

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 SUR-REPLY

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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.

PATENT OWNER’S EXHIBIT LIST

Tab	Description
2001	Declaration of Michael Wueste in Support of Motion for Admission <i>Pro Hac Vice</i>
2002	Declaration of Kevin Goon in Support of Motion for Admission <i>Pro Hac Vice</i>
2003	D. Endy, <i>Reconstruction of the Genomes</i> , SCIENCE (Feb. 28, 2009)
2004	July 17, 2025 Declaration of Gregory Porreca, Ph.D.
2005	July 18, 2025 Declaration of Patrick Waller, Ph.D., J.D.
2006	March 6, 2009 Draft Provisional Application
2007	March 6, 2009 Draft Provisional Application Figure 1
2008	March 6, 2009 Draft Provisional Application Figure 2
2009	Metadata Associated with March 6, 2009 Draft Provisional Application
2010	Metadata Associated with March 6, 2009 Draft Provisional Application Figure 1
2011	Metadata Associated with March 6, 2009 Draft Provisional Application Figure 2
2012	April 24, 2009 Email Thread between Gregory Porreca, Patrick Waller, and Daniel Young
2013	April 30, 2009 Email Thread between Gregory Porreca, Patrick Waller, and Eric Boutin
2014	May 6, 2009 Email Thread between Gregory Porreca, Patrick Waller, and Daniel Young
2015	May 14, 2009 Email Thread between Gregory Porreca, Patrick Waller, and Daniel Young
2016	May 15, 2009 Email Thread between Gregory Porreca, Patrick Waller, and Daniel Young
2017	<i>Invitae Acquiring Good Start Genetics and CombiMatrix, Adding Comprehensive Reproductive Health Capabilities to Serve Every Stage of Life</i> , INVITAE (Jul. 31, 2017)
2018	J.D. Keasling et al., <i>Production of the antimalarial drug precursor artemisinic acid in engineered yeast</i> , NATURE (Apr. 13, 2006) (“Keasling 2006”)
2019	J.D. Keasling, <i>Synthetic Biology for Synthetic Chemistry</i> , ACS CHEMICAL BIOLOGY (Jan. 18, 2008) (“Keasling 2008”)
2020	C.A. Hutchison, R.Y. Chuang, J.C. Venter (Mar. 16, 2016) (“Hutchison”)

Tab	Description
2021	March 6, 2009 Email Thread between Gregory Porreca, Patrick Waller, Daniel Young, and Eric Boutin
2022	M.P. Weiner, S.B. Gabriel, and J.C. Stephens, <i>Genetic Variation: A Laboratory Manual</i> , COLD SPRING HARBOR LABORATORY PRESS (2007) (excerpted)
2023	July 18, 2025 Declaration of Joseph Puglisi, Ph.D.
2024	July 9, 2025 Deposition Transcript of Stacey Gabriel, Ph.D.
2025	November 6, 2025 Deposition Transcript of Stacey Gabriel, Ph.D.
2026	Signed Diagram 1 Introduced as Exhibit 2026 During the November 6, 2025 Deposition of Stacey Gabriel, Ph.D.
2027	Signed Diagram 2 Introduced as Exhibit 2027 During the November 6, 2025 Deposition of Stacey Gabriel, Ph.D.

All citations to Exhibits refer to stamped exhibit page numbers.

I. Introduction

Petitioner's Reply fails to meaningfully remedy the Petition's deficiencies. *First*, for Grounds 1-3 based on Chee, Petitioner attacks the evidence Patent Owner (PO) provided showing prior conception and diligence. But Petitioner applies an unsupported interpretation of "error" and an unreasonably high bar for diligence. Those arguments cannot make Chee prior art. And Petitioner still fails to show that Chee discloses all claim limitations or establish a motivation to combine Chee with Gahan. Thus, Grounds 1-3 fail. *Second*, for Grounds 4-7 based on Bignell and McCloskey, Petitioner fails to establish a motivation to combine by failing to address Bignell's rejection of a fundamental premise of McCloskey's approach and the combination's cost. And Petitioner still does not show that the combination discloses using the claimed step of collapsing tag and target sequence combinations. Thus, Grounds 4-7 fail.

II. Grounds 1-3: The Challenged Claims Are Patentable Over Chee Alone Or In View Of Gahan

A. Chee Is Not Prior Art To Claims 1-3 And 9.

The inventors conceived of claims 1-3 and 9 in a March 6, 2009 document (EX2006, EX2007, and EX2008) (collectively, the "March 6 Application"), *before* Chee's alleged priority date of April 30, 2009. POR, 37. Petitioner argues that the March 6 Application does not disclose conception of a single limitation—"correcting for errors or bias"—and that the inventors and attorneys did not exercise

reasonable diligence. Reply, 20-27. But the evidence shows otherwise, and both arguments fail.

1. The March 6 Application Shows Conception Of “Correcting For Errors Or Bias.”

The only claim element Petitioner argues was missing from the March 6 Application is “correcting for errors or bias.” Reply, 20-21; EX2025, 111:11-113:17. But Petitioner applies an unsupported interpretation of the claims to carve this limitation out of the March 6 Application, and their sole argument on conception fails.

As an initial matter, Petitioner incorrectly suggests that a wholly separate “method of correcting for errors” needed to be described in addition to a “method of correcting” for conception. Reply, 21 (“Therefore, to demonstrate prior conception, Molecular Loop must show conception of *both* a method for correcting errors *and* a method for correcting bias.”) (emphasis in original). That is not what the claims require. They merely recite a “method for correcting for errors or bias” and a step of “correcting for errors or bias.” EX1001, Claim 1. The steps in the claimed method, and the manner in which the correcting step is performed, do not differ based on whether “error” or “bias” is being corrected. The claims cover one method that can correct for either. Indeed, while Petitioner states that error and bias must be “different” (Reply, 22), they never assert that “error” and “bias” are mutually

exclusive. Nor could they, as the specification describes them as overlapping concepts. EX1001, 4:57-66 (describing “systematic and random errors (bias)”), 5:8-11 (describing “reduc[ing] errors caused by bias, or the risk of bias”). While Petitioner admits that the March 6 Application discloses “correcting for bias,” they complain that it does not separately recite “correcting for errors.” Reply, 21. But as explained further below, the March 6 Application describes correcting for errors, even if it does not use the words “correcting for error” verbatim.¹ Thus, all evidence PO provided in the March 6 Application for “correcting for errors or bias” applies equally to show conception of the claimed method of correcting for either. POR, 24-29; EX2023, ¶¶67-72, 78-84, 86-91, 99.

Even accepting Petitioner’s view of the claims, the March 6 Application discloses “correcting for errors.” Dr. Gabriel agrees that the traditional understanding of “error” as used in the ’730 Patent is an “inaccurate result”:

Q. When you were rendering your opinions on the ’730 patent in the course of this inter partes review, were you applying a different definition of “error” than the traditional understanding of an inaccurate result?

A. I don’t think so. No.

¹ Petitioner incorrectly argues that “the word ‘error’ does not appear in the March 6 Application.” Reply, 21. The March 6 Application discusses “error,” and detecting such errors, including “synthesis errors.” EX2006, 5; EX2025 at 124:3-6.

EX2025, 30:7-13. The March 6 Application discloses detecting and correcting for such errors. For example, the March 6 Application discloses using its methods to correct for overrepresentation, which is a type of error. EX2006, 5 (“However, if we also have information on random barcodes, this situation could be averted, because the *over-represented allele would be seen to also have an over-represented random barcode* (i.e., the sequences with the overrepresented barcode all originated from the same single molecule).”); EX2023, ¶72 (Dr. Puglisi explaining that the March 6 Application discloses using tag:sequence combinations to correct for issues related to over- and under-representation). Dr. Gabriel agrees that such overrepresentation is “error.” EX2025, 27:20-28:5 (“Q. *Is overrepresentation a type of error?* A. Well, generally, anything that is not -- *if it’s not a true representation of what your original molecule was, then there’s an inaccurate result*. Again, just semantics. *We can say an inaccurate result is an error.*”); EX1066, 11:19-25 (agreeing that overrepresentation is a “common source of error”).

There is nothing in the ’730 patent that says “bias” cannot overlap with “error” or that otherwise carves out particular types of errors—including “overrepresentation errors”—from the claimed “errors.” Accordingly, the March 6 Application’s description of correcting overrepresentation errors further demonstrates conception of Claims 1-3 and 9 of the ’730 Patent, including “correcting for errors or bias.”

2. Petitioner Applies An Erroneous Interpretation Of “Error.”

Petitioner applies an unduly narrow definition of “error” to argue against conception in the March 6 Application. Petitioner essentially argues that “errors” are limited to errors that “occur in DNA synthesis during amplification or sequencing in which a nucleotide is incorrectly incorporated in the complementary strand.” Reply, 22. That interpretation is inconsistent with the intrinsic and extrinsic evidence, and it runs contrary to Petitioner’s expert’s testimony.

Neither the intrinsic nor extrinsic evidence supports Petitioner’s narrow interpretation of “error.” Reply, 21-22. Tellingly, Petitioner does not cite *any* intrinsic evidence to support such an interpretation. The claim language does not require that error occur “during amplification or sequencing,” as required by Petitioner’s interpretation. The plain language of the claims requires only “errors or bias” that are “introduced during nucleic acid analysis workflow.” EX1001, Claim 1. Both experts agree that a POSA would have understood that a “nucleic acid analysis workflow” would include at least four steps, only two of which are amplification or sequencing: (1) library preparation, including synthesis of primers; (2) amplification; (3) sequencing; and (4) subsequent analysis of sequenced reads. EX1005, ¶¶58-60; EX2024, 47:7-48:18; EX2023, ¶37; EX1066, 56:13-24. Indeed, Dr. Gabriel included library preparation and synthesis of oligonucleotides as steps comprising a sequencing workflow. EX1005, ¶¶58-60. And dependent claim

language confirms that the “error” recited in Claim 1 must be broader than only sequencing or amplification errors. Dependent Claim 3 recites an additional step of “determining the presence of a ***sequencing or amplification error*** based upon a number of said differentiator tag sequences.” EX1001, Claim 3. Therefore, the “error” recited in Claim 1 is broader than the “sequencing or amplification error” recited in Claim 3. *Alcon Rsch., Ltd. v. Apotex, Inc.*, 687 F.3d 1362, 1367 (Fed. Cir. 2012). Accordingly, the plain language of the claims does not support Petitioner’s narrower interpretation.

The specification also does not suggest that an “error” must be an “error in a sequence that arises from amplification or sequencing.” Instead, the specification explains that systematic and random errors may themselves be bias, or bias may cause an error. For example, the ’730 patent explains that its “methods [] overcom[e] problems associated with ***systematic and random errors (bias)*** in genome capture, amplification and sequencing method.” EX1001, 4:57-66, 5:8-11 (claimed methods “***reduce errors caused by bias***, or the risk of bias, associated with the capture, amplification and sequencing of genetic loci, e.g., for diagnostic purposes”); EX1068, 142:14-22, 143:11-19. Accordingly, Petitioner’s narrower interpretation is inconsistent with the specification.

Instead of intrinsic evidence, Petitioner relies on Dr. Gabriel and mischaracterizations of Dr. Porreca’s and Dr. Puglisi’s testimony. Reply, 22;

EX1065, ¶¶38-43, EX1005, ¶¶75-76. Dr. Gabriel’s first declaration simply explains, without any citations to the ’730 Patent, that errors to the sequence can arise during amplification and sequencing, not that the claimed errors exclude certain types of errors (e.g., quantitative errors), or that errors and bias must be mutually exclusive. EX1005, ¶¶75-76. And in her second declaration, Dr. Gabriel merely states her unsupported opinion improperly interpreting “errors,” which runs contrary to her testimony that the traditional understanding of error is “an inaccurate result.” EX1065, ¶¶38-43; EX2025, 27:20-28:19, 29:22-30:6. Thus, Dr. Gabriel’s testimony undermines Petitioner’s narrower interpretation.

Petitioner also mischaracterizes testimony from Dr. Porreca and Dr. Puglisi. Reply, 21-22. Neither testified that the meaning of “error” is a “sequencing” error or that “bias” is entirely different from “error.” EX1066, 95:5-8, 96:3-17, 96:18-22, 103:25-104:7, 105:7-13; EX1068, 139:16-140:20, 144:2-151:21. Instead, consistent with Dr. Gabriel’s testimony, Dr. Porreca explained that an “error” is “something that’s not right.” EX1068, 143:11-19. And Dr. Puglisi explained that “[t]here can be other forms of bias that would be more systematic errors,” such that “error” in the context of the claims is not limited only to only errors in the sequence. EX1066, 95:17-21, 96:18-22.

Petitioner also twists Dr. Puglisi’s testimony to argue that he agreed that the March 6 Application did not disclose a “sequencing error.” Reply, 21-22. Dr. Puglisi

said no such thing. Rather, he testified that the figures of the March 6 Application show correction for amplification errors. EX1066, 57:22-58:2; EX2007-2008. He also explained that, though there is not a sequencing error explicitly shown in EX2008, that is “because [in EX2008] you have the right representation of the original population.... *And so [a sequencing error] would be reflected in an incorrect population after the collapsing of the barcodes.*” EX1066, 58:6-13. In other words, Dr. Puglisi does not “admit[] that sequencing errors are not disclosed in the March 6 Application or accompanying figures” as Petitioner contends (Reply, 21-22), but instead explains that EX2008 does not specifically show a sequencing error because it depicts a correct representation of the original population.

Accordingly, Petitioner fails to sufficiently rebut PO’s evidence showing prior conception of Claims 1-3 and 9 of the ’730 Patent.

3. PO Showed Reasonably Continuous Diligence.

PO showed that the inventors and prosecuting attorneys exercised reasonably continuous diligence during the 20-day critical period from April 29, 2009 (before the earliest claimed priority date of Chee) through constructive reduction to practice on May 18, 2009. POR, 31-34. Petitioner’s counter argument centers on the assertion that there is “no evidence showing that any prosecution work was performed on 12 days of the 20-day critical period,” and therefore no diligence, with a chart

purporting to summarize those days. Reply, 23, 25-26. Petitioner is wrong on both the facts and the law.

Petitioner's chart of the critical period listing days with "[n]o evidence of activity" (Reply, 25-26) ignores significant portions of the evidence PO submitted. Petitioner's complaints that there is "no evidence" on twelve days fails because they (1) demand an unreasonably high requirement of constant seven-days-per-week work by ignoring that *five of the twelve days are weekend days*; (2) improperly ignore evidence on certain days or dismiss it as not showing *enough* work on that day;² and (3) ignore evidence in communications on days surrounding the alleged inactive days that show that work *was* being done on the days between the communications. Remedying those errors for the twelve days Petitioner focuses on shows that there was no lack of reasonably continuous diligence, as explained below.

² Petitioner dismisses certain evidence of status checks and calls as "ministerial communications," which it alleges "are not included as a prosecution activity." Reply, 25 n.9. That is incorrect. In *Perfect Surgical Techniques, Inc. v. Olympus America, Inc.*, the Federal Circuit cited similar contemporaneous calls to discuss a draft application as evidence of a diligent reduction to practice, explaining that further details about the specific content of the discussions was "unnecessary." 841 F.3d at 1010-1011 (Fed. Cir. 2016).

- May 1-4: Petitioner ignores that two of these days (May 2-3) were a weekend. Petitioner also ignores that on April 30, the inventors emailed the attorneys paragraphs to insert into the developing application, explaining that there were placeholders for ongoing modeling work for which “Uri is still calculating the actual numbers.” EX2012, 1-2. Then at 7:59AM on May 5, the inventors said “[w]e’re finished working out Uri’s example” and provided the results of the work. EX2012, 1. Obviously, work that went into the modeling/calculating results was done in the days in between (May 1-4) and evidence activity during those days.
- May 6-8. Petitioner improperly dismisses evidence of activity during these days as not being substantive enough, but they are evidence of ongoing work. On May 6, communications between the inventors and attorneys mention the ongoing work for “wrapping up Uri’s application,” including “completing the histogram for [the] application.” EX2014, 4. And communications on May 8 again mention the ongoing work and set a time to discuss the status the following day (May 9, a Saturday). EX2014, 2-3.
- May 10: Petitioner ignores that this was a Sunday. It also falls between a Saturday when the inventors and counsel met to discuss the developing application (EX2014, 2-3) and a Monday when the attorneys indicated they were continuing to work on the application (EX2014, 1).

- May 12-13: Petitioner ignores that on May 11, the attorneys emailed the inventors and stated “[w]e are working on the two drafts,” which included the provisional that was eventually filed May 18. EX2014, 1. And on May 14, the attorneys followed up sending the “draft of Uri’s application” that they had been working on. EX2016, 1. Obviously, work that went into that draft application was done in the days in between (May 12-13) and evidence activity being done during those days.
- May 16-17: Petitioner ignores that these two days were a weekend.

Petitioner applies an unreasonably heightened bar to the diligence analysis, which requires only “*reasonably continuous* diligence” during the critical period. *Perfect Surgical*, 841 F.3d at 1009. Accordingly, “[a] patent owner need not prove the inventor *continuously* exercised reasonable diligence throughout the critical period;” rather, “an inventor is not required to work on reducing his invention to practice every day during the critical period,” and “*periods of inactivity* within the critical period do not automatically vanquish a patent owner’s claim of reasonable diligence.” *Perfect Surgical*, 841 F.3d at 1009 (emphasis in original). Petitioner’s piecing together of a handful of days—including weekends—during which it alleges there is no evidence of activity is exactly the kind of “fixat[ion] on the portions of the critical period where [patent owner] did not provide evidence of [the inventor’s]

specific activities” that the Federal Circuit has rejected. *Perfect Surgical*, 841 F.3d at 1010.

Petitioner’s remaining attacks on Dr. Waller and Dr. Porreca fare no better. Petitioner argues that Dr. Waller’s testimony is irrelevant because he allegedly “did not work on” the application and instead delegated work to Dr. Young. Reply, 24. But Dr. Waller testified about his own diligent work throughout the critical period, including that he worked closely with Dr. Young on the application, did work on it himself, and did not merely hand it off to Dr. Young without oversight. EX1067, 30:8-14, 30:19-31:4, 37:5-18, 38:17-22, 45:20-46:1, 46:14-47:13, 49:11-13, 57:7-15, 57:21-58:8; POR, 33. The documentary record reflects corroborating communications and drafts from Dr. Waller’s work on the application. EX2013, 1; EX2014, 1-5; EX2015, 1-2. Similar evidence—including an attorney declaration and copies of emails, even where such emails omitted drafts of the application—is exactly the type of evidence found sufficient to demonstrate diligence in *Ex Parte Koji Murayama*. 2020 WL1663636, at *5 (PTAB April 1, 2020).

Petitioner also attempts to discredit Dr. Waller and Dr. Porreca for not recalling their specific activities during each day of the critical period, which was *sixteen years ago*. Reply, 23-24. But nothing requires inventors or attorneys to recount each activity they performed years earlier to show diligence when the contemporaneous documentation corroborates what they do remember. *Perfect*

Surgical, 841 F.3d at 1010-11 (finding that memory of specific activities performed each day was “unnecessary” when the record showed the inventor and attorneys were exchanging drafts, responding to edits, and meeting throughout the critical period). Further, Dr. Porreca testified that while he may not have remembered the specific date and content of a particular call or email off the top of his head, he does remember the work they did on the applications leading to the ’730 Patent, and that memory was consistent with and reaffirmed by reviewing the documentary record. EX1068, 157:15-159:1; *see also* EX1067, 37:11-18. And, although Petitioner takes issue with Dr. Porreca’s statements that are “based on [his] review” of documents, there is nothing wrong with an inventor or attorney’s “review” of written records to confirm specific details and dates for work they did on an application many years earlier. *Perfect Surgical*, 841 F.3d at 1010 (finding an inventor need not have independent memory of detailed activities reflected in supporting evidence); *Olympus America, Inc. v. Perfect Surgical Techniques, Inc.*, No. IPR2014-00233, at EX2010, ¶¶13-16 (PTAB Oct. 3, 2014) (testimony at issue in *Perfect Surgical* explaining “[b]ased on my review of written correspondence and billing statements ... I submitted comments to [prosecuting attorney] on the initial draft of the application on March 2, 1998.”), *see also id.* at EX2012, ¶¶9-11.

B. Petitioner Fails To Show That Chee Discloses The “Collapsing” Step.

Petitioner does not show that Chee discloses the “collapsing” step because Petitioner points to only a single step—determining a consensus read—for each of the separate “collapsing” and “determining a consensus base sequence” steps in the claims. POR, 41-42. Petitioner does not meaningfully address that claim-required distinction. Instead, Petitioner still points only to portions of Chee that determine a consensus read, but do *not* collapse.

The claims require “correcting for error or bias introduced during said workflow *by collapsing target:differentiator tag combinations.*” The two mechanisms in Chee that Petitioner identifies do not disclose the claimed collapsing. Petitioner relies on (1) Chee’s determination of a consensus sequence, which Petitioner alleges corrects for “sequencing” errors; and (2) Chee’s alleged “counting” or “grouping” molecules with the same unique identifier, which Petitioner alleges corrects for amplification bias.³ Reply, 11-14. Petitioner assumes that Chee’s alleged disclosures of correcting for error necessarily also disclose

³ Petitioner is inconsistent, first alleging that “collapsing” just means “counting” (Reply, 12-14), but then asserting “collapsing” means “grouping” by “binning” (Reply, 15). In either case, Petitioner does not and cannot point to any part of Chee that explains “collapsing.”

collapsing, but that is incorrect. Instead, Petitioner’s Reply proves PO’s point: Chee does not provide any actual method of *collapsing* to correct for any alleged “sequencing errors” or amplification bias. Reply, 12-14, 15-17; EX1066, 117:1-4.

First, Petitioner’s argument that Chee necessarily collapses by determining a consensus sequence is incorrect. Instead, Petitioner points to the same single step, determining a consensus base call from multiple clonal copies of a single molecule, to show both “collapsing” *and* “determin[ing] a consensus base sequence.” Reply, 14-15. Although Petitioner and Dr. Gabriel allege that “determining a consensus base call” is *part* of the process of identifying errors, neither points to any portion of Chee actually showing “collapsing.” Reply, 14-15; EX2025, 102:9-13. Accordingly, Petitioner improperly conflates distinct limitations of Claims 1 and 2, as PO explained. POR, 45-46.

Second, Petitioner’s argument that Chee discloses a method to correct for amplification bias and thus collapses by “counting” or “grouping” also fails. Each of Chee’s disclosures simply conclude that Chee’s method *quantifies* molecules to correct for amplification bias. EX1010, 23:59-64 (“quantification of the molecules [to] be corrected to reflect [amplification] bias”); EX1066, 120:1-5. But quantifying molecules to correct for amplification bias does not, without more, disclose collapsing “target:differentiator tag combinations” into a single count as required by the claims. Nor does Petitioner point to any evidence to say that using a unique

identifier to count each molecule discloses collapsing in the manner required by the Challenged Claims. Reply, 13; EX1010, 10:41-46.

Petitioner’s argument that Chee “groups” or “bins” multiple clonal copies of a construct using their shared unique identifier (Reply, 15) mischaracterizes Dr. Puglisi’s testimony. Dr. Puglisi did not testify that Chee performs the same type of “binning” as would be understood in the Challenged Claims of the ’730 Patent. Instead, he explained that *after* Chee has determined a consensus base sequence by reading multiple reads of the same identical molecule, it aligns the sequence to build part of a genome. EX1066, 113:3-114:13; EX1010, 9:29-39. But this does not mean that Chee “bins” to correct for errors before determining a consensus sequence. And neither Petitioner nor Dr. Gabriel can point to any part of Chee that says it uses a “grouping” or “binning” method. Reply, 15; EX1065 ¶26; EX1010, 14:46-50, 9:29-39.

Thus, Petitioner fails to show that Chee discloses the “collapsing” step in the Challenged Claims.

C. Petitioner Fails To Show That Chee Discloses Collapsing Before Making A “Consensus Base Call” As Required By Claim 2.

Petitioner fails to cite to any disclosure in Chee that discloses performing any of Chee’s alleged genotyping methods (which Petitioner cites as allegedly making consensus base calls) *after* collapsing, as required by Claim 2. Petitioner’s quibble

that a “consensus base call” does not refer to making a genotype call (Reply, 16) misses the point. Dr. Gabriel asserts that Chee’s “binning” occurs before making a consensus base call, but that unsupported assertion fails because (1) Chee’s “binning” is not collapsing as explained above; and (2) Dr. Gabriel cites to the same portion of Chee—describing determining a consensus base call—for both alleged steps. Reply, 16; EX1065 ¶26 (citing EX1010, 9:29-39). Accordingly, Petitioner does not show that Chee “collapses” at all, let alone collapses before performing a consensus base call.

D. Chee Is Not Entitled To Its Provisional Date.

Petitioner argues that Chee’s provisional describes using its technique on biological samples for humans. Reply, 18. But Petitioner cites nothing in Chee’s provisional that says its biological samples are *naturally-occurring*. Instead, as PO showed, Chee’s provisional focuses entirely on applying its method to samples that are *synthetically* created, and therefore not naturally-occurring. POR, 35-41. Petitioner ignores that the language disclosing use of Chee’s purported invention on naturally-occurring biological samples was not added until *after* the April 30, 2009 provisional. POR, 37. And though Petitioner points to portions of the Chee Provisional that say its methods can be used for “clinical” and “diagnostic” purpose (Reply, 19), Petitioner ignores that synthetically-created biological samples can be analyzed for such purposes. EX2023, ¶¶40-43.

Petitioner also incorrectly claims that PO's argument is based on only one passage in Chee. Reply, 19. Petitioner ignores the many additional citations provided by PO and Dr. Puglisi showing that the invention in the Chee Provisional is directed to *synthetically-created* biological samples. POR, 35-41; EX1011 [0001], [0003]-[0005], [0066], [0129], [0130]; EX2023 ¶¶164-169; EX2025, 107:6-109:4.

Thus, Chee is not entitled to its provisional date of April 30, 2009.

III. Grounds 4-7: The Challenged Claims Are Patentable Over McCloskey And Bignell

A. Petitioner Fails To Show A Motivation To Combine McCloskey And Bignell.

There is no motivation to combine McCloskey and Bignell. Petitioner does not persuasively counter PO's showing that (1) the proposed combination would frustrate Bignell's goals of tagging every molecule from multiple different samples with the same tag to increase throughput and reduce costs; and (2) the combination would greatly increase costs, something both Petitioner and Dr. Gabriel failed to consider at all. POR, 56-61. Petitioner's Grounds 4-7—all of which depend upon the McCloskey-Bignell combination—thus fail.

First, Petitioner fails to remedy the fact that Bignell identifies and rejects an approach that individually tags each molecule with a separate tag—like McCloskey's approach. A POSA would have understood that Bignell is focused on multiplexing samples together and thus attaches the same tag to each nucleic acid

from a single sample to accurately sequence nucleic acids from multiple different samples in a single sequencing run. EX1013, 1:24-28; EX2025, 83:9-20. Because Bignell sought to attach the same tag to every sample, it highlighted challenges with a prior approach by Brenner that tagged each individual molecule with a different tag. EX1013, 3:32–35 (“Whilst this is ideal for treating one sample such that each individual molecule in the sample carries a different tag, *it does not permit attachment of the same tag to every molecule in the sample.*”). Dr. Gabriel agrees. EX2025, 82:5–9 (“For what [Bignell’s] trying to accomplish here, [Bignell’s] saying there was a problem with the Brenner approach.”).

McCloskey, similar to the Brenner method identified in Bignell, labels nucleic acid molecules “with distinct sequence tags,” and thus follows the same prior art approach that Bignell sought to avoid. EX1012, [0005]. A POSA would not have looked to an approach that Bignell already considered and rejected, something Dr. Gabriel admitted at deposition and which Petitioner fails to meaningfully rebut. EX2024, 76:7-14 (“If the goal is being able to tell one sample from another sample, *you wouldn’t want to have different tags applied within a sample.*”).

Petitioner points out that McCloskey also discloses using a “batch-stamp” that “may identify a sample, a patient, and/or an analysis date” by “provid[ing] a unique identity” to the sample, but this misses the point. Reply, 8; EX1012, [0027]. Bignell mentions prior approaches that provided molecule-specific tags like McCloskey and

Brenner and *rejected their use for its applications*. A POSA would not have looked to McCloskey's molecule-specific approach in the face of Bignell's rejection of such approaches. And a POSA starting with McCloskey would not have looked to Bignell's method because McCloskey already used batch-stamps. EX1012, [0027]; EX1013, 6:36–48; Reply, 8. Combining McCloskey with Bignell would thus result in a redundant combination, which does not evidence a motivation to combine. *S.-Tek Sys., LLC v. Engineered Corrosion Sols., LLC*, 748 F. App'x 1003, 1007 (Fed. Cir. 2018).

Second, Petitioner fails to show why a POSA using Bignell would have accepted the extra costs required by McCloskey's approach. As Dr. Gabriel agrees, Bignell is directed towards *reducing* relative costs while maintaining *sample-specific*—not molecule-specific—information in NGS runs involving millions of sequences. EX1013, 2:3–8; EX2025, 87:11-15; EX2023, ¶¶196–197. Unlike McCloskey's Sanger sequencing method, next-generation sequencing like Bignell can sequence millions of sequences from multiple different samples in a single sequencing run, each of which would have required its own unique barcode in a molecule-specific approach. Pet., 4; Reply, 10; EX1013, 3:28–32. Petitioner admits that using molecule-specific tags would have generated an additional cost to the sequencing workflow, which is antithetical to Bignell's goal of reducing relative costs. Reply, 9; EX1065, ¶20; EX1013, 2:3–8; EX2025, 87:11-15; EX2023, ¶¶196–

197. Thus, the costs and labor of designing and incorporating millions of unique tags would dissuade a POSA from combining McCloskey and Bignell. EX2023, ¶¶195-197.

Petitioner does not deny that Dr. Gabriel never even considered, let alone analyzed, the costs of the McCloskey-Bignell combination. Pet., 46–51; EX2025, 91:19–92:7. Rather than adduce any such evidence, Petitioner argues that PO “provides no evidence showing how much it would have cost to add McCloskey’s unique barcodes to Bignell.” Reply, 9; EX1065, ¶20. But it is *Petitioner’s* burden, not PO’s, to provide evidence showing both a motivation to combine McCloskey and Bignell and a reasonable expectation of success in doing so. *Unified Pats. Inc. v. Velos Media, LLC*, No. IPR2019-00710, 2020 WL 5135433, at *5 (P.T.A.B. Aug. 31, 2020) (citing *Dynamic Drinkware, LLC. V. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1478 (Fed. Cir. 2105)).

Petitioner claims, without analysis, that “a POSA would have understood that synthesizing and adding McCloskey’s unique barcodes would not have significantly increased the cost of NGS sequencing.” Reply, 9 (citing EX1065, ¶20). But neither Petitioner nor Dr. Gabriel cite anything other than her bare opinion as evidence for such an assertion, which is insufficient. *Boragen, Inc. v. Syngenta Participations AG*, No. IPR2020-00124, 2020 WL 4680031, at *3 (PTAB Aug. 10, 2020) (diminishing expert’s testimony where “there was no documented factual support in

the record to buttress [expert's] bare opinion"). And Dr. Gabriel's testimony is suspect because she admits that incurring an additional cost—like in the proposed combination—"may or may not be" worth it "depending upon what a person was trying to do" in a given experiment, but also admits that she provides *no* identification or analysis of what experiments a POSA would use the McCloskey-Bignell combination for or what goals they would be trying to achieve. EX2025, 91:10-13, 92:8-14; EX1065, ¶¶20-21. Thus, Dr. Gabriel's conclusory and unsupported opinion does not remedy Petitioner's failure to address the costs of its combination.

Third, Petitioner's argument that the "industry trends provided a motivation to adapt conventional sequencing techniques for use in NGS systems" (Reply, 10) does not save Petitioner's combination in the face of Bignell's rejection of approaches like McCloskey's, for the reasons explained above in this Section III.A.

Fourth, Petitioner cannot show evidence of simultaneous invention (Reply, 10-11) because Chee does not disclose the claimed invention for the reasons explained above in Section II. And in Petitioner's cited *Univ. Cal. v. Broad Inst. Inc.* case—which concerned a finding of no interference-in-fact, not obviousness—the Federal Circuit affirmed a Board finding that evidence of simultaneous invention did not actually "indicate an expectation of success" when considered "along with evidence regarding the state of the art, the statements of the inventors, failures

involving similar technologies, and the remainder of the record evidence.” 903 F.3d 1286, 1295-96 (Fed. Cir. 2018). Petitioner has not addressed how Chee’s alleged “simultaneous invention” fits in with any of those additional criteria, and so its argument carries little, if any, weight.

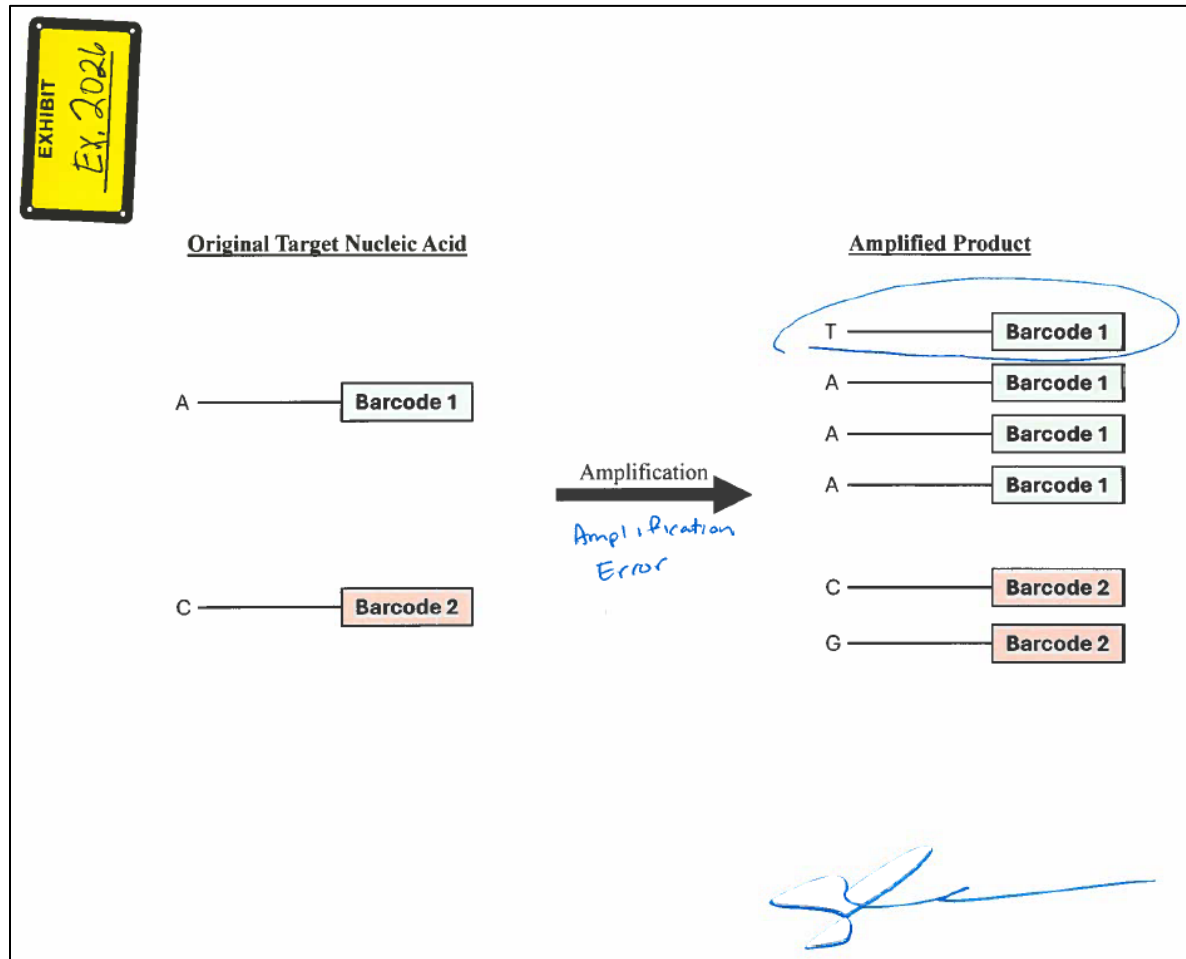
B. Petitioner Fails To Show That The Combination Discloses The “Collapsing Target:Differentiator Tag Combinations” Step of Claim 1.

Unlike the claims of the ’730 Patent, McCloskey counts *only* its unique barcodes to authenticate sequences, rather than collapsing barcode:sequence combinations to correct for errors. EX1012, [0009]; POR, 52–56; Reply, 5. Petitioner does not—and cannot—meaningfully dispute this. Dr. Gabriel agrees that McCloskey uses the barcode alone. EX2025, 67:14-17 (“Q. In your opinion, McCloskey identifies target:barcode combinations *using the barcode alone. Correct? A. Yes.*”). Accordingly, because McCloskey does not disclose use of “target:differentiator tag *combinations*,” and because Petitioner relies solely on McCloskey for the “collapsing target:differentiator tag” limitation, Grounds 4-7 fail.

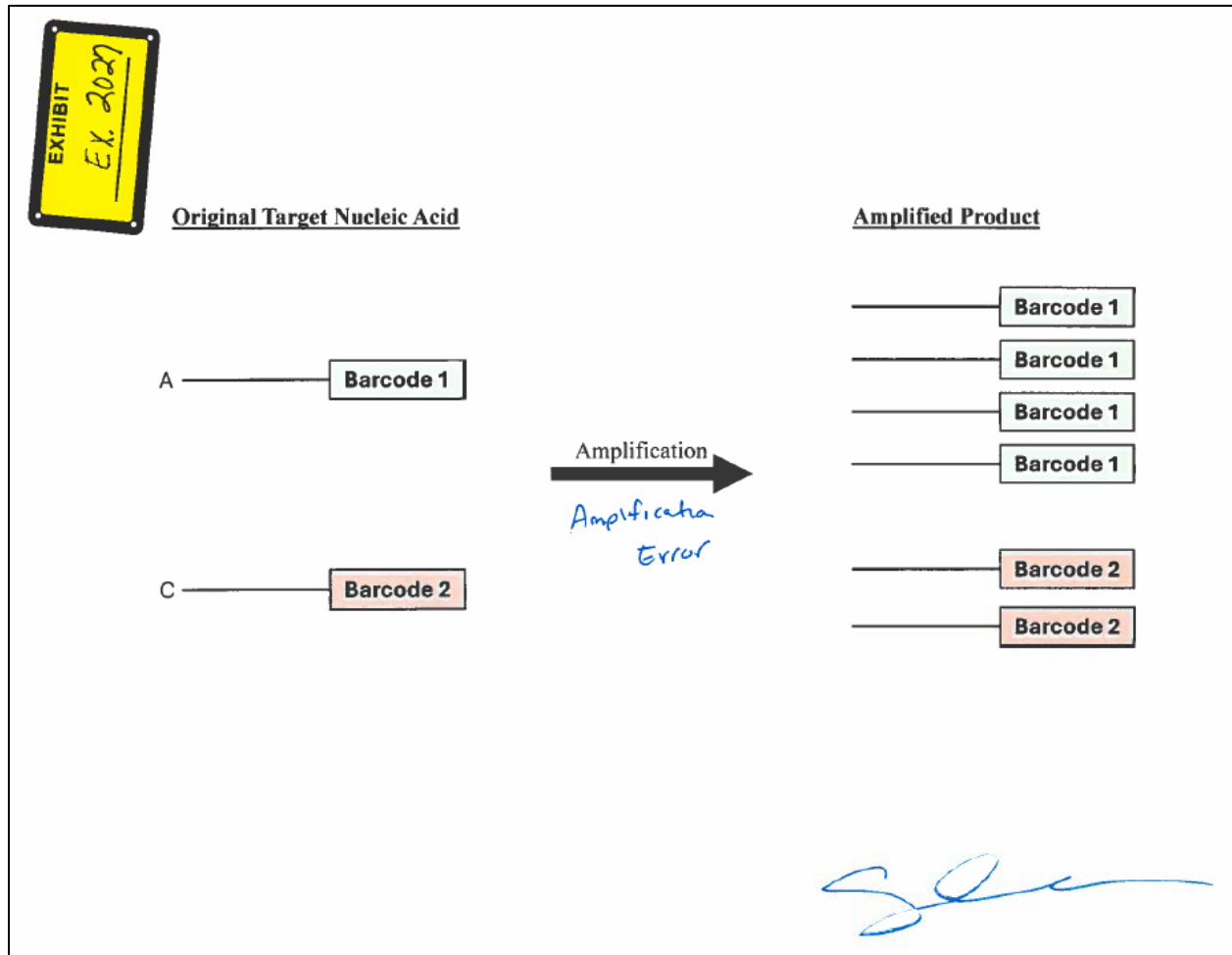
Petitioner’s arguments do not rectify this failure. *First*, Petitioner argues, incorrectly, that the “target:differentiator tag combinations” limitation of independent claim 1 is met by use of barcodes alone because dependent claim 2 recites “said correcting step further comprises collapsing all sequence reads comprising a same differentiator tag *into a single read before determining a*

consensus base call for the target nucleic acid molecule sequences.” Reply, 4. Petitioner’s argument fails because the plain language of Claim 1 requires “target:differentiator tag *combinations*,” not tags alone. Claim 1, therefore, collapses target:differentiator tag combinations, while claim 2 further requires that collapsing said combinations must occur before determining a consensus base call. EX1066, 143:23–144:5. Claim 2’s additional step after “collapsing” does not justify misreading the “target:differentiator tag *combinations*” limitation to require tags alone.

Second, Petitioner claims that “Molecular Loop’s argument is inconsistent with McCloskey” by pointing out that McCloskey “us[es] the barcodes to identify duplicates and count the duplicates as one distinct read.” Reply, 5. This argument assumes that using the barcodes alone will have the same result as using “target:differentiator tag combinations.” But Dr. Gabriel admitted that this is not true. When Dr. Gabriel was presented with information that included both target sequences and barcodes—like that claimed by the ’730 Patent—Dr. Gabriel was able to identify product sequences subject to amplification errors:



EX2026; EX2025, 46:22-50:8. But when Dr. Gabriel was presented with information that included barcodes alone—like in McCloskey’s method—she was unable to do so.



EX2027; EX2025, 53:14–54:21. Accordingly, the '730 Patent's recitation of collapsing "target:differentiator tag combinations" instead of barcodes alone creates real advantages in accuracy when subsequently correcting for errors, making genotype calls, or determining consensus base sequences. EX1001, 1:23-24, 5:1-11, 5:33-45, 6:5-13, 72:50-73:5, 131:47–49, Figure 5. And the distinction between the methods of the '730 Patent and McCloskey makes sense, because McCloskey is primarily directed not to error correction or genotyping, but authentication. EX1012, [0004], [0009]; EX2025, 71:22-74:7. Dr. Gabriel agreed that there are "certain types

of experiments called ‘counting applications’ where you can analyze the barcode to understand how many molecules are there,” and explained that those are “a different type of experiment” and “a different application” than using the barcode and the sequence to correct for errors or bias. EX2025, 53:14–54:21. Similarly, authenticating—which requires only barcodes alone—is a different type of experiment and a different application than correcting for errors or bias.

Third, contrary to Petitioner’s misrepresentation (Reply, 6-7), PO agrees that Claim 1 of the ’730 Patent does not recite making genotype calls. But what the ’730 Patent does require—collapsing “target:differentiator tag combinations” instead of barcodes alone—provides advantages when later making genotype calls, as described above, that highlight the difference between the claimed methods and the prior art. McCloskey does not recite making genotype calls, as Dr. Gabriel agrees (EX2025, 79:7-14), because that is not the purpose of its barcode-alone method for *authenticating* sequences, and therefore its method neither discloses collapsing “target:differentiator tag combinations” nor provides the advantages of the inventive method of the ’730 Patent.

Accordingly, McCloskey does not disclose collapsing “target:differentiator tag combinations.”

IV. Conclusion

For the foregoing reasons, the Challenged Claims are patentable.

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

Dated: November 21, 2025

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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 5,587 words as counted by Microsoft Word 365, the word-processing system used to prepare this paper.

Dated: November 21, 2025

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), the undersigned certifies that on November 21, 2025, a complete copy of the foregoing and corresponding exhibits were 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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