

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. 10,068,051 B2

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PETITIONER’S EXHIBIT LIST

Exhibit #	Description
EX1001	U.S. Patent No. 10,068,051 “’051 patent”
EX1002	Declaration of Carl A. Batt, Ph.D.
EX1003	Joint Claim Construction Statement, filed on June 18, 2024, Dkt No. 65, <i>ChromaCode, Inc. v. Bio-Rad Laboratories et al.</i> , 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 Allowability from Prosecution File History of U.S. Patent No. 10,068,051 filed on August 5, 2014
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	U.S. Patent Application Publication No. US 2008/0124705 A1 “Kramer”
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. 10,068,051 Infringement Claim Charts from Infringement Contentions, served on March 21, 2024, <i>ChromaCode, Inc. v. Bio-Rad Laboratories et al.</i> , 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/

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EX1014	Pamela M. Holland, et al., “Detection of specific polymerase chain reaction product by utilizing the 5’ → 3’ exonuclease activity of <i>Thermus aquaticus</i> DNA polymerase,” <i>Proc. Natl. Acad. Sci. USA</i> , 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	U.S. Patent No. 9,222,128 “128 patent”
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, <i>ChromaCode, Inc. v. Bio-Rad Laboratories et al.</i> , 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, <i>ChromaCode, Inc. et al. v. Bio-Rad Laboratories</i> , Case No. 2:23-cv-08417, C.D. Cal.
EX1025	Applicant Response from Prosecution File History of U.S. Patent No. 10,068,051 filed on May 1, 2017
EX1026	Office Action Summary from Prosecution File History of U.S. Patent No. 10,068,051 filed on August 5, 2014

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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, <i>ChromaCode, Inc. v. Bio-Rad Laboratories et al.</i> , 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, <i>ChromaCode, Inc. et al. v. Bio-Rad Laboratories</i> , Case No. 2:23-cv-08417, C.D. Cal.
EX1029	Applicant Remarks from Prosecution File History of U.S. Patent No. 10,068,051 filed on November 6, 2017
EX1030	Office Action Summary from Prosecution File History of U.S. Patent No. 10,068,051 filed on August 5, 2014
EX1031	Notice of Allowance and Fee(s) Due from Prosecution File History of U.S. Patent No. 10,068,051 filed on August 5, 2014
EX1032	Information Disclosure Statement from Prosecution File History of U.S. Patent No. 10,068,051 filed on August 5, 2014
EX1033	U.S. Patent No. 9,441,266 “Larson patent”
EX1034	Applicant Remarks from Prosecution File History of U.S. Patent No. 10,068,051 filed on August 11, 2017
EX1035	Advisory Action from Prosecution File History of U.S. Patent No. 10,068,051 filed on August 5, 2014
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,” <i>Diagnostic Molecular Pathology</i> , 2024

I. INTRODUCTION

Bio-Rad Laboratories, Inc., (“Petitioner”) requests *inter partes* review of claims 1-9 of United States Patent No. 10,068,051 (“the ’051 patent”), issued on September 4, 2018. The ’051 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 ’051 patent are novel or non-obvious over the prior art.

For decades, DNA molecules had been straightforwardly 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 light 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 relied upon herein and owned by Petitioner.

To the extent the '051 patent identifies any arguable novelty, it is little more than the straightforward extension of prior art concepts to a larger number of targets. The '051 patent, for instance, specifically claims detecting “the presence or absence of at least seven 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 1-4 are unpatentably obvious in view of Saxonov, alone or in combination with Kramer and/or Larson, and claims 5-9 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 nucleic acids such as DNA. EX1002 ¶¶ 29-34. Many biotechnology applications rely on base-pairing complementary nucleic acid sequences and the related ability of single-strands to serve as templates for synthesis of complementary strands. *Id.* ¶ 34. One such application is the polymerase chain reaction (“PCR”), wherein DNA fragments/sequences are amplified in repeated cycles. *Id.* ¶¶ 35-38.

PCR generally involves three steps. *Id.* ¶ 36. First, double-stranded DNA is denatured into single strands. *Id.* Next, DNA 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 molecules serve as templates in subsequent PCR cycles. *Id.*

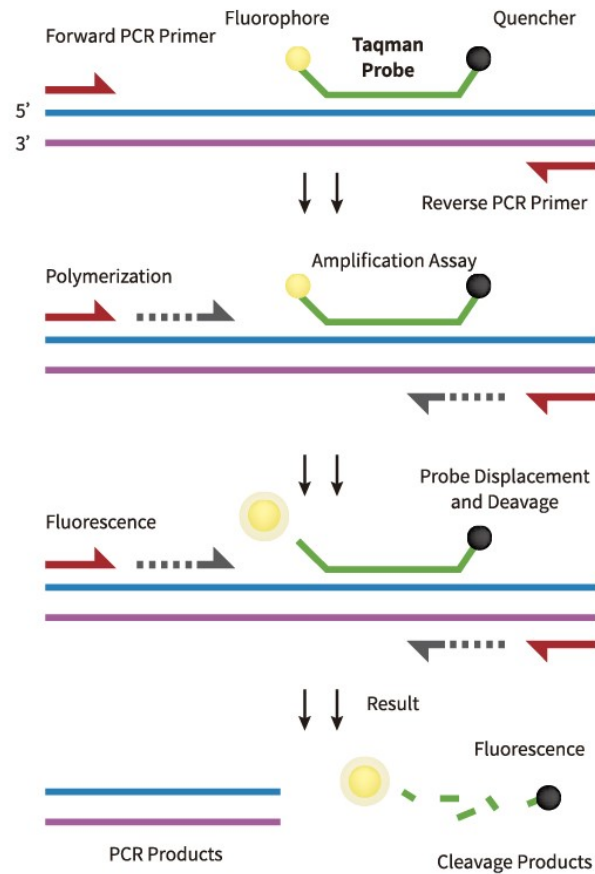
Multiplex PCR amplifies multiple polynucleotide sequences using multiple primer pairs for multiple target sequences in a single reaction volume concurrently. *Id.* ¶ 38. Multiplex PCR was well-known in the art and understood to be faster, less expensive, and more convenient than amplifying polynucleotide sequences separately in individual PCR reactions. *Id.*

B. Fluorescence Signals and Detection of Polynucleotide Analytes

Base-pairing of complementary sequences was also used to generate color signals to detect polynucleotides. EX1002 ¶ 39. Methods include hybridizing labeled oligonucleotides to specific polynucleotide sequence(s) before measuring the label's signal. *Id.* ¶¶ 39-40.

One well-known technique uses labeled oligonucleotides modified after hybridization to generate a detectable color signal, such as by cleaving the oligonucleotide. *Id.* ¶¶ 40-41. An example is the TaqMan assay, which uses oligonucleotide probes that bind to a target sequence and have a fluorophore and a

quencher at opposite ends. During PCR, the exonuclease activity of the polymerase separates the fluorophore and quencher of bound probes by cleaving the probe:



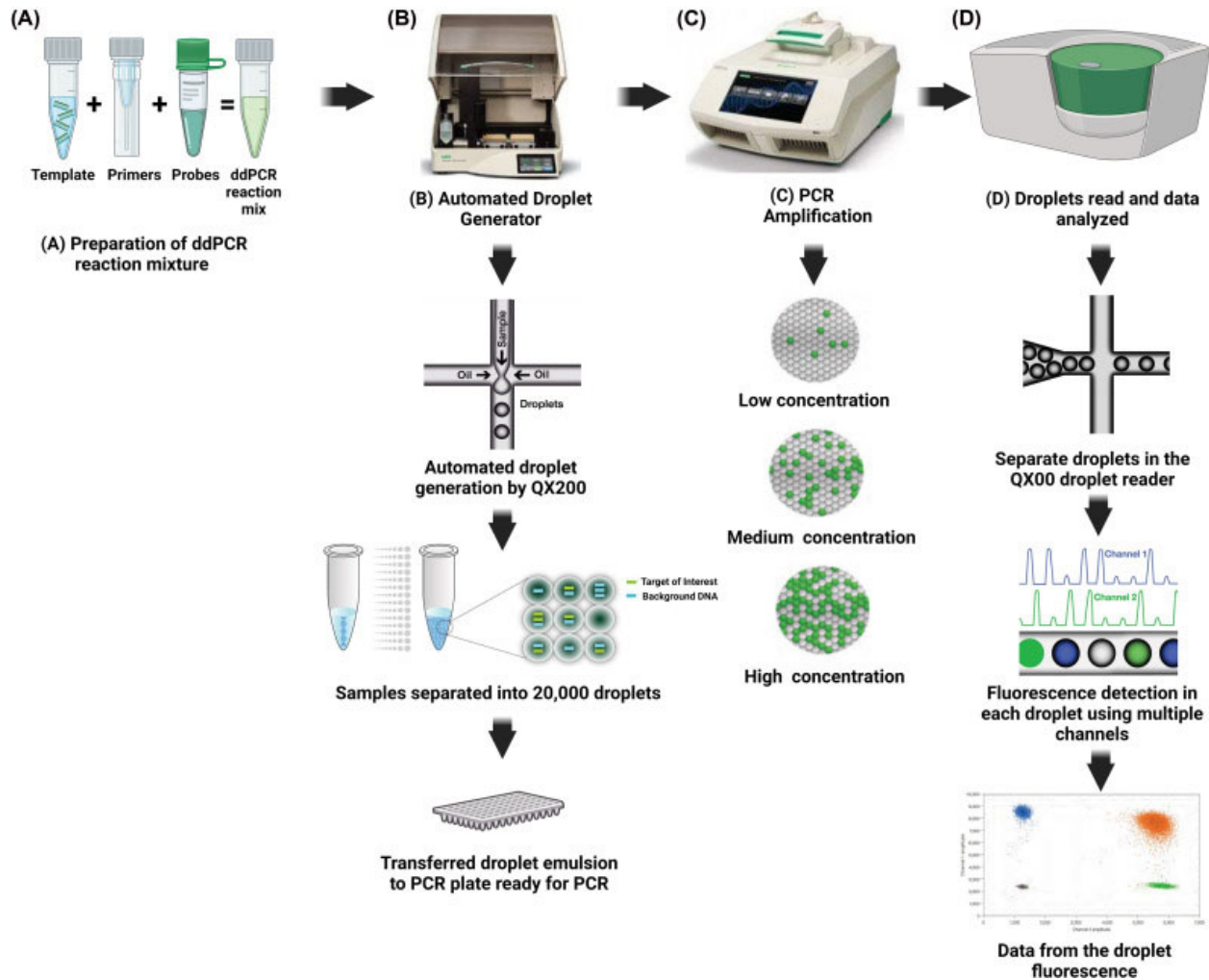
EX1013 at 6; EX1014 Fig. 1; EX1002 ¶¶ 40-41.

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 ¶¶ 42-46. 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 proportional to the amount of the target polynucleotide in a sample, allowing quantification of analytes. *Id.* ¶ 45.

In dPCR, the PCR solution including sample is diluted into small partitions, where separate PCR reactions occur. *Id.* ¶ 46. The same TaqMan probes, as described for qPCR, can be used. *Id.* Reactions can be multiplexed. *Id.* The degree of dilution is optimized so only a fraction of partitions include any one particular target, so that where there is a signal, there is typically only a single copy of one target. *Id.* 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 partitions 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 ¶ 46.

III. OVERVIEW OF THE '051 PATENT

The '051 patent issued September 4, 2018, claiming benefit of a February 3, 2012, provisional application. EX1001, codes (45), (63), 1:6-11. For purposes of only this proceeding, it is assumed herein that the '051 patent is entitled to a February 3, 2012, priority date.

A. Specification

The '051 patent purports to describe multiplex detection of polynucleotide analytes using fewer different sequence-specific labeled probes than analytes. EX1001 at 7:62-8:9, 10:26-50, 14:5-17; EX1002 ¶¶ 49-66. 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.* ¶¶ 49-54.

The '051 patent discloses coding schemes employing signals of differing intensities of the same colors to distinguish polynucleotides. *See, e.g.*, EX1001 at 23:59-24:20; EX1002 ¶¶ 55-56. An example of such a coding scheme is reproduced:

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

Example of encoding method using one color and one intensity per analyte, but different intensities among analytes.					
Tier	Analyte	B	G	Y	R
2	C	4	0	0	0
	D	8	0	0	0
	E	0	1	0	0
	F	0	2	0	0
	G	0	4	0	0
3	H	0	8	0	0
	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

EX1001 at 23:60-24:19 (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 24:31-36. 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 25:1-19; EX1002 ¶¶ 57-58.

In addition to the use of intensity to distinguish targets, the '051 patent also contemplates the prior art approach of using more than one color per analyte. EX1002 ¶¶ 59-62. 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 one or more additional 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 14:5-17. The blue “control” signal provides a measure of the total number of analytes present in a given sample and allows distinguishing 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 and another with analytes B and C can be distinguished by the doubled intensity of blue in the latter sample compared to the former. EX1002 ¶¶ 59-62.

In this approach, however, certain combinations of analytes unavoidably provide the same cumulative signals. *Id.* ¶ 63. 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 '051 patent suggests

nothing more than ignoring one or more analytes, removing them from the coding scheme to reduce or eliminate this degeneracy. EX1001 at 14:41-43, Table 4; EX1002 ¶¶ 63-64.

B. Challenged Claims

All claims of the '051 patent are challenged. A full listing of claims is included as Appendix A.

IV. LEVEL OF ORDINARY SKILL IN THE ART OF THE '051 PATENT

A person having ordinary skill in the art (“POSA”) relevant to the '051 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 ¶¶ 70-72. 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. ¶ 73.

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 '051 patent, as well as for the related patents—U.S. Patent Nos. 10,770,170 and 11,827,921. EX1002 ¶ 74; 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 assays detecting multiple target polynucleotides in single samples using dPCR. EX1007, Title; EX1002 ¶¶ 74-76. Samples having multiple targets are contacted with fluorophore-labeled probes that report the presence of targets by generating signals during PCR. *Id.* 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. *Id.* at 9:5-10 (“aspects of light, such as the intensity...may include data collected in one or more different [colors]”).

Like the '051 patent, the '013 provisional discloses using probes labeled with the same color at different intensities to distinguish among different polynucleotide analytes. *Id.* 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 in the sample, 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 that 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 analyte 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; <i>see also id.</i> 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” (<i>id.</i> at 7:11); “the partitions may be droplets” (<i>id.</i> at 7:17); “reactions may be performed in the partitions” (<i>id.</i> at 8:11); “the reaction may be an amplification reaction” (<i>id.</i> at 8:19); “[s]ignals may be created for each of the partitions...from reporters for two or more distinct targets” (<i>id.</i> at 9:4-8); <i>id.</i> at 7:3-5.
detecting a signal from the droplets representing combined emission of light from the reporters for the targets,	“[s]ignals may be created for each of the partitions” (<i>id.</i> at 9:4); “signals may represent aspects of light, such as the

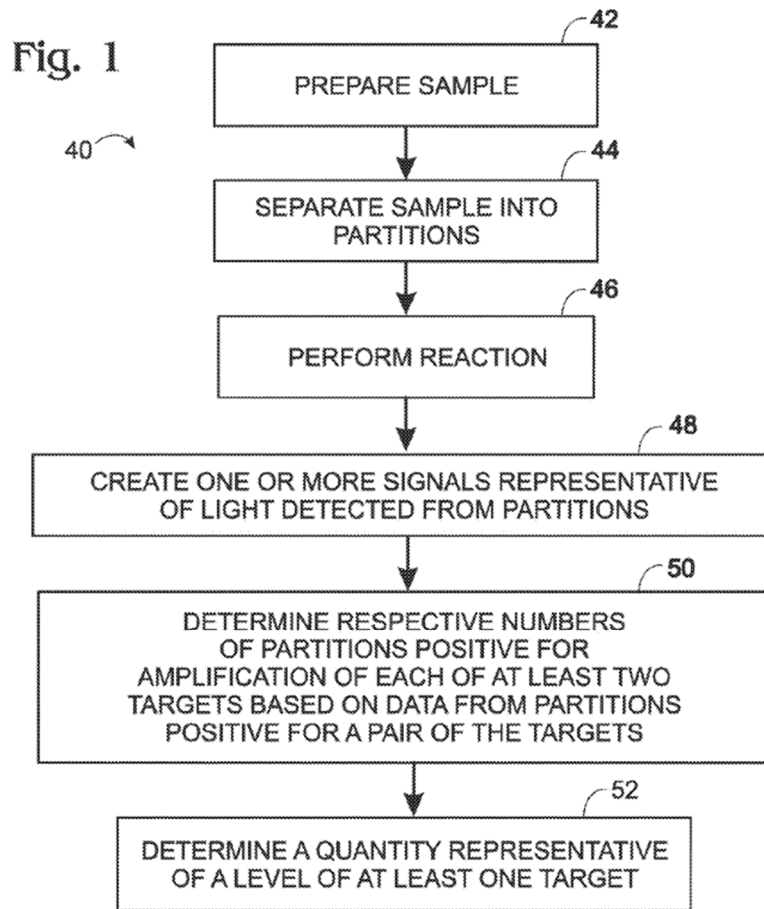
Saxonov	'013 Provisional Disclosure
wherein each reporter provides a portion of the signal having an intensity that varies according to whether or not the corresponding target is present in a droplet, and wherein a plurality of the droplets contain more than one target and have a distinguishable intensity of the signal relative to droplets containing only one target;	intensity” (<i>id.</i> 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” (<i>id.</i> 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” (<i>id.</i> 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” (<i>id.</i> at 16:26-27); <i>see also id.</i> 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...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” (<i>id.</i> 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” (<i>id.</i> at 16:26-27); “statistical methods...may be used to estimate the number of droplets or peaks associated with each outcome” (<i>id.</i> at 16:32-17:2); “droplets that included the RPP30 gene but did not include the C61 gene” (<i>id.</i> at 18:16-17); “droplets that included the C61 gene but did not include the RPP30 gene” (<i>id.</i> at 18:11-12); <i>id.</i> 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	<i>See</i> preceding section; “droplets that are positive for RPP30 and C61...droplets that included both genes” (<i>id.</i> at 18:19-20).
determining a quantity representative of a level of at least one target.	“ <u>Example 3</u> ...describes a first exemplary digital PCR assay, in which multiplexing in a single channel is used to assess copy number of the C61 gene” (<i>id.</i> at 17:4-6); “There are 4033 droplets containing RPP30...There are 4022 droplets containing C61...Thus, because RPP30 is known to have two copies per genome, C61 must also have two copies.” (<i>id.</i> 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 ¶¶ 77-78.

Saxonov depicts the steps of the method:



EX1004 Fig. 1.

Briefly, Saxonov teaches that a prepared sample may be partitioned into droplets. *Id.* ¶ 28. Each droplet may contain small numbers of target polynucleotide(s). *Id.* Reactions such as PCR (including with use of fluorophore-labeled probes) can be performed in the droplets. *Id.* ¶¶ 32-34, 28-29; EX1002 ¶¶ 79-82.

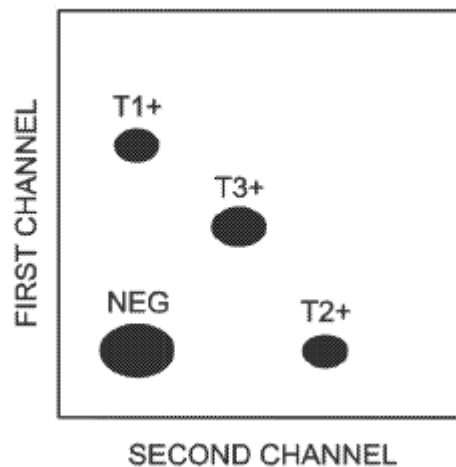
PCR can be used to generate a signal, for example, by using a fluorophore. EX1004 ¶ 36. The fluorophore can be used in conjunction with a quencher on the same probe that suppresses the fluorophore signal. *Id.* ¶ 52. When the fluorophore-labeled probe is bound to a target and cleaved during amplification, the fluorophore is separated from the quencher, allowing the fluorophore to generate a detectable signal. *See id.*; EX1002 ¶¶ 83-84.

Droplets with a generated signal are 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 ¶¶ 85-86.

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 ¶ 87; EX1004 ¶ 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), Fig. 5.

Saxonov further teaches using multiple fluorophores and multiple intensities to identify greater numbers of analytes. *Id.* ¶¶ 20, 76-79; EX1002 ¶¶ 88-90. 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 ¶ 91. Figure 10 depicts signals of different colors for the same target, as well as of different signal intensities for that target compared to others, 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 lower intensity.

Fig. 10



EX1004 Fig. 10, ¶¶ 18, 79; EX1002 ¶ 92. Whether each target is identified by a single color, or by multiple colors, Saxonov further teaches detecting light from different labeled probes with the same sensor at the same time and that the composite signal may represent “two, three, four, or more targets.” EX1004 ¶ 36; EX1007 at 9:11-15; EX1002 ¶ 93.

B. Kramer

1. Kramer is Prior Art

Kramer, US 2008/0124705 A1, entitled “Homogeneous Multiplex Screening Assays and Kits,” is the publication of patent application No. 10/426,556, published on May 29, 2008. EX1008, codes (10), (12), (21), (43). Kramer is § 102(b) prior art because it was published more than one year prior to the earliest possible effective filing date for the '051 patent, February 3, 2012. EX1001, codes (60), (63), 1:6-11.

2. Kramer Overview

Kramer discloses assays for simultaneously detecting numerous polynucleotide targets using fluorescent hybridization probes that have unique codes for each target. EX1008, Abstract, ¶ 8; EX1002 ¶¶ 95-97. The nucleic acid targets are detected in the reaction solution without segregating targets spatially and without washing away any unbound hybridization probes. EX1008 ¶ 9. Each hybridization “probe is specific to one target among the multitude of possible targets being screened.” *Id.* ¶ 10. Kramer discloses various techniques that rely on hybridization between fluorescent hybridization probes and polynucleotide targets, including the molecular beacon technique and the TaqMan assay. *Id.* ¶ 31.

Kramer teaches the use of combinations of differently colored fluorophores (“combinatorial coding”), combinations of different amounts of each fluorophore (“ratio coding”), or both in combination, to differentiate among analytes. *Id.* ¶¶ 3,

11 (combinatorial coding relies on analytes’ “unique pattern of different labels...colors”); *id.* ¶ 14 (“In ratio coding, different amounts of the same label are used for differentiation.”); EX1002 ¶¶ 98-99. Kramer teaches providing multiple colors and/or intensities for a particular target by creating portions of each probe type, labeling the individual portions differently, and mixing the different portions together so that when they are hybridized to the target, they will generate the unique color signal pattern for the analyte. EX1008 ¶ 12. Color signal patterns for analytes can be single colors, multiple colors, and either one with multiple color signal intensities, with the colors selected from four different colors. *Id.* ¶ 31.

In Figure 1, Kramer discloses “distinguishable combinations obtained using two or three colors per probe [type] and panels of 4-8 distinguishable fluorophores” (*id.* ¶ 22):

Kramer teaches assays that include multiple polynucleotides in the same sample. EX1008 ¶ 39 (“[T]wo or even more than two targets...in a sample.”); EX1002 ¶¶ 101-103. Kramer teaches how to decipher the signal in such cases by relying on the colors and intensities of colors in the resulting signal(s). EX1008 ¶¶ 39-42. Kramer further discloses that when “the colors encoding each probe will appear at the same time,” in some instances, “it may not be possible to unambiguously identify each code,” that is, to identify each individual signal pattern in the combined signal. *Id.* ¶ 42. Kramer addresses this problem by using a “repeat assay utilizing an alternative coding scheme for the targets” to “resolve the ambiguity.” *Id.* Kramer teaches, accordingly, the problem of degeneracy resulting from multiple combinations of probe sets including colors in common that generate the same cumulative color and intensity signal. *Id.*

C. 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 ’051 patent, February 3, 2012.

2. Larson Overview

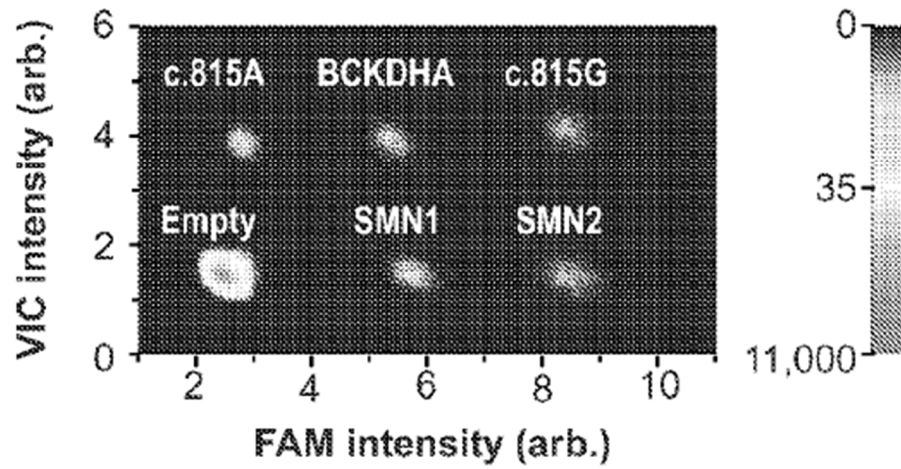
Larson discloses multiplex detection of target polynucleotide analytes using fewer color labels than targets. EX1017 Abstract, ¶¶ 119-122, 138-140; EX1002 ¶¶ 104-108. Droplets are formed containing zero, one, or more targets, and merged with others containing PCR reagents. EX1017 ¶¶ 52, 68-69, 74. Larson teaches the use of fluorogenic hybridization probes, including a TaqMan assay. *Id.* ¶¶ 47, 89, 97, 132-134.

Larson teaches three methods for identifying targets to achieve reactions higher-plex than one color per target (EX1002 ¶¶ 109-113): using different intensities of the same color (EX1017 ¶ 138); using multiple colors simultaneously in addition to multiple intensities of a single color (*id.* ¶ 139); and using “both colors and intensities” to identify each target (*id.* ¶ 140).

Larson teaches how to implement 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; EX1002 ¶¶ 114-117.

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

FIG. 14a



Id. Fig. 14a;

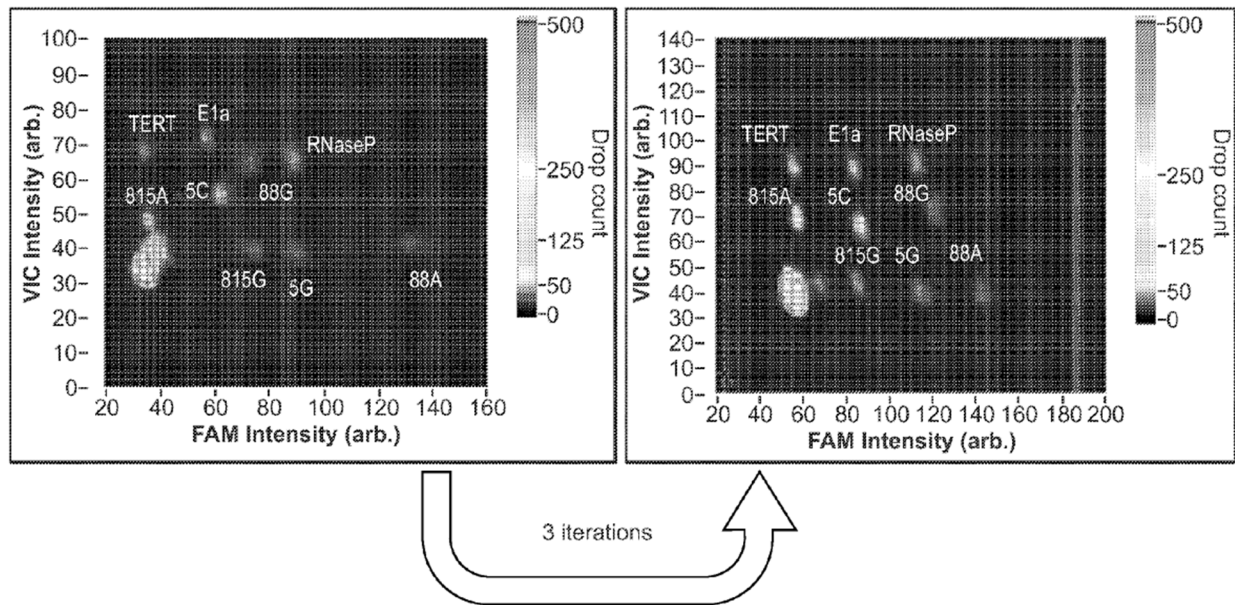


FIG. 15

Id. Fig. 15; *id.* ¶¶ 34, 145-153; EX1002 ¶ 118.

D. Secondary References Relied Upon Herein

The following references are analogous art to the '051 patent and to Saxonov, Kramer, and Larson, and are utilized herein in challenging claims 5-9 not subject to Grounds 1 and 5:

- **Silverbrook:** published in 2011. EX1009; EX1002 ¶¶ 119-123. Silverbrook is thus prior art to the '051 patent under at least § 102(a).
- **Maltezos:** published in 2008. EX1010; EX1002 ¶¶ 124-125. Maltezos is thus prior art to the '051 patent under ¶ 102(b).
- **Oh:** published in 2010. EX1011; EX1002 ¶¶ 126-129. Oh is thus prior art to the '051 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 '051 patent is involved in *ChromaCode, Inc. et al. v. Bio-Rad Laboratories, Inc.*, 5:23-cv-06360 (N.D. Cal.) (“parallel proceeding”). A related 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. 10,770,170 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.

Lead Counsel	Back-Up Counsel
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VII. GROUNDS FOR STANDING

Petitioner certifies that the '051 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	1-4	Saxonov
2	§ 103	5-6	Saxonov, Silverbrook
3	§ 103	7	Saxonov, Maltezos
4	§ 103	8-9	Saxonov, Maltezos, Oh
5	§ 103	1-4	Saxonov, Kramer and/or Larson
6	§ 103	5-6	Saxonov, Kramer and/or Larson, Silverbrook
7	§ 103	7	Saxonov, Kramer and/or Larson, Maltezos

Ground	35 U.S.C. Section (Pre-AIA)	Claims	References
8	§ 103	1-4	Saxonov, Kramer and/or Larson

IX. CLAIM CONSTRUCTION

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

- “degenerate” or “degeneracy” [as] mean[ing] a situation where a legitimate result is not definitive, because it can indicate more than one possibility in terms of the presence or absence of an analyte.” EX1003 at 9; *see e.g.*, ’051 patent, claim 1. Also, conversely, “non-degenerately.” EX1003 at 9.
- “each [of the at least seven] hybridization probe[s]” means “each collection of hybridization probes specific for a polynucleotide analyte.” *Id.* at 11; *see e.g.*, ’051 patent, claim 1.
- “cumulative intensity signal(s)” means “the signal or collection of signals from the probes that contact a given analyte.” EX1003 at 14; *see e.g.*, ’051 patent, claim 1.
- “cumulative signal measurement” means “the signal or collection of signals from the probes that contact the present analytes.” EX1003 at 16; *see e.g.*, ’051 patent, claim 1.

- “single sample solution volume” is non-limiting. EX1003 at 19; *see e.g.*, ’051 patent, claim 1.
- “wherein said method non-degenerately detects the presence or absence of the at least seven polynucleotide analytes in said single sample solution volume, in any combination of presence or absence” is non-limiting. EX1003 at 23; *see e.g.*, ’051 patent, claim 1.

Other terms, as used herein, are consistent with Patent Owner’s arguments and positions in the parallel proceeding.¹ EX1003. Specifically, for purposes of this 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 ’051 Patent is allegedly infringed by Petitioner. *See Hospira, Inc. v. Amgen Inc.*, IPR2021-00528, Paper 7

¹ In the parallel proceeding, Bio-Rad contends that the phrases “providing a sample solution volume...comprising at least seven hybridization probes” and “contacting ...” (EX1003 at 6) and “non-degenerately,” “degenerate” or “degeneracy” (*id.* at 9) in claim 1 are indefinite. 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 these terms are not indefinite. EX1012 at 3-60.

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. EX1002 ¶¶ 130-133.

X. GROUND 1: OBVIOUSNESS OF CLAIMS 1-4 IN VIEW OF SAXONOV

The ’051 patent claims a method of detecting the presence of at least seven polynucleotide analytes using at least seven hybridization probes that are labeled with one or more of four different fluorophores. EX1001 at claim 1; EX1002 ¶¶ 134-135. At its core, the ’051 patent 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 ’051 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), 12:29-14:2, 19:35-38, 23:31-25:30; EX1004 ¶¶ 19, 20, 37; EX1002 ¶¶ 136-138.

A. Claim 1

- 1. A method of detecting the presence or absence of at least seven polynucleotide analytes, in any combination of presence or absence, in a single sample solution volume, the method comprising:**

The preamble is not limiting. EX1002 ¶¶ 139-145. If deemed limiting, a POSA would have understood Saxonov to render obvious the recited method. *Id.* 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.*

- 2. a) providing a sample solution volume**

Saxonov discloses providing a sample solution volume. *See, e.g.*, EX1004 ¶ 26 (“[P]reparation may include combining the sample with reagents for amplification.”); EX1002 ¶¶ 146-148; EX1007 at 6:21-23; *see also* EX1004 ¶ 25; EX1007 at 6:13-15. Saxonov discloses preparation of sample solution into aqueous droplets that may contain small numbers of target polynucleotide(s). EX1004 ¶ 28. Such droplets are precisely what Patent Owner contends correspond to the claimed “sample solution volumes” in parallel litigation. *See* EX1012 at 12 (“The QX600 system requires dividing each sample into a sample solution volume (e.g., a water-in-oil droplet).”); *id.* at 9 (“Samples may be further provided using a droplet generator.”); EX1002 ¶ 147.

3. comprising or potentially comprising, at least one of at least seven polynucleotide analytes, and

Saxonov discloses including multiple polynucleotide analytes within the same sample solution volume. EX1002 ¶¶ 149-162. At the outset, a POSA would have understood that the use of seven target polynucleotides as claimed is not inventive. This is confirmed in the '051 patent itself, which never identifies seven target polynucleotides as novel or non-obvious, but rather buries the possibility of seven 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 12:42-45, 37:44-48. Nonetheless, Saxonov teaches the detection of seven polynucleotide targets and, at a minimum renders obvious, detecting at least seven targets.

First, a POSA would have understood that Saxonov teaches multiplexed detection of polynucleotides (detection of multiple polynucleotides in the same experiment). EX1002 ¶ 150; EX1004 ¶ 5 (describing digital PCR to detect “nucleic acid target[s]”); *id.* ¶ 6 (“A digital PCR assay can be multiplexed to permit detect 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 seven or more targets such that it teaches the analysis of samples with seven or more targets. EX1002 ¶¶ 151-

154. Specifically, Saxonov teaches detecting multiple targets using different intensities of the same color along with the use of multiple colors. *Id.* 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. *Id.* ¶¶ 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. For three targets, three different intensities of one color “generate[s] eight clusters or populations of data, separated by intensity.” *Id.* ¶ 20. 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. EX1002 ¶¶ 155-156. 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).”).

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 seven 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 ¶ 157.

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. EX1004 ¶¶ 20, 51; EX1002 ¶ 158. 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. 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 ¶ 159.

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 ¶ EX1002 ¶ 158 160-161. 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 seven analytes and a POSA would have reasonably expected success in using either scheme contemplated in Saxonov. EX1002 ¶ 162.

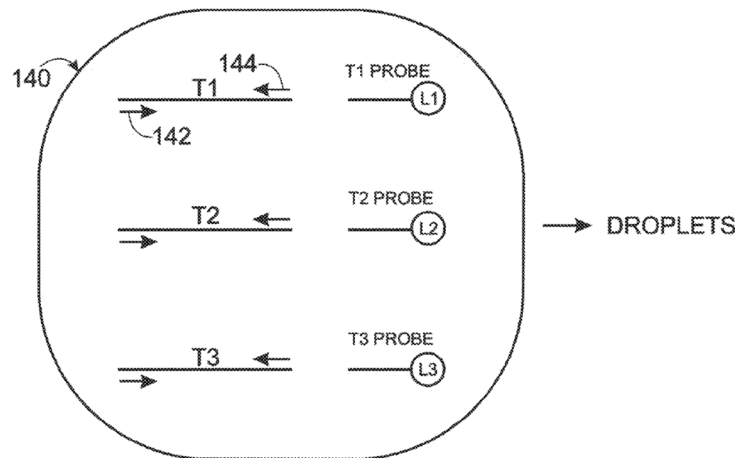
4. comprising at least seven hybridization probes, each hybridization probe corresponding to one of the at least seven polynucleotide analytes,

Saxonov discloses using hybridization probes specific for each polynucleotide analyte. EX1004 ¶¶ 50; EX1002 ¶¶ 163-167. For example, Saxonov discloses using “corresponding probes 84, 86 (‘Probe 1’ and ‘Probe 2’)” specific for “targets 80, 82

(‘Target 1’ and ‘Target 2’).” EX1004 ¶ 49, Fig. 3; EX1007 at 13:14-17; *see also* EX1004 ¶¶ 50, 63-67, Fig. 5².

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. EX1002 ¶¶ 165-166. For example, Figure 9 depicts a 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

² 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.

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 seven polynucleotides, or at a minimum renders such obvious, a POSA would likewise have understood Saxonov teaches using at least seven corresponding hybridization probes. EX1002 ¶ 167.

5. wherein each hybridization probe comprises at least one fluorophore selected from four fluorophores, and

Saxonov discloses using at least seven hybridization probes, each comprising at least one of four fluorophores. EX1002 ¶¶ 168-174. As discussed, at least seven hybridization probes labeled with at least one of four fluorophores is sufficient to detect seven targets. *See supra* Sections X.A.3, X.A.4.

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 teaches labeling each probe with one or more of these fluorophores. EX1002 ¶ 169; 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 a range of different number of fluorophores, including up to four, can be used. EX1002 ¶ 170. Indeed, Saxonov would have just stated “up to three,” or something similar, if it intended to use no more than three fluorophores. *Id.*

Labeling probes with at least one fluorophore selected from four different fluorophores would have been an obvious design choice for a POSA in light of the instruments available at the time. EX1002 ¶¶ 171-172. Indeed, the ’051 patent acknowledges that four is the natural number of different fluorophores to select from because this was the number of colors 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.

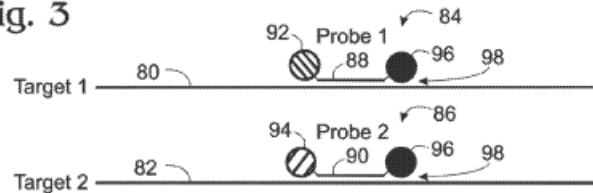
EX1001 at 37:27-32. This limitation of four-color instruments alone would have motivated a POSA to label probes with no more than four fluorophores—one for each color. EX1002 ¶ 173. Notably, nowhere does the specification suggest that it would be novel or inventive to use the four colors that were available on “widely used” instruments or that four is a novel or inventive number of fluorophores. *Id.*

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 or colors for multiplex detection of biological targets. *Id.* ¶ 174. Moreover, as explained above, using four colors with each at two intensities results in four clusters or populations of signal data for the possible combinations for each of the colors used that must be distinguished, rather than eight populations when using three intensities. *See supra* Section X.A.3; 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 ¶ 174.

6. wherein each hybridization probe, when excited and when contacted with its corresponding polynucleotide analyte, generates a cumulative intensity signal,

Saxonov discloses that each hybridization probe, when excited and when contacted with its corresponding polynucleotide analyte, generates a cumulative intensity signal. EX1002 ¶¶ 175-179; EX1004 ¶¶ 49-52. For instance, Saxonov discloses probes that hybridize to their targets and that include fluorescent labels detectable by excitation:

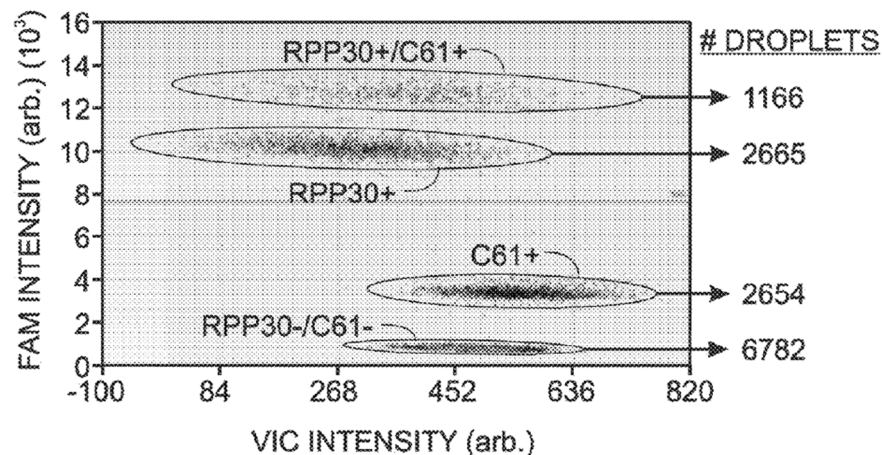
Fig. 3



EX1004 Fig. 3. 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 ¶ 176.

Saxonov discloses numerous examples of signals generated from excitation of fluorophores present in 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 ¶¶ 177-179.

7. further wherein each generated cumulative intensity signal comprises at least one signal generated by excitement of at least one of the four fluorophores;

Saxonov discloses that each generated cumulative intensity signal comprises signal generated by exciting at least one fluorophore label of the hybridization probes. EX1002 ¶¶ 180-185; EX1004 ¶ 37. For example, each positive droplet (C61+, RPP30+, and RPP30+/C61+) in Figure 5 includes signal from the FAM fluorophore label. EX1004 ¶¶ 63-67, Fig. 5; EX1007 at 17:4-19:9, 18:5-21; 5:19-6:3. As Dr. Batt explains, Saxonov discloses the exact type of fluorophore-bearing probes that Patent Owner contends infringe the claims. EX1002 ¶ 183. A POSA would understand that the signals from these fluorophores are generated by excitation and that they lead to the claimed cumulative intensity signals. *Id.*

Likewise, Saxonov teaches generating cumulative intensity signals comprising signals from different fluorophores used to label probes for the same target. Figure 10, for instance, illustrates cumulative intensity signals comprising signals from two different fluorophores used to label sequence-specific probes for

three different targets. EX1004 ¶¶ 77, 79, Fig. 10; EX1007 at 2:15-3:3, 3:15-4:15, 9:4-10:3; EX1002 ¶ 184.

A POSA would have understood that a cumulative intensity signal generated using a probe comprising fluorophores would include at least one color signal generated by excitement of at least one fluorophore. EX1002 ¶ 185.

8. b) contacting said sample solution volume with the plurality of hybridization probes and

Saxonov discloses contacting the sample solution volume with the plurality of hybridization probes in disclosing a sample having a volume comprising polynucleotide analytes and probes that hybridize to them. EX1002 ¶¶ 186-189; EX1004 ¶¶ 17-18, 77, Fig. 9; EX1007 at 6:21-7:10, 12:21-13:8.

This disclosure meets the construction apparently urged by Patent Owner in related proceedings because, as Dr. Batt explains, Patent Owner accuses Petitioner of infringing claim 1 wherein the sample solution is contacted with the various hybridization probes through the process described above for providing the sample solution. EX1002 ¶ 188; EX1012 at 28-42.

9. exciting the hybridization probes to generate the cumulative intensity signal(s) if one or more of the at least seven polynucleotide analytes is present in the sample volume; and

Saxonov discloses exciting labels of hybridization probes to generate cumulative intensity signal(s) signaling the presence of polynucleotide analytes in

the sample volume. EX1002 ¶¶ 190-194; EX1004 ¶¶ 5, 20, 37, 79, Figs. 4-8, 10; EX1007 at 12:21-13:8.

A POSA would have also understood from Saxonov that the hybridization probes for the at least seven polynucleotide analytes that a POSA would have included, as discussed above, would generate cumulative intensity signal(s) if the corresponding polynucleotides were present and excited as intended to generate detectable signal(s). EX1002 ¶¶ 192-194.

10. c) measuring the cumulative intensity signal(s), thereby generating a cumulative signal measurement,

Saxonov teaches measuring cumulative intensity signal(s) to generate a cumulative signal measurement. EX1002 ¶¶ 195-200. For example, Saxonov Figure 4 depicts measuring signals in its graphical trace of light signal(s) from probes in a digital PCR assay and Figure 5 graphs measured intensities of different signals in droplets, including the intensities for C61+, RPP30+, and RPP30+/C61+, which constitutes cumulative signal measurement. EX1002 ¶¶ 197-199; 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, 9:4-15, 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; 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 ¶ 200; EX1004 ¶¶ 12, 20, 53, 76-78, Figs. 4-5, 10; EX1007 at 9:4-15. Thus, a POSA would have understood Saxonov to teach obtaining a cumulative signal measurement including each signal of the potential signals from the included probes to identify and quantify the polynucleotide analyte(s) present. EX1002 ¶ 200.

11. wherein the cumulative signal measurement non-degenerately indicates the presence or absence of the at least seven polynucleotide analytes, in any combination of presence or absence,

Saxonov renders obvious the cumulative signal measurement non-degenerately indicating the presence or absence of the at least seven polynucleotide analytes, in any combination of presence or absence. EX1002 ¶¶ 201-207. This claim element merely reflects the results of analyzing the claimed “at least seven” polynucleotides using the components that are already as part of the method steps discussed above. *See supra* Sections X.A.3-X.A.5. As such, the basis for why this element would have been obvious in the context of the remaining claim elements is amply set forth above. *See id.*

Briefly, Saxonov discloses the unambiguous detection of multiple analytes using multiple different colors and signal intensities to distinguish among polynucleotides. EX1002 ¶ 203; *supra* Section X.A.3; 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 emit one of two or three different intensities to distinguish the presence or absence of any combination of nine targets. EX1002 ¶ 203; EX1004 ¶ 13, 20, 60-67, Fig. 5; EX1007 at 5:19-6:3; *supra* Section X.A.3. A POSA would have understood Saxonov to teach and/or render obvious selecting color labels from four different colors. EX1002 ¶ 204. Saxonov likewise teaching to use two or three different intensities per color provides more than seven distinct labels. *Id.*; *see supra* Sections X.A.3, X.A.5. 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.3, X.A.5; EX1004 ¶ 20 (describing that “an assay for three targets may generate eight clusters...separated by intensity”). 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. EX1002 ¶¶ 205-206; EX1001 at 25:1-2, 23:41-43, 23:59-24:19 (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.3; EX1002 ¶ 207. A POSA would have had a reasonable expectation of success because using multiple single color probes of varying intensities was well-known. *Id.*

12. wherein said method non-degenerately detects the presence or absence of the at least seven polynucleotide analytes in said single sample solution volume, in any combination of presence or absence,

“A whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.” *Minton v. Nat'l Ass'n of Sec. Dealers, Inc.*, 336 F.3d 1373, 1381 (Fed. Cir. 2003). Given that this clause merely states the desired outcome of the claim and is redundant of prior claim elements, it is not entitled to any patentable weight. EX1002 ¶ 208.

To the extent this clause is nonetheless deemed a limitation, it is disclosed in Saxonov for the reasons stated above. *See* Section X.A.11. Briefly, Saxonov discloses techniques non-degenerately detecting the presence of, for instance, eight different targets in a droplet by associating the targets with different intensity/color combinations. *Id.* 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 ¶¶ 209-210; *see infra* Section X.A.13.

To the extent Patent Owner contends that “single sample solution volume” in this clause does not encompass a droplet and instead refers only to a “sample

volume” that is used to generate droplets, the claim remains invalid because Saxonov teaches using the total number of droplets that are positive and negative for the target with Poisson statistics to “determine the concentration” of each 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.”). This allows one to non-degenerately detect the presence or absence of any number of polynucleotide analytes in the single sample solution volume, in any combination of presence or absence. As Dr. Batt explains, this is how Patent Owner contends the products that are accused of infringing operate. EX1002 ¶ 211.

13. without requiring any step of immobilization of said polynucleotide analytes, physical separation of said polynucleotide analytes, or mass spectrometry.

Saxonov teaches the detection of multiple polynucleotide analytes without immobilization of the polynucleotide analytes or mass spectrometry. EX1002 ¶¶ 212-213. As to no physical separation, Saxonov discloses forming droplets. *Id.* ¶ 214. But as Patent Owner construes the claims, this presents no barrier to invalidity. *Id.* ¶¶ 215-217. Saxonov expressly teaches detecting and measuring multiple polynucleotide analytes and multiple copies of the same polynucleotide analytes in the same droplet. *See supra* Sections X.A.2-X.A.12; EX1004 ¶¶ 78-79, Figs. 9-10; EX1007 at 13:10-13, 17:4-19:23 (Example 3), 4:17-20, 5:19-6:5, 9:4-15,

2:15-3:3, 12:21-13:8, Examples 2-4, Fig. 5. Indeed, the very products that Patent Owner accuses of infringing in parallel litigation include droplet formation, such that Patent Owner cannot in this proceeding credibly contend that the use of droplets in Saxonov prevents it from rendering the claims obvious. EX1002 ¶ 215. Further, Saxonov expressly teaches detecting and measuring multiple polynucleotide analytes and multiple copies of the same polynucleotide analytes in the same droplet. *Id.* ¶ 216; EX1004 ¶¶ 78-79, Figs. 9-10 EX1007 at 13:10-13, 17:4-19:23 (Example 3), 4:17-20, 5:19-6:5, 9:4-15, 2:15-3:3, 12:21-13:8, Examples 2-4, Fig. 5.

B. Claim 2: The method of claim 1, wherein said hybridization probes comprise an identical fluorophore, and wherein said plurality of hybridization probes are specific for different polynucleotide analytes.

Saxonov teaches using hybridization probes that include an identical fluorophore where the hybridization probes are specific for different polynucleotide analytes. *See supra* Section X.A.4, 11; EX1002 ¶¶ 218-225. As discussed above, specifically, Saxonov teaches an assay using sets of hybridization probes specific for different polynucleotide analytes that include single color labels of different intensity. *See supra* Sections X.A.3, X.A.5.

A POSA would have understood that generating signals with the same colors using the same fluorophores would have been straightforward relative to methods using different fluorophores, even if they were similar, to minimize differences in the generated signals. EX1002 ¶¶ 221-224; EX1004 ¶ 51.

Having two or more probes labeled using the same fluorophore that are specific for different polynucleotide analytes meets the claim construction urged by Patent Owner in related proceedings, as Dr. Batt explains, in which Patent Owner contends that probes labeled with the same FAM fluorophore with a low intensity signal for one polynucleotide analyte and a high intensity signal for a second polynucleotide analyte in an accused product infringe claim 2. EX1012 at 60-61; EX1002 ¶ 225. Specifically, Patent Owner accuses Petitioner of infringing claim 2 because one of Petitioner's assays allegedly includes two hybridization probes singly-labeled with the same FAM fluorophore label to generate different intensity signals (probes for PLA1 at low intensity and CCND1 at high intensity), along with additional singly-labeled probes using different fluorophore labels for different polynucleotide analytes. *Id.*; EX1012 at 60-61, 96-97.

C. Claim 3: The method of claim 1, wherein said detecting is performed with a plurality of hybridization probes comprising different fluorophores, wherein said plurality of hybridization probes are specific for different analytes.

Saxonov discloses performing the detecting of claim 1 with a plurality of hybridization probes comprising different fluorophores wherein the plurality of hybridization probes are specific for different analytes. *See supra* Sections X.A.4-5, 11, X.B; *see, e.g.*, EX1004 ¶¶ 20, 51; EX1007 at 2:11-17, 3:15-20, 7:9-10, 13:14-16, Fig. 3; EX1002 ¶¶ 226-229. Using a plurality of hybridization probes including different fluorophores where the different probes are specific for different

polynucleotide analytes to detect and identify the different analytes was well-known in the art. EX1002 ¶ 229.

D. Claim 4: The method of claim 1, wherein said cumulative intensity signal(s) are generated during a polymerase chain reaction.

Saxonov discloses generating the cumulative intensity signal(s) during a polymerase chain reaction. EX1002 ¶¶ 230-235; EX1004 ¶ 5; EX1007 at 2:7-9, Figs. 3-4. In Saxonov, a probe that includes fluorophore label(s) and a quencher is hybridized to the PCR template, wherein the polymerase extending through the target sequence during the primer extension reaction cleaves the bound hybridization probe, uncoupling the fluorophore(s) from the quencher, and thereby generates a color signal. 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 this uncoupling occurs during the polymerase chain reaction. EX1002 ¶¶ 232-235; EX1004 ¶¶ 52-53, Figs. 3-4; *see supra* Section II.

XI. GROUND 2: OBVIOUSNESS OF CLAIMS 5-6 IN VIEW OF SAXONOV AND SILVERBROOK

A. Claim 5: The method of claim 1, further comprising transmitting information concerning the presence or absence of said polynucleotide analytes through a computer network.

Saxonov, as described above, renders obvious the method of claim 1. *See supra* Section X.A. Claim 5 would have been obvious in further view of Silverbrook's teaching of a nucleic acid testing device and method that employs PCR

and hybridization to identify what analytes are present in a sample and transmitting results of the testing through a computer network. EX1002 ¶¶ 236-247; 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 ¶ 253.

B. Claim 6: The method of claim 1, further comprising providing information concerning the presence or absence of said polynucleotide analytes to a health care professional, wherein the health care professional makes a clinical decision based on said information.

To the extent that Saxonov, as described above, does not disclose the further limitations of claim 6, they would have been obvious in further view of Silverbrook’s teaching that quantifying the starting amount of different nucleic acids in patient samples 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

¶¶ 248-253. 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. *Id.*

XII. GROUND 3: OBVIOUSNESS OF CLAIM 7 IN VIEW OF SAXONOV AND MALTEZOS

Saxonov discloses that at least one step of the method is performed using a computer. EX1002 ¶¶ 254-262. Saxonov discloses that apparatus for performing its method includes a “data processing assembly,” which a POSA would have understood to be a computer that is used to perform calculations required for steps of the method, including measuring and thereby generating a cumulative signal measurement. EX1002 ¶¶ 255-256; EX1004 ¶ 45; EX1007 at 12:21-13:8 (citing US 2010/0173394, incorporated by reference). To the extent Patent Owner contends that Saxonov, as applied to claim 1, as set forth above, 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. EX1002 ¶ 257.

Maltezos discloses an apparatus 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 the detection region 1113 of the apparatus in which fluorescence measurements from the PCR are detected. EX1010 ¶¶ 12, 60, Fig. 11; EX1002 ¶ 258. A POSA would have understood

Maltezos' control assembly to include a computer based on the disclosure of the control assembly and detection electronics and would have further understood it to teach that the computer performs the detecting and/or measuring step. EX1002 ¶ 259.

Given the teachings of Saxonov and Maltezos, a POSA would have found it obvious to use a computer to perform the measuring (and calculating) step. *Id.* ¶ 260. A POSA would have been motivated to use a computer to facilitate operations and calculations necessary to measure cumulative intensity signal(s) and determine the presence of the seven polynucleotide analytes. *Id.* ¶ 261. A POSA would have also had a reasonable expectation of success. *Id.* ¶ 262.

XIII. GROUND 4: OBVIOUSNESS OF CLAIMS 8-9 IN VIEW OF SAXONOV, MALTEZOS, AND OH

A. Claim 8: The method of claim 7, 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...may be operatively connected to one another.” EX1004 ¶ 45 (describing Fig. 2); EX1007 at 12:2-9; EX1002 ¶¶ 263-272.

A POSA would have understood “operatively connected” to include remote connection such as by the “computer [being] located on a remote server.” EX1002 ¶ 265. To the extent Patent Owner contends that Saxonov, alone or with Maltezos (as applied to claim 7), does not disclose or render obvious locating the computer on a remote server, this would have been obvious in further view of Oh. *Id.* ¶ 267.

Oh discloses a PCR module and method, wherein the module includes a computing unit 41 that “performs appropriate computation based on 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 ¶ 268. A POSA would have understood the “appropriate computation” that remote host computer 50 performs to include computations for detecting and/or measuring steps. EX1002 ¶ 269.

Given the teachings of Saxonov and Oh, a POSA would have found it obvious to use a remote computer to perform the measuring (and calculating) step. EX1002 ¶ 270. A POSA would have understood that computers for performing analytical processes are routinely located remotely from analytical equipment for numerous benefits, including to allow performing analyses for a number of analytical devices, and would have had a reasonable expectation of success. EX1002 ¶¶ 271-272.

B. Claim 9: The method of claim 7, wherein said computer is located on a thermal cycler.

Saxonov teaches locating the computer on a thermal cycler. EX1002 ¶¶ 273-276. Saxonov discloses an exemplary apparatus for the assay that includes a “thermal incubation assembly, such as a thermocycler” and “a processor.” EX1004 ¶ 45; EX1007 at 11:14-12:11. Saxonov further discloses that the processor “may be, or may be included in, a controller that communicates with and controls operation of any suitable combination of assemblies.” EX1004 ¶ 45. Saxonov also discloses that the combination of assemblies “may be operatively connected to one another and/or...unconnected to the other assemblies.” *Id.*

To the extent Patent Owner contends that Saxonov, as set forth above for claim 1, does not disclose or render obvious locating the computer on a thermal cycler, this would have been obvious in further view of Oh. EX1002 ¶¶ 277-281. Oh discloses a PCR module and method of using the module, wherein the module is “a combined PCR thermal cycler and PCR product detector” that includes “heater 20...to apply heat to the PCR tube[s]” and a computing unit 41 that “performs appropriate computation based on the data received from...sensors.” EX1011 ¶¶ 17, 58, Abstract. A POSA would have understood included computing unit 41 to be located on the thermal cycler as it is part of the same combined apparatus, i.e., the PCR module. EX1002 ¶ 279. A POSA would have further been motivated to locate

the computer on the thermal cyclers for the benefits discussed above and would have had a reasonable expectation of success. EX1002 ¶¶ 280-281.

XIV. GROUND 5: OBVIOUSNESS OF CLAIMS 1-4 IN VIEW OF SAXONOV IN FURTHER VIEW OF KRAMER AND/OR LARSON

As documented above, Saxonov discloses or renders obvious claims 1-4. *See supra* Sections X.A-X.D. The claims would also have been obvious based on Saxonov in further view of Kramer and/or Larson. EX1002 ¶¶ 282-310.

This ground is identical in all respects to Ground I, except that the teachings of Kramer and/or Larson are used with respect to three specific claim elements that pertain to the claimed numbers of targets and fluorophores:

- “comprising or potentially comprising, at least one of at least seven polynucleotide analytes”
- “wherein each hybridization probe comprises at least one fluorophore selected from four fluorophores”
- “wherein the cumulative signal measurement non-degenerately indicates the presence or absence of the at least seven polynucleotide analytes, in any combination of presence or absence”

As set forth below, to the extent one contends that the foregoing claim elements are not taught or rendered obvious by Saxonov alone, a POSA would have found it obvious to modify Saxonov’s methods based on the teachings of Kramer and/or Larson so as to achieve a method that includes these elements. EX1002 ¶ 283.

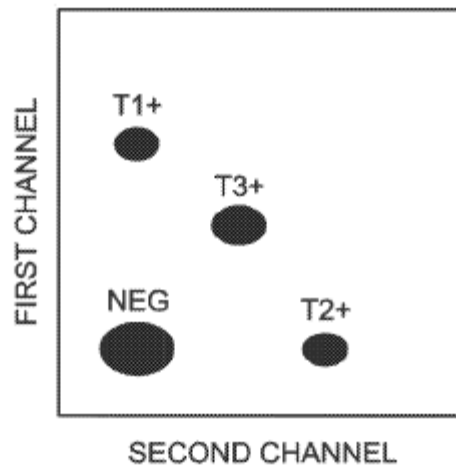
Saxonov, Kramer, and Larson are analogous art to the '051 patent—and to each other—because they are within the same field of endeavor: multiplex detection of polynucleotide analytes using color-labeled sequence-specific probes, including where there are fewer different colors than analytes. EX1001 at code (57), 12:29-14:2, 19:35-38, 23:31-25:30; EX1004 ¶¶ 19, 20, 37; EX1008 ¶¶ 8-12, 14, 22, 31, Fig. 1; EX1017 ¶¶ 34, 35, 138-153; EX1002 ¶ 284.

A. Claim 1: comprising or potentially comprising, at least one of at least seven polynucleotide analytes, and

As documented above, Saxonov alone discloses this element. *See supra* Section X.A.3. To the extent Patent Owner contends otherwise, it would have nonetheless been obvious to analyze at least seven analytes further in view of Kramer and/or Larson. EX1002 ¶¶ 285-294.

Saxonov already teaches a multiplexing method wherein multiple colors can be used to distinguish targets. *Id.* ¶¶ 286-287. Specifically, Figure 10 of Saxonov teaches an approach to detecting three targets based on just two colors, wherein a first target (T1) is identified by a first color signal, a second target (T2) is identified by a second color signal, and a third target (T3) is identified by the presence of both color signals:

Fig. 10



EX1004 Fig. 10, ¶¶ 18, 78-79. This approach wherein targets are detected and distinguished from one another based on combinations of colors is similarly taught in the '013 provisional, which teaches that signals can be “collected in one or more different channels” from “the same” target. *See* EX1007 at 9:8-10. Importantly, Saxonov contemplates that if droplets are generated that have combinations of multiple targets, the droplets with the different combinations of targets can be distinguished from one another. *See, e.g., id.* ¶ 78 (“To simplify the presentation, double-positive populations (T1+/T2+, T1+/T3+, and T2+/T3+) and the triple-positive population (T1+/T2+/T3+) are not shown.”).

Kramer, for its part, teaches that Saxonov’s approach of using combinations of different colors to distinguish targets can be extended to even larger numbers of targets. EX1002 ¶ 288. As Kramer states, for instance, “[a]ssays according to this invention are highly multiplexed assays...capable of detecting any of at least six,

preferably at least 10, and in certain embodiments 30-60 and even possibly more target sequences.” EX1008 ¶ 8; *see also id.* ¶¶ 30. As documented above, Kramer achieves these highly multiplexed assays by using larger numbers of colors to distinguish larger numbers of targets:

TWO COLORS PER PROBE:

PANEL OF 4(a, b, c, d), 5(+e), 6(+f), 7(+g) or 8(+h) FLUOROPHORES

[illegible]

THREE COLORS PER PROBE:

PANEL OF 5(a, b, c, d, e), 6(+f), 7(+g) or 8(+h) FLUOROPHORES

[illegible]

FIGURE 1

EX1008 at Fig. 1; *see also supra* Part V.B.2.

Larson, like Kramer and Saxonov, also teaches higher-plex assays for seven or more polynucleotide analytes. EX1002 ¶¶ 289-291; EX1017 ¶ 150 (disclosing a nine-plex assay using “just two colors (probes containing FAM and VIC fluorophores)”). Larson further teaches adding additional colors to further expand multiplexing. EX1017 ¶ 153 (“multiplexing capacity exceeding 50x can be envisioned”); *id.* ¶ 47 (“adding multiple colors increases the number of possible reactions geometrically”); EX1002 ¶ _____. Importantly, in Figure 15, Larson teaches that differences in intensity can be used to distinguish droplets with different target types, showing data for an assay that distinguishes droplets nine different types of targets:

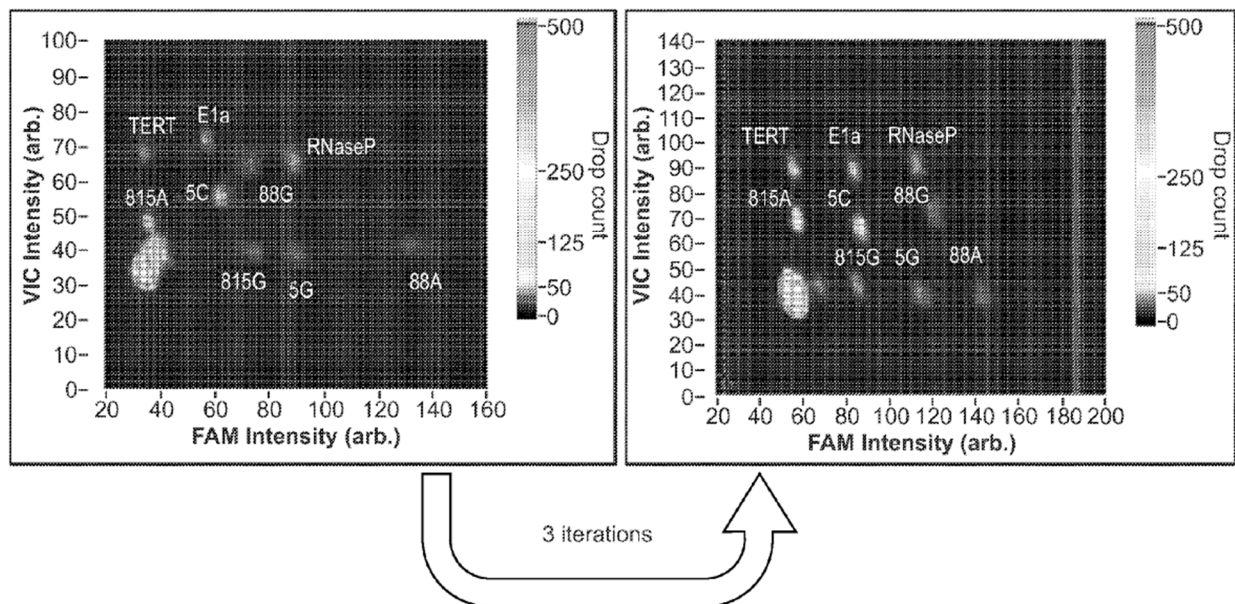


FIG. 15

EX1017 at Fig. 15; *id.* ¶¶ 34, 145-153.

It would have been obvious to modify the two-color approach in Figure 10 of Saxonov, which is used for three targets, for the detection of at least seven targets. EX1002 ¶ 292. One would have done this by increasing the number of colors and then using intensity as needed to distinguish droplet types, as taught in Kramer and Larson. *See infra* Section XIV.C.

A POSA would have been highly motivated to do this. EX1002 ¶ 293. A POSA would have understood the benefits of a higher-plex assay, including increased throughput while using less sample and reagents. *Id.* For example, Kramer discloses that treatment of the HIV-1 virus requires determining which of about 30 mutations may be present. EX1008 ¶ 4. As pertains to this and other diseases, a POSA would be motivated to increase an assay's throughput "to screen for an early indication of one of numerous possible infectious agents that may be the cause of the patient's symptoms." EX1002 ¶ 293. Similarly, Larson explains "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 success in modifying Saxonov because such higher-plex assays are in the prior art. EX1002 ¶ 294. Both

Kramer and Larson teach higher multiplex for greater numbers of targets. EX1008 ¶¶ 8, 22, 31, Fig. 1; EX1017 ¶¶ 108, 138-43, 150-53, Fig. 15. In addition, Kramer teaches techniques analogous with those in Saxonov that enables higher-plex assays. *See, e.g.*, EX1008 Fig. 1 (mapping combinations of colors to targets); *id.* ¶ 11 (panel of four fluorophores); *id.* ¶¶ 11, 31 (types of fluorophores); *id.* ¶ 42 (avoiding degeneracy). Moreover, Larson teaches distinguishing at least nine targets using combinations of two colors and varying intensities. EX1017 ¶¶ 134-138, 150-151, Figs. 12, 15. A POSA would have reasonably expected success in so modifying Saxonov.

B. Claim 1: wherein each hybridization probe comprises at least one fluorophore selected from four fluorophores, and

As discussed above, Saxonov already discloses multiple fluorophore types, and in Figure 10 specifically teaches an approach that uses two fluorophores to detect and distinguish among three targets and droplets containing combinations thereof. *See supra* Part XIV.A. To the extent Patent Owner contends Saxonov does not disclose using four fluorophores, it would have been obvious to modify Saxonov in view of Kramer and/or Larson to use four fluorophores. EX1002 ¶¶ 295-300.

Kramer, for instance, teaches using four fluorophores. EX1008 ¶ 11 (“The different fluorophores are from a panel of at least four distinguishable fluorophores.”); *see also id.* ¶¶ 22, 30-31, Fig. 1. So too does Larson. 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. A POSA would have understood that four fluorophores is sufficient to create combinations of colors and/or intensities for detecting at least seven polynucleotide analytes. EX1002 ¶¶ 296-298.

A POSA would have been motivated to label hybridization probes with at least one of four fluorophores as taught in Kramer and Larson. EX1002 ¶ 299. Indeed, Kramer and Larson already proposed precisely this. This is unsurprising because, as summarized above, increasing the number of fluorophores, would allow for one to increase the number of targets one can detect. *See supra* Section XIV.A. Further, as discussed above, the use of four fluorophores would have been an obvious design choice because, as the '051 patent acknowledges, widely available instruments already came pre-packaged with four-color detection capability. *See supra* Sections XIV.A, X.A.3, X.A.5; *see also* EX1008 ¶ 20; EX1017 ¶ 5.

A POSA would have expected the use of four fluorophores to succeed for a variety of reasons. EX1002 ¶ 300; *see supra* Section XIV.A. Most important, Kramer and Larson already expressly taught the use of four fluorophores, which is confirmation that the skilled artisans had long believed the approach of using four fluorophores would be successful. Saxonov itself already discloses at least five well-known fluorophores suitable for labeling hybridization probes, including FAM, VIC, ROX, TAMRA, and JOE, from which a POSA would have easily been able to

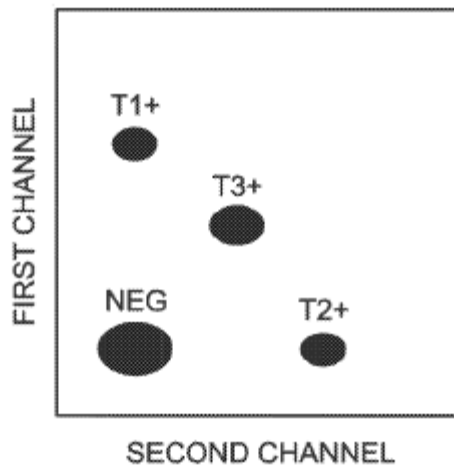
select four for target detection. EX1004 ¶¶ 49, 51, Fig. 3; EX1007 at 14:20-21, 4:20-23. There is likewise no question that four fluorophores would be successful from an instrumentation and hardware perspective because, as the '051 patent itself acknowledges, widely used instrumentation already used four different colors.

C. Claim 1: wherein the cumulative signal measurement non-degenerately indicates the presence or absence of the at least seven polynucleotide analytes, in any combination of presence or absence,

As documented above, Saxonov alone discloses this element. *See supra* Section X.A.11. To the extent Patent Owner contends otherwise, a skilled artisan would be motivated to modify the approach of Figure 10 of Saxonov based on the teachings of Kramer and/or Larson to include additional colors so as to allow for the non-degenerate detection of at least seven targets in any combination of presence or absence. EX1002 ¶¶ 301-310. A skilled artisan would have further had a reasonable expectation of successfully making such a modification. *Id.*

As discussed above, Figure 10 of Saxonov discloses an approach for the detection of three targets using just two colors. Saxonov contemplates that when combinations of targets are present in a droplet, the different combinations of droplets will yield cumulative intensity signals that can be distinguished from one another. This is shown in Figure 10, which shows how droplets with different targets will yield different signals:

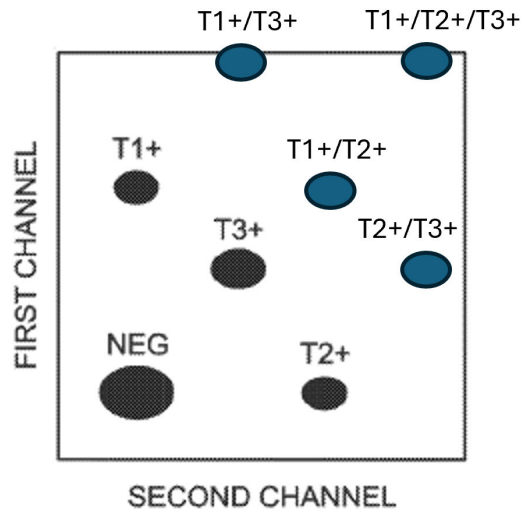
Fig. 10



EX1004 Fig. 10, ¶¶ 18, 78-79; EX1002 ¶ 302.

Though the figure does not show the signals for the droplets that have multiple targets, the text nonetheless contemplates that one will be able to distinguish droplets any combinations of targets. *See, e.g., id.* ¶ 78 (“To simplify the presentation, double-positive populations (T1+/T2+, T1+/T3+, and T2+/T3+) and the triple-positive population (T1+/T2+/T3+) are not shown.”). Indeed, based on the intensities in the figure above, one can extrapolate and modify the figure to show where the populations of droplets with all the different combinations of targets would appear in the figure, had they been included:

Fig. 10



EX1002 ¶ 302. As this modified figure shows, any combination of three targets can easily be uniquely identified. Saxonov itself teaches precisely this, stating that “three targets may generate eight clusters or populations of data, *separated by intensity*.” EX1004 ¶ 20.

As discussed above, a POSA would have been motivated to identify seven or more targets in any combination of presence or absence. *See supra* Part XIV.A. A skilled artisan would have been motivated to do this through a straightforward modification of Saxonov based on the teachings of Kramer, which teaches using greater numbers of colors. Kramer, for instance, teaches distinguishable combinations using two or three colors per set of probes for polynucleotide analytes, with colors chosen from a panel of four colors. *See supra* Section XIV.B; EX1008 ¶¶ 22, 30, Fig. 1. Kramer, in fact, teaches using even more than four colors. *See* EX1008 Fig. 1.

Nevertheless, the detection of seven targets using four colors, as taught in Kramer, would be straightforward by any one of many different approaches, and something that a skilled artisan would have reasonably expected would succeed. For instance, a skilled artisan would have easily used the pre-existing approach of Saxonov. A skilled artisan would have used two of the four colors for three targets using the approach of Figure 10 of Saxonov, and the remaining two distinct colors would then be used for another three targets, also using the approach of Figure 10. A seventh target would, as an example, be detected by the presence of three colors at a third intensity. EX1002 ¶¶ 302-304.

A skilled artisan would understand that the signals from such targets could be easily distinguished based on intensity, just as in Figure 10 of Saxonov, with the intensity of single color, two-color, and three-color labels all differing from one another. *Id.* ¶ 305. In this regard, Larson teaches tuning the intensity of probes corresponding to different targets to optimize their detection, in the same manner as in Saxonov. *Id.* ¶¶ 134-137 (describing methods to adjust probe intensity); EX1004 ¶¶ 51-52. Using this approach, Larson teaches distinguishing nine different types of droplets, as shown in Figure 15. EX1017 at Fig. 15.

To the extent one nonetheless encounters overlap in the signals arising from different combinations of targets (*i.e.*, degeneracy) when seeking to modify Saxonov, a skilled artisan would have followed the teachings of Kramer to address

the problem. EX1002 ¶¶ 306-308. Kramer teaches that degeneracy can be overcome, when it occurs, by using a “repeat assay utilizing an alternative coding scheme for the targets.” EX1008 ¶ 42. Indeed, a POSA would understand that Kramer’s teachings to this effect are little different from those in the ’051 patent, which proposes to address potential degeneracies simply by removing the problematic targets from the experiment. *See* EX1001 at 14:41-43, 19:28-34, 41:56-58; EX1002 ¶ 309. As in Kramer, this would necessitate modifying the coding scheme by removing degenerate potential signals and performing an additional assay(s) to detect any targets that could not otherwise be distinguished due to degeneracy. *Id.*

Notably, as confirmation that overcoming degeneracy would have been obvious, Patent Owner itself contends in parallel district court litigation that Larson can be combined with references detailing statistical approaches to overcome degeneracy. *See* EX1019 at 4-8; EX1020; EX1021; EX1002 ¶ 310.

XV. GROUNDS 6-8: OBVIOUSNESS OF CLAIMS 6-9

As documented above in Grounds 2-4, claims 6-9 is disclosed in Saxonov in view of Silverbrook (claims 5-6), Maltezos (claim 7), and Maltezos and Oh (claims 8-9). *See supra* Sections XI-XIII. For the same reasons in Grounds 2-4, claims 6-9 are also rendered obvious by the combination of Saxonov with Kramer and/or Larson, in further view of Silverbrook, Maltezos, and Oh. EX1002 ¶¶ 311-312.

XVI. 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 and Kramer were nominally of record during examination, based on IDSs filed March 23, 2018 and August 12, 2016. EX1032 at 1, 3, 5, 15. A continuation of Larson was also submitted in an IDS EX1032 at 9, 13; EX1022; EX1033; EX1001. But none of these references were 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 Nie et al., alone or in combination with other references, grounded on its disclosed use of multicolor quantum dots within microbeads, which applicant overcame by amending the claims to recite that the method is carried out “without a step of ‘immobilization of said analytes, physical separation of said analytes, or mass spectrometry.’” EX1030 at 7-10; EX1025 at 2-6; EX1026 at 5. The Examiner then rejected then-pending claims

over Lin et al., alone or in combination with other references, grounded on its disclosed use of barcode probes in an assay that relies on detecting colors without regard to intensity, which applicant overcame by amending the claims to recite a step of measuring a cumulative intensity signal. EX1026 at 7-16; EX1034 at 10-13; EX1035 at 2-4; EX1029 at 5-6; EX1031 at 8.

Accordingly, the “the overlap between the arguments made during examination” and arguments made in this petition is minimal. *See 3Shape A/S v. Align Tech., Inc.*, IPR2019-00160, Paper No. 9 at 39-42 (PTAB June 11, 2019).

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 and Kramer, or in references related to Larson.

In the Notice of Allowance, the Examiner did not discuss or cite any teaching from either Saxonov or Kramer (or references related to Larson), instead they stated only that the “claims recite a new and non-obvious assay to detect the presence/absence pattern of seven different analytes using non-degenerate hybridization techniques.” EX1031 at 8. Saxonov, Kramer, and Larson, however, disclose non-degenerate hybridization techniques to detect the presence/absence of more than seven different analytes. *See supra* Sections X.A, XIV; EX1002 ¶¶ 281-

310. Accordingly, the stated reasons for allowance show material error by the Examiner.

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 incomplete and there is no trial date. Courts in the Northern District of California 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. *See, e.g., 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)³ (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 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).

³ The parallel litigation here is also before Judge Davila. EX1019 at 1.

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).⁴ 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).

XVII. CONCLUSION

Petitioner respectfully requests cancellation of the '051 patent.

⁴ 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.

Petition for *Inter Partes* Review of U.S. 10,068,051

Dated: July 15, 2024

Respectfully submitted,

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APPENDIX A: LISTING OF CHALLENGED CLAIMS

No.	Limitation
1	A method of detecting the presence or absence of at least seven polynucleotide analytes, in any combination of presence or absence, in a single sample solution volume, the method comprising: a) providing a sample solution volume comprising or potentially comprising, at least one of at least seven polynucleotide analytes, and comprising at least seven hybridization probes, each hybridization probe corresponding to one of the at least seven polynucleotide analytes, wherein each hybridization probe comprises at least one fluorophore selected from four fluorophores, and wherein each hybridization probe, when excited and when contacted with its corresponding polynucleotide analyte, generates a cumulative intensity signal, further wherein each generated cumulative intensity signal comprises at least one signal generated by excitement of at least one of the four fluorophores; b) contacting said sample solution volume with the plurality of hybridization probes and exciting the hybridization probes to generate the cumulative intensity signal(s) if one or more of the at least seven polynucleotide analytes is present in the sample volume; and c) measuring the cumulative intensity signal(s), thereby generating a cumulative signal measurement, wherein the cumulative signal measurement non-degenerately indicates the presence or absence of the at least seven polynucleotide analytes, in any combination of presence or absence, wherein said method non-degenerately detects the presence or absence of the at least seven polynucleotide analytes in said single sample solution volume, in any combination of presence or absence, without

No.	Limitation
	requiring any step of immobilization of said polynucleotide analytes, physical separation of said polynucleotide analytes, or mass spectrometry.
2	The method of claim 1, wherein said hybridization probes comprise an identical fluorophore, and wherein said plurality of hybridization probes are specific for different polynucleotide analytes.
3	The method of claim 1, wherein said detecting is performed with a plurality of hybridization probes comprising different fluorophores, wherein said plurality of hybridization probes are specific for different analytes.
4	The method of claim 1, wherein said cumulative intensity signal(s) are generated during a polymerase chain reaction.
5	The method of claim 1, further comprising transmitting information concerning the presence or absence of said polynucleotide analytes through a computer network.
6	The method of claim 1, further comprising providing information concerning the presence or absence of said polynucleotide analytes to a health care professional, wherein the health care professional makes a clinical decision based on said information.
7	The method of claim 1, wherein at least one step of said method is performed using a computer.
8	The method of claim 7, wherein said computer is located on a remote server.
9	The method of claim 7, wherein said computer is located on a thermal cycler.

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 13,944 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/
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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of **PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 10,068,051 B2** WITH PETITIONER'S EXHIBIT LIST, POWER OF ATTORNEY, AND EXHIBITS 1001-1038 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

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