

**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 IPR2025-01353

Patent 12,234,510

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**PATENT OWNER'S PRELIMINARY RESPONSE**

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**EXHIBIT LIST**

| <b>Exhibit No.</b> | <b>Description</b>                                                                                                                                                                                                       |
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| 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                                                                                      |
| 2013               | July 31, 2025 Memorandum from Director Coke Morgan Stewart titled “Enforcement and Non-Waiver of 37 C.F.R. § 42.104(b)(4)                                                                                                |
| 2014               | Supporting Information for 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)  |
| 2015               | Reinartz, Jeannette, et al., <i>Massively parallel signature sequencing (MPSS) as a tool for in-depth quantitative gene expression profiling in all organisms</i> . Briefings in Functional Genomics 1.1 (2002): 95-104. |

## **I. INTRODUCTION**

Patent Owner Cold Spring Harbor Laboratory (“CSHL” or “PO”) is a not-for-profit research institution that has been investing in research at the cutting edge of biomedical science since its founding in 1890. CSHL is recognized as one of only seven National Cancer Institute-designated Basic Laboratory Cancer Centers and has been particularly influential in investigating relationships between cancer and genomics.

U.S. Patent No. 12,234,510 (“the ‘510 Patent”) is an example of the important discoveries that have come out of CSHL’s research. It covers innovative methods that allow for obtaining accurate genomic copy number information, which is an important tool, particularly in the diagnosis of certain cancers. The patented technology was developed in the CSHL laboratory of Dr. Michael Wigler, a renowned scientist who has been researching at CSHL for 47 years to find ways to better detect and treat serious diseases. For several decades Dr. Wigler’s lab has studied the molecular basis of cancer, in particular the genetic mutations that drive the evolution of cancer. His lab is specifically interested in copy number and point mutations, and using them for prognostication, early detection, and building models of medical disorders.

The Petition falls short of establishing any reasonable likelihood of prevailing. Petitioner relies on five references which, regardless of how they are combined, lack

any disclosure of the two final steps of claim 1, the only challenged independent claim. Boiled down, Petitioner presents nothing more than a legally flawed argument that the claimed method was inherent in some unspecified combination of five references. Petitioner cannot prevail on any of its Grounds.

Initially, Petitioner's arguments rely on a wholly unsupported claim interpretation. This is a threshold issue for the Petitioner to prevail. Petitioner's contention that Lo teaches "obtaining relative 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" as recited in step (f) relies on Lo's disclosure of counting the number of sequences "originating from particular chromosome(s) or *chromosomal regions*."<sup>1</sup> This argument not only ignores the fact that Lo never uses tagging (or provides any reason to use "tagged nucleic acid molecules"), it requires improperly construing "location" to mean "chromosomal region" with no support. However, a "location" is not the same thing as a "region" that contains multiple locations. Petitioner does not even attempt to explain how its interpretation comports with the claim construction standards of *Phillips*. Petitioner thus cannot align its own flawed obviousness theory to the independent claim because Lo does not teach "obtaining relative copy number information [] based on

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<sup>1</sup> All emphasis herein is added, unless otherwise specified.

the number of unique tagged nucleic acid molecules that have been assigned to each of the plurality of locations in the genome” as recited in step (f).

Compounding this deficiency, none of Petitioner’s cited prior art references teach the “assigning” step (e) of claim 1, or the “obtaining relative copy number information” step (f) of claim 1. Without explanation, Petitioner alleges that each of these steps would somehow “necessarily” or “naturally” result if other steps of the method taught by primary reference Lo were modified to add amplification and tagging. As discussed below, the proposed modification of Lo’s other steps does not make sense, but even if it did, the Petition fails to provide any explanation that both step (e) and step (f) would *necessarily* result.

The deficiencies are further compounded by Petitioner’s flawed motivation theory for combining Lo with one or more secondary references. The motivation theory is fatally flawed because it ignores explicit teachings of Petitioner’s prior art that contradict Petitioner’s motivation theory. Petitioner’s entire theory is premised on the allegation that a POSA would have been motivated to use the tagging and amplification methods taught in the secondary references to improve the accuracy of molecular counting in Lo. But the idea that a POSA would be motivated to add tagging when using Lo’s method is contradicted by Lo and Chiu (EX1011), a related publication from Lo’s lab, which establish that *tagging is not used or needed* in Lo’s method despite use of PCR amplification.

Thus, Petitioner’s motivation theory rests entirely on the flawed notion of solving a problem that in fact did not exist in Lo’s methods. It is telling that Petitioner omits to address why neither Lo nor Chiu, who were sufficiently skilled at the time and knew that tagging was an available technique, did not use tagging to generate unique tagged nucleic acid molecules in Lo’s method.

*Finally*, faced with gaps in its prior art, Petitioner resorts to its expert to save its validity challenges. But that approach does not pass muster, even at the institution stage. First, Petitioner relies on conclusory and unsupported opinions of its expert to supply rationales to combine Lo’s method with methods of one or more of the secondary references—in direct contradiction with Petitioner’s own evidence. Second, the Petition impermissibly relies on the Cooper Declaration (EX1002) and generic assertions regarding “knowledge of a POSA” to supply claim limitations. Such an approach fails to specify where each element of the claim is found in the prior art, or to identify what particular combinations of the asserted prior art Petitioner is even relying on in its main Ground 1.

Each of these flaws is independently sufficient to deny institution in this matter, and when viewed collectively these issues highlight the weakness of the invalidity challenges here. For at least those reasons, explained in more detail below, the Petition fails to establish a reasonable likelihood of prevailing, and institution should be denied.

## II. BACKGROUND

### A. Overview of the ‘510 Patent

The ‘510 Patent, titled “Varietal Counting of Nucleic Acids For Obtaining Genomic Copy Number Information,” is directed to, *inter alia*, an innovative method of obtaining copy number information from a sample. In brief, copy number relates to the number of copies of a gene present in a genome which is an important tool in the diagnosis of certain cancers. EX1002, ¶80.

At the time of the invention, one method of obtaining copy number information from a genome, called “whole genome amplification” (“WGA”), involved amplification of an entire genome from DNA that may have been obtained from a single cell, followed by sequencing. One challenge that was identified by the inventors of the ‘510 Patent for obtaining accurate copy number information in this sequencing-based method was the distortions that may result from the amplification and sampling of nucleic acids. As noted in the background of the ‘510 Patent, one problem with WGA “is over-sampling of certain regions, yielding a non-uniform amplification of the genome.” EX1001, 1:39-40. Thus, “it is difficult to obtain single cell measurements, particularly when based on WGA, due to distortions that originate from stochastic sampling and amplification steps.” *Id.* at 1:53-55.

The ‘510 patent explains that its methods allow for obtaining accurate copy number information. The ‘510 patent explains that the method overcame prior

problems—as one example, amplification bias producing inaccurate copy number information—with a novel and innovative solution:

The invention provides the following advantages: (1) the method is simple; (2) with statistical analysis the confidence of a measurement can be determined with great accuracy; (3) this is a sequence based method, which in the long run will be cheaper than arrays; (4) long read lengths are not necessary, providing savings; (5) because tagged nucleic acid molecules are counted, many processing methods that create distortion in yields can be applied without major loss in the tagged nucleic acid molecule count; (6) among these processing methods are hybrid selection (aka capture microarrays), which restrict the sequence information to regions of importance, and thus reduce cost by reducing the total number of reads per sample needed for determination of the desired information; (7) the molecules from one sample can be combined with tags and a sample tag, creating sample tagged nucleic acid molecules which can then be pooled, and after processing and sequencing, the sample tags decoded, giving a profile for each sample; (8) pooling adds efficiency and uniformity; (9) the samples can be individual cells, yielding large numbers of single cell measurements cheaply.

EX1001, 30:8-29.

The inventive concepts of the '510 patent represented a significant improvement in the early detection of cancer and addressed a need in the field:

DNA prepared by WGA methods is hampered by the copy number distortions introduced by non-uniform amplification of genomic DNA. Thus, there exists a need for a method that allows for copy number determination free of distortions caused by amplification steps and which allows for accurate and efficient copy number determination of complex samples.

EX1001, 2:29–37.

## **B. Overview of the References**

### **1. Lo (EX1010)**

Lo describes a method for “determining whether a nucleic acid sequence imbalance (e.g., chromosome imbalance) exists within a biological sample obtained from a pregnant female.” EX1010, ¶14. *See also* EX1002, ¶83. The method involves receiving a “biological sample”, such as from a “pregnant female” (EX1010, ¶54), “sequencing at least a portion of a plurality of nucleic acid molecules contained in the biological sample” (*Id.* ¶55), and aligning the sequence reads “to the human reference genome sequence” so the “chromosomal origin [can be] noted.” *Id.* ¶70.

To identify “[c]hromosome gains or losses,” “the total number of individual [sequences] aligned to each chromosome [are] tabulated and compared with the relative size of each chromosome as expected from the reference human genome or non-disease representative specimens.” *Id.* ¶70. *See also* EX1002, ¶89.

As noted in Lo and acknowledged by Petitioner's expert, the sequence reads generated in Lo "form a representative profile of the mix of nucleic acid species in the original specimen" (EX1002, ¶87, *citing* EX1010, ¶ 57) such that "the dosage imbalance of the chromosome or chromosomal regions" in the original specimen can be "inferred from the percentage representation of the sequences from the region of interest among other mappable sequences obtained from the specimen." EX1010, ¶67.

*a. Lo's method involves sequencing only a "fraction" of the genome*

Lo's method relates *specifically* to sequencing only a "fraction" of the genome to determine a nucleic acid sequence imbalance. *See, e.g.*, EX1010, FIG. 1. step 120 ("Sequence ***fraction*** of genome in sample") and its associated description at ¶55 ("In step 120, at least a portion of a plurality of the nucleic acid molecules contained in the biological sample are sequenced. The portion sequenced represents a ***fraction*** of the human genome."); *Id.*, FIG. 2. step 230 ("Randomly sequence ***fraction*** of genome"); *Id.*, ¶14 ("Nucleic acid molecules of the biological sample are sequenced, such that a ***fraction*** of the genome is sequenced."); *Id.*, ¶50 ("Nucleic acid molecules of the biological sample are sequenced, such that a ***fraction*** of the genome is sequenced"); *Id.*, ¶67 ("As mentioned above, only a ***fraction*** of the genome is

sequenced.”); and claim 1, lines 9-10 (“wherein the sequenced portion represents a *fraction* of the human genome”).

Lo specifically defines the term “fraction of the human genome,” in the context of sequencing, in paragraph 48:

The term “fraction of the human genome” or “portion of the human genome” as used herein refers to less than 100% of the nucleotide sequences in the human genome which comprises of some 3 billion basepairs of nucleotides. *In the context of sequencing, it refers to less than 1-fold coverage of the nucleotide sequences* in the human genome.

EX1010, ¶48. Further, Lo specifically *contrasts* sequencing “only a fraction of the genome” as in its method, with “situations where the same pool of nucleic acids is sequenced multiple times to achieve high redundancy or several folds of coverage whereby each nucleic acid species is sequenced multiple times” (EX1010, ¶68). It explains that “[i]n such situations, the number of times a particular nucleic acid species have been sequenced relative to that of another nucleic acid species correlate with their relative concentrations in the original sample,” where “sequencing cost increases with the number of fold coverage required to achieve accurate representation of the nucleic acid species.” *Id.*

As discussed in Lo, when sequencing only a fraction of the human genome, “by statistics, *most of the maternal plasma DNA fragment species would only each*

*have been sequenced to generate one sequenced tag count.* In other words, the nucleic acid fragments present in the maternal plasma specimen were sequenced *at less than 1-fold coverage*. Thus, the total number of sequenced nucleotides for any particular chromosome would mostly correspond to the amount, proportion or length of the part of the said chromosome that has been sequenced.” EX1010, ¶76.

Thus, in contrast to “situations where the same pool of nucleic acids is sequenced multiple times to achieve high redundancy or several folds of coverage whereby each nucleic acid species is sequenced multiple times,” where “sequencing cost increases with the number of fold coverage” (EX1010, ¶68), in Lo’s method, *each nucleic acid species generally is only sequenced once*. See *id.* at ¶67 (“...among the proportion of captured nucleic acid molecules, most of each nucleic acid species is only sequenced once”) and ¶76 (“by statistics, most of the maternal plasma DNA fragment species would only each have been sequenced to generate one sequence[ ]”).

This is confirmed by Chiu (EX1011)—a “related 2008 publication by Lo” that is cited and relied on by Petitioner’s expert because it “neatly explains the method in Lo” (EX1002, ¶88)—which states that in implementing the method of Lo, “[t]he majority of DNA fragments are *sequenced once*, if at all. The relative chromosome size is then deduced by counting the relative number of sequences aligned to the chromosome. *Each of the counted DNA fragments would be of a different nucleotide*

*sequence.*” EX1011.005, left-hand column. Not surprisingly, neither Lo nor Chiu teach, suggest or even mention tagging.

**2. McCloskey, Brenner, Chee, and Porreca (EX1008, EX1014, EX1015, and EX1017) (“the Secondary References”)**

The Petition explicitly states that it relies on McCloskey, Brenner, Chee, 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. *See also* Paper 1 at 23 (alleging that “it would have nonetheless 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.”) Because the teachings of McCloskey, Chee, Brenner, and Porreca are relied upon by Petitioner in the alternative, these references are collectively referred to herein as “the secondary references.”

As discussed in PO’s Discretionary Denial Brief (Paper 6), Petitioner’s citation to four different references 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. Nevertheless, as discussed below the methods described in each reference are fundamentally at odds with Lo’s method. While Lo *successfully* detects chromosomal imbalances by sequencing DNA at less than 1-

fold coverage, such that the majority of DNA fragment species are sequenced only *once*, if at all, each of the Petition's secondary references employ tagging to help elucidate the number of original nucleic acid molecules when *several copies of the same original nucleic acid molecule are sequenced* following PCR amplification. A consequence of the fundamental differences between Lo and the secondary references is that the rationales proposed by the Petitioner for combining their teachings all fail.

*a. McCloskey (EX1008)*

McCloskey describes a method “by which molecular codes are added to single-stranded DNA or cDNA templates” prior to PCR amplification utilizing an “encoding oligonucleotide”. EX1008.002. Each encoding oligonucleotide includes, among other things, a random barcode that distinguishes among sequences arising from different cell or allele copies, and a genomic target-binding site that targets the locus to be encoded prior to amplification. *Id.* The genomic target-binding site is designed to *target a specific genetic locus* for amplification (EX1008.003-004), while the barcode sequence allows one to “*detect redundant sequences arising from the same cellular DNA template.*” EX1008.006.

McCloskey's method is fundamentally at odds with Lo's method because as noted above, in Lo's method, “by statistics, *most of the maternal plasma DNA fragment species* would only each have been *sequenced to generate one sequenced*

**tag count.”** EX1010, ¶76. Thus, in Lo’s method there are no “redundant sequences arising from the same cellular DNA template” that need to be distinguished from one another using a barcode as in McCloskey. Moreover, the genome target-binding site in the encoding oligonucleotide of McCloskey **targets a specific genetic locus** for amplification, which is incompatible with Lo’s entire method, because Lo’s method depends on generating sequence reads that “form a representative profile of the mix of nucleic acid species in the original specimen” (EX1002, ¶85, *citing* EX1010, ¶ 57). *Cf.* EX1010, ¶83 (“As the sequencing is random, a different subset (fraction) of the nucleic acid molecules (and thus the genome) may be sequenced in each analysis.”).

**b. Brenner (EX1014)**

Brenner teaches a method for estimating the number of target polynucleotides in a mixture. EX1014 at 3:15-24. In Brenner’s method, target oligonucleotides “are each associated or linked, e.g. by ligation, to an oligonucleotide tag from a population that has a much larger size than that of the target polynucleotide population.” *Id.* at 17:61-64. After the tagged polynucleotides are generated, the tags are amplified using PCR (*Id.* at 3:20-21) and the number of different oligonucleotide tags in the sample of amplified oligonucleotide tags are counted to determine the number of target polynucleotides in the starting sample. *Id.* at 3:30-34.

Like McCloskey's method, Brenner's method is fundamentally at odds with Lo's method because while Brenner relies on counting the number of unique tags to quantify the number of target polynucleotides in a sample, Lo's method quantifies "the amount, proportion or length of the part of [a] chromosome" in a sample based on "the total number of sequenced nucleotides for [that] particular chromosome." EX1010, ¶76. Lo's method is able to rely on the total number of sequenced nucleotides because "by statistics, *most of the maternal plasma DNA fragment species* would only each have been *sequenced to generate one sequenced tag count*," (*id.*) making the unique tagging of target polynucleotides completely unnecessary.

*c. Chee (EX1015)*

Chee describes a method by which "oligonucleotide constructs" containing a "region of interest" (ROI) and a "unique identifier" are amplified. EX1005, 13:21-25. Following amplification, the "oligonucleotide constructs" are sequenced to determine the sequence of the ROI and the unique identifier of each construct. *Id.* at 14:3-25. As explained in Chee, bias in amplification of certain sequences, "can be identified by determining the amounts of constructs with unique identifiers." *Id.* at 23:56-59. "[I]f a nucleic acid is either over-represented or under-represented due to amplification bias, the number of molecules comprising unique identifiers will also be over-represented or under-represented." *Id.* at 23:59-63. Thanks to the "unique

identifier” in each construct, “amplification products can be identified as originating from a single construct, even when constructs have ROIs that are very similar or identical in sequence.” *Id.* at 24:2-4.

Like McCloskey’s and Brenner’s methods, Chee’s method is fundamentally at odds with Lo’s method. While in Chee’s method a “unique identifier” included in each original construct is used to identify amplification products originating from a single construct, in Lo’s method “by statistics, *most of the maternal plasma DNA fragment species* would only each have been *sequenced to generate one sequenced tag count*” (EX1010, ¶76). Because DNA fragment species are only sequenced once in Lo’s method, inclusion of a “unique identifier” in each DNA fragment as in Chee would serve no purpose.

***d. Porreca (EX1017)***

Porreca discloses tagging target nucleic acid sequences of interest with differentiator tags (EX1017 at 29:4-6) followed by amplification and sequencing of the tagged molecules. *Id.* at 72:11-12 and 45-47. In its methods, the differentiator tags are used “to distinguish independent target molecules from each other....” *Id.* at 28:29-30. As noted in Porreca, “if each of the plurality of target molecule sequences obtained in the assay is associated with the same differentiator tag, then they probably all originated from the same target molecule due to over-representation (e.g., due to biased amplification) of this target molecule in the

assay.” *Id.* at 28:37-42. “For any target:differentiator tag combination observed more than once, all such reads are ‘collapsed’ into a single read before consensus basecalls are determined.” *Id.* at 72:67-73:2.

Like the methods of all the other secondary references, Porreca’s method is fundamentally at odds with Lo’s method. In Porreca’s method *multiple sequence reads* are obtained from copies of the same original target molecule. These sequence reads are then identified and collapsed with the aid of a differentiator tag. By contrast, in Lo’s method there is no need to use a differentiator tag to identify and collapse multiple sequence reads obtained from copies of the same original target molecule because “by statistics, *most of the maternal plasma DNA fragment species* would only each have been *sequenced to generate one sequenced tag count*” (EX1010, ¶76).

### C. The Level of Ordinary Skill in the Art

Petitioner alleges a level of ordinary skill in the art. Paper 1 at 20-21. For the purpose of this POPR, Patent Owner does not object to Petitioner’s characterization of a person of ordinary skill in the art (“POSA”), except for Petitioner’s self-serving assertion that “a POSA would have been familiar with associated tools, methods, and techniques including: (1) DNA tagging, (2) amplification, (3) use of tags to overcome amplification bias, (4) sequencing, (5) aligning and counting of sequence reads.” This addition is a transparent attempt to bring the innovative claimed

methods of the ‘510 Patent within the POSA’s routine practice by simply saying—without support—that the POSA would have known about the inventive methods. Petitioner cannot skirt the requirements of 35 U.S.C. § 311(b)—by simply alleging that claim elements were within the generic knowledge of a POSA.

Nevertheless, as discussed herein, Petitioner’s challenges fail even under its own proposed level of ordinary skill in the art.

PO reserves the right to dispute the level of ordinary skill in the art alleged by the Petitioner, and propose an alternative level, if this IPR is instituted.

### **III. PETITIONER’S GAMBIT ON CLAIM CONSTRUCTION WARRANTS DENIAL**

For the purpose of the Petition, Petitioner alleges that they interpret the claims “consistent with PO’s arguments and positions in the parallel district court proceedings.” Paper 1 at 20, *citing* EX1020. They request that “the Board understand the claims consistent with the apparent interpretations that PO is pursuing in parallel district court litigation” asserting that “[t]he portions of PO’s infringement contentions illustrating their claim interpretations are cited herein where appropriate.” *Id.*

In the Petition, PO’s infringement contentions (EX1020) are cited to argue for an interpretation of “location” as recited in step (f) of claim 1 (Paper 1 at 39), which

is nothing more than a transparent hindsight-driven attempt to read the claims onto the Lo reference.

Petitioner's approach is a strategic—and improper—attempt to skirt the requirements for establishing invalidity in a Petition by not taking a position on a claim interpretation that is critical to Petitioner's challenge. 37 C.F.R. § 42.104(b)(3) (Petitioner is required to identify “[h]ow the challenged claim is to be construed.”). Instead, Petitioner attempts to pin the broad read of “location” on PO, *without notifying the Board that it is Petitioner, and not PO, that is now proposing a construction of “location” that explicitly encompasses “chromosomal region” in the co-pending Delaware Litigation.*<sup>2</sup> Petitioner's strategic gambit on claim construction here alone warrants denial of institution because it is deficient in at least two respects.

*First*, Petitioner does not discuss any legal principle or any intrinsic evidence that supports construing the claim term in the manner Petitioner interprets it in the Petition. Petitioner's hand-waving non-specific citation to infringement contentions falls far short of providing a sufficient basis to support institution under *Phillips*. See

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<sup>2</sup> The ‘510 Patent is asserted by PO against Petitioner in *Cold Spring Harbor Laboratory v. Guardant Health, Inc.*, C.A. No. 25-263-JCG (May 1, 2025 D. Del.) (the “Delaware Litigation”).

*Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005); *see also* 37 CFR 42.104(b)(3). **Second**, the scant evidence Petitioner does cite for its interpretation of “location” (general citation to PO’s 351 page infringement contention document) provides no support for Petitioner’s broad read to encompass “chromosomal region”.

**A. Petitioner Does Not Even Attempt to Justify Its Interpretation of the Claim Term “Location” Under the *Phillips* Standard.**

Petitioner relies on Lo’s disclosure of counting the number of sequences “originating from particular chromosome(s) or *chromosomal regions*” to allege that Lo teaches “counting the number of unique tagged nucleic acid molecules that have been assigned to the same *location*.” Paper 1 at 38. But Petitioner, tacitly acknowledging that Lo’s disclosure does not match up to the challenged claim, dodges its obligation to support the claim interpretation required by its Petition. Rather than actually justify a construction of the claim term “location” to mean “chromosomal region” under *Phillips*—for example by analyzing the ordinary and customary meaning or intrinsic evidence—Petitioner merely alleges that “Lo’s mapping to a ‘chromosomal region’ is *consistent with PO’s broad reading of ‘location’* in the parallel district court litigation.” Paper 1 at 39. Petitioner’s allegation falls short of the requirement under 37 C.F.R. § 42.104(b)(3) to identify “[h]ow the challenged claim is to be construed.” Petitioner does not even mention *Phillips*, does not analyze any intrinsic evidence, and wholly fails to provide any

coherent explanation to support its claim interpretation. This is exactly the type of deficiency that warrants denial of the entire Petition. *Robert Bosch LLC v. Orbital Austl. PTY Ltd.*, IPR2015-01249, Paper 9 at 6, 8, 11 (Dec. 21, 2015) (denying institution when petition “include[d] no explanation for the proposed construction” and “no analysis of the claim language, the written description, or the prosecution history”).

Petitioner cites to *Hospira, Inc. v. Amgen Inc.*, IPR2021-00528, Paper 7 at 7 (P.T.A.B. Aug. 17, 2021) for the proposition that “all that rule [42.104(b)(3)] requires is for the Petition to identify ‘[h]ow the challenged claim is to be construed’”. Paper 1 at 20. But that is exactly the point Petitioner fails on, as specifying how the challenged claim is to be construed requires some coherent explanation (or at the very least an attempt at such explanation) with proper supporting evidence. In *Hospira* the Petitioner explicitly proposed concrete constructions of claim terms that had been advanced by the Patent Owner in a joint claim construction statement in parallel district court litigation. *Hospira, Inc. v. Amgen Inc.*, IPR2021-00528, Paper 2 at 11-14 (Feb. 10, 2021)

By contrast, here Petitioner fails to even propose a concrete construction of the term “location”, instead merely alleging “Lo’s mapping to a ‘chromosomal region’ is *consistent with PO’s broad reading of ‘location’* in the parallel district court litigation.” And instead of citing a concrete construction that was advanced by

Patent Owner in parallel district court litigation as in *Hospira*, Petitioner requests that the Board construe the term based on an interpretation that is only allegedly “apparent” from infringement contentions that did not advance any proposed construction that could align with Petitioner’s alleged interpretation here.

Moreover, even if Petitioner’s allegation is read to be an identification of “[h]ow the challenged claim is to be construed,” (i.e. that “location” is to be construed as “chromosomal region”), in making its allegation Petitioner cites **only generally** to EX1020 (PO’s Asserted Claims and Infringement Contentions for U.S. Patent Nos. 10,947,589 and 12,234,510 in the Delaware Litigation) to allege that PO has interpreted “locations” as **any** of “genes”, “genetic locus, and “start/stop positions”:

Lo’s mapping to a “chromosomal region” is consistent with PO’s broad reading of “location” in the parallel district court litigation. *See* EX1020 (interpreting locations as any of “genes,” “genetic locus,” and “start/stop positions”).

Paper 1 at 39.

The Petition’s citation to EX1020—a 351 page document—**as a whole** and without citation to a particular page of the document, much less a particular statement or set of statements, amounts to a failure to comply with 35 U.S.C. §

312(a)(3), because it fails to identify the evidence that supports the ground for the challenge “with particularity.”

Beyond the Petition failing to identify the evidence with *any* particularity, even the Cooper Declaration cites only *generally* to EX1020 (*See* EX1002 ¶188) and fails to identify any specific statement in PO’s infringement contentions that interprets “location” to mean “chromosomal region(s)” as required for Petitioner’s theory of obviousness. Without *any* explanation supporting their construction of “location,” Petitioner’s allegation fails to comply with 37 C.F.R. § 42.104(b)(3). *See, e.g., Robert Bosch LLC*, IPR2015-01249, Paper 9 at 6, 8, 11 (Dec. 21, 2015).

**B. The Alleged Interpretations in PO’s Infringement Contentions Do Not Justify Petitioner’s Hindsight-Driven Broad Interpretation of “Location”**

Moreover, a review and analysis of EX1020 (which the Petition and Dr. Cooper fail to provide) reveals *no statement* that interprets “location” as broadly as “chromosomal region(s)” as used in Lo’s method.

Although “genes,” “genetic locus,” and “start/stop positions” are mentioned in PO’s infringement contentions, the mere mention of these terms in the infringement contentions does *not* amount to an interpretation of “location” as “chromosomal region.” Indeed, Petitioner and Dr. Cooper never argue as much, only alleging that PO has interpreted “location” as “genes,” “genetic locus,” and “start/stop positions” (Paper 1 at 39) without providing any explanation *at all* of how

their generic citation to the infringement contentions and the alleged interpretation of “location” as “genes,” “genetic locus,” and “start/stop positions” support an interpretation of “location” as including “chromosomal region.” *See id.* at 39 and EX1002, ¶194.

No statement in EX1020 that mentions “genes,” “genetic locus,” or “start/stop positions” even *remotely* suggests an interpretation of “location” as recited in step (f) being as broad as an entire “chromosomal region” as used in Lo’s method. And indeed, neither Petitioner nor Dr. Cooper address statements in the ‘510 Patent that explain a “region of the genome” can be “a continuous genomic sequence comprising multiple discrete locations.” EX1001, 15:59-61.

#### **IV. PETITIONER FAILS TO SHOW A REASONABLE LIKELIHOOD OF PREVAILING ON ANY GROUND**

Petitioner has not demonstrated a reasonable likelihood of prevailing on any of its Grounds, including Ground 1, which is the only one that challenges the lone independent claim 1 of the ‘510 Patent. Because each of the Petition’s other grounds relate to dependent claims that necessarily cannot be obvious if claim 1 is not obvious, Petitioner has not demonstrated a reasonable likelihood of prevailing on *any* of its asserted grounds. Accordingly, institution should be denied.

**A. The Petition Fails to Show That the Prior Art Meets Each and Every Claim Limitation**

**1. Petitioner Fails to Establish that the Asserted Art Discloses Step (e) of the Claimed Method**

Step (e) of claim 1 recites “assigning each of the unique tagged nucleic acid molecules to a location on a genome by mapping each of the tag associated sequence reads of step (d) to a location in the genome.” The Petition alleges that Lo “teaches this claim element” (Paper 1 at 37) even though, incongruously, it acknowledges a “difference between this claim step and the method set forth in Lo is that this claim step involves mapping tagged and amplified nucleic acid molecules, whereas Lo aligns the sequences of the original sample molecules.” *Id.* The Petition then alleges that “[h]aving been motivated to modify Lo’s method to use tagging and amplification, a POSA would have *necessarily* sequenced and then aligned the sequences of the tagged and amplified molecules, according to the exact methods and techniques set forth in Lo.” *Id.* at 38.

As an initial matter, there is *no* rationale for a POSA to modify Lo’s method to use the tagging and amplification methods of the secondary references as discussed extensively in section IV.B and IV.C below. And Petitioner further fails to provide an obviousness analysis, with the requisite rationale, for performing step (e) of the claimed method in any proposed combination.

Petitioner attempts to bypass the need for an obviousness analysis by alleging that if Lo’s method was modified “to use tagging and amplification,” then that would *necessarily* lead a POSA to practice a step of “assigning each of the amplified tagged nucleic acid molecules to a location on a reference genome.” However, asserting that something would “necessarily” occur invokes the need for an inherency analysis, something that the Petition lacks entirely. *See Azurity Pharmaceuticals, Inc., v. Exelixis Inc.*, IPR2025-00210, Paper 11 at 27 (P.T.A.B. June 4, 2025) (denying institution in part because Petitioner provided no evidence that a claim element was a “necessary result” of the combined cited art.)

Accordingly, the Petition fails to show that the step of mapping an “amplified tagged nucleic acid molecules to a location on a reference genome” is obvious from the combined teachings of Lo and the secondary references.

## **2. Petitioner Fails to Establish that the Asserted Art Discloses Step (f) of the Claimed Method**

Step (f) of claim 1 recites “in a plurality of locations in the genome, obtaining relative copy number information of the genomic nucleic acids from the sample based on the *number of unique tagged nucleic acid molecules* that have been *assigned to each of the plurality of locations* in the genome.” Petitioner alleges that Lo teaches this step because it discloses “counting the number of sequenced tags, the number of sequenced nucleotides (basepairs) or the accumulated lengths of

sequenced nucleotides (basepairs) originating from *particular chromosome(s) or chromosomal regions*.” Paper 1 at 38. But, as discussed below, the claim interpretation Petitioner relies on is not supported by any evidence and its theory of obviousness relies upon a finding of inherency that Petitioner has also not supported.

***a. Petitioner’s failure to provide any coherent claim construction support dooms its assertions that Lo discloses step (f)***

As discussed in section III above, Petitioner does not even attempt to justify or substantiate their proposed construction under the *Phillips* standard. Instead, their proposed construction is based on an unsupported, conclusory misreading of PO’s infringement contentions in the Delaware Litigation. While the claimed method of the ‘510 Patent tags nucleic acid molecules to generate “unique tagged nucleic acid molecules” to assist with determining copy number based on the “number of unique tagged nucleic acid molecules that have been assigned to *each* of the plurality of locations in the genome”, as discussed above in section II.A, Lo’s method deduces chromosomal imbalance by counting DNA fragments that align to *anywhere* in a chromosome or chromosome region. Petitioner’s strategic gamble to duck its obligation to support its broad claim interpretation fails to show how Lo could meet the requirements of this claimed step and dooms the invalidity challenge.

***b. Petitioner’s assertion that step (f) is somehow inherent from a combination of the cited references is unsupported***

In the context of an obviousness analysis, where all limitations are not taught in single reference, inherency may provide a missing claim limitation only when the limitation is “the natural result of the *combination of prior art elements*.” *Persion Pharms. LLC v. Alvogen Malta Operations LTD.*, 945 F.3d 1184, 1191 (Fed. Cir. 2019) (emphasis in original). Petitioner and their expert acknowledge that step (f) is not taught in any of their cited prior art, but instead allege that “[h]aving been motivated to modify Lo’s method to use tagging and amplification, *a POSA would have naturally* counted the ‘unique’ molecules.” Paper 1 at 40. Consequently, Petitioner’s allegation relies on step (f) being a “natural result of the combination of prior art elements.” However, nothing in Lo’s method *requires* “in a plurality of locations in the genome, obtaining relative copy number information of the genomic nucleic acids from the sample based on the *number of unique tagged nucleic acid molecules* that have been *assigned to each of the plurality of locations* in the genome” as recited in step (f).

Lo's method counts ***all*** nucleic acid molecules that have been assigned to the same chromosome.<sup>3</sup> Petitioner's assertion that "[t]o count ***anything other*** than the unique molecules would defeat the purpose of using the tagging and amplification that the skilled artisan would have been motivated to use" (Paper 1 at 40) is an ***acknowledgement*** of the fact that nothing ***in Lo*** requires counting only unique tagged nucleic acid molecules and glosses over the fact that Lo counts ***all*** nucleic acid molecules that map to a chromosome.

Petitioner's further allegation that a POSA "would have naturally followed" guidance in Lo and "use ***only*** the unique sequence reads ***rather than*** counting duplicates and hence overinflating read counts" (Paper 1 at 41) is an admission that step (f) is far from the "natural result of the combination of prior art elements", but instead requires a POSA to make choices regarding what to count. Because step (f) is not the "natural result of the combination of prior art elements," Petitioner cannot prevail as to step (f) of independent claim 1. *See Azurity Pharmaceuticals*, IPR2025-00210, Paper 11 at 27 (P.T.A.B. June 4, 2025) (denying institution in part because Petitioner provided no evidence that a claim element was a "necessary result" of the

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<sup>3</sup> This is independent of whether Lo counts the number of unique nucleic acid molecules that have been assigned to each location of a plurality of locations, which Petitioner has not shown given its unsupported interpretation of the term "location."

combined cited art.) See also *Ovid Therapeutics Inc., v. Marinus Pharmaceuticals, Inc.*, IPR2024-00726, Paper 7 at 18-19 (P.T.A.B. Sept. 20, 2024) (denying institution in part because “Petitioner relies on inherency [] without providing evidence that such inherency exists.”)

*c. Petitioner’s assertion that step (f) is obvious is also contradicted by positions it has previously taken*

The deficiency of the Petition as to step (f) is underscored by the contradictory position Petitioner took in connection with its own *later-filed* patents in a District Court litigation, as explained in PO’s Discretionary Denial Brief (Paper 6) and discussed in more detail below.

Claim 1 recites 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 (P.T.A.B. 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.

Like the claim features that Guardant relied upon to allege non-obviousness of its ***later-filed*** Patents, step (f) along with step (e) of claim 1 leverage a

combination of a nucleic acid tag and a location on the reference genome. Thus, Guardant's own statements belie its assertions here that step (f) would somehow be obvious.

**B. Petitioner's Entire Theory of Obviousness Is Rebutted by Statements in Lo and Chiu**

The Petition relies heavily on Lo and asserts that its discussion of Lo is further supported by Chiu (EX1011). Chiu is a "related 2008 publication by Lo" that is cited by Petitioner's own expert because it "neatly explains the method in Lo" EX1002, ¶90. Indeed, *all three inventors of Lo*, i.e., Yuk-Ming Dennis Lo, Rossa Wai Kwun Chiu, and Kwan Chee Chan, are authors of Chiu. Chiu demonstrated that tagging (as taught in the secondary references) was *not used* and *not needed* in Lo's methods. Thus, all of Petitioner's offered reasons to combine Lo's method with the methods described in the secondary references (*see* sections IV.C.1 and IV.C.1), are contradicted by the teachings of Lo and Chiu. Yet, the Petition nowhere acknowledges much less confronts the contradictory teachings of Lo and Chiu.

Petitioner cannot prevail based on a Petition that lacks any discussion of the explicit, contradictory teachings of the primary reference and the related reference that describes implementation of its method.

**1. Chiu Implements Lo's Method With 15 Cycles of PCR Amplification and Successfully Distinguishes Between Euploid and Trisomy Cases**

Petitioner's expert explicitly relies upon the disclosure in the secondary references for the PCR amplification required by claim 1. EX1002, ¶160 (stating that PCR "is disclosed in each of Brenner, Porreca, Chee, and McCloskey" and "I rely upon that disclosure for this claim" element.) Petitioner's theory of obviousness conveniently ignores the disclosure of PCR amplification *already present* in both Lo and Chiu (EX1011), the "related 2008 publication by Lo" that is cited by Petitioner's expert because it "neatly explains the method in Lo." EX1002, ¶90.

Dependent claim 13 of Lo recites that "the nucleic acid molecules of the biological sample have been amplified using a polymerase chain reaction," demonstrating that the inventors of Lo understood that its method could be practiced with PCR amplification of the nucleic acid molecules of the biological sample (EX1010.021, claim 13). *Indeed*, Chiu demonstrates that when Lo's method was implemented by its inventors, 15 cycles of PCR amplification were used. Chiu describes testing two protocols, an "original protocol", which included 15 cycles of PCR amplification, a gel electrophoresis-based size fractionation step, and another

15 cycles of PCR amplification<sup>4</sup>, and a “new protocol” “whereby the gel electrophoresis and second amplification steps were omitted.” EX1011.004, left-hand column.

Chiu describes using the “new protocol”, employing 15 cycles of PCR amplification, to analyze maternal plasma DNA from 28 pregnancies, which included 14 women each pregnant with a euploid fetus and 14 women each pregnant with a T21 fetus:

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<sup>4</sup> See EX1011.002, right-hand column “[p]lasma samples obtained from four pregnant women carrying euploid fetuses (three males and one female) were processed using the beta ChIP-Seq protocol from Illumina, which ***included amplification*** of the adaptor-ligated DNA fragments both before and after (i.e., two rounds of amplification) a gel electrophoresis-based size fractionation step as described in supporting information (SI) Text.” See also the Supporting Information Text, EX2014, p. 1 (“The adapter-ligated DNA fragments were [] enriched using a 15-cycle PCR with standard primers. [...] [T]he enriched adapter-ligated DNA fragments in the range of 150-300 bp were size selected using 2% agarose electrophoresis. The selected DNA libraries were then additionally amplified using the same 15-cycle PCR.”)

Plasma samples were obtained in the first and second trimesters of pregnancies from 14 women each pregnant with a euploid fetus and 14 women each pregnant with a T21 fetus. [...] Plasma DNAs from the 28 pregnancies (median gestational age: 14.1 weeks) were processed by the *new protocol* and sequenced.

EX1011.004, left-hand column. Chiu's implementation of Lo's method, employing 15 cycles of PCR prior to sequencing, *successfully distinguished between every single euploid and trisomy case* using 11–50 ng of plasma DNA. See EX1011.006, left-hand column (“For plasma DNA sequencing, 11–50 ng of plasma DNA were used for DNA library construction”); and EX1011.005, left-hand column (“the quantitative estimation of % chr21 sequences was so precise and robust that the z-scores for chr21 of the T21 pregnancies were markedly different from the mean of a reference euploid sample set”).

Thus, Chiu's implementation of Lo's method *included a PCR amplification step in the absence of any of the tagging methods*<sup>5</sup> described in the secondary references and *successfully distinguished between euploid and trisomy cases*.

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<sup>5</sup> Indeed, as discussed below, despite including 15 cycles of PCR amplification in its method, “[t]he majority of DNA fragments are *sequenced once*, if at all” (EX1011.005, left-hand column), thus making tagging completely unnecessary.

Thus, despite using PCR amplification, neither Lo nor Chiu use tagging in their method.

**2. Chiu Demonstrates that Additional PCR Amplification was Unnecessary, and Indeed Potentially Counterproductive, to Detecting Fetal Trisomy Using Lo's method**

Beyond showing that tagging is unnecessary in Lo's method even when PCR amplification is used, Chiu also demonstrates that *additional* PCR amplification of DNA in the original sample is unnecessary, and indeed potentially counterproductive, to detect fetal trisomy.

As noted above, Chiu describes testing two protocols, an "original protocol," which included 15 cycles of PCR amplification, a gel electrophoresis-based size fractionation step, and another 15 cycles of PCR amplification, and a "new protocol" "whereby the gel electrophoresis and *second amplification steps were omitted.*" EX1011.003, left-hand column. After performing linear regression analyses to compare the uniquely mappable sequence reads per chromosome obtained from both the new and the original protocols against the expected genomic representation of each chromosome in the human genome, the authors of Chiu determined that "the DNA processing protocol with *just one PCR amplification step* and the omission of the gel electrophoresis procedure produced a quantitative profile of sequences that *better resembled the genomic content of each human chromosome than the original protocol.*" EX1011.004, left-hand column.

Thus, in addition to demonstrating that Lo's method can include PCR amplification without any of the tagging methods of the secondary references, Chiu demonstrates that **additional** amplification of DNA in the samples by PCR (beyond the 15 cycles used in both protocols) is **unnecessary** and indeed potentially counterproductive to the generation of a quantitative profile of sequences that resemble the genomic content of a sample. This fact cuts **directly** against the assertion on page 33 of the Petition that a POSA would modify the method of Lo to include the amplification described in the secondary references "to increase the overall amount of DNA for testing." See EX1002 ¶172.

**3. Chiu Demonstrates that Tagging is Unnecessary in its Implementation of Lo's Method, Despite Use of PCR Amplification**

Petitioner and its expert completely fail to account for the fact that when the inventors of Lo implemented Lo's method they included a PCR amplification step. Since the method of Lo is capable of detecting fetal trisomy from maternal plasma using PCR amplification **without tagging**, a POSA would not be motivated to add tagging as described in the secondary references.

Chiu itself explains why a POSA would **not** be motivated to add tagging to Lo's method, contrasting its methods with methods that involve tagging nucleic acid molecules, sequencing at high levels of coverage, and then quantifying the original number of nucleic acid molecules based on the number of tags. Chiu explains that

Lo's method "is quite unlike some previously described sequencing based methods for quantitative nucleic acid profiling that relied on sequencing *at high fold coverage*". EX1011.005, left-hand column, *citing* Reinartz et al. 2002 ("Reinartz") (EX2015). *See also*, EX1010, ¶68 ("This is contrasted from situations where the same pool of nucleic acids is sequenced multiple times to achieve high redundancy or several folds of coverage whereby each nucleic acid species is sequenced multiple times.")<sup>6</sup>

The method described in the Reinartz reference cited by Chiu involves "generating a 17-base sequence for each mRNA at a specific site upstream from its poly(A) tail. The 17-base sequence is then used as an mRNA identification 'signature'. To measure the level of expression of any given gene, the total number of signatures for that gene's mRNA is counted." EX2015, p. 2 of 10. Similar to the methods of the secondary references, the method described in Reinartz, "is based on the ability to identify *uniquely* every [original] mRNA in a sample" by using a "17-base sequence" "as an identification 'signature'." *Id.* As noted in Chiu, this form of

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<sup>6</sup> As noted above, Lo itself also contrasts its method with "situations where the same pool of nucleic acids is sequenced multiple times to achieve high redundancy or several folds of coverage whereby each nucleic acid species is sequenced multiple times." (EX1010, ¶68).

quantification “rel[ies] on sequencing at high fold coverage.” EX1011.005, left-hand column.

By contrast, despite using at least 15 cycles of PCR amplification in the implementation of Lo’s method described in Chiu, “[t]he majority of DNA fragments are *sequenced once*, if at all. The relative chromosome size is then deduced by counting the relative number of sequences aligned to the chromosome. *Each of the counted DNA fragments would be of a different nucleotide sequence.*” EX1011.005, left-hand column. Notably, Lo’s own description of its method is consistent with this discussion in Chiu. *See* EX1010, ¶67 (“among the proportion of captured nucleic acid molecules, most of each nucleic acid species is only sequenced once”) and the discussion in section II.B.1.a, *supra*.

In Lo and Chiu, the majority of DNA fragments are sequenced only once and each of the counted DNA fragments *have a different nucleotide sequence* even when PCR amplification is used. Thus, there is simply no need to tag the DNA fragments in Lo’s method.

The above directly undercuts each and every theory offered by Petitioner to modify Lo. Yet, the Petition fails to acknowledge, let alone address, any of the above explicit teachings. Consequently, Petitioner cannot prevail based on a Petition so deficient.

**C. Each of the Individual Motivations to Combine Lo with the Secondary References Offered by Petitioner is Incoherent**

As discussed in Section IV.B above, the Petitioner cannot prevail because the Petition fails to address explicit teachings of the cited prior art that tagging is not needed in the method of Lo. Nonetheless, Patent Owner below addresses each of Petitioner's purported motivations individually.

**1. Petitioner Fails to Articulate a Plausible Rationale for Why a POSA Would Have Modified Lo's Method to Use the Amplification of the Secondary References**

Petitioner alleges three (3) motivations for why a POSA would have used the amplification disclosed in the secondary references. Each purported motivation is premised on PCR amplification *not being used* in Lo's method.<sup>7</sup> But as discussed above, Chiu shows that the inventors of Lo *already used* PCR amplification when they implemented Lo's method, in the absence of tagging, to *successfully detect fetal trisomy*. All of Petitioner's motivations also ignore claim 13 of Lo, which recites that "the nucleic acid molecules of the biological sample have been amplified

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<sup>7</sup> Petitioner and their expert explicitly (and incorrectly) state that Lo's method lacks PCR amplification, stating that step (d) of claim 1 "involves sequencing tagged and amplified nucleic acid molecules whereas Lo *directly sequences the original sample molecules*." Paper 1 at 36 and EX1002, ¶175.

using a polymerase chain reaction,” and therefore demonstrates that the inventors of Lo understood that its method could be practiced with PCR amplification in the absence of tagging.

***a. Petitioner’s first purported motivation is entirely circular***

Petitioner’s first purported motivation is premised on amplification being “part and parcel of the methods in Brenner, McCloskey, Chee, and Porreca.” Paper 1 at 32. Citing to their expert, Petitioner asserts that “there is ***no reason*** to utilize tagging without subsequent amplification because ***the whole point*** of the tagging is to permit one to subsequently perform amplification and hence ensure that one captures all the molecules of interest while maintaining an avenue to avoid amplification bias.” *Id.*, citing EX1002 ¶165. On this basis, Petitioner alleges that “all the reasons set forth [] as to why a POSA would be motivated to apply tagging to Lo’s method apply equally to the use of amplification.” *Id.*

The problem with this purported rationale is that it is entirely circular—if “there is ***no reason*** to utilize tagging without subsequent amplification” (Paper 1 at 32), then utilizing tagging ***cannot*** be the reason to utilize amplification.

***b. Petitioner’s second purported motivation is unsupported and contradicted by the disclosure of Lo itself, and Chiu***

Petitioner’s second purported motivation is that “a POSA would have naturally been motivated to perform amplification to increase the overall amount of

DNA for testing” (Paper 1 at 33) noting that “there is a limited amount of DNA overall and even less DNA from the fetus that one is interested in testing” in the “exemplary samples in Lo’s method”. *Id.*

But this bare, conclusory assertion is both unsupported by any prior art reference ***and*** contradicted by the disclosure of Lo itself, and Chiu (*see* section IV.A, *supra*). Despite the exemplary samples in its methods having “limited amounts of DNA overall and even less DNA from the fetus,” Lo ***does not*** disclose ***any*** need to “increase the overall amount of DNA for testing.” To the contrary, Lo discloses that it was possible to extract 50 ng of maternal plasma DNA from only 20 mL of peripheral venous blood and that this amount was sufficient to detect fetal trisomy using its method. EX1010, ¶¶92-93 and 98. Moreover, Lo states that “[i]t is possible to start with lesser amounts such as 15 ng or 10 ng of maternal plasma DNA” (EX1010, ¶93). In Lo’s example, “[t]he maternal plasma DNA was [] used for massively parallel sequencing by the Illumina Genome Analyzer ***according to manufacturer’s instruction.***” EX1010, ¶92.<sup>8</sup>

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<sup>8</sup> Chiu also used the Illumina Genome Analyzer for sequencing, and the Supporting Information of Chiu (EX2014) demonstrates that massively parallel sequencing by the Illumina Genome Analyzer includes PCR amplification of adaptor-ligated DNA fragments. EX2014, left-hand column.

Indeed, as discussed in section IV.B above, Chiu—the “related 2008 publication by Lo” that is cited by Petitioner’s expert because it “neatly explains the method in Lo” (EX1002, ¶90)—demonstrates: (1) that 15 cycles of PCR amplification were used in the inventors’ implementation of Lo’s method and that this amount of amplification was sufficient to allow for robust detection of fetal trisomy from DNA isolated from maternal plasma, (2) that additional cycles of PCR were not only unnecessary in its method, but indeed led to a profile of sequences that was less representative of the genomic content of each human chromosome, and most importantly (3) that even with the 15 cycles of PCR amplification used in its method, “the majority of DNA fragments are *sequenced once*, if at all,” meaning that each of the counted DNA fragments “are of a different nucleotide sequence,” making tagging *completely unnecessary*. EX1011.005, left-hand column.

***c. Petitioner’s third alleged motivation for “cost-saving and efficiency” is both contradicted by Lo and Chiu and implausible***

Petitioner’s third and final motivation to utilize amplification is allegedly “within Lo itself,” because “Lo teaches multiple methods of enriching nucleic acid sequences prior to sequencing and the motivation for doing so, namely for cost-saving and efficiency.” Paper 1 at 33, citing EX1002 at ¶167. The Petition’s sole support for its allegation that a POSA would employ the amplification of the secondary references “for cost-saving and efficiency” is the conclusory,

unsupported, and incorrect assertion of their expert that the “amplification as taught by McCloskey, Brenner, Porreca or Chee” “provides the same benefit” as the enrichment taught by Lo simply because they are “another form of enrichment.” *See* Paper 1 at 34-35, citing EX1002 at ¶167-169.

The forms of enrichment in Lo for “cost saving and efficiency” cited by Petitioner all purport to *reduce sequencing costs* by enriching a sample for fetal DNA (EX1010, ¶¶77-78), or for DNA of chromosomes of interest (EX1010, ¶79), prior to the random sequencing of Lo’s method. The inventors in Lo evidently knew that PCR-based methods cannot be used to reduce sequencing costs in a similar manner, which is why, despite PCR amplification being “well-known” (Paper 1 at 7), mentioned in dependent claim 13 of Lo, and in fact employed by the inventors when they implemented Lo’s method in Chiu (*see* section IV.B), they did not suggest PCR amplification for the purpose of reducing sequencing costs.

The Petition’s conclusory statement that the amplification as taught by McCloskey, Brenner, Porreca or Chee “provides the same benefit” as the enrichment taught by Lo simply because they are “another form of enrichment” is also illogical on its face. Tagging followed by PCR amplification necessarily *adds* steps to Lo’s method and it is self-evident that *adding* steps to a process will increase the cost of the process unless costs of other steps can be reduced or eliminated. But Petitioner and their expert utterly fail to explain what costs, if any, can be reduced thanks to

the added steps. Indeed, while the forms of enrichment discussed in Lo aim to reduce costs by purportedly *reducing* the amount of sequencing needed to arrive at a diagnosis—modifying Lo’s method to tag and amplify DNA prior to sequencing as in the secondary references implies *increased* sequencing costs. Lo itself notes that in such methods, “where the same pool of nucleic acids is sequenced multiple times to achieve high redundancy,” “*sequencing cost increases* with the number of fold coverage required to achieve accurate representation of the nucleic acid species.” (EX1010, ¶68).<sup>9</sup>

Thus, the Petition’s assertion that the amplification taught by the secondary references “provides the same benefit” as the enrichment discussed in Lo because it is “another form of enrichment” (Paper 1 at 34) is demonstrably false, contrary to express teachings in Lo and entirely conclusory.

**2. Petitioner Fails to Articulate a Plausible Rationale for Why a Person of Ordinary Skill in the Art (POSA) Would Have Used the Tagging of the Secondary References**

Petitioner offers four (4) purported motivations for why a POSA would have modified the method of Lo to include tagging nucleic acid fragments to generate

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<sup>9</sup> As discussed in IV.A, Chiu contrasts Lo’s method with methods that “re[ly] on sequencing at high fold coverage” (EX1011.005, left-hand column), which is a hallmark of the methods taught by the secondary references.

unique tagged nucleic acid molecules. But none of these reasons account for the fact that Lo and Chiu demonstrate that tagging is not necessary in Lo's method. As noted above, Lo's method successfully detects chromosomal imbalances in a method where the majority of DNA fragments are sequenced only *once*, if at all, meaning that each of the counted DNA fragments are of a different nucleotide sequence. *See* EX1010, ¶76 (“by statistics, *most of the maternal plasma DNA fragment species would only each have been sequenced to generate one sequenced tag count*”); and EX1011.005, left-hand column (“[t]he majority of DNA fragments are *sequenced once*, if at all,” meaning that “[e]ach of the counted DNA fragments would be of a *different nucleotide sequence.*”)

The Petition's first two purported reasons to modify the method of Lo to include tagging are actually the same: to allegedly improve the accuracy of counting. *See* Paper 1 at 26 (“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”) and Paper 1 at 27 (“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”). But as noted above, Lo and Chiu demonstrate that Lo's method accurately identifies fetal trisomy *without tagging and without sequencing multiple PCR copies* of the same DNA fragment (*see* sections II.B.1.a and IV.B.3, *supra*).

The Petition's third purported reason to modify the method of Lo to include tagging is that Brenner, Porreca, and other prior art references "expressly contemplate using tagging and amplification with counting for determining copy number information." Paper 1 at 27. However, the Petition fails to provide *any* reason why the teachings in Brenner, Porreca, or other prior art references would motivate a POSA to modify *the method of Lo* to include tagging and amplification. Indeed, both Lo and Chiu distinguish Lo's method from the methods in the secondary references, "whereby each nucleic acid species is sequenced multiple times" (EX1010, ¶68). *See* EX1011.005, left-hand column (explaining that Lo's method "is quite unlike some previously described sequencing based methods for quantitative nucleic acid profiling that relied on sequencing *at high fold coverage*".)

The Petition's fourth purported reason to modify the method of Lo to include tagging is that because "fetal DNA is present in low absolute concentration" in maternal plasma, there is a "low signal problem." Paper 1 at 28-29, citing EX1002, ¶152. The Petition and Cooper Declaration both contain only a bare, conclusory assertion that "the amplification techniques described below in step [1C]" would "increase the signal-to-noise ratio and thereby improve the sensitivity and accuracy of detecting aneuploidy described in Lo" without bothering to explain what the "noise" is in this context or how "the amplification techniques" of the secondary references would increase the signal relative to that noise to thereby improve

sensitivity and accuracy. Nevertheless, to the extent the “signal” is the fetal DNA and the “noise” is the maternal DNA (which Petitioner does not even attempt to articulate or explain), Lo *does* explain that “the number of sequenced tags required for differentiating euploid from trisomy 21 cases would reduce as the fractional fetal concentration increases.” EX1010, ¶78.

Moreover, as noted in section IV.C.1.b, Lo discloses that the amount of fetal DNA present in 50 ng of maternal plasma DNA, extracted from only 20 mL of peripheral venous blood, is sufficient to detect fetal trisomy using its method *in the absence of the tagging and amplification of the secondary references*. EX1010, ¶¶92-93 and 98. *See also*, section IV.B, *supra* (discussing Chiu’s successful implementation of Lo’s method.) The Petition, however, fails to articulate how the tagging and PCR amplification of the secondary references can possibly enrich a sample for fetal DNA in Lo’s method. *See*, section IV.C.1.c.

Accordingly, each of Petitioner’s purported reasons to modify Lo’s method to include tagging all fail.

Tellingly, Lo and Chiu were sufficiently skilled at the time to know that tagging was an available technique, yet neither Lo nor Chiu used tagging to generate unique tagged nucleic acid molecules in their method. Indeed, Chiu *contrasts* its method with a method (described in Reinartz) that relies on tagging nucleic acids for the purpose of counting. *See* section IV.B.3, *supra*.

**V. THE PETITION IMPERMISSIBLY RELIES ON EXPERT TESTIMONY AND GENERIC ASSERTIONS REGARDING “KNOWLEDGE OF A POSA” TO FILL IN MISSING CLAIM ELEMENTS**

Faced with gaps in its prior art, Petitioner resorts to its expert to save its validity challenges. But that approach does not pass muster, even at the institution stage. *First*, Petitioner relies on conclusory and unsupported opinions of its expert to supply rationales to combine Lo’s method with methods of one or more of the secondary references—in direct contradiction with Petitioner’s own evidence. *Second*, the Petition impermissibly relies on the Cooper Declaration (EX1002) and generic assertions regarding “knowledge of a POSA” to supply claim limitations. Such an approach fails to specify where each element of the claim is found in the prior art, or to identify what particular combinations of the asserted prior art Petitioner is even relying on in its main Ground 1. That gap-filling approach is insufficient to support the challenges here and warrants denial for these independent reasons.

**A. Petitioner Improperly Relies on Conclusory Expert Testimony to Bridge Gaps in Its Obviousness Challenges.**

At multiple junctures, Petitioner’s arguments attempt to fill deficiencies in its prior art by relying on the expert opinion of Dr. Cooper. But Dr. Cooper fails to cogently explain how the various gaps would be known or obvious to a POSA, resorting instead to generic assertions devoid of supporting evidence. Such

conclusory gap-filling by the expert cannot meet Petitioner’s burden at institution. *See Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Paper 9 (PTAB Aug. 24, 2022).

As one example, Petitioner alleges that that “[c]laims 18-21 and 29-32 are obvious *in further view of the knowledge of the skilled artisan*” (emphasis added). No prior art reference is identified. Here, Petitioner relies on the opinion of its expert, Dr. Cooper, to supplement the otherwise insufficient disclosure in the references:

As shown above, the claims from which these eight claims depend are all invalid as obvious. *As Dr. Cooper further explains*, the use of tags with variable portions constructed from the claimed palettes of oligonucleotides also *would have been obvious approaches* that a POSA would have been motivated to explore.

Paper 1 at 64.

The portions of Dr. Cooper’s testimony are simply conclusory and parrot the assertions Petitioner provides in the Petition, failing to substantiate those claims with additional evidence or support. *See* EX1002 ¶284 (Dr. Cooper stating without any citation to evidence that “The use of tags with variable portions constructed from the claimed palettes of oligonucleotides also would have been obvious approaches that a POSA would have been motivated to explore.”)

As another example, Petitioner alleges that claim 4 is obvious over Lo “in view of the knowledge of a POSA, as reflected in Brenner or Porreca” (Paper 1 at 53) using Dr. Cooper to supplement deficiencies in the references it cites:

A POSA would understand that some sequencing systems require DNA fragments of a specific size and would use the known methods of mechanical shearing, heating, and sonication to adapt larger DNA molecules for sequencing systems that require smaller fragments. EX1002 ¶¶242-243. If smaller fragments were required, employing these fragmentation techniques would have been an obvious design choice with a reasonable expectation of success. *Id.*

Paper 1 at 54.

Again, the portions of Dr. Cooper’s testimony are simply conclusory and parrot the assertions Petitioner provides in the Petition, failing to substantiate those claims with additional evidence or support. *See* EX1002, ¶243 (Dr. Cooper stating without any citation to evidence that “[a] POSA would understand that some sequencing systems require DNA fragments of a specific size. Mechanical shearing, heating, and sonication were all known methods of creating smaller DNA fragments.”)

**B. Petitioner Improperly Resorts to Generic Assertions Regarding “Knowledge of a POSA” that Fail to Specify the Evidence Supporting Its Challenge or to Identify the Exact Combinations of Prior Art Being Asserted**

Petitioner bears the burden of specifying the grounds on which its challenges rest and identifying with particularity the arguments and evidence allegedly supporting those challenges. 35 U.S.C. § 311(b) limits “the basis” of any “ground” in an *inter partes* review to “prior art consisting of patents or printed publications.”

Moreover, under 35 U.S.C. § 312(a)(3), an IPR petition must identify, “in writing and with particularity, each claim challenged, the grounds on which the challenge to each claim is based, and the evidence that supports the grounds for the challenge to each claim.” Importantly, 37 C.F.R. § 42.104(b)(4) states that a petition “must specify where each element of the claim is found in the prior art patents or printed publications relied upon.” Although the prior USPTO Director’s June 9, 2022 Memorandum entitled “Updated Guidance on the Treatment of Statements of the Applicant in the Challenged Patent in Inter Partes Reviews Under § 311” (“2022 Memorandum”) provides a *limited* exemption to this rule with respect to “applicant-admitted-prior-art” (“AAPA”) (stating that 37 C.F.R. § 42.104(b)(4) “does not foreclose the limited use of admissions described in this Memorandum”), ***no such exemption*** had been promulgated by the Director which permits assertions of an Expert to be relied upon to supply missing claim limitations.<sup>10</sup>

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<sup>10</sup> A July 31, 2025 Memorandum entitled “Enforcement and Non-Waiver of 37 C.F.R. § 42.104(b)(4)” (“July 31, 2025 Memorandum”) (EX2013) rescinds the limited exemption previously afforded solely to AAPA in the Director’s 2022 Memorandum and confirms that evidence not consisting of patents or printed publications such as “expert testimony [] may not be used to supply a missing claim limitation”.

In its main Ground 1, Petitioner asserts that Lo combined with generic “knowledge of a POSA” render the claims obvious. Paper 1 at 22. As alleged support for that assertion, Petitioner repeatedly cites the four secondary references, without specifying particularly what combination (or combinations) of the prior art are actually being asserted. *Id.* That non-specific approach leaves the Board and PO to guess at what combinations are actually at issue in Petitioner’s main ground attacking the only independent claim addressed in the Petition. It is entirely unclear whether Ground 1 in the Petition is actually asserting (1) a single combination of Lo with “knowledge of a POSA”; (2) a single combination of Lo with four additional secondary references; (3) four combinations of Lo with each of the four secondary references individually; or (4) an unspecified number of combinations of Lo with any one or more of the secondary references. That nebulous approach fails to identify the invalidity grounds with the requisite specificity and warrants denial. Indeed, the Board routinely rejects challenges where petitioners assert muddled unspecified combinations that leave a PO to only guess what particular grounds it must address. *Adaptics Ltd. v. Perfect Co.*, IPR2018-01596, Paper 20 at 17-24 (P.T.A.B. Mar. 6, 2019) (denying institution due to “a lack of particularity” where “Petitioner’s reliance on up to ten references” led to “a multiplicity of grounds, none of which is presented with sufficient particularity”). By relying on the “knowledge of a POSA” and Dr. Cooper to provide his understanding of such knowledge, Guardant goes

beyond the teachings of prior art patents and publications, on which all IPRs *must* be based, and fails to specify with any particularity what combinations of that prior art are actually being asserted here. Those shortcomings warrant denial.

## **VI. CONCLUSION**

The Petition fails to show a reasonable likelihood of prevailing on any ground because its theory of obviousness based on Lo in view of McCloskey, Brenner, Chee, or Porreca is fundamentally flawed.

Patent Owner respectfully requests that the Director deny institution of this IPR.

Respectfully submitted,

/Gary J. Gershik/

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Dated: November 3, 2025

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**CERTIFICATE OF COMPLIANCE**

Pursuant to 37 C.F.R. § 42.24(d), I hereby certify that the forgoing Patent Owner's Preliminary Response complies with the type-volume limitation of 37 C.F.R. § 42.24(b)(1) permitting up to 14,000 words for a patent owner preliminary response based on 37 C.F.R. § 42.24(a)(1)(i), because, based upon the word count of the word-processing system used to prepare this petition, the number of words in this petition is 11,961. Pursuant to 37 C.F.R. §42.24(a), this word count does not include "a table of contents, a table of authorities, mandatory notices under § 42.8, a certificate of service or word count, or appendix of exhibits or claim listing."

/Darren Haber/

Dated: November 3, 2025

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Darren Haber (Reg. No. 80,964)

**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 IPR2025-01353

Patent 12,234,510

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**CERTIFICATE OF FILING AND SERVICE**

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The undersigned hereby certifies that true and correct copies of PATENT OWNER'S PRELIMINARY RESPONSE, and EXHIBITS 2013-2015 are being electronically filed via The Patent Trial and Appeal Case Tracking System (P-TACTS) system and served this 3rd day of November 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:

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Dated: November 3, 2025

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