

Case IPR2024-01419
U.S. Patent No. 11,840,730

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ILLUMINA INC.,
Petitioner

v.

MOLECULAR LOOP BIOSCIENCES, INC.,
Patent Owner

Case IPR2024-01419

U.S. Patent No. 11,840,730

PATENT OWNER'S PRELIMINARY RESPONSE

Mail Stop Patent Board
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
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All citations to 35 U.S.C. §§102 and 103 in this paper refer to the pre-AIA statute.

All emphases are added unless otherwise noted.

All citations to exhibits refer to stamped exhibit page numbers.

I. Introduction

U.S. Patent No. 11,840,730 (the “’730 Patent”) solved significant problems in the field of sequencing by improving efficiency and accuracy with scalable technologies. Prior to the ’730 Patent, errors and ambiguities were often introduced during sequencing workflows, such as during library preparation, amplification and sequencing. For example, amplification during sequencing workflows could create an over- or under-representation of particular nucleic acid sequences from a sample. Thus, there was a need for sequencing approaches that would avoid or resolve these errors and ensure accurate results while providing scalable and cost-effective sequencing technology. *See* EX1001, 1:42-53.

The inventors of the ’730 Patent discovered that using differentiator tags to tag individual nucleic acid molecules before the nucleic acids were analyzed allowed for certain errors to be recognized and reduced, thereby increasing the accuracy of the overall workflow. The inventors developed methods that incorporated differentiator tags to differentiate multiple independent target nucleic acid sequences and reduce the effects of errors and bias introduced during sequencing workflow. *See, e.g.,* EX1001, 28:49-67. For example, the differentiator tags allow for amplicons produced through amplification to be traced back to original individual nucleic acid molecule from which they originated, ensuring that different nucleic

acid molecules were accurately identified and proportionately represented. *See id.*, 28:3-24.

Petitioner fails to show a reasonable likelihood that the inventive claimed methods were known or that they would have been obvious to a POSA. Petitioner thus fails to meet its burden, and the Petition should be denied because it is deficient in several respects.

First, Petitioner fails to establish a reasonable likelihood of prevailing on its anticipation and obviousness grounds that involve the Chee reference (Grounds 1–3). For at least one claim limitation in each claim (the “introducing” steps), Petitioner relies exclusively on Chee but fails to show that Chee, or anything in its proposed grounds, discloses or renders obvious the full requirements of the challenged claims.

Second, Petitioner fails to establish a reasonable likelihood of prevailing on its obviousness grounds that rely on Bignell and McCloskey in various combinations (Grounds 4–7). For at least one claim limitation in each claim, Petitioner fails to show that its proposed combinations disclose or render obvious the requirements of the challenged claims.

Due to these deficiencies, the Petition does not establish “a reasonable likelihood that the petitioner would prevail with respect to at least one of the claims challenged in the petition.” 35 U.S.C. § 314(a). While Patent Owner reserves the right to present additional arguments, the deficiencies of the Petition noted herein

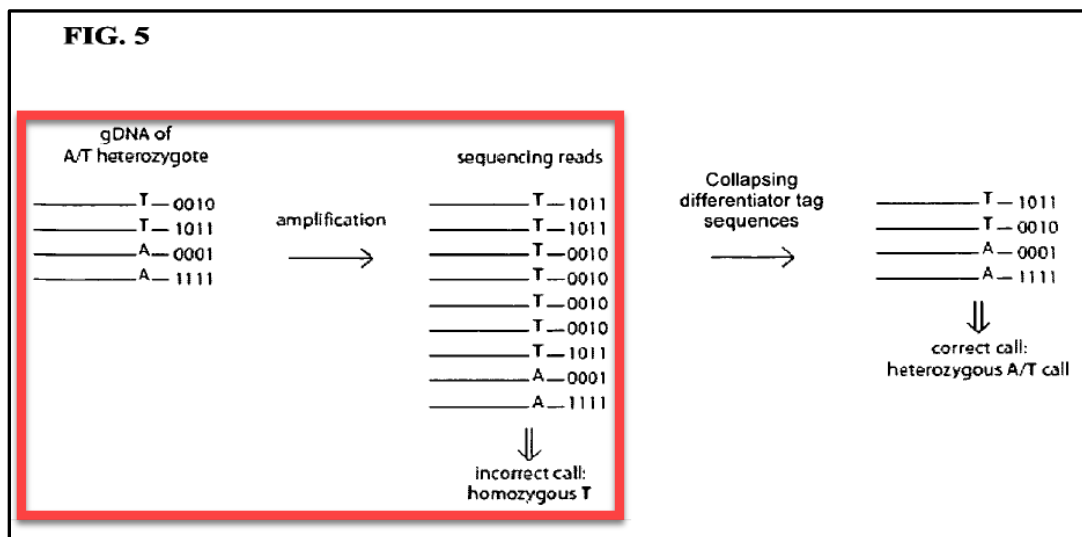
are sufficient for the Board to find that Petitioner has not met its burden and deny institution.

II. Background

A. Overview Of The '730 Patent

The '730 Patent relates to “approaches to avoid, reduce, recognize and/or resolve [] errors and ambiguities at different stages in a genetic analysis.” EX1001, 1:62-67. For example, “certain types of genetic information can be under-represented or over-represented in a genetic analysis due to a combination of stochastic variation and systematic bias in any of the preparative stages (e.g., capture, amplification, etc.), determining stages (e.g., allele-specific detection, sequencing, etc.), data interpretation stages (e.g. determining whether the assay information is sufficient to identify a subject as homozygous or heterozygous) and/or other stages.” *Id.*, 2:1-9. The '730 Patent addresses “[s]ystematic and random errors [that were] common problems associated with genome amplification and sequencing library construction techniques.” *Id.*, 27:45-47. As the '730 Patent notes, previous methods to address such errors “waste[d] resources and increase[d] the expense required to perform such experiments” or “reduced statistical confidence in certain conclusions (e.g., diagnostic calls).” *See id.*, 27:57-67. The '730 Patent provides for “high-throughput, cost-effective, yet reliable, genotyping of multiple patient samples.” *Id.*, 21:7-10.

Error or ambiguities may be introduced at different stages in a genetic analysis such as “the preparative stages (e.g. capture amplification, etc.), determining stages (e.g. allele specific detection, sequencing etc.), data interpretation stages (e.g. determining whether the assay information is sufficient to identify a subject as homozygous or heterozygous), and/or other stages.” *Id.*, 1:62-2:9. As the ’730 Patent notes, systematic and random errors “can be particularly problematic when it results in target sequences from a genome being absent or undetectable in the sequencing libraries.” *Id.*, 27:45-53. For example, such errors can result in an “over- or under-representation of particular sequences from a source genome.” *Id.*, 27:47-50. The ’730 Patent illustrates an example of this issue in Figure 5.

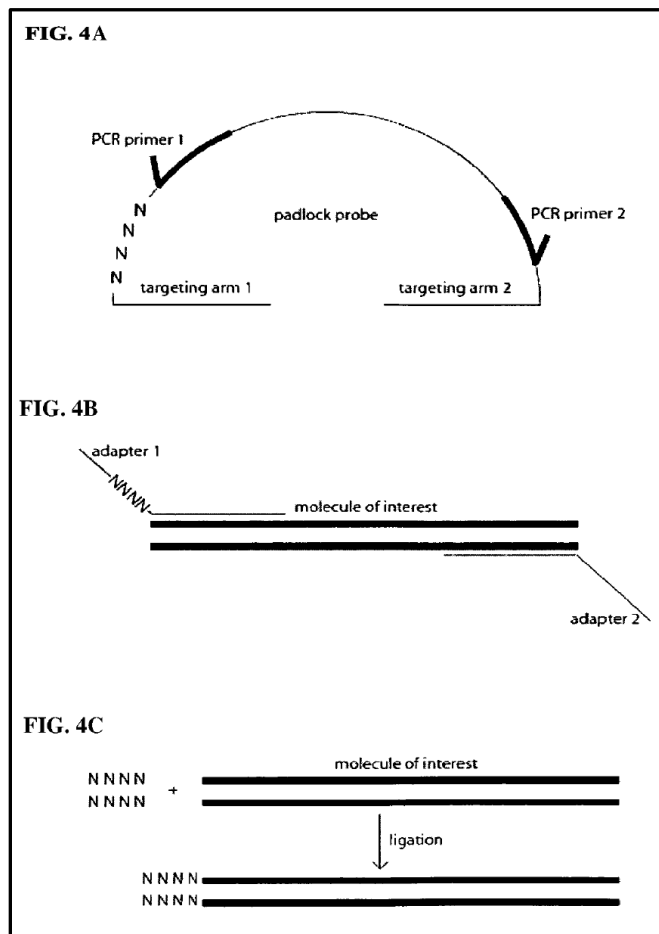


Id., Figure 5 (annotated). The ’730 Patent explains “most downstream sequencing library quantification techniques depend on stochastic counting processes, these problems have typically been addressed by sampling enough (over-sampling) to

obtain a minimum number of observations necessary to make statistically significant decisions.” *Id.*, 27:57-62. However, oversampling “wastes resources and increases the expense required to perform such experiments.” *Id.*, 27:62-65. Additionally, “oversampling can result in reduced statistical confidence in certain conclusions (e.g. diagnostic calls) based on the data.” *Id.*, 27:65-67.

The ’730 Patent addressed the shortcomings of prior approaches by incorporating “the use of differentiator tag sequences to uniquely tag individual nucleic acid molecules.” *Id.*, 28:14-17. The ’730 Patent explains that “a ‘differentiator tag sequence’ is a sequence of a nucleic acid (a preparative nucleic acid), which in the context of a plurality of different isolated nucleic acids, identifies a unique independently isolated nucleic acid.” *Id.*, 28:53-57. Introducing “the differentiator tag sequence permits the detection of bias based on the frequency with which pairs of differentiator tag and target sequences are observed in a sequencing reaction.” *Id.*, 28:18-21. For example, differentiator tags “are useful to determine whether target nucleic acid sequences identified in an assay are from independently isolated target nucleic acids or from multiple copies of the same target nucleic acid molecule (e.g. due to bias in a preparative step, for example, amplification). This information can be used to help analyze a threshold number of independently isolated target nucleic acids from a biological sample in order to obtain sequence information that is reliable and can be used to make a genotype conclusion (e.g.,

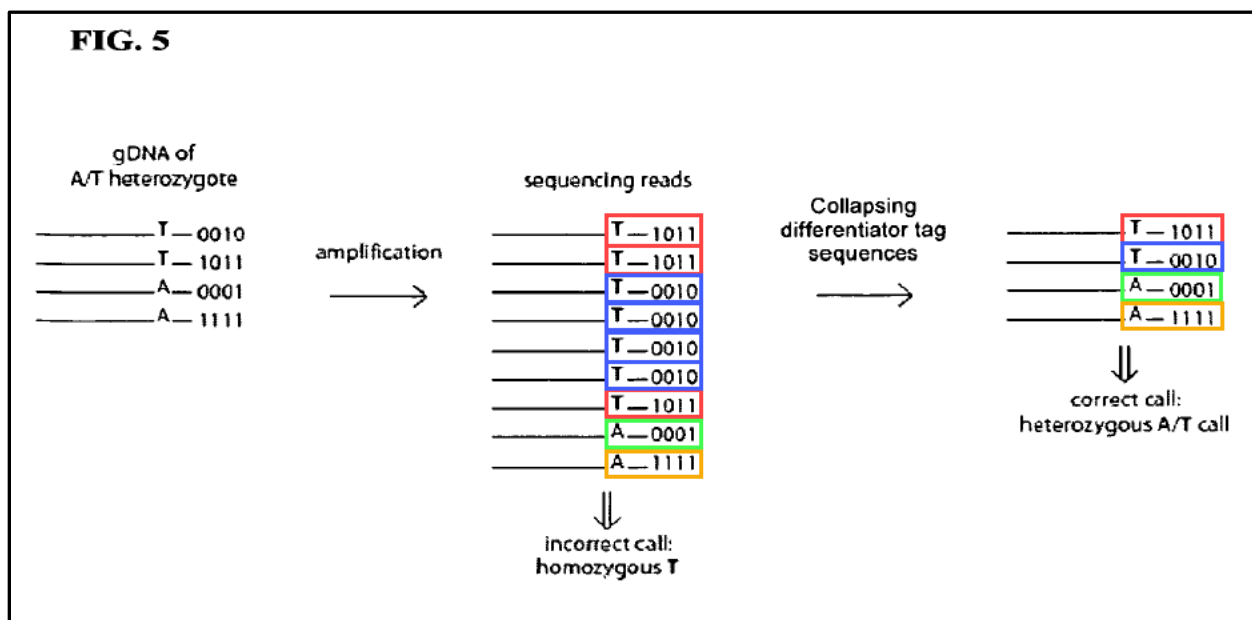
call) with a desired degree of confidence. This information also can be used to detect bias in one or more nucleic acid preparation steps.” *Id.*, 5:12-23. The ’730 Patent provides “non-limiting examples of methods for combining differentiator tag sequence and target sequences” in Figure 4. *Id.*, 19:32-34.



Id., Figure 4.

The ’730 Patent makes clear that “the differentiator tag sequence permits the detection of bias based on the occurrence of *combinations of differentiator tag and target sequences* observed in a sequencing reaction.” *See, e.g., id.*, 5:5-8. For example, “in the context of a multiplex nucleic acid amplification reaction,

differentiator tag sequences provide a basis for differentiating between multiple independent, primary amplicons of a target nucleic acid, for example. Thus, combinations of target nucleic acid and differentiator tag sequence (target:differentiator tag sequences) of an isolated nucleic acid of a preparative method provide a basis for identifying unique, independently isolated target nucleic acids.” *Id.*, 28:62-29:4. As shown in Figure 5 of the ’730 Patent, the inventive methods include correcting errors or bias in a nucleic acid analysis workflow by collapsing target:differentiator tag combinations.



Id., Figure 5 (annotated); *see also* 73:3-5 (“FIG. 5 depicts a method for making diploid genotype calls in which *repeat target:differentiator tag combination are collapsed.*”).

B. Overview Of The '730 Patent File History

The '730 Patent's application was filed on November 19, 2020, as Application No. 16/952,764, claiming priority to April 30, 2009. EX1004, 113-115; EX1001, Cover. Petitioner uses May 18, 2009, as the effective priority date of the '730 Patent for purposes of the Petition. Paper 1 ("Pet."), 15.¹

In an Office Action dated February 10, 2021, the Examiner rejected pending claims as obvious in view of Porreca (EX1031) and Wang. EX1004, 866-872. In response, Applicant submitted a declaration from inventor Dr. Greg Porreca on March 4, 2021. *Id.*, 964-967.

In his declaration, Dr. Porreca explained the '730 Patent's "application discloses tagging target individual nucleic acid molecules with differentiator tags before any amplification or sequencing steps" so that "each individual target nucleic acid molecule is tagged, and therefore associated, with a differentiator tag." *Id.*, 964. Dr. Porreca clarified that "each target:differentiator tag combination uniquely

¹ Petitioner makes various assertions regarding the priority date of the '730 Patent and the disclosures of its provisional applications. Pet., 14-15. Patent Owner does not concede those assertions. Patent Owner reserves its right to raise additional challenges to Petitioner's priority assertions and to establish an earlier priority date of the '730 Patent in future proceedings.

identifies a single nucleic acid molecule through subsequence amplification and sequencing steps.” *Id.* Dr. Porreca explained that “[b]ecause each target:differentiator tag combination can be associated back to its original, individual nucleic molecule based on the unique combination of individual nucleic acid molecules and their respective differentiator tags, the invention corrects for bias in subsequent steps.” *Id.*, 965.

The Examiner issued a final rejection on April 9, 2021, which Applicant appealed. In its appeal, the Applicant highlighted that the differentiator tags in the ’730 Patent’s application are not designed to capture a specific exon of interest and thus can differentiate between separate single molecules. *Id.*, 1070-1073, 1142-1146. Applicant reiterated none of the cited references “disclose a method comprising tagging individual nucleic acid molecules with differentiator tags prior to amplification or sequencing steps.” *Id.*, 1071, 1144. The Board reversed the Examiner’s rejection, and the claims were allowed on September 28, 2023. *Id.*, 1194-1196.

III. Overview Of The References²

A. Chee (EX1010)

Chee is U.S. Patent titled “Nucleic Acid Constructs and Methods of Use.” Chee, Cover. Chee relates to “ensuring accuracy of oligonucleotides having a desired sequence.” *Id.*, 1:55-57. Chee’s methods “provide validated sequences or sets of validated sequences corresponding to one or more *desired sequences, i.e. ‘regions of interest [ROIs].’*” *Id.*, 2:5-9. Chee explains a “fundamental element of the invention” allows for “constructs with ROIs having the correct sequence [to] be differentiated from constructs having substantially the same ROI but containing errors.” *Id.*, 2:21-28. Thus, Chee’s method relates to “ensuring the fidelity of the ROI in a particular construct” so that the correct sequence can be used in a further application. *Id.*, 9:13-18; *see also id.*, 11:49-56, 13:21-24, 14:50-56, 16:49-58, 23:36-49.

B. McCloskey (EX1012)

McCloskey is a U.S. Patent Application Publication titled “Molecular Encoding of Nucleic Acid Templates For PCR and Other Forms of Sequence

² Patent Owner does not concede that the references cited in the Petition are prior art to the ’730 Patent. Patent Owner reserves its right to raise additional challenges to the prior art status of the references in future proceedings.

Analysis.” McCloskey, Cover. McCloskey discloses using “barcodes and batch-stamps for verifying the authenticity of PCR products and other sequence information.” *Id.*, [0002]. McCloskey uses bar-coded oligonucleotides to “authenticate a nucleic acid sequence with information, such as the date of the experiment, and the sample identity.” *Id.*, [0005]. McCloskey’s method “permits the identification of valid sequences, and distinguishes the valid sequences from contaminants and redundant sequences arising from template re-cloning.” *Id.*, [0005]. McCloskey suggests “specific uses for the present invention [to] include analysis of limited amounts of template DNA for biomedical, ancient DNA, and forensic purposes.” *Id.*, [0006].

McCloskey discloses methods for “bar-coding a nucleic acid molecule” by “contacting a target nucleic acid molecule in a sample with a bar-coded oligonucleotide under suitable conditions to anneal the bar-coded oligonucleotide to the target nucleic acid molecule.” *Id.*, [0008]. Each bar-coded oligonucleotide disclosed in McCloskey comprises at least three sequences: “a first sequence complementary to the target nucleic acid molecule, a second sequence providing a random barcode, and a third sequence that is not complementary to any sequence in the sample.” *Id.*

McCloskey’s methods use the first sequence complementary to the target nucleic acid molecule to anneal the bar-coded oligonucleotide to the target nucleic

acid molecule. *See id.*, [0029]. McCloskey's methods extend the annealed bar-coded oligonucleotide using the target nucleic acid molecule as a template to produce a bar-coded target nucleic acid molecule. *Id.*, [0030]. McCloskey's methods amplify the bar-coded target nucleic acid molecule to produce an amplification product. *Id.*, [0033]. Finally, McCloskey's methods authenticate amplification products by "detecting the presence of the second sequence" in the amplification product. *See e.g., id.*, [0034].

McCloskey is cited in the '730 Patent. EX1001, 31:3-9. McCloskey was also considered by the Examiner during Prosecution of the '730 Patent. McCloskey was identified in an Information Disclosure Statement, and the Examiner signed the Statement on February 4, 2021 indicating McCloskey was considered. EX1004, 897-937.

C. Bignell (EX1013)

Bignell is U.S. Patent No. 8,053,192 titled "Methods for Indexing Samples and Sequencing Multiple Polynucleotide Templates." Bignell, Cover. Bignell describes methods to index samples during nucleic acid analysis. *Id.*, 1:24-32. Bignell discloses obtaining nucleic acids from at least two different sources and tagging nucleic acids from a given source with the same source- or sample-specific tag. *Id.*, 3:60-4:18. Bignell's methods then pool the samples together before sequencing the pooled libraries together for analysis. *Id.*, 4:19-29.

D. Gahan (EX1015)

Gahan is titled “Circulating Nucleic Acids in Plasma and Serum.” Gahan, 1. Gahan describes developments and research on circulating acids in plasma and serum. *Id.*, 1. Gahan discloses studies relating to isolated DNA or RNA from blood, serum, plasma, or urine. *Id.* Gahan additionally identifies developments in various nucleic acid analysis applications, such as fetal medicine and oncology. *See id.*, 2-5.

E. Bentley (EX1017)

Bentley is an article titled “Whole-genome re-sequencing.” Bentley, 545. Bentley reviews the “prospects for whole-genome re-sequencing using new technologies, with a focus on human genetic and medical applications.” *Id.*, 545. Bentley describes the developments, costs, throughput, accuracy, and completeness of sequencing technologies such as microelectrophoresis, sequencing by hybridization, sequencing by synthesis on arrays, and single-cell sequencing. *Id.*, 546-548.

F. Chiang (EX1033)

Chiang is an article titled “High-resolution mapping of copy-number alterations with massively parallel sequencing.” Chiang, 99. Chiang highlights the importance of copy-number alterations in discovering cancer causing genes. *Id.*, 99. Chiang discloses using massively parallel sequencing in connection with computational algorithms to estimate copy number alterations. *See id.*, 99-101.

IV. The Level Of Ordinary Skill In The Art

Petitioner proposes a level of ordinary skill in the art. Pet., 10. For the purposes of this Preliminary Response, Patent Owner does not set forth an alternative level of skill for a POSA because Petitioner fails to meet its burden even under its own proposal. Patent Owner's silence regarding the appropriate level of skill of a POSA is not an agreement with Petitioner's proposal. Patent Owner reserves the right to challenge Petitioner's proposal, and to propose an alternative or additional level of ordinary skill, in future proceedings.

V. Claim Construction

Petitioner construes various claim terms. Pet., 16-19. For the purposes of this Preliminary Response, Patent Owner does not set forth alternative constructions because Petitioner fails to meet its burden even under its own proposed constructions. Patent Owner's silence regarding the appropriate construction of any term is not an agreement with Petitioner's apparent construction of any such term. Patent Owner reserves the right to challenge Petitioner's proposed construction, and to propose alternative or additional claim constructions, in future proceedings.

VI. Institution Should Be Denied Because The Petition Does Not Establish A Reasonable Likelihood Of Prevailing On Any Ground.

A. Grounds 1-3: Petitioner Does Not Establish A Reasonable Likelihood Of Prevailing On Its Grounds Based On Chee.³

Petitioners Grounds 1-3 each rely exclusively on Chee as allegedly anticipating or rendering obvious (by itself) all limitations of the independent Claims 1 and 9. Pet., 25-39. While Petitioner adds Gahan in Ground 3, it does so only to address certain independent claims and does not rely on Gahan for any limitation of the independent claims. Pet., 42-45. But Petitioner’s mapping of the prior art does not show a reasonable likelihood that Chee discloses or renders obvious the full requirements of the “introducing” steps in Claims 1 and 9. Specifically, Petitioner’s mapping in the Petition fails to show that Chee discloses or renders obvious “one or more of said loci of origin are associated with more than one differentiator tag” as recited in Claim 1 and “any given tag is uniquely associated with said locus of

³ For the purposes of this Preliminary Response, Patent Owner addresses certain issues with Petitioner’s grounds. Patent Owner’s silence regarding any additional issue is not an agreement with Petitioner’s positions. Patent Owner reserves the right to address additional issues with this ground—including issues relating to additional claim limitations—in future proceedings.

origin” as recited in Claim 9. For at least those reasons, Petitioner failed to establish a reasonable likelihood of prevailing on Grounds 1-3 in the Petition.

1. For Claim 1, Petitioner Does Not Show That Chee Discloses Or Renders Obvious “Introducing A Set Of Differentiator Tags, Wherein Members Of Said Set Of Differentiator Tags Are Associated With Members Of Said Plurality, Such That One Or More Of Said Loci Of Origin Are Associated With More Than One Differentiator Tag.”

Claim 1 recites introducing a set of differentiator tags and that “one or more of said loci of origin are associated with more than one differentiator tag.” Petitioner relies on Chee’s disclosure that its methods can create “two constructs with substantially the same ROI and different unique identifiers” as allegedly teaching this limitation. Pet., 28 (citing Chee, 2:34-43). But Chee does not tie this disclosure to a locus of origin, and neither Petitioner’s cited portions of Chee nor the cited testimony of Dr. Gabriel sufficiently explain how the cited passages of Chee meet the claim limitation.

Chee explains that its methods provide “validated sequences” that correspond to “one or more *desired sequences, i.e., ‘regions of interest.’*” Chee, 2:5-9. In explaining how it obtains constructs having certain desired sequences (that is, the ROIs), Chee explains that one construct having “substantially the same ROI” as another construct means one construct “containing errors” relative to the other ROI. Chee, 2:23-28. In other words, a construct with “substantially the same ROI” is a construct that is almost a desired sequence (i.e., almost the ROI), except for errors

in that sequence. Nowhere does Petitioner cite disclosure in Chee tying either the desired sequence (i.e., the ROI) or a sequence having “substantially the same ROI” to a locus of origin. And while Petitioner cites testimony from Dr. Gabriel (Pet., 28), that testimony simply states in a conclusory manner that “substantially the same ROI” means “the same locus of origin on the genome.” EX1005, ¶155. But Dr. Gabriel does not provide any support for that purported meaning from Chee, and does not address Chee’s different explanation that “substantially the same ROI” refers to errors, not location, as “*ROIs having the correct sequence* can be differentiated from *constructs having substantially the same ROI but containing errors.*” Chee, 2:21-28. Moreover, neither Petitioner (Pet., 28) nor Dr. Gabriel (EX1005, ¶155) make any assertions regarding inherency absent explicit disclosure.

Additionally, while Petitioner’s Grounds 2-3 allege obviousness based on Chee, Petitioner’s obviousness assertions do not address “one or more of said loci of origin are associated with more than one differentiator tag” and do not provide any reason why, absent explicit teaching or inherent disclosure, that limitation would be obvious. Instead, Petitioner’s obviousness assertions regarding Chee address only whether Chee discloses “differentiator tags” and “unique differentiator tags.” Pet., 38-39. Therefore, Petitioner’s obviousness Grounds 2-3 fail for the same reasons as its anticipation Ground 1.

2. For Claim 9, Petitioner Does Not Show That Chee Discloses Or Renders Obvious “Introducing A Set Of Unique Differentiator Tags, Wherein Members Of Said Set Of Unique Differentiator Tags Are Randomly Associated With Members Of Said Plurality Of Target Nucleic Acid Molecules, Such That Any Given Tag Is Uniquely Associated With Said Locus Of Origin.”

Claim 9 recites introducing a set of unique differentiator tags and that “any given tag is uniquely associated with said locus of origin.” Petitioner alleges that Chee discloses only that “each unique identifier is associated with one nucleic acid ROI in the original sample.” Pet., 37 (citing Chee, 5:27-36). But as explained in the preceding section, Petitioner does not show or explain any disclosure in Chee tying its discussion of ROI constructs to a locus of origin, and neither Petitioner’s cited excerpt of Chee nor the cited testimony of Dr. Gabriel (EX1005, ¶159) sufficiently explain how the cited passages of Chee meet the claim limitation. Moreover, neither Petitioner (Pet., 36-37) nor Dr. Gabriel (EX1005, ¶159) make any allegations regarding inherency absent explicit disclosure.

Additionally, while Petitioner’s Grounds 2-3 allege obviousness based on Chee, Petitioner’s obviousness allegations do not address “any given tag is uniquely associated with said locus of origin” and do not provide any reason why, absent explicit teaching or inherent disclosure, that limitation would be obvious. Instead, Petitioner’s obviousness allegations regarding Chee address only whether Chee discloses “differentiator tags” and “unique differentiator tags.” Pet., 38-39.

Therefore, Petitioner's obviousness Grounds 2-3 fail for the same reasons as its anticipation Ground 1.

B. Grounds 4-7: Petitioner Does Not Establish A Reasonable Likelihood Of Prevailing On Its Grounds Based On McCloskey In View Of Bignell.⁴

Petitioner's Grounds 4-7 based on McCloskey and Bignell (either themselves or in further combination with Bentley, Gahan, or Chiang) fails because Petitioner fails to show the combination discloses all claimed steps. First, Petitioner relies solely on McCloskey for the "correcting" step in Claims 1 but fails to show that McCloskey meets that limitation. Second, Petitioner relies solely on McCloskey for the "introducing" step in claim 9 but fails to show how McCloskey discloses randomly associating random barcodes with nucleic acid molecules. For at least those reasons, Petitioner failed to establish a reasonable likelihood of prevailing on Grounds 4-7 in the Petition.

⁴ For the purposes of this Preliminary Response, Patent Owner addresses certain issues with Petitioner's grounds. Patent Owner's silence regarding any additional issue is not an agreement with Petitioner's positions. Patent Owner reserves the right to address additional issues with this ground—including issues relating to additional claim limitations, motivation to combine, and reasonable expectation of success—in future proceedings.

1. For Claim 1, Petitioner Does Not Show That The Combination Discloses Or Renders Obvious “Correcting For Error Or Bias Introduced During Said Workflow By Collapsing Target:Differentiator Tag Combinations Observed More Than Once Into A Single Count.”

Petitioner relies entirely on McCloskey as allegedly disclosing “correcting for error or bias introduced during said workflow by collapsing target:differentiator tag combinations observed more than once into a single count.” Pet., 56-57. In particular, Petitioner argues that “McCloskey corrects the skewing by identifying duplicate barcodes in an amplified sample.” *Id.*, 56. However, Claim 1 requires “correcting for error or bias... by collapsing *target:differentiator tag combinations* observed more than once into a single count.” EX1001, 131:47-49. Petitioner does not show disclosure in McCloskey of “correcting for error or bias... by collapsing *target:differentiator tag combinations* observed more than once into a single count.” Instead, Petitioner points to McCloskey authenticating an amplification product by “detecting the presence of the second sequence in the amplification product.” McCloskey, [0032]; *see also id.*, [0034]. Indeed, in each of McCloskey’s examples redundant sequences were identified by identifying the duplicate barcodes themselves, not a combination of the barcode and target nucleic acid molecule. *See id.* [0053]; *see also* Pet., 56. Petitioner also argues that McCloskey discloses “collapsing target:differentiator tag combinations” because McCloskey’s bar-coded oligonucleotides “allow it ‘to identify ... redundant sequences and to quantify

accurately the proportion of cells carrying a particular sequence variant by counting only distinctly tagged sequences.” Pet., 57 (citing McCloskey, [0093]). But Petitioner does not explain how this meets the ’730 Patent’s claimed limitation “collapsing target:differentiator tag combinations observed more than once into a single count.” Thus, Petitioner fails to show a reasonable likelihood that McCloskey discloses or renders obvious correcting for error or bias by “collapsing target:differentiator tag combinations.”

2. For Claim 9, Petitioner Does Not Show That The Combination Discloses Or Renders Obvious “Introducing A Set Of Unique Differentiator Tags, Wherein Members Of Said Set Of Unique Differentiator Tags Are Randomly Associated With Members Of Said Plurality Of Target Nucleic Acid Molecules, Such That Any Given Tag Is Uniquely Associated With Said Locus Of Origin.”

Claim 9 requires a “set of unique differentiator tags [that] are randomly associated with members of said plurality of target nucleic acid molecules.” EX1001, 132:44-48. Petitioner argues “McCloskey’s ‘random barcodes’ are ‘randomly associated’ with target nucleic acids.” Pet., 59. Petitioner further contends a “POSA would have understood that the unique barcodes [in McCloskey] would have been randomly associated with nucleic acids in the sample” because “McCloskey’s barcodes do not have a sequence that is complementary to any target nucleic acids, and therefore the barcodes are not destined for any particular molecule.” *Id.* Petitioner mischaracterizes McCloskey.

McCloskey does not disclose random barcodes that are *randomly associated* with nucleic acids. Instead, McCloskey discloses bar-coded oligonucleotides that are targeted to specific nucleic acid molecules. *See*, McCloskey, [0017]. McCloskey's bar-coded oligonucleotides require three components "a first sequence complementary to the target nucleic acid molecule, a second sequence providing a random barcode, and a third sequence that is not complementary to any sequence in the sample." *Id.* Because McCloskey's bar-coded oligonucleotides require "a first sequence complementary to the target nucleic acid molecule," each random barcode will be associated with the same starting sequence. *Id.* In the examples disclosed in McCloskey, each bar-coded oligonucleotide was specifically associated with a nucleic acid molecule in a targeted region. *See, e.g. id.*, [0052] (noting the sequences correspond to complementary FMR1 regions). Petitioner does not point to any disclosure in McCloskey where random barcodes are "randomly associated" with nucleic acid molecules. Instead, Petitioner cites instances in McCloskey where random barcodes are specifically associated with a targeted nucleic acid. *Pet.*, 59 (citing McCloskey [0017], [0046]-[0047]). Therefore, Petitioner fails to show how McCloskey discloses or renders obvious "unique differentiator tags [that] are *randomly associated* with members of said plurality of target nucleic acid molecules."

Petitioner's Grounds 5–7 all address claims that depend from Claim 1 and all rely on the McCloskey and Bignell combination to disclose or render obvious Claim 1. For at least the reasons discussed above, Petitioner fails to establish a reasonable likelihood that the combination of McCloskey and Bignell discloses or renders obvious Claim 1. Thus, Petitioner likewise fails to establish a reasonable likelihood of prevailing on its Grounds 5–7.

VII. Conclusion

For the foregoing reasons, Patent Owner respectfully requests that the Board deny institution of the Petition.

Dated: January 28, 2025

Respectfully submitted,

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Case IPR2024-01419
U.S. Patent No. 11,840,730

CERTIFICATION UNDER 37 C.F.R. § 42.24(d)

I hereby certify that this paper, excluding the portions exempted under 37 C.F.R. § 42.24(a), has 4,369 words as counted by Microsoft Word 365, the word-processing system used to prepare this paper.

Dated: January 28, 2025

Respectfully submitted,

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Case IPR2024-01419
U.S. Patent No. 11,840,730

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), the undersigned certifies that on January 28, 2025, a complete copy of the foregoing was served on counsel of record for Petitioner by filing this document through P-TACTS and by sending this document via electronic mail to the following addresses:

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