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10
11 **UNITED STATES DISTRICT COURT**
12 **NORTHERN DISTRICT OF CALIFORNIA**
13 **SAN JOSE DIVISION**

14 **IN RE: CHROMACODE LITIGATION**

Case No. 5:23-cv-04823-EKL
(Consolidated)

15
16 **DEFENDANT AND COUNTER-**
17 **PLAINTIFF BIO-RAD**
18 **LABORATORIES, INC.'S**
19 **INVALIDITY CONTENTIONS**
20 **UNDER PATENT L.R. 3-3**

Hon. Eumi K. Lee

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BIO-RAD'S INVALIDITY
CONTENTIONS

CASE NO. 5:23-cv-04823-EKL

1 Pursuant to Patent Local Rule 3-3, the Court’s June 18, 2025 Minute Order granting Bio-
2 Rad’s Motion to Consolidate (Dkt. No. 121), and Bio-Rad’s proposed date of serve for its Invalidity
3 Contentions within the parties’ June 30, 2025 Joint Proposed Schedule and Proposed Order (Dkt.
4 No. 123), Defendant and Counter-Plaintiff Bio-Rad Laboratories, Inc. (“Bio-Rad”) makes the
5 following disclosure of preliminary invalidity contentions for U.S. Patent No. 12,168,797 (the
6 “’797 Patent”). Plaintiff and Counter-Defendant California Institute of Technology (“Caltech,” or
7 “Plaintiff”) asserts claims 1–2, 5–11, 13–15, 18–19, and 21 of the ’797 Patent (collectively, the
8 “Asserted Claims”).

9 Bio-Rad provides these disclosures based on information ascertained to date. Bio-Rad’s
10 discovery and investigation into this matter are continuing, and Bio-Rad expects that additional
11 evidence and information will become available through discovery. Bio-Rad makes these
12 disclosures without prejudice to Bio-Rad’s right to produce evidence of any additional prior art
13 references. Bio- Rad reserves the right to supplement these invalidity contentions as Bio-Rad’s
14 investigation and discovery continue and as appropriate as the case progresses.

15 Further, these disclosures are prepared prior to the Court’s claim construction ruling on the
16 ’797 Patent and disclosure of claim construction positions from Plaintiff. Bio-Rad’s positions on
17 the invalidity of particular claims will depend, in part, on how the claims are construed by the
18 Court. Bio-Rad reserves the right to supplement or further amend its contentions based on claim
19 construction positions taken by Plaintiff or any construction adopted by the Court. Bio-Rad’s
20 contentions are made in the alternative and are not necessarily intended to be internally consistent
21 or consistent with Bio-Rad’s claim construction or non-infringement positions. Bio-Rad’s
22 contentions are not an admission that Plaintiff’s interpretation of the Asserted Claims, as
23 understood by Bio-Rad, are correct.

24 The accompanying invalidity claim charts (*see* Appendices A-B) list specific examples
25 where prior art references disclose, either expressly, implicitly in the larger context of the passage,
26 or inherently, each limitation of the asserted claims and/or examples of disclosures in view of which
27 a person of ordinary skill in the art would have considered each limitation obvious. Bio-Rad
28 endeavored to identify the most relevant portions in the references. However, the references may

1 contain additional support for particular claim limitations. Bio-Rad may rely on uncited portions
2 of the prior art references, other documents, and fact and expert testimony to provide context or to
3 aid in understanding the cited portions of the references. Where Bio-Rad cites to a particular figure
4 in a reference, the citation should be understood to encompass the caption and description of the
5 figure and the text relating to and/or describing the figure. Conversely, where Bio-Rad cites to
6 particular text referring to a figure, the citation should be understood to include the figure and
7 related figures as well.

8 **I. PATENT LOCAL RULE 3-3(A) DISCLOSURES**

9 Bio-Rad does not agree, nor does it concede that the '797 Patent is entitled to the priority
10 date asserted by Plaintiff of at least November 4, 2011, based on conception and diligent reduction
11 to practice, nor does Bio-Rad agree or concede that the '797 Patent is entitled to priority based on
12 U.S. Provisional Application No. 61/594,480 filed on February 3, 2012.

13 Based upon presently known information, pursuant to Patent Local Rule 3-3(a), Bio-Rad
14 identifies the following prior art references that invalidate the Asserted Claims by anticipation
15 and/or by rendering the Asserted Claims obvious. Bio-Rad has identified each prior art patent by
16 its inventor, title, number, country of origin, date of filing, and date of issue. To the extent any
17 prior art reference that Bio-Rad asserts anticipates one or more of the Asserted Claims is argued by
18 Plaintiff or found by the Court not to anticipate any of the Asserted Claims, Bio-Rad contends that
19 the reference nevertheless renders all of the Asserted Claims obvious either individually or in
20 combination with other references and/or in view of the knowledge of a skilled artisan and/or
21 common sense. Subject to the foregoing, based upon presently known information, the prior art
22 references that anticipate and/or render obvious the Asserted Claims include:

- 23 • U.S. Patent No. 9,921,154 ("Jouvenot")
- 24 • U.S. Patent No. 9,222,128 ("Saxonov '128")
- 25 • U.S. Patent Pub. 2013/0040841A1 ("Saxonov")
- 26 • U.S. Patent Pub. 2011/0250597A1 ("Larson")
- 27 • U.S. Patent Pub. 2008/0124705A1 ("Kramer")
- 28 • U.S. Patent No. 8,614,061 ("Brabetz")

- 1 • U.S. Patent Pub. 2012/0077692 (“Hassibi”)
- 2 • U.S. Patent Pub. 2011/0312704A1 (“Silverbrook”)
- 3 • U.S. Patent Pub. 2014/0051155A1 (“Evans”)
- 4 • U.S. Patent Pub. 2012/0100600A1 (“Slepnev”)
- 5 • U.S. Patent Pub. 2008/0003649A1 (“Maltezos”)
- 6 • U.S. Patent No. 6,814,934 (“Higuchi”)
- 7 • U.S. Patent Pub. 2009/0156415A1 (“Remacle”)
- 8 • U.S. Patent No. 5,639,428 (“Cottingham”)
- 9 • U.S. Patent No. 7,991,558 (“Kurnik”)
- 10 • U.S. Patent No. 9,044,753 (“Atwood”)
- 11 • U.S. Patent No. 8,697,433 (“Oh”)
- 12 • U.S. Patent No. 5,333,675 (“Mullis”)
- 13 • U.S. Patent Pub. 2012/0214207A1 (“Gunter”)
- 14 • U.S. Patent No. 9,207,690 (“Tverskoy”)
- 15 • U.S. Patent Pub. 2010/0311070A1 (“Oh ’070”)
- 16 • U.S. Patent Pub. 2007/0128613A1 (“Davies”)
- 17 • U.S. Patent Pub. 2011/0160288A1 (“Nakamura”)
- 18 • U.S. Patent Pub. 2007/0048750A1 (“Peck”)
- 19 • U.S. Patent No. 5,476,774 (“Wang”)
- 20 • U.S. Patent Pub. 2007/0237716A1 (“Mason”)
- 21 • U.S. RE 38,352 (“Kozal”)
- 22 • U.S. Patent Pub. 2004/0229211A1 (“Yeung”)
- 23 • U.S. Patent Pub. 2010/0267017A1 (“Hassard”)
- 24 • U.S. Patent Pub. 2009/0239308A1 (“Dube”)
- 25 • U.S. Patent Pub. 2009/0258414A1 (“Wittwer”)
- 26 • EP-0594763B1 (“Lehnen”)
- 27 • Joseph R. Lakowicz, *Principles of Fluorescence Spectroscopy* (3d ed., 2006)
- 28 (“Lakowicz”)

- 1 • Amersham Pharmacia Biotech, *Fluorescence Imaging Principles and Methods* (2000)
- 2 (“Amersham Fluorescence Publication”)
- 3 • U.S. Patent Pub. 2009/0191563 (“Steemers”)
- 4 • U.S. Patent Pub. 2010/0227386 (“Neuzil”)
- 5 • U.S. Patent Pub. 2003/0219754 (“Oleksy”)
- 6 • U.S. Patent Pub. 2008/0014589 (“Link ’589”)
- 7 • U.S. Patent Pub. 2008/0003142 (“Link ’142”)
- 8 • U.S. Patent Pub. 2010/0137163 (“Link ’163”)
- 9 • EP2047910 (“Link European Specification”)
- 10 • Bio-Rad QX100 Droplet Digital PCR System (the “QX100 System”)

11 Saxonov is 102(a), 102(e), and 102(g) prior art and Serge Saxonov, of Oakland, California,
12 Simant Dube of Pleasanton, California, and John Frederick Regan of San Mateo, California, were
13 involved in the development of the prior art reference while working at Bio-Rad.

14 Jouvenot is 102(a), 102(e), and 102(g) prior art and Yann Jouvenot of Benicia, California,
15 Serge Saxonov, of Oakland, California, Simant Dube of Pleasanton, California, and John Frederick
16 Regan of San Mateo, California, were involved in the development of the prior art reference while
17 working at Bio-Rad. The Jouvenot Patent is also continuation in part of U.S. App. No. 13/424,304,
18 filed on Mar 19, 2012, now U.S. Pat. No 9,222,128, and a continuation-in-part of U.S. App. No.
19 13/548,062, filed on Jul 12, 2012, now Pat. No. 8,951,939. The Jouvenot Patent claims further
20 priority to U.S. Provisional Application Nos. 61/454,373, filed on March 18, 2011; 61/507,082,
21 filed on July 12, 2011; 61/510,013, filed on July 20, 2011, and 61/734,296, filed on December 6,
22 2012. All disclosures relied on in these invalidity contentions were disclosed in Provisional
23 Application No. 61/507,082 and are entitled to the July 12, 2011 priority date.

24 Saxonov ’128 is 102(a), 102(e), and 102(g) prior art and Serge Saxonov, of Oakland,
25 California, Simant Dube of Pleasanton, California, Benjamin J. Hindson of Livermore, California,
26 and Adam M. McCoy of Davis, California, were involved in the development of the prior art
27 reference while working at Bio-Rad.

28 The QX100 System is 102(a) and 102(g) prior art and was developed at Bio-Rad prior to its

1 release in October, 2011.

2 The above identification of prior art by Bio-Rad is in addition to the prior art cited in the
3 prosecution history of the '797 patent and/or in the prosecution histories of any related patents or
4 patent applications, all of which are herein incorporated by reference in their entirety. Bio-Rad
5 further incorporates by reference contentions previously served or subsequently served in any
6 related litigation, including its June 17, 2024 Amended Invalidity Contentions.

7 Bio-Rad reserves the right to update its invalidity contentions to reflect the results of
8 discovery in this matter, any claim constructions provided by the Court, and/or Bio-Rad's
9 continuing investigation into the facts of this matter.

10 **II. PATENT LOCAL RULE 3-3(B) DISCLOSURES**

11 Based upon presently known information, pursuant to Patent Local Rule 3-3(b), below are
12 the grounds on which the Asserted Claims are invalid for failure to meet the requirements of both
13 35 U.S.C. §§ 102 and 103. The Asserted Claims are neither novel nor non-obvious in the field of
14 multiplexing with digital PCR assays. All aspects of the Asserted Claims were well known and
15 extensively researched well before the filing of the patent.

16 **A. Anticipation of the Asserted Claims**

17 At least the Asserted Claims of the '797 Patent are invalid as anticipated, either expressly,
18 implicitly or inherently as understood by a person having ordinary skill in the art.

- 19 • Jouvenot anticipates the '797 Patent as described, by illustrative citations, in Appendix
20 A and is 102(a), 102(e), and 102(g) prior art.
- 21 • Larson anticipates the Asserted Claims of the '797 Patent as described, by illustrative
22 citations, in Appendix B and is 102(a), 102(e), and 102(g) prior art.

23 **B. Obviousness of the Asserted Claims**

24 The Asserted Claims Would Have Been Obvious in View of the Prior Art References as
25 reflected in Appendices A and B and in the summary below. To the extent the Asserted Claims are
26 not deemed invalid under 35 U.S.C. § 112 for lack of enablement written description, or
27 indefiniteness, Bio-Rad contends that the prior art listed in Section I., whether alone or in
28 combination with each other, renders the Asserted Claims of the '797 Patent obvious under 35

1 U.S.C. § 103, as set forth in the claim charts and as described below.

2 For the reasons stated below, the Asserted Claims would have been obvious in view of
3 numerous prior art references that were available before the alleged priority date of the '797 Patent.
4 In particular, the claims of the '797 Patent would have been rendered obvious in view of the
5 combinations of prior art described below for each of the Asserted Claims. These prior art
6 combinations are not exhaustive; rather they are illustrative examples of prior art combinations
7 based on the following categories of art and specific references within these categories.

- 8 • Prior art teaching **single sample detection of multiple analytes**, for instance:
9 Jouvenot, Saxonov '128, Saxonov, and Kramer, the QX100 System, Lehnen (the
10 “Multiplexed Encoding and Detection Art”). *See, e.g.*, Appendix A.
- 11 • Prior art teaching **labeling and optimization of analytes for multiplexing**, for
12 instance: Larson, Brabetz, Jouvenot, Saxonov '128, Saxonov, Kramer, Brabetz,
13 Hassibi, the QX100 System, Steemers, Lakowicz, Amersham Fluorescence
14 Publication, Lehnen, Neuzil, Oleksy, Dube, Wittwer (the “Probe Labeling and
15 Measurement Art”). *See, e.g.*, Appendix A.
- 16 • Prior art teaching the use of **computers and networks to perform assays**, for
17 instance: Jouvenot, Saxonov, Saxonov '128, Larson, Silverbrook, Evans, Slepnev,
18 Maltezos, Higuchi, Remacle, Cottingham, Kurnik, Atwood, Oh, Mullis, Gunter,
19 Tverskoy, Oh '070, the QX100 System (the “Computer and Network Assays Art”).
- 20 • Prior art teaching the **detection of targets from biological samples**, for instance:
21 Jouvenot, Saxonov, Saxonov '128, Kramer, Larson, Davies, Nakamura, Peck, Wang,
22 Mason, Kozal, Yeung, Hassard, Link '589, Link '142, Link '163, the Link European
23 Specification (the “Biological Sample Art”).
- 24 • Prior art teaching the use of **various fluorophores**, for instance: Larson, Brabetz,
25 Jouvenot, Lakowicz Amersham Pharmacia Biotech, Maltezos, Steemers (the
26 “Fluorophore Art”).
- 27 • Prior art that teaches the use of **displays within a system**, for instance: Maltezos,
28 Slepnev, Jouvenot, Larson (the “Display Art”).

- Prior art that teaches the use of various types of hardware for **detection within a system, such as filters and detectors**, for instance: Link '589, Link '142, Link '163, the Link European Specification, Brabetz, Maltezos, Neuzil, Oleksy, Dube, Wittwer (the “Filter and Detector Art”).

To the extent that Plaintiff challenges a combination of prior art with respect to a particular element, Bio-Rad reserves the right to supplement these contentions to further specify the motivation to combine the prior art. Bio-Rad may rely on cited or uncited portions of the prior art, other documents, and/or expert testimony to establish that a person of ordinary skill in the art would have been motivated to modify or combine the prior art so as to render the Asserted Claims invalid as obvious claims 1–2, 5–11, 13–15, 18–19, and 21

1. Claims 1–2, and 19

To the extent Plaintiff contend that any of the references identified above do not disclose any or all of the limitations in Claim 1 of the '797 Patent, the limitations are obvious in light of the background knowledge possessed by a person of ordinary skill in the art, and/or the limitations can be found, for example, in one or more of the prior art references cited in the tables above. Independent claim 1 recites a system where a sample chamber has a sample and analyte-specific reagent mixtures, a detector, and a processor controlled analyzer that receives a cumulative signal from the detector and applies a decoding matrix to the cumulative signal to detect the presence or absence of at least M analytes. The reagent mixtures of claim 1 contain analyte-specific hybridization probes and multiple fluorophores. The detector is a “multi-channel” detector that detects four electromagnetic signals at four different wavelengths from each of four fluorophores in the sample chamber. The process controlled analyzer then receives a “cumulative signal” based on the electromagnetic signals detected by the multi-channel detector and applies a decoding matrix to the cumulative signal to “unambiguously detect the presence or absence of at least each of M analytes” by using the intensity and wavelength measured from the sample. The claim also requires the number of analytes detected (M) to be equal to the number of channels used (C) times the maximum cumulative intensity of the first component of the cumulative signal for any of the second

1 values when all analytes are present (F). In the terms of the claim, $M=C*\log_2 (F+1)$, and each
2 variable must be a positive integer. “C” must also be equal to four, five, or six, (F+1) must be a
3 positive integer and a power of two, and M must be greater than the number of channels. The
4 system makes its determination without immobilization, mass spectrometry, or melting curve
5 analysis.

6 Independent claim 19 is nearly identical in substance. In addition to each of the limitations
7 described above, claim 19 also includes a display and a non-transitory computer readable medium
8 storing instructions thereon. The cumulative signal data of claim 19 must come from a digital PCR
9 instrument that has a light source and rather than a sample generally, the sample must be in a
10 “sample volume.” Additionally, the system of claim 19 detects fluorescently labeled
11 polynucleotide analytes, rather than generic analytes.

12 Claim 2 is dependent on claim 1 and specifies conditions for the multi-channel detector
13 where it detects a fifth and sixth electromagnetic signal at a fifth and sixth wavelength from the
14 electromagnetic signal generated by excitement of a fifth and sixth fluorophore.

15 Claims 1, 2, and 19 of the '797 Patent are obvious because it would have been obvious for
16 one of skill in the art to combine the Multiplexed Encoding and Detection Art with the Probe
17 Labeling and Measurement Art, or combine references within each class of art for at least the
18 following reasons. For example, a POSA would have found it obvious to combine the references
19 to analyze a greater number of targets, i.e., to perform a higher order of multiplexing as taught by
20 Larson and Kramer. A POSA would have understood the need to and benefit of looking to
21 references such as those included in the table above from the teachings of Jouvenot. *See, e.g.,*
22 Jouvenot 2:21–22 (“A new approach is needed to increase the multiplex levels of digital assays”);
23 *see also* Appendices A–B. A POSA would have additionally understood the benefit of not requiring
24 immobilization, mass spectrometry, or melting curve analysis to use the systems of the alleged
25 invention to not require additional steps to use the systems. *See* Appendices A–B. Further, a POSA
26 would have found it obvious to unambiguously detect the results of such systems to provide more
27 accurate results with the system, as described in Kramer by, for example, Figure 5, which depicts
28 an unambiguous result of two targets present in combination. Kramer ¶ 26, Fig. 5; *see also*

1 Appendices A–B.

2 Kramer further teaches methods wherein probes with different numbers of unique
3 fluorophores are used to differentiate the targets in combination, “[the] combinatorial code may be
4 quadraplex coding in which the code elements comprise four colors, optionally enlarged by
5 additional code elements of three colors, two colors or one color, or some combination thereof,”
6 Kramer ¶ 11, and further methods wherein the targets are labeled with differing amounts of
7 common fluorophores to differentiate between targets, “[i]n ratio coding differing amounts of the
8 same label are used for differentiation. Combinatorial codes according to this invention may be
9 augmented with ratio coding, preferably integral ratio coding, that is, ratios of whole numbers such
10 as 2:1, 3:1, 4:1 or 5:1, and vice versa.” Kramer ¶ 14. Saxonov similarly teaches unambiguous
11 detection of targets both in a single color, such as in Figure 5, and by differentiating the colors of
12 the targets to be detected, such as in Figure 10. *See, e.g.*, Saxonov ¶¶ 78 (describing the detection
13 of three targets in any combination, the single positive populations, the “double-positive
14 populations (T1+/T2+, T1+/T2+, and T2+/T3+)” and the “triple positive population
15 (T1+/T2+/T3+).”), 60-67 (describing the detection of two analytes in any combination based on
16 intensities of signals exhibited in a single color).

17 Further, a POSA would have had a reasonable expectation of success in creating the systems
18 of the alleged invention. A POSA would have understood that a biochemical assay can be
19 multiplexed with multiple different colors by using multiple optical channels, and that more targets
20 could be analyzed, by applying the teachings of Jouvenot, e.g., Fig. 5, depicting the detection of
21 targets using intensity and multiple fluorophores (VIC and FAM). Jouvenot further teaches the
22 detection of analytes based off using more than three intensities. *See, e.g.*, Jouvenot Figure 4; *see*
23 *also id.* 14:21–15:10. A POSA would have expected success in applying Jouvenot’s teaching that
24 “signals optionally may include data collected in two or more different optical channels (e.g., in
25 different wavelength ranges (wavebands) and/or color regimes) from reporters for the same and/or
26 different targets,” 8:36–40 to, for example, four to six optical channels (colors) with two targets
27 identified in each channel to analyze the presence of eight to twelve targets in a single sample
28 solution or alternatively twelve targets in four colors with three targets per channel (or sixteen

1 targets in six colors). Larson further teaches using additional colors and that adding additional
2 colors increases detection capabilities. Larson ¶¶ 139 (“The maximum number of colors can be
3 higher than 20.”); *see also id.* ¶ 153.

4 A POSA would have further known to optimize the differentiation between the signals
5 generated by the targets, alone and in combination, as described by the teachings of Larson, which
6 allow the multiplexed detection of nine analytes. *See, e.g.,* Larson ¶¶ 35, 150 (describing Fig. 15);
7 *see also* Appendix B. A POSA would have further understood from the teachings of Kramer that
8 multiplex detection of more than ten targets can be performed in an assay via combinatorial and
9 ratio coding schemes using four unique fluorophores. *See e.g.,* Kramer ¶¶ 11, 14. Further, a POSA
10 would have been motivated by the teachings of Kramer to perform an assay wherein each
11 hybridization probe comprises an identical fluorophore to optimize the fluorescence emissions of
12 the fluorophores on a probe and thus more reliably detect and resolve which analyte(s) are present
13 in a given assay. *See, e.g.,* Kramer ¶ 13.

14 Claims 1, 2, and 19 of the ’797 Patent are also obvious because it would have been obvious
15 for one of skill in the art to combine the Multiplexed Encoding and/or Detection Art with the Probe
16 Labeling and Measurement Art and/or with the Computer and Network Assays Art, or combine
17 references within each class of art for at least the following reasons. *See, e.g.,* Jouvenot (teaching
18 a “data processing assembly,” Jouvenot 12:58-59, that “communicates with and controls operation
19 of any suitable combination of the assemblies,” Jouvenot 12:60-62, and that these assemblies may
20 be “operatively connected to one another.” Jouvenot 12:66-67; *see also* Saxonov (teaching a “data
21 processing assembly,” Saxonov ¶ 45, that “communicates with and controls operation of any
22 suitable combination of the assemblies,” *Id.*, and that these assemblies may be “operatively
23 connected to one another.” *Id.*; Saxonov ’128; (teaching a “data processing assembly,” Saxonov
24 ’128 9:7-8, that “communicates with and controls operation of any suitable combination of the
25 assemblies,” *id.* 9:10-12, and that these assemblies may be “operatively connected to one another.”
26 *Id.* 9:16-17.); Larson ¶¶ 80-85 (Larson teaches that in certain embodiments, the thermal cycling
27 may depend on a number on repeated cycles in various temperature zones, which a POSA would
28 have understood would be advantageous to use a computer to control because monitoring

1 temperature and performing cycles are actions well-suited to be performed by computers); Larson
2 ¶ 89 (Larson teaches that suitable detection apparatuses include computers and software);
3 Silverbrook ¶ 198 (“To conduct a diagnostic test, the test module 10 (or test module 11) is inserted
4 into the Micro-USB port 16 on the test module reader 12. The sterile sealing tape 22 is peeled back
5 and the biological sample (in a liquid form) is loaded into the sample macroreceptacle 24.”); Evans
6 ¶ 198 (“Computing device 104 may be provided within housing 101, or may be provided separately,
7 Such as a laptop or desktop computer, or portions of computing device 104 may be resident within
8 housing 101, while other portions are located separately and may be coupled through wiring or
9 wirelessly. Computing device 104 may be configured to load computer-readable program code for
10 controlling thermal cycler apparatus 100 and optics block 109. In one illustrative embodiment,
11 thermal cycler apparatus 100 in housing 101 may be provided in an automated system with a
12 robotics unit 105. The robotics unit 105 may be programmed to load the samples into sample wells
13 82 and then load sample plate 80 into housing 101 through opening 102.”); Slepnev ¶ 122 (“To
14 perform the PCR process, the temperature of the metal block is controlled according to prescribed
15 temperatures and times specified by the user in a PCR protocol file. A computer and associated
16 electronics then controls the temperature of the metal block in accordance with the user supplied
17 data in the PCR protocol file defining the times, temperatures, and number of cycles, etc. As the
18 metal block changes temperature, the samples in the various tubes follow with similar changes in
19 temperature.”); Maltezos ¶ 132 (in a system for detecting signals, “The detector is connected with
20 the evaluation circuit computer.”); Higuchi Fig. 8 (depicting a thermal cycler and detector
21 connected to a computer); Remacle ¶ 134 (“Data storage and data treatment are preferably
22 performed using a programmable computer which is integrated in the apparatus of the invention.
23 Data treatment can be performed at any time after data storage.”); Cottingham 15:58-16:24
24 (describing the use of networks connected to a host computer for clinical diagnostics based on
25 polynucleotide assays); Kurnik 7:18-31 (describing that performing the cycle threshold for
26 polynucleotide detection “over a network connection or direct connection to a code source or using
27 a portable medium as is well known.”); Atwood 1:19-22 (“the invention pertains to automated
28 instruments that perform the reaction simultaneously on many samples and produce very precise

1 results by using thermal cycling.”); Oh 2:59-63 (“According to an aspect of the present invention,
2 a multiple PCR system includes the PCR module; and a host computer controlling the PCR module,
3 wherein the PCR module includes a computing unit and the computing unit of the PCR module and
4 the host computer are electrically connected through a wire or wireless network.”); Mullis at
5 abstract (“There is disclosed herein a machine for performing nucleic acid amplification under
6 computer control.”); Gunter ¶ 134 (“The system 900 can be in wired or wireless communication
7 with a remote system for housing data or providing instructions for PCR (see below).
8 Communication to and from the system can be facilitated by a network interface that brings the
9 system and in communication with the remote system through an intranet or the Internet (e.g., the
10 World Wide Web).”); Tverskoy 4:14-18 (“A thermal control system 226 includes computer
11 readable storage medium such as physical memory 228 in which a predetermined set of target
12 sample temperatures and corresponding timing 230 (e.g., temperatures and timing for PCR) for a
13 loaded carrier are stored.”); Oh ’070 ¶ 71 (“the host computer 50 and the computing units 41 have
14 respective auxiliary memories 54 and 44. The auxiliary memories 54 and 44 store software
15 programs for PCR control and the software programs execute their functions. In particular, the
16 Software programs may be connected through wire or wireless network [.] Such as a pier-pier
17 network or a server-client network.”); the QX100 System (the QX100 system connects to the
18 QuantaSoft Software) https://www.biorad.com/webroot/web/pdf/lsr/literature/bulletin_10026321.pdf at 8. First, a POSA would have
19 been motivated to combine the above classes of art because A POSA would have understood that
20 to perform the steps of the alleged invention, such as detecting and measuring cumulative intensity
21 signals emitted from excited fluorophores, using a computer would provide benefits of improving
22 efficiency in collecting data and performing calculations and thermal cycling to amplify targets.
23 *See, e.g.,* Higuchi Fig. 8; *see also* Maltezos ¶¶ 12, 132.

24
25 Claims 1, 2, and 19 of the ’797 Patent are also obvious because it would have been obvious
26 for one of skill in the art to combine the Multiplexed Encoding and/or Detection Art with the
27 Computer and Network Assays Art, and/or the Display Art, or combine references within each class
28 of art for at least the following reasons. The use of a screen, as claimed in claim 19, would have

1 been no more than a routine use of screens in the art and it would have been obvious in light of the
2 foregoing. Larson, Figure 15, teaches using a display to visualize a plot of first and second values.
3 It would also have been obvious to include with the system a display so that users can visualize the
4 data results and confirm the accuracy of the reported target concentrations. Using a display for
5 such purposes was well known the art. *See, e.g.*, Maltezos ¶ 167 (“Generally, a computer comprises
6 a central processing unit, a storage or memory unit that can record and read information and
7 programs using machine-readable storage media, a communication terminal such as a wired
8 communication device or a wireless communication device, an output device such as *a display*
9 *terminal*, and an input device such as a keyboard.” (emphasis added)); Slepnev ¶ 141 (“In one
10 embodiment, the data generation device comprises a signal detector, a display monitor and a
11 computer processor coupled to the control circuit and the display monitor.”).

12 Further, a POSA would have known that performing the generation of fluorescent signals
13 representing polynucleotide analytes, the detection of such signals, and the determination of which,
14 if any, of the targets such signals represent has been performed on computers since long before the
15 alleged priority date of the ’797 Patent and a POSA would have been motivated to apply these
16 teachings to the systems of the alleged invention to enhance the efficiency and reliability of signal
17 detection and measurement. *See, e.g.*, Silverbrook ¶ 198.

18 Further still, a POSA would have known that the number of detectable analytes in a sample
19 was equal to the number of channels times a geometric progression capturing intensity (i.e.,
20 $M=C*\log_2(F+1)$). Lehnert discloses the use of binary (power-of-2) encoding (1:2:4:8) and
21 discusses multiplexing capacity as a function of channels and intensity levels. *See* Lehnert at 13:15–
22 53. Each analyte in Lehnert was encoded using bead subpopulations and powers of two to ensure
23 each possible combination yielded a unique sum. A POSA would have been motivated to use the
24 signal progression from Lehnert because its proportions allow for unique interpretation and
25 unambiguous identification of analytes. *See* Lehnert at 13:31–35. Moreover, Jouvenot expressly
26 teaches multiple methods for modulating the intensity from a target-specific probe. Jouvenot
27 explains, “the intensity associated with one fluorophore, following reaction, may be lower or higher
28 than the intensity(ies) associated with the other fluorophore(s). In some embodiments, one probe

1 may be labeled with a different number of fluorophores than the other probe, and/or the probes may
2 be located in slightly different local environments, creating a different level of fluorescence for
3 each probe following reaction. Alternatively, or in addition, both probes may be labeled with the
4 same number of fluorophores (e.g., one fluorophore), but there may be more or less of one probe
5 than the other in the sample, so that a greater or smaller signal is created when the reactions have
6 occurred.” Jouvenot 13:51–63.

7 Jouvenot and Larson further teach the use of systems that detect analytes by using varied
8 intensity values. For example, in Jouvenot the peak at 112 in Figure 4 represents the detection of
9 multiple analytes based on a cumulative intensity from a first component of a signal from a second
10 value where all analytes were present. *See* Jouvenot 14:21–15:10. And the peak at ~0.9 V that was
11 measured (but not visible in charts) in Larson Figure 11 further teaches the use of systems that
12 detect analytes using cumulative intensity. Larson ¶ 131. Thus, at the time of the alleged invention,
13 claims 1, 2, and 19 of the ’797 Patent would have been obvious to one skilled in the art based on
14 the references cited herein, at least as described above.

15 2. Claims 5 and 21

16 To the extent Plaintiff contends that any of the references identified above do not disclose
17 any or all of the limitations in Claims 5 and 21 of the ’797 Patent, the limitations are obvious in
18 light of the background knowledge possessed by a person of ordinary skill in the art, and/or the
19 limitations can be found, for example, in one or more of the prior art references cited in the tables
20 above. Claim 5 and 21 of the ’797 Patent are dependent on claims 1 and 19 respectively, which are
21 invalid for the reasons stated above. Dependent Claims 5 and 21 both claim systems where the
22 maximum cumulative intensity of the first component of the signal for a any second value when all
23 analytes are present equals three (i.e., $F=3$).

24 Claims 5 and 21 of the ’797 Patent are obvious because it would have been obvious for one
25 of skill in the art to combine the Multiplexed Encoding and Detection Art with the Probe Labeling
26 and Measurement Art, or combine references within each class of art for at least the following
27 reasons. For example, a POSA would have found it obvious to combine the references to analyze
28

1 a greater number of targets, i.e., to perform a higher order of multiplexing as taught by Larson,
2 Lehnen, and Jouvenot—individually and cumulatively.

3 Larson and Jouvenot both disclose detection of analytes using intensity values and disclose
4 $F=3$. For example, in Figure 11 of Larson, the measurement at ~ 0.9 V corresponds to droplets
5 occupied by both detected genes and represents a cumulative intensity of three. Larson ¶ 131; *see*
6 *also* Appendix B. Additionally, Figure 4 of Jouvenot discloses the same with the peak at 112,
7 which represents the presence of all analytes present and a cumulative intensity of three based on
8 the interval values used to measure intensity. *See* Jouvenot 14:21–15:10; *see also* Appendix A.

9 Further, Lehnen teaches multiplexing capacity based on the use of binary encoding and
10 discloses multiplexing capacity as a function of channels and intensity levels. *See* Lehnen at 13:15–
11 53. Thus, at the time of the alleged invention, claims 5 and 21 of the '797 Patent would have been
12 obvious to one skilled in the art based on the references cited herein, at least as described above.

13 3. Claims 6–9

14 To the extent Plaintiff contends that any of the references identified above do not disclose
15 any or all of the limitations in Claims 6–9 of the '797 Patent, the limitations are obvious in light of
16 the background knowledge possessed by a person of ordinary skill in the art, and/or the limitations
17 can be found, for example, in one or more of the prior art references cited in the tables above.
18 Claims 6–9 each specify different conditions for the fluorophores used in the claimed system.
19 Dependent Claims 6–9 each are dependent Claim 5, which is dependent on Claim 1.

20 Dependent claim 6 requires fluorophores to be selected from a blue fluorophore, a green
21 fluorophore, a yellow fluorophore, a red fluorophore, or any combinations thereof. Dependent
22 claim 7 requires the fluorophores to be selected from FAM, ROX, Cy5, Cy5.5, and any
23 combinations thereof. Dependent claim 8 requires the fluorophores to be selected from those with
24 maximum excitation wavelengths of 494 nm, about 550 nm, about 567 nm, about 650 nm, about
25 675 nm, and any combinations thereof. Dependent claim 9 requires the fluorophores to be selected
26 from those with maximum emission wavelengths of about 518 nm, about 565 nm, about 591 nm,
27 about 670 nm, about 697 nm, and any combinations thereof.
28

1 Claims 6–9 of the '797 Patent are obvious because it would have been obvious for one of
2 skill in the art to combine the Multiplexed Encoding and Detection Art with the Probe Labeling
3 and Measurement Art, and/or the Fluorophore Art or combine references within each class of art
4 for at least the following reasons. A POSA would have been motivated to combine the Multiplexed
5 Encoding and Detection Art with the Probe Labeling and Measurement Art to use the systems
6 described in the alleged invention because A POSA would have understood that reliable signal
7 generation is dependent on using a variety of wavelengths to allow them to distinguish targets. *See*,
8 *e.g.*, Jouvenot 13:24–55 (describing signals generated from two probes to identify two targets in a
9 multiplexed assay).

10 It was additionally well known that the differentiation of the fluorescent signals from the
11 probes corresponding to targets by “varying the probe and primer concentrations together [is] a
12 very simple technique to optimize relative intensities in higher-plex reactions.” *See, e.g.*, Larson
13 ¶ 134, *see also* Larson ¶¶ 137, 150. Larson further teaches the use of fluorophores that fall within
14 each of the claimed ranges. *See* Larson ¶ 90 (DAPI, FAM, ROX, Cy5, etc.). Moreover, and as
15 well described in the Fluorophore Art, each of the claimed type of fluorophores was well known in
16 the art. *See, e.g.*, Lakowicz, 657–660, 827, 848–851 (disclosing fluorophores in the claimed
17 ranges); Amersham Pharmacia Biotech, 84, 129, 132 (disclosing fluorophores in the claimed
18 ranges); *see also* Maltezos ¶¶ 142, 194 (disclosing fluorophores in the claimed ranges). Thus, at
19 the time of the alleged invention, claim 10 of the '797 Patent would have been obvious to one
20 skilled in the art based on the references cited herein, at least as described above.

21 4. Claim 10

22 To the extent Plaintiff contends that any of the references identified above do not disclose
23 any or all of the limitations in Claim 10 of the '797 Patent, the limitations are obvious in light of
24 the background knowledge possessed by a person of ordinary skill in the art, and/or the limitations
25 can be found, for example, in one or more of the prior art references cited in the tables above. Claim
26 10 is dependent on claim 5, which is dependent on claim, and specifies that the analyte-specific
27 hybridization probes must be labeled with a fluorophore of the multiple fluorophores.
28

1 Claim 10 of the '797 Patent is obvious because it would have been obvious for one of skill
2 in the art to combine the Multiplexed Encoding and Detection Art with the Probe Labeling and
3 Measurement Art, or combine references within each class of art for at least the following reasons.
4 A POSA would have been motivated to combine the Multiplexed Encoding and Detection Art with
5 the Probe Labeling and Measurement Art to use the systems described in the alleged invention
6 because A POSA would have understood that reliable signal generation is dependent on the probes
7 and the fluorophore(s) that are on the probes. *See, e.g.,* Jouvenot 13:24–55 (describing signals
8 generated from two probes to identify two targets in a multiplexed assay).

9 It would have been obvious to a skilled artisan at the time of the alleged invention to use
10 probes that are specific to target analytes, as was well known in the art. *See, e.g.,* Jouvenot 2:12–
11 14; see also Appendix A. It was further well known in the art that probes comprised one color (one
12 unique fluorophore) per probe, two colors per probe, three colors per probe, or four colors per probe
13 could be used in multiplexed assays to even further that different numbers of each unique
14 fluorophore may be placed on a single probe. *See, e.g.,* Kramer ¶¶ 3, 32; *see also*, Maltezos, Table
15 1; Appendices A–B. It was additionally well known that the differentiation of the fluorescent
16 signals from the probes corresponding to targets by “varying the probe and primer concentrations
17 together [is] a very simple technique to optimize relative intensities in higher-plex reactions.” *See,*
18 *e.g.,* Larson ¶ 134, *see also* Larson ¶¶ 137, 150. Thus, at the time of the alleged invention, claim
19 10 of the '797 Patent would have been obvious to one skilled in the art based on the references
20 cited herein, at least as described above.

21 5. Claims 11, 13-15

22 To the extent Plaintiff contends that any of the references identified above do not disclose
23 any or all of the limitations in Claims 11, 13–15 of the '797 Patent, the limitations are obvious in
24 light of the background knowledge possessed by a person of ordinary skill in the art, and/or the
25 limitations can be found, for example, in one or more of the prior art references cited in the tables
26 above. Each of these claims are dependent on claim 5, which is dependent on claim 1. These
27 claims provide limitations on the detector used within the claimed system. Particularly, claim 11
28

1 requires the detector to have four or six band pass filters, claim 13 requires four or six
2 photodetectors, claim 14 requires photodetectors that enable detection of blue, green, and red
3 fluorescent signals, and claim 15 requires photodetectors that enable detection ranges based on
4 certain wavelengths in the claim.

5 Claims 11, 13–15 of the '797 Patent are obvious because it would have been obvious for
6 one of skill in the art to combine the Multiplexed Encoding and Detection Art with the Probe
7 Labeling and Measurement Art, and/or the Filter and Detector Art, or combine references within
8 each class of art for at least the following reasons. For example, photodetectors were used in
9 Maltezos, Dube, and Wittwer. *See* U.S. Patent Publication Maltezos ¶¶ 60, 101, 144; *id.* ¶ 149
10 (“The photodetector array includes a plurality of photodetectors...”); *see also* U.S. Patent
11 Publication 2009/0239308A1 (“Dube”) ¶ 147 (“the CCD is used as an array of photodetectors
12 wherein each pixel or group of pixels corresponds to a reaction chamber...”); U.S. Patent
13 Publication 2009/0258414A1 (“Wittwer”) ¶ 375 and Figure 53 (“The emitted fluorescence signals
14 are acquired by photodetectors 466 A and 466 B.”). Moreover, photodetectors were generally well
15 known in the art.

16 It would have been obvious to a skilled artisan at the time of the alleged invention to use
17 multiple photodetectors. As discussed in detail above, Jouvenot expressly teaches using multiple
18 color channels. Specifically, Jouvenot discloses that its “assays may be extended in various ways.”
19 Jouvenot 5:19–31. Most important, Jouvenot teaches that “some targets may be analyzed in one
20 channel (e.g., a FAM channel, and other targets may be analyzed in other channels (e.g., a VIC
21 channel).” *Id.* In other words, Jouvenot teaches the use of multiple channels, which a person of
22 skill in the art would understand is a teaching of using multiple different wavelength signals from
23 multiple different fluorophores. Further, Larson uses multiple photodetectors. Larson ¶ 195
24 (“Fluorescence was detected by two H5784-20 photomultipliers...”). Larson also teaches that
25 detection can use any method known in the art. Larson ¶ 89. Larson teaches using multiple color
26 channels as well, *see* Larson ¶ 139, and a person of skill in the art would understand that teaching
27 the use of multiple colors is a teaching of using multiple different wavelength signals from multiple
28 different fluorophores. Thus, at the time of the alleged invention, claim 10 of the '797 Patent would

1 have been obvious to one skilled in the art based on the references cited herein, at least as described
2 above.

3 6. Claim 18

4 To the extent Plaintiff contends that any of the references identified above do not disclose
5 any or all of the limitations in Claim 18 of the '797 Patent, the limitations are obvious in light of
6 the background knowledge possessed by a person of ordinary skill in the art, and/or the limitations
7 can be found, for example, in one or more of the prior art references cited in the tables above. Claim
8 18 is dependent on claim 5, which is dependent on claim 1. Claim 18 requires the processor
9 controlled analyzer to have display to visualize a plot of the first and second values.

10 Based on the foregoing, and as explained in connection with claim 19, the use of a display
11 to visualize a plot of first and second values would have been routine in the art and it would have
12 been obvious to one skilled in the art to combine the Display Art with the Multiplexed Encoding
13 and Detection Art with the Probe Labeling and Measurement Art, or combine references within
14 each class of art. Larson, Figure 15, teaches using a display to visualize a plot of first and second
15 values. It would also have been obvious to include with the system a display so that users can
16 visualize the data results and confirm the accuracy of the reported target concentrations. Using a
17 display for such purposes was well known the art. *See, e.g.,* Maltezos ¶ 167 (“Generally, a
18 computer comprises a ... an output device such as a *display terminal*...” (emphasis added)). For
19 example, in Slepnev, a display monitor is disclosed as part of an apparatus for detecting and
20 quantifying polynucleotides. Slepnev ¶ 141 (“In one embodiment, the data generation device
21 comprises a signal detector, a display monitor and a computer processor coupled to the control
22 circuit and the display monitor.”).

23 **III. PATENT LOCAL RULE 3-3 (C) DISCLOSURES**

24 Based upon presently known information, pursuant to Patent Local Rule 3-3(c), Bio-Rad
25 submits the below descriptions of anticipation and obviousness in the attached appendices, which
26 are illustrative and not exhaustive of the reasons for which the Asserted Claims are invalid. *See*
27 Appendices A–B. The claim charts provide exemplary identification of how the prior art
28

1 invalidates the asserted patents, alone or in combination with other prior art. These charts are
2 provided for exemplary purposes and may not set forth all instances in each reference where a claim
3 element or limitation is disclosed. Where Bio- Rad cites a particular figure, it should be understood
4 that the citation includes the caption and all descriptions of the figure, and vice versa when Bio-
5 Rad cites a portion of a prior art reference relating to a figure.

6 Bio-Rad reserves the right to update its invalidity contentions to reflect the results of claim
7 construction and discovery in this matter.

8 **IV. PATENT LOCAL RULE 3-3 (D) DISCLOSURES**

9 Based upon presently known information, pursuant to Patent Local Rule 3-3(d), the
10 Asserted Claims of the '797 Patent are invalid under 35 U.S.C. §§ 101 and 112 for the reasons set
11 forth below.

12 **A. 35 U.S.C. § 101**

13 At least the Asserted Claims are invalid under 35 U.S.C. § 101 for failure to meet the
14 requirements for patentability. Section 101 of the Patent Act provides: “Whoever invents or
15 discovers any new and useful process, machine, manufacture, or composition of matter, or any new
16 and useful improvement thereof, may obtain a Patent therefore, subject to the conditions and
17 requirements of this title.” Section 101 precludes the patenting of mental processes and abstract
18 ideas. *See Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1293 (2012).
19 The Supreme Court has established a framework for distinguishing Patents that claim laws of
20 nature, natural phenomenon, and abstract ideas from those that claim patent-eligible applications
21 of those concepts. *Alice Corp. Pty. Ltd. v. CLS Bank Int’l*, 134 S. Ct. 2347, 2350 (2014). First, the
22 court determines whether the claim is directed to a law of nature, a natural phenomenon, or an
23 abstract idea. *Id.* at 2355. If so, the court then proceeds to step two and considers the elements of
24 the claim “‘both individually and ‘as an ordered combination’ to determine whether the additional
25 elements ‘transform the nature of the claim’ into a patent-eligible application.” *Id.* (quoting *Mayo*,
26 566 U.S. at 78, 79).

27 The Asserted Claims here are no more than such abstract ideas and include no
28 transformative elements to render the claim a patent-eligible application of such an abstract idea.

1 The Asserted Claims are directed to the abstract idea of generating coding schemes, as well as
2 decoding such schemes, to represent the amplification and detection of presence of different
3 polynucleotide analytes. The acts of generating codes for, and determining algorithms decoding
4 results of such coding schemes are inherently abstract, i.e., they are capable of being performed
5 “using a pen and paper,” which is a hallmark of an abstract idea. *In re Killian*, 45 F.4th 1373, 1382
6 (Fed. Cir. 2022). In fact, Tables 3 and 4 of the specification do exactly that—encode and decode
7 the possible results showing the presence or absence of polynucleotide analytes in an assay. *See*,
8 *e.g.*, ’797 Patent 13:52-15:50.

9 Further, the Asserted Claims describe no advance in any of the following: (1) the labeling
10 of probes with different or identical fluorophores to allow greater amounts of probe labeling or
11 better emission signals generated; (2) the hardware to produce the signals emitted from the
12 fluorophores (e.g., lasers, etc.); nor (3) the hardware to detect the signals emitted. All such
13 techniques employed were conventional and well-understood. Thus, the Asserted Claims fail to
14 add an inventive concept and are ineligible as a matter of law because the only “‘inventive concept’
15 is the application of an abstract idea using conventional and well-understood techniques.” *Simio*,
16 *LLC v. FlexSim Software Prods., Inc.*, 983 F.3d 1353, 1364 (Fed Cir. 2020).

17 **B. 35 U.S.C. § 112**

18 1. Written Description:

19 To the extent the Asserted Claims are not deemed invalid under 35 U.S.C. §§ 102 and/or
20 103 for anticipation and/or obviousness, they are necessarily invalid under 35 U.S.C. § 112 for lack
21 of written description. The first paragraph/subsection of 35 U.S.C. § 112 requires a patent
22 specification to contain “a written description of the invention.” To satisfy the written description
23 requirement, the description must “clearly allow persons of ordinary skill in the art to recognize
24 that [the inventor] invented what is claimed.” *Ariad Pharms., Inc. v. Eli Lilly and Co.*, 598 F.3d
25 1336, 1351 (Fed. Cir. 2010) (internal citation omitted). “Whether the written description
26 requirement is satisfied is a fact-based inquiry that will depend on the nature of the claimed
27 invention, and the knowledge of one skilled in the art at the time an invention is made and a patent
28 application is filed.” *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1122

(Fed. Cir. 2008) (internal citation omitted). “Whether the flaw in the specification is regarded as a failure to demonstrate that the patentee possessed the full scope of the invention recited in [the claims] or a failure to enable the full breadth of that claim, the specification provides inadequate support for the claim under section 112, paragraph one.” *LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005).

Bio-Rad lists below the grounds upon which it presently contends that certain of the Asserted Claims of the ’797 Patent is invalid under pre-AIA 35 U.S.C. § 112 ¶ 1 for failure to provide an adequate written description.

The independent claims of the ’797 Patent, and all claims dependent therefore, at least under Plaintiff’s actual and/or apparent application of the claim, are invalid under 35 U.S.C. § 112 because the specification lacks an adequate written description of the alleged invention. The inventions as a whole, as claimed, are described nowhere in the specification. Furthermore, the specifications lack any working examples to show that the inventors were in possession of the claimed inventions. *See also infra* Section IV.B.1. To the extent that a person of ordinary skill in the art would not recognize the claimed inventions from a description of the invention and the general skill in the art, the ’797 Patent also fail to fill in any gaps from the knowledge and skill in the art.

To the extent that Plaintiff argues that the written description that is missing in the ’797 Patent or the priority applications thereto may be found in patents or other documents that are incorporated by reference into the ’797 Patent or the priority applications thereto, Bio-Rad argues that such incorporations by reference are improper or otherwise fail to provide the missing written description support for the Asserted Claims.

a. Literal Lack of Support for Terms Used in Claims

The alleged invention of the ’797 Patent contains several terms which are not literally found in the specification. For independent claim 1, the terms “integer,” “integers,” “receive,” “excitement,” “house,” “power,” “fourth,” “processor,” “analyzer,” and “multi-channel” are entirely absent from the specification. For independent claim 19, the terms “integer,” “integers,” “excitement,” “power,” “fourth,” “processor,” “multi-channel,” and storing lack literal support in

1 the specification. Moreover, not only would a person of ordinary skill in the art not recognize the
2 claimed inventions from a description of the invention and the general skill in the art, the '797
3 Patent also fail to fill in any gaps from the knowledge and skill in the art.

4 **b. Lack of Support for the Full Breadth of the Claims**

5 To satisfy the written description requirement, the specification must provide written
6 description support for the “full breadth of the asserted claims.” *Rivera v. ITC*, 857 F.3d 1315,
7 1319 (Fed. Cir. 2017). The alleged invention of the '797 Patent claims to apply a decoding matrix
8 to unambiguously detect the presence or absence of “at least each of M analytes,” or “at least each
9 of the M fluorescently labeled polynucleotide analytes,” however, the specification does not
10 provide support for such detection of targets. Even the allegedly unambiguous coding schemes
11 contain ambiguity. For example, Table 6 constructs an ambiguous coding scheme. Should a
12 sample contain analyte B, C, and two copies of analyte E, it would have the same cumulate signal
13 measurement as a sample containing Analyte A, two copies of Analyte C, and Analyte G. That is,
14 both samples would produce a cumulative signal of [B,5], [G,3], [Y,1], and [R,2], including the
15 shared control fluorophore. This scheme, therefore, generates an ambiguous result. *See* '797 Patent
16 20:14-60.

17 Further, the claims are not limited in any fashion regarding the number of analytes that may
18 be detected. The '797 Patent claims lack a written description of the ability to detect “each of M
19 analytes” in signals without any limit of what number may constitute M or F, nor any maximum
20 number of analytes that corresponds to a given number of wavelength components. '797 Patent Cl.
21 1, 19; *See MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1384 (Fed. Cir. 2012).
22 The specification provides no support for methods by which the number of M analytes may be
23 expanded reliably using the detection hardware and signal generation methods of the time, which
24 were limited in the number of fluorophores that may be used within the system by spectral overlap
25 by color emission of fluorophores and limits of intensity detection for reliable differentiation and
26 provides no examples wherein greater than four fluorophores, i.e., greater than four wavelength
27 components are used within the alleged system. *See* '797 Patent claims 1-2, 19. Further, to support
28 the full breadth of the claim, the specification would need to reliably describe detection of, for

1 example, 10,000 analytes in one wavelength component by differentiation only on the basis of
2 intensity, as there is no limit on the ratio of M to F. The specification lacks description of how to
3 perform such differentiation in numbers greater than four analytes for one individual color or
4 wavelength component.

5 Related to the foregoing, the claims purportedly encompass multiplex amplification of any
6 number of targets in a single microfluidic droplet. Yet, in parallel IPR proceedings related to U.S.
7 Patent No. 11,827,921, Plaintiff has alleged that there were challenges associated with multiplex
8 amplification, including in relation to harmful interactions among primers from different reactions
9 in the multiplex. The '797 Patent, however, never mentions such challenges, let alone discloses
10 methods for addressing any challenges associated with the multiplex amplification of multiple
11 targets. In this regard, the specification fails to establish that the inventors were in possession of
12 the full breadth of their alleged invention.

13 Moreover, the specification does not contain adequate description regarding the signals that
14 satisfy the claims. The claims recite the formula $M = C \cdot \log_2(F+1)$. This formula corresponds to
15 a geometric progression of signals wherein different targets are encoded by the values 1, 2, 4, 8,
16 16, 32, etc.... The specification, however, does not describe or characterize the tolerances with
17 which the signals from targets must match the geometric progression 1, 2, 4, 8, 16, 32, etc. In its
18 infringement contentions, plaintiff accuses signal progressions that are far off from a geometric
19 progression, that are not integers, and that encompass a disparate range of intensities. Nothing in
20 the specification suggests that the inventors were in possession of the approaches used in the Bio-
21 Rad accused products, which do not use a geometric progression of target signals but are rather
22 based upon empirical separation of non-integer target intensities. The failure of written description
23 is further confirmed in view of the requirement in the claims that the value of "F" be a positive
24 integer. Nowhere does the specification describe any methods for tuning signal intensities to
25 establish integer signals (or approximate integer signals) for even a small number of targets, let
26 alone for the infinite number of targets encompassed by the claims.

27 Related to the foregoing, the claimed formula reflects an approach wherein consecutive
28 cumulative signals are distinguishable from one another by only a single intensity unit, whatever

1 that it is. The difference in the cumulative signal for a given number of targets is distinguishable
2 from the signal for one less target by an increasingly smaller percentage. The specification does
3 not describe techniques to distinguish the increasingly small signal differences need to distinguish
4 the number of targets, confirming that the inventors were not in possession of their alleged
5 invention.

6 As yet another example, the specification does not establish that the inventors were in
7 possession of the claimed “decoding matrix.” In their infringement contentions, Plaintiffs contend
8 that Bio-Rad infringes using “decoding matrices” that are two-dimensional scatter plots generated
9 by the signal intensities associated with cluster of droplets and manually specifying the intensity
10 ranges that correspond to such droplet families. Yet, nowhere does the specification contemplate
11 such approaches or suggest that the inventors were in possession of such approaches.

12 Patent Claim 1, as the specification contains no examples detecting more than sixteen
13 analytes, falls far short of the specification’s statement that the methods of the invention can
14 “encode an infinite number of analytes.” ’797 Patent 22:39-40. Thus, the specification fails to
15 provide a written description of the full scope of detecting “at least each of M analytes” or “at least
16 each of the M fluorescently labeled polynucleotide analytes” because a POSA would not have
17 understood the specification to teach how to detect an infinite number of analytes. *See MagSil*
18 *Corp.*, 687 F.3d at 1384 (finding where a claim recites an ability to perform “at least” some quantity,
19 that the specification must enable a POSA to perform more “than a small subset of the claimed
20 range.”).

21 Moreover, the ’797 Patent describes detection of analytes based on using wavelength or a
22 range of wavelengths from electromagnetic signals generated by multiple fluorophores, but the
23 specification fails to describe how to perform such detection using any wavelength component
24 other than its insufficient explanation of using light wavelength components. The specification
25 fails to describe detection based on, for example, sound, radio, gamma-rays, or x-rays to detect
26 analytes in a solution. Even further, the ’797 Patent claims the detection of “analytes,” yet the
27 specification provides written description only for the detection of “polynucleotide analytes,” and
28 fails to describe methods to detect any other class of analyte. As such, the ’797 Patent lacks written

1 description for the term “analytes.”

2 In sum, the claims are invalid for a lack of written description because the specification fails
3 to provide support for the full breadth of the claims as required by 35 U.S.C. § 112.

4 **c. Lack of Support for “unambiguous” Detection of Analytes**

5 The alleged invention of the ’797 Patent claims the unambiguous detection of “at least each
6 of M analytes” or “at least each of the M fluorescently labeled polynucleotide analytes”, however,
7 the specification does not provide support for such detection of targets. Even the allegedly
8 unambiguous exemplary coding schemes contain ambiguity. For example, ambiguity exists in the
9 coding scheme of Table 6 when, for example, the presence in combination of the control, analyte
10 B, analyte C, and two copies of analyte E produces the same cumulative signal measurement as the
11 presence of the control, analyte A, two copies of analyte C, and analyte G (a cumulative signal of
12 [5, 3, 1, 2] in fluorophores B, G, Y, and R, respectively). See ’797 Patent 20:14-60. Further, the
13 specification fails to describe any methods by which the analytes may be differentiated solely based
14 on differing intensities within the limits of detection for reliable differentiation in the
15 instrumentation available at the time of the alleged invention.

16 **d. Lack of Support for “sample volume”**

17 The ’797 Patent claims a system for detecting the presence or absence of analytes from a
18 sample volume, yet the specification does not explain what constitutes a sample volume or how to
19 obtain a sample volume. It is also unclear what the scope of the term “sample volume” is from the
20 specification. As such, the ’797 Patent fails to enable a POSA to practice the full scope of the
21 claims at least as to the term “analytes.”

22 **e. Lack of Support for Systems without “Immobilization,” “Mass
23 spectrometry,” or “Melting curve analysis”**

24 The ’797 Patent claims systems where “the determination is made without immobilization,
25 mass spectrometry or melting curve analysis.” See ’797 Patent, Cls. 1, 19. The specification,
26 however, provides no specific description of how to achieve detection of analytes in such systems.
27 Thus, the Asserted Claims are invalid for a lack of written description because the specification
28

provides no guidance as to how to perform the claimed limitations.

f. Lack of Disclosure of Claimed Invention as Integrated Whole

The Asserted Claims require unambiguous detection of the presence or absence of analytes or the presence or absence of a plurality of polynucleotide analytes. However, none of the examples in the patents discloses such an example, in theory, or implemented in practice. The examples, rather, provide sample encoding schemes that may exhibit ambiguity in certain combinations of presence, as described above in Section IV.B.1.b. Further, the specification describes no measured results from assays performed using the claimed system, nor any figures depicting actual reliably measured signals that were successfully decoded to unambiguously detect at least each of M analytes without limiting the number of detectable analytes. This makes sense as the specification fails to provide a description for the generation of probes to emit signals successfully and reliably for unambiguous detection within the limitations of detection hardware available at the time of the alleged invention.

2. Enablement:

To satisfy the enablement requirement of pre-AIA 35 U.S.C. § 112 ¶ 1, the disclosure “must teach those skilled in the art how to make and use the full scope of the claimed invention without ‘undue experimentation.’” *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997). “If a patent claims an entire class of processes, machines, manufacture, or compositions of matter, the patent’s specification must enable a person skilled in the art to make and use the entire class. In other words, the specification must enable the full scope of the invention as defined by its claims. The more one claims, the more one must enable.” *Amgen Inc. v. Sanofi*, 143 S. Ct 1243, 1254 (2023). The Federal Circuit has enumerated several factors to consider in determining whether a disclosure would require “undue experimentation”: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

The Asserted Claims describe methods to encode and decode signals and to detect analytes

1 within systems based on such signals. The scope of the claims is broader than what the specification
2 teaches. For example, the claims require unambiguous detection of the presence or absence of at
3 least M analytes or, of at least M polynucleotide analytes without any limitation on maximum
4 cumulative intensity values. '797 Patent Cls. 1, 19. The specification, however, lacks description
5 for systems that unambiguously detect analytes where multiple copies of the same analyte are
6 present, and the claims place no clear limitations on whether there may be multiple copies of a
7 given analyte-specific hybridization probe. The specification further provides little to no
8 description regarding how the allegedly unambiguous encoding schemes are put into practice, and
9 how reliable results of detection are achieved using probes labeled with fluorophores to allow the
10 allegedly described decoding methods to be performed. There is little to no description as to how
11 to perform differentiation of the emission or excitation spectra of probes, nor a description of how
12 to ensure measurement of such signals is accurate and reliable. At best, the specification provides
13 passing mentions of possible "illegitimate" results that do not correspond to a specific enumerated
14 signal combination. *See, e.g.*, '797 Patent 16:5-9. The passage describing these illegitimate,
15 results, however, states only that the control and decoding matrix provide a "means of verifying
16 that the assay is functioning properly," and that an illegitimate result may "indicate that the assay
17 malfunctioned." *Id.* There is no explanation as to how a system using such a system should be
18 modified if an illegitimate result is produced so that the system can provide a reliable output.

19 Further, the specification fails to enable a POSA to perform the full scope of the claim
20 limitations of "detecting the presence or absence of at least each of M analytes," '797 Patent Claim
21 1. The specification contains no examples detecting more than sixteen analytes, far short of the
22 specification's statement that the invention can "encode an infinite number of analytes." '797
23 Patent 22:39-40. Thus, the specification fails to enable use of the full scope of detecting "at least
24 each of M analytes" because a POSA would not have understood the specification to teach how to
25 detect an infinite number of analytes. *See MagSil Corp.*, 687 F.3d at 1384 (finding where a claim
26 recites an ability to perform "at least" some quantity, that the specification must enable a POSA to
27 perform more "than a small subset of the claimed range."). Likewise, the '797 Patent claims up
28 detection of up to six channels yet recites no working examples with more than four fluorophores

1 or for the determination of greater than 16 polynucleotide analytes. *See id.*

2 To the extent Plaintiff argues that claim 1 of the '797 Patent covers systems that detected
3 "at least each of M analytes" where " $M=C*\log_2(F+1)$," and " $C=4, 5, \text{ or } 6$ " the specification fails
4 to enable a POSA to do so. The specification recites no working examples of an assay for the
5 detection of at least each of M analytes using more than four fluorophores and does not provide
6 guidance to enable a POSA to practice the entire scope of the invention. Instead, the only examples
7 the specification provides for detecting five or more analytes each uses four fluorophores.

8 Further, the '797 Patent claims a system for detecting the presence or absence of "analytes,"
9 (Claim 1 and dependent claims) yet the specification only describes the detection of
10 "polynucleotide analytes," and fails to provide a working example or description to enable a POSA
11 to detect any other class of analyte. As such, the '797 Patent fails to enable a POSA to practice the
12 full scope of the claims at least as to the term "analytes." Additionally, the '797 Patent describes
13 detection of M analytes where "F is a positive integer and is equal to the maximum cumulative
14 intensity of the first component of the signal, for any second value, when all of the analytes are
15 present" yet the specification fails to describe how to perform such detection using an intensity
16 component other than its insufficient explanation of using light wavelength components. The
17 specification does not refer to integers in any respect and the specification fails to describe detection
18 based on, for example, sound, radio, gamma-rays, or x-rays to detect analytes in a solution, thus
19 failing to enable a POSA to practice the entire scope of the claims.

20 As yet another example, the specification is not enabled with regard to the claimed formula
21 $M = C*\log_2(F+1)$. This formula corresponds to a geometric progression of signals wherein
22 different targets are encoded by the values 1, 2, 4, 8, 16, 32, etc.... The specification, however,
23 does not enable methods of tuning signal intensities of targets so that they match the claimed
24 geometric progression of target intensities. The specification just assumes, without basis, that
25 intensities can be tuned to match specific signal intensities. Moreover, this formula reflects an
26 approach wherein consecutive cumulative signals are distinguishable from one another by only a
27 single intensity unit, whatever that it is. The difference in the cumulative signal for a given number
28 of targets is distinguishable from the signal for one less target by an increasingly smaller

1 percentage. The specification does not enable techniques to distinguish the increasingly small
2 signal differences need to distinguish the number of targets. Further, the techniques that Plaintiffs
3 accuse in Bio-Rad products based plots of droplet signal intensity and are not enabled in the '797
4 patent. The specification includes no description of such techniques, and instead relies upon
5 theoretical coding tables that utilize integer-based schemes that are not realistic in practice and are
6 not enabled.

7 Related to the foregoing, the claims purportedly encompass multiplex amplification of any
8 number of targets in a single microfluidic droplet. Yet, in parallel IPR proceedings related to U.S.
9 Patent No. 11,827,921, Plaintiff has alleged that there were challenges associated with multiplex
10 amplification, including in relation to harmful interactions among primers from different reactions
11 in the multiplex. The '797 Patent, however, never mentions such challenges, let alone discloses
12 methods for addressing any challenges associated with the multiplex amplification of multiple
13 targets. In this regard, the specification fails the full scope of the alleged invention, which
14 supposedly encompasses multiplex amplification of an infinite number of targets in a single droplet.

15 **a. Quantity of Experimentation**

16 It would take an undue amount of experimentation to practice the claimed inventions
17 because the specification has little to no disclosure for a POSA to perform the full scope of the
18 claimed methods. As detailed above, there is no description of a fully working unambiguous
19 detection scheme, nor any description on the methods of reliably detecting and practically applying
20 the allegedly described systems such as by describing methods to optimize and develop individual
21 probe labels beyond conclusory descriptions of encoding schemes. Further, there is no single
22 embodiment with all claim elements to enable a skilled artisan to practice the claimed invention.
23 A POSA, reading the description of these patents would not be able to recreate or use the systems
24 as claimed. To actually practice the full scope of any of the claims, a POSA would be required to
25 engage in extensive (infinite, based on the scope of the claims) trial-and-error experimentation,
26 testing a given scheme, determining if the results are consistent and reliable, and, if not, redesign
27 the scheme from scratch. Therefore, the specification does not enable the full scope of the claims
28 to the extent they require unambiguous detection in any combination or unique combination

1 because it would require undue experimentation for a POSA to successfully practice the full scope
2 of claims in constructing, optimizing, and implementing probe label combinations.

3 **b. Guidance in the Specification**

4 “[W]hen there is no disclosure of any specific starting material or of any of the conditions
5 under which a process can be carried out, undue experimentation is required; there is a failure to
6 meet the enablement requirement that cannot be rectified by asserting that all the disclosure related
7 to the process is within the skill of the art.” *Genentech*, 108 F.3d at 1366. There is no guidance in
8 the specification regarding how to implement the Asserted Claims in practice, i.e., how to perform
9 the claimed methods of analyte encoding and detection.

10 Specifically, the specification provides no description of how to account for the presence
11 multiple copies of a single analyte, and the ambiguities that may result from such presence in
12 combination with single copies, or multiple copies of other analytes. For example, the allegedly
13 unambiguous example to support the system allegedly described by the coding scheme in Table 6,
14 ’797 Patent 20:14-60, contains ambiguity even after eliminating identified ambiguous codes for
15 detecting analytes. For example, but not limiting, the presence of the control, analyte B, analyte C,
16 and two copies of analyte E produces the same cumulative signal measurement as the presence of
17 the control, analyte A, two copies of analyte C, and analyte G (a cumulative signal of [5, 3, 1, 2] in
18 fluorophores B, G, Y, and R, respectively). *See* ’797 Patent 20:14-60.

19 The specification also provides little to no description on how to manage noise or error. As
20 to error, the specification simply describes that “illegitimate” results, i.e., those that should not be
21 possible based on the encoding scheme and indicates a malfunction in the system. *See, e.g.*, ’797
22 Patent 16:5-9. The specification describes that noise may be minimized by encoding the “initial
23 assigned value [of a probe] to be greater than one, for example to better distinguish over noise,”
24 *see, e.g.*, ’797 Patent 50:16-19, but, again, provides no description of how to ensure such an initial
25 assigned value is generated and detected consistently using hybridization probes, let alone analyte-
26 specific hybridization probes. The specification admits that an endpoint based assay may need to
27 be “ended at a threshold number of cycles set by the limit of detection of an instrument,” ’797
28 Patent 3:53-55, i.e., ended at the limit of intensity of a signal that an instrument is able to reliably

1 detect, yet asserts, without specific support that to differentiate targets and overcome noise, initial
2 assigned values (intensities) may be “greater than one” without regarding the limits of the detection
3 hardware. ’797 Patent 50:16-19.

4 Additionally, the specification provides no

5 Further, the specification provides no description of how to use systems “without
6 immobilization, mass spectrometry or melting curve analysis.” ’797 Patent, Cls. 1, 19. Thus, the
7 specification provides insufficient guidance to perform the methods of the Asserted Claims and
8 undue experimentation would be required to perform the Asserted Claims.

9 **c. Working Examples**

10 The Asserted Claims require unambiguous detection of the presence or absence of “at least
11 each of M analytes,” or “at least each of the M fluorescently labeled polynucleotide analytes.” ’797
12 Patent, Cls. 1 and 19. However, none of the examples in the patents discloses such working
13 examples. The examples, rather, provide sample encoding schemes that may exhibit ambiguity in
14 certain combinations of presence. Further, the specification describes no measured results from
15 functioning systems, nor any figures depicting actual reliably measured signals that were
16 successfully decoded to unambiguously detect analytes in any combination of presence or absence.
17 The allegedly unambiguous example encoding scheme in Table 6, ’797 Patent 20:14-60, contains
18 ambiguity even after eliminating degeneracy in the coding scheme for detection of the presence or
19 absence of “at least each of M analytes,” or “at least each of the M fluorescently labeled
20 polynucleotide analytes.” For example, but not limited to, the presence in combination of the
21 control, analyte B, analyte C, and two copies of analyte E produces the same cumulative signal
22 measurement as the presence of the control, analyte A, two copies of analyte C, and analyte G (a
23 cumulative signal of [5, 3, 1, 2] in fluorophores B, G, Y, and R, respectively). *See* ’797 Patent
24 20:14–60.

25 **d. Nature of the Invention**

26 The alleged invention in the ’797 Patent pertain to systems that encode and decode signals
27 to detect analytes or polynucleotide analytes. The specification describes no systems, much less
28 any improvements, for the detection and methods for measuring such signals. Due to the

1 inconsistency between the claims and the specification, a skilled artisan would be unable to practice
2 the full scope of the claims without undue experimentation. Further, a skilled artisan would not be
3 enabled to practice the claimed inventions due to the broad scope of the claims and the
4 unpredictable nature of the invention. For example, the specification fails to describe methods to
5 ensure that probes in fact emit signals that are distinguishable, alone and in combination, according
6 to theoretically outlined encoding schemes.

7 **e. State of the Prior Art**

8 To the extent that the Asserted Claims are not invalid under 35 U.S.C. §§ 102 and/or 103
9 as anticipated and/or obvious in view of the prior art, the state of the prior art would have required
10 undue experimentation considering the specification. For example, in the relevant time frame,
11 methods of labeling probes with fluorophores and generating signals could result in inconsistent
12 emission spectra and/or signal detection due to inconsistent emissions or the limits of detection
13 hardware. Without guidance from the specification, it would have taken a skilled artisan undue
14 experimentation to practice the claimed invention by finding ways to permit the unambiguous
15 detection of multiple analytes in any combination of presence or absence and to optimize such
16 systems.

17 **f. Relative Skill of Those in the Art**

18 A skilled artisan at the time of the alleged invention would have been familiar with concepts
19 and techniques of labeling probes with fluorophores and detecting the presence or absence of targets
20 (or analytes) based on the presence of target-specific (or analyte-specific) probes. Nevertheless, a
21 person of skill in the art would not have had experience with the full range of parameters
22 encompassed by the claims. For example, the state of the art was such that a skilled artisan would
23 have had little experience generating probes specific for unambiguous detection of analytes in any
24 combination and for adjusting the emission spectra of such probes to perform such detection. A
25 POSA seeking to perform the claimed invention using such a system of labeled probes to identify
26 target analytes would need to start from scratch and engage in new research to identify the
27 appropriate conditions and label combinations that would in practice generate unambiguous results
28 in any combination to carry out the claimed invention. This would take undue experimentation.

1 **g. Predictability or Unpredictability of the Art**

2 As described above, the prior art discloses methods of labeling hybridization probes and
3 detecting analytes based on the signals generated by such hybridization probes. The behavior of
4 such probes is unpredictable, as is the detection of the signals generated from such probes. For
5 example, the probes may bind imperfectly or fail to bind at all, resulting in inconsistent and
6 potentially ambiguous results within a system. Further, upon inconsistent binding, the excitation
7 and emission spectra of different labels may behave differently. Indeed, neither the patent nor the
8 prior art includes any guidance regarding adjustment for the limitations of probe binding,
9 fluorophore, or other label signal emission, nor detection as limited by the ability of the systems of
10 the time to distinguish between different emission spectra, both in color and intensity.

11 **h. Breadth of the Claims**

12 As described above, the full scope of the Asserted Claims is very broad in view of the
13 specification. The specification relates to systems for detecting the presence or absence of each
14 analyte of a plurality of analytes, but provides no description, much less any improvement, as to
15 means of creating such a system beyond the use of systems that already existed. For example,
16 claims 1 and 19 of the '797 Patent describe the detection of “each of M analytes,” “M fluorescently
17 labeled polynucleotide analytes,” unlimited by any maximum number of analytes in “F,” where F
18 is “is a positive integer and is equal to the maximum cumulative intensity. . .” with no limit on
19 maximum cumulative intensity. The specification describes examples where no greater than four
20 fluorophores are used and no greater than 16 analytes are detected. The specification, however,
21 teaches no such methods for detection of over 16 analytes and even those examples contain
22 ambiguities when detecting analytes in any combination. The allegedly unambiguous example
23 encoding scheme in Table 6, '797 Patent 20:15–60, contains ambiguity even after eliminating the
24 identified “ambiguous” codes for combinations of analytes. For example, but not limited to, the
25 presence in combination of the control, analyte B, analyte C, and two copies of analyte E produces
26 the same cumulative signal measurement as the presence of the control, analyte A, two copies of
27 analyte C, and analyte G (a cumulative signal of [5, 3, 1, 2] in fluorophores B, G, Y, and R,
28 respectively). *See* '797 Patent 20:15–60.

Further, specifically as to claims 1 and 19 of the '797 Patent, to support the full breadth of the claim, the specification would need to reliably allow detection of, for example, 10,000 analytes in one component by differentiation only on the basis of intensity, as there is no limit on the ratio of M to F. The specification lacks description of how to perform such differentiation in numbers greater than four analytes for one wavelength component. The specification further lacks description of how to perform such differentiation in numbers greater than sixteen analytes for the indeterminate values of F claimed in claims 1 and 19 (and accordingly, claims dependent therefrom).

3. Indefiniteness:

Based on the information available to date and as Bio-Rad best understands Plaintiff's contentions at this time, all Claims of the '797 Patent are indefinite under 35 U.S.C. § 112(2) for at least the following reasons.

Claim 1 of the '797 Patent (and all claims that refer to claim 1) fails to satisfy the requirements of 35 U.S.C. § 112(2) because its limitations are indefinite individually and in combination. To illustrate:

- The claim term "F" is indefinite. F is described in the claims as 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." Intensity, however, is not viewed by those of skill in the art as an integer quantity and a POSA would not understand what it means for the intensity of a light signal to be an "integer." Further, to the extent F is truly intended to be an integer, it is unclear what its possible values are. On the one hand, claim 1 suggests that the minimum value of F is 3, but dependent claim 4 recites that F may take on a value of 1. Given the erroneous characterization of intensity as an "integer" and the internal inconsistencies among the claims, a person of ordinary skill in the art would not understand with reasonable certainty the scope of "F."
- The term "component" is indefinite. As Plaintiffs' expert witness in parallel proceedings confirmed based on his review of the specification, for instance, there

1 is no clarity as to whether elements of a signal that have a value of 0 count as signal
2 components. *See* 7/24/25 Struhl Tr. at 91:6-96:23. As he explained after reviewing
3 the specification, “it’s actually a little bit ambiguous, and it’s basically
4 meaningless.” *Id.* When asked to explain what “one component” is referring to in
5 a related patent, Dr. Struhl confirmed that he was not certain what the inventors were
6 referring to. *See id.* at 97:16-98:11. Likewise, the specification and claims are
7 unclear as to whether a single “component” of a “cumulative signal” reflects, for
8 instance, all the wavelengths within the signal or just one of the wavelengths. For
9 at least these reasons, a person of ordinary skill in the art would not understand with
10 certainty the scope of the term “component.”

- 11 • The term “decoding matrix” is indefinite. Nowhere does the specification or claims
12 describe what constitutes a “decoding matrix.” In particular, neither the
13 specification nor claims specify the attributes of a “matrix,” which is a term that is
14 undefined in the patent. To the extent the term “matrix” imposes a requirement for
15 a table or list, nowhere do the claims provide guidance as to the metes and bounds
16 of the claimed matrix. Plaintiffs’ infringement contentions point to the use of two-
17 dimensional scatter plots in Bio-Rad’s accused products, which a person of skill in
18 the art would not understand to be a “matrix” and which is not suggested or
19 described in the ’797 patent. Accordingly, in view of the claim language and
20 specification, a person of skill in the art would not understand with reasonable
21 certainty the scope of “decoding matrix.”
- 22 • The claim term “F is a positive integer and is equal to the maximum cumulative
23 intensity of the first component of the signal, for any second value, when all of the
24 analytes are present” is indefinite at least because a person of ordinary skill in the
25 art would not understand how to equate a “maximum cumulative intensity” with a
26 “positive integer.” Indeed, those of skill in the art generally do not view signal
27 intensities as integer quantities and would not understand what this means. To the
28 extent the claims are intended to refer to approximate integer quantities or signal

1 levels, the person of ordinary skill in the art would not understand for instance

- 2 • “sample,” is indefinite at least because there are no limitations as to what can be
3 considered a “sample,” and examples in the specification, *see* ’797 Patent 3:24–27,
4 are so broad as to render the term indefinite;
- 5 • “analyte-specific reagent mixtures of analyte-specific hybridization probes and
6 multiple fluorophores,” is indefinite at least because it has indeterminant numbers
7 of hybridization probes and fluorophores;
- 8 • “cumulative signal,” is indefinite at least because it is purportedly “based on the
9 first, second, third and fourth electromagnetic signals,” but is unclear as to whether
10 it includes permutations of those signals and/or any additional signals;
- 11 • “cumulative signal measurement,” is indefinite at least because “cumulative signal”
12 is indefinite and because it is unclear what is included within the scope of the alleged
13 “measurement;”
- 14 • “unambiguously,” is indefinite at least because it allegedly describes the detection
15 of a limitless number of analytes;
- 16 • “the presence or absence of at least each of M analytes,” is indefinite at least because
17 the number of analytes has no limit as written;
- 18 • “or range of intensities,” is indefinite at least because it lacks an antecedent basis;
- 19 • “determination,” is indefinite at least because it lacks an antecedent basis;
- 20 • “immobilization, mass spectrometry or melting curve analysis,” is indefinite at least
21 because it lacks an antecedent basis;
- 22 • “ $M=C*\log_2(F+1)$,” is indefinite at least because there is no upper limit for F or M.
23 Moreover, this formula corresponds to a geometric progression of signals wherein
24 different targets are encoded by the values 1, 2, 4, 8, 16, 32, etc.... In view of
25 Plaintiff’s infringement contentions, the claim, language, and the specification, a
26 person of skill in the art would not understand what signals satisfy the claims. For
27 instance, a person of skill in the art would not understand the tolerances with which
28 the signals from targets must match the geometric progression 1, 2, 4, 8, 16, 32, etc.

1 In its infringement contentions, plaintiff accuses signal progressions that are far off
2 from a geometric progression, that are not integers, and that encompass a disparate
3 range of intensities. In further view of the requirement in the claims that the value
4 of F be a positive integer, this establishes that a person of ordinary skill in the art
5 would not be able to ascertain with reasonable certainty the qualities of the signals
6 that satisfy the claims.

- 7 • “F is a positive integer. . .,” is indefinite at least because there is no upper limit for
8 F;
- 9 • “F+1 is a positive integer,” is indefinite at least because there is no upper limit for
10 F;
- 11 • “F+1 is a power of 2,” is indefinite at least because there is no upper limit for F;
- 12 • “M is greater than the number of second values used to encode the analytes (C),” is
13 indefinite at least because there is no limit to M and because M is equal to C when
14 F is equal to 1;
- 15 • “channels,” is indefinite at least because C is equal to 4, 5, or 6, and it is therefore
16 unclear whether the claim covers 4, 5, 6 or another number of channels; and
- 17 • “M and C are positive integers,” is indefinite at least because there is no upper limit
18 to M.
- 19 • Claims 1 and 19 are indefinite at least because the person of ordinary skill in the art
20 would not understand whether the claims pertain to systems that must only be
21 capable of performing certain functions with certain components or whether they
22 require the actual presence of those components. For instance, a POSA would not
23 understand with respect to claim 1 whether the claimed system requires the use of
24 four signals from four different fluorophores or merely requires the capability of
25 being used with four signals from four different fluorophores. Similarly, with
26 respect to claim 19, a POSA would not understand with reasonable certainty whether
27 it requires the presence of the claimed “M fluorescently labeled polynucleotide
28 analytes” or whether it requires merely the capability of functioning with “M

1 fluorescently labeled polynucleotides.” Because a POSA would not understand with
2 reasonable certainty whether the claims require actual presence of certain
3 components or the mere capability of functioning with certain components, claims
4 1 and 19 are indefinite.

5 Claim 4 of the ’797 patent is indefinite because it encompasses $F = 1$, which is inconsistent
6 with the allowed values of F as specified in independent claim 1.

7 Claim 11 of the ’797 Patent also fails to satisfy the requirements of 35 U.S.C. § 112(2)
8 because the limitation “detector” is indefinite at least because it lacks an antecedent basis.

9 Claim 18 of the ’797 Patent also fails to satisfy the requirements of 35 U.S.C. § 112(2)
10 because the limitation “first and second values” is indefinite at least because it is unclear whether
11 it claims a cumulative plot, individual plots, or something else.

12 Claim 19 of the ’797 Patent also fails to satisfy the requirements of 35 U.S.C. § 112(2)
13 because the limitations below are indefinite individually and in combination. For example,

- 14 • The claim term “ F ” is indefinite. F is described in the claims as a “positive integer”
15 and is equal to “the maximum cumulative intensity of the first component of the
16 signal, for any second value, when all of the analytes are present.” Intensity,
17 however, is not viewed by those of skill in the art as an integer quantity and a POSA
18 would not understand what it means for the intensity of a light signal to be an
19 “integer.” Further, to the extent F is truly intended to be an integer, it is unclear
20 what its possible values are. On the one hand, claim 1 suggests that the minimum
21 value of F is 3, but dependent claim 4 recites that F may take on a value of 1. Given
22 the erroneous characterization of intensity as an “integer” and the internal
23 inconsistencies among the claims, a person of ordinary skill in the art would not
24 understand with reasonable certainty the scope of “ F .”
- 25 • The term “component” is indefinite. As Plaintiffs’ expert witness in parallel
26 proceedings confirmed based on his review of the specification, for instance, there
27 is no clarity as to whether elements of a signal that have a value of 0 count as signal
28 components. *See* 7/24/25 Struhl Tr. at 91:6-96:23. As he explained after reviewing

1 the specification, “it’s actually a little bit ambiguous, and it’s basically
2 meaningless.” *Id.* When asked to explain what “one component” is referring to in
3 a related patent, Dr. Struhl confirmed that he was not certain what the inventors were
4 referring to. *See id.* at 97:16-98:11. Likewise, the specification and claims are
5 unclear as to whether a single “component” of “cumulative signal data” reflects, for
6 instance, all the wavelengths within the signal data or just one of the wavelengths.
7 For at least these reasons, a person of ordinary skill in the art would not understand
8 with certainty the scope of the term “component.”

- 9 • The term “decoding matrix” is indefinite. Nowhere does the specification or claims
10 describe what constitutes a “decoding matrix.” In particular, neither the
11 specification nor claims specify the attributes of a “matrix,” which is a term that is
12 undefined in the patent. To the extent the term “matrix” imposes a requirement for
13 a table or list, nowhere do the claims provide guidance as to the metes and bounds
14 of the claimed matrix. Plaintiffs’ infringement contentions point to the use of two-
15 dimensional scatter plots in Bio-Rad’s accused products, which a person of skill in
16 the art would not understand to be a “matrix” and which is not suggested or
17 described in the ’797 patent. Accordingly, in view of the claim language and
18 specification, a person of skill in the art would not understand with reasonable
19 certainty the scope of “decoding matrix.”

- 20 • The claim term “the six fluorescently labeled polynucleotide analytes” is indefinite.
21 As an initial matter, there is no antecedent basis for the claimed “six” fluorescently
22 labeled polynucleotides, and, on this basis alone, a POSA would not understand
23 what analytes are being referred to. Given the lack of antecedent basis, it is unclear
24 what “fluorescently labeled polynucleotides” are claimed and whether the claims
25 are limited to 6. In the claims, the only limitations on F are that it be a positive
26 integer for which $F+1$ is a power of 2, meaning that F can presumably take on any
27 positive integer value starting with 1. Indeed, dependent claim 20 recites $F=1$.
28 Given that there is likewise no limit on the value of C, the value of M can take on

any value starting with 1. Accordingly, it is unclear why the claims refer to “the six” analytes, what those analytes are, and whether the claims are limited to six analytes or encompass more than six or fewer than six analytes.

- “cumulative signal data,” is indefinite at least because it fails to distinctly claim which signals are to be summed and at which point in the process cumulative measurement is to be taken;
- “sample volume,” is indefinite at least because it applies to any kind of sample without limit;
- “M fluorescently labeled polynucleotide analytes,” is indefinite at least because there is no limit to M;
- “at least each of the M fluorescently labeled polynucleotide analytes,”
- “ $M = C \cdot \log_2(F+1)$,” is indefinite at least because M and F have no limits. Moreover, this formula corresponds to a geometric progression of signals wherein different targets are encoded by the values 1, 2, 4, 8, 16, 32, etc.... In view of Plaintiff’s infringement contentions, the claim, language, and the specification, a person of skill in the art would not understand what signals satisfy the claims. For instance, a person of skill in the art would not understand the tolerances with which the signals from targets must match the geometric progression 1, 2, 4, 8, 16, 32, etc. In its infringement contentions, plaintiff accuses signal progressions that are far off from a geometric progression, that are not integers, and that encompass a disparate range of intensities. In further view of the requirement in the claims that the value of F be a positive integer, this establishes that a person of ordinary skill in the art would not be able to ascertain with reasonable certainty the qualities of the signals that satisfy the claims. ;
- “M, C, and F are positive integers,” is indefinite at least because M, C, and F have no limits; and
- “immobilization, mass spectrometry or melting curve analytes” is indefinite at least because it lacks an antecedent basis.

1 **V. PATENT LOCAL RULE 3-4 DOCUMENT PRODUCTION**

2 Based on the foregoing and on presently known information, and as will be further specified
3 as discovery proceeds, Bio-Rad provides the following documents as indicated below:

4 • **Patent Local Rule 3-4 (a):**

5 BIO_CC CODE00006101 to BIO_CC CODE00008553

6 • **Patent Local Rule 3-4(b):**

7 BIO_CC CODE00008915 to BIO_CC CODE00009367 and BIO_CC CODE000092315 to
8 BIO_CC CODE000093941

9 • **Patent Local Rule 3-4(c):**

10 BIO_CC CODE008679 to BIO_CC CODE00008914 and BIO_CC CODE00008554 to
11 BIO_CC CODE00008677

12 • **Patent Local Rule 3-4(d):**

13 BIO_CC CODE00008678 and BIO_CC CODE000093942

14 • **Patent Local Rule 3-4(e):**

15 BIO_CC CODE008679 to BIO_CC CODE00008914 and BIO_CC CODE00008554 to
16 BIO_CC CODE00008677

17 Bio-Rad reserves the right to supplement its document production under Patent Local Rule
18 3-4 if and as warranted and to reflect the results of its investigation and discovery in this matter.

Respectfully submitted,

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By: /s/ Derek C. Walter

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Counsel for Defendant

BIO-RAD LABORATORIES, INC.

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DECLARATION OF SERVICE

I am a citizen of the United States, more than 18 years old, and not a party to this action.
My place of employment and business address is 555 California Street, 26th Floor, San Francisco, California 94104. On August 13, 2025, I caused a copy of:

**DEFENDANT BIO-RAD LABORATORIES, INC.’S INVALIDITY
CONTENTIONS**

to be served as follows:

[XX] BY ELECTRONIC SERVICE I am readily familiar with the business practice at my place of business for electronically mailing a true and correct copy through Jones Day’s electronic mail system to the e-mail address(es) set forth below, or as stated on the attached service list per agreement in accordance with Code of Civil Procedure § 1010.6.

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Executed on August 13, 2025 at San Francisco, California. I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

/s/ Sterling Gipson
Sterling Gipson

Appendix A

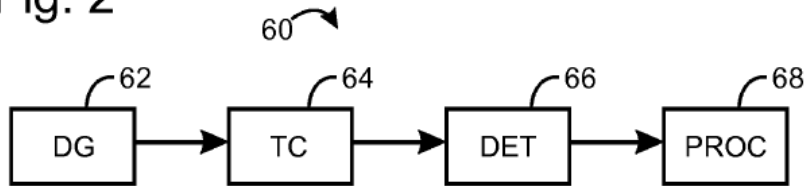
Invalidity of U.S. Patent No. 12,168,797

by U.S. Patent No. 9,921,154 (the “Jouvenot Patent”)

Based upon the claim interpretations Plaintiffs appear to be asserting and the applications of those interpretations to Bio-Rad’s products in Plaintiffs’ Patent Local Rule infringement contentions, the Jouvenot Patent, anticipates and/or renders obvious, alone or in combination with other prior art identified in Bio-Rad’s Patent Local Rule invalidity contentions, the Asserted Claims at least as described by illustrative examples, below. Other prior art is cited below as necessary, but these citations are used for example purposes and are not intended to be exclusive. These invalidity contentions are not an admission by Bio-Rad that the Accused Products, including any current or past versions of such products are covered by, or infringe these claims, particularly when they are properly construed. Nothing in these contentions should be interpreted as acquiescence to an assertion of a particular claim construction by Plaintiffs.

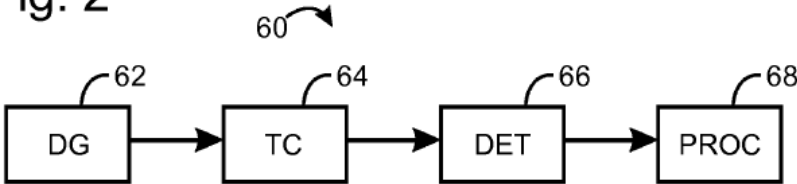
For all limitations in the asserted claims, to the extent the Jouvenot and/or other cited prior art are argued by Plaintiffs or found by the Court to not explicitly teach certain limitations in the asserted claims, such limitations would have been inherent and/or obvious as described in Bio-Rad’s invalidity contentions.

By way of summary, and as set forth in more detail in the chart below, Jouvenot Figure 4 and accompanying text teaches an intensity multiplexing encoding scheme that can distinguish between all combinations of two different targets using only a single color. A lowest intensity corresponds to no targets, a first higher intensity corresponds to a first target, a second even higher intensity corresponds to a second target, and a final highest intensity corresponds to the combination of both targets being present. Moreover, Jouvenot repeatedly contemplates the use of multiple colors at the same time. Thus, Jouvenot teaches, or at least renders obvious, using its intensity multiplexing approach for the detection of all combinations of two droplets with multiple colors. As Jouvenot teaches, or at least renders obvious, for each such color, one can analyze two distinct targets and determine precisely which combination of these two targets is present in a droplet. This is the exact type of single-color coding scheme that Plaintiffs contend satisfies the claims in their infringement contentions. To the extent the claims are interpreted to require that the progression of signals for the different combinations of targets exactly follows the progression 0, 1, 2, and 3, this is contrary to Plaintiff’s infringement contentions. Regardless, to the extent Plaintiff contends this is not taught in Jouvenot, it is taught in Lehnert and the person of ordinary skill would be motivated to use this approach with Larson for the reasons stated herein.

<u>'797 Claim Element¹</u>	<u>Invalidity Analysis</u>
1[p]. A system comprising:	To the extent the preamble is limiting, Jouvenot discloses it and the remaining elements of claim 1 (<i>see</i> below, each element recited in claim 1). Jouvenot “provides a system, including methods and apparatus, for performing a multiplexed digital assay.” Jouvenot 2:26–28; <i>see</i> Provisional App. 61/507,082 at 3:5–7 (“a system, including methods and apparatus, for performing a digital assay with multiplexed detection....”).
[1a] a sample chamber configured to house a sample and analyte-specific reagent mixtures of analyte-specific hybridization probes and multiple fluorophores;	Jouvenot teaches the use of a sample chamber configured to house a sample and analyte-specific reagent mixtures of analyte-specific hybridization probes and multiple fluorophores. For example, Jouvenot Figure 2 discloses a detector (66) and is a schematic that discloses this claim element: Fig. 2  <pre> graph LR DG[DG 62] --> TC[TC 64] TC --> DET[DET 66] DET --> PROC[PROC 68] 60((60)) -.-> TC </pre> <i>See also, e.g., id.</i> at 13:4–6 (“Detector 66 may provide a plurality of optical channels in which data can be collected.”); Provisional App. 61/507,082 at 12:6–10 (identical in substance). The detector detects signals from the droplets, which shows that the droplets are in a sample chamber configured to house a sample. Jouvenot 13:10–13; Provisional App. 61/507,082 at 12:8–10.

¹ Bracketed elements are added.

'797 Claim Element ¹	Invalidity Analysis
	Jouvenot also discloses distinguishing targets by “utilizing target-specific probes labeled with different dyes....” Jouvenot 2:14–15; Provisional App. 61/507,082 at 2:16. The “target-specific probes” are the claimed “analyte-specific hybridization probes.” In Figure 3 of the Jouvenot Provisional App., Jouvenot explains that “[e]ach probe may include an oligonucleotide 88, 90, a fluorophore 92, 94, and a quencher.” Jouvenot 13:32–34; Provisional App. 61/507,082 at 12:22–23. These fluorophore-bearing target-specific probes are shown below. Fig. 3 Jouvenot at Figure 3. Jouvenot further discloses the use of multiple fluorophores within such a sample chamber, explaining, for instance, that “[i]n some embodiments, one probe may be labeled with a different number of fluorophores....” Jouvenot 13:54–55; Provisional App. 61/507,082 at 13:15–16.
[1b] a multi-channel detector to detect:	Jouvenot discloses a detector, 66:

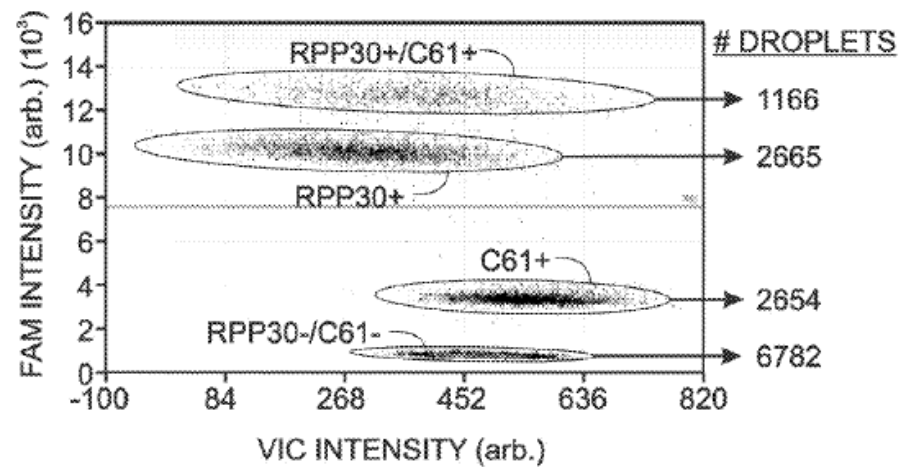
'797 Claim Element ¹	Invalidity Analysis
	Fig. 2  <pre> graph LR 62[DG] --> 64[TC] 64 --> 66[DET] 66 --> 68[PROC] 60((60)) -.-> 64 </pre> <i>See also id.</i> 13:4–6 (“Detector 66 may provide a plurality of optical channels in which data can be collected.”); Provisional App. 61/507,082 at 12:6–10 (identical in substance). Jouvenot describes collecting data from “one or more channels,” demonstrating the use of a “multi-channel detector.” Jouvenot 8:36–37; Provisional App. 61/507,082 at 9:3–5 (“The signals optionally may include data collected in one or more different channels (i.e., in different wavelength ranges (color regimes) from reporters for the same and/or different targets).”). Jouvenot also discloses assays that involve both analysis of more than two targets in the same channel and situations where targets may be analyzed in other channels. Jouvenot 5:5–18; Provisional App. 61/507,082 at 5:7–20. This disclosure further confirms the presence of the claimed “multi-channel detector” in Jouvenot.
[1b.1] 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;	Jouvenot teaches the detection from the sample chamber of four electromagnetic signals at four wavelengths from each of four fluorophores. Specifically, Jouvenot discloses that its “assays may be extended in various ways.” Jouvenot 5:19–31; Provisional App. 61/507,082 at 5:14–21. Most important, Jouvenot teaches that “some 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).” <i>Id.</i> In other words, Jouvenot teaches the use of multiple channels, which a person of skill in the art

<u>'797 Claim Element¹</u>	<u>Invalidity Analysis</u>
	would understand is a teaching of using multiple different wavelength signals from multiple different fluorophores. A person of skill in the art would further understand that this encompasses the use of at least four such channels and fluorophores. Indeed, Jouvenot states that the “signals optionally may include data collected in two or more different optical channels (e.g., in different wavelength ranges (wavebands) and/or color regimes) from reporters for the same and/or different targets). The light detected from each reporter may be light emitted from a luminophore (e.g., a fluorophore). 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 assays and thus two, three, four, or more targets.” Jouvenot 8:36–47; Provisional App. 61/507,082 at 9:3–10 (identical substantively). Jouvenot likewise expressly teaches using more than four different fluorophores <i>See</i> Jouvenot 14:1–2; Provisional App. 61/507,082 at 14:2–3 (“fluorophores that may be suitable include FAM, VIC, ROX, TAMRA, JOE, etc., among others.”). Consistent with the foregoing, as shown in Figure 5, Jouvenot shows actual data using two channels with one wavelength for some targets and another wavelength for other targets:

'797 Claim Element¹

Invalidity Analysis

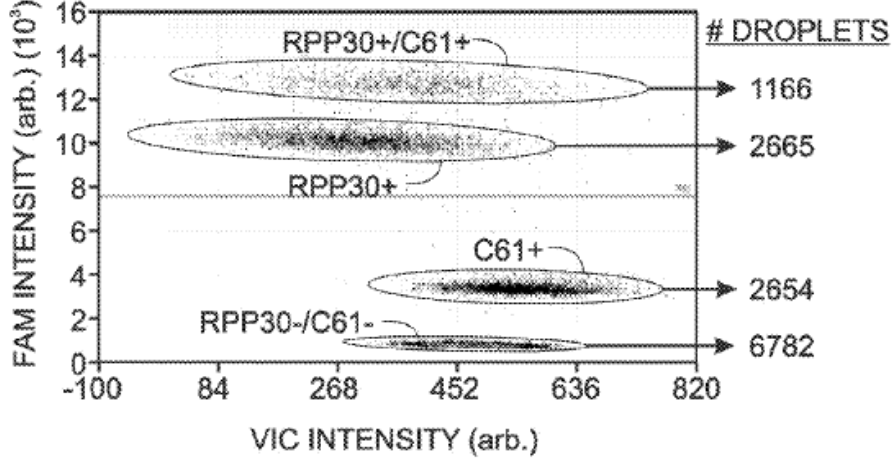
Fig. 5



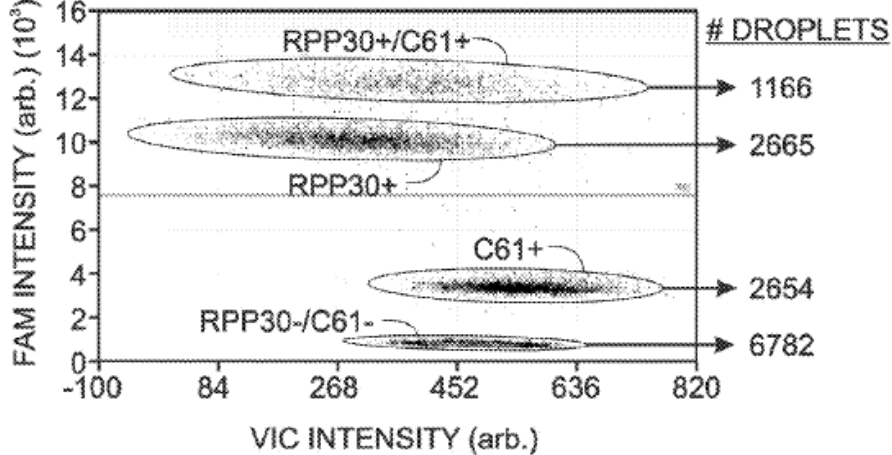
See also, e.g., *id.* at 2:52–59; Provisional App. 61/507,082 at Figure 5 and 17:1-27.

To the extent Jouvenot is deemed to not expressly disclose four or more wavelength signals from four or more fluorophores, this would have nonetheless been obvious in view of Jouvenot. As explained above, Jouvenot teaches extending its assays to detect some targets in one channel and other targets in a different channel. It shows precisely this in actual experimental data. A skilled artisan would have been motivated to use four or more color channels because he or she would have been motivated to detect larger numbers of targets at the same time. Indeed, Jouvenot expressly teaches that “many applications, especially where sample is limited, could benefit greatly from higher degrees of multiplexing.” Provisional App. 61/507,082 at 3. A POSA would have had a reasonable expectation of successfully extending Jouvenot to four or more wavelength channels and fluorophores because this would reflect nothing more than the use of multiple types of well-known fluorophores and that could be detected using

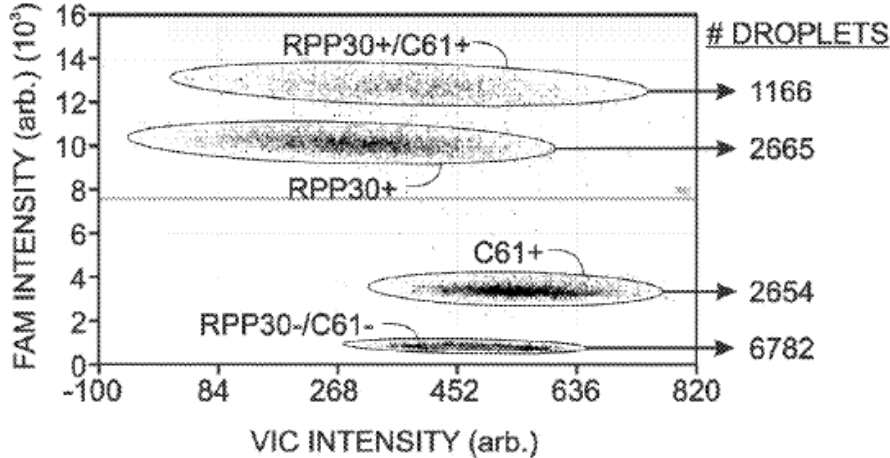
<u>'797 Claim Element¹</u>	<u>Invalidity Analysis</u>
	well-known instrumentation for the detection of multiple optical signals. <i>See, e.g.</i>, U.S. Patent Publication 2008/0003649A1 (“Maltezos”) ¶ 189 (“Various labels suitable for use in the present invention include... fluorophore-labels...”); United States Patent No. 8,614,061 (“Brabetz”) 1:61–63 (“Many DNA sequence analyzers employ. . . a special multiwavelength fluorescence detection system.”); U.S. Patent Publication 2009/0191563 (“Steemers”) ¶ 62 (in the context of fluorescently labeling nucleotides, “[a]ppropriate fluorophores are well known in the art several of which are described in further detail below.”).
[1b.2] 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;	Jouvenot teaches the detection from the sample chamber of four electromagnetic signals at four wavelengths from each of four fluorophores. Specifically, Jouvenot discloses that its “assays may be extended in various ways.” Jouvenot 5:19–31; Provisional App. 61/507,082 at 5:14–21. Most important, Jouvenot teaches that “some 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).” <i>Id.</i> In other words, Jouvenot teaches the use of multiple channels, which a person of skill in the art would understand is a teaching of using multiple different wavelength signals from multiple different fluorophores. A person of skill in the art would further understand that this encompasses the use of at least four such channels and fluorophores. Indeed, Jouvenot states that the “signals optionally may include data collected in two or more different optical channels (e.g., in different wavelength ranges (wavebands) and/or color regimes) from reporters for the same and/or different targets). The light detected from each reporter may be light emitted from a luminophore (e.g., a fluorophore). 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 assays and thus two, three, four, or more targets.” Jouvenot 8:36–47; Provisional App. 61/507,082 at 9:3–10 (identical substantively). Jouvenot likewise expressly teaches using more than four

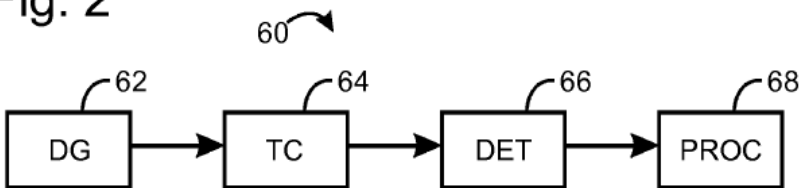
'797 Claim Element ¹	Invalidity Analysis
	different fluorophores <i>See</i> Jouvenot 14:1–2; Provisional App. 61/507,082 at 14:2–3 (“fluorophores that may be suitable include FAM, VIC, ROX, TAMRA, JOE, etc., among others.”). Consistent with the foregoing, as shown in Figure 5, Jouvenot shows actual data using two channels with one wavelength for some targets and another wavelength for other targets: Fig. 5  <i>See also, e.g., id.</i> at 2:52–59; Provisional App. 61/507,082 at Figure 5, 17:1-27. To the extent Jouvenot is deemed to not expressly disclose four or more wavelength signals from four or more fluorophores, this would have nonetheless been obvious in view of Jouvenot. As explained above, Jouvenot teaches extending its assays to detect some targets in one channel and other targets in a different channel. It shows precisely this in actual experimental data. A skilled artisan would have been motivated to use four or more color channels because he or she would have been motivated to detect

<u>'797 Claim Element¹</u>	<u>Invalidity Analysis</u>
	larger numbers of targets at the same time. Indeed, Jouvenot expressly teaches that “many applications, especially where sample is limited, could benefit greatly from higher degrees of multiplexing.” Provisional App. 61/507,082 at 3. A POSA would have had a reasonable expectation of successfully extending Jouvenot to four or more wavelength channels and fluorophores because this would reflect nothing more than the use of multiple types of well-know fluorophores and that could be detected using well-known instrumentation for the detection of multiple optical signals.
[1b.3] 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;	Jouvenot teaches the detection from the sample chamber of four electromagnetic signals at four wavelengths from each of four fluorophores. Specifically, Jouvenot discloses that its “assays may be extended in various ways.” Jouvenot 5:19–31; Provisional App. 61/507,082 at 5:14–21. Most important, Jouvenot teaches that “some 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).” <i>Id.</i> In other words, Jouvenot teaches the use of multiple channels, which a person of skill in the art would understand is a teaching of using multiple different wavelength signals from multiple different fluorophores. A person of skill in the art would further understand that this encompasses the use of at least four such channels and fluorophores. Indeed, Jouvenot states that the “signals optionally may include data collected in two or more different optical channels (e.g., in different wavelength ranges (wavebands) and/or color regimes) from reporters for the same and/or different targets). The light detected from each reporter may be light emitted from a luminophore (e.g., a fluorophore). 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 assays and thus two, three, four, or more targets.” Jouvenot 8:36–47; Provisional App. 61/507,082 at 9:3–10 (identical substantively). Jouvenot likewise expressly teaches using more than four different fluorophores <i>See</i> Jouvenot 14:1–2; Provisional App. 61/507,082 at 14:2–3

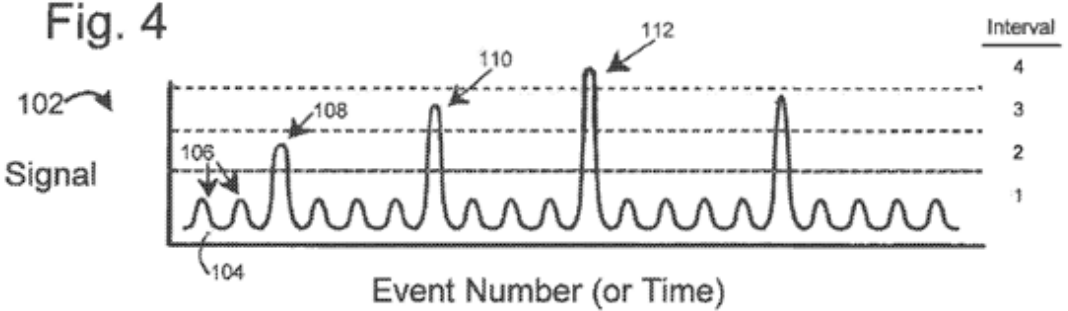
'797 Claim Element ¹	Invalidity Analysis
	("fluorophores that may be suitable include FAM, VIC, ROX, TAMRA, JOE, etc., among others."). Consistent with the foregoing, as shown in Figure 5, Jouvenot shows actual data using two channels with one wavelength for some targets and another wavelength for other targets: Fig. 5  <i>See also, e.g., id. at 2:52–59; Provisional App. 61/507,082 at Figure 5, 17:1-27.</i> To the extent Jouvenot is deemed to not expressly disclose four or more wavelength signals from four or more fluorophores, this would have nonetheless been obvious in view of Jouvenot. As explained above, Jouvenot teaches extending its assays to detect some targets in one channel and other targets in a different channel. It shows precisely this in actual experimental data. A skilled artisan would have been motivated to use

<u>'797 Claim Element¹</u>	<u>Invalidity Analysis</u>
	four or more color channels because he or she would have been motivated to detect larger numbers of targets at the same time. Indeed, Jouvenot expressly teaches that “many applications, especially where sample is limited, could benefit greatly from higher degrees of multiplexing.” Provisional App. 61/507,082 at 3. A POSA would have had a reasonable expectation of successfully extending Jouvenot to four or more wavelength channels and fluorophores because this would reflect nothing more than the use of multiple types of well-know fluorophores and that could be detected using well-known instrumentation for the detection of multiple optical signals.
[1b.4] 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;	Jouvenot teaches the detection from the sample chamber of four electromagnetic signals at four wavelengths from each of four fluorophores. Specifically, Jouvenot discloses that its “assays may be extended in various ways.” Jouvenot 5:19–31; Provisional App. 61/507,082 at 5:14–21. Most important, Jouvenot teaches that “some 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).” <i>Id.</i> In other words, Jouvenot teaches the use of multiple channels, which a person of skill in the art would understand is a teaching of using multiple different wavelength signals from multiple different fluorophores. A person of skill in the art would further understand that this encompasses the use of at least four such channels and fluorophores. Indeed, Jouvenot states that the “signals optionally may include data collected in two or more different optical channels (e.g., in different wavelength ranges (wavebands) and/or color regimes) from reporters for the same and/or different targets). The light detected from each reporter may be light emitted from a luminophore (e.g., a fluorophore). 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 assays and thus two, three, four, or more targets.” Jouvenot 8:36–47; Provisional App. 61/507,082 at 9:3–10 (identical substantively). Jouvenot likewise expressly teaches using more than four

'797 Claim Element ¹	Invalidity Analysis
	different fluorophores. <i>See</i> Jouvenot 14:1–2; Provisional App. 61/507,082 at 14:2–3 (“fluorophores that may be suitable include FAM, VIC, ROX, TAMRA, JOE, etc., among others.”). Consistent with the foregoing, as shown in Figure 5, Jouvenot shows actual data using two channels with one wavelength for some targets and another wavelength for other targets: Fig. 5  <i>See also, e.g., id.</i> at 2:52–59; Provisional App. 61/507,082 at Figure 5, 17:1-27. To the extent Jouvenot is deemed to not expressly disclose four or more wavelength signals from four or more fluorophores, this would have nonetheless been obvious in view of Jouvenot. As explained above, Jouvenot teaches extending its assays to detect some targets in one channel and other targets in a different channel. It shows precisely

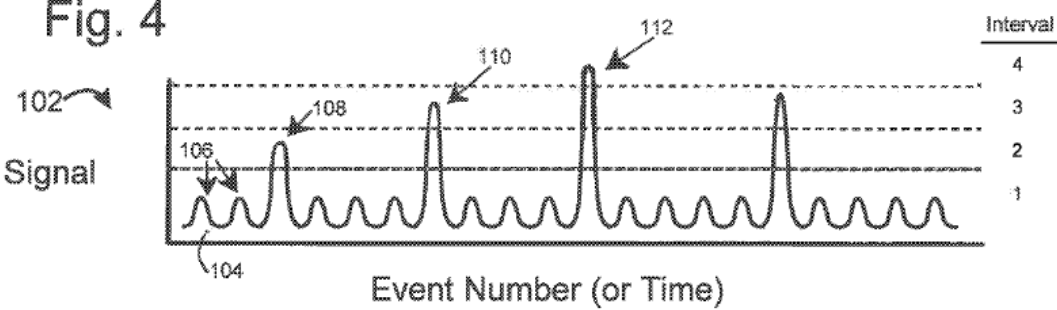
<u>'797 Claim Element¹</u>	<u>Invalidity Analysis</u>
	this in actual experimental data. A skilled artisan would have been motivated to use four or more color channels because he or she would have been motivated to detect larger numbers of targets at the same time. Indeed, Jouvenot expressly teaches that “many applications, especially where sample is limited, could benefit greatly from higher degrees of multiplexing.” Provisional App. 61/507,082 at 3. A POSA would have had a reasonable expectation of successfully extending Jouvenot to four or more wavelength channels and fluorophores because this would reflect nothing more than the use of multiple types of well-know fluorophores and that could be detected using well-known instrumentation for the detection of multiple optical signals.
[1c] a processor controlled analyzer to	Jouvenot teaches the use of a “data processing assembly (a data processor) 68.” Jouvenot 12:58–62; <i>see</i> Provisional App. 61/507,082 at 11:15–16. Fig. 2  <pre> graph LR 62[DG] --> 64[TC] 64 --> 66[DET] 66 --> 68[PROC] subgraph 60 62 64 66 68 end </pre> The processor disclosed in Jouvenot Figure 2 and discussed in Jouvenot is used to interpret signals that have been detected by detector 66. <i>See</i> Jouvenot 13:10–13; <i>see</i> Provisional App. 61/507,082 at 12:9–10 (“The signals may be processed by processor 68 to estimate concentrations of the targets”). Jouvenot Figure 2 is identical to Figure 2 disclosed in the Provisional Appl. 61/507,082.

'797 Claim Element ¹	Invalidity Analysis
[1c.1] 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	As discussed above, Jouvenot teaches, or at a minimum, renders obvious, the use of four electromagnetic wavelength signals. And Jouvenot likewise teaches a processor that receives and analyzes signals from the target molecules. Jouvenot further teaches the application of a decoding matrix to unambiguously detect the presences of at least each of M analytes. Figure 4 illustrates in graphical form the decoding matrix that is used, wherein the intensity of the signal is used to decode the particular targets that are in each droplet: Fig. 4 Specifically, the peak at 106 represents intensity zero and represents 0 analytes; the peak at 108 represents an intensity of 1 and the presence of analyte A; the peak at 110 represents the presence of analyte B and an intensity of 2; the peak at 112 represents the presence of both analytes A and B and a <i>cumulative intensity</i> of 3. The peak heights associated with each outcome were sufficiently different that each combination of analytes can be unambiguously identified and assigned. Jouvenot. <i>See</i> ¶ 14:65–15:4; Provisional App. 61/507,082 at 15:31–33. Jouvenot further presents the decoding matrix in text format. <i>See</i> Jouvenot 14:21–15:10; Provisional App. 61/507,082 at 14:17–16:7.

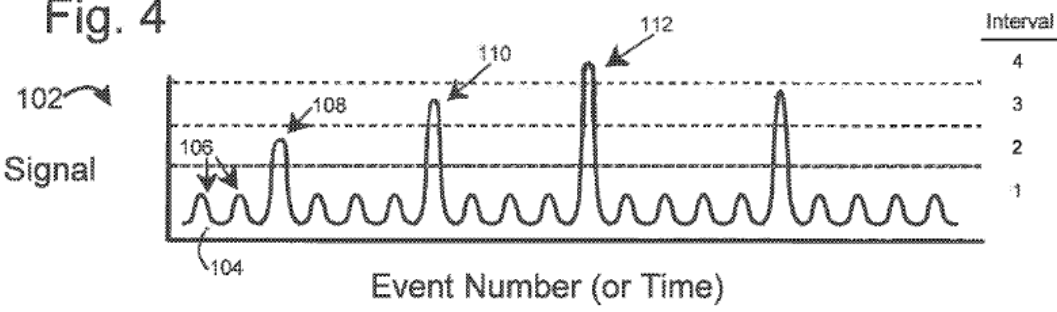
'797 Claim Element ¹	Invalidity Analysis
[1c.2] by associating, for each analyte, a first value in a first component of the cumulative signal and a second value in a second component of the cumulative signal,	Jouvenot's decoding matrix associates each analyte with a first value (e.g., intensity) in a first component of the cumulative signal and a second value (e.g., wavelength) in a second component of a cumulative signal: Fig. 4  Jouvenot at Figure 4; <i>see</i> Provisional App. 61/507,082 at Figure 4. The peaks at 106 with maxima in interval 1 correspond to droplets containing no targets; peak 108 corresponds to droplets containing target 1, but not target 2; peak 110 with maxima in interval 3 correspond to droplets containing target 2, but not target 1; and peak 112 corresponds to a cumulative signal from both targets. Put another way, the peak at 106 represents is intensity zero and represents 0 analytes; the peak at 108 represents an intensity of 1 and the presence of analyte A; the peak at 110 represents the presence of analyte B and an intensity of 2; the peak at 112 represents the presence of both analytes A and B and a <i>cumulative intensity</i> of 3. <i>See</i> Jouvenot 14:21–15:10; Provisional App. 61/507,082 at 14:17–16:7. Whether positive or negative for each target, each droplet produces an increase in cumulative signal strength that forms an identifiable peak. Jouvenot 14:36–56. While Figure 4 focuses on distinguishing targets based on intensity, the signal being measured has a wavelength as well. Moreover, as disclosed above, Jouvenot expressly teaches that its “assays may be extended in various ways.” Jouvenot 5:19–31;

<u>'797 Claim Element¹</u>	<u>Invalidity Analysis</u>
	Provisional App. 61/507,082 at 5:14–21. For example, Jouvenot discloses that “some 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).” <i>Id.</i> Accordingly, Jouvenot expressly teaches, or at a minimum, renders obvious the use of different wavelengths for different targets.
[1c.3] 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	Jouvenot’s decoding matrix associates each analyte with a first value (e.g., intensity) in a first component of the cumulative signal and a second value (e.g., wavelength) in a second component of a cumulative signal: Figure 4 is a line graph showing a signal (102) over Event Number (or Time) (104). The signal is divided into four intervals (1, 2, 3, 4) by horizontal dashed lines. Peaks are labeled: 106 (Interval 1), 108 (Interval 2), 110 (Interval 3), and 112 (Interval 4). The signal shows a series of small peaks followed by four larger peaks corresponding to the intervals. Jouvenot at Figure 4; <i>see</i> Provisional App. 61/507,082 at Figure 4. The peaks at 106 with maxima in interval 1 correspond to droplets containing no targets; peak 108 corresponds to droplets containing target 1, but not target 2; peak 110 with maxima in interval 3 correspond to droplets containing target 2, but not target 1; and peak 112 corresponds to a cumulative signal from both targets. Put another way, the peak at 106 represents is intensity zero and represents 0 analytes; the peak at 108 represents an intensity of 1 and the presence of analyte A; the peak at 110 represents the presence of analyte B and an intensity of 2; the peak at 112 represents the presence of both analytes A and B and a <i>cumulative intensity</i> of 3. <i>See</i> Jouvenot 14:21–15:10; Provisional App.

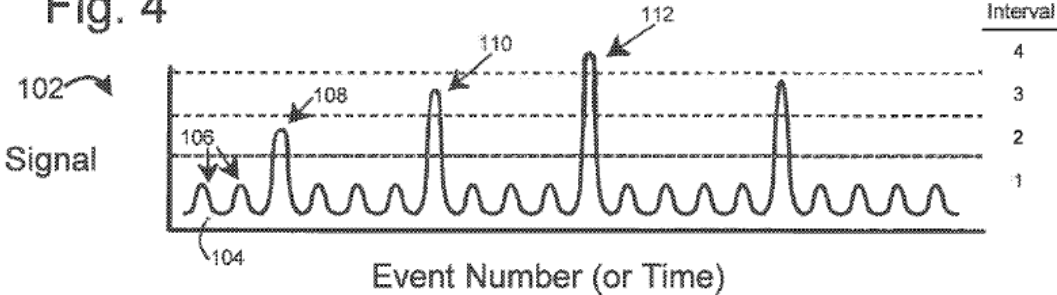
<u>'797 Claim Element¹</u>	<u>Invalidity Analysis</u>
	61/507,082 at 14:17–16:7. Whether positive or negative for each target, each droplet produces an increase in cumulative signal strength that forms an identifiable peak. Jouvenot 14:36–56. While Figure 4 focuses on distinguishing targets based on intensity, the signal being measured has a wavelength as well. Moreover, as disclosed above, Jouvenot expressly teaches that its “assays may be extended in various ways.” Jouvenot 5:19–31; Provisional App. 61/507,082 at 5:14–21. For example, Jouvenot discloses that “some 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).” <i>Id.</i> Accordingly, Jouvenot expressly teaches, or at a minimum, renders obvious the use of different wavelengths for different targets. Further, to the extent Jouvenot is deemed to not expressly disclose four or more wavelength signals from four or more fluorophores, this would have nonetheless been obvious in view of Jouvenot. As explained above, Jouvenot teaches extending its assays to detect some targets in one channel and other targets in a different channel. It shows precisely this in actual experimental data. A skilled artisan would have been motivated to use four or more color channels because he or she would have been motivated to detect larger numbers of targets at the same time. Indeed, Jouvenot expressly teaches that “many applications, especially where sample is limited, could benefit greatly from higher degrees of multiplexing.” Provisional App. 61/507,082 at 3. A POSA would have had a reasonable expectation of successfully extending Jouvenot to four or more wavelength channels and fluorophores because this would reflect nothing more than the use of multiple types of well-known fluorophores and that could be detected using well-known instrumentation for the detection of multiple optical signals.
[1c.4] the determination is made without immobilization, mass spectrometry or melting curve analysis;	Jouvenot’s methods do not use immobilization, mass spectrometry, or melting curve analysis.

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[1d] wherein for the positive integer M, $M=C*\log_2 (F+1)$,	Jouvenot figure 4 discloses a method that matches the claimed mathematical formula: Fig. 4  The peak at 106 represents intensity zero and represents 0 analytes; the peak at 108 represents an intensity of 1 and the presence of analyte A; the peak at 110 represents the presence of analyte B and an intensity of 2; the peak at 112 represents the presence of both analytes A and B and a <i>cumulative intensity</i> of 3. See Jouvenot 14:21–15:10; Provisional App. 61/507,082 at 14:17–16:7. Accordingly, $F=3$ in Figure 4, which involves a single color and a maximum cumulative intensity of 3. Accordingly, $M=(1) * \log_2 (3+1)$, or $M=2$. For the reasons explain above, it would be obvious to extend this approach to multiple colors. Specifically, Jouvenot discloses that the “assays may be extended in various ways.” Jouvenot 5:19–31; Provisional App. 61/507,082 at 5:14–21. For example, Jouvenot teaches that “some 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).” <i>Id.</i> That is, Jouvenot expressly teaches the use of multiple colors. A skilled artisan would have been motivated to use four or more color channels because he or she would have been motivated to detect larger numbers of targets at the same time. Indeed,

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	Jouvenot expressly teaches that “many applications, especially where sample is limited, could benefit greatly from higher degrees of multiplexing.” Provisional App. 61/507,082 at 3. A POSA would have had a reasonable expectation of successfully extending Jouvenot to four or more wavelength channels and fluorophores because this would reflect nothing more than the use of multiple types of well-know fluorophores and that could be detected using well-known instrumentation for the detection of multiple optical signals. To the extent one contends the individual analyte signals need to exactly follow a geometric progression of 1, 2, 4, 8... this is disclosed in European Patent Specification 0594763B1 (“Lehnen”). Lehnen discloses the use of binary (power-of-2) encoding (1:2:4:8) and discusses multiplexing capacity as a function of channels and intensity levels, which is mathematically equivalent to the formula. <i>See</i> Lehnen at 13:15–53. More specifically, each analyte is encoded using the unique proportions of bead subpopulations and powers of two to ensure that each possible combination yields a unique sum. A POSA would be motivated to use this signal progression because the proportions allow for unique interpretation and unambiguous identification of analytes, as Lehnen expressly teaches. <i>See</i> Lehnen at 13:31–35. A POSA would have a reasonable expectation of using this approach because POSA would have known how to modulate the intensity from a target-specific probe. Jouvenot expressly teaches multiple such methods for doing this. As Jouvenot explains, “the 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.” Jouvenot 13:51–63; Provisional App. 61/507,082 at 13:13–21.

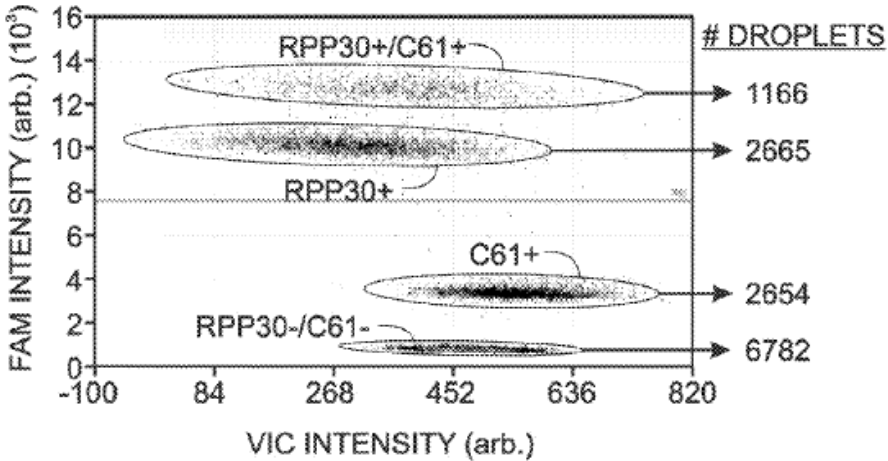
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[1d.1] F is a positive integer and is equal to the maximum cumulative intensity of the first component of the signal, for any second value, when all of the analytes are present, and	Figure 4 illustrates the detection of analytes by using various intensity values: Fig. 4  The peak at 112 represents the presence of both analytes A and B and a <i>cumulative intensity</i> for the first component of a signal for a second value where both A and B (all analytes) are present. <i>See</i> Jouvenot 14:21–15:10; Provisional App. 61/507,082 at 14:17–16:7. This peak represents a value for F of 3 and represents the maximum cumulative intensity when all targets are present at a particular wavelength. To the extent one contends the individual analyte signals need to exactly follow a geometric progression of 1, 2, 4, 8... this is disclosed in Lehen. Lehen discloses the use of binary (power-of-2) encoding (1:2:4:8) and discusses multiplexing capacity as a function of channels and intensity levels, which is mathematically equivalent to the formula. <i>See</i> Lehen at 13:15–53. More specifically, each analyte is encoded using the unique proportions of bead subpopulations and powers of two to ensure that each possible combination yields a unique sum. 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. <i>See</i> Lehen at 13:31–35. A POSA would have a reasonable expectation of using this approach because POSA would have known how to modulate the intensity from a target-specific probe. Jouvenot expressly teaches multiple such methods for doing this. As Jouvenot explains, “the intensity associated with one fluorophore, following reaction, may be

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	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.” Jouvenot 13:51–63; Provisional App. 61/507,082 at 13:13–21.
[1d.2] C=4, 5, or 6; and	To the extent that C=6 is not explicitly disclosed, it would have been obvious for the same reasons as stated above. Jouvenot specifically mentions that applications can benefit greatly from higher degrees of multiplexing (i.e., a greater number of colors). Jouvenot 2:12–20; Provisional App. 61/507,082 at 2:14–3:2. Further, Jouvenot discloses that the “assays may be extended in various ways.” Jouvenot 5:19–31; Provisional App. 61/507,082 at 5:14–21. For example, Jouvenot discloses that an assay for three targets would generate eight clusters or populations of data “separated by intensity,” and that “some 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).” <i>Id.</i>
[1d.3] wherein F+1 is a positive integer and wherein F+1 is a power of 2,	Figure 4 of Jouvenot teaches a value of F+1 that is a power of 2:

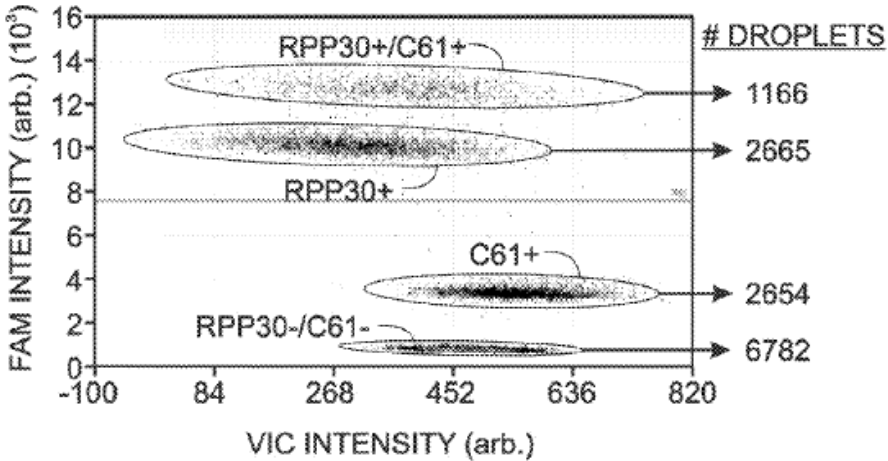
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	Fig. 4  The peak at 106 represents intensity zero and represents 0 analytes; the peak at 108 represents an intensity of 1 and the presence of analyte A; the peak at 110 represents the presence of analyte B and an intensity of 2; the peak at 112 represents the presence of both analytes A and B and a <i>cumulative intensity</i> of 3. See Jouvenot 14:21–15:10; Provisional App. 61/507,082 at 14:17–16:7. Accordingly, $F=3$ in Figure 4. With $F=3$, the value of $F+1$ is 4, which is a power of 2. To the extent one contends the individual analyte signals need to exactly follow a geometric progression of 1, 2, 4, 8... this is disclosed in Lehnert. Lehnert discloses the use of binary (power-of-2) encoding (1:2:4:8) and discusses multiplexing capacity as a function of channels and intensity levels, which is mathematically equivalent to the formula. See Lehnert at 13:15–53. More specifically, each analyte is encoded using the unique proportions of bead subpopulations and powers of two to ensure that each possible combination yields a unique sum. A POSA would be motivated to use this signal progression because the proportions allow for unique interpretation and unambiguous identification of analytes, as Lehnert expressly teaches. See Lehnert at 13:31–35. A POSA would have a reasonable expectation of using this approach because POSA would have known how to modulate the intensity from a target-specific probe. Jouvenot expressly teaches multiple such methods for doing this. As Jouvenot

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	explains, “the 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.” Jouvenot 13:51–63; Provisional App. 61/507,082 at 13:13–21.
[1d.4] 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.	In Jouvenot Figure 4, M is greater than the number of second values used to encode the analytes. Fig. 4 In Figure 4 the number of analytes present is 2 and there is a single wavelength (C) value, so M is greater than C. As explained above, it would be obvious for a POSA to duplicate this approach with multiple colors for additional targets, an approach which would increase M and C proportionally such that M would remain greater than C.

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2[p]. The system of claim 1,	<i>See</i> claim 1.
[2a] 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;	Jouvenot teaches the detection from the sample chamber of five electromagnetic signals at five wavelengths from each of five fluorophores. Specifically, Jouvenot discloses that its “assays may be extended in various ways.” Jouvenot 5:19–31; Provisional App. 61/507,082 at 5:14–21. Most important, Jouvenot teaches that “some 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).” <i>Id.</i> In other words, Jouvenot teaches the use of multiple channels, which a person of skill in the art would understand is a teaching of using multiple different wavelength signals from multiple different fluorophores. A person of skill in the art would further understand that this encompasses the use of at least five such channels and fluorophores. Indeed, Jouvenot states that the “signals optionally may include data collected in two or more different optical channels (e.g., in different wavelength ranges (wavebands) and/or color regimes) from reporters for the same and/or different targets). The light detected from each reporter may be light emitted from a luminophore (e.g., a fluorophore). 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 assays and thus two, three, four, or more targets.” Jouvenot 8:36–47; Provisional App. 61/507,082 at 9:3–10 (identical substantively). Jouvenot likewise expressly teaches using more than five different fluorophores. <i>See</i> Jouvenot 14:1–2; Provisional App. 61/507,082 at 14:2–3 (“fluorophores that may be suitable include FAM, VIC, ROX, TAMRA, JOE, etc., among others.”).

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	Consistent with the foregoing, as shown in Figure 5, Jouvenot shows actual data using two channels with one wavelength for some targets and another wavelength for other targets: Fig. 5  See also, e.g., <i>id.</i> at 2:52–59; Provisional App. 61/507,082 at Figure 5, 17:1-27. To the extent Jouvenot is deemed to not expressly disclose five or more wavelength signals from four or more fluorophores, this would have nonetheless been obvious in view of Jouvenot. As explained above, Jouvenot teaches extending its assays to detect some targets in one channel and other targets in a different channel. It shows precisely this in actual experimental data. A skilled artisan would have been motivated to use four or more color channels because he or she would have been motivated to detect larger numbers of targets at the same time. Indeed, Jouvenot expressly teaches that “many applications, especially where sample is limited, could benefit greatly from

<u>'797 Claim Element¹</u>	<u>Invalidity Analysis</u>
	higher degrees of multiplexing.” Provisional App. 61/507,082 at 3. A POSA would have had a reasonable expectation of successfully extending Jouvenot to five or more wavelength channels and fluorophores because this would reflect nothing more than the use of multiple types of well-known fluorophores and that could be detected using well-known instrumentation for the detection of multiple optical signals.
[2b] 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	Jouvenot teaches the detection from the sample chamber of six electromagnetic signals at six wavelengths from each of six fluorophores. Specifically, Jouvenot discloses that its “assays may be extended in various ways.” Jouvenot 5:19–31; Provisional App. 61/507,082 at 5:14–21. Most important, Jouvenot teaches that “some 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).” <i>Id.</i> In other words, Jouvenot teaches the use of multiple channels, which a person of skill in the art would understand is a teaching of using multiple different wavelength signals from multiple different fluorophores. A person of skill in the art would further understand that this encompasses the use of at least six such channels and fluorophores. Indeed, Jouvenot states that the “signals optionally may include data collected in two or more different optical channels (e.g., in different wavelength ranges (wavebands) and/or color regimes) from reporters for the same and/or different targets). The light detected from each reporter may be light emitted from a luminophore (e.g., a fluorophore). 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 assays and thus two, three, four, or more targets.” Jouvenot 8:36–47; Provisional App. 61/507,082 at 9:3–10 (identical substantively). Jouvenot likewise expressly teaches using more than six different fluorophores. <i>See</i> Jouvenot 14:1–2; Provisional App. 61/507,082 at 14:2–3 (“fluorophores that may be suitable include FAM, VIC, ROX, TAMRA, JOE, etc., among others.”).

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	Consistent with the foregoing, as shown in Figure 5, Jouvenot shows actual data using two channels with one wavelength for some targets and another wavelength for other targets: Fig. 5  See also, e.g., <i>id.</i> at 2:52–59; Provisional App. 61/507,082 at Figure 5, 17:1-27. To the extent Jouvenot is deemed to not expressly disclose six or more wavelength signals from four or more fluorophores, this would have nonetheless been obvious in view of Jouvenot. As explained above, Jouvenot teaches extending its assays to detect some targets in one channel and other targets in a different channel. It shows precisely this in actual experimental data. A skilled artisan would have been motivated to use four or more color channels because he or she would have been motivated to detect larger numbers of targets at the same time. Indeed, Jouvenot expressly teaches that “many applications, especially where sample is limited, could benefit greatly from

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	higher degrees of multiplexing.” Provisional App. 61/507,082 at 3. A POSA would have had a reasonable expectation of successfully extending Jouvenot to six or more wavelength channels and fluorophores because this would reflect nothing more than the use of multiple types of well-known fluorophores and that could be detected using well-known instrumentation for the detection of multiple optical signals.
[2c] wherein C=6.	Jouvenot teaches, or at a minimum, renders obvious C=6 (i.e., 6 different wavelength or color channels) for the reasons stated in connection with element [2b].
5. The system of claim 1,	See claim 1.
[5a] wherein F=3.	Figure 4 illustrates the detection of analytes by using various intensity values and discloses F=3: Fig. 4 The peak at 112 represents the presence of both analytes A and B and a <i>cumulative intensity</i> for the first component of a signal for a second value where both A and B (all analytes) are present. See Jouvenot 14:21–15:10; Provisional App. 61/507,082 at

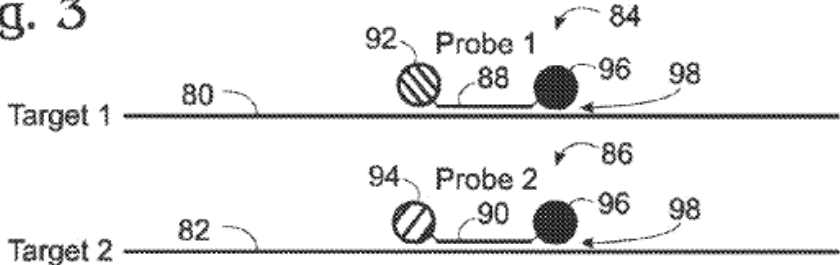
<u>'797 Claim Element¹</u>	<u>Invalidity Analysis</u>
	14:17–16:7. This peak represents a value for F of 3 and represents the maximum cumulative intensity when all targets are present at a particular wavelength. To the extent one contends the individual analyte signals need to exactly follow a geometric progression of 1, 2, 4, 8... this is disclosed in Lehnert. Lehnert discloses the use of binary (power-of-2) encoding (1:2:4:8) and discusses multiplexing capacity as a function of channels and intensity levels, which is mathematically equivalent to the formula. <i>See</i> Lehnert at 13:15–53. More specifically, each analyte is encoded using the unique proportions of bead subpopulations and powers of two to ensure that each possible combination yields a unique sum. A POSA would be motivated to use this signal progression because the proportions allow for unique interpretation and unambiguous identification of analytes, as Lehnert expressly teaches. <i>See</i> Lehnert at 13:31–35. A POSA would have a reasonable expectation of using this approach because POSA would have known how to modulate the intensity from a target-specific probe. Jouvenot expressly teaches multiple such methods for doing this. As Jouvenot explains, “the 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.” Jouvenot 13:51–63; Provisional App. 61/507,082 at 13:13–21.
6[p]. The system of claim 5,	<i>See</i> claim 5.

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[6a] 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.	In its infringement contentions, Plaintiff relies on FAM for “a green fluorophore,” HEX for “a green and yellow fluorophore,” Cy5, Cy5.5, and ATTO 590 for “a red fluorophore,” and ROX for “a yellow fluorophore.” <i>See</i> Plaintiff’s Patent L.R. 3-1 and 3-2 Disclosures, 78–84. Plaintiff does not provide a representative blue fluorophore. Regardless, following Plaintiffs infringement contentions, Jouvenot teaches exemplary green and yellow fluorophores, and combinations thereof. <i>See</i> Jouvenot 14:1–2; Provisional App. 61/507,082 at 14:2–3 (“fluorophores that may be suitable include FAM, VIC, ROX, TAMRA, JOE, etc., among others.”). FAM is a green fluorophore, VIC is a green and yellow fluorophore, ROX is a yellow fluorophore, TAMRA is a green and yellow fluorophore, and JOE is a green fluorophore. Further, Larson discloses FAM, ROX, Cy5, and Cy5.5. Larson ¶ 90. Plaintiff relies on Bio-Rad Bulletin 2421, a Fluorophore Reference Guide, <i>see</i> Plaintiff’s Patent L.R. 3-1 and 3-2 Disclosures, 78–106 (citing CT0479364), and contends that these fluorophores exhibit several of the claimed colors, excitation wavelengths, and emission wavelengths. Accordingly, under Plaintiff’s infringement theory, Larson discloses green fluorophores (such as FAM, at least), yellow fluorophores (such as ROX, at least), and red fluorophores (such Cy5 and Cy5.5, at least). Plaintiffs do not identify a blue fluorophore in their contentions, but Larson discloses this as well in the form of its disclosure of the DAPI fluorophore, which the Fluorophore Reference Guide confirms is a blue fluorophore. To the extent this claim is deemed to require disclosure of blue and red fluorophores and to the extent Jouvenot is deemed not to disclose such fluorophores, it would have nonetheless been obvious to a POSA to use further consider red and blue fluorophores because using different colored fluorophores would allow a POSA to distinguish between different targets more easily and would expand the range of available fluorophores and hence expand the multiplex capability. <i>See</i> Jouvenot 2:12–20; Provisional App. 61/507,082 at 2:14–3:2. A POSA would also have been motivated to combine Jouvenot with other fluorophore references for the same reasons. Moreover,

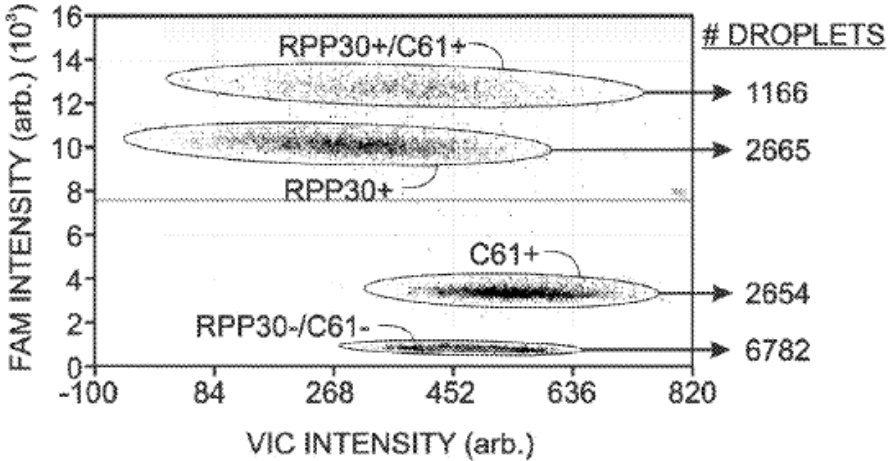
'797 Claim Element ¹	Invalidity Analysis																																																						
	such red and blue fluorophores were well-known to skilled artisans and were routinely used. Brabetz for instance, discloses blue, green, yellow, and red fluorophores, and combinations thereof: TABLE 1 <table><tr><th colspan="6">Known fluorescent dye combinations and virtual filtersets for ABI Prism ® Genetic Analyzers.</th></tr><tr><th colspan="6">Fluorescence dye combinations and colour canals</th></tr><tr><th>Blue</th><th>Green</th><th>Yellow</th><th>Red</th><th>Orange (far red)</th><th>Recommended virtual filter²</th></tr><tr><td>6-FAM</td><td>JOE</td><td>TAMRA</td><td>ROX</td><td>—</td><td>F or A</td></tr><tr><td>6-FAM</td><td>TET</td><td>HEX</td><td>TAMRA</td><td>—</td><td>C</td></tr><tr><td>5, 6-FAM</td><td>JOE</td><td>TAMRA</td><td>ROX</td><td>—</td><td>F or A</td></tr><tr><td>6-FAM</td><td>JOE</td><td>NED</td><td>ROX</td><td>—</td><td>F</td></tr><tr><td>6-FAM</td><td>HEX</td><td>NED</td><td>ROX</td><td>—</td><td>F or D</td></tr><tr><td>6-FAM</td><td>VIC</td><td>NED</td><td>PET</td><td>LIZ</td><td>G5</td></tr></table> 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). Brabetz 2:40–60; <i>see also</i> Joseph R. Lakowicz, <i>Principles of Fluorescence Spectroscopy</i>, 70 (“cascade yellow”), 722 (“blue” and “red” wavelengths), 727 (“cascade blue”), 730 (“nonspecific blue fluorophore,” “green” and “red” emissions, “yellow emission”), 770 (“green fluorophore”) (3d ed., 2006).	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 ²	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
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6-FAM	JOE	NED	ROX	—	F																																																		
6-FAM	HEX	NED	ROX	—	F or D																																																		
6-FAM	VIC	NED	PET	LIZ	G5																																																		
7[p]. The system of claim 5,	<i>See</i> claim 5.																																																						

<u>'797 Claim Element¹</u>	<u>Invalidity Analysis</u>
[7a] 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.	Jouvenot discloses FAM, VIC, ROX, TAMRA, and JOE as exemplary fluorophores that may be suitable, thus disclosing this claim element by virtue of its disclosure of FAM and ROX. To the extent this claim element is deemed to require disclosure of full group of listed fluorophores, this claim would have nonetheless been obvious. Indeed, the list of disclosed fluorophores in Jouvenot is not exhaustive. Jouvenot expressly states that “others” may be suitable. <i>See</i> Jouvenot 14:1–2; Provisional App. 61/507,082 at 14:2–3. Larson also discloses using FAM, Cy3, ROX, Cy5, and Cy5.5 for fluorescently labeled probes. Larson ¶ 90. Moreover, the claimed fluorophores other than FAM and ROX are simply well-known fluorophores that were part of the standard toolkit of the skilled artisan that a POSA would have been motivated to consider and would have had a reasonable expectation of successfully employing. <i>See</i> Joseph R. Lakowicz, <i>Principles of Fluorescence Spectroscopy</i>, 657–660, 827, 848–851(3d ed., 2006); Amersham Pharmacia Biotech, <i>Fluorescence Imaging Principles and Methods</i>, 84, 129, 132 (2000); <i>see also</i> U.S. Patent Publication 2008/0003649A1 (“Maltezos”) ¶¶ 142, 194. Accordingly, a POSA would have been motivated to combine the disclosures in Jouvenot with those in other fluorophore art to analyze a greater number of analytes based on wavelength.
8[p]. The system of claim 5,	<i>See</i> claim 5.
[8a] 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.	In its infringement contentions, Plaintiff relies on FAM for “about 494 nm,” Cy5 for “about 650 nm,” Cy5.5 for “about 675 nm,” and ROX for “about 567 nm.” <i>See</i> Plaintiff’s Patent L.R. 3-1 and 3-2 Disclosures, 97–103. Plaintiff does not provide a representative fluorophore with a maximum excitation wavelength of about 550 nm.

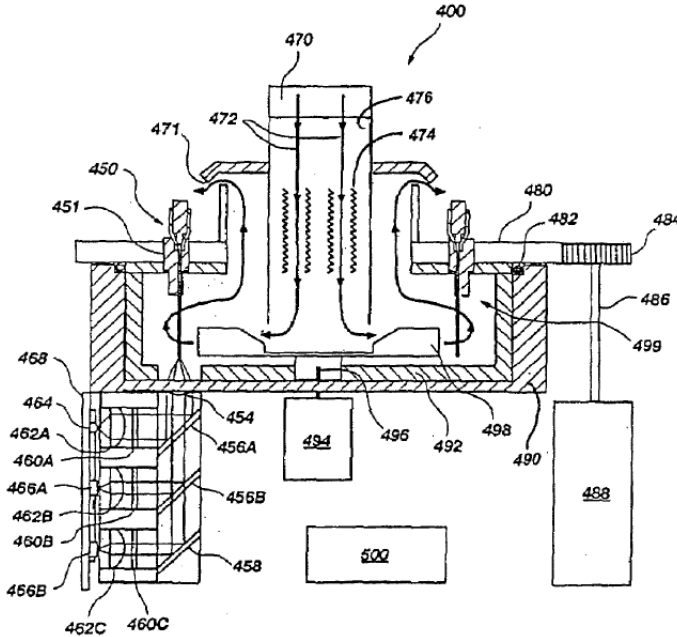
<u>'797 Claim Element¹</u>	<u>Invalidity Analysis</u>
	As discussed in connection with claim element [7a], these fluorophores are disclosed in Jouvenot or their use would have, at a minimum, been obvious. Moreover, Plaintiff relies on Bio-Rad Bulletin 2421, a Fluorophore Reference Guide, see Plaintiff's Patent L.R. 3-1 and 3-2 Disclosures, 78–106 (citing CT0479364), and contends that these fluorophores exhibit several of the claimed colors, excitation wavelengths, and emission wavelengths. Accordingly, under Plaintiff's infringement theory, each of these fluorophores is disclosed in Larson. Larson ¶ 90. Although Plaintiff has not provided a representative fluorophore in its infringement contentions, Cy3 is disclosed in Larson and it has a maximum excitation wavelength of 550 nm and was well known in the art. Larson ¶ 90; <i>see also Fluorescence Imaging Principles and Methods</i>, 84 (2000). To the extent these wavelengths are not explicitly disclosed in Jouvenot, a POSA would have been motivated to combine the disclosures in Jouvenot with disclosures of other maximum excitation wavelengths to prevent interference during detection.
9[p]. The system of claim 5,	See claim 5.
[9a] 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.	In its infringement contentions, Plaintiff relies on FAM for “about 518 nm,” Cy5 for “about 670 nm,” Cy5.5 for “about 697 nm,” and ROX for “about 591 nm.” <i>See</i> Plaintiff's Patent L.R. 3-1 and 3-2 Disclosures, 103–109. Plaintiff relies on Bio-Rad Bulletin 2421, a Fluorophore Reference Guide, <i>see</i> Plaintiff's Patent L.R. 3-1 and 3-2 Disclosures, 78–106 (citing CT0479364), and contends that these fluorophores exhibit several of the claimed colors, excitation wavelengths, and emission wavelengths. Accordingly, under Plaintiff's infringement theory, each of these fluorophores is disclosed in Larson. Larson ¶ 90. Although Plaintiff has not provided a representative fluorophore in its infringement contentions, Cy3 is disclosed in Larson and has a maximum emission wavelength of about 565 (~570 nm). Larson ¶ 90; <i>see also Fluorescence Imaging Principles and Methods</i>, 84 (2000). To the extent these fluorophores are not explicitly disclosed in Jouvenot, a POSA would have been

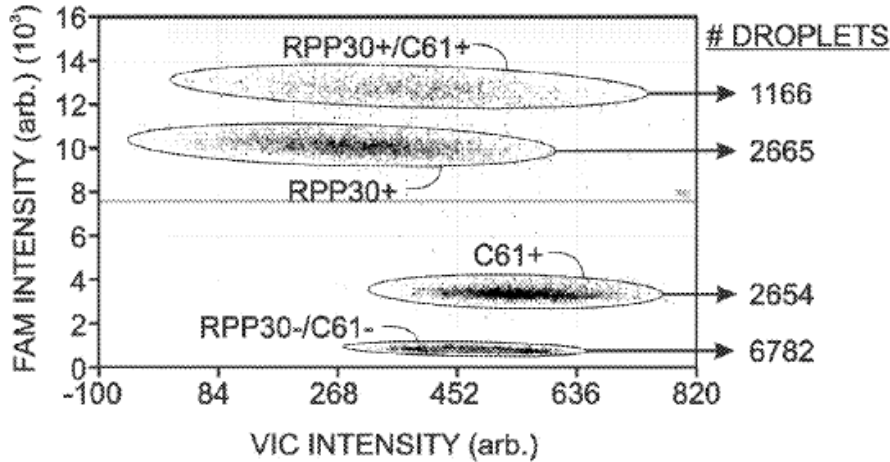
'797 Claim Element ¹	Invalidity Analysis
	motivated to combine the disclosures in Jouvenot with disclosures of fluorophores with other maximum emission wavelengths to analyze a greater number of analytes.
10[p]. The system of claim 5,	See claim 5.
[10a] wherein the analyte-specific hybridization probes are labeled with a fluorophore of the multiple fluorophores.	Jouvenot discloses probes labeled with fluorophores. Jouvenot 13:58–62; Provisional App. 61/507,082 at 13:18–21 (“both probes may be labeled with the same number of fluorophores...”). The fluorophore labeled probes are further depicted in Figure 3: Fig. 3  Jouvenot 2:39-44; Provisional App. 61/507,082 at 3:14–17. As Jouvenot states, “Figure 3 shows a pair of targets 80, 82 (‘Target 1’ and ‘Target 2’) and corresponding probes 84, 86 (‘Probe 1’ and ‘Probe 2’) that may be used to create a dedicated signal for each target in a digital PCR assay. Each probe may include an oligonucleotide 88, 90, a fluorophore 92, 94, and a quencher 96.” Provisional App. 61/507,082 at 12:20-23. Larson also discloses labeling analyte-specific hybridization probes with fluorophores and also discloses multiple fluorophores. Larson ¶ 108 (“Probes for TERT, RNaseP and E1a were labeled with the VIC dye and probes for SMN1 and SMN2 were labeled with

<u>'797 Claim Element¹</u>	<u>Invalidity Analysis</u>
	the FAM dye. The sequences for TERT RNaseP, E1a, SMN1 and SMN2 were amplified by PCR.”); <i>see also</i> ¶ 114 (“Probes for TERT and 815A were labeled with the VIC dye and probes for 815G were labeled with the FAM dye. For each of RNaseP and E1a, two probes, one labeled with the VIC dye and the other labeled with the FAM dye, were encapsulated.”); Appendix B. To the extent not explicitly disclosed in Jouvenot, using analyte-specific hybridization probes labeled with a fluorophore of multiple fluorophores would have been both a routine practice in the art and it would have been obvious to combine the disclosures in Jouvenot with other fluorophore art for the reasons discussed above.
11[p]. The system of claim 5,	<i>See</i> claim 5.
[11a] wherein the detector comprises four or six band pass filters.	Jouvenot discloses that signals may be detected with a detector. <i>See</i> Jouvenot 13:4–13; Provisional App. 61/507,082 at 12:8–9. A POSA would have found it obvious to include multiple band pass filters in the detector. Such band pass filters allow a specific range of wavelength to pass through while reducing signals outside of that range, isolating desired frequencies. A POSA would have been motivated to utilize standard band-pass filters to create different color channels for use with Jouvenot’s method because Jouvenot expressly teaches using multiple color channels. Specifically, Jouvenot discloses that its “assays may be extended in various ways.” Jouvenot 5:19–31; Provisional App. 61/507,082 at 5:14–21. Most important, Jouvenot teaches that “some 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).” <i>Id.</i> In other words, Jouvenot teaches the use of multiple channels, which a person of skill in the art would understand is a teaching of using multiple different wavelength signals from multiple different fluorophores.

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	Consistent with the foregoing, as shown in Figure 5, Jouvenot shows actual data using two channels with one wavelength for some targets and another wavelength for other targets: Fig. 5  See also, e.g., <i>id.</i> at 2:52–59; Provisional App. 61/507,082 at Figure 5, 17:1–27. That band-pass filters were standard components in fluorescent detection is confirmed by several prior art references. For instance, Brabetz discloses using band pass filters in multiple color fluorescence detection within multiplex PCR. Brabetz 1:45–2:35. Additionally, Maltezos states, “it may desirable to suppress [unwanted] luminescence even further by using optical band-pass filters.” <i>See</i> Maltezos ¶ 163. Further, U.S. Patent Publication 2010/0227386 (“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.” Neuzil ¶ 44. Even further, U.S. Patent

<u>'797 Claim Element¹</u>	<u>Invalidity Analysis</u>
	Publication 2003/0219754 (“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. Oleksy ¶ 86.
13[p]. The system of claim 5,	<i>See</i> claim 5.
[13a] wherein the multi-channel detector comprises four or six photodetectors.	Jouvenot discloses the use of fluorescent signals. As Jouvenot explains, for instance, “[a]mplification of the target can be detected optically from a fluorescent probe included in the reaction. In particular, the probe can include a dye that provides a fluorescence signal indicating whether or not the target has been amplified.” Provisional App. 61/507,082 at 2:10-13. Jouvenot further discloses the use of detectors. <i>See</i> Jouvenot 13:4–13; Provisional App. 61/507,082 at 12:8–9. Given that Jouvenot discloses detectors for detecting fluorescent signals, it discloses the use of photodetectors. At a minimum, the use of photodetectors would have been obvious because the use of fluorescent labels was well known as was the instrumentation for detecting such signals. Indeed, several prior art references disclose the use of such photodetectors. For instance, photodetectors were well known in the art. <i>See</i> U.S. Patent Publication Maltezos ¶¶ 60, 101, 144; <i>id.</i> ¶ 149 (“The photodetector array includes a plurality of photodetectors....”); <i>see also</i> U.S. Patent Publication 2009/0239308A1 (“Dube”) ¶ 147 (“the CCD is used as an array of photodetectors wherein each pixel or group of pixels corresponds to a reaction chamber....”); U.S. Patent Publication 2009/0258414A1 (“Wittwer”) ¶ 375 and Figure 53 (“The emitted fluorescence signals are acquired by photodetectors 466 A and 466 B.”).

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	 <i>Fig. 53</i> The term photodetector also includes terms like “photodiode” and photodiodes are well known in the art. Maltezos ¶ 101 (“where it is detected by a photodetector, such as a photodiode.”). As to the use of four or six photodetectors, this would have been obvious in view of Jouvenot. As discussed in detail above, Jouvenot expressly teaches using multiple color channels. Specifically, Jouvenot discloses that its “assays may be extended in various ways.” Jouvenot 5:19–31; Provisional App. 61/507,082 at 5:14–21. Most

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	important, Jouvenot teaches that “some 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).” <i>Id.</i> In other words, Jouvenot teaches the use of multiple channels, which a person of skill in the art would understand is a teaching of using multiple different wavelength signals from multiple different fluorophores. Consistent with the foregoing, as shown in Figure 5, Jouvenot shows actual data using two channels with one wavelength for some targets and another wavelength for other targets: Fig. 5  See also, e.g., <i>id.</i> at 2:52–59; Provisional App. 61/507,082 at Figure 5, 17:1-27. For the reasons explained above in connection with claims 1 and 2, a person of ordinary skill in the art would have been motivated to use six or more color channels. See, e.g., Jouvenot 8:36–37; Provisional App. 61/507,082 at pg. 9, lines 3–5 (“The signals

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	optionally may include data collected in one or more different channels (i.e., in different wavelength ranges (color regimes) from reporters for the same and/or different targets).”).To do this, a skilled artisan would have been motivated to use six or more photodetectors (one for each of the color channel) and would have had a reasonable expectation of successfully doing so because, as explained above, such photodetectors were standard components that were widely used, as reflected in several prior art references.
14[p]. The system of claim 5,	<i>See</i> claim 5.
[14a] wherein the multi-channel detector comprises photodetectors that enable the detection of blue, green, and red fluorescent signals.	As explained above in connection with claim 13, Jouvenot discloses the use of photodetectors, and it would have been obvious to use six or more photodetectors. Indeed, photodetectors, <i>see supra</i>, [13a], have excellent sensitivity such that a POSA would have been motivated to use them. <i>See</i> Maltezos ¶ 134 (“photodiode detectors have excellent sensitivity....”). Moreover, Larson discloses using a range of dyes encompassing a range of colors, <i>see</i> Larson ¶90, such that it would have been obvious to expand its use of photodetectors to cover photodetectors that cover each of the claimed colors (blue, green, and red). <i>See also</i>, Appendix B. As to the use of green and red fluorescent signals, Plaintiff relies on FAM for green, HEX for green and yellow, Cy5, Cy5.5 and ATTO 590 for red, and ROX for yellow in its infringement contentions. <i>See</i> Plaintiff’s Patent L.R. 3-1 and 3-2 Disclosures, 121–130. Plaintiff does not disclose a blue signal. Each of those is disclosed or rendered obvious in view of Jouvenot, as explained in claim [9a], above. Further, blue, green, and red signals were commonly detected. The optical assembly in Maltezos, for instance, detected blue, green, and red signals. Maltezos ¶ 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.”). Table 1 of Maltezos lays this out

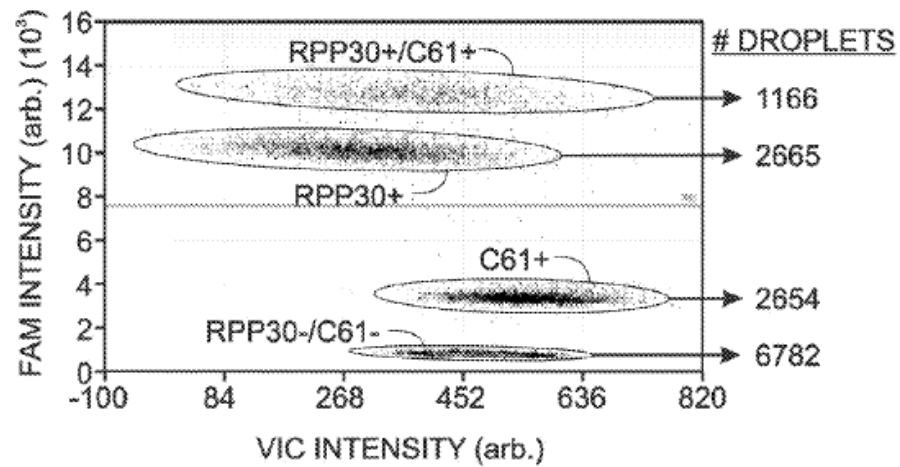
'797 Claim Element ¹	Invalidity Analysis																																							
	TABLE 1 <table><tr><th rowspan="2">Color</th><th colspan="2">Dominant wavelength (nm) or CCT (K)</th><th>Typical Luminous or Radiant flux @</th></tr><tr><th>Min.</th><th>Max.</th><th>700 mA</th></tr><tr><td>White</td><td>4500 K</td><td>8000 K</td><td>76 lm</td></tr><tr><td>Royal Blue</td><td>455 nm</td><td>465 nm</td><td>385 mW</td></tr><tr><td>Blue</td><td>465 nm</td><td>475 nm</td><td>28 lm</td></tr><tr><td>Cyan</td><td>500 nm</td><td>510 nm</td><td>75 lm</td></tr><tr><td>Green</td><td>520 nm</td><td>535 nm</td><td>80 lm</td></tr><tr><td>Amber</td><td>585 nm</td><td>595 nm</td><td>57 lm</td></tr><tr><td>Red-Orange</td><td>610 nm</td><td>620 nm</td><td>86 lm</td></tr><tr><td>Red</td><td>620 nm</td><td>635 nm</td><td>61 lm</td></tr></table>	Color	Dominant wavelength (nm) or CCT (K)		Typical Luminous or Radiant flux @	Min.	Max.	700 mA	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
Color	Dominant wavelength (nm) or CCT (K)		Typical Luminous or Radiant flux @																																					
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15[p]. The system of claim 5,	See claim 5.																																							
[15a] 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.	As explained above in connection with claims 13 and 14, Jouvenot discloses the use of photodetectors, and it would have been obvious to use six or more photodetectors. In its infringement contentions, Plaintiff relies on FAM for “about 483 nm to about 533 nm,” HEX for “about 523 nm to about 568 nm,” Cy5 and ATTO 590 for “about 615 nm to about 670 nm” ROX for “558 nm to about 610 nm.” See Plaintiff’s Patent L.R. 3-1 and 3-2 Disclosures, 131–140. As explained above in connection with claim [9a], the use of these fluorophores are either disclosed in Jouvenot or, at a minimum, rendered obvious in view of Jouvenot. Additionally, based on Plaintiff’s own infringement contentions, using fluorophores with these properties would have been obvious. Plaintiff relies on Bio-Rad Bulletin 2421, a Fluorophore Reference Guide, see Plaintiff’s Patent L.R. 3-1 and 3-2 Disclosures, 78–106 (citing CT0479364), and contends that these fluorophores exhibit several of the claimed colors, excitation wavelengths, and emission wavelengths.																																							

<u>'797 Claim Element¹</u>	<u>Invalidity Analysis</u>
	Accordingly, under Plaintiff's infringement theory, fluorophores in each of these detection ranges are disclosed in Larson or, at a minimum, rendered obvious in view of Larson. A POSA would have been motivated to combine these disclosures for the reasons discussed above.
18[p]. The system of claim 5,	<i>See</i> claim 5.
[18a] further comprising a display coupled to the processor controlled analyzer to visualize a plot of the first and second values.	Jouvenot discloses multiple examples that show that a display was coupled with the process controlled analyzer to visualize a plot of first and second values (i.e., the intensity and wavelength). In Figure 5, for instance, intensity is plotted for two different wavelength channels:

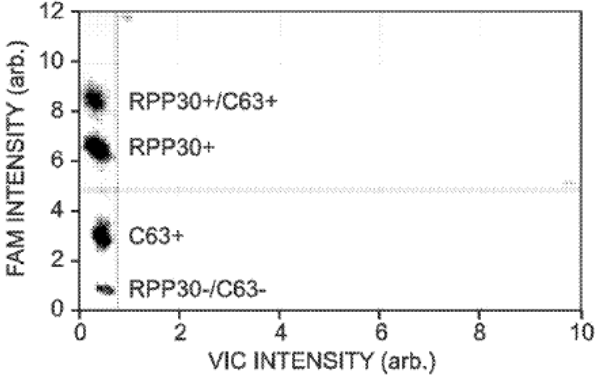
'797 Claim Element¹

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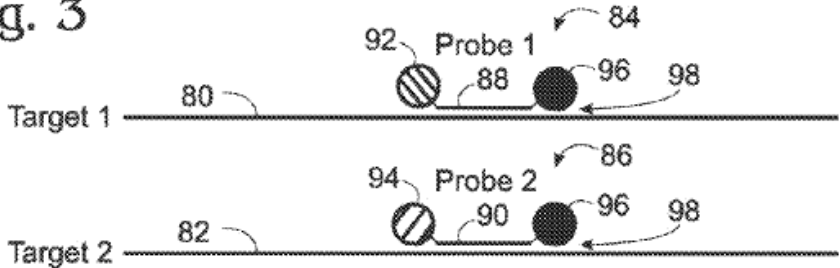
Fig. 5

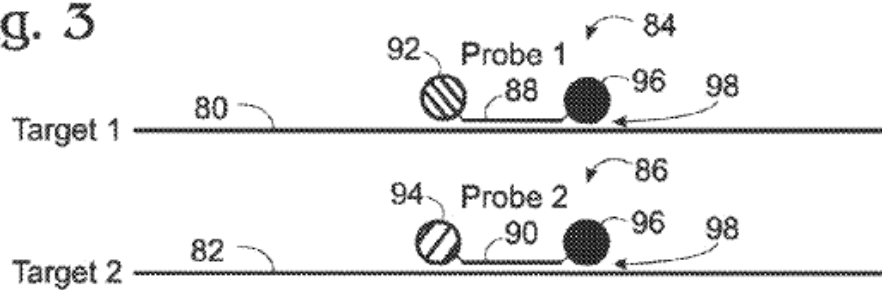


See also, e.g., *id.* at 2:52–59; Provisional App. 61/507,082 at Figure 5, 17:1-27. Figure 7 of Jouvenot includes a similar plot:

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	Fig. 7  Jouvenot at Figure 7; <i>see</i> Provisional App. 61/507,082 at Figure 7. As set forth above, Figure 2 of Jouvenot includes a data processor that may receive signal information. “The signals may be processed by processor 68 to estimate concentrations of the targets.” Provisional App. 61/507,082 at 12:9-10. It would have been obvious to include with the system a display so that users can visualize the data results and confirm the accuracy of the reported target concentrations. Moreover, using a display for such purposes was well known in the art. For example, Maltezos discloses control assemblies for various PCR applications and notes that computers for analyzing signals usually include a display terminal. Maltezos ¶ 167 (“Generally, a computer comprises 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 <i>a display terminal</i>, and an input device such as a keyboard.” (emphasis added)). In another example, Slepnev discloses using a display monitor as part of an apparatus for detecting and quantifying polynucleotides. U.S. Patent Publication 2012/0100600 (“Slepnev”) ¶ 141 (“In one embodiment, the data generation

<u>'797 Claim Element¹</u>	<u>Invalidity Analysis</u>
	device comprises a signal detector, a display monitor and a computer processor coupled to the control circuit and the display monitor.”).
19[p]. A system comprising:	To the extent the preamble is limiting, Jouvenot discloses it and the remaining elements of claim 19 (<i>see</i> below, each element recited in claim 19).
[19a] a processor;	<i>See</i> claim [1c].
[19b] a display; and	<i>See</i> claim [18a].
[19c] a non-transitory computer readable medium storing instructions thereon that, when executed by the processor, cause the processor to:	Jouvenot’s processor uses a non-transitory computer readable medium storing instructions thereon to execute the system’s functions. <i>See</i> Jouvenot 12:58–62; <i>see</i> Provisional App. 61/507,082 at 11:15–16. As Jouvenot states, “[a]pparatus 60 may include a partitioning assembly, such as a droplet generator 62 (‘DG’), a thermal incubation assembly, such as a thermocycler 64 (‘TC’), 15 a detection assembly (a detector) 66 (‘DET’), and a data processing assembly (a processor) 68 (‘PROC’), or any combination thereof, among others. The data processing assembly may be, or may be included in, a controller that communicates with and controls operation of any suitable combination of the assemblies.” Provisional App. 61/507,082 at 11:13–18
[19d] obtain cumulative signal data from a digital PCR instrument with a sample volume,	As explained above in connection with claim [1a], Jouvenot’s system includes a sample chamber or sample volume. Jouvenot discloses that its system is one for the generation and detection of cumulative signal data from a digital PCR instrument. For instance, Example 1 of Jouvenot pertains to “Digital PCR Assays with Multiplexed Detection in the Same Channel.” Provisional App. 61/507,082 at 12:15; <i>see also id.</i> at 14:17-18 (“Figure 4 shows an exemplary graph 102 of data corresponding to an exemplary digital PCR assay for Target 1 and Target 2 performed in droplets.”); <i>id.</i> at 16:8 (“Digital PCR Assay to

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	Assess Copy Number of C61.”); <i>id.</i> at 17:2-3 (“Figure 5 shows intensity in the FAM channel plotted as a function of intensity in the VIC channel for each droplet in a digital PCR assay....”); <i>id.</i> at 19:4-6 (“Like 5 Figure 5, Figure 7 shows intensity in the FAM channel plotted as a function of intensity in the VIC channel for each droplet in a digital PCR assay.”).
[19d.1] the digital PCR instrument comprising a light source and a multichannel detector with C channels,	The system disclosed in Jouvenot includes a digital PCR instrument with a light source and a multidetector channel with C channels. Figure 3 discloses a schematic view of targets being identified via emitted light using a multichannel detector within a digital PCR instrument. Jouvenot 2:39-44; Provisional App. 61/507,082 at 3:14–17. Fig. 3  As Jouvenot explains, its system is based on the detection of fluorescence. <i>See</i> Jouvenot 13:46–51; Provisional App. 61/507,082 at 13:10-13 (“Fluorophores 92, 94, which may be the same or different, 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).”). Those of skill in the art understand that such

<u>'797 Claim Element¹</u>	<u>Invalidity Analysis</u>
	systems based on the use of fluorescence require a light source for excitation of the fluorophores. <i>See, e.g.</i>, Maltezos ¶ 132 (“Optical measurement devices are known in the art. Generally, the measuring optic includes a light source.”).
[19d.2] and the sample volume comprising M fluorescently labeled polynucleotide analytes;	Jouvenot discloses sample targets (i.e., M analytes) and uses fluorescence to distinguish between targets. <i>See, e.g.</i>, Jouvenot 13:40-50; Provisional App. 61/507,082 at 13:5–13 (“Each oligonucleotide may provide target specificity by hybridization predominantly or at least substantially exclusively to only one of the two targets. Hybridization of the oligonucleotide to its corresponding target is illustrated schematically at 98. The signals may be distinguishable because an aspect of the fluorescence is different for one fluorophore than for the other fluorophore(s).”). Jouvenot Figure 3 further discloses the use of fluorescently labeled polynucleotide analytes wherein the targets are hybridized to fluorescently labeled probes. Fig. 3  The diagram illustrates two horizontal lines representing 'Target 1' and 'Target 2'. Target 1 is labeled with '80' at its left end. Target 2 is labeled with '82' at its left end. Above Target 1, a hatched circle labeled '92' (Probe 1) is hybridized to the target line at position '88'. To its right, a solid black circle labeled '96' is hybridized at position '98'. An arrow labeled '84' points from the probe 92 towards the probe 96. Above Target 2, a hatched circle labeled '94' (Probe 2) is hybridized to the target line at position '90'. To its right, a solid black circle labeled '96' is hybridized at position '98'. An arrow labeled '86' points from the probe 94 towards the probe 96.

<u>'797 Claim Element¹</u>	<u>Invalidity Analysis</u>
[19e] apply a decoding matrix to the cumulative signal data to unambiguously determine the presence or absence of at least each of the M fluorescently labeled polynucleotide analytes	<i>See</i> claim [1c.1].
[19f] by associating, for each fluorescently labeled polynucleotide analyte, a first value in a first component of the cumulative signal data and a second value in a second component of the cumulative signal data, wherein each first value is an intensity or range of intensities and each second value is a wavelength or a range of wavelengths,	<i>See</i> claims [1b.1]-[1b.4], [1c.1]-[1c.4].
[19g] wherein for a positive integer M, $M=C*\log_2 (F+1)$,	<i>See</i> claim [1d].
[19h] F is the maximum cumulative intensity of the first component of the cumulative signal data, for any second value, when all of the analytes are present,	<i>See</i> claim [1d.1].
[19i] M, C, and F are each positive integers, and	<i>See</i> claim [1d]-[1d.2].

<u>'797 Claim Element¹</u>	<u>Invalidity Analysis</u>
[19j] wherein F+1 is a positive integer and wherein F+1 is a power of 2; and	<i>See</i> claim [1d.3].
[19k] plot, on the display, a representation of the first value and the second value	<i>See</i> claim [18a].
[19l] wherein the cumulative signal data comprises:	<i>See</i> claims [1b.1]-[1b.4], [1c.1].
[19m.1] a first electromagnetic signal at a first wavelength from the sample volume, the first electromagnetic signal generated by excitement of a first fluorescently labeled polynucleotide analyte of the six fluorescently labeled polynucleotide analytes;	<i>See</i> claims [1b.1]-[1b.4], [1c.1], [2b].
[19m.2] a second electromagnetic signal at a second wavelength from the sample volume, the second electromagnetic signal generated by excitement of a second fluorescently labeled polynucleotide analyte of the six fluorescently labeled polynucleotide analytes;	<i>See</i> claims [1b.1]-[1b.4], [1c.1], [2b].

<u>'797 Claim Element¹</u>	<u>Invalidity Analysis</u>
[19m.3] a third electromagnetic signal at a third wavelength from the sample volume, the third electromagnetic signal generated by excitement of a third fluorescently labeled polynucleotide analyte of the six fluorescently labeled polynucleotide analytes;	<i>See</i> claims [1b.1]-[1b.4], [1c.1], [2b].
[19m.4] a fourth electromagnetic signal at a fourth wavelength from the sample volume, the fourth electromagnetic signal generated by excitement of a fourth first fluorescently labeled polynucleotide analyte of the six fluorescently labeled polynucleotide analytes; and	<i>See</i> claims [1b.1]-[1b.4], [1c.1], [2b].
[19n] wherein the second values comprise the first, second, third, and fourth wavelengths, and	<i>See</i> claim [1c.3].
[19o] the determination is made without immobilization, mass spectrometry or melting curve analysis.	<i>See</i> claim [1c.4]
21[p]. The system of claim 19,	<i>See</i> claim 19.

<u>'797 Claim Element¹</u>	<u>Invalidity Analysis</u>
[21a] wherein F=3.	<i>See</i> claim [5a].

Appendix B

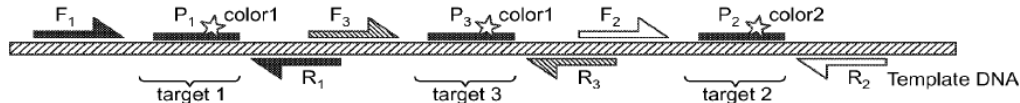
Invalidity of U.S. Patent No. 12,168,797

by U.S. Patent Publication 2011/0250597A1 (“Larson”)

Based upon the claim interpretations Plaintiffs appear to be asserting and the applications of those interpretations to Bio-Rad’s products in Plaintiffs’ Patent Local Rule infringement contentions, Larson anticipates and/or renders obvious, alone or in combination with other prior art identified in Bio-Rad’s Patent Local Rule invalidity contentions, the Asserted Claims at least as described by illustrative examples, below. These invalidity contentions are not an admission by Bio-Rad that the Accused Products, including any current or past versions of such products are covered by, or infringe these claims, particularly when they are properly construed. Nothing in these contentions should be interpreted as acquiescence to an assertion of a particular claim construction by Plaintiffs.

For all limitations in the asserted claims, to the extent the Larson and/or other cited prior art is argued by Plaintiffs or found by the Court to not explicitly teach certain limitations in the asserted claims, such limitations would have been inherent and/or obvious as described in Bio-Rad’s invalidity contentions.

By way of summary, and as set forth in more detail in the chart below, Larson Figure 11 and accompanying text teaches an intensity multiplexing encoding scheme that can distinguish between all combinations of two different targets using only a single color. A lowest intensity corresponds to no targets, a first higher intensity corresponds to a first target, a second even higher intensity corresponds to a second target, and a final highest intensity corresponds to the combination of both targets being present. Moreover, Larson repeatedly contemplates the use of multiple colors at the same time. Thus, Larson teaches, or at least renders obvious, using its intensity multiplexing approach for the detection of all combinations of two droplets with multiple colors. As Larson teaches, or at least renders obvious, for each such color, one can analyze two distinct targets and determine precisely which combination of these two targets is present in a droplet. This is the exact type of single-color coding scheme that Plaintiffs contend satisfies the claims in their infringement contentions. To the extent the claims are interpreted to require that the progression of signals for the different combinations of targets exactly follows the progression 0, 1, 2, and 3, this is contrary to Plaintiff’s infringement contentions. Regardless, to the extent Plaintiff contends this is not taught in Larson, it is taught in Lehnert and the person of ordinary skill would be motivated to use this approach with Larson for the reasons stated herein.

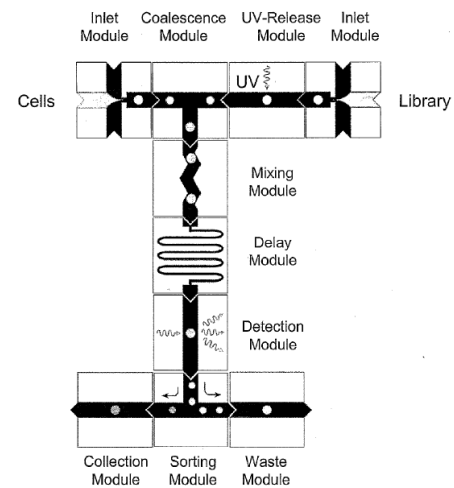
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1[p]. A system comprising:	To the extent the preamble is limiting, Larson discloses it and the remaining elements of claim 1 (<i>see</i> below, each element recited in claim 1). Larson discloses the same type of system claimed by the Asserted Claims. <i>See, e.g.</i>, Larson Abstract; Larson ¶¶ 23, 44, 64, 65, 69.
[1a] a sample chamber configured to house a sample and analyte-specific reagent mixtures of analyte-specific hybridization probes and multiple fluorophores;	Larson discloses and teaches, or at a minimum, renders obvious, a system with a sample chamber configured to house a sample and analyte-specific reagent mixtures of analyte-specific hybridization probes and multiple fluorophores. Larson ¶ 89 (“The droplets may be individually analyzed and detected using any methods known in the art, such as detecting the presence or amount of a reporter.”). The probes used in Larson “function by specific recognition of target DNA by hybridization and result in increased fluorescence on amplification of the target sequence.” Larson ¶ 93. The droplets contain the sample and use of a detector shows that the droplets are in a sample chamber configured to house a sample. <i>See id.</i> Figure 9 of Larson explains “a template DNA is amplified with three sets of primers: forward primers (F1, F2 and F3) and reverse primers (R1, R2 and R3). Probes (P1, P2 and P3) are labeled with fluorophores (color 1, color 2 and color 1) and bind to the target genetic sequences (target 1, target 2 and target 3) (Panels B and C).” Larson ¶ 121. FIG. 9A Two Colors THREE Targets 

¹ Bracketed elements are added.

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	Larson incorporates by reference Link et al. (U.S. publication numbers 2008/0014589, 2008/0003142, and 2010/0137163) and European publication number EP2047910 (collectively, “the Link Publications”) to describe additional detection modules and methods of detecting amplification. <i>See</i> Larson ¶¶ 89–93, 98, 197. For example, the Link Publications disclose detection apparatuses which “cooperate to detect a signal representative of a characteristic, marker, or reporter...” U.S. Patent Publication 2008/0003142 (“Link ’142”) ¶ 204; U.S. Patent Publication 2010/0137163 (“Link ’163”) ¶ 148. The Link Publications further teach using a detection module for identification or measurement within a droplet. Link ’142 ¶ 89; Link ’589 ¶ 103; Link ’163 ¶ 65. In the Link Publications, a Detection Module is a location in the device where small molecules are to be detected, identified, measured, etc. based on at least on predetermined characteristic. <i>See e.g.</i>, Link ’142 ¶¶ 148–169; Link ’142 ¶¶ 204–207; Link ’589 ¶¶ 219–222. Figure 1 of the Link ’163 publication shows an example of such detection module:

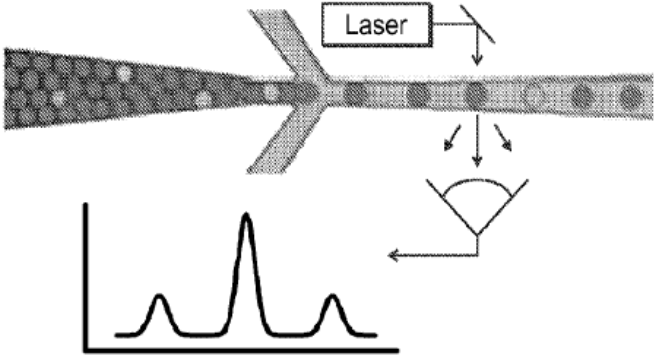
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See id. ¶¶ 17, 41.

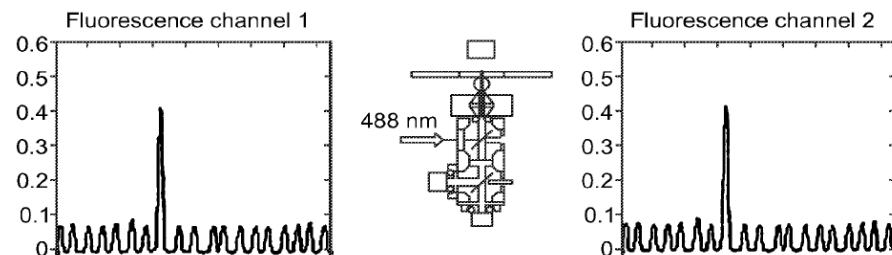
Further, Larson Figure 3c discloses detection of from individual droplets, establishing the existence of a sample chamber.

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	FIG. 3c  <i>See id.</i> ¶ 97 (“Droplets were analyzed by fluorescence while flowing through the readout chip to count the number of PCR(+) and PCR(-) droplets (See FIG. 3c”); <i>see also id.</i> ¶¶ 23, 95 (explaining that 3c depicts a cartoon of a droplet readout by fluorescence).
[1b] a multi-channel detector to detect:	Larson teaches, or at a minimum, renders obvious, multiple forms of target detection, including using a multi-channel detector for detection. Larson ¶ 89 (“The droplets may be individually analyzed and detected using any methods known in the art....”). Larson’s “Instrumentation” section discloses using band pass filters to discriminate between FAM and VIC fluorophores and using two photomultipliers to detect fluorescence. Larson ¶ 195. As an example, Figure 8c is a schematic that depicts multi-color detection.

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FIG. 8C



Additionally, Figure 3 of the Link '163 application, which Larson incorporates by reference, discloses simultaneous two color fluorescence detection:

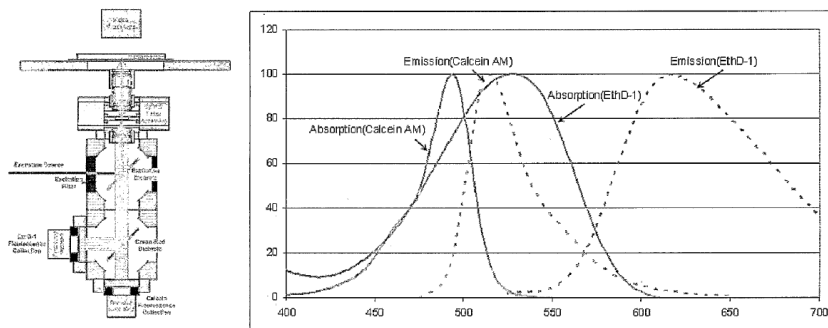


Fig. 3

See also Link '163 ¶ 211 ("FIG. 3 indicated the changes required to convert the single fluorophore station to a two color fluorescence station. The calcein fluorescence can be

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	collected using filters designed for fluorescein detection, while the EthD-1 can be monitored using filters designed for propidium iodide or Texas Red.”). Larson further states, “it is anticipated that greater numbers of colors will be used for both multiplexing and optical labels.” Larson ¶ 166. Accordingly, “embodiments of the invention include histograms of dimensionality greater than two, such as 3, or 4, or up to 10, or up to 20. Histograms of dimensionality greater than 20 are also incorporated into the invention” Larson ¶ 166. Thus, Larson is not limited to two channels and contemplates more than two channels.
[1b.1] 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;	Larson teaches, or at a minimum, renders obvious, the detection from the sample chamber of four electromagnetic signals at four wavelengths from each of four fluorophores. Larson states, “it is anticipated that greater numbers of colors will be used for both multiplexing and optical labels.” Larson ¶ 166. Accordingly, “embodiments of the invention include histograms of dimensionality greater than two, such as 3, or 4, or up to 10, or up to 20. Histograms of dimensionality greater than 20 are also incorporated into the invention” Larson ¶ 166. A person of skill in the art would understand that this encompasses the use of at least four channels and fluorophores. Indeed, Larson teaches that “[e]mbodiments of the invention include optical labels comprised of 1 fluorophore, or 2 fluorophores, or 3 fluorophores, or 4 fluorophores, or up to 10 fluorophores, or up to 20 fluorophores. Optical labels can also comprise more than 20 fluorophores.” Larson ¶ 162. Moreover, Larson discloses using multiple wavelengths. Larson ¶ 139 (“the maximum number of different colors possible is limited by spectral overlap between fluorescence emission of the different fluorophores. The maximum number of colors can be 1, or 2, or 3, or 4, or up to 10, or up to 20. The maximum number of colors can be higher than 20.”).

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Larson has multiple visual representations of scenarios where signals are generated by the excitement of particular fluorophores, including in Figure 15:

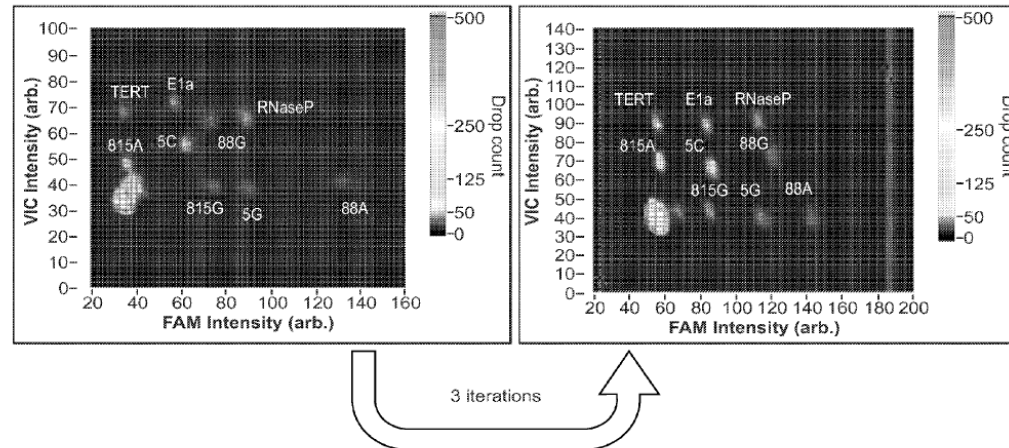


FIG. 15

See id. at Figures 5, 6, 8–10, 12, 14, 17–22; *see also* Link '163 at Figure 3.

To the extent Larson is deemed to not expressly disclose four or more wavelength signals from four or more fluorophores, this would have nonetheless been obvious in view of Larson. As explained above, Larson encourages using a greater number of colors for additional optical labeling. It shows precisely this in actual experimental data. A skilled artisan would have been motivated to use four or more color channels because he or she would have been motivated to detect larger numbers of targets at the same time. A POSA would have had a reasonable expectation of successfully extending Larson to five or more wavelength channels and fluorophores—particularly in light of its suggestion that even more than 20 colors can be used—because this would reflect nothing more than the use of multiple types of well-known fluorophores

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	and that could be detected using well-known instrumentation for the detection of multiple optical signals.
[1b.2] 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;	Larson teaches, or at a minimum, renders obvious, the detection from the sample chamber of four electromagnetic signals at four wavelengths from each of four fluorophores. Larson states, “it is anticipated that greater numbers of colors will be used for both multiplexing and optical labels.” Larson ¶ 166. Accordingly, “embodiments of the invention include histograms of dimensionality greater than two, such as 3, or 4, or up to 10, or up to 20. Histograms of dimensionality greater than 20 are also incorporated into the invention” Larson ¶ 166. A person of skill in the art would understand that this encompasses the use of at least four channels and fluorophores. Indeed, Larson teaches that “[e]mbodiments of the invention include optical labels comprised of 1 fluorophore, or 2 fluorophores, or 3 fluorophores, or 4 fluorophores, or up to 10 fluorophores, or up to 20 fluorophores. Optical labels can also comprise more than 20 fluorophores.” Larson ¶ 162. Moreover, Larson discloses using multiple wavelengths. Larson ¶ 139 (“the maximum number of different colors possible is limited by spectral overlap between fluorescence emission of the different fluorophores. The maximum number of colors can be 1, or 2, or 3, or 4, or up to 10, or up to 20. The maximum number of colors can be higher than 20.”). Larson has multiple visual representations of scenarios where signals are generated by the excitement of particular fluorophores, including in Figure 15:

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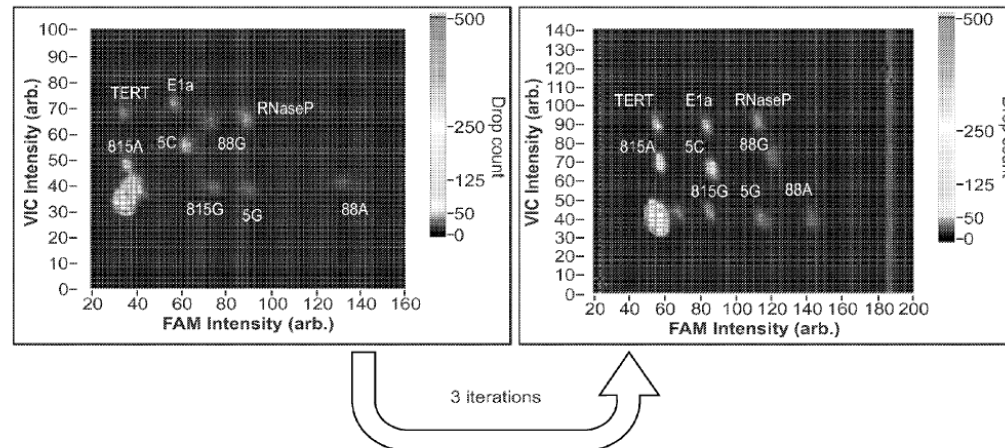


FIG. 15

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[1b.3] 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;	Larson teaches, or at a minimum, renders obvious, the detection from the sample chamber of four electromagnetic signals at four wavelengths from each of four fluorophores. Larson states, “it is anticipated that greater numbers of colors will be used for both multiplexing and optical labels.” Larson ¶ 166. Accordingly, “embodiments of the invention include histograms of dimensionality greater than two, such as 3, or 4, or up to 10, or up to 20. Histograms of dimensionality greater than 20 are also incorporated into the invention” Larson ¶ 166. “Embodiments of the invention include optical labels comprised of 1 fluorophore, or 2 fluorophores, or 3 fluorophores, or 4 fluorophores, or up to 10 fluorophores, or up to 20 fluorophores. Optical labels can also comprise more than 20 fluorophores.” Larson ¶ 162. Moreover, Larson discloses using multiple wavelengths. Larson ¶ 139 (“the maximum number of different colors possible is limited by spectral overlap between fluorescence emission of the different fluorophores. The maximum number of colors can be 1, or 2, or 3, or 4, or up to 10, or up to 20. The maximum number of colors can be higher than 20.”). Larson has multiple visual representations of scenarios where signals are generated by the excitement of particular fluorophores, including in Figure 15:

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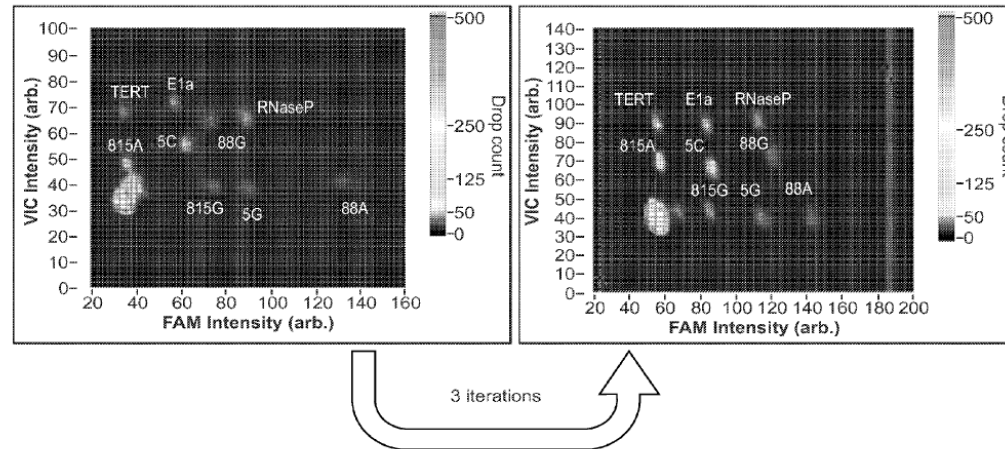


FIG. 15

See id. at Figures 5, 6, 8–10, 12, 14, 17–22; *see also* Link '163 at Figure 3.

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[1b.4] 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;	Larson teaches or at a minimum, renders obvious, the detection from the sample chamber of four electromagnetic signals at four wavelengths from each of four fluorophores. Larson states, “it is anticipated that greater numbers of colors will be used for both multiplexing and optical labels.” Larson ¶ 166. Accordingly, “embodiments of the invention include histograms of dimensionality greater than two, such as 3, or 4, or up to 10, or up to 20. Histograms of dimensionality greater than 20 are also incorporated into the invention” Larson ¶ 166. “Embodiments of the invention include optical labels comprised of 1 fluorophore, or 2 fluorophores, or 3 fluorophores, or 4 fluorophores, or up to 10 fluorophores, or up to 20 fluorophores. Optical labels can also comprise more than 20 fluorophores.” Larson ¶ 162. Moreover, Larson discloses using multiple wavelengths. Larson ¶ 139 (“the maximum number of different colors possible is limited by spectral overlap between fluorescence emission of the different fluorophores. The maximum number of colors can be 1, or 2, or 3, or 4, or up to 10, or up to 20. The maximum number of colors can be higher than 20.”). Larson has multiple visual representations of scenarios where signals are generated by the excitement of particular fluorophores, including in Figure 15:

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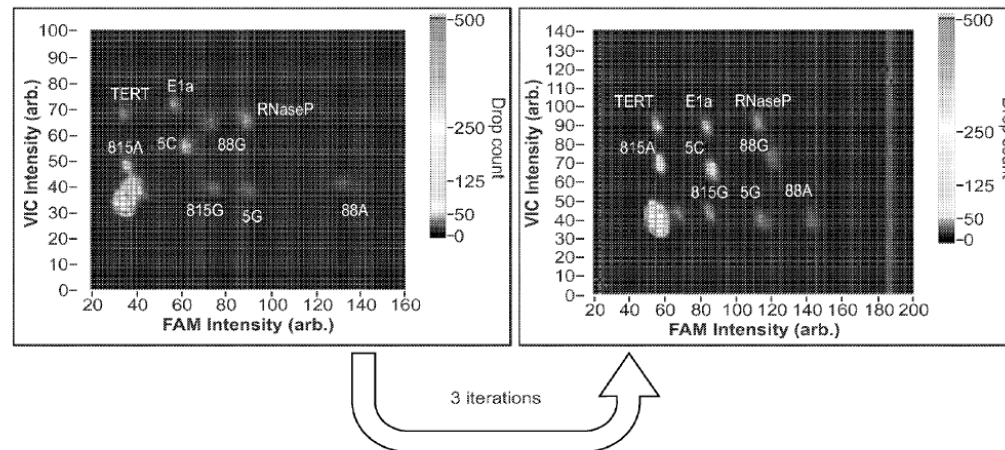


FIG. 15

See id. at Figures 5, 6, 8–10, 12, 14, 17–22; *see also* Link '163 at Figure 3.

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[1c] a processor controlled analyzer to	Larson discloses, or at a minimum, renders obvious, the use of a processor controlled analyzer (i.e., a computer). Larson ¶ 89 (“suitable detection apparatuses include optical waveguides, microscopes, diodes, light stimulating devices, (e.g., lasers), photo multiplier tubes, and processors (e.g., computers and software), and combinations thereof, which cooperate to detect a signal representative of a characteristic, marker, or reporter. . .”); <i>see also</i> Larson ¶ 196. Larson further notes that a USB-6259 data acquisition card was used to record fluorescence and that the data traces were smoothed by a seven-point, second-order Savitzky-Golay algorithm before subsequent analysis. Larson ¶ 195. The Link Publications also disclose using detection apparatuses with processors to analyze signals. <i>See, e.g.</i>, Link ¶ 148.
[1c.1] 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	As discussed above, Larson teaches, or at a minimum, renders obvious, the use of four electromagnetic wavelength signals. And Larson likewise teaches a processor that receives and analyzes signals from the target molecules. Larson further teaches application of a decoding matrix to unambiguously detect the presence of at least each of M analytes. For example, the analytes (BCKDHA and SMN2) were accurately and precisely detected with a “an excellent linear fit ($y=1.01x$) across the full range. . .” Larson ¶ 131. Thus, detection of analytes was unambiguous in Larson and a decoding matrix was applied to the cumulative signals at each intensity to accurately map each analyte. <i>Id</i>

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Figure 11 (including 11a and 11b) of Larson discloses receiving a signal based on a cumulative electromagnetic signal and applying a decoding matrix to that signal to unambiguously detect the presence or absence of at least each of certain number of analytes:

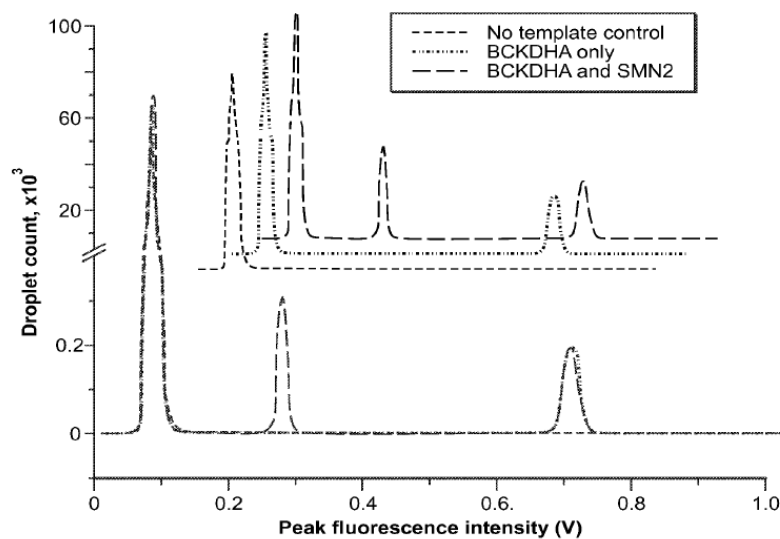
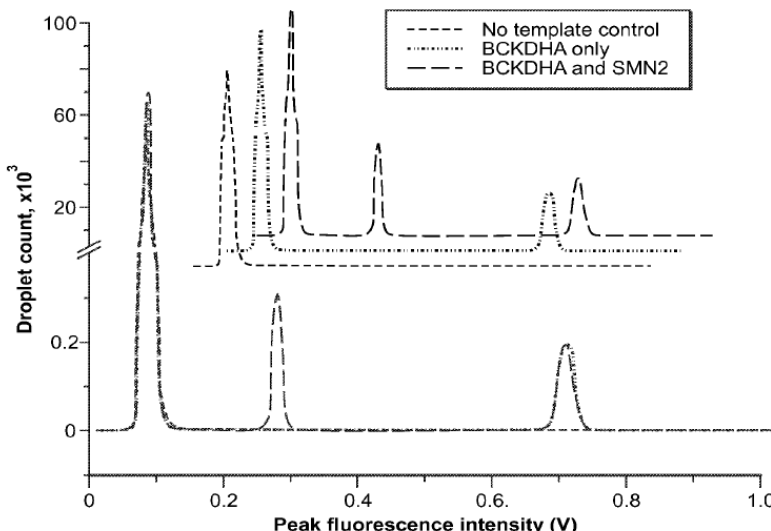


FIG. 11a

In particular, Figure 11a depicts a histogram of droplet peak fluorescence intensities. Larson ¶ 31. The small-dash line in Figure 11a represents a no template control, the dotted line represents BCKDHA and the large-dashed line represents a 1:1 ratio of BCKDHA to SMN2. Larson ¶ 131. With respect to the large-dashed line, Larson notes that three populations were readily apparent. A dominant feature appeared at 0.08 V and two smaller peaks appeared at 0.27 and 0.71 V. A very small peak appeared at ~0.9V that was not visible on the scale of Figure 11a. The .08 V peak represented

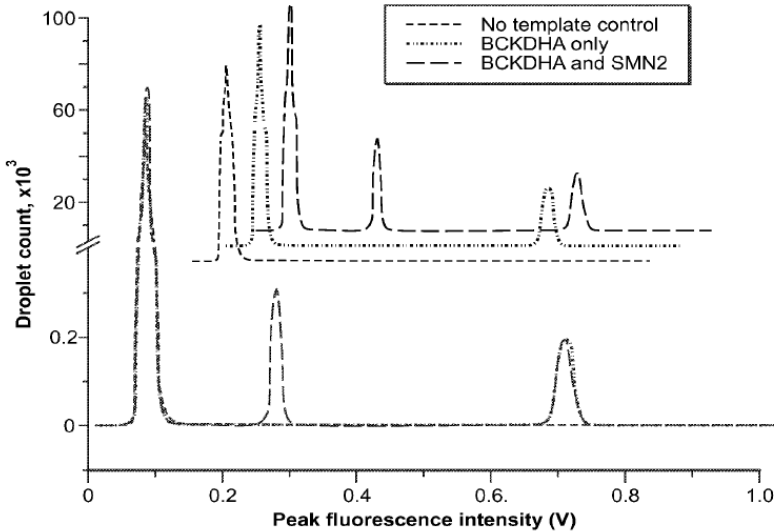
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	droplets that were negative for both BCKDHA and SMN2 and also corresponds to a representative cumulative intensity of 0. The peak at 0.71 V represented BCKDHA positive samples, and the peak at .27 V represented subsequent addition of SMN2. These two peaks represent a cumulative intensity of 1 and 2 respectively. Finally, the peak at 0.9 V corresponds to droplets occupied by both genes and represents a cumulative intensity of 3. Larson ¶ 131. Thus, Larson teaches a technique for using a decoding matrix wherein the intensity of light emitted from droplets is used to to encode which of any combination of two targets are present in a droplet (<i>i.e.</i>, lowest intensity corresponds to no targets, next highest intensity is first target, next highest intensity is second target, and highest intensity is both first and second targets). As noted above, Larson further teaches the use of multiple colors and it would have been obvious to use this same form of decoding matrix at multiple colors to detect a larger number of colors. The processor in Larson is also configured to receive signals from the detector. In Larson, a USB-6259 data acquisition card received a cumulative signal detected by photomultipliers and with VIC and FAM discriminated by using band pass filters. <i>See</i> Larson ¶ 195. Custom software was used to interpret the cumulative signal data. Larson ¶ 196. As additional support for the claimed decoding matrix, Larson also discloses the use of histogram-based data presentation and analysis for characterizing populations using both color and intensity. Larson ¶ 166. This constitutes applying a decoding matrix based on the cumulative signals to unambiguously detect analytes. To the extent that this is not an explicit disclosure of applying a decoding matrix to a cumulative signal received from a first, second, third, and fourth electromagnetic signal, it would have been obvious for a POSA to do so based on what Larson discloses.
[1c.2] by associating, for each analyte, a first value in a first component of the cumulative signal and a second value in a	Larson discloses associating for each analyte a first value in a first component of a cumulative signal (<i>i.e.</i> , intensity) with a second value (<i>i.e.</i> , wavelength) in a second

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second component of the cumulative signal,	component of a cumulative signal. For example, in Figure 11, the peak fluorescent intensity is used to distinguish analytes:  FIG. 11a In particular, Figure 11a depicts a histogram of droplet peak fluorescence intensities. Larson ¶ 31. The small-dash line in Figure 11a represents a no template control, the dotted line represents BCKDHA and the large-dashed line represents a 1:1 ratio of BCKDHA to SMN2. Larson ¶ 131. With respect to the large-dashed line, Larson notes that three populations were readily apparent. A dominant feature appeared at 0.08 V and two smaller peaks appeared at 0.27 and 0.71 V. A very small peak appeared at ~0.9V that was not visible on the scale of Figure 11a. The .08 V peak represented droplets that were negative for both BCKDHA and SMN2 and also corresponds to a

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	representative cumulative intensity of 0. The peak at 0.71 V represented BCKDHA positive samples, and the peak at .27 V represented subsequent addition of SMN2. These two peaks represent a cumulative intensity of 1 and 2 respectively. Finally, the peak at 0.9 V corresponds to droplets occupied by both genes and represents a cumulative intensity of 3. Larson ¶ 131. Thus, Larson teaches a technique for using a decoding matrix wherein the intensity of light emitted from droplets is used to to encode which of any combination of two targets are present in a droplet (<i>i.e.</i>, lowest intensity corresponds to no targets, next highest intensity is first target, next highest intensity is second target, and highest intensity is both first and second targets). As noted above, Larson further teaches the use of multiple colors and it would have been obvious to use this same form of decoding matrix at multiple colors to detect a larger number of colors. The analytes (BCKDHA and SMN2) were accurately and precisely detected with a “an excellent linear fit ($y=1.01x$) across the full range. . .” Larson ¶ 131. Thus, detection of analytes was unambiguous in Larson and a decoding matrix was applied to the cumulative signals at each intensity to accurately map each analyte. <i>Id.</i> As additional support for associating each analyte with a first value in a first component of a cumulative signal with a second value in a second component of a cumulative signal, Larson discloses using histogram-based data presentation and analysis for characterizing populations using both color and intensity. Larson ¶ 166. To the extent that this is not an explicit disclosure associating for each analyte a first value in a first component of a cumulative signal (<i>i.e.</i>, intensity) with a second value (<i>i.e.</i>, wavelength) in a second component of a cumulative signal, it would have been obvious for a POSA to do so based on what Larson discloses.
[1c.3] 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	Larson discloses detecting a first value based on intensity or a range of intensities and a second value based on wavelength or a range of wavelengths and expanding that concept to a first, second, third, fourth, etc. wavelength.

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values comprise the first, second, third, and fourth wavelengths, and	FIG. 11a Figure 11a depicts a histogram of droplet peak fluorescence intensities. Larson ¶ 31. The small-dash line in Figure 11a represents a no template control, the dotted line represents BCKDHA and the large-dashed line represents a 1:1 ratio of BCKDHA to SMN2. Larson ¶ 131. With respect to the large-dashed line, Larson notes that three populations were readily apparent. A dominant feature appeared at 0.08 V and two smaller peaks appeared at 0.27 and 0.71 V. A very small peak appeared at ~0.9V that was not visible on the scale of Figure 11a. The .08 V peak represented droplets that were negative for both BCKDHA and SMN2 and also corresponds to a representative cumulative intensity of 0. The peak at 0.71 V represented BCKDHA positive samples, and the peak at .27 V represented subsequent addition of SMN2. These two peaks represent a cumulative intensity of 1 and 2 respectively. Finally, the peak at 0.9 V

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	corresponds to droplets occupied by both genes and represents a cumulative intensity of 3. Larson ¶ 131. Thus, Larson teaches a technique for using a decoding matrix wherein the intensity of light emitted from droplets is used to encode which of any combination of two targets are present in a droplet (<i>i.e.</i>, lowest intensity corresponds to no targets, next highest intensity is first target, next highest intensity is second target, and highest intensity is both first and second targets). As noted above, Larson further teaches the use of multiple colors and it would have been obvious to use this same form of decoding matrix at multiple colors to detect a larger number of colors. Moreover, as optical signals, each intensity also has a wavelength or range of wavelengths and it would have been obvious based on other disclosures in Larson to expand this to a first, second, third, and fourth wavelength. Larson ¶ 166 (“it is anticipated that greater numbers of colors will be used for both multiplexing and optical labels” and “embodiments of the invention include histograms of dimensionality greater than two, such as 3, or 4, or up to 10, or up to 20. Histograms of dimensionality greater than 20 are also incorporated into the invention.”); <i>see also</i> Larson ¶ 139 (“the maximum number of different colors possible is limited by spectral overlap between fluorescence emission of the different fluorophores. The maximum number of colors can be 1, or 2, or 3, or 4, or up to 10, or up to 20. The maximum number of colors can be higher than 20.”). Larson also notes that adding additional colors increase detection capabilities even further. Larson ¶ 153.
[1c.4] the determination is made without immobilization, mass spectrometry or melting curve analysis;	Larson does not require immobilization, mass spectrometry, or melting curve analysis and makes no suggestions that these are necessary to the determination. For the detection and analysis of targets, Larson further notes that “droplets may be individually analyzed and detected using any methods known in the art, such as detecting the presence or amount of a reporter.” Larson ¶ 89.
[1d] wherein for the positive integer M, $M=C*\log_2 (F+1)$,	Larson matches the claimed mathematical formula, or at a minimum, renders it obvious. In particular, Larson notes that using multiple colors in addition to intensity,

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	allows the number of possible reactions to scale geometrically instead of linearly. Larson ¶ 47. Larson also discloses methods that match the claimed formula. In one embodiment, disclosed in Figure 11, the number of analytes is 3:  FIG. 11a The peak at 0.08 V represents intensity zero and represents 0 analytes; the peak at 0.27 V represents an intensity of 1 and the presence of SMN2; the peak at 0.71 V represents an intensity of 2 and the presence of BCKDHA; the peak at 0.90 represents a <i>cumulative intensity</i> of 3 and the presence of both analytes. Accordingly, $F=3$ in Figure 11a, which involves a single color and a maximum cumulative intensity of 3. Thus, $M=(1) * \log_2(3+1)$, or $M=2$. Accordingly, with a single color (C), three analytes, and a cumulative maximum intensity of 3, Larson Figure 11 satisfies the claimed equation. <i>See also</i> Larson ¶ 47.

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	Further, Larson encourages the use of additional fluorophores based on both intensity and color. <i>See supra</i>, [1b.1]–[1b.4]. If these disclosures are insufficient, the claimed progression would have nonetheless been obvious based on Larson’s disclosure that the number of detectable analytes scales geometrically as intensities and the number of colors increases. To the extent one contends the individual analyte signals need to exactly follow a geometric progression of 1, 2, 4, 8... this is disclosed in European Patent Specification 0594763B1 (“Lehnen”). Lehnen discloses the use of binary (power-of-2) encoding (1:2:4:8) and discusses multiplexing capacity as a function of channels and intensity levels, which is mathematically equivalent to the formula. <i>See</i> Lehnen at 13:15–53. More specifically, each analyte is encoded using the unique proportions of bead subpopulations and powers of two to ensure that each possible combination yields a unique sum. A POSA would be motivated to use this signal progression because the proportions allow for unique interpretation and unambiguous identification of analytes, as Lehnen expressly teaches. <i>See</i> Lehnen at 13:31–35. A POSA would have a reasonable expectation of using this approach because POSA would have known how to modulate the intensity from a target-specific probe. Larson expressly teaches multiple such methods for doing this. As an example, “[t]he one or more groups of probes can include the same detectable label which will vary in intensity upon detection, due to the varying probe concentrations.” Larson ¶ 91.
[1d.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	In at least Larson Figure 4, F is positive and equal to the maximum cumulative intensity of the first component (i.e., intensity) of a signal for a given wavelength when all analytes are present.

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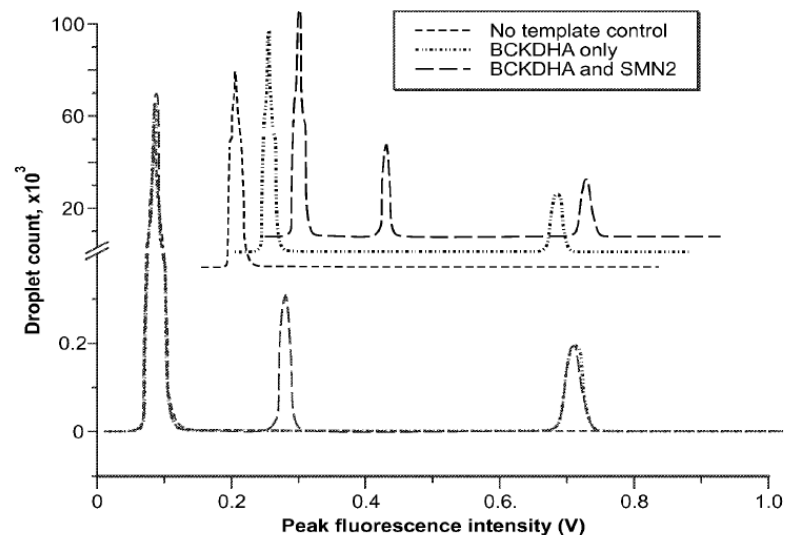
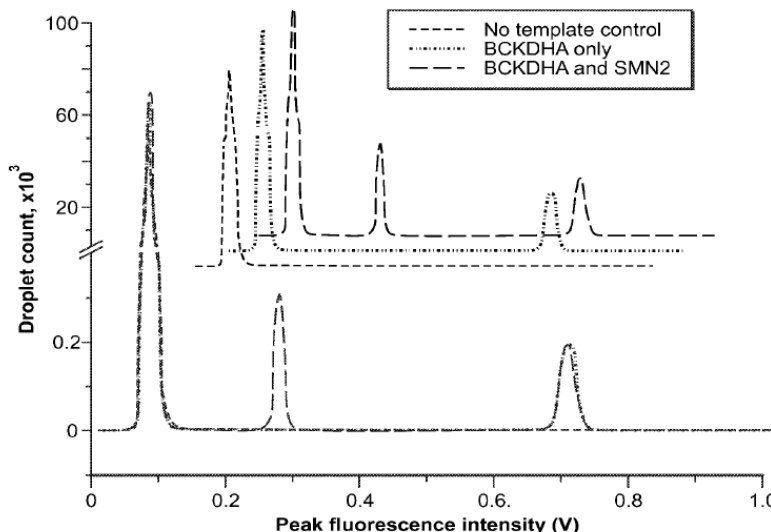


FIG. 11a

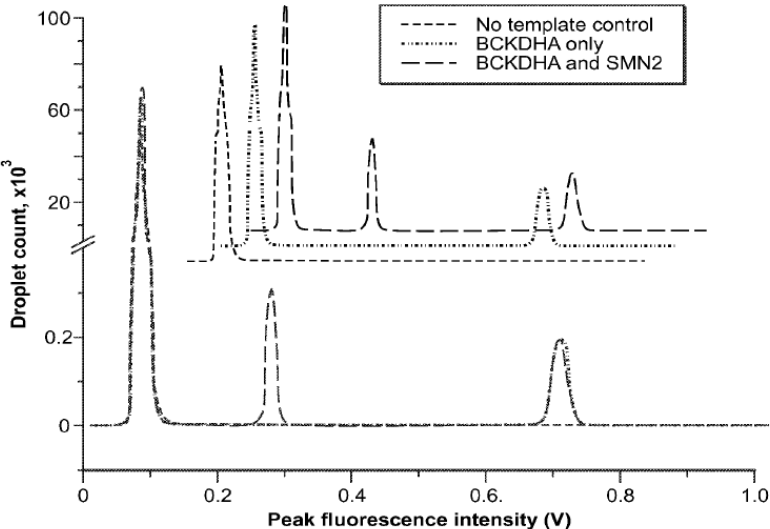
The small-dash line in Figure 11a represents a no template control, the dotted line represents BCKDHA and the large-dash line represents a 1:1 ratio of BCKDHA to SMN2. Larson ¶ 131. With respect to the large-dash line, Larson notes that three populations were readily apparent. A dominant feature appeared at 0.08 V and two smaller peaks appeared at 0.27 and 0.71 V. A very small peak appeared at ~0.9V that was not visible on the scale of Figure 11a. The .08 V peak represented droplets that were negative for both BCKDHA and SMN2 and also corresponds to a representative cumulative intensity of 0. The peak at 0.71 V represented BCKDHA positive samples, and the peak at .27 V represented subsequent addition of SMN2. These two peaks represent a cumulative intensity of 1 and 2 respectively. Finally, the peak at 0.9 V

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	corresponds to droplets occupied by both genes and represents a cumulative intensity of 3. Larson ¶ 131. Thus, Larson teaches a technique for using a decoding matrix wherein the intensity of light emitted from droplets is used to encode which of any combination of two targets are present in a droplet (<i>i.e.</i>, lowest intensity corresponds to no targets, next highest intensity is first target, next highest intensity is second target, and highest intensity is both first and second targets). To the extent one contends the individual analyte signals need to exactly follow a geometric progression of 1, 2, 4, 8... this is disclosed in Lehnert. Lehnert discloses the use of binary (power-of-2) encoding (1:2:4:8) and discusses multiplexing capacity as a function of channels and intensity levels, which is mathematically equivalent to the formula. See Lehnert at 13:15–53. More specifically, each analyte is encoded using the unique proportions of bead subpopulations and powers of two to ensure that each possible combination yields a unique sum. A POSA would be motivated to use this signal progression because the proportions allow for unique interpretation and unambiguous identification of analytes, as Lehnert expressly teaches. See Lehnert at 13:31–35. A POSA would have a reasonable expectation of using this approach because POSA would have known how to modulate the intensity from a target-specific probe. Larson expressly teaches multiple such methods for doing this. As an example, “[t]he one or more groups of probes can include the same detectable label which will vary in intensity upon detection, due to the varying probe concentrations.” Larson ¶ 91.
[1d.2] C=4, 5, or 6; and	Larson discloses using 4, 5, or 6 different wavelengths as part of a detection system. Larson ¶ 139 (“the maximum number of different colors possible is limited by spectral overlap between fluorescence emission of the different fluorophores. The maximum number of colors can be 1, or 2, or 3, or 4, or up to 10, or up to 20. The maximum number of colors can be higher than 20.”). Larson further states, “it is anticipated that greater numbers of colors will be used for both multiplexing and optical labels.” Larson ¶ 166. Accordingly, “embodiments of

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	the invention include histograms of dimensionality greater than two, such as 3, or 4, or up to 10, or up to 20. Histograms of dimensionality greater than 20 are also incorporated into the invention” Larson ¶ 166. To the extent C=4, 5, or 6 is not explicitly disclosed, this would have nonetheless been obvious in view of Larson. As explained above, Laron encourages using a greater number of colors for additional optical labeling. It shows precisely this in actual experimental data. A skilled artisan would have been motivated to use four or more color channels because he or she would have been motivated to detect larger numbers of targets at the same time. A POSA would have had a reasonable expectation of successfully extending Larson to five or more wavelength channels and fluorophores—particularly in light of its suggestion that even more than 20 colors can be used—because this would reflect nothing more than the use of multiple types of well-known fluorophores and that could be detected using well-known instrumentation for the detection of multiple optical signals.

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[1d.3] wherein F+1 is a positive integer and wherein F+1 is a power of 2,	In Larson, F+1 is a positive integer and F+1 is a power of 2:  FIG. 11a As an example, Larson discloses such a situation in Figure 11. The small-dash line in Figure 11a represents a no template control, the dotted line represents BCKDHA and the large-dashed line represents a 1:1 ratio of BCKDHA to SMN2. Larson ¶ 131. With respect to the large-dashed line, Larson notes that three populations were readily apparent. A dominant feature appeared at 0.08 V and two smaller peaks appeared at 0.27 and 0.71 V. A very small peak appeared at ~0.9V that was not visible on the scale of Figure 11a. The .08 V peak represented droplets that were negative for both BCKDHA and SMN2 and also corresponds to a representative cumulative intensity of 0. The peak at 0.71 V represented BCKDHA positive samples, and the peak at .27 V represented subsequent addition of SMN2. These two peaks represent a cumulative

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	intensity of 1 and 2 respectively. Finally, the peak at 0.9 V corresponds to droplets occupied by both genes and represents a cumulative intensity of 3. Larson ¶ 131. Because the cumulative intensity is 3, F+1 is 4, which is a power of two and is also a positive integer. To the extent one contends the individual analyte signals need to exactly follow a geometric progression of 1, 2, 4, 8... this is disclosed in Lehn. Lehn discloses the use of binary (power-of-2) encoding (1:2:4:8) and discusses multiplexing capacity as a function of channels and intensity levels, which is mathematically equivalent to the formula. See Lehn at 13:15–53. More specifically, each analyte is encoded using the unique proportions of bead subpopulations and powers of two to ensure that each possible combination yields a unique sum. A POSA would be motivated to use this signal progression because the proportions allow for unique interpretation and unambiguous identification of analytes, as Lehn expressly teaches. See Lehn at 13:31–35. A POSA would have a reasonable expectation of using this approach because POSA would have known how to modulate the intensity from a target-specific probe. Larson expressly teaches multiple such methods for doing this. As an example, “[t]he one or more groups of probes can include the same detectable label which will vary in intensity upon detection, due to the varying probe concentrations.” Larson ¶ 91.

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[1d.4] 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.	In at least Figure 11 of Larson, M is greater than the C:  FIG. 11a The small-dash line in Figure 11a represents a no template control, the dotted line represents BCKDHA and the large-dashed line represents a 1:1 ratio of BCKDHA to SMN2. Larson ¶ 131. With respect to the large-dashed line, Larson notes that three populations were readily apparent. A dominant feature appeared at 0.08 V and two smaller peaks appeared at 0.27 and 0.71 V. A very small peak appeared at ~0.9V that was not visible on the scale of Figure 11a. The .08 V peak represented droplets that were negative for both BCKDHA and SMN2 and also corresponds to a representative cumulative intensity of 0. The peak at 0.71 V represented BCKDHA positive samples, and the peak at .27 V represented subsequent addition of SMN2. These two peaks represent a cumulative intensity of 1 and 2 respectively. Finally, the peak at 0.9 V

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	corresponds to droplets occupied by both genes and represents a cumulative intensity of 3. Larson ¶ 131. Thus, Larson teaches a technique for using a decoding matrix wherein the intensity of light emitted from droplets is used to encode which of any combination of two targets are present in a droplet (<i>i.e.</i>, lowest intensity corresponds to no targets, next highest intensity is first target, next highest intensity is second target, and highest intensity is both first and second targets). As noted above, Larson further teaches the use of multiple colors and it would have been obvious to use this same form of decoding matrix at multiple colors to detect a larger number of colors. C is one in Figure 11, and M is three. Accordingly, M is greater than C, the detector has at least C channels, and M and C are positive integers. To the extent that C needs to be at least four, Larson discloses that 20 or more fluorophores can be used. Larson ¶ 139 (“the maximum number of different colors possible is limited by spectral overlap between fluorescence emission of the different fluorophores. The maximum number of colors can be 1, or 2, or 3, or 4, or up to 10, or up to 20. The maximum number of colors can be higher than 20.”). Accordingly, Larson suggests using at least four colors like the claim element. A POSA would know that applying four colors to the same experiment disclosed in Figure 11 would enable the detection of eight analytes. Thus, it would have been obvious to a POSA that the number of analytes would be greater than the number of colors when using four colors.
2[p]. The system of claim 1,	See claim 1.
[2a] 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	Larson teaches detection of a fifth electromagnetic signal at a fifth wavelength from a sample chamber where the fifth electromagnetic signal is generated by excitement of a fifth fluorophore of the multiple fluorophores. Larson states, “it is anticipated that greater numbers of colors will be used for both multiplexing and optical labels.” Larson ¶ 166. Accordingly, “embodiments of the

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excitement of a fifth fluorophore of the multiple fluorophores;	invention include histograms of dimensionality greater than two, such as 3, or 4, or up to 10, or up to 20. Histograms of dimensionality greater than 20 are also incorporated into the invention” Larson ¶ 166. “Embodiments of the invention include optical labels comprised of 1 fluorophore, or 2 fluorophores, or 3 fluorophores, or 4 fluorophores, or up to 10 fluorophores, or up to 20 fluorophores. Optical labels can also comprise more than 20 fluorophores.” Larson ¶ 162. Moreover, Larson discloses using multiple wavelengths. Larson ¶ 139 (“the maximum number of different colors possible is limited by spectral overlap between fluorescence emission of the different fluorophores. The maximum number of colors can be 1, or 2, or 3, or 4, or up to 10, or up to 20. The maximum number of colors can be higher than 20.”). A person of skill in the art would understand that this encompasses the use of five or more fluorophores and channels. Larson has multiple visual representations of scenarios where signals are generated by the excitement of particular fluorophores, including in Figure 15:

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Invalidity Analysis

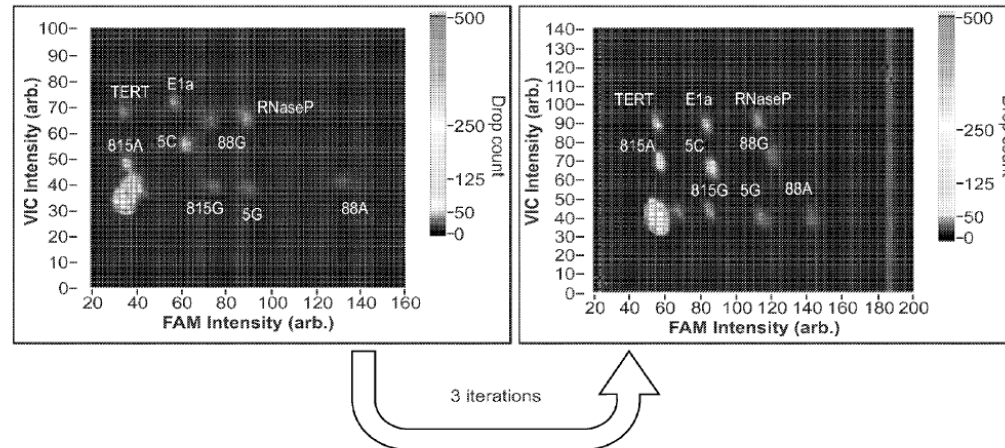


FIG. 15

See id. at Figures 5, 6, 8–10, 12, 14, 17–22; *see also* Link '163 at Figure 3.

To the extent Larson is deemed to not expressly disclose five or more wavelength signals from four or more fluorophores, this would have nonetheless been obvious in view of Larson. As explained above, Larson encourages using a greater number of colors for additional optical labeling. It shows precisely this in actual experimental data. A skilled artisan would have been motivated to use four or more color channels because he or she would have been motivated to detect larger numbers of targets at the same time. A POSA would have had a reasonable expectation of successfully extending Larson to five or more wavelength channels and fluorophores—particularly in light of its suggestion that even more than 20 colors can be used—because this would reflect nothing more than the use of multiple types of well-known fluorophores and that could be detected using well-known instrumentation for the detection of multiple optical signals.

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[2b] 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	Larson teaches detection of a sixth electromagnetic signal at a sixth wavelength from a sample chamber where the sixth electromagnetic signal is generated by excitement of a sixth fluorophore of the multiple fluorophores. Larson states, “it is anticipated that greater numbers of colors will be used for both multiplexing and optical labels.” Larson ¶ 166. Accordingly, “embodiments of the invention include histograms of dimensionality greater than two, such as 3, or 4, or up to 10, or up to 20. Histograms of dimensionality greater than 20 are also incorporated into the invention” Larson ¶ 166. “Embodiments of the invention include optical labels comprised of 1 fluorophore, or 2 fluorophores, or 3 fluorophores, or 4 fluorophores, or up to 10 fluorophores, or up to 20 fluorophores. Optical labels can also comprise more than 20 fluorophores.” Larson ¶ 162. Moreover, Larson discloses using multiple wavelengths. Larson ¶ 139 (“the maximum number of different colors possible is limited by spectral overlap between fluorescence emission of the different fluorophores. The maximum number of colors can be 1, or 2, or 3, or 4, or up to 10, or up to 20. The maximum number of colors can be higher than 20.”). A person of skill in the art would understand that this encompasses the use of six or more fluorophores and channels. Larson has multiple visual representations of scenarios where signals are generated by the excitement of particular fluorophores, including in Figure 15:

'797 Claim Element¹

Invalidity Analysis

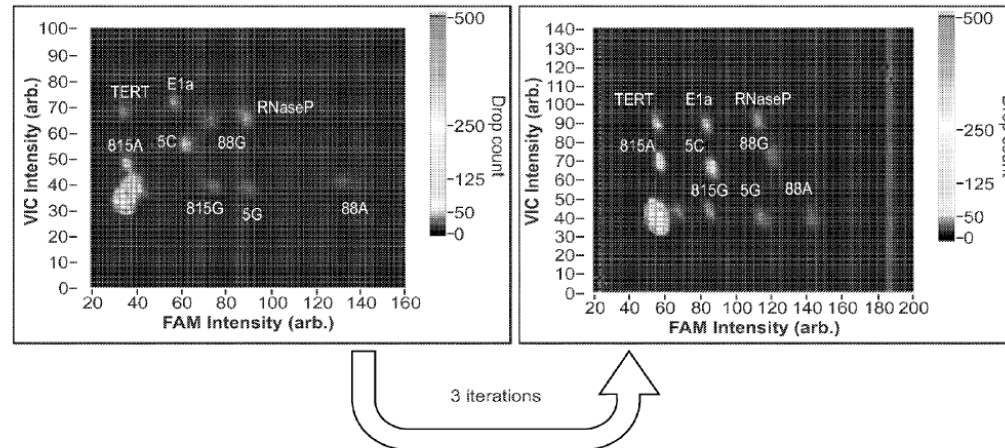
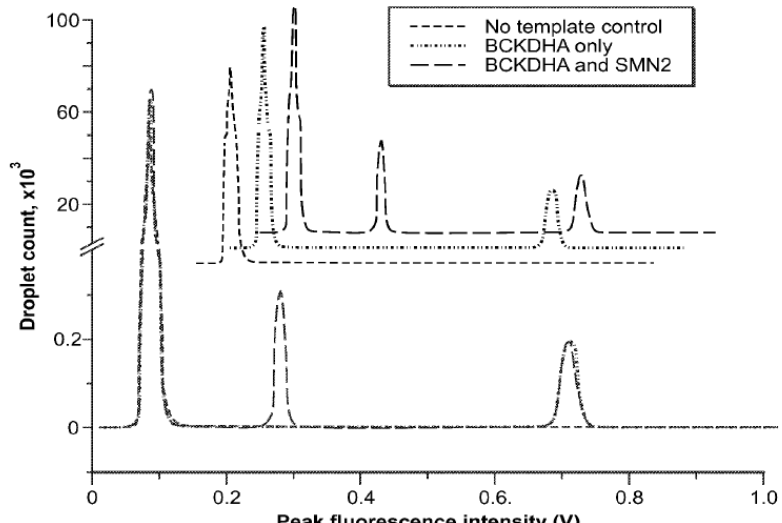


FIG. 15

See id. at Figures 5, 6, 8–10, 12, 14, 17–22; *see also* Link '163 at Figure 3.

To the extent Larson is deemed to not expressly disclose six or more wavelength signals from four or more fluorophores, this would have nonetheless been obvious in view of Larson. As explained above, Larson encourages using a greater number of colors for additional optical labeling. It shows precisely this in actual experimental data. A skilled artisan would have been motivated to use four or more color channels because he or she would have been motivated to detect larger numbers of targets at the same time. A POSA would have had a reasonable expectation of successfully extending Larson to five or more wavelength channels and fluorophores—particularly in light of its suggestion that even more than 20 colors can be used—because this would reflect nothing more than the use of multiple types of well-known fluorophores and that could be detected using well-known instrumentation for the detection of multiple optical signals.

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[2c] wherein C=6.	Larson discloses using six different wavelengths as part of a detection system. Larson ¶ 139 (“the maximum number of different colors possible is limited by spectral overlap between fluorescence emission of the different fluorophores. The maximum number of colors can be 1, or 2, or 3, or 4, or up to 10, or up to 20. The maximum number of colors can be higher than 20.”).
5. The system of claim 1,	<i>See</i> claim 1.
[5a] wherein F=3.	Larson Figure 11 illustrates the detection of analytes by using various intensity values and discloses F=3.  FIG. 11a

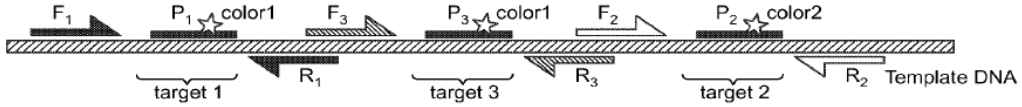
<u>'797 Claim Element¹</u>	<u>Invalidity Analysis</u>
	The small-dash line in Figure 11a represents a no template control, the dotted line represents BCKDHA and the large-dashed line represents a 1:1 ratio of BCKDHA to SMN2. Larson ¶ 131. With respect to the large-dashed line, Larson notes that three populations were readily apparent. A dominant feature appeared at 0.08 V and two smaller peaks appeared at 0.27 and 0.71 V. A very small peak appeared at ~0.9V that was not visible on the scale of Figure 11a. The .08 V peak represented droplets that were negative for both BCKDHA and SMN2 and also corresponds to a representative cumulative intensity of 0. The peak at 0.71 V represented BCKDHA positive samples, and the peak at .27 V represented subsequent addition of SMN2. These two peaks represent a cumulative intensity of 1 and 2 respectively. Finally, the peak at 0.9 V corresponds to droplets occupied by both genes and represents a cumulative intensity of 3. Larson ¶ 131. Thus, Larson teaches a technique for using a decoding matrix wherein the intensity of light emitted from droplets is used to encode which of any combination of two targets are present in a droplet (<i>i.e.</i>, lowest intensity corresponds to no targets, next highest intensity is first target, next highest intensity is second target, and highest intensity is both first and second targets). As noted above, Larson further teaches the use of multiple colors and it would have been obvious to use this same form of decoding matrix at multiple colors to detect a larger number of colors. To the extent one contends the individual analyte signals need to exactly follow a geometric progression of 1, 2, 4, 8... this is disclosed in Lehnert. Lehnert discloses the use of binary (power-of-2) encoding (1:2:4:8) and discusses multiplexing capacity as a function of channels and intensity levels, which is mathematically equivalent to the formula. See Lehnert at 13:15–53. More specifically, each analyte is encoded using the unique proportions of bead subpopulations and powers of two to ensure that each possible combination yields a unique sum. A POSA would be motivated to use this signal progression because the proportions allow for unique interpretation and unambiguous identification of analytes, as Lehnert expressly teaches. See Lehnert at 13:31–35. A POSA would have a reasonable expectation of using this approach because POSA would have known how to modulate the intensity from a target-specific probe. Larson expressly teaches multiple such methods for doing this. As an example,

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	“[t]he one or more groups of probes can include the same detectable label which will vary in intensity upon detection, due to the varying probe concentrations.” Larson ¶ 91.
6[p]. The system of claim 5,	See claim 5.
[6a] 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.	In its infringement contentions, Plaintiff relies on FAM for “a green fluorophore,” HEX for “a green and yellow fluorophore,” Cy5, Cy5.5, and ATTO 590 for “a red fluorophore,” and ROX for “a yellow fluorophore.” See Plaintiff’s Patent L.R. 3-1 and 3-2 Disclosures, 78–90. Plaintiff did not designate a blue fluorophore in its contentions. Larson discloses FAM, ROX, Cy5, and Cy5.5. Larson ¶ 90. Plaintiff relies on Bio-Rad Bulletin 2421, a Fluorophore Reference Guide, see Plaintiff’s Patent L.R. 3-1 and 3-2 Disclosures, 78–106 (citing CT0479364), and contends that these fluorophores exhibit several of the claimed colors, excitation wavelengths, and emission wavelengths. Accordingly, under Plaintiff’s infringement theory, Larson discloses green fluorophores (such as FAM, at least), yellow fluorophores (such as ROX, at least), and red fluorophores (such as Cy5 and Cy5.5, at least). Plaintiffs do not identify a blue fluorophore in their contentions, but Larson discloses this as well in the form of its disclosure of the DAPI fluorophore, which the Fluorophore Reference Guide confirms is a blue fluorophore. Moreover, such red and blue fluorophores were well-known to skilled artisans and were routinely used. Brabetz for instance, discloses blue, green, yellow, and red fluorophores, and combinations thereof:

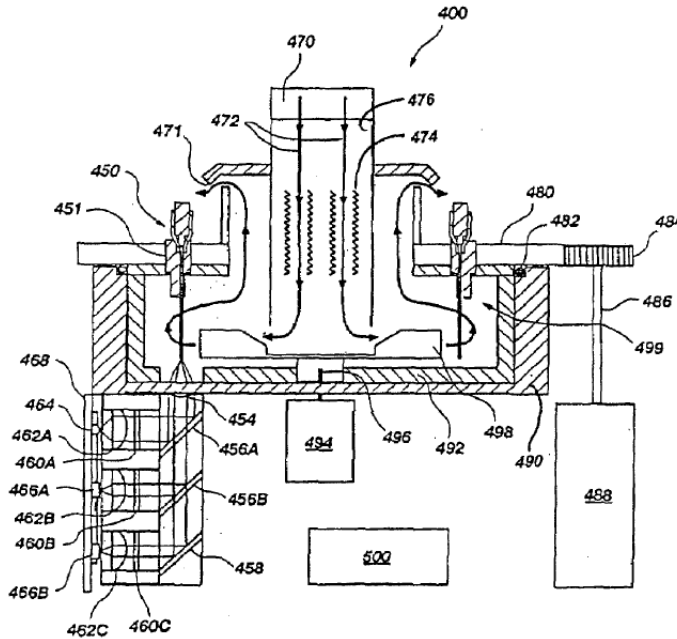
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	TABLE 1 Known fluorescent dye combinations and virtual filtersets for ABI Prism ® Genetic Analyzers. Fluorescence dye combinations and colour canals <table><tr><th>Blue</th><th>Green</th><th>Yellow</th><th>Red</th><th>Orange (far red)</th><th>Recommended virtual filterset</th></tr><tr><td>6-FAM</td><td>JOE</td><td>TAMRA</td><td>ROX</td><td>—</td><td>F or A</td></tr><tr><td>6-FAM</td><td>TET</td><td>HEX</td><td>TAMRA</td><td>—</td><td>C</td></tr><tr><td>5, 6-FAM</td><td>JOE</td><td>TAMRA</td><td>ROX</td><td>—</td><td>F or A</td></tr><tr><td>6-FAM</td><td>JOE</td><td>NED</td><td>ROX</td><td>—</td><td>F</td></tr><tr><td>6-FAM</td><td>HEX</td><td>NED</td><td>ROX</td><td>—</td><td>F or D</td></tr><tr><td>6-FAM</td><td>VIC</td><td>NED</td><td>PET</td><td>LIZ</td><td>G5</td></tr></table> 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). Brabetz 2:40–60; <i>see also</i> Joseph R. Lakowicz, <i>Principles of Fluorescence Spectroscopy</i>, 70 (“cascade yellow”), 722 (“blue” and “red” wavelengths), 727 (“cascade blue”), 730 (“nonspecific blue fluorophore,” “green” and “red” emissions, “yellow emission”), 770 (“green fluorophore”) (3d ed., 2006).	Blue	Green	Yellow	Red	Orange (far red)	Recommended virtual filterset	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
Blue	Green	Yellow	Red	Orange (far red)	Recommended virtual filterset																																						
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																																						
7[p]. The system of claim 5,	<i>See</i> claim 5.																																										
[7a] wherein the multiple fluorophores is selected from the group consisting of a	Larson discloses using FAM, Cy3, ROX, Cy5, and Cy5.5 for fluorescently labeled probes. Larson ¶ 90.																																										

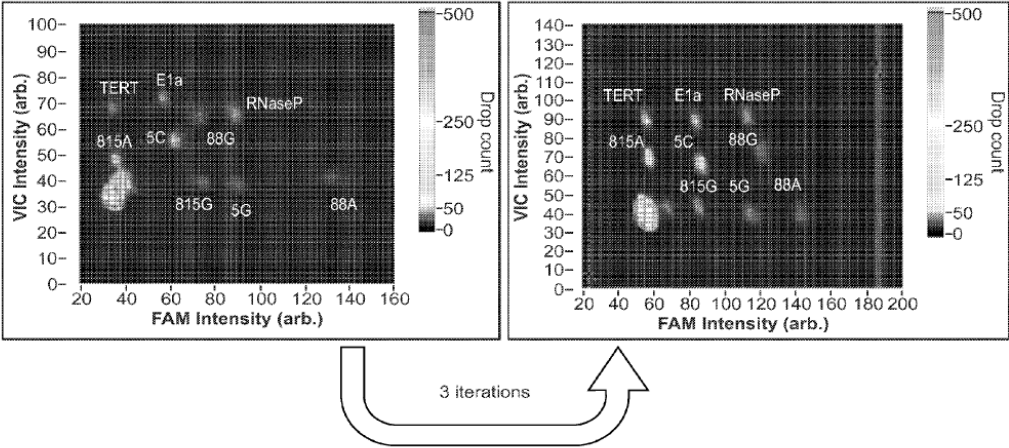
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fluorescein amidite (FAM), a cyanine 3 (Cy3), a carboxy-X-rhodamine (ROX), a cyanine 5 (Cy5), a cyanine 5.5 (Cy5.5), and any combinations thereof.	Moreover, the claimed fluorophores other than FAM and ROX are simply well-known fluorophores that were part of the standard toolkit of the skilled artisan that a POSA would have been motivated to consider and would have had a reasonable expectation of successfully employing. <i>See</i> Joseph R. Lakowicz, <i>Principles of Fluorescence Spectroscopy</i> , 657–660, 827, 848–851(3d ed., 2006); Amersham Pharmacia Biotech, <i>Fluorescence Imaging Principles and Methods</i> , 84, 129, 132 (2000); <i>see also</i> U.S. Patent Publication 2008/0003649A1 (“Maltezos”) ¶¶ 142, 194.
8[p]. The system of claim 5,	<i>See</i> claim 5.
[8a] 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.	In its infringement contentions, Plaintiff relies on FAM for “about 494 nm,” Cy5 for “about 650 nm,” Cy5.5 for “about 675 nm,” and ROX for “about 567 nm.” <i>See</i> Plaintiff’s Patent L.R. 3-1 and 3-2 Disclosures, 97–103. Plaintiff does not provide a representative fluorophore with a maximum excitation wavelength of about 550 nm. As discussed at [7a], fluorophores with these properties were well known in the art. Plaintiff relies on Bio-Rad Bulletin 2421, a Fluorophore Reference Guide, <i>see</i> Plaintiff’s Patent L.R. 3-1 and 3-2 Disclosures, 78–106 (citing CT0479364), and contends that these fluorophores exhibit several of the claimed colors, excitation wavelengths, and emission wavelengths. Accordingly, under Plaintiff’s infringement theory, each of these fluorophores is disclosed in Larson. Larson ¶ 90. Although Plaintiff has not provided a representative fluorophore in its infringement contentions, Cy3 is disclosed in Larson and it has a maximum excitation wavelength of 550 nm and was well known in the art. Larson ¶ 90; <i>see also Fluorescence Imaging Principles and Methods</i>, 84 (2000).
9[p]. The system of claim 5,	<i>See</i> claim 5.

<u>'797 Claim Element¹</u>	<u>Invalidity Analysis</u>
[9a] 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.	In its infringement contentions, Plaintiff relies on FAM for “about 518 nm,” Cy5 for “about 670 nm,” Cy5.5 for “about 697 nm,” and ROX for “about 591 nm.” <i>See</i> Plaintiff’s Patent L.R. 3-1 and 3-2 Disclosures, 103–109. Plaintiff does not provide a representative fluorophore with a maximum emission wavelength of about 565 nm. As discussed at [7a], fluorophores with these properties were well known in the art. Plaintiff relies on Bio-Rad Bulletin 2421, a Fluorophore Reference Guide, <i>see</i> Plaintiff’s Patent L.R. 3-1 and 3-2 Disclosures, 78–106 (citing CT0479364), and contends that these fluorophores exhibit several of the claimed colors, excitation wavelengths, and emission wavelengths. Accordingly, under Plaintiff’s infringement theory, each of these fluorophores is disclosed in Larson. Larson ¶ 90. Although Plaintiff has not provided a representative fluorophore in its infringement contentions, Cy3 is disclosed in Larson and has a maximum emission wavelength of about 565 (~570 nm). Larson ¶ 90; <i>see also Fluorescence Imaging Principles and Methods</i>, 84 (2000).
10[p]. The system of claim 5,	<i>See</i> claim 5.
[10a] wherein the analyte-specific hybridization probes are labeled with a fluorophore of the multiple fluorophores.	Larson discloses labeling analyte-specific hybridization probes with fluorophores and also discloses multiple fluorophores. Larson ¶ 108 (“Probes for TERT, RNaseP and E1a were labeled with the VIC dye and probes for SMN1 and SMN2 were labeled with the FAM dye. The sequences for TERT RNaseP, E1a, SMN1 and SMN2 were amplified by PCR.”); <i>see also</i> ¶ 114 (“Probes for TERT and 815A were labeled with the VIC dye and probes for 815G were labeled with the FAM dye. For each of RNaseP and E1a, two probes, one labeled with the VIC dye and the other labeled with the FAM dye, were encapsulated.”). Fluorophore labeled probes are depicted in Figure 9:

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	FIG. 9A Two Colors THREE Targets  <i>See also, id.</i> at ¶ 121. As Larson states, “Probes (P1, P2 and P3) are labeled with fluorophores (color 1, color 2 and color 1) and bind to the target genetic sequences (target 1, target 2, and target 3) (Panels B and C).” Larson ¶ 121.
11[p]. The system of claim 5,	<i>See</i> claim 5.
[11a] wherein the detector comprises four or six band pass filters.	Larson discloses using band pass filters for fluorescent discrimination. Larson ¶ 195. Moreover, Larson’s disclosure of using two band pass filters in an experiment with two colors would have made it obvious to use four or six band pass filters if four or six colors were used. Larson also discloses using a short pass filter to separate optical paths for fluorescence detection and imaging, <i>see id.</i>, which further supports that a POSA would have known and would have been motivated to use various optical filters to distinguish detectable wavelengths. The use of band-pass filters as standard components in fluorescent detection is confirmed by several prior art references. For example, Brabetz discloses using band pass filters in multiple color fluorescence detection within multiplex PCR. Brabetz 1:45–2:35. Additionally, Maltezos states, “it may desirable to suppress [unwanted] luminescence even further by using optical band-pass filters.” <i>See</i> U.S. Patent Publication 2008/0003649A1 (“Maltezos”) ¶ 163. Further, U.S. Patent Publication 2010/0227386 (“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.” Neuzil ¶ 44. Even further, U.S. Patent

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	Publication 2003/0219754 (“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. Oleksy ¶ 86. To the extent that Larson, Brabetz, and/or Maltezos do not explicitly disclose four or six band pass filters, it would have been obvious to use four or six band pass filters where four or six different wavelengths were used.
13[p]. The system of claim 5,	See claim 5.
[13a] wherein the multi-channel detector comprises four or six photodetectors.	Larson discloses using a photodetector as its detector. Larson ¶ 195 (“Fluorescence was detected by two H5784-20 photomultipliers...”). Larson further discloses that “droplets may be individually analyzed and detected using <i>any methods known in the art...</i>(emphasis added).” Larson ¶ 89. As to the use of four or six photodetectors, this would have been obvious in view of Larson. As explained here and above, Larson teaches that any method known in the art can be used for detection. Indeed, it discloses the use of photomultipliers, which are photodetectors. It also expressly teaches using multiple color channels. Larson ¶ 139 (“the maximum number of different colors possible is limited by spectral overlap between fluorescence emission of the different fluorophores. The maximum number of colors can be 1, or 2, or 3, or 4, or up to 10, or up to 20. The maximum number of colors can be higher than 20.”). A person of skill in the art would understand that teaching the use of multiple colors is a teaching of using multiple different wavelength signals from multiple different fluorophores. At a minimum, the use of photodetectors would have been obvious because the use of fluorescent labels was well known as was the instrumentation for detecting such signals. Indeed, several prior art references disclose the use of such photodetectors.

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	For instance, photodetectors were well known in the art. <i>See</i> U.S. Patent Publication Maltezos ¶¶ 60, 101, 144; <i>id.</i> ¶ 149 (“The photodetector array includes a plurality of photodetectors...”); <i>see also</i> U.S. Patent Publication 2009/0239308A1 (“Dube”) ¶ 147 (“the CCD is used as an array of photodetectors wherein each pixel or group of pixels corresponds to a reaction chamber...”); U.S. Patent Publication 2009/0258414A1 (“Wittwer”) ¶ 375 and Figure 53 (“The emitted fluorescence signals are acquired by photodetectors 466 A and 466 B.”).  Fig. 53

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	The term photodetector also includes terms like “photodiode” and photodiodes are well known in the art. Maltezos ¶ 101 (“where it is detected by a photodetector, such as a photodiode.”). Consistent with the foregoing, as shown in Figure 15, Larson shows actual data using two channels with one wavelength from some targets and another wavelength for others:  FIG. 15 <i>See id.</i> at Figures 5, 6, 8–10, 12, 14, 17–22; <i>see also</i> Link '163 at Figure 3. For the reasons explained above in connection with claims 1 and 2, a person of ordinary skill in the art would have been motivated to use six or more color channels. To do this, a skilled artisan would have been motivated to use six or more photodetectors (one for each of the color channel) and would have had a reasonable expectation of successfully doing so because, as explained above, such photodetectors

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	were standard components that were widely used, as reflected in several prior art references.
14[p]. The system of claim 5,	<i>See</i> claim 5.
[14a] wherein the multi-channel detector comprises photodetectors that enable the detection of blue, green, and red fluorescent signals.	As explained above in connection with claim 13, Larson discloses the use of photodetectors, and it would have been obvious to use six or more photodetectors. Indeed, photodetectors, <i>see supra</i>, [13a], have excellent sensitivity such that a POSA would have been motivated to use them. <i>See</i> Maltezos ¶ 134 (“photodiode detectors have excellent sensitivity....”). Moreover, Larson discloses using a range of dyes encompassing a range of colors, <i>see</i> Larson ¶90, such that it would have been obvious to expand its use of photodetectors to cover photodetectors that cover each of the claimed colors (blue, green, and red). As to the use of green and red fluorescent signals, Plaintiff relies on FAM for green, HEX for green and yellow, Cy5, Cy5.5 and ATTO 590 for red, and ROX for yellow in its infringement contentions. <i>See</i> Plaintiff’s Patent L.R. 3-1 and 3-2 Disclosures, 121–130. Plaintiff does not disclose a blue signal. Each of those is disclosed or rendered obvious in view of Larson, as explained in claim [9a], above. Further, blue, green, and red signals were commonly detected. The optical assembly in Maltezos, for instance, detected blue, green, and red signals. Maltezos ¶ 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.”). Table 1 of Maltezos lays this out:

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	TABLE 1 <table><tr><th rowspan="2">Color</th><th colspan="2">Dominant wavelength (nm) or CCT (K)</th><th>Typical Luminous or Radiant flux @</th></tr><tr><th>Min.</th><th>Max.</th><th>700 mA</th></tr><tr><td>White</td><td>4500 K</td><td>8000 K</td><td>76 lm</td></tr><tr><td>Royal Blue</td><td>455 nm</td><td>465 nm</td><td>385 mW</td></tr><tr><td>Blue</td><td>465 nm</td><td>475 nm</td><td>28 lm</td></tr><tr><td>Cyan</td><td>500 nm</td><td>510 nm</td><td>75 lm</td></tr><tr><td>Green</td><td>520 nm</td><td>535 nm</td><td>80 lm</td></tr><tr><td>Amber</td><td>585 nm</td><td>595 nm</td><td>57 lm</td></tr><tr><td>Red-Orange</td><td>610 nm</td><td>620 nm</td><td>86 lm</td></tr><tr><td>Red</td><td>620 nm</td><td>635 nm</td><td>61 lm</td></tr></table>	Color	Dominant wavelength (nm) or CCT (K)		Typical Luminous or Radiant flux @	Min.	Max.	700 mA	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
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15[p]. The system of claim 5,	See claim 5.																																							
[15a] 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.	As explained above in connection with claims 13 and 14, Larson discloses the use of photodetectors, and it would have been obvious to use six or more photodetectors. In its infringement contentions, Plaintiff relies on FAM for “about 483 nm to about 533 nm,” HEX for “about 523 nm to about 568 nm,” Cy5 and ATTO 590 for “about 615 nm to about 670 nm” ROX for “558 nm to about 610 nm.” See Plaintiff’s Patent L.R. 3-1 and 3-2 Disclosures, 131–140. As discussed above, fluorophores with these properties were well known in the art. Plaintiff relies on Bio-Rad Bulletin 2421, a Fluorophore Reference Guide, see Plaintiff’s Patent L.R. 3-1 and 3-2 Disclosures, 78–106 (citing CT0479364), and contends that these fluorophores exhibit several of the claimed colors, excitation wavelengths, and emission wavelengths. Accordingly, under Plaintiff’s infringement theory, fluorophores in each of these detection ranges are disclosed in Larson or, at a minimum, rendered obvious in view of Larson.																																							

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18[p]. The system of claim 5,	<i>See</i> claim 5.
[18a] further comprising a display coupled to the processor controlled analyzer to visualize a plot of the first and second values.	Larson discloses the use of a processor controlled analyzer (i.e., a computer). Larson ¶ 89 (“suitable detection apparatuses include optical waveguides, microscopes, diodes, light stimulating devices, (e.g., lasers), photo multiplier tubes, and processors (e.g., computers and software), and combinations thereof, which cooperate to detect a signal representative of a characteristic, marker, or reporter. . .”). Larson further discloses many examples using a display to visualize a plot of first and second values, such as Figure 15: Figure 15 consists of two side-by-side flow cytometry plots. Both plots have 'VIC Intensity (arb.)' on the y-axis and 'FAM Intensity (arb.)' on the x-axis. The left plot has a y-axis range of 0 to 100 and an x-axis range of 20 to 160. The right plot has a y-axis range of 0 to 140 and an x-axis range of 20 to 200. Both plots show a similar distribution of data points with labels for TERT, E1a, RNaseP, 815A, 5C, 88G, 815G, 5G, and 88A. A color scale for 'Drop count' is shown to the right of each plot, ranging from 0 (black) to 500 (white). A curved arrow labeled '3 iterations' points from the left plot to the right plot, indicating a process of iterative analysis or gate refinement. FIG. 15 <i>See id.</i> at Figures 5, 6, 8–10, 12, 14, 17–22; <i>see also</i> Link '163 at Figure 3.

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	It would have been obvious to include with the system a display so that users can visualize the data results and confirm the accuracy of the reported target concentrations. Moreover, using a display for such purposes was well known in the art. For example, Maltezos discloses control assemblies for various PCR applications and notes that computers for analyzing signals usually include a display terminal. Maltezos ¶ 167 (“Generally, a computer comprises 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 <i>a display terminal</i>, and an input device such as a keyboard.” (emphasis added)). In another example, Slepnev discloses using a display monitor as part of an apparatus for detecting and quantifying polynucleotides. U.S. Patent Publication 2012/0100600 (“Slepnev”) ¶ 141 (“In 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.”).
19[p]. A system comprising:	To the extent the preamble is limiting, Larson discloses it and the remaining elements of claim 19 (<i>see</i> below, each element recited in claim 19).
[19a] a processor;	<i>See</i> claim [1c].
[19b] a display; and	<i>See</i> claim [18a].
[19c] a non-transitory computer readable medium storing instructions thereon that, when executed by the processor, cause the processor to:	Larson’s processor uses a non-transitory computer readable medium storing instructions thereon to execute the system’s functions. Larson ¶ 89 (“suitable detection apparatuses include optical waveguides, microscopes, diodes, light stimulating devices, (e.g., lasers), photo multiplier tubes, and processors (e.g., computers and software), and

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	combinations thereof, which cooperate to detect a signal representative of a characteristic, marker, or reporter. . ."); <i>see also id.</i> ¶ 196.
[19d] obtain cumulative signal data from a digital PCR instrument with a sample volume,	As explained above in connection with claim [1a], Larson's system includes a sample chamber or sample volume. Larson discloses that its system is used to detect cumulative signal data from a digital PCR instrument. For example, the summary of the invention states, "the invention applies to digital amplification techniques and, in specific, embodiments enables multiplex PCR in droplets." Larson ¶ 8. And "[m]ethods of the invention are particularly useful in digital PCR...." Larson ¶ 15. Also, "suitable detection apparatuses... cooperate to detect a signal representative of a characteristic...and to determine and direct the measurement or the sorting action at a sorting module." Larson ¶ 89. Several examples in Larson demonstrate obtaining cumulative signal data from a PCR instrument. <i>See, e.g.,</i> Larson ¶¶ 113 ("At the end of the PCR, the fluorescence emission from each droplet was determined and plotted on a scattered plot based on its wavelength and intensity."), 116 ("At the end of the PCR, the fluorescence emission from each fused droplet was determined and plotted on a scattered plot based on its wavelength and intensity."), 131 ("A very small peak appeared at ~0.9V, not visible on the scale of FIG. 11a, that corresponded to droplets occupied by both genes.").

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[19d.1] the digital PCR instrument comprising a light source and a multichannel detector with C channels,	The system disclosed in Larson includes a digital PCR instrument with a light source and a multidetector channel with C channels <i>See, e.g.</i>, Larson ¶¶ 89 (“Examples of suitable detection apparatuses include optical waveguides, microscopes, diodes, light stimulating devices. . .”), 139 (“multiple colors that are spectrally separable can be used simultaneously.”), 195 (“the droplets were imaged through the same objective lens with backside illumination....”). Figure 9a discloses a schematic view of targets being identified via emitted light using a multichannel detector within a digital PCR instrument. Larson ¶¶ 120–21. FIG. 9A Two Colors THREE Targets The diagram illustrates a horizontal surface representing 'Template DNA'. Three distinct regions are marked as 'target 1', 'target 3', and 'target 2' from left to right. Above each target region, a primer (P₁, P₃, P₂) is shown binding to the template. Each primer is associated with a fluorophore (F₁, F₃, F₂) that emits light, indicated by arrows labeled R₁, R₃, and R₂ respectively. The emission from P₁ and P₃ is labeled 'color1', while the emission from P₂ is labeled 'color2'. Larson’s system is based on the detection of fluorescence. <i>See</i> Larson ¶ 120 (“Droplets containing the target sequence 1 or 2 emit fluorescence of color 1 or 2 respectively and are optically detected by laser (Panels B and C).”). Those of skill in the art understand that such systems based on the use of fluorescence require a light source for excitation of the fluorophores. <i>See, e.g.</i>, Maltezos ¶ 132 (“Optical measurement devices are known in the art. Generally, the measuring optic includes a light source.”).

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[19d.2] and the sample volume comprising M fluorescently labeled polynucleotide analytes;	Larson discloses sample targets (i.e., M analytes) and uses fluorescence to distinguish between them. <i>See, e.g.</i> Larson ¶ 168 (“Droplets that contain the variant of the target are detected based on emission from the fluorophore that is released from the probe that hybridizes to the variant of the target.”). For example, in Figure 11, BCKDHA and SMN2 are both targets in a sample volume. Both are polynucleotide analytes and both are fluorescently labeled. <i>See</i> Larson ¶¶ 31, 131. Larson Figure 9a further discloses the use of fluorescently labeled polynucleotide analytes wherein the targets are hybridized to fluorescently labeled probes.
[19e] apply a decoding matrix to the cumulative signal data to unambiguously determine the presence or absence of at least each of the M fluorescently labeled polynucleotide analytes	<i>See</i> claim [1c.1].

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[19f] by associating, for each fluorescently labeled polynucleotide analyte, a first value in a first component of the cumulative signal data and a second value in a second component of the cumulative signal data, wherein each first value is an intensity or range of intensities and each second value is a wavelength or a range of wavelengths,	<i>See</i> claims [1b.1]-[1b.4], [1c.1]-[1c.4].
[19g] wherein for a positive integer M, $M=C*\log_2(F+1)$,	<i>See</i> claim [1d].
[19h] F is the maximum cumulative intensity of the first component of the cumulative signal data, for any second value, when all of the analytes are present,	<i>See</i> claim [1d.1].
[19i] M, C, and F are each positive integers, and	<i>See</i> claim [1d]-[1d.2].
[19j] wherein F+1 is a positive integer and wherein F+1 is a power of 2; and	<i>See</i> claim [1d.3].
[19k] plot, on the display, a representation of the first value and the second value	<i>See</i> claim [18a].

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[19l] wherein the cumulative signal data comprises:	<i>See</i> claims [1b.1]-[1b.4], [1c.1].
[19m.1] a first electromagnetic signal at a first wavelength from the sample volume, the first electromagnetic signal generated by excitement of a first fluorescently labeled polynucleotide analyte of the six fluorescently labeled polynucleotide analytes;	<i>See</i> claims [1b.1]-[1b.4], [1c.1], [2b].
[19m.2] a second electromagnetic signal at a second wavelength from the sample volume, the second electromagnetic signal generated by excitement of a second fluorescently labeled polynucleotide analyte of the six fluorescently labeled polynucleotide analytes;	<i>See</i> claims [1b.1]-[1b.4], [1c.1], [2b].
[19m.3] a third electromagnetic signal at a third wavelength from the sample volume, the third electromagnetic signal generated by excitement of a third fluorescently labeled polynucleotide analyte of the six fluorescently labeled polynucleotide analytes;	<i>See</i> claims [1b.1]-[1b.4], [1c.1], [2b].

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[19m.4] a fourth electromagnetic signal at a fourth wavelength from the sample volume, the fourth electromagnetic signal generated by excitement of a fourth first fluorescently labeled polynucleotide analyte of the six fluorescently labeled polynucleotide analytes; and	<i>See</i> claims [1b.1]-[1b.4], [1c.1], [2b].
[19n] wherein the second values comprise the first, second, third, and fourth wavelengths, and	<i>See</i> claim [1c.3].
[19o] the determination is made without immobilization, mass spectrometry or melting curve analysis.	<i>See</i> claim [1c.4].
21[p]. The system of claim 19,	<i>See</i> claim 19.
[21a] wherein $F=3$.	<i>See</i> claim [5a].