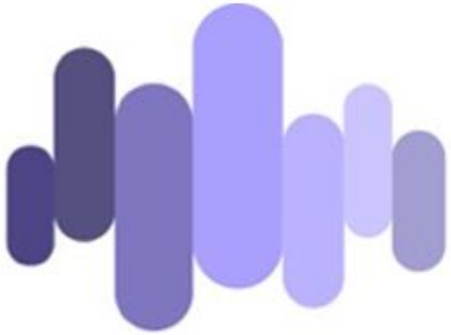


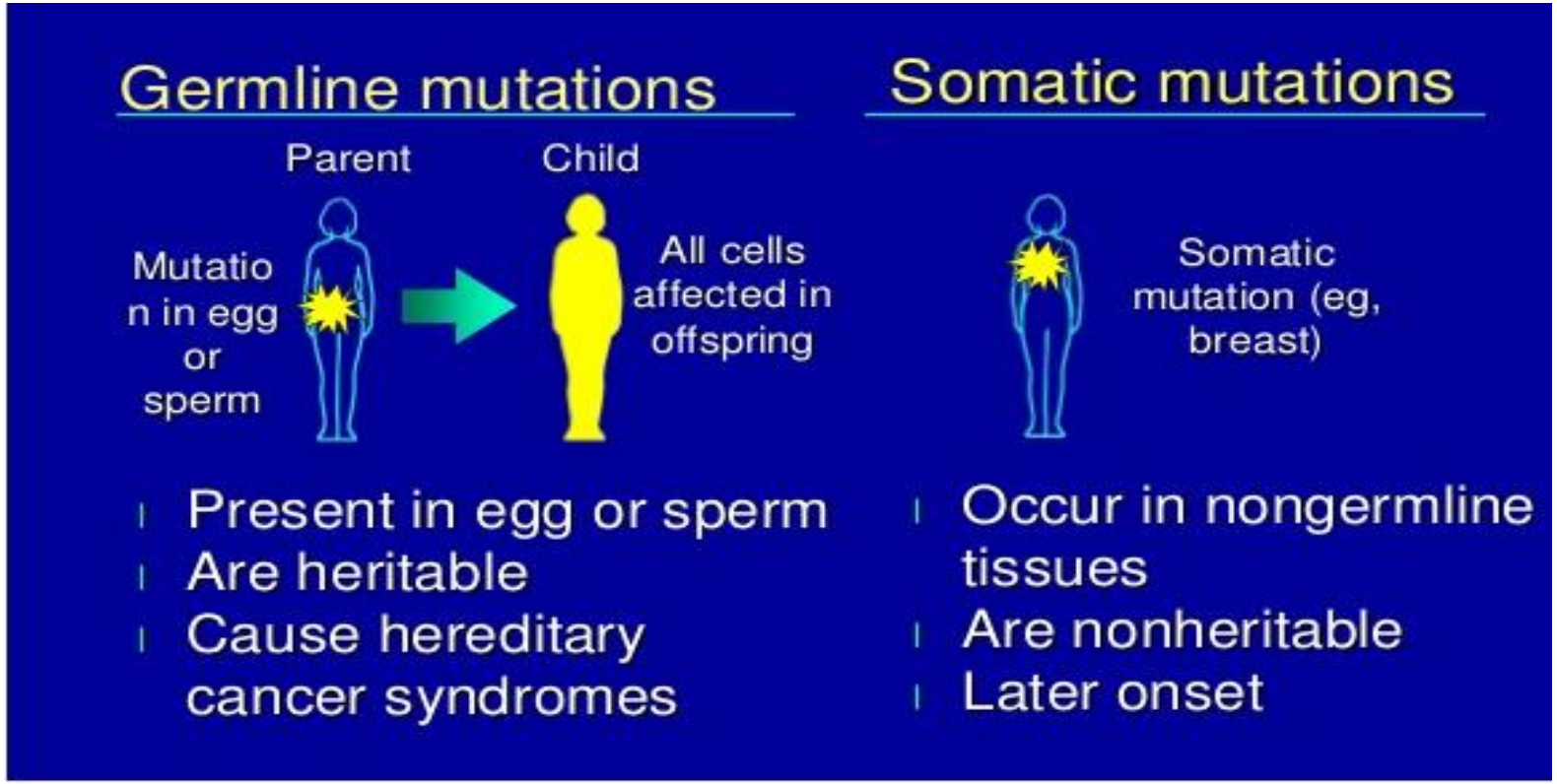
Héritas

Medicina de precisión

CIBIC + INDEAR

Héritas
Medicina de precisión
CIBIC + INDEAR

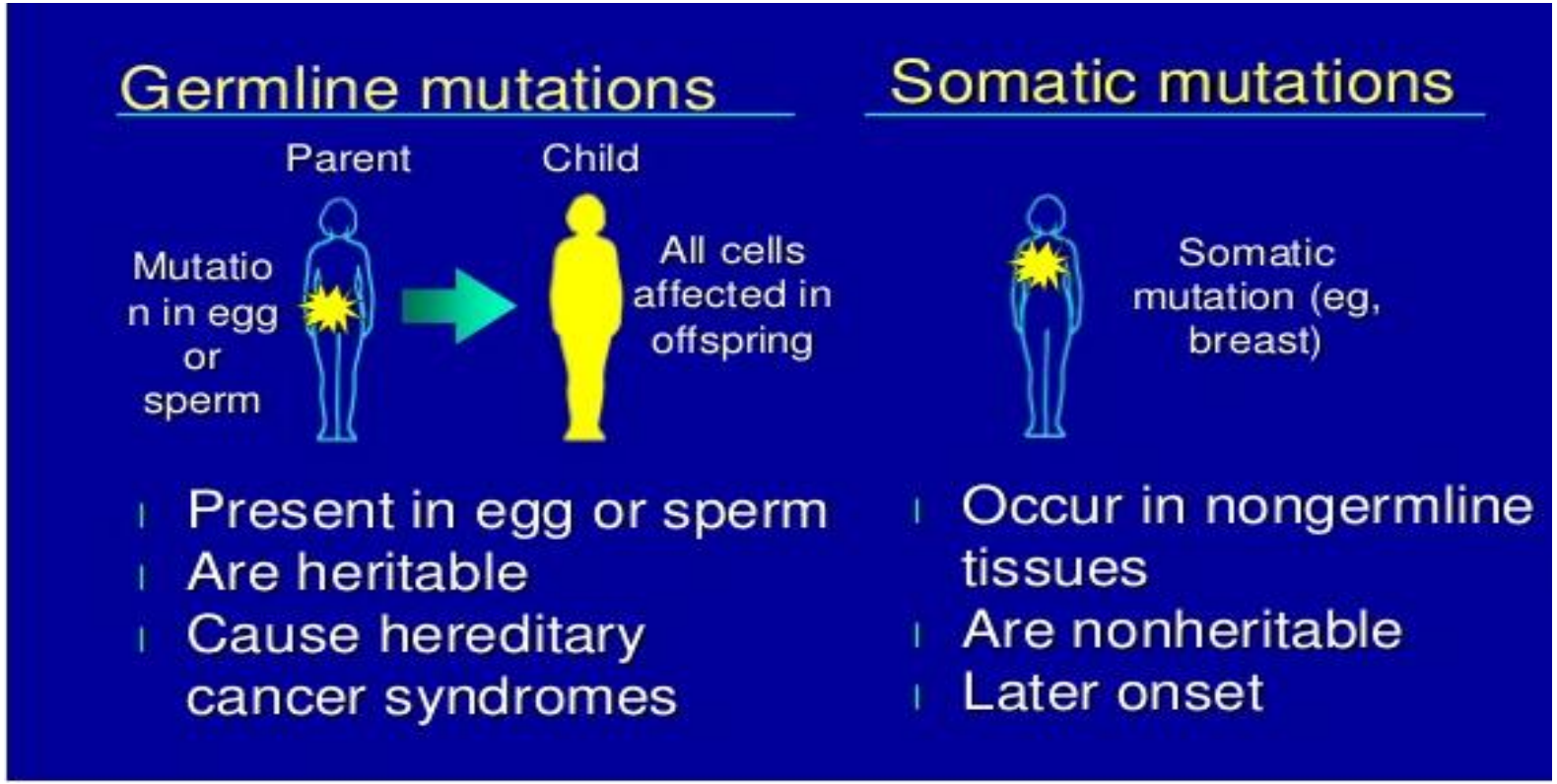
Mutaciones Germinales vs Somáticas



Mutaciones Germinales vs Somáticas

Frecuencias alélicas
50% a 100%

Datos



Frecuencias alélicas
20% a 0.1%

Datos

Héritas
Medicina de precisión
CIBIC + INDEAR

Cáncer Somático
Cómo llenar un estadio

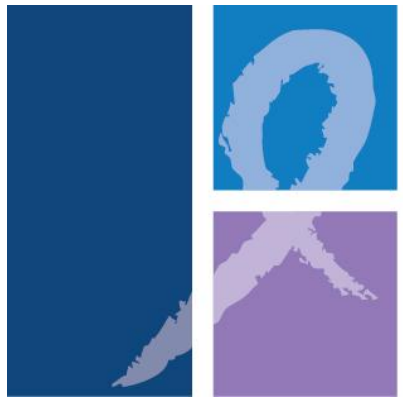
Cáncer Hereditario
Cómo llenar un bar

Big Data

¿Cuánta información genómica hace falta generar?

Héritas
Medicina de precisión
CIBIC + INDEAR

Introduction



PRECISION℠ ONCOLOGY

Biomarkers are helping personalize cancer care…

Different People's Tumours Have Different Biomarkers

Biomarkers commonly found in non-small cell lung cancer

¿La Oncología de precisión beneficia al paciente?

Has retwitteado

Tori Tomalia @lil_lytnin · 20h

I recently passed 5 yr mark w widely metastatic NSCLC. Extensive spread thru both lungs, bones, liver, brain. Today I take pills 1x/day to control the disease. I can't even begin to explain what a game changer targeted medicine and researchers behind it have been to me. #LCSM

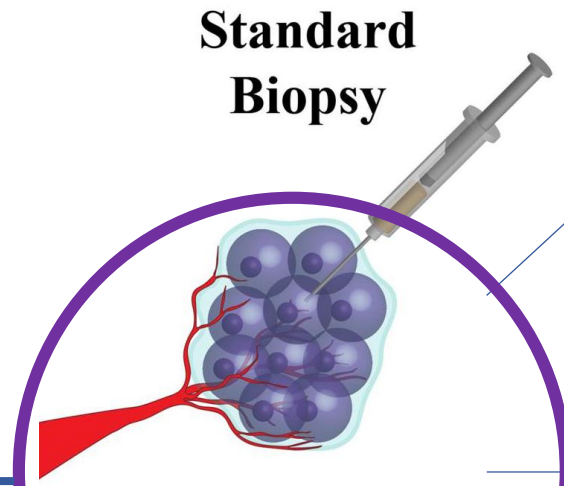
Héritas
Medicina de precisión
CIBIC + INDEAR

A todo paciente de Cancer se le debería ensayar el perfil tumoral de su ADN para acelerar diagnóstico y salvar más vidas

Sally Davis
2017
Directora Médica
Servicio Nacional de Salud (NHS), Inglaterra

2018

Why NGS for tumour profiling?



PCR
- COBAS/ddPCR
- SNVs, INDELs

EGFR 35%

IHQ
- Biomarkers
- Amplif

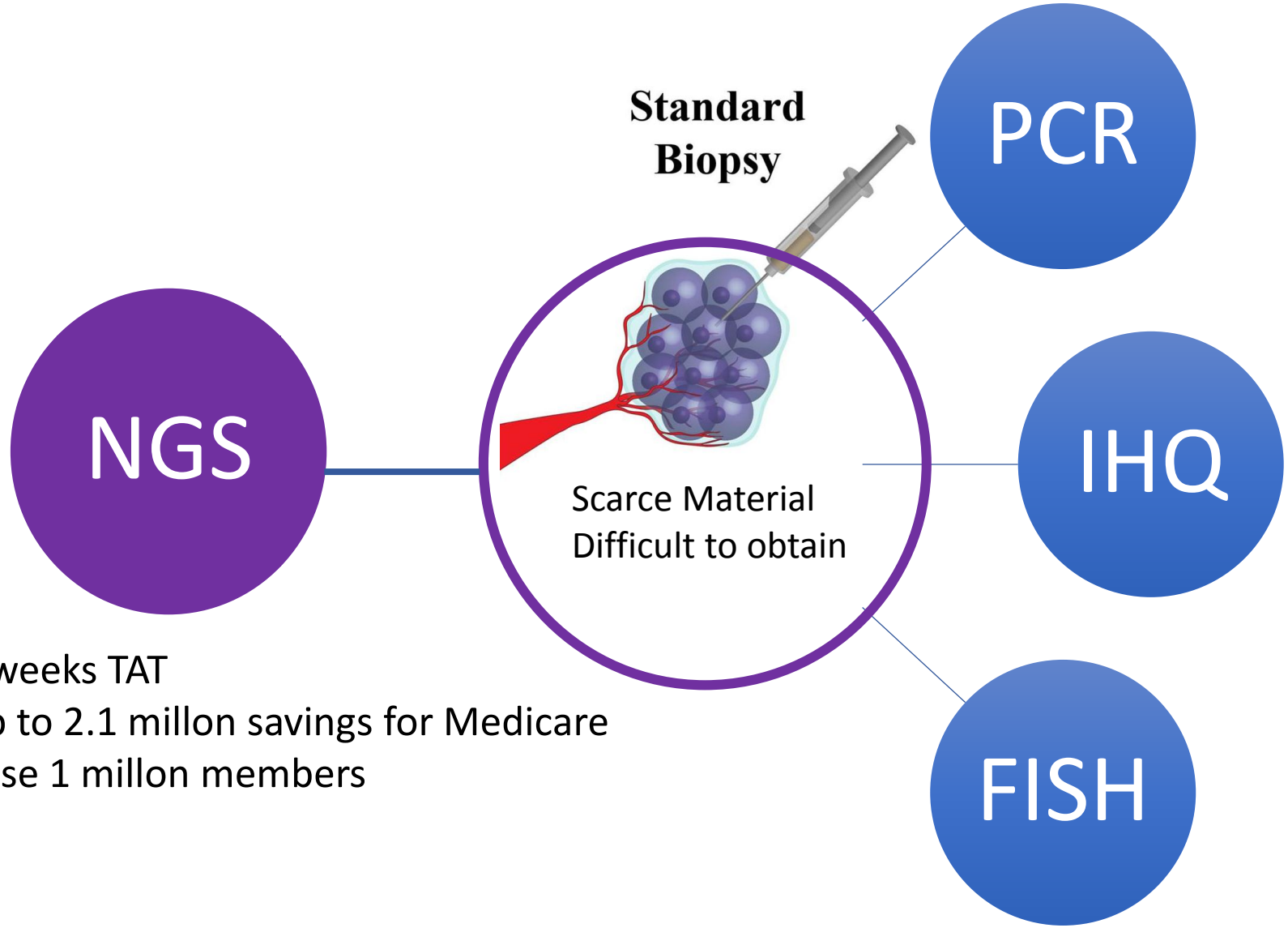
FISH
- Fusions
- Amplif

RET 1%
ROS 1%
ALK 5%

MET 3%
ERBB2 x%

NGS
- SNVs, INDELs
- FUSIONS
- Amplifications
- TMB
- MSI
- Tens to hundreds of genes

Why NGS for tumour profiling?



- 4-5 weeks TAT

- 2 weeks TAT
- Up to 2.1 millon savings for Medicare
- Base 1 millon members

ASCO May 16, 2018

Héritas
Medicina de precisión
CIBIC + INDEAR

Introduction

Tumor genomic profiling challenges

The cost of molecular-guided therapy in oncology: a prospective cost study alongside the MOSCATO trial

Arnaud Pagès, PharmD, MSc[1], Stéphanie Foulon, MD, MSc[1,2], Zhaomin Zou, PhD[1,2], Ludovic Lacroix, PharmD, PhD[3,4,5], François Lemare, PharmD, PhD[6,7], Thierry de Baère, MD[4,8], Christophe Massard, MD, PhD[9], Jean-Charles Soria, MD, PhD[4,9] and Julia Bonastre, PhD[1,2]

Tumor Profiling

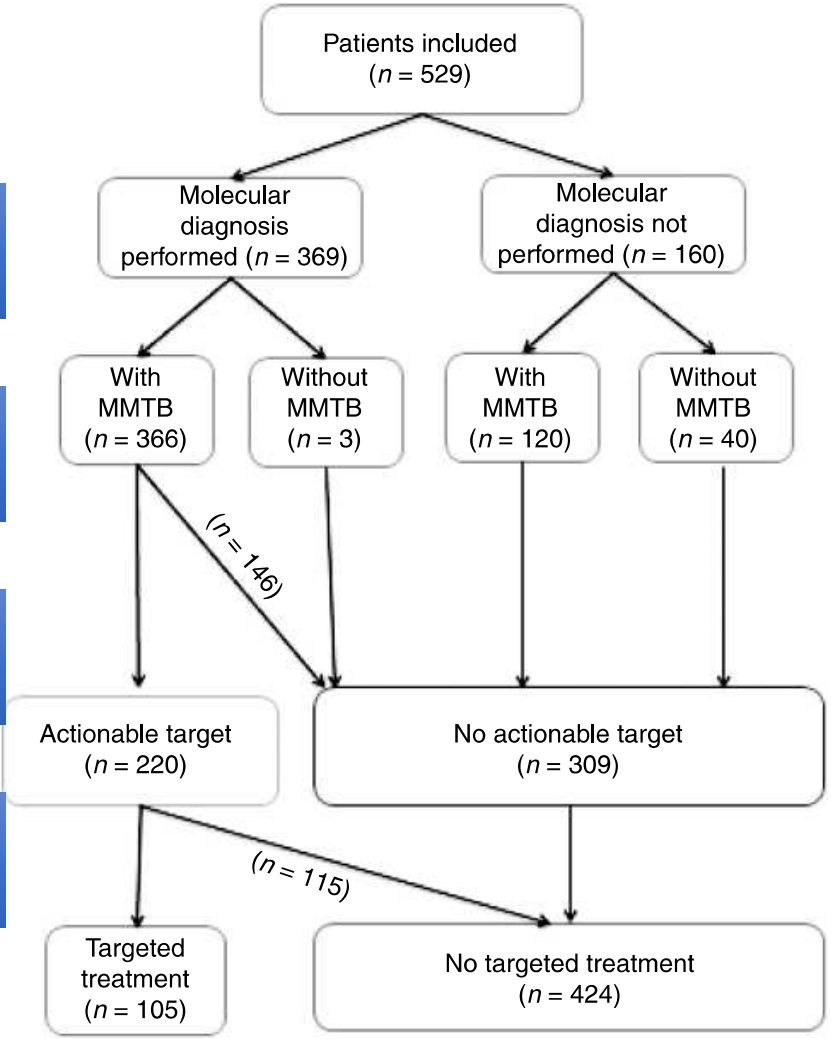
6% del costo total

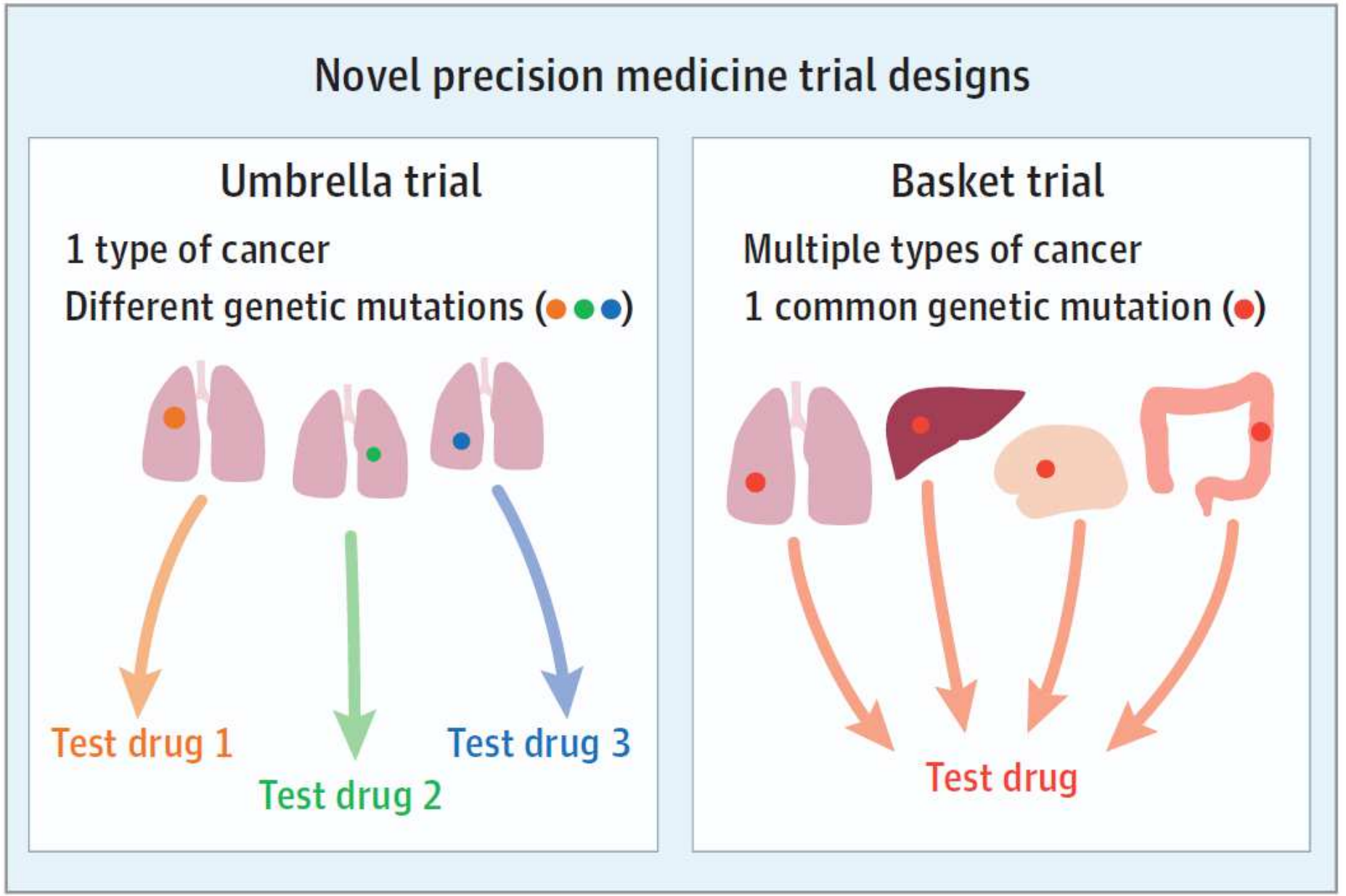
54% drogas

35% hospitalizaciones

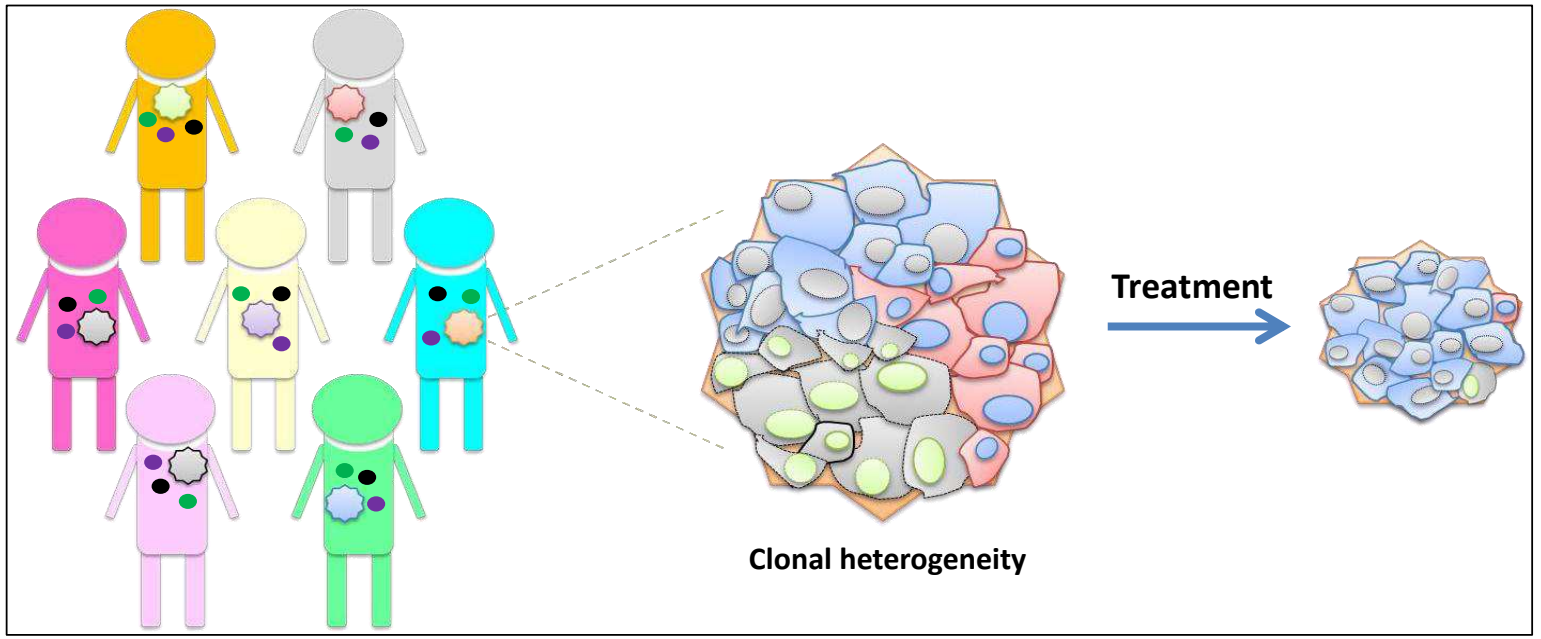
5% otros

- 1 de cada 5 recibió terapia dirigida (40% no se puedo ensayar)
- 33% de beneficio en Sobrevida
- 62% controlo su enfermedad
- El 60% tenia un target accionable off-label




Novel precision medicine trial designs
Umbrella trial
1 type of cancer
Different genetic mutations (●●●)
Test drug 1
Test drug 2
Test drug 3
Basket trial
Multiple types of cancer
1 common genetic mutation (●)
Test drug

The issue with tissue: heterogeneity



9 biopsias del mismo tumor
Solo compartieron el 39% de las mutaciones

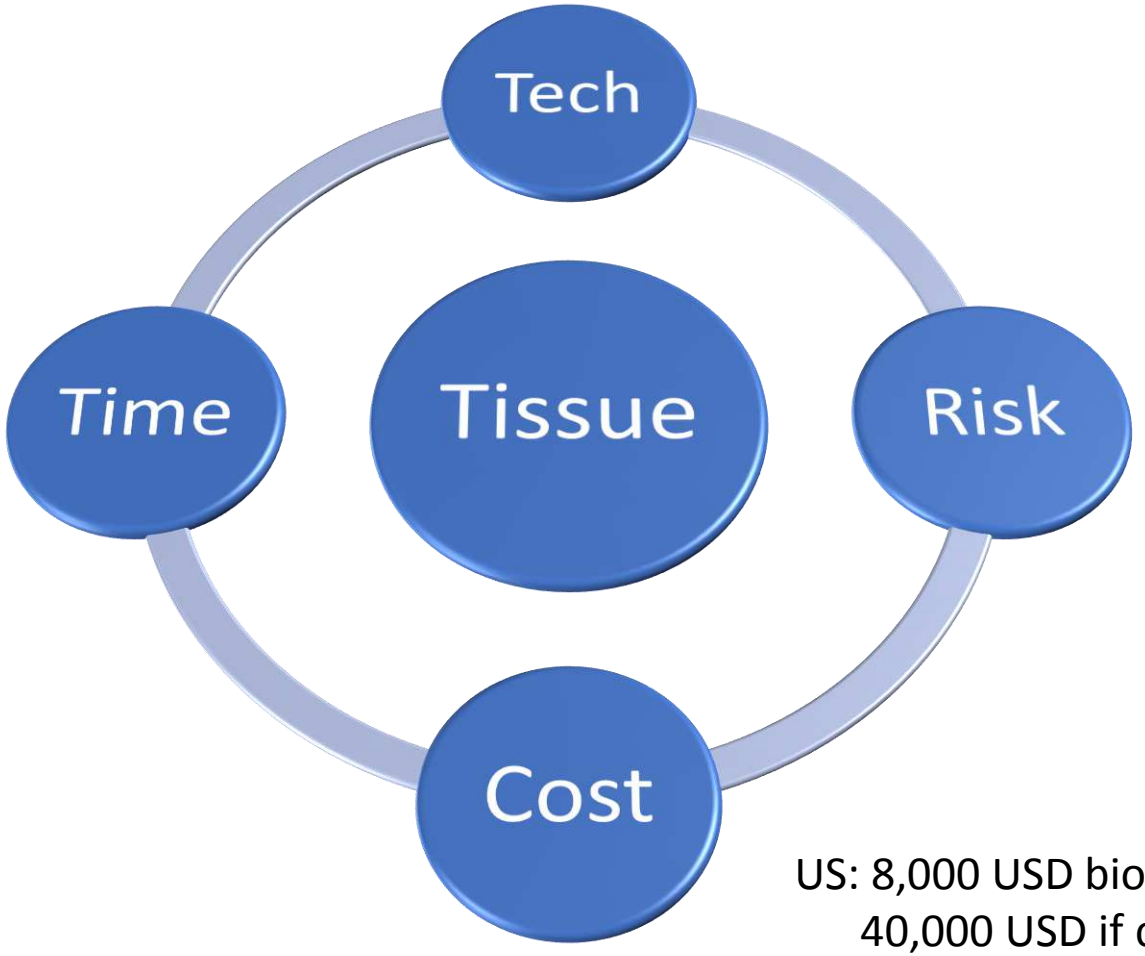
Inter-tumor heterogeneity

Intra-tumor heterogeneity

Courtesy: Andrew Nixon, PhD

Tissue vs ctDNA

Heterogeneity

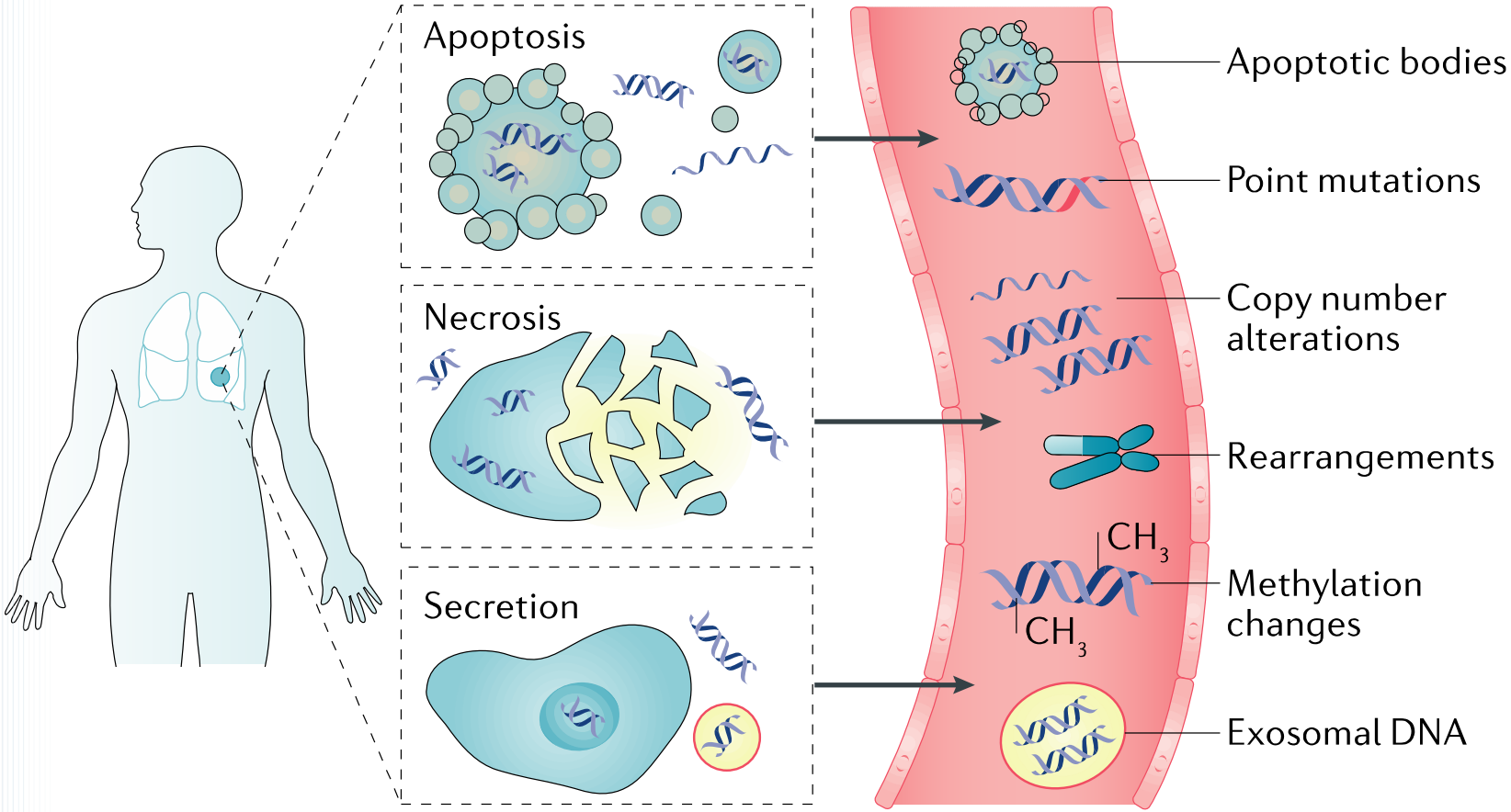


3 weeks or more

19% complication rate (lung)

US: 8,000 USD biopsy
40,000 USD if complication

ctDNA definition

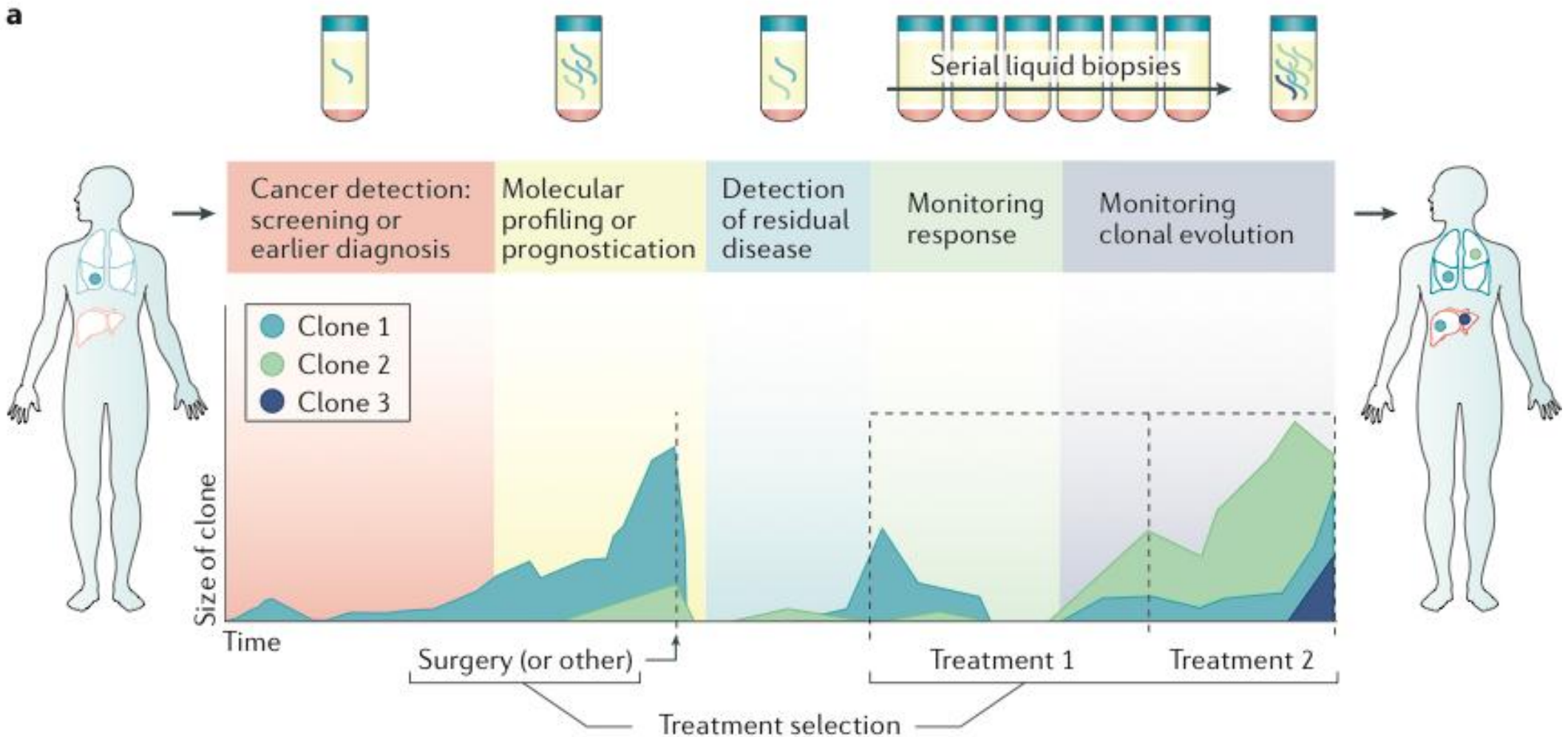


ctDNA vida media:
16 min a 2.5hs
Real-time Snapshot

ctDNA definition

- **Diagnóstico**
- **Pronóstico**
- **Predicción**

6 weeks earlier than CT scan



Héritas
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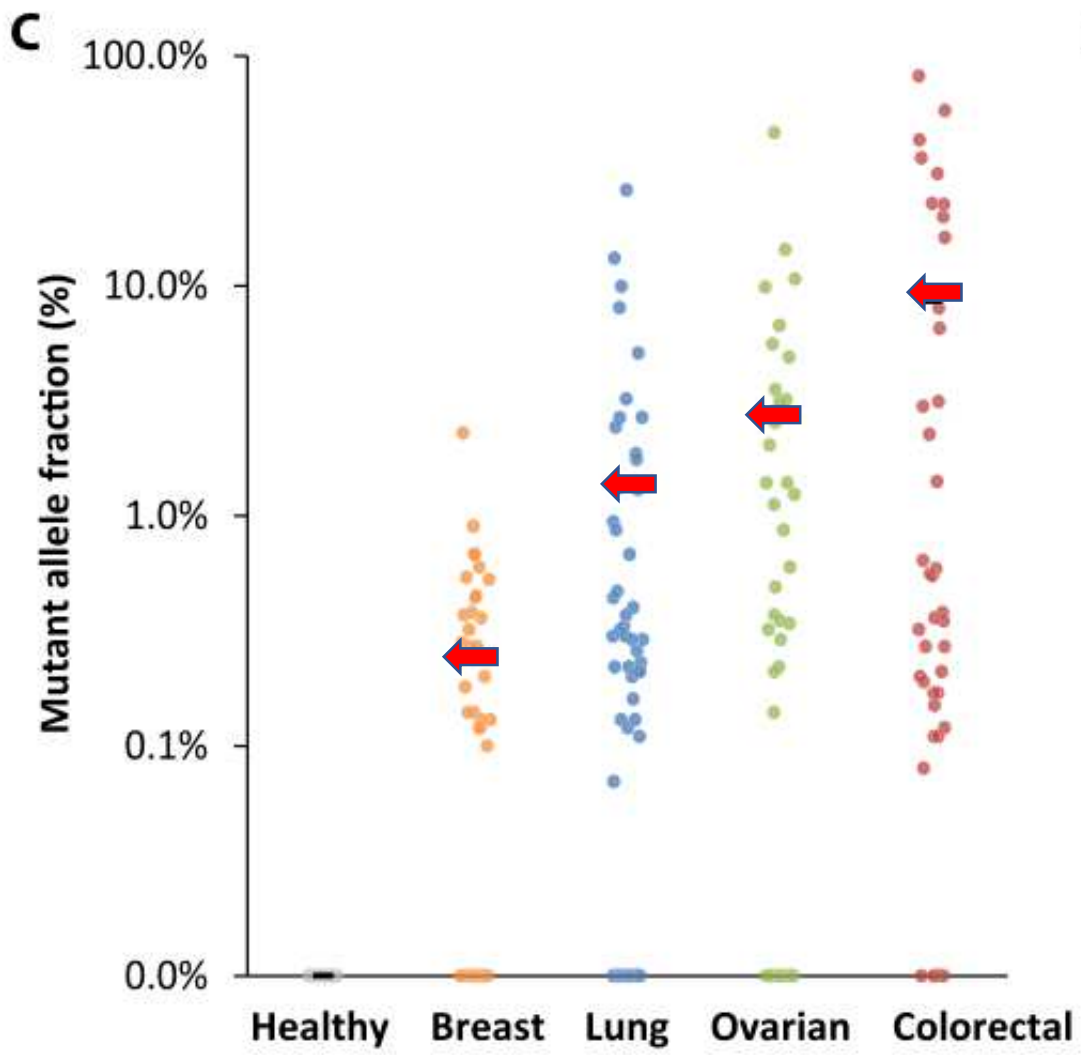
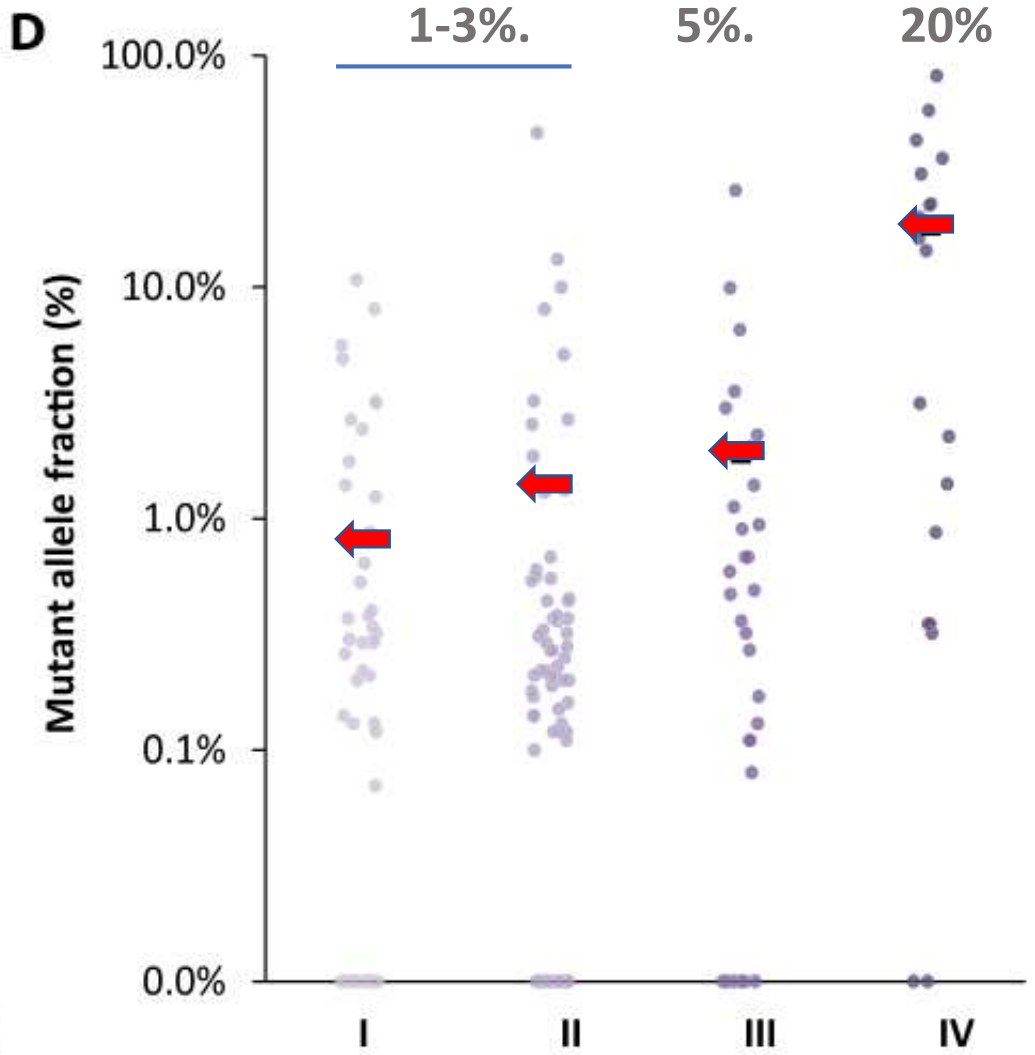
ctDNA Challenges

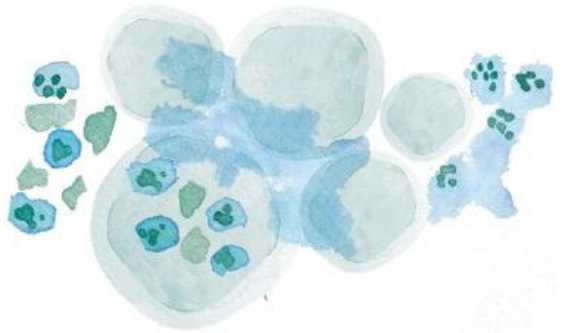




Phallen *et al.*, *Sci. Transl. Med.* **9**, eaan2415 (2017) 16 August 2017

oncoSens

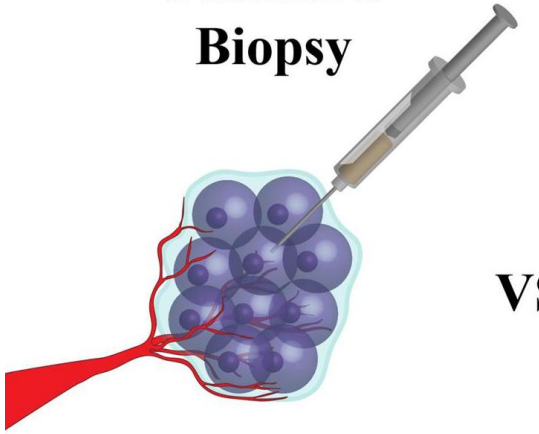
HÉRITAS BIOPSIA LÍQUIDA



Introduction

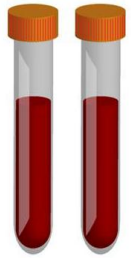
OncoSens - Hospital Aleman BA

Standard Biopsy

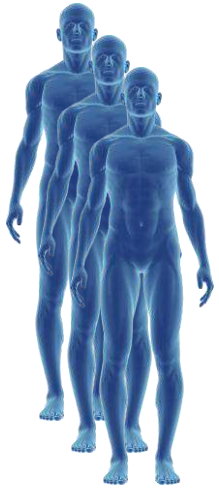


VS.

Liquid Biopsy



3 Pacientes/Tumor



Estadio IV

- ✓ Breast
- ✓ NSCLC
- ✓ CRC

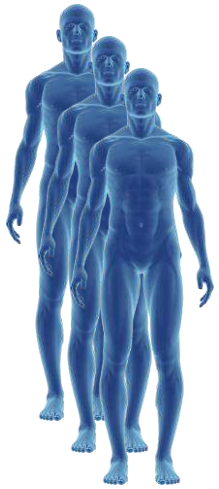
T0

Dr. Carlos bas
Dr. Gonzalo Gomez Abuin
Dra. Mercedes Tamburelli
Lab Central

Introduction

OncoSens - Hospital Aleman BA

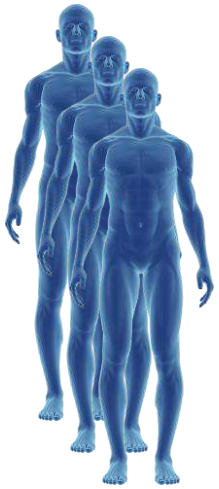
T0



Estadio IV
- ✓ Breast
- ✓ NSCLC
- ✓ CRC

Tratamiento
3 MESES

T1



Evolución ctDNA
Monitoreo

Introduction

OncoSens - Biomarkers Cáncer Mama

BREAST CANCER IN WOMEN: KNOW THE SUBTYPE

It's important for guiding treatment and predicting survival.

HR+/HER2- ····→ aka "Luminal A"

73% of all breast cancer cases

- Best prognosis
- Most common subtype for every race, age, and poverty level

HR-/HER2- ····→ aka "Triple Negative"

13% of all breast cancer cases

- Worst prognosis
- Non-Hispanic blacks have highest rate of this subtype at every age and poverty level

HR+/HER2+ ····→ aka "Luminal B"

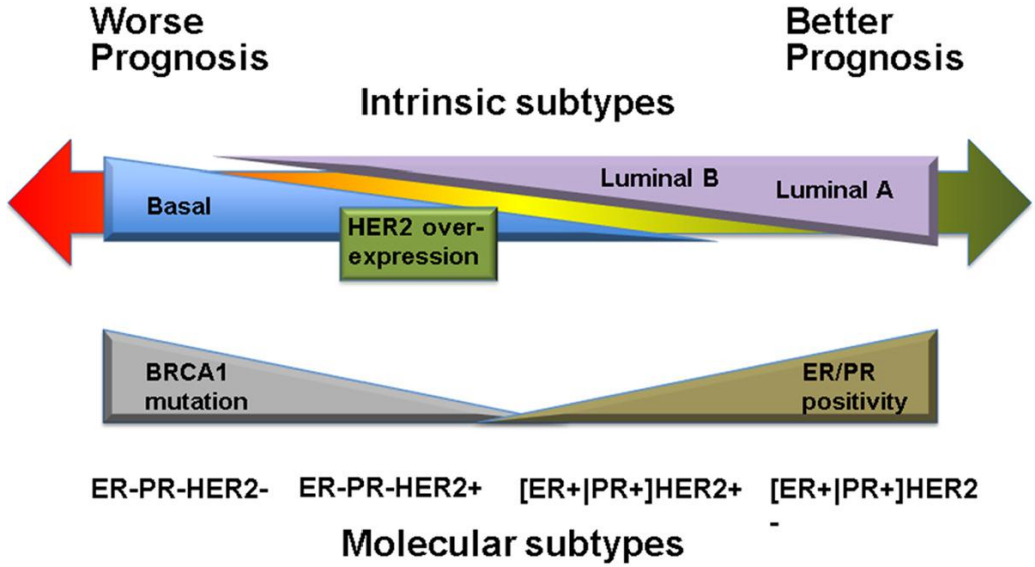
10% of all breast cancer cases

- Little geographic variation by state

HR-/HER2+ ····→ aka "HER2-enriched"

5% of all breast cancer cases

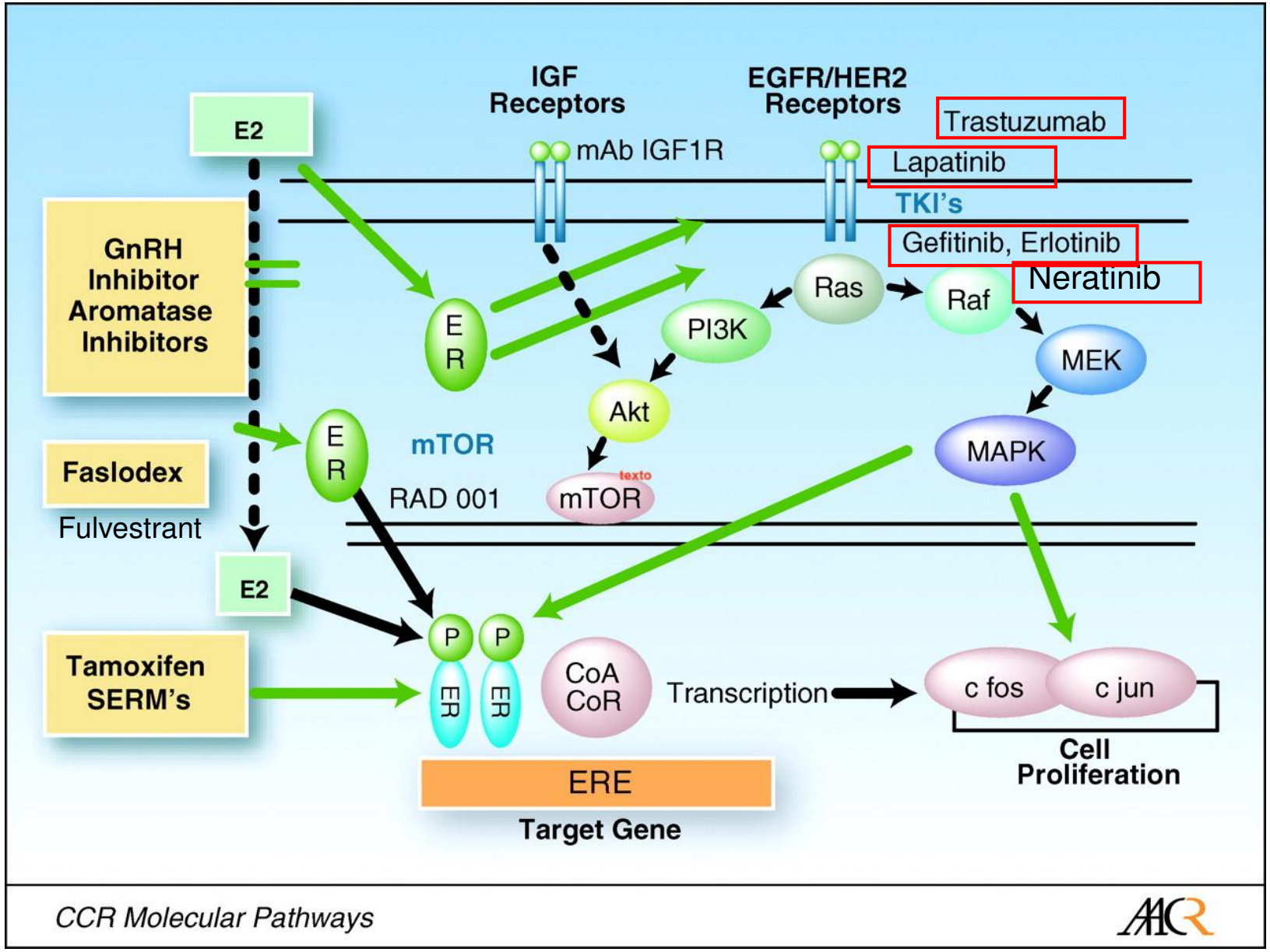
- Lowest rates for all races and ethnicities



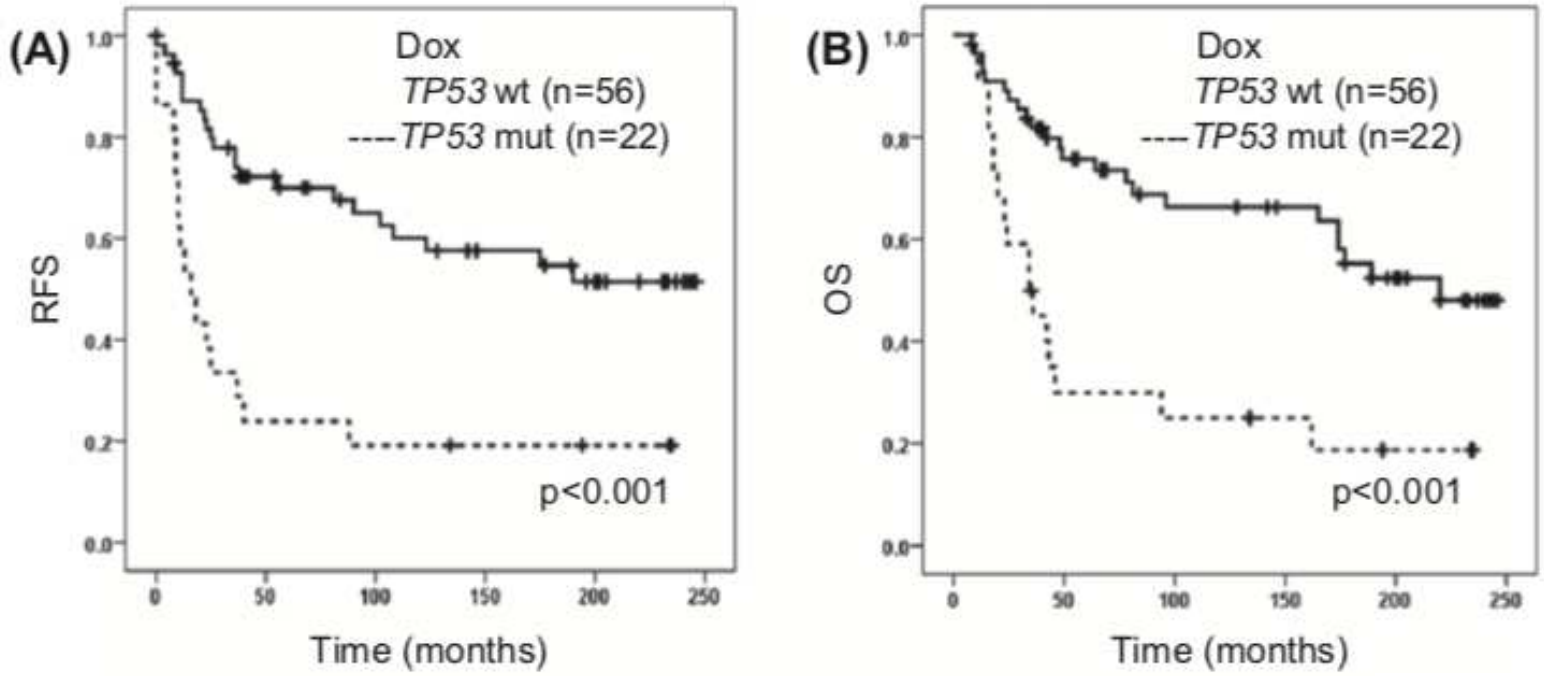
Héritas
Medicina de precisión
CIBIC + INDEAR

Introduction

OncoSens - Biomarkers Cáncer Mama



TP53 status es pronóstico de sobrevida en pacientes con cáncer de mama avanzado



- ✓ TP53 *mut* aparece en todos los subtipos de MBC
- ✓ TP53 *mut* es pronostico en HR+ con PIK3CA *mut*
- ✓ TP53 *mut* es peor pronostico de OS en HR+

2014 TP53 status predicts long-term survival in locally advanced breast cancer after primary chemotherapy

Hans P. Eikesdal, Stian Knappskog, Turid Aas & Per E. Lønning

2018 ORIGINAL REPORTS

Survival Outcomes by *TP53* Mutation Status in Metastatic Breast Cancer

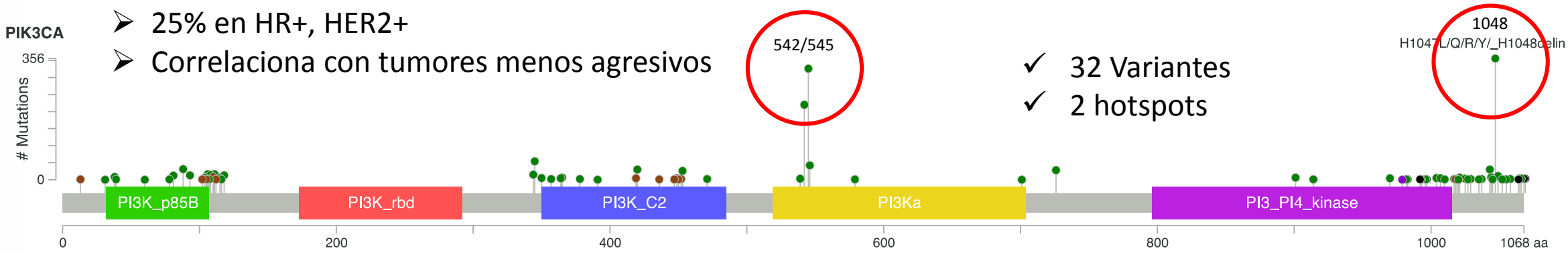
Funda Meric-Bernstam, Xiaofeng Zheng, Maryam Shariati, Senthil Damodaran, Chetna Wathoo, Lauren Brusco...

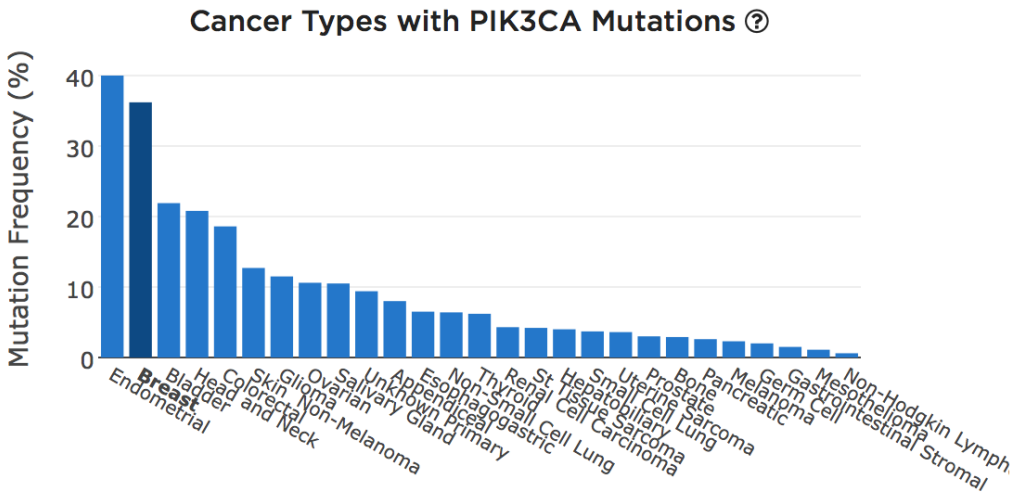
PIK3CA mut – La dinámica temprana en plasma (día 15 vs dia 1, CRD15) predice el resultado de Palbociclib + Fulvestrant

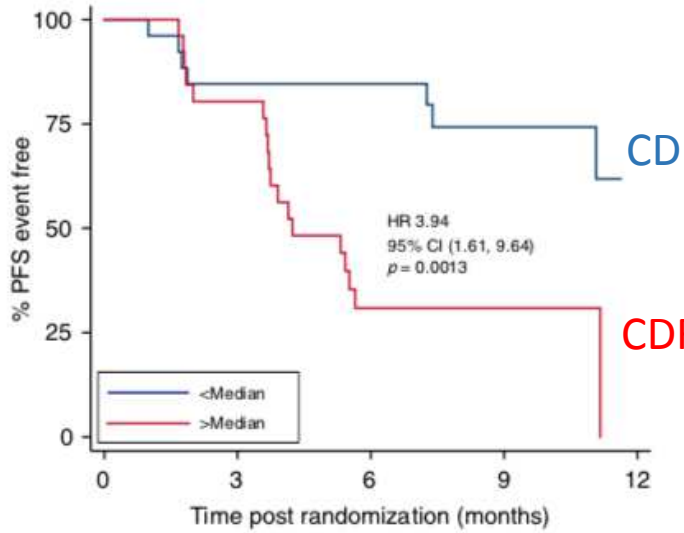
- 31% en HR+, HER2-
- 25% en HR+, HER2+
- Correlaciona con tumores menos agresivos

Hotspots

- ✓ 32 Variantes
- ✓ 2 hotspots







CDR15 bajo

Mut copies PIK3CA
day 15 to day 1
In plasma

CDR15 alto

O´Leary et al, Nat. Comms 2018, 9:896

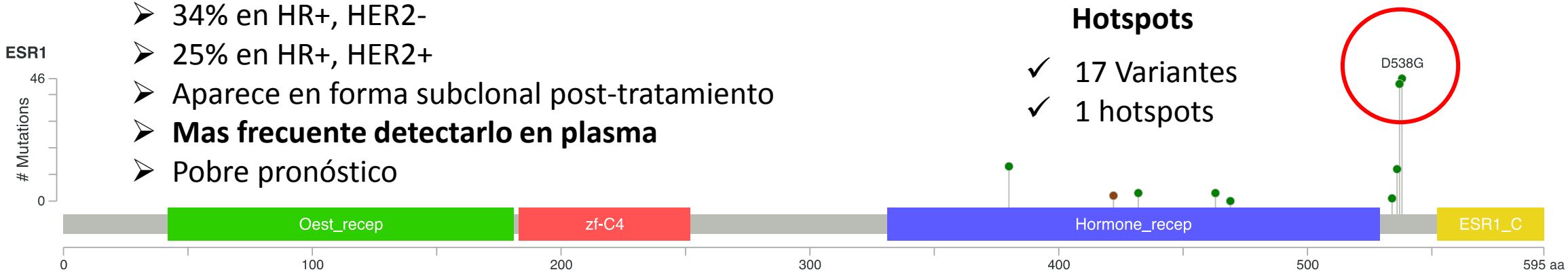
OncoSens - Biomarkers Cáncer Mama

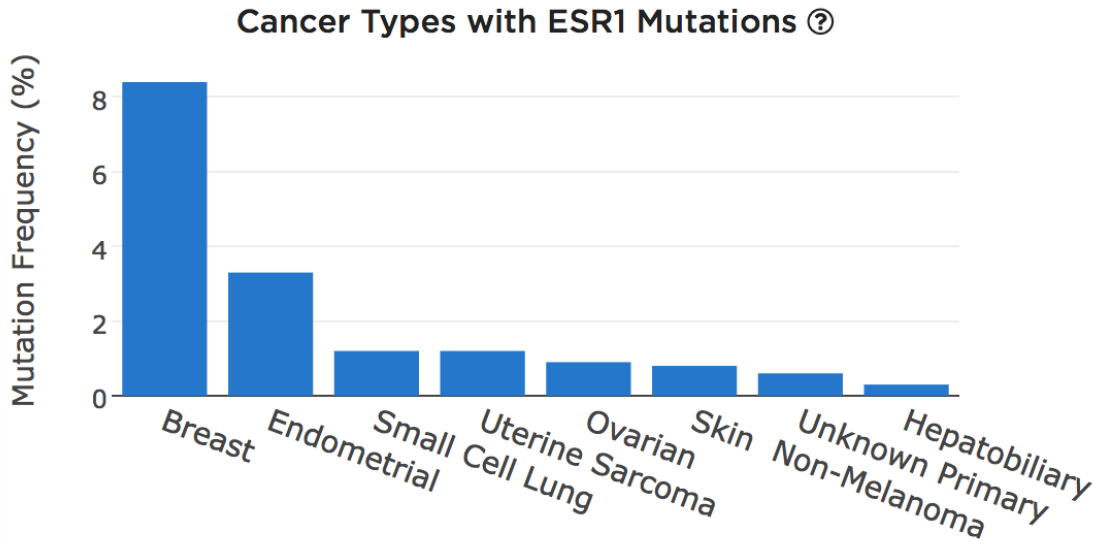
ESR1 mut predice más débilmente Palbociclib+Fulvestrant pero su persistencia en plasma asocia a falta respuesta a Tamoxifen y resistencia a inhibididor Aromatasa (Aromasin)

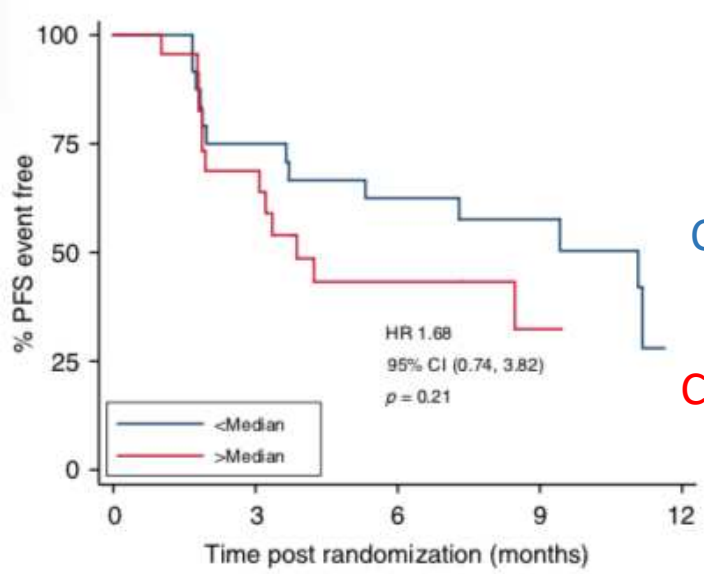
- 34% en HR+, HER2-
- 25% en HR+, HER2+
- Aparece en forma subclonal post-tratamiento
- **Mas frecuente detectarlo en plasma**
- Pobre pronóstico

Hotspots

- ✓ 17 Variantes
- ✓ 1 hotspots







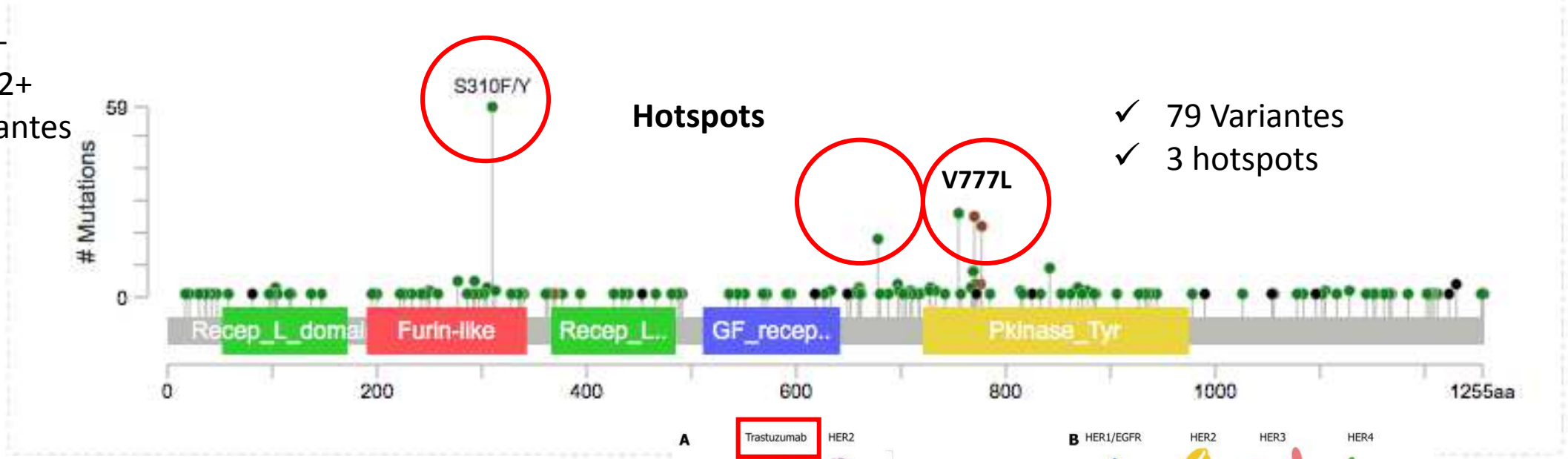
CDR15 bajo

CDR15 alto

O´Leary et al, Nat. Comms 2018, 9:896

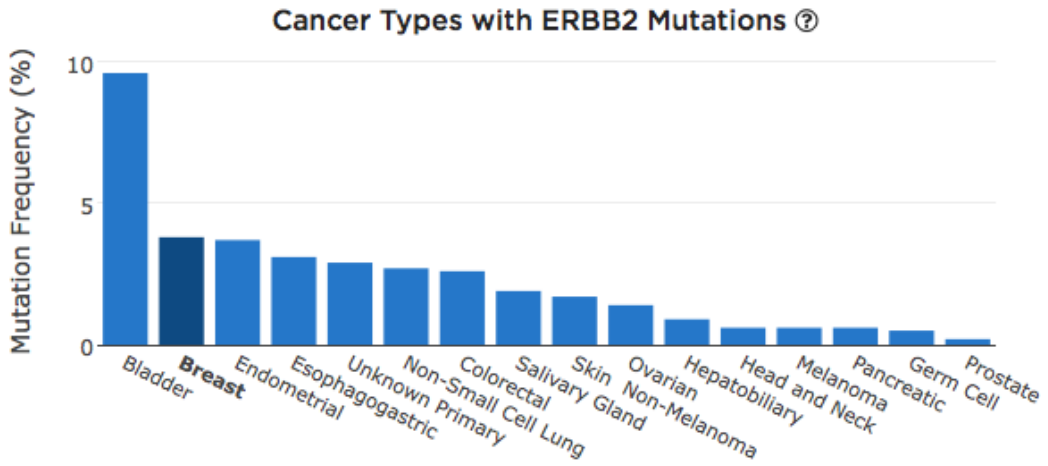
ERBB2 mut predice resistencia a Trastuzumab/Pertuzumab y sensibilidad a Neratinib/Lapatinib

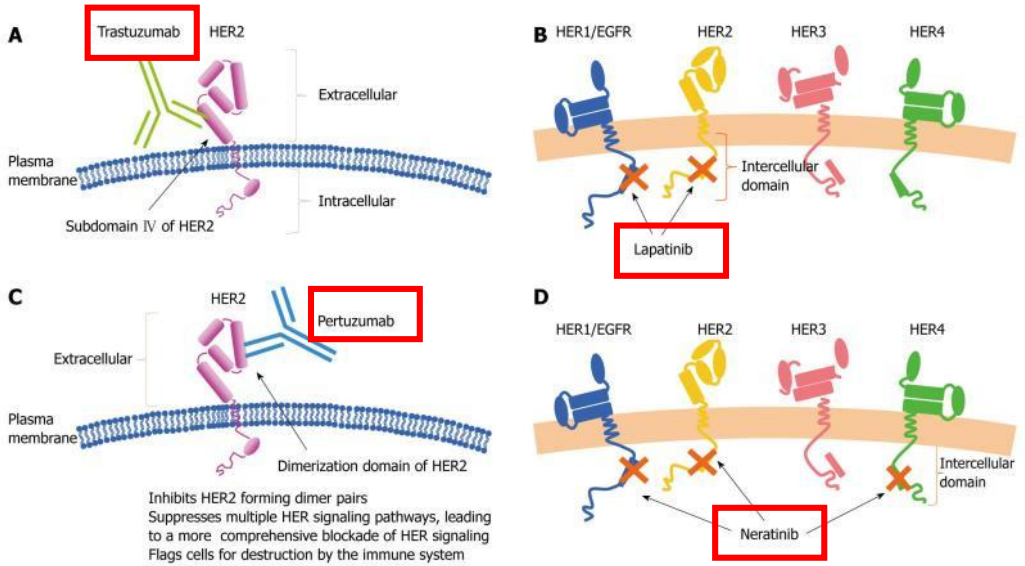
- 3% en HR+, HER2-
- 3% en HR+, HER2+
- Mutaciones activantes



Hotspots

- ✓ 79 Variantes
- ✓ 3 hotspots





Introduction

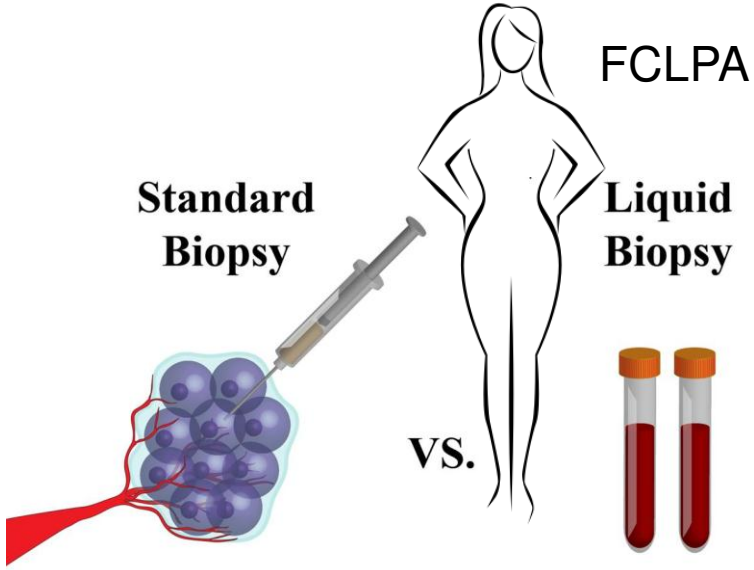
OncoSens - Hospital Aleman BA

Version 1

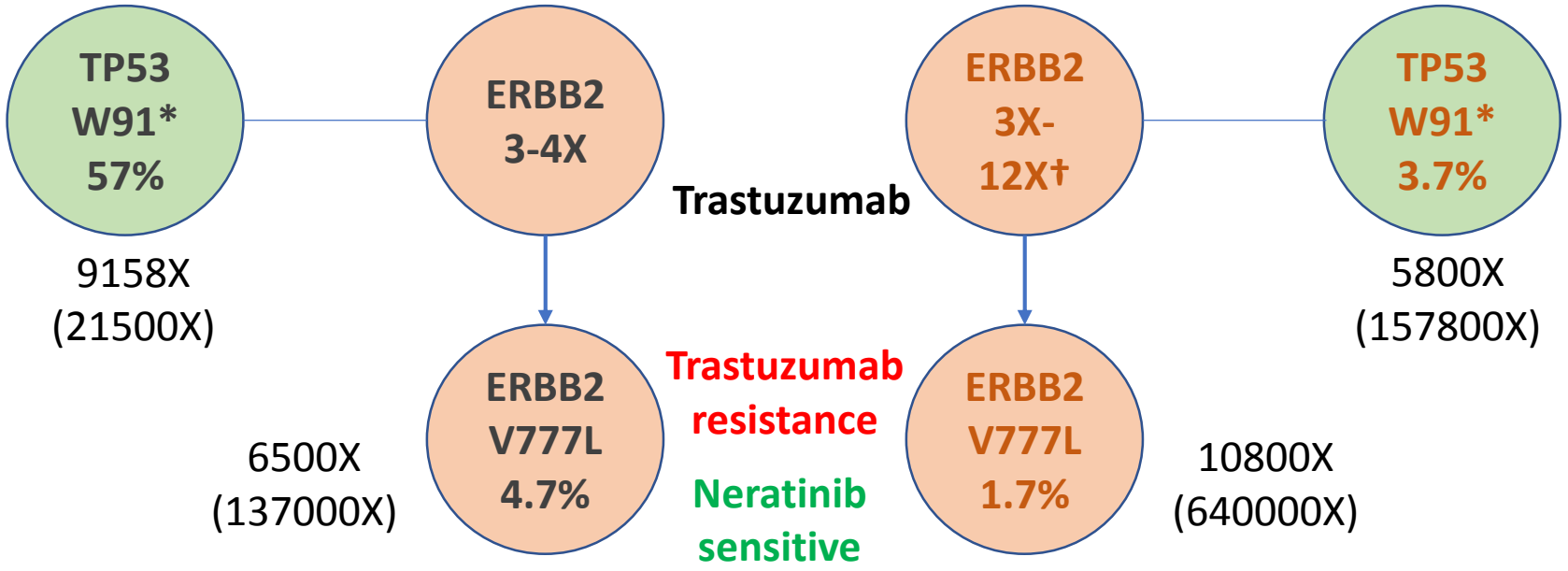
Tipo de tumor	Gen	Region target
mama	AKT1	E17K
colon, pulmón	BRAF	EXON 11,12,7,15,16
pulmón	EGFR	Focal amplification, exon 12 (partial), 18, 19, 20, 21 (partial)- insertions, deletions and indels G719/A/C/S, L858R, L861Q, S7681, T790M
mama, pulmón	ERBB2	full CDS
colon, pulmón	KRAS	exon 2 (partial), 3 (partial), 4 - codons 12,13,19,59,61,117,146
colon, pulmón	MET	EXON 19
colon	NRAS	exon 2 (partial) 3 (partial) 4 - codons 12,13,59,61,117,146
pulmón, mama	PIK3CA	full CDS
pulmón	RET	exon 16 - M918T
pulmón, colon	TP53	full CDS
pulmón	ALK	hotspots (exons 5,8,15,18,19,20,22,23,24,25,29)
pulmón	CTNNB1	hotspots (exon 3)
mama	ERBB3	hotspots (exons 2,3,7,8,9,12,23,27)
mama	ESR1	hotspots (exons 2,5,9) intron 7
pulmón, colon	RAF1	hotspots (exon 7)

FCLPA 04071977

OncoSens - Hospital Aleman BA – Patient ZERO



Patient Zero
40 years, Dx 2015
Stage IV
Invasive Breast Cancer (Her+)
Lung metastases

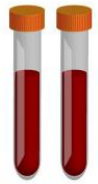


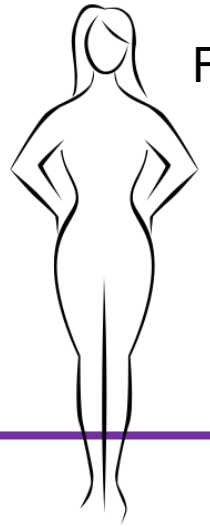
- Poor prognostic outcome
- BRCA1-related?
- Benefits: high-dose of Chemo (epirubicin)

FCLPA 04071977

OncoSens - Hospital Aleman BA – Patient ZERO

Liquid Biopsy





FCLPA 04071977

Patient Zero

40 years, Dx 2015

Stage IV

Invasive Breast Cancer (Her+)

Lung metastases

T0 → **T1**

Trastuzumab

ERBB2 3X-12X†

TP53 W91* 3.7%

5800X (157800X)

Trastuzumab resistance

Neratinib sensitive

ERBB2 V777L 1.7%

10800X (640000X)

ERBB2 1X

TP53 W91* 1.8%

609X (33684X)

Trastuzumab resistance

Neratinib sensitive

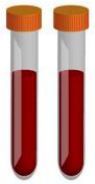
ERBB2 V777L 1.4%

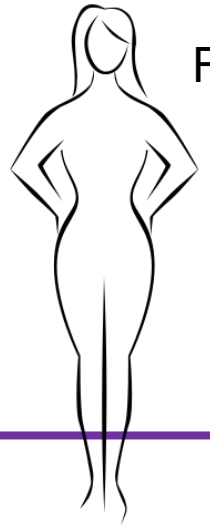
604X (41192X)

FCLPA 04071977

OncoSens - Hospital Aleman BA – Patient ZERO

Liquid Biopsy





FCLPA 04071977

Patient Zero

40 years, Dx 2015

Stage IV

Invasive Breast Cancer (Her+)

Lung metastases

T0 → **T1**

6/2017:

progresión de enfermedad (imágenes y marcador) **CA 15-3: 30**

Comienza Vinorelbine y Trastuzumab.

9/2017:

Progresión de enfermedad, aumento carga tumoral 25%.(a predominio pulmonar)

Sin respuesta a Trastuzumab

10/2017 :

Biopsia Guiada por TAC (T0)

01/2018

progresión de enfermedad a nivel pulmonar y ganglionar mediastinal.

CA 15-3: 81

Inició paclitaxel semanal.

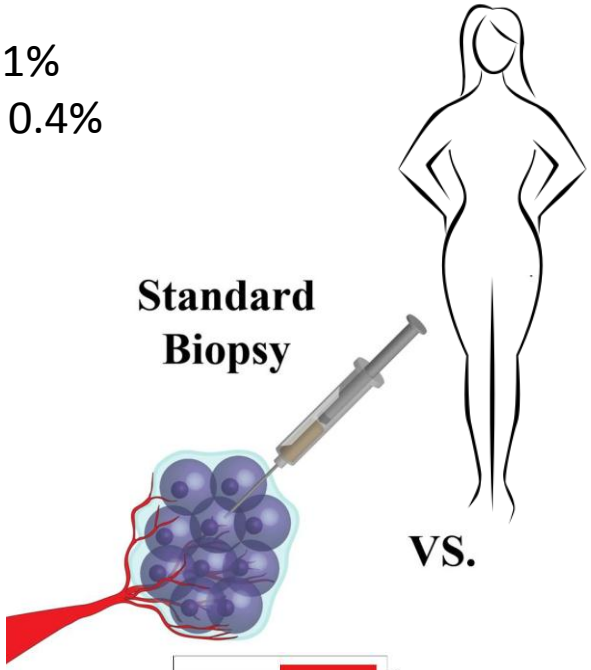
FPAPE 16111976

OncoSens - Hospital Aleman BA

Tissue cut-off : 1%
Plasma cut-off: 0.4%

FPAPE 16111976

Age: 41 years
Dx: 2011 Breast cancer
T0: 10/2017
Stage IV
Invasive Breast caner
Liver, Bone metastases



VUS

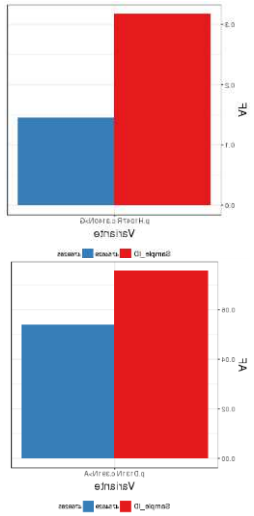
FOXL2
D131N
5.4%

55800X

Oncogenica
Sensibilidad

PIK3CA
H1047R
14.5%

27000X



PIK3CA
H1047R
31%

19600X

FOXL2
D131N
7.5%*

54000X

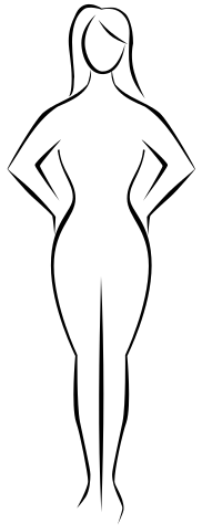
NO relevant Variants found in:

- AKT1
- ERBB2

FPAPE 16111976

OncoSens - Hospital Aleman BA –Mama 3

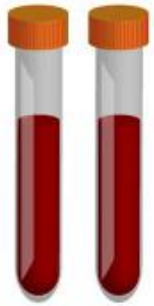
Tissue cut-off : 1%
Plasma cut-off: 0.4%



FPAPE 16111976

Age: 41 years
Dx: 2011 Breast cancer
T0: 10/2017
Stage IV
Invasive Breast caner
Liver, Bone metastases

Liquid Biopsy



T0
7.11 ng/ul

3 meses

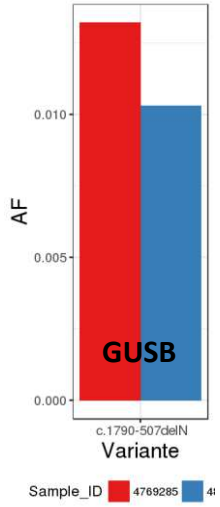
T1
1.46 ng/ul

PIK3CA H1047R 31%

19600X

FOXL2 D131N 7.5%*

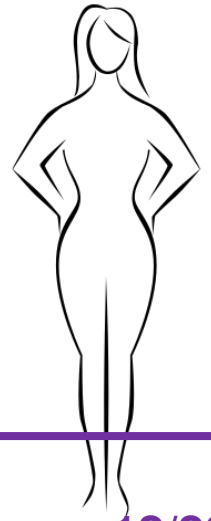
54000X



Clínica???
Interpretación?
Interacción analista-oncólogo

FPAPE 16111976

OncoSens - Hospital Aleman BA –Mama 3



FPAPE 16111976

Age: 41 years

Dx: 2011 Breast cancer, HR+, Her2-

T0: 10/2017

Stage IV

Invasive Breast caner

Liver, Bone metastases

T0 → **T1**

5/2017:

Inicia fulvestrant y zometa + Palbociclib x3C, 10/17,
con progresión hepática y ósea.

10/2017: (T0)

Bx hepática metástasis de carcinoma mamario. RE 90%, RP 10%, Her2 negativo (por FISH), Ki67 20%.

CA 15-3: 236

12/2017

Nueva línea con_Paclitaxel 90 mg/m2 DT 135 mg dia 1, 8 y 15 + bevacizumab 10 mg/kg DT 500 mg día 1 y 15 cada 28 días.

02/2018 Control Post C3

- TC TAP: - **Disminución** de tamaño de las lesiones de aspecto secundario a nivel del hígado, lesiones óseas estables + beneficio clínico.

CA 15-3: 128.8

Reporting

OncoSens - Hospital Aleman BA – Reporting

RESULTADOS DEL ANÁLISIS

2 hallazgos genómicos

HALLAZGOS SOMÁTICOS ACCIONABLES

PIK3CA **H1047R** (AF: 31.7%)

HALLAZGOS DE SIGNIFICANCIA INCIERTA

FOXL2 **D131N** (AF: 7.56%)

GENES ANALIZADOS SIN HALLAZGOS RELEVANTES

AKT1	ERBB2	TP53

Héritas
Medicina de precisión
CIBIC + INDEAR

Gracias

OncoSens 2

oncosens
HÉRITAS BIOPSIA LÍQUIDA

@HeritasArg