UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

PERKINELMER, INC., and NTD LABORATORIES, INC.	)	
Plaintiffs/Counter-Defendants,	)	
	)	**Civ. Action No. 09cv10176-NG**
v.	)	(Previously consolidated with
	)	Civ. Action No. 09cv11517-NG)
INTEMA LIMITED,	)	
Defendant/Counter-Claimant.	)	

GERTNER, D.J.

MEMORANDUM AND ORDER RE: MARKMAN CLAIM CONSTRUCTION
July 2, 2010

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I. INTRODUCTION

This action concerns U.S. Patent No. 6,573,103 ("the '103 patent"), held by the defendant, Intema Limited ("Intema"). The '103 patent describes processes for prenatal Down syndrome screening. Plaintiffs PerkinElmer, Inc. ("PerkinElmer") and its subsidiary NTD Laboratories, Inc. ("NTD") brought this action for a declaratory judgment claiming that the '103 patent is invalid and that plaintiffs have not infringed it. Separately, Intema filed suit against plaintiffs for patent infringement in the Eastern District of New York. The New York court transferred the second suit to the District of Massachusetts; this Court ordered that the two cases be consolidated. Intema's infringement claim is a counterclaim here.

Federal Circuit law provides that a court addressing patent validity and infringement questions should first "determine[] the meaning of disputed claim terms." Wavetronix v. EIS Elec. Integrated Sys., 573 F.3d 1343, 1354 (Fed. Cir. 2009); see also Smiths Indus. Med. Sys., Inc. v. Vital Signs, Inc., 183 F.3d 1347, 1353 (Fed. Cir. 1999). The parties have submitted briefs supporting their respective interpretations of various disputed terms in the '103 patent. The

Court held a Markman hearing[1] on April 29, 2010, at which Dr. Jacob Canick gave a technology tutorial on behalf of Intema, and both sides argued their interpretations. Based on all of this information, the Court issues the following order construing the disputed terms.

II. FACTS

A. Background

For many years, doctors have conducted prenatal screening to determine the chance that newborns will have Down syndrome. Scientists worked to develop increasingly accurate screening methods because the two available diagnostic tests that can definitively confirm the baby will have this condition -- chorionic villus sampling in the first trimester and amniocentesis in the second trimester -- carry significant risks of miscarriage. Doctors recommend these dangerous tests if the screening method indicates a high risk of Down syndrome. Initially, the screening methods involved looking at maternal age and certain biochemical screening markers from the second trimester of pregnancy. By the 1990s, however, doctors began considering data that they could obtain during the first trimester, including biochemical markers and measurements from ultrasounds. The patent at issue in this suit, obtained by Professor Nicholas Wald ("Wald"), describes screening methods in which doctors estimate the risk of Down syndrome using markers from *both* the first and second trimesters.

According to Intema, PerkinElmer and NTD have employed a few Down syndrome tests that infringe on this patent. In two tests allegedly employed by NTD, doctors measure one or more screening markers in the first trimester and one or more screening markers in the second trimester, where at least one of the second trimester markers was not tested in the first trimester.

[1] The term "Markman hearing" arose out of the Federal Circuit's decision in Markman v. Westview Instruments, Inc., 52 F.3d 967 (Fed. Cir. 1995), aff'd, 517 U.S. 370 (1996).

Doctors may provide an immediate risk assessment to the patient after first trimester screening, but if they perform second trimester screening, they give the patient an integrated estimate of risk based on data from both sets of screenings. Intema also alleges that PerkinElmer supplies first and second trimester screening kits to the State of California, thereby inducing infringement of the patent.

B. The '103 Patent's Scope

The main dispute concerns a phrase that appears in both Claims 1 and 20 of the patent (underlined below). Claim 1 reads as follows:

> A method of determining whether a pregnant woman is at an increased risk of having a fetus with Down's syndrome, the method comprising the steps of:
> measuring the level of at least one screening marker from a first trimester of pregnancy by:
> (I) assaying a sample obtained from the pregnant woman at said first trimester of pregnancy for at least one first biochemical screening marker;
> and/or (ii) measuring at least one first ultrasound screening marker from an ultrasound scan taken at said first trimester of pregnancy;
> measuring the level of at least one second screening marker from a second trimester of pregnancy, the at least one second screening marker from the second trimester of pregnancy being different from the at least one first screening marker from the first trimester of pregnancy, by:
> (I) assaying a sample obtained from the pregnant woman at said second trimester of pregnancy for at least one second biochemical screening marker;
> and/or (ii) measuring at least one second ultrasound screening marker from an ultrasound scan taken at said second trimester of pregnancy;
> and <u>determining the risk of Down's syndrome by comparing the measured levels of both the at least one first screening marker from the first trimester of pregnancy and the at least one second screening marker from the second trimester of pregnancy with observed relative frequency distributions of marker levels in Down's syndrome pregnancies and in unaffected pregnancies.</u>

Claim 20 states:

> A method of determining whether a pregnant woman is at an increased risk of having a fetus with Down's syndrome, the method comprising the steps of:
> measuring the level of at least one first screening marker from a first trimester of pregnancy by:
> (I) assaying a sample obtained from the pregnant woman at said first trimester of pregnancy for at least one first biochemical screening marker; and/or (ii) measuring at least one first ultrasound screening marker from an ultrasound scan taken at said first trimester of pregnancy;
> determining a first risk estimate of Down's syndrome by comparing the measured level of the at least one first screening marker level from the first trimester of pregnancy with observed relative frequency distributions of marker levels in Down's syndrome pregnancies and in unaffected pregnancies;
> comparing the first risk estimate with a predetermined cut-off level to initially classify the pregnant woman as screen-positive or screen-negative based on the comparison;
> and if the pregnant woman is initially classified as screen-negative:
> measuring the level of at least one second screening marker from a second trimester of pregnancy, the at least one second screening marker from the second trimester of pregnancy being different from the at least one first screening marker from the first trimester of pregnancy, by:
> (I) assaying a sample obtained from the pregnant woman during said second trimester of pregnancy for at least one second biochemical screening marker;
> and/or (ii) measuring at least one second ultrasound screening marker from an ultrasound scan taken during said second trimester of pregnancy;
> and <u>determining the risk of Down's syndrome by comparing the measured level of both the at least one first screening marker from the first trimester of pregnancy and the at least one second screening marker from second trimester of pregnancy with observed relative frequency distributions of marker levels in Down's syndrome pregnancies and in unaffected pregnancies.</u>

In Intema's reading, this language means that the patent covers all procedures in which doctors might determine the risk of Down syndrome using measurements obtained in both the first and second trimesters. For example, doctors could take measurements during the first trimester and put them aside; after taking additional measurements during the second trimester,

the doctors would then compute a risk estimate using both sets of data. Alternately, doctors could use the first trimester measurements to calculate a preliminary risk, which may trigger a diagnostic test; if doctors do not conduct a diagnostic test, then they would take measurements in the second trimester, and use data from both trimesters to calculate an integrated estimate. In effect, Intema believes the patent was innovative because its method allows doctors to calculate a risk estimate that is more accurate than was possible with preexisting tests that used data from only one trimester.

PerkinElmer and NTD present a very different interpretation. They note that, before this patent, doctors already conducted Down syndrome screening for some patients during both the first and second trimesters. In this prior art, doctors made the information from the first trimester test available to women, who could then decide whether to undertake diagnostic testing or wait for additional screening results in the second trimester. According to the plaintiffs, the Intema patent applies only when doctors withhold results from pregnant women during the first trimester, and instead provide a single risk estimate only after the first trimester measurements are integrated with information obtained in the second trimester. Under this view, the patent's only relevant contribution to the field was its suggestion that doctors can avoid risky diagnostic tests early in pregnancy by not telling patients any information from first trimester screening tests until after these results have been integrated with second trimester data.

In other words, Intema argues that the '103 patent covers a broad range of testing procedures that may result in an integrated risk estimate, while PerkinElmer and NTD contend that the patent covers a narrow procedure in which doctors withhold first trimester measurements and use this data solely for determining a single risk estimate later in pregnancy.

C. Other Disputed Terms

The parties also have differing views regarding six other terms in the patent. The most significant of these additional disputes is whether the patent covers procedures in which some of the tests used in the second trimester repeat tests that had been conducted in the first trimester. The phrase at issue in that dispute is "the at least one second screening marker from the second trimester of pregnancy being different from the at least one first screening marker from the first trimester of pregnancy" (claims 1, 20). The remaining disagreements concern the meaning of the following phrases:

- "assaying a sample obtained from the pregnant woman at said first trimester of pregnancy for at least one first biochemical screening marker" (claims 1, 20);
- "by comparing the measured levels of both" (claims 1, 20);
- "if the pregnant woman is initially classified as screen-negative" (claims 15, 20);
- "serum sample" (claims 7, 8); and
- "obtaining said sample from the pregnant woman" (claim 12).

The full text of the '103 patent claims that contain disputed terms can be found in an appendix to this Order. The disputed terms are underlined.

III. ANALYSIS

The following discussion explains the rules of claim construction and construes the disputed terms. A table at the end of this Order summarizes the Court's construction of each term.

A. Claim Construction Standard

Claim construction is an issue of law that must be decided by a judge, rather than a jury. Markman, 52 F.3d at 970-71. The Court should construe terms in accordance with "ordinary and customary meaning," as understood by "a person of ordinary skill in the art in question." Philips v. AWH Corp., 415 F.3d 1303, 1312-13 (Fed. Cir. 2005). When construing these terms, the

Court should consider the entire patent, with particular emphasis on the patent specification. Vitrionics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996). In addition, the Court should look at the patent's prosecution history. Philips, 415 F.3d at 1317. Clear disavowals of claim coverage in the patent specification or prosecution history may narrow claim scope. See Honeywell Int'l, Inc. v. ITT Indus., Inc., 452 F.3d 1312, 1319-20 (Fed. Cir. 2006); Omega Eng'g, Inc. v. Raytek Corp., 334 F.3d 1314, 1323-24 (Fed. Cir. 2003). If a term's meaning is ambiguous in light of all of this intrinsic evidence, the Court may also analyze extrinsic evidence, including dictionaries, treatises, and expert statements. Philips, 415 F.3d at 1318-19, 1322-24.[2]

B. Analysis of the Disputed Terms

1. Patent Scope

The first claim construction dispute relates to the overall scope of the patent. The phrase "determining the risk of Down's syndrome by comparing the measured levels of both the at least one first screening marker from the first trimester of pregnancy and the at least one second screening marker from the second trimester of pregnancy with observed relative frequency distributions of marker levels in Down's syndrome pregnancies and unaffected pregnancies" means either that doctors withhold first trimester screening results from patients until second trimester markers are available, or that doctors use information from both first and second trimester screenings in calculating risk estimates.

[2] Although the Court may consider the device or process that allegedly infringes the patent in order to concentrate on relevant aspects of the claim, it "may not use the accused product or process as a form of extrinsic evidence to supply limitations for patent claim language." Wilson Sporting Goods Co. v. Hillerich & Bradsby Co., 442 F.3d 1322, 1331 (Fed. Cir. 2006).

a. Plaintiffs' Evidence

PerkinElmer and NTD argue that this term should be construed to include only procedures in which doctors withhold information from the patient until after a second set of screening tests. In support of this construction, the plaintiffs cite language in the specification describing waiting to obtain further information, a report to the patient of a single risk estimate, and the benefits of this approach. See '103 Patent Specification Fig. 5, 1:60-64, 2:37-40, 5:26-31, 8:17-19 (document #44-1). The plaintiffs acknowledge, however, that an alternative method described in the claims and specification could be interpreted to mean that doctors calculate a risk during the first trimester and classify the woman as "screen-negative" or "screen-positive." Claims 15, 20; '103 Patent Specification at 10:36-11:43. In the plaintiffs' view, patients who are screen-positive are referred for a diagnostic test, while patients who are screen-negative do not receive a risk estimate until after second-trimester screening.[3] '103 Patent Specification at 10:41-43, 2:37-38, 5-26-31. The plaintiffs argue that even this embodiment of the patent is consistent with their interpretation because it does not, by its terms, require *providing the patient* with a risk estimate even if she is screen positive.

The plaintiffs also contend that the prosecution history supports their favored construction. The examiner questioned Wald about the patent's obviousness, and suggested that scientists in the field already knew that the risk of Down syndrome could be determined using information from the first and second trimester. See Claim Rejections at 2-4 (document #44-4). In response, Wald explained that his method was distinct because it involved holding relevant information without providing a risk estimate in the first trimester. Response Under Rule 116 at

[3] The parties separately dispute the meaning of the phrase "if the pregnant woman is initially classified as screen negative," as explained infra in Section III.B.5.

10 (document #44-5). According to the plaintiffs, this response limited the patent to situations in which women do not receive a risk estimate in the first trimester.

Moreover, an article Wald wrote and submitted to the patent office as a presentation of his "claimed invention," id. at 3, described his preferred method for Down syndrome screening, which included withholding results from first trimester tests. N.J. Wald et al., Integrated Screening for Down's Syndrome Based on Tests Performed During the First and Second Trimesters, 341 New Eng. J. Med. 461, 466 (1999) (document #44-7). The article criticized other methods of using first-trimester screening data, stating that they would cause confusion for the pregnant woman. Id. at 466-67. In addition, Wald submitted articles by other researchers that discussed his new approach, and reiterated that it withholds relevant information from patients. See, e.g., Jon Hyett & Basky Thilaganathan, First Trimester Screening for Fetal Abnormalities, 11 Current Opinion in Obstetrics and Gynecology 563, 565 (1999) (document #44-8); Integrated Test, 7 Down's Screening News 28, 28 (Summer 2000) (document #44-10). Similarly, a practice bulletin submitted with *Intema's* opening brief states that results are reported under the integrated approach only after first and second-trimester screening has been completed, and describes possible disadvantages of this approach. Screening for Fetal Chromosomal Abnormalities, ACOG Practice Bulletin 77 at 5 (Jan. 2007) (document #46 at 58).

b. Defendant's Evidence

In contrast, Intema argues that the patent applies more broadly to all methods in which doctors use information from both the first and second trimesters in calculating risk estimates. The plain language of the disputed term does not refer to withholding information from first trimester screening, and indeed the words "holding" and "withholding" do not even appear in the

claims. Furthermore, claims 15 and 20 and the specification describe a procedure in which the information obtained in the first trimester can trigger a diagnostic test without the need for additional screening in the second trimester. See '103 Patent Specification at 3:4-32; 10:36-43. The specification also provides that if screening does not immediately trigger a diagnostic test, doctors combine information from the first screening with information from the second screening to calculate a single risk estimate. Id. at 10:44-11:25. According to Intema, this alternative procedure is consistent with the more general language describing determination of the risk using information from the first and second trimester.[4] For some patients, initially classified screen-negative, doctors use data from both screenings to calculate an integrated risk estimate. For the other patients, classified screen-positive based solely on first trimester data, doctors might explain a risk estimate to the patient when recommending diagnostic testing.[5]

Intema interprets the prosecution history differently than plaintiffs, noting that Wald distinguished the patented procedure from prior art that derived risk estimates from only a single stage of pregnancy. Response Under Rule 116 at 10. In Intema's view, references in the prosecution history to "holding" information from the first risk estimate mean only that the first trimester levels are still available for use in calculating an integrated risk estimate. Id. Intema rejects the plaintiffs' references to articles submitted in support of the patent, because they only described the proposed invention "in substance." Id. at 3. These articles referred to Wald's

[4] Intema explains that the term "comprising," which is at the beginning of Claim 1, is properly construed to mean the steps described are non-exclusive. See Dow Chem. Co. v. Sumitomo Chem. Co., 257 F.3d 1364, 1380-81 (Fed. Cir. 2001). Therefore, even if the phrase "determining the risk" does not itself refer to steps in the alternative embodiments of the patent, it need not exclude those steps.

[5] If a patient characterized screen-positive decides against diagnostic testing, Intema argues that she too might have a second set of screening tests and an integrated risk estimate. See infra Section III.B.5.

preferred method rather than the full scope of the proposed patent. See Second Declaration of Jacob A. Canick ¶ 13 (document #54) [hereinafter Second Canick Declaration]. Finally, Intema offers some relevant extrinsic evidence: Genzyme has licensed the patent from Intema. It uses a version of the alternative test, in which patients receive a preliminary result in the first trimester and an integrated result in the second trimester. SequentialScreen: A New Screening Option for Down Syndrome, Trisomy 18 and Open Neural Tube Defects at 2 (document #53-4).[6]

c. Court's Construction

Ultimately, Intema has the better of this argument. Plaintiffs' approach fails to explain Claims 15 and 20, which plainly refer to the determination of some type of risk estimate based only on first trimester data. Plaintiffs' explanation of these claims -- that in procedures falling under the patent, doctors need to advise patients to obtain diagnostic screening without providing a risk estimate -- is completely illogical. In fact, the designation of a patient as "screen-positive" is itself a determination of an elevated risk of Down syndrome. Nor is there any reason to believe that a doctor who chose to provide more specific information about the risk would somehow fall outside the patent's scope. The specification's repeated references to a single estimate of risk mean only that after second trimester screening, doctors provide one integrated risk estimate. If a doctor previously offered an estimate in the first trimester, that estimate is no longer relevant because the integrated risk estimate incorporates information from both trimesters.

[6] Intema also contends that, since a different possible embodiment of the patent (claim 13) entails storing the first trimester sample without testing it, the patent must not be limited to storing the sample. This argument is not persuasive. Results can still be "held" from the patient even if the sample is tested immediately rather than stored.

Moreover, the statements in Wald's article and the other attached articles do not amount to disavowals of the '103 patent's scope. Wald undoubtedly preferred to withhold information from the patient during the first trimester, and considered this "integrated test" to be the best practice because it yielded the lowest false positive rates. Second Canick Declaration ¶ 14(d). Accordingly, he described a process in his article that included withholding information, while other researchers expressed their disagreement with this approach. Nevertheless, Wald never claimed that the articles addressed the full scope of the patent. To be sure, he referred in the prosecution history to his article describing the "presently claimed invention." Response Under Rule 116 at 3. But this statement is accurate: the article *did* explain an embodiment of the patent. It certainly does not amount to a "clear intention to limit claim scope." Abbott Labs. v. Sandoz, Inc., 566 F.3d 1282, 1288 (Fed. Cir. 2009). Although multiple references to a particular embodiment as the "invention" may amount to a disavowal of scope, Honeywell, 452 F.3d at 1318, "isolated statement[s]" that apparently disavow subject matter must be examined in the context of the prosecution history as a whole, Ecolab, Inc. v. FMC Corp., 569 F.3d 1335, 1342 (Fed. Cir. 2009). In other parts of the prosecution history, Wald sought to distinguish his invention from prior art that used information from only one trimester, a distinction which does not require withholding information.

Wald's statements about "holding" information, when read in context, refer to keeping the data so that it can be used later, not to withholding it from the patient. Wald said:

> [T]he presently claimed invention involves holding the marker levels obtained at the first stage of pregnancy until the marker levels have been measured at the second stage of pregnancy, so that both sets of marker levels may be used together to calculate a single estimate of risk. In contrast, in the prior art, risk estimates

> are only derived from measured marker levels obtained at a single stage of pregnancy.

Response Under Rule 116 at 10. Unlike in the prior art, where first trimester data was ignored when calculating estimates using second trimester data, doctors following the patented procedure keep the first trimester data and combine it with later data to determine a single risk estimate.

The Federal Circuit recently rejected an argument about disavowal that is very similar to the plaintiffs' argument about the word "holding." In i4i Ltd. P'ship v. Microsoft Corp., the language of a computer patent referred generally to "storage means" and "structures." 598 F.3d 831, 842 (Fed. Cir. 2010). In the prosecution history, the plaintiff distinguished its invention from prior art that stored information in a single file, which Microsoft argued was a disavowal of all storage means that use only one file. Id. at 843. The court disagreed, stating that, in context, the applicant had said prior art was different because it did not separate content and structure when it included all information in one file. Id. The prior art could be distinguished in this more narrow way; the applicant had not "clear[ly] inten[ded]" to limit scope to storage in multiple files. Id. at 842-843.

Similarly, reading Wald's response in context, he distinguished prior art because it used data from only one trimester at a time. As in i4i, the prior art could be distinguished on this basis alone, without further limiting the patent to withholding information.

As a result, I will construe this term essentially as requested by Intema to include all methods that may result in a single integrated estimate of risk based on data from the first and second trimesters of pregnancy. In the summary table, I employ slightly different wording than Intema for clarity, but the substance is the same. Although I am confident that this interpretation accurately represents the process that Wald sought to patent, I do not decide at this time if such a

process is indeed patentable. See Smiths, 183 F.3d at 1353. When this case reaches the stage of summary judgment, the patentability of a process for integration of prenatal screening data from more than one trimester will surely present an intriguing question. See generally Bilski v. Kappos, No. 08-964 (U.S. June 28, 2010).

2. Requirement that Screening Markers Differ

The parties also disagree about the meaning of the term "the at least one second screening marker from the second trimester of pregnancy being different from the at least one first screening marker from the first trimester of the pregnancy." This term means either that *every* marker checked in the second trimester must not have been checked in the first trimester, or that *at least one* marker in the second trimester must not have been checked in the first trimester.

PerkinElmer and NTD admit that this term is ambiguous. They assert that it is best interpreted to mean that no markers are checked during both the trimesters, because these markers would be highly correlated. The plaintiffs state that the phrasing "the at least one" rather than simply "at least one" indicates "that all the markers must be different." Pls.' Reply Brief at 13 (document #50). Moreover, the specification does not set forth any examples of procedures that violate this rule. See '103 Patent Specification tbls. 4a & 4b, 5:35-43. The specification also describes the "present method" as including markers that are "assumed to be independent of each other." Id. at 6:10-11. Finally, plaintiffs contend that Wald included the requirement for a "different" test in order to respond to the patent examiner's objection that doctors already knew to conduct the same test more than once to avoid a spurious result.

Amendment at 11 (document # 44-3). He said that the claim does not cover "duplicated measurements." Id.

Intema, on the other hand, proposes the more natural reading of the phrase: at least one marker must be checked in the second screening that was not checked in the first. The specification provides that "[a]ny markers which are effective at each stage may be selected." Id. 5:34-35. It also implies the possibility of doctors performing similar tests in the first and second trimesters by listing certain markers as usable in both trimesters. See '103 Patent Specification Tbls. 2a &3a. Indeed, claims 7 and 8 list free ß-hCG as a possible marker for both trimesters.[7] Although the specification states that it would be preferable not to use first and second trimester markers that are highly correlated, id. at 5:41-43, it also explains how doctors can correct for high correlations between first and second trimester markers. See id. at 6:10-18.

Intema's interpretation is consistent with the prosecution history. The patent examiner's objection that it would be obvious to apply all of the same tests a second time would no longer be relevant if one of the second trimester tests had not been performed in the first trimester. As Intema explains this point, "[t]o avoid mere duplication and repetition of measurements, only one marker needs to be different." Def.'s Opening Brief at 20 (document #45). In this view, Wald's response meant only that his claim does not cover processes in which second trimester tests consist only of repeated measurements. Amendment at 11. The examiner apparently interpreted the amendments in the same way when he said that the "amendments include the new

[7] The plaintiffs acknowledge that claims 7 and 8 list free ß-hCG as a possible test in each trimester, but argue that these possible tests are limited by the disputed language from claim 1. Under this interpretation, if a free ß-hCG test is applied in the first trimester, it could not be used in the second and vice versa. Although the plaintiffs' analysis represents one possible interpretation of the disputed term, I find that it is more likely the patent encompasses procedures in which some tests are used in both trimesters.

limitation that a first screening marker is measured/correlated with an ultrasound at a first stage and a second different marker is measured/correlated with an ultrasound at a second stage of the pregnancy." Office Action at 202 (document #47-4).

The plaintiffs respond by parsing the language of Intema's proposed construction, interpreting it to mean that "if the first screening markers were hypothetical markers A and B, and the second screening markers were also markers A and B, then under Intema's definition, the markers would satisfy the claim term even though they are merely duplicates. This results because marker A from the first trimester is different from marker B from the second trimester." Pls.' Reply Brief at 16-17. I interpret Intema's suggested construction differently: At least one test must be performed in the second trimester that was not performed in the first trimester. Plaintiffs' example does not fall under this definition because all of the second trimester markers were used in the first trimester.

In sum, I agree with Intema that this term means only that a test must be performed in the second trimester that was not performed in the first trimester. This interpretation accords with the plain meaning of the words, represents a logical response to the examiner's objection, and explains the specification's discussion of correcting for correlations between screening markers. In the table at the end of this Order, I use different language than proposed by Intema to preclude plaintiffs' odd interpretation of Intema's construction.

3. "Assaying a Sample"

PerkinElmer and NTD argue that the term "assaying a sample" means "determining the amount of a particular constituent of a mixture," while Intema contends that the term has the more specific meaning, "detecting and quantifying a biochemical screening marker in a sample

using a device and reagents designed for such purpose [a process which] changes the composition of the sample." According to the plaintiffs, the plain meaning of "assaying" is unambiguous, and the Court thus should not resort to extrinsic evidence. Intema responds that "assay" is ambiguous, because it could have either this general meaning or a narrower meaning that is specific to Down syndrome screening. Since both meanings appear to be consistent with the plain language, and neither party has offered intrinsic evidence to support its preferred reading, I find that the term could have either construction.[8]

Therefore, I may consider extrinsic evidence to clarify the term's meaning. See Phillips, 415 F.3d at 1324. The plaintiffs offer a technical dictionary, which defines assay as "determination of the amount of a particular constituent of a mixture." Dorland's Illustrated Medical Dictionary 149 (28th ed. 1994) (document #44-11). Moreover, the plaintiffs cite cases defining "assay" similarly in different contexts. See, e.g., General Atomics, Diazyme Labs. Div. v. Axis-Shield ASA, No. C 05-04074 SI, 2006 WL 2792428, at *6 (N.D. Cal. Sept. 27, 2006). In contrast, an Intema expert states that an assay generally "involves the use of dedicated and specialized equipment and reagents designed to test for the presence of that certain substance in the sample." First Declaration of Jacob A. Canick ¶¶ 26-27 (document #46). The addition of a reagent "changes the composition of the sample, generally enabling the measurement of the substance or making the measurement more effective." Id. ¶ 27.

It may be true that assay has the more expansive meaning offered by plaintiffs in the broader field of medicine. Moreover, courts generally should prefer technical dictionaries to

[8] Plaintiffs cite the specification's description of prior screening methods, but this discussion is consistent with either definition. See '103 Patent Specification 1:40-55. Of course, the existence of similar assays in the prior art may affect the patent's validity, but that question is not before the Court at this time.

expert testimony when looking at extrinsic evidence. See Vitrionics, 90 F.3d at 1585. In this case, however, Intema's proposed construction is more specific to the processes involved in this patent. As a result, I adopt Intema's construction of this term.

4. "Comparing the Measured Levels"

Next, the parties disagree on the meaning of "comparing the measured levels of both" in the phrase "determining the risk of Down's Syndrome by comparing the measured levels of both the at least one first screening marker from the first trimester . . . and the at least one second screening marker from the second trimester . . . with observed relative frequency distribution of marker levels." PerkinElmer and NTD argue that this term means *all* measured screening markers must be used in the determination of the Down syndrome risk. Intema, on the other hand, argues that this phrase refers only to comparing measured levels of one or more of the first screening markers that were measured and one or more of the second screening markers that were measured.

The parties first look to the language of the claim itself. Plaintiffs contend that the word "the" refers back to earlier steps, and the words "both" and "and" suggest that the comparison includes all of the screening markers. In contrast, Intema focuses on the repeated words "at least one," which may indicate that doctors could compare only one marker from each trimester even if more were measured. In the end, these textual arguments are a wash. The words plaintiffs highlight could mean simply that the comparison with relative frequency distributions includes *both* one or more first trimester markers *and* one or more second trimester markers; "the" may merely specify the markers to consider in the remainder of the process, rather than referring back

to earlier steps. Similarly, "at least one" could mean that the patent would still apply even if only one marker were measured at either stage.

The specification also provides some support for both definitions. At one point, it describes the comparison step as an analysis of "all the markers from each stage." '103 Patent Specification at 13:15-17; see also id. fig. 5 ("For each marker, calculate MoM."). Elsewhere, however, the specification states that "[a]ny markers which are effective at each particular stage may be selected." Id. at 5:34-35. It also describes a particular embodiment of the patent which does not use information from a first trimester screening marker that highly correlated with a second trimester marker. Id. at 5:35-46. Of course, this example is inconsistent with the reference to "all the markers from each stage." I find that the phrase's meaning is ambiguous in light of all the intrinsic evidence.

Only Intema offers extrinsic evidence that can resolve the ambiguity. A licensee of Intema's patent, Genzyme, measures hCG in the first trimester but does not include that marker in its integrated risk calculation. Genzyme SequentialScreen at 1 (document #53-5). In addition, there is a functional reason why a doctor following the patent procedure might not consider a particular screening marker: If the woman has a medical condition, such as uterine bleeding, which arbitrarily affects the level of a screening marker, that marker might no longer be effective in predicting the risk of Down syndrome. Second Canick Declaration ¶ 31. I adopt Intema's interpretation because it accounts for this extrinsic evidence.

5. "Initially Classified as Screen-Negative"

The claim term "if the pregnant woman is initially classified as screen-negative" appears in descriptions of alternative embodiments of the patent in which doctors make a "screen

positive" (Down syndrome likely) or "screen negative" (Down syndrome unlikely) determination after first trimester testing. In claims 15 and 20, doctors conduct second trimester measurements and provide integrated risk determinations "if the pregnant woman is initially classified as screen-negative." PerkinElmer and NTD assert that this term means the second-trimester screening is performed *only* if the pregnant woman is initially classified as screen negative, while Intema contends that second trimester screening may be performed even if the patient is initially classified as screen-positive.

The plaintiffs point out that the word "if" limits the further steps to screen-negative patients. Accordingly, the specification states that screen-positive women are referred for a diagnostic test, and screen-negative women are rescreened during the second trimester. See '103 Patent Specification at 10:41-45. Defendant's expert similarly describes claims 15 and 20. Second Canick Declaration ¶ 17. In the plaintiffs' view, there would be no need for a second screening after a test that could conclusively determine whether the fetus has Down syndrome.

Intema argues that second trimester screening and calculation of an integrated estimate may be performed under this patented process even if the patient is initially classified as screen-positive. The plaintiffs' interpretation is inconsistent with the comment in the same part of the specification that screen-positive women "*might* not be tested for screening marker levels at the second stage of the pregnancy." See '103 Patent Specification at 10:41-43 (emphasis added). Women who are referred for diagnostic screening may choose not to have a diagnostic test, and thus would have a second set of screenings and an integrated risk estimate. Intema also criticizes the plaintiffs' interpretation for failing to consider that the diagnostic testing may not occur until

the second trimester because first trimester testing is more dangerous. Second Canick Declaration ¶ 15. Furthermore, according to Intema, the word "if" need not mean "only if."

Only the plaintiffs' interpretation matches the language of the claims, because the word "if" plainly limits the circumstances in which second trimester screening occurs. Consequently, I find that the procedure described in claims 15 and 20 excludes a second screening of screen-positive women.

6. "Serum Sample"

The parties agree that the term "serum sample" (claims 7, 8) refers to a component of blood, but they disagree about whether it includes dried samples. PerkinElmer and NTD argue that the word means "the clear fluid obtained from whole blood by removing blood cells, platelets, and fibrinogen." In contrast, Intema contends that it may refer to a component of a fluid or a dried blood sample. The specification refers to drawing a blood sample and refrigerating a "separated serum," which is consistent with either construction. '103 Patent Specification at 11:50-52.

Turning to extrinsic evidence, some technical dictionaries refer to serum as a "fluid" or "liquid." Physician's Desk Reference Medical Dictionary 1603 (1995) (document # 44-12); Dorland's Illustrated Medical Dictionary, supra, at 1512. However, at least one study cited by both parties refers to "serum" analyzed "from whole blood collected as a dried dot onto card." Hyett & Thilaganathan, supra, at 565. Moreover, Intema's expert states that scientists in the field would interpret "serum sample" to include dried blood, a common substitute for fluids. Second Canick Declaration ¶ 32.

I adopt Intema's definition because the more specific extrinsic evidence suggests that individuals in the field understand "serum sample" to include dried blood.

7. "Obtaining Said Sample"

Although the parties do not agree about the meaning of the term "obtaining said sample" (claim 12), their definitions are similar. Plaintiffs think that this term refers to withdrawing blood or collecting urine, and rely on information in the patent indicating that samples are "drawn." See '103 Patent Specification at Fig. 5, 11:50-54. Nevertheless, these references are merely illustrative of particular applications of the patent, and do not claim to be exclusive of other methods. See id. at 11:44-46 ("Figs. 5 to 9 are flowcharts illustrating a specific method according to the present invention which is explained in detail below."). Intema argues that this phrase refers to obtaining a sample of any kind (including blood, urine, or cells). Indeed, the specification refers to "serum or plasma or urine or cells" as types of "biochemical samples." Id. at 5:27-28. Intema's interpretation is also consistent with the plain meaning of the terms, because "obtaining" could include receiving a sample from someone else who collected it, and "sample" need not be limited to blood and urine. Accordingly, I adopt Intema's construction.

IV. SUMMARY TABLE OF DISPUTED CLAIM TERMS AND INTERPRETATIONS

Claim Term	Plaintiffs' Proposed Construction	Defendant's Proposed Construction	Court's Construction
"determining the risk of Down's syndrome by comparing the measured levels of both the at least one first screening marker from the first trimester of pregnancy and the at least one second screening marker from the second trimester of pregnancy with observed relative frequency distributions of marker levels in Down's syndrome pregnancies and unaffected pregnancies" (Claims 1, 20)	Holding the measured level of the first trimester screening marker from the first trimester until the second trimester measurements are made and calculating and reporting the risk of Down syndrome only after obtaining the level of the second screening marker from the second trimester; the claim requires withholding from the patient the risk of having a fetus with Down syndrome based on an analysis of screening markers from only the first trimester.	Determining the risk of Down's syndrome by comparing the measured levels of both the at least one first screening marker from the first trimester of pregnancy and the at least one second screening marker from the second trimester of pregnancy with observed relative frequency distributions of marker levels in Down's syndrome pregnancies and in unaffected pregnancies by a calculation using the measured levels of both the at least one first screening marker and the at least one second screening marker, whether or not a first trimester risk determination of Down's syndrome is separately made based only on the measured level of the at least one first screening marker; this limitation does not exclude or require providing a first trimester risk assessment.	Determining the risk of Down syndrome by comparing the measured levels of at least one screening marker from the first trimester of pregnancy and at least one marker from the second trimester of pregnancy with distributions of marker levels in Down syndrome pregnancies and unaffected pregnancies by a calculation using measurements from both trimesters; this limitation does not exclude or require providing a separate risk determination based only on information obtained in the first trimester.

Claim Term	Plaintiffs' Proposed Construction	Defendant's Proposed Construction	Court's Construction
"the at least one second screening marker from the second trimester of pregnancy being different from the at least one first screening marker from the first trimester of pregnancy" (Claims 1, 20)	Every one of the measured markers from the second trimester is different from every one of the measured markers in the first trimester.	At least one first screening marker is different than at least one second screening marker; only one, but possibly more, markers need to be different in the two trimesters, not every second screening marker must be different than every first screening marker (i.e., this claim term does not exclude a second screening marker being the same as a first screening marker).	At least one measured marker from the second trimester must be different from all measured markers in the first trimester; this claim term does not exclude other second screening markers from being the same as first trimester markers.
"assaying a sample obtained from the pregnant woman at said first trimester of pregnancy for at least one first biochemical screening marker" (Claims 1, 20)	Determining the amount of a particular constituent of a mixture.	Detecting and quantifying a biochemical screening marker in a sample using a device and reagents designed for such purpose; assaying of a sample changes the composition of the sample.	Detecting and quantifying a biochemical screening marker in a sample using a device and reagents designed for such purpose; assaying of a sample changes the composition of the sample.
"by comparing the measured levels of both" (Claims 1, 20)	All of the screening markers that were measured are used in the determination of the risk of Down syndrome.	The claim comprises comparing the measured levels of at least one first trimester marker and at least one second trimester marker; the claim does not require all measured marker levels be used to determine the recited risk estimate.	The claim comprises comparing the measured levels of at least one first trimester marker and at least one second trimester marker; the claim does not require all measured marker levels be used to determine the recited risk estimate.

Claim Term	Plaintiffs' Proposed Construction	Defendant's Proposed Construction	Court's Construction
"if the pregnant woman is initially classified as screen-negative" (Claims 15, 20)	The steps of measuring the second trimester screening marker and determining the risk of Down syndrome are performed only if the pregnant woman is initially classified as "screen-negative, " and not performed if the pregnant woman is initially classified as "screen-positive. "	If the pregnant woman is initially classified as "screen-negative," then the recited measuring of at least one second trimester marker level and determining of risk is performed; the claim does not limit such measuring and determining to be limited to instances only if the woman is initially classified as screen negative, and does not require that the measuring and deriving not be performed if the pregnant woman is initially classified as "screen-positive."	The steps of measuring the second trimester screening marker and determining the risk of Down syndrome are performed only if the pregnant woman is initially classified as "screen-negative," and not performed if the pregnant woman is initially classified as "screen-positive."
"serum sample" (Claims 7, 8)	The clear fluid obtained from whole blood by removing blood cells, platelets and fibrinogen.	A component of whole blood; a serum sample may be a component of a fluid or a dried blood sample.	A component of whole blood; a serum sample may be a component of a fluid or a dried blood sample.
"obtaining said sample from the pregnant woman" (Claim 12)	To withdraw blood, or to collect urine, from the pregnant woman.	Obtaining a sample from the pregnant woman, such as blood, urine or cells.	Obtaining a sample from the pregnant woman, such as blood, urine or cells.

SO ORDERED.

Date: July 1, 2010 */s/ Nancy Gertner*

NANCY GERTNER, U.S.D.C.

APPENDIX: CLAIMS WITH DISPUTED TERMS

1. A method of determining whether a pregnant woman is at an increased risk of having a fetus with Down's syndrome, the method comprising the steps of:
measuring the level of at least one screening marker from a first trimester of pregnancy by:
(I) assaying a sample obtained from the pregnant woman at said first trimester of pregnancy for at least one first biochemical screening marker;
and/or (ii) measuring at least one first ultrasound screening marker from an ultrasound scan taken at said first trimester of pregnancy;
measuring the level of at least one second screening marker from a second trimester of pregnancy, the at least one second screening marker from the second trimester of pregnancy being different from the at least one first screening marker from the first trimester of pregnancy, by:
(I) assaying a sample obtained from the pregnant woman at said second trimester of pregnancy for at least one second biochemical screening marker;
and/or (ii) measuring at least one second ultrasound screening marker from an ultrasound scan taken at said second trimester of pregnancy;
and determining the risk of Down's syndrome by comparing the measured levels of both the at least one first screening marker from the first trimester of pregnancy and the at least one second screening marker from the second trimester of pregnancy with observed relative frequency distributions of marker levels in Down's syndrome pregnancies and in unaffected pregnancies.

7. A method according to claim 1, wherein said step of measuring the level of at least one first screening marker from a first trimester of pregnancy includes assaying a serum sample obtained from the pregnant woman during said first trimester of pregnancy for one selected from the group of PAPP-A, free β-hCG and both.

8. A method according to claim 7, wherein said step of measuring the level of at least one second screening marker from a second trimester of pregnancy includes assaying a serum sample obtained from the pregnant woman during said second trimester of pregnancy for one selected from the group of AFP, uE3, inhibin-A, free β-hCG, free α-hCG, total hCG and combinations thereof.

12. A method according to claim 1, further comprising the steps of:
obtaining said sample from the pregnant woman during said first trimester of pregnancy and/or taking said ultrasound scan during said first trimester of pregnancy; and
obtaining said sample from the pregnant woman during said second trimester of pregnancy and/or taking said ultrasound scan during said second trimester of pregnancy.

15. A method according to claim 1, further comprising:
determining a first risk estimate of Down's syndrome using the measured level of the at least one first screening marker from the first trimester of pregnancy;

comparing the first risk estimate with a predetermined cut-off level to initially classify the pregnant woman as screen-positive or screen-negative based on the comparison; and performing said steps of measuring the level of at least one second screening marker from a second trimester of pregnancy and determining the risk of Down's syndrome using the measured levels of the screening markers from both the first and second trimesters of pregnancy if the pregnant woman is initially classified as screen-negative.

20. A method of determining whether a pregnant woman is at an increased risk of having a fetus with Down's syndrome, the method comprising the steps of:
measuring the level of at least one first screening marker from a first trimester of pregnancy by:
(I) assaying a sample obtained from the pregnant woman at said first trimester of pregnancy for at least one first biochemical screening marker;
and/or (ii) measuring at least one first ultrasound screening marker from an ultrasound scan taken at said first trimester of pregnancy;
determining a first risk estimate of Down's syndrome by comparing the measured level of the at least one first screening marker level from the first trimester of pregnancy with observed relative frequency distributions of marker levels in Down's syndrome pregnancies and in unaffected pregnancies;
comparing the first risk estimate with a predetermined cut-off level to initially classify the pregnant woman as screen-positive or screen-negative based on the comparison;
and if the pregnant woman is initially classified as screen-negative: measuring the level of at least one second screening marker from a second trimester of pregnancy, the at least one second screening marker from the second trimester of pregnancy being different from the at least one first screening marker from the first trimester of pregnancy, by:
(I) assaying a sample obtained from the pregnant woman during said second trimester of pregnancy for at least one second biochemical screening marker;
and/or (ii) measuring at least one second ultrasound screening marker from an ultrasound scan taken during said second trimester of pregnancy;
and determining the risk of Down's syndrome by comparing the measured level of both the at least one first screening marker from the first trimester of pregnancy and the at least one second screening marker from second trimester of pregnancy with observed relative frequency distributions of marker levels in Down's syndrome pregnancies and in unaffected pregnancies.