

Supplementary Materials: Identification of More Feasible MicroRNA–mRNA Interactions within Multiple Cancers Using Principal Component Analysis Based Unsupervised Feature Extraction

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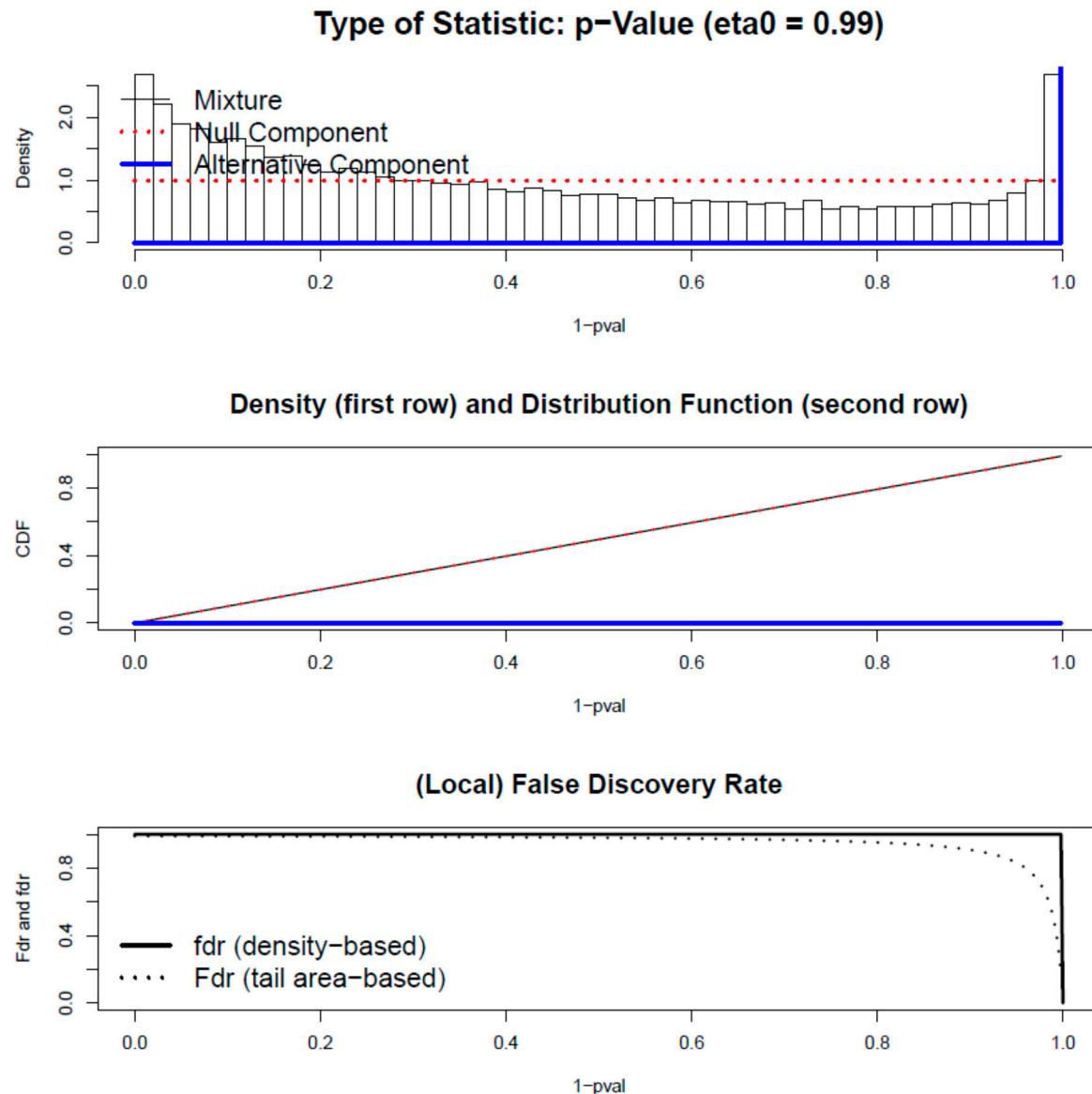


Figure S1. fdrtool's output: mRNA in HCC. **Top:** histogram of $1-P$; **Middle:** Density and cumulative density of $1-P$; **Bottom:** (Local) False Discovery Rate.

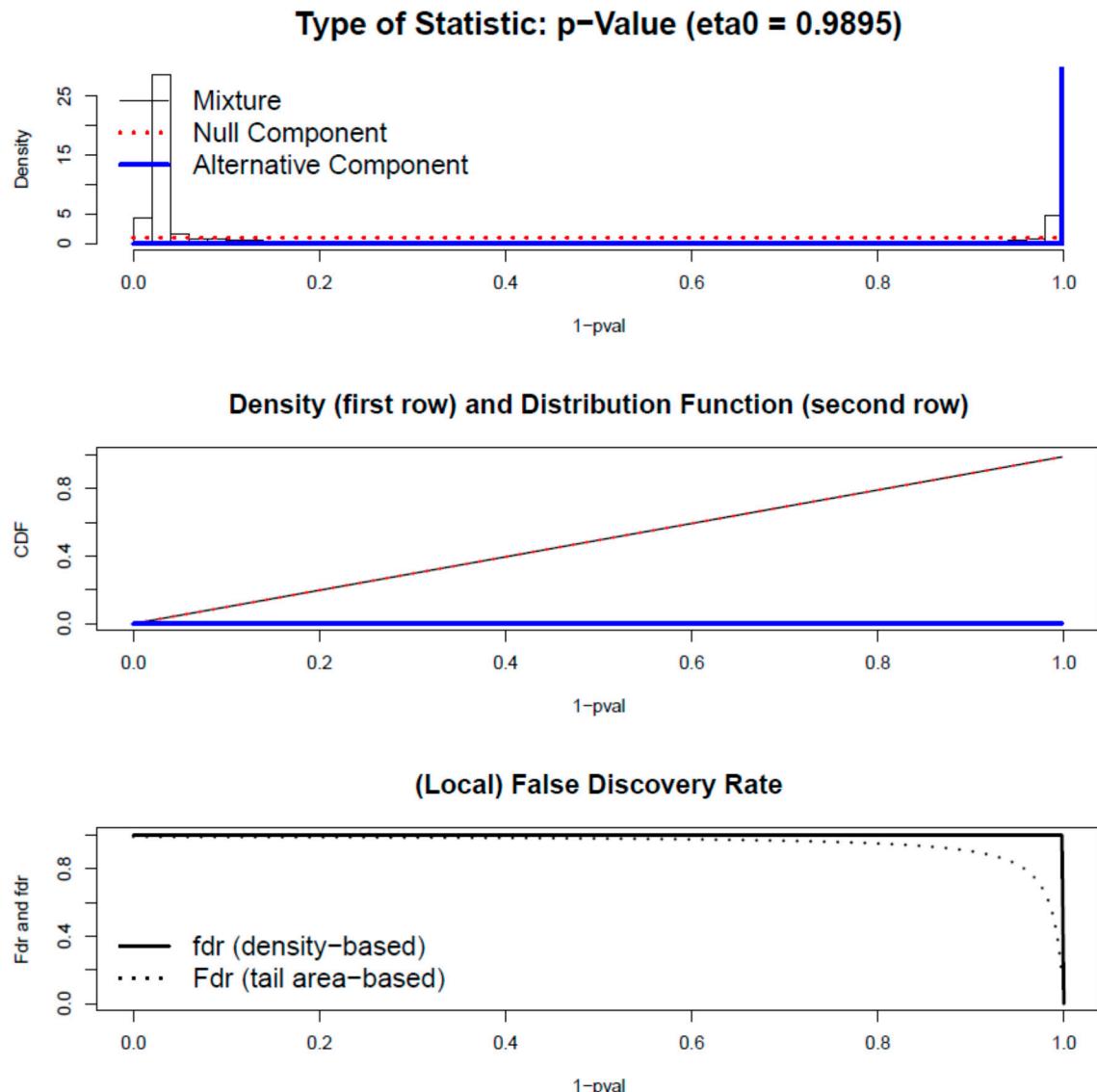


Figure S2. fdrtool's output: miRNA in HCC.

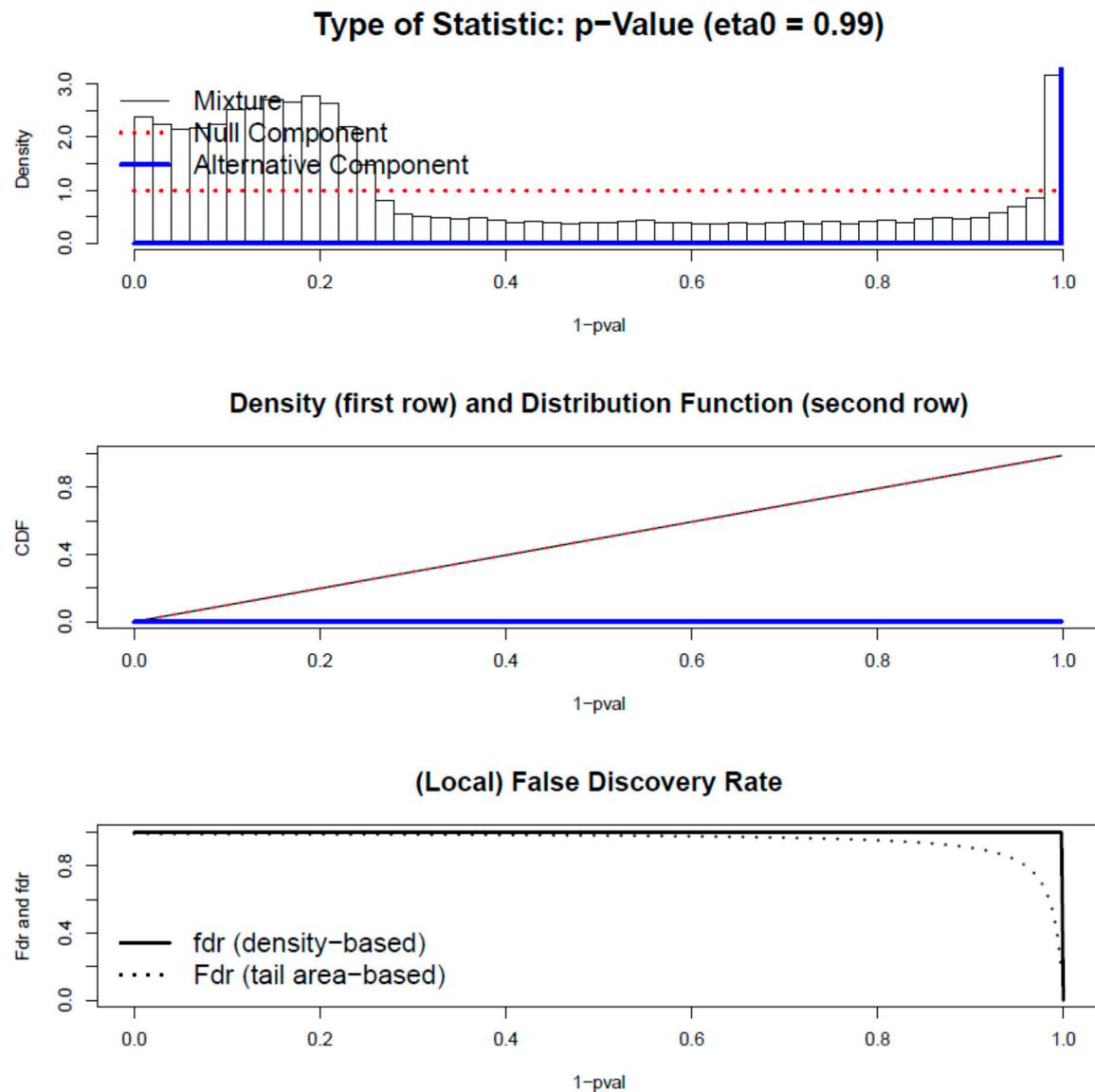


Figure S3. fdrtool's output: mRNA in NSCLC.

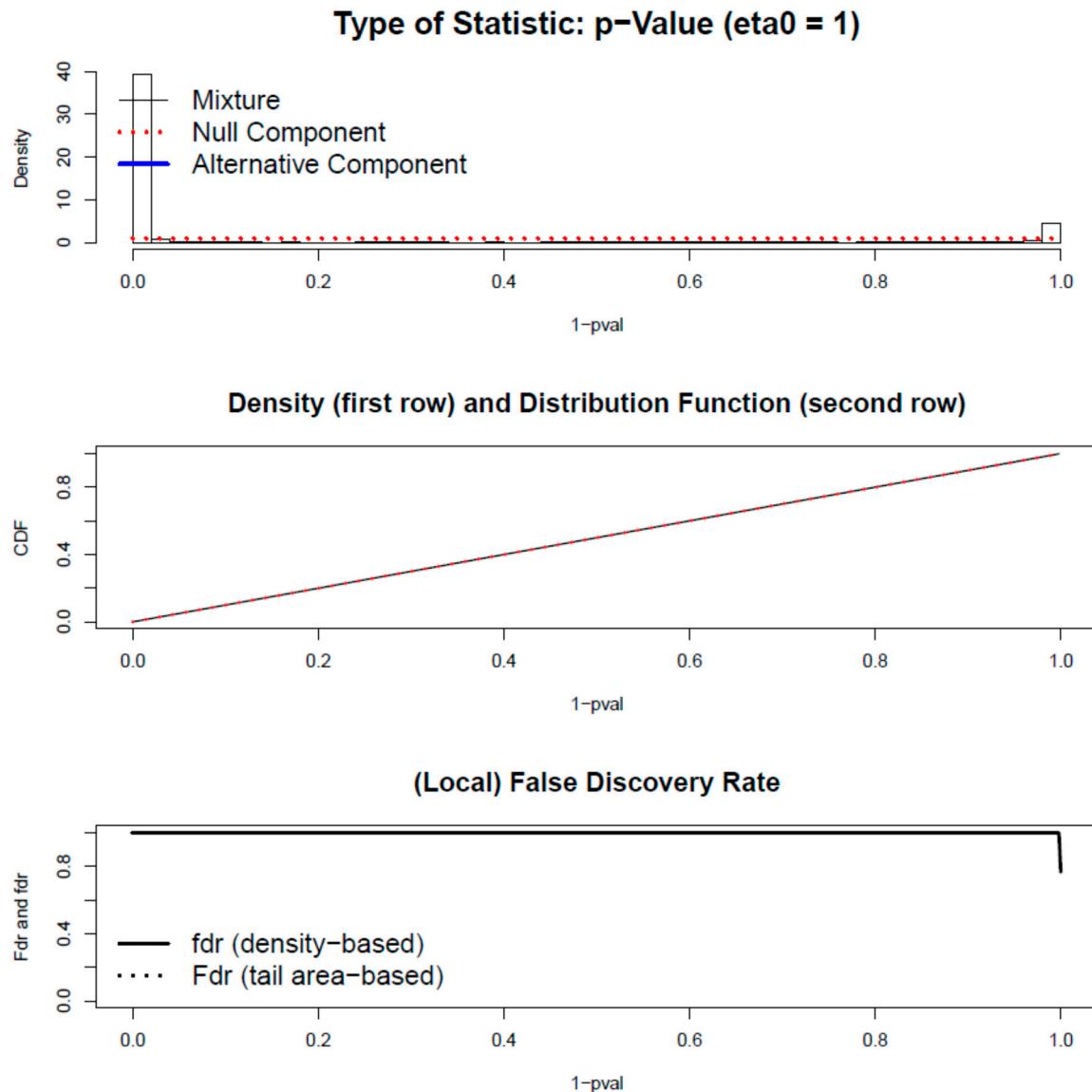


Figure S4. fdrtool's output: miRNA in NSCLC.

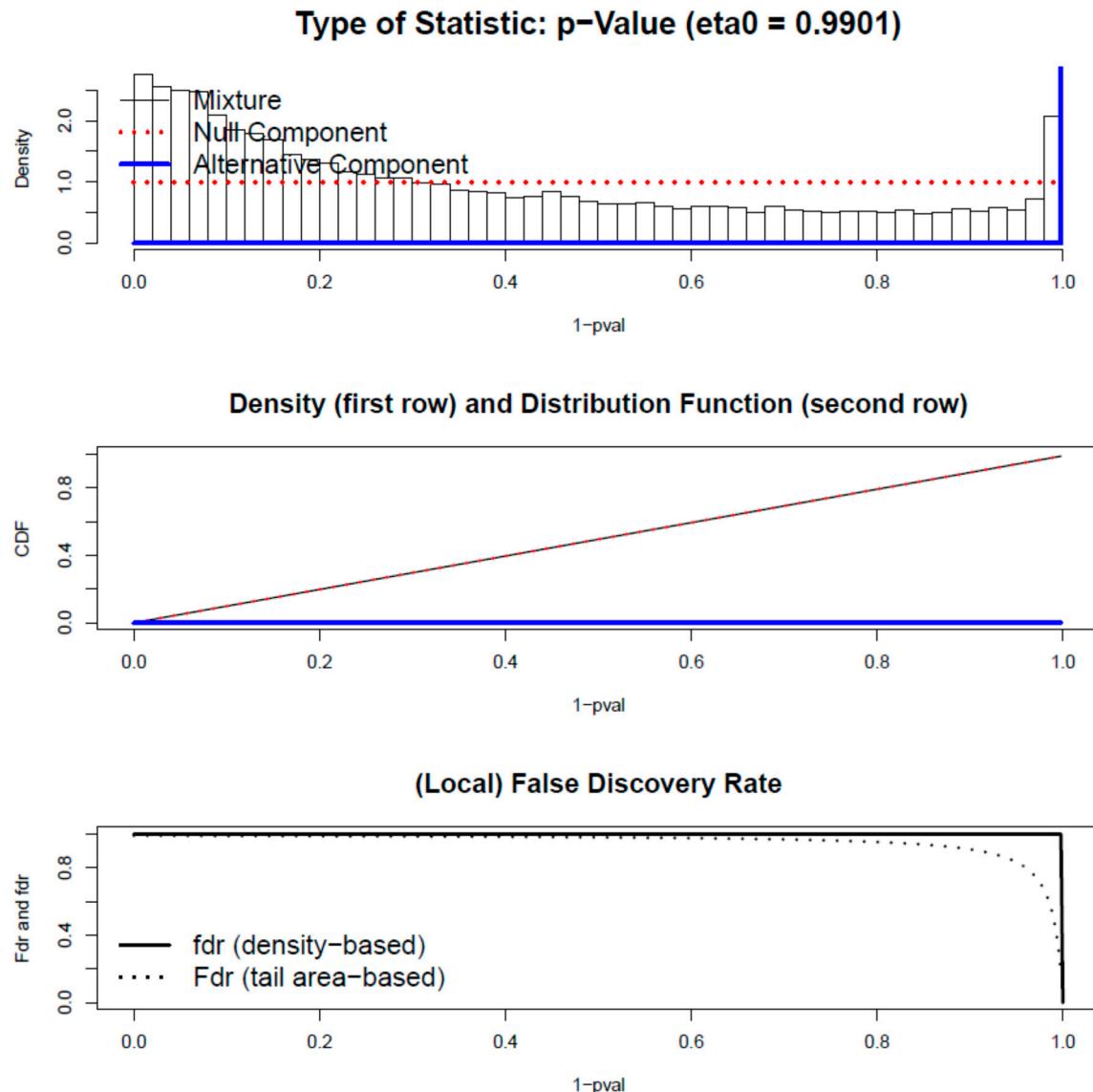


Figure S5. fdrtool's output: mRNA in ESCC.

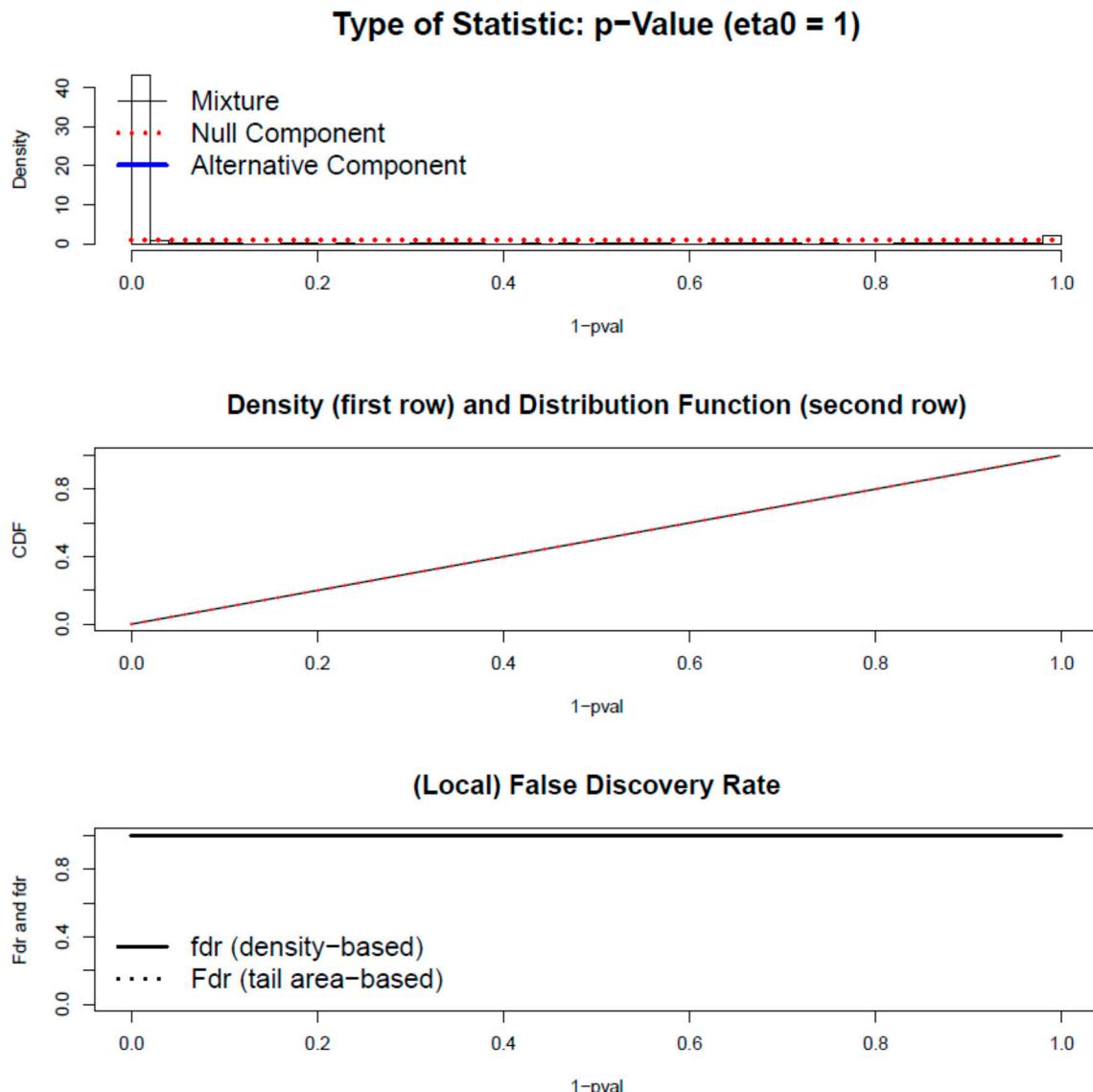


Figure S6. fdrtool's output: miRNA in ESCC.

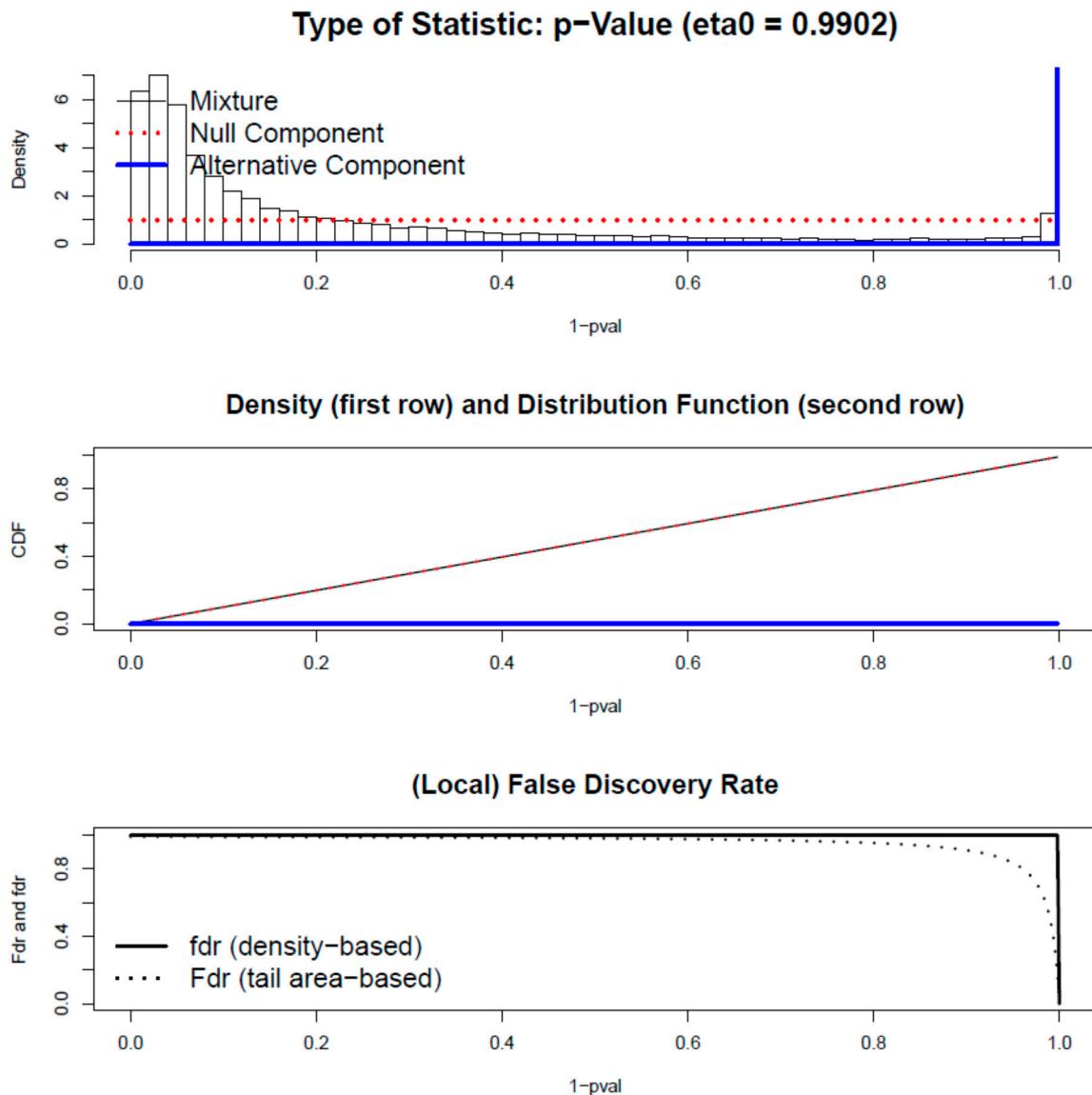


Figure S7. fdrtool's output: mRNA in prostate cancer.

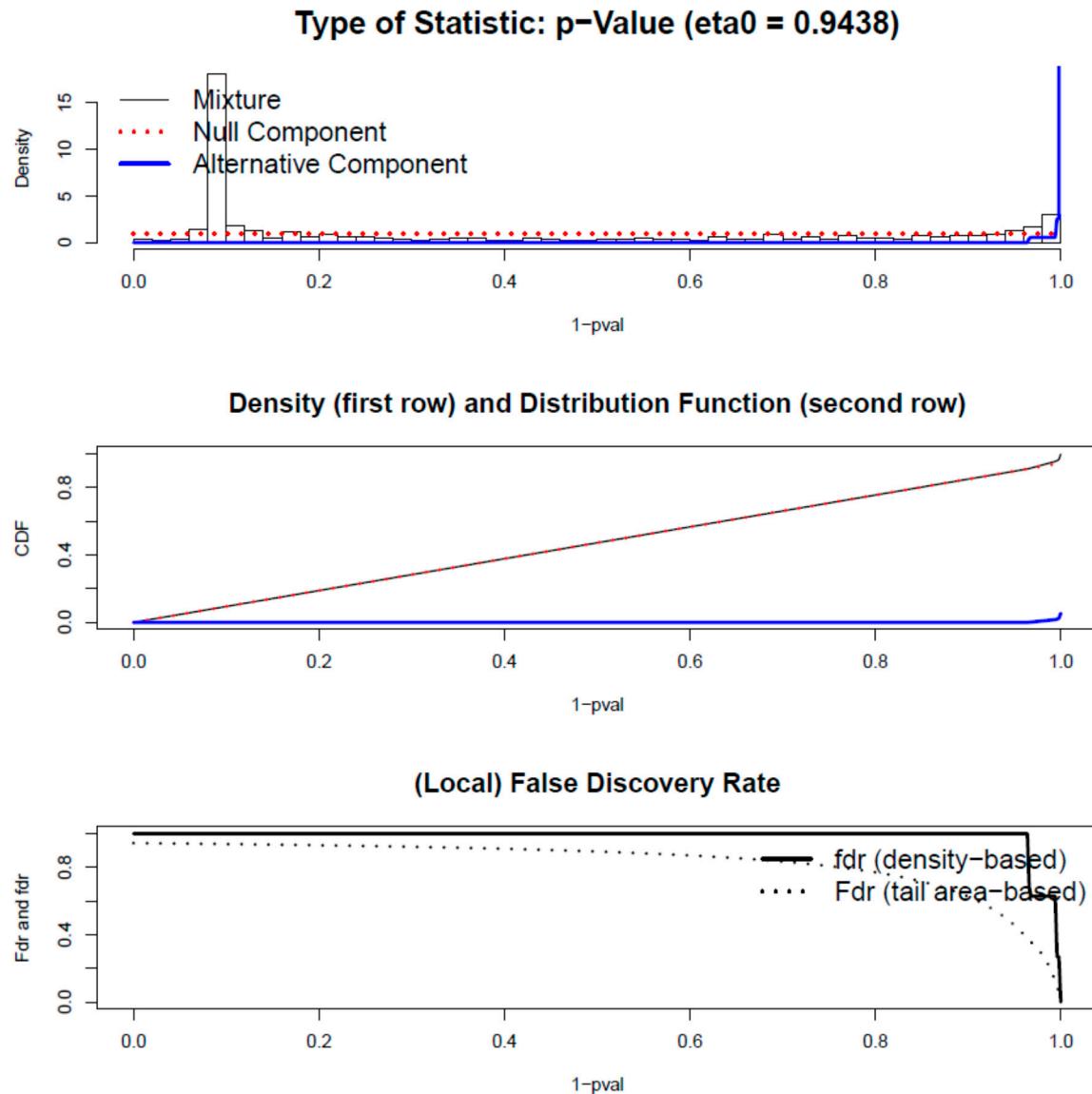


Figure S8. fdrtool's output: miRNA in prostate cancer.

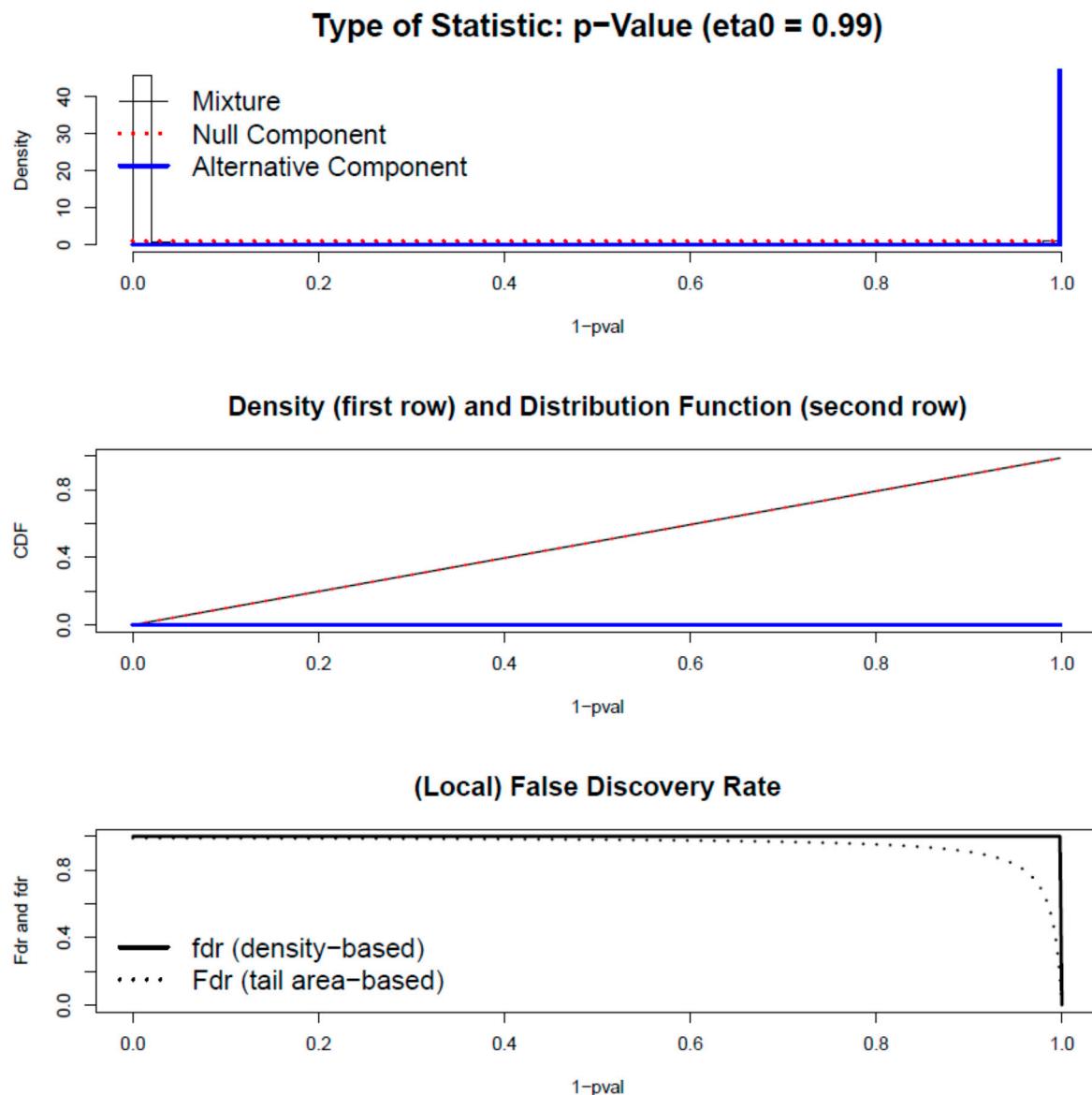


Figure S9. fdrtool's output: mRNA in colon/colorectal cancer.

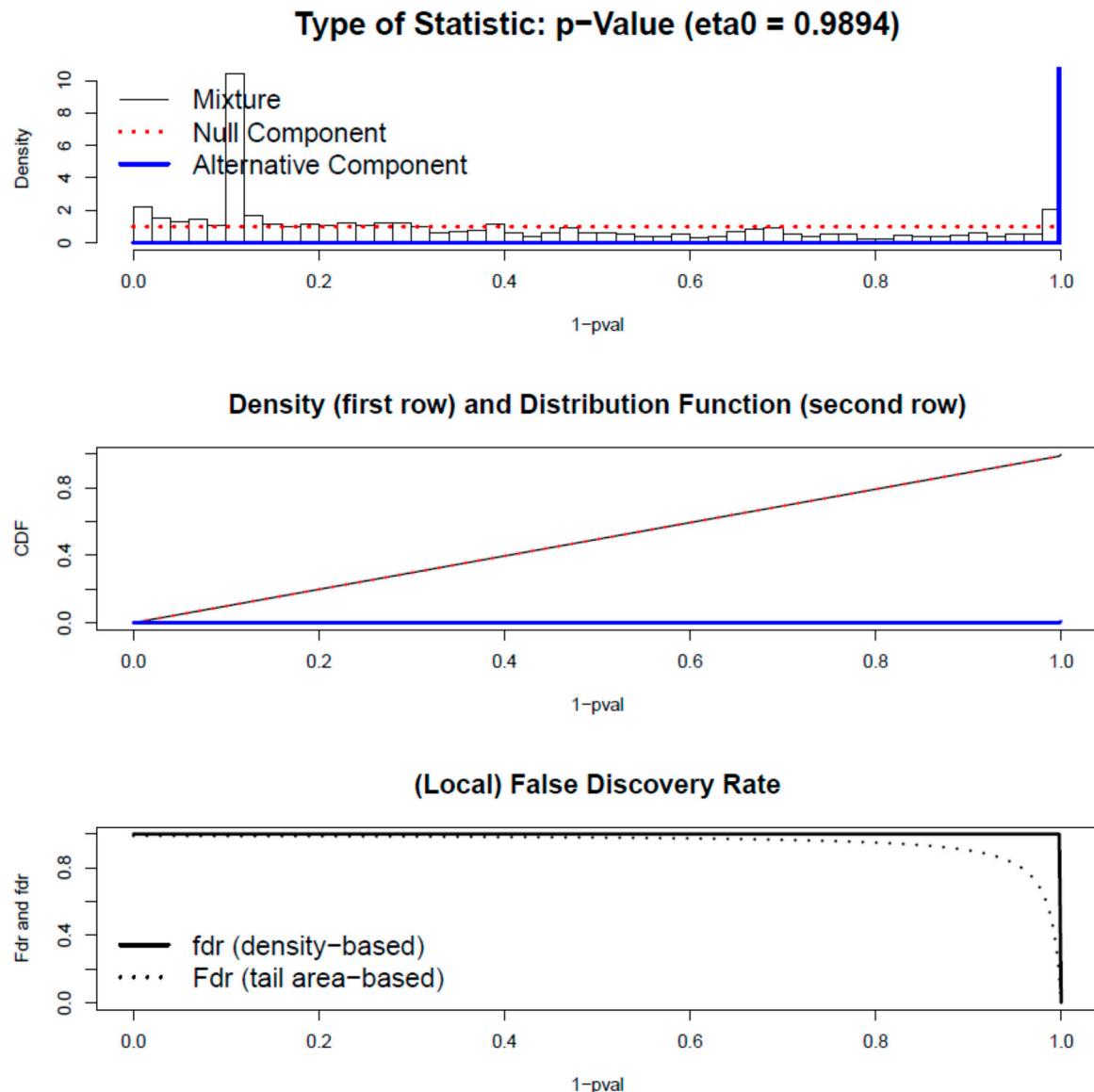


Figure S10. fdrtool's output: miRNA in colon/colorectal cancer.

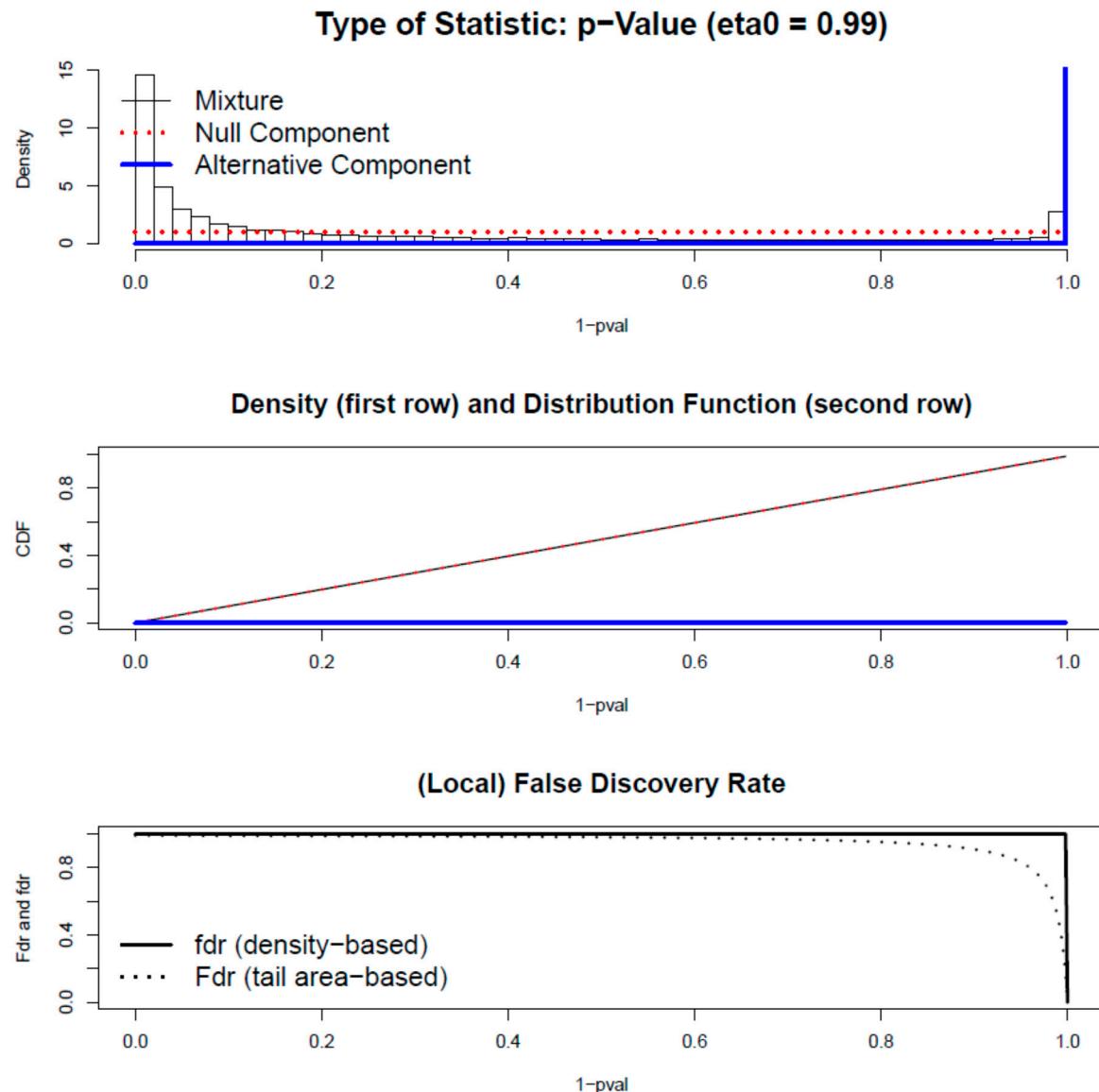


Figure S11. fdrtool's output: mRNA in breast cancer.

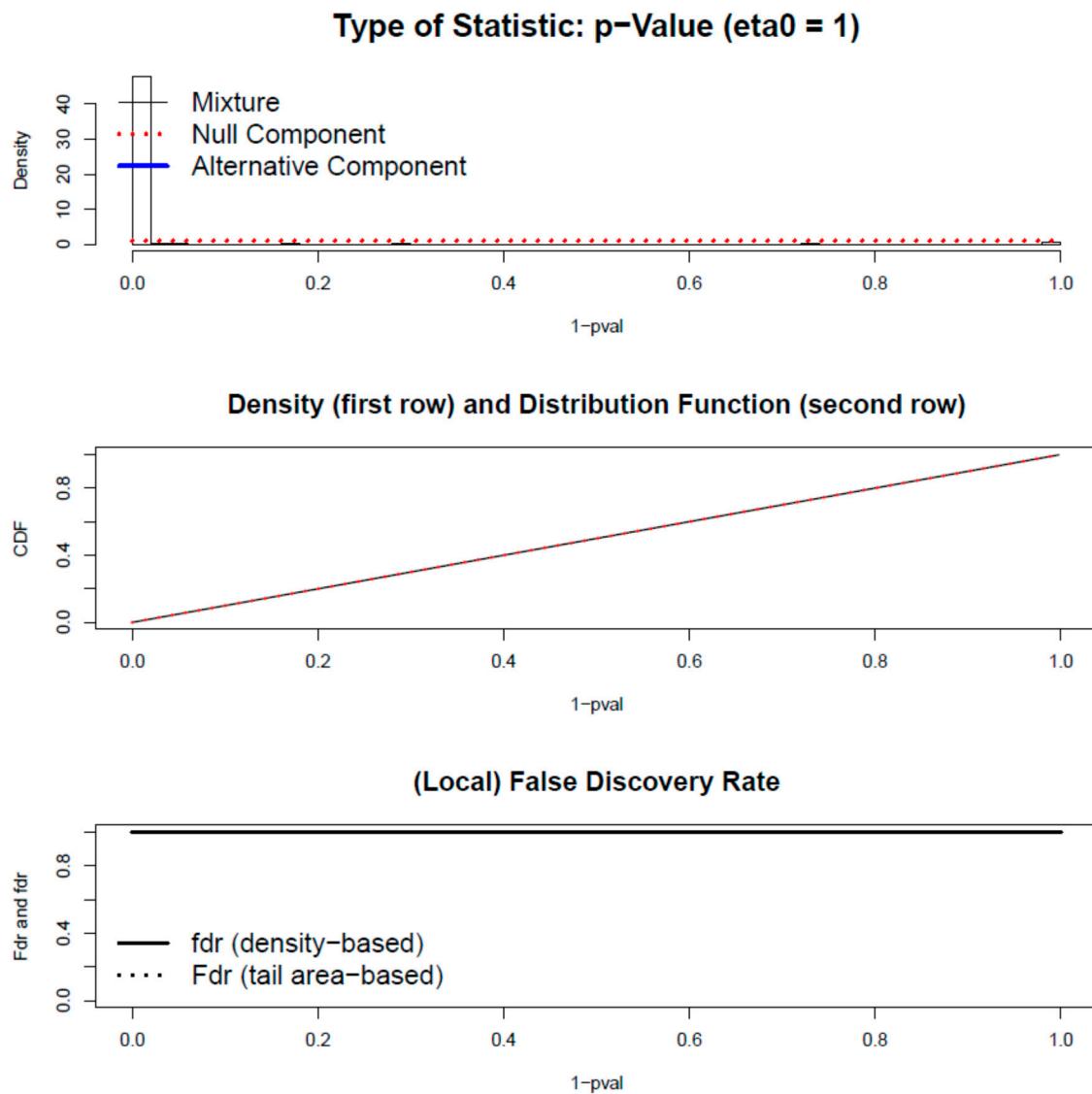


Figure S12. fdrtool's output: miRNA in breast cancer.

Table S1. miRNA–mRNA interaction pairs identified in the HCC samples. $T > N$: upregulated in tumors, $T < N$: upregulated in normal tissues. The starbase column lists the number of cancer cell lines associated with significant reciprocal correlations among the identified pairs. If several miRNAs share the same seed sequence, their numbers are stated separately and connected by a + symbol.

miRNAs ($T > N$)	Gene ($T < N$)	Function in HCC	Starbase
miR-93	activates the c-Met/PI3K/Akt pathway [1]		
	ESR1 tumor suppressor [2], promoter methylation [3]		0
	CXCL2 therapeutic target [4], promotes cell proliferation and metastasis [5]		0
miR-25	various roles [6], promotes cell growth [7]		
miR-92a	deregulation [8], contributes to tumor growth [9], preserves survival [10]		
miR-15b	CD69 CD4(+) CD69(+) CD25(−) T cells were identified in HCC tissues [11]		6 + 10
	induces endoplasmic reticulum stress and apoptosis [12]		
	see miR-25/92a		0
	related to proliferation [13], targets a long non-coding RNA that increases		
	GHR EGFR expression [14], distinct therapy treatments between positive/negative tumors [13]		0
miR-148a	GLS2 tumor suppressor [15], epigenetic silencing [16]		4
	repression of HCC cell malignancy [17]		4
miR-125b	ESR1 see miR-93		
	attenuates epithelial-mesenchymal transitions [18]		
	TAT Loss of one TAT allele [19]		0
let-7a	promising tools against systemic HCC [8]		
	STAB2 upregulation [20], downregulation suppresses tumor [20]		0
	GHR see miR-15b		0

Table S2. miRNA–mRNA interaction pairs identified in HCC samples (continued).

miRNAs ($T < N$)	Gene ($T > N$)	Function in HCC	Starbase
miR-20a	Reduced expression promotes HCC [21]		
	SLC40A1 haplotype [22]		9
	HSPA8 upregulation [23]		4
	GPR88 —		0
miR-214	PDE3B involved in development and metabolism of HCV [24]		2
	recurrence of HCC [25]		
miR-195	PEG10 upregulation [26], associated with poor survival and tumor recurrence [27], promote carcinogenesis [28]		0
	GPR88 suppresses angiogenesis and metastasis of HCC [29]		0
	GABRE upregulation [30]		0
miR-200b	suppression of HCC [31]		
miR-29c	CCNA2 AAV2 integration in CCNA2 [32], associated with low survival sub-class [33]		4
	suppression of HCC [34]		
miR-30d	B3GNT5 —		8
	B3GNT5 promotes tumor invasion and metastasis [35]		8
	see miR-29c		

Table S3. miRNA–mRNA interaction pairs identified in the NSCLC samples. $T > N$: upregulated in tumors, $T < N$: upregulated in normal tissues. For a description of the numbers in the starbase column, see Table S1.

miRNAs ($T < N$)	Gene ($T > N$)	Function in NSCLC	Starbase
miR-30a		inhibits tumor proliferation [36]	
miR-30d		inhibits tumor proliferation [37]	
	BNC1	hypermethylation [38]	0 + 0
	PIGX	candidate driver genes [39]	5 + 4
	GCLC	drug resistance [40]	3 + 2
	THBS2	correlated with decreased vascularity [41]	0 + 0
	HMGB3	overexpression as biomarker [42]	0 + 0
	PFN2	epigenetic regulation of other genes [43]	5 + 4
	FOXD1	association with poor prognosis [44]	4 + 7
	CYP24A1	independent prognostic marker of survival [45]	5 + 5
	PITX1	decreased expression [46]	7 + 7
	BMP7	reported biological impact [47]	0 + 0
	MXRA5	frequent mutation [48]	0 + 0
	SLC7A11	contributes to pathogenesis [49]	6 + 6
	FAP	clinical implications [50]	8 + 11
	BCL11A	overexpression predicts survival and relapse [51]	3 + 5
	ADAM12	diagnostic marker of proliferation, migration and invasion [52]	0 + 0
	ITGA6	downregulation in cancer stem cells [53]	5 + 4
	MARK1	inhibitor, new target agent [54]	0 + 0
	NEFL	candidate biomarker of recurrence and survival [55]	5 + 8
	GRHL1	decreased expression in cell lines [56]	0 + 0
	SLC41A2	—	3 + 6
	GDA	—	1 + 4
	CDCA7	possible subtype-specific expression [57]	9 + 6
	FRMD6	—	6 + 11
	CTHRC1	associated with tumor aggressiveness and poor prognosis [58]	10 + 8
	FBXO32	—	0 + 0
	C3orf58	—	4 + 1
	PPP1R14C	—	2 + 4
	E2F7	upregulated in NSCLC treatment [59]	10 + 5
	SIX1	target of tumor suppressor miRNA [60]	9 + 5
	FAM83F	FAM83B, which belongs to the same protein family as FAM83F, is a novel biomarker [61]	0 + 0

Table S4. miRNA–mRNA interaction pairs identified in NSCLC samples (continued).

miRNAs (T < N)	Gene (T > N)	Function in NSCLC	Starbase
miR-221	Growth inhibitor [62]		
	ATP11B —		0
	TFAP2A —		3
	FAT2 subtype-specific biomarker [63]		0
	IGF2BP2 —		0
miR-130a	targets some genes [64]		
	SLC2A1 reported polymorphisms [65]		2
	CALB1 suggested roles [66]		0
	TP63 isoform expression [67]		2
	BCL11A see miR-30a/30d		1
	SULF1 dysregulation [68]		0
	ADAM12 see miR-30a/30d		3
	CEP55 overexpression and modulation of tumor migration and invasion [69]		3
	GDA see miR-30a/30d		6
	FRMD6 see miR-30a/30d		4
	E2F7 see miR-30a/30d		2
miR-100	tumor suppressor [70]		
	FGFR3 mutation [71]		6
	GRHL1 miR-30a/30d		7
miR-223	potent tumor suppressor [72]		
	PFN2 miR-30a/30d		0
	ECT2 overexpression [73]		3
miR-143	inhibits NSCLC cell growth and metastasis [74]		
	COL1A1 overexpression [75]		0
	COL5A1 —		0
	PLAU subtype-specific expression [76]		0
	KLF5 inhibits apoptosis [77]		8
	SLC7A11 chemoresistance [78]		4
	ITGA6 miR-30a/30d		2
	GOLM1 overexpression [79]		5
	COL5A2 overexpression [80]		0
	FAM83F see miR-30a/30d		0

Table S5. miRNA–mRNA interaction pairs identified in NSCLC samples (continued).

miRNAs (<i>T < N</i>)	Gene (<i>T > N</i>)	Function in NSCLC	Starbase
miR-145		inhibits NSCLC proliferation [81]	
	ABCC1	drug resistance [82]	3
	HMGB3	miR-30a/30d	6
	TFRC	frequent amplification [83]	7
	KLF5	miR-143	4
	SULF1	see miR-130a	0
	PSAT1	sustains proliferation [84]	6
miR-125b		downregulation promotes NSCLC invasion and migration [85]	
	HMGB3	miR-30a/30d	7
	MMP11	correlated with higher-grade NSCLC [86]	0
	CYP24A1	miR-30a/30d	0
	RAPGEFL1	—	0
	GRHL1	miR-30a/30d	5
	VANGL2	—	0
miR-195	FAM83F	see miR-30a/30d	
		tumor suppressor [87]	
	ANLN	plays a critical role in NSCLC [88]	7
	AK4	promotes metastasis [88]	0
	KCNN4	associated with poor prognosis [89]	1
	CXCL10	blood biomarker [90]	1
	KIF23	overexpression [91]	8
miR-125b	PTHLH	increased in the serum and urine of NSCLC patients [92]	3
	HMGA2	overexpression [93]	8
	LRRC15	—	0
	RAPGEFL1	see miR-125b	0
	FZD10	overexpression [94]	1
	PLUNC	biomarker [95]	0
	RGMA	—	0
miR-195	SLC41A2	see miR-30a/30d	2
	KCTD1	—	5
	FAM110C	—	3
	E2F7	see miR-30a/30d	8
	PRR11	cell cycle progression [96]	0
	ODZ2	biomarker [97]	0

Table S6. miRNA–mRNA interaction pairs identified in NSCLC samples (continued).

miRNAs (T < N)	Gene (T > N)	Function in NSCLC	Starbase
miR-26a		drug resistance [98]	
	COL1A2	potential therapeutic target [99]	0
	PLOD2	prognostic variables [100]	8
	ADM	regulates NSCLC [101]	7
	LOXL2	downregulation [102]	10
	COL5A1	see miR-143	8
	COL11A1	overexpression [103]	0
	TFAP2A	see miR-221	5
	COL10A1	overexpression [104]	0
	WNT5A	promotes angiogenesis [105]	2
	CILP	—	0
	HMG A2	see miR-195	6
	JAG1	prognostic biomarkers [106]	4
	TP63	see miR-130a	0
	SLC7A11	see miR-143	6
	BCL11A	see miR-30a/30d	2
	SULF1	see miR-130a	0
	ADAM12	see miR-30a/30d	0
	ITGA6	see miR-143	5
	MARK1	see miR-30a/30d	3
	HAS3	abundant expression [107]	0
	VANGL2	see miR-125b	1
	E2F7	miR-30a/30d	8
	LPAR3	—	4
	GRHL3	—	0

Table S7. miRNA–mRNA interaction pairs identified in NSCLC samples (continued).

miRNAs (T < N)	Gene (T > N)	Function in NSCLC	Starbase
miR-29a		aberrant methylation [108] see miR-143	
	COL1A1	upregulation [109]	4
	COL3A1	—	4
	SLC16A1	—	7
	COL1A2	see miR-26a	0
	LOXL2	see miR-26a	6
	COL5A1	see miR-26a	4
	COL11A1	see miR-26a	0
	DSG3	biomarker [110] see miR-195	0
	PTHLH	a part of classifier [111]	5
	UPK1B	see miR-30a/30d	0
	BCL11A	see miR-30a/30d	4
	ADAM12	see miR-30a/30d	6
	COL4A6	frequently mutated=[48]	0
	ITGA6	see miR-30a/30d	6
	RAPGEFL1	see miR-125b	0
	COL5A2	see miR-143	6
	HAS3	see miR-26a	3
	KCTD1	see miR-195	6
	E2F7	see miR-30a/30d	9

Table S8. miRNA–mRNA interaction pairs identified in NSCLC samples (continued).

miRNAs (T > N)	Gene (T < N)	Function in NSCLC	Starbase
miR-106a		promotes growth and metastasis of NSCLC [112]	
miR-17		cancer development [113]	
	IGSF10	differently expressed [114]	0 + 0
	SLC4A4	—	0 + 0
	LMO3	cell growth and metastasis [115]	0 + 0
	NR4A2	tumor suppressor [116]	5 + 6
	HLF	—	0 + 0
	FOXF1	drives NSCLC progression [117]	8 + 9
	SMAD6	contributes to patient survival [118]	4 + 8
	CD69	detected expression [119]	6 + 9
	DLC1	tumor suppressor [120]	9 + 9
	TMEM100	downregulation [114]	9 + 8
	TBX3	overexpression [121]	5 + 6
	COL4A3	correlated with poor prognosis [122]	0 + 0
	NTN4	—	6 + 10
	SCD5	abundance [123]	4 + 5
	TMTC1	—	6 + 9
	PTPN21	mutations [124]	9 + 8
	NEDD4L	prognostic marker [125]	3 + 4
	ANKRD29	—	9 + 11
	GLDN	—	0 + 0
	ATP11A	—	6 + 3
	GPR133	mutation [126]	7 + 10
	NCKAP5	downregulation [114]	4 + 6

Table S9. miRNA–mRNA interaction pairs identified in NSCLC samples (continued).

miRNAs (T > N)	Gene (T < N)	Function in NSCLC	Starbase
miR-141		biomarker [127]	
miR-200a		targets multiple NSCLC prognostic markers [128]	
	PLCB4	downregulation [129]	0 + 0
	LMO3	see miR-106a/17	5 + 5
	HLF	see miR-106a/17	0 + 0
	GPM6B	—	0 + 0
	PDZD2	—	0 + 0
	PTCH1	suppressed by miR-212 [130]	4 + 0
	GATA6	tumor inhibitor [131]	6 + 5
	FOXA2	downregulated [132]	0 + 0
	DLC1	see miR-106a/17	11 + 9
	ATP8A1	downregulated [133]	5 + 5
	CLIC5	downregulated [134]	0 + 0
	SLC1A1	polymorphisms [65]	4 + 3
	PCDH9	possible association with NSCLC development, metastasis and prognosis [135]	11 + 8
	SOX17	promoter of methylation in plasma-circulating tumors DNA [136]	0 + 0
	SCD5	see miR-106a/17	5 + 4
	SEMA6A	downregulation [137]	0 + 0
	HSPC159	—	0 + 0
	TMTC1	see miR-106a/17	0 + 0
	SYNPO2	upregulated under HDACi treatment [138]	0 + 0
	SCN7A	associated with good survival [139]	0 + 0
	ADRB1	ADRB1-specific or non-selective drug improves survival [140]	4 + 2
	NCKAP5	see miR-106a/17	3 + 2
	PAQR5	—	2 + 3

Table S10. miRNA–mRNA interaction pairs identified in NSCLC samples (continued).

miRNAs ($T \geq N$)	Gene ($T < N$)	Function in NSCLC	Starbase
miR-200b		targets multiple NSCLC prognostic markers [128]	
miR-200c		inhibits invasion and metastasis [141]	
	DUSP1	promotes angiogenesis, invasion and metastasis [142]	7 + 10
	FHL1	downregulation [143]	10 + 9
	SLC4A4	see miR-106a/17	0 + 0
	REEP1	upregulated under both 5-dAzaC treatment and BRG1 re-expression [144]	4 + 5
	HLF	see miR-106a/17	0 + 0
	DACH1	tumor suppressor [145]	0 + 1
	FOXF1	see miR-106a/17	9 + 8
	GPM6A	differential expression [146]	7 + 8
	CHRDL1	aberrant gene expression [147]	0 + 0
	PTCH1	see miR-141/200a	2 + 3
	DLC1	see miR-106a/17	8 + 9
	KLF4	metastasis regulation [148]	4 + 2
	COL4A3	see miR-106a/17	6 + 6
	PTPN21	see miR-106a/17	7 + 8
	SEMA6D	—	5 + 3
	NEDD4L	see miR-106a/17	1 + 1
	AFF3	—	0 + 0
	GCOM1	downregulation [149]	3 + 5
	MAMDC2	aberrant methylation [150]	7 + 10
	PAQR5	see miR-141/200a	0 + 0

Table S11. miRNA–mRNA interaction pairs identified in NSCLC samples (continued).

miRNAs ($T > N$)	Gene ($T < N$)	Function in NSCLC	Starbase
miR-205		drives malignant phenotype [151]	
	LPCAT1	upregulation [152]	4
	SLC4A4	see miR-106a/17	0
	FOXF1	see miR-106a/17	7
	TBX3	see miR-106a/17	0
	SCD5	see miR-106a/17	0
	AFF3	see miR-200b/200c	0
	GCOM1	see miR-200b/200c	0
	LRRK2	—	0
miR-21		restrains cell proliferation and migration [153]	
	THBD	can be used as a part of survival prediction [154]	0
	PDZD2	see miR-141/200a	8
	CD69	see miR-106a/17	0
	PTCH1	see miR-141/200a	0
	OLR1	can be used as a part of prognosis prediction [155]	2
	LIFR	—	11
	ARHGEF26	—	0
	SOX7	downregulation [156]	7
	KCNT2	—	0

Table S12. miRNA–mRNA interaction pairs identified in NSCLC samples (continued).

miRNAs ($T > N$)	Gene ($T < N$)	Function in NSCLC	Starbase
miR-19b		circulating biomarker [157]	
	TGM2	cisplatin resistance marker [158]	9
	EDNRB	Aberrant promoter methylation [159]	8
	REEP1	see miR-200b/200c	3
	HLF	see miR-106a/17	0
	DLC1	see miR-106a/17	8
	LIMCH1	inclusion in tumorigenesis [160]	9
	PARM1	—	8
	CAB39L	—	0
	FRAS1	knockdown reduces A549 cell migration and invasion [161]	3
	HSPC159	see miR-141/200a	0
	PTPN21	see miR-106a/17	9
	VSIG10	—	2
	SEMA6D	see miR-200b/200c	4
	ARHGEF26	see miR-21	0
	SYNPO2	see miR-141/200a	0
	ADRB1	see miR-141/200a	9
	LRRK2	see miR-205	0
	ATP11A	see miR-106a/17	2
	SCN4B	—	0
	NCKAP5	see miR-106a/17	6
	KCNT2	see miR-21	0

Table S13. miRNA–mRNA interaction pairs identified in ESCC samples. $T > N$: upregulated in tumors, $T < N$: upregulated in normal tissues. For a description of the numbers in the starbase column, see Table S1.

miRNAs ($T < N$)	Gene ($T > N$)	Function in ESCC	Starbase
miR-203		G1 arrest [162], downregulation [163]	
	BIRC5	overexpression [164]	1
	TP63	tumor suppressor [165]	0
($T > N$)	($T < N$)		
miR-223		clinically significant [166]; overexpression regulates the ubiquitin ligase FBXW7 [167]	
	HLF	lineage - specifically essential for tumor growth [168]	0
	SORBS1	significantly shortened tandem 3' UTRs [169]	6

Table S14. miRNA–mRNA interaction pairs identified in prostate cancer samples. $T > N$: upregulated in tumors, $T < N$: upregulated in normal tissues. For a description of the numbers in the starbase column, see Table S1.

miRNAs ($T > N$)	Gene ($T < N$)	Function in Prostate Cancer	Starbase
miR-136	biomarker [170]		
	EIF4B	related to anticancer activity [171]	6
	HOXC10	aberrant expression [172]	0
miR-145		suppress the androgen receptor [173]	
	TFRC	biomarker [174]	7
	EIF4B	see miR-136	0
	KIAA0355	—	0
	USP31	—	2
miR-22	ZDHHC8	—	0
		overexpression in DU145 [175]	
	KIAA0355	see miR-145	7
	PTEN	genomic rearrangement [176]	2
miR-494	ZNF827	—	0
		suppress proliferation, invasion, and migration [177]	
	C14orf43	—	2
	YEATS2	—	1
	PTEN	see miR-22	1
	USP31	see miR-145	1
miR-27X	USP27X	—	0

Table S15. miRNA–mRNA interaction pairs identified in prostate cancer samples (continued).

miRNAs ($T < N$)	Gene ($T > N$)	Function in Prostate Cancer	Starbase
let-7a/7f		inclusion in tumorigenesis [178]	
	NXT2	—	0 + 1
	ANKRD12	—	1 + 2
	FOXP1	tumor suppressor [179]	3 + 1
	RTCD1	—	7 + 5
miR-200a	PLEKHG6	—	0 + 0
		tumor suppressor [180]	
	FOXP1	see let-7a/7f	6
miR-200b		tumor suppressor [180]	
	FOXP1	see let-7a/7f	0
	CADM1	inactivated by methylation promoter [181]	2
	PFN2	—	0
miR-20b		reported importance [182]	
	ANKRD12	see let-7a/7f	3
	RGNEF	—	3
	PFN2	see miR-200b	1

Table S16. miRNA–mRNA interaction pairs identified in colorectal/colon cancer samples. $T > N$: upregulated in tumors, $T < N$: upregulated in normal tissues. For a description of the numbers in the starbase column, see Table S1.

miRNAs ($T < N$)	Gene ($T > N$)	Function in Colorectal/Colon Cancer	Starbase
miR-182	FN1	deregulation promotes proliferation [183] upregulation [184]	0
miR-183	EEF2	overexpression [185] knockdown inhibits growth [186]	4
miR-96	FN1	overexpression [187] see miR-182	9
($T > N$)	($T < N$)		
miR-133a	PTPRO	tumor suppressor [188] sensitization [189]	0
miR-137	SLC25A5	tumor suppressor [190] —	3
miR-149	IGJ	tumor suppressor [191] downregulation [192]	0
miR-30a	MYH11	targets the insulin receptor [193] down-regulated expression correlates with poor prognosis [194]	0
	CEACAM1	regulates metastasis [195]	0

Table S17. miRNA–mRNA interaction pairs identified in breast cancer samples. $T > N$: upregulated in tumors, $T < N$: upregulated in normal tissues. For a description of the numbers in the starbase column, see Table S1.

miRNAs ($T > N$)	Gene ($T < N$)	Function in Breast Cancer	Starbase
let-7i	AMT	regulates self-renewal and tumorigenicity [196] subtype-specific downregulation [197]	4
	GHR	up-expression [198]	0
	HOXA9	modulates tumor phenotype [199]	0
miR-148a	CNN1	inhibits migration of breast cancer cells [200] possible therapeutic target [201]	0
	FOSB	overexpression [202]	0
	TNXB	adhesion modulation [203]	0
miR-19b	NCALD	regulates tissue factor expression [204] frequent amplification [205]	0
	HOXA9	see let-7i	1
	IRX4	—	0
	CXCL12	promotes metastasis [206]	0
miR-21	MATN2	downregulation [207] overexpression [208]	9
	MSX1	—	6
	MATN2	see miR-19b	9
miR-23a		overexpression [209]	
	SFRP1	associated with neoadjuvant chemotherapy [210]	0
	FOSB	see miR-148a	0
	CXCL12	see miR-19b	5
miR-24	NCALD	enhances tumor invasion and metastasis [211] see miR-19b	0

Table S18. miRNA–mRNA interaction pairs identified in breast cancer samples (continued).

miRNAs (T < N)	Gene (T > N)	Function in Breast Cancer	Starbase
let-7b	ICOS	regulates self-renewal and tumorigenicity [196] associated with poor prognosis [212]	0
	SYT1	possible biomarker [213]	0
	ERO1L	associated with overall good survival [214]	4
	CTSC	metastasis [215]	3
	S100A8	aggression [216]	0
	RDH10	—	4
	DUSP6	targets ARID3B [217] silencing inhibits proliferation [218]	5
miR-125b	CCR2	coordinates survival and motility [219]	0
	BIN2	also known as breast cancer-associated protein 1 [220]	0
	WARS	good prognostic marker [221]	5
	PDE7A	—	4
	GALNT7	—	5
	GLS	promotes proliferation [222] tumor suppressor [223]	0
	WHSC1	positive regulator of ERα signaling [224]	0
miR-143	ITGA6	overexpression [225]	2
	DUSP6	tumor suppressor [223]	1
	RPS6KB1	see miR-125b	3
miR-145	ITPR2	alteration [226]	0
	FOSL1	fused with ETV6 [227]	0
miR-22		biomarker [228]	2
		overexpression inhibition decreases cell growth [229]	

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