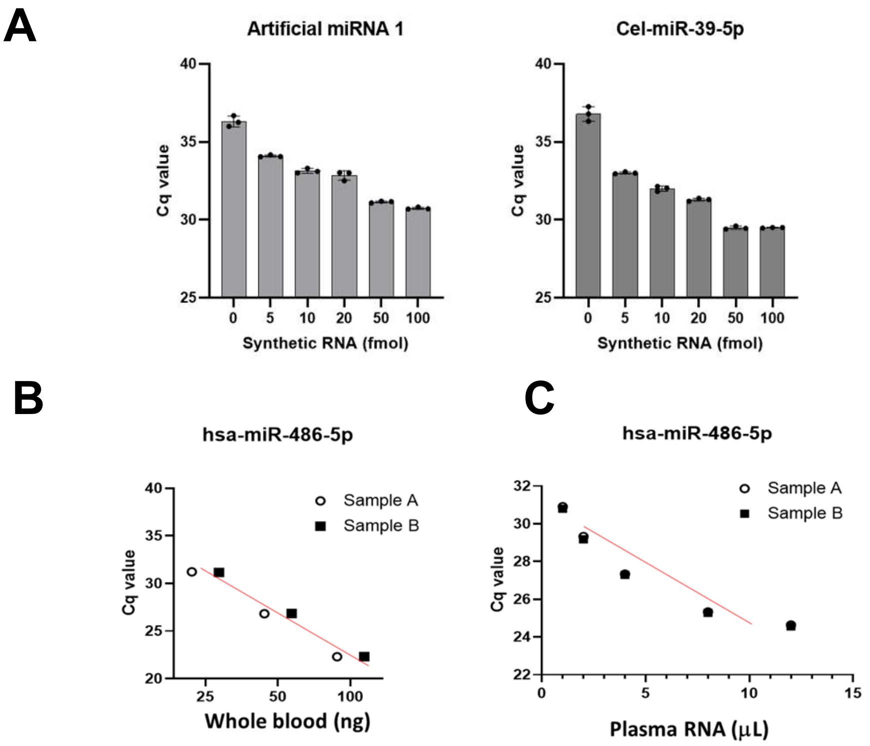
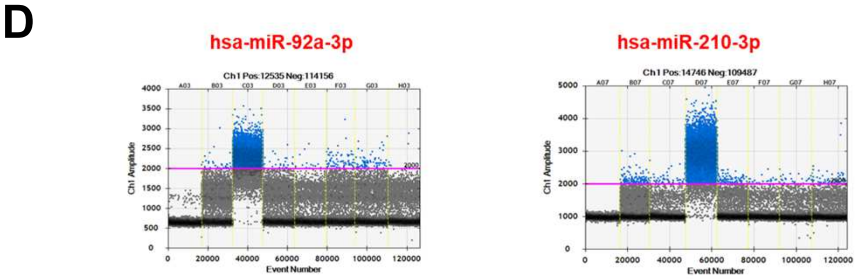
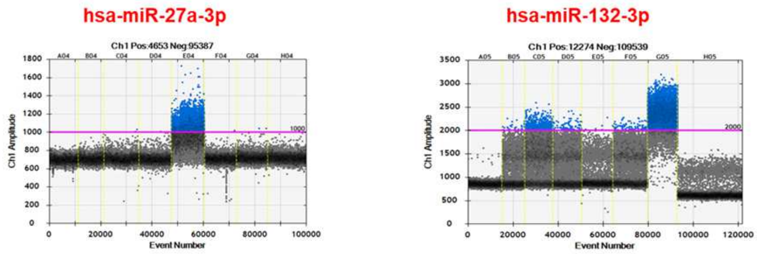




Target	Sample	Conc(copies/uL)
hsa-miR-92a-3p	NTC	0
	wo syn RNA	2.8
	syn R miR-92a-3p	**2986**
	syn R miR-210-3p	2.2
	syn R miR-27a-3p	1.1
	syn R miR-181b-5p	6.5
	syn R miR-132-3p	5.4
	syn R A1	0.74

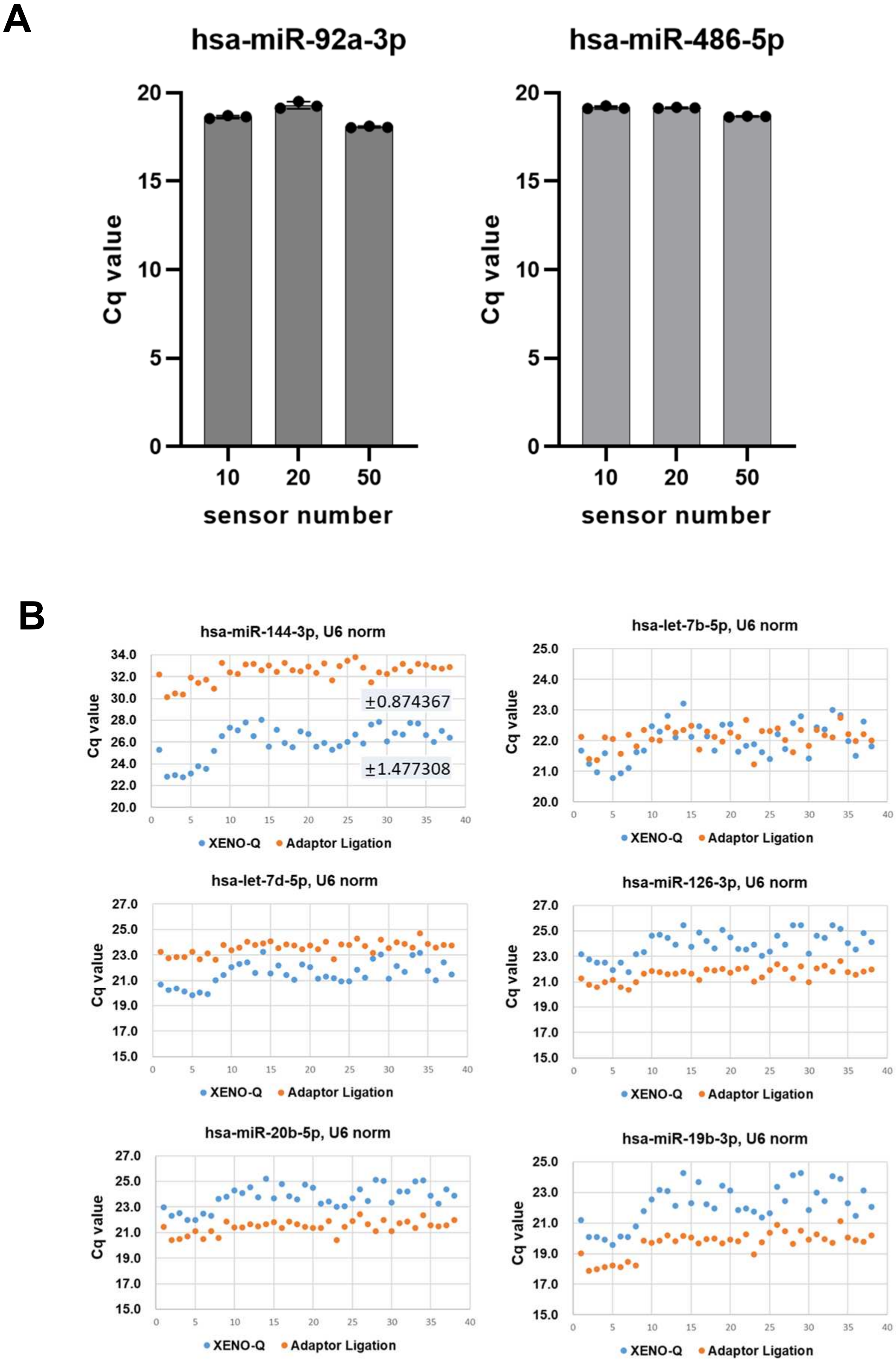
Target	Sample	Conc (copies/uL)
hsa-miR-210-3p	NTC	0
	wo syn RNA	12.7
	syn R miR-92a-3p	3.1
	syn R miR-210-3p	**3930**
	syn R miR-27a-3p	7.8
	syn R miR-181b-5p	1.7
	syn R miR-132-3p	1.9
	syn R A1	3.9



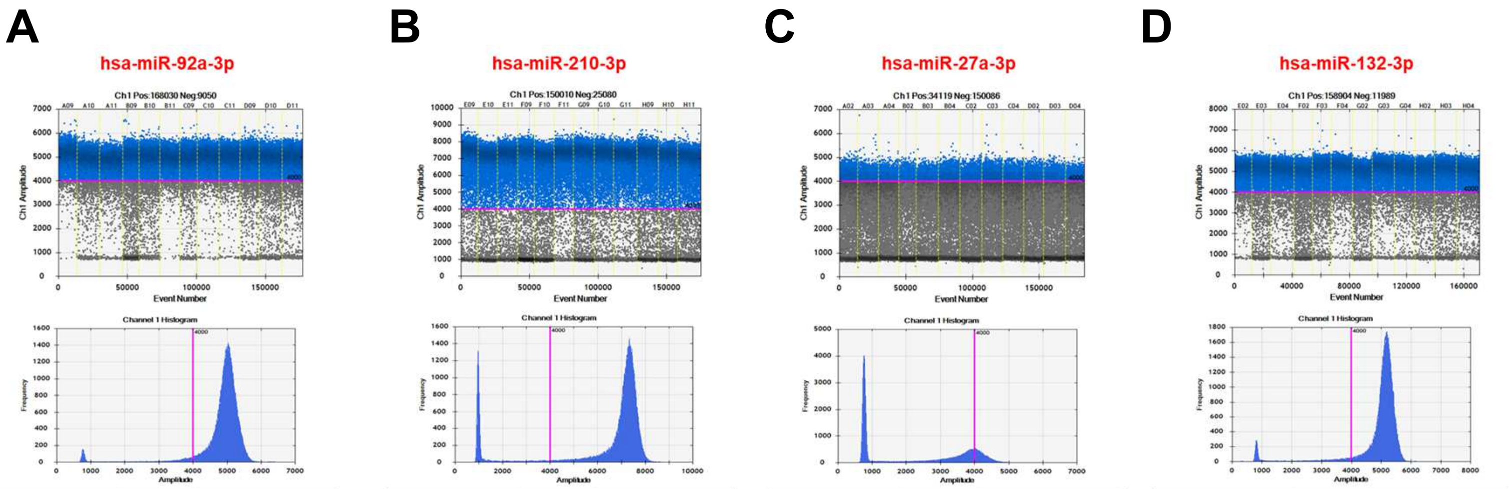
Target	Sample	Conc (copies/uL)
hsa-miR-27a-3p	NTC	0
	wo syn RNA	0
	syn R miR-92a-3p	0.17
	syn R miR-210-3p	0.09
	syn R miR-27a-3p	**1527**
	syn R miR-181b-5p	0.09
	syn R miR-132-3p	0.29
	syn R A1	0.08

Target	Sample	Conc (copies/uL)
hsa-miR-132-3p	NTC	0
	wo syn RNA	3.4
	syn R miR-92a-3p	49.6
	syn R miR-210-3p	7.8
	syn R miR-27a-3p	0.52
	syn R miR-181b-5p	7.4
	syn R miR-132-3p	**2390**
	syn R A1	0

Supplementary Figure 1. Sensitivity and specificity of the XENO-Q Method (**A**-**C**) Sensitivity of XENO-Q. (**A**) Serially diluted concentrations of synthetic miRNA (Artificial miRNA 1 and *Cel-miR-39-5p*) were used in XENO-Q reactions and detected with specific probes, demonstrating the high sensitivity of this method (Cq values are shown). (**B** and **C**) Detection of *hsa-miR-486-5p* using the XENO-Q reaction with RNA purified from serially diluted amounts of whole blood (**B**) and plasma (**C**) from two independent individuals (Samples A and B). The results show a dose-dependent change in target miRNA expression relative to the input amount of the sample. (**D**) Specificity of the XENO-Q reaction. The XENO-Q reaction was performed using six types of synthetic RNA and their corresponding target-specific Xeno-sensors. Target-specific detection was confirmed via droplet digital PCR (dd-PCR) (Conc (copies/μL)) using target-specific probes, demonstrating a highly specific reaction for the target miRNA.



Supplementary Figure 2. Characteristics and Performance of the XENO-Q Method (**A**) Comparison of miRNA Cq values based on the number of Xeno-sensors used in the XENO-Q reaction. The same RNA sample was reacted with a varying number of Xeno-sensor mixtures, and the resulting Cq values for the target miRNAs (*hsa-miR-92a-3p* and *hsa-miR-486-5p*) were compared. (**B**) Comparison of miRNA detection platforms. Results comparing miRNA detection from whole blood of 40 individuals using the XENO-Q method (blue dots) and the adapter ligation method (orange dots) for six different miRNAs.

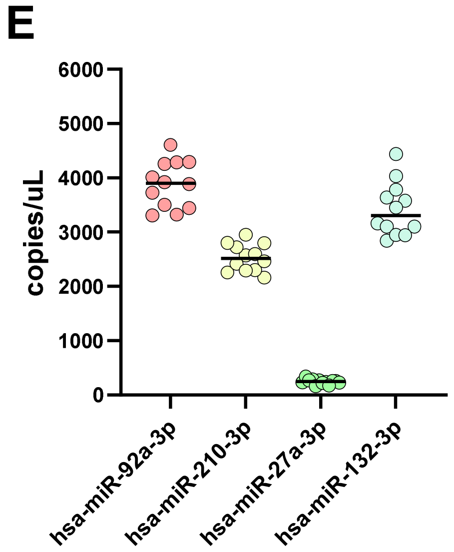


Target	Sample	Conc(copies/uL)
hsa-miR-92a-3p	ES&E 5-1	4980
	ES&E 5-2	1888
	ES&E 5-3	3530
	ES&E 5-4	3500
	ES&E 6-1	3480
	ES&E 6-2	3170
	ES&E 6-3	4810
	ES&E 6-4	3200
	ES&E 7-1	3900
	ES&E 7-2	4770
	ES&E 7-3	4450
	ES&E 7-4	3580

Target	Sample	Conc(copies/uL)
hsa-miR-210-3p	ES&E 5-1	3130
	ES&E 5-2	1002
	ES&E 5-3	2263
	ES&E 5-4	2054
	ES&E 6-1	2113
	ES&E 6-2	1788
	ES&E 6-3	3350
	ES&E 6-4	2030
	ES&E 7-1	2890
	ES&E 7-2	4040
	ES&E 7-3	3750
	ES&E 7-4	2112

Target	Sample	Conc(copies/uL)
hsa-miR-27a-3p	ES&E 5-1	394
	ES&E 5-2	128
	ES&E 5-3	207
	ES&E 5-4	231
	ES&E 6-1	195
	ES&E 6-2	172
	ES&E 6-3	436
	ES&E 6-4	201
	ES&E 7-1	189
	ES&E 7-2	321
	ES&E 7-3	287
	ES&E 7-4	159

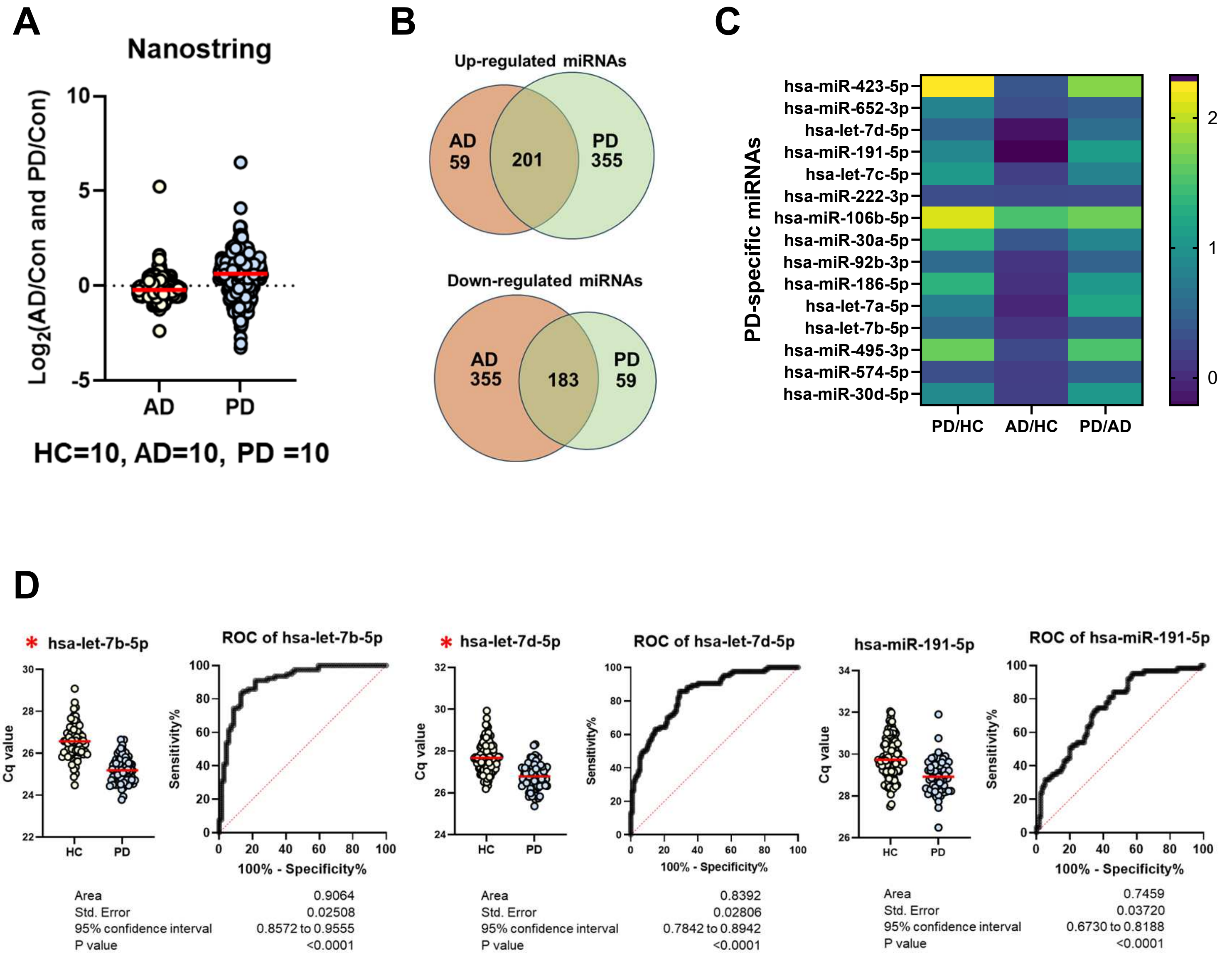
Target	Sample	Conc(copies/uL)
hsa-miR-132-3p	ES&E 5-1	4110
	ES&E 5-2	1968
	ES&E 5-3	2780
	ES&E 5-4	3190
	ES&E 6-1	2750
	ES&E 6-2	2980
	ES&E 6-3	4000
	ES&E 6-4	2820
	ES&E 7-1	3640
	ES&E 7-2	4250
	ES&E 7-3	3740
	ES&E 7-4	3180



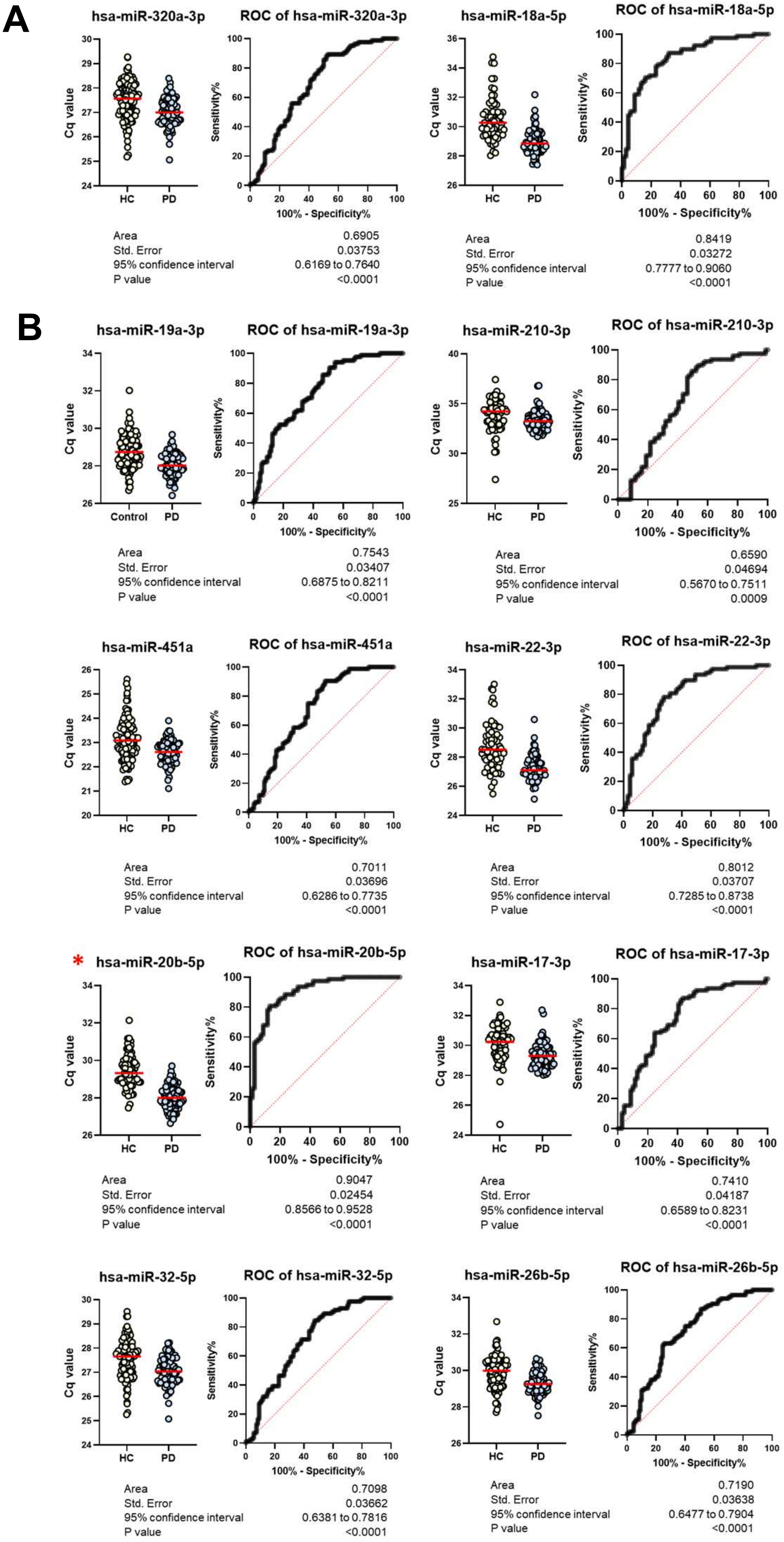
F

	hsa-miR-92a-3p	hsa-miR-210-3p	hsa-miR-27a-3p	hsa-miR-132-3p
Number of values	12	12	12	12
Minimum	3306	2163	161.0	2841
Maximum	4606	2951	338.1	4437
Range	1300	787.3	177.1	1596
Mean	3881	2528	244.6	3418
Std. Deviation	429.1	251.9	48.33	493.0
Std. Error of Mean	123.9	72.72	13.95	142.3
Lower 95% CI of mean	3608	2368	213.9	3105
Upper 95% CI of mean	4154	2688	275.4	3731
Coefficient of variation	11.06%	9.962%	19.75%	14.42%

Supplementary Figure 3. Detection of exosomal miRNA using XENO-Q and dd-PCR**.** Profiling of five miRNAs packaged into stem-cell–derived vesicles (exosomes) from human placental mesenchymal stem cells (hP-MSCs) using the XENO-Q platform. The batch-to-batch reproducibility of the target miRNA profiling was evaluated using exosomes produced from three independent culture batches (four replicates per batch, n=4). (**A**-**D**) Results of the profiling of five target miRNAs (*hsa-miR-92a-3p*, *hsa-miR-210-3p*, *hsa-miR-27a-3p*, and *hsa-miR-132-3p*) in exosomes from three different batches. Digital droplet PCR (dd-PCR) results are shown, including scatter plots of the droplets (Event Number vs. Ch1 Amplitude) and concentration tables (Copies/µL) for each target miRNA. (**E**) Graph showing the copy number per Extracellular Vesicle (EV) volume for each target miRNA. (**F**) Table summarizing the statistical measures for the target miRNAs detected, including the coefficient of variation (CV), which indicates batch-to-batch reproducibility.



Supplementary Figure 4. Nanostring-based identification of miRNAs Specific to PD vs. AD and Controls. (**A**) Scatter plots showing the expression patterns of miRNAs ($\mathrm{Log_2}$(AD/Con) and $\mathrm{Log_2}$(PD/Con)) in the Alzheimer's disease (AD) and Parkinson's disease (PD) patient groups relative to the Healthy Control (Con) group, as determined by Nanostring analysis (HC: n=10, AD: n=10, PD: n=10). (**B**) Venn diagrams illustrate the number of up-regulated and down-regulated miRNAs in AD and PD relative to Healthy Control, as identified by Nanostring. (**C**) Fold-change heatmap. The heatmap shows the $\mathrm{Log_2FC}$ comparison values for PD/HC (Parkinson's disease vs. Healthy Control), AD/HC (Alzheimer's disease vs. Healthy Control), and PD/AD (Parkinson's disease vs. Alzheimer's disease) for PD-specific miRNAs identified by Nanostring. (**D**) XENO-Q results for three target miRNAs (*hsa-let-7b-5p*, *hsa-let-7d-5p*, and *hsa-miR-191-5p*) selected through combined screening. Whole blood RNA from Healthy Controls (HC, n=112) and Parkinson's disease patients (PD, n=78) was used in the XENO-Q reaction to compare the expression patterns (Cq values) of the three miRNAs, and Receiver Operating Characteristic (ROC) curves were assessed to evaluate the diagnostic performance of each marker.



Area	0.6905
Std. Error	0.03753
95% confidence interval	0.6169 to 0.7640
P value	<0.0001

Area	0.8419
Std. Error	0.03272
95% confidence interval	0.7777 to 0.9060
P value	<0.0001

Area	0.7543
Std. Error	0.03407
95% confidence interval	0.6875 to 0.8211
P value	<0.0001

Area	0.6590
Std. Error	0.04694
95% confidence interval	0.5670 to 0.7511
P value	0.0009

Area	0.7011
Std. Error	0.03696
95% confidence interval	0.6286 to 0.7735
P value	<0.0001

Area	0.8012
Std. Error	0.03707
95% confidence interval	0.7285 to 0.8738
P value	<0.0001

Area	0.9047
Std. Error	0.02454
95% confidence interval	0.8566 to 0.9528
P value	<0.0001

Area	0.7410
Std. Error	0.04187
95% confidence interval	0.6589 to 0.8231
P value	<0.0001

Area	0.7098
Std. Error	0.03662
95% confidence interval	0.6381 to 0.7816
P value	<0.0001

Area	0.7190
Std. Error	0.03638
95% confidence interval	0.6477 to 0.7904
P value	<0.0001

Supplementary Figure 5. Expression test of selected miRNAs for PD diagnosis (**A**) XENO-Q analysis results (Cq values and ROC curves) for hsa-miR-320a-3p and hsa-miR-18a-5p, which were selected based on the Illumina sequencing results. (**B**) XENO-Q platform analysis results (Cq values and ROC curves) for established Parkinson's disease (PD)-related miRNA biomarkers reported in previous literature (*hsa-miR-19a-3p*, *hsa-miR-210-3p*, *hsa-miR-451a*, *hsa-miR-22-3p*, *hsa-miR-20b-5p*, *hsa-miR-17-3p*, *hsa-miR-32-5p*, and *hsa-miR-26b-5p*). The diagnostic performance of each marker was assessed using Receiver Operating Characteristic (ROC) curves.

hsa-let7d-5p

	Sensitivity %	Specificity %	Likelihood Ratio	AUC	Std. Error
PD vs HC	80.95	86.46	5.978	0.884	0.030
AD vs HC	83.33	77.08	3.636	0.865	0.029

hsa-miR-144-3p

	Sensitivity %	Specificity %	Likelihood Ratio	AUC	Std. Error
PD vs HC	88.89	80.21	4.491	0.931	0.019
AD vs HC	78.21	61.46	2.092	0.745	0.037

hsa-miR-107

	Sensitivity %	Specificity %	Likelihood Ratio	AUC	Std. Error
PD vs HC	77.78	75.65	3.194	0.841	0.029
AD vs HC	75.64	63.48	2.071	0.776	0.033

hsa-miR-20b-5p

	Sensitivity %	Specificity %	Likelihood Ratio	AUC	Std. Error
PD vs HC	87.30	62.61	2.335	0.797	0.033
AD vs HC	75.64	64.35	2.122	0.730	0.036

hsa-let7b-5p

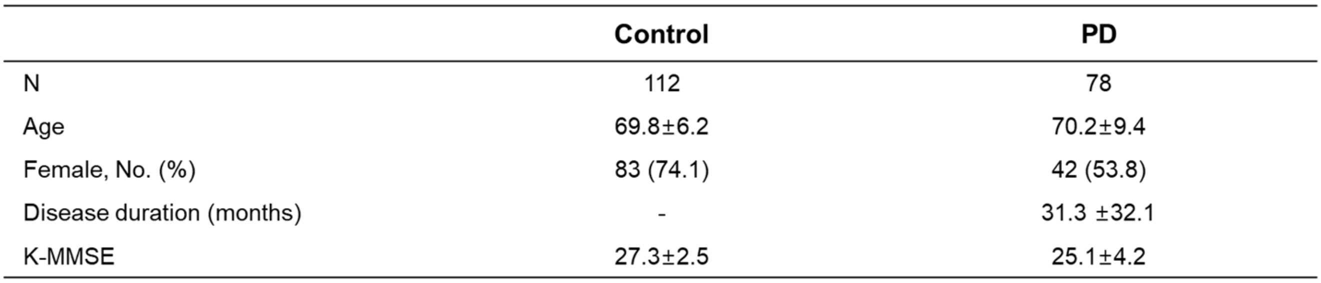
	Sensitivity %	Specificity %	Likelihood Ratio	AUC	Std. Error
PD vs HC	79.37	64.35	2.226	0.781	0.034
AD vs HC	70.51	60.00	1.763	0.675	0.038

hsa-miR-574-3p

	Sensitivity %	Specificity %	Likelihood Ratio	AUC	Std. Error
PD vs HC	63.49	52.17	1.328	0.590	0.043
AD vs HC	60.26	50.43	1.216	0.566	0.041

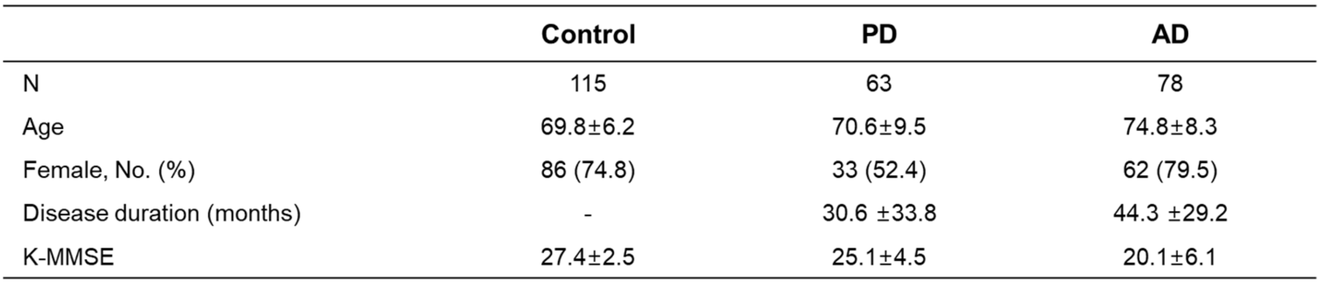
Supplementary Figure 6. Specificity, sensitivity, and AUC value of selected miRNA candidates. Validation of the five miRNA biomarker candidates (*hsa- -let7d-5p*, *hsa-miR-144-3p*, *hsa-miR-107*, *hsa-miR-20b-5p*, and *hsa-let7b-5p*) confirmed by the XENO-Q method. The table displays diagnostic performance metrics, including Sensitivity (%), Specificity (%), Likelihood Ratio (LR), Area Under the Curve (AUC), and Standard Error (Std. Error), for each marker at the optimal Youden index cut-off for the comparison groups (PD vs HC and AD vs HC).

Table S1-1 (for Figure 3e-f). Characteristics of participants analyzed in Figure 3 (Control vs. PD)



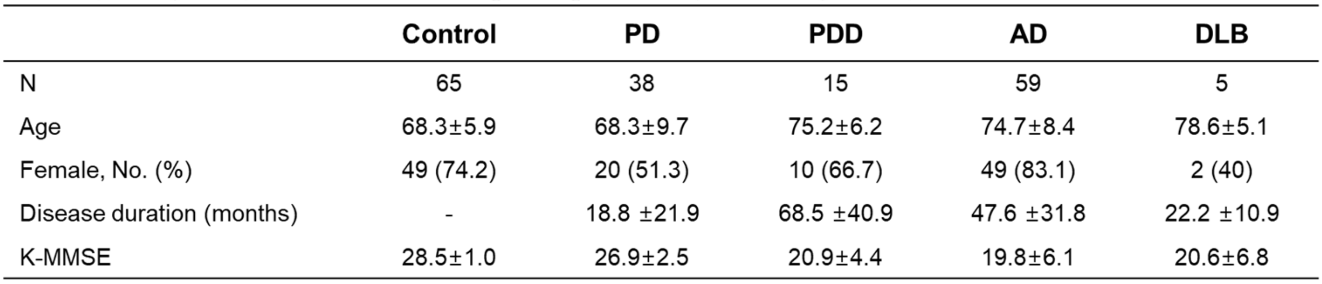
	Control	**PD**
N	112	78
Age	69.8±6.2	70.2±9.4
Female, No. (%)	83 (74.1)	42 (53.8)
Disease duration (months)	-	31.3 ±32.1
K-MMSE	27.3±2.5	25.1±4.2

Table S1-2 (for Figure 4). Characteristics of participants analyzed in Figure 4 (Control vs. PD vs. AD)



	Control	**PD**	**AD**
N	115	63	78
Age	69.8±6.2	70.6±9.5	74.8±8.3
Female, No. (%)	86 (74.8)	33 (52.4)	62 (79.5)
Disease duration (months)	-	30.6 ±33.8	44.3 ±29.2
K-MMSE	27.4±2.5	25.1±4.5	20.1±6.1

Table S1-3 (for Figure 5). Characteristics of participants analyzed in Figure 5 (Extended cohort: HC, PD/PDD, AD/DLB)



	Control	**PD**	**PDD**	**AD**	**DLB**
N	65	38	15	59	5
Age	68.3±5.9	68.3±9.7	75.2±6.2	74.7±8.4	78.6±5.1
Female, No. (%)	49 (74.2)	20 (51.3)	10 (66.7)	49 (83.1)	2 (40)
Disease duration (months)	-	18.8 ±21.9	68.5 ±40.9	47.6 ±31.8	22.2 ±10.9
K-MMSE	28.5±1.0	26.9±2.5	20.9±4.4	19.8±6.1	20.6±6.8

Supplementary Table 1. Demographic and clinical characteristics of study participants. Tables S1-1 through S1-3 provide detailed demographic and clinical data for the specific sub-populations utilized in the differential diagnostic analyses presented in Figures 3E-F, 4, and 5, respectively. Data are expressed as mean ± SD or number (%). (Abbreviations: *PD, Parkinson's disease; PDD, Parkinson's disease with dementia; AD, Alzheimer's disease; DLB, Dementia with Lewy bodies; K-MMSE, Korean Mini-Mental State Examination*)