

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ILLUMINA, INC.,
Petitioner,

v.

MOLECULAR LOOP BIOSCIENCES, INC.,
Patent Owner.

Patent No. 11,840,730

IPR2024-01419

**REPLY DECLARATION OF STACEY GABRIEL, PH. D. REGARDING
U.S. PATENT NO. 11,840,730**

Petitioner Illumina, Inc., Ex. 1065, p. i
Illumina Inc. v. Molecular Loop Biosciences, Inc.
IPR2024-01419

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I. INTRODUCTION**A. Engagement**

1. I have been retained by counsel for Illumina, Inc. as an expert witness in the above-captioned proceeding. I previously submitted a declaration in this matter in September 2024. EX1005. I have been asked to reply to certain opinions from Molecular Loop's expert witness, Joseph Puglisi, Ph.D. EX2023.

B. Background, Qualifications, and Compensation

2. A discussion of my background and qualifications can be found in my first declaration in this proceeding. *See* EX1005, ¶¶ 2-6, Exhibit A. Details of my compensation are set forth in my first declaration as well. EX1005, ¶ 7.

C. Information Considered

3. My opinions are based on my years of education, research, and experience, as well as my investigation and study of relevant materials. In forming my opinions, I have considered the materials I identify in the attached Exhibit List.

4. I may rely upon these materials and/or additional materials to respond to arguments raised by Molecular Loop. I may also consider additional documents and information in forming any necessary opinions—including documents that may not yet have been identified by me or provided to me.

5. I have responded to certain opinions from Dr. Puglisi below.

Although I have not responded to all of his opinions, my lack of response to such opinions does not mean that I agree with them.

II. LEGAL STANDARDS FOR PATENTABILITY

6. Certain basic legal principles have been explained to me by counsel for Illumina. I recorded these legal standards as they were explained to me in my first declaration. EX1005, ¶¶ 11-25.

III. Response to Certain Arguments about McCloskey and Bignell

A. McCloskey Discloses “*Correcting for Errors Or Bias Introduced During Said Workflow By Collapsing Target:Differentiator Tag Combinations Observed More than Once Into A Single Count*”

7. Dr. Puglisi asserts that McCloskey does not disclose the step of “*correcting for errors or bias introduced during said workflow by collapsing target:differentiator tag combinations observed more than once into a single count*” in claim 1 of the '730 patent. He contends that “McCloskey discloses methods that detect the barcode alone, or the barcode with a batch-stamp, to correct for skewing that can arise from PCR amplification.” EX2023(Puglisi), ¶ 179 (emphasis omitted). He also contends that “there is no disclosure in McCloskey whatsoever describing the use of barcodes or batch-stamps in combination with the target nucleic acid molecule to correct for errors or bias by collapsing those combinations into a single count.” *Id.*, ¶ 180 (emphasis omitted).

Dr. Puglisi concludes that McCloskey does not teach the “*collapsing*” step “at least *because its methods do not use the target nucleic acid sequence to correct for errors or bias.*” *Id.* (emphasis added). I disagree.

8. The claim recites “*collapsing target:differentiator tag combinations observed more than once into a single count.*” Although McCloskey uses barcodes to identify redundant sequences, she collapses the combination of the barcode and target nucleic acid into a single count. Because each target nucleic acid in a starting sample has a unique barcode, she can identify target:barcode combinations that appear more than once in the amplified sample using the barcode alone.

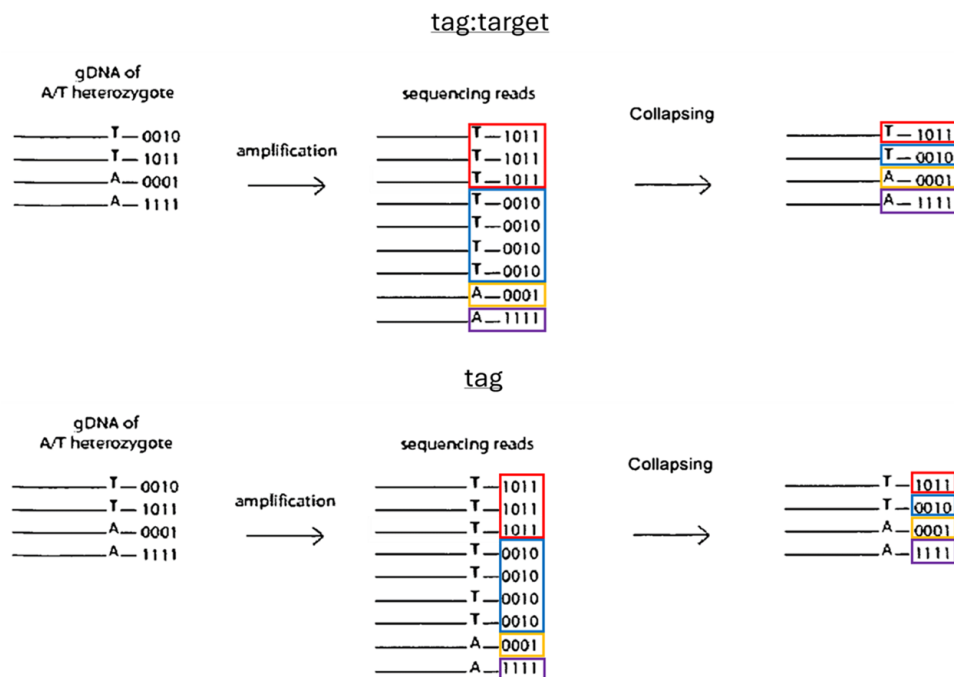
9. McCloskey explains that one use of the barcodes is to identify redundant copies of each target:barcode combination to correct for amplification bias, which allows accurately counting the number of nucleic acids in the original sample. For example, McCloskey states it uses the barcodes “to identify... redundant sequences and to quantify accurately the proportion of cells carrying a particular sequence variant by counting only distinctly tagged sequences.” EX1012(McCloskey), [0093]. To determine the proportion of the original sample that contained a sequence, McCloskey considers redundant copies of a target-barcode combination to be one instance or “count” of the target molecule in the original sample, which corrects for amplification bias.

10. McCloskey states that each barcode will “uniquely identify a target nucleic acid in an experiment.” EX1012(McCloskey), [0021]. This means that each barcode is added to only one target nucleic acid in the sample, and no barcode is added to two different target nucleic acids. When the sample is amplified, a particular barcode is always associated with the same target nucleic acid from the original sample such that each target:barcode combination is distinct. As a result, any time a barcode appears in the amplified sample, it is attached to the same target molecule. By using the barcodes to determine “redundant sequences,” meaning copies of the same original target molecule after amplification, McCloskey is identifying target:barcode combinations that appear more than once.

11. Dr. Puglisi asserts that McCloskey does not meet the claimed “*collapsing*” step because McCloskey identifies duplicates using the barcode alone. Dr. Puglisi’s analysis overlooks that each of McCloskey’s barcodes are unique and each barcode is associated with the same target nucleic acid throughout the workflow. *See, e.g.*, EX1012(McCloskey), [0009], [0093]. This means that by identifying redundant barcodes (appearing more than once), McCloskey identifies redundant target:barcode combinations.

12. Although Dr. Puglisi asserts McCloskey works differently than the claimed “*collapsing*”, it does not. This can be seen from the figure shown below.

The figure was created by simplifying EX1043.¹ The first example shows “*collapsing*” by looking at the combination of tags and target nucleic acids (seen in the boxes in color). This collapsing results in four distinct target:tag combinations. The second example shows “*collapsing*” by looking at the tags alone (seen in the boxes in color). This collapsing results in the same four distinct target:tag combinations as the first example because each tag is always associated with the same target.



13. At his deposition, Dr. Puglisi was shown a very similar figure (EX1043), and he explained that he disagreed that “*collapsing target:differentiator*

¹ I understand that EX1043 was created by modifying Figure 5 of the '730 patent.

tag combinations” functioned the same as “*collapsing*” the tags alone. Based on his answers, it appears Dr. Puglisi believes that McCloskey and the ’730 claims correct for bias in the same way, but that he believes the ’730 claims are different based on subsequent analyses that are performed on the bias-corrected reads. I have reproduced part of his explanation below. EX1066(Puglisi Tr.), 79:17-80:11 (emphasis added, objections omitted).

[Q]: If the goal is to reduce skewing, there is no difference if you collapse tags alone or tags plus target in McCloskey's system?

[A]: Again, the idea of correcting for skewing in terms of the population that you're sequencing, okay, was known in the art. I mean, that's the reason -- one of the reasons people introduced barcodes back in the day, long before even McCloskey's patent.

How that use of the barcode is used for subsequent sequence analysis, that is what differs between what is patented in the '730 patent and what McCloskey is talking about.

So I think it's important to... distinguish effects of skewing and what that does to the sample population and how subsequent sequence information is being used to correct for that skewing, if that clarifies things a little bit.

14. Claim 1 of the ’730 patent specifies correcting for errors or bias. It does not require performing any additional or subsequent analysis. Therefore, I

disagree that any subsequent sequence analysis that Dr. Puglisi references is a difference between how McCloskey corrects for bias and the '730 claims.

15. Regarding the additional analysis Dr. Puglisi referenced, he suggests that claim 1 allows for the ability to make genotype calls. He states that “McCloskey’s authenticating step does not use target nucleic acids and thus does not provide methods to make genotype calls or determine consensus base calls.” EX2023(Puglisi), ¶ 182. First, I disagree that claim 1 of the '730 patent requires making a genotype call or a consensus base call. Even so, I further disagree that McCloskey does not disclose a method to make genotype calls.

16. McCloskey discloses an example in which its method is used to test the FMR1 locus. EX1012(McCloskey), [0093]. A POSA would have known that the FMR1 locus is associated with Fragile X Syndrome and, for that reason, it was routinely sequenced to determine whether a female was a carrier of Fragile X Syndrome (*e.g.*, during prenatal genetic screening). McCloskey explains that its methods are useful for sequencing the FMR1 locus because its barcodes allow it “to quantify accurately the proportion of cells carrying a particular sequence variant by counting only distinctly tagged sequences.” EX1012(McCloskey), [0093]. This information would be used to make a genotype call: whether the

person carries two normal alleles, two abnormal alleles, or one of each.²

Therefore, a POSA would have understood that McCloskey discloses that its methods both allow for and are used to improve genotype calls.

B. A POSA Would Have Been Motivated to Combine Bignell and McCloskey

1. Bignell and McCloskey's Methods Are Compatible

17. Dr. Puglisi contends that “[my] analysis of the motivation to combine McCloskey and Bignell is flawed because of McCloskey’s and Bignell’s goals and methods for adding tags to molecules are antithetical to each other and teach away from each other.” EX2023(Puglisi), ¶ 184. He asserts that Bignell “rejects the concept of applying a different tag to each molecule because it does not allow for attaching the same tag to every molecule in a sample set comprising millions of sequences,” and cites a single passage of Bignell in support. *Id.* I have reproduced the cited excerpt from Bignell below. EX1013(Bignell), 3:28-35.

The problem with enabling the method for individual samples rather than individual molecules is that the tags are synthesized in a

² Fragile X Syndrome is a genetic disorder that stems from mutation of the FMR1 gene, which is located on the X chromosome. The syndrome is associated with developmental delays, disabilities, and other issues. Fragile X Syndrome primarily affects males because males have one X chromosome and one copy of the FMR1 gene. Females have two X chromosomes, with an FMR1 gene on each. Females can be carriers of the syndrome by having one normal FMR1 allele and one with the mutation.

combinatorial manner, meaning that all 16,777,216 different sequences are obtained in a single mixture in the same tube. *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.*

18. I disagree that Bignell rejects the concept of applying a tag to every molecule. The goal of Bignell was to differentiate samples using sample-specific tags. In the passage reproduced above, Bignell is simply explaining that one known method for using molecule-specific tags would not accomplish that goal. Bignell's comment is not relevant to McCloskey, which teaches use of both molecule-specific tags (barcodes) and sample-specific tags (batch-stamp). Bignell's comment above would not have dissuaded a POSA from combining Bignell with McCloskey.

2. Cost Would Not Have Dissuaded A POSA from the Combination

19. Dr. Puglisi further contends that combining Bignell and McCloskey “would have been cost-prohibitive” since “they are directed to different sequencing technologies.” EX2023(Puglisi), § XII.B.2 (heading capitalization omitted). Dr. Puglisi states that McCloskey used Sanger sequencing (*id.*, ¶ 187) and “a POSA reading McCloskey would thus be interested in keeping costs low and throughput high” (*id.*, ¶ 190). Dr. Puglisi states that Bignell used next-generation sequencing and that “[a] POSA using next-generation sequencing would thus be looking for

ways to limit costs and increase throughput.” *Id.*, ¶191. Dr. Puglisi then asserts that “a POSA would **not** have been motivated to incur the additional cost of synthesizing and incorporating random barcodes for millions of sequencing reads with next-generation sequencing technologies.” *Id.*, 197. I disagree.

20. Dr. Puglisi does not state how much it would have cost to add McCloskey’s unique barcodes to Bignell. Synthesizing random unique oligo barcodes would not have been a significant expense, as was known in the art. McCloskey describes several techniques for synthesizing oligos that were within the skill of those in the art. EX1012(McCloskey), [0021]. I have extensive experience in managing the costs of sequencing and addressing trade-offs between cost and quality based on the goals of an experiment, as I run the largest sequencing lab in the United States, and have done so for the past 13 years. In my experience, adding random barcodes to the sequence reads would not have significantly increased the cost of next-generation sequencing, and to the extent that some additional cost is incurred in use cases where high accuracy is required, the added cost is warranted by the improved analytic accuracy. In any event, it would still be significantly less expensive to use McCloskey’s unique barcodes with next-generation sequencing than with Sanger sequencing.

21. Regardless, those in the art could balance trade-offs between sequencing accuracy and costs. Even Dr. Puglisi admits that increasing sequencing

costs may be worthwhile when accuracy is important. EX1066(Puglisi Tr.), 87:22-88:11. A POSA interested in correcting for errors or bias would therefore not have been dissuaded from combining Bignell and McCloskey due to sequencing costs.

IV. Response to Certain Arguments about Chee

A. Chee Discloses Correcting Amplification Bias³ by “*Collapsing Target:Differentiator Tag Combinations Observed More than Once Into A Single Count*”

22. Dr. Puglisi asserts that Chee’s process for correcting amplification bias does not disclose the “*collapsing*” step because Chee does not explain how the process works. Dr. Puglisi states “Chee also broadly discloses that associating the unique identifier with each construct can be used to determine the number of starting molecules of each initial ROI present (EX1010(Chee), 10:41-46), but this again does not explain how to reduce skewing errors through collapsing identical sequence reads into one prior to subsequent analysis.” EX2023(Puglisi), ¶ 153. I disagree.

23. Chee states that its technique allows it to determine “the number of starting molecules” in a sample. EX1010(Chee), 10:41-46; *id.*, 9:5-9. Chee can do this because it associates a unique identifier with each nucleic acid in the starting

³ In my first declaration, I explained how Chee’s technique for correcting sequencing errors met this limitation as well.

sample (*id.*, 5:31-33), and when it later sequences constructs with the same unique identifier, Chee knows they are copies of the same nucleic acid from the starting sample (*id.*, 5:33-36, 9:29-39). A POSA would have known that what Chee is describing is “*collapsing*” reads of constructs that have the same combination of unique identifier and region of interest into a single read. Chee explains that amplification bias is one of several problems its technique can address. *Id.*, 10:21-28. Chee can also address amplification bias separately from sequencing errors. *See id.*, 23:50-64.

24. Dr. Puglisi states that Chee does not explain how it uses the unique identifiers to reduce skew (amplification bias). EX2023, ¶ 151. I disagree. Chee recognizes that constructs in the amplified sample that have the same unique identifier all correspond to the same molecule in the original sample, and therefore, together count as one ROI from the original sample. That is why Chee says that uses of its unique identifiers allows “quantification of the molecules [to] be corrected to reflect [amplification] bias.” EX1010(Chee), 23:59-64; *id.*, 9:5-9, 9:18-21. Quantification in this context means counting the number of molecules in the starting sample. A POSA would have known how to count the distinct unique identifiers, and how to use only one copy of a construct with a particular unique identifier to quantify the molecules in the starting sample based on Chee’s disclosure.

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

25. Dr. Puglisi asserts that Chee’s process for correcting sequencing errors does not disclose claim 2. He asserts that I “incorrectly conflate the collapsing step with determining a consensus base call for remedying sequence errors.” EX2023(Puglisi), ¶ 146. Dr. Puglisi contends that “[a] POSA would understand ‘collapsing’ to have a separate and distinct meaning from ‘determining a consensus base call.’” *Id.*, ¶ 132. For instance, Dr. Puglisi contends that “dependent claim 2 of the ’730 patent requires determining a consensus base call *after* the collapsing step of claim 1 has been performed.” *Id.*, ¶ 133. I disagree that Chee does not meet claim 2.

26. Chee’s process works in two steps. First, Chee identifies constructs that have the same unique identifier and groups them as being identical by descent.⁴ EX1010(Chee), 9:29-39. This grouping “*collapses*” the identical constructs because the bin represents a single count of the ROI in the original sample. Chee then uses the multiple reads of the grouped constructs to generate a

⁴ Dr. Puglisi referred to this step as putting the clonal copies into their own “bin.” EX1066(Puglisi Tr.), 113:18-114:13.

consensus sequence. EX1010(Chee), 9:29-39. Although claim 2 has two steps, the two steps can be part of the same process.

27. Dr. Puglisi also contends that a consensus base call refers to “determining a sample’s genotype at a given locus.” EX2023(Puglisi), ¶ 135; *see also id.*, ¶ 137. In my opinion, a POSA would have understood a consensus base call to refer to the type of process described in Bentley, where “multiple reads from the same sample can be aligned and used to derive a consensus base-call at each position,” rather to a genotype call. EX1017(Bentley), 549.

28. Even if Dr. Puglisi’s contention that claim 2 requires a genotype call is accepted, Chee also discloses a genotype call or at least renders it obvious. For instance, Chee discloses that its methods can be used to identify a “minor allelic variant... in a sample containing DNA from multiple individuals” as well as confirm the presence of polymorphisms in genomic samples. Both disclosures imply (or involve) genotyping. EX1010(Chee), 9:42-52; EX1011, [00024]. Allelic variation refers to the different alleles that appear in a population – determining “different alleles” is genotyping. Detecting a minor allelic variant refers to sequencing sample from a population of people, and identifying an uncommon allele at a locus. A polymorphism in this context refers to variations in the alleles at a given locus. For example, whether a person has a BB, bb, or Bb

alleles. *See* EX1042, 1-2. A POSA would therefore have understood that both examples in Chee’s disclosure are processes that include a genotype call.

C. Chee’s Provisional Discloses Its Methods Apply To “Biological Samples From Natural Sources” And “Naturally-Occurring Nucleic Acids”

29. Dr. Puglisi explains that he “understand[s] Chee’s provisional application to be directed to a method for synthetic biology without disclosing performing the inventions on naturally-occurring DNA.” EX2023(Puglisi), ¶ 166. He further contends that “[a]lthough the ’442 Provisional makes reference to analyzing ‘nucleic acids derived from a biological sample,’ it “does not describe the biological sample as being naturally-occurring.” *Id.*, ¶ 167 (quoting EX1011) (emphasis omitted). Dr. Puglisi therefore concludes that “[he] do[es] not understand Chee’s April 30, 2009, [sic] provisional application as disclosing performance of its invention on naturally-occurring biological samples.” *Id.*, ¶ 169. I disagree.

30. Chee’s Provisional discloses that it “addresses two primary sources of error encountered in conventional synthetic biology *and analysis of nucleic acid in biological samples*.” EX1011, [00060] (emphasis added). Therefore, a POSA would have understood that Chee’s Provisional discloses biological samples derived from synthetic biology *and* biological samples from natural sources (“naturally-occurring nucleic acids”).

31. Chee's Provisional discloses that its methods can be used to analyze "nucleic acids derived *from a biological sample*." A POSA would have understood that "nucleic acids derived from a biological sample" refers to "nucleic acids which originated from or were obtained from a biological sample." I disagree with Dr. Puglisi's opinion that "derived from" in Chee's Provisional means "nucleic acids derived from a *synthetically-created* biological sample." EX2023(Puglisi), ¶ 167. He provides no explanation of this opinion other than how he believes that sentence would be "[r]ead in the context of the rest of the '442 Provisional." *Id.*

32. Other portions of Chee's Provisional show that Chee disclosed using its techniques on naturally-occurring nucleic acids (*e.g.*, human DNA isolated from blood). Chee explains that its methods can be applied to "diagnostic use [or] clinical use." EX1011, [00066]. A POSA would have understood that "clinical" uses in Chee's Provisional refers to sequencing DNA from human patients, which are "naturally-occurring biological molecules." A POSA also would have understood that "diagnostic" use refers to sequencing DNA to diagnose a living being, most likely a human. I note that Dr. Puglisi agrees that the term "clinical involves human patients and diseases" and "diagnosis" involves "living organisms." EX1066(Puglisi Tr.), 32:15-22, 34:14-35:1.

33. Chee's Provisional further discloses that its methods are useful in polymorphism screening (EX1011, [0007]) which a POSA would have understood would have involved a sample from a human patient or some other living organism and looking for variants of a particular allele. A POSA would have understood that these samples from "human patients" and "living organisms" disclosed by Chee's Provisional would have been "naturally-occurring biological molecules."

D. A POSA Would Have Been Motivated to Combine Chee and Gahan

34. Dr. Puglisi asserts that a POSA looking "to accurately perform Chee's method would not look to a paper [like Gahan] describing inconsistencies on how to isolate a substantial amount of cell-free DNA to even perform the method." EX2023(Puglisi), ¶ 174 (emphasis omitted). I disagree. A POSA would have understood how to practice Chee's methods with both relatively large and relatively small amounts of cell-free DNA, and therefore, would not have been deterred by Gahan's disclosure.

35. For relatively large amounts of cell-free DNA, a POSA would have understood that, in order to practice Chee's methods, there needed to be enough unique identifiers to uniquely identify nucleic acid molecules in a sample. Dr. Puglisi's opinion overlooks that Chee describes creating "a *large excess* of possible identifiers relative to the ROIs in a given set." EX1010(Chee), 9:54-60

(emphasis added). Chee also discloses a method of creating unique identifiers such that each is generated by randomly adding bases until a certain length is reached (*id.*, 11:14-18), which would be useful especially when a relatively larger number of identifiers is needed. Therefore, a POSA would have understood that Chee describes how to create a large number of unique identifiers so there is an excess of identifiers compared to nucleic acid molecules.

36. For relatively small amounts of cell-free DNA, a POSA would have understood that the nucleic acid molecules could be subjected to additional rounds of amplification during the amplification step to generate a large enough population for sequencing. Therefore, a POSA would have understood that Chee's method can be used even with small amounts of cell-free DNA.

37. Dr. Puglisi also overlooks the disclosure in Gahan which recognizes that cell-free DNA extracted from blood had been used for diagnostic purposes. For instance, Gahan states that "[m]any studies have shown the successful application of CNAPS [circulating nucleic acids in plasma and serum] in the diagnosis and monitoring of cancer and in prenatal diagnosis, as well as in other diseases." EX1015(Gahan), 3. Therefore, a POSA would have recognized that the nucleic acids isolated from blood as Gahan could be used with Chee, especially since Chee discloses that its methods can be used for diagnostic purposes. *E.g.*, EX1010(Chee), 11:60-63.

V. The March 6, 2009 Draft Application Does Not Disclose “*Correcting for Errors*”

38. Dr. Puglisi contends that “the inventors [of the ’730 patent] conceived of the claimed invention in claims 1-3 and 9 by at least March 6, 2009” (EX2023(Puglisi), ¶ 64) because “[a] POSA would have understood that the disclosures of the March 6, 2009 application demonstrate conception of claims 1-3, and 9 of the ’730 patent” (*id.*, ¶ 66 (referencing EX2006)). I disagree, however, that the March 6, 2009 application discloses every element of claim 1 of the ’730 patent. Based on my review of the March 6 Application (EX2006), it does not disclose a method for “*correcting for errors.*”

39. Claim 1 recites a method of “*correcting for errors or bias*”. As I explained in my prior declaration, a POSA would have understood errors and bias to refer to different problems that can arise in the nucleic acid workflow. EX1005, ¶¶ 75-77. The claims separately recite error and bias, which I interpret as meaning that an error is something distinct from bias.

40. Errors can occur when nucleotides are incorrectly incorporated when making a copy of DNA by synthesizing a complementary strand. This type of error can occur during amplification. It can also occur during the sequencing step, such as during sequencing by synthesis which also involves copying DNA by making complementary strands. Sequencing error also can occur when the

nucleotide was correctly incorporated in the complementary strand, but subsequently mis-read by the sequencing machine. A POSA would consider these to be errors—not bias. In contrast, bias generally refers to uneven amplification of target molecules which results in some molecules being over- or under-represented following amplification as compared to the original sample. In the context of the claims, bias is distinct from error.

41. Dr. Puglisi ignores the difference between errors and bias in his analysis. He contends that “[t]he March 6 Application explains that *biases and errors* can be introduced ‘into the sequencing libraries, generally due to biases in enzyme function or to the exponential and stochastic nature of the amplification methods like PCR.’” EX2023(Puglisi), ¶ 72 (citing EX2006, 1) (emphasis added). Noticeably absent from the March 6, 2009 application, however, is any disclosure of “error.” The word “error” does not appear.

42. To support his opinion, Dr. Puglisi only refers to the March 6 Application’s disclosure of bias—not error. *E.g.*, EX2023(Puglisi), ¶ 72 (citing EX2006 generally). Dr. Puglisi further contends that the figures associated with the March 6 Application disclose “correct[ing] for errors *or* bias.” *Id.*, ¶ 72 (citing EX2007; EX2008) (emphasis added). But the figures only refer to correcting bias—they are labeled “Figure 1 *bias*_detecting_barcodes_fig1” (EX2007) and

“Figure 2 ***bias***_detecting_barcodes_fig2” (EX2008). (emphases added). Neither figure discloses correcting for errors.

43. Therefore, a POSA would not have understood the March 6, 2009 Application or its associated figures to disclose a method of correcting for errors.

* * *

I, Stacey Gabriel, do hereby declare and state, that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, under Section 1001 of Title 18 of the United States Code.



Executed on: October 10, 2025

Exhibit List

The list of exhibits that I relied upon in forming my opinions is below.

Exhibit #	Reference Name
1001	U.S. 11,840,730 (“’730 patent)
1002	’862 Application FH
1003	’687 Application FH
1004	’764 Application FH
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. McCloskey, 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 2006, 16:545-552 (2006)
1018	US Pub. 2008/0261204 to Lexow
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)

Exhibit #	Reference Name
1025	S. Arcinas et al., PCR-Induced Sequence Artifacts and Bias: Insights from Comparison of Two 16S rRNA Clone Libraries Constructed from the Same Sample, APPLIED AND ENVIRONMENTAL MICROBIOLOGY, Dec. 2005, p. 8966-69, Vol. 71, No. 12
1029	Ronaghi, US Pub. 2006/0008824
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)
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)
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
1066 [NEW]	Transcript of the Deposition of Joseph Puglisi, Sept. 17, 2025