UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BIO-RAD LABORATORIES, INC.,
Petitioner,

v.

CALIFORNIA INSTITUTE OF TECHNOLOGY,
Patent Owner

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 10,770,170 B2

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Patent Trial and Appeal Board
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1. A method of unambiguously detecting any unique combination of presence or absence of at least five polynucleotide analytes in a plurality of droplets, the method comprising: 27

2. (a) providing a sample comprising, or potentially comprising, at least one of said at least five polynucleotide analytes; 28

3. (b) forming a mixture of said sample and at least five hybridization probes, ... 32

4. wherein each of said at least five hybridization probes further comprises at least one fluorophore and at most four fluorophores; 33

5. (c) partitioning said mixture into said plurality of droplets; 36

6. (d) exciting said at least one fluorophore to generate one or more signals if one or more of said at least five polynucleotide analytes is present in said plurality of droplets, wherein said one or more signals comprise at least one signal generated by excitement of said at least one fluorophore; 36

7. (e) measuring said one or more signals to generate a cumulative intensity measurement, ... 38

8. wherein said cumulative intensity measurement corresponds to the presence of a unique combination of presence or absence of said at least five polynucleotide analytes in said sample; and 39

9. (f) determining whether each of said [at] least five polynucleotide analytes is present, in any unique combination of presence or absence, based on said cumulative intensity measurement, ... 42

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PETITIONER'S EXHIBIT LIST

Exhibit #	Description
EX1001	U.S. Patent No. 10,770,170 "'170 patent"
EX1002	Declaration of Carl A. Batt, Ph.D.
EX1003	Joint Claim Construction Statement, filed on June 18, 2024, Dkt No. 65, *ChromaCode, Inc. v. Bio-Rad Laboratories et al.*, Case No. 5:23-cv-06360, N.D. Cal
EX1004	U.S. Patent Application Publication No. US 2013/0040841 A1 "Saxonov"
EX1005	Information Disclosure Statement noting Saxonov from Prosecution File History of U.S. Patent No. 10,068,051 filed on August 5, 2014
EX1006	Notice of Allowance from Prosecution File History of U.S. Patent No. 10,770,170 filed on March 7, 2018
EX1007	U.S. Patent Provisional Application No. 61/510,013 (filed July 20, 2011) (Serge Saxonov, Simant Dube, John F. Regan, applicants) ("'013 Provisional")
EX1008	Intentionally Left Blank
EX1009	U.S. Patent Application Publication No. US 2011/0312704 A1 "Silverbrook"
EX1010	U.S. Patent Application Publication No. US 2008/0003649 A1 "Maltezos"
EX1011	U.S. Patent Application Publication No. US 2010/0311070 A1 "Oh"
EX1012	U.S. Patent No. 10,770,170 Infringement Claim Charts from Infringement Contentions, served on March 21, 2024, *ChromaCode, Inc. v. Bio-Rad Laboratories et al.*, Case No. 5:23-cv-06360, N.D. Cal.
EX1013	Synbio Technologies, Precision and Accuracy with TaqMan Probes, https://synbio-tech.com/precision-and-accuracy-with-taqman-probes/

Exhibit #	Description
EX1014	Pamela M. Holland, et al., "Detection of specific polymerase chain reaction product by utilizing the 5' → 3' exonuclease activity of *Thermus aquaticus* DNA polymerase," *Proc. Natl. Acad. Sci. USA*, Vol. 88, pp. 7276-7280, August 1991 Biochemistry "TaqMan Paper"
EX1015	Information Disclosure Statement from Prosecution File History of U.S. Patent No. 10,770,170 filed on March 7, 2018
EX1016	Information Disclosure Statement from Prosecution File History of U.S. Patent No. 11,827,921 filed on May 1, 2020
EX1017	U.S. Patent Application Publication No. US 2011/0250597 A1 "Larson"
EX1018	Intentionally Left Blank
EX1019	Plaintiff and Counter-Defendant Chromacode Inc.'s Amended Patent L.R. 3-5 Disclosure of Preliminary Invalidity Contentions; Patent L.R. 3-4 Document Production, served on February 29, 2024, *ChromaCode, Inc. v. Bio-Rad Laboratories et al.*, Case No. 5:23-cv-04823, N.D. Cal.
EX1020	Simant Dube, et al., "Mathematical Analysis of Copy Number Variation in a DNA Sample Using Digital PCR on a Nanofluidic Device," PLoS One, Volume 3, Issue 8, August 2008 "Dube Paper"
EX1021	U.S. Patent No. 9,487,822 "Dube patent"
EX1022	U.S. Patent No. 9,366,632 "Link"
EX1023	Federal Judicial Caseload Statistics (2023), at https://www.uscourts.gov/statistics-reports/analysis-reports/federal-judicial-caseload-statistics
EX1024	Civil Minutes - General, filed on December 7, 2023, Dkt No. 34, *ChromaCode, Inc. et al. v. Bio-Rad Laboratories*, Case No. 2:23-cv-08417, C.D. Cal.
EX1025	U.S. Patent Application Publication No. US 2011/0160288 A1 "Nakamura"
EX1026	U.S. Patent Application Publication No. US 2010/0173394 A1 "Colston"

Exhibit #	Description
EX1027	Joint Stipulation and Order Regarding Filing of Second Amended Complaint and Amended Case Schedule, filed on March 27, 2024, Dkt No. 53, *ChromaCode, Inc. v. Bio-Rad Laboratories et al.*, Case No. 5:23-cv-06360, N.D. Cal
EX1028	Amended Complaint for Patent Infringement of U.S. Patent Nos. 10,068,051 and 10,770,170, filed on October 13, 2023, Dkt No. 12, *ChromaCode, Inc. et al. v. Bio-Rad Laboratories*, Case No. 2:23-cv-08417, C.D. Cal.
EX1029	U.S. Patent No. 8,730,479 "Application No. 13/341,678" (as issued)
EX1030	Office Action Summary from Prosecution File History of U.S. Patent No. 10,770,170 filed on March 7, 2018
EX1031	Amendment and Response to Final Office Action and Request for Continued Examination from Prosecution File History of U.S. Patent No. 10,770,170 filed on January 21, 2020
EX1032	Information Disclosure Statement from Prosecution File History of U.S. Patent No. 10,770,170 filed on March 7, 2018
EX1033	References Cited by Applicant and Considered by Examiner from Prosecution File History of U.S. Patent No. 10,770,170 filed on March 7, 2018
EX1034	Intentionally Left Blank
EX1035	Intentionally Left Blank
EX1036	Nucleic Acids, https://www.genome.gov/genetics-glossary/Nucleic-Acids, updated July 7, 2024
EX1037	Introduction of Molecular Beacons, https://molecular-beacons.org/MB_introduction.html
EX1038	Shivaprasad H. Sathyanarayana and Lauren M. Wainman, "Chapter 2, Laboratory approaches in molecular pathology: the polymerase chain reaction," Diagnostic Molecular Pathology, 2024

I. INTRODUCTION

Bio-Rad Laboratories, Inc., ("Petitioner") requests *inter partes* review of claims 1-20 of United States Patent No. 10,770,170 ("the '170 patent"), issued on September 8, 2020. The '170 patent, entitled "Signal Encoding and Decoding in Multiplexed Biochemical Assays," relates to detecting multiple polynucleotides in the same experiment. Nothing about the techniques described and claimed in the '170 patent, however, are novel or non-obvious relative to the prior art.

For decades, DNA molecules had been detected using probes labeled with a light-emitting compound such that the probes would emit a characteristic light signal upon binding to their DNA targets. Detecting multiple DNA molecules by this method was easily done using a set of probes, wherein each probe corresponded to a unique target and emitted its own unique signal.

In addition, it was similarly well-understood that one was not limited to such a one-target-to-one-color approach. The prior art taught detecting more targets than distinct colors available. For instance, ***different intensities*** of one color can be used to detect ***three*** different targets by mapping each intensity to a target. Alternatively, with two detection colors, one can detect ***three*** different targets by mapping two colors to two targets and the combination of the two colors to a third target.

Both of the foregoing concepts for detecting more targets than the number of colors by using different intensity levels or mixing color signals had been reported

and used in the field of nucleic acid analysis, most notably in the Saxonov prior art reference that is relied upon herein and is owned by Petitioner.

To the extent the '170 patent identifies any arguable point of novelty, it is little more than the straightforward extension of these prior art concepts to more targets. The '170 patent, for instance, specifically claims detecting the "presence or absence of at least five polynucleotide analytes." EX1001 at claim 1. This is not achieved through new breakthroughs in detection hardware or optics, but simply through the prior art concepts of mapping combinations of color signals and intensities to targets.

As is proven herein and in the accompanying declaration of Dr. Batt, claims 1-9 and 20 are unpatentably obvious in view of Saxonov, alone or in combination with Larson, and claims 10-19 in combination with further references. All claims should be canceled.

II. TECHNOLOGY BACKGROUND

A. Multiplex PCR Amplification

To the extent the Board is not familiar, Petitioner's expert, Dr. Batt, provides an overview of the chemical structure of nucleic acids, such as DNA. EX1002 ¶¶ 30-35. Many applications of biotechnology rely on base-pairing of complementary nucleic acid sequences, and the related ability of single-strands to serve as templates for synthesis of complementary strands. *Id.* ¶¶ 35-45. One such application is the

polymerase chain reaction ("PCR"), wherein DNA fragments/sequences are amplified in repeated cycles. *Id.* ¶¶ 36-39.

PCR generally involves three steps. *Id.* ¶ 37. First, double-stranded DNA is denatured into single strands. *Id.* Next, primer pairs bind to specific complementary regions of the single strands. *Id.* Then, DNA polymerase extends each primer by adding nucleotides according to the base-pairing rules to form strands complementary to the single-stranded template. *Id.* The resulting double-stranded DNA serve as templates in subsequent PCR cycles. *Id.*

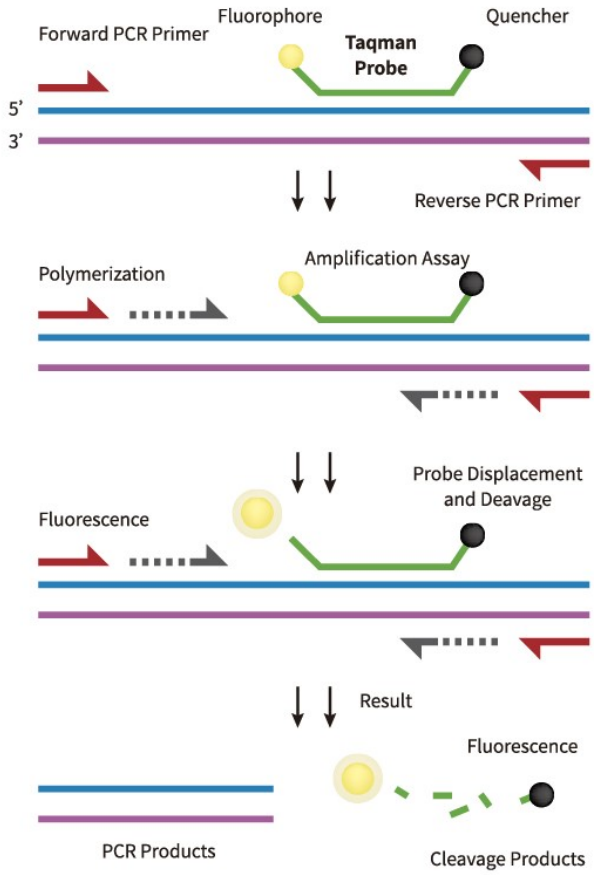
Multiplex PCR amplifies multiple polynucleotide sequences using multiple primer pairs for multiple target sequences in a single reaction volume concurrently. *Id.* ¶ 39. Multiplex PCR was well-known in the art and understood to be faster, less expensive, and more convenient than amplifying each polynucleotide sequence separately in individual PCR reactions. *Id.*

B. Fluorescence Signals and Detection of Polynucleotide Analytes

Base-pairing of complementary sequences was also used in methods to generate color signals to detect polynucleotides. EX1002 ¶ 40. Methods include hybridizing labeled oligonucleotides to specific polynucleotide sequence(s) before measuring the label's signal. *Id.* ¶¶ 40-42.

One well-known technique uses labeled oligonucleotides modified after hybridization to generate a detectable color signal, such as by cleavage of the

oligonucleotide. *Id.* ¶¶ 41-42. An example is the TaqMan assay, which uses oligonucleotide probes that bind to a target sequence and that have a fluorophore and a quencher at opposite ends. During PCR, the exonuclease activity of the polymerase enzyme separates the fluorophore and quencher of bound probes by cleaving the probe:



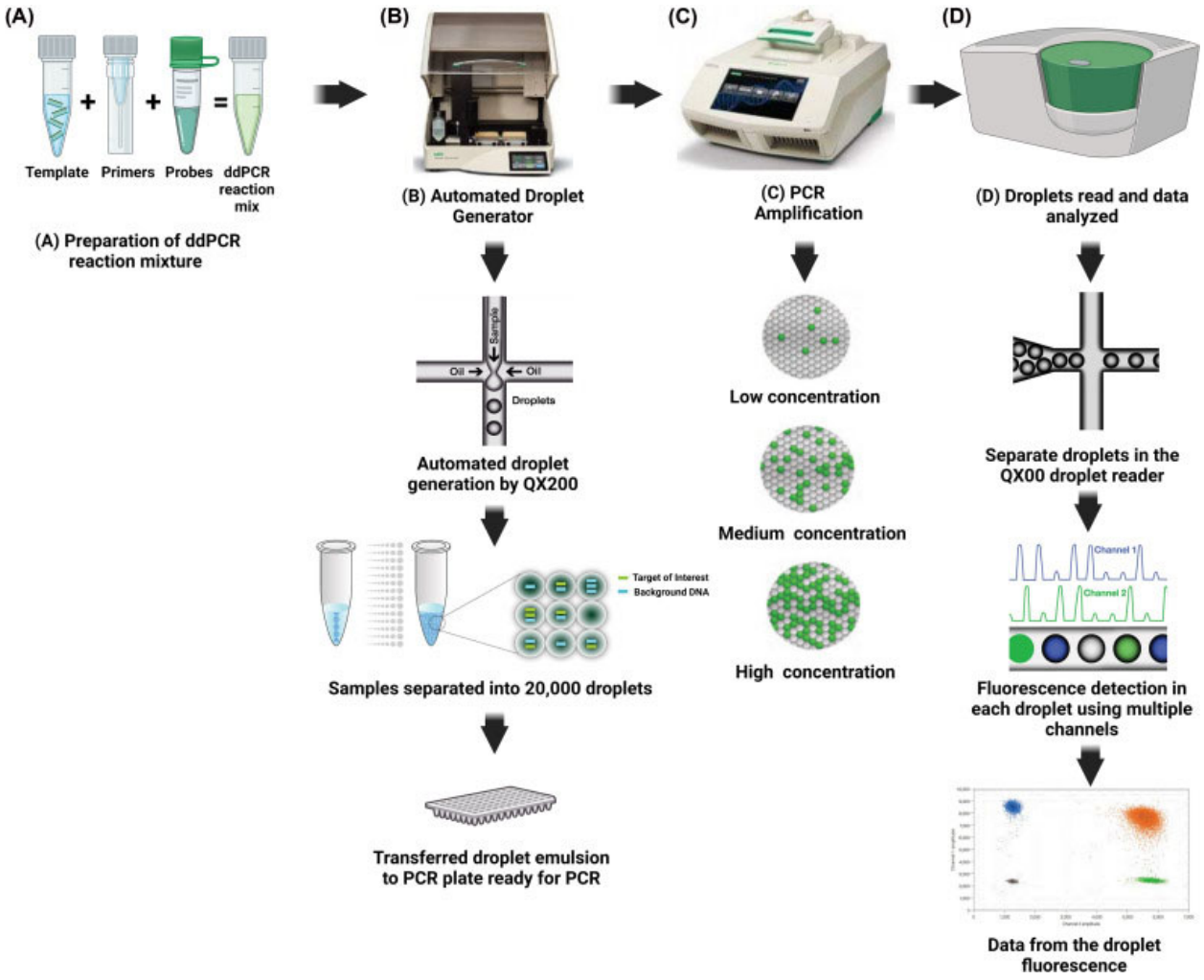
EX1013 at 6; EX1014 Fig. 1; EX1002 ¶¶ 41-42.

C. Quantitative and Digital PCR

Certain PCR techniques can be used to determine the amount (or number) of target sequences within a sample. These techniques include quantitative PCR

("qPCR") and digital PCR ("dPCR"). EX1002 ¶¶ 43-47. One form of qPCR uses a TaqMan probe that hybridizes to the target sequence and generates a signal when degraded by a polymerase. The signal generated is proportionate to the amount of the target polynucleotide in a sample, allowing quantification of analytes. *Id.* ¶ 46.

In dPCR, the PCR solution including sample is partitioned into small droplets, where separate PCR reactions occur. *Id.* ¶ 47. The same TaqMan probes, as described for qPCR, can be used. *Id.* ¶¶ 42-47. Reactions can be multiplexed. *Id.* ¶ 39. The degree of dilution is optimized so only a fraction of droplets include any one particular target, so that where there is a signal, there is typically only a single copy of the target. EX1002 ¶ 47. Based on this, and on molecules following the Poisson distribution (a random distribution based on probability), the amount of any target in the original sample can be determined by quantifying the fraction of the droplets generating a corresponding signal. *Id.* An image showing the workflow for performing dPCR using Petitioner's droplet-based products is shown below:



EX1038 at 12; EX1002 ¶ 47.

III. OVERVIEW OF THE '170 PATENT

The '170 patent issued on September 8, 2020, claiming the benefit of a February 3, 2012, provisional application. EX1001, codes (45), (63), 1:6-12. For purposes of only this proceeding, it is assumed herein that the '170 patent is entitled to a February 3, 2012, priority date.

A. Specification

The '170 patent purports to describe multiplex detection of polynucleotide analytes using fewer different sequence-specific labeled probes than analytes. EX1001 at 8:29-9:15. A coding scheme employing signals generated from labeled probes is used to map different combinations of signals to different combinations of analytes present in a sample. *Id.*

The '170 patent discloses coding schemes employing signals of differing intensities of the same colors to distinguish polynucleotides. *See, e.g.*, *id.* at 22:1-22. An example of such a coding scheme is reproduced below:

TABLE 8

Example of encoding method using one color and one intensity per analyte, but different intensities among analytes.

Tier	Analyte	B	G	Y	R
1	A	1	0	0	0
	B	2	0	0	0
	C	4	0	0	0
	D	8	0	0	0
2	E	0	1	0	0
	F	0	2	0	0
	G	0	4	0	0
	H	0	8	0	0
3	I	0	0	1	0
	J	0	0	2	0
	K	0	0	4	0
	L	0	0	8	0
4	M	0	0	0	1
	N	0	0	0	2
	O	0	0	0	4
	P	0	0	0	8
		15	15	15	15

Id. at 22:1-22 (Table 8). In the table, analytes A, B, C, and D all yield only a blue signal; different targets can nonetheless be distinguished because each target has a different signal intensity. Specifically, analytes A, B, C, and D have an intensity of 1, 2, 4, and 8, respectively. The same approach is used to code targets E-H, I-L, and M-P, using the colors green, yellow, and red, respectively.

This coding scheme is purportedly advantageous because the one-color signals of lesser intensity do not sum up to a greater intensity specific for another analyte. *Id.* at 22:32-37. For instance, the sum of the signals for targets A and B is 3, which is less than the signal for target C, which is 4. Accordingly, the cumulative signals are ***non-degenerate*** and purportedly allow unambiguous determination of the polynucleotide analytes without needing to eliminate various labeled probes (or sets of probes). *Id.* at 23:1-19; EX1002 ¶¶ 50-59.

In addition to the use of intensity to distinguish targets, the ’170 patent also contemplates the prior art approach of using more than one color per analyte. This is disclosed in, for example, Table 3. There, a blue “control” label is included in the probe for each of seven different polynucleotide targets (A through G). The probes for these targets also include an additional label or combination of labels:

TABLE 3

Encoding of eight analytes (including control) with four colors and up to four colors per analyte.

	Blue	Green	Yellow	Red
Ctrl. (p)	1	0	0	0
A	1	0	0	1
B	1	0	1	0
C	1	1	0	0
D	1	0	1	1
E	1	1	0	1
F	1	1	1	0
G	1	1	1	1

EX1001 at 13:44-58. The blue "control" signal provides a measure of the total number of analytes present in a given sample and allows one to distinguish certain combinations of analytes that might yield the same combination of green, yellow, and red signals. *Id.* at 13:44-14:19. For instance, the signals from a sample with analyte F (blue, green and yellow) and a sample with analytes B (blue and yellow) and C (blue and green) can be distinguished by the doubled intensity of blue in the latter sample compared to the former. EX1002 ¶¶ 55, 60-65.

In this approach, however, certain combinations of analytes unavoidably provide the same cumulative signals. *Id.* ¶ 64. For example, a sample with analytes B and G and another with D and F would yield the same signals—3 blue, 1 green, 2 yellow, and 1 red. EX1001 Table 4. To address this potential degeneracy, where the signals do not unambiguously identify the analytes, the '170 patent suggests nothing more than ignoring one or more analytes, removing them from the coding scheme to reduce or eliminate this degeneracy. *Id.* at 14:16-19, Table 4; EX1002 ¶¶ 64-65; *see also* EX1002 ¶ 66.

B. Challenged Claims

All claims of the ’170 patent are challenged. A full listing of claims is included as Appendix A.

IV. LEVEL OF ORDINARY SKILL IN THE ART OF THE ’170 PATENT

A person having ordinary skill in the art (“POSA”) relevant to the ’170 patent as of February 3, 2012, would have had a Ph.D. in molecular biology, genetics, biochemistry, or a related discipline, with at least a year of experience in quantitative and/or digital PCR and fluorescence-based analyte detection. EX1002 ¶ 73. Alternatively, a POSA would have been someone with greater relevant experience sufficient to compensate for having less relevant formal education. *Id.*

A POSA would have understood the following technologies and techniques:

- Multiplex PCR and its application in detecting and measuring polynucleotide analytes.
- The design and use of fluorescent-labeled oligonucleotides, including use of quenchers, and use in conjunction with multiplex PCR.
- The quantitative detection and measurement of polynucleotide analytes using fluorescent-labeled oligonucleotides in multiplex applications.
- Techniques for labeling probes and detecting multiple targets using fewer differently colored fluorophores than polynucleotide targets.

- Quantitative PCR (qPCR) and digital PCR (dPCR) and their application in detecting and measuring polynucleotide analytes, including in multiplex applications.

Id. ¶ 74.

V. THE CITED PRIOR ART

A. Saxonov

1. Saxonov is § 102(e) Prior Art

Saxonov et al., US 2013/0040841 A1, entitled "Digital Assays With Multiplexed Detection of Two or More Targets in the Same Optical Channel," is the publication of patent application No. 13/548,062, dated February 14, 2013. EX1004, codes (10), (21), (43), (54). The '062 application was filed July 12, 2012, and claims the benefit of provisional application Nos. 61/507,082 and 61/510,013 ("the '013 provisional"), filed July 12, 2011, and July 20, 2011, respectively. *Id.*, codes (22), (60).

Saxonov is § 102(e) prior art as of at least the filing of the '013 provisional, July 20, 2011, because the '013 provisional supports Saxonov's method of performing a digital assay recited in its claim 1. *See* MPEP § 2136; *Dynamic Drinkware, LLC. v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1382 (Fed. Cir. 2015); *In re Giacomini*, 612 F.3d 1380, 1383 (Fed. Cir. 2010).

Applicant identified Saxonov in an IDS during examination of the application that issued as the '170 patent, as well as for the related patents—U.S. Patent Nos. 10,068,051 and 11,827,921. EX1002 ¶ 75; EX1005 at 1; EX1015 at 2; EX1016 at 11. Applicant did not contest the prior art status in any of these proceedings.

The '013 provisional discloses an assay for detecting multiple target polynucleotides in single samples using digital PCR. EX1007, Title; EX1002 ¶¶ 75-77. Samples having multiple targets are contacted with fluorophore-labeled probes that report the presence of targets by generating signals during PCR. EX1007 at 6:21-23, 7:9-10. Saxonov states that signals for particular analytes may be based on the signal's color, intensity, or both. EX1007 at 9:5-10 ("aspects of light, such as the intensity...may include data collected in one or more different channels").

Like the '170 patent, the '013 provisional discloses using probes labeled with the same color at different intensities to distinguish among different polynucleotide analytes. EX1007 at 5:19-6:3, 13:9-19:23 (Examples 2-3), Fig. 4 (depicting different intensity signals 108, 110, and 112). Measuring the color signal(s) intensity generated from the labeled probes identifies the particular polynucleotides present, distinguishing different polynucleotides (or combinations of polynucleotides) based on signal intensity. *Id.* at 5:19-6:3, 13:9-19:23 (Examples 2-3), Figs. 4-5. The signal intensities of probes for different polynucleotides are selected so that all combinations of positive results for targets provide populations or clusters of signals

can be distinguished from one another, as described for one, two, and three target systems. *Id.* at 5:19-6:3, 10:8-11:3.

The ’013 provisional also discloses using multiple colors to identify the same polynucleotide in stating that the different color signals collected can be from reporters for the same target. *Id.* at 9:4-15. Each and every limitation of claim 1 of Saxonov is disclosed by the ’013 provisional:

Saxonov	’013 Provisional Disclosure
1. A method of performing a digital assay, comprising:	“The present disclosure provides a system, including methods…for performing a digital assay with multiplexed detection of two or more distinct targets in the same channel.” EX1007 at 3:6-8; *see also id.* at 3:10-14, 4:17-20, Figs. 1-2.
amplifying two or more targets in droplets containing a reporter for each target;	“The sample may be separated into partitions” (*id.* at 7:11); “the partitions may be droplets” (*id.* at 7:17); “reactions may be performed in the partitions” (*id.* at 8:11); “the reaction may be an amplification reaction” (*id.* at 8:19); “[s]ignals may be created for each of the partitions…from reporters for two or more distinct targets” (*id.* at 9:4-8); *id.* at 7:3-5.
detecting a signal from the droplets representing combined emission of light from the reporters for the targets, wherein each reporter provides a portion of the signal having an intensity that varies according to	“[s]ignals may be created for each of the partitions” (*id.* at 9:4); “signals may represent aspects of light, such as the intensity” (*id.* at 9:5-6); “the signal may be a composite signal that represents two, three, four, or more reactions and thus two, three, four, or more targets”

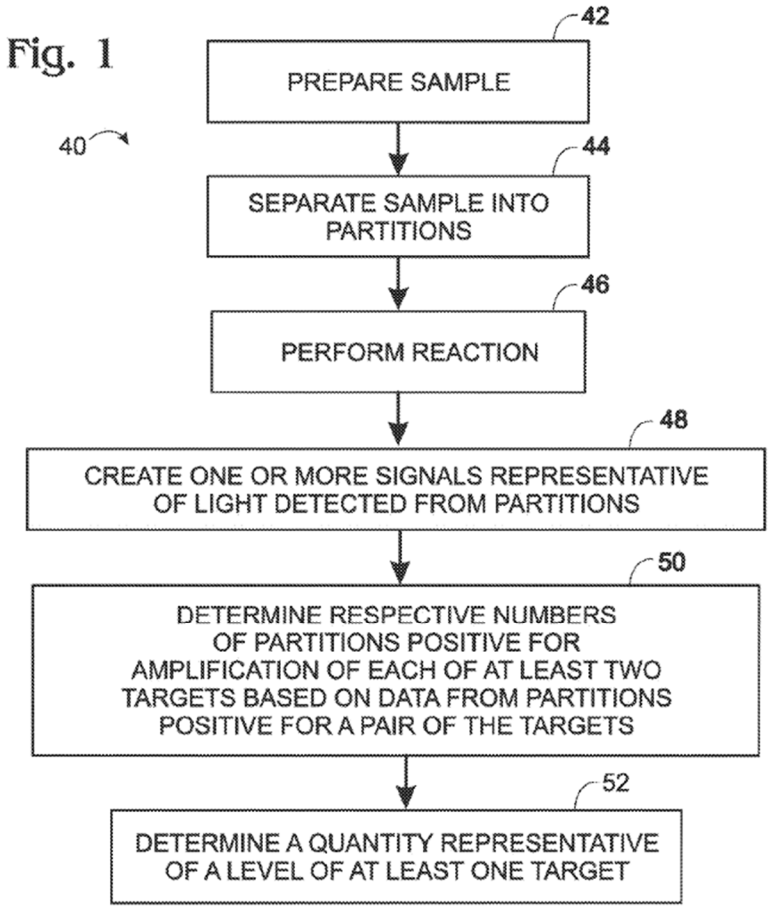
Saxonov	'013 Provisional Disclosure
whether or not the corresponding target is present in a droplet, and wherein a plurality of the droplets contain more than one target and have a distinguishable intensity of the signal relative to droplets containing only one target;	(*id.* at 9:14-15); "[t]he signal may be analyzed to determine whether neither Target, Target 1 alone, Target 2 alone, or both Targets 1 and 2 are present in each droplet" (*id.* at 15:17-19); "assignment of a droplet to a particular outcome (i.e., to one of T1-/T2-, T1+/T2-, T1-/T2+, and T1+/T2+) may be performed using any suitable algorithm" (*id.* at 16:26-27); *see also id.* at 12:17-20:22 (Examples 1-4), 5:19-6:3, 16:21-23.
determining for each target a number of droplets that are positive for only one of the targets;	"signal is created from light detected over time in a single channel from a fluid stream containing the droplets and flowing through an examination region of the channel. The signal may be analyzed to determine whether neither Target, Target 1 alone, Target 2 alone, or both Targets 1 and 2 are present in each droplet" (*id.* at 15:15-19); "assignment of a droplet to a particular outcome (i.e., to one of T1-/T2-, T1+/T2-, T1-/T2+, and T1+/T2+) may be performed using any suitable algorithm" (*id.* at 16:26-27); "statistical methods such as expectation maximization algorithms may be used to estimate the number of droplets or peaks associated with each outcome" (*id.* at 16:32-17:2); "droplets that included the RPP30 gene but did not include the C61 gene" (*id.* at 18:16-17); "droplets that included the C61 gene but did not include the RPP30 gene" (*id.* at 18:11-12); *id.* at 17:4-19:23, 18:5-19:1.

Saxonov	'013 Provisional Disclosure
determining at least one number of droplets that are positive for more than one target; and	*See* preceding section; "droplets that are positive for RPP30 and C61 (i.e., droplets that included both genes" (*id.* at 18:19-20).
determining a quantity representative of a level of at least one target.	"Example 3. [titled 'Digital PCR Assay to Assess Copy Number of C61"]…describes a first exemplary digital PCR assay, in which multiplexing in a single channel is used to assess copy number of the C61 gene" (*id.* at 17:4-6); "There are 4033 droplets containing RPP30 (i.e., that are positive for RPP30, irrespective of whether they are positive or negative for C61)…There are 4022 droplets containing C61 (i.e., that are positive for C61, irrespective of whether they are positive or negative for RPP30)…Thus, because RPP30 is known to have two copies per genome, C61 must also have two copies (i.e., the copy number of C61 is two)." (*id.* at 19:1-9)

2. Saxonov Overview

Saxonov is directed to an assay using multiplexed detection of signals from labeled probes for two or more targets where the labels for different targets can share colors. EX1004 ¶¶ 19, 20, 37; EX1002 ¶¶ 78-79.

Saxonov depicts the steps of the method:



Id. Fig. 1.

Briefly, Saxonov teaches that a prepared sample may be partitioned into a series of droplets. *Id*. ¶ 28. Each droplet may contain small numbers of target polynucleotide(s). *Id.* Reactions such as PCR (including with use of fluorescent labeled probes) can be performed in the droplets. *Id*. ¶¶ 32-34, 28-29; EX1002 ¶¶ 78-82.

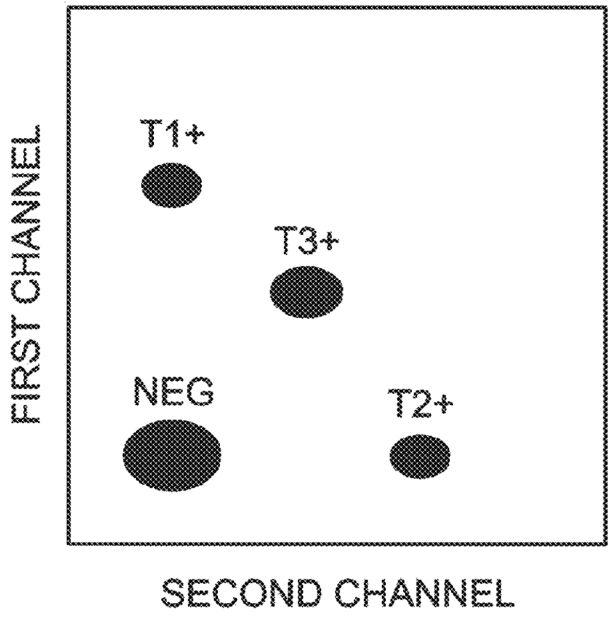
PCR can be used to generate a signal, for example, by using a fluorophore. EX1004 ¶ 36. The fluorophore can be used in conjunction with a quencher on the same probe that suppresses the fluorophore signal. *Id*. ¶ 52. When the probe with a fluorophore is bound to a target and cleaved during amplification, the fluorophore can be separated from the quencher allowing the fluorophore to generate a detectable signal. *See id*.; EX1002 ¶¶ 83-85.

Droplets with a generated signal are then marked as positive, meaning the target is present, while droplets without a signal are marked negative, meaning the target is absent. EX1004 ¶ 41. This data can be used to determine the amount of the target that is present in the original sample. *Id*. ¶ 43; EX1002 ¶¶ 86-87.

Saxonov describes an assay where signal intensity is used to distinguish among different polynucleotide analytes, and to detect the presence of multiple analytes in the droplet based on the cumulative signal intensity. EX1002 ¶¶ 88-89; EX1004 Fig. 5, ¶ 51 ("one probe may be labeled with a different number of fluorophores…creating a different level of fluorescence for each probe following reaction"); *id.* ¶ 20 (describing that "an assay for three targets may generate eight clusters or populations of data [in a single color], separated by intensity"); *id.* ¶¶ 63-67 (describing assay for two targets that may generate four clusters or populations of data in a single color separated by intensity).

Saxonov further teaches using multiple fluorophores and multiple intensities to identify greater numbers of analytes. *Id.* ¶¶ 20, 76-79; EX1002 ¶¶ 89-93. Signals from labels may be different colors or different intensities and may be from reporters, i.e., labeled probes, "for the same and/or different targets." EX1004 ¶ 36; EX1007 at 9:5-11; EX1002 ¶¶ 88-94. As to using different colors for the same target, Figure 10 depicts signals of different colors for the same target, as well as of different intensities than signals for that target than for other targets, in using label L1 in a first channel for target T1, label L2 in a second channel for target T2, and a label L3 in both the first and second channels at lesser intensity.

Fig. 10



EX1004 Fig. 10, ¶¶ 18, 78-79, Fig. 9 (depicting probes for T1, T2, and T3, wherein the T3 probe generates signals in two channels); EX1002 ¶¶ 91-93. Whether each target is identified by a single color signal, or by multiple colors, Saxonov further

teaches detecting light with the same sensor at the same time from different labeled probes and that the composite signal may represent "two, three, four, or more targets." EX1004 ¶ 36; EX1007 at 9:11-15; EX1002 ¶ 94.

B. Larson

1. Larson is § 102(a) Prior Art

Larson et al., US 2011/0250597 A1, entitled "Digital Analyte Analysis," is the publication of patent application No. 13/026,120, dated October 13, 2011. EX1017, codes (10), (21), (43), (54). Larson is § 102(a) prior art because it was published prior to the earliest effective filing date for the '170 patent, February 3, 2012.

2. Larson Overview

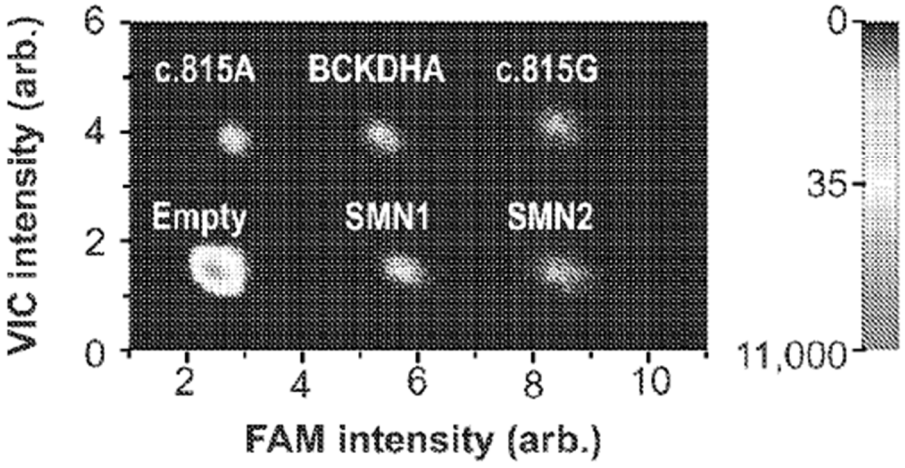
Larson, like Saxonov, is a reference based on the use of droplets that discloses multiplex detection of target polynucleotide analytes using fewer color labels than targets. EX1017 Abstract, ¶¶ 119-122, 138-140. In Larson, droplets are formed containing zero, one, or more targets, and merged with others containing reagents necessary for PCR. *Id.* ¶¶ 52, 68-69, 74. Larson teaches the use of fluorogenic hybridization probes, including a TaqMan assay. *Id.* ¶¶ 47, 97, 132-134. Fluorescence signals from the probes of each droplet can be readily detected. *Id.* ¶¶ 89, 97.

Larson describes a traditional dPCR method of "a single labeled probe specific for an individual target." *Id.* ¶¶ 119-120, Figs. 7A, 8A. Similar to the '051 patent, Larson teaches three methods to achieve higher-plex reactions. First, different intensities of the same color can be used to identify different targets. *Id.* ¶ 138. Second, in addition to multiple intensities of a single color, "multiple colors that are spectrally separable can be used simultaneously." *Id.* ¶ 139. Third, a "unique signature" of "both colors and intensities" are used to identify each target. *Id.* ¶ 140.

Larson teaches how to implement its multiplex assays, including how to tune the signal intensities corresponding to different target polynucleotide analytes, and to minimize difficulties that can arise when multiple targets are present in the same droplet. *Id.* ¶¶ 18, 20, 45, 68, 100, 134-137, 141.

Larson provides experimental data applying its methods in a 5-plex and 9-plex assay:

FIG. 14a



Id. Fig. 14a;

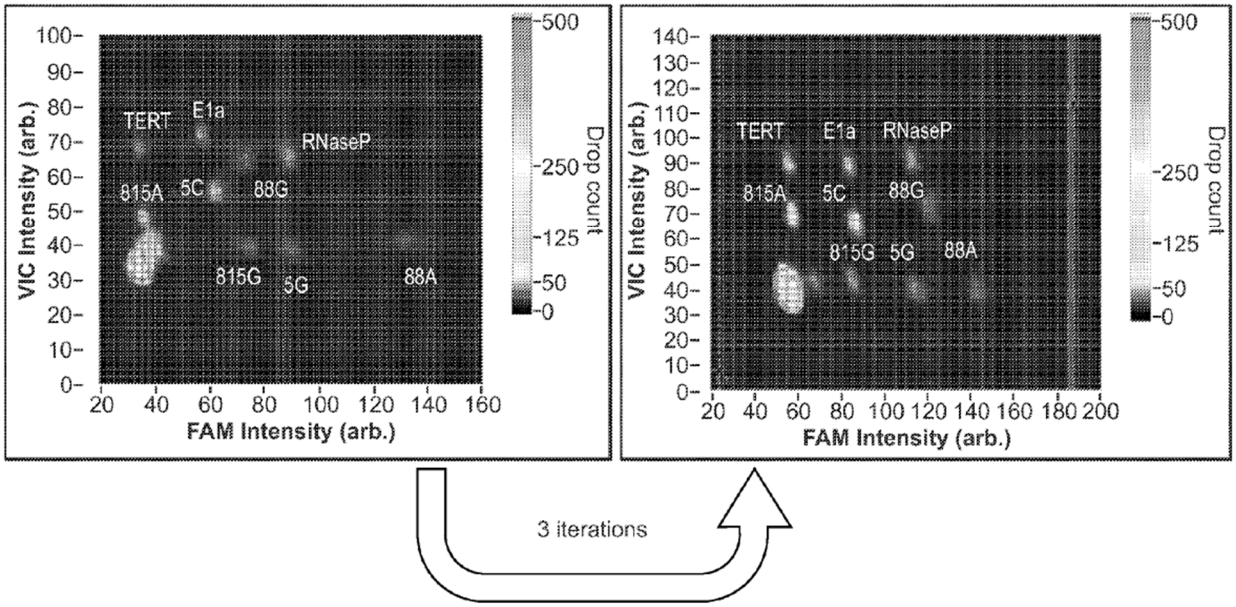


FIG. 15

Id. Fig. 15; *id.* ¶¶ 34, 145-153.

C. Secondary References Relied Upon Herein

The following references are analogous art to the '170 patent and to Saxonov and Larson, and are utilized herein in challenging remaining claims 10-19 not subject to Ground 1 and 6:

- **Nakamura**: published in 2011. EX1025; EX1002 ¶ 110. Nakamura is thus prior art to the '170 patent under at least § 102(b).
- **Silverbrook**: published in 2011. EX1009; EX1002 ¶ 114. Silverbrook is thus prior art to the '170 patent under at least § 102(a).
- **Maltezos**: published in 2008. EX1010; EX1002 ¶ 119. Maltezos is thus prior art to the '170 patent under § 102(b).
- **Oh**: published in 2010. EX1011; EX1002 ¶ 121. Oh is thus prior art to the '170 patent under § 102(b).

VI. MANDATORY NOTICES

A. Real Party-in-Interest

The real party-in-interest is Bio-Rad Laboratories, Inc.

B. Related Matters

The '170 patent is involved in district court litigation in *ChromaCode, Inc. et al. v. Bio-Rad Laboratories, Inc.*, 5:23-cv-06360 (N.D. Cal.) ("parallel

proceeding").[1] A related district court case involving two of Bio-Rad's patents is co-pending. *ChromaCode, Inc. v. Bio-Rad Laboratories, Inc.*, Case No. 23-cv-4823 (N.D. Cal. Filed September 20, 2023).

Also, a petition for *inter partes* review challenging U.S. Patent No. 10,068,051 is being filed concurrently with this petition.

C. Lead and Back-Up Counsel and Service Information

Petitioner provides the following designation of Lead and Back-Up Counsel.

[1] Originally filed as ChromaCode, Inc. v. Bio-Rad Laboratories, Inc., Case No. 23-cv-8417 (C.D. Cal. Filed October 5, 2023) before transfer to the Northern District of California. EX1024.

Lead Counsel	**Back-Up Counsel**
Derek C. Walter Registration No. 74,656 (derek.walter@weil.com) Weil, Gotshal & Manges LLP 201 Redwood Shores Parkway Redwood Shores, CA 94065 T: 650-802-3934 F: 650-802-3100	Adrian C. Percer Reg. No. 46,986 (adrian.percer@weil.com) Weil, Gotshal & Manges LLP 201 Redwood Shores Parkway Redwood Shores, CA 94065 T: 650-802-3124; F: 650-802-3100

VII. GROUNDS FOR STANDING

Petitioner certifies that the '170 patent is available for *inter partes* review and that Petitioner is not barred or estopped from requesting *inter partes* review challenging the patent claims on the grounds identified in this Petition.

VIII. STATUTORY GROUNDS FOR THE CHALLENGES

Ground	**35 U.S.C. Section (Pre-AIA)**	**Claims**	**References**
1	§ 103	1-9, 20	Saxonov
2	§ 103	10-12	Saxonov Nakamura
3	§ 103	13-16	Saxonov, Silverbrook
4	§ 103	17, 19	Saxonov, Maltezos
5	§ 103	18	Saxonov, Maltezos, Oh
6	§ 103	1-9, 20	Saxonov, Larson
7	§ 103	10-12	Saxonov, Larson, Nakamura
8	§ 103	13-16	Saxonov, Larson, Silverbrook
9	§ 103	17, 19	Saxonov, Larson, Maltezos
10	§ 103	18	Saxonov, Larson, Maltezos, Oh

IX. CLAIM CONSTRUCTION

Petitioner has identified terms and proposed constructions in the parallel proceedings, as follows:

- "each [of said at least 5] hybridization probe[s]" means "each collection of hybridization probes specific for a polynucleotide analyte." EX1003 at 11; *see e.g.*, '170 patent, claim 1.
- "cumulative intensity measurement" means "the signal or collection of signals from the probes that contact the present analytes." EX1003 at 16; *see e.g.*, '170 patent, claim 1.
- "exciting said at least one fluorophore to generate one or more signals if one or more of said at least five polynucleotide analytes is present in said plurality of droplets" means "exciting said at least one fluorophore to generate one or more signals if one or more of said at least five polynucleotide analytes contacts at least one probe in said plurality of droplets." EX1003 at 21; *see e.g.*, '170 patent, claim 1.

Other terms, as used herein, are consistent with Patent Owner's arguments and positions in the parallel proceeding.[2] EX1003. Specifically, for purposes of this

[2] In the parallel proceeding, Bio-Rad contends that the phrase "corresponds to the presence of a unique combination of presence or absence of said at least five

Petition, Petitioner requests that the Board understand the claims consistent with the apparent interpretations that Patent Owner is pursuing in parallel litigation, particularly in view of its contentions regarding how the '170 Patent is allegedly infringed by Petitioner. *See Hospira, Inc. v. Amgen Inc.*, IPR2021-00528, Paper 7 at 7 (PTAB Aug. 17, 2021) ("all that rule [42.104(b)(3)] requires is for the Petition to identify '[h]ow the challenged claim is to be construed").

Petitioner has applied its constructions above and Patent Owner's apparent interpretations throughout, reserving the right to respond to any proposed constructions raised by Patent Owner. *See also* EX1002 ¶¶ 125-128.

X. GROUND 1: OBVIOUSNESS OF CLAIMS 1-9, 20 IN VIEW OF SAXONOV

The '170 patent claims a method of detecting the presence of at least five polynucleotide analytes using at least five hybridization probes that are labeled with one to four different fluorophores. EX1001 at claim 1. At its core, the '170 patent

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polynucleotide analytes in said sample" is indefinite. EX1003 at 4; EX1001, claim 1. Because indefiniteness cannot be raised in an IPR proceeding, Petitioner addresses claim 1 based on Patent Owner's apparent interpretation in view of its infringement contentions, and without conceding that the term is not indefinite. EX1012 at 40-53.

relies on nothing more than the concept of detecting a number of targets that exceeds the number of available colors simply by mixing color signals and/or using different signal intensities to provide composite signals that unambiguously identify which analytes are present in a sample. As detailed below, however, this approach is rendered obvious by Saxonov, which includes numerous teachings of these concepts.

Saxonov is analogous art to the '170 patent because they are within the same field of endeavor: multiplex detection of polynucleotide analytes using color-labeled sequence-specific probes, including where there are fewer different colors than analytes. EX1001 at code (57), 12:28-14:3, 17:57-60, 21:39-23:30; EX1004 ¶¶ 19, 20, 37; EX1002 ¶¶ 131-133.

A. Claim 1

1. A method of unambiguously detecting any unique combination of presence or absence of at least five polynucleotide analytes in a plurality of droplets, the method comprising:

The preamble is not limiting. EX1002 ¶ 134. If deemed limiting, a POSA would have understood Saxonov to render obvious the recited method. *Id.* ¶¶ 135-139. The preamble is wholly redundant to the elements set forth in the claim body and is, accordingly, fully addressed below in setting forth the ground as to each limitation. *Id.* ¶¶ 140.

2. (a) providing a sample comprising, or potentially comprising, at least one of said at least five polynucleotide analytes;

Saxonov discloses analyzing a sample comprising, or potentially comprising, at least one of at least five polynucleotide analytes. EX1002 ¶¶ 141-156.

As an initial matter, a POSA would have understood that the use of five target polynucleotides as claimed in the '170 patent is not inventive. This is confirmed in the '170 patent itself, which never identifies five target polynucleotides as novel or non-obvious, but rather buries the possibility of five targets among a range of possible target numbers, including "at least 1.5, 1.6,…4, 5, 6, 7,…48, 49, or 50 analytes may be detected per fluorophore." EX1001 at 12:42-46, 37:44-48; EX1002 ¶¶ 142-143. Nonetheless, Saxonov teaches the analysis of samples with at least five polynucleotide targets. At a minimum, Saxonov renders obvious the analysis of samples with at least five targets.

First, a POSA would have understood that Saxonov teaches multiplexed detection of polynucleotides (*i.e.*, detection of multiple polynucleotides in the same experiment). *See* EX1002 ¶ 144; EX1004 ¶ 5 (describing digital PCR to detect "nucleic acid target[s]"); *id.* ¶ 6 ("A digital PCR assay can be multiplexed to permit detection of two or more different targets within each partition."); *id.* Fig. 10 (depicting signals for detection of three or more analytes); *id.* ¶ 77, Fig. 5; EX1007 at 13:9-13, 15:12-22, 3:6-8, 17:4-10, Fig. 5.

Second, a POSA would have understood that Saxonov contemplates not just multiplexed detection, but also multiplexed detection of five or more targets such that it teaches the analysis of samples with five or more targets. Specifically, Saxonov teaches detecting multiple targets using different intensities of the same color along with the use of multiple colors. EX1002 ¶¶ 145-148. Saxonov teaches "performing a digital assay with multiplexed detection of two or more distinct targets in the same optical channel," including "three or more distinct targets." EX1004 ¶¶ 8, 17. This "analysis of more than two targets in the same channel" is achieved by using different intensities of the same color. EX1004 ¶¶ 19-20, 36, 47-48, 77, 60-67; EX1007 at 5:19-6:3, 10:18-11:3. For example, for two targets, Saxonov teaches that two intensities of the same color results in four possible populations of intensities: droplets with no target, target 1 alone, target 2 alone, and both targets. EX1004 ¶¶ 41, 53-59, 63-68, Figs. 4-7. Similarly, for three targets, three different intensities of one color can be used to "generate eight clusters or populations of data, separated by intensity." *Id.* ¶ 20; *see also id.* ¶ 78 and Fig. 10 (describing the eight different droplet types that can be distinguished by intensity). In general, "all permutations of positives will generally fall into 2^N populations or clusters, where N is the number of targets," which is also the number of distinguishable intensities that must be detected. *Id.* ¶ 41.

Meanwhile, Saxonov also teaches the use of at least three colors, wherein multiple analytes are detected with different intensities of each color. Specifically, Saxonov teaches the use of "one channel" plus "one or more other channels," which is an express disclosure of at least three colors. EX1004 Fig. 5, ¶¶ 6, 8, 20 ("some targets may be analyzed in one channel (e.g., a FAM channel), and one or more other targets may be analyzed in one or more other channels (e.g., a VIC channel)."); EX1002 ¶¶ 149-150.

Thus, a POSA would have understood from Saxonov's disclosure of at least three colors ***and*** two or three analytes per color that it is contemplating the analysis of samples that include more than five targets. For example, three colors and three intensities per color would allow the non-degenerate identification of ***nine*** different analytes:

	Color 1	**Color 2**	**Color 3**
Intensity 1	Analyte 1	Analyte 4	Analyte 7
Intensity 2	Analyte 2	Analyte 5	Analyte 8
Intensity 3	Analyte 3	Analyte 6	Analyte 9

EX1002 ¶ 151.

Saxonov's disclosure of "one or more other channels" in addition to a first channel also encompasses using four colors, consistent with selecting fluorophores from Saxonov's listing of at least five fluorophores. *See* EX1004 ¶¶ 20, 51 ("Exemplary fluorophores that may be suitable include FAM, VIC, ROX, TAMRA, JOE, etc., among others."). A POSA would also have understood that using four colors is preferable, due to the pre-existing availability of four-color instrumentation, and the lessened requirements to distinguish two different intensities versus three or more. *See infra* Section X.A.5; EX1002 ¶¶ 152-153. Thus, using four colors, with two intensities per color, ***eight*** analytes can be unambiguously detected:

	Color 1	**Color 2**	**Color 3**	**Color 4**
Intensity 1	Analyte 1	Analyte 3	Analyte 5	Analyte 7
Intensity 2	Analyte 2	Analyte 4	Analyte 6	Analyte 8

EX1002 ¶ 153.

A POSA would have understood that resolving two intensities per color is preferable to resolving three intensities per color, since Saxonov teaches using an additional color rather than an additional intensity level so that the data is "more easily resolvable." EX1004 ¶ 20; EX1002 ¶ 154. Regardless, both schemes described—three colors at three intensities and four colors at two intensities—allow for the analysis of samples that have at least five analytes and a POSA would have

had a reasonable expectation of success in using either scheme that is contemplated in Saxonov. EX1002 ¶¶ 154-156.

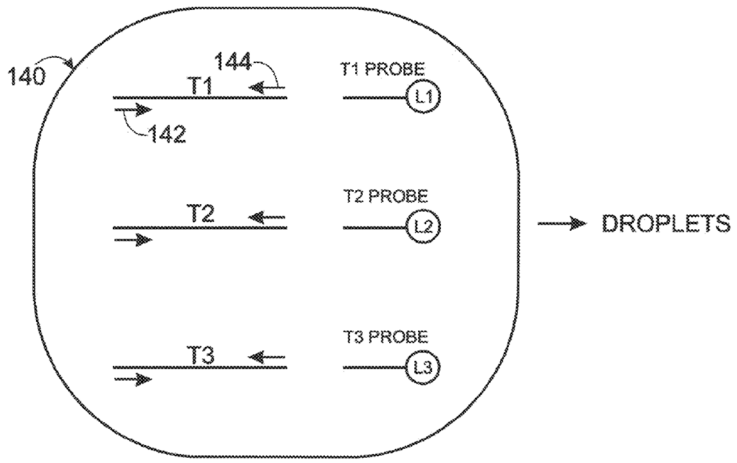
3. (b) forming a mixture of said sample and at least five hybridization probes,

Saxonov discloses forming a mixture of the sample with at least five hybridization probes. EX1004 ¶¶ 49-50; EX1002 ¶¶ 157-162.

Saxonov teaches "preparation of the sample may include combining the sample with reagents for amplification and for reporting whether or not amplification occurred." EX1004 ¶ 26. A POSA would have understood hybridization probes as a reagent for reporting whether amplification occurred. EX1002 ¶ 160.

In addition, a POSA would have known to use at least as many hybridization probes as different polynucleotide analytes, because at least one probe is needed for each analyte, as taught by Saxonov and as commonsense dictates. *Id.* ¶¶ 161-162; EX1004 ¶¶ 50, 63-67, Fig. 5. For example, Figure 9 depicts a hybridization probe for each target:

Fig. 9



EX1004 Fig. 9; *id.* ¶ 77 (describing "an exemplary bulk phase mixture 140" that "may include a reporter for amplification of each target (such as a T1 probe, a T2 probe, and a T3 probe)"); *id.* ¶ 49 (disclosing "corresponding probes" specific for each target).

As a POSA would have understood that Saxonov discloses detection of at least five polynucleotides, or at a minimum renders such obvious, a POSA would likewise have understood that Saxonov teaches using at least five corresponding hybridization probes. EX1002 ¶ 162.

4. wherein each of said at least five hybridization probes further comprises at least one fluorophore and at most four fluorophores;

Saxonov discloses using at least five hybridization probes, each comprising at least one and at most four fluorophores. EX1002 ¶ 163. As discussed, at least five hybridization probes labeled with at least one fluorophore is sufficient to detect five

targets. *See supra* Sections X.A.2-X.A.3. Further, it would have been obvious to use "at most" four fluorophores

Saxonov discloses multiple fluorophores suitable for labeling hybridization probes, including FAM, VIC, ROX, TAMRA, and JOE. EX1004 ¶¶ 49, 51, Fig. 3; EX1007 at 14:20-21, 4:20-23. Saxonov also teaches labeling each probe with one or more of these fluorophores. EX1002 ¶ 164; EX1004 ¶ 26 ("The reporters each may be a labeled probe that includes a nucleic acid (e.g., an oligonucleotide) labeled with a luminophore, such as a fluorophore."); *id.* ¶ 20 (describing targets analyzed in one color and additional targets in "one or more other [colors]"); *id.* ¶ 79 (target "detectable in two or more [colors]"); *see also id.* ¶¶ 13, 36, 63-67, 76-78, Figs. 5, 9-10. A POSA would have understood Saxonov's teaching of using "two or more" colors to be a broad disclosure that one can use any one of a range of a different number of fluorophores, including up to four. EX1002 ¶ 165. Indeed, Saxonov would have just stated "up to three," or something similar, if it intended to use no more than three fluorophores. *Id.* ¶¶ 165-166.

Labeling of probes with one to four fluorophores would have been an obvious design choice for a POSA in light of the instruments available at the time. *Id.* ¶ 167. Indeed, the '170 patent acknowledges that four is the natural number of fluorophores to select from because this was the number of colors that was pre-packaged on "instruments widely used in the art:"

> Many real-time PCR and quantitative PCR instruments comprise an excitation light source and band pass filters that enable the detection of fluorescent signals in four colors (e.g., blue, green, yellow, and red). Therefore, the methods of the invention can be readily applied using instruments widely used in the art.

EX1001 at 35:19-24. This limitation of instruments that can only detect four colors alone would have motivated a POSA to label probes with no more than four fluorophores—one for each color. EX1002 ¶¶ 168-169. Notably, nowhere does the specification suggest that it would be novel or inventive to use the four colors that were available on "widely used" instruments or that four is a novel or inventive number of fluorophores. *Id.* ¶ 168.

Further, as Dr. Batt explains, given that "widely used" instruments already employed four colors to detect targets, a POSA would have had a reasonable expectation of being able to successfully use four fluorophores (one associated with each color) for multiplex detection of biological targets. *Id.* ¶ 169. Moreover, as explained above, when using four colors with each at two intensities, there are only four resulting clusters or populations of signal data for the possible combinations for each of the colors used that must be distinguished, rather than eight when using three intensities. *Id.*; *see supra* Section X.A.2; EX1004 ¶¶ 20, 41 (explaining that data with all permutations of positives for each color fall into 2^N populations where N is the number of targets); *id.* ¶ 60-67. A POSA would have, accordingly, been

motivated to use four colors rather than three for the benefit of more straightforward distinction among the clusters or populations of data for each color used. EX1002 ¶ 169.

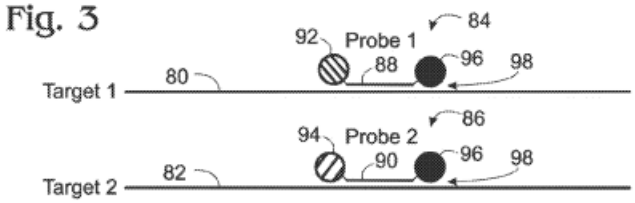
5. (c) partitioning said mixture into said plurality of droplets;

Saxonov discloses partitioning the mixture into a plurality of droplets. EX1002 ¶¶ 170-171. As depicted in Figure 1, Saxonov teaches an exemplary method in which a sample is separated into partitions. *See* EX1004 Fig. 1, ¶ 28 ("In some embodiments, the partitions may be droplets disposed in a continuous phase, such that the droplets and the continuous phase collectively form an emulsion."). Saxonov also teaches a plurality of methods for forming droplets, including "with a fluid dispenser, such as a pipette, with a droplet generator, by agitation of the sample (e.g., shaking, stirring, sonication, etc.), and/or the like." *Id.* ¶ 29; *see also id.* ¶¶ 25-30, 78. Such droplets correspond precisely to what Patent Owner contends in parallel litigation. *See* EX1012 at 34, 116-117.

6. (d) exciting said at least one fluorophore to generate one or more signals if one or more of said at least five polynucleotide analytes is present in said plurality of droplets, wherein said one or more signals comprise at least one signal generated by excitement of said at least one fluorophore;

Saxonov discloses that each hybridization probe, when excited and when contacted with its corresponding polynucleotide analyte, generates a signal when the fluorophore on the probe is excited. EX1002 ¶¶ 172-175; EX1004 ¶¶ 49-52. For

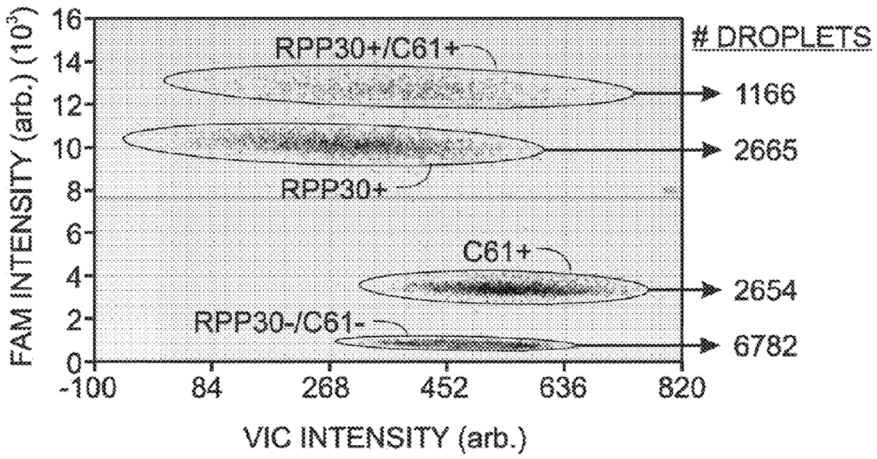
instance, Saxonov discloses in Figure 3 probes that hybridize to their targets and that include fluorescent labels detectable upon excitation:



EX1004 Fig. 3; EX1002 ¶ 174. Specifically, Saxonov teaches that "light detected from the fluorophore may increase when the associated oligonucleotide 88 or 90 binds to the amplified target…or when the probe is cleaved and the fluorophore and quencher become uncoupled during target amplification, among others." EX1004 ¶ 52; *see also id.* ¶ 37. Moreover, the probes in Figure 3 of Saxonov wherein "the probe is cleaved" are the same types of probes that Patent Owner accuses of infringing in parallel litigation. EX1002 ¶ 174.

Saxonov discloses numerous examples of signals generated from excitation of fluorophores present in a plurality of droplets. For example, Figure 5 depicts the FAM signal from droplets with C61+, RPP30+, or both:

Fig. 5



EX1004 Fig. 5; *id.* ¶¶ 63-67; EX1007 at 17:4-19:9, 18:5-21; 5:19-6:3. A POSA would have understood that a signal generated using a probe comprising fluorophores would include at least one color signal generated by exciting at least one fluorophore. EX1002 ¶ 175.

7. (e) measuring said one or more signals to generate a cumulative intensity measurement,

Saxonov teaches measuring one or more signals to generate a cumulative intensity measurement. EX1002 ¶¶ 176-181; *see supra* Section X.A.2 (describing how Saxonov teaches using multiple colors and multiple intensities per color to generate distinguishable signals specific for different analytes). For example, Saxonov Figure 4 depicts measuring signals in its graphical trace of light signal(s) from probes in droplets and Figure 5 graphs measured intensities of different signals in droplets, including the intensities for C61+, RPP30+, and RPP30+/C61+, which constitutes cumulative intensity measurement. EX1002 ¶¶ 177-180; EX1004 ¶¶ 12-

13, 20, 41, 53, 63-67, Figs. 4-5; *see also* EX1007 at 13:10-13, 17:4-19:23 (Example 3), 4:17-20, 5:19-6:5, 9:4-21, 10:8-11:3, 2:15-3:3, 12:21-13:8, Fig. 5. Saxonov further discloses measuring cumulative intensities for signals from three probes of different intensity in the same color, and for two probes in the same color and one in a second color. EX1004 ¶¶ 20, 41; *see also* EX1007 at 5:19-6:5, 10:8-11:3. A POSA would have understood that the measured signals include both different colors and intensities, as also taught by Saxonov. EX1002 ¶ 181; EX1004 ¶¶ 12, 20, 53, 76-78, Figs. 4-5, 10; EX1007 at 9:4-15.

As this claim step relates to the sample (*see infra* § X.A.8), the collection of signals collected, such as that plotted in Figure 5, constitutes "cumulative intensity measurement." A POSA would have understood Saxonov to teach obtaining a cumulative intensity measurement including each of the potential signals from the included probes over a plurality of droplets to identify and quantify the polynucleotide analyte(s) present. EX1002 ¶ 181.

8. wherein said cumulative intensity measurement corresponds to the presence of a unique combination of presence or absence of said at least five polynucleotide analytes in said sample; and

Saxonov teaches the cumulative intensity measurement corresponding to the unique combination of presence or absence of at least five polynucleotide analytes in a sample. EX1002 ¶¶ 182-188.

Saxonov teaches that probes for multiple analytes generate clusters or populations of data that are "separated by intensity." EX1004 ¶ 20. A POSA would have understood that the overall pattern of colors and intensities can be used to determine the analytes present in the sample. EX1002 ¶¶ 182-184. For example, a POSA would have understood from the presence of signals at ~13,000 arbitrary units in Figure 5 that both RPP30 and C61 were present in the sample. Notably, data of the types set forth in Figure 5 is precisely the type of data that Patent Owner contends corresponds to the "cumulative intensity signal" in Petitioner's products. *See id.* ¶¶ 142, 185-188.

While Figure 5 only involves two analytes, Saxonov nonetheless expressly contemplates using the exact same type of data (*i.e.*, different patterns of colors and intensity) to analyze five or more targets in the sample. The manner in which Saxonov teaches precisely this is set forth above in detail in § X.A.2. Briefly, as documented above, Saxonov teaches the use of multiple intensities at each of multiple colors to allow for the detection of distinct droplet types that contain unique combinations of targets. *See id.*

While the foregoing establishes that Saxonov discloses this claim element, Saxonov further teaches using Poisson statistics with the total number of droplets that are positive and negative for each analyte to determine the concentration of each individual analyte in the sample. EX1004 ¶ 19 ("Concentrations for each target may

be estimated based on the number of droplets positive for each target and the total number of droplets, for example, using Poisson statistics."). Of course, the act of determining the precise concentration of each analyte in a sample falls within the scope of determining the unique combination of presence or absence of each analyte in a sample. EX1002 ¶¶ 47, 188. Indeed, this involves not just determining which targets are present, but determining how much of each target is present. *Id.* ¶¶ 176-181.

To the extent Patent Owner argues that this claim step requires determining the presence or absence of analytes on a per-droplet basis, that is also met by Saxonov. As discussed above, Saxonov discloses the unambiguous detection of multiple analytes using multiple different colors and signal intensities to distinguish the polynucleotides present in a droplet. *Id.* ¶¶ 142-156; *see supra* Section X.A.2; EX1004 ¶¶ 13, 17-18, 20, 63-67, 76-79, Figs. 5, 9-10; EX1007 at 2:15-3:3; 3:15-4:20, 5:19-6:5, 9:4-10:3, 12:21-19:29, Fig. 5. Saxonov, for instance, teaches using target-specific probes that are each of a single color and that emit one of two or three different intensities to distinguish the presence or absence of any combination of nine targets. EX1002 ¶¶ 145-151; EX1004 ¶ 13, 20, 60-67, Fig. 5; EX1007 at 5:19-6:3; *supra* Section X.A.2. A POSA would have understood Saxonov to teach and/or render obvious selecting color labels from four different colors. EX1002 ¶¶ 152-155, 164-169. Saxonov likewise teaching to use two or three different intensities

per color likewise provides more than seven distinct labels, respectively. *Id.* ¶ 141-156, 163-169; *supra* Sections X.A.2, X.A.4. Further, Saxonov teaches selecting intensity values for labels such that the combined intensity for each color for any combination of targets is "separated by intensity" so that it can be uniquely mapped to the combination of targets. *See supra* Sections X.A.2, X.A.4; EX1004 ¶ 20 (describing that "an assay for three targets may generate eight clusters…separated by intensity"); EX1002 ¶ 141-156, 163-169, 182-186. Saxonov thus teaches assays that are non-degenerate by design in the same manner, and for the same reasons, as the analogous assays using single color labels of varying intensity disclosed in the '051 patent. *Id.* ¶¶ 186-187; EX1001 at 23:1-2, 21:49-52, 22:1-21 (Table 8).

A POSA informed by Saxonov would have been motivated to use single color probes of different intensities that can be distinguished from one another, selecting from four colors and two or three intensities, because the resulting assay would allow non-degenerate determination of useful numbers of polynucleotide analytes. *See supra* Sec. X.A.2; EX1002 ¶ 188. A POSA would have had a reasonable expectation of success because using multiple single color probes of varying intensities was well-known. *Id.*

9. (f) determining whether each of said [at] least five polynucleotide analytes is present, in any unique

combination of presence or absence, based on said cumulative intensity measurement,

This claim limitation corresponds to nothing more than reading the cumulative intensity signal corresponding to the different combinations of analytes. This claim limitation is disclosed in Saxonov for the reasons stated in the immediately preceding section. *See supra* Section X.A.8; EX1002 ¶¶ 189-192. Briefly, as discussed, Saxonov teaches distinguishable populations or clusters that can be used to determine the presence or absence of analytes in a sample and Poisson statistics to determine the concentration of analytes in the sample. *See supra* Section X.A.8.

To the extent Patent Owner argues that the cumulative intensity measurement must be used to determine the presence of analytes in each droplet, Saxonov likewise meets this. EX1002 ¶¶ 191-192. Saxonov discloses techniques wherein one can non-degenerately detect the presence of, for instance, eight different targets in a droplet by associating the targets with different intensity/color combinations. *See supra* Sections X.A.2, X.A.7-X.A.8. As Dr. Batt explains, the assays in Saxonov using droplets are the exact same types of assays detecting the presence of polynucleotide analytes in droplets that Patent Owner accuses of infringing in parallel litigation. EX1002 ¶ 192; *see also id.* ¶¶ 142, 172-175; *see supra* Section X.A.6.

10. wherein the method does not require any step of immobilization of said at least five polynucleotide analytes or mass spectrometry.

Saxonov teaches the detection of multiple polynucleotide analytes without immobilization of the polynucleotide analytes or mass spectrometry. EX1002 ¶¶ 193-195. As Dr. Batt explains, the polynucleotide analytes in Saxonov are not immobilized and there is no mass spectrometry. EX1002 ¶¶ 194-195.

B. Claim 2: The method of claim 1, wherein each of said at least five hybridization probes is complementary to one of said at least five polynucleotide analytes.

Saxonov discloses using hybridization probes that are specific and complementary for each polynucleotide analyte. EX1004 ¶ 50; EX1002 ¶¶ 196-199. For example, Saxonov discloses using "corresponding probes 84, 86 ('Probe 1' and 'Probe 2')" with "oligonucleotide 89, 90" that "provide target specificity by hybridization." EX1004 ¶¶ 49-50, Fig. 3; EX1007 at 13:14-17; *see also* EX1004 ¶¶ 63-67, Fig. 5[3]; EX1002 ¶¶ 197-198.

[3] Although there is a specific probe for each analyte, some of the probes may share a common fluorophore, such as disclosed by Saxonov wherein multiple analytes are encoded using a FAM fluorophore. *See, e.g.*, EX1004 ¶¶ 13, 14, 63-67, Fig. 5; EX1007 at 4:1-7, 17:20-19:9, Fig. 5.

As discussed, a POSA would have known to use at least as many hybridization probes as different polynucleotide analytes, because at least one probe is needed for each analyte, as taught by Saxonov and as commonsense dictates. *See supra* Section X.A.3; EX1002 ¶ 199.

C. Claim 3: The method of claim 1, wherein said at least five hybridization probes comprise one or more fluorophores selected from one, two, three, or four fluorophores.

Saxonov teaches the use of hybridization probes with one or more fluorophores selected from multiple fluorophores. EX1002 ¶ 201. As discussed, a POSA would have chosen probes with one or more fluorophores selected from at most four fluorophores because widely available instruments detected four colors and at least eight analytes can be detected. *See supra* Sections X.A.2, X.A.4; EX1002 ¶¶ 200-202.

As such, a POSA would have been motivated to use hybridization probes that include at least one fluorophore selected from up to four fluorophores because this provides a suitable number of different distinct probes, including at least five, and a POSA would have had a reasonable expectation of success based on the teachings. EX1002 ¶ 202.

D. Claim 4: The method of claim 1, wherein, in (b), a droplet of said plurality of droplets comprises said at least five hybridization probes.

Saxonov discloses droplets that contain the at least five hybridization probes. EX1002 ¶ 204; EX1004 ¶¶ 17-18, 77-78, Figs. 9, 10. As discussed, Saxonov discloses assays detecting at least five targets and, accordingly, assays with at least five corresponding hybridization probes. *See supra* Sections X.A.2-X.A.3. Saxonov also discloses a variety of ways to generate droplets. *See supra* Section X.A.5. From this disclosure, a POSA would have understood that droplets are generated such that reagents necessary to perform the reaction, including all of the hybridization probes, are contained within the droplet in accordance with methods known in the art. EX1002 ¶ 205; EX1004 ¶ 25 ("Preparation of the sample may include rendering the sample competent for subsequent performance of one or more reactions."); *id.* ¶ 26 ("In some embodiments, preparation of the sample may include combining the sample with reagents for amplification and for reporting whether or not amplification occurred."); *id.* ¶ 30 ("The partitions, when formed, may be competent for performance of one or more reactions in the partitions.").

Thus, a POSA would have understood from Saxonov that each droplet includes each of the hybridization probes corresponding to each of the polynucleotide analytes. EX1002 ¶ 206.

E. Claim 5: The method of claim 1, wherein, in (b), a droplet of said plurality of droplets comprises one or more of said at least five polynucleotide analytes.

Saxonov discloses droplets that comprise polynucleotide analytes. EX1002 ¶¶ 208-209; EX1004 ¶¶ 12-18, 41, 46, 53-59, 63-68, 72-75, 77-78, Figs. 4-10. For example, Saxonov discloses droplets containing three polynucleotide analytes in a single droplet. EX1004 ¶ 78. A POSA would have understood that if droplets are generated from a sample containing polynucleotide analytes, some of the droplets would contain at least one of the analytes. EX1002 ¶ 210.

F. Claim 6: The method of claim 1, wherein, in (b), a droplet of said plurality of droplets comprises at most one of said at least five polynucleotide analytes.

Saxonov discloses droplets that contain only a single polynucleotide. EX1002 ¶¶ 212-214; EX1004 ¶¶ 12-18, 41, 46, 53-59, 63-68, 72-75, 77-78, Figs. 4-10. Saxonov discloses that "[p]reparation of the sample may include any suitable manipulation of the sample, such as…dilution…" *Id.* ¶ 25. Further, "a sample is separated into a set of partitions, generally of equal volume, with each containing, on average, less than about one copy of the analyte." *Id.* ¶ 3. Thus, "some partitions should contain no copies" and "others only one copy." *Id.*; *id.* Fig. 5. As such, a POSA would have understood that a sample may be sufficiently diluted such that some droplets contains at most one polynucleotide analyte. EX1002 ¶ 214.

G. Claim 7: The method of claim 1, wherein said one or more signals is generated during a polymerase chain reaction.

Saxonov discloses generating one or more signals during a polymerase chain reaction. EX1002 ¶¶ 215-216; EX1004 ¶ 5; EX1007 at 2:7-9, Figs. 3-4. Saxonov teaches a TaqMan assay within droplets wherein probes emit signals during PCR. EX1004 ¶¶ 5, 52, 77-78, Figs. 3-4, 9; EX1007 at 2:7-9, 13:14-17, 14:22-15:4, Figs. 3-4. A POSA would have known that the TaqMan probe is cleaved during PCR, as disclosed by Saxonov. EX1002 ¶ 216; EX1004 ¶¶ 52-53, Figs. 3-4; *see supra* Section II.

H. Claim 8: The method of claim 1, wherein said at least five polynucleotide analytes are at least seven polynucleotide analytes.

Saxonov discloses the potential detection of at least eight or nine analytes. *See supra* Section X.A.2; EX1002 ¶¶ 217-218.

I. Claim 9: The method of claim 1, wherein said at least five hybridization probes are at least seven hybridization probes.

Just as Saxonov discloses the detection of at least eight or nine analytes, it also discloses at least seven hybridization probes. EX1002 ¶¶ 157-162, 219-220. For the same reasons discussed above, it would have been obvious to use at least seven hybridization to detect at least seven targets. *See supra* Section X.A.3.

J. Claim 20: The method of claim 1, wherein each of said at least five hybridization probes are provided at a given concentration such that said cumulative intensity measurement corresponds to said presence of said unique combination.

Saxonov discloses providing hybridization probes at a given concentration such that the cumulative intensity measurement corresponds to the presence of the combination of polynucleotide analytes. EX1002 ¶¶ 222-223.

Saxonov teaches that the probe concentration is a variable to adjust the signal. *See* EX1004 ¶ 51 ("[B]oth probes may be labeled with the same number of fluorophores (e.g., one fluorophore), but there may be more or less of one probe than the other in the sample, so that a greater or smaller signal is created when the reactions have occurred."). Moreover, as discussed, Saxonov teaches preparing the sample by combining it with reagents, including probes. *See supra* Section X.D; EX1004 ¶¶ 25-26, 30. Saxonov also discloses that the collected cumulative signal reveals which analytes are present. *See supra* Sections X.A.6-X.A.8; EX1004 ¶ 36 (The "signal may be a composite signal that represents two, three, four, or more reactions and thus two, three, four, or more targets of the reactions."). Accordingly, a POSA would have understood from Saxonov to adjust the concentrations of hybridization probes such that the cumulative intensity measurement corresponds to the presence of polynucleotide analytes. EX1002 ¶ 223.

XI. GROUND 2: OBVIOUSNESS OF CLAIMS 10-12 IN VIEW OF SAXONOV AND NAKAMURA

A. Claim 10: The method of claim 1, wherein said one or more of said at least five polynucleotide analytes comprise cell-free nucleic acid, tumor nucleic acid, fetal nucleic acid, viral nucleic acid, or any combination thereof.

Saxonov discloses assays that detect cell-free, tumor, and virus nucleic acids. EX1002 ¶ 225; EX1004 ¶ 1; EX1007 at 1:5-8. For example, Saxonov (and the '013 Provisional) incorporates Colston by reference, which discloses using sample droplets including nucleic acids that are cell-free, and from a tumor or virus. *See* EX1004 ¶ 2; EX1026 ¶¶ 13, 156-157, 1141, 1144.

Further, to the extent Patent Owner argues Saxonov does not disclose the limitations of this claim, a POSA would have found it obvious in view of Nakamura. EX1002 ¶¶ 226-227. Nakamura teaches performing PCR assays on a "tumor-specific" basis, i.e., on samples derived from a subject harboring tumors, including by using probes "labeled with a suitable label, such as dyes, fluorescent and isotopes." EX1025 ¶¶ 51-52, 57, 328, 523, 536-538, Figs. 1-2, 7.

A POSA would have been motivated to apply the teachings of Saxonov and Nakamura to the recited polynucleotide analytes and would have had a reasonable expectation of success because using assays with probes specific for different polynucleotide sequences was well known and it would have been desirable to detect

nucleic acids potentially associated with disease, such as cancer nucleic acids. EX1002 ¶¶ 227-228; *see supra* Section II.

B. Claim 11: The method of claim 1, wherein said sample is a biological sample derived from a subject.

As detailed above, the combination of Saxonov and Nakamura discloses using biological samples derived from a subject. EX1002 ¶ 230; *see supra* Section XI.A; EX1025 ¶¶ 46, 64, 307, 311, 321-324.

C. Claim 12: The method of claim 11, wherein detecting the presence or absence of said at least five polynucleotide analytes indicates the presence of cancer or an infection with a pathogen in said subject.

As detailed above, Saxonov and Nakamura disclose detecting viral and cancer analytes, including samples directly from a patient. EX1002 ¶¶ 231-233; *see supra* Sections XI.A-XI.B. For example, Colston, incorporated by reference, teaches detecting analytes for diagnostic purposes relating to infectious diseases and cancer. EX1026 ¶ 157 ("Samples may be collected for diagnostic purposes (e.g., the quantitative measurement of…an infectious agent)."); *id.* ¶ 1028 (discussing "detection of a disease"); *id.* ¶ 1144 (teaching that the assays "may be used for screening, diagnosis, monitoring, and/or designing treatment of diseases such as cancer.").

To the extent Patent Owner argues that this claim limitation is not obvious in view of Saxonov, which incorporates Colston, Nakamura discloses that the

polynucleotide analyte may indicate the presence of cancer or "indicates that the subject suffers from or is at risk of developing lung and/or esophageal cancer." EX1025 ¶ 46; *id.* at Abstract, ¶¶ 227, 307, 334; EX1002 ¶ 233. A POSA would have been motivated to detect the presence or absence of at least five polynucleotide analytes to cast a wide net for determining whether a subject has cancer or an infection and would have had a reasonable expectation of success. EX1002 ¶ 233.

XII. GROUND 3: OBVIOUSNESS OF CLAIMS 13-16 IN VIEW OF SAXONOV AND SILVERBROOK

A. Claim 13: The method of claim 1, further comprising transmitting information concerning the presence or absence of said at least five polynucleotide analytes through a computer network.

Saxonov, as described above, renders obvious the method of claim 1. *See supra* Section X.A. EX1002 ¶¶ 234-239. Claim 13 would have also been obvious in further view of Silverbrook's teaching of a nucleic acid testing device and method employing PCR and hybridization to identify what analytes are present in a sample and transmitting test results through a computer network. EX1002 ¶¶ 240-243; EX1009 ¶ 195 ("Test module 10…uses a fluorescence-based detection technique to identify target molecules."); *id.* ¶ 198 (describing test module 10 as amplifying target nucleic acids, and generating fluorescent signals using labeled hybridization probes); *id.* ¶ 201 ("data generated by the test module 10 can be used to update, via…network 125,…electronic medical records"), Fig. 99. A POSA would have been motivated to transmit information through a computer network as taught by

Silverbrook for the benefit of providing information remotely to databases of medical records and would have had a reasonable expectation of success. EX1002 ¶¶ 244-245.

B. Claim 14: The method of claim 1, further comprising providing information concerning the presence or absence of said at least five polynucleotide analytes to a health care professional, wherein said health care professional makes a clinical decision based on said information.

To the extent that Saxonov does not disclose the further limitations of claim 14, they would have been obvious in further view of Silverbrook's teaching both that quantifying the starting amount of different nucleic acids in samples from patients is "particularly useful in molecular diagnostics where treatment options may differ depending on the pathogen load" (EX1009 ¶ 34) and that such molecular diagnostic data from testing at various locations facilitates "clinical management decisions such as infection control and antibiotic use" (*id.* ¶¶ 56-62). EX1002 ¶¶ 247-249. A POSA would have been motivated to provide information concerning the presence or absence of polynucleotide analytes to a healthcare professional to facilitate clinical decisions for improved treatment and would have had a reasonable expectation of success. EX1002 ¶ 250.

C. Claim 15: The method of claim 14, wherein said clinical decision is a treatment decision.

This claim is obvious as discussed immediately above. *See supra* Section XII.B. To the extent argued otherwise, a POSA would have understood that clinical

decisions made in the normal course of care necessarily includes decisions as to treatment, i.e., a treatment decision, as well as it being obvious to a POSA who would have had a reasonable expectation of success. EX1002 ¶¶ 251-252; *see supra* Section XII.B.

D. Claim 16: The method of claim 15, wherein said treatment decision comprises treatment with an antibiotic or an anticancer therapeutic.

A POSA would have understood Silverbrook to teach both treatment decisions that include treatment with an antibiotic and with an anticancer therapeutic. EX1002 ¶¶ 254-255. Silverbrook discloses molecular diagnostic tools for the "immediate facilitation of treatment and improved quality of care." EX1009 ¶ 57. Silverbrook further discloses detecting various infectious diseases and forms of cancer including ovarian, colon carcinoma, multiple endocrine neoplasia, retinoblastoma, and turcot syndrome. *Id.* ¶¶ 206-243.

It would have been obvious to a POSA to administer an antibiotic in response to the presence of an infection and to administer an appropriate anticancer therapeutic in response to detection of a cancer. EX1002 ¶ 256.

XIII. GROUND 4: OBVIOUSNESS OF CLAIMS 17, 19 IN VIEW OF SAXONOV AND MALTEZOS

A. Claim 17: The method of claim 1, wherein at least part of said method is performed using a computer.

Saxonov discloses the method of claim 1 wherein at least one step is performed using a computer. EX1002 ¶¶ 257-258. Saxonov discloses an apparatus for performing its method that includes a "data processing assembly," which a POSA would have understood to be a computer to perform calculations required for steps of the method, including measuring and thereby generating a cumulative intensity measurement. EX1002 ¶¶ 257-258, 272-273; EX1004 ¶ 45; EX1007 at 12:21-13:8. To the extent Patent Owner contends that Saxonov does not disclose or render obvious performing a step of the method using a computer, this would have been obvious in further view of Maltezos.

Maltezos discloses an apparatus and method for performing PCR analysis that includes "a control assembly that controls…operation of the optical assembly" and describes detection electronics 1115 to evaluate the signal from detection region 1113 of the apparatus in which fluorescence measurements from the PCR are detected. EX1010 ¶¶ 12, 60, Fig. 11; EX1002 ¶¶ 259-260. A POSA would have understood Maltezos's control assembly to include a computer based on the disclosure of the control assembly and detection electronics and to teach that the computer performs the detecting and/or measuring step. EX1002 ¶ 261.

Given the teachings of Saxonov and Maltezos, a POSA would have found it obvious to use a computer to perform the measuring (and determining) step. EX1002 ¶ 262. A POSA would have been motivated to use a computer to facilitate the operations and calculations necessary to measure cumulative intensity measurement and determine the presence of the five polynucleotide analytes, and would have had a reasonable expectation of success. EX1002 ¶¶ 263-264.

B. Claim 19: The method of claim 17, wherein said computer is located on a droplet reader.

Saxonov teaches that the recited computer is located on a droplet reader in describing Figure 2. EX1004 ¶ 45 (disclosing "a detection assembly (a detector)" for detecting signals from droplets/partitions and "a data processing assembly (a processor) 68 ("PROC"),…[that] may be, or may be included in, a controller that communicates with and controls operation of any suitable combination of the assemblies….[where] [a]ny suitable combination of the assemblies may be operatively connected to one another."); EX1007 at 12:2-9; EX1002 ¶¶ 266-267. The signals may be "detected from the droplets with [the] detector" and "processed by [the] processor." EX1004 ¶ 46. A POSA would have understood the detection assembly and detector to be a droplet reader. EX1002 ¶¶ 267-269.

A POSA would have understood "operatively connected" to include that via physical connection such as by the "computer [being] located on a droplet reader." *Id.* ¶ 270. Further, Saxonov incorporates by reference U.S. Patent Application No.

13/341,678, which teaches a processor located on a droplet reader. EX1004 ¶ 2; EX1029 at 15:21-27, 23:13-26, Figs. 2, 3, 5, 7; EX1002 ¶¶ 271-272. The incorporated reference discloses, for example, that "a continuous signal may be processed digitally by [a] processor" and that the signal detected may come from a droplet. *Id.* at 16:38-46, 23:4-12, 24:26-27.

XIV. GROUND 5: OBVIOUSNESS OF CLAIM 18 IN VIEW OF SAXONOV, MALTZOS, AND OH

A. Claim 18: The method of claim 17, wherein said computer is located on a remote server.

Saxonov teaches that the computer is located on a remote server in disclosing "a data processing assembly (a processor) 68 ("PROC"),…[that] may be, or may be included in, a controller that communicates with and controls operation of any suitable combination of the assemblies….[where] [a]ny suitable combination of the assemblies may be operatively connected to one another." EX1004 ¶ 45 (describing Fig. 2); EX1007 at 12:2-9; EX1002 ¶¶ 273-275.

A POSA would have understood "operatively connected" to include remote connection such as by the "computer [being] located on a remote server." EX1002 ¶ 275. To the extent Patent Owner contends that Saxonov, alone or in combination with Maltezos, does not disclose or render obvious locating the computer on a remote server, this would have been obvious in further view of Oh. EX1002 ¶¶ 274-280.

Oh discloses a PCR module and its use, wherein the module includes a computing unit 41 that "performs appropriate computation based on the data received from [] sensors" or, if computing unit 41 is not included in the module, as also contemplated, a remote host computer 50 performs that function. EX1011 ¶¶ 17, 58, 66, 71; EX1002 ¶ 276. A POSA would have understood remote host computer 50's "appropriate computation" to include computations for the detecting and/or measuring steps. EX1002 ¶ 277.

Informed by Saxonov and Oh, a POSA would have found it obvious to use a remote computer to perform the measuring (and calculating) step. EX1002 ¶ 278. A POSA would have been motivated to use a remote computer to perform analytical processes because they would have understood that computers can be, and routinely are, located remotely from analytical equipment, for the numerous benefits of conducting analysis at a remote location, such as at a central location to perform analyses for a number of analytical devices, and would have had a reasonable expectation of success. EX1002 ¶¶ 279-280.

XV. GROUND 6: OBVIOUSNESS OF CLAIMS 1-9, 20 IN VIEW OF SAXONOV IN FURTHER VIEW OF LARSON

As documented above, Saxonov discloses or renders obvious claims 1-9 and 20. *See supra* Sections X.A-X.J. To the extent Patent Owner contends otherwise, these claims would have been obvious in further view of Larson. EX1002 ¶¶ 281-283.

This ground is identical to Ground I in all respects except that the teachings of Larson are used for three claim elements:

- "providing a sample comprising, or potentially comprising, at least one of said at least five polynucleotide analytes"
- "wherein each of said at least five hybridization probes further comprises at least one fluorophore and at most four fluorophores"
- "wherein said cumulative intensity measurement corresponds to the presence of a unique combination of presence or absence of said at least five polynucleotide analytes in said sample"

To the extent Patent Owner contends that Saxonov does not disclose or render these claim elements obvious, it would have been obvious to modify Saxonov in view of Larson to yield a method that includes these claim elements. Because this Ground is identical to Ground I except with regard to the treatment of these elements, only these elements are addressed below.

Saxonov and Larson are analogous art to the '170 patent—and to each other—because they are within the same field of endeavor: multiplex detection of polynucleotide analytes using color-labeled sequence-specific probes, including where there are fewer different colors than analytes. EX1001 at code (57), 12:28-14:3, 17:57-60, 21:39-23:30; EX1004 ¶¶ 19, 20, 37; EX1017 ¶¶ 34, 35, 138-153; EX1002 ¶ 284.

A. Claim 1: (a) providing a sample comprising, or potentially comprising, at least one of said at least five polynucleotide analytes;

As documented above, Saxonov alone discloses this element. *See supra* Section X.A.2. To the extent Patent Owner contends otherwise, it would have been obvious in view of Larson to analyze five or more polynucleotide analytes, including even nine polynucleotides. EX1002 ¶¶ 285-290.

Larson teaches a nine-plex assay using "just two colors (probes containing FAM and VIC fluorophores)." EX1002 ¶ 286; EX1017 ¶ 150, Fig. 15. Larson further teaches that adding more colors to an assay would expand even further the capabilities of multiplexing, including that "multiplexing capacity exceeding 50x can be envisioned." EX1017 ¶ 153; *id.* ¶ 47; EX1002 ¶ 287.

A POSA would have been motivated to rely on the related teachings of Larson, if necessary, to modify Saxonov to detect at least five polynucleotide analytes. EX1002 ¶¶ 287-289. Indeed, the two references both are digital PCR references based on the use of droplets, making their teachings interrelated. EX1002 ¶ 290. Further, a POSA would have understood the benefits of a higher-plex assay, including increased throughput while using less sample and reagents. For example, Larson explains that "the need for higher throughput in analyzing multiple targets in parallel continues to escalate in the fields of genomics and genetics." EX1017 ¶ 5. In addition, multiplexing allows "the simultaneous increase in the number of PCR

droplets while keeping the amount of input DNA the same or lower…without the consumption of more DNA." *Id.* ¶¶ 8, 104.

A POSA would have had a reasonable expectation of successfully modifying Saxonov using Larson because both references are based on the same approach (*i.e.*, droplets) and Larson teaches higher multiplex for greater targets, showing experimental results. EX1002 ¶ 290; EX1017 ¶¶ 108, 138-43, 150-53, Fig. 15. Most notably, in Figure 15, Larson teaches distinguishing nine targets with combinations of two colors and intensities, along with techniques for tuning the signal from each droplet. As the figure shows, the nine different targets are distinguished by having different combinations of intensity in two color channels:

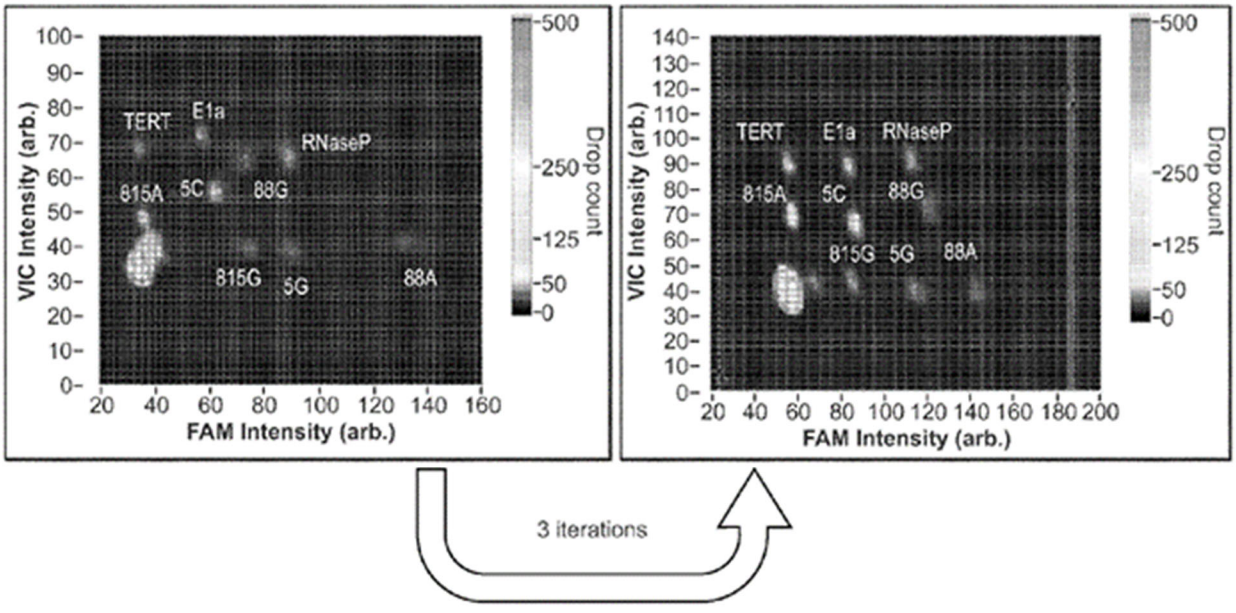


FIG. 15

EX1017 ¶¶ 134-138, 150-151, Figs. 12, 15. Accordingly, a POSA would have reasonably expected success in so modifying Saxonov.

B. Claim 1: wherein each of said at least five hybridization probes further comprises at least one fluorophore and at most four fluorophores;

As documented above, Saxonov alone discloses this element. *See supra* Section X.A.4. To the extent Patent Owner contends otherwise, it would have nonetheless been obvious in view of Larson to use hybridization probes with at most four fluorophores to detect at least five targets. EX1002 ¶ 291.

Indeed, Larson teaches using probes labeled with one or more fluorophores chosen from four fluorophores to encode each target. EX1002 ¶¶ 292-293; EX1017 ¶ 139 ("The maximum number of colors can be 1, or 2, or 3, or 4…"); *id.* ¶ 153 ("Adding extra colors would increase the capability even further"); *id.* ¶¶ 5, 35, 37, 47, 90, 145, 156, 164, Figs. 14-15, 17. Most important, Larson teaches in Figure 15 using just two different types of fluorophores to detect and distinguish among nine different targets:

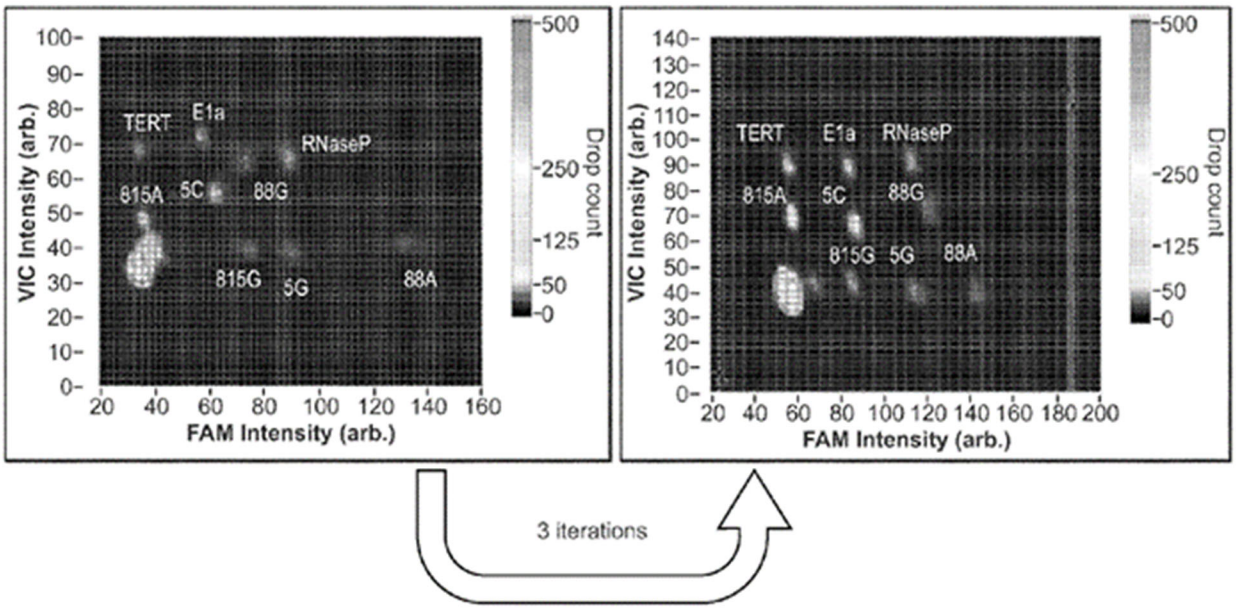


FIG. 15

EX1017 at Fig. 15. As the figure shows, the nine different types of targets that can be present in droplets are detected and distinguished from one another based solely on signals from just two fluorophores.

A POSA would have been motivated to follow the foregoing teaches of Larson and label hybridization probes with one to four fluorophores to detect at least five targets. EX1002 ¶¶ 294-297. As discussed above, the '170 patent itself acknowledges that four-color instruments were widely available. Using a maximum of four fluorophores thus would be an obvious design choice given the capabilities of available instruments. *See supra* Section X.A.4. Moreover, given that one can detect nine targets using just two colors, a POSA would have been motivated to consider up to four targets so as to detect even more targets. *See supra* Sections

XV.A, X.A.2, X.A.4; *see also* EX1017 ¶ 5. As Larson states, "[a]dding extra colors would increase the capability even further." *Id.* ¶ 153.

A POSA would have expected probes with one to four fluorophores to succeed because it is taught in the prior art. EX1002 ¶ 298; *see supra* Section XIV.A. Most important, Larson teaches in Figure 15 the detection of nine different targets using just two fluorophores, showing experimental data proving success of the approach. *See* EX1017 at Fig. 15. As Larson stated, "we have found to be generally true for this method of multiplexing, the assay worked immediately with well resolved or at least distinguishable populations for each target." *Id.* ¶ 146. Based on this, there can be no dispute on reasonable expectation of success.

C. Claim 1: wherein said cumulative intensity measurement corresponds to the presence of a unique combination of presence or absence of said at least five polynucleotide analytes in said sample; and

As documented above, Saxonov alone discloses this element. *See supra* Section X.A.8. To the extent Patent Owner contends otherwise, it would have nonetheless been obvious in view of Larson to determine a cumulative intensity measurement from a plurality of droplets that corresponds to the presence of a unique combination of presence or absence of at least five polynucleotide analytes in a sample. EX1002 ¶ 299.

Indeed, as noted above, Larson discloses in Figure 15 that one can detect the presence or absence of nine different targets in the sample by measuring the signals from a series of droplets using just two colors:

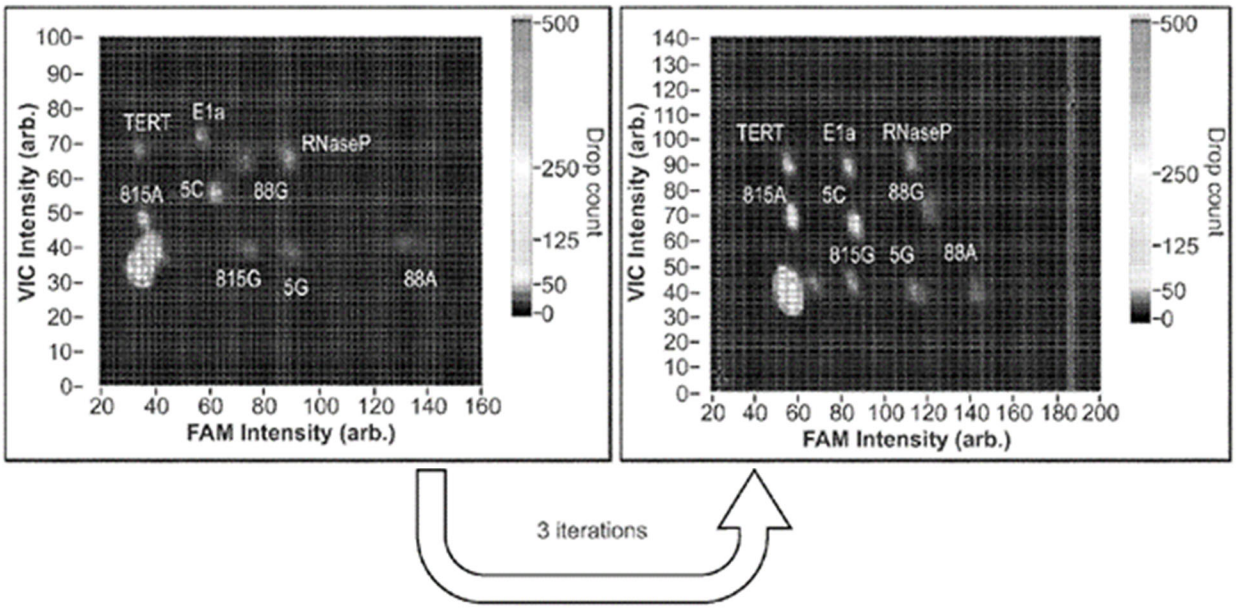


FIG. 15

EX1017 at Fig. 15. As the figure shows, there are nine distinct clusters of droplets corresponding to nine different targets that may or may not be present in the sample. As Larson states, with just a small amount of optimization, "all of the target populations were well resolved from each other, and well resolved from the empty droplets." *Id.* ¶ 150; EX1002 ¶ 300.

As discussed, a POSA would have been motivated to detect at least five analytes and have had a reasonable expectation of success. *See supra* Section XV.A.2; EX1002 ¶¶ 300-302.

D. Claim 4

As documented above, Saxonov alone discloses the limitations of this claim. See supra Section X.D. To the extent Patent Owner contends otherwise, it would have nonetheless been obvious to have a droplet that comprises at least five hybridization probes because Larson teaches including the hybridization probes for each polynucleotide target. See, e.g., EX1017 ¶ 9 ("Preferably, the droplet contains two or more probes, e.g., 2, 3, 4, 5…500, or more probes.").

E. Claim 20

As documented above, Saxonov alone discloses the limitations of this claim. See supra Section X.J. To the extent Patent Owner contends otherwise, it would have nonetheless been obvious to provide hybridization probes at concentrations such that the cumulative intensity measurement corresponds to said presence of said unique combination of analytes because the prior art specifically teaches modifying probe concentrations as a way to "tune" intensity levels to better resolve the collected signals. EX1002 ¶ 304; EX1017 Fig. 12, ¶¶ 134-37.

XVI. GROUNDS 7-10: OBVIOUSNESS OF CLAIMS 10-19

As documented above in Grounds 2-5, claims 10-19 are obvious by Saxonov in view of Nakamura (claims 10-12), Silverbrook (claims 13-16), Maltezos (claims 17, 19), and Maltezos and Oh (claims 18). *See supra* Sections XI-XIV. For the same reasons in Grounds 2-5, claims 10-19 are also rendered obvious by the

combination of Saxonov with Larson, in further view of Nakamura, Silverbrook, Maltezos, and Oh. EX1002 ¶¶ 305-306.

XVII. THE BOARD SHOULD REACH THE MERITS OF THIS PETITION

A. The Facts and Law Weigh Against Discretionary Denial Under § 325(d)

The *Advanced Bionics* test does not support discretionary denial of institution under § 325(d). *See Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 (PTAB Feb. 13, 2020) (precedential) (discussing *Becton, Dickinson* factors).

1. Factors (a), (b) and (d): The Office Has Not Considered the Same or Substantially the Same Art or Arguments

None of the asserted references were considered substantively by the Examiner. Saxonov was nominally of record during examination, based on an Information Disclosure Statement (IDS) filed March 22, 2018. EX1015 at 2. Larson itself was not submitted, although an IDS submitted on April 26, 2018, listed both U.S. Patent No. 9,366,632 by Link et al., identified as a continuation-in-part of Larson, and U.S. Patent No. 9,441,266 by Larson et al., identified as a continuation of Larson. EX1032 at 1; EX1033 at 1; EX1022; EX1017; EX1001. None of these references, however, was the basis of any rejection.

Then-pending claims were subject to prior art rejections over other references. First, the Examiner rejected then-pending claims over Han et al., Lin et. al., and

Vogelstein et al., grounded on disclosures regarding multicolor quantum dots within microbeads, which applicant overcame by amending the claims to recite a step of measuring signals to obtain a cumulative intensity measurement. EX1030 at 5-8; EX1031 at 2.

Accordingly, the "the overlap between the arguments made during examination" and arguments made in this petition is minimal, as no arguments were made during examination with respect to either Saxonov nor Larson, let alone the references in combination as set forth above. *See 3Shape A/S v. Align Tech., Inc.*, IPR2019-00160, Paper 9 at 39-42 (PTAB June 11, 2019). Also, as discussed above, and supported by the testimony of Dr. Batt, the combination of Saxonov discloses measuring the cumulative intensity signal. *Supra* Section X.A.7; EX1002 ¶¶ 176-181.

2. Factors (c), (e), and (f): The Examiner Erred by Not Considering the Art and Relevant Teachings Therein

Even if the Board determines that the same or substantially the same art or arguments were before the Office, the Examiner materially erred by not considering the relevant teachings in Saxonov.

In the Notice of Allowance, the Examiner did not discuss or cite any teaching from Saxonov, instead they stated only that the "claims recite the new and non-obvious limitation of determining a unique presence and absence pattern of at least five polynucleotides in a sample using a cumulative intensity value of fluorophores

and without using immobilization or mass spectrometry." EX1006 at 6. As discussed, however, Saxonov and Larson disclose non-degenerate hybridization techniques to detect the presence/absence of more than five polynucleotides by measuring cumulative intensity signals. *See supra* Sections X.A, XV; EX1002 ¶¶ 281-302. Accordingly, the stated reasons for allowance show material error by the Examiner in allowing the claims during examination.

B. *Fintiv* Does Not Support Discretionary Denial

The parallel district-court proceedings do not justify discretionary denial under the factors identified in *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 (PTAB Mar. 20, 2020) (precedential) ("*Fintiv*").

1. Factor 1: Likelihood Of A Stay

This factor weighs in favor of institution because Petitioner will seek a stay if IPR is instituted and stays are favored in the Northern District of California. *Zomm, LLC v. Apple Inc.*, 391 F. Supp. 3d 946, 956 (N.D. Cal. 2019) (granting stay for IPR and recognizing "a liberal policy in favor of granting motions to stay"). Further, all the factors that courts in Northern District of California consider in deciding whether to grant a stay weigh in favor of a stay. *See id.*

As discussed below for *Fintiv* Factors 2 and 3, discovery is not complete and there is no trial date. Courts in the district have granted stays pending IPR when fact discovery was in its early stages, and where a trial date had not yet been set, even

where infringement, damages, and invalidity contentions, as well as preliminary claim constructions, had been served. *Synthego Corp. v. Agilent Techs., Inc.*, No. 5:21-CV-07801-EJD, 2022 WL 2704121 at *2 (N.D. Cal. July 12, 2022) (J. Davila)[4] (finding such progress amounts to "no material progress" in a litigation). Further, given the early stage of the district court proceeding, a stay would not unduly prejudice Patent Owner. *See Zomm*, 391 F. Supp. 3d at 956.

In sum, there is no reason the district court should deny a stay if IPR is instituted. This factor favors institution.

2. Factor 2: Proximity Of Trial Date To Final Written Decision

This factor favors institution. There is no scheduled trial date in the district court case. EX1027 at 5. The median time to trial from filing for civil actions in Northern District of California is 48.9 months. EX1023 at 66. Here, Patent Owner filed a complaint for infringement in Central District of California on October 5, 2023. EX1028. The case was then transferred to the Northern District of California, where it is currently pending as *ChromaCode, Inc. v. Bio-Rad Laboratories, Inc.*, Case No. 5:23-cv-06360. EX1024. Relying on even the earliest filing date, the estimated trial date based on median time to trial statistics would be 48.9 months after October 5, 2023, or approximately November 2027. EX1023 at 66; *Mylan*

[4] The parallel district court proceeding here is also before Judge Davila. EX1012.

Pharms. Inc. v. Bayer Pharma Aktiengesellschaft, IPR2022-00517, Paper 15 at 8-9 (PTAB Aug. 9, 2022) (evaluating median time to trial for factor 2).

Petitioner expects a decision on institution within approximately seven months (six months following a filing date being accorded), giving a projected statutory deadline for a final written decision of about December 2025, which would be approximately two years before the estimated district court trial date. Therefore, this factor favors institution.

3. Factor 3: Investment In The Parallel Proceeding

This factor favors institution. The investment analysis focuses on work "completed at the time of the institution decision" that concerns "the merits of the invalidity positions." *Fintiv* at 9-10; *Sand Revolution II, LLC v. Cont'l Intermodal Group – Trucking LLC*, IPR2019-01393, Paper 24 at 10 (PTAB June 16, 2020) (informative).

At this time there has been modest investment in the district court case. The parties have engaged in discovery and begun the claim construction process, but the claim construction hearing is not scheduled until August 28, 2024, and a claim construction order will not be expected for some time following that hearing. EX1027 at 4. No depositions have been taken, and expert discovery has not yet begun. *Id.* Further, deadlines for filing opening dispositive and *Daubert* motions are not until February 18, 2025, with briefing for these motions to be complete by

March 24, 2025. *Id.* Expert discovery does not close until February 20, 2025. *Id.* Thus, "the most burdensome parts of the case—filing and responding to pretrial motions, preparing for trial, going through the trial process, and engaging in post-trial motions practice—all lie in the future." *CyWee Grp. Ltd. v. Samsung Elecs. Co. Ltd.*, No. 2:17-cv-00140-WCB-RSP, 2019 WL 11023976, at *6 (E.D. Tex. Feb. 14, 2019). Thus, this third factor favors institution.

4. Factor 4: Overlap of Issues

While the same prior art is at issue in the district court, this factor is neutral given the extensive additional art and issues being litigation in the district court.

5. Factor 5: Whether Petitioner And Defendant In Parallel Proceeding Are The Same

This factor is neutral, because it is often the case for a patent asserted in district court to be challenged at the Board.

6. Factor 6: Other Circumstances, Including the Merits

This factor strongly favors institution. As set forth above, the Petition sets forth "[c]ompelling, meritorious challenges…in which the evidence, if unrebutted at trial, would plainly lead to a conclusion that one or more claims are unpatentable by a preponderance of the evidence." *OpenSky Indus., LLC v. VLSI Tech. LLC*,

IPR2021-01064, Paper 102 at 49 (PTAB Oct. 4, 2022) (precedential).[5] Thus, the Board should institute *inter partes* review because "compelling, meritorious challenges will be allowed to proceed at the PTAB even where district court litigation is proceeding in parallel." *Id.* (quoting Memorandum at 4).

XVIII. CONCLUSION

Petitioner respectfully requests cancellation of the '170 patent.

[5] *See also* the USPTO Memorandum, Interim Procedure for Discretionary Denials in AIA Post-Grant Proceedings with Parallel District Court Litigation ("Memorandum") (June 21, 2022), available at https://www.uspto.gov/sites/default/files/documents/interim_proc_discretionary_denials_aia_parallel_district_court_ litigation_ memo_20220621_.pdf.

Dated: July 15, 2024

Respectfully submitted,

/Derek C. Walter/

Derek C. Walter
Lead Counsel for Petitioner
Registration No. 74,656
Weil, Gotshal & Manges LLP
201 Redwood Shores Parkway
Redwood Shores, CA 94065

APPENDIX A: LISTING OF CHALLENGED CLAIMS

No.	Limitation
1	A method of unambiguously detecting any unique combination of presence or absence of at least five polynucleotide analytes in a plurality of droplets, the method comprising: (a) providing a sample comprising, or potentially comprising, at least one of said at least five polynucleotide analytes; (b) forming a mixture of said sample and at least five hybridization probes, wherein each of said at least five hybridization probes further comprises at least one fluorophore and at most four fluorophores; (c) partitioning said mixture into said plurality of droplets; (d) exciting said at least one fluorophore to generate one or more signals if one or more of said at least five polynucleotide analytes is present in said plurality of droplets, wherein said one or more signals comprise at least one signal generated by excitement of said at least one fluorophore; (e) measuring said one or more signals to generate a cumulative intensity measurement, wherein said cumulative intensity measurement corresponds to the presence of a unique combination of presence or absence of said at least five polynucleotide analytes in said sample; and (f) determining whether each of said least five polynucleotide analytes is present, in any unique combination of presence or absence, based on said cumulative intensity measurement, wherein the method does not require any step of immobilization of said at least five polynucleotide analytes or mass spectrometry.
2	The method of claim 1, wherein each of said at least five hybridization probes is complementary to one of said at least five polynucleotide analytes.
3	The method of claim 1, wherein said at least five hybridization probes comprise one or more fluorophores selected from one, two, three, or four fluorophores.

No.	Limitation
4	The method of claim 1, wherein, in (b), a droplet of said plurality of droplets comprises said at least five hybridization probes.
5	The method of claim 1, wherein, in (b), a droplet of said plurality of droplets comprises one or more of said at least five polynucleotide analytes.
6	The method of claim 1, wherein, in (b), a droplet of said plurality of droplets comprises at most one of said at least five polynucleotide analytes.
7	The method of claim 1, wherein said one or more signals is generated during a polymerase chain reaction.
8	The method of claim 1, wherein said at least five polynucleotide analytes are at least seven polynucleotide analytes.
9	The method of claim 1, wherein said at least five hybridization probes are at least seven hybridization probes.
10	The method of claim 1, wherein said one or more of said at least five polynucleotide analytes comprise cell-free nucleic acid, tumor nucleic acid, fetal nucleic acid, viral nucleic acid, or any combination thereof.
11	The method of claim 1, wherein said sample is a biological sample derived from a subject.
12	The method of claim 11, wherein detecting the presence or absence of said at least five polynucleotide analytes indicates the presence of cancer or an infection with a pathogen in said subject.
13	The method of claim 1, further comprising transmitting information concerning the presence or absence of said at least five polynucleotide analytes through a computer network.
14	The method of claim 1, further comprising providing information concerning the presence or absence of said at least five polynucleotide analytes to a health care professional, wherein said health care professional makes a clinical decision based on said information.

No.	Limitation
15	The method of claim 14, wherein said clinical decision is a treatment decision.
16	The method of claim 15, wherein said treatment decision comprises treatment with an antibiotic or an anticancer therapeutic.
17	The method of claim 1, wherein at least part of said method is performed using a computer.
18	The method of claim 17, wherein said computer is located on a remote server.
19	The method of claim 17, wherein said computer is located on a droplet reader.
20	The method of claim 1, wherein each of said at least five hybridization probes are provided at a given concentration such that said cumulative intensity measurement corresponds to said presence of said unique combination.

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24 et seq., the undersigned certifies that this document complies with the type-volume limitations. This document contains 13,981 words as calculated by the "Word Count" feature of Microsoft Word 2016, the word processing program used to create it.

Respectfully submitted,

WEIL, GOTSHAL AND MANGES LLP

Dated: July 15, 2024

By: */Derek C. Walter/*
Derek C. Walter
Lead Counsel for Petitioner
Reg. No. 74,656

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of **PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 10,770,170 B2 WITH PETITIONER'S EXHIBIT LIST, POWER OF ATTORNEY, AND EXHIBITS 1001-1007, 1009-1017, 1019-1033, AND 1036-1038** are being served on July 15, 2024, via Priority Express Mail (Fed Ex) pursuant to 37 C.F.R. § 42.105 and § 42.6(e) to the Patent Owner at the address below:

California Institute of Technology
1200 East California Boulevard
Pasadena, California 91125

Patent Owner's Address of Record

Additional Addresses Known as Likely to Effect service

Dated: July 15, 2024

By: */Derek C. Walter/*
Derek C. Walter
Lead Counsel for Petitioner
Reg. No. 74,656