

CLAIMS

1. A method of analyzing a biological sample of an organism for deletions or amplifications in one or more chromosomal regions associated with cancer, the biological sample including cell-free nucleic acid molecules originating from non-malignant cells and potentially from tumor cells associated with cancer, the method comprising:

receiving sequences obtained from a random sequencing of nucleic acid molecules contained in the biological sample;

aligning at least a portion of the sequences to a human genome;

determining a first amount of sequences identified as aligning to a first chromosomal region that is part of a first chromosome, wherein an aberration in the first chromosomal region is associated with cancer;

determining a second amount of sequences identified as aligning to one or more second chromosomal regions;

determining a first parameter from the first amount and the second amount, wherein the parameter represents a relative amount between the first and second amounts; and

comparing the first parameter to one or more cutoff values to determine a classification of whether the first chromosomal regions exhibits a deletion and/or an amplification associated with cancer.

2. The method of claim 1, wherein the classification includes whether the first chromosomal region is amplified, and wherein a classification of amplification is made when the first parameter is greater than a first cutoff value of the one or more cutoff values.

3. The method of claim 1, wherein the classification includes whether the first chromosomal region has a deletion, and wherein a classification of deletion is made when the first parameter is less than a first cutoff value of the one or more cutoff values.

4. The method of claim 1, further comprising:

determining a third amount of sequences identified as aligning to a third chromosomal region, wherein an aberration in the third chromosomal region is associated with cancer;

determining a second parameter for a third chromosomal region, wherein the second parameter represents a relative amount between the third and second amounts;

comparing the second parameter to one or more cutoff values to determine a classification of whether the third chromosomal region exhibits a deletion and/or an amplification associated with cancer; and

using the classifications of the first and third chromosomal regions to detect whether the organism has cancer.

5. The method of claim 1, wherein the biological sample is blood, plasma, serum, urine or saliva.

6. The method of claim 1, wherein the biological sample is transcervical lavage fluid.

7. The method of claim 1, wherein the first parameter is calculated from a ratio that includes the first amount.

8. The method of claim 7, wherein the ratio provides a percentage of the sequences identified as aligning to the first chromosomal region among the sequences.

9. The method of claim 7, wherein the ratio is obtained from any one or more of a fractional count of the number of sequenced tags, a fractional number of sequenced nucleotides, and a fractional length of accumulated sequences.

10. The method of claim 7, wherein the sequences that are used to determine the first amount are selected to be less than a specified number of bases.

11. The method of claim 10, wherein the specified number of bases is 300 bases, 200 bases, or 100 bases.

12. The method of claim 1, wherein the nucleic acid molecules of the biological sample have been enriched for sequences originating from the first chromosomal region.

13. The method of claim 1, wherein the nucleic acid molecules of the biological sample have been enriched for sequences less than 300 bases.

14. The method of claim 1, wherein the nucleic acid molecules of the biological sample have been enriched for sequences less than 200 bases.

15. The method of claim 1, wherein the nucleic acid molecules of the biological sample have been amplified using a polymerase chain reaction.
16. The method of claim 1, wherein the aligned portion represents at least a pre-determined fraction of the human genome.
17. The method of claim 1, wherein the fraction represents at least 0.1% of the human genome.
18. The method of claim 1, wherein the fraction represents at least 0.5% of the human genome.
19. The method of claim 1, wherein at least one of the cutoff values is derived from a percentage of tumor cells in the biological sample.
20. The method of claim 1, wherein at least one of the cutoff values is a reference value established in a normal biological sample.
21. The method of claim 20, wherein the at least one cutoff value is determined from a mean of the value of the first parameter in a plurality of normal biological samples.
22. The method of any one of claims 1, wherein the one or more cutoff values are derived from a normal value for the relative amount between the first and second amounts.
23. The method of claim 1, further comprising:
identifying an amount of tumor DNA in the biological sample; and
calculating a number N of sequences to be analyzed based on a desired accuracy.
24. The method of claim 1 to 23, wherein the sequences identified as aligning to the first chromosomal region uniquely align to the first chromosomal region.
25. The method of claim 1 to 24, wherein the sequences identified as aligning to the one or more of the second chromosomal regions uniquely align to only one of the second chromosomal regions.

26. The method of claim 1 to 25, wherein the human genome is repeat-masked.
27. The method of any one of claims 1 to 26, wherein the first amount is determined based on a pool of sequenced tags that align to a plurality of positions of the first chromosomal region.
28. The method of claim 27, wherein which part of the human genome that the sequenced tags are aligned is not pre-determined.
29. The method of claim 28, wherein the part of the human genome corresponding to the sequenced tags aligned to the first chromosomal region is not pre-determined.
30. The method of claim 1, wherein the first parameter is a fractional representation of sequences identified as aligning to the first chromosomal region, the fractional representation being a measure of a proportion of nucleic acid molecules in the biological sample that are from the first chromosomal region.
31. The method of claim 30, wherein the one or more cutoff values take into account a size of the first chromosomal region relative to a size of the one or more second chromosomal regions.
32. The method of claim 1, wherein the sequencing includes paired-end sequencing, and wherein aligning each sequence includes aligning paired-end sequences.
33. The method of claim 1, further comprising:
performing the random sequencing of nucleic acid molecules contained in the biological sample to obtain the sequences.
34. A computer program product comprising a computer readable medium encoded with a plurality of instructions for controlling a computing system to perform the method of any one of claims 1 to 32.

WHAT IS CLAIMED IS:

- 1 1. A method for performing prenatal diagnosis of a fetal chromosomal
2 aneuploidy in a biological sample obtained from a pregnant female subject, wherein the
3 biological sample includes nucleic acid molecules, the method comprising:
4 receiving the biological sample;
5 sequencing at least a portion of a plurality of the nucleic acid molecules
6 contained in the biological sample, wherein the sequenced portion represents a fraction of the
7 human genome;
8 based on the sequencing:
9 determining a first amount of a first chromosome from sequences
10 identified as originating from the first chromosome;
11 determining a second amount of one or more second chromosomes
12 from sequences identified as originating from one of the second chromosomes;
13 determining a parameter from the first amount and the second amount;
14 comparing the parameter to one or more cutoff values; and
15 based on the comparison, determining a classification of whether a fetal
16 chromosomal aneuploidy exists for the first chromosome.
- 1 2. The method of claim 1, wherein the sequencing is performed randomly
2 on a portion of the nucleic acid molecules contained in the biological sample.
- 1 3. The method of claim 1, wherein the biological sample is maternal
2 blood, plasma, serum, urine or saliva
- 1 4. The method of claim 1, wherein the biological sample is transcervical
2 lavage fluid.
- 1 5. The method of claim 1, wherein the first chromosome is chromosome
2 21, chromosome 18, chromosome 13, chromosome X, or chromosome Y.
- 1 6. The method of claim 1, wherein the parameter is a ratio of sequences
2 that originate from the first chromosome.

1 7. The method of claim 6, wherein the ratio is obtained from any one or more of a
2 fractional count of the number of sequenced tags, a fractional number of sequenced
3 nucleotides, and a fractional length of accumulated sequences.

1 8. The method of claim 6, wherein the sequences that originate from the
2 first chromosome are selected to be less than a specified number of base pairs.

1 9. The method of claim 8, wherein the specified number of base pairs is
2 300bp, 200bp, or 100bp.

1 10. The method of claim 1, wherein the nucleic acid molecules of the
2 biological sample have been enriched for sequences originating from at least one particular
3 chromosome.

1 11. The method of claim 1, wherein the nucleic acid molecules of the
2 biological sample have been enriched for sequences less than 300 bp.

1 12. The method of claim 1, wherein the nucleic acid molecules of the
2 biological sample have been enriched for sequences less than 200 bp.

1 13. The method of claim 1, wherein the nucleic acid molecules of the
2 biological sample have been amplified using a polymerase chain reaction.

1 14. The method of claim 1, wherein the sequenced portion represents at
2 least a pre-determined fraction of the human genome.

1 15. The method of claim 1, wherein the fraction represents at least 0.1% of
2 the human genome.

1 16. The method of claim 1, wherein the fraction represents at least 0.5% of
2 the human genome.

1 17. The method of claim 1, wherein at least one of the cutoff values is
2 related to the fractional concentration of fetal DNA in the biological sample.

1 18. The method of claim 17, wherein the fractional concentration of fetal
2 DNA in the biological sample is determined by any one or more of a proportion of Y

3 chromosome sequences, a fetal epigenetic marker, or using single nucleotide polymorphism
4 analysis.

1 19. The method of claim 1, wherein a cutoff value is a reference value
2 established in a normal biological sample.

1 20. The method of claim 1, further comprising:
2 identifying an amount of fetal DNA in the biological sample; and
3 calculating a number N of sequences to be analyzed based on a desired
4 accuracy.

1 21. A computer program product comprising a computer readable medium
2 encoded with a plurality of instructions for controlling a computing system to perform an
3 operation for performing prenatal diagnosis of a fetal chromosomal aneuploidy in a biological
4 sample obtained from a pregnant female subject, wherein the biological sample includes
5 nucleic acid molecules, the operation comprising the steps of:

6 receiving data from a random sequencing of a portion of the nucleic acid
7 molecules contained in the biological sample obtained from a pregnant female subject,
8 wherein the biological sample includes nucleic acid molecules, wherein the portion represents
9 a fraction of the human genome;

10 based on the data from the random sequencing:

11 determining a first amount of a first chromosome from sequences
12 identified as originating from the first chromosome;

13 determining a second amount of one or more second chromosomes
14 from sequences identified as originating from one of the second chromosomes;

15 determining a parameter from the first amount and the second amount;

16 comparing the parameter to one or more cutoff values; and

17 based on the comparison, determining a classification of whether a fetal
18 chromosomal aneuploidy exists for the first chromosome.

1 22. A method for performing prenatal diagnosis of a fetal chromosomal
2 aneuploidy in a biological sample obtained from a pregnant female subject, wherein the
3 biological sample includes nucleic acid molecules, the method comprising:
4 receiving the biological sample;

5 ~~calculating a number N of sequences to be analyzed based on a desired~~
6 accuracy;
7 randomly sequencing at least N of the nucleic acid molecules contained in the
8 biological sample, wherein the portion represents a fraction of the human genome;
9 based on the random sequencing:
10 determining a first amount of a first chromosome from sequences
11 identified as originating from the first chromosome;
12 determining a second amount of one or more second chromosomes
13 from sequences identified as originating from one of the second chromosomes;
14 determining a parameter from the first amount and the second amount;
15 comparing the parameter to one or more cutoff values; and
16 based on the comparison, determining a classification of whether a fetal
17 chromosomal aneuploidy exists for the first chromosome.

1 23. The method of claim 22, further comprising:
2 identifying a percentage of fetal DNA in the biological sample, wherein
3 calculating a number N of sequences to be analyzed based on a desired accuracy is based on
4 the percentage.