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BIOPSIA LÍQUIDA · LIQUID BIOPSY

EL CAMINO A LA ONCOLOGÍA DE PRECISIÓN · THE WAY TO PRECISION MEDICINE

25, 26 Y 27 DE ENERO · JANUARY 25th, 26th and 27th

CIRCULATING TUMOR DNA REVEALS COMPLEX BIOLOGICAL FEATURES WITH CLINICAL IMPACT IN METASTATIC BREAST CANCER

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DECLARATION OF INTERESTS

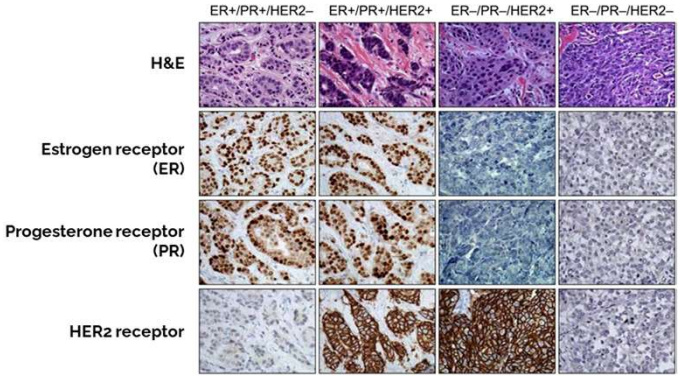
Consultancy/speaker: Reveal Genomics

Research funding (my institution): Novartis, Roche, AstraZeneca, Daiichi-Sankyo, PUMA

Patents: HER2DX (filed), DNADX (filed), TNBCDX (filed)

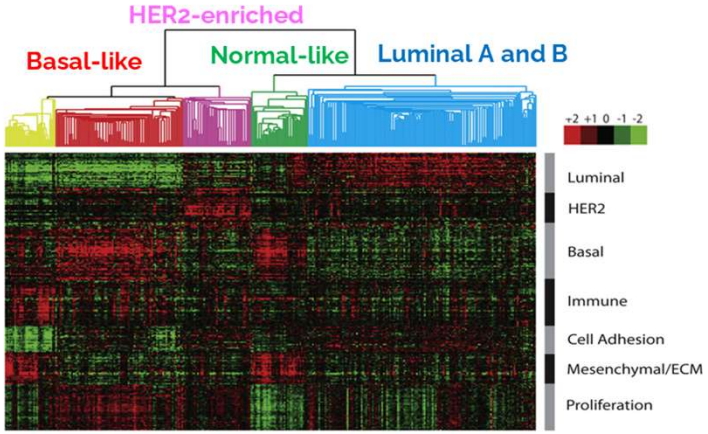
BACKGROUND. BREAST CANCER

- ✓ Breast cancer is a highly heterogeneous disease.
- ✓ Traditionally classified based on the expression of ER, PR and HER2.
- ✓ RNA-based profiling in tumor tissue:
  - ✓ Identification of complex biological processes.
  - ✓ Identification of predictive and prognostic subtypes.
  - ✓ Clinically useful in early-stage breast cancer.
  - ✓ Becoming a promising prognostic and predictive tool in metastatic disease.



Rivenbark et al., Am J Pathol., 2013

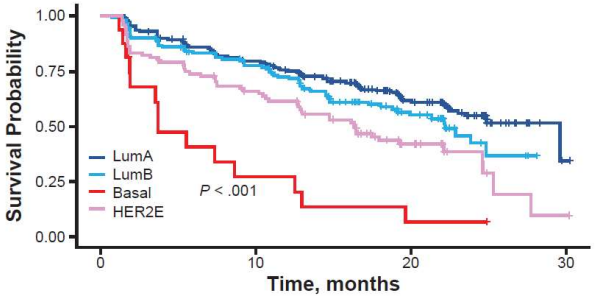
PAM50 molecular subtypes



Prat et al. BCR 2010; Prat & Perou Mol Oncol 2011; Prat et al. Breast 2015

Endocrine therapy + CDK4/6 inhibitors in HR+/HER2- metastatic breast cancer.

	n	Events, n	Median PFS	95% CI
LumA	320	114	29.60	23.03-NA
LumB	154	66	22.21	18.79-NA
Basal	16	14	3.71	1.91-13.0
HER2E	95	56	16.39	12.71-24.6



Prat et al. JCO 2021

Tumor biopsies in the metastatic setting are not always available

- Invasive: difficult/impossible to obtain, potential risks (pain, bleeding…).
- Do not address heterogeneity across metastasic sites.

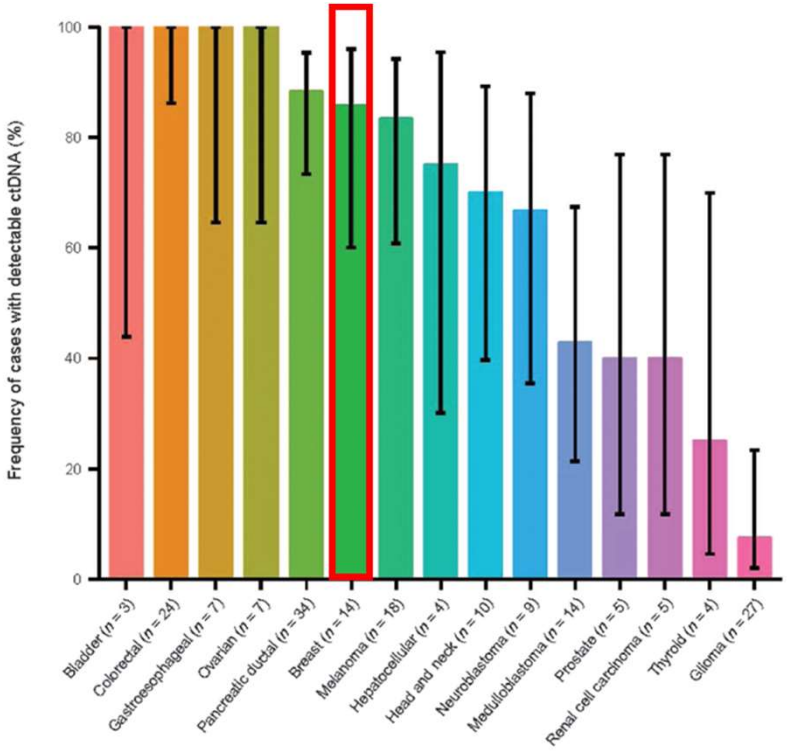
BACKGROUND. LEVERAGING LIQUID BIOPSIES FOR METASTATIC BREAST CANCER

Liquid biopsies are non-invasive

- Option for molecular analysis
- Fast and easy to obtain
- Repeatable (monitorization)
- Capture tumor heterogeneity

Can we track complex biological processes such as those identified by RNA profiling using ctDNA?

✓ ctDNA detected in aprox 80% of patients with metastatic breast cancer



Bettegowda Sci Transl Med. 2014

BACKGROUND. COPY NUMBER-BASED PREDICTORS OF TUMOR PHENOTYPES

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-019-13588-2 OPEN

Genetic determinants of the molecular portraits of epithelial cancers

Youli Xia[1,2,3], Cheng Fan[3], Katherine A. Hoadley[2,3], Joel S. Parker[2,3] & Charles M. Perou[1,2,3,4*]

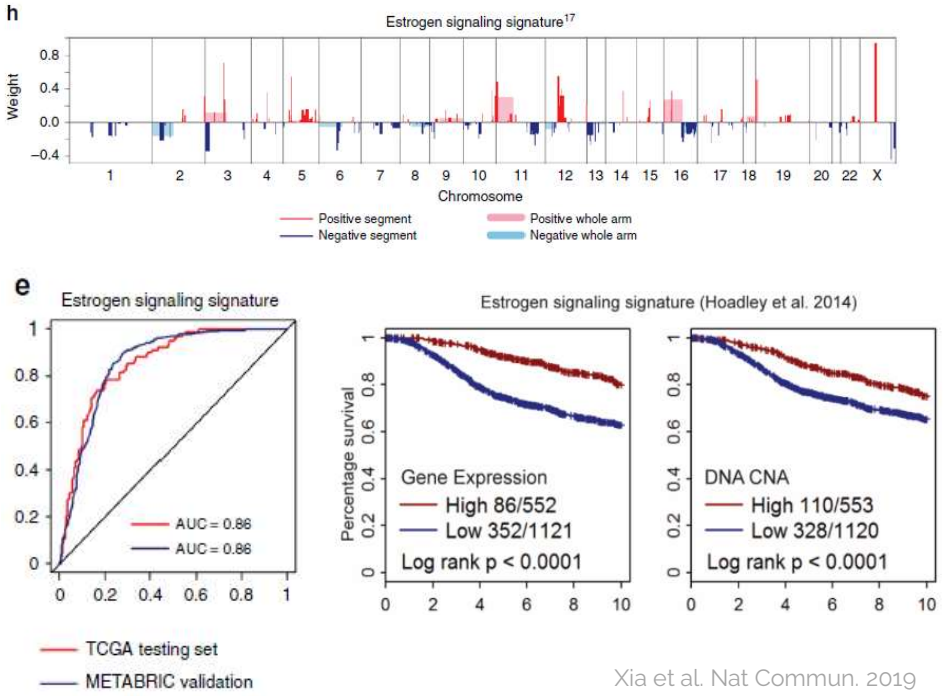
TCGA

Cancer Genome Atlas Network, Nature 2012

DNA copy-number profiles ⟷

- ✓ **Gene expression signatures**
- ✓ **Protein expression**
- ✓ **Mutation**

150 **copy number-based signatures** that tracked a variety of **biological processes** in breast cancer tissue with high accuracy (AUC ROC>0.75)

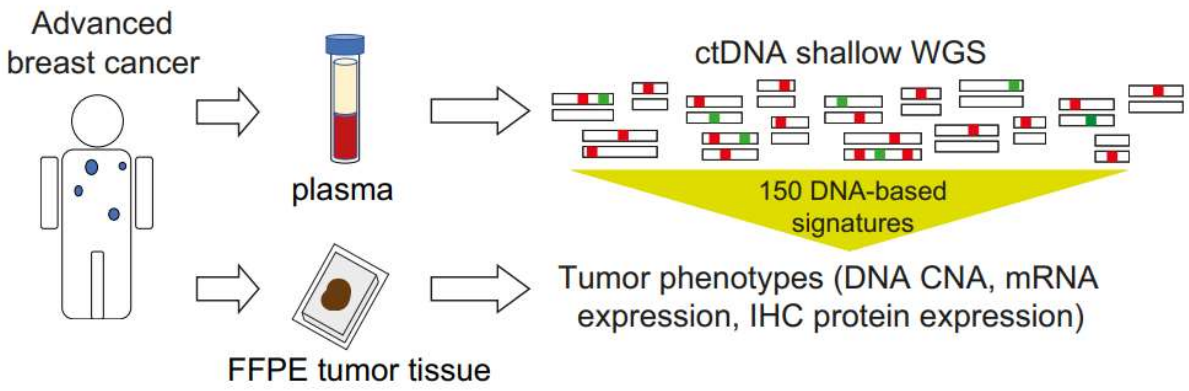


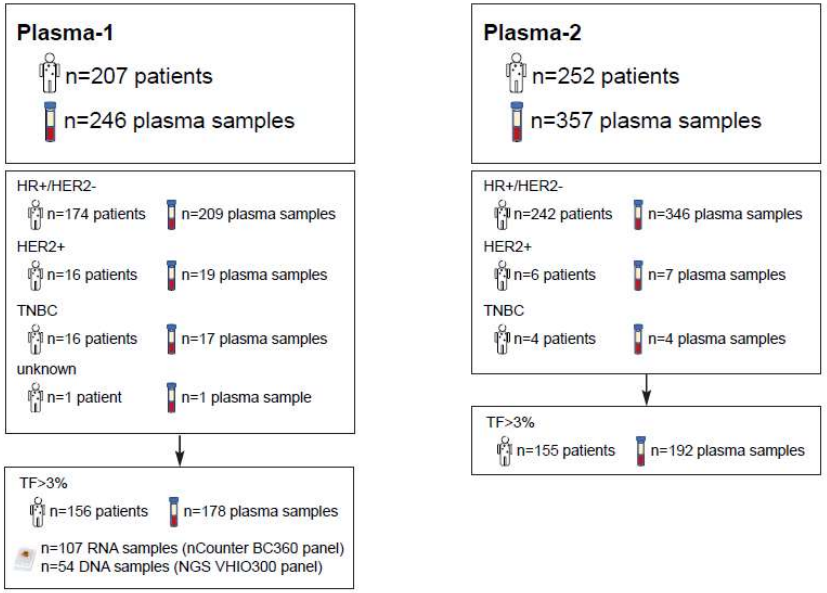
Xia et al. Nat Commun. 2019

We hypothesized that copy number-based signatures:

- ✓ **could be detected reliably in plasma ctDNA**
- ✓ **could be clinically relevant**
- ✓ **could identify subtypes with clinical relevance**

OUR APPROACH





- ✓ ctDNA analyzed using shWGS from 603 plasma samples from 2 cohorts of metastatic breast cancer.
- ✓ DNA sequencing data available for 54 FFPE tumor tissue samples.
- ✓ PAM50 molecular subtype available for 107 FFPE tumor tissue samples.

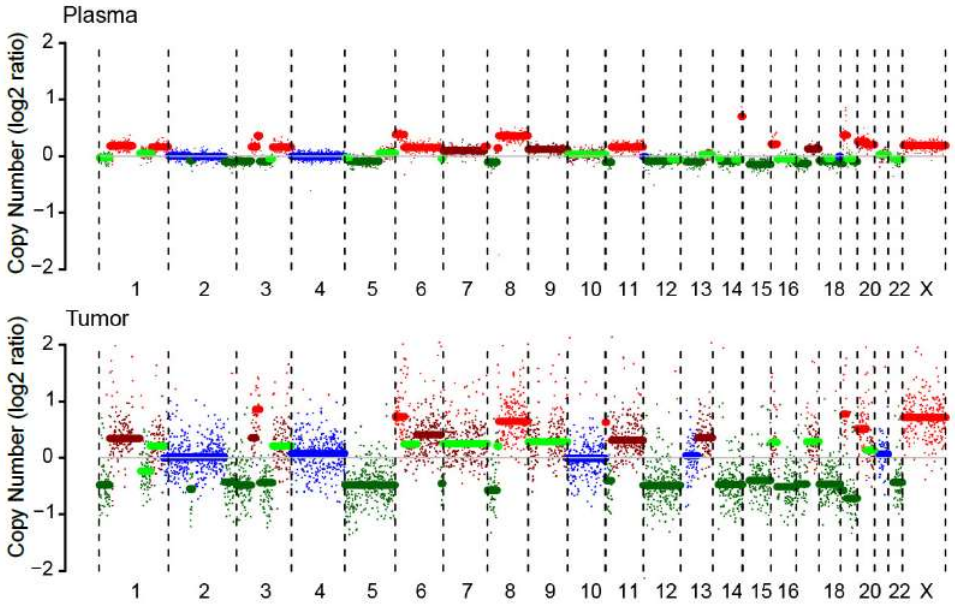
61.4% samples had a tumor fraction (TF)>3%*

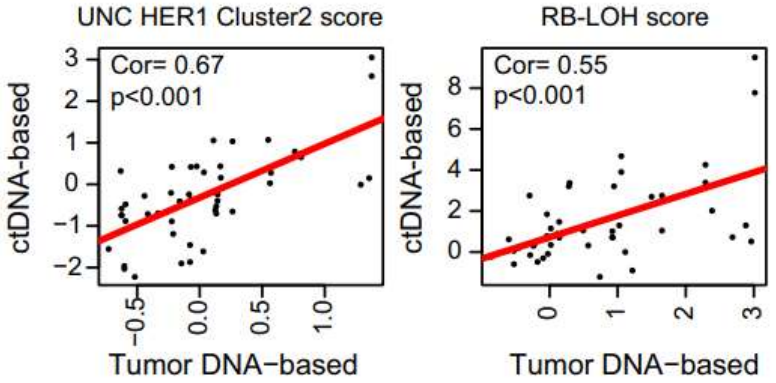
*TF cutoff of 3% by ichorCNA tool for detecting presence of tumor
Adalsteinsson et al. Nat Commun. 2017

Prat, Brasó-Maristany, Martínez-Sáez et al. Nat Commun. 2023

ASSOCIATION BETWEEN CTDNA-BASED AND TUMOR DNA-BASED SIGNATURES ACROSS TIMEPOINTS

Copy-number profiles of a patient with HR+/HER2- metastatic breast cancer

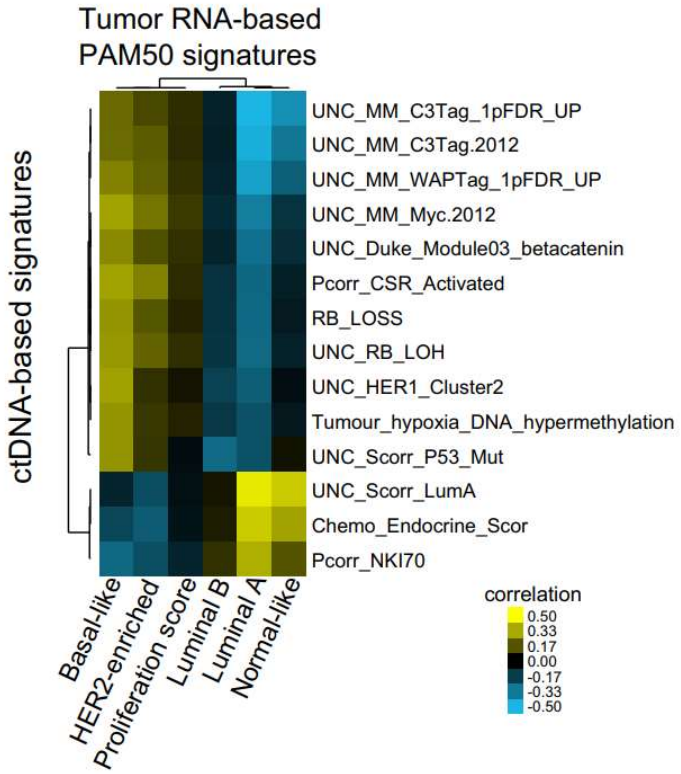


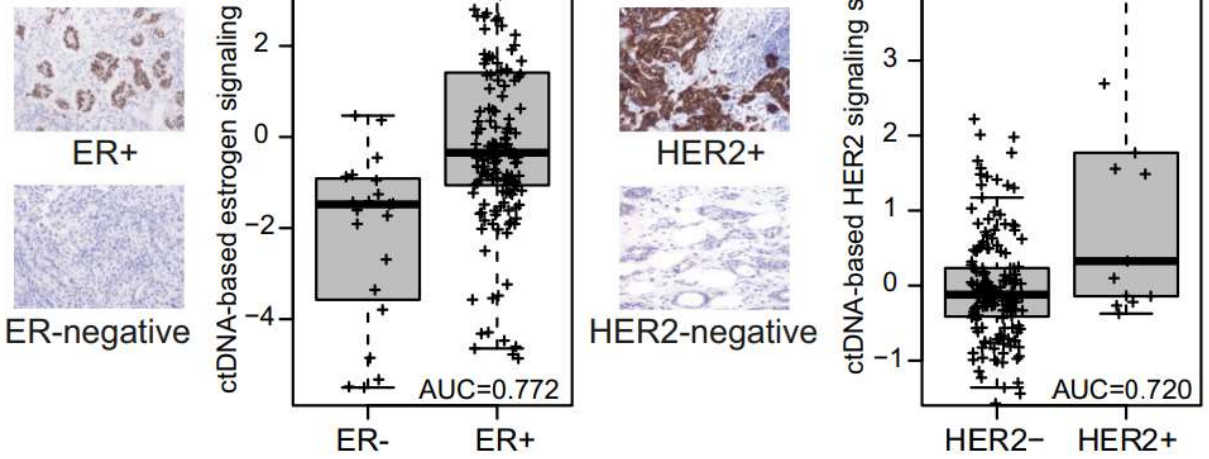


Time between plasma and tumor samples	Signatures with Cor>0.5 p<0.05
All timepoints (n=54)	40 (27%)
≤ 8-weeks (n=27)	**63 (42%)**
>8-weeks (n=27)	29 (19%)

Prat, Brasó-Maristany, Martínez-Sáez et al. Nat Commun. 2023

CTDNA-BASED SIGNATURES TRACK SPECIFIC BREAST CANCER PHENOTYPIC TRAITS SUCH AS PAM50 BIOLOGY, ER AND HER2 STATUS

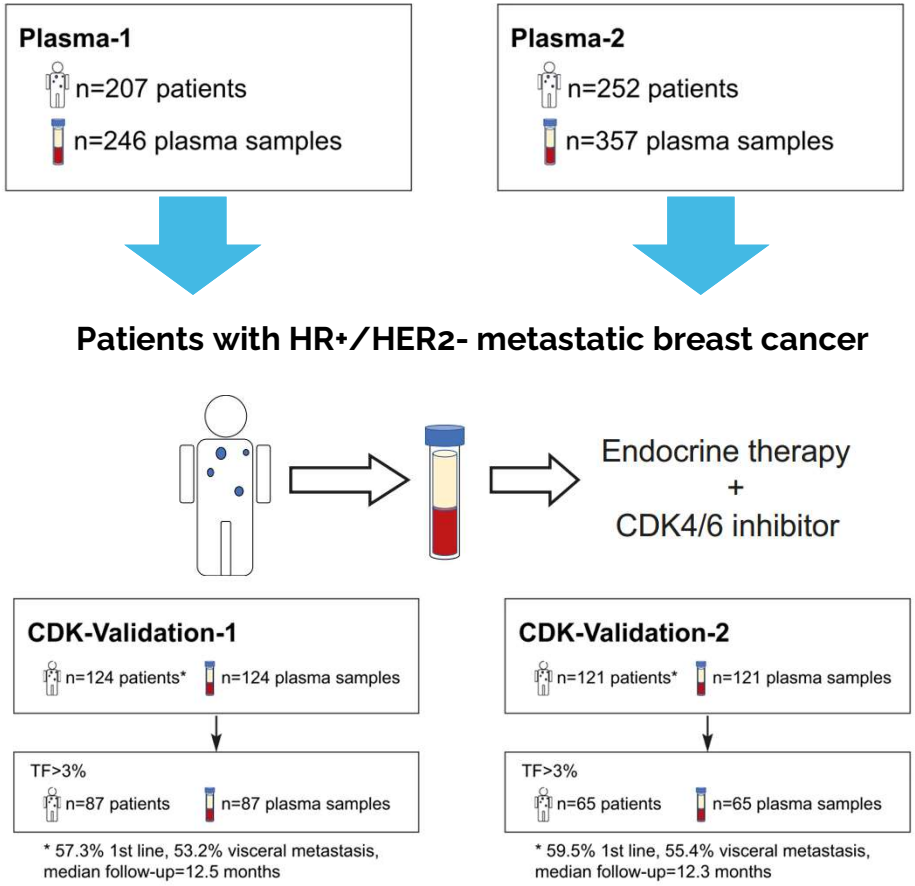


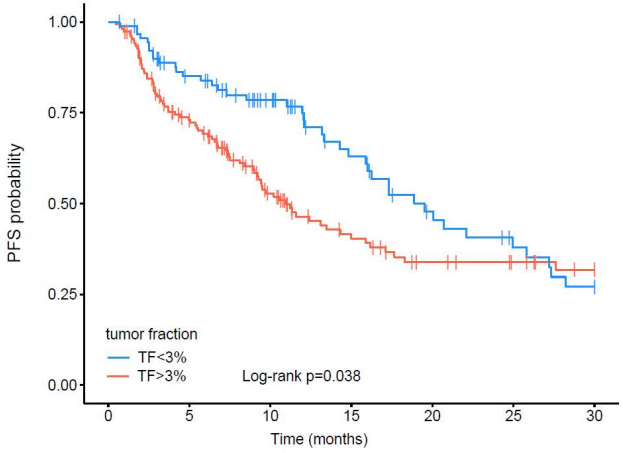


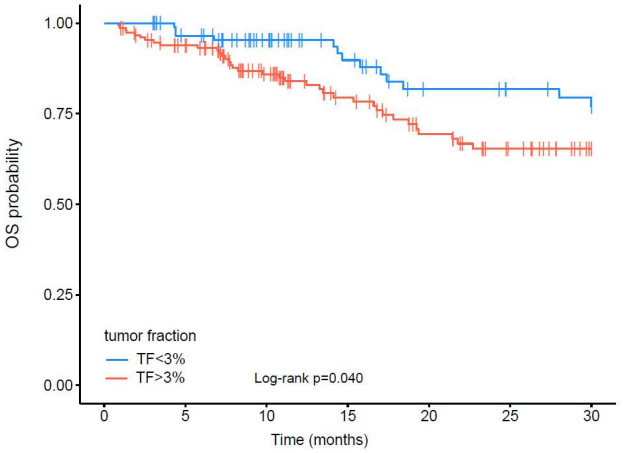
✓ copy number-based signatures can be detected reliably in plasma ctDNA

Prat, Brasó-Maristany, Martínez-Sáez et al. Nat Commun. 2023

PROGNOSTIC CTDNA-BASED SIGNATURES IN METASTATIC HR+/HER2- DISEASE TREATED WITH ENDOCRINE THERAPY + CDK4/6 INHIBITORS







PFS HR (95% CI)= 3.48 (1.55–7.80), p=0.003

OS HR (95% CI)= 11.19 (3.73–33.62), p<0.001

62% samples had a TF>3%

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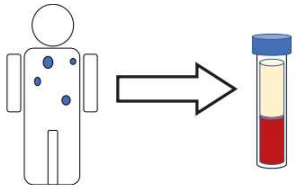
PROGNOSTIC CTDNA-BASED SIGNATURES IN METASTATIC HR+/HER2- DISEASE TREATED WITH ENDOCRINE THERAPY + CDK4/6 INHIBITORS

Plasma-1
n=207 patients
n=246 plasma samples

Plasma-2
n=252 patients
n=357 plasma samples

Patients with HR+/HER2- metastatic breast cancer



Endocrine therapy
+
CDK4/6 inhibitor

CDK-Validation-1
n=124 patients* n=124 plasma samples

TF>3%
n=87 patients n=87 plasma samples

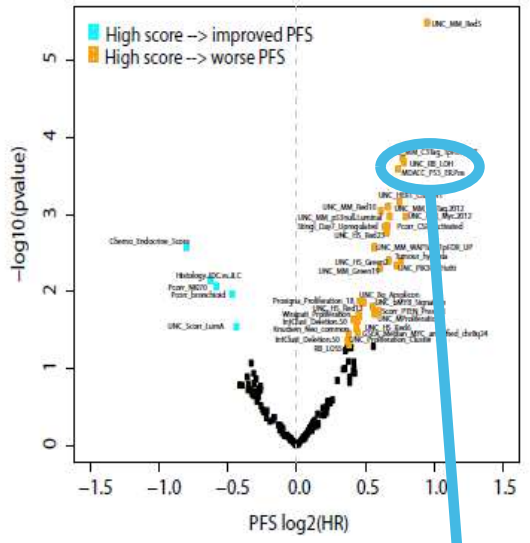
* 57.3% 1st line, 53.2% visceral metastasis, median follow-up=12.5 months

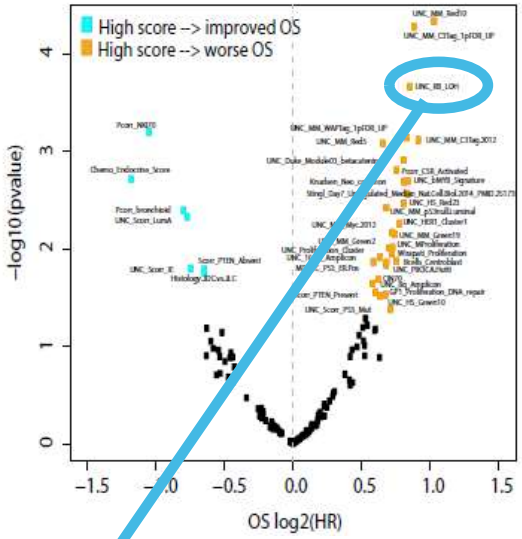
CDK-Validation-2
n=121 patients* n=121 plasma samples

TF>3%
n=65 patients n=65 plasma samples

* 59.5% 1st line, 55.4% visceral metastasis, median follow-up=12.3 months

27 ctDNA-based signatures were significantly associated with PFS and OS





RB-LOH signature

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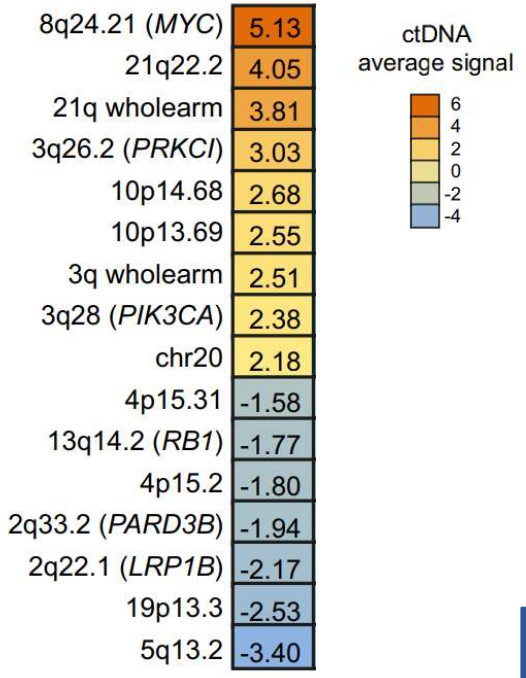
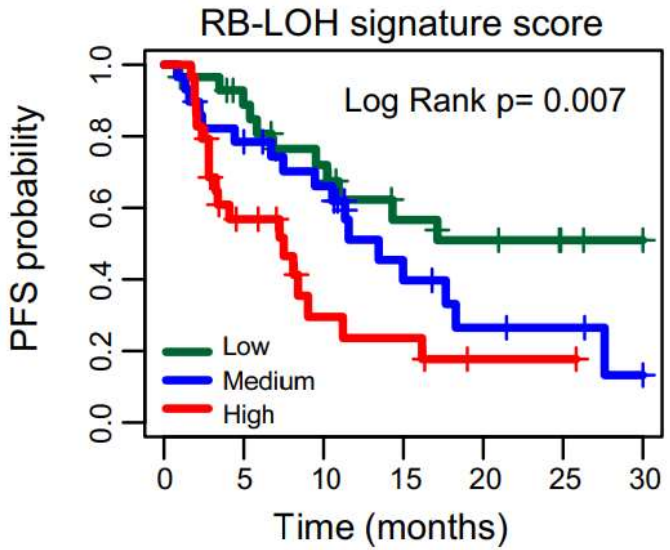
Prat, Brasó-Maristany, Martínez-Sáez et al. Nat Commun. 2023

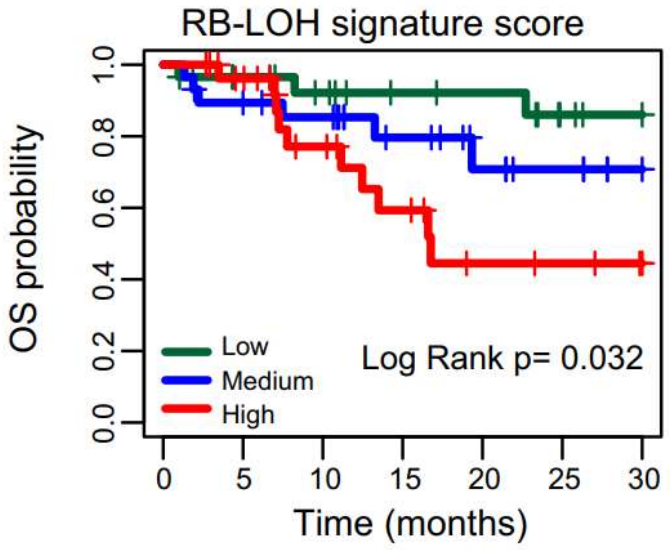
THE RB-LOH SIGNATURE CAPTURES LOSS OF RB AND IS ASSOCIATED WITH RESPONSE TO ENDOCRINE THERAPY + CDK4/6 INHIBITOR

Features of the RB-LOH signature





PFS HR (95% CI)=1.72 (1.29-2.30), p<0.001



OS HR (95% CI)=1.81 (1.32-2.47), p<0.001

✓ **copy number-based signatures detected in plasma are clinically relevant**

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Prat, Brasó-Maristany, Martínez-Sáez et al. Nat Commun. 2023

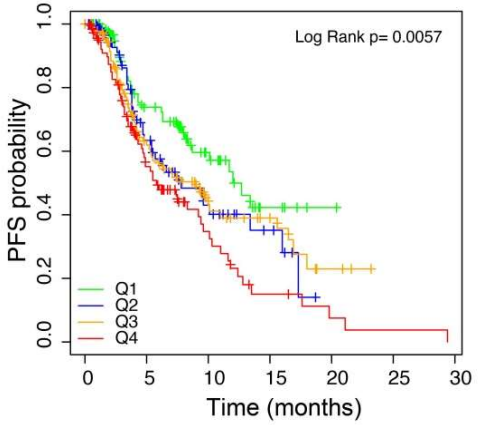
INDEPENDENT VALIDATION OF THE RB-LOH SIGNATURE IN A TUMOR TISSUE COHORT

MSKCC – 381 patients with HR+/HER2- metastatic breast cancer treated with ET+CDK4/6i

Razavi et al., Cancer Cell. 2018

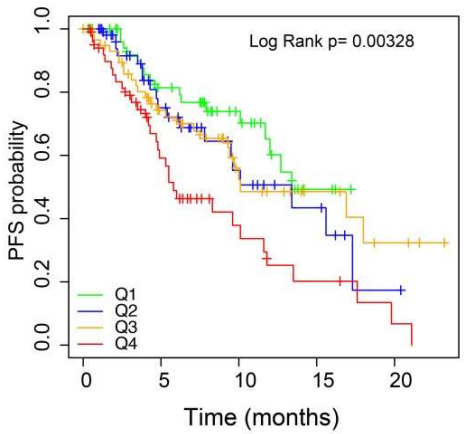
Time between biopsy and treatment initiation

All (n=381)



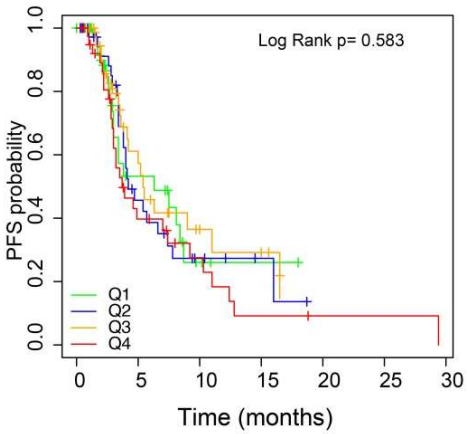
PFS HR (95% CI)= 1.41 (1.21–1.64), p<0.001

≤ 1 year (n=223)



PFS HR (95% CI)= 1.61 (1.32–1.96), p < 0.001

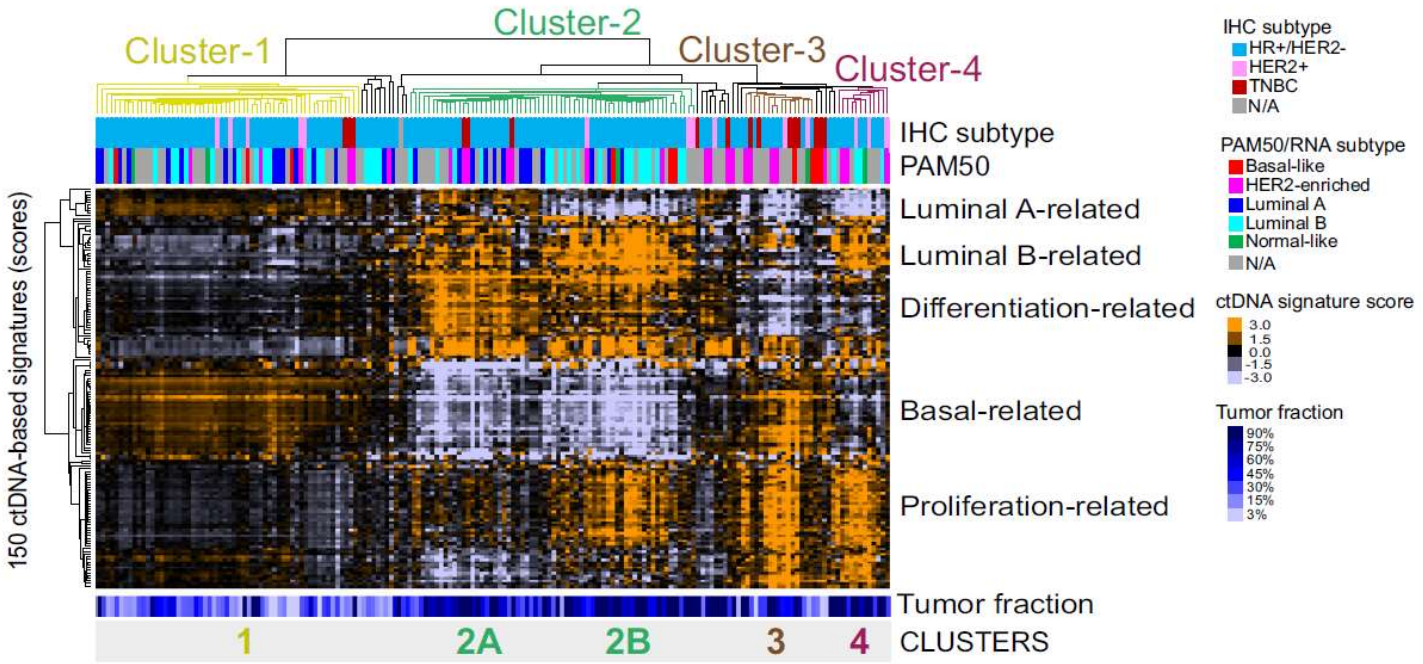
> 1 year (n=158)



PFS HR (95% CI)= 1.23 (0.97–1.56), p=0.083

Prat, Brasó-Maristany, Martínez-Sáez et al. Nat Commun. 2023

UNSUPERVISED ANALYSES IDENTIFIED NEW COPY NUMBER-BASED SUBTYPES IN PLASMA

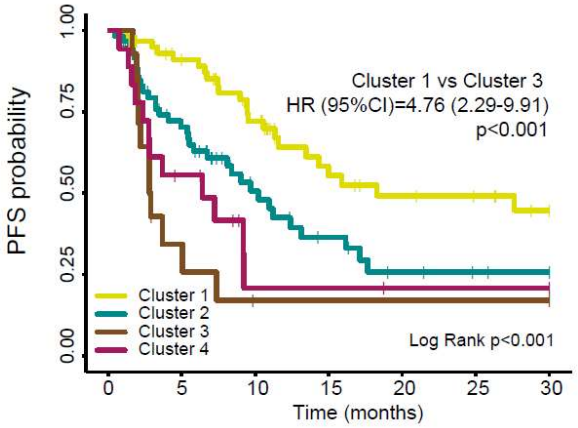


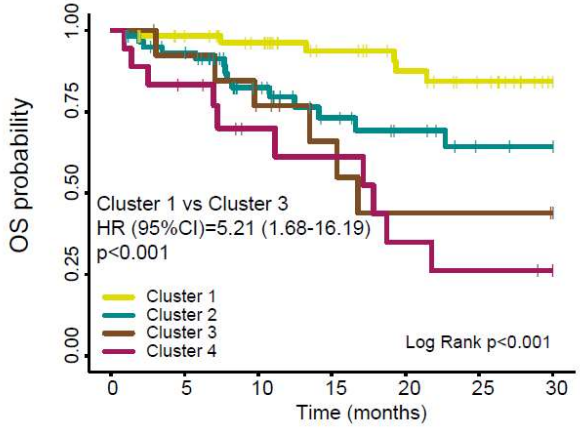
- ✓ **Cluster 1: luminal A-like**
  - ✓ high luminal A-related signatures
  - ✓ low proliferation and luminal B-related signatures
  - ✓ lower TF
- ✓ **Cluster 2: luminal B-like**
  - ✓ high differentiation and luminal B-related signatures
  - ✓ low basal-like related biology
- ✓ **Cluster 3: non-luminal**
  - ✓ high proliferation and basal-like-related signatures
  - ✓ low differentiation and luminal A-related signatures
- ✓ **Cluster 4: non-luminal**
  - ✓ high proliferation-related signatures
  - ✓ low differentiation and luminal A and basal-like-related signatures

Prat, Brasó-Maristany, Martínez-Sáez et al. Nat Commun. 2023

THE NEW COPY NUMBER-BASED SUBTYPES IDENTIFIED IN PLASMA ARE PROGNOSTIC

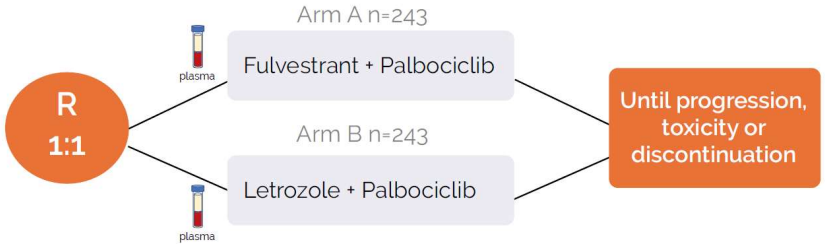
Patients with HR+/HER2- metastatic breast cancer treated with ET+CDK4/6i (n=152)

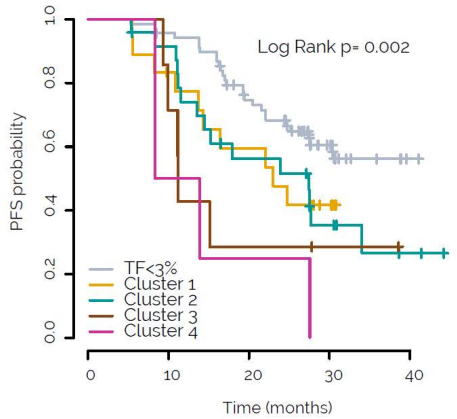




PARSIFAL trial

Llombart-Cussac et al. JAMA Oncol. 2021





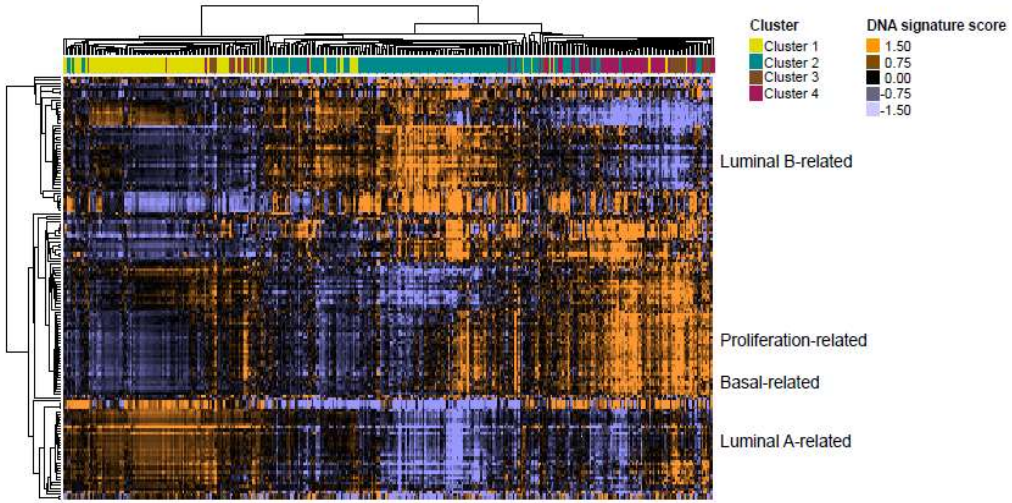
✓ **copy number-based signatures detected in plasma identify clinically relevant subtypes**

Prat, Brasó-Maristany, Martínez-Sáez et al. Nat Commun. 2023; Brasó-Maristany et al., SABCS 2023

INDEPENDENT VALIDATION OF COPY NUMBER-BASED SUBTYPES IN TUMOR TISSUE

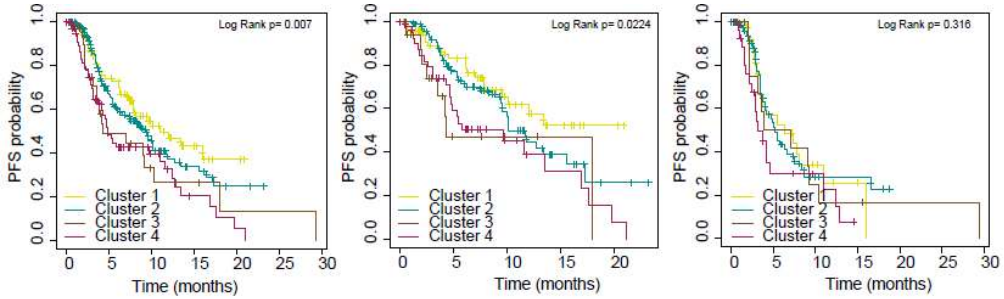
MSKCC

Razavi et al., Cancer Cell. 2018



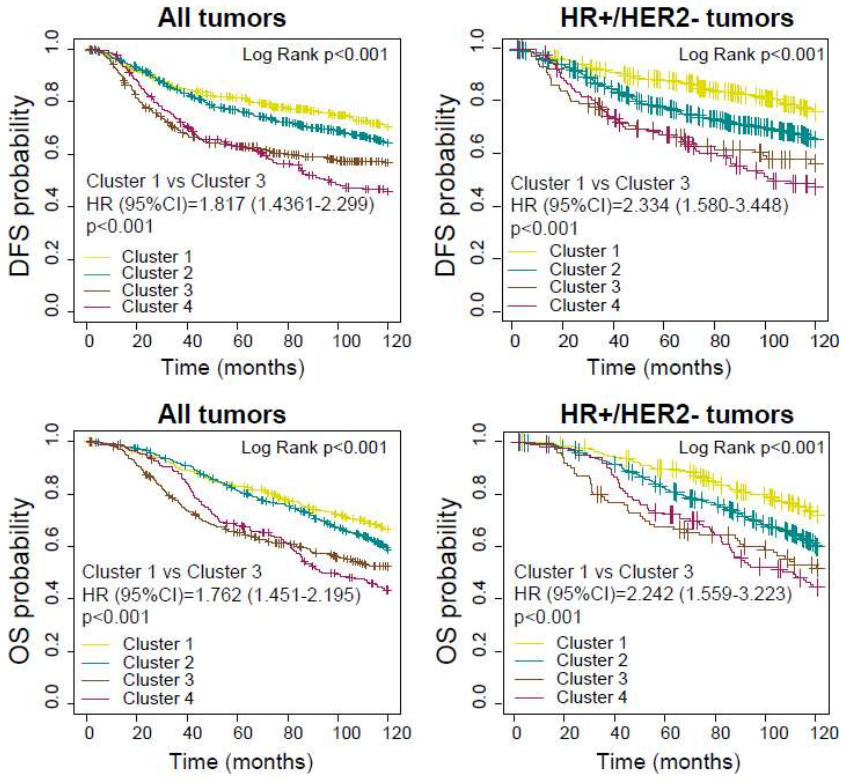
Time between biopsy and treatment initiation

All timepoints (n=381) | ≤ 1 year (n=223) | > 1 year (n=158)



METABRIC

Curtis et al., Nature 2012



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Prat, Brasó-Maristany, Martínez-Sáez et al. Nat Commun. 2023

CONCLUSIONS

- ✓ DNA copy number-based phenotypic signatures capture relevant biological and clinical information in plasma and tumor tissue.
- ✓ The RB-LOH signature and 4 new copy number-based subtypes measured in tumor tissue or plasma might help identify patients with poor survival outcomes following endocrine therapy plus CDK4/6 inhibitors.
- ✓ Our approach opens new opportunities for the discovery of multi-feature genomic predictors coming from DNA-based data.

nature communications

Article

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Circulating tumor DNA reveals complex biological features with clinical relevance in metastatic breast cancer

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Check for updates

Aleix Prat[1,2,3,4,5,6,16] ✉, Fara Brasó-Maristany[1,16], Olga Martínez-Sáez[1,3,4,16], Esther Sanfeliu[1,7], Youli Xia[2], Meritxell Bellet[6,8,9], Patricia Galván[1], Débora Martínez[1], Tomás Pascual[1,3,6,10], Mercedes Marín-Aguilera[2], Anna Rodríguez[1,3], Nuria Chic[1,3], Barbara Adamo[1,3,4], Laia Paré[2], Maria Vidal[1,3,4], Mireia Margelí[11], Ester Ballana[12], Marina Gómez-Rey[13], Mafalda Oliveira[6,8,9], Eudald Felip[11,12], Judit Matito[13], Rodrigo Sánchez-Bayona[14], Anna Suñol[8,9], Cristina Saura[6,8,9], Eva Ciruelos[14], Pablo Tolosa[14], Montserrat Muñoz[1,3,4,6], Blanca González-Farré[1,7], Patricia Villagrasa[2], Joel S. Parker[15], Charles M. Perou[15] & Ana Vivancos[13]

REVEAL GENOMICS

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- ✓ Dr. Ana Vivancos lab
- ✓ Funders

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Translational genomics and targeted therapies in solid tumors

European Commission

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AGAUR Agència de Gestió d'Ajuts Universitaris i de Recerca

asociación española contra el cáncer

Cris contra el cáncer

fundación fero Investigando por un futuro sin cáncer

BCRF Breast Cancer Research Foundation

Fundació La Marató de TV3

CMM Cáncer de Mama Metastásico Asociación

SEOM Sociedad Española de Oncología Médica

REVEAL GENOMICS

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IX Simposio · Symposium | 2024 Biopsia Líquida · Liquid Biopsy
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