

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

Case No. IPR2025-01546

PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 12,168,797 B2

Mail Stop "PATENT BOARD"
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

TABLE OF CONTENTS

	Page
I. INTRODUCTION	1
II. TECHNOLOGY BACKGROUND.....	3
A. Multiplex PCR Amplification	3
B. Fluorescent Signals and Detection of Polynucleotide Analytes	3
C. Quantitative and Digital PCR.....	5
III. OVERVIEW OF THE '797 PATENT	7
A. The Claimed Coding Scheme.....	7
B. The Challenged Claims	10
IV. LEVEL OF ORDINARY SKILL IN THE ART OF THE '797 PATENT	11
V. PO'S INFRINGEMENT CONTENTIONS IN PARALLEL DISTRICT COURT LITIGATION.....	12
VI. CITED PRIOR ART.....	13
A. Jouvenot.....	13
B. Larson	21
C. Secondary References Relied Upon Herein.....	22
VII. MANDATORY NOTICES	24
A. Real Party-in-Interest	24
B. Related Matters.....	24
C. Lead and Back-Up Counsel and Service Information	24
VIII. GROUNDS FOR STANDING.....	24
IX. STATUTORY GROUNDS FOR THE CHALLENGES	25
X. CLAIM CONSTRUCTION	26
XI. GROUND 1: CLAIMS 1-2, 5-6, 10, AND 18 ARE OBVIOUS IN VIEW OF JOUVENOT.....	28
A. Claim 1	28

B.	Claim 2: The system of claim 1, wherein the multi-channel detector is further configured to detect: a fifth electromagnetic signal at a fifth wavelength from the sample chamber, the fifth electromagnetic signal generated by excitement of a fifth fluorophore of the multiple fluorophores; a sixth electromagnetic signal at a sixth wavelength from the sample chamber, the sixth electromagnetic signal generated by excitement of a sixth fluorophore of the multiple fluorophores; and wherein C=6.	48
C.	Claim 5: The system of claim 1, wherein F=3.....	48
D.	Claim 6: The system of claim 5, wherein the multiple fluorophores is selected from the group consisting of a blue fluorophore, a green fluorophore, a yellow fluorophore, a red fluorophore, and any combinations thereof.	48
E.	Claim 10: The system of claim 5, wherein the analyte-specific hybridization probes are labeled with a fluorophore of the multiple fluorophores.	49
F.	Claim 18: The system of claim 5, further comprising a display coupled to the processor controlled analyzer to visualize a plot of the first and second values.	50
XII.	GROUND 1(A): CLAIMS 6-9 ARE FURTHER OBVIOUS IN VIEW OF LARSON, BRABETZ, AND/OR LAKOWICZ.....	52
A.	Claim 6: The system of claim 5, wherein the multiple fluorophores is selected from the group consisting of a blue fluorophore, a green fluorophore, a yellow fluorophore, a red fluorophore, and any combinations thereof.	52
B.	Claim 7: The system of claim 5, wherein the multiple fluorophores is selected from the group consisting of a fluorescein amidite (FAM), a cyanine 3 (Cy3), a carboxy-X-rhodamine (ROX), a cyanine 5 (Cy5), a cyanine 5.5 (Cy5.5), and any combinations thereof.	55

C.	Claim 8: The system of claim 5, wherein the multiple fluorophores has a maximum excitation wavelength selected from the group consisting of about 494 nm, about 550 nm, about 567 nm, about 650 nm, about 675 nm, and any combinations thereof.	56
D.	Claim 9: The system of claim 5, wherein the multiple fluorophores has a maximum emission wavelength selected from the group consisting of about 518 nm, about 565 nm, about 591 nm, about 670 nm, about 697 nm, and any combinations thereof.	57
XIII.	GROUND 1(B) CLAIM 11 IS FURTHER OBVIOUS IN VIEW OF LARSON, BRABETZ, MALTEZOS, NEUZIL, AND/OR OLEKSY	58
	Claim 11: The system of claim 5, wherein the detector comprises four or six band pass filters.	58
XIV.	GROUND 1(C): CLAIM 13 IS FURTHER OBVIOUS IN VIEW OF LARSON, MALTEZOS, DUBE, AND/OR WITTWER.....	60
	Claim 13: The system of claim 5, wherein the multi-channel detector comprises four or six photodetectors.	60
XV.	GROUND 1(D): CLAIM 14 IS FURTHER OBVIOUS IN VIEW OF LARSON AND/OR MALTEZOS	62
	Claim 14: The system of claim 5, wherein the multi-channel detector comprises photodetectors that enable the detection of blue, green, and red fluorescent signals.	62
XVI.	GROUND 1(E): CLAIM 15 IS FURTHER OBVIOUS IN VIEW OF LARSON, BRABETZ, LAKOWICZ, MALTEZOS, DUBE, AND/OR WITTWER	65
	Claim 15: The system of claim 5, wherein the multi-channel detector comprises photodetectors that enable the detection ranges selected from the group consisting of from about 483 nm to about 533 nm, from about 523 nm to about 568 nm, from about 558 nm to about 610 nm, from about 615 nm to about 670 nm, and any combinations thereof.	65
XVII.	GROUND 1(F) CLAIM 18 IS FURTHER OBVIOUS IN VIEW OF LARSON, MALTEZOS, AND/OR SLEPNEV.....	67

Claim 18: The system of claim 5, further comprising a display
coupled to the processor controlled analyzer to visualize a plot
of the first and second values.67

XVIII. ...GROUNDS 2-2(F): CLAIMS 1-2, 5-11, 13-15, AND 18 ARE OBVIOUS
IN FURTHER VIEW OF LEHNEN68

XIX. CONCLUSION.....70

TABLE OF AUTHORITIES

	Page
CASES	
<i>Allen Eng’g Corp. v. Bartell Indus., Inc.</i> , 299 F.3d 1336 (Fed. Cir. 2002)	28
<i>Aptiv Servs. US, LLC v. Microchip Tech., Inc.</i> , IPR2024-00646, Paper 11 (P.T.A.B. Sept. 25, 2024).....	27
<i>Bio-Rad Inc. v. California Inst. of Tech.</i> , IPR2024-01451, Paper 11 (P.T.A.B. Mar. 27, 2025)	24
<i>Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.</i> , 800 F.3d 1375 (Fed. Cir. 2015)	14
<i>Hospira, Inc. v. Amgen Inc.</i> , IPR2021-00528, Paper 7 (P.T.A.B. Aug. 17, 2021)	26
<i>In re ChromaCode Litigation</i> , 5:23-cv-04823-EKL (N.D. Cal.).....	24
<i>In re Giacomini</i> , 612 F.3d 1380 (Fed. Cir. 2010)	14
<i>Intel Corp. v. Qualcomm Inc.</i> , 21 F.4th 801 (Fed. Cir. 2021)	27
<i>PLR Worldwide Sales Ltd. v. Flip Phone Games, Inc.</i> , IPR2024-00209, Paper 9 (P.T.A.B. May 10, 2024)	27
STATUTES	
35 U.S.C. § 102	21, 22, 23
35 U.S.C. § 103	25, 26

MPEP § 213614

PETITIONER’S EXHIBIT LIST

Exhibit #	Description
EX1001	U.S. Patent No. 12,168,797 “the ’797 patent”
EX1002	Declaration of Carl A. Batt, Ph.D.
EX1003	U.S. Patent No. 9,921,154 “Jouvenot”
EX1004	U.S. Patent Provisional Application No. 61/507,082 (filed July 13, 2011) (Serge Saxonov, Simant Dube, John F. Regan, applicants) (“the ’082 Provisional”)
EX1005	Declaration of Kevin Struhl, Ph.D., <i>Bio-Rad Labs., Inc. v. Cal. Inst. Tech.</i> , IPR2024-01451, EX2001 (Dec. 30, 2024)
EX1006	Joseph R. Lakowicz, <i>Principles of Fluorescence Spectroscopy</i> (3d. 2006)
EX1007	Petition for <i>Inter Partes</i> Review of U.S. Patent No. 11,827,921, <i>Bio-Rad Labs., Inc. v. Cal. Inst. Tech.</i> , IPR2024-01451, Paper 1 (Sept. 16, 2024)
EX1008	U.S. Patent No. 8,614,061 “Brabetz”
EX1009	U.S. Patent No. 12,168,797 Infringement Claim Charts from Infringement Contentions, served on July 2, 2025, <i>In re ChromaCode</i> , Case No. 5:23-cv-04823, N.D. Cal.
EX1010	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.
EX1011	Pamela M. Holland, et al., “Detection of specific polymerase chain reaction product by utilizing the 5’ → 3’ exonuclease activity of <i>Thermus aquaticus</i> DNA polymerase,” <i>Proc. Natl. Acad. Sci. USA</i> , Vol. 88, pp. 7276-7280, August 1991 Biochemistry “TaqMan Paper”

Exhibit #	Description
EX1012	U.S. Patent Application Publication No. US 2008/0003649 A1 “Maltezos”
EX1013	U.S. Patent Application Publication No. US 2011/0250597 A1 “Larson”
EX1014	Complaint for Patent Infringement of U.S. Patent Nos. 12,168,797, filed on February, 18 2025, Dkt No. 1, <i>Cal. Inst. of Tech. v. Bio-Rad, Laby’s, Inc.</i> , Case No. 6:25-cv-01701, consolidated into <i>In re ChromaCode Litigation</i> , Case No. 5:23-cv-04823-EKL (N.D. Cal.).
EX1015	Shivaprasad H. Sathyanarayana and Lauren M. Wainman, “Chapter 2, Laboratory approaches in molecular pathology: the polymerase chain reaction,” <i>Diagnostic Molecular Pathology</i> , 2024
EX1016	Deposition of Kevin Struhl, Ph.D., <i>Bio-Rad Labs., Inc. v. Cal. Inst. Tech.</i> , IPR2024-01451 (July 24, 2025)
EX1017	U.S. Patent Application Publication No. US 2010/0227386 A1 “Neuzil”
EX1018	U.S. Patent Application Publication No. US 2003/0219754 A1 “Oleksy”
EX1019	U.S. Patent Application Publication No. US 2009/0239308 A1 “Dube”
EX1020	U.S. Patent Application Publication No. US 2009/0258414 A1 “Wittwer”
EX1021	U.S. Patent Application Publication No. US 2012/0100600 A1 “Slepnev”
EX1022	European Patent Specification 0,594,763 B1 “Lehnen”
EX1023	Nucleic Acids, https://www.genome.gov/genetics-glossary/Nucleic-Acids , updated September 2, 2025
EX1024	Introduction of Molecular Beacons, https://molecularbeacons .

Exhibit #	Description
	org/MB_introduction.html (downloaded July 10, 2024)
EX1025	Notice of Allowance from Prosecution File History of U.S. Patent No. 12,168,797, filed on November 18, 2024
EX1026	Final Rejection of U.S. Patent No. 12,168,797, filed on July 13, 2023
EX1027	Information Disclosure Statement noting Saxonov from Prosecution File History of U.S. Patent No. 10,068,051 filed on August 5, 2014
EX1028	Information Disclosure Statement from Prosecution File History of U.S. Patent No. 10,770,170 filed on March 7, 2018
EX1029	Information Disclosure Statement from Prosecution File History of U.S. Patent No. 11,827,921 filed on May 1, 2020
EX1030	Information Disclosure Statement from Prosecution File History of U.S. Patent No. 12,168,797 filed on July 13, 2023
EX1031	Declaration of Maria P Garcia, IP Research Librarian

I. INTRODUCTION

Bio-Rad Laboratories, Inc., (“Petitioner”) requests *inter partes* review of claims 1-2, 5-11, 13-15, and 18 of United States Patent No. 12,168,797 (“the ’797 patent”), which issued on December 17, 2024. The ’797 patent, entitled “Signal Encoding and Decoding in Multiplexed Biochemical Assays,” relates to detecting multiple nucleic acid analytes, such as DNA molecules, in the same experiment. As proven herein, the ’797 patent claims are directed to a straightforward prior art technique for the detection of multiple target molecules, albeit performed in replicate fashion. Merely replicating a prior art process, however, is hardly novel or inventive, and nothing in the claims or specification of the ’797 patent suggests otherwise.

The facts showing obviousness here are straightforward. According to the contentions of Patent Owner (“PO”) in parallel district court litigation, the claims of the ’797 patent cover a system wherein nucleic acid targets are encoded for detection using both the wavelength and intensity of electromagnetic signals. At a given wavelength, two targets may be detected: a first target is detected using a first light intensity, and a second target is detected using twice (or roughly twice) the first intensity. If both targets are present, one detects triple (or roughly triple) the first intensity. Thus, at every wavelength, one can determine which of the two targets are present, whether individually or in combination. The challenged claims cover nothing more than the replication of this process across a minimum of four different

wavelengths of light.

Yet, the exact encoding scheme claimed in the '797 patent wherein, for a given wavelength, a first target is encoded by a first intensity and a second target is encoded by double that intensity had long since been taught in the prior art, including in both the Jouvenot and Larson references relied upon herein. And these very references also taught that one should use not just use a single wavelength, but that one should use multiple wavelengths of light to detect more targets. While the claims recite the use of a peculiar equation, this equation is nothing more than a mathematical expression of the replicated coding scheme summarized above. As such, the system claimed in the '797 patent based on replicating a known coding scheme across multiple wavelengths is obvious.

The '797 patent never once suggests that the inventors had achieved any breakthrough in optics or signal detection to make such replication possible. Far from it, the '797 patent admits that “[m]any real-time PCR and quantitative PCR instruments comprise an excitation light source and band pass filters that enable the detection of fluorescent signals in four colors (e.g., blue, green, yellow, and red). Therefore, the methods of the invention can be readily applied using instruments widely used in the art.” EX1001 at 35:30-35. If anything, the '797 patent specification confirms obviousness.

The challenged claims should thus be cancelled.

II. TECHNOLOGY BACKGROUND

A. Multiplex PCR Amplification

Petitioner's expert, Dr. Batt, provides an overview of the chemical structure of nucleic acids. EX1002 ¶¶ 30-35. Many biotechnology applications rely on base-pairing of complementary nucleic acid sequences and the 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 regions of the single strands. *Id.* Then, DNA polymerase extends each primer by adding nucleotides 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.

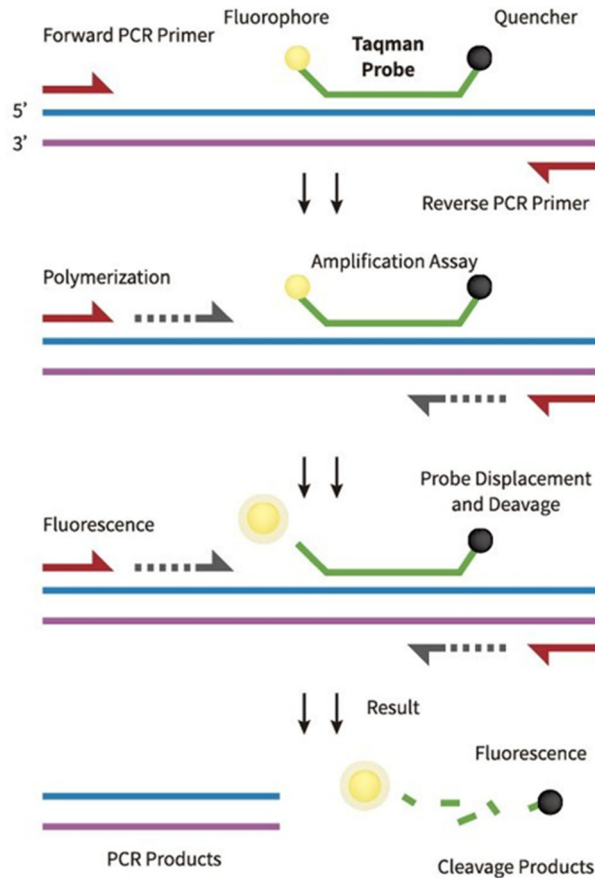
Multiplex PCR amplifies multiple polynucleotide sequences using multiple primer pairs for multiple target sequences in a single reaction volume concurrently. *Id.* ¶ 39. Multiplex PCR was well-known in the art and understood to be faster, less expensive, and more convenient than amplifying each polynucleotide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

B. Fluorescent Signals and Detection of Polynucleotide Analytes

Base-pairing of complementary sequences was also used 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 by cleaving the probe:



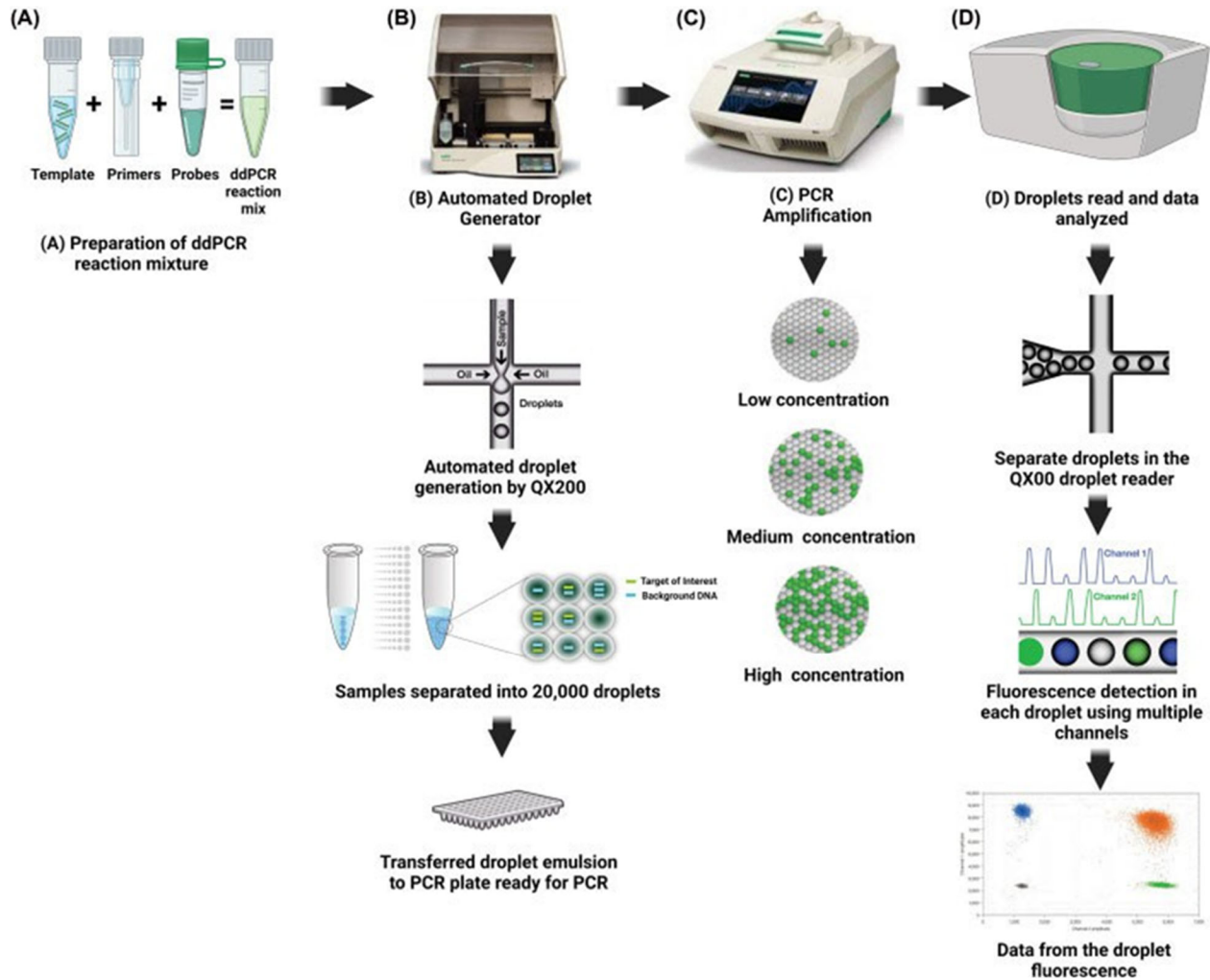
EX1010 at 6; EX1011 (describing assay); EX1002 ¶ 42.

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 target polynucleotide in a sample, allowing analyte quantification. *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, meaning multiple reactions can be performed simultaneously. *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.* The image below shows the workflow for performing dPCR using Petitioner's droplet-based products:



EX1015 at 12; EX1002 ¶ 47.

III. OVERVIEW OF THE '797 PATENT

The '797 patent issued on December 17, 2024, claiming the benefit of a February 3, 2012 provisional application. EX1001 at codes (45), (60), 1:6-15. For the purposes of this proceeding, it is assumed that the '797 patent is entitled to a February 3, 2012 priority date.

A. The Claimed Coding Scheme

The '797 patent purports to describe detection of polynucleotide analytes

using a so-called “cumulative” signal that can be decoded to determine what combination of target analytes is present in a single sample volume. EX1001 at Abstract. These coding schemes employ signals generated from labeled probes to map different combinations of signals to different combinations of analytes present in a sample. EX1002 ¶¶ 46-49, 58-61; EX1001 at 25:56-67.

Table 8 depicts an exemplary coding scheme in matrix form:

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 22:9-30. Here, the decoding matrix assigns an intensity at a wavelength to each analyte. *Id.*; EX1002 ¶¶ 58-61, 126-28, 131. In other words, “[e]ach analyte is represented by a code in a single color.” EX1001 at 22:40-41. The Table 8 scheme is an embodiment of the ’797 patent’s claims, which require the use of a “decoding matrix.” *Id.* at Claim 1; EX1002 ¶¶ 59, 125-27, 143. Decoding signal data using Table 8 purportedly allows unambiguous detection of analytes A-P based on

“cumulative intensities.” EX1001 at Claim 1; EX1002 ¶¶ 59, 126-27.

The scheme of Table 8 uses four different colors (blue, green, yellow, and red). Each color is used independently to detect a distinct set of analytes. In Table 8, blue, green, yellow, and red are used for A-D, E-H, I-L, and M-P, respectively. Because each color is used independently of the others, no analyte is detected using multiple colors. Table 8 confirms this, as each analyte has a non-zero entry for only a single color.

The specific analytes detected using a given color are distinguished from one another based on signal intensities. EX1002 ¶¶ 59, 61. The spacing between intensities supposedly allows analyte differentiation during a multiplex experiment. *Id.* For example, for the color blue in Table 8, intensities of 1, 2, 4, or 8 mean that analytes A, B, C, or D are present alone. *Id.* But an intensity of 3 means that A and B are present ($1+2=3$), an intensity of 7 means that A, B, and C are present ($1+2+4=7$), and an intensity of 15 means that all analytes are present ($1+2+4+8=15$). *Id.* This progressive pattern prevents overlap of intensities—each value is “equal to the sum of all previous values plus one.” EX1001 at 22:40-43; EX1002 ¶ 59. If C was assigned to 3 instead of 4, it could not be differentiated from A+B. *Id.*

The specification further states that the decoding scheme can be governed by the relationship between three variables, the number of analytes (M), the number of wavelengths or colors of fluorophores used in detection (C), and the maximum

cumulative intensity of any given wavelength (F), according to the following equation:

$$M = C * \log_2(F + 1)$$

Id. at 2:11-17. In Table 8 above, M has a value of 16 (analytes A through P may be detected), C has a value of 4 (the number of different colors, blue, green, yellow, and red), and F has a value of 15 (the maximum cumulative signal for any given color, 1+2+4+8=15). As explained below, this equation also appears in the challenged claims. Regardless, this mathematical formula is nothing more than a restatement of the use of signal intensities for analytes that follow the geometric progression 1, 2, 4, 8, 16, and so on

B. The Challenged Claims

Claims 1-2, 5-11, 13-15, and 18 of the '797 patent are challenged. A full listing of challenged claims is included as Appendix A. Claim 1 (from which claims 2, 5-11, and 18 depend), although verbose, merely relates to using a sample chamber and multi-channel detector to detect four types of electromagnetic signals at four different wavelengths from four different fluorophores (mixed with hybridization probes), and that the variables M, C, and F (described above) be related by the equation set forth in the previous section. *Id.* at Claim 1. Claim 1 further specifies certain mathematical requirements for these three variables:

- C=4, 5, or 6

- $F+1$ is a positive integer and a power of 2
- $M > C$
- M and C are positive integers

Id.

In other words, claim 1 requires little more than using the scheme above in Table 8 to identify analytes based on the signal wavelength and intensity data detected by a multi-channel detector.

IV. LEVEL OF ORDINARY SKILL IN THE ART OF THE '797 PATENT

A person having ordinary skill in the art (“POSA”) relevant to the '797 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 ¶¶ 65-68. Alternatively, a POSA would have been someone with greater relevant experience sufficient to compensate for having less relevant formal education. *Id.* ¶ 67.

A POSA would have been familiar with and 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 ¶ 68. PO and its expert witness in IPR2024-01451, Dr. Kevin Struhl, have accepted this definition. EX1005 ¶ 18 (Struhl declaration adopting definition), EX1007 (listing definition).

V. PO'S INFRINGEMENT CONTENTIONS IN PARALLEL DISTRICT COURT LITIGATION

PO is asserting the '797 patent against Petitioner in the Northern District of California. EX1014.

PO's infringement contentions presuppose that Petitioner's products perform multiplex target detection based on signal wavelength and intensity within six channels, with two analytes per channel. That is, PO contends Petitioner's products use the scheme expressed in Table 8 of the '797 patent, albeit using six colors and only two intensity levels at each color. Based on this interpretation, PO purports to derive the below decoding matrix:

Analyte	FAM	HEX	Cy5	Cy5.5	ROX	ATTO 590
a	1	0	0	0	0	0
b	2	0	0	0	0	0
c	0	1	0	0	0	0
d	0	2	0	0	0	0
e	0	0	1	0	0	0
f	0	0	2	0	0	0
g	0	0	0	1	0	0
h	0	0	0	2	0	0
i	0	0	0	0	1	0
j	0	0	0	0	2	0
k	0	0	0	0	0	1
l	0	0	0	0	0	2

EX1009 at 56-57; EX1002 ¶ 131.

This table further illustrates that Petitioner’s products detect two analytes per channel within six channels, and that analyte detection within each channel is decoupled from analyte detection within the five other channels. For example, analytes “a” and “b” are detected by intensity levels 1 and 2 in the wavelength of light emitted by the FAM fluorophore, “c” and “d” are detected by intensity levels 1 and 2 in the wavelength of light emitted by the HEX fluorophore, etc. Therefore, as PO’s infringement contentions acknowledge, Petitioner’s products essentially do the same thing six times across six separate color channels.

VI. CITED PRIOR ART

A. Jouvenot

1. Jouvenot Is § 102(e) Prior Art

Jouvenot et al., U.S. Patent No. 9,921,154 B2 issued on March 20, 2018.

EX1003 at codes (10), (45); EX1002 ¶ 74. Jouvenot is analogous art because it

pertains to the same field of endeavor as the '797 patent, specifically, the detection of target analytes (including nucleic acids) in a sample. Jouvenot claims the benefit of provisional application No. 61/507,082 (“the '082 provisional”), filed July 20, 2011. *Id.* at codes (22), (60). Jouvenot is § 102(e) prior art as of at least the filing of the '082 provisional, July 20, 2011, because the '082 provisional supports Jouvenot’s method of performing a multiplexed digital assay recited in its claim 11. *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).

The '082 provisional discloses assays detecting multiple target polynucleotides in single samples using dPCR. EX1004 at Title; EX1002 ¶¶ 74-77. Samples having multiple targets are contacted with fluorophore-labeled probes that report the presence of targets by generating signals during PCR. EX1004 at 4:15-5:13, 8:22-9:3; EX1002 ¶ 80. Like Jouvenot, the '082 provisional states that signals for particular analytes may be based on the signal’s color, intensity, or both. EX1004 at 9:1-4 (“aspects of light, such as the intensity...may include data collected in one or more different [colors]”); EX1002 ¶ 80.

Like the '797 patent, the '082 provisional discloses using probes labeled with the same color at different intensities to distinguish different polynucleotide analytes (or combinations of polynucleotides). EX1004 at 5:14-21, 10:3-11:12, 16:8-19:18 (Examples 2-3), Fig. 4 (depicting intensity signals 108, 110, and 112).

The '082 provisional also discloses using multiple colors to identify the same polynucleotide analyte, stating that the different color signals collected can be from reporters for the same target. *Id.* at 8:22-9:10. The disclosure relied upon herein as invalidating the claims of the '797 patent was all carried over from the '082 provisional to Jouvenot itself, as established herein by concurrent citations to both the '082 provisional and Jouvenot.

Further, each and every limitation of at least claim 11 of Jouvenot is disclosed by the '082 provisional:

Jouvenot	'082 Provisional Disclosure
11. A method of performing a multiplexed digital assay, the method comprising:	“The present disclosure provides a system, including methods and apparatus, for performing a digital assay with multiplexed detection of two or more distinct targets in the same channel.” EX1004 at 3:5-7; <i>id.</i> at 3:9-13, 4:15-19, Figs. 1-2.
forming partitions that collectively contain R targets;	“The sample may be separated into partitions.” <i>Id.</i> at 7:6; <i>see id.</i> at 6:21-23, 7:12, 8:6, 8:14, 8:22-23. “Partitions may be analyzed and signals created at any suitable time(s).” <i>Id.</i> at 9:22; <i>see id.</i> at 10:3-11:11.
amplifying the R targets in the partitions;	“[P]reparation of the sample may render the sample (or partitions thereof) capable of amplification of each of one or more targets, if present, in the sample (or a partition thereof)” <i>Id.</i> at 6:21-23, <i>see id.</i> at 7:12, 8:6, 8:14.

	<p>“The signal may be analyzed to determine whether neither Target, Target 1 alone, Target 2 alone, or both Targets 1 and 2 are present in each droplet” <i>Id.</i> at 14:22-15:1; <i>see id.</i> at 12:11-19:23 ,15:30-31, 15:25-27, Examples 1-4.</p>
<p>collecting data representing amplification of each of the R targets in the partitions, all of the data being collected in fewer than R optical channels;</p>	<p>The “assays may involve analysis of more than two targets in the same channel.” <i>Id.</i> at 5:14-15. “[S]ome targets may be analyzed in one channel (e.g., a FAM channel), and other targets may be analyzed in other channels (e.g., a VIC channel). Three targets, two in a first channel and one in a second channel, would again generate eight clusters or populations of data.” <i>Id.</i> at 5:17-20; <i>see id.</i> at 2:10-13, 8:6, 8:14, 8:22-9:3, 9:3-6, 9:11-13.</p> <p>From Example 1, “Fluorophores 92, 94, which <i>may be the same or different</i>, create detectable but distinguishable signals in the same channel, allowing multiplexing in that channel. The signals may be distinguishable because an aspect of the fluorescence is different for one fluorophore than for the other fluorophore(s).... In some embodiments, <i>one probe may be labeled with a different number of fluorophores than the other probe</i>, and/or the probes may be located in slightly different local environments, creating a different level of fluorescence for each probe following reaction. Alternatively, or in addition, both probes may be labeled <i>with the same number of fluorophores</i> (e.g., one fluorophore), but there may be</p>

	<p><i>more or less of one probe</i> than the other in the sample, so that a greater or smaller signal is created when the reactions have occurred.” <i>Id.</i> at 13:10-15 (emphasis added); <i>see id.</i> at 14:16-15:29, Fig. 4.</p>
<p>identifying from the data a plurality of partition populations each positive for a different combination of the R targets, wherein the step of identifying includes a step of resolving each partition population that is positive for exactly two of the R targets from each partition population that is positive for only one of the R targets; and</p>	<p>“[S]ignal is created from light detected over time in a single channel from a fluid stream containing the droplets and flowing through an examination region of the channel. The signal may be analyzed to determine whether neither Target, Target 1 alone, Target 2 alone, or both Targets 1 and 2 are present in each droplet.” <i>Id.</i> at 14:20-15:1.</p> <p>“[A]ssignment of a droplet to a particular outcome (i.e., to one of T1-/T2-, T1+/T2-, T1-/T2+, and T1+/T2+) may be performed using any suitable algorithm.” <i>Id.</i> at 15:30-31; <i>see id.</i> at 16:4-6, 16:8-18:17, 17:23-24, 18:18-19:18, Fig. 4.</p> <p>“Number of positives. A number of partitions that are positive (or negative) for each target may be determined for the signal.... The signal detected from each partition, and the partition itself, may be classified as being positive or negative for each of the reactions/targets contributing to the signal. Classification may be based on the strength (and/or other suitable aspect) of the signal. If the signal/partition is classified as positive (+), for a given target, the reaction corresponding to that target is deemed to have occurred and at least one copy of the target is deemed to be present in the partition. In contrast, if</p>

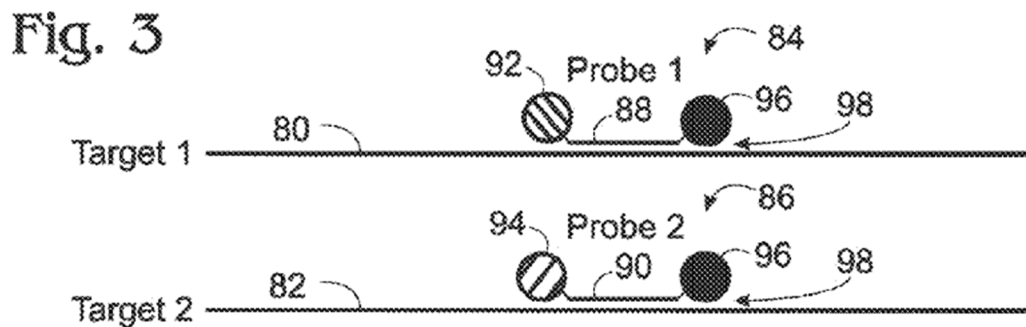
	<p>the signal/partition is classified as negative (-), for a given target, the reaction corresponding to that target is deemed not to have occurred and no copy the target is deemed to be present in the partition (i.e., the target is deemed to be absent from the partition). The data including all permutations of positives will generally fall into 2N populations or clusters, assuming that each population is distinguishable.” <i>Id.</i> at 10:3-15; <i>see id.</i> at 2:3-5, 5:4-8, 14:16-15:29, Fig. 4.</p>
<p>determining a respective level of each of the R targets from the data, wherein each level is specific for a single target of the R targets, and wherein the level determined for at least one of the R targets is based in part on a partition count for a partition population positive for two of the R targets.</p>	<p>“A concentration of each target may be estimated.... The concentration of each target may be estimated based on the respective numbers of partitions positive for the target alone and for the target in combination with any other target(s). The calculation may be based on each target having a Poisson distribution among the droplets. The concentrations may, for example, be estimated by finding solutions to a series of linear equations. The total number of partitions may be counted or, in some cases, estimated.” <i>Id.</i> at 11:2-7; <i>see id.</i> at 14:16-15:29, Fig. 4.</p>

2. Jouvenot Overview

Jouvenot discloses a system for multiplexed analyte detection. EX1003 at 2:26-28, 13:7-13; EX1004 at 3:5-7, 12:6-10. Jouvenot discloses several working examples, including Example 1. EX1003 at 13:19-15:10; EX1004 at 12:15-16:7. Example 1 “describes an exemplary digital PCR assay with multiplexed detection of

two targets, using two probes, analyzed in the same channel.” EX1003 at 13:24-26; EX1004 at 12:15-17.

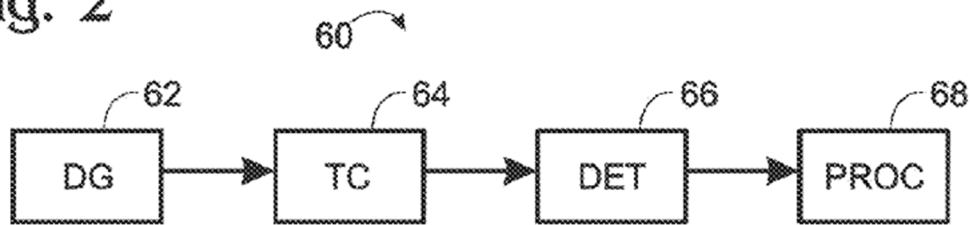
In Example 1, Jouvenot discloses “a fluid stream containing the droplets and flowing through an examination region.” EX1003 at 14:26-31; EX1004 at 14:20-22. These droplets contain a sample mixture including “a pair of targets 80, 82 (‘Target 1’ and ‘Target 2’) and corresponding probes 84, 86 (‘Probe 1’ and ‘Probe 2’).” This is depicted in Jouvenot Figure 3:



EX1003 at 13:29-32, Fig. 3; EX1004 at 12:20-23, Fig. 3; EX1002 ¶¶ 80, 95, 98, 161. The probes include oligonucleotides (labeled 88 and 90) and fluorophores (labeled 92 and 94). EX1003 at 13:32-33, Fig. 3; EX1004 at 12:22-23, Fig. 3.

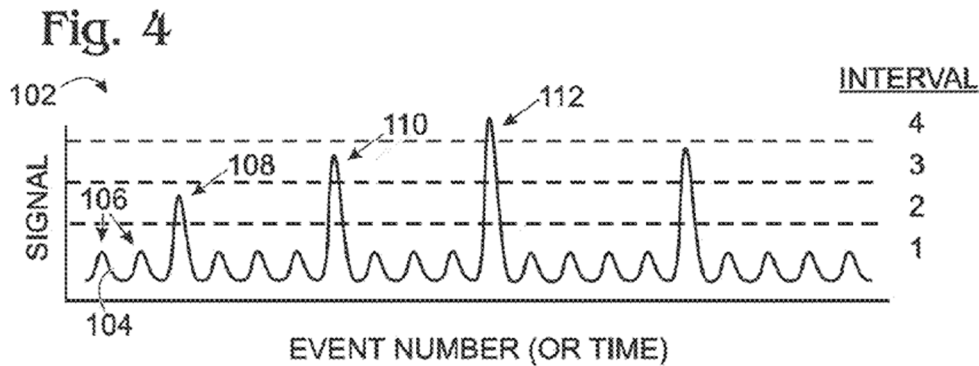
The system disclosed by Jouvenot, including Example 1, incorporates a data “processor 68 to determine numbers of droplets and/or target levels.” EX1003 at 13:7-13; *see* EX1004 at 12:6-10; EX1002 ¶¶ 80, 116-18. The data processor is depicted as part of the Jouvenot system in Figure 2:

Fig. 2



EX1003 at Fig. 2; EX1004 at Fig. 2; EX1002 ¶¶ 80, 116.

Example 1 includes Figure 4, which shows the detection of signal intensity in a single channel (at a common wavelength):



EX1003 at Fig. 4, 14:21-15:10; EX1004 at Fig. 4, 14:14-16:7. In Figure 4, analytes are identified based on signal intensity. EX1002 ¶ 81. Specifically, assignments are made based on the interval (1, 2, 3, or 4) the analyte falls into. EX1003 at 14:36-56; EX1002 ¶¶ 81, 90, 128, 136.

According to PO's expert witness in IPR2024-01451, Dr. Struhl, Jouvenot Example 1, Figure 4 uses a decoding matrix wherein "interval 1" or intensity 0 is no targets, "interval 2" or intensity 1 is the first target, "interval 3" or intensity 2 is the second target, and "interval 4" or intensity 3 (1+2) is both targets. See EX1016 at

174:25-175:11. This is the same coding scheme that PO accuses of infringing Claim 1 of the '797 patent. *See supra* § V (accusing purported decoding matrix using intensity 1 for the first targets and intensity 2 for second targets as infringing); EX1002 ¶¶ 129-32.

B. Larson

Larson was published in October 2011. EX1013 at code (43); EX1002 ¶ 82. Larson is therefore prior art to the '797 patent under pre-AIA 35 U.S.C. § 102(a) and 102(e). Larson is analogous art because it pertains to the same field of endeavor as the '797 patent, specifically, the detection of target analytes (including nucleic acids) in a sample or are, at a minimum, reasonably pertinent to this field.

As Dr. Batt explains, *see* EX1002 ¶ 83, Larson Figure 11a discloses a scheme virtually identical to that of Jouvenot Figure 4 for detecting all combinations of two targets in a single color channel. Specifically, in Figure 11a, Larson teaches an experiment using two targets, wherein “three populations” of droplets “were readily apparent,” with peaks at 0.08 V, 0.27 V, and 0.71 V. EX1013 ¶ 131. Most notably, Larson further discloses that a “very small peak appeared at ~0.9 V, not visible on the scale of FIG. 11a, that corresponded to droplets occupied by *both genes*.” *Id.* ¶¶ 130-31. Larson further repeatedly teaches increasing the number of color channels used to increase the number of targets. *See, e.g.*, EX1013 ¶¶ 47, 139-40, 152, 166.

C. Secondary References Relied Upon Herein

While the Petitioner relies principally on Jouvenot, the following references are used herein as support for secondary challenges to the same claims and challenges to the remaining claims—claims 7-9, 11, 13-15—not subject to Ground 1. All of the reference below are analogous art because they to the same field of endeavor as the '797 patent, specifically, the detection of target analytes (including nucleic acids) in a sample.

- **Lakowicz:** published in 2006. EX1006 at 3; EX1002 ¶ 84. Lakowicz is therefore prior art to the '797 patent under pre-AIA 35 U.S.C. § 102(a).
- **Dube:** published in 2009. EX1019 at code (43); EX1002 ¶ 84. Dube is therefore prior art to the '797 patent under pre-AIA 35 U.S.C. § 102(a) and 102(e).
- **Wittwer:** published in 2009. EX1020 at code (43); EX1002 ¶ 84. Wittwer is therefore prior art to the '797 patent under pre-AIA 35 U.S.C. § 102(a) and 102(e).
- **Brabetz:** was filed via PCT application in 2009, published via PCT in 2010, and published in the United States in December 2011. EX1008 at codes (22), (87), (65); 1002 ¶ 84. Brabetz is therefore prior art to the '797 patent under pre-AIA 35 U.S.C. § 102(a) and 102(e).

- **Maltezos:** published in 2008. EX1012 at code (43); EX1002 ¶ 84. Maltezos is therefore prior art to the '797 patent under pre-AIA 35 U.S.C. § 102(a) and 102(e).
- **Neuzil:** published in 2010. EX1017 at code (43); EX1002 ¶ 84. Neuzil is therefore prior art to the '797 patent under pre-AIA 35 U.S.C. § 102(a) and 102(e).
- **Oleksy:** published in 2003. EX1018 at code (43); EX1002 ¶ 84. Oleksy is therefore prior art to the '797 patent under pre-AIA 35 U.S.C. § 102(a) and 102(e).
- **Slepnev:** published in April 2012, was filed in December 2011, and has a priority date of at least June 19, 2003. EX1021 at codes (22), (43), (63); EX1002 ¶ 84. Slepnev is therefore prior art to the '797 patent under pre-AIA 35 U.S.C. § 102(a) and 102(e).
- **Lehnen:** published in 1992, was internationally published (and available in the US) in 1993, and again published via European Patent Office Bulletin in 1994. EX1022 at codes (22), (30), (86), (87); EX1002 at ¶ 84. Lehnen is therefore prior art to the '797 patent under pre-AIA 35 U.S.C. § 102(a) and 102(e).

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 '797 patent is involved in district court litigation in *In re ChromaCode Litigation*, 5:23-cv-04823-EKL (N.D. Cal.).

Also, Bio-Rad's petition for *inter partes* review of a related patent has been instituted: IPR2024-01451 (challenging U.S. Patent No. 11,827,921).

C. Lead and Back-Up Counsel and Service Information

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

Lead Counsel	Back-Up Counsel
Derek C. Walter Registration No. 74,656 dwalter@jonesday.com Jones Day 555 California Street 26 th Floor San Francisco, CA 94104 T: 415-875-5791 F: 415-875-5700	Matthew W. Johnson Registration No. 59,108 (mwjohnson@jonesday.com) Jones Day 500 Grant Street Suite 4500 Pittsburgh, PA 15219 T: 412-394-9524 F: 412-394-7959

VIII. GROUNDS FOR STANDING

Petitioner certifies that the '797 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	§ 103	1-2, 5-6, 10, 18	Jouvenot
1(a)	§ 103	6-9	Jouvenot, Larson, Brabetz, Lakowicz
1(b)	§ 103	11	Jouvenot, Larson, Brabetz, Maltezos, Neuzil, Oleksy
1(c)	§ 103	13	Jouvenot, Larson, Maltezos, Dube, Wittwer
1(d)	§ 103	14	Jouvenot, Larson, Maltezos
1(e)	§ 103	15	Jouvenot, Larson, Brabetz, Lakowicz, Maltezos, Dube, Wittwer
1(f)	§ 103	18	Jouvenot, Larson, Maltezos, Slepnev
2	§ 103	1-2, 5-6, 10, 18	Jouvenot, Lehnen
2(a)	§ 103	6-9	Jouvenot, Larson, Brabetz, Lakowicz, Lehnen
2(b)	§ 103	11	Jouvenot, Larson, Brabetz, Maltezos, Neuzil, Oleksy, Lehnen
2(c)	§ 103	13	Jouvenot, Larson, Maltezos, Dube, Wittwer, Lehnen
2(d)	§ 103	14	Jouvenot, Larson, Maltezos, Lehnen

2(e)	§ 103	15	Jouvenot, Larson, Brabetz, Lakowicz, Maltezos, Dube, Wittwer, Lehen
2(f)	§ 103	18	Jouvenot, Larson Maltezos, Slepnev, Lehen

X. CLAIM CONSTRUCTION

Generally, the claim terms are interpreted consistent with PO’s arguments and positions in the parallel district court proceeding. Specifically, for purposes of this Petition, Petitioner requests that the Board understand the claims consistent with the apparent interpretations that PO is pursuing in parallel district court litigation, particularly in view of its contentions regarding how the ’797 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’”); EX1009.

Nevertheless, in the parallel district court litigation, Petitioner will contend that the claim term “F” is indefinite due to, *inter alia*, various inconsistencies within the claims such that, although one can determine that prior art is within the scope of the claims, the skilled artisan would not understand the outer bounds of “F” with reasonable certainty. As an example, consider that in claim 1, the minimum value of “F” is 3. This is because the minimum allowed value of C in the claims is 4 and there is an additional requirement that M be greater than C, such that F can only be

3 or greater. Yet, claim 4 strangely allows for “F” to be 1. *See* EX1001 at claims 1, 4. Despite this inconsistency, a patentability determination can still be made because, as disclosed herein, the prior art teaches F=3, which, as documented herein, is the value of F that PO contends is present in the accused products.

These circumstances do not preclude institution because, as the Federal Circuit has explained, “indefiniteness of a limitation...precludes a patentability determination only when the indefiniteness renders it logically impossible for the Board to reach such a decision.” *See Intel Corp. v. Qualcomm Inc.*, 21 F.4th 801, 813 (Fed. Cir. 2021); *see also Aptiv Servs. US, LLC v. Microchip Tech., Inc.*, IPR2024-00646, Paper 11 at 11-12 (P.T.A.B. Sept. 25, 2024) (instituting IPR besides district court indefiniteness allegation because “we see no evidence at this stage of such a logical impossibility”); *PLR Worldwide Sales Ltd. v. Flip Phone Games, Inc.*, IPR2024-00209, Paper 9 at 17 (P.T.A.B. May 10, 2024) (“In this proceeding, even if full scope of ‘non-promotional’ is indefinite because the specification does not provide a sufficient boundary between promotional and non-promotional...that does not prevent us from making a determination that a teaching is well within that boundary.”).

Further, in view of the ’797 patent’s express definition of “probe,” the claim term “analyte specific hybridization probes” would be understood by a skilled artisan to refer to “a reagent capable of generating a signal in the presence of a particular

analyte and that hybridizes to the analyte.” *See* EX1001 at 11:19-50. Likewise, given the disclosure in the specification and the mathematical formulae in the claims, a POSA would understand the term “associating, for each analyte, a first value in a first component of the cumulative signal” to contemplate associating analytes with signal values for the first component that correspond to a progression 1, 2, 4, 8, 16 and so on. *See id.* at 21:47-23:27.

XI. GROUND 1: CLAIMS 1-2, 5-6, 10, AND 18 ARE OBVIOUS IN VIEW OF JOUVENOT

A. Claim 1

1. A system comprising:

“Generally, the preamble does not limit the claims.” *Allen Eng’g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1346 (Fed. Cir. 2002). If the preamble is nonetheless deemed limiting, a POSA would have understood Jouvenot to disclose a “system.” Jouvenot expressly discloses “a system, including methods and apparatuses for performing a multiplexed digital assay.” EX1003 at 2:26-28; EX1004 at 3:5-7; EX1002 ¶¶ 94-97; *see also* EX1003 at 13:7-13; *see also id.* Fig. 2; EX1004 at 12:6-10; EX1009 at 6.

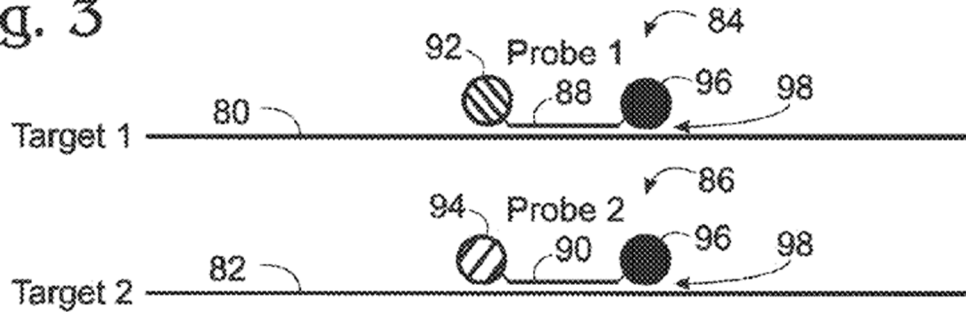
2. a sample chamber configured to house a sample and analyte-specific reagent mixtures of analyte-specific hybridization probes and multiple fluorophores;

Jouvenot Example 1 is a working example of the disclosed system. EX1003 at 13:19-15:10 (“This example describes an exemplary digital PCR assay.”);

EX1004 at 12:15-20; EX1002 ¶¶ 97-98. In Example 1, Jouvenot discloses an “examination region,” which functions as the claimed “sample chamber” by housing the sample and reagent mixtures during detection. EX1003 at 14:26-31 (disclosing “a fluid stream containing the droplets and flowing through an examination region”); EX1004 at 12:20-23; EX1002 ¶¶ 98-99, 105-07. Further, element 3 (*see infra* § XI.A.3) requires that the detector detect signals that originate “from the sample chamber.” EX1001 at Claim 1 (“a multi-channel detector to detect: a first electromagnetic signal at a first wavelength *from the sample chamber*”). In the Jouvenot system, “[s]ignals may be detected from the droplets with detector 66.” EX1003 at 13:7-13; EX1004 at 12:9-10; EX1002 ¶ 101. This confirms there is a chamber housing the droplets from which the signals come. *Id.*

Further, Jouvenot confirms that its sample chamber includes the listed components. Example 1 describes “an exemplary digital PCR assay with multiplexed detection of two targets, using two probes, analyzed in the same channel.” EX1003 at 13:24-26; EX1004 at 12:16-17; EX1002 ¶ 98. Jouvenot Figure 3 depicts a sample mixture for an exemplary experiment using the Example 1 protocol, showing “a pair of targets 80, 82 (‘Target 1’ and ‘Target 2’) and corresponding probes 84, 86 (‘Probe 1’ and ‘Probe 2’)”:

Fig. 3



EX1003 at 13:29-32, Fig. 3; EX1004 at 12:20-23, Fig. 3; EX1002 ¶ 104. Jouvenot further explains that the probes include an oligonucleotide (labeled 88 and 90) and a fluorophore (labeled 92 and 94). EX1003 at 13:32-33, Fig. 3; EX1004 at 12:22-23; EX1002 ¶ 104.

Additionally, these oligonucleotide portions of the probes are adapted to hybridize to corresponding targets. EX1003 at 13:43-45, Fig. 3; EX1004 at 13:6-9; EX1002 ¶¶ 40, 102. These oligonucleotides are analyte-specific. EX1002 ¶¶ 102-04. Example 1 further states that Target 1 and Target 2 are detected in droplets that flow through an examination region. EX1003 at 14:21-28; EX1004 at 14:17-23.

Accordingly, the examination region of Example 1 is a sample chamber configured to house droplets comprising samples (Targets 1 and 2) and analyte-specific reagent mixtures of analyte-specific hybridization probes (labeled 88 and 90) and multiple fluorophores (labeled 92 and 94).

In its district court infringement contentions, PO further contends that the location in an instrument for introducing a sample along with probes and reagents constitutes the claimed “sample chamber.” *See, e.g.*, EX1009, Appendix B at 15.

This location in the instrument holds the sample before PCR amplification or analyte detection. *See* EX1002 ¶ 105. To the extent this location may be deemed the claimed “sample chamber,” this is further disclosed in the prior art. Figure 2 of Jouvenot, for instance, teaches a “partitioning assembly” integrated with a thermocycler and detector. *See* EX1003 at 12:53-62; EX1004 at 11:12-16. A POSA would know that the partitioning assembly includes the alleged “sample chamber” so that the sample may be maintained for partitioning. *See* EX1002 ¶¶ 101, 106. Similarly, and as further evidence that a POSA would have been motivated to use such “sample chambers” with a reasonable expectation of success, consider Larson, which teaches a digital PCR system as in Jouvenot. EX1002 ¶ 82-83, 106. Larson discloses both a tube in a Bio-Rad thermal cycler and a location on a “readout chip” that holds the sample before and after amplification, respectively. *See* EX1013 ¶¶ 79, 86, 156, 193-94. Either location satisfies the claimed “sample chamber” under the interpretation of this term as reflected in PO’s infringement contentions. *See, e.g.*, EX1009 at 6, 15, 77, 81.

3. a multi-channel detector to detect:

a first electromagnetic signal at a first wavelength from the sample chamber, the first electromagnetic signal generated by excitement of a first fluorophore of the multiple fluorophores;

a second electromagnetic signal at a second wavelength from the sample chamber, the second electromagnetic

signal generated by excitement of a second fluorophore of the multiple fluorophores;

a third electromagnetic signal at a third wavelength from the sample chamber, the third electromagnetic signal generated by excitement of a third fluorophore of the multiple fluorophores;

a fourth electromagnetic signal at a fourth wavelength from the sample chamber, the fourth electromagnetic signal generated by excitement of a fourth fluorophore of the multiple fluorophores;

These elements require nothing more than using four different optical channels¹ to detect light from four different fluorophores in the sample chamber. EX1002 ¶ 108. Fluorophores are designed to generate electromagnetic signals at particular wavelengths when excited. EX1002 ¶¶ 40, 108-15. These electromagnetic signals are detected by the multi-channel detector. *Id.*

Jouvenot discloses, or at a minimum, renders obvious the use of four or more optical channels. Jouvenot discloses the use of a detector having “a plurality of optical channels,” which is a multi-channel detector. EX1003 at 12:53-13:6;

¹ Jouvenot explains that optical channels “represent a particular detection regime... characterized by a waveband (i.e., a wavelength regime) for detection of emitted light.” EX1003 at 8:17-20; *see* EX1004 at 5:14-19; EX1002 ¶ 49. This is consistent with a POSA’s understanding that different optical channels allow the detection of different wavelengths or wavelength regimes. EX1002 ¶ 49.

EX1002 ¶¶ 49, 151. In this regard, Jouvenot teaches that its assays “may be extended in various ways.” EX1003 at 5:19; EX1004 at 5:14. Most important, Jouvenot expressly discloses the use of multiple color channels in the same experiment, wherein different channels are used for different targets:

In some embodiments, the assays may involve detection of more than two targets in the same optical channel....In the same or other embodiments, *some targets may be analyzed in one channel (e.g., a FAM channel), and one or more other targets may be analyzed in one or more other channels (e.g., a VIC channel).*

EX1003 at 5:18-31; EX1004 at 5:14-19; EX1002 ¶ 109. Jouvenot also contemplates the use of the disclosed multi-channel detectors to detect “data collected in two or more different optical channels (e.g., in different wavelength ranges (wavebands) and/or color regimes).” EX1003 at 8:36-40; *see* EX1004 at 9:3-5; EX1002 ¶¶ 49, 109-15. By teaching that its “assays may be extended in various ways” and then expressly instructing that one may use multiple color channels wherein one uses different channels for different targets, Jouvenot unambiguously contemplates the use of multiple color channels, just as recited in this “multi-channel detector” claim element.

As further confirmation that a POSA would have been motivated to use multiple color channels and expected success in doing so in a system like Example 1 of Jouvenot, consider Larson. As noted above, Larson teaches in Figure 11a

scheme just like Jouvenot's Figure 4 and Example 1. Throughout, Larson contemplates increasing the number of targets that can be detected by increasing the number of color channels, including up to more than 20 color channels. *See, e.g.*, EX1013 ¶¶ 47, 139-40, 152, 166.

A POSA looking at Jouvenot Example 1 and Larson Figure 11a would have been interested in increasing the multiplex by to four or more channels and fluorophores. EX1002 ¶¶ 112-15, . This motivation is evident from Jouvenot itself, and Larson lends additional support. Jouvenot, for instance, states that “many applications, especially where sample is limited, could benefit greatly from higher degrees of multiplexing.” EX1003 at 2:18-20; EX1004 at 2:23-3:2; EX1002 ¶ 113. Likewise, Larson teaches that “adding multiple colors increases the number of possible reactions geometrically” and otherwise repeatedly contemplates increased number of colors, up to 20 or more. *See* EX1013 ¶¶ 47, 139-40, 152, 166.

The '797 patent, in its discussion of the prior art, provides further evidence of a POSA's motivation, explaining that multi-channel detectors were widely available in the art:

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

EX1001 at 35:30-35.

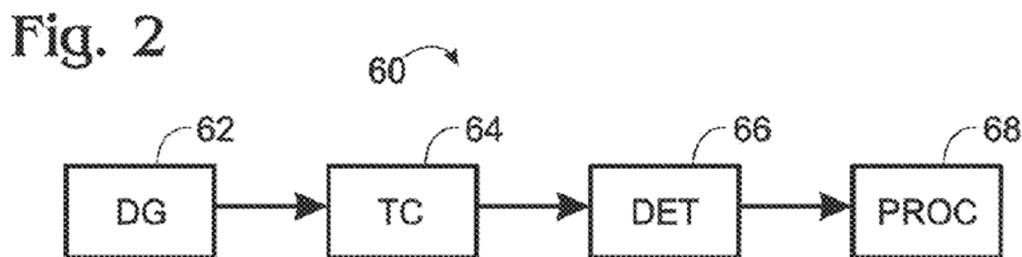
Finally, Jouvenot discloses the use of a variety of fluorophores, including FAM, VIC, ROX, TAMRA, and JOE. EX1003 at 13:46-14:2; EX1004 at 14:2-3; EX1002 ¶¶ 111, 158. A POSA would have understood that, following excitement, each fluorophore emits an electromagnetic signal at a distinct wavelength. EX1002 ¶¶ 108-11 (FAM, VIC, ROX, TAMRA, and JOE fluoresce at around 520, 543, 591, 563, and 554 nanometers respectively). A POSA would understand that these fluorophores would be suitable for generating electromagnetic signals at wavelengths for detection. EX1002 ¶ 111. Importantly, Jouvenot is clear that these fluorophores are merely “exemplary” “among others.” EX1003 at 13:67-14:2; EX1004 at 14:2-3. In other words, Jouvenot is not just teaching the use of five specific fluorophores but makes clear that one may use the range of different fluorophores known to the skilled artisan. Larson, just like Jouvenot, also includes a comprehensive listing of numerous fluorophores that can be used, including most of those already disclose in Jouvenot. *See* EX1013 ¶ 90.

Given Jouvenot’s independent teaching of multiple channels and a range of different fluorophores, and the additional support from Larson, a POSA would have found it obvious to expand Jouvenot Example 1 to use four or more different color channels and fluorophores. EX1002 ¶¶ 111-15. A POSA would have had a reasonable expectation of success in this approach because Jouvenot and Larson

independently teach the use of multiple channels and fluorophores for use with the disclosed system, of which Jouvenot Example 1 and Larson Figure 11a are embodiments. EX1002 ¶¶ 83, 114, 128-35. Nowhere does the '797 patent suggest that in the relevant time frame there were any impediments to implementing optical detection machinery for analysis in four colors. Just the opposite, the '797 patent states “the methods of the invention can be readily applied using instruments widely used in the art.” EX1001 at 35:34-35.

4. a processor controlled analyzer to

As set forth above, the system disclosed by Jouvenot incorporates a data “processor 68 to determine numbers of droplets and/or target levels.” *See supra* § XI.A.1; EX1003 at 13:7-13; EX1004 at 12:6-10; EX1002 ¶ 116. The data processor is depicted as part of the system in Figure 2:



EX1003 at Fig. 2; EX1004 at Fig. 2; EX1002 ¶ 116.

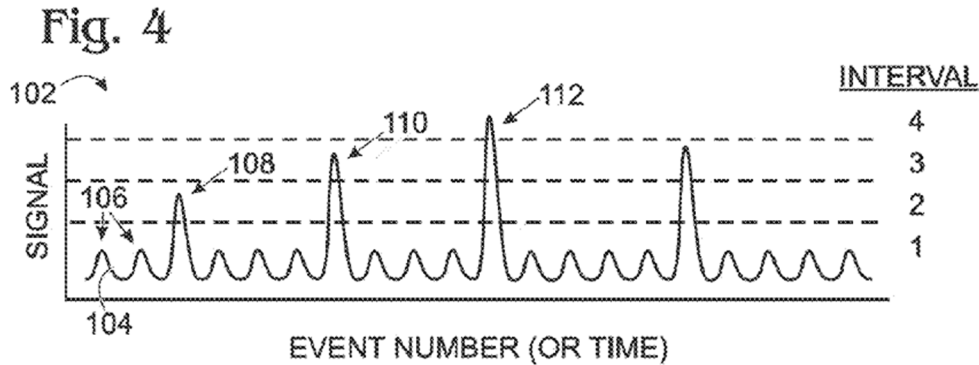
Example 1 provides an “exemplary digital PCR assay” according to the Jouvenot system and likewise incorporates a data processor. EX1003 at Fig. 2; EX1004 at Fig. 2; EX1002 ¶ 116. Further, Example 1 specifies that the “assignment

of a droplet to a particular outcome (e.g., to one of T1-/T2-, T1+/T2-, T1-/T2+, and T1+/T2+) may be performed using any suitable algorithm.” EX1003 at 14:63-65; EX1004 at 15:30-31; EX1002 ¶ 116. A POSA would have understood that using an algorithm suitable for decoding data from a digital PCR assay would be conducted with a processor-controlled analyzer. *See, e.g.*, EX1003 at 14:26-28 (“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”); EX1004 at 14:22-15:1; EX1002 ¶¶ 116-17.

- a. **receive, from the multichannel detector, a cumulative signal based on the first, second, third, and fourth electromagnetic signals and**

As Dr. Batt explains, this claim element merely pertains to the detection of the combination of the four electromagnetic signals above. EX1002 ¶¶ 119-23.

Example 1 of Jouvenot provides a cumulative signal (composed of intensity and wavelength) for a single channel. EX1003 at 13:24-26 (“This example describes an exemplary digital PCR assay with multiplexed detection of two targets, using two probes, *analyzed in the same channel.*”); EX1004 at 12:17-19; EX1002 ¶¶ 91, 95, 120, 127. This is shown in Figure 4, which shows detection of cumulative signal intensity in a single channel as part of Example 1:

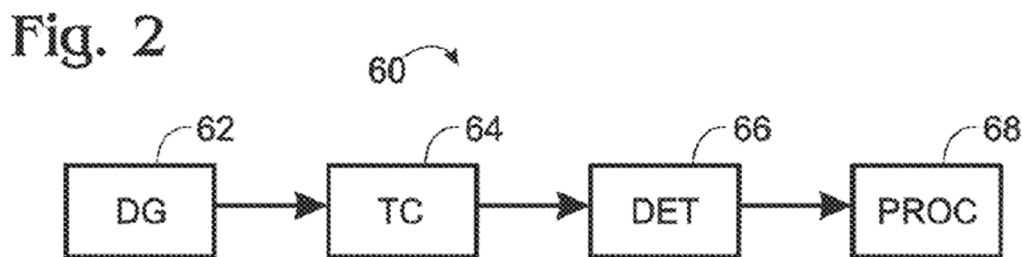


EX1003 at Fig. 4; EX1004 at Fig. 4; *see* EX1002 ¶¶ 120-23. Here, the “light detected in a given channel may be detected such that light from different reporters is *summed or accumulated* without attribution to a particular reporter. Thus, the signal for a given channel may be a *composite signal* that represents ... two, three, four, or more targets.” EX1003 at 8:40-47; *see also id.* at 4:56-60 (“light from *two or more fluorophores can be collected simultaneously* in the same optical channel”); EX1004 at 9:6-10; *see also id.* at 4:19-22; EX1002 ¶¶ 137-39. Notably, as discussed above, this exact scheme for detecting two targets in a single wavelength channel is also taught in Larson Figure 11a. *See* EX1013 at Fig. 11a; *id.* ¶¶ 30, 130-31; EX1002 ¶¶ 83, 129.

While Jouvenot Figure 4 and Larson Figure 11a use only a single wavelength, as set forth above, it would have been obvious in view of express disclosure in Jouvenot and Larson for a POSA to expand this to a four-channel assay based on four separate electromagnetic signals using a multi-channel detector. *See supra* § XI.A.3. This expansion would reflect nothing more than the straightforward

duplication of the schemes in Larson Example 1 and Jouvenot Figure 11a for use with four or more colors instead of just one so that more targets could be detected. See EX1002 ¶¶ 108, 113, 133. This four channel data from the multi-channel detector constitutes a cumulative signal based on the first, second, third, and fourth electromagnetic signals, and as detailed below, would allow the unambiguous detection of the specific combination of at least eight different target analytes present in a droplet (i.e., two targets for each of the four color channels). *Id.* ¶¶ 119-23.

Further, Jouvenot states that the signals are received by the processor from the multichannel detector. EX1003 at 13:7-13; EX1004 at 12:6-10; EX1002 ¶ 121. This can be seen in Figure 2, a flow chart showing data transfer from detector (DET, 66) to processor (PROC, 68):



EX1003 at Fig. 2; *see also id.* at 12:62-66 (“The arrows between the assemblies indicate movement or transfer of...signals/data, between the assemblies.”); EX1004 at 11:18-12:1; EX1002 ¶ 121.

b. apply a decoding matrix to the cumulative signal to unambiguously detect the presence or absence of at least each of M analytes

Example 1 involves a processor applying a decoding matrix to the cumulative signal to unambiguously detect the presence or absence of analytes. EX1002 ¶¶ 127-29. As set forth below, the scheme of Example 1 follows the mathematical requirements of Claim 1, including that M analytes are detected. *See infra* § XI.A.6.

To understand how Jouvenot discloses the decoding matrix, it is helpful to consider Table 8, which is the only exemplary decoding matrix for Claim 1 in the '797 patent:

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 22:9-29; EX1002 ¶¶ 127-29. “Table 8...illustrat[es] four tiers of encoding based on four colors and intensities 1, 2, 4, and 8.” EX1001 at 21:65-67.

The “coding scheme illustrated in Table 8 uses both intensity and color to encode each of the 16 analytes.” *Id.* at 23:10-12. “Each analyte is represented by a code in a single color, wherein the value of the code in that single color equal to the sum of all previous values plus one.” *Id.* at 22:40-43. Thus, the Table 8 decoding matrix uses four colors and encodes four analytes per color. EX1002 ¶¶ 59-61, 127-29.

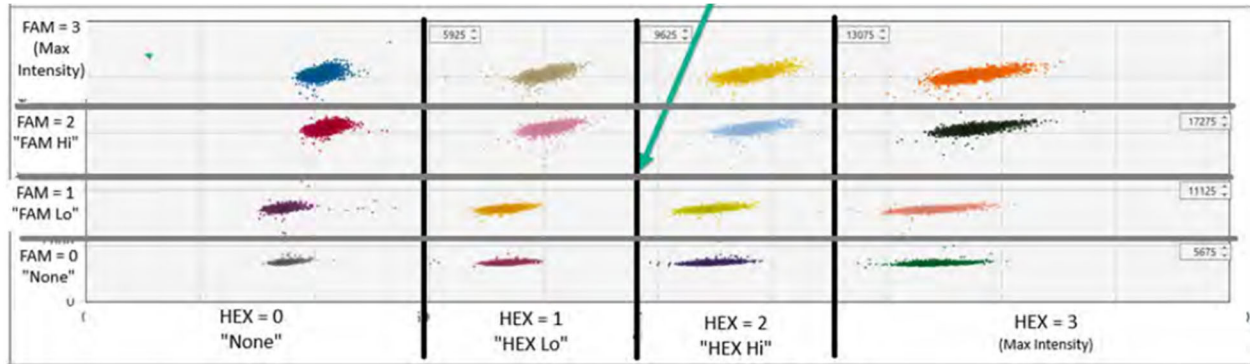
According to PO’s district court infringement contentions, Example 1 of Jouvenot utilizes this same type of decoding matrix. EX1009 at 56-57; EX1002 ¶¶ 127-29. In particular, PO alleges that Petitioner’s QX 600 product infringes Claim 1 based on the below decoding matrix (the “Contentions Matrix”):

Analyte	FAM	HEX	Cy5	Cy5.5	ROX	ATTO 590
a	1	0	0	0	0	0
b	2	0	0	0	0	0
c	0	1	0	0	0	0
d	0	2	0	0	0	0
e	0	0	1	0	0	0
f	0	0	2	0	0	0
g	0	0	0	1	0	0
h	0	0	0	2	0	0
i	0	0	0	0	1	0
j	0	0	0	0	2	0
k	0	0	0	0	0	1
l	0	0	0	0	0	2

EX1009 at 56-57; EX1002 ¶ 127. This is the same type of decoding matrix as Table 8. EX1002 ¶ 128. The differences are that Table 8 has four color channels instead of six and Table 8 has four analytes per channel instead of just two. EX1002 ¶¶ 127-29. But both decoding matrices use the same progression within each channel—0 means no analyte is present, 1 means a first analyte is present, 2 means

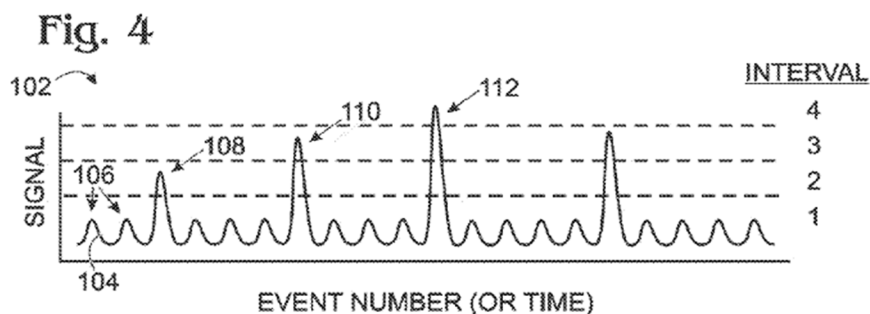
a second analyte is present, and 3 means both the first and second analytes within that channel are present. *Id.*

PO contends that the Contentions Matrix is derived from the 2D scatter plot depicted below:



EX1009 at 50. Briefly, as indicated by PO's annotations along the axes, PO contends that the horizontal and vertical divisions correspond to the intensity levels 0, 1, 2, and 3. *See id.*

Jouvenot Example 1 uses the same approach of identifying analytes within droplets based on intensity ranges. EX1002 ¶¶ 127-29. The use of this approach is evident from Jouvenot's Figure 4, depicting signal intensity data collected from an experiment using the Example 1 protocol:



EX1003 at Fig. 4; EX1004 at Fig. 4; EX1002 ¶ 128. Jouvenot explains how the intensity ranges in Figure 4 (part of Example 1) can be used to identify signals in one channel:

Peaks 106 with maxima in Interval 1 correspond to droplets containing no Target (T1-/T2-). The measured signal corresponds to background (e.g., background fluorescence, scattering, etc.) and does not reflect the presence or amplification of either Target.

Peaks 108 with maxima in Interval 2 correspond to droplets containing Target 1 but not containing Target 2 (T1+/T2-). The measured signal corresponds to signal from Target 1 plus background and reflects amplification of Target 1 implying the presence of Target 1.

Peaks 110 with maxima in Interval 3 correspond to droplets containing Target 2 but not containing Target 1 (T1-/T2+). The measured signal corresponds to signal from Target 2 plus background and reflects amplification of Target 2 implying the presence of Target 2.

Peaks 112 with maxima in Interval 4 correspond to droplets containing both Targets 1 and 2 (T1+/T2+). The measured signal corresponds to signal from both Targets 1 and 2 plus background and reflects amplification of Targets 1 and 2 implying the presence of Targets 1 and 2.

EX1003 at 14:36-56; EX1004 at 15:5-24; EX1002 ¶ 128.

According to PO's expert witness in IPR2024-01451, Dr. Struhl, Jouvenot Example 1, Figure 4 uses a decoding matrix wherein "interval 1" or intensity 0 is no targets, "interval 2" or intensity 1 is the first target, "interval 3" or intensity 2 is the

second target, and “interval 4” or intensity 3 (1+2) is both targets:

Q. The droplets that are -- have no targets, that’s 106. That is like intensity zero?

A. Yes.

Q. And then 108 with one target is like intensity 1?

A. Yes.

Q. And 110 with the other target, that’s like, intensity 2?

A. Yes.

Q. And then 112 is both targets; that’s like 3?

A. Yes.

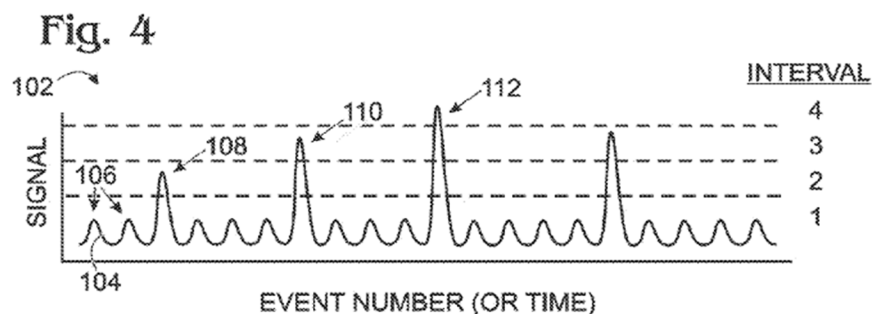
EX1016 at 174:25-175:11. This is the same coding scheme that PO accuses of infringing Claim 1 of the ’797 patent. EX1002 ¶¶ 130-32.

As further evidence of the prior art status of this approach and that a POSA would have been motivated to pursue it with reasonable expectation of success as of the alleged priority date, look no further than Larson. As noted above, Larson teaches this exact same approach in Figure 11a. *See* EX1013 at Fig. 11a; *id.* ¶¶ 30, 130-131. There, Larson teaches an experiment using two targets, wherein “three populations” of droplets “were readily apparent,” with peaks at 0.08 V, 0.27 V, and 0.71 V. *Id.* Most notably, Larson further discloses that a “very small peak appeared at ~0.9 V, not visible on the scale of FIG. 11a, that corresponded to droplets occupied by *both genes*.” *Id.* ¶¶ 130-31.

As described above, it would have been obvious to a POSA to increase the plex of Jouvenot Example 1 and Larson Figure 11 by simply duplicating the number of channels/fluorophores to at least four. *See supra* § XI.A.3; EX1002 ¶¶ 133, 138. Correspondingly, the single-channel decoding matrix (0, 1, 2) would likewise be duplicated across channels, leading to the same decoding matrix that PO accuses of infringing.

- c. **by associating, for each analyte, a first value in a first component of the cumulative signal and a second value in a second component of the cumulative signal, wherein each first value is an intensity or range of intensities and each second value is a wavelength or a range of wavelengths, and wherein the second values comprise the first, second, third, and fourth wavelengths, and**

This element is disclosed in Jouvenot Figure 4:



EX1003 at Fig. 4; EX1004 at Fig. 4; EX1002 ¶¶ 136. In Figure 4, the “signal is created from light detected over time *in a single channel.*” EX1003 at 14:26-28; EX1004 at 14:20-21. Accordingly, each analyte in Figure 4 is encoded by a wavelength in one channel. EX1002 ¶¶ 136-38. Further, targets are assigned based

on “the strength or *intensity of the signal*,” which is “divided or thresholded into four intervals.” EX1003 at 14:31-56; EX1004 at 15:1-2. So, for a given wavelength, the two analytes are encoded by different intensities or ranges of intensity (i.e., the intervals). EX1002 ¶¶ 136-38.

As further confirmation of the obviousness of this approach, consider Larson, which teaches the exact scheme of Jouvenot Figure 4 in Figure 11a. There, all combinations of two targets (*i.e.*, no targets, target 1 alone, target 2 alone, and both targets together) are detected in a color channel by four intensities. *See* EX1013 at Fig. 11a; *id.* ¶¶ 30, 130-131.

As described above, it would have been obvious to a POSA to increase the plex of Jouvenot Example 1 and Larson Figure 11a by increasing the number of channels/fluorophores to at least four. *See supra* § XI.A.3; EX1002 ¶¶ 133, 138-39. As also explained above, the single-channel decoding matrix (based on signal wavelength and intensity) would correspondingly be duplicated across channels. *See supra* § XI.A.4.b. This expanded decoding matrix would “comprise the first, second, third, and fourth wavelengths” as claimed. EX1002 ¶ 139.

5. the determination is made without immobilization, mass spectrometry or melting curve analysis;

As is evident, and as Dr. Batt confirms, Example 1 of Jouvenot does not involve immobilization, mass spectrometry, or melting curve analysis. EX1002 ¶¶ 140-41.

6. wherein for the positive integer M ,

$$M=C*\log_2(F+1),$$

F is a positive integer and is equal to the maximum cumulative intensity of the first component of the signal, for any second value, when all of the analytes are present, and

$C=4, 5, \text{ or } 6$; and

wherein $F+1$ is a positive integer and

wherein $F+1$ is a power of 2,

wherein M is greater than the number of the second values used to encode the analytes (C),

the multi-channel detector comprises C channels, and

M and C are positive integers.

The obvious four channel version of Jouvenot Example 1 and Larson Fig. 11a described here satisfies all these requirements:

- $C=4$ (four channels)
- $F=3$ (maximum cumulative intensity at any wavelength when all analytes are present (*see supra* § XI.A.4.b; *see also* EX1016 at 175:10-11 (“112 is both targets; that’s like 3”)))
- $F+1=4$, a positive integer and a power of 2 ($2^2=4$)
- $M=C*\log_2(F+1)=4*\log_2(3+1)=8$ (number of analytes detectable, two targets per channel across four channels)
- $M > C$ ($8 > 4$)
- M and C are positive integers (8 and 4)

EX1002 ¶¶ 142-47.

- B. Claim 2: The system of claim 1, wherein the multi-channel detector is further configured to detect: a fifth electromagnetic signal at a fifth wavelength from the sample chamber, the fifth electromagnetic signal generated by excitement of a fifth fluorophore of the multiple fluorophores; a sixth electromagnetic signal at a sixth wavelength from the sample chamber, the sixth electromagnetic signal generated by excitement of a sixth fluorophore of the multiple fluorophores; and wherein $C=6$.**

As explained above, it would have been obvious to a POSA to expand Example 1 to incorporate four channels and four fluorophores. *See supra* § XI.A.3. For the same reasons provided above with respect to Claim 1, it would have been obvious to a POSA to expand Example 1 to incorporate a total of six channels and fluorophores. *See* EX1003 at 5:19-31 (“assays may be extended in various ways.”); EX1004 at 5:14-21. As C is the number of channels, $C=6$ for this obvious system.

- C. Claim 5: The system of claim 1, wherein $F=3$.**

As explained above, $F=3$ for the obvious four-channel version of Example 1. *See supra* § XI.A.6.

- D. Claim 6: The system of claim 5, wherein the multiple fluorophores is selected from the group consisting of a blue fluorophore, a green fluorophore, a yellow fluorophore, a red fluorophore, and any combinations thereof.**

As explained above, Jouvenot discloses the use of fluorophores including “FAM, VIC, ROX, TAMRA, JOE, etc., among others” suitable for use with the approach of Example 1. *See supra* § XI.A.3; EX1003 at 14:1-2; EX1004 at 14:2-3. Thus, Jouvenot discloses at least five different fluorophores. As Dr. Batt explains,

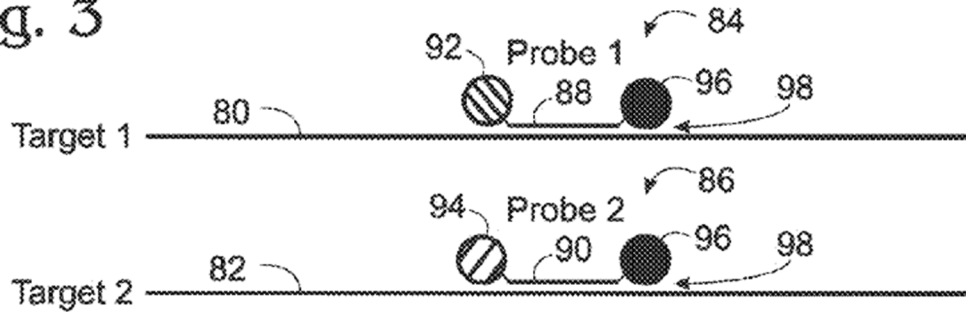
FAM is a green fluorophore, VIC is a green and yellow fluorophore, ROX is an orange fluorophore, TAMRA is a green and yellow fluorophore, and JOE is a green and yellow fluorophore. EX1002 ¶ 158.

A POSA implementing a four-channel version of Example 1 would have been motivated to use Jouvenot's fluorophores and would have had a reasonable expectation of success because these fluorophores were well-known off-the-shelf components in the art and were known to work well for PCR analysis. EX1002 ¶¶ 158-60. Moreover, because Jouvenot discloses only green and yellow fluorophores (FAM, VIC, ROX, TAMRA, and JOE), any combination of four Jouvenot-disclosed fluorophores would all be either green and/or yellow. *Id.* Therefore, a POSA using any combination of the five fluorophores disclosed by Jouvenot with the obvious four-channel version of Example 1 would meet this claim. *Id.*

E. Claim 10: The system of claim 5, wherein the analyte-specific hybridization probes are labeled with a fluorophore of the multiple fluorophores.

As explained above (*see supra* § XI.A.2), Jouvenot's Example 1 probes incorporate analyte-specific oligonucleotide hybridization probes (labeled 88 and 90 in Figure 3) and a fluorophore (labeled 92 and 94 in Figure 3). EX1003 at 13:32-33, Fig. 3; EX1004 at 12:22-23; EX1002 ¶¶ 161-62. Figure 3 depicts this:

Fig. 3



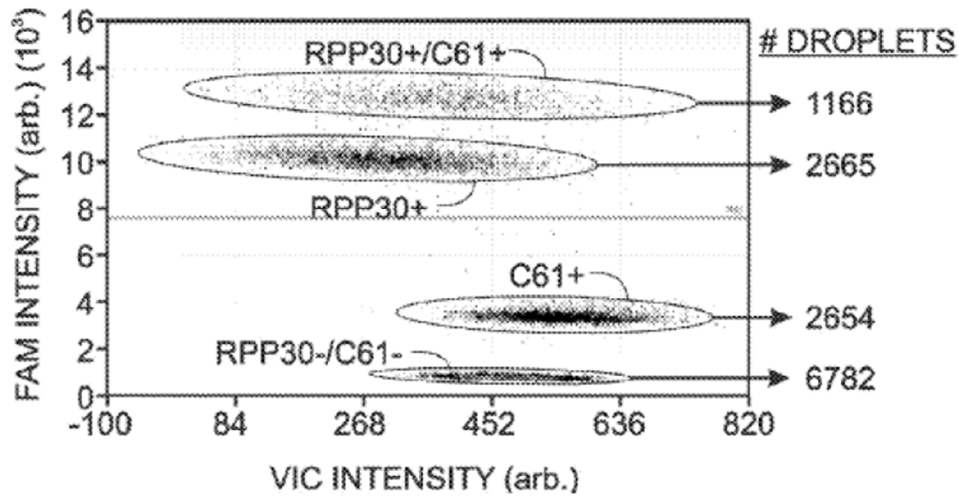
EX1003 at 13:29-32, Fig. 3; EX1004 at 12:20-22, Fig. 3; EX1002 ¶ 161.

Accordingly, the obvious four-channel version of Example 1 described above includes analyte-specific hybridization probes labeled with a fluorophore of the multiple fluorophores. *See supra* § XI.A.

F. Claim 18: The system of claim 5, further comprising a display coupled to the processor controlled analyzer to visualize a plot of the first and second values.

It would have been obvious to a POSA using the multi-channel detector in the obvious four-channel version of Example 1 to use a display coupled to the processor controlled analyzer to visualize a plot of the wavelengths and intensities (the first and second values). EX1002 ¶¶ 163-64. A POSA's motivation to visualize the data is evident from Jouvenot's disclosure of multiple examples that show that a display was coupled with the processor-controlled analyzer to visualize a plot of first and second values (i.e., the intensity and wavelength). *Id.* ¶ 164. In Figure 5, for instance, intensity is plotted for two different wavelength channels:

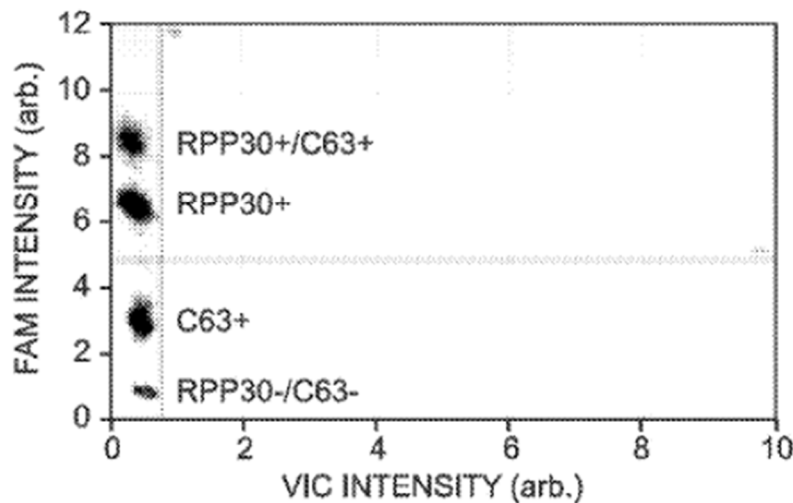
Fig. 5



EX1003 at Fig. 5; *see also id.* at 2:52-59; EX1004 at Figure 5, 17:1-27; EX1002

¶ 163. Figure 7 of Jouvenot includes a similar plot:

Fig. 7



EX1003 at Figure 7; EX1004 at Figure 7; EX1002 ¶ 163. A POSA also would have been aware that visualizing fluorescence data is standard in the art. EX1002 ¶ 164.

Accordingly, it would have been obvious to a POSA to use a display coupled

to the processor controlled analyzer to visualize a plot of the wavelengths and intensities (the first and second values) for use with the obvious four-channel version of Example 1. EX1002 ¶¶ 163-64.

XII. GROUND 1(a): CLAIMS 6-9 ARE FURTHER OBVIOUS IN VIEW OF LARSON, BRABETZ, AND/OR LAKOWICZ

Claims 6-9 are additionally obvious in view of Jouvenot in combination with Larson, Brabetz, and/or Lakowicz.

A. Claim 6: The system of claim 5, wherein the multiple fluorophores is selected from the group consisting of a blue fluorophore, a green fluorophore, a yellow fluorophore, a red fluorophore, and any combinations thereof.

To the extent this claim would not have been obvious based on Jouvenot, it would have been obvious based on Jouvenot in combination with Larson, Brabetz, and/or Lakowicz.

In addition to the fluorophores disclosed by Jouvenot, a POSA would have been aware of a variety of additional suitable fluorophores, including blue and red fluorophores. EX1002 ¶¶ 168-71. For example, Larson discloses FAM, ROX, DAPI, Cy3, Cy5, and Cy5.5. EX1013 ¶ 90. A POSA would have understood DAPI to be a blue fluorophore suitable for use with Jouvenot Example 1 and Cy5 and Cy5.5 to be red fluorophores suitable for Example 1. EX1002 ¶ 168. Brabetz likewise discloses blue, green, yellow, and red fluorophores, and combinations thereof suitable for use with Example 1:

TABLE 1

Known fluorescent dye combinations and virtual filtersets for ABI Prism ® Genetic Analyzers.					
Fluorescence dye combinations and colour canals					
Blue	Green	Yellow	Red	Orange (far red)	Recommended virtual filter set
6-FAM	JOE	TAMRA	ROX	—	F or A
6-FAM	TET	HEX	TAMRA	—	C
5, 6-FAM	JOE	TAMRA	ROX	—	F or A
6-FAM	JOE	NED	ROX	—	F
6-FAM	HEX	NED	ROX	—	F or D
6-FAM	VIC	NED	PET	LIZ	G5

5, 6-FAM: 5- and 6-carboxyfluorescein;
6-FAM: 6-carboxyfluorescein;
JOE: 6-carboxy-4', 5'-dichloro-2', 7'-dimethoxy-fluorescein;
HEX: 4,7,2',4',5',7'-hexachloro-6-carboxy-fluorescein;
TET: 4,7,2',7'-tetrachloro-6-carboxy-fluorescein;
TAMRA: 6-carboxytetramethyl-rhodamine;
VIC: 2'-chloro-7'phenyl-1,4-dichloro-6-carboxy-fluorescein;
NED: 2'-chloro-5'-fluoro-7',8'-benzo-1,4-dichloro-6-carboxyfluorescein;
ROX: 5- and 6-carboxy-X-rhodamin;
PET and LIZ are unpublished proprietary dyes of Applied Biosystems (Foster City, CA, USA).

EX1008 at 2:40-60; EX1002 ¶ 169. Finally, Lakowicz also discloses yellow, blue, red, and green fluorophores suitable for use with Example 1. EX1006 at 70, 722, 727, 730, 770; EX1002 ¶ 170. A POSA would have been motivated to select from the red, green, blue, and yellow fluorophores disclosed in Larson, Brabetz, and/or Lakowicz and would have had a reasonable expectation of success of doing so because, as Dr. Batt explains, the red, blue, green, and yellow fluorophores disclosed in these references were well-known, commonly-used fluorophores that had already been successfully and routinely applied for PCR analysis. *See* EX1002 ¶ 158; *supra* XI.D. As Dr. Batt explains, these fluorophores all worked well. *See* EX1002 ¶ 158.

Indeed, as explained above in connection with claim 6 in Ground 1, the '797 patent itself does not characterize the claimed fluorophores as novel or inventive but rather treats them as well-known prior art fluorophores that could be used without difficulty. *See* EX1001 at 34:57-61.

A POSA following the Jouvenot's direction that higher degrees of multiplexing are beneficial in certain applications, *see* EX1003 at 2:18-20, would look to references like Larson because they are in the same field, and Larson discloses even more suitable fluorophores than Jouvenot discloses. EX1013 ¶ 90. Indeed, Larson provides an entire non-exclusive list of available fluorophores. EX1013 ¶ 90. Having varied fluorophores available allows a POSA to have more precision when distinguishing analytes because it reduces the risk of overlap between emission and/or excitation wavelengths. Spectral overlap increases as fluorescence bleeds across channels. EX1002 ¶ 172 . Accordingly, a POSA would have been motivated to combine a greater number of spectrally resolvable fluorophores in Larson with the teachings of Jouvenot.

A POSA viewing Jouvenot would have been motivated to combine its teachings with those of Larson, Brabetz, and Lakowicz with a reasonable expectation of success because they all pertain to fluorophores suitable for use with PCR experiments like Jouvenot Example 1. EX1002 ¶ 172; EX1006 at 70, 722, 727, 730, 770; EX1008 at 2:40-60; EX1013 ¶ 90. A POSA would have understood that

the fluorophores disclosed by Larson, Brabetz, and Lakowicz would have worked with the obvious four-channel version of Example 1, and would have been further motivated to use them because they were standard fluorophores in the art. EX1002 ¶¶ 166-72. A POSA would have likewise had a reasonable expectation of success because these are standard fluorophores well-known in the art to work in various PCR experiments. EX1002 ¶ 171; EX1006 at 70, 657-660, 827, 848-851; EX1008 at 2:40-60; EX1013 ¶ 90.

B. Claim 7: The system of claim 5, wherein the multiple fluorophores is selected from the group consisting of a fluorescein amidite (FAM), a cyanine 3 (Cy3), a carboxy-X-rhodamine (ROX), a cyanine 5 (Cy5), a cyanine 5.5 (Cy5.5), and any combinations thereof.

As explained above for Claim 6 in connection with Ground 1, Jouvenot discloses FAM and ROX, and that these fluorophores are suitable for use with the obvious four-channel version of Example 1. *See supra* § XI.D. Similarly, as explained in the immediately preceding section for Claim 6, a POSA would have been aware of FAM, Cy3, ROX, Cy5, and Cy5.5 and that these fluorophores are suitable for use with the obvious four-channel version of Example 1. *See supra* § XII.A. As explained, a POSA would have been motivated to use these fluorophores and would have had a reasonable expectation of success. *See id.*

Indeed, Cy3, Cy5, and Cy5.5 were well-known, routinely used fluorophores that had already been successfully and routinely applied for PCR analysis. EX1002

¶ 175-76. As Dr. Batt explains, these fluorophores all worked well. *See id.* The '797 patent itself does not characterize the claimed fluorophores as novel or inventive but rather treats them as well-known prior art fluorophores that could be used without difficulty. *Id.* For example, the '797 patent discusses Cy3 and Cy5 as part of routine PCR experiments using commercial instruments. EX1001 at 45:19-35; EX1002 ¶ 176. Likewise, the '797 patent repeatedly refers to Cy3, Cy5, and Cy5.5 by name without providing a definition, which shows that they were well-known in the art prior to the patent. EX1001 at 33:67, 34:8, 45:29-30, 48:50, 49:10, 49:14, 49:33; EX1002 ¶ 176. Further, these fluorophores were regularly referenced in the literature. EX1013 ¶ 90; *see* EX1002 ¶¶ 51, 158, 171.

C. Claim 8: The system of claim 5, wherein the multiple fluorophores has a maximum excitation wavelength selected from the group consisting of about 494 nm, about 550 nm, about 567 nm, about 650 nm, about 675 nm, and any combinations thereof.

As explained above for claims 6 and 7, Jouvenot discloses both FAM and ROX, and a POSA would have been aware of FAM, Cy3, ROX, Cy5, and Cy5.5 as suitable for use with the obvious four-channel version of Example 1. *See supra* § XII.A. In its infringement contentions, PO alleges that Petitioner's products infringe this claim based on the use of FAM for "about 494 nm," Cy5 for "about 650 nm," Cy5.5 for "about 675 nm," and ROX for "about 567 nm." EX1009 at 97-103. A POSA would have been aware of the fluorophore excitation wavelengths in PO's contentions and that Cy3 has an excitation wavelength of roughly 550. EX1002

¶ 180. As explained above for claim 7, a POSA would have found it obvious to use four fluorophores selected from FAM, Cy3, ROX, Cy5, and Cy5.5 with the obvious four-channel version of Example 1. In doing so, a POSA would also be using fluorophores having maximum excitation wavelengths selected from the claimed set of wavelengths because these are the excitation wavelengths of FAM, Cy3, ROX, Cy5, and Cy5.5. EX1002 ¶¶ 178-82. Claim 8 would have therefore been obvious for the same reason as claim 7. *See supra* § XII.B; EX1002 ¶¶ 174-82; *see also* EX1003 at 14:1-2 (“other” fluorophores may be suitable); EX1004 at 14:2-3 (same).

D. Claim 9: The system of claim 5, wherein the multiple fluorophores has a maximum emission wavelength selected from the group consisting of about 518 nm, about 565 nm, about 591 nm, about 670 nm, about 697 nm, and any combinations thereof.

As explained above for claims 6 and 7, Jouvenot discloses both FAM and ROX, and a POSA would have been aware of FAM, Cy3, ROX, Cy5, and Cy5.5 as suitable for use with the obvious four-channel version of Example 1. *See supra* § XII.A. In its infringement contentions, PO alleges that Petitioner’s products infringe this claim based on the use of FAM for “about 518 nm,” Cy5 for “about 670 nm,” Cy5.5 for “about 697 nm,” and ROX for “about 591 nm.” EX1009 at 103-109. A POSA would have been aware of the fluorophore emission wavelengths in PO’s contentions and that Cy3 has an emission wavelength of roughly 565. EX1002 ¶¶ 184-85. As explained above for claim 7, a POSA would have found it obvious to use four fluorophores selected from FAM, Cy3, ROX, Cy5, and Cy5.5 with the

obvious four-channel version of Example 1. In doing so, a POSA would also be using fluorophores having maximum emission wavelengths selected from the claimed set of wavelengths because these are the excitation wavelengths of FAM, Cy3, ROX, Cy5, and Cy5.5. EX1002 ¶¶ 184-85. Claim 9 would have therefore been obvious for the same reasons as claim 7. *See supra* § XII.B; EX1002 ¶¶ 174-86; *see also* EX1003 at 14:1-2 (“other” fluorophores may be suitable); EX1004 at 14:2-3 (same).

XIII. GROUND 1(b) CLAIM 11 IS FURTHER OBVIOUS IN VIEW OF LARSON, BRABETZ, MALTEZOS, NEUZIL, AND/OR OLEKSY

Claim 11 is additionally obvious in view of Jouvenot in combination with Larson, Brabetz, Maltezos, Neuzil, and/or Oleksy.

Claim 11: The system of claim 5, wherein the detector comprises four or six band pass filters.

Band-pass filters were standard components in fluorescent detection that allow a specific range of wavelength to pass through while reducing signals outside of that range, isolating desired frequencies. Brabetz, Maltezos, Neuzil, and Oleksy all disclose such filters and motivation their use, further showing that a POSA would have reasonably expected success in using such components. EX1002 ¶ 189. For example, Brabetz discloses using band pass filters in multiple color fluorescence detection within multiplex PCR. EX1008 at 1:45-2:35. Additionally, Maltezos states, “it may desirable to suppress [unwanted] luminescence even further by using

optical band-pass filters.” EX1012 ¶ 163. Further, Neuzil discloses that the excitation filter used to detect emissions from fluorophores by its compact optical detection system “may be a band pass filter, and such filters are known.” EX1017 ¶ 44. Even further, Oleksy discloses that band pass filters can be used to select the wavelength range of interest for an excitation light when detecting different sequences within a reaction sample. EX1018 ¶ 86.

A POSA viewing Jouvenot and Larson would have been motivated to combine their teachings with those of Brabetz, Maltezos, Neuzil, and Oleksy with a reasonable expectation of success because they all pertain to PCR experiments (like Jouvenot Example 1 and Larson Figure 11) involving optical detection of lights signals from fluorophores. EX1002 ¶¶ 189-91; EX1008 at 2:12-60; EX1012 ¶¶ 60, 101, 142, 144, 163, 194; EX1017 ¶¶ 11-35, 36, 44, 49; EX1018 ¶ 86, 103, 157, 169-82. A POSA would have understood that the optical components, such as band pass filters, disclosed by Brabetz, Maltezos, Neuzil, and Oleksy would have worked with the obvious four-channel version of Example 1, and would have been motivated to use them because they were standard components in the art useful for creating multi-channel detection systems. *See supra* § XI.A.3 (discussing creating multi-channel systems from band-pass filters and photodetectors); EX1002 ¶¶ 187-92. A POSA would have likewise had a reasonable expectation of success because these are standard optical components well-known in the art to work with a variety of PCR

experiments. EX1002 ¶ 189; EX1008 at 1:45-2:35; EX1012 ¶¶ 60, 101, 144; EX1017 ¶¶ 11-35, 36, 44, 49; EX1018 ¶¶ 5-51, 86.

As if the foregoing were not enough, the '797 patent acknowledges that “band pass filters are commonly employed in a variety of laboratory instrumentation, including quantitative PCR machines.” EX1001 at 28:11-13. It likewise acknowledges that “[m]any real-time PCR and quantitative PCR instruments comprise an excitation light source and band pass filters that enable the detection of fluorescent signals in four colors (e.g., blue, green, yellow, and red).” *Id.* at 35:30-33. Because the use of such band pass filters were commonly used in existing systems for the detection of four colors and were known to work well, and because a POSA would have been motivated to implement four-channel version of Example 1, a POSA would have been motivated to utilize four or six band pass filters for this purpose with a reasonable expectation of success. *See supra* § XI.A.3; EX1002 ¶ 190.

XIV. GROUND 1(c): CLAIM 13 IS FURTHER OBVIOUS IN VIEW OF LARSON, MALTEZOS, DUBE, AND/OR WITTWER

Claim 13: The system of claim 5, wherein the multi-channel detector comprises four or six photodetectors.

This claim would have been obvious based on Jouvenot in combination with Larson, Maltezos, Dube, and/or Wittwer.

As explained above, Jouvenot discloses that signals may be detected with a

multi-channel detector and a POSA would have found it obvious to utilize a four-channel version of Example 1. *See supra* § XI.A.3; EX1003 at 13:4-13; EX1004 at 12:8-9. A POSA would have found it obvious to include four or six photodetectors in the multi-channel detector. EX1002 ¶¶ 194-96. A POSA would have understood that photodetectors were standard components in fluorescent detection that allow the detection of a specific range of wavelength. EX1002 ¶¶ 196. The Maltezos, Dube, and Wittwer references, for instance, not only disclose such detectors but motivate their use and substantiate reasonable expectation of success of using such components. EX1002 ¶ 196.

For example, Maltezos discloses a “photodetector array” that includes “a plurality of photodetectors.” EX1012 ¶ 149; *see also id.* ¶¶ 60, 101, 144 (further disclosing the use of photodetectors). Likewise, Dube discloses “an array of photodetectors wherein each pixel or group of pixels corresponds to a reaction chamber.” EX1019 ¶ 147. Finally, Wittwer discloses a system where “emitted fluorescence signals are acquired by photodetectors.” EX1020 ¶ 375 and Figure 53.

A POSA viewing Jouvenot and Larson would have been motivated to combine their teachings with those of Maltezos, Dube, and Wittwer because they all pertain to PCR experiments (like Jouvenot Example 1 and Larson Figure 11) involving optical detection of lights signals from fluorophores. EX1002 ¶¶ 195-96; EX1012 ¶¶ 60, 101, 142, 144, 163, 194; EX1019 ¶¶ 133-47, 155-57; EX1020 ¶¶ 34-

120, 375-83. A POSA would have understood that the optical components, such as photodetectors, disclosed by Maltezos, Dube, and Wittwer would have worked with the obvious four-channel version of Example 1, and would have been motivated to use them because they were standard components in the art useful for creating multi-channel detection systems. *See supra* § XIII (discussing creating multi-channel systems from band-pass filters and photodetectors); EX1002 ¶ 196. A POSA would have likewise had a reasonable expectation of success because these are standard optical components well-known in the art to work with various PCR experiments. EX1002 ¶ 196; EX1012 ¶¶ 60, 101, 134, 144, 149; EX1019 ¶¶ 147-152; EX1020 ¶¶ 375, 379. Indeed, the '797 patent admits that the “wavelength and intensity may also be determined using a combination of a photodetector and band pass filters. This configuration is used in several thermal cyclers known in the art.” EX1001 at 35:59-62.

XV. GROUND 1(d): CLAIM 14 IS FURTHER OBVIOUS IN VIEW OF LARSON AND/OR MALTEZOS

Claim 14: The system of claim 5, wherein the multi-channel detector comprises photodetectors that enable the detection of blue, green, and red fluorescent signals.

This claim would have been obvious based on Jouvenot in combination with Larson and/or Maltezos.

As explained above for claims 6-9, it would have been obvious to a POSA to use blue, green, and red fluorophores as part of the obvious four-channel version of

Example 1. *See supra* §§ XI.A.3, XI.D, XII. And, as explained above for claim 13, it would have been obvious for a POSA to utilize four or six photodetectors to detect the signal from different color channels as part of the multi-channel detector for use with the obvious four-channel version of Example 1. *See supra* § XIV. A POSA would have further understood that to use blue, green, and red fluorophores as part of the obvious four-channel version of Example 1, it would be necessary to include photodetectors enabling the detection of blue, green, and red fluorescent signals. EX1002 ¶¶ 199-203.

As explained above, a POSA also would have been aware of photodetectors that enable the detection of blue, green, and red fluorescent signals. *See supra* §§ XI.A.3, XI.D, XII. Maltezos provides further motivation to employ photodetectors that enable the detection of blue, green, and red fluorescent signals with the obvious four-channel version of Example 1. *See, e.g.*, EX1012 ¶ 135 (“optical assemblies are configured to provide excitation(light source)/emission (detector) at wavelengths such as: 365/460, 470/510, 530/555, 585/610, 625/660, 680/712 nm.”); EX1002 ¶¶ 199-201. Maltezos Table 1 further demonstrates this:

TABLE 1

Color	Dominant wavelength (nm) or CCT (K)		Typical Luminous or Radiant flux @ 700 mA
	Min.	Max.	
White	4500 K	8000 K	76 lm
Royal Blue	455 nm	465 nm	385 mW
Blue	465 nm	475 nm	28 lm
Cyan	500 nm	510 nm	75 lm
Green	520 nm	535 nm	80 lm
Amber	585 nm	595 nm	57 lm
Red-Orange	610 nm	620 nm	86 lm
Red	620 nm	635 nm	61 lm

EX1012 at Table 1; EX1002 ¶ 200.

As explained above for claim 13, a POSA would have been motivated to combine Jouvenot and Larson with Maltezos and would have reasonably expected success. *See supra* § XIV. A POSA would have been motivated to use the Maltezos photodetectors that detect blue, green, and red fluorescent signals because a POSA would have understood that these photodetectors would be useful to create a multi-channel detector for use with the obvious four-channel version of Example 1 set forth in claims 6-9, which involve the detection of particular colors. *See supra* §§ XII (discussing creating multi-channel systems from band-pass filters and photodetectors), XIII.

Indeed, the patent itself admits motivation and reasonable expectation of success with respect to this claims, stating the alleged invention can be

“accomplished by measuring the intensity of a signal across a spectrum of wavelengths, or by using band pass filters that restrict the passage of certain wavelengths of light, thereby allowing only light of certain wavelengths to reach a photodetector. Many real-time PCR and quantitative PCR instruments comprise an excitation light source and band pass filters that enable the detection of fluorescent signals in four colors (e.g., blue, green, yellow, and red).” EX1001 at 35:26-33. The ’797 patent concludes in view of this that “the methods of the invention can be readily applied using instruments widely used in the art.” *Id.* at 35:34-35.

XVI. GROUND 1(e): CLAIM 15 IS FURTHER OBVIOUS IN VIEW OF LARSON, BRABETZ, LAKOWICZ, MALTEZOS, DUBE, AND/OR WITTWER

Claim 15: The system of claim 5, wherein the multi-channel detector comprises photodetectors that enable the detection ranges selected from the group consisting of from about 483 nm to about 533 nm, from about 523 nm to about 568 nm, from about 558 nm to about 610 nm, from about 615 nm to about 670 nm, and any combinations thereof.

This claim would have been obvious based on Jouvenot in combination with Larson, Brabetz, Lakowicz, Maltezos, Dube, and/or Wittwer.

As explained above in connection with claims 6-9, it would have been obvious to use fluorophores having maximum emission wavelengths selected from the group consisting of about 518 nm, about 565 nm, about 591 nm, and about 670 nm as part of the obvious four-channel version of Example 1. *See supra* §§ XI.A.3, XII.D; *see also* EX1001 at 45:19-35; EX1008 at 2:40-60; EX1013 ¶ 90; EX1006 at 70, 722,

727, 730, 770. These four wavelengths fall within the ranges set forth in claim 15. EX1002 ¶¶ 206-07; *see also* EX1009. Because using these four wavelengths would have been obvious, a POSA would have been motivated to use emission ranges that encompass emissions in the claimed ranges. This is because, as Dr. Batt explains, fluorophore emissions are not sharply focused on a specific wavelength, but rather encompass a range of wavelengths and a POSA would have been motivated to try and capture a greater portion of the light emitted by the fluorophore. *See* EX1002 ¶ 206. Further, as Dr. Batt explains, and as confirmed in PO's infringement contentions, the claimed emission wavelength ranges correspond to nothing more than the emission wavelength ranges for the FAM, HEX, Cy5, ROX, and ATTO 590 fluorophores, which were well-known, off-the-shelf fluorophores were known to work well for PCR that POSAs would be motivated to use with a reasonable expectation of success and that had long since been disclosed in Larson. *See id.* To the extent such fluorophores are obvious, so to is claim 13.

And, as explained above for claim 13, it would have been obvious to utilize four or six photodetectors to detect the signal from the different color channels as part of the multi-channel detector for use with the obvious four-channel version of Example 1. *See supra* §§ XI.A.3, XIV; EX1012 ¶ 149; EX1019 ¶ 147.

A POSA would have further understood that using fluorophores having maximum emission wavelengths selected from the group consisting of about 518

nm, about 565 nm, about 591 nm, and about 670 nm as part of the obvious four-channel version of Example 1, required photodetectors that enable the detection of these fluorescent signals. EX1002 ¶¶ 206-07. As explained above for claim 14, a POSA would have been aware of common photodetectors in the art and would have been motivated to combine the references that disclose those photodetectors with Jouvenot with a reasonable expectation of success. *See supra* §§ XI.A.3, XV.

XVII. GROUND 1(f) CLAIM 18 IS FURTHER OBVIOUS IN VIEW OF LARSON, MALTEZOS, AND/OR SLEPNEV

Petitioner incorporates Ground 1 by reference. Claim 18 is additionally obvious in view of Jouvenot in combination with Larson, Maltezos, and/or Slepnev.

Claim 18: The system of claim 5, further comprising a display coupled to the processor controlled analyzer to visualize a plot of the first and second values.

To the extent this claim would not have been obvious based on Jouvenot and/or Larson, it would have been obvious based on Jouvenot and Larson in combination with Maltezos and/or Slepnev.

As explained above, a POSA would have been aware that visualizing fluorescence data is standard in the art. *See supra* § XI.F. Maltezos and Slepnev provide further motivation to a POSA. EX1002 ¶¶ 209-11. For example, Maltezos discloses that computers for use with PCR applications may comprise “a central processing unit, a storage or memory unit that can record and read information and programs using machine-readable storage media, a communication terminal such as

a wired communication device or a wireless communication device, an output device such as *a display terminal*, and an input device such as a keyboard.” EX1012 ¶ 167. Likewise, Slepnev, which is directed to polynucleotide quantification, states that “[i]n one embodiment, the data generation device comprises a signal detector, *a display monitor* and a computer processor coupled to the control circuit and the display monitor.” EX1021 ¶ 141.

A POSA viewing Jouvenot and Larson would have been motivated to combine their teachings with those of Maltezos and Slepnev with a reasonable expectation of success because they all pertain to polynucleotide quantification experiments such as Jouvenot Example 1 and Larson Figure 11. EX1002 ¶ 211; EX1012 ¶¶ 173-98; EX1021 ¶ 12, 54, 102-04. A POSA would have understood that the displays disclosed by Maltezos and Slepnev would have worked with the obvious four-channel version of Example 1, and would have been motivated to use such a display because they were standard tools in the art for visualizing, analyzing, and understanding experimental data. EX1002 ¶ 211. A POSA would have likewise had a reasonable expectation of success because these are standard components well-known in the art to work with PCR experiments. EX1002 ¶ 211; EX1012 ¶¶ 12, 116, 132, 147, 165-72, 212; EX1021 ¶ 141-43.

**XVIII.GROUNDS 2-2(F): CLAIMS 1-2, 5-11, 13-15, AND 18 ARE OBVIOUS
IN FURTHER VIEW OF LEHNEN**

Grounds 2-2(f) are based on the same logic and rationale as grounds 1-1(f).

The sole change is the addition of Lehen. Briefly, to the extent Jouvenot and/or Larson are deemed to not disclose encoding analytes by the geometric progression of 1, 2, 4, 8, etc. because the signals in Jouvenot Example 1 and Larson Figure 11 do not exactly match this progression, the use of this exact progression would have nonetheless been obvious based on Lehen. EX1002 ¶¶ 213-17.

Lehen discloses the use of binary (power-of-2) encoding (1:2:4:8) based on signal intensity and discusses multiplexing capacity as a function of channels and intensity levels, which matches the geometric progression and satisfies the claimed formula. *See* EX1022 at 13:15-53; EX1002 ¶ 215. In particular, Lehen discusses:

- “[R]eagent of proportions 1:2:4”
- “[R]eagent of proportions 1:2:4:8”
- That the “algorithm $n: 2n: 4n: 8n \dots :2^{(m1)}n$ can be utilized”

EX1022 at 13:15-53.

In Lehen, each analyte is encoded using a unique proportions of bead subpopulations and powers of two to ensure that each possible combination yields a unique sum. EX1002 ¶ 216. Lehen describes this approach as “uniquely interpretable.” EX1022 13:31-35; EX1002 ¶ 216. A POSA would be motivated to use this signal progression because the proportions allow for unique interpretation and unambiguous identification of analytes, as Lehen expressly teaches. *See* EX1022 at 13:31-35; EX1002 ¶¶ 214-17. A POSA would have a reasonable

expectation of success in using this approach because a POSA would have known how to modulate the intensity from a target-specific probe. EX1002 ¶ 217. Jouvenot teaches multiple such methods for doing this:

[T]he intensity associated with one fluorophore, following reaction, may be lower or higher than the intensity(ies) associated with the other fluorophore(s). In some embodiments, one probe may be *labeled with a different number of fluorophores* than the other probe, and/or the probes may be *located in slightly different local environments*, creating a different level of fluorescence for each probe following reaction. Alternatively, or in addition, both probes may be labeled with the same number of fluorophores (e.g., one fluorophore), but there may be *more or less of one probe than the other in the sample*, so that a greater or smaller signal is created when the reactions have occurred.

EX1003 at 13:51-63; EX1004 at 13:13-21.

XIX. CONCLUSION

The challenged claims should be cancelled.

Petition for *Inter Partes* Review
U.S. Patent No. 12,168,797

Dated: September 15, 2025

By: */Derek C. Walter/*
Derek C. Walter
Lead Counsel for Petitioner
Reg. No. 74,656
Jones Day
555 California Street
26th Floor
San Francisco, CA 94104

APPENDIX A: LISTING OF CHALLENGED CLAIMS

No.	Limitation
1	<p>A system comprising:</p> <ul style="list-style-type: none">a sample chamber configured to house a sample and analyte-specific reagent mixtures of analyte-specific hybridization probes and multiple fluorophores;a multi-channel detector to detect:<ul style="list-style-type: none">a first electromagnetic signal at a first wavelength from the sample chamber, the first electromagnetic signal generated by excitement of a first fluorophore of the multiple fluorophores;a second electromagnetic signal at a second wavelength from the sample chamber, the second electromagnetic signal generated by excitement of a second fluorophore of the multiple fluorophores;a third electromagnetic signal at a third wavelength from the sample chamber, the third electromagnetic signal generated by excitement of a third fluorophore of the multiple fluorophores;a fourth electromagnetic signal at a fourth wavelength from the sample chamber, the fourth electromagnetic signal generated by excitement of a fourth fluorophore of the multiple fluorophores;a processor controlled analyzer to receive, from the multi-channel detector, a cumulative signal based on the first, second, third, and fourth electromagnetic signals and apply a decoding matrix to the cumulative signal to unambiguously detect the presence or absence of at least each of M analytes by associating, for each analyte, a first value in a first component of the cumulative signal and a second value in a second component of the cumulative signal, wherein each first value is an intensity or range of intensities and each second value is a wavelength or a range of wavelengths, and wherein the second values comprise the first, second, third, and fourth wavelengths, and the determination is made without immobilization, mass spectrometry or melting curve analysis; <p>wherein for the positive integer M, $M=C*\log_2 (F+1)$,</p>

No.	Limitation
	<p>F is a positive integer and is equal to the maximum cumulative intensity of the first component of the signal, for any second value, when all of the analytes are present, and</p> <p>C=4, 5, or 6; and</p> <p>wherein F+1 is a positive integer and wherein F+1 is a power of 2,</p> <p>wherein M is greater than the number of the second values used to encode the analytes (C), the multi-channel detector comprises C channels, and M and C are positive integers.</p> <p>Independent claim</p>
2	<p>The system of <i>claim 1</i>, wherein the multi-channel detector is further configured to detect:</p> <p>a fifth electromagnetic signal at a fifth wavelength from the sample chamber, the fifth electromagnetic signal generated by excitement of a fifth fluorophore of the multiple fluorophores;</p> <p>a sixth electromagnetic signal at a sixth wavelength from the sample chamber, the sixth electromagnetic signal generated by excitement of a sixth fluorophore of the multiple fluorophores; and</p> <p>wherein C=6.</p>
5	<p>The system of <i>claim 1</i>, wherein F=3.</p>
6	<p>The system of <i>claim 5</i>, wherein the multiple fluorophores is selected from the group consisting of a blue fluorophore, a green fluorophore, a yellow fluorophore, a red fluorophore, and any combinations thereof.</p>
7	<p>The system of <i>claim 5</i>, wherein the multiple fluorophores is selected from the group consisting of a fluorescein amidite (FAM), a cyanine 3 (Cy3), a carboxy-X-rhodamine (ROX), a cyanine 5 (Cy5), a cyanine 5.5 (Cy5.5), and any combinations thereof.</p>
8	<p>The system of <i>claim 5</i>, wherein the multiple fluorophores has a maximum excitation wavelength selected from the group consisting of about 494 nm, about 550 nm, about 567 nm, about 650 nm, about 675 nm, and any combinations thereof.</p>

No.	Limitation
9	The system of <i>claim 5</i> , wherein the multiple fluorophores has a maximum emission wavelength selected from the group consisting of about 518 nm, about 565 nm, about 591 nm, about 670 nm, about 697 nm, and any combinations thereof
10	The system of <i>claim 5</i> , wherein the analyte-specific hybridization probes are labeled with a fluorophore of the multiple fluorophores.
11	The system of <i>claim 5</i> , wherein the detector comprises four or six band pass filters.
13	The system of <i>claim 5</i> , wherein the multi-channel detector comprises four or six photodetectors.
14	The system of <i>claim 5</i> , wherein the multi-channel detector comprises photodetectors that enable the detection of blue, green, and red fluorescent signals.
15	The system of <i>claim 5</i> , wherein the multi-channel detector comprises photodetectors that enable the detection ranges selected from the group consisting of from about 483 nm to about 533 nm, from about 523 nm to about 568 nm, from about 558 nm to about 610 nm, from about 615 nm to about 670 nm, and any combinations thereof.
18	The system of <i>claim 5</i> , further comprising a display coupled to the processor controlled analyzer to visualize a plot of the first and second values.

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 14,000 words as calculated by the “Word Count” feature of Microsoft Word 2016, the word processing program used to create it.

Respectfully submitted,

JONES DAY

Dated: September 15, 2025

By: /Derek C. Walter/

Derek C. Walter

Lead Counsel for Petitioner

Reg. No. 74,656

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 12,168,797 B2** WITH PETITIONER'S EXHIBIT LIST, POWER OF ATTORNEY, AND EXHIBITS 1001-1031 are being served tomorrow on September 16, 2025, via Priority Express Mail (Fed Ex) pursuant to 37 C.F.R. § 42.105 and § 42.6(e) to the PO at the address below:

SHEPPARD, MULLIN, RICHTER & HAMPTON LLP
650 Town Center Drive, 10th Floor
Costa Mesa, CA 92626

*Additional Addresses Known as Likely
to Effect service*

PO's Address of Record

Dated: September 15, 2025

By: /Daniel C. Sloan/
Daniel C. Sloan