

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SPECTRUM SOLUTIONS LLC
Petitioner,

v.

LONGHORN VACCINES & DIAGNOSTICS, LLC
Patent Owner.

IPR2021-00857
Patent 9,212,399 B2

Before GEORGIANNA W. BRADEN, ZHENYU YANG, and
WESLEY B. DERRICK, *Administrative Patent Judges*.

BRADEN, *Administrative Patent Judge*.

JUDGMENT

Adverse Judgment

Ordering All Challenged Claims Cancelled Based on Adverse Judgment

Final Written Decision

Determining All Challenged Claims Unpatentable
Denying Patent Owner's Contingent Motion to Amend
35 U.S.C. § 318(a)

Denying-in-Part and Dismissing-in-Part Patent Owner's Motion to Exclude
37 C.F.R. § 42.64(c)

Denying Patent Owner's Motion to Seal
37 C.F.R. §§ 42.54, 42.55

Executive Summary:

In our concurrently-filed Sanctions Order (Paper 106), we determine that Patent Owner failed to meet its duty of candor and fair dealing in its actions before the Board. As detailed in that Order, Patent Owner conducted, and relied on, biological testing in an attempt to distinguish the asserted Birnboim reference in this and related *inter partes* review proceedings, but selectively and improperly withheld material results that were inconsistent with its arguments. For the reasons set forth in our Sanctions Order, we order, as adverse judgment, that all challenged claims of the U.S. Patent No. 9,212,399 are cancelled.

For the sake of completeness, we also address the merits of the Petition. In so doing, we further determine that Petitioner has demonstrated by a preponderance of the evidence that all challenged claims are unpatentable under either 35 U.S.C. § 102 or 35 U.S.C. § 103. Petitioner also has shown by a preponderance of the evidence that the proposed substitute claims are unpatentable under 35 U.S.C. § 103. We, therefore, deny Patent Owner's Revised Motion to Amend on the merits and, additionally, as a further sanction consistent with our Sanctions Order.

I. INTRODUCTION

A. Procedural Background

Spectrum Solutions LLC (“Petitioner” or “Spectrum”) filed a Petition for an *inter partes* review of claims 1–35 of U.S. Patent No. 9,212,399 B2 (“the ’399 patent,” Ex. 1001). Paper 1 (“Pet.”). Longhorn Vaccines & Diagnostics, LLC (“Patent Owner” or “Longhorn”) timely filed a Preliminary Response. Paper 6 (“Prelim. Resp.”). With our authorization (*see* Paper 3001), Petitioner filed a Reply to the Preliminary Response (Paper 7) and Patent Owner filed a corresponding Sur-reply to the Preliminary Response (Paper 9, “Prelim. Sur-reply”).

In view of the then-available, preliminary record, we concluded that Petitioner satisfied the burden, under 35 U.S.C. § 314(a), to show that there was a reasonable likelihood that Petitioner would prevail with respect to at least one of the challenged claims. Accordingly, on behalf of the Director (37 C.F.R. § 42.4(a) (2018)), and in accordance with *SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1353 (2018) and the Office’s Guidance on the Impact of *SAS* on AIA Trial Proceedings (Apr. 26, 2018) (“Guidance”),¹ we instituted an *inter partes* review of claims 1–35 on all the asserted grounds. Paper 12 (“Inst. Dec.”), 46–47.

After institution, Patent Owner filed a Patent Owner Response to the Petition. Paper 21 (“Original POR.”). Petitioner filed a Reply to Patent Owner’s Response (Paper 37, “Reply”) and Patent Owner filed a respective (corrected) Sur-reply (Paper 101, “Sur-reply”).

¹ <https://www.uspto.gov/patents-application-process/patent-trial-and-appeal-board/trials/guidance-impact-sas-aia-trial>.

Pursuant to our authorization, Patent Owner submitted an Amended (and subsequently corrected) Patent Owner Response along with an Amended Supplemental Expert Report of its technical expert. Paper 100, “AmPOR.”; Ex. 2033 (Amended Supplemental Expert Report of Dr. Louis DeFilippi); Paper 59 (authorizing amendments to Patent Owner Response and Supplemental DiFilippi Declaration); *see also*, Paper 50, Appx. A and B (red-lined documents showing authorized amendments)). Unless otherwise specified, we cite herein to the Amended Patent Owner Response (“AmPO Resp.”) and the Amended Supplemental DeFilippi Declaration (“Ex. 2033”).

Patent Owner filed a Contingent Motion to Amend (Paper 20, “MTA”); Petitioner opposed the Motion (Paper 38, “Opp. MTA”); and we provided Preliminary Guidance (Paper 47, “Prelim. Guid.”). Patent Owner subsequently filed a Revised Contingent Motion to Amend. Paper 53, “RMTA.” Petitioner opposed the revised motion (Paper 66, “Opp. RMTA”); Patent Owner filed a Reply in support (Paper 76, (Reply RMTA”); and Petitioner responded with a Sur-reply (Paper 92, “Sur-reply RMTA.”).

Patent Owner filed a motion to exclude evidence (Paper 80, “MTE”; Petitioner opposed (Paper 86, “Opp. Mot. Exclude”); and Patent Owner filed a reply in support of its motion (Paper 94, “Reply MTE”).

Patent Owner filed a motion to seal (Paper 40, Mot. Seal”); Petitioner opposed (Paper 48, “Opp. Mot. Seal”); and Patent Owner filed a Reply in support of its motion (Paper 60, “Reply Mot. Seal”).

On August 19, 2022, the parties presented arguments at oral hearing, the transcript of which is of record.² Paper 103 (“Tr.”).

² The referenced transcript is for the hearing on the merits for this and related cases. Petitioner filed a Motion for Sanctions (Paper 54); Patent Owner opposed (Paper 74); and Petitioner filed a Reply in support of its

B. Adverse Judgment

Petitioner moved for sanctions, seeking: (1) judgment against Patent Owner; (2) holding that a particular reference meets particular claim limitations; and (3) compensatory expenses, including attorney fees. Paper 54, 1–2. We considered the issue after further briefing (Papers 74, 82) and a hearing on the motion (Paper 103). The briefing and accompanying evidence show that Patent Owner conducted, and relied on, biological testing in an attempt to distinguish the asserted Birnboim reference in this and related IPRs, but selectively and improperly withheld material results that were inconsistent with its arguments. Accordingly, as set forth under separate cover and issued concurrently, we determine Patent Owner has failed to meet its duty of candor and fair dealing in its actions before the Board under 37 C.F.R. § 1.56, §§ 11.106(c), 11.303, 42.11(a), 42.51(b)(1)(iii). *See* Paper 106 (“Sanctions Order”).

Under 37 C.F.R. §§ 42.5, 42.11, and 42.12, and based on the Sanctions Order and determinations made therein, we enter Adverse Judgment against Patent Owner as to all challenged original claims and deny Patent Owner’s Revised Contingent Motion to Amend. *See* Paper 106, 59–60. Nonetheless, for the sake of completeness, and to add further context to our Sanction’s Order, we address below the merits of the Petition and the Revised Contingent Motion to Amend.

motion (Paper 82). On August 16, 2022, the panel held a hearing on the sanctions motion, and the transcript of that hearing also is of record. Paper 99 (“Mot. Tr.”). Concurrent with this Decision, we separately issue our ruling on the sanctions motion. *See* Paper 106.

C. Real Parties-in-Interest

Petitioner identifies itself, Spectrum Solutions LLC as a real party-in-interest. Pet. 1. Petitioner further identifies two companies having a financial interest in, or potentially substantially affected by the outcome of, this proceeding: its parent company, Spectrum Holdco LLC, and Spectrum Intermediate LLC. *Id.* Petitioner does not expressly identify those companies as real parties-in-interest.

Patent Owner identifies only itself, Longhorn Vaccines & Diagnostics, LLC, as the real party-in-interest in this proceeding. Paper 3 (“Patent Owner’s Mandatory Disclosures”), 2.

D. Related Matters

Petitioner concurrently challenges claims of related U.S. Patents Nos. 8,084,443 (“the ’443 patent”); 8,293,467; 8,415,330; 8,669,240; and 9,683,256, in IPR2021-00847, -00850, -00851, -00854, and -00860, respectively. According to the parties, the same patents are at issue in *Longhorn Vaccines & Diagnostics, LLC v. Spectrum Solutions LLC*, C.A. No. 2:20-cv-00827 (D. Utah). Pet. 1; Paper 3, 1; Ex. 1007 ¶¶ 9–15.

E. Asserted Challenges to Patentability and Evidence of Record

Petitioner challenges the patentability of claims 1–35 on the following basis (Pet. 11):

Claim(s) Challenged	35 U.S.C. §³	Reference(s)/Basis
1, 4, 6, 8, 10, 11, 16,	102	Birnboim ⁴

³ The Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. §§ 102 and 103, effective March 16, 2013. The ’399 patent issued before the effective date of the AIA.

⁴ Birnboim, US 2004/0038269 A1, published Feb. 26, 2004 (“Birnboim,” Ex. 1003).

Claim(s) Challenged	35 U.S.C. § ³	Reference(s)/Basis
21–30, 32, 35		
1, 2, 4–8, 10–14, 16, 21–32, 35	103	Birnboim
3	103	Birnboim, Chen ⁵
9	103	Birnboim, Reed ⁶
15	103	Birnboim, Mori ⁷
16	103	Birnboim, Helftenbein ⁸
17	103	Birnboim, Chirgwin ⁹
18–20	103	Birnboim, Chen, Das ¹⁰ , Wanh ¹¹
31	103	Birnboim, Koller ¹²
33	103	Birnboim, Birnboim2006 ¹³

⁵ Chen et al., US 2007/0202511 A1, published Aug. 30, 2007. (“Chen,” Ex. 1027).

⁶ Reed et al., WO 00/77235 A1, published Dec. 21, 2000. (“Reed,” Ex. 1017).

⁷ Mori, WO 2005/111210 A1, published Nov. 24, 2005. (“Mori,” Ex. 1011).

⁸ Helftenbein, U.S. Patent No. US 6,776,959 B1, filed Aug. 12, 1999, issued Aug. 17, 2004. (“Helftenbein,” Ex. 1019).

⁹ Chirgwin et al., *Isolation of Biologically Active Ribonucleic Acid from Sources Enriched in Ribonuclease*, 18 Biochemistry 5294 (1979). (“Chirgwin,” Ex. 1015).

¹⁰ Das et al., US 2005/0123928 A1, published Jun. 9, 2005. (“Das,” Ex. 1008).

¹¹ Wanh et al., WO 2004/104181 A2, published Dec. 2, 2004. (“Wanh,” Ex. 1022).

¹² Koller, WO 91/02740 A1, published Mar. 7, 1991. (“Koller,” Ex. 1016).

¹³ Birnboim et al., WO 2006/096973 A1, published Sept. 21, 2006. (“Birnboim2006,” Ex. 1023).

Claim(s) Challenged	35 U.S.C. §³	Reference(s)/Basis
34	103	Birnboim, Chirgwin, Farrell ¹⁴

In support of its patentability challenge, Petitioner relies on, inter alia, the Declarations of Richard F. Taylor, Ph.D. (Exs. 1002, 1071 “Dr. Taylor”). Patent Owner relies on, inter alia, the Declaration of Louis DeFilippi Ph.D. (Ex. 2001, “Dr. DeFilippi”), and on Dr. DeFilippi’s Amended Supplemental Expert Report (Ex. 2033).

In support of its Revised Motion to Amend, Patent Owner relies on the Supplemental Declaration of Dr. DeFilippi. Ex. 2033. Correspondingly, Petitioner relies on Dr. Taylor’s Supplemental Declaration (Ex. 1082) and the Declaration of Christopher M. Beausoleil (Ex. 1077).

F. The ’399 Patent and Related Background

The ’399 patent, titled “Biological Specimen Collection and Transport System and Method of Use,” issued to Fischer et al., on Dec. 15, 2015, from U.S. Application No. 14/149,278, filed January 7, 2014, via a series of continuation actions first filed on October 1, 2009 and further claims priority to Provisional Application No. 60/976,728 filed on October 1, 2007.¹⁵ Ex. 1001, codes (21), (45), (54), (60), (63), (72), 1:8–21. In addressing the art of record, the parties presume the earliest possible priority date (October 1, 2007). *See, e.g.*, Pet. 4; Ex. 1002 ¶ 1. Patent Owner does not dispute the prior art status of the asserted references. AmPOR4.

¹⁴ Robert E. Farrell, Jr., Ph.D., “RNA Methodologies: A Laboratory Guide for Isolation and Characterization,” (3rd Ed., 2005). (“Farrell,” Ex. 1026).

¹⁵ Petitioner claims the earliest possible priority date as October 1, 2007. Pet. 4.

1. Background and Specification

The '399 patent relates to “aqueous compositions for collection, transport, and storage of a biological specimen containing a population of nucleic acids in a single reaction vessel, which can then be purified and/or analyzed using conventional molecular biology methods.” Ex. 1001, 1:35–39. The '399 patent acknowledges that prior art methods existed, but states such methods could result in the degradation of nucleic acids, even when stored under freezing temperatures, and had the potential for exposure to infectious agents during collection, transfer, and testing. *Id.* at 1:55–2:36. The '399 patent also states that “clinical laboratory methods for pathogen detection were labor-intensive, expensive processes that required highly knowledgeable and expert scientists with specific experience.” *Id.* at 2:37–40.

Against this background, the '399 patent purports to disclose “new and useful compositions . . . that may advantageously improve conventional collection, lysis, transport and storage methods for the preparation of nucleic acids from one or more biological sources.” *Id.* at 3:21–26. In particular, the '399 patent discloses a one-step, aqueous composition that:

a) inactivates viruses or microbes in the sample, b) lyses the biological cells or tissues to free the nucleic acids from cellular debris and extraneous biomolecules, c) protects the nucleic acids from degradation by endonuclease activity, d) facilitates collection and handling of the sample at ambient temperatures, and e) preserves the nucleic acids for subsequent isolation, detection, amplification, and/or molecular analysis.

Id. at 3:41–51; *see id.* at 6:44–52.

The Specification further discloses exemplary compositions comprising a buffered solution of nuclease-free water containing:

- a chaotrope, e.g., guanidine thiocyanate, guanidine hydrochloride, or guanidine isocyanate;
- a detergent, e.g., sodium dodecyl sulfate (SDS), lithium dodecyl sulfate (LDS), sodium taurodeoxycholate (NaTDC), sodium taurocholate (NaTC), sodium glycocholate (NaGC), sodium deoxycholate (NaDC), sodium cholate, sodium alkybenzene sulfonate (NaABS), or N-lauroyl sarcosine (NLS);
- a reducing agent, e.g., β -mercaptoethanol (β -ME), dithiothreitol (DTT), dimethylsulfoxide (DMSO), formamide, or phosphine (TCEP);
- a chelator, e.g., EGTA, HEDTA, DTPA, NTA, EDTA, citrate anhydrous, sodium citrate, calcium citrate, ammonium citrate, ammonium bicitrate, citric acid, diammonium citrate, ferric ammonium citrate, or lithium citrate); and
- a surfactant/ defoaming agent, e.g., a silicone polymer such as Antifoam A®, or a polysorbate such as Tween®.

Id. at 4:21–5:31. In certain embodiments, the composition further includes a short chain alkanol, e.g., methanol, ethanol, propanol, butanol, pentanol, hexanol (*id.* at 5:59–67) as well as buffer to control the pH of the solution (*id.* at 5:48–58).

According to the Specification, an exemplary composition containing the sample suspected of containing nucleic acids will:

stabilize the nucleic acids to the extent that they either remain at least substantially non-degraded (i.e., at least substantially stable) even upon prolonged storage of the composition at ambient, refrigerator, or sub-zero temperatures. It will be desirable that this stability provides that at least about 70%, at least about 85%, more preferably at least about 90%, more preferably at least about 95%, or even more preferably, at least about 98% of the polynucleotides contained within the stored sample will not be degraded upon prolonged storage of the sample. In certain embodiments, substantially all of the polynucleotides contained within the sample will be stabilized such that the original integrity of the polynucleotides is preserved

during the collection, lysis, storage, and transport of the processed sample.

Id. at 9:63–10:11; *see also id.* at 10:42–45 (asserting that “no more than about 1 or 2% of the sample will be degraded even when the composition is stored at a temperature from 0° C. to about 40° C. for periods of several days to several weeks”).

2. *Challenged Claims*

As noted above, the Petition challenges independent claim 1, as well as dependent claims 2–35. Claim 1 illustrates the challenged subject matter at issue and is reproduced below.

1. A stock solution of an aqueous composition comprising:
 - a chaotrope,
 - a detergent,
 - a reducing agent,
 - a chelator, and
 - a buffer,wherein the stock composition, when diluted with a sample containing nucleic acids, nucleases and proteins, denatures the proteins of the sample, inactivates the nucleases of the sample, kills pathogens that may be present in the sample, and does not degrade the nucleic acids of the sample.

Ex. 1001, 31:44–50. Dependent claims 21 and 35 recite a method for obtaining a nucleic acid from a sample using the stock solution of claim 1.

Id. at 33:25–30, 34:46–58. Dependent claim 34 is directed to a method of preparing the stock solution of claim 1. *Id.* at 34:19–46.

Depending from claim 1, claims 2, 4, 5, and 7 are particularly relevant to our analysis. Claim 2 defines the reducing agent as mercaptoethanol, tris(2-carboxyethyl) phosphine, dithiothreitol, dimethylsulfoxide, or any combination thereof,” while claim 4 defines that the reducing agent is

“present in an amount from 0.05 M to 0.3 M.” Claim 5 requires that “the chaotrope comprises guanidine thiocyanate, guanidine isocyanate, guanidine hydrochloride or a combination thereof.” Claim 7 recites that the “chelator comprises ethylene glycol tetra acetic acid, hydroxyethylethyl enediaminetriacetic acid, diethylene triamine pentaacetic acid, N,N-bis (carboxymethyl)glycine, ethylenediaminetetraacetic, citrate anhydrous sodium citrate calcium citrate, ammonium citrate, ammonium bicitrate, citric acid diammonium citrate, ferric ammonium citrate, lithium citrate or a combination thereof.”

II. ANALYSIS

A. Legal Standards

“In an IPR, 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) (requiring *inter partes* review petitions to identify “with particularity . . . the evidence that supports 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).

Petitioner contends that each claim of the ’399 patent is invalid as obvious under § 103(a). The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), reaffirmed the framework for determining obviousness set forth in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). The *KSR* Court summarized the four factual inquiries set forth in *Graham*, 383 U.S. at 17–18, that are applied in determining whether a claim is unpatentable as obvious under 35 U.S.C. § 103 as follows: (1) determining the scope and content of the prior art; (2) ascertaining the differences

between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the art; and (4) considering objective evidence indicating obviousness or non-obviousness, if present.¹⁶ *KSR*, 550 U.S. at 406.

“[W]hen a patent ‘simply arranges old elements with each performing the same function it had been known to perform’ and yields no more than one would expect from such an arrangement, the combination is obvious.” *Id.* at 417 (quoting *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 282 (1976)). Prior art references must be “considered together with the knowledge of one of ordinary skill in the pertinent art.” *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994) (citing *In re Samour*, 571 F.2d 559, 562 (CCPA 1978)). But in analyzing the obviousness of a combination of prior art elements, it can also 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.” *Id.* at 418.

“[I]n considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom.” *In re Preda*, 401 F.2d 825, 826 (CCPA 1968). Moreover, a precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *KSR*, 550 U.S. at 418. 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

¹⁶ Patent Owner does not identify evidence of objective indicia of non-obviousness.

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 International, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (quotations and citations omitted).

B. Level of Ordinary Skill in the Art

In determining the level of skill in the art, we consider the type of problems encountered in the art, the prior art solutions to those problems, the rapidity with which innovations are made, the sophistication of the technology, and the educational level of active workers in the field. *See Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986); *see also Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1011 (Fed. Cir. 1983).

In our Institution Decision, we applied Petitioner’s then-unopposed definition of one of ordinary skill in that art at the relevant time as:

A person of ordinary skill in the art (“POSA”) would have had (1) a Ph.D. in microbiology, molecular biology, biochemistry, or related discipline; (2) at least two years of post-graduate experience in the area of nucleic acid extraction and analysis; and (3) experience with the development or use of nucleic acid extraction formulations, and the literature concerning nucleic acid extraction and analysis. Ex. 1002 ¶¶ 37–38

Inst. Dec. 10 (citing Pet. 9).

Patent Owner now argues that the above definition is flawed for two reasons.¹⁷ First, because “a POSA would not have experience with the

¹⁷ At oral argument, counsel for Patent Owner could not identify any issue that turned on the precise wording of one of ordinary skill in the art. *See* Tr. 89:15–87:88:3.

‘development’ of nucleic acid extraction formulations.” AmPOR 3 (citing Ex. 2020, 104:1–9). Patent Owner’s argument is not persuasive. Patent Owner’s sole support for this proposition derives from Dr. Taylor’s statement that his research at the Arthur D. Little consulting company did not require the development of new methods for extracting DNA. Ex. 2020, 104:1–9. That Dr. Taylor personally may not have been involved with this type of assay or formulation development hardly speaks to the breadth knowledge of one of ordinary skill in the art. Moreover, that the art of record is directed largely to the development of formulations and methods for extracting nucleic acids is contrary to Patent Owner’s position. *See e.g.*, Exs. 1003, 1008, 1010, 1011, 1015, 1026, 1027; *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)).

Patent Owner further takes issue with the requirement that one of ordinary skill in the art have “*experience* with . . . the literature concerning nucleic acid extraction and analysis,” as allegedly ambiguous. AmPOR 3 (citing Ex. 2033 ¶¶ 82–83) (*italics added*). One of ordinary skill in the art is a “hypothetical person who is presumed to be aware of all the pertinent prior art.” *Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985). To the extent the above definition may be misconstrued, we substitute “awareness” for “experience.” As such, we define one of ordinary skill in the relevant art as having had:

- (1) a Ph.D. in microbiology, molecular biology, biochemistry, or related discipline; (2) at least two years of post-graduate experience in the area of nucleic acid extraction and analysis; and

(3) experience with the development or use of nucleic acid extraction formulations; and (4) awareness of the literature concerning nucleic acid extraction and analysis.

We note this level of skill is consistent with the level demonstrated in the cited prior art references. *See Okajima*, 261 F.3d at 1355. We further note that, at the hearing, counsel for both parties acknowledged that neither aspect of the dispute over the skill level affects the patentability analysis. *See* Tr. 84:18–85:5, 107:11–108:10.

C. Claim Construction

We interpret a claim “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(b) (2020). Under this standard, we construe the claim “in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” *Id.*; *see Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc).

1. “*stock solution*”

The independent claim before us is directed to stock solutions and methods and kits employing the same. *See* Ex. 1001, claim 1. Petitioner contends that we should apply the plain and ordinary meaning of “stock solution” as meaning “a formulated supply of solution for future use,” which, in the context of the instant claims, refers to “the aqueous composition before it is mixed with a sample.” Pet. 7 (citing Ex. 1029; Ex. 1002 ¶ 40–44). Patent Owner does not contest this construction. AmPOR 3. For the sake of clarity, we apply the plain and ordinary meaning of this term as Petitioner proposes.

2. “*kills pathogens*”

Independent claim 1 is directed to a stock solution which, “when diluted with a sample containing nucleic acids, nucleases and proteins, denatures the proteins of the sample, inactivates the nucleases of the sample, kills pathogens that may be present in the sample, and does not degrade the nucleic acids of the sample.” The Specification does not expressly define “kills pathogens” and the parties did not formally address the meaning of this language prior to institution. In its Preliminary Response, however, Patent Owner appeared to equate this term with complete sterilization of a sample “to prevent ‘dissemination of live infections pathogens.’” Prelim. Resp. 15.

On the limited record before us, we concluded that plain language of “the claims do[es] not require killing every potential pathogen in a sample,” and made clear that we did not otherwise “read the challenged claims as suggesting that *every* pathogenic agent including, for example, prions and bacterial spores, must be so susceptible.” DI 19–20 (citations omitted). Applying the plain and ordinary meaning, we provisionally determined that “kill pathogens” merely requires that at least some potential pathogens are killed in the extraction process, and invited further briefing. *Id.* 20–21, 24–25, 28. For the reasons discussed below, we further refine our initial construction.

As an initial matter, we now address what pathogens are contained within the scope of “kills pathogens.” At oral argument, Patent Owner’s counsel clarified that “kills pathogens” only applies to those classes of pathogen disclosed in the Specification. Tr. 114:12–116:1, 122:9–123:13, 147:15–19. According to Patent Owner’s counsel, those classes are “viruses, bacteria, and spores.” *Id.* 122:15; 134:9–135:4.

By way of explanation, some bacteria have the capacity to form spores (endospores) under adverse environmental conditions. *See* Ex. 1046, 50:6–23; Ex. 1064, 63:6–64:1. This spore stage is generally more resistant to inactivation than the corresponding vegetative-stage bacteria. *See, e.g.*, Ex. 1096, 1005:4–1008:1 (Dr. DeFillipi explaining spore resilience); Ex. 2003, 9–10, 34, 102 (CDC Guidance discussing difficulty of eliminating bacterial spores and prions as opposed to, for example, lipid encapsulated viruses and vegetative bacteria); Ex. 1008 ¶ 38 (characterizing spores as among “the toughest cells”); Tr. 128:16–19; Ex. 1046, 56:19–56:3 (testimony that spores are more resistant to desiccation and disinfection);

Contrary to the assertion of Patent Owner’s counsel that the Specification disclosed spores, we do not identify any disclosure of bacterial spores in the ’399 patent. Consistent with our understanding of the ’399 Specification, Patent Owner’s technical expert, Dr. DeFilippi testified that he “do[es] not believe spores were addressed in the specifications.” Ex. 1064, 185:9–186:5. Additionally, Patent Owner’s counsel was unable to point to such evidence at oral argument and conceded that, to the extent the Specification does not disclose spores, the claims do not encompass killing or inactivating spores.¹⁸ *See* Tr. 123:19–125:5, 136:1–137:8. Also pertinent to our understanding of “kills pathogens,” Dr. DeFilippi testified that “a spore in the form of a spore is not pathogenic” but a “pre-pathogen.” *Id.* at 186:19–187:10.

¹⁸ For the purpose of our analysis in this Decision, we consider inactivation synonymous with killing.

The Specification, largely focused on killing bacteria and inactivating viruses,¹⁹ states that “it may also be desirable to include one or more additional anti-microbial, anti-viral, or anti-fungal agents to the compositions to render them substantially non-pathogenic.” Ex. 1001, 9:41–44; *see also id.* at 18: 39–58 (listing various microorganisms that may be present in a biological sample); claim 16 (“wherein the pathogen comprises bacteria, virus, or a fungus”); claim 33 (“wherein the pathogen is an infectious pathogen, a virus, a bacterium, a parasite, a yeast, a fungal cell, a eukaryotic cell, a prokaryotic cell, a bioterrorism agent, a vector, or a microorganism”). In light of the above, we understand “kills pathogens” to encompass the killing or inactivation of at least fungi, viruses, and vegetative bacteria capable of causing disease—but excluding bacterial spores, which are neither “pathogens” (according to Dr. DeFilippi), nor disclosed in the ’399 Specification.

Having address the scope of “pathogens” encompassed by independent claim 1, we turn to Patent Owner’s contention that “kills pathogens” further means “rendering the sample substantially non-pathogenic²⁰ so that the regulations for transporting “Infectious Substances” would not apply—i.e., so that pathogens could not cause disease if exposure to the sample occurs.” AmPOR 9–10 (citing Ex. 2033 ¶¶ 8–11); *see also id.* at 19, n.1 (alternatively defining the term “as rendering the sample (that may

¹⁹ Petitioner aptly distinguishes killing bacteria from inactivating viruses on the basis that “[v]iruses are never alive to begin with.” Tr. 13:11–14:6.

²⁰ The ’399 patent defines “substantially non-pathogenic” as “leaving less than about 10 percent, less than about 5 percent, etc., of the pathogenic activity.” Ex. 1001, 20: 10–15. Thus, we agree with Petitioner “substantially non-pathogenic” would render the claims indefinite. *See* Reply 1 n.1 (citing Ex. 1001, 20: 10–15).

contain pathogens safe for shipment and handling ‘non-pathogenic’”);
Tr. 102:13–104:1, 132:16–133:3.

In support of its construction(s), Patent Owner points to U.S. regulatory standards and exceptions for transport of Division 6.2 infectious substances, and an Emergency Use Authorization (EUA) Memorandum for SDNA-1000 Saliva Collection Device indicating that USDOT packaging requirement UN3373 “was in place at the time of the invention.” AmPOR 9–11 (citing 49 C.F.R. §§173.124(a)(1)(iii), and 173.124(b)(4), (5); Ex. 2016, 7). Neither 49 C.F.R. §173 nor the USDOT packaging requirement is referenced in the ’399 Specification.

Patent Owner further contends that “rendering samples potentially containing dangerous pathogens safe for unsecured shipment to laboratory facilities” is a “fundamental purpose” of the ’399 patent. Sur-Reply 5 13–14 (citing AmPOR 8–11; Ex. 2033 ¶¶ 8–10); AmPOR 9–11 (further citing Ex. 1001, 2:13–27). As such, Patent Owner attempts to draw a parallel with the Federal Circuit’s holding in *Praxair, Inc. v ATMI, Inc.*, 543 F.3d 1306 (Fed. Cir. 2008). AmPOR 6–8; Sur-reply 5.

In addressing the term “flow restrictor,” the *Praxair* Court found that “the specification teaches that the flow restriction must be sufficient to achieve the overall object of the invention—that is, to prevent a hazardous release of gas.” 543 F.3d at 1324. The court therefore construed “flow restrictor” as “a structure that serves to restrict the rate of flow sufficiently to prevent a hazardous situation,” because “[t]he fundamental object of the invention disclosed by the . . . specification is to prevent a hazardous situation from the uncontrolled discharge of gas.” *Id.* Notably, however, the court rejected a construction requiring a “severe restriction of gas flow”

because the specification made clear that “severe restriction” pertained only to specific, albeit the most common, embodiments rather than the full scope of the invention. *Id.* at 1323.

Considering the court’s reasoning in *Praxair*, we do not find Patent Owner’s argument availing for at least the reasons set forth at pages 1–3 of Petitioner’s Reply. We further note that the ’399 patent describes compositions and methods “that may advantageously improve conventional collection, lysis, transport and storage methods for the preparation of nucleic acids from one or more biological sources.” Ex. 1001, 3:24–26. The Specification states, for example, that the

invention advantageously can provide a collection and preservation formulation to inactivate and lyse a biological specimen containing nucleic acids, and preserve nucleic acids (RNA/DNA) within the biological specimen, preferably all in a single reaction vessel, such that the integrity of the nucleic acids is at least substantially maintained, and preferably entirely maintained, so that a portion of the nucleic acids are readily available for molecular diagnostic analysis.

Id. at 3:27–35. As such, and considering the Specification as a whole, the fundamental goal of the invention—to the extent one can be assigned—is the extraction and preservation of nucleic acids for molecular diagnostic analysis. And while the Specification also discusses the desirability of killing or inactivating pathogens “to facilitate safe handling of the sample,” we agree with Petitioner that such language points to preferred embodiments, as opposed to some fundamental object of the invention. *See* Reply 1–2 (citing Ex. 1001, 9:31–37, 16:1–16); Tr. 26:8–28:8.

Illustrative of this point, the Specification discloses an embodiment having three distinct and alternative goals:

A clinical or veterinary specimen or a forensic or environmental sample collection system . . . for efficiently:

- 1) obtaining a high yield of suitable specimen beyond what is currently available in the art;
- 2) inactivating potentially infectious biological pathogens so that they are no longer viable and can be handled; shipped, or transported with minimal fear of pathogen release or contamination; *or*
- 3) effectively stabilizing and preserving lysed ‘naked’ RNA/ DNA polymers from hydrolysis or nuclease degradation for prolonged periods at ambient temperatures until samples can be processed at a diagnostic laboratory, and

preferably for achieving two or more, or all three, of these goals.

Ex. 1001, 14:64–15:9 (paragraphing and emphasis added); *see also* 16:1–16 (similar); 15:12–29 (“Exemplary benefits include, without limitation, *one or more* of the following,” including “[i]nactivion, killing, and/or lysis of microbes, viruses, or pathogens.”) (emphasis added).

In sum, having determined that the “pathogens” at issue are limited to fungi, viruses and vegetative bacteria (excluding spores), we find to no reason to otherwise depart from the plain and ordinary meaning of “kills pathogens.” Accordingly, we define the term as meaning that at least some viral or vegetative bacterial pathogens in a sample are killed or inactivated.

3. *“inactivates the nucleases”*

Patent Owner contends that “inactivates the nucleases” should be construed to mean that substantially all DNases²¹ and RNases in a sample should be inactivated. AmPOR 15–17; Sur-reply 1–5. In support of its

²¹ The prior art, the ’399 Patent, and the parties’ briefs inconsistently capitalize these enzymes as “RNase”/“RNase” and “DNase”/“DNase.” We consider the two conventions interchangeable.

position, Patent Owner relies on the intrinsic record, the opinion of its technical expert, Dr. DeFilippi, and the deposition testimony of Petitioner's expert, Dr. Taylor, that he understands "that both DNA and RNA nucleases are involved" because "[n]ucleases is plural." Ex. 2033 ¶¶ 19–22 (citing Ex. 1001, 6:44–52; 14:64–15:7, 25:46–54; Ex. 2020, 298:16–26).

Considering the totality of the evidence, however, we agree with Petitioner that "inactivates nucleases" more broadly encompasses inactivating DNases or RNases (or both) in a sample. *See* Reply 4–5.

The present controversy arises from the claim term's use of the plural "nucleases" which, Patent Owner asserts, "requires inactivation of both RNA and DNA nucleases." Tr. 93:13–15. But it is undisputed that there are entire families of both RNases and DNases such that "inactivates nucleases" can also apply to the inactivation of multiple RNases or multiple DNases. *See* Tr. 95:3–7, 30:17–31:6; Reply 4 (citing Ex. 1064, 144:4–21, 145:16–146:16); Ex. 1011, 62 (RNase H); Ex. 1206, 48 ("RNases are a family of enzymes present in virtually all living cells."); Ex. 1015, 5294 (RNase A); Ex. 1009, 3:65–4:3 (RNases A, T1, and S1)).

As noted by Patent Owner, the Specification refers to the "stabiliz[ation of] "DNA/RNA." *See* AmPOR 15–16 (citing Ex. 1001, 6:44–52; 14:64–15:7, 25:46–54). Patent Owner initially argued that we should interpret this convention as meaning "DNases *and* RNases," as opposed to "DNases *and/or* RNases" *See id.* at 16 (citing Ex. 2033 ¶¶ 19–21).

Challenged at trial, however, Patent Owner's counsel conceded that the use of "DNA/RNA" in the Specification was not necessarily conjunctive. Tr. 95:8–21). Indeed, an understanding of the "DNA/RNA" convention as

referring to the inactivation of either DNases or RNases, is consistent with the Specification's disclosure that

The compositions of the present invention will typically at least substantially inactivate, and preferably entirely inactivate, any endogenous or exogenous RNases or DNases present in the sample such that the nucleic acids of the sample are substantially free of any degradation, and preferably do not degrade, or lose integrity, during the collection, lysis, storage, and transport of the sample for subsequent in vitro or in vivo analyses."

Ex. 1001, 6:32–39. First, by including the word "typically" the Specification indicates, at best, that "substantial[] inactiv[ation]" of RNases or DNases present in the sample is a preferred, but not absolute requirement. Second, we understand the above-quoted passage's reference to inactivation of "RNases *or* DNases" to reflect the underlying purpose of the invention in providing samples for molecular analysis of RNA (e.g., RT-PCR analysis) or DNA (e.g., PCR analysis). *See* Reply 4; Ex. 1001, 6:32–39 (emphasis added), 2:48–65 (discussing molecular analysis techniques).

Petitioner also contends that, "Claim 1 of the '339 patent recites "inactivate nucleases" but dependent claim 14 adds "free of RNase *or* DNase activity." Reply 4. Therefore, Petitioner argues that "the term 'inactivate nucleases' cannot be construed to require inactivating DNase *and* RNase, rendering the dependent claim broader than the independent cla[i]m." *Id.* (citing 35 U.S.C. § 112(d); *Baxalta Inc. v. Genentech, Inc.*, 972 F.3d 1341, 1346 (Fed. Cir. 2020)). Patent Owner responds that Petitioner's claim differentiation argument fails because claim 14 requires the *composition* rather than the resulting sample to be free of RNase and DNase activity. *See* Sur-Reply 2.

Although Patent Owner is correct that claim 14 is directed to the composition prior to the addition of a biological sample, Petitioner's argument is, nevertheless, consistent with its construction "inactivate nucleases." The "free of RNase or DNase" language of claim 14 implicitly permits the composition to contain, for example, RNase activity. Adding such a composition to a biological sample would, therefore, be expected to degrade RNA in the sample. Accordingly, the term "inactivate nucleases" recited in claim 1 cannot mean that the composition must inactivate both RNase and DNase in the sample because dependent claim 14, permits the presence of RNase activity.

We also find informative certain other claims of the '399 patent. In particular, claim 21 incorporates a "stock solution in accordance with claim 1" which, "inactivates the nucleases of the sample." Depending from claim 21, claim 26 requires that "the sample further comprises one or more nucleases, at least a portion of which is at least substantially inactivated by the stock solution." In this respect, the inactivation of at least a portion of the nucleases in a sample is consistent with the inactivation of DNase or RNase, but not both.

Considering the totality of the evidence of record, we interpret "inactivates nucleases" to mean that at least one of RNase or DNase in a sample is inactivated.

4. *"does not degrade the nucleic acids of the sample"*

Independent claim 1 recites a stock solution that, "when diluted with a sample containing nucleic acids . . . kills pathogens . . . and does not degrade the nucleic acids of the sample."²² Ex. 1001, 31:44–50. On its face, the

²² To clarify, "a sample" contains "nucleic acids, nucleases and proteins."

phrase “without degrading nucleic acids of the sample” potentially has enormous breadth of scope as it can be read as requiring the protection of *all* nucleic acids in the sample (100% protection), or as requiring the protection of *at least some* nucleic acids in the sample (e.g., an amount sufficient for detection). Consistent with our construction above of “inactivates nucleases,” we interpret the “nucleic acids” in this phrase as referring to at least one of RNA or DNA.

As we understand Patent Owner’s position, one of ordinary skill in the art would understand the term to mean “as stable as possible,” such that “no more than about 1 or 2% of the sample will be degraded” as “discussed in the best-preserved embodiments taught in the ’399 patent.” AmPOR 11–15 (citing Ex. 2033 ¶¶ 13–17; Ex. 1001, 31:44–50, 10:42–43, 9:62–10:11, 10:4–6, 10:40–45; Ex. 2018, 37.; Ex. 2020, 314:17–317:23); Sur-reply 1–4.

As Petitioner points out, however, Patent Owner arrives at this construction by focusing on “the most stable embodiments” of the ’399 patent to the exclusion of its broader teachings. Reply 3 (quoting AmPOR 13). In this respect, Petitioner argues that Patent Owner “cannot arbitrarily impose limits of ‘even more preferabl[e]’ embodiments to the exclusion of other disclosed embodiments.” *Id.* at 3–4 (quoting *Conoco, Inc. v. Energy & Envtl. Int’l, L.C.*, 460 F.3d 1349, 1357-1358 (Fed. Cir. 2006)). We agree with Petitioner that the intrinsic record, which we address below, does not support Patent Owner’s narrow reading of the claim term.

As an initial matter, during prosecution of the related ’443 patent, the Examiner rejected claims reciting the “prevent[ion]” of polynucleotide degradation under 35 U.S.C § 112, first paragraph, because “preventing ‘total polynucleotide degradation . . . from happening does not appear to be

the tenor of the present specification, and nowhere in the present specification is it shown that polynucleotide degradation may totally be kept from ever occurring.” Ex. 1045, 3–5. Rather, the Examiner found, the Specification “makes clear that total protection to the polynucleotides is not expected to occur, i.e., at least some small degree of degradation and hydrolysis, etc., will occur.” *Id.* at 3. Accordingly, we understand that “without degrading nucleic acids of the sample” does entail absolute protection from degradation.

In support of its position, Patent Owner points to the following passage in support of its construction:

In some instances, the population of nucleic acids prepared by the present methods may be maintained with sufficient integrity such that no more than about 1 or 2% of the sample will be degraded even when the composition is stored at a temperature from 0°C. to about 40°C. for periods of several days to several weeks.

AmPOR 13 (quoting Ex. 1001, 10:40–45). But as Petitioner’s counsel points out, “you can’t import a numerical range simply because you want to avoid the prior art.” Tr. 32:16–18. The “[i]n some instances” language of the above passage clearly indicates that limiting degradation to “1 or 2%” merely represents one possible embodiment. In this respect, a related passage makes clear that a similar measure of polynucleotide stability—“at least about 98%”—is merely a preferred embodiment, and not indicative of the full scope of the invention.

In certain embodiments, substantially all of the polynucleotides contained within the sample will be stabilized such that the original integrity of the polynucleotides is preserved during the collection, lysis, storage, and transport of the processed sample. It will be desirable that this stability provides that at least about 70%, at least about 85%, more preferably at least about 90%,

more preferably at least about 95%, or even more preferably, at least about 98% of the polynucleotides contained within the stored sample will not be degraded upon prolonged storage of the sample.

Id. at 9:67–10:11.

The above passage indicates that the scope of the invention includes an embodiment in which “at least about 70%” of the polynucleotides are not degraded upon prolonged storage. This does not define the lower limit encompassed by “without degrading nucleic acids of the sample.” Rather, the Specification discloses a preferred embodiment wherein

the composition containing the sample is at least sufficiently stable, or is entirely stable, to permit storage of the sample in the composition at ambient temperature or colder at least substantially (or entirely) from the time of collection to the time of analyzing a population of polynucleotides from the sample.

Id. at 9:62–67.

Consistent with the underlying goal of the invention to isolate and preserve nucleic acids for analysis in “conventional molecular biology methods,” the above passage explains that the composition must merely render the target nucleic acids “sufficiently stable” for analysis. *See id.* at 1:35–46, 9:46–51; Tr. 25:21–26:1 (“[t]he fundamental goal of this invention is to stabilize nucleic acid”).²³ The Specification describes known

²³ Absent evidence, Patent Owner’s counsel appeared to take the position that, at least with respect to RNA, “without degrading nucleic acids in the sample” required the preservation of intact molecules, because “[i]f the molecule is cut in half, it’s not preserved and you can’t use the RNA for any sort of nucleic acid test or assay.” Tr. 80:16–81:3. We take judicial notice that the detection of nucleic acids by PCR, for example, does not require an intact RNA or DNA molecule. *See id.* at 81:3–82:1; Ex. 1008 ¶ 90 (designing PCR primers to amplify 373 base pair fragment of bacterial genome); Ex. 1010 (indicating that RT-PCR was well-known in the art);

nucleic acid detection strategies as including PCR (polymerase chain reaction), RT-PCR (reverse-transcriptase PCR), and advanced detection methodologies including “transcription-mediated amplifications, ligase chain reaction (LCR), microarrays, and pathogen gene chips.” *Id.* at 2:48–65, 11:65–67, 12:19–24 (RNA samples analyzed using real-time RT-PCR on an Applied Biosystems ABI 7500 instrument).

Considering the record before us, we construe “without degrading nucleic acids of the sample” as meaning that the sample contains sufficient RNA or DNA for analysis using nucleic acid detection methodologies known to those of ordinary skill in the art as of the time of the invention.

D. Overview of Prior Art References Cited and of Record

Petitioner’s challenges rely on combinations of Birnboim, Chen, Reed, Mori, Helftenbein, Chirgwin, Das, Wangh, Koller, Birnboim2006, and Farrell. *See* Pet. 11. In responding to Patent Owners Revised Motion to Amend, Petitioner further raises Casas,²⁴ Donofrio,²⁵ Laulier,²⁶ and Zinkevich.²⁷ *See* Opp. RMTA 4. As these references are pertinent to the

Ex. 3009 (Mullis KB. “*The unusual origin of the polymerase chain reaction*,” 264(4) *Sci Am.* 56–61 (1990).

²⁴ Casas, et al., “New Method for the Extraction of Viral RNA and DNA from Cerebrospinal Fluid for Use in the Polymerase Chain Reaction Assay,” *Journal of Virological Methods* 53: 25-36 (1995). Ex. 1052.

²⁵ Donofrio, et al., “Detection of Influenza A and B in Respiratory Secretions with the Polymerase Chain Reaction,” *PCR Methods and Applications* 1:263-268 (1992). Ex. 1056.

²⁶ Laulier, et al., “An Easy Method for Preserving Nucleic Acids in Field Samples for Later Molecular and Genetic Studies Without Refrigerating,” *J. Evol. Biol.*, 8:657-663 (1995). Ex. 1060.

²⁷ Zinkevich and Beech, “Isolation of Intact High Molecular Weight Chromosomal DNA from *Desulfovibrio* spp.,” *Molecular Biology Today*, 1(1): 29-33 (2000). Ex. 1054.

knowledge of one of ordinary skill in the art, and raised in Petitioners' Opposition to the Revised Motion to Amend, we briefly review them here.

1. Overview of Birnboim (Exhibit 1003)

Birnboim discloses “compositions and methods for preserving nucleic acids at room temperature for extended periods of time and for simplifying the isolation of nucleic acids,” most particularly, DNA or RNA from sputum or saliva. Ex. 1003 ¶¶ 2, 27. According to Birnboim, nucleic acid isolated can be that of the sputum or saliva donor or “from a bacterium or a virus that is residing in the buccal, nasal, or respiratory passages of the subject.” *Id.* ¶ 27; *see id.* ¶ 43 (defining “nucleic acid” as meaning “a chain of the nucleotides, including deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), typically found in chromosomes, mitochondria, ribosomes, bacteria, or viruses”); ¶ 18 (“The nucleic acid to be preserved can be . . . viral RNA.”); ¶ 27 (“If the nucleic acid is RNA, desirably it is mRNA or viral RNA.”) ¶ 45 (discussing quantitation of “high molecular weight nucleic acid (DNA, RNA, mRNA, or viral RNA)”); claims 7, 16.

Birnboim discloses stock solutions (“nucleic acid preserving compositions”) for use in a one-step method to lyse nucleic acid-containing cells or viruses, release the nucleic acids into the composition, inactivate nucleases in the sample, and stabilize the extracted nucleic acid for future analysis. *See generally, id.* ¶¶ 11, 22, 27, 64, 114–122. With respect to stability of the extracted nucleic acid, Birnboim defines “stable” as meaning “that at least about 50% of the initial amount of high molecular weight nucleic acid (DNA, RNA, mRNA, or viral RNA) contained in a sample is still present after storing the sample at ambient temperature (i.e., 20° C. to 25°C.) for the Specified time period.” *Id.* ¶ 45.

Birnboim further teaches “inclusion of an inhibitor of ribonuclease in the composition of the invention . . . when the nucleic acid to be preserved is RNA, desirably mRNA, or when the nucleic acid to be preserved is from a virus or a bacterium.” *Id.* ¶ 22; *see also id.* ¶ 68 (stating that in addition to the use of various denaturing agents, “reagents such as heparin, heparian sulfate, or oligo(vinylsulfonic acid) . . . are known to inhibit the action of deoxynucleases and /or ribonucleases”).

Birnboim explains:

When sputum is mixed with a composition of the present invention, cells are disrupted, nucleic acids are liberated from the cells, membranous material is solubilized, proteins are stripped from the nucleic acids, and protein digestion begins If transferred to a laboratory soon after collection, incubation at 55° C. for 4 to 16 hours is sufficient to allow the activated protease to digest the majority of protein to small peptides or amino acids. Under such conditions, nucleic acids and polysaccharides remain relatively intact.

Once digestion is complete, nucleic acid isolation can be performed using any technique known in the art.

Id. ¶¶ 84–85.

Example 1 discloses an embodiment wherein a subject spits saliva into a collection tube which is mixed with an equal volume of stock solution.

Id. ¶¶ 107–109. Once the container is capped and the contents shaken, the nucleic acid is “in an intermediate preserved state” and “can be maintained in a frozen state or at any temperature up to about 60° C.” *Id.* ¶ 110.

Alternatively, “[t]he container can be mailed back to the testing lab at room temperature.” *Id.* ¶ 111.

Example 3 discloses the collection and extraction of DNA using a stock solution comprising “33 mM TRIS-HCl, 0.67 M urea, 0.67 M LiCl, 0.6% sodium dodecyl sulfate, 3.3 mM CDTA, 30% ethanol, and 0.25 M

sodium ascorbate, all adjusted to a final pH of 8.0.” *Id.* ¶¶ 114–122 (“Formulation 1”). Birnboim further discloses that a similar composition comprising “0.3 M TRIS-HCl, 0.67 M urea, 0.67 M NaOAc, 0.6% sodium dodecyl sulfate, 3.3 mM CDTA, 30% ethanol, and 0.1 M sodium ascorbate, all adjusted to a final pH of 8.0, stabilizes DNA for longer periods of time.” *Id.* ¶ 115 (“Formulation 2”).

In Example 4, Birnboim subjects the DNA of Example 3 to agarose gel electrophoresis, where ethidium bromide staining reveals “the characteristic band of chromosomal DNA present in all samples.” *Id.* ¶ 117, Fig. 1; *see also id.* ¶ 13 (disclosing preferred reducing agents erythiorbate, N-acetylcysteine, dithiothreitol, 2-mercaptoethanol and, “most desirably. . . ascorbic acid”), ¶ 25 (disclosing that isolated DNA is preferably stable for “more than 60 days” and “when . . . the composition does not contain ascorbic acid, the DNA is stable for more than 60 days, and desirably more than 360 days”).

In Examples 5 and 6, Birnboim prepares “[m]inimally purified DNA” from samples prepared using the nucleic acid-preserving solution by centrifuging the samples to remove insoluble material and precipitating the DNA with ethanol prior to using “Real Time” polymerase chain reactions to detect the DNA. *Id.* ¶¶ 118–121.

2. Overview of Chen (Exhibit 1027)

Chen discloses extraction compositions and methods for the isolation of small RNA molecules from a biological sample. Ex. 1027, code (57). Chen discloses aqueous solutions designed to preserve nucleic acids. *Id.* The aqueous solution includes: a chaotrope, a metal agent, a pH buffer, a detergent, a reducing agent, an anti-foaming agent, and a bulking agent. *Id.*

¶¶ 12–27. A suitable reducing agent disclosed by Chen includes “tris(2-carboxyethyl) phosphine” (“TCEP”).

3. *Overview of Reed (Exhibit 1017)*

Reed discloses solutions and methods for isolating nucleic acids from biological materials. Ex.1017, code (57). Reed further discloses including a surfactant as part of the solution promotes “solubilization of contaminating proteins,” with polysorbates as a preferred surfactant. *Id.* at 15:15–18 (“preferred surfactants are non-ionic detergents such as . . . polysorbates.”).

4. *Overview of Mori (Exhibit 1011)*

Mori discloses the isolation of nucleic acids from a test sample (e.g., bodily fluids, plants, animals, bacteria, viruses, and cultured cells) by treating the sample with a “nucleic acid-solubilizing reagent,” which “dissolves cell membranes and nuclear membrane, and solubilizes nucleic acid.” Ex. 1011, 57.²⁸ Exemplary nucleic acid-solubilizing reagents may include “a chaotropic salt, a surfactant, a defoaming agent, a protease and a nucleic acid stabilizing agent.” *Id.* at 58; *see also id.* at 63 (indicating that the nucleic acid stabilizing agent assists in inactivating nuclease activity).

According to Mori, preferred chaotropic salts are guanidine hydrochloride, guanidine isothiocyanate and guanidine thiocyanate, but “[i]t is possible to use a chaotropic substance such as urea instead of a chaotropic salt.” *Id.* at 61. Mori further discloses that the nucleic acid stabilizing agent is a reducing agent, and preferably a mercapto compound such as mercapto ethanol (*id.* at 63); and that the defoaming agent may be any number of silicon-, alcohol-, ether-, fatty oil-, fatty acid-phosphate ester-, amine-, or

²⁸ Where possible, we refer to native pagination.

amide-based compounds, “preferably in a range of 0.1 to 10% by weight” (*id.* at 64).

With respect to the surfactant, Mori teaches the use of a wide variety of compounds including an anionic surfactant, an amphoteric surfactant and, preferably, either a nonionic or cationic surfactant. *Id.* at 61.

Nonionic surfactants include a polyoxyethylene alkyl phenyl ether-based surfactant, a polyoxyethylene alkyl ether-based surfactant, and fatty acid alkanolamide, and the preferable one is a polyoxyethylene alkyl ether-based surfactant. Among the polyoxyethylene (POE) alkyl ether surfactant, POE decylether, POE lauryl ether, POE tridecyl ether, POE alkylendecyl ether, POE sorbitan monolaurate, POE sorbitan monooleate, POE sorbitan monostearate, tetraoleic polyoxyethylene sorbit, POE alkyl amine, and POE acetylene glycol are more preferred.

Cationic surfactants include cetyl trimethyl ammonium bromide, dodecyl trimethyl ammonium chloride, tetradecyl trimethyl ammonium chloride, cetyl pyridinium chloride.

Id. at 61–62. With respect to surfactant concentration, Mori states: “The concentration of the surfactant in the nucleic acid-solubilizing reagent is preferably from 0.1 to 20% by weight.” *Id.* at 62.

5. Overview of Farrell (*Exhibit 1026*)

Farrell is a laboratory guide describing the isolation and characterization of ribonucleic acids. Ex. 1026, Title. Farrell discloses that it was widely known that nucleases, which are enzymes that degrade nucleic acids, should be purged from solutions when trying to isolate RNA. *Id.* at 48–49. Farrell discloses that numerous compounds have been used to inhibit RNase activity including, vanadyl ribonucleoside complexes, RNasin, heparin, iodoacetate, polyvinyl (dextran) sulfate, cationic surfactant, macaloid and bentonite clays, and hydrogen peroxide.

Farrell further states that “stock solutions and buffers prepared in the laboratory can be treated, directly or indirectly, with the potent chemical RNase inhibitor DEPC” or diethylpyrocarbonate. *Id.* at 55. Farrell notes that “DEPC is an efficient, nonspecific inhibitor of RNase,” but “must be destroyed completely” since “[e]ven trace amounts of residual DEPC will result in chemical modification of the base adenine” and, thus, should not be added directly to cell suspensions or lysates containing RNAs to be purified. *Id.* at 55. Farrell discloses that there are additional “legitimate reasons” not to use DEPC in the laboratory and that making solutions with nuclease-free water is a more desirable alternative for solutions that isolate nucleic acids. *Id.* 57. In this respect, Farrell states:

A suitable alternative to DEPC treatment of water to render it nuclease-free is to simply buy nuclease-free water from one’s favorite vendor. For those laboratories affiliated with hospitals, it is interesting to note that water labeled “sterile water for irrigation,” is free of contaminants and is good for RNA work. Purified RNA may be rehydrated in this water and stored at -80°C . This water is also excellent for making dilutions of nuclease-free stock solutions.

Id.

6. *Overview of Das (Exhibit 1008)*

Das is directed to techniques for detecting *Mycobacterium Tuberculosis* in clinical samples using PCR amplification. Ex. 1008 ¶¶ 1, 29, 37–38. Das specifically discloses “methods of nucleic acid extraction and mix of reagents to lyse mycobacteria and purify nucleic acid from a clinical specimen.” *Id.* ¶ 38. Das discloses a modified lysis buffer to lyse the mycobacteria cells in a specimen sample and extract the nucleic acid, where the lysis buffer contains a chaotrope (guanidinium isothiocyanate), detergent

(N lauryl sarcosyl), reducing agent (2-mercaptoethanol), chelator (EDTA), and buffer (Tris). *Id.* ¶¶ 63–64, 89. Das discloses that “most proteins are denatured in this buffer leading to through lysis of the mycobacteria present in the specimens.” *Id.* ¶ 39. In one embodiment, Das obtains saliva samples from tuberculosis patients and using the modified lysis buffer to lyse the mycobacteria cells in the samples, extract the bacteria nucleic acid, and analyze the extracted DNA using PCR. *Id.* ¶¶ 83–85, 89–98. According to Das:

The modified lysis buffer . . . uses a strong chaotropic agent i.e guanidinium isothiocyanate. This helps to inactivate all mycobacteria present in a clinical specimen, lyse tough mycobacterial cell and denature and remove proteins thus results into cleaner preparation of DNA (Table 3) and also ensure safety for the operator. By heating specimen in modified lysis buffer even the toughest cells and objects like spores and baculovirus polyhedra are lysed easily.

Id. ¶ 38. Das further explains that the modified lysis buffer can “precipitate even minute amount[s] of DNA” and “results in clear DNA preparation with improved yield.” *Id.* ¶ 39.

7. Overview of Helftenbein (Exhibit 1019)

Helftenbeim discloses a vessel for withdrawing blood containing a defined volume of nucleic acid stabilizing solution comprising: a guanidinium salt (preferably guanidinium thiocyanate and/or guanidinium chloride); a buffer comprising, e.g., TRIS, HEPES, MOPS, citrate, or phosphate; a reducing agent (e.g., DTT, β -ME, or TCEP), and a detergent (e.g., Triton X-100, NP40- Tween 20, or polidocanol). Ex. 1019, 2:28–44, 3:4–48. In one embodiment, and equal amount of blood is drawn into the vessel and mixed with the stabilizing solution such that “[t]he nucleic acids

contained in the inflowing blood were immediately converted into a stable form.” *Id.* at 4:47–5:6 (Example 1).

According to Helftenbein, “[t]he nucleic acid-Stabilizing Substance may have added thereto an internal Standard. This permits the control of the whole method from the moment of sampling up to the detection of nucleic acids.” *Id.* at 2:60–63. Helftenbein illustrates this embodiment in Examples 6–8, which discloses adding naked MS2-RNA to the vessel as a positive control. *Id.* at 6:48–8:36, 8:64–9:5. Helftenbein states, for example, that

MS2-RNA is not stable in serum. Already 2 minutes after addition of RNA to the serum the RNA is completely degraded. By the addition of Stabilizing Solution to the Serum in the ratio of 1:1, this process can be stopped immediately, and a stabilization of the RNA can be achieved at the time when the stabilizing solution is added.

Id. at 7:1–6.

8. *Overview of Chirgwin (Exhibit 1015)*

Chirgwin discloses that disruption of cells “results in the rapid mixing of RNA and RNase. One way to eliminate nucleolytic denaturation of RNA is to denature all of the cellular proteins including RNase.” *Id.* at 5294. In this respect, “[t]he rate of denaturation is maximized by the combined use of a strong denaturant, guanidinium thiocyanate, in which both cation and anion are potent chaotropic agents (Jencks, 1969), and a reductant to break protein disulfide bonds which are essential for RNase activity (Sela et al., 1956).” *Id.*

Chirgwin describes a method for preparing “[i]ntact ribonucleic acid (RNA) . . . from tissues rich in ribonuclease such as rat pancreas by efficient homogenation in a 4 M solution of the potent protein denaturant

guanidinium thiocyanate plus 0.1 M 2-mercaptoethanol to break protein disulfide bonds.” Ex. 1015, Abstract. In particular, Chirgwin’s formulation contains: 4M guanidine thiocyanate, 0.1 M β -mercaptoethanol, 0.1% w/v Antifoam A, 25 mM sodium citrate, and 0.5% w/v of the detergent sodium N-lauroylsarcine (NLS). *Id.* at 5294–95.

Chirgwin further teaches that, after denaturation, the RNA may be “isolated free of protein by ethanol precipitation or by sedimentation through cesium chloride,” though “these steps can be varied according to the specific circumstances.” *Id.* Abstract, 5296. Chirgwin similarly notes that “for some cultured cells no homogenization is needed since the cells lyse upon addition of guanidine solution.” *Id.* at 5296

9. Overview of Wangh (Exhibit 1022)

Wangh discloses solutions and method for the preparation of nucleic acids to make them available for subsequent uses such as detection, modification or manipulation with or without amplification. Ex. 1022. 1:1–5. Wangh’s disclosed solutions include many of the same classes of reagents as disclosed by Birnboim, such as detergents, chaotropes, and reducing agents. *See id.* ¶¶ 11–20.

10. Overview of Koller (Exhibit 1016)

Koller discloses “methods and compositions for isolation of nucleic acids” Ex. 1016, code (57). Koller’s compositions include a chaotrope, a detergent, a reducing agent, and a salt. *Id.* at 7:1–3.

11. Overview of Birnboim2006

Birnboim2006 discloses compositions for extracting and preserving nucleic acids from degradation at room temperature. Ex. 1023, Field of the

Invention. Birnboim2006 discloses gathering a sample for nucleic acid isolation from the inside of a patient's cheek using a "buccal swab." *Id.* at 1023.

12. Overview of Casas (Exhibit 1052)

Casas discloses the simultaneous extraction of viral RNA and DNA from cerebrospinal fluid for use in a PCR assay. Ex. 1052, Title, Abstract, 26. Casas employed a formulation similar to Chirgwin's comprising 4M guanidine thiocyanate, 1 mM DTT, 25 mM sodium citrate, and 0.5% N-lauroylsarcine (NLS). Casas further added glycogen as a carrier and precipitated the isolated nucleic acid with isopropyl alcohol. *Id.* at 27.

13. Overview of Donofrio (Exhibit 1056)

Donofrio discloses the isolation and detection of influenza RNA from respiratory sequences using RT-PCR. Ex. 1056, Abstract. According to Donofrio, "[n]ine parts of denaturing solution containing 4 M guanidinium isothio-cyanate, 25 mM sodium citrate, 0.5% sarcosyl, and 0.1 M 2-mercaptoethanol was added directly to one part of frozen or unfrozen sample." *Id.* at 264. Donofrio then added yeast tRNA as a carrier, extracted the mixture with phenol, and precipitated the RNA with ethanol. *Id.*

14. Overview of Laulier (Exhibit 1060)

Citing Chirgwin, Laulier used a buffered solution of "4 M guandium-thiocyanate/2% N-lauroyl-sarcosine/50 mM Tris-HCl, pH7.4/50 mM EDTA/0.01% 2-mercaptoethanol," to preserve nucleic acids from "field collected samples of viruses, bacteria, yeasts, invertebrates and vertebrates." Ex. 1060, Abstract, 658. According to Laulier, "Proteins were removed by extraction, with saturated phenol, followed by chloroform-isoamyl alcohol (19/1) at 20-25 °C. Nucleic acids were precipitated by adding 1/10 volume

3 M sodium acetate, 2.5 volumes ethanol.” *Id.* at 658. “The DNA and RNA from samples kept up to 41 days without refrigeration in this way were suitable for PCR and reverse transcription PCR.” *Id.* Abstract.

15. *Overview of Zinkevich (Exhibit 1054)*

Zinkevich discloses the isolation of high molecular weight bacterial DNA using lysis buffer containing “5M guanidine isothiocyanate, 50mM Tris-HCl (pH 7.5), 10m M EDTA, 140 mM 2-mercaptoethanol, 2% of N-lauroylsarcosine.” Ex. 1054, Abstract, 30. Zinkevich further purified the DNA using a CsCl gradient prior to visualization by gel electrophoresis or PCR amplification. *Id.* at 30–33.

E. Alleged Anticipation of Claims 1, 4, 6, 8, 10–11, 16, 21–30, 32, and 35 over Birnboim

Petitioner relies on Birnboim to allege anticipation of claims 1, 4, 6, 8, 10–11, 16, 21–30, and 35. Pet. 7. Patent Owner opposes and disputes that Birnboim establishes every element of the challenged claims of the ’399 patent. AmPOR 17. For reasons that follow, we determine Petitioner has shown by a preponderance of the evidence that the challenged claims are anticipated by Birnboim under 35 U.S.C. § 102.

1. *Analysis of Birnboim as Applied to Challenged Independent Claim 1*

a. *“A stock solution of an aqueous composition”*

Claim 1’s preamble recites “a stock solution of an aqueous composition” Ex. 1003, 41:44. Petitioner contends that if the preamble of claim 1 were limiting, then Birnboim plainly discloses the limitation. Pet. 17.

“Whether to treat a preamble term as a claim limitation is determined on the facts of each case in light of the claim as a whole and the invention described in the patent.” *Am. Med. Sys., Inc. v. Biolitec, Inc.*, 618 F.3d 1354,

1358 (Fed. Cir. 2010) (internal quotation marks omitted). “Absent clear reliance on the preamble in the prosecution history, or in situations where it is necessary to provide antecedent basis for the body of the claim, the preamble generally is not limiting.” *Symantec Corp. v. Computer Assoc. Int’l, Inc.*, 522 F.3d 1279, 1288 (Fed. Cir. 2008) (internal quotation marks omitted). Furthermore, where “the body of the claim fully and intrinsically sets forth the complete invention, including all of its limitations, and the preamble offers no distinct definition of any of the claimed invention's limitations, but rather merely states, for example, the purpose or intended use of the invention, then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation.” *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999). Yet, when the limitations in the body of the claim rely upon or derive essential structure from the preamble, then the preamble acts as a necessary component of the claimed invention and is limiting. *See Eaton Corp. v. Rockwell Int’l Corp.*, 323 F.3d 1332, 1339 (Fed. Cir. 2003).

Patent Owner disputes Petitioner’s contention that Birnboim discloses a stock solution of an aqueous composition. Nonetheless, the burden remains on Petitioner to demonstrate unpatentability. *See Dynamic Drinkware*, 800 F.3d at 1378.

Based on the entirety of the trial record, which shows that the Birnboim discloses a “stock solution of an aqueous composition,” we determine Petitioner has shown that Birnboim meets the preamble to the extent it is limiting.

b. “a chaotrope, a detergent, a reducing agent, a chelator, and buffer”

Claim 1 recites “A stock solution of an aqueous composition comprising: a chaotrope, a detergent, a reducing agent, a chelator, and a buffer” Ex. 1003, 41:44–46.

Petitioner contends Birnboim teaches this limitation by disclosing “stock solutions with the same components in the same amounts claimed by the ’399 patent to achieve the same claimed purpose.” Pet. 12.

Petitioner argues that Birnboim discloses denaturing agents that “lyse cells, denature proteins, and inactivate nucleases.” In addition to providing antimicrobial properties. Pet. 13 (citing Ex. 1003 ¶¶ 41, 64, 68, 84). According to Petitioner, the ’399 patent discloses these same reagents disclosed by Birnboim under the labels chaotrope or detergent. *Id.* Petitioner points out that Birnboim, in its illustrative examples, discloses the same specific reagents present in the claims of the ’399 patent. *Id.* For example, Birnboim discloses urea, sodium dodecyl sulfate and guanidinium thiocyanate as denaturing agents, which the ’399 patent claims as a chaotrope, a detergent, and a chaotrope respectively. *Compare* Ex. 1003 ¶¶ 20, 68, *with* Ex. 1001, 4:44–47; 31:65–66, 32:24–25; Ex. 1003 ¶ 115. Additionally, Petitioner argues Birnboim discloses reducing agents, chelating agents, and buffers. Pet. 14.

As Petitioner points out, Birnboim teaches that its compositions stabilize nucleic acids and inhibit nucleases and microbial growth. Pet. 10 (citing Ex. 1003 ¶ 64). Birnboim teaches that its compositions contain (1) denaturing agents to lyse cells, denature proteins, inactivate nucleases, and inhibit microbial growth (*id.* (citing, e.g., Ex. 1003 ¶¶ 64, 68, 73, 84)); (2) reducing agents to prevent nucleic acid degradation (*id.* at 11

(citing Ex. 1003 ¶¶ 13, 14, 70–72)); (3) chelating agents to stabilize nucleic acids and inhibit microbial growth (*id.* (citing Ex. 1003 ¶¶ 64, 67, 68, 73)); and (4) buffers to maintain an appropriate pH to prevent nucleic acid degradation (*id.* (citing Ex. 1003 ¶ 64)). *See id.* at 17 (summarizing reagents and their functions in Birnboim’s compositions). Patent Owner does not dispute, and we agree with Petitioner, that these well-known reagents perform well-understood functions. *See* Ex. 1003 ¶¶ 64–74; *see generally* AmPOR.

Based on the explicit disclosure of Birnboim, we find it discloses a stock solution comprising a chaotrope, a detergent, a chelating act, a reducing agent and a buffer to be adequate for institution. Additionally, we note that Das (Ex. 1008 ¶¶ 38–39, 89), Goldrick (Ex. 1009, 1:39–54, 7:30–8:54), Farrell (Ex. 1026, 58, 59), and Koller (Ex. 1016, 7:1–5, 7:19–25, 8:8–15) demonstrate the wide-spread and well-known nature of the combination of reagents specified in claim 1 of the ’399 patent.

Accordingly, we determine Petitioner has shown by a preponderance of the evidence that Birnboim discloses the challenged claim limitations of a stock solution containing the aforementioned reagents as required by challenged claim 1.

- c. *“wherein the stock composition, when diluted with a sample containing nucleic acids, nucleases and proteins, denatures the proteins of the sample, inactivates the nucleases of the sample, kills pathogens that may be present in the sample, and does not degrade the nucleic acids of the sample”*

Claim 1 recites “wherein the stock composition, when diluted with a sample containing nucleic acids, nucleases and proteins, denatures the proteins of the sample, inactivates the nucleases of the sample, kills pathogens

that may be present in the sample, and does not degrade the nucleic acids of the sample.” Ex. 1003, 4:44–50.

i. “denatures the proteins of the sample”

Petitioner contends Birnboim anticipates this limitation because Birnboim’s disclosed denaturing agents that denature proteins. Pet. 21 (citing Ex. 1002 ¶ 107). Specifically, Petitioner argues that Birnboim discloses creating a balance between the concentration of denaturing agents that will inhibit DNases/RNases and those that will inhibit proteolytic enzymes that are needed to the purification of nucleic acids. *Id.* (citing Ex. 1003 ¶ 69 (“Thus, a balance must be struck between the concentration of denaturing agents that will . . . denature other proteins in saliva”).

Patent Owner does not address this limitation directly. *See generally* AMPOR. Nonetheless, the burden remains on Petitioner to demonstrate unpatentability. *See Dynamic Drinkware*, 800 F.3d at 1378.

We have considered carefully all Petitioner’s citation (specifically Ex. 1003 ¶ 69) and we agree with Petitioner’s analysis and we credit Dr. Taylor’s testimony supporting Petitioner’s position. In sum, based on this record, we find Petitioner has shown by a preponderance of the evidence that Birnboim discloses “denatures the proteins of the sample.”

ii. “inactivates the nucleases of the sample”

Petitioner contends Birnboim anticipates this limitation because Birnboim’s discloses inactivate nucleases. Pet. 21. Specifically, Petitioner

argues that Birnboim discloses protecting nucleic acid from “breakdown” by nucleases. *Id.* at 35 (citing Ex. 1003 ¶ 68). We agree with Petitioner.

Under our construction, the term “inactivate nucleases” means inactivating RNase or DNase. *See supra* Section II.C.3. The parties do not dispute that Birnboim discloses inactivating DNase. *See* Ex. 1003 ¶ 68 (teaching that strong chelators and denaturing agents inactivate DNases). For this reason alone, Birnboim discloses “inactivate nucleases.” Moreover, Birnboim explicitly teaches that its composition may “include[] an inhibitor of ribonuclease.” *Id.* ¶ 22. According to Birnboim, “[t]he inclusion of an inhibitor of ribonuclease in the composition of the invention is particularly desirable when the nucleic acid to be preserved is RNA, desirably mRNA, or when the nucleic acid to be preserved is from a virus or a bacterium.” *Id.* Birnboim explains that the activity of DNases and RNases “can also be inhibited by denaturing agents that will destroy the complex structures of these enzymes (proteins).” *Id.* ¶ 68. Thus, Birnboim discloses including denaturing agents, such as urea, SDS, guanidinium chloride, and guanidinium thiocyanate, in “the nucleic acid preserving composition” of its invention. *Id.*

Patent Owner contends that, in an unrelated district-court proceeding, Petitioner admitted that Birnboim is not enabled for inactivating RNases to preserve RNA. AmPOR 26–27 (citing Ex. 2033 ¶¶ 22, 26). Petitioner counters that the statements Patent Owner relies on were “made by the **assignee** of the Birnboim reference.” Reply 9 (citing Ex. 2013 ¶¶ 85, 122, 123, 131). It is our opinion, Petitioner embraced those statements to support an argument that patents having the same specification as Birnboim were prosecuted in bad faith. *See, e.g.,* Ex. 2013 ¶¶ 75, 133–141, 155. Petitioner’s

arguments and reliance on these statements is not dispositive as to what Birnboim discloses to the skilled artisan. Thus, despite Petitioner embracing those statements, as explained below, we find Birnboim, when understood in the context of the prior art as whole, discloses inactivating RNases to preserve RNA. In this case, other prior art of record show that the reagents taught in Birnboim inactivate RNases. Indeed, Birnboim specifically discloses denaturing agents, including guanidinium chloride and guanidinium thiocyanate, can inhibit RNase activity. Ex. 1003 ¶ 68. As discussed below, denaturing agents such guanidinium chloride and guanidinium thiocyanate were known to inactive RNases.

Farrell lists reagents “commonly used to minimize or eliminate RNase activity.” Ex. 1026, 58. According to Farrell, “[f]or cells enriched in RNase, and even those that are not, homogenization in lysis buffers consisting of guanidinium thiocyanate or guanidinium hydrochloride is widely accepted as the method of choice.” *Id.* Farrell teaches that “[a]t a working concentration of about 4 to 6 M (in water),” guanidinium hydrochloride is “an excellent inhibitor of RNase activity during purification of nucleic acids.” *Id.* at 59. Farrell further teaches that guanidinium thiocyanate, as “a stronger protein denaturant than guanidine hydrochloride,” “is the denaturant of choice for the preparation of RNA from sources enriched in RNase activity, especially pancreatic tissue (Chirgwin *et al.*, 1979).” *Id.* Farrell states that guanidinium thiocyanate “routinely used at a working concentration of 4 M in water and appears repeatedly in the literature and in various commercial formulations, usually along with a reducing agent (e.g., β -mercaptoethanol [β -ME]) and an ionic detergent (e.g., sarkosyl [N-laurylsarcosine]).” *Id.*; *see also* Ex. 1004, 189 (teaching making 4 M

guanidinium isothiocyanate to inactivate RNase); Ex. 1015, 5294, 5298 (teaching preparing intact RNA “from tissues rich in ribonucleases such as the rat pancreas by efficient homogenization in a 4 M solution of the potent protein denaturant guanidinium thiocyanate plus 0.1 M 2-mercaptoethanol”). Thus, we find that Birnboim discloses inactivating, not only DNases, but also RNases.

Patent Owner argues that “Birnboim’s Example 3 composition does not deactivate RNases.” AmPOR 26. As support, Patent Owner relies on ABL testing data, allegedly showing “a solution prepared according to Birnboim’s Example 3 allows RNA in a sample to fully degrade within hours, demonstrating that the RNases in the sample were not effectively deactivated.” *Id.* at 27 (citing Ex. 2016 ¶ 26; Ex. 2033 ¶¶ 24–26).

Relying on Dr. Taylor’s testimony, Petitioner contends “PO’s results are unsurprising as its testing artificially spiked the RNase activity in the test samples to over 30,000 times that ordinarily found in saliva.” Reply 10 (citing Ex. 1071 ¶ 35; Ex. 1073, 70:20–72:4; Ex. 1201; Ex. 1206; Ex. 1208, 207). We credit Dr. Taylor’s testimony that ABL tested RNase “many thousands fold higher than the appropriate amount” because it is supported by the cited evidence. *See* Ex. 1071 ¶ 35 (citing Exs. 1075, 1208).

Patent Owner does not squarely address this issue in its Sur-reply. While making another argument, however, Patent Owner does contend that “inactivation [of RNase] turns on the number of RNA molecules.” Sur-reply 3. This argument supports Petitioner’s position that Patent Owner’s testing data are unreliable because ABL tested an artificially high number of RNases. *See* Reply 9; *see also* Ex. 1071 ¶ 35 (Dr. Taylor testifying “it is not possible to conclude that Assured Bio’s RNase inactivation experimental

design would provide any reliable experimental evidence of Birnboim's solution not being capable of inactivating RNases or preventing degradation of RNA in a sample containing saliva"). Thus, we find Patent Owner's results on the inhibition of RNase activity to have limited probative value.

Furthermore, Dr. DeFilippi's testimony supports our finding that Birnboim teaches inactivating RNases. Indeed, pointing to the claim language "sufficient to denature proteins," Dr. DeFilippi testified: "So I'm denaturing proteins in general. And included in that would be inactivation of the nucleases." Ex. 1064, 525:1–4; *see also id.* at 525:15–20 ("We are denaturing proteins, and the result of denaturing proteins would be destroying the activity of enzymes."); Ex. 2020, 239:21–240:14. Specifically, Dr. DeFilippi testified that "I would not suspect that one DNase or RNase in particular would be denatured relative to the other one not being denatured because we're denaturing proteins." *Id.* at 523:14–17.

In sum, based on this record, we find Petitioner has shown by a preponderance of the evidence that Birnboim discloses "inactivate nucleases."

iii. "kills pathogens that may be present in the sample"

Petitioner asserts that Birnboim's compositions inhibit and kill microbes in the sample. Pet. 20–21, 22, 37 (citing Ex. 1003 ¶¶ 21, 64, 73). Patent Owner counters that "Applying the Correct Claim Construction, Birnboim Does Not Teach 'Kills Pathogens.'" AmPOR 18. As support, Patent Owner submits data from tests conducted by ABL of compositions prepared according to Birnboim Example 3. *Id.* at 19–20. Patent Owner asserts that "[t]esting showed that Birnboim's composition failed to kill both viral (MS2) and bacterial (*B. subtilis*) pathogen organisms in a sample." *Id.*

Thus, Patent Owner concludes “Birnboim’s compound did not render a sample substantially non-pathogenic.” *Id.* (citing Ex. 2033 ¶¶ 11-12, 24–26). We disagree with Patent Owner’s conclusions and analysis.

We explained in our Decision on Institution that “Birnboim expressly discloses isolating nucleic acid from bacteria and viruses.” DI 19 (citing Ex. 1003 ¶¶ 18, 22, 27, 30). It does not “suggest such isolation is non-destructive, and we presume that at least some pathogens are ‘killed’ in the extraction process according to the plain and ordinary meaning of the term.” *Id.* In other words, Birnboim’s instruction to isolate nucleic acid “from a bacterium or a virus that is residing in the buccal, nasal, or respiratory passages of the subject” would kill the bacterium or the virus. *See* Ex. 1003 ¶ 27. Consistent with our interpretation, Birnboim further teaches that its compositions may be “bactericidal,” i.e., capable of killing bacteria. Ex. 1003 ¶ 21. Thus, Birnboim discloses that its compositions “kill[] pathogens.”

Additional evidence of record supports our determination. Indeed, ABL test data initially withheld by Patent Owner [REDACTED]
[REDACTED]
[REDACTED]. Ex. 1202–1204; Ex. 1069, 272:13–173:7; Ex. 1071 ¶¶ 15–23.

Patent Owner downplays these data. AmPOR 19 (“Even if Petitioner could show that Birnboim teaches a compound that would lyse some small subset of individual pathogen cells from a sample, that is a far cry from, and nothing in Birnboim teaches, rendering a sample substantially non-pathogenic.”). Instead, it emphasizes other ABL test data showing

Birnboim's compositions do not kill MS2 and *B. subtilis*. *Id.* at 19–20 (citing Ex. 2033 ¶¶ 12, 24–26); Sur-reply 5 (citing Ex. 2019).

As a preliminary matter, we note MS2 is a bacteriophage. Ex. 2019, 1. Other than ABL stating MS2 is “commonly used as a surrogate for human pathogenic virus” (*id.*), Patent Owner does not directly address whether MS2 is the type of pathogens contemplated in the Specification. In addition, ABL apparently included spores in its testing of *B. subtilis*. As explained above, under our construction, “kill pathogens” does not encompass the killing or inactivation of spores. *See supra* Section II.C.2. Thus, ABL's data on these two microorganisms have limited probative value in our analysis.

Nonetheless, taking Patent Owner's assertion that “Birnboim's composition failed to kill both viral (MS2) and bacterial (*B. subtilis*) pathogen organisms in a sample” at its face value, we reject its conclusion that “Birnboim does not teach killing pathogens.” *See* AmPOR 17–18. Indeed, as explained above, “kill pathogens” does not require that every pathogen in sample is killed. Instead, it merely requires killing or inactivating some fungal, viral, or vegetative bacterial pathogens in a sample. *See supra* Section II.C.2. [REDACTED]

[REDACTED]

[REDACTED]

Accordingly, based on the record before us, we determine that Petitioner has shown by a preponderance of the evidence that Birnboim discloses the claim limitation of “kills of pathogens.”

iv. “does not degrade the nucleic acids in the sample”

Petitioner contends Birnboim discloses this limitation because its compositions “preserve sufficient quantities of nucleic acids for subsequent

analysis.” Pet. 14, 21, 32–33 (citing Ex. 1003 ¶¶ 88, 116–121). Petitioner notes that Birnboim’s Examples 4–6, when using the solution of Example 3, successfully preserved and stabilized the DNA in saliva samples at room temperature for up to 62 days. *Id.* at 15 (citing Ex. 1003 ¶¶ 114–122). Patent Owner, however, contends that nothing in Birnboim teaches this limitation because its compositions do not preserve RNA and only preserve 50% of the DNA in a sample. AmPOR 22. Based on the entire record, we agree with Petitioner’s position.

Birnboim is directed to isolating nucleic acids from a sample and stabilizing the isolated nucleic acids for future analysis. *See* Ex. 1003 ¶¶ 11, 22, 27, 64, 114–122. Birnboim defines “stable” as meaning “that at least about 50% of the initial amount of high molecular weight nucleic acid (DNA, RNA, mRNA, or viral RNA) contained in a sample is still present after storing the sample at ambient temperature (i.e., 20° C. to 25° C.) for the specified time period.” *Id.* ¶ 45; *see also id.* ¶ 2 (teaching its compositions are “for preserving nucleic acids at room temperature for extended periods of time”); ¶ 25 (teaching that, in one embodiment, the isolated DNA is stable “for more than 14 days, desirably more than 30 days, and more desirably more than 60 days,” and in another embodiment, when its composition does not contain ascorbic acid, a specific reducing agent, “the DNA is stable for more than 60 days, and desirably more than 360 days”).

As explained above, the ’399 patent does not define the lower limit of the nucleic acid that must be preserved to be encompassed by “not degrade nucleic acid.” *See supra* Section II.C.4 (citing Ex. 1001, 10:1–2 (stating preserving “at least about 70%” polynucleotides is “desirable”). Instead, the term “not degrade nucleic acid” means preserving sufficient RNA or DNA

for analysis using conventional nucleic acid detection methods known to an ordinarily skilled artisan at the time of the invention. *Id.* Under our construction, Birnboim's compositions satisfy this limitation.

Indeed, Birnboim discloses isolating nucleic acids “for any application requiring a nucleic acid sample,” including, for example, “forensic applications, medical applications (including genetic screening and disease typing), and paternity testing.” Ex. 1003 ¶ 88. In addition, as Petitioner correctly points out, “Birnboim Examples 4–6 establish that the DNA is successfully stabilized and preserved sufficiently to analyze the DNA via gel electrophoresis (Example 4) and via PCR (Examples 5 and 6).” Pet. 15 (citing Ex. 1003 ¶¶ 116–122). Thus, we determine that Birnboim's compositions do “not degrade nucleic acid” beyond the extent allowed by the challenged claims.

Patent Owner counters that Birnboim's Example 3 includes NaOAc (sodium acetate) and LiCl (lithium chloride) in the composition.²⁹ AmPOR 25. Patent Owner argues that these ingredients, not recited in challenged claim 1, are responsible for the preservation of DNA. *Id.* We do not agree.

As a preliminary matter, we note that Petitioner relies on not only Example 3, but also the general teachings of Birnboim and its “series of examples” including Examples 4–6. *See* Pet. 14–15 (citing Ex. 1003 ¶¶ 107–130). And the general teachings of Birnboim do not suggest either NaOAc or LiCl must be present in the composition.

²⁹ Claim 1 is directed to an aqueous composition “comprising” five categories of reagents. Because of the open-ended transition phrase “comprising,” the claimed composition includes the listed reagents but does not exclude others.

Nonetheless, in our Decision to Institute, we explained that an ordinarily skilled artisan would have understood the roles of NaOAc and LiCl. DI 23. Patent Owner argues that is not true. AmPOR 25. According to Patent Owner, the parties' experts propose competing hypotheses of why Birnboim includes LiCl and NaOAc. *Id.* at 25–26 (citing Ex. 2001 ¶ 39; Ex. 2020, 201:1–2, 201:21–203:2). We disagree.

NaOAc and LiCl are salts frequently used in the art, often in the context of promoting nucleic acid precipitation from aqueous samples. *See, e.g.*, Ex. 1004, 192 (using NaOAc to wash/precipitate nucleic acids); Ex. 1009, 1:66–68 (same); Ex. 1013, 4.3.1 (“separation of RNA from DNA and other impurities by selective precipitation using [2M and 8M] LiCl”), 4.5.2 (0.15 M LiCl as a wash buffer component, precipitating “RNA by adjusting the salt concentration to 0.3M sodium acetate”); Ex. 1018, 15:55–67 (discussing commercial RNA extraction kits comprising LiCl in combination with guanidine or urea).

In Birnboim's Example 3, the formulation with NaOAc “stabilizes DNA for *longer periods of time*” than the formulation with LiCl. Ex. 1003 ¶ 115 (emphasis added). That result, however, does not mean a formulation without NaOAc does not sufficiently stabilize sufficient DNA “for analysis using conventional nucleic acid detection methods known to an ordinarily skilled artisan at the time of the invention,” which is all that is required to satisfy the limitation of “not degrade nucleic acid.” *See supra* Section II.C.4. In addition, Koller teaches nucleic acid releasing compositions comprising “a chaotropic agent, salt, detergent, and reducing agent.” Ex. 1016, 7:1–3. Koller explains that salt is “at a concentration effective to aid in the dissociation, purification and eventual dissolution of the isolated nucleic

acids.” *Id.* at 8:27–29. The type of salt included in the composition, Koller continues, “is not critical.” *Id.* at 8:33–34; *see also id.* at 8:35–9:2 (“For example[,] sodium chloride, sodium acetate, potassium acetate, ammonium acetate or other derivatives thereof, would suffice, however, optimum results are obtained with either sodium chloride or sodium acetate.”). Patent Owner does not present sufficient evidence or otherwise explain adequately how NaOAc and LiCl might be responsible for preserving DNA.

In sum, we find Petitioner has met its burden in showing that the ingredients recited in claim 1, as taught in Birnboim, do “not degrade nucleic acid.”

d. Summary regarding Analysis of Birnboim as Applied to Challenged Independent Claim 1

We have considered carefully all arguments and supporting evidence in light of the limitations recited in challenged independent claim 1. As discussed above, we determine Petitioner has shown by a preponderance of the evidence that Birnboim discloses each claim limitation of claim 1, thereby rendering claim 1 anticipated under 35 U.S.C § 102.

2. Analysis of Birnboim as Applied to Challenged Dependent Claim 4.

Claim 4 depends from claim 1, and further recites the concentration ranges for the five ingredient categories (chaotrope, detergent, reducing agent, chelator, and buffer). Petitioner argues that Birnboim Example 3 teaches “a specific composition with a chaotrope, detergent, reducing agent, and buffer in amounts that fall within the claimed ranges.” Pet. 23–24 (comparing the ranges recited in claim 4 with the amounts taught in Birnboim) (citing Ex. 1003 ¶ 115). Acknowledging that “the concentration of the chelator (CDTA) in Birnboim’s Example 3, at 3.3mM, is higher than the range in claim 2 (0.01-1mM),” Petitioner refers to Birnboim’s teaching

elsewhere that for CDTA, “concentrations in the 1–20 mM range are sufficient” and “other concentrations would work.” *Id.* at 24 (citing Ex. 1003 ¶ 67). Thus, Petitioner contends that “the chelator concentration disclosed in Birnboim, like the concentrations for the chaotrope, detergent, reducing agent, and buffer, all satisfy the concentration limitations in claim 4.” *Id.* (citing Ex. 1002 ¶ 114).

Patent Owner counters that “Birnboim provides no suggestion to reduce the concentration of CDTA by more than two-thirds.” AmPOR 28 (citing Ex. 2033 ¶ 33). We disagree.

Birnboim teaches that

The amount or concentration of chelator will depend upon the strength of the chelator, which would need to be determined empirically. For CDTA, concentrations in the 1–20 mM range are sufficient, however other concentrations would work, and the compositions of the invention are not intending to be limited to this range.

Ex. 1003 ¶ 67. CDTA is the chelator in Example 3. *Id.* ¶ 115. Thus, contrary to Patent Owner’s assertion, Birnboim does explicitly disclose using CDTA at the concentration of 1–20 mM because it overlaps with the “about 0.01 mM to about 1 mM” range recited in claim 4.

In cases involving overlapping ranges, the Federal Circuit has “consistently held that even a slight overlap in range establishes a *prima facie* case of obviousness.” *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003); *see also In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997) (concluding a prior art reference that teaches the range 100–600 Å renders obvious a claimed invention with the range 50–100 Å); *In re Woodruff*, 919 F.2d 1575, 1578 (CCPA 1990) (concluding a prior art reference that

teaches the range “about 1–5%” renders obvious a claimed invention with the range “more than 5% to about 25%”).

A prior art reference that discloses an overlapping but different range than the claimed range can be anticipatory, even where the prior art range only partially or slightly overlaps with the claimed range. *See Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1222, 1338 (Fed. Cir. 2020) (citing *Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 870–71 (Fed. Cir. 2015) (affirming summary judgment of anticipation of patent claims for composition with “0.05 to 0.5% by weight of at least one saturated fatty acid amide” lubricant in view of a prior art reference disclosing the same class of lubricant in an overlapping range of “0.1 to 5 parts by weight,” and the parties agreed that a measurement in “% by weight” was equivalent to one in “parts by weight”)). Patent Owner cites to *Genentech* (AmPOR 29) but fails to either (1) distinguish its holding regarding overlapping ranges and (2) demonstrate the criticality of the claimed range in the ’399 patent as required by the court in *Genentech, Inc.*, 946 F.3d at 1338 (holding that “[o]nce the patent challenger has established, through overlapping ranges, its prima facie case of anticipation, ‘the court must evaluate whether the patentee has established that the claimed range is critical to the operability of the claimed invention.’”); *see also E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1008 (Fed. Cir. 2018) (“‘where there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence’ of . . . criticality”) (quoting *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013)).

Given that Birnboim discloses CDTA at the concentration of 1–20 mM, which overlaps with the claimed range of 0.01–1 mM (Ex. 1003 ¶ 67), we find that Petitioner demonstrates by a preponderance of the evidence that Birnboim discloses all limitations of claim 4

3. Analysis of Birnboim as Applied to Challenged Dependent Claims 6, 8, 10–11, 21–30, 32, and 35

Petitioner contends dependent claims 6, 8, 10–11, 21–30, 32 and 35 of the '399 patent are unpatentable as anticipated under 35 U.S.C. § 102 in view of Birnboim and provides specific arguments for each claim. Pet. 26–27, 28–36 (citing Ex.1002 ¶¶118–127, 135–173). Patent Owner does not address the additional limitations of the dependent claims in its Response. Thus, we agree with Petitioner (Reply 5) that Patent Owner has waived any argument for these challenged dependent claims. *See In re NuVasive, Inc.*, 842 F.3d 1376, 1380–1381 (Fed. Cir. 2016) (holding party waived arguments on issues not raised in its response after institution). Nonetheless, the burden remains on Petitioner to demonstrate unpatentability. *See Dynamic Drinkware*, 800 F.3d at 1378.

We have considered carefully all arguments and supporting evidence in light of the limitations recited in challenged dependent claims 6, 8, 10–11, 16, 21–30, 32 and 35. Based on the entire trial record, we agree with Petitioner's analysis and we credit Dr. Taylor's testimony supporting Petitioner's position. Accordingly, we conclude Petitioner has demonstrated by a preponderance of the evidence that the challenged dependent claims are anticipated under 35 U.S.C. § 102 in view of Birnboim.

4. Analysis of Birnboim as Applied to Challenged Dependent Claim 16.

Claim 16 depends from claim 1 and recites a population of isolated polynucleotides that comprises RNA, DNA, or a combination thereof.

Petitioner contends dependent claim 16 of the '399 patent is unpatentable as anticipated under 35 U.S.C. § 102 in view of Birnboim and provides specific arguments for each claim. Pet. 27–28. Petitioner specifically construes “a population of isolated polynucleotides” to be a component of the “sample” of claim 1 as opposed to the “stock solution” recited in claim 1. *Id.* at 27 (citing Ex. 1001, 6:28–31 (“Preferably, the collected samples will include one or more populations of nucleic acids that are isolated from a biological sample, specimen, or source, including, for example, RNAs and DNAs.”))).

Petitioner relies on Birnboim’s disclosure regarding “obtaining sputum from a subject, and contacting the sputum with a composition of the invention, thus preserving the nucleic acid” that is then mixed with the nucleic acid-preserving solution of Birnboim’s Example 3. *Id.* at 28 (citing Ex. 1003 ¶¶ 24, 115). Petitioner notes that Birnboim discloses stock solutions that isolate a population of polynucleotides from samples, including sputum samples. *Id.* (citing Ex. 1003, code (57) (“The invention extends to methods of using the compositions of the invention to preserve and isolate nucleic acids from saliva as well as to containers for the compositions of the invention.”); ¶ 88 (“The methods of the present invention can be used to isolate nucleic acids from sputum for any application requiring a nucleic acid sample.”)). Petitioner further relies on Birnboim’s Examples 4-6, which Petitioner argues “confirm that the stock solution of Birnboim’s Example 3 comprises a population of isolated polynucleotides when diluted with a saliva sample because DNA obtained from the samples was successfully detected via electrophoresis and PCR.” *Id.* (citing Ex. 1003 ¶¶ 114–122; Ex. 1002 ¶¶ 128–32).

Patent Owner counters that Petitioner’s argument is inconsistent with the claim language, which states the *stock solution* of claim 1, further comprising a population of isolated polynucleotides. AmPOR 30. According to Patent Owner, “the population of isolated polynucleotides is part of the stock solution, not the sample (which appears nowhere in claim 16).” *Id.* Patent Owner argues that Petitioner’s argument is also inconsistent with its own claim construction of “stock solution” as “a formulated supply of solution for future use.” *Id.* (citing Pet. 8). Patent Owner contends that Birnboim teach or suggest inclusion of saliva in a “stock solution.” *Id.* (citing Ex. 2033 ¶ 49).

Patent Owner further contends that a person of ordinary skill in the art would not have understood saliva to comprise “a population of isolated polynucleotides” because polynucleotides in saliva are not isolated. *Id.* at 30–31 (citing Ex. 2033 ¶ 50). Patent Owner then notes that, “as Petitioner explains, Birnboim discloses method to extract polynucleotides from saliva.” *Id.* at 31 (citing Pet. 29; Ex. 1003 ¶¶ 107–122).

We agree with Patent Owner. The plain language of claim 16 requires that the population of isolated polynucleotides be part of the stock solution and not the sample. Accordingly, we conclude Petitioner has failed to show by a preponderance of the evidence that challenged dependent claim 16 is anticipated under 35 U.S.C. § 102 in view of Birnboim. We, nevertheless, find for Petitioner for the reasons set forth in our Decision on Sanctions.

5. Conclusion Regard Alleged Anticipation of Claims 1, 2, 4–8, 10–14, 16, 21–30, 32, 35 by Birnboim

For reasons that follow, we determine Petitioner has shown by a preponderance of the evidence that the challenged claims 1, 2, 4–8, 10–14, 21–30, 32, 35 are anticipated by Birnboim under 35 U.S.C. § 102. We also

determine Petitioner has not shown by a preponderance of the evidence that challenged dependent claim 16 is anticipated by Birnboim under 35 U.S.C. § 102. We, nevertheless, find for Petitioner for the reasons set forth in our Decision on Sanctions.

F. Alleged Obviousness of Claims 1, 2, 4–8, 10–14, 16, 21–30, 31, 32, 35 over Birnboim

Petitioner relies on teachings of Birnboim to allege claims 1, 2, 4–8, 10–14, 16, 21–30, 31, 32, 35 of the '399 patent are unpatentable under 35 U.S.C. § 103 in view of Birnboim. *See* Pet. 36–46. Patent Owner opposes and argues that Petitioner fails to show on what basis any missing elements of claim 1 can be found in Birnboim. Prelim. Resp. 33.

For reasons that follow, we determine Petitioner has shown by a preponderance of the evidence that the challenged claims 1, 2, 4–8, 10–14, 21–30, 32, 35 would have been obvious in view of Birnboim under 35 U.S.C. § 103. We also determine Petitioner has not shown by a preponderance of the evidence that challenged dependent claim 16 would have been obvious in view of Birnboim under 35 U.S.C. § 103. We, nevertheless, find for Petitioner for the reasons set forth in our Decision on Sanctions.

1. Analysis of Birnboim as Applied to Challenged Independent Claim 1

Petitioner contends that both the '399 patent and Birnboim: (1) are in the same field of endeavor; (2) have the same objective; (3) accomplish their objective through performing the same several basic functions; (4) employ a combination of the same well known-reagents; (5) use those reagents in accordance with their well understood functions to achieve the desired objective; and (6) achieve the same result. Pet. 38. Therefore, according to

Petitioner the '399 patent uses a combination of familiar elements according to known methods and would have been obvious as it yields predictable results. *Id.* (citing KSR, 550 U.S. at 401).

Patent Owner does not address Petitioner's arguments directed toward specific claims, but argues that Petitioner fails to provide proper analysis as to why the '399 patent would have been obvious in light of Birnboim.

AmPOR 32. Instead, according to Patent Owner, Petitioner simply assumes the '399 patent is anticipated by Birnboim and fails to analyze "whether, how, or on what basis the functional limitations common to all claims but missing from Birnboim can be filled in through any combination or a single-reference obviousness analysis, and does not rely on any other reference in its combinations for these functions." *Id.*

Patent Owner further argues that (1) Petitioner fails to establish that a person of ordinary skill in the art at the critical time would have been aware of "Chaotropes" in the context of Birnboim Example 3 (*id.* at 34–36), (2) Dr. Taylor's conclusory opinions regarding motivation and reasonable expectation of success are entitled to no weight (*id.* at 32–34), and (3) modifying Birnboim Example 3 is "experimentation" with no reasonable expectation of success (*id.* at 36–37). We address each of these issues in turn.

a. Chaotropes

As Petitioner points out, Birnboim teaches that its compositions stabilize nucleic acids and inhibit nucleases and microbial growth. Pet. 13 (citing Ex. 1003 ¶ 64). Birnboim teaches that its compositions contain (1) denaturing agents to lyse cells, denature proteins, inactivate nucleases, and inhibit microbial growth (*id.* (citing, e.g., Ex. 1003 ¶¶ 64, 68, 73, 84)); (2) reducing agents to prevent nucleic acid degradation (*id.* at 11

(citing Ex. 1003 ¶¶ 13, 14, 70–72)); (3) chelating agents to stabilize nucleic acids and inhibit microbial growth (*id.* (citing Ex. 1003 ¶¶ 64, 67, 68, 73)); and (4) buffers to maintain an appropriate pH to prevent nucleic acid degradation (*id.* (citing Ex. 1003 ¶ 64)). *See id.* at 6, 13–14 (summarizing reagents and their functions in Birnboim’s compositions). Patent Owner does not dispute, and we agree with Petitioner, that these well-known reagents perform well-understood functions. *See* Ex. 1003 ¶¶ 64–74.

Birnboim’s Example 3 teaches a composition comprising urea, which is a chaotrope, and SDS, which is a detergent. Ex. 1003 ¶ 115. Patent Owner contends that the Petitioner oversimplifies Birnboim, because Birnboim uses the term “denaturing agent” differently in different sections of its disclosure and uses the term extremely broadly to mean any substance that “alters the natural state of that to which it was added.” AmPOR 34 (citing Ex. 1003 ¶ 41). According to Patent Owner, Birnboim ultimately provides examples of denaturing agents that include “urea, soluble salts of dodecyl sulfate and other strong detergents, guanidinium chloride, guanidinium thiocyanate, soluble salts of perchlorate, alcohols, such as ethanol, above 10%,” and states that the denaturing agents may be used alone or in combination. *Id.* (citing Ex. 1003 ¶ 68).

Patent Owner further contends that Birnboim neither teaches the use of chaotropes and detergents as individual and separate components, nor which denaturing agents should be used in combination with one another. *Id.* at 35 (citing Ex.2033 ¶ 27). Patent Owner argues that a person of ordinary skill in the art would have “no idea how to cobble together the Birnboim disclosure to arrive at the claimed composition in view of the Birnboim disclosure.” *Id.* (citing Ex.2033 ¶ 27).

We do not agree with Patent Owner that an ordinarily skilled artisan would not have been aware of or had a reason to select both a chaotrope and a detergent (as shown in Birnboim Example 3), or to modify Birnboim's Example 3 to use other chaotropes or detergents. Rather, we determine that ordinarily skilled artisan would have understood the individual properties and uses of, as well as relevant differences between, a chaotrope and a detergent as this information is shown in the prior art. Indeed, in explaining the difference between these two classes of denaturing agents, Dr. DeFilippi testifies that:

Detergent molecules each have a hydrophobic tail and a hydrophilic head. Detergents bring the hydrophobic portions of the protein into the aqueous phase because the hydrophobic tail of the detergent binds to hydrophobic regions of the proteins while the hydrophilic portion of the detergent interacts directly with the aqueous phase. Chaotropes disrupt the hydrogen bonding network between water molecules and reduce the stability of the native state of proteins by weakening the hydrophobic effect, permitting the hydrophobic regions of the protein that are normally internal to the protein to be turned outwards.

Ex. 2033 ¶ 27.

Dr. DeFilippi, however, asserts, without any support, that “a POSA at the time of the invention was not aware of the relevance of this distinction.” *Id.* That statement is contradicted by the prior art of record. Das, for example, teaches a lysis buffer containing the detergent N lauryl Sarcosyl and the chaotrope guanidinium isothiocyanate. *See, e.g.*, Ex. 1008 ¶ 89. Das explains that a “[d]etergent helps in solubilization of cell wall lipid and of protein and thus result in complete lysis of the mycobacterial cell wall, which is rich in different types of complex lipids,” whereas “a strong chaotropic agent i.e[.] guanidinium isothiocyanate . . . helps to inactivate all

mycobacteria present in a clinical specimen, lyse tough mycobacterial cell and denature and remove proteins thus results into cleaner preparation of DNA . . . and also ensure safety for the operator.” *Id.* ¶¶ 38–39.

Similarly, Goldrick teaches isolating RNA using a mixture of, among other reagents, a chaotropic agent (guanidinium chloride or guanidinium thiocyanate) and a detergent (e.g., N-lauroyl sarcosine or SDS). *See e.g.*, Ex. 1009, 7:30–8:54. Goldrick explains that the chaotropic agent is for inactivating nucleases, and the detergent and other ingredients, such as reducing agents, “aid in the inactivation of the nucleases.” *Id.* at Abstract, 1:39–54; *see also* claim 8 (reciting “the nuclease inactivation enhancing detergent is SDS or N-lauroyl sarcosine”).

In addition, Farrell similarly discusses “homogenization in lysis buffers consisting of guanidinium thiocyanate or guanidinium hydrochloride is widely accepted as the method of choice.” Ex. 1026, 58. Farrell explains that “[s]olutions containing guanidine HCl or guanidine thiocyanate (GTC) are often referred to as chaotropic buffers because of their biologically disruptive nature.” *Id.* at 59; *see also* Ex. 1004, 189–190 (1982 Maniatis Laboratory Manual teaching solution for isolating RNA comprising guanidinium isothiocyanate, sodium lauryl sarkosinate, β -ME, and EDTA).

Furthermore, Koller teaches nucleic acid releasing compositions containing a chaotrope, detergent, reducing agent, and chelator salt. Ex. 1016, 7:1–5. According to Koller, “[t]he chaotropic component of the nucleic acid releasing composition is both an effective protein denaturant and a strong inhibitor of nucleases. The effect of a chaotropic agent on growing cells is an almost instantaneous dissolution of the cells.” *Id.* at 7:19–23. Koller teaches urea as a useful chaotropic agent. *Id.* at 7:23–25.

Koller also teaches that for the nucleic acid releasing composition, it is “beneficial to incorporate a surface-active anionic detergent to further aid in lysis and disruption of the cells,” and SDS is such a detergent. *Id.* at 8:8–15.

Thus, a preponderance of the evidence shows that an ordinarily skilled artisan at the time of the invention would have understood the identity, as well as the individual properties and use, of the various chaotropes and detergents (and other reagents), as well as the benefits of combining them in a single composition for isolating nucleic acids.

b. Reason to Modify and Reasonable Expectation of Success

Patent Owner contends Dr. Taylor’s opinions and testimony regarding a rational to modify Birnboim’s Example 3 are entitled to no weight because Dr. Taylor could “not say what the effect would be of modifying Birnboim’s Example 3. AmPOR 32–33 (citing Ex. 2020, 399:22–400:12). Patent Owner further notes that Dr. Taylor “saw no reason to change Example 3 until one tried it, but he never tried it.” *Id.* at 33 (citing Ex. 2020, 198:14–199:2, 156:25–157:7).

Patent Owner further contends that Dr. Taylor’s opinions regarding reasonable expectation of success similarly are entitled to no weight. *Id.* Patent Owner cites to Dr. Taylor’s statement that, even if a person of ordinary skill in the art “had a reason to modify Example 3, the effect would be unknown and testing would be necessary: ‘testing out the concentrations, the various components would need to be done by laboratory work, yes.’” *Id.* at 34 (citing Ex. 2020 199:4–22).

Patent Owner then contends both experts agree that modifying Birnboim example 3 would require experimentation. AmPOR 36. According to Patent Owner, altering the “components, or concentrations, or both, of a complex composition, like that of Birnboim Example 3, is a matter

of experimentation,” because a person of ordinary skill in the art “would not know the outcome without testing the performance of the altered composition as to each desired function.” *Id.*

We do not agree with Patent Owner because, for its obviousness challenge, Petitioner relies on not only Example 3, but also the general teachings of Birnboim. *See* Pet. 36–39 (citing Ex. 1003 ¶¶ 2, 21, 63, 64–74, 84, 88, 114–121, 115, 175–181).

Claim 1 of the ’443 patent recites five general categories of reagents: chaotropes, detergents, reducing agents, chelators, and buffers. It requires these reagents to perform recited functions: denature proteins, inactivate nucleases, kill pathogens, and not degrade nucleic acid. As explained above, Petitioner has shown that Birnboim teaches all the reagents recited, and those reagents together perform the recited functions. *See supra* Sections II.E.2.a.(1)–(a)(4).

The Federal Circuit has held that combining teachings in a single prior art reference “does not require a leap of inventiveness.” *Bos. Sci. Scimed, Inc. v. Cordis Corp.*, 554 F.3d 982, 991 (Fed. Cir. 2009). This is especially true when the claimed composition is used for the identical purpose taught by the prior art. *Id.*

Such is the case here. Petitioner argues, and we agree, Birnboim teaches “employ[ing] a combination of well-known compounds and use them in accordance with their well-understood functions” to “yield predictable results.” *See* Pet. 38. “If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability.” *KSR*, 550 U.S. at 417. Therefore, regardless of the weight given to Dr. Taylor’s testimony

regarding this issue, Petitioner would still carry its burden of demonstrative obviousness of the challenged claims.

Additionally, because we determine Petitioner has shown by a preponderance of the evidence that the challenged claims are anticipated by Birnboim, and Patent Owner does not present any objective indicia of non-obviousness, we conclude Petitioner has demonstrated by a preponderance of the evidence that the challenged claims would have been obvious under 35 U.S.C. § 103 in view of Birnboim. *See Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542 (Fed. Cir. 1983) (quoting *In re Fracalossi*, 681 F.2d 792, (CCPA 1982)) (“a disclosure that anticipates under § 102 also renders the claim invalid under § 103, for ‘anticipation is the epitome of obviousness.’”).

2. *Analysis of Birnboim as Applied to Challenged Dependent Claims 2, 4–8, 10–14, 16, 21–30, 32, 35*

Petitioner contends dependent claims 2, 4–8, 10–14, 16, 21–30, 32, and 35 of the ’399 patent are unpatentable as obvious under 35 U.S.C. § 103 in view of Birnboim and provides specific arguments for each claim. Pet. 22–36. Patent Owner provides specific arguments contending that dependent claims 2, 4, 5, 7, 16, and 31 would not have been obvious to a person of skill in the art at the time of the invention. AmPOR 38–48. We address claims 1, 4, 5, 7, 16, and 31 in detail below.

a. *Claims 2, 5, and 7*

Claim 2 depends from claim 1 and further recites specific reducing agents, including β -ME and DTT. Petitioner argues that Birnboim teaches β -ME and DTT as exemplary reducing agents for use with its compositions. Pet. 39 (citing Ex. 1003 ¶ 13).

Claim 5 depends from claim 1 and further recites specific chaotropes, including guanidine thiocyanate and guanidine hydrochloride. Petitioner argues that Birnboim teaches guanidine thiocyanate and guanidine hydrochloride in its compositions. *Id.* at 40 (citing Ex. 1003 ¶¶ 20, 68).

Claim 7 depends from claim 1 and further recites specific chelators, including ethylenediamine tetraacetic acid (EDTA) and diethylene triamine pentaacetic acid (DTPA). Petitioner argues that Birnboim teaches using either EDTA or DTPA as the chelator in its compositions. *Id.* at 41 (citing Ex. 1003 ¶¶ 15, 67). Petitioner also contends that an ordinarily skilled artisan would have been motivated to use the specific reducing agents, chaotropes, or chelators at the concentration ranges recited in claim 4, and would have had a reasonable expectation of success in doing so. *Id.* at 42 (citing Ex. 1003 ¶¶ 13, 67, 115).

Patent Owner points out that Birnboim's Example 3 uses sodium ascorbate (a salt of ascorbic acid) as the reducing agent, urea as the chaotrope, and CDTA as the chelator, none of which is recited in claims 3, 5, and 7. AmPOR 38–39, 41–42, 44–45 (citing Ex. 1003 ¶ 115). According to Patent Owner, Birnboim does not teach or suggest substituting these reagents with those recited in claims 3, 5, and 7, and an ordinarily skilled artisan would not have had a reasonable expectation of success when doing so. *Id.* at 38–45. We disagree with Patent Owner.

Again, as noted above, for its obviousness challenge, Petitioner relies on not only Example 3, but also the general teachings of Birnboim. *See supra* Section II.E.2. As such, Birnboim itself teaches using the specific reducing agent, chaotrope, or chelator recited in claim 2, 5, or 7. *See* Ex. 1003 ¶ 13 (exemplary reducing agents including ascorbic acid, β -ME,

and DTT); ¶¶ 20, 68 (known chaotropes urea, guanidine thiocyanate, and guanidine chloride), ¶ 16, 67 (exemplary chelators including EDTA, CDTA, and DTPA).

In addition, other prior art of record also makes clear that numerous such reagents may be used for essentially the same purpose as those recited in the challenged claims. With respect to the specific chaotropes of claim 5, Das, Mori, Goldrick, Maniatis, and Chirgwin, for example, all teach using guanidinium compounds for the isolation of nucleic acids. *See, e.g.*, Ex. 1004, 189–190; Ex. 1008 ¶ 89; Ex. 1009, 7:30–8:54; Ex. 1011, 61; Ex. 1015, Abstract. Specifically, Mori teaches guanidinium salt as the preferred chaotropic salt, and guanidine thiocyanate as especially preferred. Ex. 1011, 61. Mori, however, states that “[i]t is possible to use a chaotropic substance such as urea instead of a chaotropic salt.” *Id.*

With respect to the specific reducing agents of claim 2 and the specific chelators of claim 7, Goldrick, for example, teaches isolating RNA using a composition comprising a guanidinium compound, a detergent, a reducing agent such as β -ME or DTT and, optionally, a chelator such as EDTA. Ex. 1009, 7:30–8:54, 4:31–34. Similarly, Maniatis teaches a solution comprising guanidinium isothiocyanate, the detergent sodium lauryl sarkosinate, “reducing agents like β -mercaptoethanol,” and the chelator EDTA for simultaneously disrupting cells and inactivating nucleases. *See* Ex. 1004, 189; *see also* Ex. 1008 ¶ 63 (lysis buffer comprising guanidinium isothiocyanate, N lauryl sarcosyl, β -ME, and EDTA).

According to Patent Owner, Birnboim prefers ascorbic acid³⁰ as the “most desirabl[e]” reducing agent, and prefers other, non-guanidine denaturing agents ahead of guanidine compounds. AmPOR 38–39 (citing Ex. 1003 ¶¶ 13, 20). But, “the fact that a specific embodiment is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered.” *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989); *see also In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012) (“[J]ust because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes.”).

Thus, based on the prior art of record, we find an ordinarily skilled artisan were familiar with the use and combinations of reagents recited in the challenged claims. *See* Ex. 1002 ¶¶ 54–68 (Dr. Taylor’s review of the state of the art). Thus, we find claims 2, 5, and 7 would have been obvious because they each “recites a combination of elements that were all known in the prior art, and all that was required to obtain that combination was to substitute one well-known . . . agent for another.” *See Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1364 (Fed. Cir. 2012).

Patent Owner argues that any substitution of known reagents for those in Birnboim’s Example 3 is unpredictable and, thus, undercuts any reasonable expectation of success in arriving at the claimed invention. AMPOR28–30, 32–33, 35–40; Sur-reply 12–15. We disagree because necessary experimental work an ordinarily skilled artisan routinely employs to verify the expected properties of the substitute reagents does not

³⁰ According to Patent Owner, sodium ascorbate, which is used in Birnboim’s Example 3, “is the same thing as ascorbic acid.” AmPOR 38 n.3.

undermine a reasonable expectation of success. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) (holding “obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.”).

Patent Owner argues that there would not have been a reasonable expectation of success because its “test results show that substitution of guanidine in Birnboim’s Example 3 causes the Example 3 composition to form a precipitate, removing the precipitated reagents from the aqueous composition and making the composition unusable for collection of nucleic acid.” AMPOR42–43 (citing Ex. 2033 ¶¶ 41–43, 25–26; Ex. 2019).

We acknowledge the results in Exhibit 2019 but disagree with the conclusion Patent Owner draws from it. Patent Owner argues that “[t]he guanidine compounds are active compounds that are likely to react with other reagents in the composition.” *Id.* at 43 (citing Ex. 2033 ¶ 42; Ex. 2020, 224:17–225:7). For example, Dr. DeFilippi notes that “DTT is chemically reactive with guanidinium and would not function in composition with guanidinium salts such as those listed in Birnboim.” Ex. 2033 ¶ 28. This interaction, however, was well-known in the art. *See, e.g.*, Ex. 1015, 5296 (Chirgwin teaching that in place of β -ME, “[d]ithiothreitol can be used with the guanidine hydrochloride stock . . . but it undergoes a chemical reaction with the thiocyanate anion to produce hydrogen sulfide and a green color”).

Considering the level of skill in the art and the extensive use of guanidinium compounds in combination with reducing agents, detergents, and chelators as discussed above, we find an ordinarily skilled artisan would have been aware of such complications and known how to avoid them. Indeed, as Patent Owner points out, Dr. Taylor testified that an ordinarily

skilled artisan “should account for the reactivity of guanidinium before combining it with other reagents.” AMPOR 43 (citing Ex. 2020, 223:17–224:15). Yet, Patent Owner does not show that it has taken this well-known reactivity into account when considering a simple substitution of 0.67 M guanidine thiocyanate for the 0.67 M urea in Birnboim’s Example 3.

In addition, Patent Owner focuses on the composition in Birnboim’s Example 3 as the starting material. We repeat that, for its obviousness challenge, Petitioner relies on not only Example 3, but also the general teachings of Birnboim. *See supra* Section II.E.2. When an ordinarily skilled artisan is not limited to start from Example 3, other prior art of record shows that guanidine compounds have been used routinely in compositions for extracting and preserving nucleic acids. *See supra* Section II.E.1.c.

For example, Das teaches a lysis buffer containing about 4 M guanidinium isothiocyanate (chaotrope), about 1 % N lauryl Sarcosyl (detergent), about 10 mM β -ME (reducing agent), about 1 mM EDTA (chelator), and about 50 mM Tris.Cl pH 7.6 (buffer). Ex. 1008 ¶ 64; *see also id.* ¶ 63 (teaching guanidinium isothiocyanate in the range of about 0.5–8 M). Thus, we accord limited value to the results in Exhibit 2019 in view of both the limitations of its experimental design and the prior art teachings of successful use of guanidine compounds. *See supra* Section II.E.1.c.

To the extent some substitutions might fail, it is important to keep in mind that expectation of success need only be reasonable, not absolute. *Pfizer*, 480 F.3d at 1364. With respect to the substitution of well-known reagents in Birnboim’s Example 3 formulations, Dr. Taylor testified that adjusting denaturing agents, for example, “is something that a freshman

college student could do with a little bit of direction,” and that substituting chaotropes or detergents is “just a standard methodology.” *See* Ex. 2020, 191:10–17, 338:15–20, 487:15–22.

In sum, Petitioner demonstrates by a preponderance of the evidence that Birnboim teaches or suggests all limitations of claims 2, 5, and 7, and that an ordinarily skilled artisan would have had a reason to implement these teachings to arrive at the subject matter of these claims with a reasonable expectation of success. Patent Owner does not present evidence on objective indicia of nonobviousness. Thus, for the reasons discussed above, we determine Petitioner demonstrates by a preponderance of the evidence that claims 2, 5, and 7 would have been obvious over Birnboim.

b. Claim 4

Claim 4 depends from claim 1, and further recites the concentration ranges for the five ingredient categories (chaotrope, detergent, reducing agent, chelator, and buffer) where the chelator range (0.01 to 1.0 mM) that is lower than Birnboim’s Example 3 (CDTA at 3.3 mM). Patent Owner contends that “Birnboim provides no suggestion to reduce the concentration of CDTA by more than two-thirds.” AmPOR 39 (citing Ex. 2033 ¶¶ 33–34). As discussed previously, Section II.E.2, we disagree.

Birnboim teaches that

The amount or concentration of chelator will depend upon the strength of the chelator, which would need to be determined empirically. For CDTA, concentrations in the 1–20 mM range are sufficient, however other concentrations would work, and the compositions of the invention are not intending to be limited to this range.

Ex. 1003 ¶ 67. CDTA is the chelator in Example 3. *Id.* ¶ 115. Thus, contrary to Patent Owner’s assertion, Birnboim does explicitly disclose using CDTA

at the concentration of 1–20 mM because it overlaps with the “about 0.01 mM to about 1 mM” range recited in claim 4.

In cases involving overlapping ranges, the Federal Circuit has “consistently held that even a slight overlap in range establishes a *prima facie* case of obviousness.” *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003); *see also In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997) (concluding a prior art reference that teaches the range 100–600 Å renders obvious a claimed invention with the range 50–100 Å); *In re Woodruff*, 919 F.2d 1575, 1578 (CCPA 1990) (concluding a prior art reference that teaches the range “about 1–5%” renders obvious a claimed invention with the range “more than 5% to about 25%”).

The case for obviousness based on encompassing or overlapping ranges shifts the burden of production to the patentee to rebut the case, and this is applicable in the context of an *inter partes* review. *See E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1008 (Fed. Cir. 2018) (“[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls on the patentee to come forward with evidence of teaching away, unexpected results, or other pertinent evidence of nonobviousness.”) (quoting *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013)). Likewise, there is a rebuttable presumption grounded on a claimed range overlapping a range disclosed in the prior art. *Id.*

“The presumption [of obviousness] can be rebutted if it can be shown that the prior art teaches away from the claimed range, or the claimed range produces new and unexpected results.” *Ormco Corp. v. Align Tech., Inc.*,

463 F.3d 1299, 1311 (Fed. Cir. 2006); *see also Peterson*, 315 F.3d at 1330–31 (the same). Here, Patent Owner has done neither.

Patent Owner contends “[t]he Petition and Taylor Declaration conclude that a POSA would try other concentrations and expect them to work without explaining why this motivates a POSA to reduce the chelator concentration to less than a third of the concentration in Example 3.”

AmPOR 40 (citing Pet. 39; Ex. 1002 ¶ 180). We, again, disagree.

Both Petitioner and Dr. Taylor cite Birnboim for teaching CDTA at the concentration of 1–20 mM, which overlaps with the claimed range of 0.01–1 mM. Pet. 39 (citing Ex. 1003 ¶ 67); Ex. 1002 ¶ 180 (citing Ex. 1003 ¶ 67). As the Federal Circuit explained, “[s]uch overlap itself provides sufficient motivation to optimize the ranges.” *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012); *See also Peterson*, 315 F.3d at 1330 (“The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of . . . ranges is the optimum combination.”). Indeed, Birnboim’s teaching that “[t]he amount or concentration of chelator . . . would need to be determined empirically” underscores the guidance of our reviewing court. *See* Ex. 1003 ¶ 6.

Moreover, both Petitioner and Dr. Taylor cite Das and Goldrick as examples of prior art that teaches an ordinarily skilled artisan “to use a chelator such as CDTA or EDTA at a concentration within the claimed range in aqueous solutions further comprising a chaotrope, a detergent, a reducing agent, and a buffer to preserve and stabilize nucleic acids.” Pet. 39 (citing Ex. 1008 ¶¶ 63–64, claims 6–7; Ex. 1009, 5:5–11, 7:33–47, 11:64–68); Ex. 1002 ¶ 179 (citing the same). Thus, Petitioner has shown

sufficiently that an ordinarily skilled artisan would have had a reason to change the concentration of the chelator in Birnboim's Example 3.

Accordingly, for the reasons discussed above, we determine Petitioner demonstrates by a preponderance of the evidence that claim 4 would have been obvious over Birnboim.

c. Claim 16

Petitioner contends Birnboim anticipates claim 16. Pet. 45. Petitioner also argues that “[e]ven if not anticipated, claim 16 would have been obvious over Birnboim” because a person of ordinary skill in the art “would have found the claimed solution obvious, as Birnboim discloses solutions comprising a population of isolated polynucleotides when diluted with a saliva sample.” *Id.* (citing Ex. 1003 code (57) ¶¶ 24, 88, 114–122; Ex. 1002 ¶¶ 207–09).

Patent Owner counters that Petitioner's obviousness argument for claim 16 fails for the same reason its anticipation argument fails. Specifically, Patent Owner contends Petitioner's own claim construction of “stock solution” is “a formulated supply of solution for future use” and Birnboim does not teach or suggest inclusion of saliva in a “stock solution.” AmPOR 30 (citing Pet. 8; Ex. 2033 ¶ 49). According to Patent Owner, “Birnboim uses its compositions to collect ‘saliva DNA from different donors,’” which means the “saliva samples do not themselves include saliva and thus do not disclose a ‘stock solution’ (a formulated supply of solution for future use”) that comprises saliva.” *Id.* (citing Ex. 1003 ¶ 119; Ex. 2033 ¶ 49).

For the same reason discussed previously, Section II.E.4., regarding Petitioner's anticipation argument for claim 16, we agree with Patent Owner. The plain language of claim 16 requires that the population of isolated

polynucleotides be part of the stock solution and not the sample.

Accordingly, we conclude Petitioner has failed to show by a preponderance of the evidence that challenged dependent claim 16 would have been obvious under 35 U.S.C. § 103 in view of Birnboim. We, nevertheless, find for Petitioner for the reasons set forth in our Decision on Sanctions.

d. Claim 31

Claim 31 depends from claim 21, and further recites “wherein less than about 5% of the population of polynucleotides contained in the sample is degraded after the composition comprising the sample has been stored at a temperature of from about 10° C. to about 40° C. for a period of about 7 to about 30 days.”

Petitioner contends that Birnboim renders claim 31 obvious.³¹ Pet. 62–64. Petitioner argues that “as explained for claims 1 and 4,” Birnboim teaches using the same categories of reagents at the same concentration ranges as the ’339 patent discloses. *Id.* at 63. Petitioner asserts that in Examples 4 and 6, Birnboim teaches contacting samples with Example 3’s compositions and maintaining the mixtures at room temperature for periods of 14 days and 30 days, respectively, which satisfies the duration and temperature limitations of claim 37. *Id.* (citing Ex. 1003 ¶¶ 117, 121). According to Petitioner, Birnboim then confirms, via electrophoresis and

³¹ Petitioner argues that the ’339 patent “would not have guided a POSA to use any different constituents or concentrations from those recited in claim 1 to achieve the specified level of degradation” because it “never discloses having achieved any of the[] ‘desirable’ preservation levels, nor explains how a POSA would achieve one preferred level versus another, and even fails to disclose how one would quantify the nucleic acid preservation percentages.” Pet. 62–63 (citing Ex. 1002 ¶ 276).

PCR, that nucleic acids are not degraded, and remain stable over these time periods. *Id.* (citing Ex. 1003 ¶¶ 117, 121).

Patent Owner disagrees. PO Resp. 46–48. According to Patent Owner, “Birnboim is silent regarding the percentage of polynucleotides preserved,” and thus, “[a] POSA would have to assume—without basis—that less than 5% of the population of polynucleotides was degraded.” *Id.* at 47 (citing Ex. 2033 ¶¶ 52, 53). Patent Owner also argues that Petitioner relies on other prior art, such as Koller, to fill gaps. But, according to Patent Owner “Koller uses a different composition than Birnboim Example 3, and a POSA would expect different results.” *Id.* at 47–48 (citing Ex. 2033 ¶ 57). We, again, find Petitioner’s arguments more persuasive.

First, Birnboim teaches its compositions “for preserving nucleic acids at room temperature for extended periods of time.” Ex. 1003 ¶ 2. This suggests that, contrary to Patent Owner’s argument, the nucleic acids preserved with Birnboim’s compositions are stable.

Second, we repeat that Petitioner relies on Birnboim’s general teachings, and not just Example 3. Thus, Patent Owner’s concern regarding other prior art, specifically Koller, is irrelevant. Instead, as Petitioner points out, Koller teaches nucleic acid releasing compositions containing chaotropes, detergents, reducing agents, and chelator salts (*see* Pet. 64 (citing Ex. 1016, 1:15–2:11, 7:1–5, 12:17–25, 19:19–24, 20:16–27)), the same categories of reagents as Birnboim’s and as claimed.

In sum, we determine Petitioner demonstrates by a preponderance of the evidence that claim 33 would have been obvious over Birnboim.

e. Claims 6, 8, 10–14, 21–30, 32, 35

Petitioner contends dependent claims 6, 8, 10–14, 21–30, 32, and 35 of the ’399 patent are unpatentable as obvious under 35 U.S.C. § 103 in view

of Birnboim and provides specific arguments for each claim. Pet. 41, 45–46 (citing Ex.1002 ¶¶190–192, 210–217). Patent Owner does not address the additional limitations of the dependent claims in its Response. Thus, we agree with Petitioner (Reply 16) that Patent Owner has waived any argument for these challenged dependent claims. *See In re NuVasive, Inc.*, 842 F.3d 1376, 1380–1381 (Fed. Cir. 2016) (holding party waived arguments on issues not raised in its response after institution). Nonetheless, the burden remains on Petitioner to demonstrate unpatentability. *See Dynamic Drinkware*, 800 F.3d at 1378.

We have considered carefully all arguments and supporting evidence in light of the limitations recited in challenged dependent claims 6, 8, 10–14, 21–30, 32, and 35. Based on the entire trial record, we agree with Petitioner’s analysis and we credit Dr. Taylor’s testimony supporting Petitioner’s position. Accordingly, we conclude Petitioner has demonstrated by a preponderance of the evidence that the challenged dependent claims would have been obvious under 35 U.S.C. § 103 in view of Birnboim.

f. Conclusion Regard Alleged Obviousness of Claims 1, 2, 4–8, 10–14, 16, 21–30, 31, 32, 35 by Birnboim

For reasons that follow, we determine Petitioner has shown by a preponderance of the evidence that the challenged claims 1, 2, 4–8, 10–14, 16, 21–30, 31, 32, 35 would have been obvious in view of Birnboim under 35 U.S.C. § 103. We also determine Petitioner has not shown by a preponderance of the evidence that challenged dependent claim 16 would have been obvious in view of Birnboim under 35 U.S.C. § 103. We, nevertheless, find for Petitioner for the reasons set forth in our Decision on Sanctions.

G. Alleged Obviousness of Claim 3 over Birnboim and Chen

Claim 3 depends from claim 2 and recites “the stock solution of claim 2, wherein the reducing agent comprises tris(2-carboxy-ethyl)phosphine” also known as TCEP. Birnboim does not disclose TCEP as a reducing agent. *See* Ex. 1002; *see generally* Ex. 1003.

Petitioner contends dependent claim 3 of the ’399 patent is unpatentable as obvious under 35 U.S.C. § 103 in view of Birnboim in combination with Chen. Pet. 47–48. Petitioner further argues that it was well known that TCEP was a desirable reducing agent for aqueous solutions directed at preserving nucleic acids. *Id.* at 48. According to Petitioner, claim 3 is “merely the predictable result of a simple substitution of known elements[]” and therefore would have been obvious. *Id.* (citing *KSR*, 550 U.S. at 416).

Patent Owner contends Birnboim does not teach modifying the reducing agent of Example 3 and, “[a]lthough Birnboim provides a list of other reducing agents generally” it “makes no mention of TCEP.” AmPOR 49 (citing Ex.1003 ¶ 13, 115; Ex. 2020 516:16–517:1). Patent Owner then argues that Birnboim prefers sodium ascorbate, *i.e.*, ascorbic acid, “most desirably,” because it is inexpensive, non-toxic, and stable in the presence of chelators and denaturing agents that are included in the compositions of the invention. *Id.* (citing Ex.1003 ¶¶ 13, 72). Therefore, Patent Owner concludes there would be no reason for a person of ordinary skill in the art to modify Birnboim or use TCEP or have reasonable success in making such a change. *Id.* at 50.

We agree with Petition that it would have been obvious to substitute TCEP for sodium ascorbate or other reagents agents. First, as we have discussed *supra* Section II.E.1.c.iv., Petitioner relies on not only Example 3,

but also the general teachings of Birnboim and its “series of examples” including Examples 4–6. *See* Pet. 47 (Ex. 1003 ¶ 70). Second, Birnboim discloses that in addition to “ β -mercaptoethanol and dithiothreitol,” there are also “many biochemically relevant reducing agents are capable of reacting in solution with dissolved oxygen.” Ex. 1003 ¶ 9. Birnboim further discloses that other “desirable reducing agents...include...thiols, and phenols.” *Id.* ¶ 14. Therefore, we find that Birnboim expressly contemplated the suitability of other reducing agents in addition to “ β -mercaptoethanol and dithiothreitol.”

Chen discloses: “Suitable thiol-reducing agents include dithiothreitol (DTT), 2-mercaptoethanol, 2-mercaptoethylamine, and tris(carboxyethyl) phosphine (TCEP).” Ex. 1027 ¶ 23. Given then disclosure, we find that it would have been obvious to a person of ordinary skill in the art to substitute the thiol reducing agent, TCEP, disclosed in Chen to achieve the same function set forth in Birnboim, Chen, and the ’399 patent.

Accordingly, we conclude Petitioner has demonstrated by a preponderance of the evidence that the challenged dependent claim 3 would have been obvious under 35 U.S.C. § 103 in view of Birnboim and Chen.

H. Alleged Obviousness of Claim 9 over Birnboim and Reed

Claim 9 depends from claim 1 and recites, “The stock solution of claim 1, further comprising a surfactant that comprises a silicone polymer, a polysorbate, or any combination thereof.” Ex. 1001, 41:45–47.

Petitioner contends claim 9 of the ’399 patent is unpatentable as obvious under 35 U.S.C. § 103 in view of Birnboim in combination with Reed. Pet. 49–50. Petitioner further argues that the use of surfactants in nucleic acid stabilization was well-known in the prior art, and that Reed discloses using such a surfactant, a polysorbate, as a “preferred surfactant.”

Pet. 49; Ex. 1017, 15:15–18. Therefore, according to Petitioner, a person of ordinary skill in the art at the time of the alleged invention would have been motivated to use a polysorbate surfactant as disclosed in Reed in combination with Birnboim’s stock solution with a reasonable expectation of success, rendering claim 9 obvious. Pet. 50.

Patent Owner does not address the additional limitations of the dependent claims in its Response. Thus, we agree with Petitioner (Reply 21) that Patent Owner has waived any argument for these challenged dependent claims. *See In re NuVasive, Inc.*, 842 F.3d 1376, 1380–1381 (Fed. Cir. 2016) (holding party waived arguments on issues not raised in its response after institution). Nonetheless, the burden remains on Petitioner to demonstrate unpatentability. *See Dynamic Drinkware*, 800 F.3d at 1378.

We have considered carefully all arguments and supporting evidence in light of the limitations recited in challenged dependent claim 9. We agree with Petitioner’s analysis as supported by Dr. Taylor’s testimony regarding the specific limitations recited in this claim. Accordingly, we conclude Petitioner has demonstrated by a preponderance of the evidence that the challenged dependent claim 9 would have been obvious under 35 U.S.C. § 103 in view of Birnboim and Reed.

I. Alleged Obviousness of Claim 15 over Birnboim and Mori

Claim 15 depends from claim 1 and recites, “The stock solution of claim 1, further comprising a defoaming agent that comprises a silicon polymer or a polysorbate.” Ex. 1001, 32:61–63. Petitioner contends that the use of defoaming agents to reduce foaming in nucleic acid preserving solutions was well-known in the prior art. Pet. 52. Petitioner further argues, a person of ordinary skill in the art at the time of the invention would have expected success in using a defoaming agent along with the stock solution

disclosed by Birnboim. *Id.* at 53. Therefore, according to Petitioner, an ordinarily skilled artisan would have had reason to use a defoaming agent disclosed by Mori, in combination with Birnboim's stock solution and have a reasonable expectation of success in doing so, thus rendering claim 15 obvious. *Id.*

Patent Owner does not address the additional limitations of the dependent claims in its Response. Thus, we agree with Petitioner (Reply 21) that Patent Owner has waived any argument for these challenged dependent claims. *See In re NuVasive, Inc.*, 842 F.3d 1376, 1380–1381 (Fed. Cir. 2016) (holding party waived arguments on issues not raised in its response after institution). Nonetheless, the burden remains on Petitioner to demonstrate unpatentability. *See Dynamic Drinkware*, 800 F.3d at 1378.

We have considered carefully all arguments and supporting evidence in light of the limitations recited in challenged dependent claim 15. We agree with Petitioner's analysis as supported by Dr. Taylor's testimony regarding the specific limitations recited in this claim. Accordingly, we conclude Petitioner has demonstrated by a preponderance of the evidence that the challenged dependent claim 15 would have been obvious under 35 U.S.C. § 103 in view of Birnboim and Mori.

J. Alleged Obviousness of Claim 16 over Birnboim and Helftenbein

Claim 16 depends from claim 1 and recites "further comprising a population of isolated polynucleotides that comprises RNA, DNA or a combination thereof." Ex. 1001, 32:63–65. Petitioner contends that claim 16 of the '399 patent is unpatentable as obvious under 35 U.S.C. § 103. Pet. 54. Petitioner argues that Helftenbein discloses the use of carrier DNA or RNA in a solution designed to extract nucleic acids as a positive control, while Birnboim discloses a stock solution of an aqueous composition for the

extraction of nucleic acids. *Id.* According to Petitioner an ordinarily skill artisan would had reason to use carrier RNA or DNA, i.e. isolated populations of polynucleotides, as a positive control in Birnboim's composition, which is a stock solution analogous to claim 1 of the '399 patent. *See id.* In view of Helftenbein, Petitioner contends a person of ordinary skill in the art at the time of the alleged invention would have had reason to combine Birnboim's disclosure and Helftenbein's disclosure with a reasonable expectation of success, thus rendering claim 16 obvious. *Id.*

Patent Owner contends Petition has failed to demonstrate a reason to combine Helftenbein with Birnboim. AmPOR 51. Patent Owner first argues that Birnboim uses control DNA as a control for the PCR assay, but it is added *after* the mixing of the sample with Birnboim Example 3 composition. *Id.* (citing Ex. 2015 ¶ 65). According to Patent Owner, "[t]here is no suggestion in Birnboim to put control DNA or RNA into the composition of Example 3," which is what Helftenbein teaches. *Id.* (citing Ex. 1019, 6:27–9:37; Ex. 2015 ¶ 66). Patent Owner further contends that "Helftenbein does not provide a motivation to modify Birnboim" because "Helftenbein's Examples 5–8 disclose testing Helftenbein's 'serum' on separate samples of MS2-RNA as a control, *not including the MS2-RNA in the serum itself.*" *Id.* (citing Ex. 1019, 6:27–9:37; Ex. 2033 ¶ 69). Thus, Patent Owner argues that the MS2-RNA "does not operate as an internal control." Sur-reply 20.

Patent Owner then argues that Dr. Taylor's testimony supports its position. According to Patent Owner, "Dr. Taylor testified that a POSA would not have any reason to change Example 3 and could only speculate as to what effect a change of concentrations or substitution of components would have on Birnboim's Example 3." AmPOR 51 (citing Ex. 1019, 6:27–

9:37). Patent Owner, therefore, concludes that a person of ordinary skill in the art at the time of the invention “would not deduce from Helftenbein a teaching or other reason to include a population of isolated polynucleotides that comprises RNA, DNA, or a combination thereof, in Birnboim’s Example 3 and would not reasonably expect success in such change.” *Id.* (citing Ex. 2015 ¶ 67). For the reasons explained below, we find Petitioner’s arguments more persuasive.

First, Patent Owner argues claim 16 requires internal controls. *See* PO Resp. 51; Sur-reply 20. Patent Owner is mistaken. Claim 15 only recites that “the stock solution of claim 1, further comprising a population of isolated polynucleotides that comprises RNA, DNA, or a combination thereof,” it does not mention an internal control. Petitioner argues that Helftenbein teaches the “nucleic acid-stabilizing substance may have added thereto an internal standard” and that this internal standard can be the predetermined nucleic acid sequence of MS2-RNA. Reply 21 (citing Ex. 1019, 2:60–61,6:27–9:37). Patent Owner does not dispute these assertions.

We have considered carefully all arguments and supporting evidence in light of the limitations recited in challenged dependent claim 16. Based on the entirety of the evidence, we agree with Petitioner’s analysis as supported by Dr. Taylor’s testimony. Thus, we determine Petitioner demonstrates by a preponderance of the evidence that claim 16 would have been obvious under 35 U.S.C. § 103 in view of Birnboim and Helftenbein.

K. Alleged Obviousness of Claim 17 over Birnboim and Chirgwin

Claim 17 depends from claim 1 and recites “the stock solution of claim 1, which, when diluted for use, comprises: a) about 4 M guanidine thiocyanate; b) about 30 mM sodium citrate; c) about 0.25% (wt./vol.)

sodium dodecyl sulfate; d) about 0.25% (wt./vol.) N-lauroyl sarcosine, sodium salt; e) about 0.1 M 2-mercaptoethanol; and f) about 0.1% silicon polymer (wt./vol).” Ex. 1001, 32:66–33:4.

Petitioner contends claim 17 of the ’399 patent would have been obvious under 35 U.S.C. § 103. Pet. 55. Petitioner argues that only insubstantial differences exist between the composition disclosed by claim 17 and the composition disclosed by Chirgwin. *Id.* at 57. Petitioner further argues that that ’399 patent is a compilation of well-known reagents in the field used according to their well-understood functions and accordingly, it would have been obvious to integrate the use of Chirgwin’s disclosed reagents, which are well-known, with Birnboim’s stock solution. *Id.* In doing so, an ordinarily skilled artisan at the time of the invention would have had a reasonable expectation of success and a motivation to combine Birnboim and Chirgwin, rendering claim 17 obvious.

Patent Owner contends that for the same reasons regarding claims 2, 4, 5, and 7, a person of ordinary skill in the art would not have been “motivated to modify any one of the reducing agent, chelator concentration, chaotrope, or chelator of Birnboim Example 3, much less all four of them together.” AMPOR 52. Patent Owner argues that there is “no motivation to modify Birnboim with the reagents of Chirgwin.” *Id.* at 53 (citing Pet. 61–64; Ex. 1002 ¶¶ 252–258). According to Patent Owner, all Petitioner has done is “lists reagents from Chirgwin alongside claim 17 (Petition, 62), with hindsight, omitting the diethyl pyrocarbonate necessary in Chirgwin to avoid degrading nucleic acids,” . . . “but offers no reason why a POSA would make those substitutions.” *Id.* (citing Pet. 64; Ex. 1002 ¶ 257). Patent Owner then argues that the “context of Chirgwin (extraction of mRNA for a single

enzyme alpha amylase from mammalian pancreas) is so distinct from that of Birnboim (extraction of DNA from bodily fluids, e.g. sputum) that a POSA would not consider either as providing relevant guidance for the other's context." *Id.* (citing Ex. 2015 ¶ 69).

Again, as noted above, for its obviousness challenge, Petitioner relies on not only Example 3, but also the general teachings of Birnboim. *See supra* Section II.E.2. As such, Birnboim itself teaches using the specific reducing agent, chaotrope, or chelator recited in claim 17. *See* Ex. 1003 ¶ 13 (exemplary reducing agents including ascorbic acid, β -ME, and DTT); ¶¶ 20, 68 (known chaotropes urea, guanidine thiocyanate, and guanidine chloride), ¶ 16, 67 (exemplary chelators including EDTA, CDTA, and DTPA). In addition, Chirgwin makes clear that numerous such reagents may be used for essentially the same purpose as those recited in the challenged claims and were well-known prior to the '399 patent. Ex. 1015, Abstract, 5294–95. Thus, based on the prior art of record, we find an ordinarily skilled artisan were familiar with the use and combinations of reagents recited in the challenged claims. *See* Ex. 1002 ¶¶ 54–68 (Dr. Taylor's review of the state of the art). Thus, we find claim 17 would have been obvious because they each "recites a combination of elements that were all known in the prior art, and all that was required to obtain that combination was to substitute one well-known . . . agent for another." *See Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1364 (Fed. Cir. 2012).

We do not agree with Patent Owner argument that the Petition is using "hindsight reconstruction" and "pick[ing] and choos[ing] among isolated disclosures in the prior art to deprecate the claimed invention." AMPOR 55. Given that the full formulation is disclosed, near verbatim, in Chirgwin, it

appears that Petitioner did not pick from “isolated Disclosures.” The fact that the same reagents also are disclosed in Birnboim and used to fulfill the claimed functions on pathogenic samples further supports Petitioner’s position.

In sum, Petitioner demonstrates by a preponderance of the evidence that Birnboim and Chirgwin teach or suggest all limitations of claim 17, and that an ordinarily skilled artisan would have had a reason to implement these teachings to arrive at the subject matter of this claim with a reasonable expectation of success. Patent Owner does not present evidence on objective indicia of nonobviousness. Thus, for the reasons discussed above, we determine Petitioner demonstrates by a preponderance of the evidence that claim 17 would have been obvious over Birnboim and Chirgwin.

L. Alleged Obviousness of Claims 18–20 over Birnboim, Chen, Das, and Wangh

Claims 18–20 depend from claim 1 and recite specific reagents for claim 1’s stock solution. Ex. 1001, 33:5–24. Petitioner contends that claims 18–20 are unpatentable as obvious under 35 U.S.C. § 103. Pet. 59. Petitioner argues that Birnboim discloses the stock solution of claim 1 and that Das, Chen, and Wangh disclose the claimed reagents and concentrations of claims 18–20. *Id.* at 59–61. Petitioner further argues that because the prior art discloses the claimed reagents and concentration, it would have been obvious for a POSA to employ them as a “matter of routine optimization.” *Id.* at 61.

Patent Owner contends that for the same reasons regarding claims 2, 4, 5, and 7, a person of ordinary skill in the art would not have been “motivated to modify any one of the reducing agent, chelator concentration,

chaotrope, or chelator of Birnboim Example 3, much less all four of them together.” AMPOR 55. Patent Owner argues “Petitioner provides no reason why a POSA would undertake to modify each one of the chaotrope, chelator, and reducing agent of Birnboim’s Example 3 together while also adding a defoaming agent as recited in claims 18–20.” *Id.* at 55–56. According to Patent Owner, “Petitioner picks and chooses reagents and concentrations from three different references, Das, Chen, and Wangh against claims 18–20, and states that it would have been obvious to a POSA to use those reagents ‘as a matter of routine optimization’ to achieve a composition according to ’399 claims 18, 19, and 20.” *Id.* at 55 (citing Pet. 67; Ex. 1002 ¶ 272).

Again, as noted above, for its obviousness challenge, Petitioner relies on not only Example 3, but also the general teachings of Birnboim. *See supra* Section II.E.2. As such, Birnboim itself teaches using the specific reducing agent, chaotrope, or chelator recited in claim 17. *See* Ex. 1003 ¶ 13 (exemplary reducing agents including ascorbic acid, β -ME, and DTT); ¶¶ 20, 68 (known chaotropes urea, guanidine thiocyanate, and guanidine chloride), ¶ 16, 67 (exemplary chelators including EDTA, CDTA, and DTPA). In addition, Das, Chen, and Wangh make clear that numerous such reagents may be used for essentially the same purpose as those recited in the challenged claims and were well-known prior to the ’399 patent. *See* Ex. 1008 ¶¶ 38, 63–64, 83–85, 89; Ex. 1022, 6:9–15, 8:8–18; Ex. 1027 ¶¶ 12, 13, 23, 24, 26). Thus, based on the prior art of record, we find an ordinarily skilled artisan were familiar with the use and combinations of reagents recited in the challenged claims. *See* Ex. 1002 ¶¶ 54–68 (Dr. Taylor’s review of the state of the art). Therefore, we find claims 18–20

would have been obvious because they each “recites a combination of elements that were all known in the prior art, and all that was required to obtain that combination was to substitute one well-known . . . agent for another.” *See Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1364 (Fed. Cir. 2012).

In sum, Petitioner demonstrates by a preponderance of the evidence that Birnboim, Chen, Das, and Wangh teach or suggest all limitations recited in challenged dependent claims 18–20, and that an ordinarily skilled artisan would have had a reason to implement these teachings to arrive at the subject matter of these claims with a reasonable expectation of success. Patent Owner does not present evidence on objective indicia of nonobviousness.

M. Alleged Obviousness of Claim 31 over Birnboim and Koller

Claim 31 depends from claim 21 and recites “wherein less than about 5% of the population of polynucleotides contained in the sample is degraded after the stock solution comprising the sample has been stored at a temperature from about 10° C. to about 40° C. for a period of about 7 to about 30 days.” Ex. 1001, 34:8–12. Petitioner contends that claim 31 of the ’399 patent is unpatentable as obvious under 35 U.S.C. § 103. Pet. 62. Petitioner argues that the ’399 patent does not disclose how to achieve the desired preservation levels of nucleic acids, e.g. how to ensure a percentage of the sample “will not be degraded upon prolonged storage” *Id.* (citing Ex. 1001, 10:12–45).

According to Petitioner, because (1) the ’399 patent fails to disclose how to achieve this goal, and (2) Birnboim discloses using the same reagents as the ’399 patent, a person of ordinary skill in the art at the time of the

alleged invention would have recognized that Birnboim would not cause more than 5% degradation of the isolated nucleic acids as recited by claim 31. *Id.* at 62–63. Petitioner further argues that Koller, in utilizing a similar composition, disclosed that the “isolated DNA was essentially intact and . . . not degraded.” *Id.* at 63 (citing Ex. 1016, 23:10–15). Because an ordinarily skilled artisan would have understood Koller’s disclosure of nucleic acids as not degraded, and would have reasonably expected success in combining these teachings of Koller with the composition of Birnboim, claim 31 would have been obvious in view of Birnboim and Koller. *Id.* at 64.

Patent Owner contends Birnboim does not teach the limitations of claim 31. AMPOR 46. According to Patent Owner, “Birnboim teaches generally that ‘stable’ means at least 50% of the nucleic acid after storage at ambient temperature for a specified time period” but does not show whether its Examples provide such “stable” storage of nucleic acids. *Id.* at 47 (citing Ex. 2015 ¶ 45; Ex. 1003 ¶¶ 115–122). Patent Owner argues that any reliance on Koller is misplaced because “Koller uses a different composition than Birnboim Example 3, and a POSA would expect different results.” *Id.* at 47–48 (citing Ex. 2015 ¶ 58; Ex. 2020, 399:22–400:12).

As Petitioner notes, Patent Owner does not dispute that Koller shows less than 5% degradation of nucleic acids under the storage conditions in claim 31. Sur-Reply 20 (citing AMPOR, 46–48). And, like Birnboim, Koller discloses a solution comprising a chaotrope, chelator, detergent, reducing agent, and buffer, as required by claim 31. *See Pet.*, 5, 62–64. Koller also states that the disclosed composition preserves DNA “at room temperature up to 6–8 months and perhaps longer without degradation of nucleic acids.”

Ex. 1016, 12:23–25. We, therefore, find that Koller discloses each element of claim 31.

Given that Birnboim and the other prior art references of record demonstrate that compositions encompassed by Birnboim degrade less than 5% of nucleic acid under the claimed conditions, we determine that a person of ordinary skill in the art would have would reasonably expected the compositions disclosed in Birnboim to meet the less than 5% degradation limitation as explicitly disclosed in Koller. Ex. 1060, 658–59; Ex. 1050, 308; Ex. 1071 ¶¶ 47, 51. Accordingly, we conclude Petitioner has shown by a preponderance of the evidence that the challenged dependent claim would have been obvious under 35 U.S.C. § 103 in view of Birnboim and Koller.

N. Alleged Obviousness of Claim 33 over Birnboim and Birnboim2006

Claim 33 depends from claim 32 and recites, “The sample collection system of claim 32, furthering comprising a swab, curette, or culture loop.” Ex. 1001, 34:17–18. Petitioner contends claim 32 is unpatentable as obvious under 35 U.S.C. § 103. Pet. 64–65. Petitioner argues that Birnboim discloses a collection vessel, while Birnboim2006 discloses a buccal swab. *Id.* at 65 (citing Ex. 1023, 2). Therefore, a person of ordinary skill in the art would have been motivated to use Birnboim2006’s buccal swab with Birnboim’s disclosed collection vessel and solution with a reasonable expectation of success rendering claim 32 obvious. *Id.*

Patent Owner does not address the additional limitations of the dependent claims in its Response. Thus, we agree with Petitioner (Reply 24) that Patent Owner has waived any argument for these challenged dependent claims. *See In re NuVasive, Inc.*, 842 F.3d 1376, 1380–1381 (Fed. Cir. 2016) (holding party waived arguments on issues not raised in its response after

institution). Nonetheless, the burden remains on Petitioner to demonstrate unpatentability. *See Dynamic Drinkware*, 800 F.3d at 1378.

We have considered carefully all arguments and supporting evidence in light of the limitations recited in challenged dependent claim 33. Based on the entirety of the evidence, we agree with Petitioner's analysis as supported by Dr. Taylor's testimony. Accordingly, we conclude Petitioner has demonstrated by a preponderance of the evidence that the challenged dependent claim would have been obvious under 35 U.S.C. § 103 in view of *Birnboim and Birnboim* 2006.

O. Alleged Obviousness of Claim 34 over Birnboim, Chirgwin, and Farrell

Claim 34 discloses a method of preparing the stock solution of claim 1. Ex. 1001, 34:19–46. Claim 34 recites 8 steps, 4 of which are optional and need not be considered for the purpose of obviousness analysis. *See In re Johnston*, 435 F.3d 1381, 1384 (Fed. Cir. 2006); Ex. 1001, 34:19–46. The limitations recited by claim 34 are: [a] combining one or more chaotropes with nuclease-free water at a temperature of about 20°C to 90°C; [b] combining the dissolved one or more chaotropes with one or more reducing agents, one or more chelators and one or more detergent to form an intermediate composition; [d] combining a sufficient amount of buffer to the intermediate composition so as to maintain a pH of about 5 to 7; [f] increasing the temperature of the second intermediate composition to about 60 °C to 95 °C for about 1 to 30 minutes and lowering the temperature to ambient conditions. *Id.*

Petitioner contends that claim 34 is unpatentable as obvious under 35 U.S.C. § 103. Pet. 66. Petitioner argues that Chirgwin satisfies limitations [a] and [b] via disclosing the mixing of a chaotrope, a chelator, a reducing

agent, and a detergent in deionized water. *Id.* at 67. Petitioner also relies on the testimony of Dr. Taylor that it would have been obvious as a design choice to combine the chaotrope (guanidinium thiocyanate) with water, prior to the other reagents at room temperature, then raise the temperature to dissolve the reagents. *Id.* (citing Ex. 1002 ¶ 294). Petitioner further argues that Farrell discloses that DEPC had become undesirable for nucleic acid isolation due to its carcinogenic properties. *Id.* 68 (citing Ex. 1026, 55, 57). According to Petitioner, Farrell also discloses nuclease-free water as a desirable alternative to DEPC treated water, which a person of ordinary skill in the art at the time of the invention would have been motivated to use in the composition taught by Birnboim. *Id.*

Additionally, Petitioner argues that in light of Chirgwin, it would have been obvious for an ordinarily skill artisan to include a buffer to obtain a pH between 5 and 7 in the solution, because Chirgwin discloses adjusting the pH of its nucleic acid isolation solution to 7, and Birnboim discloses the use of a buffer to maintain a pH between 5 and 7. *Id.* (citing Ex. 1003 ¶ 19; Ex. 1015, 5295) ([for RNA preservation,] “a pH from about 5.0 to about 7.0, desirably from about 6.5 to about 6.8 can be used.”). Therefore, according to Petitioner, Birnboim, in combination with Chirgwin, satisfies limitation [d]. *Id.* at 68.

Finally, regarding limitation [f] Petitioner argues that Chirgwin discloses warming and stirring the solution, followed by returning the solution to room temperature. *Id.* According to Petitioner, it would have been obvious to raise the temperature of the solution to between 65 °C and 95 °C as it was an obvious consideration to dissolve the reagents.

Therefore, according to Petitioner, Birnboim meets this limitation and claim 34 would have been obvious. *Id.* at 68–69.

Patent Owner contends that Petitioner fails to show any composition that meets the composition of claim 1 (from which claim 34 depends). AMPOR 56–57. Thus, Patent Owner concludes that “even if Chirgwin in view of Farrell taught a method of preparing a stock solution, Petitioner has not shown that such method would prepare a stock solution meeting the limitations of claim 1.”

For all the reasons discussed regarding claim 1, *see supra* Sections II.E.1. and II.F.1., we agree with Petitioner that Birnboim discloses and teaches a composition that meets the limitations of claim 1, and therefore, claim 34. Additionally, we have considered carefully all arguments and supporting evidence in light of the other limitations recited in challenged dependent claim 34 and we agree Petitioner’s analysis as supported by Dr. Taylor’s testimony that the combined teachings of Birnboim, Chirgwin, and Farrell read on each limitation. Accordingly, we conclude Petitioner has demonstrated by a preponderance of the evidence that the challenged dependent claim would have been obvious under 35 U.S.C. § 103 in view of Birnboim, Chirgwin, and Farrell

III. REVISED CONTINGENT MOTION TO AMEND

Having determined that Petitioner has shown by a preponderance of the evidence that original claims 1–35 of the ’399 patent are unpatentable, we proceed to address Patent Owner’s Revised Contingent Motion to Amend. Patent Owner proposes substitute claims 36–70 to replace original claims 1–35. RMTA 1.

For the reasons below, we find Petitioner shows by a preponderance of the evidence that proposed substitute claims 36–70 are unpatentable under 35 U.S.C. § 103(a). Accordingly, we deny Patent Owner’s Contingent Motion to Amend.

A. Principles of Law Concerning A Motion to Amend

In an *inter partes* review, amended claims are not added to a patent as of right, but rather must be proposed as a part of a motion to amend.

35 U.S.C. § 316(d). Ordinarily, the petitioner “bears the burden of persuasion to show, by a preponderance of the evidence, that any proposed substitute claims are unpatentable.”³² 37 C.F.R. § 42.121(d)(2);

Lectrosonics, Inc. v. Zaxcom, Inc., IPR2018-01129, Paper 15, 3–4 (PTAB Feb. 25, 2019) (precedential); *Bosch Auto. Serv. Sols. LLC v. Iancu*, 878 F.3d 1027, 1040 (Fed. Cir. 2017).

b. Proposed Substitute Claims

Patent Owner proposes substitute claim 36 to replace original claim 1, substitute claim 56 to replace original claim 21, and substitute claim 70 to replace original claim 35. RMTA 2–3. Patent Owner asserts that “[a]ll other amendments update the dependencies of certain dependent claims to depend from a corresponding substitute claim.” *Id.* at 3. The proposed substitute claims are substantially the same as the corresponding original claims but for

³² Patent Owner bears the burden of persuasion to show that the Revised MTA meets the statutory and regulatory requirements set forth in 35 U.S.C. § 316(d) and 37 C.F.R. § 42.121. In this case, we do not need to decide whether the Revised MTA meets those requirements because, as explained below, Petitioner has shown the unpatentability of the proposed substitute claims over the prior art, regardless of whether Patent Owner has met this burden.

the addition of four new limitations which, for convenience, we refer to as the “entirely pathogenic,” “endogenous and exogenous nucleases,” “without further separation,” and “one step” limitations. *See id.* at 2–3, App’x A. We address these new limitations below and refer to Section II for all other elements.

1) Entirely Non-Pathogenic (claim 36)

Proposed substitute claim 36 requires that “[a] stock solution of an aqueous composition comprising: a chaotrope, a detergent, a reducing agent, a chelator, and a buffer, wherein the stock composition, when diluted with a sample containing nucleic acids, nucleases and proteins, denatures the proteins of the sample, inactivates the nucleases of the sample, kills pathogens that may be present in the sample thereby rendering the sample entirely non-pathogenic and safe for human handling, and does not degrade the nucleic acids of the sample.” RMTA, App’x A. Patent Owner asserts that the ’278 application, from which the ’399 patent issued, provides written description support for this additional limitation. RMTA 4 (citing Ex. 2024, ¶¶ 4, 14–15, 18, 24, 48, 80–82).

The relied-upon passage states:

It is also desirable in the practice of the present methods that when one or more microbes, viruses, and/or pathogens are present in, on, or about the sample when collected, such microbes, viruses, and/or pathogens will be killed or sufficiently inactivated by one or more components of the composition to facilitate safe handling of the sample by the practitioner. Preferably, one or more components of the disclosed composition are effective to render a pathogenic sample substantially, or preferably entirely, non-pathogenic without the need for adding additional components to the composition. However, in certain applications, it may also be desirable to include one or more additional anti-microbial, anti-viral, or anti-

fungus agents to the compositions to render them substantially non-pathogenic, and thus, same for handling by the practitioner. Ex. 2024 ¶ 48. Neither above paragraph nor the Revised MTA, however, explain what “entirely non-pathogenic” means. But at Oral Hearing, Patent Owner’s counsel offered that the term encompasses something more than “substantially nonpathogenic,” proposing that we construe the term as meaning “zero pathogenic activity,” such that the sample “could not infect someone, rendering it safe for handling.” Tr. 148:3–20.

We look to the ’399 patent to interpret the limitations added in the Revised MTA. In Example 8, the Specification discloses “Killing of MRSA (ATCC33592) in PrimeStore™ Solution.”³³ Ex. 1001, 26:37–40. According to this example, “the effectiveness of the PrimeStore™ Solution (ver. 2.2) in killing a potential bacterial contaminant,” MRSA strain ATCC33592, is demonstrated when “the bacteria suspended in PrimeStore™ Solution and plated onto blood agar plates had no detectable colonies.” *Id.* at 27:29–31, *see also id.* at 28:34–35 (same).

Similarly, Example 9 demonstrates that “the disclosed composition could quickly kill or inactiv[at]e microorganisms in the sample” of chicken cloacal. *Id.* at 28:48–52. According to the ’399 patent, this result is illustrated in Figure 7B, which shows chicken cloacal samples “immersed in PrimeStore™ Solution (top row) or water (bottom row) and subsequently plated onto blood agar plates.” *Id.* at 28:53–59. Although the image quality is not ideal, it appears the plates with samples treated with the disclosed composition have no detectable colonies. *See id.* at Fig. 7B.

³³ According to the ’399 patent, the formulations of the compositions disclosed therein are alternatively referred to as “PrimeStore™ Solution,” versions 1 and 2. Ex. 1001, 20:33–36, 21:30–35, 22:19–22.

Thus, in view of the disclosures of the '399 patent, we conclude that a sample is rendered “entirely non-pathogenic” when the treated sample forms no detectable colonies or plaques on an applicable plate assay.

That, however, does not resolve completely the issue because the parties disagree over whether rendering a sample “entirely non-pathogenic” requires the composition to kill or inactivate all types of pathogens disclosed in the '399 patent. As noted in section II.C.2, we defined the scope of “pathogens” as disclosed in the '399 patent as comprising fungi, viruses, and vegetative bacteria, exclusive of spores.

Patent Owner argues that the prior art does not disclose or render obvious the “entirely non-pathogenic” limitation. *See generally* RMTA 9–12; Reply RMTA 3–5. Petitioner, however, presents substantial argument and evidence to the contrary. Opp. RMTA 5–7 (*citing* Ex. 1008 ¶ 38 (“The modified lysis buffer...helps to inactivate all mycobacteria present in a clinical specimen, lyse tough mycobacterial cell[s] and denature and remove proteins ... and also ***ensure safety for the operator.***”); Ex. 1083, 50 (“The strong chaotropic properties of GTC (Chirgwin et al., 1979) ... ***renders the sample non-infectious and safe to handle.***”)); Ex. 1082 ¶ 18–38; Sur-reply RMTA, 3–5 (citing, e.g., Ex. 1083, 50) (Chirgwin’s teaching that guanidinium thiocyanate “renders the sample non-infections and safe to handle”) Ex. 1089 ¶ 38; Ex. 1016, 7:19–23.³⁴

Petitioner further argues that data from tests conducted by Assured Bio Labs (ABL) for Patent Owner [REDACTED]

³⁴ Although not necessary to our analysis, Petitioner also argues that construing the claims to inactivate *all* pathogens would render them indefinite, non-operative, and invalid for lack of written description. *See* Opp. RMTA 16–20; Reply RMTA 9–12.

[REDACTED] Opp. RMTA 5 (citing e.g., Exs. 1201–1204; Ex. 1069, 272:13–273:7; Ex. 1082 ¶¶ 16–17). This, Petitioner contends, demonstrate that the tested samples were rendered “entirely non-pathogenic.” *Id.*

Patent Owner counters that data from the ABL report show Birnboim’s composition did not inactivate two [REDACTED] types of pathogens. RMTA 3 (citing Ex. 2033 ¶ 24, n.1; Ex. 2019 ¶ 15); Thus, Patent Owner asserts, regardless of whether Birnboim’s composition kills or biologically inactivates some types of viruses or bacteria, it “fails to biologically inactivate so as to render the sample entirely non-pathogenic and safe for human handling.” *Id.*

Based on this record, and as explained below, we agree with Petitioner’s argument. As Petitioner points out, and Patent Owner does not dispute, ABL’s test data from show [REDACTED]

[REDACTED]³⁵ Opp. RMTA 5 (citing Exs. 1201–1204; Ex. 1069, 272:13–273:7); *see also* Ex. 1069, 245:5–246:16 (Dr. Birkebak at ABL testifying [REDACTED]
[REDACTED]); 247:13–248:21 (similar testimony [REDACTED]
[REDACTED]). We agree with Petitioner that when a pathogen in a sample is no longer detectable in the sample, the sample is biologically inactivated and rendered entirely non-pathogenic and safe for human handling. *See* Second MTA Opp. 5 (citing Ex. 1082 ¶ 16–17).

³⁵ Unreported validation testing on *E. coli* by ABL showed Birnboim’s composition also inactivated *E. coli*. *See* Ex. 1069, 236:11–237:15.

In sum, Petitioner has shown, by a preponderance of the evidence, that Birnboim explicitly discloses that its compositions inactivate the sample contacted and render the sample “entirely non-pathogenic and safe for human handling” as recited in proposed amended claim 36.

2) Endogenous and Exogenous Nucleases (claim 56)

Proposed substitute claim 56 requires that a “method for obtaining a population of polynucleotides from a sample suspected of containing nucleic acids, comprising contacting the sample with an amount of the stock solution in accordance with claim 36, under conditions effective to obtain the population of polynucleotides containing DNA and RNA from the sample, wherein the amount of the stock solution inactivates endogenous and exogenous nucleases to prevent degradation of the population of polynucleotides in the sample.” RMTA App’x.

Petitioner contends that the “inactivates endogenous and exogenous nucleases” and the “containing DNA and RNA” limitations are disclosed in Birnboim and numerous other prior art references. Opp. RMTA 1–5, 7-8; Sur-Reply RMTA 1–3. Patent Owner contends that Birnboim does not disclose inactivating exogenous nucleases, which come from different sources than an endogenous nuclease. RMTA 13–14; Reply RMTA 2–3. Considering the entirety of art and argument of record, we agree with Petitioner.

Focusing on Birnboim, the reference explains that, in the digestive tract, DNases and RNases are found in secretions of the pancreas and cells of the salivary gland and buccal mucosa. Ex. 1003 ¶ 68. In addition, according to Birnboim, “microorganisms resident in the mouth or from recently ingested foods may contain” DNases and RNases. *Id.* Birnboim states that chelators, including EDTA, and those stronger than EDTA, such

as cyclohexane diaminetetraacetate (CDTA) and diethylenetriamine pentaacetic acid (DTPA), inhibit pancreatic DNases. *Id.* ¶¶ 16, 67, 68. In addition, the activity of DNases and RNases “can also be inhibited by denaturing agents that will destroy the complex structures of these enzymes (proteins).” *Id.* ¶ 68. Thus, Birnboim explicitly discloses including denaturing agents, such as urea, SDS, guanidinium chloride, and guanidinium thiocyanate, in “the nucleic acid preserving composition” of its invention. *Id.*

Relying on these disclosures, Dr. Taylor testifies that “Birnboim expressly discloses that its compositions inactivate nucleases that are internal or external to the target cell.” Ex. 1082 ¶ 6 (citing Ex. 1003 ¶ 68). Petitioner, citing Dr. Taylor’s testimony, argues that “Birnboim discloses the inactivation of endogenous and exogenous nucleases.” Opp. RMTA 2 (citing Ex. 1003 ¶ 68; Ex. 1082 ¶¶ 5–8).

Patent Owner does not address Dr. Taylor’s testimony or Petitioner’s argument on this point. Instead, Patent Owner disputes Petitioner’s contention that “there is no difference in inactivating an endogenous or exogenous nuclease.” Reply RMTA 2. According to Patent Owner, endogenous and exogenous nucleases are not equivalent because “coming from different sources, they may have different rates of activity and susceptibility to inactivation.” *Id.* (citing Ex. 2042 ¶ 11; Ex. 2044³⁶). We address below Patent Owner’s reliance on Dr. DeFilippi’s testimony (Ex. 2042).

³⁶ Exhibit 2044, titled “Biofilms: Survival Mechanisms of Clinically Relevant Microorganisms,” is a 27-page document. Patent Owner does not direct us any specific disclosure that supports its argument, absent such guidance, we do not apprehend how this reference supports its position.

With respect to Patent Owner’s reliance on its expert’s testimony, Dr. DeFilippi states:

One cannot equate the properties, and thus sensitivity to denaturing conditions, of endogenous and exogenous nucleases, which may include different specific enzymes from different biological sources that may be in different types of biofilms (particularly relevant in the context of a sputum sample) and thus may have different rates of activity and different rates and susceptibility to inactivation (and which may differ depending on the specific method of inactivation at issue).

Ex. 2042 ¶ 11 (citing Ex. 2044, 168). Page 168 of Exhibit 2044—or for that matter, the Exhibit in its entirety—however, does not appear to discuss nucleases. Instead, as Dr. DeFilippi testified, Exhibit 2044 “mostly related to biofilms,” and did not make any reference to nucleases.³⁷ Ex. 1096, 1065:18–1066:6.

More importantly, we find Petitioner’s argument and Dr. DeFilippi’s testimony here inconsistent with the position they took elsewhere. For example, in its Sur-reply for the case-in-chief, Patent Owner argued that inactivation of RNases “turns on the number of RN[ase] molecules, not their activity level.” Sur-Reply, 3. As Petitioner points out, Patent Owner does not reconcile this argument with its attempt here to distinguish endogenous and exogenous nucleases inactivation, even if the enzymes “may have different rates of activity.” *See* Sur-reply RMTA, 1–2.

Similarly, pointing to the claim language “sufficient to denature proteins,” Dr. DeFilippi testified: “So I’m denaturing proteins in general. And included in that would be inactivation of the nucleases.” Ex. 1064,

³⁷ To the extent Dr. DeFilippi emphasizes “different types of biofilms” (Ex. 1096, 1067:2–10; Ex. 2042 ¶ 11), neither he, nor Petitioner, sufficiently explains the relevance of biofilms to the proposed substitute claims at issue.

525:1–4; *see also id.* at 525:17–19 (“We are denaturing proteins, and the result of denaturing proteins would be destroying the activity of enzymes.”). Birnboim and other prior art, confirms this testimony, that is, denaturing agents, by destroying protein structures, inactivate nucleases (which are proteins), regardless of their type or source. *See, e.g.*, Ex. 1003 ¶ 68; *see also* Ex. 1015, 5296 (“Since the early steps of the procedure are always carried out in the presence of denaturants, sterile procedures and glassware are unnecessary, but as soon as the RNA is no longer in the presence of guanidine, stringent precautions against adventitious³⁸ nucleases must be taken.”). Thus, Dr. DeFilippi’s own testimony that denaturants inactivate nucleases, which is consistent with the express teachings of the prior art, contradicts his opinion that exogenous nucleases may not be inactivated merely because they are from “different biological sources.”

Patent Owner emphasizes that, in Example 7, Birnboim added ribonuclease to digest and remove the majority of RNA present in the sample. RMTA 13. According to Patent Owner, this ribonuclease is an exogenous nuclease, and it is “clearly not inactivated.” *Id.* Thus, Patent Owner concludes “Birnboim composition cannot be said to inactivate both endogenous and exogenous nucleases.” *Id.* We disagree.

Example 7 teaches incubating a saliva sample with Birnboim’s composition. Ex. 1003 ¶ 124. It is after this incubation that Birnboim added additional, exogenous ribonuclease to digest RNA. *Id.* The ’399 patent, on

³⁸ Dr. DeFilippi appears to have misunderstood the term “adventitious.” *See* Ex. 1096, 985:22–986:1 (testifying that the term “[A]dventitious” means it takes advantage of the situation”). In fact, the term means “coming from another source and not inherent or innate” and, thus, in the present context, is synonymous with exogenous. *See* <https://www.merriam-webster.com/dictionary/adventitious>.

the other hand, discloses that its compositions “typically at least substantially inactivate, and preferably entirely inactivate, any endogenous or exogenous RNases or DNases present *in the sample*.” Ex. 1001, 6:32–35 (emphasis added). Thus, the ’399 patent does not contemplate inactivating nucleases added to the sample, such as the additional ribonuclease added in Birnboim Example 7, which is unrelated to the biological sample studied.³⁹ *See id.* at 9:19–27 (disclosing inactivating “exogenous or endogenous nucleases that may be *present in, on, or about the sample itself*”) (emphasis added).

In sum, Petitioner has shown, by a preponderance of the evidence, that compositions taught and suggested by Birnboim “inactivate endogenous and exogenous nucleases,” as required by proposed substitute claim 56.

3) *Without Further Separation (claim 70)*

Proposed substitute claim 70 requires that, “released polynucleotides are compatible with a nucleic acid test without further separation from the sample.” RMTA 14–15. The “without further separation” limitation was first presented in the original MTA. *See* MTA 3, 15–17.

Petitioner argues, in its Opposition to the original MTA, that Birnboim discloses this additional limitation because, in Example 7, Birnboim discloses contacting a sample with its composition, incubating the treated sample, digesting the sample with ribonuclease to remove RNA, and applying the sample to an agarose gel. OPP. MTA 8 (citing Ex. 1003 ¶ 124).

³⁹ Were it otherwise, the proposed substitute claims reciting inactivating exogenous nucleases would lack written description support. Those claims also would be indefinite because they do not limit the amount of the extra nucleases. Further, the ’256 patent does not teach how to inactivate an overwhelmingly large amount of added nucleases, and thus, does not enable the proposed substitute claims.

According to Petitioner, the target “DNA is not separated from the sample prior to running the samples on the agarose gel.” *Id.*; *see also id.* at 13 (“To reduce the time and labor necessary to preliminarily test if the sample includes the target nucleic acid, a POSA would have been motivated to add a nuclease to digest the non-target nucleic acid in the sample (as Birnboim discloses in Example 7), then proceed directly to running the sample on an agarose gel. Ex. 1003, ¶124; Ex. 1071, ¶37.”). In the Preliminary Guidance, we found Petitioner’s argument persuasive. *See* PG 13–14. We explained that Birnboim’s addition of ribonuclease to remove (i.e., digest) extraneous RNA does not equate to separation of the sample, as presently excluded by the language of proposed substitute claim 35. *Id.* at 14 (“We do not find that adding a ribonuclease to remove RNA causes separation of the sample.”).

In the Revised MTA, Patent Owner does not address Birnboim’s Example 7 as it relates to the “no further separation” limitation.⁴⁰ In the RMTA Reply, Patent Owner contends “Birnboim’s use of RNase in Ex. 7 is a separation step used prior to DNA testing using gel electrophoresis that separates hydrolyzed RNA fragments from the intact DNA. Reply RMTA 5 (citing Ex. 2042 ¶¶ 16, 39–40).

For the reasons set forth below and as argued by Petitioner, Patent Owner’s argument is unavailing. *See* Opp. RMTA 6–9; Sur-reply RMTA 5–6. Proposed substitute claim 70 requires first, “the lysis of “cells in the sample to release polynucleotides” and second, that “the released polynucleotides are compatible with a nucleic acid test without further separation *from the sample*.” Claim 70, thus, makes clear that it requires

⁴⁰ *But see* RMTA 7 (Patent Owner discussing Example 7 as it relates to “inactivates endogenous and exogenous RNases and DNases”).

lysis of cells in the sample, and is agnostic as to lysis of polynucleotides, insofar as the sample contains sufficient polynucleotides for detection. In Birnboim's Example 7, the sample is saliva. Thus, even if we were to agree with Patent Owner that "Birnboim's use of RNase . . . separates hydrolyzed RNA fragments from the intact DNA," such separation would not be "*from the sample*." We apply essentially the same analysis in rejecting Patent Owner's contention that "Birnboim's use of Proteinase K in Example 4 is a separation step." *See* Reply RMTA 5; Sur-reply 5–6.

In considering the "without separation" limitation, we are not unmindful that proposed substitute claim 70 recites that the DNA detection methodology is "PCR amplification" rather than the agarose gel of Birnboim's Example 7. Birnboim, however, repeatedly discloses the use of well-known PCR techniques. *See e.g.*, Ex. 1003 ¶¶ 53, 54, 79, 118–121. Although Birnboim's exemplification of PCR amplification appear to include centrifugation and precipitation steps (*see e.g., id.* ¶ 119), Petitioner argues persuasively that the necessity of such additional separation steps is "purely a function of the prior art nucleic acid tests, not the claimed solution." Opp. RMTA 9; *see also* Ex. 1015, 5296 (disclosing that post-lysis centrifugation and precipitation "steps can be varied according to the specific circumstances."

In this respect, Petitioner points to the '399 patents disclosure of conventional nucleic acid tests, including the commercially-available Tigris DTS platform, which "automates the entire detection process." *Id.* at 7 (citing Ex. 1001, 1:21–25, 2:57–62, 9:48–51, 15:12–13, 16:31–35.). Petitioner, and its expert Dr. Taylor presents evidence that the Tigris DTS platform (and other integrated nucleic acid test systems), were available for

performing testing on samples treated with prior art solutions such as Birnboim's without further separation from the sample. *Id.* (citing e.g., Ex. 1088, 450, 452, 455; Ex. 1089, 94; 1090; 4, 10); Ex. 1082 ¶¶ 25–26.

Although it is undisputed that the Tigris DTS platform performs PCR amplification as required by claim 35 (*see* Ex. 1089, 94), Patent Owner argues that Petitioner does not adequately “support its assertion that the TIGRIS or similar systems could be used with any composition described in Birnboim or Chirgwin or why a POSA would be motivated to do so.” Reply RMTA 5–6 (citing Ex. 2042 ¶¶ 41–45). Considering the record as a whole, including Birnboim's teaching to use its disclosed compositions to perform PCR, the scope of the prior art and the skill of one of ordinary skill in the art, we do not agree with Patent Owner's argument. *See e.g.* Section II.B, above; *see also* Opp. RMTA 10–11 (citing *In re Epstein*, 32 F.3d 1559, 1568 (Fed. Cir. 1994) (“[T]he Board's observation that appellant did not provide the type of detail in his specification that he now argues is necessary in prior art references supports the Board's finding that one skilled in the art would have known how to implement the features of the references and would have concluded that the reference disclosures would have been enabling.”)).

In sum, Petitioner has shown, by a preponderance of the evidence that the prior art teaches or suggests the “without further separation” limitation of proposed substitute claim 70.

4) One Step (claim 70)

Proposed substitute claim 70 further recites that contacting the biological sample with the stock solution is “effective to, in one step” to effect the functional limitations of the claim. As with the “without further separation” limitation, the “one step” limitation was first presented in the original MTA. *See* MTA 3, 13–14. To the extent the parties expressly

address the “one step” limitation, their arguments and evidence is coincident with, if not subsumed by, their discussion of “without further separation.” *See* RMTA 12–14; Opp. RMTA 6–9; Reply RMTA 5–6; Sur-reply RMTA 5–6. As such, our analysis of the two limitations is substantially the same. *See* Section III.B.3, above; *see* Prelim Guid. 13–14.

In short, evidence adduced at trial confirms our initial determination that “Birnboim discloses stock solutions (“nucleic acid preserving compositions”) for use in a one-step method to lyse nucleic acid-containing cells or viruses, release the nucleic acids into the composition, inactivate nucleases in the sample, and stabilize the extracted nucleic acid for future analysis.” DI 13. In Section III.B.2, above, we determined that Birnboim’s compositions “inactivate endogenous and exogenous nucleases.” In Section III.B.3, we determined that one of ordinary skill in the art would be motivated, with a reasonable expectation of success to analyze nucleic acid extracted using Birboim’s stock solution (or obvious modification thereof) using PCR amplification, and without further separation from the sample. Taken together, Petitioner has shown by a preponderance of the evidence that the “one step” limitation of claim 70 is taught or suggested by the prior art.

5) Proposed Substitute Dependent Claims 37–55 and 57–69

Substitute claims 37–55 and 57–69 depend from substitute claim 36. RMTA App’x. Patent Owner contends proposed substitute claims 37–55 differ from original claims 2–20 and 22–34, respectively, only in that they depend from proposed substitute claim 36. RMTA 12, 13–14.

Petitioner contends the following:

- (1) that proposed substitute claims 37, 40–43, and 49 are anticipated by each of Chirgwin, Casas, Donofrio, Laulier, Zinkevich, and Das (Opp. RMTA 15);
- (2) proposed substitute claim 38 would have been obvious in view of Chen with any of the compositions of Chirgwin, Casas, Donofrio, Laulier, Zinkevich, or Das (*id.*);
- (3) proposed substitute claim 39 is anticipated by Das (*id.*);
- (4) proposed substitute claims 44 and 50 is anticipated by Chirgwin and would have been obvious in view of Casas, Donofrio, Laulier, Zinkevich, and Das in view of Chirgwin (*id.* at 15–16);
- (5) proposed substitute claims 45–47 would have been obvious over each of Chirgwin, Casas, Donofrio, Laulier, Zinkevich, and Das in view of Birnboim (*id.* at 16);
- (6) proposed substitute claims 48 would have been obvious to Birnboim’s stable pH range for RNA in each of the compositions in Das, Chirgwin, Casas, Donofrio, Laulier, and Zinkevich (*id.*);
- (7) proposed substitute claims 51 would have been obvious over Chirgwin, Casas, Donofrio, Laulier, Zinkevich, and Das in view of each of Helftenbein and Goldrick (*id.* at 16–17);
- (8) proposed substitute claim 52 is anticipated or rendered obvious by Chirgwin, and also is obvious in view of Donofrio and Chirgwin (*id.* at 17);

- (9) proposed substitute claims 53–55 would have been obvious over Chirgwin (*id.* at 17–18);
- (10) proposed substitute claims 57 and 63 are anticipated or would have been obvious in view of Birnboim, and also would have been obvious over Zinkevich, Donofrio, Laulier, and Das in view of Birnboim (*id.* at 18);
- (11) proposed substitute claims 58–60, 64 and 65 would have been obvious over Laulier in view of Birnboim (*id.* at 19);
- (12) proposed substitute claims 61 and 62 are anticipated or would have been obvious in view of Birnboim, and also would have been obvious over Zinkevich, Donofrio, Laulier, and Das in view of Birnboim (*id.*);
- (13) proposed substitute claim 66 would have been obvious over Laulier in view of Birnboim (*id.*);
- (14) proposed substitute claims 67 and 68 are anticipated or would have been obvious in view of Birnboim, and also would have been obvious over Chirgwin, Casas, Donofrio, Laulier, Zinkevich, and Das in view of Birnboim (*id.* at 19–20); and
- (15) proposed substitute claim 69 would have been obvious in view of Chirgwin with Birnboim and Farrell (*id.* at 20).

For the reasons set for in Sections II.E. and II.F. (with respect to the limitations common to claim 1), and in Section III.B. (further with respect to the newly-added limitations of claim 36), we agree with Petitioner.⁴¹ For

⁴¹ As such, we need not address Petitioner’s other obviousness arguments, including that Chirgwin’s formulation inherently provides the claimed functional limitations as claimed because it is substantially similar to the

additional reasons discussed in Sections II.E–O, above, and in view of the record as a whole, we further agree that proposed dependent claims 37–55 and 57–69 are unpatentable as obvious over the prior art. *See e.g.*, Opp. RMTA 12–15.

Accordingly, considering the entirety of the record, we determine Petitioner has shown by a preponderance of the evidence that proposed substitute claims 36–70 are unpatentable as obvious in view of the prior art, including Birnboim, Chen, Chirgwin, Das, Farrell, and Helftenbein.

IV. MOTION TO EXCLUDE

Patent Owner filed a Motion to Exclude Evidence. Paper 80 (“MTE”). Specifically, Patent Owner moves to exclude Birnboim, the primary prior art reference relied on in the Petition. MTE 1–2. Patent Owner also moves to exclude certain test results from ABL, the third-party laboratory Patent Owner engaged to perform tests on several biological samples, as well as the deposition transcripts of three ABL employees. *Id.* at 6–8, 11–15. Patent Owner further moves to exclude test results from Nelson Labs, a third-party laboratory Petitioner engaged to perform tests on two biological samples. *Id.* at 4–5. Additionally, Patent Owner moves to exclude certain declarations of Petitioner’s expert witness, Dr. Taylor. *Id.* at 6–8. Patent Owner also moves to exclude numerous articles published in peer-reviewed journals and published U.S. patent applications. *Id.* at 2–4, 8–11.

Patent Owner, as the party moving to exclude evidence, bears the burden of proving that it is entitled to the relief requested, namely, that the material sought to be excluded is inadmissible under the Federal Rules of

sole stock solution disclosed in ’728 provisional application and to Example 2 of the ’399 patent. Opp RMTA 11; Opp. MTA 1–2 (citing Ex. 1049, 9; Ex. 1015, 5294–95; Ex. 1001, 21:37–58).

Evidence. *See* 37 C.F.R. §§ 42.20(c), 42.62(a). For the reasons explained below, Patent Owner has not met that burden. Thus, Patent Owner's MTE is dismissed-in-part and denied-in-part.

1. Ex. 1003

Exhibit 1003 is Birnboim, the primary reference Petitioner relies on. Patent Owner moves to exclude Birnboim “to the extent Petitioner relies on Birnboim’s specification to *prove the truth* of testing data stated and described therein without submitting an affidavit by an individual having first-hand knowledge of how the data was generated, which contravenes 37 C.F.R. §42.61(c).” MTE 1. According to Patent Owner, Petitioner cannot rely on the test results reported in Birnboim’s specification and figures because Petitioner has not provided any affidavit from a person with first-hand knowledge of the experiments discussed therein. *Id.* We are not persuaded.

Petitioner relies on Birnboim, a U.S. patent application, to prove what its specification describes, which renders Birnboim admissible. *See* 37 C.F.R. § 42.61(c) (stating a patent application is admissible as evidence “only to prove what the specification or drawing describes”); *see also* 77 Fed. Reg. 48,612, 48,624 (Aug. 14, 2012) (explaining that § 42.61(c) addresses the “problem in which a party mistakenly relies on a specification to prove a fact other than what the specification says”).

In seeking to exclude Birnboim, Patent Owner faults Petitioner for “repeatedly rel[ying] on *other references*” to support the arguments “regarding Birnboim’s performance of functional limitations.” MTE 1 (emphasis added). This appears to be counter to Patent Owner’s argument

that “Petitioner relies on *Birnboim’s specification to prove the truth* of testing data stated and described therein.” *Id.* (the first emphasis added).

The examples Patent Owner points to do not show that Petitioner relies on Birnboim’s specification to prove a fact other than what the specification describes. Indeed, Patent Owner points to Paper 68, Petitioner’s second MTA Opposition, where Petitioner allegedly “incorporat[ed] by reference argument in Taylor Decl. (Ex. 1082 ¶ 5) purporting to interpret and rely upon Birnboim ¶¶ [0020] and [0068].” MTE 2 (citing second MTA Opp. 2). In his Declaration, Dr. Taylor testified that “Birnboim discloses compositions that ‘inactivate nucleases’— including DNases and RNases.” Ex. 1082 ¶ 5 (citing Ex. 1003 ¶¶ 20, 68). In paragraph 68, Birnboim teaches “[t]he action of deoxyribonucleases and ribonucleases can also be inhibited by denaturing agents that will destroy the complex structures of these enzymes (proteins). Hence, denaturing agents are included in the nucleic acid preserving composition of the invention.” Ex. 1003 ¶ 68. It goes on to list examples of denaturing agents. *Id.*; *see id.* ¶ 20. Thus, Petitioner and Dr. Taylor rely on Birnboim to prove what its specification describes, as permitted under 37 C.F.R. § 42.61(c).

Because Petitioner relies on Birnboim to show what its specification describes, we deny Patent Owner’s Motion to Exclude Exhibit 1003.

2. *Exhibits 1008, 1015, 1050, 1052, 1054, 1056–1058, 1060, 1083, 1085–1092, 1095*

Each of these cited documents are either U.S. patent publication or a publication from a scientific peer-reviewed journal. Patent Owner argues Petitioner impermissibly relies on the cited documents for the truth of the data they report. Paper 80, 2–3 (citing 37 C.F.R. § 42.61(c)), 8–11. Patent

Owner further argues that these documents are irrelevant and prejudicial but fails to explain why. *Id.* at 3, 8–11.

We do not rely on Exhibits 1050, 1052, 1054, 1056–1058, 1060, 1083, 1085–1092, and 1095 in rendering this Decision. Thus, we dismiss this aspect of Patent Owner’s Motion to Exclude as moot.

For Exhibit 1015 (Chirgwin), we find Rule § 42.61(c) does not apply because it is an article published in a scientific journal. *See* 37 C.F.R. § 42.61(c) (discussing the admissibility of “specification or drawing of a United States patent application or patent”). Thus, we deny Patent Owner’s Motion to Exclude Exhibit 1015.

Although Rule § 42.61(c) does apply to Das, a published U.S. patent application, Patent Owner does not identify what “data” in Das Petitioner attempts to prove the truth of. Indeed, Patent Owner cites “Petition, 45, 62; Paper 40, 19; Paper 41, 2–3, 5–6” in support of its argument to exclude nine references, including Das. MTE 3. Because Patent Owner has not met its burden of proving that it is entitled to the relief requested, we deny Patent Owner’s Motion to Exclude Exhibits 1008. *See* 37 C.F.R. §§ 42.20(c), 42.62(a).

3. *Exhibit 1068*

Exhibit 1068 is a testing report from a third-party laboratory, BioScience. Patent Owner moves to exclude this testing report as improper hearsay (FRE 802), unsupported lay or expert opinion testimony (FRE 701/702), and improper expert testimony/testing data. Paper 80, 4 (citing 37 C.F.R. §§ 42.65; 42.61(c)).

We do not rely on Exhibit 1068 in rendering this Decision. Thus, we dismiss this aspect of Patent Owner's Motion to Exclude Exhibit 1068 as moot.

4. *Ex. 1069*

Exhibit 1069 is the deposition transcript of Joshua M. Birkebak, Ph.D. ("Dr. Birkebak"). Dr. Birkebak is the employee of third-party, Assured Bio Labs, LLC. *See* Ex. 2048 ¶ 3. Dr. Birkebak was involved in verifying test results for Patent Owner. *Id.* ¶ 4, Ex. B.

Patent Owner moves to exclude sections of Dr. Birkebak's April 26, 2022, deposition transcript that describe the consulting testing and exhibits reflecting the consulting testing that Patent Owner asserts constitute its protected work product. Paper 80, 6 (citing Ex. 1069, 200:1–278:12). Yet, Patent Owner fails to explain exactly how or why the information constitutes work product.

Having reviewed the transcript, it appears the information provided in the entirety of Dr. Birkebak's deposition, not just the cited portions, relays facts specifically related to tests run by Assured Bio Labs, LLC with solutions that are identical to or variations of the compounds disclosed in Birnboim. *See e.g.*, Ex. 1069, 217:1–222:8. It appears Patent Owner initially only produced test results that supports Patent Owner's position in its Response (Paper 21). Following an order from the Board (Paper 32), Patent Owner then produced tested results that are averse to its position. Now Patent Owner claims the adverse test results are protected by work product privilege. Paper 80, 6. Patent Owner's argument is unavailing. The test results and the corresponding deposition testimony from Dr. Birkebak relay

facts not attorney trial strategy and, therefore, do not qualify as work product.

Accordingly, we deny Patent Owner's Motion to Exclude Exhibit 1069.

5. Exhibits 1071 and 1082

Exhibits 1071 and 1082 are Declarations of Richard F. Taylor, Ph.D. ("Dr. Taylor"). Dr. Taylor's Declarations discuss the testing performed by Assured Bio Labs, LLC and refers to Birnboim as well as other references.

Patent Owner moves to exclude because the testing report is work product while Birnboim and the other references do not have supporting affidavits. Paper 80, 6–7, 8. For the same reasons discussed above regarding Birnboim (Ex. 1003) and Exhibit 1069, we are unpersuaded by Patent Owner's arguments.

Accordingly, we deny Patent Owner's Motion to Exclude Exhibits 1071 and 1082.

6. Exhibits 1072 and 1073

Exhibit 1072 is the deposition transcript of Ms. Anna Tolli. Ms. Tolli is an employee of Assured Bio Labs, LLC and signed the Quality Inspection Statement for the test results for Patent Owner. *See* Exhibit 2049 ¶ 4, Ex. B. Exhibit 1073 is the deposition transcript of Mr. David L. Grant. Mr. Grant is an employee of Assured Bio Labs, LLC and "performed and oversaw the testing that was part of the lab report" for Patent Owner. Ex. 1073, 19:15–21.

Patent Owner moves to exclude sections of Exhibits 1072 and 1073 that describe the testing and exhibits reflecting the testing as being protected work product. Paper 80, 7. Specifically, Patent Owner moves to exclude the

following portions of these transcripts: Ex. 1072, 79:21–92:6; Ex. 1073, 180:6, 182:18–229:22. *Id.*

While Patent Owner cites specific portions of the deposition transcripts, Patent Owner fails to explain exactly how or why the information constitutes work product. Having reviewed the transcript, it appears the information provided in the entirety of both depositions, not just the cited portions, relays facts specifically related to tests run by Assured Bio Labs, LLC with compounds that are identical to or variations of the compounds disclosed in Birnboim.

As discussed above with regards to Exhibit 1069, it appears Patent Owner initially only produced test results that support Patent Owner's position in its Response (Paper 21). Following an order from the Board (Paper 32), Patent Owner then produced tested results that are averse to its position. Now Patent Owner claims the adverse test results are protected by work product privilege. Paper 80, 6. Patent Owner's argument is unavailing. The test results and the corresponding deposition testimony from Ms. Tolli and Mr. Grant relay facts not attorney trial strategy and, therefore, do not qualify as work product.

Accordingly, we deny Patent Owner's Motion to Exclude Exhibits 1072 and 1073.

7. Exhibit 1200

Patent Owner moves to exclude Exhibit 1200 but this exhibit does not exist. Accordingly, we consider Patent Owner's request moot.

8. Exhibits 1205, 1208

Exhibit 1205 is a publicly available spreadsheet listing tested organisms, testing solutions, and the resulting organism concentration.

Exhibit 1208 is a publicly available reproduction of a peer-reviewed scientific article by Eichel et al. published in the Archives of Biochemistry and Biophysics in 1964.

Patent Owner moves to exclude Exhibits 1205, 1208 as being protected work product. Paper 80, 11–15. Exhibits 1205 and 1208 are publicly available, however, and Patent Owner does not appear to object specifically to these two exhibits as being work product. Patent Owner further fails to explain how the information disclosed in Exhibits 1205, 1208 constitute work product.

Accordingly, we deny Patent Owner's Motion to Exclude Exhibits 1205 and 1208.

9. Exhibits 1201–1204, 1206, and 1207–1211

Exhibit 1201 is a list of reagents and amounts used to create solutions used for testing by Assured Bio Labs LLC. Exhibit 1202 is a spreadsheet listing tested organisms, testing solutions, and the resulting organism concentration. Exhibit 1203 is a graphic representation of testing results of solutions used on specific tested organisms. Exhibit 1204 is a graphic representation of testing results of solutions used on specific tested organisms. Exhibit 1206 is a standard operating procedure on how to perform testing protocol at Assured Bio Labs LLC. Exhibit 1207 is a spreadsheet [REDACTED]. Exhibit 1209 is a [REDACTED] spreadsheet. Exhibit 1210 is a product testing data sheet from Assured Bio Labs LLC. Exhibit 1211 is a spreadsheet showing data analysis of several runs of quantitative PCR assays determining the impact of the presence of [REDACTED] RNase.

Patent Owner moves to exclude Exhibits 1201–1204, 1206, and 1207–1211 as being protected work product. Paper 80, 11–15.

Having reviewed the exhibits, it appears the information provided therein relays facts specifically related to tests run by Assured Bio Labs, LLC with compounds that are identical to or variations of the compounds disclosed in Birnboim. As discussed above with regards to Exhibit 1069, it appears Patent Owner initially only produced test results that supports Patent Owner’s position in its Response (Paper 21). Following an order from the Board (Paper 32), Patent Owner then produced tested results that are averse to its position. Cherry picking test results that support your position, while simultaneously withholding results that undermine your position is specifically prohibited by our rules. *See* 37 C.F.R. § 42.51(b)(1)(iii).

Under Rule § 42.51(b)(1)(iii),

a party must serve relevant information that is inconsistent with a position advanced by the party during the proceeding concurrent with the filing of the documents or things that contains the inconsistency. This requirement does not make discoverable anything otherwise protected by legally recognized privileges such as attorney-client or attorney work product. This requirement extends to inventors, corporate officers, and persons involved in the preparation or filing of the documents or things.

In an attempt to circumvent our rules, Patent Owner claims the adverse test results are protected by work product privilege. Paper 80, 11–15. To support its argument Patent Owner argues it is allowed to “explored different theories and options in preparing its response to the Petition.” *Id.* at 14. Patent Owner further argues that Assure Bio Labs LLC was testing “a variety of hypotheses in consultation with Longhorn’s counsel to assist in

this process. Such testing is quintessentially consulting expert work product immune from discovery.” *Id.*

Patent Owner’s argument is unavailing. Patent Owner does not appear to have “tested a variety of hypothesis” so much as it tested all the compounds, solutions, and organisms disclosed in Birnboim in an attempt to discredit Birnboim. Several of the compounds, however, produced results inconsistent to Patent Owner’s arguments in its Response. Simply because a test produces results contrary to a party’s initial hope, does not mean the party was exploring different theories and options. Rather, Patent Owner tested one theory—that Birnboim would not work. When it did, Patent Owner knowingly withheld those inconsistent test results.

The test protocols and test results conducted by Assured Bio Labs LLC relay the specific facts of the tests, not attorney trial strategy and, therefore, does not qualify as work product. Accordingly, we deny Patent Owner’s Motion to Exclude Exhibits 1201, 1202, 1204, 1206, and 1208.

We do not rely on Exhibits 1203, 1207, and 1209–1211 in rendering this Decision. Thus, we dismiss this aspect of Patent Owner’s Motion to Exclude Exhibits 1203, 1207, and 1209–1211 as moot.

V. PATENT OWNER’S MOTION TO SEAL

Patent Owner filed an unopposed Motion for entry of a Protective Order. Paper 35. According to Patent Owner, the parties have agreed upon a protective order that deviates from the Board’s default protective order. *Id.* Patent Owner filed a marked-up comparison of the proposed and default protective orders. Ex. 2030. and a clean copy of the proposed protective order. Paper 37. The Protective Order as set forth in Paper 37 is hereby

entered. It shall govern the conduct of the proceeding unless otherwise modified.

Patent Owner filed Motion to Seal. Paper 41 (“Mot.”). Petitioner filed an Opposition to the Motion (Paper 49, “Opp. Mot.”), and Patent Owner filed a Reply in support of its Motion to Seal (Paper 61).

There is a strong public policy for making all information filed in an *inter partes* review open to the public, especially because the proceeding determines the patentability of claims in an issued patent and, therefore, affects the rights of the public. Generally, all papers filed in an *inter partes* review shall be made available to the public. *See* 35 U.S.C. § 316(a)(1); 37 C.F.R. § 42.14. Our rules, however, “aim to strike a balance between the public’s interest in maintaining a complete and understandable file history and the parties’ interest in protecting truly sensitive information.”

Consolidated Patent Trial Practice Guide (“Trial Practice Guide”)⁴² 19.

Thus, a party may move to seal certain information (37 C.F.R. § 42.14); but only “confidential information” is protected from disclosure (35 U.S.C. § 326(a)(7)). Confidential information means trade secret or other confidential research, development, or commercial information. 37 C.F.R. § 42.2.

The standard for granting a motion to seal is “for good cause.” 37 C.F.R. § 42.54(a). The party moving to seal bears the burden of proof and must explain why the information sought to be sealed constitutes confidential information. 37 C.F.R. § 42.20(c).

As we understand the motion, Patent Owner seeks to seal the entirety of Exhibits 1202–1204, 1206, 1207, 1209, and 1201, which relate to the

⁴² Available at <https://www.uspto.gov/TrialPracticeGuideConsolidated>.

ABL testing Patent Owner originally withheld from discovery and is at issue in the copending Order on Sanctions. *See* Mot. 1–2; Opp. Mot. 6–11. As we further understand the motion, Patent Owner seeks to partially seal Exhibits 1069–1073, 1201, and 1211, which includes additional data relating to the originally withheld testing (Exs. 1201, 1211), deposition testimony of ABL employees (Exs. 1069, 1072, 1073), portions of Dr. Taylor’s Second Declaration (Ex. 1071). *See* Opp. Mot. 11–15.

Patent Owner asserts that good cause for sealing these materials exists “to preserve Patent Owner’s ability to appeal the overruling of its privilege/work product objections to disclosure and production of the information and documents proposed to be sealed.” Mot. 2, 3. Petitioner does not oppose the motion in principle, but argues—with justification—that Patent Owner provides insufficient detail or justification for the full scope of material it seeks to seal. Opp. Mot. 1–2. Petitioner asserts that

Patent Owner’s Motion to Seal falls far short of providing “a detailed discussion” that “[e]xplains why good cause exists” for blocking this information from the public. *See Garmin* at 4. Patent Owner’s request to keep this information from the public domain should be denied, subject to Patent Owner (a) providing a more specific justification for sealing the information, and (b) providing redacted documents in which the extent of redactions is no more than necessary to preserve, pending appeal, the confidentiality of information that is the subject of Patent Owner’s privilege assertions.

Id. at 6. Petitioner then provides a detailed plan for how each item of the subject documents should be treated. *Id.* at 6–15.

Patent Owner disagrees, suggesting that Petitioner is trying to set a “waiver trap” and, for the first time, describes adequately the material sought to be sealed and, with some degree of particularity, the reasons therefore. *See Seal Reply* 2–5. Specifically, Patent Owner seeks to seal the entirety of

Exhibits 1202–1204, 1206, 1207, 1209, 1210, and 1211, and seal portions of Exhibits 1069, 1071–1073, and 1201. *Id.*

Patent Owner seeks to seal Exhibit 1071, one of the Declarations of Dr. Taylor, because he discusses Exhibits 1202–1204, 1206, 1207, 1210, and 1211, as well as “consulting testing PO asserts as its protected work product.” Seal Reply 4. Similarly, Patent Owner seeks to seal portions of Exhibits 1069, 1072, and 1073, the three ABL employees’ deposition transcripts. *Id.* at 4–5. According to Patent Owner, although the reopened depositions were “taken precisely to allow Petitioner to ask about the information PO contends is subject to work product immunity,” “PO limited its redactions to testimony regarding that consulting testing.” *Id.* at 4–5.

As explained above in connection with our decision on the Motion to Exclude, the work-product doctrine is not designed to protect factual information in Exhibits 1201–1204, 1206, 1207, and 1209–1211. *See supra* Section VII.D.3. As such, Patent Owner’s reasoning for sealing Exhibits 1069 and 1071–1073 is not persuasive either. Thus, Patent Owner’s Motion to Seal is denied.

We note, however, Patent Owner appears to request sealing of the identified Exhibits only “long enough to allow PO to appeal after a final written decision.” Seal Reply 5; *see also* Seal Mot. 3 (“Patent Owner seeks to seal this information to preserve its opportunity to seek appellate review of the Board’s Order as to Patent Owner’s privilege/work product objections.”). That request is granted, and Exhibits 1069, 1071–1073, 1201–1204, 1206, 1207, 1209–1211 will remain sealed until the completion of all appeals. Depending on the outcome of the appeals, Patent Owner may renew its Motion to Seal within thirty days of the conclusion of all appeals.

In the event that Patent Owner does not timely renew its Motion to Seal, the documents filed under seal in this proceeding will be unsealed forty-five days after the conclusion of all appeals.

We also note that numerous papers in this case were filed as “Board and Parties Only,” with no corresponding motion to seal. For example, in its Reply in support of the Motion to Seal, Patent Owner states “Petitioner has since filed as Board/Parties Only briefs and transcripts discussing the same information, which should likewise remain sealed.” Seal Reply 2–3. There, Patent Owner identifies Petitioner’s Reply (Paper 37), the first MTA Opposition (Paper 38), and the Motion for Sanctions (Paper 54).⁴³ Such a single sentence does not amount to a motion to seal, which is required under the Trial Practice Guide. *See* TPG 19 (“A party intending a document or thing to be sealed may file a motion to seal concurrent with the filing of the document or thing.”). Other Papers, including Petitioner’s Opposition to Patent Owner’s Motion to Seal (Paper 48) as well as Patent Owner’s Reply in Support of the Motion to Seal (Paper 60), were filed as “Board and Parties Only,” without even a sentence mentioning any basis for sealing these Papers.

If desired, within ten business days, either party, or both parties jointly,⁴⁴ may file a motion to seal any document filed as Board and Parties Only but not presently accompanied by a motion to seal. Any such motion shall explain in detail and on a document-by-document basis what good

⁴³ Petitioner filed a redacted version of the Reply (Paper 43), the first MTA Opposition (Paper 73), and the Motion for Sanctions (Paper 58).

⁴⁴ We encourage the parties to meet and confer regarding the extent of redactions, and if possible, to file any motion to seal either unopposed or jointly.

cause supports granting the motion. In addition, the moving party or parties shall provide redacted versions of any document not requested to be sealed in its entirety, or explain where such redacted versions are available in the record. Any redactions must be limited to the minimum necessary.

See TPG 91.

The parties may, within ten business days of this Decision, jointly propose redactions for this Final Written Decision. In the absence of such proposal, at the expiration of ten business days from the date of this Decision, the entirety of the Final Written Decision will be made available to the public.

VI. CONCLUSION⁴⁵

Under 37 C.F.R. §§ 42.5, 42.11, and 42.12, and based on the Sanctions Order and determinations made therein, we enter Adverse Judgment against Patent Owner as to all challenged original claims and deny Patent Owner's Revised Contingent Motion to Amend.

On the merits, after reviewing the entire record and weighing evidence offered by both parties, we determine that Petitioner has demonstrated by a preponderance of the evidence that claims 1–35 of the '399 patent are unpatentable in view of the cited prior art.

⁴⁵ Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner's attention to the April 2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding*. *See* 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. § 42.8(a)(3), (b)(2).

In summary:

Claim(s)	35 U.S.C. §	Reference(s)	Claims Shown Unpatentable	Claims <u>Not</u> shown Unpatentabl e
1, 4, 6, 8, 10, 11, 16, 21– 30, 32, 35	102(b)	Birnboim	1, 4, 6, 8, 10, 11, 21–30, 32, 35	16
1, 2, 4–8, 10– 14, 16, 21– 32, 35	103(a)	Birnboim	1–9, 15–17, 29–39	16
3	103(a)	Birnboim, Chen	3	
9	103(a)	Birnboim, Reed	9	
15	103(a)	Birnboim, Mori	15	
16	103(a)	Birnboim, Helftenbein,	16	
17	103(a)	Birnboim, Chirgwin	17	
18–20	103(a)	Birnboim, Das, Chen, Wangh	18–20	
31	103(a)	Birnboim, Koller	31	
33	103(a)	Birnboim, Birnboim 2006	33	
34	103(a)	Birnboim, Chirgwin, Farrell	34	
Overall Outcome			1–35	

We also determine that Petitioner has demonstrated by a preponderance of the evidence that proposed substitute claims 36–70 are unpatentable under 35 U.S.C. § 103 as obvious over the assert prior art. In summary:

Revised Motion to Amend Outcome	Claim(s)
Original Claims Cancelled by Amendment	
Substitute Claims Proposed in the Amendment	36–70
Substitute Claims: Motion to Amend Granted	
Substitute Claims: Motion to Amend Denied	36–70
Substitute Claims: Not Reached	

VII. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Adverse Judgment is entered against Patent Owner;

FURTHER ORDERED that all challenged claims of the '399 patent will be cancelled;

FURTHER ORDERED that Petitioner has demonstrated by a preponderance of the evidence that claims 1–35 of the '399 patent are unpatentable under 35 U.S.C. § 103;

FURTHER ORDERED that Patent Owner's Revised Contingent Motion to Amend is denied;

FURTHER ORDERED that Patent Owner's Motion to Exclude Exhibits 1003, 1008, 1015, 1052, 1054, 1056, 1060, 1068, 1069, 1071–1073, 1082, 1088, 1089, and 1200–1211 is denied;

FURTHER ORDERED that Patent Owner's Motion to Exclude Exhibits 1050, 1057–1058, 1083, 1085–1087, 1090–1092, and 1095 is dismissed as moot;

FURTHER ORDERED that the Protective Order (Paper 36) is hereby entered;

FURTHER ORDERED that Patent Owner's Motion to Seal Exhibits 1069, 1071–1073, 1201–1204, 1206, 1207, and 1209–1211 is denied;

FURTHER ORDERED that within ten (10) business day of this Order, either party may file a motion to seal any document filed as Board and Parties Only but not presently accompanied by a motion to seal;

FURTHER ORDERED that this Order, as well as Exhibits 1202–1204, 1206, 1207, 1209, and 1210, and unredacted versions of Exhibits 1069–1073, 1201, 1211, Paper 43, and Paper 44 will remain sealed until the completion of all appeals;

FURTHER ORDERED that Patent Owner may renew its Motion to Seal within thirty days of the conclusion of all appeals;

FURTHER ORDERED that within ten (10) business days of this Order, the parties shall jointly propose a minimally redacted version for public dissemination; and

FURTHER ORDERED that, because this is a Final Written Decision, parties to this proceeding seeking judicial review of our Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

IPR2021-00857
Patent 9,212,399 B2

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