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(54) Title: NUCLEIC ACID BIOMARKERS FOR PLACENTAL DYSFUNCTION

(57) Abstract: The present invention provides compositions and methods for determining a pregnant female's risk of develop-
ing placental dysfunction later in the pregnancy, e.g. preeclampsia. The present invention also provides compositions and meth-
ods for determining a pregnant female's risk of developing placental dysfunction early in the pregnancy or throughout the pregnan-
cy. The compositions are based on miRNA biomarkers and pairs of miRNA biomarkers. The micro RNA biomarkers may be hsa-
miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa- miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d,
hsa- miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-
miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, hsa- miR-941, hsa-miR-517a-3p, hsa-miR-517b-3p, hsa-miR-760,
hsa- miR-6852-5p, hsa-miR-1323, hsa-miR-155-5p, hsa-miR-6747-3p, hsa- miR-6747-3p, hsa-miR-4446-3p, hsa-miR-30c-5p, hsa-
miR-6842-3p and hsa-miR-485-5p.

NUCLEIC ACID BIOMARKERS FOR PLACENTAL DYSFUNCTION

BACKGROUND

[0001] Placental dysfunction, most commonly manifested as preeclampsia or intrauterine growth restriction, is an important cause of maternal and fetal morbidity and mortality in both the developing and developed world. placental insufficiency. In particular, placental dysfunction linked to preterm birth (PTB), preeclampsia, intrauterine growth restriction, preterm labor, preterm premature rupture of membranes, late spontaneous abortion and abruption placentae. It is thought that placental dysfunction arises from abnormal trophoblast differentiation and/or invasion, events that occur in the first trimester of pregnancy, but become clinically apparent only in the late second and third trimesters. Optimal surveillance and management of placental dysfunction, as well as the development of effective therapies, have been hampered by the lack of methods for early and accurate identification of pregnancies at risk for this disorder. MicroRNAs (miRNAs) are non-coding, 21-25 nucleotide, regulatory RNAs that affect the stability and/or translational efficiency of messenger-RNA (mRNAs). There is a need to develop a maternal blood-based assay for quantification of extracellular microRNA (miRNA) biomarkers present in the maternal serum during the second trimester of pregnancy in order to determine a pregnant female's risk of developing placental dysfunction later in the pregnancy. The present invention addresses this need and provides related advantages.

SUMMARY

[0002]   The present invention provides compositions and methods for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy.

[0003]   In one aspect, the invention provides a panel of isolated nucleic acid biomarkers comprising two or more of the nucleic acid biomarkers listed in Tables 3, 4 or 5.

[0004]   In one aspect, the invention provides a panel of isolated nucleic acid biomarkers comprising two or more of the nucleic acid biomarkers listed in Table 3.

[0005]   In one aspect, the invention provides a biomarker panel comprising two or more of the isolated nucleic acid biomarkers selected from the group consisting of hsa-miR-516b-5p, hsa-

miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[0006] In some embodiments, the biomarker panel comprises isolated nucleic acid biomarkers comprising hsa-miR-1-3p, hsa-miR-181d-5p, hsa-miR-378d, hsa-miR-4433b-5p, and/or hsa-miR-27a-5p. In some embodiments, the biomarker panel comprises isolated nucleic acid biomarkers comprising hsa-miR-516b-5p and/or hsa-miR-30c-5p . In some embodiments, the biomarker panel comprises isolated nucleic acid biomarkers comprising hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, and/or hsa-miR-331-3p . In some embodiments, the biomarker panel comprises isolated nucleic acid biomarkers comprising hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, and/or hsa-miR-181d-5p.

[0007]   In one aspect, the invention provides a panel of isolated nucleic acid biomarkers comprising two or more of the nucleic acid biomarkers listed in Table 4.

[0008]   In one aspect, the invention provides a panel of isolated nucleic acid biomarkers comprising a pair of biomarkers selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-

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5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[0009]   In some embodiments, the biomarker panel comprises isolated nucleic acid biomarkers comprising hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-4433b-5p/hsa-

miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-24-3p, and/or hsa-miR-378c/hsa-miR-148a-5p.

[0010]   In some embodiments, the biomarker panel comprises isolated nucleic acid biomarkers comprising hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, and/or hsa-miR-484/hsa-miR-516b-5p.

[0011]   In some embodiments, the biomarker panel comprises isolated nucleic acid biomarkers comprising hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, and/or hsa-miR-30c-5p/hsa-miR-7-5p.

[0012]   In some embodiments, the biomarker panel comprises isolated nucleic acid biomarkers comprising hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, and/or hsa-miR-485-5p/hsa-miR-516b-5p.

[0013]   In some embodiments, the biomarker panel comprises isolated nucleic acid biomarkers comprising hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-516b-5p/ hsa-miR-423-5p and/or hsa-miR-155-5p/ hsa-let-7i-5p.

[0014]   In one aspect, the invention provides a panel of isolated nucleic acid biomarkers comprising at least one of the nucleic acid biomarkers listed in Table 5.

[0015]   In another aspect, the invention provides a panel of isolated nucleic acid biomarkers comprising at least one of the nucleic biomarkers selected from the group consisting of hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, hsa-miR-1323, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p.

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[0016]   In some embodiments, the biomarker panel comprises isolated biomarkers comprising hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, and hsa-miR-1323.

[0017]   In some embodiments, the biomarker panel comprises isolated biomarkers comprising hsa-miR-30c-5p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p.

[0018]   In some embodiments, the biomarker panel comprises isolated biomarkers comprising hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-760, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p.

[0019]   In one aspect, the invention provides a composition of labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to two or more of the nucleic acid biomarkers listed in Tables 3, 4 or 5.

[0020]   In one aspect, the invention provides a composition of labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to two or more of the nucleic acid biomarkers listed in Table 3.

[0021]   In one aspect, the invention provides a composition of labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to two or more nucleic acid biomarkers selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[0022]   In some embodiments, the invention provides a composition of labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to nucleic acid biomarkers hsa-miR-1-3p, hsa-miR-181d-5p, hsa-miR-378d, hsa-miR-4433b-5p, and/or hsa-miR-27a-5p. In some embodiments, the invention provides a composition of labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to nucleic acid biomarkers hsa-miR-516b-5p and/or hsa-

miR-30c-5p. In some embodiments, the invention provides a composition of labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to nucleic acid biomarkers hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, and/or hsa-miR-331-3p. In some embodiments, the invention provides a composition of labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to nucleic acid biomarkers hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, and/or hsa-miR-181d-5p.

[0023]   In one aspect, the invention provides a composition of labeled and/or amplified nucleic acid molecules that correspond to a pair of biomarkers selected from the group consisting of the biomarker pairs listed in Table 4.

[0024]   In one aspect, the invention provides a composition of labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to a pair of biomarker selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-

484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[0025]   In some embodiments, of the pair of biomarkers or panel of biomarkers comprising a pair of biomarkers, the pair of biomarkers is selected from the group consisting of hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-24-3p, and hsa-miR-378c/hsa-miR-148a-5p.

[0026]   In some embodiments, of the pair of biomarkers or panel of biomarkers comprising a pair of biomarkers, the pair of biomarkers is selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, and hsa-miR-484/hsa-miR-516b-5p .

[0027]   In some embodiments, of the pair of biomarkers or panel of biomarkers comprising a pair of biomarkers, the pair of biomarkers is selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, and hsa-miR-30c-5p/hsa-miR-7-5p.

[0028]   In some embodiments, of the pair of biomarkers or panel of biomarkers comprising a pair of biomarkers, the pair of biomarkers is selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, and hsa-miR-485-5p/hsa-miR-516b-5p.

[0029]   In some embodiments, of the pair of biomarkers or panel of biomarkers comprising a pair of biomarkers, the pair of biomarkers is selected from the group consisting of hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-516b-5p/ hsa-miR-423-5p and hsa-miR-155-5p/ hsa-let-7i-5p.

[0030]   In one aspect, the invention provides a composition of labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to at least one of the biomarkers selected from the group consisting of the biomarkers listed in Table 5.

[0031]   In one aspect, the invention provides a composition of labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to at least one of the biomarkers selected from the group consisting of hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, hsa-miR-1323, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p.

[0032]   In some embodiments, the at least one biomarker is selected from the group consisting of hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, and hsa-miR-1323.

[0033]   In some embodiments, the at least one biomarker is selected from the group consisting of hsa-miR-30c-5p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p.

[0034]   In some embodiments, the at least one biomarker is selected from the group consisting of hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-760, hsa-miR-6747-3p, hsa-miR-181d-5p and hsa-miR-4446-3p.

[0035]   In one aspect, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising measuring the amount of two or more of the nucleic acid biomarkers listed in Tables 3, 4 or 5 in a biological sample obtained from the pregnant female, and calculating a risk score based upon the measured amounts of the nucleic acid biomarkers to determine the pregnant female's risk of developing placental dysfunction. In some embodiments, the method further comprises the step of providing a score corresponding to the pregnant female's risk of developing placental dysfunction.

[0036]   In one aspect, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising producing labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to two or more of the nucleic acid biomarkers listed in Tables 3, 4 or 5 in a biological sample obtained from the pregnant female; measuring the levels of expression of the labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules; calculating a risk score based upon the measured levels of the labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, to determine the pregnant female's risk of developing placental dysfunction. In some embodiments, the method further comprises the step of providing a score corresponding to the pregnant female's risk of developing placental dysfunction.

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[0037]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction, wherein the biological sample is obtained between 17 and 28 weeks of gestational age at blood draw.

[0038]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction, wherein the biological sample is obtained between 19 and 27 weeks of gestational age at blood draw.

[0039]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction, wherein the biological sample is obtained between 17 and 36 weeks of gestational age at blood draw.

[0040]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction, wherein the biological sample is obtained more than 17, more than 18, more than 19, more than 20, more than 21, more than 22, more than 23, more than 24, more than 25, more than 26, more than 27, more than 28, more than 29, more than 30, more than 31, more than 32, more than 33, more than 34, or more than 35 weeks of gestational age at blood draw.

[0041]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction, wherein the biological sample is obtained between 119-153 days, 154-196 days, and/or 119-202 days.

[0042]   In one aspect, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising measuring the amount of two or more of the nucleic acid biomarkers selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941 in a biological sample obtained from the pregnant female, calculating a risk score based upon the measured amounts of the nucleic acid biomarkers to determine the pregnant female's risk of developing placental dysfunction, and providing a score corresponding to the pregnant female's risk of developing placental dysfunction.

[0043]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising measuring the amount of two or more of the nucleic acid biomarkers selected from the group consisting of hsa-miR-1-3p, hsa-miR-181d-5p, hsa-miR-378d, hsa-miR-4433b-5p, and hsa-miR-27a-5p.

[0044]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising measuring the amount of two or more of the nucleic acid biomarkers selected from the group consisting of hsa-miR-516b-5p and hsa-miR-30c-5p.

[0045]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising measuring the amount of two or more of the nucleic acid biomarkers selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, and hsa-miR-331-3p.

[0046]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising measuring the amount of two or more of the nucleic acid biomarkers selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, and hsa-miR-181d-5p. In one aspect, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising producing labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to two or more of the nucleic acid biomarkers selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941 in a biological sample obtained from the pregnant female; measuring the levels of expression of the labeled and/or amplified nucleic acid molecules; calculating a risk score based upon the measured levels of the labeled and/or amplified nucleic acid molecules to determine the pregnant female's risk of developing placental dysfunction.

[0047]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising producing labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to hsa-miR-1-3p, hsa-miR-181d-5p, hsa-miR-378d, hsa-miR-4433b-5p, and/or hsa-miR-27a-5p.

[0048]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising producing labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to hsa-miR-516b-5p and/or hsa-miR-30c-5p.

[0049]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising producing labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, and/or hsa-miR-331-3p.

[0050]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising producing labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, and/or hsa-miR-331-3p.

[0051]   In one aspect, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising measuring the amount of a pair of biomarkers selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-

5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a in a biological sample obtained from the pregnant female, calculating a risk score based upon the measured amounts of the nucleic acid biomarker pair to determine the pregnant female's risk of developing

placental dysfunction, and providing a score corresponding to the pregnant female's risk of developing placental dysfunction.

[0052]   In some embodiments, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising measuring the amount of a pair of biomarkers selected from the group consisting of hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-24-3p, and hsa-miR-378c/hsa-miR-148a-5p.

[0053]   In some embodiments, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising measuring the amount of a pair of biomarkers selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, and hsa-miR-484/hsa-miR-516b-5p.

[0054]   In some embodiments, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising measuring the amount of a pair of biomarkers selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, and hsa-miR-30c-5p/hsa-miR-7-5p.

[0055]   In some embodiments, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising measuring the amount of a pair of biomarkers selected from the group consisting of hsa-miR-140-3p/hsa-

miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, and hsa-miR-485-5p/hsa-miR-516b-5p.

[0056]   In some embodiments, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising measuring the amount of a pair of biomarkers selected from the group consisting of hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-516b-5p/ hsa-miR-423-5p and hsa-miR-155-5p/ hsa-let-7i-5p.

[0057]   In one aspect, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising producing labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to a pair of biomarkers selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-361-5, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p,

hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a in a biological sample obtained from the pregnant female; measuring the levels of expression of the labeled and/or amplified nucleic acid molecules; calculating a risk score based upon the measured levels of the labeled and/or amplified nucleic acid molecules to determine the pregnant female's risk of developing placental dysfunction. in a biological sample obtained from the pregnant female; measuring the levels of expression of the labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules; calculating a risk score based upon the measured levels of the labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, to determine the pregnant female's risk of developing placental dysfunction. In some embodiments, the method further comprises the step of providing a score corresponding to the pregnant female's risk of developing placental dysfunction.

[0058]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising producing

labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to of hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-24-3p, and/or hsa-miR-378c/hsa-miR-148a-5p.

[0059]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising producing labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, and/or hsa-miR-484/hsa-miR-516b-5p.

[0060]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising producing labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, and/or hsa-miR-30c-5p/hsa-miR-7-5p.

[0061]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising producing labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-

516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, and/or hsa-miR-485-5p/hsa-miR-516b-5p.

[0062]   In some embodiments, invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising producing labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-516b-5p/ hsa-miR-423-5p and/or hsa-miR-155-5p/ hsa-let-7i-5p.

[0063]   In some embodiments of methods of the invention, the risk score is calculated based on a ratio of data values. In some embodiments of methods of the invention, data transformation is applied before or after the ratio is determined.

[0064]   In one aspect, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction comprising measuring the amount of at least one of the nucleic acid biomarkers selected from the group consisting of hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, hsa-miR-1323, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p in a biological sample obtained from the pregnant female, calculating a risk score based upon the measured amounts of the nucleic acid biomarkers to determine the pregnant female's risk of developing placental dysfunction, and providing a score corresponding to the pregnant female's risk of developing placental dysfunction.

[0065]   In some embodiments, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction comprising measuring the amount of at least one biomarker selected from the group consisting of hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, and hsa-miR-1323.

[0066]   In some embodiments, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction comprising measuring the amount of at least one biomarker selected from the group consisting of hsa-miR-30c-5p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p.

[0067]   In some embodiments, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction comprising measuring the amount of at least one biomarker selected from the group consisting of hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-760, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p.

[0068]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction across the full window of gestation. In some embodiments, the full gestation window of gestation is between 119-202 days of gestation.

[0069]   In some embodiments, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction early in the pregnancy. In some embodiments, early pregnancy is between 119-153 days of gestation.

[0070]   In some embodiments, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy. In some embodiments, late pregnancy is between 154-196 days of gestation.

[0071]   In one aspect, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction comprising producing labeled and/or amplified nucleic acid molecules that correspond to at least one of the nucleic acid biomarkers selected from the group consisting of hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, hsa-miR-1323, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p in a biological sample obtained from the pregnant female; measuring the levels of expression of the labeled and/or amplified nucleic acid molecules; calculating a risk score based upon the measured levels of the labeled and/or amplified nucleic acid molecules to determine the pregnant female's risk of developing placental dysfunction.

[0072]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction comprising producing labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to

hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, and hsa-miR-1323.

[0073]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction comprising producing labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to hsa-miR-30c-5p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p.

[0074]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction comprising producing labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-760, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p.

[0075]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction across the full window of gestation. In some embodiments, the full gestation window of gestation is between 119-202 days of gestation.

[0076]   In some embodiments, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction early in the pregnancy. In some embodiments, early pregnancy is between 119-153 days of gestation.

[0077]   In some embodiments, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy. In some embodiments, late pregnancy is between 154-196 days of gestation.

[0078]   In one aspect, the invention provides a method of treating or preventing placental dysfunction in a pregnant female, the method comprising: (a) detecting a panel of isolated nucleic acid biomarkers in a biological sample obtained from a pregnant female, wherein at least one of the isolated nucleic acid biomarkers is selected from the group consisting of hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, hsa-miR-1323, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p, (b) calculating a risk score based upon the

measured levels of the isolated nucleic acid biomarkers; and (c) administering one or more therapies to the pregnant female based on the risk score, to treat or prevent placental dysfunction.

[0079]   In some embodiments, the invention provides a method of treating or preventing placental dysfunction wherein at least one of the biomarkers is selected from the group consisting of hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, and hsa-miR-1323.

[0080]   In some embodiments, the invention provides a method of treating or preventing placental dysfunction wherein at least one of the biomarkers of hsa-miR-30c-5p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p.

[0081]   In some embodiments, the invention provides a method of treating or preventing placental dysfunction wherein at least one of the biomarkers hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-760, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p.

[0082]   In some embodiments, the isolated nucleic acid biomarkers are normalized. In further embodiments, normalization comprises a reversal. In some embodiments, the reversal comprises an upregulated biomarker and a downregulated biomarker. In some embodiments, the reversal comprises a numerator and a denominator. In further embodiments, the downregulated biomarker is hsa-miR-485-5p. In other embodiments, the denominator is hsa-miR-485-5p.

[0083]   In some embodiments, the invention provides a method wherein the risk score is calculated based on the reversal of data values.

[0084]   In some embodiments, the method further comprises a step of determining gestational age at blood draw (GABD). In further embodiments, the method comprises determining GABD before detecting the biomarker. In some embodiments, GABD is between 119-153 days, 154-196 days and/or 119-202 days.

[0085] In some embodiments, the invention provides a method of treating or preventing placental dysfunction across the full window of gestation. In some embodiments, the full gestation window of gestation is between 119-202 days of gestation.

[0086] In some embodiments, the invention provides a method of treating or preventing placental dysfunction early in the pregnancy. In some embodiments, early pregnancy is between 119-153 days of gestation.

[0087] In some embodiments, the invention provides a method of treating or preventing placental dysfunction later in the pregnancy. In some embodiments, late pregnancy is between 154-196 days of gestation.

[0088] In some embodiments, the placental dysfunction is preeclampsia.

[0089] Other features and advantages of the invention will be apparent from the detailed description, and from the claims.

DETAILED DESCRIPTION

[0090] The present disclosure is based, generally, on the discovery that the concentration of certain extracellular microRNA (miRNA) biomarkers present in the maternal circulation during pregnancy predicts subsequent risk of developing placental dysfunction later in the pregnancy. For each of the miRNA biomarkers disclosed herein, the concentration of miRNA in the maternal circulation is altered in women who subsequently develop placental dysfunction. Advantageously, expression levels of these miRNA biomarkers can be measured from blood samples, thereby providing a minimally-invasive means for prediction of placental dysfunction, which can manifest as preeclampsia, intrauterine growth restriction, preterm birth (PTB), preterm labor, preterm premature rupture of membranes, late spontaneous abortion and abruption placentae.

[0091] The present disclosure is further specifically based, in part, on the unexpected discovery that single-miRNA biomarker and pairs of miRNA biomarkers disclosed herein can be utilized in methods of predicting a pregnant female's risk of developing placental dysfunction later in the pregnancy. Each of the miRNA biomarkers and clinical variables disclosed herein,

either alone or as components of pairs, ratios and/or reversal pairs serve as biomarkers for determining a pregnant women's risk of developing placental dysfunction later in the pregnancy.

[0092]   A reversal value is the ratio of the abundance of an up regulated biomarker over a down regulated biomarker and serves to both normalize variability and amplify diagnostic signal. The invention lies, in part, in the selection of particular biomarkers that, when paired together, can accurately determine a pregnant female's risk of developing placental dysfunction later in the pregnancy. Accordingly, it is human ingenuity in selecting the specific biomarkers that are informative upon being paired, for example, in novel reversals, and/or the data transformations, for example the ratio of log values, in forming said reversals, that underlies the present invention.

[0093]   The disclosure provides single-miRNA biomarkers and pairs of miRNA biomarkers as well as associated panels, methods and kits for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy.

[0094]   In addition to the specific miRNA biomarkers identified in this disclosure, for example, by name, sequence, or reference, the invention also contemplates use of biomarker variants that are at least 90% or at least 95% or at least 97% identical to the exemplified sequences and that are now known or later discovered and that have utility for the methods of the invention. These variants may represent polymorphisms, splice variants, mutations, and the like. In this regard, the instant specification discloses multiple art-known analytes in the context of the invention and provides exemplary peptide sequences that can be used to identify these analytes. However, those skilled in the art appreciate that additional sequences or other information can easily be identified that can provide additional characteristics of the disclosed biomarkers and that the exemplified references are in no way limiting with regard to the disclosed nucleic acid.

[0095]   As described herein, various techniques and reagents find use in the methods of the present invention. Suitable samples in the context of the present invention include, for example, blood, plasma, serum, amniotic fluid, vaginal secretions, saliva, and urine. In some embodiments, the biological sample is selected from the group consisting of whole blood, plasma, and serum. In a particular embodiment, the biological sample is serum. As described herein, nucleic acid can be detected through a variety of assays and techniques known in the art.

[0096]   The miRNA biomarkers that can be components of reversal pairs described herein include, for example, the miRNA biomarkers listed in Table 4.

[0097]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy, the method comprising measuring in a biological sample obtained from the pregnant female a reversal value for one or more of the biomarker pairs listed in Table 4.

[0098]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy, the method comprising measuring in a biological sample obtained from the pregnant female a reversal value for one pair of biomarkers selected from the biomarker pairs listed in Table 4.

[0099]   In some embodiments, the invention provides a pair of isolated biomarkers selected from the biomarker pairs listed in Table 4, wherein the pair of biomarkers exhibits a higher ratio in pregnant females that will develop placental dysfunction later in the pregnancy relative to pregnant females that will not develop placental dysfunction.

[00100]   In one embodiment, the present invention provides a composition comprising a pair of isolated biomarkers selected from the group consisting of the biomarker pairs listed in Table 4, wherein the pair of biomarkers exhibits a higher ratio in pregnant females that will develop placental dysfunction later in the pregnancy relative to pregnant females that will not develop placental dysfunction.

[00101]   In one embodiment, the biological sample is selected from the group consisting of whole blood, plasma, and serum. In one embodiment, the biological sample is serum. In some embodiments, the sample is obtained between 17 and 28 weeks of gestational age at blood draw (GABD). In some embodiments, the samples is obtained between 17 and 29 weeks. In some embodiments, the sample is obtained between 19 and 27 weeks. In some embodiments, the sample is obtained between 18 and 21 weeks. In further embodiments, the sample is obtained between 23 and 28 weeks of GABD. In some embodiments, the sample is obtained between 18 and 28 weeks of GABD. In some embodiments, the sample is obtained between 18 and 36 weeks of GABD. In further embodiments the sample is obtained between 19 and 21 weeks of GABD.

In some embodiments, the sample is obtained between 20 and 22 weeks of GABD. In some embodiments, the sample is obtained between 21 and 23 weeks of GABD. In further embodiments, the sample is obtained between 22 and 24 weeks of GABD. In additional embodiments, the sample is obtained between 23 and 25 weeks of GABD. In some embodiments, the sample is obtained between 24 and 26 weeks of GABD. In further embodiments, the sample is obtained between 25 and 27 weeks of GABD. In additional embodiments, the sample is obtained between 26 and 28 weeks of GABD. In some embodiments, the sample is obtained between 27 and 29 weeks of GABD. In further embodiments, the sample is obtained between 28 and 30 weeks of GABD. In additional embodiments, the sample is obtained between 29 and 31 weeks of GABD. In some embodiments, the sample is obtained between 30 and 32 weeks of GABD. In further embodiments, the sample is obtained between 31 and 33 weeks of GABD. In additional embodiments, the sample is obtained between 32 and 34 weeks of GABD. In some embodiments, the sample is obtained between 33 and 35 weeks of GABD. In further embodiments, the sample is obtained between 34 and 36 weeks of GABD. In additional embodiments, the sample is obtained between 17 and 36 weeks. In further embodiments, the sample is obtained more than 17, more than 18, more than 19, more than 20, more than 21, more than 22, more than 23, more than 24, more than 25, more than 26, more than 27, more than 28, more than 29, more than 30, more than 31, more than 32, more than 33, more than 34 or more than 35 weeks of GABD.

[00102]   In some embodiments, the sample is obtained between 119 and 202 days of GABD. In further embodiments, the sample is obtained between 119 and 152 days of GABD. In some embodiments, the sample is obtained between 119 and 153 days of GABD. In some embodiments, the sample is obtained between 138 and 172 days of GABD. In further embodiments, the sample is obtained between 154 and 196 days of GABD. In other embodiments, the samples is obtained between 156 and 196 days of GABD. In additional embodiments, the sample is obtained between 119 and 252 days. In further embodiments, the sample is obtained more than 119, more than 126, more than 133, more than 140, more than 147, more than 154, more than 161, more than 168, more than 175, more than 182, more than 189, more than 196, more than 203, more than 210, more than 217, more than 224, more than 231, more than 238, or more than 245 days of GABD.

[00103] In addition to the specific biomarkers, the disclosure further includes biomarker variants that are about 90%, about 95%, or about 97% identical to the exemplified sequences. Variants, as used herein, include polymorphisms, splice variants, mutations, and the like. Although described with reference to nucleic acid biomarkers, changes in reversal value can be identified at the gene expression level or protein level for pairs of biomarkers.

[00104] The compositions and methods of the invention also can include clinical variables, including but not limited to, maternal characteristics, medical history, past pregnancy history, and obstetrical history. Such additional clinical variables can include, for example, previous low birth weight or preterm delivery, multiple 2nd trimester spontaneous abortions, prior first trimester induced abortion, familial and intergenerational factors, history of infertility, parity, nulliparity, placental abnormalities, cervical and uterine anomalies, short cervical length measurements, gestational bleeding, intrauterine growth restriction, in utero diethylstilbestrol exposure, multiple gestations, infant sex, short stature, low prepregnancy weight, low or high body mass index, diabetes, diabetes mellitus, chronic diabetes, chronic diabetes mellitus, chronic hypertension, urogenital infections (i.e. urinary tract infection), asthma, anxiety and depression, asthma, hypertension, hypothyroidism, high body mass index (BMI), low BMI, BMI. Demographic risk indicia for preterm birth can include, for example, maternal age, race/ethnicity, single marital status, low socioeconomic status, maternal age, employment-related physical activity, occupational exposures and environment exposures and stress. Further clinical variables can include, inadequate prenatal care, cigarette smoking, use of marijuana and other illicit drugs, cocaine use, alcohol consumption, caffeine intake, maternal weight gain, dietary intake, sexual activity during late pregnancy and leisure-time physical activities. (Preterm Birth: Causes, Consequences, and Prevention, Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes; Behrman RE, Butler AS, editors. Washington (DC): National Academies Press (US); 2007). Additional clinical variables useful for as markers can be identified using learning algorithms known in the art, such as linear discriminant analysis, support vector machine classification, recursive feature elimination, prediction analysis of microarray, logistic regression, CART, FlexTree, LART, random forest, MART, and/or survival analysis regression, which are known to those of skill in the art and are further described herein.

[00105]   The present disclosure describes and exemplifies various models and corresponding biomarkers that perform at high levels of accuracy and precision in determining a pregnant female's risk of developing placental dysfunction later in the pregnancy. In some embodiments, the markers disclosed herein are predictive across the entire GABD range. In some embodiments, the entire GABD range represents from 17 to 36 weeks. In further embodiments, the entire GABD range represents more than 17, more than 18, more than 19, more than 20, more than 21, more than 22, more than 23, more than 24, more than 25, more than 26, more than 27, more than 28, more than 29, more than 30, more than 31, more than 32, more than 33, more than 34 or more than 35 weeks. In additional embodiments, the entire GABD range represents more than 119, more than 126, more than 133, more than 140, more than 147, more than 154, more than 161, more than 168, more than 175, more than 182, more than 189, more than 196, more than 203, more than 210, more than 217, more than 224, more than 231, more than 238, or more than 245 days of GABD

[00106]   It will be understood by those of skill in the art, that other models are known in the art that can be used to practice the claimed inventions and that the performance of a model can be evaluated in a variety of ways, including, but not limited to accuracy, precision, recall/sensitivity, weighted average of precision and recall. Models known in the art include, without limitation, linear discriminant analysis, support vector machine classification, recursive feature elimination, prediction analysis of microarray, logistic regression, CART, FlexTree, LART, random forest, MART, and/or survival analysis regression.

[00107]   In some embodiments, performance of a model can be evaluated based on accuracy. For example, accuracy can be expressed as the percentage of time, for example, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 80% or more that a model accurately predicts a pregnant female's risk of developing placental dysfunction later in the pregnancy.

[00108]   The present disclosure is based in part on the surprising discovery that the selection of certain biomarkers and/or clinical variables enables determining a pregnant female's risk of developing placental dysfunction later in the pregnancy.

[00109] It must be noted that, as used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the content clearly dictates otherwise and are used interchangeably with "at least one" and "one or more." Thus, for example, reference to "a biomarker" includes a mixture of two or more biomarkers, and the like.

[00110] The term "about," particularly in reference to a given quantity, is meant to encompass deviations of plus or minus five percent.

[00111] As used herein, the terms "comprises," "comprising," "includes," "including," "contains," "containing," and any variations thereof, are intended to cover a non-exclusive inclusion, such that a process, method, product-by-process, or composition of matter that comprises, includes, or contains an element or list of elements does not include only those elements but can include other elements not expressly listed or inherent to such process, method, product-by-process, or composition of matter.

[00112] As used herein, the term "panel" refers to a composition, such as an array or a collection, comprising one or more biomarkers. The term can also refer to a profile or index of expression patterns of one or more biomarkers described herein. The number of biomarkers useful for a biomarker panel is based on the sensitivity and specificity value for the particular combination of biomarker values. The term can also refer to a profile or index of expression patterns of two or more biomarkers described herein. The number of biomarkers useful for a biomarker panel can, in some embodiments, be based on the sensitivity and specificity value for the particular combination of biomarker values. Biomarkers in a panel, or the panel as a unit, can be combined in some embodiments of the invention with other markers, including other biomarkers and/or clinical or demographic variables (e.g., BMI, GABD). Such combinations can be used to derive combined scores predictive of, and which can in turn be used to treat, pregnancy dysfunction.

[00113] As used herein, and unless otherwise specified, the terms "isolated" and "purified" generally describes a composition of matter that has been removed from its native environment (e.g., the natural environment if it is naturally occurring), and thus is altered by the hand of man from its natural state so as to possess markedly different characteristics with regard to at least

one of structure, function and properties. An isolated protein or nucleic acid is distinct from the way it exists in nature and includes synthetic nucleic acids, peptides and proteins.

[00114]   The term "biomarker" refers to a biological molecule, a fragment of a biological molecule, or a clinical variable the change and/or the detection of which can be correlated with a particular physical condition or state. The terms "marker" and "biomarker" are used interchangeably throughout the disclosure. For example, the biomarkers of the present invention are associated with a discrimination power between pregnant females that will develop placental dysfunction later in the pregnancy versus those that will not develop placental dysfunction. Such biomarkers include any suitable analyte, but are not limited to, biological molecules comprising nucleotides, nucleic acids, nucleosides, amino acids, sugars, fatty acids, steroids, metabolites, peptides, polypeptides, proteins, carbohydrates, lipids, hormones, antibodies, regions of interest that serve as surrogates for biological macromolecules and combinations thereof (*e.g.*, glycoproteins, ribonucleoproteins, lipoproteins). The term also encompasses miRNAs and portions or fragments of a miRNAs.

[00115]   As used herein, the term "reversal" refers to the ratio of the measured value of one or more analytes (or some conversion or representation thereof) over that of one or more analytes, wherein the analytes provide some partially independent information. In some embodiments, the analyte value (or its representation) is itself a normalized value of the measured endogenous analyte relative to, e.g., values in the same processing batch referred to herein as: response ratio or relative ratio. For example, as exemplified herein, hsa-miR-516-5p/hsa-miR-485-5p is a ratio of an up-regulated analyte in the numerator and a down-regulated analyte in the denominator, which is defined herein as a "reversal pair." A ratio of two up-regulated analytes in the numerator and one down-regulated analyte in the denominator, which is within the definition of a "reversal triplet" defined herein. In some embodiments, "/" is inclusive of but not limited to division, taking a root or difference. In other embodiments, "+" is inclusive of but not limited to addition, taking a power or multiplication. In all instances, one analyte in a reversal may serve to normalize another analyte (*e.g.* decrease variability due to biomedical conditions not of interest, or sample pre-analytical or analytical variability). In the particular case of a ratio that is a "reversal" both amplification of diagnostic signal and normalization are possible. It is

understood, that the methods of the invention are not limited to the subset of reversals, but also encompass ratios of biomarkers.

[00116] As used herein, the term "reversal pair" refers to biomarkers in pairs where a mathematical combination of the values of the pair exhibits a change in value between the classes being compared. The detection of reversals in analyte (*i.e.* miRNA) concentrations eliminates the need for data normalization or the establishment of population-wide thresholds, and requires only that the levels of two or more biomarkers change relative to each other. Encompassed within the definition of any reversal pair is the corresponding reversal pair wherein individual biomarkers are switched between the numerator and denominator. One skilled in the art will appreciate that such a corresponding reversal pair is equally informative with regard to its predictive power.

[00117] The term "reversal value" refers to the ratio of the abundance of two analytes and serves to both normalize variability and amplify diagnostic signal. In some embodiments, a reversal value refers to the ratio of the abundance of an up-regulated (interchangeably referred to as "over-abundant," up-regulation as used herein simply refers to an observation of abundance) analyte over a down-regulated analyte (interchangeably referred to as "under-abundant," down-regulation as used herein simply refers to an observation of relative abundance). In some embodiments, a reversal value refers to the ratio of an up-regulated analyte over an up-regulated analyte, where one analyte differs in the degree of up-regulation relative the other analyte. In some embodiments, a reversal value refers to the ratio a down-regulated analyte over a down-regulated analyte, where one analyte differs in the degree of down-regulation relative the other analyte. In some embodiments a reversal value refers to the ratio of a regulated analyte (up or down) and an analyte that is un-regulated. In this case the un-regulated analyte can still serve to normalize. In some embodiments, a reversal value refers to the ratio of two analytes that are un-regulated or whose directions of regulation are unknown. In this case, the un-regulated analytes can still serve to normalize each other and to reveal a diagnostic signal.

[00118] One advantageous aspect of a reversal is the presence of complementary information in the two analytes, so that the combination of the two is more diagnostic of the condition of

interest than either one alone. Preferably the combination of the two analytes increases signal-to-noise ratio by compensating for biomedical conditions not of interest, pre-analytic variability and/or analytic variability. Out of all the possible reversals within a narrow window, a subset can be selected based on individual univariate performance. Additionally, a subset can be selected based on bivariate or multivariate performance in a training set, with testing on held-out data or on bootstrap iterations. For example, logistic or linear regression models can be trained, optionally with parameter shrinkage by L1 or L2 or other penalties, and tested in leave-one-out, leave-pair-out or leave-fold-out cross-validation, or in bootstrap sampling with replacement, or in a held-out data set. As disclosed herein, the ratio of the abundance of two analytes, for example, the ratio of an up-regulated biomarker over a down-regulated biomarker, referred herein as a reversal value, can be used to identify robust and accurate classifiers and predict a pregnant female's risk of developing placental dysfunction later in the pregnancy

[00119] Use of a ratio of biomarkers in the methods disclosed herein corrects for variability that is the result of human manipulation after the removal of the biological sample from the pregnant female. Such variability can be introduced, for example, during sample collection, processing, depletion, digestion or any other step of the methods used to measure the biomarkers present in a sample and is independent of how the biomarkers behave in nature. Accordingly, the invention generally encompasses the use of a reversal pair in a method of diagnosis or prognosis to reduce variability and/or amplify, normalize or clarify diagnostic signal.

[00120] While the term reversal value can refer to the ratio of the abundance of an up regulated analyte over a down regulated analyte and serves to both normalize variability and amplify diagnostic signal, it is also contemplated that a pair of biomarkers of the invention could be treated in a classifier by any other means, for example, by subtraction, addition or multiplication of abundances. In addition, it is contemplated that a value can be mathematically converted to a different value and used to determine a ratio. For example, as disclosed herein, reversals can be constructed as the ratios of the logarithm (log) values. Similarly, ratios can be mathematically converted, for example, as the log of the ratioed values. The methods disclosed herein encompass the measurement of biomarker pairs by such other means. A person skilled in the art will readily understand suitable data transformations that can be applied to identify biomarkers predictive of placental dysfunction, including the data transformations disclosed

herein. Exemplary transformations include, but are not limited to, box-cox, root, inverse, rank and log. Such data transformations are well known in the art, for example, root (where the root transformation is selected as appropriate for the data set, such as 2, 3, 4, and higher, as appropriate), inverse (1/X), rank (assigning to an ordered list based on appropriate criteria), and so forth, as is well known in the art.

[00121] This method is advantageous because it provides the simplest possible classifier that may be independent of data normalization, helps to avoid overfitting, and results in a very simple experimental test that is easy to implement in the clinic. In some uses of the term "reversal" it refers to the identification of analyte pairs where the relative expression (rank order) of each member of a pair reverses in the two conditions studied (e.g. cancer vs not cancer, placental dysfunction vs not). Reversal, as it is used here, allows for there to be opposing regulation of the two members of the pair (e.g., up or down), but does not require that their rank order in abundance to "reverse" in the different clinical conditions. The use of marker pairs based on changes in reversal values that are independent of data normalization enabled the development of the clinically relevant biomarkers disclosed herein. Because quantification of any single analyte is subject to uncertainties caused by measurement variability, normal fluctuations, and individual related variation in baseline expression, identification of pairs of markers that may be under coordinated, systematic regulation enables robust methods for diagnosis and prognosis.

[00122] While the specification discloses embodiments directed to measuring the particular pairs of biomarkers disclosed in Table 4, the invention is not restricted to the particular pairs recited in Table 4 and individual biomarkers disclosed herein, for example, in Table 3, as well as any pair or panel of the individual biomarkers is also encompassed by the present invention, as are methods comprising one or more pairs of biomarkers, for example, pairs of biomarkers comprising the biomarkers of Tables 3, 4 or 5. It is understood that the univariate and bivariate biomarkers disclosed herein, for example, in Tables 3, 4 or 5, can be used as biomarkers, either singly, in combinations of 2 or more biomarkers, as panels, or in combination with other variables (for example, proteins, metabolites, other molecules, clinical factors, and/or demographic factors) to predict placental dysfunction, such as preeclampsia, as disclosed herein. A person skilled in the art can readily contemplate these and/or additional parameters that can be combined with the biomarkers disclosed herein to predict placental dysfunction.

[00123]   In addition to biomarkers, measurable features can further include clinical variables including, for example, maternal characteristics, age, race, ethnicity, medical history, past pregnancy history, obstetrical history. For a risk indicium, a measurable feature can include, for example, previous low birth weight or preterm delivery, multiple 2nd trimester spontaneous abortions, prior first trimester induced abortion, familial and intergenerational factors, history of infertility, nulliparity, placental abnormalities, cervical and uterine anomalies, short cervical length measurements, gestational bleeding, intrauterine growth restriction, in utero diethylstilbestrol exposure, multiple gestations, infant sex, short stature, low prepregnancy weight/low body mass index, diabetes, hypertension, urogenital infections, hypothyroidism, asthma, low educational attainment, cigarette smoking, drug use and alcohol consumption, prior miscarriage, prior stillbirth, Body Mass Index (BMI), maternal age, parity, gravidity, fetal gender, height and weight separately from BMI, race and socioeconomic status. Additional markers can include, for example, previous low birth weight or preterm delivery, multiple 2nd trimester spontaneous abortions, prior first trimester induced abortion, familial and intergenerational factors, history of infertility, nulliparity, gravidity, primigravida, multigravida, placental abnormalities, cervical and uterine anomalies, short cervical length measurements, gestational bleeding, intrauterine growth restriction, in utero diethylstilbestrol exposure, multiple gestations, infant sex, short stature, low prepregnancy weight, low or high body mass index, diabetes, hypertension, urogenital infections (i.e. urinary tract infection), asthma, anxiety and depression, asthma, hypertension, hypothyroidism, low educational attainment, drug use and alcohol consumption. Demographic risk indicia for preterm birth can include, for example, maternal age, race/ethnicity, single marital status, low socioeconomic status, maternal age, employment-related physical activity, occupational exposures and environment exposures and stress. Further risk indicia can include, inadequate prenatal care, cigarette smoking, use of marijuana and other illicit drugs, cocaine use, alcohol consumption, caffeine intake, maternal weight gain, dietary intake, sexual activity during late pregnancy and leisure-time physical activities. (Preterm Birth: Causes, Consequences, and Prevention, Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes; Behrman RE, Butler AS, editors. Washington (DC): National Academies Press (US); 2007). Additional risk indicia useful for as markers can be identified using learning algorithms known in the art, such as linear discriminant analysis, support vector machine classification, recursive feature elimination,

prediction analysis of microarray, logistic regression, CART, FlexTree, LART, random forest, MART, and/or survival analysis regression, which are known to those of skill in the art and are further described herein.

[00124]   In some embodiments, the methods of the invention comprise calculation of body mass index (BMI).

[00125]   As used herein, the term "risk score" refers to a score that can be assigned based on comparing the amount of one or more biomarkers or reversal values in a biological sample obtained from a pregnant female to a standard or reference score that represents an average amount of the one or more biomarkers calculated from biological samples obtained from a random pool of pregnant females. Alternatively, the calculated "risk score" can be compared to the average population risk (prevalence of the outcomes). As will be apparent to one of skill in the art, a risk score can represent the positive predictive value (PPV) of the pregnant female's one or more biomarkers or reversal values for occurrence of the event, i.e., placental dysfunction. A risk score can also represent the probability of occurrence of the event given the pregnant female's one or more biomarkers or reversal values. In a simple embodiment, the pregnant female's risk prior to measurement of biomarkers (pre-test risk) is assigned to be the average population risk (prevalence of the event). Her risk is updated upon measurement of biomarkers and to a post-test risk by calculation of the risk score. An individual pre-test risk can also be assigned to a pregnant female based her standard clinical and demographic data, or on individual, family or ancestral health history or genetic data. For example, a pregnant female with a history of prior preeclampsia may have a greater individual risk for placental dysfunction than the average population risk. The calculated risk based on biomarkers can then be an updated (post-test) risk for the current pregnancy, beyond that individual pre-test risk. A calculated risk of placental dysfunction can also be updated by events or information gathered after the test is applied in the current pregnancy. For example, a pregnant female with a calculated risk of placental dysfunction of 30%, but exhibiting later signs or symptoms (e.g., moderately elevated blood pressure) may have an even higher risk of placental dysfunction (>30%) given the combination of the test and the later sign or symptom. In some embodiments, the risk score is expressed as the log of the reversal value, i.e. the ratio of the relative intensities of the individual biomarkers. One skilled in the art will appreciate that a risk score can be expressed based on a

various data transformations as well as being expressed as the ratio itself. Furthermore, with particular regard to reversal pairs, one skilled in the art will appreciate that any ratio is equally informative if the biomarkers in the numerator and denominator are switched or that related data transformations (*e.g.*, subtraction) are applied. Because the level of a biomarker may not be static throughout pregnancy, a standard or reference score has to have been obtained for the gestational time point that corresponds to that of the pregnant female at the time the sample was taken. The standard or reference score can be predetermined and built into a predictor model such that the comparison is indirect rather than actually performed every time the probability is determined for a subject. A risk score can be a standard (*e.g.*, a number) or a threshold (*e.g.*, a line on a graph). The value of the risk score correlates to the deviation, upwards or downwards, from the average amount of the one or more biomarkers calculated from biological samples obtained from a random pool of pregnant females.

[00126] In some embodiments, the methods of the invention can be practiced with samples obtained from pregnant females with a specified BMI. Briefly, BMI is an individual's weight in kilograms divided by the square of height in meters. BMI does not measure body fat directly, but research has shown that BMI is correlated with more direct measures of body fat obtained from skinfold thickness measurements, bioelectrical impedance, densitometry (underwater weighing), dual energy x-ray absorptiometry (DXA) and other methods. Furthermore, BMI appears to be as strongly correlated with various metabolic and disease outcome as are these more direct measures of body fatness. Generally, an individual with a BMI below 18.5 is considered underweight, an individual with a BMI of equal or greater than 18.5 to 24.9 normal weight, while an individual with a BMI of equal or greater than 25.0 to 29.9 is considered overweight and an individual with a BMI of equal or greater than 30.0 is considered obese. In some embodiments, the predictive performance of the claimed methods can be improved with a BMI stratification of equal or greater than 18, equal or greater than 19, equal or greater than 20, equal or greater than 21, equal or greater than 22, equal or greater than 23, equal or greater than 24, equal or greater than 25, equal or greater than 26, equal or greater than 27, equal or greater than 28, equal or greater than 29 or equal or greater than 30. In other embodiments, the predictive performance of the claimed methods can be improved with a BMI stratification of equal or less than 18, equal or less than 19, equal or less than 20, equal or less than 21, equal or less than 22, equal or less than

23, equal or less than 24, equal or less than 25, equal or less than 26, equal or less than 27, equal or less than 28, equal or less than 29 or equal or less than 30.

[00127] In the context of the present invention, the term "biological sample," encompasses any sample that is taken from pregnant female, and particularly from a pregnant human, and contains one or more of the biomarkers disclosed herein. Suitable samples in the context of the present invention include, for example, blood, plasma, serum, amniotic fluid, vaginal secretions, saliva, and urine. In some embodiments, the biological sample is selected from the group consisting of whole blood, plasma, and serum. In a particular embodiment, the biological sample is serum. As will be appreciated by those skilled in the art, a biological sample can include any fraction or component of blood, without limitation, T cells, monocytes, neutrophils, erythrocytes, platelets and microvesicles such as exosomes and exosome-like vesicles. In a particular embodiment, the biological sample is serum.

[00128] The term "amount" or "level" as used herein refers to a quantity of a biomarker that is detectable or measurable in a biological sample and/or control. The quantity of a biomarker can be, for example, the quantity of nucleic acid (*i.e.* miRNA), the quantity of a polypeptide, the quantity of nucleic acid, or the quantity of a fragment or surrogate. The term can alternatively include combinations thereof. The term "amount" or "level" of a biomarker is a measurable feature of that biomarker.

[00129] In some embodiments, nucleic acid amplification methods can be used to detect a polynucleotide biomarker. For example, the oligonucleotide primers and probes of the present invention can be used in amplification and detection methods that use nucleic acid substrates isolated by any of a variety of well-known and established methodologies (e.g., Sambrook *et al.*, Molecular Cloning, A laboratory Manual, pp. 7.37-7.57 (2nd ed., 1989); Lin *et al.*, in Diagnostic Molecular Microbiology, Principles and Applications, pp. 605-16 (Persing *et al.*, eds. (1993); Ausubel *et al.*, Current Protocols in Molecular Biology (2001 and subsequent updates)). Methods for amplifying nucleic acids include, but are not limited to, for example the polymerase chain reaction (PCR) and reverse transcription PCR (RT-PCR) (see e.g., U.S. Pat. Nos. 4,683,195; 4,683,202; 4,800,159; 4,965,188), ligase chain reaction (LCR) (see, e.g., Weiss, Science 254:1292-93 (1991)), strand displacement amplification (SDA) (see e.g., Walker *et al.*, Proc.

Natl. Acad. Sci. USA 89:392-396 (1992); U.S. Pat. Nos. 5,270,184 and 5,455,166),

Thermophilic SDA (tSDA) (see e.g., European Pat. No. 0 684 315), digital PCR (see, e.g.,

Salipante *et al.*, Clin. Chem. doi: 10.1373/clinchem.2019.304048 (2019)), and methods described

in U.S. Pat. No. 5,130,238; Lizardi *et al.*, BioTechnol. 6:1197-1202 (1988); Kwoh *et al.*, Proc.

Natl. Acad. Sci. USA 86:1173-77 (1989); Guatelli *et al.*, Proc. Natl. Acad. Sci. USA 87:1874-78

(1990); U.S. Pat. Nos. 5,480,784; 5,399,491; US Publication No. 2006/46265.

[00130]   In some embodiments, measuring mRNA in a biological sample can be used as a

surrogate for detection of the level of the corresponding protein biomarker in a biological

sample. Thus, any of the biomarkers, biomarker pairs or biomarker reversal panels described

herein can also be detected by detecting the appropriate RNA. Levels of mRNA can measured by

reverse transcription quantitative polymerase chain reaction (RT-PCR followed with qPCR). RT-

PCR is used to create a cDNA from the mRNA. The cDNA can be used in a qPCR assay to

produce fluorescence as the DNA amplification process progresses. By comparison to a standard

curve, qPCR can produce an absolute measurement such as number of copies of mRNA per cell.

Digital PCR is a special case of qPCR, where PCR is performed in many discrete partitions of

the sample, and can be more sensitive and reliable than traditional qPCR (see, e.g., Salipante *et

al.*, Clin. Chem. doi: 10.1373/clinchem.2019.304048 (2019)). Northern blots, microarrays,

Invader assays, and RT-PCR combined with capillary electrophoresis have all been used to

measure expression levels of mRNA in a sample. See Gene Expression Profiling: Methods and

Protocols, Richard A. Shimkets, editor, Humana Press, 2004.

[00131]   In one aspect, the invention provides a panel of isolated nucleic acid biomarkers

comprising two or more of the nucleic acid biomarkers listed in Tables 3, 4 or 5.

[00132]   In a further aspect, the invention provides a panel of isolated nucleic acid biomarkers

comprising two or more of the nucleic acid biomarkers listed in Table 3.

[00133]   In some embodiments, a panel described herein comprises hsa-miR-516b-5p. In

some embodiments, a panel described herein comprises hsa-miR-30c-5p. In some embodiments,

a panel described herein comprises hsa-miR-1-3p. In some embodiments, a panel described

herein comprises hsa-miR-331-3p. In some embodiments, a panel described herein comprises

hsa-miR-485-5p. In some embodiments, a panel described herein comprises hsa-miR-181d-5p.

In some embodiments, a panel described herein comprises hsa-miR-23a-3p. In some embodiments, a panel described herein comprises hsa-miR-378d. In some embodiments, a panel described herein comprises hsa-miR-155-5p. In some embodiments, a panel described herein comprises hsa-miR-99b-3p. In some embodiments, a panel described herein comprises hsa-miR-1249-3p. In some embodiments, a panel described herein comprises hsa-miR-142-3p. In some embodiments, a panel described herein comprises hsa-miR-4433b-5p. In some embodiments, a panel described herein comprises hsa-miR-1273h-3p. In some embodiments, a panel described herein comprises hsa-miR-18a-3p. In some embodiments, a panel described herein comprises hsa-miR-4746-5p. In some embodiments, a panel described herein comprises hsa-miR-27a-5p. In some embodiments, a panel described herein comprises hsa-miR-654-3p. In some embodiments, a panel described herein comprises hsa-miR-7-5p. In some embodiments, a panel described herein comprises hsa-miR-941.

[00134]   In some embodiments, a panel described herein comprises hsa-miR-516b-5p and at least one biomarker selected from the group consisting of hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00135]   In some embodiments, a panel described herein comprises hsa-miR-30c-5p and at least one biomarker selected from the group consisting of hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00136]   In some embodiments, a panel described herein comprises hsa-miR-1-3p and at least one biomarker selected from the group consisting of hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00137]   In some embodiments, a panel described herein comprises hsa-miR-516b-5p and at least one pair of biomarkers selected from the group consisting of hsa-miR-140-3p/hsa-miR-

516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-

5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00138]   In some embodiments, a panel described herein comprises hsa-miR-30c-5p and at least one pair of biomarkers selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-

5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00139] In some embodiments, a panel described herein comprises hsa-miR-1-3p and at least one pair of biomarkers selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-

5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00140] In one aspect, the invention provides a biomarker panel comprising two or more of the isolated nucleic acid biomarkers selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00141] In some embodiments, the biomarker panel comprises isolated nucleic acid biomarkers comprising hsa-miR-1-3p, hsa-miR-181d-5p, hsa-miR-378d, hsa-miR-4433b-5p, and/or hsa-miR-27a-5p. In some embodiments, the biomarker panel comprises isolated nucleic

acid biomarkers comprising hsa-miR-516b-5p and/or hsa-miR-30c-5p . In some embodiments, the biomarker panel comprises isolated nucleic acid biomarkers comprising hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, and/or hsa-miR-331-3p . In some embodiments, the biomarker panel comprises isolated nucleic acid biomarkers comprising hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, and/or hsa-miR-181d-5p.

[00142]   In one aspect, the invention provides a panel of isolated nucleic acid biomarkers comprising two or more of the nucleic acid biomarkers listed in Table 4.

[00143]   In some embodiments, a panel described herein comprises hsa-miR-140-3p/hsa-miR-516b-5p. In some embodiments, a panel described herein comprises hsa-miR-155-5p/hsa-miR-625-3p. In some embodiments, a panel described herein comprises hsa-miR-30c-5p/hsa-miR-27b-3p. In some embodiments, a panel described herein comprises hsa-miR-25-5p/hsa-miR-516b-5p. In some embodiments, a panel described herein comprises hsa-miR-484/hsa-miR-516b-5p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-let-7b-5p. In some embodiments, a panel described herein comprises hsa-miR-30c-5p/hsa-miR-7-5p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-486-5p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-150-5p. In some embodiments, a panel described herein comprises hsa-miR-485-5p/hsa-miR-516b-5p. In some embodiments, a panel described herein comprises hsa-miR-7-5p/hsa-miR-485-5p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-let-7g-5p. In some embodiments, a panel described herein comprises hsa-miR-30c-5p/hsa-miR-16-5p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-423-5p. In some embodiments, a panel described herein comprises hsa-miR-30c-5p/hsa-miR-30a-5p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-92a-3p. In some embodiments, a panel described herein comprises hsa-miR-186-5p/hsa-miR-516b-5p. In some embodiments, a panel described herein comprises hsa-miR-155-5p/hsa-miR-27b-3p. In some embodiments, a panel described herein comprises hsa-miR-30e-5p/hsa-miR-516b-5p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-let-7d-5p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-103a-3p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-126-3p. In some embodiments, a panel described herein comprises hsa-miR-99b-3p/hsa-miR-486-3p. In some

embodiments, a panel described herein comprises hsa-miR-6741-5p/hsa-miR-760. In some embodiments, a panel described herein comprises hsa-miR-20a-5p/hsa-miR-485-5p. In some embodiments, a panel described herein comprises hsa-miR-23a-3p/hsa-miR-27b-3p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-151a-3p. In some embodiments, a panel described herein comprises hsa-miR-30a-5p/hsa-miR-485-5p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-let-7a-5p. In some embodiments, a panel described herein comprises hsa-miR-30c-5p/hsa-miR-27a-3p. In some embodiments, a panel described herein comprises hsa-miR-485-5p/hsa-miR-7-5p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-222-3p. In some embodiments, a panel described herein comprises hsa-miR-23a-3p/hsa-miR-30a-5p. In some embodiments, a panel described herein comprises hsa-miR-433-3p/hsa-miR-345-5p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-let-7f-5p. In some embodiments, a panel described herein comprises hsa-miR-485-5p/hsa-miR-183-5p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-185-5p. In some embodiments, a panel described herein comprises hsa-let-7i-5p/hsa-miR-485-5p. In some embodiments, a panel described herein comprises hsa-miR-4433b-5p/hsa-miR-516b-5p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-191-5p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-3615. In some embodiments, a panel described herein comprises hsa-miR-100-5p/hsa-miR-516b-5p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-10b-5p. In some embodiments, a panel described herein comprises hsa-miR-485-5p/hsa-miR-27a-3p. In some embodiments, a panel described herein comprises hsa-miR-99a-5p/hsa-miR-485-5p. In some embodiments, a panel described herein comprises hsa-miR-99b-3p/hsa-miR-6852-5p. In some embodiments, a panel described herein comprises hsa-miR-363-3p/hsa-miR-485-5p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-484. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-let-7i-5p. In some embodiments, a panel described herein comprises hsa-miR-23a-3p/hsa-miR-181a-5p. In some embodiments, a panel described herein comprises hsa-miR-7-5p/hsa-miR-516b-5p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-328-3p. In some embodiments, a panel described herein comprises hsa-miR-181a-5p/hsa-miR-485-5p. In some embodiments, a panel described herein comprises hsa-miR-155-5p/hsa-miR-30a-5p. In some

embodiments, a panel described herein comprises hsa-miR-155-5p/hsa-let-7i-5p. In some embodiments, a panel described herein comprises hsa-miR-98-5p/hsa-miR-485-5p. In some embodiments, a panel described herein comprises hsa-miR-485-5p/hsa-miR-127-3p. In some embodiments, a panel described herein comprises hsa-miR-320b/hsa-miR-485-5p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-25-3p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-148a-3p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-128-3p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-320a. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-744-5p. In some embodiments, a panel described herein comprises hsa-miR-30c-5p/hsa-miR-186-5p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-629-5p. In some embodiments, a panel described herein comprises hsa-miR-23a-3p/hsa-miR-93-5p. In some embodiments, a panel described herein comprises hsa-miR-127-3p/hsa-miR-485-5p. In some embodiments, a panel described herein comprises hsa-miR-155-5p/hsa-miR-451a. In some embodiments, a panel described herein comprises hsa-miR-30c-5p/hsa-miR-26b-5p. In some embodiments, a panel described herein comprises hsa-miR-4732-3p/hsa-miR-516b-5p. In some embodiments, a panel described herein comprises hsa-miR-7-5p/hsa-miR-941. In some embodiments, a panel described herein comprises hsa-miR-451a/hsa-miR-485-5p. In some embodiments, a panel described herein comprises hsa-miR-374b-5p/hsa-miR-885-3p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-1307-3p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-30d-5p. In some embodiments, a panel described herein comprises hsa-miR-3605-5p/hsa-miR-425-3p. In some embodiments, a panel described herein comprises hsa-miR-501-3p/hsa-miR-516b-5p. In some embodiments, a panel described herein comprises hsa-miR-125b-5p/hsa-miR-485-5p. In some embodiments, a panel described herein comprises hsa-miR-26b-5p/hsa-miR-485-5p. In some embodiments, a panel described herein comprises hsa-miR-30c-5p/hsa-miR-99a-5p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-127-3p. In some embodiments, a panel described herein comprises hsa-miR-501-3p/hsa-miR-485-5p. In some embodiments, a panel described herein comprises hsa-miR-30c-5p/hsa-miR-451a. In some embodiments, a panel described herein comprises hsa-miR-21-5p/hsa-miR-485-5p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-423-3p. In some

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embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-146b-5p. In some embodiments, a panel described herein comprises hsa-miR-330-5p/hsa-miR-92b-5p. In some embodiments, a panel described herein comprises hsa-miR-4443/hsa-miR-485-5p. In some embodiments, a panel described herein comprises hsa-miR-30c-5p/hsa-let-7i-5p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-425-5p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-24-3p. In some embodiments, a panel described herein comprises hsa-miR-146b-5p/hsa-miR-485-5p. In some embodiments, a panel described herein comprises hsa-miR-760/hsa-miR-378g. In some embodiments, a panel described herein comprises hsa-miR-3615/hsa-miR-485-5p. In some embodiments, a panel described herein comprises hsa-miR-140-3p/hsa-miR-485-5p. In some embodiments, a panel described herein comprises hsa-miR-30c-5p/hsa-miR-125a-5p. In some embodiments, a panel described herein comprises hsa-miR-378c/hsa-miR-148a-5p. In some embodiments, a panel described herein comprises hsa-let-7b-5p/hsa-miR-485-5p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-146a-5p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-451a.

[00144]   In some embodiments, a panel described herein comprises hsa-miR-140-3p/hsa-miR-516b-5p and at least one biomarker pair selected from the group consisting of hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-

516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00145]   In some embodiments, a panel described herein comprises hsa-miR-155-5p/hsa-miR-625-3p and at least one biomarker pair selected from the group consisting of hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-

486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00146]   In some embodiments, a panel described herein comprises hsa-miR-30c-5p/hsa-miR-27b-3p and at least one biomarker pair selected from the group consisting of hsa-miR-25-5p/hsa-

miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-

miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00147]   In some embodiments, a panel described herein comprises hsa-miR-140-3p/hsa-miR-516b-5p and at least one biomarker selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00148]   In some embodiments, a panel described herein comprises hsa-miR-155-5p/hsa-miR-625-3p and at least one biomarker selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00149]   In some embodiments, a panel described herein comprises hsa-miR-30c-5p/hsa-miR-27b-3p and at least one biomarker selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00150]   In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-516b-5p/hsa-miR-423-5p and hsa-miR-155-5p/ hsa-let-7i-5p.

[00151]   In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-let-7b-5p and at least one biomarker pair selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-

5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-

miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00152] In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-423-5p and at least one biomarker pair selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-

miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00153] In some embodiments, a panel described herein comprises hsa-miR-155-5p/ hsa-let-7i-5p and at least one biomarker pair selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-

5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00154]　In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-let-7b-5p and at least one biomarker selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00155]　In some embodiments, a panel described herein comprises hsa-miR-516b-5p/hsa-miR-423-5p and at least one biomarker selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-

23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00156] In some embodiments, a panel described herein comprises hsa-miR-155-5p/ hsa-let-7i-5p and at least one biomarker selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00157] In one aspect, the invention provides a panel of isolated nucleic acid biomarkers comprising a pair of biomarkers selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-

485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00158] In some embodiments, the biomarker panel comprises isolated nucleic acid biomarkers comprising hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-24-3p, and/or hsa-miR-378c/hsa-miR-148a-5p.

[00159]   In some embodiments, the biomarker panel comprises isolated nucleic acid biomarkers comprising hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, and/or hsa-miR-484/hsa-miR-516b-5p.

[00160]   In some embodiments, the biomarker panel comprises isolated nucleic acid biomarkers comprising hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, and/or hsa-miR-30c-5p/hsa-miR-7-5p.

[00161]   In some embodiments, the biomarker panel comprises isolated nucleic acid biomarkers comprising hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, and/or hsa-miR-485-5p/hsa-miR-516b-5p.

[00162]   In a further aspect, the invention provides a panel of isolated nucleic acid biomarkers comprising at least one of the nucleic acid biomarkers listed in Table 5. In additional aspects, the invention provides a panel of isolated nucleic acid biomarkers comprising at least one pair of the nucleic acid biomarkers listed in Table 5.

[00163]   In some embodiments, a panel described herein comprises nucleic acid molecules selected from the group consisting of hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, hsa-miR-1323, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p.

[00164]   In some embodiments, a panel described herein comprises hsa-miR-30c-5p- In some embodiments, a panel described herein comprises hsa-miR-6842-3p. In some embodiments, a panel described herein comprises hsa-miR-485-5p. In some embodiments, a panel described herein comprises hsa-miR-331-3p. In some embodiments, a panel described herein comprises hsa-miR-517a-3p-hsa-miR-517b-3p. In some embodiments, a panel described herein comprises hsa-miR-516b-5p. In some embodiments, a panel described herein comprises

hsa-miR-760. In some embodiments, a panel described herein comprises hsa-miR-6852-5p. In some embodiments, a panel described herein comprises hsa-miR-1323. In some embodiments, a panel described herein comprises hsa-miR-155-5p. In some embodiments, a panel described herein comprises hsa-miR-6747-3p. In some embodiments, a panel described herein comprises hsa-miR-181d-5p. In some embodiments, a panel described herein comprises hsa-miR-4446-3p.

[00165]   In some embodiments, a panel described herein comprises hsa-miR-485-5p and at least one biomarker selected from the group consisting of hsa-miR-7-5p, hsa-miR-501-3p, hsa-miR-363-3p, hsa-miR-182-5p, hsa-miR-127-3p, hsa-miR-140-3p, hsa-miR-26b-5p.

[00166]   In some embodiments, a panel described herein comprises hsa-miR-485-5p and at least one pair biomarker selected from the group consisting of hsa-miR-27b-3p, hsa-let-7i-5p, hsa-miR-99a-5p, hsa-miR-409-3p.

[00167]   In some embodiments, a panel described herein comprises hsa-miR-485-5p and two or more biomarkers selected from the group consisting of the additional miRNAs in Table 5.

[00168]   In one aspect, the invention provides a composition of labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to two or more of the nucleic acid biomarkers listed in Tables 3, 4 or 5.

[00169]   In one aspect, the invention provides a composition of labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to two or more of the nucleic acid biomarkers listed in Table 3.

[00170]   In some embodiments, a composition described herein comprises hsa-miR-516b-5p. In some embodiments, a composition described herein comprises hsa-miR-30c-5p. In some embodiments, a composition described herein comprises hsa-miR-1-3p. In some embodiments, a composition described herein comprises hsa-miR-331-3p. In some embodiments, a composition described herein comprises hsa-miR-485-5p. In some embodiments, a composition described herein comprises hsa-miR-181d-5p. In some embodiments, a composition described herein comprises hsa-miR-23a-3p. In some embodiments, a composition described herein comprises hsa-miR-378d. In some embodiments, a composition described herein comprises hsa-miR-155-5p. In some embodiments, a composition described herein comprises hsa-miR-99b-3p. In some

embodiments, a composition described herein comprises hsa-miR-1249-3p. In some embodiments, a composition described herein comprises hsa-miR-142-3p. In some embodiments, a composition described herein comprises hsa-miR-4433b-5p. In some embodiments, a composition described herein comprises hsa-miR-1273h-3p. In some embodiments, a composition described herein comprises hsa-miR-18a-3p. In some embodiments, a composition described herein comprises hsa-miR-4746-5p. In some embodiments, a composition described herein comprises hsa-miR-27a-5p. In some embodiments, a composition described herein comprises hsa-miR-654-3p. In some embodiments, a composition described herein comprises hsa-miR-7-5p. In some embodiments, a composition described herein comprises hsa-miR-941.

[00171] In some embodiments, a composition described herein comprises hsa-miR-516b-5p and at least one biomarker selected from the group consisting of hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00172] In some embodiments, a composition described herein comprises hsa-miR-30c-5p and at least one biomarker selected from the group consisting of hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00173] In some embodiments, a composition described herein comprises hsa-miR-1-3p and at least one biomarker selected from the group consisting of hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00174] In some embodiments, a composition described herein comprises hsa-miR-516b-5p and at least one pair of biomarkers selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-

30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p,

hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00175] In some embodiments, a composition described herein comprises hsa-miR-30c-5p and at least one pair of biomarkers selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-

3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00176] In some embodiments, a composition described herein comprises hsa-miR-1-3p and at least one pair of biomarkers selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-

miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00177]   In one aspect, the invention provides a composition of labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to two or more nucleic acid biomarkers selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00178]   In some embodiments, the invention provides a composition of labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to nucleic acid biomarkers hsa-miR-1-3p, hsa-miR-181d-5p, hsa-miR-378d, hsa-

miR-4433b-5p, and/or hsa-miR-27a-5p. In some embodiments, the invention provides a composition of labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to nucleic acid biomarkers hsa-miR-516b-5p and/or hsa-miR-30c-5p. In some embodiments, the invention provides a composition of labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to nucleic acid biomarkers hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, and/or hsa-miR-331-3p. In some embodiments, the invention provides a composition of labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to nucleic acid biomarkers hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, and/or hsa-miR-181d-5p.

[00179]   In one aspect, the invention provides a composition of labeled and/or amplified nucleic acid molecules that correspond to a pair of biomarkers selected from the group consisting of the biomarker pairs listed in Table 4.

[00180]   In some embodiments, a composition described herein comprises hsa-miR-140-3p/hsa-miR-516b-5p. In some embodiments, a composition described herein comprises hsa-miR-155-5p/hsa-miR-625-3p. In some embodiments, a composition described herein comprises hsa-miR-30c-5p/hsa-miR-27b-3p. In some embodiments, a composition described herein comprises hsa-miR-25-5p/hsa-miR-516b-5p. In some embodiments, a composition described herein comprises hsa-miR-484/hsa-miR-516b-5p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-let-7b-5p. In some embodiments, a composition described herein comprises hsa-miR-30c-5p/hsa-miR-7-5p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-486-5p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-150-5p. In some embodiments, a composition described herein comprises hsa-miR-485-5p/hsa-miR-516b-5p. In some embodiments, a composition described herein comprises hsa-miR-7-5p/hsa-miR-485-5p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-let-7g-5p. In some embodiments, a composition described herein comprises hsa-miR-30c-5p/hsa-miR-16-5p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-423-5p. In some embodiments, a composition described herein comprises hsa-miR-30c-5p/hsa-miR-30a-5p. In some embodiments, a composition described herein comprises hsa-miR-516b-

5p/hsa-miR-92a-3p. In some embodiments, a composition described herein comprises hsa-miR-186-5p/hsa-miR-516b-5p. In some embodiments, a composition described herein comprises hsa-miR-155-5p/hsa-miR-27b-3p. In some embodiments, a composition described herein comprises hsa-miR-30e-5p/hsa-miR-516b-5p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-let-7d-5p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-103a-3p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-126-3p. In some embodiments, a composition described herein comprises hsa-miR-99b-3p/hsa-miR-486-3p. In some embodiments, a composition described herein comprises hsa-miR-6741-5p/hsa-miR-760. In some embodiments, a composition described herein comprises hsa-miR-20a-5p/hsa-miR-485-5p. In some embodiments, a composition described herein comprises hsa-miR-23a-3p/hsa-miR-27b-3p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-151a-3p. In some embodiments, a composition described herein comprises hsa-miR-30a-5p/hsa-miR-485-5p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-let-7a-5p. In some embodiments, a composition described herein comprises hsa-miR-30c-5p/hsa-miR-27a-3p. In some embodiments, a composition described herein comprises hsa-miR-485-5p/hsa-miR-7-5p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-222-3p. In some embodiments, a composition described herein comprises hsa-miR-23a-3p/hsa-miR-30a-5p. In some embodiments, a composition described herein comprises hsa-miR-433-3p/hsa-miR-345-5p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-let-7f-5p. In some embodiments, a composition described herein comprises hsa-miR-485-5p/hsa-miR-183-5p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-185-5p. In some embodiments, a composition described herein comprises hsa-let-7i-5p/hsa-miR-485-5p. In some embodiments, a composition described herein comprises hsa-miR-4433b-5p/hsa-miR-516b-5p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-191-5p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-3615. In some embodiments, a composition described herein comprises hsa-miR-100-5p/hsa-miR-516b-5p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-10b-5p. In some embodiments, a composition described herein comprises hsa-miR-485-5p/hsa-miR-27a-3p. In some embodiments, a composition described herein comprises

hsa-miR-99a-5p/hsa-miR-485-5p. In some embodiments, a composition described herein comprises hsa-miR-99b-3p/hsa-miR-6852-5p. In some embodiments, a composition described herein comprises hsa-miR-363-3p/hsa-miR-485-5p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-484. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-let-7i-5p. In some embodiments, a composition described herein comprises hsa-miR-23a-3p/hsa-miR-181a-5p. In some embodiments, a composition described herein comprises hsa-miR-7-5p/hsa-miR-516b-5p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-328-3p. In some embodiments, a composition described herein comprises hsa-miR-181a-5p/hsa-miR-485-5p. In some embodiments, a composition described herein comprises hsa-miR-155-5p/hsa-miR-30a-5p. In some embodiments, a composition described herein comprises hsa-miR-155-5p/hsa-let-7i-5p. In some embodiments, a composition described herein comprises hsa-miR-98-5p/hsa-miR-485-5p. In some embodiments, a composition described herein comprises hsa-miR-485-5p/hsa-miR-127-3p. In some embodiments, a composition described herein comprises hsa-miR-320b/hsa-miR-485-5p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-25-3p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-148a-3p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-128-3p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-320a. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-744-5p. In some embodiments, a composition described herein comprises hsa-miR-30c-5p/hsa-miR-186-5p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-629-5p. In some embodiments, a composition described herein comprises hsa-miR-23a-3p/hsa-miR-93-5p. In some embodiments, a composition described herein comprises hsa-miR-127-3p/hsa-miR-485-5p. In some embodiments, a composition described herein comprises hsa-miR-155-5p/hsa-miR-451a. In some embodiments, a composition described herein comprises hsa-miR-30c-5p/hsa-miR-26b-5p. In some embodiments, a composition described herein comprises hsa-miR-4732-3p/hsa-miR-516b-5p. In some embodiments, a composition described herein comprises hsa-miR-7-5p/hsa-miR-941. In some embodiments, a composition described herein comprises hsa-miR-451a/hsa-miR-485-5p. In some embodiments, a composition described herein comprises hsa-miR-374b-5p/hsa-miR-885-3p. In some embodiments, a composition

described herein comprises hsa-miR-516b-5p/hsa-miR-1307-3p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-30d-5p. In some embodiments, a composition described herein comprises hsa-miR-3605-5p/hsa-miR-425-3p. In some embodiments, a composition described herein comprises hsa-miR-501-3p/hsa-miR-516b-5p. In some embodiments, a composition described herein comprises hsa-miR-125b-5p/hsa-miR-485-5p. In some embodiments, a composition described herein comprises hsa-miR-26b-5p/hsa-miR-485-5p. In some embodiments, a composition described herein comprises hsa-miR-30c-5p/hsa-miR-99a-5p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-127-3p. In some embodiments, a composition described herein comprises hsa-miR-501-3p/hsa-miR-485-5p. In some embodiments, a composition described herein comprises hsa-miR-30c-5p/hsa-miR-451a. In some embodiments, a composition described herein comprises hsa-miR-21-5p/hsa-miR-485-5p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-423-3p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-146b-5p. In some embodiments, a composition described herein comprises hsa-miR-330-5p/hsa-miR-92b-5p. In some embodiments, a composition described herein comprises hsa-miR-4443/hsa-miR-485-5p. In some embodiments, a composition described herein comprises hsa-miR-30c-5p/hsa-let-7i-5p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-425-5p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-24-3p. In some embodiments, a composition described herein comprises hsa-miR-146b-5p/hsa-miR-485-5p. In some embodiments, a composition described herein comprises hsa-miR-760/hsa-miR-378g. In some embodiments, a composition described herein comprises hsa-miR-3615/hsa-miR-485-5p. In some embodiments, a composition described herein comprises hsa-miR-140-3p/hsa-miR-485-5p. In some embodiments, a composition described herein comprises hsa-miR-30c-5p/hsa-miR-125a-5p. In some embodiments, a composition described herein comprises hsa-miR-378c/hsa-miR-148a-5p. In some embodiments, a composition described herein comprises hsa-let-7b-5p/hsa-miR-485-5p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-146a-5p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-451a.

[00181]   In some embodiments, a composition described herein comprises hsa-miR-140-3p/hsa-miR-516b-5p and at least one biomarker pair selected from the group consisting of hsa-

miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-

miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00182]   In some embodiments, a composition described herein comprises hsa-miR-155-5p/hsa-miR-625-3p and at least one biomarker pair selected from the group consisting of hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-

3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00183]   In some embodiments, a composition described herein comprises hsa-miR-30c-5p/hsa-miR-27b-3p and at least one biomarker pair selected from the group consisting of hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p,

hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00184]   In some embodiments, a composition described herein comprises hsa-miR-140-3p/hsa-miR-516b-5p and at least one biomarker selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00185]   In some embodiments, a composition described herein comprises hsa-miR-155-5p/hsa-miR-625-3p and at least one biomarker selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-

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142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00186] In some embodiments, a composition described herein comprises hsa-miR-30c-5p/hsa-miR-27b-3p and at least one biomarker selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00187] In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-516b-5p/hsa-miR-423-5p and hsa-miR-155-5p/ hsa-let-7i-5p.

[00188] In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-let-7b-5p and at least one biomarker pair selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-

miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00189] In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-423-5p and at least one biomarker pair selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p,

hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00190] In some embodiments, a composition described herein comprises hsa-miR-155-5p/hsa-let-7i-5p and at least one biomarker pair selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-

miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-

miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00191] In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-let-7b-5p and at least one biomarker selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00192] In some embodiments, a composition described herein comprises hsa-miR-516b-5p/hsa-miR-423-5p and at least one biomarker selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00193] In some embodiments, a composition described herein comprises hsa-miR-155-5p/hsa-let-7i-5p and at least one biomarker selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00194] In one aspect, the invention provides a composition of labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to a pair of biomarker selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-

5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p,

hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00195]   In some embodiments of the pair of biomarkers or panel of biomarkers comprising a pair of biomarkers, the pair of biomarkers is selected from the group consisting of hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-24-3p, and hsa-miR-378c/hsa-miR-148a-5p.

[00196]   In some embodiments of the pair of biomarkers or panel of biomarkers comprising a pair of biomarkers, the pair of biomarkers is selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, and hsa-miR-484/hsa-miR-516b-5p .

[00197]   In some embodiments of the pair of biomarkers or panel of biomarkers comprising a pair of biomarkers, the pair of biomarkers is selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, and hsa-miR-30c-5p/hsa-miR-7-5p.

[00198]   In some embodiments of the pair of biomarkers or panel of biomarkers comprising a pair of biomarkers, the pair of biomarkers is selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, and hsa-miR-485-5p/hsa-miR-516b-5p.

[00199]   In one aspect, the invention provides a composition of labeled and/or amplified nucleic acid molecules that correspond to at least one of the nucleic acid biomarkers listed in Table 5. In an additional aspect, the invention provides a composition of labeled and/or amplified nucleic acid molecules that correspond to at least one pair of the nucleic acid biomarkers listed in Table 5

[00200]   In some embodiments, a composition described herein comprises nucleic acid molecules selected from the group consisting of hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, hsa-miR-1323, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p

[00201]   In some embodiments, a composition described herein comprises hsa-miR-30c-5p. In some embodiments, a composition described herein comprises hsa-miR-6842-3p. In some embodiments, a composition described herein comprises hsa-miR-485-5p. In some embodiments, a composition described herein comprises hsa-miR-331-3p. In some embodiments, a composition described herein comprises hsa-miR-517a-3p-hsa-miR-517b-3p. In some embodiments, a composition described herein comprises hsa-miR-516b-5p. In some embodiments, a composition described herein comprises hsa-miR-760. In some embodiments, a composition described herein comprises hsa-miR-6852-5p. In some embodiments, a composition described herein comprises hsa-miR-1323. In some embodiments, a composition described herein comprises hsa-miR-155-5p. In some embodiments, a composition described herein comprises hsa-miR-6747-3p. In some embodiments, a composition described herein comprises hsa-miR-181d-5p. In some embodiments, a composition described herein comprises hsa-miR-4446-3p.

[00202]   In some embodiments, a composition described herein comprises hsa-miR-485-5p and at least one biomarker selected from the group consisting of hsa-miR-7-5p, hsa-miR-501-3p, hsa-miR-363-3p, hsa-miR-182-5p, hsa-miR-127-3p, hsa-miR-140-3p, hsa-miR-26b-5p.

[00203]   In some embodiments, a composition described herein comprises hsa-miR-485-5p and at least one pair biomarker selected from the group consisting of hsa-miR-27b-3p, hsa-let-7i-5p, hsa-miR-99a-5p, hsa-miR-409-3p.

[00204]　　　In some embodiments, a composition described herein comprises hsa-miR-485-5p and two or more biomarkers selected from Table 5.

[00205]　　In one aspect, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising measuring the amount of two or more of the nucleic acid biomarkers listed in Tables 3, 4 or 5 in a biological sample obtained from the pregnant female, and calculating a risk score based upon the measured amounts of the nucleic acid biomarkers to determine the pregnant female's risk of developing placental dysfunction. In some embodiments, the method further comprises the step of providing a score corresponding to the pregnant female's risk of developing placental dysfunction.

[00206]　　In one aspect, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising producing labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to two or more of the nucleic acid biomarkers listed in Tables 3, 4 or 5 in a biological sample obtained from the pregnant female; measuring the levels of expression of the labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules; calculating a risk score based upon the measured levels of the labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, to determine the pregnant female's risk of developing placental dysfunction. In some embodiments, the method further comprises the step of providing a score corresponding to the pregnant female's risk of developing placental dysfunction.

[00207]　　In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p. In some embodiments, a method described herein comprises hsa-miR-30c-5p. In some embodiments, a method described herein comprises hsa-miR-1-3p. In some embodiments, a method described herein comprises hsa-miR-331-3p. In some embodiments, a method described herein comprises hsa-miR-485-5p. In some embodiments, a method described herein comprises hsa-miR-181d-5p. In some embodiments, a method described herein comprises hsa-miR-23a-3p. In some embodiments, a method described herein comprises hsa-miR-378d. In some embodiments, a method described herein comprises hsa-miR-155-5p. In some embodiments, a method described herein comprises

hsa-miR-99b-3p. In some embodiments, a method described herein comprises hsa-miR-1249-3p. In some embodiments, a method described herein comprises hsa-miR-142-3p. In some embodiments, a method described herein comprises hsa-miR-4433b-5p. In some embodiments, a method described herein comprises hsa-miR-1273h-3p. In some embodiments, a method described herein comprises hsa-miR-18a-3p. In some embodiments, a method described herein comprises hsa-miR-4746-5p. In some embodiments, a method described herein comprises hsa-miR-27a-5p. In some embodiments, a method described herein comprises hsa-miR-654-3p. In some embodiments, a method described herein comprises hsa-miR-7-5p. In some embodiments, a method described herein comprises hsa-miR-941.

[00208] In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p and at least one biomarker selected from the group consisting of hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00209] In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-30c-5p and at least one biomarker selected from the group consisting of hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00210] In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-1-3p and at least one biomarker selected from the group consisting of hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00211] In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p and at least one pair of

biomarkers selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-

485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00212] In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-30c-5p and at least one pair of biomarkers selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-

320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00213]   In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-1-3p and at least one pair of biomarkers selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-

191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00214]   In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-140-3p/hsa-miR-516b-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-155-5p/hsa-miR-625-3p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-30c-5p/hsa-miR-27b-3p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-25-5p/hsa-miR-516b-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-484/hsa-

miR-516b-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-let-7b-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-30c-5p/hsa-miR-7-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-486-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-150-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-485-5p/hsa-miR-516b-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-7-5p/hsa-miR-485-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-let-7g-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-30c-5p/hsa-miR-16-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-423-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-30c-5p/hsa-miR-30a-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-92a-3p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-186-5p/hsa-miR-516b-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-155-5p/hsa-miR-27b-3p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-30e-5p/hsa-miR-516b-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-let-7d-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-103a-3p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that

correspond to hsa-miR-516b-5p/hsa-miR-126-3p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-99b-3p/hsa-miR-486-3p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-6741-5p/hsa-miR-760. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-20a-5p/hsa-miR-485-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-23a-3p/hsa-miR-27b-3p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-151a-3p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-30a-5p/hsa-miR-485-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-let-7a-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-30c-5p/hsa-miR-27a-3p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-485-5p/hsa-miR-7-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-222-3p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-23a-3p/hsa-miR-30a-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-433-3p/hsa-miR-345-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-let-7f-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-485-5p/hsa-miR-183-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-185-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-let-7i-5p/hsa-miR-485-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic

acid molecules that correspond to hsa-miR-4433b-5p/hsa-miR-516b-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-191-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-3615. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-100-5p/hsa-miR-516b-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-10b-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-485-5p/hsa-miR-27a-3p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-99a-5p/hsa-miR-485-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-99b-3p/hsa-miR-6852-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-363-3p/hsa-miR-485-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-484. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-let-7i-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-23a-3p/hsa-miR-181a-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-7-5p/hsa-miR-516b-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-328-3p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-181a-5p/hsa-miR-485-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-155-5p/hsa-miR-30a-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-155-5p/hsa-let-7i-5p. In some embodiments, a method described herein comprises

producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-98-5p/hsa-miR-485-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-485-5p/hsa-miR-127-3p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-320b/hsa-miR-485-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-25-3p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-148a-3p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-128-3p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-320a. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-744-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-30c-5p/hsa-miR-186-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-629-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-23a-3p/hsa-miR-93-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-127-3p/hsa-miR-485-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-155-5p/hsa-miR-451a. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-30c-5p/hsa-miR-26b-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-4732-3p/hsa-miR-516b-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-7-5p/hsa-miR-941. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-451a/hsa-miR-485-5p. In some embodiments, a

method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-374b-5p/hsa-miR-885-3p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-1307-3p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-30d-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-3605-5p/hsa-miR-425-3p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-501-3p/hsa-miR-516b-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-125b-5p/hsa-miR-485-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-26b-5p/hsa-miR-485-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-30c-5p/hsa-miR-99a-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-127-3p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-501-3p/hsa-miR-485-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-30c-5p/hsa-miR-451a. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-21-5p/hsa-miR-485-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-423-3p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-146b-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-330-5p/hsa-miR-92b-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-4443/hsa-miR-485-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-30c-

5p/hsa-let-7i-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-425-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-24-3p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-146b-5p/hsa-miR-485-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-760/hsa-miR-378g. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-3615/hsa-miR-485-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-140-3p/hsa-miR-485-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-30c-5p/hsa-miR-125a-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-378c/hsa-miR-148a-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-let-7b-5p/hsa-miR-485-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-146a-5p. In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-451a.

[00215]   In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-140-3p/hsa-miR-516b-5p and at least one biomarker pair selected from the group consisting of hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-

miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00216]   In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-155-5p/hsa-miR-625-3p and at least one biomarker pair selected from the group consisting of hsa-miR-25-5p/hsa-miR-516b-5p,

hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-

516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p,

hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p,

hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-

5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00217]   In some embodiments, a method described herein comprises producing labeled and/or

amplified nucleic acid molecules that correspond to hsa-miR-30c-5p/hsa-miR-27b-3p and at least

one biomarker pair selected from the group consisting of hsa-miR-25-5p/hsa-miR-516b-5p, hsa-

miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p,

hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-

miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-

5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-

miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-

27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-

5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-

miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p,

hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-

7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-

miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-

516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p,

hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-

191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-

5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-

miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-

484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-

516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-

5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-

485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-

miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-

320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-

5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-

miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-

5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00218] In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-140-3p/hsa-miR-516b-5p and at least one biomarker selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00219] In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-155-5p/hsa-miR-625-3p and at least one biomarker selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00220] In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-30c-5p/hsa-miR-27b-3p and at least one biomarker selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-

378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00221]   In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-516b-5p/hsa-miR-423-5p and hsa-miR-155-5p/ hsa-let-7i-5p.

[00222]   In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-let-7b-5p and at least one biomarker pair selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-

miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00223] In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-423-5p and at least one biomarker pair selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-

miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00224] In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-155-5p/ hsa-let-7i-5p and at least one biomarker pair selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-

30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p,

hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

[00225] In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-let-7b-5p and at least one biomarker selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00226] In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-516b-5p/hsa-miR-423-5p and at least one biomarker selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00227] In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-155-5p/ hsa-let-7i-5p and at least one biomarker selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

[00228] In one aspect, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction comprising producing labeled and/or amplified nucleic acid molecules selected from the group consisting of hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, hsa-miR-1323, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p. In some embodiments, a method described herein comprises producing

labeled and/or amplified nucleic acid molecules that correspond to at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, at least twelve, or at least 13 of the nucleic acid molecules selected from the group consisting of hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, hsa-miR-1323, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p.

[00229]   In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that corresponds to hsa-miR-30c-5p. In some embodiments, a method described herein comprises hsa-miR-6842-3p. In some embodiments, a method described herein comprises hsa-miR-485-5p. In some embodiments, a method described herein comprises hsa-miR-331-3p. In some embodiments, a method described herein comprises hsa-miR-517a-3p-hsa-miR-517b-3p. In some embodiments, a method described herein comprises hsa-miR-516b-5p. In some embodiments, a method described herein comprises hsa-miR-760. In some embodiments, a method described herein comprises hsa-miR-6852-5p. In some embodiments, a method described herein comprises hsa-miR-1323. In some embodiments, a method described herein comprises hsa-miR-155-5p. In some embodiments, a method described herein comprises hsa-miR-6747-3p. In some embodiments, a method described herein comprises hsa-miR-181d-5p. In some embodiments, a method described herein comprises hsa-miR-4446-3p.

[00230]   In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-485-5p and at least one biomarker selected from the group consisting of hsa-miR-7-5p, hsa-miR-501-3p, hsa-miR-363-3p, hsa-miR-182-5p, hsa-miR-127-3p, hsa-miR-140-3p, hsa-miR-26b-5p.

[00231]   In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-485-5p and at least one pair biomarkers selected from the group consisting of hsa-miR-27b-3p, hsa-let-7i-5p, hsa-miR-99a-5p, hsa-miR-409-3p.

[00232]   In some embodiments, a method described herein comprises producing labeled and/or amplified nucleic acid molecules that correspond to hsa-miR-485-5p and two or more biomarkers selected from Table 5.

[00233]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction, wherein the biological sample is obtained between 17 and 28 weeks of gestational age at blood draw.

[00234]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction, wherein the biological sample is obtained between 19 and 27 weeks of gestational age at blood draw.

[00235]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction, wherein the biological sample is obtained between 17 and 36 weeks of gestational age at blood draw.

[00236]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction, wherein the biological sample is obtained more than 17, more than 18, more than 19, more than 20, more than 21, more than 22, more than 23, more than 24, more than 25, more than 26, more than 27, more than 28, more than 29, more than 30, more than 31, more than 32, more than 33, more than 34, or more than 35 weeks of gestational age at blood draw.

[00237]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction, wherein the biological sample is obtained between 119-153 days, 154-196 days, and/or 119-202 days.

[00238]   In one aspect, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising measuring the amount of two or more of the nucleic acid biomarkers selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941 in a biological sample obtained from

the pregnant female, calculating a risk score based upon the measured amounts of the nucleic acid biomarkers to determine the pregnant female's risk of developing placental dysfunction, and providing a score corresponding to the pregnant female's risk of developing placental dysfunction.

[00239] In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising measuring two or more of the nucleic acid biomarkers selected from the group consisting of hsa-miR-1-3p, hsa-miR-181d-5p, hsa-miR-378d, hsa-miR-4433b-5p, and hsa-miR-27a-5p.

[00240] In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising measuring the amount of two or more of the nucleic acid biomarkers selected from the group consisting of hsa-miR-516b-5p and hsa-miR-30c-5p.

[00241] In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising measuring the amount of two or more of the nucleic acid biomarkers selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, and hsa-miR-331-3p.

[00242] In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising measuring the amount of two or more of the nucleic acid biomarkers selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, and hsa-miR-181d-5p.

[00243] In one aspect, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction comprising measuring the amount of nucleic acid molecules selected from the group consisting of hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, hsa-miR-1323, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p in a biological sample obtained from the pregnant female, calculating a risk score based upon the measured amounts of the nucleic acid biomarkers to determine the pregnant

female's risk of developing placental dysfunction, and providing a score corresponding to the pregnant female's risk of developing placental dysfunction. In some embodiments, a method described herein comprises measuring the amount of at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, at least twelve, or at least 13 nucleic acid molecules selected from the group consisting of hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, hsa-miR-1323, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p.

[00244]   In some embodiments, a method for determining a pregnant female's risk of developing placental dysfunction comprises measuring a nucleic acid molecule that corresponds to hsa-miR-30c-5p. In some embodiments, a method described herein comprises hsa-miR-6842-3p. In some embodiments, a method described herein comprises hsa-miR-485-5p. In some embodiments, a method described herein comprises hsa-miR-331-3p. In some embodiments, a method described herein comprises hsa-miR-517a-3p-hsa-miR-517b-3p. In some embodiments, a method described herein comprises hsa-miR-516b-5p. In some embodiments, a method described herein comprises hsa-miR-760. In some embodiments, a method described herein comprises hsa-miR-6852-5p. In some embodiments, a method described herein comprises hsa-miR-1323. In some embodiments, a method described herein comprises hsa-miR-155-5p. In some embodiments, a method described herein comprises hsa-miR-6747-3p. In some embodiments, a method described herein comprises hsa-miR-181d-5p. In some embodiments, a method described herein comprises hsa-miR-4446-3p.

[00245]   In some embodiments, a method described herein comprises measuring nucleic acid molecules that correspond to hsa-miR-485-5p and at least one biomarker selected from the group consisting of hsa-miR-7-5p, hsa-miR-501-3p, hsa-miR-363-3p, hsa-miR-182-5p, hsa-miR-127-3p, hsa-miR-140-3p, hsa-miR-26b-5p.

[00246]   In some embodiments, a method described herein comprises measuring nucleic acid molecules that correspond to hsa-miR-485-5p and at least one pair biomarkers selected from the group consisting of hsa-miR-27b-3p, hsa-let-7i-5p, hsa-miR-99a-5p, hsa-miR-409-3p.

[00247]   In some embodiments, a method described herein comprises measuring nucleic acid molecules that correspond to hsa-miR-485-5p and two or more biomarkers selected from Table 5.

[00248]   In one aspect, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising producing labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to two or more of the nucleic acid biomarkers selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941 in a biological sample obtained from the pregnant female; measuring the levels of expression of the labeled and/or amplified nucleic acid molecules; calculating a risk score based upon the measured levels of the labeled and/or amplified nucleic acid molecules to determine the pregnant female's risk of developing placental dysfunction.

[00249]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising producing labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to hsa-miR-1-3p, hsa-miR-181d-5p, hsa-miR-378d, hsa-miR-4433b-5p, and/or hsa-miR-27a-5p.

[00250]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising producing labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to hsa-miR-516b-5p and/or hsa-miR-30c-5p.

[00251]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising producing labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, and/or hsa-miR-331-3p.

[00252]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising producing labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond tohsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, and/or hsa-miR-331-3p.

[00253]   In one aspect, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising measuring the amount of a pair of biomarkers selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-

5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a in a biological sample obtained from the pregnant female, calculating a risk score based upon the measured amounts of the nucleic acid biomarker pair to determine the pregnant female's risk of developing placental dysfunction, and providing a score corresponding to the pregnant female's risk of developing placental dysfunction.

[00254]   In some embodiments, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising measuring the amount of a pair of biomarkers that correspond to hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-24-3p, and/or hsa-miR-378c/hsa-miR-148a-5p.

[00255] In some embodiments, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising measuring the amount of a pair of biomarkers that correspond to hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, and/or hsa-miR-484/hsa-miR-516b-5p.

[00256] In some embodiments, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising measuring the amount of a pair of biomarkers that correspond to hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, and/or hsa-miR-30c-5p/hsa-miR-7-5p.

[00257] In some embodiments, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising measuring the amount of a pair of biomarkers that correspond to hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, and/or hsa-miR-485-5p/hsa-miR-516b-5p.

[00258] In one aspect, the invention provides a method for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising producing labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to a pair of biomarkers selected from the group consisting hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p,

hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a in a biological sample obtained from the pregnant female; measuring the levels of expression of the labeled and/or amplified nucleic acid molecules; calculating a risk

score based upon the measured levels of the labeled and/or amplified nucleic acid molecules to determine the pregnant female's risk of developing placental dysfunction. in a biological sample obtained from the pregnant female; measuring the levels of expression of the labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules; calculating a risk score based upon the measured levels of the labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, to determine the pregnant female's risk of developing placental dysfunction. In some embodiments, the method further comprises the step of providing a score corresponding to the pregnant female's risk of developing placental dysfunction.

[00259]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising producing labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-24-3p, and/or hsa-miR-378c/hsa-miR-148a-5p.

[00260]   In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising producing labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, and/or hsa-miR-484/hsa-miR-516b-5p.

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[00261] In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising producing labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, and/or hsa-miR-30c-5p/hsa-miR-7-5p.

[00262] In some embodiments, the invention provides a method of determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising producing labeled and/or amplified nucleic acid molecules, for example, amplified labeled nucleic acid molecules, that correspond to hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, and/or hsa-miR-485-5p/hsa-miR-516b-5p.

[00263] In one aspect, the invention provides a method for treating or preventing placental dysfunction in a pregnant female, the method comprising (a) detecting a panel of isolated nucleic acid biomarkers in a biological sample obtained from a pregnant female, wherein at least one of the isolated nucleic acid biomarkers is selected from the group consisting of hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, hsa-miR-1323, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p; (b) calculating a risk score based upon the measured levels of the isolated nucleic acid biomarkers; and (c) administering one or more therapies to the pregnant female based on the risk score, to treat or prevent placental dysfunction. In some embodiments, a method described herein comprises detecting at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, at least twelve, or at least 13 of the nucleic acid molecules selected from the group consisting of hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, hsa-miR-1323, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p.

[00264]   In some embodiments, a method described herein comprises detecting a nucleic acid molecule that corresponds to hsa-miR-30c-5p. In some embodiments, a method described herein comprises hsa-miR-6842-3p. In some embodiments, a method described herein comprises hsa-miR-485-5p. In some embodiments, a method described herein comprises hsa-miR-331-3p. In some embodiments, a method described herein comprises hsa-miR-517a-3p-hsa-miR-517b-3p. In some embodiments, a method described herein comprises hsa-miR-516b-5p. In some embodiments, a method described herein comprises hsa-miR-760. In some embodiments, a method described herein comprises hsa-miR-6852-5p. In some embodiments, a method described herein comprises hsa-miR-1323. In some embodiments, a method described herein comprises hsa-miR-155-5p. In some embodiments, a method described herein comprises hsa-miR-6747-3p. In some embodiments, a method described herein comprises hsa-miR-181d-5p. In some embodiments, a method described herein comprises hsa-miR-4446-3p.

[00265]   In some embodiments, a method described herein comprises detecting a nucleic acid molecule that corresponds to hsa-miR-485-5p and at least one biomarker selected from the group consisting of hsa-miR-7-5p, hsa-miR-501-3p, hsa-miR-363-3p, hsa-miR-182-5p, hsa-miR-127-3p, hsa-miR-140-3p, hsa-miR-26b-5p.

[00266]   In some embodiments, a method described herein comprises detecting a nucleic acid molecule that corresponds to a nucleic acid molecule that corresponds to hsa-miR-485-5p and at least one pair biomarkers selected from the group consisting of hsa-miR-27b-3p, hsa-let-7i-5p, hsa-miR-99a-5p, hsa-miR-409-3p.

[00267]   In some embodiments, a method described herein comprises detecting a nucleic acid molecule that corresponds to a nucleic acid molecule that corresponds to hsa-miR-485-5p and two or more biomarkers selected from Table 5.

[00268]   In some embodiments of methods of the invention, the risk score is calculated based on a ratio of data values. In some embodiments of methods of the invention, data transformation is applied before or after the ratio is determined.

[00269]   The quantitation of biomarkers in a biological sample can be determined, without limitation, by the methods described above as well as any other method known in the art. The

quantitative data thus obtained is then subjected to an analytic classification process. In such a process, the raw data is manipulated according to an algorithm, where the algorithm has been pre-defined by a training set of data, for example as described in the examples provided herein. An algorithm can utilize the training set of data provided herein, or can utilize the guidelines provided herein to generate an algorithm with a different set of data.

[00270]   An analytic classification process can use any one of a variety of statistical analytic methods to manipulate the quantitative data and provide for classification of the sample. Examples of useful methods include linear discriminant analysis, recursive feature elimination, a prediction analysis of microarray, a logistic regression, a CART algorithm, a FlexTree algorithm, a LART algorithm, a random forest algorithm, a MART algorithm, machine learning algorithms; etc.

[00271]   Classification can be made according to predictive modeling methods that set a threshold for determining the probability that a sample belongs to a given class. The probability preferably is at least 50%, or at least 60%, or at least 70%, or at least 80% or higher. Classifications also can be made by determining whether a comparison between an obtained dataset and a reference dataset yields a statistically significant difference. If so, then the sample from which the dataset was obtained is classified as not belonging to the reference dataset class. Conversely, if such a comparison is not statistically significantly different from the reference dataset, then the sample from which the dataset was obtained is classified as belonging to the reference dataset class.

[00272]   The predictive ability of a model can be evaluated according to its ability to provide a quality metric, e.g. AUROC (area under the ROC curve) or accuracy, of a particular value, or range of values. Area under the curve measures are useful for comparing the accuracy of a classifier across the complete data range. Classifiers with a greater AUC have a greater capacity to classify unknowns correctly between two groups of interest. In some embodiments, a desired quality threshold is a predictive model that will classify a sample with an accuracy of at least about 0.5, at least about 0.55, at least about 0.6, at least about 0.7, at least about 0.75, at least about 0.8, at least about 0.85, at least about 0.9, at least about 0.95, or higher. As an alternative measure, a desired quality threshold can refer to a predictive model that will classify a sample

with an AUC of at least about 0.7, at least about 0.75, at least about 0.8, at least about 0.85, at least about 0.9, or higher.

[00273]   As is known in the art, the relative sensitivity and specificity of a predictive model can be adjusted to favor either the selectivity metric or the sensitivity metric, where the two metrics have an inverse relationship. The limits in a model as described above can be adjusted to provide a selected sensitivity or specificity level, depending on the particular requirements of the test being performed. One or both of sensitivity and specificity can be at least about 0.7, at least about 0.75, at least about 0.8, at least about 0.85, at least about 0.9, or higher.

[00274]   The raw data can be initially analyzed by measuring the values for each biomarker, usually in triplicate or in multiple triplicates. The data can be manipulated, for example, raw data can be transformed using standard curves, and the average of triplicate measurements used to calculate the average and standard deviation for each patient. These values can be transformed before being used in the models, e.g. log-transformed, Box-Cox transformed (Box and Cox, Royal Stat. Soc., Series B, 26:211-246(1964). The data are then input into a predictive model, which will classify the sample according to the state. The resulting information can be communicated to a patient or health care provider.

[00275]   To generate a predictive model for determining the risk of developing placental dysfunction later in the pregnancy a robust data set, comprising known control samples and samples corresponding to the birth classification of interest is used in a training set. A sample size can be selected using generally accepted criteria. As discussed above, different statistical methods can be used to obtain a highly accurate predictive model.

[00276]   In one embodiment, hierarchical clustering is performed in the derivation of a predictive model, where the Pearson correlation is employed as the clustering metric. One approach is to consider a given birth dataset as a "learning sample" in a problem of "supervised learning." CART is a standard in applications to medicine (Singer, Recursive Partitioning in the Health Sciences, Springer(1999)) and can be modified by transforming any qualitative features to quantitative features; sorting them by attained significance levels, evaluated by sample reuse methods for Hotelling's T^2 statistic; and suitable application of the lasso method. Problems in prediction are turned into problems in regression without losing sight of prediction, indeed by

making suitable use of the Gini criterion for classification in evaluating the quality of regressions.

[00277]   This approach led to what is termed FlexTree (Huang, Proc. Nat. Acad. Sci. U.S.A 101:10529-10534(2004)). FlexTree performs very well in simulations and when applied to multiple forms of data and is useful for practicing the claimed methods. Software automating FlexTree has been developed. Alternatively, LARTree or LART can be used (Turnbull (2005) Classification Trees with Subset Analysis Selection by the Lasso, Stanford University). The name reflects binary trees, as in CART and FlexTree; the lasso, as has been noted; and the implementation of the lasso through what is termed LARS by Efron *et al.* (2004) Annals of Statistics 32:407-451 (2004). See, also, Huang *et al.*, Proc. Natl. Acad. Sci. USA. 101(29):10529-34 (2004). Other methods of analysis that can be used include logic regression. One method of logic regression Ruczinski, Journal of Computational and Graphical Statistics 12:475-512 (2003). Logic regression resembles CART in that its classifier can be displayed as a binary tree. It is different in that each node has Boolean statements about features that are more general than the simple "and" statements produced by CART.

[00278]   Another approach is that of nearest shrunken centroids (Tibshirani, Proc. Natl. Acad. Sci. U.S.A 99:6567-72(2002)). The technology is k-means-like, but has the advantage that by shrinking cluster centers, one automatically selects features, as is the case in the lasso, to focus attention on small numbers of those that are informative. The approach is available as PAM software and is widely used. Two further sets of algorithms that can be used are random forests (Breiman, Machine Learning 45:5-32 (2001)) and MART (Hastie, The Elements of Statistical Learning, Springer (2001)). These two methods are known in the art as "committee methods," that involve predictors that "vote" on outcome.

[00279]   To provide significance ordering, the false discovery rate (FDR) can be determined. First, a set of null distributions of dissimilarity values is generated. In one embodiment, the values of observed profiles are permuted to create a sequence of distributions of correlation coefficients obtained out of chance, thereby creating an appropriate set of null distributions of correlation coefficients (Tusher *et al.*, Proc. Natl. Acad. Sci. U.S.A 98, 5116-21 (2001)). The set of null distribution is obtained by: permuting the values of each profile for all available profiles;

calculating the pair-wise correlation coefficients for all profile; calculating the probability density function of the correlation coefficients for this permutation; and repeating the procedure for N times, where N is a large number, usually 300. Using the N distributions, one calculates an appropriate measure (mean, median, *etc.*) of the count of correlation coefficient values that their values exceed the value (of similarity) that is obtained from the distribution of experimentally observed similarity values at given significance level.

[00280] The FDR is the ratio of the number of the expected falsely significant correlations (estimated from the correlations greater than this selected Pearson correlation in the set of randomized data) to the number of correlations greater than this selected Pearson correlation in the empirical data (significant correlations). This cut-off correlation value can be applied to the correlations between experimental profiles. Using the aforementioned distribution, a level of confidence is chosen for significance. This is used to determine the lowest value of the correlation coefficient that exceeds the result that would have obtained by chance. Using this method, one obtains thresholds for positive correlation, negative correlation or both. Using this threshold(s), the user can filter the observed values of the pair wise correlation coefficients and eliminate those that do not exceed the threshold(s). Furthermore, an estimate of the false positive rate can be obtained for a given threshold. For each of the individual "random correlation" distributions, one can find how many observations fall outside the threshold range. This procedure provides a sequence of counts. The mean and the standard deviation of the sequence provide the average number of potential false positives and its standard deviation.

[00281] In an alternative analytical approach, variables chosen in the cross-sectional analysis are separately employed as predictors in a time-to-event analysis (survival analysis), where the event is the occurrence of preterm birth, and subjects with no event are considered censored at the time of giving birth. Given the specific pregnancy outcome (preterm birth event or no event), the random lengths of time each patient will be observed, and selection of proteomic and other features, a parametric approach to analyzing survival can be better than the widely applied semi-parametric Cox model. A Weibull parametric fit of survival permits the hazard rate to be monotonically increasing, decreasing, or constant, and also has a proportional hazards representation (as does the Cox model) and an accelerated failure-time representation. All the

standard tools available in obtaining approximate maximum likelihood estimators of regression coefficients and corresponding functions are available with this model.

[00282] In addition the Cox models can be used, especially since reductions of numbers of covariates to manageable size with the lasso will significantly simplify the analysis, allowing the possibility of a nonparametric or semi-parametric approach to prediction of time to preterm birth. These statistical tools are known in the art and applicable to all manner of proteomic data. A set of biomarker, clinical and genetic data that can be easily determined, and that is highly informative regarding the probability for preterm birth and predicted time to a preterm birth event in said pregnant female is provided. Also, algorithms provide information regarding the probability for preterm birth in the pregnant female.

[00283] Survival analyses are commonly used to understand time to occurrence of an event of interest such as birth or death. Commonly, the Kaplan-Meier estimator is used to estimate the survival function, while Cox proportional hazards models are used to estimate the effects of covariates on the hazard of event occurrence. These models conventionally assume that survival time is based on risk of exactly one type of event. However a competing risk for a different event may be present that either hinders the observation of an event of interest or modifies the chance that this event occurs. Conventional methods may be inappropriate in the presence of competing risks. Alternative methods appropriate for analysis of competing risks either asses competing hazards in subdistribution hazards models or cause-specific modified Cox proportional hazards models; or estimate cumulative incidence over competing events (Jason P. Fine & Robert J. Gray. Journal of the American Statistical Association Vol. 94 , Issue 446,1999. A Proportional Hazards Model for the Subdistribution of a Competing Risk).

[00284] In the development of a predictive model, it can be desirable to select a subset of markers, *i.e.* at least 3, at least 4, at least 5, at least 6, up to the complete set of markers. Usually a subset of markers will be chosen that provides for the needs of the quantitative sample analysis, e.g. availability of reagents, convenience of quantitation, etc., while maintaining a highly accurate predictive model. The selection of a number of informative markers for building classification models requires the definition of a performance metric and a user-defined threshold for producing a model with useful predictive ability based on this metric. For example, the

performance metric can be the AUC, the sensitivity and/or specificity of the prediction as well as the overall accuracy of the prediction model.

[00285]   As will be understood by those skilled in the art, an analytic classification process can use any one of a variety of statistical analytic methods to manipulate the quantitative data and provide for classification of the sample. Examples of useful methods include, without limitation, linear discriminant analysis, recursive feature elimination, a prediction analysis of microarray, a logistic regression, a CART algorithm, a FlexTree algorithm, a LART algorithm, a random forest algorithm, a MART algorithm, and machine learning algorithms. Various methods are used in a training model. The selection of a subset of markers can be for a forward selection or a backward selection of a marker subset. The number of markers can be selected that will optimize the performance of a model without the use of all the markers. One way to define the optimum number of terms is to choose the number of terms that produce a model with desired predictive ability (*e.g.* an AUC>0.75, or equivalent measures of sensitivity/specificity) that lies no more than one standard error from the maximum value obtained for this metric using any combination and number of terms used for the given algorithm.

[00286]   The biomarkers of the invention, which have been identified in the invention disclosed herein as being useful for predicting placental dysfunction, are known in the art and are readily available in public databases. For example, the human microRNAs disclosed herein as biomarkers useful for determining a pregnant female's risk of developing placental dysfunction are available in mirBase (mirbase.org). The naming convention for microRNAs generally uses "-" in the name of the microRNA, for example, hsa-miR-423-3p. It is noted that in some instances herein a shortened nomenclature is used, in which the "-" is replaced with "." such as "hsa.miR.423.3p" instead of "hsa-miR-423-3p." A person skilled in the art will readily understand the nomenclature commonly used for microRNAs and will appreciate that the microRNAs disclosed herein are readily available in public databases. Biomarker pairs are generally denoted herein as a pair separated by a "/", for example, hsa-miR-516b-5p/hsa-miR-485-5p.

[00287]   In yet another aspect, the invention provides kits for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy. The kit can include one or more

agents for detection of biomarkers, a container for holding a biological sample isolated from a pregnant female; and printed instructions for reacting agents with the biological sample or a portion of the biological sample to detect the presence or amount of the isolated biomarkers in the biological sample. The agents can be packaged in separate containers. The kit can further comprise one or more control reference samples and reagents for performing an immunoassay.

[00288]   The kit can comprise one or more containers for compositions or reagents contained in the kit. Compositions can be in liquid form or can be lyophilized. Suitable containers for the compositions include, for example, bottles, vials, syringes, and test tubes. Containers can be formed from a variety of materials, including glass or plastic. The kit can also comprise a package insert containing written instructions for methods for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy.

[00289]   In yet another aspect, the invention provides a method of treating or preventing placental dysfunction in a pregnant female comprising (a) detecting a panel of isolated nucleic acid biomarkers in a biological sample obtained from a pregnant female, wherein at least one of the isolated nucleic acid biomarkers is selected from the group consisting of hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, hsa-miR-1323, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p; (b) calculating a risk score based upon the measured levels of the isolated nucleic acid biomarkers; and (c) administering one or more therapies to the pregnant female based on the risk score, to treat or prevent placental dysfunction.

[00290]   In some embodiments, the invention provides a method of treating or preventing placental dysfunction wherein at least one of the biomarkers is selected from the group consisting of hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, and hsa-miR-1323.

[00291]   In some embodiments, the invention provides a method of treating or preventing placental dysfunction wherein at least one of the biomarkers of hsa-miR-30c-5p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p.

[00292]   In some embodiments, the invention provides a method of treating or preventing placental dysfunction wherein at least one of the biomarkers hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-760, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p.

[00293]   In some embodiments, the isolated nucleic acid biomarkers are normalized. In further embodiments, normalization comprises a reversal. In some embodiments, the reversal comprises an upregulated biomarker and a downregulated biomarker. In some embodiments, the reversal comprises a numerator and a denominator. In further embodiments, the downregulated biomarker is hsa-miR-485-5p. In other embodiments, the denominator is hsa-miR-485-5p.

[00294]   In some embodiments, the invention provides a method wherein the risk score is calculated based on the reversal of data values.

[00295]   In some embodiments, the method further comprises a step of determining gestational age at blood draw (GABD). In further embodiments, the method comprises determining GABD before detecting the biomarker. In some embodiments, GABD is between 119-153 days, 154-196 days and/or 119-202 days.

[00296]   In some embodiments, the invention provides a method of treating or preventing placental dysfunction across the full window of gestation. In some embodiments, the full gestation window of gestation is between 119-202 days of gestation.

[00297]   In some embodiments, the invention provides a method of treating or preventing placental dysfunction early in the pregnancy. In some embodiments, early pregnancy is between 119-153 days of gestation.

[00298]   In some embodiments, the invention provides a method of treating or preventing placental dysfunction later in the pregnancy. In some embodiments, late pregnancy is between 154-196 days of gestation.

[00299]   Therapies that can be administered to treat or prevent placental dysfunction include bedrest, steroid injection, low-dose aspirin, statins, metformin, and care management/elevated care inclusive of serial blood pressure and intensive symptomatic monitoring, and lifestyle and

behavioral modification. A person skilled in the art can readily contemplate these and/or additional therapies that can be used to treat or prevent placental dysfunction.

EXAMPLES

[00300] **Example 1:** Identification of extracellular micro RNA biomarkers for Identification of Pregnancies at Risk for Placental Dysfunction

[00301] This example shows identification of extracellular miRNA biomarkers for prediction of preeclampsia: placental dysfunction affecting maternal blood pressure and renal, liver and central nervous system function.

[00302] Study Design

[00303] Unblinded samples were used for this discovery study. Additional blinded samples are reserved for future re-verification or validation.

[00304] Maternal serum samples were collected from high-risk and average-risk pregnant women between 17-28 weeks, for which pregnancy outcomes are known. The sample set comprised 212 samples, including 73 preeclampsia and 139 normal. GABD was at a minimum of 120 days to a maximum of 201 days with a mean of 163.6 days.

[00305] Table 1. Pre-specified subject classifications

Group	Range of GA at draw	Range of GA at birth	Criterion 1	Criterion 2	Criterion 3	Criterion 4	Criterion 5
UCSD cases	19-27 weeks	25-41 weeks	New-onset hypertension and new-onset proteinuria **OR**	Chronic hypertension and new-onset proteinuria **OR**	Chronic proteinuria and new-onset hypertension **OR**	New-onset or chronic hypertension and new-onset severe feature (elevated LFTs, elevated Cr, low platelets, IUGR) **OR**	New-onset or chronic proteinuria and new-onset severe feature (elevated LFTs, elevated Cr, low platelets, IUGR)

Sera PAPR cases	17 1/7 – 28 5/7 weeks	25 5/7 – 40 5/7	New-onset hypertension with or without severe features **OR**	Superimpo sed preeclamps ia with or without severe features, **OR**		Proteinuria and new-onset severe feature (elevated LFTs, elevated Cr, low platelets, IUGR)	
UCSD controls	19-27 weeks	25-41 weeks	No hypertensive disease				
Sera PAPR controls	17 1/7 – 28 5/7 weeks	37 0/7 – 41 4/7 weeks					

[00306]   Table 2. Sample, maternal, and pregnancy conditions and identifiers

Field	Description
Batch	Small RNAseq analysis batch
SampleName	Sample Name
GASampleCollection	Gestational Age at Sample Collection
GADelivery	Gestational Age at Delivery
BMI	First recorded maternal BMI during pregnancy episode
MaternalAge	Maternal Age at Delivery
Race	Maternal Race (self-reported)
Ethnicity	Maternal Ethnicity (self-reported)
Birthweight	Birthweight
Gender	Fetal sex
BW%	Birthweight Percentile (Calculated using Hadlock and Fenton)
Diagnosis	Detailed Placental Dysfunction Diagnosis
Diagnosis_simple	Simple Placental Dysfunction Diagnosis (Normal, Pree)
Diagnosis_mild_severe	Intermediate Placental Dysfunction Diagnosis (Normal, Pree_Mild, Pree_Severe)
Diagnosis_Diabetes	Diabetes Diagnosis (No Diabetes, GDM, T2DM, T1DM)
IUGR	Birthweight <10th percentile (YES, NO)

[00307]   <u>Lab Analysis</u>

[00308]   Total extracellular RNA (exRNA) from each sample was purified and subjected to small RNA sequencing.

[00309]   Total extracellular RNA was purified from 500 µL serum using the miRNeasy micro kit (Qiagen), followed by the RNA Clean and Concentrator Kit (Zymo), with a final elution volume of 12 µL. 1.2 µL of the resulting exRNA was used to prepare the Small RNAseq libraries using the NEBNext Small RNA Sequencing Library Preparation Kit, using the

manufacturer's instruction except for the following: 1. Adapters were diluted 1:6; 2. The reactions were run at $1/5^{th}$ volume using a mosquito HTS liquid handler. Up to 384 libraries were prepared in a given batch (some of the libraries for this project were prepared in the same batches as other projects), and libraries were multiplexed using the available 48 NEB Small RNAseq indices. Up to 48 samples were combined per pool, and each pool was size selected using a Pippin Prep (either 177-180 bp, or 125-160 bp). Samples were sequenced on a HiSeq 4000. Each pool of up to 48 samples was loaded onto its own lane, generating at least 350 million single-end 75 bp reads.

[00310]   Data Analysis

[00311]   Data preprocessing, including adapter trimming and mapping to miRBase (ref to miRbase version), was performed using the ExceRpt pipeline on the Genboree Workbench (which can be accessed at exRNA.org), to yield Raw Count data.

[00312]   Further filtering removed individual miRNAs with > 70% missing values. Batch normalization was carried out using Variance Stabilizing Transformation and Bias Reduction. The PEER package (Sanger Institute) was run to further to reduce batch effect and amplify preeclampsia signal. Replicate data was then collapsed to single values. AUCs were generated with the pROC package, using the Delong and bootstrap methods to establish the confidence intervals (CIs). Analysis was performed using R 3.6.3 (Robin et al., BMC bioinformatics 12:77 (2011)).

[00313]   Univariate miRNA models were fit to the entire GABD dataset range with an interaction term with GABD to allow for GABD dependence of performance. Univariate models and bivariate reversals (ratios of miRNAs) were selected by ranking performance.

[00314]   Lower 25% DeLong's CI and AUC for prediction of Preeclampsia was determined.

[00315]   Pearson correlation of score with diagnosis of Preeclampsia (1) or not (0) was determined.

[00316]   T-test p-value significance in score between cases and controls was determined.

[00317]　Numeric performance data were converted to ranks, inverted and summed to produce a final ranking.

[00318]　Top ranking reversals may be:

a) Formed into tree-like or additive (lasso) panel hypotheses of robust performance across multiple weeks.

b) Formed into combined protein / RNA hypotheses to the extent that proteomic data are available in the same samples.

c) Re-verified or validated as univariate, bivariate and panel hypotheses in a future small RNA sequencing data set, for example comprising blinded UCSD samples.

[00319]　Table 3. Top-ranked single microRNAs predicting preeclampsia as interaction terms with GABD

microRNA	Lower 25%CI of AUC	AUC	Correlation (R^2)	T-test p-value	Final ranking
hsa-miR-516b-5p	0.573	0.649	0.228	2.67E-03	1
hsa-miR-30c-5p	0.532	0.616	0.218	4.72E-03	2
hsa-miR-1-3p	0.550	0.629	0.155	2.03E-02	3
hsa-miR-331-3p	0.537	0.617	0.201	5.79E-03	4
hsa-miR-485-5p	0.525	0.606	0.207	5.13E-03	5
hsa-miR-181d-5p	0.550	0.628	0.170	1.54E-02	6
hsa-miR-23a-3p	0.531	0.612	0.197	7.33E-03	7
hsa-miR-378d	0.521	0.601	0.201	6.72E-03	8
hsa-miR-155-5p	0.531	0.610	0.176	1.28E-02	9
hsa-miR-99b-3p	0.527	0.608	0.173	1.37E-02	10
hsa-miR-1249-3p	0.521	0.602	0.179	1.14E-02	11
hsa-miR-142-3p	0.507	0.587	0.189	7.71E-03	12
hsa-miR-4433b-5p	0.525	0.604	0.180	1.44E-02	13
hsa-miR-1273h-3p	0.513	0.593	0.181	9.15E-03	14
hsa-miR-18a-3p	0.528	0.606	0.143	2.74E-02	15
hsa-miR-4746-5p	0.527	0.607	0.142	3.42E-02	16

hsa-miR-27a-5p	0.527	0.605	0.147	2.45E-02	17
hsa-miR-654-3p	0.512	0.594	0.175	1.17E-02	18
hsa-miR-7-5p	0.502	0.584	0.182	1.56E-02	19
hsa-miR-941	0.520	0.599	0.152	2.09E-02	20

[00320]   Table 4. Top ranked pairs of microRNAs predicting preeclampsia as a ratio in an interaction term with GABD

microRNA pair	Lower 25%CI of AUC	AUC	Correlation (R^2)	T-test p-value	Final ranking
hsa-miR-140-3p / hsa-miR-516b-5p	0.611	0.684	0.319	8.26E-06	1
hsa-miR-155-5p / hsa-miR-625-3p	0.610	0.685	0.201	4.23E-03	2
hsa-miR-30c-5p/ hsa-miR-27b-3p	0.596	0.674	0.337	2.12E-05	3
hsa-miR-25-5p/ hsa-miR-516b-5p	0.603	0.679	0.326	2.65E-05	4
hsa-miR-484/ hsa-miR-516b-5p	0.599	0.673	0.310	2.05E-05	5
hsa-miR-516b-5p/ hsa-let-7b-5p	0.605	0.678	0.289	1.17E-04	6
hsa-miR-30c-5p/ hsa-miR-7-5p	0.590	0.667	0.324	2.92E-05	7
hsa-miR-516b-5p/ hsa-miR-486-5p	0.605	0.679	0.282	2.02E-04	8
hsa-miR-516b-5p/ hsa-miR-150-5p	0.601	0.675	0.305	6.54E-05	9
hsa-miR-485-5p/ hsa-miR-516b-5p	0.594	0.674	0.314	4.10E-05	10
hsa-miR-7-5p/ hsa-miR-485-5p	0.595	0.672	0.317	1.01E-04	11
hsa-miR-516b-5p/ hsa-let-7g-5p	0.603	0.676	0.282	1.88E-04	12
hsa-miR-30c-5p/ hsa-miR-16-5p	0.591	0.668	0.316	8.97E-05	13
hsa-miR-516b-5p/ hsa-miR-423-5p	0.603	0.676	0.268	3.63E-04	14
hsa-miR-30c-5p/ hsa-miR-30a-5p	0.579	0.658	0.310	7.25E-05	15

hsa-miR-516b-5p/ hsa-miR-92a-3p	0.601	0.675	0.275	3.65E-04	16
hsa-miR-186-5p/ hsa-miR-516b-5p	0.594	0.669	0.298	8.50E-05	17
hsa-miR-155-5p/ hsa-miR-27b-3p	0.599	0.676	0.235	1.40E-03	18
hsa-miR-30e-5p/ hsa-miR-516b-5p	0.600	0.675	0.263	3.05E-04	19
hsa-miR-516b-5p/ hsa-let-7d-5p	0.600	0.674	0.278	3.96E-04	20
hsa-miR-516b-5p/ hsa-miR-103a-3p	0.599	0.674	0.281	2.53E-04	21
hsa-miR-516b-5p/ hsa-miR-126-3p	0.600	0.673	0.275	3.28E-04	22
hsa-miR-99b-3p/ hsa-miR-486-3p	0.593	0.670	0.288	1.19E-04	23
hsa-miR-6741-5p/ hsa-miR-760	0.579	0.657	0.300	1.29E-04	24
hsa-miR-20a-5p/ hsa-miR-485-5p	0.588	0.666	0.299	2.19E-04	25
hsa-miR-23a-3p/ hsa-miR-27b-3p	0.590	0.668	0.294	1.54E-04	26
hsa-miR-516b-5p/ hsa-miR-151a-3p	0.600	0.673	0.259	6.97E-04	27
hsa-miR-30a-5p/ hsa-miR-485-5p	0.577	0.655	0.305	3.05E-04	28
hsa-miR-516b-5p/ hsa-let-7a-5p	0.598	0.673	0.280	3.33E-04	29
hsa-miR-30c-5p/ hsa-miR-27a-3p	0.576	0.655	0.298	1.57E-04	30
hsa-miR-485-5p/ hsa-miR-7-5p	0.575	0.654	0.296	1.32E-04	31
hsa-miR-516b-5p/ hsa-miR-222-3p	0.599	0.673	0.252	8.72E-04	32
hsa-miR-23a-3p/ hsa-miR-30a-5p	0.576	0.655	0.285	1.17E-04	33
hsa-miR-433-3p/ hsa-miR-345-5p	0.597	0.671	0.268	4.74E-04	34
hsa-miR-516b-5p/ hsa-let-7f-5p	0.594	0.669	0.280	3.32E-04	35
hsa-miR-485-5p/ hsa-miR-183-5p	0.583	0.662	0.286	1.75E-04	36

hsa-miR-516b-5p/ hsa-miR-185-5p	0.597	0.672	0.252	9.93E-04	37
hsa-let-7i-5p/ hsa-miR-485-5p	0.577	0.656	0.298	4.43E-04	38
hsa-miR-4433b-5p/ hsa-miR-516b-5p	0.585	0.661	0.280	1.38E-04	39
hsa-miR-516b-5p/ hsa-miR-191-5p	0.595	0.670	0.262	5.94E-04	40
hsa-miR-516b-5p/ hsa-miR-3615	0.596	0.671	0.249	9.89E-04	41
hsa-miR-100-5p/ hsa-miR-516b-5p	0.576	0.652	0.271	1.28E-04	42
hsa-miR-516b-5p/ hsa-miR-10b-5p	0.595	0.669	0.267	6.35E-04	43
hsa-miR-485-5p/ hsa-miR-27a-3p	0.573	0.653	0.287	1.91E-04	44
hsa-miR-99a-5p/ hsa-miR-485-5p	0.568	0.648	0.298	4.88E-04	45
hsa-miR-99b-3p/ hsa-miR-6852-5p	0.583	0.659	0.281	2.14E-04	46
hsa-miR-363-3p/ hsa-miR-485-5p	0.571	0.651	0.294	3.88E-04	47
hsa-miR-516b-5p/ hsa-miR-484	0.587	0.662	0.276	2.82E-04	48
hsa-miR-516b-5p/ hsa-let-7i-5p	0.593	0.666	0.269	3.95E-04	49
hsa-miR-23a-3p/ hsa-miR-181a-5p	0.585	0.663	0.277	2.57E-04	50
hsa-miR-7-5p/ hsa-miR-516b-5p	0.583	0.658	0.269	1.90E-04	51
hsa-miR-516b-5p/ hsa-miR-328-3p	0.590	0.665	0.270	3.72E-04	52
hsa-miR-181a-5p/ hsa-miR-485-5p	0.577	0.655	0.292	5.70E-04	53
hsa-miR-155-5p/ hsa-miR-30a-5p	0.593	0.670	0.229	1.16E-03	54
hsa-miR-155-5p/ hsa-let-7i-5p	0.593	0.670	0.202	4.71E-03	55
hsa-miR-98-5p/ hsa-miR-485-5p	0.572	0.650	0.289	3.58E-04	56
hsa-miR-485-5p/ hsa-miR-127-3p	0.579	0.656	0.276	2.37E-04	57

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hsa-miR-320b/ hsa-miR-485-5p	0.565	0.644	0.294	6.13E-04	58
hsa-miR-516b-5p/ hsa-miR-25-3p	0.590	0.664	0.267	4.74E-04	59
hsa-miR-516b-5p/ hsa-miR-148a-3p	0.593	0.668	0.242	1.44E-03	60
hsa-miR-516b-5p/ hsa-miR-128-3p	0.591	0.665	0.263	6.09E-04	61
hsa-miR-516b-5p/ hsa-miR-320a	0.590	0.665	0.263	5.60E-04	62
hsa-miR-516b-5p/ hsa-miR-744-5p	0.592	0.666	0.252	8.68E-04	63
hsa-miR-30c-5p/ hsa-miR-186-5p	0.559	0.639	0.292	4.21E-04	64
hsa-miR-516b-5p/ hsa-miR-629-5p	0.588	0.664	0.259	5.52E-04	65
hsa-miR-23a-3p/ hsa-miR-93-5p	0.576	0.654	0.277	3.02E-04	66
hsa-miR-127-3p/ hsa-miR-485-5p	0.572	0.650	0.289	6.46E-04	67
hsa-miR-155-5p/ hsa-miR-451a	0.591	0.668	0.204	3.91E-03	68
hsa-miR-30c-5p/ hsa-miR-26b-5p	0.545	0.623	0.278	1.94E-04	69
hsa-miR-4732-3p/ hsa-miR-516b-5p	0.580	0.658	0.249	3.20E-04	70
hsa-miR-7-5p/ hsa-miR-941	0.589	0.665	0.257	1.05E-03	71
hsa-miR-451a/ hsa-miR-485-5p	0.570	0.650	0.288	6.74E-04	72
hsa-miR-374b-5p/ hsa-miR-885-3p	0.547	0.628	0.292	5.74E-04	73
hsa-miR-516b-5p/ hsa-miR-1307-3p	0.587	0.662	0.259	5.89E-04	74
hsa-miR-516b-5p/ hsa-miR-30d-5p	0.588	0.662	0.256	8.34E-04	75
hsa-miR-3605-5p/ hsa-miR-425-3p	0.580	0.656	0.264	3.41E-04	76
hsa-miR-501-3p/ hsa-miR-516b-5p	0.571	0.647	0.260	2.38E-04	77
hsa-miR-125b-5p/ hsa-miR-485-5p	0.573	0.652	0.286	6.26E-04	78

hsa-miR-26b-5p/ hsa-miR-485-5p	0.578	0.654	0.279	4.64E-04	79
hsa-miR-30c-5p/ hsa-miR-99a-5p	0.565	0.645	0.281	3.90E-04	80
hsa-miR-516b-5p/ hsa-miR-127-3p	0.589	0.664	0.239	1.42E-03	81
hsa-miR-501-3p/ hsa-miR-485-5p	0.564	0.643	0.287	5.90E-04	82
hsa-miR-30c-5p/ hsa-miR-451a	0.569	0.650	0.282	5.45E-04	83
hsa-miR-21-5p/ hsa-miR-485-5p	0.562	0.641	0.288	7.62E-04	84
hsa-miR-516b-5p/ hsa-miR-423-3p	0.586	0.661	0.259	7.42E-04	85
hsa-miR-516b-5p/ hsa-miR-146b-5p	0.587	0.662	0.247	9.06E-04	86
hsa-miR-330-5p/ hsa-miR-92b-5p	0.585	0.663	0.261	1.51E-03	87
hsa-miR-4443/ hsa-miR-485-5p	0.545	0.627	0.290	8.81E-04	88
hsa-miR-30c-5p/ hsa-let-7i-5p	0.559	0.642	0.285	5.10E-04	89
hsa-miR-516b-5p/ hsa-miR-425-5p	0.586	0.662	0.250	7.93E-04	90
hsa-miR-516b-5p/ hsa-miR-24-3p	0.587	0.661	0.256	8.04E-04	91
hsa-miR-146b-5p/ hsa-miR-485-5p	0.572	0.650	0.283	8.97E-04	92
hsa-miR-760/ hsa-miR-378g	0.565	0.642	0.261	3.01E-04	93
hsa-miR-3615/ hsa-miR-485-5p	0.576	0.653	0.281	9.17E-04	94
hsa-miR-140-3p/ hsa-miR-485-5p	0.564	0.644	0.281	5.23E-04	95
hsa-miR-30c-5p/ hsa-miR-125a-5p	0.566	0.647	0.280	4.74E-04	96
hsa-miR-378c/ hsa-miR-148a-5p	0.571	0.647	0.259	3.23E-04	97
hsa-let-7b-5p/ hsa-miR-485-5p	0.577	0.655	0.280	9.35E-04	98
hsa-miR-516b-5p/ hsa-miR-146a-5p	0.583	0.657	0.258	6.27E-04	99

hsa-miR-516b-5p/ hsa-miR-451a	0.583	0.658	0.259	6.90E-04	100

[00321]   **Example 2:** Identification of Extracellular micro RNA Biomarkers Across Three Gestational Windows for Identification of Pregnancies at Risk for Placental Dysfunction

[00322]   This example shows identification of extracellular miRNA biomarkers across three gestational windows for prediction of preeclampsia: placental dysfunction affecting maternal blood pressure and renal, liver and central nervous system function.

[00323]   Study Design and Lab Analysis

[00324]   Samples were collected and analyzed as described above in Example 1.

[00325]   Data Analysis

[00326]   miRNAs were evaluated across three windows of gestational age at blood draw (GABD) including early (119-153), late (154-196) and full (119-202) days of gestation. A variation of a stacking algorithm was used, in which four modeling approaches were combined with a brute force approach to rank each miRNA in the dataset within each GABD window by an inverse rank sum metric. The four algorithms were MRPC using MRPC $\geq$ 2.2.1, LASSO using glmnet $\geq$ 4.0, conditional inference trees using party $\geq$ 1.3 and gradient boosting using xgboost $\geq$ 1.2.0.1. To control for analytic variability of reversals (ratios of log counts) of miRNAs, instead of single miRNAs, were identified as predictors in candidate models for validation. To assess performance of miRNAs within reversals, a fifth, brute-force ranking based on significance of enrichment of individual miRNAs amongst the top performing reversals was added. Top reversals per GABD window were determined by first ranking all reversals by inverse rank sum, then incrementally building a matrix of reversal scores in order of ranking and selecting as a cutpoint the number of reversals in the matrix at which a plateau was reached for significance of association of the first principal component in PCA with the outcome. Each of the different learning methods ranked the miRNAs from most important to least important and the final score was determined by taking a weighted inverse rank sum across all the different models plus the brute force approach. This approach generated the list of miRNAs in Table 5.

[00327]   To further characterize miRNAs in Table 5, two additional analyses were applied. First, it was tested whether the difference in the logarithm of miRNA levels between cases and controls was significant by the Wilcoxon test in processed miRNA assay data. Second, it was tested whether the direction of median shift seen in the processed data could be reproduced in noisy data in a future assay as represented by the raw RNAseq data before processing.

[00328]   Table 5. Top ranked microRNAs predicting preeclampsia in an interaction term with GABD windows.

microRNA	Significant in Windows	Window(s), with batch-independent median shift	Cases relative to controls, full window (GABD 119-202)	Cases relative to controls, early window (GABD 119-153)	Cases relative to controls, late window (GABD 154-196)
hsa-miR-30c-5p	full, late	early	lower	lower	lower
hsa-miR-6842-3p	full	early, late	lower	lower	lower
hsa-miR-485-5p	full, late	full, late	lower	lower	lower
hsa-miR-331-3p	full, late	full, early, late	lower	lower	lower
hsa-miR-517a-3p-hsa-miR-517b-3p	early, late	early, late	lower	lower	higher
hsa-miR-516b-5p	early, late	early, late	higher	lower	higher
hsa-miR-760	full, early	full, late	lower	lower	lower
hsa-miR-6852-5p	early	full	higher	higher	lower
hsa-miR-1323	early	full, early, late	lower	lower	higher
hsa-miR-155-5p	late	full, early, late	lower	higher	lower
hsa-miR-6747-3p	full, late	full, late	lower	higher	lower
hsa-miR-181d-5p	late	full, late	lower	higher	lower
hsa-miR-4446-3p	full, late	full, early, late	lower	higher	lower

[00329]   The above analysis identified thirteen miRNAs in Table 5 that can predict preeclampsia in early, late or full gestational age in cases relative to controls. The thirteen miRNAs can predict preeclampsia singly or as reversals of one another.

[00330] From the foregoing description, it will be apparent that variations and modifications can be made to the invention described herein to adopt it to various usages and conditions. Such embodiments are also within the scope of the following claims.

[00331] The recitation of a listing of elements in any definition of a variable herein includes definitions of that variable as any single element or combination (or subcombination) of listed elements. The recitation of an embodiment herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

[00332] All patents and publications mentioned in this specification are herein incorporated by reference to the same extent as if each independent patent and publication was specifically and individually indicated to be incorporated by reference.

What is claimed is:

1.   A panel of isolated nucleic acid biomarkers comprising two or more of the nucleic acid biomarkers listed in Tables 3, 4 or 5.

2.   A panel of isolated nucleic acid biomarkers comprising two or more of the nucleic acid biomarkers listed in Table 3.

3.   A panel of isolated nucleic acid biomarkers comprising two or more of the isolated biomarkers selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

4.   The panel of claim 3, wherein the isolated biomarkers comprise hsa-miR-1-3p, hsa-miR-181d-5p, hsa-miR-378d, hsa-miR-4433b-5p, and/or hsa-miR-27a-5p.

5.   The panel of claim 3, wherein the isolated biomarkers comprise hsa-miR-516b-5p and/or hsa-miR-30c-5p.

6.   The panel of claim 3, wherein the isolated biomarkers hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, and/or hsa-miR-331-3p.

7.   The panel of claim 3, wherein the isolated biomarkers comprise hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, and/or hsa-miR-181d-5p.

8.   A panel of isolated nucleic acid biomarkers comprising a pair of biomarkers selected from the group consisting of the biomarker pairs listed in Table 4.

9.   A panel of isolated nucleic acid biomarkers comprising a pair of biomarkers selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-

5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

10. The panel of claim 9, wherein the pair of biomarkers is selected from the group consisting of hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-

30c-5p/hsa-miR-16-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-24-3p, and hsa-miR-378c/hsa-miR-148a-5p.

11. The panel of claim 9, wherein the pair of biomarkers is selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, and hsa-miR-484/hsa-miR-516b-5p.

12. The panel of claim 9, wherein the pair of biomarkers is selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, and hsa-miR-30c-5p/hsa-miR-7-5p.

13. The panel of claim 9, wherein the pair of biomarkers is selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, and hsa-miR-485-5p/hsa-miR-516b-5p.

14. The panel of claim 9, wherein the pair of biomarkers is selected from the group consisting of hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-516b-5p/ hsa-miR-423-5p and hsa-miR-155-5p/ hsa-let-7i-5p.

15. A panel of isolated nucleic acid biomarkers comprising at least one of the nucleic acid biomarkers listed in Table 5.

16. A panel of isolated nucleic acid biomarkers comprising at least one of the nucleic biomarkers selected from the group consisting of hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760,

hsa-miR-6852-5p, hsa-miR-1323, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p.

17. The panel of claim 15 or 16, wherein the biomarker is selected from the group consisting of hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, and hsa-miR-1323.

18. The panel of claim 15 or 16, wherein the biomarker is selected from the group consisting of hsa-miR-30c-5p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p.

19. The panel of claim 15 or 16, wherein the biomarker is selected from the group consisting of hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-760, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p.

20. A composition of labeled and/or amplified nucleic acid molecules, wherein said labeled and/or amplified nucleic acid molecules correspond to two or more of the nucleic acid biomarkers listed in Tables 3, 4 or 5.

21. A composition of labeled and/or amplified nucleic acid molecules, wherein said labeled and/or amplified nucleic acid molecules correspond to two or more of the nucleic acid biomarkers listed in Table 3.

22. A composition of labeled and/or amplified nucleic acid molecules, wherein said labeled and/or amplified nucleic acid molecules correspond to two or more of the nucleic acid biomarkers selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941.

23. The composition of claim 22, wherein the nucleic acid biomarkers comprise hsa-miR-1-3p, hsa-miR-181d-5p, hsa-miR-378d, hsa-miR-4433b-5p, and/or hsa-miR-27a-5p.

24. The composition of claim 22, wherein the isolated biomarkers comprise hsa-miR-516b-5p and/or hsa-miR-30c-5p.

25. The composition of claim 22, wherein the nucleic acid biomarkers hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, and/or hsa-miR-331-3p.

26. The composition of claim 22, wherein the nucleic acid biomarkers comprise hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, and/or hsa-miR-181d-5p.

27. A composition of labeled and/or amplified nucleic acid molecules, wherein said labeled and/or amplified nucleic acid molecules correspond to a pair of biomarkers selected from the group consisting of the biomarker pairs listed in Table 4.

28. A composition of labeled and/or amplified nucleic acid molecules, wherein said labeled and/or amplified nucleic acid molecules correspond to a pair of biomarkers selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-

744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a.

29.   The composition of claim 28, wherein the pair of biomarkers is selected from the group consisting of hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-24-3p, and hsa-miR-378c/hsa-miR-148a-5p.

30.   The composition of claim 28, wherein the pair of biomarkers is selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, and hsa-miR-484/hsa-miR-516b-5p.

31. The composition of claim 28, wherein the pair of biomarkers is selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, and hsa-miR-30c-5p/hsa-miR-7-5p.

32. The composition of claim 28, wherein the pair of biomarkers is selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, and hsa-miR-485-5p/hsa-miR-516b-5p.

33. The composition of claim 28, wherein the pair of biomarkers is selected from the group consisting of hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-516b-5p/ hsa-miR-423-5p and hsa-miR-155-5p/ hsa-let-7i-5p.

34. A composition of labeled and/or amplified nucleic acid molecules, wherein said labeled and/or amplified nucleic acid molecules correspond to at least one of the biomarkers selected from the group consisting of the biomarkers listed in Table 5.

35. A composition of labeled and/or amplified nucleic acid molecules comprising at least one of the nucleic biomarkers selected from the group consisting of hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, hsa-miR-1323, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p.

36. The composition of claim 34 or 35, wherein the biomarker is selected from the group consisting of hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, and hsa-miR-1323.

37. The composition of claim 34 or 35, wherein the biomarker is selected from the group consisting of hsa-miR-30c-5p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p.

38. The composition of claim 34 or 35, wherein the biomarker is selected from the group consisting of hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-760, hsa-miR-6747-3p, hsa-miR-181d-5p and hsa-miR-4446-3p.

39. A method for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising measuring the amount of two or more of the nucleic acid biomarkers listed in Tables 3, 4 or 5 in a biological sample obtained from the pregnant female, calculating a risk score based upon the measured amounts of the nucleic acid biomarkers to determine the pregnant female's risk of developing placental dysfunction, and providing a score corresponding to the pregnant female's risk of developing placental dysfunction.

40. A method for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising producing labeled and/or amplified nucleic acid molecules that correspond to two or more of the nucleic acid biomarkers listed in Tables 3, 4 or 5 in a biological sample obtained from the pregnant female; measuring the levels of expression of the labeled and/or amplified nucleic acid molecules; calculating a risk score based upon the measured levels of the labeled and/or amplified nucleic acid molecules to determine the pregnant female's risk of developing placental dysfunction.

41. The method of claim 39 or 40, wherein the biological sample is obtained between 17 and 29 weeks of gestational age at blood draw.

42. The method of claim 39 or 40, wherein the biological sample is obtained between 19 and 27 weeks of gestational age at blood draw.

43. The method of claim 39 or 40, wherein the biological sample is obtained between 17 and 36 weeks of gestational age at blood draw.

44. The method of claim 39 or 40, wherein the biological sample is obtained more than 17, more than 18, more than 19, more than 20, more than 21, more than 22, more than 23, more than 24, more than 25, more than 26, more than 27, more than 28, more than 29, more than 30, more than 31, more than 32, more than 33, more than 34, or more than 35 weeks of gestational age at blood draw.

45. The method of claim 39 or 40, wherein the biological sample is obtained between 119-153 days, 154-196 days, and/or 119-202 days.

46. A method for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising measuring the amount of two or more of the nucleic acid biomarkers selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-

miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941 in a biological sample obtained from the pregnant female, calculating a risk score based upon the measured amounts of the nucleic acid biomarkers to determine the pregnant female's risk of developing placental dysfunction, and providing a score corresponding to the pregnant female's risk of developing placental dysfunction.

47.   The method of claim 46, wherein the nucleic acid biomarkers comprise hsa-miR-1-3p, hsa-miR-181d-5p, hsa-miR-378d, hsa-miR-4433b-5p, and/or hsa-miR-27a-5p.

48.   The method of claim 46, wherein the nucleic acid biomarkers comprise hsa-miR-516b-5p and/or hsa-miR-30c-5p.

49.   The method of claim 46, wherein the nucleic acid biomarkers hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, and/or hsa-miR-331-3p.

50.   The method of claim 46, wherein the nucleic acid comprise hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, and/or hsa-miR-181d-5p.

51.   A method for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising producing labeled and/or amplified nucleic acid molecules that correspond to two or more of the nucleic acid biomarkers selected from the group consisting of hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, hsa-miR-181d-5p, hsa-miR-23a-3p, hsa-miR-378d, hsa-miR-155-5p, hsa-miR-99b-3p, hsa-miR-1249-3p, hsa-miR-142-3p, hsa-miR-4433b-5p, hsa-miR-1273h-3p, hsa-miR-18a-3p, hsa-miR-4746-5p, hsa-miR-27a-5p, hsa-miR-654-3p, hsa-miR-7-5p, and hsa-miR-941 in a biological sample obtained from the pregnant female; measuring the levels of expression of the labeled and/or amplified nucleic acid molecules; calculating a risk score based upon the measured levels of the labeled and/or amplified nucleic acid molecules to determine the pregnant female's risk of developing placental dysfunction.

52.   The method of claim 51, wherein the nucleic acid biomarkers comprise hsa-miR-1-3p, hsa-miR-181d-5p, hsa-miR-378d, hsa-miR-4433b-5p, and/or hsa-miR-27a-5p.

53.   The method of claim 51, wherein the nucleic acid biomarkers comprise hsa-miR-516b-5p and/or hsa-miR-30c-5p.

54.   The method of claim 51, wherein the nucleic acid biomarkers hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, and/or hsa-miR-331-3p.

55.   The method of claim 51, wherein the nucleic acid biomarkers comprise hsa-miR-516b-5p, hsa-miR-30c-5p, hsa-miR-1-3p, hsa-miR-331-3p, hsa-miR-485-5p, and/or hsa-miR-181d-5p.

56.   A method for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising measuring the amount of a pair of biomarkers selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-

miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a in a biological sample obtained from the pregnant female, calculating a risk score based upon the measured amounts of the nucleic acid biomarker pair to determine the pregnant female's risk of developing placental dysfunction, and providing a score corresponding to the pregnant female's risk of developing placental dysfunction.

57.   The method of claim 56, wherein the pair of biomarkers is selected from the group consisting of hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-24-3p, and hsa-miR-378c/hsa-miR-148a-5p.

58.   The method of claim 56, wherein the pair of biomarkers is selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, and hsa-miR-484/hsa-miR-516b-5p.

59. The method of claim 56, wherein the pair of biomarkers is selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, and hsa-miR-30c-5p/hsa-miR-7-5p.

60. The method of claim 56, wherein the pair of biomarkers is selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, and hsa-miR-485-5p/hsa-miR-516b-5p.

61. The method of claim 56, wherein the pair of biomarkers is selected from the group consisting of hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-516b-5p/ hsa-miR-423-5p and hsa-miR-155-5p/ hsa-let-7i-5p.

62. A method for determining a pregnant female's risk of developing placental dysfunction later in the pregnancy comprising producing labeled and/or amplified nucleic acid molecules that correspond to a pair of biomarkers selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-485-5p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7g-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-516b-5p/hsa-miR-423-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-186-5p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-516b-5p/hsa-miR-126-3p, hsa-miR-99b-3p/hsa-miR-486-3p, hsa-miR-6741-5p/hsa-miR-760, hsa-miR-20a-5p/hsa-miR-485-5p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-151a-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-30c-5p/hsa-miR-27a-3p, hsa-miR-485-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-23a-3p/hsa-miR-30a-5p, hsa-miR-433-3p/hsa-miR-345-5p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-516b-5p/hsa-miR-185-5p, hsa-let-7i-5p/hsa-miR-485-5p, hsa-miR-4433b-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-191-5p, hsa-miR-516b-5p/hsa-miR-3615, hsa-miR-100-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-485-5p/hsa-miR-27a-3p, hsa-miR-99a-

5p/hsa-miR-485-5p, hsa-miR-99b-3p/hsa-miR-6852-5p, hsa-miR-363-3p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-484, hsa-miR-516b-5p/hsa-let-7i-5p, hsa-miR-23a-3p/hsa-miR-181a-5p, hsa-miR-7-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-181a-5p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-155-5p/hsa-let-7i-5p, hsa-miR-98-5p/hsa-miR-485-5p, hsa-miR-485-5p/hsa-miR-127-3p, hsa-miR-320b/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-25-3p, hsa-miR-516b-5p/hsa-miR-148a-3p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-320a, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-30c-5p/hsa-miR-186-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-127-3p/hsa-miR-485-5p, hsa-miR-155-5p/hsa-miR-451a, hsa-miR-30c-5p/hsa-miR-26b-5p, hsa-miR-4732-3p/hsa-miR-516b-5p, hsa-miR-7-5p/hsa-miR-941, hsa-miR-451a/hsa-miR-485-5p, hsa-miR-374b-5p/hsa-miR-885-3p, hsa-miR-516b-5p/hsa-miR-1307-3p, hsa-miR-516b-5p/hsa-miR-30d-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-501-3p/hsa-miR-516b-5p, hsa-miR-125b-5p/hsa-miR-485-5p, hsa-miR-26b-5p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-99a-5p, hsa-miR-516b-5p/hsa-miR-127-3p, hsa-miR-501-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-451a, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-423-3p, hsa-miR-516b-5p/hsa-miR-146b-5p, hsa-miR-330-5p/hsa-miR-92b-5p, hsa-miR-4443/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-let-7i-5p, hsa-miR-516b-5p/hsa-miR-425-5p, hsa-miR-516b-5p/hsa-miR-24-3p, hsa-miR-146b-5p/hsa-miR-485-5p, hsa-miR-760/hsa-miR-378g, hsa-miR-3615/hsa-miR-485-5p, hsa-miR-140-3p/hsa-miR-485-5p, hsa-miR-30c-5p/hsa-miR-125a-5p, hsa-miR-378c/hsa-miR-148a-5p, hsa-let-7b-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-146a-5p, and hsa-miR-516b-5p/hsa-miR-451a in a biological sample obtained from the pregnant female; measuring the levels of expression of the labeled and/or amplified nucleic acid molecules; calculating a risk score based upon the measured levels of the labeled and/or amplified nucleic acid molecules to determine the pregnant female's risk of developing placental dysfunction.

63.   The method of claim 62, wherein the pair of biomarkers is selected from the group consisting of hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-516b-5p/hsa-miR-150-5p, hsa-miR-30c-5p/hsa-miR-16-5p, hsa-miR-30c-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-92a-3p, hsa-miR-155-5p/hsa-miR-27b-3p, hsa-miR-30e-5p/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7d-5p, hsa-miR-516b-5p/hsa-miR-103a-3p, hsa-miR-23a-3p/hsa-miR-27b-3p, hsa-miR-30a-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-let-7a-5p, hsa-miR-516b-5p/hsa-miR-222-3p, hsa-miR-516b-5p/hsa-let-7f-5p, hsa-miR-485-5p/hsa-miR-183-5p, hsa-miR-4433b-5p/hsa-miR-

516b-5p, hsa-miR-516b-5p/hsa-miR-10b-5p, hsa-miR-516b-5p/hsa-miR-328-3p, hsa-miR-155-5p/hsa-miR-30a-5p, hsa-miR-516b-5p/hsa-miR-128-3p, hsa-miR-516b-5p/hsa-miR-744-5p, hsa-miR-516b-5p/hsa-miR-629-5p, hsa-miR-23a-3p/hsa-miR-93-5p, hsa-miR-3605-5p/hsa-miR-425-3p, hsa-miR-21-5p/hsa-miR-485-5p, hsa-miR-516b-5p/hsa-miR-24-3p, and hsa-miR-378c/hsa-miR-148a-5p.

64.   The method of claim 62, wherein the pair of biomarkers is selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, and hsa-miR-484/hsa-miR-516b-5p.

65.   The method of claim 62, wherein the pair of biomarkers is selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, and hsa-miR-30c-5p/hsa-miR-7-5p.

66.   The method of claim 62, wherein the pair of biomarkers is selected from the group consisting of hsa-miR-140-3p/hsa-miR-516b-5p, hsa-miR-155-5p/hsa-miR-625-3p, hsa-miR-30c-5p/hsa-miR-27b-3p, hsa-miR-25-5p/hsa-miR-516b-5p, hsa-miR-484/hsa-miR-516b-5p, hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-30c-5p/hsa-miR-7-5p, hsa-miR-516b-5p/hsa-miR-486-5p, hsa-miR-516b-5p/hsa-miR-150-5p, and hsa-miR-485-5p/hsa-miR-516b-5p.

67.   The method of claim 62, wherein the pair of biomarkers is selected from the group consisting of hsa-miR-516b-5p/hsa-let-7b-5p, hsa-miR-516b-5p/ hsa-miR-423-5p and hsa-miR-155-5p/ hsa-let-7i-5p.

68.   The method of any one of claims 39-67, wherein the risk score is calculated based on a ratio of data values.

69.   The method of claim 68, wherein data transformation is applied before or after the ratio is determined.

70.   A method for determining a pregnant female's risk of developing placental dysfunction comprising measuring the amount of at least one of the nucleic acid biomarkers selected from the group consisting of hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, hsa-miR-1323, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p in a biological sample obtained from the pregnant female, calculating a risk score based upon the measured amounts of the nucleic acid biomarkers to determine the pregnant female's

risk of developing placental dysfunction, and providing a score corresponding to the pregnant female's risk of developing placental dysfunction.

71.   The method of claim 70, wherein the biomarker is selected from the group consisting of hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, and hsa-miR-1323.

72.   The method of claim 70, wherein the biomarker is selected from the group consisting of hsa-miR-30c-5p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p.

73.   The method of claim 70, wherein the biomarker is selected from the group consisting of hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-760, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p.

74.   The method of claim 70 or 73, wherein the method determines a pregnant female's risk of developing placental dysfunction across the full window of gestation.

75.   The method of claim 70 or 73, wherein the full gestation window of gestation is between 119-202 days of gestation.

76.   The method of claim 70 or 71, wherein the method determines a pregnant female's risk of developing placental dysfunction early in the pregnancy.

77.   The method of claim 70 or 71, wherein early pregnancy is between 119-153 days of gestation.

78.   The method of claim 70 or 72, wherein the method determines a pregnant female's risk of developing placental dysfunction later in the pregnancy.

79.   The method of claim 70 or 72, wherein late pregnancy is between 154-196 days of gestation.

80.   A method for determining a pregnant female's risk of developing placental dysfunction comprising producing labeled and/or amplified nucleic acid molecules that correspond to at least one of the nucleic acid biomarkers selected from the group consisting of hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, hsa-miR-1323, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p in a biological sample obtained from the pregnant female; measuring the levels of expression of the labeled and/or amplified nucleic acid molecules; calculating a risk score based upon the measured levels of the labeled

and/or amplified nucleic acid molecules to determine the pregnant female's risk of developing placental dysfunction.

81. The method of claim 80, wherein the biomarker is selected from the group consisting of hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, and hsa-miR-1323.

82. The method of claim 80, wherein the biomarker is selected from the group consisting of hsa-miR-30c-5p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p.

83. The method of claim 80, wherein the biomarker is selected from the group consisting of hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-760, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p.

84. The method of claim 80 or 83, wherein the method determines a pregnant female's risk of developing placental dysfunction across the full window of gestation.

85. The method of claim 84, wherein the full gestation window of gestation is between 119-202 days of gestation.

86. The method of claim 80 or 81, wherein the method determines a pregnant female's risk of developing placental dysfunction early in the pregnancy.

87. The method of claim 86, wherein early pregnancy is between 119-153 days of gestation.

88. The method of claim 80 or 82, wherein the method determines a pregnant female's risk of developing placental dysfunction later in the pregnancy.

89. The method of claim 88, wherein late pregnancy is between 154-196 days of gestation.

90. A method of treating or preventing placental dysfunction in a pregnant female, the method comprising:

(a) detecting a panel of isolated nucleic acid biomarkers in a biological sample obtained from a pregnant female, wherein at least one of the isolated nucleic acid biomarkers is selected from the group consisting of hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, hsa-miR-1323, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p;

(b)   calculating a risk score based upon the measured levels of the isolated nucleic acid biomarkers; and

(c)   administering one or more therapies to the pregnant female based on the risk score, to treat or prevent placental dysfunction.

91.   The method of claim 90, wherein the biomarker is selected from the group consisting of hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-760, hsa-miR-6852-5p, and hsa-miR-1323.

92.   The method of claim 90, wherein the biomarker is selected from the group consisting of hsa-miR-30c-5p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-517a-3p-hsa-miR-517b-3p, hsa-miR-516b-5p, hsa-miR-155-5p, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p.

93.   The method of claim 90, wherein the biomarker is selected from the group consisting of hsa-miR-30c-5p, hsa-miR-6842-3p, hsa-miR-485-5p, hsa-miR-331-3p, hsa-miR-760, hsa-miR-6747-3p, hsa-miR-181d-5p, and hsa-miR-4446-3p.

94.   The method any one of claims 90-93, wherein the isolated nucleic acid biomarkers are normalized.

95.   The method of claim 94, wherein normalization comprises a reversal of the isolated nucleic acid biomarkers.

96.   The method of claim 95, wherein the reversal comprises an upregulated biomarker and a downregulated biomarker.

97.   The method of claim 96, wherein the downregulated biomarker is hsa-miR-485-5p.

98.   The method of claim 95, wherein the reversal comprises a numerator and a denominator.

99.   The method of claim 98, wherein the denominator is hsa-miR-485-5p.

100.   The method of any one of claims 90-99, wherein the risk score is calculated based on the reversal of data values.

101.   The method of any one of claims 90-100, wherein the method further comprises a step of determining gestational age at blood draw (GABD).

102.   The method of claim 101, wherein determining GABD is performed before the detecting step of claim 90(a).

103.   The method of claim 101 or 102, wherein GABD is between 119-153 days, 154-196 days, and/or 119-202 days.

104. The method of claim 90 or 93, wherein the method determines a pregnant female's risk of developing placental dysfunction across the full window of gestation.

105. The method of claim 104, wherein the full gestation window of gestation is between 119-202 days of gestation.

106. The method of claim 90 or 91, wherein the method determines a pregnant female's risk of developing placental dysfunction early in the pregnancy.

107. The method of claim 106, wherein early pregnancy is between 119-153 days of gestation.

108. The method of claim 90 or 92, wherein the method determines a pregnant female's risk of developing placental dysfunction later in the pregnancy.

109. The method of claim 108, wherein late pregnancy is between 154-196 days of gestation.

110. The method of any one of claims 90-109, wherein the placental dysfunction is preeclampsia.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/036535

Box No. II   Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such
   an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III   Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

    see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable
   claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of
   additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers
   only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is
   restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

    1-37, 39-71, 74-81, 84-92, 94-110(all partially)

Remark on Protest   ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the
   payment of a protest fee.

   ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest
   fee was not paid within the time limit specified in the invitation.

   ☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2005)

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/6883   ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)   C12Q
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)   EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HROMADNIKOVA ILONA ET AL: "The Prediction of Gestational Hypertension, Preeclampsia and Fetal Growth Restriction via the First Trimester Screening of Plasma Exosomal C19MC microRNAs", INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES, vol. 20, no. 12, 18 June 2019 (2019-06-18) , page 2972, XP055841037, DOI: 10.3390/ijms20122972 abstract ----- -/--	1-37, 39-71, 74-81, 84-92, 94-110

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 17 September 2021	Date of mailing of the international search report 22/11/2021
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Knudsen, Henrik

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

C(Continuation).	DOCUMENTS CONSIDERED TO BE RELEVANT	
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ILONA HROMADNIKOVA ET AL: "First trimester screening of circulating C19MC microRNAs and the evaluation of their potential to predict the onset of preeclampsia and IUGR", PLOS ONE, vol. 12, no. 2, 1 January 2017 (2017-01-01), page e0171756, XP055738457, DOI: 10.1371/journal.pone.0171756 abstract -----	1-37, 39-71, 74-81, 84-92, 94-110
Y	ALEXANDER RUDOV ET AL: "Involvement of miRNAs in Placental Alterations Mediated by Oxidative Stress", OXIDATIVE MEDICINE AND CELLULAR LONGEVITY, vol. 19, no. 1-2, 1 January 2014 (2014-01-01), pages 544-7, XP055310691, US ISSN: 1942-0900, DOI: 10.1155/2014/103068 page 3, right-hand column, line 11 -----	1
Y	BENITO CHIOFALO ET AL: "Do miRNAs Play a Role in Fetal Growth Restriction? A Fresh Look to a Busy Corner", BIOMED RESEARCH INTERNATIONAL, vol. 2017, 29 March 2017 (2017-03-29), pages 1-8, XP055685237, ISSN: 2314-6133, DOI: 10.1155/2017/6073167 page 4 -----	1
Y	WANG JIAN-MEI ET AL: "Deep-sequencing identification of differentially expressed miRNAs in decidua and villus of recurrent miscarriage patients", ARCHIVES OF GYNECOLOGY AND OBSTETRICS, SPRINGER VERLAG, BERLIN, DE, vol. 293, no. 5, 15 February 2016 (2016-02-15), pages 1125-1135, XP035879067, ISSN: 0932-0067, DOI: 10.1007/S00404-016-4038-5 [retrieved on 2016-02-15] table 2 -----	1
A	WO 2009/093254 A2 (ROSETTA GENOMICS LTD [IL]; MOR RES APPLIC [IL] ET AL.) 30 July 2009 (2009-07-30) examples 1,3 -----	1-37, 39-71, 74-81, 84-92, 94-110

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C(Continuation).	DOCUMENTS CONSIDERED TO BE RELEVANT	
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2018/265929 A1 (DONG YAFENG [US] ET AL) 20 September 2018 (2018-09-20) Groups 2 and 3; paragraph [0118] -----	1-37, 39-71, 74-81, 84-92, 94-110
A	VASHUKOVA E S ET AL: "MicroRNAs Associated with Preeclampsia", RUSSIAN JOURNAL OF GENETICS, MOSCOW, RU, vol. 56, no. 1, 1 January 2020 (2020-01-01), pages 1-16, XP037012441, ISSN: 1022-7954, DOI: 10.1134/S1022795419080167 [retrieved on 2020-02-06] pages 6-8; table 2 -----	1-37, 39-71, 74-81, 84-92, 94-110
A	NEJAD REZA MOLA ALI ET AL: "Quantification of circulating miR-517c-3p and miR-210-3p levels in preeclampsia", CARDIOVASCULAR HEALTH, vol. 16, 11 March 2019 (2019-03-11), pages 75-78, XP085680747, ISSN: 2210-7789, DOI: 10.1016/J.PREGHY.2019.03.004 abstract -----	1-37, 39-71, 74-81, 84-92, 94-110
X,P	WO 2020/123404 A2 (SERA PROGNOSTICS INC [US]) 18 June 2020 (2020-06-18) claim 3 -----	1

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Patent document cited in search report			Publication date	Patent family member(s)			Publication date
WO 2009093254	A2		30-07-2009	AU	2009207291	A1	30-07-2009
				CA	2708661	A1	30-07-2009
				EP	2234483	A2	06-10-2010
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				US	2014087967	A1	27-03-2014
				WO	2009093254	A2	30-07-2009
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				EP	3894581	A2	20-10-2021
				WO	2020123404	A2	18-06-2020

FURTHER INFORMATION CONTINUED FROM   PCT/ISA/ 210

This International Searching Authority found multiple (groups of)
inventions in this international application, as follows:

1. claims: 1-37, 39-71, 74-81, 84-92, 94-110(all partially)

A panel of biomarkers which comprise two or more biomarkers
from Tables 3, 4 and 5, wherein one of the biomarkers is
miR-516b-5p. Composition of labeled and/or amplified nucleic
acid molecules which correspond to two or more nucleic acid
molecules listed in Tables 3, 4 or 5, wherein one of the
biomarkers is miR-516b-5p. Composition of labeled and/or
amplified nucleic acid molecules which correspond to at
least one of the biomarkers listed in Table 5, wherein one
of the biomarkers is miR-516b-5p. Method for determining a
pregnant female's risk of developing placental dysfunction
later in the pregnancy by measuring the amount of or by
producing labeled or amplified nucleic acid molecules that
correspond to two or more of the nucleic acid biomarkers
listed in Tables 3, 4 or 5, wherein one of the biomarkers is
miR-516b-5p. Composition of labeled and/or amplified nucleic
acid molecules which correspond to at least one of the
biomarkers listed in Table 5, wherein one of the biomarkers
is miR-516b-5p. Method for determining a pregnant female's
risk of developing placental dysfunction later in the
pregnancy by measuring the amount of or by producing labeled
or amplified nucleic acid molecules that correspond to at
least one of the biomarkers listed in Table 5, wherein one
of the biomarkers is miR-516b-5p. A method of treating or
preventing placental dysfunction in a pregnant female,
comprising detecting a panel of biomarkers, wherein one of
the biomarkers is miR-516b-5p.

2-27. claims: 1-110(partially)

idem for each of the individual miRNA biomarkers identified
in Tables 3 and 5.