

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BRUKER SPATIAL BIOLOGY, INC.,
Petitioner,

v.

PRESIDENT AND FELLOWS OF HARVARD COLLEGE and
10X GENOMICS,
Patent Owner.

IPR2024-00526
Patent 11,542,554 B2

Before ZHENYU YANG, TAWEN CHANG, and CYNTHIA HARDMAN,
Administrative Patent Judges.

CHANG, *Administrative Patent Judge.*

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

NanoString Technologies, Inc. (“NanoString”) filed a Petition for *inter partes* review of claims 36–70 of U.S. Patent No. 11,542,554 B2 (Ex. 1001, “the ’554 patent”). Paper 2 (“Pet.”). 10x Genomics, Inc. (“10x Genomics” or “Patent Owner”) filed a Preliminary Response.¹ Paper 8 (“Prelim. Resp.”). The parties further submitted an authorized Reply and Sur-Reply to the Preliminary Response. Paper 9 (“Reply”); Paper 10 (“Sur-Reply”); Ex. 3001. On July 24, 2024, we granted NanoString’s Unopposed Motion to Substitute Party, whereupon Bruker Spatial Biology, Inc. (“Petitioner”) replaced NanoString as Petitioner in this proceeding.² Paper 13.

¹ In the Preliminary Response, 10x Genomics represents that, although the President and Fellows of Harvard College (“Harvard” or “Patent Owner”) is the owner of the ’554 patent, 10x Genomics is the exclusive licensee and the real party-in-interest. Prelim. Resp. n. 1. To date, neither Petitioner nor Harvard, which has filed its own mandatory notices and power of attorney (Papers 5, 6), has disputed 10x Genomics’ right to participate on behalf of Patent Owner for purposes of this proceeding. Accordingly, we amend the caption to include both Harvard and 10x Genomics. References to Patent Owner in this proceeding are to 10x Genomics and/or Harvard as appropriate in the particular context of the reference. To the extent any party disputes 10x Genomics’ right to participate in this proceeding on behalf of Patent Owner, the party shall request authorization to brief the issue within 5 business days of this Decision.

² With respect to events occurring prior to entry of the Order Granting the Motion to Substitute Party, references to “Petitioner” in this Decision are to NanoString.

We have authority under 35 U.S.C. § 314(a), which provides that an *inter partes* review may not be instituted “unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” For the reasons discussed below, we determine Petitioner has demonstrated a reasonable likelihood that the challenged claims of the ’554 patent are unpatentable. Accordingly, we institute an *inter partes* review of all challenged claims on each of the Grounds raised in the Petition. *See SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1359–60 (2018).

A. Real Parties-in-Interest

Petitioner identifies Bruker Spatial Biology, Inc. as the real party-in-interest. Paper 12, 1.³ Petitioner further identifies Bruker Nano, Inc. and Bruker Corporation as additional real parties-in-interest “for the purpose of this IPR proceeding.” *Id.*

Patent Owner identifies, as real parties-in-interest, Harvard as the owner of the ’554 patent and 10x Genomics, Inc. as the exclusive licensee of the ’554 patent. Paper 6,⁴ 1; Paper 4, 1.

³ Although Paper 12 is erroneously titled “Patent Owner’s Updated Mandatory Notices” and refers to “Patent Owner” in several places, we understand Paper 12 to be Petitioner’s updated mandatory notices.

⁴ Paper 6 is not paginated. We refer to the pages as if numbered sequentially starting with the first page after the cover page.

B. Related Proceedings

Petitioner, Harvard, and 10x Genomics each identifies *10x Genomics, Inc. et al. v. NanoString Technologies, Inc.*, Case No. 1:22-cv-00261 (D. Del.), as a proceeding in which the '554 patent is at issue. Pet. 20; Paper 4, 1; Paper 6, 1. Petitioner indicates that this matter is now titled *10x Genomics, Inc. and President and Fellows of Harvard College v. Bruker Spatial Biology, Inc. and Bruker Nano, Inc.*, 1:22-cv-261 (D. Del). Paper 12, 2.

10x Genomics identifies pending U.S. Patent Application No. 17/956,892 as an application that “claims the benefit of the '554 patent.” Paper 4.

C. The '554 Patent (Ex. 1001)

The '554 patent, entitled “Methods and Apparatus for Volumetric Imaging,” was filed as U.S. Patent Application No. 17/395,534 on August 6, 2021, and claims the benefit of U.S. Patent Application No. 16/386,337 (now U.S. Patent No. 11,118,220), filed on April 17, 2019; U.S. Application No. 15/969,118 (now U.S. Patent No. 10,266,888), filed on May 2, 2018; PCT/US2016/060279, filed on November 3, 2016; and U.S. Provisional Application No. 62/250,182, filed on November 3, 2015. Ex. 1001, codes (54), (21), (22), (63), (60), 1:6–16.

The Specification states that, “[s]ince many gene products such as RNA and proteins are enriched in regions where they function, their location provides an important clue to their function. This property has been used for in situ fluorescent hybridization, immunohistochemistry and tissue-specific

reporter assays in numerous areas of biological research.” Ex. 1001,

1:37–42. According to the Specification, however,

[m]ost optical sequencing methods either utilize a two-dimensional solid substrate or microwells/microchambers to immobilize sequencing templates during the sequencing process in order to maintain spatial invariability for optical detection, and therefore enable reconstruction of a single nucleic acid template sequence. In both cases, optical detection of signal occurs in at most two two-dimensional planes.

Id. at 1:42–49.

The ’554 patent relates to “a method and apparatus for volumetric imaging of a three-dimensional matrix of nucleic acids where the nucleic acids have been amplified, detected and sequenced within the matrix.” Ex. 1001, 1:30–33. “According to one aspect, the three-dimensional positioning of a molecule within the three dimensional matrix is determined.” *Id.* at 1:60–62. The Specification states that “[e]xemplary volumetric imaging approaches include those described [in the Specification] and those known in the art which measures light signals . . . in three-dimensional space.” *Id.* at 2:12–15. The Specification further states that “[e]xemplary volumetric detection methods include both methods for volumetric imaging of optical sections that utilize optical sectioning (e.g. two-dimensional acquisition of images throughout a volume), as well as those that do not utilize optical sectioning (e.g. digital holography and physical sectioning).” *Id.* at 1:64–2:2.

D. Overview of Challenged Claims

Petitioner challenges claims 36–70 of the '554 patent. Claim 36, reproduced below, is the sole independent claim:

36. A system comprising:
- (a) a stage comprising:
 - (i) a sample holder configured to receive a substrate comprising a sample having a volume;
 - (ii) a temperature control apparatus operatively coupled to said sample holder; and
 - (iii) an XY motion control system;
 - (b) a fluidics system comprising:
 - (i) one or more reservoirs configured to contain one or more fluid reagents; and
 - (ii) a fluid dispenser operationally coupled to a pump, which pump is configured to provide said one or more fluid reagents from said one or more reservoirs to said sample holder; and
 - (c) an optical system comprising:
 - (i) an objective;
 - (ii) two or more light sources, wherein each light source of said two or more light sources is configured to deliver light to said volume, wherein said two or more light sources are configured to emit two or more colors of light; and
 - (iii) one or more detectors configured to receive light signals from said volume;
 - (d) a Z-axis motion control system configured for Z-motion of an objective focal plane through said volume; and
 - (e) a computing system comprising at least one computer readable storage medium having program instructions stored thereon, which program instructions are executable by at least one processor of said computing system to cause said at least one processor to perform a method comprising:
 - receiving a plurality of images of at least a portion of said volume from a plurality of read-out cycles, wherein said plurality of images comprises a plurality of light signals

received from said volume during said plurality of readout cycles, wherein said plurality of light signals is associated with one or more nucleic acid molecules within said volume, wherein each light signal of said plurality of light signals has a three-dimensional spatial position within said volume; determining a plurality of optically-encoded signals from said plurality of light signals obtained from said plurality of read-out cycles, wherein each optically-encoded signal is associated with a nucleic acid molecule of said one or more nucleic acid molecules, wherein said plurality of optically encoded signals comprises said two or more colors of light detected by said one or more detectors in series; identifying said one or more nucleic acid molecules based on said plurality of optically-encoded signals; and determining three-dimensional positional information of said one or more nucleic acid molecules.

Ex. 1001, 33:29–34:16 (claim 36).

Claims 37–70 depend directly or indirectly from independent claim 36 and recite additional features of the system.

E. Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability (Pet. 21–22):

Ground	Claim(s) Challenged	35 U.S.C §	Reference(s)/Basis
1	36–39, 43, 44, 46, 47, 54, 56, 59, 60, 63–69	103	Chen, ⁵ Cai, ⁶ Shen ⁷
2	40	103	Chen, Cai, Shen, Xiao, ⁸ Ehrlicher ⁹
3	41, 70	103	Chen, Cai, Shen, Tirichine ¹⁰
4	42, 70	103	Chen, Cai, Shen, Brileya ¹¹

⁵ Kok Hao Chen et al., *Spatially Resolved, Highly Multiplexed RNA Profiling in Single Cells*, 348 SCIENCE 412 (2015) (Ex. 1003, “Chen”). We note that Petitioner refers to Exhibit 1003 as “Zhuang.” We refer to Exhibit 1003 as “Chen,” i.e., the first author’s last name. The parties should follow this convention in their future papers.

⁶ Cai et al., U.S. Patent 10,457,980 B2, issued Oct. 29, 2019 (Ex. 1004, “Cai”).

⁷ Feimo Shen et al., *Digital Autofocus Methods for Automated Microscopy*, 414 METHODS ENZYMOLOGY 620 (2006) (Ex. 1032, “Shen”).

⁸ Jie Xiao, *Single-Molecule Imaging in Live Cells*, in HANDBOOK OF SINGLE-MOLECULE BIOPHYSICS 43–93 (Peter Hinterdorfer & Antoine van Oijen, eds., 2009) (Ex. 1027, “Xiao”).

⁹ Allen Ehrlicher et al., *Optical Neuronal Guidance*, 83 METHODS CELL BIOLOGY 495 (Ex. 1028, “Ehrlicher”).

¹⁰ Laïla Tirichine et al., *3D Fluorescent In Situ Hybridization Using Arabidopsis Leaf Cryosections and Isolated Nuclei*, 5 PLANT METHODS, Article 11 (2009) (Ex. 1049, “Tirichine”).

¹¹ Kristen A. Brileya et al., *Biofilm Growth Mode Promotes Maximum Carrying Capacity and Community Stability During Product Inhibition*

Ground	Claim(s) Challenged	35 U.S.C §	Reference(s)/Basis
5	45	103	Chen, Cai, Shen, Fang-Yen ¹²
6	48	103	Chen, Cai, Shen, Richard ¹³
7	49	103	Chen, Cai, Shen, Nikon ¹⁴
8	50, 51	103	Chen, Cai, Shen, Nikon, Skafte-Petersen ¹⁵
9	52	103	Chen, Cai, Shen, Sands ¹⁶
10	53	103	Chen, Cai, Shen, Sands, Brooker ¹⁷

Syntrophy, 5 FRONTIERS IN BIOLOGY Article 693 (2014) (Ex. 1039, “Brileya”).

¹² Christopher Fang-Yen et al., *Video-Rate Tomographic Phase Microscopy*, J. BIOMEDICAL OPTICS 011055-1 (2011) (Ex. 1029, “Fang-Yen”).

¹³ Marc J.P. Richard et al., *Cellular Mechanisms by Which Lipoic Acid Confers Protection During the Early Stages of Cerebral Ischemia: A Possible Role for Calcium*, 69 NEUROSCIENCE RES. 299 (2011) (Ex. 1030, “Richard”).

¹⁴ NIKON, *Culture Chambers for Live-Cell Imaging*, MICROSCOPY U: THE SOURCE FOR MICROSCOPY EDUC. (2015), <https://web.archive.org/web/20150810165805/http://www.microscopyu.com/articles/livecellimaging/culturechambers.html>.

¹⁵ Peder Skafte-Pedersen et al., *A Self-Contained, Programmable Microfluidic Cell Culture System with Real-Time Microscopy Access*, 14 BIOMED MICRODEVICES 385 (2012) (Ex. 1048, “Skafte-Pedersen”).

¹⁶ Gregory B. Sands et al., *Automated Imaging of Extended Tissue Volumes Using Confocal Microscopy*, 67 MICROSCOPY RSCH. & TECH. 227 (2005) (Ex. 1046, “Sands”).

¹⁷ Brooker, U.S. 2011/0090562 A1, published Apr. 21, 2011 (Ex. 1040, “Brooker”).

Ground	Claim(s) Challenged	35 U.S.C §	Reference(s)/Basis
11	55, 57, 58	103	Chen, Cai, Shen, Wessels ¹⁸
12	61	103	Chen, Cai, Shen, knowledge of POSA ¹⁹
13	62	103	Chen, Cai, Shen, Niman, ²⁰ and/or Winer ²¹

Petitioner further relies, *inter alia*, on the Declaration of Kirk Cyzmmek, Ph.D. (“Cyzmmek Declaration,” Ex. 1002).

II. ANALYSIS

A. Principles of Law

“In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.” *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (2012) (requiring *inter partes* review petitions to identify “with particularity . . . the evidence that supports

¹⁸ Johannes T. Wessels, *Light-Emitting Diodes in Modern Microscopy — From David to Goliath?*, 81A CYTOMETRY PART A 188 (2012) (Ex. 1050, “Wessels”).

¹⁹ “POSA” refers to “[a] person having ordinary skill in the art.” Pet. 13.

²⁰ Cassandra S. Niman et al., *Controlled Microfluidic Switching in Arbitrary Time-Sequences with Low Drag*, 13 LAB ON CHIP 2389 (2013) (Ex. 1044, “Niman”).

²¹ Michael H. Winer et al., *Application of a three-dimensional (3D) Particle Tracking Method to Microfluidic Particle Focusing*, 14 LAB ON CHIP 1443 (2014) (Ex. 1051, “Winer”).

the grounds for the challenge to each claim’’)). This burden of persuasion never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review). The Board may authorize an *inter partes* review if we determine that the information presented in the Petition and Patent Owner’s Preliminary Response shows a reasonable likelihood that Petitioner will prevail with respect to at least one of the claims challenged in the petition. 35 U.S.C. § 314(a).

A claim is unpatentable under 35 U.S.C. § 103 if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. *See KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In analyzing the obviousness of a combination of prior art elements, it can be important to identify a reason that would have prompted one of skill in the art “to combine . . . known elements in the fashion claimed by the patent at issue.” *KSR*, 550 U.S. at 418. A precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish

obviousness. *Id.* Rather, “any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.” *Id.* at 420. Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness must show that “a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.” *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (internal quotations omitted).

We address Petitioner’s challenges with these standards in mind, and in view of the definition of the skilled artisan and the claim constructions discussed below.

B. Person of Ordinary Skill in the Art

Factual indicators of the level of ordinary skill in the art include “the various prior art approaches employed, the types of problems encountered in the art, the rapidity with which innovations are made, the sophistication of the technology involved, and the educational background of those actively working in the field.” *Jacobson Bros., Inc. v. U.S.*, 512 F.2d 1065, 1071 (Ct. Cl. 1975); *see also Orthopedic Equip. Co. v. U.S.*, 702 F.2d 1005, 1011 (Fed. Cir. 1983) (quoting with approval *Jacobson Bros.*).

Petitioner asserts that a person having ordinary skill in the art relevant to the ’554 patent as of November 3, 2015 “would have had a Ph.D. in Molecular, Cellular, or Developmental Biology and/or Biophysics,

Bioengineering, Biochemistry, or a related discipline with 2 years of experience in the field of fluorescence imaging of biological materials, including cells and tissues.” Pet. 13–14 (citing Ex. 1002 ¶¶ 68–70). Petitioner further asserts that such a person “would have understood . . . fluorescence imaging technologies; the use of microscopes to collect and record images; and the processing of images and data to obtain 2D or 3D spatial information relating to cells or tissues”; and “would also have had some familiarity with gene amplification and sequencing technologies.” *Id.* at 14 (citing Ex. 1002 ¶¶ 69–70).

Patent Owner states that, solely for the purposes of the Preliminary Response, it has applied Petitioner’s definition of a person of ordinary skill in the art. Prelim. Resp. 16; *see also* Ex. 2002 ¶ 25.

On the current record, for purposes of this Decision, we accept Petitioner’s proposed definition, as it appears consistent with the level of skill in the art reflected in the prior art of record and the disclosure of the ’554 Patent. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (“the prior art itself [may] reflect[] an appropriate level” as evidence of the ordinary level of skill in the art) (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)).

C. Claim Construction

We construe claims “using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. [§] 282(b).” 37 C.F.R. § 42.100 (2021). Therefore, we construe the challenged claims under the framework set forth in *Phillips v. AWH Corp.*,

415 F.3d 1303, 1312–19 (Fed. Cir. 2005) (en banc). Under this framework, claim terms are given their ordinary and customary meaning, as would be understood by a person of ordinary skill in the art, at the time of the invention, in light of the language of the claims, the specification, and the prosecution history of record. *Id.*

The parties do not propose express construction for any claim term. *See* Pet. 22; Prelim. Resp. 16. We find it unnecessary to construe any claim term to decide whether Petitioner satisfies the “reasonable likelihood” standard for instituting trial. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (noting that “we need only construe terms ‘that are in controversy, and only to the extent necessary to resolve the controversy’” (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))).

Any final written decision entered in this case may include express claim constructions, or may include discussion of claim scope that differs from that provided in our analysis below. Any final claim constructions will be based on the full trial record.

D. Overview of References Asserted Against Claim 36

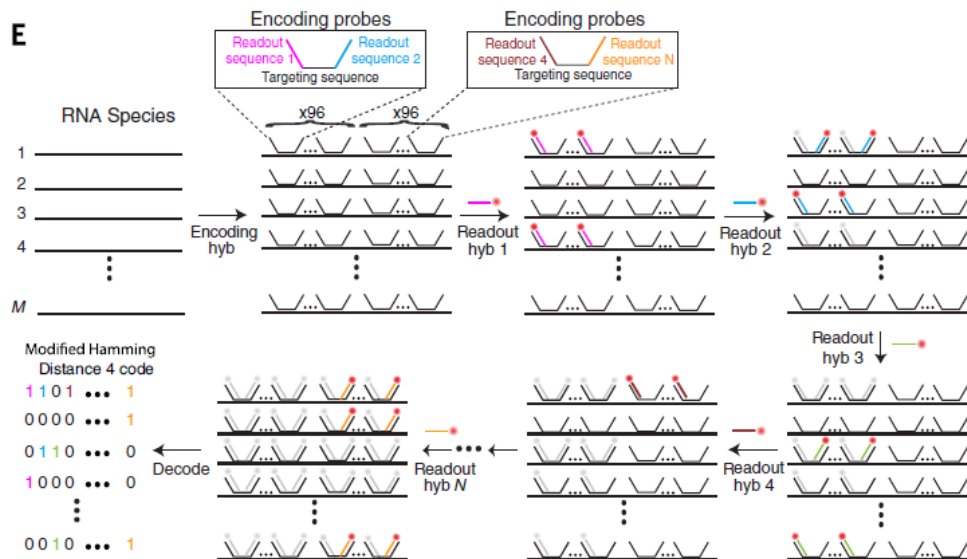
1. Overview of Chen (Exhibit 1003)

Chen is an article entitled, “Spatially resolved, highly multiplexed RNA profiling in single cells,” which appears to have been published in the journal *Science* in 2015. Ex. 1003.

Chen teaches that “[t]he copy number and intracellular localization of RNA are important regulators of gene expression,” but “the number of RNA

species that can be simultaneously imaged in individual cells has been limited,” which “makes it challenging to perform transcriptomic analysis of single cells in a spatially resolved manner.” Ex. 1003, 1.²² Chen reports “multiplexed error-robust FISH (MERFISH),” which it describes as “a single-molecule imaging method that allows thousands of RNA species to be imaged in single cells by using combinatorial [fluorescence in situ hybridization (FISH)] labeling with encoding schemes capable of detecting and/or correcting errors.” *Id.*

The combinatorial FISH labeling and encoding scheme taught in Chen is depicted in Figure 1E, reproduced below:



Ex. 1003, Fig. 1E. Figure 1E of Chen, reproduced above, is a diagram of Chen’s implementation of an encoding scheme for RNA identification. *Id.*

²² When citing to Chen, we refer to the page numbers added by Petitioner, rather than to the article’s native pagination.

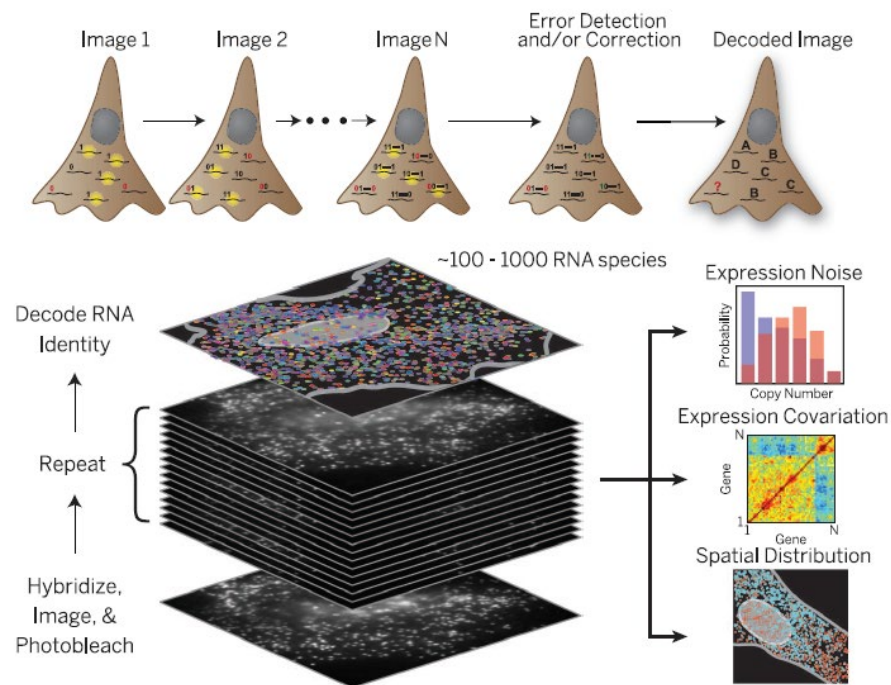
at 3. Referring to Figure 1E, Chen explains that each RNA species (RNA Species 1– M) is first labeled with encoding probes (Encoding hyb). *Id.* As shown by the callouts in Figure 1E, “[t]hese encoding probes each contain a central RNA-targeting region flanked by two readout sequences.” *Id.* Thus, hybridization with the encoding probe “convert the RNA into a specific combination of readout sequences.” *Id.*

Chen explains that the readout sequences are “drawn from a pool of N different sequences, each associated with a specific hybridization round,” and the “[e]ncoding probes for a specific RNA species contain a particular combination of four of the N readout sequences, which corresponds to the four hybridization rounds in which this RNA should read 1.” Ex. 1003, 3. Chen teaches that N subsequent rounds of hybridization with the fluorescent readout probes (Readout hyb 1–Readout hyb N in Figure 1E) are used to probe the readout sequences, with “bound probes . . . inactivated by photobleaching between successive rounds of hybridization.” *Id.* After these N rounds of hybridization with fluorescent readout probes, each RNA species should be represented by a unique binary code of N bits (a “code word”), where 1 indicates the readout sequence was detected during that particular round of hybridization, and 0 indicates it was not. *Id.*

Chen notes that, although the number of possible code words (and thus the number of addressable RNA species) “increases exponentially with N , . . . the detection error rates also grow exponentially with N .” Ex. 1003, 2. Chen explains that, to address this challenge, only a subset of possible words is used to encode RNAs in MERFISH, such that “at least four bits

must be read incorrectly to change one valid code word into another.” *Id.* According to Chen, this allows for the detection and correction of a single-bit error, which would “produce[] a word that is exclusively close to a single RNA-encoding word,” and the detection, although not the correction, of double-bit errors. *Id.*

A schematic depiction of Chen’s use of MERFISH for transcriptome imaging is reproduced below:



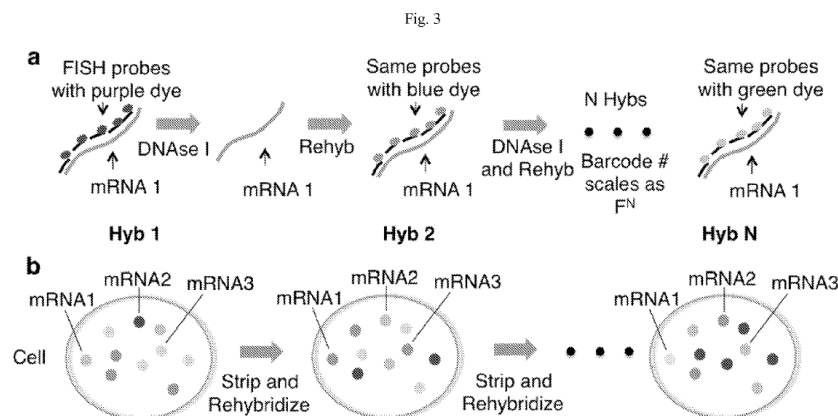
Ex. 1003, 1. The figure above is a schematic depiction of the steps and the results of applying MERFISH to a cell. Chen teaches that “[n]umerous RNA species can be identified, counted, and localized in a single cell by using MERFISH” and that “[t]his highly multiplexed measurement of individual RNAs can be used to compute . . . spatial distribution of RNAs within single cells.” *Id.*

2. Overview of Cai (Exhibit 1004)

Cai is a United States Patent, U.S. 10,457,980 B2, entitled “Multiplex Labeling of Molecules by Sequential Hybridization Barcoding,” which was issued on October 29, 2019.

Cai teaches that “[m]icroscopy imaging which can resolve multiple mRNAs in single cells can provide valuable information regarding transcript abundance and localization, which are important for understanding the molecular basis of cell [identity] and developing treatment for diseases.” Ex. 1004, 1:29–33. Cai provides “methods for high-throughput profiling of a large number of targets, such as transcripts and/or DNA loci” through sequential barcoding. *Id.* at Abstract. Cai teaches that its methods are “broadly useful, including for example for profiling of isolated cells, cells in tissues, cells in organs, and/or cells in organisms.” *Id.* at 1:44–46.

Cai’s Figure 3, reproduced below, depicts a “[s]chematic of sequential hybridization and barcoding” encompassed by Cai’s method:



Ex. 1004, Fig. 3. The figure above depicts a “[s]chematic of sequential hybridization and barcoding” (Fig. 3a) and a “[s]chematic of FISH images of

the cell” (Fig. 3b). *Id.* at 9:49–55. As shown in the figure, N rounds of hybridization was performed using the same set of probes, but the probes were labeled with a different color dye during each round of hybridization. *Id.* at Fig. 3a. Accordingly, “the same spots were detected” in each round of hybridization, “but the dye associated with the transcript changes,” and “[t]he identity of an mRNA was encoded in the temporal sequence of dyes hybridized.” *Id.* at 9:51–55.

In addition to embodiments wherein a detectably labeled oligonucleotide (i.e., a probe) directly hybridizes to its target, as depicted in Figure 3 reproduced above, Cai also teaches embodiments wherein a probe “specifically interacts with (recognizes) its target through binding or hybridization to one or more intermediate, e.g., an oligonucleotide[] that is bound, hybridized, or otherwise specifically linked to the target.” Ex. 1004, 17:24–30.

Cai teaches that the unique “barcode” for the target “after rounds of contacting and imaging” allows “information, e.g., quantitative and/or spatial information, [to] be obtained for a target.” Ex. 1004, 15:22–32.

3. Overview of Shen (Exhibit 1032)

Shen is a chapter entitled “Digital Autofocus Methods for Automated Microscopy,” which appears to have been published in the series, *Methods in Enzymology*, in 2006. Ex. 1032, 620.

Shen teaches that objectives having a high numerical aperture (NA) “characteristically have a very low depth of field (DOF),” and “only a very thin section of the specimen falls in focus in the acquired image.” Ex. 1032,

620. Shen teaches that, because of focal drift, it can be difficult to maintain focus in traditional microscopy when using objectives with high NA and low working distances. *Id.*

Shen describes “the implementation of a robust autofocus system” using “off-the-shelf materials and methods that can be engineered into any microscope for automation.” Ex. 1032, 620, 621. Shen states that, in its system,

the hardware acquires a *z* stack of images for each focus attempt. Digital image processing software determines the high-frequency content of each image in the stack and uses the results to determine a “focus index” for each image. The sharpest image is acquired at the best focus position calculated from the focus indices.

Id. at 621. Shen teaches that the hardware “needed to carry out digital autofocus in a microscopy scan” include “[h]ardware to precisely control the spacing between the objective and the specimen,” and further teaches that “various solutions are possible” for “micropositioning the objective lens in its axial, or *z* position,” including through use of a piezo-electric transducer. *Id.* at 623. Shen teaches software that “carries out the autofocus calculation instructions” and “controls the hardware, that is, stage movement, piezo movement, light path shuttering, and image acquisition via the camera.” *Id.* at 624.

E. Compliance with 35 U.S.C. § 312 and 37 C.F.R. §§ 42.22(a)(2) & 42.104

Patent Owner contends that Petitioner “fails to comply with the Board’s explicit rules requiring particularity in the Petition and forbidding

incorporation by reference.” Prelim. Resp. 51. We do not agree for the reasons discussed below.

Patent Owner first contends that the Petition “improperly cross-references its other sections without providing explanations.” Prelim. Resp. 52 (emphasis omitted). Patent Owner argues that, for example, Petitioner’s arguments in Sections X.A.1.e.iii and X.A.1.e.iv, for claim element 36(e)(iii) and 36(e)(iv), amounts to a single, conclusory sentence. Prelim. Resp. 53–54. Patent Owner further argues that “the Petition’s improper cross-reference tactics are also found throughout its arguments addressing the dependent claims,” including, e.g., Sections X.J., X.Q., and X.R. of the Petition, which discusses claims 56, 67, and 68 respectively. Prelim. Resp. 54; *see also id.* at 52.

In Section X.A.1.e.iii, the Petition states that Chen “decodes the identity of the RNA species based on the optically encoded signals” and cross-references Section X.A.1.e.ii. Pet. 41. That cross-referenced section discusses the related claim element of “determining a plurality of optically-encoded signals . . . wherein each optically-coded signal is associated with a nucleic acid molecule.” Pet. 40–41. The section explains how Chen’s method is asserted to generate “a string of light signals . . . for each RNA species,” which are “optically-encoded signals that . . . are associated with nucleic acid molecules and can be used to identify the RNA species.” *Id.* at 41.

Similarly, Section X.A.1.e.iv of the Petition states that Chen, “by itself or in view of Cai, determines the 3D positional information of the

RNA species.” Pet. 42. The cross-referenced section, Section X.A.1.e.i, discusses the related claim element of “receiving . . . a plurality of light signals . . . wherein said plurality of light signals is associated with one or more nucleic acid molecules” and “each light signal . . . has a three-dimensional spatial position within” the sample volume. *Id.* at 36–39. Section V.A.1.e.i explains how Chen is asserted to “teach[] using the MERFISH method to obtain the 3D spatial position of nucleic acid species through the entire depth of the sample volume,” as well as Petitioner’s rationale for its position that, “[t]o the extent that [Chen] is deemed to not disclose the claimed 3D feature, it would have been obvious to modify [Chen] in view of Cai to include this feature.” *Id.*

Finally, claims 56, 67, and 68 depend from claim 36 and further recite, respectively, “wherein said two or more light sources comprise one or more lasers,” “wherein at least one of the plurality of optically-encoded signals comprise two or more colors directed in series,” and “wherein said two or more light source comprise four light sources.” Pet. 45, 51–52. For these claims, the Petition cross-references Section X.A.1.c.ii (for claim 56) and Sections X.A.1.c.ii and X.A.1.e.ii (for claims 67 and 68).²³ *Id.*

Cross-referenced Section X.A.1.c.ii discusses the limitation in claim 36 regarding “two or more light sources” and specifically points to Chen’s

²³ For claim 67, the Petition cross-references Sections X.1.c.ii and X.1.e.ii. Pet. 51. Based on context, including the fact that claim 67 depends directly from claim 36 and adds a single limitation, we find it is clear that the intended cross-reference is to Sections X.A.1.c.ii and X.A.1.e.ii.

“use of three different lasers at three different wavelengths.” Pet. 29. Both cross-referenced sections also explain how Chen and/or Cai, for example in its use of “four-color FISH,” are asserted to teach “two or more light sources[] configured to deliver light of different colors to the sample,” as well as “optically encoded signals compris[ing] two or more colors of light detected . . . in series.” *Id.* at 29–30, 41.

Given the close relationship between the claim elements discussed in (1) Sections X.A.1.e.iii, X.A.1.e.iv, X.J, X.Q, and X.R, and (2) the respective sections to which they cross-reference, this is not a case where “[t]he pervasive use of internal cross-references within the Petition and the supporting . . . Declaration obfuscates the evidentiary support for the Petition’s assertions.” *Apple Inc. v. Contentguard Holdings, Inc.*, IPR2015-00450, Paper 9 (“*Apple*”), 8.

Patent Owner further argues that “[t]he Petition relies on improper incorporation by reference of its expert declaration to expand conclusory statements.” Prelim. Resp. 55 (emphasis omitted). Patent Owner cites as examples Petitioner’s arguments for claim element 36(b)(i) (“one or more reservoirs configured to contain one or more fluid reagents”), 36(c)(iii) (“one or more detectors configured to receive light signals from [the] volume[of the sample]”), 36(e)(iii) (“identifying said one or more nucleic acid molecules based on said plurality of optically-encoded signals”), and 36(e)(iv) (“determining three-dimensional positional information of said one or more nucleic acid molecules”). *Id.* at 56–57; Pet. 26–27, 30–31, 41–42. Patent Owner also argues that the Petition improperly incorporated portions

of the Cyzmmek Declaration by reference in its discussion of claims 38, 47, 48, 56, 64, and 67. Prelim. Resp. 57–58.

“It is improper to incorporate by reference arguments from one document into another document.” *Cisco Sys., Inc. v. C-Cation Tech., LLC*, IPR2014-00454, Paper 12, 10 (PTAB Aug. 29, 2014) (informative) (citing 37 C.F.R. § 42.6(a)(3)). However, not every statement made by a declarant needs to be repeated in a brief to avoid incorporation by reference. *See, e.g., Sumitomo Elec. Indus., Ltd. v. United Techs. Corp.*, IPR2017-00966, Paper 7, 11 (PTAB Sept. 13, 2017).

In discussing claim element 36(b)(i), Petitioner cites to Chen’s disclosure of “fluid reagents for use with its system” and explains that, given the “fluid reagents are repeatedly introduced to the sample in the flow chamber [in Chen’s system, Chen] teaches the fluidic system includes reservoirs for holding these fluids.” Pet. 26–27 (citing Ex. 1003, 1). For claim element 36(c)(iii), Petitioner cites to Chen’s disclosure of an EMCCD camera for detecting light signals from the sample volume. Pet. 30–31 (citing Ex. 1003, 11). Finally, as discussed above, the sections of the Petition discussing claim elements 36(e)(iii) and 36(e)(iv) cross-reference, respectively, Sections X.A.1.e.ii and X.A.1.e.i. These cross-referenced sections set out Petitioner’s arguments that Chen’s disclosures regarding MERFISH and/or Cai’s disclosure of profiling nucleic acids using sequential fluorescence in situ hybridization (“SeqFISH”) teach or suggest the limitations in question. Pet. 36–42.

In each of these cases, the paragraphs of the Cyzmmek Declaration cited in the Petition rely on similar disclosures in Chen and Cai and provide appropriate supporting technical details and/or testimony as to the understanding of a person of ordinary skill in the art. *See* Ex. 1002 ¶¶ 158–159, 176–178, 197–219. They do not offer wholly new arguments not found in the Petition. This is likewise the case with the Petition’s discussion of dependent claims 38, 47, 48, 56, 64, and 67, and the paragraphs of the Cyzmmek Declaration cited in support thereof. Accordingly, we do not find the circumstances here to amount to improper incorporation by reference or an attempt to circumvent our word count limits.

F. Analysis of Challenge to Claim 36

Petitioner asserts that claim 36 is unpatentable as obvious over Chen, Cai, and Shen. Pet. 22–42. Petitioner has provided an element-by-element analysis of the claim. *Id.*

At this stage of the proceeding, Patent Owner disputes that the asserted prior art combination teaches or suggests a system comprising “a temperature control apparatus operatively coupled to [a] sample holder,” or a pump configured to provide one or more fluid reagents from “one or more reservoirs” to the sample holder. Prelim. Resp. 18–24. Patent Owner contends that the asserted prior art combination also does not teach or suggest “determining three-dimensional positional information of one or more nucleic acid molecules, as claimed.” Prelim. Resp. 24–41.

In a similar vein, Patent Owner contends with respect to claim 36 that Petitioner “attempts . . . undeveloped inherency arguments” for the limitation relating to “two or more light sources . . . configured to emit two or more colors of light,” “one or more detectors,” and “Z-axis motion control system,” but fails to show “how the alleged claim elements ‘*necessarily must be present*’ in the prior art.” Prelim. Resp. 41, 42–44.²⁴

Finally, Patent Owner contends that Petitioner fails to establish a reason to modify Chen’s system to arrive at the claimed system with a reasonable expectation of success. Prelim. Resp. 46–51.

1. Claim Elements Allegedly Not Taught or Suggested

a) *a temperature control apparatus operatively coupled to [a] sample holder*

Petitioner contends Chen “discloses that its stage includes a Biopetechs FCS2 flow chamber, which is a system that includes temperature control capability.” Pet. 24 (citing, e.g., Ex. 1002 ¶¶ 142–143). Petitioner points to Sivaramakrishnan,²⁵ which discloses using a Biopetechs FCS2 chamber to

²⁴ Patent Owner makes similar arguments with regard to the limitations of “one or more valves downstream of [the] one or more reservoirs and upstream of [a] fluid dispenser,” “vibration control rigid foundation,” and “temperature sensor,” in dependent claims 46, 61, and 63, respectively. Prelim. Resp. 41–42, 44–45. We discuss these arguments in Section II.G below.

²⁵ Sivaraj Sivaramakrishnan et al., *Shear Stress Induced Reorganization of the Keratin Intermediate Filament Network Requires Phosphorylation by Protein Kinase C ζ* , 20 MOLECULAR BIOLOGY CELL 2755 (2009) (Ex. 1007, “Sivaramakrishnan”).

“maintain[] the cells and media at 37°C” in live cell imaging. *Id.*; Ex. 1007, 2758. Petitioner further points to Chen’s disclosure of “an oil immersion objective ‘heated to 37°C with a Bioptechs objective heater,’” arguing that, because a skilled artisan would understand that “the objective is in thermal contact with the stage holding the sample, . . . the objective heater is an additional temperature control system that becomes coupled to the stage and sample holder.” Pet. 24–25 (citing, e.g., Ex. 1002 ¶¶ 143–144).

Patent Owner contends Petitioner has not satisfied its burden of showing that Chen inherently discloses the limitation at issue. Prelim. Resp. 19–21. Patent Owner asserts Bioptechs offers “at least *two different types* of FCS2 flow chambers,” including one without temperature control, and there is no evidence that the FCS2 flow chamber used in Sivaramakrishnan is necessarily of the same type as that used in Chen. *Id.* at 20–21. Patent Owner further asserts Petitioner cannot rely on Sivaramakrishnan to meet the temperature control apparatus limitation, because it is not part of the art combination of any Ground, and Petitioner also “fails to address technical differences between the systems disclosed in Sivaramakrishnan and [Chen].” *Id.* at 19 (fn. 2), 21. Finally, Patent Owner asserts that Bioptechs’ instructions for FCS2 indicates that the objective heater used in Chen’s system is at most in thermal contact with the sample holder, rather than “operatively coupled” to it as claimed. Prelim. Resp. 22–23.

As an initial matter, based on the current record, we do not agree with Patent Owner’s narrow reading of the Petition as relying solely on a theory

that Chen inherently discloses the temperature control apparatus limitation. Instead, the Petition is based on what “a skilled artisan would understand from [Chen’s] use of a Bioptechs FCS2 flow cell and objective heater” — i.e., what would have been obvious from Chen’s disclosures. Pet. 25 (citing Ex. 1002 ¶ 144); *see also* Ex. 1002 (stating that “the use of a temperature control elements with the flow chamber was well-established in the art”).

Patent Owner cites to Exhibit 2004, which appears to be a product description of a “No-Heat Flow Cell (FCS2).” Prelim. Resp. 20–21. We note, however, that Exhibit 2004 distinguishes the No-Heat Flow Cell (FCS2) from the “standard” FCS2, stating that the No-Heat Flow Cell (FCS2) “[h]as the same optical and specimen accommodations as the *standard* FCS2 without temperature control.” Ex. 2004, 1 (emphasis added). Furthermore, Dr. Cyzmmek cites to publications suggesting that the FCS2 flow cell with temperature control was “well-known” to a skilled artisan as of the time of Chen’s publication. Ex. 1002 ¶¶ 142–143; Ex. 1007; Ex. 1015. Finally, Dr. Cyzmmek explains in his declaration that a skilled artisan would understand that Chen teaches heating the objective to 37°C because “the heated objective is in thermal contact with the sample holder,” and that “it was the cells and perfused solutions that require the temperature to be maintained at 37°C.” Ex. 1002, ¶ 144.

Based on the current record, therefore, we find that Petitioner has sufficiently established, for purposes of institution, that the asserted prior art combination teaches or suggests the limitation, “a temperature control apparatus operatively coupled to [a] sample holder.”

b) a pump configured to provide one or more fluid reagents from “one or more reservoirs” to the sample holder

Petitioner asserts Chen discloses the recited pump because it teaches a fluidics system for the purpose of controlling flow of the fluid reagents through the sample chamber, comprising both a fluid dispenser that “repeatedly introduces fluid reagents to the flow chamber” and a peristaltic pump. Pet. 27–28 (citing, Ex. 1003, 11, Ex. 1002 ¶¶ 160–162).

Patent Owner contends Petitioner fails to address “the requirement that [the] pump must provide fluid reagents from ‘one or more reservoirs’ to the sample holder.” Prelim. Resp. 24.

However, Petitioner has explained that, because “fluid reagents are repeatedly introduced to the sample in the flow chamber” in Chen’s system, Chen teaches a fluidics system that includes reservoirs for holding these reagents. Pet. 27 (citing Ex. 1002 ¶¶ 158–159). Petitioner’s declarant further testifies that the peristaltic pump used in Chen is “designed for transferring fluids” and that, “given that [Chen’s] system is entirely automated, a POSA would have understood that the computer-controlled pump is operationally coupled to an automated fluid dispenser that dispenses the fluid stored in the reservoir to the pump.” Ex. 1002 ¶¶ 161–162.

For this reason, we are also not persuaded by Patent Owner’s contention that “neither the Petition nor the Cyzmmek Declaration explains why or how [Chen’s] system *necessarily* comprises one or more reservoirs and how those same one or more reservoirs are configured to the pump.” Prelim. Resp. 42. We understand Petitioner’s position to be that, because

Chen's system involves successive dispersing of multiple fluid reagents in an automated manner (i.e., without human intervention), a skilled artisan would understand that the reagents are stored within the system itself (i.e., in "one or more reservoirs") and dispensed through the fluidics system that includes the peristaltic pump. We further read Petitioner's argument to be one of obviousness (i.e., what a skilled artisan would understand from Chen's disclosures) rather than, as Patent Owner appears to assert, an argument of inherency. Patent Owner's citation to *Floodbarrier, Inc. v. ILC Dover, LP*, IPR2019-01543, Paper 12 ("*Floodbarrier*"), is inapposite. Prelim. Resp. 24. In *Floodbarrier*, "[r]ather than identify specific teachings of [the prior art reference] relied on," the petitioner only "cites to Office Actions from the prosecution history of the [patent-in-suit] for the general proposition that '[the prior art reference] was used [by the examiner] to reject each and every pending claim until the After Final Interview.'" *Floodbarrier*, 14–15 (last bracket in original). Here, Petitioner has pointed to the portions of Chen it relies on to meet the limitation at issue.

Based on the current record, therefore, we find that Petitioner has sufficiently established, for purposes of institution, that the asserted prior art combination teaches or suggests the limitation, "a pump configured to provide one or more fluid reagents from 'one or more reservoirs' to the sample holder."

c) “two or more light sources . . . configured to emit two or more colors of light”

Petitioner asserts that Chen discloses this limitation, because it “teaches the use of three different lasers at three different wavelengths of 641 nm, 561 nm, and 405 nm, which corresponds to red, green, and violet light, respectively,” for “excitation of . . . readout probes, the fiducial beads, and nuclear counterstains, respectively.” Pet. 29 (citing Ex. 1003, 11, Ex. 1002 ¶ 168).

In the alternative, Petitioner asserts Cai “teaches profiling nucleic acids by sequential barcoding, wherein probes labeled with different detectable moieties (e.g., fluorophores or colors) are used in different cycles.” Pet. 29. Relying on the Czymmek Declaration, Petitioner asserts that “Cai’s disclosure of different color fluorophores teaches using different colors of excitation light,” and that “such multicolor detection was standard in the art at the relevant time frame.” *Id.* at 30 (citing Ex. 1002 ¶¶ 171–172)

Patent Owner contends Petitioner relies on a deficient inherency rationale in discussing this limitation, because “absent from Dr. Czymmek’s testimony is *any* underlying evidence to support his conclusory statement” that “the detection of different fluorophores as described in Cai *would have required* using different colors of excitation.” Prelim. Resp. 43.²⁶

²⁶ Patent Owner also asserts that the Petition improperly incorporates Dr. Czymmek’s testimony with respect to this limitation. Prelim. Resp. 42–43. For reasons similar to those discussed in Section II.E of this Decision, however, we are not persuaded by Patent Owner’s argument in this regard.

Patent Owner’s argument is unavailing. Dr. Cyzmmek excerpts portions of Cai showing hybridization of RNA to probes with, e.g., purple dye, blue dye, and green dye. Ex. 1002 ¶ 171. Dr. Cyzmmek explains it is “particularly the case” that different colors of excitation would need to be used to detect different fluorophores “when laser light sources are used, as taught by Cai’s listing of laser-excitables dyes, because lasers emit monochromatic light.” *Id.* ¶ 172. Furthermore, we do not read the Petitioner as relying solely on a theory of inherency with respect to this limitation. For example, Dr. Cyzmmek opines that, to the extent Cai might be deemed not to teach this limitation, “a POSA would have found it obvious to include two or more light sources, such as lasers, to provide two or more colors of light for the benefit of greater diversity of signals for generating distinct barcodes given that its use was standard prior to 2015.” Ex. 1002 ¶ 172.

Based on the current record, therefore, we find that Petitioner has sufficiently established, for purposes of institution, that the asserted prior art combination teaches or suggests the limitation, “two or more light sources . . . configured to emit two or more colors of light.”

d) “one or more detectors”

Petitioner cites to the EMCDD camera disclosed in Chen to meet this limitation. Pet. 31 (citing Ex. 1003, 11, Ex. 1002 ¶¶ 176–178).

Patent Owner contends that “Petitioner provides no explanation as to how [Chen’s] disclosure of an EMCCD (electron-multiplying charge coupled device) camera meets the claimed ‘one or more detector’ element,”

and “Dr. Cyzmek . . . provides no underlying evidence to support his conclusory statement that ‘a POSA would recognize an EMCCD camera as a detector configured to receive light signals from the volume.’” Prelim. Resp. 43.

However, Petitioner and Dr. Cyzmek both cite to the disclosure in Chen that, in its method, fluorescence from the sample was “imaged” with an EMCCD camera, which was “configured so that a pixel corresponds to 167 nm in the sample plane.” Pet. 31; Ex. 1002 ¶ 177.²⁷

Based on the current record, therefore, we find that Petitioner has sufficiently established, for purposes of institution, that the asserted prior art combination teaches or suggests the limitation, “one or more detectors.”

e) “Z-axis motion control system”

Patent Owner contends that, although “Petitioner argues that ‘to maintain a constant focus throughout an imaging process, a person of skill would understand that a Z-axis motion control system for adjusting the focal plane *would be necessary*,’” Petitioner “provides no explanation or evidence showing *why*” this would be so, and “Dr. Cyzmek’s testimony is equally deficient as he . . . provides no underlying evidence.” Prelim. Resp. 44.

²⁷ For this reason, we also disagree with Patent Owner to the extent it asserts that Petitioner relies on inherency in addressing the “one or more detectors” limitation. Prelim. Resp. 43. Instead, we understand Petitioner’s argument to be that, based on the description of the EMCCD camera and the imaging system in Chen, an ordinarily skilled artisan would understand the EMCCD camera to meet this limitation.

However, Petitioner’s arguments regarding this limitation are not limited to the alleged inherency argument. Petitioner first notes that Chen’s system is “built upon an Olympus IX-71 inverted microscope,” which includes up-down controls for moving either or both the objective or the stage, which would “move the focal plane through the sample volume.” Pet. 31 (citing, e.g., Ex. 1002 ¶¶ 180–181).

Petitioner further cites to Shen for teaching “many different systems for automating Z-axis movement,” which Petitioner asserts were “common long before the alleged invention date of the ’554 patent,” in the context of automatic focusing of microscope images. Pet. 32 (citing Ex. 1002 ¶ 185). Petitioner asserts that an ordinarily skilled artisan “would have been motivated to combine the relevant teachings in Shen with [Chen],” with a reasonable expectation of success, “because [Chen] explicitly requires an autofocus system for the MERFISH method,” and Shen teaches modifying the microscope used in Chen to accomplish this goal. *Id.* (citing Ex. 1002 ¶¶ 186–187).

Petitioner similarly asserts that, “to the extent [Chen] is deemed to not disclose the claimed Z-axis motion control system,” Cai describes a motion control system that allows scanning the sample along the z-axis, and “it would have been obvious to modify [Chen] in view of Cai to include . . . a feature” that was “standard in the art at the relevant time frame.” Pet. 32–33 (citing Ex. 1002 ¶ 188).

Based on the current record, therefore, we find that Petitioner has sufficiently established, for purposes of institution, that the asserted prior art

combination teaches or suggests the limitation, “Z-axis motion control system.”

f) “determining three-dimensional positional information of said one or more nucleic acid molecules”

Petitioner contends that Chen, “by itself or in view of Cai, determines the 3D positional information of the RNA species.” Pet. 42 (citing Section X.A.1.e.i; Ex. 1002 ¶¶ 216–219). Petitioner first contends that in Chen’s method “the light signal is detected ‘*in situ*’ only when a readout probe hybridizes to the nucleic acid molecule”; “[h]ence, the position of the light signals also reflects the spatial position of the nucleic acid molecules.” *Id.* at 38 (citing, e.g., Ex. 1002 ¶¶ 203–204). Pointing to Chen’s description of “optically section[ing] [] cells by collecting stacks of images at different focal depths through the entire depth of the cells,” Petitioner contends that “[t]his spatial position can be a 3D position within the sample volume.” *Id.*

Petitioner further argues that, to the extent Chen is found not to disclose “the claimed 3D feature, it would have been obvious to modify [Chen] in view of Cai to include this feature.” Pet. 39 (citing, e.g., Ex. 1002, ¶ 205).

Patent Owner contends that neither Chen, nor Chen combined with Cai, “discloses or suggests a system for determining three-dimensional positional information of nucleic acid molecules.” Prelim. Resp. 24 (citing Ex. 2002 ¶¶ 8–10, 54–81). Patent Owner first contends that, although Chen teaches determining *two-dimensional* positional information of RNA species in cells, it “explicitly states that its MERFISH methods are performed

without any need for optical sectioning or z-scanning.” *Id.*; *see also id.* at 25 (arguing that, because Chen relates to “imaging RNA molecules in a layer of human primary fibroblast cells” that are “relatively large and flat,” an ordinarily skilled artisan “would have understood that the fluorescently labeled RNA signals in the cells resided in *a single focal plane*”). Patent Owner further points to Chen’s “disclosure of determining only the x- and y-axis positional coordinates (*not* the z-axis coordinates)” as support. *Id.* at 26. Patent Owner contends that Chen teaches away from determining three-dimensional positional information. *Id.* at 25.

We are not persuaded by Patent Owner’s argument. Assuming the study described in Chen determined only two-dimensional positional information of RNA species in cells, “[t]he test for obviousness is not . . . that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art.” *MCM Portfolio LLC v. Hewlett-Packard Co.*, 812 F.3d 1284, 1294 (Fed. Cir. 2015) (quoting *In re Keller*, 642 F.2d 413, 425 (CCPA 1981)).

In this case, Petitioner’s declarant, Dr. Cyzmmek, explains that a skilled artisan “in possession of [Chen’s] disclosures would recognize that MERFISH has the capability for three-dimensional spatial positioning” because Chen “points to this kind of three-dimensional analysis in describing optically sectioning cells ‘by collecting stacks of images at different focal depths through the entire depth of the cells.’” Ex. 1002 ¶ 204 (quoting Ex. 1003, 12). Dr. Cyzmmek further explained that, to the extent

Chen is “deemed not to disclose . . . three-dimensional imaging,” Cai discloses it because “Cai teaches the claimed Z-axis motion control system to permit three-dimensional interrogation through a stack of focal planes” and “teaches using seqFISH to profile nucleic acid molecules and obtain ‘three-dimensional spatial information.’” Ex. 1002 ¶¶ 205–206.

Patent Owner’s arguments regarding teaching away is similarly unavailing. Chen states that, in the primary study discussed in the reference, cells were “imaged . . . without optical sectioning and z-scanning.” Ex. 1003, 12, left col. As Petitioner points out, however, Chen also describes an experiment in which cells appears to have been optically sectioned (i.e., imaged at different focal depths through the entire depth of the cells). Pet. 38; Ex. 1002 ¶ 204. Based on the current record, therefore, we are not persuaded that a skilled artisan upon reading Chen would be discouraged from optically sectioning and/or z-scanning a sample, or from determining three-dimensional positional information of one or more nucleic acid molecules. *Meiresonne v. Google, Inc.*, 849 F.3d 1379, 1382 (Fed. Cir. 2017) (explaining that “[a] reference teaches away ‘when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken’ in the claim”) (citation omitted).

Patent Owner argues that Chen’s disclosure of optically sectioning cells “relates to a separate validation experiment . . . using optical sectioning and z-scanning for *quantifying* RNAs — not for determining three-dimensional positional information.” Prelim. Resp. 27 (citing Ex. 2002 ¶ 62

(asserting that the statement in Chen of optically sectioning the cells “relates to a conventional smFISH-based (*not* MERFISH-based) quality-control experiment for confirming that there was *no need* to image the cell sample in focal planes other than the single focal plane in which [Chen’s] MERFISH-based system images the cells”)); *see also* Ex. 2002 ¶¶ 64–66.

Citing to the declaration²⁸ of Dr. Waller, Patent Owner argues that merely disclosing optical sectioning and/or z-scanning does not teach or suggest “determining three-dimensional positional information of nucleic acid molecules.” Prelim. Resp. 28–29. In particular, Dr. Waller testifies that a skilled artisan would have known that “optical sectioning” and “z-scanning” are merely techniques that allow, respectively, “acquiring images of thin slices (planes) from thick specimen” and “imaging a sample in different focal planes along the z-axis.” Ex. 2002 ¶¶ 67–68. Dr. Waller explains that, “[f]or determining three-dimensional positional information, the data obtained from optical sectioning and z-scanning must be further analyzed, and even then it may not determine three-dimensional positional information.” *Id.* ¶ 68.

Patent Owner argues that the portions of Cai relied on by the Petitioner at most teach a Z-axis motion control system without suggesting determining 3D positional information of nucleic acids. Prelim. Resp. 36. As to Cai’s statement regarding an imaging step that provides “three-dimensional spatial information of a target,” Patent Owner contends that the

²⁸ Declaration of Laura Waller, Ph.D. (“Waller Declaration,” Ex. 2002).

statement is a “mere wish.” *Id.* at 37. Citing *Raytheon Techs. Corp. v. General Electric Co.*, 993 F.3d 1374, 1380–1381 (Fed. Cir. 2021), Patent Owner argues that a prior art reference must enable a skilled artisan to make and use the claimed invention in order to render a claim obvious, and “[t]he Petition provides no explanation *how* a POSA would have purportedly determined three-dimensional positional information of nucleic acids with [Chen’s] MERFISH-based system alone or combined with Cai’s light sheet microscope approach.” Prelim. Resp. 37–38.

We are not persuaded by Patent Owner’s arguments. Even if Chen does not explicitly determine three-dimensional positional information of nucleic acid molecules in its paper, Petitioner has provided sufficient evidence, for purposes of institution, that the combination of asserted prior art would have given a skilled artisan reason to use MERFISH to “determin[e] three-dimensional positional information of . . . nucleic acid molecules,” as recited in claim 36, with a reasonable expectation of success.²⁹ Petitioner does not rely on the bare disclosure of optical sectioning and/or z-scanning to argue that the combination of asserted art suggests the limitation at issue. Rather, Dr. Cyzmmek testifies that, because Chen “had the goal of identifying ‘distinct spatial distribution pattern of RNAs,’” a skilled artisan “would have been motivated to use the MERFISH

²⁹ In this regard, we also make clear that claim 36, a system claim, does not require a step of determining three-dimensional positional information of nucleic acid molecules. Rather, it only requires program instructions that are executable by a processor to cause the processor to perform the step.

method for 3D investigation.” Ex. 1002 ¶ 207. Citing to Larsson³⁰ and Parillo,³¹ Dr. Cyzymmek further testifies that “[t]hree-dimensional FISH was routine and well-known long before the 2015 priority date.” *Id.* ¶ 208. Dr. Cyzymmek opines that, because “MERFISH was an extension of existing FISH technologies,” a skilled artisan would have reasonably expected it to also be capable of similar three-dimensional imaging.

Patent Owner contends that its position — i.e., that Chen is limited to two-dimensional imaging — is supported by publications post-dating the ’554 patent, which “reportedly ‘extended’ the MERFISH technique to three-dimensional imaging.” Prelim. Resp. 30 (citing Ex. 2002 ¶ 70). Patent Owner notes in particular that peer reviews of Fang³² described its MERFISH 3D methods as a “technical milestone” and “major technical advance.” *Id.* Patent Owner further cites to Cox³³ as explaining in 2022 that “there is *now* (seven years after [Chen]) a ‘potential’ to generate three-dimensional images using MERFISH,” arguing that this statement “confirms that [Chen] did not teach or suggest determining three-dimensional

³⁰ Chatarina Larsson et al., *In Situ Detection and Genotyping of Individual mRNA Molecules*, 7 NATURE METHODS 395 (2010) (“Larsson,” Ex. 1008).

³¹ Evan P. Perillo et al., *Enhanced 3D Localization of Individual RNA Transcripts via Astigmatic Imaging*, 8950 PROC. OF SPIE 895003-1 (2014) (“Perillo,” Ex. 1011).

³² Rongxin Fang et al., *Three-Dimensional Single-cell Transcriptome Imaging of Thick Tissues*, 2023 eLIFE 90029.1 (“Fang,” Ex. 2007).

³³ Kevin L. Cox et al., *Organizing Your Space: The Potential for Integrating Spatial Transcriptomics and 3D Imaging Data in Plants*, 188 PLANT PHYSIOLOGY 703 (2022) (“Cox,” Ex. 2010).

positional information of nucleic acid molecules.” *Id.* at 32. Finally, Patent Owner relies on Ghani³⁴ as “provid[ing] even further confirmation that [Chen’s] MERFISH-based system was only in 2D.” *Id.*

However, the post-filing publications cited by Patent Owner appear to be focused on *optimizing* imaging speed and quality for three-dimensional imaging. Fang states, for instance, that its method “enable three-dimensional (3D) single-cell transcriptome imaging of *thick tissue specimens* by integrating MERFISH with confocal microscopy for optical sectioning and deep learning *for increasing imaging speed and quality*,” and emphasized that it “demonstrated 3D MERFISH on mouse brain tissue sections of *up to 200 μm thickness* with *high detection efficiency and accuracy*.” Ex. 2007, Abstract (emphases added). Similarly, although Ghani teaches that “MERFISH analysis is currently done in 2D, where the z-data is discarded after generating maximum intensity projections,” Ghani suggests that this is in order “to decrease computation time” and acknowledges that discarding such data comes “at the cost of sub-optimal single molecule localization.” Ex. 2011, 2. Claim 36, however, contains no limitations relating to either the quality of the image or the speed of the imaging process in “determining the three-dimensional positional information of . . . one or more nucleic acid molecules.”

³⁴ Naureen Ghani & Yoh Isogai, *Optimisation of MERFISH Data Analysis and Visualization* (2019) (“Ghani,” Ex. 2011).

Accordingly, for the reasons set forth above, and based on the current record, we find that Petitioner has sufficiently established, for purposes of institution, that the asserted prior art combination teaches or suggests the limitation, “determining three-dimensional positional information of said one or more nucleic acid molecules.”

2. Reason to combine and expectation of success

Patent Owner argues that “Petitioner fails to establish a reason to modify [Chen’s] system to arrive at the claimed system with a reasonable expectation of success.” Prelim. Resp. 46 (emphasis omitted).

Patent Owner first contends that Chen “*teaches away* from determining three-dimensional positional information of one or more nucleic acid molecules,” Prelim. Resp. 47,³⁵ and that “[t]he later publications regarding MERFISH and 3D imaging well after the 554 patent’s priority date further evince the strained nature of the Petition’s reasonable expectation of success argument” with respect to this limitation, *id.* at 50. We have explained above why we are not persuaded by these arguments.

³⁵ Citing *Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1069 (Fed. Cir. 2018), Patent Owner argues that, even if Chen is not found to teach away, “‘its statements regarding preferences’ for two-dimensional imaging and analysis are ‘relevant to a finding regarding whether a skilled artisan would be motivated to combine’ [Chen] with Cai.” Prelim. Resp. 48. However, unlike in *Polaris* where it is “undisputed” that the proposed modification “would run contrary to one of [the prior art reference’s] stated purposes,” *Polaris*, 882 F.3d at 1069, and based on the current record, we do not read either Chen or Cai to express a *preference* for two-dimensional imaging and analysis.

Patent Owner also contends that Petitioner fails “to explain why or how a POSA would have modified [Chen’s] MERFISH-based system with Cai’s light sheet Microscope system to arrive at a claimed system with a reasonable expectation of success.” Prelim. Resp. 46. More particularly, citing to Dr. Waller’s testimony, Patent Owner contends that Petitioner “never explains what modifications the POSA would have made or how to make them – *e.g.*, which parts of Cai’s system are substituted into [Chen’s] system, or *vice versa*, and how those components are compatible between the two systems to provide the POSA with a reasonable expectation of success” with respect to the limitation of “determining three-dimensional positional information of . . . nucleic acid molecules.” *Id.* at 49 (citing Ex. 2002 ¶¶ 82–88); *see also id.* at 38–41.

As for a reason to combine Chen and Cai, we have noted above Petitioner’s assertion that a skilled artisan would have been motivated to use the “MERFISH method for 3D investigation in order to obtain meaningful spatial information in the z-dimension, furthering [Chen’s] goal of ‘identify[ing] distinct spatial distribution patterns of RNAs.’” Pet. 39 (citing Ex. 1003, 2; Ex. 1002 ¶ 207).

As to Patent Owner’s argument regarding expectation of success, we find Patent Owner’s (and Dr. Waller’s) focus on light sheet microscopy to be misplaced. Cai explicitly teaches that a skilled artisan would understand that “different technologies can be used for [its] imaging steps,” including, for example, “epi-fluorescence microscopy, confocal microscopy, the different types of super-resolution microscopy (PALM/STORM, SSIM/GSD/STED),

and light sheet microscopy (SPIM and etc).” Ex. 1004 21:16–22. Although Dr. Waller notes that Cai’s Figures 17 and 18 describe such a light sheet microscopy system, Ex. 2002 ¶¶ 84–85, Cai’s disclosures are not limited to particular embodiments. Similarly, Chen teaches that, “[f]rom an imaging perspective, any optical sectioning technique could be used in MERFISH to allow the imaging of RNAs in thicker cells or tissues.” Ex. 1003, 12.

Moreover, obviousness does not require features of a secondary reference to be bodily incorporated into the structure of the primary reference. *MCM Portfolio*, 812 F.3d at 1294. Thus, even if Cai only disclosed a light sheet microscopy system, we are not persuaded Petitioner must detail how to modify or combine Chen with such a system.

Instead, as discussed above, Petitioner relies on Dr. Cyzymmek’s testimony, which explains that “[t]hree-dimensional FISH was routine and well-known long before the 2015 priority date.” Pet. 39 (citing Ex. 1002 ¶ 208). As also discussed above, Dr. Cyzymmek cites to evidence that supports his testimony, including Larsson and Perillo. Ex. 1002 ¶ 208. Dr. Cyzymmek further testifies that, because MERFISH merely extended existing FISH technologies by using sequential hybridization and error correction to increase multiplexity, a skilled artisan would have known that MERFISH would not “limit 3D detection” capability of existing FISH technologies and “may even aid it.” *Id.* In this regard, we also note that expectation of success needs only be reasonable, not absolute. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007).

Accordingly, we are persuaded, at least at this stage of the proceeding and based on the present record, that Petitioner has shown sufficiently that a skilled artisan would have had a reason to modify Chen's system to use MERFISH to "determin[e] three-dimensional positional information of . . . nucleic acids molecules," as recited in claim 36, with a reasonable expectation of success.

G. Other Claims and Grounds

In *SAS*, the Supreme Court held the following:

Section 314(a) [of Title 35] does not require the Director to evaluate every claim individually. Instead, it simply requires him to decide whether the petitioner is likely to succeed on "at least 1" claim. Once that single claim threshold is satisfied, it doesn't matter whether the petitioner is likely to prevail on any additional claims; the Director need not even consider any other claim before instituting review. Rather than contemplate claim-by-claim institution, then, the language anticipates a regime where a reasonable prospect of success on a single claim justifies review of all.

SAS, 138 S. Ct. at 1356. Thus, because we have determined, based on the arguments and evidence on the present record, that there is a reasonable likelihood Petitioner would prevail with respect to claim 36, we institute an *inter partes* review of all challenged claims. *Id.*; *see also* 37 C.F.R.

§ 42.108(a) ("When instituting inter partes review, the Board will authorize the review to proceed on all of the challenged claims and on all grounds of unpatentability asserted for each claim.").

In addition, we note that Petitioner has provided an element-by-element analysis of the additional limitations in dependent claims 37–70. Pet. 107–171.

Patent Owner has argued that the Petition’s discussions of certain dependent claims contain improper internal cross-references and/or improper incorporation by reference of the Cyzmmek Declaration. We have explained above why we do not agree with these arguments. *See supra* Section II.E.

Patent Owner additionally argues that “Petitioner . . . fails to meet the required standard for inherency when addressing dependent claims 46, 61, and 63.” Prelim. Resp. 44.

More particularly, with respect to claim 46, Patent Owner argues that the Cyzmmek Declaration, on which Petitioner relies, lacks “any evidence demonstrating why or how [Chen’s] valves must *necessarily* be downstream of reservoirs and upstream of a dispenser,” as recited in that claim. *Id.* Patent Owner also argues that Petitioner fails to explain why the system in Chen, which is “merely constructed around the *body* of an Olympus IX-71,” must *necessarily* have a “vibration control rigid foundation,” as recited in claim 61. Finally, with respect to claim 63, which depends indirectly from claim 36 and additionally recites that “said temperature control apparatus further comprises a temperature sensor configured to provide a feedback signal to said thermal control system,” Patent Owner asserts that

Petitioner “fails to account for other FCS2 flow cells that do not contain a temperature control system.” *Id.* at 42.

These arguments are unavailing. As to claim 63, we have explained, in our discussion of claim 36, why Petitioner has made the requisite showing, for purposes of institution, that Chen teaches or suggests a temperature control apparatus.” *See supra* Section II.F.1.a). With respect to claim 61, Petitioner’s arguments are not confined to the alleged inherency argument. Instead, in addition to arguing that the Olympus IX-71, around which Chen’s home-built microscope was constructed, was known to include a “vibration control rigid foundation,” Petitioner argues that “[t]he inclusion of a vibration control rigid foundation would have further been obvious to improve image quality during automated imaging.” Pet. 64 (citing Ex. 1002 ¶¶ 350–353).

Finally, with respect to claim 46, Dr. Cyzymmek testifies that Chen teaches a fluidics system comprising three computer-controlled valves and a method that requires “flowing” various fluids, such as hybridization, readout, and imaging buffers, across the sample. Ex. 1002 ¶ 239. Dr. Cyzymmek further testifies that, given the above disclosures and given the automated nature of Chen’s system, a skilled artisan would have known that the valves would be “downstream of the reservoir(s) and upstream of the dispenser.” *Id.* Based on the above declaration testimony—which at this stage has not been challenged by Patent Owner’s declarant—and the portions of

Chen cited in support thereof, we find Petitioner has sufficiently established, for purposes of institution, that the asserted prior art combination teaches or suggests the limitation, “one or more valves . . . downstream of . . . one or more reservoirs and upstream of . . . fluid dispenser” that, when actuated “facilitate dispensation of fluid to [the] sample holder.”

Accordingly, having considered the arguments and evidence presented by the parties, and based on the current record, we find Petitioner has shown a reasonable likelihood that the remaining challenged claims are unpatentable for the reasons set forth in Grounds 1–13.

H. Discretionary Denial of Institution under 35 U.S.C. § 314(a)³⁶

1. Factual background

The ’554 patent is at issue in *10x Genomics et al. v. Bruker Spatial Biology, Inc. et al.*, 1:22-cv-261 (D. Del.) (“the 22-261 Litigation”). Pet. 20; Paper 4, 1; Paper 6, 1; Paper 12, 2.

The ’554 patent issued on January 3, 2023. Ex. 1001, code (45). Petitioner asserts, and Patent Owner does not dispute, that the 22-261 Litigation was first filed in February 2022 and that the ’554 patent was asserted against NanoString in the 22-261 Litigation in March 2023. Pet. 71.

³⁶ Petitioner also asserts that the Board should not exercise our discretion to deny institution under 35 U.S.C. § 325(d). Pet. 66–68. Patent Owner did not address issues relating to 35 U.S.C. § 325(d) in the Preliminary Response. Under these circumstances, we decline to exercise our discretion to deny institution under 35 U.S.C. § 325(d).

NanoString filed for Chapter 11 bankruptcy on February 4, 2024. Reply 1. The 22-261 Litigation was stayed on March 14, 2024. *Id.* On June 14, 2024, the district court lifted the bankruptcy stay and substituted Bruker Spatial Biology, Inc and Bruker Nano, Inc. for NanoString as defendants. *Id.*

2. Legal standard

Under our precedential decision in *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019 (*Fintiv*), Paper 11 (PTAB March 20, 2020), the Board, in deciding “whether efficiency, fairness, and the merits support the exercise of authority to deny institution in view of an earlier trial date in the parallel proceeding,” should consider a variety of factors, and, in evaluating these factors, “takes a holistic view of whether efficiency and integrity of the system are best served.” *Fintiv*, Paper 11 at 5–6.

In *Fintiv*, the Board set forth six factors relating to whether efficiency, fairness, and the merits support the exercise of authority to deny institution in view of an earlier trial date in the parallel proceeding:

1. Whether the court granted a stay or evidence exists that one may be granted if a proceeding is instituted;
2. Proximity of the court’s trial date to the Board’s projected statutory deadline for a final written decision;
3. Investment in the parallel proceeding by the court and the parties;
4. Overlap between issues raised in the petition and in the parallel proceeding;
5. Whether the petitioner and the defendant in the parallel proceeding are the same party; and

6. Other circumstances that impact the Board’s exercise of discretion, including the merits.

Fintiv, Paper 11 at 6. In considering these factors, we are also guided by the USPTO’s *Interim Procedure for Discretionary Denials in AIA Post-Grant Proceedings with Parallel District Court Litigation*, June 21, 2022 (the “Guidance”).³⁷

3. Analysis

We consider the above interrelated factors and Guidance, as they apply to the facts of the Petition.

- a) *Fintiv* Factor 1: whether the court granted a stay or evidence exists that one may be granted if a proceeding is instituted

Petitioner contends that this factor favors institution because the 22-261 Litigation “is at a relatively early stage, . . . making a stay realistic.” Reply Br. 2–3. Petitioner notes that, although there are five additional patents asserted in the 22-261 Litigation, “there are strong non-infringement defenses for each.” *Id.* at 2.

Patent Owner notes that the 22-261 Litigation is on a coordinated schedule with another case, *10x Genomics, Inc. et al. v. Vizgen, Inc.*, 1:22-cv-00595 (D. Del. 2022) (“22-595 Litigation”), “involving related patents and highly overlapping antitrust counterclaims that has a February 2025 trial date.” Sur-Reply 3. Patent Owner contends that Judge Kennelly,

³⁷ Available at https://www.uspto.gov/sites/default/files/documents/interim_proc_discretionary_denials_aia_parallel_district_court_litigation_memo_20220621_.pdf (last visited August 8, 2024).

who presides over the 22-261 Litigation, “expects to end his term as a visiting judge in Delaware in August 2025 and is highly motivated to complete the trial in the 22-261 litigation before his departure.” *Id.* at 1.

Patent Owner notes that Judge Kennelly has instructed the parties to submit a case schedule with the 22-261 Litigation ready for trial on or about May 19, 2025, and further contends that “Judge Kennelly is *highly unlikely* to stay the 22-261 litigation, as doing so would risk extending the 22-261 litigation beyond August 2025 against Judge Kennelly’s preference and judicial efficiency.” Sur-Reply 1, 3.³⁸

At this point in time, the 22-261 Litigation is not stayed. Although both Petitioner and Patent Owner have cited reasons why a stay of the 22-261 Litigation is “realistic” or “highly unlikely,” neither has cited to any direct evidence, such as statements by the court, as to whether a stay by the district court is likely in the event a PTAB trial is instituted.

On the present record, therefore, we decline to speculate whether a motion to stay might be successful in the event a PTAB trial is instituted. Accordingly, *Fintiv* Factor 1 is neutral. *See Sand Revolution II LLC v. Cont’l Intermodal Grp. – Trucking LLC*, IPR2019-01393, Paper 24 (“*Sand*”) at 7 (PTAB June 16, 2020) (informative) (“In the absence of specific evidence, we will not attempt to predict how the district court in the related

³⁸ Patent Owner further argues that “the parties and court will have already invested significant resources by the time the Board issues a Decision on Institution in this IPR, additionally disfavoring a stay.” Sur-Reply 3. We address this issue below with *Fintiv* Factor 3.

district court litigation will proceed because the court may determine whether or not to stay any individual case . . . based on a variety of circumstances and facts beyond our control and to which the Board is not privy.”).

- b) *Fintiv* Factor 2: proximity of the court’s trial date to the Board’s projected statutory deadline for a final written decision

Petitioner argues that there is currently no scheduled trial date, and that “[t]his fact alone weighs strongly against discretionary denial.”

Reply 3. Petitioner acknowledges “it is likely that the district court will enter a schedule soon,” but argues that this factor would still favor institution. *Id.* at 4. Petitioner argues that “Patent Owner is not even proposing that trial take place until late June or early July 2025” and notes that, even assuming no further delay, these proposed dates are “nearly a year away and . . . less than two months prior to the expected August 2025 date for the final written decision if IPR is instituted.” *Id.*³⁹

Patent Owner argues that, subsequent to the filing of the Reply, Judge Kennelly has instructed the parties that the trial in the 22-261 Litigation

³⁹ Petitioner notes that median time-to-trial statistics may not be useful in cases, such as this one, where the circumstances are not those of a typical case. Reply Br. 4. We agree that the assertion of the ’554 patent almost a year after the filing of the initial complaint in the 22-261 Litigation, and NanoString’s bankruptcy, the resultant stay of litigation, and subsequent substitution of Bruker Spatial Biology, Inc. and Bruker Nano, Inc. as defendants, render this case atypical for purposes of case scheduling. Thus, we do not rely on median time-to-trial statistics in our analysis.

“will begin ‘on or about 5/19/2025,’ before the Board’s late-August 2025 statutory deadline to issue a Final Written Decision in this IPR.”

Sur-Reply 4. Patent Owner “disagrees with Petitioner’s assertion that ‘there are strong non-infringement defenses’ in the 261 litigation.” *Id.* at 4, n. 3. Patent Owner argues that Petitioner has not raised any non-infringement arguments with respect to the ’554 patent in the 22-261 litigation and that, thus, the district court “will likely resolve the invalidity challenges to the [’]554 patent since there is virtually no chance of a summary judgment of non-infringement for the [’]554 patent.” *Id.* at 4.

We understand that no trial date has been set yet in the 22-261 Litigation. Ex. 2013, 47 (minute entry for July 8, 2014 case management conference stating that “[t]he court *anticipates* setting Case No. 22-cv-[261] for trial on or about 5/19/2025”) (emphasis added); Ex. 2023. In light of the uncertainty regarding the trial date, we find this factor to be neutral. Moreover, even if trial were scheduled for on or about May 19, 2025, as Patent Owner suggests is likely, we would find this factor to only slight favor denial of institution. In *Fintiv*, for example, the Board determined this factor only weighed “somewhat” in favor of discretionary denial, despite the fact the parallel district court trial was scheduled to begin two months before the Board’s deadline to reach a final decision. *Fintiv*, Paper 15 (PTAB May 13, 2020) (informative), at 12–13.

c) *Fintiv* Factor 3: investment in the parallel proceeding by the court and the parties

Petitioner contends that this factor favors institution because, based on the proposed schedule being discussed by the parties for the 22-261

Litigation, “[m]uch effort will remain after the date of the institution decision.” Reply 5. In particular, Petitioner notes that “discovery will not be completed and dispositive motions [will] not [be] due until well after the decision on institution,” and argues that “the most burdensome parts of the case” will all occur after the decision on institution. *Id.* (citation omitted).

Patent Owner argues that “fact discovery is well developed in the 22-261 litigation, and the parties and district court will have made substantial investments by the time the Board issues an institution decision here.” Sur-Reply 5. In particular, Patent Owner contends that “the parties have already exchanged infringement and invalidity contentions, claim construction is complete and the district court has issued [a] Markman Order, and electronically stored information discovery is substantially complete.” *Id.*

At this point, it appears, based on the parties’ submissions that, as of the institution decision date, fact discovery will still be ongoing, expert discovery will not have begun, and the deadline for filing dispositive motions will still be some time away. Furthermore, we note that, although the Court has issued a claim construction order, none of the construed terms were of the ’554 patent claims. *See generally* Ex. 2020.

Under this factor, we may also consider “facts relevant to timing.” *Fintiv*, Paper 11 at 11. In particular,

[i]f the evidence shows that the petitioner filed the petition expeditiously, such as promptly after becoming aware of the claims being asserted, this fact has weighed against exercising the authority to deny institution If, however, the evidence shows that the petitioner did not file the petition expeditiously, such as at or around the same

time that the patent owner responds to the petitioner's invalidity contentions, or even if the petitioner cannot explain the delay in filing its petition, these facts have favored denial.

Id. at 11–12.

Petitioner contends that the '554 patent was issued in January 2023 and, thus, under 35 U.S.C. § 311(c)(1), Petitioner could not file the Petition until October 2023. Petitioner filed this Petition in January 2024. Based on this timeline, we find Petitioner to have been diligent in filing the Petition, and “Patent Owner does not allege unfairness or assert that Petitioner delayed filing its Petition to gain a strategic advantage.” *See, e.g., Illumina, Inc. v. Natera, Inc.*, IPR2019-01201 (“*Illumina*”), Paper 9 (PTAB Dec. 18, 2019) at 8 (finding Petitioner to be diligent in filing the Petition where Petition was filed “several months before the statutory deadline and in response to the [patent at issue] being added to the litigation in an Amended Complaint”).

Accordingly, we find this factor weighs against discretionary denial.

- d) *Fintiv* Factor 4: overlap between issues raised in the petition and in the parallel proceeding

Under this factor, we may consider whether “the petition includes the same or substantially the same claims, grounds, arguments, and evidence as presented in the parallel proceeding.” *Fintiv*, Paper 11 at 12.

Petitioner asserts that only one of the challenged claims (independent claim 36) is at issue in the 22-261 Litigation. Pet. 71. Petitioner contends that the additional 34 dependent claims challenged in the Petition “add significant, albeit well-known, features” and that, for several of the

dependent claims, the Petition relies on additional references to disclose the features in question. *Id.* Petitioner contends that it “would be prejudiced if institution of the non-overlapping claims was denied because Patent Owner could assert these claims against Petitioner’s future products and/or customers in the future whereas the § 315(b) time bar would apply to Petitioner.” *Id.*

Patent Owner has not disputed Petitioner’s assertions or provided its view on the degree of overlap between the issues raised in the Petition and the 22-261 Litigation.

Considering the present record, we find this factor weighs against discretionary denial. *See, e.g., Illumina*, Paper 19, at 6–7.

- e) *Fintiv* Factor 5: whether the petitioner and the defendant in the parallel proceeding are the same party

Petitioner here is also a defendant in the 22-261 Litigation. This fact could weigh either in favor of, or against, exercising discretion to deny institution, depending on which tribunal was likely to address the challenged patent first. *See, e.g., Google LLC v. Proxense, LLC*, IPR2024-00233, Paper 10 (PTAB July 24, 2024). Given the current information concerning the relative timing of the proceedings, we weigh this factor as neutral or somewhat favoring denial of institution, depending on whether the proposed trial date of “on or about May 19, 2025” is adopted.

- f) *Fintiv* Factor 6: other circumstances that impact the Board’s exercise of discretion, including the merits

Under the sixth *Fintiv* factor, we consider “other circumstances that impact the Board’s exercise of discretion, including the merits.” *Fintiv*, Paper 11 at 6. As discussed below, however, *Fintiv* Factors 1–5 weighed together do not favor exercising our discretion to deny institution. Thus, there is no need to determine whether the Petition establishes compelling merits. *See* Guidance 4–5 (explaining that compelling merits can overcome what would otherwise warrant a discretionary denial under *Fintiv* analysis); *see also CommScope Techs. LLC v. Dali Wireless, Inc.*, IPR2022-01242, Paper 23 at 6 (PTAB Feb. 27, 2023) (precedential) (“The Board should first assess *Fintiv* factors 1–5; if that analysis supports discretionary denial, the Board should engage the compelling merits question.”).

Petitioner argues under this factor that, “in the interests of fairness and justice,” factors 1–3 “should not weight against institution” because “Petitioner reasonably could not have filed this petitioner early enough” where “the ’554 patent did not issue, and was not asserted, until after the district court proceeding was well underway.” Pet. 72. We have considered these facts, which are relevant to timing under Factor 3, and thus do not address them again here.

Petitioner further argues that review is warranted because the lengthy challenged claims and complex technology involved are “particularly suited for comprehensive focused review by an expert tribunal rather than limited review by a lay jury,” where “the single asserted claims of the ’554 patent

[is] among twenty asserted claims from **six total** patents” and the jury must also address “other weighty issues.” Pet. 73. We have addressed these facts to some extent under Factor 4, relating to the overlap between issues raised in the petition and in the parallel proceeding. Additionally, Petitioner has not provided evidence that the challenged claims are lengthier or involve more complex technology than the average *inter partes* review. Thus, we do not assign additional weight against denial of institution based on Petitioner’s arguments under this factor.

g) Holistic assessment of the *Fintiv* factors

We consider the above factors and take “a holistic view of whether efficiency and integrity of the system are best served by denying or instituting review.” *Fintiv*, Paper 11 at 6. The parties’ and the district court’s investment in the ’554 patent has been limited so far, and only one of the claims challenged in the Petition is also asserted in the 22-261 Litigation. Petitioner has been diligent in seeking institution of the IPR after issuance of the ’554 patent and the assertion of the patent in the 22-261 Litigation. All of the above weigh against discretionary denial of institution. Based on the current record, and in view of the uncertainty regarding the trial date for the 22-261 Litigation, the remaining factors are neutral. Further, even if trial in the 22-261 Litigation were scheduled for a date on or about May 19, 2025, our expected final written decision would be close to that date; thus, that fact would only slightly favor denial of institution. Taking a holistic view, we decline to exercise our discretion to deny the Petition under Section 314(a) based on *Fintiv*.

III. CONCLUSION

For the reasons provided above, we decline to exercise our discretion to deny institution under § 325(d) or § 314(a), and we institute *inter partes* review based on all the Grounds presented in the Petition.

We emphasize our determination in this Decision is not a final determination on the construction of any claim term or the patentability of any challenged claim and, thus, leaves undecided any factual issues necessary to determine whether sufficient evidence supports Petitioner's contentions by a preponderance of the evidence in the final written decision. *See TriVascular, Inc. v. Samuels*, 812 F.3d 1056, 1068 (Fed. Cir. 2016) (noting that “there is a significant difference between a petitioner’s burden to establish a ‘reasonable likelihood of success’ at institution, and actually proving invalidity by a preponderance of the evidence at trial”) (quoting 35 U.S.C. § 314(a) and comparing § 316(e)).

The Board will deem forfeited any issue not raised by Patent Owner in a timely response to the Petition, or as permitted in another manner during trial, even if asserted in the Preliminary Response or discussed in this Decision.

Nothing in this Decision authorizes Petitioner, in a manner not otherwise permitted by the Board's rules, to supplement the information pertaining to any ground advanced in the Petition.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 36–70 of U.S. Patent No. 11,542,554 is instituted with respect to all challenged claims and all grounds set forth in the Petition;

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial, which will commence on the entry date of this decision;

FURTHER ORDERED that, to the extent any party disputes 10x Genomics' right to participate in this proceeding on behalf of Patent Owner, the party shall request authorization to brief the issue within 5 business days of this Decision; and

FURTHER ORDERED that the caption used in this Order, reflecting the addition of 10x Genomics, be used by the parties in future filings in this proceeding.

IPR2024-00526
Patent 11,542,554 B2

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