Clinical utility of circulating tumour DNA analysis in hormone receptor positive breast cancer patients

Precision Medicine & CHANNEL RETREAT 2018
Share Knowledge. Exchange Ideas. Establish Partnerships.

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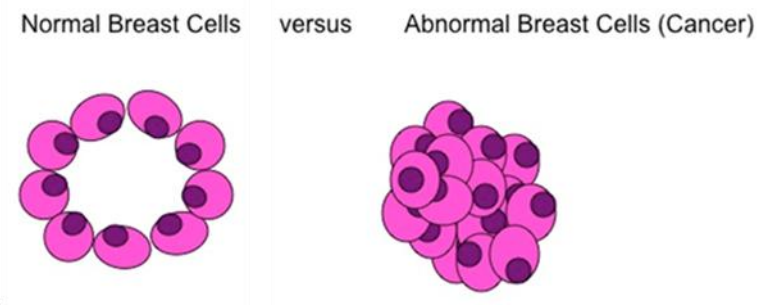
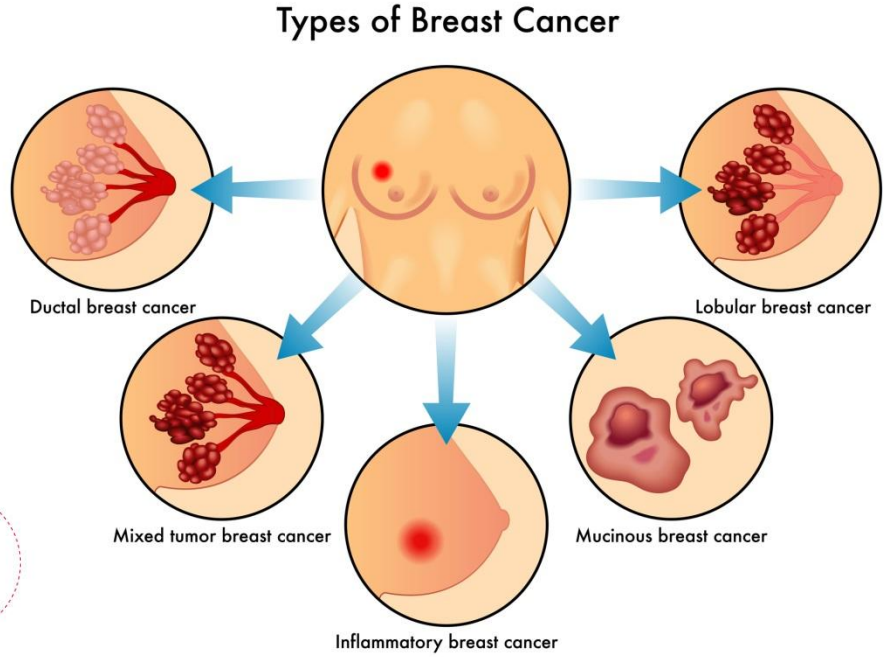
The Institute of Cancer Research, London

What is breast cancer?



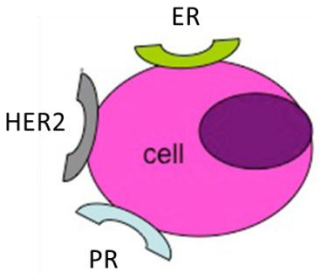


Breast cancer classification: receptor subtypes

HR+/HER2- ····→ aka "Luminal A"

73% of all breast cancer cases

- Best prognosis



HR-/HER2- ····→ aka "Triple Negative"

13% of all breast cancer cases

- Worst prognosis

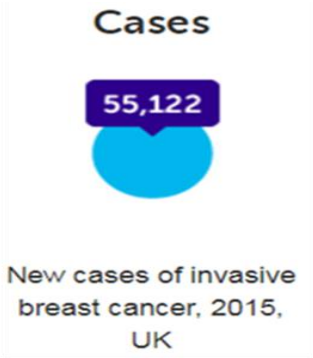
HR+/HER2+ ····→ aka "Luminal B"

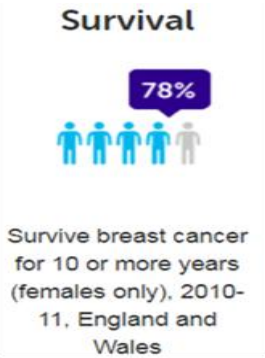
10% of all breast cancer cases

HR-/HER2+ ····→ aka "HER2-enriched"

5% of all breast cancer cases

Progress in breast cancer management

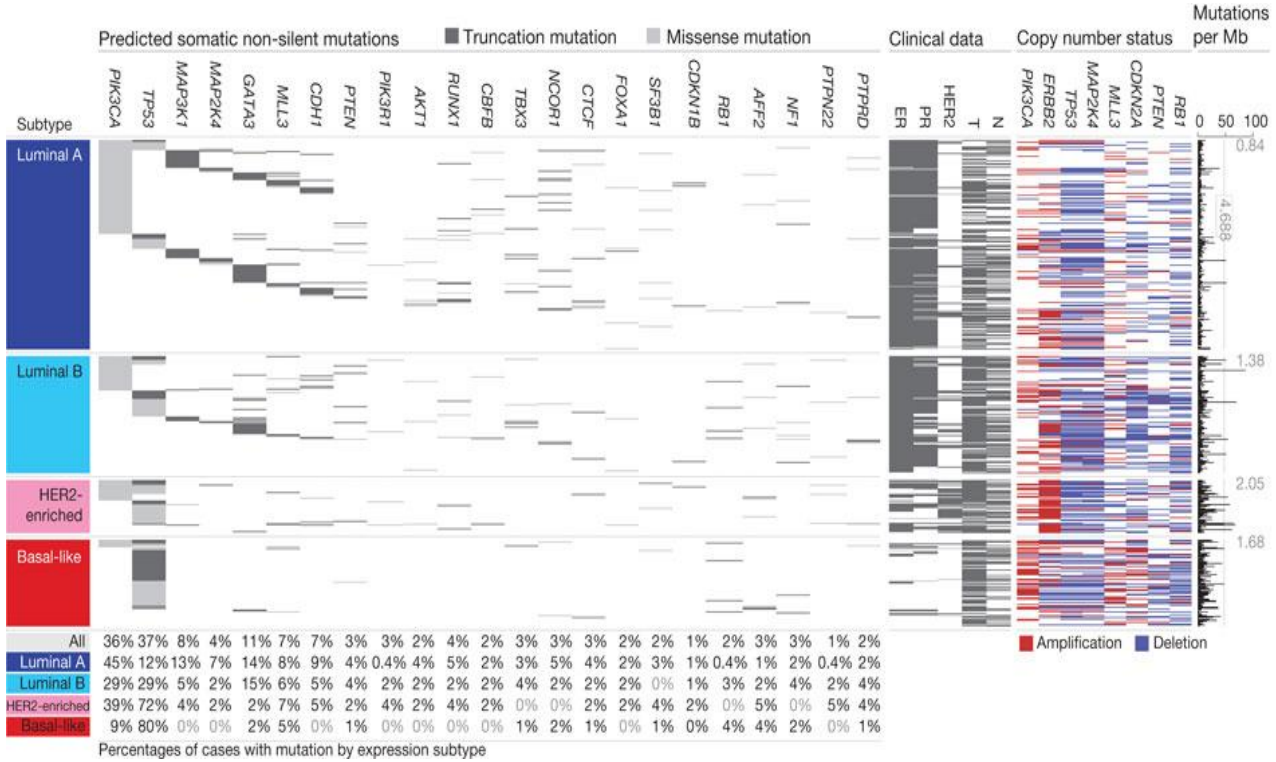




Source: CRUK

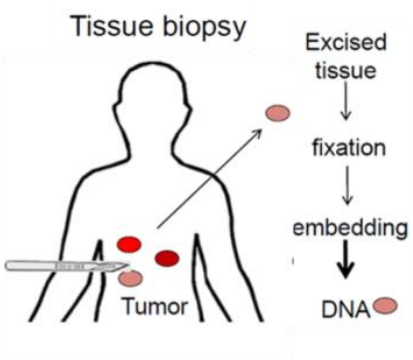
Molecular analysis of breast cancer

The spectrum of genomic alterations in breast cancer

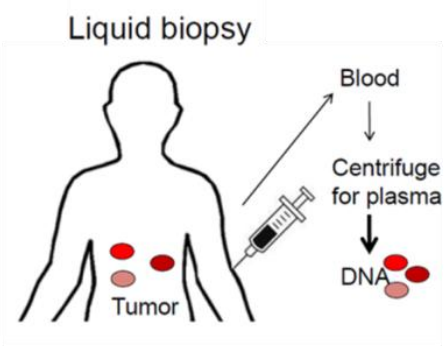


Koboldt *et al, Nature* 2012

Liquid biopsies

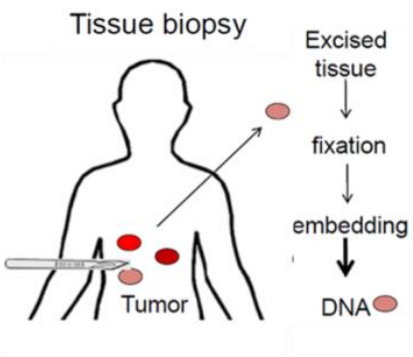


- Invasive
- Expensive
- Processing takes time



- Non-invasive assessment
- Less expensive
- Rapid purification
- Whole picture
- Surrogate when anatomic biopsies are not feasible

Liquid biopsies



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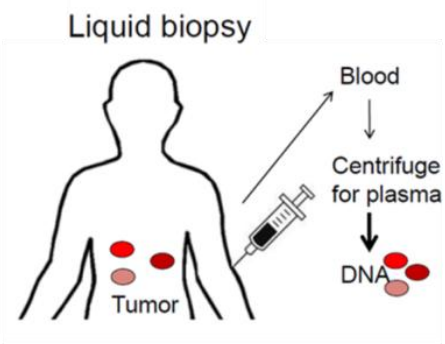

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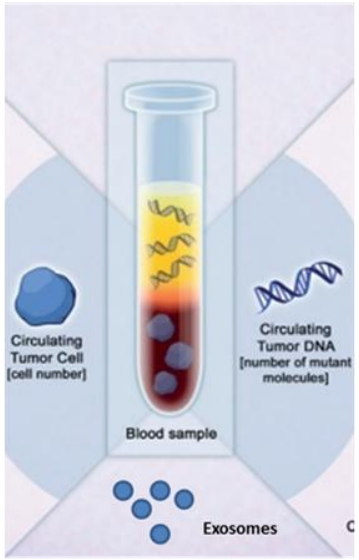
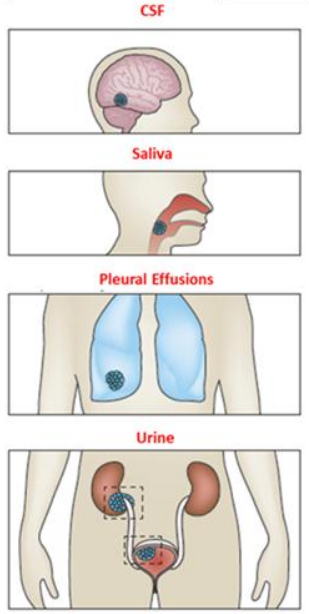
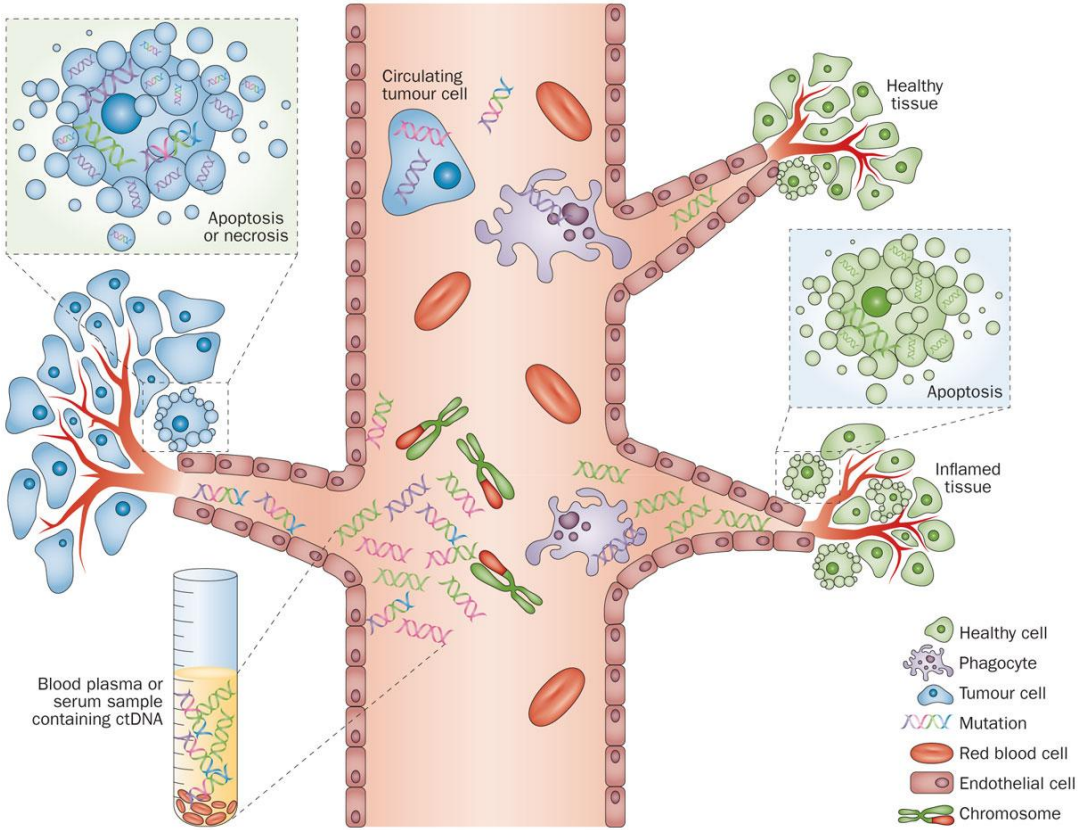




Siravegna et al, Nat Rev Clin Oncol 2017

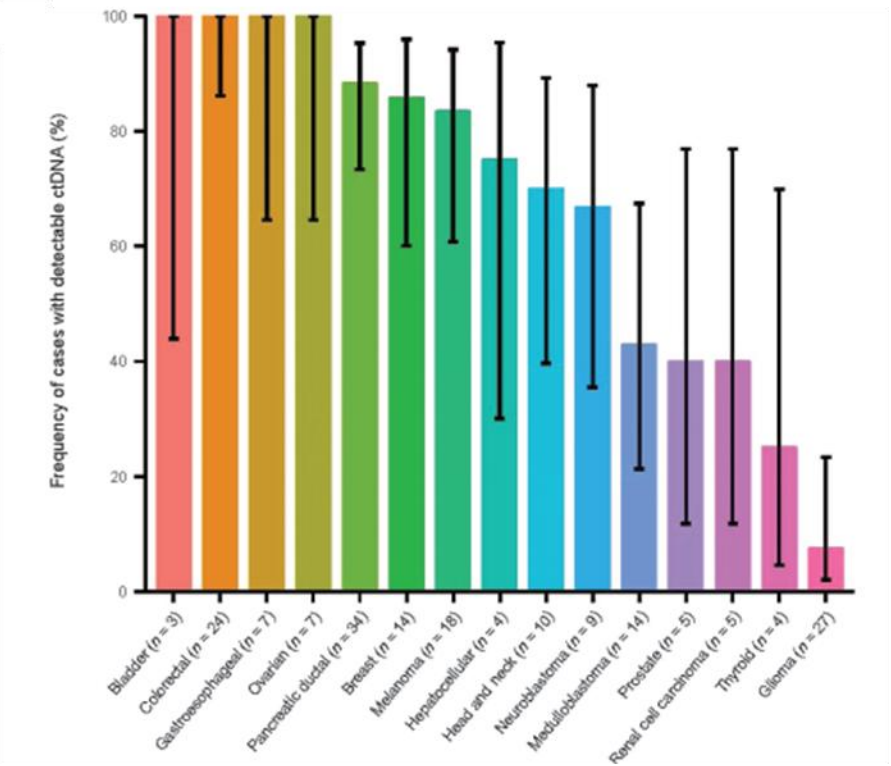
Blood, urine, saliva, CSF, other body fluids (lavages, effusions…)

Circulating tumour DNA (ctDNA)

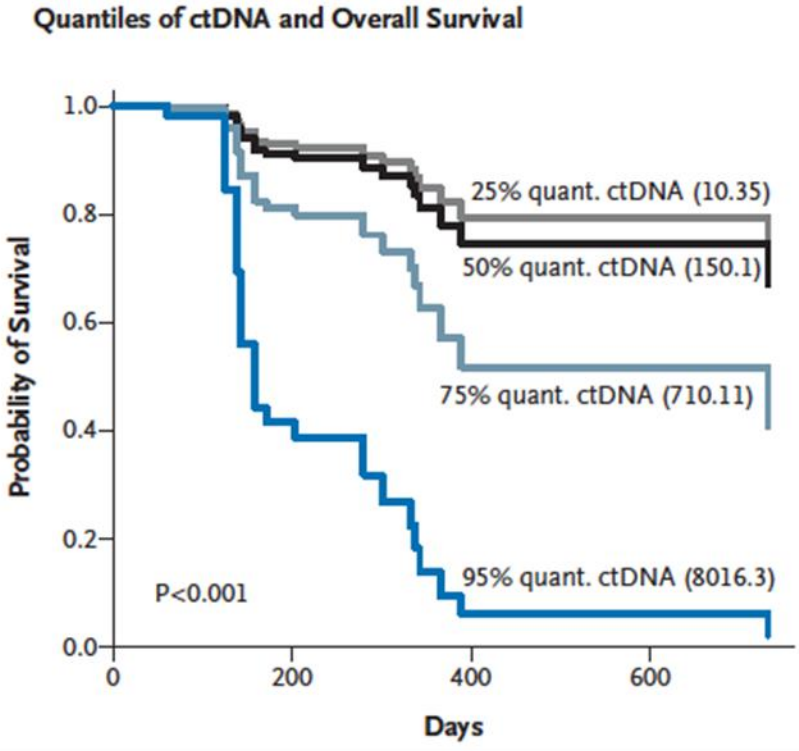


Crowley *et al* Nat Rev Clin Oncol *2013*

ctDNA in solid tumours

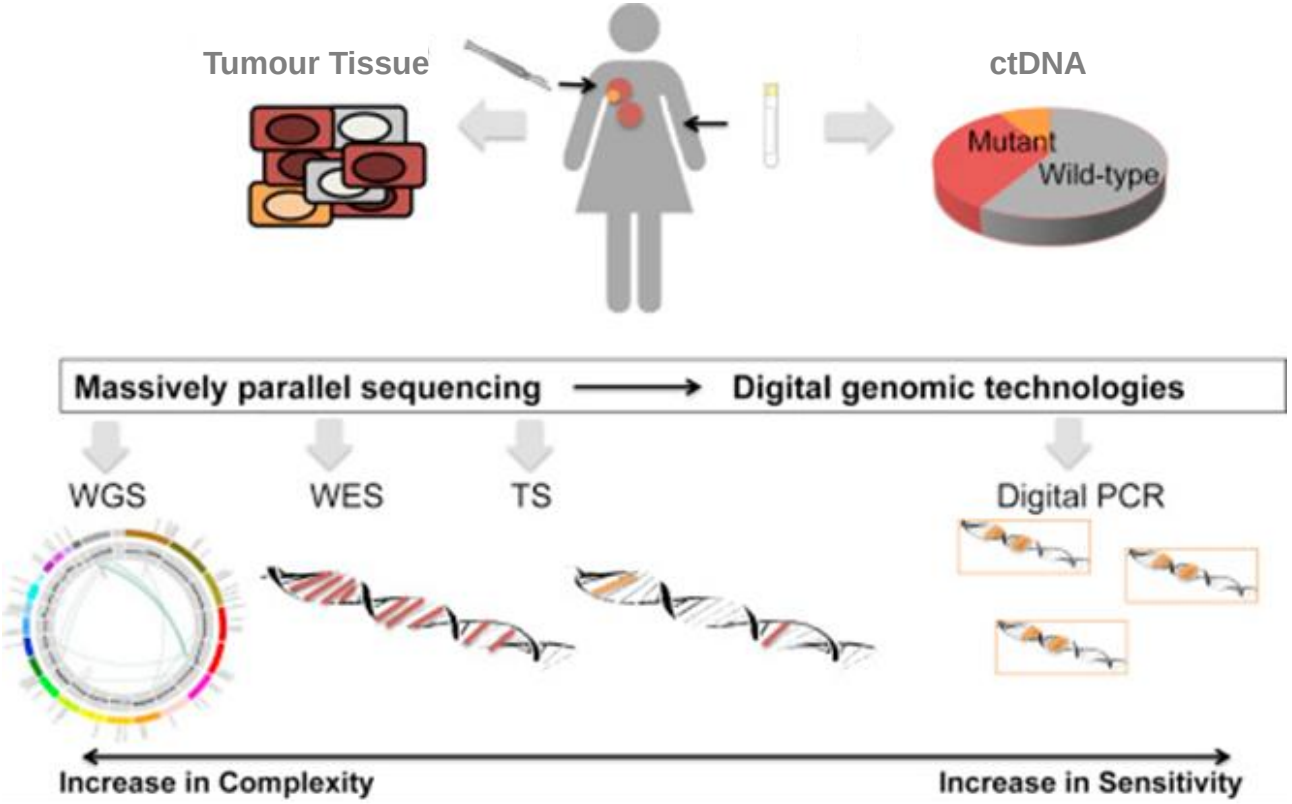


Bettegowda *et al* STM 2014



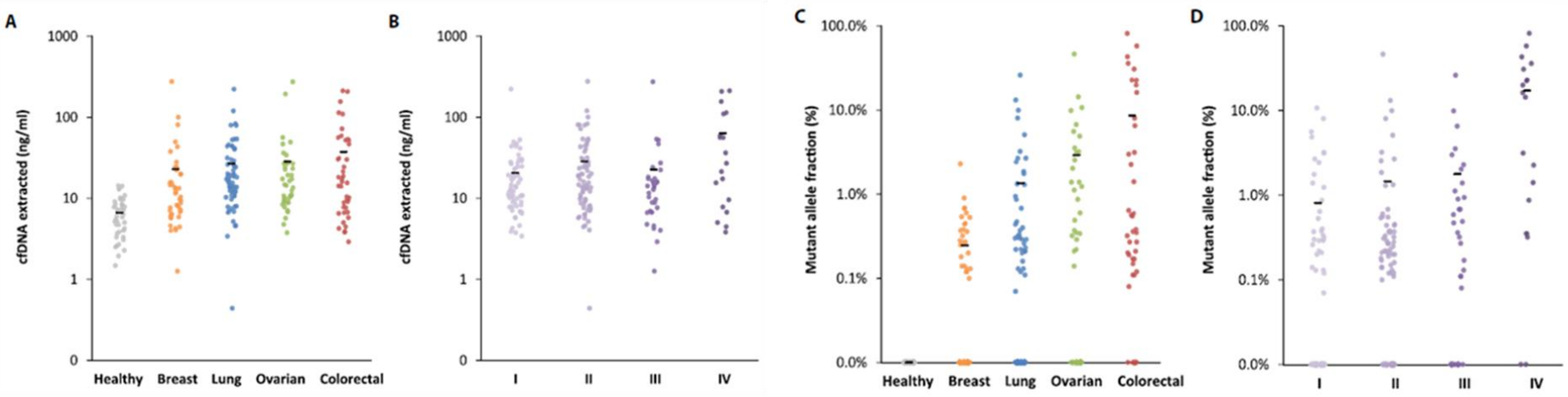
Dawson et al NEJM 2013

Molecular and genomic analysis of ctDNA



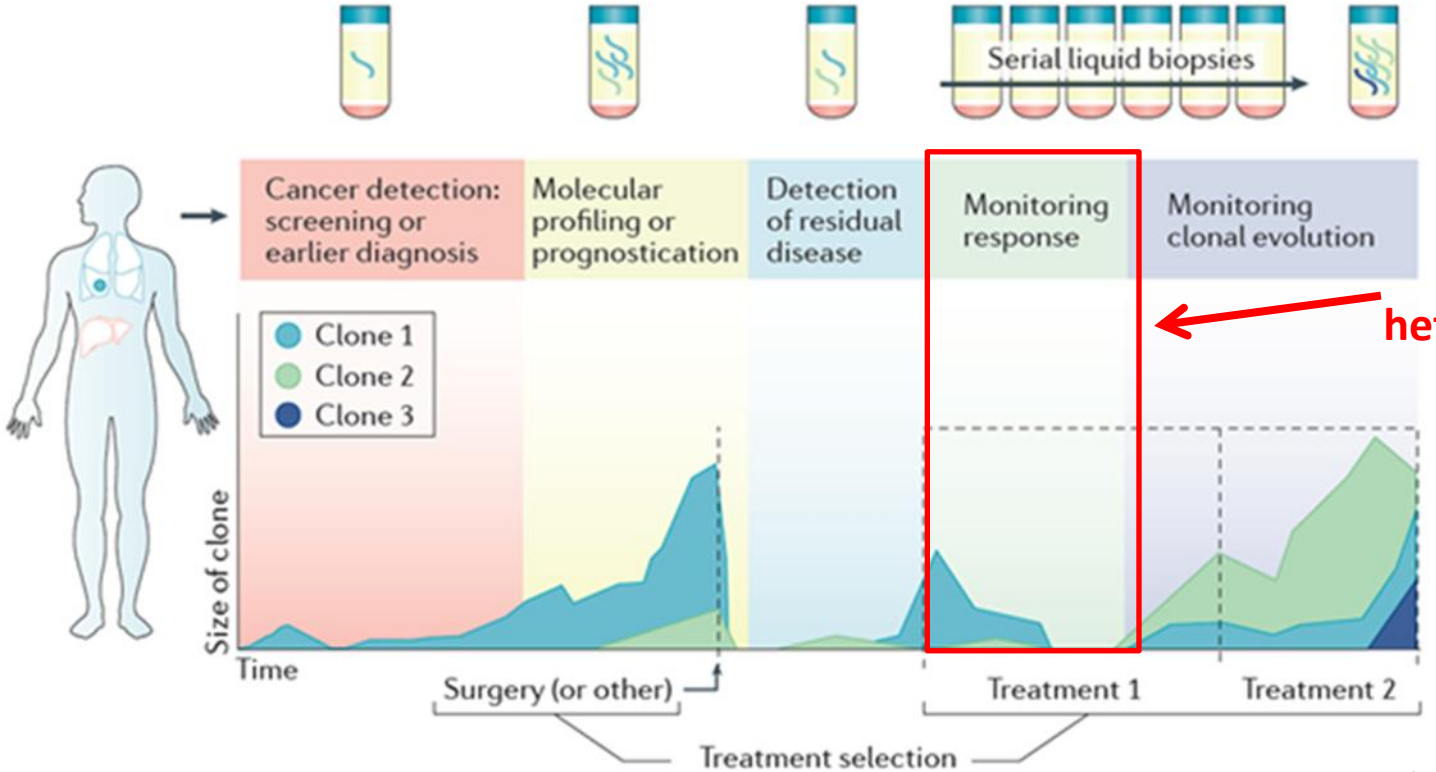
De Mattos-Arruda, Mol Oncol 2015

The challenge of low level mutation detection



Phallen *et al* STM 2017

ctDNA as clinical biomarker in cancer

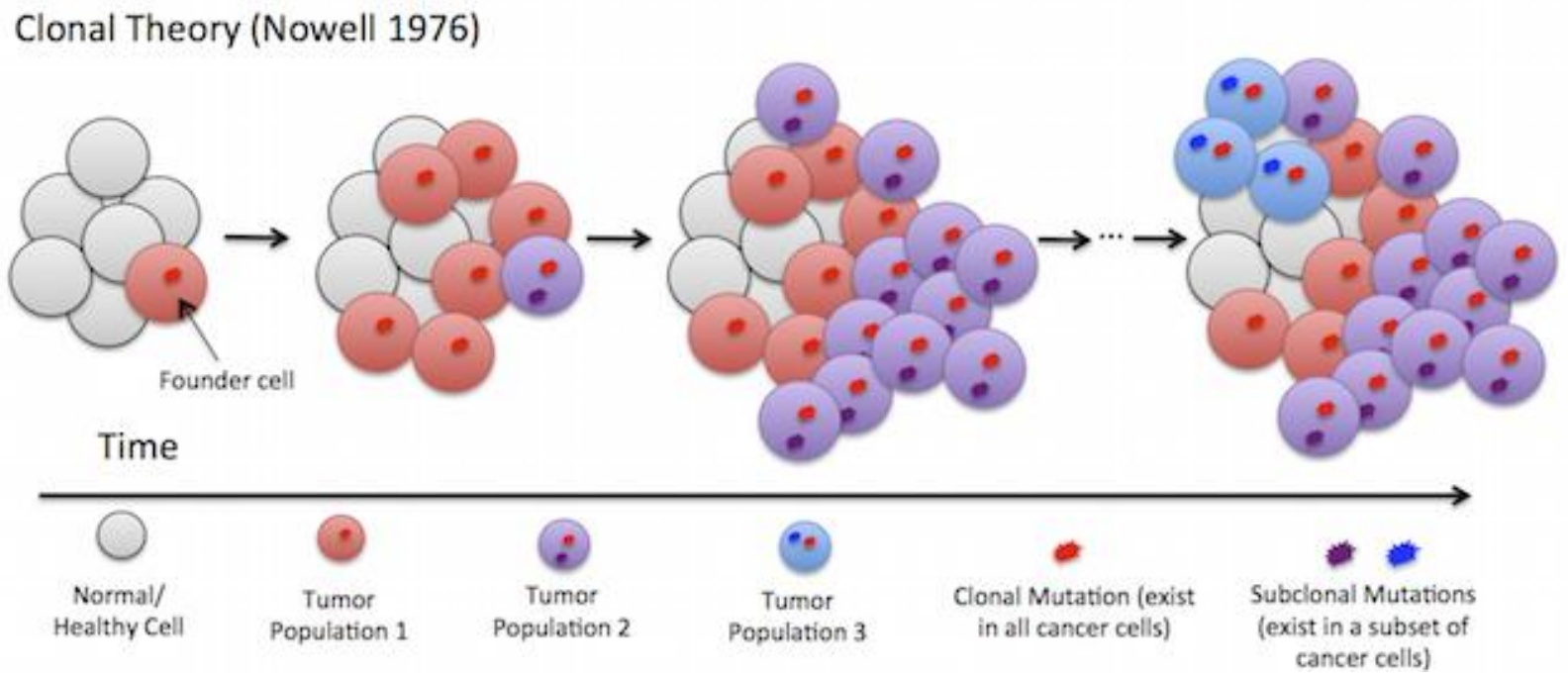


Tumour heterogeneity

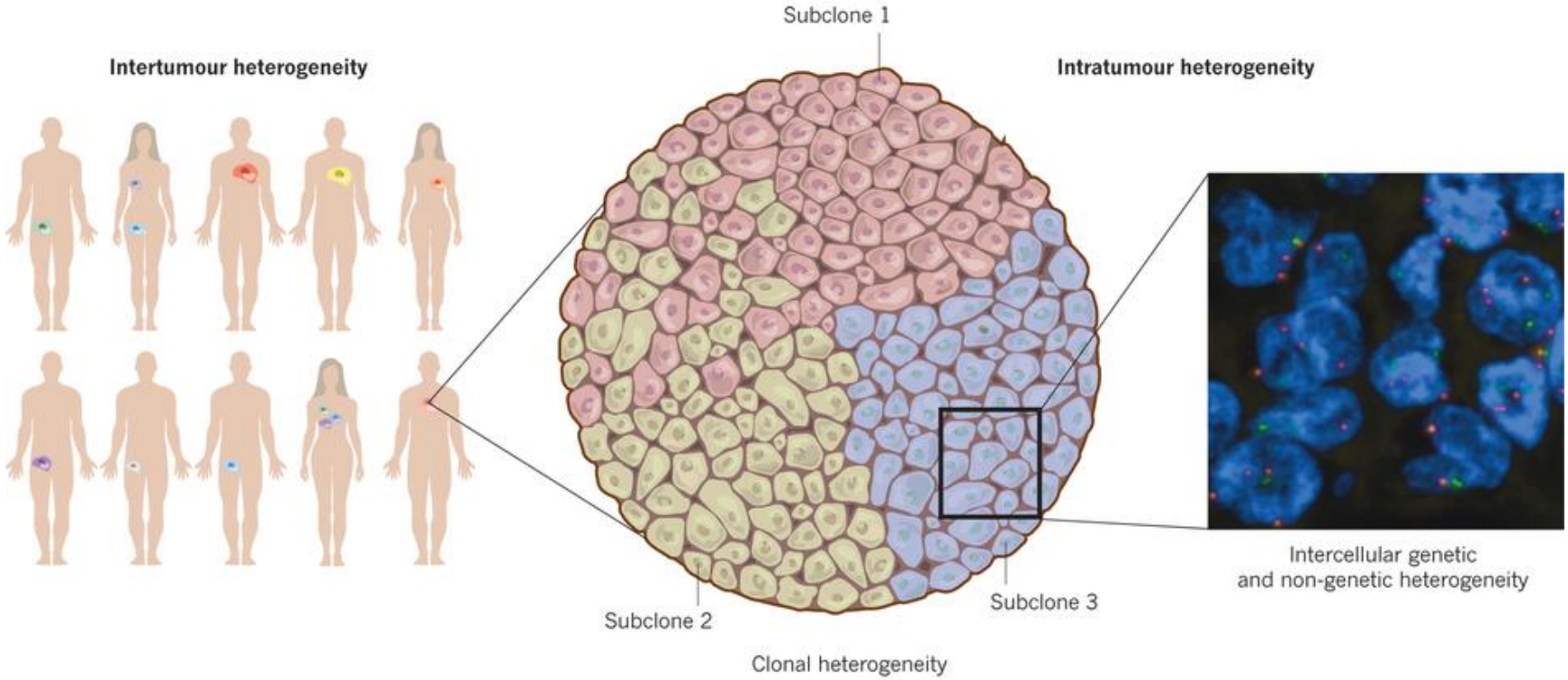
Wan *et al* Nat Rev Cancer 2017

Tumour heterogeneity

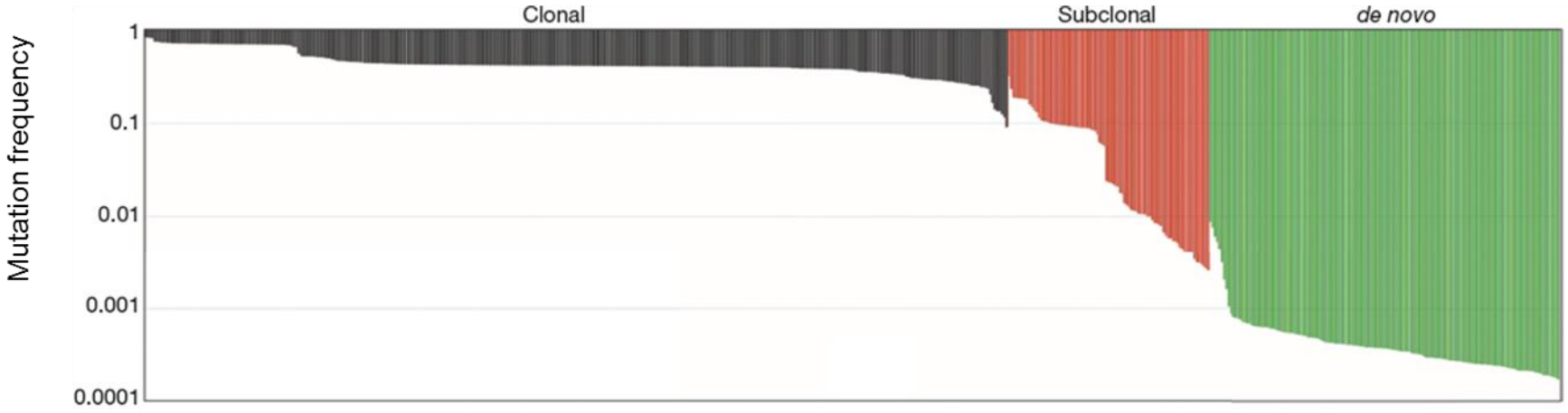
Tumour heterogeneity describes the observation that different tumour cells can show distinct morphological and phenotypic profiles, including cellular morphology, gene expression, metabolism, motility, proliferation, and metastatic potential.



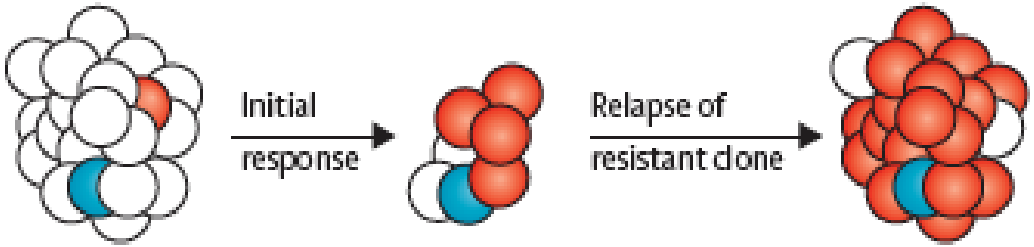
Tumour heterogeneity



Tumour heterogeneity as a driver of resistance



Wand et al, Nature 2014



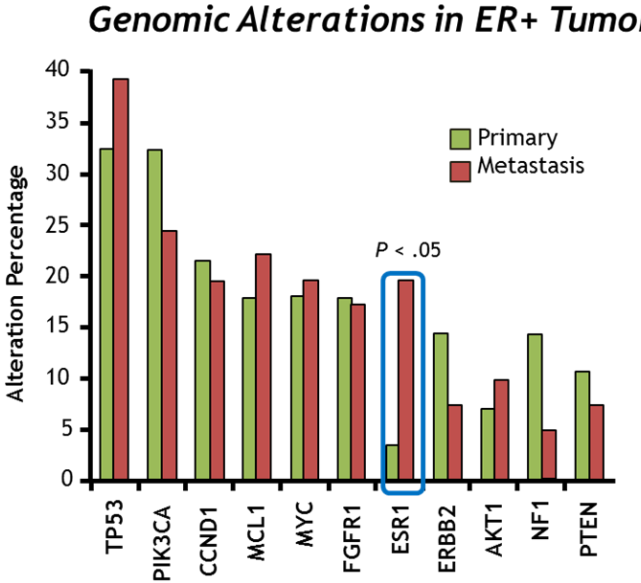
Turner et al Lancet Oncol , 2012

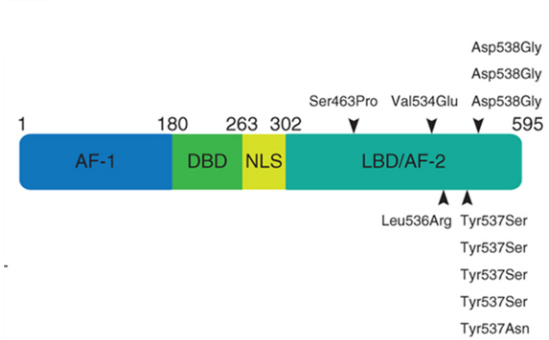
Can ctDNA analysis be used to infer resistance to therapy?

ctDNA analysis to identify mechanisms of resistance to therapy

HR+/HER2-

73% of all breast cancer cases





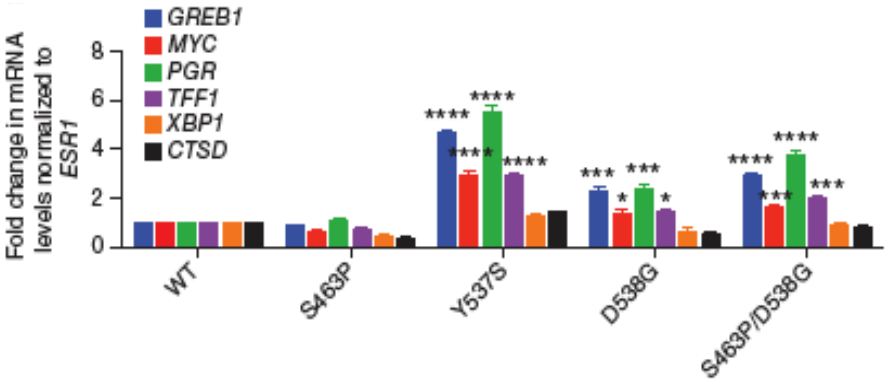
Cluster of mutations in amino acids 537-538 in ligand-binding domain(**LBD**) reported in AI pretreated patients

ESR1 mutations occur in ~20% of endocrine resistant ER positive breast cancer

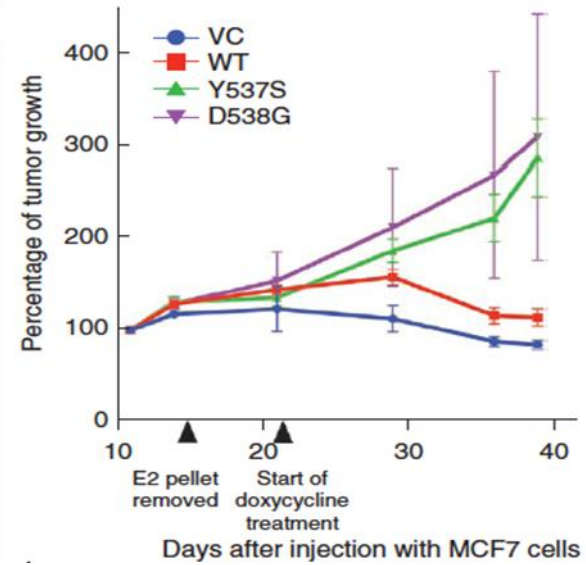
Toy *et al* Nature Genetics 2013

Robinson *et al* Nat Gen 2013

ctDNA analysis to identify mechanisms of resistance to therapy



Mutations in ligand binding domain activate ER ligand independent signalling

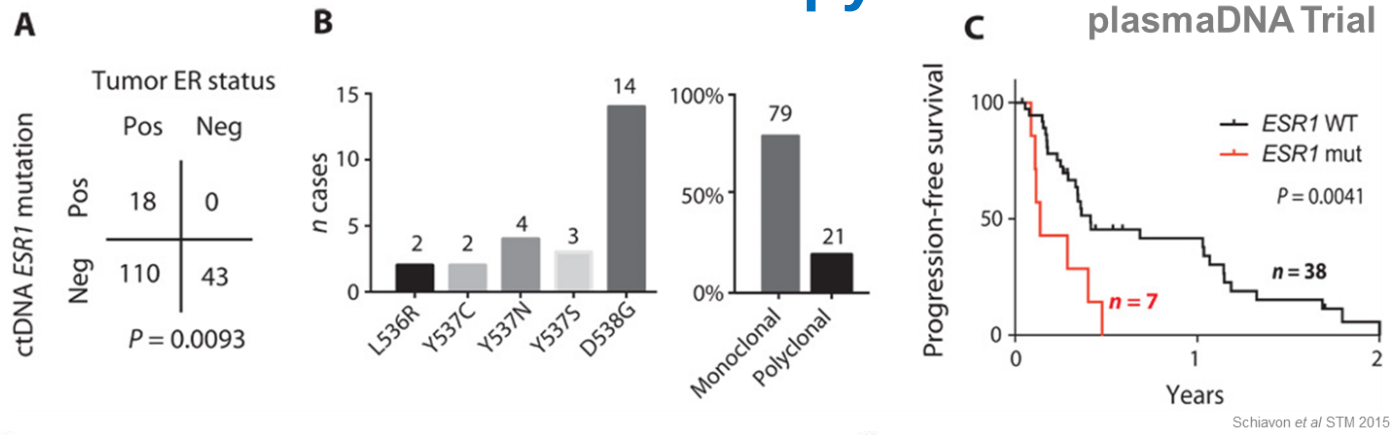


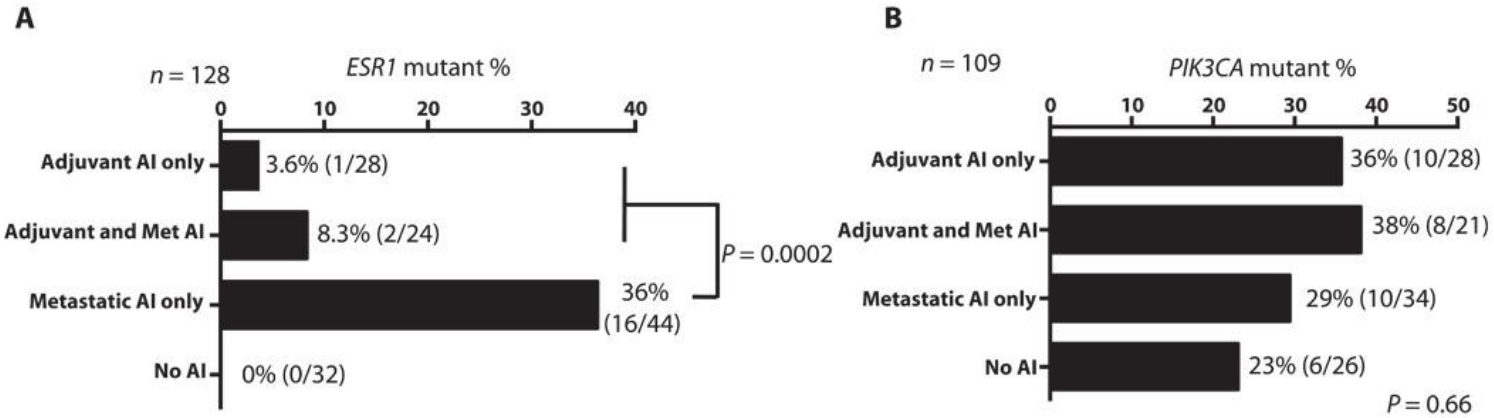
Resistance to aromatase inhibitors
Potentially sensitive to ER degraders

Toy *et al* Nature Genetics 2013

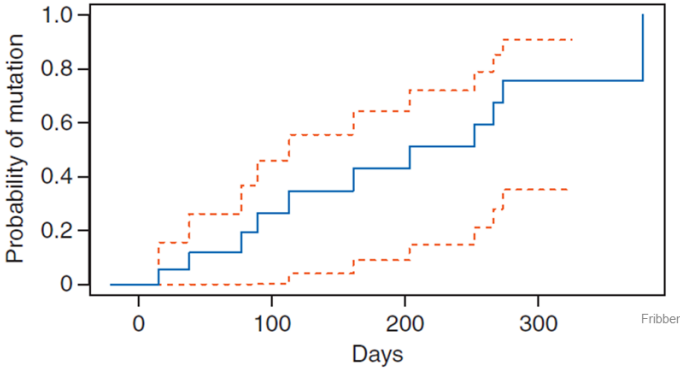
Robinson *et al* Nat Gen 2013

ctDNA analysis to identify mechanisms of resistance to therapy





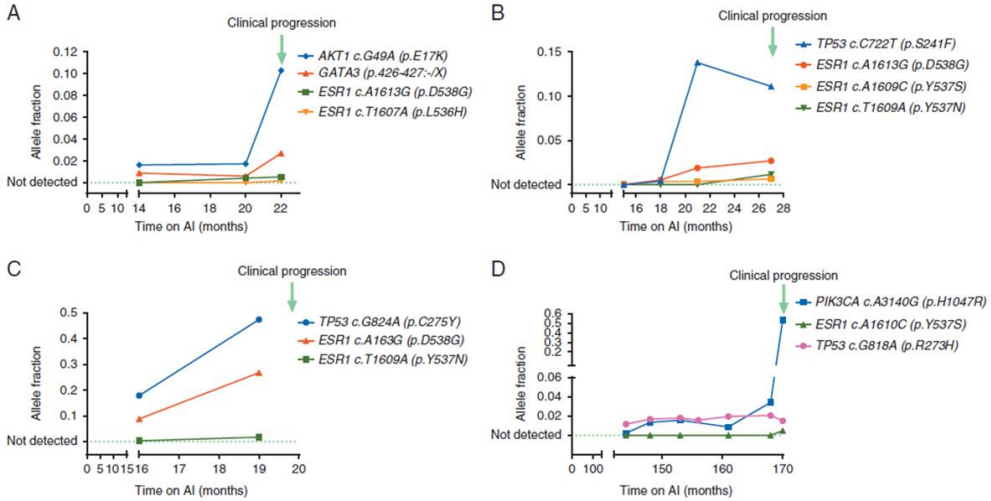
ctDNA analysis to identify mechanisms of resistance to therapy



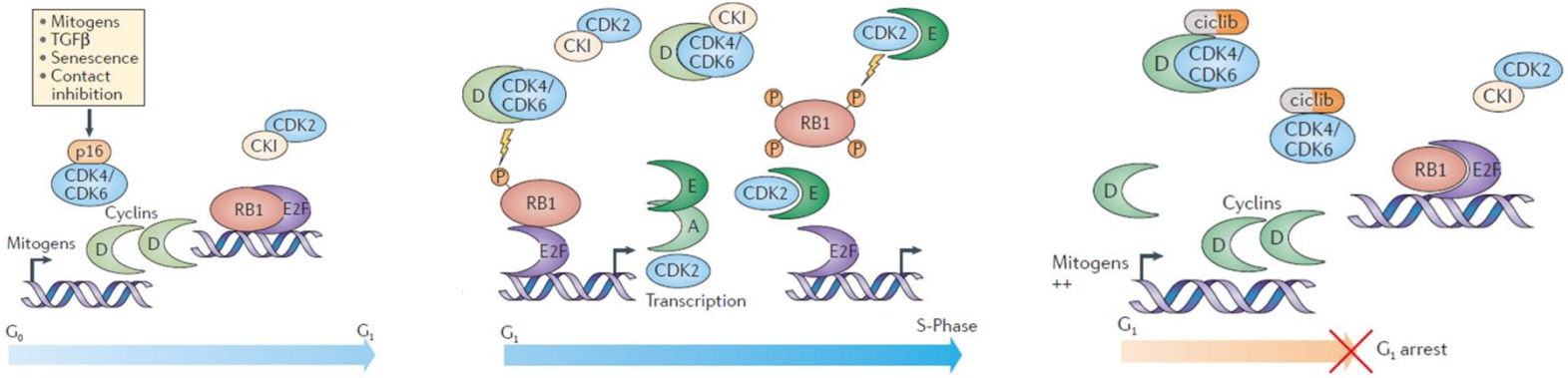
Fribbens *et al* Ann Onc 2017

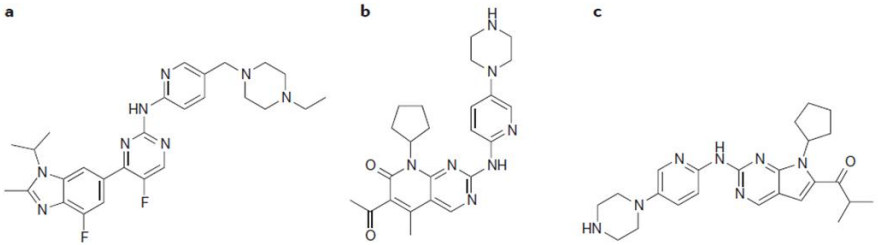
SoFEA Trial

Figure 4. Lead time to development of *ESR1* mutations. Serial tracking before progression, *ESR1* mutations were detectable in plasma median 6.7 months [95% confidence interval (CI) 3.7–NA] before clinical progression.



cdk4/6 inhibitors in HR+ breast cancer





	Abemaciclib (LY-2835219) Lilly	Palbociclib (PD-0332991) Pfizer	Ribociclib (LEE011) Novartis
IC_{50}	CDK1: >1 μM	CDK1: >10 μM	CDK1: >100 μM
	CDK2: >500 nM	CDK2: >10 μM	CDK2: >50 μM
	CDK4: 2 nM	CDK4: 9–11 nM	CDK4: 10 nM
	CDK5: ND	CDK5: >10 μM	CDK5: ND
	CDK6: 5 nM	CDK6: 15 nM	CDK6: 39 nM
	CDK7: 300 nM	CDK7: ND	CDK7: ND
	CDK9: 57 nM	CDK9: ND	CDK9: ND

Trial	*n*	Treatment	Outcomes
PALOMA-1/TRIO 18 (REF. 6)	165	Letrozole versus Letrozole + palbociclib	PFS: 10.2 months (5.7–12.6) versus 20.2 (13.8–27.5) months, HR 0.49; $P = 0.0004$*
PALOMA-3 (REFS 18,208)	521	Fulvestrant + placebo versus Fulvestrant + palbociclib	PFS: 4.6 months (3.5–5.6) versus 9.5 (9.2–11.0) months, HR 0.46; $P < 0.0001$‡

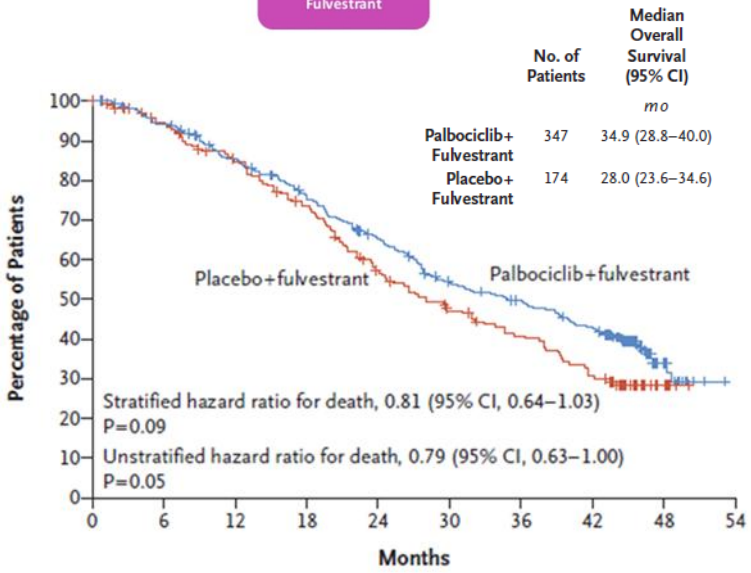
O'Leary *et al* Nat Rev Clin Onc 2016

cdk4/6 inhibitors in HR+ breast cancer: PALOMA-3 trial

- Metastatic breast cancer
- ER+/HER2-
- Tumor has shown resistance to endocrine therapy

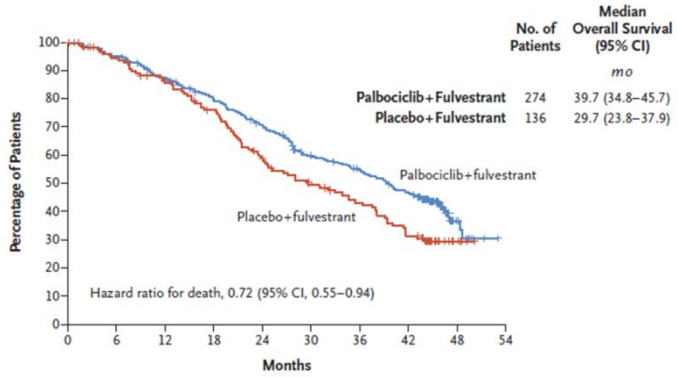
→ Palbociclib + Fulvestrant

→ Placebo + Fulvestrant

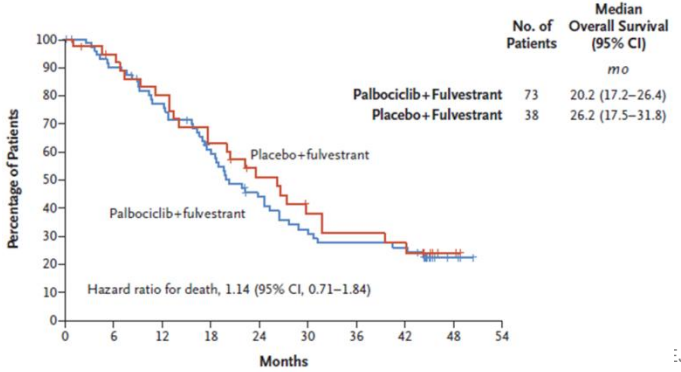


Patients do better on Palbociclib-containing regime

Sensitivity to prior endocrine therapy

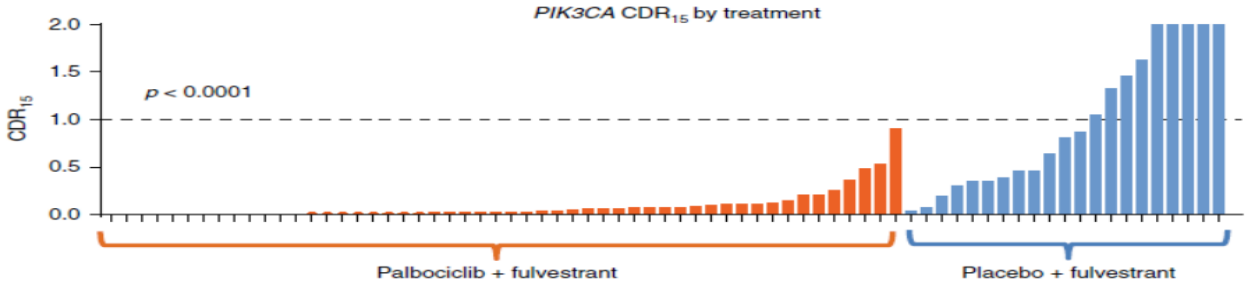


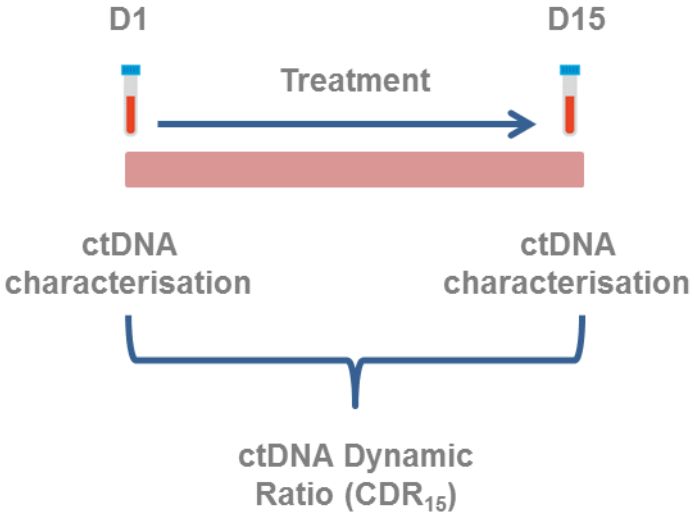
Without sensitivity to prior endocrine therapy

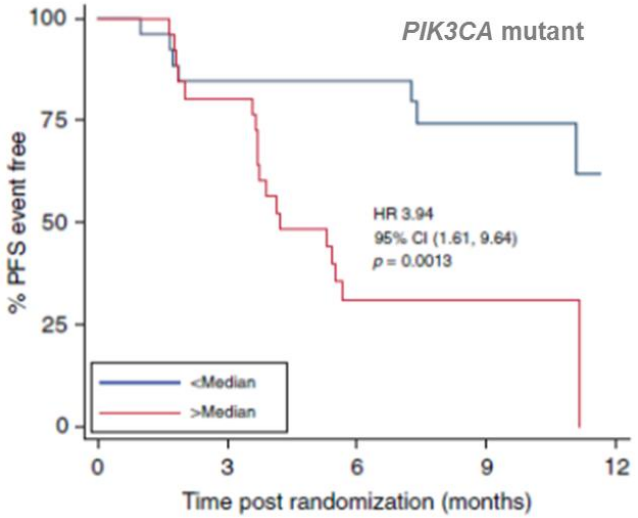


JM 2018

ctDNA analysis to predict early response on treatment







Potential marker of early response?

O'Leary *et al* Nat Comms 2018

Final remarks

- Liquid Biopsy analysis has advanced very rapidly in the last few years, particularly the analysis of ctDNA and its integration as a biomarker in clinical trials

- Several technical and clinical challenges still need to be overcome to realise the full potential of the clinical use of ctDNA

- ctDNA analysis in HR+ women can be used to identify those mutations driving resistance to the therapies used in the clinic

- Checkpoint inhibitors offer a therapeutic approach on women who relapse on standard hormone therapy but we need to identify biomarkers of response to better personalise these novel therapies

Acknowledgements

The patients that participate on the studies

The Royal Marsden Hospital

The Institute of Cancer Research

Molecular Oncology Lab

The Ralph Lauren Center for Breast Cancer Research

Center for Molecular Pathology (CMP)

ICR-CTSU

Academic and Non-Academic collaborators and Industry partners