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Genomic analysis of luminal B breast cancer

Jovanny Zabaleta, M.S., Ph.D.
Associate Professor
Department of Interdisciplinary Oncology
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LSUHSC, LCRC
New Orleans, LA 70112

LSU Health NEW ORLEANS

LSUHSC • MOFFITT SPIRIT-CHD
Southeast Partnership for Improving Research & Training in Cancer Health Disparities

INSTITUTO NACIONAL DE CANCEROLOGIA E.S.E. COLOMBIA

Silvia J. Serrano, PhD

Research Associate
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Bogotá, Colombia

Laura Fejerman, PhD

Professor
UC-Davis

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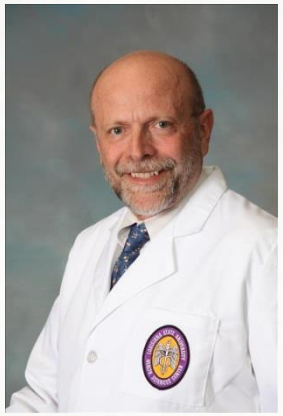
Li Li, M.D.

Jone Garai, Ph.D

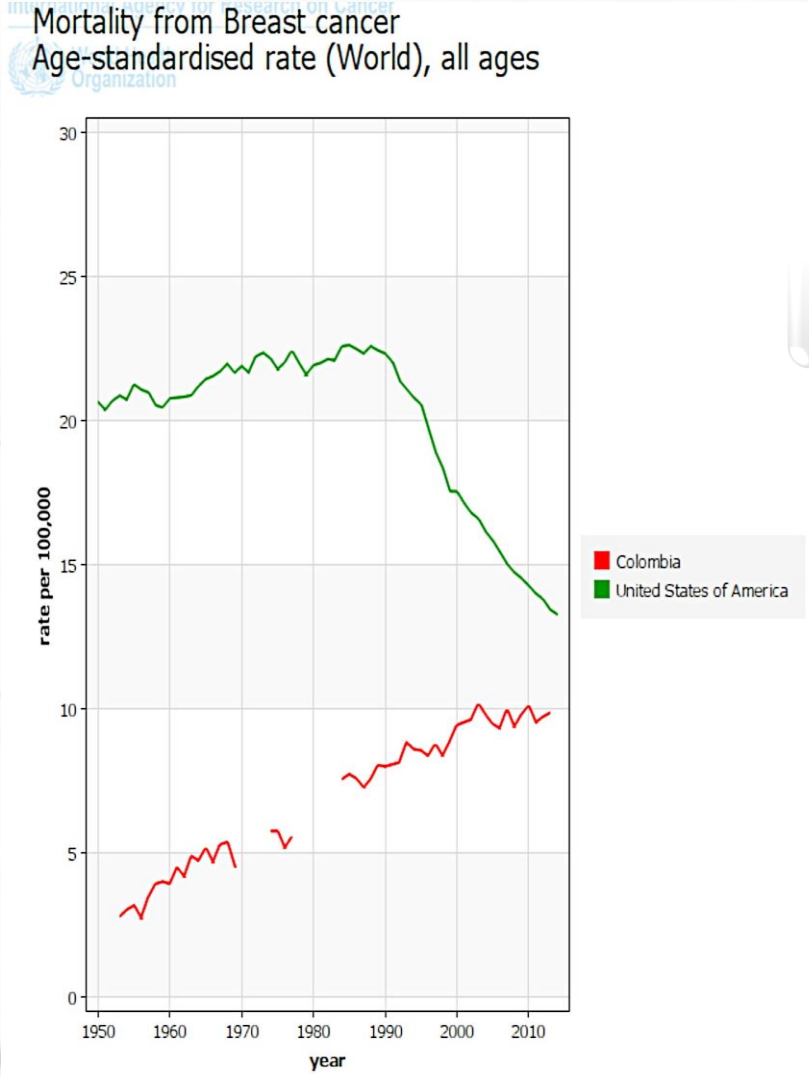


Lucio Miele, M.D, Ph.D

Professor and Department Head,
LSU School of Medicine,
Department of Genetics

P20CA202922- The Southeast Partnership for Improving Research and Training in Cancer Health Disparities (SPRIT-CHD)
1 P20 GM121288-01- Center for translational viral oncology (CTVO)
1P30GM114732-01 - Mentoring Translational Researchers in Louisiana
NCI CA 160607 - L.F

BrCa in Colombia

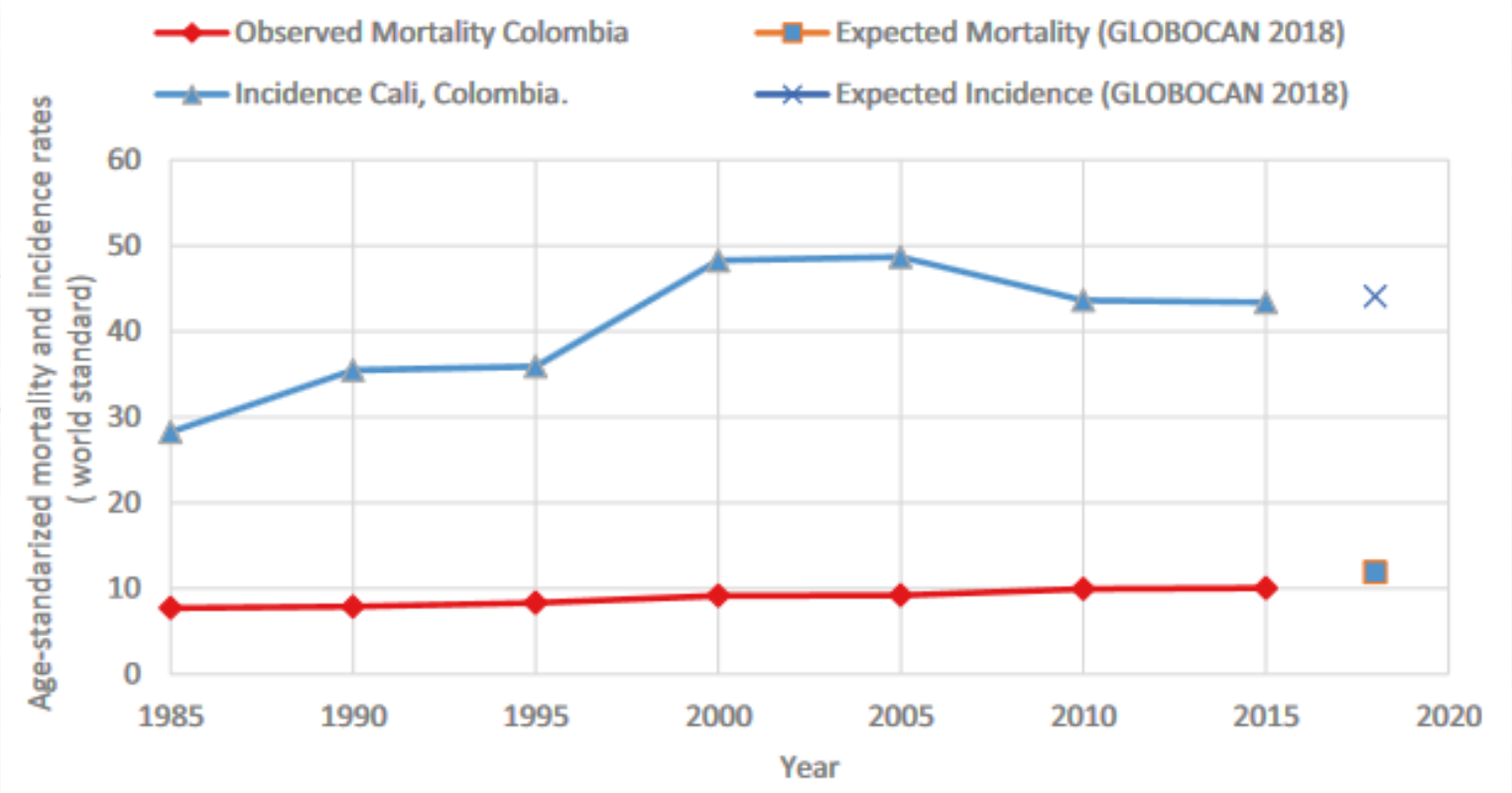


8686 new cases

2649 deaths

Increase in mortality rate over time

Some geographic regions in Colombia had higher incidence/mortality



Duarte, C et. al. Breast Ca. Res. and Treat. (2021) 186:15–24

Difference in the genetic makeup of the Colombian regions

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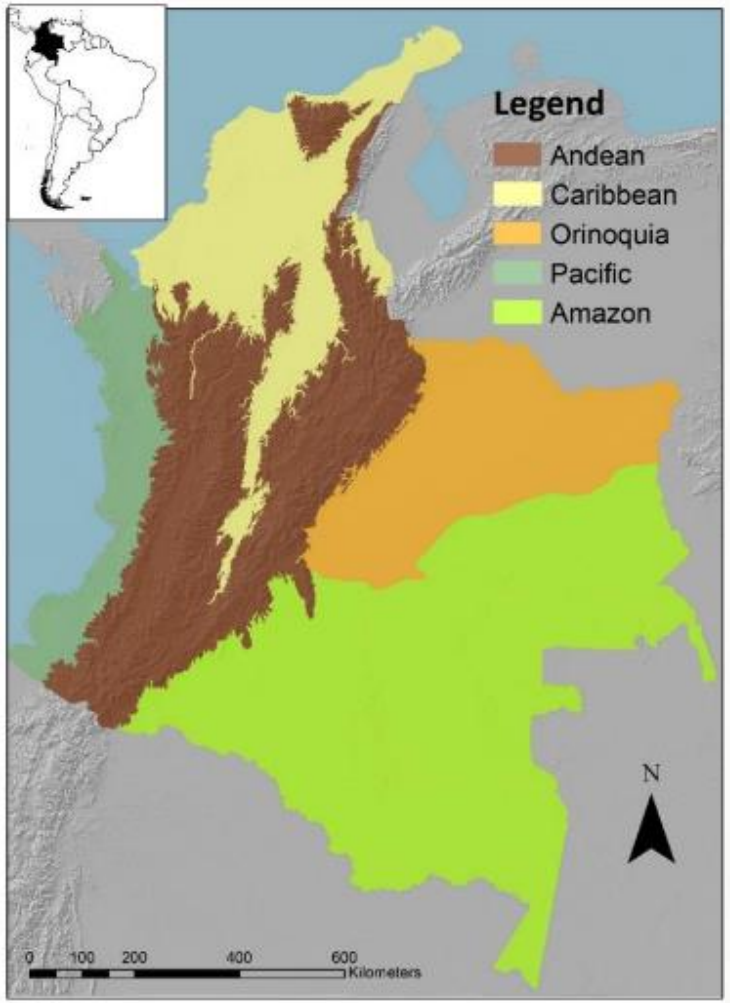


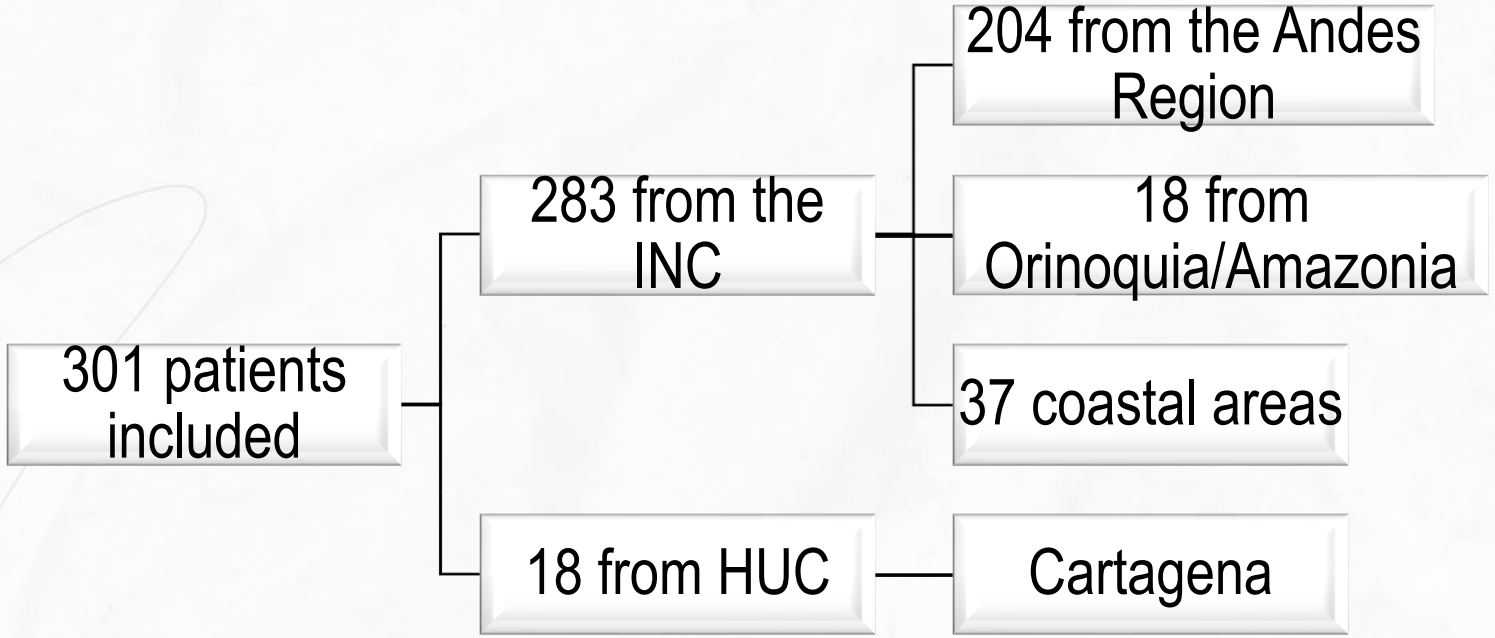
Etter et al_Colombia LRE_ Final Report 2017

Population	Estimated autosomic admixture		
	Native	European	African
Bolivar	32.9 ± 4.1	23.3 ± 3.5	43.8 ± 2.7
Magdalena	21.8 ± 12.1	50.0 ± 10.9	28.2 ± 7.6
Antioquia	26.0 ± 9.0	63.5 ± 4.8	10.6 ± 4.8
Peque	62.2 ± 5.5	32.1 ± 5.3	5.8 ± 2.6
Caldas	36.4 ± 7.7	59.3 ± 7.4	4.3 ± 32.6
Quindio	38.3 ± 7.9	57.3 ± 7.6	4.4 ± 3.3
Norte Santander	53.3 ± 6.5	42.0 ± 6.3	4.7 ± 2.9
Santander	42.4 ± 7.9	56.2 ± 7.8	1.4 ± 2.4
Cundinamarca	51.6 ± 12.1	45.4 ± 11.8	3.0 ± 4.7
Casanare	74.7 ± 6.6	24.5 ± 6.6	0.8 ± 2.0
Nariño	65.2 ± 5.2	32.1 ± 5.1	2.7 ± 2.0
Cauca	56.9 ± 7.8	19.6 ± 6.9	23.5 ± 5.0
Huila	60.8 ± 8.5	39.6 ± 8.4	0.0 ± 1.0
Valle del Cauca	39.3 ± 5.9	39.2 ± 5.4	21.5 ± 3.6
Choco	44.8 ± 9.2	46.6 ± 8.6	8.6 ± 4.6
Afro Choco	10.8 ± 10.8	21.1 ± 9.4	68.1 ± 7.1

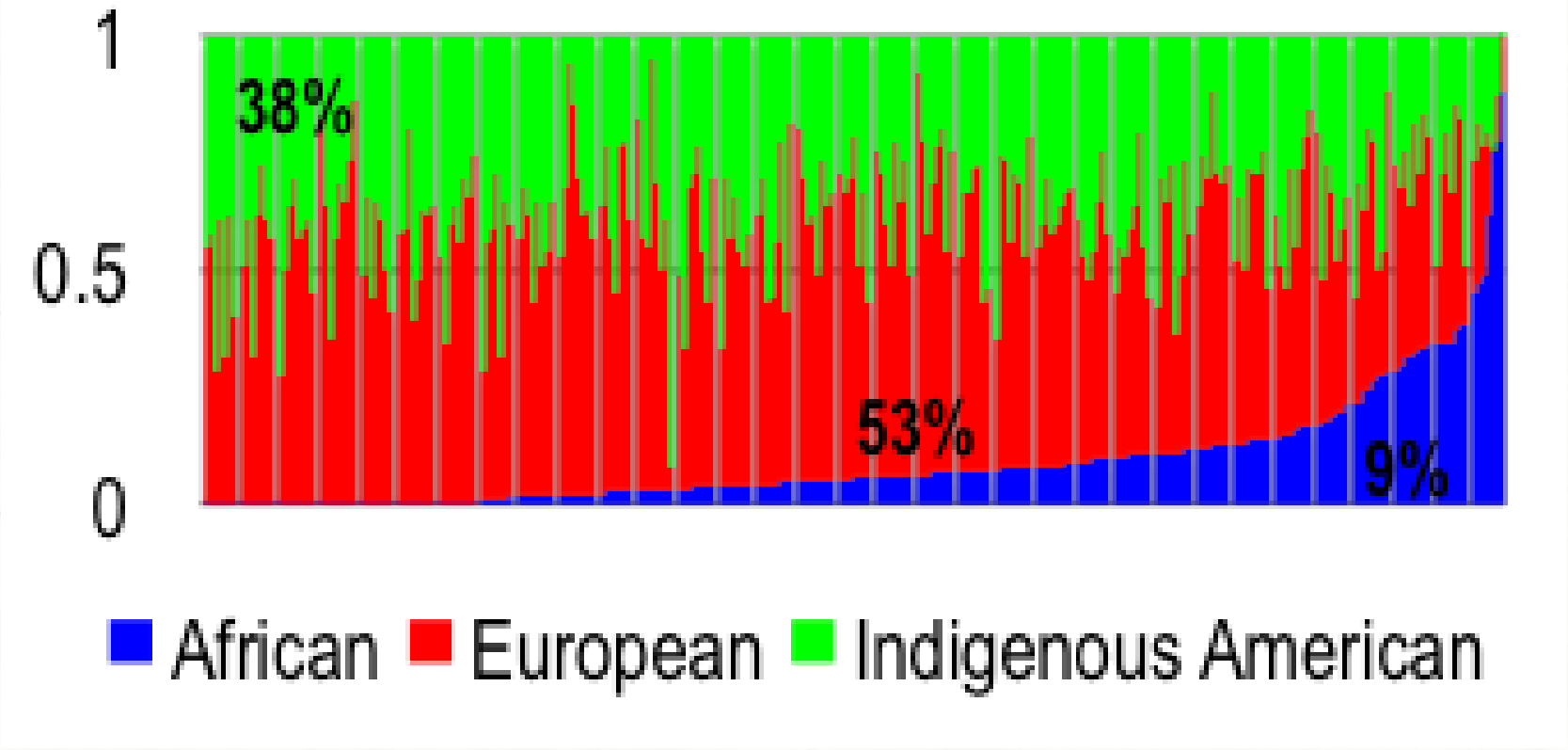
Rojas W, et. al. Am J. Phys. Anthr, 143:13-20, 2010

Are the ancestral fractions (European, African and Indigenous American) correlated with the distribution of the BrCa intrinsic subtypes in a representative sample of Colombian women with the disease?

Origins of the patients involved in the study



Genetic ancestry proportions estimated by 80 AIMS



Carcinogenesis, 2016, 1–8

Difference in the ancestral fraction among the geographic regions in Colombia

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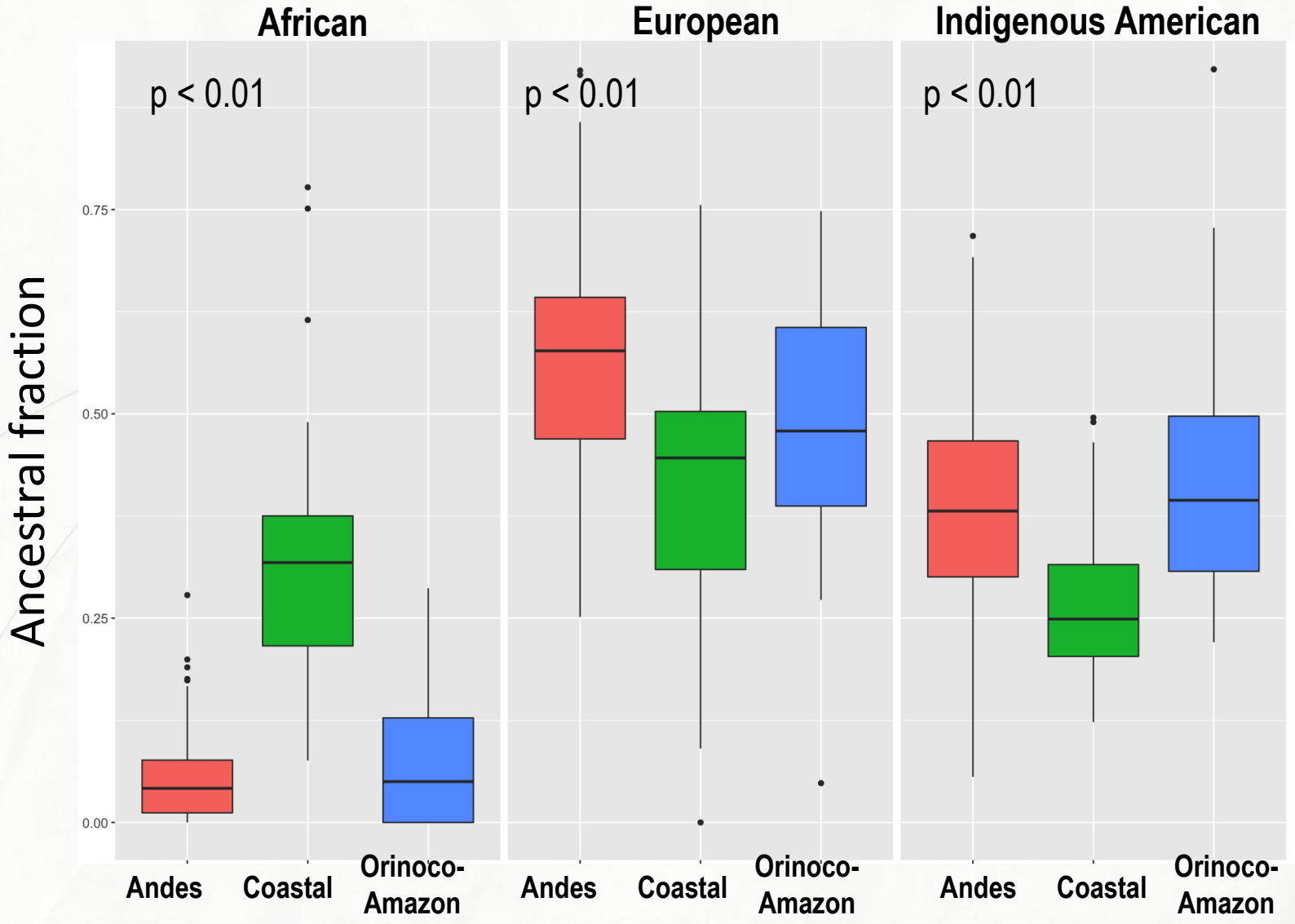
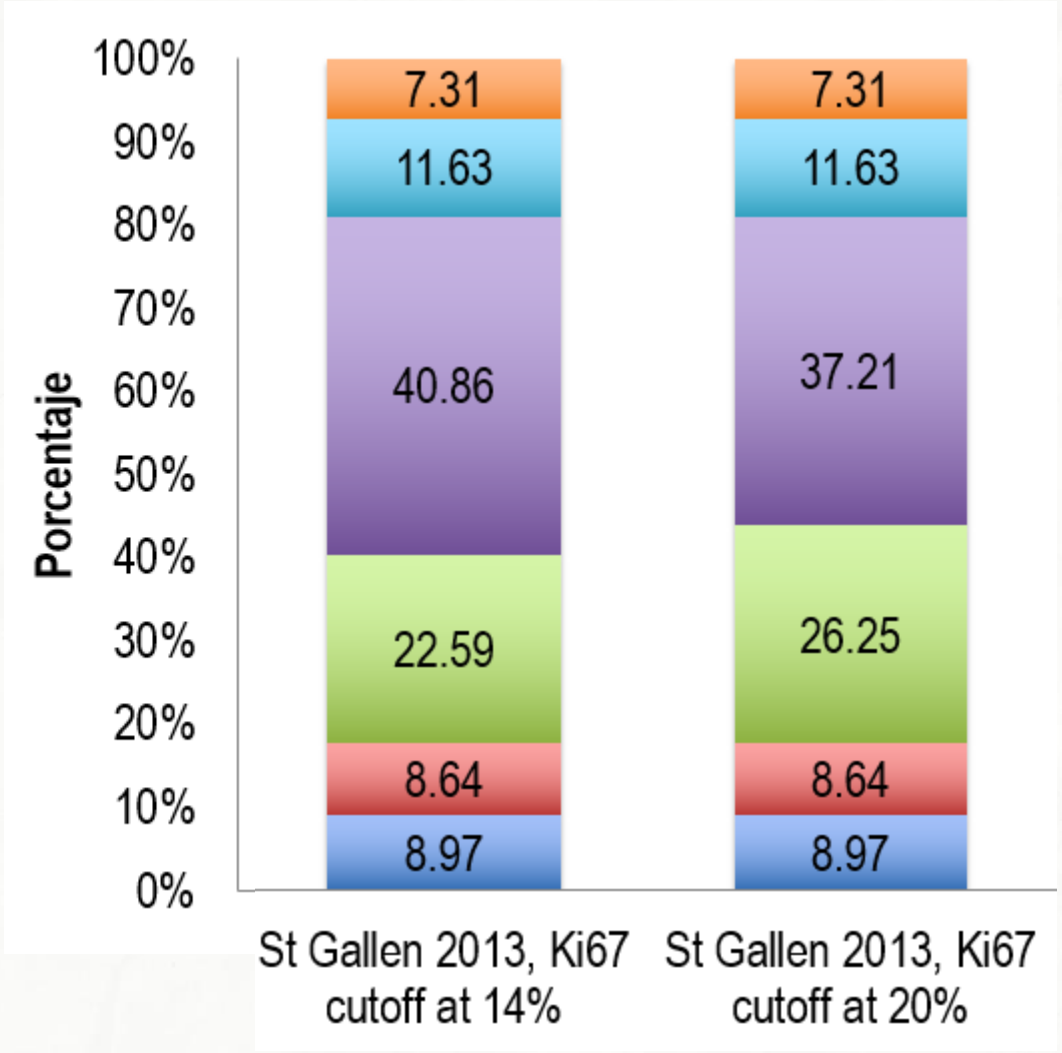


Carcinogenesis, 2016, 1–8

Distribution of BrCa intrinsic subtypes



Carcinogenesis, 2016, 1–8

Distribution of BrCa intrinsic subtypes by geographical region in Colombia

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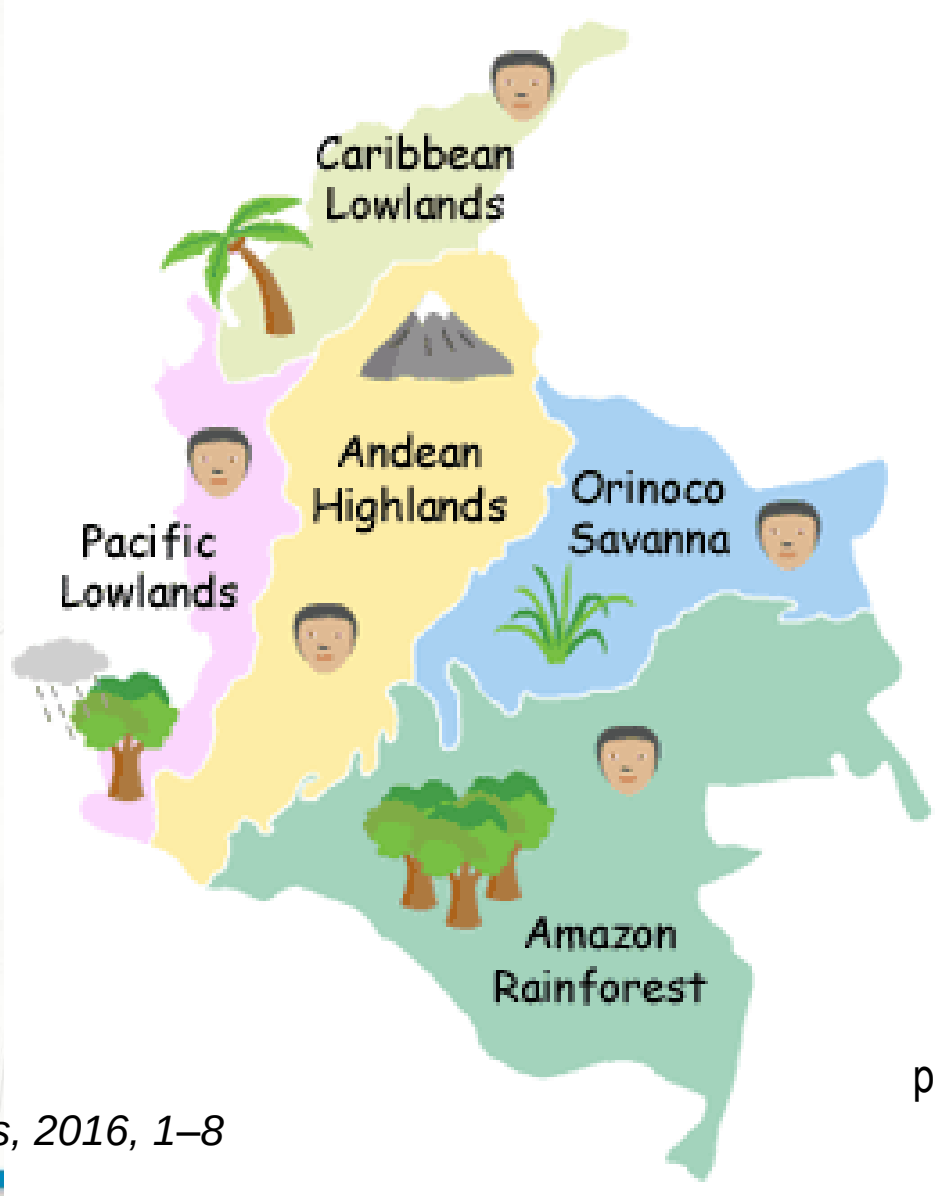

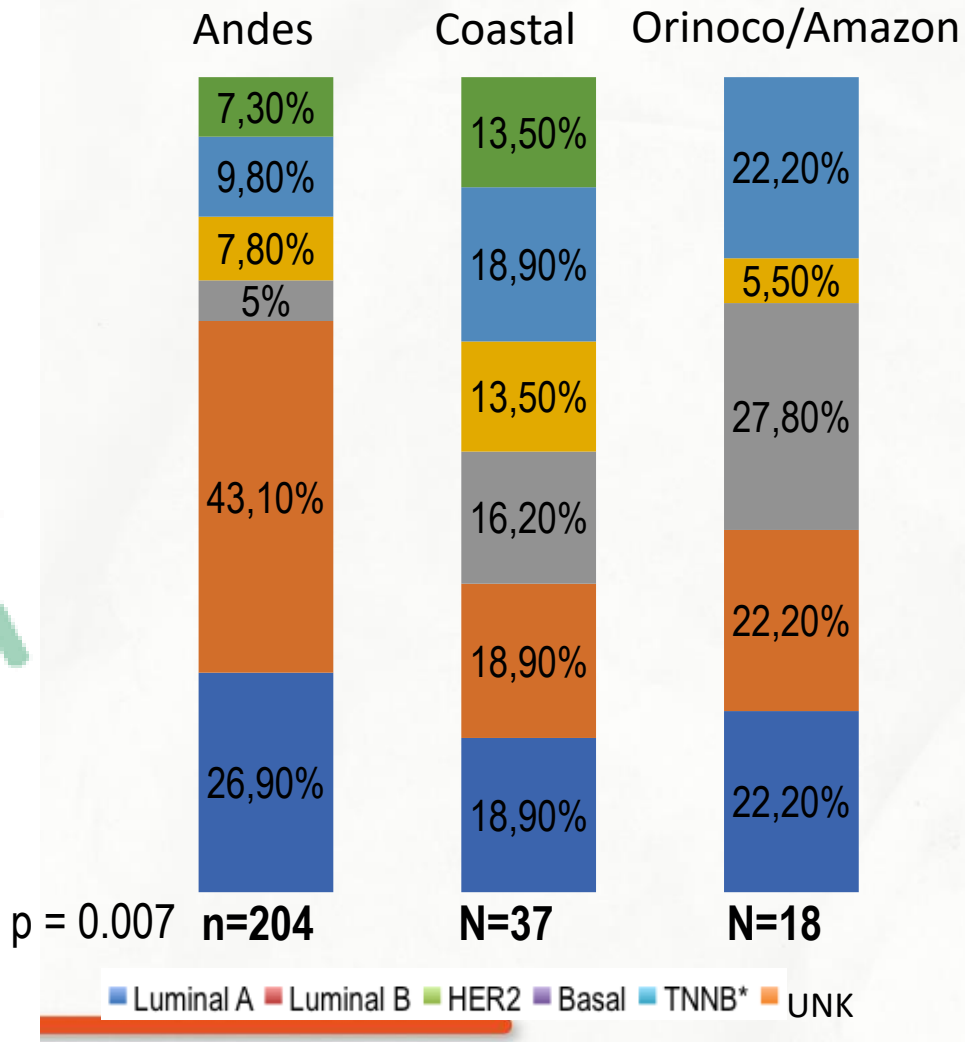

Carcinogenesis, 2016, 1–8

AGE AT DIAGNOSIS (p=0.0139)

- ✓ Mean age at diagnosis: 56.6 years
  - ✓ Younger ages observed for ER (-) tumors

LumA	LumB	HER2	Basal	NBTN
58.7	57.9	57.2	51.6	51.5

TUMOR GRADE (p < 0.001)

- ✓ Higher percentage of tumors at grade III observed in ER (-) subtypes
  - ✓ Higher percentage of grade 3 tumors in luminal B

Grade	LumA	LumB	HER2	Basal	TNBC
1	8.9%	8.0%	0	0	0
2	73.4%	58.9%	19.2%	22.2%	22.9%
3	6.3%	25%	50%	59.3%	62.9%
NA	6.3%	2.7%	0	3.7%	2.9%
Unknown	5.1%	5.4%	30.8%	14.8%	11.4%

RECURRENCE (p < 0.001)

- ✓ Systemic recurrences more likely to be observed in ER (-) tumors

Recurrence	LumA	LumB	HER2	Basal	TNBC
Systemic	7.6%	8.9%	19.2%	14.8%	5.7%

Carcinogenesis, 2016, 1–8

OXFORD

Carcinogenesis, 2016, 1–8

doi:10.1093/carcin/bgw043
Advance Access publication April 16, 2016
Original Manuscript

ORIGINAL MANUSCRIPT

High prevalence of luminal B breast cancer intrinsic subtype in Colombian women

Silvia Juliana Serrano-Gomez[1,2], Maria Carolina Sanabria-Salas[1], Gustavo Hernández-Suarez[1], Oscar García[1], Camilo Silva[1], Alejandro Romero[1], Juan Carlos Mejía[1], Lucio Miele[3,4], Laura Fejerman[5] and Jovanny Zabaleta[4,6,*]

[1]Grupo de Investigación en Biología del Cáncer, Instituto Nacional de Cancerología, Bogotá 110411001, Colombia, [2]Programa de Doctorado en Ciencias Biologicas, Pontificia Universidad Javeriana, Bogota 110231, Colombia, [3]Department of Genetics, LSUHSC, New Orleans, LA 70112, USA, [4]Stanley S. Scott Cancer Center, LSUHSC, New Orleans, LA 70112, USA, [5]Department of Medicine, Institute of Human Genetics, University of California San Francisco, San Francisco, CA 94158, USA and [6]Department of Pediatrics, LSUHSC, New Orleans, LA 70112, USA

*To whom correspondence should be addressed. Tel: +1 504 210 2979; Fax: +1 504 210 2970; Email: jzabal@lsuhsc.edu

Poster Session Abstracts

Abstract P1-08-09: Increased prevalence of luminal B subtype in Colombian women with breast cancer

SJ Serrano-Gomez, MC Sanabria, GA Hernández-Suarez, O Garcia, C Silva, A Romero, JC Mejía, L Fejerman, T Antonia, L Miele, and J Zabaleta

DOI: 10.1158/1538-7445.SABCS15-P1-08-09 Published 15 February 2016

Abstracts: Thirty-Eighth Annual CTRC-AACR San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, TX

Are there genes modulated by ancestry in the Luminal subtypes of BrCa in Colombian women

Methodology

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Whole transcriptome RNA-seq in 42 tumors

Selected according to genetic ancestry and intrinsic subtype of breast cancer

Sample selection for RNA-seq analysis

42 FFPE tumor samples

21 Luminal A

21 Luminal B

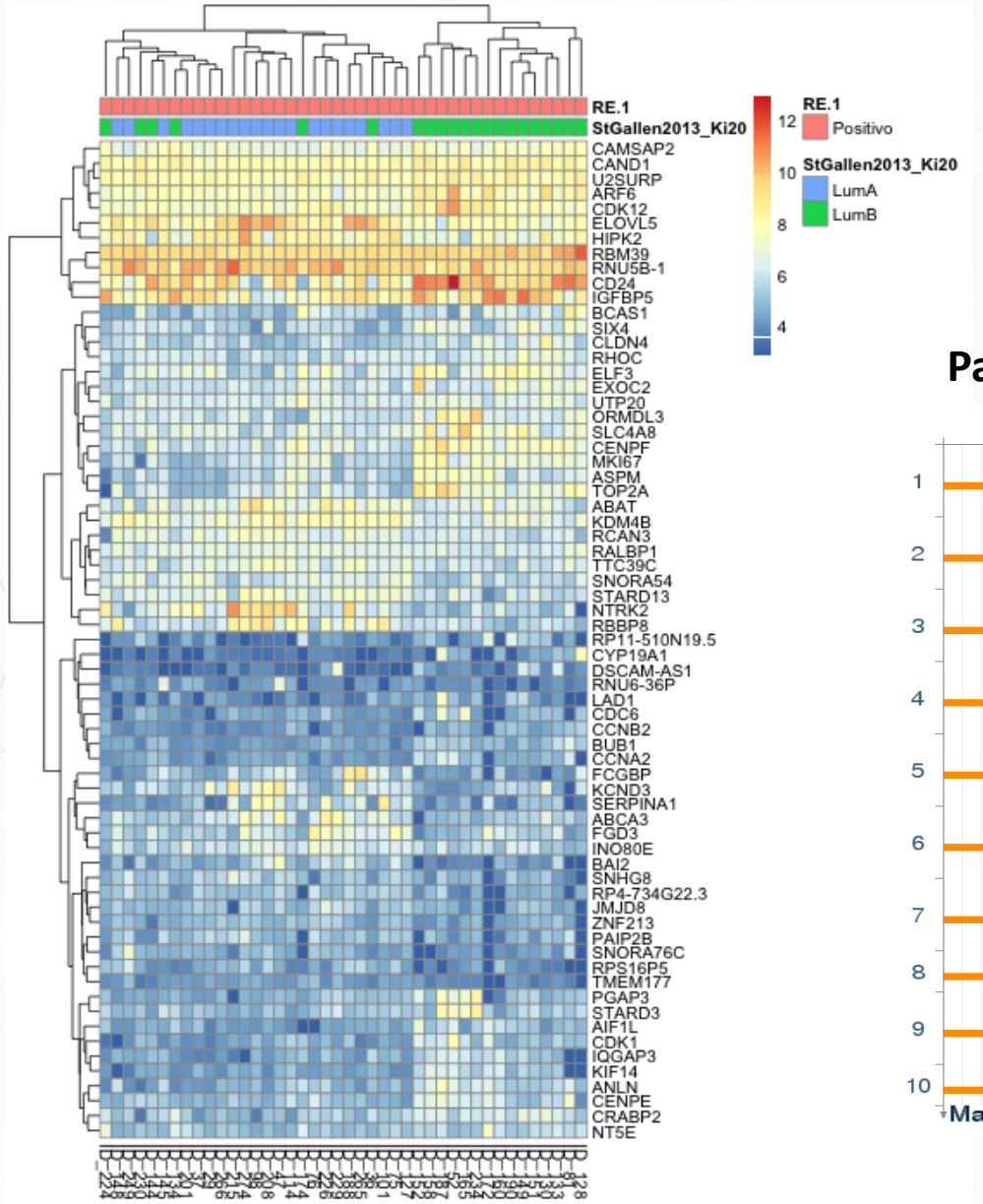
9 Low NA ancestry (25%)

12 High NA ancestry (45%)

13 Low NA Ancestry (24%)

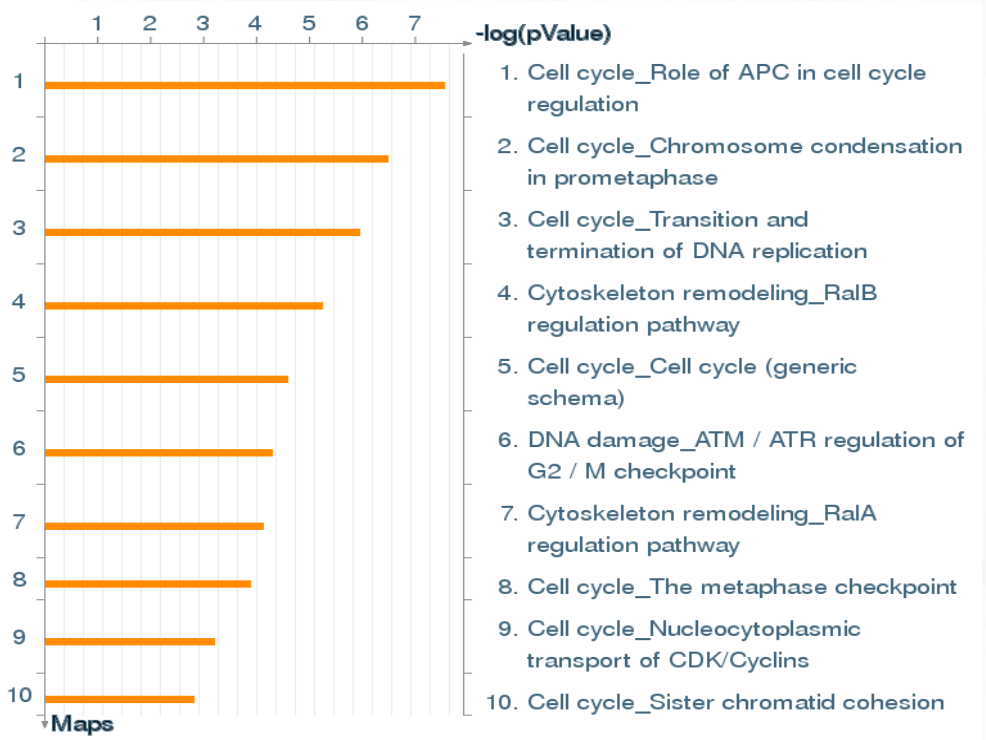
8 High NA ancestry (54%)

Molecular profile of luminal B vs. luminal A



67 genes differentially expressed

Pathways maps correlate with cell cycle



Plos One 2017, 23;12(8):e0183179

Evaluation of ancestry-modulated genes in luminal tumors

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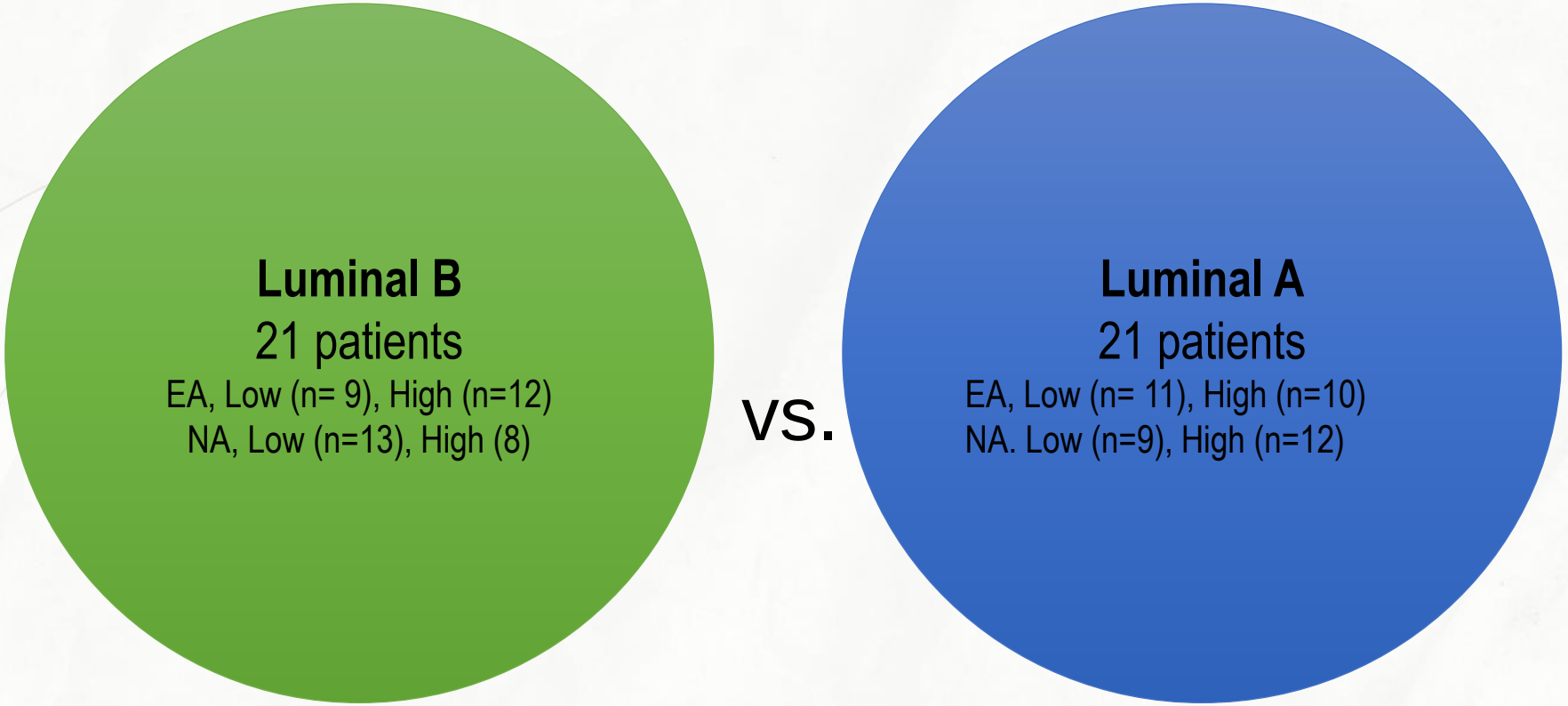
Median European Ancestry = 0.58
Median Native ancestry = 0.38



Correlation between the ancestral fraction in Colombian patients with BrCa

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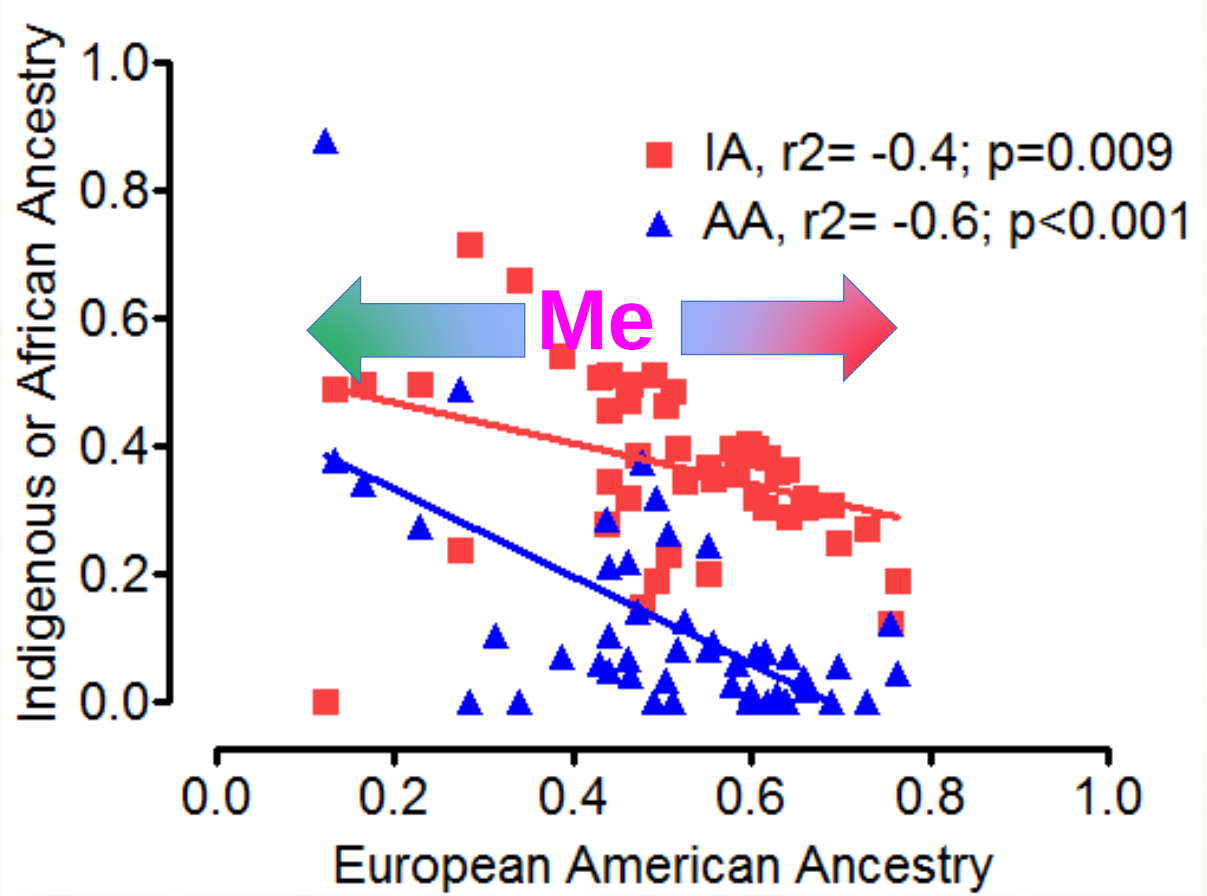

Comparison of the different gene profiles based on ancestry

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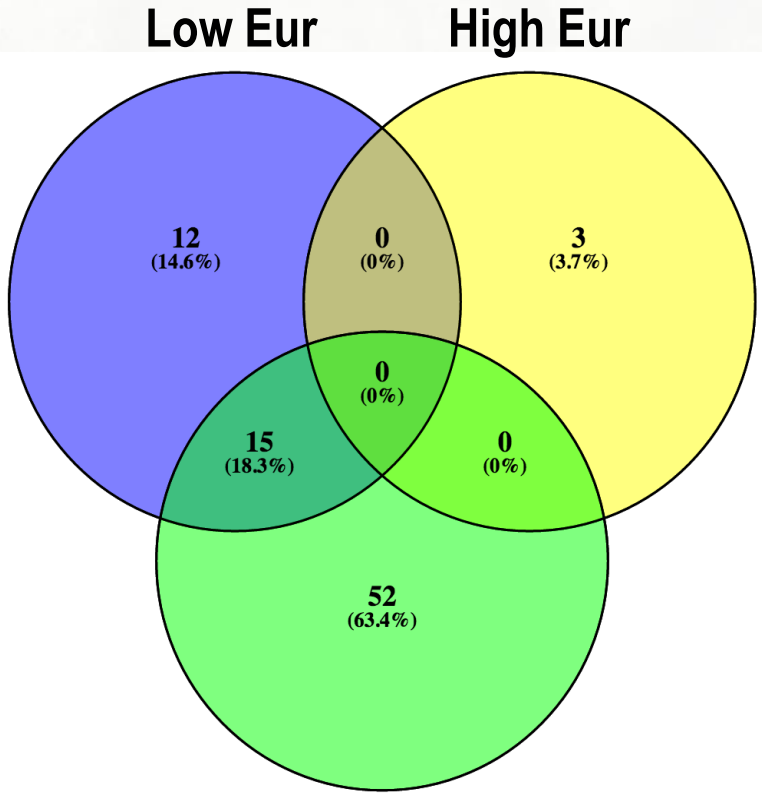
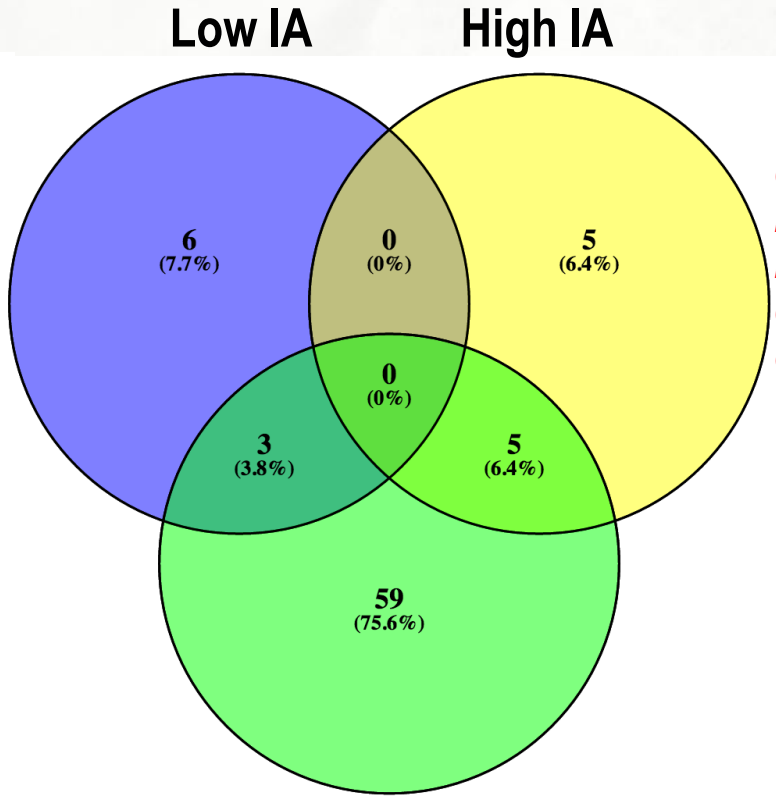
ERBB2
GRB7
MIEN1
ONECUT2
GSDMB
NUFIP2
TNFSF13
LRRC1
PSMD3
SLC23A3
ARHGAP33
HES1



67 Genes differentially expressed between luminal B y luminal A



GSDMB
MIEN1
ERBB2
GRB7
ONECUT2

67 Genes differentially expressed between luminal B y luminal A

Plos One 2017, 23;12(8):e0183179

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PLOS ONE

RESEARCH ARTICLE

Ancestry as a potential modifier of gene expression in breast tumors from Colombian women

Silvia J. Serrano-Gómez[1,2], María Carolina Sanabria-Salas[1], Jone Garay[3], Melody C. Baddoo[4], Gustavo Hernández-Suarez[1], Juan Carlos Mejía[5], Oscar García[6], Lucio Miele[7], Laura Fejerman[8☯], Jovanny Zabaleta[3,9☯*]

Ancestry as a potential modifier of gene expression in luminal B tumors among Colombian women. Ninth AACR Conference on The Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved , September 25 - 28, 2016, Fort Lauderdale, Florida, USA

Differential level of expression of genes in the MammaPrint test gene set based on ancestral fraction

Comparison of Mammaprint molecular signature based on high vs. low European/Native ancestries		
	European	Native
ABCC11	12.68	-12.03
CDCA7	-10.08	9.36
SLC16A6	-3.61	4.02
TMEM101	-4.98	4.42

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PAM50 comparison in H/L with luminal B based on BMI and ancestry

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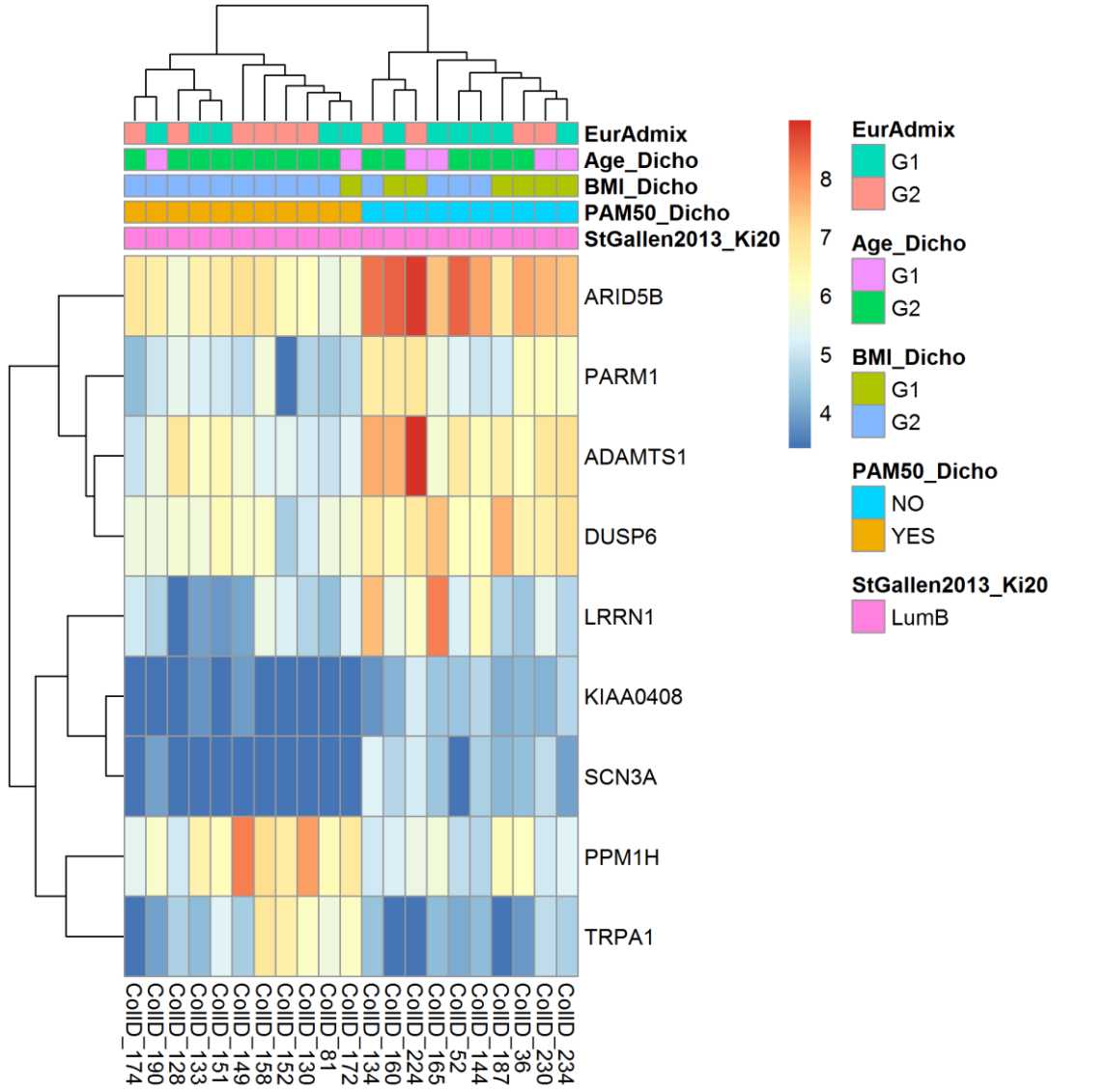

Dicho=dichotomized variable
BMI_G1= BMI<25
BMI_G2= BMI≥25
PAM50_NO=no concordance between IHC and molecular analysis by PAM50
PAM50_YES=concordance between IHC and molecular analysis by PAM50
Age_G1= <50
Age_G2 = ≥50
StGallen2013_Ki20= IHC classification of breast cancer based on the 20113 St. Gallen meeting using 20% cut-off point for Ki67

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Predicted MSC infiltration in luminal tumor tissues correlate with ancestral fraction

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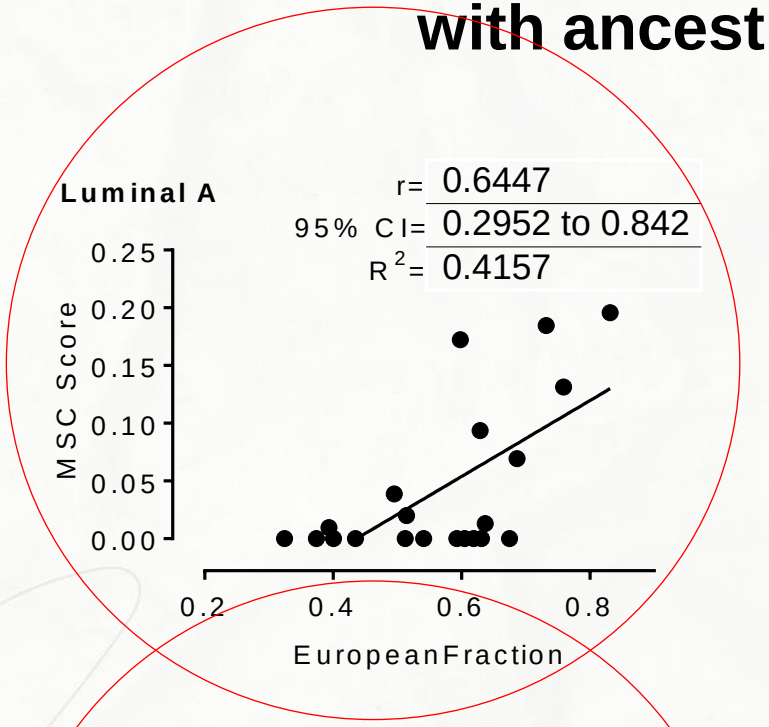

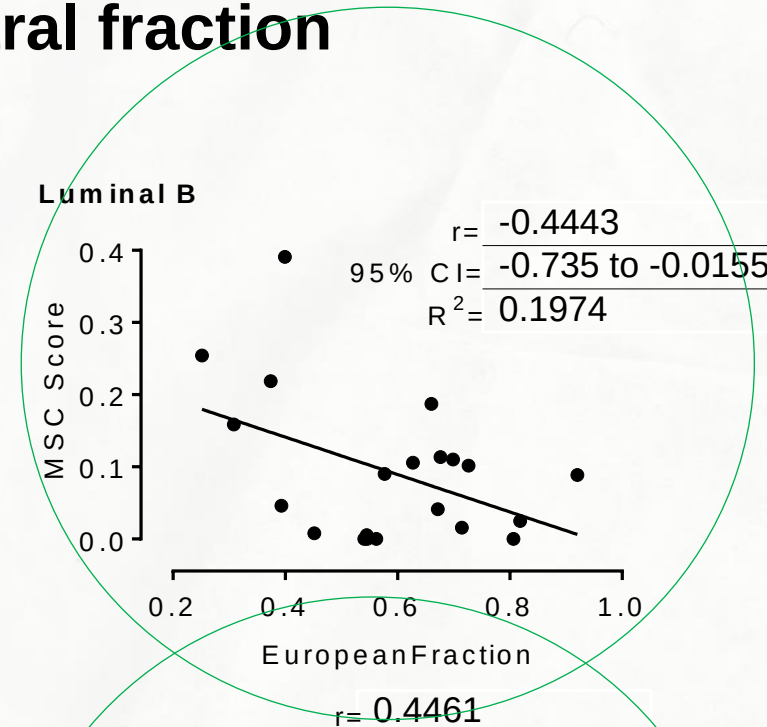

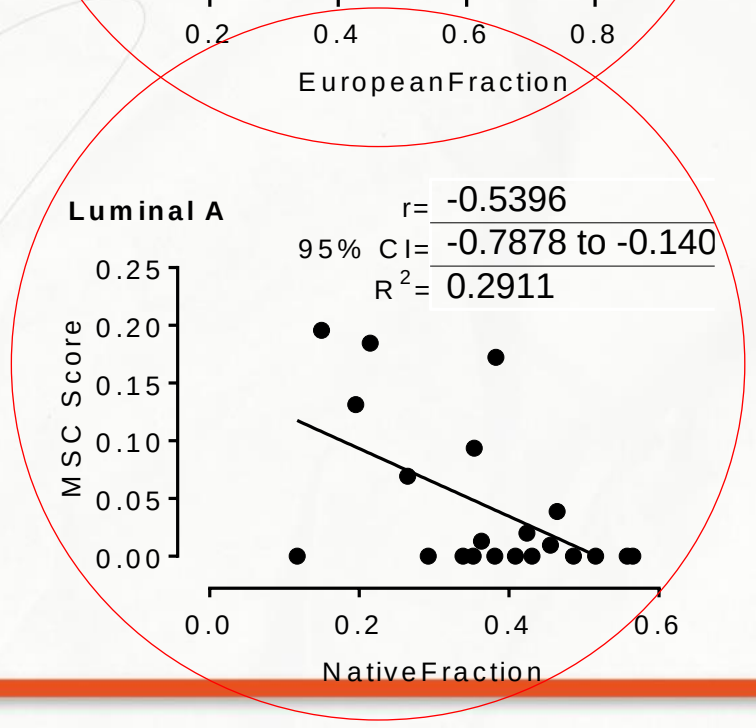

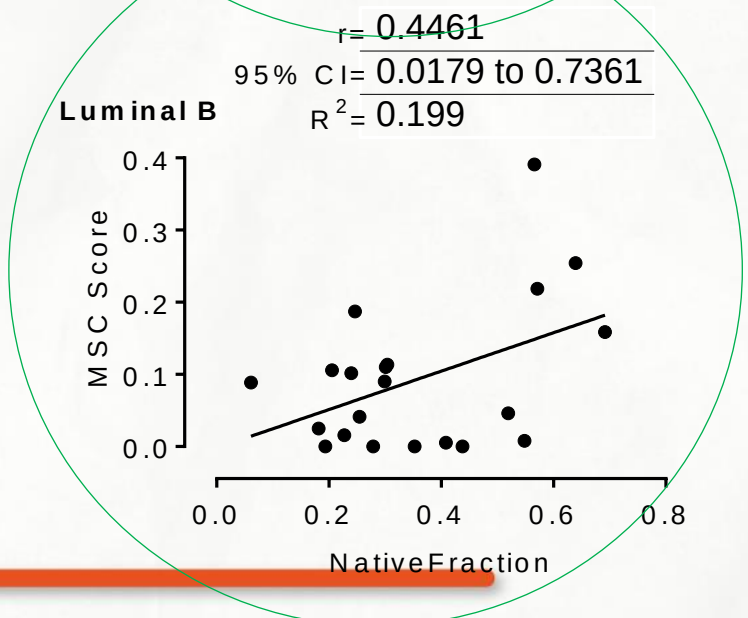

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Are these results valid in other Hispanic/Latino populations?

- **P20CA202922**

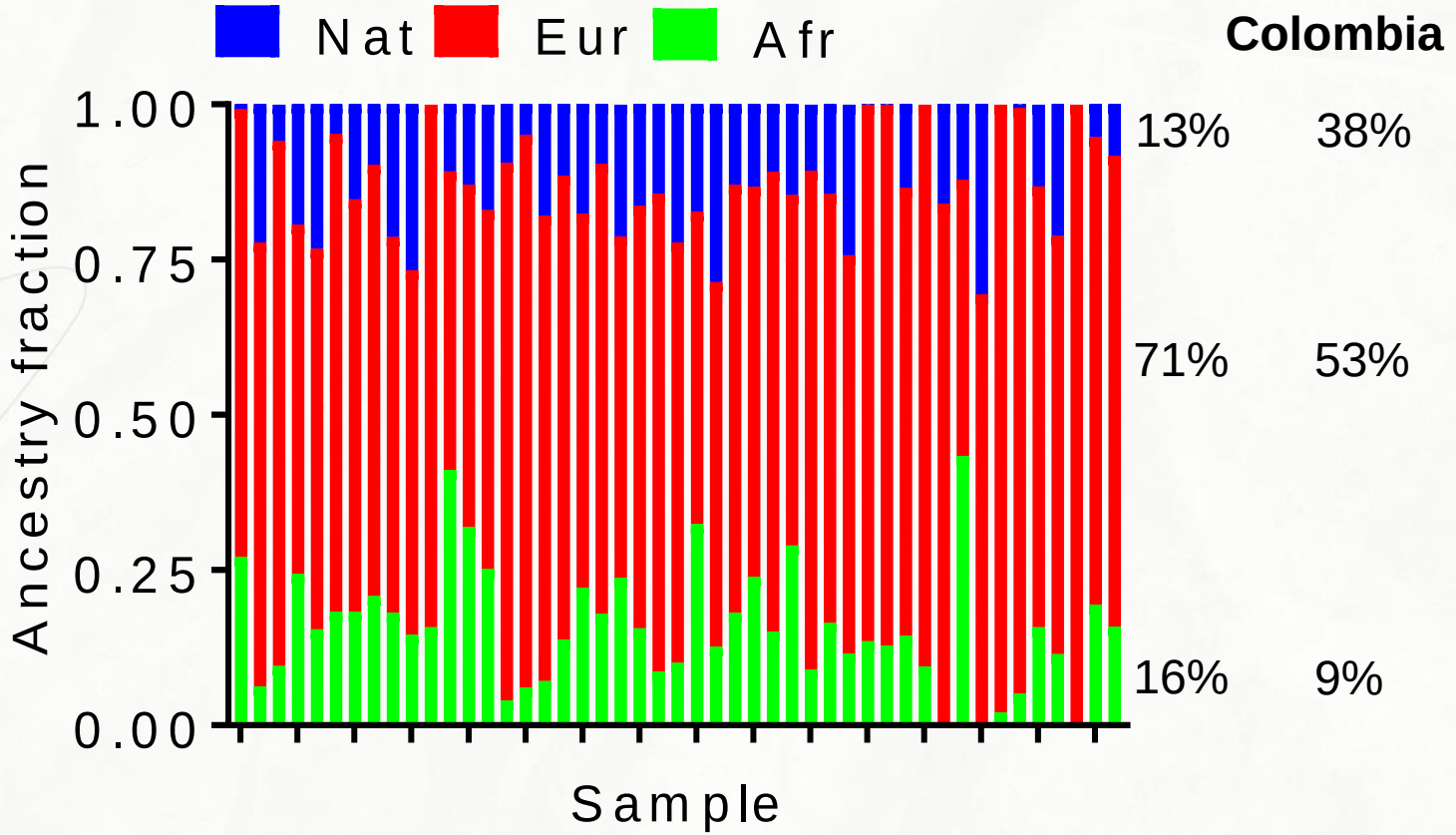
NCI-CRCHD 09/01/2017 – 08/31/2021

The Southeast Partership for Improving Research and Training in Cancer Health Disparities (SPIRIT-CHD)

Doug Cress, Ph.D

Cathy Mead, Ph.D

Different ancestral fractions in a sample of women diagnosed with PAM-50 validated luminal B tumors



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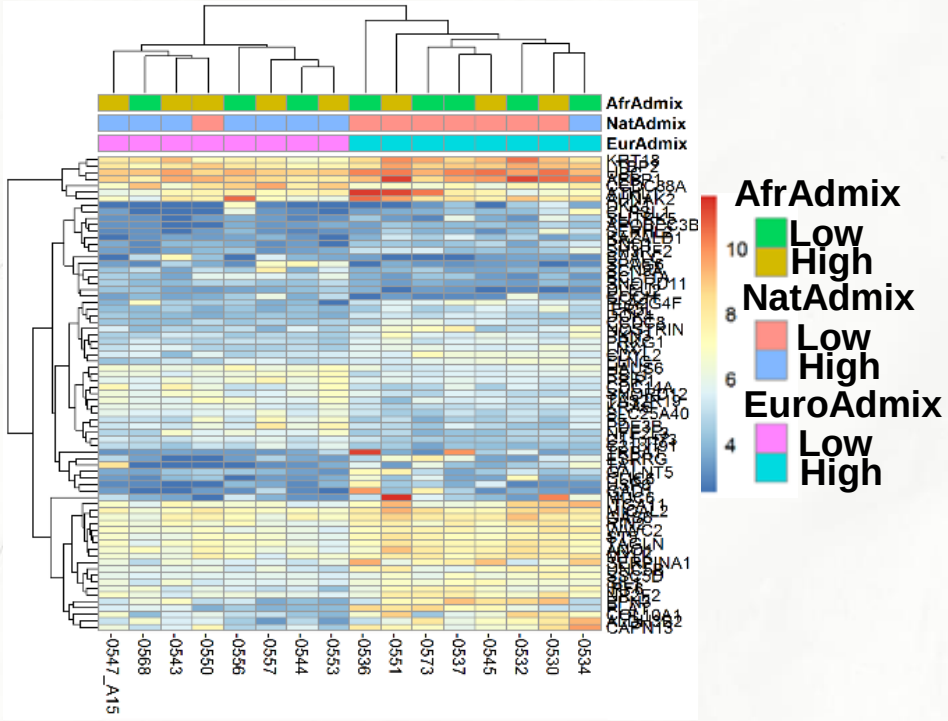
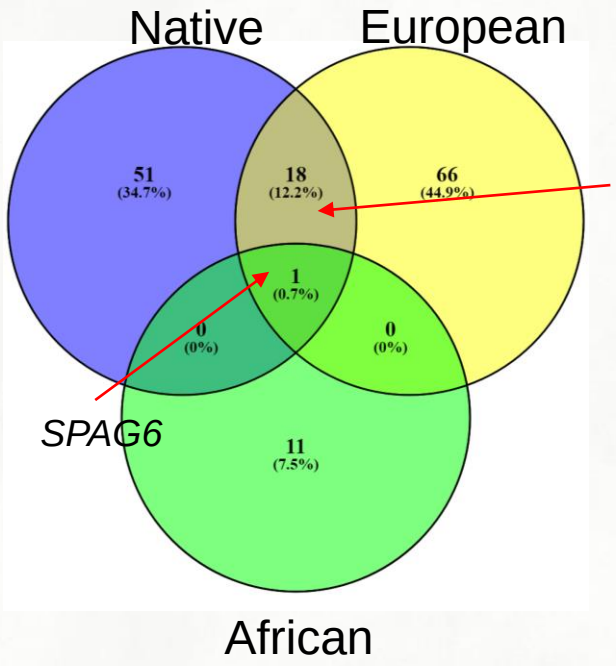
Ancestral fractions separate luminal B tumors





ANO1
ATHL1
CAPN13
CDYL2
CLIC6
EPN3
GAD1
GALNT5
GAS6
HAUS6
LTBP2
MICAL2
PLAT
RBM12
TAGLN
TRPA1
UBC
ZNF436

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Small and large luminal B tumors have different gene expression profiles

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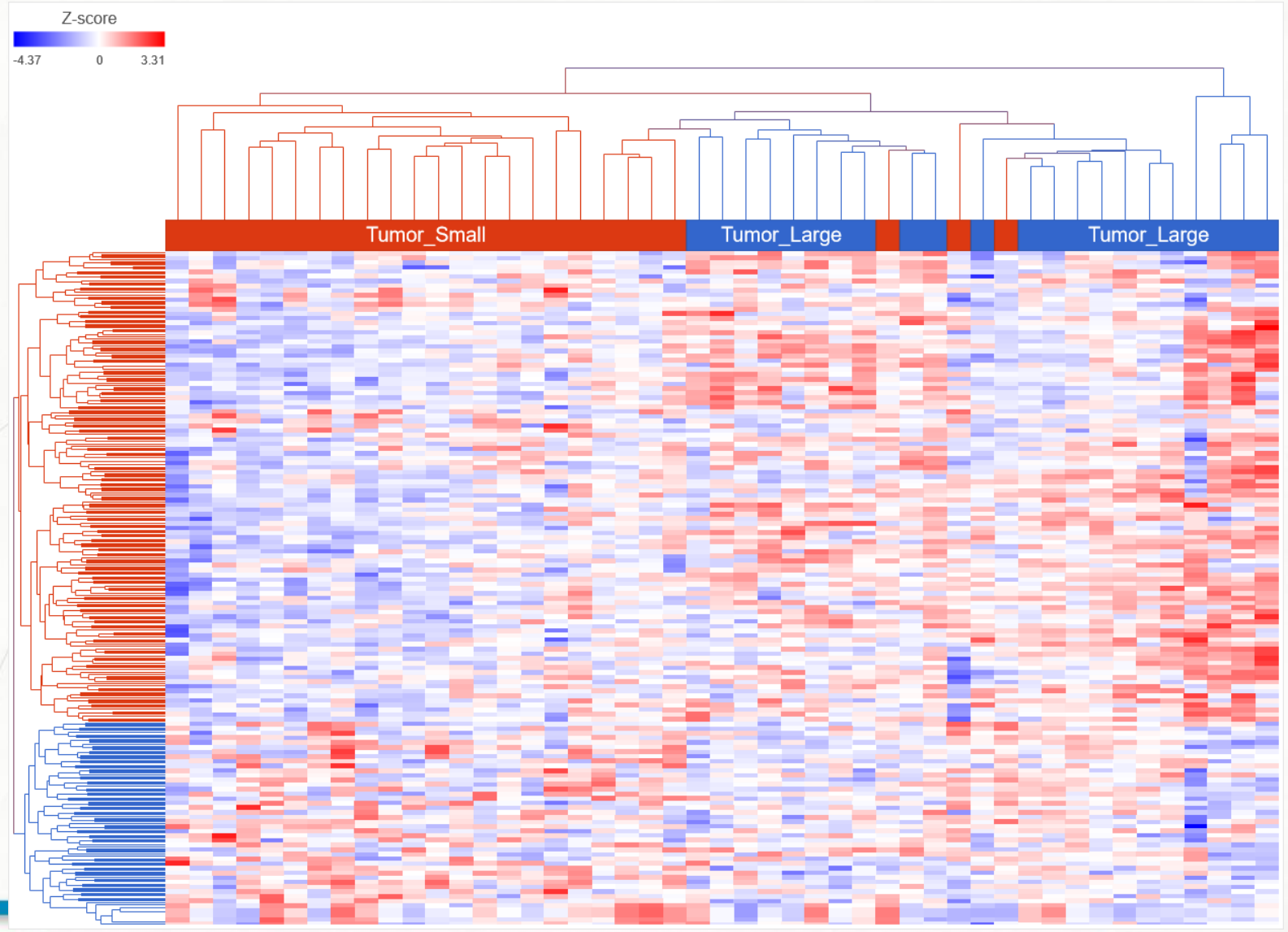

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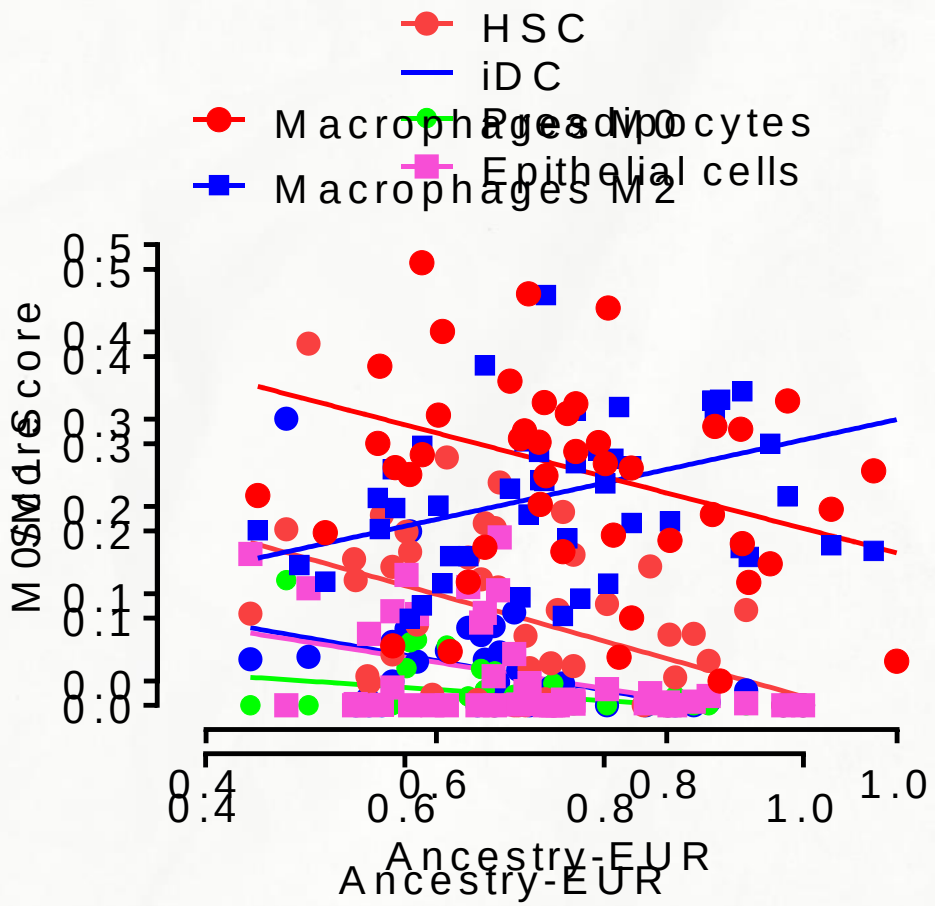
Differential infiltration of cells into luminal B tumors based on European fraction



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Frequency of M2 macrophages in the TCGA data and their effect in survival

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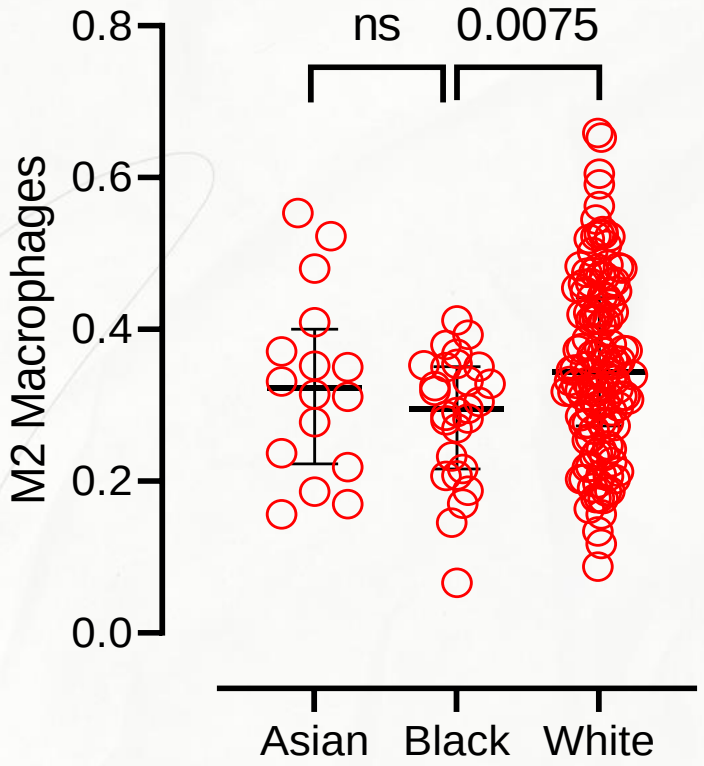

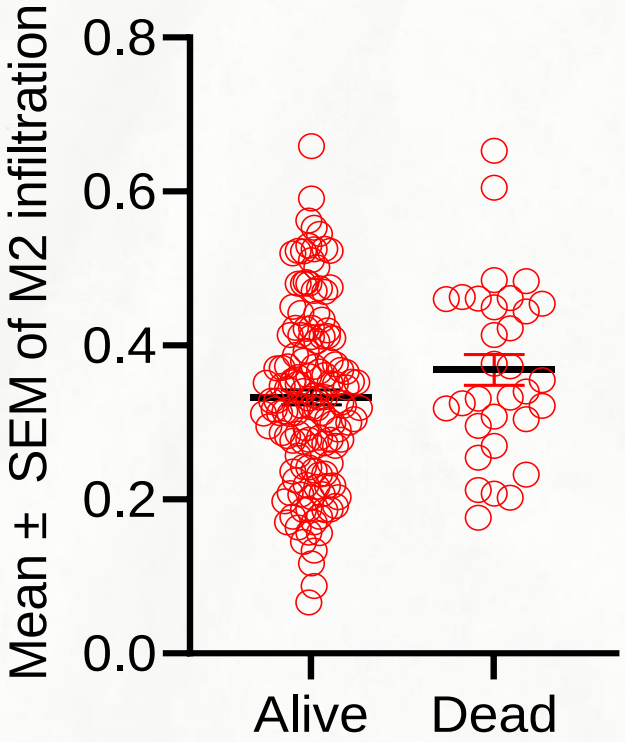

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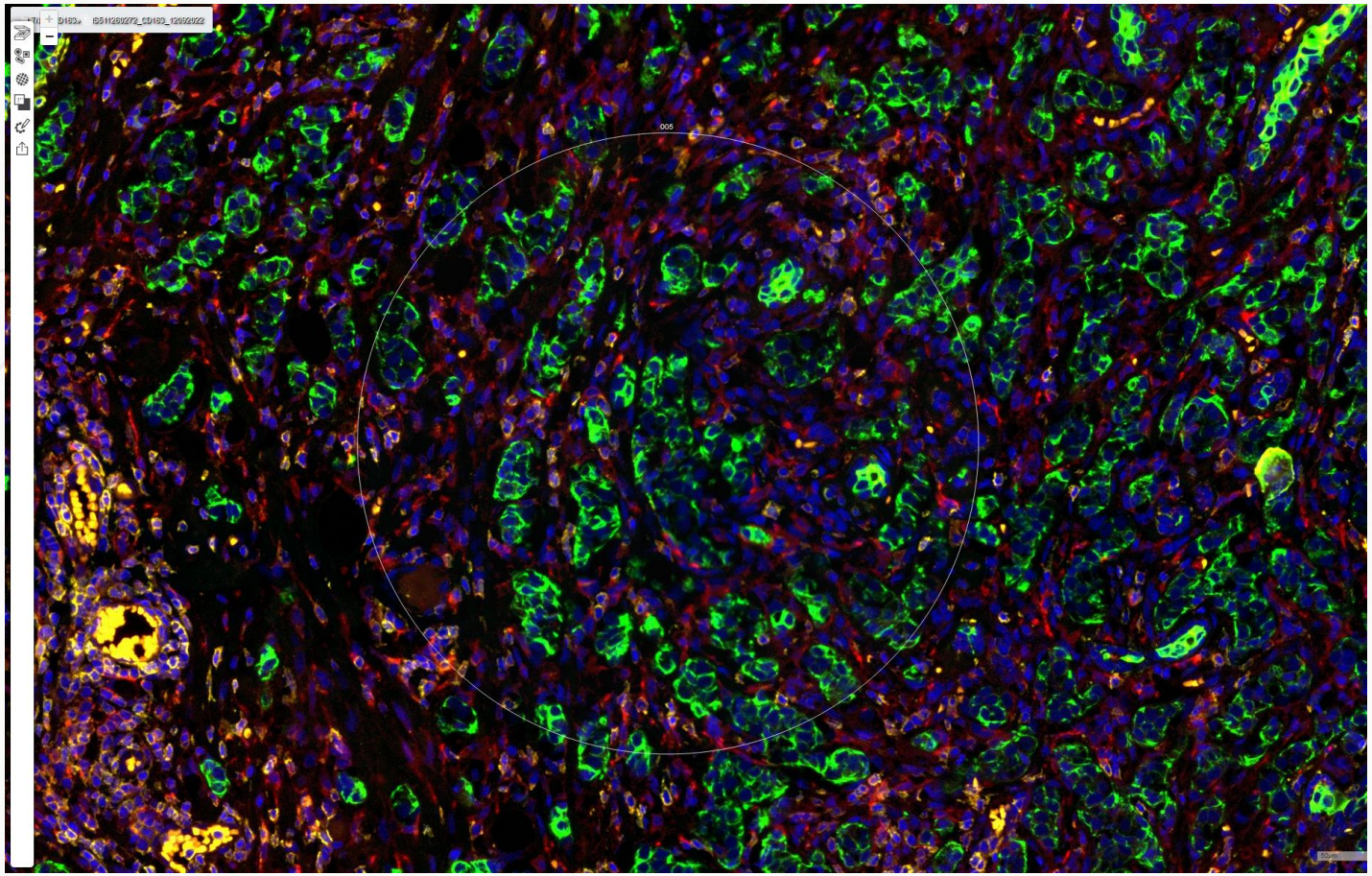
What are those M2 macrophages doing the breast tumor ME?



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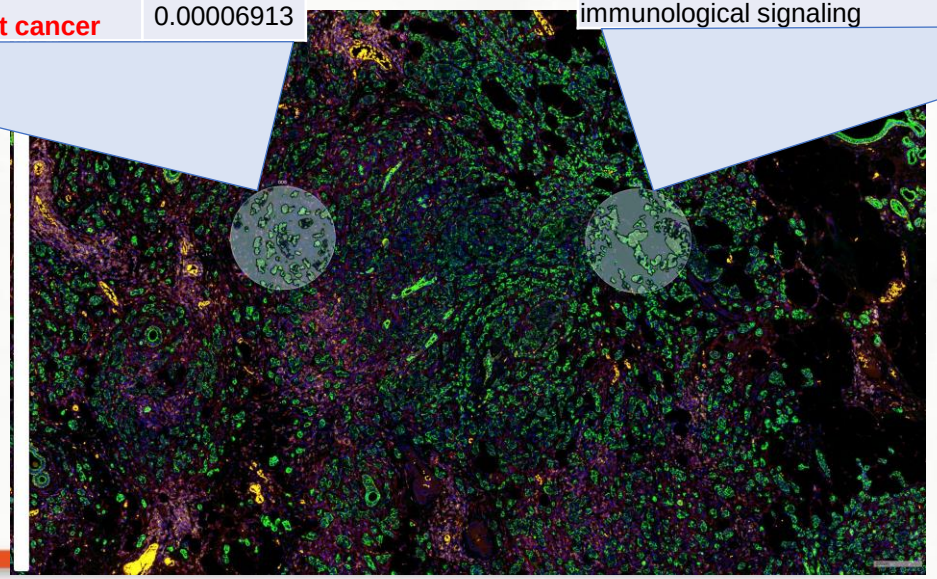
Pathways for tumor only areas	Global p-value
Development_Auditory hair cell differentiation in embryogenesis	7.429E-07
Immune response_Role of PKR in stress-induced antiviral cell response	1.7504E-06
Stem cells_Response to hypoxia in glioblastoma stem cells	0.000004942
Macrophage-induced immunosuppression in the tumor microenvironment	0.00001351
Gamma-secretase proteolytic targets	0.00003184
Interleukins-induced inflammatory signaling in normal and asthmatic airway epithelium	0.00003348
TNF-alpha and IL-1 beta induce hyperglycemia in obesity and type 2 diabetes in adipocytes	0.00005247
Interleukins-induced inflammatory response in asthmatic airway fibroblasts	0.00005247
Activation of Notch signaling in breast cancer	0.00006913

Pathways for stroma only areas	Global p-value
Chemotaxis_SDF-1/ CXCR4-induced chemotaxis of immune cells	3.251E-10
Attenuation of IFN type I signaling in melanoma cells	5.495E-10
Cooperative action of IFN-gamma and TNF-alpha on astrocytes in multiple sclerosis	8.063E-10
Immune response_IL-1 signaling	1.89154E-09
Inflammatory mechanisms of pancreatic cancerogenesis	2.717E-09
Macrophage and dendritic cell phenotype shift in cancer	7.065E-09
Immune response_IFN-gamma signaling via PI3K and NF-kB	1.375E-08
Main growth factor signaling cascades in multiple myeloma cells	1.45E-08
Immune response_Glucocorticoid receptor immunological signaling	3.409E-08



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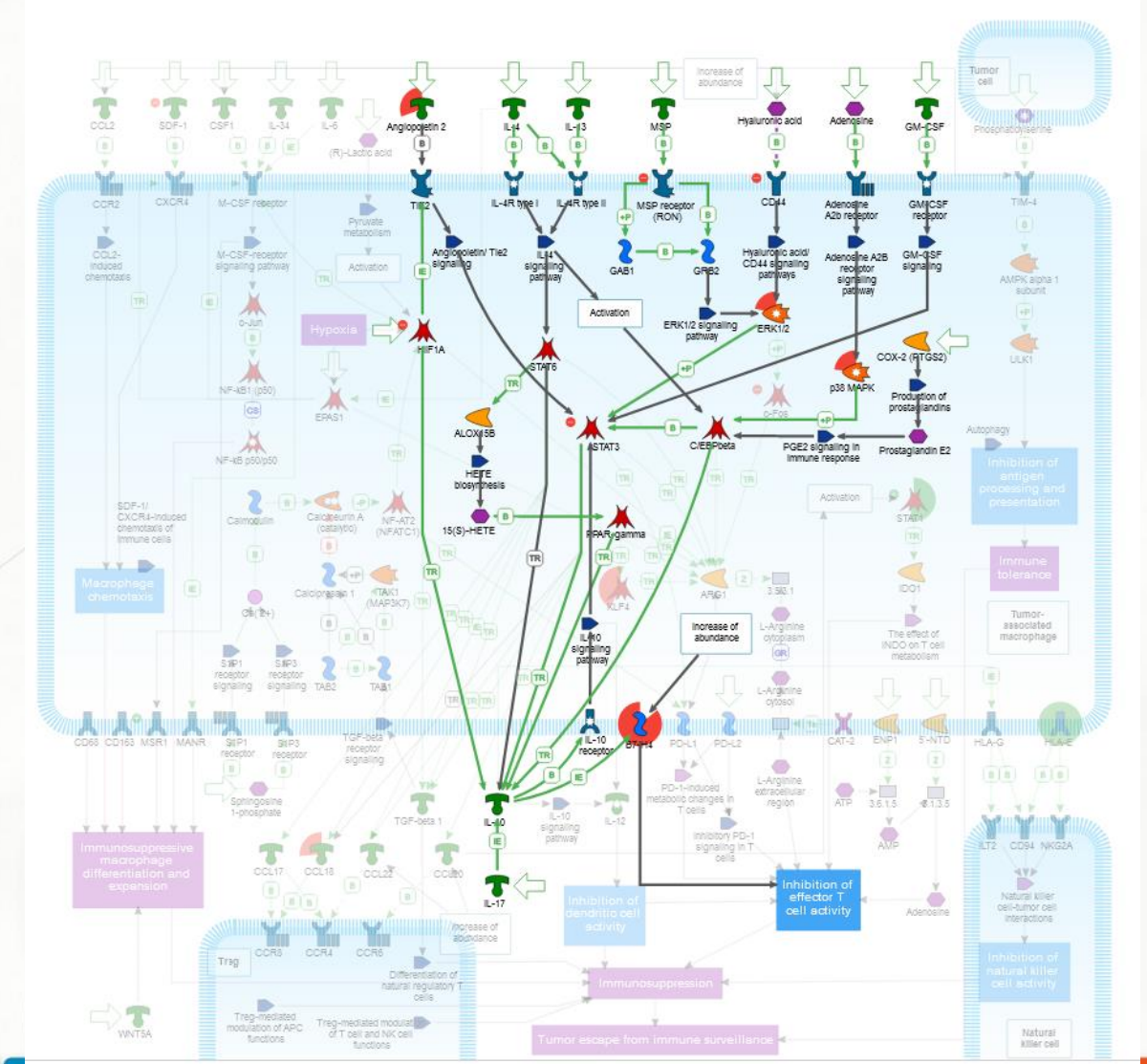
Macrophage-induced immunosuppression in the tumor microenvironment



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Differential infiltration of cells into luminal B tumors based on BMI

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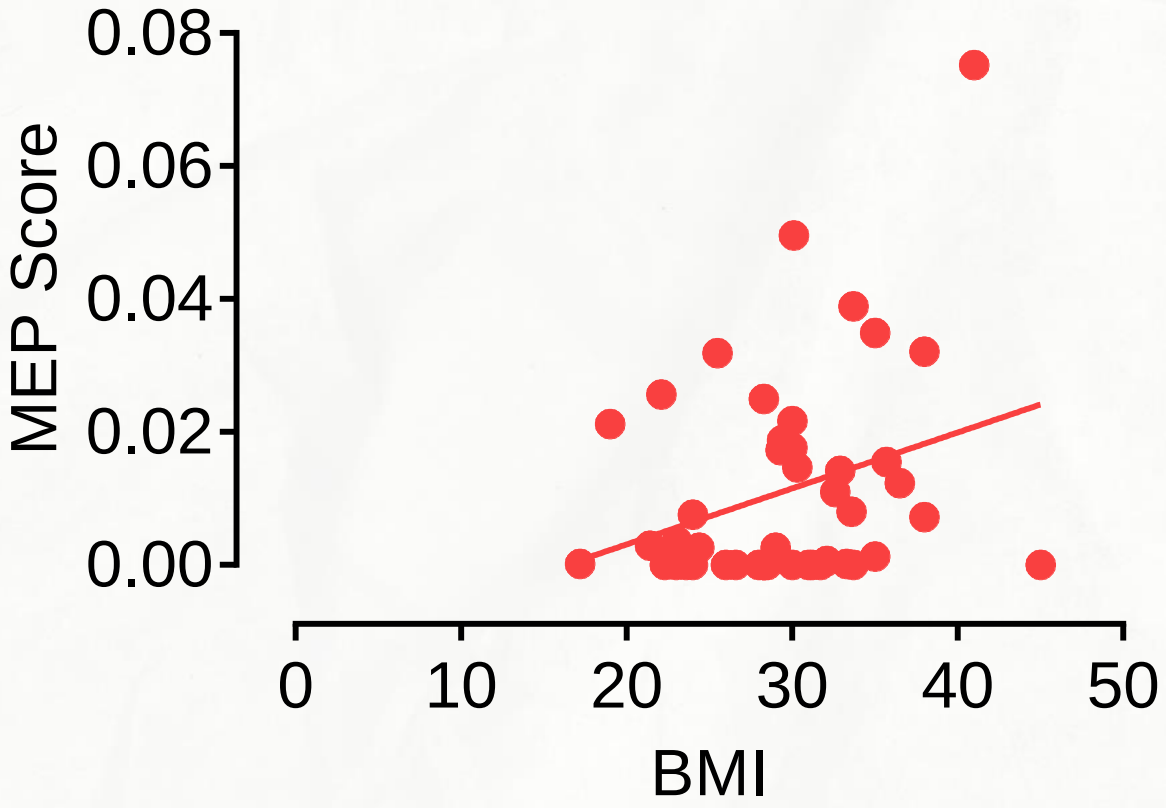

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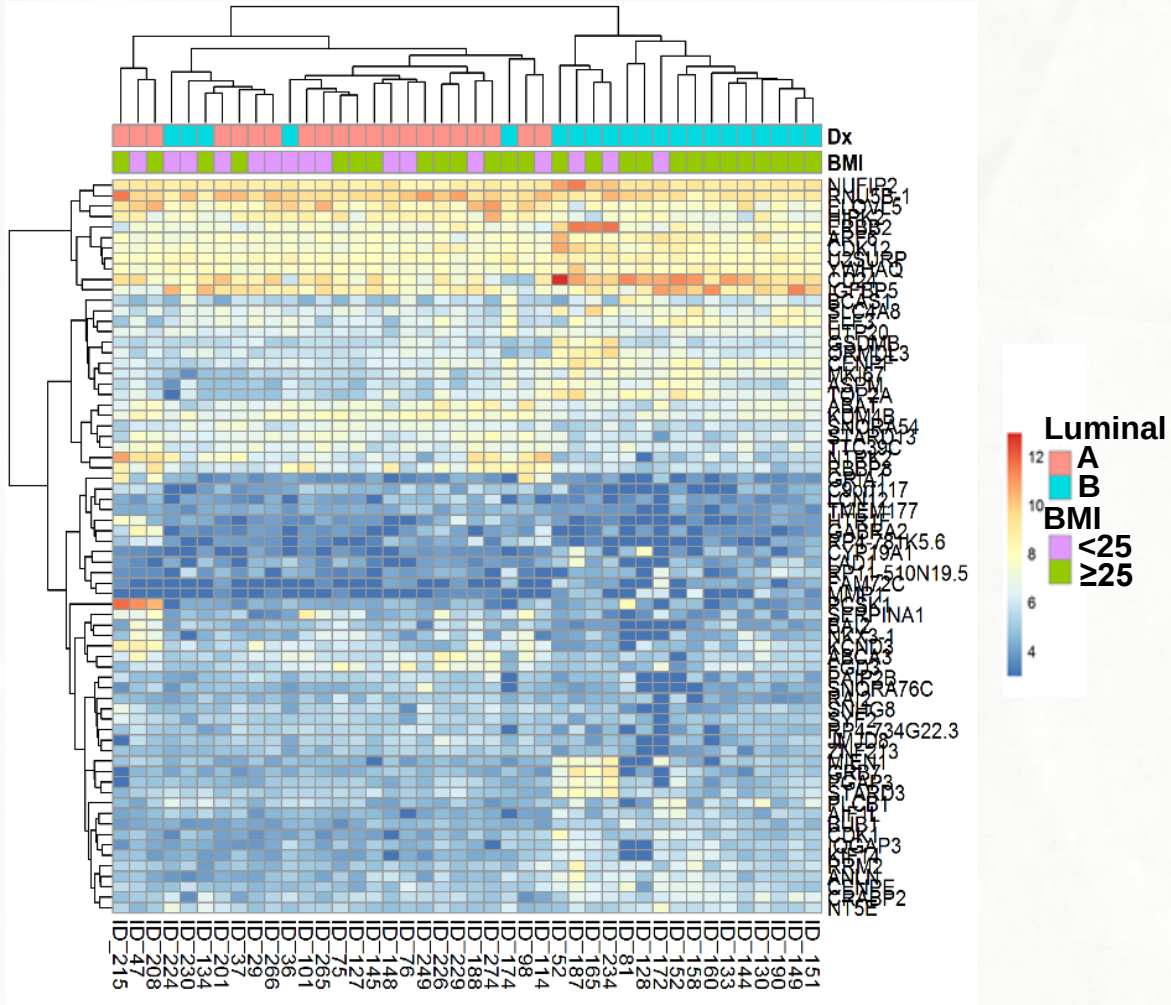

Luminal B breast cancer is associated with increased BMI (A) and with reduced European Ancestry (B)

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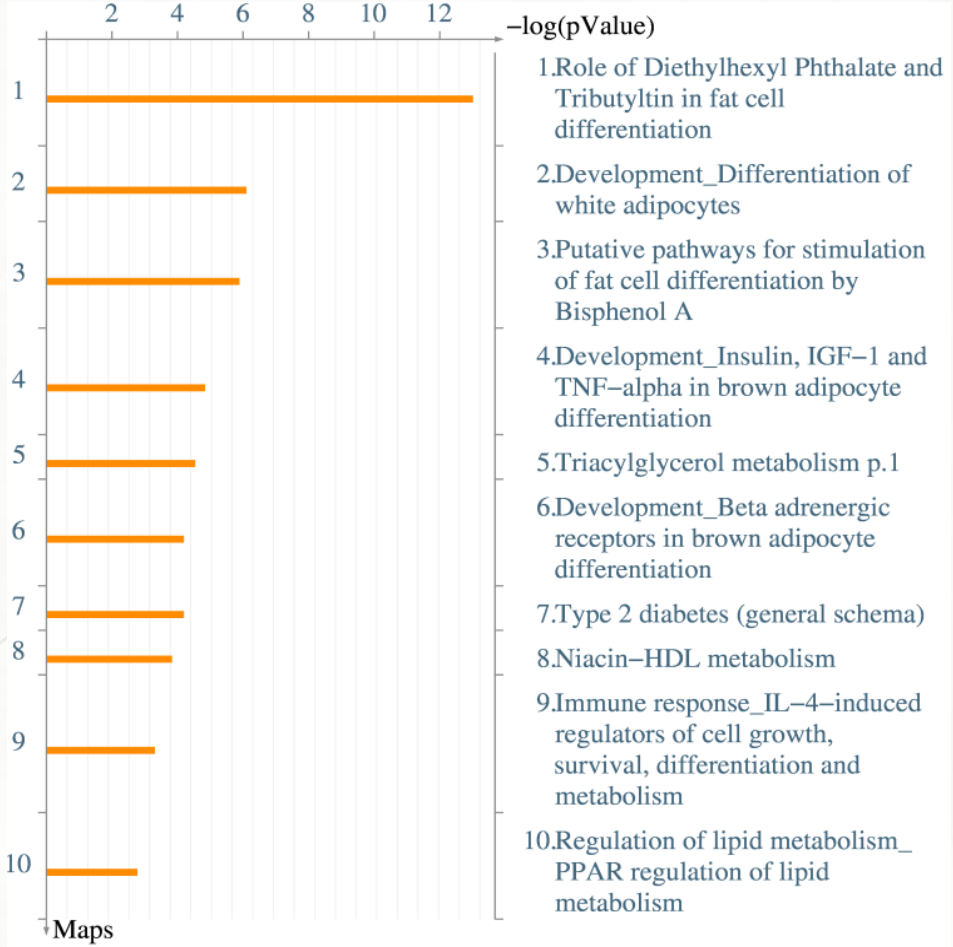
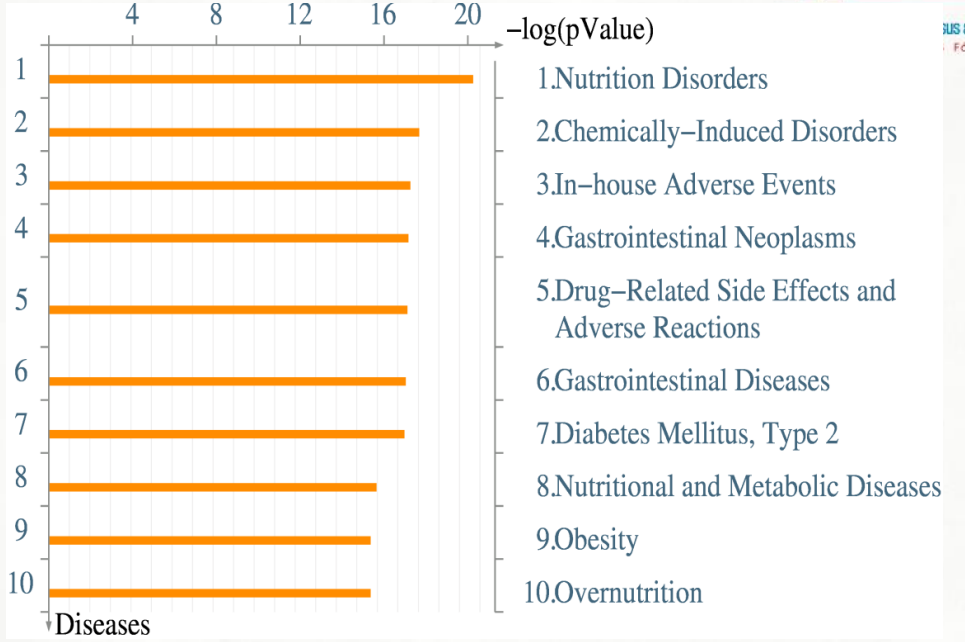
A.



B.



Pathway maps (A) and diseases (B) associated with genes differentially expressed in luminal B breast cancer vs. normals

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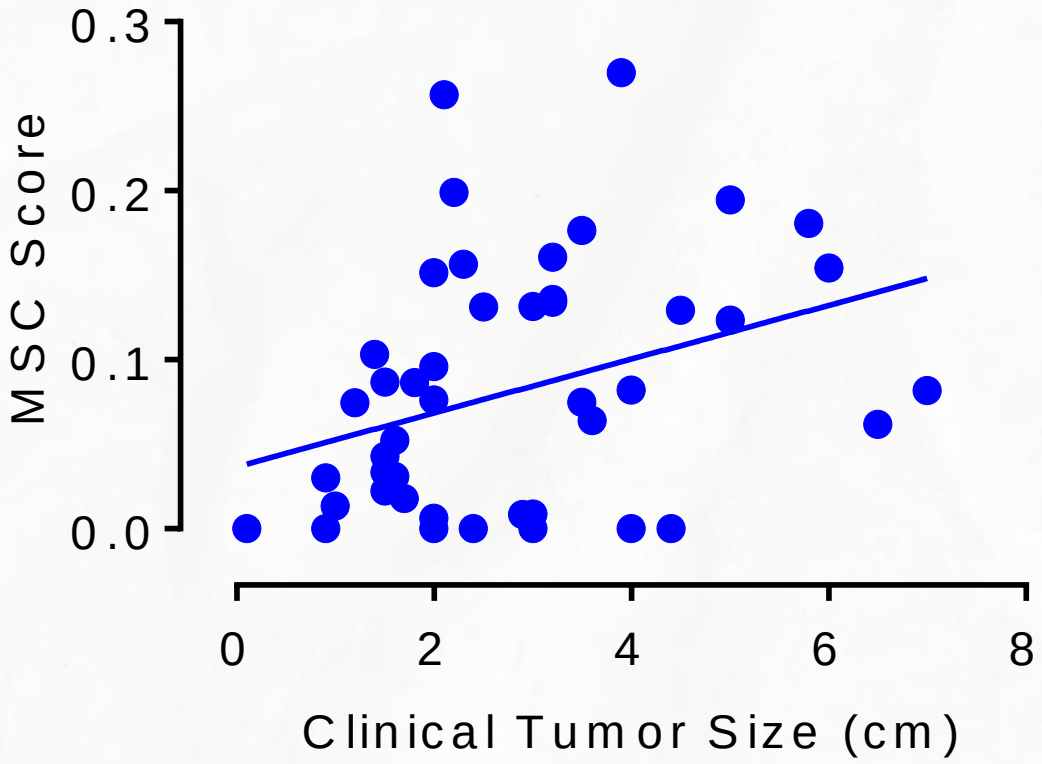
Differential infiltration of cells into luminal B tumors based on tumor size



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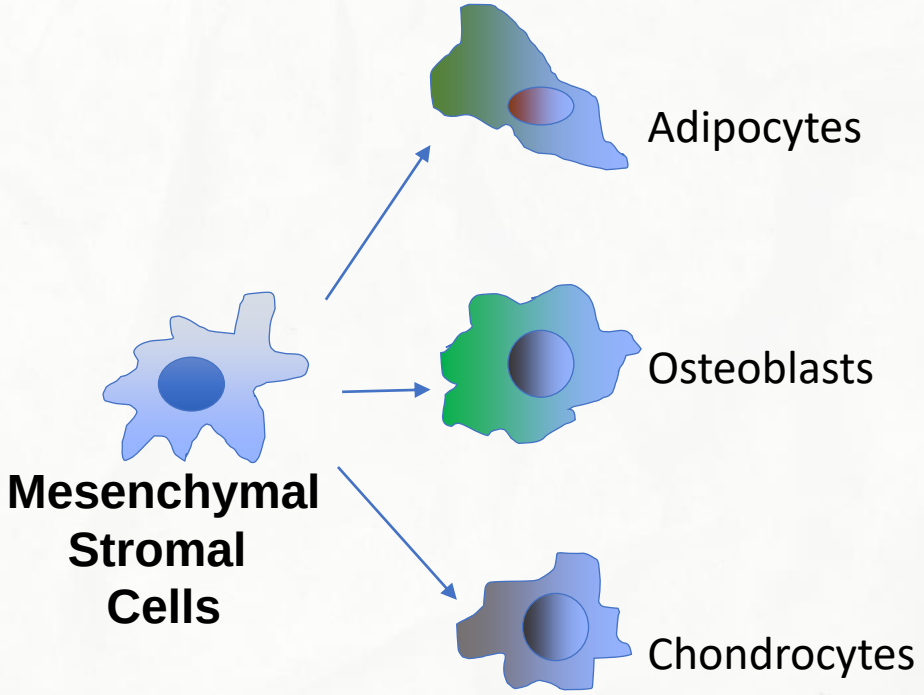
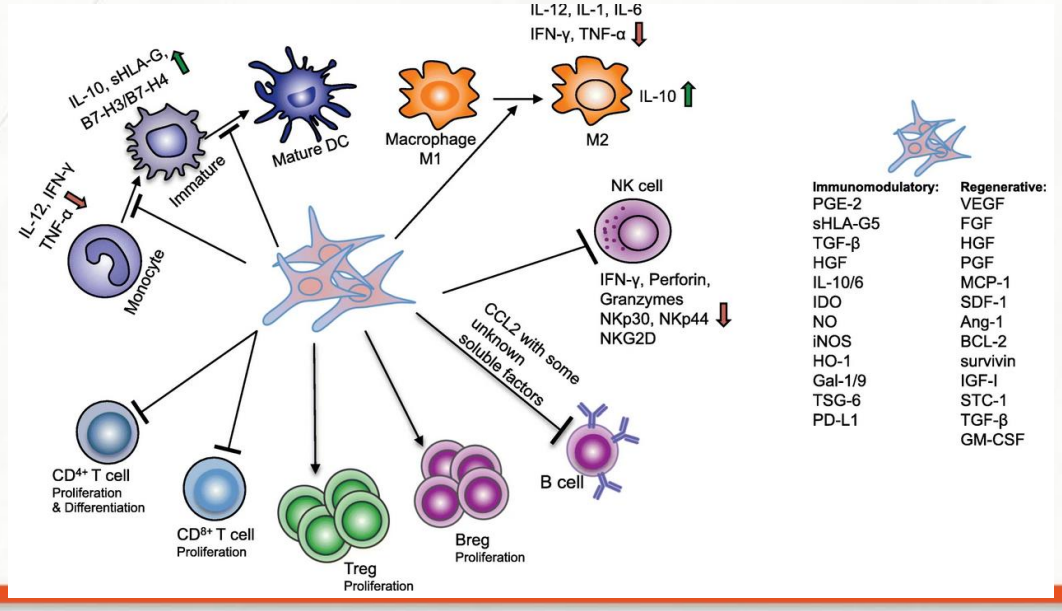
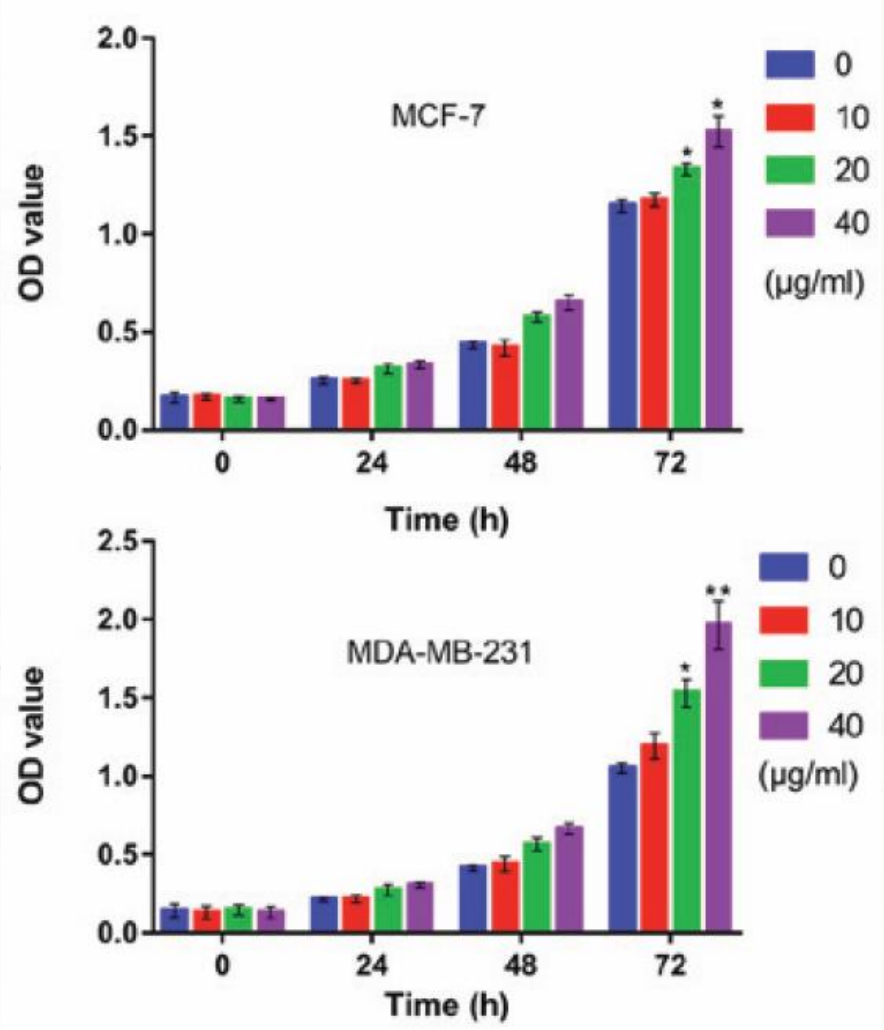
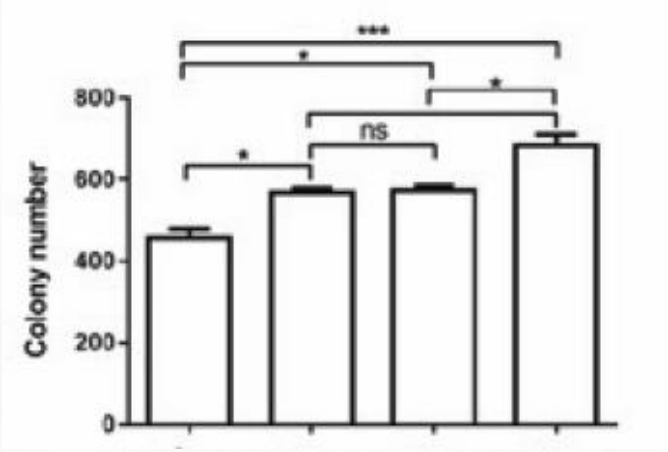


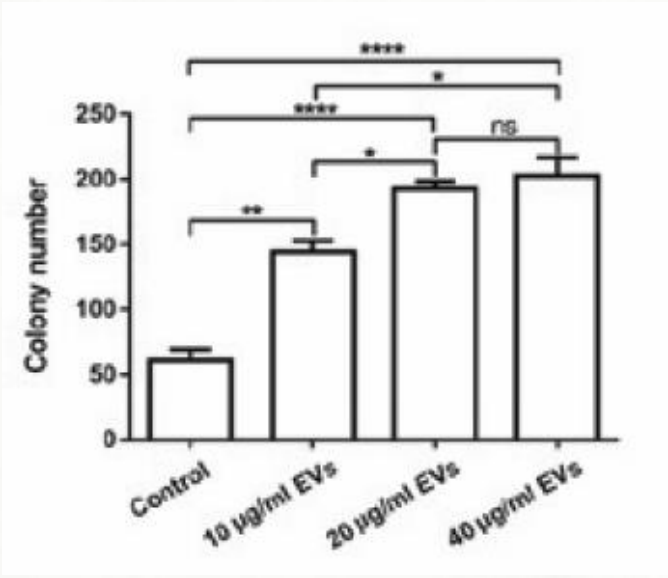


Wu X, *et. al; Stem Cell Res Ther* **11**: 345 (2020)

MSC-EVs promote breast cancer cell viability and proliferation

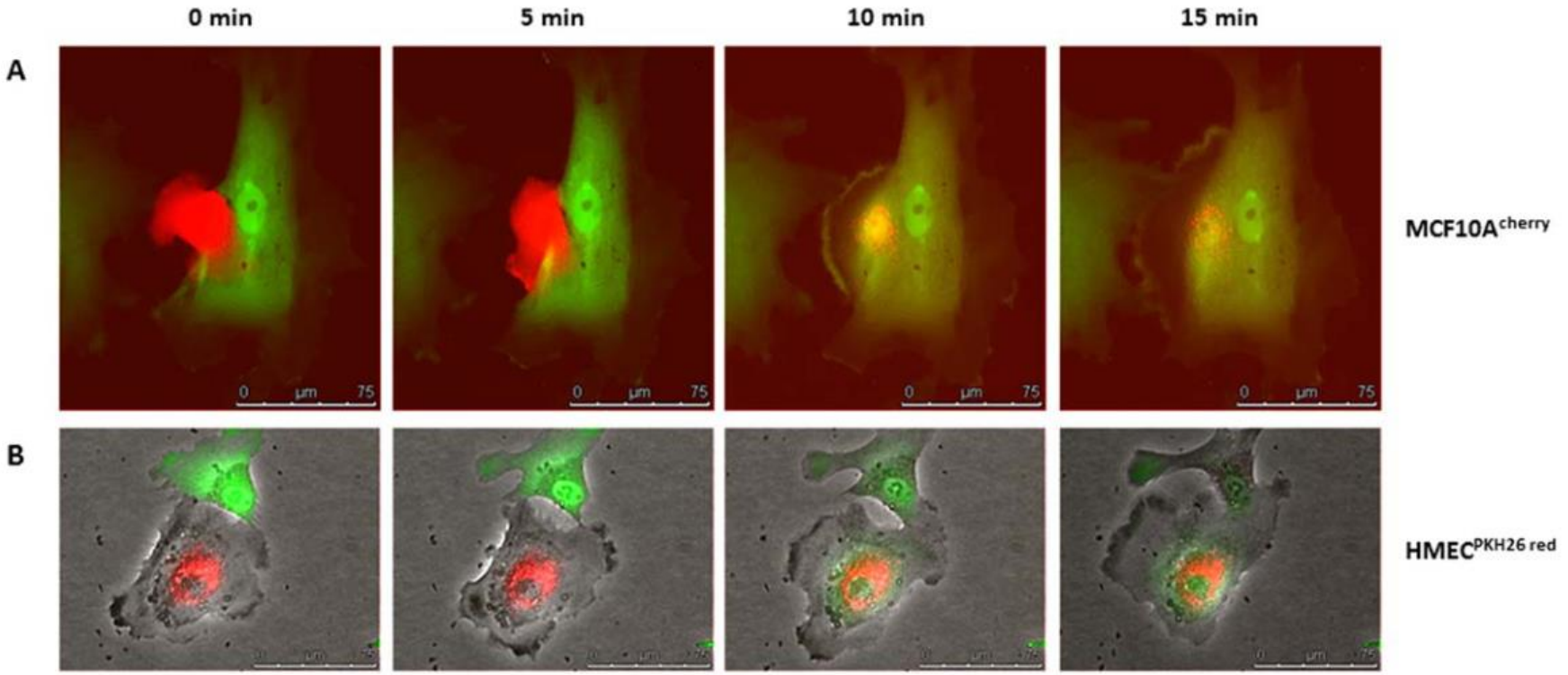






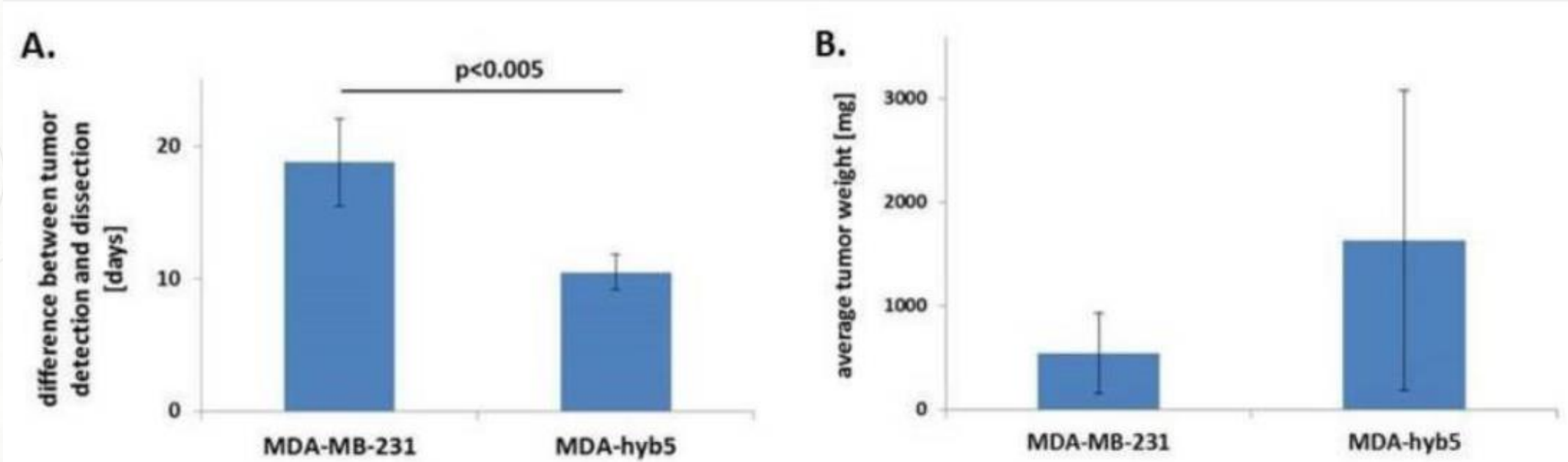
Zhou X, *et. al; Int J Oncol,* ***54***: 1843 (2019)

In vitro MSC/Breast cancer cell fusion



Melzer C, et. al; STEM CELLS 2018;36:977–989

MSC/Breast fusion cells grow faster in animal models



Melzer C, et. al; Int J Mol Sci. 2021 Jun; 22(11): 5930.

Conclusions

1. Luminal B breast cancer is the most prevalent among Colombian women;

2. Luminal tumors present differential gene expression profiles based on the ancestry fraction of the patient;

3. Ancestral fraction of luminal B breast cancer patients correlate with differential infiltration of cells into tumors

3. Differential cell infiltration is correlated with and may affect tumor size in luminal B breast cancer, especially, as suggested by our results, mesenchymal stromal cells

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GRACIAS

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