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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ARNOLD OLIPHANT, ANDREW SPARKS,
KEN SONG, and JOHN STUELPNAGEL

Appeal 2015-006686
Application 13/689,206
Technology Center 1600

Before DONALD E. ADAMS, RICHARD M. LEBOVITZ, and RICHARD J. SMITH, *Administrative Patent Judges*.

ADAMS, *Administrative Patent Judge*.

DECISION ON APPEAL[1]

This appeal under 35 U.S.C. § 134(a) involves claims 1–3, 6–12, 14–23, and 37–46 (App. Br. 4). Examiner entered rejection under 35 U.S.C. § 103(a). We have jurisdiction under 35 U.S.C. § 6(b).

We REVERSE.

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[1] Appellants identify the real party in interest as "Ariosa Diagnostics, Inc." (App. Br. 2).

STATEMENT OF THE CASE

Appellants' disclosure "relates to diagnosis of genetic abnormalities and assay systems for such diagnosis" (Spec. ¶ 2). Claim 1 is representative and reproduced below:

> 1. An assay method for providing a statistical likelihood of the presence or absence of a fetal aneuploidy comprising:
>
> providing a maternal sample comprising maternal and fetal cell free DNA;
>
> interrogating less than 2000 selected polymorphic nucleic acid regions from a first chromosome using sequence-specific oligonucleotides;
>
> isolating the selected polymorphic nucleic acid regions from the first chromosome;
>
> detecting each isolated selected polymorphic nucleic acid region from the first chromosome on average at least 100 times;
>
> quantifying total allele counts to determine a relative frequency of alleles from the isolated selected polymorphic nucleic acid regions from the first chromosome;
>
> interrogating less than 2000 selected polymorphic nucleic acid regions from a second chromosome using sequence-specific oligonucleotides;
>
> isolating the selected polymorphic nucleic acid regions from the second chromosome;
>
> detecting each isolated selected polymorphic nucleic acid region from the second chromosome on average at least 100 times;
>
> quantifying total allele counts to determine a relative frequency of the isolated selected polymorphic nucleic acid regions from the second chromosome;
>
> interrogating less than 2000 selected polymorphic nucleic acid regions from at least one chromosome different from the first and second chromosome using sequence specific oligonucleotides;

isolating the selected polymorphic nucleic acid regions from the at least one chromosome different from the first and second chromosome;

detecting each isolated selected polymorphic nucleic acid region from the at least one chromosome different from the first and second chromosome on average at least 100 times;

identifying low frequency alleles from the at least one chromosome different from the first and second chromosome using polymorphic regions where the maternal DNA is homozygous and the fetal DNA is heterozygous;

computing a sum of low frequency alleles from the isolated selected polymorphic nucleic acid regions from the at least one chromosome different from the first and second chromosome; and

calculating a statistical likelihood of the presence or absence of a fetal aneuploidy in the maternal sample, wherein the relative frequency of total alleles from the isolated selected polymorphic nucleic acid regions from the first chromosome, the relative frequency of total alleles from the isolated selected polymorphic nucleic acid regions from the second chromosome, and the sum of the low frequency alleles from the isolated selected polymorphic nucleic acid regions from the at least one chromosome different from the first and second chromosome are used to calculate statistically significant differences in chromosomal frequencies for the first and second chromosomes, and wherein a statistically significant difference in chromosomal frequency provides a statistical likelihood of the presence of a fetal aneuploidy.

(App. Br. 29–31.)

The claims stand rejected as follows:

Claims 1–3, 6–12, 14–23, and 37–46 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Lo '847,[2] Porreca,[3] Van Opstal,[4] and Lo '353.[5]

ISSUE

Does the preponderance of evidence relied upon by Examiner support a conclusion of obviousness?

FACTUAL FINDINGS (FF)

Examiner makes the following findings:

FF 1. Lo '847 discloses "methods for providing a statistical likelihood of the presence or absence of a fetal aneuploidy" from the analysis of "a maternal sample [] comprising maternal and fetal cell free DNA" using "massively parallel sequencing" (Ans. 2, citing Lo '847 ¶¶ 240, 262, 263, 266, 267, and 271).

FF 2. Lo '847 discloses

> that it is desirable to specifically target polymorphic loci and count fetal-specific alleles and common alleles from the polymorphic nucleic acid region because this informs the determination of the fractional concentration of fetal DNA[], which is used to adjust the reference range for expected

[2] Lo et al., US 2009/0087847 A1, published Apr. 2, 2009.
[3] Gregory J Porreca, et al., *Multiplex amplification of large sets of human exons*, 4 NATURE METHODS 931–936 (2007).
[4] Diane Van Opstal et al., *Rapid aneuploidy detection with multiplex ligation-dependent probe amplification: a prospective study of 4000 amniotic fluid samples*, 17 European Journal of Human Genetics 112–121 (2009).
[5] Lo et al., US 2011/0105353 A1, published May 5, 2011.

> sequence reads for a given chromosome to inform the diagnosis of a fetal aneuploidy.

(Ans. 5, citing Lo '847 ¶¶ 267 and 278; *see also* Ans. 7, citing Lo '847 ¶ 278 ("Lo [']847 teaches identifying polymorphic sites at which [a] pregnant woman is homozygous and the fetus is heterozygous," wherein "the amount of the fetal-specific allele (i.e. low frequency allele) can be compared with the amount of the common allele to determine the fractional concentration of fetal DNA (i.e. percent fetal cell free DNA)" and "determining the amount of the fetal-specific allele"); Ans. 7–8, citing Lo '847 ¶ 267 (Lo '847 discloses "identifying fetal aneuploidy by comparing the relative frequency of the nucleic acid regions to a reference range and that 'the reference range is adjusted according to the fractional concentration of fetal DNA in a particular maternal plasma sample'").)

FF 3. Lo '847 discloses "that it was known to specifically target approximately 500 polymorphic nucleic acid regions per potentially aneuploidy chromosome and then to base the determination of a chromosomal imbalance on the SNP allelic ratios for these polymorphic nucleic acid regions" (Ans. 5, citing Lo '847 ¶ 8; *see also* Ans. 7).

FF 4. Lo '847 discloses the use of "sequence-specific oligonucleotides to interrogate nucleic acid regions" on "potential[] aneuploidy chromosomes of interest includ[ing] chromosome 21, chromosome 19, or chromosome 13" (Ans. 3, citing Lo '847 ¶¶ 264, 266, 269, and 273; *see also* Ans. 5; Ans. 3 (Lo '847 ("suggests [the] use [of] oligonucleotide-based hybridization techniques to first sub-select for nucleic acid sequences from certain chromosomes")).

FF 5. Lo '847 discloses "targeting polymorphic sites at which the pregnant woman is homozygous and the fetus is heterozygous and that the amount of

the fetal-specific allele can be compared with the amount of the common allele (i.e. quantifying a relative frequency of each allele) to determine the fractional concentration of fetal DNA (i.e. percent fetal cell free DNA)" (Ans. 5–6, citing Lo '847 ¶ 278).

FF 6. Lo '847 discloses the identification of "allelic imbalance using a Bayesian-type statistical likelihood method" (Ans. 8, citing Lo '847 ¶ 88; *see also* Ans. 8, citing Lo '847 (Lo '847 discloses "that it was known to infer a fetal chromosomal imbalance by detecting a statistically significant difference between the SNP ratios between two chromosomes")).

FF 7. Lo '847 fails to disclose the interrogation of "less than 2000 polymorphic nucleic acid regions using sequence-specific oligonucleotides" or the "combination of interrogating polymorphic nucleic acid regions from a first, second, and third chromosome and further quantifying the total alleles form the polymorphic nucleic acid regions from the first and second chromosomes" (Ans. 3 and 5).

FF 8. Porreca discloses "that front-end methods to reduce the complexity of the mammalian genome to isolate subsets of interest can reduce massively parallel sequencing costs by several orders of magnitude" (Ans. 3, citing Porreca Abstract).

FF 9. Porreca discloses the use of "oligonucleotides to specifically hybridize, capture, and amplify a subset of the genome in a single multiplex reaction for massively parallel sequencing" (Ans. 3, citing Porreca Abstract, 931: col. 2, second paragraph, 932: col. 1, last paragraph, and Figure 3; *see also* Ans. 7, citing Porreca 932: col. 1, last paragraph ("Porreca explicitly teaches targeting 480 target sites (i.e. less than 2000) for massively parallel sequencing")).

FF 10. Van Opstal discloses a "method for diagnosing fetal aneuploidy by using an oligonucleotide ligation-based assay" and to disclose "that the relative amount of PCR product is proportional to the amount of target sequence" amplified (Ans. 3–4, citing Van Opstal Abstract, 113: col. 1, last paragraph, 118: col. 2, second paragraph, and Table 5; *see also* Ans. 6).

FF 11. Van Opstal suggests the use of "oligonucleotides to specifically target eight sites (i.e. less than 2000) per aneuploid chromosome to diagnose fetal aneuploidy" (Ans. 7, citing Van Opstal 114: col. 1, last paragraph).

FF 12. Lo '353 discloses "a method for target-enrichment and targeted massively parallel sequencing for non-invasive prenatal diagnosis" and "that target enrichment is an efficient way of estimating the fractional fetal DNA concentration compared with whole-genome sequencing" (Ans. 4, citing Lo '353 ¶¶ 239 and 240).

FF 13. Lo '847 fails to disclose "that the relative frequency of total alleles from the two chromosomes are used to calculate statistically significant differences in chromosomal frequencies between the first and second chromosomes" as it relates to fetal aneuploidy (Ans. 8).

FF 14. Lo '847 discloses "an embodiment in which the sequencing technique is used to detect plasma cell-free DNA in blood to detect cancer," wherein "the relative frequency of sequence reads between chromosomes [were directly compared] to identify chromosomal gains or losses" (Ans. 8, citing Lo '847 ¶ 280).

ANALYSIS

Based on the combination of Lo '847, Porreca, Van Opstal, and Lo '353, Examiner concludes that, at the time Appellants' invention was made, it would have been prima facie obvious to use "oligonucleotides [that]

specifically target and enrich for particular subsets of the genome" in Lo '847's "methods for providing a statistical likelihood of the presence or absence of a fetal aneuploidy," because, as Lo '353 discloses, "such enrichment is an efficient way of estimating the fractional fetal DNA concentration as compared to whole-genome sequencing" (Ans. 4–5).

In this regard, Examiner reasons that

> it would have been obvious to one of ordinary skill in the art at the time [Appellants' claimed] invention was made to have interrogated [less than 2000] polymorphic nucleic acid regions from [three] chromosomes because it would have merely amounted to a simple combination of prior art elements according to known methods to yield predictable results.

(Ans. 6 and 7.) Examiner further reasons that those of ordinary skill in this art "would have been motivated to have interrogated polymorphic nucleic acid regions because Lo '847 teaches that analyzing polymorphic nucleic acid regions of interest are useful because they can be used to determine the fractional concentration of fetal DNA in a maternal sample" (*id. at* 7 and 8). Specifically, Lo '847 discloses the determination of "tag counts for the nucleic acid regions from the sequencing reaction," the "amount of a fetal-specific allele and the amount of the common allele," therefore, Examiner concludes,

> one [of ordinary skill in this art] would have quantified the total allele counts by determining the tag counts from the massively parallel sequencing corresponding to the polymorphic nucleic acid regions and the relative amount of such amplified products would have been proportional to the amount of target sequence as taught by Van Opstal.

(Ans. 6, citing Lo '847 ¶¶ 272, 278 and Van Opstal 113: col. 1, last paragraph.)

Appellants contend that their

> Invention approaches the challenge of non-invasive, prenatal testing completely differently as compared to Lo [']847. Instead of sampling nucleic acids randomly or as an 'enriched population' as in Lo [']847 . . ., [Appellants'] invention samples 2000 or less targeted loci per chromosome on at least three chromosomes using sequence-specific oligonucleotides, and instead of sampling loci at a depth of coverage of less than 1x, the present invention interrogates each individual locus at a much greater depth of coverage, e.g., on average 100x.

(App. Br. 17; *see* Reply Br. 5 ("Lo [']847 [] does not clearly teach comparison of total counts from two chromosomes to identify chromosomal losses or gains" and "does not teach comparison of total counts from two chromosomes in any embodiment describing determination of fetal aneuploidies"); *see also* Reply Br. 4).

When the combination of Lo '847, Porreca, Van Opstal, and Lo '353, as relied upon by Examiner, is considered as a whole, we find that the weight of the evidence falls in favor of Appellants. In this regard, we agree with Appellants' contention

> that the scant teaching of Lo [']847 at ¶ 280 in relation to cancers—i.e., one line: "Direct comparisons or comparisons to a reference chromosome may be used[]"—and the silence of Lo [']847 regarding comparison of empirically obtained sequence counts from loci on two different chromosomes for determination of fetal aneuploidy is not a clear teaching that would lead one of ordinary skill in the art to apply Lo's cancer monitoring methods to detect fetal aneuploidies with any reasonable expectation of success.

(App. Br. 20; *cf.* Ans. 8, citing Lo '847 ¶ 280 ("Lo [']847 teaches an embodiment in which the sequencing technique is used to detect plasma cell-free DNA in blood to detect cancer").) Obviousness requires more than a mere showing that the prior art includes separate references covering each

separate limitation in a claim under examination. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). Rather, obviousness requires the additional showing that a person of ordinary skill at the time of the invention would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention. *Id.* at 421.

CONCLUSION OF LAW

The preponderance of evidence relied upon by Examiner fails to support a conclusion of obviousness.

The rejection of claims 1–3, 6–12, 14–23, and 37–46 under 35 U.S.C. § 103(a) as unpatentable over the combination of Lo '847, Porreca, Van Opstal, and Lo '353 is reversed.

REVERSED