

plasma and serum. It is therefore also desirable to have methods that allow the noninvasive detection of fetal chromosomal aneuploidy by maximizing the amount of genetic information that could be inferred from the limited amount of fetal nucleic acids which exist as a minor population in a biological sample containing maternal background nucleic acids.

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BRIEF SUMMARY

[0013a] In one aspect, there is provided a method of analyzing a biological sample of an organism for deletions or amplifications in one or more chromosomal regions associated with cancer in the organism, the biological sample being obtained from the organism and including cell-free nucleic acid molecules originating from non-malignant cells and potentially from tumor cells associated with cancer, the method comprising:

10 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 the sequences obtained from the random

15 sequencing of nucleic acid molecules contained in the biological sample that are 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 the sequences obtained from the random

sequencing of nucleic acid molecules contained in the biological sample that are identified as

20 aligning to one or more second chromosomal regions;

determining a first parameter from the first amount and the second amount,

wherein the first parameter includes a ratio 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 region exhibits a deletion and/or an amplification associated

25 with cancer in the organism.

[0014] ~~Embodiments~~Examples of this invention provide methods, systems, and apparatus for determining whether a nucleic acid sequence imbalance (e.g., chromosome imbalance) exists within a biological sample obtained from a pregnant female. This determination may be done by using a parameter of an amount of a clinically-relevant chromosomal region in relation to other non-clinically-relevant chromosomal regions (background regions) within a biological sample. In one ~~aspect~~example, an amount of chromosomes is determined from a sequencing of nucleic acid molecules in a maternal sample, such as urine, plasma, serum, and other suitable biological samples. Nucleic acid molecules of the biological sample are sequenced, such that a fraction of the genome is sequenced. One or more cutoff values are chosen for determining whether a change compared to a reference quantity exists (i.e. an imbalance), for example, with regards to the ratio of amounts of two chromosomal regions (or sets of regions).

[0015] According to one ~~exemplary embodiment~~example, a biological sample received from a pregnant female is analyzed to perform a prenatal diagnosis of a fetal chromosomal aneuploidy. The biological sample includes nucleic acid molecules. A portion of the nucleic acid molecules contained in the biological sample are sequenced. In one ~~aspect~~example, the amount of genetic information obtained is sufficient for accurate diagnosis yet not overly excessive so as to contain costs and the amount of input biological sample required.

[0016] Based on the sequencing, a first amount of a first chromosome is determined from sequences identified as originating from the first chromosome. A second amount of one or more second chromosomes is determined from sequences identified as originating from one of the second chromosomes. A parameter from the first amount and the second amount is then compared to one or more cutoff values. Based on the comparison, a classification of whether a fetal chromosomal aneuploidy exists for the first chromosome is determined. The sequencing advantageously maximizes the amount of genetic information that could be inferred from the limited amount of fetal nucleic acids which exist as a minor population in a biological sample containing maternal background nucleic acids.

[0017] According to one ~~exemplary embodiment~~example, a biological sample received from a pregnant female is analyzed to perform a prenatal diagnosis of a fetal chromosomal aneuploidy. The biological sample includes nucleic acid molecules. A percentage of fetal DNA in the biological sample is identified. A number N of sequences to be analyzed based on a desired accuracy is calculated based on the percentage. At least N of the nucleic acid molecules contained in the biological sample are randomly sequenced.

[0018] Based on the random sequencing, a first amount of a first chromosome is determined from sequences identified as originating from the first chromosome. A second amount of one or more second chromosomes is determined from sequences identified as originating from one of the second chromosomes. A parameter from the first amount and the second amount is then compared to one or more cutoff values. Based on the comparison, a classification of whether a fetal chromosomal aneuploidy exists for the first chromosome is determined. The random sequencing advantageously maximizes the amount of genetic information that could be inferred from the limited amount of fetal nucleic acids which exist as a minor population in a biological sample containing maternal background nucleic acids.

[0018a] In another aspect, there is provided a computer program product comprising a computer readable medium encoded with a plurality of instructions for controlling a computing system to perform the method as defined above.

[0019] Other ~~embodiments~~examples of the ~~invention~~disclosure are directed to systems and computer readable media associated with methods described herein.

[0020] A better understanding of the nature and advantages of the present invention may be gained with reference to the following detailed description and the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] FIG. 1 is a flowchart of a method 100 for performing prenatal diagnosis of a fetal chromosomal aneuploidy in a biological sample obtained from a pregnant female subject according to an embodiment of the present invention.

[0022] FIG. 2 is a flowchart of a method 200 for performing prenatal diagnosis of a fetal chromosomal aneuploidy using random sequencing according to an embodiment of the present invention.

[0023] FIG. 3A shows a plot of percentage representation of chromosome 21 sequences in maternal plasma samples involving trisomy 21 or euploid fetuses according to an embodiment of the present invention.