

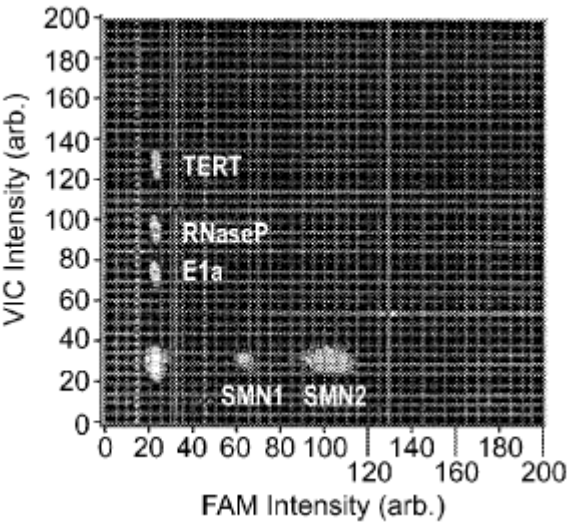
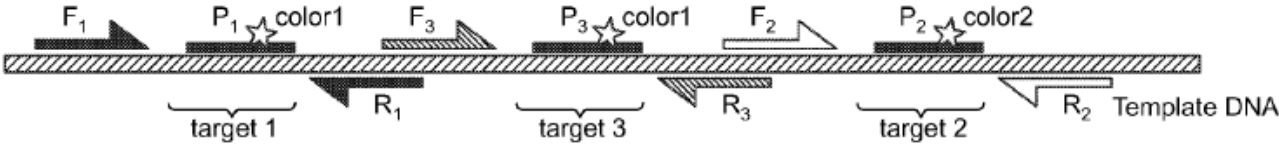
Appendix M

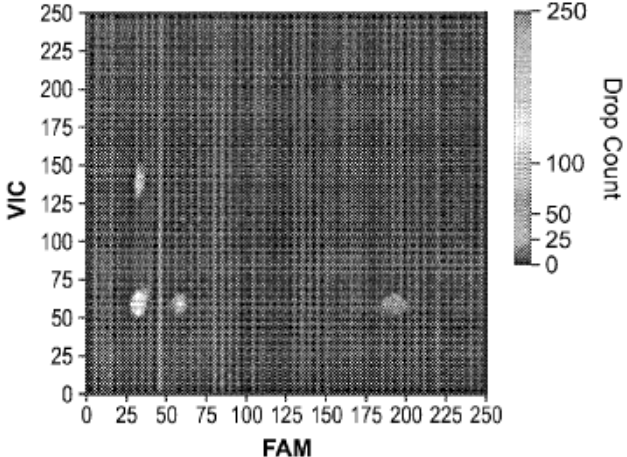
Invalidity of U.S. Patent No. 11,827,921

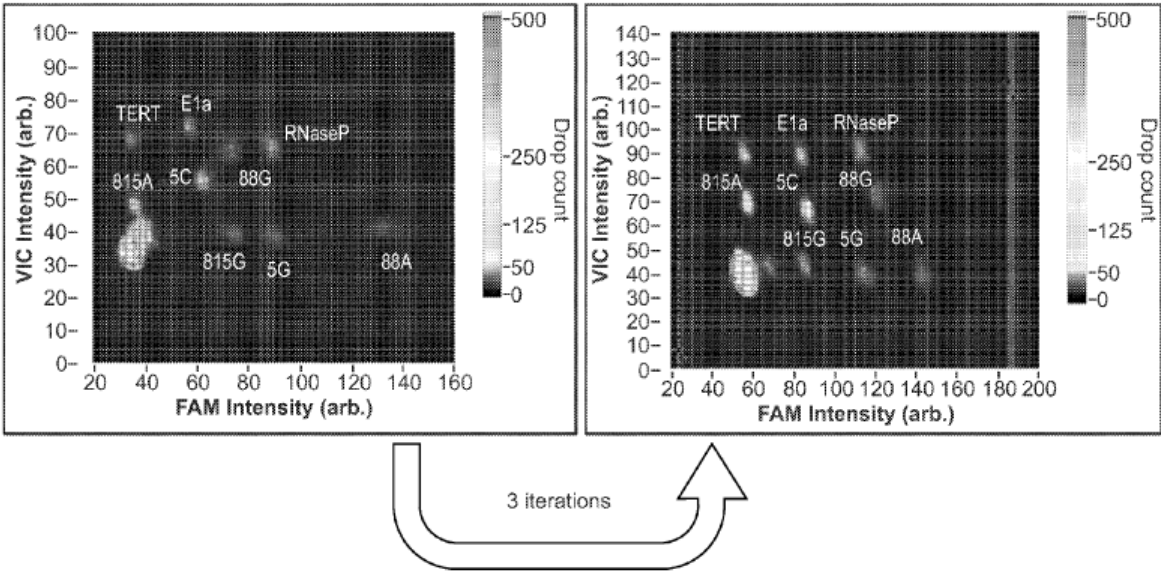
by U.S. Patent Publication 2011/0250597A1 (“Larson”)

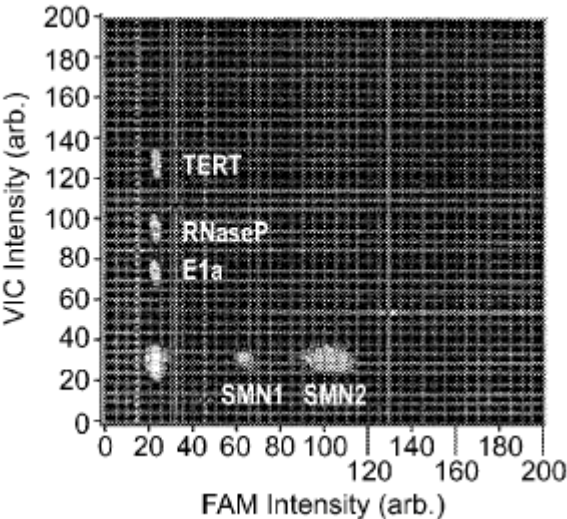
Based upon the claim interpretations Plaintiffs appear to be asserting and the applications of those interpretations to Bio-Rad’s products in Plaintiffs’ Patent Local Rule infringement contentions, Larson anticipates the ’921 Patent, or renders obvious, alone or in combination with other prior art identified in Bio-Rad’s Patent Local Rule invalidity contentions, the Asserted Claims at least as described by illustrative examples, below. These invalidity contentions are not an admission by Bio-Rad that the Accused Products, including any current or past versions of such products are covered by, or infringe these claims, particularly when they are properly construed. Nothing in these contentions should be interpreted as acquiescence to an assertion of a particular claim construction by Plaintiffs.

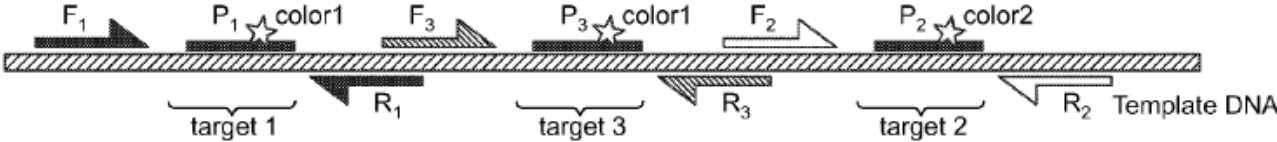
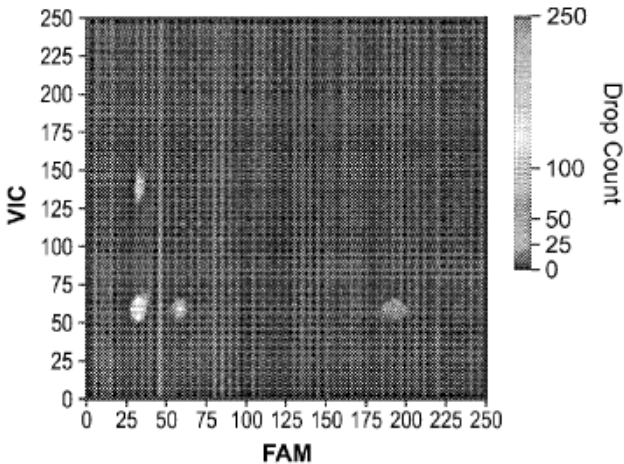
<u>Claim</u>	<u>Invalidity Analysis</u>
1. An assay that is capable of unambiguously detecting the presence or absence of each of at least M analytes,	Larson teaches detecting the presence or absence of multiple analytes in a single sample solution: For example, Larson Fig. 5c depicts the detection of five analytes in two colors:

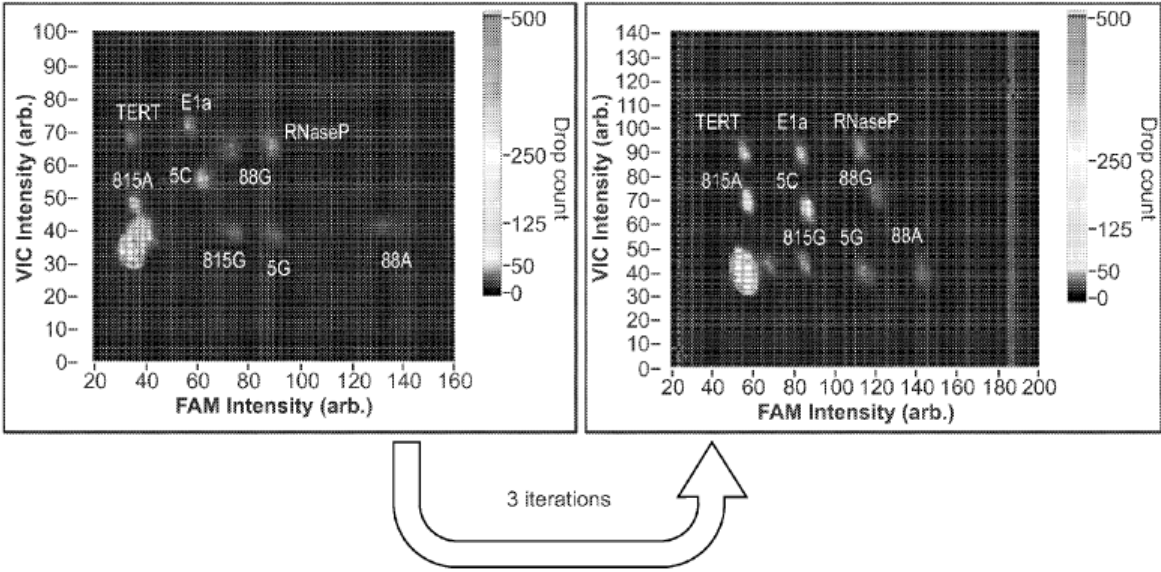
Claim	Invalidity Analysis
	FIG. 5C  Larson further depicts the detection of three targets using two colors, shown in Figures 9A and 9D. FIG. 9A Two Colors THREE Targets 

<u>Claim</u>	<u>Invalidity Analysis</u>
	FIG. 9D Histogram showing four populations of droplets; with target1, with target2, with target3 and without any of the three targets.  Larson further recites a differing description of detecting three targets in an assay than in Figure 9, reciting “Another method of the invention involves performing higher-plex assays using multiple different probe colors (i.e. fluorophores), however unlike the strategy above where each target is identified by single type of probe with a unique color and intensity, instead in this method a single target may be identified by multiple probes that constitute a unique signature of both colors and intensities. For example, a single droplet might contain four different probes for measuring three different targets (say, T1, T2, and T3). Two probes might be of color A (say, A1, and A2), and two probes might be of color B (say, B1 and B2). T1 is measured by probe A1, T2 is measured by probe B1, but T3 is measured by both probes A2 and B2. Thus, when a droplet contains T1 only increased fluorescence appears in color A. When a droplet contains T2 only increased fluorescence appears in color B. However when a droplet contains T3, increased fluorescence appears in both colors A and B.” Larson ¶ 140. Even further, Larson teaches the detection of nine analytes in two colors in Figure 15: TERT; E1a; RNaseP; 814A 5C; 88G; 815G; 5G; 88A:

Claim	Invalidity Analysis
	 FIG. 15 To the extent Larson is argued by Plaintiffs or found by the Court to not explicitly teach certain limitations in the asserted claims, such limitations would have been inherent and/or obvious as described in Bio-Rad’s invalidity contentions.
wherein each of said at least M analytes is encoded as a value of one component of a fluorescent signal, thereby generating a coding scheme,	Larson teaches assays wherein each of the detected analytes is encoded as a value of one component of a fluorescent signal: <i>See supra</i> claim 1, preamble. For example, Larson Fig. 5c depicts the detection of five analytes in two colors, each analyte being encoded as one component, either FAM or VIC:

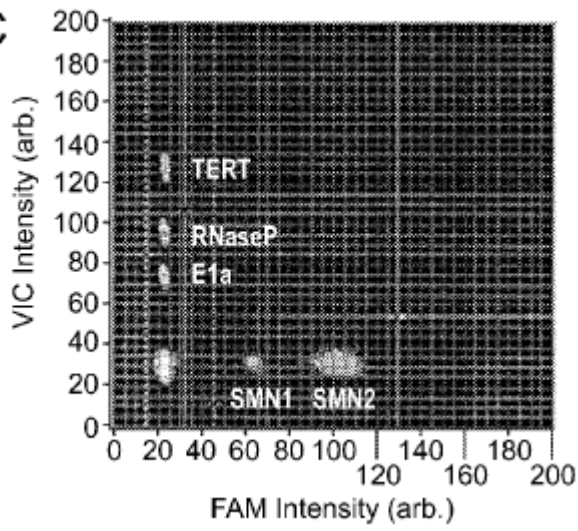
<u>Claim</u>	<u>Invalidity Analysis</u>
	FIG. 5C  <i>See also</i> Larson ¶ 113. Larson further depicts the detection of three targets, each target encoded as a either component (color) one or component (color) two as shown in Figures 9A and 9D.

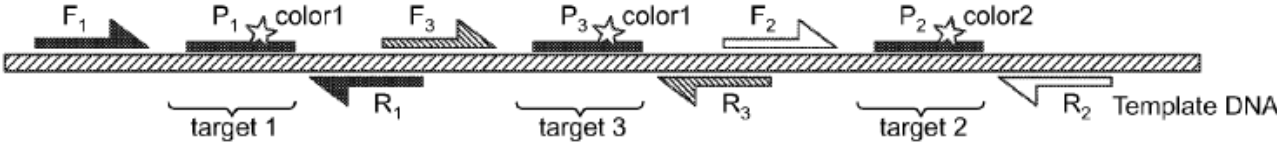
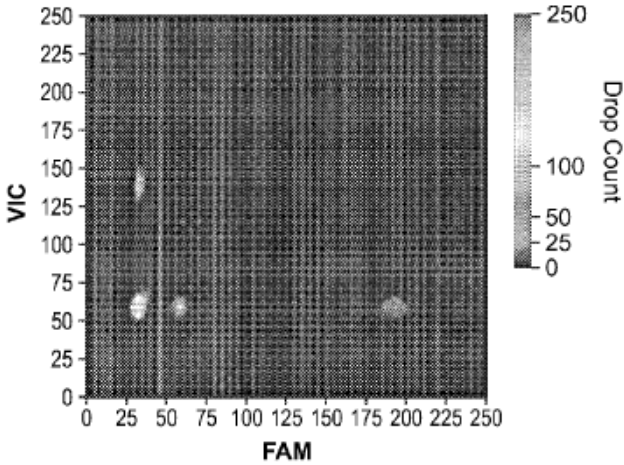
Claim	Invalidity Analysis
	FIG. 9A Two Colors THREE Targets  FIG. 9D Histogram showing four populations of droplets; with target1, with target2, with target3 and without any of the three targets.  <i>See also</i> Larson ¶¶ 29, 121. Larson further recites a differing description of detecting three targets in an assay in two wavelength components (colors), reciting “Another method of the invention involves performing higher-plex assays using multiple different

Claim	Invalidity Analysis
	probe colors (i.e. fluorophores), however unlike the strategy above where each target is identified by single type of probe with a unique color and intensity, instead in this method a single target may be identified by multiple probes that constitute a unique signature of both colors and intensities. For example, a single droplet might contain four different probes for measuring three different targets (say, T1, T2, and T3). Two probes might be of color A (say, A1, and A2), and two probes might be of color B (say, B1 and B2). T1 is measured by probe A1, T2 is measured by probe B1, but T3 is measured by both probes A2 and B2. Thus, when a droplet contains T1 only increased fluorescence appears in color A. When a droplet contains T2 only increased fluorescence appears in color B. However when a droplet contains T3, increased fluorescence appears in both colors A and B.” Larson ¶ 140. Even further, Larson teaches the detection of analytes in two components in Figure 15, a VIC and FAM component, with some target probes comprising a VIC component, some target probes comprising a FAM component, and some probes comprising both a VIC and a FAM component:  FIG. 15

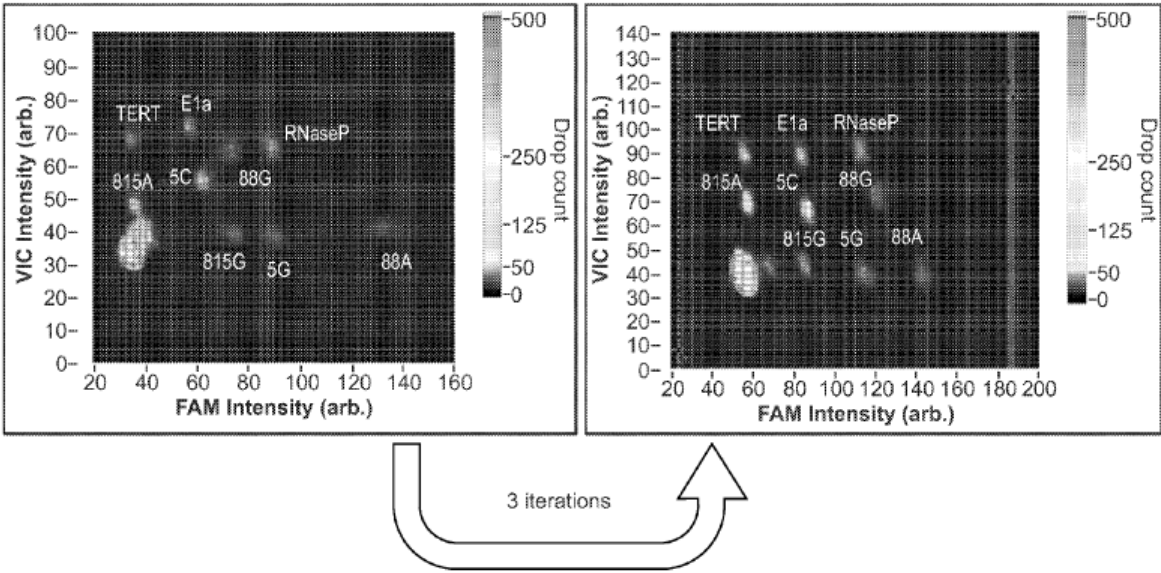
<u>Claim</u>	<u>Invalidity Analysis</u>
	<i>See also</i> Larson ¶¶ 35, 140, 150. To the extent Larson is argued by Plaintiffs or found by the Court to not explicitly teach certain limitations in the asserted claims, such limitations would have been inherent and/or obvious as described in Bio-Rad’s invalidity contentions.
wherein said fluorescent signal comprises F wavelength components, and	Larson teaches assays wherein wavelength components are used to comprise a fluorescent signal: Larson depicts assays using two channels, corresponding to two fluorophores, and thus two wavelength components in Figures 5, 6, 8-10, 14, 15, and 17-22. For example, in describing Figure 17, Larson recites “(Both panels) 2-D histograms shown as heat maps with hotter colors representing higher droplet counts. (Left panel) histogram of optical labels, i.e. fluorescence intensities of droplets measured at wavelengths for the two fluorophores comprising the optical labels. (Right panel) assay histogram, i.e. fluorescence intensities of droplets measured at wavelengths suitable for FAM detection (x-axis), and VIC detection (y-axis).” Larson ¶ 37. Larson further teaches that assays may include probes labeled with more than one fluorophore. Larson ¶ 47 (reciting, “individual reactions can be labeled with multiple fluorophores. As an example, two fluorophores (VIC and FAM) were used to distinguish five different reactions in one implementation of the invention.”). Table 2, describing probes as labeled in an exemplary assay teaches probes labeled with FAM wavelength components, VIC wavelength components, or FAM and VIC wavelength components. Larson ¶ 189.

Claim	Invalidity Analysis																																				
	TABLE 2 <table><tr><th>Target</th><th>Assay</th><th>Primers (5' to 3')</th><th>Probe (5' to 3')</th><th>5-plex assay conditions</th><th>Ref.</th></tr><tr><td>SMN1</td><td>Copy number</td><td>(f) AATGCTTTTAA- CATCCATATAAAGCT (r) CCTTAATTTAAG- GAATGTGAGCACC</td><td>FAM-CAGGGTTTC*AGACAAA- MGENFQ</td><td>0.37x</td><td>Anhuf et al., 2003</td></tr><tr><td>SMN2</td><td>Copy number</td><td>(f) AATGCTTTTAA- CATCCATATAAAGCT (r) CCTTAATTTAAG- GAATGTGAGCACC</td><td>FAM-TGATTTTGTCTA*AAA- CCC-MGBNFQ</td><td>0.76x</td><td>Anhuf et al., 2003</td></tr><tr><td>BCKDHA</td><td>Copy number</td><td>(f) CAACCTACTCTT- CTCAGACGTGTA (r) TCGAAGTGATCC- AGTGGGTAGTG</td><td>(FAM/VIC)-CAGGAGATGCCCG- CCCAGCTC-TAMRA</td><td>FAM: 0.18x VIC: 0.56x</td><td>DiMatteo et al., 2008</td></tr><tr><td>c.815A > G SNP</td><td></td><td>(f) TGCTGATGCITT- GGGAAGTATGTTA (r) TGTCAGGAAAAG- ATGCTGAGTGATT</td><td>(A) (FAM/VIC)-CATGAGTGG- CTA*TCATAC-MGBNFQ (G) FAM-ATGAGTGGCTG*TC- ATAC-MGBNFQ; VIC-CATGA- GTGGCTG*TCATAC-MGBNFQ</td><td>0.9x FAM: 0.9x VIC: 0.45x</td><td></td></tr><tr><td>RNaseP</td><td>Copy number</td><td>Unknown</td><td>unknown</td><td>n/a</td><td>Standard product, 4403326, ABI</td></tr></table> 5'-exonuclease genotyping assay design. Assay conditions in column 5 are specific to the multiplexed SMA assay. References: D. Anhuf, T. Eggermann, S. Rudnik-Schöneborn and K. Zerres, Hum Mutat., 2003, 22, 74-78; D. DiMatteo, S. Callahan and E. B. Kmiec, Exp Cell Res., 2008, 15, 878-886. Larson further teaches assays wherein three targets are detected in two colors, with two targets being encoded in one color and a third target being encoded in both colors. See Larson ¶ 140 (“For example, a single droplet might contain four different probes for measuring three different targets (say, T1, T2, and T3). Two probes might be of color A (say, A1, and A2), and two probes might be of color B (say, B1 and B2). T1 is measured by probe A1, T2 is measured by probe B1, but T3 is measured by both probes A2 and B2. Thus, when a droplet contains T1 only increased fluorescence appears in color A. When a droplet contains T2 only increased fluorescence appears in color B. However when a droplet contains T3, increased fluorescence appears in both colors A and B.”)	Target	Assay	Primers (5' to 3')	Probe (5' to 3')	5-plex assay conditions	Ref.	SMN1	Copy number	(f) AATGCTTTTAA- CATCCATATAAAGCT (r) CCTTAATTTAAG- GAATGTGAGCACC	FAM-CAGGGTTTC*AGACAAA- MGENFQ	0.37x	Anhuf et al., 2003	SMN2	Copy number	(f) AATGCTTTTAA- CATCCATATAAAGCT (r) CCTTAATTTAAG- GAATGTGAGCACC	FAM-TGATTTTGTCTA*AAA- CCC-MGBNFQ	0.76x	Anhuf et al., 2003	BCKDHA	Copy number	(f) CAACCTACTCTT- CTCAGACGTGTA (r) TCGAAGTGATCC- AGTGGGTAGTG	(FAM/VIC)-CAGGAGATGCCCG- CCCAGCTC-TAMRA	FAM: 0.18x VIC: 0.56x	DiMatteo et al., 2008	c.815A > G SNP		(f) TGCTGATGCITT- GGGAAGTATGTTA (r) TGTCAGGAAAAG- ATGCTGAGTGATT	(A) (FAM/VIC)-CATGAGTGG- CTA*TCATAC-MGBNFQ (G) FAM-ATGAGTGGCTG*TC- ATAC-MGBNFQ; VIC-CATGA- GTGGCTG*TCATAC-MGBNFQ	0.9x FAM: 0.9x VIC: 0.45x		RNaseP	Copy number	Unknown	unknown	n/a	Standard product, 4403326, ABI
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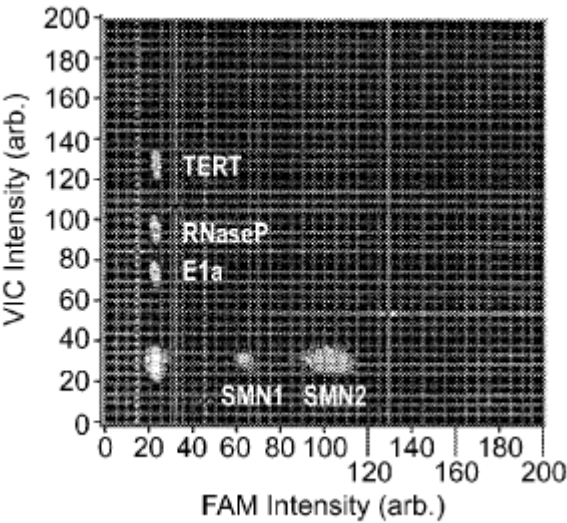
<u>Claim</u>	<u>Invalidity Analysis</u>
	To the extent Larson is argued by Plaintiffs or found by the Court to not explicitly teach certain limitations in the asserted claims, such limitations would have been inherent and/or obvious as described in Bio-Rad’s invalidity contentions.
wherein said assay is capable of unambiguously detecting the presence or absence of each of said at least M analytes, in any combination of presence or absence, in a single sample volume, based on detection of said F wavelength components, when M is greater than F,	Larson teaches assays wherein targets are unambiguously detected in any combination of presence or absence in droplets based on detection in fewer wavelength components (colors) than there are analytes: <i>See supra</i> claim 1, preamble, <i>see also supra</i>, generally. For example, Larson Fig. 5c depicts the detection of five analytes (M = 5), in two colors (F = 2). Thus, M > F: FIG. 5C  <i>See also</i> Larson ¶ 113.

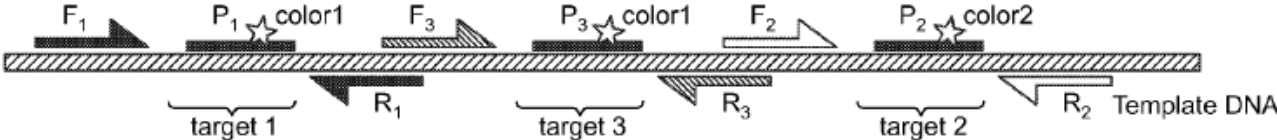
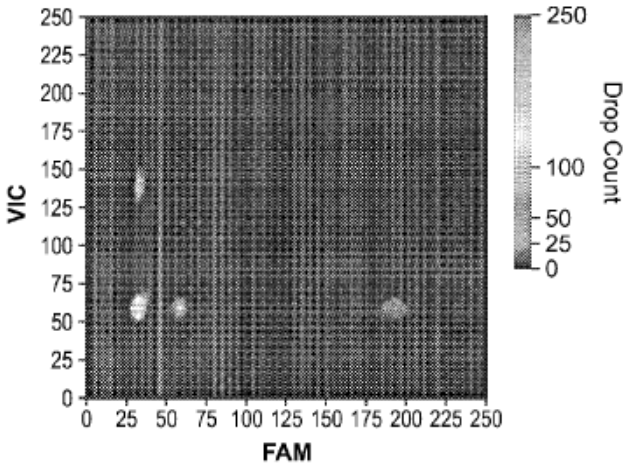
<u>Claim</u>	<u>Invalidity Analysis</u>
	Larson further depicts the detection of three targets ($M = 3$), each target encoded as a either component (color) one or component (color) two ($F = 2$) as shown in Figures 9A and 9D. Thus, $M > F$: FIG. 9A Two Colors THREE Targets  FIG. 9D Histogram showing four populations of droplets; with target1, with target2, with target3 and without any of the three targets. 

<u>Claim</u>	<u>Invalidity Analysis</u>
	<i>See also</i> Larson ¶¶ 29, 121. Larson further recites a differing description of detecting three targets ($M = 3$) in an assay in two wavelength components (colors) ($F = 2$), reciting “Another method of the invention involves performing higher-plex assays using multiple different probe colors (i.e. fluorophores), however unlike the strategy above where each target is identified by single type of probe with a unique color and intensity, instead in this method a single target may be identified by multiple probes that constitute a unique signature of both colors and intensities. For example, a single droplet might contain four different probes for measuring three different targets (say, T1, T2, and T3). Two probes might be of color A (say, A1, and A2), and two probes might be of color B (say, B1 and B2). T1 is measured by probe A1, T2 is measured by probe B1, but T3 is measured by both probes A2 and B2. Thus, when a droplet contains T1 only increased fluorescence appears in color A. When a droplet contains T2 only increased fluorescence appears in color B. However when a droplet contains T3, increased fluorescence appears in both colors A and B.” Larson ¶ 140. Thus, $M > F$. Even further, Larson teaches the detection of nine analytes ($M = 9$) in two components ($F = 2$) in Figure 15, a VIC and FAM component, with some target probes comprising a VIC component, some target probes comprising a FAM component, and some probes comprising both a VIC and a FAM component. Thus, $M > F$:

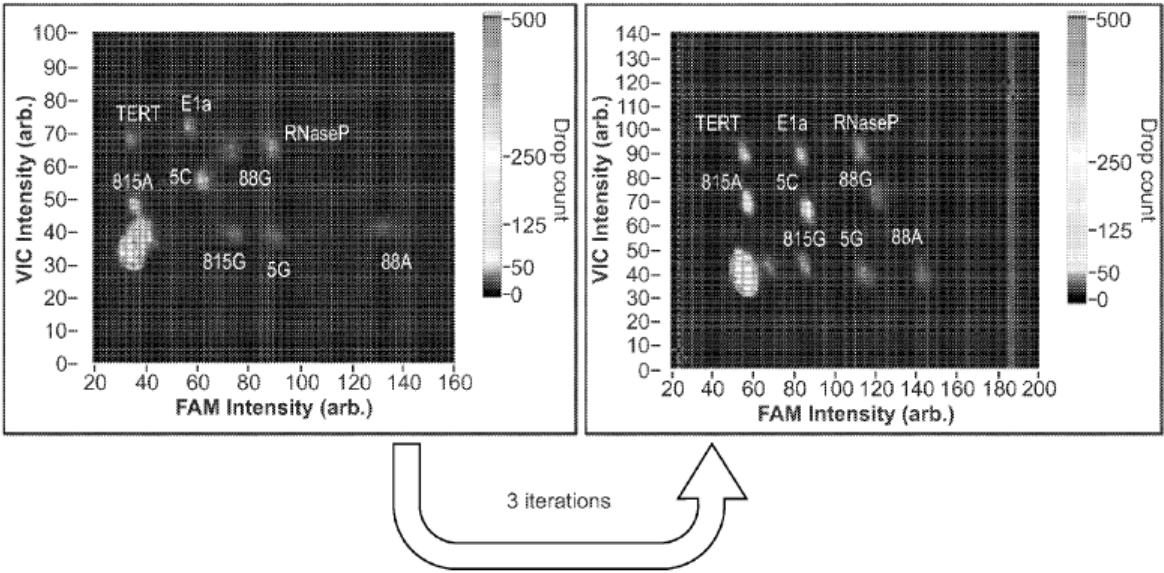
Claim	Invalidity Analysis
	 FIG. 15 To the extent Larson is argued by Plaintiffs or found by the Court to not explicitly teach certain limitations in the asserted claims, such limitations would have been inherent and/or obvious as described in Bio-Rad’s invalidity contentions.
wherein the assay does not require the use of mass spectrometry or immobilization of said at least M analytes, and	Larson teaches the performance of the described assays without immobilization, physical separation or mass spectrometry: <i>See supra</i>, generally.

<u>Claim</u>	<u>Invalidity Analysis</u>
	The methods to perform assays as described in Larson make no mention of mass spectrometry or immobilization. <i>See, e.g.</i>, Larson Figs. 5, 9, 14, 15. To the extent Larson is argued by Plaintiffs or found by the Court to not explicitly teach certain limitations in the asserted claims, such limitations would have been inherent and/or obvious as described in Bio-Rad’s invalidity contentions.
wherein the analytes are amplified in the single sample volume.	Larson teaches the amplification of analytes in the single sample volume: Larson discloses that “[t]he invention generally relates to the manipulation of nucleic acid in droplets, and in particular, nucleic acid amplification and detection. In one aspect, the invention provides a droplet that contains a single nucleic acid template and a plurality of primer pairs specific for multiple target sites on the template. The single nucleic acid template can be DNA (e.g., genomic DNA, cDNA, etc.) or RNA. The template is amplified in the droplet for detection; and may preferably be amplified using a plurality of primer pairs as described herein.” Larson ¶ 7, <i>see also</i> Larson ¶ 17 (“the targets are amplified in the droplets”), Figs. 5, 6, 8-10, 14, 15. To the extent Larson is argued by Plaintiffs or found by the Court to not explicitly teach certain limitations in the asserted claims, such limitations would have been inherent and/or obvious as described in Bio-Rad’s invalidity contentions.
2. The assay of claim 1, wherein each of said at least M analytes is encoded as at least one first value in a first component of said fluorescent signal and at least one second value in a second component of said fluorescent signal.	Larson teaches assays wherein each of M analytes is encoded as a value in a first component and a second value in a second component of a fluorescent signal: <i>See supra</i> Claim 1 at “wherein each of said at least M...” and “wherein said assay is capable of...” For example, Larson Fig. 5c depicts the detection of five analytes, each encoded in a value of two fluorophores, FAM and VIC:

<u>Claim</u>	<u>Invalidity Analysis</u>
	FIG. 5C  <i>See also</i> Larson ¶ 113. Larson further depicts the detection of three targets with each target encoded as a either component (color) one or component (color) two as shown in Figures 9A and 9D. Thus, each target exhibits a signal as a function of component one and component two as shown in Figure 9D.

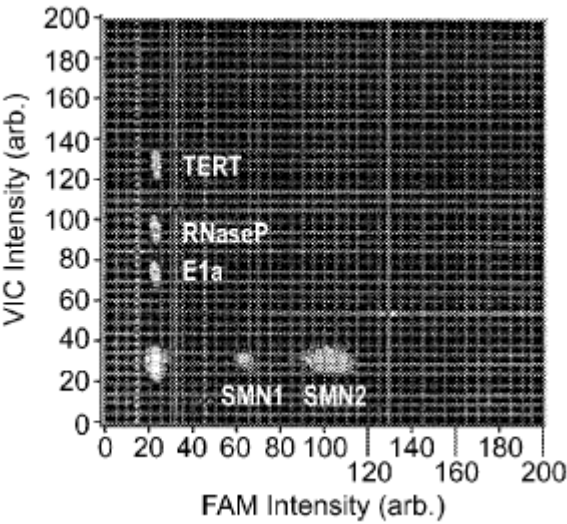
Claim	Invalidity Analysis
	FIG. 9A Two Colors THREE Targets  FIG. 9D Histogram showing four populations of droplets; with target1, with target2, with target3 and without any of the three targets.  See also Larson ¶¶ 29, 121. Larson further recites a differing description of detecting three targets in an assay in two wavelength components (colors) where each target is encoded as a value of each of the two colors “Another method of the invention involves

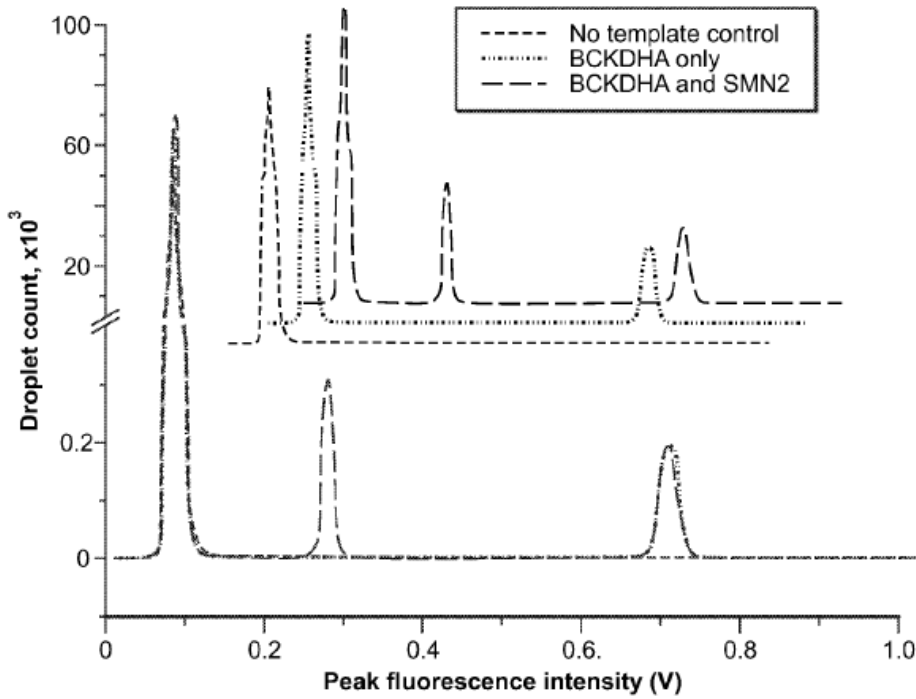
<u>Claim</u>	<u>Invalidity Analysis</u>
	performing higher-plex assays using multiple different probe colors (i.e. fluorophores), however unlike the strategy above where each target is identified by single type of probe with a unique color and intensity, instead in this method a single target may be identified by multiple probes that constitute a unique signature of both colors and intensities. For example, a single droplet might contain four different probes for measuring three different targets (say, T1, T2, and T3). Two probes might be of color A (say, A1, and A2), and two probes might be of color B (say, B1 and B2). T1 is measured by probe A1, T2 is measured by probe B1, but T3 is measured by both probes A2 and B2. Thus, when a droplet contains T1 only increased fluorescence appears in color A. When a droplet contains T2 only increased fluorescence appears in color B. However when a droplet contains T3, increased fluorescence appears in both colors A and B.” Larson ¶ 140. Thus, for example an exemplary assay that would fit the above description in paragraph 140 could have T1 encoded as a value of 1 in color A and a value of 0 in color B; T2 could be encoded as a value of 0 in color A and a value of 1 in color B; and T3 could be encoded as a value of 1 in color A and 1 in color B. Even further, Larson teaches the detection of nine analytes in two components, VIC and FAM, each of the analytes being encoded as a function of VIC and FAM, in Figure 15:

Claim	Invalidity Analysis
	 FIG. 15 To the extent Larson is argued by Plaintiffs or found by the Court to not explicitly teach certain limitations in the asserted claims, such limitations would have been inherent and/or obvious as described in Bio-Rad’s invalidity contentions.
3. The assay of claim 2, wherein said first value is an intensity or range of intensities.	Larson teaches assays wherein the first value is an intensity: <i>See supra</i>, generally; <i>see also supra</i>, claim 2.

<u>Claim</u>	<u>Invalidity Analysis</u>
	To the extent Larson is argued by Plaintiffs or found by the Court to not explicitly teach certain limitations in the asserted claims, such limitations would have been inherent and/or obvious as described in Bio-Rad’s invalidity contentions.
4. The assay of claim 2, wherein said coding scheme is made nondegenerate by enumerating every legitimate result that can be obtained from said coding scheme, identifying each legitimate result that is degenerate, and eliminating at least one potential analyte code from said coding scheme to eliminate degeneracy.	Larson teaches assays wherein the assay enumerates every legitimate result and produces results with no degeneracy: <i>See supra</i> claim 1 at “wherein each of said at least M...” and “wherein said assay is capable of...” Larson teaches enumerating every legitimate result and identifying all degenerate combinations, if any. For example, <i>see, e.g.</i>, Figure 15 (depicting elimination of degeneracy). Further, Larson identifies another method to generate nondegenerate assays for three targets in two components, “[f]or example, a single droplet might contain four different probes for measuring three different targets (say, T1, T2, and T3). Two probes might be of color A (say, A1, and A2), and two probes might be of color B (say, B1 and B2). T1 is measured by probe A1, T2 is measured by probe B1, but T3 is measured by both probes A2 and B2. Thus, when a droplet contains T1 only increased fluorescence appears in color A. When a droplet contains T2 only increased fluorescence appears in color B. However when a droplet contains T3, increased fluorescence appears in both colors A and B.” Larson ¶ 140. A POSA would have understood to eliminate the degenerate results. To the extent Larson is argued by Plaintiffs or found by the Court to not explicitly teach certain limitations in the asserted claims, such limitations would have been inherent and/or obvious as described in Bio-Rad’s invalidity contentions.
5. The assay of claim 1, wherein said detecting is performed with reagents comprising hybridization probes.	Larson teaches assays that detect analytes using hybridization probes: <i>See supra</i> claim 1 at “wherein said fluorescent signal comprises F wavelength components, and.”

<u>Claim</u>	<u>Invalidity Analysis</u>
	Further, Larson teaches that the invention may be performed with TaqMan probes, which are hybridization probes. Larson ¶ 154, 156. Further, the invention “encompasses the use of all fluorogenic DNA hybridization probes, such as molecular beacons, Solaris probes, scorpion probes, and any other probes that function by sequence specific recognition of target DNA by hybridization and result in increased fluorescence on amplification of the target sequence.” Larson ¶ 93, <i>see also</i> Larson ¶ 145. Further, as recited by Larson, “[f]or example, a single droplet might contain four different probes for measuring three different targets (say, T1, T2, and T3). Two probes might be of color A (say, A1, and A2), and two probes might be of color B (say, B1 and B2). T1 is measured by probe A1, T2 is measured by probe B1, but T3 is measured by both probes A2 and B2. Thus, when a droplet contains T1 only increased fluorescence appears in color A. When a droplet contains T2 only increased fluorescence appears in color B. However when a droplet contains T3, increased fluorescence appears in both colors A and B.” Larson ¶ 140. To the extent Larson is argued by Plaintiffs or found by the Court to not explicitly teach certain limitations in the asserted claims, such limitations would have been inherent and/or obvious as described in Bio-Rad’s invalidity contentions.
6. The assay of claim 5, wherein said hybridization probes comprise one or more hybridization probes specific for different analytes and comprising an identical fluorophore or combination of fluorophores.	Larson teaches assays wherein the hybridization probes comprise an identical fluorophore or combination of fluorophores: <i>See supra</i>, generally, <i>see supra</i> Claims 1, 2, 5. For example, Larson Figure 5 depicts cumulative signals for the detection of polynucleotides each encoded as a function of both FAM and VIC fluorophores, with TERT, RNaseP and E1a, each comprising a VIC fluorophore which are multiplexed in a single channel.

<u>Claim</u>	<u>Invalidity Analysis</u>
	FIG. 5C  <i>See also</i> Larson ¶ 113. To the extent Larson is argued by Plaintiffs or found by the Court to not explicitly teach certain limitations in the asserted claims, such limitations would have been inherent and/or obvious as described in Bio-Rad’s invalidity contentions.
7. The assay of claim 5, wherein said fluorescence signal from said hybridization probes are used to construct a chromatogram.	Larson teaches assays wherein the fluorescence signal detected from the probes is used to construct a chromatogram: For example, <i>see</i> Figures 3c, 4a, 4b, 5B, 7C, 7D, 8C, 9C, 11a, depicting fluorescence detected from the hybridization probes.

Claim	Invalidity Analysis
	 The figure is a flow cytometry histogram. The y-axis is labeled 'Droplet count, x10³' and has a break between 0.2 and 20. The x-axis is labeled 'Peak fluorescence intensity (V)' and ranges from 0 to 1.0. There are three data series: 'No template control' (dashed line), 'BCKDHA only' (dotted line), and 'BCKDHA and SMN2' (dash-dot line). The 'No template control' series shows a large peak at ~0.08V (count ~70) and smaller peaks at ~0.22V, ~0.45V, and ~0.72V. The 'BCKDHA only' series shows a single peak at ~0.28V (count ~0.4). The 'BCKDHA and SMN2' series shows a single peak at ~0.72V (count ~0.2). FIG. 11a To the extent Larson is argued by Plaintiffs or found by the Court to not explicitly teach certain limitations in the asserted claims, such limitations would have been inherent and/or obvious as described in Bio-Rad’s invalidity contentions.

<u>Claim</u>	<u>Invalidity Analysis</u>
8. The assay of claim 1, wherein said signal is generated during a polymerase chain reaction.	Larson teaches assays wherein the fluorescent signal is generated during a polymerase chain reaction: <i>See supra</i>, claim 5. Further, Larson teaches that the invention may be performed with TaqMan probes, which are hybridization probes that generate a fluorescence signal while cleaved from the target analyte during PCR. Larson ¶ 154, 156. Further, the invention “encompasses the use of all fluorogenic DNA hybridization probes, such as molecular beacons, Solaris probes, scorpion probes, and any other probes that function by sequence specific recognition of target DNA by hybridization and result in increased fluorescence on amplification of the target sequence.” Larson ¶ 93, <i>see also</i> Larson ¶¶ 70, 145, 156. To the extent Larson is argued by Plaintiffs or found by the Court to not explicitly teach certain limitations in the asserted claims, such limitations would have been inherent and/or obvious as described in Bio-Rad’s invalidity contentions.
9. The assay of claim 1, wherein at least one of said analytes is encoded by at least one additional value, wherein said at least one additional value is selected from the group consisting of a value from at least one additional component of said signal, a value from at least one component of an additional signal, and combinations thereof.	Larson teaches assays wherein at least one of the analytes is encoded by an additional value that is an intensity or a different wavelength component. <i>See supra</i>, generally, <i>see supra</i> claim 1 at “wherein each of said at least M...” and “wherein said assay is capable of...” <i>see also</i> claim 6. For example, Larson recites this exact scenario, in an assay detecting three analytes in two wavelength components: “[f]or example, a single droplet might contain four different probes for measuring three different targets (say, T1, T2, and T3). Two probes might be of color A (say, A1, and A2), and two probes might be of color B (say, B1 and B2). T1 is measured by probe A1, T2 is measured by probe B1, but T3 is measured by both probes A2 and B2. Thus, when a droplet contains T1 only increased fluorescence appears in color A. When a droplet contains T2 only increased fluorescence appears in color B. However when a droplet contains T3, increased fluorescence appears in both colors A and B.” Larson ¶ 140. In the above example, T3 is encoded as an additional component of the fluorescent signal, exhibiting signal components in color A and color B.

<u>Claim</u>	<u>Invalidity Analysis</u>
	Further, Figures 5, 6, 8, 14, 15, 17-22 all show more than two targets in two fluorophores, with at least one target exhibiting a signal in each of the two fluorophores. To the extent Larson is argued by Plaintiffs or found by the Court to not explicitly teach certain limitations in the asserted claims, such limitations would have been inherent and/or obvious as described in Bio-Rad’s invalidity contentions.
10. The assay of claim 1, wherein at least one of said analytes comprises a polynucleotide.	Larson teaches assays for the detection of polynucleotide analytes: <i>See supra</i>, generally, <i>see supra</i>, claims 1, 5, 6. Further, Larson recites “[t]he invention generally relates to droplet based digital PCR and methods for analyzing a target nucleic acid using the same.” Larson ¶ 2, <i>see also</i> Larson ¶15-17, 19, 20, 49, 52, 68, 69, 73, 74, 77, 79, 168, 173, Figs. 5-12, 14, 15, 17-22. To the extent Larson is argued by Plaintiffs or found by the Court to not explicitly teach certain limitations in the asserted claims, such limitations would have been inherent and/or obvious as described in Bio-Rad’s invalidity contentions.
11. The assay of claim 1, further comprising transmitting information concerning the presence or absence of at least one of said analytes through a computer network.	Larson teaches transmitting information concerning the presence or absence of polynucleotide analytes through a computer network: Larson describes suitable detection apparatuses, reciting “suitable detection apparatuses include optical waveguides, microscopes, diodes, light stimulating devices, (e.g., lasers), photo multiplier tubes, and processors (e.g., computers and software), and combinations thereof, which cooperate to detect a signal representative of a characteristic, marker, or reporter, and to determine and direct the measurement or the sorting action at a sorting module.” Larson ¶ 89, <i>see also</i> Fig. 16 (depicting an optical schematic for detection comprising a computer).

<u>Claim</u>	<u>Invalidity Analysis</u>
	Further, Larson teaches that in certain embodiments, the thermal cycling may depend on a number on repeated cycles in various temperature zones, which a POSA would have understood would be advantageous to use a computer to control because monitoring temperature and performing cycles are actions well-suited to be performed by computers. <i>See</i> Larson ¶¶ 80-85. To the extent Larson is argued by Plaintiffs or found by the Court to not explicitly teach certain limitations in the asserted claims, such limitations would have been inherent and/or obvious as described in Bio-Rad’s invalidity contentions.
13. The assay of claim 1, wherein said coding scheme is innately nondegenerate or non-degenerate by construction.	Larson teaches assays that are non-degenerate: <i>See supra</i>, generally, <i>see supra</i> claim 1 at “wherein each of said at least M...” and “wherein said assay is capable of...” and <i>see supra</i> claims 2, 4. To the extent Larson is argued by Plaintiffs or found by the Court to not explicitly teach certain limitations in the asserted claims, such limitations would have been inherent and/or obvious as described in Bio-Rad’s invalidity contentions.
14. A kit for detecting the presence or absence of at least M analytes by generating a single cumulative measurement, comprising analyte-specific reagents, wherein:	Larson teaches kits for detecting the presence or absence of analytes based on a single cumulative measurement with analyte-specific reagents: <i>See supra</i>, generally, <i>see supra</i> claim 1. To the extent Larson is argued by Plaintiffs or found by the Court to not explicitly teach certain limitations in the asserted claims, such limitations would have been inherent and/or obvious as described in Bio-Rad’s invalidity contentions.

<u>Claim</u>	<u>Invalidity Analysis</u>
a. each of said at least M analytes is encoded as a value of one component of a fluorescent signal, thereby generating a coding scheme, wherein each of said at least M analytes is represented in said coding scheme by said value, and wherein said encoding is performed in a manner that eliminates degeneracy; and	Larson teaches kits wherein M analytes are encoded as a component of a fluorescent signal in a manner that eliminates degeneracy: <i>See supra</i>, generally, <i>see supra</i> claim 1, <i>see supra</i> claims 2, 4-7. To the extent Larson is argued by Plaintiffs or found by the Court to not explicitly teach certain limitations in the asserted claims, such limitations would have been inherent and/or obvious as described in Bio-Rad’s invalidity contentions.
b. each of said analyte-specific reagents, when contacted with a sample comprising its corresponding analyte, generates the value;	Larson teaches kits wherein analyte specific reagents generate a signal value when contacted with its corresponding analytes: <i>See supra</i>, generally, <i>see supra</i> claim 1, <i>see supra</i> claims 5-7. To the extent Larson is argued by Plaintiffs or found by the Court to not explicitly teach certain limitations in the asserted claims, such limitations would have been inherent and/or obvious as described in Bio-Rad’s invalidity contentions.
wherein said kit is capable of unambiguously detecting the presence or absence of each analyte of M analytes in a single sample volume, in any combination of presence or absence, and wherein the kit does not require the use of mass spectrometry or immobilization of said M analytes, and	Larson teaches kits wherein analytes are unambiguously detected without immobilization or mass spectrometry: <i>See supra</i>, generally, <i>see supra</i> claim 1. To the extent Larson is argued by Plaintiffs or found by the Court to not explicitly teach certain limitations in the asserted claims, such limitations would have been inherent and/or obvious as described in Bio-Rad’s invalidity contentions.

<u>Claim</u>	<u>Invalidity Analysis</u>
wherein the analytes are simplified in the single sample volume.	Larson teaches amplification of targets in a sample volume: <i>See supra</i>, generally; <i>see also supra</i>, claim 1. To the extent Larson is argued by Plaintiffs or found by the Court to not explicitly teach certain limitations in the asserted claims, such limitations would have been inherent and/or obvious as described in Bio-Rad’s invalidity contentions.
15. The kit of claim 14, wherein said fluorescent signal comprises F wavelength components and said kit is capable of unambiguously detecting the presence or absence of M analytes, in any combination of presence or absence, when M is greater than F.	Larson teaches the non-degenerate detection of the presence or absence of polynucleotide analytes in a sample solution volume, in any combination of presence or absence: <i>See supra</i>, generally; <i>see also supra</i>, claim 1. To the extent Larson is argued by Plaintiffs or found by the Court to not explicitly teach certain limitations in the asserted claims, such limitations would have been inherent and/or obvious as described in Bio-Rad’s invalidity contentions.
16. The kit of claim 14, wherein said analyte-specific reagents comprise a plurality of hybridization probes.	Larson teaches the non-degenerate detection of the presence or absence of polynucleotide analytes in a sample solution volume, in any combination of presence or absence: <i>See supra</i>, generally; <i>see also supra</i>, claims 5-7 and preamble. To the extent Larson is argued by Plaintiffs or found by the Court to not explicitly teach certain limitations in the asserted claims, such limitations would have been inherent and/or obvious as described in Bio-Rad’s invalidity contentions.

<u>Claim</u>	<u>Invalidity Analysis</u>
17. The kit of claim 16, wherein said plurality of hybridization probes comprise a fluorophore, and wherein said plurality of hybridization probes are specific for different analytes.	Larson teaches the non-degenerate detection of the presence or absence of polynucleotide analytes in a sample solution volume, in any combination of presence or absence: <i>See supra</i>, generally; <i>see also supra</i>, claims 5-7 and preamble. To the extent Larson is argued by Plaintiffs or found by the Court to not explicitly teach certain limitations in the asserted claims, such limitations would have been inherent and/or obvious as described in Bio-Rad’s invalidity contentions.
19. The kit of claim 14, wherein the analyte-specific reagents are each present at a different amount in the kit.	Larson teaches a kit wherein analyte-specific reagents are present in different amounts: <i>See supra</i>, generally; <i>see also supra</i>, claims 5-7 and preamble. For example, Larson recites “[t]he plurality of probes can include one or more groups of probes at varying concentrations. The one or more groups of probes can include the same detectable label which will vary in intensity upon detection, due to the varying probe concentrations. The droplets of the invention can further contain one or more reagents for conducting a polymerase chain reaction, such as a DNA or RNA polymerase, and/or dNTPs.” Larson ¶ 9. Larson further recites “[c]ertain members of the plurality of probes include a detectable label. Members of the plurality of probes can each include the same detectable label, or a different detectable label. The detectable label is preferably a fluorescent label. The plurality of probes can include one or more groups of probes at varying concentrations. The one or more groups of probes can include the same detectable label which varies in intensity upon detection, due to the varying probe concentrations.” Larson ¶ 12. <i>See also</i> Larson ¶¶ 91, 94, 130, claim 6.

<u>Claim</u>	<u>Invalidity Analysis</u>
	To the extent Larson is argued by Plaintiffs or found by the Court to not explicitly teach certain limitations in the asserted claims, such limitations would have been inherent and/or obvious as described in Bio-Rad’s invalidity contentions.