UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CURIO BIOSCIENCE, INC.,
Petitioner

v.

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

Case IPR2025-00237
Patent 11,001,879

PATENT OWNER'S PRELIMINARY RESPONSE

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LIST OF EXHIBITS

Exhibit Number	Description
EX2001	[Reserved]
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," *Nature Genetics* 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," *Nature Methods* 2:i–iii (2005)
EX2007	Griffin et al., "Pathogenic Human Viruses in Coastal Waters," *Clin. Microbiol. Rev.* 16(1):129–143 (2003)
EX2008	Deak et al., "Molecular Characterization of Y*arrowia lipolytica* and *Candida zeylanoides* Isolated from Poultry," *Appl. Env. Microbiol.* 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"
EX2011	File History for U.S. Application No. 17/144,971

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. 11,001,879 ("'879 patent") filed by Curio Bioscience, Inc. ("Petitioner" or "Curio").

I. INTRODUCTION

Petitioner has constructed a house of cards built on misdirection and mistaken assumptions. The Board recently issued a decision denying institution ("DDI") in IPR2024-01289 ("IPR1289"), in which Petitioner relied on the same prior art and substantially the same arguments.[2] As in IPR1289, Petitioner again relies on isolated quotations and pictures that, at first blush, make the methods claimed in the '879 patent appear obvious. But closer inspection of the evidence reveals that the Petition skips over relevant teachings of the '879 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 Petitioner proposes. The Board

[1] Consistent with Petitioner's use, "PO" collectively refers to real-party-in-interest 10x Genomics, Inc. ("10x") and Prognosys Biosciences Inc. ("Prognosys").

[2] Indeed, every ground of unpatentability in IPR1289, IPR2025-00192, IPR2025-00193, IPR2025-00236, and IPR2025-00237 relies on the same art.

should deny institution here just as it denied institution in IPR1289.

Petitioner steps back in the ’879 patent’s priority chain to assert that the patent’s claims lack written-description support. But, just as it did in IPR1289, Petitioner fails to grapple with the fact that each and every application in that priority chain expressly incorporated by reference the disclosure of the provisional application. As the Board found in the IPR1289 DDI, the provisional explicitly describes the invention Petitioner calls “Figure A.” Petitioner’s ignorance of the provisional’s incorporation attempts to hide that the claim limitations have written-description support in the provisional. 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 presented in IPR1289. 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. Indeed, the Board agreed with Dr. Cantor in its DDI.

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 section. 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. As the Board recognized in IPR1289, 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 it would. Indeed, hybridization between Cantor's probes and a biological molecule in a tissue section 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 section, 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 here for the same reasons it did in IPR1289.

II. THE '879 PATENT CLAIMS A NOVEL, NONOBVIOUS METHOD FOR SPATIAL ANALYSIS

The '879 patent shares the same written description as U.S. Patent No. 10,480,022 ("'022 patent"), the subject of IPR1289. Like the '022 patent, the '879

patent discloses assays for analyzing spatial location(s) of biological molecules in a tissue sample. EX1003, 1:26-29, 2:4-9; EX2002, ¶15. Before these patents, "no practical method exist[ed] to analyze at high resolution the spatial expression patterns of large numbers of genes, proteins, or other biologically active molecules simultaneously." *Id.*

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

A simple analogy emphasizes the distinction between spatial-analysis 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*.

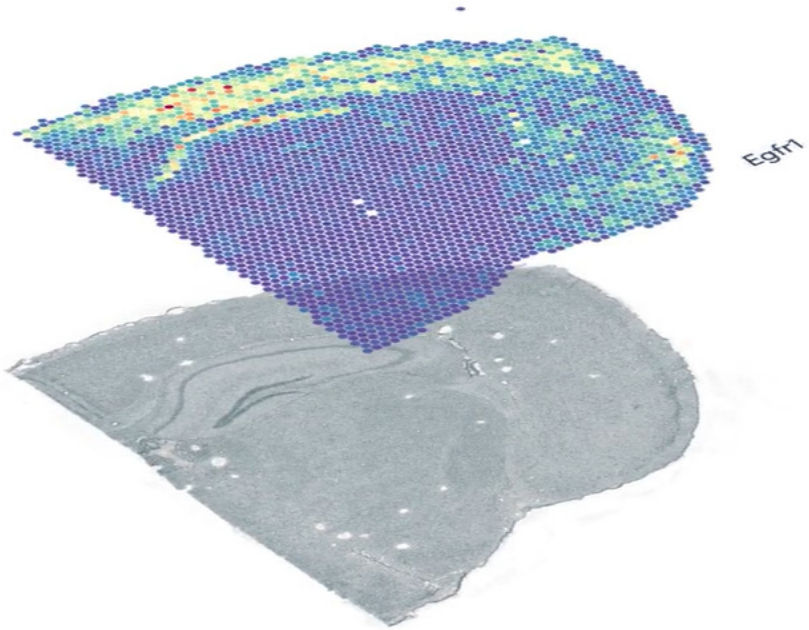
Fruit Smoothie

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 '879 patent, however, answers both questions. *Id.*

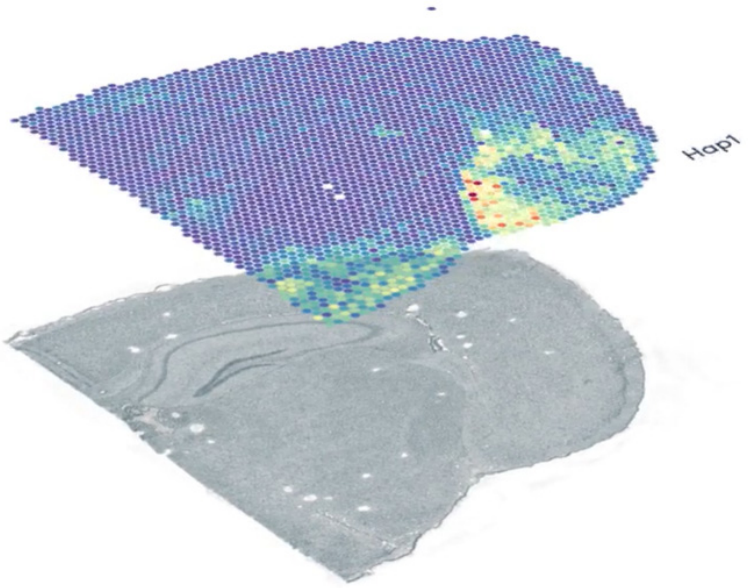
The inventions in the '879 patent addressed the "need for reproducible, high-resolution spatial maps of biological molecules in tissues." EX1003, 2:4-9; EX2002, ¶¶21-26. The '879 patent's assays utilize a spatial-encoding scheme combining molecule-specific binding agents with coding identifiers to provide 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). EX1003, 20:46-67; 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 '879 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. EX1031, [71], [75]; EX2002, ¶29.

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

¶30.

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

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

Figure 1C excerpt

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

the "sample nucleic acid"), while the primer sequence can be used for making copies. *Id*.

The identification sequence, when used, is useful for "constructing partial sequence reads into larger sequence constructions," and "may be of any length suitable for analyzing the nucleotide sequence or partial nucleotide sequence of sample nucleic acid." EX1031, 15; EX2002, ¶45. When an identification sequence is present, each solid support contains a unique identification sequence. *Id.* For example, as shown in Figure 1C, the four single-stranded nucleic acids attached to the solid support all share the same identification sequence. EX1031, 15; EX2002, ¶47. The identification sequences allow a POSA to assemble and analyze large nucleotide sequences from smaller sequence "reads" by identifying overlapping sequences. EX1031, 25, 53-55 (Example 1); EX2002, ¶45.

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

Figure 1A, excerpted below, shows a solid support where each probe on the solid support has a unique sequence P_1 through P_N. By using unique probes (i.e.,

P_1, P_2, P_3, P_N), the solid phase nucleic acid targets a different subsequence of a single target nucleic acid (i.e., subseq. 1, subseq. 2, subseq. 3, subseq. N). *Id.*

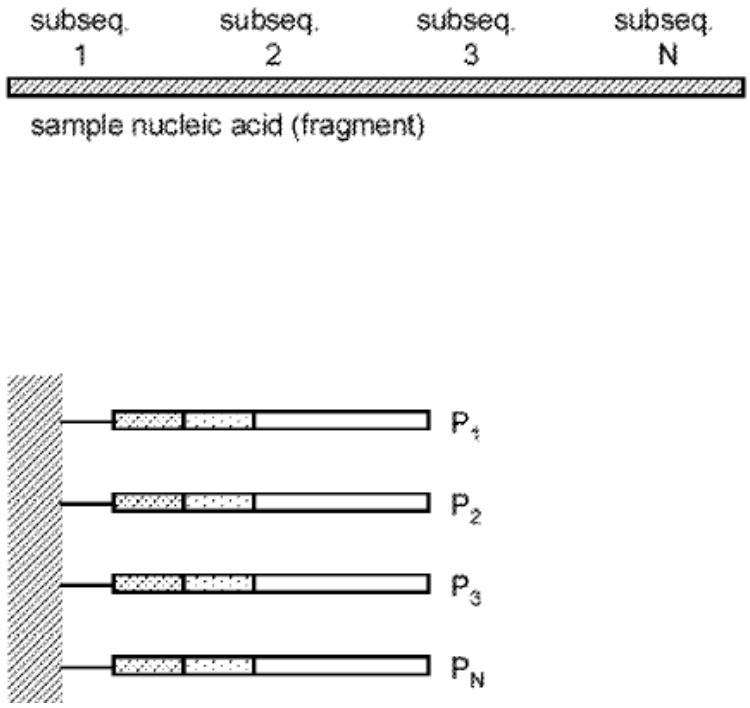


Figure 1A excerpt

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

Figure 1C excerpt

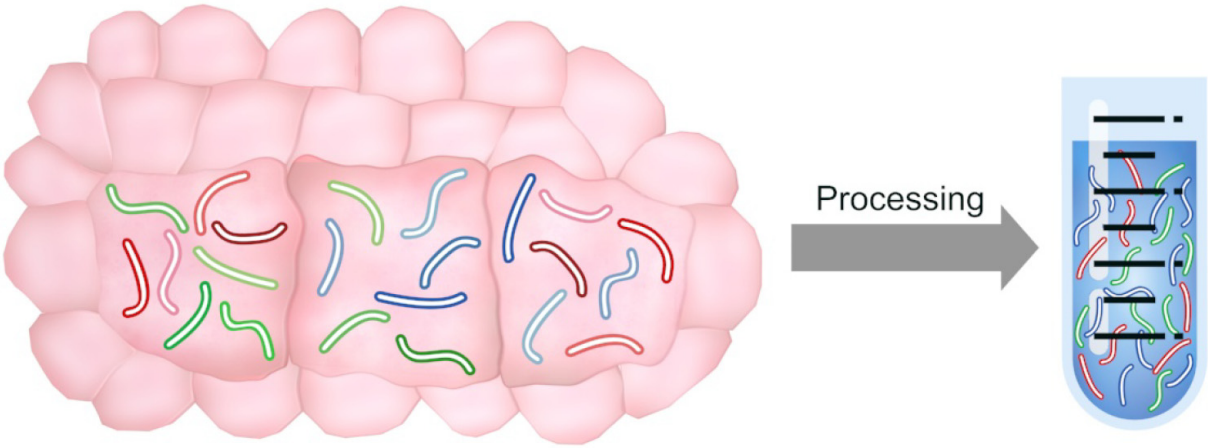
This arrangement of probes on a single solid support is also described in claim 26 of Cantor, which recites "[a] solid support comprising single-stranded solid phase nucleic acid having an identifier sequence and a probe sequence, wherein…the solid phase nucleic acid shares a common probe sequence [as in Figure 1C] or the solid phase nucleic acid does not share a common probe sequence [as in Figures 1A and 1B]." EX1031, 13-14, 60-61; EX2002, ¶¶50-51, 55-60. 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. <u>Cantor's methods analyze "sample nucleic acid," not tissue samples</u>

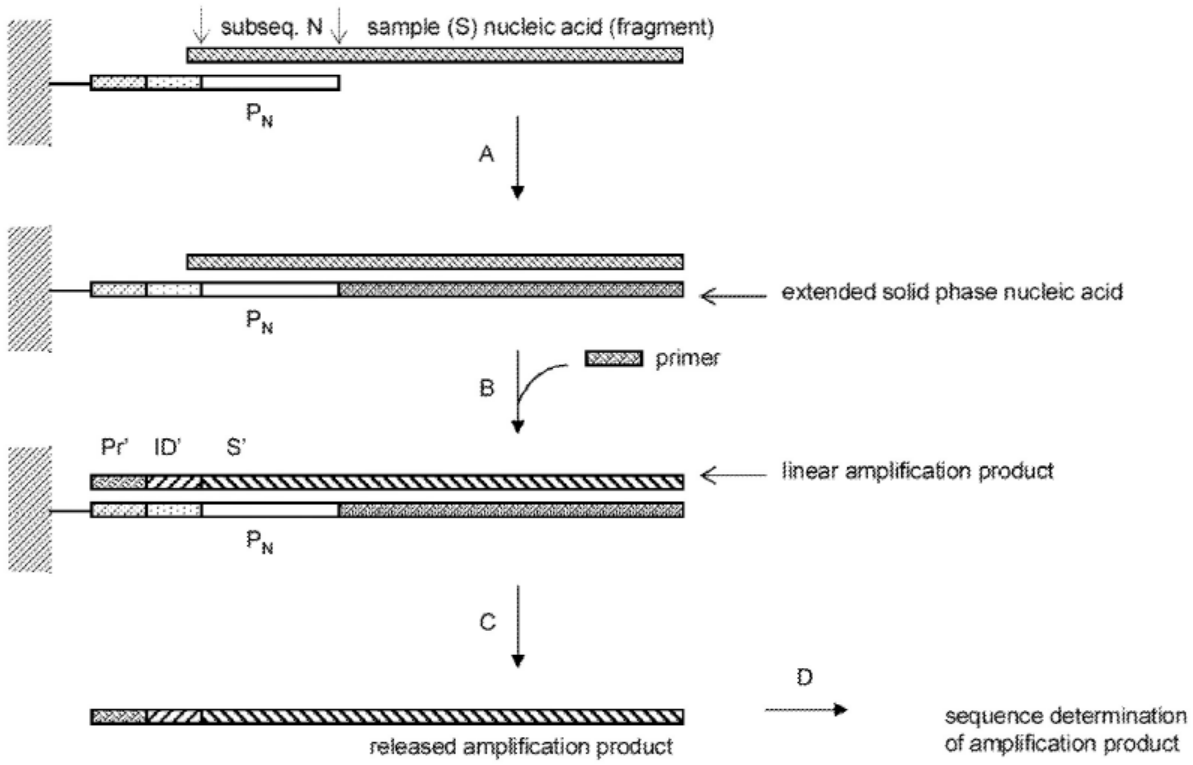
Cantor teaches that its "sample nucleic acid" may be derived from many different samples or sources, including a "biological sample"—that is, "any material obtained from a living source or formerly living source." EX1031, 6; EX2002, ¶36. The biological sample itself may have any form, including a solid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

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



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

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



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

The resulting product is called a "linear amplification product." *Id.* In steps

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

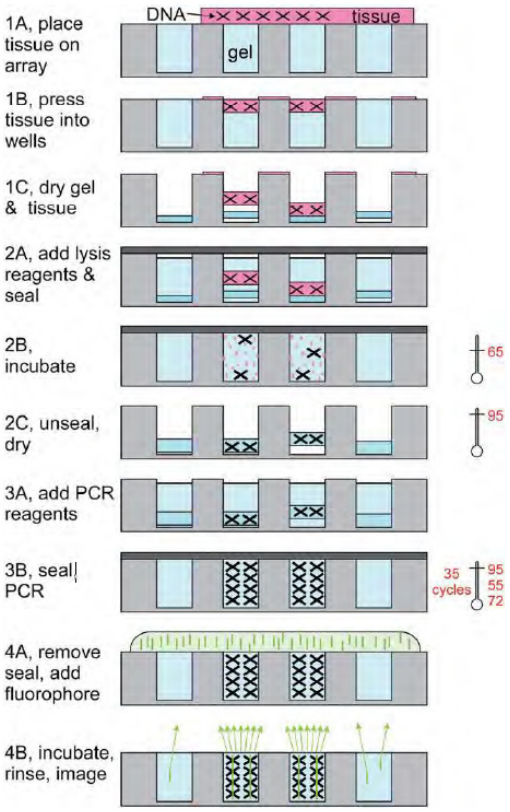
3. Cantor discloses that beads may be deposited on substrates to facilitate ease of handling for sequencing analysis and manufacturing

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, ¶¶61-69. The "array may contain one solid support species or multiple solid support species from a collection." EX1031, 4, 17; EX2002, ¶68. As Dr. Cantor explains, the use of bead arrays on substrates facilitates the ease of handling of the beads for use in the described methods. EX2002, ¶68. For example, Cantor states that an array "can be arranged on any substrate suitable for sequence analysis or manufacture processes described" in the application. EX1031, 17-18; EX2002, ¶6689. Cantor states that substrates suitable for arrays used in sequence analysis include "flat substrates, filter substrates, wafer substrates, etched substrates, substrates having multiple wells or pits …, and the like." *Id.*

B. Armani (EX1022)

Armani, titled "2D-PCR: a method of mapping DNA in tissue sections," published in October 2009. EX1022, 3526; EX2002, ¶92. Armani discloses a method for 2D-PCR. EX1031, 3526; EX2002, ¶93. Figure 2, reproduced below,

provides a step-by-step diagram of Armani's 2D-PCR. EX1031, 3527; EX2002, ¶¶94-98.



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 binds to any double-stranded DNA present in each well, allowing for imaging analysis. *Id.*

Petitioner relies on Armani for allegedly "further evidence[ing] a POSA's motivation and reasonable expectation of success in using Cantor's device and methods as set forth in the challenged claims." Pet. 51. But Armani does not disclose or contemplate using capture agents, contacting capture agents with a tissue section, or using coding tags corresponding to a location of a capture agent on an array. EX2002, ¶101.

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." EX1003, 1:64-2:3; EX2002, ¶92.

C. Frisen (EX1020)

Petitioner relies on Frisen for anticipation, but Frisen is not prior art to the Challenged Claims just as it was not prior art to the '022 patent. IPR1289, 25. Frisen's earliest possible priority date is April 13, 2011. EX1020, [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 "a capture agent that specifically binds to a nucleic acid" are irrelevant here, PO disagrees that the "specific binding" disclosed in the '879 patent does not encompass "the binding interaction between poly-T probes and the poly-A tails present on mRNA." Pet., 21-22.

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 Board found in IPR1289 that the challenged claims of the '022 patent were entitled to priority to the '124 provisional's filing date of April 5, 2010. DDI, 30. So too are the Challenged Claims of the '879 patent. Just as it did in IPR1289, Petitioner errs legally when it argues that there was a break in the priority chain barring the Challenged Claims from claiming priority. Pet., 57-59. Each application in the priority chain of the '879 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. The Board should find that the ’879 patent’s priority chain is intact just as it found “that the ’022 patent’s priority chain is intact.” DDI, 30. On the facts, an analysis of the ’124 provisional’s disclosure—which Petitioner largely ignores—shows that it provides written-description support for the claim elements that Petitioner asserts are missing. Pet., 59. Indeed, Petitioner makes the same arguments here about lack of written description that the Board rejected in IPR1289. DDI, 30.

Because the Challenged Claims of the ’879 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."[3] Both of these statutory requirements are met here.

1. The '879 patent's priority chain is intact

The '879 patent issued from Appl. No. 17/144,971 ("the '971 application," EX2011) on May 11, 2021. EX1003, [21], [22], [45]. The '971 application claims priority through a series of applications (the "intervening applications") to provisional Appl. No. 61/321,124 ("the '124 provisional," EX1009). The '124 provisional is the same provisional application that the Board analyzed in IPR1289. DDI, 25-30. PO reuses Petitioner's table showing the priority chain of the '879 patent back to the '124 provisional:

'879 Patent Priority Documents	Filing Date	Exhibit
16/988,284 (the "'284 Application")	August 7, 2020	EX1059
16/414,213 (the "'213 Application")	May 16, 2019	EX1056
16/402,098 (the "'098 Application")	May 2, 2019	EX1057
16/276,235 (the "'235 Application")[4]	February 14, 2019	EX1010
15/187,661 (the "'661 Application")	June 20, 2016	EX1011

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

[4] The '235 application matured into U.S. Patent 10,480,022, which Petitioner challenged in IPR1289.

13/080,616 (the "'616 Application")	April 5, 2011	EX1012
61/321,124 (the "'124 Provisional")	April 5, 2010	EX1009

Pet., 57. Petitioner does not and cannot dispute that each application in the '879 patent's priority chain included a "specific reference" to the earlier-filed application under §§119(e) and 120. *Id.*, 57-59.

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

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

Each of the remaining intervening applications and the '971 application were filed as continuation applications, while co-pending with their respective parent applications, and claimed priority to each of the utility applications in its priority chain under §120 and to the '124 provisional under §119(e) in an ADS by numbers and familial relationships. EX1011, 61-62; EX1010, 54-55; EX1057, 7;

EX1056, 7; EX1059, 6-7; EX2011, 6-7.

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

Each intervening application and the ’971 application expressly and unambiguously incorporated by reference the disclosure of the ’124 provisional. *See* EX1012, 5; EX1011, 2; EX1010, 6; EX1057, 15; EX1056, 16; EX1059, 14; EX2011, 14 (“Cross-Reference to Related Applications”). “Incorporation by reference provides a method for integrating material from various documents into a host document…by citing such material in a manner that makes clear that the material is effectively part of the host document as if it were explicitly contained therein.” *Droplets*, 887 F.3d at 1318 (cleaned up).

Each of these applications met all requirements for a proper incorporation of the ’124 provisional by reference. The applications use the root words “incorporate” and “reference” and “clearly identify the referenced patent, application, or publication” by serial number and filing date. *Droplets*, 887 F.3d at 1315. Thus, the disclosure of the ’124 provisional was “as much a part of the [each] application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed.” MPEP §2163.07(b).

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

The Challenged Claims are entitled to the ’124 provisional’s priority date.

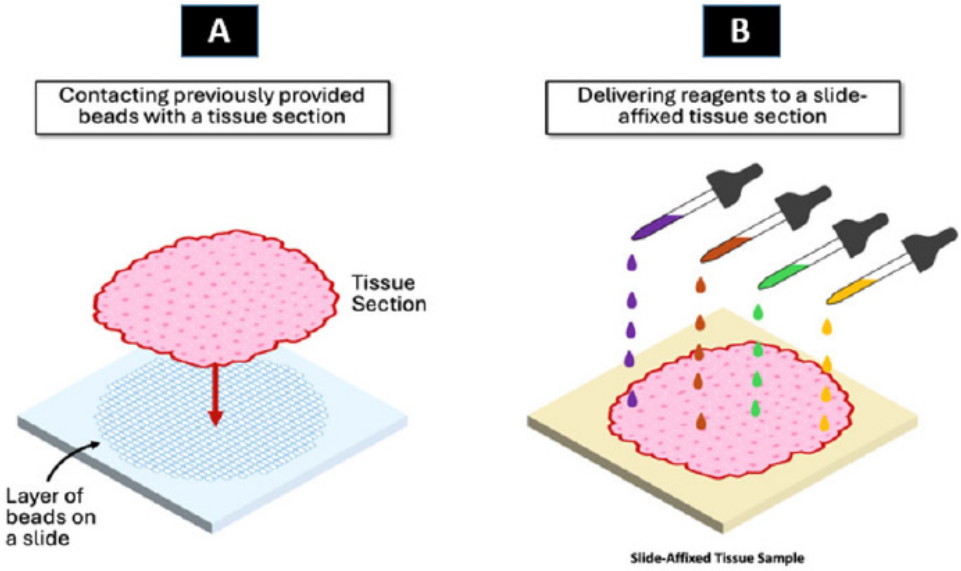
Petitioner identifies "one limitation of independent claim 1" that allegedly lacks written-description support: "contacting the tissue section with an array comprising a plurality of features." Pet., 59. The features Petitioner attacks mirror limitations that Petitioner alleged lacked written-description support in IPR1289. The Board rejected Petitioner's arguments in IPR1289 and should do the same here.

Moreover, just as it did in IPR1289, Petitioner erroneously bases its priority attack on the specification of the '661 application rather than the '124 provisional. Because the '124 provisional was incorporated by reference into the specification of the '971 application and all intervening applications, however, if the claim elements have written-description support in the '124 provisional, then they also have written-description support in the '971 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. <u>The '124 provisional supports delivering a tissue sample to a previously generated array of substrate-affixed probes</u>

The '124 provisional supports contacting substrate-affixed probes—that is, probes mounted on a substrate surface (e.g., slide)—with a tissue sample. Petitioner reuses the same illustration that it did in IPR1289 (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., 1.

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., 59-64. But the '124 provisional—which was expressly incorporated by reference into the '661 application—provides written-description support for "contacting [the claimed] array with a tissue sample by placing the tissue sample on top of the array of features (including capture probes)." (Pet., 60-61, referencing Figure A). EX2002, ¶¶111-113.

Paragraphs 17 and 18 of the '124 provisional explain that, in one

embodiment of the invention, binding agents (e.g., capture agents) are "immobilized directly or indirectly to the ***substrate*** surface."[5] EX1009, ¶¶17-18; EX1003, 22:15-23; EX2002, ¶¶114-115. And in one embodiment, a "substrate surface" is described as having "wells or channels." *Id.* As Dr. Cantor explains, a POSA would understand that a tissue section ***does not*** have features like wells or channels. EX2002, ¶115. Instead, as Dr. Cantor explains and supports with evidence, "wells or channels" are features of manufactured solid supports. *Id.* (citing EX1031). A POSA would understand that a "surface" of a "substrate" with "wells or channels" is ***not*** a tissue section, but instead is a manufactured solid support. *Id.*

Moreover, paragraphs 15-18 of the '124 provisional explain that in some embodiments, binding agents are immobilized (e.g., onto beads) and are ***then*** placed on the substrate surface, for example in wells or channels. EX2002, ¶114; *see also* EX1009, ¶17; EX1003, 22:24-35 ("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 section as depicted in "Figure A" to carry out the types of spatial distribution analyses described. EX2002, ¶114.

[5] All emphasis added throughout unless otherwise noted.

Even more passages in the ’124 provisional discuss the use of these types of pre-generated arrays—with binding agents immobilized directly or indirectly onto a “substrate surface.” EX2002, ¶116. One passage does so in the context of peptide binding agents. EX1009, ¶21; EX1003, 22:54-64; EX2002, ¶116. Another does so in the context of chemical binding agents. EX1009, ¶22; EX1003, 22:65-23:7; EX2002, ¶116.

Patent Owner presented this written-description analysis in its preliminary response for IPR1289. *See* DDI, 27-28 (quoting Prelim. Resp. 28-30). And the Board agreed that the ’124 provisional describes an array as depicted in Petitioner’s “Figure A.” *See id.*, 30 (stating that “we agree with Patent Owner’s written description analysis”).

The ’124 provisional also discloses assays and assay systems “comprising one or more agents provided in defined spatial patterns ***on a substrate*** surface….” where, in some cases, “the encoding scheme employs limited reagent delivery to the spatial patterns ***on the substrate*** surface….” EX1009, ¶¶7-8, EX1003, 21:1-17; EX2002, ¶120. The ’124 provisional discloses “[t]he primary criteria of such reagent delivery systems is the ability to direct delivery of specific agents based on spatial patterns ***on the substrate*** surface.” EX1009, ¶15, EX1003, 22:1-5; EX2002, ¶120; *see* EX1009, ¶¶47-48; EX1003, 24:4-27 (disclosing “spatially selective deposition of the binding agents on the substrate surface” and providing

"[e]xamples of methods that can be used for deposition of agents and/or coding identifiers onto the substrate surface"); EX2002, ¶121. Again, once a pre-generated array is constructed, Dr. Cantor explains, it would then be contacted with a tissue section as depicted in "Figure A" to carry out the spatial-distribution analyses described in the '124 provisional. EX2002, ¶¶111-122.

Aside from ignoring these teachings, Petitioner also argues that a "washing" step would "not make sense" in the context of probes covalently bound to beads or other surfaces. Pet., 60-61. In support, Petitioner cites to Figures 1 and 2 and paragraph 28 of the '661 application. *Id.* (citing EX1102, ¶242). That those figures and passages (which correspond to Figures 1 and 2 and column 9, line 66 to column 10, line 24 of the '879 patent) elaborate on ***additional*** types of assays also disclosed in the '879 patent, however, is irrelevant. As Dr. Cantor explains, these types of assays are ***in addition*** to the pre-generated bead arrays discussed above. EX2002, ¶¶118-119.

Petitioner cites to other portions of the '661 application describing additional embodiments. Pet., 62-63 (citing, *e.g.*, EX1011, ¶¶7, 15, 23-24, 34-35, 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 array ("Figure A"). EX2002, ¶¶118-

119.

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 '879 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).[6]

The '124 provisional (and, therefore, the intervening and '971 applications) provides written-description support for "contacting the tissue section with an array comprising a plurality of features." EX2002, ¶112. Petitioner's argument to the contrary fails and the Board should repeat its finding in IPR1289 that the '124 provisional provides adequate written-description support for this limitation here. DDI, 30.

2. <u>The '124 provisional supports contacting an array with a tissue section such that nucleic acids in the tissue section specifically bind to the capture probes</u>

As shown above, the '124 provisional discloses contacting an array with a

[6] 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.

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, ¶¶124-127 (citing EX2009, EX2010). Petitioner argues—like it did in IPR1289—that the '661 Application fails to support the claims because it does not disclose these well-known techniques. Pet., 64-66. But this argument is wrong, and the Board should reject it just like it did in IPR1289. *See* DDI, 28-30.

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., 66; EX1102, ¶264; EX2002, ¶125. 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, ¶124; 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. Again, Patent Owner presented this written-description analysis in its preliminary response for IPR1289 (*see* DDI, 28-29 (quoting Prelim. Resp. 34)), and the Board agreed (*id.*, 30).

Petitioner's argument that the '879 patent's criticism of Armani undercuts written-description support fares no better. Pet., 64-65 (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, ¶129.

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 ¶94. 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, ¶95.

This criticism of Armani has nothing to do with the POSA's knowledge of laboratory techniques. EX2002, ¶128. Methods for preparing a tissue such that the capture agent binds with the nucleic acid were well known and conventional at the time of the '124 provisional. The Board should reject Petitioner's argument just like it rejected the same argument in IPR1289. EX2002, ¶130; DDI, 30.

C. Frisen is Not Prior Art

The Board held in IPR1289 that (1) the '124 provisional provides adequate written-description support for the claim limitations at issue in that case; (2) the priority chain leading at least to the '235 Application was intact; and (3) the '022 patent was entitled to the priority date of April 5, 2010, which is before Frisen's earliest possible priority date of April 13, 2011. DDI, 25 (citing EX1020, code

[30]). Here, Petitioner presents substantially the same arguments over substantially the same claim limitations. But the '879 patent shares the same written description as the '022 patent and traces its priority back to the same '124 provisional application. *Supra,* §VI.A. Thus, the Board should find that the '879 patent's priority date is April 5, 2010, and Frisen is not prior art. And because 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). These obviousness grounds are the same as those Petitioner presented in IPR1289. The Board should find that Petitioner has failed to present a reasonable likelihood that any of the challenged claims would have been obvious just as it did in IPR1289. *See* DDI, 15 (no reasonable likelihood of success over Cantor alone), 25 (no reasonable likelihood of success over Cantor and Armani).

All of Petitioner's arguments hinge on the premise that Cantor, in view of the knowledge of a POSA, renders obvious contacting a "tissue section" with an array of beads. This is wrong, just as it was wrong in IPR1289. Cantor does not

teach or suggest contacting an array with a "tissue section," as required by the claims. That Cantor fails to teach or suggest contacting a bead array with a tissue section makes sense: as the Board recognized in IPR1289, Cantor's methods relate to ***bulk analysis*** of sample nucleic acid, ***not*** to ***spatial analysis*** (e.g., the presence or abundance of a nucleic acid at a location) of a solid material such as a tissue. DDI, 21.

Expanding on this first error, Petitioner then argues (as it did in IPR1289) that, because Cantor's beads can be placed on a substrate, they "***necessarily*** correspond to the location at which the 'probe' portion of the capture agent hybridizes with a sample nucleic acid." Pet. 32. But Cantor says nothing about placing beads in a known location on a substrate, or determining their location prior to use, 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*** "provides information about the location at which the probe interacted with the tissue section, and thus the location of the captured nucleic acid in the tissue

sample." *Id.* 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 just as it was in IPR1289. DDI, 20-25.

But even if a POSA would have constructed a bead array on a substrate and contacted it with a tissue section, 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*** determine presence or abundance of the nucleic acid at a location in the tissue section, as claimed. But, for reasons described below, Cantor's identification sequences would ***not*** "necessarily" provide the presence or abundance of a nucleic acid at a location. 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 information about the presence or abundance of a nucleic acid at a location in a tissue section, 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 nucleic acid in a tissue section using Cantor's ***bulk-analysis*** methods or collections.

Finally, as the Board also recognized in IPR1289, nothing in Armani or any "background reference" compensates for the deficiencies identified in Cantor. DDI, 24. 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 an Array With a "Tissue Section"

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 the presence or abundance of a nucleic acid at a location in ***a tissue section***." Claim 1(preamble). They require "contacting the ***tissue section*** with an array." Claim 1(a). 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. 26 (quoting EX1031, 6). But Cantor ***does not and cannot*** teach a POSA to use a tissue with its beads and methods because spatial analysis (e.g., "determining the presence or abundance of a nucleic acid at a location in a tissue section") does not matter to Cantor at all. Petitioner's grounds of unpatentability based on Cantor fails.

1. Cantor does not teach or suggest contacting bead arrays with a "tissue section"

Cantor (alone or in combination with the knowledge of a POSA) does not teach or suggest contacting its bead arrays with a tissue section. Petitioner's entire argument about "tissue section" goes like this: (1) Cantor teaches that its "sample" may be a solid material such as a tissue or a biopsy; (2) Cantor teaches that its capture agents interact with its "sample nucleic acid"; (3) a POSA would have known how to lyse cells in a tissue sample to release nucleic acid; (4) therefore, a POSA would have contacted Cantor's capture agents with a "tissue section." Pet. 25-28; *see also id.* at 23-25. But as Dr. Cantor explains and plain language of Cantor supports, Cantor's "sample nucleic acid" and is not the same as a "tissue section" and they are not interchangeable in the manner that Petitioner suggests. EX2002, ¶¶30-43, 131-135. The Board agreed with Dr. Cantor on this point in IPR1289, stating that it was "not persuaded by Petitioner's attempts to characterize Cantor's 'nucleic acid sample' as synonymous to 'tissue sample' recited in the

challenged claims." DDI, 23.

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***

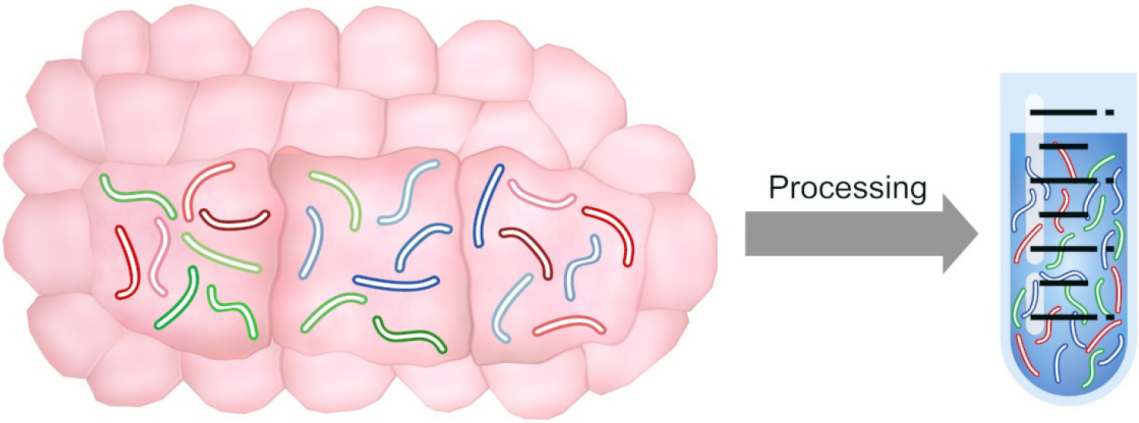
could a POSA continue to the next step of "preparing a mixture comprising sample nucleic acid and a solid support." EX1031, 1; EX2002, ¶132.

Specifically, Cantor states that "***[s]ample nucleic acid*** may be ***derived*** from one or more ***samples*** or sources." EX1031, 5; EX2002, ¶¶35, 133. 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, ¶42; 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, and the Board agreed, "[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, 134; DDI, 23 (quoting EX2002 ¶¶36, 150).[7] Cantor further teaches that deriving a "sample nucleic acid" from a sample or source is accomplished "by any means commonly known in the art,

[7] Corresponding to EX2002, ¶¶36, 134 in this proceeding.

including but not limited to cell lysis procedures using chemical, physical or electrolytic lysis methods." EX1031, 54; EX2002, ¶39; EX2006. The Board correctly found that Cantor's samples "are further processed in bulk to obtain the nucleic acid sample." DDI, 22.

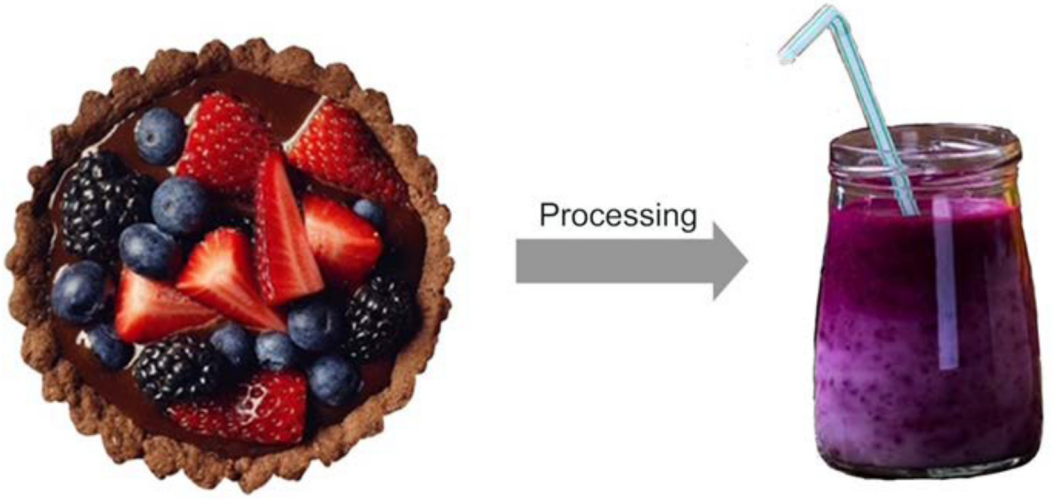
Once the "sample nucleic acid" is derived from a sample or source, a POSA would have understood that the "sample nucleic acid" exists in the form of a homogenized (blended) mixture that ***does not retain*** the original spatial distribution of nucleic acids that a solid material such as a tissue would have. EX2002, ¶¶36, 41. Again, the Board correctly found that "Cantor's nucleic acid samples are made in bulk" "without preserving their spatial distribution." DDI, 21 (citing EX2002, ¶¶17, 19).[8] 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:



[8] Corresponding to EX2002, ¶¶17, 19 in this proceeding.

EX2002, ¶¶36-38.

In this way, Dr. Cantor explains, the difference between the ’879 patent’s claimed “tissue section” and Cantor’s “sample nucleic acid” can be analogized to the difference between the fruit tart and the fruit smoothie discussed above. *Supra* §§II, III.A; EX2002, ¶¶18-20, 36-38, 134.



Fruit Tart Fruit Smoothie

The tart has many different fruits (strawberries, blueberries, blackberries) with an intact spatial distribution. *Id.* But the fruit smoothie does not: the spatial distribution of strawberries, blueberries, and blackberries has been lost because the fruit exists in a homogenized (blended) mixture. *Id.* Dr. Cantor explains that the tart is like a solid material such as a tissue, 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 acknowledges that a "tissue homogenate" cannot provide spatial information. Pet., 26. Yet, Petitioner argues that a POSA would have placed a tissue section on an array of Cantor's beads because a "POSA would have been familiar with, and would have been motivated to apply [cell lysis] techniques to intact tissue or biopsy samples" disclosed by Cantor. Pet. 29 (citing EX1102, ¶144). 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, ¶133. In any event, the sample nucleic acid, whether derived from tissue or any other biological sample, cannot provide any information about spatial location, as the Board correctly found. EX2002, ¶134; DDI, 21.

Cantor does not teach or suggest contacting a "tissue section" with an array 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 the same as in IPR1289. DDI, 20-23.

2. <u>Cantor does not teach or suggest contacting a tissue section with features such as beads at known locations to obtain spatial information</u>

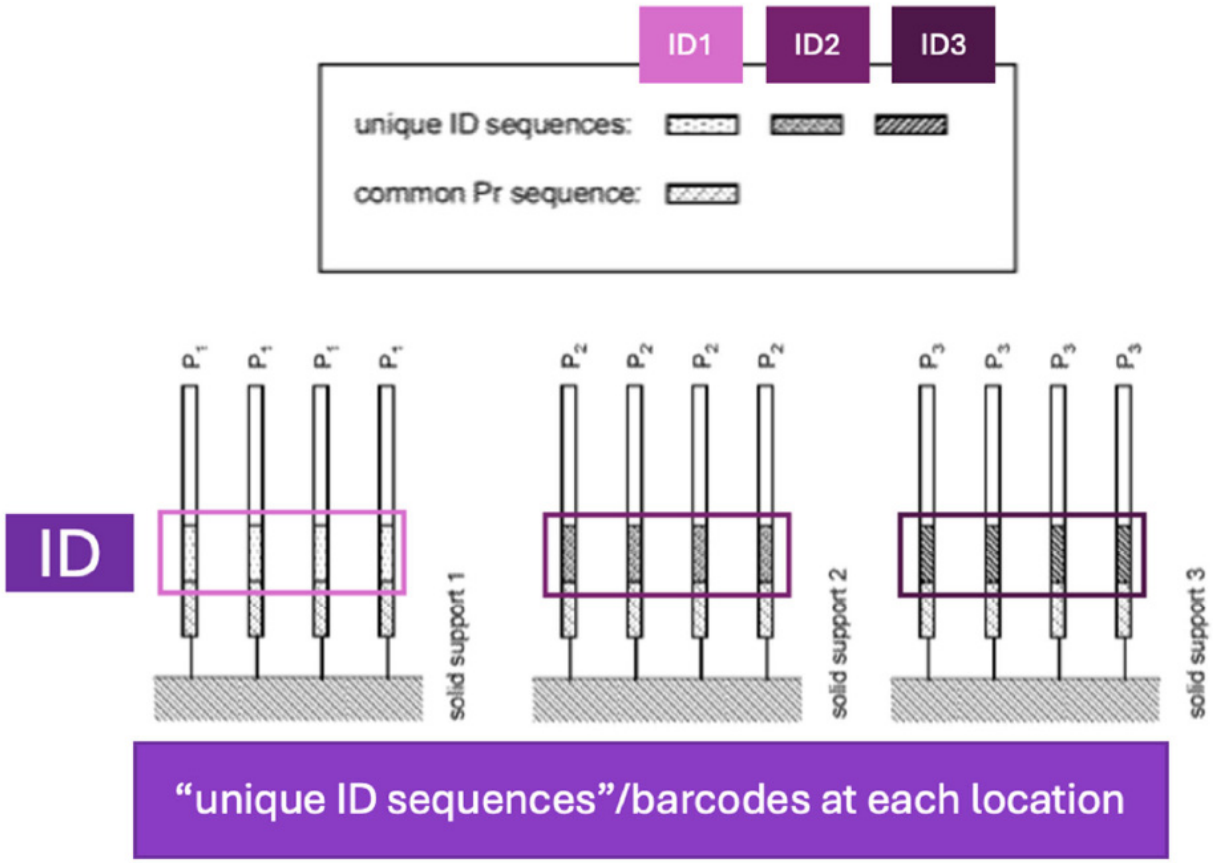
As the Board recognized in IPR1289, not only does Cantor not teach

contacting a "tissue section" with its beads, but Cantor comes nowhere close to suggesting that its beads could be contacted with a tissue section to identify spatial location. DDI, 21. 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 homogenized (blended) mixture that, because it ***does not retain*** the original spatial location of nucleic acids, cannot provide any location information. EX2002, ¶¶35-43, 134. This is 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 ¶¶136-142. 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. 4-5, 24, 39-43. That is incorrect, as the Board found in IPR1289. *See* DDI, 21-22 ("While we recognize that Cantor discloses providing the beads according to an (X,Y) array, this disclosure makes no mention of using this array to map where nucleic acids of Cantor came from relative to the original sample, let alone when that original sample is a tissue." (cleaned up)).

Cantor teaches a "collection" of solid supports that can contain multiple solid-support species (e.g., beads). EX1031, 11, 17; EX2002, ¶138. Cantor also teaches that a collection can be disposed on an array, such as an "X by Y array."

Id. ***But Cantor teaches using substrates to facilitate handling and processing.*** EX1031, 17-18 ("[t]he array can be arranged on any substrate suitable for sequence analysis or manufacture processes described herein"); EX2002, ¶¶68, 139. 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, ¶138. The Board agreed in IPR1289: "Cantor provides no teaching…regarding how to use a tissue sample with the probes and methods described in Cantor to identify where the target nucleic acids of Cantor were spatially located within the tissue sample itself." DDI, 22.

As it did in IPR1289, Petitioner simply ***assumes*** that Cantor's beads are at known locations on the substrate. And, as it did in IPR1289, Petitioner modifies Figure 1C of Cantor to reflect its mistaken assumption (excerpted below):



Pet., 25.

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, ¶¶136-143. 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, ¶140. In other words, nothing in Cantor teaches or suggests that the location of the bead on the substrate is known or even ***needs*** to be known. EX2002, ¶138. 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, ¶139.

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 presence of the nucleic acid at a location." Pet. 35-37. But, fatally for Petitioner's argument, in steps C and D of Figure 2 the linear amplification product ***is released*** from the solid support for downstream

sequencing and analysis. EX1031, 24-25; EX2002, ¶141.

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, ¶¶141-142. 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, ¶¶142-143. Again, the Board agreed with Dr. Cantor that "these types of 'bulk-analysis techniques provide no information about spatial location of biological molecules in tissue samples.'" DDI, 21 (quoting EX2002, ¶17).[9]

[9] Corresponding to EX2002, ¶17 in this proceeding.

B. In Petitioner's Proposed Arrays, the "Coding Tag" 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 "using Cantor's identification sequence to determine the location at which the capture agent interacted with the tissue section." Pet., 32. Nonetheless, Petitioner argues that this would have been inherently obvious:

> [B]ecause 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 capture agent hybridizes*** with a sample nucleic acid, and thus provides information about the location at which the probe interacted with the tissue section, and thus the location of the captured nucleic acid in the tissue sample.

Pet., 32. Put differently, Petitioner argues that Cantor's "identification sequences"

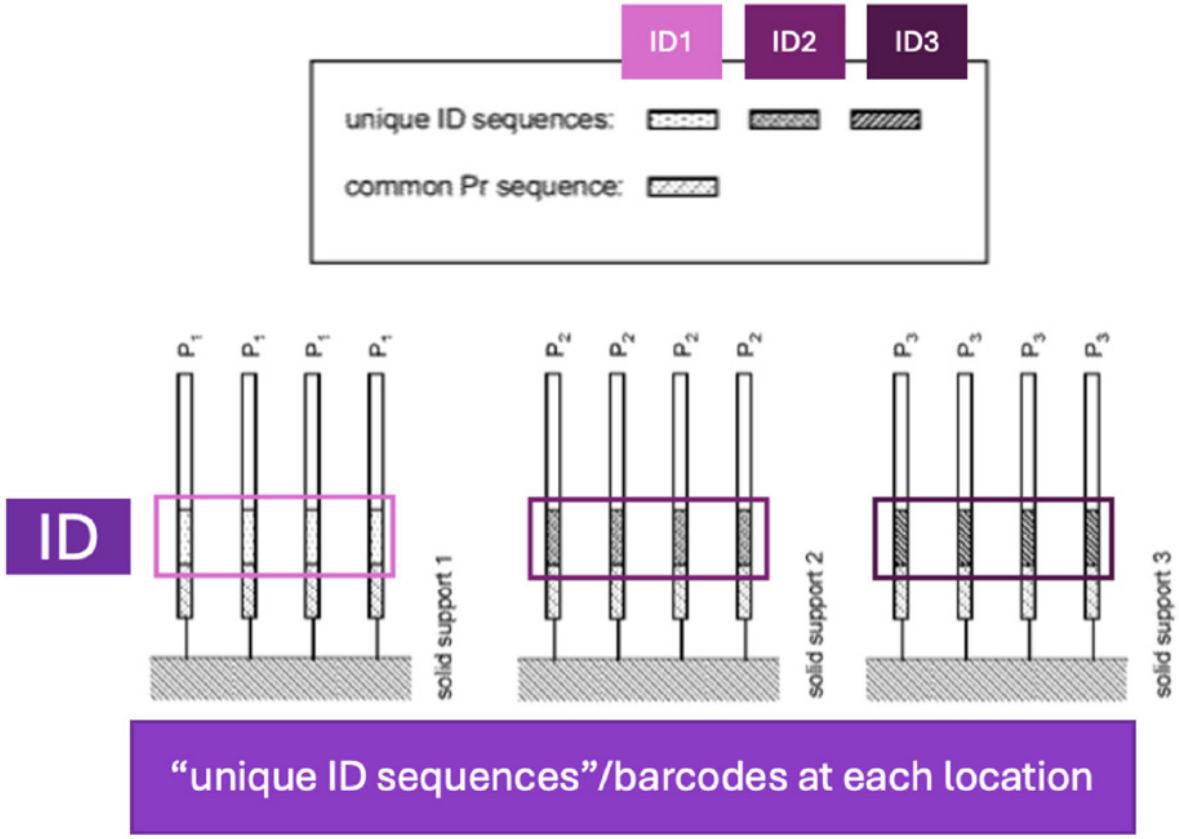
would ***necessarily*** provide spatial information (e.g., the presence or abundance of the nucleic acid at a location in the tissue section). Pet., 32; *see also id.*, 4, 24, 31, 36-37, 49, 50, 77. Petitioner's argument, however, rests on the mistaken assumption that hybridization between Cantor's probes and a nucleic acid in a tissue section 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, ¶¶55-67, 144-145. 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 presence or abundance of the nucleic acid at a location in the tissue section because hybridization does not necessarily occur between the probe and the nucleic acid in a tissue section. And without hybridization, no information about location 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.

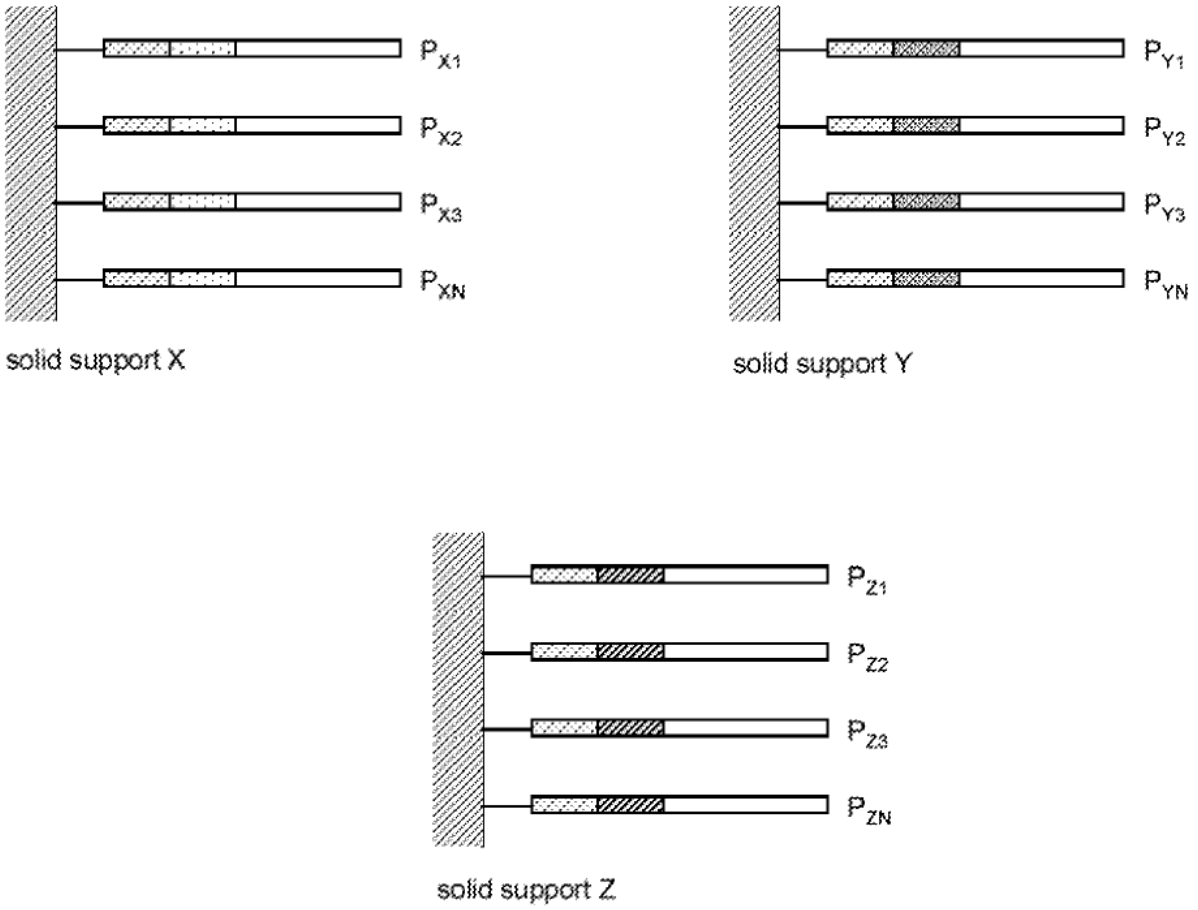
1. That Cantor's bead collections and Petitioner's proposed arrays have different probes on each bead (that are not shared between the beads) dooms Petitioner's obviousness grounds

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 nucleic acid of interest in the sample nucleic acid), not spatial information. EX2002, ¶¶145-153. As Dr. Cantor explains, the presence of ***different probes on each bead*** destroys any ability to obtain spatial information. EX2002, ¶144. Critically, Petitioner ***ignores*** that its proposed array has different probes on each bead (i.e., P_1, P_2, and P_3):



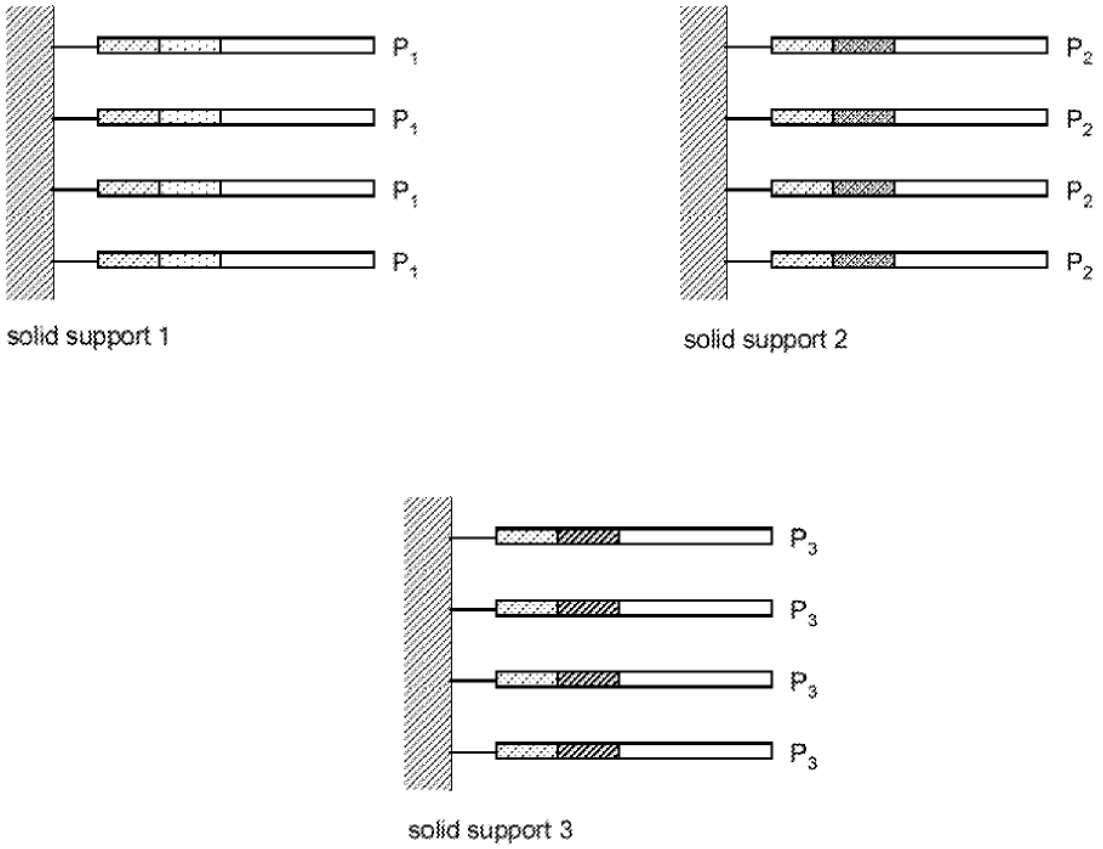
EX2002, ¶138. Each bead in Petitioner's proposed array is specific to a particular nucleic acid (or subsequences of that nucleic acid), dooming Petitioner's challenges.

Cantor describes two different types of collections. EX2002, ¶¶61-67. The first 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, ¶¶64-65. Specifically, bead "X" has probes P_{X1}-P_{XN}, bead "Y" has probes P_{Y1}-P_{YN}, and bead "Z" has probes P_{Z1}-P_{ZN}. *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):



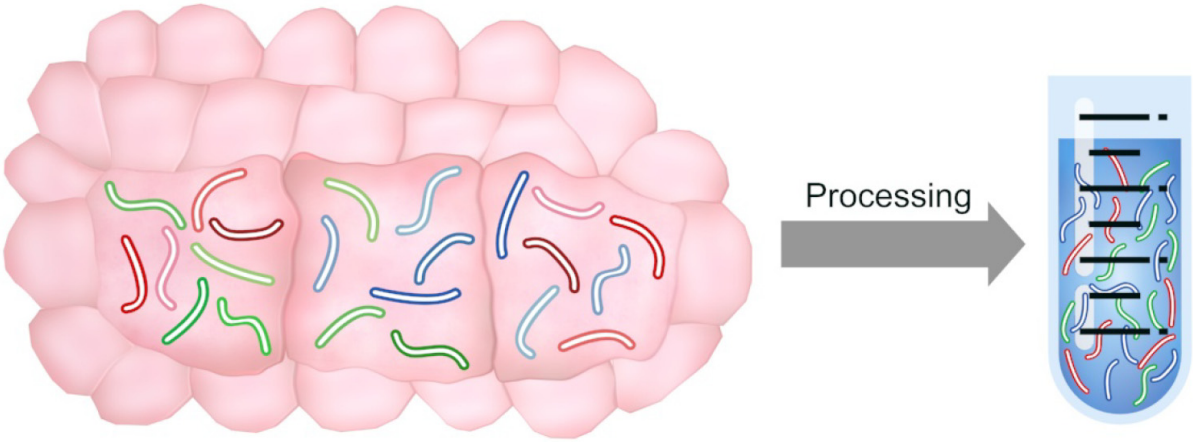
EX1031, 16-17; EX2002, ¶¶66-67. Thus, in Figure 1C, bead "1" has probes P_1, bead "2" has probes P_2, and bead "3" has probes P_3, for a total of three unique probes in the array directed at 3 different target nucleic acids (1, 2, and 3). *Id.*

Critically, in both collections ***no probe is the same between the beads***. EX2002, ¶¶63, 138.

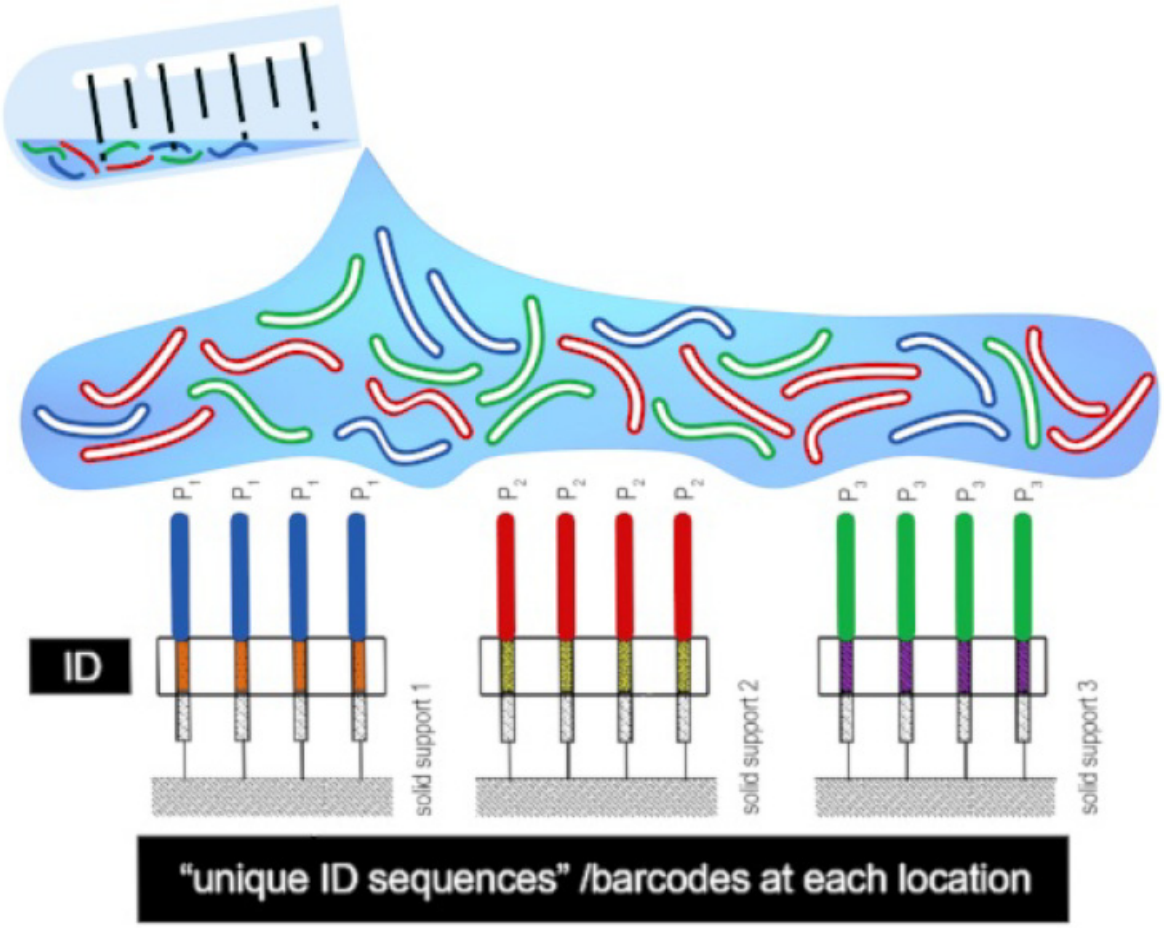
2. <u>Using Petitioner's array with Cantor's sample nucleic acid provides bulk analysis of the presence or absence of a nucleic acid, not its location in a tissue section</u>

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 section highlighting three cells containing nucleic acids depicted as differently colored outlines.



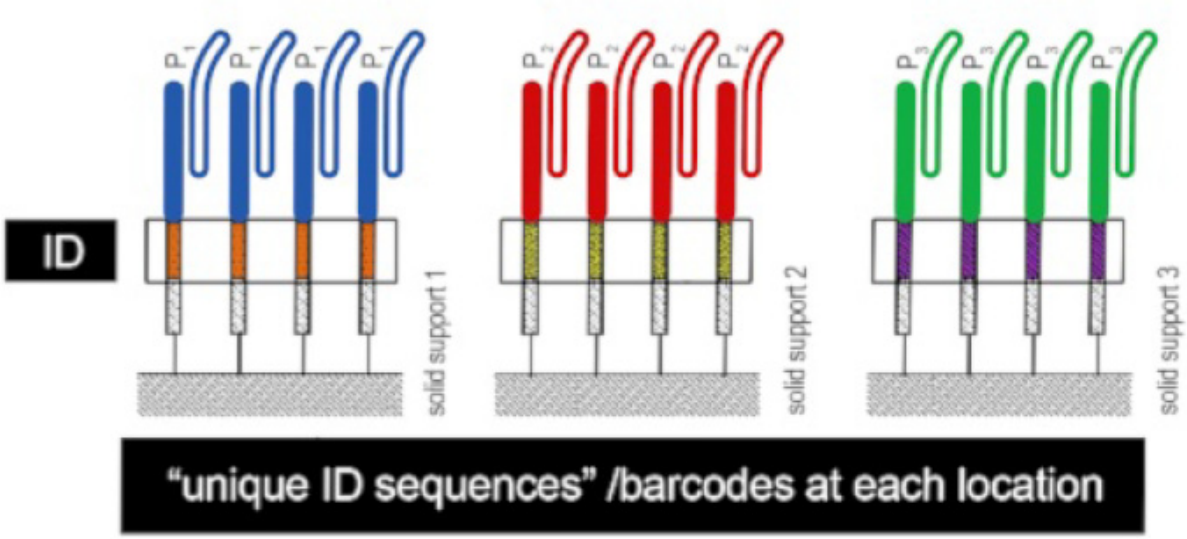
Then, the resulting sample nucleic acid is applied to Petitioner's array, where each different bead on the array has different probe sequence(s). EX1031, EX2002, ¶¶63, 138, 144-145. The mixing of sample nucleic acid with beads arranged on an array is illustrated below:



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, ¶146. 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:



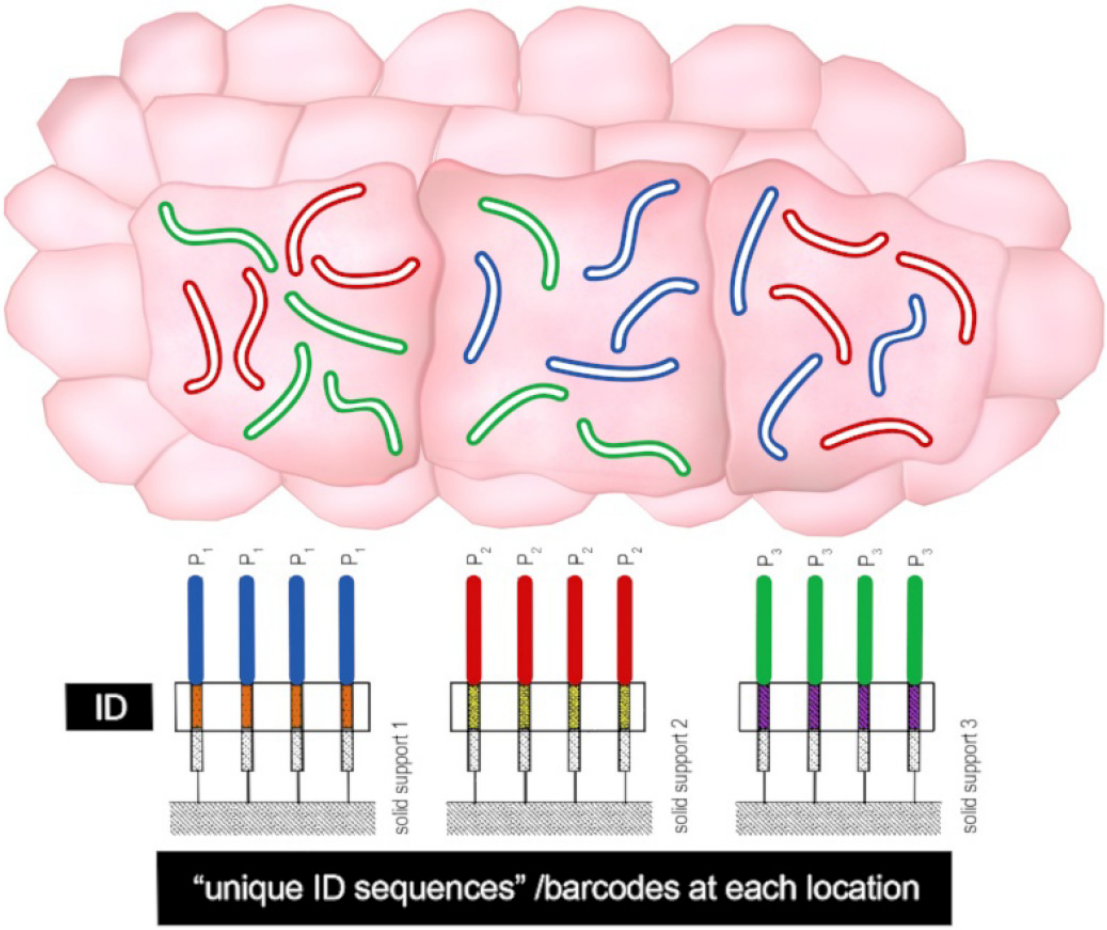
Id. Because the target nucleic acids in the sample nucleic acid are blended together (like in the fruit smoothie), the spatial distribution of the nucleic acids within the original tissue section has been lost. EX2002, ¶147. Put differently, while Cantor's collection can reveal that the **blue-outlined** 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 the presence or abundance ***at a location*** in that source. *Id.*

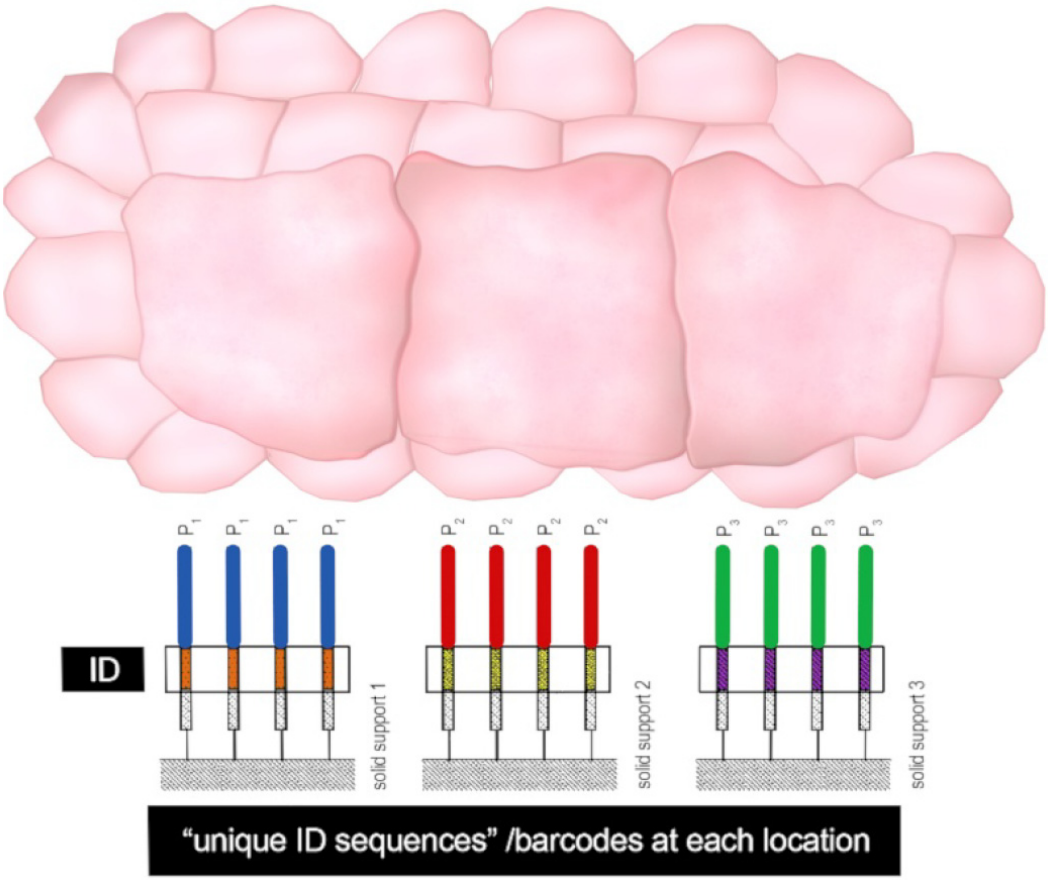
Therefore, as Dr. Cantor explains, a POSA ***could not*** have used Petitioner's array to "determin[e] presence or abundance of the nucleic acid at a location in the tissue section" as claimed. *Id.*; *see also* Claim 1(b).

3. Using Petitioner's array with a tissue section would not necessarily provide the spatial location of a nucleic acid because hybridization would not necessarily occur

Contacting Petitioner's bead array with a ***tissue section*** would not ***necessarily*** result in the spatial location of a nucleic acid. The following illustrations depict what would happen if a POSA overlaid the proposed array with a solid tissue. EX2002, ¶148; *see also* Pet., 25-26. 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, ¶149. When nucleic acids are released from a tissue section 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:

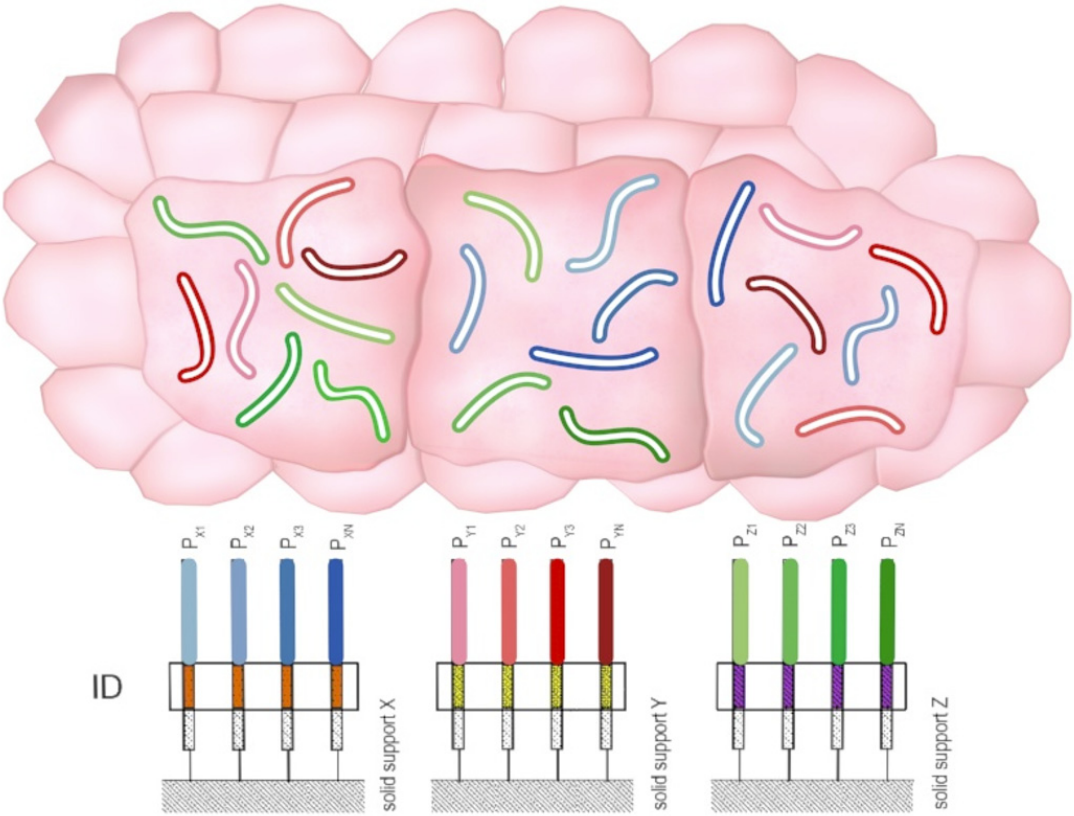


Id.

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 nucleic acids 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, ¶¶150-151. The latter array is illustrated below:

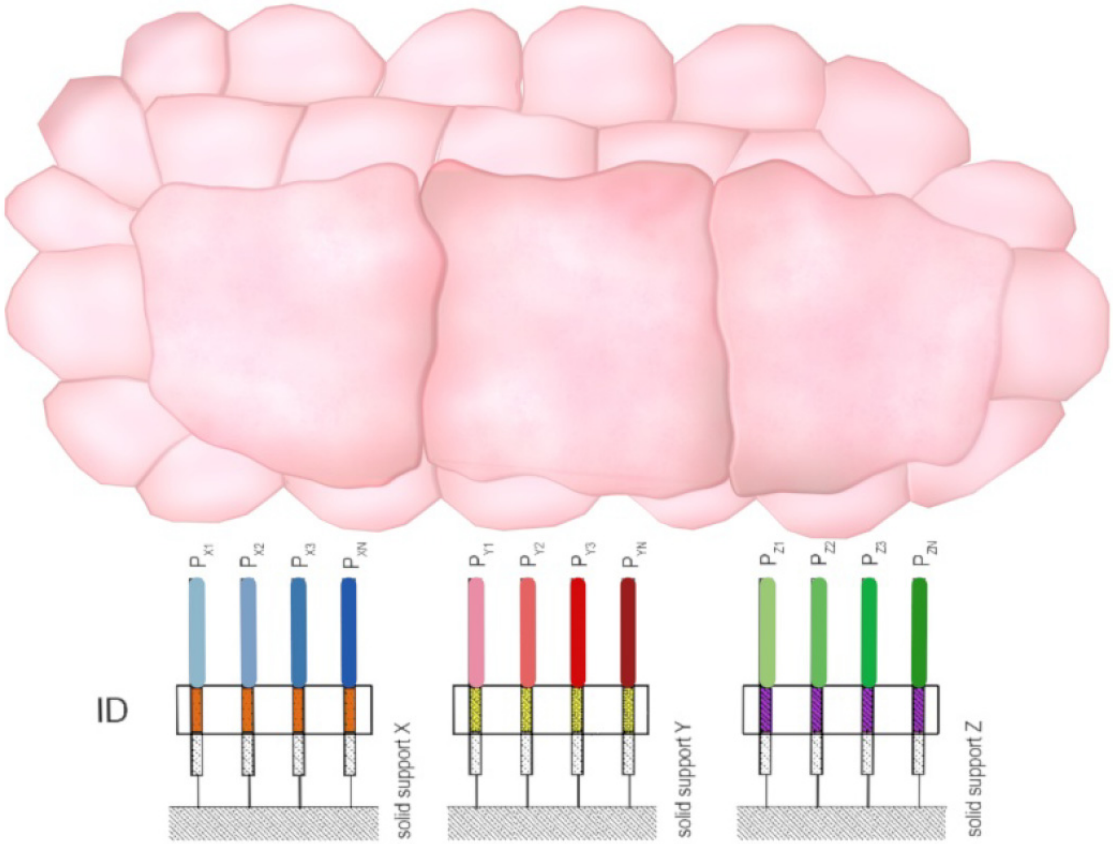


Id.

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 nucleic acids 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, ¶¶152-153.

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 nucleic acid in a tissue and thus ***necessarily*** provide information about that nucleic acid's presence or abundance at a location in the tissue section. 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 location in the tissue section 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 presence or abundance of a nucleic acid at a location in a tissue section with a reasonable expectation of success. Dr. Cantor himself explains that a POSA would have recognized the futility of attempting to obtain location information from the arrays disclosed in Cantor. EX2002, ¶154.

"[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 sections discussed in the '879 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 section (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 section those

nucleic acids 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 the presence or abundance of a nucleic acid at a 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 presence or abundance of the nucleic acid at a location in the tissue section," as claimed. EX2002, ¶155; Claim 1(b). 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 section and contact it with Petitioner's proposed array. And because contacting Petitioner's proposed array with a tissue section would not necessarily determine ***where*** a particular nucleic acid sequence is located in a tissue section, a POSA would not have had a reasonable expectation of success in using the combination of Cantor's collection of beads and a tissue section in the claimed method.

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, ¶156. 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, ¶¶140, 156. 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. EX1031, 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, ¶156. 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, ¶70-91.

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 tissue section with an array" (claim 1(a)); and using the coding tag to "determine presence or abundance of the nucleic acid at a location in the tissue section" (claim 1(b))—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 tissue section with an array comprising a plurality of features to determine a location in the tissue section using the claimed coding tag. Indeed, almost all of Petitioner's "analysis" of the purported background references (Pet., 26–28, 37-42), 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, 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 two references in any detail in the grounds: Southern and Armani. Petitioner cites to Southern as describing "techniques to . . . facilitate hybridization between the nucleic acids in [an intact tissue or biopsy sample] and the array's capture probes" and "performing spatially-defined assays." Pet. 27 (citing EX1033, 2:17-20), 37-38 (citing EX1033 1:19-20). But, like Cantor (*supra* §VII.A), Southern does ***not*** teach contacting a solid support with a ***tissue***. Rather, Petitioner's own quotation from Southern shows that

Southern contacts ***cells***[10] 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. 27 (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 nucleic acids of a tissue section. EX2002 ¶157; *see also* EX1102, ¶¶45-51.

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, ¶158.[11] Indeed, Southern teaches that it is "[a]fter ***separation*** of cells of interest from other components in the ***starting*** samples" that "the cells of interest can be analysed using the devices of the invention." *Id.*

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[10] Alternatively, Southern teaches that the released material from cells may be overlayed on the solid support. EX1033, 17; EX2002, ¶158.

[11] 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, ¶160.

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 nucleic acids*** 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, ¶¶158. 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, ¶158. 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, ¶159. 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, ¶159. But the spatial location of a nucleic acid of a tissue is not maintained. EX2002, ¶159.

In Ground 2, Petitioner combines Cantor with Armani. Pet., 51-56. But the Board "was not persuaded that Armani cures the deficiencies of Cantor discussed…with regard to Petitioner's Ground 1." DDI, 24. 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., 52-53; *see also* EX2002, ¶161. In other words, placing one of the beads of Petitioner's array in each of Armani's wells. *Id.*, 52 ("obvious to combine teachings of Cantor and 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 nucleic acid cannot be determined. *Supra* §VII.B.2; *see also* EX2002, ¶161. The Board expressly agreed with this analysis in IPR1289 (DDI 24-25), and should do the same here.

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 tag 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 just

as it denied institution of the petition in IPR1289.

Respectfully submitted,

Date: April 29, 2025

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

Under the provisions of 37 C.F.R. §42.24(d), the undersigned hereby certifies that the word count for the foregoing Patent Owner's Preliminary Response to Petition totals 13,284, which is less than the 14,000 allowed under C.F.R. §42.24(b)(1).

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CERTIFICATE OF SERVICE

Pursuant to 37 CFR § 42.6(e)(4) and 42.205(b), the undersigned certifies that on April 29, 2025, a complete and entire copy of this Patent Owner's Preliminary Response and accompanying exhibits were provided by email to Petitioner by serving the correspondence email address of record as follows:

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