

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 IPR2025-01353

Patent 12,234,510

**PATENT OWNER'S DISCRETIONARY DENIAL OF INSTITUTION
BRIEF**

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EXHIBIT LIST

<i>Exhibit No.</i>	<i>Description</i>
2001	Prosecution File History of U.S. Patent No. 12,234,510
2002	Prosecution File History of U.S. Patent No. 9,404,156
2003	March 26, 2025 Memorandum from Acting Director Coke Morgan Stewart titled “Interim Processes for PTAB Workload Management”
2004	Xie et al. (BMC Bioinformatics, 10, 80, March 6, 2009)
2005	U.S. Patent No. 8,715,967 B2 (“Casbon et al.”)
2006	<i>Foundation Medicine, Inc., v. Guardant Health, Inc.</i> IPR2019-00130, Paper 7 (June 5, 2019)
2007	Intentionally left blank
2008	Plaintiffs’ First Amended Complaint for Patent Infringement, <i>Guardant Health, Inc., v. Tempus AI, Inc.</i> 1:24-cv-00687-RGA (D. Del. filed November 4, 2024)
2009	Third Amended Scheduling Order, <i>Cold Spring Harbor Laboratory v. Guardant Health, Inc.</i> , C.A. No. 25-263-JCG (July 1, 2025 D. Del.) (No. 37)
2010	Defendant’s Opening Brief in Support of Partial Motion to Dismiss for Failure to State a Claim, <i>Cold Spring Harbor Laboratory v. Guardant Health, Inc.</i> , C.A. No. 25-263-JCG (May 1, 2025 D. Del.) (No. 25)
2011	Defendant’s Initial Invalidity Contentions, <i>Cold Spring Harbor Laboratory v. Guardant Health, Inc.</i> , C.A. No. 25-263-JCG (September 19, 2025 D. Del.)
2012	November 10, 2016 Information Disclosure Statement by Applicant filed in connection with Guardant Patent Application No. 14/712,754

I. INTRODUCTION

Patent Owner Cold Spring Harbor Laboratory (“PO” or “CSHL”) respectfully requests that the Director discretionarily deny institution of this IPR filed by Petitioner Guardant Health, Inc. (“Petitioner” or “Guardant”) against US Patent 12,234,510 (“the ‘510 Patent”). Institution should be denied because this IPR would cause the parties and the Board to incur significant inefficiencies and wasted efforts for multiple reasons explained below, and additional reasons that will be more fully elaborated in CSHL’s forthcoming Patent Owner Preliminary Response (“POPR”).

First, this Petition is one of two IPRs (IPR2025-01355 and IPR2025-01353) filed by Guardant challenging related CSHL Patents that are asserted in *Cold Spring Harbor Laboratory v. Guardant Health, Inc.*, C.A. No. 25-263-JCG (May 1, 2025 D. Del.) (the “Litigation”). In this Petition Guardant declined to challenge the validity of two claims (16 and 27) that PO has asserted. Paper 1, p. 1. Thus, the Litigation will continue even if these IPRs are instituted.

Second, the Petition is deficient on its face for multiple reasons. The Petition relies on cumulative primary and secondary references that add nothing new beyond art and arguments already considered during prosecution. Petitioner and their expert **admit** that the method described in their primary reference “**had been previously applied**” in two publications (Chiang and Wang) considered by the Examiner during

prosecution.¹ Similarly, the Petition *admits* that two of the secondary references that were considered during prosecution (Brenner and McCloskey) are relied upon for the *same* teaching as the other two secondary references (Chee and Porreca). Yet, the Petition fails to even attempt to articulate any reason why the Examiner erred when previously considering the same references and cumulative art. Petitioner also repeatedly fails to specify with particularity the reasons and evidence supporting their obviousness assertions and instead relies on the bare assertions of their expert to supply missing claim features.

Third, Guardant’s arguments in the Petition are contradicted by positions Guardant previously took to defend and enforce its own patents. The Board should deny institution of this IPR predicated on contradictory positions.

II. INSTITUTION SHOULD BE DENIED BECAUSE IT WILL NOT OBVIATE PARALLEL DISTRICT COURT LITIGATION

The Litigation has an April 19, 2027 trial date (EX2009, p. 27), which is shortly after the February 1, 2027 deadline for a final written decision in this IPR. Nonetheless, several factors weigh in favor of denying institution of this IPR.

First, the Litigation is not stayed, and Guardant has not even moved for a stay. Instead, Guardant began motion practice, seeking a limited dismissal of only

¹ All emphasis added unless otherwise indicated.

CSHL's claim of pre-suit willful infringement. That motion is fully briefed and will require the Court's attention, and even if granted would only slightly narrow the Litigation. EX2009, p. 26. The assigned Judge, Judge Choe-Groves, previously denied (without explanation) a stipulated stay where the PTAB had instituted an IPR for two out of three patents-in-suit—leaving one patent not subject to an IPR. *Data Health Partners, Inc. v. Teladoc Health, Inc.*, C.A. No. 23-160-JCG, D.I. 38 (D. Del. Oct. 7, 2024). In that case, because an IPR was not instituted on one of the three patents, the litigation needed to continue regardless of the IPR outcomes. Similarly here, Guardant declined to challenge the validity of two claims (16 and 27) (Paper 1 at 1) that PO has asserted in the Litigation. EX1020, p. 2. Thus, the Litigation will continue even if these IPRs are instituted and regardless of their outcomes.

Second, since the March 6, 2025 filing of the Litigation the parties have invested substantial resources in the case. In addition to Guardant's motion, CSHL has served its initial infringement contentions, and Guardant has served its initial invalidity contentions. *See* EX2011. Further, by the February 1, 2026 Institution Decision deadline, the parties will be proceeding through claim construction briefing. *See* EX2009, p. 26.

Third, there is substantial overlap between the issues raised in the Petition and the Litigation. All claims challenged in the Petition are also at issue in the Litigation, and Guardant has not filed any stipulation agreeing to not re-raise the same

arguments it makes here in the Litigation. To the contrary, in its invalidity contentions Guardant advanced the *exact same* prior art and arguments presented in this IPR—even incorporating these IPRs *in their entirety* into those contentions (EX2011, p. 24)—in addition to invalidity contentions based on 35 U.S.C. § 112 and § 101. *See id.*, pp. 7-23 and 40-41. CSHL will be required to defend the validity of its patents in the Litigation, including the same grounds asserted in this Petition.

III. INSTITUTION SHOULD BE DENIED UNDER 35 U.S.C. § 325(d) BECAUSE THE PETITION RAISES ONLY CUMULATIVE ART AND ARGUMENTS

The Petition relies on art that is substantially the same as the art considered by the Examiner, but Petitioner does not demonstrate material error by the Examiner. Where a petitioner (1) asserts art or arguments that were previously presented, and (2) fails to demonstrate that the Office erred in a manner material to patentability, denial is appropriate. *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GMBH*, IPR2019-01469, Paper 6, 10 (PTAB Feb. 13, 2020). Under § 325(d), “[p]reviously presented art includes art made of record by the Examiner, and art provided to the Office by an applicant, such as on an Information Disclosure Statement (IDS).” *Advanced Bionics*, Paper 6, 7-8. “[C]hallenging the claims using the same prior art that was previously presented on an IDS is sufficient to satisfy the first part of the *Advanced Bionics* framework.” *Ecto World, LLC v. RAI Strategic Holdings, Inc.*, IPR2024-01280, Paper 13, p. 4 (PTAB May 19, 2025).

If the “same or substantially the same prior art or arguments previously were presented to the Office,” then petitioner must show that the Office erred. *See, e.g., Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 24 (PTAB Dec. 15, 2017). If the Petition fails to sufficiently identify a material error by the Office, then discretionary denial of the Petition is appropriate. *Ecto World*, Paper 13 at 6. As explained in *Ecto World*, “a petitioner **must** provide an analysis even when the asserted prior art is on an IDS, but the Examiner did not apply the reference.” *Id.* at 5; *see also TankLogix, LLC v. SitePro, Inc.*, IPR2025-00761, Paper 10 (PTAB Sept. 3, 2025).

Here, all of the Petition’s Grounds rely on the same or substantially the same art as considered by the Examiner, and the Petition fails to meet its burden of showing that the Office erred in evaluating the art. The petition should be denied under § 325(d). Consolidated Trial Practice Guide, 64 (PTAB Nov. 2019).

A. The art presented in the Petition are the same or substantially the same as art previously presented during prosecution

1. The art cited in the Petition

a. US 2009/0029377 (“Lo”)

The Petition alleges that the ‘510 Patent claims are obvious over Lo “in view of the knowledge of a POSA” as allegedly reflected in a variety of other references discussed below.

Lo is cited for its teaching of “a method for determining copy number

information based on sequencing DNA from a sample, mapping the sequence reads to a reference genome, and counting the number reads that correspond to a location in the genome.” Paper 1 at 12. The Petition alleges that “[t]o the extent any aspect of the independent claims is missing in Lo, it is tagging DNA sequences to generate unique tagged nucleic acid molecules followed by amplification of these tagged nucleic acid molecules.” Paper 1 at 21.

b. McCloskey, Chee, Brenner, and Porreca

When attempting to supply the missing claim limitation of “tagging the segments ... thereby generating unique tagged nucleic acid molecules,” followed by amplification of these tagged nucleic acid molecules, the Petition explicitly relies on *any* one of McCloskey, Chee, Brenner, and Porreca *in the alternative* for the *same* teachings: “This Petition relies upon four references that teach the use of tagging, amplification, and sequencing for molecular counting: McCloskey, Chee, Brenner, and Porreca.” Paper 1 at 10; *Id.* at 23 (alleging that “it would nonetheless have been obvious to perform this step in combination with Lo in view of the knowledge of the skilled artisan, as reflected in McCloskey, Porreca, Chee, *or* Brenner”).

Petitioner’s expert, Gregory Cooper, Ph.D., similarly relies upon McCloskey, Chee, Brenner, or Porreca for the same teachings of the “general approach of tagging, amplification, and sequencing for molecular counting.” *See* EX1002 at ¶¶97, 103, 112 and 120 (Dr. Cooper states these four references all teach “the general

approach of tagging, amplification, and sequencing for molecular counting”). As discussed below, Brenner and McCloskey were well considered.

2. The art that was considered during prosecution of the grandparent 156 Patent

The '510 Patent is a continuation of U.S. Patent No. 9,404,156 (“the ‘156 Patent”), issued August 2, 2016. During prosecution of the ‘156 Patent, the same Examiner who examined the ‘510 Patent applied Brenner (US 2007/0172873)² in a rejection in an April 30, 2014 Office Action (EX2002, p. 363-364). Further, PO’s first IDS in the ‘156 Patent, containing only 14 references, included Brenner (U.S. Patent No. 7,537,897, EX1014) and McCloskey (EX1008). Finally, McCloskey and Brenner are both also discussed in the background section of the specification. EX1001, 2:23-26 and 2:16-20.

In the Examiner’s Reasons for Allowance, having considered the disclosure of Brenner, McCloskey and the other references provided by PO in its IDSs, the Examiner noted that “[n]o prior art in the record teaches a combination of steps a) to f) of claim 1 and a combination of steps a) to e) of claim 9. No prior art either

² US 2007/0172873 corresponds to U.S. Patent No. 7,537,897 (EX1014), cited in the Petition as one of four secondary references allegedly teaching “molecular counting based on tagging, amplification, and sequencing.” Paper 1, at 18; EX1002 at ¶103.

alone or in combination with other art in the record teaches or reasonably suggests a method for obtaining copy number information [] which comprise all limitations recited in claim[] 1.” EX2002, p. 692.

3. The art that was considered by the Examiner during prosecution of the ‘589 Patent

During prosecution of the ‘589 Patent, the parent of the ‘510 Patent, PO disclosed in IDSs the references previously disclosed in connection with the ‘156 Patent, including Brenner and McCloskey. EX1009, pp. 207-210 (Cite Nos. 13 and 38, respectively). PO also disclosed in an IDS an Opposition filed against the European counterpart, along with the additional references cited therein.³ EX1009, p. 318. The Opposition references included Brenner, McCloskey, and Chiang, along with subsequent briefing and additional evidence filed by the opponent, including Wang (EX1012). EX1009, pp. 318 and 540. The Examiner considered this material before allowing the ‘589 Patent. *See* EX1009, p. 255 (Brenner cited as Cite ID 13), p. 257 (McCloskey cited as Cite ID 38), p. 532 (Chiang cited as Cite ID 6); and p. 605 (Wang cited as Cite ID 6).

The same Examiner allowed this ‘510 Patent, and the ‘156 and ‘589 Patents.

³ The Opposition was filed on behalf of Guardant. *See* EX2010, p. 2 (Guardant characterizing arguments by the opponent as “*Guardant’s* arguments”).

4. The art that was considered and overcome during prosecution of the ‘510 Patent

During prosecution of this ‘510 Patent, PO submitted IDSs disclosing, and the Examiner considered, all references previously disclosed in connection with the ‘156 and ‘589 Patents. EX2001, pp. 175-178, 242, 271 and 286.

Importantly, during prosecution of the ‘510 Patent, the Examiner set forth, and subsequently withdrew, a rejection of the claims under 35 U.S.C. § 103 based on Xie (BMC Bioinformatics, 10, 80, March 6, 2009) (EX2004) in view of Casbon (U.S. Patent No. 8,715,967 B2) (EX2005) in a November 9, 2023 Final Office Action (“2023 FOA”) (EX2001, pp. 434-437). That rejection mirrored the argument for unpatentability advanced by the Petition, citing one reference (Casbon) for its teaching of tagging, amplifying, and sequencing nucleic acid molecules, and citing a second reference (Xie) for its teaching of mapping.

a. Casbon

In the 2023 FOA, the Examiner alleged that Casbon teaches “a) obtaining segments of genomic nucleic acids from a sample; b) tagging the segments with nucleic acid tags (ie., a set of adaptors), thereby generating unique tagged nucleic acid molecules, such that each of the unique tagged nucleic acid molecules comprises a segment of the segments of genomic nucleic acids from step (a) and a nucleic acid tag of the nucleic acid tags; c) subjecting the unique tagged nucleic acid

molecules (ie., a population of initial target nucleic acid molecules) to a polymerase chain reaction (PCR), thereby generating amplified unique tagged nucleic acid molecules; and d) generating tag associated sequence reads (ie., a plurality of sequence reads) by sequencing the amplified unique tagged nucleic acid molecules of step (c) as recited in claim 68...” EX2001, pp. 434-435.

b. Xie

In the 2023 FOA, the Examiner further alleged that Xie teaches “to map two sets of shotgun reads by sequence alignment on a template wherein the mapped region is analyzed using a sliding window approach and DNA copy number variations (CNVs) are detected by computing the number of reads for each individual in each of the windows, yielding ratio.” EX2001, pp. 436.

c. The § 103 rejection based on Casbon in view of Xie

In the 2023 FOA, the Examiner alleged that “it would have been obvious at the time the invention was made to have performed the method recited in claim 68 by assigning each of the amplified unique tagged nucleic acid molecules to a location on a genome and obtaining copy number information based on a count of the number of unique tagged nucleic acid molecules from the sample that have been assigned to the same location in the genome in view of the prior[] art of Casbon et al., and Xie et al.” EX2001, pp. 436-437.

After PO explained the patentability of the claimed method, the Examiner

withdrew the rejection and allowed the ‘510 Patent.

5. The art cited in the petition is substantially the same as art that was considered during prosecution

a. The teachings relied upon by Petitioner in McCloskey, Brenner, Chee, and Porreca are cumulative of the teachings of Casbon, and one another

As noted above, both McCloskey and Brenner were repeatedly cited during prosecution of the ‘510 Patent and related ‘156 Patent. The Petition and Dr. Cooper now cite to *any* one of McCloskey, Brenner, Chee and Porreca in the alternative for the same teaching: “This Petition relies upon four references that teach the use of tagging, amplification, and sequencing for molecular counting: McCloskey, Chee, Brenner, and Porreca.” Paper 1 at 10. Thus, the Petition *admits* that its two newly cited secondary references (Chee and Porreca) are being relied upon for the *same* “use of tagging, amplification, and sequencing for molecular counting” teaching as the art that was considered during prosecution (McCloskey and Brenner).

Casbon was cited by the Examiner during prosecution of the ‘510 Patent for its teaching of tagging, amplifying, and sequencing nucleic acids for molecular counting (EX2001, pp. 434-435), the same teachings for which the Petition cites McCloskey, Brenner, Chee or Porreca. In deciding to withdraw the rejection based on Casbon, the Examiner had decided the same issue that Guardant raises now.

b. Lo is cumulative to each of Wang, Chiang, and Xie

Although the primary reference Lo was not cited during prosecution of the

‘510 Patent, the teachings of Lo relied upon in the Petition are substantially the same as art that was considered during prosecution. Indeed, the Petition itself admits that the “*method described in Lo [] had been previously applied* to other sources of DNA to detect copy number information” (Paper 1 at 16), citing to Wang et al. “Digital Karyotyping” (2002) (“Wang”, EX1012) and Chiang et al. “High Resolution Mapping of Copy Number Alterations with Massively Parallel Sequencing” (2008) (“Chiang”, EX1013) as two examples where the method described in Lo had been previously applied.

Both Wang and Chiang were disclosed to the Examiner during prosecution in IDSs. Beyond not explaining how the method described in Lo *differs* from the disclosure of Chiang and Wang, the Petition *admits* Lo’s method “had been previously applied” in Chiang and Wang. Moreover, Xie was analogously applied during prosecution by the Examiner for allegedly teaching mapping “sets of shotgun reads by sequence alignment on a template wherein the mapped region is analyzed [] and DNA copy number variations (CNVs) are detected.” EX2001, pp. 436.

By citing Lo, the Petition is relying on *substantially the same art* (as Chiang, Wang, and Xie) that was already considered by the Examiner during prosecution.

B. The petition fails to identify any error by the Examiner

Despite relying on art that it *admits* is substantially the same as art considered by the Examiner during prosecution, the Petition fails to explain why or how the

Examiner erred.

Importantly, during prosecution of the ‘510 Patent, the Examiner considered *and withdrew* a rejection that mirrored the argument for unpatentability advanced by the Petition, citing one reference (Casbon) for its teaching of tagging, amplifying, and sequencing nucleic acid molecules, and citing a second reference (Xie) for its teaching of mapping sequence reads to a reference genome for the purpose of determining copy number variations.

The Petition alleges that “[d]uring prosecution, the examiner rejected the ‘510 claims as obvious over two prior art references not used in this Petition” (Paper 1 at 10), nakedly asserting that “the distinctions cited by the Patent Owner from those prior art references are obvious based on the references of Lo, McCloskey, Brenner, Chee, and Porrecca described below.” (*Id.* at 11). But the Petition does not explain what precise teachings in Lo, McCloskey, Brenner, Chee, and Porrecca go beyond the teachings of Xie and Casbon applied during prosecution.

Furthermore, the Petition ignores (1) the examination of the parent patent by the same Examiner, where there is a clear record of Brenner being applied in a rejection, and (2) the IDSs citing Brenner in this ‘510 Patent. Thus, the Petition ignores the *Ecto World* requirement that the Petition provide analysis of art disclosed in an IDS, even if not applied.

The Petition fails to identify *any* error by the Office in examining the subject

patent. Denial of institution is appropriate for that reason alone.

IV. THE WEAKNESS OF THE UNPATENTABILITY CHALLENGE WEIGHS IN FAVOR OF DENIAL

The Director’s March 26, 2025 Memorandum identifies “[t]he strength of the unpatentability challenge” and “[t]he extent of the petition’s reliance on expert testimony” as two relevant factors. EX2003 at 2. The Petition’s use of its expert to fill gaps in the prior art, and presentation of arguments that contradict previous arguments advanced by Guardant, further evidence the weakness of the Petition.

A. The Petition’s reliance on expert testimony evidences its weakness

The Petition improperly relies solely on the bare assertions of its expert to fill in pieces of its alleged obviousness rationale, as will be detailed in the POPR.

As an example, supported solely by its expert’s bare assertions, the Petition alleges that a POSA would have been motivated to combine the tagging of McCloskey, Porreca, Chee, or Brenner with the method described in Lo because “[i]t offered a known solution to a known problem: the need to improve the accuracy of counting molecules, particularly in situations where few sample DNA molecules are provided” (Paper 1 at 26, citing EX1002 at ¶¶148-149) and because “this technique was one of only a small number of options available for improving the accuracy of counting and was well within the technical grasp of a skilled artisan.” *Id.*

These opinions by the expert lack any substantiating evidence. They also

contradict Lo, who nowhere mentions any “need to improve the accuracy of counting molecules” in its methods. Notably, Lo does not cite to McCloskey, Porreca, Chee, or Brenner, let alone their tagging methods as a solution, despite these techniques being allegedly “only a small number of options available for improving the accuracy of counting.”

Further, again relying solely by its expert’s opinion, the Petition alleges that “Lo is based on counting, and therefore a POSA would naturally think to include tagging as an extension of Lo’s method because tagging was specifically intended for improving the accuracy of molecular counting.” *Id.* at 27, citing EX1002 at ¶150. Here too, the expert’s opinion lacks any substantiating evidence regarding a need “for improving the accuracy of counting molecules” in the methods of Lo or how tagging would improve the accuracy of counting in Lo.

Finally, and again supported by nothing more than its expert’s opinion, the Petition alleges that because “Lo explains that ‘fetal DNA is present in low absolute concentration’ in maternal plasma, creating a low signal problem [] a POSA would have been motivated to combine the tagging techniques known in the art with the amplification techniques described below in step [1C] to increase the signal-to-noise ratio.” *Id.* at 29, citing EX1002 at ¶152. Beyond lacking evidence, Petitioner’s expert fails to explain how the “tagging techniques known in the art” would accomplish “increas[ing] the signal-to-noise ratio” in the context of Lo.

B. The Petition fails to specify the grounds with particularity

Discretionary denial is also appropriate because the Petition fails to identify “with particularity, each claim challenged” (35 U.S.C. §312(a)(3)). Where a petition fails to meet the particularity requirement, the Board may exercise its discretion to deny the entire petition. *Adaptics Ltd. v. Perfect Co.*, IPR2018-01596, Paper No. 20 at 24 (PTAB Mar. 6, 2019) (informative).

First, the Petition inexplicably cites four secondary references McCloskey, Chee, Brenner, or Porreca *in the alternative* for the *same* teachings: “This Petition relies upon four references that teach the use of tagging, amplification, and sequencing for molecular counting: McCloskey, Chee, Brenner, and Porreca.” Paper 1 at 10; *see also* Paper 1 at 23. Citing four secondary references for the same teaching without (1) any stated reason for why one reference would not have been sufficient and (2) any indication of what possible combinations are actually asserted, is a clear failure of the Petition to present its challenges with particularity.

Second, the Cooper Declaration is 141 pages long with 284 paragraphs. The Petition repeatedly incorporates argument from the declaration rather than providing them in the Petition. *See e.g.* Paper 1 at 18 (citing 5 paragraphs from Dr. Cooper to assert that “there nothing about the method in Lo that would limit it to [] applications” of cell-free DNA from pregnant women without explanation); and *id.* at 39 (citing 4 paragraphs of the Cooper Declaration to assert that Lo “discloses how

to use the counted sequence tags to derive an estimation of relative copy number” without explanation).

This conclusory approach fails to specify the grounds with particularity, and improperly attempts to incorporate arguments from the expert declaration rather than providing them in the Petition itself. *See Cisco Systems, Inc. v. C-Cation Techs., LLC*, IPR2014-00454, Paper 12 (PTAB Aug. 29, 2014) (informative).

C. The Petition impermissibly relies on expert testimony to supply missing claim elements

37 CFR § 42.104(b)(4) requires that a petition “specify where each element of the claim is found in the prior art patents or printed publications relied upon,” and per 35 U.S.C. § 312(a)(4), the Board shall deny a petition that fails to comply with the regulations promulgated by the director, including 37 CFR § 42.104(b)(4). Here, the Petition alleges throughout that the claims “are obvious in further view of the *knowledge of the skilled artisan.*” The Petition’s failure to comply with 37 CFR § 42.104(b)(4) will be discussed in more detail in the POPR, but the Petition’s impermissible reliance on Dr. Cooper to supply missing claim elements is particularly stark in Grounds 3 and 6. *See* Paper 1 at 54 (relying solely on Dr. Cooper’s statements for obviousness of fragmentation techniques) and at 64 (relying solely on Dr. Cooper’s statements for obviousness of tags with variable portions, tags consisting of limited species of nucleotides, or consisting of sets of

dinucleotides or sets of trinucleotides). By relying on the “knowledge of a POSA” solely from Dr. Cooper’s opinion, the Petition plainly goes beyond the teachings of prior art patents and publications.

D. Petitioner’s central arguments in this IPR are inconsistent with the positions it has previously taken

Central arguments in the Petition are contradicted by positions Petitioner has taken elsewhere while defending and enforcing its own *later filed* patents, as explained below and as will be described in more detail in the POPR.

The claims here recite a step of determining copy number information based on the “number of unique tagged nucleic acid molecules that have been assigned to each of the plurality of locations in the genome.” EX1001 35:40-43. The recited “unique tagged nucleic acid molecules” each comprise “a segment of [...] the genomic nucleic acids” and “a nucleic acid tag.” *Id.* 35:25-27. Thus, the step of determining copy number information based on the “number of unique tagged nucleic acid molecules that have been assigned to each of the plurality of locations in the genome” is based on the number of molecules that have a combination of (i) a “*nucleic acid tag*” sequence and, and (ii) a sequence of the “*segment*” assigned to “a location ... by mapping.” EX1001, 35:34-36. *See also* EX1001, 15:5-14.

In the Petition, Guardant along with their expert acknowledge that a “difference between this claim step” and the prior art “is that this claim step involves

counting ‘unique tagged nucleic acid molecules.’” Paper 1 at 40. However, they allege that “a skilled artisan would have found it obvious to include tagging and amplification with Lo’s method. Having been motivated to modify Lo’s method to use tagging and amplification, a POSA would have naturally counted the ‘unique’ molecules.” *Id.* Notably, in Ground 5 Guardant asserts that “[a] POSA would have been motivated to adopt the approach where uniqueness is conferred by the combination of target sequence and tag because, although a large population of tags is beneficial, it may not be cost-effective in all cases to generate a large enough number of targets to give each target molecule a unique tag.” Paper 1 at 60.

Yet, when asserting its own *later-filed* patents in a District Court litigation, Guardant has argued that “grouping sequencing reads into families based on sequence information of the molecular barcodes,” i.e. using *nucleic acid tags*, “and beginning and end base positions of the mapped portion of progeny polynucleotides,” i.e., a *segment* sequence, “*was not routine, well-understood, or conventional*, as it leverages a *combination of barcode sequence and mapping location* [] to provide unique grouping to families using non-unique tagging.” EX2008 at 25 (Plaintiffs’ First Amended Complaint for Patent Infringement, *Guardant Health, Inc., v. Tempus AI, Inc.* 1:24-cv-00687-RGA (D. Del. filed November 4, 2024)).

Additionally, in IPR2019-00130, relying on an analogous argument, Guardant

avoided institution of an IPR against its own U.S. Patent No. 9,598,731 (with an earliest priority date of September 4, 2012) in part because it persuaded the Board that it would not have been obvious to use “non[-]unique *barcodes*”, which “*in combination with sequence data at the beginning (start) and end (stop) portions* of individual sequencing reads [] may allow for the assignment of *a unique identity* to individual sequences.” EX2006, pp. 5 and 27 (*Foundation Medicine, Inc., v. Guardant Health, Inc.* IPR2019-00130, Paper 7 (March 6, 2019)).

Thus, while defending and enforcing its later-filed patents, Guardant had argued that “grouping sequencing reads into families based on sequence information of the molecular barcodes and beginning and end base positions of the mapped portion of progeny polynucleotides” was not routine, not well-understood, and not conventional because it “leverages a *combination of barcode sequence and mapping location* [] to provide unique grouping to families” EX2008 at 25. However, in this attempt to attack CSHL’s patents that were filed years *before* those Guardant patents, Guardant takes the opposite position. Such contradiction further shows the weakness of the Petition and counsels against institution.

V. CONCLUSION

Numerous factors favor discretionary denial. Patent Owner respectfully requests that the Director deny institution of this IPR.

Respectfully submitted,

/Gary J. Gershik/

Dated: October 1, 2025

Gary J. Gershik
Registration No. 39,992
Darren Haber
Registration No. 80,964
Kenneth George
Registration No. 30,259
405 Lexington Avenue, 48th Floor
New York, NY 10174
(212) 336-8000

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 II.C.iii because this brief contains 20 pages.

/Darren Haber/

Dated: October 1, 2025

Darren Haber (Reg. No. 80,964)

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 IPR2025-01353

Patent 12,234,510

CERTIFICATE OF FILING AND SERVICE

The undersigned hereby certifies that true and correct copies of PATENT OWNER'S DISCRETIONARY DENIAL OF INSTITUTION BRIEF and EXHIBITS 2001-2006 and 2008-2012 are being electronically filed via The Patent Trial and Appeal Case Tracking System (P-TACTS) system and served this 1st day of October 2025 by electronic service by agreement between the parties pursuant to 37 C.F.R. §42.6(e)(1), via electronic mail at the email addresses listed below:

dwalter@jonesday.com

mwjohnson@jonesday.com

GH_CSH_Lab@jonesday.com

Dated: October 1, 2025

/Darren Haber/

Darren Haber (Reg. No. 80,964)