

# Will circulating biomarkers help to deliver precision medicine in CRPC?



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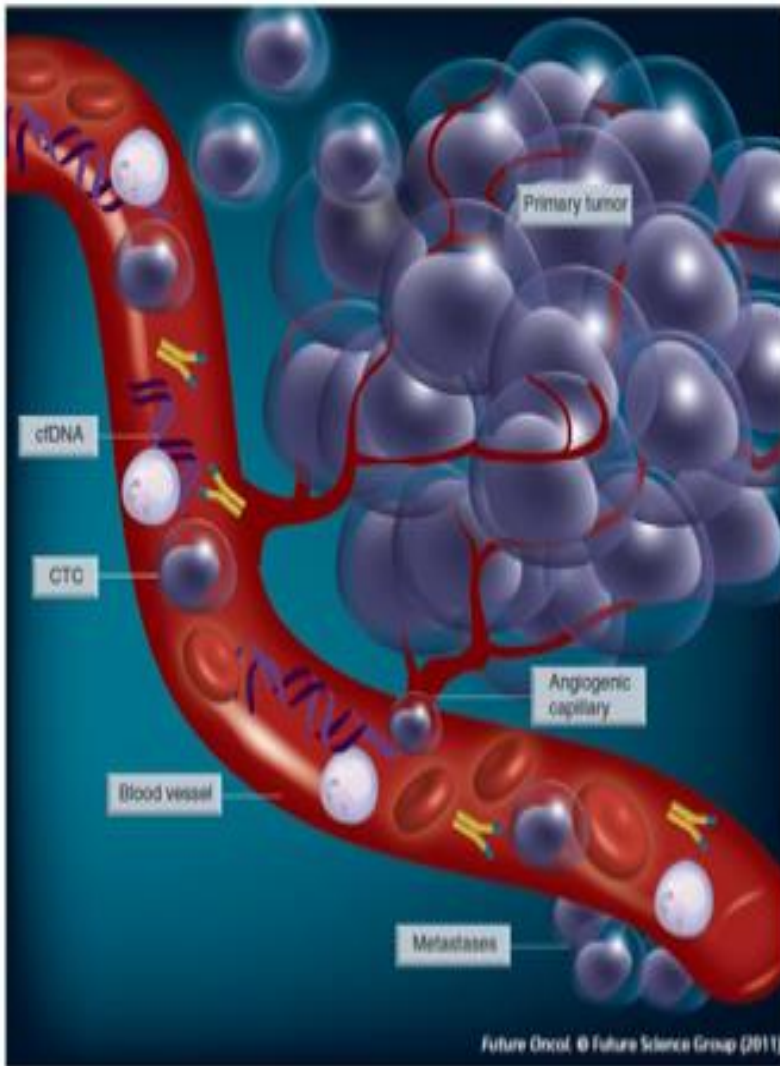
Spanish National Cancer Research Centre (CNIO) &  
Centro Integral Oncológico Clara Campal (CIOCC)

# Financial Disclosure

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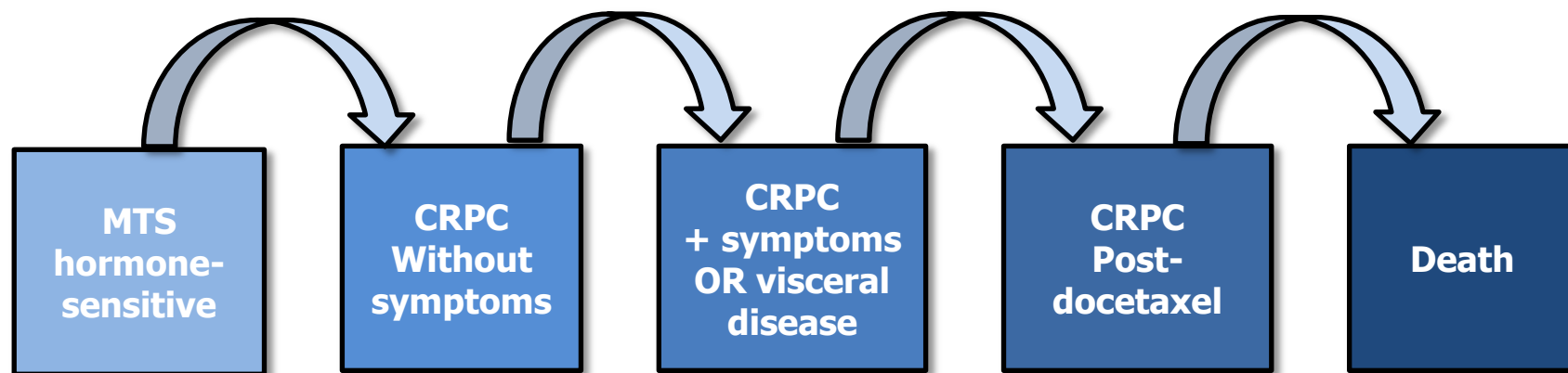
# Summary

- Why circulating Biomarkers?
- Proteins, hormones and other metabolites
- CTCs
- Nucleid Acids
- Take home message



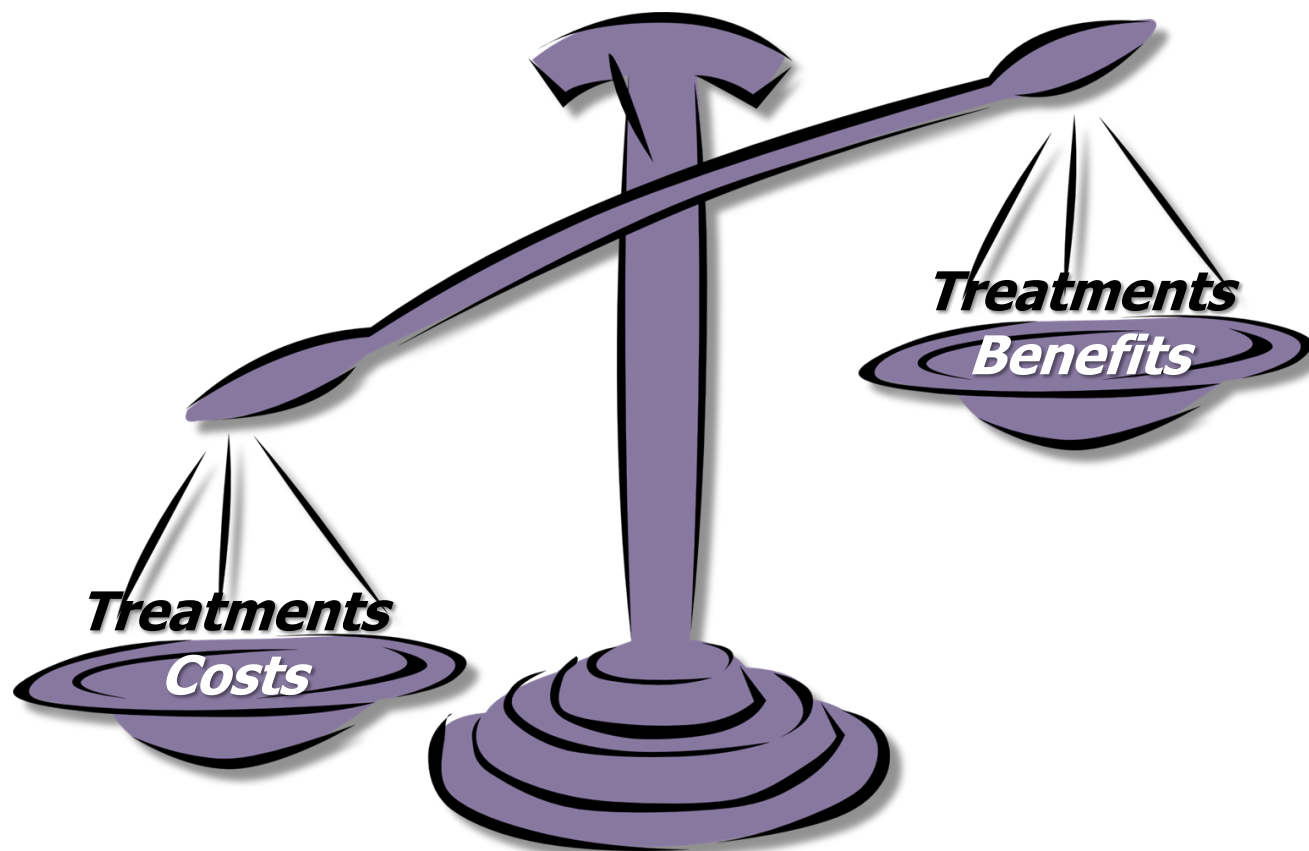
*De mattos-Arruda, Olmos, Tabernero. Future Oncol. 2011*

# Does precision medicine exist in CRPC?

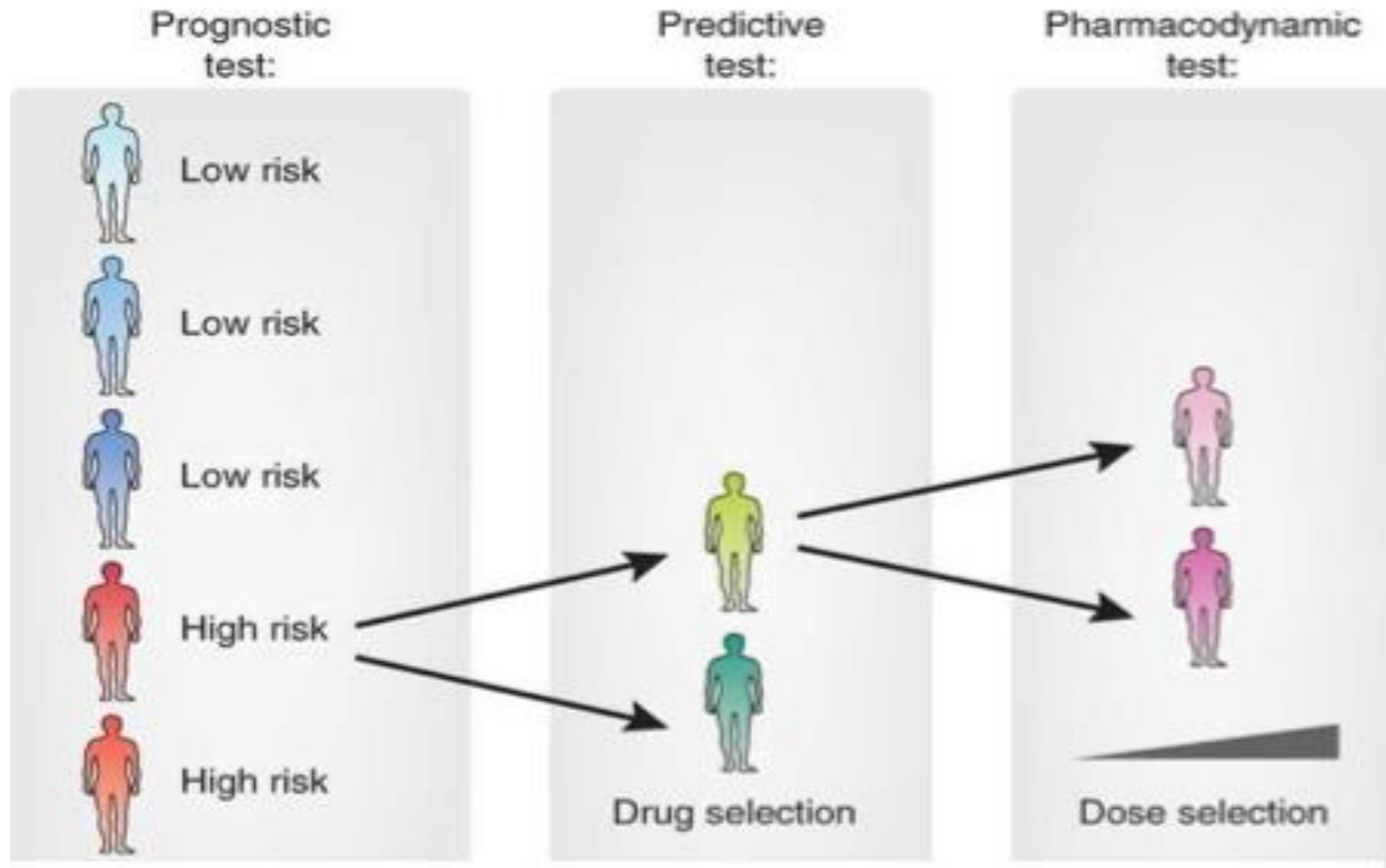


Pre 2010	<i>Classical ADT</i>	<i>2ry/3ry hormonal manipulations</i>	<i><b>Docetaxel (2004)</b></i>	<i>Mitroxantrone</i>
2010		<i><b>Spirucel T (only US)</b></i>		<i><b>Cabazitaxel</b></i>
2011				<i><b>Abiraterone</b></i>
2012		<i><b>Abiraterone</b></i>		<i><b>Enzalutamide</b></i>
2013			<i><b>Radium-223 dichloride (pre-/post-docetaxel)</b></i> <i>No visceral disease</i>	
2014	<i><b>Docetaxel</b></i>	<i><b>Enzalutamide</b></i>		

# How precision medicine could Help



# How precision medicine could Help



# Hurdles for precision medicine in CRPC

## **Traditional**

- Poor understanding of Prostate Cancer Biology
- Clinical heterogeneity and poor preclinical models
- Scarce effective treatment options
- Lack of benefit surrogate endpoints slows development

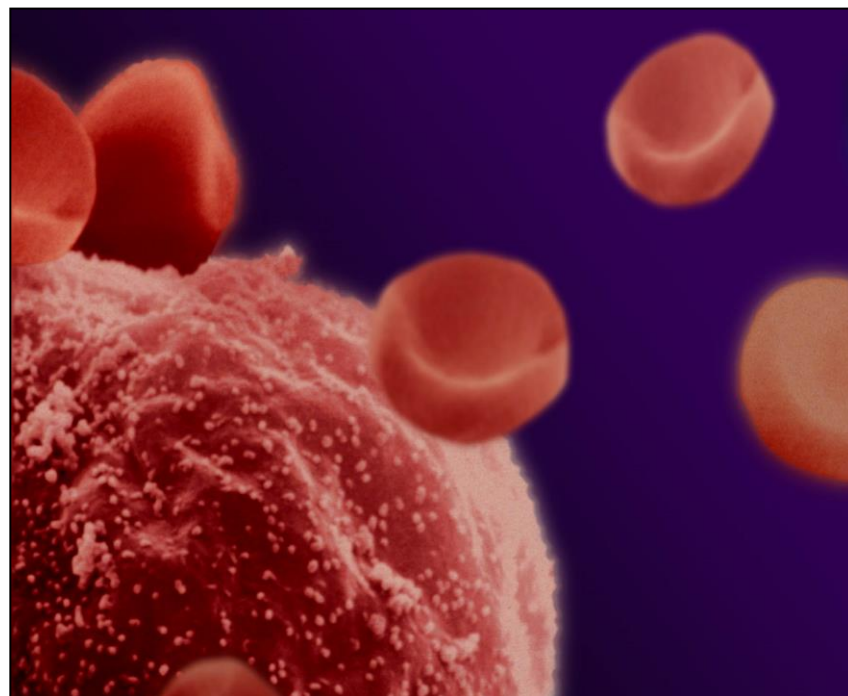
## **Ongoing hurdles**

- Limited access to tumour tissue in advanced and CRPC disease in clinical practice outside trials/academic institutions



# Advantages of Circulating biomarkers

- Blood represents an:
  - Attractive non-invasive source of tumour and host information
  - Repeatable
  - Easier implementation than tumour biopsies in:
    - Clinical trials
    - Routine practice





**Have circulating biomarkers already  
contributed in CRPC management?**

**How would they contribute in the future  
of precision medicine in CRPC?**

# Proteins, hormones and metabolites

# Proteins: serum, plasma & blood

BIOMARKER	Prognostic basal	Predictive value
Prostate Specific Antigen (PSA)	✓	✓/✗
Serum Albumin	✓	
Haemoglobin	✓	
Lactate dehydrogenase	✓	
Alkaline Phosphatase	✓/✗	

# COU-AA-301

- 1195 patients with progressive mCRPC
- Failed 1 or 2 chemotherapy regimens, 1 of which contained docetaxel

R  
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2:1

**Abiraterone 1000mg daily  
Prednisone 5mg BID  
n=797**

**Placebo daily  
Prednisone 5mg BID  
n=398**

Efficacy end points (ITT)

Primary end point:

- OS (25% improvement; HR 0.8)

Secondary end points:

- TTPP
- rPFS (Radiographic progression)
- PSA response

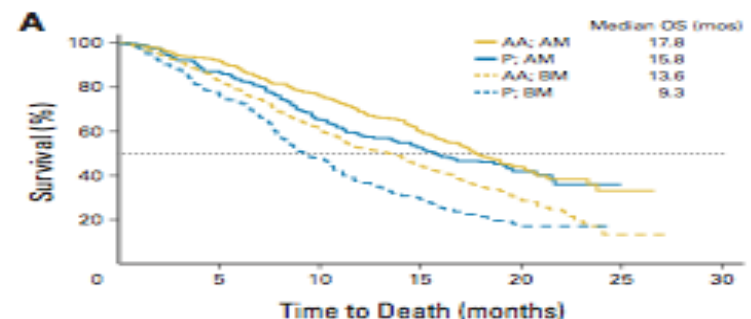
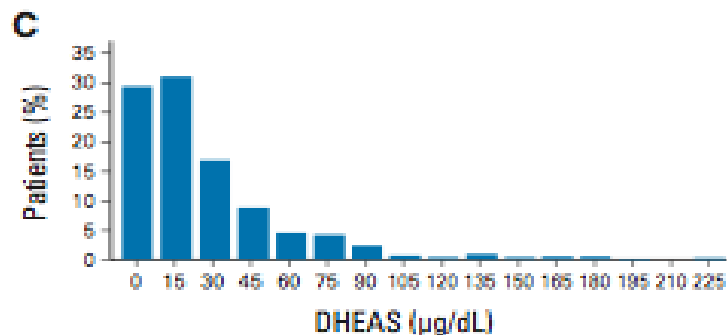
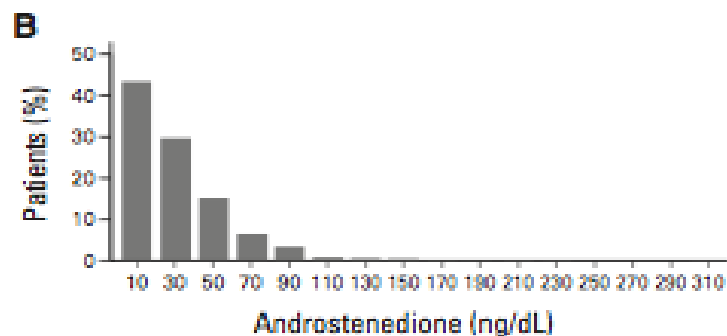
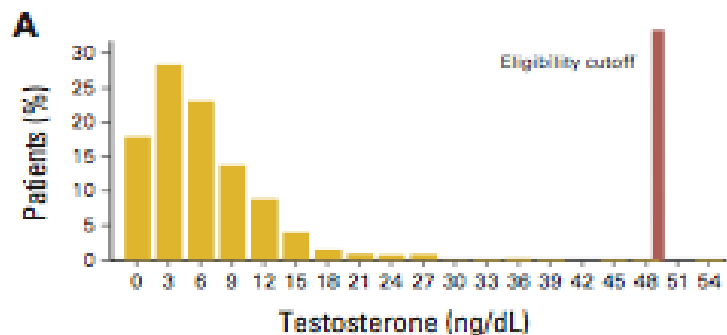
**FACT-P questionnaire**

**Prospective data collection: Day 1 of Cycles 1, 4, 7, 10, and every 6 cycles thereafter until the end of study treatment**

## Stratification by:

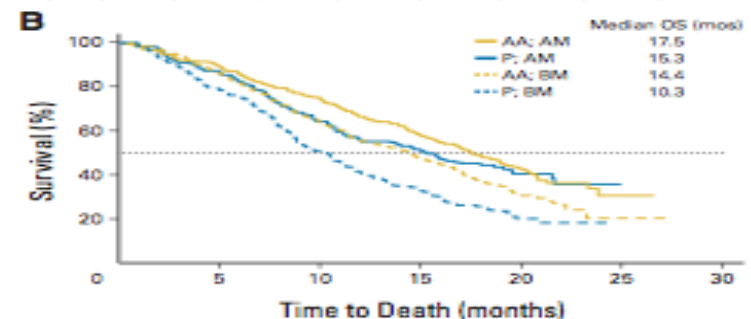
ECOG performance status	0-1 vs 2
Worst pain over previous 24 hours	BPI short form; 0-3 (absent) vs 4-10 (present)
Prior chemotherapy	1 vs 2
Type of progression	PSA only vs radiographic with or without PSA

# Serum hormones in COU-AA-301



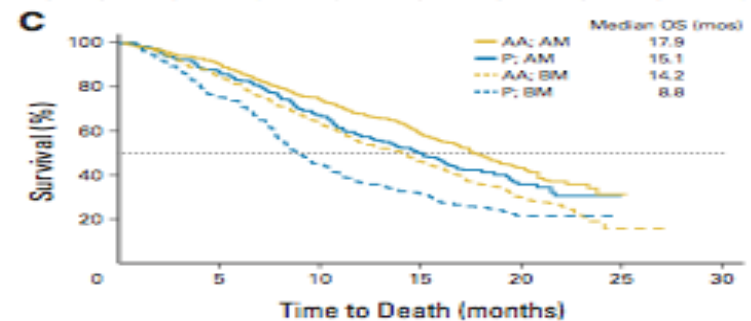
HR (95% CI)

Comparison	HR (95% CI)
AA AM v AA BM	0.64 (0.53 to 0.77)
AA AM v P AM	0.81 (0.64 to 1.03)
AA BM v P BM	0.89 (0.56 to 0.85)
P AM v P BM	0.51 (0.39 to 0.67)



HR (95% CI)

Comparison	HR (95% CI)
AA AM v AA BM	0.68 (0.56 to 0.82)
AA AM v P AM	0.80 (0.63 to 1.02)
AA BM v P BM	0.72 (0.58 to 0.89)
P AM v P BM	0.62 (0.47 to 0.81)



HR (95% CI)

Comparison	HR (95% CI)
AA AM v AA BM	0.67 (0.56 to 0.81)
AA AM v P AM	0.79 (0.62 to 0.98)
AA BM v P BM	0.72 (0.58 to 0.88)
P AM v P BM	0.62 (0.48 to 0.80)

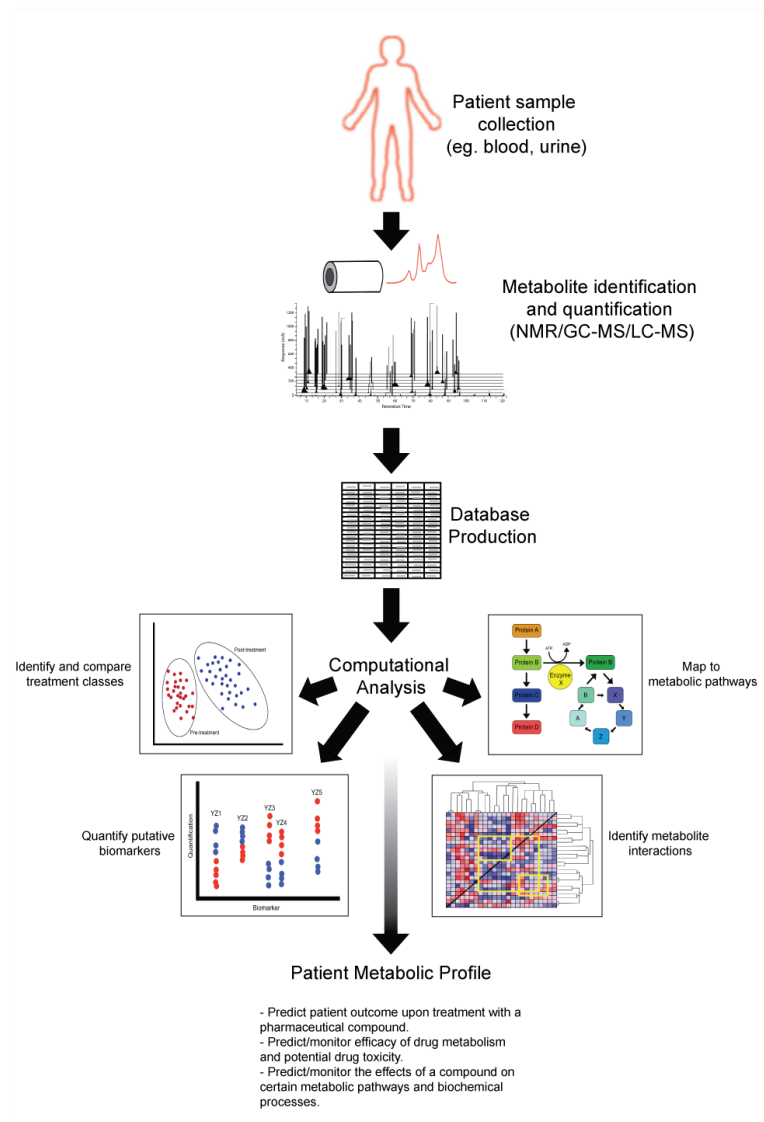
# Serum hormones in COU-AA-301

BIOMARKER	Prognostic basal	Predictive value
Testosterone	✓	✗
Androstenedione	✓	✗
DHEAS	✓	✗

*Ryan C et al. J Clin Oncol. 2011*

# Metabolomics in CRPC

- Metabolomic profiling has been proposed as a potential source for biomarker identification
- Metabolome is closer to Phenotype

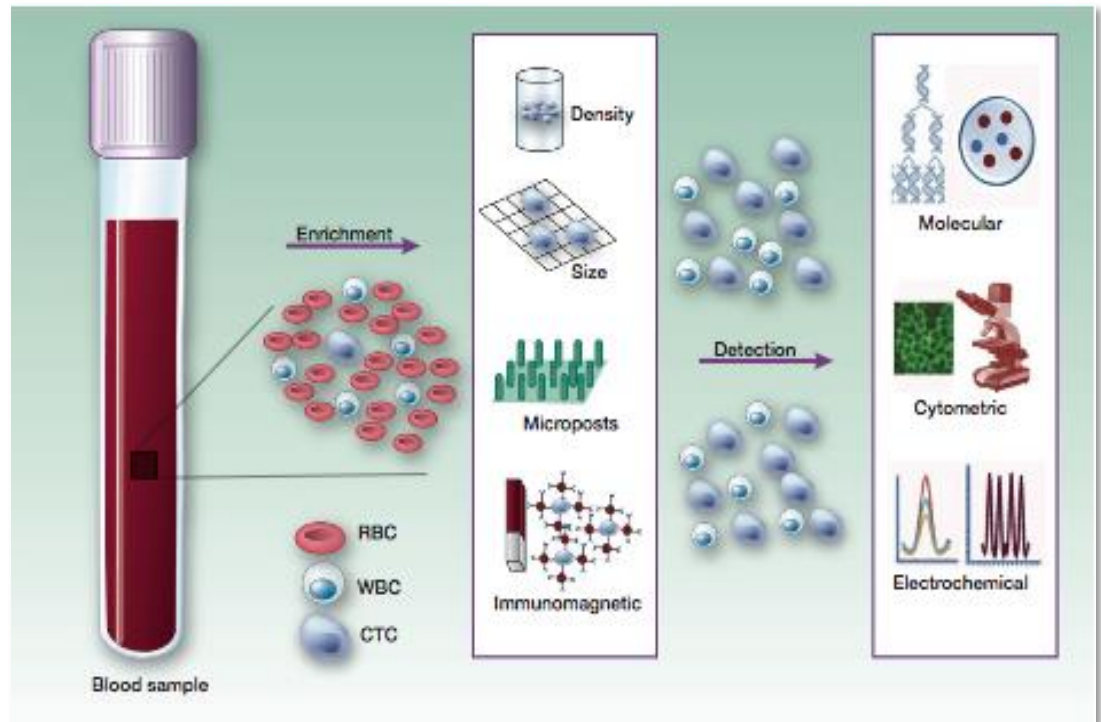




# Circulating Tumor Cells

# Circulating Tumor Cells (CTCs)

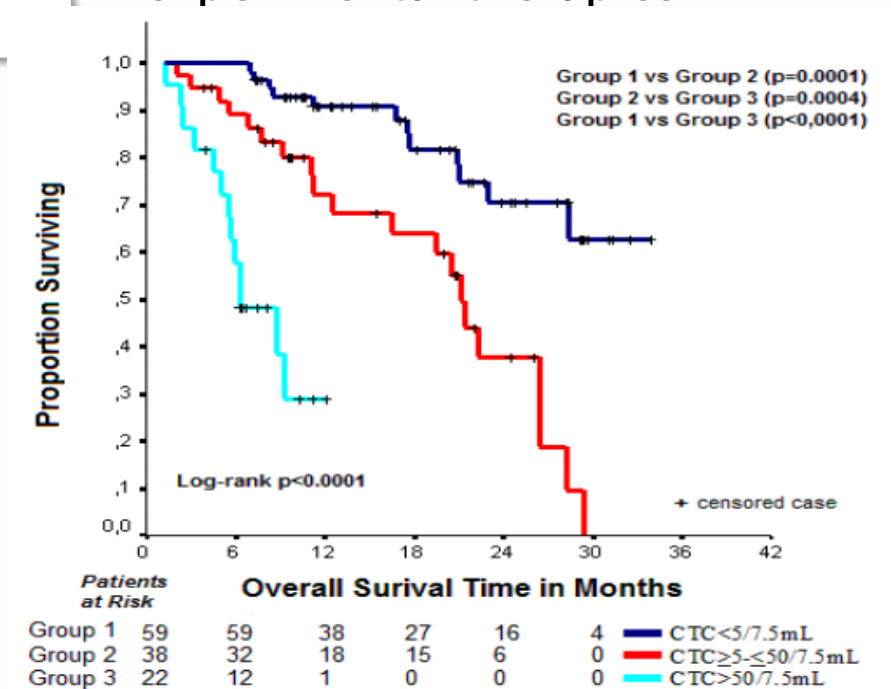
- Peripheral blood epithelial cells shed, actively or passively, from tumor surface of cancer patients
- Isolation:
  - Enrichment
  - Detection
  - Enumeration
- Profiling



*Yap, Lorente, Omlin, Olmos & de Bono. Clin Cancer Res. 2014*

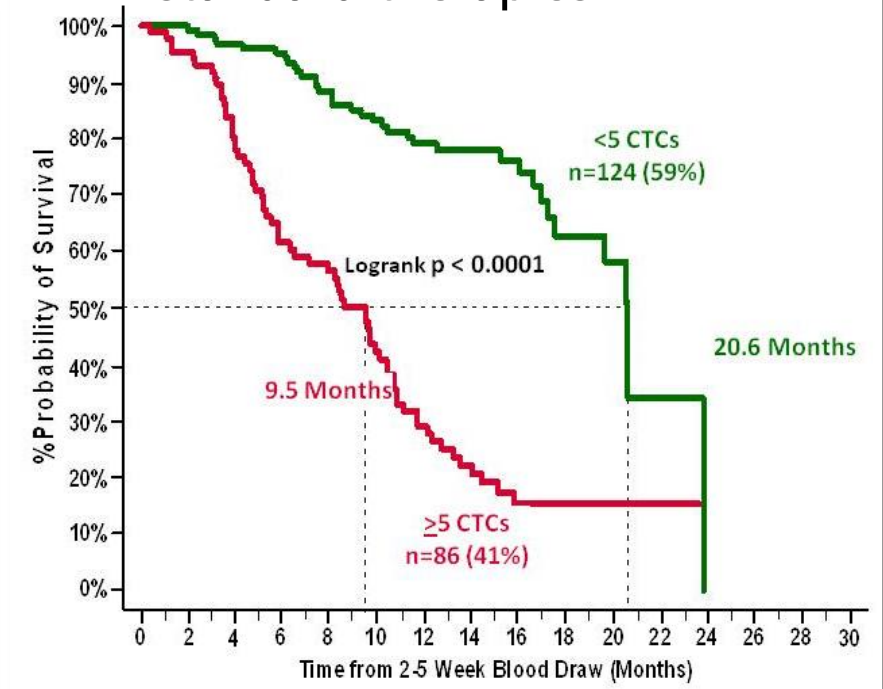
# CTCs enumeration

- Single centre study:  
experimental therapies



*Olmos D, Arkenau HT, Ang JE et al. Ann Oncol, 2008*

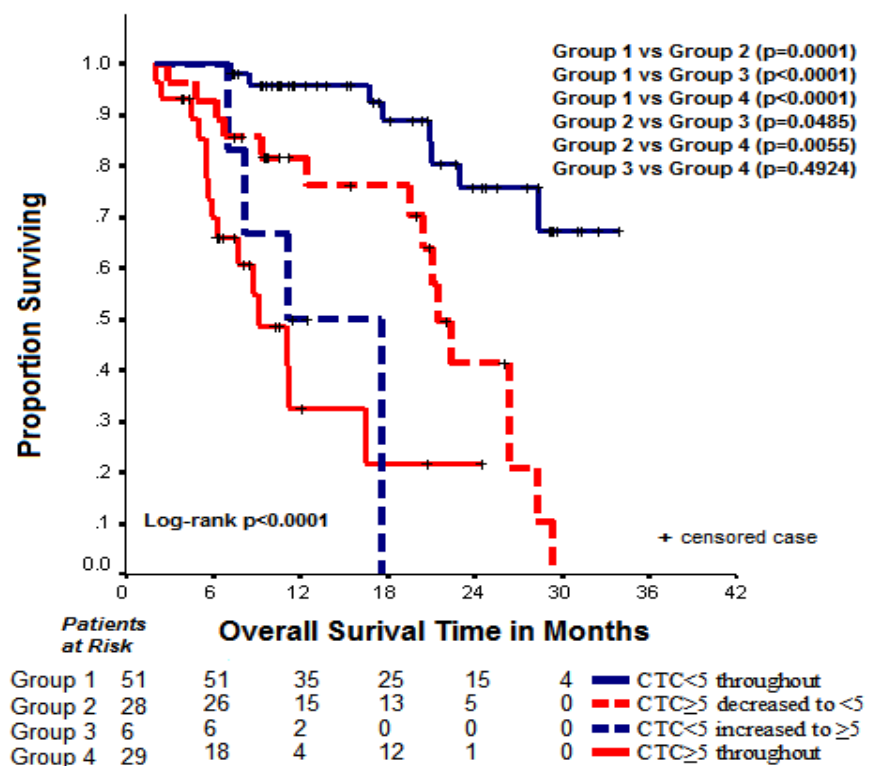
- Multicentre study:  
standard therapies



*De Bono, Scher, Montgomery et al. Clin Cancer Res, 2008*

# CTCs count changes

Conversion from  $\geq 5$  CTC to  $< 5$  CTC

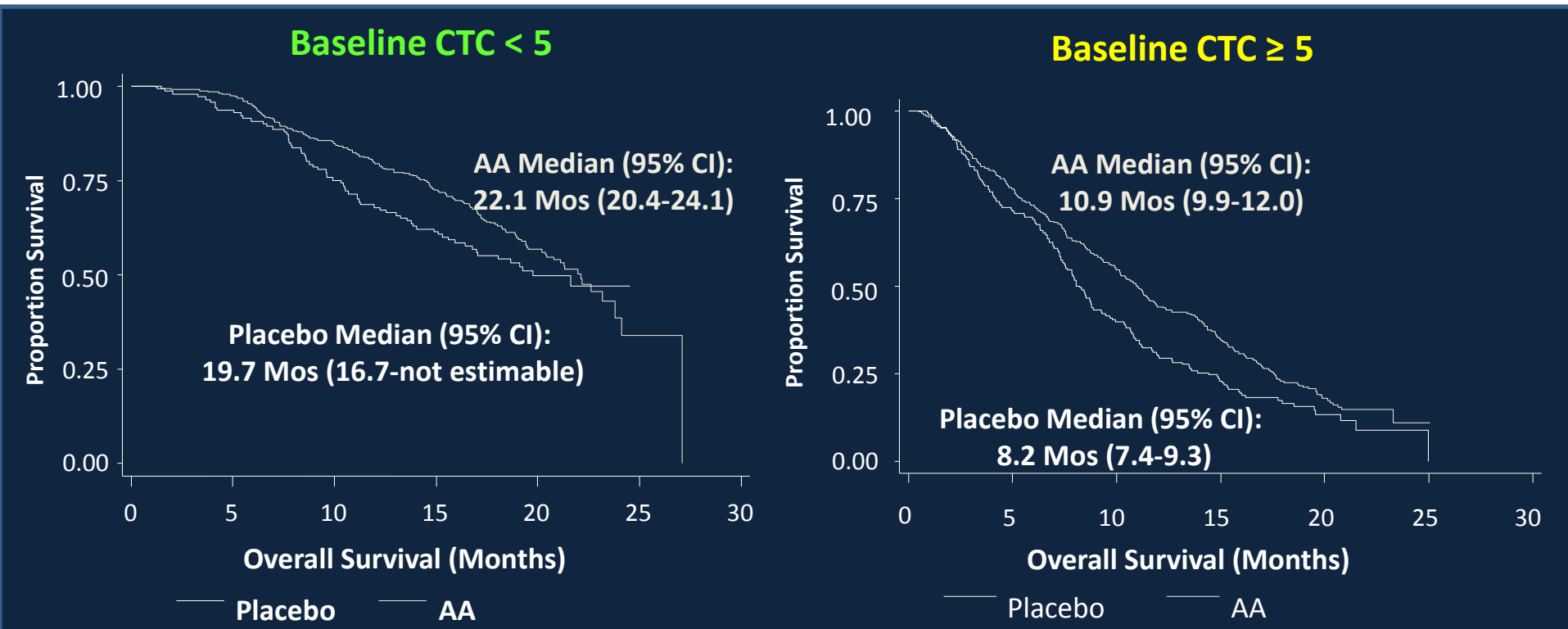


Olmos D, Arkenau HT, Ang JE et al. Ann Oncol, 2008

- CTC counts are prognostic
- CTC counts may indicate when treatment is effective
- BUT**
- This does not establish 'surrogacy'
- Prospective Phase III trials in which the evaluation of the marker (CTC number) are linked to the development of a drug are required

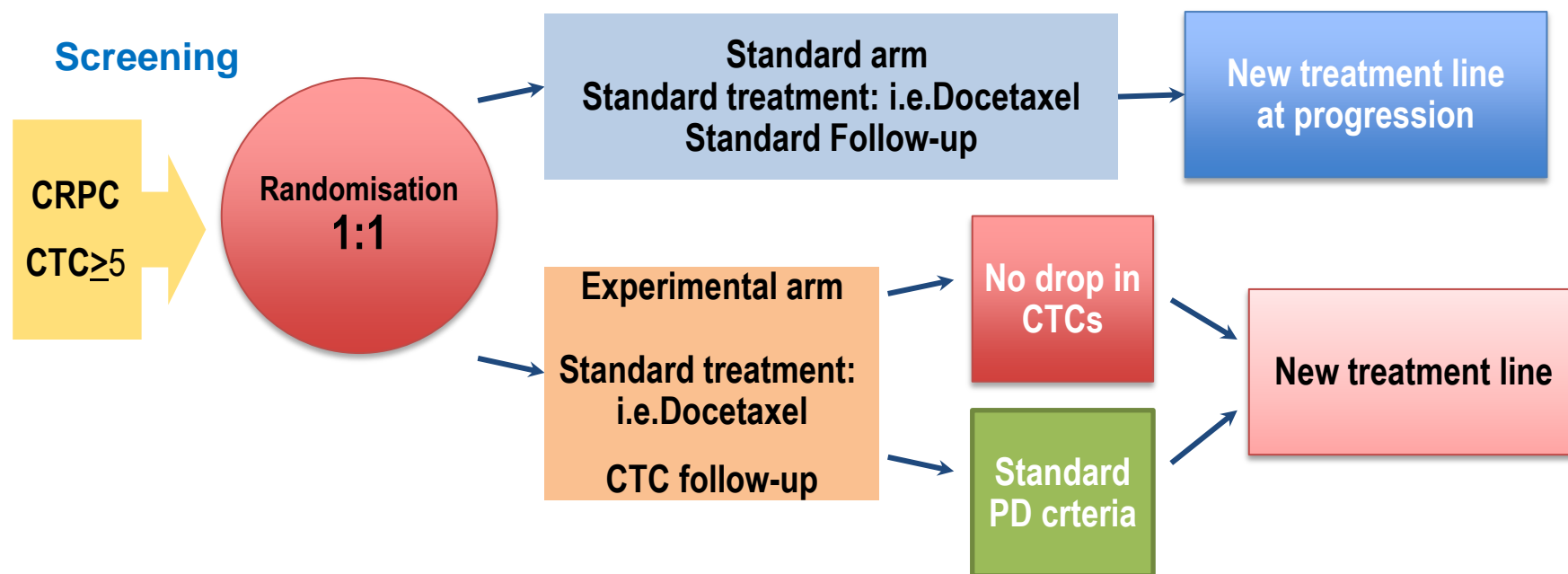
# CTCs surrogacy: COU-AA-301

- Higher conversion rates with AA relative to placebo, and benefit for favorable (CTC < 5) and unfavorable (CTC ≥ 5) CTC subgroups
- Higher percentage of ≥30% declines in AA patients.



- Independent predictive factor of OS in MVA.

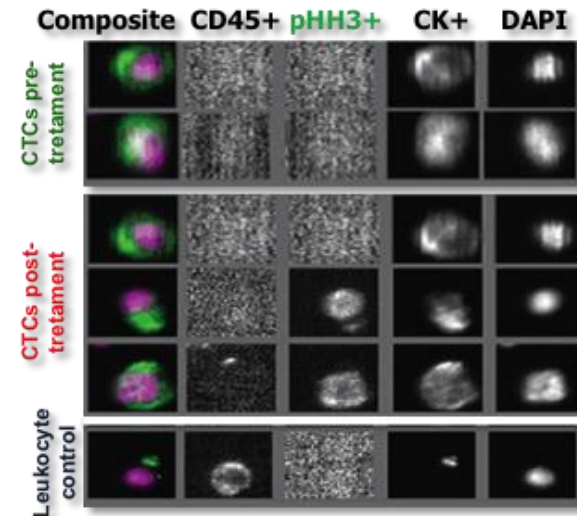
# CTCs changes – Therapy switch



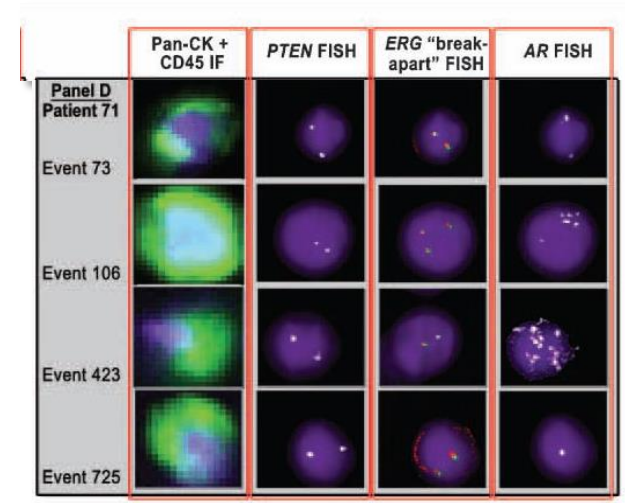
*Possible trial design to answer the question of CTCs in monitoring treatment benefit at a individual patient level*

# CTCs as surrogate tumour tissue

Protein assays	Use/Applications
AR (Nuclear/Cytoplasmic)	Target identification/Pharmacodynamic
EGFR	Target identification
HER2	Target identification
IGF-1R	Target identification
M30 (CK-M30)	Pharmacodynamic
$\gamma$ H2AX	Pharmacodynamic
pHH3	Pharmacodynamic
Genomic assays	Use/Applications
AR amplification	Marker of resistance
<i>pTEN</i> loss	Marker of resistance/Drug combinations
<i>TMPRSS2/ERG</i>	Taxonomic classification
<i>Myc</i> amplification	Tumor profiling



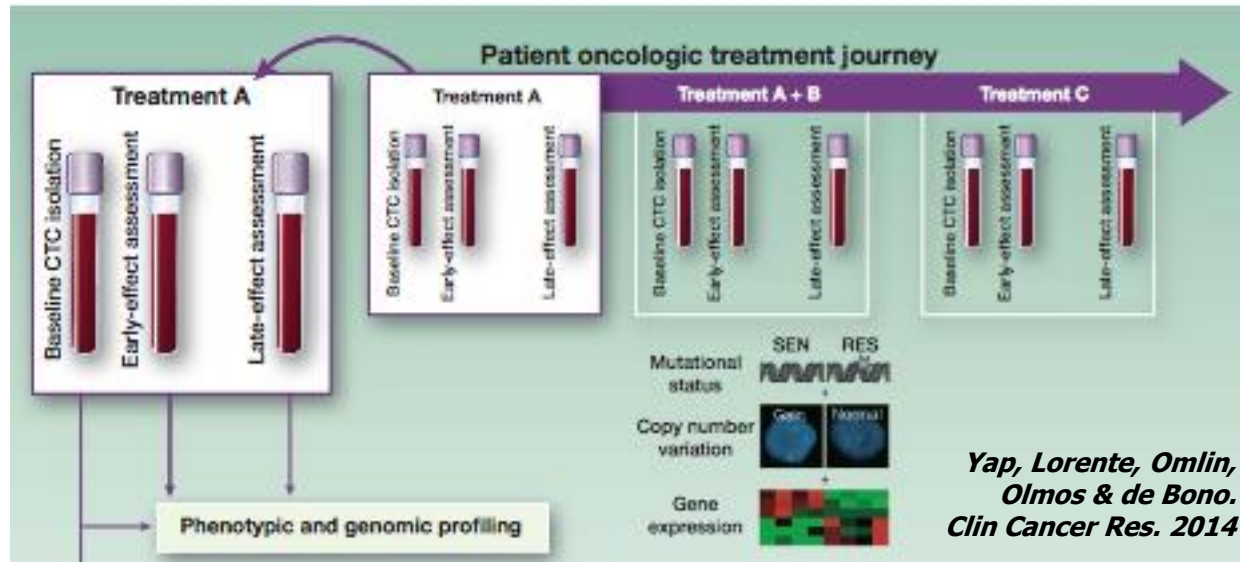
*Olmos, Barker, Sharma et al. Clin Cancer Res. 2011*



*Attard, Swennenhuis, Olmos et al. Cancer Res. 2009*

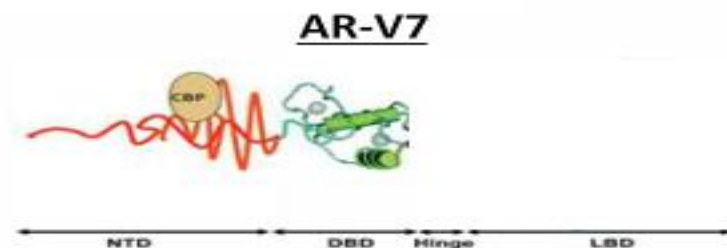
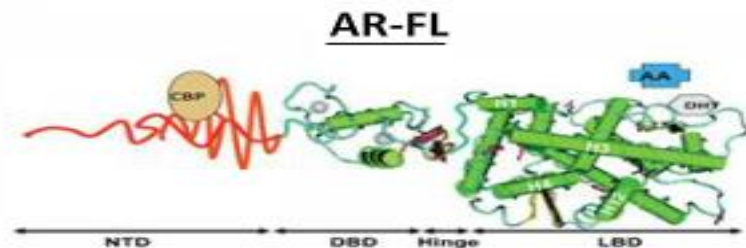


# Monitoring tumour changes in CTCs

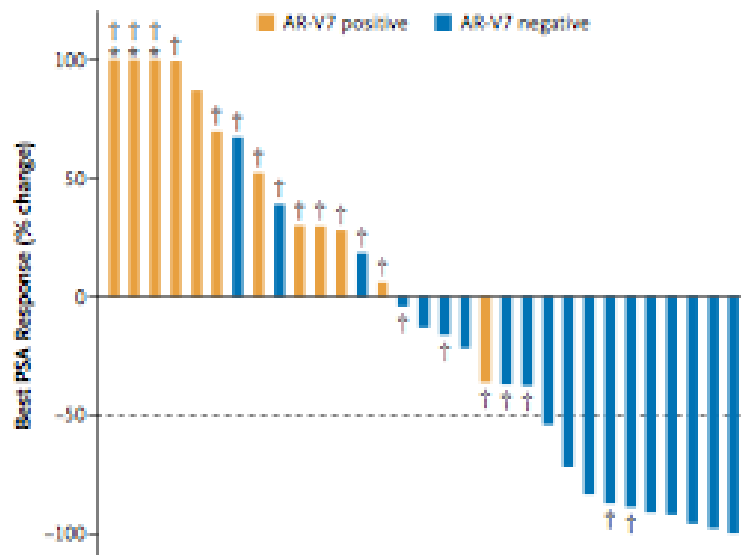


- *AR* mutations: Treatment selection and monitoring  
*Jiang Y, Palma JF, Agus DB et al. Clin Chem 2010*
- *AR* alternative splicing variants

# CTCs *AR-V7* positive: predictive marker

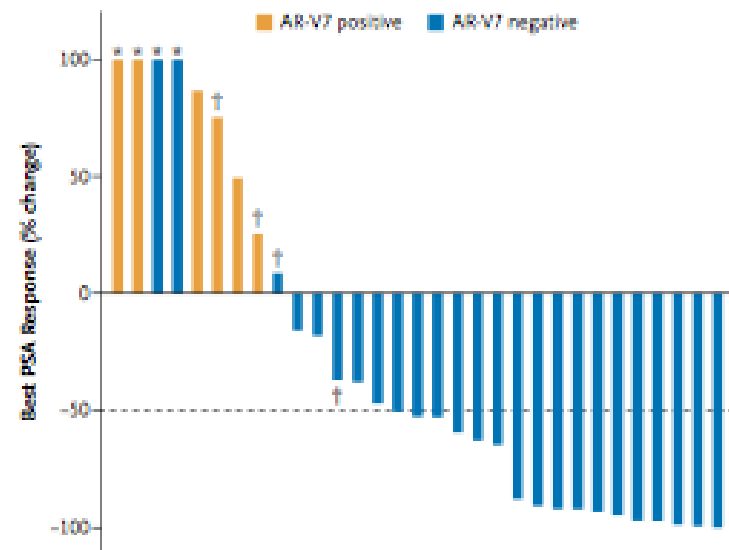


**A** Enzalutamide-Treated Patients



Antonarakis, Lu, Wang et al. *N Engl J Med.* 2014

**B** Abiraterone-Treated Patients



Genitourinary tumours, prostate 2  
Monday 29; 02:00 PM - 03:45 PM  
**Abstract 7980**

# CTCs *AR-V7* current limitations

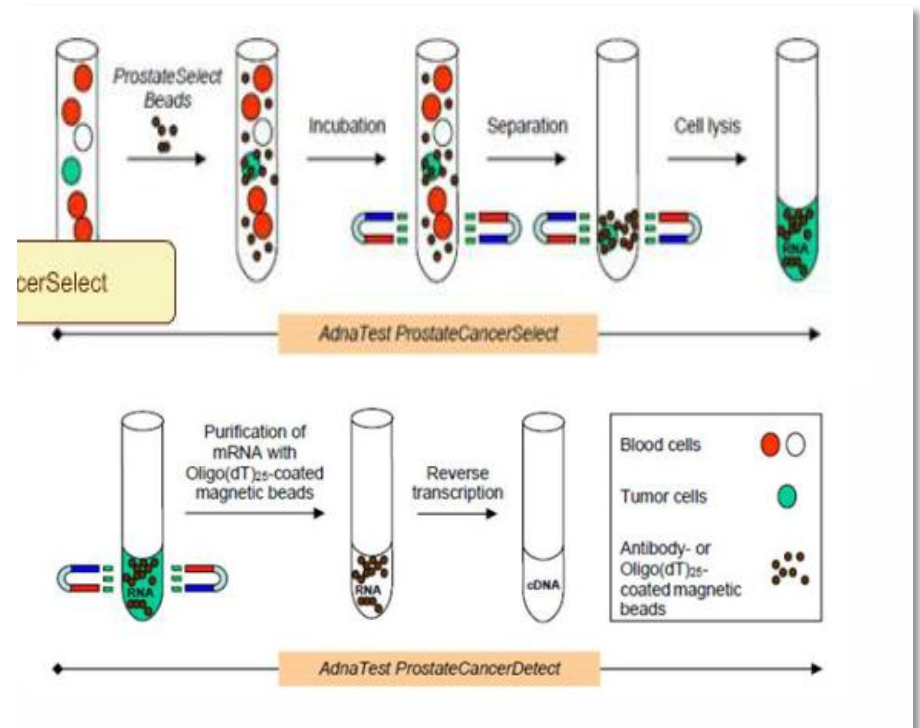
- Single-centre experience
- Require immediate initial processing
  - Enrichment CTCs
  - Lysis and RNA capture
- Haemolysis
- Novel methods

Genitourinary tumours, prostate 2  
Monday 29; 02:00 PM - 03:45 PM

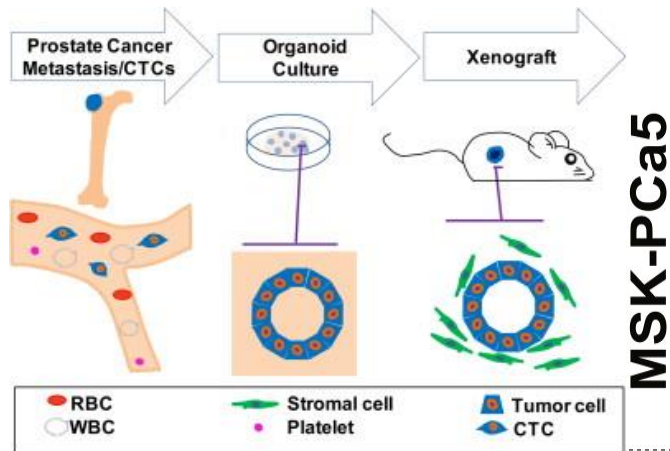
**Abstract 7570**

-Galeterone in *AR-V7*

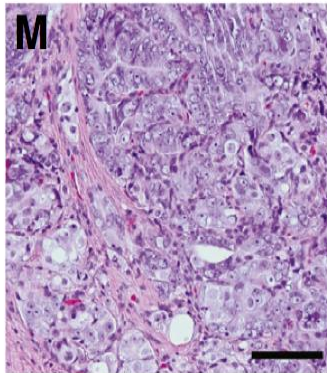
-EPIC *AR-V7* detection on CTCs



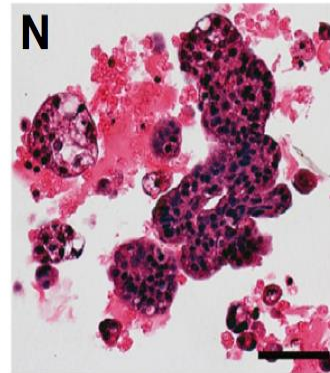
# Organoids and PDX from CTCs



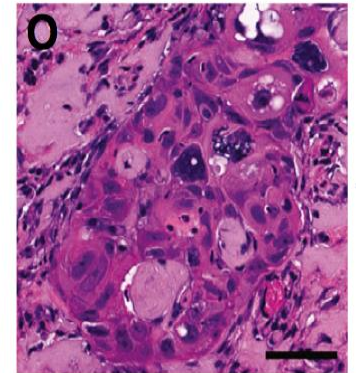
Patient Tumour



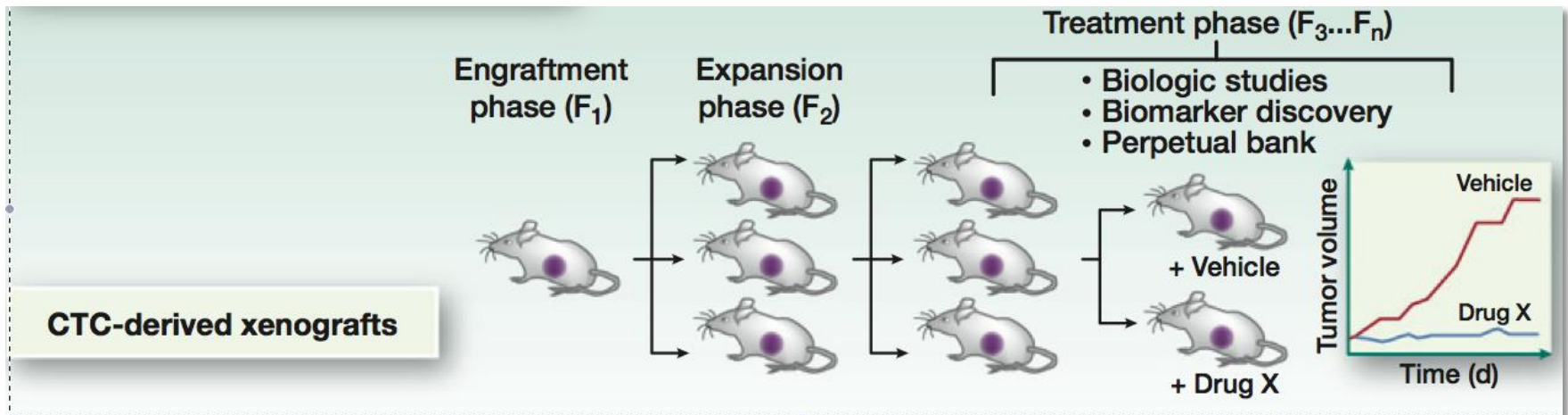
Organoid



PDX from Organoid



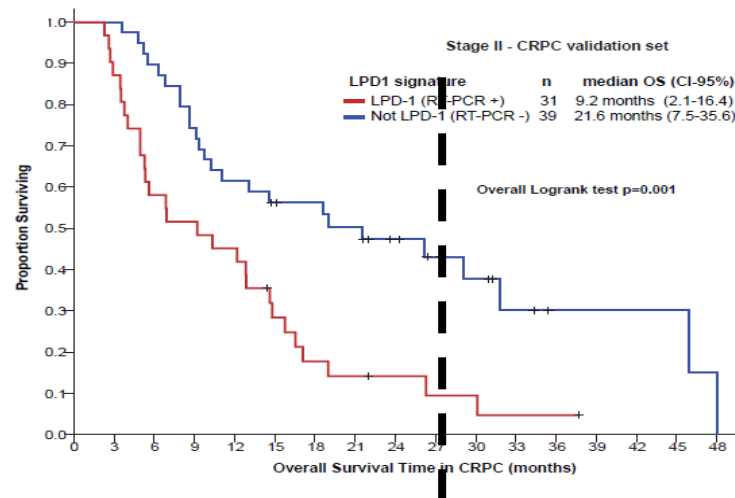
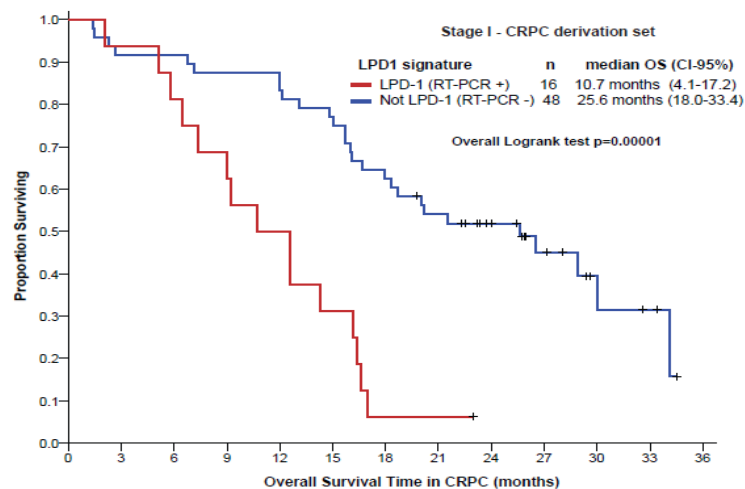
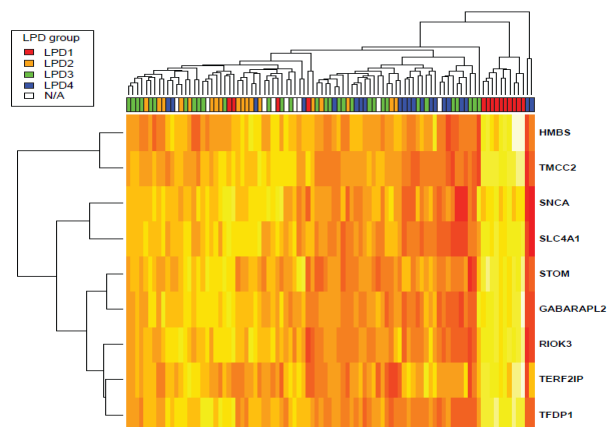
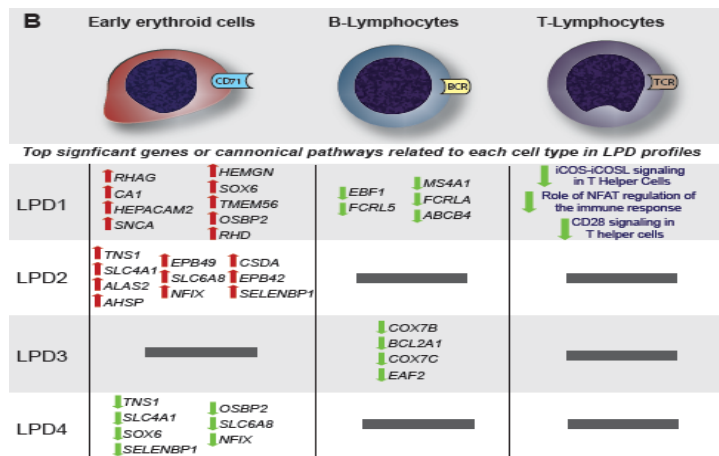
Gao, Vela, Sboner et al. *Cell*. 2014



Yap, Lorente, Omlin, Olmos & de Bono.  
*Clin Cancer Res*. 2014

# Circulating Nucleid Acids

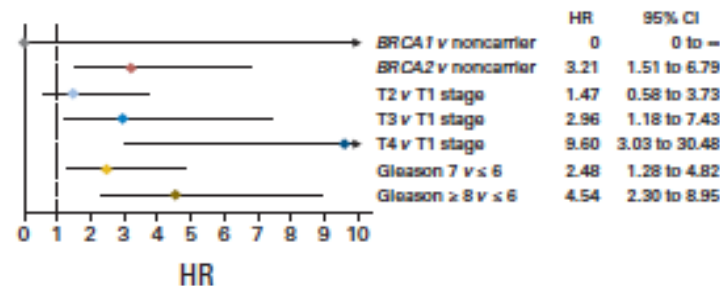
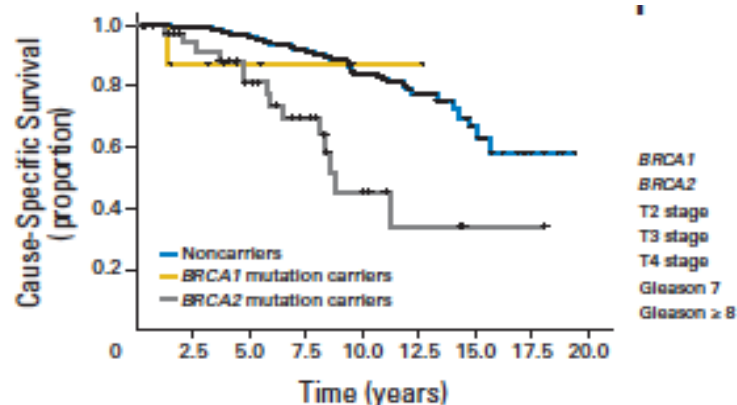
# Whole blood RNA signatures





# Germline DNA

- >100 SNPs variants associated to cancer risk, SNPs variants also associated with toxicity.
- Screening of germline *BRCA1* and *BRCA2* mutations in >2000 Pca.
- *gBRCA 2* mutations are an independent prognostic factor for survival<sup>1</sup>. PARPi are very active in this population<sup>2</sup>. Somatic?

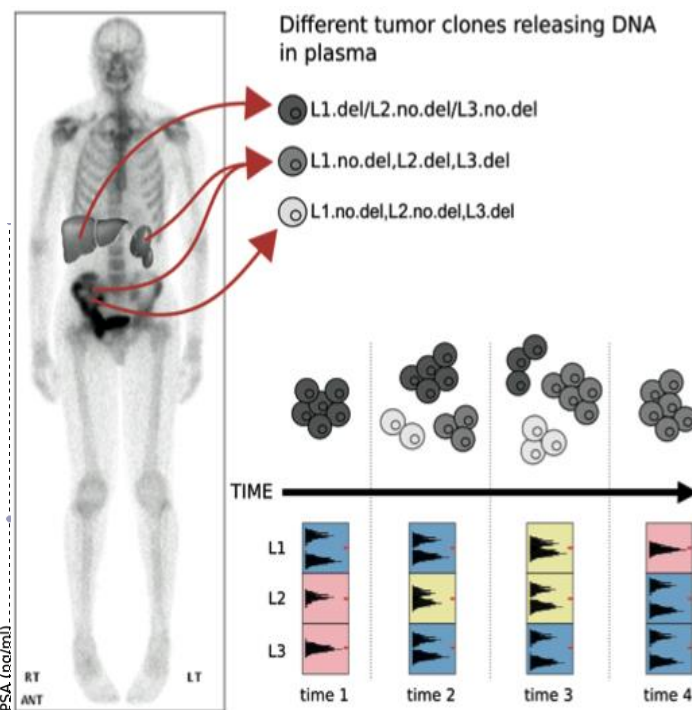
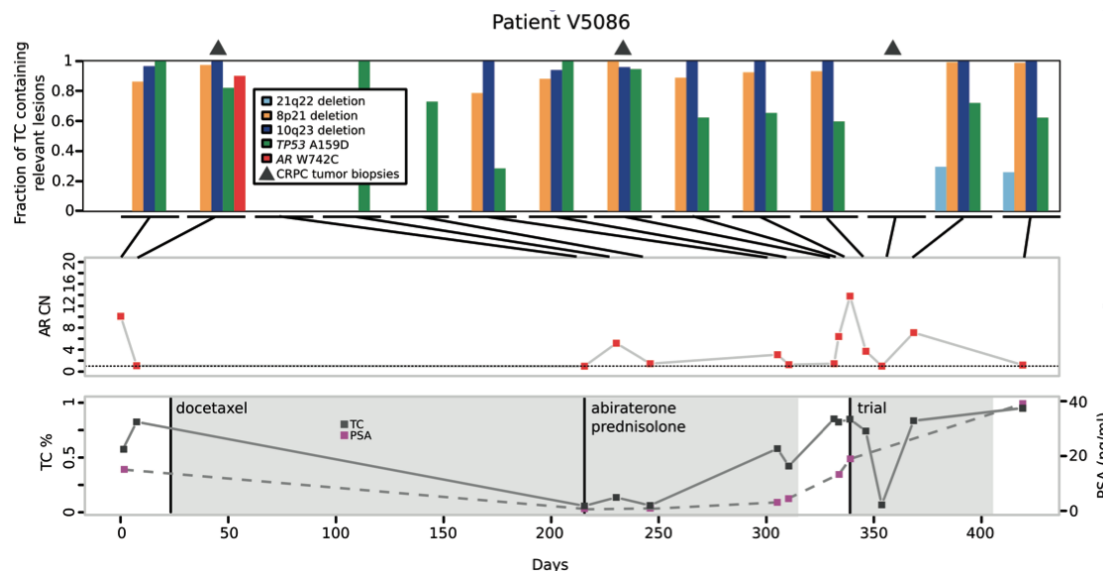


Genitourinary tumours, prostate 2, Monday 29; 02:00 PM - 03:45 PM  
**LBA 20. Olaparib in sporadic CRPC patients**



# Circulating free DNA in CRPC

- Multiple clones in metastatic disease represented in cfDNA
- Dynamic clonal architectural heterogeneity
- Monitoring of disease i.e. AR mut or Amplif



# Take home messages

- The backbone of precision medicine is about maximising benefit and minimising risk in our patients
- Circulating makers to help in the stratification and monitoring of CRPC are use everyday
- Blood is a source of information from the tumor and the host
- Novel technologies are helping in treatment selection and monitoring
- Still implementation is routine practice needs more validation work, reproducibility and efficiency

# Acknowledgments



## CNIO-CIOCC Prostate Cancer Team

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**2014 Stewart Rahr  
PCF YIA**

