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(54) **Titre :** MICRO ARN EXPRIMES PAR DIFFERENCIATION DANS LES MALADIES DU PANCREAS, ET LEUR UTILISATION
(54) **Title:** MICRORNAS DIFFERENTIALLY EXPRESSED IN PANCREATIC DISEASES AND USES THEREOF

(57) **Abrégé/Abstract:**

The present invention concerns methods and compositions for identifying a miRNA profile for a particular condition, such as pancreatic disease, and using the profile in assessing the condition of a patient.



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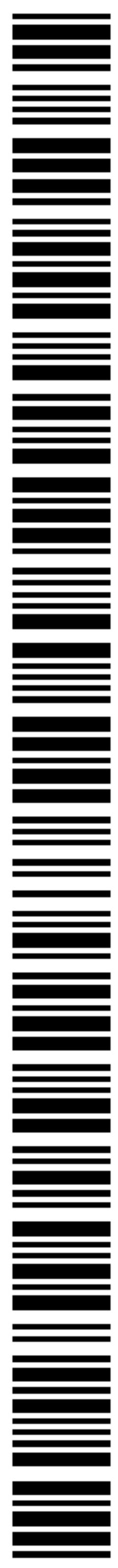
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(54) Title: MICRORNAS DIFFERENTIALLY EXPRESSED IN PANCREATIC DISEASES AND USES THEREOF

(57) Abstract: The present invention concerns methods and compositions for identifying a miRNA profile for a particular condition, such as pancreatic disease, and using the profile in assessing the condition of a patient.



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DESCRIPTION**MICRORNAS DIFFERENTIALLY EXPRESSED IN PANCREATIC****DISEASES AND USES THEREOF****BACKGROUND OF THE INVENTION**5 **I. FIELD OF THE INVENTION**

The present invention relates generally to the field of molecular biology. More particularly, it concerns methods and compositions involving microRNA (miRNAs) molecules. Certain aspects of the invention include applications for miRNAs in diagnostics, therapeutics, and prognostics of pancreatic cancer.

10 **II. BACKGROUND**

In 2001, several groups used a cloning method to isolate and identify a large group of "microRNAs" (miRNAs) from *C. elegans*, *Drosophila*, and human s (Lagos-Quintana et al., 2001; Lau et al., 2001; Lee and Ambros, 2001). Several hundreds of miRNAs have been identified in plants and animals - including humans - which do not
15 appear to have endogenous siRNAs. Thus, while similar to siRNAs, miRNAs are nonetheless distinct.

miRNAs thus far observed have been approximately 21-22 nucleotides in length and they arise from longer precursors, which are transcribed from non-protein-encoding genes. See the review of Carrington et al. (2003). The precursors form
20 structures that fold back on themselves in self-complementary regions; they are then processed by the nuclease Dicer in animals or DCL1 in plants. miRNA molecules interrupt translation through precise or imprecise base-pairing with their targets.

Many miRNAs are conserved among diverse organisms, and this has led to the suggestion that miRNAs are involved in essential biological processes throughout
25 the life span of an organism (Esquela-Kerscher and Slack, 2006). In particular, miRNAs

have been implicated in regulating cell growth and cell and tissue differentiation; cellular processes that are associated with the development of cancer. For instance, lin-4 and let-7 both regulate passage from one larval state to another during *C. elegans* development (Ambros, 2001). miR-14 and bantam are *Drosophila* miRNAs
5 that regulate cell death, apparently by regulating the expression of genes involved in apoptosis (Brennecke *et al.*, 2003, Xu *et al.*, 2003).

Research on miRNAs is increasing as scientists are beginning to appreciate the broad role that these molecules play in the regulation of eukaryotic gene expression. In particular, several recent studies have shown that expression levels of numerous
10 miRNAs are associated with various cancers (reviewed in Esquela-Kerscher and Slack, 2006). Reduced expression of two miRNAs correlates strongly with chronic lymphocytic leukemia in human s, providing a possible link between miRNAs and cancer (Calin *et al.*, 2002). Others have evaluated the expression patterns of large numbers of miRNAs in multiple human cancers and observed differential expression
15 of almost all miRNAs across numerous cancer types (Lu *et al.*, 2005). Most such studies link miRNAs to cancer only by indirect evidence. In contrast, a single study has provided more direct evidence that miRNAs may contribute directly to causing cancer. By forcing the over-expression of six miRNAs in mice, He *et al.* (2005) demonstrated a significant increase in B cell lymphomas.

20 Pancreatic cancer is a particularly challenging disease to diagnose and treat. Each year about 33,000 people in the United States are diagnosed with adenocarcinoma of the pancreas, and about 32,000 people die each year from pancreatic cancer (Jemal *et al.*, 2006). Pancreatic carcinoma ranks as the fourth leading cause of cancer deaths in the United States, and the five year survival rate
25 (~4%) is the lowest among all cancers (Jemal *et al.*, 2006).

Currently, effective diagnostic methods and/or treatments for pancreatic cancer are lacking (Monti *et al.*, 2004). Combinations of chemotherapy and radiation therapy may extend patient survival; but, only the surgical removal of part or all of the pancreas offers a potential cure for pancreatic cancer. Additional diagnostic methods
30 and therapeutic interventions are needed to address this normally incurable disease.

Distinguishing between chronic pancreatitis and pancreatic cancer can be extremely difficult. Symptoms are frequently non-specific and limited to jaundice, weight loss and bruising. Many patients with chronic pancreatitis (non-cancerous condition) exhibit the same symptoms as patients with pancreatic cancer, which are
5 mostly adenocarcinomas of the ductal epithelium (Freelove and Walling, 2006) or pancreatic ductal adenocarcinomas (PDAC). Serum levels of certain proteins may be suggestive of pancreatic adenocarcinoma but are not diagnostic; and the serum tumor marker CA19-9 can help confirm pancreatic cancer diagnosis, but is ineffective as a patient screening tool (Freelove and Walling, 2006). A need exists for additional
10 diagnostic assays that can assess the condition of the pancreas in general and distinguish chronic pancreatitis from pancreatic adenocarcinoma in particular.

SUMMARY OF THE INVENTION

The present invention overcomes these problems in the art by identifying miRNAs that are differentially expressed or mis-regulated in various states of diseased,
15 normal, cancerous, and/or abnormal tissues, including but not limited to normal pancreas, non-cancerous diseased pancreas, and pancreatic cancer (e.g., pancreatic ductal adenocarcinomas (PDAC)). Further, the invention describes a method for diagnosing diseased, normal, cancerous, and/or abnormal tissues, including but not limited to pancreatic cancer and chronic pancreatitis that is based on determining levels
20 (increased or decreased) of selected miRNAs in patient-derived samples. The invention also describes genes that the inventors contemplate are influenced by the expression or lack of expression (mis-regulation) of miRNAs in biological samples. Samples obtained and/or analyzed from patients, including but not limited to patient having or suspected of having PDAC or chronic pancreatitis, or patient suspected of having one or the other
25 condition. These genes and their regulatory pathways represent targets for therapeutic intervention by regulating their expression with miRNAs.

The term "miRNA" is used according to its ordinary and plain meaning and refers to a microRNA molecule found in eukaryotes that is involved in RNA-based gene regulation. See, e.g., Carrington et al, 2003. The term will be used to refer to the single-
30 stranded RNA molecule processed from a precursor. Individual miRNAs have been identified and sequenced

in different organisms, and they have been given names. Names of miRNAs and their sequences related to the present invention are provided herein. The methods and compositions should not be limited to miRNAs identified in the application, as they are provided as examples, not necessarily as limitations of the invention.

5 It is understood that a “synthetic nucleic acid” of the invention means that the nucleic acid does not have a chemical structure or sequence of a naturally occurring nucleic acid. Consequently, it will be understood that the term “synthetic miRNA” refers to a “synthetic nucleic acid” that functions in a cell or under physiological conditions as a naturally occurring miRNA.

10 While many of the embodiments of the invention involve synthetic miRNAs or synthetic nucleic acids, in some embodiments of the invention, the nucleic acid molecule(s) need not be “synthetic.” In certain embodiments, a non-synthetic miRNA employed in methods and compositions of the invention may have the entire sequence and structure of a naturally occurring miRNA precursor or the mature miRNA. For
15 example, non-synthetic miRNAs used in methods and compositions of the invention may not have one or more modified nucleotides or nucleotide analogs. In these embodiments, the non-synthetic miRNA may or may not be recombinantly produced. In particular embodiments, the nucleic acid in methods and/or compositions of the invention is specifically a synthetic miRNA and not a non-synthetic miRNA (that is,
20 not a miRNA that qualifies as “synthetic”); though in other embodiments, the invention specifically involves a non-synthetic miRNA and not a synthetic miRNA. Any embodiments discussed with respect to the use of synthetic miRNAs can be applied with respect to non-synthetic miRNAs, and vice versa.

 It will be understood that the term “naturally occurring” refers to something
25 found in an organism without any intervention by a person; it could refer to a naturally-occurring wildtype or mutant molecule. In some embodiments a synthetic miRNA molecule does not have the sequence of a naturally occurring miRNA molecule. In other embodiments, a synthetic miRNA molecule may have the sequence of a naturally occurring miRNA molecule, but the chemical structure of the
30 molecule, particularly in the part unrelated specifically to the precise sequence (non-sequence chemical structure) differs from chemical structure of the naturally occurring miRNA molecule with that sequence. In some cases, the synthetic miRNA

has both a sequence and non-sequence chemical structure that are not found in a naturally-occurring miRNA. Moreover, the sequence of the synthetic molecules will identify which miRNA is effectively being provided or inhibited; the endogenous miRNA will be referred to as the "corresponding miRNA". Corresponding miRNA sequences that can be used in the context of the invention include, but are not limited to, all or a portion of those sequences in SEQ ID NOs: 1-350, as well as any other miRNA sequence, miRNA precursor sequence, or any sequence complementary thereof. In some embodiments, the sequence is or is derived from or contains all or part of a sequence identified in Table 1 below to target a particular miRNA (or set of miRNAs) that can be used with that sequence.

In some embodiments, it may be useful to know whether a cell expresses a particular miRNA endogenously or whether such expression is affected under particular conditions or when it is in a particular disease state. Thus, in some embodiments of the invention, methods include assaying a cell or a sample containing a cell for the presence of one or more miRNA. Consequently, in some embodiments, methods include a step of generating a miRNA profile for a sample. The term "miRNA profile" refers to a set of data regarding the expression pattern for a plurality of miRNAs (e.g., one or more miRNA from Table 1) in the sample; it is contemplated that the miRNA profile can be obtained using a set of miRNAs, using for example nucleic acid amplification or hybridization techniques well known to one of ordinary skill in the art.

In some embodiments of the invention, a miRNA profile is generated by steps that include: (a) labeling miRNA in the sample; (b) hybridizing miRNA to a number of probes, or amplifying a number of miRNA, and (c) determining miRNA hybridization to the probes or detection miRNA amplification products, wherein a miRNA profile is generated. See, for example, U.S. Provisional Patent Application 60/575,743 and the U.S. Provisional Patent Application 60/649,584, and U.S. Patent Application Serial No. 11/141,707.

Methods of the invention involve diagnosing a patient based on a miRNA expression profile. In certain embodiments, the elevation or reduction in the level of expression of a particular miRNA or set of miRNA in a cell is correlated with a disease state compared to the expression level of that miRNA or set of miRNA in a

normal cell. This correlation allows for diagnostic methods to be carried out when that the expression level of a miRNA is measured in a biological sample being assessed and then compared to the expression level of a normal cell. It is specifically contemplated that miRNA profiles for patients, particularly those suspected of having a particular disease or condition such as pancreatitis or pancreatic cancer, can be generated by evaluating any of or sets of the miRNAs discussed in this application. The miRNA profile that is generated from the patient will be one that provides information regarding the particular disease or condition. In many embodiments, the miRNA profile is generated using miRNA hybridization or amplification, (*e.g.*, array hybridization or RT-PCR). In certain aspects, a miRNA profile can be used in conjunction with other diagnostic tests, such protein profiles in the serum, *e.g.*, CA19-9 detection.

Embodiments of the invention include methods for diagnosing and/or assessing a condition in a patient comprising measuring an expression profile of one or more miRNAs in a sample from the patient. The difference in the expression profile in the sample from the patient and a reference expression profile, such as an expression profile from a normal or non-pathologic sample, is indicative of a pathologic, disease, or cancerous condition. A miRNA or probe set comprising or identifying a segment of a corresponding miRNA can include all or part of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, 200, 250, 300, 350, or any integer or range derivable there between, of a miRNA or a probe listed in Table 1 below.

In certain aspects, the methods for diagnosing a condition in a patient comprise measuring an expression profile of one or more miRNAs in a sample from the patient, wherein a difference in the expression profile in the sample from the patient and an expression profile of a normal sample is indicative of a pathological condition; wherein the miRNA is one or more of hsa-let-7a, hsa-let-7b, hsa-let-7c, hsa-let-7d, hsa-let-7e, hsa-let-7f, hsa-let-7g, hsa-let-7i, hsa-miR-100, hsa-miR-101, hsa-miR-103, hsa-miR-106a, hsa-miR-106b, hsa-miR-107, hsa-miR-10a, hsa-miR-125a, hsa-miR-125b, hsa-miR-130a, hsa-miR-130b, hsa-miR-134, hsa-miR-140, hsa-miR-141, hsa-miR-143, hsa-miR-145, hsa-miR-146a, hsa-miR-148a, hsa-miR-148b,

hsa-miR-150, hsa-miR-154, hsa-miR-155, hsa-miR-15b, hsa-miR-17-5p, hsa-miR-18a, hsa-miR-181b, hsa-miR-182, hsa-miR-186, hsa-miR-196a, hsa-miR-196b, hsa-miR-199a, hsa-miR-199a-AS, hsa-miR-19a, hsa-miR-19b, hsa-miR-200a, hsa-miR-200b, hsa-miR-200c, hsa-miR-203, hsa-miR-21, hsa-miR-210, hsa-miR-214, hsa-miR-216, hsa-miR-217, hsa-miR-221, hsa-miR-222, hsa-miR-223, hsa-miR-224, hsa-miR-23a, hsa-miR-24, hsa-miR-25, hsa-miR-26a, hsa-miR-26b, hsa-miR-27a, hsa-miR-27b, hsa-miR-28, hsa-miR-29a, hsa-miR-29b, hsa-miR-29c, hsa-miR-30a-3p, hsa-miR-30a-5p, hsa-miR-30b, hsa-miR-30c, hsa-miR-30d, hsa-miR-30e-3p, hsa-miR-30e-5p, hsa-miR-31, hsa-miR-331, hsa-miR-335, hsa-miR-365, hsa-miR-368, hsa-miR-374, hsa-miR-375, hsa-miR-376a, hsa-miR-377, hsa-miR-379, hsa-miR-429, hsa-miR-93, hsa-miR-95, hsa-miR-96, hsa-miR-98, hsa-miR-99a, hsa-miR-99b, hsa-miR-452, hsa-miR-494, hsa-miR-497, miR-205, or ambi-miR-7105.

In a further aspect, the miRNA is one or more of miR-205, miR-29c, miR-216, miR-217, miR-375, miR-143, miR-145, miR-146a, miR-148a, miR-196b, miR-93, miR-96, miR-31, miR-210, miR-148b, miR-196a, miR-141, miR-18a, miR-203, miR-150, miR-155, miR-130b, miR-221, miR-222, miR-223, or miR-224.

In still further aspects of the invention the miRNA is miR-196a, miR-217, or both miR-196a and miR-217.

Embodiments of the invention include methods wherein differential expression of one or more miRNA is indicative of pancreatitis, wherein the miRNA is one or more of hsa-let-7a, hsa-let-7b, hsa-let-7c, hsa-let-7d, hsa-let-7e, hsa-let-7f, hsa-let-7g, hsa-let-7i, hsa-miR-100, hsa-miR-101, hsa-miR-10a, hsa-miR-125a, hsa-miR-125b, hsa-miR-130a, hsa-miR-130b, hsa-miR-141, hsa-miR-143, hsa-miR-145, hsa-miR-146a, hsa-miR-148a, hsa-miR-148b, hsa-miR-150, hsa-miR-18a, hsa-miR-182, hsa-miR-186, hsa-miR-199a hsa-miR-199a-AS, hsa-miR-19a, hsa-miR-19b, hsa-miR-200a, hsa-miR-200b, hsa-miR-200c, hsa-miR-203, hsa-miR-210, hsa-miR-214, hsa-miR-216, hsa-miR-217, hsa-miR-222, hsa-miR-223, hsa-miR-24, hsa-miR-25, hsa-miR-26a, hsa-miR-26b, hsa-miR-27b, hsa-miR-28, hsa-miR-29a, hsa-miR-29b, hsa-miR-29c, hsa-miR-30a-3p, hsa-miR-30a-5p, hsa-miR-30b, hsa-miR-30c, hsa-miR-30d, hsa-miR-30e-3p, hsa-miR-30e-5p, hsa-miR-31, hsa-miR-335, hsa-miR-365, hsa-miR-368, hsa-miR-374, hsa-miR-376a, hsa-miR-429, hsa-miR-95, hsa-miR-96, hsa-miR-98, hsa-miR-99a, hsa-miR-497, or ambi-miR-7105.

In certain aspects, an increase in expression of one or more miRNA in a patient sample is indicative of pancreatitis, wherein the miRNA is one or more of hsa-let-7i, hsa-miR-100, hsa-miR-10a, hsa-miR-125a, hsa-miR-125b, hsa-miR-143, hsa-miR-145, hsa-miR-146a, hsa-miR-150, hsa-miR-18a, hsa-miR-199a, hsa-miR-199a-AS, hsa-miR-210, hsa-miR-214, hsa-miR-222, hsa-miR-223, hsa-miR-24, hsa-miR-31, hsa-miR-99a, or hsa-miR-497.

In further aspects, a decrease in expression of one or more miRNA in a patient sample is indicative of pancreatitis, wherein the miRNA is one or more of hsa-let-7a, hsa-let-7b, hsa-let-7c, hsa-let-7d, hsa-let-7e, hsa-let-7f, hsa-let-7g, hsa-miR-101, hsa-miR-130a, hsa-miR-130b, hsa-miR-141, hsa-miR-148a, hsa-miR-148b, hsa-miR-182, hsa-miR-186, hsa-miR-19a, hsa-miR-19b, hsa-miR-200a, hsa-miR-200b, hsa-miR-200c, hsa-miR-203, hsa-miR-216, hsa-miR-217, hsa-miR-25, hsa-miR-26a, hsa-miR-26b, hsa-miR-27b, hsa-miR-28, hsa-miR-29a, hsa-miR-29b, hsa-miR-29c, hsa-miR-30a-3p, hsa-miR-30a-5p, hsa-miR-30b, hsa-miR-30c, hsa-miR-30d, hsa-miR-30e-3p, hsa-miR-30e-5p, hsa-miR-335, hsa-miR-365, hsa-miR-368, hsa-miR-374, hsa-miR-376a, hsa-miR-429, hsa-miR-95, hsa-miR-96, hsa-miR-98, or ambi-miR-7105.

In still further aspects, differential expression of one or more miRNA is indicative of pancreatic cancer, wherein the miRNA is one or more of hsa-let-7a, hsa-let-7b, hsa-let-7c, hsa-let-7d, hsa-let-7f, hsa-let-7g, hsa-let-7i, hsa-miR-100, hsa-miR-101, hsa-miR-103, hsa-miR-106b, hsa-miR-107, hsa-miR-10a, hsa-miR-125a, hsa-miR-125b, hsa-miR-130a, hsa-miR-130b, hsa-miR-134, hsa-miR-140, hsa-miR-141, hsa-miR-143, hsa-miR-145, hsa-miR-146a, hsa-miR-148a, hsa-miR-148b, hsa-miR-150, hsa-miR-154, hsa-miR-155, hsa-miR-18a, hsa-miR-181b, hsa-miR-182, hsa-miR-186, hsa-miR-196a, hsa-miR-196b, hsa-miR-199a, hsa-miR-199a-AS, hsa-miR-19a, hsa-miR-19b, hsa-miR-200a, hsa-miR-200b, hsa-miR-200c, hsa-miR-203, hsa-miR-21, hsa-miR-210, hsa-miR-214, hsa-miR-216, hsa-miR-217, hsa-miR-221, hsa-miR-222, hsa-miR-223, hsa-miR-224, hsa-miR-23a, hsa-miR-24, hsa-miR-26a, hsa-miR-26b, hsa-miR-27a, hsa-miR-27b, hsa-miR-29c, hsa-miR-30a-3p, hsa-miR-30a-5p, hsa-miR-30b, hsa-miR-30c, hsa-miR-30d, hsa-miR-30e-3p, hsa-miR-30e-5p, hsa-miR-31, hsa-miR-331, hsa-miR-335, hsa-miR-365, hsa-miR-368, hsa-miR-374, hsa-miR-375, hsa-miR-376a, hsa-miR-377, hsa-miR-379, hsa-miR-429, hsa-miR-93, hsa-miR-95,

hsa-miR-96, hsa-miR-99b, hsa-miR-452, hsa-miR-494, hsa-miR-497, miR-205, or ambi-miR-7105.

In certain aspects, an increase in expression of one or more miRNA is indicative of pancreatic cancer, wherein the miRNA is one or more of hsa-let-7i, hsa-miR-100, hsa-miR-103, hsa-miR-106b, hsa-miR-107, hsa-miR-10a, hsa-miR-125a, hsa-miR-125b, hsa-miR-140, hsa-miR-143, hsa-miR-145, hsa-miR-146a, hsa-miR-150, hsa-miR-155, hsa-miR-18a, hsa-miR-181b, hsa-miR-196a, hsa-miR-196b, hsa-miR-199a, hsa-miR-199a-AS, hsa-miR-203, hsa-miR-21, hsa-miR-210, hsa-miR-214, hsa-miR-221, hsa-miR-222, hsa-miR-223, hsa-miR-224, hsa-miR-23a, hsa-miR-24, hsa-miR-27a, hsa-miR-31, hsa-miR-331, hsa-miR-93, hsa-miR-99b, hsa-miR-452, hsa-miR-497, or ambi-miR-7105.

In a further aspect, a decrease in expression of one or more miRNA is indicative of pancreatic cancer, wherein the miRNA is one or more of hsa-let-7a, hsa-let-7b, hsa-let-7c, hsa-let-7d, hsa-let-7e, hsa-let-7f, hsa-let-7g, hsa-miR-101, hsa-miR-130a, hsa-miR-130b, hsa-miR-134, hsa-miR-141, hsa-miR-148a, hsa-miR-148b, hsa-miR-154, hsa-miR-182, hsa-miR-186, hsa-miR-19a, hsa-miR-19b, hsa-miR-200a, hsa-miR-200b, hsa-miR-200c, hsa-miR-216, hsa-miR-217, hsa-miR-26a, hsa-miR-26b, hsa-miR-27b, hsa-miR-29c, hsa-miR-30a-3p, hsa-miR-30a-5p, hsa-miR-30b, hsa-miR-30c, hsa-miR-30d, hsa-miR-30e-3p, hsa-miR-30e-5p, hsa-miR-335, hsa-miR-365, hsa-miR-368, hsa-miR-374, hsa-miR-375, hsa-miR-376a, hsa-miR-377, hsa-miR-379, hsa-miR-429, hsa-miR-95, hsa-miR-96, or hsa-miR-494.

In still another aspect, pancreatitis is distinguished from pancreatic cancer by differential expression of one or more of hsa-let-7b, hsa-let-7e, hsa-miR-103, hsa-miR-106a, hsa-miR-106b, hsa-miR-107, hsa-miR-125b, hsa-miR-130a, hsa-miR-130b, hsa-miR-141, hsa-miR-146a, hsa-miR-148a, hsa-miR-154, hsa-miR-155, hsa-miR-15b, hsa-miR-17-5p, hsa-miR-18a, hsa-miR-181b, hsa-miR-196a, hsa-miR-196b, hsa-miR-199a-AS, hsa-miR-203, hsa-miR-21, hsa-miR-210, hsa-miR-216, hsa-miR-217, hsa-miR-221, hsa-miR-222, hsa-miR-224, hsa-miR-23a, hsa-miR-24, hsa-miR-25, hsa-miR-27a, hsa-miR-28, hsa-miR-29a, hsa-miR-29c, hsa-miR-30a-3p, hsa-miR-30a-5p, hsa-miR-30b, hsa-miR-30c, hsa-miR-30d, hsa-miR-30e-5p, hsa-miR-331, hsa-miR-368, hsa-miR-375, hsa-miR-377, hsa-miR-379, hsa-miR-93, hsa-miR-452, hsa-miR-494, hsa-miR-497, or ambi-miR-7105.

A sample may be taken from a patient having or suspected of having a disease or pathological condition. In certain aspects, the sample can be, but is not limited to tissue (*e.g.*, biopsy, particularly fine needle biopsy), blood, serum, plasma, or a pancreatic juice samples. The sample can be fresh, frozen, fixed (*e.g.*, formalin
5 fixed), or embedded (*e.g.*, paraffin embedded). In a particular aspect, the sample can be a pancreatic sample.

Methods of the invention can be used to diagnose or assess a pathological condition. In certain aspect, the condition is a non-cancerous condition, such as pancreatitis or chronic pancreatitis. In other aspects the condition is cancerous
10 condition, such as pancreatic cancer and particularly pancreatic ductal adenocarcinoma (PDAC).

The methods can further comprise one or more of steps including: (a) obtaining a sample from the patient, (b) isolating nucleic acids from the sample, (c) labeling the nucleic acids isolated from the sample, and (d) hybridizing the labeled
15 nucleic acids to one or more probes. Nucleic acids of the invention include one or more nucleic acid comprising at least one segment having a sequence or complementary sequence of one or more of the miRNA sequences in Table 1. In certain aspects, the nucleic acids identify one or more miRNAs listed in Table 1. Nucleic acids of the invention are typically coupled to a support. Such supports are
20 well known to those of ordinary skill in the art and include, but are not limited to glass, plastic, metal, or latex. In particular aspects of the invention, the support can be planar or in the form of a bead or other geometric shapes or configurations.

Certain embodiments of the invention include determining expression of one or more miRNA by using an amplification assay or a hybridization assay, a variety of
25 which are well known to one of ordinary skill in the art. In certain aspects, an amplification assay can be a quantitative amplification assay, such as quantitative RT-PCR or the like. In still further aspects, a hybridization assay can include array hybridization assays or solution hybridization assays.

Aspects of the invention can be used to diagnose or assess a patient's
30 condition. For example, the methods can be used to screen for a pathological

condition, assess prognosis of a pathological condition, stage a pathological condition, or assess response of a pathological condition to therapy.

Embodiments of the invention concern nucleic acids that perform the activities of or inhibit endogenous miRNAs when introduced into cells. In certain aspects, nucleic acids are synthetic or non-synthetic miRNA. Sequence-specific miRNA inhibitors can be used to inhibit sequentially or in combination the activities of one or more endogenous miRNAs in cells, as well those genes and associated pathways modulated by the endogenous miRNA.

The present invention concerns, in some embodiments, short nucleic acid molecules that function as miRNAs or as inhibitors of miRNA in a cell. The term “short” refers to a length of a single polynucleotide that is 25, 50, 100, or 150 nucleotides or fewer, including all integers or range derivable there between.

The nucleic acid molecules are typically synthetic. The term “synthetic” means the nucleic acid molecule is isolated and not identical in sequence (the entire sequence) and/or chemical structure to a naturally-occurring nucleic acid molecule, such as an endogenous precursor miRNA or miRNA molecule. While in some embodiments, nucleic acids of the invention do not have an entire sequence that is identical to a sequence of a naturally-occurring nucleic acid, such molecules may encompass all or part of a naturally-occurring sequence. It is contemplated, however, that a synthetic nucleic acid administered to a cell may subsequently be modified or altered in the cell such that its structure or sequence is the same as non-synthetic or naturally occurring nucleic acid, such as a mature miRNA sequence. For example, a synthetic nucleic acid may have a sequence that differs from the sequence of a precursor miRNA, but that sequence may be altered once in a cell to be the same as an endogenous, processed miRNA. The term “isolated” means that the nucleic acid molecules of the invention are initially separated from different (in terms of sequence or structure) and unwanted nucleic acid molecules such that a population of isolated nucleic acids is at least about 90% homogenous, and may be at least about 95, 96, 97, 98, 99, or 100% homogenous with respect to other polynucleotide molecules. In many embodiments of the invention, a nucleic acid is isolated by virtue of it having been synthesized *in vitro* separate from endogenous nucleic acids in a cell. It will be

understood, however, that isolated nucleic acids may be subsequently mixed or pooled together.

In certain aspects, synthetic miRNA of the invention are RNA or RNA analogs. miRNA inhibitors may be DNA or RNA, or analogs thereof. miRNA and
5 miRNA inhibitors of the invention are collectively referred to as “synthetic nucleic acids.”

In some embodiments, there is a synthetic miRNA having a length of between 17 and 130 residues. The present invention concerns synthetic miRNA molecules that are, are at least, or are at most 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29,
10 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 140, 145,
15 150, 160, 170, 180, 190, 200 or more residues in length, including any integer or any range derivable therein.

In certain embodiments, synthetic miRNA have (a) a “miRNA region” whose sequence from 5’ to 3’ is identical to all or a segment of a mature miRNA sequence, and (b) a “complementary region” whose sequence from 5’ to 3’ is between 60% and
20 100% complementary to the miRNA sequence. In certain embodiments, these synthetic miRNA are also isolated, as defined above. The term “miRNA region” refers to a region on the synthetic miRNA that is at least 75, 80, 85, 90, 95, or 100% identical, including all integers there between, to the entire sequence of a mature, naturally occurring miRNA sequence. In certain embodiments, the miRNA region is
25 or is at least 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.1, 99.2, 99.3, 99.4, 99.5, 99.6, 99.7, 99.8, 99.9 or 100% identical to the sequence of a naturally-occurring miRNA.

The term “complementary region” refers to a region of a synthetic miRNA that is or is at least 60% complementary to the mature, naturally occurring miRNA sequence that the miRNA region is identical to. The complementary region is or is at
30 least 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.1, 99.2,

99.3, 99.4, 99.5, 99.6, 99.7, 99.8, 99.9 or 100% complementary, or any range derivable therein. With single polynucleotide sequences, there is a hairpin loop structure as a result of chemical bonding between the miRNA region and the complementary region. In other embodiments, the complementary region is on a
5 different nucleic acid molecule than the miRNA region, in which case the complementary region is on the complementary strand and the miRNA region is on the active strand.

In other embodiments of the invention, there are synthetic nucleic acids that are miRNA inhibitors. A miRNA inhibitor is between about 17 to 25 nucleotides in
10 length and comprises a 5' to 3' sequence that is at least 90% complementary to the 5' to 3' sequence of a mature miRNA. In certain embodiments, a miRNA inhibitor molecule is 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleotides in length, or any range derivable therein. Moreover, a miRNA inhibitor has a sequence (from 5' to 3') that is or is at least 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.1, 99.2, 99.3, 99.4, 99.5, 99.6,
15 99.7, 99.8, 99.9 or 100% complementary, or any range derivable therein, to the 5' to 3' sequence of a mature miRNA, particularly a mature, naturally occurring miRNA. Probe sequences for miRNAs are disclosed in Table 1. One of skill in the art could use a portion of the probe sequence that is complementary to the sequence of a mature miRNA as the sequence for a miRNA inhibitor. Table 1 indicates what the mature
20 sequence of a miRNA. Moreover, that portion of the probe sequence can be altered so that it is still 90% complementary to the sequence of a mature miRNA.

In some embodiments, of the invention, a synthetic miRNA contains one or more design elements. These design elements include, but are not limited to: (i) a replacement group for the phosphate or hydroxyl of the nucleotide at the 5' terminus
25 of the complementary region; (ii) one or more sugar modifications in the first or last 1 to 6 residues of the complementary region; or, (iii) noncomplementarity between one or more nucleotides in the last 1 to 5 residues at the 3' end of the complementary region and the corresponding nucleotides of the miRNA region.

In certain embodiments, a synthetic miRNA has a nucleotide at its 5' end of
30 the complementary region in which the phosphate and/or hydroxyl group has been replaced with another chemical group (referred to as the "replacement design"). In some cases, the phosphate group is replaced, while in others, the hydroxyl group has

been replaced. In particular embodiments, the replacement group is biotin, an amine group, a lower alkylamine group, an acetyl group, 2'O-Me (2'oxygen-methyl), DMTO (4,4'-dimethoxytrityl with oxygen), fluorescein, a thiol, or acridine, though other replacement groups are well known to those of skill in the art and can be used as well. This design element can also be used with a miRNA inhibitor.

Additional embodiments concern a synthetic miRNA having one or more sugar modifications in the first or last 1 to 6 residues of the complementary region (referred to as the "sugar replacement design"). In certain cases, there is one or more sugar modifications in the first 1, 2, 3, 4, 5, 6 or more residues of the complementary region, or any range derivable therein. In additional cases, there is one or more sugar modifications in the last 1, 2, 3, 4, 5, 6 or more residues of the complementary region, or any range derivable therein, have a sugar modification. It will be understood that the terms "first" and "last" are with respect to the order of residues from the 5' end to the 3' end of the region. In particular embodiments, the sugar modification is a 2'O-Me modification. In further embodiments, there is one or more sugar modifications in the first or last 2 to 4 residues of the complementary region or the first or last 4 to 6 residues of the complementary region. This design element can also be used with a miRNA inhibitor. Thus, a miRNA inhibitor can have this design element and/or a replacement group on the nucleotide at the 5' terminus, as discussed above.

In other embodiments of the invention, there is a synthetic miRNA in which one or more nucleotides in the last 1 to 5 residues at the 3' end of the complementary region are not complementary to the corresponding nucleotides of the miRNA region ("noncomplementarity") (referred to as the "noncomplementarity design"). The noncomplementarity may be in the last 1, 2, 3, 4, and/or 5 residues of the complementary miRNA. In certain embodiments, there is noncomplementarity with at least 2 nucleotides in the complementary region.

It is contemplated that synthetic miRNA of the invention have one or more of the replacement, sugar modification, or noncomplementarity designs. In certain cases, synthetic RNA molecules have two of them, while in others these molecules have all three designs in place.

The miRNA region and the complementary region may be on the same or separate polynucleotides. In cases in which they are contained on or in the same polynucleotide, the miRNA molecule will be considered a single polynucleotide. In embodiments in which the different regions are on separate polynucleotides, the synthetic miRNA will be considered to be comprised of two polynucleotides.

When the RNA molecule is a single polynucleotide, there is a linker region between the miRNA region and the complementary region. In some embodiments, the single polynucleotide is capable of forming a hairpin loop structure as a result of bonding between the miRNA region and the complementary region. The linker constitutes the hairpin loop. It is contemplated that in some embodiments, the linker region is, is at least, or is at most 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 residues in length, or any range derivable therein. In certain embodiments, the linker is between 3 and 30 residues (inclusive) in length.

In addition to having a miRNA region and a complementary region, there may be flanking sequences as well at either the 5' or 3' end of the region. In some embodiments, there is or is at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 nucleotides or more, or any range derivable therein, flanking one or both sides of these regions.

Methods of the invention include reducing or eliminating activity of one or more miRNAs in a cell comprising introducing into a cell a miRNA inhibitor; or supplying or enhancing the activity of one or more miRNAs in a cell. The present invention also concerns inducing certain cellular characteristics by providing to a cell a particular nucleic acid, such as a specific synthetic miRNA molecule or a synthetic miRNA inhibitor molecule. However, in methods of the invention, the miRNA molecule or miRNA inhibitor need not be synthetic. They may have a sequence that is identical to a naturally occurring miRNA or they may not have any design modifications. In certain embodiments, the miRNA molecule and/or a miRNA inhibitor are synthetic, as discussed above.

The particular nucleic acid molecule provided to the cell is understood to correspond to a particular miRNA in the cell, and thus, the miRNA in the cell is referred to as the "corresponding miRNA." In situations in which a named miRNA

molecule is introduced into a cell, the corresponding miRNA will be understood to be the induced miRNA. It is contemplated, however, that the miRNA molecule introduced into a cell is not a mature miRNA but is capable of becoming a mature miRNA under the appropriate physiological conditions. In cases in which a particular
5 corresponding miRNA is being inhibited by a miRNA inhibitor, the particular miRNA will be referred to as the targeted miRNA. It is contemplated that multiple corresponding miRNAs may be involved. In particular embodiments, more than one miRNA molecule is introduced into a cell. Moreover, in other embodiments, more than one miRNA inhibitor is introduced into a cell. Furthermore, a combination of
10 miRNA molecule(s) and miRNA inhibitor(s) may be introduced into a cell.

Methods include identifying a cell or patient in need of inducing those cellular characteristics. Also, it will be understood that an amount of a synthetic nucleic acid that is provided to a cell or organism is an "effective amount," which refers to an amount needed to achieve a desired goal, such as inducing a particular cellular
15 characteristic(s).

In certain embodiments of the methods include providing or introducing to a cell a nucleic acid molecule corresponding to a mature miRNA in the cell in an amount effective to achieve a desired physiological result.

Moreover, methods can involve providing synthetic or nonsynthetic miRNA
20 molecules. It is contemplated that in these embodiments, methods may or may not be limited to providing only one or more synthetic miRNA molecules or only on or more nonsynthetic miRNA molecules. Thus, in certain embodiments, methods may involve providing both synthetic and nonsynthetic miRNA molecules. In this situation, a cell or cells are most likely provided a synthetic miRNA molecule corresponding to a
25 particular miRNA and a nonsynthetic miRNA molecule corresponding to a different miRNA. Furthermore, any method articulated a list of miRNAs using Markush group language may be articulated without the Markush group language and a disjunctive article (*i.e.*, or) instead, and vice versa.

In some embodiments, there is a method for reducing or inhibiting cell
30 proliferation in a cell comprising introducing into or providing to the cell an effective amount of (i) a miRNA inhibitor molecule or (ii) a synthetic or nonsynthetic miRNA

molecule that corresponds to a miRNA sequence. In certain embodiments the methods involves introducing into the cell an effective amount of (i) a miRNA inhibitor molecule having a 5' to 3' sequence that is at least 90% complementary to the 5' to 3' sequence of one or more mature miRNA of Table 1.

5 Certain embodiments of the invention include methods of treating a pancreatic condition. In one aspect, the method comprises contacting a pancreatic cell with one or more nucleic acid, synthetic miRNA, or miRNA comprising at least one nucleic acid segment having all or a portion of a miRNA sequence. The segment may be 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30 or more
10 nucleotides or nucleotide analog, including all integers there between. An aspect of the invention includes the modulation of a miRNA or a mRNA within a target cell, such as a pancreatic cell.

Typically, an endogenous gene, miRNA or mRNA is modulated in the cell. In particular embodiments, the nucleic acid sequence comprises at least one segment that
15 is at least 70, 75, 80, 85, 90, 95, or 100% identical in nucleic acid sequence to one or more miRNA sequence listed in Table 1. Modulation of the expression or processing of an endogenous gene, miRNA, or mRNA can be through modulation of the processing of a mRNA, such processing including transcription, transportation and/or translation with in a cell. Modulation may also be effected by the inhibition or
20 enhancement of miRNA activity with a cell, tissue, or organ. Such processing may effect the expression of an encoded product or the stability of the mRNA. In still other embodiments, a nucleic acid sequence can comprise a modified nucleic acid sequence.

In particular embodiments the pancreatic cell is a pancreatic cancer cell, such
25 as a pancreatic ductal adenocarcinoma cell. Methods of the invention can further comprise administering a second therapy, such as chemotherapy, radiotherapy, surgery, or immunotherapy. The nucleic acid can be transcribed from a nucleic acid vector, such as a plasmid vector or a viral vector.

Method of treating a pancreatic condition include contacting or administering
30 to a pancreatic cell with one or more nucleic acid comprise a miRNA sequence, wherein expression of an endogenous miRNA is modulated in the pancreatic cell;

where the miRNA sequence is at least 70, 75, 80, 85% or more identical to one or more of hsa-let-7a, hsa-let-7b, hsa-let-7c, hsa-let-7d, hsa-let-7e, hsa-let-7f, hsa-let-7g, hsa-let-7i, hsa-miR-100, hsa-miR-101, hsa-miR-103, hsa-miR-106a, hsa-miR-106b, hsa-miR-107, hsa-miR-10a, hsa-miR-125a, hsa-miR-125b, hsa-miR-130a, hsa-miR-130b, hsa-miR-134, hsa-miR-140, hsa-miR-141, hsa-miR-143, hsa-miR-145, hsa-miR-146a, hsa-miR-148a, hsa-miR-148b, hsa-miR-150, hsa-miR-154, hsa-miR-155, hsa-miR-15b, hsa-miR-17-5p, hsa-miR-18a, hsa-miR-181b, hsa-miR-182, hsa-miR-186, hsa-miR-196a, hsa-miR-196b, hsa-miR-199a, hsa-miR-199a-AS, hsa-miR-19a, hsa-miR-19b, hsa-miR-200a, hsa-miR-200b, hsa-miR-200c, hsa-miR-203, hsa-miR-21, hsa-miR-210, hsa-miR-214, hsa-miR-216, hsa-miR-217, hsa-miR-221, hsa-miR-222, hsa-miR-223, hsa-miR-224, hsa-miR-23a, hsa-miR-24, hsa-miR-25, hsa-miR-26a, hsa-miR-26b, hsa-miR-27a, hsa-miR-27b, hsa-miR-28, hsa-miR-29a, hsa-miR-29b, hsa-miR-29c, hsa-miR-30a-3p, hsa-miR-30a-5p, hsa-miR-30b, hsa-miR-30c, hsa-miR-30d, hsa-miR-30e-3p, hsa-miR-30e-5p, hsa-miR-31, hsa-miR-331, hsa-miR-335, hsa-miR-365, hsa-miR-368, hsa-miR-374, hsa-miR-375, hsa-miR-376a, hsa-miR-377, hsa-miR-379, hsa-miR-429, hsa-miR-93, hsa-miR-95, hsa-miR-96, hsa-miR-98, hsa-miR-99a, hsa-miR-99b, hsa-miR-452, hsa-miR-494, hsa-miR-497, miR-205, or ambi-miR-7105.

In certain aspects, one or more miRNA sequence may include or comprise a modified nucleobase or nucleic acid sequence.

In other aspects, a pancreatic cell is a pancreatic cancer cell.

The methods may further comprise administering a second therapy. The second therapy can be, but is not limited to chemotherapy, radiotherapy, surgery, or immunotherapy.

In still further aspects, one or more miRNA are transcribed from a nucleic acid vector, such as a plasmid or viral vector.

Embodiments of the invention include methods for treating pancreatic ductal adenocarcinoma in a subject comprising administering to the subject an effective amount of one or more synthetic miRNA molecules or inhibitors having a nucleic acid segment having at least 80% nucleic acid sequence identity to hsa-let-7a, hsa-let-7b, hsa-let-7c, hsa-let-7d, hsa-let-7f, hsa-let-7g, hsa-let-7i, hsa-miR-100, hsa-miR-

101, hsa-miR-103, hsa-miR-106b, hsa-miR-107, hsa-miR-10a, hsa-miR-125a, hsa-miR-125b, hsa-miR-130a, hsa-miR-130b, hsa-miR-134, hsa-miR-140, hsa-miR-141, hsa-miR-143, hsa-miR-145, hsa-miR-146a, hsa-miR-148a, hsa-miR-148b, hsa-miR-150, hsa-miR-154, hsa-miR-155, hsa-miR-18a, hsa-miR-181b, hsa-miR-182, hsa-miR-186, hsa-miR-196a, hsa-miR-196b, hsa-miR-199a, hsa-miR-199a-AS, hsa-miR-19a, hsa-miR-19b, hsa-miR-200a, hsa-miR-200b, hsa-miR-200c, hsa-miR-203, hsa-miR-21, hsa-miR-210, hsa-miR-214, hsa-miR-216, hsa-miR-217, hsa-miR-221, hsa-miR-222, hsa-miR-223, hsa-miR-224, hsa-miR-23a, hsa-miR-24, hsa-miR-26a, hsa-miR-26b, hsa-miR-27a, hsa-miR-27b, hsa-miR-29c, hsa-miR-30a-3p, hsa-miR-30a-5p, hsa-miR-30b, hsa-miR-30c, hsa-miR-30d, hsa-miR-30e-3p, hsa-miR-30e-5p, hsa-miR-31, hsa-miR-331, hsa-miR-335, hsa-miR-365, hsa-miR-368, hsa-miR-374, hsa-miR-375, hsa-miR-376a, hsa-miR-377, hsa-miR-379, hsa-miR-429, hsa-miR-93, hsa-miR-95, hsa-miR-96, hsa-miR-99b, hsa-miR-452, hsa-miR-494, hsa-miR-497, miR-205, or ambi-miR-7105.

15 In certain aspects, a subject is administered: one or more miRNA inhibitors having a nucleic acid segment having at least 80% nucleic acid sequence identity to hsa-let-7i, hsa-miR-100, hsa-miR-103, hsa-miR-106b, hsa-miR-107, hsa-miR-10a, hsa-miR-125a, hsa-miR-125b, hsa-miR-140, hsa-miR-143, hsa-miR-145, hsa-miR-146a, hsa-miR-150, hsa-miR-155, hsa-miR-18a, hsa-miR-181b, hsa-miR-196a, hsa-miR-196b, hsa-miR-199a, hsa-miR-199a-AS, hsa-miR-203, hsa-miR-21, hsa-miR-210, hsa-miR-214, hsa-miR-221, hsa-miR-222, hsa-miR-223, hsa-miR-224, hsa-miR-23a, hsa-miR-24, hsa-miR-27a, hsa-miR-31, hsa-miR-331, hsa-miR-93, hsa-miR-99b, hsa-miR-452, hsa-miR-497, or ambi-miR-7105; and/or one or miRNAs having a nucleic acid segment having at least 80% nucleic acid sequence identity to hsa-let-7a, hsa-let-7b, hsa-let-7c, hsa-let-7d, hsa-let-7e, hsa-let-7f, hsa-let-7g, hsa-miR-101, hsa-miR-130a, hsa-miR-130b, hsa-miR-134, hsa-miR-141, hsa-miR-148a, hsa-miR-148b, hsa-miR-154, hsa-miR-182, hsa-miR-186, hsa-miR-19a, hsa-miR-19b, hsa-miR-200a, hsa-miR-200b, hsa-miR-200c, hsa-miR-216, hsa-miR-217, hsa-miR-26a, hsa-miR-26b, hsa-miR-27b, hsa-miR-29c, hsa-miR-30a-3p, hsa-miR-30a-5p, hsa-miR-30b, hsa-miR-30c, hsa-miR-30d, hsa-miR-30e-3p, hsa-miR-30e-5p, hsa-miR-335, hsa-miR-365, hsa-miR-368, hsa-miR-374, hsa-miR-375, hsa-miR-376a, hsa-miR-377, hsa-miR-379, hsa-miR-429, hsa-miR-95, hsa-miR-96, or hsa-miR-494.

In other aspects, a method for treating chronic pancreatitis in a subject comprises administering to the subject an effective amount of one or more synthetic miRNA molecules or miRNA inhibitors comprising a nucleic acid segment having at least 80% nucleic acid sequence identity to hsa-let-7a, hsa-let-7b, hsa-let-7c, hsa-let-7d, hsa-let-7e, hsa-let-7f, hsa-let-7g, hsa-let-7i, hsa-miR-100, hsa-miR-101, hsa-miR-10a, hsa-miR-125a, hsa-miR-125b, hsa-miR-130a, hsa-miR-130b, hsa-miR-141, hsa-miR-143, hsa-miR-145, hsa-miR-146a, hsa-miR-148a, hsa-miR-148b, hsa-miR-150, hsa-miR-18a, hsa-miR-182, hsa-miR-186, hsa-miR-199a, hsa-miR-199a-AS, hsa-miR-19a, hsa-miR-19b, hsa-miR-200a, hsa-miR-200b, hsa-miR-200c, hsa-miR-203, hsa-miR-210, hsa-miR-214, hsa-miR-216, hsa-miR-217, hsa-miR-222, hsa-miR-223, hsa-miR-24, hsa-miR-25, hsa-miR-26a, hsa-miR-26b, hsa-miR-27b, hsa-miR-28, hsa-miR-29a, hsa-miR-29b, hsa-miR-29c, hsa-miR-30a-3p, hsa-miR-30a-5p, hsa-miR-30b, hsa-miR-30c, hsa-miR-30d, hsa-miR-30e-3p, hsa-miR-30e-5p, hsa-miR-31, hsa-miR-335, hsa-miR-365, hsa-miR-368, hsa-miR-374, hsa-miR-376a, hsa-miR-429, hsa-miR-95, hsa-miR-96, hsa-miR-98, hsa-miR-99a, hsa-miR-497, or ambi-miR-7105.

In still a further aspect, the subject is administered one or more miRNA inhibitors having a nucleic acid segment having at least 80% nucleic acid sequence identity to hsa-let-7i, hsa-miR-100, hsa-miR-10a, hsa-miR-125a, hsa-miR-125b, hsa-miR-143, hsa-miR-145, hsa-miR-146a, hsa-miR-150, hsa-miR-18a, hsa-miR-199a, hsa-miR-199a-AS, hsa-miR-210, hsa-miR-214, hsa-miR-222, hsa-miR-223, hsa-miR-24, hsa-miR-31, hsa-miR-99a, or hsa-miR-497; and/or one or more miRNAs having a nucleic acid segment having at least 80% nucleic acid sequence identity to hsa-let-7a, hsa-let-7b, hsa-let-7c, hsa-let-7d, hsa-let-7e, hsa-let-7f, hsa-let-7g, hsa-miR-101, hsa-miR-130a, hsa-miR-130b, hsa-miR-141, hsa-miR-148a, hsa-miR-148b, hsa-miR-182, hsa-miR-186, hsa-miR-19a, hsa-miR-19b, hsa-miR-200a, hsa-miR-200b, hsa-miR-200c, hsa-miR-203, hsa-miR-216, hsa-miR-217, hsa-miR-25, hsa-miR-26a, hsa-miR-26b, hsa-miR-27b, hsa-miR-28, hsa-miR-29a, hsa-miR-29b, hsa-miR-29c, hsa-miR-30a-3p, hsa-miR-30a-5p, hsa-miR-30b, hsa-miR-30c, hsa-miR-30d, hsa-miR-30e-3p, hsa-miR-30e-5p, hsa-miR-335, hsa-miR-365, hsa-miR-368, hsa-miR-374, hsa-miR-376a, hsa-miR-429, hsa-miR-95, hsa-miR-96, hsa-miR-98, or ambi-miR-7105.

Synthetic nucleic acids can be administered to the subject or patient using modes of administration that are well known to those of skill in the art, particularly for therapeutic applications. It is particularly contemplated that a patient is human or any other mammal or animal having miRNA.

5 It will be understood in methods of the invention that a cell or other biological matter such as an organism (including patients) can be provided a miRNA or miRNA molecule corresponding to a particular miRNA by administering to the cell or organism a nucleic acid molecule that functions as the corresponding miRNA once inside the cell. The form of the molecule provided to the cell may not be the form
10 that acts as a miRNA once inside the cell. Thus, it is contemplated that in some embodiments, biological matter is provided a synthetic miRNA or a nonsynthetic miRNA, such as one that becomes processed into a mature and active miRNA once it has access to the cell's miRNA processing machinery. In certain embodiments, it is specifically contemplated that the miRNA molecule provided to the biological matter
15 is not a mature miRNA molecule but a nucleic acid molecule that can be processed into the mature miRNA once it is accessible to miRNA processing machinery. The term "nonsynthetic" in the context of miRNA means that the miRNA is not "synthetic," as defined herein. Furthermore, it is contemplated that in embodiments of the invention that concern the use of synthetic miRNAs, the use of corresponding
20 nonsynthetic miRNAs is also considered an aspect of the invention, and vice versa.

 In other embodiments, the methods involve reducing cell viability comprising introducing into or providing to the cell an effective amount of (i) a miRNA inhibitor molecule or (ii) a synthetic or nonsynthetic miRNA molecule that corresponds to a miRNA sequence. Methods for inducing apoptosis have a number of therapeutic
25 applications including, but not limited to, the treatment of cancer.

 The present invention also concerns using miRNA compositions to treat diseases or conditions or to prepare therapeutics for the treatment of diseases or conditions. It is contemplated that 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39,
30 or 40 more miRNA (or any range derivable therein) may be used for these embodiments. In certain embodiments, methods involve one or more miRNA inhibitors and/or a miRNA molecules corresponding to any of these miRNAs,

particularly for the treatment or prevention of cancer. Cancer includes, but is not limited to, malignant cancers, tumors, metastatic cancers, unresectable cancers, chemo- and/or radiation-resistant cancers, and terminal cancers.

It will be understood that shorthand notations are employed such that a generic
5 description of a miRNA refers to any of its gene family members (distinguished by a number), unless otherwise indicated. It is understood by those of skill in the art that a “gene family” refers to a group of genes having the same miRNA coding sequence. Typically, members of a gene family are identified by a number following the initial designation. For example, miR-16-1 and miR-16-2 are members of the miR-16 gene
10 family and “miR-7” refers to miR-7-1, miR-7-2 and miR-7-3. Moreover, unless otherwise indicated, a shorthand notation refers to related miRNAs (distinguished by a letter). Thus, “let-7,” for example, refers to let-7a-1, let-7a-2, let-7b, let-7c, let-7d, let-7e, let-7f-1, and let-7f-2.” Exceptions to these shorthand notations will be otherwise identified.

15 It will be understood that the term “providing” an agent is used to include “administering” the agent to a patient.

In certain embodiments, methods also include targeting a miRNA to modulate in a cell or organism. The term “targeting a miRNA to modulate” means a nucleic acid of the invention will be employed so as to modulate the selected miRNA. In
20 some embodiments the modulation is achieved with a synthetic or non-synthetic miRNA that corresponds to the targeted miRNA, which effectively provides the targeted miRNA to the cell or organism (positive modulation). In other embodiments, the modulation is achieved with a miRNA inhibitor, which effectively inhibits the targeted miRNA in the cell or organism (negative modulation).

25 In some embodiments, the miRNA targeted to be modulated is a miRNA that affects a disease, condition, or pathway. In certain embodiments, the miRNA is targeted because a treatment can be provided by negative modulation of the targeted miRNA. In other embodiments, the miRNA is targeted because a treatment can be provided by positive modulation of the targeted miRNA.

30 In certain methods of the invention, there is a further step of administering the selected miRNA modulator to a cell, tissue, organ, or organism (collectively

“biological matter”) in need of treatment related to modulation of the targeted miRNA or in need of the physiological or biological results discussed herein (such as with respect to a particular cellular pathway or result like decrease in cell viability). Consequently, in some methods of the invention there is a step of identifying a patient
5 in need of treatment that can be provided by the miRNA modulator(s). It is contemplated that an effective amount of a miRNA modulator can be administered in some embodiments. In particular embodiments, there is a therapeutic benefit conferred on the biological matter, where a “therapeutic benefit” refers to an improvement in the one or more conditions or symptoms associated with a disease or
10 condition or an improvement in the prognosis, duration, or status with respect to the disease. It is contemplated that a therapeutic benefit includes, but is not limited to, a decrease in pain, a decrease in morbidity, a decrease in a symptom. For example, with respect to cancer, it is contemplated that a therapeutic benefit can be inhibition of tumor growth, prevention of metastasis, reduction in number of metastases, inhibition
15 of cancer cell proliferation, inhibition of cancer cell proliferation, induction of cell death in cancer cells, inhibition of angiogenesis near cancer cells, induction of apoptosis of cancer cells, reduction in pain, reduction in risk of recurrence, induction of chemo- or radiosensitivity in cancer cells, prolongation of life, and/or delay of death directly or indirectly related to cancer.

20 Furthermore, it is contemplated that the miRNA compositions may be provided as part of a therapy to a patient, in conjunction with traditional therapies or preventative agents. Moreover, it is contemplated that any method discussed in the context of therapy may be applied as preventatively, particularly in a patient identified to be potentially in need of the therapy or at risk of the condition or disease for which
25 a therapy is needed.

In addition, methods of the invention concern employing one or more nucleic acids corresponding to a miRNA and a therapeutic drug. The nucleic acid can enhance the effect or efficacy of the drug, reduce any side effects or toxicity, modify its bioavailability, and/or decrease the dosage or frequency needed. In certain
30 embodiments, the therapeutic drug is a cancer therapeutic. Consequently, in some embodiments, there is a method of treating cancer in a patient comprising administering to the patient the cancer therapeutic and an effective amount of at least

one miRNA molecule that improves the efficacy of the cancer therapeutic or protects non-cancer cells. Cancer therapies also include a variety of combination therapies with both chemical and radiation based treatments. Combination chemotherapies include but are not limited to, for example, bevacizumab, cisplatin (CDDP), carboplatin, EGFR inhibitors (gefitinib and cetuximab), procarbazine, mechlorethamine, cyclophosphamide, camptothecin, COX-2 inhibitors (e.g., celecoxib) ifosfamide, melphalan, chlorambucil, busulfan, nitrosurea, dactinomycin, daunorubicin, doxorubicin (adriamycin), bleomycin, plicomycin, mitomycin, etoposide (VP16), tamoxifen, raloxifene, estrogen receptor binding agents, taxol, taxotere, gemcitabine, navelbine, farnesyl-protein transferase inhibitors, transplatinum, 5-fluorouracil, vincristin, vinblastin and methotrexate, or any analog or derivative variant of the foregoing.

Alternatively or additionally, the miRNA molecule in methods of the invention protects non-cancer cells from the cancer therapeutic and is selected from the group consisting of miR-16, miR-24, miR-30a-3p, miR-125b, miR-152, miR-194, miR-197, miR-214, and miR-331.

Generally, inhibitors of miRNAs can be given to achieve the opposite effect as compared to when nucleic acid molecules corresponding to the mature miRNA are given. Similarly, nucleic acid molecules corresponding to the mature miRNA can be given to achieve the opposite effect as compared to when inhibitors of the miRNA are given. For example, miRNA molecules that increase cell proliferation can be provided to cells to increase proliferation or inhibitors of such molecules can be provided to cells to decrease cell proliferation. The present invention contemplates these embodiments in the context of the different physiological effects observed with the different miRNA molecules and miRNA inhibitors disclosed herein. These include, but are not limited to, the following physiological effects: increase and decreasing cell proliferation, increasing or decreasing apoptosis, increasing transformation, increasing or decreasing cell viability, activating ERK, activating/inducing or inhibiting hTert, inhibit stimulation of Stat3, reduce or increase viable cell number, and increase or decrease number of cells at a particular phase of the cell cycle. Methods of the invention are generally contemplated to include providing or introducing one or more different nucleic acid molecules corresponding to one or more different miRNA

molecules. It is contemplated that the following, at least the following, or at most the following number of different nucleic acid molecules may be provided or introduced: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, or any range derivable therein. This also applies to the number of different miRNA molecules that can be provided or introduced into a cell.

The present invention also concerns kits containing compositions of the invention or compositions to implement methods of the invention. In some embodiments, kits can be used to evaluate one or more miRNA molecules. In certain embodiments, a kit contains, contains at least or contains at most 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 or more miRNA probes, synthetic miRNA molecules or miRNA inhibitors, or any range and combination derivable therein. In some embodiments, there are kits for evaluating miRNA activity in a cell.

Kits may comprise components, which may be individually packaged or placed in a container, such as a tube, bottle, vial, syringe, or other suitable container means.

Individual components may also be provided in a kit in concentrated amounts; in some embodiments, a component is provided individually in the same concentration as it would be in a solution with other components. Concentrations of components may be provided as 1x, 2x, 5x, 10x, or 20x or more.

Kits for using miRNA probes, synthetic miRNAs, nonsynthetic, and/or miRNA inhibitors of the invention for therapeutic, prognostic, or diagnostic applications are included as part of the invention. Specifically contemplated are any such molecules corresponding to any miRNA reported to influence biological activity, such as those discussed herein.

In certain aspects, negative and/or positive control synthetic miRNAs and/or miRNA inhibitors are included in some kit embodiments. The Control molecules can

be used to verify transfection efficiency and/or control for transfection-induced changes in cells.

It is contemplated that any method or composition described herein can be implemented with respect to any other method or composition described herein and that different embodiments may be combined. It is specifically contemplated that any methods and compositions discussed herein with respect to miRNA molecules or miRNA may be implemented with respect to synthetic miRNAs to the extent the synthetic miRNA is exposed to the proper conditions to allow it to become a mature miRNA under physiological circumstances. The claims originally filed are contemplated to cover claims that are multiply dependent on any filed claim or combination of filed claims.

Any embodiment of the invention involving specific miRNAs by name is contemplated also to cover embodiments involving miRNAs whose sequences are at least 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99% identical to the mature sequence of the specified miRNA.

Embodiments of the invention include kits for analysis of a pathological sample by assessing miRNA profile for a sample comprising, in suitable container means, two or more miRNA probes, wherein the miRNA probes detect one or more of hsa-let-7a, hsa-let-7b, hsa-let-7c, hsa-let-7d, hsa-let-7e, hsa-let-7f, hsa-let-7g, hsa-let-7i, hsa-miR-100, hsa-miR-101, hsa-miR-103, hsa-miR-106a, hsa-miR-106b, hsa-miR-107, hsa-miR-10a, hsa-miR-125a, hsa-miR-125b, hsa-miR-130a, hsa-miR-130b, hsa-miR-134, hsa-miR-140, hsa-miR-141, hsa-miR-143, hsa-miR-145, hsa-miR-146a, hsa-miR-148a, hsa-miR-148b, hsa-miR-150, hsa-miR-154, hsa-miR-155, hsa-miR-15b, hsa-miR-17-5p, hsa-miR-18, hsa-miR-181b, hsa-miR-182, hsa-miR-186, hsa-miR-196a, hsa-miR-196b, hsa-miR-199a, hsa-miR-199a-AS, hsa-miR-19a, hsa-miR-19b, hsa-miR-200a, hsa-miR-200b, hsa-miR-200c, hsa-miR-203, hsa-miR-21, hsa-miR-210, hsa-miR-214, hsa-miR-216, hsa-miR-217, hsa-miR-221, hsa-miR-222, hsa-miR-223, hsa-miR-224, hsa-miR-23a, hsa-miR-24, hsa-miR-25, hsa-miR-26a, hsa-miR-26b, hsa-miR-27a, hsa-miR-27b, hsa-miR-28, hsa-miR-29a, hsa-miR-29b, hsa-miR-29c, hsa-miR-30a-3p, hsa-miR-30a-5p, hsa-miR-30b, hsa-miR-30c, hsa-miR-30d, hsa-miR-30e-3p, hsa-miR-30e-5p, hsa-miR-31, hsa-miR-331, hsa-miR-335, hsa-miR-365, hsa-miR-368, hsa-miR-374, hsa-miR-375, hsa-miR-376a, hsa-miR-377,

hsa-miR-379, hsa-miR-429, hsa-miR-93, hsa-miR-95, hsa-miR-96, hsa-miR-98, hsa-miR-99a, hsa-miR-99b, hsa-miR-452, hsa-miR-494, hsa-miR-497 or ambi-miR-7105. The kit can further comprise reagents for labeling miRNA in the sample. The kit may also include the labeling reagents include at least one amine-modified nucleotide, poly(A) polymerase, and poly(A) polymerase buffer. Labeling reagents can include an amine-reactive dye.

Table 1. Listing of miRNA probes for pancreatic sample assessment.

Probe Sequence	SEQ ID NO:	miRNA	miR Base Information
UGAGGUAGUAGGUUGUAUAGUU	SEQ ID NO:1	hsa-let-7a	>hsa-let-7a MIMAT0000062
UGAGGUAGUAGGUUGUGUGGUU	SEQ ID NO:2	hsa-let-7b	>hsa-let-7b MIMAT0000063
UGAGGUAGUAGGUUGUAUGGUU	SEQ ID NO:3	hsa-let-7c	>hsa-let-7c MIMAT0000064
AGAGGUAGUAGGUUGCAUAGU	SEQ ID NO:4	hsa-let-7d	>hsa-let-7d MIMAT0000065
UGAGGUAGGAGGUUGUAUAGU	SEQ ID NO:5	hsa-let-7e	>hsa-let-7e MIMAT0000066
UGAGGUAGUAGAUUGUAUAGUU	SEQ ID NO:6	hsa-let-7f	>hsa-let-7f MIMAT0000067
UGAGGUAGUAGUUUGUACAGU	SEQ ID NO:7	hsa-let-7g	>hsa-let-7g MIMAT0000414
UGAGGUAGUAGUUUGUGCUGU	SEQ ID NO:8	hsa-let-7i	>hsa-let-7i MIMAT0000415
UGGAAUGUAAAGAAGUAUGUA	SEQ ID NO:9	hsa-miR-1	>hsa-miR-1 MIMAT0000416
AACCCGUAGAUCCGAACUUGUG	SEQ ID NO:10	hsa-miR-100	>hsa-miR-100 MIMAT0000098
UACAGUACUGUGAUAAACUGAAG	SEQ ID NO:11	hsa-miR-101	>hsa-miR-101 MIMAT0000099
AGCAGCAUUGUACAGGGCUAUGA	SEQ ID NO:12	hsa-miR-103	>hsa-miR-103 MIMAT0000101
UCAA AUGCUCAGACUCCUGU	SEQ ID NO:13	hsa-miR-105	>hsa-miR-105 MIMAT0000102
AAAAGUGCUUACAGUGCAGGUAGC	SEQ ID NO:14	hsa-miR-106a	>hsa-miR-106a MIMAT0000103
UAAAGUGCUGACAGUGCAGAU	SEQ ID NO:15	hsa-miR-106b	>hsa-miR-106b MIMAT0000680
AGCAGCAUUGUACAGGGCUAUCA	SEQ ID NO:16	hsa-miR-107	>hsa-miR-107 MIMAT0000104
UACCCUGUAGAUCCGAAUUUGUG	SEQ ID NO:17	hsa-miR-10a	>hsa-miR-10a MIMAT0000253
UACCCUGUAGAACCGAAUUUGU	SEQ ID NO:18	hsa-miR-10b	>hsa-miR-10b MIMAT0000254
UGGAGUGUGACAAUGGUGUUUGU	SEQ ID NO:19	hsa-miR-122a	>hsa-miR-122a MIMAT0000421
UUAAGGCACGCGGUGAAUGCCA	SEQ ID NO:20	hsa-miR-124a	>hsa-miR-124a MIMAT0000422
UCCCUGAGACCCUUUAACCUUGUG	SEQ ID NO:21	hsa-miR-125a	>hsa-miR-125a MIMAT0000443
UCCCUGAGACCCUAACUUGUGA	SEQ ID NO:22	hsa-miR-125b	>hsa-miR-125b MIMAT0000423
UCGUACCGUGAGUAAUAAUGC	SEQ ID NO:23	hsa-miR-126	>hsa-miR-126 MIMAT0000445
CAUUAUUACUUUUGGUACGCG	SEQ ID NO:24	hsa-miR-126-AS	>hsa-miR-126* MIMAT0000444
UCGGAUCCGUCUGAGCUUGGCU	SEQ ID NO:25	hsa-miR-127	>hsa-miR-127

			MIMAT0000446
UCACAGUGAACCGGUCUCUUUU	SEQ ID NO:26	hsa-miR-128a	>hsa-miR-128a MIMAT0000424
CUUUUUGCGGUCUGGGCUUGC	SEQ ID NO:27	hsa-miR-129	>hsa-miR-129 MIMAT0000242
CAGUGCAAUGUUAAAAGGGCAU	SEQ ID NO:28	hsa-miR-130a	>hsa-miR-130a MIMAT0000425
CAGUGCAAUGAUGAAAGGGCAU	SEQ ID NO:29	hsa-miR-130b	>hsa-miR-130b MIMAT0000691
UACAGUCUACAGCCAUGGUCG	SEQ ID NO:30	hsa-miR-132	>hsa-miR-132 MIMAT0000426
UUGGUCCCCUUAACCAGCUGU	SEQ ID NO:31	hsa-miR-133a	>hsa-miR-133a MIMAT0000427
UGUGACUGGUUGACCAGAGGG	SEQ ID NO:32	hsa-miR-134	>hsa-miR-134 MIMAT0000447
UAUGGCUUUUUAUUCCUAUGUGA	SEQ ID NO:33	hsa-miR-135a	>hsa-miR-135a MIMAT0000428
UAUGGCUUUUCAUUCCUAUGUG	SEQ ID NO:34	hsa-miR-135b	>hsa-miR-135b MIMAT0000758
ACUCCAUUUGUUUUGAUGAUGGA	SEQ ID NO:35	hsa-miR-136	>hsa-miR-136 MIMAT0000448
UAUUGCUUAAGAAUACGCGUAG	SEQ ID NO:36	hsa-miR-137	>hsa-miR-137 MIMAT0000429
AGCUGGUGUUGUGAAUC	SEQ ID NO:37	hsa-miR-138	>hsa-miR-138 MIMAT0000430
UCUACAGUGCACGUGUCU	SEQ ID NO:38	hsa-miR-139	>hsa-miR-139 MIMAT0000250
AGUGGUUUUACCCUAUGGUAG	SEQ ID NO:39	hsa-miR-140	>hsa-miR-140 MIMAT0000431
UACACUGUCUGGUAAAGAUGG	SEQ ID NO:40	hsa-miR-141	>hsa-miR-141 MIMAT0000432
UGUAGUGUUUCCUACUUUAUGGA	SEQ ID NO:41	hsa-miR-142-3p	>hsa-miR-142-3p MIMAT0000434
CAUAAAGUAGAAAGCACUAC	SEQ ID NO:42	hsa-miR-142-5p	>hsa-miR-142-5p MIMAT0000433
UGAGAUGAAGCACUGUAGCUCA	SEQ ID NO:43	hsa-miR-143	>hsa-miR-143 MIMAT0000435
UACAGUAUAGAUGAUGUACUAG	SEQ ID NO:44	hsa-miR-144	>hsa-miR-144 MIMAT0000436
GUCCAGUUUUCCCAGGAAUCCCUU	SEQ ID NO:45	hsa-miR-145	>hsa-miR-145 MIMAT0000437
UGAGAACUGAAUCCAUGGGUU	SEQ ID NO:46	hsa-miR-146a	>hsa-miR-146a MIMAT0000449
GUGUGUGGAAAUGCUUCUGC	SEQ ID NO:47	hsa-miR-147	>hsa-miR-147 MIMAT0000251
UCAGUGCACUACAGAACUUUGU	SEQ ID NO:48	hsa-miR-148a	>hsa-miR-148a MIMAT0000243
UCAGUGCAUCACAGAACUUUGU	SEQ ID NO:49	hsa-miR-148b	>hsa-miR-148b MIMAT0000759
UCUGGCUCCGUGUCUUCACUCC	SEQ ID NO:50	hsa-miR-149	>hsa-miR-149 MIMAT0000450
UCUCCCAACCCUUGUACCAGUG	SEQ ID NO:51	hsa-miR-150	>hsa-miR-150 MIMAT0000451
ACUAGACUGAAGCUCCUUGAGG	SEQ ID NO:52	hsa-miR-151	>hsa-miR-151 MIMAT0000757
UCAGUGCAUGACAGAACUUGGG	SEQ ID NO:53	hsa-miR-152	>hsa-miR-152 MIMAT0000438
UUGCAUAGUCACAAAAGUGA	SEQ ID NO:54	hsa-miR-153	>hsa-miR-153 MIMAT0000439
UAGGUUAUCCGUGUUGCCUUCG	SEQ ID NO:55	hsa-miR-154	>hsa-miR-154 MIMAT0000452
UUAAUGCUAAUCGUGAUAGGGG	SEQ ID NO:56	hsa-miR-155	>hsa-miR-155 MIMAT0000646

UAGCAGCACAUAAUGGUUUGUG	SEQ ID NO:57	hsa-miR-15a	>hsa-miR-15a MIMAT0000068
UAGCAGCACAUCAUGGUUUACA	SEQ ID NO:58	hsa-miR-15b	>hsa-miR-15b MIMAT0000417
UAGCAGCACGUAAAUAUUGGCG	SEQ ID NO:59	hsa-miR-16	>hsa-miR-16 MIMAT0000069
ACUGCAGUGAAGGCACUUGU	SEQ ID NO:60	hsa-miR-17-3p	>hsa-miR-17-3p MIMAT0000071
CAAAGUGCUUACAGUGCAGGUAGU	SEQ ID NO:61	hsa-miR-17-5p	>hsa-miR-17-5p MIMAT0000070
UAAGGUGCAUCUAGUGCAGAUUA	SEQ ID NO:62	hsa-miR-18a	>hsa-miR-18a MIMAT0000072
AACAUUCAACGCUGUCGGUGAGU	SEQ ID NO:63	hsa-miR-181a	>hsa-miR-181a MIMAT0000256
AACAUUCAUUGCUGUCGGUGGG	SEQ ID NO:64	hsa-miR-181b	>hsa-miR-181b MIMAT0000257
AACAUUCAACCUGUCGGUGAGU	SEQ ID NO:65	hsa-miR-181c	>hsa-miR-181c MIMAT0000258
UUUGGCAAUGGUAGAACUCACA	SEQ ID NO:66	hsa-miR-182	>hsa-miR-182 MIMAT0000259
UGGUUCUAGACUUGCCAACUA	SEQ ID NO:67	hsa-miR-182-AS	>hsa-miR-182* MIMAT0000260
UAUGGCACUGGUAGAAUUCACUG	SEQ ID NO:68	hsa-miR-183	>hsa-miR-183 MIMAT0000261
UGGACGGAGAACUGAUAAAGGGU	SEQ ID NO:69	hsa-miR-184	>hsa-miR-184 MIMAT0000454
UGGAGAGAAAGGCAGUUC	SEQ ID NO:70	hsa-miR-185	>hsa-miR-185 MIMAT0000455
CAAAGAAUUCUCCUUUUGGGCUU	SEQ ID NO:71	hsa-miR-186	>hsa-miR-186 MIMAT0000456
UCGUGUCUUGUGUUGCAGCCG	SEQ ID NO:72	hsa-miR-187	>hsa-miR-187 MIMAT0000262
CAUCCCUUGCAUGGUGGAGGGU	SEQ ID NO:73	hsa-miR-188	>hsa-miR-188 MIMAT0000457
GUGCCUACUGAGCUGAUUUCAGU	SEQ ID NO:74	hsa-miR-189	>hsa-miR-189 MIMAT0000079
UGAUUAUGUUUGAUUAUUAUAGGU	SEQ ID NO:75	hsa-miR-190	>hsa-miR-190 MIMAT0000458
CAACGGAAUCCCAAAGCAGCU	SEQ ID NO:76	hsa-miR-191	>hsa-miR-191 MIMAT0000440
CUGACCUAUGAAUUGACAGCC	SEQ ID NO:77	hsa-miR-192	>hsa-miR-192 MIMAT0000222
AACUGGCCUACAAAGUCCAG	SEQ ID NO:78	hsa-miR-193a	>hsa-miR-193a MIMAT0000459
UGUAAACAGCAACUCCAUGUGGA	SEQ ID NO:79	hsa-miR-194	>hsa-miR-194 MIMAT0000460
UAGCAGCACAGAAUAUUGGC	SEQ ID NO:80	hsa-miR-195	>hsa-miR-195 MIMAT0000461
UAGGUAGUUUCAUGUUGUUGG	SEQ ID NO:81	hsa-miR-196a	>hsa-miR-196a MIMAT0000226
UAGGUAGUUUCCUGUUGUUGG	SEQ ID NO:82	hsa-miR-196b	>hsa-miR-196b MIMAT0001080
UUCACCACCUUCUCCACCCAGC	SEQ ID NO:83	hsa-miR-197	>hsa-miR-197 MIMAT0000227
GGUCCAGAGGGGAGAUAGG	SEQ ID NO:84	hsa-miR-198	>hsa-miR-198 MIMAT0000228
CCCAGUGUUCAGACUACCUGUUC	SEQ ID NO:85	hsa-miR-199a	>hsa-miR-199a MIMAT0000231
UACAGUAGUCUGCACAUUGGUU	SEQ ID NO:86	hsa-miR-199a-AS	>hsa-miR-199a* MIMAT0000232
CCCAGUGUUUAGACUAUCUGUUC	SEQ ID NO:87	hsa-miR-199b	>hsa-miR-199b MIMAT0000263
UGUGCAAUUCUAUGCAAACUGA	SEQ ID NO:88	hsa-miR-19a	>hsa-miR-19a MIMAT0000073

UGUGCAAUCCAUGCAAACUGA	SEQ ID NO:89	hsa-miR-19b	>hsa-miR-19b MIMAT0000074
UAAAGUGCUUAUAGUGCAGGUAG	SEQ ID NO:90	hsa-miR-20a	>hsa-miR-20a MIMAT0000075
UAACACUGUCUGGUAACGAUGU	SEQ ID NO:91	hsa-miR-200a	>hsa-miR-200a MIMAT0000682
UAAUACUGCCUGGUAUGAUGAC	SEQ ID NO:92	hsa-miR-200b	>hsa-miR-200b MIMAT0000318
UAAUACUGCCGGGUAUGAUGG	SEQ ID NO:93	hsa-miR-200c	>hsa-miR-200c MIMAT0000617
GUGAAAUGUUUAGGACCACUAG	SEQ ID NO:94	hsa-miR-203	>hsa-miR-203 MIMAT0000264
UUCCCUUUGUCAUCCUAGCCU	SEQ ID NO:95	hsa-miR-204	>hsa-miR-204 MIMAT0000265
UCCUUCAUUCCACCGGAGUCUG	SEQ ID NO:96	hsa-miR-205	>hsa-miR-205 MIMAT0000266
UGGAAUGUAAGGAAGUGUGUGG	SEQ ID NO:97	hsa-miR-206	>hsa-miR-206 MIMAT0000462
AUAAGACGAGCAAAAAGCUUGU	SEQ ID NO:98	hsa-miR-208	>hsa-miR-208 MIMAT0000241
UAGCUUAUCAGACUGAUGUUGA	SEQ ID NO:99	hsa-miR-21	>hsa-miR-21 MIMAT0000076
CUGUGCGUGUGACAGCGGCUGA	SEQ ID NO:100	hsa-miR-210	>hsa-miR-210 MIMAT0000267
UUCCCUUUGUCAUCCUUCGCCU	SEQ ID NO:101	hsa-miR-211	>hsa-miR-211 MIMAT0000268
UAACAGUCUCCAGUCACGGCC	SEQ ID NO:102	hsa-miR-212	>hsa-miR-212 MIMAT0000269
ACCAUCGACCGUUGAUUGUACC	SEQ ID NO:103	hsa-miR-213	>hsa-miR-181a* MIMAT0000270
ACAGCAGGCACAGACAGGCAG	SEQ ID NO:104	hsa-miR-214	>hsa-miR-214 MIMAT0000271
AUGACCUAUGAAUUGACAGAC	SEQ ID NO:105	hsa-miR-215	>hsa-miR-215 MIMAT0000272
UAAUCUCAGCUGGCAACUGUG	SEQ ID NO:106;	hsa-miR-216	>hsa-miR-216 MIMAT0000273
UACUGCAUCAGGAACUGAUUGGAU	SEQ ID NO:107	hsa-miR-217	>hsa-miR-217 MIMAT0000274
UUGUGCUUGAUCUAACCAUGU	SEQ ID NO:108	hsa-miR-218	>hsa-miR-218 MIMAT0000275
UGAUUGUCCAAACGCAAUUCU	SEQ ID NO:109	hsa-miR-219	>hsa-miR-219 MIMAT0000276
AAGCUGCCAGUUGAAGAACUGU	SEQ ID NO:110	hsa-miR-22	>hsa-miR-22 MIMAT0000077
CCACACCGUAUCUGACACUUU	SEQ ID NO:111	hsa-miR-220	>hsa-miR-220 MIMAT0000277
AGCUACAUUGUCUGCUGGGUUUC	SEQ ID NO:112	hsa-miR-221	>hsa-miR-221 MIMAT0000278
AGCUACAUCUGGCUACUGGGUCUC	SEQ ID NO:113	hsa-miR-222	>hsa-miR-222 MIMAT0000279
UGUCAGUUUGUCAAAUACCCC	SEQ ID NO:114	hsa-miR-223	>hsa-miR-223 MIMAT0000280
CAAGUCACUAGUGGUUCCGUUUA	SEQ ID NO:115	hsa-miR-224	>hsa-miR-224 MIMAT0000281
AUCACAUUGCCAGGGAUUUCC	SEQ ID NO:116	hsa-miR-23a	>hsa-miR-23a MIMAT0000078
AUCACAUUGCCAGGGAUUACC	SEQ ID NO:117	hsa-miR-23b	>hsa-miR-23b MIMAT0000418
UGGCUCAGUUCAGCAGGAACAG	SEQ ID NO:118	hsa-miR-24	>hsa-miR-24 MIMAT0000080
CAUUGCACUUGUCUCGGUCUGA	SEQ ID NO:119	hsa-miR-25	>hsa-miR-25 MIMAT0000081
UUCAAGUAAUCCAGGAUAGGC	SEQ ID NO:120	hsa-miR-26a	>hsa-miR-26a MIMAT0000082

UUCAAGUAAUUCAGGAUAGGUU	SEQ ID NO:121	hsa-miR-26b	>hsa-miR-26b MIMAT0000083
UUCACAGUGGCUAAGUUCCGC	SEQ ID NO:122	hsa-miR-27a	>hsa-miR-27a MIMAT0000084
UUCACAGUGGCUAAGUUCUGC	SEQ ID NO:123	hsa-miR-27b	>hsa-miR-27b MIMAT0000419
AAGGAGCUCACAGUCUAUUGAG	SEQ ID NO:124	hsa-miR-28	>hsa-miR-28 MIMAT0000085
AGGGCCCCCCCUCAAUCCUGU	SEQ ID NO:125	hsa-miR-296	>hsa-miR-296 MIMAT0000690
UGGUUUACCGUCCCACAUACAU	SEQ ID NO:126	hsa-miR-299-5p	>hsa-miR-299-5p MIMAT0002890
UAGCACCAUCUGAAAUCGGUU	SEQ ID NO:127	hsa-miR-29a	>hsa-miR-29a MIMAT0000086
UAGCACCAUUUGAAAUCAGUGUU	SEQ ID NO:128	hsa-miR-29b	>hsa-miR-29b MIMAT0000100
UAGCACCAUUUGAAAUCGGU	SEQ ID NO:129	hsa-miR-29c	>hsa-miR-29c MIMAT0000681
CAGUGCAAUAGUAUUGUCAAGC	SEQ ID NO:130	hsa-miR-301	>hsa-miR-301 MIMAT0000688
UAAGUGCUUCCAUGUUUUGGUGA	SEQ ID NO:131	hsa-miR-302a	>hsa-miR-302a MIMAT0000684
UAAGUGCUUCCAUGUUUUAGUAG	SEQ ID NO:132	hsa-miR-302b	>hsa-miR-302b MIMAT0000715
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UUGUACAUGGUAGGCUUUCAUU	SEQ ID NO:326	hsa-miR-493	>hsa-miR-493-5p MIMAT0002813
UCUUGGAGUAGGUCAUUGGGUGG	SEQ ID NO:327	hsa-miR-432	>hsa-miR-432 MIMAT0002814
AAACAAACAUGGUGCACUUCUUU	SEQ ID NO:328	hsa-miR-495	>hsa-miR-495 MIMAT0002817
UGAAACAUAACACGGGAAACCUCUU	SEQ ID NO:329	hsa-miR-494	>hsa-miR-494 MIMAT0002816
AUUACAUGGCCAAUCUC	SEQ ID NO:330	hsa-miR-496	>hsa-miR-496 MIMAT0002818
AGGACCUGCGGGACAAGAUUCUU	SEQ ID NO:331	hsa-miR-492	>hsa-miR-492 MIMAT0002812
CAACCUGGAGGACUCCAUGCUG	SEQ ID NO:332	hsa-miR-490	>hsa-miR-490 MIMAT0002806
CAGCAGCACACUGUGGUUUUGU	SEQ ID NO:333	hsa-miR-497	>hsa-miR-497 MIMAT0002820
AAUCCUUGGAACCUAGGUGUGAGU	SEQ ID NO:334	ambi-miR-7076	>hsa-miR-362 MIMAT0000705
AAUCCUUUGUCCCUGGGUGAGA	SEQ ID NO:335	hsa-miR-501	>hsa-miR-501 MIMAT0002872
AUCCUUGCUAUCUGGGUGCUA	SEQ ID NO:336	hsa-miR-502	>hsa-miR-502 MIMAT0002873
UUUCCUAUGCAUAUACUUCUUU	SEQ ID NO:337	hsa-miR-202-AS	>hsa-miR-202* MIMAT0002810
GCAGUCCAUGGGCAUAUACAC	SEQ ID NO:338	ambi-miR-7083	
CACUCAGCCUUGAGGGCACUUUC	SEQ ID NO:339	hsa-miR-512-5p	>hsa-miR-512-5p MIMAT0002822
AGACCCUGGUCUGCACUCUAU	SEQ ID NO:340	hsa-miR-504	>hsa-miR-504 MIMAT0002875
GUGUCUUUUGCUCUGCAGUCA	SEQ ID NO:341	hsa-miR-511	>hsa-miR-511 MIMAT0002808
UCAGUCUCAUCUGCAAAGAAG	SEQ ID NO:342	hsa-miR-452-AS	>hsa-miR-452* MIMAT0001636
UAGCAGCGGGAACAGUUCUGCAG	SEQ ID NO:343	hsa-miR-503	>hsa-miR-503 MIMAT0002874
AGAGGCUGGCCGUGAUGAAUUC	SEQ ID NO:344	hsa-miR-485-5p	>hsa-miR-485-5p MIMAT0002175

UUAAGACUUGCAGUGAUGUUUAA	SEQ ID NO:345	hsa-miR-499	>hsa-miR-499 MIMAT0002870
GUCAACACUUGCUGGUUCCUC	SEQ ID NO:346	hsa-miR-505	>hsa-miR-505 MIMAT0002876
AGUGACAUCACAUAUACGGCAGC	SEQ ID NO:347	hsa-miR-489	>hsa-miR-489 MIMAT0002805
CUGGAUGGCUCCUCCAUGUCU	SEQ ID NO:348	hsa-miR-432- AS	>hsa-miR-432* MIMAT0002815
AUGCACCUGGGCAAGGAUUCUG	SEQ ID NO:349	hsa-miR-500	>hsa-miR-500 MIMAT0002871
UCCCCCAGGUGUGAUUCUGAUUU	SEQ ID NO:350	ambi-miR- 7105	

Other embodiments of the invention are discussed throughout this application. Any embodiment discussed with respect to one aspect of the invention applies to other aspects of the invention as well and vice versa. The embodiments in the

5 Example section are understood to be embodiments of the invention that are applicable to all aspects of the invention.

The terms “inhibiting,” “reducing,” or “prevention,” or any variation of these terms, when used in the claims and/or the specification includes any measurable decrease or complete inhibition to achieve a desired result.

10 The use of the word “a” or “an” when used in conjunction with the term “comprising” in the claims and/or the specification may mean “one,” but it is also consistent with the meaning of “one or more,” “at least one,” and “one or more than one.”

15 It is contemplated that any embodiment discussed herein can be implemented with respect to any method or composition of the invention, and vice versa. Any embodiment discussed with respect to a particular pancreatic disorder can be applied or implemented with respect to a different pancreatic disorder. Furthermore, compositions and kits of the invention can be used to achieve methods of the invention.

20 Throughout this application, the term “about” is used to indicate that a value includes the standard deviation of error for the device or method being employed to determine the value.

The use of the term “or” in the claims is used to mean “and/or” unless explicitly indicated to refer to alternatives only or the alternatives are mutually

exclusive, although the disclosure supports a definition that refers to only alternatives and “and/or.”

5 As used in this specification and claim(s), the words “comprising” (and any form of comprising, such as “comprise” and “comprises”), “having” (and any form of having, such as “have” and “has”), “including” (and any form of including, such as “includes” and “include”) or “containing” (and any form of containing, such as “contains” and “contain”) are inclusive or open-ended and do not exclude additional, unrecited elements or method steps.

10 Other objects, features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

15 According to a further aspect, the present disclosure comprises a method for identifying a pancreatic sample from a patient for pancreatic ductal adenocarcinoma (PDAC), the method comprising:

isolating microRNA from the pancreatic sample;

20 measuring expression of hsa-miR-196a (SEQ ID NO:81) in the isolated microRNA from the patient;

identifying the sample for PDAC by comparing the level of hsa-miR-196a expression in a normal pancreas sample or a control pancreatitis sample,

25 wherein an increase in hsa-miR-196a in the pancreatic sample as compared to the normal pancreatic sample or the control pancreatitis sample identifies the pancreatic sample as PDAC.

DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

FIG. 1. Integrity of total RNA from pancreatic tissues. About 1 µg of total RNA isolated from each of 24 individual pancreatic tissue samples was analyzed on a 1% denaturing formaldehyde agarose gel stained with ethidium bromide.

FIG. 2. Characterization of the expressed miRNome in normal pancreatic tissues. After global normalization of the raw array data from the 38 samples, the average miRNA expression in the 5 normal pancreatic tissues (N) was compared against the average miRNA expression in the 33 tissue reference set (Ref).

FIG. 3. Comparison of the expressed miRNome in normal and PDAC tissues. After normalization of the raw array data, the average miRNA expression in the 5 normal pancreatic tissues (N) was compared against the average miRNA expression in the 8 PDAC samples (Ca).

FIGs. 4A and 4B. miRNAs differentially expressed in normal (N), chronic pancreatitis (Ch) and PDAC samples (Ca). **(FIG. 4A)** Venn diagrams illustrating the relationships between sets of differentially expressed miRNAs. Circles include the total number of differentially expressed miRNAs in the direct pair-wise comparison indicated. Intersection areas correspond to the number of differentially expressed miRNAs shared between each comparison. **(FIG. 4B)** Principal Component Analysis on the 94 differentially expressed miRNAs from Table 6.

FIG. 5. Top 20 miRNAs differentially expressed in normal and diseased pancreatic tissues. miRNA candidates were selected for a $|\Delta h| > 1.6$ and $p\text{-value} < 0.0001$ between at least 2 out of the 3 primary tissue types. The graph shows mean normalized expression values and standard deviations for the 20 indicated miRNAs in the 3 sample types. (N), normal; (Ch), chronic pancreatitis; (Ca), PDAC.

FIG. 6. Principal Component Analysis of miRNAs differentially expressed in normal (N), chronic pancreatitis (Ch), PDAC (Ca) and cell line (CL) samples.

FIG. 7. miRNAs over-expressed in PDAC and cell line samples. Individual normalized miRNA expression levels and associated p-values in 5 normal (N), 6 chronic pancreatic (Ch), 8 PDAC (Ca) and 6 cell lines (CL) samples.

FIG. 8. Comparison between array and qRT-PCR data. Real time RT-PCR were performed using 25 ng of total RNA input from the 19 tissue samples previously profiled plus 2 normal (N), 2 PDAC (Ca) and 1 chronic pancreatic (Ch) samples. miRNA expression data obtained with primer sets specific for the indicated miRNAs were normalized to 5S rRNA expression level for each sample (miRNA Ct – 5S Ct). The graphs show the individual normalized miRNA expression levels determined by array (19 samples) or qRT-PCR (24 samples) method, and associated p-values.

FIGs. 9A and 9B. Expression of miR-196a and miR-217 classifies normal and diseased pancreatic tissues. **(FIG. 9A)** Real time RT-PCR were performed with primer sets specific for miR-196a and -217 using the indicated total RNA input amount from one normal (N5), one PDAC (Ca3) or one chronic pancreatic (Ch1) sample. Raw Ct values were directly used to calculate the ratio of miR-196a to miR-217 expression, *i.e.*, miR-196a Ct – miR217 Ct in the logarithmic space. **(FIG. 9B)**

Same study as in (**FIG. 9A**) with the indicated 24 individual tissue samples and 25 ng of total RNA input.

FIG. 10. Expression of miR-196a and miR-217 classifies normal and diseased pancreatic tissues. TaqMan® MicroRNA Assays (Applied Biosystems; Foster City, CA, USA) were performed on a subset of 20 frozen pancreatic tissue samples (6 N, 6 Ch and 8 Ca, Example 1). qRT-PCR reactions utilized 10 ng RNA input. RT reactions were carried out using random primers, while for PCR reactions gene-specific priming was used. The graph shows the raw Ct difference between miR-196a and miR-217 in individual samples and the associated p-value (ANOVA).

FIGs. 11A. and 11B. (**FIG. 11A.**) qRT-PCR expression data for four genes reported in the literature as differentially expressed between normal pancreas, chronic pancreatitis and pancreatic adenocarcinoma. The same sample set as in **Fig. 10** (20 frozen pancreatic tissue samples; 6 N, 6 Ch and 8 Ca) was interrogated using TaqMan® Gene Expression Assays (Applied Biosystems). qRT-PCR reactions were performed with random priming for RT reactions and gene-specific priming for PCR reactions, using 5 ng of total RNA input. For each sample, mRNA expression data were normalized to the expression of GAPDH (mRNA-X Ct – GAPDH Ct). The graphs show the individual normalized mRNA expression levels determined by qRT-PCR and associated p-values (ANOVA). (**FIG. 11B.**) Combinations of miR-196a, miR-217 and mRNA gene expression signatures improve segregation of normal pancreas, chronic pancreatitis and pancreatic cancer. These graphs show separation between the experimental groups achieved through combining the individual Ct values for markers normalized to miR-24 (miRNAs) or GAPDH (mRNAs), as well as associated p-values (ANOVA).

FIG. 12. A comparison of differential expression data for six miRNA and two mRNA genes between frozen pancreatic tissue samples (6 N, 6C h and 8 Ca) and pancreatic fine needle aspirates (FNAs, n=13). Ten FNA samples were pathologically described as PDAC (Ca FNA, solid diamonds). Of the remaining three samples (FNA), two had a non-definitive pathological description (FNA-8- solid circle and FNA-13- star), and one was consistent with neoplasia of endocrine pancreas (FNA-12, solid triangle). Real time RT-PCR reactions were performed and normalized as in FIGs. 10 and 11.

FIG. 13. Performance comparison of combinations of miR-196a, miR-217 and mRNA gene expression signatures between frozen normal pancreas, chronic pancreatitis, pancreatic cancer, pancreatic cancer FNAs (Ca FNAs, solid diamonds) and other FNAs (FNAs, FNA-8- solid circle, FNA-12- solid triangle and FNA-13- star). The graphs show the separation between the experimental groups achieved using the combination of the individual miRNA/mRNA expression signatures normalized to miR-24 (miRNAs) or GAPDH (mRNAs).

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compositions and methods relating to preparation and characterization of miRNAs, as well as use of miRNAs for therapeutic, prognostic, and diagnostic applications, particularly those methods and compositions related to assessing and/or identifying pancreatic disease.

I. miRNA Molecules

MicroRNA molecules ("miRNAs") are generally 21 to 22 nucleotides in length, though lengths of 19 and up to 23 nucleotides have been reported. The miRNAs are each processed from a longer precursor RNA molecule ("precursor miRNA"). Precursor miRNAs are transcribed from non-protein-encoding genes. The precursor miRNAs have two regions of complementarity that enables them to form a stem-loop- or fold-back-like structure, which is cleaved in animals by a ribonuclease III-like nuclease enzyme called Dicer. The processed miRNA is typically a portion of the stem.

The processed miRNA (also referred to as "mature miRNA") become part of a large complex to down-regulate a particular target gene. Examples of animal miRNAs include those that imperfectly basepair with the target, which halts translation (Olsen *et al.*, 1999; Seggerson *et al.*, 2002). siRNA molecules also are processed by Dicer, but from a long, double-stranded RNA molecule. siRNAs are not naturally found in animal cells, but they can direct the sequence-specific cleavage of an mRNA target through a RNA-induced silencing complex (RISC) (Denli *et al.*, 2003).

A. Nucleic Acids

The present invention concerns miRNAs that can be labeled, used in array analysis, or employed in diagnostic, therapeutic, or prognostic applications, particularly those related to pathological conditions of the pancreas. The RNA may have been endogenously produced by a cell, or been synthesized or produced chemically or recombinantly. They may be isolated and/or purified. The term “miRNA,” unless otherwise indicated, refers to the processed RNA, after it has been cleaved from its precursor. Table 1 indicates which SEQ ID NO correspond to the mature sequence. The name of the miRNA is often abbreviated and referred to without a hsa-, mmu-, or rno- prefix and will be understood as such, depending on the context. Unless otherwise indicated, miRNAs referred to in the application are human sequences identified as miR-X or let-X, where X is a number and/or letter.

In certain experiments, a miRNA probe designated by a suffix “5P” or “3P” can be used. “5P” indicates that the mature miRNA derives from the 5’ end of the precursor and a corresponding “3P” indicates that it derives from the 3’ end of the precursor, as described on the World Wide Web at sanger.ac.uk. Moreover, in some embodiments, a miRNA probe is used that does not correspond to a known human miRNA. It is contemplated that these non-human miRNA probes may be used in embodiments of the invention or that there may exist a human miRNA that is homologous to the non-human miRNA. While the invention is not limited to human miRNA, in certain embodiments, miRNA from human cells or a human biological sample is evaluated. In other embodiments, any mammalian cell, biological sample, or preparation thereof may be employed.

In some embodiments of the invention, methods and compositions involving miRNA may concern miRNA and/or other nucleic acids. Nucleic acids may be, be at least, or be at most 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 441,

450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, 810, 820, 830, 840, 850, 860, 870, 880, 890, 900, 910, 920, 930, 940, 950, 960, 970, 980, 990, or 1000 nucleotides, or any range derivable therein, in length.

- 5 Such lengths cover the lengths of processed miRNA, miRNA probes, precursor miRNA, miRNA containing vectors, control nucleic acids, and other probes and primers. In many embodiments, miRNA are 19-24 nucleotides in length, while miRNA probes are 19-35 nucleotides in length, depending on the length of the processed miRNA and any flanking regions added. miRNA precursors are generally
10 between 62 and 110 nucleotides in human s.

Nucleic acids of the invention may have regions of identity or complementarity to another nucleic acid. It is contemplated that the region of complementarity or identity can be at least 5 contiguous residues, though it is specifically contemplated that the region is, is at least, or is at most 6, 7, 8, 9, 10, 11,
15 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290,
20 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 441, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, 810, 820, 830, 840, 850, 860, 870, 880, 890, 900, 910, 920, 930, 940, 950, 960, 970, 980, 990, or 1000 contiguous nucleotides. It is further understood that the length
25 of complementarity within a precursor miRNA or between a miRNA probe and a miRNA or a miRNA gene are such lengths. Moreover, the complementarity may be expressed as a percentage, meaning that the complementarity between a probe and its target is 90% or greater over the length of the probe. In some embodiments, complementarity is or is at least 90%, 95% or 100%. In particular, such lengths may
30 be applied to any nucleic acid comprising a nucleic acid sequence identified in any of SEQ ID NO:1 through SEQ ID NO:350 or any other sequence disclosed herein. Each of these SEQ ID NOs is disclosed herein. The commonly used name of the miRNA is given (with its identifying source in the prefix, for example, "hsa" for human

sequences) and the processed miRNA sequence. Unless otherwise indicated, a miRNA without a prefix will be understood to refer to a human miRNA. A miRNA designated, for example, as miR-1-2 in the application will be understood to refer to hsa-miR-1-2. Moreover, a lowercase letter in the table below may or may not be
5 lowercase; for example, hsa-mir-130b can also be referred to as miR-130B. In addition, miRNA sequences with a “mu” or “mmu” sequence will be understood to refer to a mouse miRNA and miRNA sequences with a “rno” sequence will be understood to refer to a rat miRNA. The term “miRNA probe” refers to a nucleic acid probe that can identify a particular miRNA or structurally related miRNAs.

10 It is understood that a miRNA is derived from genomic sequences or a gene. In this respect, the term “gene” is used for simplicity to refer to the genomic sequence encoding the precursor miRNA for a given miRNA. However, embodiments of the invention may involve genomic sequences of a miRNA that are involved in its expression, such as a promoter or other regulatory sequences.

15 The term “recombinant” may be used and this generally refers to a molecule that has been manipulated *in vitro* or that is a replicated or expressed product of such a molecule.

The term “nucleic acid” is well known in the art. A “nucleic acid” as used herein will generally refer to a molecule (one or more strands) of DNA, RNA or a
20 derivative or analog thereof, comprising a nucleobase. A nucleobase includes, for example, a naturally occurring purine or pyrimidine base found in DNA (*e.g.*, an adenine “A,” a guanine “G,” a thymine “T” or a cytosine “C”) or RNA (*e.g.*, an A, a G, an uracil “U” or a C). The term “nucleic acid” encompasses the terms “oligonucleotide” and “polynucleotide,” each as a subgenus of the term “nucleic
25 acid.”

The term “miRNA” generally refers to a single-stranded molecule, but in specific embodiments, molecules implemented in the invention will also encompass a region or an additional strand that is partially (between 10 and 50% complementary across length of strand), substantially (greater than 50% but less than 100%
30 complementary across length of strand) or fully complementary to another region of the same single-stranded molecule or to another nucleic acid. Thus, nucleic acids

may encompass a molecule that comprises one or more complementary or self-complementary strand(s) or “complement(s)” of a particular sequence comprising a molecule. For example, precursor miRNA may have a self-complementary region, which is up to 100% complementary. miRNA probes or nucleic acids of the invention can include, can be or can be at least 60, 65, 70, 75, 80, 85, 90, 95, 96, 97, 98, 99 or 100% complementary to their target.

As used herein, “hybridization”, “hybridizes” or “capable of hybridizing” is understood to mean the forming of a double or triple stranded molecule or a molecule with partial double or triple stranded nature. The term “anneal” as used herein is synonymous with “hybridize.” The term “hybridization”, “hybridize(s)” or “capable of hybridizing” encompasses the terms “stringent condition(s)” or “high stringency” and the terms “low stringency” or “low stringency condition(s).”

As used herein “stringent condition(s)” or “high stringency” are those conditions that allow hybridization between or within one or more nucleic acid strand(s) containing complementary sequence(s), but preclude hybridization of random sequences. Stringent conditions tolerate little, if any, mismatch between a nucleic acid and a target strand. Such conditions are well known to those of ordinary skill in the art, and are preferred for applications requiring high selectivity. Non-limiting applications include isolating a nucleic acid, such as a gene or a nucleic acid segment thereof, or detecting at least one specific mRNA transcript or a nucleic acid segment thereof, and the like.

Stringent conditions may comprise low salt and/or high temperature conditions, such as provided by about 0.02 M to about 0.5 M NaCl at temperatures of about 42°C to about 70°C. It is understood that the temperature and ionic strength of a desired stringency are determined in part by the length of the particular nucleic acid(s), the length and nucleobase content of the target sequence(s), the charge composition of the nucleic acid(s), and to the presence or concentration of formamide, tetramethylammonium chloride or other solvent(s) in a hybridization mixture.

It is also understood that these ranges, compositions and conditions for hybridization are mentioned by way of non-limiting examples only, and that the desired stringency for a particular hybridization reaction is often determined

empirically by comparison to one or more positive or negative controls. Depending on the application envisioned it is preferred to employ varying conditions of hybridization to achieve varying degrees of selectivity of a nucleic acid towards a target sequence. In a non-limiting example, identification or isolation of a related target nucleic acid that does not hybridize to a nucleic acid under stringent conditions may be achieved by hybridization at low temperature and/or high ionic strength. Such conditions are termed “low stringency” or “low stringency conditions,” and non-limiting examples of low stringency include hybridization performed at about 0.15 M to about 0.9 M NaCl at a temperature range of about 20°C to about 50°C. Of course, it is within the skill of one in the art to further modify the low or high stringency conditions to suite a particular application.

1. Nucleobases

As used herein a “nucleobase” refers to a heterocyclic base, such as for example a naturally occurring nucleobase (*i.e.*, an A, T, G, C or U) found in at least one naturally occurring nucleic acid (*i.e.*, DNA and RNA), and naturally or non-naturally occurring derivative(s) and analogs of such a nucleobase. A nucleobase generally can form one or more hydrogen bonds (“anneal” or “hybridize”) with at least one naturally occurring nucleobase in manner that may substitute for naturally occurring nucleobase pairing (*e.g.*, the hydrogen bonding between A and T, G and C, and A and U).

“Purine” and/or “pyrimidine” nucleobase(s) encompass naturally occurring purine and/or pyrimidine nucleobases and also derivative(s) and analog(s) thereof, including but not limited to, those a purine or pyrimidine substituted by one or more of an alkyl, caboxyalkyl, amino, hydroxyl, halogen (*i.e.*, fluoro, chloro, bromo, or iodo), thiol or alkylthiol moiety. Preferred alkyl (*e.g.*, alkyl, caboxyalkyl, *etc.*) moieties comprise of from about 1, about 2, about 3, about 4, about 5, to about 6 carbon atoms. Other non-limiting examples of a purine or pyrimidine include a deazapurine, a 2,6-diaminopurine, a 5-fluorouracil, a xanthine, a hypoxanthine, a 8-bromoguanine, a 8-chloroguanine, a bromothymine, a 8-aminoguanine, a 8-hydroxyguanine, a 8-methylguanine, a 8-thioguanine, an azaguanine, a 2-aminopurine, a 5-ethylcytosine, a 5-methylcyosine, a 5-bromouracil, a 5-ethyluracil, a 5-iodouracil, a 5-chlorouracil, a 5-propyluracil, a thiouracil, a 2-methyladenine, a

methylthioadenine, a N,N-dimethyladenine, an azaadenines, a 8-bromoadenine, a 8-hydroxyadenine, a 6-hydroxyaminopurine, a 6-thiopurine, a 4-(6-aminoethyl/cytosine), and the like. Other examples are well known to those of skill in the art.

5 A nucleobase may be comprised in a nucleoside or nucleotide, using any chemical or natural synthesis method described herein or known to one of ordinary skill in the art. Such nucleobase may be labeled or it may be part of a molecule that is labeled and contains the nucleobase.

2. Nucleosides

10 As used herein, a “nucleoside” refers to an individual chemical unit comprising a nucleobase covalently attached to a nucleobase linker moiety. A non-limiting example of a “nucleobase linker moiety” is a sugar comprising 5-carbon atoms (*i.e.*, a “5-carbon sugar”), including but not limited to a deoxyribose, a ribose, an arabinose, or a derivative or an analog of a 5-carbon sugar. Non-limiting examples
15 of a derivative or an analog of a 5-carbon sugar include a 2'-fluoro-2'-deoxyribose or a carbocyclic sugar where a carbon is substituted for an oxygen atom in the sugar ring.

Different types of covalent attachment(s) of a nucleobase to a nucleobase linker moiety are known in the art. By way of non-limiting example, a nucleoside comprising a purine (*i.e.*, A or G) or a 7-deazapurine nucleobase typically covalently
20 attaches the 9 position of a purine or a 7-deazapurine to the 1'-position of a 5-carbon sugar. In another non-limiting example, a nucleoside comprising a pyrimidine nucleobase (*i.e.*, C, T or U) typically covalently attaches a 1 position of a pyrimidine to a 1'-position of a 5-carbon sugar (Kornberg and Baker, 1992).

3. Nucleotides

25 As used herein, a “nucleotide” refers to a nucleoside further comprising a “backbone moiety”. A backbone moiety generally covalently attaches a nucleotide to another molecule comprising a nucleotide, or to another nucleotide to form a nucleic acid. The “backbone moiety” in naturally occurring nucleotides typically comprises a phosphorus moiety, which is covalently attached to a 5-carbon sugar. The attachment
30 of the backbone moiety typically occurs at either the 3'- or 5'-position of the 5-carbon sugar. However, other types of attachments are known in the art, particularly when a

a nucleotide comprises derivatives or analogs of a naturally occurring 5-carbon sugar or phosphorus moiety.

4. Nucleic Acid Analogs

A nucleic acid may comprise, or be composed entirely of, a derivative or analog of a nucleobase, a nucleobase linker moiety and/or backbone moiety that may be present in a naturally occurring nucleic acid. RNA with nucleic acid analogs may also be labeled according to methods of the invention. As used herein a "derivative" refers to a chemically modified or altered form of a naturally occurring molecule, while the terms "mimic" or "analog" refer to a molecule that may or may not structurally resemble a naturally occurring molecule or moiety, but possesses similar functions. As used herein, a "moiety" generally refers to a smaller chemical or molecular component of a larger chemical or molecular structure. Nucleobase, nucleoside and nucleotide analogs or derivatives are well known in the art, and have been described (see for example, Scheit, 1980).

Additional non-limiting examples of nucleosides, nucleotides or nucleic acids comprising 5-carbon sugar and/or backbone moiety derivatives or analogs, include those in: U.S. Patent 5,681,947, which describes oligonucleotides comprising purine derivatives that form triple helixes with and/or prevent expression of dsDNA; U.S. Patents 5,652,099 and 5,763,167, which describe nucleic acids incorporating fluorescent analogs of nucleosides found in DNA or RNA, particularly for use as fluorescent nucleic acids probes; U.S. Patent 5,614,617, which describes oligonucleotide analogs with substitutions on pyrimidine rings that possess enhanced nuclease stability; U.S. Patents 5,670,663, 5,872,232 and 5,859,221, which describe oligonucleotide analogs with modified 5-carbon sugars (i.e., modified T-deoxyfuranosyl moieties) used in nucleic acid detection; U.S. Patent 5,446,137, which describes oligonucleotides comprising at least one 5-carbon sugar moiety substituted at the 4' position with a substituent other than hydrogen that can be used in hybridization assays; U.S. Patent 5,886,165, which describes oligonucleotides with both deoxyribonucleotides with 3'-5' internucleotide linkages and ribonucleotides with 2'-5' internucleotide linkages; U.S. Patent 5,714,606, which describes a modified internucleotide linkage wherein a 3'-position oxygen of the internucleotide linkage is replaced by a carbon to enhance the nuclease resistance of nucleic acids; U.S. Patent

5,672,697, which describes oligonucleotides containing one or more 5' methylene phosphonate internucleotide linkages that enhance nuclease resistance; U.S. Patents 5,466,786 and 5,792,847, which describe the linkage of a substituent moiety which may comprise a drug or label to the 2' carbon of an oligonucleotide to provide enhanced nuclease stability and ability to deliver drugs or detection moieties; U.S. Patent 5,223,618, which describes oligonucleotide analogs with a 2 or 3 carbon backbone linkage attaching the 4' position and 3' position of adjacent 5-carbon sugar moiety to enhanced cellular uptake, resistance to nucleases and hybridization to target RNA; U.S. Patent 5,470,967, which describes oligonucleotides comprising at least one sulfamate or sulfamide internucleotide linkage that are useful as nucleic acid hybridization probe; U.S. Patents 5,378,825, 5,777,092, 5,623,070, 5,610,289 and 5,602,240, which describe oligonucleotides with three or four atom linker moiety replacing phosphodiester backbone moiety used for improved nuclease resistance, cellular uptake, and regulating RNA expression; U.S. Patent 5,858,988, which describes hydrophobic carrier agent attached to the 2'-O position of oligonucleotides to enhanced their membrane permeability and stability; U.S. Patent 5,214,136, which describes oligonucleotides conjugated to anthraquinone at the 5' terminus that possess enhanced hybridization to DNA or RNA; enhanced stability to nucleases; U.S. Patent 5,700,922, which describes PNA-DNA-PNA chimeras wherein the DNA comprises 2'-deoxy-erythro-pentofuranosyl nucleotides for enhanced nuclease resistance, binding affinity, and ability to activate RNase H; and U.S. Patent 5,708,154, which describes RNA linked to a DNA to form a DNA-RNA hybrid; U.S. Patent 5,728,525, which describes the labeling of nucleoside analogs with a universal fluorescent label.

Additional teachings for nucleoside analogs and nucleic acid analogs are U.S. Patent 5,728,525, which describes nucleoside analogs that are end-labeled; U.S. Patent 5,637,683, 6,251,666 (L-nucleotide substitutions), and 5,480,980 (7-deaza-2'-deoxyguanosine nucleotides and nucleic acid analogs thereof).

5. Modified Nucleotides

Labeling methods and kits of the invention specifically contemplate the use of nucleotides that are both modified for attachment of a label and can be incorporated into a miRNA molecule. Such nucleotides include those that can be labeled with a dye, including a fluorescent dye, or with a molecule such as biotin. Labeled

nucleotides are readily available; they can be acquired commercially or they can be synthesized by reactions known to those of skill in the art.

Modified nucleotides for use in the invention are not naturally occurring nucleotides, but instead, refer to prepared nucleotides that have a reactive moiety on them. Specific reactive functionalities of interest include: amino, sulfhydryl, sulfoxyl, 5 aminosulfhydryl, azido, epoxide, isothiocyanate, isocyanate, anhydride, monochlorotriazine, dichlorotriazine, mono-or dihalogen substituted pyridine, mono- or disubstituted diazine, maleimide, epoxide, aziridine, sulfonyl halide, acid halide, alkyl halide, aryl halide, alkylsulfonate, N-hydroxysuccinimide ester, imido ester, hydrazine, 10 azidonitrophenyl, azide, 3-(2-pyridyl dithio)-propionamide, glyoxal, aldehyde, iodoacetyl, cyanomethyl ester, p-nitrophenyl ester, o-nitrophenyl ester, hydroxypyridine ester, carbonyl imidazole, and the other such chemical groups. In some embodiments, the reactive functionality may be bonded directly to a nucleotide, or it may be bonded to the nucleotide through a linking group. The functional moiety 15 and any linker cannot substantially impair the ability of the nucleotide to be added to the miRNA or to be labeled. Representative linking groups include carbon containing linking groups, typically ranging from about 2 to 18, usually from about 2 to 8 carbon atoms, where the carbon containing linking groups may or may not include one or more heteroatoms, e.g. S, O, N etc., and may or may not include one or more sites of 20 unsaturation. Of particular interest in many embodiments are alkyl linking groups, typically lower alkyl linking groups of 1 to 16, usually 1 to 4 carbon atoms, where the linking groups may include one or more sites of unsaturation. The functionalized nucleotides (or primers) used in the above methods of functionalized target generation may be fabricated using known protocols or purchased from commercial vendors, e.g., 25 Sigma, Roche, Ambion, Biosearch Technologies and NEN. Functional groups may be prepared according to ways known to those of skill in the art, including the representative information found in U.S. Patents 4,404,289; 4,405,711; 4,337,063 and 5,268,486, and U.K. Patent 1,529,202.

Amine-modified nucleotides are used in several embodiments of the invention. 30 The amine-modified nucleotide is a nucleotide that has a reactive amine group for attachment of the label. It is contemplated that any ribonucleotide (G, A, U, or C) or deoxyribonucleotide (G, A, T, or C) can be modified for labeling. Examples include,

but are not limited to, the following modified ribo- and deoxyribo-nucleotides: 5-(3-aminoallyl)-UTP; 8-[(4-amino)butyl]-amino-ATP and 8-[(6-amino)butyl]-amino-ATP; N6-(4-amino)butyl-ATP, N6-(6-amino)butyl-ATP, N4-[2,2-oxy-bis-(ethylamine)]-CTP; N6-(6-amino)hexyl-ATP; 8-[(6-amino)hexyl]-amino-ATP; 5-propargylamino-CTP, 5-propargylamino-UTP; 5-(3-aminoallyl)-dUTP; 8-[(4-amino)butyl]-amino-dATP and 8-[(6-amino)butyl]-amino-dATP; N6-(4-amino)butyl-dATP, N6-(6-amino)butyl-dATP, N4-[2,2-oxy-bis-(ethylamine)]-dCTP; N6-(6-amino)hexyl-dATP; 8-[(6-Amino)hexyl]-amino-dATP; 5-propargylamino-dCTP, and 5-propargylamino-dUTP. Such nucleotides can be prepared according to methods known to those of skill in the art. Moreover, a person of ordinary skill in the art could prepare other nucleotide entities with the same amine-modification, such as a 5-(3- aminoallyl)-CTP, GTP, ATP, dCTP, dGTP, dTTP, or dUTP in place of a 5-(3- aminoallyl)-UTP.

B. Preparation of Nucleic Acids

A nucleic acid may be made by any technique known to one of ordinary skill in the art, such as for example, chemical synthesis, enzymatic production or biological production. It is specifically contemplated that miRNA probes of the invention are chemically synthesized.

In some embodiments of the invention, miRNAs are recovered or isolated from a biological sample. The miRNA may be recombinant or it may be natural or endogenous to the cell (produced from the cell's genome). It is contemplated that a biological sample may be treated in a way so as to enhance the recovery of small RNA molecules such as miRNA. U.S. Patent Application Serial No. 10/667,126 describes such methods. Generally, methods involve lysing cells with a solution having guanidinium and a detergent.

Alternatively, nucleic acid synthesis is performed according to standard methods. See, for example, Itakura and Riggs (1980). Additionally, U.S. Patents 4,704,362, 5,221,619, and 5,583,013 each describe various methods of preparing synthetic nucleic acids. Non-limiting examples of a synthetic nucleic acid (*e.g.*, a synthetic oligonucleotide), include a nucleic acid made by *in vitro* chemically synthesis using phosphotriester, phosphite, or phosphoramidite chemistry and solid

phase techniques such as described in EP 266,032 or via deoxynucleoside H-phosphonate intermediates as described by Froehler et al. , 1986 and U.S. Patent 5,705,629. In the methods of the present invention, one or more oligonucleotide may be used. Various different mechanisms of oligonucleotide synthesis have been disclosed in
 5 for example, U.S. Patents 4,659,774, 4,816,571, 5,141,813, 5,264,566, 4,959,463, 5,428,148, 5,554,744, 5,574,146, 5,602,244.

A non-limiting example of an enzymatically produced nucleic acid include one produced by enzymes in amplification reactions such as PCR; (see for example, U.S. Patents 4,683,202 and 4,682,195), or the synthesis of an oligonucleotide described in
 10 U.S. Patent 5,645,897. A non-limiting example of a biologically produced nucleic acid includes a recombinant nucleic acid produced {i.e., replicated) in a living cell, such as a recombinant DNA vector replicated in bacteria (see for example, Sambrook et al, 2001).

Oligonucleotide synthesis is well known to those of skill in the art. Various different mechanisms of oligonucleotide synthesis have been disclosed in for example,
 15 U.S. Patents 4,659,774, 4,816,571, 5,141,813, 5,264,566, 4,959,463, 5,428,148, 5,554,744, 5,574,146, 5,602,244.

Basically, chemical synthesis can be achieved by the diester method, the triester method polynucleotides phosphorylase method and by solid-phase chemistry. The diester method was the first to be developed to a usable state, primarily by Khorana and
 20 co-workers. (Khorana, 1979). The basic step is the joining of two suitably protected deoxynucleotides to form a dideoxynucleotide containing a phosphodiester bond.

The main difference between the diester and triester methods is the presence in the latter of an extra protecting group on the phosphate atoms of the reactants and products (Itakura *et al.*, 1975). Purification's are typically done in chloroform solutions.
 25 Other improvements in the method include (i) the block coupling of trimers

and larger oligomers, (ii) the extensive use of high-performance liquid chromatography for the purification of both intermediate and final products, and (iii) solid-phase synthesis.

Polynucleotide phosphorylase method is an enzymatic method of DNA
5 synthesis that can be used to synthesize many useful oligonucleotides (Gillam *et al.*, 1978; Gillam *et al.*, 1979). Under controlled conditions, polynucleotide phosphorylase adds predominantly a single nucleotide to a short oligonucleotide. Chromatographic purification allows the desired single adduct to be obtained. At least a trimer is required to start the procedure, and this primer must be obtained by
10 some other method. The polynucleotide phosphorylase method works and has the advantage that the procedures involved are familiar to most biochemists.

Solid-phase methods draw on technology developed for the solid-phase synthesis of polypeptides, it has been possible to attach the initial nucleotide to solid support material and proceed with the stepwise addition of nucleotides. All mixing
15 and washing steps are simplified, and the procedure becomes amenable to automation. These syntheses are now routinely carried out using automatic nucleic acid synthesizers.

Phosphoramidite chemistry (Beaucage and Lyer, 1992) has become by far the most widely used coupling chemistry for the synthesis of oligonucleotides.
20 Phosphoramidite synthesis of oligonucleotides involves activation of nucleoside phosphoramidite monomer precursors by reaction with an activating agent to form activated intermediates, followed by sequential addition of the activated intermediates to the growing oligonucleotide chain (generally anchored at one end to a suitable solid support) to form the oligonucleotide product.

25 Recombinant methods for producing nucleic acids in a cell are well known to those of skill in the art. These include the use of vectors (viral and non-viral), plasmids, cosmids, and other vehicles for delivering a nucleic acid to a cell, which may be the target cell (*e.g.*, a cancer cell) or simply a host cell (to produce large quantities of the desired RNA molecule). Alternatively, such vehicles can be used in
30 the context of a cell free system so long as the reagents for generating the RNA

molecule are present. Such methods include those described in Sambrook, 2003, Sambrook, 2001 and Sambrook, 1989 by reference.

5 In certain embodiments, the present invention concerns nucleic acid molecules that are not synthetic. In some embodiments, the nucleic acid molecule has a chemical structure of a naturally occurring nucleic acid and a sequence of a naturally occurring nucleic acid, such as the exact and entire sequence of a single stranded primary miRNA (see Lee, 2002), a single-stranded precursor miRNA, or a single-stranded mature miRNA. In addition to the use of recombinant technology, such non- synthetic nucleic acids may be generated chemically, such as by employing technology used for creating
10 oligonucleotides.

C. Isolation of Nucleic Acids

Nucleic acids may be isolated using techniques well known to those of skill in the art, though in particular embodiments, methods for isolating small nucleic acid molecules, and/or isolating RNA molecules can be employed. Chromatography is a
15 process often used to separate or isolate nucleic acids from protein or from other nucleic acids. Such methods can involve electrophoresis with a gel matrix, filter columns, alcohol precipitation, and/or other chromatography. If miRNA from cells is to be used or evaluated, methods generally involve lysing the cells with a chaotropic (e.g., guanidinium isothiocyanate) and/or detergent (e.g., N-lauroyl sarcosine) prior to
20 implementing processes for isolating particular populations of RNA.

In particular methods for separating miRNA from other nucleic acids, a gel matrix is prepared using polyacrylamide, though agarose can also be used. The gels may be graded by concentration or they may be uniform. Plates or tubing can be used to hold the gel matrix for electrophoresis. Usually one-dimensional electrophoresis is employed
25 for the separation of nucleic acids. Plates are used to prepare a slab gel, while the tubing (glass or rubber, typically) can be used to prepare a tube gel. The phrase "tube electrophoresis" refers to the use of a tube or tubing, instead of plates, to form the gel. Materials for implementing tube electrophoresis can be readily prepared by a person of skill in the art or purchased, such as from C.B.S. Scientific Co., Inc. or Scie-Plas.

Methods may involve the use of organic solvents and/or alcohol to isolate nucleic acids, particularly miRNA used in methods and compositions of the invention. Some embodiments are described in U.S. Patent Application Serial No. 10/667,126. Generally, this disclosure provides methods for efficiently isolating small RNA molecules from cells comprising: adding an alcohol solution to a cell lysate and applying the alcohol/lysate mixture to a solid support before eluting the RNA molecules from the solid support. In some embodiments, the amount of alcohol added to a cell lysate achieves an alcohol concentration of about 55% to 60%. While different alcohols can be employed, ethanol works well. A solid support may be any structure, and it includes beads, filters, and columns, which may include a mineral or polymer support with electronegative groups. A glass fiber filter or column has worked particularly well for such isolation procedures.

In specific embodiments, miRNA isolation processes include: a) lysing cells in the sample with a lysing solution comprising guanidinium, wherein a lysate with a concentration of at least about 1 M guanidinium is produced; b) extracting miRNA molecules from the lysate with an extraction solution comprising phenol; c) adding to the lysate an alcohol solution to form a lysate/alcohol mixture, wherein the concentration of alcohol in the mixture is between about 35% to about 70%; d) applying the lysate/alcohol mixture to a solid support; e) eluting the miRNA molecules from the solid support with an ionic solution; and, f) capturing the miRNA molecules. Typically the sample is dried down and resuspended in a liquid and volume appropriate for subsequent manipulation.

II. Labels and Labeling Techniques

In some embodiments, the present invention concerns miRNA that are labeled. It is contemplated that miRNA may first be isolated and/or purified prior to labeling. This may achieve a reaction that more efficiently labels the miRNA, as opposed to other RNA in a sample in which the miRNA is not isolated or purified prior to labeling. In many embodiments of the invention, the label is non-radioactive. Generally, nucleic acids may be labeled by adding labeled nucleotides (one-step process) or adding nucleotides and labeling the added nucleotides (two-step process).

A. Labeling Techniques

In some embodiments, nucleic acids are labeled by catalytically adding to the nucleic acid an already labeled nucleotide or nucleotides. One or more labeled nucleotides can be added to miRNA molecules. See U.S Patent 6,723,509.

5 In other embodiments, an unlabeled nucleotide or nucleotides is catalytically added to a miRNA, and the unlabeled nucleotide is modified with a chemical moiety that enables it to be subsequently labeled. In embodiments of the invention, the chemical moiety is a reactive amine such that the nucleotide is an amine-modified nucleotide. Examples of amine-modified nucleotides are well known to those of skill in the art,
10 many being commercially available such as from Ambion, Sigma, Jena Bioscience, and TriLink.

In contrast to labeling of cDNA during its synthesis, the issue for labeling miRNA is how to label the already existing molecule. The present invention concerns the use of an enzyme capable of using a di- or tri-phosphate ribonucleotide or
15 deoxyribonucleotide as a substrate for its addition to a miRNA. Moreover, in specific embodiments, it involves using a modified di- or tri-phosphate ribonucleotide, which is added to the 3' end of a miRNA. The source of the enzyme is not limiting. Examples of sources for the enzymes include yeast, gram-negative bacteria such as *E. coli*, *Lactococcus lactis*, and sheep pox virus.

20 Enzymes capable of adding such nucleotides include, but are not limited to, poly(A) polymerase, terminal transferase, and polynucleotide phosphorylase. In specific embodiments of the invention, a ligase is contemplated as not being the enzyme used to add the label, and instead, a non-ligase enzyme is employed.

25 Terminal transferase catalyzes the addition of nucleotides to the 3' terminus of a nucleic acid.

Polynucleotide phosphorylase can polymerize nucleotide diphosphates without the need for a primer.

B. Labels

Labels on miRNA or miRNA probes may be colorimetric (includes visible and UV spectrum, including fluorescent), luminescent, enzymatic, or positron emitting (including radioactive). The label may be detected directly or indirectly. Radioactive
 5 labels include ^{125}I , ^{32}P , ^{33}P , and ^{35}S . Examples of enzymatic labels include alkaline phosphatase, luciferase, horseradish peroxidase, and β -galactosidase. Labels can also be proteins with luminescent properties, *e.g.*, green fluorescent protein and phicoerythrin.

The colorimetric and fluorescent labels contemplated for use as conjugates
 10 include, but are not limited to, Alexa Fluor dyes, BODIPY dyes, such as BODIPY FL; Cascade Blue; Cascade Yellow; coumarin and its derivatives, such as 7-amino-4-methylcoumarin, aminocoumarin and hydroxycoumarin; cyanine dyes, such as Cy3 and Cy5; eosins and erythrosins; fluorescein and its derivatives, such as fluorescein isothiocyanate; macrocyclic chelates of lanthanide ions, such as Quantum DyeTM;
 15 Marina Blue; Oregon Green; rhodamine dyes, such as rhodamine red, tetramethylrhodamine and rhodamine 6G; Texas Red; , fluorescent energy transfer dyes, such as thiazole orange-ethidium heterodimer; and, TOTAB.

Specific examples of dyes include, but are not limited to, those identified above and the following: Alexa Fluor 350, Alexa Fluor 405, Alexa Fluor 430, Alexa
 20 Fluor 488, Alexa Fluor 500. Alexa Fluor 514, Alexa Fluor 532, Alexa Fluor 546, Alexa Fluor 555, Alexa Fluor 568, Alexa Fluor 594, Alexa Fluor 610, Alexa Fluor 633, Alexa Fluor 647, Alexa Fluor 660, Alexa Fluor 680, Alexa Fluor 700, and, Alexa Fluor 750; amine-reactive BODIPY dyes, such as BODIPY 493/503, BODIPY 530/550, BODIPY 558/568, BODIPY 564/570, BODIPY 576/589, BODIPY 581/591,
 25 BODIPY 630/650, BODIPY 650/655, BODIPY FL, BODIPY R6G, BODIPY TMR, and, BODIPY-TR; Cy3, Cy5, 6-FAM, Fluorescein Isothiocyanate, HEX, 6-JOE, Oregon Green 488, Oregon Green 500, Oregon Green 514, Pacific Blue, REG, Rhodamine Green, Rhodamine Red, Renographin, ROX, SYPRO, TAMRA, 2',4',5',7'-Tetrabromosulfonefluorescein, and TET.

30 Specific examples of fluorescently labeled ribonucleotides are available from Molecular Probes, and these include, Alexa Fluor 488-5-UTP, Fluorescein-12-UTP,

BODIPY FL-14-UTP, BODIPY TMR-14-UTP, Tetramethylrhodamine-6-UTP, Alexa Fluor 546-14-UTP, Texas Red-5-UTP, and BODIPY TR-14-UTP. Other fluorescent ribonucleotides such as Cy3-UTP and Cy5-UTP are available from Amersham Biosciences.

5 Examples of fluorescently labeled deoxyribonucleotides include Dinitrophenyl (DNP)-1 1-dUTP, Cascade Blue-7-dUTP, Alexa Fluor 488-5-dUTP, Fluorescein- 12-dUTP, Oregon Green 488-5-dUTP, BODIPY FL-14-dUTP, Rhodamine Green-5- dUTP, Alexa Fluor 532-5-dUTP, BODIPY TMR-14-dUTP, Tetramethylrhodamine-6- dUTP, Alexa Fluor 546-14-dUTP, Alexa Fluor 568-5-dUTP, Texas Red-12-dUTP, Texas Red-
10 5-dUTP, BODIPY TR-14-dUTP, Alexa Fluor 594-5-dUTP, BODIPY 630/650- 14-dUTP, BODIPY 650/665-14-dUTP; Alexa Fluor 488-7-OBEA-dCTP, Alexa Fluor 546-1 6-OBEA-dCTP, Alexa Fluor 594-7-OBEA-dCTP, Alexa Fluor 647- 12-OBEA-dCTP.

 It is contemplated that nucleic acids may be labeled with two different labels. Furthermore, fluorescence resonance energy transfer (FRET) may be employed in
15 methods of the invention (e.g., Klostermeier et al, 2002; Emptage, 2001; Didenko, 2001).

 Alternatively, the label may not be detectable per se, but indirectly detectable or allowing for the isolation or separation of the targeted nucleic acid. For example, the label could be biotin, digoxigenin, polyvalent cations, chelator groups and the other
20 ligands, include ligands for an antibody.

C. Visualization Techniques

 A number of techniques for visualizing or detecting labeled nucleic acids are readily available. Such techniques include, microscopy, arrays, Fluorometry, Light cyclers or other real time PCR machines, FACS analysis, scintillation counters,
25 Phosphoimagers, Geiger counters, MRI, CAT, antibody-based detection methods (Westerns, immunofluorescence, immunohistochemistry), histochemical techniques, HPLC (Griffey et al., 1997), spectroscopy, capillary gel electrophoresis (Cummins et al., 1996), spectroscopy; mass spectroscopy; radiological techniques; and mass balance techniques.

When two or more differentially colored labels are employed, fluorescent resonance energy transfer (FRET) techniques may be employed to characterize association of one or more nucleic acid. Furthermore, a person of ordinary skill in the art is well aware of ways of visualizing, identifying, and characterizing labeled nucleic acids, and accordingly, such protocols may be used as part of the invention. Examples of tools that may be used also include fluorescent microscopy, a BioAnalyzer, a plate reader, Storm (Molecular Dynamics), Array Scanner, FACS (fluorescent activated cell sorter), or any instrument that has the ability to excite and detect a fluorescent molecule.

10 III. Array Preparation and Screening

A. Array Preparation

The present invention concerns the preparation and use of miRNA arrays or miRNA probe arrays, which are ordered macroarrays or microarrays of nucleic acid molecules (probes) that are fully or nearly complementary or identical to a plurality of miRNA molecules or precursor miRNA molecules and that are positioned on a support or support material in a spatially separated organization. Macroarrays are typically sheets of nitrocellulose or nylon upon which probes have been spotted. Microarrays position the nucleic acid probes more densely such that up to 10,000 nucleic acid molecules can be fit into a region typically 1 to 4 square centimeters. Microarrays can be fabricated by spotting nucleic acid molecules, *e.g.*, genes, oligonucleotides, *etc.*, onto substrates or fabricating oligonucleotide sequences *in situ* on a substrate. Spotted or fabricated nucleic acid molecules can be applied in a high density matrix pattern of up to about 30 non-identical nucleic acid molecules per square centimeter or higher, *e.g.* up to about 100 or even 1000 per square centimeter. Microarrays typically use coated glass as the solid support, in contrast to the nitrocellulose-based material of filter arrays. By having an ordered array of miRNA-complementing nucleic acid samples, the position of each sample can be tracked and linked to the original sample. A variety of different array devices in which a plurality of distinct nucleic acid probes are stably associated with the surface of a solid support are known to those of skill in the art. Useful substrates for arrays include nylon, glass, metal, plastic, and silicon. Such arrays may vary in a number of different ways, including average probe length, sequence or types of probes, nature of bond between

the probe and the array surface, e.g. covalent or non-covalent, and the like. The labeling and screening methods of the present invention and the arrays are not limited in its utility with respect to any parameter except that the probes detect miRNA; consequently, methods and compositions may be used with a variety of different types
5 of miRNA arrays.

Representative methods and apparatus for preparing a microarray have been described, for example, in U.S. Patents 5,143,854; 5,202,231; 5,242,974; 5,288,644; 5,324,633; 5,384,261; 5,405,783; 5,412,087; 5,424,186; 5,429,807; 5,432,049; 5,436,327; 5,445,934; 5,468,613; 5,470,710; 5,472,672; 5,492,806; 5,525,464;
10 5,503,980; 5,510,270; 5,525,464; 5,527,681; 5,529,756; 5,532,128; 5,545,531; 5,547,839; 5,554,501; 5,556,752; 5,561,071; 5,571,639; 5,580,726; 5,580,732; 5,593,839; 5,599,695; 5,599,672; 5,610,287; 5,624,711; 5,631,134; 5,639,603; 5,654,413; 5,658,734; 5,661,028; 5,665,547; 5,667,972; 5,695,940; 5,700,637; 5,744,305; 5,800,992; 5,807,522; 5,830,645; 5,837,196; 5,871,928; 5,847,219;
15 5,876,932; 5,919,626; 6,004,755; 6,087,102; 6,368,799; 6,383,749; 6,617,112; 6,638,717; 6,720,138, as well as WO 93/17126; WO 95/11995; WO 95/21265; WO 95/21944; WO 95/35505; WO 96/31622; WO 97/10365; WO 97/27317; WO 99/35505; WO 09923256; WO 09936760; WO0138580; WO 0168255; WO 03020898; WO 03040410; WO 03053586; WO 03087297; WO 03091426; WO03 100012; WO
20 04020085; WO 04027093; EP 373 203; EP 785 280; EP 799 897 and UK 8 803 000.

It is contemplated that the arrays can be high density arrays, such that they contain 2, 20, 25, 50, 80, 100 or more different probes. It is contemplated that they may contain 1000, 16,000, 65,000, 250,000 or 1,000,000 or more different probes. The probes can be directed to targets in one or more different organisms or cell types. The
25 oligonucleotide probes range from 5 to 50, 5 to 45, 10 to 40, 9 to 34, or 15 to 40 nucleotides in length in some embodiments. In certain embodiments, the oligonucleotide probes are 5, 10, 15, 20 to 20, 25, 30, 35, 40 nucleotides in length including all integers and ranges there between.

The location and sequence of each different probe sequence in the array are generally
30 known. Moreover, the large number of different probes can occupy a relatively small area providing a high density array having a probe density of

generally greater than about 60, 100, 600, 1000, 5,000, 10,000, 40,000, 100,000, or 400,000 different oligonucleotide probes per cm². The surface area of the array can be about or less than about 1, 1.6, 2, 3, 4, 5, 6, 7, 8, 9, or 10 cm².

Moreover, a person of ordinary skill in the art could readily analyze data
5 generated using an array. Such protocols are disclosed above, and include information found in WO 9743450; WO 03023058; WO 03022421; WO 03029485; WO 03067217; WO 03066906; WO 03076928; WO 03093810; WO 03100448A1.

B. Sample Preparation

It is contemplated that the miRNA of a wide variety of samples can be analyzed
10 using the arrays, index of miRNA probes, or array technology of the invention. While endogenous miRNA is contemplated for use with compositions and methods of the invention, recombinant miRNA - including nucleic acids that are complementary or identical to endogenous miRNA or precursor miRNA - can also be handled and analyzed as described herein. Samples may be biological samples, in which case, they
15 can be from biopsy, fine needle aspirates, exfoliates, blood, tissue, organs, semen, saliva, tears, other bodily fluid, hair follicles, skin, or any sample containing or constituting biological cells. In certain embodiments, samples may be, but are not limited to, fresh, frozen, fixed, formalin fixed, paraffin embedded, or formalin fixed and paraffin embedded. Alternatively, the sample may not be a biological sample, but be a
20 chemical mixture, such as a cell-free reaction mixture (which may contain one or more biological enzymes).

C. Hybridization

After an array or a set of miRNA probes is prepared and the miRNA in the sample is labeled, the population of target nucleic acids is contacted with the array or
25 probes under hybridization conditions, where such conditions can be adjusted, as desired, to provide for an optimum level of specificity in view of the particular assay being performed. Suitable hybridization conditions are well known to those of skill in the art and reviewed in Sambrook *et al.* (2001) and WO 95/21944. Of particular interest in many embodiments is the use of stringent conditions during hybridization. Stringent
30 conditions are known to those of skill in the art.

It is specifically contemplated that a single array or set of probes may be contacted with multiple samples. The samples may be labeled with different labels to distinguish the samples. For example, a single array can be contacted with a tumor tissue sample labeled with Cy3, and normal tissue sample labeled with Cy5.

5 Differences between the samples for particular miRNAs corresponding to probes on the array can be readily ascertained and quantified.

The small surface area of the array permits uniform hybridization conditions, such as temperature regulation and salt content. Moreover, because of the small area occupied by the high density arrays, hybridization may be carried out in extremely

10 small fluid volumes (*e.g.*, about 250 μ l or less, including volumes of about or less than about 5, 10, 25, 50, 60, 70, 80, 90, 100 μ l, or any range derivable therein). In small volumes, hybridization may proceed very rapidly.

D. Differential Expression Analyses

Arrays of the invention can be used to detect differences between two

15 samples. Specifically contemplated applications include identifying and/or quantifying differences between miRNA from a sample that is normal and from a sample that is not normal, between a cancerous condition and a non-cancerous condition, or between two differently treated samples. Also, miRNA may be compared between a sample believed to be susceptible to a particular disease or

20 condition and one believed to be not susceptible or resistant to that disease or condition. A sample that is not normal is one exhibiting phenotypic trait(s) of a disease or condition or one believed to be not normal with respect to that disease or condition. It may be compared to a cell that is normal with respect to that disease or condition. Phenotypic traits include symptoms of, or susceptibility to, a disease or

25 condition of which a component is or may or may not be genetic or caused by a hyperproliferative or neoplastic cell or cells.

An array comprises a solid support with nucleic acid probes attached to the support. Arrays typically comprise a plurality of different nucleic acid probes that are coupled to a surface of a substrate in different, known locations. These arrays, also

30 described as "microarrays" or colloquially "chips" have been generally described in the art, for example, U.S. Pat. Nos. 5,143,854, 5,445,934, 5,744,305, 5,677,195,

6,040,193, 5,424,186 and Fodor et al. (1991). These arrays may generally be produced using mechanical synthesis methods or light directed synthesis methods which incorporate a combination of photolithographic methods and solid phase synthesis methods. Techniques for the synthesis of these arrays using mechanical synthesis methods are described in, e.g., U.S. Pat. No. 5,384,261. Although a planar array surface is used in certain aspects, the array may be fabricated on a surface of virtually any shape or even a multiplicity of surfaces. Arrays may be nucleic acids on beads, gels, polymeric surfaces, fibers such as fiber optics, glass or any other appropriate substrate, see U.S. Pat. Nos. 5,770,358, 5,789,162, 5,708,153, 6,040,193 and 5,800,992. Arrays may be packaged in such a manner as to allow for diagnostics or other manipulation of an all inclusive device, see for example, U.S. Pat. Nos. 5,856,174 and 5,922,591. See also U.S. Patent Application Ser. No. 09/545,207, filed Apr. 7, 2000 for additional information concerning arrays, their manufacture, and their characteristics.

Particularly arrays can be used to evaluate samples with respect to diseases or conditions that include, but are not limited to: chronic pancreatitis; pancreatic cancer; AIDS, autoimmune diseases (rheumatoid arthritis, multiple sclerosis, insulin-dependent diabetes, non-independent diabetes, systemic lupus erythematosus and Graves disease); cancer (*e.g.*, malignant, benign, metastatic, precancer); cardiovascular diseases (heart disease or coronary artery disease, ischemic stroke, hemorrhagic stroke, rheumatic heart disease); diseases of the nervous system; and infection by pathogenic microorganisms (athlete's Foot, chickenpox, common cold, diarrheal diseases, flu, genital herpes, malaria, meningitis, pneumonia, sinusitis, skin diseases, strep throat, tuberculosis, urinary tract infections, vaginal infections, viral hepatitis); inflammation (allergy, asthma); prion diseases (*e.g.*, CJD, kuru, GSS, FFI).

Moreover, miRNA can be evaluated with respect to the following diseases, conditions, and disorders: pancreatitis, chronic pancreatitis, and/or pancreatic cancer.

Cancers that may be evaluated by methods and compositions of the invention include cancer cells particularly from the pancreas, including pancreatic ductal adenocarcinoma (PDAC), but may also include cells and cancer cells from the bladder, blood, bone, bone marrow, brain, breast, colon, esophagus, gastrointestinal, gum, head, kidney, liver, lung, nasopharynx, neck, ovary, prostate, skin, stomach, testis, tongue, or uterus. In addition, the cancer may specifically be of the following histological type, though it is not limited to these: neoplasm, malignant; carcinoma; carcinoma, undifferentiated; giant and spindle cell carcinoma; small cell carcinoma; papillary carcinoma; squamous cell carcinoma; lymphoepithelial carcinoma; basal cell carcinoma; pilomatrix carcinoma; transitional cell carcinoma; papillary transitional cell carcinoma; adenocarcinoma; gastrinoma, malignant; cholangiocarcinoma; hepatocellular carcinoma; combined hepatocellular carcinoma and cholangiocarcinoma; trabecular adenocarcinoma; adenoid cystic carcinoma; adenocarcinoma in adenomatous polyp; adenocarcinoma, familial polyposis coli; solid carcinoma; carcinoid tumor, malignant; branchiolo-alveolar adenocarcinoma; papillary adenocarcinoma; chromophobe carcinoma; acidophil carcinoma; oxyphilic adenocarcinoma; basophil carcinoma; clear cell adenocarcinoma; granular cell carcinoma; follicular adenocarcinoma; papillary and follicular adenocarcinoma; nonencapsulating sclerosing carcinoma; adrenal cortical carcinoma; endometroid carcinoma; skin appendage carcinoma; apocrine adenocarcinoma; sebaceous adenocarcinoma; ceruminous adenocarcinoma; mucoepidermoid carcinoma; cystadenocarcinoma; papillary cystadenocarcinoma; papillary serous cystadenocarcinoma; mucinous cystadenocarcinoma; mucinous adenocarcinoma; signet ring cell carcinoma; infiltrating duct carcinoma; medullary carcinoma; lobular carcinoma; inflammatory carcinoma; paget's disease, mammary; acinar cell carcinoma; adenosquamous carcinoma; adenocarcinoma w/squamous metaplasia; thymoma, malignant; ovarian stromal tumor, malignant; thecoma, malignant; granulosa cell tumor, malignant; androblastoma, malignant; sertoli cell carcinoma; leydig cell tumor, malignant; lipid cell tumor, malignant; paraganglioma, malignant; extra-mammary paraganglioma, malignant; pheochromocytoma; glomangiosarcoma; malignant melanoma; amelanotic melanoma; superficial spreading melanoma; malignant melanoma in giant pigmented nevus; epithelioid cell melanoma; blue nevus, malignant; sarcoma; fibrosarcoma; fibrous histiocytoma, malignant; myxosarcoma; liposarcoma; leiomyosarcoma; rhabdomyosarcoma; embryonal rhabdomyosarcoma;

alveolar rhabdomyosarcoma; stromal sarcoma; mixed tumor, malignant; mullerian mixed tumor; nephroblastoma; hepatoblastoma; carcinosarcoma; mesenchymoma, malignant; brenner tumor, malignant; phyllodes tumor, malignant; synovial sarcoma; mesothelioma, malignant; dysgerminoma; embryonal carcinoma; teratoma, malignant;

5 struma ovarii, malignant; choriocarcinoma; mesonephroma, malignant; hemangiosarcoma; hemangioendothelioma, malignant; kaposi's sarcoma; hemangiopericytoma, malignant; lymphangiosarcoma; osteosarcoma; juxtacortical osteosarcoma; chondrosarcoma; chondroblastoma, malignant; mesenchymal chondrosarcoma; giant cell tumor of bone; ewing's sarcoma; odontogenic tumor,

10 malignant; ameloblastic odontosarcoma; ameloblastoma, malignant; ameloblastic fibrosarcoma; pinealoma, malignant; chordoma; glioma, malignant; ependymoma; astrocytoma; protoplasmic astrocytoma; fibrillary astrocytoma; astroblastoma; glioblastoma; oligodendroglioma; oligodendroblastoma; primitive neuroectodermal; cerebellar sarcoma; ganglioneuroblastoma; neuroblastoma; retinoblastoma; olfactory

15 neurogenic tumor; meningioma, malignant; neurofibrosarcoma; neurilemmoma, malignant; granular cell tumor, malignant; malignant lymphoma; Hodgkin's disease; Hodgkin's lymphoma; paragranuloma; malignant lymphoma, small lymphocytic; malignant lymphoma, large cell, diffuse; malignant lymphoma, follicular; mycosis fungoides; other specified non-Hodgkin's lymphomas; malignant histiocytosis;

20 multiple myeloma; mast cell sarcoma; immunoproliferative small intestinal disease; leukemia; lymphoid leukemia; plasma cell leukemia; erythroleukemia; lymphosarcoma cell leukemia; myeloid leukemia; basophilic leukemia; eosinophilic leukemia; monocytic leukemia; mast cell leukemia; megakaryoblastic leukemia; myeloid sarcoma; and hairy cell leukemia. Moreover, miRNA can be evaluated in

25 precancers, such as metaplasia, dysplasia, and hyperplasia.

It is specifically contemplated that the invention can be used to evaluate differences between stages of disease, such as between hyperplasia, neoplasia, pre-cancer and cancer, or between a primary tumor and a metastasized tumor.

Moreover, it is contemplated that samples that have differences in the activity

30 of certain pathways may also be compared. These pathways include the following and those involving the following factors: antibody response, apoptosis, calcium/NFAT signaling, cell cycle, cell migration, cell adhesion, cell division,

cytokines and cytokine receptors, drug metabolism, growth factors and growth factor receptors, inflammatory response, insulin signaling, NFκ-B signaling, angiogenesis, adipogenesis, cell adhesion, viral infection, bacterial infection, senescence, motility, glucose transport, stress response, oxidation, aging, telomere extension, telomere shortening, neural transmission, blood clotting, stem cell differentiation, G-Protein Coupled Receptor (GPCR) signaling, and p53 activation.

Cellular pathways that may be profiled also include but are not limited to the following: any adhesion or motility pathway including but not limited to those involving cyclic AMP, protein kinase A, G-protein couple receptors, adenylyl cyclase, L-selectin, E-selectin, PECAM, VCAM-1, α-actinin, paxillin, cadherins, AKT, integrin-α, integrin-β, RAF-1, ERK, PI-3 kinase, vinculin, matrix metalloproteinases, Rho GTPases, p85, trefoil factors, profilin, FAK, MAP kinase, Ras, caveolin, calpain-1, calpain-2, epidermal growth factor receptor, ICAM-1, ICAM-2, cofilin, actin, gelsolin, RhoA, RAC1, myosin light chain kinase, platelet-derived growth factor receptor or ezrin; any apoptosis pathway including but not limited to those involving AKT, Fas ligand, NFκB, caspase-9, PI3 kinase, caspase-3, caspase-7, ICAD, CAD, EndoG, Granzyme B, Bad, Bax, Bid, Bak, APAF-1, cytochrome C, p53, ATM, Bcl-2, PARP, Chk1, Chk2, p21, c-Jun, p73, Rad51, Mdm2, Rad50, c-Abl, BRCA-1, perforin, caspase-4, caspase-8, caspase-6, caspase-1, caspase-2, caspase-10, Rho, Jun kinase, Jun kinase kinase, Rip2, lamin-A, lamin-B1, lamin-B2, Fas receptor, H₂O₂, Granzyme A, NADPH oxidase, HMG2, CD4, CD28, CD3, TRADD, IKK, FADD, GADD45, DR3 death receptor, DR4/5 death receptor, FLIPs, APO-3, GRB2, SHC, ERK, MEK, RAF-1, cyclic AMP, protein kinase A, E2F, retinoblastoma protein, Smac/Diablo, ACH receptor, 14-3-3, FAK, SODD, TNF receptor, RIP, cyclin-D1, PCNA, Bcl-XL, PIP2, PIP3, PTEN, ATM, Cdc2, protein kinase C, calcineurin, IKKα, IKKβ, IKKγ, SOS-1, c-FOS, Traf-1, Traf-2, IκBβ or the proteasome; any cell activation pathway including but not limited to those involving protein kinase A, nitric oxide, caveolin-1, actin, calcium, protein kinase C, Cdc2, cyclin B, Cdc25, GRB2, SRC protein kinase, ADP-ribosylation factors (ARFs), phospholipase D, AKAP95, p68, Aurora B, CDK1, Eg7, histone H3, PKAc, CD80, PI3 kinase, WASP, Arp2, Arp3, p16, p34, p20, PP2A, angiotensin, angiotensin-converting enzyme, protease-activated receptor-1, protease-activated receptor-4, Ras, RAF-1, PLCβ, PLCγ, COX-1, G-protein-coupled receptors, phospholipase A2, IP3, SUMO1, SUMO

2/3, ubiquitin, Ran, Ran-GAP, Ran-GEF, p53, glucocorticoids, glucocorticoid receptor, components of the SWI/SNF complex, RanBP1, RanBP2, importins, exportins, RCC1, CD40, CD40 ligand, p38, IKK α , IKK β , NF κ B, TRAF2, TRAF3, TRAF5, TRAF6, IL-4, IL-4 receptor, CDK5, AP-1 transcription factor, CD45, CD4, T cell receptors, MAP kinase, nerve growth factor, nerve growth factor receptor, c-Jun, c-Fos, Jun kinase, GRB2, SOS-1, ERK-1, ERK, JAK2, STAT4, IL-12, IL-12 receptor, nitric oxide synthase, TYK2, IFN γ , elastase, IL-8, epithelins, IL-2, IL-2 receptor, CD28, SMAD3, SMAD4, TGF β or TGF β receptor; any cell cycle regulation, signaling or differentiation pathway including but not limited to those involving TNFs, SRC protein kinase, Cdc2, cyclin B, Grb2, Sos-1, SHC, p68, Aurora kinases, protein kinase A, protein kinase C, Eg7, p53, cyclins, cyclin-dependent kinases, neural growth factor, epidermal growth factor, retinoblastoma protein, ATF-2, ATM, ATR, AKT, CHK1, CHK2, 14-3-3, WEE1, CDC25 CDC6, Origin Recognition Complex proteins, p15, p16, p27, p21, ABL, c-ABL, SMADs, ubiquitin, SUMO, heat shock proteins, Wnt, GSK-3, angiotensin, p73 any PPAR, TGF α , TGF β , p300, MDM2, GADD45, Notch, cdc34, BRCA-1, BRCA-2, SKP1, the proteasome, CUL1, E2F, p107, steroid hormones, steroid hormone receptors, I κ B α , I κ B β , Sin3A, heat shock proteins, Ras, Rho, ERKs, IKKs, PI3 kinase, Bcl-2, Bax, PCNA, MAP kinases, dynein, RhoA, PKAc, cyclin AMP, FAK, PIP2, PIP3, integrins, thrombopoietin, Fas, Fas ligand, PLK3, MEKs, JAKs, STATs, acetylcholine, paxillin calcineurin, p38, importins, exportins, Ran, Rad50, Rad51, DNA polymerase, RNA polymerase, Ran-GAP, Ran-GEF, NuMA, Tpx2, RCC1, Sonic Hedgehog, Crm1, Patched (Ptc-1), MPF, CaM kinases, tubulin, actin, kinetochore-associated proteins, centromere-binding proteins, telomerase, TERT, PP2A, c-MYC, insulin, T cell receptors, B cell receptors, CBP, IK β , NF κ B, RAC1, RAF1, EPO, diacylglycerol, c-Jun, c-Fos, Jun kinase, hypoxia-inducible factors, GATA4, β -catenin, α -catenin, calcium, arrestin, survivin, caspases, procaspases, CREB, CREM, cadherins, PECAMs, corticosteroids, colony-stimulating factors, calpains, adenylyl cyclase, growth factors, nitric oxide, transmembrane receptors, retinoids, G-proteins, ion channels, transcriptional activators, transcriptional coactivators, transcriptional repressors, interleukins, vitamins, interferons, transcriptional corepressors, the nuclear pore, nitrogen, toxins, proteolysis, or phosphorylation; or any metabolic pathway including but not limited to those involving the biosynthesis of amino acids, oxidation

of fatty acids, biosynthesis of neurotransmitters and other cell signaling molecules, biosynthesis of polyamines, biosynthesis of lipids and sphingolipids, catabolism of amino acids and nutrients, nucleotide synthesis, eicosanoids, electron transport reactions, ER-associated degradation, glycolysis, fibrinolysis, formation of ketone
5 bodies, formation of phagosomes, cholesterol metabolism, regulation of food intake, energy homeostasis, prothrombin activation, synthesis of lactose and other sugars, multi-drug resistance, biosynthesis of phosphatidylcholine, the proteasome, amyloid precursor protein, Rab GTPases, starch synthesis, glycosylation, synthesis of phosphoglycerides, vitamins, the citric acid cycle, IGF-1 receptor, the urea cycle,
10 vesicular transport, or salvage pathways. Additional cellular pathways include pathways that include genes and their related mRNAs identified in Table 10. It is further contemplated that nucleic acids molecules of the invention can be employed in diagnostic and therapeutic methods with respect to any of the above pathways or factors. Thus, in some embodiments of the invention, a miRNA may be differentially
15 expressed with respect to one or more of the above pathways or factors.

Phenotypic traits also include characteristics such as longevity, morbidity, appearance (*e.g.*, baldness, obesity), strength, speed, endurance, fertility, susceptibility or receptivity to particular drugs or therapeutic treatments (drug efficacy), and risk of drug toxicity. Samples that differ in these phenotypic traits may
20 also be evaluated using the arrays and methods described.

In certain embodiments, miRNA profiles may be generated to evaluate and correlate those profiles with pharmacokinetics. For example, miRNA profiles may be created and evaluated for patient tumor and blood samples prior to the patient's being treated or during treatment to determine if there are miRNAs whose expression
25 correlates with the outcome of the patient. Identification of differential miRNAs can lead to a diagnostic assay involving them that can be used to evaluate tumor and/or blood samples to determine what drug regimen the patient should be provided. In addition, it can be used to identify or select patients suitable for a particular clinical trial. If a miRNA profile is determined to be correlated with drug efficacy or drug
30 toxicity, that may be relevant to whether that patient is an appropriate patient for receiving the drug or for a particular dosage of the drug.

In addition to the above prognostic assay, blood samples from patients with a variety of diseases can be evaluated to determine if different diseases can be identified based on blood miRNA levels. A diagnostic assay can be created based on the profiles that doctors can use to identify individuals with a disease or who are at risk to develop a
 5 disease. Alternatively, treatments can be designed based on miRNA profiling.

E. Other Assays

In addition to the use of arrays and microarrays, it is contemplated that a number of difference assays could be employed to analyze miRNAs, their activities, and their effects. Such assays include, but are not limited to, nucleic amplification, polymerase
 10 chain reaction, quantitative PCR, RT-PCR, *in situ* hybridization, Northern hybridization, hybridization protection assay (HPA)(GenProbe), branched DNA (bDNA) assay (Chiron), rolling circle amplification (RCA), single molecule hybridization detection (US Genomics), Invader assay (ThirdWave Technologies), and/or Bridge Litigation Assay (Genaco).

15 IV. Kits

Any of the compositions described herein may be comprised in a kit. In a non-limiting example, reagents for isolating miRNA, labeling miRNA, and/or evaluating a miRNA population using an array, nucleic acid amplification, and/or hybridization can be included in a kit, as well reagents for preparation of samples from pancreatic
 20 samples. The kit may further include reagents for creating or synthesizing miRNA probes. The kits will thus comprise, in suitable container means, an enzyme for labeling the miRNA by incorporating labeled nucleotide or unlabeled nucleotides that are subsequently labeled. In certain aspects, the kit can include amplification reagents. In other aspects, the kit may include various supports, such as glass, nylon, polymeric
 25 beads, and the like, and/or reagents for coupling any probes and/or target nucleic acids. It may also include one or more buffers, such as reaction buffer, labeling buffer, washing buffer, or a hybridization buffer, compounds

for preparing the miRNA probes, and components for isolating miRNA. Other kits of the invention may include components for making a nucleic acid array comprising miRNA, and thus, may include, for example, a solid support.

Kits for implementing methods of the invention described herein are specifically contemplated. In some embodiments, there are kits for preparing miRNA for multi-labeling and kits for preparing miRNA probes and/or miRNA arrays. In these embodiments, kit comprise, in suitable container means, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or more of the following: 1) poly(A) polymerase; 2) unmodified nucleotides (G, A, T, C, and/or U); 3) a modified nucleotide (labeled or unlabeled); 4) poly(A) polymerase buffer; and, 5) at least one microfilter; 6) label that can be attached to a nucleotide; 7) at least one miRNA probe; 8) reaction buffer; 9) a miRNA array or components for making such an array; 10) acetic acid; 11) alcohol; 12) solutions for preparing, isolating, enriching, and purifying miRNAs or miRNA probes or arrays. Other reagents include those generally used for manipulating RNA, such as formamide, loading dye, ribonuclease inhibitors, and DNase.

In specific embodiments, kits of the invention include an array containing miRNA probes, as described in the application. An array may have probes corresponding to all known miRNAs of an organism or a particular tissue or organ in particular conditions, or to a subset of such probes. The subset of probes on arrays of the invention may be or include those identified as relevant to a particular diagnostic, therapeutic, or prognostic application. For example, the array may contain one or more probes that is indicative or suggestive of 1) a disease or condition (chronic pancreatitis and/or pancreatic cancer), 2) susceptibility or resistance to a particular drug or treatment; 3) susceptibility to toxicity from a drug or substance; 4) the stage of development or severity of a disease or condition (prognosis); and 5) genetic predisposition to a disease or condition.

For any kit embodiment, including an array, there can be nucleic acid molecules that contain or can be used to amplify a sequence that is a variant of, identical to or complementary to all or part of any of SEQ ID NOS: 1-350. In certain embodiments, a kit or array of the invention can contain one or more probes for the miRNAs identified by SEQ ID NOS:1-350. Any nucleic acid discussed above may be implemented as part of a kit.

The components of the kits may be packaged either in aqueous media or in lyophilized form. The container means of the kits will generally include at least one vial, test tube, flask, bottle, syringe or other container means, into which a component may be placed, and preferably, suitably aliquotted. Where there is more than one
5 component in the kit (labeling reagent and label may be packaged together), the kit also will generally contain a second, third or other additional container into which the additional components may be separately placed. However, various combinations of components may be comprised in a vial. The kits of the present invention also will typically include a means for containing the nucleic acids, and any other reagent
10 containers in close confinement for commercial sale. Such containers may include injection or blow molded plastic containers into which the desired vials are retained.

When the components of the kit are provided in one and/or more liquid solutions, the liquid solution is an aqueous solution, with a sterile aqueous solution being particularly preferred.

15 However, the components of the kit may be provided as dried powder(s). When reagents and/or components are provided as a dry powder, the powder can be reconstituted by the addition of a suitable solvent. It is envisioned that the solvent may also be provided in another container means. In some embodiments, labeling dyes are provided as a dried power. It is contemplated that 10, 20, 30, 40, 50, 60, 70,
20 80, 90, 100, 120, 130, 140, 150, 160, 170, 180, 190, 200, 300, 400, 500, 600, 700, 800, 900, 1000 μ g or at least or at most those amounts of dried dye are provided in kits of the invention. The dye may then be resuspended in any suitable solvent, such as DMSO.

The container means will generally include at least one vial, test tube, flask,
25 bottle, syringe and/or other container means, into which the nucleic acid formulations are placed, preferably, suitably allocated. The kits may also comprise a second container means for containing a sterile, pharmaceutically acceptable buffer and/or other diluent.

The kits of the present invention will also typically include a means for
30 containing the vials in close confinement for commercial sale, such as, *e.g.*, injection and/or blow-molded plastic containers into which the desired vials are retained.

Such kits may also include components that facilitate isolation of the labeled miRNA. It may also include components that preserve or maintain the miRNA or that protect against its degradation. Such components may be RNase-free or protect against RNases. Such kits generally will comprise, in suitable means, distinct
5 containers for each individual reagent or solution.

A kit will also include instructions for employing the kit components as well the use of any other reagent not included in the kit. Instructions may include variations that can be implemented.

Kits of the invention may also include one or more of the following: Control
10 RNA; nuclease-free water; RNase-free containers, such as 1.5 ml tubes; RNase-free elution tubes; PEG or dextran; ethanol; acetic acid; sodium acetate; ammonium acetate; guanidinium; detergent; nucleic acid size marker; RNase-free tube tips; and RNase or DNase inhibitors.

It is contemplated that such reagents are embodiments of kits of the invention.
15 Such kits, however, are not limited to the particular items identified above and may include any reagent used for the manipulation or characterization of miRNA.

V. EXAMPLES

The following examples are given for the purpose of illustrating various embodiments of the invention and are not meant to limit the present invention in any
20 fashion. One skilled in the art will appreciate readily that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those objects, ends and advantages inherent herein. The present examples, along with the methods described herein are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the
25 invention. Changes therein and other uses which are encompassed within the spirit of the invention as defined by the scope of the claims will occur to those skilled in the art. Unless otherwise designated, catalog numbers refer to products available by that number from Ambion, Inc.®, The RNA Company.

EXAMPLE 1

SAMPLE COLLECTION AND RNA ISOLATION

Six pancreatic primary ductal adenocarcinoma cell lines (IMIMPC2, PT45, PL45, SKPC1, PancTuI, PaCa44) and tissue samples from normal pancreas (N, n=7),
5 chronic pancreatitis (Ch, n=7), and pancreatic ductal adenocarcinomas (PDAC) (Ca, n=10) were collected, flash frozen and stored at -80°C. The latter two diseased tissues were macro-dissected to remove as much normal pancreatic tissue as possible. Complete pathologic analyses were performed on all 24 tissue samples (Table 2). Thirteen fine needle aspirate (FNA) samples of diseased pancreatic tissue were
10 collected during surgery and placed in RNARetain™ (Asuragen, Inc.; Austin, TX) within 30 minutes of collection and stored at 4°C.

RNA isolation was performed using the mirVana™ miRNA Isolation Kit (Ambion) according to the manufacturer's protocol. As isolation of high quality RNA from organs containing high levels of nucleases such as pancreas can be challenging,
15 the integrity of the isolated RNA was verified on a standard 1% formaldehyde agarose gel (FIG. 1). FNA samples were centrifuged at 3,000 rpm for five minutes at 4°C prior to RNA isolation to recover diseased pancreatic tissue from RNARetain™ solution. Purified total RNA was quantified using a Nanodrop® ND-1000 (Nanodrop Technologies).

Table 2. Tissue Sample Pathology Report

ID	Sex	Age	Assay	Diagnosis	Comment	Features of tissue block
Ca1	M	63	Array PCR	pancreatic ductal adenocarcinoma	Grade 3, T4N1M0	tumor content: 100%, desmoplasia: 40%, inflammatory cells: strongly neutrophils, lymphocytes
Ca2	M	62	Array PCR	pancreatic ductal adenocarcinoma	Grade 3, T4N1M0	tumor content: 100%, desmoplasia: 80%, inflammatory cells: weakly neutrophils
Ca3	F	69	Array PCR	pancreatic ductal adenocarcinoma	Grade 2, T3N0M0	tumor content: 100%, desmoplasia: 60%, inflammatory cells: weakly neutrophils
Ca4	M	71	Array PCR	pancreatic ductal adenocarcinoma	Grade 3, T3N1M0	tumor content: 100%, desmoplasia: 50%, inflammatory cells: moderately lymphocytes
Ca5	F	70	Array PCR	pancreatic ductal adenocarcinoma	Grade 3, T4N1M0	tumor content: 100%, desmoplasia: 40%, inflammatory cells: moderately neutrophils, lymphocytes, plasma cells
Ca6	F	63	Array PCR	pancreatic ductal adenocarcinoma	Grade 3, T3N1M0	tumor content: 80%, desmoplasia: 70%, inflammatory cells: weakly neutrophils
Ca7	F	71	Array PCR	pancreatic ductal adenocarcinoma	Grade 2, T3N0M0	tumor content: 100%, desmoplasia: 70%, inflammatory cells: weakly lymphocytes
Ca8	F	51	Array PCR	pancreatic ductal adenocarcinoma	Grade 2, T3N1M0	tumor content: 80%, desmoplasia: 80%, inflammatory cells: weakly neutrophils, lymphocytes
Ca9	F	77	PCR	pancreatic ductal adenocarcinoma	Grade 3, T3N1M0	tumor content: 90%, desmoplasia: 80%, inflammatory cells: weakly neutrophils
Ca10	M	80	PCR	pancreatic ductal adenocarcinoma	Grade 3, T3N0M0	tumor content: 100%, desmoplasia: 30%, no inflammatory cells
Ch1	M	58	Array PCR	chronic pancreatitis	pronounced fibrosis, formation of pseudocysts and numerous calculi	fibrosis app. 90%, moderate inflammatory activity
Ch2	M	37	Array PCR	chronic pancreatitis	scattered small pseudocyst, fibrosis, calculi	fibrosis app. 75%, moderate inflammatory activity

Ch3	F	43	Array PCR	chronic pancreatitis	pronounced fibrosis, calculi	fibrosis app. 30%, low inflammatory activity
Ch4	F	56	Array PCR	chronic pancreatitis	moderate fibrosis, few calculi	fibrosis app. 80%, low inflammatory activity, CAVE: small fragments of lymph node as well
Ch5	M	37	Array PCR	chronic pancreatitis	pronounced fibrosis, focal acute inflammation and numerous calculi	fibrosis app. 50%, low inflammatory activity
Ch6	F	58	Array PCR	chronic pancreatitis	pronounced fibrosis, calculi	fibrosis app. 50%, low inflammatory activity
Ch7	F	70	PCR	chronic pancreatitis	moderate fibrosis, no calculi	fibrosis app. 25%, moderate inflammatory activity
N1	F	35	Array PCR	histologically normal pancreas	resection because of solid pseudopapillary neoplasm	Normal
N2	M	73	Array PCR	histologically normal pancreas	resection because of ampullary carcinoma	Normal
N3	F	58	Array PCR	histologically normal pancreas	resection because of solid pseudopapillary neoplasm	fibrosis 10%
N4	M	61	Array PCR	histologically normal pancreas	resection because of bile duct carcinoma	fibrosis 10%
N5	F	47	Array PCR	histologically normal pancreas	resection because of bile duct carcinoma	fibrosis 10%
N6	M	58	PCR	histologically normal pancreas	resection because of serious cystadenoma of the pancreas	Normal
N7	F	76	PCR	histologically normal pancreas	resection because of ductal adenocarcinoma of the tail of the pancreas	Normal
FNA-1	F	74	PCR	pancreatic ductal adenocarcinoma	MX;	N/A
FNA-2	F	72	PCR	pancreatic ductal adenocarcinoma	MX;	N/A
FNA-3	F	72	PCR	pancreatic ductal adenocarcinoma	MX;	N/A
FNA-4	F	65	PCR	pancreatic ductal adenocarcinoma	MX; extensive necrosis	N/A

FNA-5	F	68	PCR	pancreatic ductal adenocarcinoma	M0;	N/A
FNA-6	F	84	PCR	pancreatic ductal adenocarcinoma	M0;	N/A
FNA-7	M	84	PCR	pancreatic ductal adenocarcinoma	MX;	N/A
FNA-8	F	59	PCR	suspect for pancreatic ductal adenocarcinoma	M0;	N/A
FNA-9	M	72	PCR	pancreatic ductal adenocarcinoma	M1;	N/A
FNA-11	F	57	PCR	pancreatic ductal adenocarcinoma	M1;	N/A
FNA-12	F	46	PCR	neoplasm of endocrine pancreas	MX;	N/A
FNA-13	M	59	PCR	Atypical	MX;	N/A
FNA-14	F	85	PCR	pancreatic ductal adenocarcinoma	MX; extensive necrosis	N/A

Ca = PDAC; Ch = chronic pancreatitis; N = normal; FNA = fine needle aspirate; MX = presence of distant metastasis cannot be assessed.

EXAMPLE 2:**MIRNA EXPRESSION PROFILING IN NORMAL AND DISEASED
PANCREATIC SAMPLES**

miRNA expression profiling was performed as previously described (Shingara
5 *et al.*, 2005), except that the miRNA fractions recovered from 10-15 µg total RNA
were labeled with Cy5 fluorescent dye (GE Healthcare Life Sciences) and hybridized
to mirVana miRNA Bioarrays (Ambion) containing 377 individual miRNA probes,
including 281 human miRNAs from the mirBase Sequence Database (on the world
wide web at microrna.sanger.ac.uk/) (Griffiths-Jones *et al.*, 2006), 33 new human
10 miRNAs (Ambi-miRs) and 63 mouse or rat miRNAs from the mirBase Sequence
Database. Following hybridization, the arrays were scanned using the Axon®
GenePix 4000B scanner and associated GenePix software. Raw array data were
normalized with the variance stabilization method (Huber *et al.*, 2002).

Six pancreatic primary ductal adenocarcinoma cell lines, five normal pancreas
15 tissue samples, six chronic pancreatitis tissue samples, and eight PDAC tissue
samples were profiled. Following array processing and normalization, the expressed
miRNomes of the 25 different samples were established (Tables 3 and 4). On average,
200 miRNAs were detected above background signal in the tissue samples and 140 in
the cell lines, corresponding to 54 and 38% respectively, of the miRNA probes
20 present on the microarray. Unsupervised clustering of samples and miRNA
expression levels showed a clear segregation between the four sample types (normal,
chronic, cancer, and cell line), indicating that miRNA expression profiles were highly
reproducible within each sample type.

Table 3. Normalized Array Data for 19 Individual Tissue Samples: 8 PDAC (Ca), 6 Chronic Pancreatitis (Ch), and 5 Normal Pancreas (N)

	Ca1	Ca2	Ca3	Ca4	Ca5	Ca6	Ca7	Ca8	Ca	Ch1	Ch2	Ch3	Ch4	Ch5	Ch6	Ch	N1	N2	N3	N4	N5	N
TV*	2.29	1.61	2.01	1.88	1.68	2.13	1.58	1.80	1.87	2.28	2.26	1.94	2.20	2.23	2.46	2.23	2.03	1.90	2.21	1.71	2.27	2.02
miRNAs > TV**	173	228	222	211	226	184	237	224	213	193	190	209	200	222	185	200	191	195	182	229	175	194
%***	45.9	60.5	58.9	56.0	59.9	48.8	62.9	59.4	56.5	51.2	50.4	55.4	53.1	58.9	49.1	53.0	50.7	51.7	48.3	60.7	46.4	51.6
									Mean							Mean						Mean
miR Name	Ca1	Ca2	Ca3	Ca4	Ca5	Ca6	Ca7	Ca8	Ca	Ch1	Ch2	Ch3	Ch4	Ch5	Ch6	Ch	N1	N2	N3	N4	N5	N
hsa-let-7a	8.89	9.41	8.51	8.92	8.76	9.01	9.19	8.51	8.90	8.83	8.91	9.16	8.84	9.17	8.48	8.90	9.42	9.68	9.24	9.56	9.61	9.50
hsa-let-7b	8.53	8.91	8.36	8.42	8.38	8.46	8.71	8.12	8.48	8.75	9.10	9.16	8.69	8.88	8.50	8.85	9.22	9.55	8.93	9.06	9.33	9.22
hsa-let-7c	8.45	9.05	8.19	8.58	8.40	8.62	8.87	8.19	8.55	8.82	8.89	9.14	8.74	8.78	8.51	8.81	9.27	9.58	9.07	9.37	9.36	9.33
hsa-let-7d	7.78	8.78	7.59	8.20	8.10	8.32	8.43	7.95	8.14	7.97	7.79	8.29	7.93	7.91	7.63	7.92	8.72	8.90	8.51	9.13	8.90	8.83
hsa-let-7e	6.45	7.04	6.14	6.63	6.73	7.04	6.79	6.79	6.70	6.39	6.32	6.45	6.01	6.16	6.28	6.27	6.82	6.97	6.92	7.92	7.05	7.14
hsa-let-7f	7.70	8.57	6.99	7.81	7.90	8.13	8.22	7.78	7.89	7.42	7.13	7.97	7.56	7.62	7.79	7.58	8.58	8.56	8.37	9.08	8.73	8.66
hsa-let-7g	7.56	7.56	6.60	7.08	7.37	7.29	7.45	7.17	7.26	6.95	6.92	7.35	7.13	7.19	6.98	7.09	7.60	7.86	7.45	7.73	7.75	7.68
hsa-let-7i	7.91	7.49	7.33	7.68	7.50	6.98	7.44	7.20	7.44	7.38	7.64	6.95	7.07	7.28	6.81	7.19	6.44	6.38	6.20	6.77	6.55	6.47
hsa-miR-1	2.43	3.77	1.27	2.24	2.92	4.80	5.70	3.74	3.36	2.39	1.90	3.38	3.12	2.57	5.01	3.06	2.42	2.53	2.55	2.67	2.22	2.48
hsa-miR-100	5.39	6.78	6.12	6.11	6.40	5.97	6.94	6.64	6.29	6.79	6.63	6.42	6.73	6.09	6.45	6.52	5.45	5.16	5.10	5.21	5.71	5.32
hsa-miR-101	4.69	4.47	3.71	3.88	4.68	4.69	4.81	4.80	4.47	4.14	4.29	4.68	4.76	4.16	4.50	4.42	5.09	4.83	5.21	5.15	4.89	5.03
hsa-miR-103	6.63	6.59	6.93	6.18	7.12	6.61	6.71	6.60	6.67	6.24	6.20	6.14	6.19	5.82	5.97	6.10	5.98	6.02	5.77	6.02	6.28	6.01
hsa-miR-105	1.34	1.24	1.18	1.21	1.25	1.24	1.53	1.01	1.25	1.11	0.77	1.04	1.28	1.49	0.70	1.06	1.20	1.12	1.88	1.61	1.23	1.41
hsa-miR-106a	6.82	6.39	6.83	6.64	6.92	6.90	6.49	6.58	6.70	6.02	5.94	6.39	6.42	5.97	6.33	6.18	6.67	6.38	6.29	6.53	6.42	6.46
hsa-miR-106b	6.17	5.14	5.51	5.70	5.59	5.69	5.49	5.53	5.60	5.11	5.18	5.19	5.29	5.01	4.85	5.11	5.15	5.15	5.00	5.34	5.07	5.14
hsa-miR-107	6.68	6.59	6.94	6.33	7.12	6.63	6.75	6.64	6.71	6.34	6.28	6.10	6.29	5.95	6.08	6.18	5.92	5.98	5.74	6.03	6.22	5.98
hsa-miR-10a	5.59	6.64	6.27	6.30	6.39	5.64	6.61	6.06	6.19	5.87	5.66	5.90	5.80	5.54	5.87	5.77	5.22	5.07	4.88	5.11	5.14	5.09
hsa-miR-10b	4.67	5.59	5.03	5.25	5.54	4.90	5.50	5.15	5.20	5.17	4.89	5.30	5.58	4.43	4.88	5.04	4.94	4.40	4.68	4.78	4.74	4.71
hsa-miR-122a	2.98	2.64	2.48	2.96	2.68	3.69	2.00	3.04	2.81	2.86	2.87	2.81	2.99	3.15	2.97	2.94	2.75	2.47	3.01	2.67	2.56	2.69
hsa-miR-124a	0.63	1.57	0.85	1.27	0.96	1.13	1.20	1.27	1.11	0.56	0.70	1.16	0.87	0.70	1.11	0.85	1.07	0.86	1.43	0.89	0.54	0.96
hsa-miR-125a	5.09	6.26	6.06	6.17	6.37	5.93	6.21	5.91	6.00	6.41	6.17	6.31	5.79	5.92	5.83	6.07	5.48	5.31	5.39	5.39	5.85	5.48
hsa-miR-125b	6.17	7.33	7.06	6.53	6.91	6.52	7.43	7.06	6.88	7.76	7.45	7.46	7.47	7.11	7.38	7.44	6.16	6.07	6.15	5.96	6.25	6.12
hsa-miR-126	7.28	7.22	7.39	7.28	7.00	7.89	7.44	7.38	7.36	7.64	7.61	7.71	8.01	7.26	7.48	7.62	7.54	7.11	7.36	7.11	7.24	7.27
hsa-miR-126-AS	2.14	3.82	3.72	3.64	3.64	4.49	3.95	3.21	3.58	3.58	2.49	4.29	4.43	3.02	2.79	3.43	4.37	3.56	4.03	4.47	4.01	4.09
hsa-miR-127	1.24	1.96	2.35	1.80	1.63	1.71	2.03	1.83	1.82	2.73	2.41	2.15	2.02	2.12	2.21	2.27	1.45	2.06	2.00	1.61	2.52	1.93
hsa-miR-128a	2.62	3.02	3.06	2.69	3.12	2.74	2.86	2.62	2.84	2.62	2.23	2.46	2.55	2.41	2.66	2.49	2.47	2.66	1.88	2.43	2.82	2.45
hsa-miR-129	1.96	1.66	2.19	1.92	1.68	1.75	1.76	1.72	1.83	2.25	2.26	1.54	2.39	2.61	3.21	2.38	1.86	1.52	2.21	1.61	2.17	1.88
hsa-miR-130a	5.68	5.49	5.71	5.09	5.77	5.34	5.84	5.71	5.58	5.82	6.16	5.95	6.11	5.79	6.02	5.98	6.24	6.34	6.08	6.34	6.00	6.20

hsa-miR-130b	4.14	3.74	4.26	3.71	3.89	3.81	3.54	3.53	3.83	4.23	4.11	5.55	5.25	5.09	5.85	5.01	6.46	6.74	6.47	6.28	6.17	6.42
hsa-miR-132	3.66	4.54	4.22	4.14	3.65	4.29	4.31	3.80	4.08	4.59	4.38	3.87	3.86	4.31	3.19	4.03	2.71	3.15	2.47	4.08	4.00	3.28
hsa-miR-133a	1.96	2.58	2.28	2.18	1.99	3.45	4.68	2.49	2.70	2.62	2.23	2.43	2.64	2.41	3.98	2.72	1.94	1.59	1.75	0.89	1.42	1.52
hsa-miR-134	2.02	2.62	2.55	2.52	2.20	2.44	2.91	2.85	2.52	3.60	2.73	2.77	2.72	2.68	2.56	2.84	3.21	3.53	2.74	2.97	3.58	3.21
hsa-miR-135a	0.34	1.41	2.17	1.02	1.97	1.24	1.31	0.96	1.30	1.89	1.90	1.82	1.04	2.54	1.81	1.83	1.94	1.79	2.11	2.93	1.74	2.10
hsa-miR-135b	1.83	2.10	2.17	2.77	3.02	1.66	1.88	2.59	2.25	1.89	2.38	1.64	1.97	1.94	1.71	1.92	0.67	1.37	1.07	1.71	1.74	1.31
hsa-miR-136	0.94	1.46	2.07	1.02	1.05	0.95	1.26	0.91	1.21	1.64	2.38	1.49	1.70	2.64	1.11	1.83	1.20	1.04	1.07	1.51	1.33	1.23
hsa-miR-137	0.94	2.49	2.22	0.96	2.01	1.13	1.37	1.60	1.59	1.56	2.02	2.01	1.97	2.07	1.99	1.94	1.07	1.29	1.07	1.15	1.33	1.18
hsa-miR-138	1.34	1.51	1.80	1.65	2.59	1.92	2.00	1.72	1.82	1.44	1.46	1.33	1.28	1.88	0.84	1.37	1.86	1.45	1.60	1.27	1.42	1.52
hsa-miR-139	1.96	1.84	1.44	2.61	1.82	2.39	2.58	2.09	2.09	2.41	2.71	2.75	2.72	2.37	2.56	2.59	2.42	2.66	2.47	2.05	2.36	2.39
hsa-miR-140	3.90	4.14	3.87	3.58	3.94	4.75	4.21	4.17	4.07	4.10	3.74	3.98	4.01	3.29	3.38	3.75	3.59	3.42	3.18	3.38	3.61	3.44
hsa-miR-141	6.57	5.14	6.01	6.37	6.32	5.87	5.54	5.82	5.95	5.94	6.30	7.23	6.67	7.07	7.11	6.72	7.47	7.84	7.90	7.64	7.41	7.65
hsa-miR-142-3p	4.17	3.51	2.83	3.98	3.73	4.05	3.47	3.74	3.68	2.93	2.46	3.35	3.88	2.12	3.01	2.96	2.53	2.32	2.86	4.50	2.63	2.97
hsa-miR-142-5p	3.72	2.28	2.24	2.39	1.97	2.56	2.25	2.12	2.44	2.45	2.67	2.70	2.58	3.09	2.51	2.67	2.36	2.53	2.68	3.22	2.27	2.61
hsa-miR-143	7.35	7.91	7.77	7.44	7.54	8.62	8.84	7.81	7.91	7.52	7.69	7.49	7.48	7.28	8.07	7.59	6.12	6.38	5.91	6.17	6.33	6.18
hsa-miR-144	0.94	1.06	0.52	0.63	0.90	1.07	0.84	1.17	0.89	1.06	0.77	0.85	0.39	0.81	0.84	0.79	1.67	0.95	0.14	1.71	1.14	1.12
hsa-miR-145	6.99	8.38	8.21	7.55	7.82	8.68	9.29	7.84	8.10	8.03	7.77	8.02	7.63	7.41	8.49	7.89	6.54	6.69	6.14	6.32	6.67	6.47
hsa-miR-146a	6.72	5.90	5.85	5.90	6.46	5.83	5.10	5.32	5.89	4.66	5.71	5.02	5.68	4.11	4.58	4.96	4.19	3.84	3.54	3.97	4.59	4.03
hsa-miR-147	1.83	1.51	1.52	1.39	1.88	3.12	1.37	1.90	1.82	1.48	1.34	1.27	1.28	2.46	0.84	1.45	0.94	1.59	2.68	1.27	1.14	1.52
hsa-miR-148a	5.49	5.57	4.80	5.45	5.66	5.05	4.90	4.94	5.23	6.45	6.18	8.23	7.24	7.60	7.57	7.21	8.39	9.12	8.98	8.83	8.29	8.72
hsa-miR-148b	2.19	3.45	2.52	2.71	3.21	2.86	3.47	2.82	2.91	2.86	2.83	4.16	2.74	2.89	3.36	3.14	4.69	5.65	5.46	5.99	4.58	5.27
hsa-miR-149	0.83	1.61	1.80	1.92	1.44	1.52	1.67	1.07	1.48	0.56	1.03	1.49	1.12	2.77	2.61	1.60	2.10	1.59	1.26	1.51	1.14	1.52
hsa-miR-150	4.70	4.37	4.43	4.30	4.35	3.65	4.88	4.13	4.35	4.64	4.13	3.61	5.66	2.61	2.34	3.83	2.67	1.90	1.26	1.89	2.82	2.11
hsa-miR-151	4.12	4.13	4.03	4.04	4.02	3.90	3.99	3.67	3.99	3.89	3.81	4.21	3.91	3.67	4.33	3.97	4.36	4.31	4.03	4.03	4.24	4.19
hsa-miR-152	4.56	5.09	5.20	5.11	5.11	5.06	5.42	5.33	5.11	5.62	5.33	5.04	4.89	5.28	4.65	5.14	4.84	5.19	4.81	4.68	5.05	4.91
hsa-miR-153	2.14	3.38	2.14	2.18	3.39	2.60	3.57	3.31	2.84	3.50	2.23	2.89	3.30	2.41	1.99	2.72	3.42	3.73	3.32	3.43	3.25	3.43
hsa-miR-154	1.68	2.06	2.62	2.33	2.01	2.36	2.77	2.40	2.28	3.79	2.61	3.22	3.53	3.25	2.21	3.10	3.71	3.39	3.25	3.25	3.75	3.47
hsa-miR-155	6.91	5.46	5.72	5.44	5.67	5.18	5.30	4.74	5.55	4.66	4.43	4.47	5.01	3.74	3.59	4.32	3.40	2.63	2.39	4.47	4.47	3.47
hsa-miR-15a	7.06	6.21	6.14	6.21	6.39	6.61	6.29	6.45	6.42	5.96	6.48	6.45	6.33	6.18	6.20	6.27	6.41	6.25	6.27	6.24	6.30	6.30
hsa-miR-15b	5.10	6.11	5.72	5.92	5.83	6.06	5.58	5.47	5.72	5.14	5.34	5.19	4.99	4.90	4.47	5.00	5.22	5.51	4.92	5.40	5.62	5.33
hsa-miR-16	8.23	8.17	8.27	8.24	8.28	8.42	8.19	8.40	8.27	7.92	8.15	8.37	8.34	7.95	7.92	8.11	8.20	8.21	8.11	8.07	8.16	8.15
hsa-miR-17-3p	3.02	2.31	2.57	2.39	3.02	2.51	2.34	2.26	2.55	2.23	2.58	2.35	2.39	1.94	2.94	2.41	2.67	2.50	2.96	2.38	2.44	2.59
hsa-miR-17-5p	6.84	6.20	6.75	6.48	6.92	6.79	6.45	6.50	6.62	5.90	5.90	6.23	6.47	5.88	6.31	6.12	6.57	6.13	6.09	6.40	6.34	6.31
hsa-miR-18a	5.22	3.41	4.47	4.14	4.27	4.39	3.72	4.27	4.24	3.40	3.55	3.54	3.68	2.71	3.01	3.32	3.00	2.77	2.47	2.93	2.95	2.83
hsa-miR-181a	4.81	5.87	5.86	6.22	5.83	5.43	5.91	5.83	5.72	5.62	5.43	5.95	4.74	5.79	5.22	5.46	5.07	5.32	5.11	5.18	5.14	5.16
hsa-miR-181b	4.51	4.97	5.45	5.52	5.07	4.65	4.91	5.01	5.01	4.60	4.81	4.80	4.15	4.72	4.01	4.51	4.29	4.61	4.36	4.58	4.78	4.52
hsa-miR-181c	2.34	2.87	2.61	2.54	3.00	2.56	3.07	3.00	2.75	2.25	2.29	2.46	2.43	2.07	2.14	2.27	2.24	2.15	2.21	2.63	2.52	2.35
hsa-miR-182	3.98	4.35	4.94	4.76	4.54	3.89	4.86	5.03	4.54	4.07	3.27	4.61	4.49	4.48	4.65	4.26	5.75	5.88	5.44	5.12	5.56	5.55
hsa-miR-182-AS	1.04	1.00	1.08	1.39	1.61	1.30	1.48	1.42	1.29	2.04	2.20	2.33	1.57	1.41	0.84	1.73	1.07	1.29	1.88	1.15	0.84	1.25
hsa-miR-183	1.34	1.88	2.74	1.27	2.04	1.57	2.56	2.18	1.95	2.43	1.67	2.08	2.46	2.94	2.07	2.28	2.47	2.66	2.39	2.05	2.60	2.43
hsa-miR-184	2.65	3.23	2.59	3.29	2.60	2.41	1.84	2.92	2.69	2.69	2.79	2.70	2.69	2.89	3.07	2.80	2.71	2.40	2.62	2.38	2.44	2.51
hsa-miR-185	4.55	4.54	5.11	4.29	4.72	4.76	4.41	4.95	4.67	4.42	4.17	4.48	4.69	4.00	4.19	4.33	4.41	4.35	4.18	4.62	4.52	4.42
hsa-miR-186	3.57	3.61	3.07	3.13	3.56	3.61	3.57	3.11	3.40	3.36	2.85	3.62	3.28	2.74	3.31	3.19	4.07	3.93	3.62	4.15	3.58	3.87
hsa-miR-187	2.02	1.57	1.74	1.60	1.94	1.71	3.33	1.51	1.93	1.44	1.90	1.54	1.76	2.01	1.90	1.76	1.33	1.45	0.67	2.32	0.94	1.34

hsa-miR-188	2.14	2.13	2.50	2.41	1.84	2.03	2.10	2.09	2.16	2.35	2.46	2.08	2.43	2.46	2.14	2.32	1.86	2.06	2.47	2.13	2.22	2.15
hsa-miR-189	2.14	2.13	2.09	2.00	2.75	2.41	2.77	2.51	2.35	2.07	2.26	2.48	2.28	2.01	2.83	2.32	2.24	2.66	1.43	1.81	2.60	2.15
hsa-miR-190	2.29	1.36	0.80	1.65	1.90	1.99	1.31	2.26	1.70	1.39	1.98	1.49	2.28	0.50	2.83	1.75	1.07	2.01	1.88	1.98	0.44	1.48
hsa-miR-191	5.78	6.17	6.29	5.85	6.36	6.15	6.04	5.65	6.04	5.81	5.73	5.80	5.97	5.51	5.85	5.78	5.93	6.13	5.69	5.76	6.03	5.91
hsa-miR-192	7.24	6.51	6.57	4.11	7.62	7.07	6.97	6.58	6.58	5.52	5.84	6.50	6.25	6.32	6.45	6.15	7.36	7.56	7.42	7.04	7.07	7.29
hsa-miR-193a	3.02	2.19	2.68	2.11	2.81	2.41	2.42	2.12	2.47	2.41	2.98	3.03	2.89	2.83	2.66	2.80	2.67	2.66	2.21	2.32	2.56	2.48
hsa-miR-194	7.73	6.95	7.20	4.43	7.90	7.60	7.54	7.35	7.09	5.58	5.91	6.16	5.87	6.07	6.56	6.03	6.81	6.92	6.93	6.50	6.75	6.78
hsa-miR-195	5.90	6.75	6.32	6.04	6.46	6.66	6.74	6.65	6.44	6.93	6.88	6.80	6.68	6.53	6.98	6.80	5.61	6.35	6.42	6.49	6.54	6.28
hsa-miR-196a	4.13	3.14	3.59	2.96	3.91	4.03	3.95	4.45	3.77	2.49	1.40	2.08	1.36	1.49	2.51	1.89	1.77	1.84	2.00	0.89	1.67	1.63
hsa-miR-196b	3.92	2.58	2.70	2.59	3.37	3.45	3.76	3.84	3.28	2.30	1.40	0.85	1.63	2.37	1.25	1.63	1.07	1.29	0.48	1.71	1.42	1.20
hsa-miR-197	2.29	3.25	2.47	2.27	1.88	1.99	2.39	1.97	2.31	2.35	2.32	2.27	2.46	1.88	2.87	2.36	1.86	2.15	2.21	2.13	2.06	2.08
hsa-miR-198	4.14	3.86	3.66	4.26	3.48	4.50	3.17	4.11	3.90	3.88	4.13	3.82	3.96	4.11	4.24	4.02	3.63	3.73	4.32	4.00	3.75	3.89
hsa-miR-199a	6.09	6.16	6.75	6.28	6.49	5.96	6.49	6.20	6.30	6.83	6.98	6.52	6.58	6.47	6.13	6.58	5.38	5.59	5.08	5.76	5.72	5.51
hsa-miR-199a-AS	7.14	6.93	7.18	7.05	7.04	6.75	7.20	6.81	7.01	7.57	7.38	7.42	7.23	7.52	7.31	7.41	6.33	6.61	6.37	7.00	6.63	6.59
hsa-miR-199b	4.65	4.46	4.86	4.75	4.58	4.01	4.82	4.26	4.55	4.94	5.13	4.69	5.27	4.94	4.28	4.87	4.55	4.54	4.44	4.78	4.33	4.53
hsa-miR-19a	4.91	3.81	3.90	4.54	4.31	4.43	4.07	4.04	4.25	3.80	3.90	4.37	4.29	4.14	4.23	4.12	4.87	4.99	5.02	5.23	4.40	4.90
hsa-miR-19b	6.56	5.65	6.24	6.38	6.29	6.25	5.97	5.94	6.16	5.86	6.09	6.20	6.45	6.32	6.39	6.22	6.81	6.89	6.76	6.44	6.39	6.66
hsa-miR-20a	6.16	5.51	6.17	6.04	6.12	6.09	5.71	5.78	5.95	5.42	5.29	5.69	5.95	5.38	5.86	5.60	6.12	5.60	5.69	5.88	5.69	5.80
hsa-miR-200a	6.03	5.60	5.87	4.91	5.98	5.39	5.41	4.65	5.48	4.93	5.25	6.02	5.84	5.91	6.19	5.69	6.74	6.88	6.95	6.63	6.44	6.73
hsa-miR-200b	6.53	6.76	7.04	6.35	7.44	6.59	6.76	5.93	6.68	5.87	5.97	6.96	6.55	6.57	7.09	6.50	7.64	7.68	7.62	7.78	7.55	7.65
hsa-miR-200c	7.30	6.74	7.76	7.30	7.46	7.38	6.80	7.11	7.23	7.00	7.34	8.02	7.71	7.93	8.04	7.67	8.80	8.84	8.60	8.61	8.86	8.74
hsa-miR-203	5.69	4.37	5.21	4.56	5.31	4.88	5.93	5.29	5.15	2.96	3.14	2.57	2.64	2.46	3.34	2.85	4.36	3.28	3.29	3.36	4.16	3.69
hsa-miR-204	0.83	2.39	1.90	1.39	1.46	1.88	2.25	2.12	1.78	2.37	1.72	1.94	2.72	2.46	2.21	2.24	2.03	2.36	1.75	2.26	2.36	2.15
hsa-miR-205	3.60	2.06	4.48	7.90	3.10	0.95	2.74	1.80	3.33	2.02	1.67	2.08	1.70	2.28	1.61	1.89	1.45	0.86	2.80	1.61	0.84	1.51
hsa-miR-206	2.29	1.57	1.96	2.27	1.88	3.10	1.62	1.47	2.02	2.53	2.67	2.05	2.28	2.89	2.66	2.51	1.56	2.01	1.75	1.98	2.12	1.88
hsa-miR-208	1.76	1.36	1.56	1.50	1.49	1.24	1.37	1.80	1.51	1.83	2.58	1.82	1.92	1.66	1.71	1.92	1.45	1.29	1.75	1.61	1.67	1.55
hsa-miR-21	9.57	9.93	9.40	10.2	9.38	10.0	9.93	9.48	9.75	9.68	8.89	9.28	8.68	9.53	9.47	9.26	8.53	8.39	8.46	9.69	9.25	8.86
hsa-miR-210	6.90	5.51	6.98	6.61	7.21	7.23	5.60	6.45	6.56	4.75	4.80	4.26	4.24	4.24	4.86	4.53	4.12	3.68	3.98	3.78	4.27	3.97
hsa-miR-211	0.83	1.12	2.09	1.02	1.44	1.30	1.02	1.07	1.24	1.79	1.94	1.16	1.28	2.01	0.98	1.53	0.41	1.37	1.75	1.27	0.73	1.11
hsa-miR-212	1.68	1.51	1.74	1.55	1.58	1.88	1.42	1.87	1.65	1.56	1.90	1.86	1.63	1.41	1.11	1.58	0.94	1.59	1.07	1.81	1.74	1.43
hsa-miR-213	0.63	1.06	1.90	1.27	1.28	1.24	1.31	1.17	1.23	1.83	2.41	1.69	1.87	2.64	2.07	2.08	1.77	1.12	0.48	1.15	0.94	1.09
hsa-miR-214	5.17	6.53	6.31	5.81	6.21	5.77	6.51	6.45	6.10	6.76	6.43	6.00	5.89	6.15	5.58	6.14	4.65	4.67	4.37	5.16	5.23	4.81
hsa-miR-215	6.14	3.54	2.50	1.70	5.09	4.19	4.45	4.05	3.96	2.21	2.23	3.21	2.67	3.04	3.21	2.76	4.33	4.28	4.46	5.40	4.02	4.50
hsa-miR-216	2.55	2.78	2.41	1.33	1.49	2.51	1.48	1.51	2.01	5.15	5.06	7.14	6.01	5.66	6.82	5.97	6.99	7.55	7.27	7.38	7.04	7.25
hsa-miR-217	3.16	3.43	1.04	2.36	1.99	2.97	1.80	2.62	2.42	5.97	5.94	7.95	6.91	6.36	7.49	6.77	7.78	8.19	8.02	8.15	7.95	8.02
hsa-miR-218	3.51	4.73	3.73	3.92	3.95	3.79	4.44	4.58	4.08	4.40	4.33	4.11	4.27	3.98	3.86	4.16	3.64	3.51	3.42	4.04	4.02	3.73
hsa-miR-219	1.14	1.51	2.14	1.15	1.33	1.52	1.37	1.32	1.44	1.68	2.09	1.82	2.20	2.18	1.99	1.99	1.77	1.79	2.00	1.39	1.42	1.67
hsa-miR-22	7.06	6.91	7.69	7.24	7.08	7.21	7.31	7.12	7.20	7.43	7.28	7.12	7.05	7.09	6.91	7.15	6.87	7.15	6.93	7.02	6.77	6.95
hsa-miR-220	1.90	1.00	1.27	1.27	1.38	1.13	1.58	1.27	1.35	1.35	2.02	1.27	1.76	1.49	0.84	1.46	1.56	1.52	1.07	1.39	1.04	1.32
hsa-miR-221	6.18	6.11	6.48	6.88	6.99	6.74	6.10	6.15	6.45	5.72	5.62	5.42	5.65	5.32	5.23	5.49	5.16	5.19	4.82	5.48	5.25	5.18
hsa-miR-222	5.35	5.61	5.79	6.49	6.45	6.40	5.56	5.89	5.94	4.90	5.04	4.60	4.88	4.56	4.34	4.72	4.27	4.15	3.39	4.36	4.34	4.10
hsa-miR-223	5.54	7.39	7.23	7.19	6.95	8.25	6.09	5.86	6.81	5.81	6.19	6.60	5.66	5.55	4.41	5.70	4.29	3.82	4.56	5.60	4.94	4.64
hsa-miR-224	4.14	3.45	4.05	3.82	3.82	3.40	4.04	3.85	3.82	2.51	2.56	2.46	2.49	3.02	2.94	2.66	2.36	2.91	2.68	3.29	2.79	2.81
hsa-miR-23a	7.13	7.76	7.93	7.51	7.61	7.79	7.91	7.34	7.62	7.35	7.37	7.09	6.88	7.03	7.20	7.15	7.01	7.19	6.88	7.04	7.21	7.07

hsa-miR-23b	6.93	7.75	7.73	7.50	7.61	7.74	7.97	7.31	7.57	7.44	7.39	7.35	6.99	7.24	7.28	7.28	7.33	7.57	7.05	7.20	7.42	7.31
hsa-miR-24	7.55	8.00	8.40	7.75	8.11	8.15	8.18	8.07	8.02	7.81	7.61	7.62	7.39	7.61	7.65	7.87	7.26	7.45	7.32	7.02	7.50	7.31
hsa-miR-25	5.59	5.73	5.43	5.92	5.58	5.81	5.42	5.67	5.64	5.10	5.01	5.49	5.34	5.05	5.19	5.12	5.69	5.66	5.40	5.53	5.65	5.58
hsa-miR-26a	8.36	8.97	8.56	8.34	9.07	8.87	8.96	8.83	8.75	8.67	8.68	9.04	8.57	8.78	8.76	8.84	9.05	9.33	9.02	8.97	9.40	9.15
hsa-miR-26b	6.54	7.25	6.41	6.74	7.08	7.31	7.04	7.10	6.93	6.55	6.26	7.24	6.82	6.41	6.67	6.66	7.64	7.65	7.55	7.62	7.63	7.62
hsa-miR-27a	7.40	7.12	7.09	7.57	7.32	7.40	7.69	7.11	7.34	7.03	7.04	7.10	6.44	7.02	6.79	6.90	6.91	7.15	6.96	7.07	7.03	7.03
hsa-miR-27b	6.66	7.12	6.90	6.93	7.27	7.16	7.57	7.07	7.09	7.11	7.02	7.20	6.83	7.38	7.33	7.14	7.62	7.98	7.55	7.38	7.60	7.62
hsa-miR-28	4.79	5.46	4.78	4.78	5.14	5.13	5.28	5.02	5.05	4.53	4.62	4.87	4.44	4.62	4.83	4.65	4.99	5.05	4.66	5.00	5.23	4.99
hsa-miR-296	1.60	1.88	1.74	1.75	1.68	1.46	1.62	1.42	1.64	1.96	2.41	2.12	2.12	2.01	1.37	2.00	1.20	1.90	1.88	1.71	2.17	1.77
hsa-miR-299-5p	1.83	2.37	1.63	2.44	1.78	1.84	2.07	2.28	2.03	2.51	2.06	1.90	2.28	1.74	2.66	2.19	2.57	2.40	2.74	2.38	2.44	2.51
hsa-miR-29a	7.64	7.56	7.26	7.83	7.51	7.79	7.55	7.49	7.58	7.26	7.43	7.51	7.21	7.24	7.08	7.29	7.52	7.76	7.75	7.84	7.64	7.71
hsa-miR-29b	6.91	6.14	5.89	6.33	6.85	6.40	6.64	6.26	6.43	5.86	5.72	6.29	6.38	5.87	6.44	6.09	6.57	6.73	6.92	6.88	6.58	6.73
hsa-miR-29c	6.53	6.82	5.66	6.19	6.52	6.63	6.83	6.41	6.45	6.61	6.39	7.60	6.95	7.21	7.37	7.02	8.31	8.65	8.74	8.34	7.98	8.40
hsa-miR-301	3.20	2.66	2.43	2.49	2.58	2.74	2.77	2.94	2.73	2.28	1.98	2.18	2.12	2.41	1.81	2.13	2.03	2.36	2.21	2.53	2.22	2.27
hsa-miR-302a	1.24	1.18	1.84	0.83	1.19	1.88	0.84	1.01	1.25	1.60	1.40	1.82	2.12	2.89	1.99	1.97	2.03	1.21	0.67	1.39	1.50	1.36
hsa-miR-302b	1.52	1.12	1.18	1.21	1.44	1.46	1.31	1.12	1.30	0.86	1.03	0.73	0.71	0.91	1.25	0.91	1.67	1.37	1.26	0.76	1.04	1.22
hsa-miR-302b-AS	1.24	1.30	1.56	1.02	0.99	0.82	1.08	0.48	1.06	1.16	0.83	1.86	0.79	3.06	2.56	1.71	1.77	1.21	0.48	0.50	0.94	0.98
hsa-miR-302c	0.73	1.06	1.63	0.76	1.08	0.82	1.02	0.69	0.97	0.96	0.45	0.67	1.20	2.46	0.31	1.01	1.67	1.37	1.75	1.02	1.04	1.37
hsa-miR-302c-AS	2.43	1.99	3.30	2.08	1.58	1.46	1.58	1.72	2.02	2.30	2.38	2.24	3.30	1.22	2.28	2.29	2.57	1.96	2.74	2.05	1.88	2.24
hsa-miR-302d	1.76	1.57	2.39	1.70	1.49	1.52	1.31	1.37	1.64	2.28	2.06	1.22	1.70	2.18	2.21	1.94	1.94	1.29	0.31	1.39	1.33	1.25
hsa-miR-30a-3p	2.34	2.51	2.88	2.63	2.59	2.70	2.89	2.40	2.62	3.08	3.16	3.99	3.51	3.52	4.03	3.55	4.29	4.42	4.40	4.21	4.03	4.27
hsa-miR-30a-5p	6.15	6.66	6.84	6.61	6.77	6.71	6.85	6.54	6.64	6.84	6.97	7.50	7.38	7.11	7.52	7.22	7.99	7.78	7.80	7.51	7.76	7.77
hsa-miR-30b	5.54	5.65	5.64	5.67	6.14	5.76	5.73	5.42	5.69	6.06	5.99	6.82	6.30	6.17	6.29	6.27	6.86	7.28	7.11	7.04	6.71	7.00
hsa-miR-30c	5.13	5.49	5.73	5.55	5.70	5.78	5.76	5.52	5.58	5.87	5.88	6.51	6.44	6.05	6.47	6.20	7.04	7.17	7.01	6.78	6.64	6.93
hsa-miR-30d	5.81	6.57	6.30	5.89	6.30	6.23	6.54	6.35	6.25	6.31	6.66	6.85	6.81	6.57	6.71	6.65	7.48	7.15	7.20	7.06	7.31	7.24
hsa-miR-30e-3p	2.08	2.47	2.35	2.27	1.90	2.68	2.51	1.83	2.26	2.32	2.02	3.37	2.77	3.02	3.10	2.77	3.66	3.86	4.01	3.97	3.36	3.77
hsa-miR-30e-5p	5.88	6.13	6.32	6.28	6.23	6.25	6.39	6.25	6.22	6.39	6.25	6.90	6.79	6.42	6.68	6.57	7.36	7.27	7.27	7.06	7.13	7.22
hsa-miR-31	5.86	6.44	2.90	9.04	7.68	7.00	6.80	7.54	6.66	6.22	6.06	5.54	4.23	5.82	6.03	5.65	4.33	3.86	4.43	3.89	3.88	4.08
hsa-miR-32	1.04	1.80	2.22	1.50	1.41	1.66	1.58	1.22	1.55	1.89	1.10	2.21	1.70	2.68	1.49	1.84	1.77	1.66	1.43	2.58	1.50	1.79
hsa-miR-320	6.15	5.84	5.57	5.52	6.14	6.44	6.11	5.87	5.96	5.70	5.93	6.15	5.68	5.69	6.13	5.88	5.86	6.08	5.66	5.93	5.79	5.86
hsa-miR-323	1.43	1.24	0.75	1.44	1.44	1.46	1.58	1.47	1.35	0.91	0.97	1.16	1.28	1.31	-0.2	0.90	1.67	1.04	1.07	1.71	1.23	1.34
hsa-miR-324-3p	2.47	2.68	3.11	2.69	2.79	2.44	2.77	2.47	2.68	2.84	2.85	2.43	2.77	2.54	2.70	2.69	1.33	1.96	2.00	1.81	2.22	1.86
hsa-miR-324-5p	1.60	1.66	1.74	1.02	1.49	1.66	1.67	1.56	1.55	1.11	1.28	1.22	1.50	2.28	1.25	1.44	1.07	1.52	1.88	1.27	1.74	1.50
hsa-miR-325	0.94	1.57	0.99	1.55	1.90	1.13	1.26	1.12	1.31	0.76	0.90	1.16	1.20	1.94	1.99	1.32	1.86	1.21	1.75	1.51	1.23	1.51
hsa-miR-326	1.68	1.88	1.99	1.39	1.25	1.46	1.48	1.07	1.52	1.92	1.72	1.54	1.12	2.50	1.90	1.78	1.33	1.37	1.26	1.15	1.50	1.32
hsa-miR-328	1.90	1.80	1.99	1.55	1.54	1.52	1.58	1.27	1.64	1.56	1.46	1.49	1.81	2.01	1.61	1.66	1.33	1.45	0.48	1.51	1.33	1.22
hsa-miR-33	1.68	1.41	0.90	1.21	1.25	1.30	1.48	1.42	1.33	1.60	0.45	1.82	1.76	2.99	0.43	1.51	1.20	1.37	0.87	1.02	1.81	1.25
hsa-miR-330	1.96	1.41	1.67	1.75	1.88	1.61	1.62	1.56	1.68	1.64	2.56	1.33	1.70	2.12	2.07	1.90	1.07	1.37	0.14	1.15	1.81	1.11
hsa-miR-331	2.69	3.61	3.93	3.01	3.62	3.37	3.79	3.70	3.46	3.30	2.58	2.66	2.32	2.37	2.56	2.63	2.53	2.36	1.60	2.13	2.63	2.25
hsa-miR-335	4.73	5.44	4.92	4.30	4.83	4.20	5.72	5.25	4.92	5.08	4.25	5.77	5.67	4.78	5.24	5.13	6.50	6.62	6.60	5.83	6.18	6.35
hsa-miR-337	0.94	1.51	1.08	1.84	1.16	0.88	1.26	0.80	1.19	0.91	0.83	1.33	1.36	0.41	0.84	0.95	1.77	1.21	0.48	1.39	0.84	1.14
hsa-miR-338	4.95	3.93	2.73	3.00	3.83	4.54	3.89	4.85	3.96	3.54	4.07	4.65	4.09	4.14	4.19	4.11	4.98	5.07	5.16	4.73	4.99	4.98
hsa-miR-339	2.34	2.28	2.48	2.81	2.43	2.46	2.58	2.38	2.47	2.78	2.81	2.55	2.79	2.18	2.61	2.62	2.57	2.71	3.14	2.43	2.60	2.69

hsa-miR-340	1.52	1.36	1.04	1.21	1.54	2.09	1.76	1.27	1.47	1.11	0.83	1.49	0.71	1.01	1.81	1.16	1.67	1.72	1.26	1.61	1.42	1.54
hsa-miR-342	6.47	6.22	6.03	6.11	6.00	5.88	6.08	6.06	6.11	6.00	5.87	5.85	6.18	5.77	6.08	5.96	6.17	6.08	6.48	6.49	5.93	6.23
hsa-miR-345	1.83	1.88	2.26	2.00	1.96	1.88	2.16	2.03	2.00	1.64	2.41	2.30	2.64	1.94	1.37	2.05	1.56	2.01	1.26	2.05	1.50	1.68
hsa-miR-346	1.34	1.41	1.08	1.80	1.33	1.01	1.20	1.01	1.27	0.76	0.83	2.41	1.63	0.23	1.25	1.18	1.07	1.12	1.43	1.02	1.42	1.21
hsa-miR-34a	6.14	5.38	6.19	5.77	6.26	5.64	6.05	5.20	5.83	5.82	5.97	5.63	5.29	5.31	5.81	5.64	4.85	6.02	5.22	5.60	5.58	5.45
hsa-miR-34b	3.75	3.68	3.38	3.68	3.95	3.72	4.04	3.36	3.70	3.54	2.95	3.49	3.05	2.97	3.26	3.21	2.62	3.99	3.71	4.64	3.46	3.68
hsa-miR-34c	1.76	1.84	2.37	1.55	2.03	1.41	2.19	1.90	1.88	1.72	1.77	1.86	1.20	2.97	2.40	1.99	1.45	1.37	0.87	1.02	1.33	1.21
hsa-miR-361	4.16	4.85	4.89	4.36	5.05	4.87	4.96	4.66	4.72	4.40	4.52	4.60	4.69	4.50	4.16	4.48	4.63	4.70	4.44	4.43	4.88	4.61
hsa-miR-365	2.08	2.44	1.74	2.63	2.13	2.34	2.16	2.06	2.20	2.69	2.16	2.77	2.43	2.18	2.34	2.43	3.68	3.58	3.69	4.29	2.82	3.61
hsa-miR-367	1.43	1.12	1.96	1.08	1.13	0.76	1.37	0.80	1.21	2.35	2.41	1.54	1.92	1.81	2.83	2.14	0.67	0.77	1.07	1.71	1.50	1.15
hsa-miR-368	4.01	4.48	4.62	4.70	3.86	4.32	4.57	4.49	4.38	5.58	4.84	5.16	5.21	5.41	4.76	5.16	5.74	5.71	5.57	5.54	6.02	5.71
hsa-miR-369-3p	0.63	1.36	0.61	1.21	0.81	0.64	1.02	0.59	0.86	0.71	0.97	1.16	0.87	1.58	1.11	1.07	1.56	1.52	0.48	1.98	1.42	1.39
hsa-miR-370	3.09	3.36	3.35	3.14	2.31	3.18	3.03	3.32	3.10	3.39	2.95	3.15	2.89	3.59	2.87	3.14	2.71	2.71	3.05	3.03	2.79	2.86
hsa-miR-371	1.90	1.00	0.85	1.33	1.28	0.88	1.20	1.64	1.26	1.99	1.62	1.54	1.12	1.49	1.61	1.56	1.33	0.86	1.75	1.39	1.04	1.27
hsa-miR-372	1.76	1.41	1.48	1.92	1.22	1.46	1.67	1.64	1.57	1.16	1.03	1.22	1.97	1.41	0.70	1.25	0.18	1.66	0.67	1.81	1.23	1.11
hsa-miR-373	1.24	1.30	1.59	1.50	1.19	1.30	1.31	1.27	1.34	1.21	1.72	1.82	1.20	2.86	2.28	1.85	1.56	1.29	1.43	1.27	0.94	1.30
hsa-miR-373-AS	2.19	2.10	1.87	2.41	2.06	2.28	2.10	2.33	2.17	1.99	2.16	1.98	2.20	1.94	1.99	2.04	2.30	2.24	2.39	2.58	2.06	2.32
hsa-miR-374	2.65	3.36	2.41	2.71	3.33	3.41	3.68	3.31	3.11	2.76	2.13	3.12	2.89	2.41	2.94	2.71	3.94	3.58	3.88	5.03	3.52	3.99
hsa-miR-375	3.40	6.11	3.92	4.04	5.00	4.10	5.91	4.96	4.68	6.28	5.11	7.26	6.83	6.67	6.91	6.51	7.55	7.59	7.57	6.75	7.38	7.37
hsa-miR-376a	3.05	3.99	3.61	4.00	3.35	3.70	4.00	3.92	3.70	4.50	3.64	4.02	4.11	4.14	3.41	3.97	4.64	4.74	4.52	5.12	4.95	4.79
hsa-miR-377	2.58	2.62	2.54	3.19	2.04	2.49	2.91	3.20	2.70	3.89	3.00	3.15	2.97	3.38	2.87	3.21	3.35	3.70	3.14	3.49	3.83	3.50
hsa-miR-378	1.14	1.71	2.09	1.08	1.49	1.71	1.80	1.07	1.51	1.11	0.90	1.98	1.36	2.32	2.40	1.68	1.94	1.21	1.60	1.27	0.84	1.37
hsa-miR-379	3.33	3.66	3.61	3.79	2.81	3.32	3.52	3.97	3.50	4.44	3.97	4.19	4.12	4.22	4.04	4.16	4.02	4.05	4.15	3.84	4.47	4.11
hsa-miR-380-3p	0.34	1.51	1.22	1.15	1.11	0.88	1.08	0.75	1.01	0.37	0.90	0.85	1.12	1.94	2.34	1.26	1.33	0.52	0.87	1.39	1.33	1.09
hsa-miR-380-5p	0.94	1.51	1.84	0.63	1.11	1.30	1.02	0.91	1.16	1.89	1.81	1.82	1.43	2.23	2.34	1.92	0.80	1.12	1.07	0.50	1.23	0.94
hsa-miR-381	1.90	1.75	2.01	1.75	1.63	1.61	1.72	1.94	1.79	2.39	2.26	2.33	2.39	3.11	2.87	2.56	2.03	2.57	2.11	2.43	2.79	2.38
hsa-miR-382	2.78	3.06	3.02	3.24	2.72	3.45	3.05	3.33	3.08	3.75	3.31	2.98	2.67	3.52	2.56	3.13	3.07	3.36	2.80	3.25	3.93	3.28
hsa-miR-383	1.43	1.51	2.07	1.70	1.36	1.66	1.37	1.42	1.57	2.18	2.26	1.27	2.12	2.46	2.34	2.11	1.77	1.37	2.31	1.27	2.12	1.77
hsa-miR-384	0.43	1.30	0.99	0.76	1.02	0.41	1.26	0.29	0.81	0.56	0.51	0.79	0.71	1.74	0.19	0.75	0.54	1.12	1.43	1.15	1.42	1.13
hsa-miR-422a	2.78	3.50	2.26	2.67	3.05	2.81	3.63	2.15	2.86	2.32	2.29	2.72	2.64	1.01	2.40	2.23	3.03	3.04	2.74	2.75	2.63	2.84
hsa-miR-422b	4.37	4.31	4.07	3.79	4.26	3.84	4.79	3.49	4.12	3.21	3.57	3.78	3.79	3.04	3.86	3.54	4.13	3.96	2.91	3.49	3.62	3.62
hsa-miR-423	2.90	4.05	4.03	4.00	3.83	4.04	3.93	3.54	3.79	3.99	3.83	3.93	2.99	3.63	3.45	3.64	3.50	3.63	3.14	2.63	3.41	3.26
hsa-miR-424	3.85	4.06	3.54	3.89	3.65	3.71	4.01	4.49	3.90	3.95	3.38	3.46	2.86	3.25	2.46	3.23	3.64	3.37	3.05	4.77	4.39	3.85
hsa-miR-425	2.24	2.28	1.99	1.84	2.48	2.09	2.07	1.68	2.08	1.79	1.86	1.39	1.76	1.74	2.46	1.83	2.10	2.36	1.43	1.71	1.59	1.84
hsa-miR-429	4.62	5.18	4.73	3.84	5.20	4.66	5.10	4.07	4.68	3.92	3.31	4.68	4.37	4.01	4.53	4.14	5.34	5.31	5.36	5.29	5.16	5.29
hsa-miR-448	1.34	1.18	0.90	0.96	1.28	1.66	1.31	1.72	1.29	0.91	1.90	1.04	0.87	0.91	0.70	1.05	1.20	1.37	2.11	1.61	1.59	1.58
hsa-miR-449	1.34	1.46	1.96	1.08	1.56	1.57	1.42	1.17	1.45	1.60	2.09	2.01	1.57	3.11	3.19	2.26	0.94	1.45	1.07	1.51	1.74	1.34
hsa-miR-450	2.19	1.61	1.93	1.84	1.70	1.79	2.03	1.97	1.88	2.23	1.77	2.12	1.28	1.66	1.49	1.76	1.56	1.37	0.87	1.98	1.50	1.46
hsa-miR-7	5.87	7.07	3.23	5.03	5.32	5.45	6.30	5.76	5.50	6.15	3.61	5.11	6.23	5.38	4.87	5.22	6.02	5.74	5.68	5.22	6.55	5.84
hsa-miR-9	1.24	1.24	2.31	1.15	1.16	1.19	1.48	1.47	1.40	1.11	2.56	1.27	2.16	2.41	2.28	1.97	0.54	1.21	0.87	1.51	1.67	1.16
hsa-miR-9-AS	2.19	1.57	2.31	1.44	1.58	1.75	1.80	2.06	1.84	1.99	2.16	1.82	1.81	2.07	2.07	1.99	2.30	1.84	1.26	1.15	1.33	1.58
hsa-miR-92	4.55	4.75	5.05	4.88	5.19	5.01	4.76	4.91	4.89	4.61	4.61	5.20	4.99	4.81	5.11	4.89	5.37	4.90	4.81	5.01	4.83	4.98
hsa-miR-93	6.29	5.22	6.08	5.72	5.90	6.05	5.97	5.95	5.90	5.09	5.33	5.09	5.37	4.91	4.64	5.07	5.21	4.78	4.67	5.22	5.09	4.99
hsa-miR-95	2.43	4.18	2.33	3.20	3.04	3.73	3.74	3.11	3.22	2.90	2.16	3.35	2.69	2.46	2.83	2.73	3.97	4.33	4.06	3.63	4.27	4.05

hsa-miR-96	2.72	3.10	2.95	3.52	3.01	2.72	3.35	3.35	3.09	2.47	2.29	3.82	2.69	3.23	3.41	2.99	4.92	5.34	5.02	4.57	4.40	4.85
hsa-miR-98	4.30	5.20	3.68	4.57	4.90	4.08	4.89	4.83	4.56	4.25	4.04	4.42	4.28	3.99	3.97	4.16	4.89	4.93	5.00	6.10	5.16	5.22
hsa-miR-99a	5.32	6.79	5.96	5.79	6.43	5.73	7.07	6.73	6.23	6.96	6.90	6.59	6.96	6.21	6.66	6.71	5.75	5.53	5.30	5.17	5.94	5.54
hsa-miR-99b	4.20	5.11	5.01	4.65	5.37	4.95	5.17	4.86	4.91	4.86	4.83	4.50	4.83	4.38	4.67	4.68	4.48	4.05	3.98	4.11	4.83	4.29
mmu-let-7d-AS	1.14	1.18	2.01	0.83	1.38	1.30	1.62	1.32	1.35	0.96	1.34	0.98	1.12	1.81	0.98	1.20	1.33	1.45	2.00	1.02	1.42	1.44
mmu-miR-101b	2.08	1.46	0.99	1.65	1.56	1.75	1.67	1.51	1.59	1.86	1.57	1.54	3.10	1.01	1.61	1.78	2.03	0.77	2.11	2.05	1.42	1.68
mmu-miR-106a	6.23	5.92	6.18	6.02	6.44	6.40	6.03	6.03	6.16	5.28	5.16	5.73	5.81	5.17	5.66	5.47	6.07	5.69	5.63	6.19	5.83	5.88
mmu-miR-129-3p	1.96	1.80	1.80	1.70	1.76	1.79	1.96	1.64	1.80	2.67	2.20	1.86	2.16	2.28	2.97	2.36	1.94	1.59	2.21	1.51	1.94	1.84
mmu-miR-140-AS	4.29	4.24	4.39	3.67	4.54	5.31	4.78	4.71	4.49	4.66	4.55	4.41	4.73	3.89	4.09	4.39	4.32	3.78	3.18	3.56	4.15	3.80
mmu-miR-151	2.87	3.26	2.07	3.11	2.92	2.79	3.00	2.73	2.84	2.32	2.16	2.53	2.67	1.94	2.75	2.40	3.42	3.43	3.01	3.32	3.29	3.29
mmu-miR-155	5.04	4.72	4.52	4.29	4.61	4.39	4.37	3.90	4.48	3.41	2.49	3.41	3.52	2.80	2.51	3.02	2.67	1.96	2.31	3.78	3.88	2.92
mmu-miR-17-3p	2.29	1.92	1.22	2.30	1.65	1.46	2.03	1.27	1.77	1.83	1.22	1.44	1.87	2.07	1.90	1.72	2.03	1.79	1.88	1.89	1.81	1.88
mmu-miR-192	7.16	6.44	6.54	3.77	7.53	7.01	6.93	6.48	6.48	5.49	5.70	6.36	6.23	6.25	6.35	6.07	7.27	7.44	7.24	6.84	6.98	7.15
mmu-miR-199b	4.49	4.97	4.91	5.10	4.91	4.62	5.27	4.72	4.87	5.21	5.08	4.99	5.08	4.67	4.21	4.88	4.31	4.42	4.25	5.35	4.42	4.55
mmu-miR-201	1.04	1.41	1.40	0.96	1.25	1.36	1.31	1.22	1.24	1.35	1.72	0.85	1.43	1.22	1.37	1.32	1.07	1.79	1.60	1.02	1.59	1.41
mmu-miR-202	3.51	3.00	3.09	3.77	3.15	3.03	2.28	3.36	3.15	2.92	3.28	2.94	3.50	2.74	3.47	3.14	3.00	2.60	3.21	2.97	2.66	2.89
mmu-miR-207	1.60	2.74	1.13	1.75	1.19	1.36	1.42	1.17	1.55	1.60	0.77	1.44	1.87	1.41	1.90	1.50	1.77	1.84	2.00	1.61	1.23	1.69
mmu-miR-211	0.83	1.18	0.90	0.70	0.93	1.13	1.14	0.75	0.94	1.48	0.97	1.59	0.55	1.58	1.25	1.24	1.33	1.52	1.26	1.61	1.59	1.46
mmu-miR-215	3.02	1.41	0.94	1.60	2.69	1.99	2.22	2.53	2.05	0.28	1.03	1.22	1.63	1.01	1.99	1.19	2.24	1.90	2.31	2.83	1.33	2.12
mmu-miR-217	3.18	3.20	1.48	2.15	1.90	2.79	1.76	2.71	2.40	5.65	5.53	7.70	6.64	5.95	7.35	6.47	7.66	7.98	7.83	8.07	7.72	7.85
mmu-miR-290	2.58	2.31	2.57	2.63	2.08	2.51	2.28	2.23	2.40	2.70	2.54	1.94	2.84	3.09	2.66	2.63	2.57	2.40	2.68	2.48	2.60	2.55
mmu-miR-291-3p	1.14	1.06	1.04	1.60	1.36	1.36	1.58	1.37	1.31	2.25	1.34	2.01	1.63	2.50	1.49	1.87	0.94	1.59	1.43	0.89	0.94	1.16
mmu-miR-291-5p	1.24	1.41	1.87	1.33	1.44	1.13	1.31	1.07	1.35	1.60	1.98	1.22	2.02	2.46	2.14	1.90	1.56	0.77	1.88	1.02	1.50	1.35
mmu-miR-292-3p	1.83	1.46	2.01	1.08	1.74	1.41	1.67	1.72	1.62	1.99	1.81	1.04	1.57	0.60	1.25	1.38	0.29	1.59	1.07	0.76	1.33	1.01
mmu-miR-292-5p	2.02	1.75	1.93	1.84	1.58	1.66	1.58	1.68	1.76	1.44	1.67	1.49	2.20	2.23	2.21	1.87	1.94	1.79	2.00	2.32	1.67	1.94
mmu-miR-293	1.43	1.12	2.26	1.60	1.08	1.24	1.14	1.37	1.41	1.99	2.49	1.94	2.07	2.61	0.98	2.01	1.45	1.12	1.26	1.15	1.23	1.24
mmu-miR-294	0.94	1.51	1.63	1.39	1.28	1.71	1.42	1.72	1.45	1.39	0.70	1.16	1.28	1.66	1.49	1.28	1.56	1.45	1.75	1.98	1.42	1.63
mmu-miR-295	1.43	1.46	1.08	1.55	1.46	1.30	1.48	1.64	1.43	1.21	1.16	1.44	0.71	1.12	1.11	1.12	1.20	0.77	1.60	1.81	1.14	1.30
mmu-miR-297	2.58	1.36	1.80	2.88	3.51	5.18	1.53	2.12	2.62	1.83	1.28	1.82	1.04	2.54	2.51	1.84	1.86	1.12	2.68	2.05	1.67	1.88
mmu-miR-298	4.05	3.63	3.36	4.06	3.49	3.82	3.21	3.84	3.68	3.52	3.74	3.60	3.86	3.83	4.22	3.80	3.77	3.73	4.11	3.99	3.70	3.86
mmu-miR-300	1.43	1.66	1.77	1.84	1.58	1.88	1.62	1.68	1.68	1.86	1.62	1.49	1.70	2.12	1.90	1.78	0.94	2.20	2.55	1.71	2.00	1.88
mmu-miR-322	0.83	1.12	2.12	1.27	1.33	1.13	1.31	0.85	1.25	2.04	2.13	1.49	2.20	2.54	1.71	2.02	0.80	0.95	0.48	0.50	1.33	0.81
mmu-miR-424	2.02	2.39	2.07	2.41	2.43	2.34	2.51	3.33	2.44	2.25	1.72	2.24	1.36	1.12	0.98	1.61	2.24	2.06	1.43	3.06	2.60	2.28
mmu-miR-325	2.14	1.18	1.35	1.96	1.94	1.61	1.67	2.33	1.77	1.92	2.26	1.86	2.12	1.01	2.14	1.89	1.33	1.52	1.75	2.26	1.33	1.64
mmu-miR-329	3.18	1.57	1.08	1.44	1.44	1.36	1.67	1.68	1.68	1.92	2.09	1.44	0.87	1.22	0.84	1.40	1.45	1.72	1.26	1.27	0.94	1.33
mmu-miR-330	1.52	1.30	1.48	1.44	1.41	1.30	1.72	1.47	1.45	0.96	1.03	0.73	1.20	1.74	1.25	1.15	1.56	1.79	1.60	1.61	1.59	1.63
mmu-miR-337	1.83	1.18	1.40	1.84	1.63	1.71	1.48	1.87	1.62	1.11	2.02	0.98	1.36	1.74	2.14	1.56	2.62	1.84	1.43	1.89	1.04	1.77
mmu-miR-341	2.29	1.51	1.08	1.88	1.92	1.99	1.48	1.83	1.75	1.01	1.28	1.22	1.76	-0.01	2.40	1.28	1.33	1.72	1.88	1.39	1.14	1.49

mmu-miR-344	1.14	1.18	2.14	0.76	1.02	1.36	1.31	0.85	1.22	1.89	2.58	1.22	1.87	2.94	2.40	2.15	1.45	1.29	0.87	1.15	0.73	1.10
mmu-miR-345	1.60	1.88	1.48	3.56	1.49	1.75	1.67	1.37	1.85	1.72	1.98	1.78	2.49	1.66	1.90	1.92	2.10	1.72	1.75	1.39	1.50	1.69
mmu-miR-346	1.34	1.46	1.27	1.39	1.51	1.52	1.31	0.91	1.34	1.06	1.28	1.27	0.47	1.01	1.49	1.10	0.94	1.04	0.67	1.51	1.04	1.04
mmu-miR-34b	1.76	1.92	2.17	1.70	1.72	1.61	1.84	1.51	1.78	1.86	2.23	1.86	2.02	2.61	1.11	1.95	1.33	1.37	1.43	1.51	2.00	1.53
mmu-miR-350	1.52	1.75	1.08	1.21	1.63	1.19	1.26	1.87	1.44	1.48	1.28	1.22	1.28	1.12	1.25	1.27	1.56	1.12	2.00	1.02	1.23	1.39
mmu-miR-351	2.08	1.18	1.40	1.70	1.68	1.57	1.26	1.51	1.55	1.64	1.86	1.82	1.76	2.41	1.49	1.83	1.33	1.84	0.87	1.89	0.84	1.35
mmu-miR-376a	1.96	1.99	2.64	2.15	1.72	1.79	2.03	1.72	2.00	2.60	2.51	1.64	1.97	2.92	2.46	2.35	2.17	2.40	2.21	3.52	2.40	2.54
mmu-miR-376b	2.47	1.36	1.35	2.15	1.96	2.09	1.48	2.28	1.89	1.44	1.57	1.04	1.63	0.70	2.46	1.47	1.67	1.52	2.47	2.05	1.74	1.89
mmu-miR-380-3p	0.53	1.46	1.13	1.02	1.13	1.19	1.37	1.51	1.17	0.86	1.46	1.16	0.71	1.31	1.81	1.22	1.86	1.45	0.31	1.61	1.14	1.27
mmu-miR-383	2.02	1.57	1.04	2.00	1.94	1.75	1.53	2.42	1.78	1.30	1.72	1.49	1.81	1.12	3.13	1.76	1.77	1.59	2.47	2.26	1.88	1.99
mmu-miR-384	1.14	0.94	2.04	0.51	1.11	0.95	1.08	0.39	1.02	1.11	1.81	1.59	1.04	1.74	1.99	1.55	0.67	0.86	1.07	0.89	0.54	0.80
mmu-miR-409	1.68	2.54	2.41	2.79	1.61	1.95	2.25	1.87	2.14	3.19	2.46	2.01	2.02	2.57	2.07	2.39	2.17	2.24	2.39	2.63	2.66	2.42
hsa-miR-410	1.04	1.57	1.90	1.75	1.44	1.24	1.76	1.72	1.55	2.25	1.52	2.15	1.97	2.61	0.84	1.89	1.94	1.84	1.43	1.98	1.88	1.82
mmu-miR-411	1.52	1.51	2.41	1.70	1.19	1.07	1.42	1.32	1.52	2.60	2.65	1.49	1.43	2.92	1.71	2.13	0.94	1.79	1.43	1.39	1.59	1.43
hsa-miR-412	0.83	1.12	0.90	1.02	0.81	0.95	1.20	0.48	0.91	0.42	0.83	0.85	1.76	0.14	1.25	0.87	0.67	0.52	0.48	1.02	0.94	0.73
mmu-miR-429	1.68	1.61	1.40	1.50	1.94	1.46	1.72	2.06	1.67	1.72	0.90	2.24	2.24	1.12	1.49	1.62	1.77	1.79	2.11	2.32	2.00	2.00
mmu-miR-7b	1.76	3.57	2.24	2.04	2.14	2.31	2.66	2.51	2.40	2.73	2.29	2.50	2.46	2.12	2.61	2.45	2.67	2.28	2.62	2.86	2.85	2.66
mo-miR-151-AS	5.08	5.86	5.38	5.40	5.63	5.37	5.39	5.39	5.44	5.33	5.30	5.42	5.17	5.37	5.35	5.32	5.35	5.36	4.89	4.95	5.48	5.20
mo-miR-20-AS	1.34	1.51	2.28	1.08	1.28	1.36	1.26	0.80	1.36	1.72	2.23	1.33	1.92	1.22	1.71	1.69	0.94	1.04	0.87	0.76	1.67	1.05
mo-miR-297	1.04	1.06	1.35	1.21	1.76	3.01	1.20	1.56	1.53	1.68	0.77	1.39	0.79	0.91	1.25	1.13	1.45	1.12	0.48	1.27	1.33	1.13
mo-miR-327	2.81	2.28	2.14	2.96	2.17	2.62	1.80	2.92	2.47	2.65	3.06	2.77	2.49	3.11	2.83	2.82	2.42	2.28	2.80	2.43	2.27	2.44
mo-miR-333	1.68	1.71	2.33	2.24	2.45	4.24	1.14	1.01	2.10	1.72	1.94	1.54	1.57	2.01	2.79	1.93	3.96	1.45	2.74	1.51	1.74	2.28
mo-miR-336	2.69	3.28	2.09	2.21	2.70	2.09	2.00	1.97	2.38	2.32	2.63	2.43	3.03	2.83	3.47	2.79	2.53	2.32	2.68	2.86	3.11	2.70
mo-miR-343	1.34	1.57	2.09	1.70	1.41	1.24	1.14	1.37	1.48	1.01	1.40	0.85	2.32	1.88	1.61	1.51	1.56	1.66	2.00	1.51	1.50	1.65
mo-miR-344	0.53	1.51	1.18	1.50	0.78	0.70	0.96	0.43	0.95	1.16	0.57	1.27	0.55	1.81	-0.2	0.86	0.94	1.52	1.60	0.89	1.42	1.27
mo-miR-346	2.08	1.41	1.56	2.21	1.74	1.92	1.20	1.60	1.71	1.64	1.57	1.59	1.92	2.18	1.71	1.77	1.56	1.29	1.75	1.61	1.33	1.51
mo-miR-347	2.55	1.46	2.55	1.96	2.04	1.30	1.62	1.83	1.92	2.30	2.56	1.73	2.24	2.77	2.46	2.34	2.47	1.84	2.39	1.61	1.59	1.98
mo-miR-349	1.68	1.36	1.27	1.08	1.44	1.46	1.14	1.72	1.39	1.48	0.83	1.16	0.96	0.81	0.19	0.90	1.20	1.52	1.88	1.39	1.23	1.45
mo-miR-352	4.62	5.39	3.97	4.72	4.88	5.11	4.77	4.83	4.79	4.22	4.10	4.44	4.12	3.99	3.94	4.14	4.87	4.91	4.47	5.79	5.09	5.03
mo-miR-421	1.68	1.18	1.44	1.15	1.51	1.57	1.14	1.90	1.45	1.35	0.90	1.64	0.63	0.50	1.11	1.02	1.45	1.04	1.07	1.27	1.50	1.27
mo-miR-7-AS	2.02	1.57	2.04	1.44	1.38	1.88	1.37	0.96	1.58	1.60	1.90	1.98	1.92	1.58	1.99	1.83	2.10	1.96	1.60	2.05	2.06	1.95
hsa-miR-522	1.34	1.75	1.31	0.51	1.22	1.01	1.14	1.27	1.19	1.44	1.34	1.27	1.28	1.94	0.19	1.25	1.67	1.12	1.60	1.27	1.42	1.42
hsa-miR-519b	1.90	1.36	2.14	1.27	1.44	1.30	1.31	1.68	1.55	2.47	1.03	1.44	1.28	2.01	1.61	1.64	1.67	1.12	2.00	0.76	0.64	1.24
hsa-miR-520c	0.94	1.61	1.67	0.96	1.38	0.82	0.96	0.91	1.16	0.91	0.70	1.49	1.76	2.89	1.25	1.50	1.45	1.21	1.60	1.15	1.23	1.33
hsa-miR-519e	1.68	1.36	2.01	0.96	1.13	1.30	1.42	1.12	1.37	1.48	2.09	0.85	1.63	2.61	2.34	1.84	1.20	1.37	1.43	1.39	0.84	1.25
hsa-miR-519d	0.83	1.80	1.84	0.89	1.05	1.41	0.90	0.59	1.16	1.60	1.77	1.98	1.43	2.61	1.90	1.88	1.20	1.12	0.31	0.63	1.74	1.00
hsa-miR-520b	2.14	1.00	1.18	1.80	1.86	1.66	1.53	2.15	1.66	1.79	1.72	1.54	1.87	1.66	1.99	1.76	0.80	1.12	1.60	1.27	1.04	1.17
hsa-miR-519c	1.60	0.82	1.04	1.21	1.70	1.46	1.62	1.60	1.38	1.30	1.46	1.54	1.43	1.31	1.11	1.36	1.94	0.86	1.07	1.27	1.33	1.30
hsa-miR-526b-AS	0.63	1.36	1.52	0.57	1.19	1.01	0.90	0.59	0.97	0.56	0.02	1.78	0.87	2.32	3.19	1.46	1.33	1.45	1.26	1.02	1.14	1.24
hsa-miR-520e	1.34	1.12	0.90	1.44	1.33	1.01	1.37	1.87	1.30	1.11	2.26	1.04	0.87	0.81	1.71	1.30	1.33	0.77	1.07	1.27	1.74	1.24
hsa-miR-520a	1.60	1.46	2.17	0.76	1.28	1.13	0.96	0.64	1.25	1.99	2.29	1.73	2.36	1.41	2.79	2.09	0.80	1.29	1.26	1.27	1.14	1.15
hsa-miR-520d	1.14	1.18	2.01	1.50	1.56	1.52	1.31	1.42	1.46	2.32	2.51	1.86	1.57	1.88	2.56	2.12	0.67	1.29	1.07	1.15	1.67	1.17

hsa-miR-520h	1.90	0.88	1.90	0.83	1.33	1.36	1.53	1.83	1.44	2.25	1.40	1.69	1.50	2.18	0.98	1.67	1.20	1.21	0.48	0.76	0.64	0.86
hsa-miR-517a	1.14	2.03	2.01	1.21	1.28	1.52	0.90	1.12	1.40	2.28	2.58	1.73	2.32	2.01	1.81	2.12	1.33	0.95	1.75	0.50	1.14	1.13
hsa-miR-518e	1.68	1.30	0.90	1.39	1.74	0.95	1.31	1.72	1.37	0.81	1.28	0.91	1.20	0.91	1.61	1.12	0.54	1.12	1.43	1.15	1.23	1.10
hsa-miR-521	0.94	1.18	1.70	1.02	1.28	0.95	1.53	1.37	1.25	1.86	1.94	1.64	0.71	1.66	2.51	1.72	1.67	1.12	1.26	1.15	0.94	1.23
hsa-miR-523	1.90	1.12	1.27	1.55	1.49	1.71	1.31	1.68	1.50	1.16	4.27	1.59	2.02	0.60	1.49	1.86	1.20	1.12	2.00	1.27	0.84	1.29
hsa-miR-518f	0.83	1.30	1.80	1.80	1.41	1.01	1.26	0.69	1.26	1.68	2.13	0.98	1.97	2.46	2.87	2.01	1.77	1.37	1.26	1.61	1.33	1.47
hsa-miR-518c	1.34	1.18	1.56	0.83	1.16	1.24	1.26	1.01	1.20	1.48	1.10	1.44	1.92	2.57	1.61	1.69	1.45	0.86	0.48	1.51	1.04	1.07
hsa-miR-518b	1.52	1.61	1.44	1.27	1.13	1.41	1.26	1.07	1.34	1.64	2.02	0.91	2.52	2.12	2.28	1.92	1.07	1.66	1.43	1.39	1.33	1.38
hsa-miR-518d	0.73	1.18	0.85	1.27	1.13	1.30	1.08	0.85	1.05	1.48	1.03	0.79	0.25	0.41	0.31	0.71	0.80	1.21	0.48	3.22	1.33	1.41
hsa-miR-525-AS	0.53	1.41	0.48	0.76	1.08	0.70	1.02	0.59	0.82	0.56	0.57	1.04	1.36	0.70	0.70	0.82	1.56	1.04	0.48	1.27	1.42	1.16
hsa-miR-524	1.83	1.24	1.87	3.01	1.38	1.61	1.26	1.56	1.72	1.30	1.10	1.73	2.12	2.12	1.25	1.60	1.07	1.45	2.00	1.02	1.50	1.41
hsa-miR-518a	1.24	1.18	1.96	1.15	1.05	1.30	1.08	0.91	1.23	1.64	1.94	1.44	0.87	1.12	2.21	1.54	0.54	1.59	0.87	1.51	1.23	1.15
hsa-miR-515-3p	1.83	1.18	1.31	0.96	1.65	1.61	1.58	1.80	1.49	0.56	1.10	1.69	1.04	1.12	1.49	1.17	0.67	1.04	1.60	1.39	1.33	1.20
hsa-miR-516-3p	1.04	1.57	1.52	1.21	1.19	1.52	1.20	1.56	1.35	1.06	1.46	1.04	0.47	0.91	1.11	1.01	0.94	1.52	2.11	0.89	1.23	1.34
ambi-miR-7026	0.83	0.82	1.63	0.89	1.22	1.19	0.78	0.80	1.02	0.86	0.90	1.78	1.87	2.46	1.37	1.54	0.67	1.04	0.48	1.02	0.73	0.79
ambi-miR-7027	1.83	1.12	1.99	1.60	1.74	1.66	1.62	2.06	1.70	1.48	1.52	2.08	1.57	0.81	1.37	1.47	1.45	1.52	0.87	2.13	2.06	1.60
hsa-miR-512-3p	1.90	1.61	1.70	1.55	1.49	1.71	1.31	1.97	1.66	1.21	1.40	1.78	1.50	1.74	1.81	1.57	1.20	1.59	2.80	1.71	1.67	1.79
ambi-miR-7029	4.75	3.77	5.62	4.92	5.14	5.77	5.31	6.83	5.26	4.15	4.54	6.30	7.37	4.76	4.96	5.35	6.88	5.08	5.95	5.31	5.45	5.74
hsa-miR-491	2.95	2.56	2.14	3.25	2.67	2.41	2.16	2.74	2.61	2.32	2.65	2.50	2.86	2.37	3.26	2.66	2.83	3.00	3.14	2.83	2.63	2.88
hsa-miR-506	2.38	1.41	1.08	2.08	1.82	1.92	1.62	2.06	1.80	0.66	2.69	1.04	1.12	0.81	1.81	1.35	1.33	1.66	2.39	2.13	1.23	1.75
hsa-miR-514	1.68	1.12	1.48	0.96	1.28	1.52	1.26	1.51	1.35	1.35	0.77	0.38	0.55	-0.15	1.71	0.77	1.07	0.95	0.87	1.02	1.23	1.03
hsa-miR-509	1.90	1.57	1.99	1.75	1.82	1.79	1.42	1.72	1.74	1.89	1.77	1.78	2.07	2.07	1.99	1.93	1.67	2.01	2.31	1.39	1.42	1.76
hsa-miR-508	1.68	1.24	1.44	1.39	1.65	1.41	1.42	2.21	1.56	2.23	1.16	1.54	2.46	2.23	3.07	2.12	1.20	1.12	2.11	2.05	1.33	1.56
hsa-miR-507	1.14	1.51	0.94	0.57	1.19	0.82	1.08	0.29	0.95	0.61	0.51	1.44	1.04	1.41	-0.1	0.82	1.45	1.04	1.07	1.71	1.74	1.40
ambi-miR-7036	1.52	1.71	2.17	1.50	1.61	1.84	1.53	2.03	1.74	1.39	2.13	2.35	1.76	1.81	1.99	1.91	2.36	2.24	2.39	1.71	2.22	2.19
hsa-miR-193b	2.43	2.93	4.07	4.27	2.82	2.53	3.47	2.79	3.17	2.85	2.98	3.32	4.02	3.29	3.45	3.32	3.56	3.15	3.14	3.12	3.11	3.21
ambi-miR-7038-1	0.34	1.46	0.90	0.89	1.54	1.07	1.20	0.75	1.02	2.04	0.90	1.16	1.57	1.12	1.71	1.42	1.07	0.86	1.26	1.15	1.59	1.19
ambi-miR-7039	4.48	2.03	3.44	2.71	3.22	1.92	3.03	2.66	2.94	2.67	3.58	2.79	3.53	2.71	3.36	3.11	3.37	3.19	2.68	2.19	3.11	2.91
hsa-miR-488	1.76	1.12	0.85	1.92	1.58	1.57	1.37	1.97	1.52	0.76	1.57	1.04	1.43	1.88	2.28	1.49	1.67	1.37	1.60	1.89	1.33	1.57
hsa-miR-510	1.68	1.75	1.27	1.15	1.22	1.01	1.26	1.01	1.29	1.39	0.90	1.39	1.20	1.22	1.11	1.20	2.17	1.37	1.26	2.05	1.50	1.67
hsa-miR-517-AS	1.52	1.41	2.28	1.33	1.28	1.30	1.26	0.91	1.41	1.72	2.13	1.54	0.96	1.49	1.81	1.61	0.67	0.69	2.11	1.51	1.59	1.31
hsa-miR-518f-AS	1.68	1.24	1.56	1.39	2.62	1.57	1.37	1.17	1.57	1.39	1.81	2.15	1.43	0.50	1.61	1.48	1.33	1.37	0.31	1.27	1.04	1.06
hsa-miR-518c-AS	3.07	2.98	2.54	3.38	2.45	2.66	2.34	2.98	2.80	2.65	2.63	2.59	2.74	3.09	2.97	2.78	3.00	2.66	2.96	2.79	2.60	2.80
hsa-miR-526c	0.08	1.41	1.04	0.96	1.13	1.30	1.26	0.54	0.96	1.21	1.03	1.33	0.87	1.31	1.37	1.19	1.77	1.29	1.43	0.89	1.33	1.34
hsa-miR-526b	2.29	2.25	2.04	2.21	1.61	1.66	1.84	1.80	1.96	2.13	1.86	1.94	2.46	2.37	2.07	2.14	2.57	2.24	2.21	2.26	2.22	2.30
hsa-miR-520a-AS	0.43	1.12	1.04	0.63	1.02	0.70	1.02	0.75	0.84	1.76	0.51	1.39	1.04	0.23	0.43	0.89	0.80	1.04	1.60	0.63	0.94	1.00
hsa-miR-525	1.04	1.80	1.35	1.60	1.11	1.52	1.08	1.27	1.35	0.81	1.16	1.04	1.12	1.01	1.11	1.04	1.86	1.52	1.43	1.61	1.74	1.63
hsa-miR-524-AS	1.52	1.00	1.74	1.55	1.63	1.66	1.67	1.07	1.48	1.83	1.03	1.33	1.63	1.81	1.81	1.57	1.07	1.66	1.43	1.71	1.42	1.46

hsa-miR-520d-AS	2.02	1.24	1.80	1.39	1.54	1.41	1.42	1.68	1.56	2.51	1.52	1.86	2.28	2.57	1.37	2.02	1.86	2.01	1.07	1.39	1.59	1.58
hsa-miR-527	1.90	1.57	1.04	2.15	1.49	1.52	1.53	1.42	1.57	1.99	1.67	1.64	2.64	2.41	2.51	2.14	1.77	1.52	2.00	2.13	1.42	1.77
hsa-miR-515-5p	1.34	1.06	2.12	0.70	1.02	1.30	0.96	1.07	1.20	1.68	1.40	1.59	1.43	1.31	1.37	1.47	1.20	1.45	1.75	1.02	1.42	1.37
hsa-miR-519e-AS	0.83	1.41	1.87	1.50	1.22	1.52	1.53	1.32	1.40	2.13	0.57	1.04	1.76	2.07	1.49	1.51	1.67	1.52	1.07	1.15	1.04	1.29
ambi-miR-7054	1.60	1.12	2.14	1.44	1.25	1.52	1.48	1.76	1.54	0.91	0.70	0.91	0.71	1.81	1.90	1.16	1.20	1.37	2.00	1.27	1.42	1.45
ambi-miR-7055	1.34	1.51	2.17	1.27	1.56	1.41	1.14	1.22	1.45	2.43	2.56	1.69	1.92	2.07	1.25	1.99	1.20	1.72	1.07	0.89	1.23	1.22
hsa-miR-498	1.76	1.57	2.26	1.27	1.30	1.52	1.67	1.27	1.58	1.96	2.02	1.90	2.12	2.01	2.14	2.02	1.56	1.29	1.26	1.39	1.74	1.45
hsa-miR-513	4.78	3.92	3.65	4.41	3.72	3.91	3.27	4.08	3.97	3.93	3.91	4.01	4.67	4.22	5.56	4.38	4.29	4.19	5.08	4.76	3.95	4.45
ambi-miR-7058	4.27	3.72	3.94	4.03	4.28	4.58	3.88	4.22	4.11	3.58	3.95	4.11	4.09	3.81	4.90	4.07	4.11	4.25	4.40	4.47	3.79	4.21
ambi-miR-7059-1	0.73	0.94	1.40	1.08	1.22	1.01	1.31	0.34	1.00	1.16	1.46	1.54	0.87	0.60	1.25	1.15	0.80	0.69	0.87	1.39	1.23	1.00
hsa-miR-452	3.48	3.02	3.66	3.45	3.53	3.29	3.21	3.85	3.44	2.81	2.97	2.57	2.46	2.12	2.21	2.52	2.67	2.79	2.91	2.67	2.63	2.73
hsa-miR-493	2.34	2.06	1.93	1.60	1.86	1.66	2.00	2.12	1.95	2.30	2.09	2.05	2.02	2.57	1.99	2.17	1.86	1.59	1.88	2.19	2.17	1.94
ambi-miR-7062	2.02	1.71	1.90	2.11	1.68	1.88	1.58	1.64	1.81	1.96	1.90	1.82	1.92	2.50	2.28	2.06	2.03	1.72	2.11	1.81	1.67	1.87
hsa-miR-432	3.09	3.35	3.23	3.44	2.57	2.89	3.15	3.49	3.15	3.92	3.54	3.35	3.48	3.49	3.19	3.50	3.18	3.04	3.39	3.25	3.66	3.30
hsa-miR-495	2.55	2.22	2.09	2.61	2.46	2.25	2.10	2.36	2.33	2.79	2.56	2.21	2.55	1.66	2.07	2.31	2.42	2.32	2.74	2.63	2.56	2.53
hsa-miR-494	7.34	4.49	4.88	5.46	4.87	5.06	4.14	4.87	5.14	6.49	5.20	7.12	7.41	6.55	8.99	6.96	7.60	7.05	8.32	7.68	5.48	7.22
ambi-miR-7066	2.02	1.24	0.85	1.75	1.74	1.75	1.67	2.12	1.64	1.21	1.34	0.98	0.96	2.23	2.14	1.48	1.56	1.37	0.48	2.19	1.33	1.39
ambi-miR-7067	1.83	1.41	2.43	1.96	1.76	1.71	1.53	1.94	1.82	2.49	1.57	2.18	2.20	2.28	1.71	2.07	2.10	1.59	1.75	1.81	1.42	1.73
ambi-miR-7068-1	0.73	1.18	1.59	0.96	1.41	1.07	1.20	0.80	1.12	0.91	1.52	1.10	1.04	1.22	1.37	1.19	1.07	0.86	1.26	1.51	1.59	1.26
hsa-miR-496	1.24	0.82	2.17	1.15	1.05	1.66	1.31	1.17	1.32	1.89	1.34	0.91	0.96	1.31	0.31	1.12	0.41	1.45	0.48	0.89	2.00	1.05
ambi-miR-7070	1.43	2.31	2.39	2.11	1.58	2.06	1.92	1.90	1.96	2.81	2.23	2.27	2.61	2.68	1.71	2.39	2.57	2.60	1.75	2.05	2.90	2.37
hsa-miR-492	1.14	1.12	1.67	0.76	1.51	1.36	1.08	1.37	1.25	1.11	0.33	0.73	0.71	0.41	0.56	0.64	1.67	1.37	1.88	1.15	1.14	1.44
hsa-miR-490	0.94	1.12	1.80	1.33	1.19	1.19	1.26	0.64	1.18	1.72	1.28	1.22	2.46	2.18	1.81	1.78	1.20	1.21	0.67	1.27	1.04	1.08
hsa-miR-497	5.33	4.52	4.99	4.32	4.91	4.71	5.12	4.70	4.83	5.40	5.81	5.03	5.24	4.87	5.36	5.29	3.79	4.25	4.41	4.14	4.24	4.17
ambi-miR-7074	1.43	1.30	1.77	1.15	1.30	0.82	1.08	1.12	1.25	1.52	2.35	1.78	1.43	1.01	1.25	1.56	1.07	1.45	0.87	0.76	1.33	1.09
ambi-miR-7075	2.72	2.22	2.04	2.63	2.64	2.28	2.36	2.66	2.44	2.21	2.54	2.55	2.49	2.46	2.75	2.50	2.36	2.57	2.47	2.53	2.76	2.54
ambi-miR-7076	2.55	3.25	2.17	2.75	3.58	2.64	3.13	2.74	2.85	2.60	2.43	2.79	2.49	2.41	2.56	2.55	2.83	3.00	2.39	2.43	2.95	2.72
hsa-miR-501	2.02	1.57	1.80	1.92	1.68	2.13	1.42	2.03	1.82	2.30	2.41	1.59	1.70	1.66	1.61	1.88	1.67	1.84	1.88	1.81	1.74	1.79
hsa-miR-502	1.83	1.92	2.07	1.75	1.56	1.66	1.31	1.76	1.73	1.92	2.06	2.21	2.07	1.88	2.51	2.11	1.77	1.84	1.60	1.71	1.33	1.65
ambi-miR-7079	2.02	1.75	2.28	1.55	1.80	2.19	2.77	2.71	2.14	2.35	1.90	2.30	2.39	2.41	1.99	2.22	2.03	1.90	1.75	1.89	2.06	1.93
ambi-miR-7080	2.24	1.36	1.67	1.80	1.58	1.92	1.53	1.64	1.72	1.11	1.90	1.64	1.63	1.58	0.84	1.45	1.86	1.45	1.75	1.39	1.23	1.54
ambi-miR-7081	2.38	2.16	2.33	2.11	2.31	2.46	2.46	2.33	2.32	2.10	2.23	2.43	2.74	2.77	2.61	2.48	1.94	1.96	1.75	2.32	2.12	2.02
hsa-miR-202-AS	0.53	0.94	1.52	0.76	1.02	1.19	1.14	0.54	0.95	0.76	0.64	0.91	0.63	2.68	2.28	1.32	1.67	0.69	1.43	1.61	1.04	1.29
ambi-miR-7083	2.78	3.25	3.50	3.71	3.37	3.88	3.22	2.57	3.28	3.26	3.37	3.23	2.46	3.04	2.61	3.00	3.00	3.56	2.39	3.17	3.44	3.11
ambi-miR-7084	1.83	1.46	2.01	1.27	1.54	1.46	1.72	1.56	1.61	2.53	1.46	1.59	1.87	2.28	2.34	2.01	1.67	1.52	1.60	2.05	1.23	1.61
ambi-miR-7085	1.34	1.61	2.19	1.60	1.56	1.19	1.62	1.72	1.60	1.99	2.35	1.54	1.20	2.50	1.99	1.93	1.77	1.29	0.87	1.39	1.42	1.35
ambi-miR-7086	0.73	1.96	1.70	1.92	1.51	1.36	1.80	1.12	1.51	1.39	0.97	1.27	1.28	1.22	0.56	1.12	1.86	1.59	1.75	2.05	2.06	1.86
hsa-miR-512-5p	1.43	1.06	1.04	1.02	1.13	1.36	1.20	1.27	1.19	1.48	1.03	2.05	0.71	0.60	0.84	1.12	1.07	1.04	1.26	1.81	1.50	1.34
hsa-miR-504	1.24	0.94	0.75	1.21	1.33	1.07	1.26	1.27	1.13	0.81	0.90	1.04	0.87	0.41	1.25	0.88	1.20	1.45	1.88	1.51	1.14	1.43
ambi-miR-7089	1.90	0.94	1.13	1.84	1.58	1.36	1.14	2.06	1.49	1.48	1.98	1.27	2.02	2.28	1.37	1.74	1.67	1.45	2.11	1.71	1.88	1.76

hsa-miR-511	0.43	1.71	1.04	1.27	1.22	1.13	1.31	0.75	1.11	1.21	0.83	0.85	0.25	1.22	1.81	1.03	1.56	0.77	1.07	1.39	1.50	1.26
hsa-miR-452-AS	1.96	1.92	1.96	2.04	2.04	2.22	1.92	2.15	2.03	0.91	1.10	1.33	0.63	0.70	1.25	0.99	1.86	1.66	2.11	1.89	1.50	1.81
hsa-miR-503	2.38	2.58	3.52	3.22	2.62	2.56	3.04	2.79	2.84	3.33	2.61	2.05	1.63	2.50	1.81	2.32	2.03	1.84	1.60	2.38	2.63	2.09
hsa-miR-485-5p	1.76	1.66	1.87	2.15	1.84	2.19	2.03	2.18	1.96	1.92	2.20	1.82	2.16	1.74	1.90	1.96	2.10	2.01	2.11	1.15	2.12	1.90
hsa-miR-499	1.68	1.51	2.61	1.33	1.25	1.61	1.48	1.42	1.61	2.32	1.40	1.49	1.63	2.37	2.75	2.00	1.77	1.52	2.00	1.98	1.42	1.74
ambi-miR-7095	2.08	1.24	1.27	1.80	1.58	1.30	1.37	1.97	1.58	1.99	1.57	1.39	2.52	1.94	0.70	1.68	0.80	1.29	1.43	1.71	1.23	1.29
hsa-miR-505	1.76	2.47	2.17	2.24	2.06	2.19	2.34	1.80	2.13	1.86	2.02	1.90	2.02	2.50	1.11	1.90	1.77	1.79	0.67	1.89	2.06	1.64
ambi-miR-7097	1.24	1.66	1.27	1.44	1.33	1.36	1.20	1.27	1.35	1.68	1.10	0.73	1.28	1.41	1.61	1.30	1.33	1.52	1.43	1.02	1.67	1.39
ambi-miR-7098	1.83	1.18	1.04	1.08	1.36	1.71	1.53	1.32	1.38	0.91	1.52	1.69	0.96	-0.2	1.25	1.02	0.80	1.37	0.67	1.71	1.14	1.14
hsa-miR-489	1.60	1.51	1.99	1.39	2.16	1.36	1.84	1.83	1.71	1.11	0.90	0.67	1.63	0.70	0.84	0.97	1.94	1.66	2.21	1.39	1.42	1.73
ambi-miR-7100	2.51	1.41	0.99	2.08	1.90	1.71	1.92	2.21	1.84	1.92	1.62	2.15	1.63	1.58	2.46	1.89	2.17	2.36	2.80	2.53	2.27	2.43
ambi-miR-7101	0.73	1.36	1.63	1.27	1.16	1.36	1.48	1.27	1.28	1.89	2.20	1.98	1.92	2.01	2.28	2.05	0.94	1.21	0.87	1.51	1.50	1.21
hsa-miR-432-AS	1.43	1.24	1.84	0.89	1.28	1.61	1.26	1.12	1.33	0.76	1.28	1.33	2.24	1.66	1.71	1.50	1.07	1.12	1.88	0.26	1.59	1.19
ambi-miR-7103	1.24	1.66	1.99	1.70	1.44	1.24	1.62	1.27	1.52	1.86	2.46	1.73	2.32	2.07	1.61	2.01	0.80	1.45	1.43	1.27	1.23	1.24
hsa-miR-500	2.29	2.28	2.04	2.11	3.08	2.31	2.51	2.31	2.37	2.18	2.54	2.30	2.39	2.32	2.56	2.38	2.42	2.20	2.21	1.39	2.60	2.16
ambi-miR-7105	3.02	3.03	3.01	2.79	3.36	2.88	3.07	3.10	3.03	2.51	2.63	2.46	2.28	2.23	2.14	2.37	2.53	2.53	2.55	2.86	2.93	2.68

*, threshold value
**, number of miRNAs above threshold value
***, percentage of miRNAs above threshold value

Table 4. Normalized Array Data for Six Individual Pancreatic Cancer Cell Lines and Three Tissue Types

miR Name	Cell Lines										Mean		%*		Mean		%*		Mean		%*	
	IMIMPC2	PT45	SKPC1	PL45	PancTul	PaCa44	CL	CL	Ca	Ca	Ca	Ch	Ch	Ch	Ch	Ch	Ch	Ch	Ch	Ch	Ch	N
hsa-let-7a	8.95	8.40	9.43	8.46	8.65	8.32	8.70	8.70	8.95	8.95	100	8.83	100	100	8.83	100	100	100	9.35	100	100	100
hsa-let-7b	8.40	7.72	8.99	7.72	7.33	7.63	7.96	7.96	8.53	8.53	100	8.78	100	100	8.78	100	100	100	9.06	100	100	100
hsa-let-7c	8.44	7.87	8.93	8.17	7.77	7.29	8.08	8.08	8.60	8.60	100	8.74	100	100	8.74	100	100	100	9.18	100	100	100
hsa-let-7d	8.05	7.73	8.34	8.31	8.07	7.53	8.01	8.01	8.19	8.19	100	7.85	100	100	7.85	100	100	100	8.68	100	100	100
hsa-let-7e	6.58	6.52	6.97	6.82	6.03	5.86	6.46	6.46	6.75	6.75	100	6.19	100	100	6.19	100	100	100	6.98	100	100	100
hsa-let-7f	7.26	7.08	7.23	8.15	7.69	6.72	7.36	7.36	7.94	7.94	100	7.51	100	100	7.51	100	100	100	8.51	100	100	100
hsa-let-7g	6.53	6.19	6.76	6.60	6.61	5.99	6.45	6.45	7.31	7.31	100	7.01	100	100	7.01	100	100	100	7.52	100	100	100
hsa-let-7i	7.52	6.59	8.91	6.91	8.88	8.95	7.96	7.96	7.49	7.49	100	7.12	100	100	7.12	100	100	100	6.31	100	100	100
hsa-miR-1	0.92	0.17	1.05	0.28	1.01	1.22	0.78	0.78	3.23	3.23	88	2.84	83	83	2.84	83	83	83	2.19	80	80	80
hsa-miR-100	7.14	6.49	6.32	7.23	7.73	7.76	7.11	7.11	6.34	6.34	100	6.44	100	100	6.44	100	100	100	5.16	100	100	100
hsa-miR-101	1.97	2.77	2.16	2.72	2.60	2.69	2.48	2.48	4.49	4.49	100	4.33	100	100	4.33	100	100	100	4.87	100	100	100
hsa-miR-103	6.14	7.33	7.36	6.75	6.62	6.63	6.80	6.80	6.72	6.72	100	6.02	100	100	6.02	100	100	100	5.86	100	100	100
hsa-miR-105	-0.03	2.33	2.27	0.92	1.47	1.59	1.42	1.42	0.50	0.50	33	0.22	0	0	0.22	0	0	0	0.81	0	0	0
hsa-miR-106a	7.09	8.19	7.55	7.68	8.46	8.50	7.91	7.91	6.74	6.74	100	6.10	100	100	6.10	100	100	100	6.30	100	100	100
hsa-miR-106b	5.88	6.06	5.97	6.28	5.88	6.06	6.02	6.02	5.65	5.65	100	5.02	100	100	5.02	100	100	100	4.98	100	100	100
hsa-miR-107	6.12	7.41	7.41	6.73	6.66	6.68	6.83	6.83	6.76	6.76	100	6.10	100	100	6.10	100	100	100	5.82	100	100	100
hsa-miR-10a	5.22	4.76	5.79	6.49	6.45	6.49	5.87	5.87	6.23	6.23	100	5.70	100	100	5.70	100	100	100	4.92	100	100	100
hsa-miR-10b	2.87	4.54	3.61	4.53	4.29	4.00	3.97	3.97	5.24	5.24	100	4.96	100	100	4.96	100	100	100	4.54	100	100	100
hsa-miR-122a	2.62	2.92	1.52	1.81	2.63	2.80	2.38	2.38	2.71	2.71	100	2.76	100	100	2.76	100	100	100	2.43	100	100	100
hsa-miR-124a	-0.15	0.85	0.59	0.92	0.44	-0.03	0.44	0.44	0.29	0.29	0	-0.06	0	0	-0.06	0	0	0	0.21	0	0	0
hsa-miR-125a	6.38	6.65	7.11	6.37	5.21	5.53	6.21	6.21	6.04	6.04	100	6.00	100	100	6.00	100	100	100	5.32	100	100	100
hsa-miR-125b	6.01	5.23	5.26	6.47	6.54	6.85	6.06	6.06	6.93	6.93	100	7.37	100	100	7.37	100	100	100	5.96	100	100	100
hsa-miR-126	3.07	2.20	3.79	4.56	4.49	4.52	3.77	3.77	7.41	7.41	100	7.54	100	100	7.54	100	100	100	7.12	100	100	100
hsa-miR-126-AS	1.63	-0.20	1.24	1.50	0.88	0.35	0.90	0.90	3.55	3.55	88	3.27	100	100	3.27	100	100	100	3.91	100	100	100
hsa-miR-127	0.92	0.17	-0.18	0.84	1.14	0.35	0.54	0.54	1.42	1.42	50	1.97	50	50	1.97	50	50	50	1.52	40	40	40
hsa-miR-128a	3.26	3.17	4.19	3.55	3.25	3.61	3.50	3.50	2.77	2.77	100	2.23	83	83	2.23	83	83	83	2.16	80	80	80
hsa-miR-129	1.16	1.41	0.90	0.75	1.47	1.59	1.21	1.21	1.46	1.46	50	2.07	50	50	2.07	50	50	50	1.44	0	0	0
hsa-miR-130a	5.39	6.66	6.46	4.07	2.67	2.36	4.60	4.60	5.62	5.62	100	5.90	100	100	5.90	100	100	100	6.04	100	100	100
hsa-miR-130b	4.56	5.00	5.77	4.42	5.08	5.06	4.98	4.98	3.84	3.84	100	4.93	100	100	4.93	100	100	100	6.27	100	100	100
hsa-miR-132	2.36	2.79	2.24	1.61	2.45	1.80	2.21	2.21	4.09	4.09	100	3.92	100	100	3.92	100	100	100	3.06	100	100	100

hsa-miR-133a	1.27	0.59	0.67	0.84	0.74	0.62	0.79	0	2.55	88	2.49	83	0.97	0
hsa-miR-134	1.16	1.21	0.75	0.92	1.88	0.62	1.09	0	2.37	88	2.65	100	2.99	100
hsa-miR-135a	-0.48	1.10	1.11	0.92	0.88	1.00	0.76	0	0.62	25	1.35	17	1.72	20
hsa-miR-135b	0.10	0.45	1.42	1.81	1.26	1.80	1.14	0	2.01	75	1.49	17	0.72	0
hsa-miR-136	0.65	0.04	0.19	0.01	1.01	0.75	0.44	0	0.42	13	1.32	33	0.57	0
hsa-miR-137	1.71	0.98	0.04	0.01	-0.13	0.62	0.54	0	1.02	38	1.51	17	0.51	0
hsa-miR-138	3.05	2.24	4.38	1.16	0.59	0.62	2.01	50	1.41	25	0.67	0	0.96	0
hsa-miR-139	1.78	0.98	1.36	2.34	1.26	0.49	1.37	17	1.81	75	2.36	100	2.09	100
hsa-miR-140	2.40	1.87	1.79	1.37	1.88	1.32	1.77	33	4.08	100	3.63	100	3.24	100
hsa-miR-141	5.81	6.28	6.46	6.53	6.33	6.63	6.34	100	6.00	100	6.65	100	7.50	100
hsa-miR-142-3p	0.79	0.72	0.67	0.92	0.88	1.22	0.87	0	3.68	100	2.76	83	2.71	100
hsa-miR-142-5p	1.37	0.17	0.35	0.47	1.14	0.75	0.71	0	2.28	100	2.44	100	2.34	80
hsa-miR-143	0.79	0.59	0.27	0.37	0.59	0.35	0.49	0	7.96	100	7.52	100	6.02	100
hsa-miR-144	0.23	1.31	1.05	0.10	0.59	-0.15	0.52	0	-0.05	0	-0.14	0	0.48	0
hsa-miR-145	1.37	0.31	0.51	0.75	0.59	0.35	0.65	0	8.15	100	7.82	100	6.32	100
hsa-miR-146a	3.01	2.37	5.33	3.95	2.01	2.09	3.13	67	5.93	100	4.87	100	3.85	100
hsa-miR-147	0.10	0.59	0.75	1.24	1.14	0.22	0.67	0	1.38	38	0.76	17	0.94	20
hsa-miR-148a	1.37	2.96	5.02	1.31	2.53	2.09	2.55	50	5.27	100	7.14	100	8.57	100
hsa-miR-148b	2.87	2.77	3.76	2.29	3.05	2.57	2.88	100	2.82	88	2.97	100	5.11	100
hsa-miR-149	1.97	2.59	2.34	1.72	1.47	1.93	2.00	33	0.90	25	0.94	33	0.96	20
hsa-miR-150	1.16	0.04	1.05	1.61	1.94	1.32	1.19	0	4.38	100	3.68	83	1.73	60
hsa-miR-151	4.24	4.35	4.87	4.65	4.65	4.94	4.62	100	4.00	100	3.86	100	4.02	100
hsa-miR-152	2.94	4.12	2.88	2.06	3.07	2.32	2.90	83	5.15	100	5.05	100	4.75	100
hsa-miR-153	1.16	0.59	1.11	1.66	2.12	1.59	1.37	0	2.73	88	2.47	67	3.23	100
hsa-miR-154	0.92	0.72	0.19	0.56	-0.13	1.50	0.63	0	2.07	88	2.92	83	3.27	100
hsa-miR-155	5.08	2.05	5.30	5.44	6.19	5.77	4.97	100	5.59	100	4.22	100	3.25	100
hsa-miR-15a	5.19	5.05	5.77	5.66	6.01	5.94	5.60	100	6.47	100	6.19	100	6.14	100
hsa-miR-15b	6.89	7.59	7.95	7.87	7.87	7.63	7.63	100	5.77	100	4.92	100	5.17	100
hsa-miR-16	8.08	8.20	8.98	8.49	8.50	8.66	8.48	100	8.32	100	8.04	100	7.99	100
hsa-miR-17-3p	2.58	3.59	3.44	2.84	3.40	4.12	3.33	100	2.43	100	2.13	67	2.31	100
hsa-miR-17-5p	6.95	8.11	7.53	7.65	8.40	8.52	7.86	100	6.66	100	6.04	100	6.15	100
hsa-miR-18a	4.16	5.72	4.94	4.38	5.69	5.98	5.14	100	4.26	100	3.17	100	2.58	100
hsa-miR-181a	6.31	6.53	6.75	5.41	6.09	6.31	6.23	100	5.76	100	5.38	100	5.00	100
hsa-miR-181b	5.86	6.54	6.47	4.59	6.24	6.24	5.99	100	5.05	100	4.42	100	4.35	100

hsa-miR-181c	2.62	3.41	2.48	2.16	2.56	1.80	2.51	67	2.65	100	1.97	50	2.04	80
hsa-miR-182	4.95	5.23	5.12	5.84	4.72	4.64	5.08	100	4.57	100	4.16	100	5.39	100
hsa-miR-182-AS	1.55	0.04	0.67	0.84	0.88	0.75	0.79	0	0.57	0	1.22	17	0.58	0
hsa-miR-183	2.55	3.59	3.35	3.56	3.43	2.88	3.23	100	1.57	63	1.94	67	2.14	100
hsa-miR-184	2.71	3.01	1.97	2.02	2.01	2.57	2.38	67	2.57	100	2.61	100	2.22	100
hsa-miR-185	4.16	4.65	5.09	3.80	4.44	4.22	4.39	100	4.70	100	4.23	100	4.25	100
hsa-miR-186	2.77	3.33	3.06	1.86	2.56	2.14	2.62	67	3.39	100	3.04	100	3.69	100
hsa-miR-187	0.23	1.31	1.18	1.16	0.59	0.22	0.78	0	1.55	25	1.25	0	0.73	20
hsa-miR-188	2.62	2.52	1.83	2.45	2.56	2.60	2.43	83	1.92	75	2.03	83	1.80	60
hsa-miR-189	0.37	0.85	1.71	4.80	1.26	0.88	1.65	17	2.17	88	2.02	50	1.78	80
hsa-miR-190	0.92	0.85	0.51	0.37	0.14	0.09	0.48	0	1.23	25	1.23	33	0.91	40
hsa-miR-191	6.13	6.37	5.86	5.68	5.20	4.97	5.70	100	6.08	100	5.70	100	5.75	100
hsa-miR-192	2.19	2.24	2.50	2.32	2.06	2.04	2.23	67	6.63	100	6.07	100	7.13	100
hsa-miR-193a	3.13	3.30	2.39	3.31	2.79	3.61	3.09	100	2.33	100	2.60	100	2.20	80
hsa-miR-194	1.85	2.05	2.52	2.40	2.45	2.36	2.27	83	7.13	100	5.95	100	6.63	100
hsa-miR-195	3.17	3.94	3.13	3.75	3.97	2.97	3.49	100	6.49	100	6.72	100	6.12	100
hsa-miR-196a	2.97	4.37	3.84	2.45	2.23	1.22	2.85	83	3.77	100	1.41	50	1.13	0
hsa-miR-196b	3.11	4.38	3.38	2.42	0.59	0.22	2.35	67	3.24	100	1.04	33	0.57	0
hsa-miR-197	4.32	4.25	4.79	2.29	3.68	3.13	3.74	100	2.11	75	2.07	83	1.72	40
hsa-miR-198	4.02	3.82	2.29	3.65	3.64	4.09	3.59	100	3.91	100	3.92	100	3.70	100
hsa-miR-199a	1.37	0.59	0.04	0.37	1.01	-0.03	0.56	0	6.35	100	6.51	100	5.35	100
hsa-miR-199a-AS	1.04	1.10	1.05	0.10	-0.13	1.12	0.71	0	7.06	100	7.33	100	6.43	100
hsa-miR-199b	0.51	0.98	0.35	0.92	0.29	1.32	0.73	0	4.58	100	4.79	100	4.36	100
hsa-miR-19a	3.60	4.70	4.11	3.98	4.90	4.82	4.35	100	4.27	100	4.02	100	4.74	100
hsa-miR-19b	5.90	6.89	6.51	6.42	6.82	7.04	6.60	100	6.20	100	6.14	100	6.50	100
hsa-miR-20a	6.02	7.04	6.46	6.92	7.46	7.67	6.93	100	5.99	100	5.52	100	5.64	100
hsa-miR-200a	5.79	5.32	6.37	5.27	5.28	5.74	5.63	100	5.52	100	5.61	100	6.57	100
hsa-miR-200b	7.34	6.77	7.76	7.01	6.76	6.94	7.10	100	6.72	100	6.43	100	7.50	100
hsa-miR-200c	8.15	8.60	8.45	8.67	8.53	8.38	8.46	100	7.28	100	7.60	100	8.59	100
hsa-miR-203	0.37	1.66	1.90	2.52	4.52	5.13	2.68	50	5.19	100	2.66	100	3.50	100
hsa-miR-204	1.16	0.17	1.05	0.28	0.59	0.75	0.67	0	1.34	38	1.90	50	1.80	60
hsa-miR-205	5.82	8.76	8.41	8.75	6.24	6.11	7.35	100	3.12	75	1.44	33	0.90	20

hsa-miR-206	1.85	1.50	1.11	1.37	1.37	1.80	1.50	0	1.69	50	2.26	100	1.47	40
hsa-miR-208	0.65	0.04	0.35	1.16	1.14	0.75	0.68	0	0.92	0	1.49	17	1.02	0
hsa-miR-21	10.06	9.69	10.33	9.66	9.40	9.51	9.77	100	9.80	100	9.18	100	8.71	100
hsa-miR-210	5.38	4.58	5.65	4.00	4.43	4.25	4.71	100	6.61	100	4.43	100	3.79	100
hsa-miR-211	0.51	0.85	0.51	1.16	1.56	1.12	0.95	0	0.47	13	0.91	0	0.43	0
hsa-miR-212	1.04	0.85	1.47	0.56	1.01	-0.46	0.75	0	1.18	13	1.00	0	0.87	20
hsa-miR-213	1.63	0.98	1.18	1.01	0.59	1.87	1.21	0	0.48	0	1.70	33	0.41	0
hsa-miR-214	1.78	2.05	1.18	2.06	2.06	2.36	1.91	33	6.14	100	6.06	100	4.65	100
hsa-miR-215	0.10	0.98	0.98	0.47	1.56	1.66	0.96	0	3.91	88	2.54	67	4.33	100
hsa-miR-216	1.91	1.31	0.75	0.56	1.26	0.49	1.05	0	1.64	50	5.90	100	7.09	100
hsa-miR-217	0.92	1.50	1.30	1.44	1.37	1.12	1.27	0	2.19	88	6.70	100	7.86	100
hsa-miR-218	2.94	2.77	1.90	1.81	2.45	1.59	2.24	50	4.10	100	4.06	100	3.54	100
hsa-miR-219	0.92	0.59	0.59	0.10	-0.48	0.88	0.43	0	0.80	13	1.59	0	1.17	0
hsa-miR-22	5.38	6.48	5.91	4.58	5.50	5.72	5.59	100	7.25	100	7.07	100	6.79	100
hsa-miR-220	0.65	0.04	0.83	0.92	1.01	0.49	0.66	0	0.66	0	0.81	0	0.69	0
hsa-miR-221	7.66	7.21	8.08	8.47	7.85	8.12	7.90	100	6.50	100	5.41	100	5.02	100
hsa-miR-222	7.14	6.81	7.70	7.62	7.12	6.90	7.22	100	5.99	100	4.63	100	3.92	100
hsa-miR-223	0.51	1.50	0.90	1.61	1.88	1.74	1.36	0	6.86	100	5.62	100	4.47	100
hsa-miR-224	2.14	2.24	5.47	5.07	5.14	5.12	4.20	100	3.83	100	2.44	100	2.56	100
hsa-miR-23a	7.92	8.35	7.93	7.89	7.96	7.65	7.95	100	7.67	100	7.08	100	6.91	100
hsa-miR-23b	7.67	7.99	7.87	7.45	7.86	7.60	7.74	100	7.62	100	7.21	100	7.16	100
hsa-miR-24	7.06	7.71	7.21	7.47	7.26	6.87	7.26	100	8.07	100	7.58	100	7.15	100
hsa-miR-25	5.83	5.58	5.90	5.98	5.32	5.37	5.66	100	5.69	100	5.10	100	5.42	100
hsa-miR-26a	7.13	7.40	8.08	7.55	7.06	7.19	7.40	100	8.80	100	8.69	100	9.00	100
hsa-miR-26b	5.15	4.70	5.27	6.18	5.50	4.89	5.28	100	6.98	100	6.58	100	7.46	100
hsa-miR-27a	7.15	7.25	6.94	7.42	7.47	7.57	7.30	100	7.39	100	6.83	100	6.87	100
hsa-miR-27b	6.36	6.17	6.78	6.38	7.20	7.57	6.74	100	7.13	100	7.07	100	7.47	100
hsa-miR-28	4.60	4.71	4.92	5.09	5.16	5.20	4.95	100	5.08	100	4.56	100	4.82	100
hsa-miR-296	1.78	0.98	1.05	1.31	1.94	1.32	1.40	0	1.16	25	1.59	33	1.32	0
hsa-miR-299-5p	1.04	1.31	1.05	1.44	1.14	1.80	1.30	0	1.73	63	1.85	50	2.22	100
hsa-miR-29a	6.90	7.09	7.52	8.80	8.02	8.08	7.73	100	7.63	100	7.22	100	7.55	100
hsa-miR-29b	5.40	5.13	5.49	6.87	6.74	6.12	5.96	100	6.48	100	6.02	100	6.58	100
hsa-miR-29c	4.27	4.59	4.78	5.68	4.44	3.84	4.60	100	6.49	100	6.95	100	8.25	100
hsa-miR-301	2.58	3.83	3.01	2.77	3.79	3.64	3.27	100	2.64	100	1.77	33	1.95	40

hsa-miR-302a	0.65	0.59	0.90	0.37	-0.26	1.12	0.56	0	0.50	0	1.50	17	0.77	0
hsa-miR-302b	0.79	0.98	0.98	1.31	1.14	1.00	1.03	0	0.58	0	0.01	0	0.56	0
hsa-miR-302b-AS	1.04	0.72	0.51	0.37	0.29	0.49	0.57	0	0.20	0	1.10	33	0.28	0
hsa-miR-302c	0.23	0.04	0.43	-0.23	0.74	1.12	0.39	0	0.07	0	0.18	17	0.75	0
hsa-miR-302c-AS	2.14	1.66	1.52	3.84	2.23	2.09	2.25	50	1.67	50	1.95	67	1.89	80
hsa-miR-302d	1.16	0.59	0.98	0.66	1.26	0.75	0.90	0	1.13	13	1.51	0	0.65	0
hsa-miR-30a-3p	4.90	2.05	4.65	4.09	3.82	3.69	3.87	100	2.51	100	3.42	100	4.10	100
hsa-miR-30a-5p	7.60	6.25	7.34	7.32	6.47	6.52	6.92	100	6.69	100	7.15	100	7.61	100
hsa-miR-30b	4.96	5.16	5.25	6.07	5.27	5.49	5.37	100	5.74	100	6.20	100	6.84	100
hsa-miR-30c	6.94	5.60	7.05	6.44	5.88	5.91	6.30	100	5.63	100	6.13	100	6.77	100
hsa-miR-30d	6.75	6.01	6.60	6.90	6.16	6.05	6.41	100	6.29	100	6.58	100	7.08	100
hsa-miR-30e-3p	3.93	2.20	3.67	3.09	2.73	2.60	3.04	100	2.06	88	2.54	83	3.58	100
hsa-miR-30e-5p	6.78	5.09	5.99	6.30	5.62	5.50	5.88	100	6.26	100	6.50	100	7.06	100
hsa-miR-31	1.55	7.35	1.57	8.66	8.42	8.81	6.06	67	6.69	100	5.57	100	3.90	100
hsa-miR-32	-0.15	1.10	0.51	0.92	1.14	0.35	0.64	0	1.00	25	1.33	33	1.32	20
hsa-miR-320	6.53	6.11	7.04	5.89	6.60	6.78	6.49	100	6.00	100	5.80	100	5.70	100
hsa-miR-323	0.23	0.04	0.27	1.66	1.94	0.88	0.84	0	0.69	0	0.06	0	0.73	0
hsa-miR-324-3p	2.52	3.84	3.12	3.27	2.56	2.95	3.04	100	2.58	100	2.47	100	1.44	40
hsa-miR-324-5p	1.46	2.05	1.24	0.75	1.56	1.50	1.43	17	1.01	25	0.73	17	0.95	0
hsa-miR-325	0.23	0.59	0.67	0.10	1.01	1.12	0.62	0	0.60	13	0.58	0	0.94	0
hsa-miR-326	0.92	1.58	1.11	1.09	1.37	0.49	1.09	0	0.95	13	1.28	17	0.71	0
hsa-miR-328	0.51	1.58	1.18	1.09	1.37	0.75	1.08	0	1.15	13	1.09	0	0.60	0
hsa-miR-33	0.79	1.31	0.67	0.56	0.74	0.88	0.83	0	0.64	0	0.89	17	0.64	0
hsa-miR-330	1.97	2.20	2.50	0.92	2.18	1.59	1.89	50	1.23	25	1.45	17	0.49	0
hsa-miR-331	3.95	4.06	4.08	3.73	4.30	3.11	3.87	100	3.45	100	2.40	100	1.91	80
hsa-miR-335	4.70	0.31	3.60	3.58	3.92	4.09	3.37	83	4.96	100	5.05	100	6.19	100
hsa-miR-337	0.92	0.45	1.05	-0.08	0.14	0.75	0.54	0	0.40	0	0.08	0	0.47	0
hsa-miR-338	0.79	-0.08	0.04	3.40	-0.13	1.74	0.96	17	3.97	100	4.01	100	4.82	100
hsa-miR-339	2.74	4.16	3.74	3.61	3.05	3.54	3.47	100	2.33	100	2.39	83	2.43	100
hsa-miR-340	0.37	0.45	1.18	0.75	0.44	-0.26	0.49	0	0.88	13	0.37	0	1.00	0
hsa-miR-342	5.37	5.66	4.09	5.17	5.64	5.49	5.24	100	6.15	100	5.88	100	6.07	100
hsa-miR-345	2.71	1.21	2.13	2.13	1.47	0.88	1.75	33	1.71	75	1.64	50	1.19	40

hsa-miR-346	0.79	-0.31	0.35	0.75	1.14	0.88	0.60	0	0.53	0	0.42	17	0.55	0
hsa-miR-34a	4.04	3.35	3.95	1.44	2.87	4.22	3.31	83	5.87	100	5.56	100	5.29	100
hsa-miR-34b	2.03	2.05	2.07	1.24	1.94	2.40	1.95	50	3.70	100	3.06	100	3.48	100
hsa-miR-34c	0.51	1.80	1.87	0.19	0.74	-0.03	0.85	17	1.51	63	1.53	17	0.56	0
hsa-miR-361	4.92	5.41	5.56	5.26	5.03	5.13	5.22	100	4.76	100	4.39	100	4.45	100
hsa-miR-365	2.62	2.89	2.91	2.97	2.87	2.44	2.78	100	1.97	75	2.16	50	3.41	100
hsa-miR-367	-0.03	0.31	0.98	1.31	1.01	0.49	0.68	0	0.43	0	1.78	50	0.48	0
hsa-miR-368	0.51	0.31	0.59	0.92	1.14	0.75	0.71	0	4.41	100	5.08	100	5.56	100
hsa-miR-369-3p	-0.27	1.21	1.71	0.01	0.29	1.22	0.69	0	-0.08	0	0.21	0	0.83	20
hsa-miR-370	2.74	3.13	2.34	2.68	2.85	2.92	2.78	100	3.05	100	2.98	100	2.62	100
hsa-miR-371	0.37	0.45	0.75	1.01	0.74	0.22	0.59	0	0.52	0	0.97	0	0.62	0
hsa-miR-372	-0.38	0.98	0.51	0.92	0.74	1.42	0.70	0	1.03	25	0.48	0	0.48	20
hsa-miR-373	0.23	0.17	1.11	0.28	0.59	0.75	0.52	0	0.64	0	1.32	17	0.66	0
hsa-miR-373-AS	2.03	2.33	1.42	1.61	1.94	1.99	1.89	17	1.94	75	1.67	17	2.00	80
hsa-miR-374	1.91	1.93	1.83	0.92	1.88	1.00	1.58	17	3.06	100	2.48	83	3.80	100
hsa-miR-375	0.51	0.72	0.19	1.76	0.59	1.32	0.85	0	4.70	100	6.43	100	7.21	100
hsa-miR-376a	0.37	0.45	0.67	0.92	1.37	1.12	0.82	0	3.70	100	3.86	100	4.63	100
hsa-miR-377	0.65	-0.08	0.19	2.34	1.01	1.00	0.85	17	2.59	100	3.05	100	3.30	100
hsa-miR-378	2.09	0.72	2.04	2.06	2.56	2.75	2.04	50	0.94	38	1.08	33	0.75	0
hsa-miR-379	2.48	1.99	1.18	1.81	2.23	2.44	2.02	67	3.49	100	4.06	100	3.93	100
hsa-miR-380-3p	0.37	0.45	1.24	0.84	1.56	0.49	0.82	0	0.14	0	0.50	0	0.40	0
hsa-miR-380-5p	1.16	0.17	0.35	0.47	1.26	-0.37	0.51	0	0.36	0	1.48	0	0.22	0
hsa-miR-381	0.92	0.98	0.75	0.75	1.14	1.22	0.96	0	1.39	38	2.31	83	2.08	60
hsa-miR-382	1.37	1.31	0.43	0.56	1.47	0.88	1.00	0	3.04	100	2.96	100	3.07	100
hsa-miR-383	1.04	0.45	1.11	0.47	1.01	1.42	0.92	0	1.02	13	1.73	17	1.29	20
hsa-miR-384	-0.15	1.10	1.05	0.01	-0.13	0.62	0.41	0	-0.12	0	-0.15	0	0.46	0
hsa-miR-422a	2.90	2.37	3.94	3.86	3.89	4.26	3.54	100	2.77	100	1.89	67	2.60	100
hsa-miR-422b	3.87	2.99	4.84	4.37	4.51	5.00	4.26	100	4.13	100	3.41	100	3.43	100
hsa-miR-423	4.90	5.07	5.35	4.99	5.10	4.98	5.07	100	3.79	100	3.51	100	3.05	100
hsa-miR-424	2.62	2.94	2.01	0.84	0.59	0.35	1.56	50	3.91	100	3.07	83	3.66	100
hsa-miR-425	2.44	2.89	2.24	1.50	1.73	2.04	2.14	50	1.82	38	1.35	0	1.39	40
hsa-miR-429	4.74	4.43	4.83	4.03	4.42	4.09	4.42	100	4.71	100	4.03	100	5.13	100
hsa-miR-448	0.65	0.45	0.27	0.47	0.88	0.09	0.47	0	0.58	0	0.24	0	1.04	0

hsa-miR-449	0.79	0.85	2.01	1.81	1.01	1.32	1.30	17	0.82	0	1.89	50	0.75	0
hsa-miR-450	0.92	0.72	1.66	1.31	1.26	1.74	1.27	0	1.54	38	1.25	17	0.90	20
hsa-miR-7	5.00	5.41	4.64	4.71	5.04	3.91	4.78	100	5.54	100	5.14	100	5.68	100
hsa-miR-9	0.23	0.59	0.51	1.24	0.00	1.22	0.63	0	0.73	13	1.50	33	0.52	0
hsa-miR-9-AS	1.37	2.65	1.47	2.68	1.47	1.93	1.93	33	1.45	38	1.59	0	1.04	20
hsa-miR-92	5.42	6.69	6.45	6.22	6.65	6.65	6.35	100	4.92	100	4.80	100	4.82	100
hsa-miR-93	6.58	6.97	6.65	7.36	6.76	6.39	6.78	100	5.94	100	4.99	100	4.83	100
hsa-miR-95	1.04	2.05	1.66	0.92	1.47	1.22	1.39	17	3.17	100	2.51	83	3.87	100
hsa-miR-96	2.68	3.20	3.49	3.96	2.76	2.51	3.10	100	3.04	100	2.79	100	4.69	100
hsa-miR-98	3.99	4.72	4.00	4.57	4.73	3.30	4.22	100	4.58	100	4.05	100	5.05	100
hsa-miR-99a	6.15	5.38	4.67	6.30	6.79	6.54	5.97	100	6.27	100	6.64	100	5.38	100
hsa-miR-99b	5.43	5.99	6.01	4.95	4.61	4.30	5.22	100	4.95	100	4.59	100	4.12	100
mmu-let-7d-AS	-0.15	0.04	0.90	0.37	0.44	-0.64	0.16	0	0.67	13	0.40	0	0.86	0
mmu-miR-101b	0.51	0.04	0.98	1.66	0.44	1.42	0.84	0	1.07	13	1.24	17	1.16	20
mmu-miR-106a	6.53	7.67	7.00	7.20	7.92	7.90	7.37	100	6.20	100	5.39	100	5.72	100
mmu-miR-129-3p	1.46	0.45	1.62	1.44	1.80	1.80	1.43	0	1.42	38	2.06	50	1.40	0
mmu-miR-140-AS	3.09	2.15	3.15	1.24	2.01	2.23	2.31	50	4.52	100	4.29	100	3.61	100
mmu-miR-151	3.54	3.56	3.91	4.01	4.10	4.06	3.86	100	2.76	100	2.11	67	3.08	100
mmu-miR-155	3.26	0.45	2.91	3.99	4.60	2.90	3.02	83	4.51	100	2.84	100	2.65	100
mmu-miR-17-3p	2.48	2.65	2.32	1.81	2.60	3.01	2.48	83	1.33	38	1.18	0	1.46	20
mmu-miR-192	1.91	2.24	2.04	2.06	2.45	2.19	2.15	50	6.52	100	5.99	100	7.00	100
mmu-miR-199b	0.51	0.59	0.67	0.84	0.59	0.88	0.68	0	4.91	100	4.79	100	4.38	100
mmu-miR-201	-0.03	-0.51	0.67	0.47	0.88	0.49	0.33	0	0.49	0	0.60	0	0.84	0
mmu-miR-202	2.65	2.68	2.22	2.57	2.76	3.27	2.69	100	3.11	100	2.98	100	2.65	100
mmu-miR-207	2.14	1.21	1.79	1.37	1.88	1.50	1.65	17	0.95	13	0.86	0	1.19	0
mmu-miR-211	1.04	-0.08	0.75	0.28	-0.13	1.00	0.48	0	0.02	0	0.49	0	0.90	0
mmu-miR-215	-0.03	0.45	0.90	-0.23	-0.13	0.35	0.22	0	1.72	50	0.43	0	1.72	60
mmu-miR-217	1.04	0.17	-0.04	1.16	1.47	0.22	0.67	0	2.17	88	6.40	100	7.70	100
mmu-miR-290	3.33	2.84	2.99	2.68	2.87	2.54	2.87	100	2.24	100	2.39	83	2.27	100
mmu-miR-291-3p	0.65	0.31	0.04	1.44	1.94	0.09	0.74	0	0.61	0	1.38	33	0.48	0
mmu-miR-291-	1.55	0.85	0.59	1.16	1.01	1.59	1.13	0	0.66	0	1.44	17	0.73	0

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mmu-miR-429	1.63	0.31	1.36	1.01	1.01	1.01	1.42	1.12	0	1.20	38	1.02	33	1.61	20
mmu-miR-7b	1.63	1.21	0.75	1.44	1.47	1.32	1.32	1.30	0	2.21	88	2.19	83	2.39	100
rno-miR-151-AS	5.52	5.77	6.30	5.95	5.91	6.20	5.94	5.94	100	5.48	100	5.24	100	5.04	100
rno-miR-20-AS	1.04	1.10	0.83	0.92	1.26	0.75	0.98	0.98	0	0.67	13	1.15	0	0.37	0
rno-miR-297	0.37	-0.60	0.51	0.37	-0.13	-0.03	0.08	0.08	0	0.90	25	0.34	0	0.47	0
rno-miR-327	2.68	2.05	1.71	2.16	1.80	2.75	2.19	2.19	50	2.30	100	2.62	100	2.14	80
rno-miR-333	1.37	0.85	0.59	0.92	1.37	1.66	1.13	1.13	0	1.71	63	1.48	17	1.86	40
rno-miR-336	2.36	2.15	1.97	1.98	2.06	2.60	2.19	2.19	67	2.20	88	2.58	100	2.44	100
rno-miR-343	0.92	0.98	0.51	1.44	0.29	1.50	0.94	0.94	0	0.87	13	0.85	17	1.14	0
rno-miR-344	1.04	0.85	1.11	0.92	1.26	1.00	1.03	1.03	0	0.07	0	0.04	0	0.64	0
rno-miR-346	0.37	1.21	0.51	0.75	1.47	0.09	0.73	0.73	0	1.25	25	1.26	0	0.94	0
rno-miR-347	2.28	1.31	1.52	0.75	1.80	2.28	1.66	1.66	17	1.55	75	2.05	67	1.56	40
rno-miR-349	0.10	0.04	0.83	1.94	1.65	0.88	0.91	0.91	0	0.73	0	0.06	0	0.86	0
rno-miR-352	4.13	4.33	4.52	5.34	5.13	4.36	4.63	4.63	100	4.82	100	4.03	100	4.86	100
rno-miR-421	-0.38	0.45	0.98	0.56	1.37	0.35	0.55	0.55	0	0.82	13	0.20	0	0.63	0
rno-miR-7-AS	2.62	1.66	2.19	1.50	2.37	2.19	2.09	2.09	50	1.05	13	1.36	17	1.56	60
hsa-miR-522	-0.03	0.17	0.59	0.66	1.14	1.32	0.64	0.64	0	0.41	13	0.54	0	0.82	0
hsa-miR-519b	1.16	1.21	1.11	0.47	0.14	1.22	0.89	0.89	0	0.98	13	1.05	17	0.58	0
hsa-miR-520c	-0.15	0.59	0.98	0.92	0.29	1.66	0.71	0.71	0	0.35	0	0.80	17	0.70	0
hsa-miR-519e	1.04	-0.60	0.19	0.84	0.44	1.12	0.50	0.50	0	0.70	0	1.33	17	0.59	0
hsa-miR-519d	0.79	0.85	0.83	1.66	1.14	0.88	1.03	1.03	0	0.38	13	1.41	33	0.33	0
hsa-miR-520b	-0.03	0.04	0.90	1.01	0.44	1.32	0.61	0.61	0	1.18	25	1.26	0	0.48	0
hsa-miR-519c	0.10	0.17	0.67	1.37	-0.26	0.35	0.40	0.40	0	0.74	25	0.65	0	0.66	0
hsa-miR-526b-AS	0.65	0.72	1.11	0.37	1.37	0.49	0.79	0.79	0	0.08	0	0.80	33	0.58	0
hsa-miR-520e	0.23	0.31	0.35	0.01	0.00	0.88	0.30	0.30	0	0.58	13	0.58	0	0.60	0
hsa-miR-520a	0.92	0.72	0.98	0.75	0.88	1.50	0.96	0.96	0	0.50	13	1.71	50	0.47	0
hsa-miR-520d	0.92	0.85	0.67	0.56	1.37	-0.15	0.70	0.70	0	0.84	0	1.76	50	0.52	0
hsa-miR-520h	1.04	0.59	1.05	0.66	0.29	0.75	0.73	0.73	0	0.82	13	1.10	0	0.11	0
hsa-miR-517a	1.27	1.10	0.83	1.31	1.47	1.22	1.20	1.20	0	0.73	13	1.76	33	0.45	0
hsa-miR-518e	0.51	0.85	0.67	0.66	-0.91	0.88	0.44	0.44	0	0.71	13	0.30	0	0.41	0
hsa-miR-521	0.79	0.17	0.43	0.10	0.59	1.12	0.53	0.53	0	0.50	0	1.21	17	0.56	0
hsa-miR-523	0.92	0.72	1.24	0.75	0.59	1.32	0.92	0.92	0	0.92	0	1.29	17	0.63	0

hsa-miR-518f	-0.15	0.72	1.11	0.66	1.47	0.35	0.69	0	0.53	0	1.57	33	0.90	0
hsa-miR-518c	1.63	0.85	0.27	0.01	1.65	0.88	0.88	0	0.41	0	1.09	17	0.38	0
hsa-miR-518b	1.27	0.31	1.30	1.37	0.88	0.75	0.98	0	0.64	0	1.45	17	0.78	0
hsa-miR-518d	0.37	-0.41	0.98	0.75	0.29	1.32	0.55	0	0.19	0	-0.17	0	0.80	20
hsa-miR-525-AS	1.97	0.17	0.98	0.19	0.29	0.75	0.73	0	-0.12	0	-0.09	0	0.51	0
hsa-miR-524	0.37	0.98	1.47	0.37	1.01	-0.03	0.70	0	1.21	13	0.98	0	0.82	0
hsa-miR-518a	-0.03	0.72	0.27	0.01	1.01	1.32	0.55	0	0.46	0	0.94	0	0.50	0
hsa-miR-515-3p	1.04	0.72	0.59	0.47	1.01	0.22	0.68	0	0.91	0	0.37	0	0.55	0
hsa-miR-516-3p	1.27	1.58	0.11	1.44	1.47	0.62	1.08	0	0.66	0	0.16	0	0.72	0
ambi-miR-7026	1.04	0.31	0.67	0.56	0.29	0.75	0.60	0	0.13	0	0.88	17	0.02	0
ambi-miR-7027	-0.15	0.72	1.47	0.84	0.74	-0.03	0.60	0	1.25	38	0.83	17	1.11	20
hsa-miR-512-3p	1.16	1.66	0.83	1.01	0.59	0.75	1.00	0	1.17	13	0.96	0	1.31	20
ambi-miR-7029	1.16	1.31	0.75	1.16	1.14	0.49	1.00	0	5.30	100	5.26	100	5.58	100
hsa-miR-491	3.15	2.71	2.48	2.13	2.49	2.44	2.57	83	2.49	100	2.44	100	2.64	100
hsa-miR-506	0.79	1.50	0.83	1.16	1.14	1.00	1.07	0	1.39	63	0.65	17	1.25	40
hsa-miR-514	-0.03	0.59	0.67	0.47	-0.13	0.35	0.32	0	0.66	0	-0.08	0	0.31	0
hsa-miR-509	1.04	1.58	0.83	0.19	1.56	1.66	1.14	0	1.32	13	1.50	0	1.28	40
hsa-miR-508	0.10	1.50	0.75	0.75	-0.13	0.88	0.64	0	0.99	13	1.69	33	1.01	20
hsa-miR-507	0.10	-0.20	0.75	0.84	0.88	1.50	0.64	0	0.05	0	-0.04	0	0.82	0
ambi-miR-7036	1.04	0.17	0.83	1.44	0.59	0.22	0.72	0	1.30	38	1.45	17	1.84	60
hsa-miR-193b	5.10	4.62	6.00	4.76	4.67	5.32	5.08	100	3.11	100	3.17	100	3.00	100
ambi-miR-7038-1	1.27	0.85	0.90	1.44	0.59	1.12	1.03	0	0.18	0	0.74	0	0.52	0
ambi-miR-7039	2.97	3.89	3.45	2.84	2.49	2.57	3.04	100	2.84	88	2.94	100	2.66	100
hsa-miR-488	0.37	1.10	0.59	1.01	-0.37	0.62	0.55	0	0.95	25	0.83	0	1.03	20
hsa-miR-510	0.37	1.10	0.90	1.16	1.37	0.35	0.88	0	0.56	13	0.41	0	1.16	40
hsa-miR-517-AS	1.37	0.72	0.59	1.01	0.29	1.32	0.88	0	0.75	13	1.05	0	0.70	0
hsa-miR-518f-AS	1.04	0.98	1.30	0.92	0.29	0.35	0.81	0	1.01	13	0.87	17	0.39	0
hsa-miR-518c-AS	2.71	2.33	1.66	2.29	2.49	2.54	2.34	83	2.71	100	2.58	100	2.55	100
hsa-miR-526c	1.04	1.41	1.05	0.66	0.29	0.35	0.80	0	0.12	0	0.39	0	0.72	0
hsa-miR-526b	1.71	2.10	1.47	1.01	1.47	1.87	1.60	17	1.64	50	1.78	33	1.98	60

hsa-miR-520a-AS	0.79	0.85	0.75	0.56	1.14	-0.26	0.64	0	-0.12	0	0.09	0	0.27	0
hsa-miR-525	1.55	1.31	0.83	0.66	1.37	1.66	1.23	0	0.65	13	0.17	0	1.13	0
hsa-miR-524-AS	1.16	0.98	0.35	0.37	1.37	0.09	0.72	0	0.89	13	0.97	0	0.90	0
hsa-miR-520d-AS	0.10	1.21	0.51	1.09	1.14	2.09	1.02	0	1.02	0	1.58	50	1.07	20
hsa-miR-527	1.16	0.85	0.43	1.24	0.59	1.00	0.88	0	1.04	13	1.77	50	1.29	20
hsa-miR-515-5p	0.23	1.21	0.67	0.84	1.26	0.49	0.78	0	0.40	13	0.82	0	0.76	0
hsa-miR-519e-AS	1.16	0.17	0.27	1.09	1.14	0.49	0.72	0	0.76	0	0.88	0	0.65	0
ambi-miR-7054	1.04	0.85	0.83	0.28	0.74	0.75	0.75	0	0.97	13	0.36	0	0.87	0
ambi-miR-7055	-0.15	0.59	0.67	0.75	0.88	1.12	0.64	0	0.82	13	1.56	33	0.58	0
hsa-miR-498	1.55	1.41	1.11	1.01	1.01	1.42	1.25	0	1.03	25	1.64	0	0.88	0
hsa-miR-513	4.04	3.76	2.62	4.17	3.49	3.74	3.64	100	3.98	100	4.29	100	4.28	100
ambi-miR-7058	4.64	4.76	5.44	4.61	4.86	4.81	4.85	100	4.13	100	3.97	100	4.03	100
ambi-miR-7059-1	1.04	0.59	0.11	0.37	1.14	0.88	0.69	0	0.14	0	0.36	0	0.28	0
hsa-miR-452	1.46	1.66	3.89	2.34	2.73	2.36	2.41	67	3.42	100	2.27	67	2.48	100
hsa-miR-493	1.91	1.58	0.19	0.37	0.88	0.88	0.97	0	1.63	63	1.83	50	1.53	20
ambi-miR-7062	1.85	1.80	1.30	1.09	1.80	1.42	1.54	17	1.43	25	1.68	17	1.43	20
hsa-miR-432	2.58	2.10	1.52	2.09	2.37	2.57	2.21	67	3.11	100	3.36	100	3.09	100
hsa-miR-495	-0.03	0.85	0.35	1.01	1.80	-0.37	0.60	0	2.15	100	2.00	67	2.25	100
hsa-miR-494	4.62	4.75	3.41	5.40	4.32	4.49	4.50	100	5.17	100	6.89	100	7.07	100
ambi-miR-7066	1.04	-0.08	0.04	0.84	0.14	0.49	0.41	0	1.16	38	0.80	0	0.81	20
ambi-miR-7067	0.79	1.10	0.98	0.84	1.37	1.59	1.11	0	1.42	50	1.67	50	1.25	40
ambi-miR-7068-1	1.16	0.72	1.18	-0.08	-0.26	0.88	0.60	0	0.30	0	0.40	0	0.62	0
hsa-miR-496	1.55	0.72	0.83	1.01	0.29	1.32	0.95	0	0.61	13	0.37	0	0.41	0
ambi-miR-7070	-0.15	0.59	0.35	0.47	1.14	1.66	0.68	0	1.63	63	2.09	67	2.06	80
hsa-miR-492	0.37	0.59	-0.18	1.31	1.01	1.00	0.68	0	0.50	0	-0.30	0	0.85	0
hsa-miR-490	0.65	1.21	0.98	0.56	0.44	1.22	0.84	0	0.40	0	1.24	17	0.38	0
hsa-miR-497	1.78	2.10	1.30	1.44	2.45	2.54	1.94	50	4.86	100	5.20	100	3.99	100
ambi-miR-7074	0.10	0.04	0.83	1.16	1.56	0.62	0.72	0	0.48	0	0.96	17	0.42	0
ambi-miR-7075	2.23	2.15	2.16	2.34	1.65	1.50	2.01	67	2.29	100	2.25	83	2.26	100

ambi-miR-7076	2.74	3.38	2.50	3.70	2.73	2.60	2.94	100	2.77	100	2.31	100	2.46	100
hsa-miR-501	1.16	1.99	1.71	1.37	0.88	1.80	1.48	17	1.43	25	1.43	33	1.34	20
hsa-miR-502	1.55	1.80	1.42	1.81	1.80	1.66	1.67	17	1.29	25	1.75	33	1.15	0
ambi-miR-7079	1.27	1.10	1.24	2.61	1.47	1.12	1.47	17	1.87	75	1.89	67	1.52	20
ambi-miR-7080	1.71	0.59	1.05	0.92	1.73	0.75	1.12	0	1.27	0	0.80	0	0.98	0
ambi-miR-7081	1.55	1.41	0.98	0.92	0.88	1.22	1.16	0	2.15	100	2.22	67	1.64	40
hsa-miR-202-AS	0.65	0.31	0.35	0.75	0.59	0.62	0.54	0	0.06	0	0.57	17	0.65	0
ambi-miR-7083	2.40	4.03	0.35	0.56	3.05	2.40	2.13	67	3.25	100	2.82	100	2.89	100
ambi-miR-7084	0.79	0.72	1.05	1.31	0.59	1.00	0.91	0	1.09	13	1.59	33	1.09	20
ambi-miR-7085	1.71	0.98	0.90	1.44	0.59	1.50	1.19	0	1.08	25	1.48	33	0.75	0
ambi-miR-7086	2.09	2.77	1.79	0.66	1.56	1.22	1.68	17	0.95	38	0.31	0	1.44	20
hsa-miR-512-5p	0.51	0.98	0.83	1.56	0.44	0.35	0.78	0	0.39	0	0.34	17	0.72	20
hsa-miR-504	0.23	0.17	0.51	0.10	0.14	0.35	0.25	0	0.32	0	-0.03	0	0.84	0
ambi-miR-7089	0.37	0.85	1.18	1.37	1.37	0.75	0.98	0	0.89	13	1.19	17	1.30	0
hsa-miR-511	0.92	1.10	1.30	0.75	0.29	0.22	0.76	0	0.31	13	0.20	0	0.63	0
hsa-miR-452-AS	1.27	0.45	2.34	1.66	1.94	1.12	1.46	17	1.75	75	0.12	0	1.35	20
hsa-miR-503	3.60	4.94	3.82	1.50	1.37	0.22	2.57	50	2.76	100	1.99	67	1.73	40
hsa-miR-485-5p	0.79	1.41	0.90	0.92	1.01	1.74	1.13	0	1.64	75	1.55	0	1.47	40
hsa-miR-499	1.27	0.85	0.98	1.01	1.37	-0.03	0.91	0	1.07	13	1.55	50	1.25	20
ambi-miR-7095	1.16	1.21	0.83	0.47	1.47	1.32	1.08	0	1.03	13	1.14	17	0.67	0
hsa-miR-505	2.58	3.81	2.93	2.09	1.94	1.66	2.50	50	1.88	75	1.45	17	1.16	20
ambi-miR-7097	1.16	1.10	0.98	1.56	1.26	1.00	1.17	0	0.65	13	0.57	0	0.81	0
ambi-miR-7098	2.19	0.04	0.98	0.92	2.23	0.62	1.16	33	0.73	0	0.24	0	0.48	0
hsa-miR-489	0.92	1.41	0.04	0.84	0.00	-0.46	0.46	0	1.25	38	0.11	0	1.23	0
ambi-miR-7100	0.23	0.04	0.11	0.84	1.01	1.12	0.56	0	1.45	63	1.44	17	2.13	80
ambi-miR-7101	1.16	0.72	0.83	0.66	-0.26	0.88	0.66	0	0.57	0	1.67	17	0.56	0
hsa-miR-432-AS	0.79	1.31	0.11	0.75	1.37	0.62	0.82	0	0.64	0	0.83	17	0.55	0
ambi-miR-7103	1.71	0.31	1.94	1.16	1.01	1.12	1.21	0	0.95	25	1.60	33	0.59	0
hsa-miR-500	1.78	2.55	2.24	2.29	1.65	1.59	2.02	50	2.19	88	2.11	83	1.80	60
ambi-miR-7105	2.40	2.37	3.47	2.45	2.70	3.27	2.78	100	2.99	100	2.10	67	2.42	100
TV**	2.09	1.66	1.94	2.1	2.12	2.28	2.04							
				6										

miRNAs > TV***	144	161	144	12 9	137	133	141
%*	38.2	42.7	38.2	34. 2	36.3	35.3	37.5

* , percentage of miRNAs above threshold value; ** , threshold value; *** , number of miRNAs above threshold value; CL = Cell Line; Ca = PDAC; Ch = chronic pancreatitis; N = normal

EXAMPLE 3:**THE PANCREATIC MIRNOME**

As no comprehensive data set about miRNA expression in normal pancreas is currently available, the inventors first characterized the normal pancreatic miRNome.

5 About 190 miRNAs were reproducibly detected above background signal in all five normal pancreas samples (Table 3, Mean (N)>2). These included 158 well characterized human miRNAs and 21 miRNAs previously identified in mouse or rat. In addition, six new human miRNAs (Ambi-miR-7029, -7039, -7058, -7076, -7083 and -7105) were detected. Ambi-miR-7029 and -7058 had a highly significant
10 expression level (Mean (N)>4). The inventors next performed a global comparison of expression data between the five normal pancreatic tissue samples and a reference set consisting of 33 different human tissues analyzed on the same array platform. The data are summarized in a global graphical representation of mean expression levels within each sample set (FIG. 2). The human reference set consisted of FirstChoice®
15 Total RNA samples (Ambion) isolated from 33 distinct tissues: adipose, adrenal, aorta, bladder, bone marrow, brain, breast, cervix, colon, duodenum, esophagus, fallopian tube, heart, ileum, jejunum, kidney, liver, lung, lymph node, muscle, ovary, pituitary, placenta, prostate, small intestine, spleen, stomach, testis, thymus, thyroid, trachea, uterus, and vena cava.

20 Statistical analyses indicated that most miRNAs had similar mean expression levels in both sample sets and that many miRNAs known to be highly expressed in all tissue types, (e.g., hsa-miR-16, -21, -24, -26 and the let-7 family members) were also very abundant in pancreas (Table 5). However, several miRNAs (hsa-miR-141, -148a, -200a, -200b, -200c, -216, -217, and -375) were found clearly enriched in
25 pancreas, whereas others (hsa-miR-133a, -143, -145, and -150) were present at lower levels in our normal pancreatic tissue set (Table 5). Notably, miR-133a was detected at significant expression levels in all of the tissues in our reference set but not in any of the five normal pancreatic tissues. Furthermore, miR-216 and 217 were found to be essentially specific to pancreas with low mean expression levels and standard
30 deviations within the reference set (Table 5). The only other tissue where both miRNAs were detected at significant levels was duodenum, albeit at an expression level 15 to 25 times lower than in pancreas.

Table 5. Normalized Array Data for Five Normal Pancreas Samples (N) and 33 Reference Tissue Samples (Ref)

miR Name	Ref			N			Δ (N-Ref)
	%*	Mean	S.D.	%*	Mean	S.D.	
hsa-miR-133a	100	7.49	2.09	0	2.86	0.83	-4.63
hsa-miR-150	97	6.75	1.42	60	3.77	0.84	-2.97
hsa-miR-145	100	10.83	0.91	100	8.32	0.36	-2.51
hsa-miR-378	94	4.98	1.04	0	2.50	0.95	-2.49
hsa-miR-143	100	10.46	0.95	100	8.02	0.31	-2.43
hsa-miR-1	97	6.58	2.40	80	4.25	0.15	-2.34
hsa-miR-324-3p	100	5.72	0.40	40	3.48	0.50	-2.24
hsa-miR-422b	100	7.64	1.24	100	5.45	0.56	-2.19
ambi-miR-7079	100	5.74	1.03	20	3.59	0.20	-2.15
hsa-miR-205	42	4.63	2.91	20	2.54	1.43	-2.09
hsa-miR-422a	97	6.66	1.34	100	4.64	0.23	-2.02
hsa-miR-505	97	5.10	0.65	20	3.10	0.98	-2.00
hsa-miR-128a	100	6.20	1.18	80	4.22	0.47	-1.98
hsa-miR-222	100	7.90	0.82	100	5.94	0.50	-1.96
hsa-miR-187	58	4.40	1.76	20	2.46	1.09	-1.94
hsa-miR-196b	48	4.16	1.98	0	2.31	0.85	-1.86
mmu-miR-140-AS	100	7.41	0.70	100	5.63	0.54	-1.78
hsa-miR-100	100	8.88	0.82	100	7.17	0.34	-1.71
hsa-miR-99a	100	9.07	1.01	100	7.38	0.40	-1.70
hsa-miR-139	97	5.81	1.24	100	4.15	0.29	-1.66
hsa-miR-328	76	4.02	0.72	0	2.39	0.79	-1.63
hsa-miR-125b	100	9.59	0.77	100	7.96	0.18	-1.63
hsa-miR-331	94	5.54	0.68	80	3.98	0.54	-1.56
hsa-miR-197	97	5.35	0.63	40	3.79	0.16	-1.56
hsa-miR-125a	100	8.87	0.72	100	7.33	0.29	-1.55
hsa-miR-124a	27	3.12	1.72	0	1.62	0.93	-1.50
hsa-miR-423	100	6.54	0.50	100	5.08	0.48	-1.46
hsa-miR-193b	100	6.48	1.03	100	5.03	0.21	-1.45
hsa-miR-221	100	8.46	0.83	100	7.02	0.32	-1.44
hsa-miR-345	91	4.64	0.61	40	3.23	0.48	-1.41
ambi-miR-7029	100	8.94	1.58	100	7.58	0.66	-1.36
hsa-miR-223	100	7.82	1.11	100	6.48	0.67	-1.34
hsa-miR-204	91	5.18	1.44	60	3.88	0.37	-1.30
hsa-miR-497	100	7.28	0.64	100	6.00	0.26	-1.27
hsa-miR-99b	100	7.40	0.62	100	6.13	0.44	-1.27
hsa-miR-10b	94	7.80	1.71	100	6.55	0.19	-1.25
hsa-miR-155	100	6.52	1.10	100	5.29	1.06	-1.23
ambi-miR-7085	64	3.83	0.56	0	2.62	0.58	-1.21
hsa-miR-132	100	6.30	0.99	100	5.10	0.81	-1.20
hsa-miR-500	88	5.03	0.65	60	3.84	0.68	-1.19
hsa-miR-15b	100	8.34	0.64	100	7.18	0.39	-1.17
hsa-miR-224	94	5.77	1.16	100	4.61	0.38	-1.16
ambi-miR-7081	97	4.83	0.60	40	3.71	0.28	-1.13
hsa-miR-126	100	10.24	0.48	100	9.12	0.17	-1.13
hsa-miR-23a	100	10.03	0.56	100	8.91	0.26	-1.12
hsa-miR-181a	100	8.11	0.84	100	7.01	0.20	-1.11
hsa-miR-330	30	3.25	0.89	0	2.16	1.12	-1.09

hsa-miR-93	100	7.92	0.56	100	6.83	0.30	-1.09
hsa-miR-503	85	4.88	1.25	40	3.79	0.54	-1.09
hsa-miR-146a	100	6.93	0.96	100	5.86	0.49	-1.07
ambi-miR-7105	100	5.52	0.49	100	4.47	0.26	-1.05
hsa-miR-23b	100	10.21	0.59	100	9.16	0.32	-1.05
hsa-miR-425	94	4.50	0.34	40	3.46	0.52	-1.04
hsa-miR-206	64	4.57	2.20	40	3.54	0.32	-1.04
hsa-miR-517a	15	3.03	1.69	0	2.01	1.07	-1.02
hsa-miR-34c	30	3.37	1.95	0	2.35	0.49	-1.02
hsa-miR-107	100	8.83	0.38	100	7.82	0.29	-1.01
ambi-miR-7083	94	5.94	1.01	100	4.93	0.57	-1.01
hsa-miR-149	67	3.90	0.79	20	2.90	0.63	-1.00
hsa-miR-103	100	8.86	0.38	100	7.86	0.30	-1.00
hsa-miR-339	100	5.46	0.77	100	4.48	0.25	-0.99
hsa-miR-189	94	4.80	0.73	80	3.85	0.70	-0.95
hsa-miR-92	100	7.76	0.54	100	6.82	0.25	-0.94
ambi-miR-7055	24	3.31	1.37	0	2.37	0.64	-0.94
mmu-miR-322	0	2.32	0.42	0	1.40	0.74	-0.92
ambi-miR-7103	39	3.30	0.51	0	2.38	0.57	-0.91
hsa-miR-212	52	3.69	0.76	20	2.78	0.71	-0.91
hsa-miR-361	100	7.36	0.46	100	6.45	0.30	-0.90
hsa-miR-199a	100	8.24	0.89	100	7.35	0.38	-0.90
hsa-miR-191	100	8.64	0.32	100	7.75	0.30	-0.89
hsa-miR-9-AS	61	3.87	1.11	20	2.98	0.76	-0.89
hsa-miR-214	100	7.54	0.89	100	6.65	0.45	-0.89
ambi-miR-7101	24	3.15	0.92	0	2.33	0.58	-0.82
hsa-miR-196a	48	3.85	1.92	0	3.05	0.89	-0.80
hsa-miR-213	18	2.76	0.67	0	1.97	0.91	-0.79
hsa-miR-520h	6	2.25	0.90	0	1.48	0.76	-0.77
hsa-miR-195	100	8.89	0.74	100	8.12	0.42	-0.77
hsa-let-7i	100	9.07	0.49	100	8.31	0.28	-0.76
hsa-miR-126-AS	100	6.64	0.54	100	5.92	0.33	-0.72
hsa-miR-16	100	10.69	0.46	100	9.99	0.17	-0.70
hsa-miR-18a	94	5.32	0.92	100	4.63	0.29	-0.70
hsa-miR-514	18	2.59	1.59	0	1.90	0.39	-0.69
hsa-miR-498	36	3.52	0.96	0	2.83	0.41	-0.69
hsa-miR-24	100	9.84	0.55	100	9.15	0.28	-0.69
mmu-miR-291-5p	15	3.14	0.61	0	2.45	1.08	-0.69
hsa-miR-140	100	5.94	0.51	100	5.26	0.27	-0.68
ambi-miR-7076	91	5.20	0.66	100	4.52	0.40	-0.68
hsa-miR-324-5p	64	3.55	0.50	0	2.88	0.58	-0.67
hsa-miR-519d	6	2.52	1.31	0	1.85	1.13	-0.67
mmu-miR-384	3	1.95	0.56	0	1.29	0.65	-0.66
ambi-miR-7068-1	18	3.03	1.07	0	2.38	0.82	-0.65
hsa-miR-320	100	8.35	0.47	100	7.70	0.25	-0.65
ambi-miR-7026	6	1.93	1.01	0	1.28	0.40	-0.65
hsa-miR-181b	100	7.01	0.80	100	6.36	0.31	-0.65
hsa-miR-181c	94	4.74	0.73	80	4.10	0.26	-0.64
hsa-miR-10a	94	7.54	1.54	100	6.93	0.22	-0.61
rno-miR-151-AS	100	7.65	0.47	100	7.05	0.38	-0.61
hsa-miR-27a	100	9.47	0.54	100	8.87	0.20	-0.60
hsa-miR-490	21	2.64	0.78	0	2.04	0.46	-0.60

hsa-miR-502	76	3.77	0.49	0	3.17	0.35	-0.60
mmu-miR-346	3	2.48	0.59	0	1.89	0.60	-0.59
hsa-miR-199a-AS	100	8.99	0.84	100	8.43	0.33	-0.55
hsa-miR-9	21	2.75	1.30	0	2.19	0.96	-0.55
ambi-miR-7075	91	4.87	0.58	100	4.32	0.23	-0.55
hsa-miR-495	97	4.85	0.99	100	4.31	0.14	-0.55
hsa-miR-22	100	9.33	0.66	100	8.79	0.20	-0.54
ambi-miR-7058	100	6.58	0.32	100	6.04	0.21	-0.54
hsa-miR-412	0	1.69	0.66	0	1.15	0.55	-0.54
hsa-miR-31	94	6.44	1.69	100	5.91	0.19	-0.53
hsa-miR-326	27	3.14	0.41	0	2.61	0.29	-0.53
hsa-miR-520d	9	2.74	1.03	0	2.23	0.77	-0.51
hsa-miR-185	100	6.73	0.61	100	6.26	0.25	-0.47
mmu-miR-34b	27	3.44	1.31	0	2.97	0.47	-0.47
mmu-miR-292-3p	0	2.34	0.40	0	1.89	1.09	-0.44
hsa-miR-152	100	7.18	0.48	100	6.75	0.31	-0.43
hsa-miR-449	18	3.03	1.80	0	2.62	0.61	-0.41
hsa-miR-138	42	3.34	1.21	0	2.93	0.40	-0.40
hsa-miR-142-5p	88	4.79	0.89	80	4.39	0.37	-0.40
hsa-miR-17-5p	100	8.54	0.60	100	8.15	0.24	-0.40
hsa-miR-509	24	3.67	1.64	40	3.29	0.55	-0.38
hsa-miR-29a	100	9.92	0.52	100	9.55	0.17	-0.38
hsa-miR-380-5p	0	2.08	0.59	0	1.71	0.70	-0.37
hsa-miR-106b	100	7.35	0.46	100	6.98	0.19	-0.37
hsa-miR-106a	100	8.66	0.62	100	8.30	0.20	-0.36
hsa-miR-342	100	8.43	0.57	100	8.07	0.15	-0.36
hsa-miR-373-AS	94	4.40	0.57	80	4.06	0.17	-0.35
ambi-miR-7074	0	2.44	0.34	0	2.10	0.64	-0.34
hsa-miR-218	100	5.90	0.76	100	5.56	0.35	-0.34
hsa-miR-517-AS	6	2.64	0.77	0	2.32	1.34	-0.33
mmu-miR-106a	100	8.05	0.61	100	7.72	0.27	-0.33
hsa-miR-515-3p	12	2.53	1.05	0	2.23	0.84	-0.30
mmu-miR-351	3	2.83	0.33	20	2.54	1.03	-0.29
hsa-miR-17-3p	85	4.66	0.54	100	4.36	0.20	-0.29
hsa-miR-337	3	2.36	0.46	0	2.07	1.02	-0.29
ambi-miR-7059-1	3	2.09	0.67	0	1.80	0.80	-0.28
hsa-miR-452	97	4.81	0.86	100	4.53	0.11	-0.28
hsa-miR-137	15	2.57	1.32	0	2.31	0.18	-0.27
hsa-miR-370	97	4.91	0.41	100	4.66	0.12	-0.26
hsa-miR-25	100	7.68	0.54	100	7.43	0.23	-0.25
mmu-miR-17-3p	64	3.77	0.64	20	3.52	0.12	-0.24
hsa-miR-373	9	2.70	0.64	0	2.45	0.64	-0.24
mmu-miR-199b	97	6.63	0.94	100	6.39	0.47	-0.24
rno-miR-20-AS	0	2.16	0.52	0	1.93	0.80	-0.23
mmu-miR-155	85	4.92	1.16	100	4.69	0.97	-0.23
mmu-miR-345	58	3.45	0.35	20	3.22	0.41	-0.22
ambi-miR-7038-1	9	2.45	1.57	0	2.23	0.76	-0.22
hsa-miR-496	0	2.13	0.56	0	1.92	1.32	-0.21
ambi-miR-7027	33	3.27	0.57	20	3.06	0.82	-0.21
hsa-miR-323	15	2.75	1.18	0	2.54	0.72	-0.21
mmu-miR-202	91	4.88	0.80	100	4.69	0.18	-0.20
hsa-miR-30c	100	8.97	0.56	100	8.77	0.23	-0.20

hsa-miR-26a	100	11.18	0.35	100	11.00	0.31	-0.19
hsa-miR-518f-AS	6	2.22	0.59	0	2.03	0.85	-0.18
hsa-miR-519b	6	2.29	1.04	0	2.12	1.29	-0.18
hsa-miR-523	6	2.48	1.03	0	2.31	0.91	-0.17
rno-miR-327	88	4.37	0.47	80	4.20	0.16	-0.17
hsa-miR-520a-AS	3	1.86	0.59	0	1.70	0.85	-0.16
hsa-miR-367	0	2.25	0.37	0	2.09	1.08	-0.15
hsa-miR-28	100	6.98	0.43	100	6.83	0.33	-0.15
hsa-miR-20a	100	7.78	0.63	100	7.64	0.20	-0.14
hsa-miR-485-5p	64	3.61	0.57	40	3.47	0.73	-0.14
hsa-miR-19b	100	8.64	0.53	100	8.50	0.24	-0.14
mmu-miR-101b	24	3.11	0.59	20	2.97	1.24	-0.14
hsa-miR-151	100	6.16	0.36	100	6.03	0.25	-0.13
mmu-miR-300	58	3.52	0.36	40	3.40	0.96	-0.12
hsa-miR-34a	100	7.40	0.67	100	7.30	0.53	-0.10
hsa-miR-452-AS	45	3.49	0.88	20	3.39	0.30	-0.10
mmu-miR-409	82	4.28	0.94	100	4.18	0.27	-0.10
hsa-miR-127	45	3.66	0.98	40	3.57	0.59	-0.09
hsa-miR-491	100	4.78	0.61	100	4.69	0.16	-0.09
hsa-miR-380-3p	6	2.13	1.08	0	2.04	1.00	-0.09
hsa-miR-519e-AS	6	2.56	0.79	0	2.47	0.60	-0.09
hsa-miR-489	33	3.32	0.94	0	3.23	0.50	-0.08
hsa-miR-518c	3	2.02	0.78	0	1.93	0.95	-0.08
ambi-miR-7098	0	2.23	0.43	0	2.14	0.79	-0.08
ambi-miR-7086	58	3.56	0.70	20	3.49	0.32	-0.07
hsa-miR-372	6	2.17	1.00	20	2.11	1.31	-0.06
mmu-miR-294	27	3.17	0.37	20	3.12	0.36	-0.05
hsa-miR-184	82	4.33	0.48	100	4.28	0.14	-0.05
hsa-miR-499	24	3.32	1.59	20	3.27	0.39	-0.05
ambi-miR-7080	9	2.98	0.98	0	2.93	0.48	-0.05
mmu-miR-329	3	2.59	0.35	0	2.55	0.69	-0.04
hsa-miR-27b	100	9.51	0.64	100	9.47	0.31	-0.04
hsa-miR-210	97	5.84	0.73	100	5.80	0.28	-0.04
hsa-miR-346	3	2.34	0.56	0	2.31	0.52	-0.04
hsa-miR-340	24	3.05	0.55	0	3.01	0.29	-0.03
hsa-miR-193a	82	4.29	0.70	80	4.26	0.30	-0.03
hsa-miR-527	21	3.34	0.98	20	3.31	0.44	-0.03
hsa-miR-30d	100	9.11	0.46	100	9.08	0.21	-0.03
hsa-miR-188	73	3.88	0.42	60	3.86	0.24	-0.02
mmu-miR-380-3p	9	2.44	0.60	0	2.42	1.11	-0.02
hsa-miR-211	0	1.99	0.48	0	1.97	1.17	-0.02
hsa-miR-302b-AS	3	1.74	0.73	0	1.72	1.09	-0.02
mmu-miR-424	61	4.01	1.24	80	4.00	0.74	-0.02
hsa-miR-30b	100	8.86	0.50	100	8.84	0.24	-0.02
hsa-miR-302d	3	2.41	0.59	0	2.39	1.08	-0.02
mmu-miR-290	88	4.32	0.47	100	4.32	0.11	0.00
rno-miR-7-AS	55	3.62	0.49	60	3.63	0.29	0.01
hsa-miR-296	30	3.34	0.78	0	3.35	0.57	0.01
mmu-miR-129-3p	33	3.41	1.05	0	3.43	0.42	0.01
hsa-miR-521	3	2.26	1.04	0	2.27	0.70	0.01
hsa-miR-518c-AS	91	4.58	0.49	100	4.60	0.12	0.02
hsa-miR-520d-AS	15	3.05	1.07	20	3.07	0.59	0.02

hsa-miR-129	33	3.45	0.80	0	3.47	0.47	0.02
hsa-miR-144	3	2.03	0.86	0	2.06	1.24	0.03
hsa-miR-524-AS	15	2.83	1.01	0	2.86	0.44	0.03
hsa-miR-526c	9	2.51	0.73	0	2.55	0.71	0.03
hsa-miR-432	97	5.09	0.87	100	5.12	0.28	0.03
hsa-miR-186	100	5.66	0.45	100	5.70	0.28	0.04
ambi-miR-7097	9	2.68	0.42	0	2.72	0.54	0.05
mmu-miR-151	100	5.07	0.52	100	5.12	0.26	0.05
hsa-miR-122a	82	4.42	1.48	100	4.47	0.14	0.05
hsa-miR-15a	100	8.08	0.51	100	8.14	0.14	0.06
hsa-miR-432-AS	3	2.12	0.66	0	2.18	1.26	0.06
hsa-miR-511	6	2.32	1.03	0	2.38	0.91	0.06
hsa-miR-302a	0	2.52	0.57	0	2.58	0.89	0.06
hsa-let-7g	100	9.46	0.52	100	9.52	0.28	0.06
hsa-miR-504	15	2.67	0.63	0	2.74	0.53	0.07
hsa-miR-199b	97	6.30	1.23	100	6.37	0.18	0.07
hsa-miR-520b	6	2.06	0.83	0	2.13	0.67	0.08
hsa-miR-518a	6	2.12	0.81	0	2.20	0.90	0.08
hsa-miR-450	18	2.73	0.72	20	2.82	0.66	0.09
ambi-miR-7084	12	2.98	1.05	20	3.07	0.49	0.09
ambi-miR-7067	30	3.18	0.80	40	3.28	0.38	0.09
hsa-let-7a	100	11.25	0.38	100	11.35	0.30	0.10
hsa-miR-219	21	3.08	1.01	0	3.19	0.40	0.11
hsa-miR-381	70	4.04	0.73	60	4.15	0.42	0.11
hsa-miR-299-5p	76	4.17	0.88	100	4.28	0.12	0.11
hsa-miR-383	30	3.15	0.77	20	3.26	0.72	0.11
ambi-miR-7066	15	2.51	1.09	20	2.63	1.06	0.11
hsa-miR-516-3p	9	2.34	0.59	0	2.46	0.90	0.12
ambi-miR-7095	6	2.34	0.65	0	2.46	0.69	0.12
hsa-miR-135b	6	2.39	0.64	0	2.52	0.91	0.13
hsa-miR-220	6	2.42	0.50	0	2.55	0.53	0.13
ambi-miR-7036	61	3.77	0.98	60	3.90	0.36	0.13
rno-miR-347	39	3.47	0.61	40	3.60	0.52	0.13
hsa-miR-198	100	5.58	0.44	100	5.72	0.21	0.14
hsa-miR-519e	6	2.22	0.93	0	2.36	0.69	0.14
hsa-miR-520a	3	2.05	0.51	0	2.19	0.46	0.15
rno-miR-346	6	2.75	0.47	0	2.89	0.40	0.15
hsa-miR-506	18	3.07	1.20	40	3.22	0.71	0.15
hsa-miR-147	0	2.60	0.38	20	2.75	1.01	0.15
ambi-miR-7062	30	3.32	0.51	20	3.48	0.24	0.16
ambi-miR-7070	67	3.97	0.93	80	4.13	0.60	0.16
hsa-miR-525-AS	3	2.02	0.97	0	2.19	0.88	0.17
hsa-miR-136	3	2.20	0.67	0	2.36	0.50	0.17
mmu-miR-298	100	5.52	0.47	100	5.69	0.09	0.17
mmu-miR-293	0	2.21	0.48	0	2.38	0.41	0.17
hsa-miR-522	9	2.53	1.20	0	2.70	0.57	0.17
hsa-miR-512-5p	9	2.37	1.16	20	2.54	0.71	0.18
hsa-miR-203	82	5.34	1.80	100	5.52	0.58	0.18
hsa-let-7c	100	10.97	0.54	100	11.17	0.30	0.20
mmu-miR-291-3p	0	1.94	0.60	0	2.14	0.78	0.20
hsa-miR-518e	6	1.82	1.32	0	2.02	0.77	0.20
hsa-let-7b	100	10.86	0.62	100	11.06	0.36	0.21

hsa-miR-515-5p	6	2.41	1.12	0	2.63	0.55	0.22
mmu-miR-411	18	2.56	0.66	0	2.79	0.61	0.22
hsa-miR-519c	3	2.17	0.69	0	2.41	0.91	0.23
hsa-miR-30a-5p	100	9.36	0.48	100	9.61	0.21	0.26
mmu-miR-341	15	2.60	0.83	0	2.85	0.55	0.26
hsa-let-7e	100	8.73	0.44	100	8.98	0.46	0.26
ambi-miR-7039	79	4.45	0.61	100	4.71	0.57	0.26
rno-miR-336	91	4.23	0.69	100	4.49	0.36	0.26
mmu-miR-344	3	1.77	0.59	0	2.04	0.74	0.26
hsa-miR-520c	6	2.27	0.77	0	2.54	0.46	0.27
hsa-miR-142-3p	85	4.48	1.09	100	4.75	0.88	0.27
hsa-miR-512-3p	9	3.02	1.23	20	3.30	0.74	0.28
hsa-miR-510	18	2.87	1.19	40	3.15	0.62	0.29
hsa-miR-508	15	2.58	1.45	20	2.87	0.83	0.29
hsa-miR-182-AS	0	1.97	0.50	0	2.26	0.83	0.29
hsa-miR-302b	0	1.98	0.55	0	2.27	0.82	0.29
hsa-miR-30e-3p	100	5.30	0.41	100	5.60	0.22	0.31
mmu-miR-295	0	2.06	0.42	20	2.38	1.00	0.32
hsa-miR-302c-AS	70	3.62	0.46	80	3.94	0.40	0.32
mmu-miR-350	3	2.22	0.60	0	2.55	0.79	0.33
hsa-miR-325	3	2.51	0.63	0	2.85	0.60	0.33
hsa-miR-526b	64	3.71	0.70	60	4.05	0.18	0.34
mmu-miR-292-5p	52	3.25	0.62	20	3.59	0.29	0.34
hsa-let-7d	100	10.32	0.42	100	10.67	0.32	0.36
hsa-miR-384	0	1.75	0.62	0	2.11	0.84	0.36
rno-miR-421	0	2.08	0.41	0	2.44	0.57	0.36
hsa-miR-29b	100	8.21	0.48	100	8.58	0.13	0.37
hsa-miR-525	9	2.78	0.85	0	3.16	0.28	0.39
hsa-miR-524	3	2.28	0.77	0	2.67	0.71	0.39
hsa-miR-526b-AS	6	2.00	1.14	0	2.40	0.41	0.39
hsa-miR-130a	100	7.64	0.69	100	8.04	0.21	0.40
hsa-miR-21	100	10.30	0.66	100	10.71	0.61	0.40
hsa-miR-492	9	2.31	0.67	0	2.71	0.64	0.40
hsa-miR-33	0	2.03	0.47	0	2.44	0.68	0.40
rno-miR-352	100	6.46	0.59	100	6.87	0.53	0.41
hsa-miR-518b	3	2.30	0.75	0	2.71	0.38	0.41
hsa-miR-202-AS	9	1.91	1.12	0	2.34	1.10	0.44
rno-miR-297	0	1.72	0.49	0	2.16	0.76	0.44
mmu-let-7d-AS	3	2.30	0.49	0	2.74	0.64	0.44
hsa-miR-34b	94	5.06	1.14	100	5.51	0.76	0.45
mmu-miR-330	12	2.72	0.63	0	3.17	0.12	0.45
hsa-miR-501	27	2.95	0.68	20	3.40	0.09	0.46
hsa-miR-520e	0	1.87	0.41	0	2.34	0.93	0.46
hsa-miR-30e-5p	100	8.58	0.42	100	9.06	0.15	0.49
rno-miR-344	0	1.91	0.63	0	2.43	0.73	0.52
hsa-miR-518d	0	1.91	0.45	20	2.43	1.57	0.52
hsa-miR-371	0	1.79	0.54	0	2.32	0.89	0.53
mmu-miR-383	27	3.09	0.85	40	3.63	0.43	0.54
hsa-miR-30a-3p	100	5.56	0.62	100	6.11	0.16	0.55
hsa-miR-105	0	2.10	0.52	0	2.65	0.64	0.55
hsa-miR-410	21	2.90	1.03	20	3.44	0.31	0.55
hsa-miR-424	88	5.12	1.34	100	5.68	0.77	0.56

ambi-miR-7054	6	2.22	0.53	0	2.78	0.49	0.56
hsa-miR-369-3p	6	2.11	0.84	20	2.68	1.00	0.57
hsa-miR-26b	100	8.88	0.50	100	9.46	0.16	0.58
mmu-miR-207	9	2.58	0.59	0	3.19	0.50	0.61
hsa-miR-382	85	4.49	0.94	100	5.11	0.53	0.62
hsa-miR-98	100	6.42	0.54	100	7.06	0.51	0.64
hsa-miR-32	15	2.71	0.56	20	3.36	0.57	0.65
ambi-miR-7100	36	3.53	0.97	80	4.18	0.21	0.65
mmu-miR-325	0	2.43	0.59	20	3.10	0.55	0.67
hsa-miR-302c	3	1.86	0.58	0	2.55	0.75	0.69
hsa-miR-183	55	3.51	1.00	100	4.20	0.34	0.69
hsa-miR-493	15	2.88	0.88	20	3.58	0.37	0.70
hsa-miR-365	94	4.73	0.86	100	5.43	0.49	0.70
mmu-miR-211	6	2.19	0.70	0	2.89	0.23	0.70
hsa-miR-95	97	5.18	1.28	100	5.89	0.36	0.71
mmu-miR-201	3	1.99	0.79	0	2.73	0.69	0.74
hsa-miR-154	76	4.55	0.96	100	5.29	0.32	0.75
hsa-miR-379	97	5.18	0.78	100	5.94	0.30	0.76
hsa-miR-507	3	1.90	0.83	0	2.68	0.75	0.78
hsa-miR-518f	3	2.05	0.69	0	2.85	0.37	0.80
hsa-miR-19a	100	5.91	0.87	100	6.74	0.27	0.83
hsa-miR-190	0	1.80	0.61	40	2.66	1.45	0.86
rno-miR-343	6	2.26	0.53	0	3.16	0.28	0.90
hsa-let-7f	100	9.59	0.51	100	10.51	0.32	0.92
hsa-miR-513	100	5.37	0.83	100	6.29	0.35	0.92
hsa-miR-208	0	2.06	0.62	0	2.99	0.39	0.93
hsa-miR-448	3	2.06	0.44	0	3.00	0.52	0.94
hsa-miR-134	64	4.08	1.03	100	5.03	0.48	0.95
mmu-miR-376b	3	2.51	0.61	40	3.48	0.47	0.97
ambi-miR-7089	3	2.35	0.55	0	3.32	0.39	0.97
hsa-miR-488	0	1.99	0.56	20	3.01	0.41	1.02
hsa-miR-368	100	6.52	0.94	100	7.56	0.29	1.04
mmu-miR-376a	39	3.26	0.82	80	4.31	0.59	1.05
hsa-miR-135a	27	2.70	1.52	20	3.77	0.54	1.07
hsa-miR-374	100	4.71	0.74	100	5.82	0.57	1.11
mmu-miR-215	18	2.61	1.94	60	3.74	0.73	1.13
rno-miR-333	9	2.70	0.82	40	3.85	1.25	1.15
rno-miR-349	0	1.62	0.50	0	2.78	0.45	1.16
hsa-miR-101	100	5.69	0.55	100	6.88	0.06	1.19
mmu-miR-429	0	2.47	0.49	20	3.67	0.27	1.20
mmu-miR-7b	21	3.21	0.94	100	4.44	0.27	1.23
hsa-miR-301	24	2.76	0.83	40	4.02	0.22	1.25
hsa-miR-377	64	3.99	0.95	100	5.33	0.39	1.34
mmu-miR-337	0	1.87	0.55	40	3.21	0.96	1.34
hsa-miR-376a	100	5.23	0.94	100	6.63	0.31	1.40
hsa-miR-148b	100	5.71	0.38	100	7.11	0.60	1.40
hsa-miR-335	100	6.77	0.90	100	8.19	0.35	1.42
mmu-miR-297	0	1.79	0.49	40	3.34	0.92	1.55
hsa-miR-153	39	3.49	1.17	100	5.26	0.25	1.76
hsa-miR-29c	100	8.37	0.51	100	10.25	0.26	1.87
hsa-miR-194	100	6.75	2.13	100	8.63	0.21	1.88
hsa-miR-96	94	4.80	0.97	100	6.69	0.38	1.89

hsa-miR-182	91	5.39	1.29	100	7.39	0.37	2.00
hsa-miR-215	42	4.09	2.37	100	6.34	0.50	2.25
hsa-miR-429	70	4.88	1.88	100	7.13	0.09	2.25
hsa-miR-494	100	6.78	0.54	100	9.07	0.97	2.28
hsa-miR-7	94	5.07	1.66	100	7.68	0.56	2.61
hsa-miR-192	97	6.47	2.25	100	9.13	0.25	2.66
mmu-miR-192	97	6.32	2.25	100	9.00	0.28	2.67
hsa-miR-130b	100	5.56	0.66	100	8.27	0.25	2.71
hsa-miR-338	58	4.09	1.31	100	6.82	0.19	2.73
hsa-miR-200b	82	6.47	2.59	100	9.49	0.14	3.02
hsa-miR-200c	94	7.37	2.65	100	10.59	0.24	3.22
hsa-miR-148a	100	7.34	1.13	100	10.57	0.36	3.23
hsa-miR-200a	67	5.31	2.78	100	8.57	0.17	3.26
hsa-miR-141	67	5.52	2.29	100	9.49	0.20	3.98
hsa-miR-375	58	4.63	2.20	100	9.21	0.39	4.59
hsa-miR-216	3	2.79	0.69	100	9.09	0.28	6.30
mmu-miR-217	6	2.37	0.89	100	9.70	0.21	7.32
hsa-miR-217	12	2.38	1.07	100	9.86	0.22	7.48

threshold value = 3.47 for Ref; threshold value = 3.70 for N; %*, percentage of miRNAs above threshold value

EXAMPLE 4:**IDENTIFICATION OF MIRNAS DIFFERENTIALLY EXPRESSED IN PDAC**

To uncover miRNAs potentially relevant to pancreatic carcinogenesis, the inventors normalized miRNA array data from eight PDAC samples together with the normal pancreas set (Table 3). A direct comparison of mea miRNA expression levels showed that miRNA expression is profoundly affected in PDAC (Table 3, FIG. 3). Interestingly, most of the miRNAs down regulated in PDAC are miRNAs strongly enriched in pancreas relatively to the 33 human tissues reference set (Tables 3 and 5). Among these miRNAs, the highly expressed, pancreas-enriched miR-216 and -217 were down-regulated more than 200-fold in PDAC samples, to levels barely detectable on the array.

Further data analysis revealed 84 miRNAs with a significant differential expression between normal pancreas and PDAC (Table 6, Flag (N vs Ca)=1). Among these miRNAs, 41 were down-regulated and 32 were up-regulated by at least 2-fold in PDAC ($|\Delta h|$ (N-Ca)>0.6). Together with miR-216 and -217, a total of 11 miRNAs were strongly down-regulated by more than 5-fold in PDAC (Δh (N-Ca)>1.6; hsa-miR-29c, -30a-3p, -96, -130b, -141, -148a, -148b, -216, -217, -375, and -494), and 11 others were strongly enriched in PDAC samples (Δh (N-Ca)<-1.6; hsa-miR-31, -143, -145, -146a, -150, -155, -196a, -196b, -210, -222, and -223).

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Table 6. miRNAs Differentially Expressed Among Normal Pancreas (N), Chronic Pancreatitis (Ch), and PDAC (Ca) Tissue Samples

miR Name	Mean Ch	Mean N	Mean Ca	p-value ANOVA	Δh Ch-N	p-value Ch vs N	Flag* Ch vs N	Δh Ch- Ca	p-value Ch vs Ca	Flag* Ch vs Ca	Δh N-Ca	p-value N vs Ca	Flag* N vs Ca
hsa-let-7a	8.90	9.50	8.90	1.97E-03	-0.60	1.58E-03	1	0.00	9.92E-01	0	0.60	2.51E-03	1
hsa-let-7b	8.85	9.22	8.48	2.84E-04	-0.37	3.53E-02	1	0.36	1.77E-02	1	0.73	2.21E-04	1
hsa-let-7c	8.81	9.33	8.55	2.03E-04	-0.52	1.81E-03	1	0.27	9.06E-02	0	0.78	3.35E-04	1
hsa-let-7d	7.92	8.83	8.14	3.95E-04	-0.91	9.38E-05	1	-0.22	2.21E-01	0	0.69	4.02E-03	1
hsa-let-7e	6.27	7.14	6.70	1.15E-03	-0.87	1.57E-03	1	-0.43	7.80E-03	1	0.44	5.59E-02	0
hsa-let-7f	7.58	8.66	7.89	6.23E-04	-1.08	1.35E-04	1	-0.30	1.85E-01	0	0.78	6.06E-03	1
hsa-let-7g	7.09	7.68	7.26	3.13E-03	-0.59	2.02E-04	1	-0.17	2.47E-01	0	0.42	2.03E-02	1
hsa-let-7i	7.19	6.47	7.44	4.78E-05	0.72	1.60E-03	1	-0.25	1.34E-01	0	-0.97	4.08E-05	1
hsa-miR-100	6.52	5.32	6.29	2.31E-04	1.19	2.96E-05	1	0.23	3.39E-01	0	-0.97	2.23E-03	1
hsa-miR-101	4.42	5.03	4.47	1.27E-02	-0.61	1.62E-03	1	-0.04	8.36E-01	0	0.57	1.74E-02	1
hsa-miR-103	6.10	6.01	6.67	8.84E-05	0.08	4.53E-01	0	-0.58	6.81E-04	1	-0.66	6.54E-04	1
hsa-miR-106a	6.18	6.46	6.70	6.89E-04	-0.28	4.24E-02	0	-0.52	6.70E-04	1	-0.24	4.19E-02	0
hsa-miR-106b	5.11	5.14	5.60	9.30E-04	-0.04	6.88E-01	0	-0.50	2.55E-03	1	-0.46	6.75E-03	1
hsa-miR-107	6.18	5.98	6.71	1.47E-05	0.20	7.46E-02	0	-0.53	4.44E-04	1	-0.73	9.89E-05	1
hsa-miR-10a	5.77	5.09	6.19	1.73E-05	0.69	1.72E-05	1	-0.41	3.24E-02	0	-1.10	9.72E-05	1
hsa-miR-125a	6.07	5.48	6.00	1.59E-02	0.59	3.05E-03	1	0.07	7.06E-01	0	-0.51	2.38E-02	1
hsa-miR-125b	7.44	6.12	6.88	1.56E-05	1.32	4.88E-07	1	0.56	1.37E-02	1	-0.76	3.07E-03	1
hsa-miR-130a	5.98	6.20	5.58	1.75E-04	-0.23	3.63E-02	1	0.40	5.49E-03	1	0.62	4.94E-04	1
hsa-miR-130b	5.01	6.42	3.83	8.26E-08	-1.41	2.02E-03	1	1.19	8.11E-04	1	2.60	1.18E-09	1
hsa-miR-134	2.84	3.21	2.52	9.05E-03	-0.36	1.41E-01	0	0.33	9.25E-02	0	0.69	3.19E-03	1
hsa-miR-140	3.75	3.44	4.07	8.46E-03	0.32	9.77E-02	0	-0.32	1.13E-01	0	-0.63	3.01E-03	1
hsa-miR-141	6.72	7.65	5.95	1.82E-05	-0.93	4.62E-03	1	0.77	1.33E-02	1	1.70	1.20E-05	1
hsa-miR-143	7.59	6.18	7.91	3.86E-06	1.41	4.01E-06	1	-0.32	2.16E-01	0	-1.73	3.17E-05	1
hsa-miR-145	7.89	6.47	8.10	1.60E-04	1.42	4.88E-05	1	-0.21	5.34E-01	0	-1.62	4.84E-04	1
hsa-miR-146a	4.96	4.03	5.89	6.66E-05	0.93	1.98E-02	1	-0.93	1.19E-02	1	-1.86	3.34E-05	1
hsa-miR-148a	7.21	8.72	5.23	9.28E-09	-1.52	3.00E-03	1	1.98	2.83E-05	1	3.49	2.32E-09	1
hsa-miR-148b	3.14	5.27	2.91	1.53E-06	-2.13	1.80E-04	1	0.24	3.90E-01	0	2.37	6.17E-06	1
hsa-miR-150	3.83	2.11	4.35	5.86E-04	1.72	2.15E-02	1	-0.52	2.82E-01	0	-2.25	5.58E-06	1
hsa-miR-154	3.10	3.47	2.28	3.24E-04	-0.37	2.27E-01	0	0.82	6.63E-03	1	1.19	3.93E-05	1
hsa-miR-155	4.32	3.47	5.55	3.19E-04	0.85	1.04E-01	0	-1.24	2.34E-03	1	-2.08	6.49E-04	1

hsa-miR-15b	5.00	5.33	5.72	2.08E-03	-0.33	9.39E-02	0	-0.72	1.38E-03	1	-0.39	5.20E-02	0
hsa-miR-17-5p	6.12	6.31	6.62	4.11E-03	-0.19	2.06E-01	0	-0.50	2.95E-03	1	-0.31	3.75E-02	0
hsa-miR-18	3.32	2.83	4.24	6.85E-05	0.49	3.04E-02	1	-0.92	3.74E-03	1	-1.41	1.74E-04	1
hsa-miR-181b	4.51	4.52	5.01	1.47E-02	-0.01	9.49E-01	0	-0.50	2.13E-02	1	-0.49	1.68E-02	1
hsa-miR-182	4.26	5.55	4.54	4.58E-04	-1.29	9.47E-04	1	-0.28	2.99E-01	0	1.01	8.44E-04	1
hsa-miR-186	3.19	3.87	3.40	3.49E-03	-0.68	4.90E-03	1	-0.21	2.01E-01	0	0.47	7.99E-03	1
hsa-miR-196a	1.89	1.63	3.77	9.61E-07	0.26	4.15E-01	0	-1.88	2.25E-05	1	-2.14	8.31E-06	1
hsa-miR-196b	1.63	1.20	3.28	8.92E-06	0.44	2.14E-01	0	-1.64	2.22E-04	1	-2.08	2.86E-05	1
hsa-miR-199a	6.58	5.51	6.30	2.36E-05	1.08	1.63E-04	1	0.28	7.96E-02	0	-0.79	2.63E-04	1
hsa-miR-199a-AS	7.41	6.59	7.01	9.52E-06	0.82	8.95E-05	1	0.39	4.14E-04	1	-0.42	4.69E-03	1
hsa-miR-19a	4.12	4.90	4.25	1.90E-03	-0.78	9.51E-04	1	-0.13	4.70E-01	0	0.65	7.37E-03	1
hsa-miR-19b	6.22	6.66	6.16	8.53E-03	-0.44	9.80E-03	1	0.06	6.78E-01	0	0.50	7.49E-03	1
hsa-miR-200a	5.69	6.73	5.48	4.11E-04	-1.04	1.67E-03	1	0.21	4.47E-01	0	1.25	2.62E-04	1
hsa-miR-200b	6.50	7.65	6.68	5.63E-04	-1.15	7.01E-04	1	-0.17	5.10E-01	0	0.98	6.23E-04	1
hsa-miR-200c	7.67	8.74	7.23	2.20E-06	-1.07	4.06E-04	1	0.44	4.79E-02	0	1.51	1.23E-06	1
hsa-miR-203	2.85	3.69	5.15	5.07E-07	-0.84	1.13E-02	1	-2.30	9.16E-07	1	-1.46	5.28E-04	1
hsa-miR-21	9.26	8.86	9.75	6.29E-03	0.39	2.12E-01	0	-0.49	2.41E-02	1	-0.89	4.39E-03	1
hsa-miR-210	4.53	3.97	6.56	1.07E-07	0.56	9.02E-03	1	-2.03	1.87E-05	1	-2.59	5.51E-06	1
hsa-miR-214	6.14	4.81	6.10	1.21E-04	1.32	3.61E-04	1	0.04	8.67E-01	0	-1.28	3.35E-04	1
hsa-miR-216	5.97	7.25	2.01	1.86E-10	-1.27	1.11E-02	1	3.97	2.97E-07	1	5.24	1.40E-09	1
hsa-miR-217	6.77	8.02	2.42	2.77E-10	-1.25	9.44E-03	1	4.35	3.68E-07	1	5.60	8.83E-09	1
hsa-miR-221	5.49	5.18	6.45	1.69E-06	0.31	4.08E-02	0	-0.96	9.55E-05	1	-1.27	2.95E-05	1
hsa-miR-222	4.72	4.10	5.94	8.14E-07	0.62	1.38E-02	1	-1.22	6.91E-05	1	-1.84	1.29E-05	1
hsa-miR-223	5.70	4.64	6.81	8.24E-04	1.06	3.62E-02	1	-1.11	3.14E-02	0	-2.17	7.94E-04	1
hsa-miR-224	2.66	2.81	3.82	1.47E-06	-0.15	4.33E-01	0	-1.16	2.91E-06	1	-1.01	9.27E-05	1
hsa-miR-23a	7.15	7.07	7.62	6.46E-04	0.09	4.23E-01	0	-0.47	4.25E-03	1	-0.56	1.83E-03	1
hsa-miR-24	7.65	7.31	8.02	1.20E-04	0.34	1.14E-02	1	-0.37	1.07E-02	1	-0.72	2.72E-04	1
hsa-miR-25	5.19	5.58	5.64	3.16E-04	-0.40	2.83E-03	1	-0.46	5.50E-04	1	-0.06	5.28E-01	0
hsa-miR-26a	8.76	9.15	8.75	1.48E-02	-0.39	5.67E-03	1	0.02	9.06E-01	0	0.41	1.75E-02	1
hsa-miR-26b	6.66	7.62	6.93	1.96E-04	-0.96	1.80E-04	1	-0.28	1.57E-01	0	0.68	8.90E-04	1
hsa-miR-27a	6.90	7.03	7.34	3.70E-03	-0.12	3.33E-01	0	-0.44	5.02E-03	1	-0.31	1.35E-02	1
hsa-miR-27b	7.14	7.62	7.09	3.00E-03	-0.48	4.54E-03	1	0.06	6.74E-01	0	0.54	3.46E-03	1
hsa-miR-28	4.65	4.99	5.05	1.08E-02	-0.34	1.55E-02	1	-0.40	6.31E-03	1	-0.06	6.73E-01	0

hsa-miR-29a	7.29	7.71	7.58	1.37E-03	-0.42	9.41E-04	1	-0.29	8.00E-03	1	0.13	1.98E-01	0
hsa-miR-29b	6.09	6.73	6.43	1.03E-02	-0.64	2.59E-03	1	-0.33	8.98E-02	0	0.31	9.90E-02	0
hsa-miR-29c	7.02	8.40	6.45	7.11E-07	-1.38	2.86E-04	1	0.58	2.51E-02	1	1.96	1.03E-06	1
hsa-miR-30a-3p	3.55	4.27	2.62	3.98E-08	-0.72	4.32E-03	1	0.93	9.37E-05	1	1.65	8.25E-09	1
hsa-miR-30a-5p	7.22	7.77	6.64	1.15E-06	-0.55	4.54E-03	1	0.58	1.17E-03	1	1.13	1.16E-06	1
hsa-miR-30b	6.27	7.00	5.69	2.84E-07	-0.73	1.42E-03	1	0.58	1.06E-03	1	1.31	3.87E-07	1
hsa-miR-30c	6.20	6.93	5.58	2.29E-07	-0.73	1.56E-03	1	0.62	7.64E-04	1	1.35	2.95E-07	1
hsa-miR-30d	6.65	7.24	6.25	4.37E-06	-0.59	4.66E-04	1	0.40	1.01E-02	1	0.99	1.61E-05	1
hsa-miR-30e-3p	2.77	3.77	2.26	1.07E-05	-1.01	3.30E-03	1	0.51	3.77E-02	0	1.51	1.74E-06	1
hsa-miR-30e-5p	6.57	7.22	6.22	2.68E-07	-0.65	5.92E-04	1	0.36	6.79E-03	1	1.00	9.08E-08	1
hsa-miR-31	5.65	4.08	6.66	8.86E-03	1.57	1.51E-03	1	-1.01	2.21E-01	0	-2.58	9.27E-03	1
hsa-miR-331	2.63	2.25	3.46	1.48E-04	0.38	1.29E-01	0	-0.83	2.06E-03	1	-1.22	3.35E-04	1
hsa-miR-335	5.13	6.35	4.92	3.98E-04	-1.21	2.37E-03	1	0.21	4.89E-01	0	1.42	2.48E-04	1
hsa-miR-365	2.43	3.61	2.20	7.58E-06	-1.18	8.46E-04	1	0.23	1.33E-01	0	1.41	4.70E-05	1
hsa-miR-368	5.16	5.71	4.38	1.16E-06	-0.55	7.65E-03	1	0.78	5.11E-04	1	1.33	2.60E-06	1
hsa-miR-374	2.71	3.99	3.11	1.34E-03	-1.28	1.96E-03	1	-0.40	1.03E-01	0	0.88	1.20E-02	1
hsa-miR-375	6.51	7.37	4.68	4.82E-05	-0.86	4.56E-02	0	1.83	2.56E-03	1	2.69	1.15E-04	1
hsa-miR-376a	3.97	4.79	3.70	1.42E-04	-0.82	2.67E-03	1	0.27	2.03E-01	0	1.09	8.06E-05	1
hsa-miR-377	3.21	3.50	2.70	3.28E-03	-0.29	1.83E-01	0	0.51	2.95E-02	1	0.81	2.03E-03	1
hsa-miR-379	4.16	4.11	3.50	5.83E-04	0.05	6.63E-01	0	0.66	1.19E-03	1	0.61	6.13E-03	1
hsa-miR-429	4.14	5.29	4.68	1.94E-03	-1.16	6.86E-04	1	-0.54	7.15E-02	0	0.62	2.23E-02	1
hsa-miR-93	5.07	4.99	5.90	3.64E-05	0.08	6.36E-01	0	-0.83	2.61E-04	1	-0.90	2.34E-04	1
hsa-miR-95	2.73	4.05	3.22	1.91E-03	-1.32	1.71E-04	1	-0.49	1.32E-01	0	0.83	2.08E-02	1
hsa-miR-96	2.99	4.85	3.09	2.27E-06	-1.86	1.90E-04	1	-0.10	6.74E-01	0	1.76	1.36E-06	1
hsa-miR-98	4.16	5.22	4.56	3.32E-03	-1.06	9.57E-04	1	-0.40	9.13E-02	0	0.66	4.25E-02	0
hsa-miR-99a	6.71	5.54	6.23	2.73E-03	1.18	1.21E-04	1	0.49	1.01E-01	0	-0.69	4.14E-02	0
hsa-miR-99b	4.68	4.29	4.91	1.23E-02	0.39	5.10E-02	0	-0.24	1.74E-01	0	-0.62	1.14E-02	1
hsa-miR-452	2.52	2.73	3.44	1.61E-05	-0.21	2.11E-01	0	-0.91	8.82E-05	1	-0.70	1.69E-04	1
hsa-miR-494	6.96	7.22	5.14	5.26E-03	-0.26	7.20E-01	0	1.82	9.59E-03	1	2.09	3.98E-03	1
hsa-miR-497	5.29	4.17	4.83	7.94E-05	1.12	1.31E-04	1	0.46	2.37E-02	1	-0.66	2.60E-03	1
ambi-miR-7105	2.37	2.68	3.03	2.02E-05	-0.30	2.75E-02	1	-0.66	1.53E-05	1	-0.35	5.31E-03	1

* Significant differential expression is indicated by a Flag = 1

EXAMPLE 5:**COMPARISON OF NORMAL VS PDAC VS CHRONIC
PANCREATITIS TISSUE SAMPLES**

Because some of the miRNA expression changes identified above may in fact
 5 be related to non-neoplastic processes, the inventors added to our analysis miRNA
 expression data from a control set consisting of six chronic pancreatitis tissue
 samples. Hierarchical clustering analysis showed that miRNA expression profiles
 from chronic pancreatitis samples are in-between the normal and PDAC profiles and
 are more similar overall to expression profiles from normal pancreas than to
 10 expression profiles from PDAC. Pair comparison of Pearson correlation values,
 calculated using mean normalized data for all the miRNAs, confirmed that global
 miRNA expression levels in chronic pancreatitis tissues are intermediate amid those
 in the normal and PDAC tissues (Table 7). Consistent with this observation, 45 out of
 the 52 miRNAs differentially expressed between PDAC and chronic tissue samples
 15 (Table 6, Flag (Ch vs Ca)=1) were also deregulated in PDAC respective to normal
 tissues (FIG. 4A, top). All of these miRNAs had expression levels in chronic samples
 that were in-between those of the normal and PDAC expression levels.

Table 7. Paired Pearson Correlation Values.

	Normal	Chronic	Cancer	Cell Line
Normal	1	0.96	0.93	0.78
Chronic	0.96	1	0.95	0.79
Cancer	0.93	0.95	1	0.84
Cell Line	0.78	0.79	0.84	1

20 Ninety-four (94) miRNAs were found differentially expressed at a significant
 level between any 2 of the 3 tissue types (Table 6). Among the 68 miRNA
 differentially expressed in chronic samples versus normal samples (Table 6, Flag (Ch
 vs N)=1), 61 were also deregulated in PDAC versus normal pancreas (FIG. 4A,
 bottom). These miRNAs whose expression is affected in both PDAC and chronic
 25 diseased tissues are more likely to reflect the desmoplastic reaction of the tumor
 rather than changes specific to PDAC. Nonetheless, Principal Component Analysis
 (PCA) using the 94 miRNAs identified above showed a perfect segregation of the

PDAC samples away from the normal pancreas and chronic disease groups showing that miRNA expression classifies pancreatic tissues (FIG. 4B).

EXAMPLE 6:

MIRNA BIOMARKERS FOR PANCREATIC DISEASES

5 To identify the best miRNA markers for PDAC, the inventors selected those most differentially expressed among the three tissue types using stringent parameters: $|\Delta h| > 1.6$ (5-fold) and $p\text{-value} < 0.0001$ between at least 2 sample types (FIG. 5). Using this subset of 20 miRNAs, a clear discrimination between the tissue types could be achieved. For example, expression of miR-29c, -96, -143, -145, -148b
10 and -150 were mis-regulated in both chronic and cancer samples while miR-196a, -196b, -203, -210, -222, -216, -217 and -375 were mis-regulated only in PDAC samples. These data indicate that expression levels of a few miRNAs can be used to classify normal, chronic pancreatitis, and PDAC tissues and discriminate between neoplastic and non-neoplastic processes in PDAC.

EXAMPLE 7:

MIRNA EXPRESSION IN PANCREATIC CARCINOMA CELL LINES

Currently, pancreatic carcinoma cell lines represent the best available cell model systems for in vitro analyses of miRNA function. Therefore, the same array profiling strategy was deployed to characterize miRNA expression in six pancreatic
20 primary ductal adenocarcinoma cell lines, IMIMPC2, PT45, PL45, SKPC1, PancTu1, and PaCa44. To compare miRNA expression profiles in cell lines and primary tissues, the inventors normalized miRNA array data from the cell lines together with the 19 tissue set (Table 4).

Hierarchical clustering analysis on the global miRNA population as well as
25 clustering and principal component analyses (FIG. 6) on the differentially expressed miRNAs showed a clear segregation of the cell line samples away from the primary tissues. This divergence resulted mainly from the lack of detectable expression of ~60 miRNAs in cancer cell line samples relative to tissue samples, including seven miRNAs from our list of top 20 differentially expressed miRNAs in PDAC (miR-143,
30 -145, -150, -216, -217, -223 and -375; FIG. 5). Array data indicate that only 140 miRNAs were detected in the cancer cell lines, and each of them was also expressed

in pancreatic tissues (see % of samples with miRNA detected above threshold value in Table 4).

Overall, the mean miRNA expression levels in cancer cell lines correlated better with PDAC than with normal or chronic tissue (Pearson correlation values of 0.84, 0.78 and 0.79 respectively; Table 7). Furthermore, 12 out the top 20 miRNAs differentially expressed in PDAC had expression levels in the cell lines that were very similar to those in PDAC. Thus, miRNA expression profiles in these cancer cell lines more closely resemble those from PDAC primary tumors than those from normal pancreatic tissues.

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EXAMPLE 8:

IDENTIFICATION OF MIRNA BIOMARKERS OVER-EXPRESSED IN PDAC AND CANCER CELL LINES

Consistent with the differences described in Example 7, 87 miRNAs were identified as differentially expressed between PDAC and the cancer cell lines, and 108 were differentially expressed between normal pancreas and the cancer cell lines (Table 8A, 8B, and 8C, Flag (Ca vs CL)=1 or Flag (N vs CL) =1). Strikingly, one miRNA, miR-205, was highly over-expressed by more than 600-fold in cell lines versus normal tissue and was also up-regulated in 5 out of 8 PDAC tissues relative to chronic or normal tissues (Table 3). This observation prompted us to look for other miRNAs highly expressed in cell lines and up-regulated in PDAC that could have escaped our initial stringent screening because of a high p-value or low Δh (Example 6). By this approach, the inventors identified five additional miRNAs: miR-18a, -31, -93, -221, and -224 (FIG. 7). These six miRNAs (FIG. 7) are over-expressed in neoplastic ductal cells both in vivo and ex vivo, and therefore, represent additional potential biomarkers for PDAC.

Table 8A. miRNAs Differentially Expressed Between Normal Pancreas (N), Chronic Pancreatitis (Ch), PDAC (Ca), and Pancreatic Cancer Cell lines (CL)

miRNA	Mean Ch	Mean N	Mean Ca	Mean CL	p-value ANOVA
hsa-let-7b	8.78	9.06	8.53	7.96	8.56E-04
hsa-let-7c	8.74	9.18	8.60	8.08	1.01E-03
hsa-let-7d	7.85	8.68	8.19	8.01	3.71E-03
hsa-let-7e	6.19	6.98	6.75	6.46	8.94E-03
hsa-let-7f	7.51	8.51	7.94	7.36	8.57E-04
hsa-let-7g	7.01	7.52	7.31	6.45	8.72E-06
hsa-let-7i	7.12	6.31	7.49	7.96	1.21E-03
hsa-miR-1	2.84	2.19	3.23	0.78	5.65E-03
hsa-miR-100	6.44	5.16	6.34	7.11	1.35E-05
hsa-miR-101	4.33	4.87	4.49	2.48	3.47E-10
hsa-miR-103	6.02	5.86	6.72	6.80	3.86E-05
hsa-miR-106a	6.10	6.30	6.74	7.91	1.34E-08
hsa-miR-106b	5.02	4.98	5.65	6.02	3.88E-08
hsa-miR-107	6.10	5.82	6.76	6.83	2.28E-05
hsa-miR-10a	5.70	4.92	6.23	5.87	5.54E-04
hsa-miR-10b	4.96	4.54	5.24	3.97	2.20E-04
hsa-miR-125b	7.37	5.96	6.93	6.06	4.23E-05
hsa-miR-126	7.54	7.12	7.41	3.77	2.53E-11
hsa-miR-126-AS	3.27	3.91	3.55	0.90	2.08E-06
hsa-miR-128a	2.23	2.16	2.77	3.50	1.53E-06
hsa-miR-130b	4.93	6.27	3.84	4.98	4.01E-08
hsa-miR-132	3.92	3.06	4.09	2.21	1.06E-05
hsa-miR-140	3.63	3.24	4.08	1.77	1.57E-09
hsa-miR-141	6.65	7.50	6.00	6.34	1.06E-05
hsa-miR-142-3p	2.76	2.71	3.68	0.87	3.52E-07
hsa-miR-143	7.52	6.02	7.96	0.49	0.00E+00
hsa-miR-145	7.82	6.32	8.15	0.65	0.00E+00
hsa-miR-146a	4.87	3.85	5.93	3.13	1.24E-05
hsa-miR-148a	7.14	8.57	5.27	2.55	1.91E-10
hsa-miR-148b	2.97	5.11	2.82	2.88	1.82E-06
hsa-miR-150	3.68	1.73	4.38	1.19	1.49E-06
hsa-miR-151	3.86	4.02	4.00	4.62	3.84E-05
hsa-miR-152	5.05	4.75	5.15	2.90	2.40E-08
hsa-miR-153	2.47	3.23	2.73	1.37	6.95E-04
hsa-miR-154	2.92	3.27	2.07	0.63	2.49E-07
hsa-miR-155	4.22	3.25	5.59	4.97	2.75E-03
hsa-miR-15a	6.19	6.14	6.47	5.60	1.48E-04
hsa-miR-15b	4.92	5.17	5.77	7.63	6.94E-11
hsa-miR-17-3p	2.13	2.31	2.43	3.33	1.60E-04
hsa-miR-17-5p	6.04	6.15	6.66	7.86	4.51E-08
hsa-miR-18a	3.17	2.58	4.26	5.14	3.68E-07
hsa-miR-181a	5.38	5.00	5.76	6.23	4.65E-04
hsa-miR-181b	4.42	4.35	5.05	5.99	1.54E-05
hsa-miR-182	4.16	5.39	4.57	5.08	5.77E-04
hsa-miR-183	1.94	2.14	1.57	3.23	3.96E-04
hsa-miR-186	3.04	3.69	3.39	2.62	1.02E-03
hsa-miR-192	6.07	7.13	6.63	2.23	5.47E-11
hsa-miR-193a	2.60	2.20	2.33	3.09	1.52E-03

hsa-miR-194	5.95	6.63	7.13	2.27	9.00E-11
hsa-miR-195	6.72	6.12	6.49	3.49	1.05E-12
hsa-miR-196a	1.41	1.13	3.77	2.85	1.00E-05
hsa-miR-196b	1.04	0.57	3.24	2.35	3.79E-04
hsa-miR-197	2.07	1.72	2.11	3.74	2.46E-05
hsa-miR-199a	6.51	5.35	6.35	0.56	0.00E+00
hsa-miR-199a-AS	7.33	6.43	7.06	0.71	0.00E+00
hsa-miR-199b	4.79	4.36	4.58	0.73	7.77E-16
hsa-miR-20a	5.52	5.64	5.99	6.93	4.27E-06
hsa-miR-200a	5.61	6.57	5.52	5.63	1.38E-03
hsa-miR-200b	6.43	7.50	6.72	7.10	1.26E-03
hsa-miR-200c	7.60	8.59	7.28	8.46	3.51E-08
hsa-miR-203	2.66	3.50	5.19	2.68	2.06E-04
hsa-miR-205	1.44	0.90	3.12	7.35	3.47E-06
hsa-miR-21	9.18	8.71	9.80	9.77	5.27E-04
hsa-miR-210	4.43	3.79	6.61	4.71	2.38E-08
hsa-miR-214	6.06	4.65	6.14	1.91	2.52E-13
hsa-miR-215	2.54	4.33	3.91	0.96	3.13E-05
hsa-miR-216	5.90	7.09	1.64	1.05	4.56E-13
hsa-miR-217	6.70	7.86	2.19	1.27	3.81E-13
hsa-miR-218	4.06	3.54	4.10	2.24	4.34E-07
hsa-miR-22	7.07	6.79	7.25	5.59	2.00E-07
hsa-miR-221	5.41	5.02	6.50	7.90	1.55E-11
hsa-miR-222	4.63	3.92	5.99	7.22	3.43E-11
hsa-miR-223	5.62	4.47	6.86	1.36	1.33E-10
hsa-miR-224	2.44	2.56	3.83	4.20	1.51E-03
hsa-miR-23a	7.08	6.91	7.67	7.95	1.62E-06
hsa-miR-23b	7.21	7.16	7.62	7.74	2.71E-03
hsa-miR-24	7.58	7.15	8.07	7.26	6.80E-06
hsa-miR-25	5.10	5.42	5.69	5.66	2.18E-04
hsa-miR-26a	8.69	9.00	8.80	7.40	2.29E-08
hsa-miR-26b	6.58	7.46	6.98	5.28	1.94E-08
hsa-miR-27a	6.83	6.87	7.39	7.30	5.46E-04
hsa-miR-27b	7.07	7.47	7.13	6.74	2.55E-02
hsa-miR-28	4.56	4.82	5.08	4.95	9.11E-03
hsa-miR-29c	6.95	8.25	6.49	4.60	1.48E-10
hsa-miR-301	1.77	1.95	2.64	3.27	1.91E-06
hsa-miR-30a-3p	3.42	4.10	2.51	3.87	1.50E-04
hsa-miR-30a-5p	7.15	7.61	6.69	6.92	1.07E-03
hsa-miR-30b	6.20	6.84	5.74	5.37	2.31E-07
hsa-miR-30c	6.13	6.77	5.63	6.30	1.71E-04
hsa-miR-30d	6.58	7.08	6.29	6.41	6.28E-04
hsa-miR-30e-3p	2.54	3.58	2.06	3.04	1.91E-04
hsa-miR-30e-5p	6.50	7.06	6.26	5.88	9.81E-05
hsa-miR-320	5.80	5.70	6.00	6.49	2.23E-03
hsa-miR-324-3p	2.47	1.44	2.58	3.04	3.63E-06
hsa-miR-331	2.40	1.91	3.45	3.87	1.48E-06
hsa-miR-335	5.05	6.19	4.96	3.37	3.25E-04
hsa-miR-338	4.01	4.82	3.97	0.96	8.80E-07
hsa-miR-339	2.39	2.43	2.33	3.47	1.37E-05
hsa-miR-342	5.88	6.07	6.15	5.24	2.21E-04
hsa-miR-34a	5.56	5.29	5.87	3.31	1.16E-06

hsa-miR-34b	3.06	3.48	3.70	1.95	3.79E-06
hsa-miR-361	4.39	4.45	4.76	5.22	1.48E-04
hsa-miR-365	2.16	3.41	1.97	2.78	6.50E-06
hsa-miR-368	5.08	5.56	4.41	0.71	0.00E+00
hsa-miR-374	2.48	3.80	3.06	1.58	4.81E-06
hsa-miR-375	6.43	7.21	4.70	0.85	1.41E-11
hsa-miR-376a	3.86	4.63	3.70	0.82	6.59E-13
hsa-miR-377	3.05	3.30	2.59	0.85	9.82E-07
hsa-miR-379	4.06	3.93	3.49	2.02	6.22E-09
hsa-miR-381	2.31	2.08	1.39	0.96	1.97E-07
hsa-miR-382	2.96	3.07	3.04	1.00	7.09E-08
hsa-miR-422a	1.89	2.60	2.77	3.54	3.60E-03
hsa-miR-422b	3.41	3.43	4.13	4.26	1.47E-02
hsa-miR-423	3.51	3.05	3.79	5.07	2.76E-07
hsa-miR-424	3.07	3.66	3.91	1.56	4.57E-05
hsa-miR-429	4.03	5.13	4.71	4.42	2.57E-03
hsa-miR-92	4.80	4.82	4.92	6.35	1.72E-08
hsa-miR-93	4.99	4.83	5.94	6.78	1.26E-09
hsa-miR-95	2.51	3.87	3.17	1.39	2.22E-06
hsa-miR-96	2.79	4.69	3.04	3.10	9.15E-06
hsa-miR-98	4.05	5.05	4.58	4.22	1.33E-02
hsa-miR-99a	6.64	5.38	6.27	5.97	1.29E-02
hsa-miR-99b	4.59	4.12	4.95	5.22	5.07E-03
ambi-miR-7029	5.26	5.58	5.30	1.00	7.87E-09
hsa-miR-193b	3.17	3.00	3.11	5.08	2.48E-06
ambi-miR-7058	3.97	4.03	4.13	4.85	3.23E-04
hsa-miR-452	2.27	2.48	3.42	2.41	9.61E-04
hsa-miR-432	3.36	3.09	3.11	2.21	3.11E-05
hsa-miR-494	6.89	7.07	5.17	4.50	2.72E-04
hsa-miR-497	5.20	3.99	4.86	1.94	3.17E-12
ambi-miR-7105	2.10	2.42	2.99	2.78	2.38E-04

Table 8B. miRNAs Differentially Expressed Between Normal Pancreas (N), Chronic Pancreatitis (Ch), PDAC (Ca), and Pancreatic Cancer Cell lines (CL)

miRNA	Ch vs N			Ch vs Ca			Ch vs CL		
	Δh	p-value	Flag	Δh	p-value	Flag	Δh	p-value	Flag
hsa-let-7b	-0.29	1.41E-01	0	0.24	1.32E-01	0	0.81	1.50E-02	1
hsa-let-7c	-0.44	1.64E-02	1	0.14	4.00E-01	0	0.66	2.62E-02	1
hsa-let-7d	-0.83	5.50E-04	1	-0.35	9.89E-02	0	-0.16	3.63E-01	0
hsa-let-7e	-0.79	4.08E-03	1	-0.55	4.46E-03	1	-0.27	2.04E-01	0
hsa-let-7f	-1.00	2.23E-04	1	-0.43	8.60E-02	0	0.15	5.20E-01	0
hsa-let-7g	-0.51	1.48E-03	1	-0.30	7.94E-02	0	0.57	1.94E-03	1
hsa-let-7i	0.80	1.97E-03	1	-0.38	4.30E-02	0	-0.84	1.01E-01	0
hsa-miR-1	0.65	2.56E-01	0	-0.39	6.41E-01	0	2.06	2.40E-03	1
hsa-miR-100	1.28	6.57E-05	1	0.10	6.78E-01	0	-0.67	3.71E-02	1
hsa-miR-101	-0.54	1.90E-03	1	-0.16	4.62E-01	0	1.84	8.66E-07	1
hsa-miR-103	0.16	2.75E-01	0	-0.70	3.00E-04	1	-0.78	4.04E-03	1
hsa-miR-106a	-0.20	1.21E-01	0	-0.64	7.38E-05	1	-1.81	2.39E-05	1
hsa-miR-106b	0.04	6.93E-01	0	-0.62	5.74E-04	1	-1.00	1.77E-06	1
hsa-miR-107	0.28	6.53E-02	0	-0.66	1.89E-04	1	-0.73	7.38E-03	1
hsa-miR-10a	0.77	4.48E-05	1	-0.54	1.26E-02	1	-0.17	5.96E-01	0
hsa-miR-10b	0.42	7.48E-02	0	-0.29	2.02E-01	0	0.98	1.11E-02	1
hsa-miR-125b	1.41	2.37E-06	1	0.44	5.93E-02	0	1.31	1.46E-03	1
hsa-miR-126	0.43	1.33E-02	1	0.14	3.66E-01	0	3.77	3.35E-06	1
hsa-miR-126-AS	-0.64	1.62E-01	0	-0.28	5.55E-01	0	2.37	4.29E-04	1
hsa-miR-128a	0.08	7.15E-01	0	-0.53	8.44E-04	1	-1.27	2.59E-05	1
hsa-miR-130b	-1.34	2.00E-03	1	1.09	9.55E-04	1	-0.05	8.74E-01	0
hsa-miR-132	0.86	7.20E-02	0	-0.17	5.05E-01	0	1.71	1.73E-04	1
hsa-miR-140	0.40	8.93E-02	0	-0.45	5.63E-02	0	1.86	1.20E-05	1
hsa-miR-141	-0.85	4.45E-03	1	0.65	2.27E-02	0	0.31	2.03E-01	0
hsa-miR-142-3p	0.05	9.27E-01	0	-0.92	1.24E-02	1	1.89	8.70E-05	1
hsa-miR-143	1.50	6.47E-06	1	-0.44	1.17E-01	0	7.02	1.97E-13	1
hsa-miR-145	1.50	6.33E-05	1	-0.33	3.52E-01	0	7.17	2.20E-11	1
hsa-miR-146a	1.03	1.80E-02	1	-1.06	5.94E-03	1	1.75	1.51E-02	1
hsa-miR-148a	-1.43	3.09E-03	1	1.86	3.58E-05	1	4.59	2.84E-05	1
hsa-miR-148b	-2.14	2.19E-04	1	0.15	6.41E-01	0	0.09	7.82E-01	0
hsa-miR-150	1.95	2.07E-02	1	-0.70	1.89E-01	0	2.49	2.35E-03	1
hsa-miR-151	-0.16	2.99E-01	0	-0.14	2.25E-01	0	-0.76	6.36E-04	1
hsa-miR-152	0.30	1.80E-01	0	-0.10	6.08E-01	0	2.16	7.33E-05	1
hsa-miR-153	-0.75	5.97E-02	0	-0.25	5.55E-01	0	1.10	1.50E-02	1
hsa-miR-154	-0.35	3.23E-01	0	0.85	2.22E-02	0	2.29	1.01E-04	1
hsa-miR-155	0.96	9.15E-02	0	-1.38	1.24E-03	1	-0.76	2.75E-01	0
hsa-miR-15a	0.05	6.09E-01	0	-0.28	7.62E-02	0	0.59	8.98E-03	1
hsa-miR-15b	-0.25	2.67E-01	0	-0.85	9.62E-04	1	-2.71	2.05E-07	1
hsa-miR-17-3p	-0.18	3.80E-01	0	-0.30	1.57E-01	0	-1.20	1.45E-03	1
hsa-miR-17-5p	-0.11	4.37E-01	0	-0.63	3.90E-04	1	-1.82	3.81E-05	1
hsa-miR-18a	0.59	3.25E-02	0	-1.09	1.50E-03	1	-1.97	2.84E-04	1
hsa-miR-181a	0.38	1.19E-01	0	-0.39	1.41E-01	0	-0.86	9.46E-03	1
hsa-miR-181b	0.06	7.66E-01	0	-0.63	7.94E-03	1	-1.57	9.14E-04	1
hsa-miR-182	-1.23	1.25E-03	1	-0.41	1.33E-01	0	-0.92	7.06E-03	1
hsa-miR-183	-0.20	4.93E-01	0	0.37	3.61E-01	0	-1.29	1.11E-03	1
hsa-miR-186	-0.65	1.10E-02	1	-0.35	8.00E-02	0	0.42	1.62E-01	0
hsa-miR-192	-1.06	1.99E-04	1	-0.56	2.53E-01	0	3.85	2.56E-10	1

hsa-miR-193a	0.40	3.78E-02	0	0.27	1.69E-01	0	-0.49	4.00E-02	0
hsa-miR-194	-0.68	1.54E-03	1	-1.18	2.92E-02	0	3.68	5.59E-10	1
hsa-miR-195	0.60	1.21E-02	1	0.24	1.78E-01	0	3.24	1.92E-08	1
hsa-miR-196a	0.28	5.14E-01	0	-2.36	2.01E-05	1	-1.43	2.89E-02	1
hsa-miR-196b	0.47	3.27E-01	0	-2.20	1.45E-04	1	-1.31	1.14E-01	0
hsa-miR-197	0.35	8.86E-02	0	-0.04	8.75E-01	0	-1.67	2.02E-03	1
hsa-miR-199a	1.16	3.52E-04	1	0.16	3.37E-01	0	5.95	7.62E-10	1
hsa-miR-199a-AS	0.90	1.34E-04	1	0.27	1.07E-02	1	6.62	1.00E-10	1
hsa-miR-199b	0.43	4.60E-02	0	0.21	2.72E-01	0	4.06	6.93E-09	1
hsa-miR-20a	-0.12	4.09E-01	0	-0.47	3.29E-03	1	-1.41	3.99E-04	1
hsa-miR-200a	-0.96	1.26E-03	1	0.09	7.33E-01	0	-0.02	9.46E-01	0
hsa-miR-200b	-1.07	6.18E-04	1	-0.30	2.57E-01	0	-0.67	2.06E-02	1
hsa-miR-200c	-0.99	4.17E-04	1	0.32	9.97E-02	0	-0.86	4.32E-04	1
hsa-miR-203	-0.84	1.82E-02	1	-2.54	6.14E-07	1	-0.03	9.74E-01	0
hsa-miR-205	0.53	2.66E-01	0	-1.69	1.15E-01	0	-5.91	2.04E-06	1
hsa-miR-21	0.48	1.49E-01	0	-0.62	1.03E-02	1	-0.59	2.17E-02	1
hsa-miR-210	0.65	7.35E-03	1	-2.17	9.55E-06	1	-0.28	3.79E-01	0
hsa-miR-214	1.41	5.77E-04	1	-0.08	7.67E-01	0	4.15	1.56E-08	1
hsa-miR-215	-1.79	2.60E-04	1	-1.37	5.99E-02	0	1.58	6.37E-04	1
hsa-miR-216	-1.19	1.35E-02	1	4.25	7.01E-07	1	4.85	3.16E-07	1
hsa-miR-217	-1.17	1.18E-02	1	4.51	1.71E-06	1	5.42	1.96E-08	1
hsa-miR-218	0.52	2.03E-02	1	-0.04	8.61E-01	0	1.81	3.05E-05	1
hsa-miR-22	0.28	5.62E-02	0	-0.18	1.87E-01	0	1.48	3.17E-04	1
hsa-miR-221	0.39	3.59E-02	0	-1.09	5.77E-05	1	-2.48	2.61E-07	1
hsa-miR-222	0.71	1.53E-02	1	-1.36	5.16E-05	1	-2.58	1.34E-07	1
hsa-miR-223	1.15	3.12E-02	0	-1.24	2.21E-02	0	4.27	6.85E-07	1
hsa-miR-224	-0.12	5.49E-01	0	-1.39	3.30E-07	1	-1.76	2.14E-02	1
hsa-miR-23a	0.17	2.54E-01	0	-0.59	2.24E-03	1	-0.87	8.03E-05	1
hsa-miR-23b	0.05	7.24E-01	0	-0.41	3.04E-02	0	-0.53	1.29E-03	1
hsa-miR-24	0.42	9.32E-03	1	-0.50	3.00E-03	1	0.31	5.64E-02	0
hsa-miR-25	-0.32	2.01E-02	1	-0.58	1.11E-04	1	-0.56	2.52E-03	1
hsa-miR-26a	-0.31	4.14E-02	0	-0.11	4.83E-01	0	1.29	1.87E-05	1
hsa-miR-26b	-0.88	4.21E-04	1	-0.40	6.53E-02	0	1.30	4.78E-04	1
hsa-miR-27a	-0.04	7.85E-01	0	-0.56	2.68E-03	1	-0.47	1.12E-02	1
hsa-miR-27b	-0.40	1.64E-02	1	-0.06	6.72E-01	0	0.33	1.99E-01	0
hsa-miR-28	-0.26	8.53E-02	0	-0.52	2.47E-03	1	-0.39	1.09E-02	1
hsa-miR-29c	-1.30	2.24E-04	1	0.45	7.08E-02	0	2.35	1.68E-05	1
hsa-miR-301	-0.17	3.45E-01	0	-0.86	2.11E-04	1	-1.50	1.82E-04	1
hsa-miR-30a-3p	-0.68	4.81E-03	1	0.91	2.27E-04	1	-0.45	3.32E-01	0
hsa-miR-30a-5p	-0.47	6.63E-03	1	0.46	5.87E-03	1	0.23	3.88E-01	0
hsa-miR-30b	-0.65	2.61E-03	1	0.46	7.43E-03	1	0.83	1.81E-03	1
hsa-miR-30c	-0.65	1.75E-03	1	0.50	3.89E-03	1	-0.18	5.25E-01	0
hsa-miR-30d	-0.51	1.04E-03	1	0.28	6.70E-02	0	0.16	3.67E-01	0
hsa-miR-30e-3p	-1.05	4.39E-03	1	0.48	9.68E-02	0	-0.50	1.93E-01	0
hsa-miR-30e-5p	-0.57	9.20E-04	1	0.24	5.77E-02	0	0.62	4.20E-02	0
hsa-miR-320	0.10	4.74E-01	0	-0.20	2.52E-01	0	-0.69	5.77E-03	1
hsa-miR-324-3p	1.04	7.28E-04	1	-0.10	4.47E-01	0	-0.57	2.71E-02	1
hsa-miR-331	0.49	1.38E-01	0	-1.04	1.41E-03	1	-1.47	1.61E-04	1
hsa-miR-335	-1.14	3.22E-03	1	0.09	7.68E-01	0	1.68	3.19E-02	1
hsa-miR-338	-0.81	1.03E-03	1	0.04	9.09E-01	0	3.05	3.99E-04	1
hsa-miR-339	-0.03	8.52E-01	0	0.06	6.76E-01	0	-1.08	1.37E-03	1

hsa-miR-342	-0.19	1.06E-01	0	-0.27	9.69E-03	1	0.65	2.69E-02	1
hsa-miR-34a	0.27	3.14E-01	0	-0.31	1.46E-01	0	2.25	5.36E-04	1
hsa-miR-34b	-0.43	2.47E-01	0	-0.64	2.11E-03	1	1.10	3.01E-04	1
hsa-miR-361	-0.06	6.74E-01	0	-0.37	4.08E-02	0	-0.83	7.48E-05	1
hsa-miR-365	-1.26	9.64E-04	1	0.18	3.90E-01	0	-0.63	3.65E-03	1
hsa-miR-368	-0.48	2.87E-02	0	0.67	2.41E-03	1	4.37	4.17E-10	1
hsa-miR-374	-1.32	2.21E-03	1	-0.57	6.22E-02	0	0.90	6.73E-03	1
hsa-miR-375	-0.78	5.79E-02	0	1.73	4.49E-03	1	5.58	4.23E-08	1
hsa-miR-376a	-0.77	8.25E-03	1	0.16	4.96E-01	0	3.04	1.68E-07	1
hsa-miR-377	-0.25	3.33E-01	0	0.46	8.57E-02	0	2.20	2.28E-04	1
hsa-miR-379	0.13	3.93E-01	0	0.57	5.30E-03	1	2.04	2.56E-06	1
hsa-miR-381	0.23	3.56E-01	0	0.92	4.15E-05	1	1.35	1.03E-05	1
hsa-miR-382	-0.11	7.49E-01	0	-0.07	7.57E-01	0	1.96	5.44E-05	1
hsa-miR-422a	-0.71	1.05E-01	0	-0.88	4.70E-02	0	-1.65	4.83E-03	1
hsa-miR-422b	-0.02	9.53E-01	0	-0.72	6.64E-03	1	-0.85	2.94E-02	1
hsa-miR-423	0.47	1.23E-01	0	-0.28	2.76E-01	0	-1.55	1.13E-05	1
hsa-miR-424	-0.59	1.93E-01	0	-0.85	6.16E-03	1	1.51	1.58E-02	1
hsa-miR-429	-1.10	8.23E-04	1	-0.68	3.37E-02	0	-0.39	1.37E-01	0
hsa-miR-92	-0.02	8.95E-01	0	-0.12	3.21E-01	0	-1.55	3.42E-05	1
hsa-miR-93	0.16	4.03E-01	0	-0.95	1.11E-04	1	-1.80	2.50E-06	1
hsa-miR-95	-1.36	4.92E-04	1	-0.66	9.37E-02	0	1.12	1.69E-03	1
hsa-miR-96	-1.90	2.51E-04	1	-0.25	3.60E-01	0	-0.31	3.91E-01	0
hsa-miR-98	-1.00	1.86E-03	1	-0.53	4.71E-02	0	-0.16	5.25E-01	0
hsa-miR-99a	1.26	2.09E-04	1	0.37	2.34E-01	0	0.67	8.83E-02	0
hsa-miR-99b	0.47	4.28E-02	0	-0.36	7.55E-02	0	-0.63	6.85E-02	0
ambi-miR-7029	-0.31	6.21E-01	0	-0.04	9.43E-01	0	4.26	8.68E-06	1
hsa-miR-193b	0.17	4.09E-01	0	0.06	8.57E-01	0	-1.91	3.32E-05	1
ambi-miR-7058	-0.06	7.77E-01	0	-0.17	4.02E-01	0	-0.89	1.98E-03	1
hsa-miR-452	-0.21	3.49E-01	0	-1.15	5.38E-05	1	-0.13	7.43E-01	0
hsa-miR-432	0.27	1.65E-01	0	0.25	1.67E-01	0	1.16	2.25E-04	1
hsa-miR-494	-0.18	7.96E-01	0	1.71	1.18E-02	1	2.39	1.71E-03	1
hsa-miR-497	1.21	1.68E-04	1	0.34	9.57E-02	0	3.27	1.89E-07	1
ambi-miR-7105	-0.32	8.49E-02	0	-0.89	1.91E-05	1	-0.68	1.37E-02	1

Significant differential expression is indicated by a Flag = 1

Table 8C. miRNAs Differentially Expressed Between Normal Pancreas (N), Chronic Pancreatitis (Ch), PDAC (Ca), and Pancreatic Cancer Cell lines (CL)

miRNA	N vs Ca			N vs CL			Ca vs CL		
	Δh	p-value	Flag	Δh	p-value	Flag	Δh	p-value	Flag
hsa-let-7b	0.53	6.62E-03	1	1.10	5.35E-03	1	0.57	3.54E-02	0
hsa-let-7c	0.58	7.45E-03	1	1.10	3.20E-03	1	0.52	5.63E-02	0
hsa-let-7d	0.48	4.50E-02	0	0.67	5.25E-03	1	0.19	3.80E-01	0
hsa-let-7e	0.23	3.08E-01	0	0.52	8.49E-02	0	0.28	1.93E-01	0
hsa-let-7f	0.57	4.31E-02	0	1.15	1.43E-03	1	0.58	5.37E-02	0
hsa-let-7g	0.21	2.50E-01	0	1.08	7.91E-05	1	0.86	3.81E-04	1
hsa-let-7i	-1.18	8.05E-06	1	-1.65	9.36E-03	1	-0.47	2.60E-01	0
hsa-miR-1	-1.04	2.09E-01	0	1.41	8.60E-05	1	2.45	5.23E-03	1
hsa-miR-100	-1.18	9.86E-04	1	-1.95	1.11E-04	1	-0.77	2.69E-02	1
hsa-miR-101	0.38	1.13E-01	0	2.39	9.82E-08	1	2.01	1.36E-06	1
hsa-miR-103	-0.86	1.56E-04	1	-0.95	2.85E-03	1	-0.08	6.80E-01	0
hsa-miR-106a	-0.44	1.37E-03	1	-1.61	1.69E-04	1	-1.17	1.34E-04	1
hsa-miR-106b	-0.67	5.10E-04	1	-1.04	1.11E-06	1	-0.37	1.24E-02	1

hsa-miR-107	-0.94	2.95E-05	1	-1.02	2.40E-03	1	-0.08	7.09E-01	0
hsa-miR-10a	-1.31	3.92E-05	1	-0.95	2.24E-02	1	0.37	2.62E-01	0
hsa-miR-10b	-0.70	2.30E-03	1	0.57	9.28E-02	0	1.27	5.34E-04	1
hsa-miR-125b	-0.97	8.80E-04	1	-0.10	7.62E-01	0	0.87	1.48E-02	1
hsa-miR-126	-0.29	5.67E-02	0	3.34	3.35E-05	1	3.63	2.76E-07	1
hsa-miR-126-AS	0.36	3.72E-01	0	3.01	1.23E-05	1	2.65	3.72E-05	1
hsa-miR-128a	-0.61	1.00E-02	1	-1.35	5.30E-04	1	-0.74	8.50E-04	1
hsa-miR-130b	2.43	1.13E-09	1	1.29	3.62E-04	1	-1.14	6.70E-05	1
hsa-miR-132	-1.03	9.27E-03	1	0.85	5.45E-02	0	1.88	1.39E-06	1
hsa-miR-140	-0.85	1.05E-03	1	1.46	4.84E-05	1	2.31	1.26E-07	1
hsa-miR-141	1.50	2.56E-05	1	1.16	3.50E-05	1	-0.34	1.33E-01	0
hsa-miR-142-3p	-0.97	2.74E-02	0	1.85	9.03E-04	1	2.81	1.20E-08	1
hsa-miR-143	-1.94	2.65E-05	1	5.53	1.52E-11	1	7.46	1.36E-12	1
hsa-miR-145	-1.83	3.22E-04	1	5.67	7.09E-10	1	7.50	3.98E-11	1
hsa-miR-146a	-2.09	1.35E-05	1	0.72	2.71E-01	0	2.81	1.14E-04	1
hsa-miR-148a	3.30	4.26E-09	1	6.02	5.64E-06	1	2.73	1.49E-04	1
hsa-miR-148b	2.29	2.74E-05	1	2.23	8.93E-05	1	-0.06	8.42E-01	0
hsa-miR-150	-2.65	6.12E-06	1	0.54	2.52E-01	0	3.19	7.12E-08	1
hsa-miR-151	0.02	8.75E-01	0	-0.60	3.14E-03	1	-0.61	1.91E-04	1
hsa-miR-152	-0.40	2.81E-02	0	1.85	4.01E-04	1	2.25	3.04E-06	1
hsa-miR-153	0.50	1.98E-01	0	1.86	4.81E-05	1	1.36	3.49E-03	1
hsa-miR-154	1.20	6.30E-04	1	2.64	6.56E-06	1	1.44	3.34E-04	1
hsa-miR-155	-2.34	3.56E-04	1	-1.72	5.94E-02	0	0.62	3.01E-01	0
hsa-miR-15a	-0.33	3.81E-02	0	0.53	1.65E-02	1	0.86	5.46E-04	1
hsa-miR-15b	-0.60	1.32E-02	1	-2.46	1.59E-06	1	-1.86	8.21E-07	1
hsa-miR-17-3p	-0.11	5.23E-01	0	-1.02	3.80E-03	1	-0.90	2.51E-03	1
hsa-miR-17-5p	-0.52	2.51E-03	1	-1.71	1.88E-04	1	-1.20	2.27E-04	1
hsa-miR-18a	-1.68	4.02E-05	1	-2.56	5.93E-05	1	-0.88	2.40E-02	1
hsa-miR-181a	-0.76	3.68E-03	1	-1.23	2.89E-04	1	-0.47	7.69E-02	0
hsa-miR-181b	-0.69	2.68E-03	1	-1.64	1.05E-03	1	-0.94	6.92E-03	1
hsa-miR-182	0.82	4.46E-03	1	0.31	2.27E-01	0	-0.51	5.09E-02	0
hsa-miR-183	0.57	1.66E-01	0	-1.09	1.01E-03	1	-1.66	6.66E-04	1
hsa-miR-186	0.30	1.01E-01	0	1.07	3.57E-03	1	0.77	6.10E-03	1
hsa-miR-192	0.51	3.35E-01	0	4.91	1.30E-11	1	4.40	4.92E-07	1
hsa-miR-193a	-0.13	5.21E-01	0	-0.89	3.35E-03	1	-0.76	4.66E-03	1
hsa-miR-194	-0.51	3.49E-01	0	4.36	1.84E-10	1	4.86	2.86E-07	1
hsa-miR-195	-0.36	1.24E-01	0	2.64	3.37E-06	1	3.00	9.57E-09	1
hsa-miR-196a	-2.64	3.99E-06	1	-1.72	1.39E-02	1	0.92	6.51E-02	0
hsa-miR-196b	-2.67	1.01E-05	1	-1.78	4.65E-02	0	0.89	1.84E-01	0
hsa-miR-197	-0.39	1.42E-01	0	-2.02	9.22E-04	1	-1.63	1.20E-03	1
hsa-miR-199a	-1.00	7.20E-05	1	4.79	3.95E-08	1	5.79	5.24E-12	1
hsa-miR-199a-AS	-0.63	4.67E-04	1	5.72	8.48E-09	1	6.35	1.10E-12	1
hsa-miR-199b	-0.22	1.56E-01	0	3.63	1.81E-08	1	3.85	9.95E-11	1
hsa-miR-20a	-0.36	1.60E-02	1	-1.29	1.53E-03	1	-0.94	1.82E-03	1
hsa-miR-200a	1.05	9.04E-04	1	0.95	1.35E-03	1	-0.11	6.83E-01	0
hsa-miR-200b	0.77	3.94E-03	1	0.40	5.26E-02	0	-0.37	1.36E-01	0
hsa-miR-200c	1.31	3.88E-06	1	0.12	2.97E-01	0	-1.19	2.66E-06	1
hsa-miR-203	-1.69	2.33E-04	1	0.82	3.61E-01	0	2.51	2.79E-03	1
hsa-miR-205	-2.22	7.67E-02	0	-6.44	1.42E-05	1	-4.23	2.34E-03	1
hsa-miR-21	-1.09	1.60E-03	1	-1.07	5.06E-03	1	0.03	8.91E-01	0
hsa-miR-210	-2.82	2.13E-06	1	-0.93	1.63E-02	1	1.90	1.80E-04	1
hsa-miR-214	-1.49	1.67E-04	1	2.73	1.64E-06	1	4.23	9.20E-10	1

hsa-miR-215	0.42	5.77E-01	0	3.37	4.18E-06	1	2.95	8.70E-04	1
hsa-miR-216	5.45	2.52E-08	1	6.04	2.98E-09	1	0.60	1.57E-01	0
hsa-miR-217	5.68	1.66E-07	1	6.59	1.50E-12	1	0.91	6.31E-02	0
hsa-miR-218	-0.56	4.59E-02	0	1.29	1.39E-03	1	1.85	2.29E-05	1
hsa-miR-22	-0.46	2.33E-03	1	1.20	2.59E-03	1	1.66	1.53E-05	1
hsa-miR-221	-1.48	1.18E-05	1	-2.88	4.44E-07	1	-1.40	3.25E-05	1
hsa-miR-222	-2.06	8.61E-06	1	-3.29	3.63E-07	1	-1.23	1.81E-04	1
hsa-miR-223	-2.39	4.27E-04	1	3.12	1.32E-05	1	5.50	1.99E-08	1
hsa-miR-224	-1.27	2.18E-05	1	-1.64	4.94E-02	0	-0.37	5.21E-01	0
hsa-miR-23a	-0.76	5.15E-04	1	-1.04	2.49E-05	1	-0.28	8.92E-02	0
hsa-miR-23b	-0.46	3.14E-02	0	-0.58	2.32E-03	1	-0.12	4.71E-01	0
hsa-miR-24	-0.92	7.49E-05	1	-0.11	5.14E-01	0	0.81	2.16E-04	1
hsa-miR-25	-0.26	2.80E-02	0	-0.24	1.31E-01	0	0.02	8.60E-01	0
hsa-miR-26a	0.20	2.61E-01	0	1.60	2.31E-05	1	1.39	8.09E-06	1
hsa-miR-26b	0.48	1.85E-02	1	2.18	7.78E-06	1	1.70	1.22E-05	1
hsa-miR-27a	-0.52	2.02E-03	1	-0.43	5.72E-03	1	0.09	5.26E-01	0
hsa-miR-27b	0.33	7.68E-02	0	0.72	2.45E-02	1	0.39	1.19E-01	0
hsa-miR-28	-0.26	1.43E-01	0	-0.12	4.52E-01	0	0.14	3.81E-01	0
hsa-miR-29c	1.75	5.23E-06	1	3.65	6.72E-07	1	1.89	1.85E-05	1
hsa-miR-301	-0.69	1.02E-03	1	-1.32	7.49E-04	1	-0.64	1.55E-02	1
hsa-miR-30a-3p	1.59	1.12E-07	1	0.23	6.25E-01	0	-1.36	3.12E-03	1
hsa-miR-30a-5p	0.93	2.08E-05	1	0.70	2.74E-02	1	-0.23	3.26E-01	0
hsa-miR-30b	1.11	4.45E-06	1	1.48	3.32E-05	1	0.37	4.73E-02	0
hsa-miR-30c	1.15	3.24E-06	1	0.47	1.32E-01	0	-0.68	1.33E-02	1
hsa-miR-30d	0.79	2.84E-04	1	0.67	6.02E-03	1	-0.12	5.33E-01	0
hsa-miR-30e-3p	1.53	1.57E-05	1	0.55	1.14E-01	0	-0.98	5.37E-03	1
hsa-miR-30e-5p	0.80	3.20E-06	1	1.18	2.06E-03	1	0.38	1.14E-01	0
hsa-miR-320	-0.30	1.13E-01	0	-0.79	4.19E-03	1	-0.49	3.52E-02	0
hsa-miR-324-3p	-1.14	1.09E-04	1	-1.60	3.30E-04	1	-0.46	4.05E-02	0
hsa-miR-331	-1.53	2.41E-04	1	-1.96	8.19E-05	1	-0.43	1.09E-01	0
hsa-miR-335	1.23	9.74E-04	1	2.82	3.36E-03	1	1.59	1.91E-02	1
hsa-miR-338	0.85	5.46E-02	0	3.86	1.78E-04	1	3.01	3.14E-04	1
hsa-miR-339	0.10	4.92E-01	0	-1.04	2.63E-03	1	-1.14	9.66E-05	1
hsa-miR-342	-0.08	4.44E-01	0	0.84	1.44E-02	1	0.92	1.16E-03	1
hsa-miR-34a	-0.58	3.89E-02	0	1.98	3.82E-03	1	2.56	3.43E-05	1
hsa-miR-34b	-0.21	4.92E-01	0	1.53	2.12E-03	1	1.74	5.33E-07	1
hsa-miR-361	-0.31	1.15E-01	0	-0.77	5.53E-04	1	-0.46	1.70E-02	1
hsa-miR-365	1.44	1.53E-04	1	0.63	2.26E-02	1	-0.81	7.95E-04	1
hsa-miR-368	1.15	2.52E-05	1	4.85	3.48E-10	1	3.70	3.89E-11	1
hsa-miR-374	0.75	4.31E-02	0	2.23	7.29E-05	1	1.48	2.34E-04	1
hsa-miR-375	2.51	3.16E-04	1	6.36	5.62E-09	1	3.85	3.08E-06	1
hsa-miR-376a	0.93	9.59E-04	1	3.81	2.09E-08	1	2.88	1.39E-08	1
hsa-miR-377	0.72	1.38E-02	1	2.45	2.09E-04	1	1.73	3.69E-04	1
hsa-miR-379	0.44	4.32E-02	0	1.91	2.83E-05	1	1.47	3.26E-05	1
hsa-miR-381	0.69	1.72E-03	1	1.12	2.40E-04	1	0.43	1.25E-03	1
hsa-miR-382	0.03	8.80E-01	0	2.07	4.91E-05	1	2.03	2.68E-07	1
hsa-miR-422a	-0.17	5.78E-01	0	-0.94	2.23E-02	1	-0.77	5.96E-02	0
hsa-miR-422b	-0.71	2.49E-02	0	-0.83	6.51E-02	0	-0.13	6.95E-01	0
hsa-miR-423	-0.75	1.56E-02	1	-2.02	3.00E-06	1	-1.27	3.02E-05	1
hsa-miR-424	-0.26	4.13E-01	0	2.10	6.06E-03	1	2.35	8.92E-05	1
hsa-miR-429	0.42	1.14E-01	0	0.71	1.00E-03	1	0.29	2.78E-01	0
hsa-miR-92	-0.10	4.21E-01	0	-1.53	1.21E-04	1	-1.42	8.10E-06	1

hsa-miR-93	-1.11	4.56E-05	1	-1.96	2.80E-06	1	-0.84	4.32E-04	1
hsa-miR-95	0.71	7.99E-02	0	2.48	1.94E-06	1	1.77	2.73E-04	1
hsa-miR-96	1.64	6.25E-06	1	1.59	4.07E-04	1	-0.06	8.20E-01	0
hsa-miR-98	0.47	1.51E-01	0	0.84	3.07E-02	1	0.37	2.44E-01	0
hsa-miR-99a	-0.90	1.70E-02	1	-0.60	1.58E-01	0	0.30	4.49E-01	0
hsa-miR-99b	-0.83	4.04E-03	1	-1.10	1.40E-02	1	-0.27	3.90E-01	0
ambi-miR-7029	0.27	5.70E-01	0	4.57	1.29E-07	1	4.30	1.02E-07	1
hsa-miR-193b	-0.11	7.67E-01	0	-2.08	1.63E-05	1	-1.97	1.50E-04	1
ambi-miR-7058	-0.10	5.18E-01	0	-0.82	7.83E-04	1	-0.72	7.04E-04	1
hsa-miR-452	-0.94	7.38E-06	1	0.07	8.60E-01	0	1.02	7.99E-03	1
hsa-miR-432	-0.01	9.38E-01	0	0.89	2.28E-03	1	0.90	5.65E-04	1
hsa-miR-494	1.89	5.80E-03	1	2.57	6.42E-04	1	0.68	1.60E-01	0
hsa-miR-497	-0.87	4.23E-04	1	2.06	2.01E-05	1	2.93	2.13E-08	1
ambi-miR-7105	-0.57	9.24E-04	1	-0.36	1.68E-01	0	0.21	2.83E-01	0

Significant differential expression is indicated by a Flag = 1

EXAMPLE 9:**26 MIRNA BIOMARKERS FOR PDAC AND OTHER PANCREATIC DISEASES**

Microarray profiling of pancreatic cell lines and normal and diseased primary
5 tissues allowed us to identify 131 mis-regulated (differentially expressed) miRNAs
among the samples (Table 8). The inventors further identified a subset of 94 miRNAs
differentially expressed between normal, chronic, and PDAC samples (Table 6), and
84 miRNAs differentially expressed between normal and PDAC samples (Table 6,
Flag (N vs Ca)=1). The inventors identified 20 miRNAs with $|\Delta h| > 1.6$ (5-fold) and
10 p-value < 0.0001 between at least 2 out of 3 primary tissue types (FIG. 5), and six
miRNAs over-expressed in neoplastic ductal cells both *in vivo* and *ex vivo* (FIG. 7).
These 26 miRNAs whose expression is significantly affected in PDAC represent
novel biomarkers and therapeutic targets for PDAC and other pancreatic diseases.
Their identity, associated array data, and chromosomal location are summarized in
15 Table 9.

Table 9 Top 26 miRNAs differentially expressed in PDAC

miRNA ID	Chr.	Mean (N)	Mean (Ch)	Mean (Ca)	Mean (CL)	p-value	Δh (Ca-N)	Δ fold	# targets
miR-205	1 q32.2	0.9	1.44	3.12	7.35	3.47E-06	2.22	9	19
miR-29c	1 q32.2	8.25	6.95	6.49	4.6	1.48E-10	-1.75	6	45
miR-216	2 p16.1	7.09	5.9	1.64	1.05	4.56E-13	-5.45	233	6
miR-217	2 p16.1	7.86	6.7	2.19	1.27	3.81E-13	-5.68	293	19
miR-375	2 q35	7.21	6.43	4.7	0.85	1.41E-11	-2.51	12	5
miR-143	5 q32	6.02	7.52	7.96	0.49	< 1E-11	1.94	7	7
miR-145	5 q32	6.32	7.82	8.15	0.65	< 1E-11	1.83	6	15
miR-146a	5 q33.3	3.85	4.87	5.93	3.13	1.24E-05	2.09	8	4
miR-148a	7 p15.2	8.57	7.14	5.27	2.55	1.91E-10	-3.3	27	28
miR-196b	7 p15.2	0.57	1.04	3.24	2.35	3.79E-04	2.67	14	7
miR-93	7 q22.1	4.83	4.99	5.94	6.78	1.26E-09	1.11	3	26
miR-96	7 q32.2	4.69	2.79	3.04	3.1	9.15E-06	-1.64	5	33
miR-31	9 p21.3	3.9	5.57	6.69	6.06	1.52E-01	2.79	16	10
miR-210	11 p15.5	3.79	4.43	6.61	4.71	2.38E-08	2.82	17	0
miR-148b	12 q13.13	5.11	2.97	2.82	2.88	1.82E-06	-2.29	10	28
miR-196a	12 q13.13	1.13	1.41	3.77	2.85	1.00E-05	2.64	14	6
miR-141	12 p13.31	7.5	6.65	6	6.34	1.06E-05	-1.5	4.5	29
miR-18a	13 q31.3	2.58	3.17	4.26	5.14	3.68E-07	1.68	5	4
miR-203	14 q32.33	3.5	2.66	5.19	2.68	2.06E-04	1.69	5	14
miR-150	19 p13.33	1.73	3.68	4.38	1.19	1.49E-06	2.65	14	6
miR-155	21 q21.3	3.25	4.22	5.59	4.97	2.75E-03	2.34	10	8
miR-130b	22 q11.21	6.27	4.93	3.84	4.98	4.01E-08	-2.43	11	41
miR-221	X p11.3	5.02	5.41	6.5	7.9	1.55E-11	1.48	4	13
miR-222	X p11.3	3.92	4.63	5.99	7.22	3.43E-11	2.06	8	12
miR-223	X q12	4.47	5.62	6.86	1.36	1.33E-10	2.39	11	10
miR-224	X q28	2.56	2.44	3.83	4.2	1.51E-03	1.27	3.5	7

EXAMPLE 10:**MICROARRAY DATA VALIDATION BY QRT-PCR**

5 To verify our array data, the inventors performed real-time PCR for 5 miRNAs with very distinct expression patterns within the 3 tissue types (miR-143, -155, -196a, -217, and -223) and one miRNA with no significant variation (miR-16). qRT-PCR reactions were performed using SuperTaq™ Polymerase (Ambion) and the mirVana™ qRT-PCR miRNA Detection Kit and Primer Sets (Ambion) following the
10 manufacturer's instructions. qRT-PCR were performed with 5 to 50 ng of total RNA input on an ABI7500 thermocycler (Applied Biosystems; Foster City, CA, USA). Data analysis was performed using 7500 Fast System SDS Software.

The inventors analyzed the 19 total RNA samples previously profiled as well as an independent set of tissues consisting of 2 normal pancreas, 2 PDAC, and one

chronic pancreatitis samples showing different extent of RNA degradation (N6, N7, Ca9, Ca10, and Ch7; FIG. 1; see Table 2 for pathology report). The relative variations of miRNA expression levels were similar for the normalized array and qRT-PCR data (FIG. 8). Moreover, all of the 24 samples had the expected miRNA expression patterns characteristic of normal, cancer and chronic tissues, thus validating our array data and further illustrating the stability of mature miRNA molecules.

EXAMPLE 11:

TISSUE CLASSIFICATION BY QRT-PCR

Analyses of global miRNA expression profiles, differentially expressed miRNAs (FIG. 4B and 6), and the 26 miRNA markers (FIG. 5, 7, and 8) indicated that miRNA expression can distinguish and classify normal and diseased pancreatic tissues. To take this classification one step further, the minimal set of miRNAs that could discriminate between neoplastic and non-neoplastic tissues were identified by applying a quantitative RT-PCR analysis of mature miRNAs. The inventors found that the difference between raw Ct values of two miRNAs (miR-196 and -217) provided a simple index to identify diseased tissues independently of the total RNA sample input (FIG. 9A). The same analysis performed on the 24 independent tissue samples showed a perfect segregation between normal, PDAC, and chronic pancreatitis samples with a p-value of 1.77E-13 (FIG. 9B). This segregation was confirmed using a different real-time PCR assay, the TaqMan® MicroRNA Assay (Applied Biosystems; Foster City, CA, USA). qRT-PCR reactions were performed with 10 ng RNA input using the 7900HT Fast Real-Time PCR System (Applied Biosystems) on a subset of 20 frozen pancreatic tissue samples (6 N, 6 Ch and 8 Ca, Example 1). RT reactions were carried out using random primers, while for PCR reactions gene-specific priming was used. Initial data analysis was done using the 7900HT Sequence Detection System Software v2.3. The inventors observed segregation between normal, cancer, and chronic tissues that was nearly identical to the previously performed assay, with a p-value of 8.18E-10 (FIG. 10).

EXAMPLE 12**MRNA EXPRESSION SIGNATURES IN CLASSIFICATION OF
DISEASED PANCREATIC TISSUE**

Several reports have described the potential diagnostic significance of
5 carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6), survivin
(BIRC5), mucin 4 (MUC4) and urokinase plasminogen activator receptor (UPAR) in
clinical samples obtained from patients with pancreatic disease (Balague *et al.*, 1995;
Bhanot *et al.*, 2006; Chen *et al.*, 2007; Duxbury *et al.*, 2004; Hollingsworth *et al.*,
1994; Lopes *et al.*, 2007). All four genes are up-regulated in pancreatic cancer and a
10 majority of pancreatic cancer cell lines, not expressed (MUC4) or elevated (survivin,
UPAR, CEACAM) in chronic pancreatitis, and not expressed or barely expressed in
normal pancreatic tissue (Jhala *et al.*, 2006; Andrianifahanana *et al.*, 2001; Friess *et al.*,
1997; Shimzu *et al.*, 1990).

The inventors interrogated the expression levels of CEACAM6, BIRC5,
15 MUC4 and UPAR in a subset of frozen tissue samples from Example 1 (6 N, 6 Ch
and 8 Ca) using real time RT-PCR. qRT-PCR reactions were carried out using 5 ng
total RNA input and the ABI TaqMan® Gene Expression Assay system (Applied
Biosystems). RT reactions used random primers, and PCR reactions used gene-
specific priming. Initial data analysis was done using the 7900HT Sequence
20 Detection System Software v2.3. The comparison of mean mRNA expression levels
for CEACAM6, BIRC5, MUC4 or UPAR between the experimental groups
demonstrated a general up-regulation of these genes in PDAC (data not shown).
However, an analysis of expression levels in individual samples revealed no clear
segregation between normal pancreas, chronic pancreatitis and PDAC sample sets, as
25 reflected by high p-values of 7.64E-03, 1.11E-02 and 2.11E-03, respectively. The
expression profiles in chronic pancreatitis samples were either intermediate between
the normal and PDAC profiles or closer to normal (FIG 11A).

EXAMPLE 13**COMBINATIONS OF MIRNA AND MRNA EXPRESSION
SIGNATURES IMPROVE CLASSIFICATION OF DISEASED PANCREATIC
TISSUE**

5 The inventors sought to determine if the individual diagnostic performance of
CEACAM6, BIRC5, MUC4 and UPAR could be improved by combining them
together or with miRNAs. The inventors found that combined expression signatures
of two or more mRNA genes did not offer any advantage in segregating between
normal pancreas, chronic pancreatitis, and pancreatic cancer samples ($p > 4.35 \times 10^{-07}$,
10 FIG. 11B), when compared with the miRNA index of miR-196a and miR-217 (p
 $= 8.18 \times 10^{-10}$, FIG. 10). However, combinations of miRNA and mRNA expression
signatures increased the separation between normal tissue and chronic pancreatitis
samples and enabled the differentiation of pancreatic cancer samples from normal,
non-malignant tissue samples. The best shown combination, 196a-217+CEACAM,
15 had p-value of 5.24×10^{-10} .

EXAMPLE 14**DETECTION OF MIRNA AND MRNA BIOMARKERS FOR
DIAGNOSIS OF PANCREATIC ADENOCARCINOMA IN PANCREATIC
20 FINE NEEDLE ASPIRATES (FNAs)**

 The inventors interrogated expression signatures of a subset of the top 20
differentially expressed miRNAs (Example 6). Because pancreatic tissues contain
high levels of ribonucleases, FNAs were collected within 30 min post surgery in
RNAretain™ (tissue collection and storage solution), kept at 4°C for up to two days,
25 and shipped on dry ice. The targets interrogated by qRT-PCR included: miR-130b, -
148a, -155, -196a, -217 and -375, as well as two mRNAs previously described in the
literature, CEACAM6 and BIRC5. qRT-PCR reactions were carried out as described
in Example 12 using 10 ng (for miRNA quantification) and 5 ng (for mRNA
quantification) total RNA input. The miRNA expression patterns in 10 PDAC FNAs
30 (Ca FNA) were consistent with the reference frozen pancreatic ductal adenocarcinoma

samples (FIG. 12). The expression levels of CEACAM6 and BIRC5 mRNAs were also consistent with PDAC, although they overlapped with chronic pancreatitis expression levels and normal pancreas specimens, as in the case of BIRC5. In the three non-PDAC FNA samples (FNA; FNA-8-solid circle, FNA-12-solid triangle and FNA-13-star), the expression patterns varied depending on the interrogated marker. Further analysis by combining two or more miRNA and/or mRNA markers, confirmed that the difference between raw Ct values of miR-196 and miR-217 improved segregation between pancreatic cancer FNA samples and normal or chronic pancreatitis specimens (FIG. 13). In addition, these miRNAs alone, or in combination with mRNA markers, enabled classification of FNA-8 (suspect for PDAC, solid circle) as a PDAC specimen. This result demonstrates that miRNAs could aid pathological evaluation of suspicious cases and become a valuable asset in definitive diagnosis of pancreatic adenocarcinoma. Additionally, the combination of miRNA and mRNA expression levels enabled an increased separation between the pancreatic cancer FNAs and frozen normal pancreas as well as chronic pancreatitis specimen.

EXAMPLE 15:

TARGET PREDICTION FOR MIRNAS POTENTIALLY INVOLVED IN PANCREATIC CARCINOGENESIS

To gain further insights into the biological pathways potentially regulated by miRNA during pancreatic carcinogenesis, the inventors performed a comprehensive comparison between the published genes known to be deregulated in pancreatic carcinoma and the predicted target genes for the 26 miRNA biomarkers described above. A representative number of published data sets reporting differentially expressed genes in PDAC was used to build a PDAC candidate gene expression database. In parallel, a search was performed on the predicted targets for the 26 miRNA biomarkers identified in our study using the publicly available PicTar web interface (<http://pictar.bio.nyu.edu>). Following comparison of both datasets, a subset of genes which were found in both datasets was generated. Lastly, miRNAs up-regulated in PDAC were linked to the common set of predicted target genes which were known to be down-regulated in PDAC. The opposite selection criteria was applied for the miRNAs down-regulated in PDAC.

Relying on the current view that miRNAs are negative regulators of gene expression, and therefore, anticipating an inverse correlation between miRNA and predicted target gene expression, the inventors identified 246 unique genes deregulated in PDAC (Table 10). Importantly, about 37% of these genes were
5 predicted to be targeted by multiple miRNAs. 47 genes are predicted to be targeted by 2 miRNAs, 21 genes by 3 miRNAs, 13 genes by 4 miRNAs, and 7 genes by up to 5 different miRNAs. These data indicate that miRNA-driven pathophysiological mechanisms may be directly involved in pancreatic diseases development and as importantly, offer new targets for diagnostic uses and therapeutic interventions.

10

Table 10 Twenty-six miRNA biomarkers and their predicted target genes differentially expressed in PDAC

	miRNA in		Target Gene	Description of Predicted Target Gene	Ensembl Gene	UniGene	Literature Source
miRNA	PDAC						
hsa-miR-145 hsa-miR-18a hsa-miR-205	up	ACTB	Actin, beta		ENSG000000075624	Hs.520640	Crnogorac-Jurcevic et al., 2001
hsa-miR-141	down	AK3	Adenylate kinase 3-like 1		ENSG000000162433	Hs.10862	Nakamura et al., 2004, Logsdon et al., 2003
hsa-miR-203 hsa-miR-205	up	AMOT	Angiomotin		ENSG000000126016	Hs.528051	Nakamura et al., 2004
hsa-miR-145	up	ANGPT2	Angiopoietin 2		ENSG000000091879	Hs.553484	Sato et al., 2003
hsa-miR-217	down	ANLN	Anillin, actin binding protein (scraps homolog, Drosophila)		ENSG000000011426	Hs.62180	Iacobuzio-Donahue et al., 2003; Nakamura et al., 2004
hsa-miR-29c	down	RND3	Rho family GTPase 3		ENSG000000115963	Hs.6838	Gress et al., 1996
hsa-miR-203 hsa-miR-93	up	ARHGAP12	Rho GTPase activating protein 12		ENSG000000165322	Hs.499264	Buchholz et al., 2005
hsa-miR-93	up	ARHGEF11	Rho guanine nucleotide exchange factor (GEF) 11		ENSG000000132694	Hs.516954	Han et al., 2002
hsa-miR-130b hsa-miR-148a hsa-miR-148b hsa-miR-375 hsa-miR-96	down	ARHGEF12	Rho guanine nucleotide exchange factor (GEF) 12		ENSG000000196914	Hs.24598	Gress et al., 1996
hsa-miR-141	down	ARPC5	Actin related protein 2/3 complex, subunit 5, 16kDa		ENSG000000162704	Hs.518609	Iacobuzio-Donahue et al., 2003; Grützmann et al., 2003
hsa-miR-29c	down	ASPH	Aspartate beta-hydroxylase		ENSG000000198363	Hs.332422	Iacobuzio-Donahue et al., 2003, Gress et al., 1996
hsa-miR-155	up	ASTN2	Astrotactin 2		ENSG000000148219	Hs.209217	Buchholz et al., 2005
hsa-miR-145	up	ATXN2	Ataxin 2		ENSG000000204842	Hs.76253	Buchholz et al., 2005
hsa-miR-205	up	AXIN2	Axin 2 (conductin, axil)		ENSG000000168646	Hs.156527	Buchholz et al., 2005
hsa-miR-145	up	BAZ2A	Bromodomain adjacent to zinc finger domain, 2A		ENSG000000076108	Hs.314263	Nakamura et al., 2004
hsa-miR-217	down	BCL2	B-cell CLL/lymphoma 2		ENSG000000171791	Hs.150749	Friess et al., 1998

hsa-miR-96				BET1 homolog (<i>S. cerevisiae</i>)	ENSG000000105829	Hs.489132	Buchholz et al., 2005
hsa-miR-150	up	BET1		Bladder cancer associated protein	ENSG000000166619	Hs.472651	Gress et al., 1996
hsa-miR-148b	down	BLCAP		Chromosome 14 open reading frame 140	ENSG000000119703	Hs.48642	Nakamura et al., 2004
hsa-miR-145	up	C14orf140		Chromosome 1 open reading frame 16	ENSG000000116698	Hs.270775	Crnogorac-Jurcevic et al., 2003
hsa-miR-150 hsa-miR-205	up	C1orf16		C1q domain containing 1	ENSG000000110888	Hs.234355	Iacobuzio-Donahue et al., 2002
hsa-miR-130b	down	C1QDC1		Chromosome 20 open reading frame 102	ENSG000000132821	Hs.517029	Nakamura et al., 2004
hsa-miR-150	up	C20orf102		Chromosome 20 open reading frame 161	ENSG000000124104	Hs.472854	Buchholz et al., 2005
hsa-miR-93	up	C20orf161		Chromosome 21 open reading frame 63	ENSG000000166979	Hs.208358	Nakamura et al., 2004
hsa-miR-205	up	C21orf63		Chromosome 2 open reading frame 17	ENSG000000144567	Hs.516707	Buchholz et al., 2005
hsa-miR-93	up	C2orf17		Chromosome 6 open reading frame 62	ENSG000000112308	Hs.519930	Gress et al., 1996
hsa-miR-130b hsa-miR-148a hsa-miR-148b	down	C6orf62		Chromosome 7 open reading frame 23	ENSG000000135185	Hs.196129	Buchholz et al., 2005
hsa-miR-31	up	C7orf23		Chromosome 8 open reading frame 4	ENSG000000176907	Hs.283683	Nakamura et al., 2004
hsa-miR-155	up	C8orf4		Chromosome 9 open reading frame 58	ENSG000000126878	Hs.4944	Buchholz et al., 2005
hsa-miR-203	up	C9orf58		Calcium channel, voltage-dependent, alpha 1G subunit	ENSG000000006283	Hs.194746	Sato et al., 2003
hsa-miR-150	up	CACNA1G		Ca2+-dependent secretion activator	ENSG000000163618	Hs.127013	Nakamura et al., 2004
hsa-miR-31	up	CADPS		Calnexin	ENSG000000127022	Hs.529890	Tan et al., 2003
hsa-miR-205	up	CANX		Caveolin 1, caveolae protein, 22kDa	ENSG000000105974	Hs.74034	Iacobuzio-Donahue et al., 2003; Crnogorac-Jurcevic et al., 2001
hsa-miR-96	down	CAV1		Caveolin 2	ENSG000000105971	Hs.212332	Iacobuzio-Donahue et al., 2003; Iacobuzio-Donahue et al., 2003; Iacobuzio-
hsa-miR-29c	down	CAV2					buzio-

hsa-miR-130b	down	CBFB		Core-binding factor, beta subunit	ENSG00000067955	Hs.460988	Donahue et al., 2002; Sato et al., 2003
hsa-miR-203	up	CCNC		Cyclin C	ENSG00000112237	Hs.430646	Buchholz et al., 2005
hsa-miR-224	up	CD28		CD28 antigen (Tp44)	ENSG00000178562	Hs.1987	Crnogorac-Jurcevic et al., 2002
hsa-miR-31	up	CD28		CD28 antigen (Tp44)	ENSG00000178562	Hs.1987	Nakamura et al., 2004
hsa-miR-148a	down	CDC25B		Cell division cycle 25B	ENSG00000101224	Hs.153752	Grützmann et al., 2003
hsa-miR-148b	down	CDC2L6		Cell division cycle 2-like 6 (CDK8-like)	ENSG00000155111	Hs.193251	Gress et al., 1996
hsa-miR-96	down	CDC37		CDC37 cell division cycle 37 homolog (S. cerevisiae)	ENSG00000105401	Hs.160958	Buchholz et al., 2005
hsa-miR-93 hsa-miR-196a hsa-miR-196b hsa-miR-221 hsa-miR-222	up	CDKN1A		Cyclin-dependent kinase inhibitor 1A (p21, Cip1)	ENSG00000124762	Hs.370771	Sato et al., 2003
hsa-miR-221 hsa-miR-222	up	CDKN1C		Cyclin-dependent kinase inhibitor 1C (p57, Kip2)	ENSG00000129757	Hs.106070	Sato et al., 2003
hsa-miR-216	down	CEBPG		CCAAT/enhancer binding protein (C/EBP), gamma	ENSG00000153879	Hs.429666	Gress et al., 1996
hsa-miR-96	down	CELSR1		Cadherin, EGF LAG seven-pass G-type receptor	ENSG00000075275	Hs.252387	Iacobuzio-Donahue et al., 2003
hsa-miR-96	down	CFL1		Cofilin 1 (non-muscle)	ENSG00000172757	Hs.170622	Nakamura et al., 2004
hsa-miR-130b hsa-miR-141 hsa-miR-148a hsa-miR-148b hsa-miR-217	down	CHD9		Chromodomain helicase DNA binding protein 9	ENSG00000177200	Hs.59159	Buchholz et al., 2005
hsa-miR-224	up	CHGB		Chromogranin B (secretogranin 1)	ENSG00000089199	Hs.516874	Crnogorac-Jurcevic et al., 2003
hsa-miR-145	up	CHKB		Choline kinase beta	ENSG00000100288	Hs.439777	Buchholz et al., 2005
hsa-miR-29c	down	CLDN1		Claudin 1	ENSG00000163347	Hs.439060	Iacobuzio-Donahue et al., 2002
hsa-miR-375	down	CLECSF2		C-type lectin domain family 2,	ENSG00000110852	Hs.85201	Friess et al., 2003

			member B				
hsa-miR-143	up	CNNM3			ENSG000000168763	Hs.150895	Nakamura et al., 2004
hsa-miR-29c	down	COL11A1	Collagen, type XI, alpha 1		ENSG000000060718	Hs.523446	Iacobuzio-Donahue et al., 2002
hsa-miR-29c	down	COL1A1	Collagen, type I, alpha 1		ENSG000000108821	Hs.172928	Iacobuzio-Donahue et al., 2002; Nakamura et al., 2004; Gress et al., 1997; Crnogorac-Jurcevic et al., 2003; Yoshida et al., 2003
hsa-miR-29c	down	COL1A2	Collagen, type I, alpha 2		ENSG000000164692	Hs.489142	Friess et al., 2003; Crnogorac-Jurcevic et al., 2002; Tan et al., 2003; Iacobuzio-Donahue et al., 2002; Nakamura et al., 2004
hsa-miR-130b hsa-miR-148a hsa-miR-148b hsa-miR-29c	down	COL2A1	Collagen, type II, alpha 1		ENSG000000139219	Hs.408182	Friess et al., 2003
hsa-miR-29c	down	COL3A1	Collagen, type III, alpha 1		ENSG000000168542	Hs.443625	Buchholz et al., 2005; Gress et al., 1997; Nakamura et al., 2004; Crnogorac-Jurcevic et al., 2001; Friess et al., 2003
hsa-miR-29c	down	COL4A2	Collagen, type IV, alpha 2		ENSG000000134871	Hs.508716	Friess et al., 2003
hsa-miR-29c	down	COL5A2	Collagen, type V, alpha 2		ENSG000000204262	Hs.445827	Gress et al., 1997
hsa-miR-29c	down	COL6A3	Collagen, type VI, alpha 3		ENSG000000163359	Hs.233240	Gress et al., 1997
hsa-miR-205	up	CROP	Cisplatin resistance-associated overexpressed protein		ENSG000000108848	Hs.130293	Grützmann et al., 2003
hsa-miR-96	down	CRR9	Cisplatin resistance related protein CRR9p		ENSG000000049656	Hs.444673	Gress et al., 1996
hsa-miR-141	down	CSNK1A1	Casein kinase 1, alpha 1		ENSG000000113712	Hs.529862	Nakamura et al., 2004
hsa-miR-375	down	CTGF	Connective tissue growth factor		ENSG000000118523	Hs.410037	Iacobuzio-Donahue et al., 2002
hsa-miR-141	down	CTNNA1	Catenin (cadherin-associated protein), alpha 1, 102kDa		ENSG000000044115	Hs.445981	Li, 2003
hsa-miR-141	down	CTNNB1	Catenin (cadherin-associated		ENSG000000168036	Hs.476018	Iacobuzio-Donahue et al.,

hsa-miR-217			protein), beta 1, 88kDa				2002; Gress et al., 1996; Li, 2003
hsa-miR-29c hsa-miR-96	down	CTNND1	Catenin (cadherin-associated protein), delta 1	ENSG000000198561	Hs.166011		Gress et al., 1996
hsa-miR-31	up	CXCL12	Chemokine (C-X-C motif) ligand 12 (stromal cell-derived factor 1)	ENSG000000107562	Hs.522891		Grützmann et al., 2003
hsa-miR-146a	up	CXYorf2	Chromosome X and Y open reading frame 2	ENSG000000169098	Hs.521856		Buchholz et al., 2005
hsa-miR-223	up	CYB5	Cytochrome b-5	ENSG000000166347	Hs.465413		Nakamura et al., 2004
hsa-miR-145	up	DAG1	Dystroglycan 1 (dystrophin-associated glycoprotein 1)	ENSG000000173402	Hs.76111		Han et al., 2002
hsa-miR-223	up	DAG1	Dystroglycan 1 (dystrophin-associated glycoprotein 1)	ENSG000000173402	Hs.76111		Han et al., 2002
hsa-miR-141	down	DEK	DEK oncogene (DNA binding)	ENSG000000124795	Hs.484813		Gress et al., 1996
hsa-miR-29c	down	DGKD	Diacylglycerol kinase, delta 130kDa	ENSG000000077044	Hs.471675		Grützmann et al., 2003
hsa-miR-224	up	DKFZp434K2435	Hypothetical protein DKFZp434K2435	ENSG000000139173	Hs.444668		Nakamura et al., 2004
hsa-miR-150	up	DKFZP586A0522	DKFZP586A0522 protein	ENSG000000185432	Hs.288771		Nakamura et al., 2004
hsa-miR-217	down	DKK1	Dickkopf homolog 1 (Xenopus laevis)	ENSG000000107984	Hs.40499		Iacobuzio-Donahue et al., 2003
hsa-miR-205	up	DLG2	Discs, large homolog 2, chapsyn-110 (Drosophila)	ENSG000000150672	Hs.503453		Friess et al., 2003
hsa-miR-217	down	DNAJA1	DnaJ (Hsp40) homolog, subfamily A, member 1	ENSG000000086061	Hs.445203		Yoshida et al., 2003
hsa-miR-29c	down	DNM3	Dynammin 3	ENSG000000197959	Hs.567444		Nakamura et al., 2004
hsa-miR-130b	down	DPYSL2	Dihydropyrimidinase-like 2	ENSG000000092964	Hs.173381		Gress et al., 1996
hsa-miR-148a hsa-miR-148b	down	DUSP1	Dual specificity phosphatase 1	ENSG000000120129	Hs.171695		Yoshida et al., 2003
hsa-miR-223	up	EFNA1	Ephrin-A1	ENSG000000169242	Hs.516664		Crnogorac-Jurcevic et al., 2001
hsa-miR-203	up	EGR1	Early growth response 1	ENSG000000120738	Hs.326035		Nakamura et al., 2004
hsa-miR-130b hsa-miR-148a hsa-miR-148b	down	EIF2C4	Eukaryotic translation initiation factor 2C, 4	ENSG000000134698	Hs.471492		Nakamura et al., 2004
hsa-miR-217	down	EIF4A2	Eukaryotic translation initiation factor 4A, isoform 2	ENSG000000156976	Hs.478553		Gress et al., 1996

hsa-miR-141	down	EIF4E	Eukaryotic translation initiation factor 4E	ENSG00000151247	Hs.249718	Gress et al., 1996
hsa-miR-141 hsa-miR-29c	down	ELF2	E74-like factor 2 (ets domain transcription factor)	ENSG00000109381	Hs.480763	Gress et al., 1996
hsa-miR-93	up	EPAS1	Endothelial PAS domain protein 1	ENSG00000116016	Hs.468410	Friess et al., 2003
hsa-miR-375	down	EPB41L2	Erythrocyte membrane protein band 4.1-like 2	ENSG000000079819	Hs.486470	Nakamura et al., 2004
hsa-miR-141	down	EPHA2	EPH receptor A2	ENSG00000142627	Hs.171596	Iacobuzio-Donahue et al., 2002
hsa-miR-130b	down	EREG	Epiregulin	ENSG00000124882	Hs.115263	Iacobuzio-Donahue et al., 2003
hsa-miR-145	up	EYA3	Eyes absent homolog 3 (Drosophila)	ENSG00000158161	Hs.185774	Buchholz et al., 2005
hsa-miR-223	up	FGFR2	Fibroblast growth factor receptor 2	ENSG000000066468	Hs.533683	Nakamura et al., 2004
hsa-miR-93	up	FLT1	Fms-related tyrosine kinase 1	ENSG00000102755	Hs.507621	Crnogorac-Jurcevic et al., 2001
hsa-miR-217	down	FN1	Fibronectin 1	ENSG00000115414	Hs.203717	Buchholz et al., 2005, Tan et al., 2003; Friess et al., 2003; Nakamura et al., 2004; Gress et al., 1997; Crnogorac-Jurcevic et al., 2003
hsa-miR-221 hsa-miR-222	up	FOS	V-fos FBJ murine osteosarcoma viral oncogene homolog	ENSG00000170345	Hs.25647	Grützmann et al., 2003; Han et al., 2002
hsa-miR-29c	down	FSTL1	Follistatin-like 1	ENSG00000163430	Hs.269512	Tan et al., 2003
hsa-miR-205	up	FXYD2	FXYD domain containing ion transport regulator 2	ENSG00000137731	Hs.413137	Buchholz et al., 2005, Nakamura et al., 2004, Crnogorac-Jurcevic et al., 2003
hsa-miR-96	down	FYN	FYN oncogene related to SRC, FGR, YES	ENSG000000010810	Hs.390567	Yoshida et al., 2003; Nakamura et al., 2004
hsa-miR-141 hsa-miR-96	down	GALNT2	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylglucosaminyltransferase 2	ENSG00000143641	Hs.567272	Nakamura et al., 2004
hsa-miR-155	up	GNAS	GNAS complex locus	ENSG000000087460	Hs.125898	Buchholz et al., 2005
hsa-miR-143 hsa-miR-224	up	HABP2	Hyaluronan binding protein 2	ENSG00000148702	Hs.422542	Nakamura et al., 2004; Grützmann et al., 2003; Friess et al., 2003

hsa-miR-93	up	HABP4	Hyaluronan binding protein 4	ENSG00000130956	Hs.494567	Buchholz et al., 2005
hsa-miR-141	down	HAPIP	Kalirin, RhoGEF kinase	ENSG00000160145	Hs.8004	Iacobuzio-Donahue et al., 2003
hsa-miR-130b hsa-miR-148a hsa-miR-148b hsa-miR-29c hsa-miR-96	down	HAS3	Hyaluronan synthase 3	ENSG00000103044	Hs.85962	Iacobuzio-Donahue et al., 2003
hsa-miR-130b	down	HECA	Headcase homolog (Drosophila)	ENSG00000112406	Hs.197644	Nakamura et al., 2004
hsa-miR-205	up	HMGB1	High-mobility group box 1	ENSG00000189403	Hs.434102	Buchholz et al., 2005
hsa-miR-196a hsa-miR-196b hsa-miR-203	up	HOXA1	Homeo box A1	ENSG00000105991	Hs.67397	Sato et al., 2003
hsa-miR-29c	down	HOXA10	Homeo box A10	ENSG00000153807	Hs.110637	Iacobuzio-Donahue et al., 2003
hsa-miR-141	down	HOXA11	Homeo box A11	ENSG00000005073	Hs.249171	Buchholz et al., 2005
hsa-miR-141	down	HOXB5	Homeo box B5	ENSG00000120075	Hs.149548	Iacobuzio-Donahue et al., 2003
hsa-miR-205	up	HS3ST1	Heparan sulfate (glucosamine) 3-O-sulfotransferase 1	ENSG00000002587	Hs.507348	Nakamura et al., 2004
hsa-miR-130b hsa-miR-148a hsa-miR-148b hsa-miR-217 hsa-miR-29c	down	HSHIN1	OTU domain containing 4	ENSG00000164164	Hs.270851	Gress et al., 1996
hsa-miR-223	up	CDH12	Cadherin 12, type 2 (N-cadherin 2)	ENSG00000154162	Hs.113684	Crnogorac-Jurcevic et al., 2003
hsa-miR-93	up	IL17E	Interleukin 17E	ENSG00000166090	Hs.302036	Buchholz et al., 2005
hsa-miR-224	up	ILF3	Interleukin enhancer binding factor 3, 90kDa	ENSG00000129351	Hs.465885	Nakamura et al., 2004
hsa-miR-29c	down	IMPDH1	IMP (inosine monophosphate) dehydrogenase 1	ENSG00000156802	Hs.558347	Nakamura et al., 2004
hsa-miR-130b hsa-miR-148a hsa-miR-148b	down	INHBB	Inhibin, beta B (activin AB beta polypeptide)	ENSG00000163083	Hs.1735	Sato et al., 2003; Iacobuzio-Donahue et al., 2003
hsa-miR-155	up	INPP5D	Inositol polyphosphate-5-phosphatase, 145kDa	ENSG00000168918	Hs.262886	Nakamura et al., 2004

hsa-miR-130b hsa-miR-148a hsa-miR-148b hsa-miR-29c	down	ITGA11	Integrin, alpha 11	ENSG000000137809	Hs.436416	Gress et al., 1997
hsa-miR-217	down	ITM1	Integral membrane protein 1	ENSG000000134910	Hs.504237	Nakamura et al., 2004
hsa-miR-130b hsa-miR-96	down	KAB	KARP-1-binding protein	ENSG000000143702	Hs.533635	Iacobuzio-Donahue et al., 2002
hsa-miR-143 hsa-miR-203 hsa-miR-93	up	KIAA0063	Josephin domain containing 1	ENSG000000100221	Hs.3094	Nakamura et al., 2004
hsa-miR-155	up	KIAA0276	DCN1, defective in cullin neddylation 1, domain containing 4 (S. cerevisiae)	ENSG000000109184	Hs.221407	Buchholz et al., 2005
hsa-miR-216 hsa-miR-29c	down	KIAA1199	KIAA1199	ENSG000000103888	Hs.459088	Iacobuzio-Donahue et al., 2003
hsa-miR-146a	up	KLF7	Kruppel-like factor 7 (ubiquitous)	ENSG000000118263	Hs.471221	Nakamura et al., 2004
hsa-miR-93	up	KLF9	Kruppel-like factor 9	ENSG000000119138	Hs.150557	Nakamura et al., 2004
hsa-miR-29c	down	LASP1	LIM and SH3 protein 1	ENSG000000002834	Hs.334851	Gress et al., 1996
hsa-miR-130b hsa-miR-148a hsa-miR-148b	down	LBR	Lamin B receptor	ENSG000000143815	Hs.435166	Gress et al., 1996
hsa-miR-96	down	LCP1	Lymphocyte cytosolic protein 1 (L-plastin)	ENSG000000136167	Hs.381099	Nakamura et al., 2004
hsa-miR-217	down	LGALS3	Lectin, galactoside-binding, soluble, 3 (galectin 3)	ENSG000000131981	Hs.531081	Iacobuzio-Donahue et al., 2003
hsa-miR-130b hsa-miR-148a hsa-miR-148b	down	MAF1	MAF1 homolog (S. cerevisiae)	ENSG000000179632	Hs.19673	Gress et al., 1996
hsa-miR-217	down	MAPK1	Mitogen-activated protein kinase 1	ENSG000000100030	Hs.431850	Gress et al., 1996
hsa-miR-203 hsa-miR-205 hsa-miR-93	up	MAPK9	Mitogen-activated protein kinase 9	ENSG000000050748	Hs.484371	Crnogorac-Jurcevic et al., 2001
hsa-miR-29c	down	MARK3	MAP/microtubule affinity-regulating kinase 3	ENSG000000075413	Hs.35828	Friess et al., 2003
hsa-miR-93	up	MASTL	Microtubule associated serine/threonine kinase-like	ENSG000000120539	Hs.276905	Buchholz et al., 2005
hsa-miR-93	up	MCL1	Myeloid cell leukemia sequence 1	ENSG000000143384	Hs.532826	Grützmann et al., 2003

			(BCL2-related)					
hsa-miR-203 hsa-miR-223 hsa-miR-93	up	MEF2C	MADS box transcription enhancer factor 2, polypeptide C (myocyte enhancer factor 2C)	ENSG000000081189	Hs.444409	Nakamura et al., 2004		
hsa-miR-18a	up	MEF2D	MADS box transcription enhancer factor 2, polypeptide D (myocyte enhancer factor 2D)	ENSG000000116604	Hs.314327	Nakamura et al., 2004		
hsa-miR-196b	up	MEIS2	Meis1, myeloid ecotropic viral integration site 1 homolog 2 (mouse)	ENSG000000134138	Hs.510989	Nakamura et al., 2004		
hsa-miR-29c	down	MFAP2	Microfibrillar-associated protein 2	ENSG000000117122	Hs.389137	Iacobuzio-Donahue et al., 2003		
hsa-miR-196a hsa-miR-196b	up	MGC61598	Similar to ankyrin-repeat protein Nrarp	ENSG000000198435	Hs.535075	Nakamura et al., 2004		
hsa-miR-141	down	MMP11	Matrix metalloproteinase 11 (stromelysin 3)	ENSG000000099953	Hs.143751	Nakamura et al., 2004; Iacobuzio-Donahue et al., 2003; Bramhall et al., 1997; Crnogorac-Jurcevic et al., 2003		
hsa-miR-29c	down	MMP2	Matrix metalloproteinase 2 (gelatinase A, 72kDa gelatinase, 72kDa type IV collagenase)	ENSG000000087245	Hs.513617	Bramhall et al., 1997; Ellenrieder et al., 2000; Gress et al., 1997		
hsa-miR-143 hsa-miR-145	up	MSI2	Musashi homolog 2 (Drosophila)	ENSG000000153944	Hs.134470	Nakamura et al., 2004		
hsa-miR-29c	down	MYBL2	V-myb myeloblastosis viral oncogene homolog (avian)-like 2	ENSG000000101057	Hs.179718	Nakamura et al., 2004		
hsa-miR-130b	down	N4BP1	Nedd4 binding protein 1	ENSG000000102921	Hs.511839	Gress et al., 1997		
hsa-miR-96	down	N4BP1	Nedd4 binding protein 1	ENSG000000102921	Hs.511839	Gress et al., 1997		
hsa-miR-29c	down	NAV2	Neuron navigator 2	ENSG000000166833	Hs.502116	Nakamura et al., 2004		
hsa-miR-29c	down	NCOA3	Nuclear receptor coactivator 3	ENSG000000124151	Hs.382168	Nakamura et al., 2004		
hsa-miR-145 hsa-miR-93	up	NEDD4L	Neural precursor cell expressed, developmentally down-regulated 4-like	ENSG000000049759	Hs.185677	Nakamura et al., 2004		
hsa-miR-223 hsa-miR-93	up	NFIB	Nuclear factor I/B	ENSG000000147862	Hs.370359	Nakamura et al., 2004		
hsa-miR-130b hsa-miR-148a	down	NHS	Nance-Horan syndrome (congenital cataracts and dental	ENSG000000188158	Hs.201623	Nakamura et al., 2004		

hsa-miR-148b hsa-miR-217			anomalies)				
hsa-miR-205	up	NPR2	Natriuretic peptide receptor B/guanylate cyclase B (atrionatriuretic peptide receptor B)	ENSG00000159899	Hs.78518	Nakamura et al., 2004	
hsa-miR-150 hsa-miR-155	up	NR2F2	Nuclear receptor subfamily 2, group F, member 2	ENSG00000185551	Hs.347991	Nakamura et al., 2004	
hsa-miR-130b hsa-miR-141	down	NR3C2	Nuclear receptor subfamily 3, group C, member 2	ENSG00000151623	Hs.163924	Gress et al., 1996	
hsa-miR-224	up	NR4A1	Nuclear receptor subfamily 4, group A, member 1	ENSG00000123358	Hs.524430	Nakamura et al., 2004	
hsa-miR-93	up	NR4A2	Nuclear receptor subfamily 4, group A, member 2	ENSG00000153234	Hs.165258	Nakamura et al., 2004	
hsa-miR-31	up	NR5A2	Nuclear receptor subfamily 5, group A, member 2	ENSG00000116833	Hs.33446	Crnogorac-Jurcevic et al., 2003	
hsa-miR-143 hsa-miR-146a hsa-miR-31	up	NUMB	Numb homolog (Drosophila)	ENSG00000133961	Hs.509909	Buchholz et al., 2005	
hsa-miR-205 hsa-miR-223	up	NUTF2	Nuclear transport factor 2	ENSG00000102898	Hs.356630	Buchholz et al., 2005	
hsa-miR-96	down	OSBPL8	Oxysterol binding protein-like 8	ENSG00000091039	Hs.430849	Iacobuzio-Donahue et al., 2002	
hsa-miR-29c	down	OXTR	Oxytocin receptor	ENSG00000180914	Hs.2820	Sato et al., 2003	
hsa-miR-130b hsa-miR-141 hsa-miR-96	down	PAFAH1B1	Platelet-activating factor acetylhydrolase, isoform Ib, alpha subunit 45kDa	ENSG00000007168	Hs.77318	Gress et al., 1996	
hsa-miR-221 hsa-miR-222 hsa-miR-93	up	PCDHA6	Protocadherin alpha subfamily C, 1	ENSG000000081842	Hs.199343	Buchholz et al., 2005	
hsa-miR-221 hsa-miR-222 hsa-miR-31	up	PCGF3	Polycomb group ring finger 3	ENSG00000185619	Hs.144309	Nakamura et al., 2004	
hsa-miR-217	down	PCNA	Proliferating cell nuclear antigen	ENSG00000132646	Hs.147433	Han et al., 2002	
hsa-miR-145	up	PDCD4	Programmed cell death 4 (neoplastic transformation inhibitor)	ENSG00000150593	Hs.232543	Tan et al., 2003	
hsa-miR-29c	down	PDGFRB	Platelet-derived growth factor	ENSG00000113721	Hs.509067	Gress et al., 1997	

hsa-miR-205	up	PHB	receptor, beta polypeptide	ENSG00000167085	Hs.514303	Nakamura et al., 2004
hsa-miR-143	up	PHF20L1	Prohibitin	ENSG00000197967	Hs.304362	Buchholz et al., 2005
hsa-miR-18a			PHD finger protein 20-like 1			
hsa-miR-203			Phospholipase D2			
hsa-miR-223			Pleckstrin 2			
hsa-miR-203	up	PLD2	Procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2	ENSG00000129219	Hs.104519	Nakamura et al., 2004
hsa-miR-31	up	PLEK2	Peroxisome proliferative activated receptor, alpha	ENSG00000100558	Hs.170473	Sato et al., 2003
hsa-miR-96	down	PLOD2	Peptidylprolyl isomerase C (cyclophilin C)	ENSG00000152952	Hs.477866	Buchholz et al., 2005
hsa-miR-93	up	PPARA	Protein phosphatase 1B (formerly 2C), magnesium-dependent, beta isoform	ENSG00000186951	Hs.275711	Nakamura et al., 2004
hsa-miR-29c	down	PPIC	Protein phosphatase 2 (formerly 2A), regulatory subunit B (PR 52), alpha isoform	ENSG00000168938	Hs.110364	Nakamura et al., 2004
hsa-miR-216	down	PPM1B	Protein phosphatase 2 (formerly 2A), regulatory subunit B (PR 52), alpha isoform	ENSG00000138032	Hs.416769	Nakamura et al., 2004
hsa-miR-141	down	PPP2R2A	Palmitoyl-protein thioesterase 2	ENSG00000104762	Hs.146339	Yoshida et al., 2003
hsa-miR-141	down	PPT2	PRO149 protein	ENSG00000168452	Hs.332138	Buchholz et al., 2005
hsa-miR-29c	down	PRO149	Protein tyrosine phosphatase type IVA, member 1	ENSG00000182831	Hs.221497	Gress et al., 1996
hsa-miR-130b	down	PTP4A1	RAB34, member RAS oncogene family	ENSG00000112245	Hs.227777	Han et al., 2002
hsa-miR-141			Ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1)			
hsa-miR-29c			Retinoic acid receptor, beta			
hsa-miR-96			RNA binding motif, single stranded interacting protein 1			
hsa-miR-130b	down	RAB34	Protein phosphatase 2 (formerly 2A), regulatory subunit B (PR 52), alpha isoform	ENSG00000109113	Hs.301853	Buchholz et al., 2005; Iacobuzio-Donahue et al., 2003
hsa-miR-148a			Palmitoyl-protein thioesterase 2			
hsa-miR-148b			PRO149 protein			
hsa-miR-96			Protein tyrosine phosphatase type IVA, member 1			
hsa-miR-96	down	RAC1	Ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1)	ENSG00000136238	Hs.413812	Crnogorac-Jurcevic et al., 2001
hsa-miR-141	down	RARB	Retinoic acid receptor, beta	ENSG00000077092	Hs.436538	Crnogorac-Jurcevic et al., 2001
hsa-miR-29c	down	RBMS1	RNA binding motif, single stranded interacting protein 1	ENSG00000153250	Hs.470412	Nakamura et al., 2004

hsa-miR-223	up	RBPSUH	Recombining binding protein suppressor of hairless (Drosophila)	ENSG00000168214	Hs.479396	Han et al., 2002
hsa-miR-196a hsa-miR-196b	up	RGL2	Ral guanine nucleotide dissociation stimulator-like 2	ENSG000000056687	Hs.509622	Nakamura et al., 2004
hsa-miR-130b hsa-miR-148a hsa-miR-148b hsa-miR-29c	down	RNPEPL1	Arginyl aminopeptidase (aminopeptidase B)-like 1	ENSG00000142327	Hs.5345	Gress et al., 1996
hsa-miR-141 hsa-miR-375	down	RUNX1	Runt-related transcription factor 1 (acute myeloid leukemia 1; aml1 oncogene)	ENSG00000159216	Hs.149261	Iacobuzio-Donahue et al., 2002; Iacobuzio-Donahue et al., 2003
hsa-miR-221 hsa-miR-222	up	SAFB	Scaffold attachment factor B	ENSG00000160633	Hs.23978	Nakamura et al., 2004
hsa-miR-141	down	SCD	Stearoyl-CoA desaturase (delta-9-desaturase)	ENSG000000099194	Hs.558396	Nakamura et al., 2004
hsa-miR-205	up	SCMH1	Sex comb on midleg homolog 1 (Drosophila)	ENSG00000010803	Hs.87464	Nakamura et al., 2004
hsa-miR-130b hsa-miR-148a hsa-miR-148b hsa-miR-217	down	SDFR1	Stromal cell derived factor receptor 1	ENSG00000156642	Hs.187866	Gress et al., 1996
hsa-miR-205	up	SEL1L	Sel-1 suppressor of lin-12-like (C. elegans)	ENSG000000071537	Hs.181300	Crnogorac-Jurcevic et al., 2003
hsa-miR-31	up	SEMA3F	Sema domain, immunoglobulin domain (Ig), short basic domain, secreted, semaphorin 3F	ENSG00000001617	Hs.32981	Nakamura et al., 2004
hsa-miR-205 hsa-miR-93	up	SENP1	SUMO1/sentrin specific peptidase 1	ENSG000000079387	Hs.371957	Nakamura et al., 2004
hsa-miR-96	down	SEPT11	Septin 11	ENSG00000138758	Hs.128199	Iacobuzio-Donahue et al., 2002
hsa-miR-141 hsa-miR-216	down	SEPT7	Septin 7	ENSG00000122545	Hs.191346	Nakamura et al., 2004
hsa-miR-221 hsa-miR-222	up	SFRP2	Secreted frizzled-related protein 2	ENSG00000145423	Hs.481022	Crnogorac-Jurcevic et al., 2001
hsa-miR-96	down	SH3BGR13	SH3 domain binding glutamic acid-rich protein like 3	ENSG00000142669	Hs.109051	Buchholz et al., 2005
hsa-miR-130b	down	SIAHBP1	Fuse-binding protein-interacting repressor	ENSG00000179950	Hs.521924	Gress et al., 1996

hsa-miR-29c	down	SLC16A1	AKR7 family pseudogene	ENSG000000155380	Hs.75231	Iacobuzio-Donahue et al., 2003
hsa-miR-141	down	SLC20A1	Solute carrier family 20 (phosphate transporter), member 1	ENSG000000144136	Hs.187946	Nakamura et al., 2004
hsa-miR-145	up	SLC25A25	Solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 25	ENSG000000148339	Hs.5476	Nakamura et al., 2004
hsa-miR-130b hsa-miR-148a hsa-miR-148b	down	SLC2A1	Solute carrier family 2 (facilitated glucose transporter), member 1	ENSG000000117394	Hs.473721	Logsdon et al., 2003; Crnogorac-Jurcevic et al., 2003; Nakamura et al., 2004; Iacobuzio-Donahue et al., 2003
hsa-miR-96	down	SLC35A1	Solute carrier family 35 (CMP-sialic acid transporter), member A1	ENSG000000055291	Hs.423163	Friess et al., 2003
hsa-miR-93	up	SLC40A1	Solute carrier family 40 (iron-regulated transporter), member 1	ENSG000000138449	Hs.529285	Nakamura et al., 2004
hsa-miR-145 hsa-miR-203 hsa-miR-221 hsa-miR-222 hsa-miR-224	up	SLC4A4	Solute carrier family 4, sodium bicarbonate cotransporter, member 4	ENSG000000080493	Hs.5462	Buchholz et al., 2005; Iacobuzio-Donahue et al., 2003; Crnogorac-Jurcevic et al., 2003; Nakamura et al., 2004
hsa-miR-96	down	SLCO3A1	Solute carrier organic anion transporter family, member 3A1	ENSG000000176463	Hs.311187	Iacobuzio-Donahue et al., 2003
hsa-miR-216	down	SMAD7	SMAD, mothers against DPP homolog 7 (Drosophila)	ENSG000000101665	Hs.465087	Kleeff et al., 1999
hsa-miR-96	down	SMAD7	SMAD, mothers against DPP homolog 7 (Drosophila)	ENSG000000101665	Hs.465087	Kleeff et al., 1999
hsa-miR-221 hsa-miR-222	up	SMARCA1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 1	ENSG000000102038	Hs.152292	Sato et al., 2003
hsa-miR-148a hsa-miR-148b	down	SMARCD1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 1	ENSG000000066117	Hs.79335	Buchholz et al., 2005
hsa-miR-130b hsa-miR-141 hsa-miR-216	down	SMC4L1	SMC4 structural maintenance of chromosomes 4-like 1 (yeast)	ENSG000000113810	Hs.58992	Nakamura et al., 2004; Iacobuzio-Donahue et al., 2003

hsa-miR-130b hsa-miR-141 hsa-miR-148a hsa-miR-148b hsa-miR-96	down	SOX5	SRY (sex determining region Y)- box 5	ENSG00000134532	Hs.434948	Tan et al., 2003
hsa-miR-155 hsa-miR-221	up	SOX6	SRY (sex determining region Y)- box 6	ENSG00000110693	Hs.368226	Nakamura et al., 2004
hsa-miR-93	up	SP8	Sp8 transcription factor	ENSG00000164651	Hs.195922	Nakamura et al., 2004
hsa-miR-29c	down	SPARC	Secreted protein, acidic, cysteine- rich (osteonectin)	ENSG00000113140	Hs.111779	Tan et al., 2003; Nakamura et al., 2004; Friess et al., 2003
hsa-miR-93	up	STAT3	Signal transducer and activator of transcription 3 (acute-phase response factor)	ENSG00000168610	Hs.463059	Han et al., 2002
hsa-miR-217	down	STRBP	Spermatid perinuclear RNA binding protein	ENSG00000165209	Hs.287659	Iacobuzio-Donahue et al., 2003
hsa-miR-130b hsa-miR-148a hsa-miR-148b	down	SULF1	Sulfatase 1	ENSG00000137573	Hs.409602	Buchholz et al., 2005; Iacobuzio-Donahue et al., 2002
hsa-miR-29c	down	SYT7	Synaptotagmin VII	ENSG00000011347	Hs.502730	Buchholz et al., 2005
hsa-miR-217 hsa-miR-96	down	TACC1	Transforming, acidic coiled-coil containing protein 1	ENSG00000147526	Hs.279245	Gress et al., 1996
hsa-miR-196a hsa-miR-196b	up	TCF7	Transcription factor 7 (T-cell specific, HMG-box)	ENSG00000081059	Hs.519580	Buchholz et al., 2005
hsa-miR-96	down	TEGT	Testis enhanced gene transcript (BAX inhibitor 1)	ENSG00000139644	Hs.35052	Nakamura et al., 2004
hsa-miR-130b	down	TIMP2	TIMP metalloproteinase inhibitor 2	ENSG00000035862	Hs.104839	Gress et al., 1996; Bramhall et al., 1997
hsa-miR-221 hsa-miR-222	up	TIMP3	TIMP metalloproteinase inhibitor 3 (Sorsby fundus dystrophy, pseudoinflammatory)	ENSG00000197047	Hs.297324	Sato et al., 2003
hsa-miR-93	up	TIPARP	TCDD-inducible poly(ADP- ribose) polymerase	ENSG00000163659	Hs.12813	Nakamura et al., 2004
hsa-miR-29c hsa-miR-96	down	TM4SF14	Tetraspanin 14	ENSG00000108219	Hs.310453	Nakamura et al., 2004
hsa-miR-130b hsa-miR-96	down	TMEPAI	Transmembrane, prostate androgen induced RNA	ENSG00000124225	Hs.517155	Iacobuzio-Donahue et al., 2002
hsa-miR-29c	down	TMPRSS3	Transmembrane protease, serine 3	ENSG00000160183	Hs.208600	Iacobuzio-Donahue et al.,

hsa-miR-130b hsa-miR-148a hsa-miR-148b hsa-miR-96	down	TMSB10	Thymosin, beta 10	ENSG000000034510	Hs.446574	2003 Tan et al., 2003; Nakamura et al., 2004
hsa-miR-130b hsa-miR-148a hsa-miR-148b hsa-miR-217	down	TMSB4X	Thymosin, beta 4, X-linked	ENSG000000188364	Hs.522584	Tan et al., 2003
hsa-miR-145	up	STEAP4	STEAP family member 4	ENSG000000127954	Hs.521008	Nakamura et al., 2004
hsa-miR-155 hsa-miR-93	up	TP53INP1	Tumor protein p53 inducible nuclear protein 1	ENSG000000164938	Hs.492261	Nakamura et al., 2004
hsa-miR-29c	down	TRIB2	Tribbles homolog 2 (Drosophila)	ENSG000000071575	Hs.467751	Nakamura et al., 2004
hsa-miR-130b hsa-miR-96	down	TTYH3	Tweety homolog 3 (Drosophila)	ENSG000000136295	Hs.440899	Buchholz et al., 2005
hsa-miR-130b	down	UBE2D2	Ubiquitin-conjugating enzyme E2D 2 (UBC4/5 homolog, yeast)	ENSG000000131508	Hs.108332	Nakamura et al., 2004
hsa-miR-221 hsa-miR-222	up	UNC84B	Unc-84 homolog B (C. elegans)	ENSG000000100242	Hs.517622	Nakamura et al., 2004
hsa-miR-29c	down	USP37	Ubiquitin specific peptidase 37	ENSG000000135913	Hs.166068	Gress et al., 1996
hsa-miR-143 hsa-miR-221 hsa-miR-222 hsa-miR-31	up	VAPB	VAMP (vesicle-associated membrane protein)-associated protein B and C	ENSG000000124164	Hs.182625	Buchholz et al., 2005
hsa-miR-130b hsa-miR-141 hsa-miR-148a hsa-miR-148b hsa-miR-29c	down	WHSC1	Wolf-Hirschhorn syndrome candidate 1	ENSG000000109685	Hs.113876	Nakamura et al., 2004
hsa-miR-130b hsa-miR-148a hsa-miR-148b	down	WNT10B	Wingless-type MMTV integration site family, member 10B	ENSG000000169884	Hs.91985	Buchholz et al., 2005
hsa-miR-18a hsa-miR-203	up	YPEL5	Yippee-like 5 (Drosophila)	ENSG000000119801	Hs.515890	Grützmann et al., 2003
hsa-miR-130b hsa-miR-148a hsa-miR-148b hsa-miR-217	down	ZCCHC2	Zinc finger, CCHC domain containing 2	ENSG000000141664	Hs.114191	Nakamura et al., 2004

hsa-miR-96	down	ZIC2	Zic family member 2 (odd-paired homolog, Drosophila)	ENSG00000043355	Hs.369063	Iacobuzio-Donahue et al., 2003
hsa-miR-145 hsa-miR-205 hsa-miR-196a hsa-miR-196b	up	ZNF462	Zinc finger protein 462	ENSG00000148143	Hs.370379	Buchholz et al., 2005

EXAMPLE 16**DIAGNOSTIC METHODS**

A patient may present for evaluation with symptoms that include one or more of jaundice, weight loss, bruising, abdominal pain, vomiting, diarrhea, and/or nausea.

5 Peripheral blood is drawn in order to evaluate the patient's plasma for the presence of CA 19-9, a cancer tumor marker that exhibits 50-75% sensitivity and 83% specificity for pancreatic cancer (Freelove and Walling, 2006). At the same time total RNA, including the miRNA fraction, are purified from a sample of the patient's plasma. The methods of the invention are used to determine if levels of miRNAs listed in

10 Table 6, Table 9 and FIG. 9A and 9B are altered in a manner that suggests pancreatic ductal adenocarcinoma or chronic pancreatitis. Typically, under these circumstances the invention will be used to diagnose a case of chronic pancreatitis.

EXAMPLE 17**DIAGNOSTIC METHODS**

15 A patient may have symptoms suggesting pancreatic cancer or chronic pancreatitis (see Example 13) and may be found to have elevated levels of the serum tumor marker CA19-9 and is scheduled for an endoscopic ultrasonography-guided fine needle aspiration (Freelove and Walling, 2006). During the procedure, fine

20 needle aspirates containing pancreatic cells are collected. Alternatively, pancreatic juice may be aspirated during the procedure. Pancreatic juice may contain sloughed pancreatic cells and contents of lysed pancreatic cells. Total RNA, including the miRNA fraction, is purified from the contents of the fine needle aspirate, fresh, frozen or fixed, or from the pancreatic juice sample. The methods of the invention are used

25 to determine if levels of miRNAs listed in Table 6, Table 9, and FIG. 9A and 9B are altered in a manner that suggests pancreatic ductal adenocarcinoma or chronic pancreatitis. Typically, under these circumstances the invention will be used to confirm a suspected diagnosis of pancreatic cancer.

EXAMPLE 18**DIAGNOSTIC METHODS**

An asymptomatic patient may be found to have a pancreatic mass on CT scan imaging. Chest x-ray and colonoscopy are normal. The patient has a family history
5 of pancreatic cancer and may have experienced some recent weight loss. Peripheral blood is drawn in order to evaluate the patient's plasma for the presence of tumor marker antigens. A sample of the plasma also may be processed to purify miRNAs. The methods of the invention then may be used to determine if levels of plasma-isolated miRNAs are altered in a manner that suggests pancreatic ductal
10 adenocarcinoma or chronic pancreatitis (Table 6, Table 9, FIG. 9A and 9B). Under these circumstances the invention can be used to provide a diagnosis of pancreatic cancer.

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CLAIMS

1. A method for identifying a pancreatic sample from a patient for pancreatic ductal adenocarcinoma (PDAC), the method comprising:
 - isolating microRNA from the pancreatic sample;
 - measuring expression of hsa-miR-196a (SEQ ID NO:81) in the isolated microRNA from the patient;
 - identifying the sample for PDAC by comparing the level of hsa-miR-196a expression in a normal pancreas sample or a control pancreatitis sample,
 - wherein an increase in hsa-miR-196a in the pancreatic sample as compared to the normal pancreatic sample or the control pancreatitis sample identifies the pancreatic sample as PDAC.
2. The method of claim 1, further comprising:
 - measuring expression of hsa-miR-217 (SEQ ID NO:107) in the isolated microRNA from the patient; and
 - comparing the level of hsa-miR-217 expression in the pancreatic sample to the normal pancreas sample or the control pancreatitis sample,
 - wherein a decrease in hsa-miR-217 expression and an increase in hsa-miR-196a in the pancreatic sample as compared to the normal pancreatic sample or the control pancreatitis sample identifies the pancreatic sample as PDAC.
3. The method of claim 1 or 2, wherein the pancreatic sample is a tissue or a pancreatic juice sample.
4. The method of claim 3, wherein the sample is fresh, frozen, fixed, or embedded.

5. The method of any one of claims 1 to 4, wherein expression of the hsa-miR-196a is determined by an amplification assay or a hybridization assay.
6. The method of claim 5, wherein the amplification assay is PCR.