

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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**GUARDANT HEALTH, INC.**

Petitioner,

v.

**COLD SPRING HARBOR LABORATORY**

Patent Owner

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Case No. IPR2025-01355

U.S. Patent No. 10,947,589

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

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## TABLE OF CONTENTS

|                                                                                                              | Page |
|--------------------------------------------------------------------------------------------------------------|------|
| TABLE OF AUTHORITIES .....                                                                                   | ii   |
| I. INTRODUCTION .....                                                                                        | 1    |
| II. THE DISTRICT COURT LITIGATION STATUS WEIGHS<br>AGAINST DISCRETIONARY DENIAL .....                        | 2    |
| A. The Delaware Court Will Likely Grant A Stay .....                                                         | 3    |
| B. Progress In The Parallel Litigation Is Minimal.....                                                       | 4    |
| C. The Overlap Between The Issues In the Petition And District<br>Court Favors Institution .....             | 5    |
| D. The Remaining <i>Fintiv</i> Factors Weigh Against Discretionary<br>Denial .....                           | 6    |
| III. THE EXAMINER’S MATERIAL ERROR AND THE PETITION’S<br>NEWLY CITED PRIOR ART FAVOR INSTITUTION .....       | 7    |
| A. The Examiner Materially Erred In Considering The Prior Art.....                                           | 7    |
| B. The Petition Contains New Art Not Considered By The<br>Examiner .....                                     | 10   |
| IV. THE PETITION’S CLEARLY ARTICULATED OBVIOUSNESS<br>ARGUMENTS WEIGH IN FAVOR OF INSTITUTION.....           | 14   |
| A. Petitioner’s Patentability Challenge Is Strong .....                                                      | 14   |
| B. The Petition Appropriately Relies On Expert Testimony .....                                               | 15   |
| C. Petitioner Has Not Taken Inconsistent Positions .....                                                     | 17   |
| V. OTHER FACTORS IDENTIFIED BY THE DIRECTOR WEIGH<br>AGAINST DENIAL .....                                    | 18   |
| A. The ’589 Patent Is Not Entitled To Settled Expectations .....                                             | 18   |
| B. Compelling Public Health Considerations Weigh Against<br>Denial .....                                     | 20   |
| C. No Forum Has Previously Adjudicated The Validity Or<br>Patentability Of The Challenged Patent Claims..... | 20   |
| VI. CONCLUSION.....                                                                                          | 20   |

## TABLE OF AUTHORITIES

|                                                                                                                                      | Page   |
|--------------------------------------------------------------------------------------------------------------------------------------|--------|
| <b>CASES</b>                                                                                                                         |        |
| <i>454 Life Scis. Corp. v. ION Torrent Sys., Inc.</i> ,<br>No. 15-595, 2016 WL 6594083 (D. Del. Nov. 7, 2016) .....                  | 3      |
| <i>Amgen v. Bristol-Myers Squibb Co.</i> ,<br>IPR2025-00601, 2025 WL 2086050 (PTAB July 24, 2025).....                               | 19     |
| <i>Apple Inc. v. Fintiv, Inc.</i> ,<br>IPR2020-00019, Paper 11 (PTAB Mar. 20, 2020) .....                                            | 5      |
| <i>BOE Technology Group Co., Ltd. V. Optronics Sciences LLC</i> ,<br>IPR2024-01130, Paper 16 (PTAB Jan. 27, 2025) .....              | 6, 8   |
| <i>Cambridge Industries USA, Inc. v. Applied Optoelectronics, Inc.</i> ,<br>IPR2025-00434, Paper 11 (PTAB Jun. 26, 2025) .....       | 18     |
| <i>Data Health Partners, Inc. v. Teladoc Health, Inc.</i> ,<br>C.A. No. 23-160-JCG, D.I. 43 (D. Del. Dec. 4, 2024) .....             | 4      |
| <i>Diamond v. Diehr</i> ,<br>450 U.S. 175 (1981).....                                                                                | 17     |
| <i>Foundation Medicine, Inc. v. Guardant Health, Inc.</i> ,<br>Case No. 1:17-cv-00807 (D. Del. Jun. 23, 2017) .....                  | 17     |
| <i>Google LLC v. Withrow Networks Inc.</i> ,<br>IPR2025-00775, Paper 10 (PTAB Aug. 14, 2025).....                                    | 19, 20 |
| <i>Guardant Health, Inc., v. Tempus AI, Inc.</i> ,<br>Case No. 1:24-cv-00687. Jun. 11, 2024) .....                                   | 17     |
| <i>Harbor Freight Tools USA, Inc. et al v. Champion Power Equipment, Inc.</i> ,<br>IPR2025-00805, Paper 20 (PTAB Sep. 19, 2025)..... | 2      |
| <i>IOENGINE, LLC v. PayPal Holdings, Inc.</i> ,<br>No. 18-452, 2019 WL 3943058 (D. Del. Aug. 21, 2019) .....                         | 3, 4   |
| <i>Rhythm Technologies, Inc. v. Welch Allyn, Inc.</i> ,<br>IPR2025-00363, Paper 10 (PTAB Jun. 6, 2025) .....                         | 16     |

|                                                                                                                                                                                                                                      |          |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| <i>Sotera Wireless, Inc. v. Masimo Corp.</i> ,<br>IPR2020-01019, Paper 12 (PTAB Dec. 1, 2020) .....                                                                                                                                  | 6        |
| <i>State Indus., Inc. v. A.O. Smith Corp.</i> ,<br>751 F.2d 1226 (Fed. Cir. 1985) .....                                                                                                                                              | 19       |
| <i>Valneva Austria GMBH v. Takeda Vaccines, Inc.</i> ,<br>IPR2025-00776, Paper 11 (PTAB Aug. 11, 2025).....                                                                                                                          | 18       |
| <b>STATUTES</b>                                                                                                                                                                                                                      |          |
| 35 U.S.C. § 315(b) .....                                                                                                                                                                                                             | 19       |
| 35 U.S.C. § 325(d) .....                                                                                                                                                                                                             | 2, 7, 10 |
| <b>OTHER AUTHORITIES</b>                                                                                                                                                                                                             |          |
| Interim Director Discretionary Process,” USPTO, III.C,<br><a href="https://www.uspto.gov/patents/ptab/interim-director-discretionary-process">https://www.uspto.gov/patents/ptab/interim-director-discretionary-</a><br>process..... | 2        |

## PETITIONER'S EXHIBIT LIST

| Exhibit # | Description                                                                                                                                                                                           |
|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| EX1001    | U.S. Patent No. 10,947,589 (“the ’589 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. 10,947,589                                                                                                                                                |
| 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    | U.S. Patent No. 8,195,415 (“Quake”)                                                                                                                                                                   |

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|--------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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 <a href="https://www.genome.gov/genetics-glossary/Nucleotide">https://www.genome.gov/genetics-glossary/Nucleotide</a>                                            |
| 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 <a href="https://www.genome.gov/geneticsglossary/Polymerase-Chain-Reaction">https://www.genome.gov/geneticsglossary/Polymerase-Chain-Reaction</a> |
| 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)                                               |

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|--------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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 | Intentionally left blank                                                                                                                                                             |
| EX1038 | Intentionally left blank.                                                                                                                                                            |
| 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 IPR2025-01353, the main differences focusing on the details of Examiner error.

The ’589 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 ’589 patent—which 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 favor of institution, and this proceeding should thus be referred to the

Board.<sup>1</sup>

## 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

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<sup>1</sup> 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 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 patent that the district court will adjudicate 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 Petitioner has not even moved for a stay.” Request at 3. 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.<sup>2</sup> These factors all favor a stay. An unpatentability finding by the Board would invalidate all asserted claims in this case and effectively end the district court litigation, 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**

PO argues that “since the March 6, 2025 filing of the Litigation the parties have invested substantial resources in the case.” Request at 4. 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

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<sup>2</sup> Internal citations omitted unless otherwise noted.

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 4. 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 Favors Institution**

PO argues that “even if these IPRs were instituted, the Litigation will need to continue, regardless of the IPR outcomes.” Request at 4. 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 potentially invalidating the claims at issue. PO’s allegations

that that “the Litigation will need to continue, regardless of the IPR 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), Petitioner will not pursue against the ’589 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 5. In fact, the Examiner erred greatly in his consideration of the art, 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 In Considering The Prior Art

As the Petition explains, Lo, when combined with McCloskey, Brenner, Chee, or Porreca, discloses all limitations of almost all claims of the ’589 patent and renders them obvious. Yet, despite *numerous* examples of tagging references in the prior art, the Examiner did not issue a single rejection based on § 103 during the prosecution of the ’589 patent. EX1009. This alone constitutes error and confirms that the initial Examination was poor. Indeed, as to prior art, it was *nonexistent*.

The Examiner, for instance, did not discuss or analyze any of the supposedly cumulative art in any Office Action—the only citations to McCloskey, Brenner, Chiang, and Wang are found in IDS documents and lists of references. *Id.* The Examiner’s failure to even discuss McCloskey and Brenner—let alone any other tagging reference—is particularly erroneous given the inventor’s admission that molecular tagging was “not a new idea.” EX1004.001.

Although PO contends that McCloskey and Brenner are not worthy of further consideration because they were cited in the '589 patent specification and thus supposedly considered during Examination, the patent's discussion of these references just substantiates Examiner error. As to Brenner, the specification distinguishes it as using "ligation, which has been found to be an inefficient reaction." EX1001 at 2:21-22. Yet, the '589 patent *claims* tagging by ligation. *Id.* at 22:43-51, claim 10. The Examiner never recognized this inconsistency. Similarly, as to McCloskey, the '589 patent criticizes it as using "template specific primers to barcode template DNA molecules prior to PCR amplification." *Id.* at 2:25-26. Yet, the specification teaches that a tag or barcode "may comprise part of an adaptor or a *primer*," and claim 1's step of "tagging the segments" makes no distinction among methods of tagging and *includes* McCloskey's barcode tags. EX1001 at 16:51-53. Again, the Examiner never recognized the inconsistency.

The Examiner erred by failing to recognize that the specification's distinctions over Brenner and McCloskey were at odds with the claim language itself and then ignoring these references for prior art purposes. Certainly, in view of the contradiction between the claim language and specification vis-à-vis McCloskey and Brenner, any suggestion that the Board should now 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 '589 patent. Request at 8. The earlier rejection, however, was based on anticipation for substantially different claims and did not analyze obviousness. EX2002.363. That rejection was made nearly *two years* before the application for the '589 patent was even filed. EX2002.363-365, EX1009.001. PO's contention that these facts establish consideration of Brenner for the purposes of the '589 patent is an unsupported stretch.

To better understand why the Examiner's consideration of the prior art was so inadequate as to be nonexistent, it is instructive to consider the prior art searches the Examiner ran, which were deeply flawed, superficial, and reflect yet more error. The Examiner ran prior art searches on at least three different dates. EX1009.260-261, EX1009.606-607, EX1009.654-655. But none of these searches focused on the key concepts in the claims, such as "copy number" or "mapping." Instead, the Examiner's search terms were loaded with overbroad, unfocused, and irrelevant terms, such as "linker," "PCR," and "amplification." It is little wonder the Examiner found nothing. The Examiner's error in missing directly on-point references such as Lo, Quake, Chee, and Porreca confirms that the searches were deficient.

The Examiner's failure to identify Lo is the most striking. As detailed in the Petition and further below, Lo provides clear and unambiguous disclosure of the

copy number, mapping, and alignment features of the claims of the '589 patent. Petition at 12-13. Lo also 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; *infra* Section III.B. The Examiner's failure to identify Lo contributed to material error in not recognizing that prior art disclosing all limitations of claims 1-18 of the '589 patent was publicly available before the priority date, rendering all challenged claims unpatentable as obvious.

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

As explained above, the Examiner clearly erred in his search for and analysis of prior art. Yet, even in the absence of material error, discretionary denial is still inappropriate under § 325(d) because the Petition relies on prior art not considered by the Examiner.

The Petition includes four new references—Lo, Quake, Chee, and Porreca—that were undisputedly not considered by the Examiner. PO acknowledges that Lo, Chee, and Porreca were not cited during the prosecution of the '589 patent. Request at 10. Additionally, U.S. Pat. No. 8,195,415 (“Quake,” EX1019) was not included in any of the IDS documents considered by the Examiner during the prosecution of the '589 patent. *See* EX1009. As documented below, 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 '589 patent is unpatentable.

### **1. Lo Is Not Cumulative**

Based on a single line in the Petition—and without engaging in any meaningful analysis—PO argues that Lo, which is the primary reference relied upon in the Petition, is cumulative of Chiang and Wang. Request at 10-11. Although Lo has some overlap with the same “basic counting method” of Chiang and Wang, the disclosures of these two references are far from coextensive. Lo, in fact, includes robust, unambiguous disclosures of several claim limitations that are simply not found in Chiang and Wang.

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 and Wang 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. A major goal of Chiang was to compare copy-number detection

performance using sequence counts with the visual intensity information provided by microarrays, a common technique before the spread of high-throughput sequencing. EX1013.001. Both Lo and the '589 patent claims work with nucleic acids of unknown 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 and Wang. *See* Petition at 26-29. Chiang and Wang both focus on whole tumor and normal cells, which provide abundant quantities of DNA samples for analysis. EX1012.003 ("We characterized 210,245 genomic tags from the lymphoblastoid cells of a normal individual...."); EX1013.003 ("For each of the six cell lines...."). 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. For example, 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." *Id.* ¶ 93. And fetal DNA further comprises only a subset of the maternal plasma DNA. *Id.* ¶ 13 ("fetal DNA is present in low absolute concentration and 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 or Chiang. *See* Petition at 26-27, 29; EX1002 ¶ 155.

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 and Wang.

## **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 '589 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. PO contends these references are duplicative of Brenner and McCloskey, which are mentioned in the background section of the '589 patent.

Yet, as shown above, the '589 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 '589 patent claims cover all methods of “tagging the segments with 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 '589 patent, the Petition relies on Chee and Porreca exclusively in combination with Lo to demonstrate the obviousness of claim 13. Petition at 54. Only Chee and Porreca teach the limitation where tagged nucleic acid molecules differing only by a single nucleotide are ignored during the counting step. 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 provides 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 14. But the volume of art cited by the Petition underscores just how well-known the tagging method described in the '589 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. The Petition further argues that the challenged claims of the '589 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 22. Each of these tagging references also 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 15. 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. For example, under Ground 2, the Petition demonstrates the obviousness claim 9 using Lo in view of Brenner or McCloskey while Ground 4 demonstrates the obviousness of claim 13 using Lo in view of Chee or Porreca. These grounds are not "conclusory," as PO argues. Request at 15. Throughout, both the Petition and Dr. Cooper's expert declaration cite to where each of the claim limitations is found in the prior art. *See* Petition at 43-44 (citing to specific disclosures in Lo for challenged claims 3 and 6); EX1002 ¶¶ 204-213. The Petition's strong arguments weigh against discretionary denial.

#### **B. The Petition Appropriately Relies On Expert Testimony**

PO contends that the Petition relies on expert testimony to “impermissibly fill gaps in the prior art” and that it “improperly relies solely on the bare assertions of its expert to fill in pieces of its alleged obviousness rationale.” Request at 12. The Petition, however, relies upon citations to the prior art to teach the claimed limitations. These disclosures are supported by Dr. Cooper’s declaration to explain the motivation to combine prior art references and to demonstrate a reasonable likelihood of success. As one example, PO argues that the Petition’s citation to paragraphs 154 and 155 of Dr. Cooper’s declaration constitutes “bare assertions” of a motivation to combine. Request at 13. 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 ’589 patent’s priority date. EX1002 ¶¶ 154-155.

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 ¶¶ 154-155. 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 18. A claim can be inventive under § 101 even if it is obvious under § 103. *Diamond v. Diehr*, 450 U.S. 175, 176 (1981).

PO also fails to understand a crucial distinction between this proceeding and the other proceedings in which Petitioner participated. The ’589 patent deals with “substantially unique tags,” EX1001 at Abstract, and “unique tagged nucleic acid molecules,” *Id.* at Claim 1. Accordingly, the Petition relies on prior art directed to unique tags. *See, e.g.*, EX1017 at 5:1-5. In contrast, both *Guardant Health, Inc., v. Tempus AI, Inc.* and *Foundation Medicine, Inc., v. Guardant Health, Inc.* centered

around *non-unique* nucleic acid barcodes. EX2008.012; EX2006.005. In *Foundation*, the Board specifically denied the petition because the prior art cited did not disclose using non-unique tags. EX2006.028, fn. 9. In neither of these proceedings did Petitioner argue that using *unique* nucleic acid tags to differentiate molecules was somehow not obvious. 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 ’589 Patent Is Not Entitled To Settled Expectations**

The Director has explained that “settled expectations” may develop on the part of a patent owner when a patent has been in force for a long time, which may weigh against institution under certain circumstances. *Valneva Austria GMBH v. Takeda Vaccines, Inc.*, IPR2025-00776, Paper 11 at 2 (PTAB Aug. 11, 2025).

PO contends that Petitioner’s “long awareness of this family of patents weighs in favor of denial of the petition.” Request at 19. But the ’589 patent has been in force only since its issue date of March 16, 2021. EX1001.001. The short lifetime of ’589 patent weighs against denying institution of the Petition. *See Cambridge Industries USA, Inc. v. Applied Optoelectronics, Inc.*, IPR2025-00434, Paper 11 at 3 (PTAB Jun. 26, 2025) (denying a discretionary denial request for patents which

issued in 2019 and 2020); *see also Google LLC v. Withrow Networks Inc.*, IPR2025-00775, Paper 10 at 2-3 (PTAB Aug. 14, 2025) (same for a 2020 patent). In addition to being in force for a short period, the '589 patent has not been commercialized or otherwise utilized 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).

PO argues that Petitioner improperly delayed in filing the petition, since it was “aware of this family of patents since at least November 2016.” Request at 19. First, there is a vast difference between awareness of the patent family or application and awareness of a patent itself since “[w]hat the scope of claims in patents that do issue will be is something totally unforeseeable.” *State Indus., Inc. v. A.O. Smith Corp.*, 751 F.2d 1226, 1236 (Fed. Cir. 1985). Second, Petitioner filed its Petition within five months of the filing of a complaint in the parallel District Court proceeding and within weeks of being served with PO’s asserted claims and infringement contentions, which was well before the one year bar statutorily prescribed in 35 U.S.C. § 315(b). EX1003.020.

Arguing that Petitioner delayed in filing its Petition, PO cites to Petitioner’s participation in a **successful** opposition proceeding challenging a related European patent for Petitioner’s knowledge of the '589 patent. Request at 19. PO even admits that it had to amend its European patent claims in the opposition. *Id.* at 20. If any

party had settled expectations here, it was Petitioner, who had defeated PO's patent and then heard nothing from PO for years in any forum until the filing of the parallel litigation in Delaware. PO has no strong settled expectations regarding the '589 patent, and this factor weighs against denial.

**B. Compelling Public Health Considerations Weigh Against Denial**

In the parallel district court litigation, PO accuses Petitioner's products of infringing the '589 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 '589 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,

/Derek C. Walter/

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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

By: /Derek C. Walter/  
Derek C. Walter  
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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<br>ggershik@arelaw.com<br>Darren Haber<br>dhaber@arelaw.com<br>Kenneth George<br>kgeorge@arelaw.com<br>Amster Rothstein & Eberstein LLP<br>405 Lexington Avenue, 48 <sup>th</sup> Floor<br>New York NY 10174 |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|

Dated: November 3, 2025

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