

Supplementary Materials: Circulating microRNAs as Promising Biomarkers in Colorectal Cancer

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Table S1. Main findings of the included studies about circulating miRNAs in patients with CRC.

Authors	Study Cohort	TNM Stage	Technique	Specimen	Molecular Profile	Sensitivity (%)	Specificity (%)	Expression Level	Normalization	Clinical Application
Ng et al. 2009 [1]	DP: 5 CRC, 5 HC VeP: 25 CRC, 20 HC VaP: 90 CRC, 50 HC, 20 IBD, 20 GC	I–IV	DP: Cancer MicroRNA Array with QuantiMir system VeP: SYBR green qRT-PCR VaP: SYBR green qRT-PCR	Plasma	miR-17-3p	64	70	▲	U6	Diagnosis
					miR-92a	89	70	▲		
Huang et al. 2010 [2]	DP: 20 CRC, 20 HC VaP: 100 CRC, 37 AA, 59 HC	I–IV	DP: qRT-PCR VaP: qRT-PCR	Plasma	miR-29a	69/62.2*	89.1/84.7*	▲	miR-16	Diagnosis
					miR-92a	84/64.9*	71.2/81.4*	▲		
Pu et al. 2010 [3]	103 CRC, 37 HC	I–IV	qRT-PCR	Plasma	miR-221	86	41	▲	No internal control	Diagnosis and prognosis
Cheng et al. 2011 [4]	DP: 74 CRC, 28 HC VaP: 111 CRC, 48 HC	I–IV	DP: qRT-PCR VaP: qRT-PCR	Plasma	miR-141	-	-	▲	cel-miR-39	Diagnosis and prognosis
Wang et al. 2012 [5]	DP: 10 CRC, 10 HC VaP: 90 CRC, 43 AA, 58 HC	I–IV	DP: miRCURY LNA™ Universal RT microRNA PCR system VaP: qRT-PCR	Plasma	miR-601	69.2/72.1*	72.4/51.7*	▼	cel-miR-39	Diagnosis
					miR-760	80/69.8*	72.4/62.1*	▼		
Wang and Gu. 2012 [6]	36 non-metastatic CRC, 38 metastatic CRC	II–IV	qRT-PCR	Serum	miR-29a	75	75	▲	miR-16	Diagnosis
Giraldez et al. 2013 [7]	DP: 20 AA, 21 CRC, 20 HC VaP: 40 AA, 42 CRC, 53 HC	I–IV	DP: SAM-Bead Array platform VaP: qRT-PCR	Plasma	miR-19a, miR-29a, miR-15b, miR-335, miR-19b	-	-	▲	miR-16	Diagnosis
					miR-18a	72*	57*	▲		
Kanaan et al. 2013 [8]	DP: 20 CRC, 9 A, 12 HC VaP: 45 CRC, 16 A, 26 HC	I–IV	DP: 380 miRNA TaqMan low-density array card VaP: qRT-PCR	Plasma	miR-15b, miR-142-3p, miR-21, miR-532, miR-331, miR-652, miR-532-3p, miR-17, miR-195, miR-431, miR-139-3p	-	-	▲	U6	Diagnosis
Chen et al. 2013 [9]	DP: 8 non-responder CRC, 8 responder CRC VaP: 36 non-responder CRC, 36 responder CRC	IV	DP: miRNA microarray VaP: qRT-PCR	Serum	miR-19a	66.7	63.9	▲	ath-miR-159	Predictive resistance to therapy
Toiyama et al. 2013 [10]	DP: 12 CRC, 12 HC VaP: 186 CRC, 43 A, 53 HC	I–IV	DP: qRT-PCR VaP: qRT-PCR	Serum	miR-21	91.9/81.13*	81.1/76.74*	▲	cel-miR-39	Diagnosis and prognosis
Liu et al. 2013 [11]	200 CRC, 50 AA, 80 HC	I–IV	qRT-PCR	Serum	miR-21	65	85	▲	miR-16	Diagnosis and prognosis
					miR-92a	65.5	82.5	▲		

Hofsli et al. 2013 [12]	DP: 30 CRC (IV), 10HC VaP: 40 CRC (I-II), 10 HC	I-II IV	DP: miRCURY LNA Universal RT miRNA PCR VaP: qRT-PCR	Serum	miR-423-5p, miR-210, miR-720, miR-320a, miR-378, miR-92a, miR-29a	-	-	▲	Geometric mean	Diagnosis
					miR-155, miR-409-3p, miR-382, let-7d, miR-221, miR-425, miR-423-3p, miR-191, miR-107, miR-151-5p, miR-199a-3p, miR-103, miR-143, miR-106a	-	-	▼		
Brunet Vega et al. 2013 [13]	30 CRC, 26 HC	III	qRT-PCR	Serum	miR-18a, miR-29a	-	-	▲	miR-103, miR-16 and miR-let-7a	Diagnosis
Kjersem et al. 2014 [14]	DP: 12 responder CRC, 12 non-responder CRC VaP: 90 responder CRC, 60 non-responder CRC	IV	DP: miRNA microarray VaP: qRT-PCR	Plasma	miR-160a, miR-484, miR-130b	-	-	▲	miR-126, miR-15b and miR-24	Predictive resistance to therapy
Zhang et al. 2014 [15]	DP: 20 responder CRC, 20 non-responder CRC TP: 20 responder CRC, 20 non-responder CRC VaP: 93 responder CRC, 80 non-responder CRC		DP: TaqMan Array Human MicroRNA A+B Cards Set v3.0 TP: qRT-PCR VaP: qRT-PCR	Serum	miR-20a, miR-130, miR-145, miR-216, miR-372	-	-	▲	serum volume	Predictive response to therapy
Yin et al. 2014 [16]	116 non-metastatic CRC, 108 metastatic CRC	I-IV	qRT-PCR	Serum	miR-126	77.78	68.97	▼	cel-miR-39	Diagnosis
					miR-141	86.11	76.11	▲		
					miR-21	73.61	66.38	▲		
Toiyama et al. 2014 [17]	DP: 24 CRC VaP: 182 CRC, 24 HC	I-IV	DP: qRT-PCR VaP: qRT-PCR	Serum	miR-200c	-	-	▲	cel-miR-39	Prognosis and tumor recurrence predictive
Lv et al. 2014 [18]	146 CRC, 60 HC	I-IV	qRT-PCR	Serum	miR-155	58.2	95	▲	miR-16	Diagnosis and prognosis
Ogata-Kawata 2014 [19]	DP: 88 CRC, 11 HC VaP: 13 CRC, 8 HC	I-IV	DP: miRNA microarray VaP: qRT-PCR	Serum	let-7a, miR-1229, miR-1246, miR-150, miR-21, miR-223, miR-23a	-	-	▲	miR-451	Diagnosis
Schou et al. 2014 [20]	138 CRC	IV	TaqMan Array Human MicroRNA cards A and B v2.0	Blood	miR-345	-	-	▲	Global mean normalization	Prognosis and predictive response to therapy
Yamada et al. 2015 [21]	DP: 24 CRN, 25 HC VaP: 136 CRN, 52 HC	NA	DP: qRT-PCR VaP: qRT-PCR	Serum	miR-21, miR-29a, miR-125b	-	-	▲	cel-miR-39	Diagnosis
Basati et al. 2015 [22]	55 CRC, 55 HC	I-IV	qRT-PCR	Serum	miR-194	72	80	▼	cel-miR-39	Diagnosis and prognosis
					miR-29b	77	75	▼		
Hur et al. 2015 [23]	169 CRC	I-IV	qRT-PCR	Serum	miR-885-5p	-	-	▲	cel-miR-39 and miR-16	Prognosis
Li et al. 2015 [24]	DP: 20 CRC, 20 HC TP: 20 CRC, 20 HC VaP: 65 CRC, 40 HC	II-III	DP: TaqMan Low Density Arrays TP: qRT-PCR	Serum	miR-17-3p, miR-106a	-	-	▲	let-7d/g/i	Diagnosis and prognosis
					miR-145	-	-	▼		

Ex-VaP: 90 CRC, 70 HC			VaP: qRT-PCR Ex-VaP: qRT-PCR							
Yuan et al. 2015 [25]	118 CRC, 61 HC	I-IV	qRT-PCR	Plasma	miR-183	73.7	88.5	▲	U6	Diagnosis, prognosis and tumor recurrence predictive
Liu et al. 2015 [26]	98 CRC, 62 HC	I-IV	qRT-PCR	Serum	miR-592	-	-	▲	U6	Prognosis
Matsumura et al. 2015 [27]	DP: 6 CRC VaP1: 90 CRC, 12 HC VaP2: 209 CRC, 16 HC	I-IV	DP: miRNA microarray VaP: qRT-PCR	Serum	miR-19a	-	-	▲	miR-16a	Prognosis and tumor recurrence predictive
Hansen et al. 2015 [28]	32 responder CRC, 31 non- responder CRC	IV	qRT-PCR	Plasma	miR-126-3p	-	-	▲	cel-miR-54 and cel-miR-238	Predictive resistance to therapy
Wang et al 2015 [29]	DP: 47 CRC, 33 HC TP: 55 CRC, 57 HC VaP: 22 CRC, 27 HC		DP: Human microRNA microarray TP: qRT-PCR VaP: qRT-PCR	Plasma	miR-7, miR-93, miR-25	-	-	▼	miR-1228	Diagnosis
					miR-409-3p	-	-	▲		
Kou et al. 2016 [30]	96 CRC, 48 HC	I-IV	qRT-PCR	Plasma	miR-23b	84.38	77.08	▼	U6	Diagnosis and prognosis
Liu et al. 2016 [31]	DP: 4 non-recurrent CRC, 3 recurrent CRC VaP: 57 non-recurrent CRC, 27 recurrent	II-III	DP: RNA-seq VaP: qRT-PCR	Serum	miR-4772-3p	-	-	▲	miR-16	Prognosis and tumor recurrence predictive
Vychitilova- Faltesjskova et al. 2016 [32]	DP: 144 CRC, 96 HC TP: 80 CRC, 80 HC VaP (diagnosis): 203 CRC, 100 HC VaP (prognosis): 261 CRC	I-IV	DP: next generation sequencing (MiSeq Illumina) TP: qRT-PCR VaP: qRT-PCR	Serum	miR-142-5p, miR-23a-3p, miR- 376c-3p, miR-27a-3p	-	-	▲	miR-93-5p	Diagnosis and prognosis
Yu et al. 2016 [33]	DP: 3 responder CRC, 3 non-responder CRC TP: 43 responder-CRC, 44 non-responder CRC VaP: 26 responder CRC, 16 non-responder CRC	II-III	DP: miRNA microarray TP: qRT-PCR VaP: qRT-PCR	Serum	miR-345	-	-	▲	cel-miR-39	Predictive tumor response and prognosis
D'Angelo et al. 2016 [34]	16 responder CRC, 22 non- responder CRC	II-III	qRT-PCR	Serum	miR-125b	-	-	▲	miR-16 and cel- miR-39	Predictive tumor response
Zekri et al. 2016 [35]	TP: 30 CRC, 18 IBD, 18 polyps, 24 HC VaP: 100 CRC, 24 HC		TP: Custom miScript miRNA PCR array VaP: qRT-PCR	Serum	miR-223, miR-17, miR-19a, miR-19b, miR-20a	-	-	▲	SNORD 68	Diagnosis
Imaoka et al. 2016 [36]	DP: 3 CRC, 3 A, 3 HC TP: 36 CRC, 12 A, 12 HC VaP: 211 CRC, 56 A, 57 HC	I-IV	DP: miRNA expression microarray TP: qRT-PCR	Serum	miR-1290	70.1/46.4*	91.2/91.2*	▲	cel-miR-39	Diagnosis, prognosis and

VaP: qRT-PCR									tumor recurrence	
Sun et al. 2016 [37]	DP: 40 CRC, 10 HC VaP: 187 CRC, 47 HC	I–IV	DP: TaqMan® Array Human MicroRNA A + B Cards Set v3.0 VaP: qRT-PCR	Plasma	miR-141, let-7f-2, miR-628-5p, miR-96, miR-148a, miR-203, miR-200b, miR-22	-	-	▲	cel-miR-39 /miR-451	Diagnosis and prognosis
Ng et al. 2017 [38]	117 CRC, 90 HC	I–IV	qRT-PCR	Serum	miR-139-3p miR-622	96.6 87.8	97.8 67.5	▼ ▲	U6 and RNU48	Diagnosis
Tsukamoto et al. 2017 [39]	DP: 3 CRC, 3 HC VaP: 326 CRC, 30 HC	I–IV	DP: miRNA microarrays VaP: qRT-PCR	Serum	miR-21	-	-	▲	miR-16a	Diagnosis and prognosis
Zhu et al. 2017 [40]	54 non-metastatic CRC and 85 metastatic CRC	I–IV	qRT-PCR	Serum	miR-200b miR-141 miR-200c	77.78 86.11 73.61	68.97 76.11 66.38	▲ ▲ ▲	cel-miR-39	Diagnosis
Pan et al. 2017 [41]	TP: 60 CRC, 60 HC VaP: 80 CRC, 80 HC	I–IV	qRT-PCR	Plasma	miR-15b miR-17 miR-21 miR-26b miR-145	50 67.5 71.25 72.50 62.50	68.75 62.5 52.50 56.25 61.25	▲ ▲ ▲ ▲ ▲	cel-miR-39 and miR-16-5p	Diagnosis
Krawczyk et al. 2017 [42]	56 CRC, 70 HC	I–II	qRT-PCR	Plasma	miR-506 miR-4316	60.7 60.9	76.8 83.9	▲ ▲	U6	Diagnosis
Wang et al. 2017 [43]	268 CRC, 102 HC	I–IV	qRT-PCR	Serum	miR-210	74.6	73.5	▲	miR-191-5p and U6	Diagnosis and prognosis
Ding et al. 2017 [44]	380 CRC, - HC	I–IV	qRT-PCR	Serum	miR-200, miR-141	-	-	▲	U6	Diagnosis
Wang et al. 2017 [45]	50 CRC, 50 HC	I–II	qRT-PCR	Plasma	miR-125a-3p, miR-320c	-	-	▲	miR-30e-5p	Diagnosis
Yan et al. 2017 [46]	DP: 3 CRC, 3HC VaP: 77 CRC, 20 HC	I–IV	DP: miRNA microarrays VaP: qRT-PCR	Serum	miR-638, miR-5787, miR-8075, miR-6869-5p, miR-548c-5p miR-486-5p, miR-3180-5p	- -	- -	▼ ▲	-	Diagnosis
Xu et al. 2017 [47]	103 CRC, 51 A, 100 HC	I–IV	qRT-PCR	Serum	miR-196b	87.38	63	▲ ▼*	U6	Diagnosis and prognosis
Hur et al. 2017 [48]	DP: 186 CRC, 24 HC VaP: 144 CRC, 24 HC	I–IV	DP: qRT-PCR VaP: qRT-PCR	Serum	miR-203	-	-	▲	-	Prognosis
Maiertaler et al. 2017 [49]	DP: 20 non-metastatic CRC and 20 metastatic CRC VaP: 309 non-metastatic CRC and 234 metastatic CRC	I–IV	DP: Custom TaqMan Array MicroRNA cards VaP: qRT-PCR	Plasma	miR-200a, miR-200b, miR-122	-	-	▲	cel-miR-39	Prognosis
Tayel et al. 2018 [50]	30 CRC, 30 polyps, 30 HC	II–IV	qRT-PCR	Blood	miR-200c	86.67	73.33	▲	RNU48	Diagnosis and prognosis
Santassusagna et al. 2018 [51]	50 CRC	I–III	qRT-PCR	Plasma	miR-200a, miR-200b, miR-429	-	-	▲	miR-484	Prognosis
	TP: 40 CRC, 40 HC	I	qRT-PCR	Plasma	miR-182	78	91	▲	cel-miR-39	Diagnosis

Liu et al. 2018 [52]	VaP: 50 CRC, 50 HC, 50 A				miR-20a	-	-	▲	and U6	
Vafaei et al. 2018 [53]	DP: 75 CRC VaP: 16 CRC, 8 HC		DP: OpenArray analysis VaP: TaqMan Array Human MicroRNA Cards Set v2.0A/B	Plasma	let-7a, miR-21, miR-25, miR-30a	-	-	-	Quantile normalization	Prognosis
Yan et al. 2018 [54]	168 CRC, 20 HC	I–IV	miRNA microarray	Serum	miR-6803-5p	-	-	▲	miR-16	Diagnosis and prognosis
Liu et al. 2018 [55]	DP: 88 CRC, 11 HC TP: 40 CRC, 40 HC VaP: 80 CRC, 40 HC Ex-VaP: 50 CRC, 50 A, 50 HC	I–IV	DP: qRT-PCR TP: qRT-PCR VaP: qRT-PCR Ex-VaP: qRT-PCR	Plasma	miR-27a miR-130a	80 70	77.5 80	▲ ▲	cel-miR-39	Diagnosis and prognosis
Fu et al. 2018 [56]	18 CRC, 10 HC	I–IV	qRT-PCR	Serum	miR-17, miR-92a	-	-	▲	cel-miR-39	Diagnosis and prognosis
Wang et al. 2018 [57]	96 CRC, 60 HC	I–IV	qRT-PCR	Serum	miR-103	80	88.5	▲	U6	Diagnosis and prognosis
Ji et al. 2018 [58]	TP: 40 CRC VaP: 226 CRC Ex-VaP: 56 CRC	I–III	TP: miRNA Ready-to-Use PCR, Human Serum/Plasma Focus miRNA PCR Panel I and Panel II V1 VaP: qRT-PCR Ex-VaP: qRT-PCR	Serum	miR-652-3p, miR-342-2p, miR-501-3p, miR-328-3p	-	-	-	miR-103-3p and miR-93-5p	Prognosis
Ulivi et al. 2018 [59]	52 CRC	I–IV	qRT-PCR	Plasma	miR-20b-5p, miR-29b-3p, miR-155-3p	-	-	▲	miR-484, miR-223-3p, cel-miR-39	Predictor tumor response and prognosis
Peng et al. 2019 [60]	108 CRC	I–IV	qRT-PCR	Serum	miR-548c-5p	-	-	▼	miR-16	Prognosis
Zhang et al. 2019 [61]	DP: 30 CRC pool, 10 HC pool TP: 30 CRC, 30 HC VaP: 79 CRC, 76 HC Ex-VaP: 30 CRC, 30 HC	I–IV	DP: Exiqon miRCURY-Ready-to-Use PCR-Human-panel-I + II-V1.M VaP: qRT-PCR Ex-VaP: qRT-PCR	Plasma	miR-17-5p, miR-181a-5p, miR-18a-5p, miR-18b-5p	-	-	▲	cel-miR-39 and miR-16-5p	Diagnosis
Herreros-Villanueva et al. 2019 [62]	96 CRC, 101 AA, 100 HC	I–IV	qRT-PCR	Plasma	miR-19a, miR-19b, miR-15b, miR-29a, miR-335, miR-18a	-	-	▲	miR-1228 and cel-miR-39	Diagnosis
Sun et al. 2019 [63]	138 CRC, 60 HC	I–IV	qRT-PCR	Serum	miR-30a-5p	77.5	78.3	▼	cel-miR-39	Diagnosis and prognosis
Jin et al. 2019 [64]	25 non-responder CRC, 18 responder CRC	III–IV	qRT-PCR	Serum	miR-21-5p, miR-1246, miR-1229-5p, miR-96-5p	-	-	▲	miR-16	Predictive resistance to therapy

DP = discovery phase; TP = training phase; VeP = verification phase; VaP = validation phase; Ex-VaP = external-validation phase; qRT-PCR = quantitative real-time PCR; CRC = colorectal cancer; HC = healthy controls, IBD = inflammatory bowel disease; GC = gastric cancer; AA = advanced adenomas; A = adenomas. *Comparison AA/A vs HC.

Table S2. List of references of Figure 2.

miRNAs	References	miRNAs	References
miR-21	[10,11,19,21,39,41,65–80]	miR-720	[12,73]
miR-29 (a/b)	[2,6,7,12,13,21,22,62,76,77,81–84]	miR-191	[12,85]
miR-92 (a)	[1,2,11,12,68,76,77,82,84–87]	miR-409	[12,29]
miR-18 (a/b)	[7,13,61,62,70,76,85,88]	miR-155	[12,18]
miR-17	[1,24,35,41,61,82]	miR-378	[12,69]
miR-19 (a/b)	[7,24,35,62,79,87]	miR-199a	[12,78]
let-7 (a/d/f/g)	[12,19,68,72,89,90]	miR-423	[12,91]
miR-145	[24,41,72,81,84]	miR-1229	[19,80]
miR-106 (a/b)	[12,24,76,92,93]	miR-24	[85,91]
miR-20 (a)	[35,52,72,76,93]	miR-375	[86,94]
miR-223	[19,35,77,85,87]	miR-182	[52,95]
miR-23 (a/b)	[19,30,32,96]	miR-22	[70,89]
miR-125 (a/b)	[21,45,77,82]	miR-203	[68,89]
miR-103 (a)	[12,57,61,73]	miR-25	[29,70]
miR-320 (a/c/d)	[12,45,91,97]	miR-143	[12,76]
miR-200 (b/c)	[17,44,72,88,89]	miR-760	[5,86]
miR-141	[4,44,89,98]	miR-548 (c/at)	[46,99]
miR-221	[3,12,85]	miR-1246	[19,80]
miR-31	[68,72,98]	miR-34a	[12,100,101]
miR-139	[8,38,99]	miR-135 (a/b)	[72,102]
miR-15b	[7,41,62]	miR-26 (a/b)	[41,103]
miR-181 (a/b)	[61,68]	miR-142	[32,103]
miR-150	[19,100]	miR-335	[7,62]
miR-151 (a)	[12,61]	miR-1290	[36,97]
miR-107	[12,99]	miR-30 (a/b/c)	[63,104]
miR-210	[12,43]	miR-27a	[32,55]

Table S3. List of references of Figure 3.

miRNAs	References	miRNAs	References
miR-200 (a/b/c)	[17,37,49,51]	miR-210	[43]
miR-141	[4,37,51]	miR-203	[48]
miR-21	[10,39,53,105]	miR-372	[32]
miR-23 (a/b)	[30,32]	miR-155	[18]
miR-106a	[24,53]	miR-92a	[11]
let-7a	[53,106]	miR-122	[49]
miR-30a	[53,63]	miR-183	[25]
miR-548c	[60]	miR-221	[3]
miR-6803	[54]	miR-27a	[55]
miR-4772	[31]	miR-130a	[55]
miR-19a	[27]	miR-196b	[47]
miR-885	[23]	miR-185	[53]
miR-29b	[22]	miR-217	[53]
miR-194	[22]	miR-25	[53]
miR-96	[37]	miR-431	[53]
miR-17	[24]	miR-483	[53]
miR-592	[26]	miR-615	[53]
miR-26a	[107]	miR-892a	[53]
miR-124	[107]	miR-501	[58]
miR-103	[57]	miR-342	[58]
miR-376c	[32]	miR-652	[58]
miR-1290	[36]	miR-328	[58]

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