

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.

IPR2025-00236
Patent No. 10,662,468

PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 10,662,468

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TABLE OF CONTENTS

	<u>Page</u>
I. INTRODUCTION	4
II. GROUNDS FOR STANDING.....	8
III. MANDATORY NOTICES	8
A. Real Party-In-Interest	8
B. Related Matters.....	8
C. Lead and Back-up Counsel and Service Information	10
D. Additional Service Information.....	10
IV. GROUNDS FOR THE CHALLENGES	11
V. THE '468 PATENT	11
VI. CITED PRIOR ART.....	13
A. Cantor	13
B. Armani.....	13
C. Frisen	13
VII. LEVEL OF ORDINARY SKILL IN THE ART	13
VIII. BACKGROUND KNOWLEDGE OF A POSA	14
A. Molecular Biology.....	14
B. Cells and Tissues	14
C. Spatial Analysis	15
1. Detection of Nucleic Acids.....	15
2. Nucleic Acid Arrays.....	16
3. Sequence Barcoding.....	17

	<u>Page</u>
D. Overview of Spatial Analysis Technologies	19
IX. CLAIM CONSTRUCTION	23
X. THE BOARD SHOULD CANCEL THE CHALLENGED CLAIMS	24
A. Ground 1: Obviousness over Cantor in view of the Knowledge of a POSA	24
1. Claim 1	24
2. Claim 2	44
3. Claim 6	45
4. Claim 7	45
5. Claims 12-13	46
6. Claim 18	46
7. Claim 20	47
8. Claim 21	47
9. Claim 23	48
10. Claims 25-26	48
11. Claim 30	49
B. Ground 2: Obviousness over Cantor in view of Armani and Knowledge of a POSA.	51
1. Claim 1	51
2. Claim 21	55
3. Claim 23	56
C. Ground 3: Anticipation by Frisen.....	58

	<u>Page</u>
1. Priority Date	58
2. Claim 1	67
3. Claim 2	72
4. Claim 6	72
5. Claim 7	72
6. Claims 12-13	73
7. Claim 18	73
8. Claim 20	74
9. Claim 21	74
10. Claim 23	75
11. Claims 25-26	75
12. Claim 30	76
XI. SECONDARY CONSIDERATIONS	77
XII. NO BASIS FOR DISCRETIONARY DENIAL	78
A. Denial Under 314(a) is Inappropriate	78
B. Denial Under 325(d) is Inappropriate	80
XIII. CONCLUSION.....	80

TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>10x Genomics, Inc. and Prognosys Biosciences Inc. v. Curio Bioscience, Inc.</i> , No. 23-cv-01375-MN (D. Del.)	8
<i>Apple Inc. v. Fintiv, Inc.</i> , IPR2020-00019, Paper 11 (PTAB March 20, 2020)	78, 79
<i>Flash-Control, LLC v. Intel Corp.</i> , No. 2020-2141, 2021 WL 2944592 (Fed. Cir. July 14, 2021)	60
<i>Gentry Gallery, Inc. v. Berkline Corp.</i> , 134 F.3d 1473 (Fed. Cir. 1998)	64
<i>Geo M. Martin Co. v. Alliance Mach. Sys. Int’l LLC</i> , 618 F.3d 1294 (Fed. Cir. 2010)	77
<i>Holmer v. Harari</i> , 681 F.3d 1351 (Fed. Cir. 2012)	59
<i>ICU Med., Inc. v. Alaris Med. Sys., Inc.</i> , 558 F.3d 1368 (Fed. Cir. 2009)	65
<i>Mylan Pharmaceuticals Inc. v. Merck Sharp & Dohme Corp.</i> , IPR2020-00040, Paper 21 (PTAB May 12, 2020)	80
<i>Novozymes A/S v. DuPont Nutrition Biosciences APS</i> , 723 F.3d 1336 (Fed. Cir. 2013)	60
<i>Nuvo Pharms. (Ir.) Designated Activity Co. v. Dr. Reddy’s Labs. Inc.</i> , 923 F.3d 1368 (Fed. Cir. 2019)	66
<i>Quake v. Lo</i> , 928 F.3d 1365 (Fed. Cir. 2019)	6, 67
<i>Rivera v. Int’l Trade Comm’n</i> , 857 F.3d 1315 (Fed. Cir. 2017)	65

IPR2025-00236
Patent No. 10,662,468

<i>Yita LLC v. MacNeil IP</i> LLC, IPR2023-00172, Paper No. 12	80
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Statutes

35 U.S.C. §119(e)	58
35 U.S.C. §120.....	58
35 U.S.C. §314(a)	79
35 U.S.C. § 315(e)(2)	78
35 U.S.C. § 325(d)	80

EX NO.	PETITIONER'S EXHIBIT LIST
EX1001	U.S. Patent No. 10,480,022 issued to Chee
EX1002	U.S. Patent No. 10,662,468 issued to Chee
EX1003	U.S. Patent No. 11,001,879 issued to Chee
EX1004	U.S. Patent No. 11,549,138 issued to Chee
EX1005	U.S. Patent No. 11,761,030 issued to Chee
EX1006	10x Genomics' Complaint for Patent Infringement, Case 1:23-cv-01375, Doc. 1, filed December 1, 2023
EX1007	Exemplary Infringement Claim Chart-U.S. Patent No. 10,480,022 Case 1:23-cv-01375, Doc. 1-11, filed December 1, 2023 (EX K)
EX1008	Reserved
EX1009	U.S. Provisional Application No. 61/321,124
EX1010	File History for U.S. Application No. 16/276,235 (2 parts)
EX1011	File History for U.S. Application No. 15/187,661
EX1012	File History for U.S. Application No. 13/080,616
EX1013	Nick J. Proudfoot, <i>et al.</i> , <i>Integrating mRNA Processing with Transcription</i> , Cell, Vol. 108, 501-512, February 22, 2002
EX1014	Uwe Kuhn <i>et al.</i> , <i>Poly(A) Tail Length Is Controlled by the Nuclear Poly(A)-binding Protein Regulating the Interaction between Poly(A) Polymerase and the Cleavage and Polyadenylation Specificity Factor</i> , The Journal of Biologic Chemistry VOL. 284, NO. 34, pp 22803-22814, August 21, 2009
EX1015	James Eberwine <i>et al.</i> , <i>Complementary DNA Synthesis in Situ: Methods and Applications</i> , Methods in Enzymology, VOL. 216, 1992

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EX1016	Laurence H. Tecott <i>et al.</i> , <i>In Situ Transcription: Specific Synthesis of Complementary DNA in Fixed Tissue Sections</i> , Science, VOL. 240, pp. 1661-1664, 1988
EX1017	Anna Ligasová and Karel Koberna, <i>In situ reverse transcription: the magic of strength and anonymity</i> , Nucleic Acids Research, 2010, Vol. 38, No. 16
EX1018	Victor Trevino <i>et al.</i> , <i>DNA Microarrays: a Powerful Genomic Tool for Biomedical and Clinical Research</i> , Mol Med 13 (9-10) 527-541, September-October 2007
EX1019	Stahl <i>et al.</i> , "Visualization and analysis of gene expression in tissue sections [sic: sections] by spatial transcriptomics," <i>Science</i> 353(6294):78-82 (July 1, 2016)
EX1020	WO 2012/140224 A1 to Frisen
EX1021	WO 2010/088517 A1 to Emmert-Buck, Armani <i>et al.</i>
EX1022	Michael Armani <i>et al.</i> , <i>2D-PCR: a method of mapping DNA in tissue sections</i> , Lab Chip, 2009, 9(24), 3526-3534; NIH Public Access Author Manuscript
EX1023	Lambda Moses and Lior Pachter, <i>Museum of spatial transcriptomics</i> , Nature Methods, VOL 19, May 2022 [534-546]
EX1024	U.S. Patent No. 11,214,796 issued to Shirai
EX1025	JP2007-14297 to Okano
EX1026	EP 2 130 913 A1 to Okano
EX1027	Franklin M. Harold, <i>Molecules into Cells: Specifying Spatial Architecture</i> , <i>Microbiology and Molecular Biology Reviews</i> , Dec. 2005, p. 544-564

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EX1028	Vanessa M. Brown <i>et al.</i> , <i>Multiplex Three-Dimensional Brain Gene Expression Mapping in a Mouse Model of Parkinson's Disease</i> , Genome Research, 12:868-884, 2002
EX1029	Michael L. Metzker, <i>Sequencing technologies-the next generation</i> , Nature Reviews Genetics, Volume 11, January 2010
EX1030	Poornima Parameswaran, <i>et al.</i> , <i>A pyrosequencing-tailored nucleotide barcode design unveils opportunities for largescale sample multiplexing</i> , Nucleic Acids Research, 2007, Vol. 35, No. 19
EX1031	WO 2009/091934 A1 Cantor
EX1032	U.S. Patent No. 6,620,584 issued to Chee
EX1033	WO 2008/075086 A1 Southern <i>et al.</i>
EX1034	Spellman Declaration EX1002 from IPR2023-01298
EX1035	10x Genomics' Opening Brief in support of Motion to Dismiss, Case 1:18-cv-01800 (D.Del), Doc. 19, filed March 1, 2019
EX1036	Norman P. Gerry, <i>et al.</i> , <i>Universal DNA Microarray Method for Multiplex Detection of Low Abundance Point Mutations</i> , J. Mol. Biol. (1999) 292, 251-262
EX1037	U.S. Patent No. 8,835,358 issued to Fodor
EX1038	U.S. No. 2007/0231824 A1 to Chee
EX1039	Jian-Bing Fan, <i>et al.</i> , <i>Illumina Universal Bead Arrays</i> , Methods in Enzymology, VOL. 410, 2006
EX1040	10X Genomics' Petition for IPR Review of Nanostring Technologies' Patent No. 11,377,689 (IPR2023-01298)

EX NO.	PETITIONER'S EXHIBIT LIST
EX1041	July 24, 2024 Email from Counsel for Patent Owner to Counsel for Petitioner
EX1042	August 16, 2024 Email from Counsel for Patent Owner to Counsel for Petitioner
EX1043	Scheduling Order, Doc #25, C.A. 23-cv-1375 (D.Del.)
EX1044	Leslie P. Gartner, Ph.D. and James L. Hiatt Ph.D., <i>Color Textbook of Histology</i> , Third Edition, Saunders Elsevier
EX1045	WO 2014/060483 A1 ("Frisen")
EX1046	Marshall S. Scicchitano <i>et al.</i> , <i>Preliminary Comparison of Quantity, Quality, and Microarray Performance of RNA Extracted From Formalin-fixed, Paraffin-embedded, and Unfixed Frozen Tissue Samples</i> , 2006, J. Histochemistry & Cytochemistry 54(11), 1229-1237.
EX1047	Stephen M. Hewitt, MD <i>et al.</i> , <i>Tissue Handling and Specimen Preparation in Surgical Pathology</i> , Arch. Pathol. Lab. Med. (2008) 132, 1929-1935.
EX1048	US6,133,436 issued to Köster
EX1049-1054	Reserved
EX1055	File History for 16/430,015 (the "'015 Application")
EX1056	File History for 16/414,213 (the "'213 Application")
EX1057	File History for 16/402,098 (the "'098 Application")
EX1058	Reserved
EX1059	File History for 16/988,284 (the "'284 Application")
EX1060	Reserved

IPR2025-00236

Patent No. 10,662,468

EX NO.	PETITIONER’S EXHIBIT LIST
EX1061	Exemplary Infringement Claim Chart-U.S. Patent No. 11,549,138 Case 1:23-cv-01375, Doc. 1-11, filed December 1, 2023 (EX N)
EX1062	Exemplary Infringement Claim Chart-U.S. Patent No. 11,761,030, Case 1:23-cv-01375, Doc. 1-11, filed December 1, 2023 (EX O)
EX1063	File History for 16/443,771 (the “771 Application”)
EX1064	File History for 16/437,726 (the “726 Application”)
EX1065	Exemplary Infringement Claim Chart-U.S. Patent No. 10,662,468, Case 1:23-cv-01375, Doc. 1-12, filed December 1, 2023 (EX L)
EX1066	Exemplary Infringement Claim Chart-U.S. Patent No. 11,001,879, Case 1:23-cv-01375, Doc. 1-12, filed December 1, 2023 (EX M)
EX1067-EX1100	Reserved
EX1101	Curriculum Vitae of Joseph D. Puglisi, Ph.D.
EX1102	Declaration of Joseph D. Puglisi, Ph.D. for IPR2025-00236 & IPR2025-00237

LISTING OF CHALLENGED CLAIMS

1. A method for determining the presence or abundance of a nucleic acid at a location in a tissue section comprising:

(a) contacting the tissue section with an array comprising a plurality of features, wherein a feature of the plurality of features comprises a capture agent, wherein the capture agent comprises:

(i) a first sequence that specifically binds the nucleic acid, and

(ii) a second sequence comprising a coding tag, wherein a sequence of the coding tag corresponds to a location of the capture agent on the array;

(b) determining all or a portion of the sequence of the coding tag, or a complement thereof, and all or a portion of the sequence of the nucleic acid specifically bound to the capture agent, or a complement thereof, and using the determined sequences to determine presence or abundance of the nucleic acid at a location in the tissue section.

2. The method of claim 1, wherein the method further comprises, between steps (a) and (b), a step of removing the tissue section from the array.

6. The method of claim 1, wherein the determining step comprises nucleic acid amplification.

7. The method of claim 1, wherein the determining step comprises sequencing all or a portion of the sequence of the coding tag, or a complement thereof, and all or a portion of the sequence of the nucleic acid specifically bound to the capture agent, or a complement thereof.

12. The method of claim 1, wherein the nucleic acid is RNA.

13. The method of claim 12, wherein the RNA is mRNA.

18. The method of claim 1, wherein the capture agent is immobilized directly or indirectly on a surface of the feature.

20. The method of claim 1, wherein the array comprises a bead array.

21. The method of claim 1, wherein the tissue section is a fresh frozen tissue section or a formalin-fixed paraffin-embedded (FFPE) tissue section.

23. The method of claim 1, wherein the method further comprises generating a map of the presence or abundance of the nucleic acid at location(s) in the tissue section.

25. The method of claim 1, wherein the array comprises greater than 500 features.

26. The method of claim 1, wherein the array comprises greater than 1,000 features.

30. The method of claim 1, wherein a feature of the plurality of features comprises greater than 100 capture agents, where each of the greater than 100

IPR2025-00236

Patent No. 10,662,468

capture agents comprises a first sequence that specifically binds to a different nucleic acid and a coding tag that corresponds to a location of the capture agent on the array.

Curio Bioscience, Inc. (“Petitioner”) requests *inter partes* review and cancellation of claims 1, 2, 6, 7, 12-13, 18, 20, 21, 23, 25-26, and 30 of U.S. Patent No. 10,662,468 (“Chee-468”), entitled “Spatially Encoded Biological Assays.” Chee-468 is owned by Prognosys, and was licensed to real-party-in-interest 10x Genomics (“10x”) in November 2018.¹

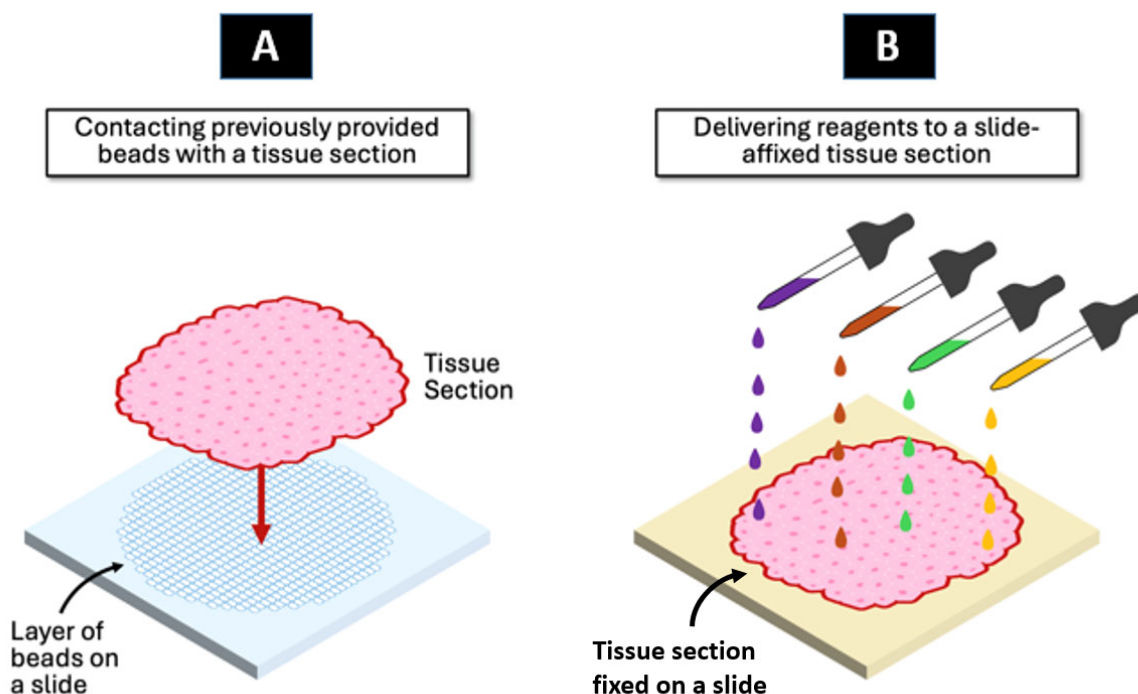
I. INTRODUCTION

The claims of Chee-468 recite “[a] method for determining the presence or abundance of a nucleic acid at a location in a tissue section” comprising contacting nucleic acid “capture agents” and “coding tags” with a tissue section, and “and using the determined sequences [of the coding tag] to determine presence or abundance of the nucleic acid at a location in the tissue section.” EX1002, cl. 1. In co-pending litigation, PO has read the claims of Chee-468 to cover methods of using nucleic acid bead arrays to analyze the spatial organization of nucleic acids in a tissue sample placed on top of the array, and using the array to tag captured mRNA with “spatial barcodes.” *See* EX1006.

Such methods are not described by Chee-468 or its priority documents. Rather, Chee-468’s specification focuses on the patterned delivery of probes to a

¹ Patent Owner (“PO”) collectively refers to 10x and Prognosys. 10x and Prognosys refer to the separate actions of each.

slide-affixed tissue sample using allegedly novel “reagent delivery systems” such as inkjet printing or photolithography, techniques Chee-468 calls “integral to the assay system of the invention.” *See* EX1002, 16:15-17. The stark contrast between the approach PO now claims (Figure A) and the approach actually described in the specification (Figure B) is illustrated below.



This disconnect exists because, starting in 2019, 10x began prosecuting the claims of Chee-468’s predecessor applications, and subsequently Chee-468, to cover implementations of technology it acquired from Spatial Transcriptomics AB (“ST”). ST is a company 10x acquired in late 2018, around the same time it licensed Chee-468 from Prognosys. In proceedings not involving Prognosys, 10x has stated:

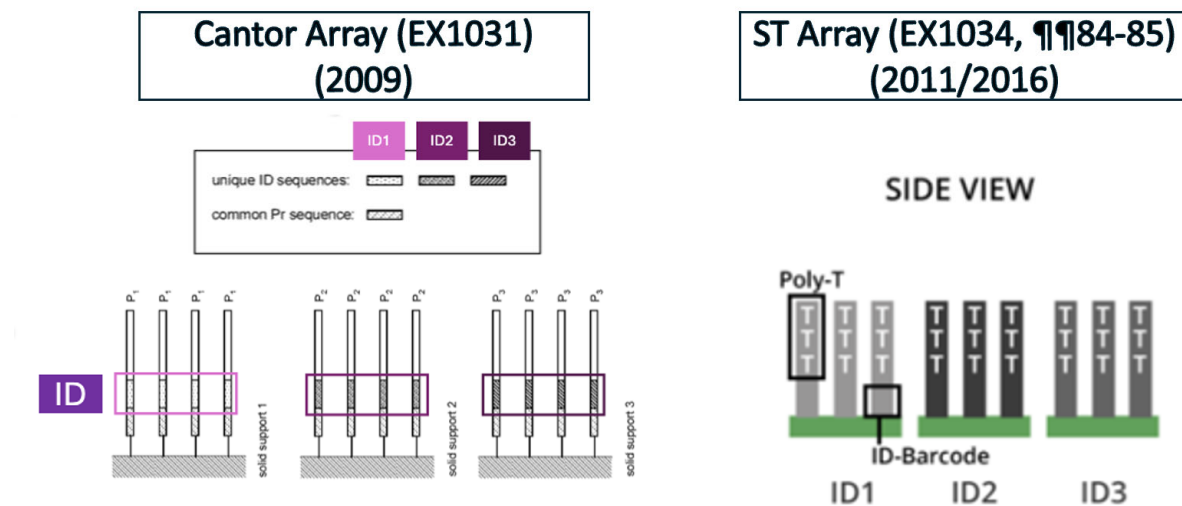
As early as 2011, Stahl et al. *developed a pioneering spatially barcoded array paradigm* for determining the locations of target mRNAs in a biological sample. *The scientists disclosed this foundational technology in a patent application filed in 2011* (WO 2012/140224; [EX1020 (Frisen)]) and subsequently published it in a 2016 article [EX1019].

EX1034, ¶82. 10x's claim that Frisen's work—filed over one year after what PO contends is Chee-468's priority date (April 2010)—was “foundational” and “pioneering” is a telling sign that Chee-468 does not support claims to spatially barcoded arrays for nucleic acid analysis. Nevertheless, shortly after taking over prosecution of the Chee-468 family in early 2019, 10x filed a substitute specification and began seeking claims to cover the “pioneering” work of ST.

The written description requirement exists precisely “to prevent an applicant from later asserting that he invented that which he did not, [which] is particularly important when, as here, claims are added later during prosecution in response to development by others.” *Quake v. Lo*, 928 F.3d 1365, 1373 (Fed. Cir. 2019) (internal quotation omitted). In this case, the lack of support for the claims in Chee-468's priority documents means that it is entitled to, at the earliest, the 2019 filing date of the claims. Accordingly, Chee-468 is anticipated by Frisen.

To be sure, before Chee-468's earliest priority date, there was nothing new about either its claims or the later-filed yet still somehow “pioneering” and

“foundational” ST array designs it purports to cover. By 2009, noted geneticist Charles Cantor had already published nucleic acid bead arrays in which each bead comprises (i) a probe sequence that binds a target nucleic acid in a tissue sample and (ii) an identification sequence (ID) (or “barcode”) that is unique for each bead. Because each bead necessarily occupies a different spatial location on a given array, each barcode necessarily corresponds to a particular location in the array. As illustrated below, Cantor’s 2009 array consists of the exact same [solid support (e.g., bead)]—[barcode]—[probe] structure as the subsequently-disclosed ST embodiment—which is claimed but not disclosed in Chee-468. EX1102, ¶¶113-115.



In Cantor’s methods, after the sample nucleic acid hybridizes to a probe at a specific location in the array, it undergoes a process of extension and amplification to generate a population of “barcoded” nucleic acids in which its bead ID/barcode

sequences are appended to the captured sample nucleic acids. These nucleic acids are then sequenced, which provides the identity and spatial location of the detected molecule. Accordingly, Cantor renders the challenged claims unpatentable.

As explained further below, and in the accompanying declaration of Joseph Puglisi, Ph.D. (EX1102), the Board should institute IPR and cancel the challenged claims.

II. GROUNDS FOR STANDING

Petitioner certifies that the '468 patent is available for *inter partes* review and that Petitioner is not barred or estopped from requesting an *inter partes* review challenging its claims on the grounds identified in this petition.

III. MANDATORY NOTICES

A. Real Party-In-Interest

Petitioner Curio Bioscience, Inc. is the real party-in-interest with respect to this petition.

B. Related Matters

On December 1, 2023, Prognosys and 10x Genomics filed a lawsuit against Petitioner in the District of Delaware. *10x Genomics, Inc. and Prognosys Biosciences Inc. v. Curio Bioscience, Inc.*, No. 23-cv-01375-MN (D. Del.) alleging infringement of US Patent Nos. 10,480,022; 10,662,468; 11,001,879; 11,549,138; and 11,761,030.

On September 11, 2024, Petitioner filed *inter partes* review petition IPR2024-01289 challenging claims 1-7, 11-15, 17, 19, and 27-29 of US Patent No. 10,480,022.

On November 15, 2024, Petitioner filed *inter partes* review petition IPR2025-00192 challenging claims 1, 5, 17, 20, 23, 28, and 29 of U.S. Patent No. 11,549,138.

On November 15, 2024, Petitioner filed *inter partes* review petition IPR2025-00193 challenging claims 1, 3, 6, 10-11, 16, 18, 21, 24-26, and 30 of U.S. Patent No. 11,761,030.

On November 27, 2024, Petitioner filed *inter partes* review petition IPR2025-00237 challenging claims 1, 2, 5, 6, 11-12, 17, 21, 23, 27, 28, and 30 of U.S. Patent No. 11,001,879.

Chee-468 issued from application No. 16/660,234 filed on October 22, 2019, which is a continuation of application No. 16/443,771, filed on June 17, 2019, which is a continuation of application No. 16/437,726, filed on June 11, 2019, which is a continuation of application No. 16/430,015, filed on June 3, 2019, which is a continuation of application No. 16/414,213, filed on May 16, 2019, which is a continuation of application No. 16/402,098, filed on May 2, 2019, now Pat. No. 10,472,669, which is a continuation of application No. 16/276,235, filed on February 14, 2019, now Pat. No. 10,480,022, which is a continuation of application No. 15/187,661, filed on June 20, 2016, now US 10,308,982, which is a continuation

of application No. 13/080,616, filed on April 5, 2011, now US 9,371,598. Chee-468 also claims priority to provisional application No. 61/321,124 filed on April 5, 2010.

C. Lead and Back-up Counsel and Service Information

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D. Additional Service Information

Please address all correspondence to the lead and back-up counsel as shown above. Petitioner consents to electronic service at: CurioIPRs@irell.com.

IV. GROUNDS FOR THE CHALLENGES

Petitioner challenges the claims of Chee-468 on grounds tabulated below. Grounds 1 and 2 are based on references that are prior art even if Chee-468 is entitled to the filing dates of its priority applications.

Ground	Challenged Claims	Basis
1	1, 2, 6, 7, 12-13, 18, 20, 21, 23, 25-26, and 30	Obviousness (pre-AIA §103) over Cantor in view of the knowledge of a POSA
2	1, 2, 6, 7, 12-13, 18, 20, 21, 23, 25-26, and 30	Obviousness (pre-AIA §103) over Cantor in view of Armani and the knowledge of a POSA
3	1, 2, 6, 7, 12-13, 18, 20, 21, 23, 25-26, and 30	Anticipation (AIA §102) by Frisen

V. THE '468 PATENT

The **ABSTRACT** of the '468 Patent states that “[t]he present invention provides assays and assay systems for use in spatially encoded biological assays,” and that the assay system of the invention is “capable of high levels of multiplexing where reagents are provided to a biological sample in defined spatial patterns; instrumentation capable of controlled delivery of reagents according to the spatial patterns; and a decoding scheme providing a readout that is digital in nature.” EX1002, Abstract.

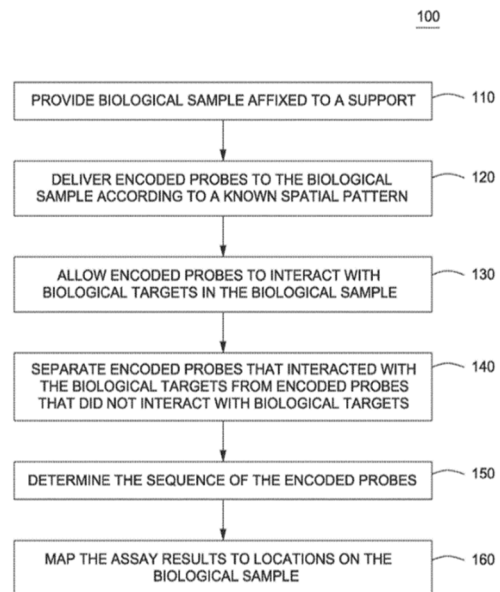


FIG. 1

To the extent any inventive subject matter is disclosed in Chee-468, it is the fluid delivery systems for spatial patterning of reagents that the specification repeatedly emphasizes as “the invention.” For example, in the section headed “The Invention in General,” the inventor wrote: “The assay systems of *the invention* provide spatially encoded, multiplexed assays comprising 1) an assay capable of high levels of multiplexing with an efficient spatial encoding scheme; 2) *instrumentation capable of delivering reagents according to a spatial pattern*; and 3) decoding determined by a readout that is digital in nature.” EX1002, 8:52-57. It continues: “The assay system further provides instrumentation *with an ability to deliver reagents in a spatially-defined pattern. This instrumentation*, together with software, reagents, and protocols, *provides a key component of the highly innovative assay system of the invention,....*” *Id.*, 8:64-9:1.

When Chee-468 discusses nucleic acid binding arrays its disclosures are unrelated to the subject matter that it now seeks to claim. Instead, it discusses them as conventional genotyping techniques; not as tools for performing “the invention.” See EX1002, 24:54-61 (“Genotyping may be performed using any technique known to those skilled in the art.... Some examples of suitable techniques involve...nucleic acid arrays, bead arrays....”). Moreover, when nucleic acid arrays are discussed in the (exclusively prophetic) examples, they are not used to demonstrate “the invention”; rather, “[a] microarray is used as *a proxy for a tissue section*.” EX1002,

30:15-32:37 (describing, e.g., delivering “a reagent droplet to an individual cell,” consistent with Figure B.)

VI. CITED PRIOR ART

A. Cantor

Cantor, WO 2009/091934, is WIPO application that was published on July 23, 2009. EX1031; EX1102, ¶¶107-109.

B. Armani

Armani et al., “2D-PCR: a method of mapping DNA in tissue sections,” is an article that was published in *Lab on a Chip* on October 12, 2009. EX1022; EX1102, ¶110.

C. Frisen

Frisen et al., WO 2012/140224, is a WIPO application that was published on October 18, 2012. EX1020, EX1102, ¶¶111-115.

VII. LEVEL OF ORDINARY SKILL IN THE ART

As Dr. Puglisi explains, a POSA in the field of Chee-468 in February 2010: would have had a doctorate degree (or equivalent) in bioengineering, genetics, genomics, chemistry, biochemistry, biophysics, molecular imaging or a related discipline with at least 2-4 years of academic, research, or industry experience in genomic technology. In the course of their training and experience, the POSA would have acquired a working knowledge of nucleic acid arrays, combinatorial chemistry techniques for making and using such arrays, nucleic acid sequencing

and sample preparation techniques, such as barcoding, imaging methods for signal detection, as well as histopathology techniques for cell permeabilization and tissue handling.

EX1102, ¶¶30-32. As of the February 2019 priority date applied in Ground 3, “a POSA would have at least the foregoing level of skill and education, plus the additional knowledge acquired and documented in the literature in the intervening years.” *Id.*, ¶34.

VIII. BACKGROUND KNOWLEDGE OF A POSA

A. Molecular Biology

The specification of Chee-468 refers to the analysis and detection of “biological molecules,” and in particular nucleic acids. The “**BACKGROUND OF THE INVENTION**” admits that prior art “gene expression and protein analysis have been useful tools in understanding mechanisms of biology,” and that “[c]onventional methods such as in situ hybridization and other multiplexed detection of different transcripts have revealed spatial patterns of gene expression and have helped shed light on the molecular basis of development and disease.” EX1002, 1:42-51. The concept of “gene expression” refers to the process by which a gene encoded by DNA gets turned on in a cell to make RNA and proteins. EX1102, ¶¶36-44.

B. Cells and Tissues

Tissues are groups of cells that function together as a unit. Important to many aspects of biological research, tissues can be in a normal, healthy state, or in a disease

state, and a POSA would have been familiar with many techniques for isolating and preparing tissue samples for further investigation. EX1102, ¶¶45-51.

C. Spatial Analysis

Chee-468 admits that “conventional methods” were used in the prior art to “reveal[] spatial patterns of gene expression and have helped shed light on the molecular basis of development and disease.” EX1002, 1:47-51.

As Dr. Puglisi explains, by April 2010 biologists found important information not only in the identity and quantitation of the genes expressed in a biological system, but also in the location at which particular genes are expressed (or not expressed). Accordingly, scientists had long been devising ways to analyze the spatial relationships of biological molecules, developing numerous tools and techniques to answer questions such as “whether there is...a spatial relationship between the position of genes and the location of their products in cell space.” EX1027, 552; EX1102, ¶¶52-57.

1. Detection of Nucleic Acids

Many nucleic acid technologies historically used fluorescence and other labelling and imaging techniques to detect the presence or absence of a target nucleic acid sequence. For example, nucleic acids are readily labeled with fluorescent dyes to form labelled probes, and when such probes are hybridized with a target, will cause the target-probe complex to be fluorescent upon exposure to an appropriate

light source, allowing detection with simple imaging or spectroscopy methods.

EX1102, ¶¶59-60.

Sequencing generally refers to techniques used to determine the order of nucleotide bases present in the DNA or RNA of a biological sample. Such techniques include high-throughput “Next Generation Sequencing” (NGS) as well as traditional Sanger sequencing. Some applications of these techniques included the use of “custom-designed oligonucleotide microarrays...for targeting regions of interest.” EX1029, 41. Such techniques may be applied in conjunction with NGS to sequence nucleic acids of interest captured using microarrays. *Id.*, 41; EX1102, ¶¶61-62.

2. Nucleic Acid Arrays

Nucleic acid arrays are a class of technologies in which DNA or other nucleic acid sequences are provided on a solid support. Because “[i]t is well known that complementary single-stranded sequences of nucleic acids form double stranded hybrids,” nucleic acid arrays leverage this property by presenting “thousands of single-stranded sequences that are complementary to target sequences,” and hybridization is then detected by fluorescence or sequencing. EX1018, 528. EX1102, ¶¶63-64.

Around the priority date, there were two main classes of solid supports on which the hybridization probes, sometimes called capture probes, were typically affixed: glass slides, similar to microscope slides, and beads. EX1018, 528. In bead

arrays, the beads would then be deposited on a support, and the position of each bead and the sequence it carried would be determined by a process called “decoding.” *Id.* EX1102, ¶65.

Well before 2010, a POSA would have been familiar with a variety of techniques for “decoding” bead arrays to determine the identity and location of each bead in an array. For example, in a 2007 publication, Dr. Chee explained that “after the array is made, a correlation of the location of an individual site in the array with the bead or bioactive agent at that particular site can be made.” EX1038, [0013]. Known processes for such decoding included “positional decoding” methods in which the beads carrying known probes were selectively placed at particular locations. *Id.*, [0043]. Other known techniques involved analyzing “identification sequences” affixed to the beads. *Id.*, [0042]. This facilitated the use of “decoding by sequencing” methods to map the location of particular beads in the array, and which “allow[] decoding to be accomplished independent of the” capture agent on the molecule. *Id.*, [0141]. EX1102, ¶¶66-71.

3. Sequence Barcoding

Multiplexing, which allows higher throughput analysis of many samples in parallel, was a key development for nucleic acid sequence analysis before the priority date. As such, a POSA would have been familiar with the concept of barcoding, including using nucleic acid sequences as barcodes to identify and

differentiate between different nucleic acid molecules or sets of molecules. *See, e.g.*, EX1037, 3:55-64. Consistent with this knowledge, it is notable that in a prior proceeding involving EX1037, 10x asserted that the concept of nucleic acid barcoding “is as old as the scientific method and is familiar to every student in any introductory science class.” EX1035, 4-5. As such, 10x asserted that the use of barcodes or tags in “the particular technological environment of DNA (and other nucleic acids) by adding ‘attaching,’ ‘amplifying,’ and ‘detecting’ steps and other similarly generic techniques were ***well-known and conventional before 2009.***” *Id.*; EX1102, ¶¶72-73.

Examples of nucleic acid barcoding approaches specifically for correlating particular spatial locations in arrays (such as X,Y coordinates) with particular nucleic acid sequences (barcodes) were disclosed in numerous references before the priority date. For example, Barany describes a barcoding scheme for microarrays, which is used to direct target nucleic acids “to specific zip-code addresses attached covalently to a three-dimensional gel-matrix array.” EX1036, 251. For example, by using tetramer (4 nucleotide) barcodes, an array may be designed that uniquely barcodes up to 256 (4^4) separate locations according to, for example, a grid pattern. EX1102, ¶¶74-75.

	2nd two bases																			
1st two bases	TT	TC	TG	TA	CT	CC	CG	CA	GT	GC	GG	GA	AT	AC	AG	AA				
TT							16'			23'		TTGA 6			TTAG 8					
TC			TCTG 1		30'	TCCC 3			TCGT 5							6'				
TG		TGTC 2		36'			TGCG 4						TGAT 7			11'				
TA					18'			TACA 36			33'									
CT	32'		CTTG 9					CTCA 11	CTGT 13							8'				
CC				CCTA 33					29'					CCAT 15						
CG	CGTT 10		12'					4'						28'		CGAA 16				
CA		34'			25'		CACG 12			CAGC 14		1'			9'					
GT					GTCT 19	24'				GTGC 22			31'							
GC	GCTT 17		14'											22'		GCAA 23				
GG		20'		GGTA 18	35'							3'		GGAC 24						
GA			GATG 34				GACC 20		2'	GAGT 21										
AT							ATCG 28	7'			15'			ATAC 31						
AC		21'			ACCT 27						ACGG 29	5'			13'					
AG			AGTG 25				AGCC 35		27'			AGGA 30			19'					
AA	AATC 26							10'		17'						AAAG 32				

Figure 2. Design of tetramers for use in zip-code arrays. The checkerboard pattern shows all 256 possible tetramers. A given square represents the two bases on the left followed by the two bases on the top of the checkerboard. To be included, each tetramer must differ from all others by at least two bases, and be non-complementary. The chosen tetramers are shown in the white boxes, while their complements are listed as (number)'. Thus, as an example, the complementary sequences GACC (20) and GGTC (20') are mutually exclusive in this scheme. In addition, tetramers that are palindromic, e.g. TCGA (off-diagonal hatched boxes) or repetitive, e.g. CACA (hatched boxes on diagonal from upper left to lower right) have been eliminated. All other sequences which differ from the 36 tetramers by only one base are shaded in light gray. Four potential tetramers were not chosen as they are either all A·T or G·C bases (open boxes).

Similarly, Chee-584 discloses barcoded bead arrays in which “a spatial or positional coding system is done.” EX1032, 28:6-7; *see also* EX1038, [0146] (“In this way, beads are tagged with fluorescent labels, i.e., barcodes of sorts, their location or identity deciphered and recorded.”). EX1102, ¶76

D. Overview of Spatial Analysis Technologies

By 2009, a POSA would have been familiar with 2D-PCR techniques in which “[a] 2d map of [a gene] was created from a tissue section and shown to correlate

with the spatial area of the sample.” EX1022 (Armani), 3526 (Abstract). These techniques were anticipated to “be easily adapted to assess the status of multiple genes within tissue sections, yielding a molecular map that directly correlates with the histology of the sample,” thus “provid[ing] investigators with a new tool to interrogate the molecular heterogeneity of tissue specimens.” *Id.* For example, Armani observed that “[v]ariations in DNA status (mutation, epigenetic modification, insertions, deletions) by location within a tissue section are of interest for elucidating their roles in biology and as clinical markers for diseases.” *Id.*, 3526. Thus, Armani noted a desire and motivation in the art to study nucleic acids in a manner that maintained their spatial organization. EX1102, ¶¶79-84.

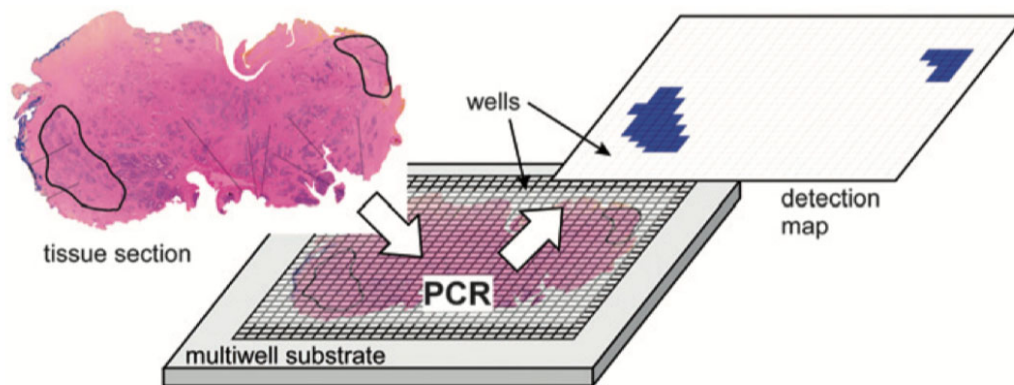


Fig. 1 2D-PCR is achieved by transferring a tissue section vertically into a multi-well array device, isolating tissue subregions. The DNA is extracted and then amplified by the polymerase chain reaction. A detection map is created by imaging the amplified DNA, for example using a DNA-intercalating dye.

Related technologies performed spatial analysis of gene expression using arrays of capture agents to immobilize mRNA in two-dimensional space and detect its presence using fluorescent or other labeled probes, including after reverse-transcription processes. EX1102, ¶¶86-92.

Shirai discloses an example of such techniques. For example, Shirai explains that it “provides a method and/or means for collecting and analyzing an individual cell in a tissue, and at the same time, quantitatively monitoring the expression levels of various genes *while keeping two-dimensional information in the tissue.*” EX1024, Abstract. Shirai describes providing a plurality of beads: “beads smaller than cells are arranged on a surface.” *Id.*, 27:5-6. These beads comprise a plurality of capture agents: “[o]n the beads surface, poly-T probes are immobilized.” *Id.*, 27:6-7. The poly-T probes immobilized on the beads’ surface are configured to interact with at least one mRNA present in a tissue sample: “On the resultant structure,” that is, an array of poly-T coated beads, “a tissue slice is mounted” and the cells are permeabilized or lysed to release their mRNA, which is then reverse transcribed into complementary cDNA molecules. *Id.*, 27:5-19. EX1102, ¶¶93-97. Shirai then discloses detecting gene expression using fluorescent probes to generate a spatial map. EX1024, 10:46-55; *see also* EX1025 (Okano). EX1102 ¶¶98-102.

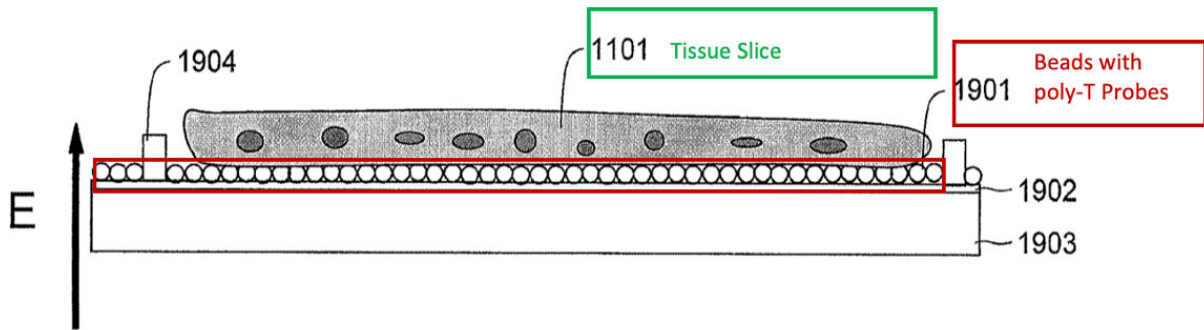


FIG. 19

Similarly, Southern discloses the detection of target nucleic acids on arrays so that “[t]he spatial arrangement of the samples is maintained” and the location of “results of the analysis [may] be matched to individual samples.” EX1033, Abstract. “One analytical procedure that can be used with” Southern’s arrays “involves capture of mRNA by hybridisation to an immobilised capture DNA, followed by reverse transcription of the mRNA.” *Id.*, 9:17-25. In this procedure, Southern discloses creating a complementary cDNA, using the captured mRNA as a template for *in situ* reverse transcription. Southern discloses using optical means, such as fluorescence, as the method for detecting the spatial location of an interaction between its capture agent and a target nucleic acid. EX1030, 27:13-28. In addition to detection by fluorescence, Southern continues by noting that “single molecule sequencing” is also a suitable readout. *Id.*, 39:25-28. EX1102, ¶¶103-104.

Approaching the priority date, a POSA would have found using sequencing-based techniques as a readout for nucleic acid assays as an alternative

for fluorescence-based detection methods to have been an obvious and natural substitution. First, sequencing methods provide a direct readout of the nucleic acid identity, without the use of probe hybridization, imaging, or microscopy to indirectly confirm the identity of a target sequence. Second, using the analogy presented by 10x in prior litigation, labelling target nucleic acids with fluorescence would have been akin to a “form of labeling such as placing one in a green cup and one in a blue cup,” whereas nucleic acid barcodes simply apply the concept of “serial numbers” to nucleic acids. EX1035, 4-5. Such approaches are illustrated in Cantor and Frisen, as discussed in the Grounds below. EX1102, ¶¶105-106.

IX. CLAIM CONSTRUCTION

The Petition applies the understanding of the claim terms applied by PO to assert infringement against Curio. PO has asserted that no claim terms require construction. EX1041-1042.

The claims of Chee-468 require a nucleic acid that specifically binds to a nucleic acid. *See* 1002, cl. 1(a)(i). In the District Court, the parties dispute whether a poly-T probe constitutes a nucleic acid sequence that “specifically binds” to a target DNA. PO contends and Petition disputes that the binding interaction between poly-T probes and the poly-A tails present on mRNA constitutes “specific binding.” Because the prior art that is the basis of Grounds 1-3 below discloses both capture agents that specifically bind a biological molecule of interest, such as gene-specific

probes, as well as probes that satisfy the broader implicit interpretation advanced by PO (such as poly-T probes), the claims are obvious and/or anticipated regardless the interpretation applied. EX1102, ¶¶117-119.

X. THE BOARD SHOULD CANCEL THE CHALLENGED CLAIMS

A. Ground 1: Obviousness over Cantor in view of the Knowledge of a POSA

1. Claim 1

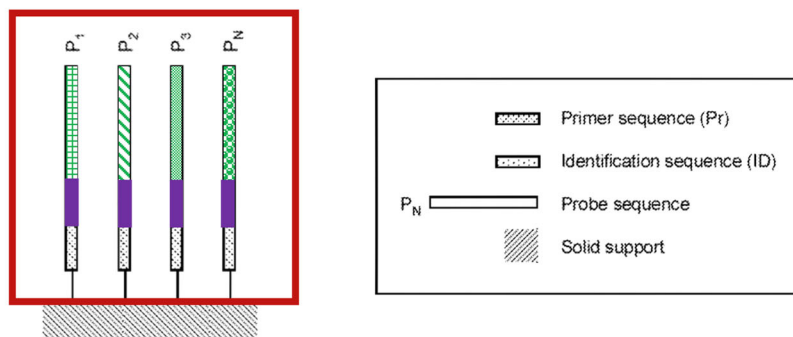
(a) “A method for determining the presence or abundance of a nucleic acid at a location in a tissue section”

To the extent the preamble, a “method for determining the presence or abundance of a nucleic acid at a location in a tissue section,” is limiting, Cantor renders it obvious by teaching each of the claimed steps.

Cantor discloses methods for analyzing biological samples using nucleic acid capture agents affixed to solid supports such as beads.² EX1031, 13 (a “solid support unit (e.g., one bead) can be selected”). Individual solid supports “may be in a collection of solid supports,” such as an array wherein each “solid support unit” is “one bead.” *Id.*, 2, 13; EX1102, ¶¶128-131.

² Cantor’s beads constitute the claimed “features.” *See* EX1002, cl. 17 (“[M]ethod of claim 1, wherein the *feature...comprises a bead,....*”).

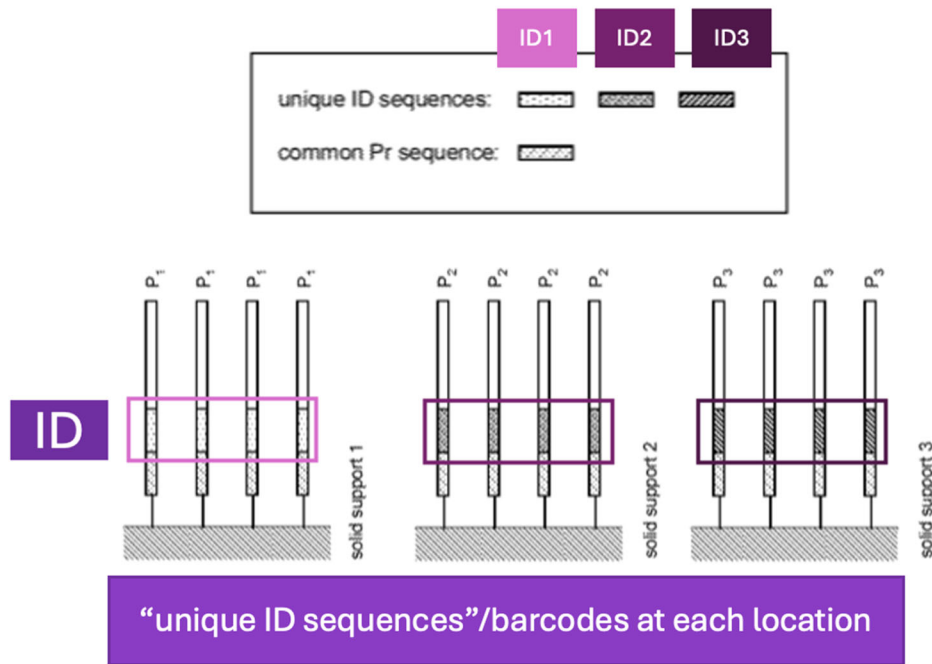
Tracking the claims, Cantor discloses that “[t]he biological sample can be...a solid material such as a tissue.” EX1031, 6. And Cantor’s plurality of beads comprise the claimed “**capture agents**” because bound to each bead are nucleic acid constructs that include a “**probe sequence**” that “**specifically binds**” with a target nucleic acid, as well as a “**coding tag**”—Cantor’s “**identification sequence**”—that identifies the specific bead, and thus location, at which a particular binding interaction occurred. Accordingly, Cantor discloses bead arrays comprising every structural element required by the claim. EX1102, ¶¶127-132. Cantor’s Figure 1A, annotated below, shows a solid support (e.g., a bead), comprising a plurality of “**capture agents**,” each having the same “**identification sequence (ID)**” and different “**probe sequences**.” EX1102, ¶132.



Cantor explains that its “[s]olid supports may be provided in an array” including “an ‘X by Y array’..., where the array includes X number of sample locations or solid supports,” such as beads, “in one dimension and Y number of sample locations or solid supports,” such as beads, “in a perpendicular dimension.”

EX1031, 17. Thus, a POSA would have understood Cantor to disclose an array of beads at which each bead is necessarily deposited at a particular (X,Y) coordinate location. Cantor explains that each bead has a unique identification sequence, such that each bead at its unique (X,Y) coordinate location would have a unique identification sequence as part of its capture agent. Such capture agents would also include a “probe” sequence as part of the same single-stranded nucleic acid. Thus, the “identification sequence” corresponds to the location at which the “probe” portion of the capture agent interacts with a tissue section contacting the array. EX1102, ¶133.

For example, Cantor’s Figure 1C depicts separate solid supports, each having “unique ID sequences” that are correlated to the specific solid supports “solid support [e.g., bead] 1,” “solid support [e.g., bead] 2,” and “solid support [e.g. bead] 3.” In other words, each capture agent on a support/bead has an IDbarcode that is different than the IDbarcode on each of the other supports/beads. EX1102, ¶134.



Because each unique ID sequence corresponds to a particular bead and thus “barcodes” a given bead (and its location in the array), the existing knowledge of a POSA would have further motivated using Cantor’s bead arrays to determine the presence or abundance of a nucleic acid at a location in a tissue section for a variety of reasons described in detail below in Section X.A.1(b). EX1102, ¶135.

(b) Step 1(a): “contacting the tissue section with an array comprising a plurality of features, wherein a feature of the plurality of features comprises a capture agent,”

Cantor discloses nucleic acid binding arrays in which the claimed capture agents are attached to beads, which constitute the claimed “features.” *See* EX1002, cl. 17; *see also* EX1065, 3 (PO’s infringement allegation requiring a bead to constitute a “feature.”); EX1102, ¶¶137-139.

Cantor discloses arrays of beads (features), explaining that its methods use “a substrate comprising a collection of beads oriented in an array, where each bead is in association with single-stranded nucleic acid” capture agents. EX1031, 4, *see also id.*, 1, 2, 10; EX1102, ¶140.

Cantor in view of the knowledge of a POSA renders obvious “contacting the tissue section with an array.” Cantor explains that its sample may be “a solid material such as a tissue...or a biopsy,” *id.*, 6, and the literature evidenced multiple reasons why a POSA would have been motivated to perform array-based nucleic acid analysis on a tissue sample (such as an intact tissue section or a biopsy sample), including because the analysis of such samples would provide information, such as spatial information, that could not be obtained through the analysis of, for example, a tissue homogenate. *See* EX1022 (Armani), 3526; EX1026 (Okano), [0008]. Thus, as explained by Dr. Puglisi, a POSA would have been motivated to contact Cantor’s array with a tissue section, rendering obvious contacting Cantor’s plurality of beads (i.e., features) with a tissue section such that the capture agents affixed to its beads interact with nucleic acids in the section. EX1102, ¶¶141-142.

Additionally, Cantor explains that its capture agents interact with the target nucleic acids by contacting the targets with the array to allow for hybridization between the capture agents and the targets. EX1031, 2. (“[T]he solid support and sample nucleic acid are contacted in the mixture under conditions that allow

hybridization of the solid phase nucleic acid,” i.e., the probe, “to the sample nucleic acid.”). Thus, Cantor motivates contacting the tissue section with the array to allow for hybridization between the solid phase nucleic acid (capture agents) and the nucleic acids in a tissue sample. EX1102, ¶143.

Cantor further explains that “[s]ample nucleic acid may be prepared by any means commonly known in the art, including but not limited to cell lysis procedures using chemical, physical or electrolytic lysis methods.” *Id.*, 53-54. A POSA would have been familiar with, and would have been motivated to apply such techniques to intact tissue or biopsy samples to facilitate hybridization between the nucleic acids in the tissue sample and the array’s capture probes. EX1102, ¶144.

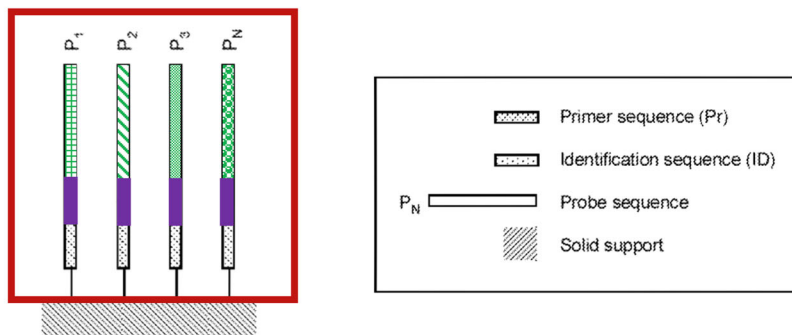
These techniques were frequently applied in the art. For example, Southern discloses that, “[i]n some methods, *samples are applied directly to the support to generate a spatial arrangement of samples*, as illustrated in Fig. 1. Thus, *when the samples are biological samples comprising cells, the step a) of applying the samples to a support may comprise: (i) applying cells to the support; then (ii) releasing material from the cells.*” EX1033, 2:17-20. A POSA would recognize that “releasing material from the cells” is synonymous with lysing the cells, as disclosed by Cantor. EX1102, ¶145.

Moreover, as Dr. Puglisi explains, a POSA would similarly have been familiar with other methods for lysing and capturing target nucleic acids from cells in a tissue

sample disposed on an array. Thus, a POSA would have been further motivated to dispose a tissue section on the array disclosed in Cantor and lyse the cells such that the probes can interact with the target nucleic acids within the tissue sample. *Id.* (discussing EX1021-1022 (Armani), EX1024 (Shirai), EX1025 (Yasuda), and EX1026 (Okano)).

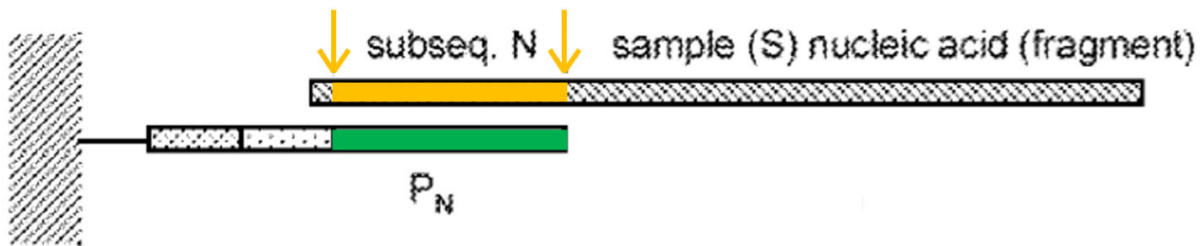
(i) Step(a)(i): “wherein the capture agent comprises: (i) a first sequence that specifically binds the nucleic acid, and”

Cantor’s “**capture agents**” are configured to “**specifically bind**” a nucleic acid at a location in a tissue section by hybridization between the target nucleic acid and Cantor’s “**probe sequences**.” EX1102, ¶¶146-148.



For example, Cantor explains that “[s]ample nucleic acid molecule (S) may include a nucleotide sequence (i.e., **subseq.N**) that hybridizes to a complementary probe sequence (P_N) of the solid phase nucleic acid.” EX1031, 24. This is depicted in Figure 2, excerpted below to show interaction between the “**probe sequence**” of

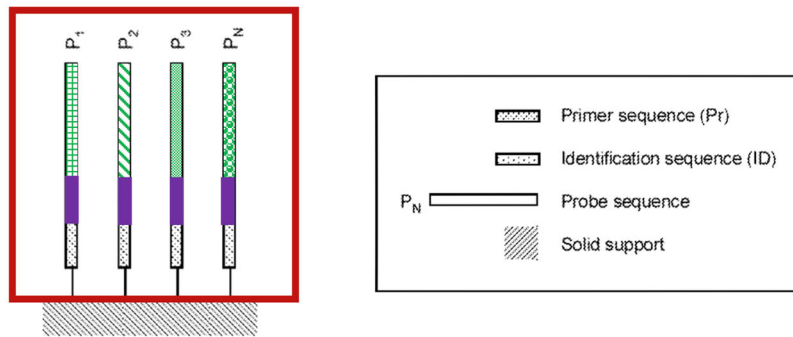
the “**capture agent**” and a portion of a “**biological molecule**,” here a **subsequence (N)** of sample nucleic acid (S). EX1102, ¶149.



Cantor’s “probe sequences” specifically bind to target nucleic acids in the tissue section because they are “complementary to subsequences in the sample nucleic acid.” EX1031, 16-17; *see also id.*, 14 (“A probe nucleotide sequence is of a length sufficient to specifically hybridize to a sample nucleic acid nucleotide sequence.”). EX1102, ¶150.

- (ii) **Step (a)(ii): “[wherein the capture agent comprises:...] (ii) a second sequence comprising a coding tag, wherein a sequence of the coding tag corresponds to a location of the capture agent on the array;”**

Cantor discloses that each “**capture agent**” includes an “**identification or identifier sequence**,” which constitutes the claimed “coding tag.” EX1102, ¶¶151-152.



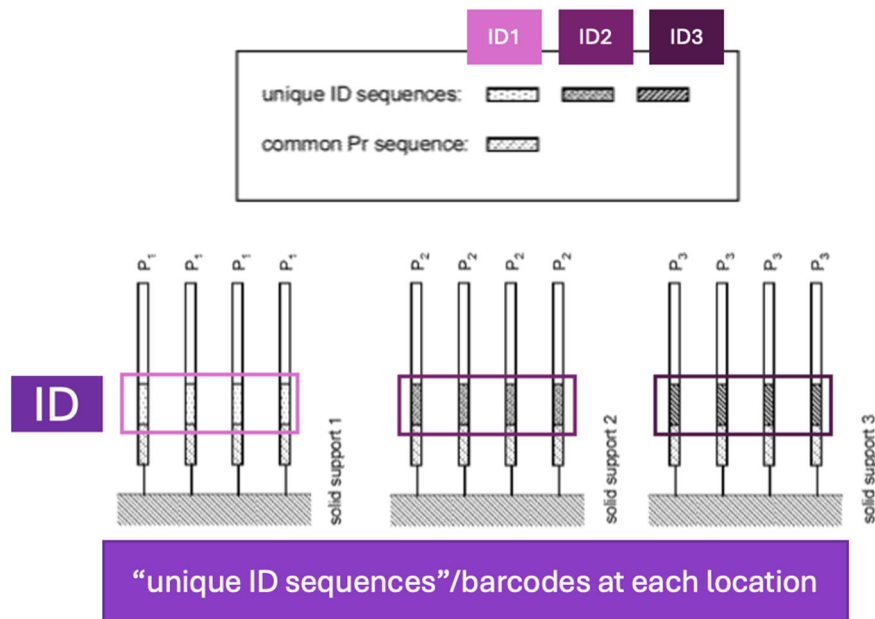
For example, Cantor states that “the solid phase nucleic acid of each of the solid supports [e.g., beads], in the collection [e.g., an array] share a unique identifier sequence different than the identifier sequence of the solid phase nucleic acid of the other solid supports [e.g., beads].” EX1031, 4. A POSA would have understood these disclosures to mean that each capture agent attached to a particular bead included the same “identification sequence,” while the capture agents attached to other beads would have a different “identification sequence.” EX1102, ¶153.

Cantor explains that these identification sequences “may be of any length suitable for analyzing the nucleotide sequence or partial nucleotide sequence of sample nucleic acid,” and “[i]n some embodiments, an identifier sequence is about 5 to about 50 contiguous nucleotides in length, sometimes about 5 to about 20 nucleotides...and at times about 10 nucleotides....” EX1031, 16; EX1102, ¶154.

Cantor’s “identification sequences” (i.e., coding tags) render obvious the claim requirement that they “correspond[] to a location of the capture agent on the array.” Cantor explains that its “[s]olid supports may be provided in an array”

including for example “an ‘X by Y array’..., where the array includes X number of sample locations or solid supports,” such as beads, “in one dimension and Y number of sample locations or solid supports,” such as beads, “in a perpendicular dimension.” EX1031, 17. Thus, a POSA would have understood Cantor to disclose a bead array where each bead is deposited at a particular (X,Y) location. Since Cantor’s “identification sequence” is “unique” for each bead, each bead at a unique (X,Y) location necessarily possesses a unique identification sequence as part of its capture agent. EX1102, ¶155.

For example, Cantor’s Figure 1C depicts separate solid supports, such as beads, each having “unique ID sequences” that correlate to the specific solid supports “solid support [e.g., bead] 1,” “solid support [e.g., bead] 2,” and “solid support [e.g., bead] 3.” EX1102, ¶156.

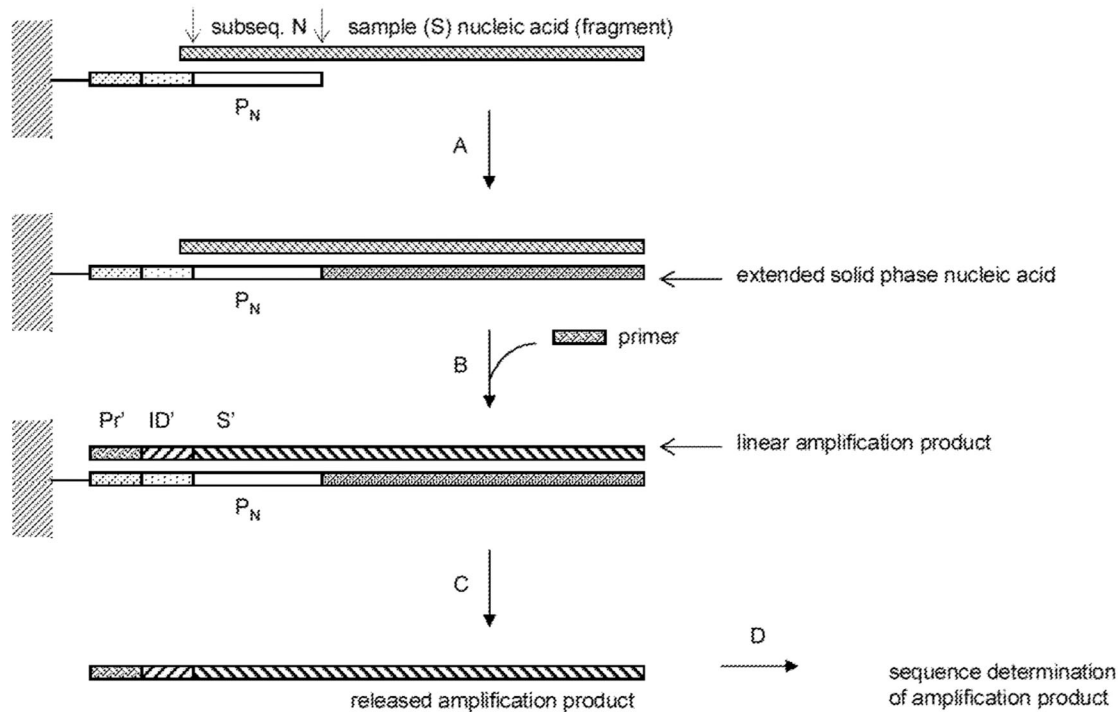


Moreover, as explained further below in connection with step 1(b), the knowledge of a POSA renders obvious using Cantor's identification sequence to determine the location at which the capture agent interacted with the tissue section. Specifically, because Cantor's capture agents include a "probe" sequence 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. EX1102, ¶157.

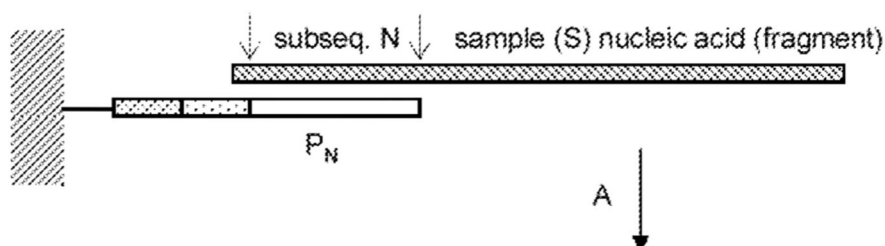
- (c) Step 1(b): "[i] determining all or a portion of the sequence of the coding tag, or a complement thereof, and [ii] all or a portion of the sequence of the nucleic acid specifically bound to the capture agent, or a complement thereof, and [iii] using the determined sequences to determine presence or abundance of the nucleic acid at a location in the tissue section."**

(i) Steps 1(b)(i) and 1(b)(ii)

Figure 2 describes how to detect target nucleic acids and determine the sequence of the target nucleic acid and the identification sequence of the capture agent on which it was captured. EX1102, ¶¶158-160.

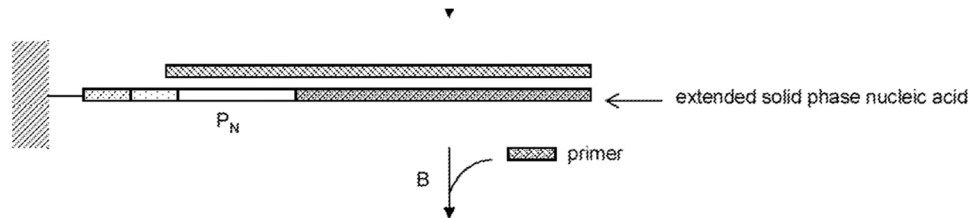


The first panel shows “specific binding” between the probe region of the capture agent and the target nucleic acid, as discussed above. EX1102, ¶¶163-164.

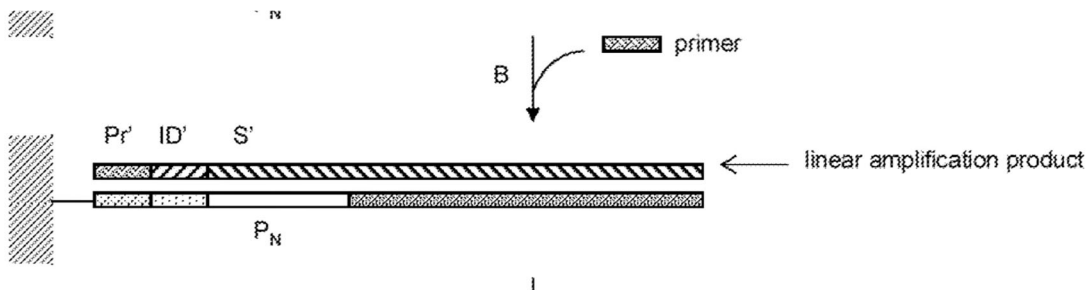


The next panel shows “extension” of the capture agent to generate a second strand complementary to the bound target nucleic acid. EX1031, 24. The nucleic acid depicted to the right of the probe sequence P_N in the figure below shows the extension of the capture agent to include “a nucleotide subsequence complementary

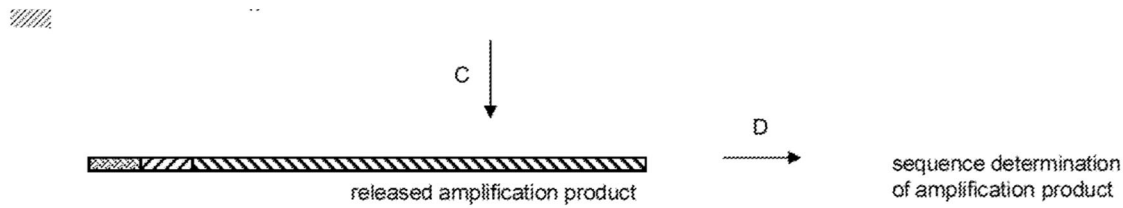
to a target nucleotide sequence in the sample nucleic acid molecule.” *Id.*; EX1102, ¶165.



Next, the “[e]xtended solid phase nucleic acid may be amplified by hybridizing primer (Pr’),....” *Id.* This amplification product, shown below, “contains the primer nucleotide sequence (Pr’), a nucleotide sequence complementary to the identification sequence in solid phase nucleic acid, and a nucleotide sequence identical to or substantially identical to a target nucleotide sequence in the sample nucleic acid molecule.” *Id.*; EX1102, ¶165.

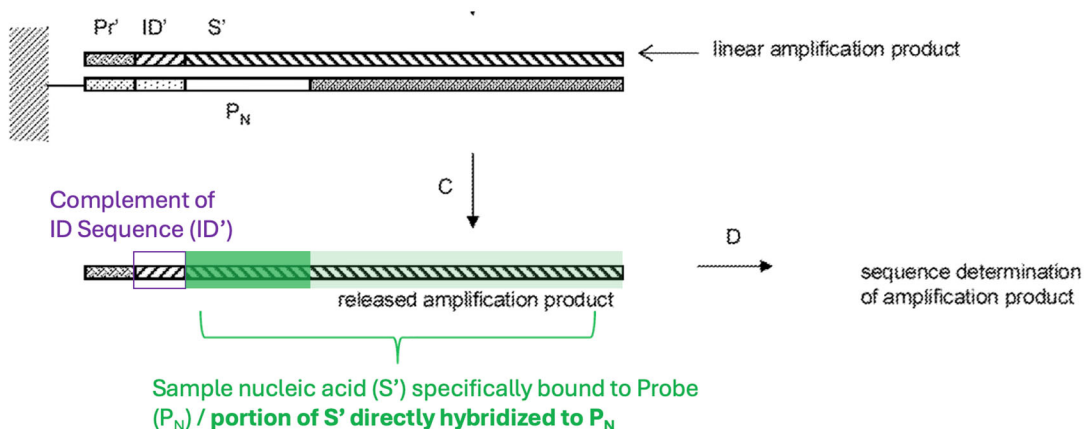


Cantor further discloses that “[t]his linear amplification product can be released from the solid support” for “sequence determination of [the] amplification product.” *Id.*, 24-25; Figure 2C, D. EX1102, ¶166.



Cantor explains that during the sequence determination step, “[t]he entire sequence or partial sequence of an amplification product can be determined...with or without further amplification.” EX1031, 25. Accordingly, Cantor discloses determining both the sequence of the strand including the original target nucleic acid molecule and its complement. EX1102, ¶¶167-169.

As Dr. Puglisi explains, a POSA would recognize that sequencing the “released amplification product” determines the sequence of a complement of the **coding tag (Cantor’s identification sequence)** and the sequence of the **nucleic acid specifically bound to the capture agent**, which includes “subseq. N” that directly hybridized to Cantor’s probe sequence, as well as additional portions of the “sample (S) nucleic acid fragment.” EX1031, 24-25; EX1102, ¶¶161-162.



Accordingly, Cantor discloses “determining [i] all or a portion of the sequence of the coding tag, or a complement thereof, and [ii] all or a portion of the sequence of the nucleic acid specifically bound to the capture agent, or a complement thereof.”

(ii) Step 1(b)(iii)

As explained above, sequencing the released amplification product depicted in Figure 2C-2D determines the sequence of (i) a target nucleic acid and its complement and (ii) an identification sequence and its complement, which necessarily determines the presence of the nucleic acid at a location (i.e., the location corresponding to the bead bearing the identification sequence). EX1102, ¶170.

A POSA’s motivation to correlate Cantor’s bead “identification sequences” with the bead’s location in array, and thus the location of the “specifically bound” nucleic acid in the tissue section, is confirmed by the knowledge of a POSA. As explained by Dr. Puglisi and set forth in Section X.A.1(b) above, multiple references disclosed the use of nucleic acid arrays, such as bead arrays, to (1) capture nucleic acids from a tissue sample through the use of complementary probes; (2) amplify the captured nucleic acid; and (3) determine the identity of the captured nucleic acid and the location at which it interacted with the complementary probe, and thus its location in a tissue sample. EX1102, ¶171.

For example, Southern discloses performing spatially-defined assays using capture arrays and nucleic acid capture and detection procedures that are analogous

to Cantor's. Southern explains that "[i]n the methods of the invention, samples are analysed by allowing them to interact with an analytical component on a support." EX1033, 1:19-20. "Target analytes," such as nucleic acids, "in the samples are detected when the sample interacts with the analytical component." EX1033, 1:19-21. Southern explains that its samples "are applied in step a) to different areas of the support to produce a spatial arrangement," which is maintained, "permitting the results of the analysis to be matched to individual samples," thus determining the spatial location of target nucleic acids. EX1102, ¶¶172-173.

Like Cantor, Southern discloses the detection of a target nucleic acid by creating a nucleic acid strand complementary to the target analyte. For example, when the target analyte is an mRNA, Southern discloses creating a complementary cDNA by extending the probe via in situ reverse transcription, using the captured mRNA as a template. Southern discloses using optical means, such as fluorescence, as the method for detecting the spatial location of an interaction between its capture agent and a target nucleic acid. EX1033, 27:12-28. Additionally, Southern observes that detection can include an "amplification reaction," *Id.*, 28:19-22, which may be used in connection with "single molecule sequencing." *Id.*, 39:25-28. EX1102, ¶174.

And as explained above, numerous other references described the successful capture and detection of nucleic acids, including mRNA, from tissue samples on

bead arrays that preserved and determined the spatial location of the captured target nucleic acids in said tissue samples. *See* Section X.A.1(b), above. EX1102, ¶175.

Moreover, a POSA's existing knowledge before the priority date further confirms the motivation and reasonable expectation of success one would have had in using the "identification sequence" present in Cantor's "capture agents" to determine the location at which the probe of a given capture agent interacted with a target nucleic acid from a tissue sample, and thus the location of the specifically bound nucleic acid in the tissue section. EX1102, ¶176.

As Dr. Puglisi explains, a POSA would have appreciated that Cantor's disclosure of a unique identification sequence for each bead constituted a unique "barcode" nucleic acid sequence to distinguish one bead from another. In addition to Cantor's express disclosures of providing the beads according to an (X,Y) array, a POSA would have found it obvious to determine the identity and location of each bead in the array before using it in Cantor's analytical procedures at least by (i) selective loading of particular beads to particular locations on the array and/or (ii) decoding the array. EX1102, ¶177 (discussing EX1038); ¶¶65-71.

Cantor discloses that its "identifier sequence is about 5[-]50 nucleotides in length." EX1031, 15. In a selective loading procedure, a POSA would have found it obvious to provide beads having, for example, 5-nucleotide identifier sequences that correspond to particular locations in Cantor's (X,Y) array. A POSA would have

reasonably expected success in correlating such sequences with particular (X,Y) coordinates given the disclosure of success in using such systems in the prior art. *See* EX1032, 7:30-33 (beads are spatially arranged in “a regular pattern of sites such that the sites may be addressed in the X-Y coordinate plane.”); EX1038, [0044] (“Once the identity of the bioactive agent and its location in the array has been fixed, the array is exposed to samples containing target analytes.”); EX1036, 251 (describing 4-nucleotide “zip-code” sequences to define spatial locations on an array in a “checkerboard” (X,Y) array pattern). EX1102, ¶¶178-180.

Alternatively, “the beads may be randomly distributed on the array,” and “can later be ‘decoded’, i.e. after the array is made, a correlation of the location of an individual site on the array with the bead or candidate agent at that particular site can be made.” EX1038, [0042]. As Dr. Puglisi explains, a POSA would have been familiar with multiple well-established techniques for decoding bead arrays, for example by sequencing or using fluorescent probes to “correlat[e] the location of an individual site in the array with the bead,” at that location. EX1038, [0013]. EX1102, ¶¶181, 65-71. A POSA would have been motivated to use a random loading procedure to simplify and expedite the array generation and fabrication process, and would have found it obvious to decode the array by using any of a number of known decoding procedures. EX1038, [0037]-[0038], [0046], Figs. 12-13. For example, Chee-824 discloses “decoding by sequencing” of bead arrays comprising probes

structured similarly to Cantor's, using procedures that allow the array to be used in analytical assays without issue following the decoding procedure. *Id.*, [0142]-[0146]. EX1102, ¶181.

When the “identification sequence” of a particular bead location is produced as a sequencing readout, a necessary result of Cantor's workflow, a POSA would then have found it obvious to map the rest of the sequence readout (i.e., the sequence of the target nucleic acid or a complement thereof) to the bead location, thereby determining a spatial location of the biological molecule of the tissue sample. A POSA would have reasonably expected success in correlating Cantor's “identification sequences” with the location of the beads to which they are bound on an array, at least based on the use of known loading and/or decoding procedures. Indeed, a POSA could have made this correlation without any modifications to Cantor's device, or the process in which it is used to capture, amplify, extend and sequence target nucleic acid. EX1102, ¶¶182-184.

Instead, correlating a particular sequence to a particular location involves (at most) only the mental step of associating a particular “identification sequence” with a “particular bead”—features already present in Cantor's device and methods—based on the routine and predictable use of well-known array decoding techniques. And in light of the knowledge in the art motivating a POSA to determine the spatial location and orientation of nucleic acids throughout a tissue sample, it also would

have been obvious to document or record the presence of a particular nucleic acid at a particular location in a tissue sample—information learned from sequencing the identification sequence—by mapping it back to the identification sequence’s decoded coordinate in the array. EX1102, ¶185.

Such mapping is illustrated by Armani, which explains that its spatial analysis technique included “the creation of a 2D detection map, showing the presence/absence of target DNA, on the millimeter scale,” that is, mapping whether target DNA was present or absent at a particular location in the X-Y plane. EX1022, 3527; EX1102, ¶186.

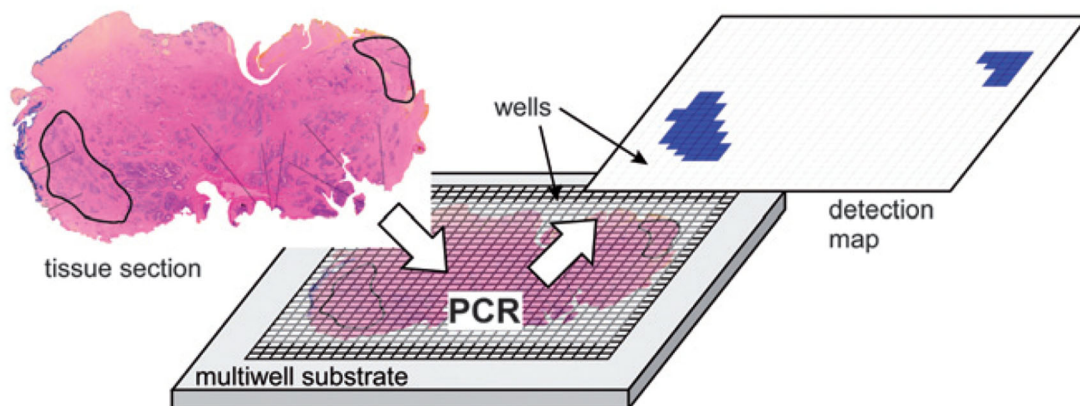


Fig. 1 2D-PCR is achieved by transferring a tissue section vertically into a multi-well array device, isolating tissue subregions. The DNA is extracted and then amplified by the polymerase chain reaction. A detection map is created by imaging the amplified DNA, for example using a DNA-intercalating dye.

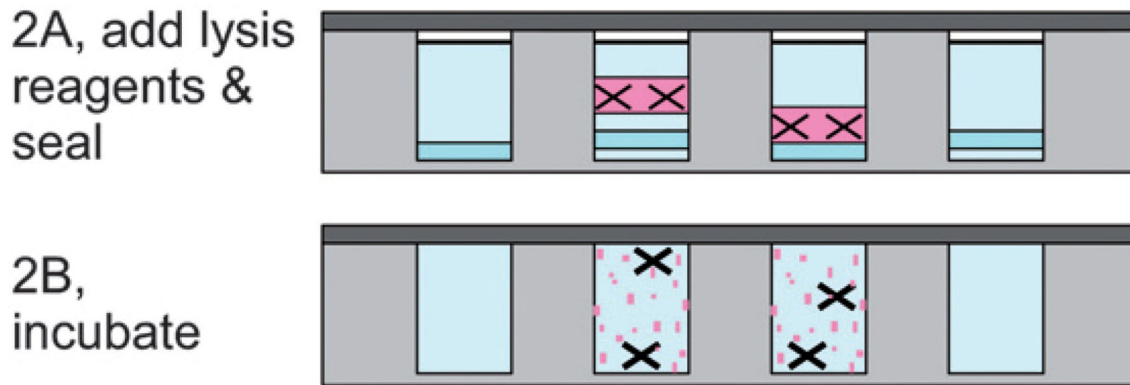
The presence of a target nucleic acid at particular locations in the tissue sample is mapped in Armani's Figure 1, with the blue squares indicating the presence of the target at a particular location. Performing this mapping based on sequencing a particular identification sequence, which correlates to a known location identified through well-known decoding procedures, would have involved routine decoding procedures, and a manual or computer-implemented process for indicating the presence of a nucleic acid at a particular location (e.g., through a check mark, or by shading in a box corresponding to the array's grid structure). EX1102, ¶186.

2. Claim 2

Cantor renders obvious "removing the tissue section from the array."

Between the contacting and determining steps, Cantor renders obvious tissue removal by using "chemical, physical, or electrolytic lysis methods" on the tissue section after it is contacted with the array and before the sample nucleic acids are analyzed. EX1031, 54. EX1102, ¶¶188-190.

As Dr. Puglisi explains, a POSA would have understood that lysis procedures remove a tissue section by breaking down cells and tissue structure, thus releasing their contents. Indeed, Armani discloses this very technique in Figure 2 below. EX1022, 3527 (Fig. 2A-2B (showing removal of tissue section (pink rectangle) following addition of lysis reagents). EX1102, ¶¶191-192.



3. Claim 6

Cantor discloses “determining step comprises nucleic acid amplification.”

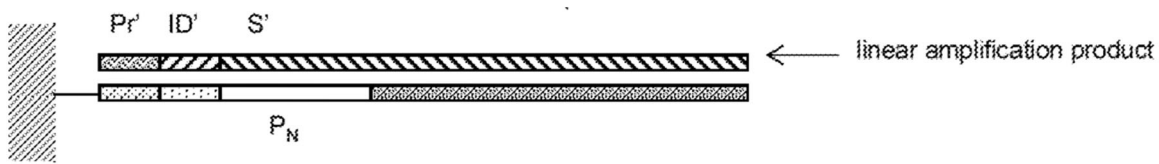
As explained in detail with respect to step 1(b) in Claim 1, Cantor discloses that “the determining step” comprises nucleic acid amplification, leading to the “sequence determination of [the] **amplification** product.” EX1102, ¶¶193-194.



4. Claim 7

Cantor discloses “wherein the determining step comprises sequencing....”

Cantor’s determining step comprises sequencing the entirety of the “released amplification product,” (depicted as the “linear amplification product” below) as well as sequencing the entirety of the complement of the “released amplification product,” (depicted as the bottom strand in the excerpt of Figure 2 below) as discussed with respect to step 1(b) in Claim 1, above. EX1102, ¶¶195-196.



Accordingly, Cantor's sequencing in the claimed "determining step" involves sequencing all or a portion of the coding tag (i.e., Cantor's identification sequence or its complement), and at least the portion of the target nucleic acid that was directly hybridized to the capture agent's probe sequence. EX1102, ¶197.

5. Claims 12-13

Cantor discloses "the nucleic acid is [mRNA/RNA.]"

Cantor discloses that the "sample nucleic acid in certain embodiments can comprise or consist essentially of...RNA (e.g., *message RNA (mRNA)*,...)." EX1031, 6; EX1102, ¶¶198-199.

6. Claim 18

Cantor discloses "the capture agent is immobilized directly or indirectly on a surface of the feature."

Cantor explains that its capture agents may be affixed to beads by covalent bonding. EX1031, 11-12 ("Solid phase nucleic acid may be in association with a solid support by a covalent linkage...."). Cantor further explains that "[n]ucleic acid may be linked to a solid support without a linker or with a linker," thereby disclosing, respectively, direct and indirect mobilization of the capture agent onto the surface of a bead. *Id.*, 12; EX1102, ¶¶200-201.

7. Claim 20

Cantor discloses “the array comprises a bead array.” As described in detail in relation to Claim 1 above, Cantor discloses bead arrays. *See, e.g.*, EX1031, 4. EX1102, ¶¶202-203.

8. Claim 21

Cantor renders obvious “the tissue section is a fresh frozen tissue section or a formalin-fixed paraffin-embedded (FFPE) tissue section.”

Cantor explains that its target/sample nucleic acid may be “a solid material *such as a tissue...or a biopsy.*” *Id.*, 6, 53-54. As Dr. Puglisi explains, there were only a handful of methods of preparing a tissue sample known in the art prior to 2010, including freezing a fresh tissue section to create a fresh frozen tissue sample and creating an FFPE tissue sample. Given the limited number of options, it would have been obvious to a POSA to try using a fresh-frozen tissue sample or FFPE tissue sample with the array disclosed in Cantor. EX1102, ¶206.

Moreover, a POSA would have been motivated to use a fresh-frozen tissue sample with the array disclosed in Cantor. In 2010, fresh-freezing tissue samples was a very common method for preserving tissue samples in a laboratory and clinical setting. Given the prominence of fresh-frozen tissue samples in the field, a POSA would have been motivated to use a fresh frozen tissue sample with Cantor’s array, including because of the convenience of using such samples. Additionally, because

fresh frozen tissue samples were known to have high RNA/nucleic acid quality, including as compared to FFPE tissues, a POSA would have been motivated to use fresh-frozen samples in implementations of Cantor's methods intended to analyze RNA/nucleic acids. EX1102, ¶207.

9. Claim 23

Cantor renders obvious “generating a map of the presence or abundance of the nucleic acid at location(s) in the tissue section.”

As explained in Section X.A.1(c)(ii), generating a map of the presence or abundance of the nucleic acid at a location in the tissue section would have been an obvious way of documenting the claimed mental step of “using the determined sequences to determine presence or abundance of the nucleic acid at a location in the tissue section.” EX1102, ¶¶208-209.

10. Claims 25-26

Cantor discloses “the array comprises greater than [500/1,000] features.”

Cantor expressly discloses arrays with up to 10,000 unique features (i.e., beads or solid supports). EX1031, 11 (“In certain embodiments, a solid support collection comprises...1000, 2000,...or 10000 unique solid support species.”); *see also* EX1032 (Chee-584) at 6:6-13 (“Arrays containing from about 2 different bioactive agents (i.e. different beads) to many millions can be made,...”); EX1038 (Chee-824), [0047] (same). EX1102, ¶211.

As noted above, Cantor's identification sequences are disclosed to be 5-50 nucleotides in length. Thus, as Dr. Puglisi explains, even when the identification sequences are 5 nucleotides in length, such a configuration allows the assignment of 1,024 (4^5) unique identification sequences, confirming a POSA's motivation and expectation of success in using Cantor's methods to create arrays with 1,000 or more beads (i.e., features). EX1102, ¶211.

11. Claim 30

Cantor discloses "a feature of the plurality of features comprises greater than 100 capture agents, where each of the greater than 100 capture agents comprises a first sequence that specifically binds to a different nucleic acid and a coding tag that corresponds to a location of the capture agent on the array."

In particular, Cantor discloses each of the plurality of beads (*i.e.*, features) containing at least 100 capture agents (*i.e.*, nucleic acid molecules). For example, Cantor discloses that the "solid phase nucleic acid density per solid support unit," *i.e.*, the number of capture probes per bead, may range from 5 to 10,000, including specifically 100 or 200. EX1031, 13. As explained above, each capture agent comprises a first sequence that specifically binds to a different nucleic acid (Cantor's probe sequence) and a coding tag (Cantor's identification sequence) that corresponds to a location of the capture agent on the array. EX1102, ¶¶212-213.

With respect to the probe sequences, Cantor expressly discloses that a given bead (i.e., one of the claimed features) may contain single stranded nucleic acids with the same bead identification sequence, but different probe sequences. *See* EX1031, 14 (“In certain embodiments, one solid support comprises about 10 to about 10,000 unique probe sequences.”); *see also id.* cls. 32-35. When each probe sequence on a given bead is different, each necessarily binds to a different nucleic acid, as claimed. EX1102, ¶214.

In addition, PO contends that the limitation “each of the greater than 100 capture agents comprises a first sequence that binds to a different nucleic acid” is allegedly satisfied in Curio’s Seeker product by multiple poly-T tails on the same bead that bind polyA tails on mRNA. To the extent this argument can be understood, it appears that PO interprets the claimed “first sequence that binds to a different nucleic acid” to be satisfied by a sequence on the capture agent that binds to any molecule present in a sample, as long as another capture probe isn’t already bound to that molecule. Thus, because nucleic acid hybridization interactions generally involve the formation of duplexes through base-pairing, each of the 100 or more probe sequences present on one of Cantor’s beads necessarily binds to a different nucleic acid under PO’s interpretation of the claims. EX1102, ¶¶215-216.

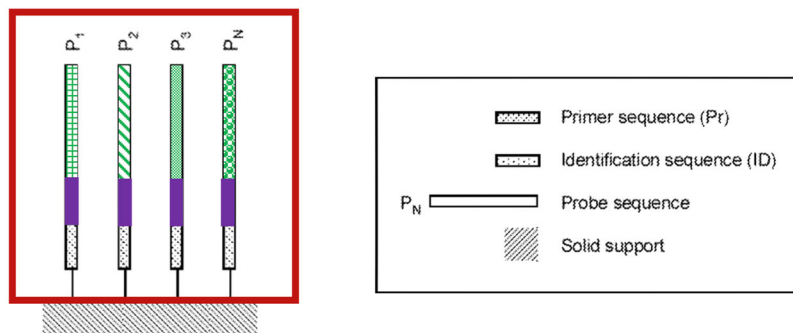
B. Ground 2: Obviousness over Cantor in view of Armani and Knowledge of a POSA.

In addition to Ground 1, which is herein incorporated, Armani further evidences a POSA's motivation and reasonable expectation of success in using Cantor's device and methods as set forth in the challenged claims. EX1102, ¶217.

1. Claim 1

Cantor in view of Armani further renders obvious claim steps 1(a) “contacting the tissue section with an array” and 1(b)(iii) “determin[ing] [the] presence or abundance of the nucleic acid at a location in the tissue section.”

As explained above, Cantor discloses providing a plurality of beads with the claimed “**capture agents**,” which include a “**probe sequence**” that “**specifically binds**” with a target nucleic acid, as well as a “**coding tag**” or “**identification sequence**” that may be used to identify the specific bead, and thus location, at which a particular binding interaction occurred. EX1102, ¶220.



Cantor further explains that its “array can be arranged on any substrate suitable for sequence analysis,” including “substrates having multiple wells or pits.”

EX1031, 17-18. Cantor explains that “[w]ells or pits of multiple well and pit substrates may contain one or more solid support units (e.g., each unit being a single bead or particle.” *Id.*, 18; *see also id.*, 19. EX1102, ¶221.

Thus, Cantor discloses providing a plurality of beads containing the claimed capture agents by arranging the beads in a multiple well plate. This arrangement is encompassed by the Chee-468 claims. *See* EX1002, cl. 17. EX1102, ¶221.

Armani further discloses methods for the analysis of nucleic acids in a tissue section. In Armani’s method, (1) “the tissue section is transferred onto the surface of the multi-well array (step 1A) and the pressed onto the surface (1B),” after which “[t]he contents of the well are dehydrated to enable the addition of lysis reagents (1C); (2) “the tissue is lysed to release genomic DNA into solution”; (3) the “DNA is amplified” using PCR; and (4) “the DNA is imaged” using fluorescent detection techniques. EX1022, 3527. This is depicted in Armani’s Figure 2. EX1102, ¶222.

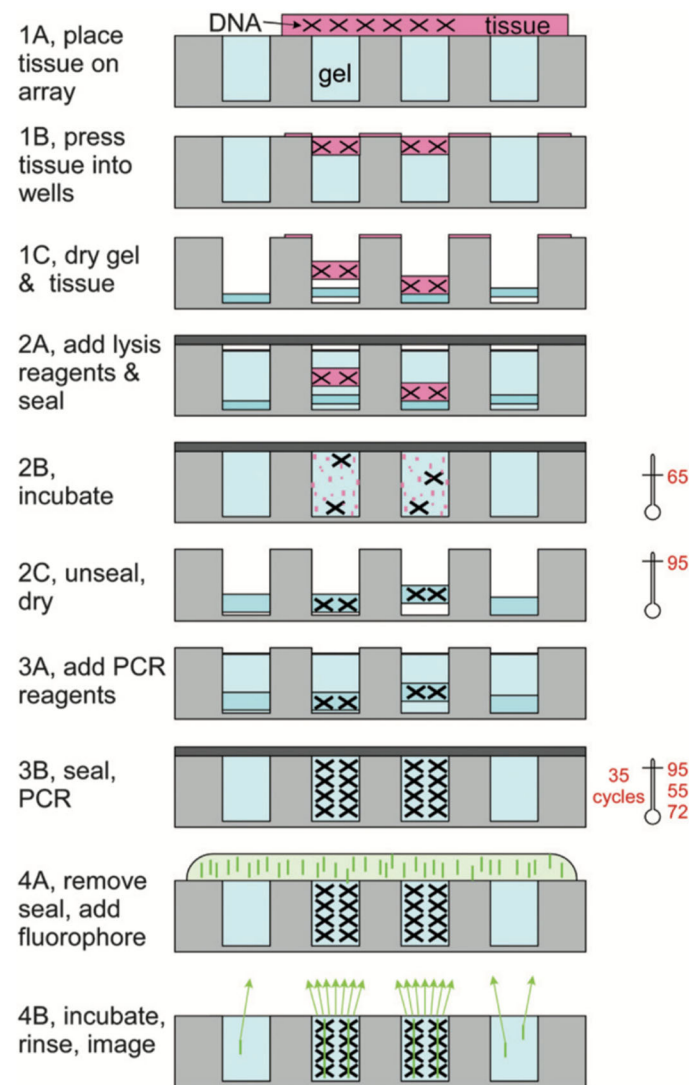


Fig. 2 Experimental protocol used to demonstrate the 2D-PCR concept. Tissue is transferred into wells, isolated, and lysed to extract the genomic DNA (represented by "x"s). PCR is performed to amplify the target DNA, and the targets are visualized with fluorescent dye (indicated by vertical lines "I").

A POSA would have found it obvious to combine the teachings of Cantor and Armani by providing Cantor's bead array with the plurality of beads disposed in wells as contemplated by Cantor, contacting that array with a tissue slice as suggested by both Cantor and disclosed in Armani, and then pressing the tissue

sample into the wells and lysing the tissue as described by Armani. EX1022, 3531 (describing “loading the tissue vertically, pressing it directly into the array of wells to isolate tissue subregions while preserving the overall 2D spatial relationship....”). EX1102, ¶223.

A POSA would then have proceeded with the nucleic acid extension, amplification, and detection by sequencing steps disclosed by Cantor. EX1102, ¶224.

A POSA reviewing Cantor and Armani would have been motivated to combine their teachings for several reasons. Cantor’s protocols facilitate the capture, amplification, and detection of mRNA by sequencing, which Armani indicates was a desirable application for spatial analysis. By using sequencing as a detection technique, rather than visualization (e.g., fluorescence), the combination would allow the detection of even low abundance mRNAs. *See* EX1022, 3532 (“We are currently working on mapping RNA from tissue, since current visualization techniques for RNA cannot reliably detect below a few dozen copies per cell in situ.”). Moreover, the use of Cantor’s methods to generate cDNA libraries of target nucleic acids coded with location information (via Cantors’ identification sequences) would simplify Armani’s detection procedure by eliminating at least the steps of unsealing the array, adding a fluorophore, incubating, rinsing, and imaging. Instead, using sequencing as a detection method would allow a POSA to simply pool

the contents of all wells together in a multiplexed sequencing procedure, where the data can then be deconvoluted and spatially mapped based on the read out of location-correlated identification sequences. EX1102, ¶225.

A POSA would have reasonably expected success in combining the teachings of Cantor and Armani. Indeed, the combination would have involved using Cantor's device and methods in the manner they are disclosed—to detect nucleic acids from a tissue sample, while specifically using the identification probes to identify the location at which beads were provided. Armani expressly motivates this mental step, and further provides additional specific implementations of how to successfully prepare and process effectively a nucleic acid sample for localized detection. EX1102, ¶226.

2. Claim 21

As described in Ground 1, Cantor in view of the knowledge of a POSA renders obvious “wherein the tissue section is a fresh frozen tissue section....”

Armani further renders obvious using a fresh-frozen tissue with Cantor's array because Armani discloses successfully placing a fresh-frozen tissue section on a multi-well array, as shown in Figure 2 above, to detect the presence of a target nucleic acid at various location throughout the tissue sample. EX1022, 3528 (“Two types of tissue were used in these studies: frozen tissue samples from a human prostate....and breast tissue with lobular carcinoma....Tissue specimens were snap

frozen....”); *id.* (“Tissue sections were transferred to the multi-well device immediately after sectioning while still frozen[.]”). EX1102, ¶230.

Thus, Armani confirms a POSA’s reasonable expectation of success in using a fresh-frozen tissue section on Cantor’s array. EX1102, ¶231.

3. Claim 23

The combination of Cantor and Armani renders obvious the step of “generating a map of the presence or abundance of the nucleic acid at location(s) in the tissue section.”

Armani further explains that its spatial analysis technique included “the creation of a 2D detection map, showing the presence/absence of target DNA, on the millimeter scale,” that is, mapping whether target DNA was present or absent at a particular location in the X-Y plane. EX1022, 3527. The presence of target nucleic acid at particular locations in the tissue sample is mapped in Armani’s Figure 1, with the blue squares indicating the presence of a target nucleic acid at a particular location. EX1102, ¶¶234-235.

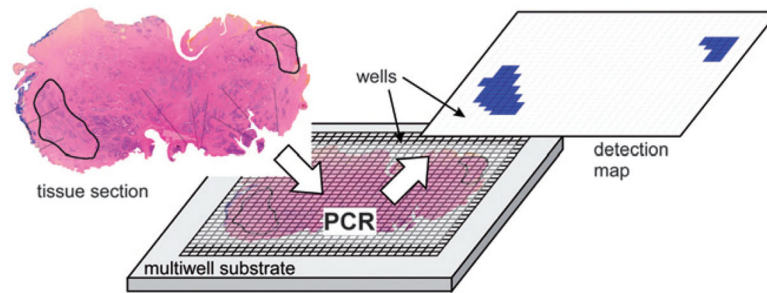


Fig. 1 2D-PCR is achieved by transferring a tissue section vertically into a multi-well array device, isolating tissue subregions. The DNA is extracted and then amplified by the polymerase chain reaction. A detection map is created by imaging the amplified DNA, for example using a DNA-intercalating dye.

Armani explains that a POSA would have been motivated to generate a map of the presence of nucleic acids at spatial locations in a tissue sample, including to “interrogate the molecular heterogeneity of tissue specimens” and create “molecular map[s]” depicting “the status of multiple genes within the tissue sample.” EX1022, 3526; EX1102, ¶¶234-235.

Additionally, as Dr. Puglisi explains, this mapping step is equally applicable to methods involving the use of Cantor’s arrays with the beads arranged on a substrate, as set forth in Ground 1, above. Thus, Cantor in view of Armani and the knowledge of a POSA renders obvious claim 23 of Chee-468. EX1102, ¶236.

C. Ground 3: Anticipation by Frisen**1. Priority Date**

The applications leading to Chee-468 are tabulated below:

'468 Patent Priority Documents	Filing Date	Exhibit
16/443,771	June 17, 2019	EX1063
16/437,726	June 11, 2019	EX1064
16/430,015	June 3, 2019	EX1055
16/414,213	May 16, 2019	EX1056
16/402,098	May 2, 2019	EX1057
16/276,235 (the “’235 Application”)	February 14, 2019	EX1010
15/187,661 (the “’661 Application”)	June 20, 2016	EX1011
13/080,616 (the “’616 Application”)	April 5, 2011	EX1012
61/321,124 (the “’124 Provisional”)	April 5, 2010	EX1009

The challenged claims are not entitled to a priority date earlier than the February 14, 2019 filing date of the ’235 Application because the claimed invention is not disclosed “in the manner provided by §112(a)” in earlier applications. 35 U.S.C. §§119(e), 120. As explained below, the ‘661 and ‘616 Applications and the ’124 Provisional (hereinafter “the Priority Documents”) do not support the challenged claims, and since “there has to be a continuous chain of copending

applications each of which satisfies the requirements of §112 with respect to the subject matter presently claimed,” this break in the priority chain precludes PO from relying on any date earlier than February 14, 2019, the filing date of the ’235 Application,³ the next application in the priority chain. *Holmer v. Harari*, 681 F.3d 1351, 1355 (Fed. Cir. 2012) (quotation omitted). EX1102, ¶240.

The ’661 Application fails to disclose the subject matter recited in the claims of Chee-468. The application preceding the ’661 Application—the ’616 Application—shares the same specification as the ’661 Application, and thus fails to provide adequate description of the subject matter recited in the challenged claims for the same reasons. Finally, the passages of the ’124 Provisional that were omitted from the ’661 and ’616 Applications also fail to describe the subject matter of the challenged claims. EX1102, ¶241.

As set forth below, the Priority Applications at most contain ambiguous disclosures of isolated aspects of the claims, with no explanation of how those disclosures are linked to other aspects of the specification. Because “[a] patent owner cannot show written description support by picking and choosing claim elements from different embodiments that are never linked together in the specification,”

³ Curio does not concede support in the ’235 Application, or any subsequent application, for the challenged claims.

Chee-468 is not entitled to the filing dates of the Priority Applications. *Flash-Control, LLC v. Intel Corp.*, No. 2020-2141, 2021 WL 2944592, at *4 (Fed. Cir. July 14, 2021); *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1349 (Fed. Cir. 2013) (“pointing to an ‘amalgam of disclosures’ from which an artisan could have created the claimed invention does not satisfy this requirement.”).

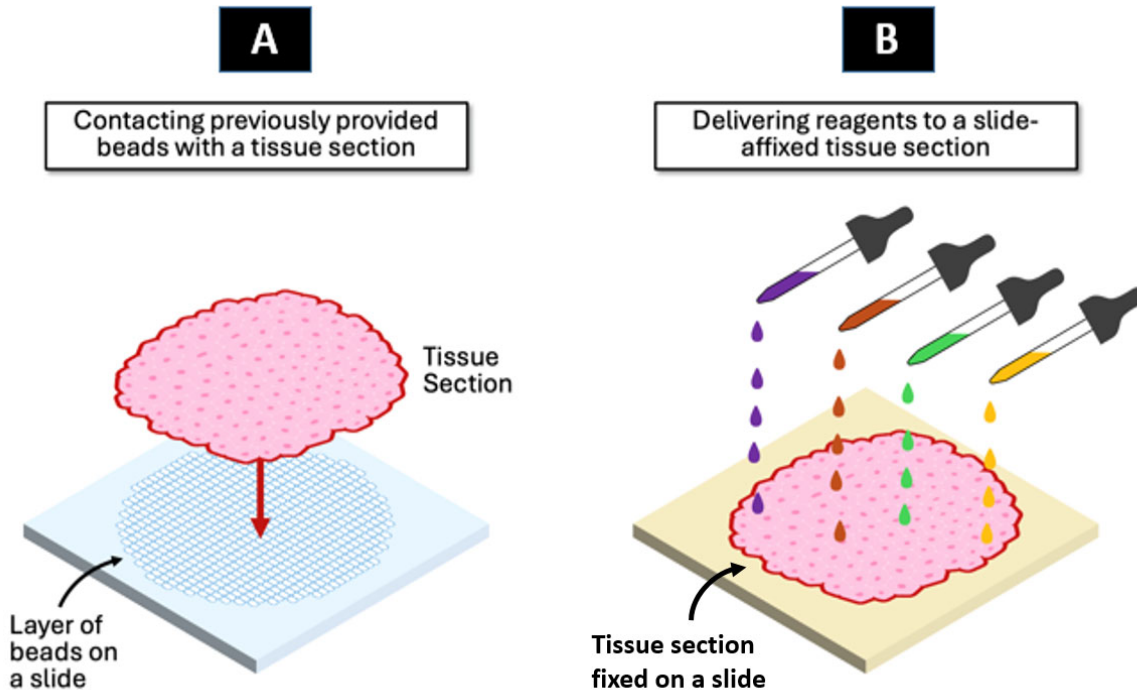
At least one limitation of independent claim 1 is not disclosed by the Priority Documents, as there is no disclosure of “contacting the tissue section with an array comprising a plurality of features.” The challenged dependent claims do not further limit claim 1 in a manner that cures this deficiency.

(a) The '661 Application discloses delivering probes to a fixed tissue sample; not delivering a tissue sample to a previously generated array of substrate-affixed probes.

Claim step 1(a) recites “contacting the tissue section with an array comprising a plurality of features, wherein a feature of the plurality of features comprises a capture agent, wherein the capture agent comprises: (i) a first sequence that specifically binds the nucleic acid.” Thus, the claims as drafted and as read by PO to assert infringement require providing an array of features, where each feature comprises a capture agent that binds a target nucleic acid. The claims also require contacting such an array with a tissue sample by placing the tissue sample on top of

the array of features (including capture probes), as depicted in Figure A below.

EX1102, ¶¶242-243.



The '661 Application discloses different methods, which uniformly require providing a tissue sample affixed to a solid support, and then delivering reagents, such as capture agents, to the support-affixed tissue sample according to a spatial pattern as shown in Figure B. EX1102, ¶243.

As Dr. Puglisi explains, the differences between these methodologies are not trivial. For example, consistent with the '661 Application's focus on fluid handling techniques for delivery of probes, it repeatedly describes the delivery of probes to tissue in solution. As a result, Chee-468 repeatedly emphasizes a step of "washing" or separating encoded probes that did not bind to a target away from the sample,

which is important for eliminating “noise” from the sequencing readout. EX1011, Figs. 1-2, [00028]. By contrast, the claims purport to encompass providing an array of solid phase probes to which a tissue sample is subsequently delivered. Such techniques require fabrication technologies and chemistries to create beads or other surfaces with the nucleic acids (such as probes) affixed to the desired locations. Here, a step of separating or washing encoded probes that did not bind to a target would not make sense in the context of these bead chemistries, because the probes are covalently bound to the beads. Moreover, such a washing step could displace beads spatially with respect to the sample, impeding the array’s function and the accuracy of its readouts. EX1102, ¶242.

Moreover, Chee-468 criticizes Armani, which provides a variation of the Figure A approach, stating that its reliance on the transfer of tissue into wells, “prevents random access to tissue samples and prevents high levels of multiplexing.” *See* EX1002, 1:66-2:5. To the extent that the disclosures of Chee-468 (but not its claims) purport to address these alleged deficiencies, it is through the delivery of reagents from above the tissue sample. EX1002, 16:15-17 (“Integral to the assay system of the invention is instrumentation that allows for spatial patterning of reagents *onto* the biological sample.”). EX1102, ¶245.

A POSA reviewing the ’661 Application would not have understood it to demonstrate that the inventor possessed methods of contacting a pre-existing array

or arrangement of binding agents, such as probes, with a tissue sample. Instead, a POSA would have understood the disclosure of the '124 Provisional to have been limited to the delivery of reagents, including binding agents and encoded probes, to a tissue sample already affixed to the solid support. EX1102, ¶246.

The '661 Application's Specification and Drawings are replete with statements confirming that its "invention" requires (i) providing a sample affixed to a support before (ii) delivering probes to the sample. These include:

- **SUMMARY OF THE INVENTION:** "The assay system comprises an assay capable of high levels of multiplexing where encoded probes *are provided to a biological sample* in a defined spatial patterns...." EX1011, [0007]. The other embodiments disclosed in this section similarly involve "providing a sample affixed to a support" and "delivering encoded probes." *E.g., id.*, [00015]; EX1102, ¶¶247-249.
- **FIGURES:** The figures require (i) providing biological samples affixed to a support, and (ii) delivering encoded probes to the biological sample. EX1011, Figs. 1-2. EX1102, ¶¶250-253.
- **"The Invention in General":** "The assay system further provides *instrumentation with an ability to deliver reagents* in a spatially-defined pattern. *This instrumentation*, together with software, reagents and protocols, *provides a key component* of the highly innovative assay

system *of the invention*....” EX1011, [00023]-[00024]. EX1102, ¶¶254-256.

- “Assays”: “The assay portion of the assay systems of *the present invention* comprise the following general steps: *delivering probes and encoding agents*” to samples, where “[t]he samples of the present invention include virtually any biological sample or samples *that can be affixed to a support*....” EX1011, [00034]-[00035]. EX1102, ¶257.

Further confirming that that the ’661 Application discloses only the delivery of reagents, including probes, to a sample affixed to a solid support, the Specification further notes that “instrumentation capable of delivering reagents according to a spatial pattern” “onto the biological sample” is “*integral to the assay system of the invention*.” EX1011, [00055]. Such techniques are disclosed to include, for example, ink jet printing and photolithographic processes. *Id.*, [00056], [00064]-[00065]; *see also* [00054] (“The reagent delivery system *of the invention* includes instrumentation that allows the *delivery* of reagents to discrete portions of the biological sample.”). A POSA would not have understood such disclosures, to demonstrate possession of methods in which a tissue sample is placed on top of an array of capture agents, as claimed. EX1102, ¶¶258-261; *see also Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479 (Fed. Cir. 1998) (finding failure of written description for claims directed to furniture with controls off the console

where “the original disclosure clearly identifies the console as the only possible location for the controls”); *Rivera v. Int’l Trade Comm’n*, 857 F.3d 1315, 1321 (Fed. Cir. 2017) (The “question is whether a pod adaptor assembly intended to allow compatibility between distinct brewing systems, also supports an undisclosed configuration that eliminates a fundamental component of one of those systems (i.e., the ‘pod’) through integration. It does not.”); *ICU Med., Inc. v. Alaris Med. Sys., Inc.*, 558 F.3d 1368, 1378 (Fed. Cir. 2009) (The “specification describes only medical valves with spikes... [A POSA] would not understand the inventor...to have invented a spikeless medical valve”).

(b) The ’661 Application does not disclose contacting an array with a tissue section such that nucleic acids in the tissue section “specifically bind” to the capture probes.

As noted above, Chee-468 and its priority applications criticize Armani’s tissue preparation procedures:

Certain PCR assays in a 2D format preserve spatial information (see [Armani, EX1022]), but these methods have low spatial resolution because they rely on physical transference of tissue into wells, which also prevents random access to tissue samples and high levels of multiplexing.

EX1011 (’661 Application), [0004]. Yet the subsequent disclosures of the ’661 Application contain no teaching on how to prepare the tissue section to allow specific binding when a tissue section is contacted with an array. EX1102, ¶262.

A POSA would understand, given the '661 Application's criticism of Armani, that the inventor did not envision or possess providing access to the nucleic acids in a tissue sample through physical transference and lysis as in Armani. But the '661 Application does not disclose any alternative techniques for "contacting" an array such that capture probes disposed on the array bind or specifically bind nucleic acids in the tissue section. Thus, a POSA would have understood the '661 Application as having disclosed at most a hope or a wish to obtain access to tissue samples without relying on transference and lysis techniques as disclosed in Armani. But given the failure of the '661 Application to expressly disclose or otherwise point to which techniques to use, a POSA would not have understood the inventor to have possessed such methods. EX1102, ¶263. *Nuvo Pharms. (Ir.) Designated Activity Co. v. Dr. Reddy's Labs. Inc.*, 923 F.3d 1368, 1381 (Fed. Cir. 2019) ("Patents are not rewarded for mere searches, but are intended to compensate their successful completion. That is why the written description requirement incentivizes actual invention, and thus a mere wish or plan for obtaining the claimed invention is not adequate written description[.]") (internal citations and markings omitted).

While, as Dr. Puglisi explains, 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, the inventor did not point to such techniques (or in the case of Armani, expressly criticizes and disclaims them). Moreover, given the inventor's

criticism and failure to point to such techniques, there is no indication to a POSA in the priority documents that the inventor possessed or even contemplated the use of such techniques. EX1102, ¶264. *Quake*, 928 F.3d at 1365-76 (specification did not communicate possession of random sequencing methods when the specification repeatedly discussed targeted sequencing but had only two references to random sequencing: “a bare citation to [a prior art reference that disclosed random sequencing] and use of the phrase ‘about 30 bp of *random* sequence information are needed to identify a sequence’”).

Thus, this is an independent reason for which the ’661 Application fails to support the challenged claims.

2. Claim 1

As described below, Frisen anticipates claim 1.

(a) “A method for determining the presence or abundance of a nucleic acid....:”

Frisen discloses the claimed “method for determining the presence or abundance of a nucleic acid at a location in a tissue section.”

For example, Frisen discloses the following workflow (hereinafter “Frisen’s Workflow”):

[A] method for localised detection of nucleic acid in a tissue sample comprising:

- (a) providing an array comprising a substrate on which multiple species of capture probes are directly or indirectly...wherein each

species of said capture probe comprises a nucleic acid molecule with 5' to 3':

- (i) a positional domain that corresponds to the position of the capture probe on the array, and
- (ii) a capture domain;
- (b) contacting said array with a tissue sample such that the position of a capture probe on the array may be correlated with a position in the tissue sample and allowing nucleic acid of the tissue sample to hybridise to the capture domain in said capture probes;
- (c) generating DNA molecules from the captured nucleic acid molecules...;
- (d) optionally generating a complementary strand of said tagged DNA and/or optionally amplifying said tagged DNA;
- (e) releasing at least part of the tagged DNA molecules...;
- (f) directly or indirectly analysing the sequence of the released DNA molecules.

EX1020, 7:14-8:5; *see also, e.g.*, Claims 1, 40, 42. EX1102, ¶¶267-268.

Frisen further explains that its methods involve the implementation “of standard arrays [that] are commercially available and both the number and size of the features may be varied.” EX1020, 15:21-22. Frisen explains that the arrays suitable for its methods include “[c]ommercial arrays...available or known for use in the context of sequence analysis and in particular in the context of NGS technologies. Such arrays may also be used as the array surface in the context of the present invention e.g. an Illumina bead array.” *Id.*, 15:30-34. Thus, Frisen discloses

providing its array of capture probes or binding agents by providing a plurality of features, such as beads. EX1102, ¶269.

As explained further below, Frisen discloses each enumerated element of Claim 1.

(b) Step 1(a)

Frisen discloses each aspect of step 1(a).

First, Frisen discloses “contacting a tissue section with an array comprising a plurality of features.” Frisen’s Workflow includes “(b) contacting [an] array with a tissue sample such that the position of a capture probe on the array may be correlated with a position in the tissue sample and allowing nucleic acid of the tissue sample to hybridise to the capture domain in said capture probes.” *Id.*, 7:25-27; cl. 1; *see also id.*, 13:7-11 (“The distinct position of each nucleic acid (oligonucleotide) spot (each species of oligonucleotide/nucleic acid molecule) is known as a ‘feature’[.]”). EX1102, ¶¶273-274.

Second, Frisen’s arrays comprise “a feature of the plurality of features comprises a capture agent.” Frisen discloses that its array surface, such as a glass slide or a plurality of beads, comprises a plurality of capture probes. Specifically, Frisen’s Workflow includes “providing an array comprising a substrate on which multiple species of capture probes are directly or indirectly immobilized such that each species occupies a distinct position on the array...wherein each species of said

capture probe comprises a nucleic acid molecule from 5' to 3' (i) a positional domain that corresponds to the position of the capture probe on the array.” EX1020, 7:16-21; *see also id.*, cl. 1; 13:7-11 (describing each nucleic acid spot as a “feature”). EX1102, ¶¶275-276.

(i) Step 1(a)(i)

Frisen discloses Step 1(a)(i). In particular, Frisen’s Workflow discloses that “each species” of capture probe comprises “a capture domain.” *Id.*, 7:24, cl. 1. Frisen discloses that the “capture domain” may be poly-T, *id.*, 18:23-26, or that “[t]he capture domain may be capable of binding selectively to a desired subtype or subset of nucleic acid,” such as “a sequence-specific capture probe, specific for a particular RNA target or group of targets.” *Id.*, 19:15-24; EX1102, ¶¶278-280.

(ii) Step 1(a)(ii)

Frisen discloses Step 1(a)(ii). Specifically, Frisen’s Workflow includes “providing an array comprising a substrate on which multiple species of capture probes are directly or indirectly immobilized such that each species occupies a distinct position on the array...wherein each species of said capture probe comprises a nucleic acid molecule from 5' to 3' (i) *a positional domain that corresponds to the position of the capture probe on the array.*” EX1020, 7:16-23, cl. 1; EX1102, ¶¶281-282.

(c) Step 1(b)

Frisen discloses Step 1(b). For example, after contacting an array with the claimed capture probes with a tissue section, Frisen's Workflow includes "(c) generating DNA molecules from the captured nucleic acid molecules using said capture probes as extension or ligation primers, wherein said extended or ligated DNA molecules are tagged by virtue of their positional domain," "(e) releasing at least part of the tagged DNA molecules and/or their complements or amplicons from the surface of the array, wherein said part includes the positional domain or a complement thereof," and "(f) directly or indirectly analyzing the sequence of the released DNA molecules." *Id.*, 6:2-7, cl. 1. For example, when the released DNA is sequenced this "results in a transcriptome with exact positional information" because each positional domain is "correlated with a position in the tissue sample." *Id.*, 6:2-7; Figure 1. "The sequence data can then be matched to a position in the tissue sample, which enables the visualization, e.g. using a computer, of the sequence data together with the tissue section, for instance to display the expression pattern of any gene of interest across the tissue section (Figure 2)." *Id.*, 6:8-11; EX1102, ¶¶283-284.

(d) Conclusion

Accordingly, Frisen anticipates claim 1.

3. Claim 2

Frisen discloses “between steps (a) and (b), a step of removing the tissue section from the array.” EX1020, 35:34-36:5 (“The tissue sample...preferably is removed prior to the step of releasing the cDNA molecules from the array.”); EX1102, ¶¶286-287.

4. Claim 6

Frisen discloses “the determining step comprises nucleic acid amplification.”

For example, Frisen discloses that its determining step “may involve sequencing, but it is not necessary to perform actual sequence determination.” EX1020, 9:5-8. “For example a sequence-specific amplification reaction may be performed, for example using primers which are specific for the positional domain and/or for a specific target sequence, e.g. a particular target DNA to be detected (i.e. corresponding to a particular cDNA/RNA or gene etc.). An exemplary analysis method is a sequence-specific PCR reaction.” *Id.* 9:9-13; EX1102, ¶¶288-289.

5. Claim 7

Frisen discloses “the determining step comprises sequencing all or a portion of the sequence of the coding tag, or a complement thereof, and all or a portion of the sequence of the nucleic acid specifically bound to the capture agent, or a complement thereof.”

As discussed with respect to claim 1, Frisen discloses performing the determining step by sequencing, for example by disclosing “(f) directly...analysing the sequence of the released DNA molecules.” EX1020, 8:4-5; cl. 1(f); *see also* 9:6-8 (“[A]ny method of nucleic acid analysis may be used in the analysis step. Typically this may involve sequencing....”). Thus, Claim 7 is anticipated for the same reasons set forth with respect to step 1(b) in Section X.C.2.(c), above. EX1102, ¶¶290-291.

6. Claims 12-13

Frisen discloses “the nucleic acid is [mRNA/RNA]”:

[T]he array of the present invention may be used to *capture RNA, e.g. mRNA of a tissue sample* that is contacted with said array.

EX1020, 11:21-22; EX1102, ¶¶292-293.

7. Claim 18

Frisen discloses “the capture agent is immobilized directly or indirectly on a surface of the feature.” For example, Frisen discloses “providing an array comprising a substrate on which multiple species of capture probes are directly or indirectly immobilized such that each species occupies a distinct position on the array.” EX1020, 7:16-21; EX1102, ¶¶294-296.

Frisen also discloses immobilizing the capture agents to beads, for example using “[c]ommerical arrays” such as “an Illumina bead array.” EX1020, 15:30-33. Frisen further explains that the “probes on a microarray may be immobilized, i.e. attached or bound, to the array preferably via the 5’ or 3’ end, depending on the

chemical matrix of the array.” *Id.*, 16:3-5. “The covalent linkage used to couple a nucleic acid probe on an array substrate may be viewed as both a direct and indirect linkage, in that although the probe is attached by a ‘direct’ covalent bond there may be a chemical moiety or linker separating the ‘first’ nucleotide of the nucleic acid probe from the, e.g, glass or silicon, substrate, i.e. an indirect linkage.” *Id.*, 16:10-14; EX1102, ¶297.

8. Claim 20

Frisen discloses “the array comprises a bead array.”

Frisen explains that its methods involve the implementation “of standard arrays [that] are commercially available and both the number and size of the features may be varied.” EX1020, 15:21-22. Frisen explains that the arrays suitable for its methods include “[c]ommercial arrays” such as “an Illumina bead array.” *Id.*, 15:30-33. Thus, a POSA would at once envisage Frisen’s array of capture probes being provided on a plurality of beads, as in an Illumina bead array. EX1102, ¶¶298-299.

9. Claim 21

Frisen discloses “the tissue section is a fresh frozen tissue section or a formalin-fixed paraffin-embedded (FFPE) tissue section.”

Frisen discloses that “[t]he tissue sample may be prepared in any convenient or desired way and the invention is not restricted to any particular type of tissue

preparation. Fresh, frozen, fixed or unfixed tissues may be used.” EX1020, 29:25-29. EX1102, ¶301.

Frisen expressly discloses fresh frozen tissue sections, EX1020, 29:30-30:8, and FFPE tissue sections, EX1020, 30:9-13, as examples of tissue types suitable for use with the disclosed arrays. EX1102, ¶¶302-303.

10. Claim 23

Frisen discloses “generating a map of the presence or abundance of the nucleic acid at location(s) in the tissue section.” In particular, Frisen discloses generating a map of gene expression, i.e., the presence or abundance of mRNAs in the tissue section: “The sequence data can then be matched to a position in the tissue sample, which enables the visualization e.g. using a computer of the sequence data together with the tissue section, for instance to display the expression pattern of any gene of interest across the tissue (Figure 2).” EX1020, 6:8-11; EX1102, ¶¶304-305.

11. Claims 25-26

Frisen discloses “wherein the array comprises greater than [500/1,000] features.” In particular, Frisen’s arrays may contain greater than 1,000 features. EX1020, 28:1-8. (“In representative embodiments of the invention, an array may contain at least...1000, 1500, 3000,...or 4200000 features.”). EX1102, ¶¶306-307.

12. Claim 30

Frisen discloses “wherein a feature of the plurality of features comprises greater than 100 capture agents, where each of the greater than 100 capture agents comprises a first sequence that specifically binds to a different nucleic acid and a coding tag that corresponds to a location of the capture agent on the array.”

Each of Frisen’s features comprises capture agents comprising a first sequence that binds to a nucleic acid and a coding tag that corresponds to the location of the capture agent on the array, as discussed above. Moreover, Frisen discloses that “[t]he typical array of...the invention may contain multiple spots, or “features”....[E]ach feature will comprise a multiplicity of probe molecules,...but...the sequence of a capture domain may differ.” EX1020, 27:4-16. Frisen further discloses that “the term ‘multiple means two or more, or at least two, e.g., 1000, 2000, 5000, 10,000, or more.” *Id.*, 12:19-25 (“[I]t is envisaged that conventional-type arrays with many hundreds, thousands, tens of thousands, hundreds of thousands or even millions of capture probes may be used.”); EX1102, ¶309.

As described by Dr. Puglisi, from these disclosures, a POSA would have understood that Frisen envisaged using high-density arrays with greater than 100 capture agents per feature, and that each of the capture probes in Frisen’s features

could have a different capture domain designed to bind a different molecule than the other capture probes present at a feature. EX1102, ¶309.

In addition, PO contends that the limitation “each of the greater than 100 capture agents comprises a first sequence that binds to a different nucleic acid” is allegedly satisfied in Curio’s Seeker product by multiple poly-T tails on the same bead that bind polyA tails on mRNA. To the extent this argument can be understood, it appears that PO is interpreting the claimed “first sequence that binds to a different nucleic acid” to be satisfied by a sequence on the capture agent that binds to any molecule present in a sample, as long as another capture probe isn’t already bound to that molecule. Thus, because nucleic acid hybridization interactions generally involve the formation of duplexes through base-pairing, each of the 100 or more probe sequences present on one of Frisen’s capture agents necessarily binds to a different nucleic acid under PO’s interpretation of the claims. EX1102, ¶¶310-311.

XI. SECONDARY CONSIDERATIONS

Petitioner is not aware of any secondary considerations of non-obviousness, and reserves the right to respond to any such issues raised by PO.

Even if Chee-468 were entitled to its 2010 provisional filing date, the contemporaneous work of Frisen, which was filed on April 13, 2011, is “strong evidence of what constitutes the level of ordinary skill in the art.” *Geo M. Martin Co. v. Alliance Mach. Sys. Int’l LLC*, 618 F.3d 1294, 1306 (Fed. Cir. 2010). As

illustrated in Ground 3, Frisen discloses all elements of the claims, and thus developed the claimed subject matter totally independent of the original applicant. This simultaneous invention and development is strong evidence of obviousness. *Id.* at 1305 (“Independently made, simultaneous inventions, made ‘within a comparatively short space of time,’ are persuasive evidence that the claimed apparatus was the product only of ordinary mechanical or engineering skill.”).

XII. NO BASIS FOR DISCRETIONARY DENIAL

A. Denial Under 314(a) is Inappropriate

As explained below, factors 1-4 and 6 of *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 at 6 (PTAB March 20, 2020) strongly favor institution, and factor 5 does not weigh against institution:

1. Likelihood of a stay – Petitioner intends to move for a stay promptly after filing this Petition. Here, each of the factors the Court will consider favors a stay: the parallel litigation is still in early stage, and discovery is still ongoing, *see* EX1043; a stay would simplify the issues in question because all of the asserted claims of Chee-468 are being challenged in this Petition, and thus the invalidity issues in the district court would be narrowed by the estoppel provisions of § 315(e)(2); and there is no evidence of prejudice to Patent Owner, which did not seek a preliminary injunction.

2. Trial date – Trial is scheduled for May 2026. If instituted, the Board’s FWD would be expected around the same time. *See* EX1040, 77 (10x (as Petitioner) asserting that “*Fintiv* simply does not apply” in IPR proceeding where FWD would post-date trial, which was scheduled “approximately two months *before* a [FWD] would be reached”).

3. Investment in the parallel proceeding – The parallel litigation is in its early stages, investment by the parties and the court has been limited. Claim construction will not be fully briefed until after the Board’s anticipated decision to institute. EX1043.

4. Overlap between issues raised – The most efficient course is for the Board to address the issues before it, and the district court to address only the issues that remain.

5. Parties – The parties are the same in this IPR and in the parallel district court proceeding.

6. Other circumstances – This Petition presents a compelling merits case that all challenged claims are unpatentable, and therefore favors institution. *See Fintiv*, Paper 11 at 14-15.

In view of the above factors, this Petition should not be denied under §314(a).

B. Denial Under 325(d) is Inappropriate

Grounds 1-2: Cantor was neither considered during prosecution nor cited in an IDS. *See Yita LLC v. MacNeil IP LLC*, IPR2023-00172, Paper No. 12 at 47 (when reference not previously presented, “the first prong of the *Advanced Bionics* framework is not satisfied and we need not consider the second prong.”).

Ground 3: The Office materially erred, because had the Examiner analyzed the lack of support for the claims in the priority documents, they would have then appreciated the relevance of Frisen as anticipatory prior art.

Moreover, the Office did not have the benefit of the detailed expert evidence submitted with this Petition, which shows why the claims are not supported and how Cantor, Frisen, and Armani confirm their unpatentability. *See* EX1102; *see also Mylan Pharmaceuticals Inc. v. Merck Sharp & Dohme Corp.*, IPR2020-00040, Paper 21 at 20 (PTAB May 12, 2020).

XIII. CONCLUSION

The Board should institute IPR and cancel the challenged claims.

Dated: November 27, 2024

Respectfully submitted,

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CERTIFICATE OF WORD COUNT

I hereby certify, pursuant to 37 C.F.R. section 42.24, that the foregoing Petition contains 13,979 words, excluding the words in the table of contents, table of authorities, exhibit list, this certificate of word count, and certificate of service. The word count is based on the word count of the Microsoft Word program used to prepare the Petition.

/Andrew E. Krause/
Andrew E. Krause

CERTIFICATE OF SERVICE

I hereby certify, pursuant to 37 C.F.R. sections 42.6 and 42.105, that a complete copy of the Petition for *Inter Partes* Review of U.S. Patent No. 10,662,468 and Exhibits are being served via Express Mail on November 27, 2024, the same day as the filing of the above-identified documents in the United States Patent and Trademark Office/Patent Trial and Appeal Board, upon the patent prosecution counsel of record for the Patent Owner:

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Courtesy copies were also sent via ShareSite to Patent Owner's counsel of record in the related district court litigation at the following addresses:

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