

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BIO-RAD LABORATORIES, INC.,
Petitioner,

v.

CALIFORNIA INSTITUTE OF TECHNOLOGY,
Patent Owner

Case No. IPR2025-01546

U.S. Patent No. 12,168,797 B2

PATENT OWNER'S PRELIMINARY RESPONSE

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EXHIBIT LIST

Exhibit No.	Description
2001	Director's Memo on Interim Processes for PTAB Workload Management, dated March 26, 2025
2002	U.S. Patent No. 11,827,921
2003	U.S. Patent No. 10,770,170
2004	U.S. Patent No. 10,068,051
2005	<i>ChromaCode Inc. v. Bio Rad Laboratories, Inc.</i> , Case No. 2-23-cv-08417, Dkt. 1 (CDCA Oct. 5, 2023)
2006	<i>ChromaCode Inc. v. Bio Rad Laboratories, Inc.</i> , Case No. 2-23-cv-08417, Dkt. 34 (CDCA Dec. 7, 2023)
2007	<i>ChromaCode Inc. v. Bio Rad Laboratories, Inc.</i> , Case No. 2-23-cv-08417, Dkt. 12 (CDCA Oct. 13, 2023)
2008	<i>California Institute of Technology v. Bio-Rad Laboratories, Inc.</i> , Case No. 5-25-cv-01701, Dkt. 1 (NDCA Feb. 18, 2025)
2009	<i>In re: ChromaCode Litigation</i> , Case No. 5-23-cv-04823, Dkt. 121 (NDCA June 18, 2025)
2010	<i>In re: ChromaCode Litigation</i> , Case No. 5-23-cv-04823, Dkt. 124 (NDCA July 2, 2025)
2011	Declaration by Jesse Salen
2012	Bio-Rad, Inc.'s Invalidity Contentions, served on August 13, 2025
2013	<i>In Re ChromaCode Litigation</i> , 5-23-cv-04823, Dkt. 125 (NDCA July 22, 2025)
2014	<i>In Re ChromaCode Litigation</i> , 5-23-cv-04823, Dkt. 151 (NDCA Sept. 22, 2025)
2015	<i>In re: ChromaCode Litigation</i> , Case No. 5-23-cv-04823, Dkt. 160 (NDCA Oct. 29, 2025)
2016	<i>In re: ChromaCode Litigation</i> , Case No. 5-23-cv-04823, Dkt. 160 (NDCA Oct. 29, 2025)
2017	<i>In Re ChromaCode Litigation</i> , 5-23-cv-04823, Dkt. 152 (NDCA Sept. 26, 2025)
2018	Case Timing Statistics for Northern District of California, exported from Docket Navigator on November 7, 2025
2019	Notice of Allowance for U.S. Patent No. 10,068,051, mailed July 11, 2018

Exhibit No.	Description
2020	Information Disclosure Statement filed for U.S. Patent Application No. 18/352,112, initialed December 30, 2023
2021	Notice of Allowance for U.S. Patent No. 10,770,170, mailed May 4, 2020
2022	Notice of Allowance for U.S. Patent No. 11,827,921, mailed October 23, 2023
2023	Notice of Allowance for U.S. Patent No. 12,168,797, mailed November 18, 2024
2024	Declaration of Bernhard H. Weigl, Ph.D.
2025	<i>Curriculum Vitae</i> of Bernhard H. Weigl, Ph.D.
2026	File history of U.S. Patent No. 12,168,797
2027	Plaintiffs California Institute of Technology and ChromaCode, Inc.'s Opening Claim Construction Brief for the '797 Patent, <i>In re: ChromaCode Litigation</i> , Case No. 5:23-cv-04823, N .D. Cal.
2028	Plaintiffs California Institute of Technology and ChromaCode, Inc.'s Responsive Claim Construction Brief for The '797 Patent, <i>In re: ChromaCode Litigation</i> , Case No. 5:23-cv-04823, N .D. Cal.

I. INTRODUCTION

The Board should not institute IPR of claims 1, 2, 5–11, 13–15, and 18 (“the challenged claims”) of U.S. Patent No. 12,168,797 (EX1001, “the ’797 Patent”) because Petitioner has not met its burden of showing it has a reasonable likelihood of prevailing on any claim.

After years of significant investment in research and development, inventors from Patent Owner the California Institute of Technology (“PO” or “Caltech”) conceived of a long-sought and powerful technology for unambiguously distinguishing multiple analytes (*e.g.*, genetic sequences) in any combination of presence or absence within a biological sample. The ’797 Patent, entitled “Signal Encoding and Decoding in Multiplexed Biochemical Assays,” is one of several Caltech patents that protect embodiments of this innovative technology. Petitioner Bio-Rad Laboratories, Inc. asserts the challenged claims in the ’797 Patent are unpatentable on the following grounds:

- Ground 1: claims 1, 2, 5, 6, 10, and 18 as allegedly being unpatentable over U.S. Patent No. 9,921,154 (EX1003, “Jouvenot”);
- Grounds 1(a)–1(f): claims 6, 9, 11, 13–15, and 18 as allegedly being unpatentable over Jouvenot in view of secondary references including U.S. Patent Application Publication No. 2011/0250597 (EX1013, “Larson”);

- Grounds 2: claims 1, 2, 5, 6, 10, and 18 as allegedly being unpatentable over Jouvenot in view of European Patent Specification 0,594,763 B1 (EX1022, “Lehnen”); and
- Grounds 2(a)–2(f): claims 6, 9, 11, 13, 14, 15, and 18 as allegedly being unpatentable over Jouvenot in view of Lehnen and other secondary references including Larson.

Petition, 25–26. However, each of Petitioner's alleged invalidity grounds fails for multiple reasons.

First, Petitioner fails to show a reasonable likelihood of demonstrating that the challenged claims are obvious over Jouvenot, whether alone or in view of the relied-upon secondary references. As explained below, Jouvenot is deficient in multiple regards. Despite—or perhaps because of—Jouvenot's deficiencies, Petitioner uses impermissible hindsight to exaggerate and reinterpret Jouvenot, disregarding significant components of Caltech's invention as though they were simple and intuitive, when just the opposite is true.

Second, in Grounds 1(a)–1(f) and 2(a)–2(f), Petitioner cites Larson as a secondary reference. As described below, Larson's disclosure would have led a person of ordinary skill in the art (POSA) away from—rather than towards—the claimed invention.

Third, in Grounds 2 and 2(a)–2(f) Petitioner relies on Lehen to make up for the deficiencies in Jouvenot. But Lehen is directed to an entirely different technology and is irrelevant despite an at most superficial resemblance to a specific embodiment in the '797 Patent.

In view of the Petition's substantial deficiencies, Petitioner has failed to demonstrate a reasonable likelihood of prevailing on any claim. The Petition should be denied.

II. BACKGROUND

A. Technology

A variety of techniques have been developed to detect a target polynucleotide, such as a particular genetic sequence, within a biological sample. EX2024, ¶27. Caltech's innovations described and claimed in the '797 Patent addressed a long-standing problem in the field: namely, as the number of analytes in a biological sample increases, it quickly becomes more complicated to identify the analytes. *See id.*, ¶40. The term "multiplexing" refers to a broad class of techniques for detecting multiple analytes. *Id.*, ¶41. Early assays used polymerase chain reaction (PCR) to amplify (create copies of) each of the target polynucleotides, and often involved gel electrophoresis to separate the various PCR products that distinguished the targets. *Id.* ¶27.

Over the years, many multiplexing techniques have been developed, and they frequently involve some type of immobilization, separation (such as chromatography), or spatial immobilization based multiplexing (*e.g.*, in an array or on beads), mass spectrometry, or melting curve analysis. EX2024, ¶¶45, 67. These techniques therefore typically require large amounts of sample materials, long assay time, additional reagents, and/or additional instruments. *Id.*

A subsequent multiplex PCR approach uses “probes” to bind to targets and fluoresce with different colorimetric labels (fluorophores) corresponding to the different analytes, with results being detected with appropriate optical channels configured to detect signals from specific wavelength(s) of light, *i.e.*, colors produced by the probes when the probes bind or “hybridize” to complimentary genetic sequences in the targets, such that a signal in each optical channel corresponds to a probe color (wavelength). EX2024, ¶28. For example, a probe is designed to be complementary to a particular genetic sequence, and the probe and sequence bind via “hybridization.” *Id.* The fluorophore emits light only if the probe has bound its target within the sample. *Id.* For example, a probe with a blue fluorophore binds analyte A and its light is observed in a blue channel; and a probe with a red fluorophore binds analyte B and its light is observed in a red channel. *Id.* Increasing the numbers of probe types (each with distinct fluorophore color) and channels (one per color) increases the number of detectable analytes. *Id.*

However, scaling up to detect more analytes in the same sample has the limitation of the number of distinct colorimetric probes and optical channels that could be assayed simultaneously. *Id.*

Some multiplexing techniques use probes with colorimetric labels (fluorophores) of the same color. EX2024, ¶29. Here, color alone does not distinguish the analytes from one another: light in the channel means an analyte is present, but does not identify *which* analyte is present. *Id.* Some techniques (*e.g.*, Larson) tried to avoid this problem by (i) highly diluting the sample, (ii) physically dividing the diluted sample into droplets, (iii) observing the intensity of light from each droplet, and (iv) drawing conclusions about the analytes based on that intensity. *Id.* For example, probes with the same color could be designed to fluoresce at different intensities, to identify the analyte using the intensity. *Id.*, ¶30.

When a dilute sample is divided into droplets, different droplets may contain different numbers of unique analyte molecules. EX2024, ¶54. The “Poisson distribution” describes the statistics of how many analyte molecules the droplets contain. EX2024, ¶55. In the “limiting dilution” regime, the majority of droplets contain zero analyte molecules, fewer droplets contain exactly one analyte molecule, even fewer contain exactly two analyte molecules, still fewer contain exactly three analyte molecules, and so on. *Id.* At terminal dilution, the sample is sufficiently diluted that the Poisson distribution basically guarantees that almost all

droplets are either empty or contain only a single analyte molecule, with droplets rarely containing multiple analyte molecules. *Id.* At terminal dilution, to best avoid droplets containing multiple analyte molecules, most droplets are empty, which wastes material and time. *Id.*

The '797 Patent refers to signals from different analytes that are indistinguishable from one another in a given assay as being “degenerate.” EX1001, 16:47–50. At the time the '797 Patent and its priority applications were filed, a significant need remained for inexpensive, material-efficient, and time-efficient multiplexing that could non-degenerately identify a higher number of analytes within a given sample, without the need to add another optical channel corresponding to each additional analyte. *Id.*, 1:35–47, 8:45–62; EX2024, ¶45.

B. The '797 Patent and the Challenged Claims

To address the above-described needs, Caltech inventors conceived of a solution—described and claimed in the '797 Patent—that enables non-degenerate detection of more polynucleotide analytes in a single sample solution volume, in any combination of presence or absence, than the number of wavelength components used to detect them. EX2024, ¶45. The application that issued as the '797 Patent was filed on July 13, 2023 as a continuation of application no. 16/937,464, filed on July 23, 2020, which was a continuation of application no. 15/914,356, filed on March 7, 2018, which was a continuation of application no.

14/451,876, filed on August 5, 2014, which was a continuation of application no. 13/756,760, filed on February 1, 2013. EX1001, §§(22), (63). The '797 Patent claims priority to provisional application nos. 61/594,480, filed on February 3, 2012, and 61/703,093, filed on September 19, 2012. EX1001, §(60).

The Caltech inventors recognized that in traditional multi-channel methods such as those described above, “the number of detectable analytes is equal to the number of spectrally resolvable fluorophores. Therefore the number of analytes may only be increased by increasing the number of spectrally resolvable fluorophores.” EX1001, 12:39–45. To overcome this limitation, the inventors developed a technique to non-degenerately identify analytes in a sample, using *fewer* fluorophores than the number of analytes (in contrast to prior multi-channel techniques). EX1001, 8:45–66. Instead, “each analyte to be detected is encoded as a value of a signal (*e.g.*, intensity),” and by “measuring one component of the signal (*e.g.*, fluorescence intensity)” from a sample, the technique can “determin[e] the presence and absence of certain analytes based on the values used to encode the presence of each analyte and the cumulative value of the signal.” *Id.*, 8:66–9:6, 9:35–40.

Table 8 of the '797 Patent, below, describes an example in which 16 analytes (A–P) are encoded using fluorescence intensities of four fluorophores (fewer fluorophores than analytes):

TABLE 8

Example of encoding method using one color and one intensity per analyte, but different intensities among analytes.					
Tier	Analyte	B	G	Y	R
1	A	1	0	0	0
	B	2	0	0	0
	C	4	0	0	0
	D	8	0	0	0
2	E	0	1	0	0
	F	0	2	0	0
	G	0	4	0	0
	H	0	8	0	0
3	I	0	0	1	0
	J	0	0	2	0
	K	0	0	4	0
	L	0	0	8	0
4	M	0	0	0	1
	N	0	0	0	2
	O	0	0	0	4
	P	0	0	0	8
		15	15	15	15

EX1001, 22:9–29; EX2024, ¶57.

In this example, the presence of analyte A is indicated by a result of 1000, the presence of analyte B is indicated by a result of 2000, and the presence of analyte E is indicated by a result of 0100. EX2024, ¶60. These results express the intensity of the signal in each color; for example, the result 1000 has one unit of signal intensity in the blue channel, and the result 2000 has twice the signal intensity in the blue channel. EX2024, ¶60.

The inventive encoding technique in this example facilitates the detection of *combinations* of different analytes in a single sample volume. For example, the following table demonstrates how combinations of analytes A, B, and E can be detected from the *cumulative* signal intensity from a single sample volume that contains a given combination of analytes:

B	G	Y	R	Analytes(s) Present
1	0	0	0	A
2	0	0	0	B
3	0	0	0	AB
1	1	0	0	AE
2	1	0	0	BE
3	1	0	0	ABE

EX2024, ¶59. This table shows only a tiny fraction of the 2^{16} (65,536) possible combinations of the 16 analytes shown in Table 8 above. EX2024, ¶58.

The '797 Patent uses the term “decoding matrix” to describe data structures, such as the table excerpted above, that enable the “conversion of a cumulative signal to information concerning the presence or absence of one or more analytes.” EX1001, 10:23–25. Conversely, the '797 Patent uses the term “encoding matrix” to describe data structures containing encoding schemes such as the one in Table 8. See EX1001, 39:50. Note that for conciseness, the '797 Patent omits the decoding matrix corresponding to Table 8 because the full decoding matrix has 65,536

entries. *See* EX2024, ¶58. The size of the decoding matrix grows exponentially as a function of the number of analytes, while the size of the corresponding encoding matrix grows linearly as a function of the number of analytes. EX2024, ¶110.

The Caltech inventors recognized by intelligently designing the encoding and decoding matrices, degenerate results are avoided (*i.e.*, avoiding a result that “can indicate more than one possibility in terms of the presence or absence of an analyte,” EX1001, 16:37–38). The '797 Patent teaches several different ways to eliminate degeneracy such that every possible combination of analytes in the decoding scheme has a unique cumulative intensity, “thereby increasing the confidence with which an analyte is detected.” EX1001, 16:57–59, 22:11–23:56. One particular coding scheme that eliminates degeneracy by design is that used in Table 8, reproduced above. Specifically, in Table 8, “each analyte is represented by a code in a single color, wherein the value of the code in that single color equal to the sum of all previous values plus one.” EX1001, 22:40–43. The example scheme shown in Table 8 encodes fluorescence intensities as powers of two. “For example, if the first code contains a 1 in a particular color, the next codes are 2, 4, 8, 16, 32, 64, 128 and so on,” although the '797 Patent contemplates other progressions as well. EX1001, 22:43–64; EX2024, ¶62.

The Caltech inventors extended inventive schemes, such as in Table 8, to describe the measurement capabilities of a system using C colors with the equation

$M = C \times \log_2 (F + 1)$, where F is the maximum cumulative intensity, for any color, when all of the analytes are present, and M is the maximum number of analytes that can be unambiguously detected using the system. EX1001, 23:21–27, 77:35–78:51; EX2024, ¶63. Claim 1 of the '797 Patent recites this equation, constraining C to be equal to 4, 5, or 6, and constraining $F+1$ to be a positive integer and a power of 2. EX1001, 78:39–51. Under these constraints, the minimum value of F is 3, based upon which the presence or absence of each of eight analytes can be unambiguously detected using the system, “without immobilization, mass spectrometry or melting curve analysis.” EX1001, 77:35–78:52; EX2024, ¶63.

C. The '797 Patent's Prosecution History

Initially, Examiner Negin rejected the claims as being obvious over Nature Biotechnology, volume 19, 2001, pages 631–835 (“Han”) in view of secondary references, or as indefinite, or as not enabled. EX2026, 1313–1321. Examiner Negin also issued double patenting rejections over U.S. Patent Nos. 8,838,394, 10,068,051, 10,770,170, and U.S. Patent Application No. 16/937,464, all of which are the '797 Patent's parents. *Id.*, 1321–1326. Following PO's response including amendments and arguments, Examiner Negin issued a Final Office Action maintaining the same rejections. *Id.*, 676–691. PO replied with arguments and a terminal disclaimer, and amended independent claim 1 as follows:

1. (Currently Amended) A system comprising:

- a sample chamber configured to house a sample and analyte-specific reagent mixtures of analyte-specific hybridization probes and multiple fluorophores;
- a multi-channel detector to detect:
 - a first electromagnetic signal at a first wavelength from the sample chamber, the first electromagnetic signal generated by excitement of a first fluorophore of the multiple fluorophores;
 - a second electromagnetic signal at a second wavelength from the sample chamber, the second electromagnetic signal generated by excitement of a second fluorophore of the multiple fluorophores;
 - a third electromagnetic signal at a third wavelength from the sample chamber, the third electromagnetic signal generated by excitement of a third fluorophore of the multiple fluorophores;
 - a fourth electromagnetic signal at a fourth wavelength from the sample chamber, the fourth electromagnetic signal generated by excitement of a fourth fluorophore of the multiple fluorophores;
- a processor controlled analyzer to receive, from the multi-channel detector, a cumulative signal based on the first, second, third, and fourth electromagnetic signals and apply a decoding matrix to the cumulative signal to unambiguously detect the presence or absence of at least

each of M analytes by associating, for each analyte, a first value in a first component of the cumulative signal and a second value in a second component of the cumulative signal, wherein each first value is an intensity or range of intensities and each second value is a wavelength or a range of wavelengths, and wherein the second values comprise the first, second, third, and fourth wavelengths, and the determination is made without immobilization, mass spectrometry or melting curve analysis;

wherein for the positive integer M,

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

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

C=4, 5, or 6; and

wherein F+1 is a positive integer and wherein F+1 is 1 or a power of 2.[sic]

wherein M is greater than the number of the second values used to encode the analytes (C), the multi-channel detector comprises C channels, and M and C are positive integers;.[sic]

EX2026, 657–658.

Examiner Negin then allowed the application, stating “[t]he claims are free of the prior art because the prior art does not teach experimentally decoding

electromagnetic signals to determine the presence and absence patterns of analytes using the equation and values input into the equation recited in the claims.”

EX2026, 595; EX2024, ¶70.

After allowance, PO further amended claim 1 as follows, into its now-granted form:

1. (Currently Amended) A system comprising:

...

wherein $F+1$ is a positive integer and wherein $F+1$ is ~~1~~ or a power of 2.*[sic]*

wherein M is greater than the number of the second values used to encode the analytes (C), the multi-channel detector comprises C channels, and M and C are positive integers[;].

EX2026, 404–405.

Notably, PO filed during prosecution an Information Disclosure Statement citing the equivalents of Jouvenot and Larson, which Examiner Negin initialed to indicate that he had considered the references before he allowed the claims.

EX2026, 1333 (showing Cite No. 060, “US-9441266,” which is a continuation to Larson), 1337 (showing Cite No. 140, “US-20140171341,” which is a pre-grant publication of Jouvenot).

D. The Ground References

All of Petitioner's grounds (including Grounds 1, 1(a)–1(f), 2, 2(a)–2(f)) rely on Jouvenot as the primary reference. Petition, 25–26. As described below in §V.A., Petitioner fails to establish the claims are unpatentable over Jouvenot, whether alone or in combination with other references.

Moreover, Petitioner's grounds 1(a)–1(f) and 2(a)–2(f) (challenging the '797 patent's dependent claims 6–9, 11, 13–15, and 18) all cite a secondary reference Larson. Petition, 25–26. As described below in §V.B., Petitioner fails to establish the claims are unpatentable over Jouvenot in combination with Larson and other secondary references.

Finally, Petitioner's grounds 2–2(f) all cite Lehnen as an additional secondary reference, which allegedly shows how it would have been obvious to “encod[e] analytes by the geometric progression of 1, 2, 4, 8, etc.” Petition, 25–26, 69. As described below in §V.C., Lehnen cannot cure the deficiencies in Jouvenot.

1. Jouvenot

Jouvenot was filed on December 6, 2013, and issued on March 20, 2018. EX1003, §§(22), (43). Jouvenot claims the benefit of several earlier applications. EX1003, §(60).

Jouvenot discloses “a system, including methods and apparatus, for performing a multiplexed digital assay.” EX1003, 2:26–28. Regarding “digital assays,” Jouvenot states:

Digital assays generally rely on the ability to detect the presence or activity of individual copies of an analyte in a sample. In an exemplary digital assay, a sample is separated into a set of partitions, generally of equal volume, with each containing, on average, less than about one copy of the analyte. If the copies of the analyte are distributed randomly among the partitions, some partitions should contain no copies, others only one copy, and, if the number of partitions is large enough, still others should contain two copies, three copies, and even higher numbers of copies. The probability of finding exactly 0, 1, 2, 3, or more copies in a partition, based on a given average concentration of analyte in the partitions, is described by a Poisson distribution.

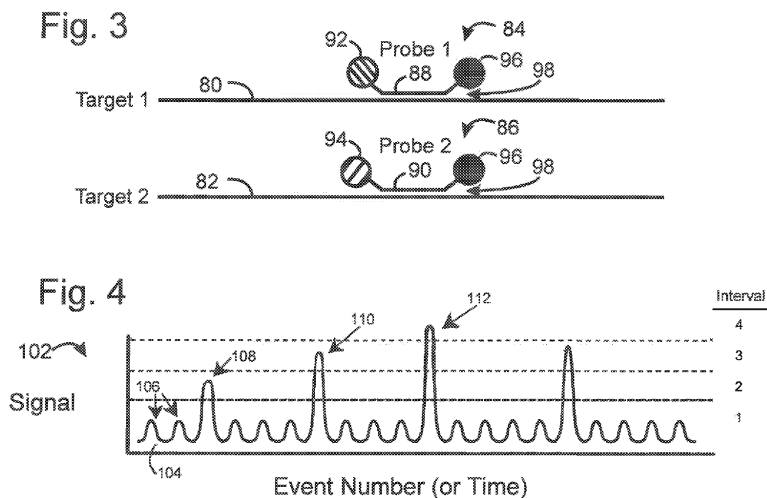
EX1003, 1:39–51; EX2024, ¶74.

According to Jouvenot, “[d]igital assays frequently rely on amplification of a nucleic acid target in partitions to enable detection of a single copy of an analyte,” and such “[a]mplification may be conducted via the polymerase chain reaction (PCR).” EX1003, 2:1–4; EX2024, ¶75. Jouvenot states “[a]mplification of the target can be detected optically from a fluorescent probe included in the reaction,”

and “the probe can include a dye that provides a fluorescence signal indicating whether or not the target has been amplified.” EX1003, 2:7–11; EX2024, ¶75.

Jouvenot identified various shortcomings in then-known multiplexing techniques, such as that “instruments with more optical channels, to detect emission from more dyes, are more expensive than those with fewer channels.” EX1003, 2:16–18; EX2024, ¶76. Therefore, according to Jouvenot, “[a] new approach is needed to increase the multiplex levels of digital assays.” EX1003, 2:21–22; EX2024, ¶76.

Jouvenot discloses in Example 1 “an exemplary digital PCR assay with multiplexed detection of two targets.” EX1003, 13:24–25. The two analytes (Target 1 and Target 2) are detected with respective probes (Probe 1 and Probe 2), each of which includes a fluorophore (92 and 94 in figure 3 below):



EX1003, Fig. 3, Fig. 4.

Jouvenot discloses that “the intensity associated with one fluorophore, following reaction, may be lower or higher than the intensity(ies),” such that “Fluorophores 92, 94 . . . create detectable but distinguishable signals in the same channel. EX1003, 13:46–48, 51–53. According to Jouvenot, in the example shown in Fig. 4, fluorophore 94 indicates the presence of Target 2 and has a signal of higher intensity than Fluorophore 92 indicating the presence of Target 1, and therefore four cases (both negative, Target 1 positive, Target 2 positive, and both positive) ostensibly may be distinguished:

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

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

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

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

EX1003, 14: 36–56.

Jouvenot's Example 1 described with reference to FIG. 4 is very simple because there are only two analytes and four possible outcomes. EX2024, ¶79. According to Jouvenot, the complexity of multiplexing increases exponentially as the number of analytes increases: for N analytes, “[t]he data including all permutations of positives will generally fall into 2^N populations or clusters, assuming that each population is distinguishable.” EX1003, 10:23–26; EX2024, ¶79. Jouvenot includes the following tables purportedly showing “[e]xemplary results for one, two, and three target systems in which data are collected in a single channel,” in which it may be seen that the one-analyte system contains two (2^1) populations, the two-analyte system contains four (2^2) populations, and the three-analyte system contains eight (2^3) populations:

	Target A	Intensity
Population 2	+	Highest
Population 1	-	Lowest

	Target A	Target B	Intensity
Population 4	+	+	Highest
Population 3	+	-	Intermediate
Population 2	-	+	Intermediate
Population 1	-	-	Lowest

	Target A	Target B	Target C	Intensity
Population 8	+	+	+	Highest
Population 7	+	+	-	Intermediate
Population 6	+	-	+	Intermediate
Population 5	-	+	+	Intermediate
Population 4	+	-	-	Intermediate
Population 3	-	+	-	Intermediate
Population 2	-	-	+	Intermediate
Population 1	-	-	-	Lowest

EX1003, 10:32–55; EX2024, ¶79.

Jouvenot expresses skepticism as to whether the four outcomes in even the simple two-analyte system can be reliably distinguished:

Specifically, the peaks are assigned based on intervals delineated by values lying between (*e.g.*, half way between) the peak heights for one outcome and the peak heights for adjacent outcomes. In other cases, the peak heights for each outcome may overlap at their extremes, so that thresholding may be neither simple nor linear.

EX1003, 15:2–7; EX2024, ¶80.

Therefore, according to Jouvenot, the range of certainty in the peak height for each outcome may be so large that neighboring ranges of certainty overlap, and thus different outcomes cannot be reliably distinguished. EX2024, ¶81.

It should be noted that Examiner Negin considered Jouvenot before he allowed the claims in the '797 Patent. EX2026, 1337 (IDS showing Cite No. 140, "US-20140171341," which is a pre-grant publication of Jouvenot). In fact, Examiner Negin examined both the '797 Patent and Jouvenot. *Compare* EX1001.001 *with* EX1003.001 (both stating "Primary Examiner — Russell S Negin").

2. Larson

Larson was filed on February 11, 2011, and issued on October 13, 2011. EX1013, §§(22), (43).

Larson discloses "droplet based digital PCR and methods for analyzing a target nucleic acid using the same." EX1013, Abstract. Larson states:

Methods of the invention involve novel strategies for performing multiple different amplification reactions on the same sample simultaneously to quantify the abundance of multiple different DNA targets, commonly known to those familiar with the art as "multiplexing". Methods of the invention for multiplexing dPCR assays promise greater plexity—the number of simultaneous reactions—than possible with existing qPCR or dPCR techniques.

EX1013, ¶45; EX2024, ¶84.

Larson states it is “based on the singular nature of amplifications at terminal or limiting dilution that arises because most often only a single target allele is ever present in any one droplet even when multiple primers/probes targeting different alleles are present.” *Id.*, ¶¶45, 98, 99. That is, that the sample is sufficiently diluted that a single analyte is located within a droplet. EX2024, ¶84.

Larson describes terminal dilution as “the vast majority of reactions contain either one or zero target DNA molecules for practical intents and purposes,” and limiting dilution as “some reactions contain zero DNA molecules, some reactions contain one molecule, and frequently some other reactions contain multiple molecules, following the Poisson distribution.” EX1013, ¶6. Larson asserts various advantages of having one allele per droplet. *See, e.g., id.*, ¶¶99–100; EX2024, ¶87.

Larson discloses digital PCR (dPCR) assays for detecting different numbers of analytes; illustratively, FIG. 15 purports to disclose a “9-plex dPCR assay for spinal muscular atrophy with only two fluorophores, showing the process of optimizing droplet intensities.” EX1013, ¶35, FIG. 15; EX2024, ¶88.

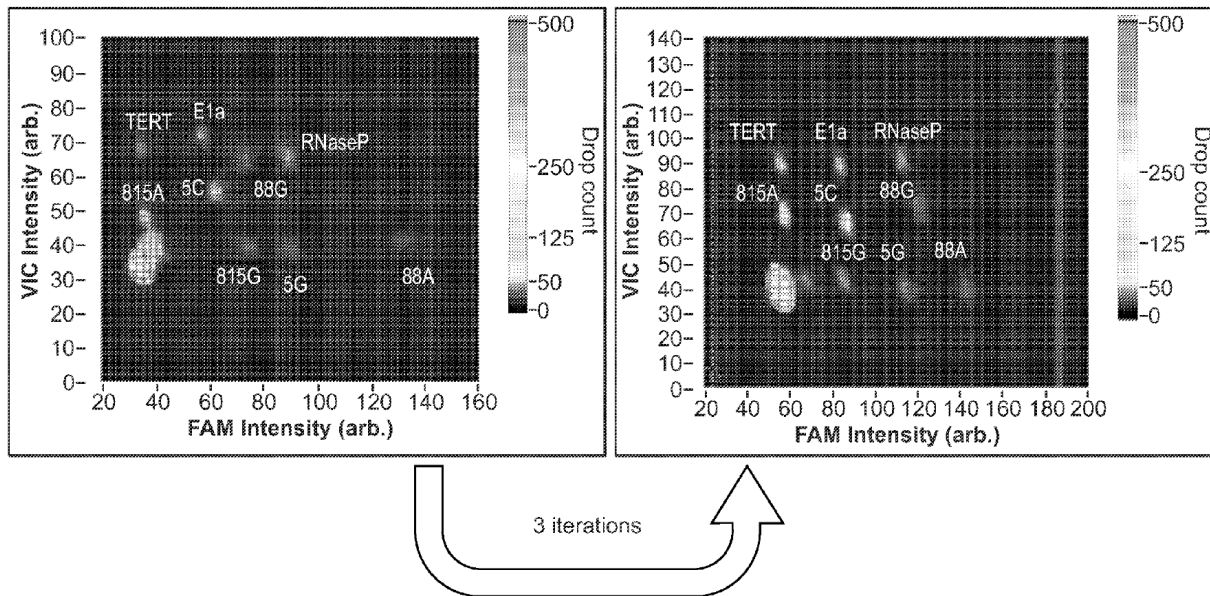


FIG. 15

However, Larson's FIG. 15 shows only single-analyte clusters (respectively TERT, 815A, E1a, 5C, 815G, RNaseP, 88G, 5G, 88A). EX1013, ¶35, FIG. 15; EX2024, ¶89. Other graphs in Larson similarly appear to show measurements from only single-analyte droplets/clusters, and conspicuously omit measurements from multi-analyte droplets/clusters. EX2024, ¶89, *citing* EX1013, FIGS. 5B, 5C, 6B, 7C, 8D, 9A–9D, 14a, 18A, 19A, 20A, 21B, 21E, 21H.

Larson discloses that “[h]igher degrees of multiplexing would require greater dilution,” because of possible unintended “cross-reactivity” between analytes in a droplet. EX1013, ¶129; EX2024, ¶90. Accordingly, Larson expressly and fundamentally relies on *increasing* sample dilution as the number of analytes increases, to *reduce* the probability that one probe overlaps any of the other probes

—that is, to reduce the probability that any droplet contains two or more analytes.

EX2024, ¶90. And, to the extent any droplets nonetheless contain more than one analyte, Larson expressly discloses *excluding* such droplets from analysis.

EX2024, ¶91. More specifically, Larson states “[m]ethods of the invention are able to detect which droplets contain a *heterogeneous population* of molecules and are able to *exclude* those droplets from the analysis.” EX1013, ¶172; EX2024, ¶91.

Larson describes a *heterogeneous* population of molecules: “[d]roplets that produce two signals are classified as droplets that contain a heterogeneous population of molecules.” EX1013, ¶173; EX2024, ¶91. A POSA considering Larson as a whole would have readily understood that droplets containing a heterogeneous population of molecules produce two signals because they contain two different analytes, and each analyte produces a different signal. EX2024, ¶91.

In contrast to heterogeneous populations that produce two signals, Larson describes a *homogeneous* population: “[d]roplets that produce only a *single* signal are classified as droplets that contain a homogeneous population of target.”

EX1013, ¶172; EX2024, ¶92. A POSA considering Larson as a whole would have readily understood that droplets containing a homogeneous population of molecules produce *one signal* because they contain only a single analyte, producing a single signal. EX2024, ¶92.

Larson describes *how* to exclude “[d]roplets that produce two signals” from analysis in a section entitled “Droplet Sorting.” EX2024, ¶93. According to Larson, “[b]ased upon the detected signal at the detection module, droplets containing a heterogeneous population of molecules are sorted away from droplets that contain a homogeneous population of molecules.” EX1013, ¶181; EX2024, ¶93. From Larson’s full disclosure, a POSA readily would have understood that Larson discloses *detecting* and *sorting* droplets based on the detected number of signals from those droplets: *two signals* from droplets containing a *heterogeneous* population of molecules, and *one signal* from droplets containing a *homogeneous* population of molecules; and *excluding* the droplets with *two signals*. EX2024, ¶93.

Larson’s reasons for excluding “multiple occupancy” droplets relate to complexities associated with “multiple occupancy”:

With multiple occupancy arises the complexity of simultaneous assays competing within the same reaction droplet, and also complexity of assigning the resulting fluorescence intensity that involves a combination of fluorescence from two different reaction products that may or may not be equal to the sum of the two fluorescence intensities of the individual reaction products. However, methods of the invention can accommodate these complications arising from multiple occupancy.

EX1013, ¶141; EX2024, ¶94.

A POSA readily would have understood, considering the above excerpt from Larson's ¶141 in view of Larson as a whole, that "multiple occupancy" droplets contain a "heterogeneous population of molecules." EX2024, ¶95. Moreover, they readily would have understood Larson's statement "methods of the invention can accommodate these complications arising from multiple occupancy" means *first*, increasing sample dilution as the number of analytes increases, reducing the probability that one probe overlaps any other probes—that is, to reduce the probability that any droplet contains two or more analytes. EX2024, ¶95; and *second*, detecting, sorting away, and excluding droplets containing heterogeneous populations of molecules based how many signals (one or two) the droplets produce. EX2024, ¶95.

Larson is replete with examples of how to identify a *single* analyte within a droplet, repeats this as a key inventive concept, and indeed a POSA reasonably would have considered identifying a *single* analyte within a droplet to be Larson's principle of operation. EX2024, ¶96, *citing* EX1013 abstract, ¶¶7, 8, 11, 13, 18–20, 45, 46, 49, 68, 99-101, 107, and claims 1, 3, 10, 11, and 15.

It should be noted that Examiner Negin considered Larson's disclosures before he allowed the claims in the '797 Patent. *See* EX2026, 1333 (IDS showing Cite No. 060, "US-9441266," which is a continuation to Larson); EX2024, ¶97.

3. Lehnen

Lehnen was published in 1994. EX1022, §(43).

Lehnen is concerned with “fluorescent immunoassays (FIAs) in which the capture matrix, or solid phase, generally is a microsphere[.]” EX1022, 2:53–54; EX2024, ¶98. According to Lehnen, the general procedure for detecting an antibody or antigen in a fluid sample is as follows:

For example a 10 micron diameter microsphere can be coated with an antigen A. When this coated microsphere is exposed to a fluid which contains antibodies to antigen A, these antibodies will specifically bind to the coated microsphere. Next a reagent which contains a fluorochrome labelled antibody which will specifically bind to antibody A is added. Thus an antibody “sandwich” arises when antibody A is present in the sample such that the fluorochrome is now bound to the microsphere via the specific antibody antigen pairing. This is an example of an “antibody capture” FIA. Alternatively the microsphere can be coated with certain antibodies and thus selectively capture antigens which might be present in the sample in an “antigen capture” immunoassay. In this manner the effective fluorescence of the 10 micron diameter microsphere is determined by how many specific antigens or antibodies are captured, *i.e.*, are present in the sample.

EX1022, 2:54–3:4; EX2024, ¶98.

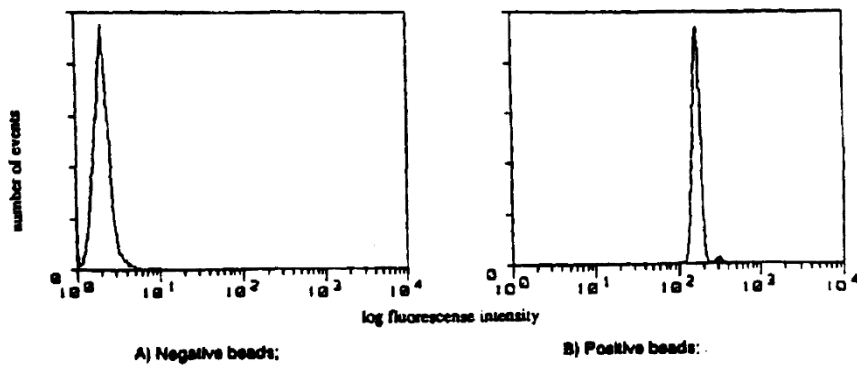
Lehnen discloses that the microspheres in a FIA are examined, one at a time, by a flow cytometer:

The reacted microspheres are passed through a flow cell which causes the microspheres to pass through a laser beam one at a time The laser [] excites the fluorescent dye specifically bound to the microsphere. The emitted light is collated The intensity of the fluorescence is recorded with the appropriate electronics and stored for future analysis.

EX1022, 2:54–3:4; EX2024, ¶99.

Lehnen discloses using a histogram to analyze the fluorescence information collected, wherein the histogram is a plot of the number of fluorescent microspheres having a certain level of fluorescence intensity on vertical axis against the level of fluorescence intensity on the horizontal axis. EX1022, 11:26–40; EX2024, ¶99. According to Lehnen, Fig. 4 shows examples of such histogram:

FIGURE THREE Fluorescence histogram of 4 micron microspheres stained with FITC anti-human IgG.



EX1022, Fig. 3; EX2024, ¶99.

Lehnen discloses a method of multiplexing FIAs that relies on known proportions of reagents “wherein each discrete ligand complex comprises a known, unique proportion of the composition and the sum of any two or more unique proportions also is unique[.]” EX1022, claim 1; EX2024, ¶100. Lehnen discloses the following example:

If a 3 part reagent were prepared in which the subpopulation proportions were 1:2:3 (16.67% : 33.33 % : 50%), and then was reacted with an unknown sample which was positive for the first two of the three target analytes as listed an indeterminant result would be possible. If the mcf values of the positive peaks were by coincidence the same or nearly so, *i.e.*, overlapping peaks, the histogram would show two peaks of equal size each comprising 50% of the total number of events analyzed. One of these peaks would be in the left hand region, or negative domain, of the histogram, and one would be in the right hand positive region. From this resulting pattern, it would not be possible to discern whether the sample was positive for both the first and second analytes as listed or positive for the third analyte only. However, if the reagent had been designed with proportions 1:2:4 (14.28%, 28.57%, 57.14%), the resulting histogram would be uniquely interpretable. A sample positive for the first two analytes as listed wherein their peaks overlapped would

show a right hand or positive peak of area 42.85% and a left hand or negative peak of 57.14%, thus correctly identifying the respective analytes unambiguously since 42.85% could only be the sum of 14.28% and 28.57%.

EX1022, 13:24–34.

Lehnen discloses devising the reagent proportions as follows:

The algorithm $n: 2n: 4n: 8n \dots :2^{(m)}n$ can be utilized to determine the proportions of unequivocal analytical utility to be used in the preparation of a reagent containing m subpopulations of coated microspheres of similar diameter, and wherein n is any number.

EX1022, 13:41–43; EX2024, ¶101.

E. Related Proceedings

PO filed an action asserting U.S. Patent No. 12,168,797 in the district court litigation proceeding *California Institute of Technology v. Bio-Rad Laboratories, Inc.*, Case No. 5:25-cv-01701-EKL (N.D. Cal.). The district court consolidated that action with PO's other pending district court litigation *In Re: ChromaCode Litigation*, Case No. 5:23-cv-04823-EKL (N.D. Cal., consolidated) filed September 20, 2023. This pending district court litigation involves the related U.S. Patent Nos. 10,068,051 ("the '051 Patent"), 10,770,170 ("the '170 Patent"), and 11,827,921 ("the '921 Patent"). The Board denied institution in *inter partes* reviews challenging the '051 and the '170 Patents; see IPR2024-01177 and

IPR2024-01178. Petitioner's request for rehearing for the Board's institution decision in IPR2024-01178 has also been denied. The Board has granted institution of *inter partes* review for a petition challenging the '921 patent, currently pending as IPR2024-01451 with the Oral Hearing scheduled for January 6, 2026.

III. PERSON OF ORDINARY SKILL IN THE ART

For purposes of this IPR proceeding, PO does not contest Petitioner's description of qualifications for a POSA set forth at Petition, 11–12.

IV. CLAIM CONSTRUCTION

Petitioner “requests that the Board understand the claims consistent with the apparent interpretations that PO is pursuing in parallel district court litigation[.]” Petition, 26. Accordingly, the Board should adopt PO's proposed constructions from the parallel litigation as follows:

Claim Term	PO's Proposed Construction	Support
<p>“F” (claims 1 & 5)</p>	<p>No construction of “F” is required for the asserted claims because the claims expressly recite that “F is a positive integer and is equal to the maximum cumulative intensity of the first component of the signal, for any second value, when all of the analytes are present, ... wherein F+1 is a positive integer and F+1 is a power of 2.”</p> <p>To the extent a construction is required, this term should be construed to mean “F, a value that scales with a constituent signal.”</p>	<p>EX2027, 10; EX2028, 2</p>
<p>“analyte specific hybridization probes” (claims 1 & 5)</p>	<p>Plain and ordinary meaning.</p> <p>If a more specific interpretation of the plain and ordinary meaning is required, this term should be construed as “a probe that binds to a portion of an analyte having a specific sequence, with the sequence generally also characterizing the analyte.”</p>	<p>EX2027, 12; EX2028, 18</p>

Claim Term	PO’s Proposed Construction	Support
“associating, for each analyte, a first value in a first component of the cumulative signal” (claim 1)	Plain and ordinary meaning. To the extent a construction is necessary, the entire term of “associating, for each analyte, a first value in a first component of the cumulative signal and a second value in a second component of the cumulative signal, wherein each first value is an intensity or a range of intensities and each second value is a wavelength or a range of wavelengths” should be construed to mean “assigning each analyte to an intensity value of the cumulative signal and a wavelength value of the cumulative signal, wherein each intensity value is an intensity or range of intensities and each wavelength value is a wavelength or a range of wavelengths.”	EX2027, 15; EX2028, 17

In any case, the Board should deny institution regardless of whether it adopts the PO's or Petitioner’s claim constructions because Petitioner’s arguments lack merit even when evaluated under its own proposed claim constructions. Furthermore, the reasoning presented by PO in the following pages does not hinge on any specific claim construction. These arguments remain robust and equally valid criticisms under Petitioner’s claim constructions, demonstrating the fundamental weaknesses in Petitioner’s case.

Notably, regarding “F,” Petitioner argued indefiniteness in the district court but then adopted PO’s construction from the district court litigation in its

Petition—that is, plain and ordinary meaning. Petition, 26–27. The Board should not allow Petitioner to advance inconsistent claim construction positions in different forums to suit its convenience. *See Tesla, Inc. v. Intellectual Ventures II LLC*, IPR2025-00340, Paper 18 (Nov. 5, 2025) (granting Director review, vacating IPR institution decision, and denying petition because “[a]llowing a petitioner to advance a claim construction before the Board when that petitioner has made inconsistent indefiniteness arguments in district court fails to further, but instead detracts from, the Office’s goal of ‘providing greater predictability and certainty in the patent system.’”).

V. THE BOARD SHOULD DENY INSTITUTION

A. Ground 1, Claims 1, 2, 5, 6, 10, and 18: The Challenged Claims Are Patentable over the Ground Reference Jouvenot

Petitioner alleges as Ground 1 that Jouvenot renders claims 1, 2, 5, 6, 10, and 18 unpatentable. Petitioner’s arguments lack merit.

Petitioner’s arguments on the basis of Jouvenot center on Jouvenot’s Example 1, *see, e.g.*, Petition, 28 *et seq.* But that example only describes detecting two analytes using a single fluorophore by a single-channel detector at one wavelength—a circumstance with only four possible outcomes. *See supra*, §II.D.1; EX2024, ¶108.

In contrast, claim 1 of the '797 Patent is directed to a system comprising “a multi-channel detector” that uses 4, 5, or 6 colors, with a minimum value of $F=3$, based on which any combination of at least 8 analytes can be detected—of which there are at least 2^8 (256) possible populations—with the number of populations growing exponentially with the number of analytes. EX1001, 77:38, 77:39, 77:53. EX2024, ¶109. There is a huge conceptual gap between Jouvenot and the invention recited in the '797 Patent claims. EX2024, ¶109. Indeed, although Jouvenot acknowledges that the number of populations increases exponentially as the number of analytes increases, Jouvenot simply does not teach or suggest how to unambiguously distinguish eight or more analytes from one another, let alone teach or suggest each and every limitation recited in the '797 Patent claims. EX2024, ¶109. Indeed, Jouvenot only “*assum[es]* that each population is distinguishable.” EX1003, 10:23–26; EX2024, ¶¶79, 109.

1. Claim 1: “apply a decoding matrix to the cumulative signal to unambiguously detect the presence or absence of at least each of M analytes”

Rather than pointing to anything in Jouvenot that teaches or suggests applying a *decoding matrix* to the cumulative signal to unambiguously detect the presence or absence of at least each of M analytes, Petitioner points to *encoding* matrices from sources *other* than Jouvenot. See Petition, 40–41; EX2024, ¶110.

For example, Petitioner points to Table 8 as being “the only exemplary *decoding* matrix for Claim 1 in the '797 Patent.” Petition, 40 (emphasis added). However, Table 8 is plainly labeled as an “Example of *encoding* method using one color and one intensity per analyte, but different intensities among analytes.” EX1001, Table 8 (emphasis added). An *encoding* matrix is not the same as a *decoding* matrix, and Petitioner does not explain why an encoding matrix should be equated with a decoding matrix. See §II.B above; EX2024, ¶111. Indeed, while the size of an *encoding* matrix grows linearly as a function of the number of analytes, the size of the corresponding *decoding* matrix grows *exponentially* as a function of the number of analytes. See §II.B above; EX2024, ¶111. For example, Table 8 in the '797 Patent is an *encoding* matrix with 16 entries corresponding to 16 analytes A–P, so its corresponding *decoding* matrix has not 16, but 2^{16} (or 65,536) entries, where each entry is used for decoding signal intensities for one particular combination of the 16 analytes. See §II.B above; EX2024, ¶111. Petitioner fails to adequately explain why it would have been obvious to expand the two-analyte, four-population system in Jouvenot's Example 1 to obtain and use a decoding matrix that is remotely as complex as recited in claim 1, illustratively, an eight-analyte, 256-population (2^8) decoding matrix using four colors (corresponding to $F=3$ and $C=4$), let alone a 16-analyte, 65,536-population (2^{16}) decoding matrix using four colors (corresponding to $F=15$ and $C=4$), let alone a 30-analyte,

1,073,741,824-population (2^{30}) decoding matrix using six colors (corresponding to $F=30$ and $C=6$). See §II.B above; EX2024, ¶111.

Further reflecting its deep confusion about the difference between encoding matrices and decoding matrices, as well as its need to rely on sources *other* than Jouvenot because of Jouvenot's utter lack of relevant teachings, Petitioner points to an *encoding* matrix which PO constructed for purposes of accusing Petitioner's QX 600 product of infringing the '797 Patent, and refers to it as a "decoding matrix" which allegedly is "the same type of decoding matrix as Table 8." Petition, 41; EX2024, ¶112. Petitioner's characterization of this "Contentions Matrix" as a decoding matrix suffers from similar flaws as its characterization of Table 8: the "Contentions Matrix" is not a decoding matrix, and indeed the corresponding decoding matrix contains 2^{12} (or 4,096) entries for the 12 listed analytes. EX2024, ¶112.

Petitioner dances around the issue because contrary to what claim 1 requires, Jouvenot simply does not teach or suggest any decoding matrix that when applied to a cumulative signal, allows the unambiguous detection of the presence or absence of each analyte. EX2024, ¶113. Indeed, Jouvenot does not even recognize the degeneracy problem, as illustrated by the following table in Jouvenot:

	Target A	Target B	Target C	Intensity
Population 8	+	+	+	Highest
Population 7	+	+	-	Intermediate
Population 6	+	-	+	Intermediate
Population 5	-	+	+	Intermediate
Population 4	+	-	-	Intermediate
Population 3	-	+	-	Intermediate
Population 2	-	-	+	Intermediate
Population 1	-	-	-	Lowest

EX1003, 10:46–55; EX2024, ¶113.

Here Jouvenot purports to tabulate eight (2³) possible outcomes for a hypothetical three-analyte multiplexing system. EX1003, 10:23–29, 46–55; EX2024, ¶113. However, according to the table, only the all-positive (“Population 8”) and the all-negative (“Population 1”) cases can be unambiguously identified as having the “Highest” or the “Lowest” intensity. EX1003, 10:48, 54; EX2024, ¶113. The remaining six cases (“Population 2” to “Population 7”) all have “Intermediate” intensities and Jouvenot does not teach how they can be unambiguously distinguished. EX1003, 10:49–53; EX2024, ¶113. Again, Jouvenot only “assum[es] that each population is distinguishable.” EX1003, 10:23–26; EX2024, ¶79. Even if, *arguendo*, a POSA were to erroneously conflate Jouvenot’s table with a decoding matrix, the Jouvenot table still is still incapable of “unambiguously detect[ing] the presence or absence of at least each of M analytes,” as recited in claim 1 of the ’797 Patent. EX1001, 77:61-62. Petitioner fails to show otherwise. EX2024, ¶113.

Given that Jouvenot does not disclose these important features of the '797 Patent's claims, Petitioner alleges that "it would have been obvious to a POSA to increase the plex of Jouvenot Example 1[.]" Petition, 45. However, Jouvenot's own teachings would have discouraged a POSA from such endeavor: Jouvenot expresses doubt as to whether even the *two*-analyte system can work reliably, and does not explain how to disambiguate *three*-analyte systems, let alone *eight*-analyte systems as recited in claim 1. See §II.D.1; EX1003, 15:1–7; EX2024, ¶114. For example, Jouvenot suggests that under some conditions, fluorescent intensities (*i.e.*, "peak heights") may be ambiguous and does not point to a definite conclusion as to which analytes are present, and a POSA would have expected far worse ambiguities even if for some reason motivated to try to "increase the plex of Jouvenot Example 1." §II.D.1; EX1003, 15:1–7; EX2024, ¶114.

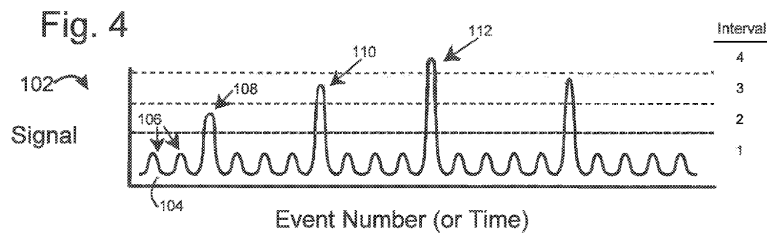
Thus, Petitioner falls well short of its burden of showing Jouvenot teaches a POSA to "apply a decoding matrix to the cumulative signal to unambiguously detect the presence or absence of at least each of M analytes," and thus fails to show that Petitioner has a reasonable likelihood of prevailing on this ground.

2. Claim 1: "M=C*log₂ (F+1) . . . wherein F+1 is a positive integer and wherein F+1 is a power of 2"

Jouvenot unquestionably fails to disclose anything that even resembles the equation and mathematical conditions recited by the '797 Patent's claim 1.

Tellingly, Petitioner does not contend otherwise. *See generally* Petition at 47; EX2024, ¶115. Petitioner instead argues that a hypothetical system (“[t]he [allegedly] obvious four channel version of Jouvenot Example 1 and Larson Fig. 11a”) would have parameters that satisfy the equation. Petition, 47. Petitioner argues that this hypothetical system would have $C=4$, $F=3$, and $M=8$, which would satisfy the equation since $4 \times \log_2(3 + 1) = 8$. *Id.*

Jouvenot, however, does not actually disclose or suggest these values. EX2024, ¶116. Rather, Petitioner clearly used sheer and impermissible hindsight to pick these particular values to fit the equation which is taught not by Jouvenot but rather by the '797 Patent. *Id.* For example, Petitioner's assertion that $F=3$ apparently comes from Petitioner's interpretation of the following Fig. 4 in Jouvenot:



Petition, 42; EX1003.004, EX2024, ¶116.

Here, Petitioner appears to interpret the height of peak 112 as “F,” and asserts $F=3$. Petition, 42–44, 47; EX2024, ¶116. However, assigning a peak height of “3” to peak 112 contradicts Jouvenot's express disclosure that:

- “Peaks 106 with a “maxima in Interval 1 correspond to droplets containing no Target[.]”
- “Peaks 108 with maxima in Interval 2 correspond to droplets containing Target 1 but not containing Target 2[.]”
- “Peaks 110 with maxima in Interval 3 correspond to droplets containing Target 2 but no containing Target 1[.]” and
- “Peaks 112 with maxima in Interval 4 correspond to droplets containing both Targets 1 and 2[.]”

EX1003, 14:36–56 (emphasis added); EX2024, ¶116.

In Jouvenot's Example 1, there are only four (2^2) possible outcomes when detecting the presence or absence of two analytes, and the peaks for Target 1, Target 2, and Target 1 + Target 2 ostensibly can be distinguished because the signals for Target 1 and Target 2 have different intensities. *Supra*, §II.D.1; EX1003, Fig. 4, 14:36–56; EX2024, ¶117. Because of this situation's utter simplicity, Jouvenot had no need to “apply a decoding matrix to the cumulative signal” as in the '797 Patent, nor any need to impose mathematical constraints on F—indeed, Jouvenot did not even recognize “F” as a concept. EX1001, 22:40–45, 77:60; EX2024, ¶117.

Even assuming, purely for the sake of argument, that the height of Jouvenot's peak 112 corresponds to “F” as Petitioner urges, Jouvenot does not

disclose any requirement that $F+1$ be an integer and also a power of two, and Petitioner does not appear to contend that Jouvenot contains such disclosure. Petition, 47; EX2024, ¶118. Instead, Jouvenot states that peak 112 has a “maxima in Interval 4,” EX1003, 14:51, EX2024, ¶116. Petitioner does not explain why, given this express disclosure of Jouvenot, a POSA would have considered F to be equal to 3 instead of the value 4 which Jouvenot expressly discloses for peak 112. Petition, 47; EX1003, 14:51, EX2024, ¶116. Petitioner also does not explain why, given Jouvenot's express disclosure of the value 4 for peak 112, a POSA would have considered it obvious that peak 112 satisfy the claimed requirement that $F+1$ be a power of 2; indeed, if $F=4$, then $F+1=5$ but this does not satisfy the mathematical requirements of claim 1 that $F+1$ be a power of 2. Petition, 47; EX2024, ¶119.

Thus, Petitioner fails to meet its burden to show that Jouvenot teaches the equation “ $M=C*\log_2(F+1)$ ” or the mathematical constraints on F , and thus fails to show that Petitioner has a reasonable likelihood of prevailing on this ground.

3. Claim 1: “ $C=4, 5, \text{ or } 6$ ”

Nothing in Jouvenot discloses the claim limitation that “ $C=4, 5, \text{ or } 6$,” despite Petitioner's argument that the limitation is satisfied by “[t]he obvious four channel version of Jouvenot Example 1.” Petition, 47; EX2024, ¶115. Let it be clear: Jouvenot does not disclose any such “four channel version.” EX2024, ¶115.

It is beyond dispute that Jouvenot's Example 1 has but a single channel (C=1).

EX2024, ¶121.

Petitioner fails to adequately explain why Jouvenot's teaching of C=1 renders obvious the limitation "C=4, 5, or 6." This is not a case where "the claimed range and the prior art range do not overlap but are close enough such that one skilled in the art would have expected them to have the same properties." *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003). On the contrary, there is an enormous difference between C=1 and C=4, 5, or 6. EX2024, ¶122.

For example, even in the least complicated case encompassed by claim 1 of the '797 Patent, where C=4 and F=3, the claimed system can still detect at least 8 analytes. EX2024, ¶121. The number of analytes M can be derived from the claimed equation $M=C*\log_2(F+1)$. *Id.* When C=4 (the lowest value of C recited by claim 1), the claimed equation becomes $M=4*\log_2(F+1)$. *Id.* Because "F+1 is a positive integer," "F+1 is a power of 2," and M is greater than C, the minimum value for F is 3 and therefore the minimum number of analytes (M) in the claimed system is 8. EX1001, 78:45–48; EX2024, ¶121. In other recited cases where C=5 or 6, the minimum number of analytes the claimed system can detect is 10 or 12, respectively. EX2024, ¶121. But again, Jouvenot's Example 1 is a single-channel system that detects only *two* analytes. EX1003, 14:29–31; EX1001, 78:45–48; EX2024, ¶121.

The technological gap between the claimed system (using the recited values of $C=4, 5, \text{ or } 6$) and Jouvenot's Example 1 ($C=1$) is much wider than the apparent numerical difference between detecting at least 8–12 analytes on the one hand, and detecting only 2 analytes on the other because the number of populations increases exponentially as a function of the number of analytes. *Supra*, §V.A.1; EX1003, 10:23–26; EX2024, ¶122.

The problem the Caltech inventors solved is far more challenging than Jouvenot's two-analyte system. EX2024, ¶123. Contrary to what Petitioner represents, a POSA would not be motivated to “simply duplicat[e] the number of channels/fluorophores to at least four” or have a reasonable expectation of success in doing so. Petition, 45; EX2024, ¶123. Again, in Jouvenot's Example 1 to which Petitioner points, only four possible outcomes need to be distinguished. EX1003, 14:63–64; EX2024, ¶123. And yet even in this simple case, Jouvenot teaches that its method is not always reliable because signal peaks can lie “half way between” or “overlap at their extremes.” EX1003, 15:1–7. EX2024, ¶123. If there are ambiguous cases when distinguishing four outcomes in a single-channel system, a POSA would not expect the problem to go away if “duplicating the number of channels/fluorophores to at least four” in the manner Petitioner proposes; instead the POSA would expect much worse problems in four channels, where 256 or more outcomes must be unambiguously distinguished. Petition, 45; EX2024, ¶123.

Petitioner does not explain why a POSA would reasonably have believed that there is no meaningful difference between distinguishing 4 outcomes and distinguishing 256 outcomes, particularly in view of the limitations in Jouvenot's method that Jouvenot itself admits. EX1003, 15:1–7. EX2024, ¶123. The claimed limitation “C=4, 5, or 6” is not obvious in view of Jouvenot. *See Dann v. Johnston*, 425 U.S. 219, 230 (1976) (the gap between the prior art and the claimed invention may not be “so great as to render the [claim] nonobvious to one reasonably skilled in the art”), *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 997 (Fed. Cir. 2009) (there was no prima facie case of obviousness because there was no evidence the necessary modifications would have been routine); *see also In re Patel*, 566 F. App'x 1005, 1010 (Fed. Cir. 2014) (“Where differences clearly exist and there is no evidence that they are either not meaningful or one of skill in the art would know to discard the limits set by the prior art, proximity alone is not enough to establish a prima facie case of obviousness.”).

4. Petitioner's Arguments Are Fraught with Impermissible Hindsight

Petitioner's conclusion of obviousness stems from its application of hindsight reasoning that the Federal Circuit has expressly prohibited for purposes of determining patent validity. EX2024, ¶124. Throughout the Petition and its supporting declaration from Dr. Batt, there is a systematic pattern of the Petitioner

using the '797 Patent as a roadmap, and then arguing *ex post* that the claimed invention is obvious. See Table 1 below; see also *TQ Delta, LLC v. CISCO Sys., Inc.*, 942 F.3d 1352, 1361 (Fed. Cir. 2019) (rejecting expert testimony that uses “the challenged patent as a roadmap to reconstruct the claimed invention”).

For example, Petitioner's hindsight bias is demonstrated by its repeated misidentification of the Caltech inventor's success, as documented in the '797 Patent's disclosure, as evidence of success that a POSA would have expected. EX2024, ¶124. According to Petitioner's logic, if the '797 Patent does not describe an arduous inventive journey, the achievement therefore must have been “easy” and therefore obvious. *Id.*; e.g., Petition, 35–36 (arguing that a POSA would have had a reasonable expectation of success because the '797 Patent does not suggest “any impediments to implementing optical detection machinery for analysis in four colors”); Petition, 54 (arguing that claim 6's use of multiple fluorophores is obvious because the '797 Patent “treats them as well-known prior art fluorophores that could be used without difficulty.”). The law, however, does not support Petitioner's distorted view of the inventive process. See pre-AIA §103(a) (“Patentability shall not be negated by the manner in which the invention was made.”).

The expert's testimony ostensibly supporting the Petition—the declaration of Dr. Batt—also suffers from the same hindsight bias. EX2024, ¶125. For example,

the '797 Patent explains that its inventive methods can be readily implemented using existing instruments having four color channels. EX1001 at 35:30–35. Dr. Batt, however, mistakes the invention's ease of implementation—that it can be readily implemented using existing instruments, *once given knowledge of the invention*, for obviousness at the time of invention:

The '797 patent, in fact, makes clear that four color instrumentation had previously existed in “many” incarnations. EX1001 at 35:30-35. In view of this, it would have been a no-brainer for a skilled artisan to simply take the scheme disclosed in Figure 4 of Jouvenot and, rather than use it in one color channel, duplicate it in four or more independent color channels to detect more targets. This would have been nothing more than the straightforward idea of, for instance, digging a hole faster and deeper by using multiple workers each with their own shovel rather than having a single worker do the task with just one shovel.

EX1002, ¶133; EX2024, ¶125. This supposed motivation is nothing but a conclusory statement. Other than alleging it to be a “no-brainer,” it does not explain *how* a POSA would “duplicate [Figure 4 of Jouvenot] in four or more independent color channels,” *how* the modified Jouvenot would operate to detect more targets,” or *how* the modified Jouvenot would render the claim limitations obvious. EX2024, ¶125. The hole-digging analogy also bears no comprehensible relation to the proposed modification of Jouvenot. *Id.* (What are the workers,

shovels, and hole supposed to represent? What is the action in a biochemical assay that is parallel to “digging a hole faster and deeper”?) The Board should reject this testimony on obviousness because it is no different from the rejected expert testimony in *ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*, 694 F.3d 1312, 1327 (Fed. Cir. 2012) (rejecting expert testimony as insufficient and fraught with hindsight bias because it was “essentially a conclusory statement that a person of ordinary skill in the art would have known, based on the ‘modular’ nature of the claimed components, how to combine any of a number of references to achieve the claimed inventions”).

There are many places in Dr. Batt's testimony where he simply cannot “resist the temptation to read into the prior art the teachings of the invention.” *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 36 (1966). An archetypical example of this is in EX1002, ¶129: in arguing that Jouvenot's Example 1 renders claim 1 obvious, Dr. Batt's purported explanation is essentially that Jouvenot's Example 1, once modified to include encoding applied as taught by Table 8 of the '797 Patent, “reflect[s] the same scheme” as Table 8. EX2024, ¶126. In other words, he argues that Jouvenot's Example 1, when combined with the teaching of the '797 Patent, renders the '797 Patent obvious.

And Dr. Batt's circular reasoning goes even further than combining the '797 Patent with prior art. Dr. Batt also argues that the '797 Patent's claimed invention

is obvious in view of its own specification. For example, Dr. Batt argues that the equation $M=C*\log_2(F+1)$ —a limitation of claim 1—is obvious because it is “an intuitive mathematical formula” that reflects Table 8 of the ’797 Patent. EX1002, ¶¶142–143; EX2024, ¶125; *see also id.* ¶146 (suffering from similar flaw when arguing that “F is a positive integer” is obvious because it is explained in the specification of the ’797 Patent).

Table 1 below summarizes the erroneous reasoning of the Petitioner and Dr. Batt, and how they rely on the ’797 Patent’s own disclosure to argue, circularly, that the ’797 Patent is obvious. EX2024, ¶127.

Table 1

Petitioner’s Citations to the ’797 Patent	What the Cited Passage in the ’797 Patent Says	What Petitioner Argues
Ground 1: Claim 1		
Petition, 34–35, <i>citing</i> EX1001, 35:30–35, 34–35	The cited text explains that the methods of the invention can be readily applied using existing instruments having four channels.	Petitioner uses the ’797 Patent’s own disclosure as ostensible evidence of how a POSA would have been motivated to expand Jouvenot to four

		<p>channels, and as evidence of a reasonable expectation of success because “[n]owhere does the ’797 patent suggest that . . . there were any impediments to implementing optical detection machinery for analysis in four colors.”</p>
<p>Batt Declaration, ¶113, citing EX1001, 35:30–35</p>	<p><i>same as above</i></p>	<p>Dr. Batt uses the ’797 Patent’s own disclosure as ostensible evidence of “pre-existing motivation” and a reasonable expectation of success for using four or more channels.</p>
<p>Batt Declaration, ¶133, citing EX1001, 35:30–35</p>	<p><i>same as above</i></p>	<p>Because the ’797 Patent discloses that four-channel instrumentation had existed, Dr. Batt argues that it would be a “no-brainer” to expand the single-channel example in Jouvenot to four channels. “This would have been nothing more than the straightforward idea of, for instance, digging a hole faster and deeper by using multiple workers.”</p>

<p>Petition, 40, <i>citing</i> EX1001, 22:9–29</p>	<p>The cited text describes an exemplary encoding matrix.</p>	<p>Petitioner uses the ’797 Patent’s own disclosure as ostensible evidence that Jouvenot somehow teaches the claimed decoding matrix.</p>
<p>Batt Declaration, ¶129, <i>citing</i> EX1001, 21:65–67</p>	<p>The cited text explains that encoding based on intensities 1, 2, 4, and 8 results in a code scheme without degeneracy.</p>	<p>In his circular reasoning, Dr. Batt applies the ’797 Patent’s teaching to expand Jouvenot, which supposedly shows how Jouvenot renders the ’797 Patent obvious.</p>
<p>Batt Declaration, ¶143, <i>citing</i> EX1001, 22:10–30</p>	<p>The cited text describes an exemplary encoding matrix.</p>	<p>Dr. Batt argues that Jouvenot renders the claimed equation $M=C*\log_2(F+1)$ obvious because the equation is “intuitive” in view of the ’797 Patent’s own embodiment.</p>
<p>Batt Declaration, ¶146, <i>citing</i> EX1001, 2:1–5</p>	<p>The cited text explains the equation $M=C*\log_2(F+1)$.</p>	<p>Dr. Batt argues that the claimed limitation “F is a positive integer” is obvious because of the explanation in the specification of the ’797 Patent itself.</p>
<p>Ground 1(a): Claim 6</p>		
<p>Petition, 54 <i>citing</i> EX1001, 34:57–61</p>	<p>The cited text explains that fluorophores not specifically named in the specification can also be used in the invention.</p>	<p>Petitioner argues that the ’797 Patent’s use of the fluorophores is not novel or inventive because the ’797 Patent “treats them</p>

		as well-known prior art fluorophores that could be used without difficulty.”
Ground 1(a): Claim 7		
Petition, 56, citing EX1001, 45:19–35, 33:67, 34:8, 45:29–30, 48:50, 49:10, 49:14, 49:33.	The cited text describes fluorophores used in exemplary embodiments (including Examples 1 and 2).	Petitioner argues that the ’797 Patent’s use of the fluorophores is not novel or inventive because they are well-known in the prior art, and the ’797 Patent does not describe any difficulty in using them.
Ground 1(b): Claim 11		
Petition, 60 citing EX1001, 28:11–13, 35:30–33.	The cited text explains that the measurements of wavelength and intensity in the invention can be accomplished using known components (band pass filters).	Petitioner uses the ’797 Patent’s own disclosure as evidence that a POSA would have been motivated to use band pass filters with a reasonable expectation of success, because the ’797 Patent supposedly “acknowledges” that band pass filters are commonly employed.
Ground 1(c): Claim 13		
Petition, 62, citing EX1001 at 35:59–62	The cited text explains that the measurements of wavelength and intensity in the invention can be accomplished using known components	Petitioner uses the ’797 Patent’s own disclosure as ostensible evidence of “a reasonable expectation of success because these are standard optical

	(photodetector and band pass filters).	components well-known in the art[.]”
Batt Declaration, ¶146, <i>citing</i> EX1001 at 35:59–62	<i>same as above</i>	Dr. Batt uses Patent’s own disclosure as ostensible evidence of “a reasonable expectation of success.
Ground 1(d): Claim 14		
Petition, 64–65, <i>citing</i> EX1001, 35:26–33, 35:34–35	The cited text explains how the methods of the invention can be readily applied using existing instruments.	Petitioner uses the ’797 Patent’s own disclosure as ostensible evidence of “motivation and reasonable expectation of success.”
Batt Declaration, ¶203, <i>citing</i> EX1001 at 35:26–33, 35:34–35	<i>same as above</i>	Dr. Batt uses Patent’s own disclosure as ostensible evidence of motivation and a reasonable expectation of success.
Ground 1(e): Claim 15		
Petition, 65, <i>citing</i> EX1001, 45:19–35	The cited text describes an exemplary embodiment (Example 1).	Petitioner uses the ’797 Patent’s own disclosure as ostensible evidence that “it would have been obvious to use fluorophores having maximum emission wavelengths selected from the group consisting of about 518 nm, about 565 nm, about 591 nm, and about 670 nm[.]”

For any and all of the above reasons, Petitioner has failed to establish a reasonable likelihood that it will prevail on Ground 1.

B. Grounds 1 and 1(a)–1(f), Claims 1, 2, 5–11, 13–15, and 18: The Challenged Claims Are Patentable over Combinations of Jouvenot, Larson, and other references

Petitioner alleges as Grounds 1(a)–1(f) that Jouvenot in various combinations with Larson and other references renders claims 6–9, 11, 13–15, and 18 unpatentable. Petition, 25–26. In addition, even though Petitioner's Ground 1 is supposed to be based on just Jouvenot, Petition, 25, Petitioner's arguments also include proposed combinations of Jouvenot and Larson, *see* Petition, 31, 33–36, 38, 39, 44–47; EX2024, ¶129. This section addresses the proposed combination of Jouvenot with Larson in the above alleged grounds (1 and 1(a)–1(f), involving claims 1, 2, 5–11, 13–15, and 18).

The proposed combination of Jouvenot and Larson is untenable for the following reasons.

1. Larson Tries to Eliminate the Need to Detect Multiple Analytes in the Same Sample

Jouvenot's disclosure ostensibly is motivated by a desire to multiplex a digital PCR assay to "permit detection of two or more different targets in each partition." EX1003, 2:12–13. Because "instruments with more detection channels, to detect more colors, are more expensive than those with fewer detection

channels,” Jouvenot discloses “a new approach . . . to increase the multiplex levels of digital assays,” EX1003, 2:16–22.

Although Larson purports to teach “multiplexing,” *e.g.*, EX1013, ¶45, its actual method of doing so is incompatible with Jouvenot. EX2024, ¶132. Indeed, a POSA considering Larson as a whole readily would have understood that Larson’s “multiplexing” refers to strategies entirely different from Jouvenot. EX2024, ¶132. First, Larson teaches increasing sample dilution as the number of analytes increases, so as to reduce the probability that any droplet contains even two analytes, let alone more than two. EX1013, ¶129; EX2024, ¶132. Second, Larson teaches detecting, sorting away, and excluding droplets containing a heterogeneous population of analyte molecules. EX1013, ¶172; *supra* §II.D.2; EX2024, ¶132.

For at least these reasons, the full teachings of Larson would, at most, have motivated that POSA to try to *eliminate* any situations of having multiple analytes in the same sample partition by *diluting* the sample to reduce the probability that any partition contains two or more analytes, and/or to *exclude* partitions that do contain two or more analytes. EX2024, ¶133. Nothing in Larson would have rationally motivated a POSA to try to modify Jouvenot to *increase* the probability of having multiple analytes in the same partition. *Id.* Larson would not motivate a POSA to “expand Jouvenot Example 1 to use four or more different color channels

and fluorophores,” as Petitioner contends. *E.g.*, Petition, 33–36; EX2024, ¶133.

Such expansion would be pointless without any partition having at least four analytes to detect, let alone at least eight analytes as encompassed in claim 1 of the '797 Patent. EX2024, ¶133.

2. Larson Teaches Away from Claim 1 of the '797 Patent

One important aspect of the '797 Patent claims is the equation $M = C * \log_2(F + 1)$. EX1001, 78:39. In Petitioner's analysis, “this mathematical formula is nothing more than a restatement of the use of signal intensities for analytes that follow the geometric progression 1, 2, 4, 8, 16, and so on[.]” Petition, 10.

Petitioner alleges that the use of this “geometric progression” is as simple as basic arithmetic:

For example, for the color blue in Table 8, intensities of 1, 2, 4, or 8 mean that analytes A, B, C, or D are present alone. *Id.* But an intensity of 3 means that A and B are present ($1+2=3$), an intensity of 7 means that A, B, and C are present ($1+2+4=7$), and an intensity of 15 means that all analytes are present ($1+2+4+8=15$). *Id.* This progressive pattern prevents overlap of intensities—each value is “equal to the sum of all previous values plus one.”

Petition, 9; EX2024, ¶134.

An unstated, but critical foundation for Petitioner's position is that fluorescent intensities must be additive. EX2024, ¶135. For example, in order for this scheme to work in the manner Petitioner describes, two analytes that

respectively have a fluorescent intensity of 1 and 2 must have a cumulative intensity of 3 (*i.e.*, $1 + 2$) when both analytes are present. *Id.* Under Petitioner's logic, if an observed cumulative intensity of 3 is not necessarily the result of $1 + 2$, then it does not lead to the identification of A and B. *Id.* In other words, under Petitioner's logic, any cumulative intensity that is not a sum of the fluorescent intensities of the individual analytes will throw off the whole encoding scheme. *Id.*

But Larson actually questions whether fluorescence intensities are even additive. EX2024, ¶136. For example, Larson discloses that one way of “performing higher-plex assays with a single probe color” is to have “each intensity level uniquely identifies a DNA target,” “[f]or example, targets T1, T2, T3, and T4 might be uniquely identified by intensity levels I1, I2, I3, and I4.” EX1013, ¶138. But Larson regards this method as having “complexity” because fluorescent intensities are not necessarily additive:

With multiple occupancy arises the . . . complexity of assigning the resulting fluorescence intensity that involves a combination of fluorescence from two different reaction products that *may or may not be equal to the sum of the two fluorescence intensities* of the individual reaction products.

EX1013, ¶141; EX2024, ¶136.

Such disclosure in Larson, therefore, would have motivated a POSA to *avoid* any encoding scheme based on fluorescent intensities because it would indeed be

difficult, if not impossible, to interpret any cumulative intensity reading when there is no guarantee that the cumulative intensity is a sum of individual fluorescence intensities as Petitioner asserts is required for the scheme to be obvious. EX2024, ¶137. And, according to Petitioner's own logic, without encoding fluorescent intensities in powers of two, a POSA would not have been able to arrive at the equation $M = C * \log_2 (F + 1)$. *Id.*

For the above reasons, Petitioner has failed to establish a reasonable likelihood that it will prevail on any ground involving Larson, including Grounds 1 and 1(a)–1(f).

C. Grounds 2 and 2(a)–2(f), Claims 1, 2, 5–11, 13–15, and 18: The Challenged Claims Are Patentable over Combinations of Jouvenot, Lehnen, and other references

Petitioner concedes that its Grounds 1 and 1(a)–1(f) are probably insufficient because Jouvenot and Larson may be “deemed to not disclose encoding analytes by the geometric progression of 1, 2, 4, 8, etc. because the signals in Jouvenot Example 1 and Larson Figure 11 do not exactly match this progression.” Petition, 69. Therefore, Petitioner re-alleges the same grounds as Grounds 2 and 2(a)–2(f), and “[t]he sole change is the addition of Lehnen.” *Id.*, 69.

Because Grounds 2 and 2(a)–2(f) “are based on the same logic and rationale as grounds 1–1(f),” Petition, 68, they suffer from the same defects as explained above in §§V.A.–B. Furthermore, Lehnen cannot remedy the defects in

Petitioner's alleged grounds because it is directed to an entirely different technology with at most superficial relevance to the system recited in the '797 Patent claims.

1. Lehnen Is Non-Analogous Art

As a threshold issue, it is improper to assert obviousness on the basis of Lehnen because it is not analogous art to the claimed invention of the '797 Patent. *See In re Klein*, 647 F.3d 1343, 1348 (Fed. Cir. 2011) (“A reference qualifies as prior art for an obviousness determination under § 103 only when it is analogous to the claimed invention.”). Lehnen is neither from the same field of endeavor as the claimed invention—as Petitioner itself has defined such field—nor is it reasonably pertinent to the problem faced by the Caltech inventors of the '797 Patent.

a. Lehnen is not in the same field of endeavor as the '797 Patent. Petitioner broadly asserts that all the secondary references cited in its Petition are analogous art “because they to [*sic*] the same field of endeavor as the '797 patent, specifically, the detection of target analytes (including nucleic acids) in a sample.” Petition, 22 (parenthesis in original); EX2024, ¶141. However, Petitioner itself defines the field of knowledge of the POSA far more narrowly than this. Petition, 11–12. This is because Petitioner defines a POSA as a person who is familiar with detecting and measuring polynucleotide analytes. Petition, 11–12; EX2024, ¶19. But the technologies and techniques discussed in Lehnen, such as

detecting antibodies and antigens and immunoassays, do not fall within the skillset of Petitioner's POSA. *See supra*, §II.D.3; Petition, 11–12; EX2024, ¶¶19, 102.

Indeed, Lehnen's fluorescent immunoassay is entirely different from all the PCR-based assays in the '797 Patent, Jouvenot, and Larson (as different as they are). EX2024, ¶102. PCR assays and immunoassays address different problems; for example, while PCR assays detect polynucleotides, immunoassays detect antibodies or antigens (usually proteins). EX2024, ¶¶19, 102. PCR assays and immunoassays are separate fields of endeavor, and both fields are rapidly evolving with constant new innovations. *Id.* Both PCR assays and immunoassays are sophisticated technology, and each must be mastered separately. *Id.* For example, one set of skills is required for designing and preparing hybridization probes for detecting polynucleotides and for running and interpreting PCR assays, while another set of skills is required to prepare antibodies and for running and interpreting immunoassays. *Id.* In other words, a person having ordinary skill in the art of detecting and measuring polynucleotides cannot be presumed to have the same ordinary level of skill in immunoassays. *Id.* Petitioner does not even mention the distinction between the two different fields of endeavor, let alone explain why the POSA *as defined by Petitioner* would be expected to possess the skillset related to immunoassays. Petition, 11–12; EX2024, ¶19; *see also In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995) (in determining the level of ordinary

skill in the art, the Board may consider various factors including “type of problems encountered in the art,” “prior art solutions to those problems,” “rapidity with which innovations are made,” and “sophistication of the technology”).

Moreover, Petitioner's broad characterization of the field of endeavor, “the detection of target analytes,” encompasses a huge range of scientific endeavors starting from the emergence of modern chemistry, medicine, and geology several centuries ago. *Id.* But Petitioner's broad characterization cannot be correct because it renders superfluous the same field of endeavor test. More specifically, the applicable field of endeavor must be determined in view of the “explanations of the invention's subject matter in the patent application, including the embodiments, function, and structure of the claimed invention.” *Airbus S.A.S. v. Firepass Corp.*, 941 F.3d 1374, 1380 (Fed. Cir. 2019). An examination of the '797 Patent reveals that the disclosed examples are all directed to the detection of polynucleotides.

EX2024, ¶142; *see* EX1001, 40:31 (Example 1 describing preparation of analytes: “[f]ive nucleic acids from organisms of clinical relevance”), 45:36–37 (Example 2 entitled “Simultaneous Detection of Polynucleotide Markers”), 50:1–2 (Example 3 similarly entitled). A POSA can also readily understand from the claims that the '797 Patent is directed to the detection of polynucleotides because all independent claims recite “hybridization probes” (which detects polynucleotides), “PCR” (which amplifies polynucleotide), and/or expressly “polynucleotide analytes.”

EX2024, ¶142; *see*, EX1001, 77:38 (independent claim 1), 79:57–61 (independent claim 19), 80:44–46 (independent claim 22).

Lehnen, on the other hand, is in the field of detecting antibodies and antigens, such as “antibodies to recombinant HIV gp4, recombinant HIV p24, Hepatitis B core protein, and recombinant HTLV re-5.” *See* EX1022, 2:8–10 (“Technical Field”); EX2024, ¶143. Lehnen discloses twelve examples, and not a single one is about detecting polynucleotides. EX2024, ¶143. The claims of Lehnen also do not recites anything like DNA, RNA, or polynucleotides, whereas claims 4, 6, 7, and 10 are directed to detecting antibodies and antigens. *Id.*

A POSA knows that detecting polynucleotides is fundamentally different from detecting antibody/antigen. EX2024, ¶144. A POSA would not regard the ’797 Patent and Lehnen to be in the same field of endeavor, especially “from the vantage point of the common sense likely to be exerted by one of ordinary skill in the art.” *Airbus S.A.S. v. Firepass Corp.*, 941 F.3d 1374, 1380 (Fed. Cir. 2019). And again, Petitioner itself has defined the field of knowledge of the POSA and that field does **not** include Lehnen’s ostensible techniques. *See supra* §III.

- b. Lehnen is not reasonably pertinent to the problem the Caltech inventors of the ’797 Patent faced

References are reasonably pertinent only if “a person of ordinary skill would reasonably have consulted those references and applied their teachings in seeking a

solution to the problem that the inventor was attempting to solve.” *Airbus S.A.S. v. Firepass Corp.*, 941 F.3d 1374, 1382 (Fed. Cir. 2019).

According to Lehn, that reference started from fluorescent immunoassays using immobilized reagents, and sought to multiplex the immunoassays without being limited by “particle size resolution.” EX1022, 2:53–3:16; EX2024, ¶146. Lehn’s ostensible method was to use different types of immobilized reagents in known ratios. *Id.*, 5:14–21; EX2024, ¶146. For example, according to Lehn, a two-analyte system can contain two types of microspheres—each type carrying immobilized reagents for detecting one analyte—present at a 1:2 ratio, where the ratio is in the number of the microspheres of each type; a three-analyte system can contain three types of microspheres present at a 1:2:4 ratio. EX1022, 13:37–38; EX2024, ¶146. According to Lehn, after reacting with microspheres with a sample, a flow cytometer is used to measure the microspheres one at a time. EX2024, ¶146; *see* EX1022, Fig. 4 (showing apparatus for detecting “fluorescence characteristics of *individual* particles moving in flow path from the sample source”).

In comparison, the Caltech inventors sought to invent ways to detect polynucleotides with “the ability to extract rich information from a sample in a fast and efficient manner,” but without complex mechanisms involving spectrally resolved fluorescence or chemiluminescence, spatially resolved signals, or

temporally resolved signals. EX1001, 1:37–49; EX2024, ¶147. Indeed, the Caltech inventors' efforts resulted in the claimed system, in which “the determination is made without immobilization, mass spectrometry or melting curve analysis.” EX1001, 78:36–37; EX2024, ¶147.

The Caltech inventors would not have consulted Lehen because that reference's microsphere-based approach essentially tried to resolve signals spatially, while its use of a flow cytometer to sequentially examine the reacted microsphere essentially tried to resolve signals temporally. EX2024, ¶148. Lehen's method involves the sequential examination of hundreds of thousands microspheres (*e.g.*, EX1022, 16:34), a technique which is neither fast and efficient. EX2024, ¶148. For these and other reasons, Lehen is not reasonably pertinent to the problem the Caltech inventors of the '797 Patent faced, and Petitioner fails to show otherwise. *Id.*

Because Lehen is neither the same field of endeavor nor reasonably pertinent, it is not analogous art to the '797 Patent. *See In re Klein*, 647 F.3d 1343, 1348 (Fed. Cir. 2011) (a reference is analogous art if it is from the same field of endeavor as the claimed invention or if the reference is reasonably pertinent to the problem faced by the inventor).

2. Lehnen Does Not Teach Any Encoding in the Cumulative Intensity of Signals Because There Is No Cumulative Intensity in Lehnen

One aspect of the '797 Patent claims relates to encoding and decoding information in the cumulative intensity of signals. EX2024, ¶149. Because the cumulative intensity is a sum of the individual fluorescence intensities of all the different analytes present, it is possible to deduce information about the different analytes even when their fluorescence signals use the same wavelength. *See* above §§II.B, V.B.2; EX1001, 78:41–44; EX2024, ¶149.

However, there is no cumulative intensity in Lehnen because fluorescence signals from different analytes are examined separately without any accumulation or summation. EX2024, ¶150. More specifically, Lehnen discloses using microspheres on which different reagents are immobilized. *Id.* For example, Lehnen discloses that one set of microspheres may be coated with a reagent to detect human antibody IgG, and another set coated with another reagent to detect HIV. EX1022, 12:44–46. Lehnen discloses reacting the microspheres with a sample, so analytes present in the sample will bind to corresponding reagents on the microspheres. EX2024, ¶150. According to Lehnen, a flow cytometer is then used to examine every microsphere, which emits a fluorescence signal when a positive binding between the reagent on the microsphere and the analyte the reagent is designed to detect. *Id.* It is important to note that a flow cytometer

measures the microspheres one at a time, *see* EX1022, Fig. 4 (showing apparatus for detecting “fluorescence characteristics of *individual* particles moving in flow path from the sample source”), and because of this, fluorescence signals from different analytes are never added. EX2024, ¶150. In other words, there is no “cumulative intensity” to speak of in Lehn. *Id.* Lehn cannot teach or suggest any encoding in a property that it does not have. *Id.*

Moreover, it should be understood that the individual examination of the microspheres in Lehn is not due to any limitation of the instrument. EX2024, ¶151. To the contrary, Lehn's method must do so in order to obtain a count of the number of microspheres at different levels of fluorescence. *Id.* As explained below in §V.C.3., Lehn extracts information about analytes from microsphere populations (*i.e.*, the numbers of microspheres having different levels of fluorescence).

3. Lehn Obtains Information From Microsphere Populations, Which Cannot Be Applied to Jouvenot

Lehn's method works in a way that is radically different from Jouvenot, Larson, or the '797 Patent (as different as those are from one another). EX2024, ¶152. Lehn discloses obtaining information from the populations of the microspheres that detect different analytes. *Id.* For example, according to Lehn, a two-analyte system can contain two types of microspheres present at a 1:2 ratio,

where the ratio is in the number of the microspheres of each type; a three-analyte system can contain three types of microspheres present at a 1:2:4 ratio. EX1022, 13:37–38. Lehnen discloses that “the algorithm $n: 2n: 4n: 8n \dots :2^{(m1)}n$ can be utilized to determine the proportions.” *Id.*, 13:41. By this, Lehnen means that there should be n microspheres with immobilized reagent for detecting a first analyte, and $2n$ microspheres with a different immobilized reagent for detecting a second analyte, etc. EX2024, ¶152. As any POSA would be able to appreciate, this ratio of “ $n: 2n: 4n: 8n \dots$ ” does not in any way relate to *intensity* of fluorescent signals. *Id.*

Moreover, Lehnen's method cannot be combined with Jouvenot. EX2024, ¶153. First, there simply are not any microspheres, particles, or solid supports, or any discrete units of solids that can be counted in Jouvenot. *Id.* Second, it would be impractical and unrealistic to apply Lehnen's method in the context of digital PCR, in which at least tens of thousands of partitions (droplets) must be examined. EX2024, ¶153. If the analysis of each partition would require reacting it with microspheres (*e.g.*, EX1022, 16:34) and then examining each microsphere one-by-one, the whole digital PCR process would be enormously time consuming and wasteful of materials because the same method involving microspheres must be repeated for every partition. EX2024, ¶153. No rational POSA would even consider it. *Id.*

4. Lehnen Teaches the Opposite of What Claim 1 Expressly Requires

Claim 1 of the '797 Patent requires that “the determination is made without immobilization[.]” EX1001, 78:36–37. Lehnen, however, teaches away such determination because Lehnen *requires* combining a sample with a “mixture containing the known proportions of multiple subpopulations of *immobilized* complementary binding moieties.” EX1022, 7:42–43; EX2024, ¶154. By “immobilized,” Lehnen means that the complementary binding moieties are attached to a solid support, such as particles of microspheres. EX1022, 6:49–50, 7:15–16; EX2024, ¶154.

Lehnen discusses microspheres, solid supports, and particulate supports throughout the reference. *E.g.*, EX1022, 2:43 (“Relevant Literature”), 3:24 (“Summary of the Invention”), 3:51 (“Brief Description of the Drawings”), 4:13 (“Brief Description of the Specific Embodiments”), 10:33 (“Examples”), 23:51 (claim 1). Indeed, Lehnen’s use of microspheres carrying immobilized reagents is not merely incidental, but an integral part of the method. EX2024, ¶155. As explained above in §§V.C.1–2, Lehnen’s method relies counting the number of microspheres by a flow cytometer. EX2024, ¶155. Without the microspheres, there would not be any discreet units to count, no ratio of different populations

could be observed, and no information could be decoded from observed population ratios. *Id.* Lehnen's method just would not work at all. *Id.*

Therefore, even if Lehnen could be combined with Jouvenot and/or Larson, the resulting combination would require the use of immobilized reagents, and would be the polar opposite of what claim 1 of the '797 Patent requires. EX2024, ¶156.

For the above reasons, Petitioner has failed to establish a reasonable likelihood that it will prevail on Grounds 2 and 2(a)–2(f).

VI. CONCLUSION

For at least these reasons, the Board should deny institution.

Respectfully submitted,

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on December 23, 2025, a copy of the foregoing PATENT OWNER'S PRELIMINARY RESPONSE was filed through the Patent Trial and Appeal Case Tracking System (P-TACTS) and was served via E-Mail on the Petitioner at the following email addresses provided by counsel of record for the Petitioner pursuant to 37 C.F.R. § 42.8(b)(4):

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**CERTIFICATE OF COMPLIANCE WITH
TYPE-VOLUME LIMITATION, TYPEFACE REQUIREMENTS,
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1. This Patent Owner's Preliminary Response complies with the type-volume limitation of 14,000 words, comprising 13,981 words, as counted using the Microsoft Word software that was used to prepare this paper, excluding the parts exempted by 37 C.F.R. § 42.24(a).

2. This Patent Owner's Preliminary Response complies with the general format requirements of 37 C.F.R. § 42.6(a) and has been prepared using Microsoft® Word in 14-point Times New Roman.

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