EDWARD R. REINES (Bar No. 135960)
edward.reines@weil.com
DEREK C. WALTER (Bar No. 246322)
derek.walter@weil.com
WEIL, GOTSHAL & MANGES LLP
Silicon Valley Office
201 Redwood Shores Parkway
Redwood Shores, CA 94065
Telephone: (650) 802-3000
Facsimile: (650) 802-3100

Attorneys for Defendant and Counter-Plaintiff
BIO-RAD LABORATORIES, INC.

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA
SAN JOSE DIVISION

CHROMACODE, INC., and CALIFORNIA INSTITUTE OF TECHNOLOGY, Plaintiffs and Counter-Defendants, v. BIO-RAD LABORATORIES, INC., Defendant and Counter-Plaintiff.	Case No. 5:23-cv-06360-EJD **DEFENDANT AND COUNTER-PLAINTIFF BIO-RAD LABORATORIES, INC.'S AMENDED INVALIDITY CONTENTIONS** Hon. Edward J. Davila

IPR2024-01177
California Institute of Technology - Ex. 2006 Page 1

Pursuant to Patent Local Rule 3-3, the Court's March 8, 2024 Patent Scheduling Order (Dkt. No. 47), and the Court's Order to Amend Patent Scheduling Order (Dkt. No. 53), Defendant and Counter-Plaintiff Bio-Rad Laboratories, Inc. ("Bio-Rad") makes the following disclosure of preliminary invalidity contentions for U.S. Patent No. 10,068,051 (the "'051 Patent"), U.S. Patent No. 10,770,170 (the "'170 Patent"), and U.S. Patent No. 11,827,921 (the "'921 Patent," collectively, the "Asserted Patents"). Plaintiffs and Counter-Defendants ChromaCode, Inc. ("ChromaCode") and California Institute of Technology ("Caltech," and collectively, "Plaintiffs") assert claims 1-9 of the '051 Patent, Claims 1-20 of the '170 Patent and claims 1-17, 19 of the '921 Patent (collectively, the "Asserted Claims").

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

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

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

IPR2024-01177
California Institute of Technology - Ex. 2006 Page 2

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

I. PATENT LOCAL RULE 3-3(a) DISCLOSURES

Bio-Rad does not agree, nor does it concede that the Asserted Patents are entitled to the priority date asserted by Plaintiffs of November 4, 2011 based on conception and diligent reduction to practice, nor does Bio-Rad agree or concede that the Asserted Patents are entitled to priority based on U.S. Provisional Application No. 61/594,480 filed on February 3, 2012.

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

- U.S. Patent No. 9,921,154 ("Youvenot")
- U.S. Patent No. 9,222,128 ("Saxonov 128")
- U.S. Patent Pub. 2013/0040841A1 ("Saxonov")
- U.S. Patent Pub. 2011/0250597A1 ("Larson")
- U.S. Patent Pub. 2008/0124705A1 ("Kramer")
- U.S. Patent No. 8,614,061 ("Brabetz")
- U.S. Patent Pub. 2012/0077692 ("Hassibi")

IPR2024-01177
California Institute of Technology - Ex. 2006 Page 3

- U.S. Patent Pub. 2011/0312704A1 ("Silverbrook")
- U.S. Patent Pub. 2014/0051155A1 ("Evans")
- U.S. Patent Pub. 2012/0100600A1 ("Slepnev")
- U.S. Patent Pub. 2008/0003649A1 ("Maltezos")
- U.S. Patent No. 6,814,934 ("Higuchi")
- U.S. Patent Pub. 2009/0156415A1 ("Remacle")
- U.S. Patent No. 5,639,428 ("Cottingham")
- U.S. Patent No. 7,991,558 ("Kurnik")
- U.S. Patent No. 9,044,753 ("Atwood")
- U.S. Patent No. 8,697,433 ("Oh")
- U.S. Patent No. 5,333,675 ("Mullis")
- U.S. Patent Pub. 2012/0214207A1 ("Gunter")
- U.S. Patent No. 9,207,690 ("Tverskoy")
- U.S. Patent Pub. 2010/0311070A1 ("Oh 070")
- U.S. Patent Pub. 2007/0128613A1 ("Davies")
- U.S. Patent Pub. 2011/0160288A1 ("Nakamura")
- U.S. Patent Pub. 2007/0048750A1 ("Peck")
- U.S. Patent No. 5,476,774 ("Wang")
- U.S. Patent Pub. 2007/0237716A1 ("Mason")
- U.S. RE 38,352 ("Kozal")
- U.S. Patent Pub. 2004/0229211A1 ("Yeung")
- U.S. Patent Pub. 2010/0267017A1 ("Hassard")
- Bio-Rad QX100 Droplet Digital PCR System (the "QX100 System")

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

Youvenot is 102(g) prior art and Yann Jouvenot of Benicia, California, Serge Saxonov, of Oakland, California, Simant Dube of Pleasanton, California, and John Frederick Regan of San Mateo,

IPR2024-01177
California Institute of Technology - Ex. 2006 Page 4

California, were involved in the development of the prior art reference while working at Bio-Rad

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

The QX100 System is 102(g) prior art and was developed at Bio-Rad prior to its release in October, 2011.

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

II. PATENT LOCAL RULE 3-3(b) DISCLOSURES

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

A. Anticipation of the Asserted Claims

At least the Asserted Claims of the '921 Patent are invalid as anticipated, either expressly, implicitly or inherently as understood by a person having ordinary skill in the art.

- Saxonov anticipates the '921 Patent as described, by illustrative citations, in Appendix I and is 102(g) prior art.
- Saxonov 128 anticipates the '921 Patent as described, by illustrative citations, in Appendix J and is 102(g) prior art.
- Kramer anticipates the Asserted Claims of the '921 Patent as described in Appendix K.
- Youvenot anticipates the '921 Patent as described, by illustrative citations, in Appendix L and is 102(g) prior art.
- Larson anticipates the Asserted Claims of the '921 Patent as described in Appendix M.
- The QX100 System anticipates the Asserted Claims of the '921 Patent as described in Appendix N.

B. Obviousness of the Asserted Claims

1. The Asserted Claims Would Have Been Obvious in View of the Prior Art References

To the extent the Asserted Claims are not deemed invalid under 35 U.S.C. § 112 for lack of enablement written description, or indefiniteness, Bio-Rad contends that the prior art listed in Section I., whether alone or in combination with each other, renders the Asserted Claims of the Asserted Patents obvious under 35 U.S.C. § 103, as set forth in the claim charts and as described below.

For the reasons stated below, the Asserted Claims would have been obvious in view of numerous prior art references that were available before the priority dates of the Asserted Patents. In particular, the claims of the Asserted Patents would have been rendered obvious in view of the combinations of prior art described below for each of the Asserted Claims. These prior art combinations are not exhaustive; rather they are illustrative examples of prior art combinations based on the following categories of art and specific references within these categories.

- Prior art teaching single sample detection of multiple analytes, for instance: Youvenot, Saxonov 128, Saxonov, and Kramer, the QX100 System (the "Multiplexed Encoding and Detection Art"). *See, e.g.*, Appendix A.
- Prior art teaching labeling and optimization of analytes for multiplexing, for instance: Larson, Brabetz, Youvenot, Saxonov 128, Saxonov, Kramer, Brabetz, Hassibi, the QX100 System (the "Probe Labeling and Measurement Art"). *See, e.g.*, Appendix A.
- Prior art teaching the use of computers and networks to perform assays, for instance: Youvenot, Saxonov, Saxonov 128, Larson, Silverbrook, Evans, Slepnev, Maltezos, Higuchi, Remacle, Cottingham, Kurnik, Atwood, Oh, Mullis, Gunter, Tverskoy, Oh 070, the QX100 System (the "Computer and Network Assays Art").
- Prior art teaching the detection of targets from biological samples, for instance: Youvenot, Saxonov, Saxonov 128, Kramer, Larson, Davies, Nakamura, Peck, Wang, Mason, Kozal, Yeung, Hassard (the "Biological Sample Art").

To the extent that Plaintiffs challenge 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

IPR2024-01177
California Institute of Technology - Ex. 2006 Page 6

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.

a. ’051 Patent:

(1) Claims 1-4

To the extent Plaintiffs contend that any of the references identified above do not disclose any or all of the limitations in Claims 1-4 of the ’051 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 method for detecting the presence or absence of at least seven polynucleotide analytes in any combination of presence or absence in a single sample volume non-degenerately by use of analyte-specific hybridization probes labeled with fluorophores. Claims 2-4 are dependent on claim 1 and specify conditions for the hybridization probes and the detection of signals, including that the signals must be generated during a polymerase chain reaction (claim 4), that each hybridization probe must comprise an identical fluorophore (claim 2), or that the hybridization probes are specific for different analytes (claim 3).

Claims 1-4 of the ’051 Patent are obvious because it would have been obvious for one of skill in the art to combine the Multiplexed Encoding and Detection Art with the Probe Labeling and Measurement Art, or combine references within each class of art for at least the following reasons. For example, a POSA would have found it obvious to combine the references to analyze a greater number of targets, i.e., to perform a higher order of multiplexing as taught by Kramer and Larson, including a total of seven or more targets. A POSA would have understood the need to and benefit of looking to references such as those included in the table above from the teachings of Saxonov. *See, e.g.*, Saxonov ¶ 7 (“A new approach is needed to increase the multiplex levels of digital assays”) and ¶ 6 (“instruments with more optical channels, to detect emission from more dyes, are more expensive than those with fewer channels”); *see also* Appendices A-D. A POSA would have additionally understood the benefit of not requiring immobilization to perform the assays of the alleged invention so as to not require additional steps to perform the assays. *See* Appendices A-D. Further, a POSA would have found it

IPR2024-01177
California Institute of Technology - Ex. 2006 Page 7

obvious to non-degenerately detect the results of such assays to provide more accurate results of the assays such as described in Kramer by, for example, Figure 5, which depicts an unambiguous result of two targets present in combination. Kramer ¶ 26, Fig. 5. Kramer further teaches methods wherein probes with different numbers of unique fluorophores are used to differentiate the targets in combination, "[the] combinatorial code may be quadraplex coding in which the code elements comprise four colors, optionally enlarged by additional code elements of three colors, two colors or one color, or some combination thereof," Kramer ¶ 11, and further methods wherein the targets are labeled with differing amounts of common fluorophores to differentiate between targets, "[i]n ratio coding differing amounts of the same label are used for differentiation. Combinatorial codes according to this invention may be augmented with ratio coding, preferably integral ratio coding, that is, ratios of whole numbers such as 2:1, 3:1, 4:1 or 5:1, and vice versa." Kramer ¶ 14. Saxonov similarly teaches unambiguous detection of targets both in a single color, such as in Figure 5, and by differentiating the colors of the targets to be detected, such as in Figure 10. *See, e.g.*, Saxonov ¶¶ 78 (describing the detection of three targets in any combination, the single positive populations, the "double-positive populations (T1+/T2+, T1+/T2+, and T2+/T3+)" and the "triple positive population (T1+/T2+/T3+)."), 60-67 (describing the detection of two analytes in any combination based on intensities of signals exhibited in a single color).

Further, a POSA would have had a reasonable expectation of success in practicing the assays of the alleged invention. A POSA would have understood that a PCR assay can be multiplexed with multiple different colors by the use of multiple optical channels, and that more than three targets could be analyzed, by applying the teachings of Saxonov, e.g., Fig. 5, depicting the detection of two distinct targets with a single color fluorophore, a FAM fluorophore. Saxonov further teaches the detection of three analytes in any combination of presence or absence in a single color based off differing intensities. *See, e.g.*, Saxonov ¶ 41. A POSA would have expected success in applying Saxonov's teaching of "performing a digital assay with multiplexed detection of two or more distinct targets in the same optical channel" ¶ 8 to, for example, four optical channels (colors) with two targets identified in each channel to analyze the presence of eight targets in a single sample solution or alternatively twelve targets in four colors with three targets per channel. A POSA would have further understood

from the teachings of Kramer that multiplex detection of more than ten targets can be performed in an assay via combinatorial and ratio coding schemes using four unique fluorophores. *See e.g.*, Kramer ¶¶ 11, 14; Appendix C. A POSA would have further known to optimize the differentiation between the signals generated by the targets, alone and in combination, as described by the teachings of Larson, which allow the multiplexed detection of nine analytes using only two fluorophores. *See*, *e.g.*, Larson ¶¶ 35, 150 (describing Fig. 15); *see also* Appendix A. Further, a POSA would have been motivated by the teachings of Kramer to perform an assay wherein each hybridization probe comprises an identical fluorophore to optimize the fluorescence emissions of the fluorophores on a probe and thus more reliably detect and resolve which analyte(s) are present in a given assay. *See, e.g.*, Kramer ¶ 13. Thus, at the time of the alleged invention, claims 1-4 of the ’051 Patent would have been obvious to one skilled in the art based on the references cited herein, at least as described above.

(2) Claims 5-9

To the extent Plaintiffs contend that any of the references identified above do not disclose any or all of the limitations in Claims 5-9 of the ’051 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. Claims 5-9 of the ’051 Patent are dependent on claim 1, which is invalid for the reasons stated above. Further, the limitations of claims 5-9 are directed to the use of computers, the placement or location of computers in performing the methods of the alleged invention and transmitting information through such a computer network.

Claims 5-9 of the ’051 Patent are obvious because it would have been obvious for one of skill in the art to combine the Multiplexed Encoding and Detection Art with the Probe Labeling and Measurement Art with the Computer and Network Assays Art”, or combine references within each class of art for at least the following reasons. *See, e.g.*, Youvenot (teaching a “data processing assembly,” Youvenot ¶ 12:58-59, that “communicates with and controls operation of any suitable combination of the assemblies,” Youvenot 12:60-62, and that these assemblies may be “operatively connected to one another.” Youvenot 12:66-67. Saxonov; (teaching a “data processing assembly,” Saxonov ¶ 45, that “communicates with and controls operation of any suitable combination of the

assemblies," *Id.*, and that these assemblies may be "operatively connected to one another." *Id.*); Saxonov 128; (teaching a "data processing assembly," Saxonov 128 9:7-8, that "communicates with and controls operation of any suitable combination of the assemblies," *id.* 9:10-12, and that these assemblies may be "operatively connected to one another." *Id.* 9:16-17.); Larson ¶¶ 80-85 (Larson teaches that in certain embodiments, the thermal cycling may depend on a number on repeated cycles in various temperature zones, which a POSA would have understood would be advantageous to use a computer to control because monitoring temperature and performing cycles are actions well-suited to be performed by computers); Silverbrook ¶ 198 ("To conduct a diagnostic test, the test module 10 (or test module 11) is inserted into the Micro-USB port 16 on the test module reader 12. The sterile sealing tape 22 is peeled back and the biological sample (in a liquid form) is loaded into the sample macroreceptacle 24."); Evans ¶ 198 ("Computing device 104 may be provided within housing 101, or may be provided separately, Such as a laptop or desktop computer, or portions of computing device 104 may be resident within housing 101, while other portions are located separately and may be coupled through wiring or wirelessly. Computing device 104 may be configured to load computer-readable program code for controlling thermal cycler apparatus 100 and optics block 109. In one illustrative embodiment, thermal cycler apparatus 100 in housing 101 may be provided in an automated system with a robotics unit 105. The robotics unit 105 may be programmed to load the samples into sample wells 82 and then load sample plate 80 into housing 101 through opening 102."); Slepnev ¶ 122 ("To perform the PCR process, the temperature of the metal block is controlled according to prescribed temperatures and times specified by the user in a PCR protocol file. A computer and associated electronics then controls the temperature of the metal block in accordance with the user supplied data in the PCR protocol file defining the times, temperatures and number of cycles, etc. As the metal block changes temperature, the samples in the various tubes follow with similar changes in temperature."); Maltezos ¶ 132 (in a system for detecting signals, "The detector is connected with the evaluation circuit computer."); Higuchi Fig. 8 (depicting a thermal cycler and detector connected to a computer); Remacle ¶ 134 ("Data storage and data treatment are preferably performed using a programmable computer which is integrated in the apparatus of the invention. Data treatment can be performed at any time after data storage."); Cottingham 15:58-16:24 (describing the use of networks

connected to a host computer for clinical diagnostics based on polynucleotide assays); Kurnik 7:18-31 (describing that performing the cycle threshold for polynucleotide detection "over a network connection or direct connection to a code source or using a portable medium as is well known."); Atwood 1:19-22 ("the invention pertains to automated instruments that perform the reaction simultaneously on many samples and produce very precise results by using thermal cycling."); Oh 2:59-63 ("According to an aspect of the present invention, a multiple PCR system includes the PCR module; and a host computer controlling the PCR module, wherein the PCR module includes a computing unit and the computing unit of the PCR module and the host computer are electrically connected through a wire or wireless network."); Mullis at abstract ("There is disclosed herein a machine for performing nucleic acid amplification under computer control."); Gunter ¶ 134 ("The system 900 can be in wired or wireless communication with a remote system for housing data or providing instructions for PCR (see below). Communication to and from the system can be facilitated by a network interface that brings the system and in communication with the remote system through an intranet or the Internet (e.g., the World Wide Web)."); Tverskoy 4:14-18 ("A thermal control system 226 includes computer readable storage medium such as physical memory 228 in which a predetermined set of target sample temperatures and corresponding timing 230 (e.g., temperatures and timing for PCR) for a loaded carrier are stored."); Oh 070 ¶ 71("the host computer 50 and the computing units 41 have respective auxiliary memories 54 and 44. The auxiliary memories 54 and 44 store software programs for PCR control and the software programs execute their functions. In particular, the Software programs may be connected through wire or wireless network Such as a pier-pier network or a server-client network."); the QX100 System (the QX100 system connects to the QuantaSoft Software) https://www.bio-rad.com/webroot/web/pdf/lsr/literature/bulletin_10026321.pdf at 8. First, a POSA would have been motivated to combine the above classes of art because A POSA would have understood that to perform the steps of the alleged invention, such as detecting and measuring cumulative intensity signals emitted from excited fluorophores, using a computer would provide benefits of improving efficiency in collecting data and performing calculations and thermal cycling to amplify targets. *See, e.g.*, Higuchi Fig. 8; *see also* Matlezos ¶¶ 12, 132.

Further, a POSA would have known that performing the generation of fluorescent signals representing polynucleotide targets, the detection of such signals, and the determination of which, if any, of the targets such signals represent has been performed on computers since long before the alleged priority date of the Asserted Patents and a POSA would have been motivated to apply these teachings to the assays of the alleged invention to enhance the efficiency and reliability of signal detection and measurement. *See, e.g.*, Silverbrook ¶ 198.

A POSA would have additionally understood that the computer may be located anywhere, including in multiple places, on the apparatus to perform the methods of the alleged invention, including remotely at another location, and on a thermal cycler. *See, e.g.*, Appendices A-D; *see also* Saxonov ¶ 45; *see also* Matlezos ¶ 12.

A POSA would have understood that transmitting such information over a computer network, specifically to a health care professional, would have been of value because, the analytes detected may be, for example, markers of disease. *See, e.g.*, Saxonov ¶¶ 63-67, Fig. 5; *see also* Silverbrook ¶ 199. Computer networks, including those for health care applications, have been well known since long before the priority date of the Asserted Patents. *See, e.g.*, Silverbrook ¶ 199. Thus, at the time of the alleged invention, claims 5-9 of the ’051 Patent would have been obvious to one skilled in the art based on the references cited herein, at least as described above.

b. ’170 Patent:

(1) Claims 1, 7-9

To the extent Plaintiffs contend that any of the references identified above do not disclose any or all of the limitations in Claims 1, 7-9 of the ’170 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 method for unambiguously detecting the presence or absence of at least five polynucleotide analytes in droplets in any combination of presence or absence in in droplets by use of hybridization probes labeled with one to four fluorophores. Claim 7 requires that the signal is generated during a polymerase chain reaction. Claims 8 and 9 require that there be at least seven polynucleotide analytes, and seven hybridization probes, respectively.

IPR2024-01177
California Institute of Technology - Ex. 2006 Page 12

Claims 1, 7-9 of the '170 Patent are obvious because it would have been obvious for one of skill in the art to combine the Multiplexed Encoding and Detection Art with the Probe Labeling and Measurement Art, or combine references within each class of art for at least the following reasons. For example, a POSA would have found it obvious to combine the references to analyze a greater number of targets, i.e., to perform a higher order of multiplexing as taught by Kramer and Larson, including a total of seven or more targets. A POSA would have understood the need to and benefit of looking to references such as those included in the table above from the teachings of Saxonov. *See, e.g.*, Saxonov ¶ 7 ("A new approach is needed to increase the multiplex levels of digital assays") and ¶ 6 ("instruments with more optical channels, to detect emission from more dyes, are more expensive than those with fewer channels"); *see also* Appendices E-H. A POSA would have additionally understood the benefit of not requiring immobilization to perform the assays of the alleged invention so as to not require additional steps to perform the assays. *See, e.g.*, Appendix N. A POSA would have further understood the benefit of performing the assays by generating the signal during a polymerase chain reaction, to enable the assays to employ commonly used hybridization probes, i.e., TaqMan probes. *See, e.g.*, Youvenot 9:15. Further, a POSA would have found it obvious to unambiguously detect the results of such assays to provide more accurate results of the assays such as described in Kramer by, for example, Figure 5, which depicts an unambiguous result of two targets present in combination. Kramer ¶ 26, Fig. 5. Kramer further teaches methods wherein probes with different numbers of unique fluorophores are used to differentiate the targets in combination, "[the] combinatorial code may be quadraplex coding in which the code elements comprise four colors, optionally enlarged by additional code elements of three colors, two colors or one color, or some combination thereof," Kramer ¶ 11, and further methods wherein the targets are labeled with differing amounts of common fluorophores to differentiate between targets, "[i]n ratio coding differing amounts of the same label are used for differentiation. Combinatorial codes according to this invention may be augmented with ratio coding, preferably integral ratio coding, that is, ratios of whole numbers such as 2:1, 3:1, 4:1 or 5:1, and vice versa." Kramer ¶ 14. Saxonov similarly teaches unambiguous detection of targets both in a single color and by differentiating the colors of the targets to be detected, such as in Figures 5 and 10. *See, e.g.*, Saxonov ¶¶ 78 (describing the detection of three targets in any combination, the single positive

populations, the "double-positive populations (T1+/T2+, T1+/T2+, and T2+/T3+)" and the "triple positive population (T1+/T2+/T3+)."), 60-67 (describing the detection of two analytes in any combination based on intensities of signals exhibited in a single color).

Further, a POSA would have had a reasonable expectation of success in practicing the assays of the alleged invention because a POSA would have understood that a digital PCR assay can be multiplexed with multiple different colors by the use of multiple optical channels and that more than three targets could be multiplexed by applying the teachings of Saxonov, e.g., Fig. 5, depicting the detection of two distinct targets in a single color fluorophore, a FAM fluorophore. Saxonov further teaches the detection of three analytes in any combination of presence or absence in a single color based off differing intensities. *See, e.g.*, Saxonov ¶ 41. A POSA would have expected success in performing the teachings of Saxonov of "performing a digital assay with multiplexed detection of two or more distinct targets in the same optical channel" ¶ 8 and applying them to, for example, four optical channels (colors) with two targets identified in each channel to analyze the presence of eight targets in a single sample solution or alternatively twelve targets in four colors with three targets per channel. A POSA would have further understood from the teachings of Kramer that multiplex detection of more than ten targets can be performed in an assay via combinatorial and ratio coding schemes using four unique fluorophores. *See e.g.*, Kramer ¶¶ 11, 14; Appendix C. A POSA would have further known to optimize the differentiation between the signals generated by the targets, alone and in combination, as described by the teachings of Larson, which allow the multiplexed detection of nine analytes using only two fluorophores. *See*, *e.g.*, Larson ¶¶ 35, 150 (describing Fig. 15); *see also* Appendix E. Thus, at the time of the alleged invention, claims 1, 7-9 of the '170 Patent would have been obvious to one skilled in the art based on the references cited herein, at least as described above.

(2) Claims 2, 3, 20

To the extent Plaintiffs contend that any of the references identified above do not disclose any or all of the limitations in Claims 2, 3, 20 of the '170 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. Claims 2-3, 20 are dependent on claim 1 and specify conditions for the hybridization probes. Claim 2 requires that

IPR2024-01177
California Institute of Technology - Ex. 2006 Page 14

the probes be complementary to one of the targets. Claim 3 requires the probes comprise one or more fluorophores, up to four fluorophores. Claim 20 requires the probes be present at a given concentration for signals to correspond to the presence of a unique combination of targets.

Claims 2, 3, 20 of the '170 Patent are obvious because it would have been obvious for one of skill in the art to combine the Multiplexed Encoding and Detection Art with the Probe Labeling and Measurement Art, or combine references within each class of art for at least the following reasons. A POSA would have been motivated to combine the Multiplexed Encoding and Detection Art with the Probe Labeling and Measurement Art to perform the assays described in the alleged invention because A POSA would have understood that reliable signal generation is dependent on the probes and the fluorophore(s) that are on the probes. *See, e.g.*, Saxonov ¶ 60 (describing signals generated from two probes to identify two targets in a multiplexed assay).

It would have been obvious to a skilled artisan at the time of the alleged invention to use probes that are specific to target analytes, as was well known in the art. *See, e.g.*, Saxonov ¶¶ 6, 50; *see also* Appendix E. It was further well known in the art that probes comprised one color (one unique fluorophore) per probe, two colors per probe, three colors per probe, or four colors per probe could be used in multiplexed assays to even further that different numbers of each unique fluorophore may be placed on a single probe. *See, e.g.*, Kramer ¶¶ 3, 32. It was additionally well known that the differentiation of the fluorescent signals from the probes corresponding to targets by "varying the probe and primer concentrations together [is] a very simple technique to optimize relative intensities in higher-plex reactions." *See, e.g.*, Larson ¶ 134, *see also* Larson ¶¶ 137, 150. Thus, at the time of the alleged invention, claims 2, 3, 20 of the '170 Patent would have been obvious to one skilled in the art based on the references cited herein, at least as described above.

(3) Claims 4-6

To the extent Plaintiffs contend that any of the references identified above do not disclose any or all of the limitations in Claims 4-6 of the '170 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. Claims 4-6 are dependent on claim 1 and specify conditions for the droplets. Claim 4 requires a droplets comprise at

least five hybridization probes. Claim 5 requires a droplet comprises one or more of at least five targets. Claim 6 requires that droplets comprise at most one target.

Claims 4-6 of the '170 Patent are obvious because it would have been obvious for one of skill in the art to combine the Multiplexed Encoding and Detection Art with the Probe Labeling and Measurement Art, or combine references within each class of art for at least the following reasons. A POSA would have been motivated to combine the Multiplexed Encoding and Detection Art with the Probe Labeling and Measurement Art to perform the assays described in the alleged invention because A POSA would have understood that in order for targets to be detected in droplets, that targets and their corresponding probes and other reaction agents would need to be with in the droplets to perform the assays. *See, e.g.*, Saxonov ¶ 30, 78; *see also* Appendix E. A POSA would have understood that in order to perform a multiplexed assay within a droplet, that the droplet would need to be capable of emitting signals corresponding to each target, which would require each probe and target combination to be present in a single droplet. *See id.* Further, it was well known and understood in the art that a sample solution could be manipulated by "dilution" of the sample to construct assays wherein at most one target is present in a droplet. *See, e.g.*, Saxonov ¶ 25; *see also* Appendix E. Thus, at the time of the alleged invention, claims 4-6 of the '170 Patent would have been obvious to one skilled in the art based on the references cited herein, at least as described above.

(4) Claims 10-12, 14-16

To the extent Plaintiffs contend that any of the references identified above do not disclose any or all of the limitations in Claims 10-12, 14-16 of the '170 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. Claims 10-12 are directed to the sample. Claim 10 requires one or more target to be cell-free nucleic acid, tumor nucleic acid, fetal nucleic acid, or viral nucleic acid. Claim 11 requires the sample to be biological and derived from a subject Claim 12 requires the presence of a target to represent the presence of cancer or an infection in the subject.

Claims 10-12, 14-16 of the '170 Patent are obvious because it would have been obvious for one of skill in the art to combine the Multiplexed Encoding and Detection Art with the Computer and

IPR2024-01177
California Institute of Technology - Ex. 2006 Page 16

Network Assays Art and/or the Biological Sample Art, or combine references within each class of art for at least the following reasons. *See supra*, Section B.1.a.(2); *see also* Youvenot 1:30 (incorporating by reference U.S. Patent Pub. No. 2010/0173394A1 (the "'394 Publication"), which recites "[c]linical samples may include nasopharyngeal wash, blood, plasma, cell-free plasma, buffy coat, saliva, urine, stool, sputum, mucous, wound swab, tissue biopsy, milk, a fluid aspirate, a swab (e.g., a nasopharyngeal swab), and/or tissue, among others. Environmental samples may include water, soil, aerosol, and/or air, among others. Research samples may include cultured cells, primary cells, bacteria, spores, viruses, small organisms, any of the clinical samples listed above, or the like." '394 Publication ¶ 156.); Saxonov ¶ 5 ("[d]igital assays frequently rely on amplification of a nucleic acid target in partitions to enable detection of a single copy of an analyte."); Saxonov 128 5:8-10 (teaches the detection of "copy number (CN), copy number variation (CNV), and the presence/abundance of single nucleotide polymorphisms (SNPs), among other quantities."); Kramer ¶ 1 (Kramer teaches an "invention [that] relates to homogenous in vitro multiplexed assays, including particularly homogeneous amplification assays, for screening biological samples for the presence of any of a large number of nucleic acid sequences."); Larson ¶ 50 ("[a] sample can also be total RNA extracted from a biological specimen, a cDNA library, viral, or genomic DNA."); Davies ¶ 2 ("The present invention relates to molecular diagnostics. In particular, the present invention relates to PCR based diagnostics for the typing of Group B streptococci."); Nakamura ¶ 227 (describing treatment options based on the presence of disease markers, including those for cancer); Peck ¶ 3 ("The present invention relates generally to methods for assessment of carcinoma cancer therapy and relapse detection, and more specifically it relates to an efficacy assessment method for lung cancer therapy to rapidly assess the outcome of lung cancer therapy so treatment with higher likelihood of success can be selected to prevent invalid treatment from wrecking patents, and a routine monitoring method for cancer relapse after the treatment."); Wang 2:27-31 ("The availability of quantitative PCR will provide valuable information in a number of research areas. More particularly, the invention provides critical information in disease diagnosis and cancer therapy"); Mason ¶ 51 ("In an embodiment, the present invention is directed to compositions, methods and kits for use in reverse transcriptase-polymerase chain reaction (RT-PCR) for detection, production, amplification, analysis and quantification of human

β-retrovirus nucleic acids from biological samples."); Kozal at abstract ("The present invention relates to methods of monitoring, via polymerase chain reaction, the clinical progression of human immunodeficiency virus infection and its response to antiretroviral therapy"); Yeung ¶ 9 ("Apart from a very sensitive methodology for detection of genetic materials, MOD may also be useful, combining with the usual multiplex real time PCR using different probe reporter dyes, as a confirmation test of certain difficult to diagnose diseases."); Hassard ¶ 11 ("The invention also provides a method for allele specific primer, PCR based, SNP validation. Creation of such a method should allow a healthcare worker to take a blood sample from a patient and rapidly (within a few minutes) make an informed choice of drug therapy based on the patient's genetic information."). A POSA would have been motivated to combine the above classes of art to perform efficient communication of assay results with interested parties and to determine the scope of the targets and samples that may be analyzed and detected with the described assays and it was well known that such targets were detectable by such assays. *See, e.g.*, Wang 10:31-35, 2:25-37.

It would have been obvious to one of ordinary skill in the art to perform an assay as described in the alleged invention wherein at least one of the targets was nucleic acid from a tumor to detect cancer in a patient, as such detection was well-known in the art. *See, e.g.*, Nakamura ¶ 227. It further would have been obvious to provide information about the presence or absence of targets detected in biological assays to a healthcare professional that may make a clinical decision on the basis of the results, including treating a patient with an antibiotic. *See, e.g.*, Davies ¶¶ 57-60, 64. Thus, at the time of the alleged invention, claims 10-12, 14-16 of the '170 Patent would have been obvious to one skilled in the art based on the references cited herein, at least as described above.

(5) Claims 13, 17-19

To the extent Plaintiffs contend that any of the references identified above do not disclose any or all of the limitations in Claims 13, 17-19 of the '170 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. Claim 13 is directed to transmitting information through a computer network. Claims 17-19 require that at least part of the method be performed on a computer and require that the computer may be located on

a remote server or on a droplet reader.

Claims 13, 17-19 of the '170 Patent are obvious because it would have been obvious for one of skill in the art to combine the Multiplexed Encoding and Detection Art with the Computer and Network Assays Art, or combine references within each class of art for at least the following reasons. *See supra*, Section B.1.a.(2). First, a POSA would have been motivated to combine the above classes of art because A POSA would have understood that to perform the steps of the alleged invention, such as detecting and measuring cumulative intensity signals emitted from excited fluorophores, using a computer would provide benefits of improving efficiency in collecting data and performing calculations and thermal cycling to amplify targets. *See, e.g.*, Higuchi Fig. 8; *see also* Matlezos ¶¶ 12, 132.

Further, a POSA would have known that performing the generation of fluorescent signals representing polynucleotide targets, the detection of such signals, and the determination of which, if any, of the targets such signals represent has been performed on computers since long before the alleged priority date of the Asserted Patents and a POSA would have been motivated to apply these teachings to the assays of the alleged invention to enhance the efficiency and reliability of signal detection and measurement. *See, e.g.*, Silverbrook ¶ 198.

A POSA would have additionally understood that the computer may be located anywhere, including in multiple places, on the apparatus to perform the methods of the alleged invention, including remotely at another location, and on a droplet reader. *See, e.g.*, Appendix E; *see also* Saxonov ¶ 45; *see also* Matlezos ¶ 132; *see also* Oh 070 ¶ 71.

A POSA would have understood that transmitting such information over a computer network, specifically to a health care professional, would have been of value because, the analytes detected may be, for example, markers of disease. *See, e.g.*, Saxonov ¶¶ 63-67, Fig. 5; *see also* Silverbrook ¶ 199. Computer networks, including those for health care applications, have been well known since long before the priority date of the Asserted Patents. *See, e.g.*, Silverbrook ¶ 199. Thus, at the time of the alleged invention, claims 13, 17-19 of the '170 Patent would have been obvious to one skilled in the art based on the references cited herein, at least as described above.

c. ’921 Patent:

(1) Claims 1-3, 8-10, 14, 15

To the extent Plaintiffs contend that any of the references identified above do not disclose any or all of the limitations in Claims 1-3, 8-10, 14, 15 of the ’921 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 method for unambiguously detecting the presence or absence of “M” analytes by encoding analytes as a value of one component of a fluorescent signal, wherein said fluorescent signal comprises “F” wavelength components, wherein the M analytes are detected in any combination of presence or absence in a sample volume based on the F wavelength components, where there are more analytes than wavelength components in the assay and the analytes are amplified in the sample volume. Claims 2 and 3 require each analytes to be encoded as a first value in a first component and a second value in a second component. Claim 8 requires that the fluorescent signal be generated during a polymerase chain reaction. Claim 9 requires at least one analyte to be encoded by an additional value. Claim 10 requires at least one analyte to be a polynucleotide. Independent claim 14 recites a kit for detecting the presence of M analytes nondegenerately by encoding analytes as a value of one component of a fluorescent signal wherein a value is generated when the analyte specific reagent is contacted with its corresponding analyte and the kit detects the presence of the analytes in any combination of presence or absence in a sample volume without mass spectrometry and the analytes are amplified in the sample volume. Claim 15 depends on claim 14 and recites that said fluorescent signal comprises F wavelength components and the kit unambiguously identifies the analytes where there are more analytes than wavelength components.

Claims 1-3, 8-10, 14, 15 of the ’921 Patent are obvious because it would have been obvious for one of skill in the art to combine the Multiplexed Encoding and Detection Art with the Probe Labeling and Measurement Art, or combine references within each class of art for at least the following reasons. For example, a POSA would have found it obvious based on the prior art to detect, as the prior art teaches, multiple polynucleotide targets unambiguously or non-degenerately. Further, a POSA would have found it obvious to unambiguously detect the results of such assays to provide more accurate

IPR2024-01177
California Institute of Technology - Ex. 2006 Page 20

results of the assays such as described in Kramer by, for example, Figure 5, which depicts an unambiguous result of two targets present in combination. Kramer ¶ 26, Fig. 5. Kramer further teaches methods wherein probes with different numbers of unique fluorophores are used to differentiate the targets in combination, "[the] combinatorial code may be quadraplex coding in which the code elements comprise four colors, optionally enlarged by additional code elements of three colors, two colors or one color, or some combination thereof," Kramer ¶ 11, and further methods wherein the targets are labeled with differing amounts of common fluorophores to differentiate between targets, "[i]n ratio coding differing amounts of the same label are used for differentiation. Combinatorial codes according to this invention may be augmented with ratio coding, preferably integral ratio coding, that is, ratios of whole numbers such as 2:1, 3:1, 4:1 or 5:1, and vice versa." Kramer ¶ 14. Saxonov similarly teaches unambiguous detection of targets both in a single color and by differentiating the colors of the targets to be detected, such as in Figures 5 and 10. *See, e.g.*, Saxonov ¶¶ 78 (describing the detection of three targets in any combination, the single positive populations, the "double-positive populations (T1+/T2+, T1+/T2+, and T2+/T3+)" and the "triple positive population (T1+/T2+/T3+)."), 60-67 (describing the detection of two analytes in any combination based on intensities of signals exhibited in a single color). A POSA would have understood that unambiguous detection of polynucleotide targets would be beneficial to more precisely determine the presence (and amount) of targets in a sample solution and that this was already known in the field. *See e.g.*, *id.*

A POSA would have further been motivated to encode each analyte as one component of a fluorescent signal to generate an encoding scheme. *See, e.g.*, Saxonov Fig. 5; Kramer ¶ 11 ("The combinatorial code may be quadraplex coding in which the code elements comprise four colors, optionally enlarged by additional code elements of three colors, two colors or one color, or some combination thereof."), Fig. 1; *see also* Appendix I; *see also* Appendix K. A POSA would have understood that it was well known in the art that analytes may be encoded by fluorescent signals for detection and would have been motivated to label analytes with fluorescent labels to enable detection. *See id.*

It would have further been obvious to a skilled artisan to use a fluorescent signal comprising F wavelength components, i.e., F colors or fluorophores as it was well known in the art at the time of the

alleged invention. *See, e.g.*, Kramer ¶ 32, Fig. 1; *see also* Appendix K. A POSA would have further been motivated to generate the signal using a polymerase chain reaction because of its compatibility with a variety of different hybridization probes. *See, e.g.*, Larson ¶ 93, *see also* Larson ¶¶ 70, 145, 156. A POSA would have expected success in generating a coding scheme with F fluorescent signals because such assays were well known and the labeling of individual probes with multiple fluorophores was well known at the time. *See, e.g.*, Saxonov ¶ 51 ("one probe may be labeled with a different number of fluorophores than the other probe" and these probes may be "the same or different").

It likewise would have been obvious to a POSA to unambiguously identify a number of targets greater than the number of colors or fluorophores used in an assay in a single sample volume without immobilization or mass spectrometry. A POSA would have understood the need to and benefit of looking to references such as those included in the table above from the teachings of Saxonov. *See, e.g.*, Saxonov ¶ 7 ("A new approach is needed to increase the multiplex levels of digital assays") and ¶ 6 ("instruments with more optical channels, to detect emission from more dyes, are more expensive than those with fewer channels"); *see also* Appendix A. Further, a POSA would have had a reasonable expectation of success because a POSA would have understood that a digital PCR assay can be multiplexed in a single color in droplets. *See, e.g.*, Saxonov Fig. 5. A POSA would have further understood that it was possible to, and would have expected predictable results in, detecting more analytes than fluorophores using more than one fluorophore, such as three analytes using two colors, as was well known in the art. *See, e.g.*, Larson ¶ 140; *see also* Appendix M; *see also* Saxonov ¶ 76-79, Figs. 9-10; *see also* Appendix I. A POSA would have understood the benefit of not requiring immobilization to be not requiring additional steps and would have expected success as none of the above-described methods, nor do any of those in the cited art in Section I. require immobilization or spectrometry. *See* Appendices I-N.

A POSA would have further found it obvious to encode each of the analytes detected as at least one first value in a first component (color) of the fluorescent signal and at least one second value in a second component of the fluorescent signal, wherein the first value is an intensity or a range of intensities. A POSA would have been motivated to encode analytes in two colors because the prior art teaches that analytes may be more easily differentiated using more fluorophores. *See, e.g.*, Larson ¶

47 (assays are expanded "geographically" using more colors); *see also* Saxonov ¶ 20. A POSA would have further understood that it was possible to, and would have expected predictable results in, detecting targets encoded as values in two colors, such as three targets encoded using two colors, as was well known in the art. *See, e.g.*, Larson ¶ 140; *see also* Appendix M; *see also* Saxonov ¶ 76-79, Figs. 9-10; *see also* Appendix I. A POSA would have further understood the benefit of encoding the targets as an intensity in a color to allow detection as was well known and regularly performed in the art at the time of the alleged invention.

Additionally, it would have been obvious to a person of ordinary skill at the time of the alleged invention that at least one of said analytes may be encoded by at least one additional value, wherein the additional value may be an additional component of said signal or a value from at least one component of an additional signal. A POSA would have understood the benefit of encoding a target in more than one component of a signal to differentiate between targets. *See, e.g.*, Larson ¶ 47 (adding more colors to an assay expands the assay "geometrically"); *see also* Saxonov ¶ 20. A POSA would have expected predictably successful results in performing such an assay because Larson teaches an assay detecting three targets in two colors, wherein one target is encoded by both colors. *See, e.g.*, Larson ¶ 140.

Thus, at the time of the alleged invention, claims 1-3, 8-10, 14, 15 of the '921 Patent would have been obvious to one skilled in the art based on the references cited herein, at least as described above.

(2) Claims 5-7, 16, 17, 19

To the extent Plaintiffs contend that any of the references identified above do not disclose any or all of the limitations in Claims 5-7, 16, 17, 19 of the '921 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. Claims 5-7, 16, 17, 19 depend on similar claims 1 and 14 and require the use of hybridization probes and provide further limitations of the composition of such probes. Claim 7 recites the generation of a chromatogram. Claim 19 requires the analyte-specific reagents (often probes, as in claims 5, 6, 16, and 17) to be present in different amounts in the kit.

Claims 5-7, 16, 17, 19 of the '921 Patent are obvious because it would have been obvious for one of skill in the art to combine the Multiplexed Encoding and Detection Art with the Probe Labeling and Measurement Art, or combine references within each class of art for at least the following reasons. It would have been obvious to one of skill in the art to perform the assays of the alleged invention using hybridization probes because the sequence-specific nature of hybridization probes would allow an assay to identify targets with increased accuracy and specificity. *See, e.g.*, Larson ¶ 93, *see also* Larson ¶ 145. A POSA would have had a reasonable expectation of success in the use of hybridization probes, including those comprising an identical fluorophore or combination of fluorophores as it was well known in the art that identical fluorophores may be used to encode different analytes, and that such coding schemes were beneficial because they would allow the use of fewer colors to perform a multiplexed assay, lowering costs. *See e.g.*, Saxonov ¶¶ 8, 51, Fig. 5; *see also* Appendix I. A POSA would have further understood that the signals generated from the hybridization probes used in the assay could be detected and used to construct a chromatogram, as was regularly done in the art long before the date of the alleged invention, and would have been motivated to do so to visualize the collected data. *See e.g.*, Saxonov Fig. 4; *see also* Appendix I.

Finally, a POSA would have been motivated to have target-specific reagents, such as hybridization probes with attached fluorophores, present at different amounts to differentiate the fluorescence signals of the targets. *See e.g.*, Saxonov ¶ 51; *see also* Larson ¶¶ 12, 91, 94, 130, claim 6. Thus, at the time of the alleged invention, claims 5-7, 16, 17, 19 of the '921 would have been obvious to one skilled in the art based on the references cited herein, at least as described above.

(3) Claims 4, 13

To the extent Plaintiffs contend that any of the references identified above do not disclose any or all of the limitations in Claims 4 and 13 of the '921 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. Claims 4 and 13 require specific conditions for the non-degeneracy of the detection. Claim 4 requires that the coding scheme be made nondegenerate by enumerating all legitimate results that may be obtained from the scheme and eliminating the degenerate results to eliminate degeneracy while claim 13 requires that

the coding scheme be innately nondegenerate or nondegenerate by construction.

Claims 4 and 13 of the ’921 Patent are obvious because it would have been obvious for one of skill in the art to combine the Multiplexed Encoding and Detection Art with the Probe Labeling and Measurement Art, or combine references within each class of art for at least the following reasons. It would have been obvious to one of ordinary skill in the art to eliminate degenerate codes generated by a coding scheme and to generate coding schemes that are non-degenerate. For example, it was well known in the art that certain combinations of targets when present together in an assay may produce results with ambiguity, and that those results may be identified based on the coding scheme. *See, e.g.*, Kramer Fig. 6. A POSA would have been motivated to remove the degeneracy to provide more precise results. Further, a POSA would have had a reasonable expectation of success because a POSA would have understood that a digital PCR assay can be multiplexed non-degenerately. *See, e.g.*, Saxonov Fig. 5. A POSA would have further expected success in generating nondegenerate coding schemes using two fluorophores to encode targets in an assay as using two fluorophores to non-degenerately detect three targets was well known in the art. *See, e.g.*, Larson ¶ 140; *see also* Appendix M; *see also* Saxonov ¶ 76-79, Figs. 9-10; *see also* Appendix I. Thus, at the time of the alleged invention, claims 4, 13 of the ’921 would have been obvious to one skilled in the art based on the references cited herein, at least as described above.

(4) Claims 11-12

To the extent Plaintiffs contend that any of the references identified above do not disclose any or all of the limitations in Claims 11-12 of the ’921 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. Claims 11-12 of the ’921 Patent are dependent on claim 1, which is invalid for the reasons stated above. Further, the limitations of claims 11-12 are directed to the use of computers, the placement or location of computers in performing the methods of the alleged invention and transmitting information through such a computer network.

Claims 11-12 of the ’921 Patent are obvious because it would have been obvious for one of skill in the art to combine the Multiplexed Encoding and Detection Art with the Probe Labeling and

Measurement Art with the Computer and Network Assays Art, or combine references within each class of art for at least the following reasons. *See supra*, Section B.1.a.(2). First, a POSA would have been motivated to combine the above classes of art because A POSA would have understood that to perform the steps of the alleged invention, such as detecting and measuring cumulative intensity signals emitted from excited fluorophores, using a computer would provide benefits of improving efficiency in collecting data and performing calculations and thermal cycling to amplify targets. *See, e.g.*, Higuchi Fig. 8; *see also* Matlezos ¶¶ 12, 132.

Further, a POSA would have known that performing the generation of fluorescent signals representing polynucleotide targets, the detection of such signals, and the determination of which, if any, of the targets such signals represent has been performed on computers since long before the alleged priority date of the Asserted Patents and a POSA would have been motivated to apply these teachings to the assays of the alleged invention to enhance the efficiency and reliability of signal detection and measurement. *See, e.g.*, Silverbrook ¶ 198.

A POSA would have additionally understood that the computer may be located anywhere, including in multiple places, on the apparatus to perform the methods of the alleged invention, including remotely at another location, and on a thermal cycler. *See, e.g.*, Appendix I; *see also* Saxonov ¶ 45; *see also* Matlezos ¶ 12.

Further, a POSA would have understood that transmitting such information over a computer network, specifically to a health care professional, would have been of value because, the analytes detected may be, for example, markers of disease. *See, e.g.*, Saxonov ¶¶ 63-67, Fig. 5; *see also* Silverbrook ¶ 199. Computer networks, including those for health care applications, have been well known since long before the priority date of the Asserted Patents. *See, e.g.*, Silverbrook ¶ 199. Thus, at the time of the alleged invention, claims 11-12 of the '921 Patent would have been obvious to one skilled in the art based on the references cited herein, at least as described above.

III. PATENT LOCAL RULE 3-3 (c) DISCLOSURES

Based upon presently known information, pursuant to Patent Local Rule 3-3(c), Bio-Rad submits the below descriptions of obviousness and the attached appendices, which are illustrative and not exhaustive of the reasons for which the Asserted Claims are invalid. *See* Appendices A-N. The

IPR2024-01177
California Institute of Technology - Ex. 2006 Page 26

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

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

IV. PATENT LOCAL RULE 3-3 (d) DISCLOSURES

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

A. 35 U.S.C. § 101

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

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

IPR2024-01177
California Institute of Technology - Ex. 2006 Page 27

are directed to the abstract idea of generating coding schemes, as well as decoding such schemes, to represent the amplification and detection of presence of different polynucleotide analytes. The acts of generating codes for, and determining algorithms decoding results of such coding schemes are inherently abstract, i.e., they are capable of being performed "using a pen and paper," which is a hallmark of an abstract idea. *In re Killian*, 45 F.4th 1373, 1382 (Fed. Cir. 2022). In fact, Tables 3 and 4 of the specification do exactly that –encode and decode the possible results showing the presence or absence of polynucleotide analytes in an assay. *See, e.g.*, '170 Patent 13:45-15:56.

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

B. 35 U.S.C. § 112

1. Written Description:

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

IPR2024-01177
California Institute of Technology - Ex. 2006 Page 28

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 Asserted Patents are invalid under pre-AIA 35 U.S.C. § 112 ¶ 1 for failure to provide an adequate written description.

The independent claims of the Asserted Patents, and all claims dependent therefore, at least under Plaintiffs' 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.2.c. 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 Asserted Patents also fail to fill in any gaps from the knowledge and skill in the art.

To the extent that Plaintiffs argue that the written description that is missing in the Asserted Patents or the priority applications thereto may be found in patents or other documents that are incorporated by reference into the Asserted Patents 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. Lack of Support for the Full Breadth of the Claims

To satisfy the written description requirement, the specification must provide written description support for the "full breadth of the asserted claims." *Rivera v. ITC*, 857 F.3d 1315, 1319 (Fed. Cir. 2017).

The alleged invention of the Asserted Patents claims the unambiguous or non-degenerate detection of targets in any combination or in unique combinations or presence or absence in a sample solution exceeding the number of fluorophores or unique labels used in the assay, however, the specification does not provide support for such detection of targets. Even the allegedly unambiguous or non-degenerate exemplary coding schemes contain degeneracy. For example, Table 6, which is

IPR2024-01177
California Institute of Technology - Ex. 2006 Page 29

present in the specifications of all three patents, constructs a degenerate coding scheme. Should a sample contain analyte B, C, and two copies of analyte E, it would have the same cumulate signal measurement as a sample containing Analyte A, two copies of Analyte C, and Analyte G. That is, both samples would produce a cumulative signal of [B,5], [G,3], [Y,1], and [R,2], including the shared control fluorophore. This scheme, therefore, is degenerate. *See* '170 Patent 20:6-53.

Further, the claims are not limited in any fashion regarding the number of analytes that may be detected. The '921 Patent claims lack a written description of the ability to detect "M analytes" in signals comprising "F wavelength components" without any limit of what number may constitute M or F, nor any maximum number of analytes that corresponds to a given number of wavelength components. '921 Patent Cl. 1, 14, 15; *See MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1384 (Fed. Cir. 2012). The specification provides no support for methods by which the number of M analytes may be expanded reliably using the detection hardware and signal generation methods of the time, which were limited in the number of fluorophores that may be used in an assay by spectral overlap by color emission of fluorophores and limits of intensity detection for reliable differentiation and provides no examples wherein greater than four fluorophores, i.e., greater than four wavelength components are used to perform an assay. *See* '921 Patent claims 1, 15. Further, to support the full breadth of the claim, the specification would need to reliably describe detection of, for example, 10,000 analytes in one wavelength 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 individual color or wavelength component.

The '170 and '051 Patents similarly lack sufficient written description for "detecting the presence or absence of at least seven polynucleotide analytes," '051 Patent Claim 1, and "detecting any unique combination of presence or absence of at least five polynucleotide analytes," '170 Patent Claim 1, as the specification contains no examples detecting more than sixteen analytes, far short of the specification's statement that the methods of the invention "can encode an infinite number of analytes." '170 Patent 22:32. Thus, the specification fails to provide a written description of the full scope of detecting "at least seven" or "at least five" analytes because a POSA would not have understood the specification to teach how to detect an infinite number of analytes. *See MagSil Corp.*,

687 F.3d at 1384 (finding where a claim recites an ability to perform "at least" some quantity, that the specification must enable a POSA to perform more "than a small subset of the claimed range.").

Moreover, the '921 Patent describes detection of analytes based on "F wavelength components," yet the specification fails to describe how to perform such detection using any wavelength component other than its insufficient explanation of using light wavelength components. The specification fails to describe detection on the basis of, for example, sound, radio, gamma-rays or x-rays to detect analytes in a solution. Even further, the '921 Patent claims the detection of "analytes," yet the specification provides written description only for the detection of "polynucleotide analytes," and fails to describe methods to detect any other class of analyte. As such, the '921 Patent lacks written description for the term "analytes."

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

b. Lack of Support for "unambiguous" or "non-degenerate" Detection of Analytes

The alleged invention of the Asserted Patents claims the unambiguous or non-degenerate detection of targets in any combination or in unique combinations or presence or absence in a sample solution exceeding the number of fluorophores or unique labels used in the assay, however, the specification does not provide support for such detection of targets. Even the allegedly unambiguous or non-degenerate exemplary coding schemes contain degeneracy. For example, degeneracy exists in the coding scheme of Table 6 when, for example, the presence in combination of the control, analyte B, analyte C, and two copies of analyte E produces the same cumulative signal measurement as the presence of the control, analyte A, two copies of analyte C, and analyte G (a cumulative signal of [5, 3, 1, 2] in fluorophores B, G, Y, and R, respectively). *See* '170 Patent 20:6-53. Further, the specification fails to describe any methods by which the analytes may be differentiated solely on the basis of differing intensities within the limits of detection for reliable differentiation in the instrumentation available at the time of the alleged invention.

c. Lack of Support for Performance of the Claimed Methods in Droplets

As Bio-Rad understands Plaintiffs' infringement contentions, Plaintiffs allege that all Asserted Claims encompass the methods of the invention performed in droplets, including the claims of the '170 Patent that specifically include the limitation of claim 1 of "partitioning said mixture into said plurality of droplets." The specification provides insufficient written description for performing the claimed methods in droplets. In fact, the specification actually *teaches away* from the use of droplets in describing the alleged invention's improvements upon the prior art:

> Whenever higher factors of multiplexing are required (i.e., [number of analytes]>[unique fluorophores]), fluorescence is generally combined with other techniques, such as aliquoting, spatial arraying, or sequential processing. These additional processing steps are labor-intensive and frequently require relatively expensive and complex optical and mechanical systems (e.g., spectrometers, mechanized microscopy stages, **microfluidics, droplet generators,** scanners, and the like).

'170 Patent 8:45-52 (emphasis added). Further, the specification merely provides a conclusory assertion that the methods of the invention are compatible with a variety of amplification methods, including those that occur within droplets. '170 Patent 36:17-26. In sum, the specification fails to provide a written description of how to implement the claimed methods of the alleged invention in assays wherein droplets and appropriate accompanying microfluidics are used.

d. Lack of Support for "contacting said sample solution volume with the plurality of hybridization probes"

The '051 Patent claims "providing a sample solution comprising . . . at least seven hybridization probes" and later "contacting said sample solution volume with the plurality of hybridization probes." The specification provides no description of what is meant by such limitations, nor how probes may be contacted with a sample solution which they allegedly already exist in. Thus, the claims of the '051 Patent are invalid for lack of written description because the specification provides no guidance as to how to perform the claimed limitations.

e. Lack of Support for assays without "immobilization," "mass spectrometry," or "physical separation"

The '051 Patent claims assays "without requiring any step of immobilization of said polynucleotide analytes, physical separation of said polynucleotide analytes, or mass spectrometry," the '170 Patent claims assays without "any step of immobilization of said at least five polynucleotide analytes or mass spectrometry," and the '921 Patent claims assays without "the use of mass spectrometry or immobilization of said at least M analytes." The specification, however, provides no specific description of how to achieve detection of analytes in such assays. Thus, the Asserted Claims are invalid for a lack of written description because the specification provides no guidance as to how to perform the claimed limitations.

f. Lack of Disclosure of a "Chromatogram"

The '921 Patent claim 7 recites the use of the detected fluorescence signal "to construct a chromatogram." '921 Patent cl. 7. The specification, however, provides no description, examples, or other disclosure of a "chromatogram" as the term is used in Plaintiffs' infringement contentions. Plaintiffs assert that a "chromatogram" encompasses a scatterplot, which is undescribed by the specification. Thus, '921 Patent claim 7 is invalid for a lack of written description because the specification provides no guidance as to how to perform the claimed limitations.

g. Lack of Disclosure of to Support the Detection of "five polynucleotide analytes" with fewer than four fluorophores

To the extent Plaintiffs argue that claim 1 of the '170 Patent includes assays that detect "at least five polynucleotide analytes" with fewer than four fluorophores, the specification lacks such written disclosure and support. The Specification recites no working examples of an assay for the detection of five or more analytes without the use of four fluorophores. Thus, the Asserted Claims of the '170 Patent are invalid for a lack of written description because the specification provides no guidance as to how to perform the claimed limitations.

h. Lack of Disclosure of Claimed Invention as Integrated Whole

The Asserted Claims require non-degenerate or unambiguous detection 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

IPR2024-01177
California Institute of Technology - Ex. 2006 Page 33

degeneracy or ambiguity in certain combinations of presence, as described above in Section IV.B.1.b. Further, the specification describes no measured results from performed assays, nor any figures depicting actual reliably measured signals that were successfully decoded to unambiguously detect analytes in any combination of presence or absence. This makes sense as the specification fails to provide a description for the generation of probes to successfully and reliably emit signals 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 polynucleotide analytes in assays based on such signals. The scope of the claims, are broader than what the specification teaches.[1] For example, the claims require "non-degenerate," '051 Patent claim 1, or "unambiguous" detection of a plurality of analytes. '170 Patent Claim 1; '921 Patent Claims 1, 14. The Asserted Claims further require that this "non-degenerate" or "unambiguous" detection is capable of being performed when the analytes are present "in any combination," '051 Patent Claim 1;

[1] The Asserted Patents share a specification as each traces back as a continuation of U.S. patent application Ser. No. 13/756,760.

’921 Patent Claim 1, or in a “unique combination of presence or absence,” ’170 Patent Claim 1. The specification, however, lacks description for assays that unambiguously detect analytes in any combination, nor in a unique combination, where multiple copies of the same analyte are present. The specification further provides little to no description regarding how the allegedly non-degenerate encoding schemes are put into practice, and how reliable results of detection are achieved by the use of probes labeled with fluorophores to allow the allegedly described decoding methods to be performed. There is little to no description as to how to perform differentiation of the emission spectra of probes, nor a description of how to ensure measurement of such signals is accurate and reliable. At best, the specification provides passing mentions of possible “illegitimate” results that do not correspond to a specific enumerated signal combination. *See, e.g.*, ’170 Patent 15:65-16:3. The passage describing these illegitimate, results, however, states only that the control and decoding matrix provide a “means of verifying that the assay is functioning properly,” and that an illegitimate result may “indicate that the assay malfunctioned.” *Id*. There is no explanation as to how the assay should be modified if an illegitimate result is produced so that the assay can provide a reliable output.

Further, the specification fails to enable a POSA to perform the full scope of the claim limitations of “detecting the presence or absence of at least seven polynucleotide analytes . . . [using] four fluorophores,” ’051 Patent Claim 1, and “detecting any unique combination of presence or absence of at least five polynucleotide analytes . . . [using] at most four fluorophores.” ’170 Patent Claim 1. The specification contains no examples detecting more than sixteen analytes, far short of the specification’s statement that the methods of the invention “can encode an infinite number of analytes.” ’170 Patent 22:32. Thus, the specification fails to enable use of the full scope of detecting “at least seven” or “at least five” analytes because a POSA would not have understood the specification to teach how to detect an infinite number of analytes. *See MagSil Corp.*, 687 F.3d at 1384 (finding where a claim recites an ability to perform “at least” some quantity, that the specification must enable a POSA to perform more “than a small subset of the claimed range.”). Likewise, the ’921 Patent claims “F wavelength components” and “M analytes” yet recites no working examples with more than four fluorophores or for the determination of greater than 16 polynucleotide analytes. *See id.* The ’051 and ’170 Patents likewise claim detection of “at least” five or seven analytes and fail to provide even

IPR2024-01177
California Institute of Technology - Ex. 2006 Page 35

allegedly enabling disclosure for a POSA to achieve detection of more than 16 analytes, far short of fully enabling the claims.

To the extent Plaintiffs argue that claim 1 of the '170 Patent covers assays that detected "at least five polynucleotide analytes" with fewer than four fluorophores, the specification fails to enable a POSA to do so. The Specification recites no working examples of an assay for the detection of five or more analytes without the use of four fluorophores and does not provide guidance to enable a POSA to practice the entire scope of the invention. Instead, the only examples the specification provides for detecting five or more analytes each uses four fluorophores.

Further, the '921 Patent claims the detection of "analytes," yet the specification only describes the detection of "polynucleotide analytes," and fails to provide a working example or description to enable a POSA to detect any other class of analyte. As such, the '921 Patent fails to enable a POSA to practice the full scope of the claims at least as to the term "analytes." Additionally, the '921 Patent describes detection of analytes based on "F wavelength components," yet the specification fails to describe how to perform such detection using any wavelength component other than its insufficient explanation of using light wavelength components. The specification fails to describe detection on the basis of, for example, sound, radio, gamma-rays or x-rays to detect analytes in a solution, thus failing to enable a POSA to practice the entire scope of the claims.

Moreover, the specification lacks enabling description of methods "to construct a chromatogram," as required by claim 7 of the '921 Patent as the term is used in Plaintiffs' infringement contentions. Plaintiffs assert that a "chromatogram" encompasses a scatterplot, which is undescribed by the specification.

Further, the specification fails to include any working examples demonstrating how the invention claimed therein would work for any of the Asserted Patents. Specifically, in addition to the above deficiencies, the Asserted Claims of the '170 Patent lack enablement as the specification fails to describe performance of the claimed invention in droplets, at least because the specification teaches away from the use of droplets. *See supra* Section IV.B.1.c. The '051 Patent fails to enable a POSA to perform the invention at least because there is no working example that includes "contacting said sample solution volume with the plurality of hybridization probes." To the extent that one of ordinary

IPR2024-01177
California Institute of Technology - Ex. 2006 Page 36

skill in the art could not make the claimed embodiments work based on ordinary skill in the art, the Asserted Patents do not contain any disclosures that would supplement one of ordinary skill in the art's ability to make the claimed embodiments work and otherwise meet the functional requirements of the claims.

a. Quantity of Experimentation

It would take an undue amount of experimentation to practice the claimed inventions because the specification has little to no disclosure for a POSA to perform the full scope of the claimed methods. As detailed above, there is no description of a fully working non-degenerate or unambiguous detection scheme, nor any description on the methods of reliably detecting and practically applying the allegedly described encoding methods, such as by describing methods to optimize and develop individual probe labels beyond conclusory descriptions of encoding schemes. Further, there is no single embodiment with all claim elements to enable a skilled artisan to practice the claimed invention. A POSA, reading the description of these patents would not be able to practice the signal encoding and decoding methods as claimed. To actually practice the full scope of any of the claims, a POSA would be required to engage in extensive trial-and-error experimentation, testing a given scheme, determining if the results are consistent and reliable, and, if not, redesign the scheme from scratch. Therefore, the specification does not enable the full scope of the claims to the extent they require non-degenerate or unambiguous detection in any combination or unique combination because it would require undue experimentation for a POSA to practice successfully the full scope of claims in constructing, optimizing, and implement probe label combinations.

b. Guidance in the Specification

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

Specifically, the specification provides no description of how to account for the presence multiple copies of a single analyte, and the degeneracies that may result from such presence in combination with single copies, or multiple copies of other analytes. For example, the allegedly non-degenerate or unambiguous example encoding scheme in Table 6, '170 Patent 20:6-53, contains degeneracy even after eliminating the identified "degenerate" codes for "any combination" of analytes. For example, but not limiting, the presence of the control, analyte B, analyte C, and two copies of analyte E produces the same cumulative signal measurement as the presence of the control, analyte A, two copies of analyte C, and analyte G (a cumulative signal of [5, 3, 1, 2] in fluorophores B, G, Y, and R, respectively). *See* '170 Patent 20:6-53.

The specification also provides little to no description on how to manage noise or error. As to error, the specification simply describes that "illegitimate" results, i.e., those that should not be possible based on the encoding scheme and indicates a malfunction in the assay. *See, e.g.*, '170 Patent 15:65-16:3. The specification describes that noise may be minimized by encoding the "initial assigned value [of a probe] to be greater than one, for example to better distinguish over noise," *see, e.g.*, '170 Patent 49:25-32, but, again, provides no description of how to ensure such an initial assigned value is generated and detected consistently using hybridization probes. The specification admits that an end-point based assay may need to be "ended at a threshold number of cycles set by the limit of detection of an instrument," '170 Patent 3:47-50, i.e., ended at the limit of intensity of a signal that an instrument is able to reliably detect, yet asserts, without specific support that to differentiate targets and overcome noise, initial assigned values (intensities) may be "greater than one" without regarding the limits of the detection hardware. '170 Patent 45:25-28.

Further, the specification provides no description of how to perform assays "without requiring any step of immobilization of said polynucleotide analytes, physical separation of said polynucleotide analytes, or mass spectrometry," '051 Patent, without "any step of immobilization of said at least five polynucleotide analytes or mass spectrometry," '170 Patent, and without "the use of mass spectrometry or immobilization of said at least M analytes." '921 Patent. Thus, the specification provides insufficient guidance to perform the methods of the Asserted Claims and undue experimentation would be required to perform the Asserted Claims.

c. Working Examples

The Asserted Claims require non-degenerate or unambiguous detection of polynucleotide analytes. However, none of the examples in the patents discloses such a working example. The examples, rather, provide sample encoding schemes that may exhibit degeneracy or ambiguity in certain combinations of presence. Further, the specification describes no measured results from performed assays, nor any figures depicting actual reliably measured signals that were successfully decoded to unambiguously detect analytes in any combination of presence or absence. The allegedly non-degenerate or unambiguous example encoding scheme in Table 6, '170 Patent 20:6-53, contains degeneracy even after eliminating the identified "degenerate" or "ambiguous" codes for "any combination" of analytes. For example, but not limited to, the presence in combination of the control, analyte B, analyte C, and two copies of analyte E produces the same cumulative signal measurement as the presence of the control, analyte A, two copies of analyte C, and analyte G (a cumulative signal of [5, 3, 1, 2] in fluorophores B, G, Y, and R, respectively). *See* '170 Patent 20:6-53.

d. Nature of the Invention

The alleged inventions in the Asserted Patents pertain to methods to encode and decode signals to detect polynucleotide analytes in assays. The specification describes no methods, much less any improvements, for the detection and methods for measuring such signals in assays. Due to the inconsistency between the claims and the specification, a skilled artisan would be unable to practice the full scope of the claims without undue experimentation. Further, a skilled artisan would not be enabled to practice the claimed inventions due to the broad scope of the claims and the unpredictable nature of the invention. For example, the specification fails to describe methods to ensure that probes in fact emit signals that are distinguishable, alone and in combination, according to theoretically outlined encoding schemes.

e. State of the Prior Art

To the extent that the Asserted Claims are not invalid under 35 U.S.C. §§ 102 and/or 103 as anticipated and/or obvious in view of the prior art, the state of the prior art would have required undue experimentation in light of the specification. For example, in the relevant time frame, methods of labeling probes with fluorophores and generating signals could result in inconsistent emission spectra

IPR2024-01177
California Institute of Technology - Ex. 2006 Page 39

and/or signal detection due to inconsistent emissions or the limits of detection hardware. Without guidance from the specification, it would have taken a skilled artisan undue experimentation to practice the claimed invention by finding ways to permit the unambiguous detection of multiple analytes in any combination of presence or absence and to optimize such assays.

f. Relative Skill of Those in the Art

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

g. Predictability or Unpredictability of the Art

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

h. Breadth of the Claims

As described above, the full scope of the Asserted Claims is very broad in view of the specification. The specification relates to methods to encode and decode signals to detect polynucleotide analytes in assays, but provides no description, much less any improvement, as to the methods for detection. For example, claims 1 and 14/15 of the '921 Patent describe the detection of "M analytes", unlimited by any maximum number of analytes in "F wavelength components" with no maximum number of wavelength components. The specification describes examples where no greater than four fluorophores are used and no greater than 16 analytes are detected. The specification, however, teaches no such methods for detection of over 16 analytes and even those examples contain degeneracy when detecting analytes in any combination. The allegedly non-degenerate or unambiguous example encoding scheme in Table 6, '170 Patent 20:6-53, contains degeneracy even after eliminating the identified "degenerate" or "ambiguous" codes for "any combination" of analytes. For example, but not limited to, the presence in combination of the control, analyte B, analyte C, and two copies of analyte E produces the same cumulative signal measurement as the presence of the control, analyte A, two copies of analyte C, and analyte G (a cumulative signal of [5, 3, 1, 2] in fluorophores B, G, Y, and R, respectively). *See* '170 Patent 20:6-53.

Further, specifically as to claims 1 and 15 of the '921 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 wavelength 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 individual color or wavelength component.

3. Indefiniteness:

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

Claim 1 of the '051 Patent fails to satisfy the requirements of 35 U.S.C. § 112(2) because the limitations "sample solution volume . . . comprising at least seven hybridization probes," and "contacting said sample solution volume with the plurality of hybridization probes" are indefinite in

IPR2024-01177
California Institute of Technology - Ex. 2006 Page 41

combination. Further, the limitations "cumulative intensity signal(s)," "cumulative signal measurement," "in any combination of presence or absence," "non-degenerately," "exciting the hybridization probes," and "physical separation of said polynucleotide analytes" are indefinite.

Claims 2 and 3 of the '051 Patent fail to satisfy the requirements of 35 U.S.C. § 112(2) because the limitations "wherein said plurality of hybridization probes are specific for different [polynucleotide] analytes" are indefinite.

Claim 4 of the '051 Patent fails to satisfy the requirements of 35 U.S.C. § 112(2) because the limitation "cumulative intensity signal(s)" is indefinite.

Claim 6 of the '051 Patent fails to satisfy the requirements of 35 U.S.C. § 112(2) because the limitation "wherein the health care professional makes a clinical decision based on said information" is indefinite.

Claim 1 of the '170 Patent fails to satisfy the requirements of 35 U.S.C. § 112(2) because the limitations "any unique combination of presence or absence" "cumulative intensity measurement" and "corresponds to the presence of a unique combination of presence or absence of said at least five polynucleotide analytes in said sample" are indefinite.

Claim 14 of the '170 Patent fails to satisfy the requirements of 35 U.S.C. § 112(2) because the limitation "wherein the health care professional makes a clinical decision based on said information" is indefinite.

Claim 15 of the '170 Patent fails to satisfy the requirements of 35 U.S.C. § 112(2) because the limitation "wherein said clinical decision is a treatment decision" is indefinite.

Claim 20 of the '170 Patent fails to satisfy the requirements of 35 U.S.C. § 112(2) because the limitation "cumulative intensity measurement corresponds to said presence of said unique combination" is indefinite.

Claims 1, 14 and 15 of the '921 Patent fail to satisfy the requirements of 35 U.S.C. § 112(2) because the limitations "one component of a fluorescent signal," "unambiguously," "M analytes," "F wavelength components," and "coding scheme" are indefinite.

Claim 2 of the '921 Patent fails to satisfy the requirements of 35 U.S.C. § 112(2) because the limitations "first value in a first component," and "second value in a second component" are indefinite.

Claim 4 of the '921 Patent fails to satisfy the requirements of 35 U.S.C. § 112(2) because the limitations "made nondegenerate by enumerating every legitimate result that can be obtained from said coding scheme," "identifying each legitimate result that is degenerate," and "eliminating at least one potential analyte code" are indefinite.

Claim 7 of the '921 Patent fails to satisfy the requirements of 35 U.S.C. § 112(2) because the limitation "construct a chromatogram" is indefinite.

Claim 9 of the '921 Patent fails to satisfy the requirements of 35 U.S.C. § 112(2) because the limitation "at least one additional value" is indefinite.

Claim 14 of the '921 Patent fails to satisfy the requirements of 35 U.S.C. § 112(2) because the limitation "wherein said encoding is performed in a manner that eliminates degeneracy" is indefinite.

4. Improper Dependency:

Based on the information available to date and as Bio-Rad best understands Plaintiffs' contentions at this time, claims 2 and 9 of the '921 Patent are invalid under 35 U.S.C. § 112(4) as improper dependent claims. Claims 2 and 9 contradict claim 1 from which they improperly depend by broadening the scope of claim 1. Claim 1 recites, in part, "each of said at least M analytes is encoded as a value of one component of a fluorescent signal," '921 Patent claim 1, while claim 2 recites "each one of at least M analytes is encoded as at least one first value in a first component of said fluorescent signal and at least one second value in a second component of said fluorescent signal" and claim 9 recites "at least one of said analytes is encoded by at least one additional value, wherein said at least one additional value is selected from the group consisting of a value from at least one additional component of said signal." *Id.* cl. 2, cl. 9. Claims 2 and 9 are improper dependents because claim 1 in no uncertain terms recites encoding each of the analytes as a value of one component of a fluorescent signal, while claims 2 and 9 broaden this limitation and permit analytes to be encoded as "at least one second value in a second component," or an "additional component of said signal." *See Multilayer Stretch Cling Film Holdings, Inc. v. Berry Plastics Corp.*, 831 F.3d 1350, 1362 (Fed. Cir. 2016) ("A dependent claim that contradicts, rather than narrows, the claim from which it depends is invalid.").

V. PATENT LOCAL RULE 3-4 DOCUMENT PRODUCTION

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

- **Patent Local Rule 3-4 (a):**

  BIO_CCODE00006101 to BIO_CCODE00008553

- **Patent Local Rule 3-4(b):**

  BIO_CCODE00008915 to BIO_CCODE00009367

- **Patent Local Rule 3-4(c):**

  BIO_CCODE008679 to BIO_CCODE00008914 and BIO_CCODE00008554 to BIO_CCODE00008677

- **Patent Local Rule 3-4(d):**

  BIO_CCODE00008678

- **Patent Local Rule 3-4(e):**

  BIO_CCODE008679 to BIO_CCODE00008914 and BIO_CCODE00008554 to BIO_CCODE00008677

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

Dated: June 17, 2024

Respectfully submitted,

WEIL, GOTSHAL & MANGES LLP

/s/ Derek C. Walter
Derek C. Walter

EDWARD R. REINES (Bar No. 135960)
DEREK C. WALTER (Bar No. 246322)
WEIL, GOTSHAL & MANGES LLP
201 Redwood Shores Parkway
Redwood Shores, CA 94065
Tel: (650) 802-3000
Fax: (650) 802-3100
edward.reines@weil.com
derek.walter@weil.com

Attorneys for Defendant and Counter-Plaintiff
BIO-RAD LABORATORIES, INC.

IPR2024-01177
California Institute of Technology - Ex. 2006 Page 45

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 201 Redwood Shores Parkway, Redwood Shores, California 94065. On June 17, 2024, I caused a copy of:

DEFENDANT AND COUNTER-PLAINTIFF BIO-RAD LABORATORIES, INC.'S AMENDED 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 Weil, Gotshal & Manges, LLP'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.

WILSON SONSINI GOODRICH & ROSATI, P.C.
ChromaCode-Bio-Rad@wsgr.com
AMY H. CANDIDO
acandido@wsgr.com
CHRISTOPHER D. MAYS
cmays@wsgr.com
SACHLI BALAZADEH-NAYERI
snayeri@wsgr.com
One Market Plaza
Spear Tower, Suite 3300
San Francisco, CA 94105-1126
Telephone: (415) 947-2000
Facsimile: (866) 974-7329

ERIC P. TUTTLE
eric.tuttle@wsgr.com
ARIEL C. GREEN ANABA
aanaba@wsgr.com
LISA D. ZANG
lzang@wsgr.com
953 East Third Street, Suite 100
Los Angeles, CA 90071
Telephone: (323) 210-2900
Facsimile: (866) 974-7329

Attorneys for Plaintiff and Counter-Defendant ChromaCode, Inc.

SHEPPARD, MULLIN, RICHTER & HAMPTON, LLP
LegalTm-CC-Caltech-v
BioRad@sheppardmullin.com
MARTIN R. BADER
mbader@sheppardmullin.com
JESSE A. SALEN
jsalen@sheppardmullin.com
12275 El Camino Real, Suite 100
San Diego, CA 92130-4092
Telephone: (858) 720-8900
Facsimile: (858) 509-3691

DARREN M. FRANKLIN
dfranklin@sheppardmullin.com
333 South Hope Street, 43rd Floor
Los Angeles, CA 90071-1422
Telephone: (213) 620-1780
Facsimile: (213) 620-1398

BRADLEY C. GRAVELINE, *pro hac vice*
bgraveline@sheppardmullin.com
321 North Clark St., 32nd Floor
Chicago, IL 60654
Telephone: (312) 499-6300
Facsimile: (312) 499-6301

Attorneys for Plaintiffs & Counter-Defendants ChromaCode, Inc. and California Institute of Technology

Executed on June 17, 2024 at Redwood Shores, California. I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

/s/ Noah Suissa
Noah Suissa

IPR2024-01177
California Institute of Technology - Ex. 2006 Page 46