United States Court of Appeals for the Federal Circuit

ARIA DIAGNOSTICS, INC.,
Plaintiff-Appellee,

v.

SEQUENOM, INC.,
Defendant-Appellant.

2012-1531

Appeal from the United States District Court for the Northern District of California No. 11-CV-6391, Judge Susan Y. Illston.

Decided: August 9, 2013

DAVID I. GINDLER, Irell & Manella LLP, of Los Angeles, California, argued for plaintiff-appellee. With him on the brief were ANDREI IANCU, AMIR NAINI, LINA F. SOMAIT and JASON W. SULLIVAN.

MICHAEL J. MALECEK, Kaye Scholer, LLP, of Palo Alto, California, argued for defendant-appellant. With him on the brief were STEPHEN C. HOLMES and JONATHAN M. ROTTER.

Before RADER, *Chief Judge,* DYK, and REYNA, *Circuit Judges.*

RADER, *Chief Judge.*

Aria Diagnostics, Inc., now known as Ariosa Diagnostics, Inc. (Ariosa) sought a declaration that its Harmony test did not infringe any claim of U.S. Patent No. 6,258,540 (the '540 patent), owned by defendant Isis Innovation Limited (Isis) and licensed by Isis exclusively to Sequenom, Inc. (Sequenom). Sequenom counterclaimed, alleging that Ariosa's Harmony test infringes the '540 patent. The United States District Court for the Northern District of California denied Sequenom's motion for a preliminary injunction to prevent Ariosa from making, using, or selling that test. *Aria Diagnostics, Inc. v. Sequenom, Inc.*, 2012 WL 2599340 (N.D. Cal. July 5, 2012). Because the district court incorrectly interpreted the asserted claims and improperly balanced factors regarding issuance of a preliminary injunction, this court vacates and remands.

I.

Genetically normal human beings have 23 pairs of chromosomes. Having the normal number of chromosomes is called "euploidy." Genetic birth defects often occur when a person has three chromosomes rather than the usual pair. Having an abnormal number of chromosomes is "aneuploidy." Aneuploidy of the three-chromosome variety is called "trisomy." Trisomy causes three major syndromes: Down's, Edwards, and Patau. Down's Syndrome is often caused by trisomy of chromosome 21.

Conventional tests for prenatal abnormalities such as trisomy relied on invasive techniques like amniocentesis to obtain fetal cells floating in the amniotic fluid. Once the fetal cells were removed, the fetal DNA could be analyzed. These invasive tests, of course, presented risks

to the fetus and the mother. *See* '540 patent col. 1, ll. 12–17.

As an alternative to invasive techniques, scientists in the 1990's developed methods to determine fetal abnormalities and other fetal traits by analyzing DNA extracted from fetal cells floating in maternal blood. These methods required detecting rare nucleated cells from the fetus that had passed through the amniotic sac into maternal blood, and then extracting and analyzing the fetal DNA in those free floating fetal cells. Among other things, these methods required separating fluids from the cells—and then discarding the fluids, either plasma or serum—and then separating fetal cells from the much more common maternal cells. *See id.* col. 1, ll. 17–37. Once the cells were separated, the remaining maternal serum or plasma was commonly discarded as waste, and the fetal DNA was extracted and analyzed. J.A. 1118.

The '540 patent discloses methods to identify fetal genetic defects by analyzing the fluid that had commonly been discarded as medical waste—the maternal plasma or serum. The '540 patent discloses that non-nucleated free-floating fetal DNA (the cffDNA) exists in maternal blood. *See* '540 patent col. 2, ll. 1–5. The specification explains that not only does analysis of cffDNA permit more efficient determination of genetic defects (for example, trisomy of chromosome 21) but that a pregnant woman carrying a fetus with certain genetic defects will have more cffDNA in her blood than do women with normal fetuses. *Id.* col. 3, ll. 30–43. In other words, the '540 patent claims methods to detect fetal genetic characteristics by analyzing cffDNA obtained from a maternal blood sample. These new tests presented fewer risks and a more dependable rate of abnormality detection.

On December 19, 2011, Ariosa filed a declaratory judgment action against Sequenom in the Northern District of California. Ariosa sought clearance to use its

Harmony test without fear of infringing the '540 patent. On March 8, 2012, Sequenom counterclaimed, alleging that the Harmony test infringes the '540 patent. On that same day, Sequenom moved for a preliminary injunction. On June 29, 2012, the district court heard oral argument on Sequenom's motion. Upon denial of that motion, Sequenom appealed. This court has jurisdiction under 28 U.S.C. § 1292(c)(1).

II.

This court reviews facts for clear error. *E.I. Du Pont De Nemours & Co. v. MacDermid Printing Solutions, LLC*, 525 F.3d 1353, 1358 (Fed. Cir. 2008). However, to reverse a denial of a preliminary injunction, the appellant "must show not only that one or more of the findings relied on by the district court was clearly erroneous, but also that denial of the injunction amounts to an abuse of the court's discretion upon reversal of the erroneous findings." *Reebok Int'l Ltd. v. J. Baker, Inc.*, 32 F.3d 1552, 1555 (Fed. Cir. 1994).

The parties dispute the proper standard of review for claim construction in the context of a preliminary injunction. This court recognizes some flexibility on this point. *Compare Chamberlain Group, Inc. v. Lear Corp.*, 516 F.3d 1331, 1340 (Fed. Cir. 2008) ("a correct claim construction is almost always a prerequisite for imposition of a preliminary injunction), *with Int'l Cmty. Materials v. Ricoh Co.*, 108 F.3d 316, 318-19 (Fed. Cir. 1997) ("We do not regard it as our function [in preliminary injunction appeals] to definitively construe" claims or to review claim construction "as if from final judgment").

In this case, the court need not reach out to comment on those alternative approaches to the question. Even under the ostensibly more relaxed standard, the district court erred in its claim construction. As a consequence, the district court erred in finding a substantial question of noninfringement.

III.

This court first examines the meaning of the phrase "paternally inherited nucleic acid." Claim 1 exemplifies the claims' use of this phrase:

> 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
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> > 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.

'540 patent, col. 23, ll. 61–67 (emphases added).

The district court held, at least at this preliminary juncture, that "paternally inherited nucleic acid" means "DNA sequence known [in advance] to be received only from the father which is not possessed by the mother." J.A. 13. The trial court did not use the bracketed "in advance" phrase in its order. The parties agree, however, that the district court's construction requires that the sequence be known "in advance" to have been received only from the father and not possessed by the mother. Under this construction, infringement can only occur after a user knows the father's gene sequence (for example, through genotyping). For reasons that follow, this construction of the phrase is incorrect.

Claim construction focuses primarily on the language of the claims. *See Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc). At the outset, the claim language recites only the term "paternally inherited nucleic acid." This term does not incorporate any inherent meaning about the timing or method of detecting the paternal

characteristic. Rather this claim term states only the origin of that particular nucleic acid however or whenever it may be identified. This language does not require pre-testing knowledge of the father's genetic sequence. The phrase "paternally inherited nucleic acid of fetal origin" connotes only nucleic acid that originates from the fetus and is inherited from the father. Had the applicant wanted to limit the claim to those nucleic acids known in advance to have come from the father, it easily could have done so, as the district court's insertion of the "known in advance" requirement shows. The applicant, however, did not limit the term in the claim.

Therefore, to incorporate that requirement into the claim, this limitation must find its source and support elsewhere. The district court attempted to find that support in one sentence from the specification, the examples, and isolated events in the '540 patent's prosecution history. J.A. 11. Taken in context, this evidence does not support the trial court's interpretation, and certainly is not clear lexicography or disavowal.

The specification does not state that "paternally inherited" means "known in advance to be paternally inherited." Instead, the single sentence in the specification on this topic suggests no limitation whatsoever: the "method according to the invention can be applied to the detection of *any* paternally-inherited sequences which are not possessed by the mother." '540 patent, col. 2, ll. 57–60 (emphasis added). This expansive sentence reflects the broad meaning of "paternally inherited nucleic acid" that is found in the claims—a meaning which does not limit them to those known in advance to have come from the father. Properly understood, this sentence describes the method of isolating and identifying *any* paternal characteristics by comparison to maternal characteristics, hardly a limitation to *only* paternal characteristics known in advance.

The district court's construction also does not adequately account for the proper teaching of the examples in the specification. At the outset, this court notes that the claims would not necessarily carry this limitation even if the patent contained only examples where the father's genetic sequence had been known prior to detection. As this court has explained, it is "not enough that the only embodiments, or all of the embodiments, contain a particular limitation to limit a claim term beyond its ordinary meaning." *Aventis Pharma S.A. v. Hospira, Inc.*, 675 F.3d 1324, 1330 (Fed. Cir. 2012). Moreover, 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." *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 906 (Fed. Cir. 2004). Instead of a clear intention to limit the claims to the embodiments in the examples, here the specification states that the examples "do not in any way limit the scope of the invention." '540 patent, col. 4, ll. 13-14.

Further, Example 3 expressly describes ascertaining, before testing, whether the mother is RhD negative, but makes no mention of detecting the RhD gene in the father. *See id.* col. 10, ll. 33–34. In sum, Example 3 describes detecting paternally-inherited genes—the RhD gene—but not a gene *known in advance* to have come from the father. Consequently, even if the specification did clearly limit the claims to the examples, the examples are not limited to sequences known in advance to have come from the father.

Similarly, the prosecution history does not support importing this "known in advance" limitation. For prosecution history to limit claim meaning, it must be clear and unmistakable that the patentee intended that limitation. *See Aventis*, 675 F.3d at 1330. The parties focus on three ambiguous events during prosecution.

First, when Isis originally filed the application that led to the '540 patent, the claims were not limited to "paternally inherited" sequences. Instead, they were directed to "detecting the presence of a nucleic acid of foetal origin in the sample . . . ." J.A. 3544.

The examiner rejected these proposed claims. J.A. 1322. Among other things, the examiner emphasized that because the amount of cffDNA before fifteen weeks of gestation was very low, "detection of a maternally inherited nucleic acid would . . . require undue experimentation." J.A. 1361; *see* J.A. 1322. The examiner stated, however, that the claims would be allowable if limited to "paternally inherited nucleic acid." J.A. 3714. Accordingly, the patentee amended the issued claims to contain the "paternal" limitation.

This record does not clearly require that the paternally inherited sequence must have been known in advance to have come from the father. The account of the prosecution history makes no reference to advance timing, let alone the clear and unmistakable disavowal required by controlling precedent.

The second event Ariosa relies upon to support the "known in advance" limitation involves statements made later, during prosecution of a continuation of the application that led to the '540 patent. After the '540 patent had been allowed but before issuance, Isis filed a continuation application. In that application, Isis sought claims that were not limited to paternally inherited sequences. In explaining to the examiner its justification for these different claims, Isis wrote:

> [T]he term 'paternally inherited' does not cover cases: (a) in which the gene is maternally inherited, yet the nucleic acid is not (in total) the same in the fetus as in the mother, and (b) in which the gene is altered spontaneously, for example, in the

> egg or sperm, i.e., by what appears to be chance or mutation.

J.A. 1776.

This passage may show that Isis understood that "paternally inherited" excluded the subject matter in (a) and (b). The passage, however, says nothing that clearly requires the claims in the parent to include the "known in advance" limitation. This passage does not approach the clear and unequivocal statement needed before prosecution history can operate to extinguish subject matter otherwise within the claims.

Third, in rejecting those proposed claims, the examiner stated that the specification did not enable a person of ordinary skill to identify a trisomy of chromosome 21 caused by maternal inheritance or genetic mutation. J.A. 2287. Once again, this ambiguous reference makes no allusion to paternal characteristics known in advance. At most, this passage suggests concerns about enablement, an argument raised below but not reached by the district court. J.A. 19 n.17.

In sum, the record does not support importation into the claims of a "known in advance" limitation. Accordingly, the district court erred in relying upon this construction to hold that Ariosa had raised a substantial question of noninfringement.

The district court also construed the term "amplifying." Again, claim 1 illustrates:

> 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.

'540 patent, col. 23, ll. 61–67 (emphases added).

The district court construed "amplifying" to mean "increasing the concentration of a paternally inherited nucleic acid relative to the other DNA in the sample." J.A. 14. The district court concluded that *only* paternally inherited nucleic acid must increase by reasoning that "amplifying" modified "paternally inherited nucleic acid." *Id.* As a result, it reasoned that this was "not the same as amplifying fetal DNA in general, or all DNA in the sample." *Id.*

To the contrary, the 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.

The remainder of the specification also undermines the district court's interpretation because it does not require amplification to change the proportions of paternal or maternal nucleic acids. Rather, the specification discloses that "enrichment" and "amplification" are distinct:

> The preparation of serum or plasma from the maternal blood sample is carried out by standard techniques. *The serum or plasma is normally then subjected to a nucleic acid extraction process*. [The patent then lists various methods.] Serum and plasma nucleic acid extraction methods allowing

> the purification of DNA or RNA from larger volumes of maternal sample increase the amount of foetal nucleic acid material for analysis and thus improve the accuracy. *A sequence-based enrichment method could also be used on the maternal serum or plasma to enrich for foetal nucleic acid sequences*.
>
> *An amplification of foetal DNA sequences in the sample is normally carried out.* Standard nucleic acid amplification systems can be used, including PCR, the ligase chain reaction, nucleic acid sequence based amplification (NASBA), branched DNA methods, and so on. Preferred amplification methods involve PCR.

'540 patent col. 2, ll. 27–48 (emphases added). In sum, the specification does not support, but instead points away from the district court's claim construction, which already is at odds with the plain language of the claim.

The prosecution history is also insufficient to overcome the broad language of the claims. Specifically, the examiner stated that detecting fetal DNA before the fifteenth week of gestation would require enriching the fetal DNA "in some manner which ha[s] not been described." J.A. 1676–77. The examiner could not have been objecting to lack of support for amplification, because amplification was described through traditional PCR and other methods. *E.g.*, '540 patent col. 5, ll. 6–29.

By defining "amplifying" to mean changing the proportion of paternally inherited DNA relative to other DNA in the sample, the district court construed the term incorrectly. Accordingly, because of the district court's erroneous constructions, this court reverses that court's conclusion that Ariosa had raised a substantial question of noninfringement.

IV.

The district court also found there was a substantial question over whether the subject matter of the asserted claims was to eligible subject matter. J.A. 16-19. Since the district court's decision, the Supreme Court decided *Association for Molecular Pathology v. Myriad Genetics, Inc.,* 133 S. Ct. 2107 (2013) (*Myriad*), which held that product claims directed to isolated DNA segments were not eligible subject matter, but that product claims directed to synthetic cDNA were patent eligible. *See id.* at 2119-20. Because the district court did not have the benefit of *Myriad* and also in light of this court's disagreement with the district court's claim construction, this court remands for the district court to examine subject matter eligibility in the first instance.

To be clear, this court offers no opinion as to whether there is or is not a substantial question regarding the subject matter eligibility of the asserted claims. This court merely concludes that in light of *Myriad* and the different claim construction, this court would benefit from the district court's initial and further consideration. On remand, the district court may once again consider this issue, as well as whether there is a substantial question of validity of the asserted claims under other defenses raised by Ariosa but not reached previously by the district court. *See* J.A. 19 n.17.

V.

On remand, if the district court finds no substantial question of validity or infringement, it must address the traditional equitable factors for a preliminary injunction. The district court correctly held that in addition to showing the likelihood of success on the merits, Sequenom must show it likely will suffer irreparable harm, that the balance of equities tips in its favor, and that an injunction is in the public interest. J.A. 9 (citing *Winter v. Natural Res. Def. Council, Inc.*, 555 U.S. 7, 20 (2008)). Because it

found substantial questions on infringement and "validity" in the form of ineligible subject matter, the district court only briefly addressed the traditional factors. J.A. 19–20. The district court erred in some aspects of its brief analysis. Accordingly, this court remands with additional guidance.

Significantly, the district found that price and market erosion would occur. *Id.* Under this court's precedent, "[p]rice erosion, loss of goodwill, damage to reputation, and loss of business opportunities are all valid grounds for finding irreparable harm." *Celsis in Vitro, Inc. v. CellzDirect, Inc.*, 664 F.3d 922, 930 (Fed. Cir. 2012). Nonetheless, the district court denied Sequenom's motion, giving four reasons.

First, the district court reasoned that the erosion to Sequenom's price and its loss of market share were not irreparable. J.A. 20. It reasoned that if Sequenom was proven correct that the '540 patent and the MaterniT21 test would set new standards of care, then Sequenom could recover the market and receive damages to compensate for the infringement. J.A. 20. While the *facts* may show that damages would be reparable, this *assumption* is not sufficient. In the face of that kind of universal assumption, patents would lose their character as an exclusive right as articulated by the Constitution and become at best a judicially imposed and monitored compulsory license.

Second, the district court reasoned that the degree of price erosion and market loss had not been adequately shown by Sequenom's expert, Dr. Rao. More specifically, the district court characterized it as a "significant deficiency" that he had not examined the "*actual* market" because he did not consider the impact of another test, sold by another company, Verinata Health, Inc. (Verinata). J.A. 19 (emphasis in original). Yet, the district court found that Verinata's tests *did not* compete in the actual

market, but only "may eventually" do so. J.A. 7. Further, even if Verinata were actually in the same market, the "fact that other infringers may be in the marketplace does not negate irreparable harm." *Pfizer, Inc. v. Teva Pharm. USA, Inc.*, 429 F.3d 1364, 1381 (Fed. Cir. 2005).

Third, the district court found that a preliminary injunction would put Ariosa out of business. J.A. 20. A record showing that the infringer will be put out of business is a factor, *Intel Corp. v. ULSI Sys. Tech., Inc.*, 995 F.2d 1566, 1568, 1570 (Fed. Cir. 1993) (finding no error in district court's determination that balance of hardships favored accused infringer where it "would in all likelihood be forced out of business" if enjoined), but does not control the balance of hardships factor. *Id.* at 1570 ("none of the factors is dispositive"); *Bell & Howell Document Mgmt. Prods. Co. v. Altek Sys.,* 132 F.3d 701, 708 (Fed. Cir. 1997) (the fact that an accused infringer would be put out of business "does not insulate it from the issuance of a preliminary injunction" if other factors weigh in favor of the relief). This court can easily imagine a situation where the loser on either side may have to close its doors. At this point, however, this court has seen no comparison of difficulties or losses Ariosa might experience weighed against the harms Sequenom might suffer without protection of its legal exclusive rights. For example, the district court made no findings on the harm that would accrue to Sequenom's R&D and investment in the technology, undermining work and money spent developing, validating, and commercializing any covered product. J.A. 6. These issues also await remand.

Finally, the district court reasoned that the public interest favored denial of the preliminary injunction. Sequenom marketed its tests only to women over 35 and at high risk both of having a fetus with Down's Syndrome and of losing a fetus through invasive testing, J.A. 4, but Ariosa marketed its products to both high- and low-risk women. Ariosa argued there was "no reason" to refuse to

serve the 3,550,000 women in the low risk category, instead of only the 750,000 in the high risk category. J.A. 6-7. After the preliminary injunction hearing, this court took judicial notice that an expert organization had warned that cffDNA tests should not, yet, be used in low-risk women. Am. Coll. of Obstetricians and Gynecologists Comm. on Genetics, *Noninvasive Prenatal Testing for Fetal Aneuploidy*, Op. No. 545 (Dec. 2012). On remand, if necessary the district court should consider this and any other evidence pertaining to the public interest anew.

This court has considered the other arguments presented by Ariosa, but does not find them persuasive. Accordingly, this court reverses and remands this case to the district court for further proceedings consistent with this opinion.

VACATED AND REMANDED