Annex

1. A method for performing prenatal diagnosis of a fetal chromosomal aneuploidy in a biological sample obtained from a female subject pregnant with a fetus, wherein the biological sample is maternal plasma or serum and wherein the sample includes cell-free nucleic acid molecules from the female subject and the fetus, the method comprising:

performing a random sequencing on at least a portion of a plurality of the nucleic acid molecules contained in the biological sample to obtain a pre-determined number of sequences, wherein the sequences represent a fraction of the human genome;

aligning, with a computer system, each sequence to a human genome;

determining a first amount of sequences identified as being aligned to a first chromosome;

determining a second amount of sequences identified as being aligned to one or more second chromosomes;

determining a 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 parameter to one or more cutoff values, to determine a classification of whether a fetal chromosomal aneuploidy exists for the first chromosome.

~~2. The method of claim 1, wherein the biological sample is maternal blood, plasma, serum, urine or saliva.~~

~~3. The method of claim 1, wherein the biological sample is transcervical lavage fluid.~~

2~~4~~. The method of claim 1, wherein the first chromosome is chromosome 21, chromosome 18, chromosome 13, chromosome X, or chromosome Y.

3~~5~~. The method of claim 1, wherein the parameter is determined from a ratio of the first amount and the second amount.

4~~6~~. The method of claim 3~~5~~, wherein the ratio is a fractional count of the number of sequences, a fractional number of sequenced nucleotides, or a fractional length of accumulated sequences.

5~~7~~. The method of claim 3~~5~~, wherein the sequences that align to the first chromosome are selected to be less than a specified number of base pairs.

6~~8~~. The method of claim 5~~7~~, wherein the specified number of base pairs is 300 bp, 200 bp, or 100 bp.

7~~9~~. The method of claim 1, wherein the nucleic acid molecules of the biological sample have been enriched for sequences originating from at least one particular chromosome.

8~~10~~. The method of claim 1, wherein the nucleic acid molecules of the biological sample have been enriched for sequences less than 300 bp.

9~~11~~. The method of claim 1, wherein the nucleic acid molecules of the biological sample have been enriched for sequences less than 200 bp.

10~~12~~. The method of claim 1, wherein the nucleic acid molecules of the biological sample, have been amplified using a polymerase chain reaction.

11~~13~~. The method of claim 1, wherein the obtained sequences represent at least a pre-determined fraction of the human genome.

12~~14~~. The method of claim 11~~13~~, wherein the fraction represents at least 0.1% of the human genome.

13~~15~~. The method of claim 11~~13~~, wherein the fraction represents at least 0.5% of the human genome.

14~~16~~. The method of claim 1, wherein at least one of the cutoff values is dependent on the fractional concentration of fetal DNA in the biological sample.

15~~17~~. The method of claim 14~~16~~, wherein the fractional concentration of fetal DNA in the biological sample is determined by any one or more of a proportion of Y chromosome sequences, a fetal epigenetic marker, or using single nucleotide polymorphism analysis.

16~~18~~. The method of claim 1, wherein a cutoff value is a reference value established from one or more normal biological samples.

17~~19~~. The method of claim 1, further comprising:

identifying an amount of fetal DNA in the biological sample; and

calculating the number of sequences to be obtained based on a desired accuracy and the amount of fetal DNA in the biological sample.

18~~21~~. The method of claim 1 further comprising;

calculating the number of nucleic acid molecules to be sequenced based on a desired accuracy.

19~~22~~. The method of claim 18~~21~~, wherein the desired accuracy is at least 95%.

20~~24~~. The method of claim 1 wherein the determined number of sequences for differentiating trisomy 21 from euploid cases is at least 120,000 when the biological sample has 20% or more fetal DNA, at least 180,000 when the biological sample has 10% or more fetal DNA, or at least 540,000 when the biological sample has 5% or more fetal DNA.

21. The method of any preceding claim wherein the nucleic acid molecules are amplified by emulsion PCR.

22. The method of any preceding claim wherein the nucleic acid molecules are DNA.

23. The method of any preceding claim wherein the fractional concentration of fetal DNA in the maternal plasma is measured and the fractional concentration of fetal DNA is used to calculate the one or more cutoff values.

24. The method of any preceding claim wherein performing a random sequencing comprises sequencing the full length of short nucleic acid fragments to determine their length.

25. The method of claim 24 further comprising focusing the data analysis on the subset of sequences corresponding to short nucleic fragments in the biological sample by post-sequencing *in silico* selection.

26. The method of any preceding claim wherein the biological sample is maternal plasma.

2720. A computer program product comprising a computer readable medium encoded with a plurality of instructions for controlling a computing system to perform an operation for performing prenatal diagnosis of a fetal chromosomal aneuploidy in a biological sample obtained from a female subject pregnant with a fetus, the biological sample is maternal plasma or serum and wherein the sample includes~~ing~~ cell-free nucleic acid molecules from the female subject and from the fetus; the operation comprising the steps of:

receiving at least a determined number of sequences from a random sequencing on at least a portion of a plurality of the nucleic acid molecules contained in the biological sample and wherein the sequences represent a fraction of the human genome;

aligning each sequence to a human genome;

determining a first amount of sequences identified as being aligned to a first chromosome;

determining a second amount of sequences identified as being aligned to one or more second chromosomes;

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

comparing the parameter to one or more cutoff values; and

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

~~23. The method of claim 1, wherein the first amount and the second amount are determined from sequences identified as being uniquely aligned to the first chromosome and the one or more second chromosomes, respectively.~~

28. The computer program product of claim 27 wherein the random sequencing uses emulsion PCR.

29. The computer program product of claim 27 or 28 wherein the nucleic acid molecules are DNA.

30. The computer program product of claims 27 to 29 wherein the operation further comprises the steps of measuring the fractional concentration of fetal DNA in the maternal plasma and using the fractional concentration of fetal DNA to calculate the one or more cutoff values.

31. The computer program product of claims 27 to 30 wherein the random sequencing comprises sequencing the full length of short nucleic acid fragments to determine their length.

32. The computer program product of claim 31 wherein the operation further comprises the step of focusing the data analysis on the subset of sequences corresponding to short nucleic fragments in the biological sample by post-sequencing *in silico* selection.

33. The computer program product of claims 27 to 32 wherein the biological sample is maternal plasma.