

Supplementary Information

Integrating analysis reveals microRNA-mediated pathway crosstalk among Crohn's disease, ulcerative colitis and colorectal cancer

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Content

Figure S1. The relationships of risk genes in different diseases	2
Figure S2. Regulation network of risk miRNAs enriched in diseases	3
Figure S3. The statistic of validated and predicted miRNA targets.....	4
Table S1: The list of common biological processes among CD, UC and CRC.....	5
Table S2. The list of consensus KEGG pathways among CD, UC and CRC.....	12
Table S3. The PubMed citation information of risk miRNAs and corresponding diseases.....	13

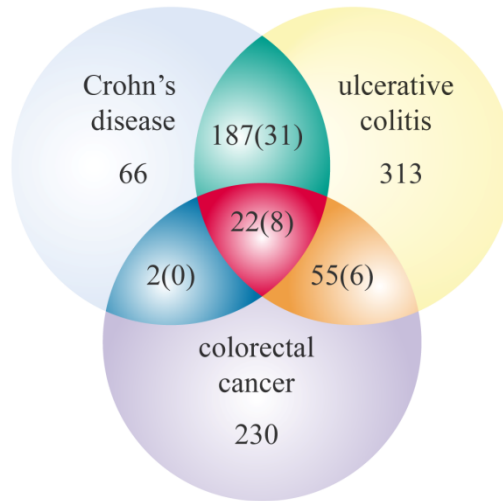


Figure S1. The relationships of risk genes in different diseases

Venn diagram illustrates the overlapping relationships of the risk genes among the three diseases. The number in the bracket represents the number of known disease genes of inflammatory bowel disease or colon cancer.

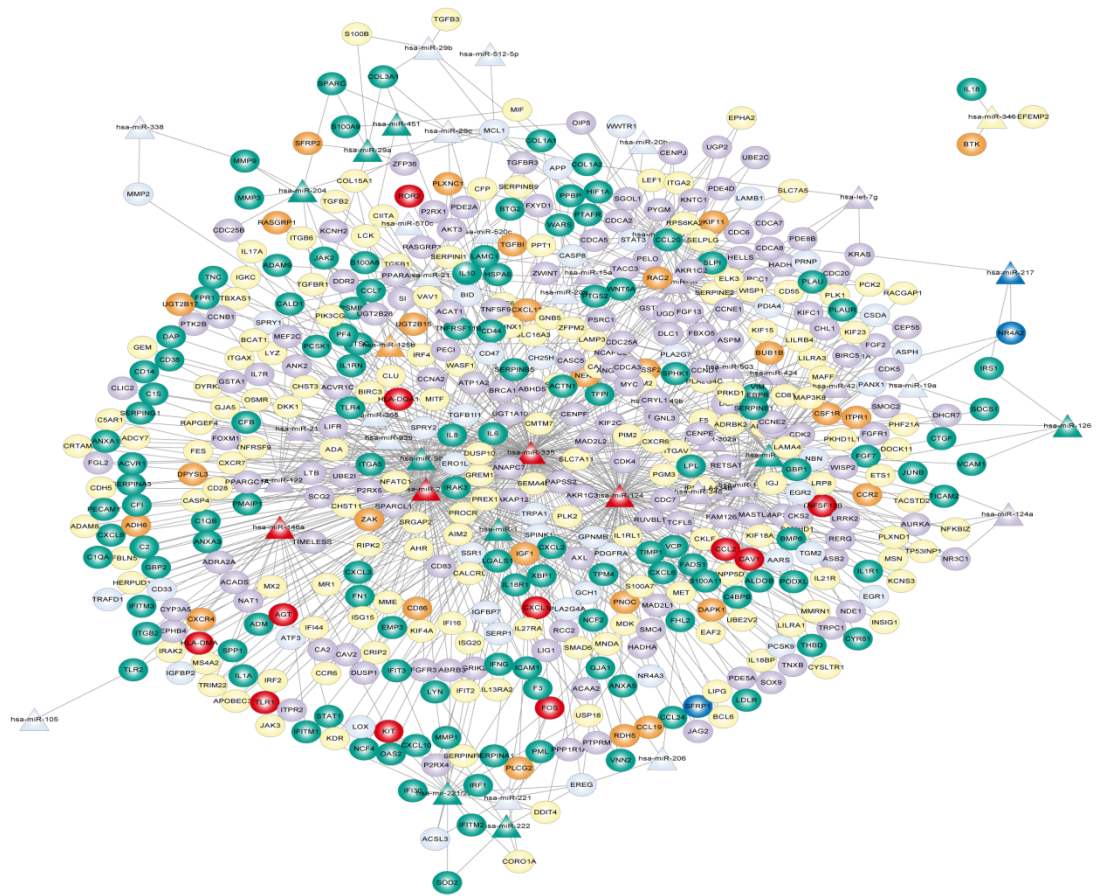


Figure S2. Regulation network of risk miRNAs enriched in diseases

A network generated by disease risk miRNAs and their validated target genes, which consists of 942 regulatory relationships between 47 miRNAs and 516 disease risk genes. A triangle node represents a miRNA and a circle node represents a gene. Colors of the nodes have the same meanings as the Venn diagram in Figure S1.

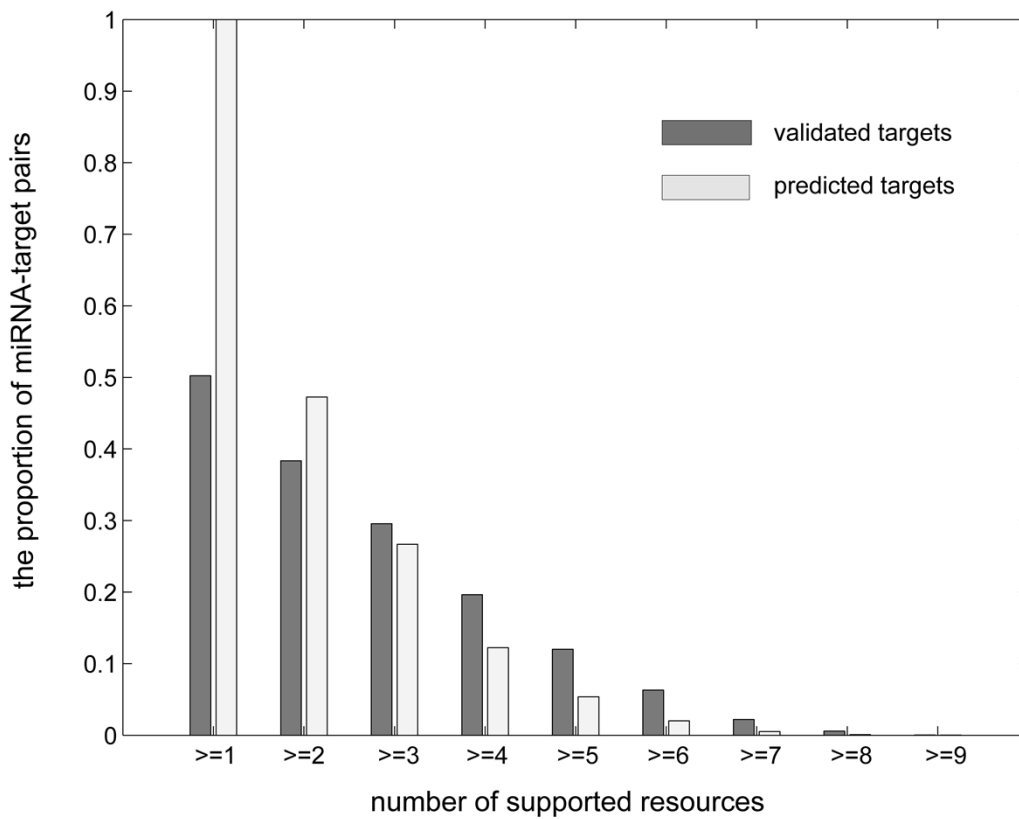


Figure S3. The statistic of validated and predicted miRNA targets.

The validated targets were collected from four considered sources including miRecords, TarBase_v6.0, miRTarBase and mir2Disease, whereas the predicted targets were obtained from ten frequently-used databases including TargetScan, miRanda, PITA, DIANA-microT, PicTar5, RNA22, mirSVR, RNAhybrid, MirTarget2 and TargetMiner. The value is the proportion of shared miRNA-targets relative to the total number of miRNA-targets.

Table S1: The list of common biological processes among CD, UC and CRC

Classes	Term name1	Term name2	No.1	No.2
CD&UC	response to organic cyclic compound	response to organic cyclic compound	7	5
	response to lipopolysaccharide	response to lipopolysaccharide	7	9
	response to lipopolysaccharide	defense response to bacterium	7	5
	response to lipopolysaccharide	response to biotic stimulus	7	5
	response to cytokine stimulus	response to organic substance	7	6
	response to cytokine stimulus	cytokine-mediated signaling pathway	7	6
	response to cytokine stimulus	response to tumor necrosis factor	7	5
	response to cytokine stimulus	response to cytokine stimulus	7	5
	response to hyperoxia	response to hypoxia	7	5
	response to glucocorticoid stimulus	response to glucocorticoid stimulus	7	5
	response to glucocorticoid stimulus	response to estradiol stimulus	7	5
	response to organic substance	response to organic substance	6	6
	response to organic substance	response to cytokine stimulus	6	5
	cellular component movement	cellular component movement	6	7
	cellular component movement	positive regulation of cellular component movement	6	6
	cellular component movement	leukocyte migration	6	6
	chemotaxis	chemotaxis	6	8
	inflammatory response	blood coagulation	6	8
	inflammatory response	inflammatory response	6	8
	inflammatory response	negative regulation of inflammatory response	6	6
	inflammatory response	response to wounding	6	6
	inflammatory response	defense response	6	5
	response to cold	response to cold	6	5
	wound healing	blood coagulation	6	8
	wound healing	inflammatory response	6	8

wound healing	response to wounding	6	6
response to wounding	blood coagulation	6	8
response to wounding	inflammatory response	6	8
response to wounding	response to wounding	6	6
response to estradiol stimulus	response to glucocorticoid stimulus	6	5
response to estradiol stimulus	response to estradiol stimulus	6	5
negative regulation of cell proliferation	cell proliferation	6	7
negative regulation of cell proliferation	negative regulation of cell proliferation	6	5
leukocyte migration	cellular component movement	5	7
leukocyte migration	leukocyte migration	5	6
cellular response to interleukin-1	response to interleukin-1	5	5
response to hydrogen peroxide	hydrogen peroxide catabolic process	5	5
anti-apoptosis	negative regulation of apoptosis	5	6
anti-apoptosis	anti-apoptosis	5	5
positive regulation of cell migration	cellular component movement	5	7
positive regulation of cell migration	positive regulation of cellular component movement	5	6
cellular response to tumor necrosis factor	response to tumor necrosis factor	5	5
positive regulation of peptidyl-serine phosphorylation	positive regulation of peptidyl-serine phosphorylation	5	5
response to bacterium	response to lipopolysaccharide	5	9
response to bacterium	response to virus	5	6
response to bacterium	defense response to Gram-positive bacterium	5	5
response to bacterium	defense response to bacterium	5	5
response to bacterium	response to biotic stimulus	5	5
response to interleukin-1	response to interleukin-1	5	5
positive regulation of inflammatory response	inflammatory response	5	8
positive regulation of	negative regulation of	5	6

inflammatory response	inflammatory response		
innate immune response	immune response	5	8
innate immune response	regulation of immune response	5	6
innate immune response	innate immune response	5	6
innate immune response	defense response	5	5
aging	aging	5	5
response to drug	response to drug	5	5
negative regulation of apoptosis	positive regulation of cell death	5	6
negative regulation of apoptosis	negative regulation of apoptosis	5	6
negative regulation of apoptosis	positive regulation of apoptosis	5	5
negative regulation of apoptosis	anti-apoptosis	5	5
negative regulation of apoptosis	apoptosis	5	5
positive regulation of cell proliferation	cell proliferation	5	7
positive regulation of cell proliferation	negative regulation of cell proliferation	5	5
response to electrical stimulus	response to electrical stimulus	5	5
cytokine-mediated signaling pathway	cytokine-mediated signaling pathway	5	6
cytokine-mediated signaling pathway	response to cytokine stimulus	5	5
acute-phase response	inflammatory response	5	8
endoplasmic reticulum unfolded protein response	endoplasmic reticulum unfolded protein response	5	5
response to hypoxia	response to hypoxia	5	5
acute inflammatory response	inflammatory response	5	8
protein secretion	positive regulation of cytokine secretion	5	6
protein secretion	negative regulation of cytokine secretion	5	5
activation of caspase activity	negative regulation of endopeptidase activity	5	8
activation of caspase activity	activation of caspase activity	5	6
activation of caspase	negative regulation of	5	6

activity	caspase activity		
defense response to Gram-positive bacterium	defense response to Gram-positive bacterium	5	5
defense response to Gram-positive bacterium	defense response to bacterium	5	5
platelet activation	blood coagulation	4	8
platelet activation	response to wounding	4	6
positive regulation of endothelial cell migration	positive regulation of cellular component movement	4	6
blood coagulation	blood coagulation	4	8
blood coagulation	inflammatory response	4	8
blood coagulation	response to wounding	4	6
cellular response to lipopolysaccharide	response to lipopolysaccharide	4	9
neutrophil chemotaxis	leukocyte migration	4	6
cellular response to hydrogen peroxide	hydrogen peroxide catabolic process	4	5
positive regulation of cell death	positive regulation of cell death	4	6
positive regulation of cell death	negative regulation of apoptosis	4	6
positive regulation of cell death	induction of apoptosis	4	5
positive regulation of cell death	positive regulation of apoptosis	4	5
positive regulation of cell death	apoptosis	4	5
negative regulation of endopeptidase activity	negative regulation of endopeptidase activity	4	8
negative regulation of endopeptidase activity	activation of caspase activity	4	6
negative regulation of endopeptidase activity	negative regulation of caspase activity	4	6
positive regulation of protein phosphorylation	positive regulation of peptidyl-serine phosphorylation	4	5
immune response	immune response	4	8
immune response	regulation of immune response	4	6
immune response	innate immune response	4	6
cell-cell signaling	cell-cell signaling	4	7
cell-cell signaling	signal transduction	4	6
cellular response to	cellular response to glucose	4	5

	glucose stimulus	stimulus		
	hydrogen peroxide catabolic process	superoxide anion generation	4	6
	hydrogen peroxide catabolic process	hydrogen peroxide catabolic process	4	5
	inner ear development	inner ear development	4	5
	fatty acid biosynthetic process	leukotriene biosynthetic process	4	5
	positive regulation of membrane protein ectodomain proteolysis	positive regulation of membrane protein ectodomain proteolysis	4	5
	response to copper ion	response to copper ion	4	5
	response to heat	response to cold	4	5
	hemopoiesis	erythrocyte differentiation	4	6
	hemopoiesis	hemopoiesis	4	5
	calcium ion homeostasis	elevation of cytosolic calcium ion concentration	4	6
	positive regulation of caspase activity	negative regulation of endopeptidase activity	4	8
	positive regulation of caspase activity	activation of caspase activity	4	6
	positive regulation of caspase activity	negative regulation of caspase activity	4	6
	response to tumor necrosis factor	response to tumor necrosis factor	4	5
	response to tumor necrosis factor	response to cytokine stimulus	4	5
	NF-kappaB cascade	NF-kappaB cascade	4	5
	positive regulation of tumor necrosis factor production	positive regulation of tumor necrosis factor production	4	5
	positive regulation of interleukin-6 production	negative regulation of interleukin-6 production	4	5
	positive regulation of interleukin-1 beta secretion	positive regulation of cytokine secretion	4	6
	positive regulation of interleukin-1 beta secretion	negative regulation of cytokine secretion	4	5
UC&CRC	blood coagulation	platelet activation	8	3
	cell proliferation	regulation of cell proliferation	7	3
	cell proliferation	cell proliferation	7	3
	cell-cell signaling	signal transduction	7	3

	signal transduction	signal transduction	6	3
	response to wounding	platelet activation	6	3
	cytokine-mediated signaling pathway	cellular response to hormone stimulus	6	3
	elevation of cytosolic calcium ion concentration	cytosolic calcium ion homeostasis	6	3
	elevation of cytosolic calcium ion concentration	cellular calcium ion homeostasis	6	3
	elevation of cytosolic calcium ion concentration	positive regulation of calcium ion transport into cytosol	6	3
	elevation of cytosolic calcium ion concentration	regulation of membrane potential	6	3
	NF-kappaB cascade	intracellular protein kinase cascade	5	3
	prostanoid metabolic process	fatty acid metabolic process	5	3
	negative regulation of cell proliferation	regulation of cell proliferation	5	3
	negative regulation of cell proliferation	cell proliferation	5	3
	xenobiotic metabolic process	xenobiotic metabolic process	5	3
	hydrogen peroxide catabolic process	cellular response to reactive oxygen species	5	3
	anti-apoptosis	positive regulation of anti-apoptosis	5	3
	regulation of insulin secretion	negative regulation of insulin secretion	5	3
	ERK1 and ERK2 cascade	MAPKKK cascade	5	4
CD&CRC	response to peptide hormone stimulus	cellular response to hormone stimulus	6	3
	wound healing	platelet activation	6	3
	response to wounding	platelet activation	6	3
	negative regulation of cell proliferation	regulation of cell proliferation	6	3
	negative regulation of cell proliferation	cell proliferation	6	3
	JAK-STAT cascade	intracellular protein kinase cascade	5	3
	response to hydrogen	cellular response to reactive	5	3

peroxide	oxygen species		
anti-apoptosis	positive regulation of anti-apoptosis	5	3
cellular response to starvation	response to starvation	5	3
positive regulation of cell proliferation	regulation of cell proliferation	5	3
positive regulation of cell proliferation	cell proliferation	5	3
cytokine-mediated signaling pathway	cellular response to hormone stimulus	5	3
platelet activation	platelet activation	4	3
blood coagulation	platelet activation	4	3
positive regulation of endothelial cell proliferation	negative regulation of endothelial cell proliferation	4	3
response to insulin stimulus	cellular response to hormone stimulus	4	3
cellular response to hydrogen peroxide	cellular response to reactive oxygen species	4	3
response to inorganic substance	cellular response to reactive oxygen species	4	3
cell-cell signaling	signal transduction	4	3
hydrogen peroxide catabolic process	cellular response to reactive oxygen species	4	3
fatty acid biosynthetic process	fatty acid metabolic process	4	3
positive regulation of peptidyl-tyrosine phosphorylation	peptidyl-tyrosine phosphorylation	4	3
calcium ion homeostasis	cytosolic calcium ion homeostasis	4	3
calcium ion homeostasis	cellular calcium ion homeostasis	4	3
calcium ion homeostasis	positive regulation of calcium ion transport into cytosol	4	3
calcium ion homeostasis	regulation of membrane potential	4	3
positive regulation of cell division	cell division	4	3
NF-kappaB cascade	intracellular protein kinase cascade	4	3

Note: Term name1 represents the terms enriched in the first disease (for example, CD for CD&UC), and the No.1 is the corresponding number of enriched datasets. Term name2 and No.2 correspond to the other disease (UC for CD&UC). The term pairs have the similarity score larger than 0.8.

Table S2. The list of consensus KEGG pathways among CD, UC and CRC

classes	Functional category	KEGG pathway name	No. total	No. UC	No. CD/CRC
CD&UC	Signaling Molecules and Interaction	Cytokine-cytokine receptor interaction	14	8	6
	Infectious Diseases	Pertussis	15	8	7
	Infectious Diseases	Leishmaniasis	13	7	6
	Infectious Diseases	Malaria	12	6	6
	Immune System Diseases	Rheumatoid arthritis	13	7	6
	Infectious Diseases	Staphylococcus aureus infection	11	6	5
	Infectious Diseases	Tuberculosis	10	5	5
	Infectious Diseases	Toxoplasmosis	10	5	5
	Infectious Diseases	African trypanosomiasis	11	6	5
	Infectious Diseases	Chagas disease	10	6	4
	Immune System	NOD-like receptor signaling pathway	12	7	5
	Immune System	Complement and coagulation cascades	10	5	5
	Immune System	Chemokine signaling pathway	13	8	5
	Immune System	Antigen processing and presentation	9	5	4
	Development	Osteoclast differentiation	11	7	4
	Immune System	Toll-like receptor signaling pathway	11	7	4
UC&CRC	Xenobiotics Biodegradation and Metabolism	Drug metabolism - cytochrome P450	10	6	4
	Xenobiotics Biodegradation and Metabolism	Metabolism of xenobiotics by cytochrome P450	8	5	3
	Metabolism of Cofactors and Vitamins	Retinol metabolism	9	5	4
	Excretory System	Proximal tubule bicarbonate reclamation	8	5	3
	Immune System	Intestinal immune network for IgA production	8	5	3

Note: CD&UC represents CD and UC, likewise UC&CRC represents UC and CRC. The last three columns display the number of significantly enriched datasets, "No" represents the number. In the last column, No.CD is used for the first class, whereas No.CRC is used for the second.

Table S3. The PubMed citation information of risk miRNAs and corresponding diseases.

Class	miRNA	Relation	First authors	Refs
CRC	miR-124	colorectal cancer	Zhang Y; Zhang J; Sun Y; Liu K	1-4
	miR-146a	colorectal cancer	Mao Y; Du W; Hwang WL; Wan D	5-8
	miR-26b	colorectal cancer	Ma YL; Zhang C	9, 10
	miR-335	colorectal cancer	Vickers MM; Wang YX	11, 12
	miR-125b	colorectal cancer	Nishida N; Ak S; Gong J; Lin M	13-16
	let-7g	colorectal cancer	Wang J; Xi Y; Salendo J	17-19
	miR-122	colorectal cancer	Iino I; Kunte DP; Kanaan Z	20-22
	miR-124a	colorectal cancer	Deng G; Nakano H	23, 24
	miR-15a	colorectal cancer	Shi L; Dai L; Wang X	25-27
	miR-16	colorectal cancer	Qian J; Shi L; Ma Q; Young LE	25, 28-30
	miR-192	colorectal cancer	Chiang Y; Boni V; Yu XF; Balaguer F	31-34
	miR-212	colorectal cancer	Meng X	35
	miR-34b*	colorectal cancer	Oh J;; Wu XD; Gao LB Kalimutho M	36-39
	miR-34c	colorectal cancer	Toyota M; Gao LB; Wu XD; Kalimutho M	37-40
	miR-424	colorectal cancer	Wang S; Guo ST; Wang X; Wang YX	12, 27, 41, 42
	miR-449a	colorectal cancer	Chen S; Rudolf E	43, 44
	miR-449b	colorectal cancer	Fang Y	45
	miR-503	colorectal cancer	Kunte DP	21
	miR-217	gastrointestinal cancer	Stuckenholz C	46
	miR-193b	gastrointestinal cancer	Du Y	47
miR-425	gastrointestinal cancer	Hummel R	48	
miR-302a	predicted			
CD	miR-146a	Crohn's disease	Lin J; Gazouli M	49, 50
	miR-126	Crohn's disease	Paraskevi A	51
	miR-29a	Crohn's disease	Paraskevi A	51
	miR-206	Crohn's disease	Lin J	49
	miR-29b	Crohn's disease	Nijhuis A	52
	miR-29c	Crohn's disease	Nijhuis A	52
	miR-221	Crohn's disease	Fujioka S	53
	miR-21	Crohn's disease	Ludwig K; Sohn JJ	54, 55
	miR-338	inflammatory bowel disease	Dalal SR	56
	miR-155	inflammation	Wu R	57

	miR-520c	inflammation	Keklikoglou I	58
	miR-939	inflammation	Semaan N	59
	miR-335	inflammation	Zhu L	60
	miR-1	inflammation	Georgantas RW	61
	miR-204	inflammation	Li G	62
	miR-222	inflammation	Dentelli P	63
	miR-20a	inflammation	Zhu D	64
	miR-365	inflammation	Ha TY.	65
	miR-217	inflammation	Dinh H	66
	mir-221/222	inflammation	Zhu N	67
	miR-451	inflammation	Podolska A	68
	miR-19a	ulcerative colitis	Chen B	69
	miR-124	ulcerative colitis	Koukos G	70
	miR-26b	ulcerative colitis	Coskun M	71
	miR-98	ulcerative colitis	Coskun M	71
	miR-105	ulcerative colitis	Coskun M	71
	miR-20b	ulcerative colitis	Coskun M	71
	miR-512-5p	predicted		
	miR-570c	predicted		
UC	miR-124	ulcerative colitis	Koukos G	70
	miR-146a	ulcerative colitis	Lin J	49
	miR-26b	ulcerative colitis	Coskun M	71
	miR-126	ulcerative colitis	Feng X	72
	miR-155	ulcerative colitis	Min M;Takagi T; Paraskevi A	51, 73, 74
	miR-98	ulcerative colitis	Coskun M	71
	miR-1	inflammation	Georgantas RW	61
	miR-204	inflammation	Li G	62
	miR-125b	inflammation	Wang Z	75
	mir-221/222	inflammation	Zhu N	67
	miR-451	inflammation	Podolska A	68
	miR-335	inflammation	Zhu L	60
	miR-29a	Crohn's disease	Paraskevi A	51
	miR-222	colorectal cancer	Xu K	76
	miR-346	predicted		

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