UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TWINSTRAND BIOSCIENCES, INC.
Petitioner,

v.

GUARDANT HEALTH
Patent Owner.

Inter Partes Review Case No. IPR2022-01115

U.S. Patent No. 10,801,063

DECLARATION OF PAUL T. SPELLMAN, Ph.D.

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B. Schmitt (EX1009), Schmitt-623 (EX1083) 77
C. Meyer (EX1005) 83
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XII. GROUND 1: CLAIMS 1-7, 9-11, 15-18, AND 22-28 WOULD HAVE BEEN OBVIOUS OVER NARAYAN, SCHMITT, AND MEYER 85

A. Claim 1 85

1. A method for classifying consensus sequences generated from sequencing reads derived from double-stranded cell-free deoxyribonucleic acid (cfDNA) molecules from a sample of a human subject, the method comprising 86

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2. (a) non-uniquely tagging a population of double-stranded cfDNA molecules from the sample with more than a 10x molar excess of adapters comprising molecular barcodes, relative to the double-stranded cfDNA molecules in the population, to generate non-uniquely tagged parent polynucleotides 87

3. wherein the double-stranded cfDNA molecules that map to a mappable base position of a reference sequence are tagged with a number of different molecular barcodes ranging from at least 2 to fewer than a number of double-stranded cfDNA molecules that map to the mappable base position, and 91

4. wherein at least 20% of the double-stranded cfDNA molecules are non-uniquely tagged with the adapters comprising the molecular barcodes at both ends of a molecule of the double-stranded cfDNA molecules 93

5. (b) amplifying a plurality of the non-uniquely tagged parent polynucleotides to produce progeny polynucleotides; 94

6. (c) enriching a plurality of the progeny polynucleotides for target regions of interest to generate enriched progeny polynucleotides; 95

7. (d) sequencing a plurality of the enriched progeny polynucleotides to produce a set of sequencing reads; 96

8. (e) mapping a plurality of sequencing reads from the set of sequencing reads to the reference sequence; 97

9. (f) grouping a plurality of the mapped sequencing reads into families of mapped sequencing reads based at least on (i) sequence information from the molecular barcodes and (ii) a beginning base position and an ending base position of the mapped sequencing reads 100

10. (g) generating a consensus sequence for each family from among one or more of the families to produce a set of consensus sequences; and 101

11. (h) classifying one or more consensus sequences from among the set of consensus sequences as (1) paired

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consensus sequences generated from sequencing reads representing a Watson strand and a Crick strand of a non-uniquely tagged parent polynucleotide or (2) unpaired consensus sequences generated from sequencing reads representing only one of either a Watson strand or a Crick strand of a non-uniquely tagged parent polynucleotide. 102

B. Motivation to combine 103

1. A POSA would have been motivated to use Schmitt's 3-mer hybrid tagging approach to "non-uniquely" tag a population of cfDNA molecules. 105

2. A POSA would have been motivated to use "more than a 10x molar excess." 108

3. A POSA would also have been motivated to generate "at least 20%" adapter-ligated cfDNA molecules. 111

4. A POSA would have been motivated to use a number of different molecular barcodes ranging from at least 2 to fewer than a number of double-stranded cfDNA molecules that map to the mappable base position. 113

5. A POSA would have been motivated to amplify, enrich, sequence, map, group, generate a consensus sequence, and classify the consensus sequence as recited in claim 1. ... 113

C. Reasonable expectation of success 118

1. A POSA would have reasonably expected to successfully sequence cfDNA disclosed in Narayan with Schmitt's Duplex Sequencing method because of knowledge in the art that a routine blood draw contains more than sufficient quantities of cfDNA. 119

2. A POSA would have reasonably expected to successfully "non-uniquely" tag cfDNA molecules. 121

3. A POSA would have reasonably expected success in using "more than a 10x molar excess" of adapters. 122

4. A POSA would also have reasonably expected success in generating "at least 20%" adapter-ligated cfDNA molecules. 122

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