



US 20250257392A1

(19) **United States**

(12) **Patent Application Publication**
Kang et al.

(10) **Pub. No.: US 2025/0257392 A1**

(43) **Pub. Date: Aug. 14, 2025**

(54) **KIT FOR DETERMINING ENDOMETRIAL STATUS AND METHOD OF DETERMINING MIRNA EXPRESSION PROFILE OF ENDOMETRIAL SAMPLE**

(71) Applicant: **Inti Taiwan, Inc.**, Hsinchu County (TW)

(72) Inventors: **Shih-Ting Kang**, Hsinchu County (TW); **Wei-Ming Chen**, Hsinchu County (TW)

(73) Assignee: **Inti Taiwan, Inc.**, Hsinchu County (TW)

(21) Appl. No.: **19/186,584**

(22) Filed: **Apr. 22, 2025**

Related U.S. Application Data

(62) Division of application No. 18/733,895, filed on Jun. 5, 2024, which is a division of application No. 16/914,040, filed on Jun. 26, 2020, now abandoned.

(60) Provisional application No. 62/869,574, filed on Jul. 2, 2019.

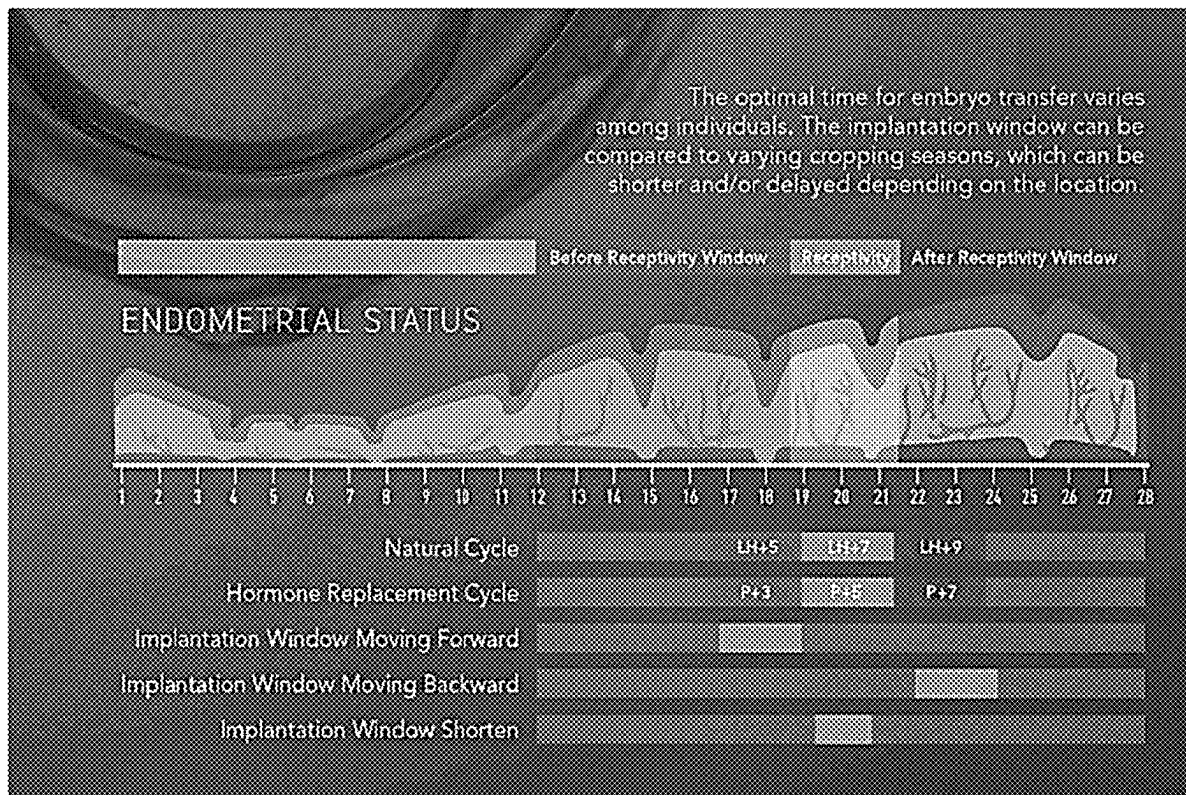
Publication Classification

(51) **Int. Cl.**
C12Q 1/686 (2018.01)
C12Q 1/6883 (2018.01)
G06F 17/18 (2006.01)
(52) **U.S. Cl.**
CPC **C12Q 1/686** (2013.01); **C12Q 1/6883** (2013.01); **C12Q 2600/112** (2013.01); **C12Q 2600/178** (2013.01); **G06F 17/18** (2013.01)

(57) **ABSTRACT**

The disclosure relates to a kit for determining an endometrial status and a method of determining a miRNA expression profile of an endometrial sample. The kit comprises: (a) one or more microRNA (miRNA) profiling chips targeting a plurality of miRNAs, and (b) instructions on (i) determining a miRNA expression profile of an endometrial sample from a woman, using the one or more miRNA profiling chips, and (ii) obtaining a receptivity predictive score based on the miRNA expression profile, using a computer-based algorithm, wherein the plurality of miRNAs comprise at least 167 miRNA s having the sequences of SEQ ID NOs: 1-167, respectively.

Specification includes a Sequence Listing.



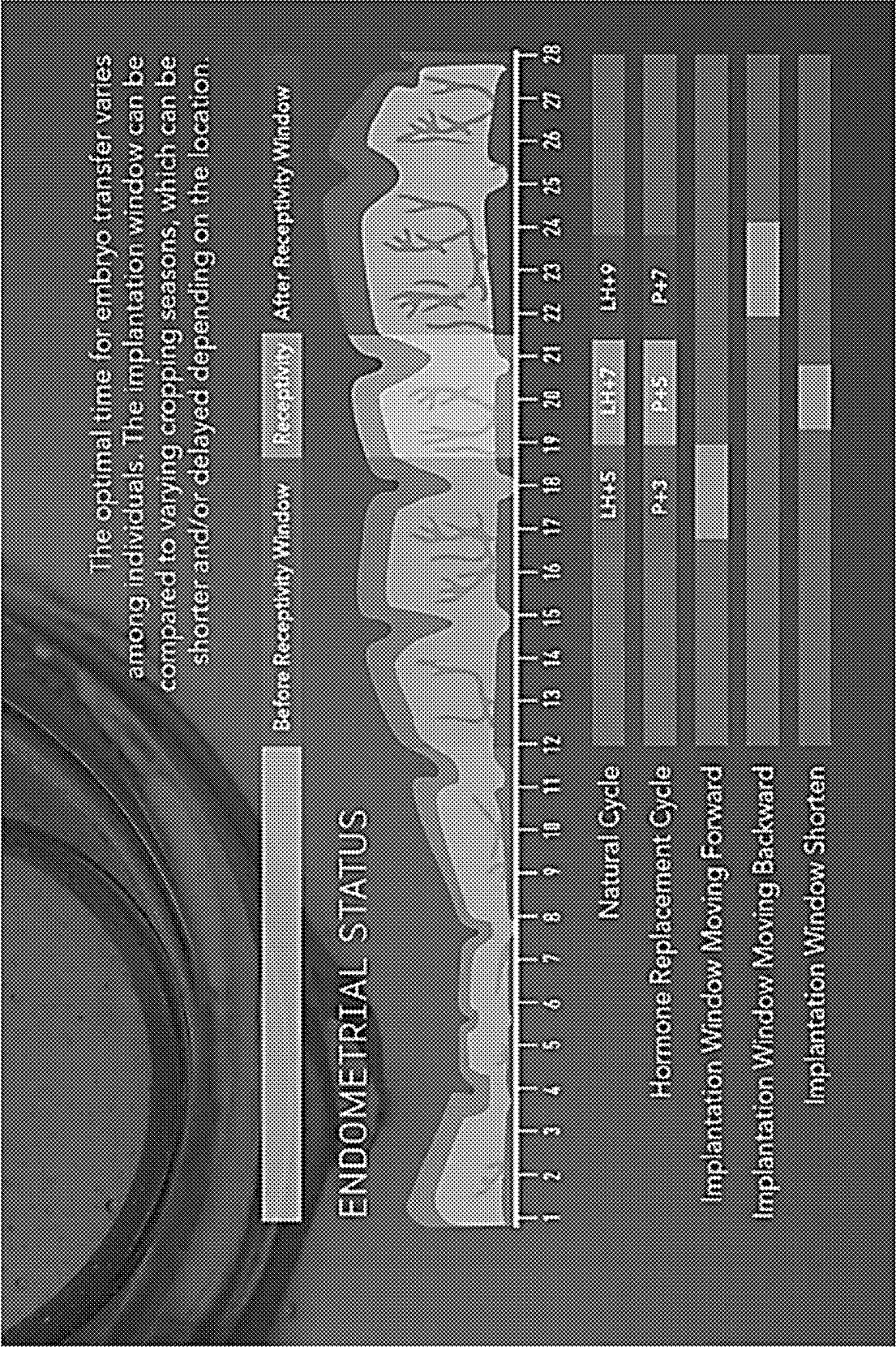


FIG. 1

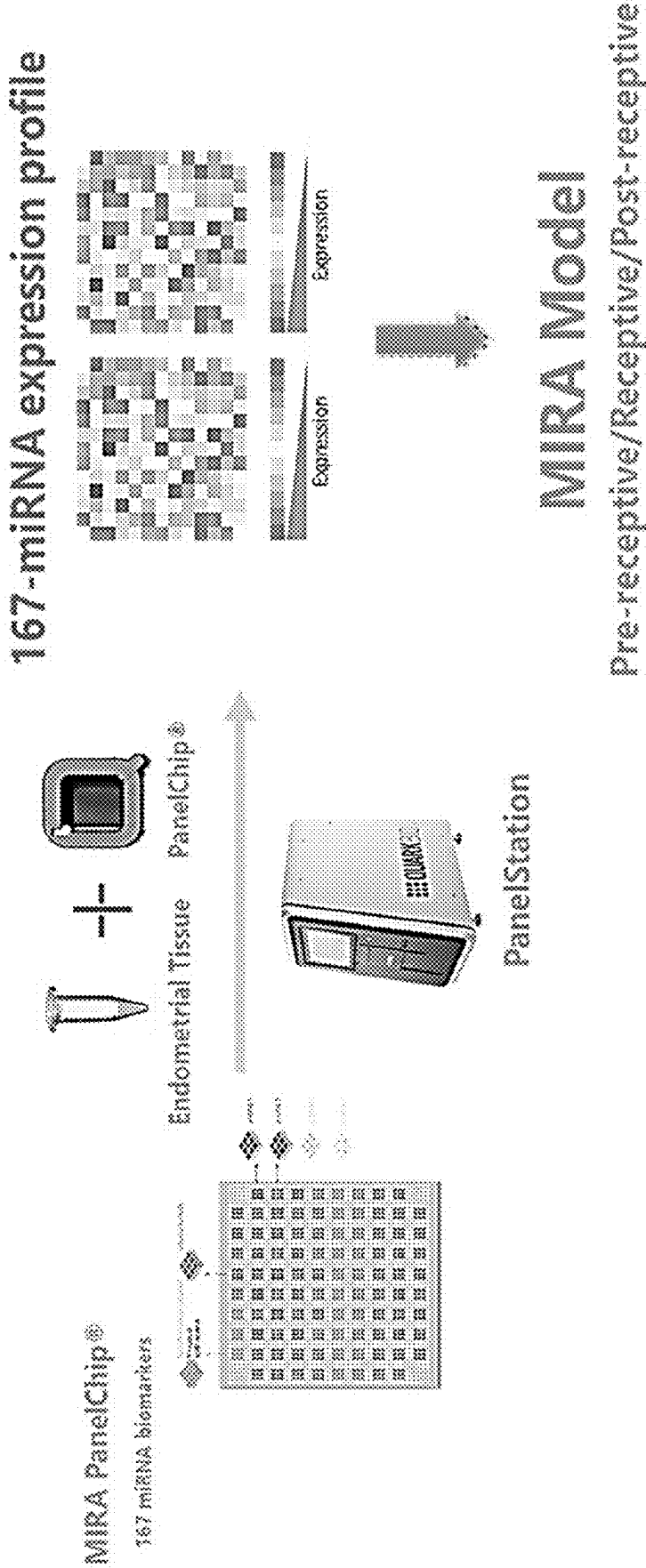


FIG. 2

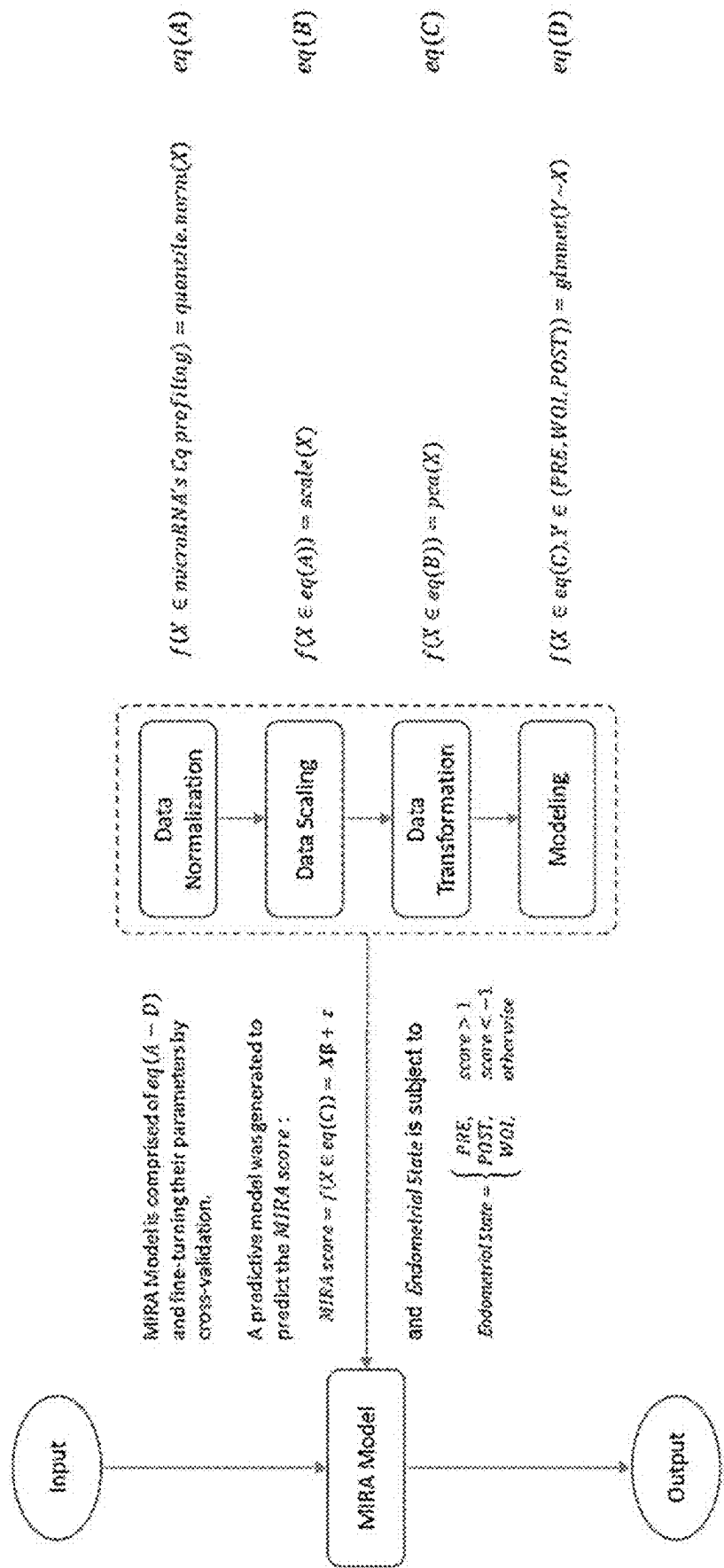
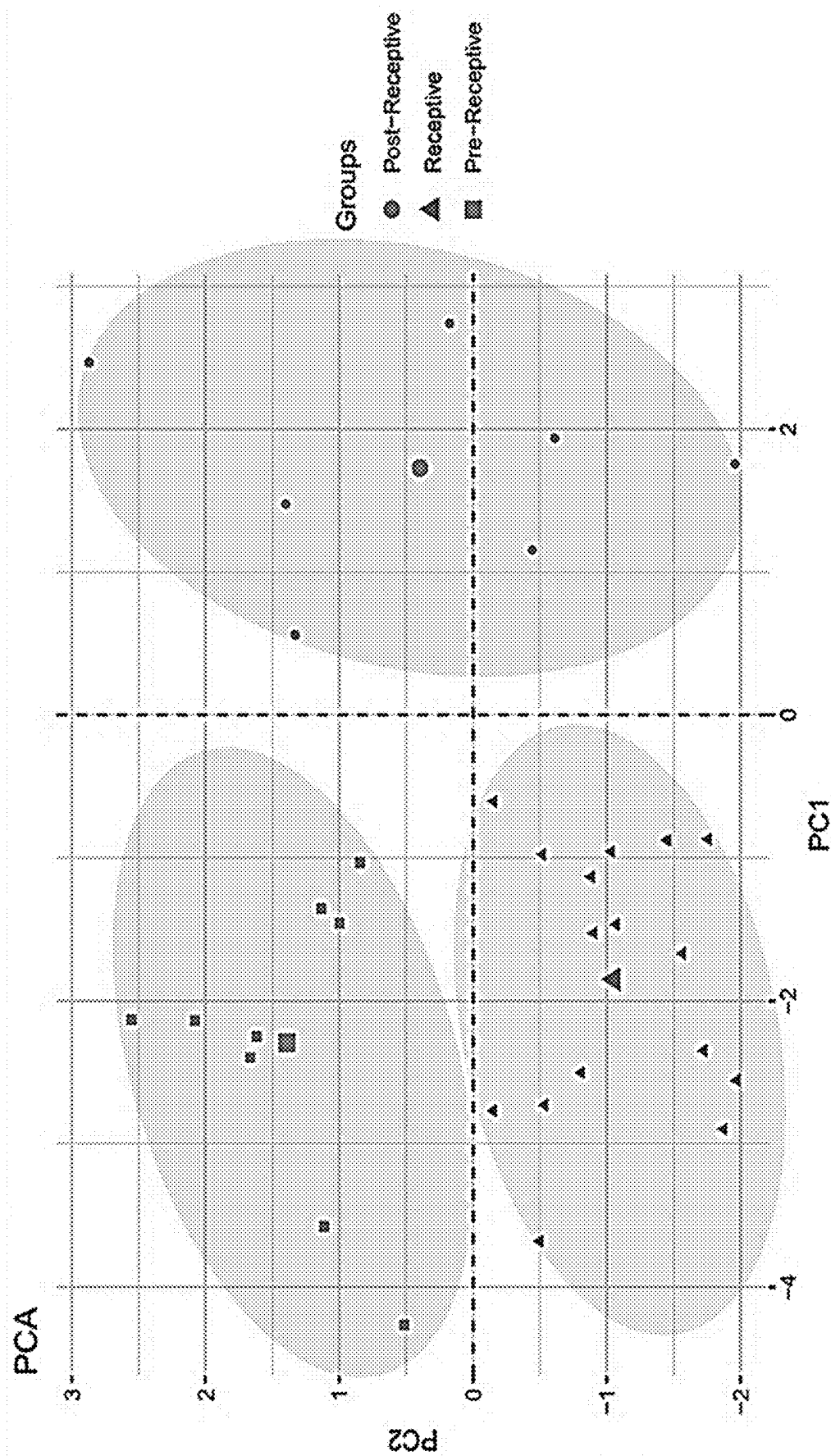


FIG. 3



	MIRA Prediction	
	Validation set	Test set
Total Patient	14	24
Receptive (R)	10	13
Pre-receptive (Pre)	2	11
Post-receptive (Post)	2	0

Clinical pregnancy rate percentage		
Receptive (R)	9/10 (90 %)	13/13 (100 %)
Pre-receptive (Pre)	1/2 (50%)	3/11 (27 %)
Post-receptive (Post)	0/2 (0 %)	0/0 (0 %)

FIG. 4B

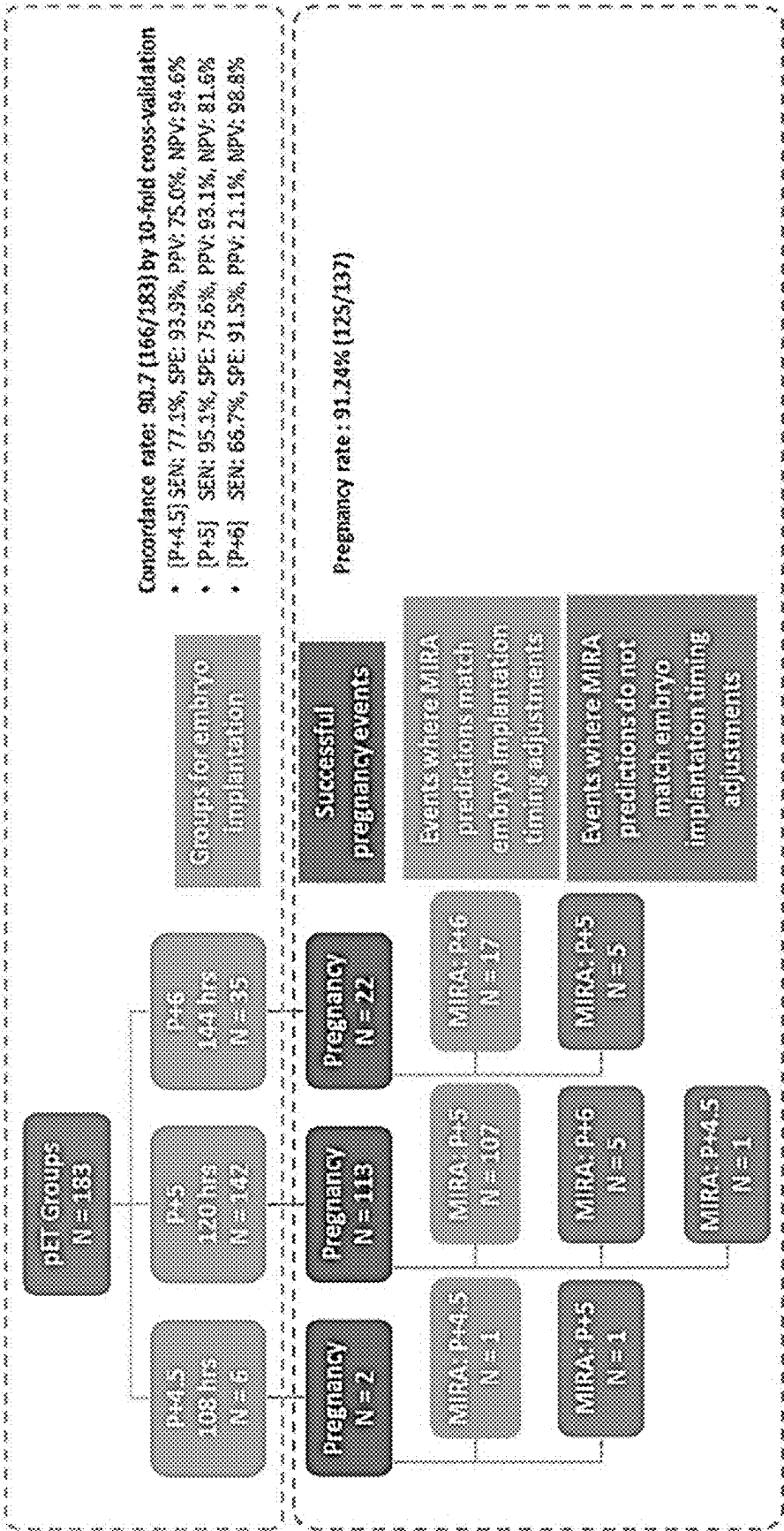


FIG. 5

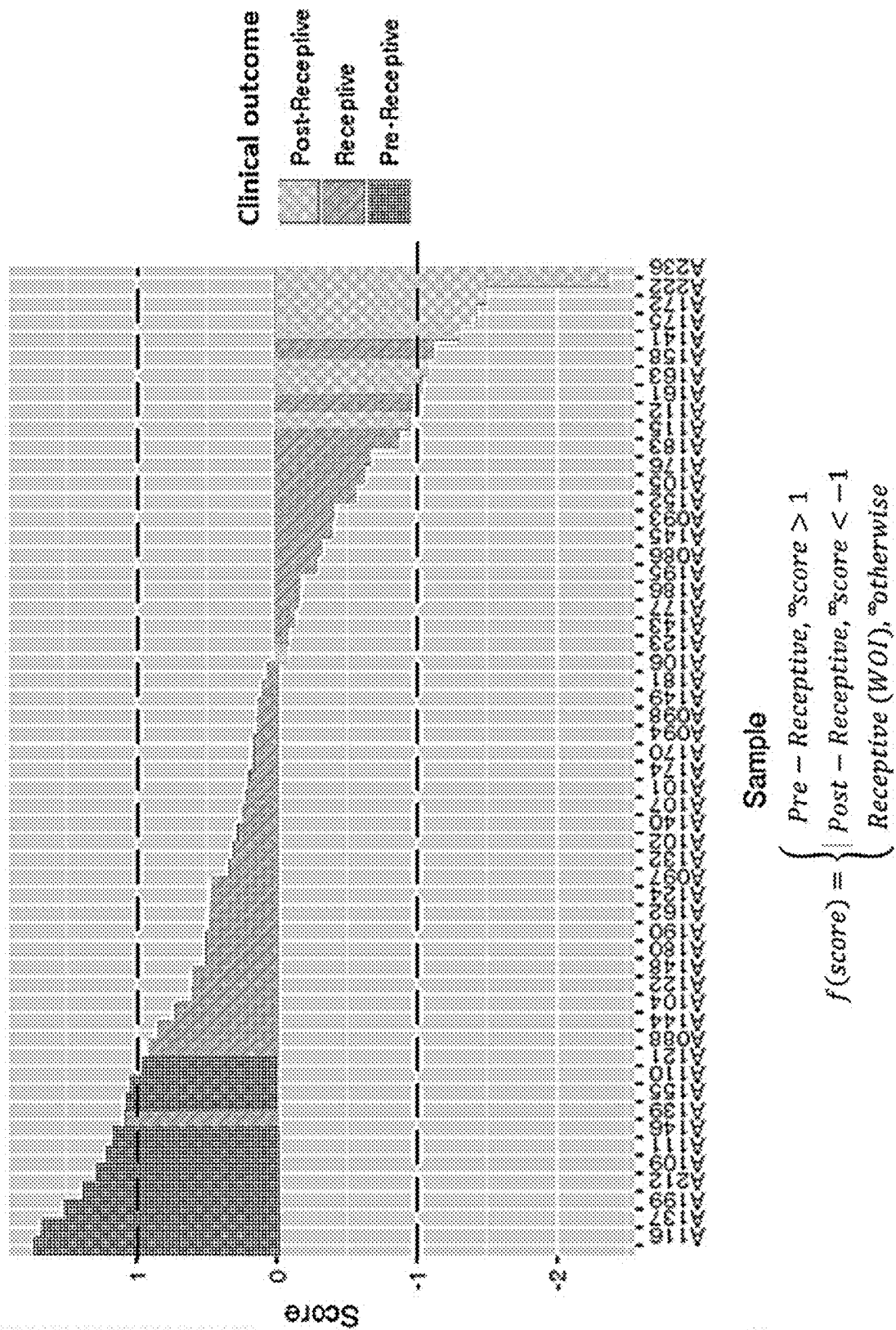


FIG. 6

KIT FOR DETERMINING ENDOMETRIAL STATUS AND METHOD OF DETERMINING MIRNA EXPRESSION PROFILE OF ENDOMETRIAL SAMPLE

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application is a divisional application of and claims the priority benefit of a prior application Ser. No. 18/733,895, filed on Jun. 5, 2024. The prior application Ser. No. 18/733,895 is a divisional application of and claims the priority benefit of a prior application Ser. No. 16/914,040, filed on Jun. 26, 2020. The prior application Ser. No. 16/914,040 claims the priority benefit of U.S. Provisional Application No. 62/869,574, filed on Jul. 2, 2019. The entirety of each of the above-mentioned patent applications is hereby incorporated by reference herein and made a part of this specification.

REFERENCE TO A SEQUENCE LISTING

[0002] The instant application contains a Sequencing Listing which has been submitted electronically in XML file and is hereby incorporated by reference in its entirety. Said XML copy, created on Apr. 15, 2025, is named 087210-1-1-US-sequence listing and is 212,368 bytes in size.

BACKGROUND

Technical Field

[0003] The disclosure relates to methods for determining the endometrial receptivity of a woman using (a) a microRNA (miRNA) expression profile comprising expression levels of a plurality of miRNAs, for example, 167 miRNAs, and (b) a computer-based algorithm that classifies the endometrial status of the woman based on the miRNA expression profile. Aspects of the disclosure further relate to kits suitable for performing the methods, as well as uses of the kits for diagnostic and therapeutic purposes. In some embodiments, the methods and/or kits are

used to classify a woman's responsiveness to an in vitro fertilization (IVF) treatment.

Description of Related Art

[0004] Assisted reproductive technologies, including IVF, emerged as potential approaches to address a lack of reproductive success. A major factor in the success rates of IVF is the receptive state of the endometrium. An endometrium is receptive only for a relatively short period referred to as window of implantation (WOI). This usually occurs around days 19-21 of the menstrual cycle. There is a longstanding need for monitoring the status of the endometrium not only based on the calendar approach, which tends to be unreliable, but also directly by examining the endometrium itself, which would indicate the opportunity for embryo implantation in a more reliable way.

[0005] Human endometrium is a tissue cyclically regulated by both proteins and miRNAs. The human genome comprises more than 2500 miRNAs, some of which have been shown to play roles in reproductive cycles. For example, recent literature demonstrated that certain miRNAs regulate the expression of genes involved in the establishment and progression of WOI.

[0006] Traditionally, histological and imaging methods were used to assess the status of the endometrium. However, it was long recognized that they are time consuming and often cannot clearly distinguish between the receptive and non-receptive states of the endometrium. Methods based on the examination of gene expression levels have also been developed. Early studies focused on a few marker genes. Igenomix developed an "Endometrial Receptivity Analysis" (ERA) test, relying on a microarray of specific 238 genes involved in endometrial receptivity. However, microarray-based ERA test has certain drawbacks. For example, it is known that microarray-based gene expression measurements require significant amounts of tissue samples. In addition, microarray technology generally has lower specificity as compared to quantitative polymerase chain reaction (qPCR) technology. Next-generation sequencing (NGS)-based ERA test is only emerging.

[0007] Thus, there remains a need for improved methods of determining endometrial receptivity that require less tissue input and/or provide more reliable determination of the receptive or non-receptive status of the endometrium in a woman.

SUMMARY

[0008] The disclosure relates to methods for determining endometrial receptivity using a sample, for example, an endometrial biopsy, from a woman, comprising: (a) performing an assay on the endometrial sample from the woman to determine a miRNA expression profile of the endometrial sample, wherein the miRNA expression profile comprises expression levels of a plurality of miRNAs, for example, 167 miRNAs having the sequences of SEQ ID NOs: 1-167, respectively; and (b) analyzing the miRNA expression profile to obtain a receptivity predictive score, wherein the receptivity predictive score determines the woman's endometrial receptivity status. Aspects of the disclosure further relate to kits suitable for performing the methods, as well as uses of the kits for determining an endometrial status of a woman.

[0009] Certain embodiments of the present disclosure are summarized in the following paragraphs. This list is only exemplary and not exhaustive of all of the embodiments provided by this disclosure.

[0010] Embodiment 1. A method of determining an endometrial status, comprising: (a) performing an assay on an endometrial sample from a woman to determine a miRNA expression profile of the endometrial sample, wherein the miRNA expression profile comprises expression levels of a plurality of miRNAs; and (b) analyzing the miRNA expression profile to obtain a receptivity predictive score, wherein the receptivity predictive score classifies the endometrial status of the woman, and wherein the endometrial status comprises a pre-receptive state, a receptive state, or a post-receptive state, and wherein the plurality of miRNAs comprise at least 50, 75, 100, 125, 150, or 200 miRNAs, and preferably at least 167 miRNAs having the sequences of SEQ ID NOs: 1-167, respectively.

[0011] Embodiment 2. The method of embodiment 1, wherein the endometrial sample is obtained from the uterine cavity of the woman.

[0012] Embodiment 3. The method of embodiment 1 or embodiment 2, wherein the endometrial sample comprises an endometrial biopsy, an endometrial lavage, or combination thereof.

[0013] Embodiment 4. The method of any one of embodiments 1-3, wherein the endometrial sample is obtained (i) seven days after an endogenous luteinizing hormone (LH) surge in the woman or (ii) five days after a progesterone administration in the woman.

[0014] Embodiment 5. The method of any one of embodiments 1-4, wherein the miRNA expression profile is determined by qPCR, sequencing, microarray, or RNA-DNA hybrid capture technology.

[0015] Embodiment 6. The method of embodiment 5, wherein the miRNA expression profile is determined by qPCR performed on a cDNA preparation synthesized from the miRNAs in the endometrial sample.

[0016] Embodiment 7. The method of embodiment 6, wherein the cDNA synthesis is performed using a universal reverse transcription primer having a nucleotide sequence represented by the following general formula: 5'-R-(dT)_nVN-3', wherein R comprises SEQ ID NO: 168, (dT)_n is an n number of continuous thymine residues, wherein n is 19, V is an adenine residue, a guanine residue, or a cytosine residue, and N is an adenine residue, a guanine residue, a cytosine residue, or a thymine residue.

[0017] Embodiment 8. The method of any one of embodiments 1-7, wherein the receptivity predictive score is a value produced by a computer-based algorithm and calculated using the equation of $MIRA\ score = f(X \in eq(C)) = X\beta + \epsilon$, β being a vector of coefficients, and ϵ being an error.

[0018] Embodiment 9. The method of embodiment 8, where the computer-based algorithm is established by performing one or more of the following steps: data normalization, data scaling, data transformation, prediction modeling, and cross-validation.

[0019] Embodiment 10. The method of embodiment 8 or embodiment 9, wherein a receptivity predictive score greater than 1 indicates the pre-receptive state, a receptivity predictive score less than -1 indicates the post-receptive state, and a receptivity predictive score from -1 to 1 indicates the receptive state.

[0020] Embodiment 11. The method of any one of embodiments 1-10, wherein if the endometrial status is determined to be at the pre-receptive state or the post-receptive state, further comprising: repeating steps (a) and (b) at least once or until the endometrial status is determined to be at the receptive state.

[0021] Embodiment 12. The method of any one of embodiments 1-11, wherein the woman suffers or suffered from an implantation failure.

[0022] Embodiment 13. The method of any one of embodiments 1-12, wherein the woman is subject to an IVF treatment.

[0023] Embodiment 14. The method of embodiment 13, wherein the receptivity predictive score further classifies the woman's responsiveness to the IVF treatment.

[0024] Embodiment 15. A method of detecting endometrial receptivity for embryo implantation in a woman, comprising: (a) performing an assay on an endometrial sample from the woman to determine a miRNA expression profile of the endometrial sample, wherein the miRNA expression profile comprises expression levels of a plurality of miRNAs; and (b) analyzing the miRNA expression profile to obtain a receptivity predictive score, wherein the receptivity predictive score determines whether the woman has endometrial receptivity for embryo implantation, and wherein the plurality of miRNAs comprise at least 50, 75, 100, 125, 150,

or 200 miRNAs, and preferably at least 167 miRNAs having the sequences of SEQ ID NOs: 1-167, respectively.

[0025] Embodiment 16. The method of embodiment 15, wherein the endometrial sample is obtained from the uterine cavity of the woman.

[0026] Embodiment 17. The method of embodiment 15 or embodiment 16, wherein the endometrial sample comprises an endometrial biopsy, an endometrial lavage, or combination thereof.

[0027] Embodiment 18. The method of any one of embodiments 15-17, wherein the endometrial sample is obtained (i) seven days after an endogenous luteinizing hormone (LH) surge in the woman or (ii) five days after a progesterone administration in the woman.

[0028] Embodiment 19. The method of any one of embodiments 15-18, wherein the miRNA expression profile is determined by qPCR, sequencing, microarray, or RNA-DNA hybrid capture technology.

[0029] Embodiment 20. The method of embodiment 19, wherein the miRNA expression profile is determined by qPCR performed on a cDNA preparation synthesized from the miRNAs in the endometrial sample.

[0030] Embodiment 21. The method of embodiment 20, wherein the cDNA synthesis is performed using a universal reverse transcription primer having a nucleotide sequence represented by the following general formula: 5'-R-(dT)_nVN-3', wherein R comprises SEQ ID NO: 168, (dT)_n is an n number of continuous thymine residues, n is 19, V is an adenine residue, a guanine residue, or a cytosine residue, and N is an adenine residue, a guanine residue, a cytosine residue, or a thymine residue.

[0031] Embodiment 22. The method of any one of embodiments 15-21, wherein the receptivity predictive score is a value produced by a computer-based algorithm and calculated using the equation of $MIRA\ score = f(X \in eq(C)) = X\beta + \epsilon$, β being a vector of coefficients, and ϵ being an error.

[0032] Embodiment 23. The method of embodiment 22, where the computer-based algorithm is established by performing one or more of the following steps: data normalization, data scaling, data transformation, prediction modeling, and cross-validation.

[0033] Embodiment 24. The method of embodiment 22 or embodiment 23, wherein a receptivity predictive score from -1 to 1 indicates that the woman has endometrial receptivity for embryo implantation.

[0034] Embodiment 25. The method of any one of embodiments 15-24, wherein the woman suffers or suffered from an implantation failure.

[0035] Embodiment 26. A kit comprising: (a) one or more miRNA profiling chips targeting a plurality of miRNAs, and (b) instructions on (i) determining a miRNA expression profile of an endometrial sample from a woman, optionally using the one or more miRNA profiling chips, and (ii) obtaining a receptivity predictive score based on the miRNA expression profile, using a computer-based algorithm, wherein the plurality of miRNAs comprise at least 50, 75, 100, 125, 150, or 200 miRNAs, and preferably at least 167 miRNAs having the sequences of SEQ ID NOs: 1-167, respectively.

[0036] Embodiment 27. The kit of embodiment 26, wherein the one or more miRNA profiling chips comprise primers for detection of expression levels of the plurality of miRNAs.

[0037] Embodiment 28. The kit of embodiment 27, wherein the miRNA profiling chips are suitable for performing a qPCR, sequencing, microarray, or RNA-DNA hybrid capture assay, preferably qPCR, to detect the expression levels of the plurality of miRNAs.

[0038] Embodiment 29. Use of the kit of embodiment 27 or embodiment 28 for determining an endometrial status of a woman.

[0039] Embodiment 30. The use of embodiment 29, wherein the woman suffers or suffered from an implantation failure and/or is subject to an IVF treatment.

BRIEF DESCRIPTION OF THE DRAWINGS

[0040] FIG. 1 depicts the endometrial status of a woman in a natural cycle or a hormone replacement therapy cycle. LH+5: five days after an endogenous luteinizing hormone (LH) surge in the woman; LH+7: seven days after an endogenous LH surge in the woman; and LH+9: nine days after an endogenous LH surge in the woman. P+3: three days after a progesterone administration in the woman; P+5: five days after a progesterone administration in the woman; and P+7: seven days after a progesterone administration in the woman.

[0041] FIG. 2 depicts a workflow of an endometrial receptivity test, using MIRA PanelChip targeting the 167 miRNAs according to this disclosure.

[0042] FIG. 3 depicts processes on how a computer-based algorithm (MIRA Model) is built and how MIRA Model produces a test result.

[0043] FIG. 4A shows an exemplary analysis of endometrium receptivity that classifies the endometrial status into one of the three states: a pre-receptive state, a receptive state, or a post-receptive state.

[0044] FIG. 4B shows exemplary implantation results in women classified under the three receptive states.

[0045] FIG. 5 shows a 10-fold cross-validation and pregnancy rate using miRNA expression profiles comprising expression levels of 167 miRNAs from 183 endometrial samples. SEN: Sensitivity=True Positives/(True Positives+False Negatives); SPE: Specificity=True Negatives/(True Negatives+False Positives); PPV: precision or positive predictive value=True Positives/(True Positives+False Positives); and NPV: negative predictive value=True Negatives/(True Negatives+False Negatives). P+6: embryo implantation six days after a progesterone administration in a woman whose endometrium was previously determined to be in the pre-receptive state; P+5: embryo implantation five days after a progesterone administration in a woman whose endometrium was previously determined to be in the receptive state; and P+4.5: embryo implantation 4.5 days (i.e., 108 hours) after a progesterone administration in a woman whose endometrium was previously determined to be in the post-receptive state.

[0046] FIG. 6 shows the MIRA scoring system, classifying the endometrial samples into one of the three states: a pre-receptive state, a receptive state, or a post-receptive state, depending on the value of the receptivity predictive score.

DESCRIPTION OF THE EMBODIMENTS

[0047] The disclosures and embodiments set forth herein are to be construed as exemplary only and not as limiting the scope of the invention. Although specific terms are

employed herein, unless otherwise noted, they are used in a generic and descriptive sense only and not for purposes of limitation.

Definitions

[0048] As used herein, the singular forms “a,” “an,” and “the” are intended to include the plural forms as well, unless the context clearly indicates otherwise.

[0049] The term “cDNA” refers to complementary DNA generated by performing reverse transcription on an RNA preparation using a reverse transcriptase. In some embodiments, the RNA preparation contains miRNAs extracted from an endometrial tissue sample. See Example 1.

[0050] The terms “comprise,” “have” and “include” are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as “comprises,” “comprising,” “has,” “having,” “includes,” and “including,” are also open-ended. For example, any method that “comprises,” “has” or “includes” one or more steps is not limited to possessing only those one or more steps and can also cover other unlisted steps. Similarly, any composition or kit that “comprises,” “has” or “includes” one or more features is not limited to possessing only those one or more features and can cover other unlisted features. The use of any and all examples, or exemplary language (e.g., “such as”) provided with respect to certain embodiments herein is intended merely to better illuminate the present disclosure and does not pose a limitation on the scope of the present disclosure otherwise claimed.

[0051] The term “expression” refers to the transcription and/or accumulation of RNA molecules in a biological sample, for example, an endometrial tissue sample from a woman. In this context, the term “miRNA expression” refers to the amount of one or more miRNAs in a biological sample, and the miRNA expression can be detected by using suitable methods known in the art. See, e.g., Example 1.

[0052] The term “microRNA” or “miRNA” refers to a class of approximately 18 to 25 nucleotide long non-coding RNA derived from an endogenous gene. miRNAs function as post-transcriptional regulators of gene expression by base pairing to the 3' untranslated regions (UTR) of their target mRNAs for mRNA degradation or translation inhibition.

[0053] The terms “nucleic acid,” “nucleotide” and “polynucleotide” are used interchangeably and refer to a polymer of DNA or RNA in either single or double stranded form. Unless otherwise noted, these terms encompass polynucleotides containing known analogues of natural nucleotides that have similar binding properties as the reference nucleic acid and are metabolized in a manner similar to naturally occurring nucleotides.

[0054] The term “primer” refers to an oligonucleotide which acts to initiate synthesis of a complementary nucleic acid strand when placed under conditions in which synthesis of a primer extension product is induced, e.g., in the presence of nucleotides and a polymerization-inducing agent such as a DNA or RNA polymerase and at a suitable temperature, pH, metal ion concentration, and salt concentration.

[0055] The term “probe” refers to a structure comprising a polynucleotide, which contains a nucleic acid sequence complementary to a nucleic acid sequence present in the target nucleic acid analyte (e.g., a nucleic acid amplification product). The polynucleotide regions of probes may be composed of DNA, and/or RNA, and/or synthetic nucleotide

analogs. Probes are generally of a length compatible with their use in specific detection of all or a portion of a target sequence of a target nucleic acid.

[0056] The term “qPCR” or “quantitative PCR” refers to an experimental method of using polymerase chain reaction to amplify and quantify target DNA and/or RNA at the same time. Quantification is performed using a plurality of chemical substances (including, for instance, fluorescent dye of SY BR® green or fluorescent reporter oligonucleotide probe of Taqman probe), and real-time quantification is performed by measuring the amplified DNA and/or RNA in the reaction after one or more amplification cycles.

[0057] The term “targeting” refers to the selection of suitable nucleotide sequences that hybridize to a nucleic acid sequence of interest. In some embodiments, the nucleic acid sequence of interest includes a miRNA having the sequence of any one of SEQ ID NOs: 1-167. See Example 1.

Overview of the Methods for Determining Endometrial Status

[0058] Endometrial receptivity is the state in which a woman's endometrium is prepared for embryo implantation. This occurs in all menstrual cycles in a time period referred to as WOI. As shown in FIG. 1, in a natural cycle, ovulation occurs after the LH surge, and the WOI is around seven days after the LH surge (LH+7). In a hormone replacement therapy cycle, the WOI is around five days after a progesterone administration (P+5). These estimates give probable information on endometrial receptivity. However, the ultimate answer for the endometrium status can only be provided by an examination of the endometrium itself.

[0059] To that end, an endometrial sample can be collected from the uterine cavity of a woman either five days after a progesterone administration (P+5) in a hormone replacement therapy cycle or seven days after an endogenous LH surge (LH+7) in a natural cycle. The sample is then subject to a molecular diagnostic tool that analyzes the endometrial receptivity status. In the methods of determining an endometrial status according to this disclosure, the molecular diagnostic tool analyzes the miRNA expression profile of the endometrial sample.

[0060] As shown in FIG. 2, the present disclosure provides methods of determining an endometrial status, comprising: (a) performing an assay on an endometrial sample to determine a miRNA expression profile of the endometrial sample, wherein the miRNA expression profile comprises expression levels of a plurality of miRNAs, for example, 167 miRNAs having the sequences of SEQ ID NOs: 1-167, respectively; and (b) analyzing the miRNA expression profile with a computer-based algorithm to obtain a receptivity predictive score, wherein the receptivity predictive score classifies the endometrial status into a pre-receptive state, a receptive state, or a post-receptive state.

[0061] The pre-receptive state indicates that the endometrium is not yet ready to receive the embryo and embryo implantation at this time may be too early. The receptive state (WOI) indicates that the endometrium is at an optimal time for embryo implantation. The post-receptive state indicates that the endometrium already passed the optimal stage for embryo implantation.

Analyzing miRNA Expression Profile to Determine Endometrial Receptivity

[0062] The present disclosure determines an endometrial sample's miRNA expression profile. In some embodiments,

the miRNA expression profile comprises expression levels of a plurality of miRNAs, for example, at least 10, 25, 50, 75, 100, 125, 150, or 200 miRNAs, all of which may be implicated in the regulation of endometrial receptivity. In preferred embodiments, the present disclosure provides a selection of 167 miRNAs, whose expression levels have been implicated in the regulation of endometrial receptivity. See Example 1. These 167 miRNAs were chosen by first identifying genes involved in the reproductive diseases from the Human Disease Ontology database, and then selecting potential regulator miRNAs using miRTARBase, TargetScan, and miRDB.

[0063] In order to determine an endometrial status, the methods according to this disclosure comprise performing an assay to determine the miRNA expression profile of the endometrial sample, wherein the miRNA expression profile comprises expression levels of the 167 miRNAs shown in Table 1.

TABLE 1

Names and sequences of the 167 miRNAs.		
Name	Sequence	SEQ ID NO
hsa-miR-155-5p	UUA AUGCUAAUCGUGAUAGGGGUU	1
hsa-miR-145-5p	GUCCAGUUUCCCAGGAUCCCU	2
hsa-miR-34a-5p	UGGCAGUGUCUAGCUGGUUGU	3
hsa-miR-21-5p	UAGCUUAUCAGACUGAUUGA	4
hsa-miR-125b-5p	UCCUGAGACCCUAAUCUGUGA	5
hsa-miR-29a-3p	UAGCACCAUCUGAAUCGGUUA	6
hsa-miR-29b-3p	UAGCACCAUUUGAAUCAGUGUU	7
hsa-miR-200c-3p	UAAUACUGCCGGUAAUGAUGGA	8
hsa-miR-24-3p	UGGCUCAGUUCAGCAGGAACAG	9
hsa-miR-9-5p	UCUUUGGUUAUCUAGCUGAUGA	10
hsa-miR-146a-5p	UGAGAACUGAAUCCAUUGGGUU	11
hsa-miR-26a-5p	UUCAAGUAAUCCAGGAUAGGCU	12
hsa-miR-17-5p	CAAAGUGCUUACAGUGCAGGUAG	13
hsa-miR-200b-3p	UAAUACUGCCUGGUAUGAUGA	14
hsa-miR-221-3p	AGCUACAUGUCUGCUGGGUUUC	15
hsa-miR-181a-5p	AACAUUAACGUCUGCGGUGAGU	16
hsa-miR-122-5p	UGGAGUGUGACAAUGGUGUUUG	17
hsa-miR-199a-5p	CCCAGUGUUCAGACUACCGUUC	18
hsa-miR-29c-3p	UAGCACCAUUUGAAUCGGUUA	19
hsa-miR-31-5p	AGGCAAGAUUGCUGGCAUAGCU	20
hsa-miR-1-3p	UGGAAUGUAAAGAAGUAUGUUAU	21
hsa-miR-20a-5p	UAAAGUGCUUAUAGUGCAGGUAG	22
hsa-miR-27a-3p	UUCACAGUGGCUAAGUCCGC	23
hsa-miR-203a-3p	GUGAAUGUUUAGGACCACUAG	24

TABLE 1-continued

Names and sequences of the 167 miRNAs.		
Name	Sequence	SEQ ID NO
hsa-miR-141-3p	UAACACUGUCUGGUAAGAUGG	25
hsa-miR-200a-3p	UAACACUGUCUGGUAACGAUGU	26
hsa-miR-22-3p	AAGCUGCCAGUUGAAGAACUGU	27
hsa-miR-101-3p	UACAGUACUGUGAUAAACUGAA	28
hsa-miR-16-5p	UAGCAGCAGCUAAUAUUGGCG	29
hsa-miR-182-5p	UUUGGCAAUGGUAGAACUCACACU	30
hsa-miR-210-3p	CUGUGCGUGUGACAGCGGUGA	31
hsa-miR-125a-5p	UCCUGAGACCCUUUAACUGUGA	32
hsa-let-7a-5p	UGAGGUAGUAGGUUGUAUAGUU	33
hsa-miR-23a-3p	AUCACAUUGCCAGGGAUUUCC	34
hsa-miR-19a-3p	UGUGCAAUUCUAUGCAAACUGA	35
hsa-miR-223-3p	UGUCAGUUUGUCAAUACCCCA	36
hsa-miR-143-3p	UGAGAUGAAGCACUGUAGCUC	37
hsa-miR-205-5p	UCCUUCAUUCCACCGAGUCUG	38
hsa-miR-30a-5p	UGUAAACAUCCUCGACUGGAAG	39
hsa-miR-133a-3p	UUUGGUCCCCUUAACCGAGCUG	40
hsa-miR-126-3p	UCGUACCGUGAGUAUAUUGCG	41
hsa-miR-128-3p	UCACAGUGAACCGUCUCUUU	42
hsa-miR-222-3p	AGCUACAUCUGGCUACUGGGU	43
hsa-miR-214-3p	ACAGCAGGCACAGACAGGCAGU	44
hsa-miR-133b	UUUGGUCCCCUUAACCGAGCUA	45
hsa-miR-181b-5p	AACAUUCAUUGCUGUCGGUGGGU	46
hsa-miR-15a-5p	UAGCAGCACAUAAUGGUUUGUG	47
hsa-miR-106a-5p	AAAAGUGCUCUACAGUGCAGGUAG	48
hsa-miR-429	UAAUACUGUCUGGUAACCCGU	49
hsa-miR-7-5p	UGGAAGACUAGUGAUUUUGUUGUU	50
hsa-miR-106b-5p	UAAAGUGCUGACAGUGCAGAU	51
hsa-miR-10b-5p	UACCCUGUAGAACCAGAAUUGUG	52
hsa-miR-192-5p	CUGACCUAUGAAUUGACAGCC	53
hsa-miR-195-5p	UAGCAGCACAGAAUAUUGGC	54
hsa-miR-30c-5p	UGUAAACAUCCUACACUCUCAGC	55
hsa-miR-335-5p	UCAAGAGCAAUAACGAAAAAUGU	56
hsa-let-7b-5p	UGAGGUAGUAGGUUGUGUGGUU	57
hsa-miR-224-5p	UCAAGUCACUAGUGGUUCCGUUAG	58
hsa-miR-135a-5p	UAUGGCUUUUAUCCUAUGUGA	59

TABLE 1-continued

Names and sequences of the 167 miRNAs.		
Name	Sequence	SEQ ID NO
hsa-miR-206	UGGAAUGUAAGGAAGUGUGUGG	60
hsa-miR-92a-3p	UAUUGCACUUGUCCCGGCCUGU	61
hsa-miR-150-5p	UCUCCCAACCCUUGUACCAGUG	62
hsa-miR-15b-5p	UAGCAGCACAUCAUGGUUUACA	63
hsa-miR-130a-3p	CAGUGCAAUGUUAAGGGCAU	64
hsa-miR-130b-3p	CAGUGCAAUGAUGAAGGGCAU	65
hsa-miR-140-5p	CAGUGGUUUUACCCUAUGGUAG	66
hsa-miR-18a-5p	UAAGGUGCAUCUAGUGCAGAUAG	67
hsa-let-7c-5p	UGAGGUAGUAGGUUGUAUGGUU	68
hsa-miR-196a-5p	UAGGUAGUUUCAUGUUUGGGG	69
hsa-miR-199a-3p	ACAGUAGUCUGCACAUUGGUUA	70
hsa-miR-103a-3p	AGCAGCAUUGUACAGGGCUAUGA	71
hsa-miR-129-5p	CUUUUUGCGGUCUGGGCUUGC	72
hsa-miR-152-3p	UCAGUGCAUGACAGAACUUGG	73
hsa-miR-144-3p	UACAGUAUAGAUGAUGUACU	74
hsa-miR-183-5p	UAUGGCACUGGUAGAAUUCACU	75
hsa-miR-93-5p	CAAAGUGCUGUUCGUGCAGGUAG	76
hsa-miR-100-5p	AACCCGUAGAUCGGAACUUGUG	77
hsa-miR-19b-3p	UGUGCAAUCCAUUGCAAACUGA	78
hsa-miR-30b-5p	UGUAAACAUCCUACACUCAGCU	79
hsa-miR-373-3p	GAAGUGCUCUAGUUUUGGGUGU	80
hsa-miR-451a	AAACCGUUACCAUACUGAGUU	81
hsa-miR-142-3p	UGUAGUGUUUCCUACUUUAUGGA	82
hsa-miR-20b-5p	CAAAGUGCUCUAGUGCAGGUAG	83
hsa-miR-30d-5p	UGUAAACAUCCCGACUGGAAG	84
hsa-miR-372-3p	AAAGUGCUGCGACAUUUGAGCGU	85
hsa-miR-135b-5p	UAUGGCUUUUAUCCUAUGUGA	86
hsa-miR-193a-3p	AACUGGCCUACAAGUCCCGAGU	87
hsa-miR-409-3p	GAAUGUUGCUCGGUGAACCCCU	88
hsa-let-7g-5p	UGAGGUAGUAGUUUGUACAGUU	89
hsa-miR-10a-5p	UACCCUGUAGAUCGAAUUGUG	90
hsa-miR-191-5p	CAACGGAAUCCAAAAGCAGCUG	91
hsa-let-7f-5p	UGAGGUAGUAGAUUGUAUAGUU	92
hsa-miR-134-5p	UGUGACUGGUUGACCAGAGGGG	93
hsa-miR-146b-5p	UGAGAACUGAAUCCAUAGGCUG	94
hsa-miR-127-3p	UCGGAUCCGUCUGAGCUUGGCU	95

TABLE 1-continued

Names and sequences of the 167 miRNAs.		
Name	Sequence	SEQ ID NO
hsa-miR-196b-5p	UAGGUAGUUUCCUGUUGUUGGG	96
hsa-miR-302d-3p	UAAGUGCUUCCAUGUUUGAGUGU	97
hsa-miR-663a	AGGCGGGGCGCCGCGGGACCGC	98
hsa-miR-326	CCUCUGGGCCCUUCCUCCAG	99
hsa-miR-486-5p	UCCUGUACUGAGCUGCCCCGAG	100
hsa-miR-17-3p	ACUGCAGUGAAGGCACUUGUAG	101
hsa-miR-30e-5p	UGUAAACAUCUUGACUGGAAG	102
hsa-let-7d-5p	AGAGGUAGUAGGUUGCAUAGUU	103
hsa-miR-193b-3p	AACUGGCCCCUCAAGUCCCGCU	104
hsa-miR-202-3p	AGAGGUUAUGGGCAUGGGAA	105
hsa-miR-216a-5p	UAAUCUCAGCUGGCAACUGUGA	106
hsa-miR-376c-3p	AACAUAAGAGGAAAUUCCACGU	107
hsa-miR-198	GGUCCAGAGGGAGAUAGGUUC	108
hsa-miR-215-5p	AUGACCUAUGAAUUGACAGAC	109
hsa-miR-197-3p	UUCACCACCUUCCACCCAGC	110
hsa-miR-29a-5p	ACUGAUUUUUUUGGUGUUCAG	111
hsa-miR-425-5p	AAUGACACGAUCACUCCGUUGA	112
hsa-miR-574-3p	CACGCUAUGCACACCCACA	113
hsa-miR-18b-5p	UAAGGUGCAUCUAGUGCAGUUG	114
hsa-miR-483-5p	AAGACGGGAGGAAAGAAGGGAG	115
hsa-miR-625-5p	AGGGGGAAAGUUUAUAGUCC	116
hsa-miR-338-5p	AACAAUAUCCUGGUCUGAGUG	117
hsa-miR-539-5p	GGAGAAAUAUCCUUGGUGUGU	118
hsa-miR-151a-3p	CUAGACUGAAGCUCUUGAGG	119
hsa-miR-208b-3p	AUAAGACGAACAAAAGGUUUGU	120
hsa-miR-330-5p	UCUCUGGGCCUGUGUCUAGGC	121
hsa-miR-382-5p	GAAGUUGUUCGUGGUGGAUUCG	122
hsa-miR-499a-5p	UUAAGACUUGCAGUGAUGUUU	123
hsa-miR-223-5p	CGUGUAUUUGACAAGCUGAGUU	124
hsa-miR-31-3p	UGCUAUGCCAACAUUUGCCAU	125
hsa-miR-361-5p	UUAUCAGAAUCUCCAGGGUAC	126
hsa-miR-423-3p	AGCUCGGUCUGAGGCCCUACAGU	127
hsa-miR-885-5p	UCCAUUACACUACCCUGCCUCU	128
hsa-miR-95-3p	UUCAACGGGUUUUAUUGAGCA	129
hsa-miR-99b-5p	CACCCGUAGAACCGACCUUGCG	130

TABLE 1-continued

Names and sequences of the 167 miRNAs.		
Name	Sequence	SEQ ID NO
hsa-miR-299-5p	UGGUUUACCGUCCACAUACAU	131
hsa-miR-378a-5p	CUCCUGACUCCAGGUCCUGUGU	132
hsa-miR-500a-5p	UAAUCCUUGCUACCGGGUGAGA	133
hsa-miR-518a-5p	CUGCAAAGGGAAGCCUUUC	134
hsa-miR-589-5p	UGAGAACCACGUCUGCUCUGAG	135
hsa-miR-718	CUUCCGCCCCGCCGGGCGUCG	136
hsa-miR-940	AAGGCAGGGCCCCCGCUCCCC	137
hsa-miR-28-3p	CACUAGAUUGUGAGCUCCUGGA	138
hsa-miR-411-5p	UAGUAGACCGUAUAGCGUACG	139
hsa-miR-423-5p	UGAGGGGCAGAGAGCGAGAUUU	140
hsa-miR-450a-5p	UUUUGCGAUGUGUCCUAAUUAU	141
hsa-miR-484	UCAGGCUCAGUCCCUCCCGAU	142
hsa-miR-593-5p	AGGCACCAGCCAGGCAUUGCUCAGC	143
hsa-miR-652-3p	AAUGGCGCCACUAGGGUUGUG	144
hsa-miR-760	CGGCUCUGGGUCUGUGGGGA	145
hsa-miR-1228-5p	GUGGGCGGGGCAGGUGUGUG	146
hsa-miR-1254	AGCCUGGAAGCUGGAGCCUGCAGU	147
hsa-miR-1290	UGGAUUUUUGGAUCAGGGA	148
hsa-miR-574-5p	UGAGUGUGUGUGUGAGUGUGU	149
hsa-miR-579-3p	UUCAUUUGGUUAUAAACCGCAUU	150
hsa-miR-596	AAGCCUGCCCGGCUCUCCGGG	151
hsa-miR-601	UGGUCUAGGAUUGUUGGAGGAG	152
hsa-miR-660-5p	UACCCAUUGCAUAUCGAGAUUG	153
hsa-let-7d-3p	CUAUACGACCUCUGCCUUUCU	154
hsa-miR-1225-3p	UGAGCCCCUGUGCCGCCCCAG	155
hsa-miR-1248	ACCUUCUUGUAUAAGCACUGUCUAAA	156
hsa-miR-1972	UCAGGCCAGGCACAGUGGCUCA	157
hsa-miR-1973	ACCGUGCAAAGGUAGCAUA	158
hsa-miR-2114-3p	CGAGCCUCAAGCAAGGGACUU	159
hsa-miR-217-5p	UACUGCAUCAGGAACUGAUUGGA	160
hsa-miR-320a-3p	AAAAGCUGGGUUGAGAGGGCGA	161
hsa-miR-375-3p	UUUGUUCGUUCGGCUCGCGUGA	162
hsa-miR-425-3p	AUCGGGAUUGUCGUGUCCGCC	163
hsa-miR-4306	UGGAGAGAAAGGCAGUA	164
hsa-miR-452-3p	CUCAUCUGCAAAGAAGUAAGUG	165

TABLE 1-continued

Names and sequences of the 167 miRNAs.		
Name	Sequence	SEQ ID NO
hsa-miR-4772-3p	CCUGCAACUUUGCCUGAUCAGA	166
hsa-miR-520b-3P	AAAGUGCUUCCUUUAGAGGG	167

[0064] The expression levels of the miRNAs can be analyzed with quantitative methods known in the art. In some embodiments, to facilitate the analysis, one or more miRNA profiling chips targeting these 167 miRNAs can be used. For example, in Example 1, two miRNA profiling chips are designed and developed to analyze the expression levels of these 167 miRNAs. In some embodiments, the one or more chips additionally target certain RNA sequences, e.g., 18s rRNA, that can be used as the endogenous controls for the miRNA expression analysis. See Example 1.

[0065] The present disclosure provides methods of determining the miRNA expression profile of an endometrial sample. The method generally comprises (i) obtaining or having obtained an endometrial sample from a woman's uterine cavity, (ii) performing an assay to determine a miRNA expression profile of the endometrial sample, wherein the miRNA expression profile comprises expression levels of a plurality of miRNA s, for example, 167 miRNA s having the sequences of SEQ ID NOs: 1-167, respectively.

[0066] In some embodiments, the endometrial sample may be obtained via an invasive method, for example, by taking a small biopsy from the endometrium. See Example 1. In some embodiments, the endometrial sample may be obtained via a less invasive method, for example, by collecting the detached cells present in the uterine lavage. Without wishing to be bound by any theory, it is believed that the claimed qPCR-based miRNA expression profiling method provides higher specificity and sensitivity as compared to the microarray-based miRNA expression profiling method, such that a significantly less amount of the endometrial sample may be needed in the methods according to this disclosure. See Wang et al., "Large scale real-time PCR validation on gene expression measurements from two commercial long-oligonucleotide microarrays," BMC Genomics, 2006, 7:59-75.

[0067] In some embodiments, the endometrial sample is obtained seven days after an endogenous LH surge (LH+7) in the woman. In some embodiments, the endometrial sample is obtained five days after a progesterone administration (P+5) in the woman.

[0068] The miRNAs in the endometrial sample can be extracted and enriched using methods known in the art. For example, miRNA can be extracted from the endometrial tissue using the miRNeasy Micro Kit (QIAGEN) following the manufacturer's instructions. See Example 1. The miRNA-enriched preparations can be stored at -80° C. The quantity and quality of the miRNA can be analyzed using methods known in the art. For example, the miRNA can be analyzed using a commercially available Agilent bioanalyzer.

[0069] The expression level of each miRNA can be quantified by methods known in the art, including qPCR, sequencing, microarray, or RNA-DNA hybrid capture technology. In some embodiments, the methods according to this

disclosure use a qPCR reaction, which generally has higher sensitivity and specificity than northern blot hybridization and/or microarray gene chip analysis. To that end, cDNA can be synthesised from the extracted and enriched miRNAs in a reverse transcription reaction, and a qPCR reaction can be performed to quantify the expression levels of the miRNAs. Thus, in some embodiments, the miRNA expression profile is determined by qPCR, optionally using one or more miRNA profiling chips disclosed herein. See Example 1.

[0070] Currently, qPCR assays can be divided into two types. The first type is performing cDNA synthesis using a stem-loop reverse transcription primer, and quantifying miRNA using a miRNA specific probe or a universal probe. The second method is to perform cDNA synthesis using a linear universal reverse transcription primer and quantify miRNA using a miRNA specific forward primer, a reverse transcription-primer specific reverse primer, and a double-stranded DNA intercalating dye.

[0071] In some embodiments, the cDNA synthesis is performed using a universal reverse transcription primer as disclosed in U.S. Pat. No. 10,590,478, which is incorporated herein by reference. In some embodiments, the cDNA synthesis is performed using a universal reverse transcription primer having a nucleotide sequence represented by the following general formula: 5'-R-(dT) nVN-3', wherein R comprises the sequence of CAACTCAGGTCGTAGGCAATTCGT (SEQ ID NO:168), (dT) n is an n number of continuous thymine residues, wherein n is 19, V is an adenine residue, a guanine residue, or a cytosine residue, and N is an adenine residue, a guanine residue, a cytosine residue, or a thymine residue.

[0072] To reduce cost and for ease of use, in some embodiments, the qPCR reactions can be performed using one or more miRNA profiling chips that target all of the 167 miRNAs according to this disclosure. See Example 1. In some embodiments, each of the miRNA profiling chips is preloaded with suitable primers and/or probes capable of concurrently analyzing the expression of at least 20, 30, 40, 50, 60, 60, 70, 80, 90, 95, 96, 97, 98, 99, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, or 200 miRNAs. In some embodiments, the miRNA profiling chip contains a multiplex slide plate as disclosed in U.S. Pat. Nos. 9,724,692, 10,415,084, Appl. No. 16/191,451 and application Ser. No. 16/233,121 which are incorporated herein by reference.

[0073] The qPCR reactions can be performed using methods known in the art. In some embodiments, the qPCR reactions can be carried out using a thermal cycler device as disclosed in U.S. Pat. No. 9,168,533 and application Ser. No. 16/559,642, which are incorporated herein by reference. See also Example 1.

miRNA Analysis Algorithm and its Use for Determining Endometrial Receptivity

[0074] According to the methods of this disclosure, the miRNA expression profile can be used to generate a receptivity predictive score, using a computer-based miRNA analysis algorithm. The receptivity predictive score classifies the endometrial status into one of the following three states: a pre-receptive state, a receptive state, or a post-receptive state.

[0075] The computer-based miRNA analysis algorithm is a mathematical prediction classifier which uses the miRNA expression data and learns to distinguish classes according to different receptivity states.

[0076] To build the algorithm, the raw data on miRNA expression levels is divided into a training set and a validation set. The training set is used to train the prediction classifier and the validation set is used to evaluate and refine the performance of the prediction classifier. As shown in FIG. 3, one or more of the following steps are performed to build and validate the algorithm: data normalization, data scaling, data transformation, prediction modeling, and cross-validation.

[0077] In order to make distributions identical in statistical properties, the data can be normalized by Quantile Normalization, as described in Bolstad et al., “A comparison of normalization methods for high density oligonucleotide array data based on variance and bias,” *Bioinformatics*, 2003, 19 (2): 185-193. Furthermore, to ensure that the objective functions are working properly, the data can be standardized the range of value to make data having zero-mean and unit-variance.

[0078] For both reasons of data reduction and feature extraction, a principal component analysis (PCA) can be used to condense the information from a large number of original variables and generate a small set of new features by linearly combining the original variables.

[0079] The PCA-transformed data can be used to further build a generalized linear model with elastic net regularization, which is a regularized regression method that linearly combined the L1 and L2 penalties of lasso and ridge methods, as described in Zou et al., “Regularization and variable selection via the elastic net,” *J. R. Statist. Soc. B*, 2005, 67, part 2, 301-320. Additional information on glmnet is known and available at glmnet.stanford.edu.

[0080] The k-fold cross-validation method, for example, a 10-fold cross-validation, can be used to assess the computer-based miRNA analysis algorithm's predictive value before finalizing it. See FIG. 5. In a k-fold cross-validation, the original sample is randomly partitioned into k equal size subsamples. Of the k subsamples, a single subsample is retained as the validation data for testing the model, and the remaining k-1 subsamples are used as training data. The cross-validation process is then repeated k times (the folds), with each of the k subsamples used exactly once as the validation data. The k results from the folds can then be averaged (or otherwise combined) to produce a single estimation.

[0081] Pregnancy rates can be used to assess the predictive value of the computer-based miRNA analysis algorithm. See Example 2.

[0082] After validation and refinement, a computer-based miRNA analysis algorithm is generated. Running the algorithm generates a receptivity predictive score that classifies the endometrial status of the woman into one of the three states as follows: if the score is greater than 1, the woman's endometrium is in the pre-receptive state; if the score is less than -1, the woman's endometrium is in the post-receptive state; and if the score is from -1 to 1, the woman's endometrium is in the receptive state. See FIG. 6.

Applications of the Methods According to this Disclosure

[0083] The present disclosure provides methods for determining an endometrial status, using a sample, for example, an endometrial biopsy, comprising: (a) performing an assay on the endometrial sample from a woman to determine a miRNA expression profile of the endometrial sample, wherein the miRNA expression profile comprises expression levels of a plurality of miRNAs, for example, 167 miRNAs

having the sequences of SEQ ID NOs: 1-167, respectively; and (b) analyzing the miRNA expression profile to obtain a receptivity predictive score using, for example, a computer-based algorithm.

[0084] Methods of the present disclosure can be used for various diagnostic and therapeutic purposes, including but not limited to IVF treatment. For example, in some embodiments, based on the endometrial results, the methods may further include implanting an embryo in the woman or administering one or more treatments to the woman who suffers or suffered from an implantation failure. In some embodiments, the present disclosure provides methods of detecting endometrial receptivity for embryo implantation, comprising: (a) performing an assay on an endometrial sample from a woman to determine a miRNA expression profile of the endometrial sample, wherein the miRNA expression profile comprises expression levels of a plurality of miRNAs, for example, 167 miRNAs having the sequences of SEQ ID NOs: 1-167, (b) analyzing the miRNA expression profile to obtain a receptivity predictive score, wherein the receptivity predictive score determines whether the woman has endometrial receptivity, and (c) transferring an embryo to the endometrium of the woman determined to have endometrial receptivity.

[0085] In some embodiments, the methods of determining an endometrial status can be used to determine the timing of embryo implantation in a woman. In some embodiments, if the endometrial status is at the receptive state, the woman is considered suitable for embryo implantation. If the endometrial status is at the pre-receptive or the post-receptive state, the woman is considered not suitable for embryo implantation. In some embodiments, when the endometrial status is determined to be at the pre-receptive state or the post-receptive state, the present disclosure provides methods for embryo implantation based on the information on the endometrial status. For example, if the endometrial status is determined to be at the pre-receptive state, during the next cycle, embryo implantation can be performed between 5.5 and 7.5 days, for example, 5.5, 6, 6.5, 7, or 7.5 days after a progesterone administration. Alternatively, if the endometrial status is determined to be at the post-receptive state, during the next cycle, embryo implantation can be performed between 2.5 and 4.5 days, for example, 2.5, 3, 3.5, 4, or 4.5 days after a progesterone administration.

[0086] In cases where the endometrium shows a non-receptive state at the time of the sampling, the information gained is instructive, such that the method can be repeated by taking an endometrial sample at another time, modified in line with the results of the first determination. By way of example, if the endometrial status is at the pre-receptive state, the next time point of taking the endometrial sample can be more than seven days after an endogenous LH surge or more than five days after a progesterone administration. For example, the next point of taking the endometrial sample can be between 7.5 and 10.5 days, for example, 7.5, 8, 8.5, 9, 9.5, 10, or 10.5 days after an endogenous LH surge or between 5.5 and 7.5 days, for example, 5.5, 6, 6.5, 7, or 7.5 days after a progesterone administration. Alternatively, if the endometrial status is at the post-receptive state, the next time point of taking the endometrial sample can be fewer than seven days after an endogenous LH surge or fewer than five days after a progesterone administration. For example, the next point of taking the endometrial sample can be between 3.5 and 6.5 days, for example, 3.5, 4, 4.5, 5, 5.5, 6, or 6.5

days after an endogenous LH surge or between 2.5 and 4.5 days, for example, 2.5, 3, 3.5, 4, or 4.5 days after a progesterone administration. By following these procedures, a receptive state can be found, and the success rate of the IVF treatment can be improved. For any one of these uses, the woman suffers or suffered from an implantation failure. In some embodiments, the woman is subject to an IVF treatment.

[0087] In some embodiments, if the endometrial status is determined to be at the pre-receptive state or the post-receptive state, the method of determining an endometrial status can be repeated at least once or until the endometrial status is determined to be at the receptive state.

[0088] In some embodiments, the methods of determining an endometrial status according to this disclosure can be used to determine the WOI of a woman. In some embodiments, the methods according to this disclosure can be used to classify a woman's responsiveness to the IVF treatment. For any one of these uses, in some embodiments, the woman suffers or suffered from an implantation failure. In some embodiments, the woman is subject to an IVF treatment.

[0089] In some embodiments, the methods of determining an endometrial status according to this disclosure can be used as a valuable tool for investigating the effects of pregnancy drugs on the endometrium of a woman. In these embodiments, the woman suffers or suffered from an implantation failure. In some embodiments, the woman is subject to an IVF treatment.

Kits

[0090] Another aspect of this disclosure relates to kits for carrying out the methods of determining an endometrial status. In some embodiments, the kits comprise primers and/or probes suitable for the detection of the expression levels of a plurality of miRNAs, for example, the 167 miRNAs having the sequences of SEQ ID NOs: 1-167, respectively. See Example 1. In some embodiments, the primers and/or probes are suitable for performing qPCR reactions to detect the expression levels of the 167 miRNAs. In some embodiments, the kits comprise one or more miRNA profiling chips targeting the 167 miRNAs. In some embodiments, the one or more chips additionally target RNA sequences, e.g., 18s rRNA, that can be used as the endogenous controls for the miRNA expression analysis.

[0091] The kits may additionally contain instructions on (i) determining a miRNA expression profile of an endometrial sample from a woman, optionally using the one or more miRNA profiling chips, and/or (ii) obtaining a receptivity predictive score based on the miRNA expression profile, using a computer-based algorithm. In some embodiments, the kits contain instructions on how to interpret and use the receptivity predictive score.

[0092] In some embodiments, the kits are useful for diagnostic and therapeutic purposes, including but not limited to IVF treatment.

EXAMPLES

Example 1

Materials and Methods for Generating a miRNA Expression Profile

[0093] Endometrial biopsy. An endometrial biopsy was collected from the uterine cavity of a woman using Pipelle

Endometrial Suction Curette (Cooper Surgical, Inc.) either five days after a progesterone administration (P+5) in a hormone replacement therapy cycle or seven days after an endogenous luteinizing hormone surge (LH+7) in a natural cycle. Endometrial tissues were stored in RNA later immediately.

[0094] RNA extraction and miRNA enrichment. Total RNA was isolated from the endometrial tissue using the miRNeasy Micro Kit (QIAGEN) following the manufacturer's instructions. Briefly, five mg of the endometrial tissue was disrupted and homogenized in liquid nitrogen with a motor and pestle. 700 μ l of QIAzol Lysis Reagent was added to the homogenized tissue and the resulting sample was incubated at room temperature for five min to promote the dissociation of nucleoprotein complexes. 140 μ l of chloroform per 700 μ l of QIAzol Lysis Reagent was added to the tube, and the tube was shaken vigorously by hand for 15 seconds and incubated at room temperature for 2-3 min. The sample was centrifuged at 12,000 g for 15 min at 4° C. After the centrifugation, the upper aqueous phase was transferred to a new tube, one volume of 70% ethanol was added to the tube, and the tube was vortexed thoroughly. The sample was transferred into a RNeasy MinElute spin column and centrifuged at 8,000 g for 15 s at room temperature. The flow-through was pipetted into a 2 ml tube, 0.65 volume of 100% ethanol was added to the flow-through, and the resulting sample was vortexed thoroughly. The sample was then transferred into a RNeasy M inElute spin column and centrifuged at 8,000 g for 15 s at room temperature. The flow-through was discarded, 700 μ l Buffer RWT was added to the RNeasy MinElute spin column, and the column was centrifuged for 15 s at 8000 g to wash the column. The flow-through was discarded, 500 μ l Buffer RPE was added into the RN easy M inElute spin column, and the column was centrifuged for 15 s at 8,000 g to wash the column. The flow-through was discarded, 500 μ l of 80% ethanol was added to the RNeasy M inElute spin column, and the column was centrifuged for 2 min at 8,000 g to dry the spin column membrane. The RNeasy M in Elute spin column was placed into a new 2 ml collection tube and centrifuged for 5 min at 8,000 g. The RNeasy M inElute spin column was placed into a 1.5 ml collection tube, 14-20 μ l nuclease-free water was added onto the spin column membrane, and the column was centrifuged for 1 min at 8,000 g to elute the miRNA-enriched fraction. The miRNA-enriched fraction was stored at -80° C.

[0095] cDNA synthesis. ≥ 2 ng of miRNA-enriched fraction from endometrial tissue was used to synthesize cDNA in a 20 μ l reverse transcription reaction. Reverse transcription was performed using the QuarkBio microRNA Universal RT Kit (Quark Biosciences Taiwan, Inc.) following the manufacturer's instructions. Briefly, poly-A tails were added to the miRNA using poly-A polymerase, followed by cDNA synthesis. cDNA synthesis was subsequently performed using the following program: 42° C. for 60 min and 95° C. for 5 min, and then 4° C. until completion of program. The synthesized cDNA was stored at -20° C.

[0096] miRNA expression profiling using the NextA mp Analysis System and the MIRA PanelChip set. The MIRA PanelChip set contains a total of 167 miRNA assays. The sequences for the 167 miRNAs are shown in Table 1. In addition, RNU6B, RNU43, and 18 s rRNA were used as endogenous controls. Three exogenous spike-in controls were used to monitor miRNA extraction, cDNA synthesis,

and qPCR efficiency (Quark Biosciences Taiwan, Inc.). The cDNA was analyzed with the MIRA PanelChip set. cDNA (equivalent to 0.1 ng of miRNA-enriched fraction) was added to the mixture containing 30 μ l of 2 \times SYBR Master Mix (Quark Biosciences Taiwan, Inc.), and nuclease-free water was added to the mixture to obtain a final volume of 60 μ l. The mixture was mixed by hand thoroughly and briefly spun down to collect the liquid at the bottom. 60 μ l of the mixture was dispensed using a Pipetman along the edge of the chip and the mixture was then applied across the entire surface of the MIRA PanelChip via a scraping motion with a glass slide. Each chip was then submerged into a tray containing Channeling Solution (Quark Biosciences Taiwan, Inc.), with reaction wells facing the bottom of the tray. Each tray was then placed into Q Station, which is a thermocycler (see PanelStation in FIG. 2) for MIRA PanelChip applications and includes built-in sample management database and a analysis platform, such that the MIRA PanelChip assays and data analysis can be performed conveniently and quickly. The MIRA PanelChip analysis was subsequently performed according to the following program: 95° C. for 36 s and 60° C. for 72 s, for 40 cycles.

Example 2

Computer-Based miRNA Analysis Algorithm and its Use

[0097] As shown in FIG. 3, the computer-based miRNA analysis algorithm (MIRA) was built by performing one or more of the following steps: data normalization, data scaling, data transformation, prediction modeling, and cross-validation.

[0098] Data normalization. For making distributions identical in statistical properties, the data was normalized by Quantile Normalization. See equation (A) in FIG. 3; see also Bolstad et al., “A comparison of normalization methods for high density oligonucleotide array data based on variance and bias,” *Bioinformatics*, 2003, 19 (2): 185-193.

[0099] Data scaling. To ensure that the objective functions are working properly, the data was standardized the range of value to make data having zero-mean and unit-variance. See equation (B) in FIG. 3.

[0100] Data transformation. For the reasons of data reduction and feature extraction, the PCA condensed the information from a large number of original variables and generated a small set of new features by linearly combining the original variables. See equation (C) in FIG. 3. Modeling. The PCA-transformed data was used to further build a generalized linear

[0101] model with elastic net regularization, which was a regularized regression method that linearly combined the L1 and L2 penalties of lasso and ridge methods. See equation (D) in FIG. 3; see also Zou et al., “Regularization and variable selection via the elastic net,” *J. R. Statist. Soc. B*, 2005, 67, part 2, 301-320.

[0102] Cross-validations were performed to assess the computer-based miRNA analysis algorithm’s predictive value before finalizing the MIRA model. As shown in FIG. 4A, using the miRNA expression profile containing the expression levels of 167 miRNA s having the sequences of SEQ ID NOs: 1-167 shown in Table 1, the MIRA model was able to successfully classify the clinal samples into one of the three status groups: a pre-receptive state, a receptive state, or a post-receptive state. Furthermore, as shown in FIG. 4B, preliminary validation showed a 100% pregnancy rate in women classified under the receptive state (Test set).

[0103] Data from 183 women were divided into 10 subsets to achieve the 10-fold cross-validation for model assessment. FIG. 5 shows a 10-fold cross-validation and pregnancy rate using miRNA expression profiles comprising expression levels of 167 miRNA s from 183 endometrial samples. In these tests, in the first cycle, each woman’s endometrial status was determined. If a woman’s endometrium was determined to be in the pre-receptive state, embryo implantation was performed six days after a progesterone administration in the next cycle (P+6 group; 35 women). If a woman’s endometrium was determined to be in the receptive state, embryo implantation was performed five days after a progesterone administration in the next cycle (P+5 group; 142 women). If a woman’s endometrium was determined to be in the post-receptive state, embryo implantation was performed 4.5 days after a progesterone administration in the next cycle (P+4.5 group; 6 women). In addition, FIG. 5 shows the sensitivity, specificity, PPV, NPV, and overall concordance rate of the 10-fold cross-validation results.

[0104] Among the three groups, 137 pregnancy events were detected, with 22 events from the P+6 group, 113 events from the P+5 group, and 2 events from the P+4.5 group. See FIG. 5. With respect to the predictive evaluation of the computer-based miRNA analysis algorithm, among all 137 pregnancy events, 1 out of 2 from the P+4.5 group, 107 out of 113 from the P+5 group, and 17 out of 22 from the P+6 group showed correct embryo implantation timing adjustments determined by the algorithm and resulted in a 91.24% pregnancy rate (125/137). See FIG. 5. MIRA Model. Taking into account all of the parameters described in this example (see

[0105] FIG. 3, eq (A-D) and subsequent fine-tuning their parameters based on cross-validation), a prediction model was generated which classifies all samples into three distinct endometrial states. Running MIRA generated a receptivity predictive score (MIRA score), calculated using the following equation: $\text{MIRA score} = f(X \in \text{eq}(C)) = X\beta + \epsilon$, where β is a vector of coefficients, and ϵ is an error, both being produced by gimnet through the cross-validation (FIG. 3). This model could be applied to any qPCR profiling of an endometrium to predict the endometrial status.

[0106] As shown in FIG. 6, running the computer-based miRNA analysis algorithm generated a receptivity predictive score that classifies the endometrial status of the woman into one of the three states: if the score is greater than 1, the woman’s endometrium is in the pre-receptive state; if the score is less than -1, the woman’s endometrium is in the post-receptive state; and if the score is from -1 to 1, the woman’s endometrium is in the receptive state (WOI).

[0107] While the disclosure has been particularly shown and described with reference to specific embodiments, it should be understood by those having skill in the art that various changes in form and detail may be made therein without departing from the spirit and scope of the present disclosure.

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SEQUENCE LISTING

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SEQUENCE: 61		
tattgcactt gtcccgccct gt		22
SEQ ID NO: 62	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-150-5p	
source	1..22 mol_type = genomic RNA organism = Homo sapiens	
SEQUENCE: 62		
tctccaacc cttgtaccag tg		22
SEQ ID NO: 63	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-15b-5p	
source	1..22 mol_type = genomic RNA organism = Homo sapiens	
SEQUENCE: 63		
tagcagcaca tcatgggtta ca		22
SEQ ID NO: 64	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-130a-3p	
source	1..22 mol_type = genomic RNA organism = Homo sapiens	
SEQUENCE: 64		
cagtgcaatg ttaaaagggc at		22

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SEQ ID NO: 65      moltype = RNA  length = 22
FEATURE           Location/Qualifiers
misc_feature       1..22
                   note = hsa-miR-130b-3p
source            1..22
                   mol_type = genomic RNA
                   organism = Homo sapiens

SEQUENCE: 65
cagtgcattg atgaaagggc at                               22

SEQ ID NO: 66      moltype = RNA  length = 22
FEATURE           Location/Qualifiers
misc_feature       1..22
                   note = hsa-miR-140-5p
source            1..22
                   mol_type = genomic RNA
                   organism = Homo sapiens

SEQUENCE: 66
cagtgggttt accctatggt ag                               22

SEQ ID NO: 67      moltype = RNA  length = 23
FEATURE           Location/Qualifiers
misc_feature       1..23
                   note = hsa-miR-18a-5p
source            1..23
                   mol_type = genomic RNA
                   organism = Homo sapiens

SEQUENCE: 67
taaggtgcat ctagtgcaga tag                             23

SEQ ID NO: 68      moltype = RNA  length = 22
FEATURE           Location/Qualifiers
misc_feature       1..22
                   note = hsa-let-7c-5p
source            1..22
                   mol_type = genomic RNA
                   organism = Homo sapiens

SEQUENCE: 68
tgaggtagta ggttgatgg tt                               22

SEQ ID NO: 69      moltype = RNA  length = 22
FEATURE           Location/Qualifiers
misc_feature       1..22
                   note = hsa-miR-196a-5p
source            1..22
                   mol_type = genomic RNA
                   organism = Homo sapiens

SEQUENCE: 69
taggtagttt catgttggtg gg                             22

SEQ ID NO: 70      moltype = RNA  length = 22
FEATURE           Location/Qualifiers
misc_feature       1..22
                   note = hsa-miR-199a-3p
source            1..22
                   mol_type = genomic RNA
                   organism = Homo sapiens

SEQUENCE: 70
acagtagtct gcacattggt ta                             22

SEQ ID NO: 71      moltype = RNA  length = 23
FEATURE           Location/Qualifiers
misc_feature       1..23
                   note = hsa-miR-103a-3p
source            1..23
                   mol_type = genomic RNA
                   organism = Homo sapiens

SEQUENCE: 71
agcagcattg tacagggcta tga                             23

SEQ ID NO: 72      moltype = RNA  length = 21
FEATURE           Location/Qualifiers
misc_feature       1..21
                   note = hsa-miR-129-5p
source            1..21

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	mol_type = genomic RNA organism = Homo sapiens	
SEQUENCE: 72		
ctttttgcgg tctgggcttg c		21
SEQ ID NO: 73	moltype = RNA length = 21	
FEATURE	Location/Qualifiers	
misc_feature	1..21	
	note = hsa-miR-152-3p	
source	1..21	
	mol_type = genomic RNA organism = Homo sapiens	
SEQUENCE: 73		
tcagtgcattg acagaacttg g		21
SEQ ID NO: 74	moltype = RNA length = 20	
FEATURE	Location/Qualifiers	
misc_feature	1..20	
	note = hsa-miR-144-3p	
source	1..20	
	mol_type = genomic RNA organism = Homo sapiens	
SEQUENCE: 74		
tacagtattag atgatgtact		20
SEQ ID NO: 75	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-183-5p	
source	1..22	
	mol_type = genomic RNA organism = Homo sapiens	
SEQUENCE: 75		
tatggcactg gtagaattca ct		22
SEQ ID NO: 76	moltype = RNA length = 23	
FEATURE	Location/Qualifiers	
misc_feature	1..23	
	note = hsa-miR-93-5p	
source	1..23	
	mol_type = genomic RNA organism = Homo sapiens	
SEQUENCE: 76		
caaagtgcctg ttcgtgcagg tag		23
SEQ ID NO: 77	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-100-5p	
source	1..22	
	mol_type = genomic RNA organism = Homo sapiens	
SEQUENCE: 77		
aaccgtaga tccgaacttg tg		22
SEQ ID NO: 78	moltype = RNA length = 23	
FEATURE	Location/Qualifiers	
misc_feature	1..23	
	note = hsa-miR-19b-3p	
source	1..23	
	mol_type = genomic RNA organism = Homo sapiens	
SEQUENCE: 78		
tgtgcaaattc catgcaaaac tga		23
SEQ ID NO: 79	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-30b-5p	
source	1..22	
	mol_type = genomic RNA organism = Homo sapiens	
SEQUENCE: 79		
tgtaaacattc ctacactcag ct		22
SEQ ID NO: 80	moltype = RNA length = 23	

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FEATURE	Location/Qualifiers	
misc_feature	1..23	
	note = hsa-miR-373-3p	
source	1..23	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 80		
gaagtgccttc gattttgggg tgt		23
SEQ ID NO: 81	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-451a	
source	1..22	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 81		
aaaccgttac cattactgag tt		22
SEQ ID NO: 82	moltype = RNA length = 23	
FEATURE	Location/Qualifiers	
misc_feature	1..23	
	note = hsa-miR-142-3p	
source	1..23	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 82		
tgtagtggtt cctactttat gga		23
SEQ ID NO: 83	moltype = RNA length = 23	
FEATURE	Location/Qualifiers	
misc_feature	1..23	
	note = hsa-miR-20b-5p	
source	1..23	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 83		
caaagtgcctc atagtgcagg tag		23
SEQ ID NO: 84	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-30d-5p	
source	1..22	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 84		
tgtaaacatc cccgactgga ag		22
SEQ ID NO: 85	moltype = RNA length = 23	
FEATURE	Location/Qualifiers	
misc_feature	1..23	
	note = hsa-miR-372-3p	
source	1..23	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 85		
aaagtgcctgc gacatttgag cgt		23
SEQ ID NO: 86	moltype = RNA length = 23	
FEATURE	Location/Qualifiers	
misc_feature	1..23	
	note = hsa-miR-135b-5p	
source	1..23	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 86		
tatggctttt cattcctatg tga		23
SEQ ID NO: 87	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-193a-3p	
source	1..22	
	mol_type = genomic RNA	
	organism = Homo sapiens	

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SEQUENCE: 87
aactggccta caaagtccca gt 22

SEQ ID NO: 88 moltype = RNA length = 22
FEATURE Location/Qualifiers
misc_feature 1..22
 note = hsa-miR-409-3p
source 1..22
 mol_type = genomic RNA
 organism = Homo sapiens

SEQUENCE: 88
gaatgttgct cggtgaaccc ct 22

SEQ ID NO: 89 moltype = RNA length = 22
FEATURE Location/Qualifiers
misc_feature 1..22
 note = hsa-let-7g-5p
source 1..22
 mol_type = genomic RNA
 organism = Homo sapiens

SEQUENCE: 89
tgaggtagta gttgtacag tt 22

SEQ ID NO: 90 moltype = RNA length = 23
FEATURE Location/Qualifiers
misc_feature 1..23
 note = hsa-miR-10a-5p
source 1..23
 mol_type = genomic RNA
 organism = Homo sapiens

SEQUENCE: 90
taccctgtag atccgaattt gtg 23

SEQ ID NO: 91 moltype = RNA length = 23
FEATURE Location/Qualifiers
misc_feature 1..23
 note = hsa-miR-191-5p
source 1..23
 mol_type = genomic RNA
 organism = Homo sapiens

SEQUENCE: 91
caacggaatc ccaaaagcag ctg 23

SEQ ID NO: 92 moltype = RNA length = 22
FEATURE Location/Qualifiers
misc_feature 1..22
 note = hsa-let-7f-5p
source 1..22
 mol_type = genomic RNA
 organism = Homo sapiens

SEQUENCE: 92
tgaggtagta gattgtatag tt 22

SEQ ID NO: 93 moltype = RNA length = 22
FEATURE Location/Qualifiers
misc_feature 1..22
 note = hsa-miR-134-5p
source 1..22
 mol_type = genomic RNA
 organism = Homo sapiens

SEQUENCE: 93
tgtgactggt tgaccagagg gg 22

SEQ ID NO: 94 moltype = RNA length = 23
FEATURE Location/Qualifiers
misc_feature 1..23
 note = hsa-miR-146b-5p
source 1..23
 mol_type = genomic RNA
 organism = Homo sapiens

SEQUENCE: 94
tgagaactga attccatagg ctg 23

SEQ ID NO: 95 moltype = RNA length = 22
FEATURE Location/Qualifiers
misc_feature 1..22

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source	note = hsa-miR-127-3p 1..22 mol_type = genomic RNA organism = Homo sapiens	
SEQUENCE: 95		
tcggatccgt ctgagcttgg ct		22
SEQ ID NO: 96	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-196b-5p	
source	1..22 mol_type = genomic RNA organism = Homo sapiens	
SEQUENCE: 96		
taggtagttt cctgttggtg gg		22
SEQ ID NO: 97	moltype = RNA length = 23	
FEATURE	Location/Qualifiers	
misc_feature	1..23	
	note = hsa-miR-302d-3p	
source	1..23 mol_type = genomic RNA organism = Homo sapiens	
SEQUENCE: 97		
taagtgttc catgtttgag tgt		23
SEQ ID NO: 98	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-663a	
source	1..22 mol_type = genomic RNA organism = Homo sapiens	
SEQUENCE: 98		
aggcggggcg ccgcgggacc gc		22
SEQ ID NO: 99	moltype = RNA length = 20	
FEATURE	Location/Qualifiers	
misc_feature	1..20	
	note = hsa-miR-326	
source	1..20 mol_type = genomic RNA organism = Homo sapiens	
SEQUENCE: 99		
cctctgggcc cttcctccag		20
SEQ ID NO: 100	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-486-5p	
source	1..22 mol_type = genomic RNA organism = Homo sapiens	
SEQUENCE: 100		
tcctgtactg agctgccccg ag		22
SEQ ID NO: 101	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-17-3p	
source	1..22 mol_type = genomic RNA organism = Homo sapiens	
SEQUENCE: 101		
actgcagtga aggcacttgt ag		22
SEQ ID NO: 102	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-30e-5p	
source	1..22 mol_type = genomic RNA organism = Homo sapiens	
SEQUENCE: 102		
tgtaaacatc cttgactgga ag		22

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SEQ ID NO: 103	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-let-7d-5p	
source	1..22	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 103		
agaggtagta ggttgcatag tt		22
SEQ ID NO: 104	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-193b-3p	
source	1..22	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 104		
aactggccct caaagtcccg ct		22
SEQ ID NO: 105	moltype = RNA length = 20	
FEATURE	Location/Qualifiers	
misc_feature	1..20	
	note = hsa-miR-202-3p	
source	1..20	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 105		
agaggtatag ggcattgggaa		20
SEQ ID NO: 106	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-216a-5p	
source	1..22	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 106		
taatctcagc tggcaactgt ga		22
SEQ ID NO: 107	moltype = RNA length = 21	
FEATURE	Location/Qualifiers	
misc_feature	1..21	
	note = hsa-miR-376c-3p	
source	1..21	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 107		
aacatagagg aaattccacg t		21
SEQ ID NO: 108	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-198	
source	1..22	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 108		
ggtccagagg ggagataggt tc		22
SEQ ID NO: 109	moltype = RNA length = 21	
FEATURE	Location/Qualifiers	
misc_feature	1..21	
	note = hsa-miR-215-5p	
source	1..21	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 109		
atgacctatg aattgacaga c		21
SEQ ID NO: 110	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-197-3p	
source	1..22	

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	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 110		
ttcaccacct tctccaccca gc		22
SEQ ID NO: 111	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-29a-5p	
source	1..22	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 111		
actgatttct tttggtgttc ag		22
SEQ ID NO: 112	moltype = RNA length = 23	
FEATURE	Location/Qualifiers	
misc_feature	1..23	
	note = hsa-miR-425-5p	
source	1..23	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 112		
aatgacacga tcaactccgt tga		23
SEQ ID NO: 113	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-574-3p	
source	1..22	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 113		
cacgctcatg cacacaccca ca		22
SEQ ID NO: 114	moltype = RNA length = 23	
FEATURE	Location/Qualifiers	
misc_feature	1..23	
	note = hsa-miR-18b-5p	
source	1..23	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 114		
taaggtgcat ctagtgcagt tag		23
SEQ ID NO: 115	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-483-5p	
source	1..22	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 115		
aagacgggag gaaagaaggg ag		22
SEQ ID NO: 116	moltype = RNA length = 21	
FEATURE	Location/Qualifiers	
misc_feature	1..21	
	note = hsa-miR-625-5p	
source	1..21	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 116		
agggggaaaag ttctatagtc c		21
SEQ ID NO: 117	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-338-5p	
source	1..22	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 117		
aacaatatcc tgggtgtgag tg		22
SEQ ID NO: 118	moltype = RNA length = 22	

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FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-539-5p	
source	1..22	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 118		
ggagaaatta tccttggtgt gt		22
SEQ ID NO: 119	moltype = RNA length = 21	
FEATURE	Location/Qualifiers	
misc_feature	1..21	
	note = hsa-miR-151a-3p	
source	1..21	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 119		
ctagactgaa gctccttgag g		21
SEQ ID NO: 120	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-208b-3p	
source	1..22	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 120		
ataagacgaa caaaaggttt gt		22
SEQ ID NO: 121	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-330-5p	
source	1..22	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 121		
tctctgggcc tgtgtcttag gc		22
SEQ ID NO: 122	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-382-5p	
source	1..22	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 122		
gaagttgttc gtggtggatt cg		22
SEQ ID NO: 123	moltype = RNA length = 21	
FEATURE	Location/Qualifiers	
misc_feature	1..21	
	note = hsa-miR-499a-5p	
source	1..21	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 123		
ttaagacttg cagtgatgtt t		21
SEQ ID NO: 124	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-223-5p	
source	1..22	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 124		
cgtgtatttg acaagctgag tt		22
SEQ ID NO: 125	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-31-3p	
source	1..22	
	mol_type = genomic RNA	
	organism = Homo sapiens	

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SEQUENCE: 125
tgctatgccacacatattgcc at 22

SEQ ID NO: 126      moltype = RNA length = 22
FEATURE            Location/Qualifiers
misc_feature        1..22
                    note = hsa-miR-361-5p
source              1..22
                    mol_type = genomic RNA
                    organism = Homo sapiens

SEQUENCE: 126
ttatcagaat ctccagggt ac 22

SEQ ID NO: 127      moltype = RNA length = 23
FEATURE            Location/Qualifiers
misc_feature        1..23
                    note = hsa-miR-423-3p
source              1..23
                    mol_type = genomic RNA
                    organism = Homo sapiens

SEQUENCE: 127
agctcgtct gaggccctc agt 23

SEQ ID NO: 128      moltype = RNA length = 22
FEATURE            Location/Qualifiers
misc_feature        1..22
                    note = hsa-miR-885-5p
source              1..22
                    mol_type = genomic RNA
                    organism = Homo sapiens

SEQUENCE: 128
tcattacac taccctgct ct 22

SEQ ID NO: 129      moltype = RNA length = 22
FEATURE            Location/Qualifiers
misc_feature        1..22
                    note = hsa-miR-95-3p
source              1..22
                    mol_type = genomic RNA
                    organism = Homo sapiens

SEQUENCE: 129
ttcaacgggt atttattgag ca 22

SEQ ID NO: 130      moltype = RNA length = 22
FEATURE            Location/Qualifiers
misc_feature        1..22
                    note = hsa-miR-99b-5p
source              1..22
                    mol_type = genomic RNA
                    organism = Homo sapiens

SEQUENCE: 130
caccgtaga accgaccttg cg 22

SEQ ID NO: 131      moltype = RNA length = 22
FEATURE            Location/Qualifiers
misc_feature        1..22
                    note = hsa-miR-299-5p
source              1..22
                    mol_type = genomic RNA
                    organism = Homo sapiens

SEQUENCE: 131
tggttaccg tccacatac at 22

SEQ ID NO: 132      moltype = RNA length = 22
FEATURE            Location/Qualifiers
misc_feature        1..22
                    note = hsa-miR-378a-5p
source              1..22
                    mol_type = genomic RNA
                    organism = Homo sapiens

SEQUENCE: 132
ctcctgactc caggctcctgt gt 22

SEQ ID NO: 133      moltype = RNA length = 23
FEATURE            Location/Qualifiers
misc_feature        1..23

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source	note = hsa-miR-500a-5p 1..23 mol_type = genomic RNA organism = Homo sapiens	
SEQUENCE: 133		
taatccttgc tacctgggtg aga		23
SEQ ID NO: 134	moltype = RNA length = 20	
FEATURE	Location/Qualifiers	
misc_feature	1..20	
	note = hsa-miR-518a-5p	
source	1..20 mol_type = genomic RNA organism = Homo sapiens	
SEQUENCE: 134		
ctgcaaaggg aagccctttc		20
SEQ ID NO: 135	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-589-5p	
source	1..22 mol_type = genomic RNA organism = Homo sapiens	
SEQUENCE: 135		
tgagaaccac gtctgtcttg ag		22
SEQ ID NO: 136	moltype = RNA length = 21	
FEATURE	Location/Qualifiers	
misc_feature	1..21	
	note = hsa-miR-718	
source	1..21 mol_type = genomic RNA organism = Homo sapiens	
SEQUENCE: 136		
cttcgcgccc gccgggcgtc g		21
SEQ ID NO: 137	moltype = RNA length = 21	
FEATURE	Location/Qualifiers	
misc_feature	1..21	
	note = hsa-miR-940	
source	1..21 mol_type = genomic RNA organism = Homo sapiens	
SEQUENCE: 137		
aaggcagggc ccccgctccc c		21
SEQ ID NO: 138	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-28-3p	
source	1..22 mol_type = genomic RNA organism = Homo sapiens	
SEQUENCE: 138		
cactagattg tgagctcctg ga		22
SEQ ID NO: 139	moltype = RNA length = 21	
FEATURE	Location/Qualifiers	
misc_feature	1..21	
	note = hsa-miR-411-5p	
source	1..21 mol_type = genomic RNA organism = Homo sapiens	
SEQUENCE: 139		
tagtagaccg tatagcgtac g		21
SEQ ID NO: 140	moltype = RNA length = 23	
FEATURE	Location/Qualifiers	
misc_feature	1..23	
	note = hsa-miR-423-5p	
source	1..23 mol_type = genomic RNA organism = Homo sapiens	
SEQUENCE: 140		
tgaggggcag agagcgagac ttt		23

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SEQ ID NO: 141      moltype = RNA  length = 22
FEATURE            Location/Qualifiers
misc_feature        1..22
                    note = hsa-miR-450a-5p
source              1..22
                    mol_type = genomic RNA
                    organism = Homo sapiens

SEQUENCE: 141
ttttgcatg tgttctaata at                               22

SEQ ID NO: 142      moltype = RNA  length = 22
FEATURE            Location/Qualifiers
misc_feature        1..22
                    note = hsa-miR-484
source              1..22
                    mol_type = genomic RNA
                    organism = Homo sapiens

SEQUENCE: 142
tcaggctcag tccccctccg at                               22

SEQ ID NO: 143      moltype = RNA  length = 25
FEATURE            Location/Qualifiers
misc_feature        1..25
                    note = hsa-miR-593-5p
source              1..25
                    mol_type = genomic RNA
                    organism = Homo sapiens

SEQUENCE: 143
aggcaccagc caggcattgc tcagc                             25

SEQ ID NO: 144      moltype = RNA  length = 21
FEATURE            Location/Qualifiers
misc_feature        1..21
                    note = hsa-miR-652-3p
source              1..21
                    mol_type = genomic RNA
                    organism = Homo sapiens

SEQUENCE: 144
aatggcgcca ctagggttgt g                                21

SEQ ID NO: 145      moltype = RNA  length = 20
FEATURE            Location/Qualifiers
misc_feature        1..20
                    note = hsa-miR-760
source              1..20
                    mol_type = genomic RNA
                    organism = Homo sapiens

SEQUENCE: 145
cggctctggg tctgtgggga                                  20

SEQ ID NO: 146      moltype = RNA  length = 21
FEATURE            Location/Qualifiers
misc_feature        1..21
                    note = hsa-miR-1228-5p
source              1..21
                    mol_type = genomic RNA
                    organism = Homo sapiens

SEQUENCE: 146
gtgggcgggg gcagggtgtg t                                21

SEQ ID NO: 147      moltype = RNA  length = 24
FEATURE            Location/Qualifiers
misc_feature        1..24
                    note = hsa-miR-1254
source              1..24
                    mol_type = genomic RNA
                    organism = Homo sapiens

SEQUENCE: 147
agcctggaag ctggagcctg cagt                             24

SEQ ID NO: 148      moltype = RNA  length = 19
FEATURE            Location/Qualifiers
misc_feature        1..19
                    note = hsa-miR-1290
source              1..19

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-continued

SEQUENCE: 148	mol_type = genomic RNA	
tggaatttttg gatcagggga	organism = Homo sapiens	19
SEQ ID NO: 149	moltype = RNA length = 23	
FEATURE	Location/Qualifiers	
misc_feature	1..23	
source	note = hsa-miR-574-5p	
	1..23	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 149		
tgagtgtgtg tgtgtgagtg tgt		23
SEQ ID NO: 150	moltype = RNA length = 23	
FEATURE	Location/Qualifiers	
misc_feature	1..23	
source	note = hsa-miR-579-3p	
	1..23	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 150		
ttcatttggt ataaaccgcg att		23
SEQ ID NO: 151	moltype = RNA length = 21	
FEATURE	Location/Qualifiers	
misc_feature	1..21	
source	note = hsa-miR-596	
	1..21	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 151		
aagcctgccc ggctcctcgg g		21
SEQ ID NO: 152	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
source	note = hsa-miR-601	
	1..22	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 152		
tggcttagga ttgttgagg ag		22
SEQ ID NO: 153	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
source	note = hsa-miR-660-5p	
	1..22	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 153		
taccattgc atatcgagtg tg		22
SEQ ID NO: 154	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
source	note = hsa-let-7d-3p	
	1..22	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 154		
ctatacgacc tgctgccttt ct		22
SEQ ID NO: 155	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
source	note = hsa-miR-1225-3p	
	1..22	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 155		
tgagccctg tgccgcccc ag		22
SEQ ID NO: 156	moltype = RNA length = 27	

-continued

FEATURE	Location/Qualifiers	
misc_feature	1..27	
	note = hsa-miR-1248	
source	1..27	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 156		
accttcttgtg ataagcactg tgctaaa		27
SEQ ID NO: 157	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-1972	
source	1..22	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 157		
tcaggccagg cacagtggct ca		22
SEQ ID NO: 158	moltype = RNA length = 19	
FEATURE	Location/Qualifiers	
misc_feature	1..19	
	note = hsa-miR-1973	
source	1..19	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 158		
accgtgcaaa ggtagcata		19
SEQ ID NO: 159	moltype = RNA length = 21	
FEATURE	Location/Qualifiers	
misc_feature	1..21	
	note = hsa-miR-2114-3p	
source	1..21	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 159		
cgagcctcaa gcaagggact t		21
SEQ ID NO: 160	moltype = RNA length = 23	
FEATURE	Location/Qualifiers	
misc_feature	1..23	
	note = hsa-miR-217-5p	
source	1..23	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 160		
tactgcatca ggaactgatt gga		23
SEQ ID NO: 161	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-320a-3p	
source	1..22	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 161		
aaaagctggg ttgagagggc ga		22
SEQ ID NO: 162	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-375-3p	
source	1..22	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 162		
ttgttcggt cggtcgcgt ga		22
SEQ ID NO: 163	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-425-3p	
source	1..22	
	mol_type = genomic RNA	
	organism = Homo sapiens	

-continued

SEQUENCE: 163		
atcggaatg tcgtgcgc cc		22
SEQ ID NO: 164	moltype = RNA length = 17	
FEATURE	Location/Qualifiers	
misc_feature	1..17	
	note = hsa-miR-4306	
source	1..17	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 164		
tggagagaaa ggcagta		17
SEQ ID NO: 165	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-452-3p	
source	1..22	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 165		
ctcatctgca aagaagtaag tg		22
SEQ ID NO: 166	moltype = RNA length = 22	
FEATURE	Location/Qualifiers	
misc_feature	1..22	
	note = hsa-miR-4772-3p	
source	1..22	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 166		
cctgcaactt tgctgatca ga		22
SEQ ID NO: 167	moltype = RNA length = 21	
FEATURE	Location/Qualifiers	
misc_feature	1..21	
	note = hsa-miR-520b-3P	
source	1..21	
	mol_type = genomic RNA	
	organism = Homo sapiens	
SEQUENCE: 167		
aaagtgcttc ctttagagg g		21
SEQ ID NO: 168	moltype = DNA length = 24	
FEATURE	Location/Qualifiers	
misc_feature	1..24	
	note = Synthetic	
source	1..24	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 168		
caactcaggt cgtaggcaat tcgt		24

What is claimed is:

1. A kit for determining an endometrial status, comprising: (a) one or more microRNA (miRNA) profiling chips targeting a plurality of miRNAs, and (b) instructions on (i) determining a miRNA expression profile of an endometrial sample from a woman, using the one or more miRNA profiling chips, and (ii) obtaining a receptivity predictive score based on the miRNA expression profile, using a computer-based algorithm, wherein the plurality of miRNAs comprise at least 167 miRNAs having sequences of SEQ ID NOs: 1-167, respectively.

2. The kit of claim 1, wherein the one or more miRNA profiling chips comprise primers for detection of expression levels of the plurality of miRNAs.

3. The kit of claim 2, wherein the miRNA profiling chips are suitable for performing a quantitative PCR (qPCR), sequencing, microarray, or RNA-DNA hybrid capture assay, to detect the expression levels of the plurality of miRNAs.

4. A method of determining a miRNA expression profile of an endometrial sample, comprising:

- (i) obtaining the endometrial sample of a woman; and
- (ii) performing an assay to determine a miRNA expression profile of the endometrial sample,

wherein the miRNA expression profile comprises expression levels of a plurality of miRNAs, and the plurality of miRNAs comprise 167 miRNAs having sequences of SEQ ID NOs: 1-167, respectively, whose expression levels are implicated in a regulation of endometrial receptivity.

5. The method of claim 4, wherein the endometrial sample is obtained from a uterine cavity of the woman.

6. The method of claim 4, wherein the endometrial sample comprises an endometrial biopsy, an endometrial lavage, or combination thereof.

7. The method of claim 4, wherein the endometrial sample is obtained (i) seven days after an endogenous luteinizing

hormone (LH) surge in the woman or (ii) five days after a progesterone administration in the woman.

8. The method of claim 4, wherein the miRNA expression profile is determined by quantitative PCR (qPCR), sequencing, microarray, or RNA-DNA hybrid capture technology.

9. The method of claim 8, wherein the miRNA expression profile is determined by qPCR performed on a cDNA preparation synthesized from the miRNAs in the endometrial sample.

10. The method of claim 9, wherein the cDNA synthesis is performed using a universal reverse transcription primer having a nucleotide sequence represented by the following general formula: 5'-R-(dT) nVN-3', wherein R comprises SEQ ID NO:168, (dT) n is an n number of continuous thymine residues, wherein n is 19, V is an adenine residue, a guanine residue, or a cytosine residue, and N is an adenine residue, a guanine residue, a cytosine residue, or a thymine residue.

11. The method of claim 4, wherein the woman suffers or suffered from an implantation failure.

12. The method of claim 4, wherein the woman is subject to an in vitro fertilization (IVF) treatment.

13. The method of claim 4, wherein the miRNA expression profile comprises expression levels of the 167 miRNAs shown in following table:

TABLE 1

Names and sequences of the 167 miRNAs.		
Name	Sequence	SEQ ID NO
hsa-miR-155-5p	UUAAUGCUAUCGUAUAGGGUU	1
hsa-miR-145-5p	GUCCAGUUUUCCAGGAUCCCU	2
hsa-miR-34a-5p	UGGCAGUGUCUAGCUGGUUGU	3
hsa-miR-21-5p	UAGCUUAUCAGACUGAUGUUGA	4
hsa-miR-125b-5p	UCCUGAGACCCUAACUUGUGA	5
hsa-miR-29a-3p	UAGCACCAUCUGAAUCGGUUA	6
hsa-miR-29b-3p	UAGCACCAUUUGAAUCAGUGUU	7
hsa-miR-200c-3p	UAAUACUGCCGGUAAUGAUGGA	8
hsa-miR-24-3p	UGGCUCAGUUCAGCAGGAACAG	9
hsa-miR-9-5p	UCUUUGGUUAUCUAGCUGUAUGA	10
hsa-miR-146a-5p	UGAGAACUGAAUCCAUGGGUU	11
hsa-miR-26a-5p	UUCAAGUAAUCCAGGAUAGGCU	12
hsa-miR-17-5p	CAAAGUGCUUACAGUGCAGGUAG	13
hsa-miR-200b-3p	UAAUACUGCCUGGUAAUGAUGA	14
hsa-miR-221-3p	AGCUACAUGUCUGCUGGGUUUC	15
hsa-miR-181a-5p	AACAUUCAACGCUGUCGGUGAGU	16
hsa-miR-122-5p	UGGAGUGUGACAAUGGUGUUUG	17
hsa-miR-199a-5p	CCCAGUGUUCAGACUACCUGUUC	18
hsa-miR-29c-3p	UAGCACCAUUUGAAUCGGUUA	19

TABLE 1-continued

Names and sequences of the 167 miRNAs.		
Name	Sequence	SEQ ID NO
hsa-miR-31-5p	AGGCAAGAUGCUGGCAUAGCU	20
hsa-miR-1-3p	UGGAAUGUAAAGAAGUAUGUUAU	21
hsa-miR-20a-5p	UAAAGUGCUUAUAGUGCAGGUAG	22
hsa-miR-27a-3p	UUCACAGUGGCUAAGUUCGCG	23
hsa-miR-203a-3p	GUGAAAUGUUUAGGACCACUAG	24
hsa-miR-141-3p	UAAACUGUCUGGUAAGAUGG	25
hsa-miR-200a-3p	UAAACUGUCUGGUAACGAUGU	26
hsa-miR-22-3p	AAGCUGCCAGUUGAAGAACUGU	27
hsa-miR-101-3p	UACAGUACUGUGAUACUGAA	28
hsa-miR-16-5p	UAGCAGCACGUAUUAUUGGCG	29
hsa-miR-182-5p	UUUGGCAAUGGUAAGACUCACACU	30
hsa-miR-210-3p	CUGUGCGUGUGACAGCGGUGA	31
hsa-miR-125a-5p	UCCUGAGACCCUUUAACUGUGA	32
hsa-let-7a-5p	UGAGGUAGUAGGUUGUAUAGUU	33
hsa-miR-23a-3p	AUCACAUUGCCAGGGAUUUCC	34
hsa-miR-19a-3p	UGUGCAAUUCUAUGCAAAACUGA	35
hsa-miR-223-3p	UGUCAGUUUGUCAAUACCCCA	36
hsa-miR-143-3p	UGAGAUGAAGCACUGUAGCUC	37
hsa-miR-205-5p	UCCUUAUUCACCGGAGUCUG	38
hsa-miR-30a-5p	UGUAAACAUCUCGACUGGAAG	39
hsa-miR-133a-3p	UUUGGUCCCCUUAACACGUG	40
hsa-miR-126-3p	UCGUACCGUGAGUAAUAAUGCG	41
hsa-miR-128-3p	UCACAGUGAACCGUCUCUUU	42
hsa-miR-222-3p	AGCUACAUCUGGCUACUGGGU	43
hsa-miR-214-3p	ACAGCAGGCACAGACAGGCAGU	44
hsa-miR-133b	UUUGGUCCCCUUAACACGCUA	45
hsa-miR-181b-5p	AACAUUAUUGCUGUCGGUGGGU	46
hsa-miR-15a-5p	UAGCAGCACAUAAUGGUUUGUG	47
hsa-miR-106a-5p	AAAAGUGCUUACAGUGCAGGUAG	48
hsa-miR-429	UAAUACUGUCUGGUAACCGU	49
hsa-miR-7-5p	UGGAAGACUAGUGAUUUUGUUGU	50
hsa-miR-106b-5p	UAAAGUGCUGACAGUGCAGAU	51
hsa-miR-10b-5p	UACCCUGUAGAACCAGAAUUGUG	52
hsa-miR-192-5p	CUGACCUAUGAAUUGACAGCC	53
hsa-miR-195-5p	UAGCAGCACAGAAUUAUUGGC	54
hsa-miR-30c-5p	UGUAAACAUCUACACUCUCAGC	55

TABLE 1-continued

Names and sequences of the 167 miRNAs.		
Name	Sequence	SEQ ID NO
hsa-miR-335-5p	UCAAGAGCAAUAACGAAAAUGU	56
hsa-let-7b-5p	UGAGGUAGUAGGUUGUGUGGUU	57
hsa-miR-224-5p	UCAAGUCACUAGUGGUUCCGUUUAG	58
hsa-miR-135a-5p	UAUGGCUUUUAUCCUAUGUGA	59
hsa-miR-206	UGGAAGUAAGGAAGUGUGUGG	60
hsa-miR-92a-3p	UAUUGCACUUGUCCCGGCCUGU	61
hsa-miR-150-5p	UCUCCCAACCCUUGUACAGUG	62
hsa-miR-15b-5p	UAGCAGCACAUCAUGGUUUACA	63
hsa-miR-130a-3p	CAGUGCAAUGUUAAAAGGGCAU	64
hsa-miR-130b-3p	CAGUGCAAUGAUGAAAGGGCAU	65
hsa-miR-140-5p	CAGUGGUUUUACCCUAUGGUAG	66
hsa-miR-18a-5p	UAAGGUGCAUCUAGUGCAGAUAG	67
hsa-let-7c-5p	UGAGGUAGUAGGUUGUAUGGUU	68
hsa-miR-196a-5p	UAGGUAGUUUCAUGUUGUUGGG	69
hsa-miR-199a-3p	ACAGUAGUCUGCACAUUGGUUA	70
hsa-miR-103a-3p	AGCAGCAUUGUACAGGGCUAUGA	71
hsa-miR-129-5p	CUUUUUGCGGUCUGGGCUUGC	72
hsa-miR-152-3p	UCAGUGCAUGACAGAACUUGG	73
hsa-miR-144-3p	UACAGUAUAGAUGAUGUACU	74
hsa-miR-183-5p	UAUGGCACUGGUAGAAUUCACU	75
hsa-miR-93-5p	CAAAGUGCUGUUCGUGCAGGUAG	76
hsa-miR-100-5p	AACCCGUAGAUCGGAACUUGUG	77
hsa-miR-19b-3p	UGUGCAAUCCAUGCAAACUGA	78
hsa-miR-30b-5p	UGUAAACAUCCUACACUCAGCU	79
hsa-miR-373-3p	GAAGUGCUCGAUUUUGGGGUGU	80
hsa-miR-451a	AAACCGUUACCAUUACUGAGUU	81
hsa-miR-142-3p	UGUAGUGUUUCCUACUUUAUGGA	82
hsa-miR-20b-5p	CAAAGUGCUCUAGUGCAGGUAG	83
hsa-miR-30d-5p	UGUAAACAUCCCGACUGGAAG	84
hsa-miR-372-3p	AAAGUGCUGCGACAUUUGAGCGU	85
hsa-miR-135b-5p	UAUGGCUUUUAUCCUAUGUGA	86
hsa-miR-193a-3p	AACUGGCCUACAAAGUCCAGU	87
hsa-miR-409-3p	GAAUGUUGCUCGGUGAACCCCU	88
hsa-let-7g-5p	UGAGGUAGUAGUUUGUACAGUU	89
hsa-miR-10a-5p	UACCCUGUAGAUCGGAUUUGUG	90

TABLE 1-continued

Names and sequences of the 167 miRNAs.		
Name	Sequence	SEQ ID NO
hsa-miR-191-5p	CAACGGAAUCCAAAAGCAGCUG	91
hsa-let-7f-5p	UGAGGUAGUAGAUUGUAUAGUU	92
hsa-miR-134-5p	UGUGACUGGUUGACCAGAGGGG	93
hsa-miR-146b-5p	UGAGAACUGAAUCCAUAGGCUG	94
hsa-miR-127-3p	UCGGAUCCGUCUGAGCUUGGCU	95
hsa-miR-196b-5p	UAGGUAGUUUCCUGUUGUGGG	96
hsa-miR-302d-3p	UAAGUGCUUCCAUUUUAGUGUGU	97
hsa-miR-663a	AGGCGGGGCGCCGCGGACCGC	98
hsa-miR-326	CCUCUGGGCCCUUCCUCCAG	99
hsa-miR-486-5p	UCCUGUACUGAGCUGCCCCGAG	100
hsa-miR-17-3p	ACUGCAGUGAAGGCACUUGUAG	101
hsa-miR-30e-5p	UGUAAACAUCUUGACUGGAAG	102
hsa-let-7d-5p	AGAGGUAGUAGGUUGCAUAGUU	103
hsa-miR-193b-3p	AACUGGCCCUCAAAGUCCCGCU	104
hsa-miR-202-3p	AGAGGUUAGGGCAUGGGAA	105
hsa-miR-216a-5p	UAAUCUCAGCUGGCAACUGUGA	106
hsa-miR-376c-3p	AACAUAGAGGAAAUUCCACGU	107
hsa-miR-198	GGUCCAGAGGGAGAUAGGUUC	108
hsa-miR-215-5p	AUGACCUAUGAAUUGACAGAC	109
hsa-miR-197-3p	UUCACCACCUUCCACCCAGC	110
hsa-miR-29a-5p	ACUGAUUUUUUUGGUGUUCAG	111
hsa-miR-425-5p	AAUGACACGAUCACUCCGUUGA	112
hsa-miR-574-3p	CACGCUCAUGCACACACCCACA	113
hsa-miR-18b-5p	UAAGGUGCAUCUAGUGCAGUUAG	114
hsa-miR-483-5p	AAGACGGGAGGAAGAAGGGAG	115
hsa-miR-625-5p	AGGGGGAAGUUCUUAUGUCC	116
hsa-miR-338-5p	AACAAUAUCCUGGUGCUGAGUG	117
hsa-miR-539-5p	GGAGAAUUAUCCUUGGUGUGU	118
hsa-miR-151a-3p	CUAGACUGAAGCUCCUUGAGG	119
hsa-miR-208b-3p	AUAAGACGAACAAAGGUUUUGU	120
hsa-miR-330-5p	UCUCUGGGCCUGUGUCUUAGGC	121
hsa-miR-382-5p	GAAGUUGUUCUGGUGGAUUCG	122
hsa-miR-499a-5p	UUAAGACUUGCAGUGAUUUU	123
hsa-miR-223-5p	CGUGUAUUUGACAAGCUGAGUU	124
hsa-miR-31-3p	UGCUAUGCCAACAUAUUGCCAU	125
hsa-miR-361-5p	UUAUCAGAAUCCACGGGGUAC	126

TABLE 1-continued

Names and sequences of the 167 miRNAs.		
Name	Sequence	SEQ ID NO
hsa-miR-423-3p	AGCUCGGUCUGAGCCCCUCAGU	127
hsa-miR-885-5p	UCCAUUACACUACCCUGCCUCU	128
hsa-miR-95-3p	UUCAACGGGUAUUUAUUGAGCA	129
hsa-miR-99b-5p	CACCCGUAGAACCGACCUUGCG	130
hsa-miR-299-5p	UGGUUUACCGUCCCAUACAU	131
hsa-miR-378a-5p	CUCCUGACUCCAGGUCCUGUGU	132
hsa-miR-500a-5p	UAAUCCUUGCUACCGGUGAGA	133
hsa-miR-518a-5p	CUGCAAAGGGAAGCCUUUC	134
hsa-miR-589-5p	UGAGAACCACGUCGUCUCUGAG	135
hsa-miR-718	CUUCCGCCCCCGCGGCGUCG	136
hsa-miR-940	AAGGCAGGGCCCCGCUCCCC	137
hsa-miR-28-3p	CACUAGAUUGAGCUCUUGGA	138
hsa-miR-411-5p	UAGUAGACCGUAUAGCGUACG	139
hsa-miR-423-5p	UGAGGGGCAGAGAGCGAGACUUU	140
hsa-miR-450a-5p	UUUUGCGAUGUGUCCUAAUAU	141
hsa-miR-484	UCAGGCUCAGUCCCCUCCCGAU	142
hsa-miR-593-5p	AGGCACCAGCCAGGCAUUGCUCAGC	143
hsa-miR-652-3p	AAUGGCGCCACUAGGGUUGUG	144
hsa-miR-760	CGGCUCUGGGUCUGUGGGGA	145
hsa-miR-1228-5p	GUGGGCGGGGCAGGUGUGUG	146
hsa-miR-1254	AGCCUGGAAGCUGGAGCCUGCAGU	147

TABLE 1-continued

Names and sequences of the 167 miRNAs.		
Name	Sequence	SEQ ID NO
hsa-miR-1290	UGGAUUUUUGGAUCAGGGA	148
hsa-miR-574-5p	UGAGUGUGUGUGUGAGUGUGU	149
hsa-miR-579-3p	UUCAUUUGGUAUAAACCGCAUU	150
hsa-miR-596	AAGCCUGCCCGGCCUCCGCGG	151
hsa-miR-601	UGGUCUAGGAUUGUGGAGGAG	152
hsa-miR-660-5p	UACCCAUUGCAUAUCGGAGUUG	153
hsa-let-7d-3p	CUAUACGACCUCUGCCUUUCU	154
hsa-miR-1225-3p	UGAGCCCCUGUGCCGCCCCAG	155
hsa-miR-1248	ACCUUCUUGUAUAAGCACUGUCUAAA	156
hsa-miR-1972	UCAGGCCAGGCACAGUGGCUCA	157
hsa-miR-1973	ACCGUGCAAAGGUAGCAUA	158
hsa-miR-2114-3p	CGAGCCUCAAGCAAGGGACUU	159
hsa-miR-217-5p	UACUGCAUCAGGAACUGAUUGGA	160
hsa-miR-320a-3p	AAAAGCUGGGUUGAGAGGGCGA	161
hsa-miR-375-3p	UUUGUUCGUUCGGCUCGCGUGA	162
hsa-miR-425-3p	AUCGGGAUUGUGUGUCCGCC	163
hsa-miR-4306	UGGAGAGAAAGGCAGUA	164
hsa-miR-452-3p	CUCAUCUGCAAAGAAGUAAGUG	165
hsa-miR-4772-3p	CCUGCAACUUUGCCUGAUCAGA	166
hsa-miR-520b-3P	AAAGUGCUUCUUUUAGAGGG	167

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