

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CURIO BIOSCIENCE, INC.,
Petitioner

v.

PROGNOSYS BIOSCIENCES INC. AND 10X GENOMICS, INC.,
Patent Owner and Real Party in Interest

Case IPR2025-00193
Patent 11,761,030

PATENT OWNER'S PRELIMINARY RESPONSE

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LIST OF EXHIBITS

Exhibit Number	Description
EX2001	[RESERVED]
EX2002	Declaration of Dr. Charles R. Cantor
EX2003	Curriculum Vitae of Dr. Charles R. Cantor
EX2004	Web Capture of https://www.10xgenomics.com/products/spatial-gene-expression (December 18, 2024)
EX2005	Khaliq et al., “Spatial Transcriptomic Analysis of Primary and Metastatic Pancreatic Cancers Highlights Tumor Microenvironmental Heterogeneity,” <i>Nature Genetics</i> 56:2455–2465 (2024)
EX2006	Latham and Peltier, “MELT™ Total Nucleic Acid Isolation System: a new technology for hands-free tissue disruption, RNA preservation and total nucleic acid purification,” <i>Nature Methods</i> 2:i–iii (2005)
EX2007	Griffin et al., “Pathogenic Human Viruses in Coastal Waters,” <i>Clin. Microbiol. Rev.</i> 16(1):129–143 (2003)
EX2008	Deak et al., “Molecular Characterization of <i>Yarrowia lipolytica</i> and <i>Candida zeylanoides</i> Isolated from Poultry,” <i>Appl. Env. Microbiol.</i> 66(10):4340–4344 (2000)
EX2009	[RESERVED]
EX2010	[RESERVED]
EX2011	[RESERVED]
EX2012	Gunderson et al., “Decoding Randomly Ordered DNA Arrays,” <i>Genome Research</i> 14:870–77 (2004)
EX2013	U.S. Application No. 18/074,992

Patent Owner (“PO”) submits this Preliminary Response to the Petition for Inter Partes Review (“IPR”) of U.S. Patent No. 11,761,030 (“’030 patent”) filed by Curio Bioscience, Inc. (“Petitioner”).

I. INTRODUCTION

Petitioner once again constructs a house of cards built on misdirection and mistaken assumptions.¹ Petitioner relies on isolated quotations and pictures that, at first blush, make the claims of the ’030 patent appear obvious. But closer inspection reveals that the Petition skips over relevant teachings of the ’030 patent’s priority chain, makes assumptions about the prior-art teachings that are either wholly absent or taken out of context, and ignores that a POSA would *not* have constructed the arrays Petitioner proposes.

Petitioner steps back in the ’030 patent’s priority chain to assert that the patent’s claims lack written-description support. But Petitioner fails to grapple with the fact that each and every application in that priority chain expressly incorporated by reference the disclosure of the provisional application. The provisional explicitly describes the invention Petitioner calls “Figure A.” Petitioner’s ignorance of the provisional’s incorporation attempts to hide that the

¹ Each of Petitioner’s grounds relies on the same art asserted in IPR2024-01289, IPR2025-00192, IPR2025-00236, and IPR2025-00237.

claim limitations have written-description support in the provisional. Moreover, Petitioner's own characterizations of the prior art directly contradicts and refutes its assertion that the provisional does not teach "the plurality of beads was previously positioned on the substrate in a random pattern." Because the challenged claims have a priority date before Frisen (Petitioner's §102 reference), Frisen cannot anticipate.

Petitioner's obviousness challenges continue the pattern of misdirection and mistaken assumptions. Petitioner's arguments as to most Challenged Claims *depend* on the assertion that Cantor (Petitioner's §103 reference) teaches contacting a "tissue" with its beads. Petitioner is wrong. Cantor actually teaches that tissue is merely a *source* for Cantor's "sample nucleic acid." In Cantor's bulk-analysis methods, nucleic acids may be extracted from tissue to create a "sample nucleic acid"—a solution containing nucleic acids that can be mixed with beads. The creation of sample nucleic acid destroys any spatial information from tissue, making it impossible for Cantor's bulk-analysis methods to provide spatial analysis. Dr. Cantor's testimony and the Cantor application could not be clearer on this point.

Moreover, Petitioner fails to call its obviousness theory what it actually is: obviousness based on inherency. Petitioner avoids using the term "inherency" but nonetheless argues that Cantor's "identification sequences" would *necessarily*

identify the unique location of a bead on the array. But Cantor teaches that its beads and optional identification sequences facilitate *sequence analysis* of a sample nucleic acid to determine *if* a particular nucleic acid was present in the sample (not *where* in the sample). *Nothing* in Cantor teaches or suggests that the location of a bead and its corresponding identification sequence (if used) is known (it isn't) or *even* needs to be known (it doesn't).

Petitioner simply states that a POSA would have “correlate[d] the identification sequence . . . and [the] bead’s location on the array” using just one of two options: (1) selective loading or (2) random loading and decoding. But what Petitioner fails to state is that a POSA would have chosen *neither* if knowledge of the physical location of the bead was not required for the assay. The sequencing and other processes used in Cantor’s bulk-analysis methods do *not* require knowledge of the physical location of the bead and to have determined it would have been counterproductive.

Dr. Charles Cantor himself—the sole inventor of Cantor and the “noted geneticist” to whom Petitioner refers—testifies that none of Petitioner’s assumptions have support in Cantor or the knowledge of a POSA.

But even if Petitioner’s obviousness theory is *not* based on inherency (it is), it still fails for the same technical reasons that Petitioner’s inherent obviousness theory fails. A POSA would *not* have been motivated to arrange Cantor’s bead

collections—which require neither a coding identifier nor identification of a unique location on the substrate—to generate Petitioner’s proposed array (or deposit a tissue sample on it).

None of the Petition’s asserted grounds of unpatentability stand up to scrutiny. Instead, they collapse like the house of cards. The Board should deny institution.

II. THE ’030 PATENT CLAIMS A NOVEL, NONOBVIOUS SPATIAL-ANALYSIS ARRAY

The ’030 patent discloses assay systems for analyzing spatial location(s) of biological molecules in a tissue sample. EX1005, 1:38-41, 2:16-21, 20:60-21:14; EX2002, ¶15. Before the ’030 patent, “no practical method exist[ed] to analyze at high resolution the spatial expression patterns of large numbers of genes, proteins, or other biologically active molecules simultaneously.” *Id.*

Cantor (EX1031) is a “bulk-analysis” technique that provides no information about spatial location in a tissue sample. In bulk analysis, a mixture of nucleic acids is derived from a sample of interest (such as tissue). The mixture is then analyzed to determine if a particular nucleic acid is present or not. And while spatial analysis methods can determine both if a biological molecule was present in a sample and where the molecule was in that sample, bulk-analysis methods can determine if, but not where. EX2002, ¶¶16-20, 31-34.

A simple analogy emphasizes the distinction between spatial-analysis on the one hand, and bulk-analysis on the other. EX2002, ¶¶18-20. A tissue sample has many different cells containing many different nucleic acids (biological molecules) in a spatial pattern, like fruit in a fruit tart. *Id.* As shown below, the tart has many different fruits (strawberries, blueberries, blackberries) with an intact spatial distribution. *Id.*



Fruit Tart

Spatial-analysis methods can determine if a blueberry was present in the tart and where that blueberry was located within the tart. Bulk-analysis methods, however, can only determine if a blueberry was present in the fruit tart, not where. This is because in bulk-analysis methods, the nucleic acids are extracted from the different cells of the tissue without preserving their spatial distribution—like taking strawberries, blueberries, and blackberries from the tart and making a fruit smoothie. *Id.*



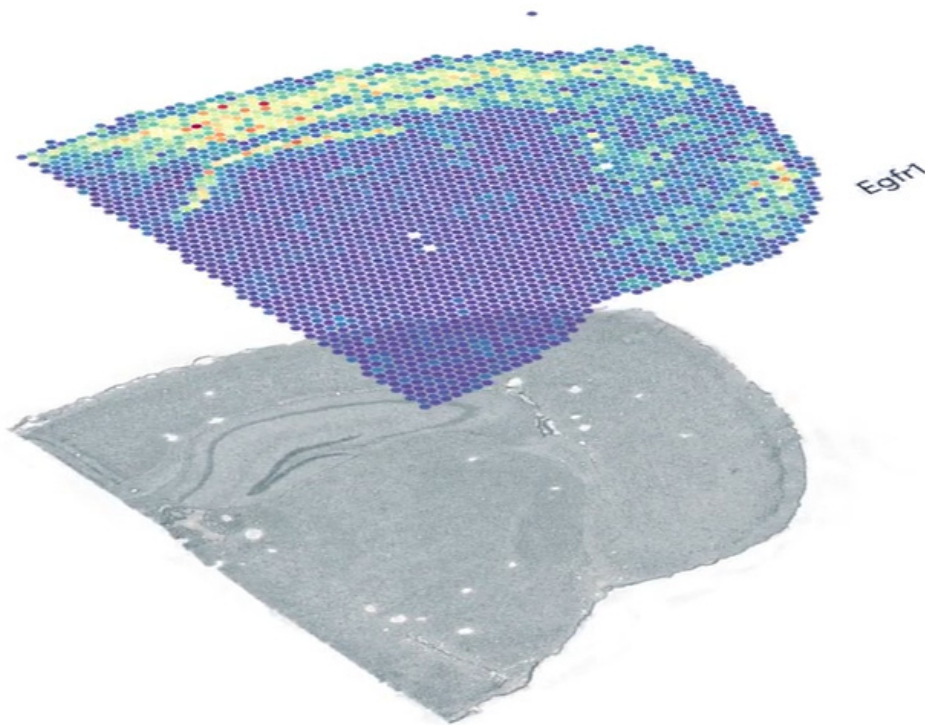
Fruit Smoothie

Thus, with bulk-analysis, a POSA could answer the question: did this fruit tart have any blueberries in it? But the POSA could not answer: where in this tart were the blueberries located? *Id.* The spatial-analysis technology claimed in the '030 patent, however, answers both questions. *Id.*

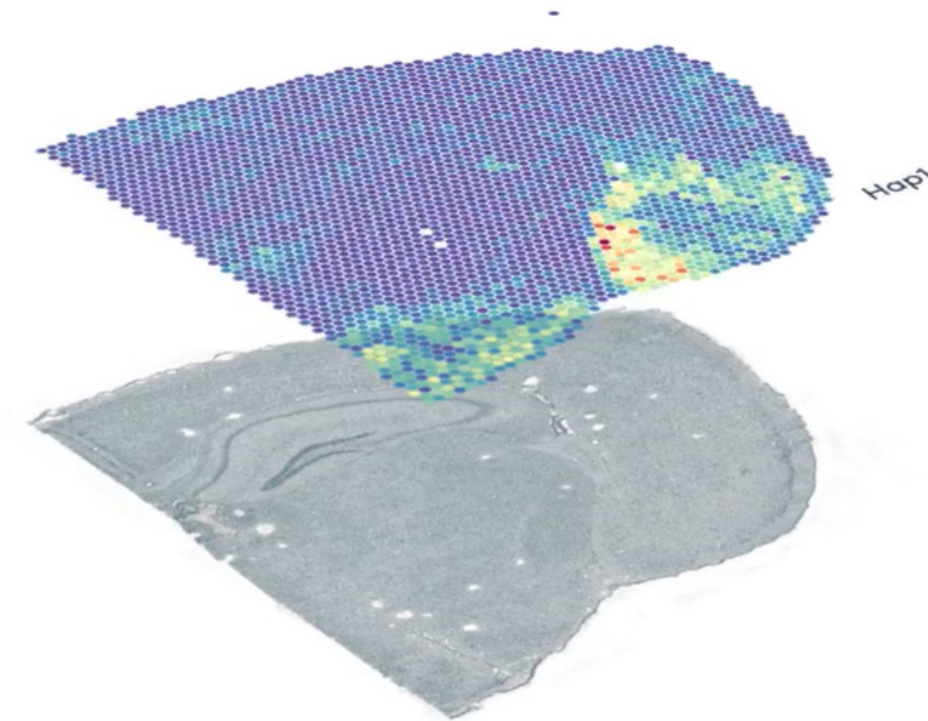
The inventions in the '030 patent addressed the “need for reproducible, high-resolution spatial maps of biological molecules in tissues.” EX1005, 2:16-21; EX2002, ¶¶21-26. The '030 patent’s assay systems utilize a spatial-encoding scheme utilizing molecule-specific binding agents together with coding identifiers to provide a practical and cost-effective determination of information on multiple biological molecules, including specific positional information of such molecules in a biological sample (e.g., tissue). EX1005, 20:60-21:14; EX2002, ¶21. This “unique encoding scheme” allows “multiple molecules and their respective

multiple locations to be identified in a single system using a unique encoding scheme.” *Id.*

PO commercialized the technology described in the '030 patent in its Visium® line of products for spatial analysis of tissues. EX2002, ¶22; EX2004. This powerful technology allows researchers to assay gene-expression patterns across an entire tissue sample for the entire transcriptome (i.e., mRNA of all expressed genes in the genome). *Id.* An example gene-expression pattern across a tissue for one gene (EGFR1) is depicted below. The upper image is a “heatmap” depicting EGFR1 expression in the tissue sample and the lower image is a picture of the tissue itself. Warmer colors in the heatmap indicate higher EGFR1 expression.



The gene expression pattern across the same tissue sample for a differently expressed gene (HAP1) is depicted below.



Utilizing the claimed invention, these types of spatial analyses became possible, allowing researchers to understand things like variation among different cells within a single tumor (the tumor “microenvironment”), which provides valuable information for developing new therapeutics. EX2002, ¶¶23-26; EX2005.

III. PETITIONER’S REFERENCES

A. Cantor (EX1031)

Cantor is the publication (WO 2009/091934) of PCT/US2009/031169, titled “Single Molecule Nucleic Acid Sequence Analysis Processes and Compositions,” published on July 23, 2009. Cantor identifies Dr. Cantor as the sole inventor.

EX1031, [71], [75]; EX2002, ¶29.

Cantor relates to “the field of nucleic acid sequence analysis and methodology and components for use in such analysis.” EX1031, 1; EX2002, ¶30. Cantor’s improvements relate to “efficiently preparing” copies of nucleic-acid molecules of interest for later sequencing and analyses through the use of single-stranded nucleic acid(s) linked to a solid support (e.g., bead or particle). *Id.* To aid in Cantor’s sequencing and analyses, some single-stranded nucleic acid(s) optionally include an “identification sequence.” EX1031, 15; EX2002, ¶30. Using solid supports and improved methods, Cantor “minimize[s] the number of steps required by” other prior-art methods for sequence analysis. EX1031, 1; EX2002, ¶30.

1. Cantor discloses “solid phase nucleic acids” on beads to capture biological molecules of interest

Cantor starts with preparation of a “sample nucleic acid” from, e.g., a biological sample. EX1031, 5; EX2002, ¶¶35-43. Next, target nucleic-acid molecules of interest from the “sample nucleic acid” are captured using what Cantor refers to as “solid phase nucleic acids,” which are single-stranded nucleic acid(s) attached to a solid support. EX1031, 1; EX2002, ¶¶44-46. Figure 1C, excerpted below, illustrates a “solid phase nucleic acid” with four single-stranded solid phase nucleic acids attached to a solid support. EX2002, ¶¶46-47.



Figure 1C excerpt

Each single-stranded nucleic acid has two or three components (shown left to right in Figure 1C): a primer sequence, an optional identification sequence, and a probe sequence. EX1031, 13-17; EX2002, ¶45. The probe sequence is used to hybridize to a target nucleic acid (and thus capture the nucleic acid of interest from the “sample nucleic acid”), while the primer sequence can be used for making copies. *Id.*

The identification sequence, when used, is useful for “constructing partial sequence reads into larger sequence constructions,” and “may be of any length suitable for analyzing the nucleotide sequence or partial nucleotide sequence of sample nucleic acid.” EX1031, 15; EX2002, ¶45. When an identification sequence is present, each solid support contains a unique identification sequence. *Id.* For example, as shown in Figure 1C, the four single-stranded nucleic acids attached to the solid support all share the same identification sequence. EX1031,

15; EX2002, ¶47. The identification sequences allow a POSA to assemble and analyze large nucleotide sequences from smaller sequence “reads” by identifying overlapping sequences. EX1031, 25, 53-55 (Example 1); EX2002, ¶45.

Cantor teaches that the probe sequence is designed to be complementary to the target nucleic acid, so that hybridization between the probe and the target can occur. EX1031, 13-14; EX2002, ¶¶48-51. Each probe sequence on a single solid support (e.g., one bead) is either unique (e.g., for hybridizing to different subsequences of a single target nucleic acid) or identical (e.g., for hybridizing to the same subsequence of a single target nucleic acid). *Id.*

Figure 1A, excerpted below, shows a solid support where each probe on the solid support has a unique sequence P_1 through P_N . By using unique probes (i.e., P_1, P_2, P_3, P_N), the solid phase nucleic acid targets a different subsequence of a single target nucleic acid (i.e., subseq. 1, subseq. 2, subseq. 3, subseq. N). *Id.*

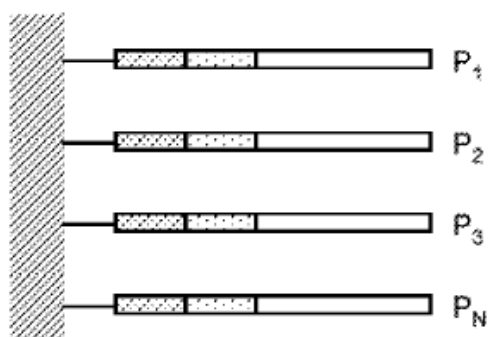
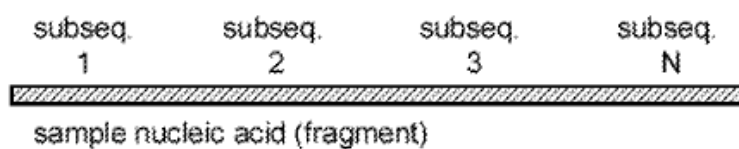


Figure 1A excerpt

Figure 1C, excerpted below, shows a solid support where each probe has the same sequence P_1 .



Figure 1C excerpt

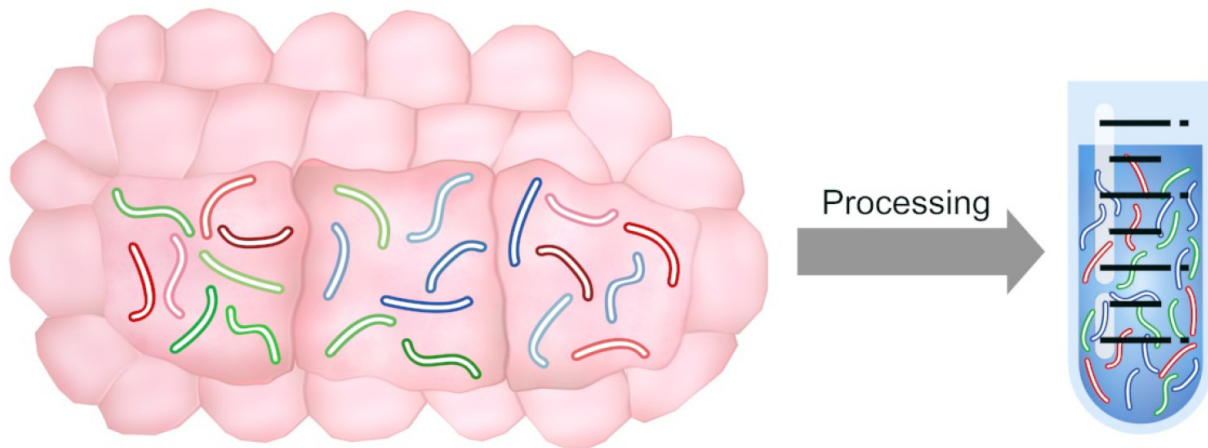
This arrangement of probes on a single solid support is also described in claim 26 of Cantor, which recites “[a] solid support comprising single-stranded solid phase nucleic acid having an identifier sequence and a probe sequence, wherein...the solid phase nucleic acid shares a common probe sequence [as in Figure 1C] or the solid phase nucleic acid does not share a common probe sequence [as in Figures 1A and 1B].” EX1031, 13-14, 60-61; EX2002, ¶¶50-51, 55-61. In either case, however, “the solid phase nucleic acid shares a common identifier sequence.” *Id.*

Claims 31 and 32 separate these two arrangements—the arrangement in Figure 1C into claim 31 (“the solid phase nucleic acid of each support share a common probe sequence”) and the arrangement in Figures 1A and 1B into claim 32 (“the solid phase nucleic acid of each solid support do not share a common probe sequence”). *Id.*

2. Cantor’s methods analyze “sample nucleic acid,” not tissue samples

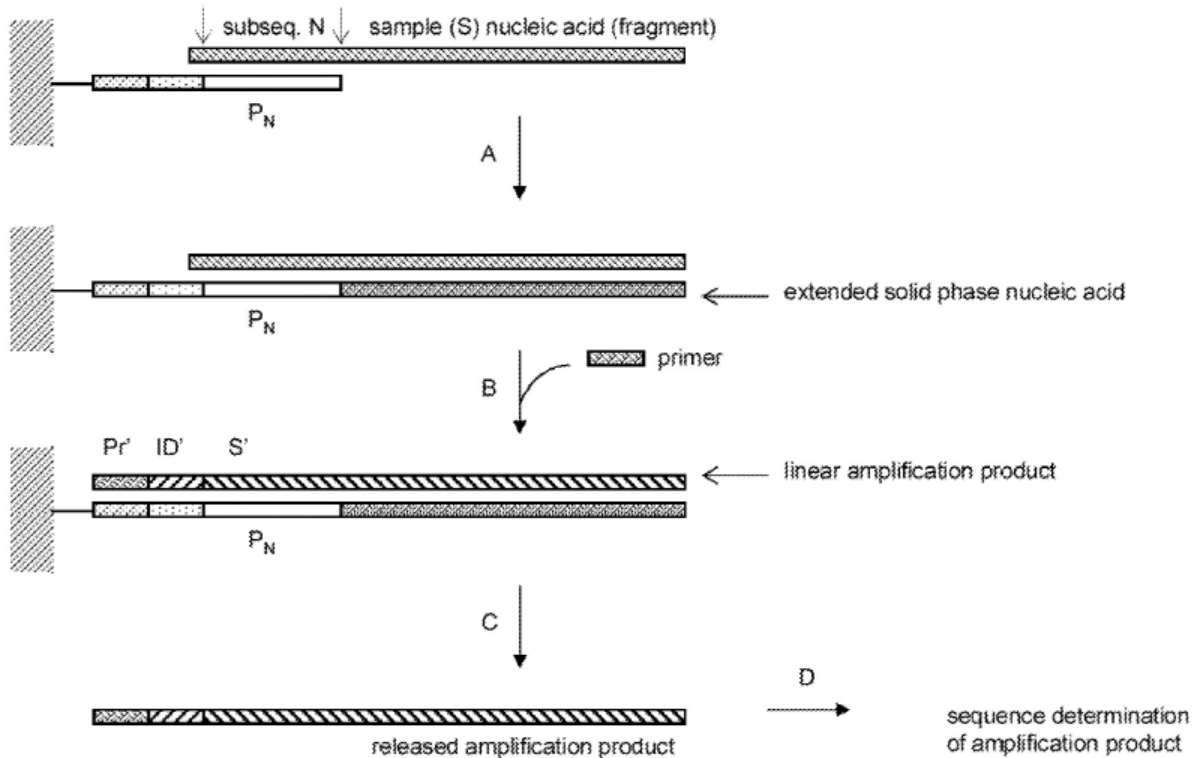
Cantor teaches that its “sample nucleic acid” may be derived from many different samples or sources, including a “biological sample”—that is, “any material obtained from a living source or formerly living source.” EX1031, 6; EX2002, ¶36. The biological sample itself may have any form, including a solid form (e.g., tissue, cell, etc.) and a fluid form (e.g., urine, blood, etc.). *Id.* But the biological sample is not the sample nucleic acid assayed in Cantor’s methods.

EX2002, ¶36. Instead, nucleic acids are extracted from the sample/source (e.g., a biological sample) and mixed together in bulk to create the sample nucleic acid. EX1031, 1, 5-6; EX2002, ¶36. This sample nucleic acid is then mixed with the solid phase nucleic acids to capture molecule(s) from the sample nucleic acid for sequencing and analysis. EX2002, ¶¶34, 44. Whatever the source, the sample nucleic acid is a solution—not a solid material such as tissue. EX2002, ¶36. This process is illustrated in the drawing (with three cells of a tissue highlighted to show the nucleic acids present in those cells) below.



As shown, the spatial relationship between the nucleic acids in the tissue sample is lost when nucleic acids are extracted from the tissue and mixed to create sample nucleic acid. *Id.*, ¶38.

Figure 2, reproduced below, is a simplified illustration of how Cantor copies nucleic-acid molecules of interest for later sequencing and analyses. EX2002, ¶¶52-54.



First, a single target nucleic acid molecule in the sample nucleic acid hybridizes to the probe of a solid phase nucleic acid. EX1031, 24-25; EX2002, ¶44. After the target nucleic acid hybridizes, in step A, the single-stranded solid phase nucleic acid is extended to form an “extended solid phase nucleic acid.” EX1031, 24-25; EX2002, ¶53. The extended solid phase nucleic acid is complementary to the sequence of the captured single molecule. *Id.* Next, in step B, a primer is added that hybridizes to the primer sequence on the single-stranded solid phase nucleic acid, to extend (copy) the entire extended solid phase nucleic acid. EX1031, 24-25; EX2002, ¶54.

The resulting product is called a “linear amplification product.” *Id.* In steps C and D, the linear amplification product is released from the solid support into solution for further sequencing and analysis. *Id.*

3. Cantor discloses that beads may be deposited on substrates to facilitate ease of handling for sequence analysis and manufacturing

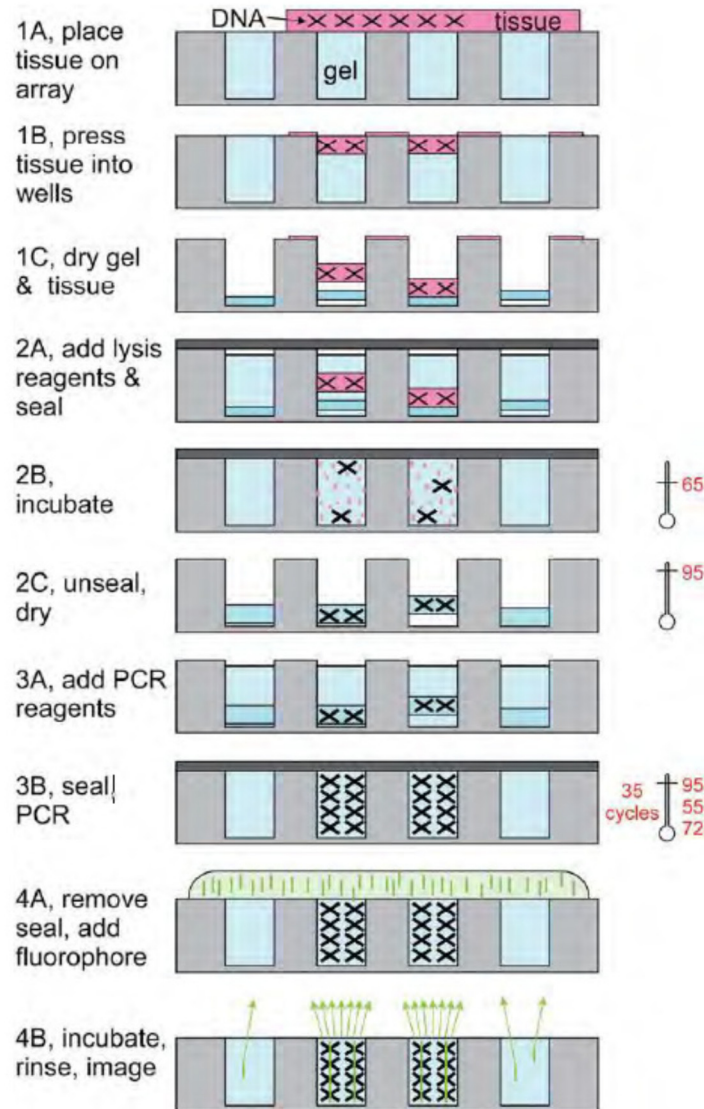
Cantor discloses that “the invention in part provides a substrate comprising a collection of beads oriented in an array.” EX1031, 4; *see also id.*, 17 (“Solid supports may be provided in an array in certain embodiments....”); EX2002, ¶¶61-69. The “array may contain one solid support species or multiple solid support species from a collection.” EX1031, 4, 17; EX2002, ¶68. As Dr. Cantor explains, the use of bead arrays on substrates facilitates the ease of handling of the beads for use in the described methods. EX2002, ¶68. For example, Cantor states that an array “can be arranged on any substrate suitable for sequence analysis or manufacture processes described” in the application. EX1031, 17-18; EX2002, ¶68. Cantor states that substrates suitable for arrays used in sequence analysis include “flat substrates, filter substrates, wafer substrates, etched substrates, substrates having multiple wells or pits ..., and the like.” *Id.*

B. Armani (EX1022)

Armani, titled “2D-PCR: a method of mapping DNA in tissue sections,” published in October 2009. EX1022, 3526; EX2002, ¶¶92-93. Armani discloses a

method for 2D-PCR. *Id.* Figure 2, reproduced below, provides a diagram of

Armani's 2D-PCR. EX1022, 3527; EX2002, ¶¶94-100.



Armani starts with sectioning a tissue and transferring it to a multi-well array device (step 1A). In steps 1B-1C, the tissue is physically pressed into the wells of the array and dried in agarose gel. Each well therefore contains only sub-portions of the tissue sample immobilized in the well. Any genetic information in

those portions of the tissue sample that does not end up in a well is lost. From that point on, separate reactions take place in each individual well. *Id.*

In steps 2A-2C, reagents are added to each well to lyse the tissue and release genomic DNA into solution, which are represented by “x”s. After the solution is dried, PCR reagents are added to each well in steps 3A-3B and genomic DNA is amplified (now represented by multiple “x”s). In steps 4A-4B, an intercalating fluorophore is incubated in each well and the resulting fluorescence is imaged. The intercalating fluorophore binds to any double-stranded DNA present in each well, allowing for imaging analysis. *Id.*

Petitioner relies on Armani for allegedly providing “additional information rendering obvious disposing the tissue section on the array as recited by Claim 16 and the tissue section being a fresh-frozen tissue section as required by Claim 24.” Pet. 43. But Armani does not disclose or contemplate using capture probes, contacting capture probes with a tissue section, or using capture probes comprising a nucleic acid sequence that identifies a unique location on the substrate. EX2002, ¶101.

Armani’s assays, unlike the claimed arrays, provides “low spatial resolution because they rely on physical transference of tissues into wells, which also prevents random access to tissue samples and high levels of multiplexing.” EX1005, 2:9-15; EX2002, ¶92.

C. Frisen (EX1020)

Petitioner relies on Frisen for anticipation, but Frisen is not prior art to the Challenged Claims. Frisen's earliest possible priority date is April 13, 2011. *Id.*, [30]. But this date is after the Challenged Claims priority date of April 5, 2010.

IV. CLAIM CONSTRUCTION

PO submits, solely for a decision on institution, that no claim terms require explicit construction. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017). Although Petitioner's statements about infringement of "target-nucleic acid binding domain" are irrelevant here, PO disagrees that the "target-nucleic acid binding" disclosed in the '030 patent does not encompass "the interaction of poly-T probes and poly-A tails present on typical mRNA molecules." Pet., 22-23.

V. LEVEL OF ORDINARY SKILL IN THE ART

For this Preliminary Response, PO does not dispute Petitioner's definition of a POSA. PO reserves its right to challenge Petitioner's definition and to provide its own definition, should trial be instituted.

VI. INSTITUTION ON GROUND 3 SHOULD BE DENIED BECAUSE PETITIONER'S PRIORITY ATTACK IS LEGALLY AND FACTUALLY INSUFFICIENT

The Challenged Claims of the '030 patent are entitled to priority to the '124 provisional's filing date of April 5, 2010. Petitioner errs legally when it argues that there was a break in the priority chain barring the Challenged Claims from

claiming priority. Pet., 51. Each application in the priority chain of the '030 patent included a specific reference to its co-pending preceding application as required by 35 U.S.C. §§119(e) and 120, and each application properly incorporated the disclosure of the '124 provisional by reference. Petitioner ignores that PO met all the legal requirements for priority. An analysis of the '124 provisional's disclosure—which Petitioner largely ignores—shows that it provides written-description support for the claim elements that Petitioner asserts are missing. Pet., 52.

Because the Challenged Claims of the '030 patent are entitled to the filing date of the '124 provisional—both legally and factually—Frisen is not prior art and does not anticipate the claims. Petitioner cannot correct its legal and factual errors at trial, and institution on Ground 3 should be denied.

A. Petitioner's Priority Attack is Legally Insufficient Because Each Application in the Priority Chain Contained a Specific Reference to Its Co-Pending Preceding Application and the '124 Provisional was Properly Incorporated by Reference into Every Application

“Priority claims are governed by statute.” *Droplets Inc. v. E*TRADE Bank*, 887 F.3d 1309, 1315 (Fed. Cir. 2018). Relevant here, 35 U.S.C. §§119(e) and 120 require that each application in a priority chain include a “specific reference” to the earlier-filed preceding application and disclose the claimed invention “in the

manner provided by §112.”² Both of these statutory requirements are met here.

1. The ’030 patent’s priority chain is intact

The ’030 patent issued from Appl. No. 18/074,992 (“the ’992 application,” EX2013) on September 19, 2023. EX1005, [21], [22], [45]. The ’992 application claims priority through a series of applications (the “intervening applications”) to provisional Appl. No. 61/321,124 (“the ’124 provisional,” EX1009). PO reuses Petitioner’s table showing the priority chain of the ’030 patent back to the ’124 provisional:

’030 Patent Priority Documents	Filing Date	Exhibit
17/850,538 (the “’538 Application”)	June 27, 2022	EX1049
17/480,914 (the “’914 Application”)	September 21, 2021	EX1050
17/321,090 (the “’090 Application”)	May 14, 2021	EX1051
17/145,210 (the “’210 Application”)	January 8, 2021	EX1052
16/669,246 (the “’246 Application”)	October 30, 2019	EX1053
16/437,637 (the “’637 Application”)	June 11, 2019	EX1054
16/430,015 (the “’015 Application”)	June 3, 2019	EX1055
16/414,213 (the “’213 Application”)	May 16, 2019	EX1056

² Petitioner does not dispute that each application in the priority chain was properly co-pending with its preceding application.

16/402,098 (the “’098 Application”)	May 2, 2019	EX1057
16/276,235 (the “’235 Application”)	February 14, 2019	EX1010
15/187,661 (the “’661 Application”)	June 20, 2016	EX1011
13/080,616 (the “’616 Application”)	April 5, 2011	EX1012
61/321,124 (the “’124 Provisional”)	April 5, 2010	EX1009

Pet., 50. Petitioner does not and cannot dispute that each application in the ’030 patent’s priority chain included a “specific reference” to the earlier-filed application under §§119(e) and 120. *Id.*, 50-52.

The Office’s regulations provide that the “specific reference” include each prior-filed application’s application number and the familial relationship. 37 C.F.R. §1.78; *Droplets*, 887 F.3d at 1315. For pre-AIA applications, “specific reference” could be included either on an application data sheet (“ADS”) or in the first sentence(s) of the specification. For post-AIA applications, the ADS controls the priority claim. 37 C.F.R. §§1.55, 1.76, 1.78. The ADS is a form that contains bibliographic data arranged in a format specified by the Office in 37 C.F.R. §1.76.

The ’616 application was filed as a utility application on April 5, 2011, one year after the co-pending ’124 provisional, and claimed priority under §119(e) to the ’124 provisional in an ADS by number and familial relationship. EX1012, 1-3.

Each of the remaining intervening applications and the ’992 application were filed as continuation applications, while co-pending with their respective

parent applications, and claimed priority to each of the utility applications in its priority chain under §120 and to the '124 provisional under §119(e) in an ADS by numbers and familial relationships. EX1011, 61-62; EX1010, 54-55; EX1057, 7; EX1056, 7; EX1055, 11-12; EX1054, 7-8; EX1053, 5-6; EX1052, 6-7; EX1051, 4-5; EX1050, 6-7; EX1049, 6-7; EX2013, 6-7.

2. The disclosure of the '124 provisional was incorporated by reference into each application

Each intervening application and the '992 expressly and unambiguously incorporated by reference the disclosure of the '124 provisional. *See* EX1011, 2; EX1010, 6; EX1057, 15; EX1056, 16; EX1055, 21; EX1054, 15; EX1053, 15; EX1052, 16; EX1051, 19; EX1050, 14; EX1049, 14; 2013, 14 (“Cross-Reference to Related Applications”). “Incorporation by reference provides a method for integrating material from various documents into a host document...by citing such material in a manner that makes clear that the material is effectively part of the host document as if it were explicitly contained therein.” *Droplets*, 887 F.3d at 1318 (cleaned up).

Each of these applications met all requirements for a proper incorporation of the '124 provisional by reference. The applications use the root words “incorporate” and “reference” and “clearly identify the referenced patent, application, or publication” by serial number and filing date. *Droplets*, 887 F.3d at 1315. Thus, the disclosure of the '124 provisional was “as much a part of the

[each] application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed.” MPEP §2163.07(b).

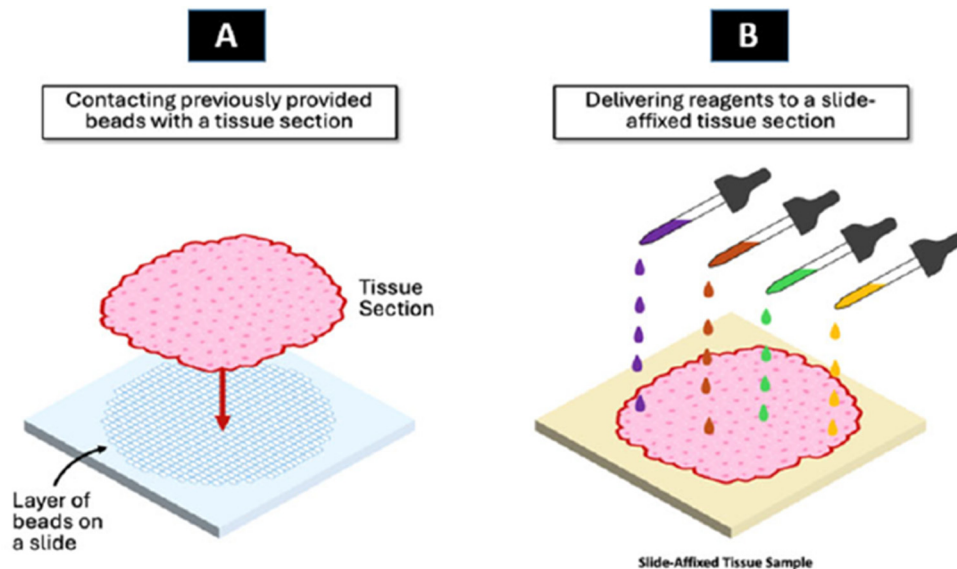
B. Petitioner’s Priority Attack is Factually Insufficient Because the ’124 Provisional Provides Written-Description Support for the Challenged Claim Elements

The Challenged Claims are entitled to the provisional application’s priority date. Petitioner identifies “two key elements of independent claims 1 and 16” that allegedly lack written-description support: (1) “the plurality of beads/capture probes being attached to a substrate,” and (2) “beads that (i) have a capture probe with a nucleic acid sequence that identifies a unique location on the substrate and (ii) are randomly distributed on the substrate.” Pet., 52-60. But Petitioner erroneously bases its priority attack on the specification of the ’661 application—not the ’124 provisional. Because the ’124 provisional was incorporated by reference into the specification of the ’992 application and all intervening applications, if the claim elements have written-description support in the ’124 provisional, then they also have written-description support in the ’992 application and all intervening applications. The ’124 provisional provides written-description support under §112 for each challenged claim element and Petitioner’s priority challenge fails.

1. The ’124 provisional supports “the plurality of beads/capture probes being attached to a substrate”

The ’124 provisional supports attaching a plurality of bead-affixed capture

probes mounted on a substrate surface (e.g., slide). Petitioner creates an illustration (reproduced below) depicting an allegedly “stark contrast between the approach and devices PO now claims (Figure A) and the approach actually described in the specification (Figure B).” Pet., 4-5. The alleged dichotomy is between two types of approaches—one that involves “[c]ontacting previously provided beads with a tissue section” (Figure A) and one that involves “[d]elivering reagents to a slide-affixed tissue section” (Figure B). *Id.*, 5.



Petitioner argues that, while the approach depicted in Figure B has written-description support in the '661 application, the approach in Figure A does not. Pet., 53. But the '124 provisional—which was expressly incorporated by reference into the '661 application—supports “disposing a tissue on top of” an “an array of beads attached to a substrate, where each bead comprises a capture probe that

binds a target nucleic acid.” (Pet., 53, referencing Figure A). EX2002, ¶¶111-113.

The ’124 provisional discloses an array of capture probes attached to a substrate in, for example, paragraphs 15-18, which discuss delivering reagents, such as binding agents (which bind to a molecule of interest), on the surfaces of a substrate—either directly or via beads. EX1009, ¶¶7-8, 15-18. These passages describe an array as depicted in Petitioner’s “Figure A” because, once constructed, a tissue section would be disposed on it as depicted in “Figure A” to carry out the types of spatial distribution analyses described. EX2002, ¶114.

Paragraphs 17 and 18 explain that, in one embodiment of the invention, binding agents (e.g., capture probes) are “immobilized directly or indirectly to the **substrate** surface.” EX1009, ¶¶17-18; EX1005, 22:29-49; EX2002, ¶114. And in one embodiment, a “substrate surface” is described as having “wells or channels.” *Id.* As Dr. Cantor explains, a POSA would understand that a tissue section **does not** have features like wells or channels. EX2002, ¶115. Instead, as Dr. Cantor explains and supports with evidence, “wells or channels” are features of manufactured solid supports. *Id.* (citing EX1031). A POSA would understand that a “surface” of a “substrate” with “wells or channels” is **not** a tissue section, but instead is a manufactured solid support. *Id.*

Moreover, paragraphs 15-18 of the ’124 provisional explain that in some embodiments, binding agents are immobilized onto beads that are **then** placed on

the substrate surface, for example in wells or channels. EX2002, ¶114; *see also* EX1009, ¶17; EX1005, 22:29-37. These passages describe an array as depicted in Petitioner’s “Figure A” because, once constructed, that array would then be contacted with a tissue sample as depicted in “Figure A” to carry out the types of spatial distribution analyses described. EX2002, ¶114.

Even more passages in the ’124 provisional discuss the use of pre-generated arrays—with beads immobilized directly or indirectly onto a “substrate surface.” EX2002, ¶116. One passage does so in the context of peptide binding agents; another does so in the context of chemical binding agents. EX1009, ¶¶21-22; EX1005, 23:1-22; EX2002, ¶116.

The ’124 provisional also discloses assays and assay systems “comprising one or more agents provided in defined spatial patterns *on a substrate* surface....” where, in some cases, “the encoding scheme employs limited reagent delivery to the spatial patterns *on the substrate* surface....” EX1009, ¶¶7-8, EX1005, 20:60-21-29; EX2002, ¶120. The ’124 provisional discloses “[t]he primary criteria of such reagent delivery systems is the ability to direct delivery of specific agents based on spatial patterns *on the substrate* surface.” EX1009, ¶15, EX1005, 22:15-19; EX2002, ¶120; *see* EX1009, ¶¶47-48; EX1005, 24:20-53 (disclosing “spatially selective deposition of the binding agents on the substrate surface” and providing “[e]xamples of methods that can be used for deposition of agents and/or coding

identifiers onto the substrate surface”); EX2002, ¶121. Again, once a pre-generated bead array is constructed, Dr. Cantor explains, it would then be contacted with a tissue section as depicted in “Figure A” to carry out the spatial-distribution analyses described in the ’124 provisional. EX2002, ¶¶114-122.

Aside from ignoring these teachings, Petitioner argues that a “washing” step would “not make sense” in the context of probes covalently bound to a substrate such as a slide or beads. Pet., 54. In support, Petitioner cites to Figures 1 and 2 and paragraph 28 the ’661 application. *Id.* (citing EX1011, Figs. 1-2, ¶28). That those figures and passages (which correspond to Figures 1 and 2 and column 10, lines 8 to 32 of the ’030 patent) elaborate on **additional** types of assays also disclosed in the ’030 patent, however, is irrelevant. As Dr. Cantor explains, these types of assays are in **addition** to the pre-generated bead arrays discussed above. EX2002, ¶118.

Petitioner cites to other portions of the ’661 application describing additional embodiments. Pet., 55-57 (citing, e.g., EX1011, ¶¶7, 15, 23-24, 35, 54-56, 64-65, Figs. 1-2). But again, Petitioner errs by looking to only the ’661 application without accounting for incorporation by reference of the ’124 provisional. None of these figures and passages in the ’661 application negate that the ’124 provisional teaches a pre-generated array (“Figure A”). EX2002, ¶¶119-121.

Petitioner does not cite to a legal prohibition against the **disclosure** of **multiple** inventions in one application—here, disclosure of both “Figure A” and “Figure B” (as well as other types of assays) in the ’030 patent. Nor could it, as the Federal Circuit has observed that a written description describing multiple inventions may not be relevant “in toto” to each of those inventions. *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1311 (Fed. Cir. 1999).³

The ’124 provisional (and, therefore, the intervening and ’992 applications) provides written-description support for “disposing a tissue on top of” an “array of beads attached to a substrate, where each bead comprises a capture probe that binds a target nucleic acid” (Pet., 53). EX2002, ¶122.

2. The ’124 provisional supports beads that (i) have a capture probe with a nucleic-acid sequence that identifies a unique location on the substrate and (ii) are randomly distributed on the substrate.

As discussed in §VI.B.1, the ’124 provisional discloses “disposing a tissue on top of” an “array of beads attached to a substrate, where each bead comprises a capture probe that binds a target nucleic acid.” It also supports “each of the capture probes of the plurality of capture probes comprises...a nucleic acid sequence that identifies a unique location on the substrate” and “the plurality of

³ That the Office might limit the **claims** of an application to only **one** invention (out of multiple) does not change the analysis. *See* 35 U.S.C. §121.

beads was previously positioned on the substrate in a random pattern.”

- a) The '124 provisional supports “beads that have a capture probe with a nucleic acid sequence that identifies a unique location on the substrate”

The '124 provisional expressly teaches embodiments using both binding agents and coding identifiers (here, nucleic acid capture probes comprising a target nucleic acid-binding domain and a “nucleic acid sequence that identifies a unique location on the substrate” (*see* Pet. 60)) such that the coding identifiers are not superfluous. EX2002, ¶123. For example, the '124 provisional discloses that its “unique coding scheme” uses “both molecule-specific binding agents and coding identifiers to provide a practical and cost-effective determination of information on multiple biological molecules, including specific positional information of such molecules in a biological sample, e.g., a tissue section.” EX1009, ¶7; EX1005, 20:60-21:14; EX2002, ¶124. The unique encoding scheme allows “multiple molecules and their respective multiple locations to be identified in a single system.” *Id.* And here the presence or absence and specific positional information of the biological molecules is based on detection of both the binding agent, the coding identifier, and the knowledge of the location of the binding agents (and thus coding identifier) on the substrate. EX1009, ¶¶7, 18; EX2002, ¶¶125-126.

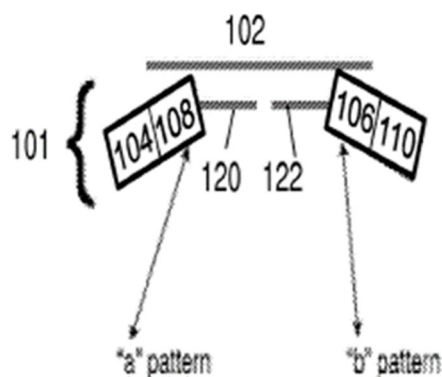
The '124 provisional provides explicit disclosure of an embodiment in which the “binding agents are nucleic acids,” and “the nucleic acids may be

immobilized directly or indirectly onto beads.” EX1009, ¶18; EX1005, 22:38-49; EX2002, ¶127. It teaches that, in this embodiment, the spatial-encoding scheme is decoded using “nucleic acid sequencing, and preferably next-generation sequencing.” EX1009, ¶¶18-19; EX1005, 22:38-57; EX2002, ¶128. Dr. Cantor explains that when nucleic-acid sequencing is used to decode the spatial-encoding scheme, a POSA would have understood that the coding identifier itself is a nucleic acid. EX2002, ¶129. Otherwise, the coding identifier could not be sequenced using nucleic-acid sequencing. *Id.*

In this way, Petitioner’s logic—that identifier sequences are superfluous—is wrong on its face. Pet., 59-60. Petitioner’s logic is that because the ’124 provisional’s beads are “provided in known locations on the substrate surface” it follows that “there would be no purpose for such an identifier.” Pet., 60. But if a nucleic-acid binding agent was attached to a bead at a known location on the substrate ***and no coding identifier was used at all***, a POSA would have understood that it would have been impossible to obtain spatial information for captured target nucleic acids by nucleic-acid sequencing. EX2002, ¶130. This is because in the absence of a coding identifier, any location information would be lost in the process of sequencing when the nucleic acid is separated from the substrate. *Id.* As Dr. Cantor explains, “even if the beads were provided in known locations, it would not, as Dr. Puglisi suggests, ‘obviate[] the need for the use of coding

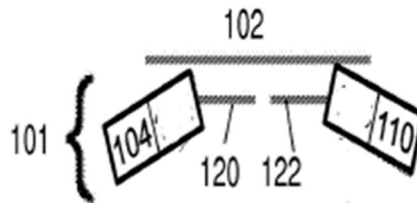
identifiers.” EX1103, ¶226; EX2002, ¶123.

This is illustrated in Figure 1 of the '124 provisional (corresponding to Figure 4 of the '030 patent), partially excerpted below. In Figure 1, both the binding agent and the coding identifier are part of the same molecule. EX1009, ¶46; EX1005, 24:1-19; EX2002, ¶¶131-132. The coding identifiers (106 and 108) are associated with the binding agents (120 and 122) that capture the target nucleic acid (102). *Id.*



The coding identifiers are also associated with universal priming sites (104 and 110) that ***facilitate sequencing***—the preferred method in the '124 provisional for decoding spatial locations. EX1009, ¶¶18, 19, 46; EX1005, 22:38-57, 24:1-19; EX2002, ¶132. The sequencing results include both sequences of the binding agent and coding identifier, where the ***sequence of the coding identifier provides the specific position on the substrate*** where the target nucleic acid hybridized to the binding agent—provided that the location of the binding agents (and therefore coding identifiers) is known or determined prior to using the assay system. *Id.*

As Dr. Cantor explains, a POSA would have understood that if the coding identifiers (106 and 108) in this example were removed, then there would have been no way to recover any specific positional information when nucleic-acid sequencing is used to decode the spatial-encoding scheme because there would have been no coding identifier present when sequenced. EX2002, ¶¶133-135. This is illustrated in a modified version of Figure 1 (without the coding identifiers 106 and 108), below:



In this case, the sequencing results would have the sequence of the binding agent **but not** that of the coding identifier. *Id.* And, without using any coding identifier at all, the specific position on the substrate where the target nucleic acid hybridized to the binding agent could not be determined. *Id.* This would be true even if the binding agents were at known locations on the array, because—as any POSA would readily understand—sequencing requires release of the captured target nucleic acid from the substrate. *Id.* Petitioner’s arguments lack evidentiary support and are contrary to the well-known sequencing techniques in the art. EX2002, ¶134.

b) The '124 provisional supports beads “randomly distributed on the substrate”

First, as Petitioner points out, the '124 provisional discloses providing beads on a substrate at locations that are either *known* or *determined prior to use*. Pet., 59; EX1009, ¶¶17-18; EX2002, ¶¶137-138. Petitioner argues, however, that neither of these two alternatives refers to beads that are *randomly* distributed. Pet., 59. This argument is not only a mischaracterization of the '124 provisional's teachings, but also *directly contradictory* to Petitioner's own characterization of how a POSA would have constructed a spatial-analysis array.

Elsewhere in the Petition, Petitioner describes two alternatives for placement of beads comprising identification sequences onto a spatial-analysis array: (1) “selective loading” or (2) “randomly loading” and “decoding”:

[A] POSA would have known that there are two options to correlate the identification sequence on the nucleic acid attached to a given bead and the beads location on the array: (i) selective loading of particular beads to particular locations on the array and/or (ii) *randomly loading the beads* and then decoding the array prior to use.

Pet., 33.

Dr. Cantor agrees. EX2002, ¶¶138-139. As Dr. Cantor explains, a POSA would have understood the '124 provisional's disclosure that beads are provided at locations that are either *known* or *determined prior to use* refers precisely to the two alternative strategies Petitioner identifies. *Id.*

As discussed in §VI.B.1, the '124 provisional teaches pre-generated bead arrays in which binding agents and coding identifiers (e.g., capture probes) are deposited onto substrate at “discrete, independent measureable” locations. EX1009, ¶47; EX1005, 24:20-43; EX2002, ¶137. It also teaches that their location “is known or determined prior to use of the substrate surface in the assay system.” EX1009, ¶¶17-18; EX1005, 22:29-49; EX2002, ¶137. That is, they are placed onto “discrete, independent measurable” locations and their location is either known (e.g., placed on the array knowing where each particular bead would bind to the array) or determined prior to use (e.g., placed on the array randomly, without prior knowledge of where each particular bead would bind to the array and later “decoded.”)

In the context of obviousness, Petitioner asserts that these two options render obvious “fabricating [Cantor’s] bead arrays by randomly positioning [Cantor’s] beads on the substrate,” stating that “a POSA would appreciate that ‘the beads may be randomly distributed on the array,’ and ‘can later be decoded’, i.e. after the array is made, a correlation of the location of an individual site on the array with the bead or candidate agent at that particular site can be made.” Pet., 32, 35 (quoting EX1038, ¶42). Yet, in the context of priority, Petitioner does an about-face and asserts that *both* refer to “providing beads at *known locations* on the substrate”:

The Provisional's disclosures solely involve providing beads at *known locations* on the substrate—i.e., at locations that are *known or determined prior to use*.” In sharp contrast, the claims of Chee-030 expressly recite that the beads are *randomly* distributed.

Pet., 59 (emphases in original).

As Petitioner acknowledges, the Provisional's disclosure teaches providing beads “at locations that are known *or* determined prior to use.” Pet., 59. And, as Petitioner also acknowledges, a POSA would have understood that beads could be “*randomly distributed on the array*” and “later decoded.” Pet., 35. Petitioner offers no reasoning or support for its assertion that “known or determined prior to use” refers only to “providing beads at *known locations* on the substrate” (e.g., “selective loading”) and does not also encompass providing them at *random loading* followed by “decoding” procedures, in which they are deposited on the substrate randomly and their location is determined prior to use (e.g., to identify a unique location on the substrate.” The argument is not only unsupported, but also is non-sensical. EX2002, ¶¶139-143. The Board should reject Petitioner's attempt to mischaracterize the teachings of the '124 provisional.

C. Frisen is Not Prior Art

Frisen's earliest possible priority date is April 13, 2011, EX1020, [30], which is after the '030 patent's priority date of April 5, 2010. Because Frisen is not prior art and Petitioner cannot cure this defect at trial, the Board should deny

institution of Ground 3.

**VII. INSTITUTION ON GROUNDS 1 AND 2 SHOULD BE DENIED
BECAUSE PETITIONER HAS NOT SHOWN A REASONABLE
LIKELIHOOD THAT IT WOULD PREVAIL IN PROVING
OBVIOUSNESS**

All of Petitioner's arguments hinge on at least one fatally flawed premise:

(1) that Cantor expressly teaches contacting a “*tissue section*” with its beads, and/or (2) that Cantor's “identification sequences” would *necessarily* provide *unique location* information. Both are wrong. Petitioner's arguments are simply an attempt to mold the prior art to fit the Challenged Claims. The Board should reject Petitioner's mix-and-match styling of the prior art.

Cantor does not teach or suggest contacting its beads with a “tissue section,” as required by claim 16 and its dependent claims. That Cantor fails to teach or suggest contacting its beads with a tissue sample makes sense: Cantor's methods relate to *bulk analysis* of sample nucleic acid, *not* to *spatial analysis* of a solid material such as a tissue section. Accordingly, Petitioner's challenge to the majority of Challenged Claims (i.e., 16, 18, 21, 24, 25, 26, and 30) fails.

Petitioner's challenge to all Challenged Claims (including claims 1, 3, 6, 10, and 11) fails because Cantor does not teach that its “identification sequences” *necessarily* provide *unique location* information, as required by all claims.

Petitioner argues that, because Cantor's beads can be placed on a substrate, “each identification sequence *necessarily* corresponds to, and thus identifies, *the unique*

location (such as an (X,Y) coordinate) of the bead on the array.” Pet. 29.⁴ In this way, Petitioner’s obviousness grounds are predicated on an unsaid “inherent obviousness” theory. Petitioner argues that a POSA would have **necessarily** correlated the identification sequence with a unique location on the array, choosing between two options: (1) placing the beads at a pre-determined location on the substrate (“selective loading”), or (2) placing the beads on the substrate randomly and then “decoding” them to determine their location. *Id.*, 33.

But Cantor says nothing about correlation. And Cantor says nothing about either selective loading or decoding. At no point does Cantor express any interest in knowing or determining the location of any bead. Indeed, as Dr. Cantor explains, a POSA would not have considered **either** of Petitioner’s options for Cantor’s arrays, and thus **would not** necessarily have correlated the identification sequence with the location of the beads. EX2002, ¶¶171-172. Therefore, Cantor’s identification sequence would not **necessarily** “identif[y] a unique location on the substrate,” which is not enough to meet the exacting standard of inherent obviousness.

Even if Petitioner’s theory of obviousness is not based on inherency (it is), it still fails for the same technical reasons that Petitioner’s inherent obviousness theory fails. A POSA would not have had a reason to use Cantor’s bulk-analysis

⁴ All emphasis added throughout unless otherwise noted.

bead collections—which did not provide or seek to provide spatial information—to construct arrays or dispose a tissue section on one. As Dr. Cantor explains, a POSA would have recognized the futility of attempting to obtain spatial location of a biological molecule in a tissue sample using Cantor’s bulk-analysis methods or collections. EX2002, ¶¶166, 180.

Finally, nothing in Armani or any “background reference” compensates for the deficiencies in Cantor. Petitioner has never set forth in the Petition with sufficient detail or clarity how or why a POSA would have bridged that divide that stands between Petitioner’s prior art and what is claimed.

A. Cantor Fails to Teach a “Tissue Section” as Required by the Majority of Challenged Claims

Cantor is directed to bulk analysis of “sample nucleic acid”—not solid material such as a tissue section. But claim 16 and its dependent claims—the majority of the Challenged Claims—are directed to “[a] composition comprising...*a tissue section*.” EX1005, 34:8-11. Petitioner’s arguments are predicated on Cantor teaching that its “sample may be ‘a solid material such as a tissue...or a biopsy.’” Pet. 38 (quoting EX1031, 6).

But Cantor does not and cannot teach a POSA to use a tissue section with its beads and methods because spatial information does not matter to Cantor at all. Because Petitioner’s grounds of unpatentability based on Cantor fails for the majority of Challenged Claims, the Board should deny institution on Grounds 1

and 2. *See Chevron Oronite Co. v. Infineum USA L.P.*, IPR2018-00923, Paper 9 at 10–11 (PTAB Nov. 7, 2018) (informative); *Deeper, UAB v. Vexilar, Inc.*, IPR2018-01310, Paper 7 at 41–43 (PTAB Jan. 24, 2019) (informative).

1. Cantor does not perform array-based nucleic-acid analysis on a “tissue section”

Cantor does not teach or suggest contacting its beads with a tissue section to perform array-based nucleic-acid analysis. Petitioner’s entire argument about “tissue section” goes like this: (1) Cantor teaches that the solid phase nucleic acid hybridizes to a “sample nucleic acid”; (2) Cantor teaches that its “sample” may be a solid material such as a tissue or a biopsy; (3) therefore, Cantor ***must teach*** contacting its capture probes with a “tissue section” to perform array-based nucleic-acid analysis Pet. 37-38; *see also id.*, 40, 42, 49. But this argument conflates Cantor’s “sample nucleic acid” (which is mixed with beads) with Cantor’s “sample or source” (from which the “sample nucleic acid” is ***derived***). As Dr. Cantor explains and plain language of Cantor supports, they are not the same. EX2002, ¶¶30-43, 145-148.

Cantor teaches preparing a “***sample nucleic acid***” and contacting that sample nucleic acid to solid supports (e.g., beads). Indeed, every time Cantor describes “the invention,” it is with respect to a “sample nucleic acid”—not a solid material such as a tissue section:

- “Certain improvements are directed to efficiently preparing nucleic acids that

comprise nucleotide sequences identical to or substantially identical to one or more target nucleotide sequences *of a sample nucleic acid*, or complement thereof.” EX1031, 1;

- “The invention in part provides a method for preparing *sample nucleic acid* complements, which comprises: (a) *preparing a mixture comprising sample nucleic acid and a solid support....*” *Id.*;
- “[T]he invention in part provides collections of solid supports and methods in which a collection of *solid supports is contacted with sample nucleic acid....*” *Id.*, 2;
- “The invention also in part provides a method for sequence analysis, which comprises: (a) *preparing a mixture comprising sample nucleic acid a solid support....*” *Id.*;
- “Also, the invention in part provides a method for obtaining sequence information of a target nucleic acid, which comprises: (a) *preparing a mixture comprising sample nucleic acid and a solid support....*” *Id.*;
- “The invention also in part provides a solid support comprising single-stranded solid phase nucleic acid having an identifier sequence and a probe sequence, where: *the probe sequence hybridizes to sample nucleic acid....*” *Id.*, 3;
- “Also, the invention in part provides a substrate comprising a collection of beads oriented in an array, where: each bead is in association with single-

stranded nucleic acid; the solid phase nucleic acid comprises an identifier sequence and a probe sequence; *the probe sequence hybridizes to sample nucleic acid* when the probe sequence is complementary to a nucleotide sequence in the sample nucleic acid....” *Id.*, 4;

- “The invention also in part provides a kit comprising a solid support having single-stranded solid phase nucleic acid, one or more agents that can extend solid phase nucleic acid *hybridized to sample nucleic acid*....” *Id.*, 4.

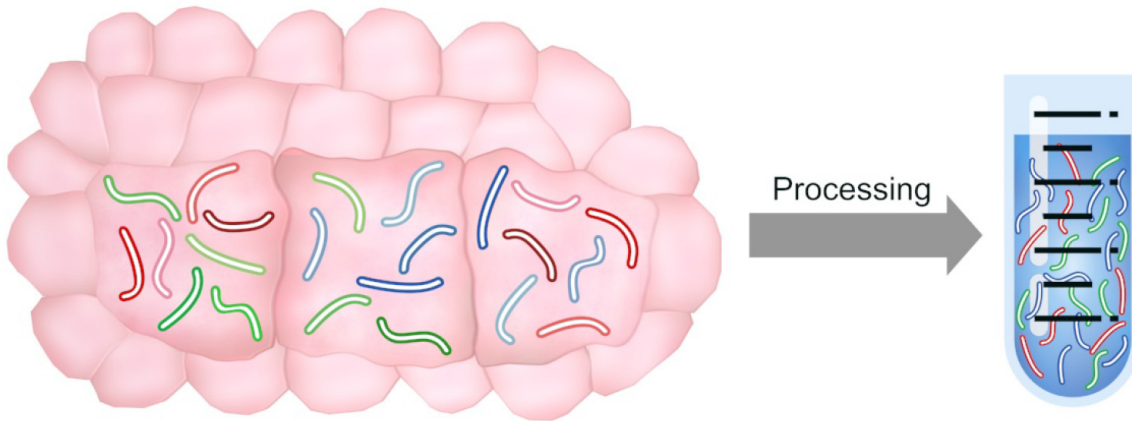
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Dr. Cantor explains that a POSA would have understood that, to carry out the steps of Cantor’s methods, the POSA would first have to derive the sample nucleic acid from a sample or source. EX2002, ¶35; see EX1031, 5. *Only then* could a POSA continue to the next step of “preparing a mixture comprising sample nucleic acid and a solid support.” EX1031, 1; EX2002, ¶145.

Cantor states that “[s]ample nucleic acid may be *derived* from one or more *samples* or sources.” EX1031, 5; EX2002, ¶¶35, 146. Cantor defines “sample” as the thing that contains the sample nucleic acid (EX1031, 5) and explains “[a] *sample* may be collected from an organism.” EX1031, 6; EX2002, ¶42. When a “sample” comes from a living (or formerly living) source, Cantor states, that sample is a “*biological sample*.” Cantor then states that the “biological sample can be in any form, including without limitation a *solid material such as a tissue*...or a

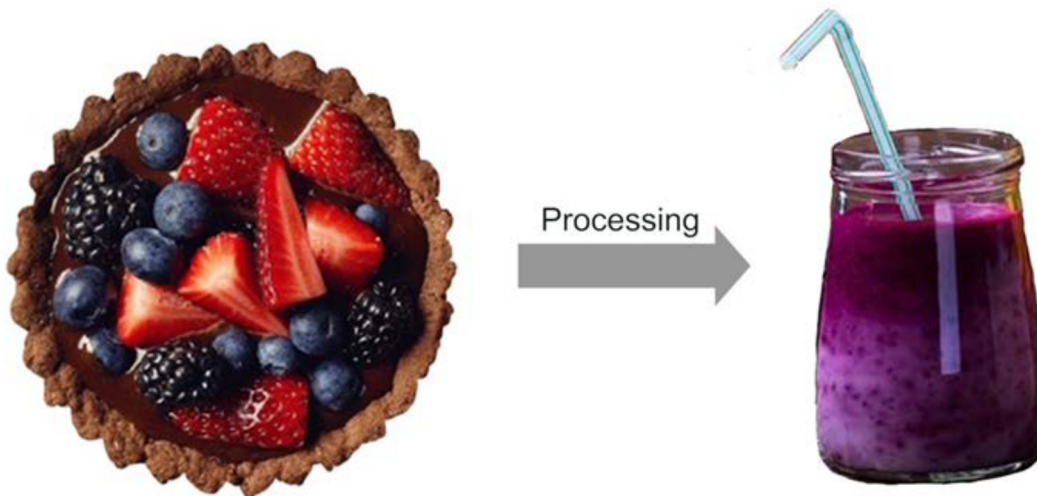
biological fluid such as urine, blood, saliva, amniotic fluid....” *Id.* Finally, the “sample nucleic acid may be a result of nucleic acid purification or isolation and/or amplification of nucleic acid molecules **from the sample.**” EX1031, 7; EX2002, ¶¶40; EX2007; EX2008. In other words, Cantor teaches deriving the sample nucleic acid from a solid material such as tissue or from a biological fluid. As Dr. Cantor explains, “[a] tissue is simply the **source** of the sample nucleic acid used in [Cantor’s] methods”—it is not the sample nucleic acid itself. EX2002, ¶¶43, 147-148. Cantor further teaches that deriving a “sample nucleic acid” from a sample or source is accomplished “by any means commonly known in the art, including but not limited to cell lysis procedures using chemical, physical or electrolytic lysis methods.” EX1031, 54; EX2002, ¶39; EX2006.

Once the “sample nucleic acid” is derived from a sample or source, a POSA would have understood that the “sample nucleic acid” exists in the form of a homogenized (blended) mixture that **does not retain** the original spatial distribution of nucleic acids that a solid material such as a tissue section would have. EX2002, ¶¶36-41. This can be visualized by the following drawing that shows processing of solid tissue section (with three cells of the tissue highlighted to show the nucleic acids present in those cells) into sample nucleic acid:



EX2002, ¶¶36-38.

In this way, Dr. Cantor explains, the difference between the '138 patent's claimed "tissue section" and Cantor's "sample nucleic acid" can be analogized to the difference between the fruit tart and the fruit smoothie. *Supra* §§II, III.A; EX2002, ¶¶18-20, 36-38, 147.



Fruit Tart

Fruit Smoothie

The tart has many different fruits (strawberries, blueberries, blackberries) with an intact spatial distribution. *Id.* But the fruit smoothie does not: the spatial

distribution of strawberries, blueberries, and blackberries has been lost because the fruit exists in a homogenized (blended) mixture. *Id.* Dr. Cantor explains that the tart is like a solid material such as a tissue section, which has many different cells expressing many different nucleic acids with an intact spatial distribution. *Id.* Conversely, the smoothie is like Cantor’s “sample nucleic acid,” which does not have an intact spatial distribution of nucleic acids. *Id.*

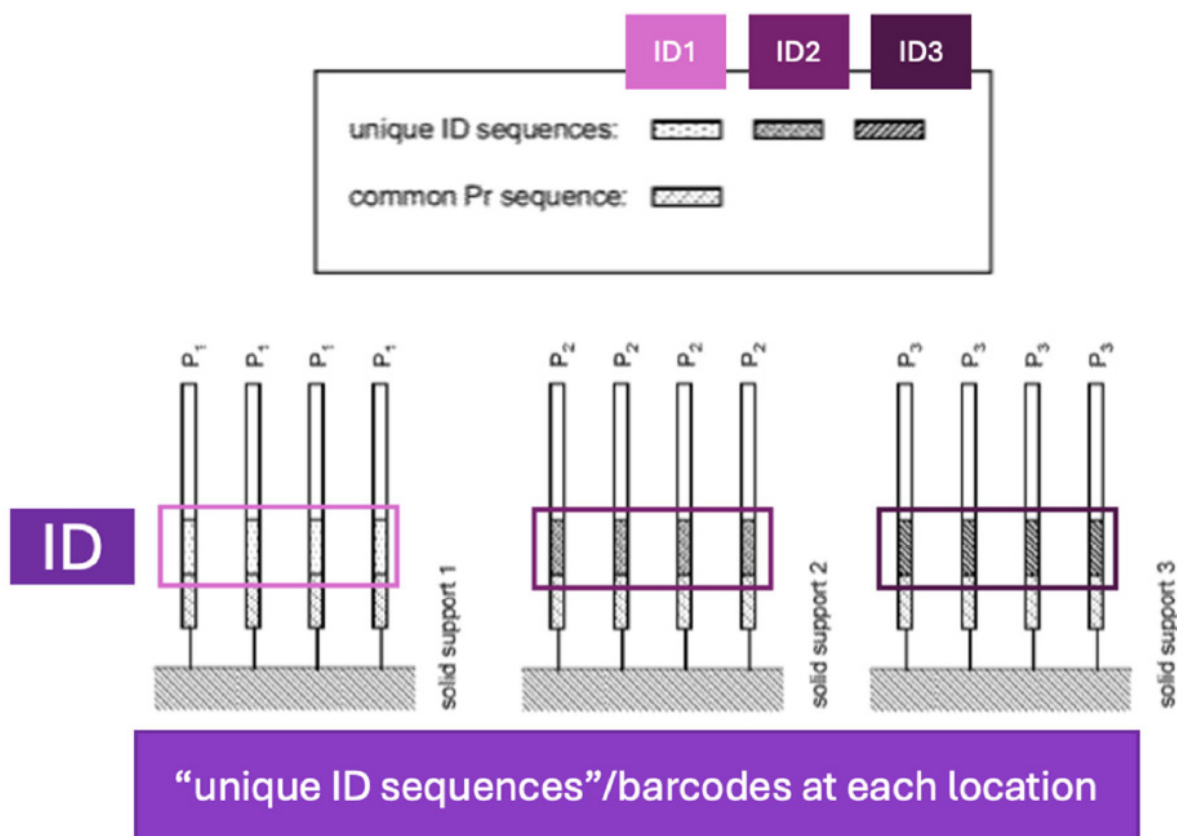
Petitioner argues that a POSA would have placed a tissue section on an array of Cantor’s beads because a “POSA would have been familiar with, and would have been motivated to apply such [cell lysis] techniques to the tissue or biopsy samples” disclosed by Cantor. Pet. 39 (citing EX1103, ¶164). But Petitioner fails to appreciate that Cantor performs cell lysis to *derive* the sample nucleic acid from the sample or source before contacting the sample nucleic acid with solid supports. EX2002, ¶146. In any event, the sample nucleic acid, whether derived from tissue or any other biological sample, cannot provide any information about spatial location. EX2002, ¶147.

Cantor does not teach contacting a “tissue section” with beads. Instead, Cantor teaches that “a solid material such as a tissue” may be merely a source of the “sample nucleic acid,” and it is the “sample nucleic acid”—not the tissue itself—that is mixed with solid supports. EX1031, 1. For this reason alone, Ground 1 fails with respect to almost all of the Challenged Claims.

2. That Cantor's bead collections and Petitioner's proposed arrays have different probes on each bead (that are not shared between the beads) dooms Petitioner's obviousness grounds

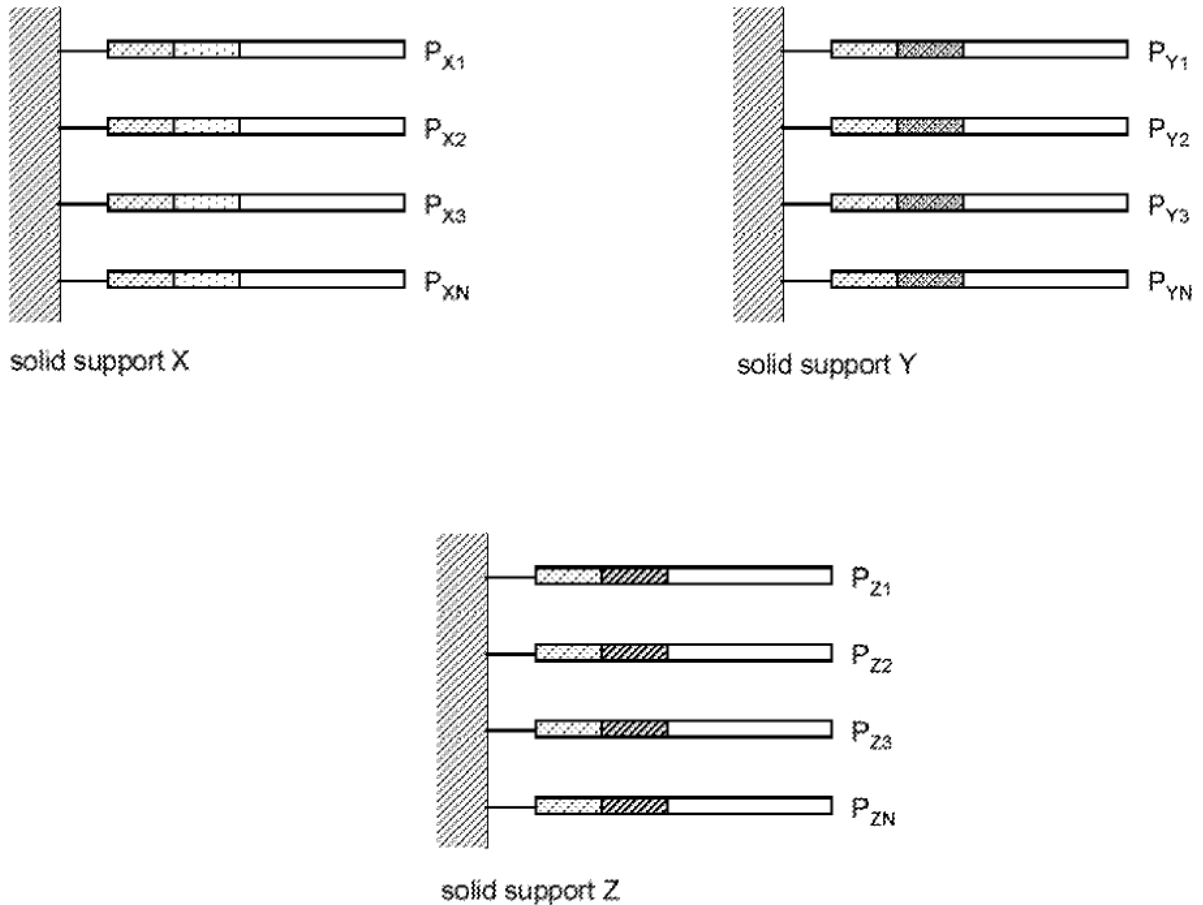
All Challenged Claims (including claim 1 and its dependent claims) require *arrays*. In analyzing the Challenged Claims, however, Petitioner largely focuses on Cantor's *individual beads* and ignores that Cantor's arrays would still be limited to bulk analysis (the presence or absence of the biological molecule of interest in the sample nucleic acid), not spatial information. Pet., 23-32, 37-38, 44-45; EX2002, ¶¶149-166. As Dr. Cantor explains, the presence of *different probes on each bead* destroys any ability to obtain spatial information from a tissue section. EX2002, ¶157. Thus, a POSA would have had no reason "to perform array-based nucleic acid analysis on a tissue sample" as Petitioner alleges. Pet. 38.

Critically, Petitioner ignores that its proposed array has different probes on each bead (i.e., P1, P2, and P3):



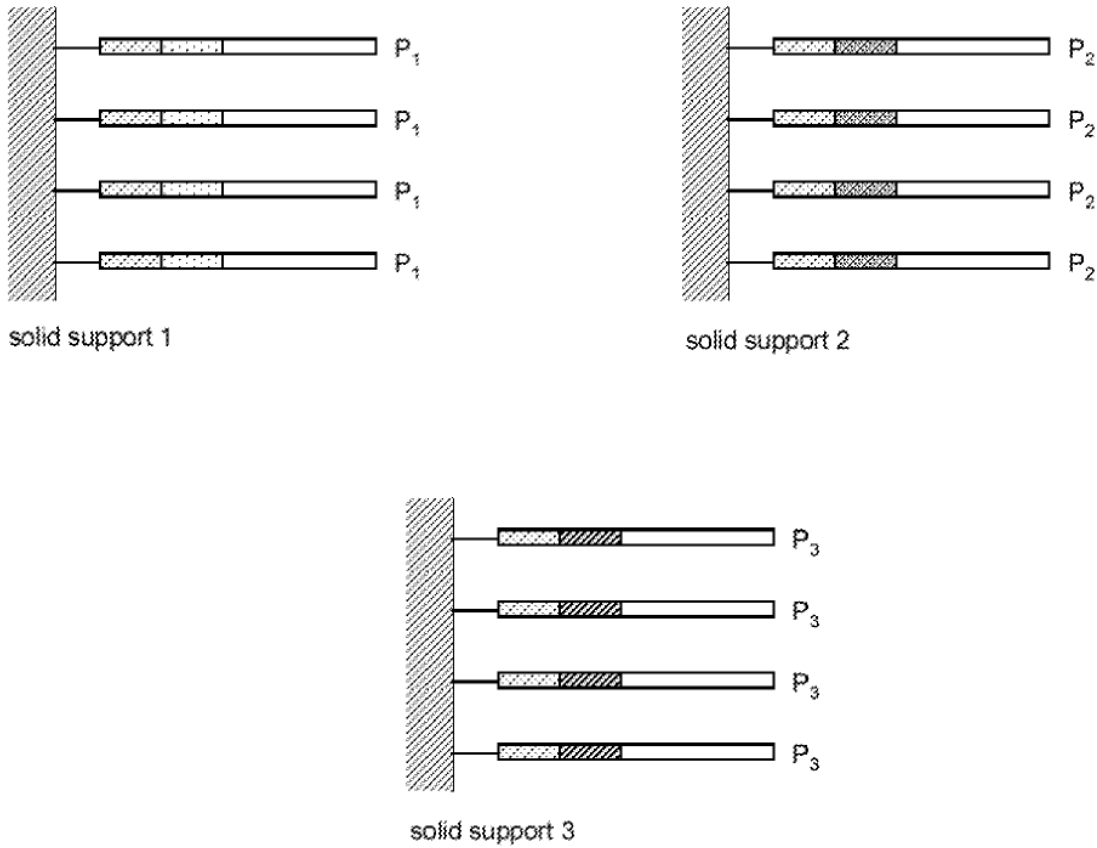
Pet. 30; EX2002, ¶151. Each bead in Petitioner's array is specific to a particular nucleic acid (or subsequences of that nucleic acid), dooming Petitioner's challenges.

Cantor describes two different types of collections. EX2002, ¶¶61-67. The first has solid support species (e.g., beads) that have multiple probes per bead directed to different subsequences of the same target nucleic acid (depicted in Figure 1B):



EX1031, 16-17; EX2002, ¶¶64-65. Specifically, bead “X” has probes P_{X1} - P_{XN} , bead “Y” has probes P_{Y1} - P_{YN} , and bead “Z” has probes P_{Z1} - P_{ZN} . Each probe on bead “X” targets a different subsequence of the “X” nucleic acid. The same is true of the “Y” and “Z” beads. Put differently, Figure 1B depicts a bead collection with twelve unique probes directed to subsequences of 3 different target nucleic acids (X, Y, and Z). *Id.*

The second has solid support species that have multiple probes per bead directed to the same target nucleic acid (depicted in Figure 1C):



EX1031, 16-17; EX2002, ¶¶66-67. Thus, in Figure 1C, bead “1” has probes P1, bead “2” has probes P2, and bead “3” has probes P3, for a total of three unique probes in the array directed at 3 different target nucleic acids (1, 2, and 3). *Id.*

Critically, in both *collections no probe is the same between the beads.*

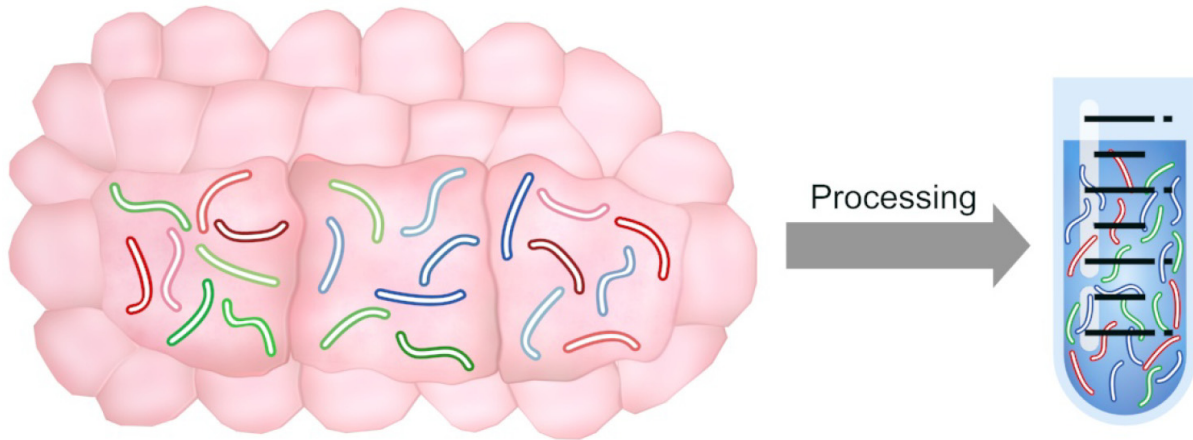
EX2002, ¶¶64, 151.

3. Using Petitioner’s array with Cantor’s sample nucleic acid provides bulk analysis of the presence or absence of a biological molecule, not its spatial location

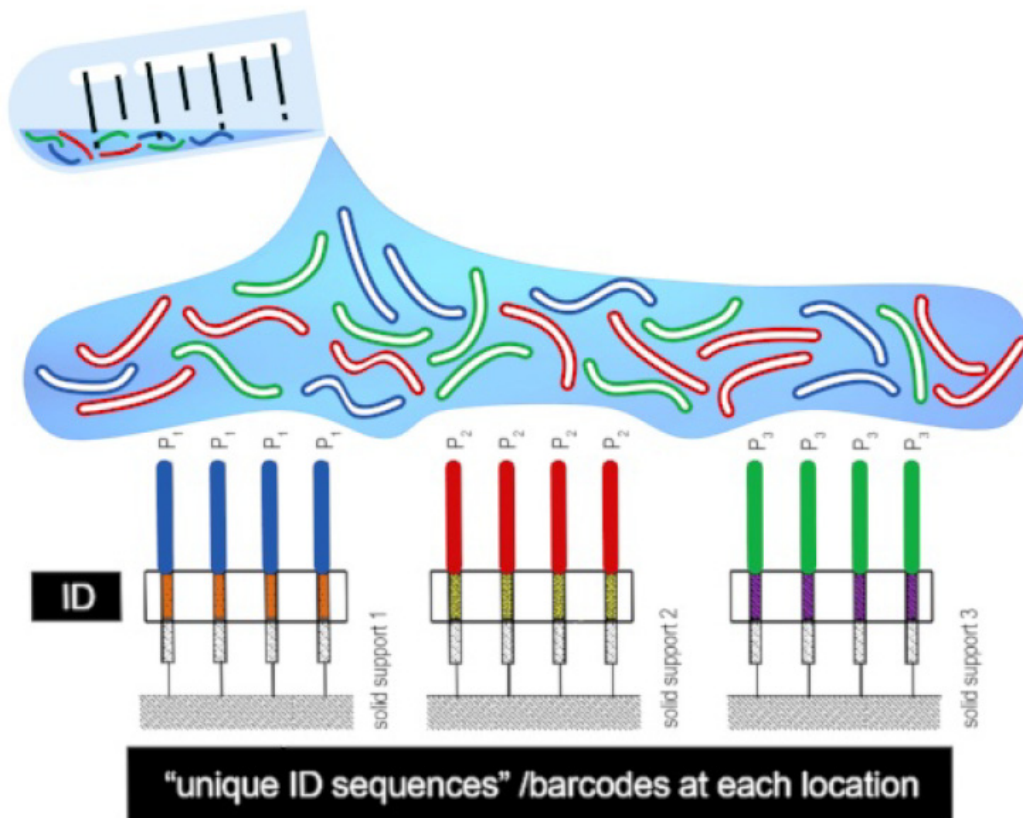
Cantor’s bead collections, designed for bulk analysis, would not work for spatial analysis. A POSA would not have been motivated to perform array-based nucleic acid analysis on a tissue sample, as Petitioner argues. Pet. 38. As

discussed in §VII.A.2., each bead in Petitioner's proposed array is designed to hybridize with a particular nucleic acid or a subsequence of that particular nucleic acid. EX2002, ¶¶55-67, 152-166. Therefore, each bead in Petitioner's proposed array is focused on a specific nucleic-acid sequence or a subsequence of that specific sequence. In other words, each bead in the array would hybridize with one target nucleic acid (or subsequences of that target nucleic acid). Thus, hybridization would not necessarily occur between the probe and the biological molecule in a tissue section. And without hybridization, no spatial information can be obtained. Any spatial information that might result from overlaying a tissue section over Petitioner's array would be the result of *pure chance*.

The results from contacting Petitioner's array with Cantor's sample nucleic acid is illustrated below. Again, a "sample nucleic acid" is first derived from, e.g., tissue. EX1031, 5-6; EX2002, ¶¶35-36. This is depicted below as a tissue sample highlighting three cells containing nucleic acids depicted as differently colored outlines.

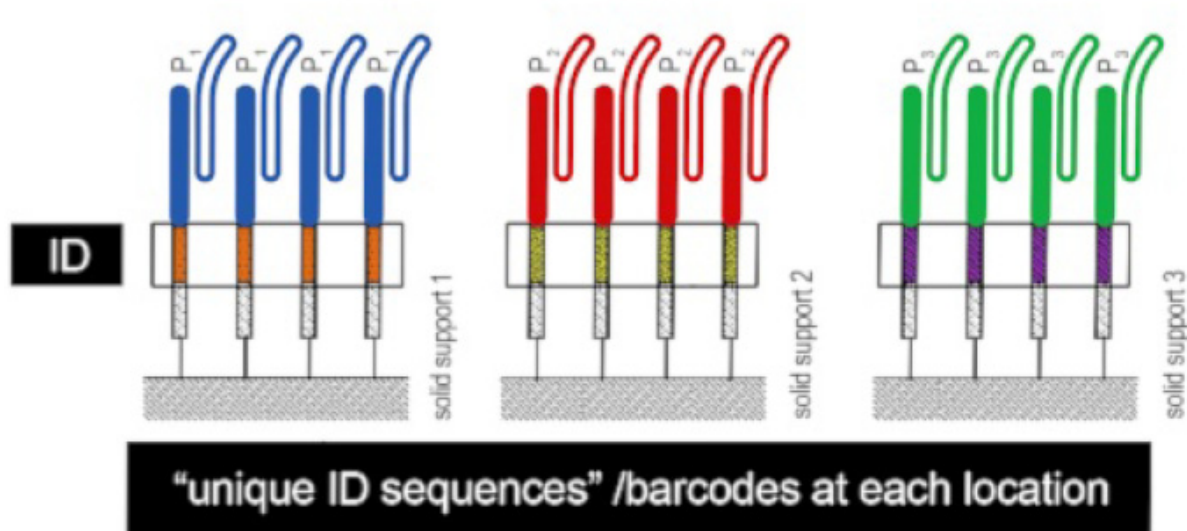


Then, the resulting sample nucleic acid is applied to Petitioner's array, where each different bead on the array has different probe sequence(s). EX1031, EX2002, ¶¶64, 151, 157. The mixing of sample nucleic acid with beads arranged on an array is illustrated below:



The probes of bead 1 are **solid blue**, the probes of bead 2 are **solid red**, and the probes of bead 3 are **solid green**. EX2002, ¶¶158-159. The **solid blue** probes are designed to hybridize to the **blue-outlined** nucleic acids in the sample nucleic acid; the **solid red** probes to the **red-outlined** nucleic acids; the **solid green** probes to the **green-outlined** nucleic acids. *Id.*

Because the nucleic acids are free to flow across the entire array, they hybridize to their corresponding probes regardless of where the nucleic acid was located in the original tissue. *Id.* Thus, hybridization between the probes and the target nucleic acids is depicted in the following illustration:

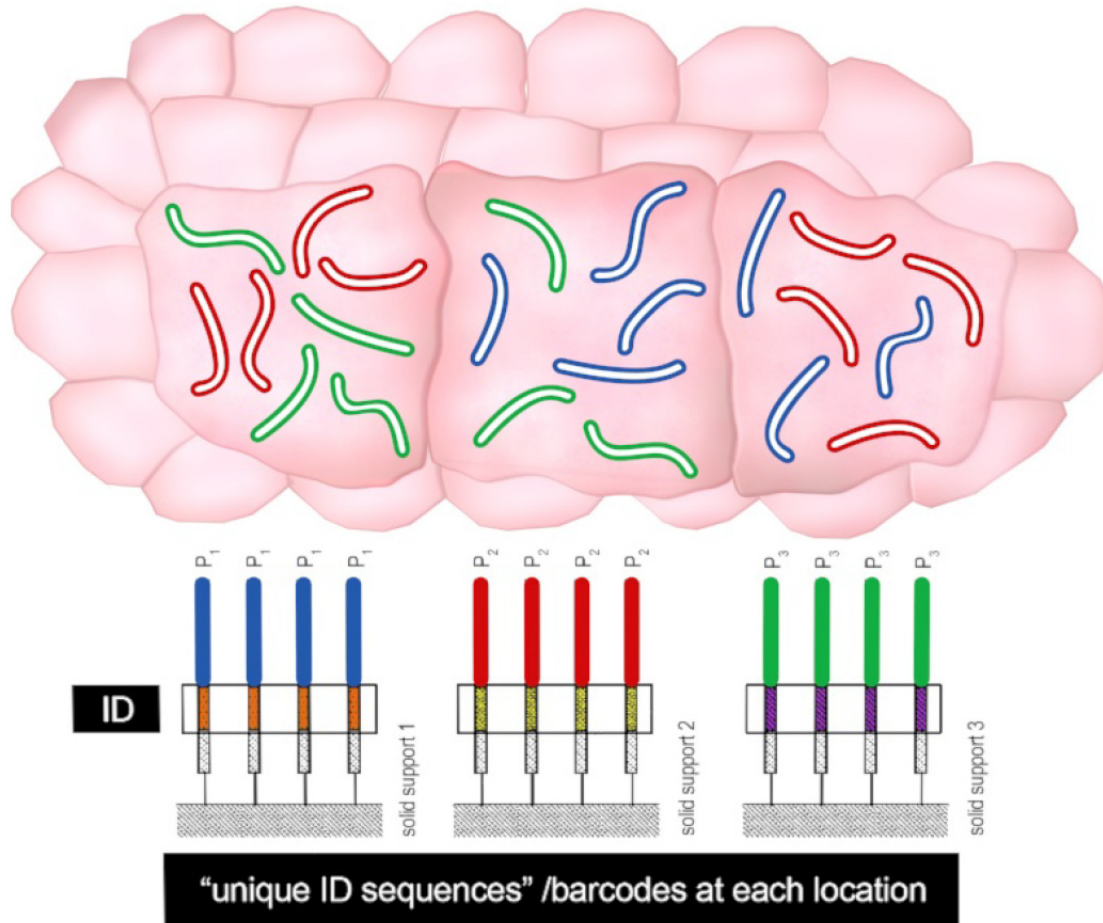


Id. Because the target nucleic acids in the sample nucleic acid are blended together (like in the fruit smoothie), the spatial distribution of the nucleic acids within the original tissue sample has been lost. EX2002, ¶¶160. Put differently, while

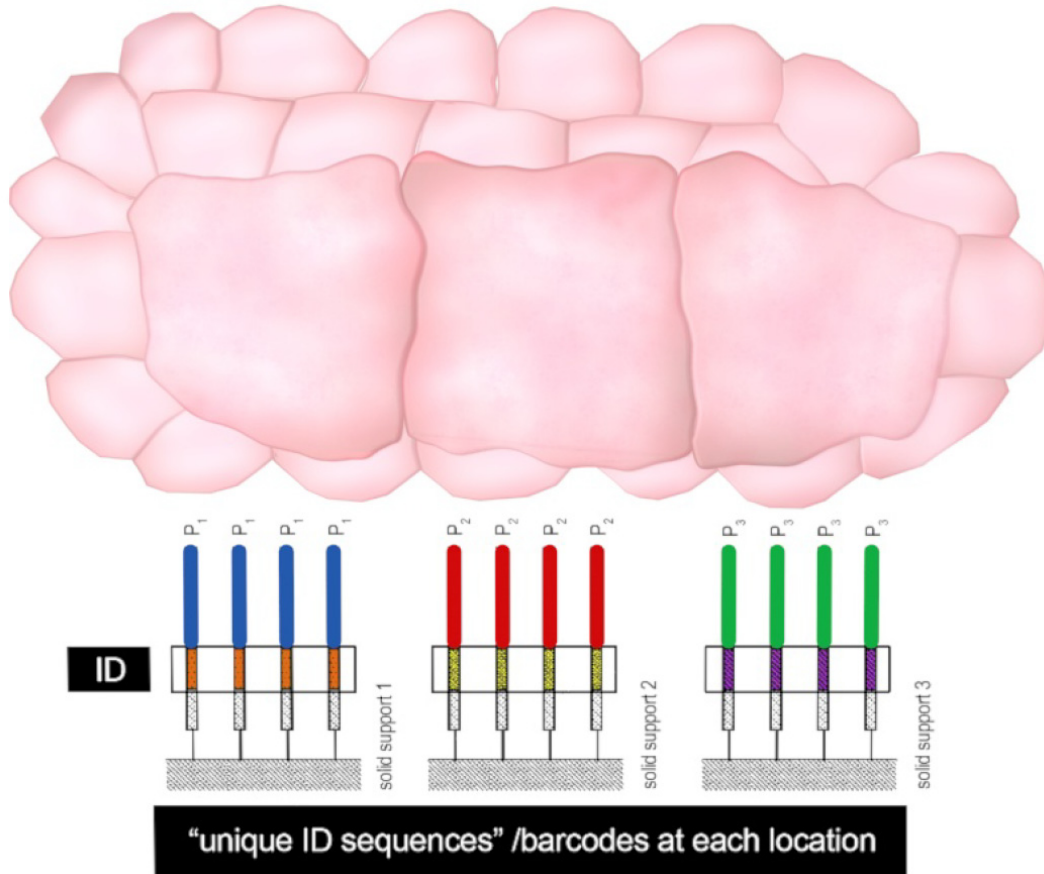
Cantor's collection can reveal that the **blue-outlined** nucleic acids hybridized to the **solid blue** probes of bead 1 (and thus was *present* in the sample), it cannot reveal *where* in a tissue section that **blue-outlined** nucleic acid was spatially located (like in the fruit tart). *Id.*

Accordingly, any hybridization between Cantor's solid phase nucleic acid (having a probe and an identification sequence) would indicate the *presence or absence* of a target nucleic acid in the original source (e.g., a solid material such as a tissue), but not *location* in that source. *Id.*

Contacting Petitioner's bead array with a *tissue section* would not necessarily result in the spatial information about a biological molecule. The following illustrations depict what would happen if a POSA overlaid the proposed array with a solid tissue. EX2002, ¶161; *see* Pet., 23-24. In the first illustration, the probes of bead 1 are **solid blue** (designed to hybridize to the **blue-outlined** nucleic acids in the tissue), the probes of bead 2 are **solid red** (designed to hybridize to the **red-outlined** nucleic acids in the tissue), and the probes of bead 3 are **solid green** (designed to hybridize to the **green-outlined** nucleic acids in the tissue). *Id.*



As shown, the target nucleic acids are non-uniformly distributed in the tissue *and* the probes are not repeated across the array. EX2002, ¶¶162-163. When nucleic acids are released from a tissue sample onto the array, they can only be captured by probes that are underneath the location where the nucleic acid was released from the tissue. *Id.* Thus, a target nucleic acid will hybridize to the array *only if* that target nucleic acid *just happens* to be present in the spatial location of the tissue that overlays its corresponding probe, as the next illustration shows:

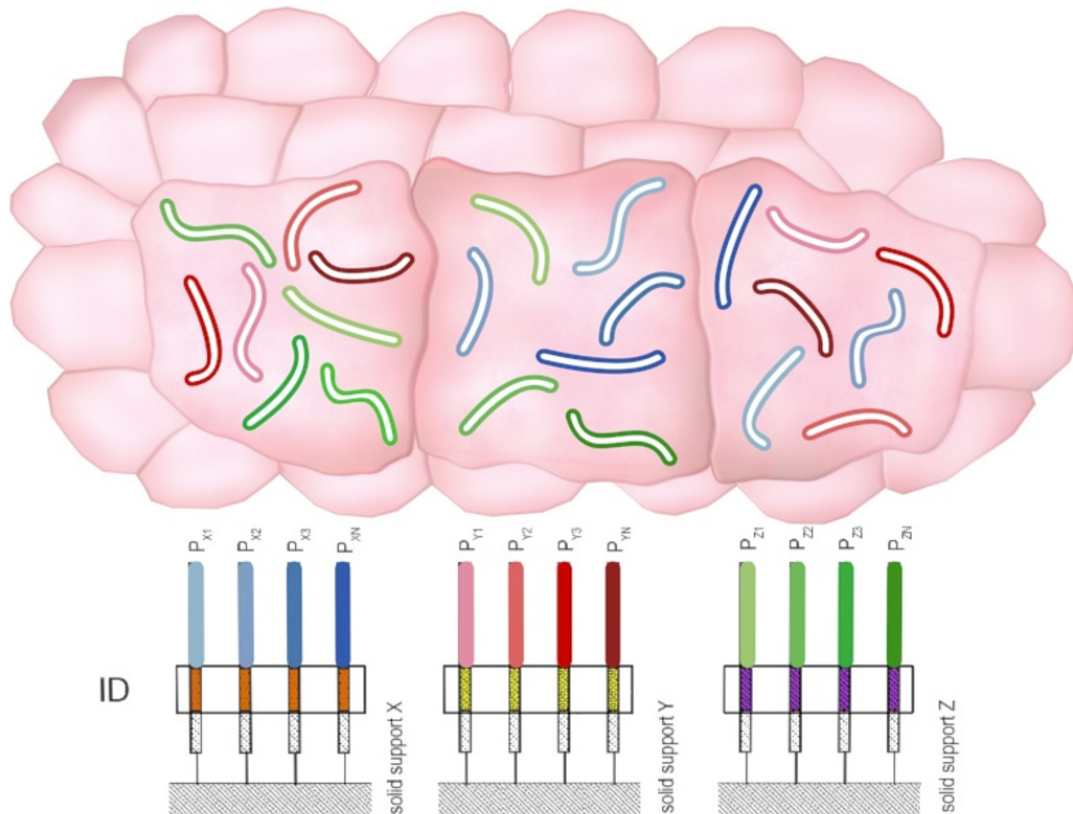


Id.

Here, even though **blue-outlined**, **red-outlined**, and **green-outlined** target nucleic acids were *present* in tissue (as shown in the first illustration), the results of the assay would nevertheless show *no* spatial information for these nucleic acids (as shown by the lack of any binding between the probes and any nucleic acids in the second illustration). This is because the spatial location of these target nucleic acids in the tissue *just happened* to not overlay the beads containing each target's corresponding **solid blue**, **solid red**, and **solid green** probes. *Id.* Put differently, target nucleic acids were not in a spatial location where they could hybridize to

their corresponding probes and no spatial location of the biological molecules is *necessarily* obtained from the array. *Id.*

The same results would occur whether Petitioner's array had a single type of probe per bead (as depicted above) or the array had multiple different subsequence probes per bead (as depicted in Cantor's Figure 1B). EX2002, ¶¶164-165. The latter array is illustrated below:

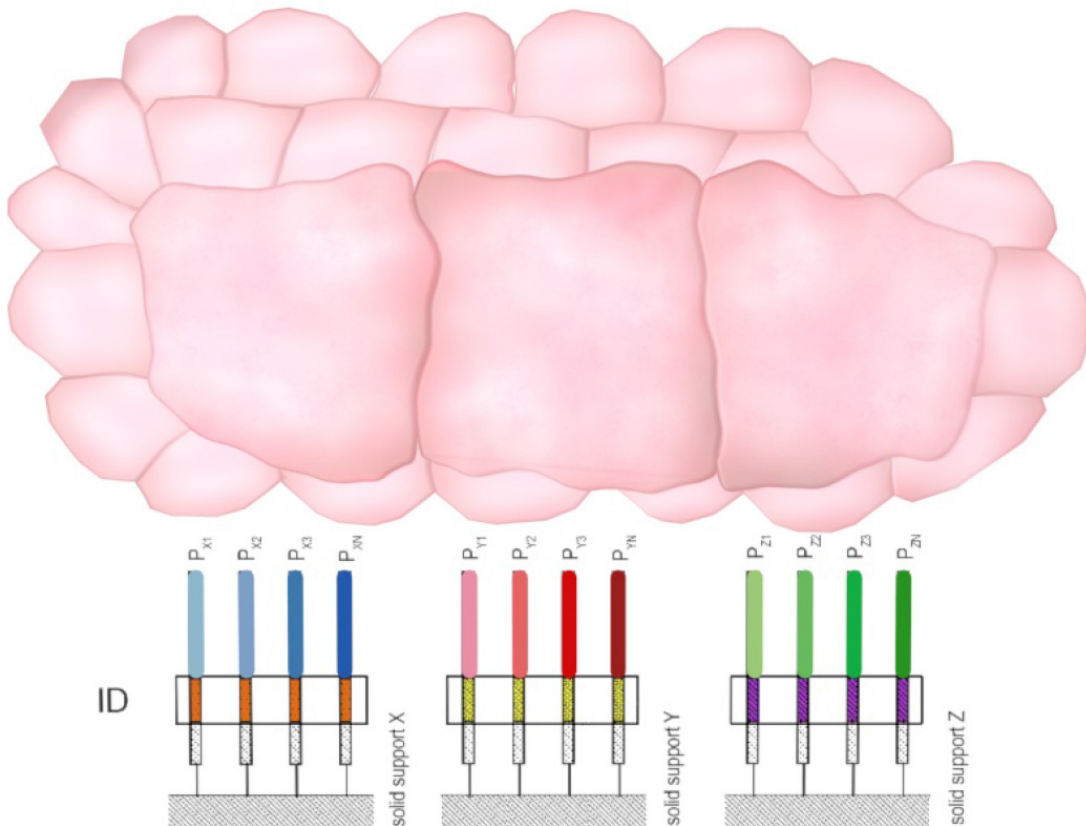


Id.

Here, the probes of bead X are various **shades of blue** (designed to hybridize to the various **shades of blue-outlined** nucleic acids in the tissue). The

probes of bead Y are various **shades of red** (designed to hybridize to the various **shades of red-outlined** nucleic acids in the tissue), and the probes of bead Z are various **shades of green** (designed to hybridize to the various **shades of green-outlined** nucleic acids in the tissue). *Id.*

As the next illustration shows, however, *if* the target nucleic acid is not present in a spatial location of the tissue section that overlays its corresponding probe, then *no* hybridization will occur, and *no* spatial information about the biological molecules is obtained from the array.



Id.

Even though various shades of blue-outlined, red-outlined, and green-outlined target nucleic acids were *present* in the tissue section (as shown in the first illustration), the results of the assay would nevertheless show *no* spatial information for these nucleic acids (as shown by the lack of any binding between the probes and any nucleic acids in the second illustration). *Id.*

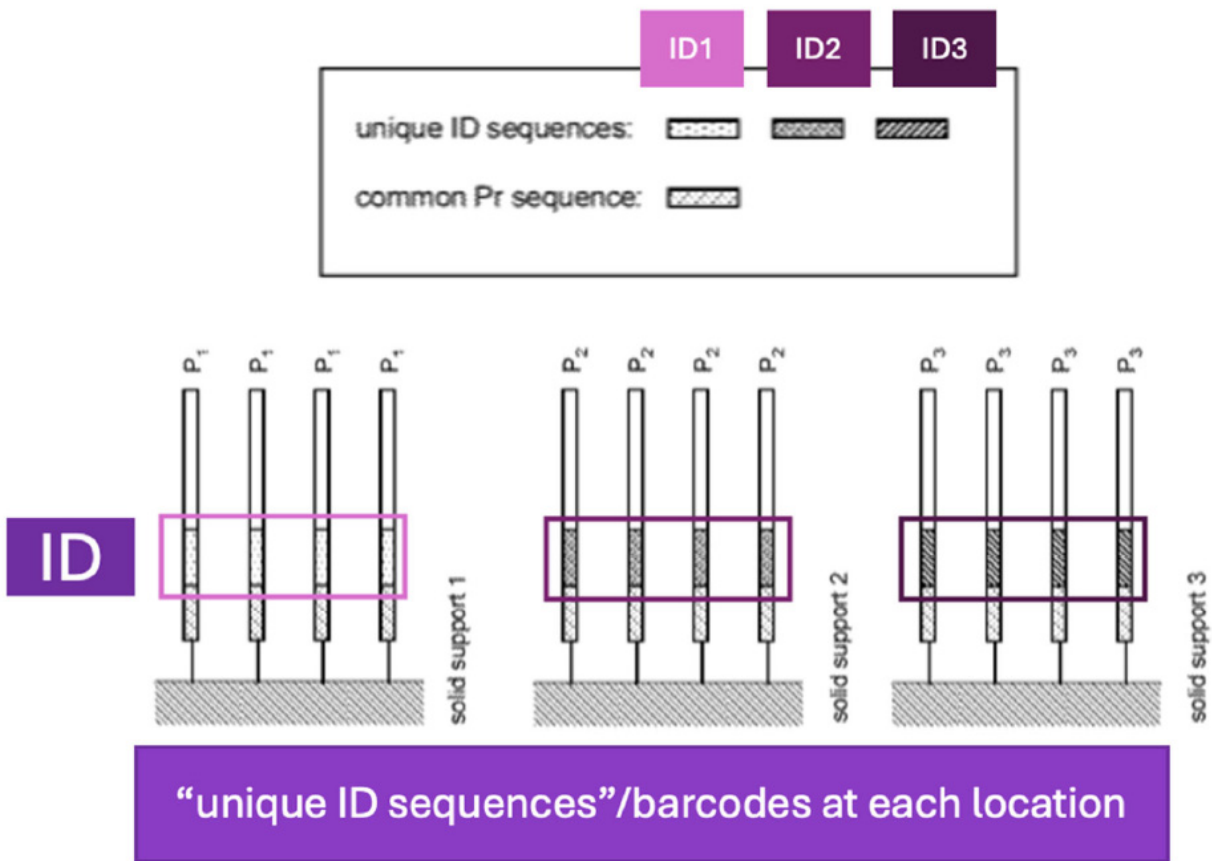
At most, hybridization “*may* result from a given set of circumstances” (e.g., a tissue section was, by chance, overlaid in exactly the right location over Petitioner’s array). A POSA simply *would not* have disposed a tissue section onto Petitioner’s array because Cantor *does not and cannot* teach a POSA to use a tissue section with its beads and methods. Spatial analysis does not matter to Cantor at all. Contrary to Petitioner’s argument (Pet. 38-40), therefore, a POSA would not have had a reason to perform array-based nucleic-acid analysis by contacting Cantor’s array with a tissue section. EX2002, ¶166. Because these critical flaws cannot be cured during trial, institution on Ground 1 should be denied.

B. Cantor Fails to Teach an Identification Sequence that “Identifies a Unique Location on the Substrate” as Required by All Challenged Claims

Not only does Cantor not teach contacting a “tissue section” with beads, it also comes nowhere close to suggesting that beads, with optional coding identifiers, could or even *should* be arranged at locations on a substrate that are

known or determined prior to use to “*identif[y] a unique location on the substrate.*” EX1005, 33:23-24 (claim 1), 34:15-16 (claim 16); EX2002, ¶¶167-179. Again, Cantor’s solid supports and methods answer the question of whether a biological molecule of interest is present in a sample nucleic acid—a simple “yes or no” determination achieved through *bulk analysis*. Dr. Cantor explains that Cantor’s substrates are used to ease handling of its solid supports (beads) for use in its described methods. EX2002 ¶173.

But Cantor *never* teaches or suggests that the beads and their corresponding identification sequences (if present) are either placed at a known location or placed randomly, with locations determined prior to use so that the identification sequence can be *traced back* to a unique location on the substrate. EX2002, ¶168. Petitioner simply *assumes* so, and modifies and rearranges Figure 1C of Cantor to reflect its mistaken assumptions (excerpted below):



Pet., 29. Specifically, Petitioner argues this modified figure shows that Cantor’s identification sequences “necessarily correspond to, and thus identifies, the unique location (such as an (X,Y) coordinate) of the bead on the array.” *Id.* But this modified and rearranged figure only highlights Petitioner’s mistaken assumptions about Cantor’s arrays.

Cantor does not teach that “each of the capture probes” comprises “(ii) a nucleic acid sequence that identifies a unique location on the substrate and is not configured to hybridize to a target nucleic acid that binds to a target nucleic acid binding domain.” Pet., 28-29. Nonetheless, Petitioner argues that this would have

been inherently obvious:

[A] POSA would understand that Cantor discloses a bead array in which each bead is necessarily deposited at a particular (X, Y) coordinate location, and thus, each identification sequence ***necessarily*** corresponds to, and thus identifies, the unique location (such as an (X,Y) coordinate) of the bead on the array.

Id., 29. Put differently, Petitioner argues that Cantor’s “identification sequences” would ***necessarily*** provide ***unique location*** information. *Id.*, 29; *see also id.*, 6-7.

Petitioner’s argument, however, rests on the mistaken assumption that, because Cantor’s beads can be arranged on a substrate, a POSA would have ***necessarily*** correlated the identifier sequence with the bead’s location by: (1) placing the beads at known locations (“selective loading”) or (2) randomly placing the beads with subsequent “decoding.”

But Cantor does not teach or suggest that the location of beads on an array is known (it isn’t) or even needs to be known (it doesn’t). EX2002, ¶172. And in the context of Cantor’s bulk-analysis methods, if a POSA would have placed the beads on an array at all, it would only make sense for a POSA to have done so ***without*** either selective loading or randomly loading and decoding—regardless of whether an identification sequence was present or not. *Id.*

The critical flaw in Petitioner’s argument is that Petitioner ***just assumes*** that a POSA would have chosen between these two options to correlate the identifier

sequence with the bead's location. Pet., 33-36. But, as Dr. Cantor explains, a POSA **would not** have loaded Cantor's beads onto an array either selectively or randomly followed by decoding so that the identification sequence would "identif[y] a unique location on the substrate." EX2002, ¶174. Put differently, although a POSA would have known that a bead (having a unique identification sequence and probe(s) to a particular target nucleic acid) was present **somewhere** on the substrate, the POSA would not have known the **location** of that bead on the substrate. Nor would a POSA have had a reason to determine the location of a bead because that information would have been completely irrelevant to Cantor's bulk-analysis methods. *Id.*

Petitioner does not offer any evidence to support its assumption, and—as explained below—its assumption is incorrect. Petitioner has not shown that "a nucleic acid sequence **that identifies a unique location on the substrate**" would be "necessarily present, or the natural result of the combination of elements explicitly disclosed by" Cantor. *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014). Petitioner's obviousness theory cannot meet the high standard of inherent obviousness. *Id.*, 1195-96 ("A party must...meet a **high standard** in order to rely on inherency to establish the existence of a claim limitation in the prior art in an obviousness analysis—the limitation at issue **necessarily** must be present.").

1. Cantor does not teach that the location of its beads on a substrate is known or even needs to be known

Cantor pertains to “nucleic acid sequence analysis [i.e., determining a nucleotide sequence of an amplification product] and methodology and components for use in such analysis.” EX1031, 1; EX2002, ¶30. Cantor teaches a “collection” of solid supports that can contain multiple solid-support species (e.g., beads). EX1031, 11, 17; EX2002, ¶¶55-60, 157. Cantor also teaches that a collection can be disposed on an array, such as an “X by Y array.” *Id.* ***But Cantor teaches using substrates to facilitate handling and processing.*** EX1031, 17-18 (“[t]he array can be arranged on any substrate suitable for sequence analysis or manufacture processes described herein”); EX2002, ¶¶68, 173. Cantor discusses how to physically attach beads to arrays. EX2002, ¶¶172; *see also* EX1048 (incorporated by reference in Cantor). But Cantor does not teach placing beads on the array in a known physical location—whether at the time of placement (e.g., selective loading), or determined prior to use (e.g., random loading followed by decoding). EX2002, ¶168.

Dr. Cantor explains that sequencing and other processes used in bulk analysis are easier when solid supports are arranged in an array on a substrate. Rather than having to manipulate numerous individual solid supports during multi-step preparation and sequencing processes, a POSA could simply manipulate a single substrate that holds numerous individual solid supports. EX2002, ¶152.

Cantor describes that its *optional* identification sequences are for assembly of large nucleotide sequences from smaller sequence “reads” by identifying overlapping sequences. *Id.*, 25, 53-55 (Example 1); EX2002, ¶45. The location of a bead on the substrate is completely irrelevant to that use. EX2002, ¶153. Put differently, nothing in Cantor teaches or suggests that the location of the bead on the substrate is known or even *needs* to be known. EX2002, ¶172.

2. A POSA would not have chosen to correlate the identifier sequence with the bead’s location and thus would not have been limited to “selective loading” or random loading with “decoding”

Petitioner’s mistaken assumption—that “each identification sequence necessarily correspond to, *and thus identifies*, the unique location...of the bead on the array”—becomes clear when considering Petitioner’s unsubstantiated assertion that a POSA would have chosen between two options to construct an array and correlate the identifier sequence with the bead’s location: (1) either “selective loading”, or (2) random loading followed by “decoding.”. Pet., 33-36. But that assumption is not supported by Cantor, which uses arrays for ease of handling beads and has no reason to care about the location of the beads on the array. EX2002, ¶¶68, 152, 167, 173.

Petitioner does not identify any teachings in Cantor suggesting that a POSA would have chosen between selective loading and random loading followed by decoding when constructing Cantor’s arrays, instead relying solely on Dr. Puglisi’s

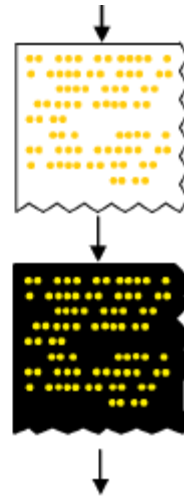
unsupported testimony. Pet., 33; EX1103, ¶¶ 66-71, 321; EX2002, ¶174. As Dr.

Cantor explains and supports with evidence, however, Petitioner's two proposed alternatives relate to the arrangement of probes on array sensors such as DNA microarrays, which generate a signal, e.g., fluorescence, directly on the array (i.e., *in situ*) when a target nucleic acid molecule hybridizes to a probe. EX2002, ¶¶174-179; EX1018; EX2012. These are *distinct* from Cantor's *sequence* analysis processes and compositions. EX2002, ¶175.

In a DNA microarray, the identity of the probe at each location on the array is *known prior to use* so that the signal generated on the array by hybridization of a target nucleic acid to a corresponding probe can provide the identity of the target nucleic-acid molecule that hybridize. EX2002, ¶¶175-177. For example, nucleic acids are processed to prepare a bulk nucleic-acid sample (e.g., as described above in §§II and III.A), labeled with fluorescent dye, and then applied to an array spotted with different DNA probes at known locations. *Id.* The presence and/or amount of a target nucleic acid—as well as its identity—is determined by imaging the array to detect fluorescence *at the physical location of the probe that hybridized to the target nucleic acid.* *Id.* This is depicted below, in an excerpt from Figure 1 of Petitioner's EX1018:

Microarray

Digital
Image

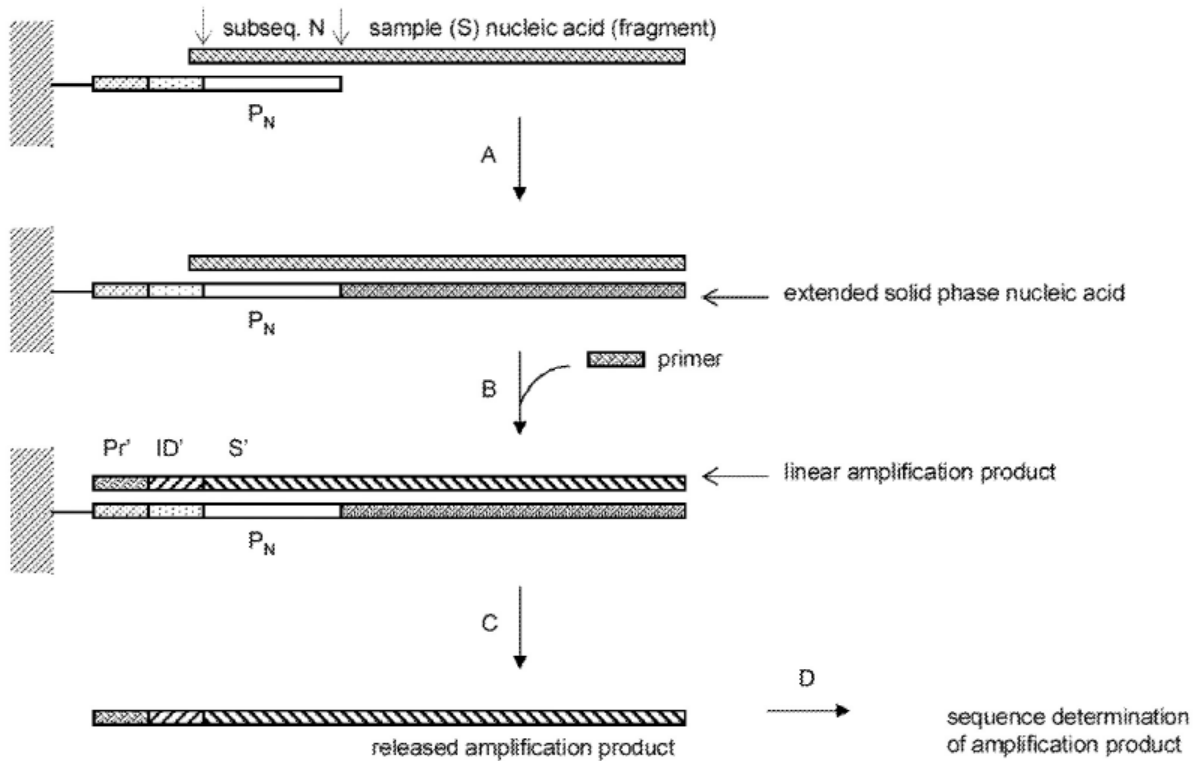


Id.

If a POSA did not know which probe was at a given physical location on the array, a POSA could ***not*** use the image to determine presence and/or absence of a given target nucleic acid. EX2002, ¶177. Thus, for this type of array, a POSA ***would*** have had to choose one of Petitioner’s two alternatives—either selectively loading the DNA probes onto the array or randomly loading them and determining where they landed before using the array (decoding). *Id.* But not to “correlate the identification sequence” with a “location on the array” that is known or determined prior to use and ***necessarily “identif[y] a unique location on the substrate.”*** Pet., 33; EX2002, ¶177. Rather, a POSA would have used one of these two procedures to determine the physical location of the probe on the DNA microarray. EX2002, ¶177. Cantor, however, is not a DNA microarray, does not use *in situ* signal detection in this manner, and Petitioner’s two choices are irrelevant to Cantor. EX2002, ¶178.

Petitioner's mistaken assumption also becomes clear when considering

Cantor's Figure 2:



In contrast to DNA microarrays, Cantor's beads are not imaged to determine presence and/or amount of a target nucleic acid. Rather, in steps C and D, the linear amplification product *is released* from the solid support for downstream *sequencing and analysis*. EX1031, 24-25; EX2002, ¶¶178-179.

Dr. Cantor explains that once the linear amplification product is released, any information about where the bead was located on the substrate is lost. *Id.* Once the linear amplification products are released into solution for sequencing, they no longer retain any physical relationship with the beads. They have only a

copy of the captured target nucleic acid and (if used) the identification sequence.

Id. Cantor describes that its identification sequences—***if they are used at all***—are for assembly of large nucleotide sequences from smaller sequence “reads” by identifying overlapping sequences. EX1031, 25, 53-55 (Example 1); EX2002, ¶45. The location of the bead, binding agent, and (if used) coding identification sequence on the substrate is irrelevant to Cantor’s sequence-analysis methods. *Id.*

Moreover, even if Cantor suggested that an identification sequence would be used ***and*** could be traced back to a location ***of a bead on the substrate***, it ***would not*** and ***could not*** correlate to the location of the target nucleic-acid sequence in the original ***tissue sample***. ***It could not***, because, as described in §§II and III.A, any information about the spatial location of a target nucleic acid in the tissue was lost when Cantor’s sample nucleic acid was prepared. EX2002, ¶¶35-43, 176. Because these critical flaws cannot be cured during trial, institution on Ground 1 should be denied.

C. The Challenged Claims Would Not Have Been Obvious Because a POSA Would Not Have Been Motivated to Generate Petitioner’s Proposed Array

Even if Petitioner’s theory of obviousness is ***not*** based on inherency, it still fails for the same technical reasons discussed above. At the time of the invention, a POSA would ***not*** have had a reason to construct Petitioner’s array, determine the locations of the beads on the array, or dispose a tissue section on it. Dr. Cantor

himself explains that a POSA would have recognized the futility of doing so.

EX2002, ¶¶180-182.

“[O]bviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention.” *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015). Here, as Dr. Cantor explains, the technology in Cantor “does not relate to preparation or analysis of intact tissue samples discussed in the ’138 patent (i.e., for spatial analysis).” EX2002, ¶31. Instead, Cantor’s solid supports and methods are used to answer *whether* biological molecules of interest are present in a *sample nucleic acid* (the “fruit smoothie”) *derived* from solid material such as a tissue (the “fruit tart”). *Id.* A POSA could not have and would not have arranged Cantor’s beads into an array as Petitioner suggests to answer *where* those biological molecules of interest are located because, as explained above, those locations are lost in the process of going from a tissue sample (fruit tart) to sample nucleic acid (fruit smoothie). *Supra* §VII.A.

As Dr. Cantor explains, Petitioner’s obviousness case requires the POSA to modify Cantor to trace back its identification sequences to locations on a substrate (by selective loading of capture probes to locations on the array and/or randomly loading the capture probes and then decoding). EX2002, ¶151. As described above in §VII.B, Cantor does not teach or suggest doing so. It would be

unnecessary and contradictory to Cantor's objective of "efficiently preparing"

copies of nucleic-acid molecules of interest for bulk analysis. EX2002, ¶173.

Likewise, Cantor does not teach or suggest its identification sequences (for assembling large nucleotide sequences from smaller sequence "reads" by identifying overlapping sequences) could provide spatial information. *Id.*, 25, 53-55 (Example 1); EX2002, ¶45. Petitioner's myopic view on how Cantor's beads can be "arranged" is inappropriately narrowed to options for sensor arrays, such as DNA microarrays, which Cantor is not, and can only have been based on hindsight. EX2002, ¶¶180-182.

Petitioner's obviousness case requires a POSA to *further* modify Cantor to switch out Cantor's sample nucleic acid with a tissue section and dispose it on Petitioner's proposed array. But the binding of a target nucleic acid in Petitioner's proposed arrays would happen only by chance or not at all. *Supra* §VII.A. Thus, a POSA would have had neither motivation nor reasonable expectation of success in making such a modification. Such "by chance" hybridization would be at cross purposes to bulk analysis. *Supra* §VII.A.

The Federal Circuit has held that a POSA lacks motivation when petitioner's proposed modification to a prior-art device would undermine the very reason a POSA would have used that device in the first place. *Medtronic, Inc. v. Teleflex Innovations S.a.r.l.*, 69 F.4th 1341, 1348-50 (Fed. Cir. 2023); *Polaris Indus. v.*

Arctic Cat, Inc., 882 F.3d 1056, 1061, 1067-69 (Fed. Cir. 2018). For the reasons discussed above, a POSA would not have modified Cantor in the manner that Petitioner suggests. EX2002, ¶¶180-182. This is supported by the plain language of Cantor itself; of the several dozen uses that Cantor *does* identify for its solid supports and methods, none are for nucleic acid analysis that could provide spatial information. EX1031, 5, 30-52; EX2002, ¶¶70-91; 181.

D. None of Petitioner’s “Background References” (Ground 1) or Armani (Ground 2) Compensate for the Deficiencies of Petitioner’s Obviousness Case

Petitioner relies on these “background references” to supply at least two independent claim limitations: that “the plurality of beads was previously positioned on the substrate in a random pattern” and a “tissue section is disposed on the array.” Pet., 32-36, 38-40, 43-44; *id.* at 42-43 (claim 20). The Board has recognized that doing so—without any explanation as to why a POSA would have combined those references with Cantor—is improper. *Intel Corp. v. PACT XPP Schweiz AG*, IPR2020-00535, Paper 33 at 52–53 (PTAB Aug. 9, 2021), *aff’d Intel Corp. v. PACT XPP Schweiz AG*, Appeal No. 2023-1537, slip op. at 3-4 (Fed. Cir. Dec. 11, 2024).

To the extent Petitioner includes *some* parenthetical explanations (Pet., 35-36, 39-40), this lacks sufficient particularity. The Board has held that simply “provid[ing] a string-citation to many pages of the different, unrelated references

that purportedly comprise the background knowledge art, with very little substantive explanation” is insufficient at institution to “satisfy Petitioner's obligation to explain why a person of ordinary skill in the art would have modified [the prior art] based on the background knowledge in the art.” *Cisco Sys., Inc. v. Video Sols. Pte. Ltd.*, IPR2024-00922, Paper 7 at 13-14 (PTAB Nov. 12, 2024); 37 C.F.R. §42.22(a)(2) (Petition must “includ[e] a detailed explanation of the significance of the evidence”).

But even if the Board considers those “background references,” Petitioner has failed to explain sufficiently for institution how *any* would have led a POSA to “correlate the identification sequence” with a “location on the array” that are known or determined prior to use and *necessarily “identify] a unique location on the substrate”* as Petitioner suggests. Indeed, Petitioner’s “analysis” of the purported background references (e.g., Pet., 33) rest on the bald, unsupported assertion that “a POSA would have known that there are two options to correlate the identification sequence on the nucleic acid attached to a given bead and the bead’s location on the array” (i.e., selective loading or random loading/decoding). Pet., 33; EX1103, ¶¶66-71, 141. Neither Petitioner nor Dr. Puglisi explain why a POSA would “correlate the identification sequence” with a “location on the array” at all, much less be limited to Petitioner’s two options. *Supra* §VII.B; *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016) (a petitioner

does not satisfy its burden by employing “mere conclusory statements,” but “must instead articulate specific reasoning, based on evidence of record, to support the legal conclusion of obviousness”).

Other than Cantor, only a few are described in any detail in the grounds. With respect to Ground 1, claims 1 and 16, Petitioner cites Chee-584 (EX1032), Chee-824 (EX1038), and Barany 1999 (EX1036) when discussing selective loading versus random loading/decoding. Pet., 33-34. What Petitioner does not say, however, is that of the two options, only random loading/decoding could even *possibly* be relevant to the Challenged Claims. EX2002, ¶183. This is because “selective loading” is incompatible with being “immobilized on the substrate in a random pattern” as claimed. *Id.* And the only reference that Petitioner refers to regarding random loading/decoding is Chee-824. But Chee-824 relates to an array sensor that uses on-substrate imaging. *Id.* As discussed in §VII.B, Cantor is an entirely different type of array and a POSA would not have been constrained to Petitioner’s two options for arranging Cantor’s beads because a POSA would have had no reason to “correlate the identification sequence” with a “location on the array” at all.

As to Ground 1, claim 16, Petitioner also discusses Southern. Pet., 39-40. But Southern, like Cantor, does *not* teach contacting a solid support with a *tissue*. Rather, Petitioner’s own quotations from Southern show that Southern contacts

cells (or materials released from cells) with the support: “Thus, when the samples are biological samples comprising *cells*, the step a) of applying the samples to a support may comprise: (i) *applying cells to the support*; then (ii) releasing material from the cells.” Pet. 39-40 (citing EX1033, 2:17-27). As Dr. Cantor explains and supports with evidence, a POSA would understand that cells are not a tissue and do not maintain the spatial relationship of the biological molecules of a tissue.

EX2002 ¶184; *see also* EX1103, ¶¶45-51.

Southern mentions “tissue samples” only once in the context of using the sample to *derive* the cells that are *then* applied to the support. EX1033, 16:26-17:10; EX2002, ¶¶185-187.⁵ Southern teaches that it is “[a]fter *separation* of cells of interest from other components in the *starting* samples” that “the cells of interest can be analysed using the devices of the invention.” *Id.*

Finally, although Southern uses the phrase “spatial arrangement,” that spatial arrangement is of the *samples* themselves on the support, not the spatial arrangement of *target biological molecules* of a tissue. Southern describes an array in which individual samples are placed on a surface at known locations,

⁵ Southern discloses the use of “tissues” in some of its Examples. A POSA would readily understand that these “tissues” are paper tissues used for wetting membranes or blotting excess liquid. *See, e.g.*, EX1033, 40:19; EX2002, ¶187.

creating an array of individual samples. EX1033, 22:20-31; EX2002, ¶185. The array can be used to simultaneously analyze multiple samples (i.e., cells of interest separated from the other components in the tissue) by different methods. EX1033, 26:19-32; EX2002, ¶185. As Dr. Cantor explains, this is similar to how a POSA might arrange test tubes in a particular order in a rack—where each test tube contains a single sample—and then maintain that arrangement of test tubes throughout subsequent testing. EX2002, ¶186. In this case, “[t]he spatial arrangement of the samples is maintained” so that the location of “results of the analysis [may] be match[ed] to individual samples”—i.e., the location of that test tube in the rack. EX1033, 17:6-10; EX2002, ¶186. But spatial location of a tissue’s biological molecule is not maintained. EX2002, ¶186.

Petitioner also cites Shirai for the proposition that a POSA “would similarly have been familiar with methods for releasing and capturing target nucleic acid from cells in a tissue sample disposed on an array, including a bead array.” Pet., 40. But Petitioner fails to mention that Shirai is a *post-filing date* reference not known to a POSA as of the ’030 patent’s filing date. Shirai was filed and published in 2017—*several years after* the ’030 patent’s priority date. EX1024, [21], [22]. Petitioner fails to provide *any analysis whatsoever* of Shirai’s priority

date.⁶ Because Petitioner failed its burden, the Board should disregard Petitioner's arguments about Shirai. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015).

In Ground 2, Petitioner combines Cantor with Armani. Pet., 43. But Petitioner's combination of Cantor and Armani *still presumes* that a POSA would construct Petitioner's array. Pet., 47; *see also* EX2002, ¶189. But even if a POSA would have done so, Ground 2 still suffers from the same critical flaws as Ground 1. *Supra* §VII; EX2002, ¶189.

Armani's methods do not involve using capture probes, contacting capture probes with a tissue section, or using capture probes comprising a nucleic-acid sequence that identifies a unique location on the substrate. *Supra* §III.B. Rather, Armani's methods rely on forcing portions of a tissue sample into discrete wells forming individual samples, performing individual well-by-well PCR reactions on the individual samples in the wells, and then imaging them in place. Armani does

⁶ For example, although Shirai purports to claim priority to a *post-filed* PCT application (EX1024, [63]), Petitioner fails to provide a copy of that document or allege that it provides §112 support for the teachings of Shirai. Shirai's foreign-priority application does not qualify as a pre-AIA 35 U.S.C. §102(e) prior art. *In re Hilmer*, 359 F.2d 859, 862 (1966).

not need to use a coding identifier because Armani's method preserves the physical location of the individual samples during imaging. *Id.*

VIII. CONCLUSION

PO respectfully requests that the Board deny institution of the Petition.

Respectfully submitted,

Date: February 25, 2025

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CERTIFICATION UNDER 37 C.F.R. §42.24(d)

Under the provisions of 37 C.F.R. §42.24(d), the undersigned hereby certifies that the word count for the foregoing Patent Owner's Preliminary Response to Petition totals 13,994, which is less than the 14,000 allowed under C.F.R. §42.24(b)(1).

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CERTIFICATE OF SERVICE

Pursuant to 37 CFR § 42.6(e)(4) and 42.205(b), the undersigned certifies that on February 25, 2025, a complete and entire copy of this Patent Owner's Preliminary Response and accompanying exhibits were provided by email to Petitioner by serving the correspondence email address of record as follows:

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