

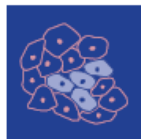
**Biomarcatori e Tecniche di
Diagnostica per Immagini
nella Valutazione
dell'Infiammazione in
Oncologia**

2° Edizione

Correlazione tra i parametri di imaging diagnostico ed i dati molecolari: un nuovo approccio integrato per migliorare la gestione dei pazienti oncologici

Aviano, 20 Febbraio 2020

Mariarosaria Incoronato, PhD








cancers

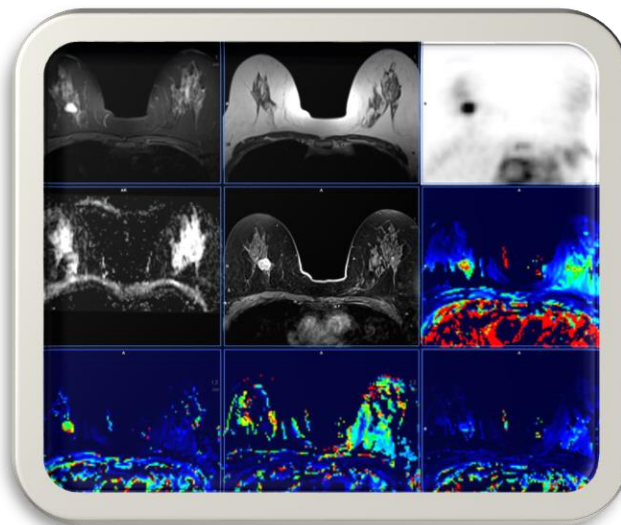


Article

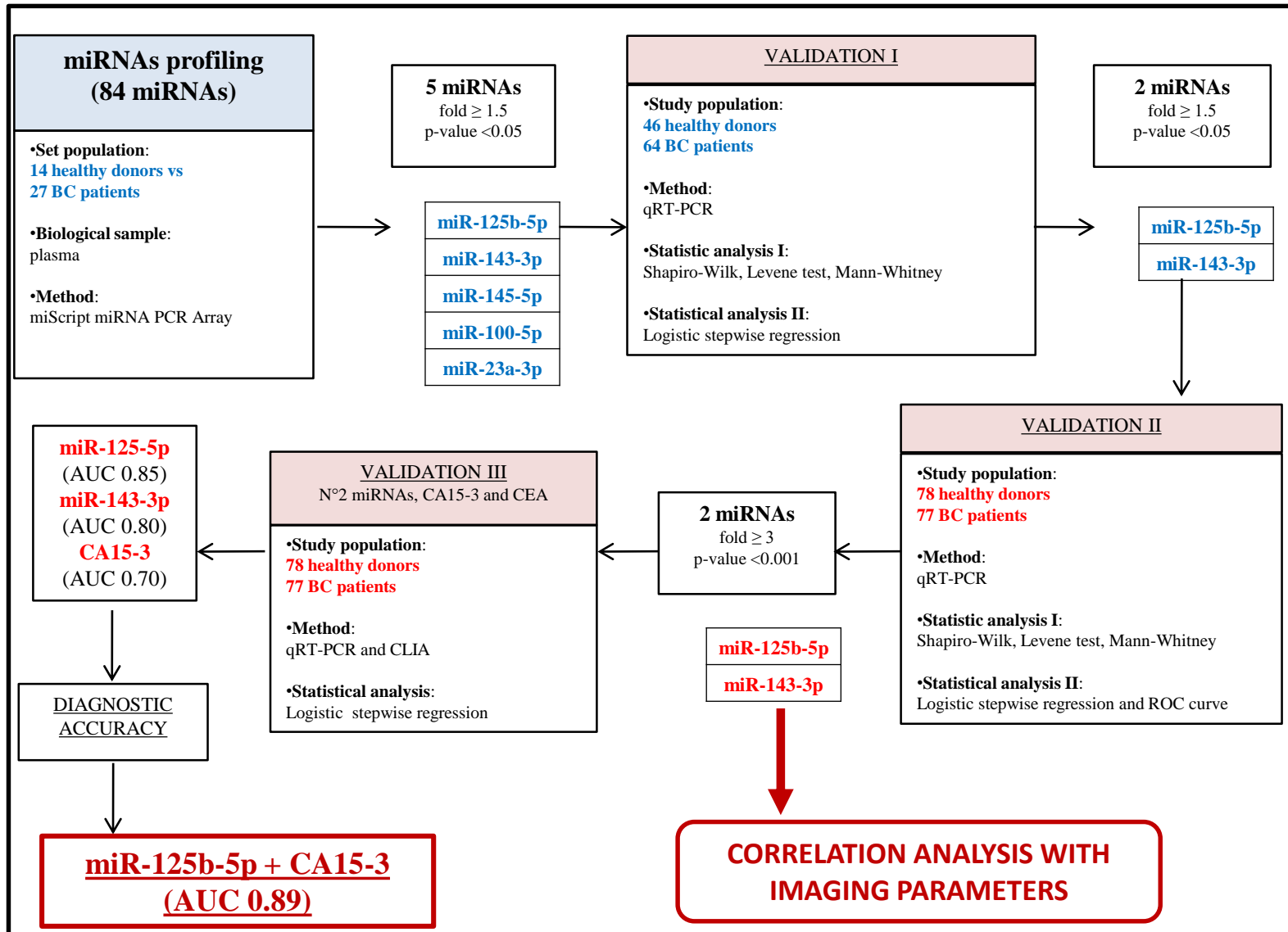
Circulating miRNAs in Untreated Breast Cancer: An Exploratory Multimodality Morpho-Functional Study

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 Daniela Russo ², Andrea Soricelli ^{1,3}, Onofrio Antonio Catalano ^{4,*} and Marco Salvatore ¹ 

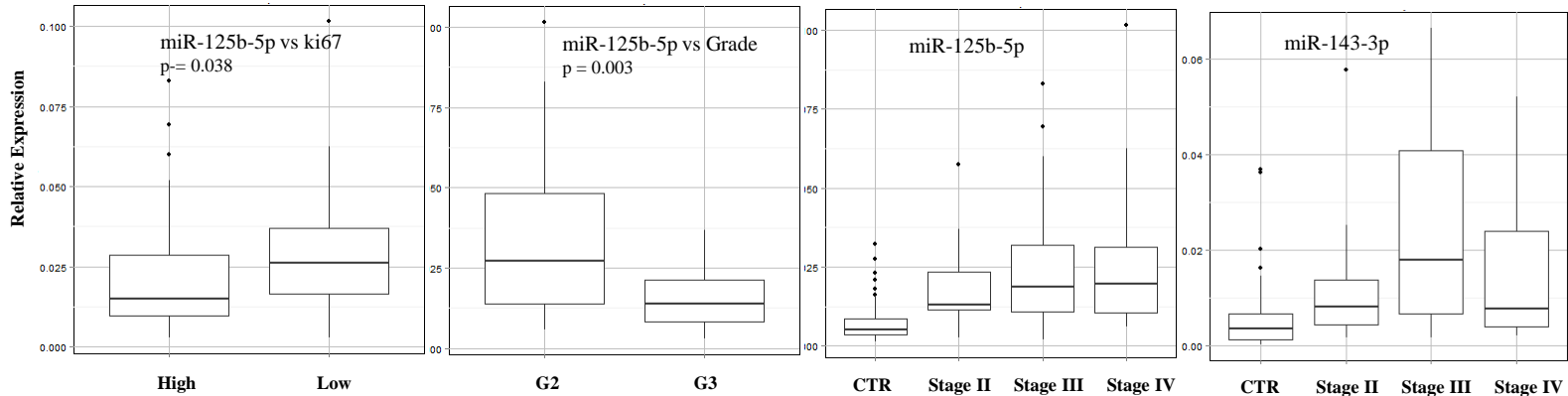
Purpose: The aim of this study was to identify new disease-related circulating miRNA with high diagnostic accuracy for breast cancer (BC), and to correlate their deregulation with morpho-functional characteristics of tumor, as assessed in vivo by positron emission tomography/magnetic resonance (PET/MR) imaging.



Study design



Correlation analysis of circulating miRNAs with quantitative imaging parameters of tumor lesions



- **iAUC**: initial area under the concentration curve
- **Ktrans**: forward volume transfer constant
- **Ve**: extravascular extracellular space volume
- **Kep**: reverse efflux volume transfer constant
- **SUV**: metabolic standardized uptake value
- **ADC**: apparent diffusion coefficient
- **Lesion size**

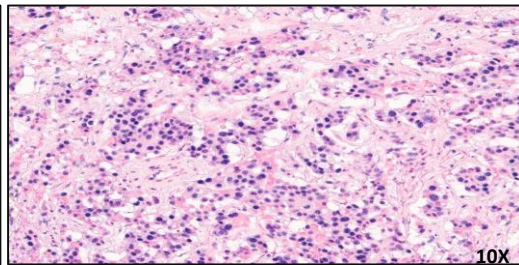
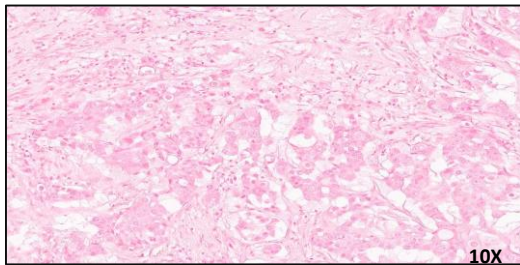
	Stage II				Stage III		Stage IV	
	iAUC _{mean}	ki67	Kep _{mean}	SUV _{max}	iAUC _{mean}	ki67	ki67	Ktrans _{mean}
miR-125-5p	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	-0.513 p-value 0.029	-0.421 p-value 0.040
miR-143-3p	0.943 p-value 0.005	<i>ns</i>	0.943 p-value 0.005	0.829 p-value 0.042	0.938 p-value 0.044	<i>ns</i>	<i>ns</i>	<i>ns</i>

- **miR-143-3p** overexpression in plasma samples of BC patients could be linked to tumor angiogenesis
- Highest concentration of **miR-125b-5p** could be correlated to a better prognosis

In Situ Hybridization experiments

Scramble

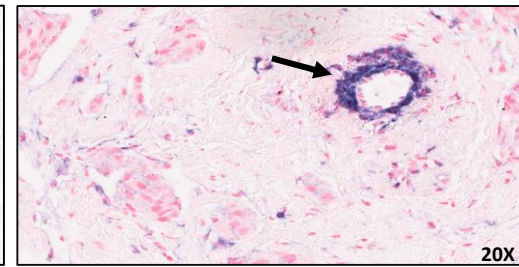
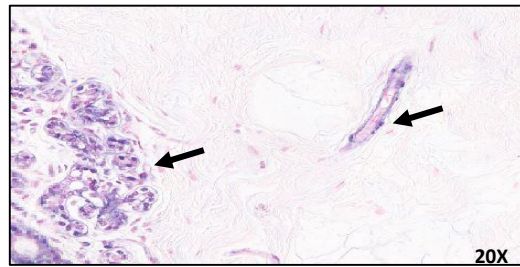
U6



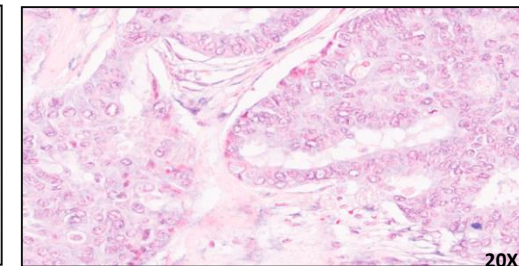
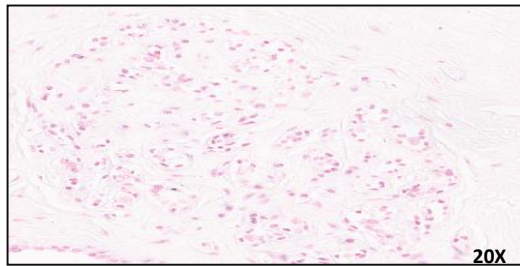
Normal

Cancer

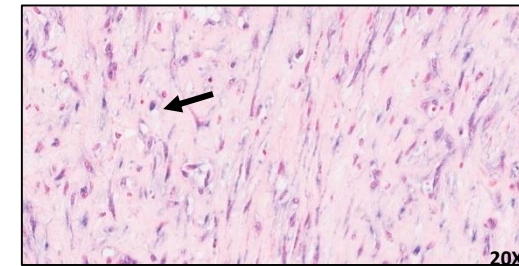
miR-143-3p



miR-125b-5p



miR-125b-5p



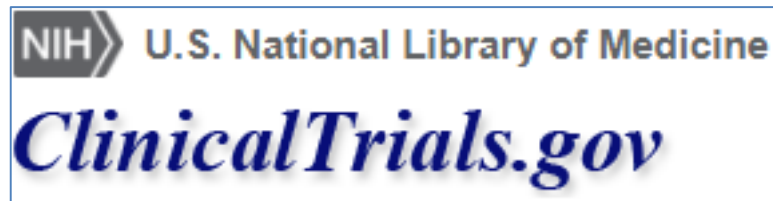
CONCLUSIONS

This is the first study that correlates circulating miRNAs with in vivo quantified tumor biology through PET/MR biomarkers. **This integration helped to understand the link between the plasmatic increase of these two potential circulating biomarkers and the biology of untreated breast cancer.**

In the last two decades, many circulating miRNAs have emerged as promising BC diagnostic biomarkers

Circulating miRNAs have not been applied in clinical practice

How many clinical trials are in place?



1. Approximately **39 clinical** trials involved miRNAs and of these, 24 were interventional and 15 were observational studies. Most of them aimed to evaluate the effect of miRNAs in predicting response to therapeutic treatments;
2. Restricting search only at circulating miRNAs we found only **7 studies**, summarized in Table.

Identifier	Status	Study type	Study start date	Title	Interventions
NCT01612871	Completed	Interventional	2012	Circulating miRNAs as Biomarkers of Hormone Sensitivity in Breast Cancer	Drugs: - Tomoxifen - Letrozole - Anastrozole - Exemestane
NCT01722851	Recruiting	Observational	2011	Circulating miRNAs. ICORG 10-11, V2	- none
NCT03779022	Recruiting	Observational	2015	miRNA and Relevant Biomarkers of BC Patients Undergoing Neoadjuvant Treatment	Genetic: - microRNA
NCT02618538	Enrolling by invitation	Observational	2015	The Andromeda Study. Predictive Value of Combined Criteria to Tailor Breast Cancer Screening.	- none
NCT03255486	Completed	Interventional	2013	Identification and Evaluation of Biomarkers of Resistance to Neoadjuvant Chemotherapy (IDEA SEIN)	Biological: - blood sample
NCT03528473	Recruiting	Interventional	2019	Adapted Physical Activity (APA) in a Breast Cancer Population.	Behavioural: - Exercise
NCT03118882	Completed	Interventional	2010	STI.VI. Study: How to Improve Lifestyles in Screening Contexts	Behavioural: - Diet - Physiological activity

Two pivotal and essential requirements for the clinical validity of identified miRNAs for BC diagnosis:

- i) **specificity,**
- ii) **concordance between blood and tissue**

To investigate the claim that circulating miRNAs are truly specific for BC

Any circulating miRNAs displaying altered levels in the blood of oncology patients should also be altered in the tumor tissue and show the same trend (upregulated or downregulated)

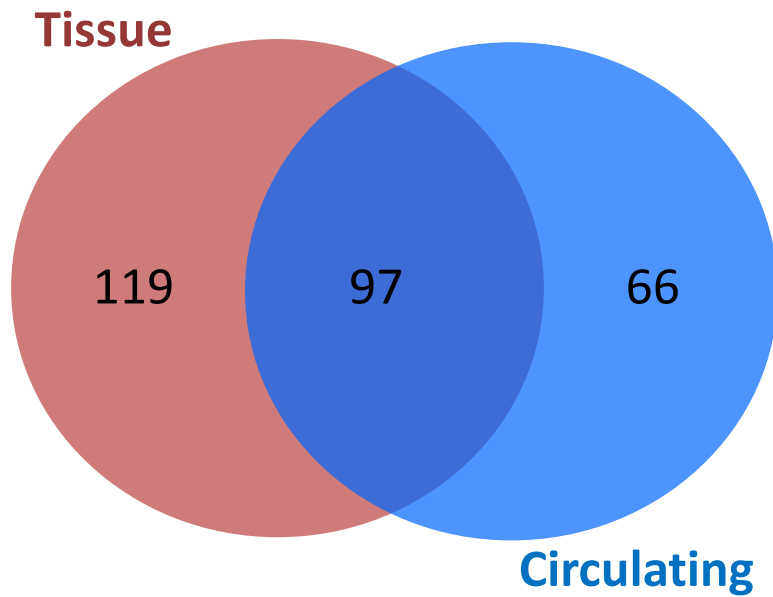
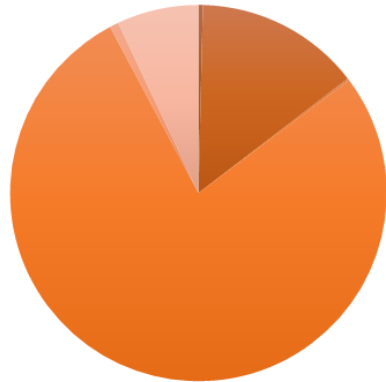


HMDD v3.2: the **H**uman **m**icroRNA **D**isease **D**atabase version 3.2

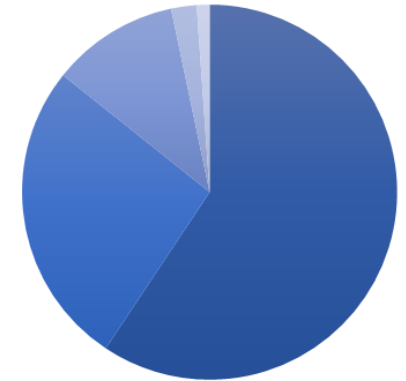
Home Browse Search miR-Target Network Causality Download Submit Help



- Breast Adenocarcinoma
- Breast Carcinoma
- Breast Ductal Carcinoma
- Breast Neoplasma
- Early stage Breast Carcinoma
- Hereditary Breast Carcinoma
- Triple Negative Breast Carcinoma



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Tissue miRNA	Frequency
miR-21	36
miR-155	21
miR-10b	15
miR-200c	11
miR-200b, miR-145	10

Circulating miRNA	Frequency
miR-21	24
miR-155	8
miR-222	6
miR-10b, miR-107, miR-195, miR-373	5

281 different BC-associated miRNAs

216 were reported to be deregulated in BC **tissues** in 182

163 were reported as deregulated **circulating** miRNAs in 91 publications

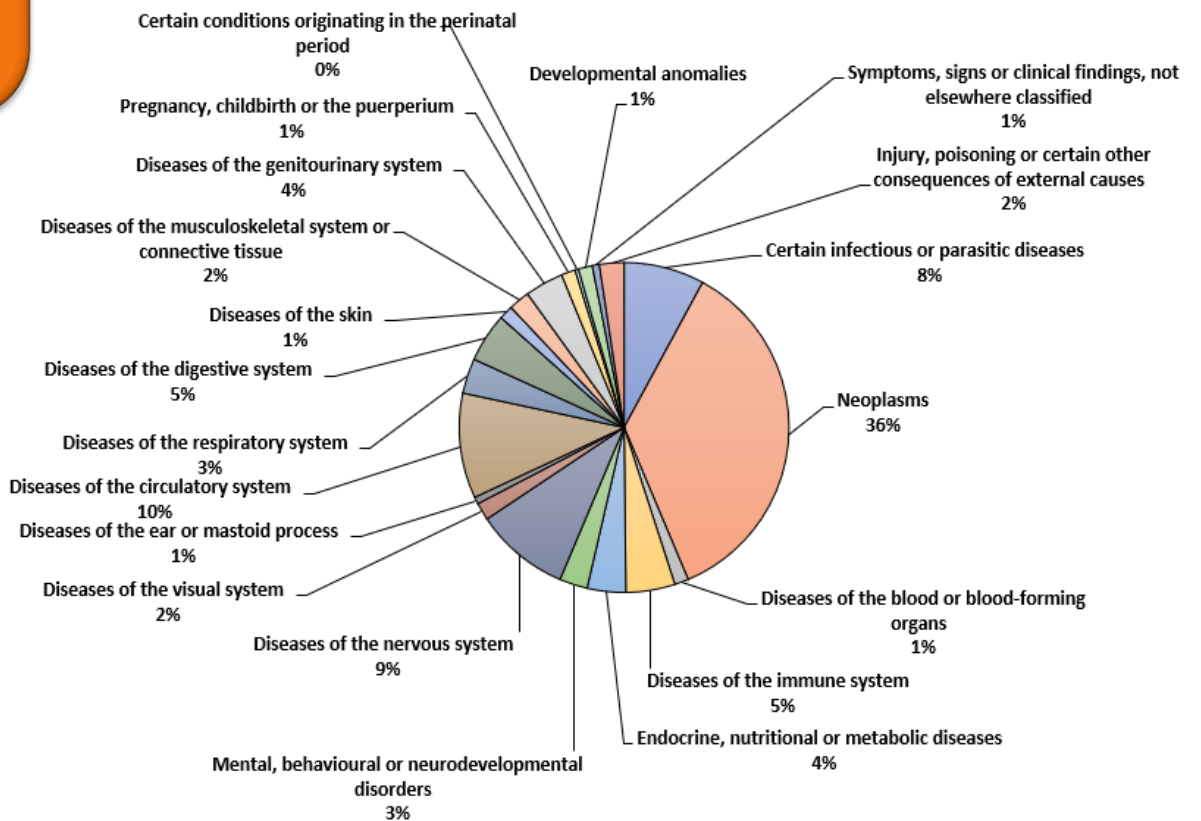
97 miRNAs were **shared** between these two categories

To assess the specificity of the **163 BC-associated circulating miRNA.....**

HMDD v3.0:

88% were deregulated in 291 different additional human diseases

Circulating miRNA	Shared
miR-21	108/291 (54% neoplastic)
miR-155	75/291 (43% neoplastic)
miR-223	58/291 (48% neoplastic)
miR-16	42/291 (50% neoplastic)

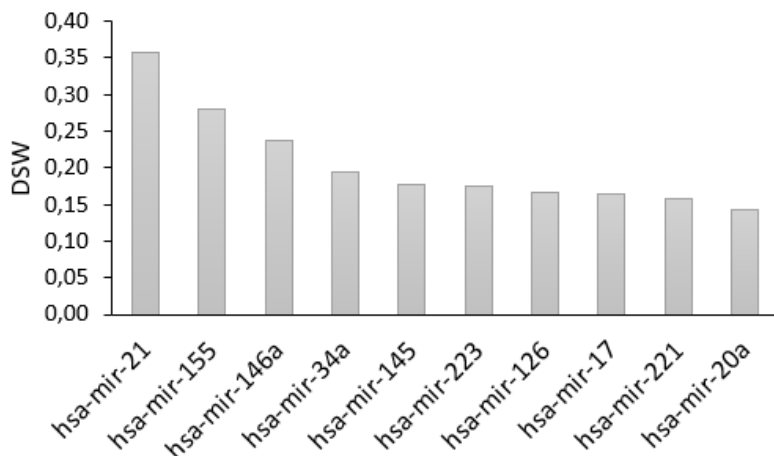


HMDD v3.0:

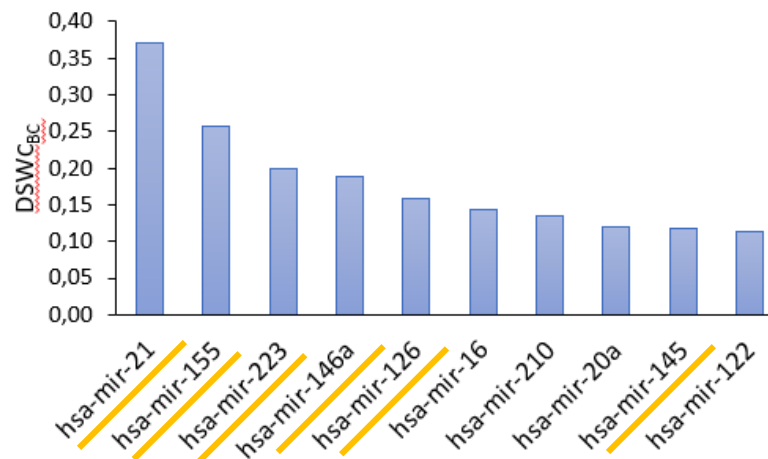
“DISEASE SPECTRUM WIDTH” (DSW)

The ratio between the number of diseases associated with miRNA and the total number of diseases.

A higher score indicates a greater number of pathologies in which the miRNA was identified



The engagement of a miRNA in human diseases



The engagement of the **163 BC-associated circulating miRNA** in human diseases

Among all 163 BC-associated circulating miRNAs, the only circulating miRNAs that were specifically associated with the early detection of BC were:

DOWNREGULATED

miR-526
miR-1469
miR-1471
miR-2355
miR-3130-1
miR-3130-2
miR-3186

UPREGULATED

miR-922
miR-1323
miR-4257
miR-801
miR-6861

... each of these molecules was reported in only one paper, making their validation for diagnostic purposes improper and premature.

The most obvious hypothesis proposed by researchers aiming to assign a function of tumor markers to circulating miRNAs is that these molecules are generated from and secreted by the tumor cells into the bloodstream

How many BC-associated miRNAs were screened in both the bloodstream and tissue in the same paper?

Only 8,6% of the studies (n°19) validated the expression levels of the selected miRNAs in both the tumor tissues and blood samples of patients with BC



- n°6 = plasma
- n° 11 = serum
- n° 1 = whole blood
- n° 1 = both plasma and serum



miR-21
miR-155

List of miRNAs analysed in the bloodstream and in tissue in separate studies

A. Concordant						
miRNA	Total Studies (n°)	Circulating Expression		Tissue Expression		
		Up	Down	Up	Down	
mir-155	16	4	-	12	-	
mir-373	6	3	-	3	-	
mir-20a-b	6	4	-	2	-	
mir-181b	5	1	-	4	-	

B. Partially Concordant						
miRNA	Total Studies (n°)	Circulating Expression		Tissue Expression		
		Up	Down	Up	Down	
mir-21	38	10	1	25	2	
mir-10b	12	2	1	5	4	
mir-200c	10	1	1	3	5	
mir-145	11	-	3	1	7	
mir-222	8	3	2	3	-	
mir-200b	6	1	-	2	3	
mir-195	5	1	2	-	2	
mir-210	6	1	1	3	1	
mir-182	8	2	2	2	2	
mir-19a	5	1	1	1	2	

miR-21 and miR-155

CONCLUSIONS

A circulating miRNA signature for BC diagnosis is currently unavailable because the most frequently studied circulating miRNA, BC-associated miRNAs (**miR-155, miR-21, miR-195, and miR-145**), are the most non-specific BC-associated miRNAs



“
INSANITY: DOING THE SAME
THING OVER AND OVER
AGAIN AND EXPECTING
DIFFERENT RESULTS

ALBERT EINSTEIN

”

