CLAIMS

What is claimed is:

1. A method of testing for an abnormal distribution of a specified chromosome portion in a sample obtained from a subject, wherein the sample is a mixture of fetal and maternal DNA in a maternal plasma sample, comprising:

(a) obtaining sequences from multiple chromosome portions of the mixed sample by massively parallel sequencing to obtain a number of sequence tags of sufficient length of determined sequence to be assigned to a chromosome location within a human reference genome;

(b) assigning the sequence tags to corresponding chromosome portions including at least one normally distributed chromosome portion and the specified chromosome portion, by comparing the sequences of the tags to a human reference genomic sequence and assigning the sequence tags to a certain chromosome and to a certain position along the chromosome;

(c) determining values for numbers of sequence tags mapping to chromosome portions by using a number of windows of defined length within the at least one normally distributed chromosome portion to obtain a first value from the number of sequence tags mapped to the at least one normally distributed chromosome portion and within the specified chromosome portion to obtain a second value from the number of sequence tags mapped to the specified chromosome portion, wherein the first value and the second value are calculated using the windows to account for intra-chromosomal and inter-chromosomal variation in the distribution of the sequence tags; and

(d) using the values from step (c) to determine a differential, between the first value and the second value, which is determinative of the over-representation or under-representation of the specified chromosome portion in the mixture of maternal and fetal DNA, wherein the method further includes correcting for GC bias of the sequence reads from the massively parallel sequencing, by:

(i) dividing the human reference genome into a number of windows of defined length within each chromosome and calculating the GC content of each window;

(ii) calculating the relationship between sequence coverage and GC content of each window by determining a number of reads per a given window

and a GC content of that window; and

(ii) assigning a weight to said number of reads per a given window based on GC content, where the weight has a relationship to GC content such that increasing numbers of reads with increasing GC content results in decreasing weight per increasing GC content.

2. The method of claim 1, wherein to determine a differential includes the step of comparing a normalized sequence tag density of the specified DNA chromosome portion to a normalized sequence tag density of another DNA chromosome portion in said mixed sample, wherein all autosomes are used to calculate the normalized sequence tag density.

3. The method of claim 1 or claim 2, wherein the windows of defined length for GC correction in steps (i)-(iii) are smaller in length than the windows of defined length in step (c).

4. The method of any preceding claim, wherein the abnormal distribution is a fetal aneuploidy, and optionally wherein the abnormal distribution is an aneuploidy of at least one of chromosomes 13, 18 and 21, such as trisomy 13, trisomy 18 or trisomy 21.

5. The method of any preceding claim, wherein the step of assigning sequence tags to corresponding chromosome portions allows one mismatch.

6. The method of any preceding claim, wherein the sequence tags are about 25-100 bp in length.

7. The method of claim 6 wherein at least about 1 million sequence tags are obtained.

8. The method of claim 6 further comprising the steps of calculating a normalized sequence tag density of the specified DNA chromosome portion and a normalized sequence tag density of another DNA chromosome portion in said mixed sample, wherein all autosomes are used to calculate the normalized sequence tag density.

9. The method of claim 8 wherein the step of calculating a differential includes the step of comparing a normalized sequence tag density of the specified DNA chromosome portion to a normalized sequence tag density of another DNA chromosome portion in said mixed sample, wherein all autosomes are used to calculate the normalized sequence tag density.

10. The method of claim 8 further comprising the step of measuring over- and under-representation of a chromosome by determining a sequence tag density for each chromosome in the sample, namely chromosomes 1-22, X and also chromosome Y if

present.

11. The method of claim 1 wherein said calculating a differential comprises obtaining a sequence density of an abnormally distributed chromosome and comparing it to a sequence density of a disomic chromosome.

12. The method of any preceding claim, wherein said number of windows of defined length in step (c) are comprised of sliding non overlapping windows of 10-100 kb extending along substantially an entire chromosome.

13. The method of any preceding claim, wherein said number of windows of defined length in step (i) are 10-30 kb in length.

14. The method of claim 2, further comprising the step of calculating a t statistic for each chromosome relative to other chromosomes in the mixed sample, whereby each t statistic indicates a value of a chromosome relative to other chromosomes in a sample, said value being indicative of disomy.

15. The method of claim 2, further comprising the step of calculating a normalized value for chromosome X and, if present, Y.