PATENT TRIAL AND APPEAL BOARD
UNITED STATES PATENT AND TRADEMARK OFFICE

Illumina, Inc.

v.

Molecular Loop Biosciences, Inc.

January 29, 2026

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

molecularloop

IPR2024-01419
Illumina Inc., v. Molecular Loop Biosciences, Inc.
Molecular Loop's Exhibit 2028

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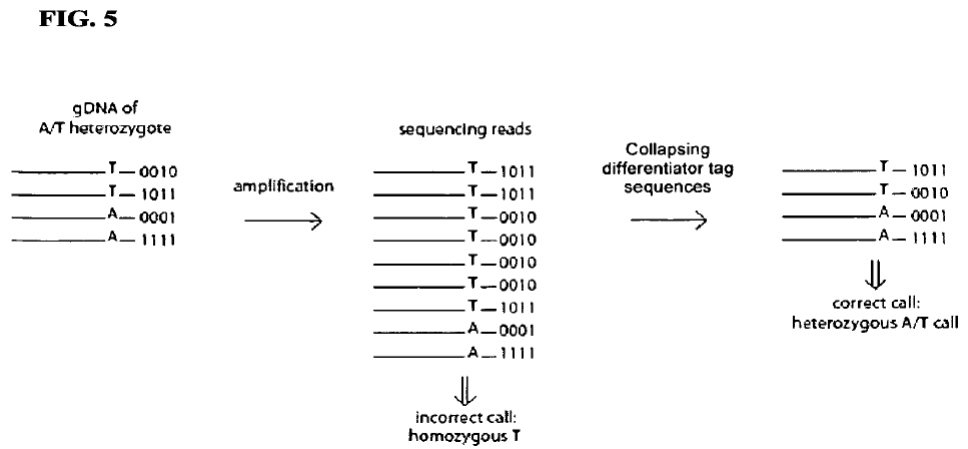
Outline

A Overview of Molecular Loop's '730 Patent

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The Molecular Loop '730 Patent Introduced A New Method Of Collapsing Sequence Reads And Determining Consensus Basecalls



EX1001, FIG 5.

"For any target:differentiator tag combination observed more than once, ***all such reads are 'collapsed' into a single read before consensus basecalls are determined***. ***This will cancel the effect of bias on consensus basecall accuracy***. FIG. 5 depicts a method for making diplod genotype calls in which repeat target:differentiator tag combination[s] are collapsed."

EX1001, 72:67-73:5.

"[I]n the context of a multiplex nucleic acid amplification reaction, differentiator tag sequences provide a basis for differentiating between multiple independent, primary amplicons of a target nucleic acid, for example. Thus, combinations of target nucleic acid and differentiator tag sequence (target:differentiator tag sequences) of an isolated nucleic acid of a preparative method provide a basis for identifying unique, independently isolated target nucleic acids."

EX1001, 28:62-29:4.

Outline

A Overview of the Molecular Loop Patents

B Overview of the Prior Art

C Disputed Issues

Prior Art: Chee Focuses On Synthetic Biology And Ways For Validating Synthetically Constructed Sequences That Match A Desired Sequence For Building Oligos

"***Synthetic biology*** is a promising new field at the interface of engineering and biology," but "construction of multi-kilobase scale DNA molecules remains difficult and costly, largely because that ***de novo chemical synthesis of the DNA building blocks*** is quite error-prone."

EX1010, 1:23-41.

There remains a need to select ***error-free synthesized oligonucleotides for use in synthetic biology*** and other analytical methods. The present invention addresses this need by providing constructs, sets of constructs, and methods for ensuring accuracy of ***oligonucleotides having a desired sequence***.

EX1010, 1:53-58.

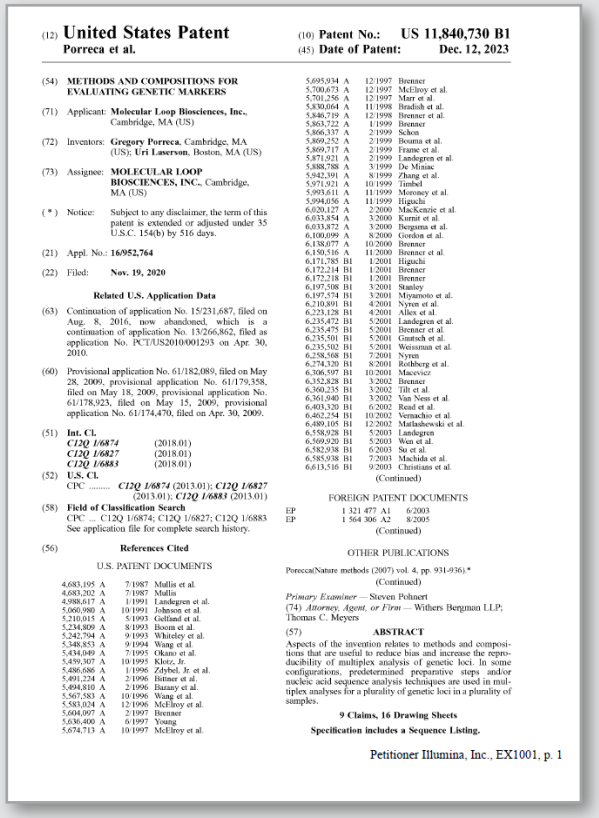
It is a fundamental element of the invention that the unique identifier is associated with a construct, not the ROI; thus, ***constructs with ROIs having the correct sequence can be differentiated from constructs having substantially the same ROI but containing errors***.

EX1010, 2:23-28.

By obtaining long, highly pure ***oligos of desired sequence***, it will be possible to ***assemble relatively long constructs by annealing the oligos together*** so that hybridization ensures that correct sequences are brought together.

EX1010, 23:36-39.

Prior Art: The Applicant Disclosed McCloskey To The Patent Office During Prosecution



(12) **United States Patent**
Porreca et al.

(10) **Patent No.: US 11,840,730 B1**
(45) **Date of Patent: Dec. 12, 2023**

(54) **METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS**

(71) Applicant: **Molecular Loop Biosciences, Inc.**, Cambridge, MA (US)

(72) Inventors: **Gregory Porreca**, Cambridge, MA (US); **Uri Laserson**, Boston, MA (US)

(73) Assignee: **MOLECULAR LOOP BIOSCIENCES, INC.**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 516 days.

(21) Appl. No.: **16/952,764**

(22) Filed: **Nov. 19, 2020**

Related U.S. Application Data

(63) Continuation of application No. 15/231,687, filed on Aug. 8, 2016, now abandoned, which is a continuation of application No. 13/266,862, filed as application No. PCT/US2010/001293 on Apr. 30, 2010.

(60) Provisional application No. 61/182,089, filed on May 28, 2009, provisional application No. 61/179,358, filed on May 18, 2009, provisional application No. 61/178,923, filed on May 15, 2009, provisional application No. 61/174,470, filed on Apr. 30, 2009.

(51) **Int. Cl.**
C12Q 1/6874 (2018.01)
C12Q 1/6827 (2018.01)
C12Q 1/6883 (2018.01)

(52) **U.S. Cl.**
CPC ***C12Q 1/6874*** (2013.01); ***C12Q 1/6827*** (2013.01); ***C12Q 1/6883*** (2013.01)

(58) **Field of Classification Search**
CPC ... C12Q 1/6874; C12Q 1/6827; C12Q 1/6883
See application file for complete search history.

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Primary Examiner — Steven Pohnert
(74) *Attorney, Agent, or Firm* — Withers Bergman LLP; Thomas C. Meyers

(57) **ABSTRACT**

Aspects of the invention relates to methods and compositions that are useful to reduce bias and increase the reproducibility of multiplex analysis of genetic loci. In some configurations, predetermined preparative steps and/or nucleic acid sequence analysis techniques are used in multiplex analyses for a plurality of genetic loci in a plurality of samples.

9 Claims, 16 Drawing Sheets
Specification includes a Sequence Listing.

Petitioner Illumina, Inc., EX1001, p. 1

2007/0009925	A1	1/2007	Fang et al.	
2007/0020640	A1	1/2007	McCloskey et al.	
2007/0042369	A1	2/2007	Reese et al.	EX1001, 2.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	13266862
Filing Date	2012-03-13
First Named Inventor	Gregory Porreca
Art Unit	1634
Examiner Name	S. C. Pohnert
Attorney Docket Number	GSGE-002/01US 29258/20

71	20070020640	A1	2007-01-25	McCloskey et al.	EX1002, 824.

Prior Art: McCloskey Is Primarily Directed To Authenticating PCR Products Using Barcodes

"There is a need in the art for methods for ***verifying the authenticity of PCR products***. The present invention addresses this and other needs."

EX1012, [0004].

"The bar-coded oligonucleotide further comprises a ***second sequence that provides a random barcode***."

EX1012, [0021].

"The fourth sequence is a predetermined nucleic acid sequence providing a batch-stamp or experiment verification information…. [A] batch-stamp ***may identify a sample***, a patient, and/or an analysis date."

EX1012, [0027].

"In step (d) of the methods, the amplification product is ***authenticated by detecting the presence of the second sequence*** in the amplification product."

EX1012, [0034].

Prior Art: McCloskey's Invention Describes Use Of Sanger Sequencing Techniques, In Examples Producing Low Numbers of Reads Per Run

"Verified SPCR reactions were then cleaned with Microclean (Gel Company) and sequenced on an ***ABI 3100*** with Big Dye."

EX1012, [0049].

[0053] 132 sequences were obtained from this experiment.

EX1012, [0053].

[0063] 46 sequences were obtained from this experiment.

EX1012, [0063].

[0076] 107 sequences were obtained from this experiment.

EX1012, [0076].

[0104] Within 142 barcodes recovered from multiple reactions with FMR], the average nucleotide composition was 54% T, 26% G and 19% A. This bias is similar to that

EX1012, [0104].

Prior Art: Bignell Is Directed To Identifying Nucleic Acid Samples From Multiple Sources In Large Scale Pooled Sample Sequencing

"The invention relates to methods for ***indexing samples*** during the sequencing of polynucleotide templates, resulting in the attachment of ***tags specific to the source of each nucleic acid sample*** such that after a sequencing run, ***both the source and sequence of each polynucleotide can be determined***."

EX1013, 1:24–28.

"Pooling therefore represents an effective technique for analysing ***large quantities of samples*** in a facile manner."

EX1013, 1:63-65.

Prior Art: Bignell Uses Sample-Specific Tags Applied To Multiple Sequences From The Same Sample, Instead Of Molecule-Specific Tags, In Order To Maintain Cost Efficiencies

"However ***large-scale genotyping is demanding in terms of the cost*** of both materials and labour involved, ***and the time taken to perform the study***, ***especially if the methodology employed involves separate serial analysis of individual DNA samples***. One shortcut is to pool DNA from many individuals and to determine parameters such as the ratio of changes at certain positions in the genome."

EX1013, 1:51-58.

"***One disadvantage of pooling samples prior to analysis is that information pertaining to individual DNA samples is lost***; only global information such as allele frequencies is gathered, as there is no easy method for discerning which individuals gave rise to a particular genotype." EX1013, 1:66–2:3.

"An ability to genotype ***large populations*** in a small number of reactions, while ***retaining the information relating to the source of the individual samples would yield the information content of a full non-pooled population screen in the time and at the cost of a pooled reaction***."

EX1013, 2:3-8.

Prior Art: Bignell Considered And Rejected Small-Scale Approaches Using Molecule-Specific Tags

"DNA from more than one source can be sequenced on an array if ***each DNA sample is first tagged to enable its identification*** after it has been sequenced. Many low scale DNA-tag methodologies already exist, for example fluorescent labelling (Haughland, Handbook of Fluorescent Probes and Research Products, Invitrogen/Molecular Probes), but ***these are limited in scope to less than 10 or so reactions in parallel***."

EX1013, 3:4-11.

"The ***problem with enabling the method for individual samples rather than individual molecules*** is that the tags are synthesized in a combinatorial manner is that the tags are synthesized in a combinatorial manner, meaning that all ***16,77216 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***."

EX1013, 3:28–35.

Outline

A Overview of the Molecular Loop Patents

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C Disputed Issues

Petitioner's Grounds

IPR2024-01419

Ground	Challenged Claims	References
1	1-4, 9	Chee (Anticipation)
2	1-4, 7, 9	Chee (Obviousness)
3	5-6, 8	Chee and Gahan
4	1, 4-6, 9	Bignell and McCloskey
5	2, 3	Bignell, McCloskey, and Bentley
6	6, 8	Bignell, McCloskey, and Gahan
7	7	Bignell, McCloskey, and Chiang

Disputed Issues

1. Chee is not prior art to the '730 Patent. (Grounds 1-3)
2. Chee does not disclose the "collapsing target:differentiator tag combinations" limitation. (Grounds 1-3)
3. Petitioner does not show a motivation to combine Chee and Gahan. (Ground 3)
4. Petitioner does not show a motivation to combine Bignell and McCloskey. (Grounds 4-7)
5. Bignell-McCloskey does not disclose the "correcting" step. (Grounds 4-7)

Disputed Issues

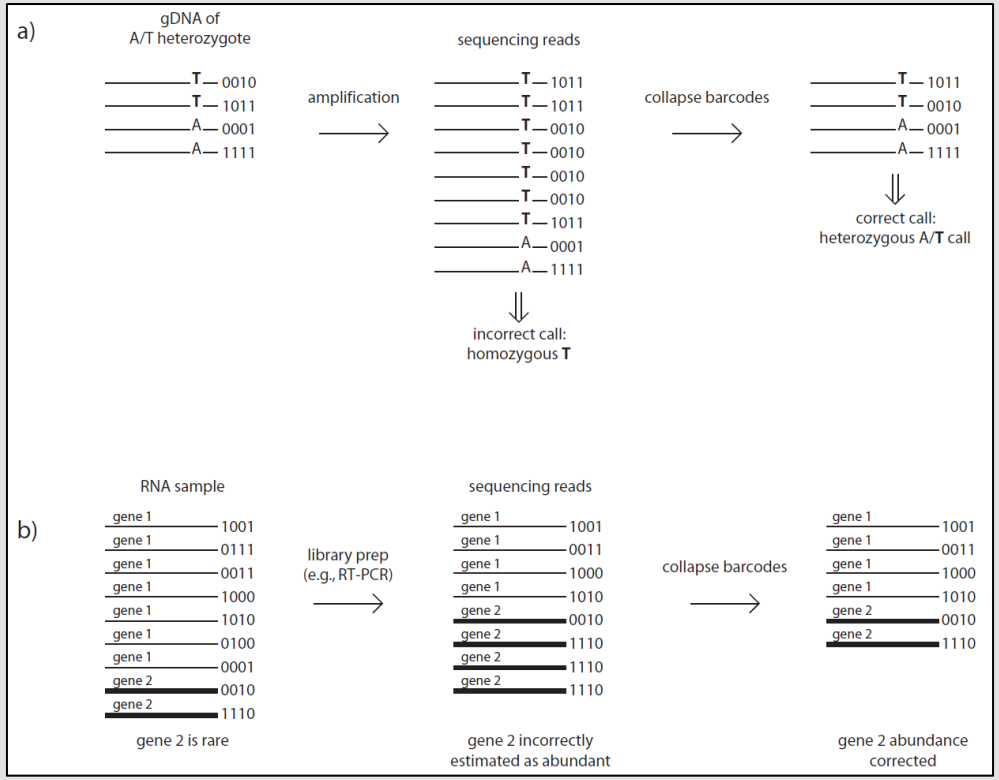
1. **Chee is not prior art to the ’730 Patent. (Grounds 1-3)**
2. Chee does not disclose the “collapsing target:differentiator tag combinations” limitation. (Grounds 1-3)
3. Petitioner does not show a motivation to combine Chee and Gahan. (Ground 3)
4. Petitioner does not show a motivation to combine Bignell and McCloskey. (Grounds 4-7)
5. Bignell-McCloskey does not disclose the “correcting” step. (Grounds 4-7)

The ‘730 Patent Is Entitled To An Earlier Priority Date Than Chee

- Claims 1-3 and 9 were conceived and documented in the inventors’ March 6, 2009 draft and figures. POR, 23-30; Sur-Reply, 2-8.
- Claims 1-3 and 9 were constructively reduced to practice with reasonably continuous diligence during the critical period of April 29, 2009 through May 18, 2009. POR 31-34; Sur-Reply 8-13.
- For all claims, Petitioner relies on portions of Chee that were not included in the Chee Provisional Application. POR 35-41; Sur-Reply 17-18.

The Inventors' March 6, 2009 Documents Demonstrate Conception Of Claims 1-3 And 9

- Patent Owner provided evidence explaining how the draft and figures of the inventors' March 6, 2009 documents demonstrate conception of each element of Claim 1. EX2006-2008.



EX2008, 1.

- Dr. Puglisi analyzed that evidence and explained how it demonstrates conception for every limitation in Claim 1. EX2023, ¶¶ 61-73, 84.

POR, 23-30; Sur-Reply, 2-8.

The Inventors' March 6, 2009 Documents Demonstrate Conception Of Claims 1-3 And 9 (Cont'd)

- Patent Owner provided evidence explaining how the draft and figures of the inventors' March 6, 2009 documents demonstrate conception of the additional elements of Claims 2-3. EX2006-2008.
  - The figures of the March 6, 2009 document show a "***collapse*** barcodes" step performed before a "***correct call***: heterozygous A/T call" step, as claimed in Claim 2. EX2008.
  - The draft of the March 6, 2009 document explains "random barcode sequences are used to ***detect and correct biases*** in the final read-out of the library," as claimed in Claim 3. EX2006, 2.

- Patent Owner provided evidence explaining how the draft and figures of the inventors' March 6, 2009 documents demonstrate conception of the additional elements of Claim 9. EX2006-2008.
  - The draft of the March 6, 2009 document explains that the "incorporation of the barcode at a given step allows the ***detection and correction of biases***" and that "the barcodes are ***randomly incorporated***," as claimed in Claim 9. EX2006, 2-3.

- Dr. Puglisi analyzed that evidence and explained how it demonstrates conception for every limitation in Claims 2-3 and 9. EX2023, ¶¶ 74-84.

POR, 23-30; Sur-Reply, 2-8.

Petitioner Disputes Only Whether There Was Conception Of "Correcting For Error"

- Petitioner does not dispute much of Patent Owner's evidence of conception, and in particular ***does not dispute***:
  - That March 6, 2009 is the correct date of the inventors' draft and figures (EX2006-2008);
  - That the March 6, 2009 date is sufficiently corroborated by metadata for the inventors' draft and figures (EX2009-2011);
  - That the inventors provided the March 6, 2009 draft and figures to prosecution counsel to prepare the patent application that was eventually filed on May 18, 2009 (EX2004, ¶¶ 8-9; EX2005 ¶7); and
  - That the March 6, 2009 draft and figures demonstrates conception of the additional limitations of Claims 2-3 and 9.

- Petitioner's lone argument against prior conception is its incorrect claim that the evidence does not "show prior conception of '*correcting for errors or bias*'" as claimed. Reply, 20.

Reply, 20-23.

Conception Requires Disclosure Sufficient For A POSA To Reduce The Invention To Practice, Not Verbatim Disclosure Of Every Claim Limitation



Federal Circuit:

"[C]onception is complete when 'the idea is so clearly defined in the inventor's mind that ***only ordinary skill would be necessary to reduce the invention to practice*** without extensive research or experimentation."

Spansion, Inc. v. Int'l Trade Comm'n, 629 F.3d 1331, 1356 (Fed Cir. 2010) (quoting *Burroughs Wellcome Co. V. Barr Lab'ys, Inc.*, 40 F.3d 1223, 1228 (Fed Cir. 1994)).

- Petitioner's arguments against conception demand more than is required by that Federal Circuit precedent.

POR, 23.

Petitioner Reads "Error" Too Narrowly And Incorrectly Suggests That Two Different Methods Must Be Disclosed To Demonstrate Conception

- Petitioner suggests that two wholly separate methods ("***both*** a method for correcting for errors ***and*** a method for correcting for bias") are required for conception. Reply, 21.
  - Petitioner's arguments limit "errors" to those that "occur in DNA synthesis during amplification or sequencing in which a nucleotide is incorrectly incorporated in the complementary strand." Reply, 22.

- The claims are not so limited. They require a "method for correcting for errors or bias" and a step of "correcting for errors or bias." EX1001, Claim 1.
  - The specification explains that error and bias are overlapping concepts, and ***the same*** method can correct for both. EX1001, 4:57-66, 5:8-11.

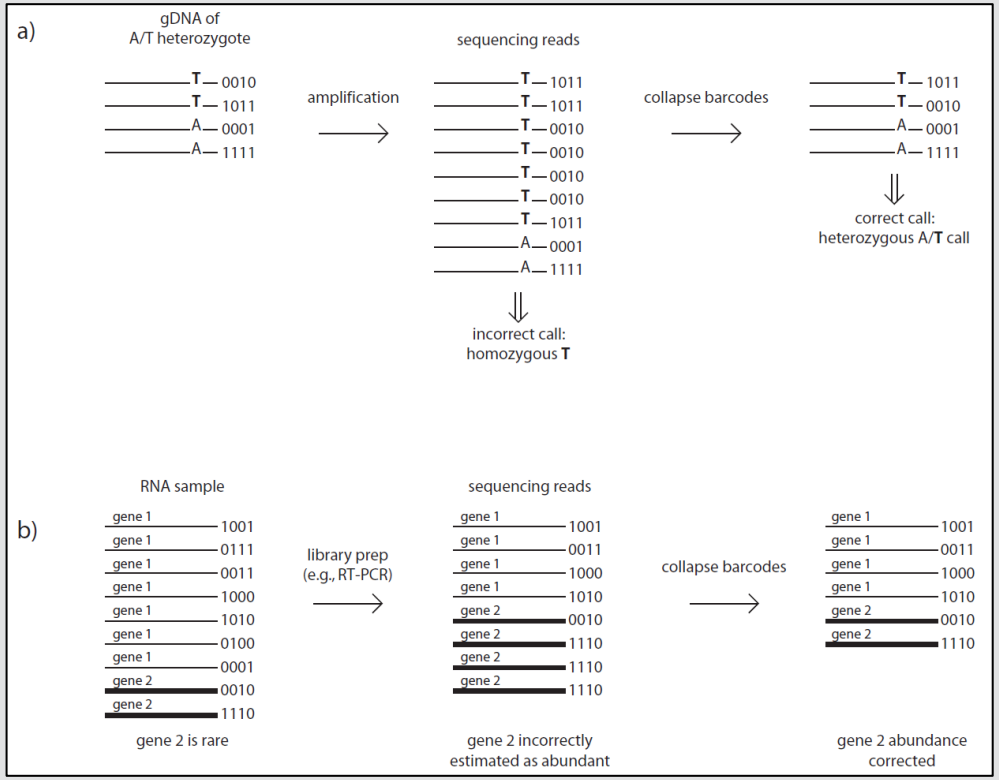
- Dr. Gabriel acknowledged that the claims are not as limited as Petitioner reads them, confirming she understood "error" in the '730 Patent consistent with the "traditional understanding of an inaccurate result." EX2025, 30:7-13.

- Dr. Puglisi explained how the inventors' March 6, 2009 documents disclosed correcting for "overrepresentation," which Dr. Gabriel agrees is a type of error. EX2023, ¶72; EX2025, 27:20-28:5.

Sur-Reply, 3-6.

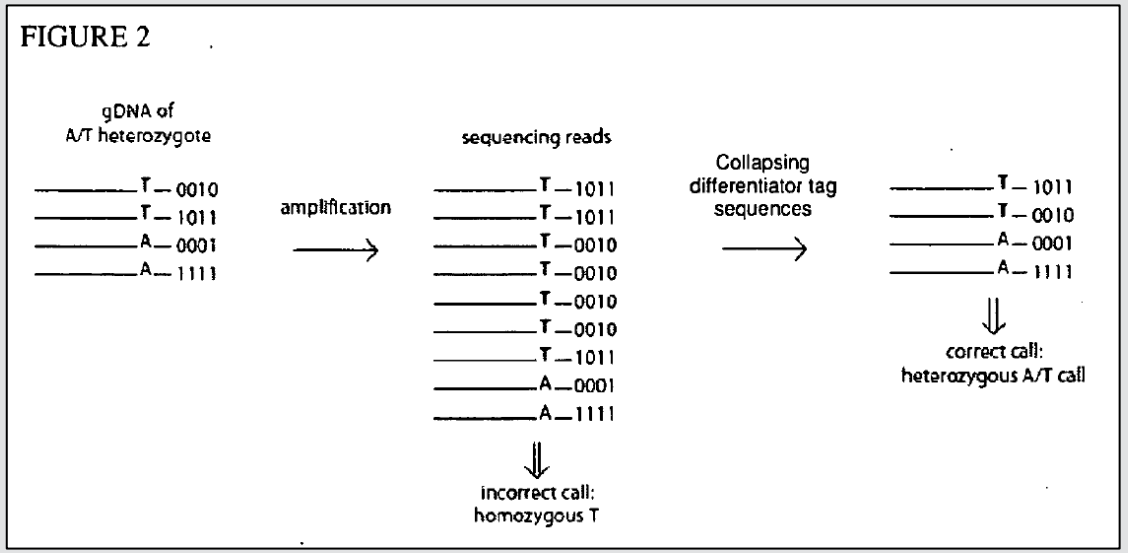
The Main Figure Demonstrating The Claimed Method In The May 18, 2009 Provisional Application Was Included In The March 6, 2009 Figures

- March 6, 2009 Figure:



EX2008, 1.

- May 18, 2009 Provisional Application Figure:



EX1008, 49.

POR, 24-29; Sur-Reply 2-3.

Patent Owner Is Required To Show Only "Reasonably Continuous Diligence" During The Critical Period



Federal Circuit:

"A patent owner need not prove the inventor continuously exercised reasonable diligence throughout the critical period; it must show there was ***reasonably continuous diligence***."

- An "inventor is ***not required to work on reducing his invention to practice every day*** during the critical period."
- "Periods of inactivity within the critical period" ***do not "automatically vanquish a patent owner's claim for reasonable diligence***."
- "[T]he absence of evidence that an inventor and his attorney revised or discussed the application on a daily basis is alone ***insufficient to determine that the invention was abandoned or unreasonably delayed***."

Perfect Surgical Techniques, Inc. v. Olympus America, Inc., 841 F.3d 1004, 1009 (Fed. Cir 2016).

- Patent Owner's evidence of the inventors' and prosecution counsel's activity throughout the short critical period meets those standards.

POR, 21, 31; Sur-Reply, 11-12.

Patent Owner Demonstrated Reasonably Continuous Diligence From Chee's Provisional Date To The Constructive Reduction To Practice

- Patent Owner demonstrated reasonably continuous diligence through the activities of the inventors and prosecution counsel, both working to prepare the '358 provisional application that constructively reduced the claimed invention to practice on May 18, 2009.

- Patent Owner provided testimony from both the inventor Dr. Porreca (EX2004) and prosecution counsel Dr. Waller (EX2005) explaining their practices and describing certain events during the critical period.

- Patent Owner provided documentation (EX2004-2017, EX2021) corroborating the testimony of Dr. Porreca and Dr. Waller and highlighting the diligent activity that occurred during the critical period.

POR, 31-34; Sur-Reply, 8-13.

The Documented Timeline Of Activities Demonstrates Reasonably Continuous Diligence

- April 29, 2009 (Wednesday)
  - Inventors and counsel schedule a call and discuss claim set and comments for provisional application. EX2012, 2-3.
- April 30, 2009 (Thursday)
  - Inventors email paragraphs for draft application, including placeholders. For placeholders, inventors write "***Uri [co-inventor] is still calculating the actual numbers***, but in the interest of time we decided to get this to you now, and will drop those in when available." EX2012, 1-2.
  - Inventors email to identify inventorship of the provisional application ("'Uri's' disclosure"). EX2013, 1.
- May 5, 2009 (Tuesday)
  - Inventors email they "finished working out Uri's example" that was discussed in April 30 email and provide updated paragraph. EX2012, 1.
  - Counsel email back with questions, and inventors respond addressing questions the same day. EX2012, 1.
- May 6, 2009 (Wednesday)
  - Inventors email regarding "next steps," including for "Uri's application." Inventors explain that "Uri is completing the histogram for his application this morning." EX2014, 4.

POR, 31-34; Sur-Reply, 8-13.

The Documented Timeline Of Activities Demonstrates Reasonably Continuous Diligence (Cont'd)

- May 8, 2009 (Friday)
  - Inventors email regarding applications to "schedule a time to discuss current status." EX2014, 3.
  - Counsel responds and schedule a call for May 9, 2009 to discuss status. EX2014, 2-3.
- May 9, 2009 (Saturday)
  - Inventors and counsel discuss application status by phone. EX2014, 2 ("Glad we were able to connect Saturday morning.").
- May 11, 2009 (Monday)
  - Inventors email to inquire about status of provisional applications and for date estimate. EX2014, 2.
  - Counsel responds they "are working to get them to you as soon as possible." EX2014, 1.
- May 13, 2009 (Wednesday)
  - Inventors email to ask when to expect provisional "to be ready for final review and filing." EX2014, 1.
  - Counsel responds that they expect to send provisional application ("Uri's") "tomorrow during the day" and request to "schedule a time tomorrow to go over any questions or comments." EX2014, 1.

POR, 31-34; Sur-Reply, 8-13.

The Documented Timeline Of Activities Demonstrates Reasonably Continuous Diligence (Cont'd)

- May 14, 2009 (Thursday)
  - Counsel emails to indicate they are still working and are "finalizing Uri's application." Counsel requests to set up a call that afternoon to go over the applications. EX2014, 1.
  - Counsel emails draft of provisional application. EX2015, 1 ("Attached is a draft of Uri's application."). The draft includes "some specific questions in bold" for the inventors. EX2015, 1.
- May 15, 2009 (Friday)
  - Inventors email edits to the draft provisional application, indicating "[a]ttached is my edited version" and "I used track changes." Inventors summarize a short paragraph that was added in the edits. EX2015, 1.
  - Inventors email additional suggested edits and "look forward to getting this one on file soon." EX2015, 1.
- May 18, 2009 (Monday)
  - Inventors email to "confirm that we're still on track to file Uri's application today." EX1064, 1.
  - Counsel responds with "updated application," indicating they "have revised the claims," changed a term, and "are updating the supporting specification to reflect this new terminology and the additional claims in preparation for filing this evening." EX1064, 1.
  - Provisional application is filed, constructively reducing the claimed inventions to practice. EX1008.

POR, 31-34; Sur-Reply, 8-13.

Petitioner's Attack On Cherry-Picked Days During The Critical Period Do Not Overcome Patent Owner's Evidence Of Diligence

- Petitioner's main argument nitpicks individual days to reach the incorrect assertion that "Molecular Loop cannot show any activity on 12 of 20 days," claiming "gaps" of "over 50% of the critical period." Reply, 27.

- That argument imposes a standard much higher than precedent requires because it (1) ignores the multiple weekends in Petitioner's count of alleged inactive days, (2) ignores evidence of activity even on the alleged inactive days, and (3) ignores surrounding evidence showing work done on the alleged inactive days.

- In addition to being incorrect, Petitioner's argument is exactly the type of "fixat[ion] on the portions of the critical period" that lack "evidence of [inventor's] specific activities" that the Federal Circuit has rejected.

Perfect Surgical Techniques, Inc. v. Olympus America, Inc., 841 F.3d 1004, 1010 (Fed. Cir 2016).

Sur-Reply, 8-12.

Petitioner's Attacks On Witnesses' Memories Of Specific Events Sixteen Years Ago Do Not Overcome Patent Owner's Evidence Of Diligence

- Petitioner faults Dr. Porreca and Dr. Waller for not recalling specific details about the application drafting that occurred 16 years ago. Reply, 23-24.

- That argument imposes an improperly high standard requiring specific independent recollection of details (e.g., specific dates and activities performed) regarding the diligent activity during the critical period.

Perfect Surgical Techniques, Inc. v. Olympus America, Inc., 841 F.3d 1004, 1010-11 (Fed. Cir 2016).

- Witness testimony that is "[b]ased on [] review or written correspondence" to confirm certain specific details is exactly the type of testimony that has been found to support reasonably continuous diligence.

Olympus America, Inc. v. Perfect Surgical Techniques, Inc., IPR2014-00233, EX2010, at ¶¶13-16 (PTAB Oct. 3, 2014).

Sur-Reply, 12-13.

Chee Is Not Prior Art For The Additional Reason That Its Provisional Does Not Include Disclosure Relied On In Petitioner's Grounds (All Claims)

- Petitioner relies on Chee's disclosure of "naturally-occurring nucleic acids (e.g., DNA or RNA or fragments thereof that are isolated from a sample)" to argue that Chee discloses the claimed step of "obtaining a biological sample comprising a plurality of target nucleic acid molecules." Pet., 26 (citing EX1010, 11:51-54).

- Chee's disclosure of "naturally-occurring nucleic acids" does not appear in Chee's provisional, and Dr. Puglisi explained how Chee's provisional lacks support for that portion of Chee relied on in Petitioner's Grounds that are based on Chee. EX2023, ¶¶164-169.

- Thus, Petitioner fails to establish Chee as prior art to any claims because it fails to identify in Chee's Provisional "written description support ***for the specific portions of the patent specification identified and relied on***" in its invalidity challenge.

In re Riggs, 131 F.4th 1377, 1384 (Fed. Cir. 2025).

POR, 35-41; Sur-Reply, 17-18.

Chee's Provisional Repeatedly Describes Synthetic Biology Applications And Contains No Discussion Of Naturally-Occurring Nucleic Acids

- Chee's Provisional repeatedly highlights that its descriptions relate to ***synthetic biology***. EX2023, ¶¶166-168.
  - The invention "relates to the field of oligonucleotide selection and ***synthetic biology***." EX1011, ¶1.
  - The background says "***synthetic biology*** is a promising new field at the interface of engineering and biology." EX1011, ¶3.
  - The problem addressed is that "***construction*** of multi-kilobase scale DNA molecules remains difficult and costly, largely because that ***de novo chemical synthesis*** of the DNA building blocks is quite error-prone." EX1011, ¶4.
  - The invention sought to fill the "need to select error-free synthesized oligonucleotides for use in ***synthetic biology*** and other analytical methods." EX1011, ¶5.

- Dr. Gabriel agrees that Chee's repeated and consistent discussion of "synthetic biology" refers to "synthesizing nucleic acid fragments," which would be "***an artificial nucleic acid sequence as opposed to a naturally occurring one***." EX2024, 59:21-60:7.

POR, 38-41; Sur-Reply, 17-18.

Comparing The Key Disclosure In Chee's Provisional And Its Later Patent Application Highlights The Lack Of Provisional Support

- Chee's 2009 Provisional:

[00066] Although the present invention is primarily described in the context of synthetic biology and quantitative analysis, the constructs and methods can be used more generally to identify and obtain any desired sequence from a collection of nucleic acid molecules. For example, the methods of the invention can be used to create a large collection of smaller nucleic acids with extremely high fidelity for any discovery research, diagnostic use, clinical use or other development techniques.

EX1011, ¶66.

- Chee's 2010 Specification:

In a specific aspect, the constructs and methods can be used more generally to identify and obtain any desired sequence from a collection of nucleic acid molecules. For example, the methods of the invention can be used to determine the sequence of naturally-occurring nucleic acids (e.g., DNA or RNA or fragments thereof that are isolated from a sample). These molecules can be used to create a master set of ROIs for sequence determination. When the starting nucleic acid is quite large, e.g., a genome or a complex mixture of nucleic acids, the sequences can optionally be assembled to result in one or more contiguous sequences containing two or more ROIs from the set. In other aspects, the ROIs can be used to create a large collection of smaller nucleic acids with extremely high sequence fidelity for any discovery research, diagnostic use, clinical use or other development techniques.

EX1010, 11:49-63.

POR, 38-41; Sur-Reply, 17-18.

Disputed Issues

1. Chee is not prior art to the '730 Patent. (Grounds 1-3)

2. **Chee does not disclose the "collapsing target:differentiator tag combinations" limitation. (Grounds 1-3)**

3. Petitioner does not show a motivation to combine Chee and Gahan. (Ground 3)

4. Petitioner does not show a motivation to combine Bignell and McCloskey. (Grounds 4-7)

5. Bignell-McCloskey does not disclose the "correcting" step. (Grounds 4-7)

The '730 Patent Claims Separate Steps Of "Collapsing Target:Differentatior Tag Combinations" And "Determining A Consensus Base Call"

1. A method for correcting for errors or bias introduced during nucleic acid analysis workflow, the method comprising the steps of:

obtaining a biological sample comprising a plurality of target nucleic acid molecules from more than one locus of origin;

introducing a set of differentiator tags, wherein members of said set of differentiator tags are associated with members of said plurality, such that one or more of said loci of origin are associated with more than one differentiator tag;

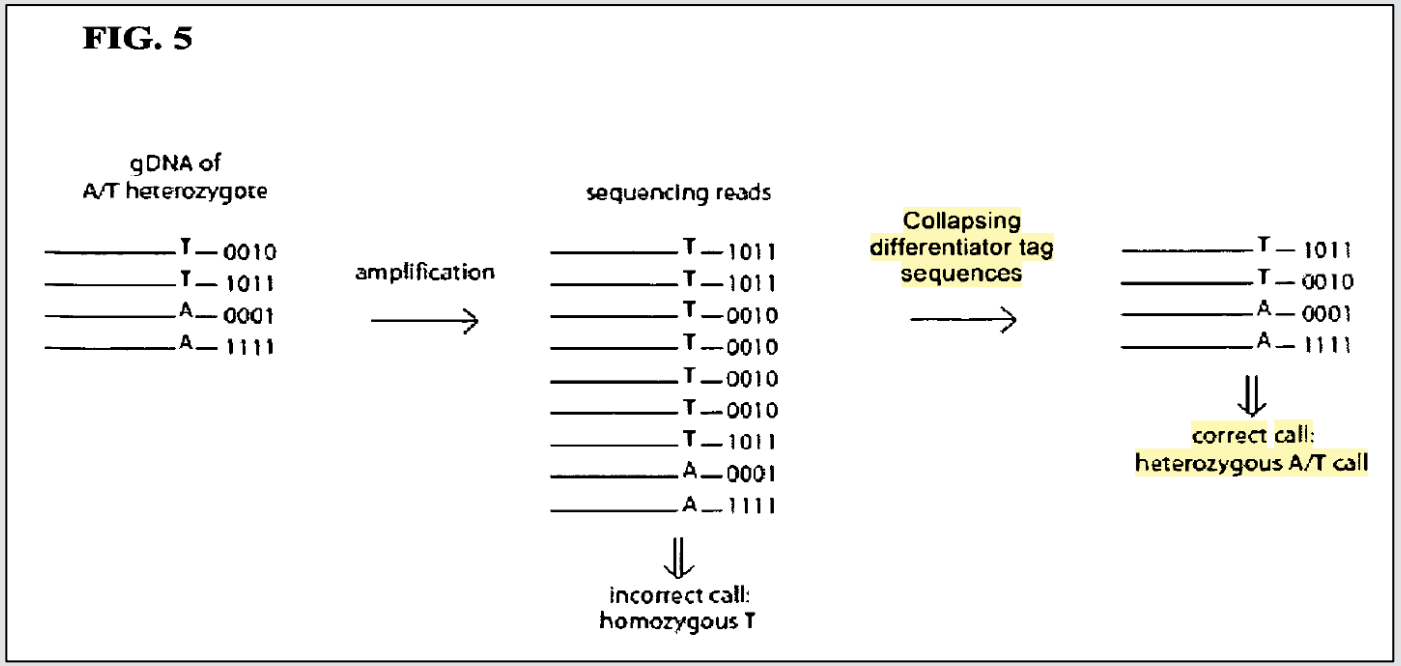
amplifying each of the plurality of tagged target nucleic acid molecules to generate amplicons;

sequencing the amplicons obtained in said amplifying step to obtain sequence reads of each of the amplicons, wherein each of the sequence reads comprises a target nucleic acid molecule sequence and a differentiator tag sequence; and

correcting for error or bias introduced during said workflow by collapsing target:differentiator tag combinations observed more than once into a single count.

2. The method of claim 1, wherein 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.

EX1001, Claim 1.



EX1001, Fig. 5.

POR, 42-45; Sur-Reply, 14-16; EX2023, ¶¶132-144.

Chee Generally Discusses "Technical Bias" And "Consensus Sequences" But Does Not Disclose Specific Methods For Either

- Petitioner cites Chee disclosures about identifying technical bias generally, without discussion of a particular method that includes the claimed "collapsing." EX2023, ¶¶145-157.
  - Chee states that its methods "can identify technical bias" and that "the number of starting molecules can be inferred" without detail on how it would do so. EX1010, 10:41-46.
  - Chee states that if nucleic acid is over- or under-represented, "the quantification of the molecules can be corrected to reflect this manner of bias" without detail on how it would do so. EX1010, 23:59-64.
  - Chee states that "differences in the amount and/or composition of amplification products can be detected and quantified" without detail on how it would do so. EX1010, 24:5-8

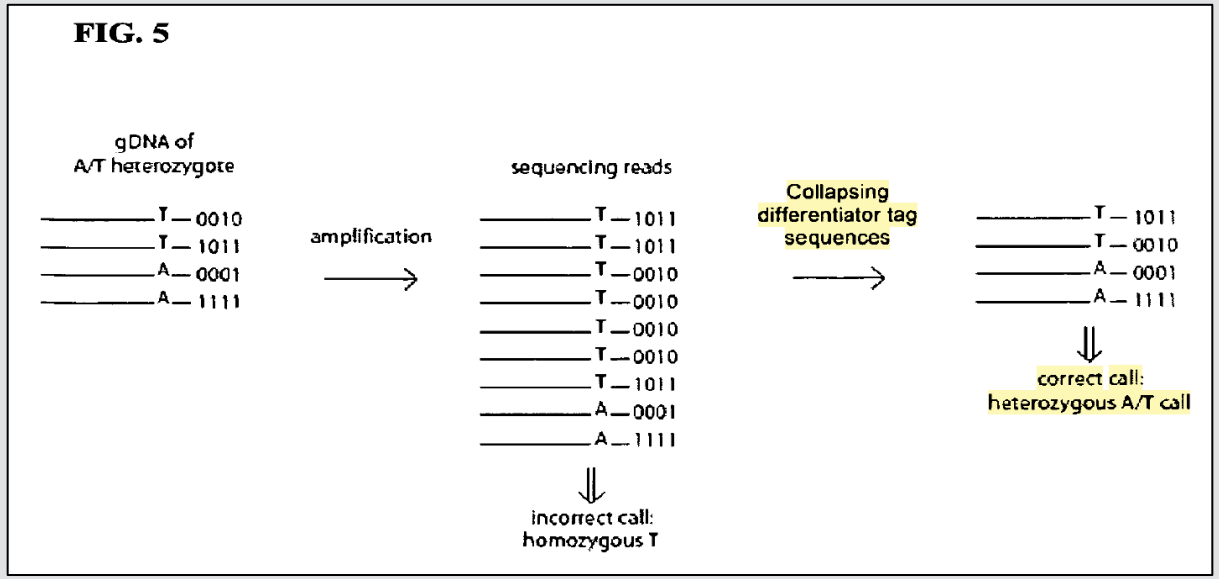
- Petitioner cites Chee disclosure about "consensus sequences" generally, but if anything points only to disclosure of determining those sequences ***without collapsing***. EX2023, ¶¶158-163.
  - For example, Chee explains that rather than collapsing it identifies "a variation in the sequence of a single copy of a construct" to be "a synthesis or sequencing error if it differs from a consensus sequence derived from ***multiple clonal copies of the construct***." EX1010, 14:39-50.

POR, 46–48; Sur-Reply, 15-16

Petitioner Does Not Tie Together Alleged Disclosure Of "Collapsing" With A Next Step Of "Determining A Consensus Base Call" In Chee (Claim 2)

- Claim 2 recites "***collapsing*** all sequence reads comprising a same differentiator tag into a single read ***before determining a consensus base call***." EX1001, Claim 2.

- Even under Petitioner's interpretations of Chee for the "collapsing" step, Petitioner never identifies disclosure in Chee of collapsing sequence reads in a first step and then determining a consensus base call in a second step, contrary to the claimed method.



EX1001, Fig. 5.

POR, 48-49; Sur-Reply, 16-17.

Disputed Issues

1. Chee is not prior art to the '730 Patent. (Grounds 1-3)
2. Chee does not disclose the "collapsing target:differentiator tag combinations" limitation. (Grounds 1-3)
3. **Petitioner does not show a motivation to combine Chee and Gahan. (Ground 3)**
4. Petitioner does not show a motivation to combine Bignell and McCloskey. (Grounds 4-7)
5. Bignell-McCloskey does not disclose the "correcting" step. (Grounds 4-7)

Petitioner Has Not Established Motivation To Combine Chee With Gahan (Ground 3)

A POSA would not have been motivated to combine Chee and Gahan because:

- (1) Petitioner ignores the focus and purpose of Chee's methods, validating "building blocks" for constructing synthetic oligos; and
- (2) Applying Chee's methods, in which "the number of nucleic acid constructs in a set should be ***large enough to ensure a high probability of obtaining at least one correct sequence*** or to confirm a correct sequence associated with a particular unique identifier" (EX1010, 2:44-51) run counter to Gahan's methods in biological samples that are "***far from*** consistent, and if there are to be reliable protocols for diagnostic purposes, there needs to be a form of quality assurance for these procedures" (EX1015, 3).

POR, 49-51; EX2023, ¶¶170-176.

Disputed Issues

1. Chee is not prior art to the '730 Patent. (Grounds 1-3)
2. Chee Does Not Disclose the "collapsing target:differentiator tag combinations" limitation. (Grounds 1-3)
3. Petitioner does not show a motivation to combine Chee and Gahan. (Ground 3)
4. **Petitioner does not show a motivation to combine Bignell and McCloskey. (Grounds 4-7)**
5. Bignell-McCloskey does not disclose the "correcting" step. (Grounds 4-7)

Each Of Petitioner's Grounds 4-7 Is Based On McCloskey And Bignell

Ground	Challenged Claims	Basis	References
1	1-4, 9	§102	Chee
2	1-4, 7, 9	§103	Chee
3	5-6, 8	§103	Chee + Gahan
4	1, 4-6, 9	§103	Bignell + McCloskey
5	2-3	§103	Bignell + McCloskey + Bentley
6	6, 8	§103	Bignell + McCloskey + Gahan
7	7	§103	Bignell + McCloskey + Chiang

Pet., 3.

There Is No Motivation To Combine Bignell With McCloskey

A POSA would not have been motivated to combine Bignell and McCloskey because:

- (1) Petitioner ignores the cost increases required to use McCloskey's molecule-specific tags with Bignell's pooled sample runs.
- (2) Adapting techniques based in McCloskey's Sanger-sequencing to Bignell's NGS sequencing would invoke trade-offs between accuracy and cost, but neither Plaintiff nor Dr. Gabriel performed that analysis.
- (3) Bignell's stated goals—cost reduction and analysis efficiency—for sample-specific sequence tags conflict with McCloskey's more detailed but more expensive molecule-specific tags.

POR, 56-61; Sur-Reply, 18-23.

Petitioner's Only Stated Reason For Combining McCloskey And Bignell Is A Conclusory, Unsupported Assumption That A POSA Needed References Regarding NGS Techniques

EX1012(McCloskey), [0002], [0106]. McCloskey does not require a specific sequencing technology, but notes that methods for "sequencing are standard in the art." *Id.*, [0034]. To implement McCloskey's method, a POSA would have looked to other references for details on known, standard sequencing technologies. EX1005, ¶248. One such reference is Bignell.

Pet., 47.

46:45-47:3, 6:36-43. By early 2009, several recent developments in the DNA sequencing field, including the release of Next-Gen sequencing technologies, "undeniably reinvigorat[ed] this field" and increased the "incentive for developing entirely new strategies for DNA sequencing." EX1014, 1135. A POSA would have been motivated to combine McCloskey specifically with a Next-Gen sequencing technique such as the ones taught in Bignell. EX1005, ¶¶249-50.

Pet., 47.

But McCloskey already discloses sequencing techniques for DNA analysis—Sanger-style techniques.

"Verified SPCR reactions were then cleaned with Microclean (Gel Company) and ***sequenced*** on an ***ABI 3100*** with Big Dye."

EX1012, [0049].

POR, 56-59; Sur-Reply. 18-22 .

McCloskey's Molecule-Specific Sanger Sequencing Techniques Are Detailed, But Have Lower Throughput

Dr. Gabriel Deposition (EX2024)

Q. Okay. So for the record, in the mid-2000 time frame, next-generation sequencing technologies were capable of millions of sequence reads on a single instrument run, compared to hundreds of reads for a first-generation technology like Sanger sequencing?

A. Correct.

EX2024, 12:9-16.

Dr. Puglisi Declaration (EX2023)

However, the Sanger method suffers from drawbacks including limited throughput (bases sequenced per run or unit time), time consuming sample preparation, and the cost per nucleotide sequenced. These aspects

EX2023, ¶ 30.

McCloskey's examples are all limited to Sanger-style sequence runs of less than 150 sequence reads:

"Verified SPCR reactions were then cleaned with Microclean (Gel Company) and sequenced on an ***ABI 3100*** with Big Dye."

EX1012, [0049].

POR, 3-5, 56-59; Sur-Reply, 20-22.

Bignell Seeks Cost Efficient And High Throughput Pooled NGS Sequencing, Compared To Sequencing Sequences One At A Time

"An ability to genotype large populations in a small number of reactions, while ***retaining the information relating to the source of the individual samples would yield the information content of a full non-pooled population screen in the time and at the cost of a pooled reaction***."

EX1013, 2:3-8.

"However ***large-scale genotyping is demanding in terms of the cost*** of both materials and labour involved, ***and the time taken to perform the study***, ***especially if the methodology employed involves separate serial analysis of individual DNA samples***. One shortcut is to pool DNA from many individuals and to determine parameters such as the ratio of changes at certain positions in the genome."

EX1013, 1:51-58.

Bignell's method is designed to provide better information using the sample-specific barcode at a lower relative cost than sequencing all of those DNAs one at a time. Is that right?

A. Yeah.

EX2025, 87:11-15.

POR, 16-17, 59-61; Sur-Reply, 20-22.

Dr. Gabriel—Petitioner's Expert—Concludes That NGS Cost-Efficiency Would Lead To A Motivation To Combine, But Never Acknowledges Or Analyzes The Costs Of The Proposed Combination

the ones described in Bignell. As I explained above, by early 2009, Next-Gen sequencing technologies were widely adopted because they provided sequencing methods which were both cost-effective and highly efficient. *See, e.g.*, EX1014, 1135. Next-Gen sequencing technologies have been praised for "undeniably reinvigorating this field" and creating "the incentive for developing entirely new strategies for DNA sequencing." *Id.* It made sequencing more affordable and available for all types of experiments and analyses. Thus, a person of ordinary skill in the art would have been motivated to implement a Next-Gen sequencing technique, such as the technique described by Bignell, with McCloskey's method.

EX1005, (Gabriel Decl), ¶ 250.

Q. You'd agree that your reply declaration contains no mention of the point at which an increase in quality is worth an increase in cost based upon the intent of an experiment in the McCloskey-Bignell combination. Correct?

A. The only thing -- I've made the point here that if very high accuracy is required, that can warrant additional costs. They haven't given what that cost is or an example of what that could be. We can talk about that, but that's not what I've given here in this paragraph.

EX2025, 91:19-92:7.

POR, 59-61; Sur-Reply, 20-22.

Petitioner Does Not Carry Its Burden To Provide Evidence Showing A Motivation To Combine McCloskey And Bignell



***Unified Patents Inc. v. Velos Media, LLC*, IPR2019-00710, 2020 WL 5135433, at *5 (P.T.A.B. Aug. 31, 2020)**

"***It is not Patent Owner's burden, however, to disprove Petitioner's alleged motivation***. Rather, ***Petitioner must demonstrate*** by a preponderance of the evidence that the claims are unpatentable. 35 U.S.C. § 316(e). This burden of persuasion never shifts to Patent Owner."

- Neither Petitioner nor Dr. Gabriel consider the costs of the proposed McCloskey-Bignell combination.

POR; 59-61; Sur-Reply, 20-21.

Petitioner And Dr. Gabriel Argue That A POSA Might Be Willing To Trade Increased Costs For Increased Accuracy, But Admit That The Trade Is Situation-Dependent

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.

EX1065, ¶20.

Q. And if very high accuracy was not the intent of the experiment using the McCloskey-Bignell combination, then the cost would not be worth it. Correct?

A. It may or may not be, depending upon what a person was trying to do.

EX2025, 92:8-14.

Sur-Reply, 20-22.

Petitioner And Dr. Gabriel Admit That They Did Not Do The Analysis To Determine When Increased Accuracy Is Worth Increased Costs In McCloskey-Bignell

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.

EX1065, ¶21.

Q. And you don't list out what somebody might be trying to accomplish in your reply declaration. Correct?

A. I don't list that out. No.

EX2025, 91:10-13.

Q. You'd agree that your reply declaration contains no mention of the point at which an increase in quality is worth an increase in cost based upon the intent of an experiment in the McCloskey-Bignell combination. Correct?

A. The only thing -- I've made the point here that if very high accuracy is required, that can warrant additional costs. They haven't given what that cost is or an example of what that could be. We can talk about that, but that's not what I've given here in this paragraph.

EX2025, 91:19-92:7.

Sur-Reply, 20-22.

Petitioner Does Not Carry Its Burden To Provide Evidence Showing A Motivation To Combine McCloskey And Bignell



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- Neither Petitioner nor Dr. Gabriel consider the costs of the proposed McCloskey-Bignell combination.
- Neither Petitioner nor Dr. Gabriel provide any evidence or analysis showing when the tradeoff between costs and accuracy would be worth it.

POR, 59-61; Sur-Reply, 20-22.

Petitioner's Failure To Consider The Whys And Hows Of Its Proposed Combination Led It To Ignore Bignell's Rejection Of McCloskey's Approach.

- McCloskey's molecule-specific barcodes were designed to solve issues with the ***authenticity*** of PCR products by barcoding ***each sequence*** in a sample with a different barcoded oligonucleotide.
  - "The present invention permits the ***identification of valid sequences***, and ***distinguishes the valid sequences from contaminants and redundant sequences*** arising from template re-cloning." EX1012, [0002].

- Bignell's sample-specific tags were designed to pool multiple samples together, sequence the pooled samples on NGS sequencers in a single sequencing run, and trace the sequences back to each original sample based on the sample-specific tags.
  - Bignell's "invention relates to methods for indexing samples … resulting in the ***attachment of tags specific to the source of each nucleic acid sample*** such that after a sequencing run, both the source and sequence of each polynucleotide can be determined**.**" EX1013, 1:24-28.

POR, 56–58; Sur-Reply, 27.

Petitioner's Failure To Consider The Whys And Hows Of Its Proposed Combination Led It To Ignore Bignell's Rejection Of McCloskey's Approach.

- For that reason, Bignell rejected approaches that tagged molecules one by one:

> "However ***large-scale genotyping is demanding in terms of the cost*** of both materials and labour involved, ***and the time taken to perform the study***, ***especially if the methodology employed involves separate serial analysis of individual DNA samples***. One shortcut is to pool DNA from many individuals and to determine parameters such as the ratio of changes at certain positions in the genome."
>
> EX1013, 1:51-58.

such that each bead contains multiple copies of a single amplified target sequence (Brenner et al., (2000) Nature Biotechnology, 18, 630). In this application the tags are not sequenced, so the method does not provide a method of analysing targets from multiple samples, but rather a method of sorting a mixture of amplified templates from a single sample. The problem with enabling the method for individual samples rather than individual molecules is that the tags are synthesised in a 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.

EX1013, 3:22-35

POR, 56–59; Sur-Reply, 18-22

Dr. Gabriel Agrees That Applying Different Tags To Each Molecule Within A Sample Does Not Make Sense For Bignell's Goal

Q. It wouldn't make sense to apply different tags to every molecule in the sample if your goal -- if Bignell's goal was identifying the source of the sample, right?

A. 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.

EX2024, 76:7-14

Q. You disagree that Bignell has a problem with the Brenner approach?

A. For what she's trying to accomplish here, she's saying there was a problem with the Brenner approach.

EX2025, 82:5-9.

POR, 58–59; Sur-Reply, 18-20.

There Is No Motivation To Combine Bignell With McCloskey

- Petitioner now argues in Reply that "[b]ecause McCloskey adds a sample-specific tag to each molecule, it is completely consistent with Bignell's goals of using tags to identify and distinguish samples." Reply, 8 (emphasis in original).
  - But that ignores the cost of the combination and Bignell's rejection of similar prior art approaches.
  - Petitioner has no analysis or reasoning for why a POSITA looking at Bignell would add molecule-specific tags that do not serve its goals and increase costs.
- And even if Petitioner is right, then Petitioner's proposed combination is redundant and there is no need to add Bignell—McCloskey alone supplies both (1) a molecule-specific tag; and (2) a sample-specific tag.

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).

EX1065, ¶18.

POR 56-58; Reply, 8–9; Sur Repy, 18-22..

Petitioner Does Not Carry Its Burden To Provide Evidence Showing A Motivation To Combine McCloskey And Bignell



***Unified Patents Inc. v. Velos Media, LLC*, IPR2019-00710, 2020 WL 5135433, at *5 (P.T.A.B. Aug. 31, 2020)**

"***It is not Patent Owner's burden, however, to disprove Petitioner's alleged motivation***. Rather, ***Petitioner must demonstrate*** by a preponderance of the evidence that the claims are unpatentable. 35 U.S.C. § 316(e). This burden of persuasion never shifts to Patent Owner."

- Neither Petitioner nor Dr. Gabriel consider the costs of the proposed McCloskey-Bignell combination.
- Neither Petitioner nor Dr. Gabriel provide any evidence or analysis showing when the tradeoff between costs and accuracy would be worth it.
- Petitioner and Dr. Gabriel fail to address Bignell's rejection of molecule-specific approaches.

POR, 58-61; Sur-Reply, 18-22.,

Disputed Issues

1. Chee is not prior art to the ’730 Patent. (Grounds 1-3)
2. Chee Does Not Disclose the “collapsing target:differentiator tag combinations” limitation. (Grounds 1-3)
3. Petitioner does not show a motivation to combine Chee and Gahan. (Ground 3)
4. Petitioner does not show a motivation to combine Bignell and McCloskey. (Grounds 4-7)
5. **Bignell-McCloskey does not disclose the “correcting” step. (Grounds 4-7)**

Petitioner Relies Solely On McCloskey For The "Correcting" Step

Bignell fails to address "correcting," which makes sense, because Bignell is directed to sample identification, not to error or bias correction.

Bignell discloses adding a tag to each nucleic acid in a sample. EX1013(Bignell), 7:59-64, 9:41-52, 9:59-10:4. *See also id.*, 13:16-22, 13:32-35, 21:18-22. Bignell's tags include a sample identifier that is the same for every nucleic acid in a sample. *Id.*, 9:46-52. The tags can be incorporated into an

Pet., 53.

Therefore, in order to accomplish its goal of identifying the source of a sample of a molecule, Bignell describes attaching the same tag to every molecule from a given sample, correct?

A. Right. The goal is to assign sequence data to samples.

EX2024, 77:15-21.

Therefore, Petitioner relies on McCloskey alone—and not Bignell—for the "correcting" step:

f) correcting for error or bias introduced during said workflow by collapsing target:differentiator tag combinations observed more than once into a single count.

As explained with respect to the claim preamble, McCloskey teaches "*correcting for errors or bias*." EX1012(McCloskey), [0002].

Pet., 56.

Pet., 56-57; POR 52.

But McCloskey Uses Barcodes Alone, As Petitioner Admits

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

Reply, 3-4.

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

Reply, 5.

In your opinion, McCloskey identifies target:barcode combinations using the barcode alone. Correct?

A. Yes.

EX2025 (Gabriel Deposition), 67:14-17.

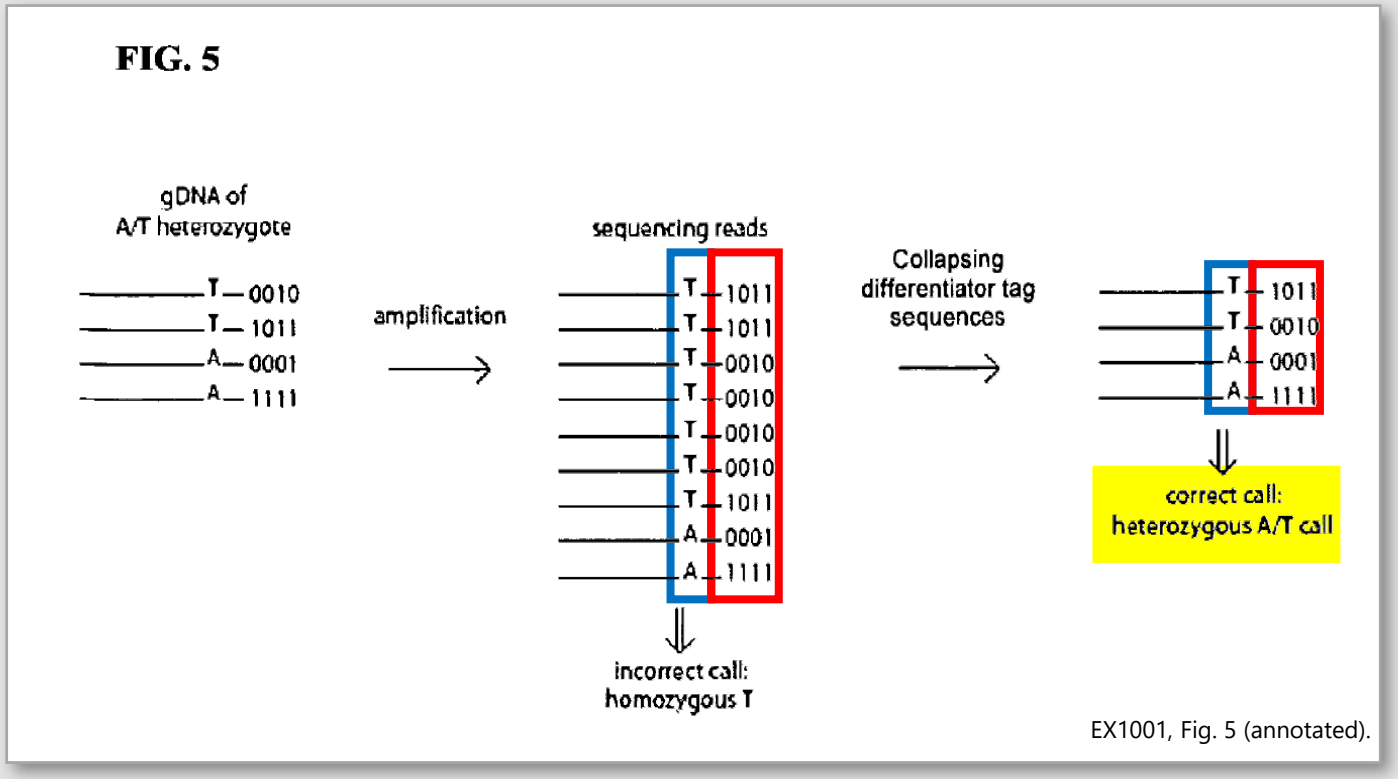
POR 52-54; Sur-Reply, 23-27.

Petitioner Argues That McCloskey's Barcodes Alone Disclose The Claimed "Collapsing" Step, But The Claims Require Combinations.

correcting for error or bias introduced during said work-flow by collapsing target:differentiator tag combinations observed more than once into a single count.

EX1001, Claim 1

- This is important, because using information for both the **differentiator tag** ***and*** the **target sequence** itself allows for correction of bias ***and*** more accurate genotyping and consensus base calls.



EX1001, Fig. 5 (annotated).

POR 52-55; Sur-Reply, 23-27.

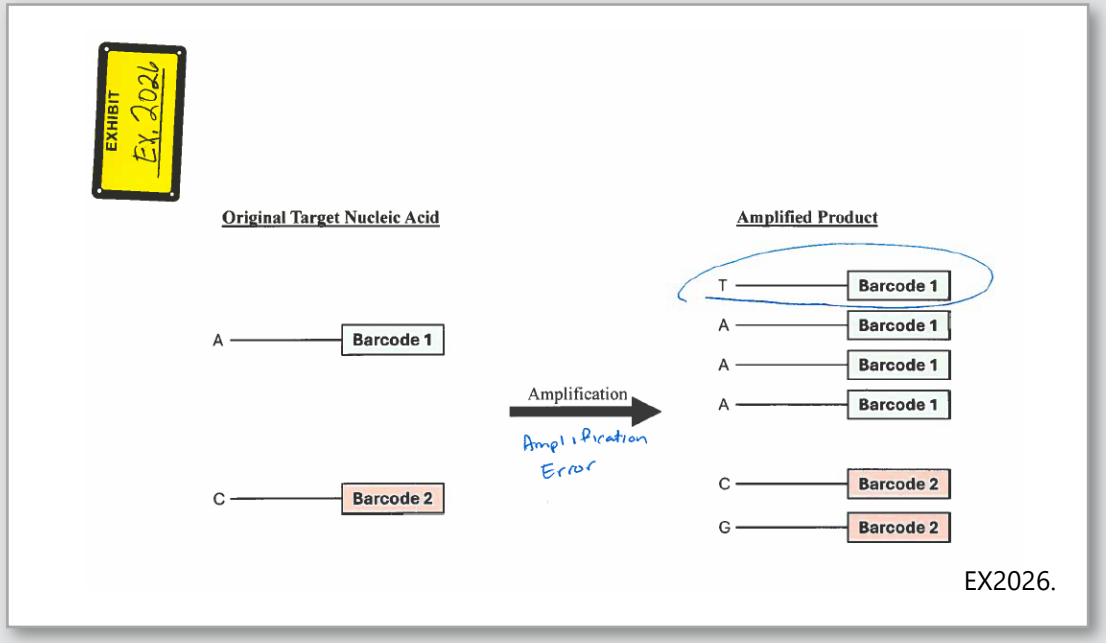
Petitioner's Arguments—All Of Which Rely On Use Of Barcodes Alone—Therefore Fail To Show That McCloskey Discloses The Claims

- Petitioner argues in the Petition "McCloskey teaches 'correcting for errors or bias.' . . . McCloskey corrects the skewing ***by identifying duplicate barcodes*** in an amplified sample," which "allows McCloskey to determine that there are 'multiple amplified sequences derived from a single original molecule.'" Pet., 56-57.
- Petitioner argues in the Reply "McCloskey uses the barcodes to identify redundant copies so it can accurately quantify the number of molecules in the starting sample." Reply, 3-4.

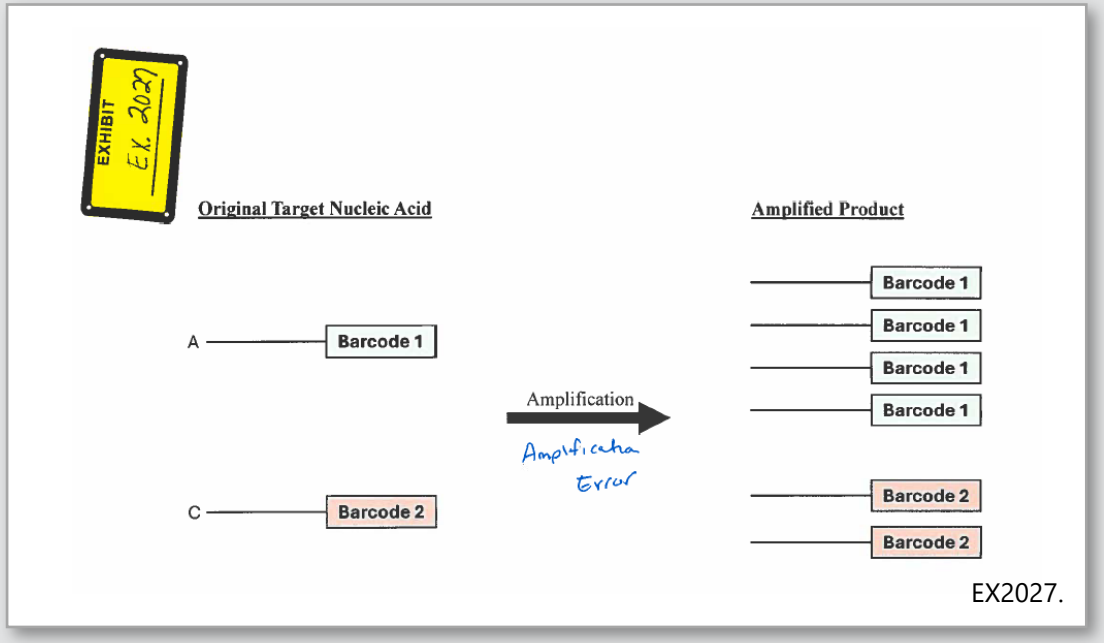
- Neither of these arguments holds water, because both rely on the ***barcode alone***.

Sur-Reply, 23-27.

Dr. Gabriel Admits That Using Barcodes Alone Does Not Provide The Information Necessary To Detect Authentication Errors



EX2026.



EX2027.

But again, depending on how you analyze the data, you can look at the -- you can look at these reads themselves and understand that "T" is -- there's one outlier "T" where you have a bunch of "As".

Q. Right. But that's because I'm looking at both the sequence and -- I have the sequence information in my results. Right? And that's what I'm looking at?

A. That's what you're looking at, yeah.

EX2025, 49:21-50:8.

Sur-Reply, 24-27.

Experiments That Use Barcodes Alone—Like McCloskey's Authentication Experiments—Are Not Intended To Identify Error

Q. So in the scenario in which you're using just the barcode alone, like in a counting application, you would not be able to identify error. Correct?

A. You wouldn't be trying to.

A. It's a different type of experiment.

That's a different application. Yeah.

Dr. Gabriel (EX2025), 54:14-21.

"There is a need in the art for methods for ***verifying the authenticity of PCR products***. The present invention addresses this and other needs."

EX1012, [0004].

"The bar-coded oligonucleotide further comprises a ***second sequence that provides a random barcode***."

EX1012, [0021].

"In step (d) of the methods, the amplification product is ***authenticated by detecting the presence of the second sequence*** in the amplification product."

EX1012, [0034].

POR, 53-54; Sur-Reply, 24-27.

McCloskey's Use Of Barcodes Alone Does Not Disclose The Claimed Target:Differentiator Tag Combinations

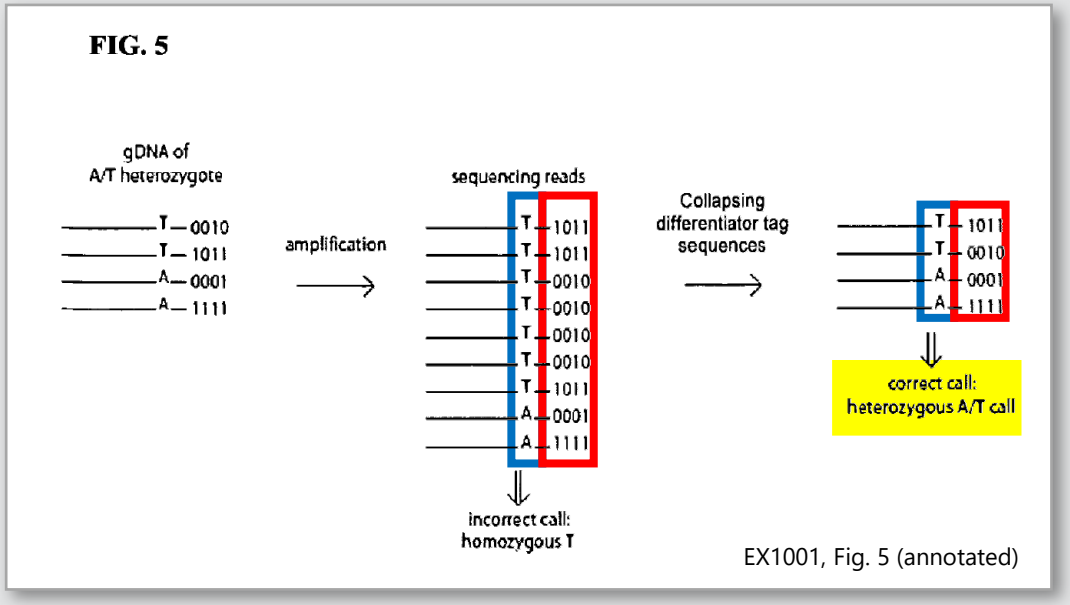
correcting for error or bias introduced during said work-flow by collapsing target:differentiator tag combinations observed more than once into a single count.

EX1001, Claim 1

In your opinion, McCloskey identifies target:barcode combinations using the barcode alone. Correct?

A. Yes.

EX2025 (Gabriel Deposition), 67:14-17.



EX1001, Fig. 5 (annotated)

POR, 52-56; Sur-Reply, 23-27.