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. 11,827,921 B2

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3. wherein said fluorescent signal comprises F wavelength components, and.....28

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c. b. each of said analyte-specific reagents, when contacted with a sample comprising its corresponding analyte, generates the value; 42

3. wherein said kit is capable of unambiguously detecting the presence or absence of each analyte of M analytes in a single sample volume, in any combination of presence or absence, and wherein the kit does not require the use of mass spectrometry or immobilization of said M analytes, and 42

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PETITIONER'S EXHIBIT LIST

Exhibit #	Description
EX1001	U.S. Patent No. 11,827,921 "the '921 patent"
EX1002	Declaration of Carl A. Batt, Ph.D.
EX1003	Joint Claim Construction Statement, filed on June 18, 2024, Dkt No. 65, *ChromaCode, Inc. v. Bio-Rad Laboratories et al.*, Case No. 5:23-cv-06360, N.D. Cal
EX1004	U.S. Patent Application Publication No. US 2013/0040841 A1 "Saxonov"
EX1005	Information Disclosure Statement noting Saxonov from Prosecution File History of U.S. Patent No. 10,068,051 filed on August 5, 2014
EX1006	Notice of Allowance from Prosecution File History of U.S. Patent No. 11,827,921 filed on August 10, 2023
EX1007	U.S. Patent Provisional Application No. 61/510,013 (filed July 20, 2011) (Serge Saxonov, Simant Dube, John F. Regan, applicants) ("the '013 Provisional")
EX1008	Intentionally Left Blank
EX1009	U.S. Patent Application Publication No. US 2011/0312704 A1 "Silverbrook"
EX1010	Intentionally Left Blank
EX1011	Intentionally Left Blank
EX1012	U.S. Patent No. 11,827,921 Infringement Claim Charts from Infringement Contentions, served on March 21, 2024, *ChromaCode, Inc. et al. v. Bio-Rad Laboratories, Inc.*, Case No. 5:23-cv-06360, N.D. Cal.

Exhibit #	Description
EX1013	Internet Archive WayBackMachine, Feb. 22, 2024, archived copy of Synbio Technologies, Precision and Accuracy with TaqMan Probes, https://synbio-tech.com/precision-and-accuracy-with-taqman-probes/, https://web.archive.org/web/20240519044916/https://synbio-tech.com/precision-and-accuracy-with-taqman-probes/, accessed Sept. 12, 2024.
EX1014	Pamela M. Holland, et al., "Detection of specific polymerase chain reaction product by utilizing the 5' → 3' exonuclease activity of *Thermus aquaticus* DNA polymerase," *Proc. Natl. Acad. Sci. USA*, Vol. 88, pp. 7276-7280, August 1991 Biochemistry "TaqMan Paper"
EX1015	Information Disclosure Statement from Prosecution File History of U.S. Patent No. 10,770,170 filed on March 7, 2018
EX1016	Information Disclosure Statement from Prosecution File History of U.S. Patent No. 11,827,921 filed on May 1, 2020
EX1017	U.S. Patent Application Publication No. US 2011/0250597 A1 "Larson"
EX1018	Intentionally Left Blank
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EX1020	Intentionally Left Blank
EX1021	Intentionally Left Blank
EX1022	U.S. Patent No. 9,366,632 "Link"
EX1023	Federal Judicial Caseload Statistics (2023), at https://www.uscourts.gov/statistics-reports/analysis-reports/federal-judicial-caseload-statistics
EX1024	Civil Minutes - General, filed on December 7, 2023, Dkt No. 34, *ChromaCode, Inc. et al. v. Bio-Rad Laboratories*, Case No. 2:23-cv-08417, C.D. Cal.
EX1025	Patent Owner's Response to Non-Final Office Action from Prosecution File History of U.S. Patent No. 11,827,921 filed on March 28, 2023

Exhibit #	Description
EX1026	Final Rejection from Prosecution File History of U.S. Patent No. 11,827,921 filed on May 10, 2023
EX1027	Joint Stipulation and Order Regarding Filing of Second Amended Complaint and Amended Case Schedule, filed on March 27, 2024, Dkt No. 53, *ChromaCode, Inc. v. Bio-Rad Laboratories et al.*, Case No. 5:23-cv-06360, N.D. Cal
EX1028	Amended Complaint for Patent Infringement of U.S. Patent Nos. 10,068,051 and 10,770,170, filed on October 13, 2023, Dkt No. 12, *ChromaCode, Inc. et al. v. Bio-Rad Laboratories*, Case No. 2:23-cv-08417, C.D. Cal.
EX1029	Patent Owner's Response to Final Office Action from Prosecution File History of U.S. Patent No. 11,827,921 filed on July 10, 2023
EX1030	Non-Final Rejection from Prosecution File History of U.S. Patent No. 11,827,921 filed on December 28, 2022
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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 (downloaded July 10, 2024)
EX1038	Shivaprasad H. Sathyanarayana and Lauren M. Wainman, "Chapter 2, Laboratory approaches in molecular pathology: the polymerase chain reaction," Diagnostic Molecular Pathology, 2024
EX1039	U.S. Patent No. 10,068,051 Infringement Claim Charts from Infringement Contentions, served on March 21, 2024, *ChromaCode, Inc. et al. v. Bio-Rad Laboratories*, Case No. 5:23-cv-06360, N.D. Cal.

Exhibit #	Description
EX1040	U.S. Patent No. 10,770,170 Infringement Claim Charts from Infringement Contentions, served on March 21, 2024, *ChromaCode, Inc. et al. v. Bio-Rad Laboratories*, Case No. 5:23-cv-06360, N.D. Cal.
EX1041	Order of Consolidation filed August 16, 2024, Dkt. No. 77, *ChromaCode, Inc. v. Bio-Rad Laboratories, Inc.*, Case No. 5:23-cv-04823, N.D. Cal.
EX1042	Order Reassigning Case filed August 20, 2024, Dkt. No. 78, *In re: ChromaCode Litigation*, Case No. 5:23-cv-04823, Dkt. No. 78, N.D. Cal.

I. INTRODUCTION

Bio-Rad Laboratories, Inc., ("Petitioner") requests *inter partes* review of claims 1-19 of United States Patent No. 11,827,921 ("the '921 patent"), which issued on November 28, 2023. The '921 patent, entitled "Signal Encoding and Decoding in Multiplexed Biochemical Assays," relates to detecting multiple polynucleotides in the same experiment. More specifically, as Patent Owner has confirmed in parallel district court proceedings, the '921 patent encompasses detecting three polynucleotide targets using just two distinct signals. This process, where a single signal is used for each of two targets and the combination of signals is used for a third target, had long been disclosed in Petitioner's own previous patent filings, including the Larson reference principally relied upon herein.

Because Patent Owner's overbroad claims read on Petitioner's own prior art patent filings and otherwise include no novel elements, all claims of the '921 patent should be canceled.

II. TECHNOLOGY BACKGROUND

A. Multiplex PCR Amplification

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

of complementary strands. *Id.* ¶¶ 36-42. One such application is the polymerase chain reaction ("PCR"), wherein DNA fragments/sequences are amplified in repeated cycles. *Id.* ¶¶ 36-39.

PCR involves three steps. *Id.* ¶ 37. First, double-stranded DNA is denatured into single strands. *Id.* Next, primer pairs bind to specific complementary regions of the single strands. *Id.* Then, DNA polymerase extends each primer by adding nucleotides according to the base-pairing rules to form strands complementary to the single-stranded template. *Id.* The resulting double-stranded DNA serve as templates in subsequent PCR cycles. *Id.* RNA may also be the polynucleotide of interest in PCR. *Id.* ¶ 38.

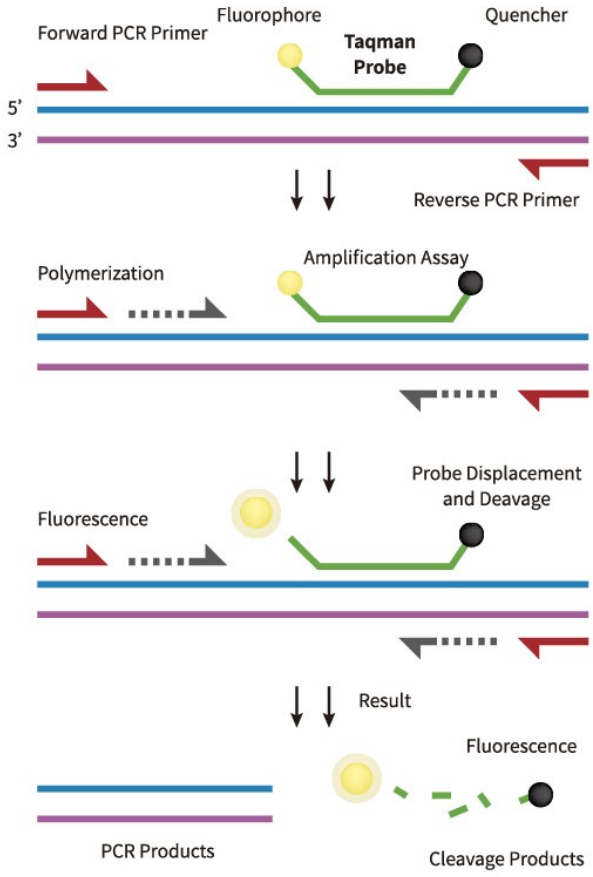
Multiplex PCR amplifies multiple polynucleotide sequences using multiple primer pairs for multiple target sequences in a single reaction volume concurrently. *Id.* ¶ 39. Multiplex PCR was well-known in the art and understood to be faster, less expensive, and more convenient than amplifying each polynucleotide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

B. Fluorescent Signals and Detection of Polynucleotide Analytes

Base-pairing of complementary sequences was also used in methods to generate color signals to detect polynucleotides. EX1002 ¶ 40. Methods include

hybridizing labeled oligonucleotides to specific polynucleotide sequence(s) before measuring the label's signal. *Id.* ¶¶ 40-42.

One well-known technique uses labeled oligonucleotides modified after hybridization to generate a detectable color signal, such as by cleavage of the oligonucleotide. *Id.* ¶¶ 40-42. An example is the TaqMan assay, which uses oligonucleotide probes that bind to a target sequence and that have a fluorophore and a quencher at opposite ends. *Id.* During the extension step of PCR, the exonuclease activity of the polymerase enzyme separates the fluorophore and quencher of bound probes are separated by cleaving the probe:

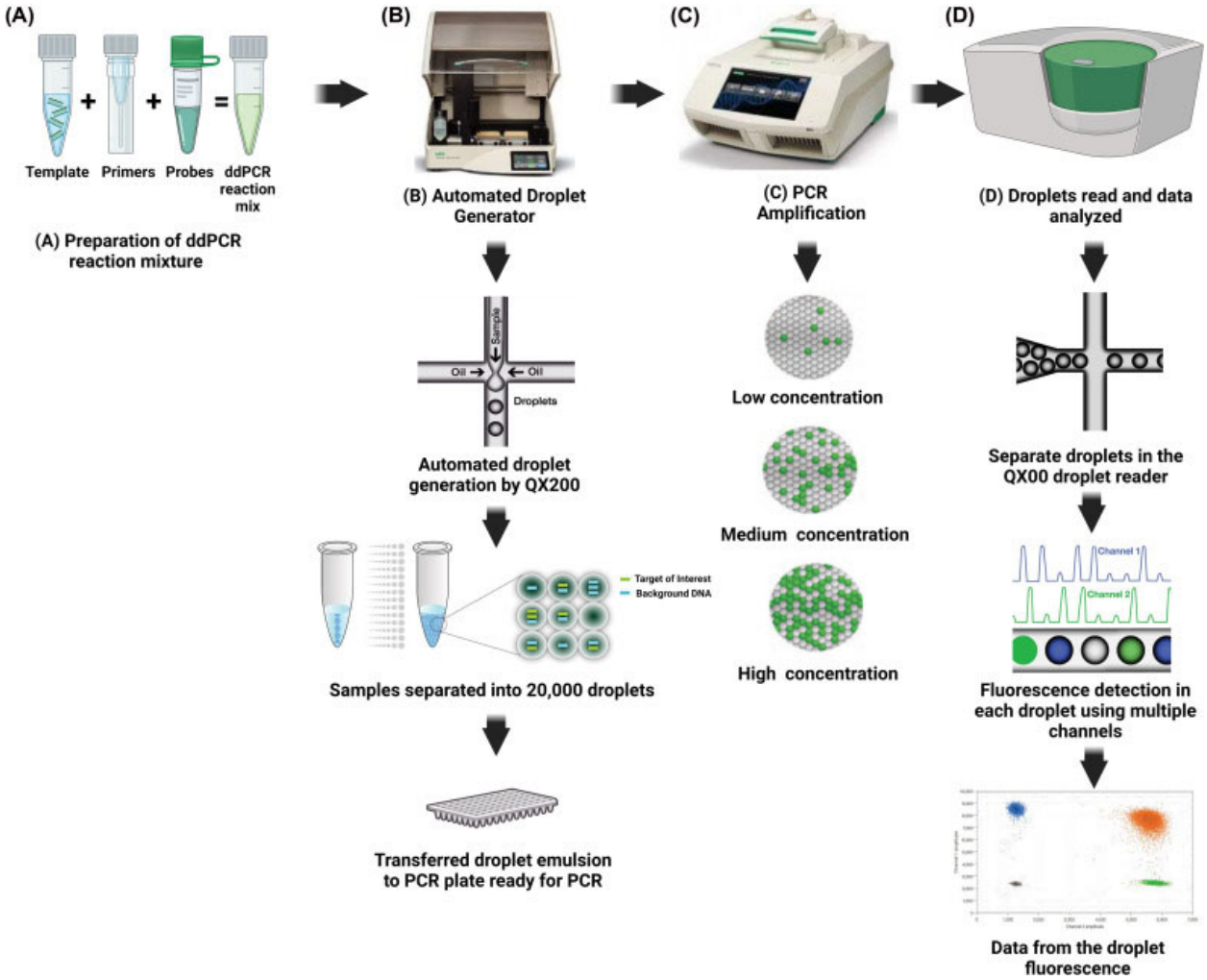


EX1013 at 6; EX1014 (describing assay); EX1002 ¶ 42.

C. Quantitative and Digital PCR

Certain PCR techniques can determine the amount (or number) of target sequences within a sample. These techniques include quantitative PCR ("qPCR") and digital PCR ("dPCR"). EX1002 ¶¶ 43-47. One form of qPCR uses TaqMan probes that hybridize to the target sequence and generate a signal when degraded by a polymerase. *Id*. ¶ 45. The signal generated is proportional to the amount of the target polynucleotide in a sample, allowing quantification of analytes. *Id.* ¶ 46.

In dPCR, the PCR solution including sample is partitioned into small droplets or other partitions, where separate PCR reactions occur. *Id.* ¶ 47. TaqMan probes can also be used for dPCR applications. *Id.* ¶¶ 43-47. Reactions can be multiplexed, which means that multiple reactions can be performed at the same time. *Id.* ¶ 37. The degree of dilution is optimized so only a fraction of droplets include any one particular target, so that where there is a signal, there is typically only a single copy of the particular target. *Id*. ¶ 47. Based on this, and on molecules following the Poisson distribution (a random distribution based on probability), the amount of any target in the original sample can be determined by quantifying the fraction of the droplets generating a corresponding signal. *Id.* An image showing the workflow for performing dPCR using Petitioner's droplet-based products is shown below:



EX1038 at 12; EX1002 ¶ 47.

III. OVERVIEW OF THE '921 PATENT

The '921 Patent issued on November 28, 2023, claiming the benefit of a February 3, 2012 provisional application. EX1001 at codes (45), (60), 1:6-15. For the purposes of only this proceeding, it is assumed herein that the '921 patent is entitled to a February 3, 2012, priority date.

A. Specification

The ’921 patent purports to describe multiplex detection of polynucleotide analytes using fewer different colors in the sequence-specific labeled probes than polynucleotide analytes. EX1001 at Abstract, 8:1-15, 10:31-55, 13:57-14:8; EX1002 ¶¶ 48-50. 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. EX1002 ¶¶ 51-53; EX1001 at 26:18-28.

The ’921 patent discloses coding schemes employing signals of differing intensities of the same colors to distinguish polynucleotides. *See, e.g.*, EX1001 at 22:9-23:67; EX1002 ¶¶ 54-58. An example of such a coding scheme follows:

TABLE 8

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

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

EX1001 at 22:38-58 (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. Thus, a single color can be used to distinguish two, three, or four analytes, where analytes A, B, C, and D have an intensity of 1, 2, 4, and 8, respectively. EX1002 ¶¶ 56-57. The same approach is used to code targets E-H, I-L, and M-P, using the colors green, yellow, and red, respectively. *Id.*

The specification purports to teach multiple such coding schemes that purportedly allow for the detection of multiple targets simultaneously. EX1002 ¶¶ 59-62.

B. Claims

Claims 1-19 of the ’921 patent are challenged. A full listing of challenged claims is included as Appendix A.

IV. LEVEL OF ORDINARY SKILL IN THE ART OF THE ’921 PATENT

A person having ordinary skill in the art (“POSA”) relevant to the ’921 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 dPCR and fluorescence-based analyte detection. EX1002 ¶¶ 66-68. Alternatively, a POSA would have been someone with greater relevant experience sufficient to compensate for having less relevant formal education. *Id.* ¶ 68.

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

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

EX1002 ¶ 69.

V. THE PARALLEL DISTRICT COURT LITIGATION

Patent Owner is asserting the '921 patent against Petitioner in the Northern District of California. *In re ChromaCode Litigation*, Case No. 5:23-cv-04823-EKL (N.D. Cal. Filed October 5, 2023)[1]. Patent Owner accuses several of Petitioner's assays and kits of infringement, including those detecting three target sequences using only two different fluorophores. *See, e.g.*, EX1012 at 14, 21, 25, 30-33, 38, 50, 52-53; EX1002 ¶ 70.

One such accused assay/kit is the SARS-CoV-2 Kit. *See, e.g.*, EX1012 at 10. The SARS-CoV-2 Kit detects three target DNA sequences (genes): N1, N2, and RP. *Id.*; EX1002 ¶ 71. The sequence-specific probes for these targets are labeled with FAM and HEX fluorophores. Probes for N1 are labeled with FAM fluorophore, probes for RP are labeled with HEX fluorophore, and probes for N2 are labeled with both fluorophores. *Id.* Patent Owner contends that "each analyte is encoded as a

[1] The case was originally filed as *ChromaCode, Inc. v. Bio-Rad Laboratories, Inc.*, Case No. 2:23-cv-08417-RGK (C.D. Cal.), and was subsequently transferred to the Northern District as *ChromaCode, Inc. v. Bio-Rad Laboratories, Inc.*, Case No. 5:23-cv-06360-EJD (N.D. Cal.), EX1024, and was later consolidated with a related case to reach its current status. EX1041.

value of one component of a fluorescence signal (corresponding to a specific wavelength as defined by the fluorophore…)" and that the assay uses a coding scheme "as follows":

Analyte	FAM	HEX
N1	1	0
N2	1	1
RP	0	1

Id. Patent Owner contends, thus, that the '921 patent is infringed by these assays (or assay kits) that generate droplets from a sample solution, amplify targets in the droplets to generate signal(s), and monitor signal(s) from the droplets to unambiguously detect three analytes using two fluorophores without mass spectrometry or immobilization techniques. *See* EX1012 at 3, 9-10, 16, 21, 25-26, 27-29; EX1002 ¶¶ 72-74.

Another such assay/kit alleged to infringe is the SARS-CoV-2 Wastewater Quantification Kit ("Wastewater Kit"). *See* EX1012 at 10-11; EX1002 ¶ 71. This ddPCR assay similarly pairs analytes with fluorophores, i.e., analyte N2 with FAM fluorophore, analyte MHV with HEX fluorophore, and analyte E with both FAM and HEX fluorophores. *Id.* According to Patent Owner's infringement contentions, the Wastewater kit includes the same coding scheme as the SARS-CoV-2 Kit:

Analyte	FAM	HEX
N2	1	0
E	1	1
MHV	0	1

EX1012 at 11; EX1002 ¶ 75.

VI. CITED PRIOR ART

A. Larson

1. Larson Is § 102(a) Prior Art

Larson et al., US 2011/0250597 A1, is the October 13, 2011, publication of application No. 13/026,120. EX1017, codes (10), (21), (43), (54); EX1002 ¶ 76. Larson is § 102(a) prior art because it was published prior to the earliest effective filing date for the '921 patent, February 3, 2012.

2. Larson Overview

Larson discloses use of digital PCR using droplets for multiplex detection of target polynucleotide analytes using fewer color labels than targets. EX1017 at Abstract, ¶¶ 119-122, 138-140; EX1002 ¶ 77. Larson teaches forming droplets from a sample solution, wherein the droplets may contain varying numbers of polynucleotide targets. EX1017 ¶ 52; EX1002 ¶ 78. These droplets are merged with droplets that contain reagents for PCR, such as primers, which can be used to amplify polynucleotide targets in the sample solution droplets, and labeled probes, which can

be used to generate detectable signals. *Id*. ¶¶ 47, 68-69, 74, 97, 113, 132-134, Fig. 5A; EX1002 ¶¶ 77-78.

Like the '921 patent specification, in addition to simply using different color labels for each polynucleotide analyte (EX1017 ¶¶ 119-120, Figs. 7A, 8A), Larson also teaches identifying different targets by generating different intensities of the same color (*id.* ¶ 138), multiple intensities of multiple different colors (*id.* ¶ 139), and "unique signature[s]" of "both colors and intensities" (*id.* ¶ 140). EX1002 ¶¶ 79-83.

B. Saxonov

1. Saxonov is § 102(e) Prior Art

Saxonov et al., US 2013/0040841 A1, published February 14, 2013, is the publication of application No. 13/548,062. EX1004, codes (10), (21), (43), (54). The '062 application, filed July 12, 2012, 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 '921 patent, as well as for the related patents—U.S. Patent Nos. 10,068,051 and 10,770,170. EX1002 ¶ 84; 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 ¶¶ 85-86. Samples having multiple targets are contacted with fluorophore-labeled probes that report the presence of targets by generating signals during PCR. EX1007 at 6:21-23, 7:9-10; EX1002 ¶ 85. Saxonov states that signals for particular analytes may be based on the signal's color, intensity, or both. EX1007 at 9:5-10 ("aspects of light, such as the intensity...may include data collected in one or more different [colors]"); EX1002 ¶ 85.

Like the '921 patent, the '013 provisional discloses using probes labeled with the same color at different intensities to distinguish among different polynucleotide analytes (or combinations of polynucleotides). EX1007 at 5:19-6:3, 10:8-11:13, 13:9-19:23 (Examples 2-3), Fig. 4 (depicting different intensity signals 108, 110, and 112).

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; *id.* at 3:10-14, 4:17-20, Figs. 1-2.
amplifying two or more targets in droplets containing a reporter for each target;	"The sample may be separated into partitions" (*id.* at 7:11); "the partitions may be droplets" (*id.* at 7:17); "reactions may be performed in the partitions" (*id.* at 8:11); "[t]he reaction may be an amplification reaction" (*id.* at 8:19); "[s]ignals may be created for each of the partitions…from reporters for two or more distinct targets" (*id.* at 9:4-8); *id.* at 7:3-5.
detecting a signal from the droplets representing combined emission of light from the reporters for the targets, wherein each reporter provides a portion of the signal having an intensity that varies according to 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;	"[s]ignals may be created for each of the partitions" (*id.* at 9:4); "signals may represent aspects of light, such as the intensity" (*id.* at 9:5-6); "the signal may be a composite signal that represents two, three, four, or more reactions and thus two, three, four, or more targets" (*id.* at 9:14-15); "[t]he signal may be analyzed to determine whether neither Target, Target 1 alone, Target 2 alone, or both Targets 1 and 2 are present in each droplet" (*id.* at 15:17-19); "assignment of a droplet to a particular outcome (i.e., to one of T1-/T2-,

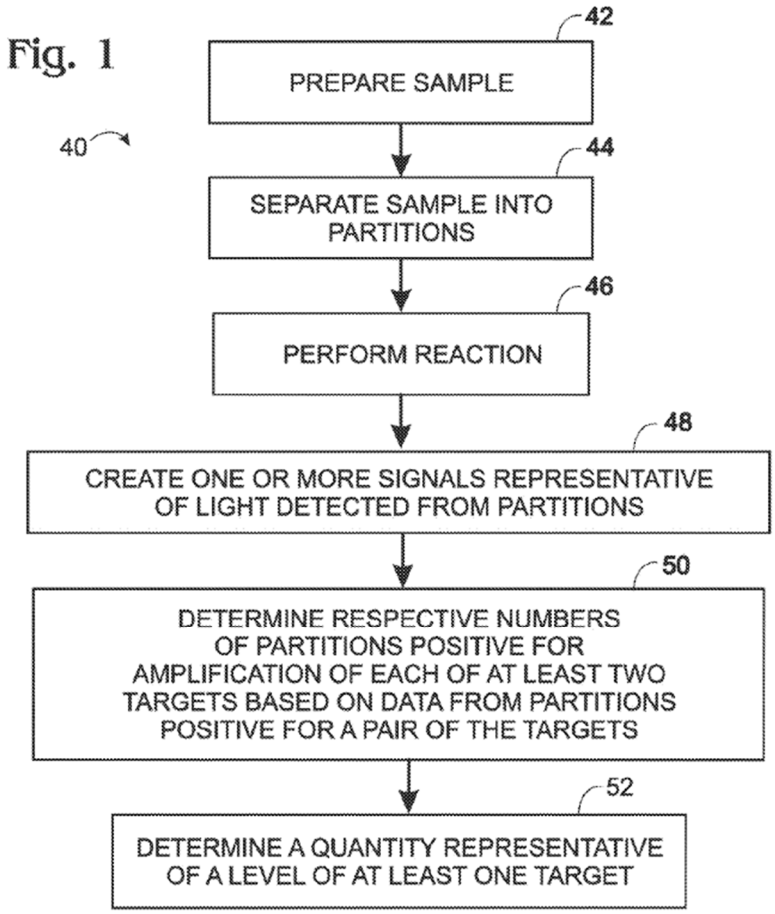
Saxonov	’013 Provisional Disclosure
	T1+/T2-, T1-/T2+, and T1+/T2+) may be performed using any suitable algorithm” (*id.* at 16:26-27); *id.* at 12:17-20:22 (Examples 1-4), 5:19-6:3, 16:21-23.
determining for each target a number of droplets that are positive for only one of the targets;	“signal is created from light detected over time in a single channel from a fluid stream containing the droplets…The signal may be analyzed to determine whether neither Target, Target 1 alone, Target 2 alone, or both Targets 1 and 2 are present in each droplet” (*id.* at 15:15-19); “assignment of a droplet to a particular outcome (i.e., to one of T1-/T2-, T1+/T2-, T1-/T2+, and T1+/T2+) may be performed using any suitable algorithm” (*id.* at 16:26-27); “statistical methods…may be used to estimate the number of droplets or peaks associated with each outcome” (*id.* at 17:1-2); “droplets that included the RPP30 gene but did not include the C61 gene” (*id.* at 18:16-17); “droplets that included the C61 gene but did not include the RPP30 gene” (*id.* at 18:11-12); *id.* at 17:4-19:23, 18:5-19:1
determining at least one number of droplets that are positive for more than one target; and	*See* preceding section; “droplets that are positive for RPP30 and C61…droplets that included both genes” (*id.* 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”

Saxonov	'013 Provisional Disclosure
	(*id.* 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." (*id.* at 19:1-9)

2. Saxonov Overview

Saxonov is directed to an assay using multiplexed detection of signals from labeled probes for two or more targets where the labels for different targets can share colors. EX1004 ¶¶ 19, 20, 37; EX1002 ¶¶ 87-96.

Saxonov depicts the steps of the method in Figure 1:



EX1004 Fig. 1. As shown above, Saxonov teaches that a prepared sample may be partitioned, such as 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 ¶¶ 89-93.

Droplets with a generated signal are marked as positive, meaning one or more targets are present, while droplets without a signal are marked negative, meaning the

target(s) are absent. EX1004 ¶ 41; EX1002 ¶ 94. This data can be used to determine the amount of each target that is present in the original sample. *Id*. ¶ 43; EX1002 ¶¶ 95-96.

C. Silverbrook

1. Silverbrook is § 102(a) Prior Art

Silverbrook et al., US2011/0312704 A1, published December 22, 2011, is the publication of patent application No. 13/150,037. EX1009, codes (10), (21), (43); EX1002 ¶ 97. Silverbrook is § 102(a) prior art because it was published prior to the earliest effective filing date for the '921 patent, February 3, 2012.

2. Silverbrook Overview

Silverbrook is directed to apparatus for low volume PCR, including assays based generating fluorescent signals, and transmitting results to update medical databases, including through a computer network. EX1009 ¶¶ 195, 198, 201, Fig. 99; EX1002 ¶¶ 98-101.

VII. MANDATORY NOTICES

A. Real Party-in-Interest

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

B. Related Matters

As of the filing date of this Petition, the ’921 patent is involved in district court litigation in *In re ChromaCode Litigation*, 5:23-cv-04823-EKL (N.D. Cal.) (“district court litigation”).[2]

Also, two petitions for *inter partes* review of related patents have been filed: IPR2024-01178 (challenging U.S. Patent No. 10,770,170, the parent of the ’921 patent); and IPR2024-01177 (challenging U.S. Patent No. 10,068,051, the parent of the ’170 patent).

C. Lead and Back-Up Counsel and Service Information

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

[2] This case was originally filed as *ChromaCode, Inc. v. Bio-Rad Laboratories, Inc.*, Case No. 2:23-cv-08417 (C.D. Cal. Filed October 5, 2023), but was transferred to the Northern District of California. EX1024. The district court litigation has also been consolidated with a related district court case involving two of Bio-Rad’s patents, *ChromaCode, Inc. v. Bio-Rad Laboratories, Inc.*, Case No. 5:23-cv-04823 (N.D. Cal. Filed September 20, 2023). EX1041.

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VIII. GROUNDS FOR STANDING

Petitioner certifies that the ’921 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.

IX. STATUTORY GROUNDS FOR THE CHALLENGES

Ground	35 U.S.C. Section (Pre-AIA)	Claims	References
1	§ 102	1-10, 13-19	Larson
2	§ 103	4, 6-7, 14-19	Larson
3	§ 103	1-10, 12-19	Larson, Saxonov
4	§ 103	11	Larson, Saxonov, Silverbrook

X. CLAIM CONSTRUCTION

Petitioner has identified terms and proposed constructions in the parallel proceedings, as follows: “non-degenerately,” “degenerate” or “degeneracy” where

"'degenerate' or 'degeneracy' means 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.*, '921 patent at claims 4, 13, 14.

All other claim terms are interpreted consistent with Patent Owner's arguments and positions in the parallel district court proceeding. 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 district court litigation, particularly in view of its contentions regarding how the '921 Patent is allegedly infringed. *See Hospira, Inc. v. Amgen Inc.*, IPR2021-00528, Paper 7 at 7 (P.T.A.B. 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'"); EX1012.

XI. GROUND 1: CLAIMS 1-10 AND 13-19 ARE ANTICIPATED BY LARSON

The '921 patent claims an assay and kit for an assay capable of unambiguously detecting the presence or absence of at least M analytes based on detection of F wavelength components of fluorescent signals wherein M is greater than F. EX1001 at claims 1, 14; EX1002 ¶ 106. At its core, the '921 patent relies on nothing more than the concept of detecting a number of targets exceeding the number of colors used in labels simply by mixing color signals to obtain multi-color labels

and/or using different signal intensities to provide composite signals that unambiguously identify which analytes are present in a sample. EX1002 ¶ 107. As detailed below, this approach is anticipated by Larson. *Id.* ¶ 110.

Larson is analogous art to the '921 patent because it is in the same field of endeavor: multiplex detection of polynucleotides using color-labeled sequence-specific probes, including where there are fewer colors than analytes. EX1001 at code (57), 12:37-14:22, 18:10-13, 22:9-23:67; EX1017 ¶¶ 15, 29, 32, 121, 135, 140; EX1002 ¶¶ 108-109.

A. Claim 1

1. An assay that is capable of unambiguously detecting the presence or absence of each of at least M analytes

The value for "M" can be as small as two. This is because the only restriction the claim places on the value of "M" is that it be greater than "F," where "F" is the number of wavelength components in the assay. *See* EX1001 at claim 1. The value of "F," is unrestrained and can be as small as 1, meaning the minimum value of "M" is 2. EX1002 ¶ 111.

With this in mind, Larson discloses dPCR assays that detect the presence or absence of two or more polynucleotide analytes. *See* EX1001 at 26:18-28 (the analytes are "selected from the group consisting of any 2, 3, 4,…100 or more"); EX1017 ¶¶ 26 (five-plex assay), 116 (same), 28, 120, 29 (describing Figure 9's

depicted two-color detection of three sequences), 121 (same), 32 (describing different signal intensity to distinguish sequences (Fig. 12)), 135 (same); EX1002 ¶ 112.

Most important for the purposes of the present petition, in paragraph 140, Larson describes detecting three target polynucleotides using two colors. A single-color probe of the first color is used to detect the first analyte, a second single-color probe of the second color is used to detect the second analyte, and one or more probes collectively including both the first and second colors is used to detect the third analyte. *Id.* ¶ 140; EX1002 ¶ 113. The particular assay format set forth in paragraph 140 of Larson is relied upon throughout this petition and corresponds to the exact assay format used in Bio-Rad's Wastewater and SARS-CoV-2 kits that Patent Owner accuses of infringing in parallel district court proceedings. *See* EX1012; EX1002 ¶ 113.

As to detection of two or more analytes "unambiguously," Larson teaches this as well, as detailed below describing claim elements specifically requiring the "unambiguous" detection of analytes. *See infra* Sections XI.A.4, XIII.A.4; EX1002 ¶ 114.

2. wherein each of said at least M analytes is encoded as a value of one component of a fluorescent signal, thereby generating a coding scheme

Larson discloses dPCR assays using two colors to detect three analytes. EX1002 ¶¶ 115-116; *see supra* Section VI.A.2; EX1017 ¶ 140. Specifically, in ¶ 140 Larson teaches the following:

> [A] single droplet might contain four different probes for measuring three different targets (say, T1, T2, and T3). Two probes might be of color A (say, A1, and A2), and two probes might be of color B (say, B1 and B2). Tl is measured by probe A1, T2 is measured by probe B1, but T3 is measured by both probes A2 and B2. Thus, when a droplet contains T1 only increased fluorescence appears in color A. When a droplet contains T2 only increased fluorescence appears in color B. However when a droplet contains T3, increased fluorescence appears in both colors A and B.

EX1017 ¶ 140. As set forth above, a first target is measured by color "A," a second target is measured by color "B," and a third target is measured by colors "A" and "B" together. EX1002 ¶ 120. Thus, Larson discloses a scheme where M is 3, and

each of the three targets is encoded by a value of one component of a fluorescent signal (i.e., the individual color components A and B).[3] EX1017 ¶ 121.

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[3] This invalidity theory is based not just on how Patent Owner interprets the claims in parallel district court litigation, but also in view of how Patent Owner drafted dependent claims 2 and 9, which confirm that Patent Owner construes claim 1 as encompassing situations wherein individual targets are detected by combinations of multiple individual colors. Indeed, dependent claim 2 recites the "assay of claim 1, wherein ***each*** of said at least M analytes is encoded as at least one first value in a ***first*** component of said fluorescent signal ***and*** at least one ***second*** value in a second component of said fluorescent signal." Referring to "each" analyte being detected by a "first" "and" "second" signal component, claim 2 covers detecting analytes through the use of two signal components, which means Patent Owner necessarily construes such approaches to be within the scope of claim 1. Claim 9 includes language similar to claim 2, calling for "at least one" of the analytes to be "encoded by at least one ***additional*** value, wherein said at least one additional value is selected from the group consisting of a value from at least one additional component of said signal, a value from at least one component of an additional signal, and combinations thereof." Thus, claim 9 is further confirmation that Patent Owner intends for claim

As Dr. Batt explains, this is the exact coding scheme based on the use of two colors to detect three analytes that Patent Owner contends satisfies the claims in district court. EX1002 ¶¶ 117-122. In the parallel district court litigation, Patent Owner alleges dPCR assays using a single-color probe for a first analyte, a second single-color probe for a second analyte, and multi-color probe(s) including both colors for a third analyte infringe claim 1. *See* EX1012 at 2-4 (contending SARS-CoV-2 Kit and SARS-CoV-2 Wastewater Quantification Kit ("Wastewater Kit") infringe claim 1), 9-11; EX1002 ¶¶ 117-118. For instance, Patent Owner contends the following coding scheme used in Bio-Rad's SARS-CoV-2 Kit satisfies the claims:

Analyte	FAM	HEX
N1	1	0
N2	1	1
RP	0	1

EX1012 at 10. In this scheme, the signal from the FAM fluorophore corresponds to N1 target, the signal from the HEX fluorophore corresponds to RP target, and signal from ***both*** FAM and HEX fluorophores corresponds to N2 target. EX1002 ¶ 119.

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1 to encompass situations wherein individual targets are detected by combinations of multiple colors.

Because the exact coding scheme that Patent Owner now contends infringes is present in Larson, Patent Owner should not be heard to contend that Larson does not disclose this claim element.

3. wherein said fluorescent signal comprises F wavelength components, and

Larson discloses assays wherein the fluorescent signal comprises a number of wavelength components, i.e., colors. *See supra* Sections XI.A.1-2; EX1002 ¶¶ 123-128; EX1017 ¶¶ 28-29, 32, 120-121, 135, 140, Figs. 8-9, 12. The claim places no restriction on F and the number of wavelength components can be as small as 1. EX1002 ¶ 124. In the assay set forth in paragraph140 of Larson for detecting three targets, two different colors are used, specifically, "colors A and B." *See* EX1017 ¶ 140. As such, in the assay of paragraph 140 of Larson, F is 2. *See id.*; EX1002 ¶¶ 125-126.

This is the same mapping that Patent Owner accuses of infringement. *See supra* Section XI.A.2; EX1002 ¶ 127; EX1012 16-17, 9-11.

4. wherein said assay is capable of unambiguously detecting the presence or absence of each of said at least M analytes, in any combination of presence or absence, in a single sample volume, based on detection of said F wavelength components, when M is greater than F,

Larson discloses assays performing this limitation. EX1002 ¶¶ 129-138. As documented above, Larson discloses in ¶ 140 using two colors to identify three target

analytes, relying on the combination of two colors as the multi-color label for one analyte, with each of the two colors individually as a label for the other two targets. *See supra* Sections X.A.1-3; EX1017 ¶ 140; EX1002 ¶ 130. Here, M is three and F is two. EX1002 ¶ 130. Larson discloses detecting whether these three targets are present in a "sample volume," specifically, a portion of a sample solution that is subsequently partitioned into droplets. *See id.* ¶¶ 131-132; EX1017 ¶¶ 11, 13-17, 21-23, 52-68, 154, 164, Figs. 1-3.

Larson discloses conducting the digital PCR assay in paragraph 140 under conditions of terminal dilution, where the probability of a single target molecule in droplets is much greater than, and overwhelms that of, multiple targets. EX1017 ¶¶ 141 (describing the method of paragraph 140 is simplest to implement at terminal dilution), 6 (describing terminal dilution); EX1002 ¶ 130. Under these conditions, the detectable signal generated for each potential analyte is distinct and readily distinguishable, providing "unambiguous" detection of the analytes. EX1017 ¶¶ 140, 141; EX1002 ¶ 130. Also, the "unambiguous" detection of the presence or absence of targets, the approach in paragraph 140 of Larson based on using two colors to detect three targets is the same approach that Patent Owner contends is used by the assays accused of infringing and providing "unambiguous" detection. EX1012 at 17-25; EX1002 ¶¶ 133-137. Patent Owner contends that for "all of Bio-

Rad's infringing ddPCR assays and kits, the detection is unambiguous in that it detects the presence of the nucleic acid target sequences based on a coding scheme where the same detection signal(s) event cannot represent two or more analytes." *Id.* at 19. These accused ddPCR assays such as the SARS-CoV-2 Kit and Wastewater Kit include using a first color for a first analyte, a second color for a second analyte, and both colors for a third analyte, just as in ¶ 140 of Larson. *See supra* Section V; EX1002 ¶¶ 133-135; EX1012 at 21.

As to the claimed "sample volume," Larson discloses partitioning a portion of a sample mixture into droplets using various means. *See* EX1017 ¶¶ 11, 16, 23, 52-68, Fig. 3; EX1002 ¶ 32. This portion of sample solution that is subsequently partitioned into droplets is precisely what Patent Owner contends satisfies the claims. Patent Owner, for instance, contends in parallel district court litigation that Petitioner's accused products infringe because "the detection is performed in a single ***sample volume*** that is ***subsequently*** partitioned into multiple droplets." EX1012 at 20; EX1002 ¶ 137.

5. wherein the assay does not require the use of mass spectrometry or immobilization of said at least M analytes, and

Larson discloses assays for detecting multiple polynucleotide analytes that do not require mass spectrometry or immobilization of the analytes. EX1002 ¶¶ 139-

143. Larson rather teaches amplification and detection of polynucleotide analyte sequences in droplets, including the generation of color signal, without mass spectrometry or immobilization of the analytes. *Id.* ¶¶ 139-141; EX1017 ¶¶ 47, 52-54, 69, 70-72, 83, 89, Fig. 1-3.

This is the same mapping as Patent Owner contends infringes by relying on PCR amplification and detection of sequences in droplets generated by fractionating the sample solution volume to determine the fraction of positive droplets in the original sample and using Poisson statistical formulas to determine the absolute quantity. EX1012 at 26; EX1002 ¶ 142.

6. wherein the analytes are amplified in the single sample volume.

Larson discloses PCR assays that amplify target polynucleotide analytes in a single sample volume, specifically a portion of the reaction mixture that is subsequently partitioned into droplets. *See supra* Sections X.A.1, 5; EX1002 ¶¶ 144-147.

As detailed above, Patent Owner relies on Petitioner's droplet digital PCR assays as infringing and contends that the claimed "sample volume" is a portion of the sample mixture that is subsequently partitioned into droplets. EX1002 ¶ 145. As Patent Owner states with regard to Petitioner's products, "the detection is performed in a single ***sample volume*** that is ***subsequently*** partitioned into multiple

droplets." EX1012 at 20. Patent Owner goes on to state that "analytes are amplified in the single sample volume" where "the single sample is partitioned into individual droplets" and that "[f]ollowing droplet generation, the sample is amplified in a thermal cycler" prior to reading "each droplet to determine the fraction of positive droplets in the original sample and us[ing] Poisson statistical formulas to determine the absolute quantity." *Id.* at 27-29. Thus, Larson again discloses the exact thing that Patent Owner now accuses of infringing in district court. EX1017 ¶¶ 2, 9, 11, 13, 14, 16, 17, 20, 47, 49, 91, 93, 119-121, 150, 195, Figs. 1-4, 7-11, 15; EX1002 ¶ 146.

B. Claim 2: The assay of claim 1, wherein each of said at least M analytes is encoded as at least one first value in a first component of said fluorescent signal and at least one second value in a second component of said fluorescent signal.

Claim 2 is anticipated by Larson. EX1002 ¶¶ 148-154. As detailed above, paragraph 140 of Larson discloses assays using a single-color probe for a first analyte, a second single-color probe for a second analyte, and multi-color probe(s) including both colors for a third analyte. *See supra* Sections VI.A.2, XI.A.1; EX1017 ¶ 140; EX1002 ¶¶ 151-153. As such, paragraph 140 of Larson discloses an assay where M is 3 and each of the targets is detected by a first and second component of a fluorescent color signal (i.e., colors A and B).

As Dr. Batt explains, this assay format is the exact approach that Patent Owner accuses of infringing. EX1002 ¶¶ 150-151. In the parallel litigation, Patent Owner alleges that the SARS-CoV2 Kit and Wastewater Kit infringe because "each analyte…is encoded as a 0 or 1 value for each of at least two component [sic] of the fluorescent signal (i.e. the fluorophore)," that is, FAM and HEX fluorophores. EX1012 at 30; EX1002 ¶ 150.

C. Claim 3: The assay of claim 2, wherein said first value is an intensity or range of intensities.

As detailed above in Sections XI.A, B, Larson discloses assays wherein the first value in a first component for which an analyte is encoded may be an intensity or range of intensities. EX1002 ¶¶ 155-161; EX1017 ¶¶ 34-42, 47, 52, 121, 139-141, 145, 150, 153-154, 162, Figs. 14-15. In particular, Larson teaches in ¶ 140 an assay wherein "when a droplet contains T1 only increased fluorescence appears in color A. When a droplet contains T2 only increased fluorescence appears in color B. However when a droplet contains T3, increased fluorescence appears in both colors A and B." EX1017 ¶ 140. Referring to detecting targets by "increase fluorescence," Larson discloses using values that are intensities or ranges of intensities. *See* EX1002 ¶ 160.

In the parallel litigation, Patent Owner contends, "for each infringing Bio-Rad assay or kit, the value is an intensity based on fluorescent signal and its wavelength,"

incorporating by reference its contentions for claim 2. EX1012 at 32; EX1002 ¶ 158. As detailed above, Patent Owner contends that the SARS-CoV2 Kit and Wastewater Kit infringe because the analytes for these kits allegedly are encoded as a 0 or 1 value for the FAM and HEX fluorophore signals. *See supra* Sections XI.A.1, X.B; EX1012 at 30; EX1002 ¶¶ 158-159. As Dr. Batt explains, these values of 1 in the accused products correspond to increased fluorescence (i.e., intensity), just as disclosed in Larson. *See* EX1002 ¶¶ 159-160; EX1017 ¶ 140. Again, the exact feature that Patent Owner now accuses of infringing corresponds to what is disclosed in the prior art. EX1002 ¶¶ 158-159.

D. Claim 4: The assay of claim 2, wherein said coding scheme is made nondegenerate by enumerating every legitimate result that can be obtained from said coding scheme, identifying each legitimate result that is degenerate, and eliminating at least one potential analyte code from said coding scheme to eliminate degeneracy.

Claim 4 is anticipated by Larson. *See supra* Sections XI.A.1-2, 4; EX1002 ¶¶ 162-166. Larson discloses adjusting the intensity values from color labels to avoid potentially ambiguous results, particularly to avoid overlap between signals for two different populations. EX1017 ¶¶ 35, 146 (describing optimizing intensities to adjust positions of signals in histograms), 150, Fig. 15; EX1002 ¶ 163. Larson thus discloses identifying the possible combinations of signals that may arise from the different droplets and, where signals for individual analytes result in ambiguity,

i.e., are degenerate, then adjusting the intensity of signals so that they are not degenerate. EX1002 ¶ 164. This adjustment of intensity eliminates a potential analyte code from the coding scheme because each analyte is also encoded by intensity of color signals. *See supra* Section XI.A.2; EX1002 ¶ 165; EX1017 ¶ 35, 140, Fig. 15.

E. Claim 5: The assay of claim 1, wherein said detecting is performed with reagents comprising hybridization probes.

As detailed above, Larson discloses using labeled hybridization probes in its assays to detect analytes. *Id.*; *see, e.g.*, EX1017 ¶ 140; EX1002 ¶¶ 167-172; *supra* Section XI.A.1.

F. Claim 6: The assay of claim 5, wherein said hybridization probes comprise one or more hybridization probes specific for different analytes and comprising an identical fluorophore or combination of fluorophores.

Larson discloses using sets of hybridization probes including one or more probes specific for different analytes that include an identical fluorophore. EX1002 ¶¶ 173-181; EX1017 ¶¶ 121 ("Methods…involve…using probes with the same fluorophore."), 135, 140, Figs. 9A, 12B. In the two-color, three-analyte assay set forth in paragraph 140 of Larson, hybridization probes specific for the first and third analytes comprise the same fluorophore, as do probes for the second and third analytes. EX1017 ¶ 140; EX1002 ¶ 177.

Importantly, in the parallel litigation, Patent Owner contends infringement of this claim by assays using single color labels for first and second analytes, and combinations for a third and using single colors at varying intensity. EX1012 at 44 (citing Appendix B1 (EX1040), claim 3); EX1040 at 67 (disclosing triplex assays using "probes that correspond to FAM, HEX, FAM/HEX, Cy5, Cy5.5, Cy5/Cy5.5, ROX, ATTO590, and ROX/ATTO590"), 68-69 (disclosing using multiple single-color labels at different intensity). Again, the exact thing that Patent Owner contends infringes in district court is disclosed in Larson. EX1002 ¶¶ 178-181.

G. Claim 7: The assay of claim 5, wherein said fluorescence signal from said hybridization probes are used to construct a chromatogram.

Larson discloses using the fluorescence signal from the hybridization probes to construct a chromatogram. EX1002 ¶¶ 182-191.

Larson broadly discloses using "scattered plot[s]" constructed by plotting "the fluorescence emission from each droplet [that] was determined and plotted on a scattered plot based on its wavelength and intensity." *Id.* ¶ 185; EX1017 ¶¶ 113, 116. Examples are depicted with a signal cluster for each analyte. EX1017 Figs. 5C, 6B, 9, 10, 14a, 15; EX1002 ¶ 185. In addition to droplets that each include only one of the analytes, Larson also discloses droplets that include multiple polynucleotide analytes. EX1002 ¶ 186. Larson explains that while there is

typically one analyte per droplet, the assay follows the Poisson distribution of analytes in droplets meaning some droplets have multiple analytes:

> The distribution from background of target DNA molecules among the reactions follows Poisson statistics, and at so called "terminal dilution" the vast majority of reactions contain either one or zero target DNA molecules for practical intents and purposes. In another case, at so called ***"limiting dilution"*** some reactions contain zero DNA molecules, some reactions contain one molecule, and ***frequently some other reactions contain multiple molecules***, following the Poisson distribution.

EX1017 ¶ 6 (emphasis added). Larson discloses using its multiplex assay at limiting dilution. *Id.* ¶ 45; EX1002 ¶ 187. Such droplets at limiting dilution as disclosed in Larson frequently contain multiple target molecules. *Id.* ¶¶ 187-188.

As the assays detailed above include those for two or three polynucleotide targets, a POSA would have understood Larson disclosing droplets with multiple targets to be a disclosure of assays with reactions in droplets that include all possible combinations of the target polynucleotide sequences, necessarily including those with all targets in the same droplet. *Id.* ¶ 188. The scattered plots for these sets of droplets would, accordingly, have included the combined signals for every combination of the targets, thus, also providing a chromatogram according to the claim. *Id.* ¶ 189.

In the parallel litigation, Patent Owner alleges infringement based on the exact types of scattered plots set forth in Larson, including, for example, scattered plots generated based on data allegedly taken using Petitioner's SARS-CoV-2 Kit and Wastewater Kit assays. EX1012 at 45; EX1002 ¶ 190; EX1017 Fig. 15.

H. Claim 8: The assay of claim 1, wherein said signal is generated during a polymerase chain reaction.

Larson discloses methods for generating fluorescence signals during assays using PCR amplification, e.g., TaqMan. *See supra* Sections II.B., XI.A; EX1002 ¶¶ 192-195; EX1017 ¶ 47, Fig. 5.

In the parallel litigation, Patent Owner alleges infringement based on the accused assays allegedly using "reagents and workflows similar to those used for most standard Taqman probe-based assays" that also generate signals during assays using PCR amplification. EX1012 at 49-50; EX1002 ¶ 194.

I. Claim 9: The assay of claim 1, wherein at least one of said analytes is encoded by at least one additional value, wherein said at least one additional value is selected from the group consisting of a value from at least one additional component of said signal, a value from at least one component of an additional signal, and combinations thereof.

Claim 9 is anticipated by Larson. EX1002 ¶¶ 196-201. As detailed above, Larson discloses in paragraph 140 encoding analytes using a color signal (or signal(s)), just as in the '921 patent. *See supra* Sections X.A.1-2, X.B; EX1001 at 1:66-2:8; EX1002 ¶ 198. In the two-color assay for three analytes—relying on a

first color for one analyte, a second color for a second analyte, and both colors for a third analyte—the third analyte is encoded by a value of at least one additional component, as the third analyte is encoded by two colors. EX1017 ¶ 140; EX1002 ¶¶ 198, 200.

In the parallel litigation, Patent Owner alleges infringement based on assays just like those disclosed in Larson, including those using two positive color signals for particular analytes, as in the SARS-CoV-2 Kit, where "the N2 Target [being] encoded by a positive signal of both FAM and HEX" and the Wastewater Kit, "the E Target [being] encoded by a positive signal of both FAM and HEX." EX1012 at 50-51; EX1002 ¶ 199.

J. Claim 10: The assay of claim 1, wherein at least one of said analytes comprises a polynucleotide.

Disclosed. *See supra* Section XI.A; EX1002 ¶¶ 202-205.

K. Claim 13: The assay of claim 1, wherein said coding scheme is innately nondegenerate or non-degenerate by construction.

As documented above, Larson discloses, including in paragraph 140, assays that are innately non-degenerate or non-degenerate by construction. *Id.*; EX1002 ¶¶ 206-213; *see, e.g.*, EX1017 ¶¶ 29, 32, 121, 135, 140, Figs. 9, 12B, 15; *supra* Sections XI.A.4, XI.B, XI.D.

In the parallel litigation, Patent Owner relies on alleged infringement of claim 13 by Bio-Rad's SARS-CoV-2 Kit and Wastewater Kit, asserting that the

"coding scheme is innately nondegenerate or non-degenerate by construction," citing elements of claim 1 and claims 2 and 4. EX1012 at 64 (citing *id.* at 9-16 (element [1a] in chart), 17-25 (element [1c] in chart), 30-31 (claim 2), 32-40 (claim 4)). Again, Patent Owner accuses of infringement the precise approach set forth in Larson. *See* EX1002 ¶¶ 209-212.

L. Claim 14

Claim 14 is anticipated by Larson. EX1002 ¶¶ 214-254.

1. A kit for detecting the presence or absence of at least M analytes by generating a single cumulative measurement, comprising

The "description of a 'kit' that 'can be assembled for home use in the preamble is the exact type of intended use" that the Federal Circuit has "consistently held does not limit claim scope." *In re Rudy*, 778 Fed. App'x. 940, 946 (Fed. Cir. 2019). The preamble is otherwise wholly redundant to the specific elements in the claim body. The preamble thus does not limit the claims. *See Catalina Marketing Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (preamble not limiting where it only states intended use and claim body otherwise recites "structurally complete" invention); EX1002 ¶¶ 215-216.

If deemed limiting, a POSA would have understood Larson to disclose the recited kit. *Id.* ¶¶ 214-254. As documented below, every element recited in the

preamble is redundant to some non-preamble claim element and disclosed in Larson fully as set forth below with respect to each limitation. *Id.* ¶¶ 218-219.

2. analyte-specific reagents, wherein:

Larson discloses analyte-specific reagents in disclosing the second sample fluid containing PCR primers and labeled probes, each specific for the polynucleotide analytes. *See supra* Sections XI.A, XI.E; EX1017 ¶¶ 68, 74; EX1002 ¶¶ 222-226; *see also* EX1017 ¶¶ 26, 28-29, 32, 116, 120-121, 135, 140, Figs. 6, 8-9, 12.

a. a. each of said at least M analytes is encoded as a value of one component of a fluorescent signal, thereby generating a coding scheme, wherein each of said at least M analytes is represented in said coding scheme by said value, and

Disclosed. *See supra* Section XI.A.1-2, XI.B, XI.E, XI.F; EX1002 ¶ 227-232. Larson discloses assays wherein analytes are encoded as a value of one component of a fluorescent signal thus generating a coding scheme. EX1002 ¶ 228-232. Each of the analytes is represented in that coding scheme by the value of the component of the signal. EX1002 ¶¶ 231-232.

b. wherein said encoding is performed in a manner that eliminates degeneracy; and

Disclosed. *See supra* Sections XI.A.1-4, XI.B, XI.D; EX1002 ¶ ¶¶ 233-239. Larson discloses encoding in a manner that eliminates degeneracy. *Id.* ¶ 234; EX1017 ¶ 5; *see also* EX1017 ¶¶ 121, 131, 135, 140, Figs. 9, 12B.

c. b. each of said analyte-specific reagents, when contacted with a sample comprising its corresponding analyte, generates the value;

Disclosed. *See supra* Sections XI.A, XI.E, XI.H, XI.L.2; EX1002 ¶¶ 240-245. Larson discloses the use of PCR assays using forward and reverse primers and sequence-specific probes that generate a fluorescent signal during PCR, i.e., a TaqMan assay, if the polynucleotide target is present. EX1002 ¶ 241. Generating the fluorescent signal, they likewise generate the value of one component of the fluorescent signal. *Id.* Such reagents are the precise reagents that Patent Owner accuses of infringing in parallel district court litigation. *See* EX1012 at 40-44; EX1002 ¶ 244.

3. wherein said kit is capable of unambiguously detecting the presence or absence of each analyte of M analytes in a single sample volume, in any combination of presence or absence, and wherein the kit does not require the use of mass spectrometry or immobilization of said M analytes, and

Disclosed. *See supra* Section XI.A.; EX1002 ¶¶ 246-251. Larson teaches assays that unambiguously detect the presence or absence of multiple analytes, e.g.,

two or three, in any combination of presence or absence in a single sample volume. *See supra* Sections XI.A.4, 6; EX1002 ¶ 247; EX1017 ¶¶ 120-121, 135, 140, Figs. 9, 12. Larson does so without requiring the use of mass spectrometry or immobilization of the analytes. *See supra* Section XI.A.5; EX1002 ¶ 247.

4. wherein the analytes are [amplified] in the single sample volume.

Disclosed. *See supra* Section XI.A.1, 5, 6; EX1002 ¶¶ 252-254; EX1017 ¶¶ 47, 52-54, 69-72, 83, 89, 96-97.

M. Claim 15: The kit of claim 14, wherein said fluorescent signal comprises F wavelength components and said kit is capable of unambiguously detecting the presence or absence of M analytes, in any combination of presence or absence, when M is greater than F.

Disclosed. *See supra* Sections XI.A.3-4; EX1002 ¶¶ 255-261.

N. Claim 16: The kit of claim 14, wherein said analyte-specific reagents comprise a plurality of hybridization probes.

Disclosed. *See supra* Sections XI.L.2, XI.A.1-4, XI.E; EX1002 ¶¶ 262-266.

O. Claim 17: The kit of claim 16, wherein said plurality of hybridization probes comprise a fluorophore, and wherein said plurality of hybridization probes are specific for different analytes.

Disclosed. *See supra* Sections XI.A, XI.F, XI.H, XI.L.2, XI.N; EX1002 ¶¶ 267-272.

P. Claim 18: The kit of claim 17, wherein said number of hybridization probes in the kit is greater than M.

Disclosed. *See supra* Section XI.A.1, XI.O; EX1017 ¶ 140; EX1002 ¶¶ 273-278. Larson teaches assays using a greater number of hybridization probes than polynucleotide analytes, i.e., M analytes. EX1017 ¶ 140; EX1002 ¶ 276.

Q. Claim 19: The kit of claim 14, wherein the analyte-specific reagents are each present at a different amount in the kit.

Larson teaches using analyte-specific reagents at different concentrations. *See* EX1017 ¶ 130 (disclosing using "1x and 0.5x primers and probes respectively"), ¶ 193 (similar); EX1002 ¶¶ 279-285.

In the parallel litigation, Patent Owner contends that assays with final concentrations of primers/probes of 900 nM/250 nM infringe claim 19. EX1012 at 67-68; EX1002 ¶ 282.

Larson also discloses using different concentrations of different primers and different probes. *See* EX1017 ¶ 137 (disclosing "varying the probe, forward, and reverse primers concentrations in any way"); *see also id.* ¶¶ 9, 12, 91, 94, 130, 146, 150-151, Figs. 9, 12B, claim 6; EX1002 ¶ 283.

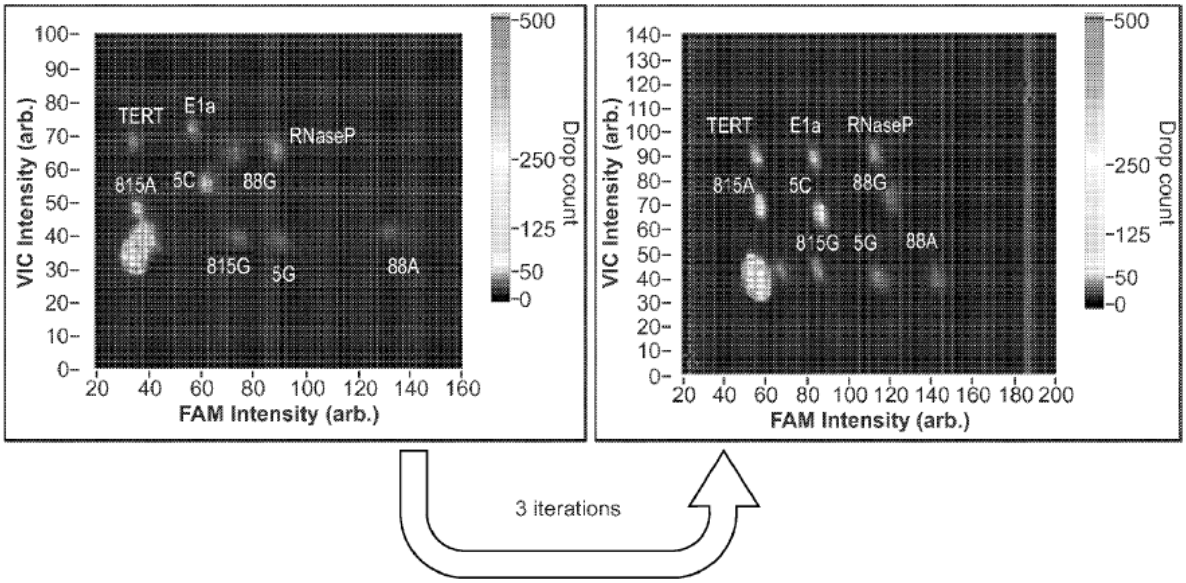
XII. GROUND 2: CLAIMS 2, 4, 6-7, AND 14-19 ARE OBVIOUS IN VIEW OF LARSON

A. Claim 4: The assay of claim 2, wherein said coding scheme is made nondegenerate by enumerating every legitimate result that can be obtained from said coding scheme, identifying each legitimate result that is degenerate, and eliminating at least one

potential analyte code from said coding scheme to eliminate degeneracy.

Larson alone, as described above, discloses the assay of claim 2. *See supra* Sections XI.A, B; EX1002 ¶¶ 286-293. Larson also further discloses the method of claim 4 wherein the coding scheme is made nondegenerate. *See supra* Section XI.D; EX1002 ¶ 288.

As detailed by Dr. Batt, Larson renders obvious that, "said coding scheme is made nondegenerate by enumerating every legitimate result that can be obtained from said coding scheme, identifying each legitimate result that is degenerate, and eliminating at least one potential analyte code from said coding scheme to eliminate degeneracy." EX1002 ¶¶ 286-293. First, a POSA would have understood Larson to teach that detecting multiple analytes in a sample was desirable, and that this was known. *Id.* ¶ 289; EX1017 ¶¶ 139-145, 5 (the "need for higher throughput in analyzing multiple targets in parallel continues to escalate."). Second, Larson discloses "enumerating every legitimate result that can be obtained from said coding scheme," as required by the claim, in its depicted scattered plots, including in Figure 15.



EX1017 Fig. 15; EX1002 ¶ 290. Third, Figure 15 also depicts, as shown above, results before (left-hand panel) and after (right-hand panel) optimization of a nine-plex assay. EX1017 ¶ 150, Fig. 15. The increased separation between different signals reduces ambiguity to eliminate degeneracy because overlap in signals is reduced or eliminated. EX1002 ¶ 291.

Larson's optimization process is functionally no different than eliminating an analyte code that is degenerate to remove the degeneracy. *Id.* ¶ 292. A POSA would have understood that in the process of optimization, the optimized analyte codes are necessarily eliminated, and subsequently replaced, to detect the targets unambiguously. *Id.*

Thus, it would have been obvious to a POSA in view of Larson to enumerate every legitimate result, identify degenerate results, and eliminate at least one potential analyte code from the coding scheme to eliminate such degeneracy because it would allow detection unambiguous detection of analytes within the same assay and they would have had a reasonable expectation of success because Larson discloses doing so. EX1002 ¶ 290.

B. Claim 6: The assay of claim 5, wherein said hybridization probes comprise one or more hybridization probes specific for different analytes and comprising an identical fluorophore or combination of fluorophores.

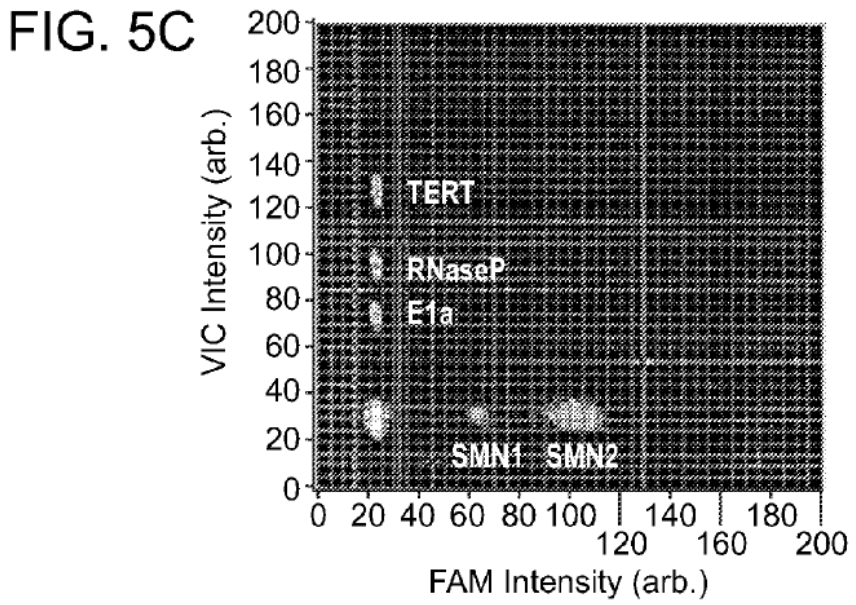
As documented above, Larson anticipates claims 1 and 5. *See supra* Sections XI.A, XI.E. To the extent Patent Owner contends claim 6 is not anticipated, it is rendered obvious in view of Larson, which explicitly teaches using sets of hybridization probes including one or more probes specific for different analytes that include an identical fluorophore. *See supra* XI.F; EX1002 ¶¶ 294-299; EX1017 ¶ 121, Fig. 9A; *see also id.* ¶¶ 135, 140, Figs. 9A, 9C, 12B. Given this explicit teaching, it would have been obvious for a POSA to have used the identical fluorophore on different probes specific for different analytes in obtaining same-color signals, such as taught in paragraph 140. EX1002 ¶ 298. A POSA would have been motivated to use the same fluorophore in such an assay because they would have understood the relative ease of obtaining the same color signals when using the

same fluorophore and would have had a reasonable expectation of success. EX1002 ¶ 299; EX1017 ¶ 121, Figs. 9A, 9C.

C. Claim 7: The assay of claim 5, wherein said fluorescence signal from said hybridization probes are used to construct a chromatogram.

As documented above, Larson anticipates claims 1, 5, and 7. *See supra* Sections XI.A, XI.E, XI.G. To the extent Patent Owner contends claim 7 is not anticipated, it is rendered obvious in view of Larson. EX1002 ¶¶ 300-308.

Larson depicts "scattered plots" of signal clusters representative of each analyte as a function of color and intensity. EX1017 ¶¶ 113, 116, Figs. 5C, 6B, 9, 10, 14a, 15; EX1002 ¶¶ 303-304; *see supra* Section XI.G. Figure 5 depicts fluorescent signal(s) from probes in VIC and FAM colors at different intensities:



id. Fig. 5C, ¶ 113. This "scattered plot" is a chromatogram of exactly the type relied on by Patent Owner in its infringement contentions. *See supra* Section XI.G; EX1012 at 42; EX1002 ¶ 304.

As explained herein, Larson teaches in paragraph 140 assays involving three targets and two colors of the type that Patent Owner contends infringe the claims. EX1002 ¶ 305. To the extent Patent Owner contends that Larson does not teach generating a chromatogram in connection with such assays, a POSA would have nonetheless been motivated, in view of Larson, to generate a chromatogram using the fluorescent signal(s) of the assay. *Id.* Indeed, Larson teaches the value of visual representations of fluorescence data collected from hybridization probes in allowing one to quickly ascertain which targets are present and the relative amounts at which the various targets are present. *Id.* Additionally, the plots allow assessment of the fidelity with which the assay distinguishes among targets as reflected in the spacing between clusters. *Id.*; *see, e.g.*, EX1017 Figs. 5, 10, 14, 15, 17.

A POSA would have had a reasonable expectation of success in generating a chromatogram, including in the form Larson depicts. EX1002 ¶¶ 306-307; EX1017 Fig. 15. As Dr. Batt explains, it is a straightforward and routine matter to plot data obtained from a PCR experiment. *Id.* ¶ 307.

D. Claims 14-19

Claims 14-19 recite "a kit." As noted above, the requirement for a "kit" is not limiting. *See, e.g.*, *In re Rudy*, 778 Fed. App'x. at 946. To the extent Patent Owner contends that Larson does not disclose a "kit," it would have been obvious to combine the components disclosed in Larson together in a "kit." As Dr. Batt explains, a POSA would have been motivated to do this to streamline performance of the assay and would have expected success in doing so. *See* EX1002 ¶¶ 309-317.

Claim 19, reciting that "the analyte-specific reagents are each present at a different amount in the kit," is further obvious because Larson teaches using analyte-specific reagents in different amounts. *Id.* ¶¶ 312-317.

Larson teaches use of primers and labeled sequence-specific probes—all sequence-specific—at differing concentrations, including by varying primer and probe concentrations for increased resolution. *See supra* Section XI.Q; EX1017 ¶¶ 9, 12, 91, 94, 130, 134, 137, 146, 150, 151, Figs. 9, 12C; EX1002 ¶¶ 312-313. Larson teaches adjusting relative positions of signal populations for target molecules within a histogram by varying concentrations of sequence-specific primers and probes to optimize the pattern of colors and intensities used to detect targets. EX1017 ¶¶ 150-151; EX1002 ¶ 313. A POSA would have been motivated to change probe and primer concentrations, i.e., use different concentrations in optimizing to

enhance resolution and would have had a reasonable expectation of success given the extensive teaching of Larson. EX1002 ¶ 314.

XIII. GROUND 3: OBVIOUSNESS OF CLAIMS 1-10 AND 12-19 IN VIEW OF LARSON AND SAXONOV

As documented above, the claims require "unambiguously detecting the presence or absence" of analytes in a "single sample volume." The claimed "single sample volume" encompasses nothing more than a portion of an original sample solution, which may be ***later*** partitioned into sub-volumes for amplification. Patent Owner admits this in district court, stating, for instance, that the claimed "single sample volume" can be a portion of an original reaction mixture that is "***subsequently*** partitioned into multiple droplets." *See* EX1012 at 19-20; EX1002 ¶ 318. As proven above, claims 1-10 and 13-19 are invalid under this interpretation advanced by Patent Owner in district court. *See supra* Sections XI.A-Q.

Nevertheless, to the extent Patent Owner changes its tune and contends that the claimed "single sample volume" is limited to a single partition from the original sample solution (e.g., a single droplet), the claims are still invalid. EX1002 ¶ 319. This is because Larson, alone or in combination with Saxonov, at a minimum renders obvious the "unambiguous" detection of the "presence or absence" of multiple analytes in such individual sub-volumes. *Id.*

Saxonov and Larson are analogous art to the '921 patent—and to each other—because they are within the same field of endeavor: multiplex detection of polynucleotides using color-labeled sequence-specific probes, including where there are fewer colors than analytes. EX1001 at code (57), 12:28-14:3, 17:57-60, 21:39-23:30; EX1004 ¶¶ 19, 20, 37; EX1017 ¶¶ 34, 35, 138-153; EX1002 ¶¶ 109, 284, 320.

Indeed, Larson expressly teaches that there may be multiple targets in a single individual droplet and that its methods accommodate such "multiple occupancy" situations. *See* EX1017 ¶¶ 129, 141; EX1002 ¶ 321. Larson's assays use conditions and parameters that do precisely this. EX1002 ¶ 321. While this alone proves obviousness, the contemporaneous Saxonov reference likewise teaches such "multiple occupancy" situations and that one can easily distinguish among droplets having different combinations of targets based on their intensity in different color channels. Dr. Batt confirms a POSA would have at least found it obvious to incorporate Saxonov's teachings into Larson to do this. EX1002 ¶¶ 318-352.

A. Claim 1

1. An assay…M analytes

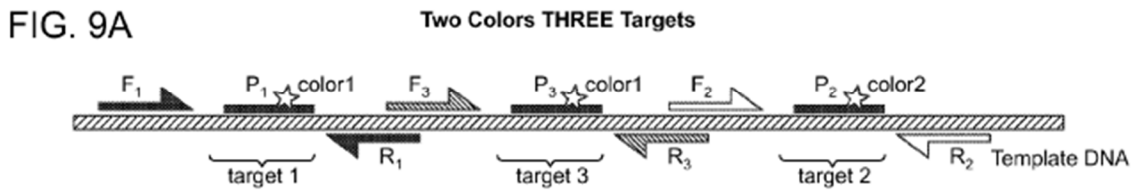
As documented above, Larson's assays detect the presence or absence of at least M analytes. *See supra* Section XI.A.1; EX1002 ¶ 322. The manner in which Larson "unambiguously" detects these M analytes," either alone or in combination

with Saxonov, is further documented below. *See infra* Section XIII.A.4; EX1002 ¶ 323.

2. wherein each…coding scheme

As documented above, Larson teaches a scheme wherein each of two or three analytes is encoded by an intensity of light in either one or two colors. *See supra* Section XI.A.1-4; EX1002 ¶¶ 324-327.

For example, Larson teaches a coding scheme wherein one detects three targets using only two colors, as depicted in Fig. 9:



EX1017 Fig. 9A. As shown, targets 1-3 are detected using corresponding forward and reverse primer pairs F_{1-3} and R_{1-3}, respectively, and labeled probes P_{1-3} for each of targets 1, 2, and 3. *Id.* ¶ 121. The probes for targets 1 and 3, probes P_1 and P_3, are labeled with the same color (color1), but provide different intensity signals, and probe P_2 is labeled with a different color (color2). *Id.* ¶ 121; EX1002 ¶ 325. This scheme is an example of an approach wherein each of the three analytes are encoded

by an intensity of fluorescent light (which is a component of a fluorescent signal) in one of two wavelengths. EX1002 ¶¶ 326-327.

3. wherein said…components, and

As documented above, Larson teaches assays where there are fluorescent signals that comprise two different wavelength components. *See supra* Sections XI.A.1-2, 4; EX1002 ¶¶ 328-329.

4. wherein said…than F,

To the extent this ground differs from Ground 1, it is primarily in the identification of the "single sample volume" disclosed in the prior art. Whereas in Ground 1 the "single sample volume" is taken to be a portion of the original sample mixture prior to it being partitioned into droplets, here the "single sample volume" is an individual droplet generated by partitioning the sample mixture. Under this mapping, the claims are obvious in view Larson alone or in further combination with Saxonov. EX1002 ¶¶ 330-348.

a. Larson Alone Renders Obvious Unambiguously Detecting Multiple Targets In A Single Droplet

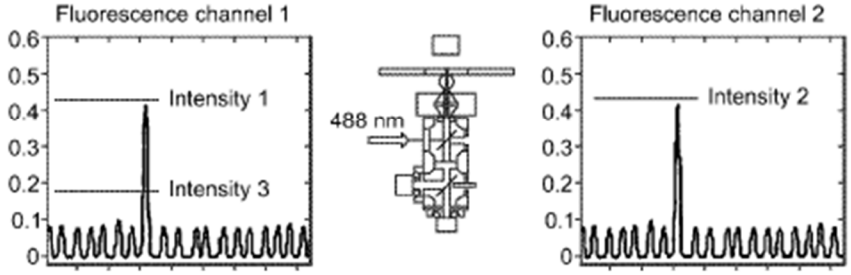
While Larson focuses on scenarios where droplets have only one target, it also teaches scenarios where individual droplets have multiple targets. Specifically, Larson teaches that the number of targets present in droplets will follow a Poisson distribution. EX1017 ¶ 6; EX 1002 ¶ 331. As Larson explains, in a so-called

"limiting dilution" regime, "some reactions contain zero DNA molecules, some reactions contain one molecule, and ***frequently some other reactions contain multiple molecules***, following the Poisson distribution." EX1017 ¶ 6. Larson goes on to state that "the invention is compatible with all distributions of DNA loading that conform to limiting or terminal dilution." *Id.* ¶ 52. Thus, by explaining that the invention is compatible with "limiting" dilution, Larson makes clear that the invention works in situations where droplets may contain multiple targets. Indeed, Larson later refers to the possibility of such "multiple occupancy" situations, and, while noting that complications may arise, says that "methods of the invention can accommodate these complications arising from multiple occupancy." *Id.* ¶ 141; EX1002 ¶ 332.

And, in fact, Larson teaches an assay that would do precisely this in Figure 9, which is an assay involving three targets and two colors, wherein one color is used to identify two of the targets and a second color identifies the third target. EX1017 ¶ 121, Fig. 9A; EX1002 ¶ 333.

Larson discloses specifically how this works in Figure 9C. As Larson explains, target 1 has a signal in a first color channel of a little above 0.4, target 3 has a signal in the same color channel of slightly less than 0.2, and target 2 has a signal in a different color channel of slightly greater than 0.4:

FIG. 9C



EX1017 Fig. 9C, ¶ 121; EX1002 ¶ 334. In tabular format, the signal signatures for the three individual targets in Figure 9 may be represented as follows:

	Color 1	**Color 2**
Intensity slightly less than 0.2	Target 3	NA
Intensity slightly greater than 0.4	Target 1	Target 2

EX1002 ¶ 335. Thus, each target has its own unique color/intensity signature that is not overlapping with that of the other two targets. *Id.*

Critically, consistent with Larson's teaching that its assays can accommodate "multiple occupancy," the foregoing coding scheme allows for determination of precisely which targets are present in a droplet even when multiple targets are present in a droplet. *See* EX1002 ¶¶ 335-337. As Dr. Batt explains, a POSA would recognize that the "Intensity 1" of slightly greater than 0.4 and "Intensity 3" of slightly less than 0.2 are such that a multiple of the lesser "Intensity 3" could be distinguished from the higher "Intensity 1" or multiples of it, as well as from

combinations of "Intensity 1" and "Intensity 3." *Id.* ¶ 336. Put another way, a POSA would have understood that the various combinations of analytes would result in distinguishable signals for the three analytes because the signals from P_1, P_2, P_3, P_1+P_2, P_1+P_3, P_2+P_3, $P_1+P_2+P_3$, and so on have different intensities as the combinations are additive and would each sum to unique values in each of the two colors used. EX1002 ¶ 336; EX1017 Fig. 9C.

Thus, Larson alone renders obvious to a skilled artisan assays unambiguously determining the presence or absence of three different targets (and combinations thereof) in individual droplets. EX1002 ¶ 337. In view of Larson, one of skill in the art would have had a reasonable expectation of successfully determining precisely which targets (or combinations of targets) are present or absent in an individual droplet as Larson teaches assays that perform this limitation. *See* EX1002 ¶¶ 331-338. Further, as Dr. Batt explains, a POSA would have been highly motivated to identify unambiguously which targets (or combinations thereof) are present in a droplet so that one extracts the maximum amount of information from the experiment and adequately deals with the "multiple occupancy" situations that arise with loading of targets into droplets with a Poisson distribution. *See id.* ¶¶ 337-338.

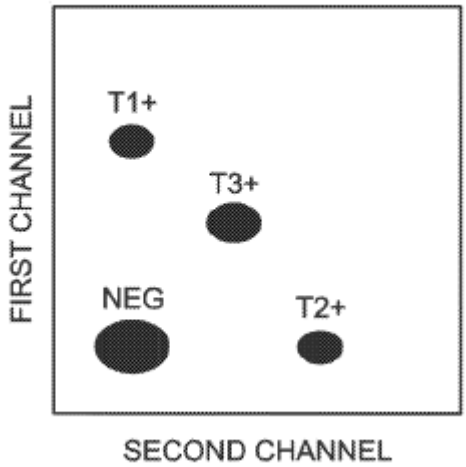
b. Larson In Combination With Saxonov Renders Obvious Unambiguously Detecting Multiple Targets In A Single Droplet

To the extent Patent Owner contends that Larson alone does not render obvious the unambiguous detection of multiple targets in a single droplet, it would have been obvious in further view of Saxonov. EX1002 ¶¶ 339-348.

Saxonov, like Larson, teaches loading of droplets with targets according to a Poisson distribution, contemplating the possibility of multiple targets in a droplet. Saxonov states the "probability of finding exactly 0, 1, 2, 3, or more copies in a partition, based on a given average concentration of analyte in the partitions, is described by a Poisson distribution." EX1004 ¶ 3, *see also id.* ¶ 43; EX1002 ¶ 340.

Importantly, Saxonov's Figure 10 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

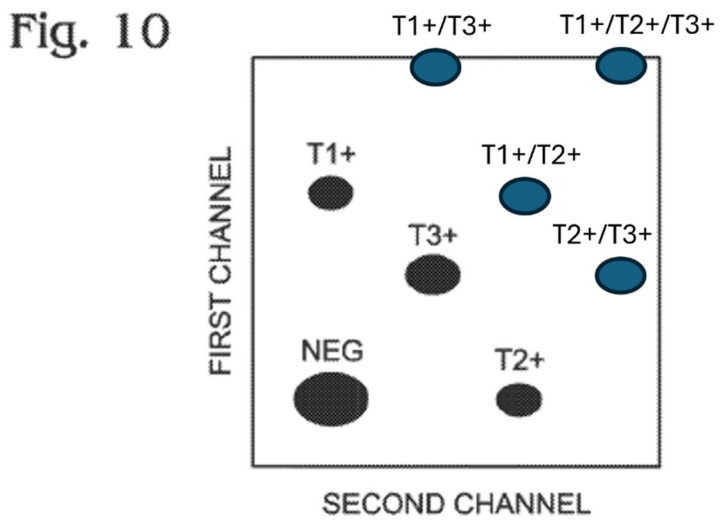


EX1004 Fig. 10, ¶¶ 18, 78-79; EX1002 ¶ 341.[4] This is the exact approach already taught in Larson, which is relied upon in Ground 1 above and that Patent Owner accuses of infringing. *See supra* Section XI.A.4; EX1002 ¶ 341.

Though the figure does not show the signals for the droplets that have multiple targets, Saxonov contemplates that one will be able to distinguish droplets any combinations of targets. *See, e.g.*, EX1004 ¶ 78 ("To simplify the presentation, double-positive populations (T1+/T2+, T1+/T3+, and T2+/T3+) and the triple-

[4] This approach wherein targets are detected and distinguished from one another based on combinations of colors is similarly taught in the provisional to which Saxonov claims priority, which teaches that signals can be "collected in one or more different channels" from "the same" target. *See* EX1007 at 9:8-10.

positive population (T1+/T2+/T3+) are not shown."); EX1002 ¶ 342. 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:



EX1002 ¶ 342. 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; EX1002 ¶ 343.

To the extent Patent Owner contends that Larson alone does not contemplate unambiguously distinguishing among droplets with different combinations of droplets, it would have been obvious to use the approach in Figure 10 of Saxonov with Larson. As Dr. Batt explains, a POSA would have been naturally motivated to

make this combination because Larson already teaches the same approach utilized in Figure 10 of Saxonov, using a distinct color for each of two targets and a combination of two colors for a third target. EX1002 ¶¶ 344-346. Incorporating Saxonov's teachings that droplets with different combinations of targets can be "separated by intensity" would have been a no-brainer and something a POSA would have been highly motivated to extract the most information possible from the experiment and address "multiple occupancy" situations. *Id.*

Further, a POSA would have had a reasonable expectation of successfully doing this. A POSA would understand that the signals from droplets with different combinations of targets could be easily distinguished based on intensity, just as in Figure 10 of Saxonov. EX1004 ¶ 78, Fig. 10; EX1002 ¶¶ 347-348. Larson already teaches tuning the intensity of probes corresponding to different targets to optimize their detection, in the same manner as in Saxonov. EX1017 ¶¶ 134-137; EX1004 ¶¶ 51-52; EX1002 ¶ 347. Using this approach, Larson teaches distinguishing ***nine*** different types of droplets, as shown in Figure 15 with genuine experimental data. EX1017 at Fig. 15; EX1002 ¶ 347. Given that Larson had already taught that intensity could be easily adjusted to distinguish among different droplet types, a skilled artisan would have had no question of being able to implement the approach of Figure 10 of Saxonov with Larson. EX1002 ¶¶ 347-348.

5. wherein the…analytes, and

Disclosed. *See supra* Section XI.A.5; EX1002 ¶¶ 349-351.

6. wherein the…sample volume

As Dr. Batt explains, the assays in Larson use PCR amplification of analytes in droplets. *See* EX1002 ¶ 352. An individual microfluidic droplet falls within the scope of "single sample volume." *Id.*

B. Claims 2-10

Disclosed and/or rendered obvious. *See supra* Sections XI.B-J, XII.A, B, C; EX1002 ¶ 353.

C. Claim 12: The assay of claim 1, wherein at least one step of said assay is performed using a computer and wherein said computer is connected to a thermal cycler.

Larson discloses that at least one step of the method is performed using a computer connected to a thermal cycler. EX1002 ¶¶ 354-361. Larson discloses apparatus for its assays including "processors (e.g., computers and software)" which a POSA would have understood to be a computer to perform calculations required for steps of the method, including to detect/measure a signal and to control the thermal cycler required for the PCR, where controlling the thermal cycler requires that the computer is necessarily at least operatively connected to the thermal cycler. EX1002 ¶ 355; EX1017 ¶ 89 ("[S]uitable detection apparatuses include[s]…processors (e.g., computers and software), and combinations [including

processors]…which cooperate to detect a signal representative of a characteristic, marker, or reporter, and to determine and direct the measurement."); *id.* ¶¶ 5, 78-79, 82-85, 137; EX1002 ¶ 356.

To the extent Patent Owner contends that Larson does not contemplate performing at least one step of the assay using a computer that is connected to a thermal cycler, it would have been obvious in further light of Saxonov. EX1002 ¶ 357. Saxonov discloses an apparatus 60 for performing its assay that includes:

> [A] partitioning assembly, such as a droplet generator 62 ("DG"), a thermal incubation assembly, such as a thermocycler 64 ("TC"), a detection assembly (a detector) 66 ("DET"), and a data processing assembly (a processor) 68 ("PROC"), or any combination thereof, among others. ***The data processing assembly may be***, or may be included in, ***a controller that*** communicates with and ***controls operation of any suitable combination of the assemblies***….Any suitable combination of the assemblies may be operatively connected to one another.

EX1004 ¶ 45; EX1002 ¶ 358. Saxonov further discloses that processor 68 can be used to process signals generated in the assay(s). *Id.* ¶ 46; EX1002 ¶ 359. Moreover, being a part of apparatus 60 that includes the thermal incubation assembly, and controlling the thermal cycling carried out by the thermal cycler, the computer (processor 68) is connected to the thermal cycler (thermocycler 64). *Id.* ¶¶ 45-46; EX1002 ¶ 359.

Given the teachings of Larson and Saxonov, a POSA would have found it obvious to use a computer to perform the steps of droplet generation, thermal incubation, detection, and data processing, as set forth in Saxonov, for the benefit of improved control and convenience, as well as to perform the required processing of the data. EX1002 ¶ 360. Control of the detection apparatus during detection of signals and data processing steps meet the recited detection step and a POSA would have had a reasonable expectation of success given that both references carry out such. A POSA would have further understood that the computer was connected to the thermal cycler, as it controls the thermal cycler, as well as it being obvious to include the computer and thermal cycler in the same apparatus, as taught by Saxonov. Given Saxonov and Larson disclose such use of a computer, a POSA would have had a reasonable expectation of success. EX1002 ¶ 361.

D. Claim 13

Disclosed. *See supra* Section XI.K; EX1002 ¶¶ 362-363.

E. Claim 14

To the extent Patent Owner contends that Larson does not anticipate or alone render the claimed kit obvious, it would have been obvious in further view of Saxonov. *See supra* Sections XI.L, XII.D; EX1002 ¶¶ 364-385.

1. A kit…measurement, comprising

The preamble is not limiting and, if deemed limiting, is disclosed or rendered obvious in view of Larson alone. *See supra* Sections XI.L.1, XII.D; EX1002 ¶¶ 365-366.

2. analyte-specific reagents,…the value;

Disclosed. *See supra* Section XI.L.2; EX1002 ¶ 367.

3. wherein said kit…analytes, and

Disclosed and/or rendered obvious by Larson alone or in further view of Saxonov. *See supra* Sections XI.L.3, XIII.A.4-5; EX1002 ¶¶ 368-379.

4. wherein the analytes…sample volume.

Disclosed and/or rendered obvious by Larson alone or in further view of Saxonov. *See supra* Sections XI.L.4, XIII.A.6; EX1002 ¶¶ 380-385.

F. Claims 15-18

Disclosed and/or rendered obvious by Larson. *See supra* Sections XI.M-P, XII.D; EX1002 ¶ 386.

G. Claim 19: The kit of claim 14, wherein the analyte-specific reagents are each present at a different amount in the kit.

Disclosed and/or rendered obvious by Larson. *See supra* Sections XI.Q, XII.D; EX1002 ¶ 387.

XIV. GROUND 4: CLAIM 11 IS OBVIOUS IN VIEW OF LARSON, SAXONOV, AND SILVERBROOK

A. Claim 11: The assay of claim 1, further comprising transmitting information concerning the presence or absence of at least one of said analytes through a computer network.

Larson anticipates and/or renders obvious alone, or in combination with Saxonov, minimum renders obvious the assay of claim 1. *See supra* Sections XI.A, XII.A; EX1002 ¶ 388. Claim 11 would have been obvious in further view of Silverbrook. EX1002 ¶¶ 388-393.

Silverbrook is analogous art to Larson, Saxonov, and the '921 patent because it also relates to detecting nucleic acid analyte detection/testing employing PCR and hybridization. EX1009 at code (57), ¶¶ 195-243, Fig. 99; EX1002 ¶ 389.

Claim 11 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 which analytes are present in a sample and transmitting results of the testing through a computer network. EX1002 ¶ 390; 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 provide databases of medical records and would have had a reasonable expectation of success. EX1002 ¶¶ 391-393.

XV. 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). S*ee Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 7-11 (P.T.A.B. Feb. 13, 2020), Paper 6 at 7-11 (precedential) (citing *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17-18 (P.T.A.B. Dec. 15, 2017) (precedential)). As documented below, the same art and arguments presented herein were not previously presented to the Office in any meaningful or relevant way. In addition, the Examiner erred by not considering the relevant teachings in Larson. As such, application of *Becton* overwhelmingly confirms that the Board should not exercise its discretion to deny institution under § 325(d).

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

None of the asserted references were considered substantively by the Examiner. Saxonov was nominally of record during examination, based on an IDS

filed March 25, 2021. EX1016 at 7. Larson itself was not submitted, although an IDS filed March 25, 2021, included in its listing of references both U.S. Patent No. 9,366,632 by Link et al., identified as a continuation-in-part of Larson, and U.S. Patent No. 9,441,266 by Larson et al., identified as a continuation of Larson. EX1016 at 7; EX1022; EX1017; EX1033; EX1001. None of these references, however, were the basis of any rejection by the Examiner.

Then-pending claims were subject to prior art rejections over Han et al. in view of Lin et al, and in further combination with additional references, grounded on Han's disclosed use of multicolor quantum dots and alleged immobilization, which applicant overcame by arguing that Han (and the combinations) did not disclose or suggest an assay according to the claims without immobilization. EX1030 at 5-9; EX1025 at 6-7; EX1026 at 2-9; EX1029 at 6-12; EX1006 at 6.

Accordingly, "the overlap between the arguments made during examination" and arguments made in this petition is minimal, as no arguments were made during examination with respect to Larson. *See 3Shape A/S v. Align Tech., Inc.*, IPR2019-00160, Paper No. 9 at 39-42 (P.T.A.B. June 11, 2019). Also, as discussed above, and supported by the testimony of Dr. Batt, Larson discloses its assays that unambiguously detect the presence or absence of multiple polynucleotide analytes without immobilizing the analytes. *See supra* Section X.A.6.; EX1002 ¶¶ 144-147.

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 Larson.

In the Notice of Allowance, the Examiner did not discuss or cite any teaching from Larson, instead they stated only that the "claims recite an empirical assay detecting the presence and absence of M analytes with F wavelength components wherein M is greater than F without using mass spectrometry or immobilization." EX1006 at 6. As discussed above, however, Larson discloses such assays without use of analyte immobilization. *See supra* Section X.A.5.; EX1002 ¶¶ 139-143. Accordingly, the stated reasons for allowance show material error by the Examiner in allowing the claims during examination.

B. *Fintiv* Does Not Support Discretionary Denial

The parallel district-court proceedings do not justify discretionary denial under the factors identified in *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 (P.T.A.B. 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).

The Northern District of California applies a three factor test for granting a stay pending an IPR: "(1) whether discovery is complete and whether a trial date has been set; (2) whether a stay will simplify the issues in question and trial of the case; and (3) whether a stay would unduly prejudice or present a clear tactical disadvantage to the non-moving party." *See id.* at 956. All three factors favor a stay here.

As discussed below for *Fintiv* Factors 2 and 3, discovery is not complete and there is no trial date. Courts in the district have granted stays pending IPR when fact discovery was in its early stages, and where a trial date had not yet been set, even where infringement, damages, and invalidity contentions, as well as preliminary claim constructions, had been served. *Synthego Corp. v. Agilent Techs., Inc.*, No. 5:21-CV-07801-EJD, 2022 WL 2704121 at *2 (N.D. Cal. July 12, 2022) (J. Davila)[5]

[5] The parallel district court proceeding here is also before Judge Davila. *See, e.g.*, EX1003.

(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 an initial complaint for infringement, which ***did not*** include the '921 patent, 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 *In re ChromaCode*, Case No. 5:23-cv-04823, after consolidation with another case. EX1024; EX1041. Relying on the earliest filing date of the consolidated case, September 20, 2023, the estimated trial date based on median time to trial—48.9 months later—is approximately October 2027. EX1023 at 66; *Mylan Pharms. Inc. v. Bayer Pharma Aktiengesellschaft*, IPR2022-00517, Paper 15 at 8-9 (P.T.A.B. Aug. 9, 2022) (evaluating median time to trial for factor 2). Complicating the matter

further is that the district court schedule was recently vacated and the matter was transferred to a new judge. EX1042.

Petitioner expects a decision on institution within approximately seven months, giving a projected statutory deadline for a final written decision of about April 2026, which would be approximately 1.5 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 (P.T.A.B. 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 originally scheduled for August 28, 2024, was first delayed and has now been vacated, and a claim construction order will not be expected for some time following that, as of this date, unscheduled hearing. EX1027 at 4; EX1042. Indeed, as noted the entire district court schedule was recently vacated and the matter was transferred to a new judge, who has not yet entered a new

schedule. EX1042. No depositions have been taken, and expert discovery has not yet begun. EX1027 at 4. Likewise, neither dispositive nor *Daubert* motions have been filed. In fact, there are not even scheduled dates for these events.

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). This factor favors institution.

4. Factor 4: Overlap of Issues

While the same prior art is at issue in the district court, there are extensive additional art and issues being litigated and Claim 18 is not being asserted. Claim 18 adds that the "number of hybridization probes…is greater than" the number of polynucleotide analytes, which is a meaningful additional limitation that will not be otherwise be adjudicated if institution is denied. EX1001 at 68:50-51; *see* EX1012 at 67. Thus, this factor favors institution.

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 (P.T.A.B. Oct. 4, 2022) (precedential). 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.* at 6.

XVI. CONCLUSION

Petitioner respectfully requests cancellation of the '921 patent.

Dated: September 16, 2024

Respectfully submitted,

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APPENDIX A: LISTING OF CHALLENGED CLAIMS

No.	Limitation
1	An assay that is capable of unambiguously detecting the presence or absence of each of at least M analytes, wherein each of said at least M analytes is encoded as a value of one component of a fluorescent signal, thereby generating a coding scheme, wherein said fluorescent signal comprises F wavelength components, and wherein said assay is capable of unambiguously detecting the presence or absence of each of said at least M analytes, in any combination of presence or absence in a single sample volume, based on detection of said F wavelength components, when M is greater than F, wherein the assay does not require the use of mass spectrometry or immobilization of said at least M analytes, and wherein the analytes are amplified in the single sample volume.
2	The assay of claim 1, wherein each of said at least M analytes is encoded as at least one first value in a first component of said fluorescent signal and at least one second value in a second component of said fluorescent signal.
3	The assay of claim 2, wherein said first value is an intensity or range of intensities.
4	The assay of claim 2, wherein said coding scheme is made nondegenerate by enumerating every legitimate result that can be obtained from said coding scheme, identifying each legitimate result that is degenerate, and eliminating at least one potential analyte code from said coding scheme to eliminate degeneracy
5	The assay of claim 1, wherein said detecting is performed with reagents comprising hybridization probes.

No.	Limitation
6	The assay of claim 5, wherein said hybridization probes comprise one or more hybridization probes specific for different analytes and comprising an identical fluorophore or combination of fluorophores.
7	The assay of claim 5, wherein said fluorescence signal from said hybridization probes are used to construct a chromatogram.
8	The assay of claim 1, wherein said signal is generated during a polymerase chain reaction.
9	The assay of claim 1, wherein at least one of said analytes is encoded by at least one additional value, wherein said at least one additional value is selected from the group consisting of a value from at least one additional component of said signal, a value from at least one component of an additional signal, and combinations thereof.
10	The assay of claim 1, wherein at least one of said analytes comprises a polynucleotide.
11	The assay of claim 1, further comprising transmitting information concerning the presence or absence of at least one of said analytes through a computer network.
12	The assay of claim 1, wherein at least one step of said assay is performed using a computer and wherein said computer is connected to a thermal cycler.
13	The assay of claim 1, wherein said coding scheme is innately nondegenerate or non-degenerate by construction.
14	A kit for detecting the presence or absence of at least M analytes by generating a single cumulative measurement, comprising analyte-specific reagents, wherein: a. each of said at least M analytes is encoded as a value of one component of a fluorescent signal, thereby generating a coding scheme, wherein each of said at least M analytes is represented in said coding scheme by said value, and wherein said

No.	Limitation
	encoding is performed in a manner that eliminates degeneracy; and b. each of said analyte-specific reagents, when contacted with a sample comprising its corresponding analyte, generates the value; wherein said kit is capable of unambiguously detecting the presence or absence of each analyte of M analytes in a single sample volume, in any combination of presence or absence, and wherein the kit does not require the use of mass spectrometry or immobilization of said M analytes, and wherein the analytes are simplified [sic, amplified] in the single sample volume.
15	The kit of claim 14, wherein said fluorescent signal comprises F wavelength components and said kit is capable of unambiguously detecting the presence or absence of M analytes, in any combination of presence or absence, when M is greater than F.
16	The kit of claim 14, wherein said analyte-specific reagents comprise a plurality of hybridization probes.
17	The kit of claim 16, wherein said plurality of hybridization probes comprise a fluorophore, and wherein said plurality of hybridization probes are specific for different analytes.
18	The kit of claim 17, wherein said number of hybridization probes in the kit is greater than M.
19	The kit of claim 14, wherein the analyte-specific reagents are each present at a different amount in the kit.

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 13,948 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: September 16, 2024

By: */Derek C. Walter/*
Derek C. Walter
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Reg. No. 74,656

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 11,827,921 B2** WITH PETITIONER'S EXHIBIT LIST, POWER OF ATTORNEY, AND EXHIBITS 1001-1007, 1009, 1012-1017, 1022-1030, 1033 and 1036-1042 are being served on September 16, 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: September 16, 2024

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