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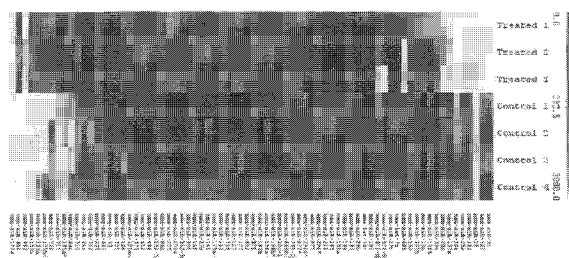


FIG. 3.

(57) Abstract: Methods, compositions, and devices are disclosed which use microRNA to detect, predict, treat, and monitor physiological conditions such as disease or injury. microRNA are isolated and their differential expression is measured to provide diagnostic information. This information may then be utilized for evaluation and/or treatment purposes.

METHODS, COMPOSITIONS, AND DEVICES UTILIZING MicroRNA TO DETERMINE PHYSIOLOGICAL CONDITIONS

BACKGROUND

[0001] This application claims priority to U.S. Provisional Patent Application Serial No. 61/112,985, filed November 10, 2008. That provisional application is hereby fully incorporated by reference in its entirety.

[0002] Disclosed herein are various methods, compositions, and devices utilizing microRNA, such as microRNA-based markers, to detect, predict, treat, or monitor various physiological or pathological conditions.

[0003] The ideal diagnostic marker has to fulfill certain key requirements including being specific, sensitive, robust, and non-invasive. Current disease diagnoses are primarily based on two different but complementary approaches—physical imaging and biomolecular profiling. Both approaches currently suffer from a lack of specificity and early detection capability. Tissue-specific blood biomarkers can increase the specificity to selected organs. However, the levels of these tissue-specific biomarkers are usually low in blood. In addition, the difficulty of developing suitable capture agents for proteins makes the identification and development of new molecular diagnostic markers difficult.

[0004] It would be desirable to provide new methods, compositions, and devices for diagnosing physiological and pathological conditions.

BRIEF DESCRIPTION

[0005] The present disclosure relates, in different embodiments, to the use of the levels of microRNA sequences (miRNA) in body fluids to establish correlations with the body's pathophysiological conditions. Exemplary body fluids include, but are not limited to, serum, plasma, saliva, urine, tears, amniotic fluid, sweat, cerebrospinal fluid, seminal fluid (semen), lung mucus (e.g. from bronchial lavage), pleural fluid, peritoneal fluid, colostrums, and breast milk. These levels can then provide diagnostic and/or predictive information with regard to important issues of health and disease.

[0006] Disclosed are methods of using microRNA sequences to detect a physiological condition. The methods comprise: isolating microRNA sequences from a

biological sample; generating a microRNA profile from the isolated microRNA sequences, the profile including the levels of expressed microRNA sequences in the biological sample; comparing the microRNA profile with a reference to identify differentially expressed microRNA sequences; and detecting the physiological condition based on the identity or the levels of the differentially expressed microRNA sequences.

[0007] The biological sample may be a biopsy material, tissue, or body fluid. In embodiments, the biological sample comprises a body fluid selected from the group consisting of serum, plasma, lymph, saliva, urine, tears, sweat, semen, synovial fluid, cervical mucus, amniotic fluid, cerebrospinal fluid, and breast milk.

[0008] The microRNA sequences may be isolated by extracting the biological sample with an organic solvent to obtain an aqueous phase containing the microRNA sequences; and purifying the aqueous phase through a silica membrane to isolate the microRNA sequences.

[0009] The microRNA profile can be generated using hybridization to identify a microRNA sequences; or by using a quantitative polymerase chain reaction to identify the level of a microRNA sequences.

[0010] The reference can be a table of the levels of expressed microRNA sequences in a normal person, or a reference sample.

[0011] The biological sample may be from a microbe, such as a virus, bacterium, fungus, protozoan, or parasite.

[0012] The isolated microRNA sequences may be specific to a biological pathway, a cell type, or a tissue.

[0013] The physiological condition may be a disease, injury, or infection.

[0014] Also disclosed are methods of using microRNA sequences to detect or predict a physiological condition. These methods also comprise: generating a microRNA profile from a biological sample, the profile including the levels of expressed microRNA sequences in the biological sample; and comparing the microRNA profile with a reference to identify differentially expressed microRNA sequences. The physiological condition could then be detected or predicted based on the identity or the levels of the differentially expressed microRNA sequences. Alternatively, the

physiological condition can be identified, and a treatment can then be administered based on the identity of the physiological condition.

[0015] Further disclosed are methods of using microRNA sequences to monitor a physiological condition, comprising: generating a first microRNA profile from a first biological sample of a patient; administering a treatment to the patient; generating a second microRNA profile from a second biological sample of the patient; comparing the second microRNA profile with the first microRNA profile to identify differentially expressed microRNA sequences; and identifying a change in the physiological condition based on the identity or the amounts of the differentially expressed microRNA sequences.

[0016] Additionally disclosed are methods of using microRNA sequences to treat a physiological condition. The methods comprise: identifying at least one microRNA sequence based on the physiological condition; and manipulating the level of the at least one microRNA sequence to treat the physiological condition. Manipulating the level of the at least one microRNA sequence may comprise: constructing a specific DNA or RNA sequence related to the at least one microRNA sequence; and delivering the specific DNA or RNA sequence to a targeted cell, tissue, or organ.

[0017] Also disclosed are methods of using microRNA sequences to detect, predict, or treat a physiological condition. The methods comprise: generating a microRNA profile from a biological sample; identifying at least one differentially expressed microRNA sequence by comparing the microRNA profile to a reference; and detecting, predicting, or treating the physiological condition based on the identity or the levels of the at least one differentially expressed microRNA sequence. In alternative embodiments, at least two differentially expressed microRNA sequences are identified.

[0018] Other methods of detecting or predicting a physiological condition comprise generating a microRNA profile from a biological sample, wherein the microRNA profile comprises at least one specific microRNA sequence; and comparing the microRNA profile to a reference to provide information useful for detecting or predicting the physiological condition. In alternative embodiments, the microRNA profile comprises at least two specific microRNA sequences.

[0019] A differentially expressed microRNA sequence can be identified by comparing the amount of a particular microRNA sequence in the microRNA profile with the amount of that particular microRNA sequence in the reference. A differentially expressed microRNA sequence is identified when the ratio of the amount in the microRNA profile to the amount in the reference is at least 1.5, or at least 3.

[0020] When the physiological condition is related to liver disease or liver injury, in some embodiments, the microRNA profile or the specific microRNA sequence(s) may comprise at least one microRNA sequence selected from the group consisting of mmu-miR-122, mmu-miR-486, mmu-miR-125b-5p, mmu-let-7d*, mmu-miR-101a, mmu-miR-101b, mmu-miR-1224, mmu-miR-124, mmu-miR-125a-3p, mmu-miR-125a-5p, mmu-miR-127, mmu-miR-130a, mmu-miR-133a, mmu-miR-133b, mmu-miR-135a*, mmu-miR-141, mmu-miR-193, mmu-miR-193b, mmu-miR-199a-5p, mmu-miR-199b*, mmu-miR-200c, mmu-miR-202-3p, mmu-miR-205, mmu-miR-22, mmu-miR-23b, mmu-miR-26a, mmu-miR-27b, mmu-miR-291a-5p, mmu-miR-294*, mmu-miR-29b, mmu-miR-30a, mmu-miR-30c-1*, mmu-miR-30e, mmu-miR-320, mmu-miR-327, mmu-miR-339-3p, mmu-miR-342-3p, mmu-miR-370, mmu-miR-375, mmu-miR-451, mmu-miR-466f-3p, mmu-miR-483, mmu-miR-494, mmu-miR-574-5p, mmu-miR-652, mmu-miR-671-5p, mmu-miR-685, mmu-miR-710, mmu-miR-711, mmu-miR-712, mmu-miR-714, mmu-miR-720, mmu-miR-721, mmu-miR-877, mmu-miR-877*, mmu-miR-882, mmu-miR-93, mmu-miR-99a, and human orthologs thereof.

[0021] In other embodiments where the physiological condition is related to liver disease or liver injury, the microRNA profile or the specific microRNA sequence may comprise at least one microRNA sequence selected from the group consisting of mmu-miR-122, mmu-miR-486, mmu-miR-125b-5p, mmu-let-7d*, mmu-miR-101a, mmu-miR-101b, mmu-miR-1224, mmu-miR-124, mmu-miR-125a-3p, mmu-miR-125a-5p, mmu-miR-133a, mmu-miR-133b, mmu-miR-135a*, mmu-miR-193, mmu-miR-193b, mmu-miR-199a-5p, mmu-miR-199b*, mmu-miR-202-3p, mmu-miR-291a-5p, mmu-miR-294*, mmu-miR-30c-1*, mmu-miR-30e, mmu-miR-327, mmu-miR-339-3p, mmu-miR-342-3p, mmu-miR-375, mmu-miR-466f-3p, mmu-miR-483, mmu-miR-574-5p, mmu-miR-652, mmu-miR-671-5p, mmu-miR-685, mmu-miR-710, mmu-miR-711, mmu-miR-712, mmu-

miR-714, mmu-miR-720, mmu-miR-721, mmu-miR-877, mmu-miR-877*, mmu-miR-882, and human orthologs thereof.

[0022] In particular embodiments, the at least one differentially expressed microRNA sequence or the at least one specific sequence comprises hsa-miR-122. In more specific embodiments, they comprise hsa-miR-122 and either hsa-miR-486-3p or hsa-miR-486-5p (i.e. the human orthologs to mmu-miR-486). The ratio of the amount of miR-122 to the amount of miR-486 may be greater than 4.0, including greater than 6.0.

[0023] When the physiological condition is neurological disease or neurological injury, in some embodiments, the microRNA profile or the specific microRNA sequence may comprise at least one microRNA sequence selected from the group consisting of mmu-let-7g, mmu-miR-298, mmu-miR-1, mmu-miR-101a*, mmu-miR-101b, mmu-miR-1224, mmu-miR-126-5p, mmu-miR-127, mmu-miR-128, mmu-miR-129-3p, mmu-miR-133b, mmu-miR-136, mmu-miR-138, mmu-miR-138*, mmu-miR-139-3p, mmu-miR-140, mmu-miR-140*, mmu-miR-142-3p, mmu-miR-143, mmu-miR-146a, mmu-miR-146b, mmu-miR-148b, mmu-miR-150, mmu-miR-15a*, mmu-miR-15b, mmu-miR-181b, mmu-miR-181d, mmu-miR-183, mmu-miR-185, mmu-miR-186, mmu-miR-191*, mmu-miR-194, mmu-miR-19a, mmu-miR-200a, mmu-miR-200b, mmu-miR-200b*, mmu-miR-202-3p, mmu-miR-206, mmu-miR-208a, mmu-miR-21, mmu-miR-211, mmu-miR-221, mmu-miR-222, mmu-miR-223, mmu-miR-27a, mmu-miR-27b*, mmu-miR-28*, mmu-miR-290-5p, mmu-miR-291a-5p, mmu-miR-297a, mmu-miR-299, mmu-miR-29b, mmu-miR-29c*, mmu-miR-301b, mmu-miR-302c*, mmu-miR-30c, mmu-miR-31, mmu-miR-322, mmu-miR-323-3p, mmu-miR-324-3p, mmu-miR-324-5p, mmu-miR-326, mmu-miR-328, mmu-miR-331-5p, mmu-miR-341, mmu-miR-34b-5p, mmu-miR-34c*, mmu-miR-369-3p, mmu-miR-374, mmu-miR-376b, mmu-miR-379, mmu-miR-380-3p, mmu-miR-382, mmu-miR-384-5p, mmu-miR-409-5p, mmu-miR-411, mmu-miR-411*, mmu-miR-423-5p, mmu-miR-425, mmu-miR-429, mmu-miR-434-5p, mmu-miR-450b-3p, mmu-miR-451, mmu-miR-455, mmu-miR-465c-3p, mmu-miR-466d-5p, mmu-miR-467e*, mmu-miR-484, mmu-miR-486, mmu-miR-487b, mmu-miR-497, mmu-miR-505, mmu-miR-511, mmu-miR-539, mmu-miR-540-3p, mmu-miR-551b, mmu-miR-568, mmu-miR-654-5p, mmu-miR-669a, mmu-miR-686, mmu-miR-688, mmu-miR-699, mmu-miR-701, mmu-miR-706, mmu-miR-708, mmu-miR-720, mmu-miR-721, mmu-miR-744*, mmu-miR-760,

mmu-miR-770-5p, mmu-miR-7a, mmu-miR-7b, mmu-miR-881*, mmu-miR-93, mmu-miR-96, mghv-miR-M1-6, mghv-miR-M1-9, and human orthologs thereof.

[0024] In other embodiments where the physiological condition is neurological disease or neurological injury, the microRNA profile or the specific microRNA sequence may comprise at least one microRNA sequence selected from the group consisting of mmu-let-7g, mmu-miR-298, mmu-miR-101a*, mmu-miR-101b, mmu-miR-1224, mmu-miR-126-5p, mmu-miR-128, mmu-miR-129-3p, mmu-miR-133b, mmu-miR-138*, mmu-miR-139-3p, mmu-miR-140*, mmu-miR-146a, mmu-miR-148b, mmu-miR-15a*, mmu-miR-15b, mmu-miR-181b, mmu-miR-181d, mmu-miR-185, mmu-miR-186, mmu-miR-191*, mmu-miR-19a, mmu-miR-200b*, mmu-miR-202-3p, mmu-miR-208a, mmu-miR-211, mmu-miR-27b*, mmu-miR-28*, mmu-miR-290-5p, mmu-miR-291a-5p, mmu-miR-297a, mmu-miR-299, mmu-miR-29c*, mmu-miR-301b, mmu-miR-302c*, mmu-miR-322, mmu-miR-323-3p, mmu-miR-324-3p, mmu-miR-324-5p, mmu-miR-326, mmu-miR-328, mmu-miR-331-5p, mmu-miR-341, mmu-miR-34b-5p, mmu-miR-34c*, mmu-miR-369-3p, mmu-miR-374, mmu-miR-376b, mmu-miR-379, mmu-miR-380-3p, mmu-miR-382, mmu-miR-384-5p, mmu-miR-409-5p, mmu-miR-411, mmu-miR-411*, mmu-miR-423-5p, mmu-miR-425, mmu-miR-429, mmu-miR-434-5p, mmu-miR-450b-3p, mmu-miR-465c-3p, mmu-miR-466d-5p, mmu-miR-467e*, mmu-miR-505, mmu-miR-511, mmu-miR-539, mmu-miR-540-3p, mmu-miR-551b, mmu-miR-568, mmu-miR-654-5p, mmu-miR-669a, mmu-miR-686, mmu-miR-688, mmu-miR-699, mmu-miR-701, mmu-miR-706, mmu-miR-720, mmu-miR-721, mmu-miR-744*, mmu-miR-760, mmu-miR-770-5p, mmu-miR-7a, mmu-miR-7b, mmu-miR-881*, mmu-miR-96, mghv-miR-M1-6, mghv-miR-M1-9, and human orthologs thereof.

[0025] When the physiological condition is related to lung disease or lung injury, in some embodiments, the microRNA profile or the specific microRNA sequence may comprise at least one microRNA sequence selected from the group consisting of hsa-miR-135a*, hsa-miR-10b, hsa-miR-1224-3p, hsa-miR-1224-5p, hsa-miR-1225-3p, hsa-miR-1225-5p, hsa-miR-1226*, hsa-miR-1227, hsa-miR-1228, hsa-miR-1229, hsa-miR-1234, hsa-miR-1237, hsa-miR-1238, hsa-miR-124, hsa-miR-129*, hsa-miR-129-3p, hsa-miR-136*, hsa-miR-187*, hsa-miR-188-5p, hsa-miR-190b, hsa-miR-198, hsa-miR-22, hsa-miR-220b, hsa-miR-300, hsa-miR-301b, hsa-miR-30e, hsa-miR-338-3p, hsa-

miR-33a*, hsa-miR-33b, hsa-miR-33b*, hsa-miR-34c-3p, hsa-miR-34c-5p, hsa-miR-363*, hsa-miR-371-3p, hsa-miR-371-5p, hsa-miR-375, hsa-miR-377*, hsa-miR-423-5p, hsa-miR-424, hsa-miR-424*, hsa-miR-429, hsa-miR-448, hsa-miR-449a, hsa-miR-449b, hsa-miR-450b-3p, hsa-miR-452, hsa-miR-454*, hsa-miR-455-3p, hsa-miR-483-3p, hsa-miR-483-5p, hsa-miR-491-3p, hsa-miR-491-5p, hsa-miR-493, hsa-miR-493*, hsa-miR-494, hsa-miR-497, hsa-miR-498, hsa-miR-500, hsa-miR-503, hsa-miR-505, hsa-miR-507, hsa-miR-513a-3p, hsa-miR-513a-5p, hsa-miR-513b, hsa-miR-513c, hsa-miR-515-5p, hsa-miR-518b, hsa-miR-518c*, hsa-miR-518d-3p, hsa-miR-518d-5p, hsa-miR-518e*, hsa-miR-520d-5p, hsa-miR-520h, hsa-miR-541, hsa-miR-545*, hsa-miR-548d-3p, hsa-miR-548d-5p, hsa-miR-551a, hsa-miR-551b, hsa-miR-552, hsa-miR-554, hsa-miR-556-5p, hsa-miR-557, hsa-miR-559, hsa-miR-561, hsa-miR-564, hsa-miR-572, hsa-miR-575, hsa-miR-576-3p, hsa-miR-578, hsa-miR-583, hsa-miR-586, hsa-miR-589, hsa-miR-589*, hsa-miR-591, hsa-miR-595, hsa-miR-601, hsa-miR-602, hsa-miR-609, hsa-miR-610, hsa-miR-612, hsa-miR-613, hsa-miR-614, hsa-miR-615-3p, hsa-miR-616, hsa-miR-619, hsa-miR-622, hsa-miR-623, hsa-miR-624*, hsa-miR-627, hsa-miR-633, hsa-miR-634, hsa-miR-638, hsa-miR-639, hsa-miR-640, hsa-miR-642, hsa-miR-644, hsa-miR-647, hsa-miR-648, hsa-miR-652, hsa-miR-654-5p, hsa-miR-658, hsa-miR-659, hsa-miR-662, hsa-miR-663, hsa-miR-665, hsa-miR-671-5p, hsa-miR-675, hsa-miR-708, hsa-miR-708*, hsa-miR-744*, hsa-miR-760, hsa-miR-765, hsa-miR-766, hsa-miR-767-3p, hsa-miR-802, hsa-miR-874, hsa-miR-876-3p, hsa-miR-876-5p, hsa-miR-877, hsa-miR-877*, hsa-miR-885-3p, hsa-miR-885-5p, hsa-miR-886-3p, hsa-miR-890, hsa-miR-891b, hsa-miR-892b, hsa-miR-920, hsa-miR-922, hsa-miR-923, hsa-miR-92b, hsa-miR-92b*, hsa-miR-933, hsa-miR-934, hsa-miR-935, hsa-miR-936, hsa-miR-937, hsa-miR-939, hsa-miR-940, hsv1-miR-H1, hsv1-miR-LAT, kshv-miR-K12-12, kshv-miR-K12-3, kshv-miR-K12-3*, kshv-miR-K12-4-5p, kshv-miR-K12-6-5p, kshv-miR-K12-8, kshv-miR-K12-9, kshv-miR-K12-9*, ebv-miR-BART10*, ebv-miR-BART12, ebv-miR-BART13, ebv-miR-BART13*, ebv-miR-BART15, ebv-miR-BART1-5p, ebv-miR-BART16, ebv-miR-BART18-5p, ebv-miR-BART19-3p, ebv-miR-BART19-5p, ebv-miR-BART20-5p, ebv-miR-BART2-5p, ebv-miR-BART3*, ebv-miR-BART5, ebv-miR-BART6-5p, ebv-miR-BART7, ebv-miR-BART7*, ebv-miR-BHRF1-1, ebv-miR-BHRF1-3, hcmv-miR-UL148D, hcmv-miR-UL22A, hcmv-miR-UL22A*, hcmv-miR-UL70-3p, hcmv-miR-UL70-5p, hcmv-

miR-US25-1, hcmv-miR-US25-2-3p, hcmv-miR-US25-2-5p, hcmv-miR-US4, hiv1-miR-H1, hiv1-miR-N367, and human orthologs thereof.

[0026] In other embodiments where the physiological condition is related to lung disease or lung injury, the microRNA profile or the specific microRNA sequence may comprise at least one microRNA sequence selected from the group consisting of hsa-miR-135a*, hsa-miR-1224-3p, hsa-miR-1224-5p, hsa-miR-1225-3p, hsa-miR-1225-5p, hsa-miR-1226*, hsa-miR-1227, hsa-miR-1228, hsa-miR-1229, hsa-miR-1234, hsa-miR-1237, hsa-miR-1238, hsa-miR-124, hsa-miR-129*, hsa-miR-129-3p, hsa-miR-136*, hsa-miR-187*, hsa-miR-188-5p, hsa-miR-190b, hsa-miR-220b, hsa-miR-300, hsa-miR-301b, hsa-miR-30e, hsa-miR-338-3p, hsa-miR-33a*, hsa-miR-33b, hsa-miR-33b*, hsa-miR-34c-3p, hsa-miR-34c-5p, hsa-miR-363*, hsa-miR-371-3p, hsa-miR-371-5p, hsa-miR-375, hsa-miR-377*, hsa-miR-423-5p, hsa-miR-424*, hsa-miR-429, hsa-miR-448, hsa-miR-449a, hsa-miR-449b, hsa-miR-450b-3p, hsa-miR-452, hsa-miR-454*, hsa-miR-455-3p, hsa-miR-483-3p, hsa-miR-483-5p, hsa-miR-491-3p, hsa-miR-491-5p, hsa-miR-493, hsa-miR-493*, hsa-miR-500, hsa-miR-505, hsa-miR-507, hsa-miR-513a-3p, hsa-miR-513a-5p, hsa-miR-513b, hsa-miR-513c, hsa-miR-515-5p, hsa-miR-518c*, hsa-miR-518d-3p, hsa-miR-518d-5p, hsa-miR-518e*, hsa-miR-520d-5p, hsa-miR-541, hsa-miR-545*, hsa-miR-548d-3p, hsa-miR-548d-5p, hsa-miR-551b, hsa-miR-552, hsa-miR-554, hsa-miR-556-5p, hsa-miR-557, hsa-miR-559, hsa-miR-561, hsa-miR-564, hsa-miR-575, hsa-miR-576-3p, hsa-miR-578, hsa-miR-583, hsa-miR-586, hsa-miR-589, hsa-miR-589*, hsa-miR-591, hsa-miR-595, hsa-miR-602, hsa-miR-609, hsa-miR-610, hsa-miR-612, hsa-miR-613, hsa-miR-614, hsa-miR-615-3p, hsa-miR-616, hsa-miR-619, hsa-miR-623, hsa-miR-624*, hsa-miR-633, hsa-miR-638, hsa-miR-639, hsa-miR-640, hsa-miR-642, hsa-miR-644, hsa-miR-647, hsa-miR-652, hsa-miR-654-5p, hsa-miR-658, hsa-miR-659, hsa-miR-665, hsa-miR-671-5p, hsa-miR-675, hsa-miR-708*, hsa-miR-744*, hsa-miR-760, hsa-miR-765, hsa-miR-766, hsa-miR-767-3p, hsa-miR-768-3p, hsa-miR-768-5p, hsa-miR-801, hsa-miR-802, hsa-miR-874, hsa-miR-876-3p, hsa-miR-876-5p, hsa-miR-877, hsa-miR-877*, hsa-miR-885-3p, hsa-miR-885-5p, hsa-miR-886-3p, hsa-miR-890, hsa-miR-891b, hsa-miR-892b, hsa-miR-920, hsa-miR-922, hsa-miR-923, hsa-miR-92b*, hsv1-miR-H1, hsv1-miR-LAT, kshv-miR-K12-12, kshv-miR-K12-3, kshv-miR-K12-3*, kshv-miR-K12-4-5p, kshv-miR-K12-6-5p, kshv-miR-K12-8, kshv-miR-K12-

9, kshv-miR-K12-9*, ebv-miR-BART10*, ebv-miR-BART12, ebv-miR-BART13, ebv-miR-BART13*, ebv-miR-BART15, ebv-miR-BART1-5p, ebv-miR-BART16, ebv-miR-BART18-5p, ebv-miR-BART19-3p, ebv-miR-BART19-5p, ebv-miR-BART20-5p, ebv-miR-BART2-5p, ebv-miR-BART3*, ebv-miR-BART5, ebv-miR-BART6-5p, ebv-miR-BART7, ebv-miR-BART7*, ebv-miR-BHRF1-1, ebv-miR-BHRF1-3, hcmv-miR-UL148D, hcmv-miR-UL22A, hcmv-miR-UL22A*, hcmv-miR-UL70-3p, hcmv-miR-UL70-5p, hcmv-miR-US25-1, hcmv-miR-US25-2-3p, hcmv-miR-US25-2-5p, hcmv-miR-US4, hiv1-miR-H1, hiv1-miR-N367, and human orthologs thereof.

[0027] The physiological condition may also be a lung disease or lung injury, such as chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF), also known as interstitial lung disease (ILD).

[0028] In embodiments, the at least one differentially expressed microRNA sequence or at least one specific microRNA sequence is selected from the group consisting of hsa-miR-630, hsa-miR-134, hsa-miR-1225-5p, hsa-miR-135a*, hsa-miR-150*, hsa-miR-22, hsa-miR-223, hsa-miR-448, hsa-miR-451, hsa-miR-483-5p, hsa-miR-575, hsa-miR-638, hsa-miR-923, hsa-miR-92a-2*, hsa-miR-939, hsa-miR-940, hsv1-miR-H1, kshv-miR-K12-3, hsv1-miR-LAT, hcmv-miR-UL70-3p, hsv1-miR-H1, hsv1-miR-LAT, kshv-miR-K12-3, hcmv-miR-UL70-3p, and human orthologs thereof.

[0029] In other embodiments, the biological sample is plasma and the at least one differentially expressed microRNA sequence or at least one specific microRNA sequence is selected from the group consisting of hsa-miR-630, hsa-miR-134, hsa-miR-1225-5p, hsa-miR-135a*, hsa-miR-150*, hsa-miR-22, hsa-miR-223, hsa-miR-483-5p, hsa-miR-575, hsa-miR-638, hsa-miR-923, hsa-miR-939, hsa-miR-940, hsv1-miR-H1, hsv1-miR-LAT, kshv-miR-K12-3, hcmv-miR-UL70-3p, and human orthologs thereof. In some particular embodiments, the microRNA profile consists of only a selection of at least two of these microRNA sequences, i.e. the microRNA profile does not look at other microRNA sequences.

[0030] In yet other embodiments, the biological sample is plasma and the at least one differentially expressed microRNA sequence or at least one specific microRNA sequence is selected from the group consisting of hsa-miR-630, hsa-miR-134, hcmv-miR-UL70-3p, hsa-miR-1225-5p, hsa-miR-135a*, hsa-miR-150*, hsa-miR-483-5p, hsa-

miR-575, hsa-miR-638, hsv1-miR-H1, hsv1-miR-LAT, and human orthologs thereof. In some particular embodiments, the microRNA profile consists of only a selection of at least two of these microRNA sequences, i.e. the microRNA profile does not look at other microRNA sequences.

[0031] In some alternate embodiments, the biological sample is plasma and at least two differentially expressed microRNA sequences or specific microRNA sequences are identified. At least one of the at least two differentially expressed microRNA sequences or specific microRNA sequences is selected from the group consisting of hsa-miR-630, hcmv-miR-UL70-3p, hsa-miR-1225-5p, hsa-miR-134, hsa-miR-135a*, hsa-miR-150*, hsa-miR-483-5p, hsa-miR-575, hsa-miR-638, hsv1-miR-H1, hsv1-miR-LAT, and human orthologs thereof. The other one of the at least two differentially expressed microRNA sequences or specific microRNA sequences is selected from the group consisting of hsa-miR-451, hsa-miR-448, hsa-miR-92a-2*, and human orthologs thereof. In some particular embodiments, the microRNA profile consists of only a selection of these microRNA sequences, i.e. the microRNA profile does not look at other microRNA sequences.

[0032] In yet other embodiments, the biological sample is lung tissue and the at least one differentially expressed microRNA sequence is selected from the group consisting of hsa-miR-451, hsa-miR-923, hsa-miR-1225-5p, hsa-miR-22, hsa-miR-223, hsa-miR-638, kshv-miR-K12-3, and human orthologs thereof. In some particular embodiments, the microRNA profile consists of only a selection of these microRNA sequences.

[0033] In still other embodiments, the biological sample is plasma and the at least one differentially expressed microRNA sequence is selected from the group consisting of hsa-miR-940, hsa-miR-134, hsa-miR-135a*, hsa-miR-150*, hsa-miR-483-5p, hsa-miR-575, hsa-miR-939, hsv1-miR-H1, kshv-miR-K12-3, hsv1-miR-LAT, hcmv-miR-UL70-3p, and human orthologs thereof. In some particular embodiments, the microRNA profile consists of only a selection of these microRNA sequences, i.e. the microRNA profile does not look at other microRNA sequences.

[0034] Also disclosed are methods of using microRNA sequences to detect a lung condition, comprising: generating a microRNA profile from a biological sample; and detecting the lung condition based on the levels of at least one overexpressed

microRNA sequence and at least one underexpressed microRNA sequence. The at least one overexpressed microRNA sequence is selected from the group consisting of hsa-miR-630, hcmv-miR-UL70-3p, hsa-miR-1225-5p, hsa-miR-134, hsa-miR-135a*, hsa-miR-150*, hsa-miR-483-5p, hsa-miR-575, hsa-miR-638, hsv1-miR-H1, hsv1-miR-LAT, and human orthologs thereof. The at least one underexpressed microRNA sequence is selected from the group consisting of hsa-miR-451, hsa-miR-448, and hsa-miR-92a-2*, and human orthologs thereof. In some particular embodiments, the microRNA profile examines only a selection of these listed microRNA sequences.

[0035] Also disclosed are methods of detecting or predicting certain physiological conditions in a patient. Those methods comprise generating a microRNA profile from a biological sample provided by the patient; identifying at least one differentially expressed microRNA sequence by comparing the microRNA profile to a reference; and detecting or predicting the physiological condition based on the identity or the amounts of the at least one differentially expressed microRNA sequence. The biological sample comprises (i) serum or plasma; and (ii) an additional body fluid specific to a particular location of the body that is relevant to the particular physiological condition. In a first embodiment, the biological sample further comprises amniotic fluid and the physiological condition is the health status of a fetus being carried by the patient. In a second embodiment, the biological sample further comprises urine and the physiological condition is the health status of a bladder or a kidney of the patient. In a third embodiment, the biological sample further comprises breast milk and the physiological condition is the health status of a breast of the patient. In a fourth embodiment, the biological sample further comprises saliva and the physiological condition is the health status of the head and neck region of the patient. In a fifth embodiment, the biological sample further comprises tears and the physiological condition is the health status of an eye of the patient. In a sixth embodiment, the biological sample further comprises semen and the physiological condition is the health status of a prostate or male reproductive organ of the patient. In a seventh embodiment, the biological sample further comprises synovial fluid and the physiological condition is the health status of a joint of the patient. In an eighth embodiment, the biological sample further comprises sweat and the physiological

condition is the health status of the skin of the patient. In a ninth embodiment, the biological sample further comprises cerebrospinal fluid and the physiological condition is the health status of the central nerve system of the patient.

[0036] Also disclosed are methods of diagnosing a physiological condition. The methods comprise taking a sample of a body fluid and a sample of a body tissue from a patient. A first microRNA profile is generated from the body fluid sample, and a second microRNA profile is generated from the body tissue sample. At least two differentially expressed microRNA sequences are identified in the first microRNA profile by comparing the first microRNA profile to a first reference. At least two differentially expressed microRNA sequences are identified in the second microRNA profile by comparing the second microRNA profile to a second reference. The physiological condition is then diagnosed based on the differentially expressed microRNA sequences identified. In particular, the differentially expressed microRNA sequences in the first microRNA profile are different from the differentially expressed microRNA sequences in the second microRNA profile. This difference in the differentially expressed microRNA sequences between the body fluid and the body tissue increases the probability of a correct diagnosis.

[0037] Also included are assays for detecting the identity and/or levels of the various combinations of microRNA sequences described above.

[0038] These and other non-limiting aspects and/or objects of the disclosure are more particularly described below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0001] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0002] The following is a brief description of the drawings, which are presented for the purposes of illustrating the disclosure set forth herein and not for the purposes of limiting the same.

[0039] **FIGs. 1A-1B** are electropherograms of RNA.

[0040] FIG. 2 is a microRNA profile showing changes in specific microRNA expression levels over time in the liver after exposing the animal to a high dose of acetaminophen.

[0041] For reference, the text on the right-hand side of FIG. 2 reads, in order from top to bottom: mmu-miR-720, mmu-miR-1224, mmu-miR-122, mmu-miR-494, mmu-miR-609, mmu-miR-21, mmu-miR-22, mmu-miR-451, mmu-miR-466f-3p, mmu-miR-574-5p, mmu-let-7a, mmu-let-7f, mmu-miR-192, mmu-miR-194, mmu-miR-212, mmu-let-7g, mmu-miR-29b, mmu-miR-26a, mmu-miR-30c, mmu-miR-29a, mmu-miR-188-5p, mmu-miR-709, mmu-miR-466g, mmu-miR-574-3p, mmu-miR-125a-3p, mmu-miR-125b-5p, mmu-miR-29c, mmu-miR-483, mmu-miR-600, mmu-miR-705, mmu-miR-721, mmu-miR-376b, mmu-miR-706, mmu-miR-710, mmu-miR-711, mmu-let-7c-2*, mmu-miR-376a, mmu-miR-891, mmu-miR-452, mmu-miR-467a*, mmu-miR-718, mmu-miR-500, mmu-miR-669c, mmu-miR-714, mmu-miR-290-5p, mmu-miR-134, mmu-miR-27b, mmu-miR-671-5p, mmu-miR-135a*, and mmu-miR-877*.

[0042] FIG. 3 is a microRNA profile showing differences in specific microRNA levels between plasma samples from a treated group and a control group.

[0043] For reference, the text on the right-hand side of FIG. 3 reads, in order from top to bottom: mmu-miR-21, mmu-miR-122, mmu-miR-22, mmu-miR-192, mmu-miR-29a, mmu-miR-30a, mmu-miR-130a, mmu-miR-29c, mmu-miR-30a, mmu-miR-148a, mmu-miR-19b, mmu-miR-101b, mmu-miR-15a, mmu-miR-685, mmu-let-7g, mmu-miR-27b, mmu-miR-574-5p, mmu-miR-671-5p, mmu-miR-107, mmu-let-7d*, mmu-miR-29b, mmu-miR-193, mmu-miR-194, mmu-miR-101a, mmu-miR-185, mmu-miR-221, mmu-miR-294*, mmu-miR-877, mmu-miR-291a-5p, mmu-miR-877*, mmu-miR-339-3p, mmu-miR-466f-3p, mmu-miR-30c-1*, mmu-miR-199b, mmu-miR-199a-5p, mmu-miR-193b, mmu-miR-370, mmu-miR-882, mmu-miR-327, mmu-miR-127, mmu-miR-714, mmu-miR-150, mmu-miR-125a-5p, mmu-miR-141, mmu-miR-23b, mmu-miR-145, mmu-miR-320, mmu-miR-342-3p, mmu-miR-200c, mmu-miR-223, mmu-miR-99a, mmu-miR-202-3p, mmu-miR-494, mmu-miR-652, mmu-miR-375, mmu-miR-125a-3p, mmu-miR-124, mmu-miR-721, mmu-miR-93, mmu-miR-483, mmu-miR-205, mmu-miR-712, mmu-miR-26a, mmu-miR-710, mmu-miR-23a, mmu-miR-135a*, mmu-miR-711, mmu-miR-720,

mmu-miR-125b-5p, mmu-miR-133a, mmu-miR-133b, mmu-miR-451, mmu-miR-486, and mmu-miR-1224.

[0044] FIG. 4 is a graph of intensities for two selected microRNA sequences, mir-122 and mir-486 in plasma after exposing the animal to different doses of acetaminophen.

[0045] FIG. 5 is a graph of the ratio between mir-122 and mir-486 (either median or average intensities) for the same data as FIG. 4.

[0046] FIG. 6 is a microRNA profile showing differences in microRNA expression levels between normal brain tissue and diseased brain tissue.

[0047] FIG. 7 is a microRNA profile showing differences in microRNA expression levels as a disease progressed in lung tissue.

[0048] FIG. 8 is a microRNA profile showing differences in microRNA expression levels between serum and urine samples.

[0049] FIG. 9 is a graph comparing miRNA expression levels in control plasma samples with ILD plasma samples.

[0050] FIGs. 10A-10B are graphs showing the signal strength in the ILD and control plasma samples of FIG. 9.

[0051] FIG. 11 is a graph showing the signal strength for all oligonucleotide probes used to target certain microRNA sequences.

[0052] FIG. 12 is a graph showing the difference in the signal strength for certain microRNA sequences in the ILD and control plasma samples of FIG. 9.

[0053] FIG. 13 is a graph showing the degree of overexpression in certain microRNA sequences in the ILD and control plasma samples of FIG. 9.

[0054] FIG. 14 is a graph comparing miRNA expression levels in ILD tissue samples with ILD plasma samples.

[0055] FIG. 15 is a graph comparing miRNA expression levels in control lung tissue samples with ILD lung tissue samples.

[0056] FIG. 16 is a graph showing the effect of normalization on data in a data analysis method.

[0057] FIGs. 17A-17B are graphs showing the effect of normalization on the quality of data.

[0058] FIG. 18 is a graph clustering normalized miRNA data.

[0059] FIG. 19 is a graph showing the p-value distribution of all miRNA in a sample.

[0060] FIG. 20 is a collection of charts showing the selection of panels that separates data.

DETAILED DESCRIPTION

[0061] A more complete understanding of the processes and apparatuses disclosed herein can be obtained by reference to the accompanying drawings. These figures are merely schematic representations based on convenience and the ease of demonstrating the existing art and/or the present development, and are, therefore, not intended to indicate relative size and dimensions of the assemblies or components thereof.

[0062] Although specific terms are used in the following description for the sake of clarity, these terms are intended to refer only to the particular structure of the embodiments selected for illustration in the drawings, and are not intended to define or limit the scope of the disclosure. In the drawings and the following description below, it is to be understood that like numeric designations refer to components of like function.

[0063] MicroRNAs (also known as miRNA) are small but potent regulatory non-coding ribonucleic acid (RNA) sequences first identified in *C. elegans* in 1993. miRNA may be about 21 to about 23 nucleotides in length. Through sequence complementation, microRNA interacts with messenger RNA (mRNA) and affects the stability of mRNA and/or the initiation and progression of protein translation. It has been estimated that over 30% of the mRNAs are regulated by microRNA. Like mRNA, some of the microRNAs also display restricted tissue distribution. The biological function of microRNA is yet to be fully understood; however, it has been shown that microRNA sequences are involved in various physiological and pathological conditions, including differentiation, development, cancer, and neurological disorders. Unlike mRNA and proteins, microRNA is reasonably well conserved across different species. Thus, a specific microRNA sequences which is shown to correlate to a particular condition, such as disease or injury, in one species, should also correlate to that particular condition in other species, particularly humans (i.e. *Homo sapiens*). This correlation provides useful diagnostic content.

[0064] MicroRNAs can also be manipulated with commonly used molecular biology techniques including complementary DNA (cDNA) synthesis, polymerase chain reactions, Northern blotting, and array based hybridization. This makes it possible to easily investigate the function(s) of a given microRNA sequences of interest.

[0065] A microRNA is encoded by a gene. When the DNA of the gene is transcribed into RNA, the RNA is not subsequently translated into protein. Instead each primary transcript (a pri-mir) is processed into a short stem-loop structure (a pre-mir) and finally into a mature sequence, designated miR. The primary transcript can form local hairpin structures, which ordinarily are processed such that a single microRNA sequence accumulates from one arm of a hairpin precursor molecule. Sometimes the primary transcript contains multiple hairpins, and different hairpins give rise to different microRNA sequences.

[0066] The microRNA sequences discussed herein are named according the miRBase database available at <http://microrna.sanger.ac.uk/> and maintained by the Wellcome Trust Sanger Institute (now redirected to <http://www.miRBase.org/>). Generally speaking, microRNA sequences are assigned sequential numerical identifiers, with the numerical identifier based on sequence similarity. A 3- or 4-letter prefix designates the species from which the microRNA sequence came. For example, the hsa in hsa-miR-101 refers to homo sapiens.

[0067] Orthologous sequences, or orthologs, refer to microRNA sequences that are in different species but are similar (i.e. homologous) because they originated from a common ancestor. Generally speaking, orthologs have the same numerical identifier and are believed to serve a similar function. For example, mmu-miR-101 and hsa-miR-101 are in mouse and human, respectively, and are orthologs to each other. In this disclosure, microRNA sequences are referred to without the prefix designating the species, and should be construed as preferentially referring to the human microRNA sequence and the murine sequence. For example, miR-101 should be construed as referring to hsa-miR-101 and mmu-miR-101.

[0068] Paralogous sequences, or paralogs, are microRNA sequences that differ from each other in only a few positions. Paralogs occur within a species. Paralogs are designated with letter suffixes. For example, mmu-miR-133a and mmu-miR-133b are

paralogs.

[0069] Identical microRNA sequences that originate from separate genomic loci are given numerical suffixes, such as hsa-miR-26a-1 and hsa-miR-26a-2.

[0070] Sometimes, two different mature microRNA sequences are excised from opposite arms of the same hairpin precursor. The two microRNA sequences can be designated in at least two ways. First, when it is possible to determine which arm gives rise to the predominantly expressed miRNA sequence, an asterisk has been used to denote the less predominant form, such as hsa-let-7b and hsa-let-7b*. Alternatively, they are named to designate whether they come from the 5' or 3' arm, such as hsa-miR-125a-3p and hsa-miR-125a-5p.

[0071] Specific microRNA sequences have been identified in the blood that are associated with liver injuries. Thus, the levels of selected microRNA sequences can be used to detect, predict, or diagnose diseases, predict and monitor therapeutic responses, and/or predict disease outcomes.

[0072] MicroRNA-based blood markers offer superior properties over existing markers. Such markers are sensitive, in part because microRNA signals can be amplified using standard polymerase chain reactions (PCR) while protein-based markers cannot be easily amplified. Because the sequence and expression profile of microRNAs are largely conserved across species, discoveries made in animal models can be easily translated to and adapted for use in humans. MicroRNA assays can be quickly performed and developed with standard PCR or array based systems; therefore, beside PCR primers, there is no need to develop special detection agents. Finally, since microRNA can be easily accessed in various body fluids, obtaining such diagnostic information can be done non-invasively.

[0073] The level of specific microRNA sequences(s) in a cell, tissue, or body fluid(s) can be used to monitor the physiopathological conditions of the body.

[0074] Sets of microRNA sequences in the tissue and the serum have been identified that are associated with liver injuries, lung injuries, and lung diseases. The combination of information from multiple microRNA expression level changes can further enhance the sensitivity and specificity of disease/injury detection, including using the ratio of paired microRNA sequences.

[0075] MicroRNA profiles, for example a microRNA profile of tissue-specific microRNA sequences, could be used to monitor the health status of that tissue. Those microRNA sequences could also be used as therapeutic targets for diseases associated with the tissue.

[0076] MicroRNA sequences from microbes or infectious agents, such as bacteria and viruses, could be used as an indication of infection. Host responses could be monitored by using the combination of microRNA sequences from infectious agents and the host as measured from the host's body fluids.

[0077] Biological processes occurring in a number of cell types or tissues could be monitored by the use of microRNA profiles specific to a process or network. These specific microRNA sequences could also be used as therapeutic targets for diseases associated with the biological processes.

[0078] The methods of the present disclosure could be used to detect, predict, monitor, or treat a physiological condition such as a disease, injury, or infection. Generally, the methods include: (a) isolating microRNA sequences from a biological sample; (b) generating a microRNA profile from the isolated microRNA sequences, the profile including the levels of expressed microRNA sequences in the biological sample; and (c) comparing the microRNA profile with a reference to identify differentially expressed microRNA sequences. Based on the identity or the levels of the differentially expressed microRNA sequences, the physiological condition could be detected, predicted, or monitored; or a treatment could be indicated, administered, or monitored accordingly.

[0079] The biological sample is generally non-invasive, and may be, for example, a biopsy material, tissue, or body fluid. Exemplary body fluids include serum, plasma, lymph, saliva, urine, tears, sweat, semen, synovial fluid, cervical mucus, amniotic fluid, cerebrospinal fluid, and breast milk.

[0080] Combinations of different biological samples are also contemplated for providing more specific diagnoses. For example, plasma and serum would provide some general indicators of health, while a specific body fluid could be included for specific information. For example, if one wanted to assess the health status of a fetus being carried by the mother, one might test the amniotic fluid along with the mother's

plasma or serum. As another example, one might test the urine to assess the health status of a bladder or a kidney. Testing the breast milk would help assess the health status of a breast of the patient providing the biological sample. Testing the saliva would help assess the health status of the head and neck region. Testing the tears would help assess the health status of an eye of the patient providing the biological sample. Testing semen would help assess the health status of a prostate or male reproductive organ. Testing the synovial fluid would help assess the health status of a joint of the patient providing the biological sample. Testing the sweat would help assess the health status of the skin. Testing the cerebrospinal fluid would help assess the health status of the central nerve system. The term "health status" refers only to the physiological condition of the given body part, and has no specific meaning otherwise.

[0081] Isolating microRNA can be done by various methods. For example, the biological sample may be extracted with an organic solvent to obtain an aqueous phase containing the microRNA sequences. The aqueous phase is then purified through a silica membrane to isolate the microRNA sequences.

[0082] A microRNA profile can then be generated from the isolated microRNA sequences. Generally speaking, the microRNA profile provides the identity of specific microRNA sequences and/or the expression level (i.e. amount) of each specific microRNA sequence. An exemplary microRNA profile is seen in **FIG. 2**, which shows the expression levels for several microRNA sequences from several different liver samples that have been exposed to a high dose of acetaminophen. The microRNA profile of **FIG. 2** has six columns, but a microRNA profile may be simply one column (along with the identifying microRNA). The expression level can be displayed either as a sliding color scale or simply as numerical values. The microRNA profile can be generated by using hybridization to identify the microRNA sequences and/or using quantitative PCR (qPCR) to identify the levels of one or more particular microRNA sequences. It should be noted that the diagnostic information may be in the identity of the microRNA sequences themselves, or in the absolute or relative levels of the microRNA sequence, either between two microRNA sequences in a given sample or between two samples for a given microRNA sequence. A reference table could be provided, for example from a reference sample taken from the patient or from a table of

levels of expressed microRNA sequences in a normal (healthy) person or a table compiled from the expressed microRNA sequences over a large sample of people. Differentially expressed microRNA sequences can then be identified by comparing the microRNA profile of the biological sample with the reference sample or table to obtain diagnostic information. The term “differentially expressed” refers only to the fact that the amount or expression level has changed. The direction of change (i.e. upwards or downwards, overexpressed or underexpressed) is not significant, except as otherwise stated.

[0083] In particular embodiments, it is contemplated that identifying at least one specific microRNA sequence as being differentially expressed would be sufficient to identify a particular physiological condition as occurring. In other embodiments, at least two differentially expressed microRNA sequences are identified. This provides for an additional degree of confirmation in the identity of the physiological condition.

[0084] In using the terms “generating” and “identifying,” it is contemplated that these actions may be performed directly or indirectly. For example, a laboratory technician may perform the actions that directly “generate” a microRNA profile. The physician who ordered the microRNA profile that was directly “generated” by the laboratory technician may be considered to have indirectly “generated” the microRNA profile.

[0085] Because microRNA sequences and expression levels are generally conserved across species, it is contemplated that sequences and levels from other species would contain useful diagnostic information. For example, the biological sample may be from a microbe, such as a virus, bacterium, fungus, protozoan, or parasite.

[0086] It has been found that microRNA sequences and their expression levels can differ depending on their location in the body. In other words, they can be specific to a biological pathway, cell type, or tissue. This fact can provide powerful diagnostic information as well.

[0087] Table 1 lists some microRNA sequences which have been found to be specific to certain tissues in the human body.

Table 1.

Tissue	Human tissue specific miRNA	Tissue	Human tissue specific miRNA
Adipose	hsa-miR-452	Placenta	hsa-miR-527
Adipose	hsa-miR-196a	Placenta	hsa-miR-377
Adipose	hsa-miR-224	Placenta	hsa-miR-526c
Adipose	hsa-miR-335	Placenta	hsa-miR-524*
Adipose	hsa-miR-452*	Placenta	hsa-miR-517*
Adipose	hsa-miR-432*	Placenta	hsa-miR-450
Adrenal	hsa-miR-409-5p	Placenta	hsa-miR-503
Adrenal	hsa-miR-494	Placenta	hsa-miR-526b*
Adrenal	hsa-miR-485-5p	Placenta	hsa-miR-371
Adrenal	hsa-miR-360-5p	Placenta	hsa-miR-519b
Adrenal	hsa-miR-154	Placenta	hsa-miR-516-3p
Adrenal	hsa-miR-370	Placenta	hsa-miR-526a
Adrenal	hsa-miR-381	Placenta	hsa-miR-523
Adrenal	hsa-miR-369	Placenta	hsa-miR-518a-2*
Adrenal	hsa-miR-485-3p	Placenta	hsa-miR-518c*
Adrenal	hsa-miR-134	Placenta	hsa-miR-520b
Adrenal	hsa-miR-323	Placenta	hsa-miR-518d
Adrenal	hsa-miR-7N	Placenta	hsa-miR-524
Adrenal	hsa-miR-382	Placenta	hsa-miR-519a
Adrenal	hsa-miR-7	Placenta	hsa-miR-520a
Adrenal	hsa-miR-405	Placenta	hsa-miR-521
Adrenal	hsa-miR-127	Placenta	hsa-miR-522
Adrenal	hsa-miR-493	Placenta	hsa-miR-520d
Adrenal	hsa-miR-379	Placenta	hsa-miR-525
Adrenal	hsa-miR-432	Placenta	hsa-miR-512-5p
Adrenal	hsa-miR-299	Placenta	hsa-miR-520a*
Adrenal	hsa-miR-433	Placenta	hsa-miR-519a*
Adrenal	hsa-miR-376a	Placenta	hsa-miR-517a
Adrenal	hsa-miR-202*	Placenta	hsa-miR-517b
Adrenal	hsa-miR-137	Placenta	hsa-miR-515-5p
Adrenal	hsa-miR-501	Placenta	hsa-miR-525*
Adrenal	hsa-miR-202	Placenta	hsa-miR-518
Adrenal	hsa-miR-491	Placenta	hsa-miR-512-3p
Bladder	hsa-miR-451	Placenta	hsa-miR-517c
Brain	hsa-miR-330	Placenta	hsa-miR-518a
Brain	hsa-miR-219	Placenta	hsa-miR-519d
Brain	hsa-miR-124	Placenta	hsa-miR-518c
Brain	hsa-miR-9	Placenta	hsa-miR-518e
Brain	hsa-miR-9*	Placenta	hsa-miR-520g
Brain	hsa-miR-124a	Placenta	hsa-miR-519c
Brain	hsa-miR-129	Placenta	hsa-miR-515-3p
Brain	hsa-miR-124b	Placenta	hsa-miR-520b

Tissue	Human tissue specific miRNA	Tissue	Human tissue specific miRNA
Brain	hsa-miR-137	Placenta	hsa-miR-372
Brain	hsa-miR-383	Placenta	hsa-miR-520a
Brain	hsa-miR-433	Placenta	hsa-miR-520c
Brain	hsa-miR-348	Placenta	hsa-miR-373
Brain	hsa-miR-323	Placenta	hsa-miR-520b
Brain	hsa-miR-153	Placenta	hsa-miR-154*
Brain	hsa-miR-128b	Placenta	hsa-miR-520c
Brain	hsa-miR-128a	Placenta	hsa-miR-493
Brain	hsa-miR-485-5p	Placenta	hsa-miR-381
Brain	hsa-miR-370	Placenta	hsa-miR-151
Brain	hsa-miR-485-3p	Placenta	hsa-miR-495
Brain	hsa-miR-181b	Placenta	hsa-miR-474
Brain	hsa-miR-338	Placenta	hsa-miR-369-5p
Brain	hsa-miR-154*	Placenta	hsa-miR-184
Brain	hsa-miR-149	Placenta	hsa-miR-489
Brain	hsa-miR-213	Placenta	hsa-miR-376a
Brain	hsa-miR-340	Placenta	hsa-miR-500
Brain	hsa-miR-181bN	Placenta	hsa-miR-369
Brain	hsa-miR-181d	Placenta	hsa-miR-135b
Brain	hsa-miR-491	Placenta	hsa-miR-432
Brain	hsa-miR-184	Placenta	hsa-miR-27aN
Brain	hsa-miR-138	Placenta	hsa-miR-198
Brain	hsa-miR-132	Placenta	hsa-miR-224
Brain	hsa-miR-181c	Placenta	hsa-miR-452*
Brain	hsa-miR-204	Placenta	hsa-miR-433
Brain	hsa-miR-328	Placenta	hsa-miR-193b
Brain	hsa-miR-181a	Placenta	hsa-miR-494
Brain	hsa-miR-432	Placenta	hsa-miR-502
Brain	hsa-miR-379	Placenta	hsa-miR-335
Brain	hsa-miR-324-5p	Placenta	hsa-miR-299
Brain	hsa-miR-122	Placenta	hsa-miR-149
Brain	hsa-miR-134	Placenta	hsa-miR-213
Brain	hsa-miR-342	Placenta	hsa-miR-30d
Breast	hsa-miR-452	Placenta	hsa-miR-141
Breast	hsa-miR-205	Placenta	hsa-miR-301
Breast	hsa-miR-489	Placenta	hsa-miR-485-3p
Colon	hsa-miR-490	Placenta	hsa-miR-141N
Colon	hsa-miR-363	Placenta	hsa-miR-379
Colon	hsa-miR-338	Placenta	hsa-miR-130a
Colon	hsa-miR-31	Placenta	hsa-miR-382
Colon	hsa-miR-215	Placenta	hsa-miR-99b
Colon	hsa-miR-200a*	Placenta	hsa-miR-370

Tissue	Human tissue specific miRNA	Tissue	Human tissue specific miRNA
Colon	hsa-miR-200a	Placenta	hsa-miR-130b
Colon	hsa-miR-196b	Placenta	hsa-miR-27a
Colon	hsa-miR-196a	Placenta	hsa-miR-200cN
Colon	hsa-miR-194	Placenta	hsa-miR-24
Colon	hsa-miR-192	Placenta	hsa-miR-30a-5p
Colon	hsa-miR-141N	Placenta	hsa-miR-30bN
Colon	hsa-miR-141	Placenta	hsa-miR-221
Small Intestine	hsa-miR-490	Placenta	hsa-miR-200c
Small Intestine	hsa-miR-451	Placenta	hsa-miR-320
Small Intestine	hsa-miR-429	Placenta	hsa-miR-127
Small Intestine	hsa-miR-31	Placenta	hsa-miR-485-5p
Small Intestine	hsa-miR-215	Placenta	hsa-miR-30b
Small Intestine	hsa-miR-200bN	Placenta	hsa-miR-90a-3p
Small Intestine	hsa-miR-200b	Placenta	hsa-miR-181a
Small Intestine	hsa-miR-200a*	Placenta	hsa-miR-222
Small Intestine	hsa-miR-198	Placenta	hsa-miR-362
Small Intestine	hsa-miR-194	Placenta	hsa-miR-125a
Small Intestine	hsa-miR-192	Placenta	hsa-miR-323
Small Intestine	hsa-miR-138	Placenta	hsa-miR-451
Cervix	hsa-miR-196b	Placenta	hsa-miR-409-5p
Cervix	hsa-miR-99a	Placenta	hsa-miR-452
Heart	hsa-miR-1	Placenta	hsa-miR-518b
Heart	hsa-miR-107	Placenta	hsa-miR-515-5p
Heart	hsa-miR-133a	Placenta	hsa-miR-130aN
Heart	hsa-miR-189	Skeletal Muscle	hsa-miR-206
Heart	hsa-miR-221	Skeletal Muscle	hsa-miR-95
Heart	hsa-miR-23bN	Skeletal Muscle	hsa-miR-133b

Tissue	Human tissue specific miRNA	Tissue	Human tissue specific miRNA
Heart	hsa-miR-302a	Skeletal Muscle	hsa-miR-133a
Heart	hsa-miR-302b	Skeletal Muscle	hsa-miR-128b
Heart	hsa-miR-302c	Skeletal Muscle	hsa-miR-1
Heart	hsa-miR-302d	Skeletal Muscle	hsa-miR-489
Heart	hsa-miR-300-3p	Skeletal Muscle	hsa-miR-378
Heart	hsa-miR-367	Skeletal Muscle	hsa-miR-422a
Heart	hsa-miR-378	Skeletal Muscle	hsa-miR-128a
Heart	hsa-miR-422a	Skeletal Muscle	hsa-miR-196a
Heart	hsa-miR-422b	Skeletal Muscle	hsa-miR-502
Heart	hsa-miR-452	Spleen	hsa-miR-223
Heart	hsa-miR-490	Spleen	hsa-miR-139
Heart	hsa-miR-491	Lymph Node	hsa-miR-150
Heart	hsa-miR-409	Lymph Node	hsa-miR-142-3p
Heart	hsa-miR-7a	Lymph Node	hsa-miR-146b
Pericardium	hsa-miR-188	Lymph Node	hsa-miR-146
Pericardium	hsa-miR-369	Lymph Node	hsa-miR-155
Pericardium	hsa-miR-305	Lymph Node	hsa-miR-363
Pericardium	hsa-miR-452	PBMC	hsa-miR-128a
Pericardium	hsa-miR-224	PBMC	hsa-miR-124b
Pericardium	hsa-miR-511	PBMC	hsa-miR-124a
Pericardium	hsa-miR-199b	PBMC	hsa-miR-137
Kidney	hsa-miR-500	PBMC	hsa-miR-431
Kidney	hsa-miR-204	PBMC	hsa-miR-129
Kidney	hsa-miR-480	PBMC	hsa-miR-128b
Kidney	hsa-miR-190	PBMC	hsa-miR-138
Kidney	hsa-miR-501	Thymus	hsa-miR-183
Kidney	hsa-miR-196a	Thymus	hsa-miR-96
Kidney	hsa-miR-211	Thymus	hsa-miR-128b
Kidney	hsa-miR-363	Thymus	hsa-miR-213
Kidney	hsa-miR-502	Thymus	hsa-miR-205
Kidney	hsa-miR-184	Thymus	hsa-miR-128a
Liver	hsa-miR-122a	Thymus	hsa-miR-181bN
Liver	hsa-miR-30a-3p	Thymus	hsa-miR-182

Tissue	Human tissue specific miRNA	Tissue	Human tissue specific miRNA
Lung	hsa-miR-223	Thymus	hsa-miR-181b
Esophagus	hsa-miR-203	Thymus	hsa-miR-181d
Esophagus	hsa-miR-205	Thymus	hsa-miR-181a
Esophagus	hsa-miR-145	Thymus	hsa-miR-181c
Esophagus	hsa-miR-210N	Thymus	hsa-miR-20b
Esophagus	hsa-miR-143	Thymus	hsa-miR-383
Esophagus	hsa-miR-31	Thymus	hsa-miR-17-5p
Esophagus	hsa-miR-187	Thymus	hsa-miR-142-3p
Trachea	hsa-miR-34b	Stomach	hsa-miR-211
Trachea	hsa-miR-205	Stomach	hsa-miR-188
Trachea	hsa-miR-34cN	Stomach	hsa-miR-346
Trachea	hsa-miR-34c	Stomach	hsa-miR-200a*
Prostate	hsa-miR-363	Stomach	hsa-miR-375
Prostate	hsa-miR-205	Stomach	hsa-miR-148a
Prostate	hsa-miR-196b	Stomach	hsa-miR-200a
Ovary	hsa-miR-502	Stomach	hsa-miR-200b
Ovary	hsa-miR-383	Stomach	hsa-miR-200c
Fallopian Tube	hsa-miR-34bN	Stomach	hsa-miR-200bN
Fallopian Tube	hsa-miR-34b	Stomach	hsa-miR-212
Fallopian Tube	hsa-mi-34cN	Stomach	hsa-miR-31
Fallopian Tube	hsa-miR-449	Stomach	hsa-miR-7
Fallopian Tube	hsa-miR-34c	Stomach	hsa-miR-153
Fallopian Tube	hsa-miR-135a	Stomach	hsa-miR-429
Pancreas	hsa-miR-217	Stomach	hsa-miR-107
Pancreas	hsa-miR-216	Stomach	hsa-miR-200cN
Pancreas	hsa-miR-375	Stomach	hsa-miR-502
Pancreas	hsa-miR-98	Stomach	hsa-miR-203
Pancreas	hsa-miR-163	Testicle	hsa-miR-202
Pancreas	hsa-miR-141N	Testicle	hsa-miR-506
Pancreas	hsa-miR-148a	Testicle	hsa-miR-507
Pancreas	hsa-miR-141	Testicle	hsa-miR-510
Pancreas	hsa-miR-7N	Testicle	hsa-miR-514
Pancreas	hsa-miR-494	Testicle	hsa-miR-513
Pancreas	hsa-miR-130b	Testicle	hsa-miR-508
Pancreas	hsa-miR-200cN	Testicle	hsa-miR-509
Pancreas	hsa-miR-148b	Testicle	hsa-miR-202*

Tissue	Human tissue specific miRNA	Tissue	Human tissue specific miRNA
Pancreas	hsa-miR-182	Testicle	hsa-miR-449
Pancreas	hsa-miR-200a	Testicle	hsa-miR-34c
Thyroid	hsa-miR-138	Testicle	hsa-miR-432*
Thyroid	hsa-miR-135a	Testicle	hsa-miR-184
Thyroid	hsa-miR-206	Testicle	hsa-miR-520c
Thyroid	hsa-miR-95	Testicle	hsa-miR-520l
Thyroid	hsa-miR-1	Testicle	hsa-miR-34cN
Thyroid	hsa-miR-7	Testicle	hsa-miR-34b
Uterus	hsa-miR-10b	Testicle	hsa-miR-520b
Uterus	hsa-miR-196b	Testicle	hsa-miR-135b
Uterus	hsa-miR-502	Testicle	hsa-miR-383
Testicle	hsa-miR-204	Testicle	hsa-miR-34bN

[0088] It has been found that microRNA sequences and their expression levels can differ depending on their location in different types of body fluid samples. In other words, they can be specific to a biological pathway, cell type, or tissue. This fact can provide powerful diagnostic information as well.

[0089] Table 2 lists some microRNA sequences which have been found to be highly abundant in different body fluids. The sequences in bold font are unique to the listed body fluid.

Table 2.

Tears	Urine	Breast Milk	Seminal Fluid	Saliva	Amniotic Fluid
miR-518e	miR-515-3p	miR-518e	miR-518e	miR-335*	miR-518e
miR-335*	miR-335*	miR-26a-2*	miR-590-3p	miR-515-3p	miR-335*
miR-137	miR-892a	miR-335*	miR-588	miR-545*	miR-302c
miR-515-3p	miR-509-5p	miR-490-5p	miR-873	miR-492	miR-515-3p
miR-509-5p	miR-223*	miR-181d	miR-590-5p	miR-892a	miR-452
miR-873	miR-302d	miR-26a-1*	miR-137	miR-518e	miR-892a
miR-223*	miR-873	miR-137	miR-197	miR-27a	miR-671-5p
miR-892a	miR-923	miR-524-5p	miR-515-5p	miR-923	miR-515-5p
miR-590-3p	miR-616*	miR-509-5p	miR-515-3p	miR-509-5p	miR-590-3p
miR-302d	miR-483-5p	miR-513c	miR-218	miR-873	miR-593*
miR-616*	miR-134	miR-595	miR-20b	miR-483-5p	miR-873
miR-590-5p	miR-589	miR-515-3p	miR-410	miR-616*	miR-137
miR-101*	miR-556-3p	miR-515-5p	miR-335*	miR-580	miR-410
miR-130a	miR-101*	miR-598	miR-617	miR-609	miR-548d-5p
miR-410	miR-138	miR-130a	miR-671-5p	miR-302d	miR-223*
miR-195	miR-652	miR-181b	miR-524-5p	miR-25*	miR-590-5p
miR-675	miR-325	miR-671-5p	miR-892a	miR-134	miR-616*
miR-325	let-7i	miR-892a	miR-181d	miR-92b	miR-302d
miR-134	miR-377*	miR-578	miR-545*	miR-598	miR-509-5p
miR-29b	miR-545*	miR-580	miR-1	let-7a	miR-210

Table 2 cont.

Bronchial Lavage	CSF	Pleural Fluid	Peritoneal Fluid	Colostrum	Plasma
miR-515-3p	miR-515-3p	miR-515-3p	miR-892a	miR-509-5p	miR-335*
miR-335*	miR-335*	miR-892a	miR-518e	miR-181d	miR-325
miR-509-5p	miR-892a	miR-509-5p	miR-515-3p	miR-335*	miR-377*
miR-483-5p	miR-223*	miR-134	miR-134	miR-518e	miR-586
miR-892a	miR-873	miR-590-5p	miR-509-5p	miR-515-5p	miR-518e
miR-223*	miR-509-5p	miR-515-5p	miR-223*	miR-223*	let-7i
miR-873	miR-302d	miR-873	miR-515-5p	miR-671-5p	miR-539
miR-1225-3p	miR-616*	miR-335*	miR-616*	miR-873	miR-616*
miR-302d	miR-134	miR-920	miR-137	miR-483-5p	miR-302d
miR-545*	miR-483-5p	miR-616*	miR-873	miR-186	miR-589
miR-324-3p	miR-325	miR-302d	miR-483-5p	miR-515-3p	miR-556-3p
miR-616*	miR-151-5p	miR-518e	miR-518c	miR-616*	miR-151-3p
miR-92b	miR-589	miR-923	miR-92b	miR-134	miR-548b-3p
miR-25*	miR-377*	miR-589	miR-923	miR-892a	miR-192
miR-539	miR-923	miR-377*	miR-302d	miR-590-5p	miR-151-5p
miR-923	miR-652	miR-410	miR-374a	miR-590-3p	miR-598
miR-192	miR-518e	miR-137	miR-598	miR-425	miR-187
miR-134	miR-556-3p	miR-671-5p	miR-937	miR-454	miR-873
miR-371-3p	miR-767-3p	miR-151-5p	miR-335*	miR-101*	miR-218
miR-580	miR-505	miR-223*	miR-885-5p	miR-132	miR-923

[0090] With the diagnostic information obtained, a physiological condition could be detected, identified, predicted, treated, and/or monitored. For example, a treatment could be administered based on the identity of the physiological condition. A particular treatment could be monitored by taking a first sample, administering the treatment, taking a second sample, and comparing the microRNA profiles of the two samples to identify and/or track changes resulting from the treatment. Those changes could include the amounts of a particular microRNA sequence, or the identity of the differentially expressed microRNA sequences that have changed between the two samples.

[0091] It is also contemplated that manipulating the levels of microRNA sequences might itself be a treatment for a physiological condition. The microRNA level could be

altered by constructing a specific DNA or RNA sequence related to the microRNA sequences, then delivering that DNA or RNA sequence to a targeted cell, tissue, or organ expressing the targeted microRNA sequences.

[0092] As discussed below, specific microRNA sequences are identified that may be useful in diagnosing and/or treating liver disease or injury, lung disease or injury, and neurological disease or injury. Such conditions include chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF) (also known as interstitial lung disease (ILD)).

[0093] Other methods embodied herein include generating a microRNA profile from a biological sample. The microRNA profile comprises the amounts of specific microRNA sequences. The amounts of those specific microRNA sequences are then compared to a reference to provide information for detecting or predicting the lung condition. In this regard, the microRNA profile may include those specific microRNA sequences identified below in the examples, or a subset thereof. Such microRNA profiles would be smaller, faster, and provide the same diagnostic information as larger test kits.

[0094] The following examples are provided to illustrate the devices and methods of the present disclosure. The examples are merely illustrative and are not intended to limit the disclosure to the materials, conditions, or process parameters set forth therein.

EXAMPLES

ISOLATION OF microRNA

[0095] microRNA can be isolated using glass filter based methods to selectively bind RNA in a high salt buffer. The unwanted biomolecules can then be washed off by using high salt buffers containing at least 50% alcohol. The bound pure RNA can then eluted off the glass membrane with low salt buffer or RNase-free water.

[0096] 1). *Isolating microRNA from solid tissues*

[0097] Briefly, total RNA, including microRNA, was isolated using commercial kits such as miRNeasy mini kit (Qiagen Inc. Valencia, CA). Approximately 5 mg to 50 mg tissue samples were excised from flash-frozen tissue. After placing the tissue sample

into a Dounce tissue grinder, 700 microliter (μ l) QIAzol lysis reagent was added to the grinder and the tissue was homogenized immediately. For every 700 μ l QIAzol lysis reagent used, 140 μ l chloroform was added to the tissue lysate to extract the water soluble content. After mixing for 15 seconds, the lysate was placed in a centrifuge and spun at 12000x g for 15 minutes at room temperature. The upper aqueous phase (containing the RNA) was then transferred to a new collection tube, and 1.5 volumes of ethanol was added. The sample was then transferred to a cartridge containing a glass filter (i.e. silica membrane) so that RNA could attach to the glass filter. The contaminants were washed off the silica membrane by applying different high salt washing buffers included in the miRNeasy kit. The bound pure RNA was then eluted off the membrane with water or low salt buffer.

[0098] 2). *Isolating microRNA from liquid samples*

[0099] Approximately, 800 μ l of QIAzol lysis reagent was added to 200 μ l liquid sample. The sample was mixed in a tube followed by adding 200 μ l of chloroform. After mixing rigorously for 15 seconds, the sample was then centrifuged at 12,000x g for 15 minutes. The upper aqueous phase was carefully transferred to a new collection tube, and 1.5 total volumes of ethanol was added. The sample was then applied directly to a glass membrane containing column and the RNA was bound and purified by three contiguous washing to remove unwanted contamination. The immobilized RNA was then collected from the membrane with a low salt elution buffer.

[0100] The yield of microRNA from different amount of liquid samples used in these protocols was tested. The best ratio was found to be 4 volumes of lysis buffer with 1 volume of liquid sample.

[0101] The quality and quantity of RNA isolated was evaluated by RNA by NanoDrop 1000 spectrophotometer (Thermo Fisher Scientific Inc. Waltham, MA) and the Agilent 2100 Bioanalyzer (Agilent Inc. Santa Clara, CA).

[0102] **FIG. 1A** shows an electropherogram of RNA isolated from solid tissue, while **FIG. 1B** shows an electropherogram of RNA isolated from a liquid sample. The 18S and 28S peaks are clearly visible and marked. The microRNA are located on the left of both electropherograms. This region also contains all degraded RNA.

ARRAY HYBRIDIZATION AND QUANTITATIVE PCR

[0103] Agilent's human and mouse microRNA microarray kits (Agilent Inc. Santa Clara, CA) were used as the array platform; however, arrays from different companies including Affymetrix and Exiqon have also been used. The human microRNA microarray contained probes for 723 human and 76 human viral microRNAs from the Sanger database v 10.1. The mouse microRNA microarray contained probes for 567 mouse and 10 mouse herpes virus microRNA sequences from the Sanger database v 10.1. Cyanine 3-pCp labeled RNA (i.e. RNA labeled with Cyanine 3-Cytidine bisphosphate) for array hybridization was generated by 100 nanograms (ng) of total RNA using Agilent's microRNA complete labeling and hybridization kit. All the steps, including labeling, hybridization, washing, scanning and feature extraction were performed in accordance with the manufacturer's instructions.

[0104] In brief, 100 ng of total RNA was dephosphorylated with calf intestinal alkaline phosphatase, then heat and DMSO treated to yield denatured RNA. Cyanine 3-Cytidine bisphosphate was joined to the microRNA by T4 RNA ligase. MicroBioSpin 6 columns were used to desalt the samples and remove any unincorporated fluorophores. The samples were hybridized to 8x15K Agilent Human microRNA (V2) or Mouse microRNA microarrays in a rotating hybridization oven for 20 hours at 55°C and 10 rpm. The arrays were washed for 5 minutes in Agilent GE Wash Buffer 1 with Triton X-102 and then for another 5 minutes in Agilent GE Wash Buffer 2 with Triton X-102.

[0105] After washing, all slides were immediately scanned using a PerkinElmer ScanArray Express at 5 micron resolution. The resulting images were quantified using Agilent's Feature Extraction software. The differentially expressed microRNA sequences were then identified using a standard protocol developed for gene array data processing. The sample or gene clustering and array hybridization heatmap were generated using MeV4 software package from The Institute for Genomic Research (TIGR) (available at <http://www.tigr.org/tdb/microarray/>).

[0106] Quantitative PCR (QPCR) with microRNA specific primer sets were used to confirm the results from array hybridization. In brief, a SYBR Green based method, miScript real-time PCR (Qiagen Inc. Valencia, CA, USA), or TaqMan primer set from Apply Biosystems, was used with 50 ng of total RNA from each sample. The first strand

cDNA was generated according to the manufacturer's instruction. Approximately 2.5 ng of cDNA was used in the PCR reaction. The yield of 18 to 20 base pair fragments (based on SYBR Green intensity) corresponding to the specific microRNA species was monitored with the 7900HT fast real-time PCR system from Applied Biosystems (Applied Biosystems, Foster City, CA). QPCR results were analyzed by SDS 2.2.2, with a manual C_T threshold value of 0.2.

EXAMPLE 1

[0107] This example showed that microRNA sequences could be used as a marker to detect liver injury. Mice were used as the experimental model.

[0108] 6-month-old male C57/B6 mice were grouped into control and treatment groups with 4 animals in each group. The mice then fasted for 24 hours prior to a single intraperitoneal injection of either (a) 300mg/kg of acetaminophen in phosphate buffer saline (PBS) (treatment group); (b) or PBS (control group). Mice were sacrificed at different time points post-exposure (12 hr, 24 hr, 48 hr, 72 hr, and 120 hr) and plasma and liver samples were collected. Part of the liver samples were sectioned and examined by a pathologist and the serum alanine transaminase (ALT) levels were also determined to confirm as well as assess the severity of liver injury.

[0109] Total RNA was isolated from collected samples to conduct comprehensive microRNA analyses. To assess the level of microRNA in liver tissues, a microRNA array from Agilent was used. The RNA samples were labeled and processed according to the manufacturer's recommended protocols. The data from each array were extracted, normalized and compared following a standard gene expression microarray method.

[0110] The expression levels of various microRNA sequences in the liver tissues were used to generate a microRNA profile and used to assess tissue injury. Differentially expressed microRNA sequences were clustered using the Hierarchical clustering method and the result is shown in **FIG. 2**. The different time points are indicated on the top, while the identity of individual microRNA sequences is listed on the right. (The identifying labels correspond to those in the miRNA Registry maintained at the Sanger Institute.) The hybridization intensity of individual microRNA sequences is

represented in different colors as indicated on top of the figure (yellow representing the highest expression and blue representing the lowest expression signal). The microRNA profile clearly indicates that the levels of some microRNA sequences were changed by the exposure to acetaminophen.

EXAMPLE 2

[0111] This example showed that the levels of specific microRNA sequences in the serum or plasma could be used to assess drug-induced liver injury.

[0112] The male C57/B6 mice were randomly grouped into two groups, a treatment group (3 animals) and control group (4 animals). They fasted for 24 hours prior to a single intraperitoneal injection of either (a) 300mg/kg of acetaminophen in PBS (treatment group); or (b) PBS (control group). Mice were sacrificed at 24 hours post exposure, the plasma samples were collected and RNA was isolated.

[0113] The expression levels of microRNA sequences in the serum were used to make a microRNA profile. The differentially expressed microRNA sequences between the treatment group and the control group were clustered with the Hierarchical clustering method and is shown in **FIG. 3**. The result clearly indicated that the levels of certain microRNA sequences in the serum could be used as an indication of the acetaminophen toxicity.

EXAMPLE 3

[0114] This example showed that the levels of specific microRNA sequences in the serum or plasma could be used as an early indication of drug-induced liver injury.

[0115] The male C57/B6 mice were randomly grouped into nine different groups with 4 animals in each group. They fasted for 24 hours prior to a single intraperitoneal injection with either (a) 75 mg/Kg of acetaminophen in PBS (treatment 1); (b) 150 mg/Kg of acetaminophen in PBS (treatment 2); (c) 300mg/Kg of acetaminophen in PBS (treatment 3); or (d) PBS (control group). Mice were sacrificed and plasma samples were collected at 1, 3 and 24 hours post-exposure. The nine groups were: 1) 1 hour control; 2) 1 hour treatment 1; 3) 1 hour treatment 2; 4) 1 hour treatment 3; 5) 3 hour control; 6) 3 hour treatment 1; 7) 3 hour treatment 2; 8) 3 hour treatment 3; and 9) 24

hour treatment 3. The group at 24 hr post-exposure received only the highest dose (300 mg/kg) to serve as a positive control. The expression levels of two different microRNA sequences, mir-486 and mir-122, in the serum were profiled by quantitative polymerase chain reactions (Q-PCR).

[0116] The median intensities (Z-axes) from each group (X-axis) at PCR cycle number 19 were plotted. This graph is shown in **FIG. 4**. Both mir-486 (red bars) and mir-122 (green bars) intensities showed dose-dependent changes at 3 hr post-exposure. The intensity of mir-122 at 300 mg/kg was almost the same between 3 hr and 24 hr post-exposure. Clear changes were observed in the samples obtained at one hour post-acetaminophen injection. The results clearly indicated that the levels of selected microRNA sequences, such as mir-122 and mir-486, in the serum could be used as an early indication of tissue injury.

[0117] Next, the ratios of the median intensities (green bars) and average intensities (blue bars) from each group at PCR cycle number 19 were plotted. This graph is shown as **FIG. 5**. As expected, the ratios of both median and average intensities showed dose-dependent changes at 3 hr post-exposure. The ratio also clearly indicated the difference between 3 hr and 24 hr post-exposure. This result clearly indicated the ratio of selected microRNA sequences, such as mir-122 and mir-486, in the serum could be used as an early indication of tissue injury.

EXAMPLE 4

[0118] This example showed that microRNA could be used in assessing neurological disorders. The microRNA expression patterns in brain tissues obtained from normal and prion infected animals were profiled as described above. The results are shown in **FIG. 6**. The result clearly indicated differences between normal and diseased samples.

EXAMPLE 5

[0119] This example showed that microRNA could be used in assessing the health status of lungs. The microRNA expression patterns in lung tissues obtained from normal and diseased animals were profiled as described above. The results are shown in **FIG. 7**. The result clearly indicated there were differences on microRNA expression

as the disease progressed (from 1 to 6 where 6 has the most serious disease condition) and a number of microRNA sequences are different between normal and disease samples. Thus, specific microRNA sequences or a panel of microRNA sequences could be used as a tool to assess the health status of lungs.

EXAMPLE 6

[0120] This example showed that different biological pathways or compartments had very different microRNA profiles. The microRNA profiles in serum and urine samples obtained from a normal mouse were profiled as described above, then compared. The result is shown in **FIG. 8**. The result clearly revealed a significant difference in the microRNA composition in different body fluids. This would allow the development of different biomarkers to be used in different body fluids to assess the health status of tissues. In addition, microRNA sequences in a specific body fluid can be used as a reliable tool to assess the health status of tissues intimately associated with that body fluid, e.g. bladder and kidney tissues to the urine.

EXAMPLE 7

[0121] miRNA profiles from lung tissue and plasma from ILD patients and COPD patients were compared to a control set of miRNA profiles from uninvolved lung tissue obtained from lung cancer resections (controls) and a control set of miRNA profiles from plasma samples obtained from clinically normal donors (collected by the Marsh lab). The miRNA profiles were compared in various pairwise combinations to determine which miRNA sequences were overexpressed and thus useful for diagnostic purposes. The miRNA profiles were obtained using a microarray kit available from Agilent, which generally detected a given miRNA with usually two independent oligonucleotide (oligo) targets and four or more in some cases.

[0122] **FIG. 9** shows the graph comparing miRNA expression levels in control plasma with ILD plasma. Note the log scale. MiRNA with expression values that differ substantially between the two samples reside away from the diagonal line (i.e. $y=x$) that would represent equivalent expression in the two samples. This graph indicated that many miRNAs in ILD plasma are expressed at substantially higher levels than in the

control plasma. There also appear to be a few miRNAs in the control profile that were expressed at relatively lower levels than in the ILD profile.

[0123] Next, in order to reduce the complexity of the data, the similarity of the signals returned by the different oligos that were present on the Agilent array and designed to detect a given miRNA were examined. For example, miRNA 1225-5p (i.e. mir-1225-5p) was about 3-fold over expressed in ILD plasma. For mir-1225-5p, four probe oligos were used in the Agilent array. **FIG. 10A** shows the signal in the ILD plasma samples (n=24). **FIG. 10B** shows the signal in the control plasma samples (n=6). As seen, all four probe oligos gave signals in the ILD and control plasma samples. In addition, the signal strengths were within a factor of about two to each other, even though these oligos differ slightly in sequence.

[0124] 17 miRNA sequences were identified that appeared to be overexpressed in the ILD plasma samples. **FIG. 11** shows the signal strength for all of the oligos that targeted these 17 sequences. The ILD plasma signals are shown as blue diamonds and the control plasma signals are shown as pink squares. As seen, the signal strengths for all of the independent oligo probes were reasonably close (i.e. within a factor of 2.5).

[0125] Since the signals from the independent probes were close, the data from all probes was combined. Then, the mean expression level for each miRNA was calculated and miRNA sequences which were relatively overexpressed in the ILD plasma samples were identified. (An alternative analysis path could have been to choose the data from one or two of the independent probes and identify overexpressed miRNA sequences based on that data.)

[0126] **FIG. 12** shows the resulting graph with the mean and one standard deviation identified. Again, the ILD plasma signals are shown as blue diamonds and the control plasma signals are shown as pink squares. The expression of the displayed microRNAs was at least two-fold higher in the ILD plasma samples than in the control plasma samples (2x was an arbitrary value). Table 3 lists the specific data of **FIG. 12**.

Table 3.

microRNA sequence	mean level (ILD)	St. Dev. (ILD)	mean level (control)	St. Dev. (control)	mean ILD/ mean control
hsv1-miR-H1	371	100	207	13.9	1.8
hsa-miR-223	688	317	338	105	2.0
hsa-miR-575	416	17	198	21.4	2.1
hsa-miR-483-5p	589	179	259	70.1	2.3
hsa-miR-150*	659	142	267	35.6	2.5
hsa-miR-22	958	589	376	91	2.5
hsa-miR-1225-5p	3361	873	1201	324.4	2.8
hsa-miR-939	644	463	224	36.5	2.9
hsa-miR-135a*	499	127	172	33.2	2.9
hsa-miR-940	1316	906	341	45.6	3.9
hsa-miR-134	830	9	201	50	4.1
hcmv-miR-UL70-3p	721	129	166	25.2	4.3
hsa-miR-630	3349	65	683	100.3	4.9
hsv1-miR-LAT	1250	490	223	64.2	5.6
kshv-miR-K12-3	3542	2912	588	422.3	6.0
hsa-miR-638	18055	11123	1670	716.2	10.8
hsa-miR-923	42215	40796	310	9883.1	136.2

[0127] Based on the standard deviations, the 17 miRNAs that met this criterion can be divided into three groups. 11 miRNAs (UL70-3p, 1225-5p, 134, 135a*, 150*, 483-5p, 575, 630, 638, H1, and LAT) were likely to be differentially expressed between ILD and control with high confidence. There was intermediate confidence for 4 miRNAs (mir-22, 223, 939, and 940); and lower confidence for miRNAs 923 and K12-3.

[0128] The degree of over expression displayed by these miRNAs varied over 100-fold, as shown in **FIG. 13**. Note the log scale.

[0129] Next, the miRNA that were expressed at a higher level in control plasma than ILD plasma were investigated. An arbitrary expression level of 250 or greater and 3.0 fold or greater relative overexpression as used to screen out marginal miRNA candidates. Three miRNA sequences passed this screen as shown in Table 4.

Table 4.

microRNA sequence	mean level (ILD)	St. Dev. (ILD)	mean level (control)	St. Dev. (control)	mean control/mean ILD
hsa-miR-451 oligo 1	729	1695.917	5274	5362.923	7
hsa-miR-451; oligo 2	487	1096.762	3527.167	3421.076	7
hsa-miR-451; oligo 1 w/o outlier	390	375	5274		13.5
hsa-miR-451; oligo 2 w/o outlier	268	243	3527		13.1
hsa-miR-448	64	38.3	253	93	4
hsa-miR-92a-2*	78	46.94568	253.6667	109.7154	3

[0130] hsa-miR-448 and hsa-miR-92-a-2* were just over the threshold for inclusion and showed low absolute expression. The standard deviation for hsa-miR-451 was rather large when all samples (n=24) were used. However, when one outlier was removed (n=23), the standard deviations improved, as did the ratios. hsa-miR-451 was expressed ten times higher in control plasma relative to ILD plasma.

[0131] One of the miRNAs that is overexpressed in control serum relative to ILD serum, in combination with a miRNA that is overexpressed in ILD serum relative to control serum, could be used in a simple “top scoring pair” test for ILD.

EXAMPLE 8

[0132] Using the same data as in Example 7, the expression of miRNA in both ILD plasma and ILD tissue was examined. That graph is shown in **FIG. 14**. While many miRNAs that were expressed in ILD plasma had little or no expression in ILD tissue, most of those that were expressed in tissue had at least some expression in plasma. Those miRNA sequences that had signal strength of at least 1000 in both tissue and plasma (an arbitrarily chosen value) are listed in Table 5. The ratio of the expression for the miRNA sequence was also compared to the average expression of all the miRNAs in the sample and is labeled as “overexpression ratio.”

Table 5.

microRNA sequence	mean level (plasma)	overexpression ratio	mean level (tissue)	overexpression ratio
hsa-miR-1225-5p	4043	9.8	1189.0	3.1
hsa-miR-21	455	1.1	9938.7	26.0
hsa-miR-22	1374	3.3	5555.8	14.5
hsa-miR-223	835	2.0	1303.4	3.4
hsa-miR-451	729	1.8	6564.4	17.2
hsa-miR-638	25920	62.6	1084.6	2.8
hsa-miR-923	71062	171.7	6114.7	16.0
kshv-miR-K12-3	5602	13.5	498.0	1.3

[0133] hsa-miR-21 was present here, but not in Tables 3 or 4, while the other seven were also listed in either Table 3 or 4.

EXAMPLE 9

[0134] Using the same data as in Example 7, the expression of miRNA in both ILD lung tissue and control lung tissue was examined. That graph is shown in **FIG. 15**. The expression levels for certain miRNA sequences, as well as those overexpressed in ILD lung tissue, are listed below in Table 6.

Table 6.

microRNA sequence	mean level (ILD)	mean level (control)	mean ILD/ mean control
hsa-miR-923	6114.7	22421.33	0.3
hsa-miR-22	5555.8	4771.83	1.2
hsa-miR-29a	4881.6	2183.67	2.2
hsa-miR-145	3759.9	1449.50	2.6
hsa-miR-26a	3187.3	1123.33	2.8
hsa-let-7c	4405.5	1336.33	3.3
hsa-miR-23a	4396.1	1144.83	3.8
hsa-miR-21	9938.7	2450.83	4.1
hsa-miR-125b	3843.2	939.17	4.1
hsa-miR-27a	3090.2	720.50	4.3
hsa-let-7a	5709.2	1039.33	5.5
hsa-let-7f	3352.5	504.83	6.6
hsa-miR-451	6564.4	383.33	17.1

[0135] miRNA hsa-miR-923 was over 130-fold over-expressed in ILD plasma relative to control plasma (Table 3), but it is under-expressed in ILD lung tissue relative to control lung tissue (Table 6). This suggests the tissue or cell of origin for this miRNA may be within the blood itself, or at least not the ILD lung. Similarly, miRNA hsa-miR-22 is expressed three times higher in ILD plasma compared to control plasma (Table 3), but is expressed at nearly the same level in ILD lung and control lung tissue (Table 6). Other miRNAs that are characteristic of ILD, such as miRNA-451, were elevated in ILD lung tissue (17x in Table 6) but not in ILD plasma (see Table 4).

[0136] In total 17 miRNA sequences were identified as containing diagnostic information related to ILD. Those 17 sequences are listed in Table 3.

EXAMPLE 10

[0137] The plasma sample data (control, COPD, and ILD) was separately analyzed using the Panorama suite of tools and consisted of the following steps: (A) Normalization; (B) Quality Control; (C) Cluster Analysis; (D) Panel Selection; and (E) Comparison. Each step is explained in more detail below.

[0138] In Normalization, the following steps occurred. First, missing values were left unchanged instead of imputing a value. Second, each sample was normalized independently of other samples. Third, the natural log was applied to the values for each sample; then the values were adjusted by the median and standard deviation. **FIG. 16** shows the results of normalization.

[0139] In Quality Control, the quality of the data was assessed before and after normalization. **FIG. 17A** shows the Pearson correlation distribution before normalization. This figure correlated the score for each miRNA across the samples to the total miRNA expression level across the samples. This figure showed that the vast majority of miRNA sequences had the same expression profile across the samples, and furthermore, this expression profile is the total miRNA level per sample – this is the dominant feature of the dataset. **FIG. 17B** shows the Pearson correlation distribution after normalization. Normalization improved the quality of the dataset. The distribution in **FIG. 17B** was much less skewed than that of **FIG. 17A**.

[0140] In Cluster Analysis, the normalized miRNA data was clustered using multi-dimensional scaling (MDS); the results are presented in **FIG. 18**. This was an unsupervised analysis without samples being identified by group or miRNA selected that differentiated the groups. There were several notable features of this plot. First, the samples within each group clustered together showing uniformity in miRNA expression. The exception was IPF tissue where a few outliers occurred, likely due to sample handling. Second, the tissue groups cluster away from the plasma groups. Third, within the plasma groups, the COPD and ILD plasma samples overlapped and were clustered away from the plasma control samples.

[0141] Performing a T-test at significance level 0.01, 194 miRNA were found to separate the plasma control samples from the ILD plasma samples. Performing 50 permutation tests revealed that the expected number of miRNA, by chance alone, was 21.5, yielding a false discovery rate of 11%. The p-value distribution of all miRNA is shown in **FIG. 19**. There was a uniform distribution over most p-values, except an increase below 0.05. This was consistent with the hypothesis that there are miRNA that segregate the two sample groups.

[0142] In Panel Selection, panels that segregated the control plasma samples from the ILD plasma samples were selected using Area Under the Curve (AOC). AOC is a measure of diagnostic segregation. It ranges from 0 to 1 where 1 indicates perfect segregation. The AUC of individual miRNA can be determined independently of each other allowing for straightforward selection of the best segregating miRNA. In addition, the combined AUC of panels of miRNA can be calculated to assess how well groups of miRNA work together to segregate control plasma samples from ILD plasma samples.

[0143] To calculate the combined AUC, a combination rule must be established. The combination rule used here was majority consensus: if the strict majority of miRNA classified a sample as diseased (i.e. ILD or IPF) then the sample was classified diseased, otherwise, the sample was classified as normal.

[0144] **FIG. 20** is three charts showing the distribution of directional bias (upper left), the AUC distribution (upper right), and the standard deviation for the ILD group (lower left). The number of miRNA higher in the control samples than the ILD samples was essentially the same as the opposite direction. The distribution of AUC scores for all

miRNA was centered about 0.6 which is expected. A small rise around 0.95 indicated the presence of miRNA that distinguish the control and ILD samples. The distribution of miRNA expression standard deviations showed that overall, variability was similar across miRNA (note that normalization is done by sample, not by miRNA).

[0145] In Comparison, the data was analyzed. Using an AUC threshold of 0.95, 57 out of 2421 (2.4%) miRNA probes were selected. Table 7 contains the oligo probe used for the miRNA, the corresponding miRNA, p-value, AUC, and number of panels of 3 miRNA above combined AUC 0.99 that each miRNA participated in. If the miRNA was expressed higher in the control sample than the ILD sample, the column "Control>ILD" was marked with a Y.

Table 7.

Probe	miRNA	Control > ILD	P-value	AUC	St. Dev.	# Panels
A_25_P00010804	hsa-miR-518d-3p	Y	9.96E-06	1.00	0.42	945
A_25_P00013406	hsa-miR-135a*	N	1.56E-09	1.00	0.55	681
A_25_P00013825	hiv1-miR-H1	N	4.98E-06	1.00	0.66	656
A_25_P00011724	hcmv-miR-UL70-3p	N	1.23E-13	1.00	0.62	621
A_25_P00013407	hsa-miR-135a*	N	1.41E-12	1.00	0.62	615
A_25_P00013090	hsa-miR-940	N	8.13E-09	1.00	0.88	581
A_25_P00012074	hsa-miR-139-3p	N	3.27E-07	1.00	0.63	572
A_25_P00013689	kshv-miR-K12-3	N	1.09E-11	1.00	0.60	572
A_25_P00012231	hsa-miR-134	N	9.11E-11	1.00	0.64	548
A_25_P00012230	hsa-miR-134	N	6.22E-13	1.00	0.65	539
A_25_P00010345	hsa-miR-557	N	2.47E-06	1.00	0.55	534
A_25_P00013829	hsv1-miR-LAT	N	1.52E-11	1.00	0.77	500
A_25_P00011725	hcmv-miR-UL70-3p	N	6.62E-13	1.00	0.65	463
A_25_P00013830	hsv1-miR-LAT	N	1.42E-12	1.00	0.65	449
A_25_P00013831	hsv1-miR-LAT	N	2.62E-09	1.00	0.84	449
A_25_P00013087	hsa-miR-939	N	3.19E-13	1.00	0.53	362
A_25_P00013453	hsa-miR-150*	N	1.67E-08	1.00	0.58	362
A_25_P00014907	hsa-miR-1224-5p	N	6.43E-07	1.00	0.47	344
A_25_P00013326	hsa-miR-187*	N	1.24E-06	1.00	0.70	324
A_25_P00013828	hsv1-miR-LAT	N	1.33E-12	1.00	0.80	299
A_25_P00011853	ebv-miR-BART13	N	4.09E-08	0.99	0.47	435
A_25_P00015004	hsa-miR-1226*	N	2.14E-06	0.99	0.66	362
A_25_P00010687	hsa-miR-498	N	7.82E-08	0.99	0.46	498
A_25_P00011096	hsa-miR-572	N	3.25E-08	0.99	0.81	420
A_25_P00010808	hsa-miR-575	N	2.42E-07	0.99	0.85	415
A_25_P00014908	hsa-miR-1224-5p	N	4.81E-07	0.99	0.60	344
A_25_P00014896	hsa-miR-575	N	4.23E-07	0.99	0.82	316
A_25_P00010641	hsa-miR-601	N	2.63E-08	0.99	0.49	218

Probe	miRNA	Control > ILD	P-value	AUC	St. Dev.	# Panels
A_25_P00013086	hsa-miR-939	N	1.09E-07	0.99	0.49	179
A_25_P00013450	hsa-miR-150*	N	2.91E-08	0.99	0.67	178
A_25_P00010344	hsa-miR-557	N	5.45E-06	0.98	0.65	684
A_25_P00013327	hsa-miR-187*	N	1.06E-05	0.98	0.65	347
A_25_P00015003	hsa-miR-1226*	N	2.15E-06	0.98	0.61	179
A_25_P00013451	hsa-miR-150*	N	1.39E-06	0.98	0.67	178
A_25_P00014906	hsa-miR-1224-5p	N	2.03E-07	0.97	0.55	330
A_25_P00012059	hsa-miR-198	N	1.13E-05	0.97	0.67	296
A_25_P00011799	hsv1-miR-H1	N	6.61E-07	0.97	0.98	268
A_25_P00011097	hsa-miR-572	N	6E-05	0.97	0.60	203
A_25_P00013452	hsa-miR-150*	N	8.41E-07	0.97	0.62	179
A_25_P00010669	hsa-miR-326	N	7.84E-05	0.97	0.83	177
A_25_P00014892	hsa-miR-539	N	0.000543	0.97	0.59	722
A_25_P00010444	hsa-miR-448	N	6.72E-05	0.97	0.58	581
A_25_P00012030	hsa-miR-92a	N	1.18E-05	0.97	0.86	343
A_25_P00013448	hsa-miR-149*	N	1.95E-05	0.97	0.58	260
A_25_P00014861	hsa-miR-483-5p	N	2.9E-07	0.97	0.62	144
A_25_P00010228	hsa-miR-623	N	5.7E-05	0.96	0.79	356
A_25_P00012419	hsa-miR-423-5p	N	0.000569	0.96	0.87	336
A_25_P00011796	hsv1-miR-H1	N	2.96E-06	0.96	0.69	268
A_25_P00011854	ebv-miR-BART13	N	0.000141	0.96	0.73	268
A_25_P00011719	ebv-miR-BART7	N	7.87E-05	0.96	0.57	224
A_25_P00012459	hsa-miR-483-5p	N	2.03E-07	0.96	0.66	178
A_25_P00013449	hsa-miR-149*	N	1.55E-06	0.96	0.66	164
A_25_P00012262	hsa-miR-320	N	5.41E-05	0.96	0.73	84
A_25_P00011342	hsa-miR-765	N	5.08E-06	0.96	0.38	57
A_25_P00013324	hsa-miR-187*	N	5.29E-05	0.95	0.68	477
A_25_P00010227	hsa-miR-623	N	4.89E-05	0.95	0.97	362
A_25_P00012031	hsa-miR-92a	N	2.59E-05	0.95	1.07	343

[0146] Interestingly, only 3 of the 57 miRNA were higher in the control samples than the ILD samples, despite the near equivalence of miRNA higher in control samples over ILD samples, as compared to the opposite among all miRNA (see **FIG. 20**). 20 of the 57 miRNA had a perfect AUC score of 1.00. Not shown here is the fact that there were also many panels of three miRNA that had a perfect AUC score of 1.00.

[0147] There were also unique miRNA among the 57 miRNA probes, which illustrated a strong redundancy among probes. This redundancy could be used as a selection criterion.

[0148] 11 of the 17 miRNA sequences listed in Table 3 of Example 7 also appear in Table 7. They are shown in bold text in Table 7.

[0149] The claims refer to identifying “at least one” or “at least two” differentially expressed microRNA sequences in a microRNA profile, wherein the differentially expressed microRNA sequences are selected from a list. This language should be construed as meaning that the microRNA sequence selected from the list is identified as a differentially expressed microRNA sequence in the microRNA profile.

[0150] It is contemplated that assays or microRNA profiles would test for only specific microRNA sequences, such as those identified above.

[0151] In some embodiments, an assay or microRNA profile tests for at least two microRNA sequences selected from the group consisting of miR-630, miR-134, hcmv-miR-UL70-3p, miR-1225-5p, miR-135a*, miR-150*, miR-22, miR-223, miR-483-5p, miR-575, miR-638, miR-923, miR-939, miR-940, hsv1-miR-H1, hsv1-miR-LAT, kshv-miR-K12-3, and human orthologs thereof. In other embodiments, at least three of these sequences is tested for. In particular embodiments, all 17 of these sequences are tested for. Specific pairs of these 17 microRNA sequences include those listed in Table 8:

Table 8.

miR-630, miR-134	miR-630, hcmv-miR-UL70-3p
miR-630, miR-1225-5p	miR-630, miR-135a*
miR-630, miR-150*	miR-630, miR-22
miR-630, miR-223	miR-630, miR-483-5p
miR-630, miR-575	miR-630, miR-638
miR-630, miR-923	miR-630, miR-939
miR-630, miR-940	miR-630, hsv1-miR-H1
miR-630, hsv1-miR-LAT	miR-630, kshv-miR-K12-3
miR-134, hcmv-miR-UL70-3p	miR-134, miR-1225-5p
miR-134, miR-135a*	miR-134, miR-150*
miR-134, miR-22	miR-134, miR-223
miR-134, miR-483-5p	miR-134, miR-575
miR-134, miR-638	miR-134, miR-923
miR-134, miR-939	miR-134, miR-940
miR-134, hsv1-miR-H1	miR-134, hsv1-miR-LAT
miR-134, kshv-miR-K12-3	hcmv-miR-UL70-3p, miR-1225-5p
hcmv-miR-UL70-3p, miR-135a*	hcmv-miR-UL70-3p, miR-150*
hcmv-miR-UL70-3p, miR-22	hcmv-miR-UL70-3p, miR-223
hcmv-miR-UL70-3p, miR-483-5p	hcmv-miR-UL70-3p, miR-575
hcmv-miR-UL70-3p, miR-638	hcmv-miR-UL70-3p, miR-923

hcmv-miR-UL70-3p, miR-939	hcmv-miR-UL70-3p, miR-940
hcmv-miR-UL70-3p, hsv1-miR-H1	hcmv-miR-UL70-3p, hsv1-miR-LAT
hcmv-miR-UL70-3p, kshv-miR-K12-3	miR-1225-5p, miR-135a*
miR-1225-5p, miR-150*	miR-1225-5p, miR-22
miR-1225-5p, miR-223	miR-1225-5p, miR-483-5p
miR-1225-5p, miR-575	miR-1225-5p, miR-638
miR-1225-5p, miR-923	miR-1225-5p, miR-939
miR-1225-5p, miR-940	miR-1225-5p, hsv1-miR-H1
miR-1225-5p, hsv1-miR-LAT	miR-1225-5p, kshv-miR-K12-3
miR-135a*, miR-150*	miR-135a*, miR-22
miR-135a*, miR-223	miR-135a*, miR-483-5p
miR-135a*, miR-575	miR-135a*, miR-638
miR-135a*, miR-923	miR-135a*, miR-939
miR-135a*, miR-940	miR-135a*, hsv1-miR-H1
miR-135a*, hsv1-miR-LAT	miR-135a*, kshv-miR-K12-3
miR-150*, miR-22	miR-150*, miR-223
miR-150*, miR-483-5p	miR-150*, miR-575
miR-150*, miR-638	miR-150*, miR-923
miR-150*, miR-939	miR-150*, miR-940
miR-150*, hsv1-miR-H1	miR-150*, hsv1-miR-LAT
miR-150*, kshv-miR-K12-3	miR-22, miR-223
miR-22, miR-483-5p	miR-22, miR-575
miR-22, miR-638	miR-22, miR-923
miR-22, miR-939	miR-22, miR-940
miR-22, hsv1-miR-H1	miR-22, hsv1-miR-LAT
miR-22, kshv-miR-K12-3	miR-223, miR-483-5p
miR-223, miR-575	miR-223, miR-638
miR-223, miR-923	miR-223, miR-939
miR-223, miR-940	miR-223, hsv1-miR-H1
miR-223, hsv1-miR-LAT	miR-223, kshv-miR-K12-3
miR-483-5p, miR-575	miR-483-5p, miR-638
miR-483-5p, miR-923	miR-483-5p, miR-939
miR-483-5p, miR-940	miR-483-5p, hsv1-miR-H1
miR-483-5p, hsv1-miR-LAT	miR-483-5p, kshv-miR-K12-3
miR-575, miR-638	miR-575, miR-923
miR-575, miR-939	miR-575, miR-940
miR-575, hsv1-miR-H1	miR-575, hsv1-miR-LAT
miR-575, kshv-miR-K12-3	miR-638, miR-923
miR-638, miR-939	miR-638, miR-940
miR-638, hsv1-miR-H1	miR-638, hsv1-miR-LAT
miR-638, kshv-miR-K12-3	miR-923, miR-939
miR-923, miR-940	miR-923, hsv1-miR-H1
miR-923, hsv1-miR-LAT	miR-923, kshv-miR-K12-3
miR-939, miR-940	miR-939, hsv1-miR-H1
miR-939, hsv1-miR-LAT	miR-939, kshv-miR-K12-3

miR-940, hsv1-miR-H1	miR-940, hsv1-miR-LAT
miR-940, kshv-miR-K12-3	hsv1-miR-H1, hsv1-miR-LAT
hsv1-miR-H1, kshv-miR-K12-3	hsv1-miR-LAT, kshv-miR-K12-3

[0152] In other embodiments, an assay or microRNA profile tests for at least two microRNA sequences selected from the group consisting of miR-630, miR-134, hcmv-miR-UL70-3p, miR-1225-5p, miR-135a*, miR-150*, miR-483-5p, miR-575, miR-638, hsv1-miR-H1, hsv1-miR-LAT, and human orthologs thereof. In other embodiments, at least three of these sequences is tested for. In particular embodiments, all 11 of these sequences are tested for. Specific pairs of these 11 microRNA sequences include those listed in Table 9:

Table 9.

miR-630, miR-134	miR-630, hcmv-miR-UL70-3p
miR-630, miR-1225-5p	miR-630, miR-135a*
miR-630, miR-150*	miR-630, miR-483-5p
miR-630, miR-575	miR-630, miR-638
miR-630, hsv1-miR-H1	miR-630, hsv1-miR-LAT
miR-134, hcmv-miR-UL70-3p	miR-134, miR-1225-5p
miR-134, miR-135a*	miR-134, miR-150*
miR-134, miR-483-5p	miR-134, miR-575
miR-134, miR-638	miR-134, hsv1-miR-H1
miR-134, hsv1-miR-LAT	hcmv-miR-UL70-3p, miR-1225-5p
hcmv-miR-UL70-3p, miR-135a*	hcmv-miR-UL70-3p, miR-150*
hcmv-miR-UL70-3p, miR-483-5p	hcmv-miR-UL70-3p, miR-575
hcmv-miR-UL70-3p, miR-638	hcmv-miR-UL70-3p, hsv1-miR-H1
hcmv-miR-UL70-3p, hsv1-miR-LAT	miR-1225-5p, miR-135a*
miR-1225-5p, miR-150*	miR-1225-5p, miR-483-5p
miR-1225-5p, miR-575	miR-1225-5p, miR-638
miR-1225-5p, hsv1-miR-H1	miR-1225-5p, hsv1-miR-LAT
miR-135a*, miR-150*	miR-135a*, miR-483-5p
miR-135a*, miR-575	miR-135a*, miR-638
miR-135a*, hsv1-miR-H1	miR-135a*, hsv1-miR-LAT
miR-150*, miR-483-5p	miR-150*, miR-575
miR-150*, miR-638	miR-150*, hsv1-miR-H1
miR-150*, hsv1-miR-LAT	miR-483-5p, miR-575
miR-483-5p, miR-638	miR-483-5p, hsv1-miR-H1
miR-483-5p, hsv1-miR-LAT	miR-575, miR-638
miR-575, hsv1-miR-H1	miR-575, hsv1-miR-LAT
miR-638, hsv1-miR-H1	miR-638, hsv1-miR-LAT
hsv1-miR-H1, hsv1-miR-LAT	

[0153] In some embodiments, an assay or microRNA profile tests for two or more microRNA sequences. At least one of the microRNA sequences tested for is selected from the group consisting of miR-630, hcmv-miR-UL70-3p, miR-1225-5p, miR-134, miR-135a*, miR-150*, miR-483-5p, miR-575, miR-638, hsv1-miR-H1, hsv1-miR-LAT, and human orthologs thereof. At least one of the microRNA sequences tested for is selected from the group consisting of miR-451, miR-448, and miR-92a-2*. In particular embodiments, miR-451 is one of the microRNA sequences tested for. Specific pairs of these microRNA sequences include those listed in Table 10:

Table 10.

miR-630, miR-451	miR-630, miR-448
miR-630, miR-92a-2*	hcmv-miR-UL70-3p, miR-451
hcmv-miR-UL70-3p, miR-448	hcmv-miR-UL70-3p, miR-92a-2*
miR-1225-5p, miR-451	miR-1225-5p, miR-448
miR-1225-5p, miR-92a-2*	miR-134, miR-451
miR-134, miR-448	miR-134, miR-92a-2*
miR-135a*, miR-451	miR-135a*, miR-448
miR-135a*, miR-92a-2*	miR-150*, miR-451
miR-150*, miR-448	miR-150*, miR-92a-2*
miR-483-5p, miR-451	miR-483-5p, miR-448
miR-483-5p, miR-92a-2*	miR-575, miR-451
miR-575, miR-448	miR-575, miR-92a-2*
miR-638, miR-451	miR-638, miR-448
miR-638, miR-92a-2*	hsv1-miR-H1, miR-451
hsv1-miR-H1, miR-448	hsv1-miR-H1, miR-92a-2*
hsv1-miR-LAT, miR-451	hsv1-miR-LAT, miR-448
hsv1-miR-LAT, miR-92a-2*	

[0154] In some embodiments, an assay or microRNA profile tests for at least two microRNA sequences selected from the group consisting of miR-451, miR-923, miR-1225-5p, miR-22, miR-223, miR-638, kshv-miR-K12-3, and human orthologs thereof. In other embodiments, at least three of these sequences is tested for. In particular embodiments, all seven of these sequences are tested for. Specific pairs of these seven microRNA sequences include those listed in Table 11:

Table 11.

miR-451, miR-923	miR-451, miR-1225-5p
miR-451, miR-22	miR-451, miR-223
miR-451, miR-638	miR-451, kshv-miR-K12-3
miR-923, miR-1225-5p	miR-923, miR-22
miR-923, miR-223	miR-923, miR-638
miR-923, kshv-miR-K12-3	miR-1225-5p, miR-22
miR-1225-5p, miR-223	miR-1225-5p, miR-638
miR-1225-5p, kshv-miR-K12-3	miR-22, miR-223
miR-22, miR-638	miR-22, kshv-miR-K12-3
miR-223, miR-638	miR-223, kshv-miR-K12-3
miR-638, kshv-miR-K12-3	

[0155] In some embodiments, an assay or microRNA profile tests for at least two microRNA sequences selected from the group consisting of miR-940, miR-134, miR-135a*, miR-150*, miR-483-5p, miR-575, miR-939, hsv1-miR-H1, kshv-miR-K12-3, hsv1-miR-LAT, hcmv-miR-UL70-3p, and human orthologs thereof. In other embodiments, at least three of these sequences is tested for. In particular embodiments, all 11 of these sequences are tested for. Specific pairs of these 11 microRNA sequences include those listed in Table 12:

Table 12.

miR-940, miR-134	miR-940, miR-135a*
miR-940, miR-150*	miR-940, miR-483-5p
miR-940, miR-575	miR-940, miR-939
miR-940, hsv1-miR-H1	miR-940, kshv-miR-K12-3
miR-940, hsv1-miR-LAT	miR-940, hcmv-miR-UL70-3p
miR-134, miR-135a*	miR-134, miR-150*
miR-134, miR-483-5p	miR-134, miR-575
miR-134, miR-939	miR-134, hsv1-miR-H1
miR-134, kshv-miR-K12-3	miR-134, hsv1-miR-LAT
miR-134, hcmv-miR-UL70-3p	miR-135a*, miR-150*
miR-135a*, miR-483-5p	miR-135a*, miR-575
miR-135a*, miR-939	miR-135a*, hsv1-miR-H1
miR-135a*, kshv-miR-K12-3	miR-135a*, hsv1-miR-LAT
miR-135a*, hcmv-miR-UL70-3p	miR-150*, miR-483-5p
miR-150*, miR-575	miR-150*, miR-939
miR-150*, hsv1-miR-H1	miR-150*, kshv-miR-K12-3
miR-150*, hsv1-miR-LAT	miR-150*, hcmv-miR-UL70-3p
miR-483-5p, miR-575	miR-483-5p, miR-939

miR-483-5p, hsv1-miR-H1	miR-483-5p, kshv-miR-K12-3
miR-483-5p, hsv1-miR-LAT	miR-483-5p, hcmv-miR-UL70-3p
miR-575, miR-939	miR-575, hsv1-miR-H1
miR-575, kshv-miR-K12-3	miR-575, hsv1-miR-LAT
miR-575, hcmv-miR-UL70-3p	miR-939, hsv1-miR-H1
miR-939, kshv-miR-K12-3	miR-939, hsv1-miR-LAT
miR-939, hcmv-miR-UL70-3p	hsv1-miR-H1, kshv-miR-K12-3
hsv1-miR-H1, hsv1-miR-LAT	hsv1-miR-H1, hcmv-miR-UL70-3p
kshv-miR-K12-3, hsv1-miR-LAT	kshv-miR-K12-3, hcmv-miR-UL70-3p
hsv1-miR-LAT, hcmv-miR-UL70-3p	

[0156] Appendix A provides a listing of the RNA sequences for all of the microRNA discussed herein, including human orthologs thereof.

Appendix A.

miRNA name	Accession Number	RNA Sequence	SEQ ID No:
ebv-miR-BART10*	MIMAT0004817	gccaccucuuugguucuguaca	1
ebv-miR-BART12	MIMAT0003423	uccugugguguuuggugugguu	2
ebv-miR-BART13	MIMAT0003424	uguaacuugccagggacggcuga	3
ebv-miR-BART13*	MIMAT0004818	aaccggcucguggcucguacag	4
ebv-miR-BART15	MIMAT0003713	gucagugguuuuuguuuccuuga	5
ebv-miR-BART1-5p	MIMAT0000999	ucuuaguggaagugacgugcugug	6
ebv-miR-BART16	MIMAT0003714	uuagauagagugggugugugcucu	7
ebv-miR-BART18-5p	MIMAT0003717	ucaaguucgcacuuccuauaca	8
ebv-miR-BART19-3p	MIMAT0003718	uuuuguuuugcuugggaugcu	9
ebv-miR-BART19-5p	MIMAT0004836	acauuccccgcaaacaugacaug	10
ebv-miR-BART20-5p	MIMAT0003719	uagcaggcaugucucauucc	11
ebv-miR-BART2-5p	MIMAT0001000	uaauuucugcauucgcccugc	12
ebv-miR-BART3*	MIMAT0003410	accuaguguuaguguugugcu	13
ebv-miR-BART5	MIMAT0003413	caaggugaauauagcugcccaucg	14
ebv-miR-BART6-5p	MIMAT0003414	uaagguugguccaauccauagg	15
ebv-miR-BART7	MIMAT0003416	caucauaguccaguguccagg	16
ebv-miR-BART7*	MIMAT0004815	ccuggaccuugacuaugaaaca	17
ebv-miR-BHRF1-1	MIMAT0000995	uaaccugaucagccccggaguu	18
ebv-miR-BHRF1-3	MIMAT0000998	uaacgggaaguguguaagcaca	19
hcmv-miR-UL148D	MIMAT0001578	ucguccuccccuucucaccg	20

miRNA name	Accession Number	RNA Sequence	SEQ ID No:
hcmv-miR-UL22A	MIMAT0001574	uaacuagccuucccgugaga	21
hcmv-miR-UL22A*	MIMAT0001575	ucaccagaaugcuaguuguag	22
hcmv-miR-UL70-3p	MIMAT0003343	ggggaugggucggcgcgcg	23
hcmv-miR-UL70-5p	MIMAT0003342	ugcgucucggccucguccaga	24
hcmv-miR-US25-1	MIMAT0001581	aaccgcucaguggcucggacc	25
hcmv-miR-US25-2-3p	MIMAT0001583	auccacuuggagagcucccgcg	26
hcmv-miR-US25-2-5p	MIMAT0001582	agcggucuguucagguggauga	27
hcmv-miR-US4	MIMAT0003341	cgacauggacgugcagggggau	28
hiv1-miR-H1	MIMAT0004480	ccagggaggcgugccugggc	29
hiv1-miR-N367	MIMAT0004478	acugaccuuuggauggugcucaa	30
hsa-miR-1	MIMAT0000416	ggaauguaaagaaguauguau	31
hsa-miR-10b	MIMAT0000254	uaccucugaagaaccgaauuug	32
hsa-miR-122	MIMAT0000421	uggagugugacaaugguguuug	33
hsa-miR-1224-3p	MIMAT0005459	ccccaccuccucuccucag	34
hsa-miR-1224-5p	MIMAT0005458	gugaggacucgggaggugg	35
hsa-miR-1225-3p	MIMAT0005573	ugagccccugugccgccccag	36
hsa-miR-1225-5p	MIMAT0005572	guggguacggcccaguggggg	37
hsa-miR-1226*	MIMAT0005576	gugagggcaugcaggccuggaugggg	38
hsa-miR-1227	MIMAT0005580	cgugccacccuuuuccccag	39
hsa-miR-1228	MIMAT0005583	ucacaccugccucgcccccc	40
hsa-miR-1229	MIMAT0005584	cucucaccacugcccucccacag	41
hsa-miR-1234	MIMAT0005589	ucggccugaccacccacccac	42
hsa-miR-1237	MIMAT0005592	uccuucugcuccgucccccag	43
hsa-miR-1238	MIMAT0005593	cuuccucgucugucugcccc	44
hsa-miR-124	MIMAT0000422	uaaggcacgcggugaaugcc	45
hsa-miR-125a-3p	MIMAT0004602	acaggugagguucuugggagcc	46
hsa-miR-125a-5p	MIMAT0000443	ucccugagacccuuuaaccuguga	47
hsa-miR-127-3p	MIMAT0000446	ucggauccgucugagcuuggcu	48
hsa-miR-127-5p	MIMAT0004604	cugaagcucagagggcucugau	49
hsa-miR-128	MIMAT0000424	ucacagugaaccggucuuuu	50
hsa-miR-129*	MIMAT0004548	aagcccuuaccccaaaaaguau	51
hsa-miR-129-3p	MIMAT0004605	aagcccuuaccccaaaaagcau	52
hsa-miR-130a	MIMAT0000425	cagugcaauguuaaaagggcau	53
hsa-miR-133a	MIMAT0000427	uuugguccccuucaaccagcug	54
hsa-miR-133b	MIMAT0000770	uuugguccccuucaaccagcua	55
hsa-miR-134	MIMAT0000447	ugugacugguugaccagagggg	56
hsa-miR-135a*	MIMAT0004595	uauagggauuggagccguggcg	57

miRNA name	Accession Number	RNA Sequence	SEQ ID No:
hsa-miR-136	MIMAT0000448	acuccauuuuuuuugaugaugga	58
hsa-miR-136*	MIMAT0004606	caucaucgucucaaaugagucu	59
hsa-miR-138	MIMAT0000430	agcugguguugugaauccaggccg	60
hsa-miR-139-3p	MIMAT0004552	ggagacgcggcccuguuggagu	61
hsa-miR-140-3p	MIMAT0004597	uaccacagggguagaaccacgg	62
hsa-miR-140-5p	MIMAT0000431	cagugguuuuuacccuaugguag	63
hsa-miR-141	MIMAT0000432	uaacacugucugguaaagaugg	64
hsa-miR-142-3p	MIMAT0000434	uguaguguuuuccuacuuuauugga	65
hsa-miR-143	MIMAT0000435	ugagaugaagcacuguagcuc	66
hsa-miR-146a	MIMAT0000449	ugagaacugaauuccauggguu	67
hsa-miR-146b-3p	MIMAT0004766	ugcccuguggacucaguucugg	68
hsa-miR-146b-5p	MIMAT0002809	ugagaacugaauuccauaggcu	69
hsa-miR-148b	MIMAT0000759	ucagugcaucacagaacuuugu	70
hsa-miR-150	MIMAT0000451	ucucccaacccuuguaccagug	71
hsa-miR-150*	MIMAT0004610	cugguacaggccugggggacag	72
hsa-miR-15a*	MIMAT0004488	caggccauauugugcugccuca	73
hsa-miR-15b	MIMAT0000417	uagcagcacaucaugguuaca	74
hsa-miR-181b	MIMAT0000257	aacauucauugcugucggugggu	75
hsa-miR-181d	MIMAT0002821	aacauucauuguugucggugggu	76
hsa-miR-183	MIMAT0000261	uauggcacugguagaauucacu	77
hsa-miR-185	MIMAT0000455	uggagagaaaggcaguuccuga	78
hsa-miR-186	MIMAT0000456	caaagaauucuccuuuugggcu	79
hsa-miR-187*	MIMAT0004561	ggcuacaacacaggaccggggc	80
hsa-miR-188-5p	MIMAT0000457	caucccuugcaugguggagggg	81
hsa-miR-190b	MIMAT0004929	ugauauguuugauauuggguu	82
hsa-miR-191*	MIMAT0001618	gcugcgcuuggauuucgucccc	83
hsa-miR-193b	MIMAT0002819	aacuggcccucuaagucccgcu	84
hsa-miR-194	MIMAT0000460	uguaacagcaacuccaugugga	85
hsa-miR-198	MIMAT0000228	gguccagaggggagauagguuc	86
hsa-miR-199a-5p	MIMAT0000231	cccaguguucagacuaccuguuc	87
hsa-miR-19a	MIMAT0000073	ugugcaaaucuaugcaaaacuga	88
hsa-miR-200a	MIMAT0000682	uaacacugucugguaacgaugu	89
hsa-miR-200b	MIMAT0000318	uaauacugccugguaaugga	90
hsa-miR-200b*	MIMAT0004571	caucuacugggcagcauugga	91
hsa-miR-200c	MIMAT0000617	uaauacugccggguaaugga	92
hsa-miR-205	MIMAT0000266	uccuucuuuccaccggagucug	93
hsa-miR-206	MIMAT0000462	uggaauquaaggaaguguggg	94
hsa-miR-208a	MIMAT0000241	auaagacgagcaaaaagcuugu	95
hsa-miR-21	MIMAT0000076	uagcuuaucagacugauguuga	96

miRNA name	Accession Number	RNA Sequence	SEQ ID No:
hsa-miR-211	MIMAT0000268	uucccuuugucauccuucgccu	97
hsa-miR-22	MIMAT0000077	aagcugccaguugaagaacugu	98
hsa-miR-220b	MIMAT0004908	ccaccaccgugucugacacuu	99
hsa-miR-221	MIMAT0000278	agcuacauugucugcuggguuuc	100
hsa-miR-222	MIMAT0000279	agcuacauugcugcugcugggu	101
hsa-miR-223	MIMAT0000280	ugucaguuugucaaaauacccca	102
hsa-miR-23b	MIMAT0000418	aucacauugccagggaauuacc	103
hsa-miR-26a	MIMAT0000082	uucaaguaauccaggauaggcu	104
hsa-miR-27a	MIMAT0000084	uucacaguggcuaaguuccgc	105
hsa-miR-27b	MIMAT0000419	uucacaguggcuaaguucugc	106
hsa-miR-27b*	MIMAT0004588	agagcuuagcugauuggugaac	107
hsa-miR-299-3p	MIMAT0000687	uaugugggaugguaaaccgcuu	108
hsa-miR-299-5p	MIMAT0002890	ugguuuaccguccacauacau	109
hsa-miR-29b	MIMAT0000100	uagcaccuuugaaaucaguguu	110
hsa-miR-29c*	MIMAT0004673	ugaccgauuucuccugguguuc	111
hsa-miR-300	MIMAT0004903	uauacaagggcagacucucucu	112
hsa-miR-301b	MIMAT0004958	cagugcaaugauauugucaaaagc	113
hsa-miR-302c*	MIMAT0000716	uuuaacauggggguaccugcug	114
hsa-miR-30a	MIMAT0000087	uguaaacauccucgacuggaag	115
hsa-miR-30c	MIMAT0000244	uguaaacauccuacacucucagc	116
hsa-miR-30c-1*	MIMAT0004674	cuggggagagggguuguuuacucc	117
hsa-miR-30e	MIMAT0000692	uguaaacauccuugacuggaag	118
hsa-miR-31	MIMAT0000089	aggcaagaugcuggcuaugcu	119
hsa-miR-323-3p	MIMAT0000755	cacauuacacggucgaccucu	120
hsa-miR-324-3p	MIMAT0000762	acugccccaggugcugcugg	121
hsa-miR-324-5p	MIMAT0000761	cgcauccccuagggcuauggugu	122
hsa-miR-326	MIMAT0000756	ccucuggggccuuccuccag	123
hsa-miR-328	MIMAT0000752	cuggcccucucugcccuuccgu	124
hsa-miR-331-5p	MIMAT0004700	cuagguaugguccagggaucc	125
hsa-miR-338-3p	MIMAT0000763	uccagcaucagugauuuuguug	126
hsa-miR-339-3p	MIMAT0004702	ugagcgccucgacgacagagccg	127
hsa-miR-33a*	MIMAT0004506	caauguuuccacagugcaucac	128
hsa-miR-33b	MIMAT0003301	gugcauugcuguugcauugc	129
hsa-miR-33b*	MIMAT0004811	cagugccucggcagugcagccc	130
hsa-miR-342-3p	MIMAT0000753	ucucacacagaaaucgcacccgu	131
hsa-miR-34c-3p	MIMAT0004677	aaucacuaaccacacggccagg	132
hsa-miR-34c-5p	MIMAT0000686	aggcaguguaguauagcugauugc	133
hsa-miR-363*	MIMAT0003385	cggguggaucacgaugcauuuu	134
hsa-miR-369-3p	MIMAT0000721	aaauaacauggguugaucuuu	135

miRNA name	Accession Number	RNA Sequence	SEQ ID No:
hsa-miR-370	MIMAT0000722	gccugcugggguggaaccuggu	136
hsa-miR-371-3p	MIMAT0000723	aagugccgccaucuuuugagugu	137
hsa-miR-371-5p	MIMAT0004687	acucaaacugugggggcacu	138
hsa-miR-375	MIMAT0000728	uuuguucguucggcucgcguga	139
hsa-miR-376b	MIMAT0002172	aucauagaggaaaauccauguu	140
hsa-miR-377*	MIMAT0000730	aucacacaaaggcaacuuuugu	141
hsa-miR-379	MIMAT0000733	ugguagacuuggaacguagg	142
hsa-miR-382	MIMAT0000737	gaaguuguucgugggguuucg	143
hsa-miR-409-5p	MIMAT0001638	agguuacccgagcaacuuugcau	144
hsa-miR-411	MIMAT0003329	uaguagaccguauagcguacg	145
hsa-miR-411*	MIMAT0004813	uauguaacacgguccacuaacc	146
hsa-miR-423-5p	MIMAT0004748	ugaggggcagagagcgagacuuu	147
hsa-miR-424	MIMAT0001341	cagcagcaauucauguuuugaa	148
hsa-miR-424*	MIMAT0004749	caaaacgugaggcgugcuau	149
hsa-miR-425	MIMAT0003393	aaugacacgaucacucccgua	150
hsa-miR-429	MIMAT0001536	uaauacugucugguaaaaccgu	151
hsa-miR-448	MIMAT0001532	uugcauauguaggauugccau	152
hsa-miR-449a	MIMAT0001541	uggcaguguauuguuagcuggu	153
hsa-miR-449b	MIMAT0003327	aggcaguguauuguuagcuggc	154
hsa-miR-450b-3p	MIMAT0004910	uugggaucauuuugcauccaua	155
hsa-miR-451	MIMAT0001631	aaaccguuaccuuacugaguu	156
hsa-miR-452	MIMAT0001635	aacuguuugcagaggaaacuga	157
hsa-miR-454*	MIMAT0003884	accuaucaauauugucucugc	158
hsa-miR-455-3p	MIMAT0004784	gcaguccaugggcauauacac	159
hsa-miR-455-5p	MIMAT0003150	uaugugccuuuggacuacaucg	160
hsa-miR-483-3p	MIMAT0002173	ucacuccucuccucccgucuu	161
hsa-miR-483-5p	MIMAT0004761	aagacgggaggaaagaaggag	162
hsa-miR-484	MIMAT0002174	ucaggcucaguccccucccgau	163
hsa-miR-486-3p	MIMAT0004762	cggggcagcucaguacaggau	164
hsa-miR-486-5p	MIMAT0002177	uccuguacugagcugccccgag	165
hsa-miR-487b	MIMAT0003180	aaucguacagggucauccacuu	166
hsa-miR-491-3p	MIMAT0004765	cuuaugcaagauucccuucac	167
hsa-miR-491-5p	MIMAT0002807	aguggggaacccuuccaugagg	168
hsa-miR-493	MIMAT0003161	ugaaggucuacugugugccagg	169
hsa-miR-493*	MIMAT0002813	uuguacaugguaggcuuucuu	170
hsa-miR-494	MIMAT0002816	ugaaacauacacgggaaaccuc	171
hsa-miR-497	MIMAT0002820	cagcagcacacugugguuugu	172
hsa-miR-498	MIMAT0002824	uuucaagccagggggcguuuuuc	173
hsa-miR-500	MIMAT0004773	uaauccuugcuaccugggugaga	174

miRNA name	Accession Number	RNA Sequence	SEQ ID No:
hsa-miR-503	MIMAT0002874	uagcagcggaacaguucugcag	175
hsa-miR-505	MIMAT0002876	cgucaacacuugcugguuuccu	176
hsa-miR-507	MIMAT0002879	uuuugcaccuuuuggagugaa	177
hsa-miR-511	MIMAT0002808	gugucuuuugcucugcaguca	178
hsa-miR-513a-3p	MIMAT0004777	uaaauuucaccuuucugagaagg	179
hsa-miR-513a-5p	MIMAT0002877	uucacagggaggugucau	180
hsa-miR-513b	MIMAT0005788	uucacaaggaggugucauuuau	181
hsa-miR-513c	MIMAT0005789	uucucaaggaggugucguuuau	182
hsa-miR-515-5p	MIMAT0002826	uucuccaaaagaaagcacuuucug	183
hsa-miR-518b	MIMAT0002844	caaagcgcuuccuuuagaggu	184
hsa-miR-518c*	MIMAT0002847	ucucuggagggaagcacuuucug	185
hsa-miR-518d-3p	MIMAT0002864	caaagcgcuuccuuuaggagc	186
hsa-miR-518d-5p	MIMAT0005456	cucuagagggaagcacuuucug	187
hsa-miR-518e*	MIMAT0005450	cucuagagggaagcgcuuucug	188
hsa-miR-520d-5p	MIMAT0002855	cuacaaagggaagcccuuc	189
hsa-miR-520h	MIMAT0002867	acaagugcuuccuuuagagu	190
hsa-miR-539	MIMAT0003163	ggagaaauuauccuuggugugu	191
hsa-miR-541	MIMAT0004920	uggugggcacagaauucuggacu	192
hsa-miR-545*	MIMAT0004785	ucaguaaauguuuuuuagauga	193
hsa-miR-548d-3p	MIMAT0003323	caaaaaccacaguuuuuuugc	194
hsa-miR-548d-5p	MIMAT0004812	aaaaguaauugugguuuuugcc	195
hsa-miR-551a	MIMAT0003214	gcgaccacucuugguuucca	196
hsa-miR-551b	MIMAT0003233	gcgaccacauacuugguuucag	197
hsa-miR-552	MIMAT0003215	aacaggugacugguuagacaa	198
hsa-miR-554	MIMAT0003217	gcuaguccugacucagccagu	199
hsa-miR-556-5p	MIMAT0003220	gaugagcucuuuguaauaugag	200
hsa-miR-557	MIMAT0003221	guuugcacgggugggcuugucu	201
hsa-miR-559	MIMAT0003223	uaaaguaaaauugcaccaaaa	202
hsa-miR-561	MIMAT0003225	caaaguuuuagaucuuugaagu	203
hsa-miR-564	MIMAT0003228	aggcacggugucagcaggc	204
hsa-miR-568	MIMAT0003232	auguauaaauguauacacac	205
hsa-miR-572	MIMAT0003237	guccgcucggcgugggcca	206
hsa-miR-574-5p	MIMAT0004795	ugagugugugugugugagugugu	207
hsa-miR-575	MIMAT0003240	gagccaguuggacaggagc	208
hsa-miR-576-3p	MIMAT0004796	aagauguggaaaaauuggaauc	209
hsa-miR-578	MIMAT0003243	cuucuugugcucuaggauugu	210
hsa-miR-583	MIMAT0003248	caaagaggaaggucccauac	211
hsa-miR-586	MIMAT0003252	uaugcauuguaauuuuaggucc	212
hsa-miR-589	MIMAT0004799	ugagaaccacgucugcucugag	213

miRNA name	Accession Number	RNA Sequence	SEQ ID No:
hsa-miR-589*	MIMAT0003256	ucagaacaaaugccgguucccaga	214
hsa-miR-591	MIMAT0003259	agaccauggguucucuuugu	215
hsa-miR-595	MIMAT0003263	gaagugugccguggugugucu	216
hsa-miR-601	MIMAT0003269	uggucuaggauuguuggaggag	217
hsa-miR-602	MIMAT0003270	gacacgggcgacagcugcgccc	218
hsa-miR-609	MIMAT0003277	aggguuuucucucaucucu	219
hsa-miR-610	MIMAT0003278	ugagcuaaaugugugcuggga	220
hsa-miR-612	MIMAT0003280	gcugggcagggcuucugagcuccuu	221
hsa-miR-613	MIMAT0003281	aggaauguuccuucuuugcc	222
hsa-miR-614	MIMAT0003282	gaacgccuguucuuugccaggugg	223
hsa-miR-615-3p	MIMAT0003283	uccgagccugggucucccucu	224
hsa-miR-616	MIMAT0004805	agucuuuggaggguuugagcag	225
hsa-miR-619	MIMAT0003288	gaccuggacauguuugugcccagu	226
hsa-miR-622	MIMAT0003291	acagucugcugagguuggagc	227
hsa-miR-623	MIMAT0003292	aucccuugcaggggcuguugggu	228
hsa-miR-624*	MIMAT0003293	uaguaccaguaccuuguguuca	229
hsa-miR-627	MIMAT0003296	gugagucucuaagaaaagagga	230
hsa-miR-630	MIMAT0003299	aguauucuguaccaggggaaggu	231
hsa-miR-633	MIMAT0003303	cuaauaguaucuaaccacaauaaa	232
hsa-miR-634	MIMAT0003304	aaccagcaccccaacuuuggac	233
hsa-miR-638	MIMAT0003308	agggaucgcgggcggguggcgccu	234
hsa-miR-639	MIMAT0003309	aucgcugcgguugcgagcgcu	235
hsa-miR-640	MIMAT0003310	augauccaggaaccugccucu	236
hsa-miR-642	MIMAT0003312	guccucuccaaaugugucuug	237
hsa-miR-644	MIMAT0003314	aguguggcuucuuagagc	238
hsa-miR-647	MIMAT0003317	guggcugcacucacuuccuuc	239
hsa-miR-648	MIMAT0003318	aagugugcagggcacuggu	240
hsa-miR-652	MIMAT0003322	aauggcgccacuagguugug	241
hsa-miR-654-5p	MIMAT0003330	uggugggccgcagaacaugugc	242
hsa-miR-658	MIMAT0003336	ggcggagggaaguaggucguuggu	243
hsa-miR-659	MIMAT0003337	cuugguucagggaggguccca	244
hsa-miR-662	MIMAT0003325	ucccacguugggcccagcag	245
hsa-miR-663	MIMAT0003326	aggcgggcgccggggaccgc	246
hsa-miR-665	MIMAT0004952	accaggaggcugaggcccu	247
hsa-miR-671-5p	MIMAT0003880	aggaagcccuggaggggcuggag	248
hsa-miR-675	MIMAT0004284	uggugcgagagggccacagug	249
hsa-miR-708	MIMAT0004926	aaggagcuuacaauagcuggg	250
hsa-miR-708*	MIMAT0004927	caacuagacugugagcuucua	251
hsa-miR-711	MIMAT0012734	gggaccaggagagacguaag	252

miRNA name	Accession Number	RNA Sequence	SEQ ID No:
hsa-miR-720	MIMAT0005954	ucucgcuggggccucca	253
hsa-miR-744*	MIMAT0004946	cuguugccacuaaccucaaccu	254
hsa-miR-760	MIMAT0004957	cggcucugggucugugggga	255
hsa-miR-765	MIMAT0003945	uggaggagaaggaaggugaug	256
hsa-miR-766	MIMAT0003888	acuccagccccacagccucagc	257
hsa-miR-767-3p	MIMAT0003883	ucugcucauaccccaugguuucu	258
hsa-miR-770-5p	MIMAT0003948	uccaguaccacgugucagggccca	259
hsa-miR-802	MIMAT0004185	caguaacaaagauucauccuugu	260
hsa-miR-874	MIMAT0004911	cugcccuggcccaggaggaccga	261
hsa-miR-876-3p	MIMAT0004925	uggugguuuacaaaguaauuca	262
hsa-miR-876-5p	MIMAT0004924	uggauuucuuuugugaaucacca	263
hsa-miR-877	MIMAT0004949	guagaggagauggcgcaggg	264
hsa-miR-877*	MIMAT0004950	uccucuuccuccuccuccag	265
hsa-miR-885-3p	MIMAT0004948	aggcagcgggguguaguggaua	266
hsa-miR-885-5p	MIMAT0004947	uccauuacacuacccugccucu	267
hsa-miR-886-3p	MIMAT0004906	cgcgggugcuuacugacccuu	268
hsa-miR-890	MIMAT0004912	uacuuggaaaggcaucaguug	269
hsa-miR-891b	MIMAT0004913	ugcaacuaccugagucuuuga	270
hsa-miR-892b	MIMAT0004918	cacuggcuccuuucuggguaga	271
hsa-miR-920	MIMAT0004970	ggggagcuguggaagcagua	272
hsa-miR-922	MIMAT0004972	gcagcagagaauaggacuacguc	273
hsa-miR-923	none	GUCAGCGGAGGAAAAGAAA CU	274
hsa-miR-92a-2*	MIMAT0004508	ggguggggauuuguugcauuac	275
hsa-miR-92b	MIMAT0003218	uauugcacucgucccgccucc	276
hsa-miR-92b*	MIMAT0004792	agggacgggacgcggugcagug	277
hsa-miR-93	MIMAT0000093	caaagugcuguucgugcagguag	278
hsa-miR-933	MIMAT0004976	ugugcgcaggagaccucuccc	279
hsa-miR-934	MIMAT0004977	ugucuacuacuggagacacugg	280
hsa-miR-935	MIMAT0004978	ccaguuaaccguuccgcuaccgc	281
hsa-miR-936	MIMAT0004979	acaguagaggagggaauccgag	282
hsa-miR-937	MIMAT0004980	auccgcgcucugacucucugcc	283
hsa-miR-939	MIMAT0004982	uggggagcugaggcucuggggug	284
hsa-miR-940	MIMAT0004983	aaggcaggggcccccgcucccc	285
hsa-miR-96	MIMAT0000095	uuuggcacuagcacauuuuugcu	286
hsa-miR-99a	MIMAT0000097	aaccguagauccgaucuugug	287
hsv1-miR-H1	MIMAT0003744	uggaaggacgggaaguggaag	288
hsv1-miR-LAT	none	uggcgggccggccggggcc	289
kshv-miR-K12-12	IMAT0003712	accaggccaccauuccucuccg	290

miRNA name	Accession Number	RNA Sequence	SEQ ID No:
kshv-miR-K12-3	MIMAT0002193	ucacauucugaggacggcagcgga	291
kshv-miR-K12-3*	MIMAT0002194	ucgcggucacagaaugugaca	292
kshv-miR-K12-4-5p	MIMAT0002191	agcuaaaccgcaguacucuagg	293
kshv-miR-K12-6-5p	MIMAT0002188	ccagcagcaccuaauccaucgg	294
kshv-miR-K12-8	MIMAT0002186	uaggcgcgacugagagagcacg	295
kshv-miR-K12-9	MIMAT0002185	cuggguauacgcagcugcguaa	296
kshv-miR-K12-9*	MIMAT0002184	accagcugcguaaaccgccu	297
mghv-miR-M1-6	MIMAT0001569	ugaaacugugugaggugguuuu	298
mghv-miR-M1-9	MIMAT0001573	ucacauuugccuggaccuuuuu	299
mmu-let-7d*	MIMAT0000384	cuauacgaccugcugccuuucu	300
mmu-let-7g	MIMAT0000121	ugagguaguaguuuuguacaguu	301
mmu-miR- 298	MIMAT0000376	ggcagaggagggcuguucuccc	302
mmu-miR-1	MIMAT0000123	uggaauguaaagaaguauguau	303
mmu-miR-101a	MIMAT0000133	uacaguacugugauaacugaa	304
mmu-miR-101a*	MIMAT0004526	ucaguuaucacagugcugaugc	305
mmu-miR-101b	MIMAT0000616	uacaguacugugauagcugaa	306
mmu-miR-122	MIMAT0000246	uggagugugacaaugguguuug	307
mmu-miR-1224	MIMAT0005460	gugaggacuggggagguggag	308
mmu-miR-124	MIMAT0000134	uaaggcacgcgggugaauGCC	309
mmu-miR-125a-3p	MIMAT0004528	acaggugagguucuugggagcc	310
mmu-miR-125a-5p	MIMAT0000135	ucccugagaccuuuaaccuguga	311
mmu-miR-125b-5p	MIMAT0000136	ucccugagaccuaacuuguga	312
mmu-miR-126-5p	MIMAT0000137	auuauuacuuuugguacgCG	313
mmu-miR-127	MIMAT0000139	ucggauccgucugagcuuggcu	314
mmu-miR-128	MIMAT0000140	ucacagugaaccggucucuuu	315
mmu-miR-129-3p	MIMAT0000544	aagccuuaccacaaaagcau	316
mmu-miR-130a	MIMAT0000141	cagugcaauguuaaaaggcau	317
mmu-miR-133a	MIMAT0000145	uuuggucccuucaaccagcug	318
mmu-miR-133b	MIMAT0000769	uuuggucccuucaaccagcua	319
mmu-miR-135a*	MIMAT0004531	uauagggauuggagccguggcg	320
mmu-miR-136	MIMAT0000148	acuccauuuuguuuugaugg	321
mmu-miR-138	MIMAT0000150	agcugguguugugaauccaggccg	322
mmu-miR-138*	MIMAT0004668	ggcuacuucacaacaccagg	323
mmu-miR-139-3p	MIMAT0004662	uggagacgCGGCCUGUUGGAG	324
mmu-miR-140	MIMAT0000151	cagugguuuuaccuauugguag	325
mmu-miR-140*	MIMAT0000152	uaccacaggguagaaccacgg	326
mmu-miR-141	MIMAT0000153	uaacacugucugguaaagaugg	327
mmu-miR-142-3p	MIMAT0000155	uguaguguuuuccuacuuuauuga	328
mmu-miR-143	MIMAT0000247	ugagaugaagcacuguagcuc	329

miRNA name	Accession Number	RNA Sequence	SEQ ID No:
mmu-miR-146a	MIMAT0000158	ugagaacugaauuccauggguu	330
mmu-miR-146b	MIMAT0003475	ugagaacugaauuccauaggcu	331
mmu-miR-148b	MIMAT0000580	ucagugcaucacagaacuuugu	332
mmu-miR-150	MIMAT0000160	ucucccaacccuuguaccagug	333
mmu-miR-15a*	MIMAT0004624	caggccauacugugcugccuca	334
mmu-miR-15b	MIMAT0000124	uagcagcacaucaugguuaca	335
mmu-miR-181b	MIMAT0000673	aacauucauugcugucggugggu	336
mmu-miR-181d	MIMAT0004324	aacauucauuguugucggugggu	337
mmu-miR-183	MIMAT0000212	uauggcacugguagaauucacu	338
mmu-miR-185	MIMAT0000214	uggagagaaaggcaguuccuga	339
mmu-miR-186	MIMAT0000215	caaagaauucuccuuuugggcu	340
mmu-miR-191*	MIMAT0004542	gcugcacuuggauuucguuccc	341
mmu-miR-193	MIMAT0000223	aacuggccuacaaagucccagu	342
mmu-miR-193b	MIMAT0004859	aacuggcccacaaagucccgcu	343
mmu-miR-194	MIMAT0000224	uguaacagcaacuccaugugga	344
mmu-miR-199a-5p	MIMAT0000229	cccaguguucagacuaccuguuc	345
mmu-miR-199b*	MIMAT0000672	cccaguguuuagacuaccuguuc	346
mmu-miR-19a	MIMAT0000651	ugugcaaaucuaugcaaaacuga	347
mmu-miR-200a	MIMAT0000519	uaacacugucugguaacgaugu	348
mmu-miR-200b	MIMAT0000233	uaauacugccugguaaugga	349
mmu-miR-200b*	MIMAT0004545	caucuacugggcagcauugga	350
mmu-miR-200c	MIMAT0000657	uaauacugccggguaaugga	351
mmu-miR-202-3p	MIMAT0000235	agagguaauagcgcaugggaaga	352
mmu-miR-205	MIMAT0000238	uccuucuuuccaccggagucug	353
mmu-miR-206	MIMAT0000239	uggaauquaaggaagugugugg	354
mmu-miR-208a	MIMAT0000520	auaagacgagcaaaaagcuugu	355
mmu-miR-21	MIMAT0000530	uagcuuaucagacugauguuga	356
mmu-miR-211	MIMAT0000668	uucccuuugucauccuuugccu	357
mmu-miR-22	MIMAT0000531	aagcugccaguugaagaacugu	358
mmu-miR-221	MIMAT0000669	agcuacauugucugcuggguuuc	359
mmu-miR-222	MIMAT0000670	agcuacauucuggcuacugggu	360
mmu-miR-223	MIMAT0000665	ugucaguuugucaaaauaccca	361
mmu-miR-23b	MIMAT0000125	aucacauugccagggaauacc	362
mmu-miR-26a	MIMAT0000533	uucaaguaauccaggauaggcu	363
mmu-miR-27a	MIMAT0000537	uucacaguggcuaaguuccgc	364
mmu-miR-27b	MIMAT0000126	uucacaguggcuaaguucugc	365
mmu-miR-27b*	MIMAT0004522	agagcuuagcugauugggugaac	366
mmu-miR-28*	MIMAT0004661	cacuagauugugagcugcugga	367
mmu-miR-290-5p	MIMAT0000366	acucaaacuaugggggcacuuu	368

miRNA name	Accession Number	RNA Sequence	SEQ ID No:
mmu-miR-291a-5p	MIMAT0000367	caucaaaguggaggcccucucu	369
mmu-miR-294*	MIMAT0004574	acucaaaauggaggcccuaucu	370
mmu-miR-297a	MIMAT0000375	auguaugugugcaugugcaugu	371
mmu-miR-299	MIMAT0004577	uauguggggacgguaaaccgcuu	372
mmu-miR-29b	MIMAT0000127	uagcaccauuugaaaucaguguu	373
mmu-miR-29c*	MIMAT0004632	ugaccgauuucuccugguguuc	374
mmu-miR-301b	MIMAT0004186	cagugcaaugguauugucaaagc	375
mmu-miR-302c*	MIMAT0003375	gcuuaaacauggggguuaccugc	376
mmu-miR-30a	MIMAT0000128	uguaaacauccucgacuggaag	377
mmu-miR-30c	MIMAT0000514	uguaaacauccuacacucucagc	378
mmu-miR-30c-1*	MIMAT0004616	cugggagagggguuguuuacucc	379
mmu-miR-30e	MIMAT0000248	uguaaacauccuugacuggaag	380
mmu-miR-31	MIMAT0000538	aggcaagaugcuggcauagcug	381
mmu-miR-320	MIMAT0000666	aaaagcuggguugagagggcgga	382
mmu-miR-322	MIMAT0000548	cagcagcaauucauguuuugga	383
mmu-miR-323-3p	MIMAT0000551	cacauuacacggucgaccucu	384
mmu-miR-324-3p	MIMAT0000556	ccacugccccaggugcugcu	385
mmu-miR-324-5p	MIMAT0000555	cgcauccccuagggaauuggugu	386
mmu-miR-326	MIMAT0000559	ccucuggggcccuuccuccagu	387
mmu-miR-327	MIMAT0004867	acuugaggggcaugaggau	388
mmu-miR-328	MIMAT0000565	cuggcccucucugcccuuccgu	389
mmu-miR-331-5p	MIMAT0004643	cuagguaugguccagggaucc	390
mmu-miR-339-3p	MIMAT0004649	ugagcgccucggcgacagagccg	391
mmu-miR-341	MIMAT0000588	ucggucgaucggucggucggu	392
mmu-miR-342-3p	MIMAT0000590	ucucacacagaaucgcacccgu	393
mmu-miR-34b-5p	MIMAT0000382	aggcaguguaauuagcugauugu	394
mmu-miR-34c*	MIMAT0004580	aaucacuaaccacacagccagg	395
mmu-miR-369-3p	MIMAT0003186	aaauaauacaugguugaucuuu	396
mmu-miR-370	MIMAT0001095	gccugcugggguggaaccuggu	397
mmu-miR-374	MIMAT0003727	auauaauacaaccugcuaagug	398
mmu-miR-375	MIMAT0000739	uuuguucguucggcucgcguga	399
mmu-miR-376b	MIMAT0001092	aucuaagaggaacauccacuu	400
mmu-miR-379	MIMAT0000743	ugguagacuauggaacguagg	401
mmu-miR-380-3p	MIMAT0000745	uauguaguaugguccacauuu	402
mmu-miR-382	MIMAT0000747	gaaguuguucguggggaauucg	403
mmu-miR-384-5p	MIMAT0004745	uguaaacaauuccuaggcaaugu	404
mmu-miR-409-5p	MIMAT0004746	agguuacccgagcaacuugcau	405
mmu-miR-411	MIMAT0004747	uaguagaccguauagcguacg	406
mmu-miR-411*	MIMAT0001093	uauguaacacgguccacuaacc	407

miRNA name	Accession Number	RNA Sequence	SEQ ID No:
mmu-miR-423-5p	MIMAT0004825	ugagggggcagagagcgagacuuu	408
mmu-miR-425	MIMAT0004750	aaugacacgaucacucccgguuga	409
mmu-miR-429	MIMAT0001537	uaauacugucugguaaugccgu	410
mmu-miR-434-5p	MIMAT0001421	gcucgacucaugguuugaacca	411
mmu-miR-450b-3p	MIMAT0003512	auugggaacauuuugcaugcau	412
mmu-miR-451	MIMAT0001632	aaaccguuaccuuacugaguu	413
mmu-miR-455	MIMAT0003742	gcaguccacgggcgauauacac	414
mmu-miR-465c-3p	MIMAT0004874	gaucaggggccuuucuaaguaga	415
mmu-miR-466d-5p	MIMAT0004930	ugugugugcguacauguacaug	416
mmu-miR-466f-3p	MIMAT0004882	cauacacacacacauacacac	417
mmu-miR-467e*	MIMAT0005294	auauacauacacacaccuauau	418
mmu-miR-483	MIMAT0004782	aagacgggagaagagaaggagg	419
mmu-miR-484	MIMAT0003127	ucaggcucaguccccucccgau	420
mmu-miR-486	MIMAT0003130	uccuguacugagcugccccgag	421
mmu-miR-487b	MIMAT0003184	aaucguacagggucauccacuu	422
mmu-miR-494	MIMAT0003182	ugaaacauacacgggaaaccuc	423
mmu-miR-497	MIMAT0003453	cagcagcacacugugguuugua	424
mmu-miR-505	IMAT0003513	cgucaacacuugcugguuuucu	425
mmu-miR-511	MIMAT0004940	augccuuuugcucugcacuca	426
mmu-miR-539	MIMAT0003169	ggagaaaauuauccuuggugugu	427
mmu-miR-540-3p	MIMAT0004786	caaggguaccccucugacucugu	428
mmu-miR-551b	MIMAT0003890	gcgaccacauacuugguuucag	429
mmu-miR-568	MIMAT0004892	auguauaaauguauacacac	430
mmu-miR-574-5p	MIMAT0004893	ugagugugugugugugagugugu	431
mmu-miR-652	MIMAT0003711	aauggcgccacuagguugug	432
mmu-miR-654-5p	MIMAT0004897	ugguaagcugcagaacaugugu	433
mmu-miR-669a	MIMAT0003477	aguugugugugcauguucaugu	434
mmu-miR-671-5p	MIMAT0003731	aggaagcccuggaggggcuggag	435
mmu-miR-685	MIMAT0003463	ucaauggcugaggugaggcac	436
mmu-miR-686	MIMAT0003464	auugcuucccagacggugaaga	437
mmu-miR-688	MIMAT0003467	ucgcaggcgacuacuauuc	438
mmu-miR-701	MIMAT0003491	uuagccgcugaaaauagaugga	439
mmu-miR-706	MIMAT0003496	agagaaacccugucucaaaaaa	440
mmu-miR-708	MIMAT0004828	aaggagcuuacaaucuaucuggg	441
mmu-miR-710	MIMAT0003500	ccaagucuuggggagaguugag	442
mmu-miR-711	MIMAT0003501	gggacccggggagagauguaag	443
mmu-miR-712	MIMAT0003502	cuccuucacccgggcgguacc	444
mmu-miR-714	MIMAT0003505	cgacgagggcgguucggucgc	445
mmu-miR-720	MIMAT0003484	aucucgcuggggccucca	446

miRNA name	Accession Number	RNA Sequence	SEQ ID No:
mmu-miR-721	MIMAT0003515	cagugcaauuaaaagggggaa	447
mmu-miR-744*	MIMAT0004820	cuguugccacuaaccucaaccu	448
mmu-miR-760	MIMAT0003898	cggcucugggucugugggga	449
mmu-miR-770-5p	MIMAT0004822	agcaccacgugucugggccacg	450
mmu-miR-7a	MIMAT0000677	uggaagacuagugauuuuguugu	451
mmu-miR-7b	MIMAT0000678	uggaagacuugugauuuuguugu	452
mmu-miR-877	MIMAT0004861	guagaggagauggcgcaggg	453
mmu-miR-877*	MIMAT0004862	uguccucuuccuccucccca	454
mmu-miR-881*	MIMAT0004845	cagagagauaacagucacau	455
mmu-miR-882	MIMAT0004847	aggagagaguagcgcauuagu	456
mmu-miR-93	MIMAT0000540	caaagugcuguucgugcagguag	457
mmu-miR-96	MIMAT0000541	uuuggcacuagcacauuuugcu	458
mmu-miR-99a	MIMAT0000131	aaccgguagaucggaucuugug	459

[0157] The devices and methods of the present disclosure have been described with reference to exemplary embodiments. Obviously, modifications and alterations will occur to others upon reading and understanding the preceding detailed description. It is intended that the exemplary embodiments be construed as including all such modifications and alterations insofar as they come within the scope of the appended claims or the equivalents thereof.

What is claimed is:

1. A method of detecting or predicting a lung condition, comprising:
generating a microRNA profile from a biological sample;
identifying at least one differentially expressed microRNA sequence by
comparing the microRNA profile to a reference; and
detecting or predicting the lung condition based on the identity or the
amounts of the at least one differentially expressed microRNA sequence.

2. The method of claim 1, wherein the microRNA profile comprises at least one microRNA sequence selected from the group consisting of miR-135a*, miR-10b, miR-1224-3p, miR-1224-5p, miR-1225-3p, miR-1225-5p, miR-1226*, miR-1227, miR-1228, miR-1229, miR-1234, miR-1237, miR-1238, miR-124, miR-129*, miR-129-3p, miR-136*, miR-187*, miR-188-5p, miR-190b, miR-198, miR-22, miR-220b, miR-300, miR-301b, miR-30e, miR-338-3p, miR-33a*, miR-33b, miR-33b*, miR-34c-3p, miR-34c-5p, miR-363*, miR-371-3p, miR-371-5p, miR-375, miR-377*, miR-423-5p, miR-424, miR-424*, miR-429, miR-448, miR-449a, miR-449b, miR-450b-3p, miR-452, miR-454*, miR-455-3p, miR-483-3p, miR-483-5p, miR-491-3p, miR-491-5p, miR-493, miR-493*, miR-494, miR-497, miR-498, miR-500, miR-503, miR-505, miR-507, miR-513a-3p, miR-513a-5p, miR-513b, miR-513c, miR-515-5p, miR-518b, miR-518c*, miR-518d-3p, miR-518d-5p, miR-518e*, miR-520d-5p, miR-520h, miR-541, miR-545*, miR-548d-3p, miR-548d-5p, miR-551a, miR-551b, miR-552, miR-554, miR-556-5p, miR-557, miR-559, miR-561, miR-564, miR-572, miR-575, miR-576-3p, miR-578, miR-583, miR-586, miR-589, miR-589*, miR-591, miR-595, miR-601, miR-602, miR-609, miR-610, miR-612, miR-613, miR-614, miR-615-3p, miR-616, miR-619, miR-622, miR-623, miR-624*, miR-627, miR-633, miR-634, miR-638, miR-639, miR-640, miR-642, miR-644, miR-647, miR-648, miR-652, miR-654-5p, miR-658, miR-659, miR-662, miR-663, miR-665, miR-671-5p, miR-675, miR-708, miR-708*, miR-744*, miR-760, miR-765, miR-766, miR-767-3p, miR-802, miR-874, miR-876-3p, miR-876-5p, miR-877, miR-877*, miR-885-3p, miR-885-5p, miR-886-3p, miR-890, miR-891b, miR-892b, miR-920, miR-922, miR-923, miR-92b, miR-92b*, miR-933, miR-934, miR-935, miR-936, miR-937, miR-939, miR-940,

hsv1-miR-H1, hsv1-miR-LAT, kshv-miR-K12-12, kshv-miR-K12-3, kshv-miR-K12-3*, kshv-miR-K12-4-5p, kshv-miR-K12-6-5p, kshv-miR-K12-8, kshv-miR-K12-9, kshv-miR-K12-9*, ebv-miR-BART10*, ebv-miR-BART12, ebv-miR-BART13, ebv-miR-BART13*, ebv-miR-BART15, ebv-miR-BART1-5p, ebv-miR-BART16, ebv-miR-BART18-5p, ebv-miR-BART19-3p, ebv-miR-BART19-5p, ebv-miR-BART20-5p, ebv-miR-BART2-5p, ebv-miR-BART3*, ebv-miR-BART5, ebv-miR-BART6-5p, ebv-miR-BART7, ebv-miR-BART7*, ebv-miR-BHRF1-1, ebv-miR-BHRF1-3, hcmv-miR-UL148D, hcmv-miR-UL22A, hcmv-miR-UL22A*, hcmv-miR-UL70-3p, hcmv-miR-UL70-5p, hcmv-miR-US25-1, hcmv-miR-US25-2-3p, hcmv-miR-US25-2-5p, hcmv-miR-US4, hiv1-miR-H1, hiv1-miR-N367, and human orthologs thereof.

3. The method of claim 1, wherein the at least one differentially expressed microRNA sequence is selected from the group consisting of miR-630, miR-134, miR-1225-5p, miR-135a*, miR-150*, miR-22, miR-223, miR-448, miR-451, miR-483-5p, miR-575, miR-638, miR-923, miR-92a-2*, miR-939, miR-940, hsv1-miR-H1, kshv-miR-K12-3, hsv1-miR-LAT, hcmv-miR-UL70-3p, hsv1-miR-H1, hsv1-miR-LAT, kshv-miR-K12-3, hcmv-miR-UL70-3p, and human orthologs thereof.

4. The method of claim 1, wherein the biological sample is plasma and wherein the at least one differentially expressed microRNA sequence is selected from the group consisting of miR-630, miR-134, hcmv-miR-UL70-3p, miR-1225-5p, miR-135a*, miR-150*, miR-22, miR-223, miR-483-5p, miR-575, miR-638, miR-923, miR-939, miR-940, hsv1-miR-H1, hsv1-miR-LAT, kshv-miR-K12-3, and human orthologs thereof.

5. The method of claim 1, wherein the biological sample is plasma and wherein the at least one differentially expressed microRNA sequence is selected from the group consisting of miR-630, miR-134, hcmv-miR-UL70-3p, miR-1225-5p, miR-135a*, miR-150*, miR-483-5p, miR-575, miR-638, hsv1-miR-H1, hsv1-miR-LAT, and human orthologs thereof.

6. The method of claim 1, wherein the biological sample is plasma and at least two differentially expressed microRNA sequences are identified;

wherein at least one of the at least two differentially expressed microRNA sequences is selected from the group consisting of miR-630, hcmv-miR-UL70-3p, miR-1225-5p, miR-134, miR-135a*, miR-150*, miR-483-5p, miR-575, miR-638, hsv1-miR-H1, hsv1-miR-LAT, and human orthologs thereof; and

wherein at least one of the at least two differentially expressed microRNA sequences is selected from the group consisting of miR-451, miR-448, miR-92a-2*, and human orthologs thereof.

7. The method of claim 1, wherein the biological sample is lung tissue and wherein the at least one differentially expressed microRNA sequence is selected from the group consisting of miR-451, miR-923, miR-1225-5p, miR-22, miR-223, miR-638, kshv-miR-K12-3, and human orthologs thereof.

8. The method of claim 1, wherein the biological sample is plasma and wherein the at least one differentially expressed microRNA sequence is selected from the group consisting of miR-940, miR-134, miR-135a*, miR-150*, miR-483-5p, miR-575, miR-939, hsv1-miR-H1, kshv-miR-K12-3, hsv1-miR-LAT, hcmv-miR-UL70-3p, and human orthologs thereof.

9. The method of claim 1, wherein a differentially expressed microRNA sequence is identified by comparing an amount of a particular microRNA sequence in the microRNA profile with an amount of the particular microRNA sequence in the reference, wherein a differentially expressed microRNA sequence is identified when the ratio of the amount in the microRNA profile to the amount in the reference is at least 1.5.

10. The method of claim 9, wherein a differentially expressed microRNA sequence is identified when the ratio of the amount in the microRNA profile to the amount in the reference is at least 3.

11. The method of claim 1, wherein the reference is a table of the amounts of expressed microRNA sequences in a healthy person.

12. A method of detecting or predicting a liver condition, comprising:
generating a microRNA profile from a biological sample;
identifying at least one differentially expressed microRNA sequence by comparing the microRNA profile to a reference; and
detecting or predicting the liver condition based on the identity or the amounts of the at least one differentially expressed microRNA sequence.

13. The method of claim 12, wherein the microRNA profile comprises at least one microRNA sequence selected from the group consisting of miR-122, miR-486, miR-125b-5p, let-7d*, miR-101a, miR-101b, miR-1224, miR-124, miR-125a-3p, miR-125a-5p, miR-127, miR-130a, miR-133a, miR-133b, miR-135a*, miR-141, miR-193, miR-193b, miR-199a-5p, miR-199b*, miR-200c, miR-202-3p, miR-205, miR-22, miR-23b, miR-26a, miR-27b, miR-291a-5p, miR-294*, miR-29b, miR-30a, miR-30c-1*, miR-30e, miR-320, miR-327, miR-339-3p, miR-342-3p, miR-370, miR-375, miR-451, miR-466f-3p, miR-483, miR-494, miR-574-5p, miR-652, miR-671-5p, miR-685, miR-710, miR-711, miR-712, miR-714, miR-720, miR-721, miR-877, miR-877*, miR-882, miR-93, miR-99a, and human orthologs thereof.

14. The method of claim 12, wherein the at least one differentially expressed microRNA sequence comprises miR-122 and human orthologs thereof.

15. The method of claim 12, wherein the at least one differentially expressed microRNA sequence comprises miR-122, miR-486, and human orthologs thereof.

16. The method of claim 15, wherein the ratio of the amount of miR-122 to the amount of miR-486 is greater than 4.0.

17. The method of claim 15, wherein the ratio of the amount of miR-122 to the amount of miR-486 is greater than 6.0.

18. A method of detecting or predicting a neurological condition, comprising:
generating a microRNA profile from a biological sample;
identifying at least one differentially expressed microRNA sequence by comparing the microRNA profile to a reference; and
detecting or predicting the neurological condition based on the identity or the levels of the at least one differentially expressed microRNA sequence.

19. The method of claim 18, wherein the microRNA profile comprises at least one microRNA sequence selected from the group consisting of let-7g, miR-298, miR-1, miR-101a*, miR-101b, miR-1224, miR-126-5p, miR-127, miR-128, miR-129-3p, miR-133b, miR-136, miR-138, miR-138*, miR-139-3p, miR-140, miR-140*, miR-142-3p, miR-143, miR-146a, miR-146b, miR-148b, miR-150, miR-15a*, miR-15b, miR-181b, miR-181d, miR-183, miR-185, miR-186, miR-191*, miR-194, miR-19a, miR-200a, miR-200b, miR-200b*, miR-202-3p, miR-206, miR-208a, miR-21, miR-211, miR-221, miR-222, miR-223, miR-27a, miR-27b*, miR-28*, miR-290-5p, miR-291a-5p, miR-297a, miR-299, miR-29b, miR-29c*, miR-301b, miR-302c*, miR-30c, miR-31, miR-322, miR-323-3p, miR-324-3p, miR-324-5p, miR-326, miR-328, miR-331-5p, miR-341, miR-34b-5p, miR-34c*, miR-369-3p, miR-374, miR-376b, miR-379, miR-380-3p, miR-382, miR-384-5p, miR-409-5p, miR-411, miR-411*, miR-423-5p, miR-425, miR-429, miR-434-5p, miR-450b-3p, miR-451, miR-455, miR-465c-3p, miR-466d-5p, miR-467e*, miR-484, miR-486, miR-487b, miR-497, miR-505, miR-511, miR-539, miR-540-3p, miR-551b, miR-568, miR-654-5p, miR-669a, miR-686, miR-688, miR-699, miR-701, miR-706, miR-708, miR-720, miR-721, miR-744*, miR-760, miR-770-5p, miR-7a, miR-7b, miR-881*, miR-93, miR-96, mghv-miR-M1-6, mghv-miR-M1-9, and human orthologs thereof.

20. A method of detecting or predicting a physiological condition in a patient, comprising:
- generating a microRNA profile from a biological sample provided by the patient;
 - identifying at least one differentially expressed microRNA sequence by comparing the microRNA profile to a reference; and
 - detecting or predicting the physiological condition based on the identity or the amounts of the at least one differentially expressed microRNA sequence;
- wherein the biological sample comprises serum or plasma; and
- wherein
- (i) the biological sample further comprises amniotic fluid and the physiological condition is the health status of a fetus being carried by the patient; or
 - (ii) the biological sample further comprises urine and the physiological condition is the health status of a bladder or a kidney of the patient; or
 - (iii) the biological sample further comprises breast milk and the physiological condition is the health status of a breast of the patient; or
 - (iv) the biological sample further comprises saliva and the physiological condition is the health status of the head and neck region of the patient; or
 - (v) the biological sample further comprises tears and the physiological condition is the health status of an eye of the patient; or
 - (vi) the biological sample further comprises semen and the physiological condition is the health status of a prostate or male reproductive organ of the patient; or
 - (vii) the biological sample further comprises synovial fluid and the physiological condition is the health status of a joint of the patient; or
 - (viii) the biological sample further comprises sweat and the physiological condition is the health status of the skin of the patient; or
 - (ix) the biological sample further comprises cerebrospinal fluid and the physiological condition is the health status of the central nerve system of the patient.

21. A method of using microRNA to monitor a physiological condition, comprising:

- generating a first microRNA profile from a first biological sample of a patient;
- administering a treatment to the patient;
- generating a second microRNA profile from a second biological sample of the patient;
- comparing the second microRNA profile with the first microRNA profile to identify differentially expressed microRNA sequences; and
- identifying a change in the physiological condition based on the identity or the amounts of the differentially expressed microRNA sequences.

22. A method of diagnosing a physiological condition, comprising:

- generating a first microRNA profile from a body fluid sample of a patient;
- generating a second microRNA profile from a body tissue sample of the patient;
- identifying at least two differentially expressed microRNA sequences in the first microRNA profile by comparing the first microRNA profile to a first reference;
- identifying at least two differentially expressed microRNA sequences in the second microRNA profile by comparing the second microRNA profile to a second reference; and
- diagnosing the physiological condition;

wherein the differentially expressed microRNA sequences in the first microRNA profile are different from the differentially expressed microRNA sequences in the second microRNA profile.

23. A method of detecting or predicting a lung condition, comprising:
generating a microRNA profile from a biological sample, wherein the microRNA profile comprises the amount of at least one specific microRNA sequence;
and

comparing the amount of the at least one specific microRNA sequence to a reference to provide information for detecting or predicting the lung condition;

wherein the at least one specific microRNA sequence is selected from the group consisting of miR-630, hcmv-miR-UL70-3p, miR-1225-5p, miR-134, miR-135a*, miR-150*, miR-22, miR-223, miR-448, miR-451, miR-483-5p, miR-575, miR-638, miR-923, miR-92a-2*, miR-939, miR-940, hsv1-miR-H1, kshv-miR-K12-3, hsv1-miR-LAT, hcmv-miR-UL70-3p, hsv1-miR-H1, hsv1-miR-LAT, kshv-miR-K12-3, and human orthologs thereof.

24. The method of claim 23, wherein the microRNA profile comprises at least two specific microRNA sequences; and wherein the at least two specific expressed microRNA sequences are selected from the group consisting of miR-630, miR-134, hcmv-miR-UL70-3p, miR-1225-5p, miR-134, miR-135a*, miR-150*, miR-22, miR-223, miR-483-5p, miR-575, miR-638, miR-923, miR-939, miR-940, hsv1-miR-H1, hsv1-miR-LAT, kshv-miR-K12-3, and human orthologs thereof.

25. The method of claim 24, wherein the at least two specific microRNA sequences comprise hsa-miR-630, hsa-miR-134, hcmv-miR-UL70-3p, hsa-miR-1225-5p, hsa-miR-135a*, hsa-miR-150*, hsa-miR-22, hsa-miR-223, hsa-miR-483-5p, hsa-miR-575, hsa-miR-638, hsa-miR-923, hsa-miR-939, hsa-miR-940, hsv1-miR-H1, hsv1-miR-LAT, and kshv-miR-K12-3.

26. The method of claim 23, wherein the microRNA profile comprises at least two specific microRNA sequences; and wherein the at least two specific microRNA sequences are selected from the group consisting of miR-630, miR-134, hcmv-miR-UL70-3p, miR-1225-5p, miR-135a*, miR-150*, miR-483-5p, miR-575, miR-638, hsv1-miR-H1, hsv1-miR-LAT, and human orthologs thereof.

27. The method of claim 26, wherein the at least two specific microRNA sequences comprise hsa-miR-630, hsa-miR-134, hcmv-miR-UL70-3p, hsa-miR-1225-5p, hsa-miR-135a*, hsa-miR-150*, hsa-miR-483-5p, hsa-miR-575, hsa-miR-638, hsv1-miR-H1, and hsv1-miR-LAT.

28. The method of claim 23, wherein the microRNA profile comprises at least two specific microRNA sequences;

wherein at least one of the at least two specific microRNA sequences is selected from the group consisting of miR-630, hcmv-miR-UL70-3p, miR-1225-5p, miR-134, miR-135a*, miR-150*, miR-483-5p, miR-575, miR-638, hsv1-miR-H1, hsv1-miR-LAT, and human orthologs thereof; and

wherein at least one of the at least two specific microRNA sequences is selected from the group consisting of miR-451, miR-448, and miR-92a-2*.

29. The method of claim 23, wherein the microRNA profile comprises at least two specific microRNA sequences; and wherein the at least two specific microRNA sequences are selected from the group consisting of miR-451, miR-923, miR-1225-5p, miR-22, miR-223, miR-638, kshv-miR-K12-3, and human orthologs thereof.

30. The method of claim 29, wherein the at least two specific microRNA sequences comprise hsa-miR-451, hsa-miR-923, hsa-miR-1225-5p, hsa-miR-22, hsa-miR-223, hsa-miR-638, and kshv-miR-K12-3.

31. The method of claim 23, wherein the at least two specific microRNA sequences are selected from the group consisting of miR-940, miR-134, miR-135a*, miR-150*, miR-483-5p, miR-575, miR-939, hsv1-miR-H1, kshv-miR-K12-3, hsv1-miR-LAT, hcmv-miR-UL70-3p, and human orthologs thereof.

32. The method of claim 31, wherein the at least two specific microRNA sequences comprise hsa-miR-940, hsa-miR-134, hsa-miR-135a*, hsa-miR-150*, hsa-miR-483-5p, hsa-miR-575, hsa-miR-939, hsv1-miR-H1, kshv-miR-K12-3, hsv1-miR-LAT, and hcmv-miR-UL70-3p.

33. A method of detecting or predicting a liver condition, comprising:
generating a microRNA profile from a biological sample, wherein the microRNA profile comprises the amount of at least one specific microRNA sequence;
and

comparing the amount of the at least one specific microRNA sequence to a reference to provide information for detecting or predicting the lung condition;

wherein the at least one specific microRNA sequence is selected from the group consisting of miR-122, miR-486, miR-125b-5p, let-7d*, miR-101a, miR-101b, miR-1224, miR-124, miR-125a-3p, miR-125a-5p, miR-127, miR-130a, miR-133a, miR-133b, miR-135a*, miR-141, miR-193, miR-193b, miR-199a-5p, miR-199b*, miR-200c, miR-202-3p, miR-205, miR-22, miR-23b, miR-26a, miR-27b, miR-291a-5p, miR-294*, miR-29b, miR-30a, miR-30c-1*, miR-30e, miR-320, miR-327, miR-339-3p, miR-342-3p, miR-370, miR-375, miR-451, miR-466f-3p, miR-483, miR-486-3p, miR-486-5p, miR-494, miR-574-5p, miR-652, miR-671-5p, miR-685, miR-710, miR-711, miR-712, miR-714, miR-720, miR-721, miR-877, miR-877*, miR-882, miR-93, miR-99a, and human orthologs thereof.

34. The method of claim 33, wherein the at least one specific microRNA sequence comprises hsa-miR-122.

35. The method of claim 33, wherein the at least one specific microRNA sequence comprises hsa-miR-122 and either hsa-miR-486-3p or hsa-miR-486-5p.

36. The method of claim 35, wherein the ratio of the amount of miR-122 to the amount of miR-486 is greater than 4.0.

37. The method of claim 35, wherein the ratio of the amount of miR-122 to the amount of miR-486 is greater than 6.0.

38. A method according to any preceding claim, comprising recording the output/result of the diagnostic method on a data storage medium.

A) TOTAL RNA AND MICRO RNA ISOLATED FROM SOLID TISSUES

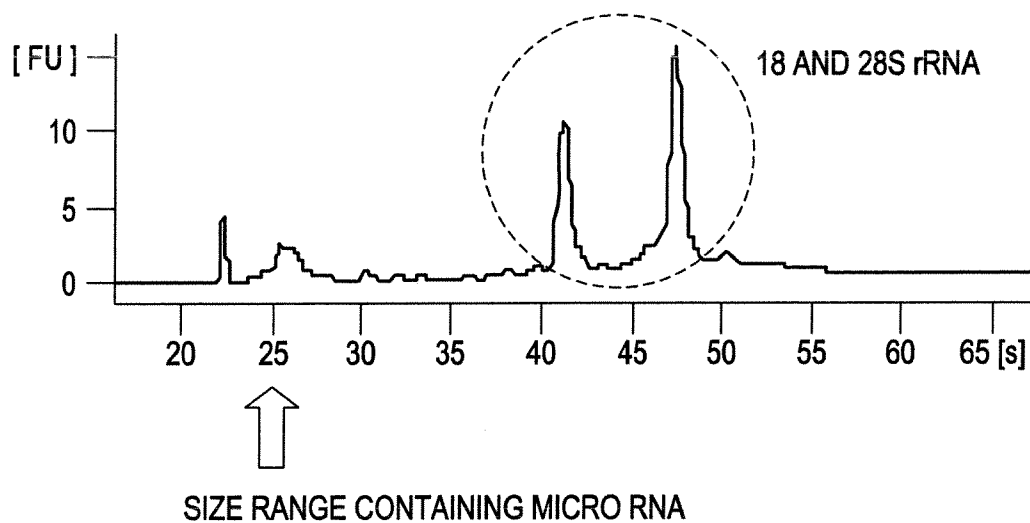


FIG. 1A

B) MICRO RNA ISOLATED FROM LIQUID SAMPLES

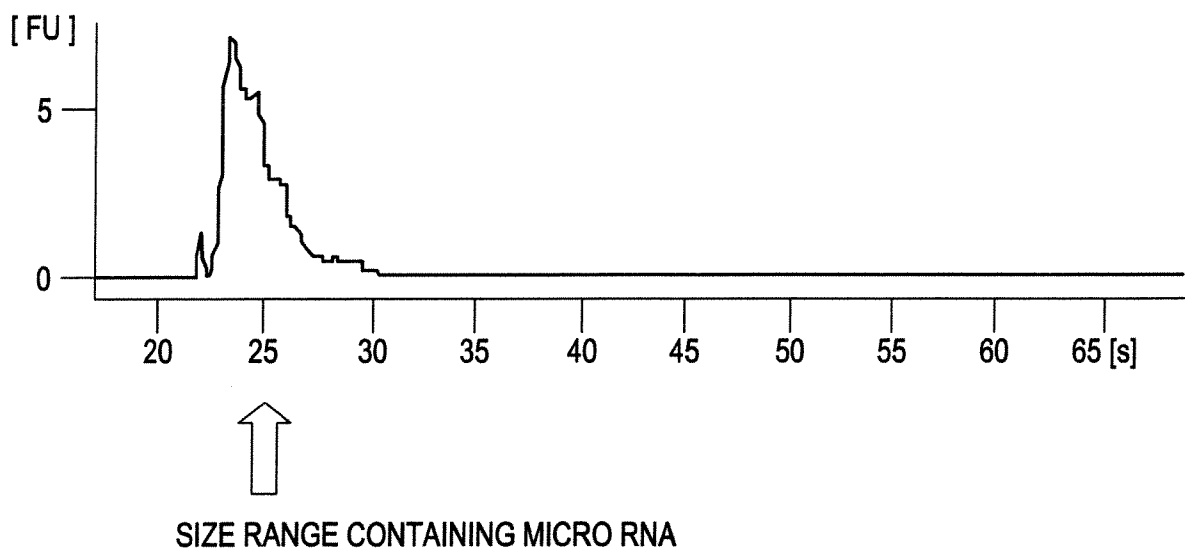


FIG. 1B

FIG. 2.

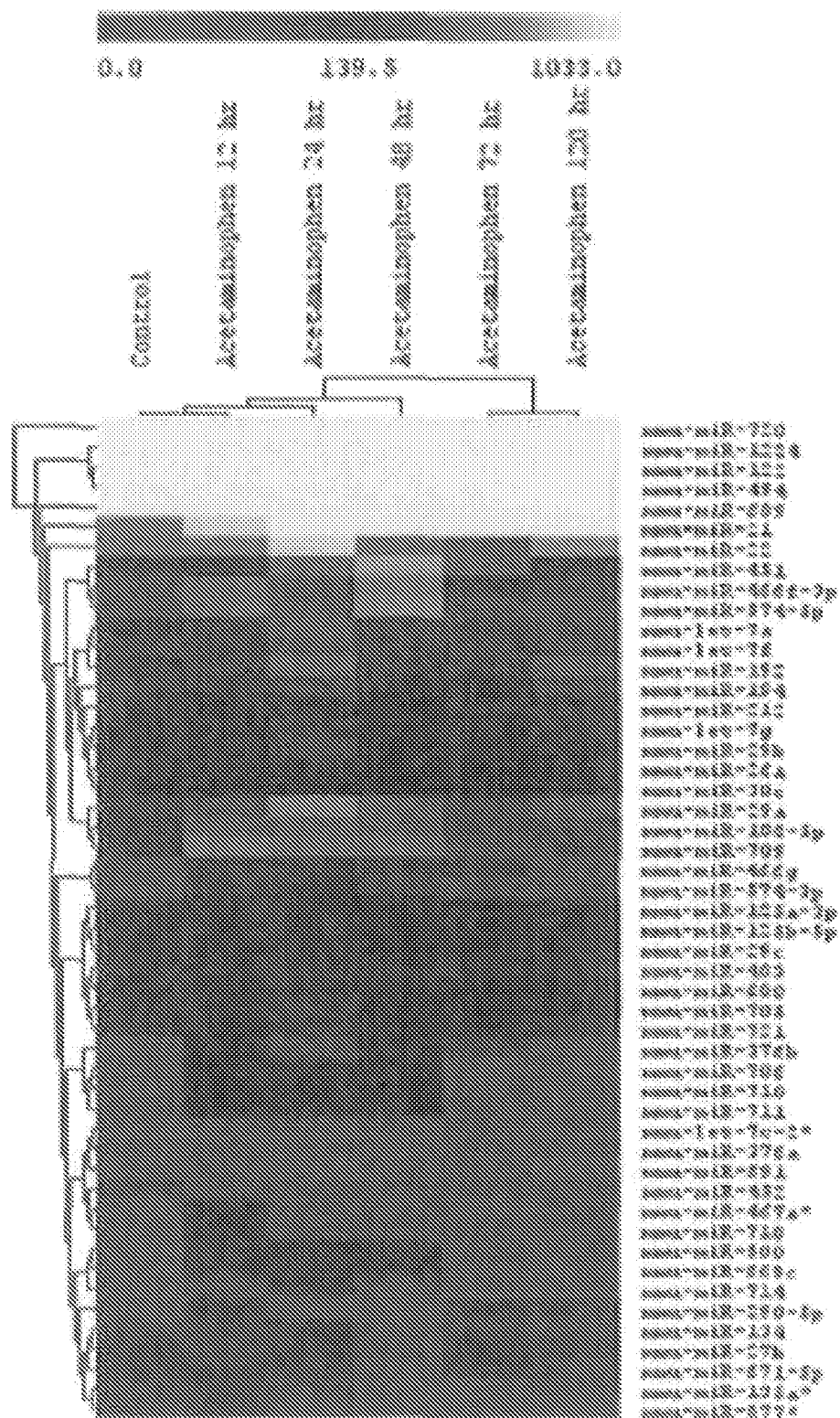
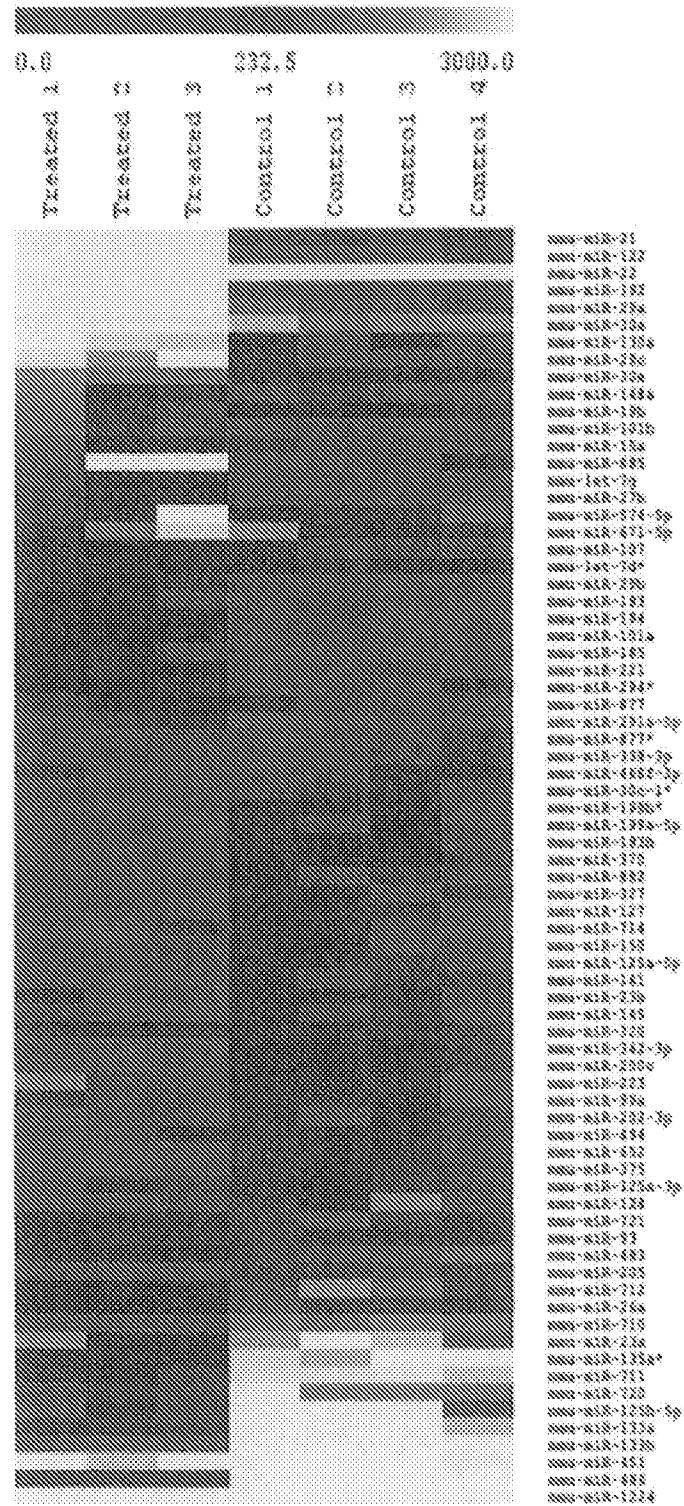


FIG. 3.



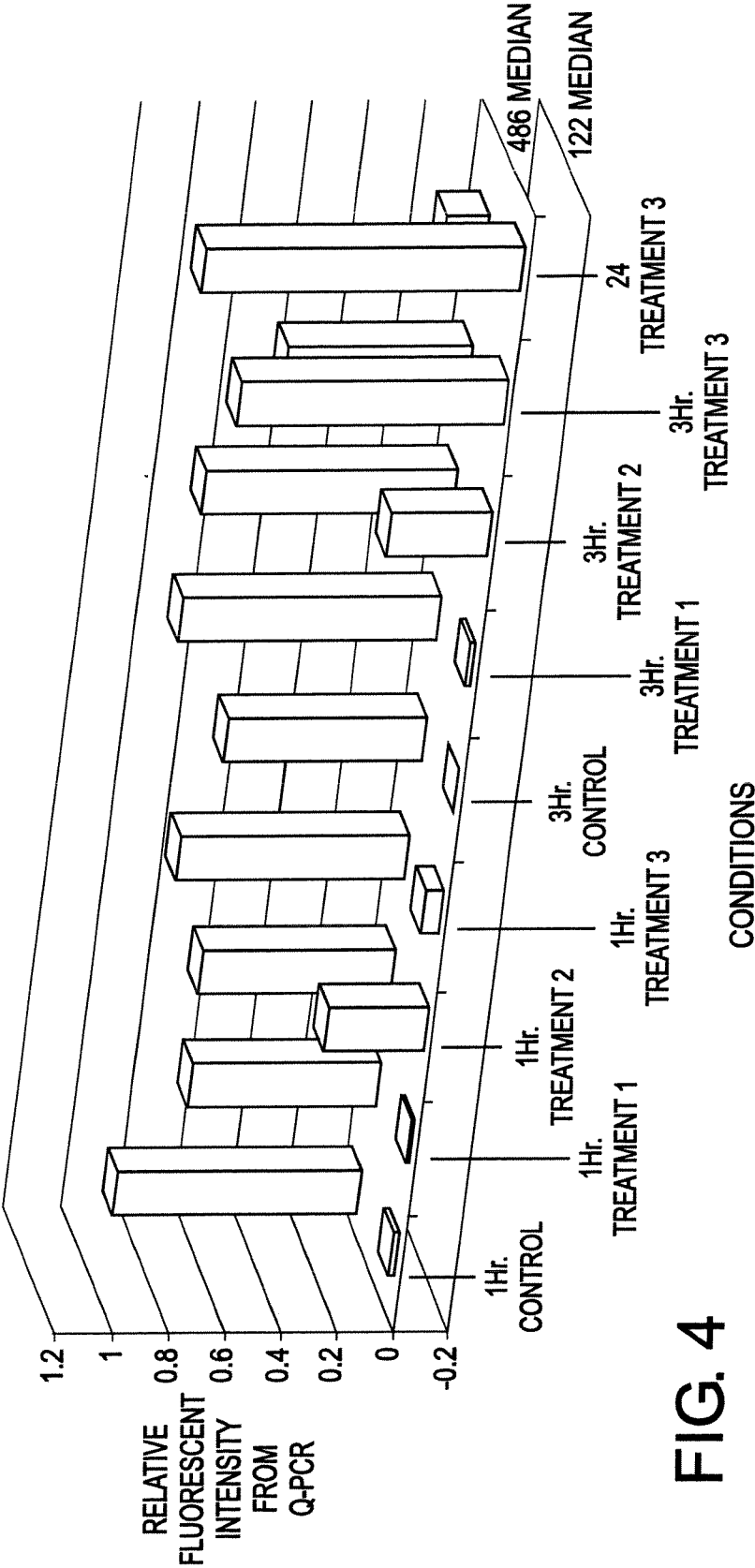


FIG. 4

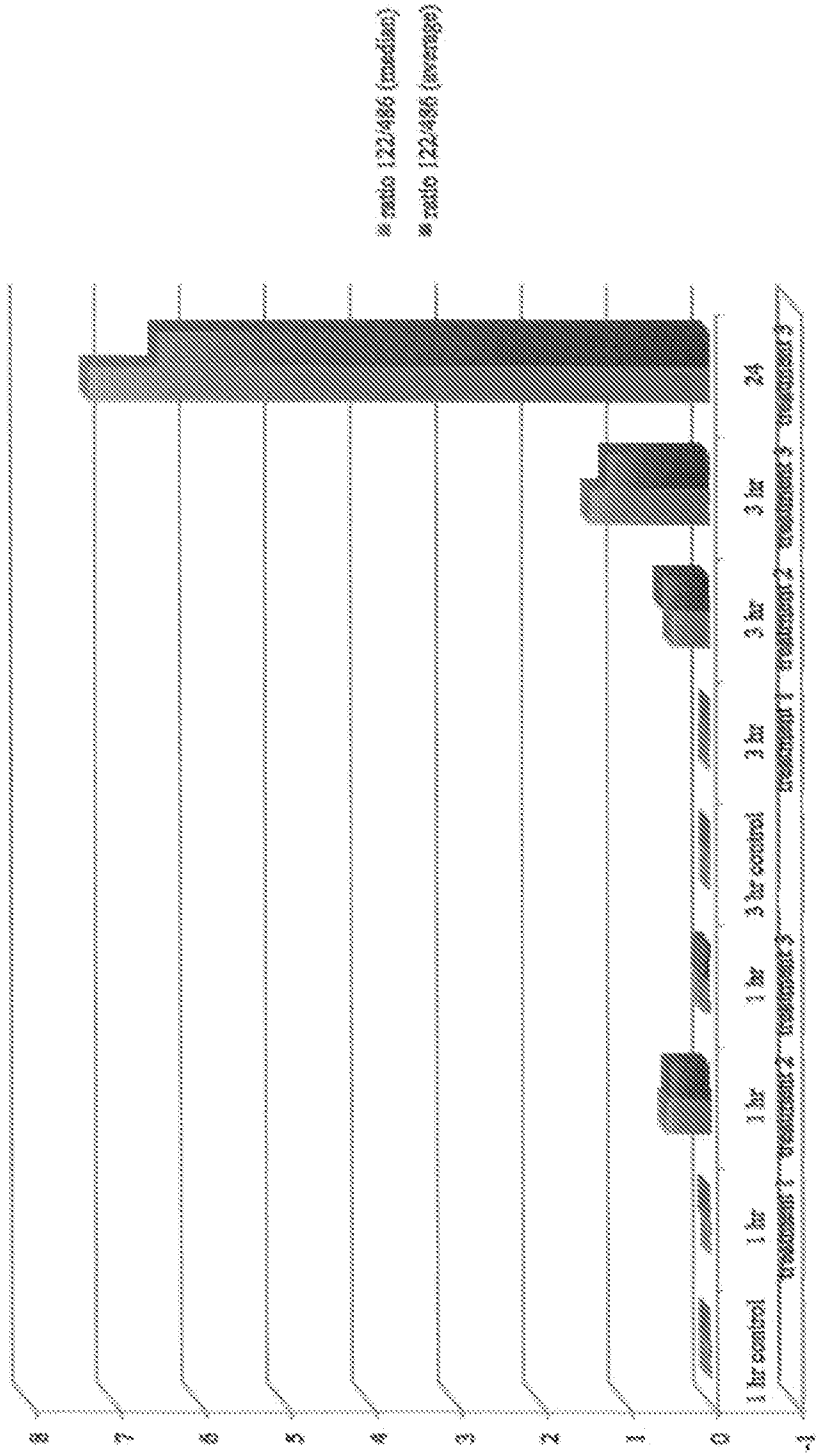


FIG. 5.

FIG. 6.

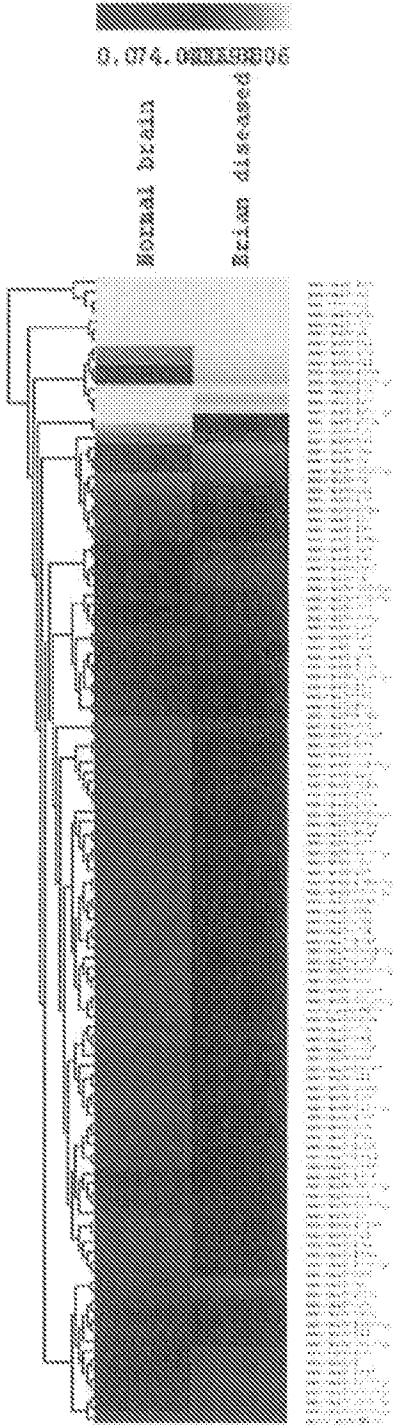


FIG. 7.

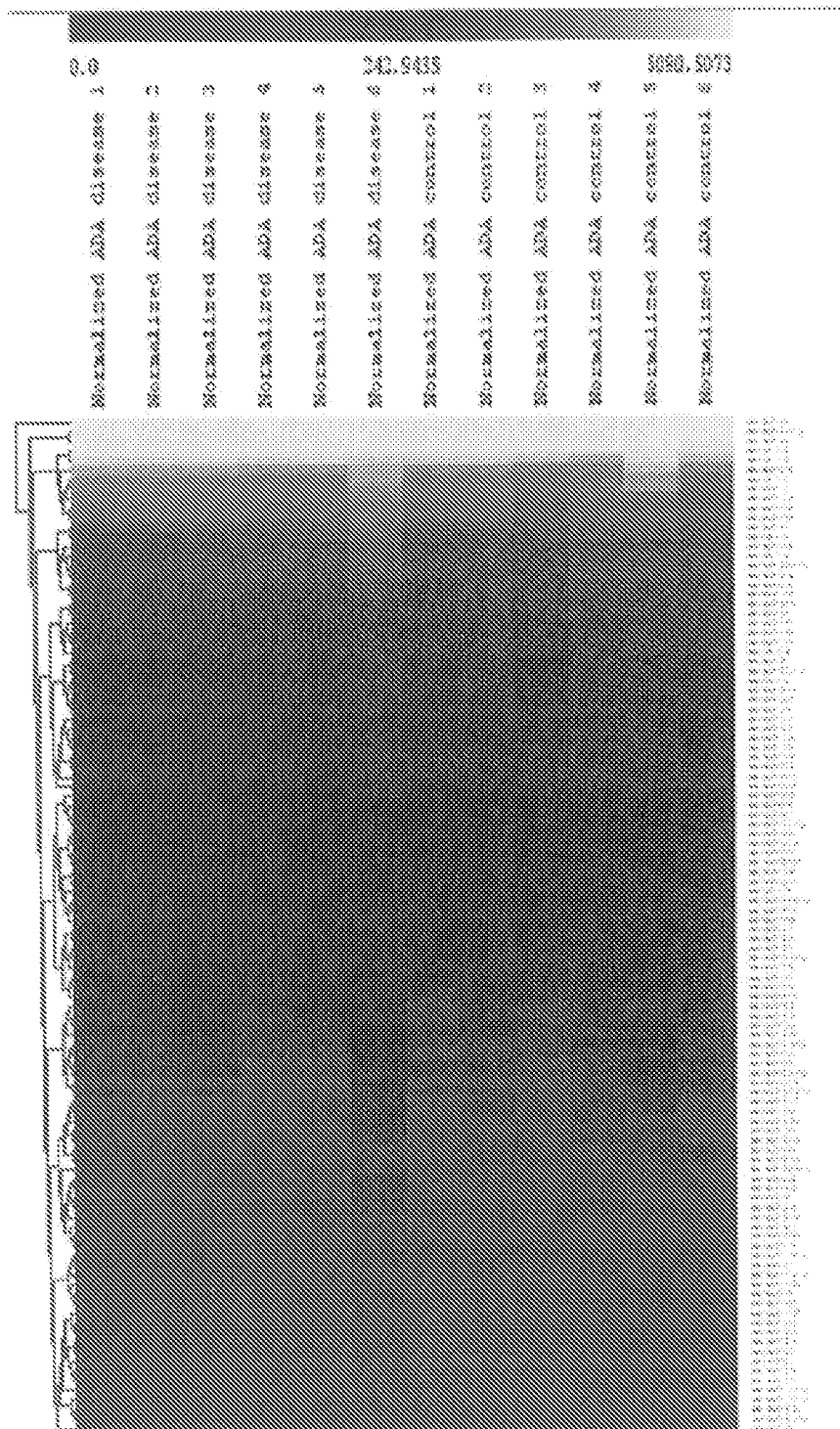


FIG. 8.

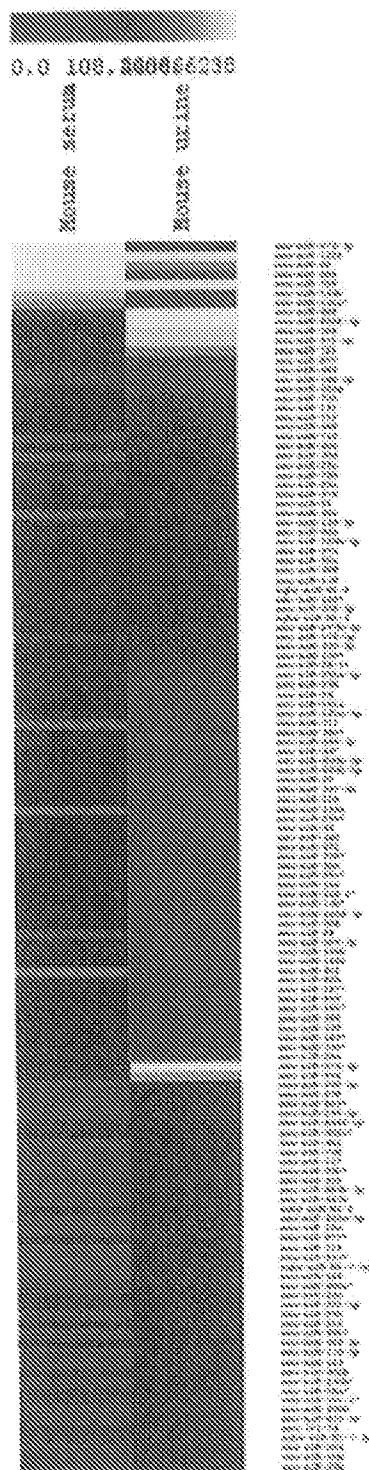


FIG. 9.

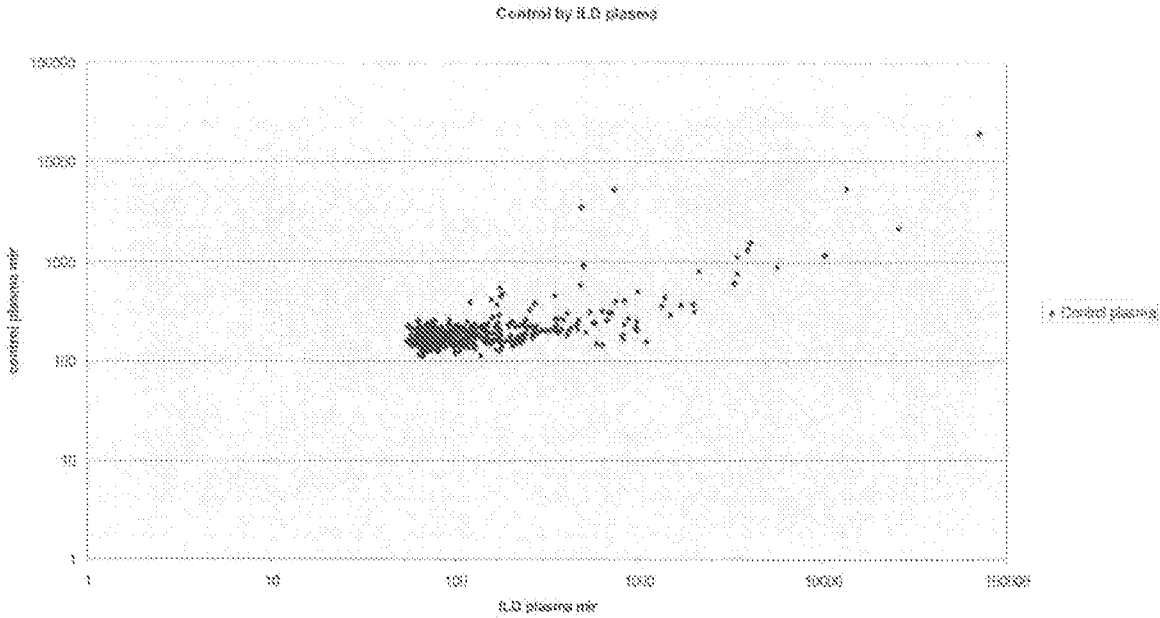


FIG. 10A.

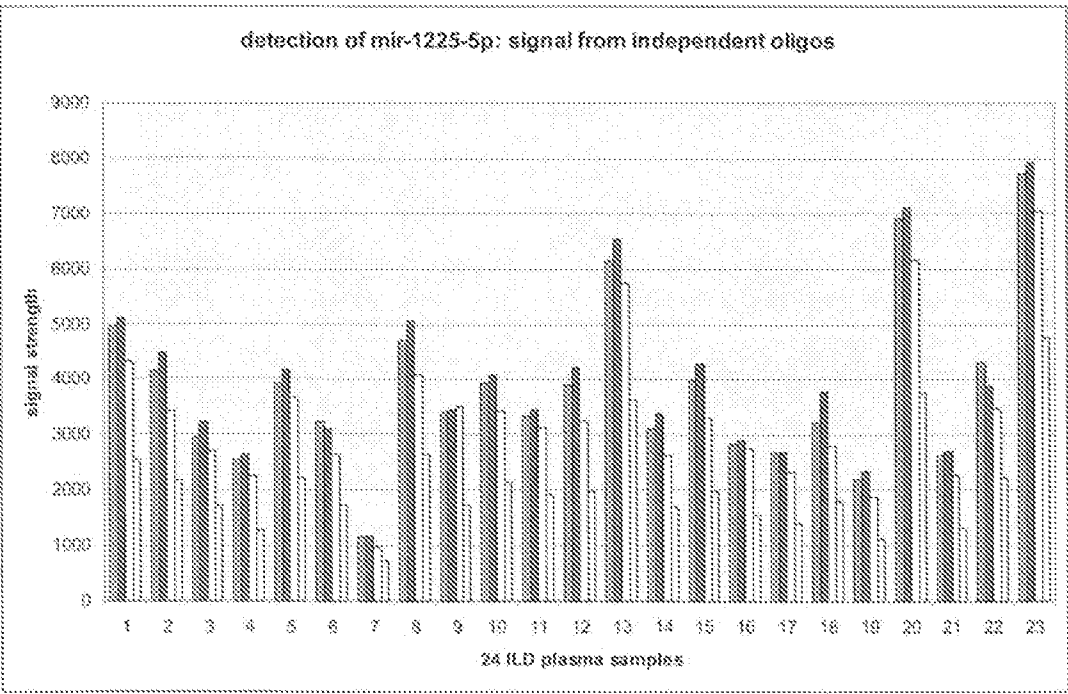


FIG. 10B.

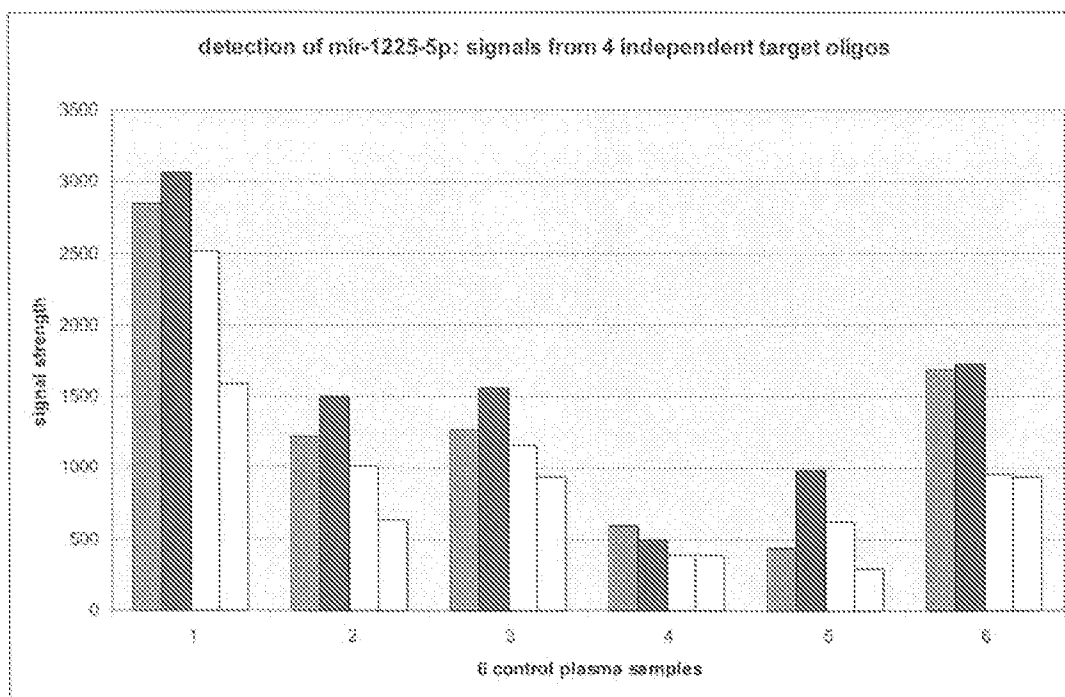


FIG. 11.

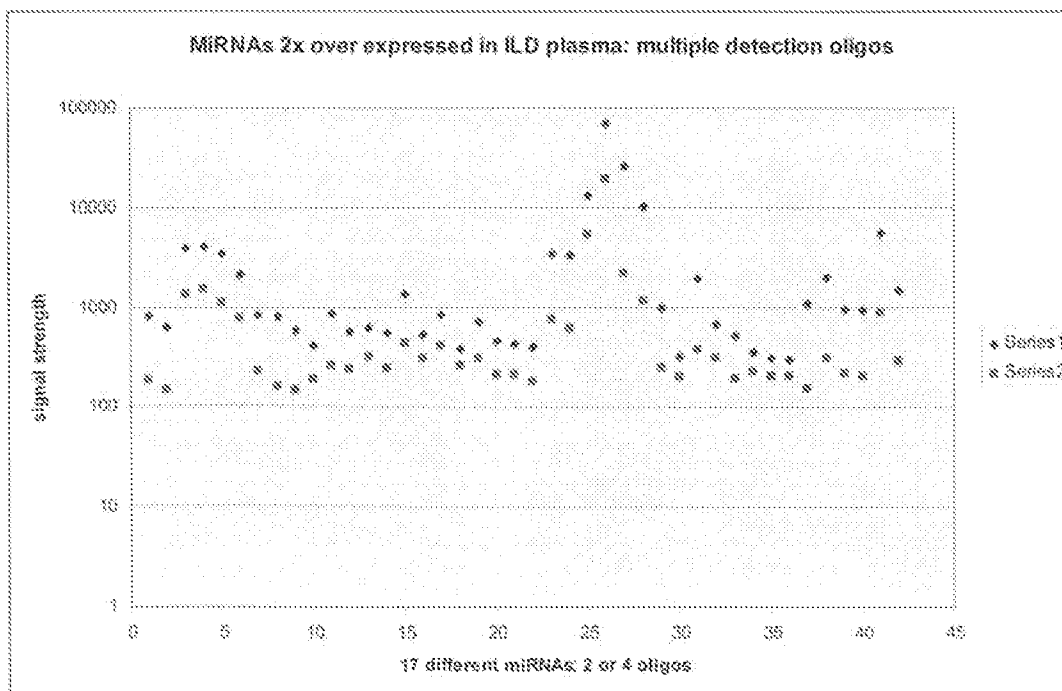


FIG. 12.

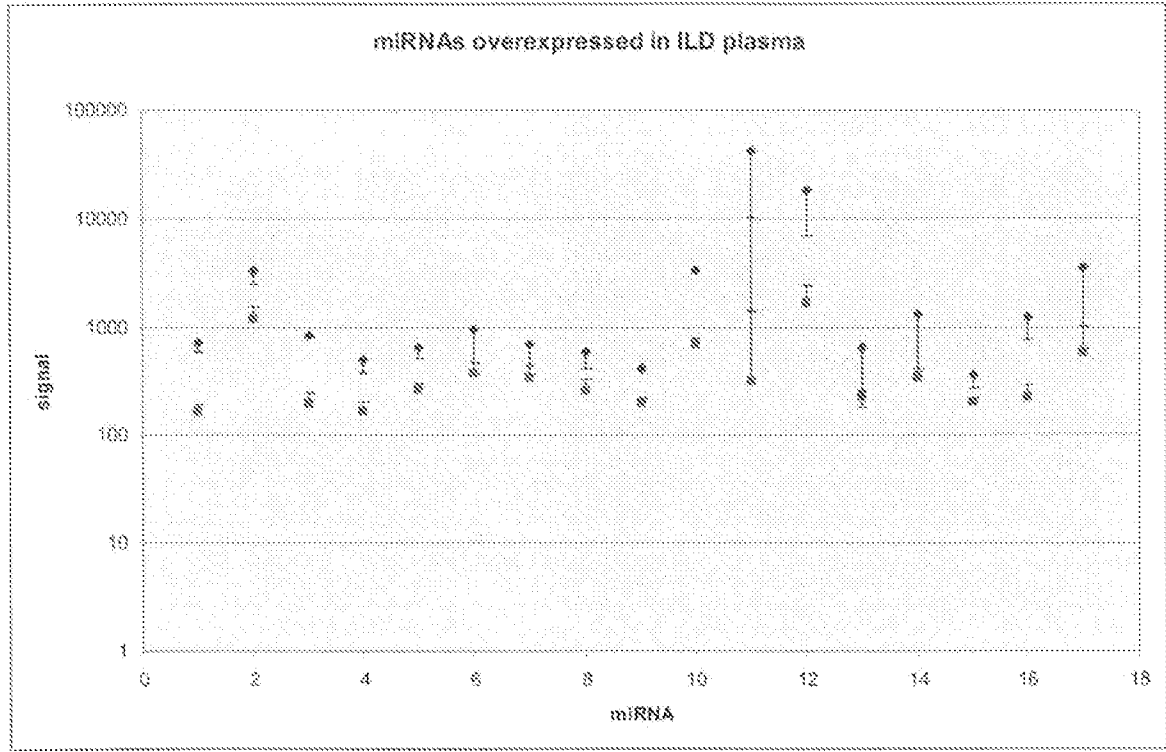


FIG. 13.

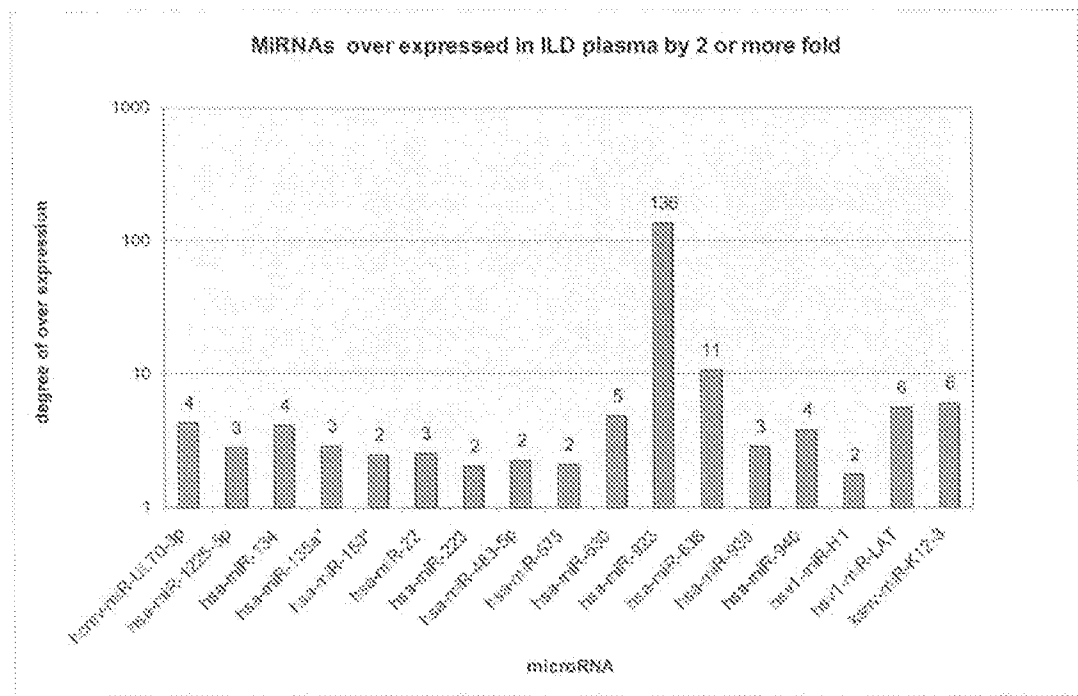


FIG. 14.

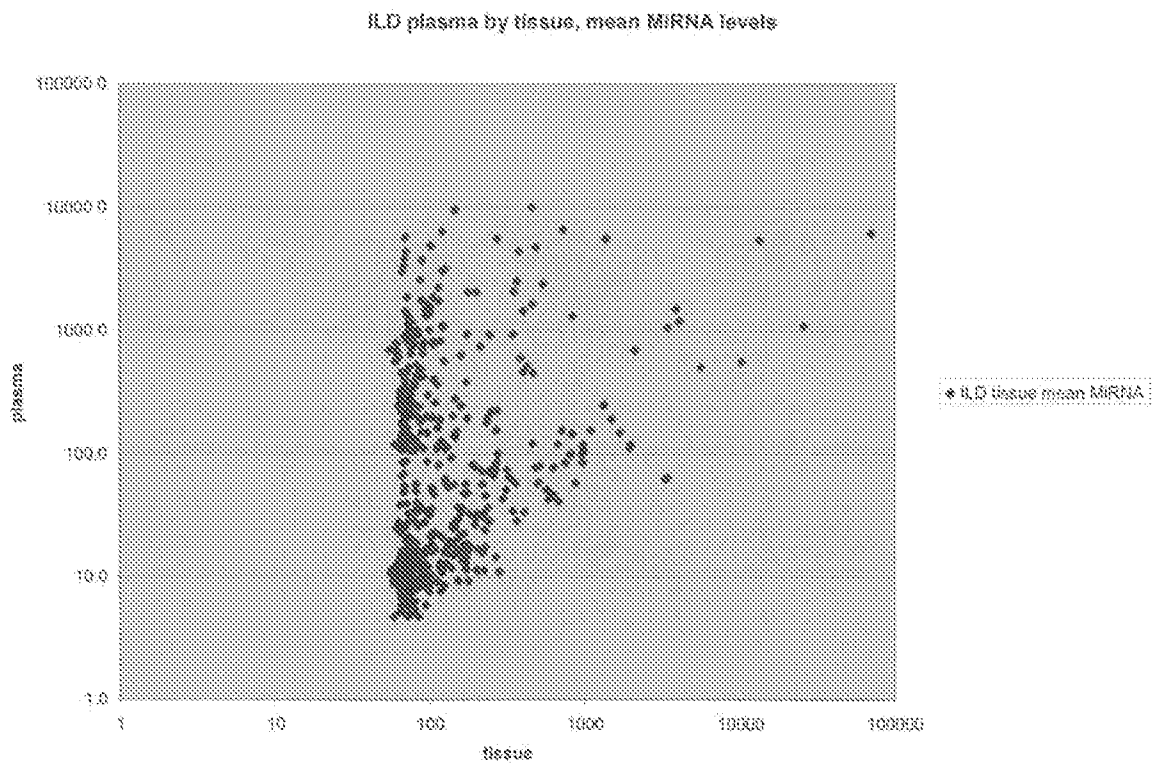


FIG. 15.

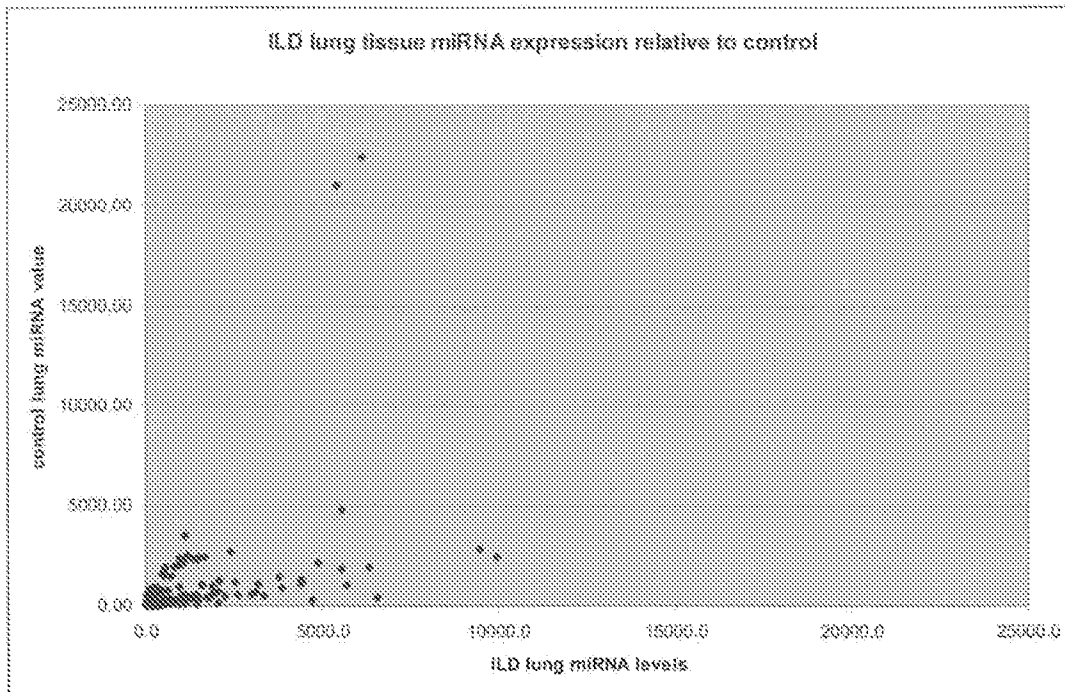


FIG. 16.

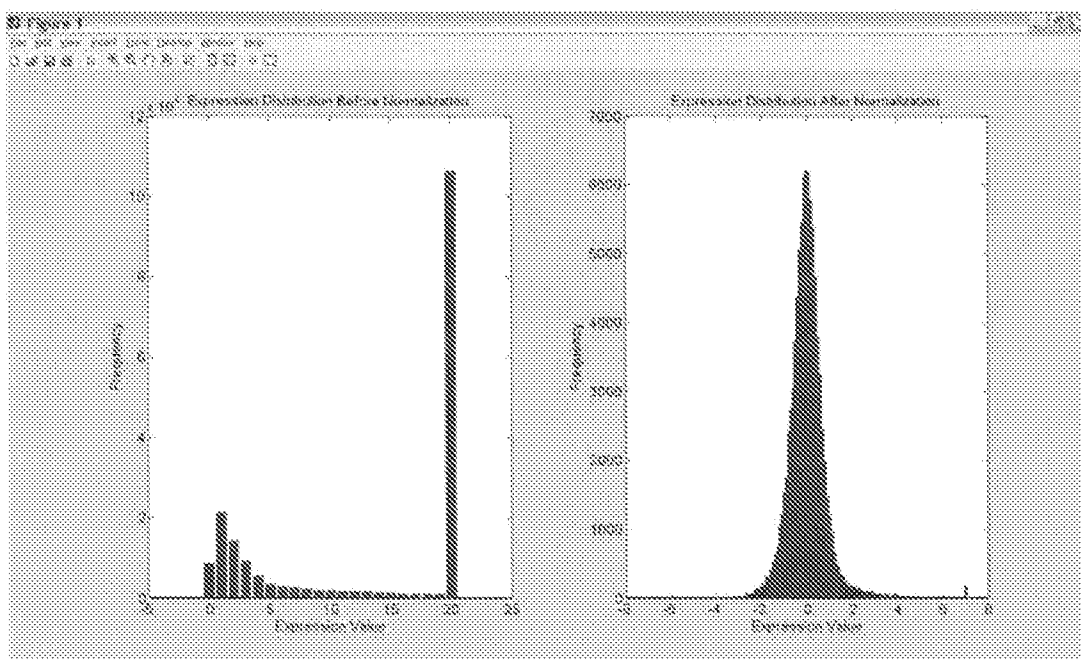


FIG. 17A.

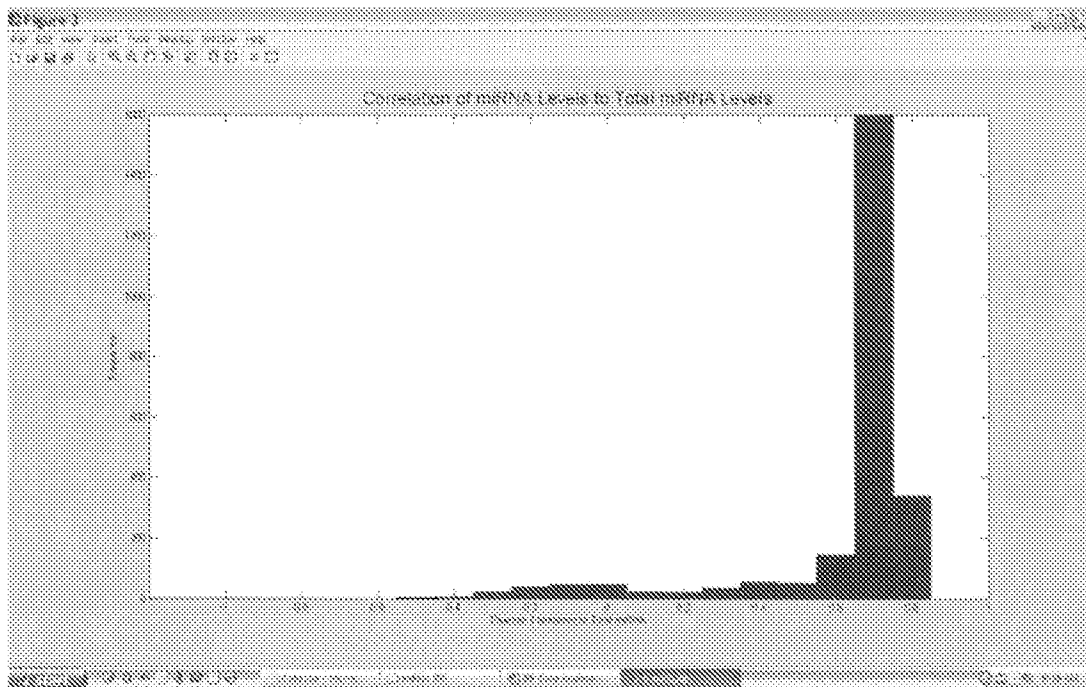


FIG. 17B.

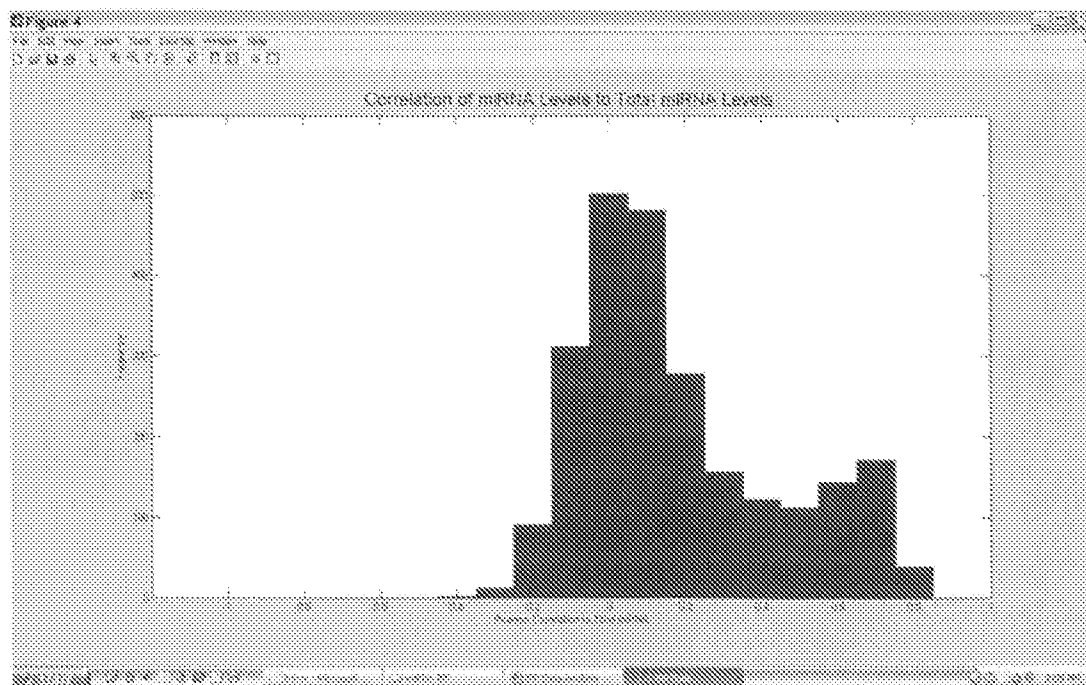


FIG. 18.

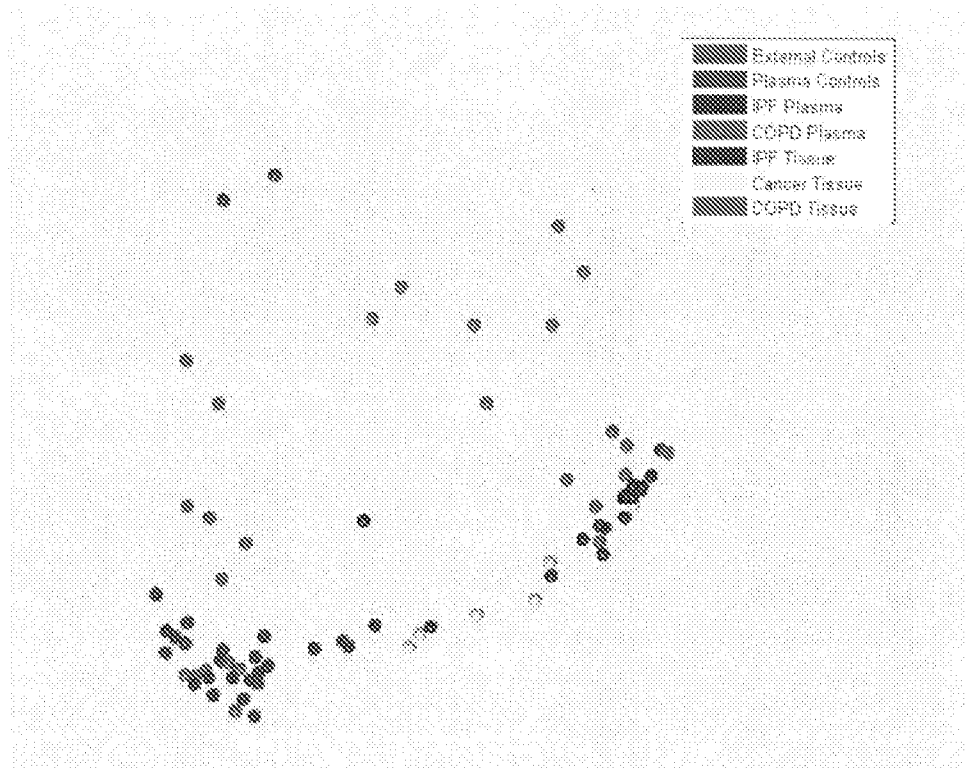


FIG. 19.

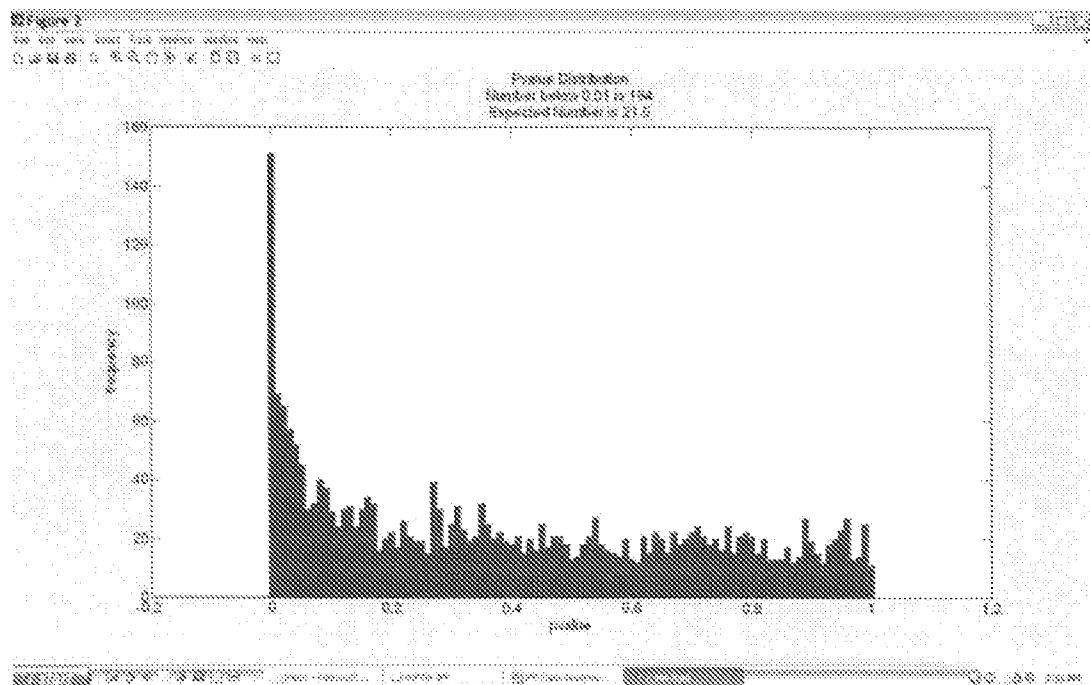


FIG. 20

