Supplementary Materials

METHODS

Nanoparticle tracking analysis (NTA)

We evaluated the quality of extracellular vesicles isolated from 3 mL of urine using the Total Exosome Isolation Reagent (from urine) via the NTA system. The number and size of extracellular vesicles were analyzed using a nanoparticle tracking analysis (NTA) system (Malvern Panalytical, NanoSight NS300) according to the manufacturer's protocols. After appropriate dilutions in 1X PBS, video data were collected 5 times for a 60 second time period for each video. Camera level and detection threshold were set to 10 and 3, respectively. Data analysis was performed automatically by NanoSight NTA 3.4 software.

RT-qPCR

Reverse transcription of miRNAs was conducted using the TaqMan Advanced miRNA cDNA Synthesis Kit (Applied Biosystems) according to the manufacturer's instructions. For each miRNA and sample, 5·0 μL of miRNA-enriched eluate was utilized in the initial reverse transcription step. Complementary DNA was pre-amplified as recommended by the kit. Real-time PCR was carried out using the FAST Advanced PCR mix (Applied Biosystems) on the QuantStudio 5 System (Applied Biosystems). Signal detection and analysis were performed with QuantStudio software (Applied Biosystems), and the threshold cycle (Ct) values were determined from the fixed threshold values for each probe as specified by the software. Ct values were not assigned to the measurements with poor amplification according to the amplification status provided by the software, and were removed from the analyses. Ct values of technical replicates (n=3) were averaged after excluding outliers (defined as values deviating ±1 or more from the median). miRNA expression levels were quantified using delta Ct values by subtracting from the average values of two reference miRNAs (hsa-miR-374a-5p and hsa-miR-30d-5p), and the $\log_2$ fold change values were calculated as the difference of the average values of delta Ct in the non-cancer group from that in the pancreatic cancer group. Student’s t test was performed for the comparisons of the pancreatic cancer and non-cancer groups.

Performance of prediction model with reduced feature sets

To explore the feasibility of modeling with a smaller feature set, we performed a feature reduction approach with the recursive feature elimination (RFE) analysis with the linear support vector classifier (SVC) model as estimator. RFE employs a backward feature elimination approach. It initiates with the full set of features and iteratively constructs models, each time excluding the least important feature based on the model's performance metrics. This process continues until the desired number of features is reached, effectively ranking features by their predictive power and identifying the optimal subset for the target variable. We obtained performance curves for both the train and test sets by evaluating the model’s area under the curve (AUC) of the receiver operating characteristic (ROC) curve against reduced feature sizes. In the train set, we conducted five-fold cross-validation repeated 100 times to obtain out-of-fold performance metrics. For the test set, we fitted the model using the entire train set and assessed its performance, allowing us to evaluate the generalization capabilities of reduced feature sets. To determine the minimum number of features while maintaining model performance, we conducted Student's t-tests comparing each point of the train set's performance curve with the full feature size of 183. Additionally, we performed Student's t-tests against reference AUC values of 0·90 and 0·95. All tests were upper one-sided, with $p < 0{\cdot}05$ considered statistically significant.

RESULTS and DISCUSSIONS

Nanoparticle tracking analysis (NTA)

The particle size (mode) ranged from 50 nm to 150 nm, corresponding to exosomes (Supplementary Fig. 1), and the particle concentration was approximately $1–3\times10^{10}$ (Supplementary Fig. 1). These results indicate that our precipitation method for extraction of extracellular vesicles provides comparable particle size ranges with superior yields (10^{10} particles / mL from only 3 mL of urine) compared to previous reports using ultracentrifugation, polyethylene glycol (PEG), and size exclusion chromatography (SEC) for exosome isolation.[1-3]

Learning curve analysis of the prediction model

To assess the potential risk of overfitting and evaluate our model's generalization capability, we conducted a learning curve analysis for our prediction model. As shown in Supplementary Fig. 5, the performance of the out-of-fold prediction on the validation set improved with an increase in the training set size, while the performance of the in-fold prediction on the training set remained almost constant. When the sample size was small, we observed a significant gap between the validation and training performances, indicating that the model was initially overfitted to the training set, and demonstrated poor generalizability to the out-of-fold data. As the training set size grew, we noted a gradual improvement in performance, suggesting that the model was acquiring greater generalizability with the addition of more training samples. The learning curve also indicated a gradual slowdown in performance improvement, likely approaching a saturation point with an AUC greater than 0·95. Although it remains possible that the curve could show further growth with an even larger training set, this trend implies that the model effectively fitted the training set and achieved strong generalization, resulting in high performance in the out-of-fold prediction for the validation set. Given that the training set size in the current study was N = 315, which exceeds the saturation point, we conclude that our model was well-fitted to the train set and demonstrated robust generalization capabilities. These findings support the robustness of our prediction model and mitigate concerns about its generalizability.

Evaluation of urinary bilirubin impact on miRNA assay performance

We investigated urinary bilirubin using a simple test strip method (Aution Sticks 10EA, Arkray, Japan). Of the 99 and 54 pancreatic cancer cases in the train and test sets, 5 (Early stage: 2, Late stage: 2, Unknown: 1) and 2 (Late stage: 2) cases were bilirubin positive, respectively. All of the seven bilirubin-positive cases were positive in the urinary miRNA assay. In summary, a low incidence of bilirubin-positive cases was observed in the current pancreatic cancer cases, and those cases were successfully classified as pancreatic cancer positive in our urinary miRNA assay.

Verification of DEMs train vs test

To confirm the consistency of the results in the train and test sets, we performed differential expression analysis independently for the train and test sets. As shown in Supplementary Fig. 6, the log2 fold change values were highly correlated with each other (Pearson’s $r = 0{\cdot}74$, $p < 0{\cdot}0001$). Of the 26 up-regulated and 19 down-regulated DEMs in the train set, 19 and 5 were consistently differentially expressed in the test set, respectively (Supplementary Table 1).

Verification of DEMs by RT-qPCR

We selected 30 pancreatic cancer and 30 non-cancer cases from the training set and targeted 15 miRNA probes for qPCR analysis using the TaqMan Assay. These probes were chosen based on prior confirmation of their detection among the 45 differentially expressed miRNAs (DEMs) identified through differential expression analysis (DEA) with small RNA-seq. The normalized Ct values showed a negative correlation (Pearson’s $r = -0.68$) with the normalized count from NGS, indicating that the overall miRNA expression levels were consistent (Supplementary Fig 7 (a)). DEA for the normalized Ct values revealed that 3 of the 8 up-regulated miRNAs identified in small RNA-seq exhibited a log2 fold change greater than 0·5 in qPCR (Supplementary Fig 7 (b) and Supplementary Table 5), indicating consistency between the small RNA sequencing and qPCR results.

Performance of prediction model with reduced feature sets

To explore the feasibility of modeling with a smaller feature set, we implemented a recursive feature elimination analysis. As shown in Supplementary Fig. 8 (a), reducing the feature set size from the full M = 183 did not significantly affect model performance until it reached M = 96 (Supplementary Fig. 8 (b)). Further reduction led to a gradual decline in performance, but the AUC was not significantly lower than 0·95 until M = 43 (Supplementary Fig. 8 (c)). Below this threshold, the decline in performance accelerated, with AUC dropping below 0·90 at M = 10. Although the model showed reasonable performance with only 10 features, at least 43 features were necessary to maintain a high AUC of approximately 0·95. While the model performed comparably with 95 features in the training set, the full feature set demonstrated the most robust performance in the test set. These findings suggest that our modeling approach offers a robust prediction with the small RNA-seq assay.

Prediction performance in samples with storage conditions.

To evaluate the potential confounding effect of urine storage conditions on our urinary miRNA assay, we compared specificity values for non-cancer samples stored at –80°C (Hokuto Hospital) and –20°C (Omiya City Clinic), as described in the Methods section. As shown in Supplementary Fig. 9, there were no statistically significant differences in specificity between the storage conditions of –80°C and –20°C, both in the training set (chi-squared test, p = 0·566) and the test set (chi-squared test, p = 1·0).

References

1 Street JM, Koritzinsky EH, Glispie DM, Yuen PST. Urine Exosome Isolation and Characterization. In: Gautier J-C (ed). *Drug Safety Evaluation*. Springer New York: New York, NY, 2017, pp 413–423.

2 Gheinani AH, Vögeli M, Baumgartner U *et al.* Improved isolation strategies to increase the yield and purity of human urinary exosomes for biomarker discovery. *Sci Rep* 2018; **8**: 3945.

3 Cho S, Yang HC, Rhee WJ. Development and comparative analysis of human urine exosome isolation strategies. *Process Biochem* 2020; **88**: 197–203.

Supplementary Tables

Supplementary Table 1. Differentially expressed miRNAs (DEMs) in urine. (a) Upregulated miRNAs (b) Downregulated miRNAs.

(a) Upregulated miRNAs

miRNA	Train			Test		
	Base mean	**Log2 fold change**	**P-adjusted**	**Base mean**	**Log2 fold change**	**P-adjusted**
hsa-miR-514a-3p	36·7	2·35	<0·0001	74.4	2.97	<0.0001
hsa-miR-194-5p	553·1	1·17	<0·0001	767.2	1.09	<0.0001
hsa-miR-100-5p	61·2	1·05	<0·0001	74.1	0.90	<0.0001
hsa-miR-508-3p	12·0	1·96	<0·0001	13.9	1.72	<0.0001
hsa-miR-192-5p/215-5p	2135·3	1·02	<0·0001	2832.8	0.86	<0.0001
hsa-miR-146a-5p	335·8	1·41	<0·0001	272.3	0.99	<0.0001
hsa-miR-509-3p	21·7	1·62	<0·0001	23.8	1.38	4.7x10^{-4}
hsa-miR-21-5p	7528·9	0·71	<0·0001	9701.1	0.60	7.8x10^{-4}
hsa-miR-181b-5p	42·4	0·52	<0·0001	52.4	0.32	5.0x10^{-2}
hsa-miR-135a-5p	60·2	0·97	<0·0001	70.0	0.49	7.7x10^{-2}
hsa-miR-378a-5p	7·3	0·87	<0·0001	9.1	1.18	<0.0001
hsa-miR-378a-3p/378c/378d/378e	146·2	0·80	<0·0001	185.6	0.79	2.5x10^{-3}
hsa-miR-424-5p	113·1	0·52	<0·0001	145.9	0.68	<0.0001
hsa-miR-486-5p	68·5	1·39	<0·0001	77.4	-0.01	9.9x10^{-1}
hsa-miR-1246	57·6	1·37	<0·0001	45.6	-0.80	1.1x10^{-1}
hsa-miR-501-3p	37·9	0·53	<0·0001	49.1	0.70	6.7x10^{-4}
hsa-miR-653-5p	5·8	0·55	<0·0001	9.2	0.61	1.4x10^{-2}
hsa-miR-132-3p	19·5	0·50	6.7x10^{-4}	23.7	0.55	4.2x10^{-3}
hsa-miR-338-3p	43·8	0·61	9.2x10^{-4}	55.1	0.50	4.0x10^{-2}
hsa-miR-15a-5p	47·5	0·50	2.1x10^{-3}	65.0	0.97	<0.0001
hsa-miR-484	20·8	0·59	2.5x10^{-3}	26.6	0.44	1.2x10^{-1}

hsa-miR-1269a-3p	7·8	0·62	$2.7x10^{-3}$	7.5	0.82	$3.5x10^{-3}$
hsa-miR-142-5p	168·8	0·97	$9.1x10^{-3}$	270.6	1.50	$9.5x10^{-3}$
hsa-miR-378i	6·4	0·60	$1.1x10^{-2}$	6.8	0.49	$1.9x10^{-1}$
hsa-miR-199a-3p/199b-3p	122·7	0·62	$3.1x10^{-2}$	115.2	1.38	<0.0001
hsa-miR-143-3p	85·4	0·73	$4.5x10^{-2}$	100.3	1.27	$2.0x10^{-2}$

(b) Downregulated miRNAs

	Train			Test		
miRNA	**Base mean**	**Log2 fold change**	**P-adjusted**	**Base mean**	**Log2 fold change**	**P-adjusted**
hsa-let-7e-5p	3689·7	-0·91	<0.0001	4228.4	-0.57	$1.2x10^{-3}$
hsa-let-7g-5p	1555·0	-0·80	<0.0001	1954.4	-0.50	$2.5x10^{-3}$
hsa-let-7f-5p	16371·0	-0·54	<0.0001	19893.1	-0.38	$1.3x10^{-3}$
hsa-let-7a-5p/7c-5p	32531·7	-0·58	<0.0001	38745.7	-0.36	$1.5x10^{-2}$
hsa-let-7d-5p	569·5	-0·63	<0.0001	645.9	-0.43	$3.5x10^{-3}$
hsa-miR-744-5p	121·5	-0·70	<0.0001	120.6	-0.26	$4.0x10^{-2}$
hsa-miR-4728-3p	9·7	-0·95	<0.0001	10.6	-0.41	$7.7x10^{-2}$
hsa-miR-331-3p	36·9	-0·79	<0.0001	42.0	-0.24	$2.5x10^{-1}$
hsa-miR-1306-5p	31·2	-0·72	<0.0001	34.0	-0.42	$1.7x10^{-2}$
hsa-miR-551b-3p	6·3	-0·75	<0.0001	9.0	-0.52	$5.0x10^{-2}$
hsa-miR-92b-5p	9·6	-0·65	<0.0001	9.2	-0.01	$9.9x10^{-1}$
hsa-miR-30c-1-3p	5·9	-0·50	<0.0001	6.9	-0.24	$1.8x10^{-1}$
hsa-miR-934	75·5	-0·51	<0.0001	103.1	-0.46	$1.7x10^{-2}$
hsa-miR-574-3p	133·0	-0·59	$3.2x10^{-4}$	137.6	-0.51	$2.5x10^{-2}$
hsa-miR-296-3p	4·3	-0·57	$3.8x10^{-4}$	4.4	-0.05	<0.0001
hsa-miR-574-5p	98·5	-0·58	$8.9x10^{-4}$	92.6	-0.62	$9.5x10^{-3}$
hsa-miR-582-5p	4·3	-0·51	$9.7x10^{-4}$	5.7	-0.30	<0.0001
hsa-miR-30b-3p	2·6	-0·52	$1.2x10^{-3}$	2.6	0.20	<0.0001
hsa-miR-888-5p	6·2	-0·58	$1.5x10^{-2}$	8.3	-0.31	$3.9x10^{-1}$

Supplementary Table 2. Overrepresented pathways of DEMs in urine. (a) 36 overrepresented pathways in KEGG (*p*-adjusted <0·05) (b) Top 100 overrepresented GO terms according to $-\log_{10}$ (*p*-adjusted) (*p*-adjusted <0·05).

(a)

Category	Subcategory	Enrichment	P-value	P-adjusted	Expected	Observed	Ratio	miRNAs/precursors
KEGG (miRPathDB)	Pancreatic cancer	over-represented	3.79E-06	5.72E-04	4.943	16	3.237	hsa-miR-21-5p; hsa-miR-378a-3p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-378i; hsa-miR-486-5p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7g-5p; hsa-miR-574-3p; hsa-miR-582-5p; hsa-miR-888-5p
KEGG (miRPathDB)	Proteoglycans in cancer	over-represented	2.19E-05	1.65E-03	5.614	16	2.850	hsa-miR-21-5p; hsa-miR-194-5p; hsa-miR-378a-3p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-132-3p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7g-5p; hsa-miR-744-5p; hsa-miR-574-3p; hsa-miR-331-3p; hsa-miR-582-5p
KEGG (miRPathDB)	Colorectal cancer	over-represented	5.21E-05	2.29E-03	4.660	14	3.004	hsa-miR-21-5p; hsa-miR-378a-3p; hsa-miR-146a-5p; hsa-miR-1246; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-378i; hsa-miR-142-5p; hsa-let-7g-5p; hsa-miR-574-3p; hsa-miR-582-5p; hsa-miR-888-5p
KEGG (miRPathDB)	Prostate cancer	over-represented	7.57E-05	2.29E-03	6.885	17	2.469	hsa-miR-21-5p; hsa-miR-194-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-486-5p; hsa-let-7a-5p; hsa-miR-744-5p; hsa-miR-574-3p; hsa-miR-582-5p
KEGG (miRPathDB)	MicroRNAs in cancer	over-represented	7.38E-05	2.29E-03	9.215	20	2.170	hsa-miR-21-5p; hsa-miR-194-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-574-3p
KEGG (miRPathDB)	Non-small cell lung cancer	over-represented	1.05E-04	2.64E-03	4.307	13	3.018	hsa-miR-21-5p; hsa-miR-378a-3p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7g-5p; hsa-miR-744-5p; hsa-miR-574-3p; hsa-miR-331-3p
KEGG (miRPathDB)	FoxO signaling pathway	over-represented	2.02E-04	3.85E-03	5.931	15	2.529	hsa-miR-21-5p; hsa-miR-194-5p; hsa-miR-378a-3p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-486-5p;

								hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-miR-574-3p
KEGG (miRPathDB)	Renal cell carcinoma	over-represented	2.04E-04	3.85E-03	3.354	11	3.280	hsa-miR-21-5p; hsa-miR-194-5p; hsa-miR-378a-3p; hsa-miR-424-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-378i; hsa-miR-142-5p; hsa-miR-574-3p
KEGG (miRPathDB)	Pathways in cancer	over-represented	2.65E-04	4.45E-03	7.556	17	2.250	hsa-miR-21-5p; hsa-miR-194-5p; hsa-miR-378a-3p; hsa-miR-146a-5p; hsa-miR-1246; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-486-5p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7g-5p; hsa-miR-574-3p; hsa-miR-582-5p
KEGG (miRPathDB)	Endometrial cancer	over-represented	3.44E-04	5.20E-03	4.166	12	2.880	hsa-miR-21-5p; hsa-miR-378a-3p; hsa-miR-146a-5p; hsa-miR-1246; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-miR-744-5p
KEGG (miRPathDB)	Hippo signaling pathway	over-represented	5.61E-04	7.71E-03	3.142	10	3.182	hsa-miR-21-5p; hsa-miR-378a-3p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-934; hsa-miR-744-5p; hsa-miR-574-3p
KEGG (miRPathDB)	Focal adhesion	over-represented	8.14E-04	9.45E-03	4.555	12	2.635	hsa-miR-194-5p; hsa-miR-378a-3p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-486-5p; hsa-miR-142-5p; hsa-miR-744-5p; hsa-miR-574-3p
KEGG (miRPathDB)	HIF-1 signaling pathway	over-represented	8.08E-04	9.45E-03	3.283	10	3.046	hsa-miR-21-5p; hsa-miR-194-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-132-3p; hsa-miR-486-5p; hsa-let-7a-5p; hsa-miR-574-3p
KEGG (miRPathDB)	mTOR signaling pathway	over-represented	1.12E-03	1.13E-02	2.260	8	3.540	hsa-miR-21-5p; hsa-miR-378a-3p; hsa-miR-424-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-378i; hsa-miR-142-5p; hsa-miR-744-5p
KEGG (miRPathDB)	Ribosome	over-represented	1.07E-03	1.13E-02	0.847	5	5.901	hsa-miR-100-5p; hsa-miR-484; hsa-let-7a-5p; hsa-miR-744-5p; hsa-miR-331-3p
KEGG (miRPathDB)	Epstein-Barr virus infection	over-represented	1.34E-03	1.16E-02	3.495	10	2.861	hsa-miR-21-5p; hsa-miR-378a-3p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-let-7a-5p; hsa-let-7e-5p; hsa-miR-744-5p; hsa-miR-331-3p

KEGG (miRPathDB)	Epithelial cell signaling in Helicobacter pylori infection	over-represented	1.30E-03	1.16E-02	0.883	5	5.665	hsa-miR-194-5p; hsa-miR-146a-5p; hsa-let-7a-5p; hsa-let-7g-5p; hsa-miR-574-3p
KEGG (miRPathDB)	Wnt signaling pathway	over-represented	1.38E-03	1.16E-02	2.330	8	3.433	hsa-miR-194-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-miR-15a-5p; hsa-miR-744-5p; hsa-miR-574-5p; hsa-miR-574-3p
KEGG (miRPathDB)	MAPK signaling pathway	over-represented	1.46E-03	1.16E-02	3.531	10	2.832	hsa-miR-21-5p; hsa-miR-378a-3p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-378i; hsa-miR-142-5p; hsa-miR-574-3p
KEGG (miRPathDB)	Tuberculosis	over-represented	1.57E-03	1.18E-02	0.918	5	5.447	hsa-miR-21-5p; hsa-miR-146a-5p; hsa-miR-135a-5p; hsa-miR-143-3p; hsa-miR-574-3p
KEGG (miRPathDB)	PI3K-Akt signaling pathway	over-represented	1.86E-03	1.34E-02	4.978	12	2.411	hsa-miR-21-5p; hsa-miR-378a-3p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-let-7a-5p; hsa-let-7g-5p; hsa-miR-574-3p; hsa-miR-582-5p
KEGG (miRPathDB)	Leishmaniasis	over-represented	2.80E-03	1.84E-02	0.636	4	6.294	hsa-miR-21-5p; hsa-miR-146a-5p; hsa-miR-199a-3p; hsa-miR-143-3p
KEGG (miRPathDB)	Hepatitis B	over-represented	2.76E-03	1.84E-02	5.931	13	2.192	hsa-miR-21-5p; hsa-miR-378a-3p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7g-5p; hsa-miR-574-3p; hsa-miR-888-5p
KEGG (miRPathDB)	Small cell lung cancer	over-represented	3.78E-03	2.38E-02	3.990	10	2.507	hsa-miR-21-5p; hsa-miR-378a-3p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-486-5p; hsa-miR-574-3p
KEGG (miRPathDB)	Malaria	over-represented	4.08E-03	2.46E-02	0.353	3	8.497	hsa-miR-21-5p; hsa-miR-146a-5p; hsa-miR-143-3p
KEGG (miRPathDB)	NF-kappa B signaling pathway	over-represented	4.72E-03	2.74E-02	1.165	5	4.291	hsa-miR-21-5p; hsa-miR-146a-5p; hsa-miR-135a-5p; hsa-miR-143-3p; hsa-let-7a-5p

KEGG (miRPathDB)	Cell cycle	over-represented	5.67E-03	3.17E-02	5.649	12	2.124	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-378a-3p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-501-3p; hsa-miR-15a-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7g-5p; hsa-miR-574-3p
KEGG (miRPathDB)	Rap1 signaling pathway	over-represented	6.84E-03	3.44E-02	2.366	7	2.959	hsa-miR-378a-3p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-132-3p; hsa-miR-378i; hsa-miR-142-5p; hsa-miR-574-3p
KEGG (miRPathDB)	Neurotrophin signaling pathway	over-represented	6.43E-03	3.44E-02	3.601	9	2.499	hsa-miR-21-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-miR-744-5p
KEGG (miRPathDB)	Regulation of actin cytoskeleton	over-represented	6.84E-03	3.44E-02	2.366	7	2.959	hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-miR-143-3p; hsa-miR-132-3p; hsa-let-7a-5p; hsa-miR-574-3p
KEGG (miRPathDB)	Jak-STAT signaling pathway	over-represented	7.44E-03	3.62E-02	2.401	7	2.916	hsa-miR-21-5p; hsa-miR-194-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-let-7f-5p; hsa-let-7g-5p
KEGG (miRPathDB)	Bladder cancer	over-represented	8.47E-03	4.00E-02	4.449	10	2.248	hsa-miR-21-5p; hsa-miR-378a-3p; hsa-miR-146a-5p; hsa-miR-135a-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-132-3p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7g-5p
KEGG (miRPathDB)	p53 signaling pathway	over-represented	9.14E-03	4.18E-02	5.225	11	2.105	hsa-miR-21-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-15a-5p; hsa-miR-486-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-miR-582-5p; hsa-miR-888-5p
KEGG (miRPathDB)	Amoebiasis	over-represented	1.12E-02	4.77E-02	0.494	3	6.069	hsa-miR-21-5p; hsa-miR-146a-5p; hsa-miR-143-3p
KEGG (miRPathDB)	Chronic myeloid leukemia	over-represented	1.14E-02	4.77E-02	6.143	12	1.953	hsa-miR-21-5p; hsa-miR-378a-3p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-378i; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7g-5p; hsa-miR-574-3p
KEGG (miRPathDB)	African trypanosomiasis	over-represented	1.13E-02	4.77E-02	0.177	2	11.329	hsa-miR-21-5p; hsa-miR-146a-5p

(b)

Category	Subcategory	Enrichment	P-value	P-adjusted	Expected	Observed	Ratio	miRNAs/precursors
Annotations derived over miRTarBase (Gene Ontology)	positive regulation of glucose metabolic process GO0010907	over-represented	1.05E-10	7.03E-07	4.895	22	4.495	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-338-3p; hsa-miR-135a-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-378i; hsa-miR-484; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-934; hsa-miR-744-5p; hsa-miR-92b-5p; hsa-miR-331-3p; hsa-miR-888-5p
Annotations derived over miRTarBase (Gene Ontology)	B cell proliferation GO0042100	over-represented	1.20E-10	7.03E-07	3.933	20	5.085	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-194-5p; hsa-miR-181b-5p; hsa-miR-146a-5p; hsa-miR-135a-5p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-486-5p; hsa-miR-484; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-1306-5p; hsa-miR-574-5p; hsa-miR-331-3p
Annotations derived over miRTarBase (Gene Ontology)	negative regulation of long-chain fatty acid import across plasma membrane GO0010748	over-represented	1.40E-09	5.44E-06	3.521	18	5.113	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-378a-3p; hsa-miR-100-5p; hsa-miR-338-3p; hsa-miR-135a-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-132-3p; hsa-miR-378i; hsa-miR-484; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-92b-5p
Annotations derived over miRTarBase (Gene Ontology)	activation of protein kinase activity GO0032147	over-represented	1.09E-08	1.87E-05	11.077	29	2.618	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-338-3p; hsa-miR-135a-5p; hsa-miR-501-3p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-378i; hsa-miR-484; hsa-miR-378a-5p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-574-5p; hsa-miR-331-3p; hsa-miR-582-5p; hsa-miR-30c-1-3p; hsa-miR-296-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	response to UV-A GO0070141	over-represented	1.08E-08	1.87E-05	5.599	21	3.751	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-378a-3p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-338-3p; hsa-miR-135a-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-378i; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-574-5p; hsa-miR-574-3p
Annotations derived over miRTarBase (Gene Ontology)	response to iron ion GO0010039	over-represented	1.60E-08	1.87E-05	5.719	21	3.672	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-424-5p; hsa-miR-338-3p; hsa-miR-135a-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-484; hsa-miR-378a-5p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p;

								hsa-let-7d-5p; hsa-miR-582-5p; hsa-miR-30c-1-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	MAP kinase kinase kinase activity GO0004709	over-represented	1.34E-08	1.87E-05	3.091	16	5.176	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-509-3p; hsa-miR-132-3p; hsa-miR-484; hsa-let-7a-5p; hsa-let-7g-5p; hsa-miR-574-3p; hsa-miR-331-3p; hsa-miR-582-5p
Annotations derived over miRTarBase (Gene Ontology)	SMAD protein complex GO0071141	over-represented	1.02E-08	1.87E-05	6.784	23	3.390	hsa-miR-194-5p; hsa-miR-181b-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-486-5p; hsa-miR-653-5p; hsa-miR-484; hsa-miR-508-3p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-574-5p; hsa-miR-574-3p; hsa-miR-30c-1-3p; hsa-miR-888-5p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	regulation of cell death GO0010941	over-represented	1.58E-08	1.87E-05	3.589	17	4.736	hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-484; hsa-miR-378a-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-331-3p; hsa-miR-296-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	regulation of lipid metabolic process GO0019216	over-represented	1.20E-08	1.87E-05	9.583	27	2.817	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-378a-3p; hsa-miR-100-5p; hsa-miR-424-5p; hsa-miR-338-3p; hsa-miR-135a-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-509-3p; hsa-miR-132-3p; hsa-miR-514a-3p; hsa-miR-484; hsa-miR-378a-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-1306-5p; hsa-miR-331-3p; hsa-miR-582-5p; hsa-miR-30c-1-3p; hsa-miR-296-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	ATP synthesis coupled electron transport GO0042773	over-represented	1.76E-08	1.87E-05	0.343	7	20.380	hsa-miR-21-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-143-3p; hsa-let-7a-5p; hsa-miR-744-5p; hsa-miR-296-3p
Annotations derived over miRTarBase (Gene Ontology)	tRNA aminoacylation for protein translation GO0006418	over-represented	2.27E-08	2.21E-05	3.675	17	4.626	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-100-5p; hsa-miR-424-5p; hsa-miR-484; hsa-miR-378a-5p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-574-5p; hsa-miR-331-3p; hsa-miR-4728-3p; hsa-miR-296-3p

Annotations derived over miRTarBase (Gene Ontology)	I-SMAD binding GO0070411	over-represented	4.15E-08	3.60E-05	7.282	23	3.159	hsa-miR-21-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-1246; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-486-5p; hsa-miR-653-5p; hsa-miR-484; hsa-miR-142-5p; hsa-let-7f-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-574-5p; hsa-miR-574-3p; hsa-miR-331-3p; hsa-miR-30c-1-3p; hsa-miR-888-5p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	embryonic digestive tract development GO0048566	over-represented	4.32E-08	3.60E-05	3.349	16	4.778	hsa-miR-21-5p; hsa-miR-378a-3p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-338-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-378i; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-574-5p
Annotations derived over miRTarBase (Gene Ontology)	SMAD protein signal transduction GO0060395	over-represented	4.84E-08	3.77E-05	16.298	34	2.086	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-338-3p; hsa-miR-135a-5p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-378i; hsa-miR-486-5p; hsa-miR-653-5p; hsa-miR-484; hsa-miR-378a-5p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-934; hsa-miR-744-5p; hsa-miR-574-5p; hsa-miR-574-3p; hsa-miR-331-3p; hsa-miR-4728-3p; hsa-miR-582-5p; hsa-miR-30c-1-3p; hsa-miR-888-5p; hsa-miR-296-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	phosphate-containing compound metabolic process GO0006796	over-represented	5.97E-08	4.10E-05	3.916	17	4.342	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-181b-5p; hsa-miR-146a-5p; hsa-miR-1246; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-484; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-574-3p
Annotations derived over miRTarBase (Gene Ontology)	positive regulation of glycogen biosynthetic process GO0045725	over-represented	5.91E-08	4.10E-05	8.089	24	2.967	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-378a-3p; hsa-miR-100-5p; hsa-miR-424-5p; hsa-miR-338-3p; hsa-miR-135a-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-509-3p; hsa-miR-378i; hsa-miR-484; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-miR-744-5p; hsa-miR-574-5p; hsa-miR-92b-5p; hsa-miR-4728-3p; hsa-miR-582-5p; hsa-miR-30c-1-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	positive regulation of epithelial to mesenchymal transition GO0010718	over-represented	7.69E-08	4.87E-05	15.577	33	2.119	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-1246; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-514a-3p; hsa-miR-378i; hsa-miR-486-5p; hsa-miR-484; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-

								744-5p; hsa-miR-574-5p; hsa-miR-574-3p; hsa-miR-331-3p; hsa-miR-4728-3p; hsa-miR-582-5p; hsa-miR-30c-1-3p; hsa-miR-888-5p; hsa-miR-296-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	regulation of JNK cascade GO0046328	over-represented	7.92E-08	4.87E-05	8.913	25	2.805	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-194-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-486-5p; hsa-miR-484; hsa-miR-378a-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-574-3p; hsa-miR-331-3p; hsa-miR-4728-3p; hsa-miR-582-5p; hsa-miR-296-3p
Annotations derived over miRTarBase (Gene Ontology)	enzyme inhibitor activity GO0004857	over-represented	8.56E-08	5.00E-05	11.232	28	2.493	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-194-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-378i; hsa-miR-653-5p; hsa-miR-484; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-1306-5p; hsa-miR-574-5p; hsa-miR-574-3p; hsa-miR-331-3p; hsa-miR-582-5p; hsa-miR-888-5p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	regulation of cell size GO0008361	over-represented	1.01E-07	5.57E-05	9.755	26	2.665	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-194-5p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-338-3p; hsa-miR-199a-3p; hsa-miR-15a-5p; hsa-miR-486-5p; hsa-miR-484; hsa-miR-378a-5p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-574-5p; hsa-miR-574-3p; hsa-miR-331-3p; hsa-miR-582-5p; hsa-miR-296-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	TOR signaling GO0031929	over-represented	1.05E-07	5.57E-05	9.034	25	2.767	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-424-5p; hsa-miR-338-3p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-378i; hsa-miR-653-5p; hsa-miR-484; hsa-miR-378a-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7d-5p; hsa-miR-934; hsa-miR-744-5p; hsa-miR-574-5p; hsa-miR-92b-5p; hsa-miR-296-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	NF-kappaB binding GO0051059	over-represented	1.44E-07	5.84E-05	7.763	23	2.963	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-194-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-1246; hsa-miR-15a-5p; hsa-miR-653-5p; hsa-miR-484; hsa-miR-378a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-

								5p; hsa-miR-1306-5p; hsa-miR-574-5p; hsa-miR-574-3p; hsa-miR-30c-1-3p; hsa-miR-296-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	odontogenesis GO0042476	over-represented	1.23E-07	5.84E-05	5.788	20	3.456	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-194-5p; hsa-miR-378a-3p; hsa-miR-1246; hsa-miR-424-5p; hsa-miR-15a-5p; hsa-miR-378i; hsa-miR-653-5p; hsa-miR-484; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-574-5p; hsa-miR-4728-3p; hsa-miR-30c-1-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	secondary palate development GO0062009	over-represented	1.45E-07	5.84E-05	6.457	21	3.252	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-378a-3p; hsa-miR-146a-5p; hsa-miR-1246; hsa-miR-424-5p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-378i; hsa-miR-486-5p; hsa-miR-484; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-574-5p; hsa-miR-574-3p; hsa-miR-582-5p; hsa-miR-888-5p
Annotations derived over miRTarBase (Gene Ontology)	regulation of signal transduction by p53 class mediator GO1901796	over-represented	1.44E-07	5.84E-05	14.976	32	2.137	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-194-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-424-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-509-3p; hsa-miR-132-3p; hsa-miR-514a-3p; hsa-miR-378i; hsa-miR-653-5p; hsa-miR-484; hsa-miR-378a-5p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-miR-934; hsa-miR-744-5p; hsa-miR-1306-5p; hsa-miR-574-5p; hsa-miR-574-3p; hsa-miR-331-3p; hsa-miR-582-5p; hsa-miR-30c-1-3p; hsa-miR-888-5p; hsa-miR-296-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	cytolytic granule membrane GO0101004	over-represented	1.27E-07	5.84E-05	1.511	11	7.278	hsa-miR-378a-3p; hsa-miR-378i; hsa-miR-484; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-934; hsa-miR-30c-1-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	positive regulation of intrinsic apoptotic signaling pathway GO2001244	over-represented	1.43E-07	5.84E-05	8.450	24	2.840	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-194-5p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-484; hsa-miR-378a-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-934; hsa-miR-744-5p; hsa-miR-331-3p; hsa-miR-888-5p; hsa-miR-296-3p; hsa-miR-30b-3p

Annotations derived over miRTarBase (Gene Ontology)	cysteine-type endopeptidase activity involved in execution phase of apoptosis GO0097200	over-represented	1.18E-07	5.84E-05	0.893	9	10.078	hsa-miR-192-5p; hsa-miR-146a-5p; hsa-miR-143-3p; hsa-miR-132-3p; hsa-miR-484; hsa-let-7a-5p; hsa-let-7g-5p; hsa-miR-582-5p; hsa-miR-888-5p
Annotations derived over miRTarBase (Gene Ontology)	STAT family protein binding GO0097677	over-represented	1.55E-07	6.04E-05	3.177	15	4.721	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-194-5p; hsa-miR-181b-5p; hsa-miR-424-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-574-5p; hsa-miR-574-3p; hsa-miR-331-3p; hsa-miR-296-3p
Annotations derived over miRTarBase (Gene Ontology)	respiratory chain complex IV GO0045277	over-represented	1.66E-07	6.05E-05	4.190	17	4.057	hsa-miR-21-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-135a-5p; hsa-miR-143-3p; hsa-miR-132-3p; hsa-miR-484; hsa-miR-378a-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-30c-1-3p; hsa-miR-296-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	fibroblast growth factor binding GO0017134	over-represented	1.71E-07	6.05E-05	7.162	22	3.072	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-424-5p; hsa-miR-338-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-484; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-1306-5p; hsa-miR-574-5p; hsa-miR-331-3p; hsa-miR-30c-1-3p; hsa-miR-296-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	positive regulation of G2M transition of mitotic cell cycle GO0010971	over-represented	1.71E-07	6.05E-05	12.400	29	2.339	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-338-3p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-378i; hsa-miR-486-5p; hsa-miR-653-5p; hsa-miR-484; hsa-miR-378a-5p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-1306-5p; hsa-miR-574-5p; hsa-miR-331-3p; hsa-miR-296-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	negative regulation of amyloid-beta formation GO1902430	over-represented	2.13E-07	6.96E-05	7.247	22	3.036	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-378a-3p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-miR-199a-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-484; hsa-miR-378a-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-1306-5p; hsa-miR-574-5p; hsa-miR-574-3p; hsa-miR-30c-1-3p; hsa-miR-30b-3p

Annotations derived over miRTarBase (Gene Ontology)	positive regulation of mitochondrial membrane potential GO0010918	over-represented	2.14E-07	6.96E-05	1.958	12	6.129	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-378i; hsa-let-7g-5p; hsa-miR-744-5p; hsa-miR-92b-5p; hsa-miR-296-3p
Annotations derived over miRTarBase (Gene Ontology)	regulation of nuclear-transcribed mRNA catabolic process, nonsense-mediated decay GO2000622	over-represented	2.14E-07	6.96E-05	1.958	12	6.129	hsa-miR-378a-3p; hsa-miR-484; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-331-3p; hsa-miR-30c-1-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	satellite DNA binding GO0003696	over-represented	2.27E-07	7.17E-05	1.597	11	6.887	hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-15a-5p; hsa-miR-486-5p; hsa-miR-484; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-296-3p
Annotations derived over miRTarBase (Gene Ontology)	positive regulation of G1S transition of mitotic cell cycle GO1900087	over-represented	2.52E-07	7.73E-05	10.957	27	2.464	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-338-3p; hsa-miR-135a-5p; hsa-miR-501-3p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-378i; hsa-miR-484; hsa-miR-378a-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-1306-5p; hsa-miR-574-3p; hsa-miR-331-3p; hsa-miR-582-5p
Annotations derived over miRTarBase (Gene Ontology)	macromolecule biosynthetic process GO0009059	over-represented	3.17E-07	9.05E-05	1.649	11	6.672	hsa-miR-194-5p; hsa-miR-424-5p; hsa-miR-484; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-331-3p; hsa-miR-582-5p
Annotations derived over miRTarBase (Gene Ontology)	exon-exon junction complex GO0035145	over-represented	3.18E-07	9.05E-05	2.439	13	5.331	hsa-miR-21-5p; hsa-miR-378a-3p; hsa-miR-484; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-331-3p; hsa-miR-30c-1-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	lipopolysaccharide-mediated signaling pathway GO0031663	over-represented	3.02E-07	9.05E-05	5.496	19	3.457	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-143-3p; hsa-miR-132-3p; hsa-miR-653-5p; hsa-miR-378a-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-1306-5p; hsa-miR-574-5p; hsa-miR-574-3p; hsa-miR-30c-1-3p; hsa-miR-30b-3p

Annotations derived over miRTarBase (Gene Ontology)	filopodium membrane GO0031527	over-represented	3.69E-07	1.00E-04	4.980	18	3.614	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-181b-5p; hsa-miR-338-3p; hsa-miR-199a-3p; hsa-miR-132-3p; hsa-miR-514a-3p; hsa-miR-486-5p; hsa-miR-484; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-574-5p; hsa-miR-331-3p; hsa-miR-30c-1-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	glutamatergic synapse GO0098978	over-represented	3.68E-07	1.00E-04	19.630	36	1.834	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-194-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-1246; hsa-miR-424-5p; hsa-miR-338-3p; hsa-miR-135a-5p; hsa-miR-501-3p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-486-5p; hsa-miR-484; hsa-miR-508-3p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-934; hsa-miR-744-5p; hsa-miR-1306-5p; hsa-miR-574-5p; hsa-miR-92b-5p; hsa-miR-574-3p; hsa-miR-331-3p; hsa-miR-582-5p; hsa-miR-30c-1-3p; hsa-miR-296-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	cadmium ion binding GO0046870	over-represented	4.17E-07	1.11E-04	2.078	12	5.775	hsa-miR-146a-5p; hsa-miR-143-3p; hsa-miR-484; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-574-5p; hsa-miR-582-5p; hsa-miR-30c-1-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	positive regulation of receptor binding GO1900122	over-represented	4.37E-07	1.12E-04	1.700	11	6.470	hsa-miR-21-5p; hsa-miR-338-3p; hsa-miR-501-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-378a-5p; hsa-miR-142-5p; hsa-let-7e-5p; hsa-miR-582-5p; hsa-miR-888-5p
Annotations derived over miRTarBase (Gene Ontology)	hormone-mediated signaling pathway GO0009755	over-represented	4.40E-07	1.12E-04	7.539	22	2.918	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-15a-5p; hsa-miR-509-3p; hsa-miR-132-3p; hsa-miR-653-5p; hsa-miR-484; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-574-5p; hsa-miR-574-3p; hsa-miR-331-3p; hsa-miR-30c-1-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	cardiac muscle cell proliferation GO0060038	over-represented	4.57E-07	1.14E-04	2.095	12	5.727	hsa-miR-21-5p; hsa-miR-378a-3p; hsa-miR-424-5p; hsa-miR-15a-5p; hsa-miR-378i; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-582-5p

Annotations derived over miRTarBase (Gene Ontology)	negative regulation of cellular senescence GO2000773	over-represented	4.70E-07	1.14E-04	12.091	28	2.316	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-194-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-338-3p; hsa-miR-501-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-486-5p; hsa-miR-484; hsa-miR-378a-5p; hsa-miR-508-3p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-331-3p; hsa-miR-30c-1-3p; hsa-miR-888-5p; hsa-miR-296-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	G protein-coupled receptor binding GO0001664	over-represented	5.26E-07	1.25E-04	13.001	29	2.231	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-338-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-486-5p; hsa-miR-653-5p; hsa-miR-484; hsa-miR-378a-5p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-1306-5p; hsa-miR-574-5p; hsa-miR-92b-5p; hsa-miR-331-3p; hsa-miR-582-5p; hsa-miR-30c-1-3p; hsa-miR-296-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	transforming growth factor beta receptor binding GO0005160	over-represented	5.33E-07	1.25E-04	5.101	18	3.529	hsa-miR-21-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-378i; hsa-miR-486-5p; hsa-miR-484; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-582-5p
Annotations derived over miRTarBase (Gene Ontology)	viral exocytosis GO0046754	over-represented	5.90E-07	1.30E-04	1.391	10	7.189	hsa-miR-378a-3p; hsa-miR-378i; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-934; hsa-miR-30c-1-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	antigen processing and presentation following phagocytosis GO0002747	over-represented	5.90E-07	1.30E-04	1.391	10	7.189	hsa-miR-378a-3p; hsa-miR-378i; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-934; hsa-miR-30c-1-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	antigen processing and presentation of polysaccharide antigen via MHC class II GO0002505	over-represented	5.90E-07	1.30E-04	1.391	10	7.189	hsa-miR-378a-3p; hsa-miR-378i; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-934; hsa-miR-30c-1-3p; hsa-miR-30b-3p

Annotations derived over miRTarBase (Gene Ontology)	positive regulation of endothelial cell migration GO0010595	over-represented	6.38E-07	1.36E-04	18.892	35	1.853	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-194-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-338-3p; hsa-miR-135a-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-509-3p; hsa-miR-132-3p; hsa-miR-378i; hsa-miR-486-5p; hsa-miR-484; hsa-miR-378a-5p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-574-5p; hsa-miR-92b-5p; hsa-miR-574-3p; hsa-miR-331-3p; hsa-miR-582-5p; hsa-miR-30c-1-3p; hsa-miR-888-5p; hsa-miR-296-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	peptidyl-tyrosine autophosphorylation GO0038083	over-represented	6.39E-07	1.36E-04	7.024	21	2.990	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-194-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-1246; hsa-miR-135a-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-132-3p; hsa-miR-486-5p; hsa-miR-484; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-574-3p
Annotations derived over miRTarBase (Gene Ontology)	positive regulation of histone deacetylation GO0031065	over-represented	6.88E-07	1.44E-04	5.187	18	3.471	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-1246; hsa-miR-424-5p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-484; hsa-miR-378a-5p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-331-3p
Annotations derived over miRTarBase (Gene Ontology)	response to progesterone GO0032570	over-represented	7.89E-07	1.53E-04	7.110	21	2.954	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-194-5p; hsa-miR-378a-3p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-199a-3p; hsa-miR-15a-5p; hsa-miR-509-3p; hsa-miR-132-3p; hsa-miR-514a-3p; hsa-miR-378i; hsa-miR-484; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-574-3p
Annotations derived over miRTarBase (Gene Ontology)	alphav-beta3 integrin-IGF-1-IGF1R complex GO0035867	over-represented	8.01E-07	1.53E-04	5.839	19	3.254	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-194-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-338-3p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-486-5p; hsa-miR-484; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-574-5p; hsa-miR-30c-1-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	dendritic shaft GO0043198	over-represented	7.79E-07	1.53E-04	7.780	22	2.828	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-194-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-1246; hsa-miR-424-5p; hsa-miR-338-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-486-5p; hsa-miR-484; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-574-5p; hsa-miR-30c-1-3p; hsa-miR-296-3p; hsa-miR-30b-3p

Annotations derived over miRTarBase (Gene Ontology)	positive regulation of microtubule nucleation GO0090063	over-represented	7.72E-07	1.53E-04	4.105	16	3.898	hsa-miR-21-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-199a-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-653-5p; hsa-miR-484; hsa-miR-378a-5p; hsa-let-7a-5p; hsa-miR-744-5p; hsa-miR-331-3p; hsa-miR-582-5p; hsa-miR-296-3p
Annotations derived over miRTarBase (Gene Ontology)	ventricular cardiac muscle tissue morphogenesis GO0055010	over-represented	7.77E-07	1.53E-04	4.654	17	3.653	hsa-miR-21-5p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-15a-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-574-5p; hsa-miR-574-3p; hsa-miR-582-5p; hsa-miR-888-5p; hsa-miR-296-3p
Annotations derived over miRTarBase (Gene Ontology)	alanine-tRNA ligase activity GO0004813	over-represented	8.58E-07	1.57E-04	0.206	5	24.261	hsa-miR-484; hsa-miR-378a-5p; hsa-miR-744-5p; hsa-miR-331-3p; hsa-miR-296-3p
Annotations derived over miRTarBase (Gene Ontology)	alanyl-tRNA aminoacylation GO0006419	over-represented	8.58E-07	1.57E-04	0.206	5	24.261	hsa-miR-484; hsa-miR-378a-5p; hsa-miR-744-5p; hsa-miR-331-3p; hsa-miR-296-3p
Annotations derived over miRTarBase (Gene Ontology)	atrial septum morphogenesis GO0060413	over-represented	8.38E-07	1.57E-04	3.607	15	4.159	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-miR-15a-5p; hsa-miR-378i; hsa-miR-142-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-4728-3p; hsa-miR-582-5p
Annotations derived over miRTarBase (Gene Ontology)	positive regulation of extracellular matrix assembly GO1901203	over-represented	8.85E-07	1.59E-04	0.824	8	9.705	hsa-miR-21-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-142-5p; hsa-miR-744-5p; hsa-miR-574-3p
Annotations derived over miRTarBase (Gene Ontology)	centrosome localization GO0051642	over-represented	9.21E-07	1.63E-04	5.891	19	3.225	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-194-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-424-5p; hsa-miR-15a-5p; hsa-miR-484; hsa-miR-378a-5p; hsa-let-7a-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-miR-744-5p; hsa-miR-574-5p; hsa-miR-92b-5p; hsa-miR-30c-1-3p; hsa-miR-296-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	polyubiquitin modification-dependent protein binding GO0031593	over-represented	9.49E-07	1.66E-04	7.866	22	2.797	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-424-5p; hsa-miR-338-3p; hsa-miR-501-3p; hsa-miR-15a-5p; hsa-miR-486-5p; hsa-miR-484; hsa-miR-378a-5p; hsa-miR-508-3p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-

								let-7d-5p; hsa-miR-744-5p; hsa-miR-574-5p; hsa-miR-331-3p; hsa-miR-296-3p
Annotations derived over miRTarBase (Gene Ontology)	epicardium-derived cardiac fibroblast cell development GO0060939	over-represented	1.14E-06	1.85E-04	1.151	9	7.822	hsa-miR-21-5p; hsa-miR-424-5p; hsa-miR-15a-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-582-5p
Annotations derived over miRTarBase (Gene Ontology)	response to follicle-stimulating hormone GO0032354	over-represented	1.14E-06	1.85E-04	1.151	9	7.822	hsa-miR-21-5p; hsa-miR-424-5p; hsa-miR-15a-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-582-5p
Annotations derived over miRTarBase (Gene Ontology)	response to luteinizing hormone GO0034699	over-represented	1.14E-06	1.85E-04	1.151	9	7.822	hsa-miR-21-5p; hsa-miR-424-5p; hsa-miR-15a-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-582-5p
Annotations derived over miRTarBase (Gene Ontology)	BMP signaling pathway GO0030509	over-represented	1.14E-06	1.85E-04	15.251	31	2.033	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-194-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-338-3p; hsa-miR-135a-5p; hsa-miR-199a-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-378i; hsa-miR-653-5p; hsa-miR-484; hsa-miR-378a-5p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-574-5p; hsa-miR-574-3p; hsa-miR-4728-3p; hsa-miR-582-5p; hsa-miR-30c-1-3p; hsa-miR-888-5p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	transforming growth factor beta receptor activity, type III GO0070123	over-represented	1.14E-06	1.85E-04	1.151	9	7.822	hsa-miR-21-5p; hsa-miR-424-5p; hsa-miR-15a-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-582-5p
Annotations derived over miRTarBase (Gene Ontology)	insulin receptor binding GO0005158	over-represented	1.16E-06	1.86E-04	10.940	26	2.377	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-194-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-424-5p; hsa-miR-338-3p; hsa-miR-135a-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-486-5p; hsa-miR-484; hsa-miR-378a-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-574-5p; hsa-miR-331-3p;

								hsa-miR-4728-3p; hsa-miR-30c-1-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	negative regulation of mitochondrial depolarization GO0051902	over-represented	1.18E-06	1.87E-04	2.284	12	5.254	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-181b-5p; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p
Annotations derived over miRTarBase (Gene Ontology)	positive regulation of signaling receptor activity GO2000273	over-represented	1.22E-06	1.89E-04	4.242	16	3.772	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-194-5p; hsa-miR-424-5p; hsa-miR-338-3p; hsa-miR-135a-5p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-378a-5p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-582-5p
Annotations derived over miRTarBase (Gene Ontology)	protein tyrosine kinase activity GO0004713	over-represented	1.24E-06	1.90E-04	21.588	37	1.714	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-194-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-1246; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-509-3p; hsa-miR-132-3p; hsa-miR-378i; hsa-miR-486-5p; hsa-miR-653-5p; hsa-miR-484; hsa-miR-378a-5p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-934; hsa-miR-744-5p; hsa-miR-1306-5p; hsa-miR-92b-5p; hsa-miR-574-3p; hsa-miR-331-3p; hsa-miR-4728-3p; hsa-miR-582-5p; hsa-miR-30c-1-3p; hsa-miR-296-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	transcription coactivator binding GO0001223	over-represented	1.29E-06	1.94E-04	16.281	32	1.965	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-194-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-1246; hsa-miR-424-5p; hsa-miR-338-3p; hsa-miR-135a-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-509-3p; hsa-miR-486-5p; hsa-miR-653-5p; hsa-miR-484; hsa-miR-378a-5p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-574-5p; hsa-miR-574-3p; hsa-miR-331-3p; hsa-miR-30c-1-3p; hsa-miR-888-5p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	definitive erythrocyte differentiation GO0060318	over-represented	1.29E-06	1.94E-04	1.168	9	7.707	hsa-miR-21-5p; hsa-miR-424-5p; hsa-miR-15a-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-582-5p

Annotations derived over miRTarBase (Gene Ontology)	histone H2AXY142 kinase activity GO0140801	over-represented	1.38E-06	2.04E-04	0.223	5	22.395	hsa-miR-21-5p; hsa-miR-100-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p
Annotations derived over miRTarBase (Gene Ontology)	positive regulation of histone methylation GO0031062	over-represented	1.43E-06	2.10E-04	4.294	16	3.727	hsa-miR-192-5p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-1246; hsa-miR-424-5p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-484; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-331-3p; hsa-miR-296-3p
Annotations derived over miRTarBase (Gene Ontology)	fatty acid beta-oxidation GO0006635	over-represented	1.69E-06	2.44E-04	4.912	17	3.461	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-378a-3p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-miR-15a-5p; hsa-miR-484; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-331-3p; hsa-miR-30c-1-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	smoothened signaling pathway GO0007224	over-represented	1.82E-06	2.52E-04	8.158	22	2.697	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-424-5p; hsa-miR-338-3p; hsa-miR-15a-5p; hsa-miR-509-3p; hsa-miR-132-3p; hsa-miR-484; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-miR-934; hsa-miR-744-5p; hsa-miR-574-5p; hsa-miR-331-3p; hsa-miR-582-5p; hsa-miR-30c-1-3p; hsa-miR-296-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	endocardial cushion morphogenesis GO0003203	over-represented	1.90E-06	2.52E-04	10.408	25	2.402	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-378a-3p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-338-3p; hsa-miR-135a-5p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-514a-3p; hsa-miR-378i; hsa-miR-486-5p; hsa-miR-484; hsa-miR-508-3p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-574-5p; hsa-miR-331-3p; hsa-miR-4728-3p; hsa-miR-582-5p
Annotations derived over miRTarBase (Gene Ontology)	phosphatidylinositol 3-kinase binding GO0043548	over-represented	1.89E-06	2.52E-04	8.175	22	2.691	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-194-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-424-5p; hsa-miR-338-3p; hsa-miR-135a-5p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-486-5p; hsa-miR-484; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-331-3p; hsa-miR-30c-1-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	cell-cell contact zone GO0044291	over-represented	1.77E-06	2.52E-04	6.784	20	2.948	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-100-5p; hsa-miR-424-5p; hsa-miR-15a-5p; hsa-miR-653-5p; hsa-miR-484; hsa-miR-378a-5p; hsa-miR-508-3p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-574-5p; hsa-

								miR-582-5p; hsa-miR-30c-1-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	phagosome-lysosome fusion GO0090385	over-represented	1.88E-06	2.52E-04	4.379	16	3.653	hsa-miR-378a-3p; hsa-miR-100-5p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-378i; hsa-miR-508-3p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-934; hsa-miR-744-5p; hsa-miR-30c-1-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	chordate embryonic development GO0043009	over-represented	1.85E-06	2.52E-04	1.958	11	5.618	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-181b-5p; hsa-miR-146a-5p; hsa-miR-1246; hsa-miR-424-5p; hsa-miR-15a-5p; hsa-miR-484; hsa-let-7e-5p; hsa-miR-744-5p; hsa-miR-296-3p
Annotations derived over miRTarBase (Gene Ontology)	response to prostaglandin E GO0034695	over-represented	1.88E-06	2.52E-04	1.219	9	7.381	hsa-miR-21-5p; hsa-miR-424-5p; hsa-miR-15a-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-582-5p
Annotations derived over miRTarBase (Gene Ontology)	positive regulation of phosphatidylinositol 3-kinase activity GO0043552	over-represented	1.93E-06	2.53E-04	6.818	20	2.933	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-574-3p; hsa-miR-331-3p; hsa-miR-582-5p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	negative regulation of G2M transition of mitotic cell cycle GO0010972	over-represented	1.95E-06	2.53E-04	0.910	8	8.789	hsa-miR-21-5p; hsa-miR-338-3p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-331-3p
Annotations derived over miRTarBase (Gene Ontology)	positive regulation of DNA damage response, signal transduction by p53 class mediator GO0043517	over-represented	1.98E-06	2.54E-04	6.183	19	3.073	hsa-miR-192-5p; hsa-miR-194-5p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-378a-5p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-934; hsa-miR-1306-5p; hsa-miR-331-3p; hsa-miR-888-5p

Annotations derived over miRTarBase (Gene Ontology)	nuclear inner membrane GO0005637	over-represented	2.02E-06	2.56E-04	9.669	24	2.482	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-194-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-1246; hsa-miR-424-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-378i; hsa-miR-484; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7e-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-331-3p; hsa-miR-582-5p; hsa-miR-30c-1-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	positive regulation of phosphatidylinositol 3-kinase signaling GO0014068	over-represented	2.15E-06	2.68E-04	17.603	33	1.875	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-194-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-509-3p; hsa-miR-132-3p; hsa-miR-514a-3p; hsa-miR-378i; hsa-miR-486-5p; hsa-miR-484; hsa-miR-378a-5p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-1306-5p; hsa-miR-574-5p; hsa-miR-331-3p; hsa-miR-582-5p; hsa-miR-30c-1-3p; hsa-miR-296-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	positive regulation of cyclin-dependent protein serinethreonine kinase activity GO0045737	over-represented	2.14E-06	2.68E-04	11.266	26	2.308	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-338-3p; hsa-miR-135a-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-132-3p; hsa-miR-378i; hsa-miR-484; hsa-miR-378a-5p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-miR-574-5p; hsa-miR-574-3p; hsa-miR-888-5p
Annotations derived over miRTarBase (Gene Ontology)	methionine-tRNA ligase activity GO0004825	over-represented	2.28E-06	2.72E-04	0.653	7	10.726	hsa-miR-484; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-296-3p
Annotations derived over miRTarBase (Gene Ontology)	methionyl-tRNA aminoacylation GO0006431	over-represented	2.28E-06	2.72E-04	0.653	7	10.726	hsa-miR-484; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-296-3p
Annotations derived over miRTarBase (Gene Ontology)	epithelial to mesenchymal transition GO0001837	over-represented	2.28E-06	2.72E-04	15.680	31	1.977	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-194-5p; hsa-miR-378a-3p; hsa-miR-181b-5p; hsa-miR-146a-5p; hsa-miR-1246; hsa-miR-424-5p; hsa-miR-338-3p; hsa-miR-135a-5p; hsa-miR-199a-3p; hsa-miR-15a-5p; hsa-miR-378i; hsa-miR-486-5p; hsa-miR-484; hsa-miR-508-3p; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-let-7g-5p; hsa-let-7d-5p; hsa-miR-744-5p; hsa-

								miR-574-5p; hsa-miR-574-3p; hsa-miR-331-3p; hsa-miR-582-5p; hsa-miR-30c-1-3p; hsa-miR-888-5p; hsa-miR-296-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	negative regulation of fat cell differentiation GO0045599	over-represented	2.22E-06	2.72E-04	12.108	27	2.230	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-181b-5p; hsa-miR-146a-5p; hsa-miR-1246; hsa-miR-424-5p; hsa-miR-135a-5p; hsa-miR-199a-3p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-509-3p; hsa-miR-132-3p; hsa-miR-486-5p; hsa-miR-484; hsa-miR-142-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-let-7e-5p; hsa-miR-744-5p; hsa-miR-574-5p; hsa-miR-574-3p; hsa-miR-331-3p; hsa-miR-4728-3p; hsa-miR-582-5p; hsa-miR-30c-1-3p; hsa-miR-296-3p; hsa-miR-30b-3p
Annotations derived over miRTarBase (Gene Ontology)	DNA repair complex GO1990391	over-represented	2.34E-06	2.76E-04	3.383	14	4.138	hsa-miR-21-5p; hsa-miR-192-5p; hsa-miR-181b-5p; hsa-miR-100-5p; hsa-miR-146a-5p; hsa-miR-424-5p; hsa-miR-143-3p; hsa-miR-15a-5p; hsa-miR-484; hsa-miR-378a-5p; hsa-let-7a-5p; hsa-let-7f-5p; hsa-miR-1306-5p; hsa-miR-331-3p
Annotations derived over miRTarBase (Gene Ontology)	cellular response to staurosporine GO0072734	over-represented	2.39E-06	2.80E-04	1.254	9	7.179	hsa-miR-192-5p; hsa-miR-146a-5p; hsa-miR-132-3p; hsa-miR-484; hsa-miR-378a-5p; hsa-let-7a-5p; hsa-let-7g-5p; hsa-miR-582-5p; hsa-miR-888-5p

Supplementary Table 3. Coefficients of the multiple regression analysis with the generalized linear model with logit link function.

Variable	Value	Train			Test		
		Coefficient	Standard Error	P-adjusted	Coefficient	Standard Error	P-adjusted
Intercept		-4.66	1.72	0.026	-10.2	3.49	0.014
Cancer status	**Pancreatic cancer**	5.13	0.58	<0.0001	5.10	0.882	<0.0001
Age		0.552	0.54	0.49	-1.17	0.818	0.20
BMI		-0.618	0.49	0.42	1.03	0.717	0.20
Alcohol	**Yes**	-0.016	0.61	0.98	1.81	0.888	0.09
Smoking history	**Past used**	-0.179	0.73	0.92	0.233	0.980	0.81
	Current use	0.007	0.017	0.88	0.0174	0.032	0.67

BMI, Body Mass Index.

Supplementary Table 4. Lists of overlap between urinary DEMs and organoid DEMs. (a) Upregulated miRNAs in urine (b) Downregulated miRNAs in urine.

(a) Upregulated miRNAs in urine

miRNA	Urinary-miRNA AUC (Train set)	Organoid_match (1 vs 1)	Organoid_all (3 vs 3)
hsa-miR-338-3p	0.667	Up	Up
hsa-miR-100-5p	0.764	Up	Down
hsa-miR-378a-5p	0.732	Up	<0·5
hsa-miR-378i	0.704	Up	>-0·5
hsa-miR-378a-3p/378c/378d/378e	0.754	Up	<0·5
hsa-miR-486-5p	0.661	Up	<0·5
hsa-miR-484	0.666	Up	<0·5
hsa-miR-194-5p	0.824	Up	<0·5
hsa-miR-199a-3p/199b-3p	0.649	Up	>-0·5
hsa-miR-424-5p	0.633	<0·5	<0·5
hsa-miR-142-5p	0.623	<0·5	Up
hsa-miR-192-5p/215-5p	0.804	<0·5	Up
hsa-miR-143-3p	0.672	<0·5	Up
hsa-miR-15a-5p	0.689	<0·5	Down
hsa-miR-501-3p	0.674	<0·5	>-0·5
hsa-miR-1246	0.752	>-0·5	Down
hsa-miR-132-3p	0.692	Down	<0·5
hsa-miR-21-5p	0.753	Down	Down
hsa-miR-135a-5p	0.717	Down	Down
hsa-miR-181b-5p	0.715	Down	Down
hsa-miR-146a-5p	0.730	Down	Down
hsa-miR-509-3p	0.803	-	-
hsa-miR-514a-3p	0.865	-	-
hsa-miR-653-5p	0.694	-	-

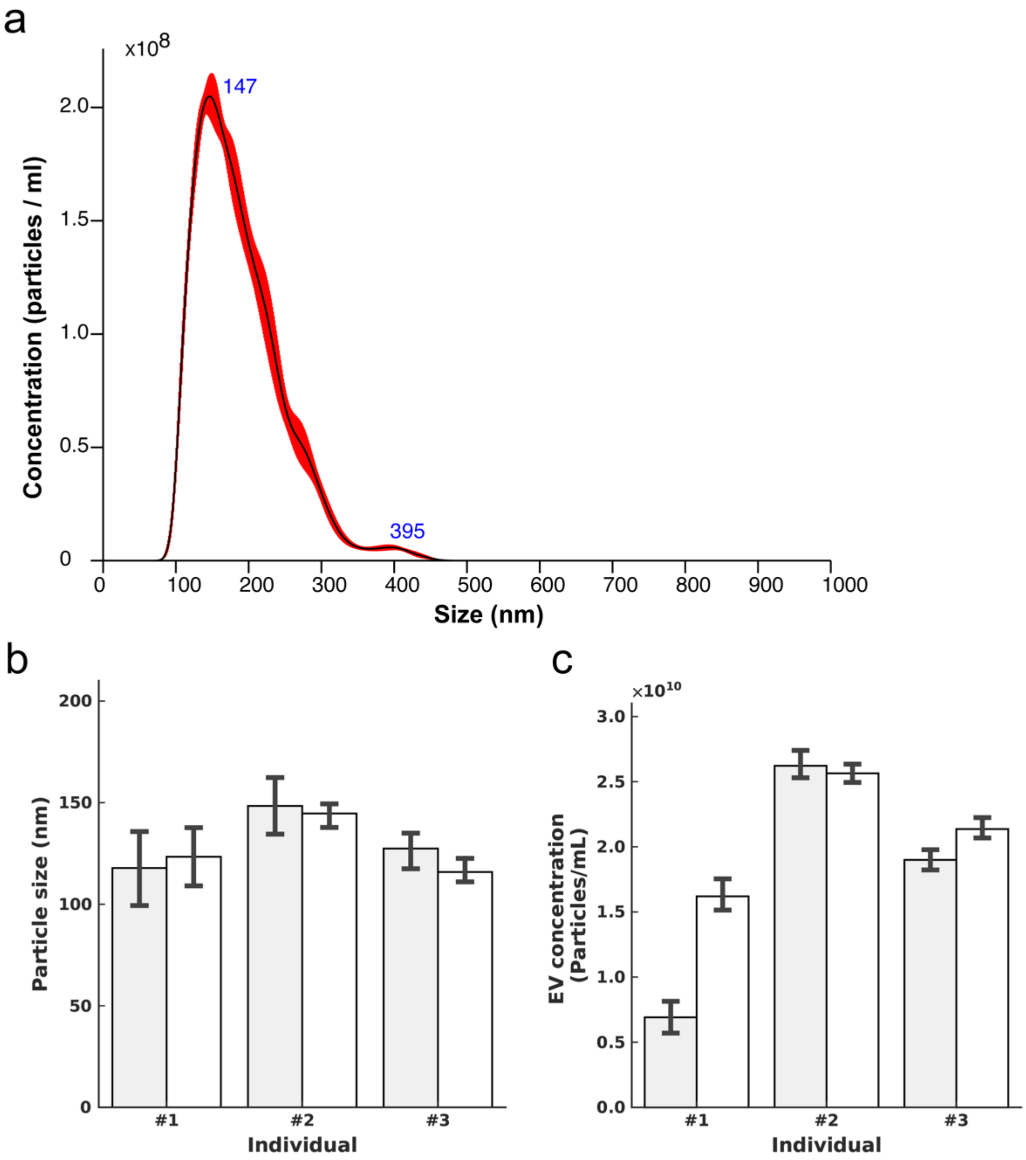
hsa-miR-508-3p	0.818	-	-
hsa-miR-1269a-3p	0.642	-	-

(b) Downregulated miRNAs in urine

miRNA	Urinary-miRNA AUC (Train set)	Organoid_match (1 vs 1)	Organoid_all (3 vs 3)
hsa-miR-92b-5p	0.579	Down	>-0·5
hsa-miR-574-3p	0.542	Down	<0·5
hsa-miR-574-5p	0.591	Down	>-0·5
hsa-miR-744-5p	0.664	Down	Up
hsa-let-7g-5p	0.711	Down	<0·5
hsa-let-7a-5p/7c-5p	0.695	Down	<0·5
hsa-let-7d-5p	0.664	Down	>-0·5
hsa-miR-1306-5p	0.688	>-0·5	Up
hsa-let-7f-5p	0.729	>-0·5	Up
hsa-miR-296-3p	0.569	>-0·5	Up
hsa-miR-331-3p	0.641	Up	Up
hsa-let-7e-5p	0.730	Up	Up
hsa-miR-934	0.631	-	-
hsa-miR-4728-3p	0.653	-	-
hsa-miR-582-5p	0.549	-	-
hsa-miR-30c-1-3p	0.606	-	-
hsa-miR-888-5p	0.535	-	-
hsa-miR-551b-3p	0.590	-	-
hsa-miR-30b-3p	0.504	-	-

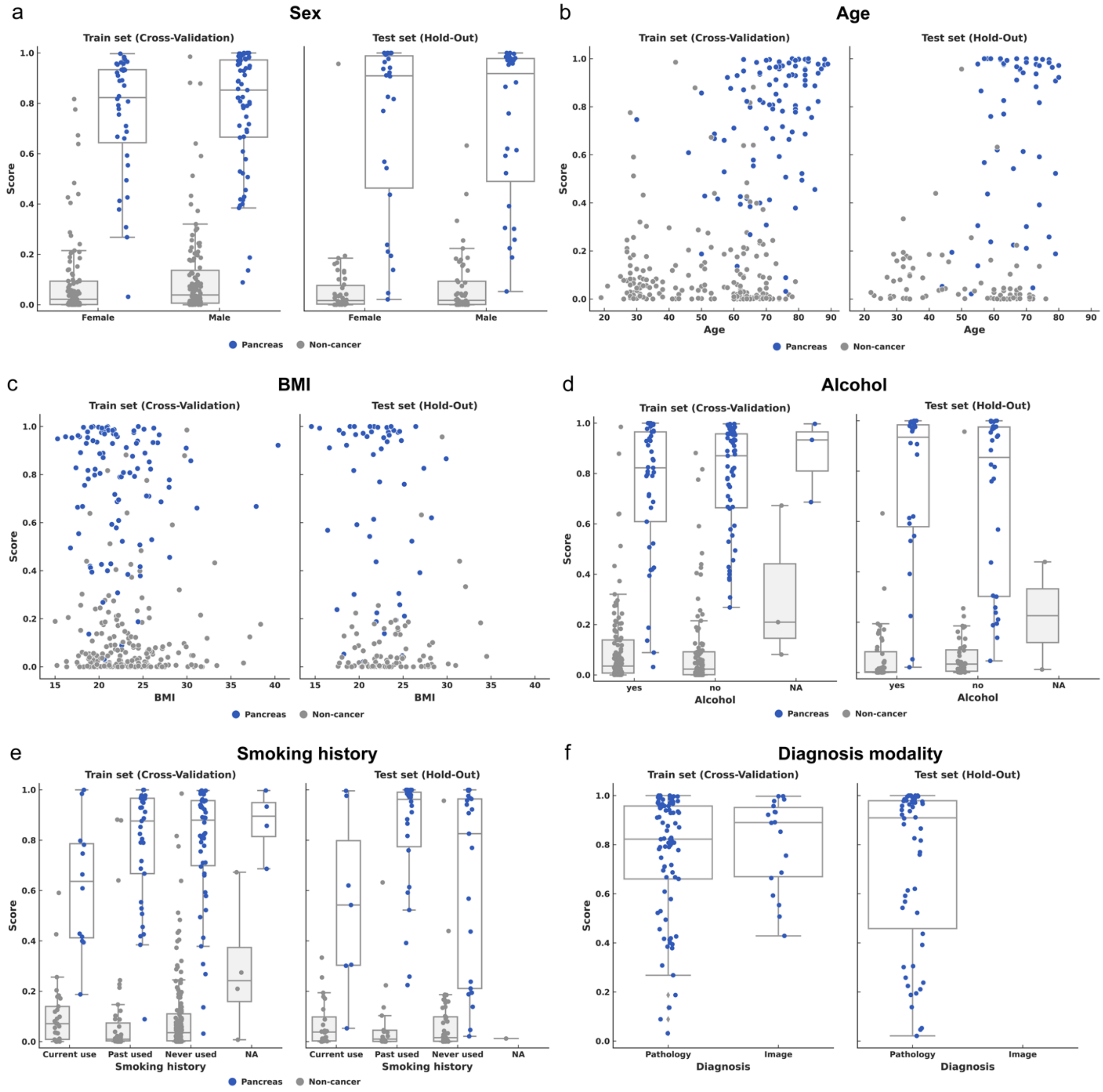
Supplementary Table 5. Verification of 15 DEMs in qPCR.

miRNA	Small RNA-seq	RT-qPCR			
	DEA	Mean Ct	Mean delta Ct	Log2 fold change	P-value
hsa-miR-146a-5p	Up-regulated	24.6	0.25	0.74	0.098
hsa-miR-194-5p	Up-regulated	24.9	0.55	1.05	0.0091
hsa-miR-100-5p	Up-regulated	24.5	0.11	-0.13	0.65
hsa-miR-192-5p	Up-regulated	24.2	-0.20	0.82	0.0052
hsa-miR-378a-5p	Up-regulated	27.2	3.31	0.08	0.91
hsa-miR-338-3p	Up-regulated	30.0	5.93	0.24	0.67
hsa-miR-181b-5p	Up-regulated	25.6	1.23	-0.01	0.97
hsa-miR-15a-5p	Up-regulated	21.2	-2.69	0.06	0.90
hsa-miR-574-5p	Down-regulated	22.4	-1.98	-0.01	0.97
hsa-let-7a-5p	Down-regulated	18.5	-5.91	-0.20	0.59
hsa-let-7d-5p	Down-regulated	22.0	-2.38	-0.31	0.37
hsa-miR-551b-3p	Down-regulated	24.8	1.35	-0.39	0.36
hsa-miR-331-3p	Down-regulated	24.0	-0.20	0.16	0.66
hsa-let-7g-5p	Down-regulated	24.1	-0.32	-0.26	0.10
hsa-let-7e-5p	Down-regulated	20.3	-3.94	-0.23	0.51

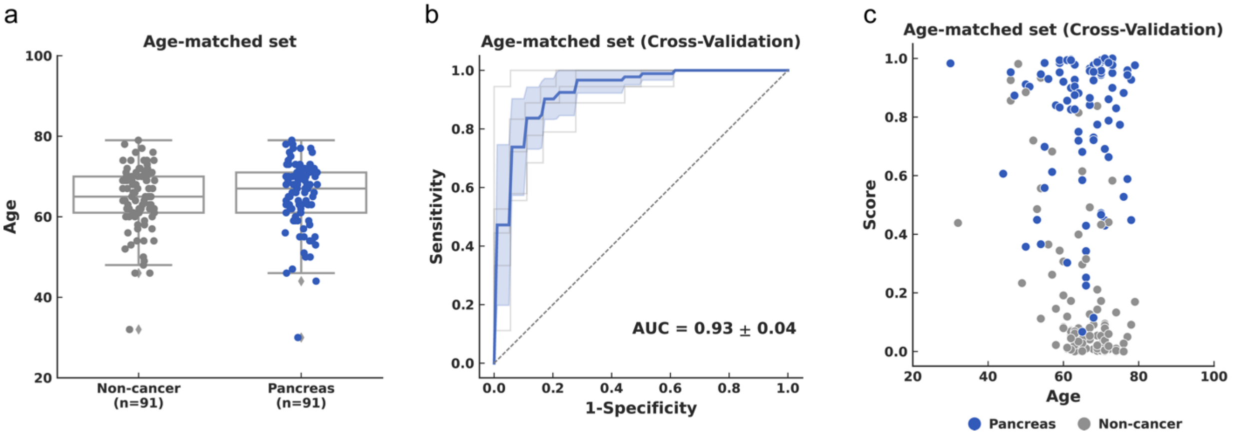


Supplementary Figure 1. Nanoparticle tracking assay for urinary-EV. (a) Particle size distribution of a representative EV sample (#2). The shaded region indicates the standard error of five repeated measurements. (b) Particle size estimated from the mode of the distribution, plotted for three biological replicates and two technical replicates. Error bars represent the standard error of five repeated measurements. (c) EV concentration estimated from the area of the distribution, plotted similarly to (b).

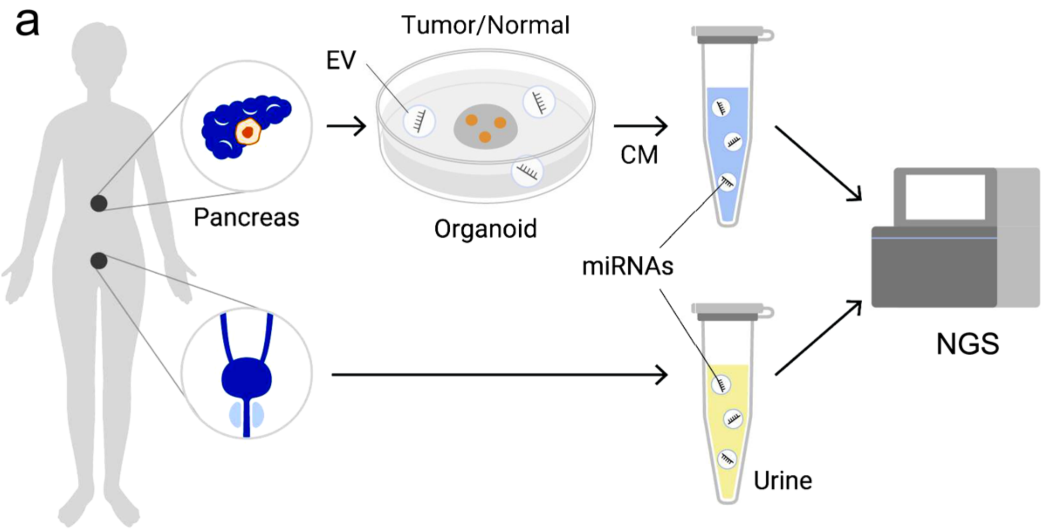
EV, Extracellular vesicle.



Supplementary Figure 2. Prediction score across demographic characteristic factors. Prediction scores were plotted against values of (a) Sex, (b) Age, (c) BMI, (d) Alcohol, (e) Smoking history, and (f) Diagnosis modality.
BMI, Body Mass Index.



Supplementary Figure 3. Performance of the model developed for the age-match dataset. (a) Box plot showing age was matched between groups in the age-match dataset. (b) ROC curve for SVC model with linear kernel developed in the age-matched. The mean value of five-folds is shown as the solid blue line, with standard deviations shown as the blue-shaded region. (c) Prediction scores obtained via cross-validation were plotted against age.

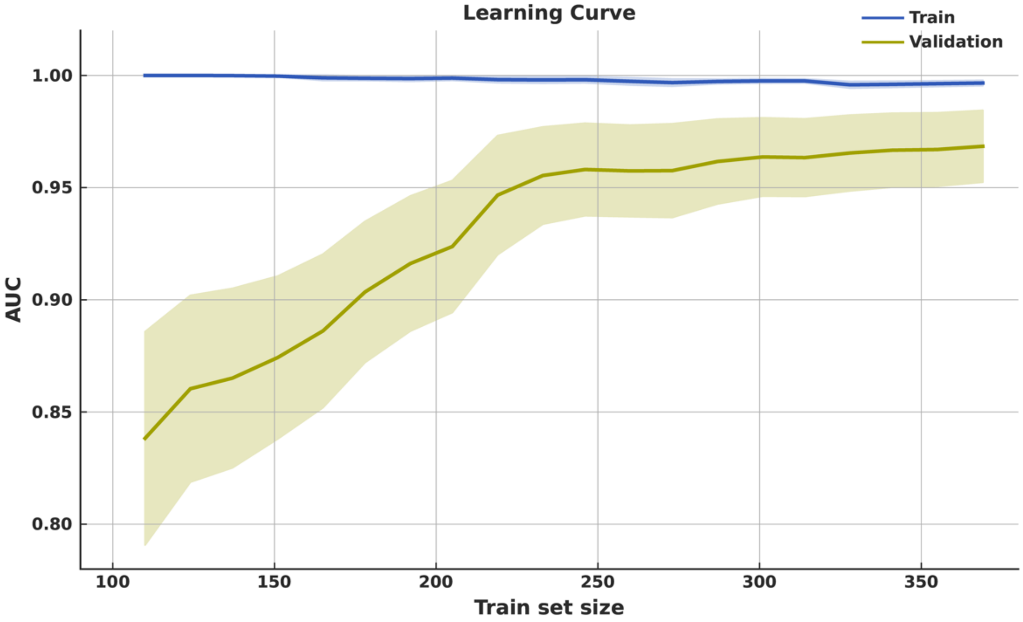


b

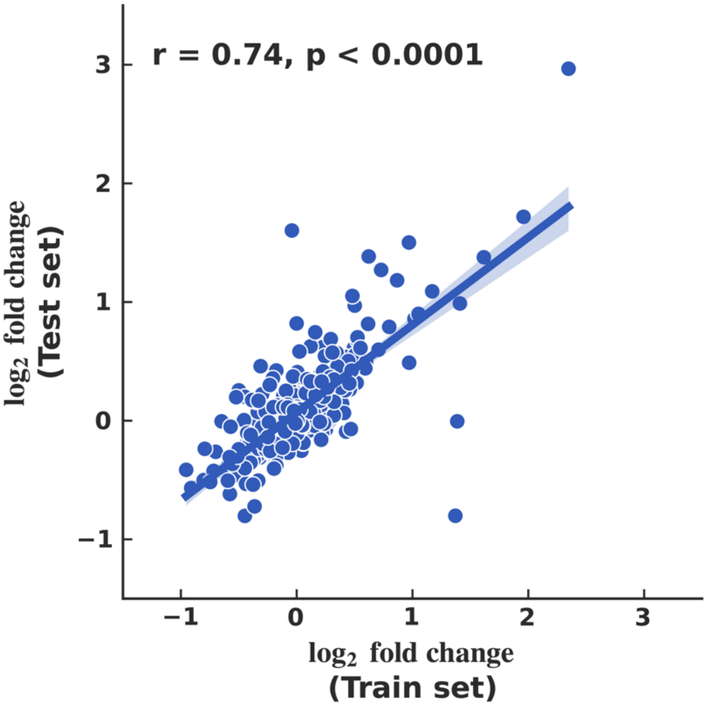
	Patient ID	Clinical diagnosis	Sex	Age	Source of cells
Pancreatic cancer organod	PC1*	PC	Male	64	Tumor
	PC2	PC	Male	55	Tumor
	PC3	PC	Male	53	FNA
Normal tissue organoide	PC1*	PC	Male	64	Normal tissue
	PC4	PC	Male	84	Normal tissue
	NC1	Common bile duct stone	Male	78	Pancreatic juice

*Identical patient

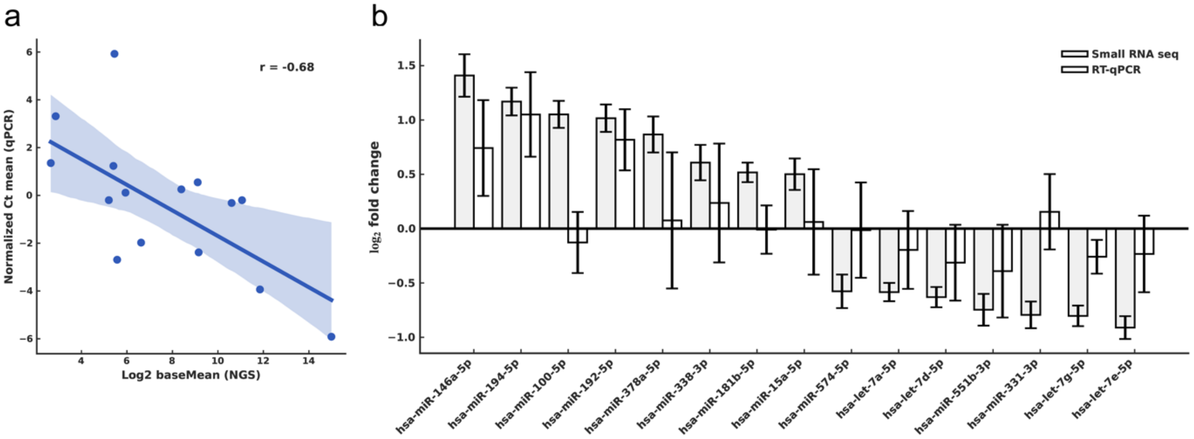
Supplementary Figure 4. Organoid analysis. (a) Schematic overview of the organoid analysis. (b) Donor characteristics of the organoid analysis. *Identical patient.



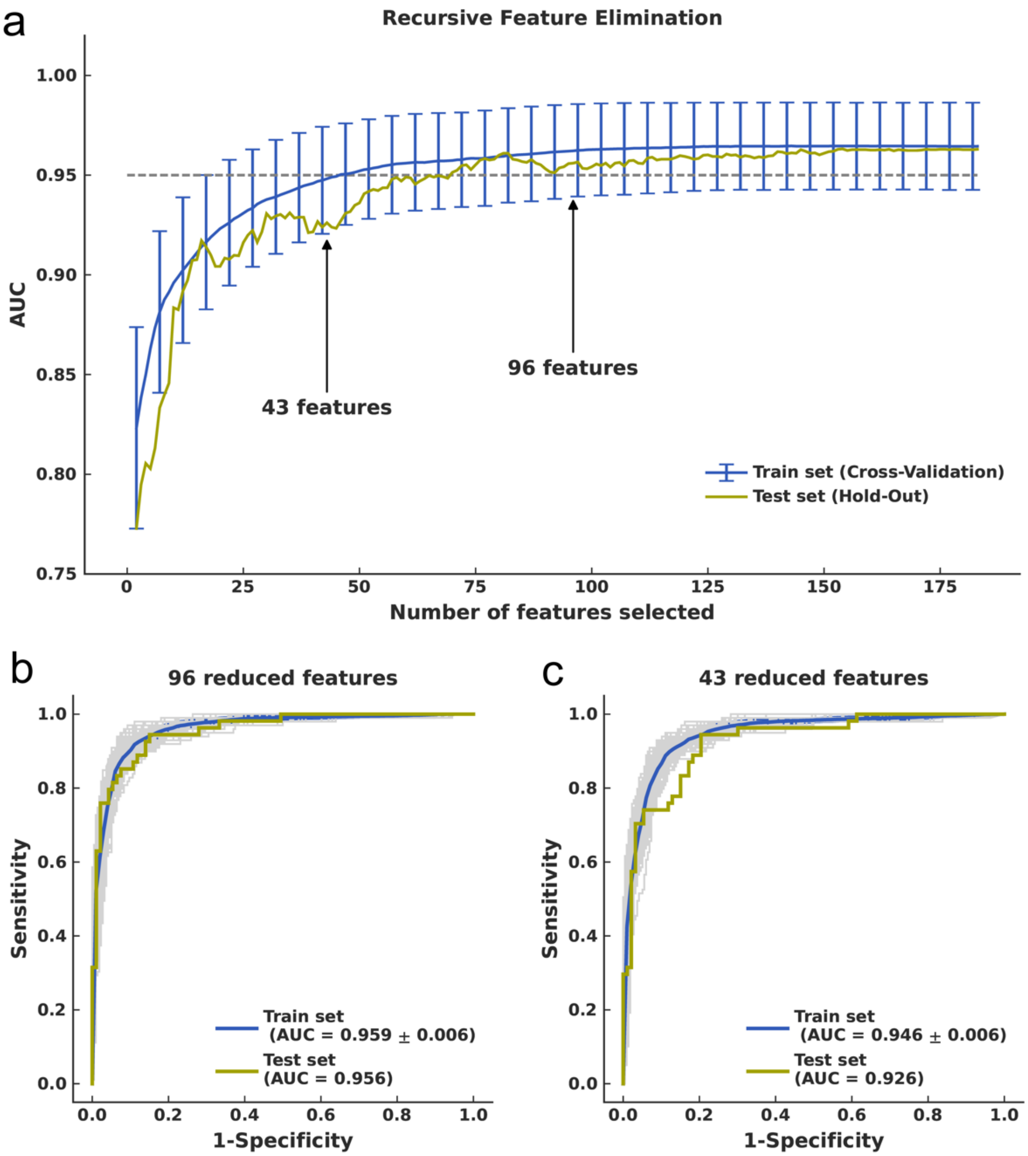
Supplementary Figure 5. Learning curve analysis of the prediction model. The AUC values were plotted against varying train set sizes. Each point represents the mean AUC from 100 repetitions of five-fold cross-validation, with solid lines indicating mean values and regions representing standard deviations. Blue and Yellow lines denote the performance on the training and validation sets, respectively.



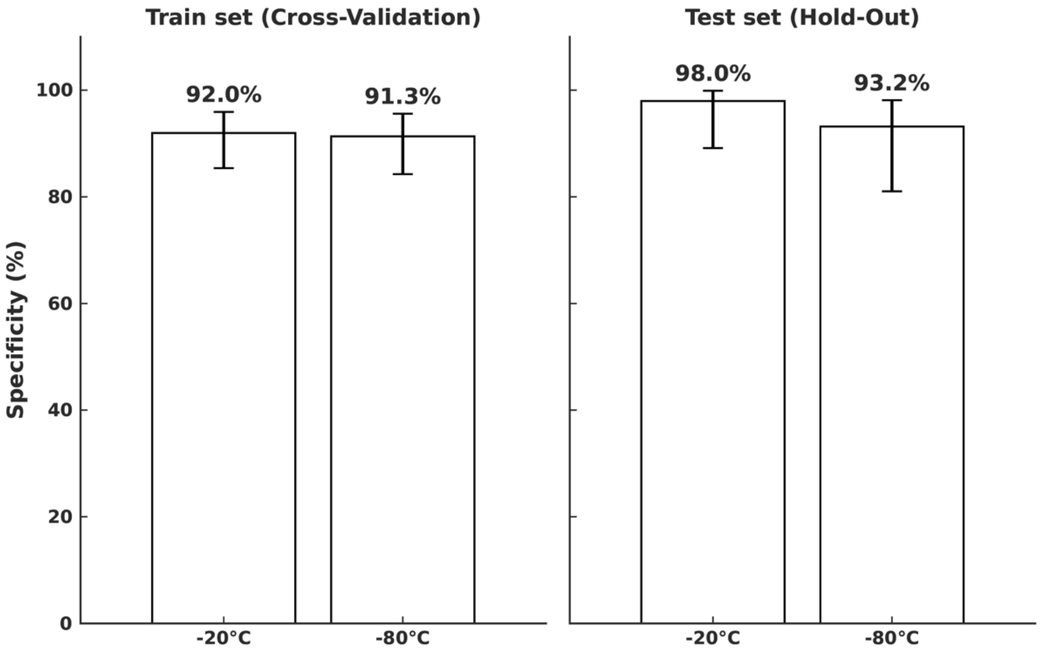
Supplementary Figure 6. Comparison of DEMs between training and test sets. Differential expression analyses were conducted independently for the training and test sets. Log2 fold change values were plotted on a scatter plot, with the horizontal axis representing the train set and the vertical axis representing the test set. Each point corresponds to a single miRNA. The solid line shows the regression line, with the shaded region representing the 95% confidence interval. Pearson's correlation coefficient (r) and its associated p-value were displayed in the upper left corner of the plot.



Supplementary Figure 7. Verification of DEMs by the qPCR assay. Pancreatic cancer (N=30) and non-cancer (N=30) cases in the train set were subjected to qPCR analysis, and the results were compared with the small RNA-seq results. (a) Normalized miRNA expression levels were compared for 15 target miRNAs, with the horizontal and vertical axes indicating the delta Ct values and the log2 transformed base mean values from DESeq2. The solid line shows the regression line, with the shaded region representing the 95% confidence interval. Pearson's correlation coefficient (r) was displayed in the upper right corner of the plot. (b) Log2 fold change values of 15 target miRNAs were plotted for both the small RNA-seq and qPCR. Error bars indicate the standard errors.



Supplementary Figure 8. Feature reduction analysis of the prediction model. (a) The AUC values were plotted against reducing the feature set size by employing the recursive feature elimination analysis. The blue line indicates the AUC values evaluated with out-of-fold prediction through 100 repetitions of five-fold cross-validation in the train set, with solid lines indicating mean values and error bars representing standard deviations. The yellow line indicates the AUC value of the out-of-fold prediction in the test set. (b) ROC curve of the model with the reduced feature size of 96. (c) ROC curve of the model with the reduced feature size of 43.



Supplementary Figure 9. Performance comparison of storage conditions. Specificity values were plotted against the storage temperature for the non-cancer cases in the train and test sets, respectively. Error bars indicate 95% confidence intervals.