

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GUARDANT HEALTH, INC.

Petitioner,

v.

COLD SPRING HARBOR LABORATORY

Patent Owner

Case No. IPR2025-01353

U.S. Patent No. 12,234,510

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

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PETITIONER'S EXHIBIT LIST

Exhibit #	Description
EX1001	U.S. Patent No. 12,234,510 (“the ’510 patent”)
EX1002	Declaration of Gregory Cooper, Ph.D.
EX1003	Plaintiff’s First Amended Complaint for Patent Infringement, <i>Cold Spring Harbor Laboratory v. Guardant Health, Inc.</i> , C.A. No. 25-263-JCG (May 1, 2025 D. Del.) (No. 15)
EX1004	Dan Levy et al., <i>Facilitated sequence counting and assembly by template mutagenesis</i> , PNAS (October 13, 2014) (“Levy-Wigler”)
EX1005	Final Written Decision, <i>Parse Biosciences, Inc., v. 10X Genomics, Inc.</i> , IPR2023-00958 (February 3, 2025) (Paper 48)
EX1006	Petition for <i>Inter Partes</i> Review of U.S. Patent No. 10,697,013, <i>Parse Biosciences, Inc., v. 10X Genomics, Inc.</i> , IPR2023-00958 (May 25, 2023) (Paper 1)
EX1007	Brooks E. Miner et al., <i>Molecular barcodes detect redundancy and contamination in hairpin-bisulfite PCR</i> , 32 Nucleic Acids Research 1-4 (2004) (“Miner”)
EX1008	Megan L McCloskey et al., <i>Encoding PCR Products with Batch-Stamps and Barcodes</i> , 45 Biochemical Genetics, 761-767 (2007) (“McCloskey”)
EX1009	Prosecution File History of U.S. Patent No. 12,234,510
EX1010	U.S. Patent Application 2009/0029377 (“Lo”)
EX1011	Rossa W. K. Chiu et al., <i>Noninvasive prenatal diagnosis of fetal chromosomal aneuploidy by massively parallel genomic sequencing of DNA in maternal plasma</i> , PNAS (December 23, 2008) (“Chiu”)
EX1012	Tian-Li Wang et al., <i>Digital karyotyping</i> , PNAS (December 10, 2002) (“Wang”)
EX1013	Derek Y. Chiang et al., <i>High-resolution mapping of copy-number alterations with massively parallel sequencing</i> , Nature Methods, Vol 6. No. 1 (January 2009) (“Chiang”)
EX1014	U.S. Patent No. 7,537,897 (“Brenner”)
EX1015	U.S. Patent No. 9,085,798 (“Chee”)
EX1016	WO 2010/127186 (filed on April 29, 2010) (“Chee PCT”)
EX1017	U.S. Patent No. 11,840,730 (“Porreca”)
EX1018	WO 2010/126614 (filed on April 30, 2010) (“Porreca PCT”)
EX1019	Intentionally left blank

EX1020	Plaintiff’s Disclosure of Asserted Claims and Infringement Contentions for U.S. Patent Nos. 10,947,589 and 12,234,510, <i>Cold Spring Harbor Laboratory v. Guardant Health, Inc.</i> , C.A. No. 25-263-JCG (July 11, 2025 D. Del.)
EX1021	U.S. Patent No. 8,741,606
EX1022	DE 10 2008 025 656 B4 Translation
EX1023	Curriculum Vitae of Gregory Cooper
EX1024	U.S. Patent No. 10,697,013
EX1025	Decision Granting Petitioner’s request on Rehearing of Decision Denying Institution of <i>Inter Partes</i> Review, <i>Parse Biosciences, Inc., v. 10X Genomics, Inc.</i> , IPR2023-00958 (February 5, 2024) (Paper 9)
EX1026	PCT Patent Publication No. WO 2010/117620 to Linnarsson et al. (“Linnarsson”)
EX1027	U.S. Patent Application 2007/0020640 (“McCloskey II”)
EX1028	Declaration of Gregory Cooper, Ph.D. In Support of Petitioner for <i>Inter Partes</i> Review, <i>Parse Biosciences, Inc., v. 10X Genomics, Inc.</i> , IPR2023-00958 (May 24, 2023) (Exhibit 1002)
EX1029	National Human Genome Research Institute, Nucleotide (March 21, 2023) at https://www.genome.gov/genetics-glossary/Nucleotide
EX1030	Gerald Schochetman et al., Polymerase Chain Reaction, 158 J. of Infectious Diseases 1154-1157 (1988) (“Schochetman”)
EX1031	National Human Genome Research Institute, Polymerase Chain Reaction (March 21, 2023) at https://www.genome.gov/geneticsglossary/Polymerase-Chain-Reaction
EX1032	Severine A Degrelle et al., Amplification biases: possible difference among deviating gene expressions, 9 BMC Genomics 1-15 (2008) (“Degrelle”)
EX1033	H.C. Yang et al., A genome-wide study of preferential amplification/hybridization in microarray-based pooled DNA experiments, 34 Nucleic Acids Research 1-11 (2006) (“Yang”)
EX1034	Elaine R. Mardis, The impact of next-generation sequencing technology on genetics, 24(3) Trends in Genetics 133-141 (2008) (“Mardis”)
EX1035	Andy Itsara et al., <i>Population Analysis of Large Copy Number Variants and Hotspots of Human Genetic Disease</i> , The American Journal of Human Genetics 84, 148-161 (February 13, 2009)

EX1036	Heather C. Mefford et al., <i>A method for rapid, targeted CNV genotyping identifies rare variants associated with neurocognitive disease</i> , Genome Research (June 8, 2009)
EX1037	U.S. Patent No. 7,794,984
EX1038	Jingdong Tian et al., <i>Advancing high-throughput gene synthesis technology</i> , Molecular BioSystems 5, 714-722 (2009)
EX1039	Roche Technical Bulletin for Genome Sequencer FLX System, TCB No. 004-2009 (April 2009)
EX1040	DE 10 2008 025 656 B4
EX1041	DE 10 2008 025 656 B4 Translator Certification
EX1042	Juliane C. Dohm et al., Substantial biases in ultra-short read data sets from high-throughput DNA sequencing, Nucleic Acids Research, 2008, Vol. 36, No. 16 e105 (December 21, 2007)

I. INTRODUCTION

Petitioner Guardant Health, Inc. (“Petitioner”) submits this opposition to Patent Owner Cold Spring Harbor Laboratory (“PO”)’s Discretionary Denial of Institution Brief (Paper 6, “Request”). For the convenience of the Board, Petitioner notes that the content of this brief tracks its corresponding brief in IPR2025-01355, the main differences focusing on the details of Examiner error.

The ’510 patent claims a method of modifying sample DNA molecules with “tags” so that one can accurately count the molecules. EX1001 at 19:33-55. But inventor Michael Wigler admitted after filing his patent that “[m]odifying molecules to facilitate counting is not a new idea.” EX1004.001. He acknowledged, for instance, that before the priority date, there were “several protocols in which a sequence of random nucleotides [was] appended to the template molecules before amplification and sequencing.” *Id.* The claims of the ’510 patent—which at their core are admittedly based on a concept that is “not a new idea”—cry out for Board review, particularly in view of the poor showing that PO makes for discretionary denial. The early status of the parallel district court litigation, examiner error during prosecution, new art used by the Petition, the strength of the Petition, and numerous additional factors all weigh in favor of institution, and this proceeding should thus

be referred to the Board.¹

II. THE DISTRICT COURT LITIGATION STATUS WEIGHS AGAINST DISCRETIONARY DENIAL

As its lead argument, PO points to three of the *Fintiv* factors relating to the status of district court litigation. As detailed below, however, these factors all weigh overwhelmingly *against* discretionary denial. The remaining *Fintiv* factors—which PO ignores—further weigh against denial, including the most important factor: the timing of trial compared to the deadline for a final written decision. It is undisputed that a final written decision will issue more than two months before any district court

¹ PO argues that the Petition is deficient for failure to “articulate any reason why the Examiner erred when previously considering the same references and cumulative art.” Request at 1-2. The Director has made clear, however, that this brief is where such issues should be addressed. See “Interim Director Discretionary Process,” USPTO, III.C, <https://www.uspto.gov/patents/ptab/interim-director-discretionary-process> (“A petitioner’s brief should be responsive to the arguments raised in patent owner’s discretionary denial brief and should raise any discretionary issues, including issues relating to 35 U.S.C. § 325(d)”; see also *Harbor Freight Tools USA, Inc. et al v. Champion Power Equipment, Inc.*, IPR2025-00805, Paper 20 (PTAB Sep. 19, 2025) (referring petition to Board where petitioner first addressed discretionary denial criteria in opposing request for discretionary denial).

trial. *See* Request at 3. This is thus not a case where the Board risks wasting its precious resources on a case that the district court will handle more rapidly, but rather one where the Board is ideally suited to provide a more efficient resolution for the parties and Court.

A. The Delaware Court Will Likely Grant A Stay

PO states that “the Litigation is not stayed, and Guardant has not even moved for a stay.” Request at 2. In the District of Delaware, however, courts “almost invariably deny requests for stays pending IPR proceedings when the stay requests are filed before the IPR is instituted.” *IOENGINE, LLC v. PayPal Holdings, Inc.*, No. 18-452, 2019 WL 3943058, at *6 (D. Del. Aug. 21, 2019). On the other hand, as former Chief Judge Stark explained, “generally the ideal time at which to file such a request” is following institution. *See 454 Life Scis. Corp. v. ION Torrent Sys., Inc.*, No. 15-595, 2016 WL 6594083, at *4 (D. Del. Nov. 7, 2016). If the Board grants institution, Petitioner will immediately seek a stay and will likely receive one.

Indeed, the facts here all align strongly in favor of a stay. Delaware district courts “consider three factors when determining whether to grant a stay pending *inter partes* review of the patent in suit: ‘(1) whether granting the stay will simplify the issues for trial; (2) the status of the litigation, particularly when discovery is complete and a trial date has been set; and (3) whether a stay would cause the non-movant to suffer undue prejudice from any delay, or allow the movant to gain a clear

tactical advantage.”” *IOENGINE* at *2.² These factors all favor a stay. An unpatentability finding by the Board would invalidate all but two asserted claims in this case and effectively end the district court litigation,³ reflecting the maximum possible simplification. As detailed further below, the district court litigation is in its earliest stages. Finally, PO would not suffer undue prejudice because the Petition was promptly submitted, Petitioner would promptly request a stay, and PO, as a non-profit research entity, does not commercially compete with Petitioner.

PO nonetheless cites a decision by Judge Choe-Groves, the presiding judge in the parallel litigation, where Judge Choe-Groves initially denied a stipulated stay pending an instituted IPR. Request at 3. PO, however, only tells half the story. Just a few months after her original decision, Judge Choe-Groves reversed herself and granted the parties’ stipulated stay. *See Data Health Partners, Inc. v. Teladoc Health, Inc.*, C.A. No. 23-160-JCG, D.I. 43 (D. Del. Dec. 4, 2024). PO’s reliance on such inapt authority underscores the weakness of its lead argument.

B. Progress In The Parallel Litigation Is Minimal

² Internal citations omitted unless otherwise noted.

³ PO argues that the parallel litigation will continue because the Petition does not challenge claims 16 and 27. These claims, however, recite features that are not present in the accused products, such that the validity status of these claims is ultimately irrelevant to the parties’ dispute.

PO argues that “since the March 6, 2025 filing of the Litigation the parties have invested substantial resources in the case.” Request at 3. Nonsense. As of the filing of this paper, fact discovery is in its early stages, and the parties have only just exchanged proposed claim construction terms. Petitioner has received no discovery requests from PO. There has been no expert discovery nor summary judgment briefs. Additionally, the Board will issue an institution decision before the scheduled claim construction hearing on April 2, 2026. “If, at the time of the institution decision, the district court has not issued orders related to the patent at issue in the petition, this fact weighs against exercising discretion to deny institution.” *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 at 10 (PTAB Mar. 20, 2020).

PO cites to the service of initial infringement contentions as a substantial investment of resources in the parallel litigation. Request at 3. But initial infringement contentions are indeed *initial* and reflect only an early step in the proceeding. PO does not cite to any case law that suggests otherwise or where the mere service of initial infringement contentions favored discretionary denial.

C. The Overlap Between The Issues In the Petition And District Court Favor Institution

PO argues that “the Litigation will continue even if these IPRs are instituted and regardless of their outcomes.” Request at 3. In the same breath, however, PO argues that there is “substantial overlap between” the issues raised in the IPR and the district court action. *Id.* As PO acknowledges, “[a]ll claims challenged in the

Petition are also at issue in the Litigation....” *Id.* These considerations do not support discretionary denial but rather establish that the Board’s work would have the effect of eliminating the need for the district court litigation entirely by invalidating the claims at issue. PO’s allegations that that “the Litigation will continue even if these IPRs are instituted and regardless of their outcomes” is without merit. In fact, as documented above, if IPR is instituted, the litigation will likely be stayed and will never recommence if the claims are found invalid.

Nevertheless, to eliminate any concerns over duplication of efforts, Petitioner stipulates that if the Board institutes (unless institution is later vacated, reversed, or withdrawn), it will not pursue against the ’510 patent any ground “that was raised or could have been reasonably raised” during this IPR proceeding in the parallel litigation, removing any overlap between the proceedings. *Sotera Wireless, Inc. v. Masimo Corp.*, IPR2020-01019, Paper 12 at 13 (PTAB Dec. 1, 2020) (precedential as to § II.A.). This factor favors institution.

D. The Remaining *Fintiv* Factors Weigh Against Discretionary Denial

As noted, the remaining *Fintiv* factors, which PO ignores, weigh against discretionary denial. Most important, the final written decision deadline of February 3, 2027, is scheduled well before the April 19, 2027 trial date in the parallel litigation, which weighs heavily in favor of institution. Further, both Petitioner and PO are parties in the district court. This factor weighs against discretionary denial

when the projected statutory deadline for a final written decision is before the district court trial date and when a stay of the district court litigation is likely if the Petition is instituted, as is the case here. *See BOE Technology Group Co., Ltd. v. Optronic Sciences LLC*, IPR2024-01130, Paper 16 at 13-14 (PTAB Jan. 27, 2025).

III. THE EXAMINER’S MATERIAL ERROR AND THE PETITION’S NEWLY CITED PRIOR ART FAVOR INSTITUTION

PO asserts that institution should be denied under § 325(d) because the “Petition relies on art that is substantially the same as art considered by the Examiner, but Petitioner does not demonstrate material error by the Examiner.” Request at 4. In fact, the Examiner erred greatly in his consideration of the art, and Petitioner relies upon art substantially different from that which the Examiner considered. As detailed below, both prongs of § 325(d) favor institution.

A. The Examiner Materially Erred When Considering The Prior Art

As the Petition explains, Lo, when combined with McCloskey, Brenner, Chee, or Porreca, discloses all limitations of most claims of the ’510 patent and renders them obvious. Even if, as PO argues, the art in the Petition is cumulative of that considered by the Examiner (it is not, *see infra* Section III.B), the Examiner materially erred in his consideration of the prior art. After several flawed rounds of prior art searching, the Examiner made a single § 103 rejection using the combination of Casbon and Xie, only to later abandon the objection without explanation. As detailed below, this abandonment followed PO’s

mischaracterization of the prior art and was erroneous. The Examiner further erred by then failing to identify key prior art references, like Lo, Chee, and Porreca that would have made clear that the claims were unpatentable as obvious.

Consider first the Examiner's abandonment of his § 103 rejection, which cited Casbon as teaching tagging and amplifying. *See* Request at 9. In response to this rejection, PO amended the claims to recite “**randomly** tagging segments of genomic nucleic acids to generate the unique tagged nucleic acid molecules” and then emphasized this new feature of the claims as the distinguishing feature over the art. *See* EX2001.452-53. Casbon, however, teaches precisely this limitation, stating that “a degenerate base region (DBR) is also attached to the polynucleotides...[and] can have a variable base composition or sequence (which may be considered as ‘**random**’) as compared to other tagged polynucleotides in the sample.” EX2005 at 15:19-27. By failing to recognize that Casbon teaches “randomly tagging the segments” and then abandoning his rejection, the Examiner erred.

Even assuming Casbon did not teach “random” tagging, the Examiner should have at least considered whether this trivial concept was obvious in view of Casbon and/or other references. But the Examiner did not do this either and thus committed further error. In fact, “random” tagging was widespread before the priority date. As detailed in the Petition, at least four additional prior art references—McCloskey, Brenner, Chee, and Porreca—all teach “randomly tagging.” *See* Petition at 23-26.

As the Petition explains, each reference teaches “not just tagging, but *random* tagging because they all teach the use of *random* sequences that are paired up with target nucleic acids through *random* stochastic processes during solution-phase reactions, such as primer extension or ligation...” Petition at 26. McCloskey, for example, teaches a tag that includes a “*random* barcode” which “distinguishes among sequences arising from different cell or allele copies.” EX1008 at 762. As to each of McCloskey, Brenner, Chee, and Porreca, the Petition proves their disclosure of random tagging with citations to both expert witness testimony and the references themselves. *See* Petition at 26; EX1002 ¶¶ 140, 143, 145-46. The Examiner, however, did not find any of this disclosure in the art.

The reason for this is simple. To wit, the Examiner did not even look for “random” tagging in the prior art. After PO amended the claims to include “randomly tagging,” none of the search terms in the Examiner’s subsequent prior art searches included “random” or “randomly.” EX2001.518. This is inexplicable and is part of a long pattern of flawed searches. Although the Examiner ran prior art searches on at least six different dates (EX2001.221-222, EX2001.272-273, EX2001.310, EX2001.424-425, EX2001.491-494, EX2001.518), the Examiner did not identify Lo, Chee, or Porreca as prior art because the Examiner’s search terms were loaded with overbroad, unfocused, and irrelevant terms such as “linker,” “PCR,” and “amplification.” *See, e.g.*, EX2001.424.

The Examiner's failure to identify Lo is particularly striking. In response to the Examiner's § 103 rejection, PO alleged that the '510 patent's method improved on the prior on by "**mapping** each tag associated sequence read to a location on the genome." EX2001.453. Lo, however, expressly discloses the mapping and alignment steps of the '510 patent. Petition at 12-14. As detailed in the Petition, Lo further provides a strong motivation for a POSA to combine the method in Lo with any of the tagging references identified in the Petition. Petition at 26-29. The Examiner missed this all entirely.

As to McCloskey and Brenner, PO contends they are not worthy of further consideration because they were cited in the '510 patent specification and thus supposedly considered during Examination. But the patent's discussion of these references just substantiates Examiner error. The specification distinguishes Brenner as using "ligation, which has been found to be an inefficient reaction." EX1001 at 2:21-22. Yet, the '510 patent claims undeniably encompass ligation; this is what PO accuses of infringing. The Examiner, however, never recognized the inconsistency. Similarly, the '510 patent criticizes McCloskey as using "template specific primers to barcode template DNA." *Id.* at 2:25-26. Yet, the specification teaches that a tag "may comprise a part of an adaptor or a **primer**." *Id.* at 16:51-53. Claim 1's step of "tagging the segments" makes no distinction among tagging methods and **includes** both Brenner's ligated tags and McCloskey's barcode tags.

Again, the Examiner never recognized the inconsistency.

The Examiner's failure to recognize that the specification's distinctions over Brenner and McCloskey were at odds with the claim language was error and is consistent with his blindness to these references for obviousness. *See* Petition at 30. Certainly, given the contradiction between the claim language and specification vis-à-vis McCloskey and Brenner, any suggestion that the Board should disregard these references is without merit, particularly because, as detailed below, the Petition relies on additional non-cumulative references such as Porreca and Chee.

PO nonetheless argues that the same Examiner's invalidity rejection based on Brenner for a different patent years earlier in 2014 means that Brenner was considered for the '510 patent. Request at 7. The earlier rejection, however, was based on anticipation for substantially different claims and did not analyze obviousness. EX2002.363. That rejection was made nearly *five years* before the application for the '510 patent was even filed. EX2002.363-365, EX2001.001. PO's contention that these facts establish consideration of Brenner for the purposes of the '510 patent is an unsupported stretch.

B. The Petition Contains New Art Not Considered By The Examiner

As explained above, the Examiner erred in his search for and analysis of prior art. Even in the absence of such error, discretionary denial is still inappropriate because the Petition relies on prior art not considered by the Examiner.

The Petition includes three new references—Lo, Chee, and Porreca—that were undisputedly not considered by the Examiner because, as PO acknowledges. Request at 11. These references are neither continuations-in-part nor alternative versions of documents of record that petitioners often rely upon to skirt criticism that they are using previously considered art. They are rather wholly distinct references having considerably different teachings that would have made clear to the Examiner that the ’510 patent is unpatentable.

1. Lo Is Not Cumulative

Based on a single line in the Petition—and without analysis of the references—PO argues that Lo, which is the primary reference in the Petition, is cumulative of Chiang, Wang, and Xie. Request at 11-12. Although Lo has some overlap with the “basic counting method” of Chang, Wang, and Xie, these three references are far from coextensive. Lo, in fact, has robust, unambiguous disclosures of several claim limitations that are simply not found in Chiang, Wang, and Xie.

Lo, for example, discloses sequence alignment to an external control reference (claim 1), EX1010 ¶¶ 58, 70, 93; hybrid capture (claims 7-8), *id.* ¶ 72; nucleic acids from blood samples (claim 17), *id.* ¶ 92; and tumor cell DNA in bodily fluids (claim 18), *id.* ¶ 52. These latter limitations are especially relevant because here the products accused of infringement use cell-free DNA to detect cancer. *See* EX1003.015. To the extent Chiang, Wang, and Xie disclose mapping and

alignment, they rely on outdated methods used before the advent of high-throughput sequencing. In Wang, genomic DNA molecules are broken down enzymatically into segments 21 base-pairs long, whose sequences could be predicted before sequencing. EX1012.003. Chiang and Xie compared copy-number detection performance using sequence counts with the visual intensity information provided by microarrays, a technique that predates high-throughput sequencing. EX1013.001; EX2004 at 3. Both Lo and the '510 patent claims work with unknown nucleic acid sequences and do not rely on microarrays for counting.

Perhaps most important, though, Lo's disclosure provides a motivation to combine that is simply absent from Chiang, Wang, and Xie. *See* Petition at 26-29. Chiang and Wang all focus on whole tumor and normal cells, which provide abundant quantities of DNA samples for analysis. EX1012.002 (using "tags from the lymphoblastoid cells of a normal individual"); EX1013.003 (using "both normal and tumor cell lines"). And Xie did not even use samples, but rather simulated data and previously generated data downloaded from a website. *See* EX2004 at 6-7.

The method described in Lo, while applicable to many types of DNA samples, is particularly effective for applications using cell-free DNA. EX1010 ¶¶ 93-94. As the Petition explains, cell-free DNA samples are usually present in very small concentrations in the blood or serum of the patient. Petition at 33. Lo describes experiments working with as little as "50 ng of maternal plasma DNA" and discusses

“lesser amounts such as 15 ng or 10 ng.” EX1010 ¶ 93. And fetal DNA further comprises only a subset of the maternal plasma DNA. *Id.* ¶ 13 (“fetal DNA...represent a minor portion of all DNA sequences in maternal plasma and serum”). The motivation to combine Lo with the tagging references disclosed is straightforward: with limited input material, accuracy is crucial, and tagging was a known solution to improve accuracy. This is detailed in the Petition at length and is an important argument that does not stem from Wang, Chiang, or Xie. *See* Petition at 26-29; EX1002 ¶ 149.

Because Lo contains additional limitations, provides a strong motivation to combine, and is compatible with the widespread tagging method described in the tagging references, Lo is not substantially similar to Chiang, Wang, or Xie.

2. Chee And Porreca Are Not Cumulative

Chee and Porreca are two prior art references not considered by the Examiner during the prosecution of the '510 patent that teach a method of counting nucleic acids in a sample using nucleic acid tagging, PCR amplification, and DNA sequencing. Petition at 24-25, 31-32. CSHL contends these references are duplicative of Brenner and McCloskey, which are mentioned in the background section of the '510 patent.

Yet, as shown above, the '510 patent claims contradict the specification's background discussion of McCloskey and Brenner. *See supra* Section III.A.

McCloskey and Brenner teach molecular tagging by PCR primers and ligation, respectively. The distinctions identified in the specification may have been relevant for claims previously prosecuted, but the '510 patent claims cover all methods of “randomly tagging the segments of genomic nucleic acids with different nucleic acid tags,” including via ligation. EX1001 at claims 1, 10. These inconsistencies negate any contention that McCloskey and Brenner ought to be disregarded along with Chee and Porreca as having already been considered.

Moreover, although the Petition uses Chee and Porreca interchangeably with McCloskey and Brenner to demonstrate the obviousness of claim 1 of the '510 patent, the Petition uses Chee and Porreca differently to show the obviousness of each dependent claim. For example, Chee clearly discloses the predefined tag sequences required by claim 3, and Porreca has the clearest disclosure of mechanical shearing required by claim 4. *See* Petition at 52, 54. Therefore, Chee and Porreca are not cumulative of McCloskey and Brenner.

IV. THE PETITION’S CLEARLY ARTICULATED OBVIOUSNESS ARGUMENTS WEIGH IN FAVOR OF INSTITUTION

Contrary to PO’s assertions, the Petition lays out a clear, concise, and strong argument that develops the obviousness of the challenged claims. This also weighs heavily against discretionary denial.

A. Petitioner’s Patentability Challenge Is Strong

PO argues that the “Petition fails to specify the grounds with particularity,”

since multiple references are cited “*in the alternative* for the *same* teachings.” Request at 16. But the volume of art cited by the Petition underscores just how well-known the tagging method described in the ’510 patent was to skilled artisans. The Petition cites four distinct prior art references (Chee, Porreca, Brenner and McCloskey), which all teach molecular counting using nucleic acid tags to overcome amplification distortion in sequencing methods. Petitioner’s inclusion of these four references highlights that the tagging method was widespread before the priority date and underscores Examiner error. The Petition demonstrates that the challenged claims of the ’510 patent are obvious in view of Lo, which discusses mapping and counting of DNA sequences to generate copy number information, in combination with the well-known tagging method. Petition at 21-22. Each of the tagging references discloses different limitations for the challenged dependent claims.

PO further argues that Petitioner’s invalidity arguments use four references “without...any indication of what possible combinations are actually asserted.” Request at 16. The Petition, however, identifies the prior art combination for each of the grounds used to demonstrate the obviousness of the challenged claims. Petition at 5. Under Ground 2, the Petition demonstrates the obviousness of claim 3 using Lo in view of McCloskey, Brenner, or Chee. Ground 3 demonstrates the obviousness of claim 4 using Lo in view of Brenner or Porreca. These grounds are not “conclusory,” as PO argues. Request at 17. Both the Petition and Dr. Cooper’s

declaration explain where each of the claim limitations is found in the prior art and support each argument. *See* Petition at 16-18 (citing to disclosures in Wang and Chiang to explain why Lo’s method is not limited to pregnant women); EX1002 ¶¶ 93-94 (same); *see also* Petition at 39 (citing to disclosures in Lo to show Lo teaches deriving copy number information); EX1002 ¶¶ 184-186 (same). The Petition’s strong arguments weigh against discretionary denial.

B. The Petition Appropriately Relies On Expert Testimony

PO contends that the Petition “impermissibly relies on expert testimony to supply missing claim elements” and that it “improperly relies solely on the bare assertions of its expert to fill in pieces of its alleged obviousness rationale.” Request at 14, 17. The Petition, however, relies upon citations to the prior art to teach the claimed limitations. In one example, PO argues that the Petition relies “solely on Dr. Cooper’s statements for obviousness of fragmentation techniques.” Request at 17. But both the Petition and Dr. Cooper’s declaration cite to disclosures in Brenner and Porreca to show that fragmentation was a known and obvious technique. *See* Petition at 54; EX1002 ¶ 242.

Dr. Cooper’s declaration supports these disclosures by explaining the motivation to combine prior art references and demonstrating a reasonable likelihood of success. PO argues that the Petition’s use of paragraphs 148 and 149 of Dr. Cooper’s declaration constitutes “bare assertions” of a motivation to combine.

Request at 14. Those paragraphs, however, do not impermissibly fill gaps in the prior art but instead provide Dr. Cooper's opinion regarding the relevant knowledge of a POSA as of the '510 patent's priority date. EX1002 ¶¶ 148-149.

Dr. Cooper relies on evidence presented in McCloskey, Brenner, Chee and Porreca for his opinion that tagging molecules to overcome amplification distortion was "well within the technical grasp of a skilled artisan." EX1002 ¶¶ 148-149. The Petition, like any other petition based on obviousness, relies on the opinions of an expert, here, Dr. Cooper, to explain why a POSA would be motivated to combine prior art references and why such a combination would have had a reasonable likelihood of success. The Petition, therefore, uses expert testimony properly, which confirms its strength and weighs against discretionary denial. *See Rhythm Technologies, Inc. v. Welch Allyn, Inc.*, IPR2025-00363, Paper 10, (PTAB Jun. 6, 2025) (stating that expert testimony should not be used to "to fill gaps in the prior art" but is appropriate "to explain the background knowledge of a person of ordinary skill in the art [where the] expert provides citations to evidence in support.").

C. Petitioner Has Not Taken Inconsistent Positions

PO asserts that Petitioner's arguments are inconsistent with arguments that Petitioner made in two other proceedings. Request at 18-19. Both of these proceedings, however, pertained to claims for more complex analyses than mere counting, including determining consensus reads and identifying single nucleotide

variations. EX2008.024; EX2006.005. Additionally, in citing Petitioner’s allegation that grouping sequencing reads “was not routine, well-understood, or conventional,” PO confuses the test for obviousness under § 103 with the test for patent eligibility under § 101. Request at 19. A claim can be inventive under § 101 even if it is obvious under § 103. *Diamond v. Diehr*, 450 U.S. 175, 176 (1981).

Petitioner does not now take an inconsistent position. The ’510 patent deals with “substantially *unique* tags,” EX1001 at Abstract, and “*different* ... tagged nucleic acid molecules,” *Id.* at Claim 1, and the Petition relies on prior art directed to unique tags. *See, e.g.*, EX1017 at 5:1-5. Both proceedings cited by PO centered around *non-unique* nucleic acid barcodes. EX2008.012; EX2006.005. Ultimately, the relevance of these arguments to this IPR is intensely factual and not useful at the discretionary denial stage.

V. OTHER FACTORS IDENTIFIED BY THE DIRECTOR WEIGH AGAINST DENIAL

Additional factors identified by the Acting Director in the Office’s March 26, 2025 memorandum further weigh against discretionary denial. EX2003.

A. The ’510 Patent Is Not Entitled To Settled Expectations

The ’510 patent has been in force only since its issue date of February 25, 2025. EX1001.001. Given the short lifetime of the ’510 patent, PO has no settled expectations regarding the ’510 patent, and this factor weighs against denial. *See Cambridge Industries USA, Inc. v. Applied Optoelectronics, Inc.*, IPR2025-00434,

Paper 11 at 3 (PTAB Jun. 26, 2025) (denying a denial request for patents which issued in 2019 and 2020). The '510 patent has not been commercialized by PO or any other party, which further weighs against denial. *See Amgen v. Bristol-Myers Squibb Co.*, IPR2025-00601, 2025 WL 2086050 (PTAB July 24, 2025).

B. Compelling Economic And Public Health Considerations Weigh Against Denial

In the parallel district court litigation, PO accuses Petitioner's products of infringing the '510 patent and seeks a permanent injunction against Petitioner. EX1003.029. Petitioner's products include FDA-approved tests used to diagnose and treat many varieties of cancer by providing key information to oncologists. EX1003.015. Several of Petitioner's products are non-invasive and require only a blood sample. *Id.* If Petitioner is found to infringe the '510 patent, the healthcare space could lose an important and niche diagnostic and treatment tool in the fight against cancer. This factor weighs against discretionary denial.

C. No Forum Has Previously Adjudicated The Validity Or Patentability Of The Challenged Patent Claims

The Board has not adjudicated the validity or patentability of the challenged claims nor has any other forum, weighing against discretionary denial.

VI. CONCLUSION

PO's request for discretionary denial should be rejected.

Dated: November 3, 2025

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

Pursuant to the Interim Director Discretionary Process, the undersigned hereby certifies that this brief complies with the type-volume limitation of Section III.C.iii because this brief contains 20 pages.

Dated: November 3, 2025

Respectfully submitted,

JONES DAY

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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of **PETITIONER'S
OPPOSITION TO PATENT OWNER'S REQUEST FOR DISCRETIONARY
DENIAL** is being served on November 3, 2025, via email pursuant to 37 C.F.R.
§ 42.6(e) to the Patent Owner at the address below:

Gary J. Gershik ggershik@arelaw.com Darren Haber dhaber@arelaw.com Kenneth George kgeorge@arelaw.com Amster Rothstein & Eberstein LLP 405 Lexington Avenue, 48 th Floor New York NY 10174	
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Dated: November 3, 2025

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