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Paper 166
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ARIOSA DIAGNOSTICS,
Petitioner,

v.

ISIS INNOVATION LIMITED,
Patent Owner.

Case IPR2012-00022[1]
Patent 6,258,540

Before LORA M. GREEN, FRANCISCO C. PRATS, and JEFFREY B. ROBERTSON, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

A. Background

Petitioner, Ariosa Diagnostics ("Ariosa"), filed a Petition for *inter partes* review of claims 1, 2, 4, 5, 8, 19–22, 24, and 25 of U.S. Patent No. 6,258,540 ("the '540 Patent") pursuant to 35 U.S.C. §§ 311–319. Paper 1 ("Pet."). Patent Owner, Isis Innovation Limited ("Isis"), filed a Preliminary

[1] This Case has been joined with IPR2013-00250.

Response. Paper 18 ("Prelim. Resp."). On March 19, 2013, we instituted trial as to all of the challenged claims. Paper 24 ("Dec. Institute").

After institution of trial in IPR2012-00022, Ariosa filed a second Petition for *inter partes* review of claims 3, 8, 12, 13, 15, and 18 of the '540 patent. IPR2013-00250, Paper 1. Ariosa also filed a Motion for Joinder, seeking joinder of that proceeding with IPR2012-00022. IPR2013-00250, Paper 4. On September 3, 2013, we instituted trial as to all of the claims challenged in the second Petition (IPR2013-00250, Paper 26), and joined the proceeding with IPR2012-00022 (IPR2013-00250, Paper 25). Thus, claims 1–5, 8, 12, 13, 15, 18–22, 24, and 25 are subject to *inter partes* review in the joined proceeding.

Isis filed a Patent Owner Response in the joined proceeding. Paper 89 ("PO Resp."). Isis filed also a contingent Motion to Amend by submitting proposed substitute new claims 28–30, or substitute new claims 31–33, for claims 1, 24, and 25, respectively. Paper 88 ("Mot. to Amend"). Ariosa filed a Reply to the Patent Owner Response (Paper 114; "Reply"), and also an opposition to Isis's Motion to Amend (Paper 115; "Opp."). Isis then filed a Reply in support of its Motion to Amend. Paper 130 ("Reply Mot. to Amend").

Isis filed a Motion to Exclude. (Paper 135; "Isis's Motion to Exclude"); and Ariosa filed an Opposition to that Motion (Paper 155). Oral hearing was held on January 24, 2014. Paper 165[2] ("Tr.).

[2] We note that the pages of the oral hearing transcript are not numbered. We, thus, designate the first page on which argument appeared, entitled "PROCEEDINGS," as page 1, and number the remaining pages sequentially therefrom.

The Board has jurisdiction under 35 U.S.C. § 6(c). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

Ariosa has demonstrated, by a preponderance of the evidence of record, the unpatentability of claims 1, 2, 4, 5, 8, 19, 20, 24, and 25 under 35 U.S.C. § 102(b). Ariosa, however, has not met its burden to show by a preponderance of the evidence of record that claims 3, 12, 13, 15, 18, 21, and 22 are unpatentable under 35 US.C. § 103(a).

Isis's Motion to Amend is *denied.*

B. Related Proceedings

Claims 1, 2, 4, 5, 8, 19–22, 24, and 25 of the '540 patent were declared invalid in *Ariosa Diagnostics v. Sequenom*, Civ. No. 12-00132-SI (N.D. Cal.). Paper 107, 1 (citing Ex. 2224). The district court granted summary judgment on the basis that the claims were drawn to patent ineligible subject matter under 35 U.S.C. § 101. Ex. 2224, 20. The district court's decision is currently on appeal to the Court of Appeals for the Federal Circuit in *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, Appeal Nos. 14-1139, 14-1142, and 14-1144. Paper 163, 1.

C. The '540 Patent

The '540 patent issued on July 10, 2001, with Yuk-Ming Dennis Lo and James Stephen Wainscoat as the listed co-inventors. The '540 patent is drawn to "prenatal detection methods using non-invasive techniques," and,

in particular, "to prenatal diagnosis by detecting foetal nucleic acids in serum or plasma from a maternal blood sample." Ex. 1001,[3] col. 1, ll. 6–9.

According to the '540 patent, it was unexpected that fetal DNA "is detectable in maternal serum or plasma samples." *Id.* at col. 1, ll. 50–51. The concentration of fetal DNA in serum or plasma samples has been measured from 0.39% (early pregnancy) to 11.4% (late pregnancy), whereas the concentration of fetal cells in the cellular fraction is generally from 0.001% to 0.025%. *Id.* at col. 1, ll. 59–64. The '540 patent thus "provides a detection method performed on a maternal serum or plasma sample from a pregnant female, which method comprises detecting the presence of nucleic acid of foetal origin in the sample." *Id.* at col. 2, ll. 1–4. "[P]renatal diagnosis" is defined by the '540 patent as covering the "determination of any maternal or foetal condition or characteristic which is related to either the foetal DNA itself or to the quantity or quality of the foetal DNA in the maternal serum or plasma." *Id.* at col. 2, ll. 6–10.

The '540 patent also teaches that the "preparation of serum or plasma from the maternal blood sample is carried out by standard techniques," and that "[s]tandard nucleic acid amplification systems can be used." *Id.* at col. 2, ll. 26–27 and ll. 43–47. Polymerase chain reaction ("PCR") is one of the standard nucleic acid amplification systems disclosed by the '540 patent. *Id.* at col. 2, ll. 44–48. According to the '540 patent, "[s]ex determination has successfully been performed on pregnancies from 7 to 40 weeks of gestation." *Id.* at col. 3, ll. 60–62.

[3] Throughout the decision, quotations to the '540 patent (Ex. 1001) include the British spelling of several words. We, otherwise, use the American spelling; for example, "foetal" versus "fetal."

The ’540 patent teaches further that the plasma or serum-based prenatal diagnostic method may be used to determine fetal rhesus D status in rhesus negative mothers, such that the detection of the rhesus D gene in the negative mother is indicative of a rhesus D positive fetus. *Id.* at col. 2, l. 57–col. 3, l. 3. The diagnostic methods may be used also to detect haemoglobinopathies or other paternally-inherited DNA polymorphisms. *Id.* at col. 3, ll. 4–24.

According to the ’540 patent, the non-invasive methods may be used also to screen for Down’s syndrome and other chromosomal aneuploidies. *Id.* at col. 3, ll. 25–28. The ’540 patent teaches that it was known that the level of circulating fetal cells is higher in pregnancies with chromosomal aneuploidies, such as Down’s syndrome, and it was further determined that the level of fetal DNA in maternal plasma and serum is also higher. *Id.* at col. 3, ll. 30–40. Thus, the ’540 patent teaches that quantitative detection of fetal DNA in maternal plasma or serum may be used to screen for fetal aneuploidies. *Id.* at col. 3, ll. 40–43. Another method disclosed by the ’540 patent for use in screening fetal aneuploidies is quantifying fetal DNA markers on different chromosomes, such as quantification of fetal chromosomal 21-derived DNA. *Id.* at col. 3, ll. 44–51.

Example 2 of the ’540 patent describes quantitative analysis of fetal DNA in maternal serum, wherein the pregnancy is an aneuploidy pregnancy. *Id.* at col. 5, ll. 55–57. Plasma and serum samples were obtained from pregnant women undergoing prenatal testing, and DNA was extracted from those samples. *Id.* at col. 6, ll. 14–34. The DNA then was amplified using real time quantitative PCR using primers for the SRY gene. *Id.* at col. 6, l. 35–col. 7, l. 3. The inventors report that the concentration of fetal DNA is

elevated in aneuploid pregnancies. *Id.* at col. 8, ll. 33–36. The same test, using the same primers, was used to screen for pre-eclampsia, wherein the concentration of fetal DNA is higher in patients with pre-eclamptic pregnancies. *Id.* at col. 11, l. 38–col. 12, l. 49, Example 4.

The SRY gene is male specific, being found on the Y chromosome. *Id.* at col. 25, ll. 6–7, claim 7. The '540 patent teaches that the "[r]eal time quantitative SRY system was insensitive to the existence of background female DNA from 0 to 12,800 female genome-equivalents." *Id.* at col. 14, ll. 46–48. In addition, samples from women bearing female fetuses did not provide a positive SRY signal. *Id.* at col. 15, ll. 63–67.

According to the '540 patent,

> For selected disorders, foetal genetic information could be acquired more economically and rapidly from maternal plasma or serum than by using foetal cells isolated from maternal blood. We envisage that foetal DNA analysis in maternal plasma and serum would be most useful in situations where the determination of foetal-derived paternally inherited polymorphisms/mutations or genes would be helpful in clinical prenatal diagnosis. Examples include foetal sex determination for the prenatal diagnosis of sex-linked disorders, foetal rhesus D status determination in sensitized rhesus negative pregnant women, autosomal dominant disorders in which the father carries the mutation and autosomal recessive genetic disorders in which the father and mother carry different mutations, e.g., certain hemoglobinopathies and cystic fibrosis. Due to the much reduced maternal background and high foetal DNA concentration in maternal plasma and serum, we predict that this type of analysis would be much more robust compared with their application for detecting unsorted foetal cells in maternal blood. The ability for allelic discrimination allows the homogeneous TaqMan assay to be used for this purpose.

Id. at col. 17, ll. 32–54 (citations omitted).

As for the application of the method to female fetuses, the '540 patent teaches:

> [I]t has been demonstrated (Example 2) that the foetal DNA concentration in maternal plasma and serum is . . . elevated in [aneuploid] pregnancies. This provides a new screening test for foetal chromosomal disorders. For this application, foetal DNA quantitation systems can be developed for polymorphic markers outside the Y chromosome so that quantitation can be applied to female foetuses. Autosomal polymorphic systems which may be used for this purpose have already been described. However, foetal cell isolation techniques would still be necessary for a definitive cytogenetic diagnosis. Similarly, foetal cell isolation would also be required for direct mutational analysis of autosomal recessive disorders caused by a single mutation. It is likely that foetal cell isolation and analysis of foetal DNA in maternal plasma/serum would be used as complementary techniques for non-invasive prenatal diagnosis.

Id. at col. 17, l. 59–col. 18, l. 8 (citations omitted).

D. Illustrative Claim

Claims 1, 21, 24, and 25 of the '540 patent are independent. Claim 1 is illustrative, and is reproduced below:

> 1. A method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises
>
> amplifying a paternally inherited nucleic acid from the serum or plasma sample and
>
> detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample.

E. Instituted Challenges

Claims	Basis	References
1–5, 12, 13, 15, 18–22, 24, and 25	§ 102(a)	Lo[4]
8	§ 103(a)	Lo and Simpson[5]
1, 2, 4, 5, 8, 19, 20, 24, and 25	§ 102(b)	Kazakov[6]
3, 12, 13, 15, and 18	§ 103(a)	Kazakov and Bianchi[7]
1, 2, 4, 5, 19–22, 24, and 25	§ 103(a)	Simpson, Schallhammer,[8] and Kazakov
3, 12, 13, 15, and 18	§ 103(a)	Simpson, Schallhammer, Kazakov, and Bianchi

In regard to the challenge of claims 1–5, 12, 13, 15, 18–22, 24, and 25 as being anticipated under 35 U.S.C. § 102(a) by Lo, as well as the challenge of claim 8 as being rendered obvious under 35 U.S.C. § 103(a) over the combination of Lo and Simpson, we note that Ariosa stated during oral argument that it is no longer pursuing those challenges. Tr., 10:9–20. Without a further developed record, we decline to address those challenges further in this Decision.

[4] Lo et al., *Presence of Fetal DNA in Maternal Plasma and Serum*, 350 LANCET 485–487 (1997) (Ex. 1016).
[5] Simpson et al., *Isolating Fetal Cells in Maternal Circulation for Prenatal Diagnosis*, 14 PRENATAL DIAGNOSIS 1229–1242 (1994) (Ex. 1025).
[6] Kazakov et al., *Extracellular DNA in the Blood of Pregnant Women*, 37(3) CYTOLOGY (TSITOLOGIA) 232–236 (1995) (Ex. 1014).
[7] Bianchi et al., *Fetal Cells in Maternal Blood: Determination of Purity and Yield by Quantitative Polymerase Chain Reaction*, 171 AM. J. OBST. GYNECOL. 922–26 (1994) (Ex. 1043).
[8] Schallhammer et al., *Phenotypic Comparison of Natural Killer Cells from Peripheral Blood and from Early Pregnancy Decidua*, 3 EARLY PREGNANCY: BIOLOGY AND MEDICINE 15–22 (1997) (Ex. 1022).

II. ANALYSIS

A. 35 U.S.C. § 315(a)(1)

Isis argues that Ariosa lacks standing on the basis of Ariosa's filing of a civil action challenging the validity of the '540 patent before filing of the Petition for *Inter Partes* Review. PO Resp. 59 (citing IPR2012-00022, Prelim. Resp.). In the Preliminary Response, Isis asserted that Ariosa, prior to filing its Petition, filed a civil action against Sequenom, the exclusive licensee of the '540 patent, seeking a declaration that it did not infringe any claim of the '540 patent. Prelim. Resp. 3–4. Sequenom counterclaimed for infringement, and Ariosa answered by raising the affirmative defense of invalidity of the '540 patent. *Id.* at 4. We responded to that argument before institution of the IPR2021-00022 proceeding. *See generally* Paper 20. As this proceeding is at Final Decision, we summarize our Decision that addressed the issue of whether Ariosa lacked standing to bring to bring the IPR2012-00022 proceeding under 35 U.S.C. § 315(a)(1).

Specifically, in its Preliminary Response in IPR2012-00022, Isis argued that it "is of no moment" that Ariosa's challenge of the validity of the '540 patent in civil litigation is in the form of an affirmative defense. Prelim. Resp. 6. Isis asserted that the bar in § 315 does not require that the challenge be placed in the complaint, but "is directed to a petitioner-initiated 'civil action'—in other words the entire civil lawsuit—that challenges patent validity." *Id.* at 6–7.

Isis argued further that the exception in § 315(a)(3) does not apply, as that exception is limited to a counterclaim. *Id.* at 7. According to Isis, Ariosa only could have brought a counterclaim for invalidity if Isis and Sequenom had initiated the civil action. *Id.* Isis cited *Leatherman v.*

Tarrant County Narcotics Intelligence & Coordination Unit, 507 U.S. 163, 168 (U.S. 1993) ("*Expressio unius est exclusio alterius*") for the "canon of statutory interpretation 'the express mention of one thing excludes all others,'" arguing that canon excludes additional exceptions, such as the filing of an affirmative defense of patent invalidity. *Id.* at 7–8.

Isis also asserted that to allow Ariosa to file an *inter partes* review proceeding would thwart the intent of Congress. *Id.* at 5–6. According to Isis, § 315 was enacted to "avoid patent-owner harassment and to further the central purpose of IPRs to provide a cost-effective alternative to district-court patent validity litigation." *Id.* at 5. Thus, Isis asserted, a "key directive" of the statute is that the party that wishes to challenge the validity of a patent "must choose a single forum," with the only narrow exception being if the challenge is in the form of a counterclaim in a patent owner-initiated civil action. *Id.* at 5–6.

The issue we thus addressed before instituting *inter partes* review in IPR2012-00022 was

> whether filing a Declaratory Judgment of non-infringement in District Court bars Ariosa from later filing a petition for Inter Partes Review under 35 U.S.C. § 315(a), and whether the express mention of a counterclaim of invalidity in 35 U.S.C. § 315(a)(3) mandates interpreting the statute such that raising an affirmative defense of invalidity in response to a compulsory counterclaim of infringement deprives Ariosa of standing to file for inter partes review.

Paper 20, 3–4.

We noted in our Decision that statutory construction "'begins with 'the language of the statute.' And where the statutory language provides a

clear answer, it ends there as well.'" *Id.* at 4 (quoting *Hughes Aircraft Co. v. Jacobson*, 525 U.S. 432, 438 (1999) (citations omitted)).

> "Beyond the statute's text, [the 'traditional tools of statutory construction'] include the statute's structure, canons of statutory construction, and legislative history." *Timex V.I. v. United States*, 157 F.3d 879, 882 (Fed.Cir.1998) (quoting *Chevron U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 843 n. 9, 104 S.Ct. 2778, 81 L.Ed.2d 694 (1984)). "If a court, employing traditional tools of statutory construction, ascertains that Congress had an intention on the precise question at issue, that intention is the law and must be given effect," *Chevron*, 467 U.S. at 843 n. 9, 104 S.Ct. 2778.

Bull v. U.S., 479 F.3d 1365, 1376 (Fed. Cir. 2007).

We first addressed the issue of what is meant by "the petitioner or real party in interest filed a civil action challenging the validity of a claim of the patent" in § 315(a)(1) of the statute. Paper 20, 4. Under Isis's interpretation of the statute, "filing" extends beyond the commencement of the civil action and includes raising the affirmative defense of invalidity. *Id.* We looked to the Federal Rules of Civil Procedure as a guide to interpreting the plain meaning of the statute. *Id.*

We noted that Rule 2 of the Federal Rules of Civil Procedure[9] states that "[t]here is one form of action—the civil action," and Rule 3 states that "[a] civil action is commenced by filing a complaint with the court." *Id.* at 5. Defenses are raised in answer to the complaint or in answer to a counterclaim. *Id.* (citing Fed. R. Civ. P. 12). We concluded, therefore, that when the statute refers to filing a civil action, it refers to filing a complaint with the court to commence the civil action. *Id.*; *see, e.g., Baldwin Cnty. Welcome Ctr. v. Brown*, 466 U.S. 147, 149 (1984) (citing Fed. R. Civ. P. 3

[9] As amended December 1, 2010.

for the proposition that a civil action is brought upon the filing of a complaint with the court).

The next issue we addressed was whether the above interpretation of what constitutes filing a civil action for purposes of § 315(a)(1) can be reconciled with the explicit exception of filing a counterclaim for invalidity in § 315(a)(3). Paper 20, 5.

In our Decision addressing this issue, we noted that the Supreme Court has distinguished an affirmative defense of invalidity from a counterclaim of invalidity in *Cardinal Chem. Co. v. Morton Int'l, Inc.*, 508 U.S. 83 (1993). Paper 20, 5–6. The question before the Court in that case was whether the Court of Appeals for the Federal Circuit properly vacated a declaratory judgment of invalidity after finding that there was no infringement. *Cardinal Chem.*, 508 U.S. at 85. Quoting *Altvater v. Freeman*, 319 U.S. 359, 363–364 (1943), the Court stated:

> "To hold a patent valid if it is not infringed is to decide a hypothetical case. But the situation in the present case is quite different. We have here not only bill and answer but a counterclaim. Though the decision of non-infringement disposes of the bill and answer, it does not dispose of the counterclaim which raises the question of validity . . . . [T]he issue of validity may be raised by a counterclaim in an infringement suit. The requirements of case or controversy are of course no less strict under the Declaratory Judgments Act (48 Stat. 955, 28 U.S.C. § 400) than in case of other suits. But we are of the view that the issues raised by the present counterclaim were justiciable and that the controversy between the parties did not come to an end on the dismissal of the bill for non-infringement, since their dispute went beyond the single claim and the particular accused devices involved in that suit."

Cardinal Chem. Co., 508 U.S. at 94. The Court noted, however, that *Altvater* did not answer the question of whether, in the absence of an ongoing infringement dispute between the parties, an adjudication of invalidity would be moot. *Id.* at 95.

In answering that question, the Court observed that "[a] party seeking a declaratory judgment of invalidity presents a claim independent of the patentee's charge of infringement." *Id.* at 96. The Court also emphasized that there are public policy reasons to resolve questions of patent validity. *Id.* at 100–101. The Court, thus, rejected the Federal Circuit's practice of vacating a declaratory judgment of invalidity after a finding of noninfringement. *Id.* at 102.

Thus, it is clear from *Cardinal Chem. Co.* that there is a fundamental difference between an affirmative defense of invalidity and a counterclaim of invalidity. The affirmative defense of invalidity is tied to the claim of infringement, whereas a counterclaim of invalidity is independent from the claim of infringement and survives a finding of noninfringement. Section 315(a)(3) makes clear that if a party is faced with a claim of infringement, it can bring the independent claim of invalidity as a counterclaim and still avail itself of *inter partes* review.

Given the above analysis as a backdrop, we concluded that the statutory language provides a clear answer to the issue of whether filing a civil action for a declaratory judgment of noninfringement by a party deprives that party of standing to file an *inter partes* review as a result of raising the affirmative defense of invalidity in response to a counterclaim of infringement. Paper 20, 6.

As discussed above, the statute clearly defines which civil actions, when filed, bar a party from filing an *inter part*es review—civil actions challenging the validity of a patent. A civil action for a declaratory judgment of non-infringement is not a civil action challenging the validity of a patent. Moreover, as discussed above, asserting an affirmative defense of invalidity is treated differently than a counterclaim for invalidity, and thus for the purposes of § 315(a)(1) cannot be considered a filing of a civil action for invalidity. And as also discussed above, that interpretation of § 315(a)(1) does not conflict with the explicit exclusion in § 315(a)(3) of filing a counterclaim for invalidity.

We considered Isis's argument that to allow Ariosa to file a declaratory judgment action for noninfringement and also file a Petition for *inter partes* review allows Ariosa to thwart the intent of Congress, but it did not convince us otherwise.

In reviewing the legislative history of the America Invents Act[10] ("AIA") (Paper 20, 7–8), we noted that Senator Kyl stated in discussing the Act:

> Another set of changes made by the House bill concerns the coordination of inter partes and postgrant review with civil litigation. The Senate bill, at proposed sections 315(a) and 325(a), would have barred a party or his real party in interest from seeking or maintaining an inter partes or postgrant review after he has filed a declaratory-judgment action challenging the validity of the patent. The final bill will still bar seeking IPR or PGR after a declaratory-judgment action has been filed, but will allow a declaratory-judgment action to be filed on the same day or after the petition for IPR or PGR was filed. Such a declaratory-judgment action, however, will be automatically

[10] Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011).

> stayed by the court unless the patent owner countersues for infringement. The purpose of allowing the declaratory-judgment action to be filed is to allow the accused infringer to file the first action and thus be presumptively entitled to his choice of venue.

157 Cong. Rec. S5429 (daily ed. Sept. 8, 2011)).

Thus, as made clear by Senator Kyl, § 315(a) was amended to allow a petitioner to file an *inter partes* review, and still have a choice of venue by allowing the petitioner to file a declaratory judgment action that same day.

Moreover, a party cannot bring a declaratory judgment action of noninfringement without any basis for doing so.

> Although there is no bright line rule to determine whether a declaratory judgment action satisfies Article III's case-or-controversy requirements, the dispute must be "definite and concrete, touching the legal relations of parties having adverse legal interests," "real and substantial," and "admi[t] of specific relief through a decree of a conclusive character, as distinguished from an opinion advising what the law would be upon a hypothetical state of facts." "Basically, the question in each case is whether the facts alleged, under all the circumstances, show that there is a substantial controversy, between parties having adverse legal interests, of sufficient immediacy and reality to warrant the issuance of a declaratory judgment." *Id.*.

3M Co. v. Avery Dennison Corp., 673 F.3d 1372, 1376 (Fed. Cir. 2012) (citations omitted). And even when there is a case or controversy, the district court still has discretion in deciding whether it will entertain the declaratory judgment action. *Id.*

We concluded, therefore, that allowing a party to file both a declaratory judgment action for noninfringement and an inter partes review does not constitute harassment of a patent owner, because in order to bring

the declaratory judgment action for noninfringement, a party must still satisfy Article III's case-or-controversy requirements. Paper 20, 8.

We, thus, concluded that 35 U.S.C. § 315(a) does not deprive Ariosa of standing to bring the instant *inter partes* review. *Id.*

B. 35 U.S.C. § 315(b)

Isis argues further that this *inter partes* review is barred under 35 U.S.C. § 315(b). PO Resp. 59 (citing IPR2013-00250, Prelim. Resp.). In its Preliminary Response filed in IPR2013-00250, Isis contended that under 35 U.S.C. § 315(b), the "Office may not institute *inter partes* review if the petitioner filed its petition more than one year after being served with a complaint alleging infringement of the patent." IPR2013-00250, Prelim. Resp. 42. According to Isis, Aria Diagnostics, Inc., now Ariosa, accepted service of a complaint alleging infringement of the '540 patent, more than a year before the IPR2013-00250 Petition filing date of April 19, 2013. *Id.*

Isis acknowledged that the parties later agreed to dismissal of the civil action without prejudice. *Id.* Isis argued, however, that § 315(b) leaves no room for discretion, as it states that "*inter partes* review 'may not be instituted if the petition requesting the proceeding is filed more than 1 year after the date on which the petitioner . . . is served with [the] complaint'" *Id.* (alteration in original). According to Isis, the fact that the infringement suit was dismissed without prejudice was immaterial to whether or not Ariosa was barred from bringing the instant *inter partes* review against Isis. *Id.* at 42–44.

In the Decision to Institute in IPR2013-00250, we noted that that argument had already been considered by the Board in *Macauto U.S.A. v.*

BOS GMBH & KG, Case IPR2012-00004 (PTAB January 24, 2013) (Paper 18). IPR2013-00250, Paper 26, 4. In that proceeding, the panel noted that the bar of filing an *inter partes* review under 35 U.S.C. § 315(b) did not attach to a complaint of infringement that was voluntarily dismissed without prejudice. *See Macauto*, slip. op. at 14–16. We agree with that reasoning, discussed below.

Specifically, the panel in that case looked to the Federal Rules of Civil Procedure in making its determination. *Id.* at 15. As to the requirement of service, the panel noted that the infringement suit was voluntarily dismissed without prejudice under Fed. R. Civ. P. 41(a). *Id.* The panel noted further that the Court of Appeals for the Federal Circuit has consistently interpreted the effect of such dismissals as leaving the parties as though the action had never been brought. *Id.* (citing *Graves v. Principi*, 294 F.3d 1350, 1356 (Fed. Cir. 2002) ("The dismissal of an action without prejudice leaves the parties as though the action had never been brought"); *Bonneville Associates, Ltd. Partnership v. Baram*, 165 F.3d 1360, 1364 (Fed. Cir. 1999) ("The rule in the federal courts is that '[t]he effect of a voluntary dismissal without prejudice pursuant to Rule 41(a) is to render the proceedings a nullity and leave the parties as if the action had never been brought.'") (citations and internal quotes omitted.)); *Accord*, Wright, Miller, Kane, and Marcus, 9 Federal Prac. & Proc. Civ. § 2367 (3d. ed.) ("[A]s numerous federal courts have made clear, a voluntary dismissal without prejudice under Rule 41(a) leaves the situation as if the action never had been filed.") (footnote omitted).

As in the *Macauto* case, we agreed that the dismissal without prejudice leaves the parties as if the action had never been brought, and

concluded that Ariosa was not barred from filing its Petition in IPR2013-00250 under 35 U.S.C. § 315(b). IPR2013-00250, Paper 26, 3. As a result, we did not address Isis's arguments (IPR2013-00250, Prelim. Res. 44–46) regarding joinder in the context of the bar under § 315(b). *Id.*

C. 35 U.S.C. § 315(c)

Isis also argues the joinder statute only allows joinder of parties, not joinder of issues. PO Resp. 60 (citing IPR2013-00250, Prelim. Resp. 44–46).

Ariosa's Motion for Joinder under 37 C.F.R. § 42.122(b) requested that proceeding IPR2013-00250, involving the same parties and patent as IPR2012-00022, be joined with that proceeding. IPR2013-00250, Paper 4. The Joinder Motion was timely filed within one month after institution of this trial in accordance with § 42.122(b). Isis opposed the Motion on the ground that the enabling joinder statute, 35 U.S.C. § 315(c), allows only joinder of parties, not joinder of issues. IPR2013-00250, Prelim. Resp. 44–45; IPR2012-00022, Paper 72, 6–8.

The statute governing joinder of *inter partes* review proceedings, 35 U.S.C. § 315(c), provides:

> (c) JOINDER.—If the Director institutes an inter partes review, the Director, in his or her discretion, may join as a party to that inter partes review any person who properly files a petition under section 311 that the Director, after receiving a preliminary response under section 313 or the expiration of the time for filing such a response, determines warrants the institution of an inter partes review under section 314.

In its Response to the Petition, Isis maintains that the language in § 315(c) addresses joinder of a "party" to a proceeding, rather than the

situation present in this case, where Ariosa essentially seeks the "joinder" of additional grounds by the same party. PO Resp. 60.

In addressing that argument previously (IPR2013-00250, Paper 25, 4), we noted that the Board has allowed routinely joinder of additional grounds by the same party, citing to *Microsoft Corp. v. Proxycann, Inc.*, Case IPR2013-00109 (PTAB February 25, 2013) (Paper 15), and the Board has continued to do so. *See, e.g., Samsung Elecs. Co., Ltd. v. Virginia Innovation Scis., Inc.*, Case IPR2014-00557, slip. op. at 16 (PTAB June 13, 2014) (Paper 10), and cases cited therein. As we now consider the Joinder Motion at the Final Decision stage of the two involved proceedings, we take this opportunity to re-examine this issue.

While the plain language of the statute mentions joinder of "a party" and does not specifically articulate the joinder of issues, it states that "any person who properly files a petition under section 311" may be joined at the Director's discretion. Thus, there does not appear to be any language in the statute directly prohibiting the joinder of issues by the same party.

The legislative history of this section provides little guidance as to the scope of this statutory section. As the final Committee Report noted, under §§ 315(c) and 325(c), "[t]he Director may allow other petitioners to join an inter partes or post-grant review." *See* H.R. Rep. No. 112-98, pt.1, at 76 (2011). During the Senate's March 2011 debates on the AIA, Senator Kyl stated that the USPTO expected to allow liberal joinder of reviews:

> The Office anticipates that joinder will be allowed as of right—if an inter partes review is instituted on the basis of a petition, for example, a party that files an identical petition will be joined to that proceeding, and thus allowed to file its own briefs and make its own arguments. If a party seeking joinder also presents additional challenges to validity that satisfy the

> threshold for instituting a proceeding, the Office will either join that party and its new arguments to the existing proceeding, or institute a second proceeding for the patent.

157 Cong. Rec. S 1376 (daily ed. Mar. 8, 2011) (statement of Sen. Kyl). Senator Kyl, thus, contemplated the joinder of issues as well as the joinder of parties.

In addition to noting that §§ 315(c) and 325(c) give the USPTO discretion over whether to allow joinder, Sen. Kyl observed that "[t]his safety valve will allow the Office to avoid being overwhelmed if there happens to be a deluge of joinder petitions in a particular case." *Id.* The Board will determine whether to grant joinder on a case-by-case basis, taking into account the particular facts of each case, substantive and procedural issues, and other considerations. *See* 157 Cong. Rec. S1376 (daily ed. Mar. 8, 2011) (statement of Sen. Kyl) (when determining whether and when to allow joinder, the Office may consider factors including "the breadth or unusualness of the claim scope" and claim construction issues). These remarks highlight the discretion given to the USPTO in joinder matters. 35 U.S.C. § 315(c). We, thus, conclude that there is nothing in the language of the statute governing joinder, 35 U.S.C. § 315(c), nor does there appear to be anything in the legislative history, which limits joinder to the joinder of parties only.

We also look to our rule that governs joinder in *inter partes* review, 37 C.F.R. § 42.122, which states:

> *Request for joinder.* Joinder may be requested by a patent owner or petitioner. Any request for joinder must be filed, as a motion under § 42.22, no later than one month after the institution date of any *inter partes* review for which joinder is

> requested. The time period set forth in § 42.101(b) shall not apply when the petition is accompanied by a request for joinder.

The policy basis for construing our rules for governing these proceedings, which were prescribed as mandated by 35 U.S.C. § 316, is set forth in the Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,758 (Aug. 14, 2012): "The rules are to be construed so as to ensure the just, speedy, and inexpensive resolution of a proceeding." *See also* 37 C.F.R. § 42.1(b) (the rules "shall be construed to secure the just, speedy, and inexpensive resolution of every proceeding."). We concluded that under the present circumstances, that policy was best served by granting Ariosa's Motion for Joinder, which resulted in the joinder of this proceeding with IPR2013-00250. The proceedings involve the same patent and parties, and there is significant overlap in the asserted prior art, as well as the experts relied upon. Ariosa was diligent and timely in filing the Motion, such that there has been no discernible prejudice to either party.

Moreover, while Ariosa is not barred under 35 U.S.C. § 315(b), if Ariosa had been barred, and if joinder of the same party were not allowed, the panel would not have the discretion to address the patentability of the additional claims challenged in IPR2013-00250 (i.e., those which are dependent on the independent claims challenged in IPR2012-00022, on which trial already had been instituted). One of the purposes of the AIA was to "limit unnecessary and counterproductive litigation costs." 157 Cong. Rec. S1349 (daily ed. March 8, 2011) (statement of Sen. Leahy). Thus, even if the independent claims were to be found unpatentable in this proceeding, by not having the ability to join the dependent claims, the case would have to go back to the district court for a determination of validity as to those

dependent claims, which would be a waste of judicial resources, and would increase the litigation costs to both parties.

Isis asserts further that Ariosa should not "have a second bite of the apple for claim 8." PO Resp. 60. As set forth in 35 U.S.C. § 325(d), "[i]n determining whether to institute or order a proceeding under this chapter, chapter 30, or chapter 31 [chapter providing for *inter partes* review], the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office." Thus, again, it was at our discretion as to whether Ariosa should be able to present substantially the same arguments and prior art as those presented in IPR2012-00022. We conclude it was appropriate use of our discretion to institute Ariosa's anticipation challenge as to claim 8 for the same policy and efficiency considerations discussed above with respect to exercising our discretion to allow joinder under 35 U.S.C. § 315(c).

D. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 100(b); Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,766 (Aug. 14, 2012). Claim terms are also given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). If an inventor acts as his or her own lexicographer, the definition must be set forth in the specification with reasonable clarity, deliberateness,

and precision. *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1249 (Fed. Cir. 1998).

1. "Detecting"

Claim 1 comprises two steps, an amplification step, and a detecting step, wherein a paternally inherited nucleic acid is amplified, and its presence is detected. In the Decision to Institute, we construed the amplification step as including "a step of amplifying nucleic acid from a serum or plasma sample from a pregnant female, such as by PCR. The amplified nucleic acid would necessarily include fetal nucleic acid, and the fetal nucleic acid necessarily includes paternally inherited nucleic acid." Dec. Institute, 7–8.

That interpretation is consistent with the construction given that step by the Court of Appeals for the Federal Circuit in *Aria Diagnostics, Inc. v. Sequenom, Inc.*, 726 F.3d 1296, 1303 (Fed. Cir. 2013), where the Court stated:

> [T]he claim language requires "amplifying" paternally inherited nucleic acid, without any mention of an effect on the quantity of other nucleic acid. Thus, the claim as written stands infringed without regard to whether, or not, other nucleic acid is amplified. A party that amplifies paternally inherited nucleic acid satisfies this claim limitation without regard to amplification beyond other nucleic acid. The claim does not state that paternally inherited nucleic acid is "selectively" or "only" amplified.

Id.

We acknowledge that in district court, the principles set forth in *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) govern claim construction, and that would have been the standard applied by the Federal

Circuit in the *Aria Diagnostics* case, discussed above. In *inter partes* review, the claim construction standard is set forth in 37 C.F.R. § 42.100(b), which states that "[a] claim in an unexpired patent shall be given its broadest reasonable construction in light of the specification of the patent in which it appears." The use of the standard set forth in *Phillips* is regarded to result in a narrower construction than the use of the broadest reasonable interpretation standard. *See, e.g.*, *In re Rambus, Inc.*, 753 F.3d 1253, 1255–56 (Fed. Cir. 2014) (noting that broadest reasonable interpretation standard is justified, in part, by the ability to amend the claims, whereas claims in an expired patent are subject to the claim construction principles in *Phillips* as amendments can no longer be made). Thus, we find it incongruous to adopt a narrower construction in this proceeding, wherein the claims are construed using the broadest reasonable interpretation standard, than was adopted in *Aria Diagnostics*, in which a narrower, *Phillips* construction standard applied.

We then interpreted the "detecting" step of claim 1 as not requiring that the nucleic acid specifically is identified as being inherited from the father or even as being from the fetus, only that it be identified as containing some level of nucleic acid. Dec. Institute 8. As noted by Ariosa in its Reply, that interpretation was consistent with the interpretation of the Declaration of Dr. Mark I. Evans (Ex. 1033), Isis's expert in the co-pending case before the Northern District of California. Reply, 4 (citing Paper 24, 8 (Dec. Institute); Ex. 1033, ¶ 95; Ex. 2223, 9).

Isis contends that "detecting" requires that one determine that the "detected paternally inherited nucleic acid of fetal origin . . . is not possessed by the pregnant female." PO Resp. 15. Specifically, Isis argues that one

cannot "detect the presence of paternally inherited nucleic acid of fetal origin," as required by claim 1, without doing that determination. *Id.* According to Isis, the whole point of the Specification is to identify paternally inherited nucleic acid of fetal origin, and that determining step must be performed in order to determine a fetal or maternal construction based on paternally inherited nucleic acid of fetal origin. *Id.* (citing Ex. 1001, 1:6–10; 2:6–18).

Notably, however, Isis does not appear to contest the interpretation of the amplification step in the Institution Decision. Both the amplification step and the detecting step of claim 1, however, use very similar language. That is, the amplifying step requires "amplifying a paternally inherited nucleic acid from the serum or plasma sample," and the detecting step requires "detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample." Applicants could have added "only," such that the claim read as "*only* detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample," but they chose not to do so. *See, e.g.*, *Aria*, 726 F.3d at 1301 (noting as to the claim limitation of "paternally inherited nucleic acid" that during prosecution before the examiner the inventors could have limited the claims to those nucleic acids that were known in advance to come from the father). Thus, when the "detecting" step is construed in conjunction with the use of "comprising" as the transitional phrase, there is nothing in the language of claim 1 that limits the detecting step to also determining or identifying the detected nucleic acid as being of fetal origin and not being possessed by the pregnant female.

In addition, as to Isis's contention that any other interpretation is inconsistent with the Specification, the Specification specifically states that

the examples "do not in any way limit the scope of the invention." Ex. 1001, col. 4, ll. 13–14; *see also Aria Diagnostics*, 726 F.3d at 1301 (noting the same). Moreover, almost all of the examples perform a PCR amplification using primers that are specific to the Y chromosome, to specifically detect fetal DNA. Ex. 1001, col. 5, ll. 6–26 (Example 1, using primers designed to amplify a single copy Y sequence); col. 6, l. 60–col. 7, l. 3 (Example 2, using SRY specific primers); col. 12, ll. 24–38 (Example 4, using SRY specific primers); col. 15, ll. 18–48 (Example 5, using SRY specific primers). The remaining example, Example 3, uses primers specific for the RhD gene in women known to be RhD negative. *Id.* at col. 10, ll. 39–51. Thus, the examples are limited to the amplification and detection of fetal sequences that are known not to be possessed by the pregnant female. That limitation, however, also was not added to the claims during prosecution by Applicants, and we decline to read the claim language that narrowly. *See also Aria Diagnostics*, 726 F.3d at 1301 (noting that "even if a specification has only one embodiment, its claims will not be confined to that example 'unless the patentee has demonstrated a clear intention to limit the claim scope using words or expression of manifest exclusion or restriction.'" (quoting *Liebel–Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 906 (Fed. Cir. 2004)).

Thus, we decline to interpret the "detecting" step as narrowly as advocated by Isis. Instead, we interpret "detecting" as we did on institution, that is, as not requiring that the nucleic acid that is isolated from the plasma or serum of the pregnant female be specifically identified as being inherited from the father or even as being from the fetus; rather, only that it be

identified as containing some level of nucleic acid, which would include nucleic acid from the fetus that was inherited from the father.

E. Patentability of the Original Claims

To prevail on its challenges to the patentability of claims, Petitioner must establish facts supporting its challenges by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d).

1. Anticipation of claims 1, 2, 4, 5, 8, 19, 20, 24, and 25 by Kazakov

In order for a prior art reference to serve as an anticipatory reference, it must disclose every limitation of the claimed invention, either explicitly or inherently. *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997). We must analyze prior art references as a skilled artisan would. *See Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991), *overruled on other grounds by Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282 (Fed. Cir. 2009) (to anticipate, "[t]here must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention").

> A single prior art reference that discloses, either expressly or inherently, each limitation of a claim invalidates that claim by anticipation. Thus, a prior art reference without express reference to a claim limitation may nonetheless anticipate by inherency. "Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claims limitations, it anticipates." Moreover, "[i]nherency is not necessarily coterminous with knowledge of those ordinary skill in the art. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art."

Perricone v. Medicis Pharm. Corp., 432 F.3d 1368, 1375–76 (Fed. Cir. 2005) (citations omitted). In addition, "[i]t is a general rule that merely discovering and claiming a new benefit of an *old* process cannot render the process again patentable." *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990); *see also Perricone*, 432 F.3d at 1377–78 (noting that the realization of a new benefit of an old process does not render that process patentable); *Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001) (stating in the context of a claimed process that was drawn to the same use comprising the same steps of the prior art, "[n]ewly discovered results of known processes directed to the same purpose are not patentable because such results are inherent.").

We acknowledge:

> Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient. [Citations omitted.] If, however, the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient.

In re Oelrich, 666 F.2d 578, 581 (CCPA 1981) (quoting *Hansgirg v. Kemmer*, 102 F.2d 212, 214 (CCPA 1939)) (emphasis and bracketed material in original).

> Because inherency places subject matter in the public domain as well as an express disclosure, the inherent disclosure of the entire claimed subject matter anticipates as well as inherent disclosure of a single feature of the claimed subject matter. The extent of the inherent disclosure does not limit its anticipatory effect. In general, a limitation or the entire invention is inherent and in the public domain if it is the

> 'natural result flowing from' the explicit disclosure of the prior art.

Schering Corp. v. Geneva Pharms., Inc., 339 F.3d 1373, 1379 (Fed. Cir. 2003).

Ariosa contends that Kazakov anticipates the claimed methods because Kazakov inherently detected paternally inherited nucleic acid of fetal origin. Pet. 43–48; Reply 3–7. According to Ariosa, Kazakov amplified the DNA in serum that was obtained from pregnant women in their first and third trimesters of pregnancy. Pet. 43–44. One set of primers used by Kazakov were the B1 and C1 primers, which Ariosa asserts amplify sequences throughout the human genome, including sequences unique to the Y chromosome. *Id.* at 44 (citing Ex. 1006 (Kazakov Decl.) ¶¶ 11, 26). Ariosa then relies on the Declarations of Dr. Elaine S. Mansfield and Dr. Vasily Ivanovich Kazakov to show that inter-Alu sequences were also amplified, as Alu repeats are present everywhere in the human genome. *Id.* at 44–45 (citing Ex. 1007 (Mansfield Decl.) ¶¶ 46, 51–69; Ex. 1006 (Kazakov Decl.) ¶¶ 20–22).

The Kazakov reference teaches that it is known that extracellular DNA is contained in the blood of humans and animals. Ex. 1014, 232. According to Kazakov, the "level of extracellular DNA increases in the blood of women during pregnancy." Ex. 1014, Abstract. Kazakov studied the sera from blood of women in both the first and third trimesters of pregnancy, as well as women with late toxicosis of pregnancy. *Id.* at 233. Kazakov then performed PCR using DNA preparations from the serum using primers for Alu repeats. *Id.* The primers used by Kazakov were the

Tc65, B1, and C2 primers. *Id.* Kazakov then detected the DNA using gel electrophoresis. *Id.* at Inset VIII.

Kazakov reported that during pregnancy, there is initially an increase in concentration of low-molecular weight DNA, and that inter-Alu repeats have been detected only in the blood of women in the first trimester of pregnancy. *Id.* at 234. Kazakov notes that both the cells of the fetus (trophoblasts) and the mother (cells of the endometrium and lymphocytes) may excrete DNA. *Id.* at 235.

Kazakov discloses the same method of claim 1. That is, as discussed above in the section on claim construction, all that is required by the amplification step of claim 1 is a step of amplifying nucleic acid from a serum or plasma sample from a pregnant female, such as by PCR, as such amplified nucleic acid would necessarily include fetal nucleic acid, and the fetal nucleic acid necessarily includes paternally inherited nucleic acid. Moreover, as also discussed above, the detecting step does not require that the detected nucleic acid specifically be identified as being inherited from the father or even as being from the fetus, only that it be identified as containing some level of nucleic acid, which would include, necessarily, nucleic acid from the fetus that was inherited from the father. Here, Kazakov performs both of those steps: That is, DNA from the serum of pregnant women is amplified using PCR, and the amplified DNA is detected using gel electrophoresis, as demonstrated by Figures 1 and 2 of Kazakov.

Moreover, Kazakov specifically notes that the levels of extracellular DNA increases in the blood of women during pregnancy. Further, as acknowledged by Isis, "[m]aternal serum and plasma, *in vivo*, inherently contain [paternally inherited fetal nucleic acid]," as shown by the '540

patent. PO Resp. 19. Thus, if the ordinary artisan were to follow the teachings of Kazakov, and perform PCR on the serum obtained from the blood obtained from a pregnant female, that blood would inherently contain paternally inherited fetal nucleic acid. That nucleic acid would be amplified and detected by the experiments of Kazakov as such a result is necessarily inherent. That is, the amplification and detection of paternally inherited fetal nucleic acid would be a new benefit of a known process.

In that regard, we credit the testimony of Dr. Robert Nussbaum[11] (Ex. 1215), who states that as of 1995, the techniques used by Kazakov, such as the serum preparation and PCR, were all conventional. *Id.* ¶ 17. According to Dr. Nussbaum:

> Although I agree that the Kazakov publication provided to me had very poor reproductions of the data from the PCR experiments conducted, especially the gel reproduced as Figure 2, I find it very difficult to believe that the experiments performed by Kazakov did not amplify and detect <u>any</u> paternally inherited DNA, as the serum samples would contain at least some fetal cell-free DNA and the primers used specifically annealed to human sequences that would have been found in the fetal cell free DNA. I can think of no reason why the 50% of Alus in the fetal genome that are of paternal origin would fail specifically to amplify with these primers. In other words, if any amplification occurred, some of it was perforce paternally derived fetal DNA. Therefore, I believe that Kazakov did amplify some paternally-inherited cell-free DNA, even if it was a very low amount.

Id. ¶ 18.

[11] Dr. Nussbaum has worked in the field of medicine, pediatrics, and medical genetics for over 30 years, and is familiar with DNA detection techniques, chromosomal anomalies, and genetic analysis. Ex. 1215 ¶¶ 3–10.

That finding is supported by the Deposition of Dr. Prescott Deininger (Ex. 1197). When asked "if one were to use cell-free DNA obtained from serum in a PCR reaction with the B1/C2 primers, would you expect to obtain amplification products from the fetal cell-free DNA in that sample," Dr. Deininger responded that "I would think it would be likely that you would get some amplification. I do not think it would be likely that it would meet what I would consider criteria for detection." Ex. 1197, 122:10–123:7. Dr. Deininger's criteria for detection is that one would be able to determine that the DNA is of fetal origin in some way. *Id.* at 123:9–12. As construed above, the claims do not require any recognition that the DNA being detected is paternally inherited fetal nucleic acid, or even that it is of fetal origin. As we have declined to adopt Isis's proposed construction of the claims, we do not find persuasive Isis's contention that Kazakov does not anticipate the claims when the term "detecting" is properly construed. PO Resp. 14–15.

According to Isis, inherency is a strict doctrine, and "[i]t cannot be established by mere possibilities or even probabilities." PO Resp. 16 (citing *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993)). Isis contends also that paternally inherited nucleic acid of fetal origin was not necessarily amplified by Kazakov, and thus Kazakov cannot inherently anticipate the claims. *Id.* (citing Ex. 2175 ¶¶ 33–35; Ex. 2127 ¶¶ 44, 51, 60).

Specifically, Isis contends that PCR does not always work, and even if it does work, amplified product cannot necessarily be detected. PO Resp. 19. Moreover, Isis argues that Kazakov does not provide sufficient details as to the performance of the experiments, and Isis asserts further that Kazakov obtained data of poor quality. *Id.* Thus, Isis contends that the

ordinary artisan would not have concluded that Kazakov necessarily amplified and detected paternally inherited nucleic acid of fetal origin. *Id.* Although the '540 patent demonstrates that maternal serum and plasma *inherently* contains paternally inherited nucleic acid of fetal origin, Isis argues that Kazakov's samples "likely" contained little or no paternally inherited nucleic acid of fetal origin. *Id.* at 19–20.

Isis contends further that Kazakov "failed to amplify [cell-free] DNA using TC65 primer in at least one of the samples from first trimester pregnant women." PO Resp. 18. In fact, Isis asserts, Dr. Kazakov himself could not confirm whether the lanes in Figure 2 of Kazakov, which corresponded to those samples, contained detectable bands. *Id.* at 18–19 (citing Ex. 2113, 210:4–17).

Isis's position is, thus, that, even though fetal DNA is necessarily present in maternal serum, as there may have been experimental errors in some or all the results reported by Kazakov, whether due to errors in the way the PCR reaction was performed, contamination, or something else, Kazakov cannot, under the law of inherency, anticipate the claimed method.

We do not read the doctrine of inherency so strictly. We find the Federal Circuit's decision in *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331 (Fed. Cir 2005) to be instructive. The claims at issue in that case were drawn to paroxetine hydrochloride ["PHC"] hemihydrate. *Id.* at 1334. In finding that the claims were inherently anticipated, the Federal Circuit noted that the district court used a too exacting standard in determining that the claims were not anticipated. *Id.* at 1343. According to the court, all that is required is that the claimed product is the "'natural result flowing from the operation as taught [in the prior art].'" *Id.* (alteration in

original). The district court did not take into account that the prior art does not require an actual reduction to practice, but only requires an enabling disclosure. *Id.* at 1345. Thus, the Federal Circuit held:

> [W]hether it was actually possible to make pure PCH anhydrate before the critical date of the . . . patent [at issue] is irrelevant. The [prior art] patent suffices as an anticipatory prior art reference if it discloses in an enabling manner the production of PHC hemihydrate. The [prior art] patent discloses a method of manufacturing PHC anhydrate that naturally results in the production of PHC hemihydrate. Consequently, applying the facts as found by the district court to the correct standard, this court holds that claim 1 of the . . . patent [at issue] is invalid for anticipation by the [prior art] patent.

Id. at 1344 (citations omitted).

Moreover, in *King Pharmaceuticals, Inc. v. Eon Labs, Inc.*, 616 F.3d 1267 (Fed. Cir. 2010), the Federal Circuit held that "[t]o anticipate, the prior art need only meet the inherently disclosed limitation to the extent the patented method does." *Id.* at 1276. In that case, the claim at issue was drawn to a method of increasing the bioavailability of the therapeutic, metaxolone, by administering it with food. *Id.* at 1274. The patent owner, King, argued that the prior art's disclosure of taking metaxalone with food to reduce gastric discomfort was too vague as to the condition under which the food was administered, and thus the district court erred in finding that an increase in bioavailability was "necessarily disclosed." *Id.*

The Federal Circuit noted that while the written description of the patent at issue disclosed specific conditions for food consumption, the claims only recited taking metaxalone "with food," and that "[i]t would be improper to limit the broad terms used in the . . . patent's claims to the specific food conditions disclosed in the written description." *Id.* at 1275.

The court concluded, that given the broad disclosure of the patent, an increase in bioavailability of metaxolone naturally occurs when taken with food. *Id.* That is, according to the Federal Circuit, the "prior art methods in their 'normal and usual operation . . . perform the function which [King] claims,'" then the patent "'will be considered, to have been anticipated by the [prior art].'" *Id.* at 1275–76 (alterations in original).

The above cases do not support Isis's position that because experimental mistakes may have been made by Kazakov, Kazakov cannot anticipate the claimed methods. The natural result that flows from amplifying nucleic acid in the serum of blood obtained from a pregnant woman is that fetal nucleic acid, which both parties agree would inherently be present, would be amplified, which would include nucleic acid that the fetus inherited from the father. The '540 patent does not specify any conditions under which the amplification or detection steps need be practiced, such as particular Mg^{2+} levels, and we decline to read such limitations into the claim.

We do not find *Perricone* to be inconsistent with our finding of inherent anticipation. In that case, the Federal Circuit found that claims directed to treatment of sunburn were not inherently anticipated, as the prior art did not teach application to sunburn. *Perricone,* 432 F.3d at 1378–79. According to the court, "there is an important distinction between topical application to skin for the purpose of avoiding sunburn, and the much narrower topical application to skin sunburn." *Id.* at 1379. In contrast, Kazakov clearly discloses performing an amplification reaction, PCR, on the nucleic acid from serum obtained from pregnant woman, and then detects the results of that reaction using gel electrophoresis. Thus, Kazakov teaches

performing PCR on a sample of serum obtained from a pregnant woman, which necessarily includes an amplification and a detection step, and thus teaches the method steps specified by claim 1 of the ’540 patent.

Based on the above, whether or not Dr. Mansfield in fact exactly duplicated the experiments in the Kazakov reference is irrelevant to the analysis. Isis does not dispute that it was well within the level of the skilled artisan to perform an amplification reaction properly, such as by PCR, on a serum sample obtained from the blood of a pregnant female. In fact, according to Isis, the level of the person ordinary skill in the art

> would . . . have had knowledge and skill about the principles and use of amplification and detection techniques for fetal nucleic acids from maternal blood, e.g., polymerase chain reaction (PCR). This includes knowledge and skill about the equipment, processes and techniques for isolating nucleic acids from biological samples and analyzing the isolated or amplified nucleic acids.

Mot. to Amend 4. Thus, the ordinary artisan, following the teachings of Kazakov, would amplify and detect the nucleic acid contained in the serum sample obtained from a pregnant woman. The fact that the artisan may not have appreciated that paternally inherited nucleic acid from the fetus was part of the nucleic acid being amplified and detected is irrelevant to the analysis, because the claim as construed herein does not require a step of identifying the source of the nucleic acid.

We have considered Isis’s arguments that the testimony of Dr. Mansfield is not reliable, as well as the arguments that the Kazakov reference provides insufficient detail as to the conditions of the amplification reaction. *See* PO Resp. 16–29. We do not find those arguments convincing, however, for the reasons set forth above.

We conclude, therefore, that Ariosa has demonstrated by a preponderance of the evidence that claim 1 is anticipated under 35 U.S.C. § 102(b) by Kazakov. Isis presents no additional arguments as to claims 2, 19, and 20, other than those discussed above as to claim 1. Based on our review of the evidence presented by Ariosa, we conclude that Ariosa has established by a preponderance of the evidence that Kazakov anticipates those claims as well.

Isis contends further, without providing additional argument,[12] that Kazakov does not meet the limitations of claims 4, 5, 8, 24, or 25. PO Resp. 29. We have reviewed those claims, as well as the evidence presented by Ariosa, and determine that the preponderance of the evidence of record demonstrates that those claims are anticipated by Kazakov as well.

2. Obviousness of Claims 1, 2, 4, 5, 19–22, 24, and 25 over the Combination of Simpson, Schallhammer, and Kazakov

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level

[12] We note that Isis cites Exhibit 2161, ¶¶ 34–77, but provides no argument in the Patent Owner response. PO Resp. 29. Isis's citation to Exhibit 2161, therefore, amounts to improper incorporation by reference, and we thus decline to consider the cited paragraphs of that Exhibit in this context. *See* 37 C.F.R. 42.6(a)(3).

of skill in the art; and (4) where in evidence, so-called secondary considerations. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). The level of ordinary skill in the art usually is evidenced by the references themselves. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995); *In re Oelrich*, 579 F.2d 86, 91 (CCPA 1978).

For an obviousness analysis, 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) (quoting *In re Samour*, 571 F.2d 559, 562 (CCPA 1978)). Moreover, "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). That is because an obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418; *see also In re Translogic Tech., Inc.*, 504 F.3d. at 1259.

As an initial matter, we note that Isis contends that Schallhammer is not prior art. PO Resp. 30. Ariosa, in response, does not argue Isis's contention that Schallhammer is not prior art to the claims, but argues that, although the trial was instituted on the combination of Simpson, Schallhammer, and Kazakov, we only expressly relied on the teachings of Simpson and Kazakov to institute trial. Reply 8–9. As we agree that the teachings of Schallhammer are cumulative to those of Simpson and Kazakov, we conclude that Ariosa's failure to continue to rely on

Schallhammer in arguing the challenge, in and of itself, is not fatal to the obviousness challenge. Thus, we only address the challenge further to the extent that it relies on Simpson and Kazakov.

Ariosa contends that the combination of Simpson and Kazakov renders obvious claims 1, 2, 4, 5, 8, 19–22, 24, and 25 of the '540 patent. Pet. 49–52; Reply 9. According to Ariosa, Simpson teaches that fetal cells, or at least fetal DNA, are present in maternal blood. Pet. 49.

Specifically, Simpson teaches that fetal cells may be recovered from maternal blood, and that various chromosomal abnormalities, such as trisomies, have been detected using fetal cells. Ex. 1025, Abstract. According to Simpson, Lo demonstrated that "fetal cells, or at least fetal DNA, indeed existed in maternal blood." *Id.* at 1230, col. 1. Simpson teaches that the sensitivity required in making that demonstration was achieved by using nested PCR to amplify for Y sequences, and women that were carrying a male fetus were more likely to show a Y-chromosome specific signal. *Id.* at 1230, paragraph bridging the cols. The sample used was unsorted nucleated cells. *Id.*

Ariosa relies on Kazakov as demonstrating that the levels of extracellular DNA increases in the blood of pregnant females. Pet. 50 (citing Ex. 1007 (Mansfield Decl.) ¶ 95). The teachings of Kazakov are discussed above.

Isis responds that Kazakov in combination with Simpson does not render obvious the claimed methods, as Kazakov does not teach that cell-free DNA of fetal origin increases in pregnancy, but teaches only that there is increased cell-free DNA in the first trimester. PO Resp. 42 (citing Ex. 2175 ¶ 34). And although Dr. Kazakov relies on the disclosure at page 234

of the Kazakov reference in his Declaration to support the obviousness challenge. (*id.* (citing Ex. 2127 ¶¶ 72–73)), that paragraph discusses maternal cells, not fetal cells.

Isis argues further that a person of ordinary skill in the art would not have had a reasonable expectation of success of detecting paternally inherited fetal nucleic acid in the serum or plasma obtained from a pregnant female. *Id.* (citing Ex. 2127, ¶¶ 100–109; Ex. 2175 ¶¶ 63–65; Ex. 2161 ¶¶ 114–119). Isis argues that the prior art, such as Simpson, taught examining the DNA in isolated fetal cells, and routinely discarded the cell-free portion of the blood, *i.e.*, the plasma and the serum. PO Resp. 37 (citing Ex. 2175 ¶¶ 66, 68; Ex. 2127 ¶ 100, 101). Simpson relies on two Lo papers in making the statement that fetal DNA was found in maternal blood. *Id.* at 38. Those papers, according to Isis, used whole blood to detect DNA, and thus the ordinary artisan would have understood that the source of the detected DNA was fetal cells, and not plasma or serum. *Id.* (citing Ex. 2127 ¶¶ 89–93).

Isis contends further that the prior art taught that "fetal cells were vanishingly rare and not present in all pregnant women." PO Resp. 38 (citing Ex. 2127 ¶¶ 103–104; Ex. 2175 ¶ 73; Ex. 2185 ¶¶ 28–31). Because those cells were so rare in maternal blood, Isis argues that the ordinary artisan "would have expected that DNA released from such cells would also have been rare, if it existed at all." *Id.* at 39 (citing Ex. 2127 ¶¶ 103–104; Ex. 2175 ¶ 64).

The primary focus of Simpson, as discussed above, is the analysis of DNA from fetal cells isolated from maternal blood. Ex. 1025, Abstract. In determining that Ariosa had established a reasonable likelihood that the

combination of Simpson and Kazakov would have rendered obvious the claimed methods, we noted that "Simpson suggests that the DNA would be found in levels sufficient to be determined using amplification reactions, such as PCR, by teaching that Y specific signals were seen in women carrying a male fetus (Simpson 1230, bridging ¶)." Dec. Institute 31.

The paragraph we relied upon in the Simpson reference cited to two papers by Lo. As noted by Isis's expert, Dr. Robert Williamson,[13] it was the cellular component of maternal blood that contained fetal DNA. Ex. 2127 ¶¶ 89–93. The Lo 1990[14] article states that blood samples from pregnant females were analyzed, but does not discuss using only the serum or plasma from the samples. Ex. 1044, 1463. Lo 1989[15] discusses the use of PCR to detect male fetal cells, in which PCR was extracted from the blood samples. Ex. 1045, 1363–64. Moreover, Simpson states that the work of Lo was performed on unsorted nuclear cells. Ex. 1025, 1230, col. 2. Thus, the preponderance of evidence supports a finding that when Simpson reported that Lo demonstrated that fetal DNA could be found in maternal blood (*id.* at col. 1), the source of that DNA would have been understood by the ordinary artisan to be fetal cells, and not cell-free DNA.

In addition, the preponderance of evidence of record supports a finding that the presence of fetal cells in maternal blood is a rare occurrence.

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[13] Dr. Williamson is an expert in the fields of molecular biology and molecular genetics (Ex. 2127 ¶¶ 6–16), and based on his credentials, which do not appear to be contested by Ariosa, we consider him competent to testify as to the subject matter in his Declaration.

[14] Lo et al., *Detection of Single-Copy Fetal DNA Sequence from Maternal Blood*, 335 LANCET 1463–64 (1990) (Ex. 1044).

[15] Lo et al., *Prenatal Sex Determination by DNA Amplification from Maternal Peripheral Blood*, 2 LANCET 1363–65 (Ex. 1045).

As testified by Dr. Williamson, "fetal cells in maternal blood were a scarce commodity." Ex. 2127, ¶ 103. That is supported by the Bianchi reference, relied upon by Ariosa, which teaches that "[f]etal cells are rare in the maternal circulation; all current methods used for their isolation also yield maternal cells." Ex. 1043,[16] Abstract.

Moreover, as noted by Isis, although Kazakov teaches that the "level of extracellular DNA increases in the blood of women during pregnancy," (Ex. 1014, Abstract), Kazakov concludes:

> Thus, in the early stages of pregnancy in humans, cells of the fetus (trophoblasts) and the mother (cells of the endometrium and lymphocytes) may excrete DNA. In view of the above, and also considering the transposonic and recombinogenic nature of the Alu repeats, it can be conjectured that the inter-Alu repeats discovered by us in the blood serum of pregnant women may play some kind of regulatory role in the early stages of pregnancy. The cloning and sequencing of these fragments is of particular interest. What has been said does not rule out the presence of other inter-Alu repeats in the blood of pregnant women, which can be identified by means of other primers and may have their own features of distribution in the blood in the course of pregnancy.

Id. at 235 (citation omitted). Thus, it is clear that Kazakov does not consider fetal DNA to be the only source of the increased DNA in maternal serum during the first trimester, but also considers maternal sources, and does not rule out the possibility that the DNA being amplified is only from maternal sources. That position is supported by the testimony of Dr. Williamson, who states that, as set forth by the Kazakov reference, the origin of the extracellular DNA "is completely left to conjecture." Ex. 2127 ¶ 97.

[16] All references to Ex. 1043 are to the exhibit as filed in IPR2013-00250.

Based on the above, we conclude that the ordinary artisan would not have used the serum sample of Kazakov, which is a cell-free sample, for the whole blood sample of Simpson, which contains the cellular fraction, for the analysis of fetal DNA as taught by Simpson. The ordinary artisan would not have had a reasonable expectation that the fetal DNA would have been present in maternal serum in sufficient quantities for detection using amplification methods such as PCR given the understanding in the art that fetal cells were a rare occurrence in maternal blood. Moreover, Kazakov's lack of teaching that the increase in extracellular DNA in the serum of pregnant females is due to the presence of cell-free fetal DNA in the serum further supports that conclusion.

We have considered Ariosa's arguments in response, but they do not persuade us otherwise. Ariosa argues that the experts agree "that techniques taught in Simpson would have successfully amplified [cell-free] DNA in the maternal serum as suggested by Kazakov." Reply 8 (citing Ex. 1200 ¶ 67; Ex. 1215 ¶¶ 42–43). According to Ariosa, the "explicit suggestion by Kazakov that maternal serum may contain fetal DNA cannot be overcome by a generalized belief . . . that fetal DNA was not present in appreciable quantities in maternal serum or plasma." *Id.* (citing Ex. 1200, ¶¶ 63–64). Ariosa contends that Isis's arguments, such as those based on the Declaration testimony of Dr. Fisk, are "premised upon the erroneous belief that the term 'detect' requires [paternally inherited fetal nucleic acid] to be distinctly distinguished from maternal DNA." *Id.* at 12.

Kazakov, Ariosa contends, specifically states that there are two potential sources of cell-free DNA, that is, fetal and maternal. *Id.* at 13 (citing Ex. 1014). Ariosa relies on the Declaration of Dr. Nussbaum, who

stated that Kazakov's results "'would have been intriguing to a person working in prenatal diagnosis as it would have signaled that maternal plasma or serum might be a potential new source for fetal DNA.'" *Id.* at 14 (quoting Ex. 1215 ¶¶ 40, 41); *see also* Ex. 1200 ¶ 64 (Ariosa's expert, Dr. Valeri Vasioukhin opining that "researchers in prenatal molecular diagnosis would have appreciated the implications of the Kazakov results and incorporated this newly identified source of fetal DNA into existing prenatal molecular diagnostic techniques.").

We agree with Ariosa that "detect" as used in the claimed methods does not require identification of the detected DNA as paternally inherited DNA, or even as fetal DNA. Simpson, however, analyzes fetal DNA for purposes of prenatal diagnosis of chromosomal abnormalities. Ex. 1025, Abstract. Thus, the only reason for one to use the serum of Kazakov in the method of Simpson would also be to detect fetal chromosomal abnormalities, which would have required some level of realization that fetal nucleic acid was in fact being detected.

Moreover, we have considered the evidence cited by Ariosa, but again, conclude that it does not establish by a preponderance of the evidence of record that the combination of Simpson and Kazakov would have rendered obvious the method of the challenged claims. As stated by Dr. Vasioukhin:

> I believe a researcher working in prenatal molecular diagnostics would have a very high expectation of success if the maternal serum samples did indeed contain fetal cell free-nucleic acids, which we now know such serum samples from pregnant women naturally do. The use of the specific primers taught in Simpson 1993 (*e.g.*, the Y1.7 and Y1.8 primers) would have resulted in the amplification and detection of

> paternally inherited nucleic acids if PCR using these primers had been carried out using cell-free DNA template from a pregnant woman.

Ex. 1200 ¶ 67 (footnote omitted).

While we agree with Dr. Vasioukhin that it would have been well within the level of skill of the ordinary artisan to use the primers of Simpson on the serum sample of Kazakov, that does not address the question as to whether the ordinary artisan would have expected there to be sufficient quantities of cell-free DNA in maternal DNA for the detection of fetal chromosomal abnormalities as taught by Simpson. That opinion presupposes that the ordinary artisan would have understood from the Kazakov reference that the analyzed serum contained fetal DNA. There is no recognition in the Kazakov reference, however, that the serum did in fact contain fetal DNA. Rather, the Kazakov reference theorizes that it may come from maternal and/or fetal sources. Given the evidence that demonstrates that the presence of fetal cells in maternal blood is a rare event, we conclude that the ordinary artisan would not have read the Kazakov reference as demonstrating that fetal DNA was present in the serum of pregnant women in sufficient quantities such that the serum could be used as a source of fetal DNA in the methods of analyzing fetal DNA for chromosomal abnormalities as taught by Simpson.

In fact, Dr. Kazakov testified on cross-examination that the Kazakov reference "do[es] not describe any quantitative data." Ex. 2113, 233, ll. 9–10. Dr. Kazakov testified further that what he states in his Declaration (Ex. 1006), "that the amount of fetal DNA increases with pregnancy, is based on my current data." Ex. 2113, 233, ll. 16–21.

In addition, Dr. Robert Nussbaum testified,

> Isis argues that a person of ordinary skill in the art at the time of the invention would have no reason to combine Kazakov with Simpson or Bianchi. Even if skeptical of the results provided in Kazakov, I believe these results would have been intriguing to a person working in prenatal diagnosis as it would have signaled that maternal plasma or serum might be a potential new source for fetal DNA. Based on these findings, a person combining the techniques of Simpson and Bianchi (discussed below) with Kazakov would have a reasonable chance of success in amplifying and detecting fetal cell-free DNA from a maternal serum sample.

Ex. 1215 ¶ 41.

Dr. Nussbaum goes on to testify that because of the scarcity of fetal cells, a potential source of fetal DNA would have been of great interest. *Id.* ¶ 42. The problem with that analysis, is that it does not explain why the ordinary artisan would have been expecting fetal cell-free DNA to be present in serum or plasma samples in greater quantities than the fetal cells, given the teaching of Kazakov that the increased levels of DNA in maternal serum during the first trimester may be either from maternal or fetal sources. Accordingly, Ariosa has not demonstrated by a preponderance of the evidence that claims 1, 2, 4, 5, 19–22, 24, and 25 would have been rendered obvious by the combination of Simpson and Kazakov.

3. Obviousness of Claims 3, 12, 13, 15, and 18 Over the Combination of Kazakov and Bianchi or the Combination of Simpson, Schallhammer, Kazakov, and Bianchi

Ariosa relies on Kazakov, as well as the combination of Simpson and Kazakov, as discussed above. IPR2013-00250, Pet. 24–28, 43–48.

Ariosa then relies on Bianchi for its teaching of primers that are specific for Y chromosomes in a male fetus, as well as methods for detecting fetal aneuploidy. *Id.*

Bianchi teaches the detection of fetal aneuploidy and gene mutations by the analysis of fetal cells isolated from maternal blood. Ex. 1043, Abstract. According to Bianchi, "[f]etal cells are rare in the maternal circulation; all current methods used for their isolation also yield maternal cells." *Id.* Bianchi teaches that "[w]ith the possible exception of polymerase chain reaction amplification of exclusively paternally inherited genes, in most cases enrichment and purification procedures are necessary to detect fetal cells." *Id.* at 922, col. 1. According to Bianchi, current techniques used for fetal cell isolation "result in fetal cell purity and yields that are still generally too low for routine clinical diagnosis." *Id.* at 925, col. 1.

Bianchi, however, does not remedy the deficiencies of the combination of Simpson and Kazakov, as discussed above. In addition, the combination of Kazakov and Bianchi suffers from the same deficiencies discussed above with respect to the combination of Simpson and Kazakov. We, thus, conclude that Ariosa has not demonstrated by a preponderance of the evidence that claims 3, 12, 13, 15, and 18 would have been rendered obvious by the combination of Kazakov and Bianchi or the combination of Simpson, Schallhammer, Kazakov, and Bianchi.

F. Isis's Motion to Amend Claims

Isis filed a Contingent Motion to Amend. Paper 88 ("Mot. to Amend"). Isis presents two set of claims, stating that "[i]f claims 1, 24, and

25 are found to be unpatentable, then Isis moves to replace them with claims 28–30, respectively. If claims 28–30 are found unpatentable, then Isis moves to replace them with claims 31–33." Mot. to Amend 1. As the moving party, Isis bears the burden of proof to establish that it is entitled to the relief requested. 37 C.F.R. § 42.20(c). The proposed amendment is not entered automatically, but only upon Isis having demonstrated the patentability of those substitute claims.

Proposed substitute independent claims 28[17] and 31[18] are reproduced below, with underlined text indicating material inserted relative to claim 1, and brackets indicating material removed relative to that claim:

> 28. A method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises
>
> amplifying a paternally inherited nucleic acid from the serum or plasma sample, and
>
> detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample by determining that the paternally inherited fetal nucleic acid contains a sequence not possessed by the pregnant female.
>
> 31. A method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises
>
> amplifying a paternally inherited nucleic acid from the serum or plasma sample, [and]
>
> detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample by determining that the

[17] Isis added a similar "detecting" limitation to proposed substitute claim 29, which is a proposed substitute for original claim 24.
[18] Isis added a similar "detecting" limitation to proposed substitute claim 32, which is a proposed substitute for proposed substitute claim 29.

> paternally inherited nucleic acid of fetal origin contains a sequence not possessed by the pregnant female,
> and
> determining fetal sex, fetal chromosomal aneuploidy, fetal mutation, fetal RhD status, or fetal paternally-inherited DNA polymorphism.

Mot. to Amend 1–2. Claim 28 is proposed to be a substitute for original claim 1, while claim 31 is proposed to be an alternative substitute for original claim 1. *Id.*

According to Isis, the "determining" limitation was added "in view of Ariosa's unreasonably broad construction of the 'detecting step.'" *Id.* at 7. According to Isis, the "by determining" phrase "requires manipulation of the paternally inherited nucleic acid to determine that it contains a sequence not possessed by the pregnant female." *Id.* Isis contends further that the Specification of the '540 patent describes a number of ways in which that manipulation could be done. *Id.* at 7–8.

1. No Broadening of Scope

Proposed substitute claims may not enlarge the scope of the original patent claims. 35 U.S.C. § 316(d)(3); 37 C.F.R. § 42.121(a)(2)(ii). Proposed substitute claims 28–30 and 31–33 merely add features to the claims for which they substitute, and do not remove any limitation therefrom. Accordingly, no issue exists with regard to the prohibition against broadening original patent claims.

2. *Patentability*

An *inter partes* review is neither a patent examination proceeding nor a patent reexamination proceeding. The substitute claims proposed in a

motion to amend are not entered automatically and then subject to examination. Rather, the proposed substitute claims will be added directly to the patent, without examination, *if* the patent owner's motion to amend is granted. In a motion to amend, the patent owner is not rebutting a rejection in an office action, as though this proceeding were a patent examination or a reexamination. Instead, the patent owner, as the movant, bears the burden of establishing the patentability of the proposed substitute claims.

a. Patentability under 35 U.S.C. § 101

As discussed above in the section discussing the related proceedings, on October 30, 2013, claims 1, 2, 4, 5, 8, 19–22, 24, and 25 of the patent at issue in the instant proceeding, which includes independent claims 1, 24, and 25, were declared invalid in *Ariosa Diagnostics, Inc. v. Sequenom, Inc.* Ex. 2224. The district court was instructed by the Federal Circuit to "examine subject matter eligibility of the asserted claims in the first instance in light of the Supreme Court's recent decision in *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013) and the Federal Circuit's claim construction holdings." *Id.* at 4.

Ariosa Diagnostics was decided by the Federal Circuit on August 9, 2013, before Isis filed its Motion to Amend on October 9, 2013. Isis did not address, however, the issue of whether its proposed substitute claims met the requirements of 35 U.S.C. § 101. In fact, Isis stated during oral argument that they need not address any issues other than those of written description and the prior art, as those were the only issues discussed in the rules governing these proceedings, such as 37 C.F.R. § 42.121, as well as in cases such as *Oracle Corp. v. Clouding IP, LLC*, Case IPR2013-00088, slip. op. at

2 (PTAB July 15, 2013) (Paper 16) (citing *Idle Free Systems, Inc. v. Bergstrom, Inc*, Case IPR2012-00027, slip. op. at 3–9 (PTAB June 11, 2013) (Paper 26)). Tr., 66–67.

The moving party has the burden of proof to establish that it is entitled to the relief requested. 37 C.F.R. § 42.20(c). In the context of a motion to amend, that requires patent owner, the moving party, to demonstrate the patentability of the claims by a preponderance of the evidence. *Inter partes* review is an adjudicatory proceeding, not a prosecutorial proceeding, before the Office. H.R. Rep. No. 112-98 Part 1 (2011) at 46–47 ("The [AIA] converts inter partes reexamination *from an examinational to an adjudicative proceeding*, and renames the proceeding 'inter partes review.'"; emphasis added); *see also id.* at 75 ("Subsections (a) and (d) [of Section 6 of the AIA] enact new chapters 31 and 32, which create *adjudicative* systems of post-grant and inter partes review;" emphasis added). Thus, when considering a motion to amend, we do not *examine* and *allow* or *reject* the substitute claims, but determine whether the patent owner has met its burden of establishing that it is entitled to the substitute claims that it seeks in its motion to amend.

Although we agree with Isis that an *inter partes* review cannot be instituted using 35 U.S.C. § 101 as the basis for a challenge brought by a petitioner, *see* 35 U.S.C. § 311(b) ("A petitioner in an inter partes review may request to cancel as unpatentable 1 or more claims of a patent only on a ground that could be raised under section 102 or 103 and only on the basis of prior art consisting of patents or printed publications."), in a motion to amend, the patent owner has the burden of demonstrating the patentability of the claims (*see* 37 C.F.R. § 42.20(c) ("The moving party has the burden of

proof to establish that it is entitled to the relief requested.")). And while the panel in *Idle Free Systems* focused its analysis on patentability over the prior art, we do not think that was an exhaustive list of the issues that we must consider in determining whether a patent owner, in this case Isis, has demonstrated the patentability of the proposed substitute claims. Moreover, in a case such as this, where the claims have been determined to be invalid by a district court, we decline to enter an amendment to claims where the patent owner did not explain how the proposed amendments addressed the district court's concerns regarding the validity of the claims.

We acknowledge that the district court's decision as to invalidity was issued after Isis filed its Motion to Amend in this case. Isis was on notice, however, that both the district court and the Federal Circuit had considered the question as to whether the claims of the '540 patent were patent ineligible under § 101. *Aria Diagnostics*, 726 F.3d at 1304. And Isis did file a Reply to Ariosa's opposition to the Motion to Amend (Paper 130) on December 23, 2013, after the district court issued its decision that claims 1, 2, 4, 5, 8, 19–22, 24, and 25 were invalid as being drawn to patent ineligible subject matter, and again did not explain how the proposed substitute claims addressed the district court's subject matter eligibility concerns.

Moreover, we do not think that allowing Isis to amend the claims under these facts would serve the purpose of these post-grant proceedings; that is, "establish[ing] a more efficient and streamlined patent system that will improve patent quality and limit unnecessary and counterproductive litigation costs." 77 Fed. Reg. 48,612 (August 14, 2012). If we were to allow Isis to amend the claims of the '540 patent, without requiring Isis to explain how the proposed substitute claims overcome the district court's

finding that the claims are drawn to patent ineligible subject matter under 35 U.S.C. § 101, the claims that are currently on appeal before the Federal Circuit from the district court's finding of invalidity would no longer be the claims in the patent. Such a result would thwart the purpose of limiting counterproductive litigation costs, and wasting judicial resources.

We conclude, therefore, that Isis has not met its burden of demonstrating the patentability of the claims.

3. Written Description Support

Because Isis has not shown patentability of the proposed substitute claims, we do not reach whether it has shown that the proposed substitute claims have written description support in the '540 patent application as filed.

Isis has not, in its motion, set forth a prima facie case for the relief requested—that independent proposed substitute independent claims 28–30, or proposed substitute claims 31–33, are patentable—and thus has not satisfied its burden of proof. Isis's Motion to Amend is, therefore, *denied*.

G. Isis's Motion to Exclude Evidence

Isis filed a Motion to Exclude Evidence (Paper 135) seeking to exclude (1) the first Declaration of Dr. Mansfield (Ex. 1007) on the basis that it contains unreliable and irrelevant expert opinions; (2) the second Declaration of Dr. Mansfield (Ex. 1047) on the same basis as the first Declaration of Dr. Mansfield; (3) Exhibits 1134–1168 and 1170–1183 as lacking foundation; and Exhibits 1184 and 1199 as being untimely served; (4) the first Declaration of Dr. Morassa Mohseni (Ex. 1184); (5) the second

Declaration of Dr. Mohseni (Ex. 1199); and (6) portions of the Deposition of Dr. Nicholas M. Fisk (Ex. 1196).

A party wishing to challenge the admissibility of evidence must identify the grounds of the objection and explain why the evidence is not admissible. 37 C.F.R. § 42.64(c). As to Isis's objections to the two declarations of Dr. Mansfield (*see* Paper 135, 1–9), we note that the objections go more to the weight that those Declarations should be afforded, rather than admissibility. It is within our discretion to assign the appropriate weight to be accorded to Dr. Mansfield's testimonial evidence. We thus decline to exclude the two Declarations of Dr. Mansfield (Exs. 1007, 1047).

As we did not rely on Exhibits 1134–1168 and 1170–1183 in making our final determination, we conclude it is unnecessary to consider Isis's objections to the admissibility of those exhibits. As we also did not rely on the two Declarations of Dr. Mohseni (Exs. 1184, 1199), we also conclude it is unnecessary to consider Isis's objections to the admissibility of those exhibits.

As to the cross-examination of Dr. Fisk, Isis contends that in the portion of the deposition it seeks to exclude, "the question was presented in an improper form that would cause undue confusion and unduly prejudice patent owner under FRE 403." Paper 135, 12 (citing Ex. 1196, 132, l. 22–133, l. 3). Isis states that it had objected to the question during deposition. *Id.*

Specifically, according to Isis:

> Dr. Fisk was asked the following question: "So then would you say that the quantity of fetal cell-free DNA present in the plasma or serum of a pregnant woman is diagnostic of an aneuploidy?" EX1196:133:22–25. The use of the phrase

> "diagnostic of" is inherently confusing because the phrase implies definitive clinical standards and is more stringent than the patent's use of "diagnosis," which encompasses less stringent screening standards. Consideration of an answer to this question will therefore cause confusion in consideration of the '540 patent claims.

Id. at 13.

We have considered Isis's objection, but do not find that the question causes undue confusion or was unduly prejudicial to Patent Owner. The PTAB, sitting as a non-jury tribunal with administrative expertise, is well-positioned to determine and assign appropriate weight to evidence presented. In this case, we understand that there may be differences in how "diagnosis" may be used by a practitioner in the field and how it is used in the '540 patent, and find that there is no discernable prejudice to Patent Owner in this proceeding. We, thus, deny Isis's motion to the extent it seeks exclusion of that portion of Dr. Fisk's deposition testimony.

In view of the foregoing, Isis's Motion to Exclude is *denied* to the extent it seeks to exclude Exhibits 1007, 1047, as well as a portion of Exhibit 1196, and is *dismissed as moot* to the extent it seeks the exclusion of Exhibits 1134–1168, 1170–1183, 1184, and 1199.

H. Ariosa's Motion for Observation Regarding Cross Examination of Isis's Reply Witnesses

In addition, Ariosa moved for observations on certain portions of certain cross-examinations of Isis's reply witnesses, contingent on our consideration of Exhibits 2230, 2240, and 2243. Paper 142, 1. Isis contends that we should not consider Ariosa's motion. Paper 147, 1. As we did not

rely on Exhibits 2230, 2240, and 2243 in our final decision, we dismiss Ariosa's motion (Paper 142) as moot.

III. CONCLUSION

Ariosa has not shown by a preponderance of the evidence that claims 3, 12, 13, 15, 18, 21, and 22 are unpatentable.

Ariosa has shown by a preponderance of the evidence that claims 1, 2, 4, 5, 8, 19, 20, 24, and 25 of the '540 patent are unpatentable under 35 U.S.C. § 102(b).

Isis has not demonstrated by a preponderance of the evidence of record that its proposed substitute claims 28–30, or proposed substitute claims 13–33, are patentable.

IV. ORDER

ORDERED that claims 1, 2, 4, 5, 8, 19, 20, 24, and 25 of the '540 patent are determined to be shown unpatentable by a preponderance of the evidence of record;

FURTHER ORDERED that Petitioner has not shown by a preponderance of the evidence that claims 3, 12, 13, 15, 18, 21, and 22 are unpatentable;

FURTHER ORDERED that Isis's Motion to Amend Claims is *denied*;

FURTHER ORDERED that Isis's Motion to Exclude Evidence is *denied* to the extent it seeks to exclude Exhibits 1007, 1047, as well as a portion of Exhibit 1196, and *dismissed* as moot as to the extent it seeks the exclusion of Exhibits 1134–1168, 1170–1183, 1184 and 1199.

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