

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ILLUMINA INC.,
Petitioner,

v.

MOLECULAR LOOP BIOSCIENCES, INC.,
Patent Owner.

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

PETITIONER'S REPLY

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Exhibit List

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1001	U.S. 11,840,730 (“’730 patent)
1002	’862 Application FH
1003	’687 Application FH
1004	’764 Application FH
1005	Declaration of Stacey Gabriel, Ph. D.
1006	Provisional Appl. No. 61/174,470
1007	Provisional Appl. No. 61/178,923
1008	Provisional Appl. No. 61/179,358
1009	Provisional Appl. No. 61/182,089
1010	US 9,085,798 to Chee
1011	Provisional Appl. No. 61/174,442
1012	US Pub. US2007/0020640 to McCloskey
1013	US 8,053,192 to Bignell
1014	J. Shendure & H. Ji, Next-Generation DNA Sequencing, Nature Biotechnology, Vol. 26, No. 10 (Oct. 2008)
1015	Gahan, Circulating Nucleic Acids in Plasma and Serum, Ann. N.Y. Acad. Sci. (2008)
1016	Weiner, Gabriel, Stephens, Eds. (2007), Genetic Variation: A Laboratory Manual (excerpts)
1017	D. Bentley, Whole-Genome Re-Sequencing, Current Opinion in Genetics & Development, 16:545-552 (2006)
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1019	US 6,172,214 to Brenner
1020	Brenner et al., <i>In vitro</i> Cloning of Complex Mixtures of DNA on Microbeads: Physical Separation of Differentially Expressed cDNAs, PNAS, Vol. 97, No. 4 (Feb. 2000)

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1022	Annals of the New York Academy of Sciences ordering page for the <i>Circulating Nucleic Acids in Plasma and Serum</i> article by Gahan (Archive.org: Sept. 12, 2008), available at: http://web.archive.org/web/20080912061421/http://www.nyas.org/annals/detail.asp?annalID=934
1023	J. Shendure et al., <i>Next-generation DNA sequencing</i> , Nature Biotechnology, Nature Biotechnology, Vol. 26, No. 10 (Oct. 2008) (Archive.org: Jan. 24, 2009), available at: https://web.archive.org/web/20090124152730/http://nature.com/nbt/journal/v26/n10/full/nbt1486.html
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1032	Voelkerding et al., Next-Generation Sequencing: From Basic Research to Diagnostics, Clinical Chemistry, Vol 55, No. 4 (April 2009)
1033	D. Chiang et al., High-resolution mapping of copy-number alterations with massively parallel sequencing, Nature Methods Vol. 6 No. 1 (Jan. 2009)

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1034	Print out of Polymerase Chain Reaction (PCR), Genome.gov, available at: https://www.genome.gov/genetics-glossary/Polymerase-Chain-Reaction
1035	Commings et al., Computational Biology Methods and Their Application to the Comparative Genomics of Endocellular Symbiotic Bacteria of Insects, Biological Procedures Online, Vol. 11, No. 1 (March 2009)
1036	Molecular Loop's Complaint, Case 1:24-cv-00680-UNA, Filed June 10, 2024
1037	Declaration of Nathaniel E. Frank-White, Internet Archive (September 26, 2024)
1038	Current Opinion in Genetics & Development, Vol. 16, No. 6 (Dec. 2006) (on file with the A. R. Mann Library at Cornell Univ. in Ithaca, NY)
1039	D. Chiang et al., Abstract, High-resolution mapping of copy-number alterations with massively parallel sequencing, Nature Methods Vol. 6 No. 1 (Jan. 2009) (Archive.org: Feb. 13, 2009), available at: https://web.archive.org/web/20090213081827/http://www.nature.com/nmeth/journal/v6/n1/abs/nmeth.1276.html
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1041	Declaration of Thomas A. Broughan III
1042 [NEW]	Print out of Allele, Genome.gov, available at: https://www.genome.gov/genetics-glossary/Allele
1043 [NEW]	Modified Version of Figure 5 of the '730 Patent
1044 [NEW]	Modified Version of Figure 5 of the '730 Patent to Include Error Correction
1045 [NEW]	Emails from Daniel Young to Greg Porreca (Apr. 24, 2009) and Attachment (ML-IPR-000415-17)
1046 [NEW]	Emails between Daniel Young and Greg Porreca (Apr. 24, 2009-Apr. 28, 2009) and Attachments (ML-IPR-000427-49)
1047 [NEW]	Emails between Daniel Young and Greg Porreca (Apr. 24, 2009-Apr. 29, 2009) (ML-IPR-000463-65)

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1048 [NEW]	Emails between Daniel Young and Greg Porreca (May 14, 2009) (ML-IPR-000061-99)
1049 [NEW]	Emails between Daniel Young and Greg Porreca (Apr. 24, 2009) and Attachments (ML-IPR-000418-21)
1050 [NEW]	Email between Daniel Young, Greg Porecca, and Patrick Waller (May 14, 2009) (ML-IPR-000022-24)
1051 [NEW]	Emails between Daniel Young, Greg Porreca, and Patrick Waller (May 14, 2009) (ML-IPR-000610)
1052 [NEW]	Emails between Daniel Young and Greg Porreca (May 15, 2009) and Attachment (ML-IPR-000789-823)
1053 [NEW]	Email from Greg Porreca to Eric Boutin (March 6, 2009), Email from Eric Boutin to Patrick Waller (March 6, 2009), and Attachments (ML-IPR-000001-21)
1054 [NEW]	Emails between Daniel Young, Greg Porreca, and Patrick Waller (Apr. 7, 2009-April 23, 2009) (ML-IPR-000375-83)
1055 [NEW]	Emails between Daniel Young and Greg Porreca (Apr. 24, 2009) and Attachment (ML-IPR-000415-17) ¹
1056 [NEW]	Emails between Daniel Young, Greg Porreca (Apr. 24, 2009-Apr. 27, 2009) (ML-IPR-000422-23)
1057 [NEW]	Emails between Daniel Young, Greg Porreca, and Patrick Waller (Apr. 24, 2009-Apr. 30, 2009) (ML-IPR-000479-80)
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1060 [NEW]	Emails between Patrick Waller and Greg Porreca (May 5, 2009-May 11, 2009) (ML-IPR-000550-54)
1061 [NEW]	Emails between Daniel Young and Greg Porreca (May 14, 2009) and Attachments (ML-IPR-000061-99)
1062 [NEW]	Emails between Daniel Young and Greg Porreca (May 14, 2009-May 15, 2009) and Attachment (ML-IPR-000027-60)
1063 [NEW]	Emails between Daniel Young and Greg Porreca (May 14, 2009-May 15, 2009) (ML-IPR-000690-91)

¹ EX1055 and EX1045 are the same document, but were given different Exhibit numbers during the depositions.

Exhibit#	Reference Name
1064 [NEW]	Emails between Daniel Young and Greg Porreca (May 15, 2009-May 18, 2009) and Attachment (ML-IPR-000875-913)
1065 [NEW]	Reply Declaration of Stacey Gabriel, Ph. D.
1066 [NEW]	Transcript of the Deposition of Joseph Puglisi, Sept. 17, 2025
1067 [NEW]	Transcript of the Deposition of Patrick Waller, Sept. 26, 2025
1068 [NEW]	Transcript of the Deposition of Gregory Porreca, Sept. 30, 2025
1069 [NEW]	Sherman et al., Fragile X Syndrome: Diagnostic and Carrier Testing, ACMG Practice Guidelines, Vol. 7, No. 8 (Oct. 2005)

I. Introduction

Patent Owner Molecular Loop's Response presents two primary arguments: that (1) neither Chee (Grounds 1-3) nor McCloskey (Grounds 4-6) discloses the claimed "*collapsing*" step and (2) Chee is not prior art to claims 1-3 and 9 of the '730 patent. Both arguments fail, and none of Molecular Loop's remaining arguments changes the outcome.

First, Molecular Loop incorrectly asserts the patent's method of "*collapsing*" is novel because it uses unique tags to trace duplicate copies of molecules back to the original sample and considers the copies as one count. POR, 1-2. It contends this solves problems with skewing caused by amplification bias, where amplification makes more copies of some nucleic acids in a sample than others. But both Chee and McCloskey recognize the *exact same* amplification bias problem and both propose the *exact same* solution: using unique tags/barcodes to identify all duplicate copies of a nucleic acid so that each nucleic acid from the original sample is counted only once. There is nothing new about the problem or solution. Even Molecular Loop's own expert admits that "the idea of correcting for skewing... was known in the art... that's... one of the reasons people introduced barcodes." EX1066, 79:22-80:2; *see id.*, 120:1-5.

Second, Molecular Loop seeks to swear behind Chee for claims 1-3 and 9, but it is unable to patch numerous gaps in its required proof. On conception,

Molecular Loop's conception document fails to show "*correcting for errors*," an element in every claim. With respect to diligence in constructive reduction to practice, during the 20-day critical period, Molecular Loop provides no evidence showing any prosecution activity on 12 of those days. Although it submitted a declaration from named prosecuting attorney Patrick Waller, Dr. Waller did not draft the relevant provisional application (the "'358 Provisional")—a junior patent agent did—and Dr. Waller has no recollection of what work was done on the provisional application during the critical period.

Molecular Loop's other arguments also fail. It incorrectly contends Chee is not entitled to its April 30, 2009 provisional date because Chee's provisional application allegedly does not disclose a "*biological sample*" and is limited to synthetic biology. Chee's provisional in fact discloses sequencing biological samples for "clinical" and "diagnostic" purposes, both of which involve samples from humans. Molecular Loop also incorrectly argues a POSA would not have been motivated to combine Chee or McCloskey with other references. Its arguments, however, are based on inaccurate descriptions of the references. In view of the actual disclosures, the motivation to combine is unquestionable.

For these reasons, the Board should find all claims unpatentable.

II. Grounds 4-7: Bignell and McCloskey Alone or With Bentley, Gahan, or Chiang

Molecular Loop's attempt to swear behind Chee does not apply to Bignell and McCloskey alone (Ground 4) or with additional references (Grounds 5-7). Because swearing behind Chee does not impact these grounds, Illumina addresses them first.

With respect to Ground 4 (claims 1, 4-6, and 9), Molecular Loop does not contest that Bignell and McCloskey teach the additional elements of dependent claims 4-6 and every element of claim 9. Molecular Loop makes only two challenges to this combination: that (1) it does not teach “*collapsing target:differentiator tag combinations*” into a single count (claim 1), and (2) a POSA would not have been motivated to combine Bignell and McCloskey. Both arguments fail.

With respect to Grounds 5-7 (claims 2-3 and 6-8), Molecular Loop's only argument is that these fail for the same reasons Ground 4 fails. Thus, Grounds 4-7 rise and fall together.

A. Claim 1: McCloskey Discloses “*Collapsing Target:Differentiator Tag Combinations Observed More than Once Into A Single Count*”

McCloskey teaches a technique for correcting amplification bias when sequencing DNA by adding unique barcodes to each molecule in a starting sample. EX1012(McCloskey), [0005], [0093], [0106]. After amplification and sequencing,

McCloskey uses the barcodes to identify redundant copies so it can accurately quantify the number of molecules in the starting sample. *Id.*, [0053], [0093]. Even Dr. Puglisi admits that McCloskey “use[s] barcodes as a way to correct for amplification bias. That, there’s no doubt about.” EX1066, 85:21-86:13. This process “*collapses*” barcoded nucleic acids observed more than once into a single count. Pet., 56-57.

Molecular Loop contends there are three reasons McCloskey does not teach this element, all of which are wrong.

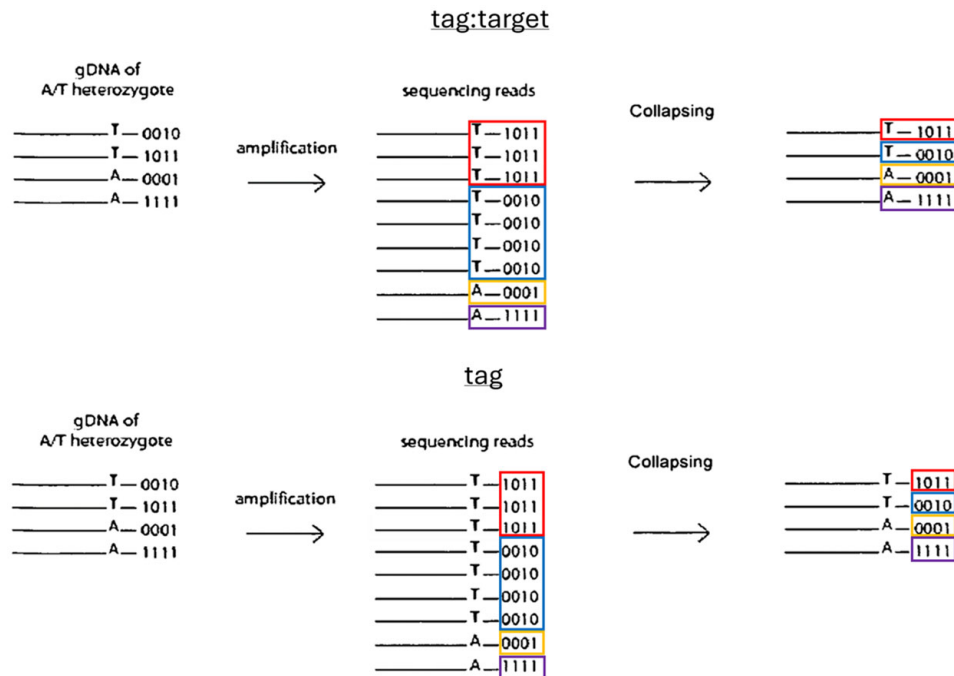
First, Molecular Loop argues McCloskey collapses using barcodes (“*differentiator tags*”) alone, rather than “*target:differentiator tag combinations*,” so it cannot meet the claim. Its argument is inconsistent with dependent claim 2, which requires “*collapsing*” on the tags alone.² Claim 2 provides: “*said correcting step further comprises **collapsing all sequence reads comprising a same differentiator tag into a single read** before determining a consensus base call.*” Because claim 1 must encompass claim 2, claim 1’s step of “*collapsing... into a single read*” must encompass collapsing using the differentiator tags alone.

Littlefuse, Inc. v. Mersen USA EP Corp., 29 F.4th 1376, 1380 (Fed. Cir. 2022) (“if

² Under the Board’s construction (not challenged by Molecular Loop), each “*differentiator tag*” must be unique. Inst. Decision, 6-7.

a dependent claim reads on a particular embodiment..., the corresponding independent claim must cover that embodiment as well”). Likewise, the specification shows collapsing on tags alone. The specification states Figure 5 depicts that “repeat target:differentiator tag combinations are collapsed.” EX1001, 73:3-5. Figure 5 shows collapsing on tags alone, labeling the step “collapsing differentiator tag sequences” (not combinations), and shows the result is one count of each target:tag combination. EX1001, Fig. 5; Inst. Dec., 23-24.

Molecular Loop's argument also is inconsistent with McCloskey. In McCloskey, each “barcode” will “uniquely identify a target nucleic acid in an experiment,” and thus, each barcode and target combination is necessarily also unique. EX1012(McCloskey), [0021]; EX1065(Gabriel), ¶10. Consequently, when the sample is amplified, a particular barcode is always associated with the same target nucleic acid. *Id.* By using the barcodes to identify duplicates and count the duplicates as one distinct read, McCloskey “*collapses*” the barcode-target combinations. *Id.*, ¶11. In the figure below, the top shows using target:tag combinations (the color boxes) to identify copies, and the bottom shows using tags alone (the color boxes). The result is the same: each distinct target:tag combination is collapsed to a single count. EX1065(Gabriel), ¶12.



Id., ¶12.³

Second, Molecular Loop argues the claimed “*collapsing*” is different because it provides “the ability to ‘make diploid genotype calls.’” POR, 54. That argument is irrelevant to claim 1, which does not require making genotype calls, as even Dr. Puglisi admits. EX1066, 83:2-6. Even if the ability to make genotype calls were required (it is not), McCloskey discloses its barcodes can improve making genotype calls on the FMR1 locus. EX1065(Gabriel), ¶¶13-16. FMR1 testing was commonly done to determine whether a female carried an allele

³ The figure is a modified version of EX1001, Fig. 5.

associated with Fragile X Syndrome, which could be passed to a male child.⁴

EX1065(Gabriel), ¶16; EX1069, 1. McCloskey describes an example of testing the FMR1 locus, and explains that barcodes allow it “to quantify accurately the proportion of cells carrying a particular sequence variant by counting only distinctly tagged sequences.” EX1012(McCloskey), [0093]. That process determines a genotype. EX1065(Gabriel), ¶16; *see also* EX1001, 55:60-56:53.

Third, Molecular Loop admits McCloskey uses barcodes to identify redundant sequences and count only distinct tags, but argues doing so does not “‘collaps[e]’ reads together.” POR, 54. But when trying to distinguish Chee, Molecular Loop asserts that the purpose of “*collapsing*” is “to remove redundant sequences prior to counting.” POR, 46. Removing duplicates prior to counting is exactly what McCloskey does. EX1012(McCloskey), [0053], [0093]; EX1065(Gabriel), ¶¶8-9. Contrary to Molecular Loop’s argument, claim 1 does not require combining reads “together”; it only requires that duplicates be counted once (“*a single count*”). McCloskey does exactly this.

⁴ Fragile X Syndrome is an abnormality on the X chromosome that is associated with developmental delays and other issues. It primarily affects males because males have one X chromosome. Females have two X chromosomes and can be carriers by having one normal FMR1 allele and one with the mutation.

B. A POSA Had Reasons to Combine Bignell and McCloskey

Molecular Loop's contention that a POSA would not have been motivated to combine McCloskey and Bignell is based on two incorrect premises. POR, 56.

First, Molecular Loop contends that McCloskey's technique for adding a unique barcode to each molecule in a sample is inconsistent with Bignell, which adds an identical sample tag to each molecule in a sample. POR, 56-58.

Molecular Loop ignores that McCloskey teaches adding *two* identifiers to each nucleic acid: a unique barcode to identify the molecule *and* an identical "batch-stamp" to identify the sample. EX1012(McCloskey), [0021], [0027]; EX1066, 61:2-62:5, 65:16-25 (Puglisi agreeing McCloskey teaches both sample-specific and molecule-specific tags). Thus, just like Bignell, McCloskey discloses adding an identical sample tag to every nucleic acid in a sample. EX1005(Gabriel), ¶252. Because McCloskey adds a sample-specific tag to each molecule, it is completely consistent with Bignell's goal of using tags to identify and distinguish samples. McCloskey's further provision of a molecule-specific barcode provided powerful advantages, as even Dr. Puglisi admitted. EX1066, 69:7-12.

Molecular Loop incorrectly asserts that Bignell teaches using unique identifiers is "at odds" with using sample tags, citing to Bignell's discussion of an article by Brenner. POR, 58. Bignell says no such thing. Bignell simply observes that Brenner adds a random unique identifier to each nucleic acid in a sample, and

because that approach does not add the same tag to each nucleic acid, it does not enable multiplexing (simultaneously sequencing DNA from multiple samples/patients). EX1013(Bignell), 3:28-35; EX1065(Gabriel), ¶¶17-18. Bignell did not state that unique identifiers cannot be used with sample identifiers, only that unique identifiers alone did not achieve its goal. EX1013(Bignell), 3:28-35. Those comments are irrelevant to McCloskey, which teaches tagging nucleic acids with *both* molecule-specific *and* sample-specific identifiers, which provides the ability to identify and distinguish between samples and would enable multiplexing. EX1065(Gabriel), ¶18.

Second, Molecular Loop argues a POSA would not have had a reasonable expectation of success because the combination allegedly would have been too expensive. POR, 59. Molecular Loop, however, provides no evidence showing how much it would have cost to add McCloskey's unique barcodes to Bignell. On the contrary, a POSA would have understood that synthesizing and adding McCloskey's unique barcodes would not have significantly increased the cost of NGS sequencing. EX1065(Gabriel), ¶20; EX1005(Gabriel), ¶255. Even with a moderate cost increase, NGS overall costs would still have been only a fraction of the costs of Sanger sequencing. EX1065(Gabriel), ¶20. And Dr. Puglisi admits that, when accuracy is important, it may be worthwhile to increase the sequencing costs. EX1066, 87:22-88:11; EX1017, 548; *see* EX1065(Gabriel), ¶21.

Therefore, the alleged cost increase would not have dissuaded a POSA from the combination.

Molecular Loop also criticizes the combination because McCloskey is directed toward Sanger sequencing whereas Bignell involves NGS. But, as explained in the Petition, industry trends provided a motivation to adapt conventional sequencing techniques for use in NGS systems. Pet., 47. Molecular Loop does not contest the trends in the industry in 2009. Nor does Molecular Loop contest that Illumina's NGS (which Bignell discloses using) used multiple amplification processes that could cause bias. See EX1005(Gabriel), ¶¶62, 67, 252. A POSA would have known that the amplification processes used in NGS introduced bias, and would have looked for known techniques, *e.g.*, McCloskey's technique, to address that issue. Pet., 46-48; EX1005(Gabriel), ¶¶248-52.

Finally, Molecular Loop fails to address the evidence of simultaneous invention, which is objective indicia of obviousness. Pet., 50-51. Simultaneous inventions are "evidence that persons of ordinary skill in the art understood the problem and a solution to that problem." *Univ. Cal. v. Broad Inst. Inc.*, 903 F.3d 1286, 1295 (Fed. Cir. 2018). Chee conceived of attaching unique identifiers to each nucleic acid in a starting sample to correct for amplification bias in NGS sequencing, such as on an Illumina sequencer. EX1010(Chee), 2:21-25, 4:1-3, 10:2-7. Molecular Loop contends that Dr. Porreca came up with the same idea

within a few weeks of when Chee's Provisional was filed. Others also had the idea of using unique identifiers to correct amplification bias in NGS sequencing around the same time as well. *E.g.*, EX1018, [0002], [0005], [0028]-[0029], [0088]-[0090]; EX1005, ¶81. The existence of simultaneous inventions is “evidence of the motivation to combine,” and is another reason a POSA would have combined McCloskey and Bignell. *Univ. Cal.*, 903 F.3d at 1296.

III. Grounds 1-3: Chee Alone or in View of Gahan

Regarding Grounds 1-2, Molecular Loop does not contest that Chee discloses the additional elements of dependent claims 3-4, 7, and every element of claim 9. The only two limitations it alleges Chee does not teach are claim 1's “*collapsing*” step and claim 2's step of “*determining a consensus base call*.” Chee discloses both.

Regarding Ground 3, Molecular Loop asserts there is no rationale to combine Chee with Gahan (claims 5-6 and 8) by arguing Chee solely discloses synthetic biology techniques, but Molecular Loop ignores that Chee also discloses sequencing naturally-occurring nucleic acids.

A. Claim 1: Chee Discloses “*Collapsing Target:Differentiator Tag Combinations Observed More than Once Into a Single Count*”

Chee teaches two processes that meet the “*collapsing*” step. One process can “*correct[] for [amplification] bias*” and the other can “*correct[] for*

[sequencing] errors.” Pet., 31-32; *see, e.g.*, EX1010(Chee), 10:21-28. Molecular Loop incorrectly asserts that neither process meets the claim.

In Chee's process, after obtaining an initial sample, it adds a unique identifier to each nucleic acid in the sample to create constructs. EX1010(Chee), 4:1-3, 10:41-46. Each construct includes a unique identifier and a target nucleic acid (region of interest, “ROI”). *Id.*, 2:34-38. The sample is amplified (*e.g.*, using PCR), creating multiple copies of each construct, and the amplified constructs are sequenced. *Id.*, 3:10-17, 13:20-61. Chee explains that if multiple constructs have the same unique identifier, those constructs are “identical by descent,” meaning they are copies of the same molecule from the original sample. *Id.*, 5:27-36, 14:42-46.

Correcting Amplification Bias. Molecular Loop admits Chee discloses correcting amplification bias,⁵ but argues Chee does not disclose a “precise method” for “counting the number of original starting molecules.” POR, 47. Molecular Loop is wrong. Chee explains that its unique identifiers allow

⁵ Chee observes that “amplification bias” can cause some nucleic acids to be “either over-represented or under-represented.” EX1010(Chee), 23:59-64.

Molecular Loop asserts that the '730 patent identifies and solves the same problem with “over- or under-amplification.” POR, 10, 43.

“quantification of the molecules [to] be corrected to reflect [amplification] bias.”

EX1010(Chee), 23:59-64. It explicitly states it can determine “*the number of starting molecules*” in a sample by using the fact that “each initial ROI present in a sample [was associated] with its unique identifier.” EX1010(Chee), 10:41-46; *id.*, 5:31-36, 9:29-39; EX1066, 120:1-5, 121:12-20.

Chee can correct the “quantification” and determine “the number of starting molecules” because it recognizes that reads with the same unique identifier correspond to the same nucleic acid from the original sample and counts those once. EX1010(Chee), 10:41-46, 23:59-64; EX1005(Gabriel), ¶¶173-74. A POSA would have understood that “where [Chee] reads multiple sequences with the same unique identifier, it only counts those as one instance of the ROI (not multiple instances).” EX1005(Gabriel), ¶173; *see* EX1066, 122:9-20. Thus, Chee’s process “*collapses*” sequences with the same unique identifier into “*a single count*.” EX1010(Chee), 9:34-39, 14:46-50; EX1005(Gabriel), ¶¶175-78.

Molecular Loop argues only that Chee does not disclose how to “use this information to count the number of original starting molecules” in a sample nor “an actual method of counting.” POR, 47-48. In other words, Molecular Loop contends that a POSA would not know *how to count* distinct unique identifiers. But a POSA would have been able to do so. EX1065(Gabriel), ¶¶23-24. The ability to count is most certainly within the skill of a POSA, who would have had a

master's or Ph.D. *Impax Labs. v. Aventis Pharms.*, 468 F.3d 1366, 1381 (Fed. Cir. 2006) (prior art's description sufficient if a POSA "could have combined the publication's description of the invention with his own knowledge to make the claimed invention").

Correcting Sequencing Errors. Chee teaches that its unique identifiers also can be used to correct sequencing errors⁶ by comparing reads from copies of the same molecule and using them to create a "consensus" sequence.

EX1010(Chee), 9:34-39, 10:54-57, 14:39-50; *see* EX1005(Gabriel), ¶¶177-78.

Illumina explained how this process met the claim in the Petition. Pet., 32.

Molecular Loop argues that Chee's process for correcting sequencing errors by "determin[ing] a consensus base call" is different than the claimed "*collapsing*." POR, 46. It argues for the first time in its Response that the "*collapsing*" element corrects only quantitative errors by removing redundant sequences and that it must do so *without* making any base call or correcting sequencing errors. POR, 46; EX1066, 140:24-141:17; EX1044.

⁶ An example of a sequencing error is a misread nucleotide (*e.g.*, the sequencer erroneously determined a nucleotide was a 'C' instead of a 'G').

EX1005(Gabriel), ¶76. Such errors can be corrected by comparing multiple sequence reads of the same target. *E.g., id.*, ¶¶105, 176-78.

Even under Molecular Loop's new construction of "*collapsing*," Chee still anticipates or renders obvious claim 1. As explained above, Chee's technique for correcting amplification bias corrects quantitative errors without correcting sequencing errors or making consensus base calls.

B. Claim 2: Chee Discloses "*Collapsing All Sequence Reads Comprising a Same Differentiator Tag Into a Single Read Before Determining a Consensus Base Call*"

As explained in the petition, Chee's process for correcting sequencing errors generates a consensus sequence that meets claim 2. Pet., 33. Chee's process can be divided into two steps. EX1065(Gabriel), ¶26. First, Chee "*collapses*" multiple clonal copies of a construct by grouping them using their shared unique identifier, with the understanding that they constitute only one count. EX1010(Chee), 14:46-50, 9:29-39. Dr. Puglisi described this as putting all of the clonal copies into their own "bin." EX1066, 113:18-114:13.⁷ The bin corresponds to a single molecule from the original sample. After binning the copies, Chee uses standard techniques to determine a consensus sequence (*e.g.*, Bentley's technique). EX1005(Gabriel), ¶¶177-78, 185; EX1066, 113:3-9 (Puglisi testifying that Chee uses the process

⁷ He also stated that the '730 patent's process "bin[s]" molecules with the same barcode. EX1066, 117:5-10.

shown in Bentley), 91:1-4; EX1017(Bentley), 549 (“multiple reads from the same sample can be aligned and used to derive a consensus base-call at each position”).

Molecular Loop argues that a “*consensus base call*” refers to making a genotype call. POR, 10, 44; EX2023(Puglisi), ¶135 (“determining a sample’s genotype at a given locus by performing a consensus base call”), ¶137 (“determining the consensus base call for genotyping”). It argues Chee does not disclose a “*consensus base call*” so-construed because Chee creates a consensus sequence using multiple reads of copies of the *same* molecule (to correct sequencing errors), and thus, cannot determine a genotype based on reads of *multiple* molecules. POR, 47-48; EX1066, 116:24-117:14.

Even if Molecular Loop’s new construction of “*consensus base call*” to mean “genotype call” were accepted, Chee discloses or at least renders it obvious because Chee discloses processes that include making genotype calls.

EX1065(Gabriel), ¶28. A genotype refers to the combination of alleles (one from each parent) a person has for a gene. EX1066, 13:12-25, 18:23-19:10, 20:16-21:19; EX1042, 1-2. Chee discloses, for example, sequencing a sample containing DNA from multiple individuals and identifying a “minor allelic variant.”

EX1010(Chee), 9:42-52. That process involves determining the genotype of each individual and identifying uncommon alleles. EX1065(Gabriel), ¶28. Chee also discloses identifying polymorphisms. *Id.*; EX1010(Chee), 9:42-52; EX1011,

[00024]. Identifying a polymorphism in this context refers to identifying variation in alleles a person has. EX1065(Gabriel), ¶28; *see* EX1066, 26:1-12, 28:12-29:8, 15:15-20.

C. Ground 3: A POSA Would Have Been Motivated to Combine Chee and Gahan

Molecular Loop incorrectly argues a POSA would not have been motivated to combine Chee and Gahan, inaccurately asserting that Chee is directed solely to synthetic biology. POR, 50.

Chee, however, explicitly teaches analyzing ***both*** synthetic and naturally-occurring DNA: “The ROI for the present invention can be isolated from a ***natural*** or non-natural source.” EX1010(Chee), 3:51-53; *id.*, 11:51-54 (“determine the sequence of ***naturally-occurring nucleic acids*** (e.g., DNA or RNA... isolated from a sample)”), 10:21-24 (“analysis of nucleic acids in ***biological samples***”), 9:42-52 (“a sample containing ***DNA from multiple individuals***”). Chee also explains that its method of sequencing can be used for “***diagnostic*** use” or “***clinical*** use.” *Id.*, 11:60-63.

Molecular Loop incorrectly argues a POSA would not have combined Chee and Gahan because (i) Chee needs to provide a sufficient number of constructs to correctly sequence nucleic acids, and (ii) Gahan states protocols for extracting DNA from blood are “far from consistent,” potentially resulting in a lot or a little DNA. POR, 51. A POSA would have been able to choose a sufficient number

unique identifiers to create the constructs. EX1065(Gabriel), ¶¶35. Chee provides an excess of unique identifiers, so it could handle larger samples. *Id.* It also teaches amplifying a sample, so it could handle smaller amounts of DNA. *Id.*, ¶36. Moreover, Gahan states that free DNA extracted from blood had already been used for diagnostic purposes, showing POSAs knew how to handle any variability. EX1015(Gahan), 3; EX1065(Gabriel), ¶37. Dr. Gabriel explains that Gahan's statement about consistency would not have deterred a POSA from applying Chee's methods to nucleic acid isolated from blood. EX1065(Gabriel), ¶34.

D. Chee Is Entitled to Its Provisional Date

Molecular Loop does not contest that Chee's provisional application ("Chee's Provisional," EX1011) provides written description support for at least one claim in the Chee patent. It asserts, however, that Illumina relied on Chee's disclosure of a "biological sample," that Chee's Provisional does not disclose such a sample, and therefore Chee's discussion of "biological samples" is not entitled to the provisional's date. POR, 37-38.

Molecular Loop is wrong. Chee's Provisional describes using its technique on "biological samples" and doing so for humans. It expressly states it addresses "sources of error encountered in conventional synthetic biology *and analysis of nucleic acid in biological samples.*" EX1011, [00060] (emphasis added). Chee's Provisional further teaches its techniques can be applied to "diagnostic use [or]

clinical use,” (EX1011, [00066]), and can be used with “diagnostic methods” and “the discovery or analysis of polymorphisms or mutations in a sample,” (EX1011, [00024]). A POSA would have understood that Chee’s references to “clinical” and “diagnostic” use referred to use on human patients. EX1065(Gabriel), ¶32; EX1066, 32:15-22 (Puglisi agreeing “‘clinical’ involves human patients and diseases”), 34:14-35:1 (agreeing that “diagnosis” is done to “living organisms” such as human patients). Similarly, a POSA would have understood that discovering or analyzing polymorphisms in a sample refers to analyzing a sample from a living being. EX1065(Gabriel), ¶33.

Molecular Loop admits that Chee discloses a “biological sample,” but asserts the sample is a “synthetic biological sample” and not a “naturally-occurring biological sample.” POR, 38. First, the distinction is irrelevant to the ’730 patent claims, which recite “biological sample” not a “naturally-occurring biological sample.” Second, Molecular Loop’s argument is based on one passage in Chee’s Provisional that refers to “nucleic acids *derived from* a biological sample.” EX1011, [00069] (emphasis added). According to Molecular Loop, the phrase “derived from” refers to synthetic biological samples, (POR, 38-39), but Molecular Loop’s argument is unfounded. Dr. Gabriel explains that a POSA would have understood that “derived from” in this context means extracted from a sample. EX1065(Gabriel), ¶31. Nucleic acids extracted from a biological sample are not

synthetic DNA. *Id.* Moreover, Molecular Loop ignores Chee's Provisional's disclosure of sequencing DNA for clinical and diagnostic uses, which involve getting a DNA sample from humans (naturally-occurring DNA). *Id.*, ¶¶32-33.

Molecular Loop also contends that Chee's Provisional does not disclose performing Chee's method on the specific types of samples recited in claims 4-6 and 8. POR, 35-36. Illumina did not rely on Chee to teach the additional elements of claims 5-6 and 8; it relied on Gahan, and its prior art status is unchallenged. For claim 4 (sample from blood or tissue), Illumina relied on the *Genetic Variation Manual*, incorporated-by-reference into Chee. Pet., 35. That manual is also is incorporated-by-reference into Chee's Provisional. EX1011, [00050].

E. Molecular Loop Failed to Show Earlier Conception and Diligence in Reduction to Practice

1. Molecular Loop Failed to Show Prior Conception

Molecular Loop asserts earlier invention than Chee for only claims 1-3 and 9 (but not claims 4-8). It contends that “each limitation in claims 1-3 and 9 of the '730 patent is described in the March 6 Application [‘EX2006’] and therefore was conceived of by the inventors by at least March 6, 2009.” POR, 24. It argues that Chee, therefore, is not prior art because “Chee's provisional application was not filed until April 30, 2009.” POR, 35.

Molecular Loop, however, failed to show prior conception of “*correcting for errors or bias*” which is a required element of claims 1-3 and 9. POR, 24, 28-29.

Although Dr. Porreca's March 6 Application (EX2006) discusses "*correcting for bias*," neither the March 6 Application nor any other evidence shows an earlier conception of a method for "*correcting for errors*." And Dr. Porreca does not recall anything about what he allegedly conceived on March 6, 2009, beyond what is stated in the document. EX1068, 58:18-59:9, 71:3-72:20.

Conception "refer[s] to a concept that is complete, rather than merely one that is 'substantially complete.'" *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 66 (1998). An invention's conception therefore "must encompass all limitations of the claimed invention." *Singh v. Brake*, 222 F.3d 1362, 1367 (Fed. Cir. 2000). Conception must show that the claimed limitations were "so clearly defined in the inventor's mind that only ordinary skill would be necessary to reduce the invention to practice." *Burroughs Wellcome Co. v. Barr Lab'ys, Inc.*, 40 F.3d 1223, 1228 (Fed. Cir. 1994). Therefore, to demonstrate prior conception, Molecular Loop must show conception of ***both*** a method for correcting errors ***and*** a method for correcting bias.

The March 6 Application, which is entitled "Methods for Reducing Bias in Preparations of Nucleic Acids," discloses at most a method for correcting bias. EX2006, 1. The word "error" does not appear in the March 6 Application. Although Dr. Puglisi suggested the application discloses correcting sequencing errors (EX2023, ¶76), he admitted that sequencing errors are not disclosed in the

March 6 Application or accompanying figures (EX1066, 57:22-59:1). *See* EX2006-EX2008.

Molecular Loop also cannot credibly argue that “bias” is a type of “error.” Within the context of the claims, “error” must be different than “bias.” The claims recite “[a] method for correcting for *errors or bias*.” If bias was simply a type of error, then the claim term “bias” would be a “merely superfluous, nonlimiting elaboration.” *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 950 (Fed. Cir. 2006) (“claims are interpreted with an eye toward giving effect to all terms in the claim”); *Wasica Finance GmbH v. Continental Auto. Sys., Inc.*, 853 F.3d 1272, 1288 n.10 (Fed. Cir. 2017) (“It is highly disfavored to construe terms in a way that renders them void, meaningless, or superfluous”). Even Dr. Porreca was unable to testify that “bias” and “error” are the same. EX1066, 139:16-140:20, 144:2-151:21. As Dr. Gabriel explains, errors can occur in DNA synthesis during amplification or sequencing in which a nucleotide is incorrectly incorporated in the complementary strand. EX1005(Gabriel), ¶¶75-76. These errors are distinct from bias, which occurs when molecules are over- or under-amplified in the amplification step. EX1065(Gabriel), ¶¶38-43. Dr. Puglisi agrees that, in the context of claim 1, errors and bias are different. EX1066, 96:3-17; *see id.*, 95:5-8, 96:18-22, 103:25-104:7, 105:7-13.

The March 6 Application does not disclose “[a] method for correcting for errors,” and therefore, Molecular Loop has not established an earlier conception date.

2. Molecular Loop Has Not Shown Diligence in Reduction to Practice

Molecular Loop argues it acted diligently in constructively reducing the invention to practice for the 20-day critical period, starting April 29, 2009 (one day before Chee's Provisional was filed) and running to May 18, 2009 (when the '358 Provisional was filed). POR, 21-22. Molecular Loop cannot show diligence because it provides no evidence showing that any prosecution work was performed on 12 days of the 20-day critical period.

To show diligence, Molecular Loop relies almost entirely on emails⁸ exchanged between Dr. Porreca and Wolf Greenfield (the prosecuting firm). Neither of its two declarants (Drs. Porreca and Waller) recalls details beyond the emails. In Dr. Porreca's declaration, he merely repeats what is in the documents. EX2004(Porreca), ¶¶10-21 (each paragraph starting “Based on my review of written correspondence...”).

⁸ It also relies on a generalized, non-specific statement by Dr. Waller that Dr. Porreca was “conscientious” and “diligently” provided feedback. EX2005(Waller), ¶23.

Dr. Waller, the named prosecution attorney, also submitted a declaration. EX2005(Waller), ¶¶3-5. However, the evidence shows that Dr. Waller did not work on the '358 Provisional, and instead delegated preparation of it to Dan Young, a patent agent at the time. *E.g.*, EX1067, 57:17-58:21; EX1045; EX1028; EX1054. Dr. Waller has no recollection of drafting or editing the '358 Provisional during the critical period, and no recollection of substantively discussing the provisional or its claims with either Dr. Porreca or Dr. Young. *Id.*, 30:8-18, 38:17-22, 42:19-43:21, 45:10-47:13, 49:5-10, 54:5-55:6, 56:6-13, 57:17-58:21. Dr. Waller's testimony about his general practices or hours worked is not relevant to diligence on the '358 Provisional because he did not draft it.

Molecular Loop did not submit a declaration from Dr. Young, who still works at Wolf Greenfield. EX1067, 72:12-18. Nor did Molecular Loop submit any billing records. *See* EX1068, 31:7-32:9. Beyond the emails, the record contains no evidence of what prosecution work, if any, Dr. Young did during the critical period. Most prosecution work could have been done before the critical period, in the 53 days between March 6 and April 28. Dr. Waller did not do the work, and cannot recall what work was done, so his testimony cannot fill in gaps in the record. Thus, this case is unlike *Ex Parte Koji Muramaya*, 2020 WL 1663636 (PTAB Apr. 1, 2020) where attorney testimony could fill certain gaps in the documentary record.

The table below summarizes all documented prosecution-related activities⁹ on the 358 Provisional (“Uri’s application”)¹⁰ during the critical period. Notably, there is no evidence of any activity by anyone on 12 of the 20 days, and minimal activity most other days (*e.g.*, a phone call, an email sent to the attorneys).

<u>Date</u>	<u>Inventor Activity</u>	<u>Attorney Activity</u>
4/29/09	Phone call between Young and Porreca. EX2012, 2-3. • Waller does not know what was discussed. EX1067, 43:9-21. • Porreca does not know either. EX1068, 112:3-114:10.	
4/30/09	Porreca sends Waller inventorship information. EX2013.	No evidence of activity.
5/1/09	No evidence of activity.	
5/2/09	No evidence of activity.	
5/3/09	No evidence of activity.	
5/4/09	No evidence of activity.	
5/5/09	Porreca sends Young two paragraphs to Young for inclusion in provisional. EX2012.	Young asks Porreca a question. EX2012. Waller call with Porreca. EX2014, 4.
5/6/09	No evidence of activity. ¹¹	

⁹ Ministerial communications such as scheduling a call (*e.g.*, May 8), or making a status inquiry (*e.g.*, May 13) are not included as a prosecution activity. *See, e.g.*, EX2014 (message history).

¹⁰ *See* EX2005(Waller), ¶10; EX1067, 29:5-9.

¹¹ On May 6, Dr. Waller sent Dr. Porreca draft claims for a different provisional (’089 Provisional) directed to estimating the length of a nucleic acid. EX2014, 4-5. No evidence shows Dr. Waller doing any work on the ’358 Provisional that day.

<u>Date</u>	<u>Inventor Activity</u>	<u>Attorney Activity</u>
5/7/09	No evidence of activity.	
5/8/09	No evidence of activity.	
5/9/09	Phone call between Waller and Porreca. EX2014, 2. Waller does not recall what was discussed. EX1067, 56:6-13.	
5/10/09	No evidence of activity.	
5/11/09	Porreca stated "Uri's [application] probably doesn't need further revision." EX2014, 2.	No evidence of activity.
5/12/09	No evidence of activity.	
5/13/09	No evidence of activity.	
5/14/09	No evidence of activity.	Young sends draft of '358 Provisional to Porreca.
5/15/09	Porreca sends edits to Young. EX2015-EX2016.	No evidence of activity.
5/16/09	No evidence of activity.	
5/17/09	No evidence of activity.	
5/18/09	'358 Provisional filed.	

With respect to work by the attorneys, there are no documented activities on 15 of 20 days. Of the five days with activity, on two the only activity was a phone call, but there is no evidence of what was discussed or if the discussion involved the '358 Application. Although Dr. Young sent a draft provisional on May 14, no evidence shows when Dr. Young actually drafted the provisional, or how much, if any, drafting occurred during the critical period. In fact, evidence shows that Drs. Young and Porreca exchanged partial drafts in early April, and that in response to an April 22 status inquiry from Dr. Porreca, Dr. Waller stated they had all of the information they needed and would send "updated drafts." EX1054; EX1068, 91:5-92:2. Thus, most drafting could have been done in the 53 days between

March 6 and April 28. Molecular Loop therefore has failed to provide sufficient evidence to establish reasonable diligence during the critical period.

Molecular Loop argues that diligence only needs to be “reasonably continuous,” citing *Perfect Surgical Techniques v. Olympus America, Inc.*, 841 F.3d 1004, 1007 (Fed. Cir. 2016). But *Perfect Surgical* stands for the proposition that the PTO should not hunt for small gaps where the evidence overall showed diligence. *Id.*, 1011, 1012. Here, Molecular Loop cannot show any activity on 12 of 20 days. The “gaps” here comprise over 50% of the critical period, which is hardly small. Molecular Loop cannot show an overall pattern of diligence because no evidence shows how much, if any, of the '358 Provisional was actually drafted during the critical period, or what work was done when. *Perfect Surgical* does not excuse Molecular Loop's failure to provide evidence of diligence. Thus, Molecular Loop's attempt to swear behind Chee fails.

IV. Conclusion

Accordingly, the Challenged Claims should be found unpatentable.

Dated: October 10, 2025

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CERTIFICATE OF COMPLIANCE

I hereby certify that this brief complies with the type-volume limitations of 37 C.F.R. §42.24, because it contains 5,594 words (as determined by the Microsoft Word word-processing system used to prepare the brief), excluding the parts of the brief exempted by 37 C.F.R. §42.24.

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I hereby certify that on this 10th day of October, 2025, copies of this
Petitioner's Reply and all new Exhibits have been served in their entirety on
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