duplex tags [that] are attached to both ends of a molecule of the plurality of the cfDNA molecules" recited in '306 Patent claim 1. EX1027.16 Based on this argument, the Board found that the end portions of the DNA fragments were not "attached to both ends" of the cfDNA molecule, but rather those end portions "are the pre-existing, endogenous ends of that molecule." EX1027.23 (emphasis in original).

The finding by the Board in the 1400IPR is irrelevant to this Petition for several reasons. First, the Petition here does not rely solely on the hybrid embodiment in Schmitt. Instead, the Petition primarily relies on the main embodiment in Schmitt, which teaches attaching barcodes of between 3 to 20 nucleotides in length to both ends of the DNA molecules. Petition at 35-36, 62. Patent Owner does not argue, nor can it, that these limitations are not disclosed by Schmitt's main embodiment. For this reason alone, Patent Owner's arguments (DD Request at 4-5), which focus solely on the hybrid embodiment, fail.

Second, the challenged '916 Patent claims do not require "duplex tags," which is the claim language at issue in the 1400IPR. Instead, the challenged '916 Patent claims require "ligating molecular barcodes . . . to a plurality of the cell-free nucleic acid molecules" (claim 13) and attaching "a molecular barcode . . . to both ends of a

molecule of the plurality of the cfDNA molecules” (claim 30). The Petition does not contend that end portions of the DNA fragments are part of the molecular barcodes; it contends that the molecular barcodes are the polynucleotide sequences attached (or ligated) to the ends of the cfDNA molecules. Petition at 35-36. Again, Patent Owner does not dispute that the molecular barcodes in Schmitt are ligated, or attached, to ends of the cfDNA molecules.

C. The *Advanced Bionics* Factors Do Not Support Discretionary Denial

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, are not substantially the same as the prior art the Examiner applied, and the grounds in the Petition identify specific teachings that “impact patentability of the challenged claims.” *See Ecto World, LLC v. Rai Strategic Holdings, Inc.*, IPR2024-01280, Paper 13 at 5-6 (Director May 19 2025). Indeed, all of the factors 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. *See id.* Accordingly, *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.³

³ Those factors are: (c) the extent to which the asserted art was evaluated

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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. EX1002.28-128, 226, 241. The Examiner did not cite or discuss any of the references as a basis for rejection of the claims. Instead, the Examiner rejected Guardant's claims for obviousness-type double patenting in view of patents and applications related to the '916 Patent (and '822 Patent) in view of Sacko, but later withdrew the rejection based on a terminal disclaimer. EX1002.542-547, 675-679, 737-742. Although the Board's Final Written Decision for the related '822 Patent invalidating claims reflecting the same subject matter was submitted in an IDS during the '916 prosecution, there is no suggestion that the Examiner substantively considered the arguments about Schmitt and Forshew that the Board relied on in the 652IPR in light of the Examiner's own finding about Sacko's teachings of MSIs. 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 (PTAB May 12, 2020); *Ecto World*, IPR2024-

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 (PTAB Feb. 13, 2020) (designated precedential Mar. 24, 2020); *see also Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17-18 (PTAB Dec. 15, 2017).

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01280, Paper 13 at 5-7; *Anthony Inc. v. ControlTec, LLC*, IPR2025-00559, Paper 12 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.”).⁴

Patent Owner points to prosecutions in “co-pending cases” to argue that the references cited in the grounds were “repeatedly” before the Patent Office. DD Request at 9. None of these “co-pending” cases is related to the '916 Patent. These wholly unrelated file history excerpts do not show that the references cited in the grounds were ever considered in the prosecution of the '916 claims. In fact, the prosecution of these applications demonstrate that the '916 claims would not have issued had Schmitt and Forshew not been overlooked:

- 15/669,779 – In response to the Examiner's rejection of pending claims in view of Schmitt as well as Forshew (EX2003.2-13), the applicant cancelled all rejected claims in the next office action response. EX1088.3, 5-6.

⁴ 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 Dr. Michael Metzker. Petition at 4 n.4; EX1003.

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- 16/601,168 – Similarly, the applicant did not overcome the rejection in view of Schmitt and Sacko (EX2004.4-5) without amending the rejected claims. Notably, the applicant offered no challenge to the examiner's finding that Schmitt discloses “tagging double-stranded DNA molecules with a set of duplex tags comprising barcodes.” EX1089.2-8, 10.
- 16/672,267 – In response to the Examiner's rejection of claims in view of Schmitt and Sacko (EX2005.4-5), the applicant cancelled the rejected claims in the next office action response. EX1090.2, 7.

Thus, the Patent Owner's citations demonstrate that, had Schmitt not been overlooked by the Examiner, the challenged claims would not have been allowed.

Similarly, the Patent Owner's argument about the examiner's reliance on Porreca in a different application (DD Request at 9-10) falls flat. There, after the related application 15/828,099 (“'099 application”) claims were rejected in view of Porreca and Schmitt (EX2009.19-20), the applicant amended the claims (EX2009.7-10) and argued that Porreca and Schmitt did not disclose “detecting a presence or absence of a somatic genetic variant from a sample comprising cfDNA molecules”—a limitation not present in the challenged claims of the '916 Patent (EX2009.12-13). In a Nov. 13, 2019 Office Action, the Examiner found that the amended claims were “free of the prior art.” EX2009.5. In Feb. 14, 2020, during the

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prosecution of the '916 claims, the Examiner rejected the claims for obviousness type double patenting based on that amended '099 application in view of Sacko. EX1002.360. The applicant overcame the rejection by filing a terminal disclaimer. EX1002.1233. The applicant made no effort to note that Schmitt and Porreca had been relied on to reject the original '099 claims—and there was no indication that the Examiner did so.

Indeed, the fact that no unamended claims of these cited applications overcame Schmitt, Forshew, or Porreca confirms that these references were not considered by the Examiner during the '916 prosecution.

In view of the fact that the references cited in the grounds disclose each and every element of the challenged claims, there can be no legitimate dispute that the Examiner overlooked the teachings of those references.

Patent Owner argues that the Examiner “was well-aware” of the cited references because they appeared on IDSs, in invalidity contentions, and in Office Actions from unrelated applications. DD Request at 8-10. But Patent Owner conflates “awareness” with “substantive consideration.” Under *Advanced Bionics*, Step 2 requires showing that the Examiner “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 failed to

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

The fact that references appeared on an IDS does not mean they were substantively considered, particularly when—as here—they were buried among 750 other references cited on the same day. *Scientific Design Co., Inc. v. Shell Oil Co.*, IPR2022-00158, Paper 7 at 25 (PTAB April 4, 2022). The Petition identifies specific teachings from the cited references that teach claim limitations the Examiner never analyzed. *See, e.g.*, Petition at 1, n.1.

Patent Owner's citations to Office Actions from unrelated applications (15/669779, 16/601168, 16/672267) actually undermine its position. In each of these prosecutions, when the Examiner actually applied Schmitt in a substantive rejection, the applicant either cancelled the rejected claims or amended them to overcome the rejection. This demonstrates that had the Examiner substantively considered Schmitt's teachings in the context of the '916 claims, those claims would not have issued in their current form. This is precisely the type of material error that warrants institution under *Advanced Bionics*.

D. Patent Owner's Arguments About Schmitt's Applicability Go to the Merits, Not Discretionary Denial

Patent Owner devotes significant space to arguing that “Schmitt lacks the requisite sensitivity” for detecting somatic variants in cfDNA and that “the Office

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has never accepted Schmitt as applicable to microsatellite changes in cfDNA.” DD Request at 11-13. These are merits arguments dressed up as discretionary denial arguments, and they fail on both fronts.

Patent Owner mischaracterizes the Petition's grounds in arguing against the applicability of Schmitt to the '916 claims. The question of whether Schmitt was “applicable to microsatellite changes in cfDNA” was never before the Office. Moreover, as shown in the Petition, Schmitt's method expressly teaches that “the ability to indirectly infer that damage is present on the DNA could be a useful biomarker” including “for cancer risk, cancer metabolic state, mutator phenotype related to defective damage repair.” EX1005, 15:42-51; Petition at 27. Schmitt's reference to “mutator phenotype related to defective damage repair” clearly demonstrates that Schmitt is “applicable to microsatellite changes in cfDNA.” Microsatellite changes were not at issue in the 1400IPR. Patent Owner's arguments regarding the Board's findings in the 1400IPR are inapposite. Similarly, the prosecution of other Guardant patent applications cited by the Patent Owner do not address whether Schmitt teaches detection of microsatellite changes. Patent Owner's unsupported arguments that findings limited to detection of somatic genetic variations could be extended to the challenged claims relating to detecting microsatellite changes goes to the merits of the Petition and are not a basis for discretionary denial.

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Even if the Patent Owner's identified discussions regarding the applicability of Schmitt to detecting somatic genetic variations in cfDNA were relevant to the '916 Patent, as explained in the Petition, the Board has previously found that the combination of Schmitt and ForsheW discloses "detecting, at one or more loci, at least one single nucleotide variant, at least one gene fusion and at least one copy number variant." EX1083.43-44. Thus, Patent Owner's reliance on characterizations of the disclosures of Schmitt alone are irrelevant.

Patent Owner's citations to the Kennedy reference and alleged "operability" issues with tag lengths less than 12 nucleotides (DD Request at 6-7) are factual disputes that go to the merits of obviousness, not discretionary denial. Whether the Petition's proposed combination would have worked is precisely the type of technical dispute that should be resolved through full IPR proceedings, not summarily dismissed at the institution stage. Moreover, Kennedy's guidance pertains to its specific protocol and Illumina platform configuration in 2014—over a year after Schmitt's priority date. Kennedy does not establish that Schmitt's disclosed embodiments were non-functional or that a POSA could not have implemented them successfully as set forth in the Petition's grounds.

Next, Patent Owner cites statements made by Tempus relating to the Examiner's rejection under 35 U.S.C. 101 of a Tempus patent application in support of its arguments about Schmitt. DD Request at 12-15. There, Tempus made general

arguments about conventional techniques regarding determining MSI status, not Schmitt's teachings of the challenged limitations of the '916 Patent. Guardant omits that the Examiner disagreed with Tempus's arguments and maintained the rejection. EX2013.30-31. Arguments made to overcome an abstract idea rejection have no bearing on whether Schmitt teaches the challenged limitations of the '916 Patent.

None of the arguments cited by Guardant demonstrate that Schmitt's teachings relating to detecting microsatellite instability were ever considered by the Office during the prosecution of the '916 Patent. In sum, Patent Owner's technical arguments about Schmitt's alleged deficiencies are precisely the types of disputes that warrant full IPR proceedings, not discretionary denial at the threshold.

E. The Board's Institution and Invalidation in the 652IPR Weighs Against "Settled Expectations."

Patent Owner cannot have "settled expectations" when the Board previously found a related patent from the same family invalid based on Schmitt and Forshev—the same core references at issue here. The Board previously found one patent from the same family as the '916 Patent to be invalid based on Schmitt and Forshev, among other references, in the 652IPR. *See* EX1083. In the 652IPR, the Board instituted review and issued a Final Written Decision finding claims of the '822 Patent unpatentable over Schmitt, Forshev, and other references. *See* EX1083. The '822 Patent shares a common parent application with the '916 Patent. Petition at 11.

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The fact that the Federal Circuit later vacated the 652IPR decision does not restore “settled expectations.” The vacatur occurred on May 5, 2023—less than three years ago—and the Federal Circuit rejected Guardant’s appeal on all grounds except one narrow issue regarding the presumption of nexus for objective indicia, remanding solely for additional fact-finding on that issue. *Guardant Health, Inc. v. Vidal*, No. 2021-1104, 2023 U.S. App. LEXIS 11037, at *1-2 (Fed. Cir. May 5, 2023); DD Request at 14. The Federal Circuit did not disturb any of the Board’s analysis of the prior art teachings. After remand, the proceeding terminated pursuant to settlement without any findings by the Board on remand. EX1084.2-3.

This history weighs against discretionary denial. The institution or invalidation of other patents in the same family as the ’916 Patent weighs against “settled expectations.” See *Mercedes-Benz Group G v. The Phelan Group, LLC*, IPR2025-00413, Paper 13 (Director June 25, 2025), at 2 (finding that “claims of a related patent were recently found unpatentable” among “factors weigh[ing] against discretionary denial. On balance, discretionary denial is not appropriate in this case.”).

Patent Owner’s attempt to distinguish the ’822 claims from the ’916 claims (DD Request at 14-15) further undermines its settled expectations argument. Yet Patent Owner simultaneously argues that Guardant360 provides objective indicia of nonobviousness for the ’916 Patent. If the claims are so different that the 652IPR

findings do not apply, then they are too different for Guardant360's commercial success to apply either. Patent Owner cannot have it both ways.

Further, as discussed above, there are no known objective indicia of nonobviousness for the '916 Patent. While Guardant now points to Guardant360, there is no evidence to show that Guardant360 practices the '916 Patent. Indeed, the '916 Patent issued six years after the commercialization of Guardant360. Further, as Patent Owner admits, detection of microsatellite changes was not present in the '822 claims—and no evidence was offered in the 652IPR of any secondary indicia of nonobviousness of claims with those limitations. DD Request at 14. The absence of such evidence in the 652IPR confirms there are no settled expectations for the '916 Patent's specific claim scope.

F. Petitioner Has Not Advanced “Inconsistent” Claim Constructions

Patent Owner argues for discretionary denial based on the false assertion that Petitioner has taken different claim construction positions in this proceeding and the parallel district court proceeding. DD Request at 16-20. The claim construction process in the district court is barely in its infancy. Although the parties have exchanged preliminary lists of terms and constructions, they have not 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

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construction and proposed constructions until March 27, 2026. EX1091.17. 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, and likely not before the final written 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. Moreover, as Patent Owner 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.*

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Prisua 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's preliminary constructions in the district court are "irreconcilable with the claim mapping presented in the petition" (DD Request at 18) is totally unsupported. There is no inconsistency, nor any "conflict" for the Board to resolve. Patent Owner claims Petitioner argued in district court that claim 30's "amplifying" step requires amplifying "every one" of the tagged polynucleotides, while the Petition maps this limitation to prior art that amplifies only "a set" of molecules. DD Request at 18. This mischaracterizes the Petition and goes to the merits of the Petition rather than whether discretionary denial is appropriate. The Petition cites Schmitt's disclosure of "amplifying the double-stranded SMI-target nucleic acid complex, resulting in a set of amplified SMI-target nucleic acid products." EX1005, 3:10-20; *see* Petition at 27. Patent Owner has not shown that Schmitt's disclosure is inconsistent with the previously proposed construction of the "amplifying" step of Claim 30 as "amplifying every one of the tagged parent polynucleotides." DD Request at 18. Indeed, Schmitt does not recite amplifying only "a set" of molecules, but rather "amplifying the double-stranded SMI-target nucleic acid complex, **resulting in a set** of amplified SMI-target nucleic acid products." EX1005, 3:10-20 (emphasis added). There is no inconsistency.

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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.

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:

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