more cells. One recent study found a mean value of 37 fetal lymphocytes per milliliter of blood. (Huang, *Prenatal Diagnosis* 2008 28: 892-899).

[0008] Thus, there is a need for improved methods and tools for detecting fetal alleles and fetal genetic variations.

SUMMARY OF THE INVENTION

[0008A] In one aspect, there is provided an *in vitro* method of obtaining and analyzing a fetal genome from a mixture of maternal and fetal cells, comprising: enriching a sample comprising a mixture of maternal and fetal cells; dividing said enriched sample into at least about 100 subsamples; performing whole genome amplification on each at least about 100 subsamples to provide an amplified product for each subsample, wherein each amplified product has an amplified genome from an average of about one cell; dividing each of said amplified product into aliquots, wherein each aliquot contains at least one copy of said amplified genome from said cell; screening or genotyping an aliquot for the presence of a fetal identifier, wherein said screening or genotyping comprises: screening or genotyping said aliquot for a genotype differing from a maternal genotype at at least one target locus, wherein the presence of said genotype differing from said maternal genotype indicates the presence of an informative paternal allele in said aliquot; identifying the presence of fetal cell in at least one subsample whose aliquot contains an informative paternal allele; and analyzing another aliquot from said at least one subsample identified as containing fetal cell to detect genetic variation in said genome of said fetal cell.

[0009] Examples of the present disclosure relate to methods and genotyping panels for detecting fetal alleles and fetal genetic variations. One example of the disclosure is a method of detecting a fetal identifier, comprising: obtaining a sample comprising a mixture of maternal and fetal cells; dividing the sample into subsamples; screening or genotyping a subsample for the presence of a fetal identifier; and identifying the presence of at least one fetal identifier from a fetal cell in at least one subsample.

[0010] Examples of the disclosure can and may comprise one or more of the following: a method further comprising performing subsample amplification on at least one subsample to provide an amplified product; a method further comprising dividing the amplified product into aliquots, where screening or genotyping a subsample for the presence of at least one fetal identifier comprises

screening an aliquot for the presence of a fetal identifier; a method where subsample amplification comprises a method selected from the group consisting of: whole genome amplification, whole transcriptome amplification, targeted nucleic acid amplification, amplification of a nucleic acid sequence other than the fetal identifier, generation of a proxy for a nucleic acid sequence, and cell division; a method where preamplification comprises whole genome amplification or whole transcriptome amplification; a method where preamplification comprises targeted nucleic acid amplification, amplification of a nucleic acid sequence other than the fetal identifier, generation of a proxy for a nucleic acid sequence, and cell division; a method further comprising determining whether the genetic material of the maternal cells is homozygous or heterozygous at a set of target loci to determine a maternal genotype, where screening or genotyping an aliquot or subsample for a fetal identifier comprises screening or genotyping the aliquot or subsample for a genotype differing from the maternal genotype at at least one target locus, where the presence of the genotype differing from the maternal genotype indicates the presence of an informative paternal allele in the amplified product, and where identifying the presence of at least one fetal identifier comprises identifying an informative paternal

where the amplified product comprises genomic DNA or complementary DNA; a method where determining a maternal genotype comprises using a panel of SNPs to genotype a sample of maternal genetic material from the same individual that is the source of the maternal cells; a method where the source of the maternal genetic material is selected from the group consisting of blood, serum, plasma, urine, a cervical swab, tears, saliva, buccal swab, or skin; a method where the source of the maternal genetic material is selected from the group consisting of blood or a buccal swab; a method where the mixture of maternal and fetal nucleic acids is a mixture of cell-free nucleic acids; a method where the source of the maternal and fetal cell-free nucleic acid sample is blood, serum, plasma, urine, cervical swab, cervical lavage, uterine lavage, or culdocentesis from a pregnant female; a method comprising selecting and screening or genotyping more than one test locus in a single aliquot or subsample, selecting and screening or genotyping more than one test locus in more than one aliquot or subsample, or selecting and screening or genotyping one test locus in more than one aliquot or subsample; a method comprising selecting and screening or genotyping a second target locus in at least a second subsample following the identification of an informative paternal allele in a first aliquot or subsample; a method where the samples are divided to generate subsamples with a Poisson or a Non-Poisson distribution of cells; a method where each subsample comprises not more than one cell; a method further comprising pooling aliquots from two or more subsamples prior to screening or genotyping; a method where pooling comprises the use of an indexed system of rows and columns of wells comprising the aliquots; a method further comprising enriching the sample for the fetal cells prior to dividing into subsamples; a method where enriching comprises differential expansion of the fetal cells over the maternal cells; a method where a homogeneous portion of the amplified product is divided into the aliquots; and a method where a non-homogeneous portion of the amplified product is divided into the aliquots.

[0011] Yet another example of the disclosure is a single nucleotide polymorphism (SNP) panel for detecting a fetal allele, comprising at least one chromosome-specific panel comprising about 5 to about 100 unique SNPs specific for a single chromosome, where each of the SNPs has a frequency in the range of about 30% to about 50% as measured across all major population groups; and where the total number of SNPs in the SNP panel is between about 5 and about 100 SNPs.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

WHAT IS CLAIMED IS:

1. An *in vitro* method of obtaining and analyzing a fetal genome from a mixture of maternal and fetal cells, comprising:

enriching a sample comprising a mixture of maternal and fetal cells;

dividing said enriched sample into at least about 100 subsamples;

performing whole genome amplification on each at least about 100 subsamples to provide an amplified product for each subsample, wherein each amplified product has an amplified genome from an average of about one cell;

dividing each of said amplified product into aliquots, wherein each aliquot contains at least one copy of said amplified genome from said cell;

screening or genotyping an aliquot for the presence of a fetal identifier, wherein said screening or genotyping comprises:

screening or genotyping said aliquot for a genotype differing from a maternal genotype at at least one target locus, wherein the presence of said genotype differing from said maternal genotype indicates the presence of an informative paternal allele in said aliquot;

identifying the presence of fetal cell in at least one subsample whose aliquot contains an informative paternal allele; and

analyzing another aliquot from said at least one subsample identified as containing fetal cell to detect genetic variation in said genome of said fetal cell.

2. The method of Claim 1, further comprising determining whether the genetic material of said maternal cells is homozygous or heterozygous at a set of target loci to determine a maternal genotype.

3. The method of Claim 2, further comprising selecting said target loci prior to determining whether the genetic material of said maternal cells is homozygous or heterozygous.

4. The method of Claim 3, further comprising selecting a test locus from said target loci, wherein said screening or genotyping comprises screening or genotyping an aliquot or subsample for a genotype differing from said maternal genotype at said test locus.

5. The method of Claim 4, wherein said selection of said test locus comprises screening a sample of mixed maternal and fetal nucleic acids for a genotype differing from said maternal genotype at a target locus, and selecting as said test locus a target locus with a non-maternal genotype in said sample of mixed maternal and fetal nucleic acids.

6. The method of Claim 1, wherein said genetic variation is a fetal genetic variation selected from the group consisting of a chromosomal rearrangement, a copy number variation, and a polymorphism.

7. The method of Claim 1, wherein said analysis comprises determining a ratio of maternally- and paternally-inherited alleles in an aliquot comprising said informative paternal allele, wherein said ratio is analyzed to determine the presence of a genetic variation.

8. The method of Claim 1, wherein said analysis comprises determining a copy number of alleles in an aliquot comprising said informative paternal allele, wherein said copy number of alleles is analyzed to determine the presence of a genetic variation.

9. The method of Claim 2, wherein said target loci are all homozygous for said maternal genotype, are all heterozygous for said maternal genotype, or comprise a mixture of homozygous and heterozygous loci for said maternal genotype.

10. The method of Claim 5, wherein said target loci are all homozygous for said maternal genotype.

11. The method of Claim 2 or 5, wherein said determining a maternal genotype comprises using a panel of SNPs to genotype a sample of maternal genetic material from the same individual that is the source of said maternal cells.

12. The method of Claim 11, wherein the source of said maternal genetic material is selected from the group consisting of blood, serum, plasma, urine, a cervical swab, tears, saliva, buccal swab, or skin.

13. The method of Claim 11, wherein the source of said maternal genetic material is selected from the group consisting of blood or a buccal swab.

14. The method of claim 5, wherein said mixture of maternal and fetal nucleic acids is a mixture of cell-free nucleic acids.

15. The method of Claim 14, wherein the source of said maternal and fetal cell-free nucleic acid sample is blood, serum, plasma, urine, cervical swab, cervical lavage, uterine lavage, or culdocentesis from a pregnant female.

16. The method of Claim 4 or 5, comprising selecting and screening or genotyping more than one test locus in a single aliquot or subsample, selecting and screening or genotyping more than one test locus in more than one aliquot or subsample, or selecting and screening or genotyping one test locus in more than one aliquot or subsample.

17. The method of Claim 4 or 5, comprising selecting and screening or genotyping a second target locus in at least a second subsample following the identification of an informative paternal allele in a first aliquot or subsample.

18. The method of Claim 1, further comprising pooling an aliquot from two or more subsamples prior to screening or genotyping an aliquot for the presence of a fetal identifier, wherein said screening or genotyping comprises:

screening or genotyping said pooled aliquots for a genotype differing from a maternal genotype at least one target locus, wherein the presence of said genotype differing from said maternal genotype indicates the presence of an informative paternal allele in said pooled aliquots; and

wherein said identifying the presence of a fetal cell in at least one subsample comprises individually screening or genotyping a second aliquot from the subsamples whose pooled aliquots contained an informative paternal allele.

19. The method of Claim 18, wherein said pooling comprises the use of an indexed system of rows and columns of wells comprising said aliquots.

20. The method of Claim 1, wherein aliquots from two or more subsamples identified as containing a fetal cell are pooled prior to said analyzing another aliquot from said at least one subsample identified as containing fetal cell to detect a genetic variation in said fetal cell.

21. The method of Claim 18, wherein aliquots from two or more subsamples identified as containing a fetal cell are pooled prior to said analyzing another aliquot from said at least one subsample identified as containing fetal cell to detect a genetic variation in said fetal cell.

22. The method of Claim 1, wherein said enriched sample is divided into at least about 1536 subsamples.

23. The method of Claim 1, wherein said enriched sample is divided into at least about 3456 subsamples.