Proposed unconditional amendments to EP (UK) 1 524 321 B2

Annex A

1. A fraction of a sample of the blood plasma or serum of a pregnant woman in which, as the result of said sample having been submitted to a DNA extraction, followed by a size separation, of the extracellular DNA, the extracellular DNA present therein substantially consists of DNA consisting of 500 base pairs or less.

2. A sample-fraction according to claim 1 which, before extraction and size separation of the extracellular DNA, is substantially cell-free.

3. A sample-fraction, according to claim 1 or 2 wherein the size separation was carried out by chromatography or electrophoresis, by density gradient centrifugation or by methods utilising nanotechnological means.

4. A sample-fraction according to claim 3 wherein the chromatography and, respectively, electrophoresis was chromatography on agarose or polyacrylamide gels, ion-pair reversed-phase high performance liquid chromatography (IP RP HPLC), capillary electrophoresis in a self-coating, low-viscosity polymer matrix, selective extraction in microfabricated electrophoresis devices, microchip electrophoresis on reduced viscosity polymer matrices or adsorptive membrane chromatography.

5. A sample-fraction according to claim 3 wherein the method utilizing nanotechnological means was making use of microfabricated entropic trap arrays.

6. The use of a sample-fraction according to any one of claims 1 to 5 for the non-invasive detection of fetal genetic traits.

7. The use according to claim 6 wherein the fetal genetic trait to be detected is the fetal RhD gene in a pregnancy at risk for HDN (hemolytic disease of the fetus and the newborn) or a fetal Y chromosome-specific sequence in a pregnancy at risk for an X chromosome-linked disorder.

8. The use according to claim 6 wherein the fetal genetic trait to be detected is ~~a chromosomal aberration,~~ a hereditary Mendelian genetic disorder and, respectively, a genetic marker associated therewith, or a fetal genetic trait which may be decisive when paternity is to be determined.

9. The use according to claim 7 wherein the X chromosome-linked disorder is hemophilia or fragile X syndrome.

~~10. The use according to claim 8 wherein the chromosomal aberration is aneuploidy.~~

~~11. The use according to claim 8 wherein the chromosomal aberration is associated with Down's syndrome.~~

~~12~~10. The use according to claim 8 wherein the hereditary Mendelian genetic disorder is a single gene disorder.

~~13~~11. The use according to claim ~~12~~10 wherein the single gene disorder is cystic fibrosis or a hemoglobinopathy.

~~14~~12. The use according to any one of claims 6 to ~~13~~11 wherein the detection of the fetal genetic traits is carried out by PCR (polymerase chain reaction) technology, ligand chain reaction or probe hybridisation techniques or by means of nucleic acid arrays.

~~15~~13. A process for performing non-invasive detection of fetal genetic traits which comprises subjecting a sample of the blood plasma or serum of a pregnant woman to a DNA extraction, followed by a size separation, of the extracellular DNA so as to obtain a fraction of said sample in which the extracellular DNA present therein substantially consists of DNA consisting of 500 base pairs or less, and determining the fetal genetic trait(s) to be detected by submitting such fraction to PCR (polymerase chain reaction) technology, ligase chain reaction or probe hybridisation techniques, or to nucleic acid arrays.

~~16~~14. A process according to claim ~~15~~13 wherein the fetal genetic trait to be detected is the fetal RhD gene in a pregnancy at risk for HDN (haemolytic disease of the fetus and the newborn) or a fetal Y chromosome-specific sequence in a pregnancy at risk for an X chromosome-linked disorder.

~~17~~15. A process according to claim ~~15~~13 wherein the fetal genetic trait to be detected is ~~a chromosomal aberration,~~ a hereditary Mendelian genetic disorder and, respectively,

a genetic marker associated therewith, or a fetal genetic trait which may be decisive when paternity is to be determined.

~~18~~16. A process according to claim ~~16~~14 wherein the X chromosome-linked disorder is hemophilia or fragile X syndrome.

~~19. A process according to claim 17 wherein the chromosomal aberration is an aneuploidy.~~

~~20. A process according to claim 17 wherein the chromosomal aberration is associated with Down's syndrome.~~

~~21~~17. A process according to claim ~~17~~15 wherein the hereditary Mendelian genetic disorder is a single gene disorder.

~~22~~18. A process according to claim ~~21~~17 wherein the single gene disorder is cystic fibrosis or a hemoglobinopathy.

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Annex B

1. A fraction of a sample of the blood plasma or serum of a pregnant woman in which, as the result of said sample having been submitted to a DNA extraction, followed by a size separation, of the extracellular DNA, the extracellular DNA present therein substantially consists of DNA consisting of 500 base pairs or less.

2. A sample-fraction according to claim 1 which, before extraction and size separation of the extracellular DNA, is substantially cell-free.

3. A sample-fraction, according to claim 1 or 2 wherein the size separation was carried out by chromatography or electrophoresis, by density gradient centrifugation or by methods utilising nanotechnological means.

4. A sample-fraction according to claim 3 wherein the chromatography and, respectively, electrophoresis was chromatography on agarose or polyacrylamide gels, ion-pair reversed-phase high performance liquid chromatography (IP RP HPLC), capillary electrophoresis in a self-coating, low-viscosity polymer matrix, selective extraction in microfabricated electrophoresis devices, microchip electrophoresis on reduced viscosity polymer matrices or adsorptive membrane chromatography.

5. A sample-fraction according to claim 3 wherein the method utilizing nanotechnological means was making use of microfabricated entropic trap arrays.

6. The use of a sample-fraction according to any one of claims 1 to 5 for the non-invasive detection of fetal genetic traits, wherein the fetal genetic traits to be detected are paternally inherited polymorphisms.

7. The use ~~according to claim 6~~ of a sample-fraction according to any one of claims 1 to 5 for the non-invasive detection of fetal genetic traits, wherein the fetal genetic trait to be detected is the fetal RhD gene in a pregnancy at risk for HDN (hemolytic disease of the fetus and the newborn) or a fetal Y chromosome-specific sequence in a pregnancy at risk for an X chromosome-linked disorder.

8. The use ~~according to claim 6~~ of a sample-fraction according to any one of claims 1 to 5 for the non-invasive detection of fetal genetic traits, wherein the fetal genetic

trait to be detected is a hereditary Mendelian genetic disorder and, respectively, a genetic marker associated therewith, or a fetal genetic trait which may be decisive when paternity is to be determined.

9. The use according to claim 7 wherein the X chromosome-linked disorder is hemophilia or fragile X syndrome.

10. The use according to claim 8 wherein the hereditary Mendelian genetic disorder is a single gene disorder.

11. The use according to claim 10 wherein the single gene disorder is cystic fibrosis or a hemoglobinopathy.

12. The use according to any one of claims 6 to 11 wherein the detection of the fetal genetic traits is carried out by PCR (polymerase chain reaction) technology, ligand chain reaction or probe hybridisation techniques or by means of nucleic acid arrays.

13. A process for performing non-invasive detection of fetal genetic traits which comprises subjecting a sample of the blood plasma or serum of a pregnant woman to a DNA extraction, followed by a size separation, of the extracellular DNA so as to obtain a fraction of said sample in which the extracellular DNA present therein substantially consists of DNA consisting of 500 base pairs or less, and determining the fetal genetic trait(s) to be detected by submitting such fraction to PCR (polymerase chain reaction) technology, ligase chain reaction or probe hybridisation techniques, or to nucleic acid arrays, where the fetal genetic traits to be detected are paternally inherited polymorphisms.

14. A process for performing non-invasive detection of fetal genetic traits which comprises subjecting a sample of the blood plasma or serum of a pregnant woman to a DNA extraction, followed by a size separation, of the extracellular DNA so as to obtain a fraction of said sample in which the extracellular DNA present therein substantially consists of DNA consisting of 500 base pairs or less, and determining the fetal genetic trait(s) to be detected by submitting such fraction to PCR (polymerase chain reaction) technology, ligase chain reaction or probe hybridisation techniques, or to nucleic acid arrays, ~~according to claim 13~~ wherein the fetal genetic trait to be detected is the fetal RhD gene in a pregnancy at risk for HDN (haemolytic

disease of the fetus and the newborn) or a fetal Y chromosome-specific sequence in a pregnancy at risk for an X chromosome-linked disorder.

15. A process for performing non-invasive detection of fetal genetic traits which comprises subjecting a sample of the blood plasma or serum of a pregnant woman to a DNA extraction, followed by a size separation, of the extracellular DNA so as to obtain a fraction of said sample in which the extracellular DNA present therein substantially consists of DNA consisting of 500 base pairs or less, and determining the fetal genetic trait(s) to be detected by submitting such fraction to PCR (polymerase chain reaction) technology, ligase chain reaction or probe hybridisation techniques, or to nucleic acid arrays, ~~according to claim 13~~ wherein the fetal genetic trait to be detected is a hereditary Mendelian genetic disorder and, respectively, a genetic marker associated therewith, or a fetal genetic trait which may be decisive when paternity is to be determined.

16. A process according to claim 14 wherein the X chromosome-linked disorder is hemophilia or fragile X syndrome.

17. A process according to claim 15 wherein the hereditary Mendelian genetic disorder is a single gene disorder.

18. A process according to claim 17 wherein the single gene disorder is cystic fibrosis or a hemoglobinopathy.