

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 IPR2024-01289
Patent 10,480,022

PATENT OWNER'S PRELIMINARY RESPONSE

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	THE '022 PATENT CLAIMS A NOVEL, NONOBVIOUS METHOD FOR SPATIAL ANALYSIS	4
III.	PETITIONER'S REFERENCES	9
	A. Cantor (EX1031)	9
	1. Cantor discloses "solid phase nucleic acids" on beads to capture biological molecules of interest.....	10
	2. Cantor's methods analyze "sample nucleic acid," not tissue samples	14
	3. Cantor discloses that beads may be deposited on substrates to facilitate ease of handling for sequencing analysis and manufacturing ...	17
	B. Armani (EX1022).....	17
	C. Frisen (EX1020)	19
IV.	CLAIM CONSTRUCTION	20
V.	LEVEL OF ORDINARY SKILL IN THE ART	20
VI.	INSTITUTION ON GROUND 3 SHOULD BE DENIED BECAUSE PETITIONER'S PRIORITY ATTACK IS LEGALLY AND FACTUALLY INSUFFICIENT	20
	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.....	21
	1. The '022 patent's priority chain is intact	22
	2. The disclosure of the '124 provisional was incorporated by reference into each of the '616, '661, and '235 applications	24
	3. PO's filing of a substitute specification was proper	26
	B. Petitioner's Priority Attack is Factually Insufficient Because the '124 Provisional Provides Written-Description Support for the Challenged Claim Elements	27

1. The '124 provisional supports delivering a tissue sample to a previously generated array of bead-affixed probes	27
2. The '124 provisional supports contacting a plurality of beads with a tissue section “such that the binding agent interacts with the biological molecule”	33
3. The '124 provisional supports “providing a plurality of beads, wherein the plurality of beads...(i) comprises a coding identifier having a nucleic acid sequence”	36
C. Frisen is Not Prior Art	40
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.....	41
A. Cantor Fails to Teach Contacting a Plurality of Beads With a “Tissue Sample”	43
1. Cantor does not teach contacting beads with a “tissue sample”	44
2. Cantor does not teach or suggest contacting a tissue sample with beads at known locations to obtain spatial information	50
B. In Petitioner’s Proposed Arrays, the “Coding Identifier” Does Not Inherently Render the Challenged Claims Obvious.....	54
1. 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	56
2. 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.....	60
3. Using Petitioner’s array with a tissue sample would not necessarily provide the spatial location of a biological molecule because hybridization would not necessarily occur.....	63
C. The Challenged Claims Would Not Have Been Obvious Because a POSA Would Not Have Been Motivated to Use Cantor’s Arrays With a Reasonable Expectation of Success	69

D. None of Petitioner’s “Background References” (Ground 1) or Armani (Ground 2) Compensate for the Deficiencies of Petitioner’s Obviousness Case	72
VIII. CONCLUSION.....	77

LIST OF EXHIBITS

Exhibit Number	Description
EX2001	Declaration of Paul Ehrlich in Support of Pro Hac Vice Admission
EX2002	Declaration Charles R. Cantor
EX2003	Curriculum Vitae of 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	PCR PRIMER: A LABORATORY MANUAL (Carl W. Dieffenbach and Gabriela S. Dveksler, eds. (2003)), Section 2, “Sample Preparation”
EX2010	PCR PRIMER: A LABORATORY MANUAL (Carl W. Dieffenbach and Gabriela S. Dveksler, eds. (2003)), Chapter 19, “Reverse Transcriptase In Situ PCR”

Per 37 C.F.R. § 42.107(a), Patent Owner (“PO”)¹ submits this Preliminary Response to the Petition for Inter Partes Review (“IPR”) of U.S. Patent No. 10,480,022 (“’022 patent”) filed by Curio Bioscience, Inc. (“Petitioner” or “Curio”).

I. INTRODUCTION

The Petition constructs a house of cards built on misdirection and mistaken assumptions. Petitioner relies on isolated quotations and pictures that, at first blush, make the methods claimed in the ’022 patent appear obvious. But closer inspection of the evidence reveals that the Petition skips over relevant teachings of the ’022 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 arrived at the claimed invention if she constructed the arrays proposed by Petitioner.

Petitioner steps just one application back in the ’022 patent’s priority chain to assert that the claims of the ’022 patent lack written-description support. But Petitioner fails to grapple with the fact that each and every application in that priority chain—the application leading to the ’022 patent, the parent application,

¹ Consistent with Petitioner’s use, “PO” collectively refers to real-party-in-interest 10x Genomics, Inc. (“10x”) and Prognosys Biosciences Inc. (“Prognosys”).

and grandparent application—expressly incorporated by reference the disclosure of the provisional application. The provisional explicitly describes the invention Petitioner calls “Figure A.”

PO *also* submitted a substitute specification during prosecution that included text from the provisional. Despite Petitioner’s criticisms, PO had the right to submit a substitute specification and followed every Office rule in doing so. Petitioner’s misdirection—accusing PO of foul play and ignoring the incorporation of the provisional—attempts to hide the fact that the claim limitations have written-description support in the provisional application. And because the challenged claims have a priority date before Frisen (Petitioner’s §102 reference), Frisen does not anticipate.

Petitioner’s obviousness challenges continue the pattern of misdirection and mistaken assumptions. All of Petitioner’s arguments *depend* on the assertion that Cantor (Petitioner’s §103 reference) teaches using a “tissue” with its beads. But 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 the tissue, making it impossible for Cantor’s bulk-analysis methods to provide spatial analysis. Dr. Cantor’s

testimony and the Cantor application itself 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 spatial location of a biological molecule of a tissue sample. But Cantor teaches that its beads and corresponding 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). And, because Cantor has *nothing* to do with spatial analysis, it follows that *nothing* in Cantor teaches or suggests that the location of a bead and its corresponding identification sequence is known (it isn’t) or *even* needs to be known (it doesn’t in bulk analysis).

Similarly, Petitioner mischaracterizes Cantor’s description of arrays. As Dr. Cantor explains, the sequencing and other processes used in bulk analysis are easier when solid supports are arranged in an array on a substrate. Rather than manipulating 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. Putting Cantor’s beads on a substrate does not teach or suggest spatial analysis.

Dr. Charles Cantor himself—the sole inventor of Cantor and the “noted geneticist” to whom Petitioner refers in its Introduction—testifies that none of

Petitioner's assumptions have support in either Cantor or the knowledge of a POSA as of the filing date. Dr. Cantor explains that, *even if* a POSA set up an array in the manner Petitioner urges *and* made the same assumptions Petitioner makes, the array would *not* necessarily provide the spatial information Petitioner says they would. Indeed, hybridization between Cantor's probes and a biological molecule in a tissue sample in the arrangement concocted by Petitioner would occur only by *pure chance if at all*. And pure chance falls far from the satisfying the demanding standard of inherent obviousness.

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 use Cantor's bead collections—which did not provide or seek to provide spatial information—to obtain spatial location of a biological molecule of a tissue sample, nor a reasonable expectation of success.

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

II. THE '022 PATENT CLAIMS A NOVEL, NONOBVIOUS METHOD FOR SPATIAL ANALYSIS

The '022 patent discloses assays for analyzing spatial location(s) of

biological molecules in a tissue sample. EX1001, 1:12-15, 57-62; EX2002, ¶15.

Before the '022 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, for example, 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 methods on the one hand, and bulk-analysis methods 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 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.*



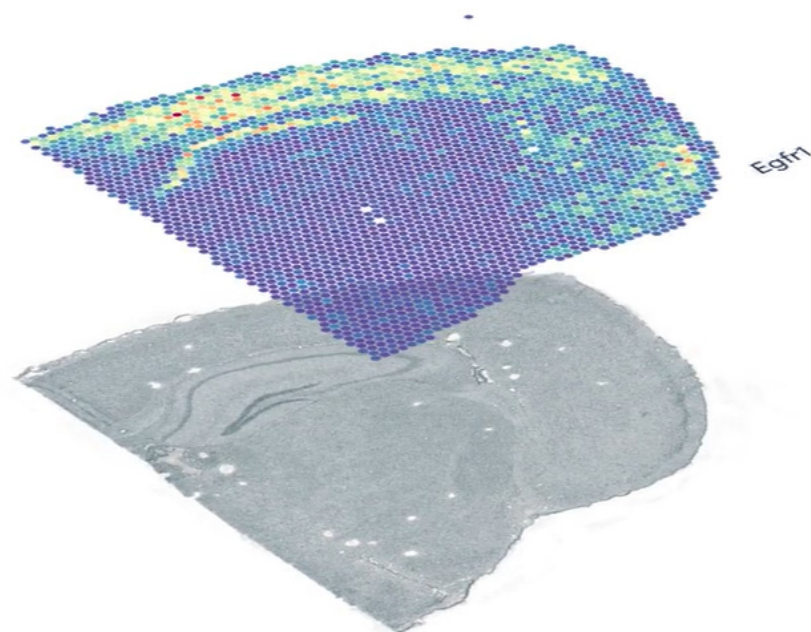
Fruit Smoothie

Thus, with a bulk-analysis experiment, 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 '022 patent, however, answers both questions. *Id.*

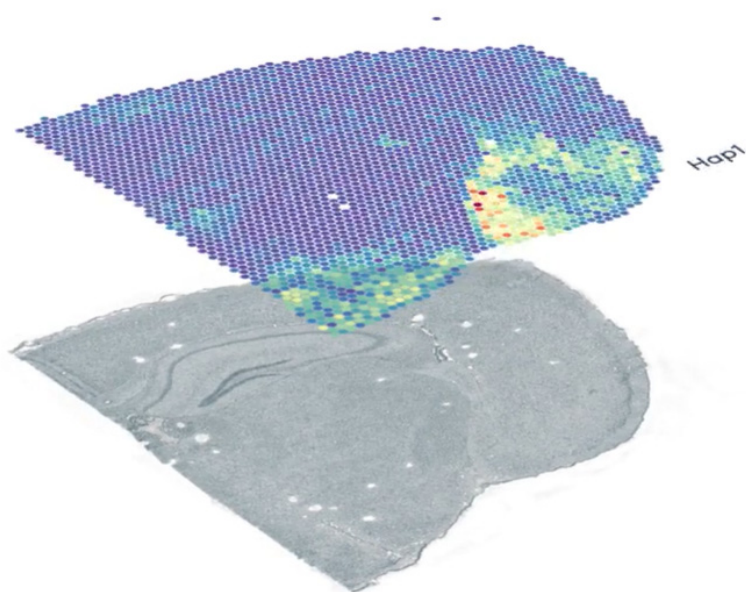
The inventions described in the '022 patent addressed the “need for reproducible, high-resolution spatial maps of biological molecules in tissues.” *Id.* 1:60-62; EX2002, ¶¶21-26. The '022 patent's assays utilize a spatial-encoding scheme utilizing molecule-specific binding agents together with coding identifiers to provide a practical and cost-effective determination of information on multiple biological molecules, including specific position information of such molecules in a biological sample (e.g., tissue). EX1001, 20:29-50; 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 '022 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., the mRNA of all expressed genes in the genome). *Id.* An example of the gene-expression pattern across a tissue for one gene (EGFR1) is depicted below. The upper image is a “heatmap” depicting EGFR1 expression in various parts of the tissue sample and

the lower image is 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 the 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. *Id.*, codes [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.*

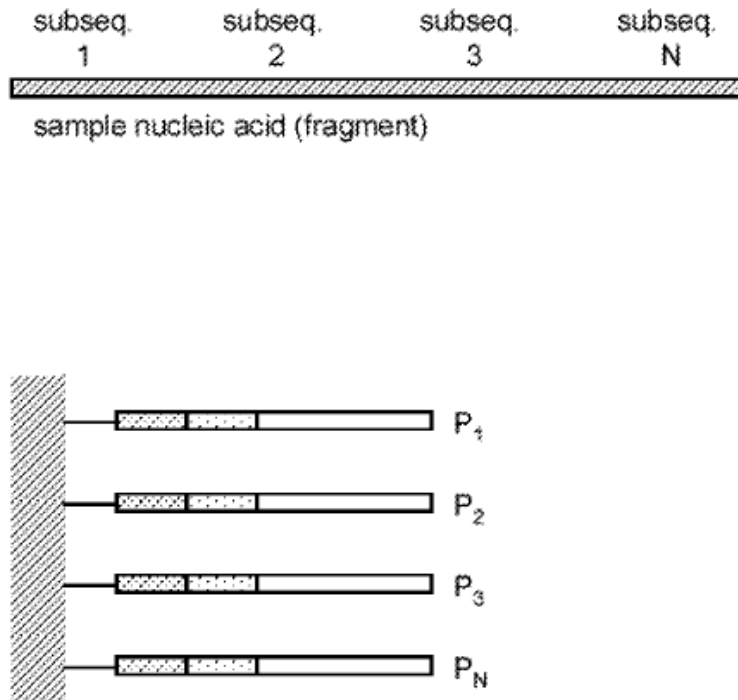


Figure 1A excerpt

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



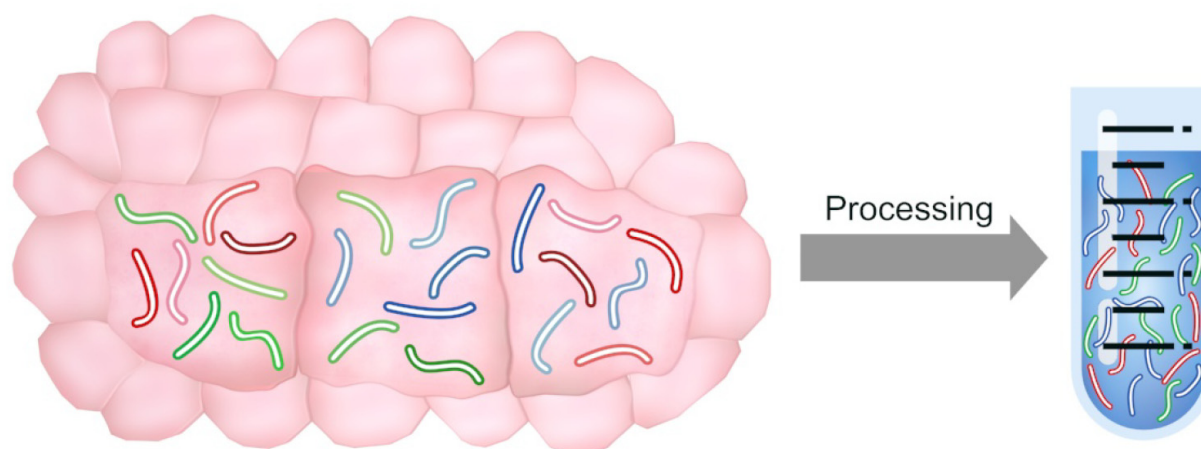
Figure 1C excerpt

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.*

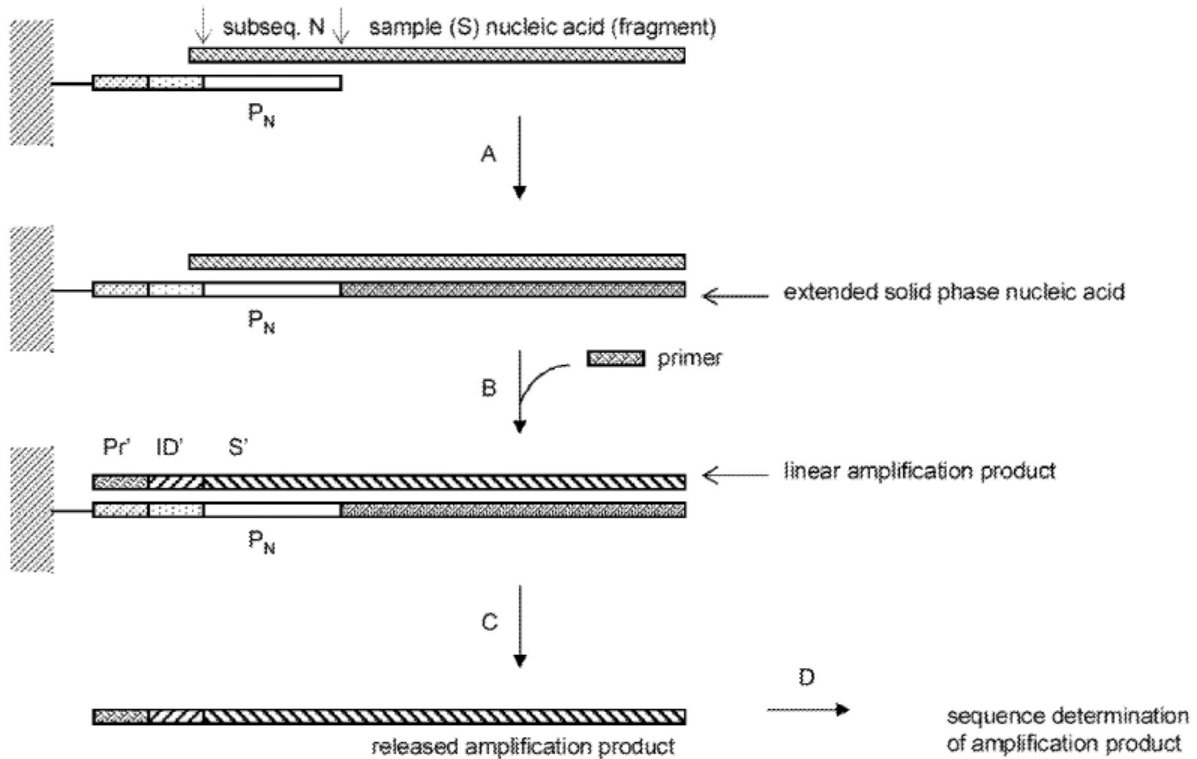
2. Cantor's methods analyze "sample nucleic acid," not tissue samples

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 D and C, the linear amplification product is released from the solid support into solution for further sequencing and analysis. *Id.*

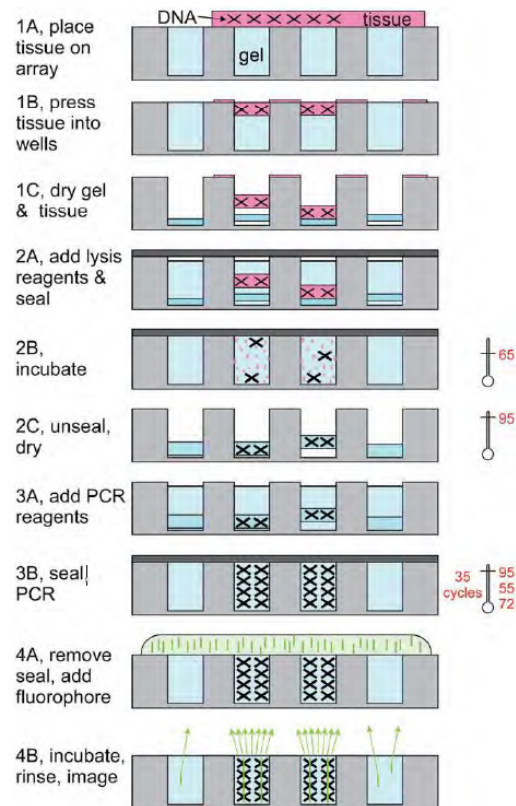
3. Cantor discloses that beads may be deposited on substrates to facilitate ease of handling for sequencing analysis and manufacturing

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, ¶¶62-70. The “array may contain one solid support species or multiple solid support species from a collection.” EX1031, 4, 17; EX2002, ¶69. 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, ¶69. 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, ¶69. 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, ¶93. Armani discloses a

method for 2D-PCR. EX1031, 3526; EX2002, ¶¶94. Figure 2, reproduced below, provides a step-by-step diagram of Armani's 2D-PCR. EX1031, 3527; EX2002, ¶¶95-99.



Armani starts with sectioning a tissue and transferring it to a multi-well array device (step 1A). *Id.* In steps 1B-1C, the tissue is physically pressed into the wells of the array and dried in agarose gel. *Id.* Each well therefore contains only sub-portions of the tissue sample immobilized in the well. *Id.* Any genetic information in those portions of the tissue sample that does not end up in a well is lost. *Id.* 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. *Id.* 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). *Id.* In steps 4A-4B, intercalating fluorophore is incubated in each well and the resulting fluorescence is imaged. *Id.* The intercalating fluorophore non-specifically 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 the step of contacting a plurality of beads with a tissue section such that the binding agents interact with nucleic acids of the tissue sample.” Pet. 49. But Armani does not disclose or contemplate using beads, contacting beads with a tissue section, or using binding agents comprising a coding identifier to interact with nucleic acids of the tissue sample. EX2002, ¶102.

As noted in the '022 patent, Armani’s methods, unlike the claimed methods, have “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.” EX1001, 1:50-56; EX2002, ¶93.

C. Frisen (EX1020)

Frisen is a WIPO publication titled “Method and Product for Localised or Spatial Detection of Nucleic Acid in a Tissue.” EX1020, code [54]. 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.*, code [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 "binding agent" are irrelevant to here, PO disagrees that the "specific binding" disclosed in the '022 patent does not encompass "the interaction of poly-T probes with the poly-A tails present on typical mRNA molecules." Pet., 20-21.

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 '022 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., 54-55. Each application in the priority chain of the '022 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 in the priority chain properly incorporated the disclosure of the '124 provisional by reference.

Petitioner ignores that PO met all the legal requirements for priority. On the facts, an analysis of the '124 provisional's disclosure—which Petitioner largely ignores—shows that it provides written-description support for the elements of claim 1 that Petitioner asserts are missing. Pet., 55-56.

Because the Challenged Claims of the '022 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 a 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 ’022 patent’s priority chain is intact

The ’022 patent issued from Appl. No. 16/276,235 (“the ’235 application,” EX1010) on November 19, 2019. EX1001, codes [21], [22], [45]. The ’235 application is a continuation of Appl. No. 15/187,661 (“the ’661 application” or “parent,” EX1011), which in turn is a continuation of Appl. No. 13/080,616 (“the ’616 application” or “grandparent,” EX1012). EX1001, code [63]. The ’022 patent claims priority through these applications to provisional Appl. No. 61/321,124 (“the ’124 provisional,” EX1009). For ease of reference, PO reuses Petitioner’s table showing the priority chain of the ’022 patent back to the ’124 provisional:

’022 Patent Priority Documents	Filing Date	Exhibit
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., 54. Petitioner does not and cannot dispute that each application in the ’022

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

patent's priority chain included a "specific reference" to the earlier-filed application under §§119(e) and 120. Pet., 54-55.

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; *see also 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 (grandparent) application. The '616 application was filed as a utility application on April 5, 2011, one year after the co-pending '124 provisional. EX1012, 1-3. The '616 application claimed priority under §119(e) to the '124 provisional in an ADS by number and familial relationship. *Id.*, 2.

The '661 (parent) application. The '661 application was filed as a continuation of the '616 application on June 20, 2016, while the '616 application was pending. EX1011, 48. The '661 application claimed priority to the '616 application under §120 and the '124 provisional under §119(e) in an ADS by numbers and familial relationships. *Id.*, 61-62.

The '235 application. The '235 application was filed as a continuation of

the '661 application on February 14, 2019, while the '661 application was pending. EX1010, 1-3. The '235 application claimed priority to the '661 and '616 applications under §120, and the '124 provisional under §119(e), by numbers and familial relationships in an ADS. *Id.*, 54-55.

2. The disclosure of the '124 provisional was incorporated by reference into each of the '616, '661, and '235 applications

Each of the '616, '661, and '235 applications expressly and unambiguously incorporated by reference the disclosure of the '124 provisional. “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).

The '616 (grandparent) application. The '616 application's specification incorporated the '124 provisional into the specification by reference:

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of United States Provisional Patent Application No. 61/321,124, filed April 5, 2010 and is incorporated herein by reference.

EX1012, 5.

The '661 (parent) application. The '661 application's specification as filed incorporated the '124 provisional into the specification by reference:

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of United States Provisional Patent Application No. 61/321,124, filed April 5, 2010 and is incorporated herein by reference.

EX1011, 2.

The '235 application. The '235 application's specification as filed incorporated the '124 provisional into the specification by reference:

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of United States Provisional Patent Application No. 61/321,124, filed April 5, 2010 and is incorporated herein by reference.

EX1010, 6.

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 (cleaned up). 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).

3. PO's filing of a substitute specification was proper

Not only did PO incorporate the disclosure of the '124 provisional into the '235 application by reference, PO also submitted a substitute specification that amended the '235 application to include text from the '124 provisional:

Amendments to the Specification:

The present application claims priority to and incorporates by reference the entire text of U.S. Provisional Application Serial No. 61/321,124, filed April 5, 2010. The present specification has been amended herein to include text from U.S. Provisional Application Serial No. 61/321,124. A marked-up and clean copy of the substitute specification in accordance with 37 C.F.R. § 1.125 is provided herewith.

EX1010, 69.

The Office allows the filing of a substitute specification under 37 C.F.R. §1.125 “[i]f the number or nature of the amendments...renders it difficult to consider the application, or to arrange the papers for printing or copying.” Here, PO's substitute specification simply included text from the incorporated '124 provisional, making it easier to consider the application. PO complied with §1.125 by submitting both clean and marked-up copies of the substitute specification. *See* EX1010, 69 (preliminary amendment), 76-124 (marked-up copy), 127-170 (clean copy).

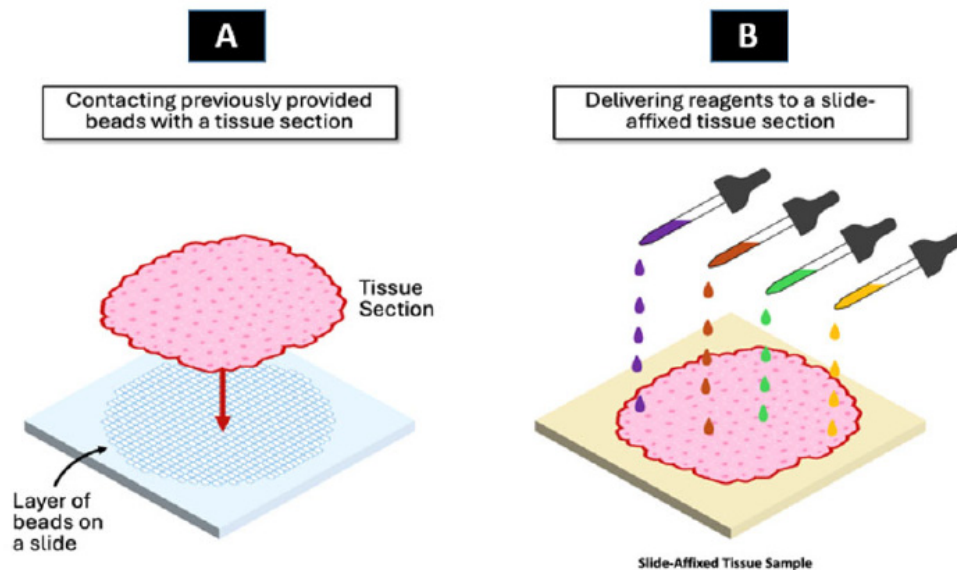
B. Petitioner’s Priority Attack is Factually Insufficient Because the ’124 Provisional Provides Written-Description Support for the Challenged Claim Elements

The Challenged Claims are entitled to the provisional application’s priority date. Petitioner identifies “three key elements of independent claim 1” that allegedly lack written-description support. Pet., 54-65. 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 ’235 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 ’235 application and all intervening applications. The ’124 provisional provides written-description support under §112 for each challenged claim element and, accordingly, Petitioner’s priority challenge fails.

1. The ’124 provisional supports delivering a tissue sample to a previously generated array of bead-affixed probes

The ’124 provisional supports contacting bead-affixed probes mounted on a substrate surface (e.g., slide) with a tissue sample. Petitioner creates an illustration (reproduced below) depicting an allegedly “stark contrast between the approach PO now claims (Figure A) and the approach actually described in the specification (Figure B).” Pet., 2. 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.*



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., 56-61. But the '124 provisional—which was expressly incorporated by reference into the '661 application—provides written-description support for delivering a tissue sample to a pre-generated array of bead-affixed probes (Figure A). EX2002, ¶¶112-114.

Both Petitioner and Dr. Puglisi acknowledge that the '124 provisional discloses bead arrays, citing paragraph 18. Pet., 60; EX1100, ¶268; EX2002, ¶115. But Petitioner wrongly argues that this passage “give[s] no indication that they

refer to providing beads in an array as claimed, as opposed to depositing beads comprising a binding agent to a tissue sample that was previously affixed to a solid support using the disclosed ‘reagent delivery systems.’ Pet., 60.

Petitioner misconstrues paragraph 18 by failing to read it in context of preceding paragraphs 15-17. EX2002, ¶116. Paragraph 18 states that, in one embodiment of the invention, immobilizing binding agents (including nucleic acid binding agents) are “provided in known locations on the *substrate surface*.”³ EX1009, ¶18; EX1001, 22:7-18; EX2002, ¶116. That “substrate surface” is described in the preceding paragraphs as having “wells or channels.” EX1009, ¶17; EX1001, 21:65-22:6; EX2002, ¶116. As Dr. Cantor explains, a POSA would understand that a tissue sample *does not* have features like wells or channels. EX2002, ¶117. Instead, as Dr. Cantor explains and supports with evidence, “wells or channels” are features of manufactured solid supports. EX2002, ¶117 (citing EX1031). Thus, a POSA would understand that the “substrate surface” discussed in paragraphs 15-18 of the ’124 provisional is *not* a tissue sample, but instead is a manufactured solid support. *Id.*

Moreover, paragraphs 15-18 of the ’124 provisional explain that binding agents are immobilized onto beads that are *then* placed on the substrate surface, for

³ All emphasis added throughout unless otherwise noted.

example in wells or channels. EX2002, ¶116; *see also* EX1009, ¶17; EX1001, 21:65-22:6 (“In another aspect, the binding agents are immobilized onto beads or other separate structural elements that are *then* provided in known locations on the substrate surface.”). 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, ¶116.

Even more passages in the ’124 provisional discuss the use of these types of pre-generated bead arrays—with beads immobilized directly or indirectly onto a “substrate surface.” EX2002, ¶118. One passage does so in the context of peptide binding agents. EX1009, ¶21; EX1001, 22:37-47; EX2002, ¶118. Another does so in the context of chemical binding agents. EX1009, ¶22; EX1001, 22:48-57; EX2002, ¶118.

The ’124 provisional also discloses assays and assay systems “comprising one or more agents provided in defined spatial patterns *on a substrate surface....*” (EX1009, ¶7; EX1001, 20:29-33; EX2002, ¶122) and that in some cases “the encoding scheme employs limited reagent delivery to the spatial patterns *on the substrate surface....*” (EX1009, ¶8, EX1001, 20:63-65; EX2002, ¶122). Indeed, 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, EX1001 21:51-55; EX2002, ¶122; *see also* EX1009, ¶¶ 47-48; EX1001, 23:52-24:18 (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, ¶123. Again, once a pre-generated bead array is constructed, as Dr. Cantor explains, it would then be contacted with a tissue sample as depicted in “Figure A” to carry out the types of spatial-distribution analyses described in the ’124 provisional. EX2002, ¶¶118-123.

Aside from mischaracterizing the bead-related disclosures of the ’124 provisional and ignoring other pre-generated array teachings, Petitioner also argues that a “washing” step would “not make sense” in the context of probes covalently bound to beads. Pet., 57. 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 9, line 53 to column 10, line 10 of the ’022 patent) elaborate on *additional* types of assays also disclosed in the ’022 patent, however, is irrelevant. As Dr. Cantor explains, these types of assays are *in addition* to the pre-generated bead arrays discussed above. EX2002, ¶¶120-121.

Likewise, Petitioner cites to other portions of the '661 application describing additional embodiments. Pet., 58-59 (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 taking into account the incorporation by reference of the '124 provisional's disclosure. None of these figures and passages in the '661 application negate that the '124 provisional teaches a pre-generated bead array ("Figure A"). EX2002, ¶¶120-121.

Petitioner does not and cannot 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 '022 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).⁴

The '124 provisional (and, therefore, the '616, '661, and '235 applications) provides written-description support for "delivering a tissue sample to a previously generated array of bead-affixed probes." EX2002, ¶111. Petitioner's argument to

⁴ 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.

the contrary fails.

2. The '124 provisional supports contacting a plurality of beads with a tissue section “such that the binding agent interacts with the biological molecule”

As shown above, the '124 provisional discloses contacting a plurality of beads with a tissue sample. And, as Dr. Cantor testifies and supports with evidence, techniques for preparing tissues to interact with biological molecules were well known to a POSA by April 5, 2010, and therefore would not have needed to be explained to a POSA in the specification. EX2002, ¶¶125-126 (citing EX2009, EX2010). Petitioner's argument that the '661 Application fails to support the claims because it does not disclose these well-known techniques is wrong. *See* Pet., 62.

A “patent need not teach, and preferably omits, what is well known in the art.” *Falkner v. Inglis*, 448 F.3d 1357, 1365 (Fed. Cir. 2006) (cleaned up); *see also Capon v. Eshhar*, 418 F.3d 1349, 1358 (Fed. Cir. 2005) (“The ‘written description’ requirement must be applied in the context of the particular invention and the state of the knowledge.”); *Zoltek Corp. v. United States*, 815 F.3d 1302, 1308 (Fed. Cir. 2016) (“The written description need not include information that is already known and available to the experienced public.” (cleaned up)). Likewise, the Office affirmatively advises applicants that when processes are “conventional and generally widely known in the field of the invention described, and their exact

nature or type is not necessary for an understanding and use of the invention by a person skilled in the art, they should not be described in detail.” MPEP §608.01(a).

Both Petitioner and Dr. Puglisi *agree* with Dr. Cantor stating: “techniques for local release of nucleic acids or other biological molecules from tissue samples for capture on probes in bead or other arrays were known” to a POSA at the time the ’124 provisional was filed. Pet., 62-63; EX1100, ¶273; EX2002, ¶127. As Dr. Cantor elaborates, conventional techniques such as *in situ* hybridization (referenced in the ’124 provisional) have been around since the 1970s and would not need to have been explained to a POSA circa 2010. EX2002, ¶126; EX1009, ¶3. The ’124 provisional itself points a POSA to “standard laboratory manuals” that describe such conventional techniques. *Id.* One of those manuals includes detailed protocols for liberating nucleic acids from a variety of different samples, including the local release of nucleic acids from tissue samples for *in situ* analysis. *Id.*; EX2009; EX2010.

Instead of addressing the caselaw on point, Petitioner deflects by calling these well-known methods merely “obvious” and “insufficient to establish possession of the claimed invention.” Pet., 62-63 (citing *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1349 (Fed. Cir. 2013)). But *Novozymes* and similar cases analyzed the written description of a *broad genus of*

unpredictable species. This is not a case where the claims recite a specific species of a broad genus of unpredictable compounds; instead, the '124 provisional takes advantage of the **undisputed fact** that certain laboratory techniques (i.e., techniques for “local release of nucleic acids or other biological molecules from tissue samples for capture on probes in bead or other arrays”) were well known in the art. Pet., 62-63; EX1100, ¶273; EX2002, ¶¶127-129. The Board should reject Petitioner’s attempt to mischaracterize the facts here.

Petitioner’s argument that the '022 patent’s criticism of Armani undercuts written-description support fares no better. Pet., 62 (citing EX1011, ¶4). As Dr. Cantor explains, a POSA would have understood that passage to criticize the **low-spatial resolution** that Armani’s 2D-PCR provides:

Certain PCR assays in a 2D format preserve spatial information (Armani, M et al (2009) *Lab on a Chip*, 9(24): 3526-34 (2009)), **but these methods have 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.

EX1009, ¶4. EX2002, ¶131.

Armani’s low-spatial resolution results from physically pressing the tissue into the individual wells of the array. Therefore, each discrete well contains **only sub-portions of the tissue** immobilized in that well. EX1022, 3527; EX2002 ¶95. As Dr. Cantor explains, spatial information relating to genetic information in those

portions of the tissue that are not immobilized in an individual well is lost.

EX2002, ¶96.

This criticism of Armani has nothing to do with the POSA's knowledge of laboratory techniques. EX2002, ¶130. Methods for preparing a tissue "such that the binding agent interacts with the biological molecule" were well known and conventional at the time of the '124 provisional. Petitioner's argument should be rejected. EX2002, ¶132.

3. The '124 provisional supports "providing a plurality of beads, wherein the plurality of beads...(i) comprises a coding identifier having a nucleic acid sequence"

The '124 provisional expressly teaches that the disclosed assays and methods use both binding agents and coding identifiers, and that the coding identifiers are not superfluous. EX2002, ¶133. 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; EX1001, 20:37-46; EX2002, ¶134. The unique encoding scheme allows "multiple molecules ***and their respective multiple locations*** to be identified in a single system." *Id.* And the presence or absence and specific positional information of the biological molecules is based on detection of both the

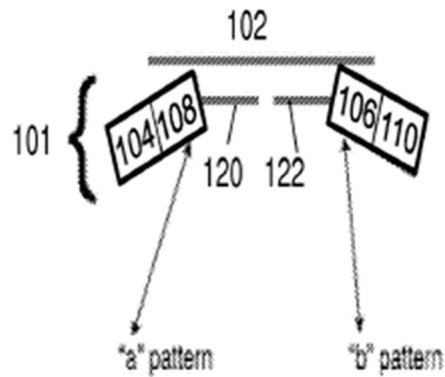
binding agent, the coding identifier, and the knowledge of the location of the binding agents (and thus coding identifier) on the substrate surface. EX1009, ¶¶7, 18; EX2002, ¶135.

A POSA would have understood that the '124 provisional provides written-description support for embodiments in which the binding agents attached to the beads are nucleic acids having a coding identifier. EX2002, ¶¶130-137. 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; EX1001, 22:7-18; EX2002, ¶137. The '124 provisional teaches that, in this embodiment, the spatial-encoding scheme is decoded using “nucleic acid sequencing, and preferably next-generation sequencing.” EX1009, ¶18-19; EX1001, 22:19-23; EX2002, ¶138. 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 also a nucleic acid. EX2002, ¶139. Otherwise, the coding identifier could not be sequenced using nucleic-acid sequencing. *Id.*

In this way, Petitioner’s logic—that coding identifiers are superfluous—is wrong on its face. Pet., 63-64. Petitioner’s logic is that “[b]ecause the '124 Provisional’s disclosures pertaining to beads involve providing them at known locations,” it follows that “a POSA would have understood these disclosures to

have obviated the need for the use of coding identifiers as claimed in the '022 Patent.” Pet., 64. But if a nucleic-acid binding agent was attached to a bead at a known location on the substrate surface *without* a coding identifier, a POSA would have understood that it would have been impossible to obtain “specific positional information” for captured target nucleic acids by the nucleic-acid sequencing disclosed in the '124 provisional. EX2002, ¶140. This is because without 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 Petitioner suggests, ‘obviate[] the need for the use of coding identifiers.’” EX2002, ¶133.

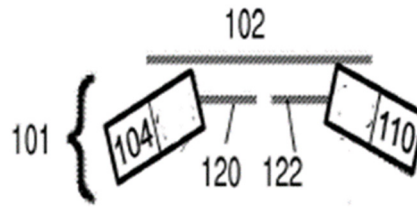
This is illustrated in Figure 1 of the '124 provisional (corresponding to Figure 4 of the '022 patent), partially excerpted below. In Figure 1, both the binding agent and the coding identifier are part of the same molecule. EX1009, ¶46; EX2002, ¶¶141-142. The coding identifiers (106 and 108) are associated with the binding agents (120 and 122) that capture the target nucleic acid (102). EX1009, ¶46; EX1001, 22:34-51; EX2002, ¶141.



The coding identifiers are also associated with universal priming sites (104 and 110) that *facilitate sequencing*—again, the preferred method in the '124 provisional for decoding spatial locations. EX1009, ¶¶18, 19, 46; EX1001, 23:7-24; EX2002, ¶142. 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 surface* 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) were removed (as shown in the modified version of Figure 1, below), *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. EX2002, ¶¶143-145. 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 the coding identifier, the specific position on the substrate surface 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 surface. *Id.* Petitioner’s arguments otherwise lack evidentiary support and are contrary to the well-known sequencing techniques in the art. EX2002, ¶139. 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, code [30]. This date is after the ’022 patent’s priority date of April 5, 2010. Because Frisen is not prior art and Petitioner cannot cure this defect in the Petition 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**

Petitioner has not shown a reasonable likelihood that it would prevail in proving the obviousness of any challenged claim on either Ground 1 (Cantor alone) or Ground 2 (Cantor and Armani).

All of Petitioner's arguments hinge on the premise that Cantor expressly teaches contacting a "tissue sample" with its beads. This is wrong. Cantor does not teach or suggest contacting its beads with a "tissue sample," as required by the 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.

Expanding on this first error, Petitioner then argues that, because Cantor's beads can be placed on a substrate, the beads are at a "known location" and Cantor's identification sequence identifies the location where the bead interacted with the tissue sample. But Cantor says nothing about placing beads in a "known location" on a substrate because Cantor's beads contact a sample nucleic acid, which itself has no spatial information. Rather, Cantor states that beads are arranged on the substrate in a manner suitable for the sequencing and manufacturing processes disclosed.

Petitioner doesn't stop its faulty analysis there, arguing that because a tissue sample contacts a bead at a known location and each bead has a unique identification sequence, then Cantor's identification sequence necessarily identifies the known location. But Cantor expressly teaches that its beads and corresponding identification sequences facilitate sequence analysis of a sample nucleic acid to determine *if* a particular nucleic acid of interest was present in a sample (but not where in the sample). Cantor has *nothing* to do with spatial analysis, and *nothing* in Cantor teaches or suggests that the location of a bead and its corresponding identification sequence is known (it isn't) or *even* needs to be known (it doesn't in bulk analysis). Petitioner's obviousness arguments all hinge on these false bases and institution on Grounds 1 and 2 should be denied.

But even if a POSA would have constructed a bead array on a substrate and contacted it with a tissue sample, as Petitioner proposes, both Grounds 1 and 2 would still fail. Petitioner's obviousness grounds are predicated on an unsaid "inherent obviousness" theory. Although not expressly using that term, Petitioner nonetheless argues that Cantor's identification sequences would *necessarily* provide the spatial location of a biological molecule of a tissue sample. But, for reasons described below, Cantor's identification sequences would *not* "necessarily" provide spatial location information. Instead, obtaining any spatial information would be by *pure chance*, which is not enough to meet the exacting

standard of inherent obviousness.

And 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 bead collections—which did not provide or seek to provide spatial information—to obtain the spatial location of a biological molecule of a tissue sample, nor a reasonable expectation of success in doing so. 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.

Finally, nothing in Armani or any “background reference” compensates for the deficiencies identified 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 Contacting a Plurality of Beads With a “Tissue Sample”

Cantor's solid supports and methods are directed to bulk analysis of “sample nucleic acid”—*not* solid material such as tissue. The Challenged Claims, however, are directed to “method[s] for determining a spatial location of a biological molecule of *a tissue sample*.” Claim 1(preamble). They require “contacting the

plurality of beads with *the tissue sample*.” Claim 1(b). Petitioner’s arguments about the claims are predicated on Cantor teaching “that its sample may be ‘a solid material such as a tissue...or a biopsy.’” Pet. 31 (quoting EX1031, 6). But Cantor does *not and cannot* teach a POSA to use a tissue with its beads and methods because spatial analysis does not matter to Cantor at all. Petitioner’s grounds of unpatentability based on Cantor fails.

1. Cantor does not teach contacting beads with a “tissue sample”

Cantor does not teach or suggest contacting its beads with a tissue sample. Petitioner’s entire argument about “tissue sample” 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 binding agents with a “tissue sample.” Pet. 31; *see also id.* at 23, 28. But this argument conflates Cantor’s “sample nucleic acid” (which is mixed with Cantor’s 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, 147-151.

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:

- “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.

* * *

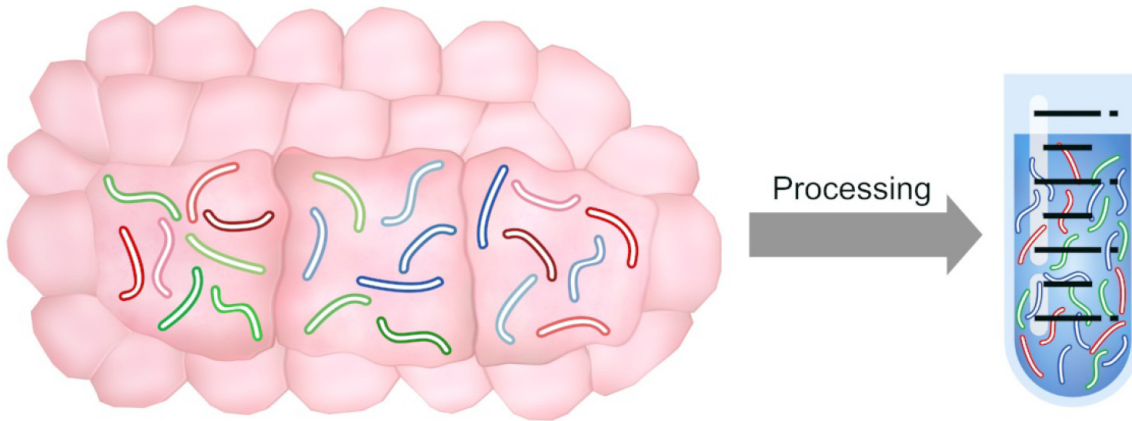
Dr. Cantor explains that a POSA would have understood that, to carry out the steps of Cantor’s methods, the POSA would *first* have to derive the sample nucleic acid from a sample or source. EX2002 ¶35; see EX1031, 5. *Only then* could a POSA continue to the next step of “preparing a mixture comprising sample nucleic acid and a solid support.” EX1031, 1; EX2002, ¶148.

Specifically, Cantor states that “[s]ample nucleic acid may be *derived* from one or more *samples* or sources.” EX1031, 5; EX2002, ¶¶35, 149. 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, ¶¶36, 150. 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.

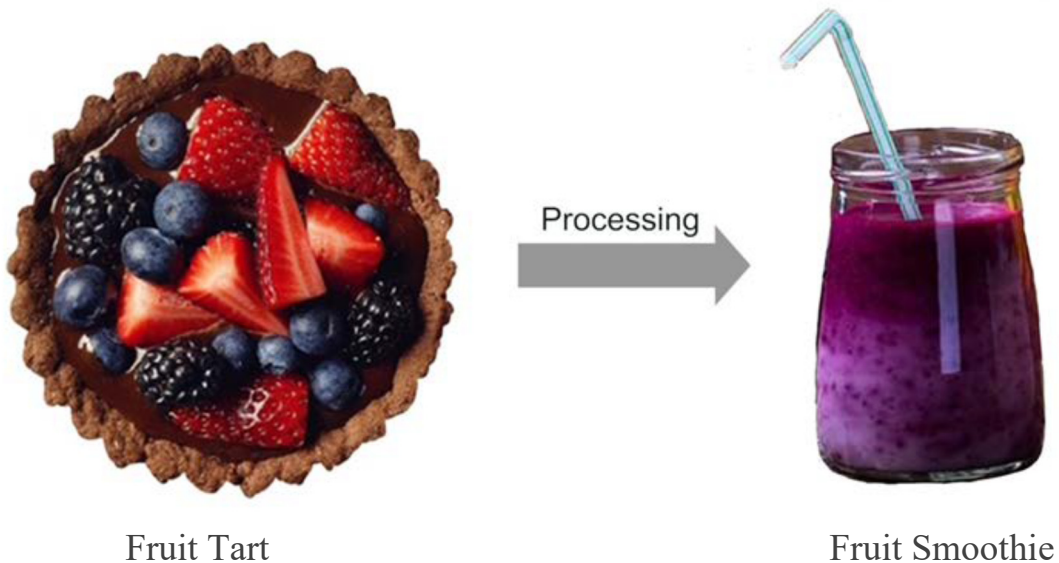
Once the “sample nucleic acid” is derived from a sample or source, a POSA would have understood that the “sample nucleic acid” exists in the form of a homogenized (blended) mixture that **does not retain** the original spatial distribution of nucleic acids that a solid material such as a tissue would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

processing of solid tissue (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 '022 patent's claimed "tissue sample" and Cantor's "sample nucleic acid" can be analogized to the difference between the fruit tart and the fruit smoothie discussed above. *Supra* §§II, III.A; EX2002, ¶¶18-20, 36-38, 150.



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, 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 sample 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. 31 (citing EX1100, ¶149). 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, ¶149. In any event, the sample nucleic acid, whether derived from tissue or any other biological sample, cannot provide any information about spatial location. EX2002, ¶150.

Cantor does not teach contacting the “tissue sample” with beads as required by the Challenged Claims. 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 Cantor’s solid supports.

EX1031, 1. For this reason, Ground 1 fails.

2. Cantor does not teach or suggest contacting a tissue sample with beads at known locations to obtain spatial information

Not only does Cantor not teach contacting a “tissue sample” with beads, but Cantor comes nowhere close to suggesting that its beads could be contacted with a tissue sample to identify spatial location. 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 ¶¶152-155. Petitioner argues, however, that Cantor’s arrays could *also* provide spatial location because Cantor’s identification sequences could allegedly be traced back to a bead at a unique X,Y location on an array. *E.g.*, Pet. 3-4, 33-34. That is incorrect.

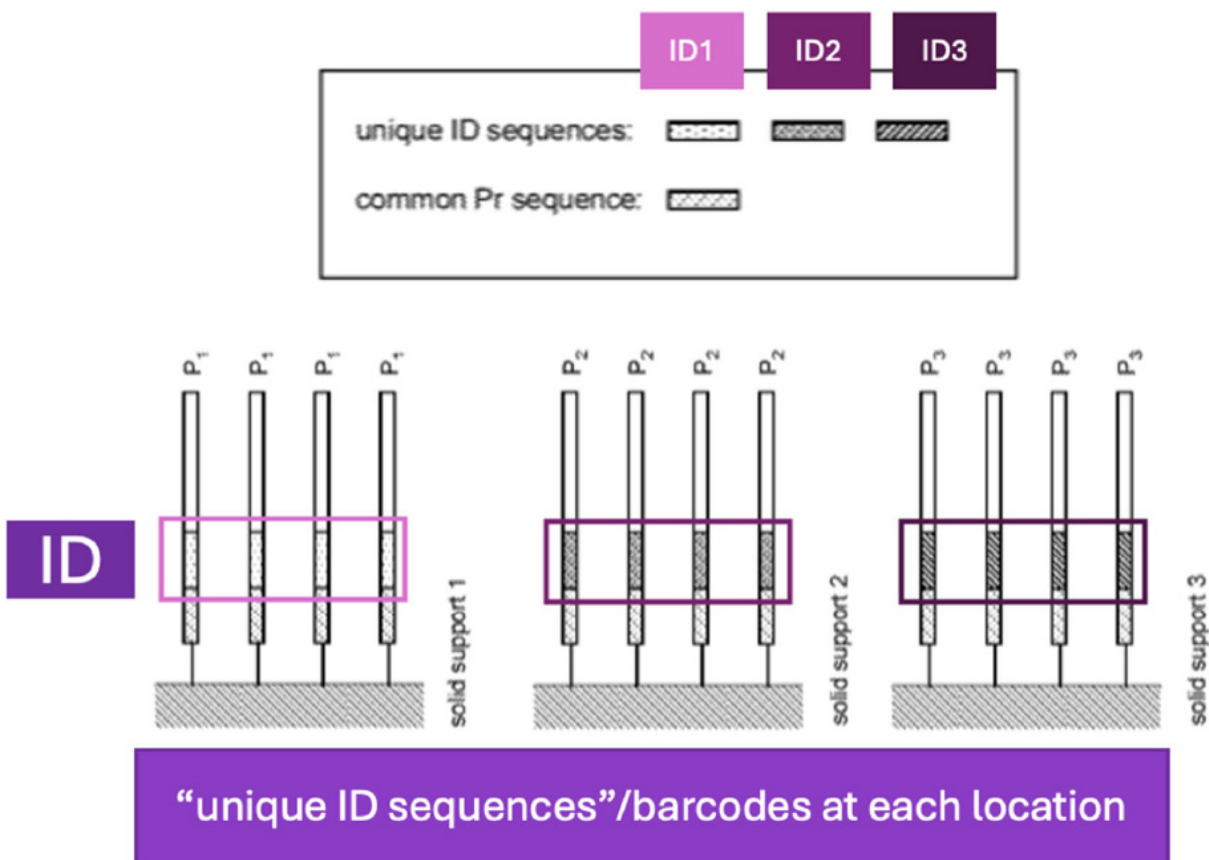
Cantor teaches a “collection” of solid supports that can contain multiple solid-support species (e.g., beads). EX1031, 11, 17; EX2002, ¶154. Cantor also teaches that a collection can be disposed on an array, such as an “X by Y array.”

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, ¶¶69, 155. Cantor *never* teaches or suggests that the beads and their corresponding identification sequences are at a known location so that the identification sequence can be *traced back* to a unique location on the substrate. EX2002, ¶154.

Petitioner simply *assumes* that Cantor’s beads are at known locations on the substrate. And Petitioner modifies Figure 1C of Cantor to reflect its mistaken assumption (excerpted below):



Pet., 24. Petitioner refers to this modified figure as “Cantor’s bead arrays.” *Id.*

As Dr. Cantor explains, however, the fundamental flaw in Petitioner's modified figure is that Cantor does not teach or suggest that "each location" is, in fact, known. EX2002, ¶¶152-158. 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. *Id.* 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.*

Specifically, Cantor describes that its 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, ¶156. 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, ¶154. 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, ¶155.

Petitioner's mistaken assumption—that “each location” of a bead in an array on a substrate would have been known—becomes clear when considering that Petitioner expressly relies on “Figure 2 and associated discussion” as proof that spatial location can be deduced from Cantor's bead collections. Pet. 33. Petitioner argues that “sequencing the released amplification product” shown in Figure 2 “would necessarily determine the sequence of a target nucleic acid and at least the complement of the identification sequence corresponding to a particular (X,Y) location of a bead in the array.” Pet. 34. Petitioner concludes that, once those sequences are determined, a POSA would “thereby determine the spatial location at which the binding agent interacted with the tissue sample.” Pet. 34. But, fatally for Petitioner's argument, in steps D and C of Figure 2 the linear amplification product *is released* from the solid support for downstream sequencing and analysis. EX1031, 24-25; EX2002, ¶157.

Dr. Cantor explains that once the linear amplification product is released, any information about where the bead was located on the substrate is lost. EX2002, ¶¶157-158. Once the linear amplification products are released into solution for sequencing, they no longer retain any physical relationship with the beads. *Id.* They have only a copy of the captured target nucleic acid and (if used) the identification sequence. *Id.* Cantor describes that its 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.

But even if Cantor suggested that an identification sequence could be traced back to a location *of a bead on the substrate* (it does not), 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 any information about the spatial location of a target nucleic acid in the tissue sample was lost when the sample nucleic acid was prepared. EX2002, ¶¶158-159.

B. In Petitioner’s Proposed Arrays, the “Coding Identifier” Does Not Inherently Render the Challenged Claims Obvious

Petitioner’s obviousness theory cannot meet the high standard of inherent obviousness. Inherency may supply a missing claim limitation in an obviousness analysis where the limitation at issue is “the natural result of the combination of prior art elements.” *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014). But “[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.” *Id.*, 1195–96. Mere “probabilities or possibilities” are insufficient. *Id.*, 1195.

Petitioner admits that Cantor does not expressly teach that the “coding identifier corresponds to a location at which the binding agent interacts with a biological molecule of a tissue sample.” Pet., 29. Nonetheless, Petitioner argues

that this would have been inherently obvious:

Because Cantor's binding agents include a 'probe' sequence as part of the same single-stranded nucleic acid as the 'identification sequence,' Cantor's 'identification sequence' *necessarily corresponds to the location at which the 'probe' portion of the binding agent hybridizes* with sample nucleic acid present in a tissue sample.

Pet., 30. Put differently, Petitioner argues that Cantor's "identification sequences" would *necessarily* provide spatial location of a biological molecule of a tissue sample. Pet., 30; *see also id.*, 3, 4, 23, 30, 34, 41. Petitioner's argument, however, rests on the mistaken assumption that hybridization between Cantor's probes and a biological molecule in a tissue sample will *necessarily* occur. But as shown below, hybridization will not necessarily occur.

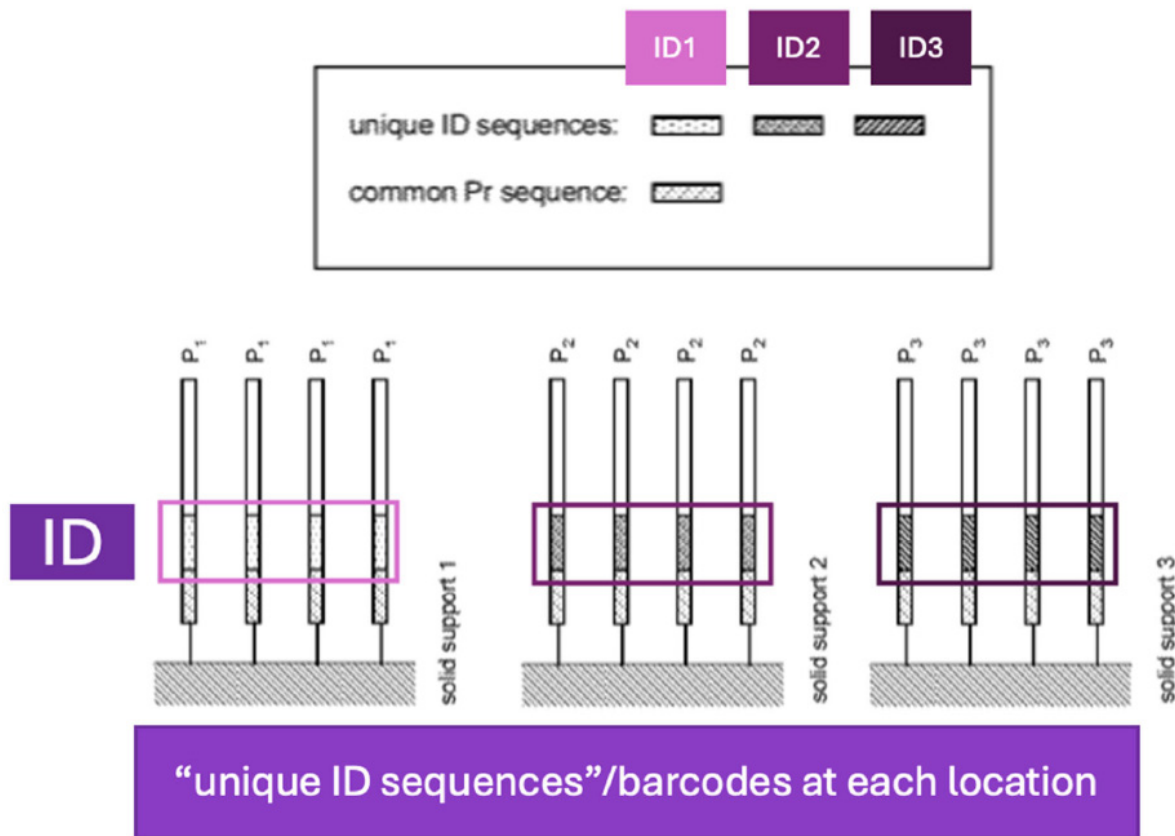
Cantor's bead collections, designed for bulk analysis, would not work for spatial analysis. Each bead of the array proposed by Petitioner was designed to hybridize with a particular nucleic acid or a subsequence of that particular nucleic acid. EX2002, ¶¶55-68, 160-161. Therefore, each bead in Petitioner's proposed arrays 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).

Accordingly, Petitioner's proposed array would *not* "necessarily" provide the spatial location of a biological molecule because hybridization does not

necessarily occur between the probe and the biological molecule in a tissue sample. And without hybridization, no spatial information can be obtained. Any spatial information that might result from overlaying a tissue over Petitioner's array would be the result of *pure chance*, which is not enough to meet the exacting standard of inherent obviousness.

1. 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

Even if Cantor's beads were provided in an array as Petitioner proposes in its modified Figure 1C—with each bead having a known X,Y location as well as a unique identification sequence—the resulting information 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. EX2002, ¶¶162-170. As Dr. Cantor explains, the presence of *different probes on each bead* destroys any ability to obtain spatial information. EX2002, ¶160. Critically, Petitioner *ignores* that its proposed array has different probes on each bead (i.e., P₁, P₂, and P₃):

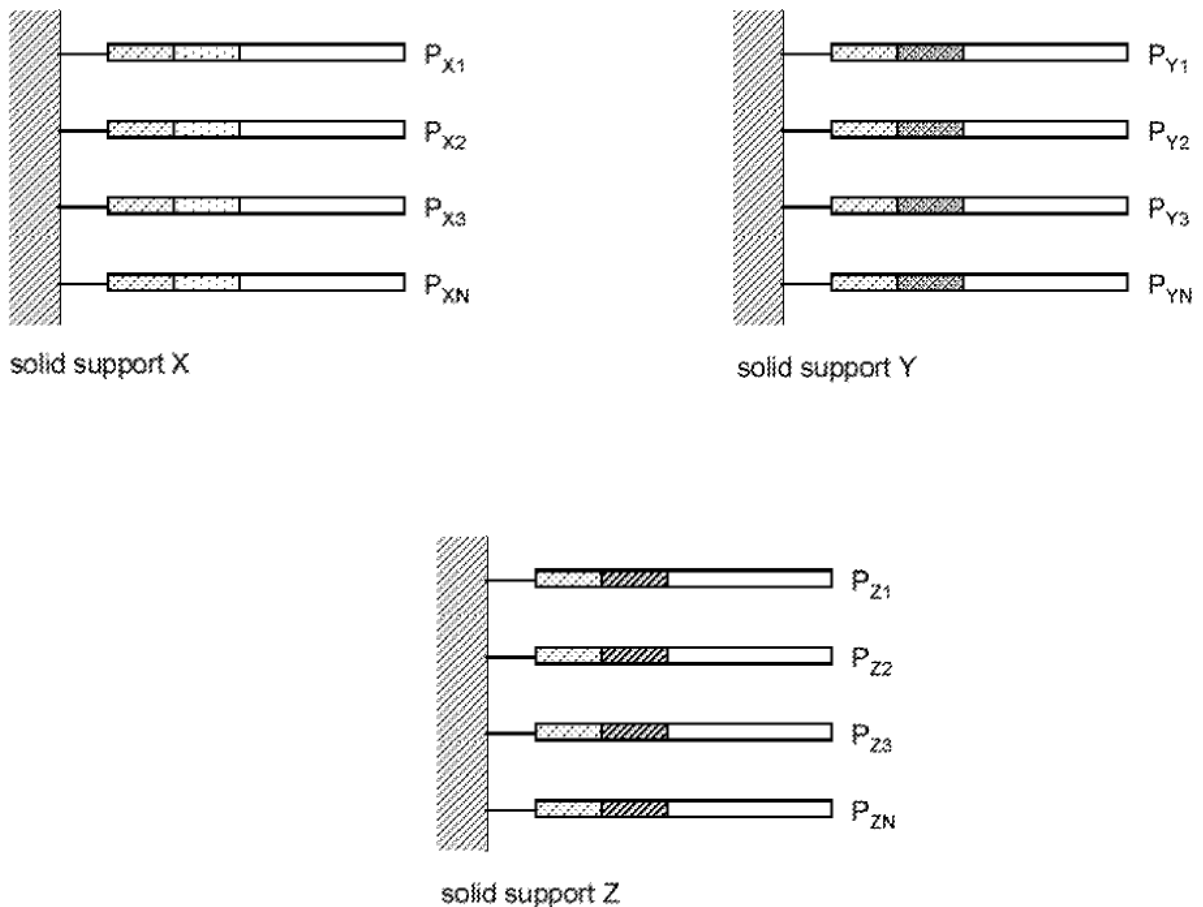


EX2002, ¶154.⁵ Each bead in Petitioner’s proposed array is specific to a particular

⁵ In a footnote, Petitioner wrongly asserts—citing claims 31 and 32—that “Cantor discloses both arrays in which the probe sequence is the same at each position, and arrays in which the probe sequence is not the same at each position.” Pet., 29 n.2. That is incorrect. As Dr. Cantor explains, a POSA would understand that claims 31 and 32 refer to the arrangement of the probes on a solid support (e.g., bead) rather than across a collection or an array, and depend only from claims directed to a “solid support.” EX2002, ¶59.

nucleic acid (or subsequences of that nucleic acid), dooming Petitioner's challenges.

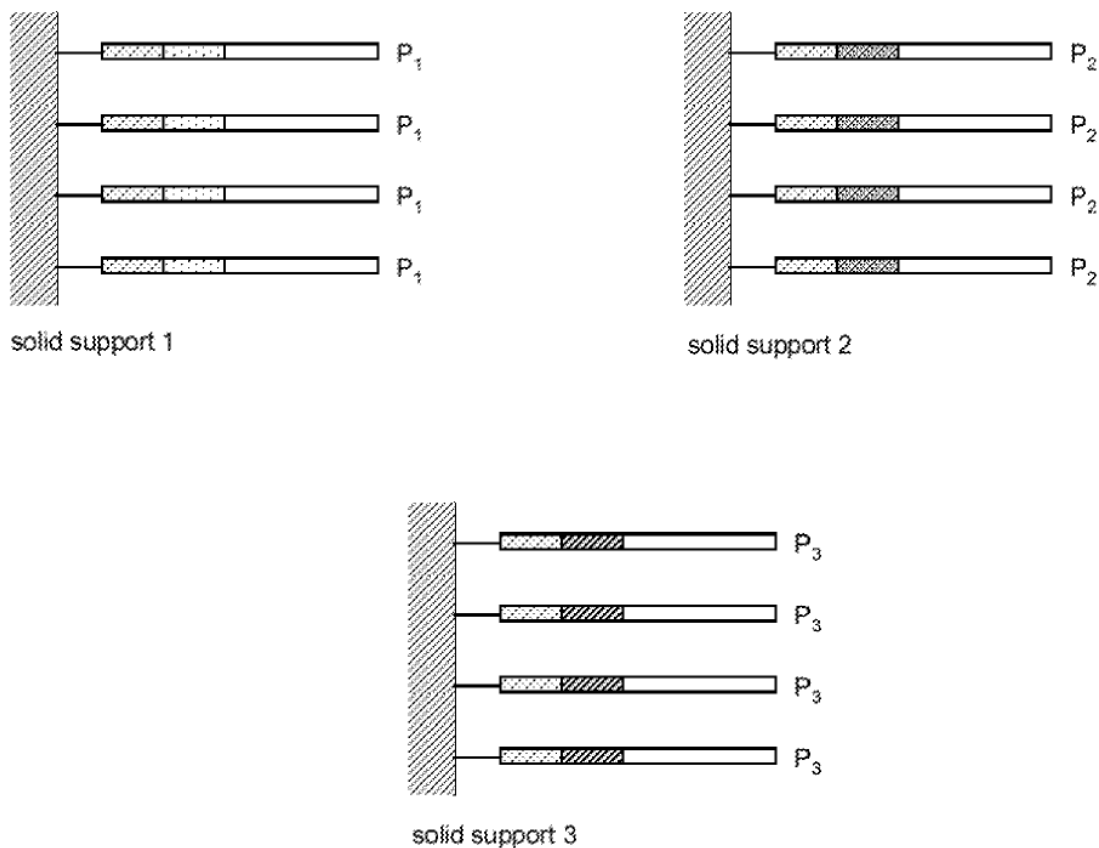
Cantor describes two different types of collections. EX2002, ¶¶62-28. The first type has solid support species (e.g., beads) that have multiple probes per bead directed to different subsequences of the same target nucleic acid (depicted in Figure 1B):



EX1031, 16-17; EX2002, ¶¶65-66. 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} . *Id.* Each probe on bead “X” targets a different subsequence of the “X” nucleic acid. *Id.* The same is true

of the “Y” and “Z” beads. *Id.* 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 type has solid support species that have multiple probes per bead directed to the same target nucleic acid (depicted in Figure 1C):



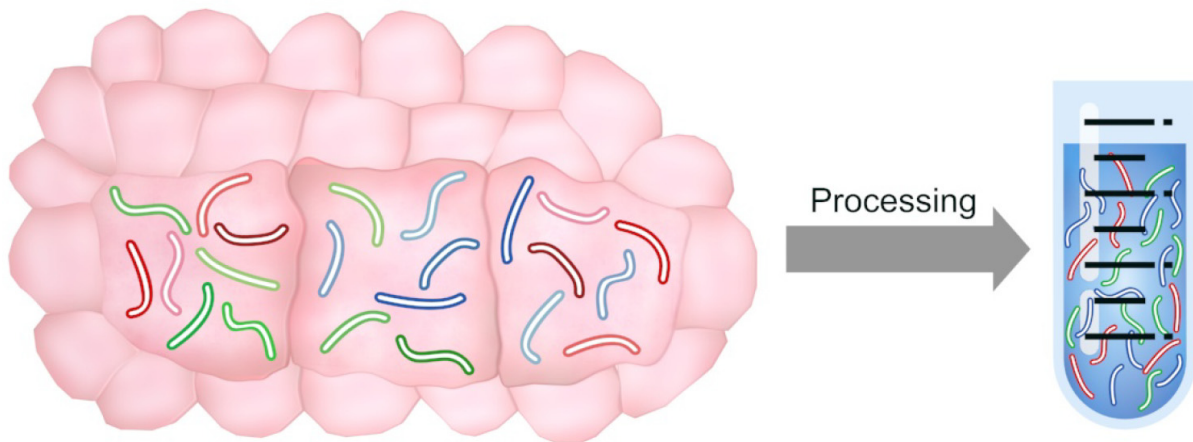
EX1031, 16-17; EX2002, ¶¶67-68. Thus, in Figure 1C, bead “1” has probes P₁, bead “2” has probes P₂, and bead “3” has probes P₃, for a total of three unique probes in the array directed at 3 different target nucleic acids (1, 2, and 3). *Id.*

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

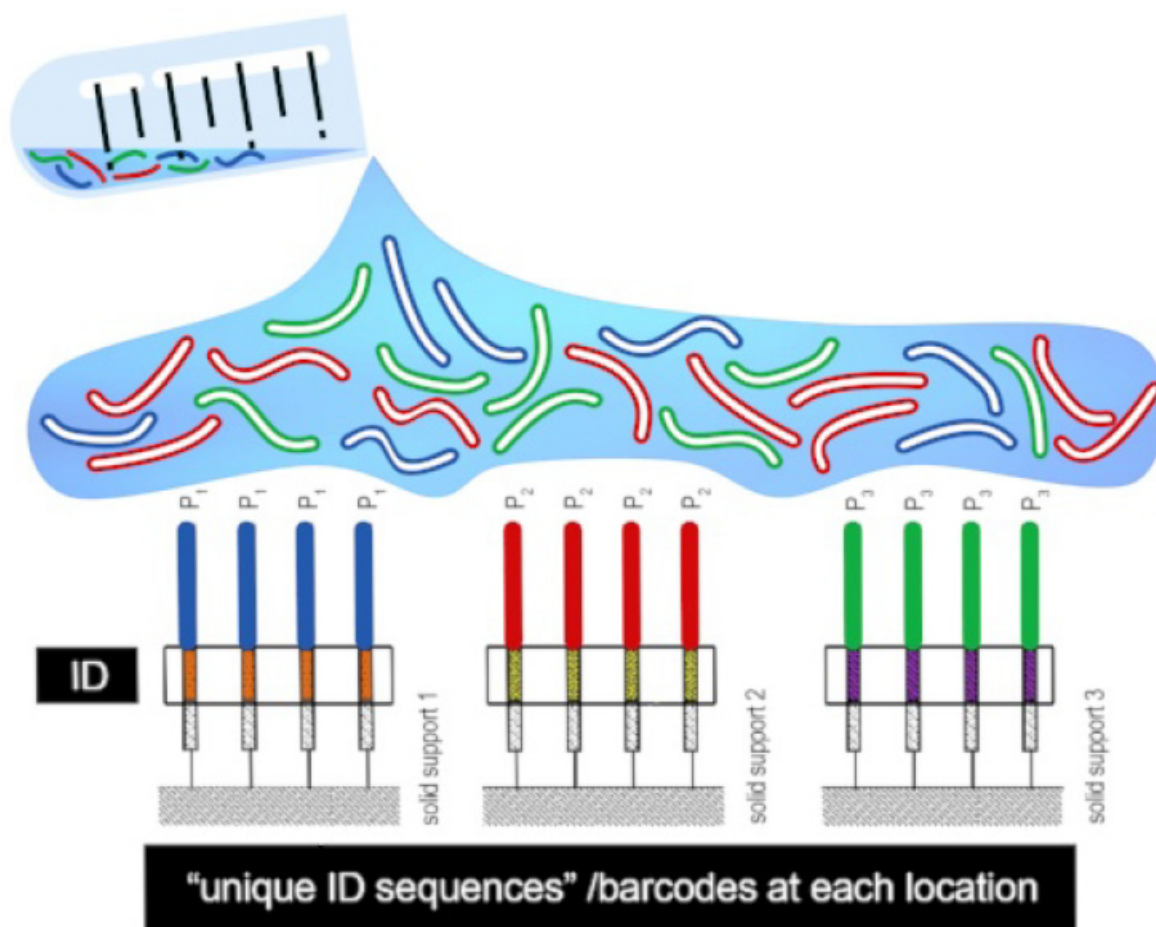
EX2002, ¶¶64, 154.

2. 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

The results from contacting Petitioner's array with Cantor's sample nucleic acid is illustrated below. Again, according to Cantor's teachings, 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.



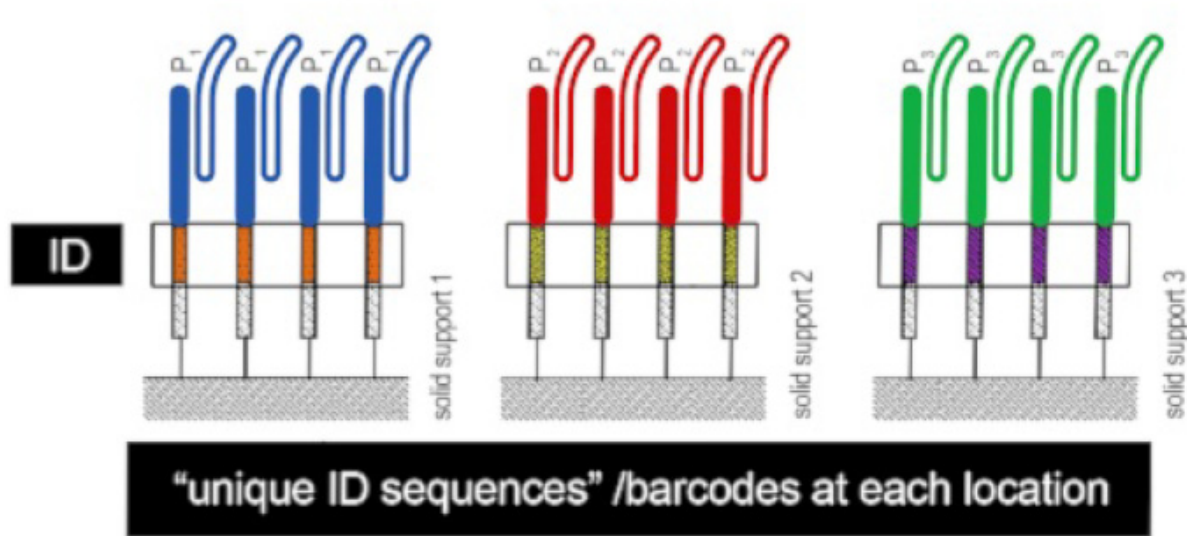
Then, the resulting sample nucleic acid is applied to Petitioner's array, where each different bead on the array has different probe sequence(s). EX1031, EX2002, ¶¶64, 154, 160-162. The mixing of sample nucleic acid with beads arranged on an array is illustrated below:



In this illustration, 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, ¶163. 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 can 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:



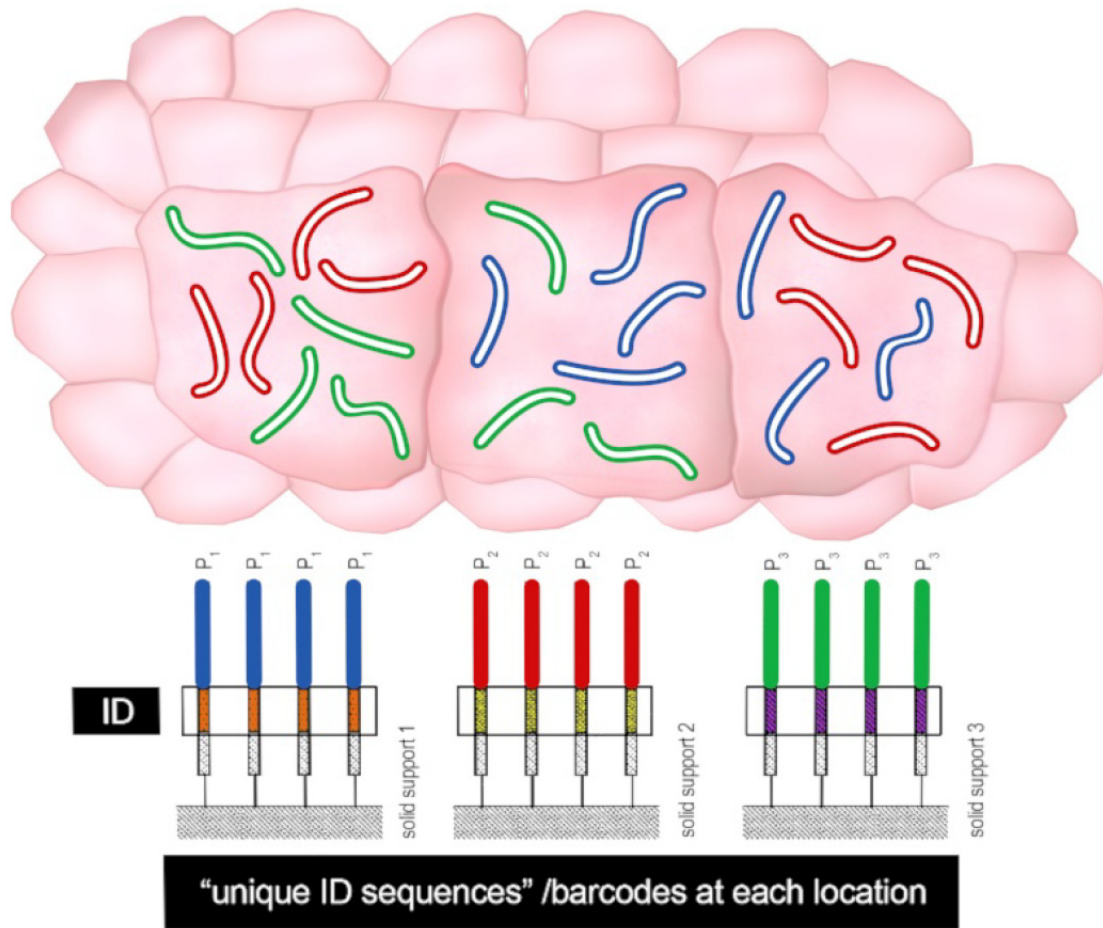
Id. Because the target nucleic acids in the sample nucleic acid are blended together (like in the fruit smoothie), the spatial distribution of the nucleic acids within the original tissue sample has been lost. EX2002, ¶164. Put differently, while Cantor's collection can reveal that the **blue-outlined** 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 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.* Therefore, as Dr. Cantor explains, a

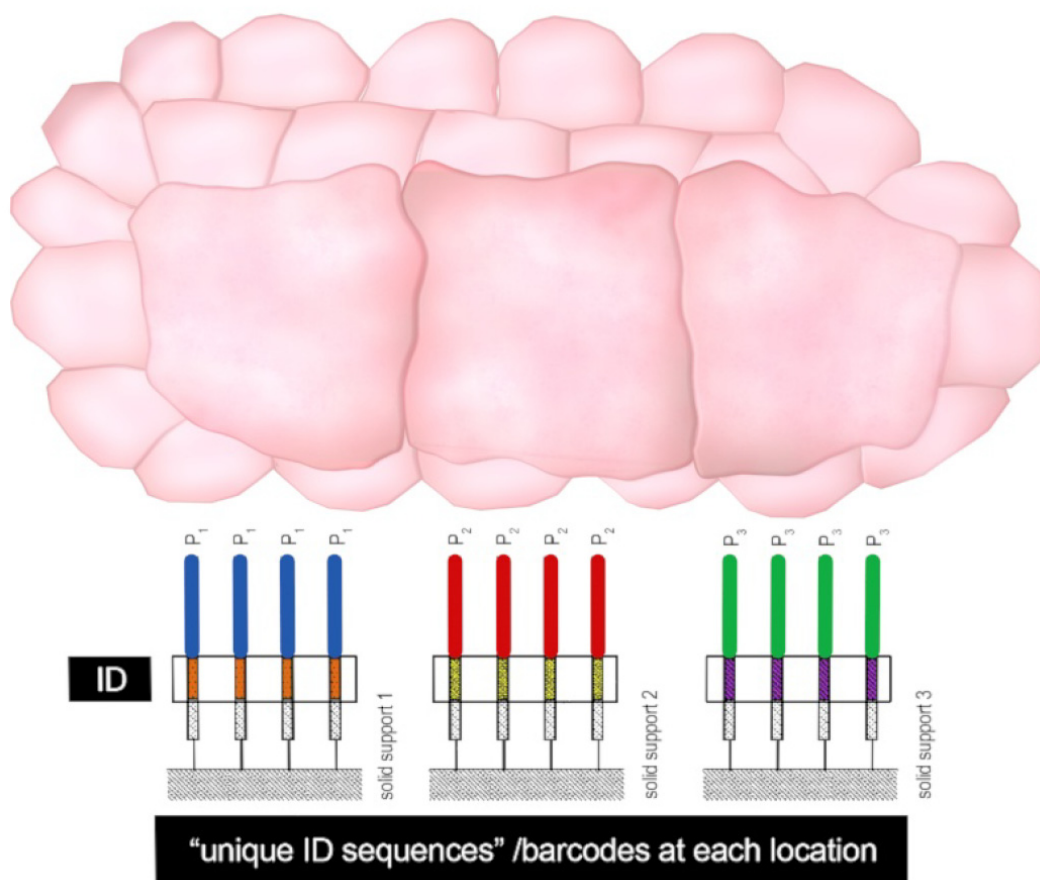
POSA ***could not*** have used Petitioner's array to "determin[e] a spatial location of the biological molecule of the tissue sample" as claimed. *Id.*; *see also* Claim 1(c).

3. Using Petitioner's array with a tissue sample would not necessarily provide the spatial location of a biological molecule because hybridization would not necessarily occur

Contacting Petitioner's bead array with a ***tissue sample*** would not ***necessarily*** result in the spatial location of a biological molecule. The following illustrations depict what would happen if a POSA overlaid the proposed array with a solid tissue. EX2002, ¶165; *see also* Pet., 24-25. 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 in this illustration, the target nucleic acids are non-uniformly distributed in the tissue *and* the probes are not repeated across the array. EX2002, ¶166. 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:

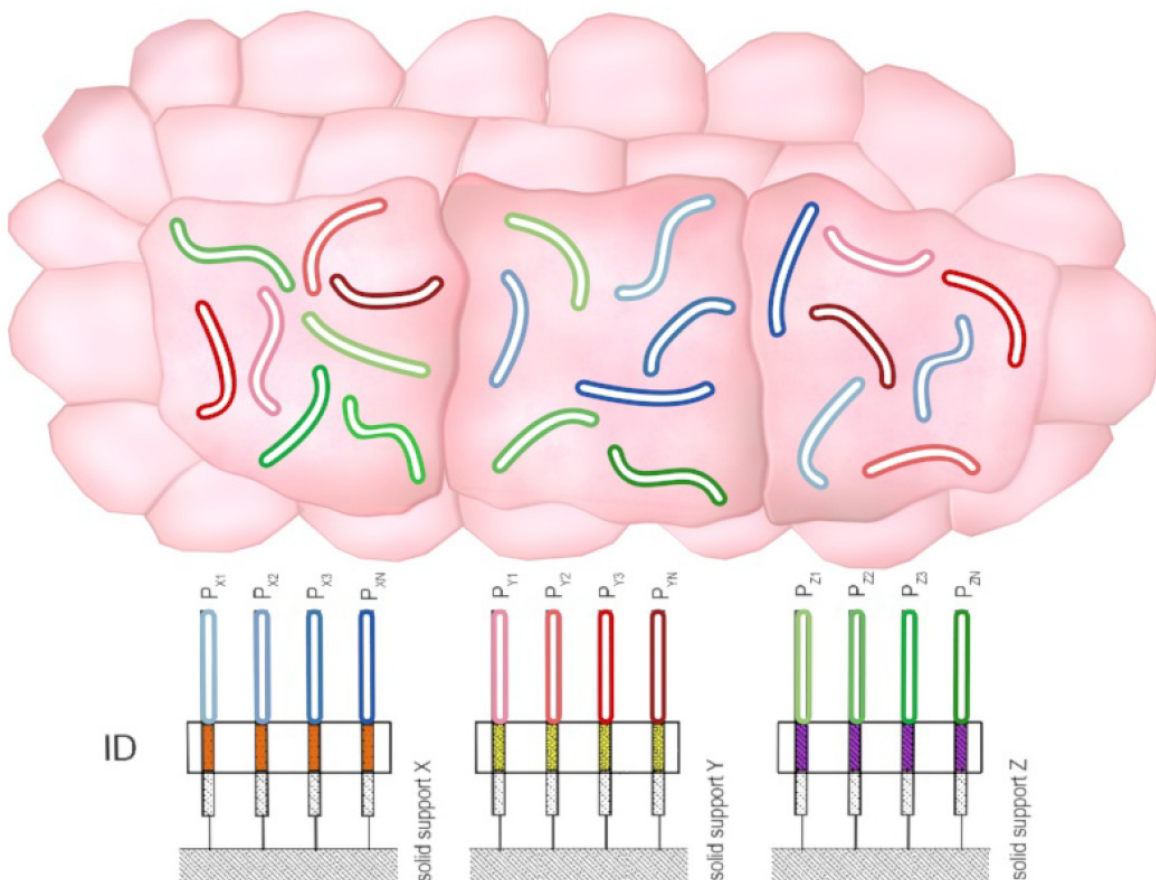


Id.

Here, even though **blue-outlined**, **red-outlined**, and **green-outlined** target nucleic acids were *present* in the 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, the 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, ¶168. The latter array is illustrated below:

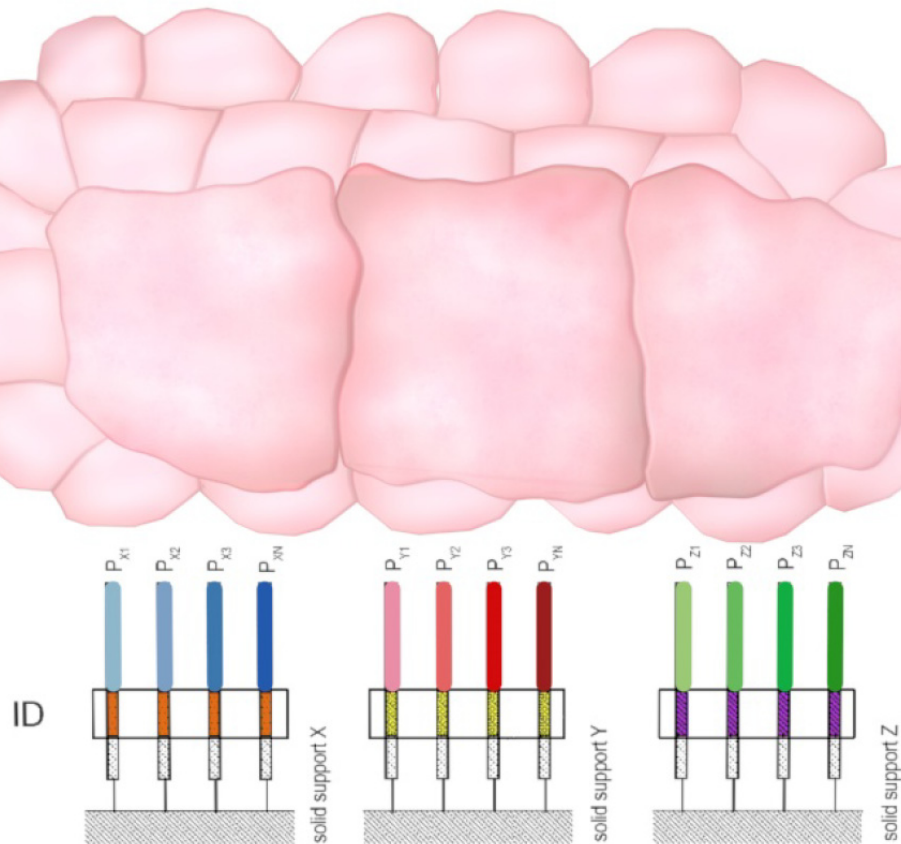


Id.

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).

Similarly, 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 that overlays its corresponding probe, then *no* hybridization will occur, and *no* spatial location of the biological molecules is obtained from the array.



Id.

Again, even though various shades of **blue-outlined**, **red-outlined**, and **green-outlined** target nucleic acids were *present* in the 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). EX2002, ¶¶169-170.

The critical flaw in the Petitioner’s argument is that it *just assumes* that its array will result in hybridization between a probe and a biological molecule in a tissue and thus *necessarily* provide a spatial location. But Petitioner does not offer any evidence to support that assumption, and—as the above illustrations show and Dr. Cantor supports—that assumption is incorrect. Petitioner has not shown that the spatial location recited in claim 1 would be “necessarily present, or the natural result of the combination of elements explicitly disclosed by” Cantor. At most, hybridization “*may* result from a given set of circumstances” (e.g., a tissue was, by chance, overlayed in exactly the right location over Petitioner’s array), but that “is not sufficient to render the result inherent.” *PAR Pharm.*, 773 F.3d at 1195. 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 Use Cantor’s Arrays With a Reasonable Expectation of Success

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 use Cantor’s bead collections—taught and used for bulk analysis—to determine the spatial location of a biological molecule of a tissue sample with a reasonable expectation of success in doing so. Dr. Cantor himself explains that a POSA would have recognized the futility of attempting to obtain spatial location of biological molecules from the arrays disclosed in Cantor. EX2002, ¶171.

“[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 described in Cantor “does not relate to preparation or analysis of intact tissue samples discussed in the ’022 patent (i.e., for spatial analysis).” EX2002, ¶31. Instead, Cantor’s solid supports and methods are used to answer the question of *whether* biological molecules of interest are present in a *sample nucleic acid* (the “fruit smoothie”) *derived* from a solid material such as a tissue (the “fruit tart”). *Id.* A POSA could not have and would not have used Cantor’s solid supports and

methods to answer the question of *where* in a tissue sample 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.B.1.

Moreover, the binding in Petitioner's proposed arrays (and therefore spatial location) would happen only by chance or not at all. *Supra* §VII.B.2. Thus, a POSA would have had neither motivation nor reasonable expectation of success in using Cantor's bead collections to "determine[e] a spatial location of a biological molecule of the tissue sample," as claimed. EX2002, ¶172; Claim 1(c). Such "by chance" hybridization would be at cross purposes to bulk analysis. *Supra* §III.A.

Put simply: a POSA would not have had any motivation to modify Cantor to switch out Cantor's sample nucleic acid with a tissue sample and contact it with Petitioner's proposed array. And because contacting Petitioner's proposed array with a tissue sample would not necessarily determine *where* a particular nucleic acid sequence is present in a tissue sample, a POSA would not have had a reasonable expectation of success in using the combination of Cantor's collection of beads and a tissue sample in a method for determining a spatial location of a biological molecule of a tissue sample, as claimed.

What's more, as Dr. Cantor explains, Petitioner's obviousness case requires the POSA to *further* modify Cantor to trace back its identification sequences to

locations on a substrate (by placing the beads in known locations or determining their location before use). EX2002, ¶173. As described above in §VIII.A.2, 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, ¶¶156, 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 any spatial information. *Id.*, 25, 53-55 (Example 1); EX2002, ¶45.

The Federal Circuit has repeatedly 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) (vacating Board decision that failed to consider whether modifying prior art reference would undermine its goal of constructing stable all-terrain vehicles). For all the reasons discussed above, a POSA would not have modified Cantor in the manner that Petitioner suggests, let alone with a reasonable expectation of success. EX2002, ¶173. This is supported by the plain language of Cantor itself; of the several dozen uses that Cantor **does** identify for its methods, none are for spatial analysis.

EX1031, 5, 30-52; EX2002, ¶¶71-92.

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

Petitioner’s “background references” do not cure the deficiencies of the Petition. Petitioner’s reliance on these “background references” to supply missing claim limitations—e.g., “contacting the plurality of beads with the tissue sample” (claim 1(b)); and using the coding identifier to “determin[e] a spatial location of the biological molecule of the tissue sample” (claim 1(c))—should be rejected. *Supra* §VII.A. 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).

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 contact a plurality of beads with a tissue sample to determine spatial location using the claimed coding identifier. Indeed, almost all of Petitioner’s “analysis” of the purported background references (Pet., 24–25) consists of string-cites to Dr. Puglisi’s Declaration, which is improper. *See* 37 C.F.R. §42.6(a)(3); *see also Nearmap US, Inc. v. Pictometry Int’l Corp.*, IPR2024-00729, Paper 9 at 21-22

(PTAB Oct. 10, 2024) (denying institution where the petitioner string-cited to 13 pages of explanation found only in the expert declaration).

To the extent Petitioner includes *some* parenthetical explanations (Pet., 39-41), this too 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); *see also* 37 C.F.R. §42.22(a)(2) (Petition must “includ[e] a detailed explanation of the significance of the evidence”).

Other than Cantor, the Petition discusses only three references in any detail in the grounds: Southern, Shirai, and Armani. Petitioner cites to Southern as “similarly disclos[ing] the spatial analysis of nucleic acid molecules by contacting tissue samples with a binding agent affixed to a solid support.” Pet. 32 (citing EX1033, 16:28-30; 7:3-7). But Petitioner mischaracterizes the teachings of Southern’s “tissue samples”, Pet. 32 (citing EX1033, 16:28-30; 7:3-7), just like it did the teachings of Cantor’s “solid material such as a tissue.” *Supra* §VII.A.

Southern, like Cantor, does **not** teach contacting a solid support with a **tissue**. Rather, Petitioner's own quotation from Southern shows that Southern contacts **cells**⁶ 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. 32 (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 ¶174; *see also* EX1100, ¶¶45-50.

Moreover, the only time Southern mentions "tissue samples," it is in the context of using that sample to **derive** the cells that are **then** applied to the support. EX1033, 16:26-17:10; EX2002, ¶175.⁷ Indeed, Southern teaches that it is "[a]fter

⁶ Alternatively, Southern teaches that the released material from cells may be overlaid on the solid support. EX1033, 17; EX2002, ¶175.

⁷ As Dr. Cantor explains, Southern also discloses the use of "tissues" in some of its Examples. But 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, ¶177.

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, creating an array of individual samples. EX1033, 22:20-31; EX2002, ¶¶175. The array can be used to simultaneously analyze multiple samples (i.e., cells of interest separated from the other components in the tissue) by a variety of methods. EX1033, 26:19-32; EX2002, ¶175. 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, ¶176. 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, ¶176. But the spatial location of a biological molecule of a tissue is not maintained. EX2002, ¶176.

Petitioner also cites to 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., 32. But Petitioner fails to mention that Shirai is a *post-filing date* reference, the contents of which would not have been known to a POSA as of the ’022 patent’s filing date. Indeed, Shirai was filed and published in 2017—*several years after* the ’022 patent’s priority date. EX1024, codes [21], [22]. Petitioner fails to provide *any analysis whatsoever* of Shirai’s priority date.⁸ 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).

Finally, in Ground 2, Petitioner combines Cantor with Armani. Pet., 49. But Petitioner’s combination of Cantor and Armani *still presumes* that a POSA would construct Petitioner’s array with beads at known locations—this time with “the plurality of beads disposed in wells” of a multi-well plate. Pet., 50-51; *see also* EX2002, ¶179. In other words, placing one of the beads of Petitioner’s array in each of Armani’s wells. *Id.*, 51 (“obvious to combine teachings of Cantor and

⁸ For example, although Shirai purports to claim priority to a *post-filed* PCT application (EX1024, code [30]), 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).

Armani by providing Cantor's bead array with a plurality of beads disposed in wells"). But even if a POSA would have done so, Ground 2 still suffers from the same critical flaws as Ground 1: because the target nucleic acids are non-uniformly distributed in the tissue sample *and* the probes of Cantor's bead collections are not repeated, hybridization will only happen by chance (or not at all) and the spatial location of the biological molecule cannot be determined. *Supra* §VII.B.2; *see also* EX2002, ¶179.

Armani's methods do not use beads, binding agents, coding identifiers, or sequencing. *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 using a fluorophore. *Id.* Armani does 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: December 24, 2024

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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 13,914, which is less than the 14,000 allowed under C.F.R. §42.24(b)(1).

Respectfully submitted,

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CERTIFICATE OF SERVICE

Pursuant to 37 CFR § 42.6(e)(4) and 42.205(b), the undersigned certifies that on December 24, 2024, 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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