



Real-time assessment of cancer in the blood: the concept of a liquid biopsy in castration-resistant prostate cancer

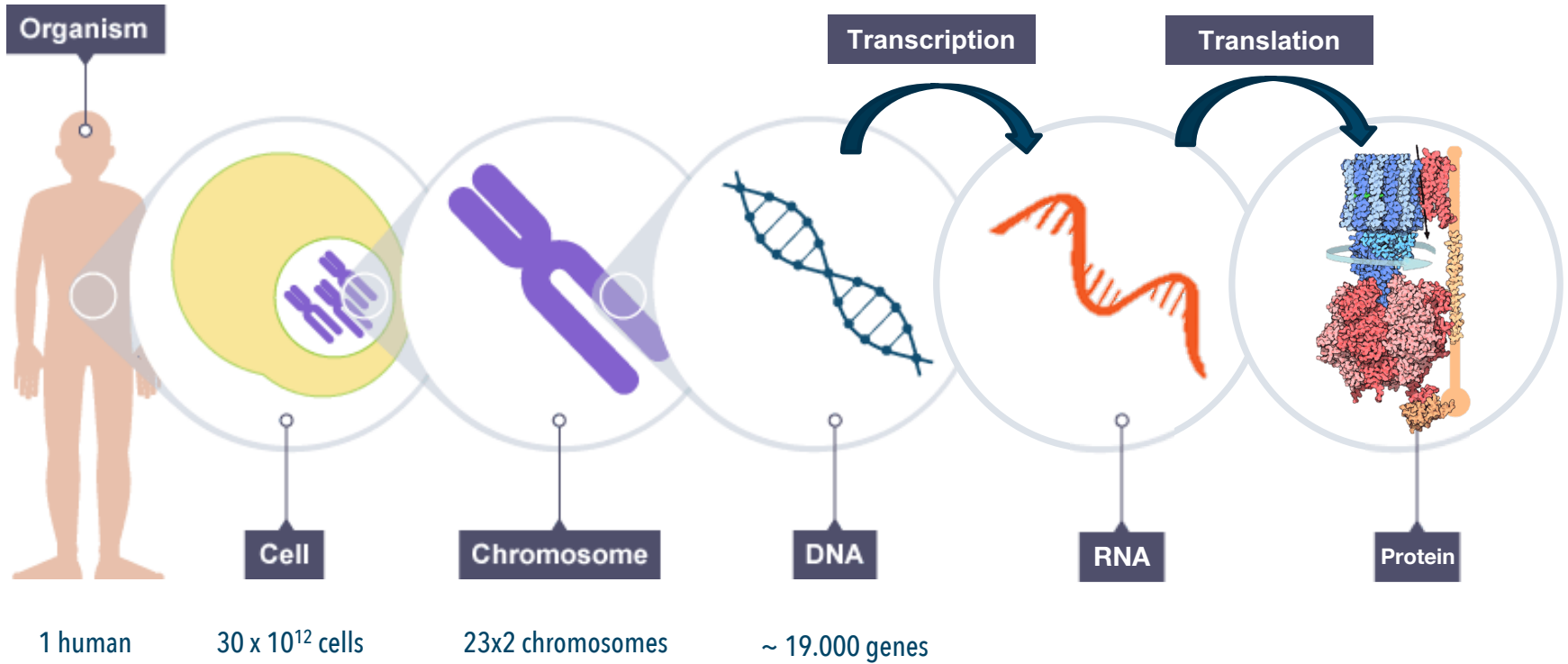
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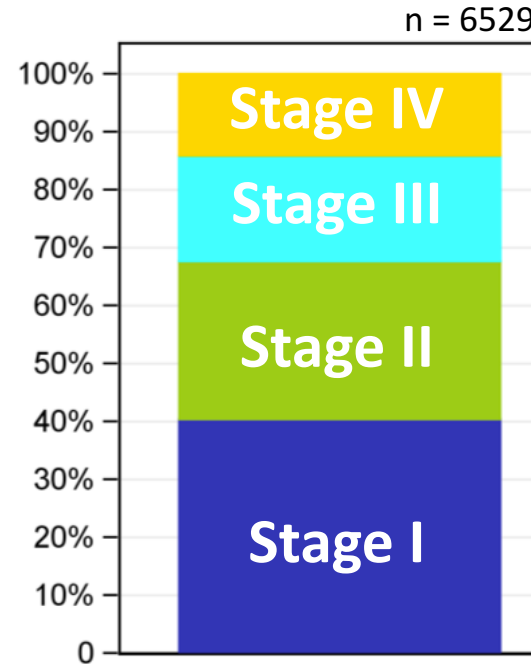
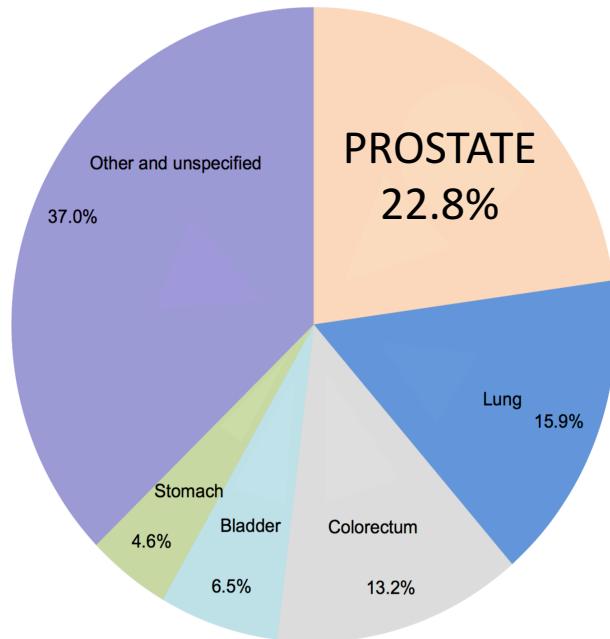
 **Karolinska
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Central dogma of the molecular biology

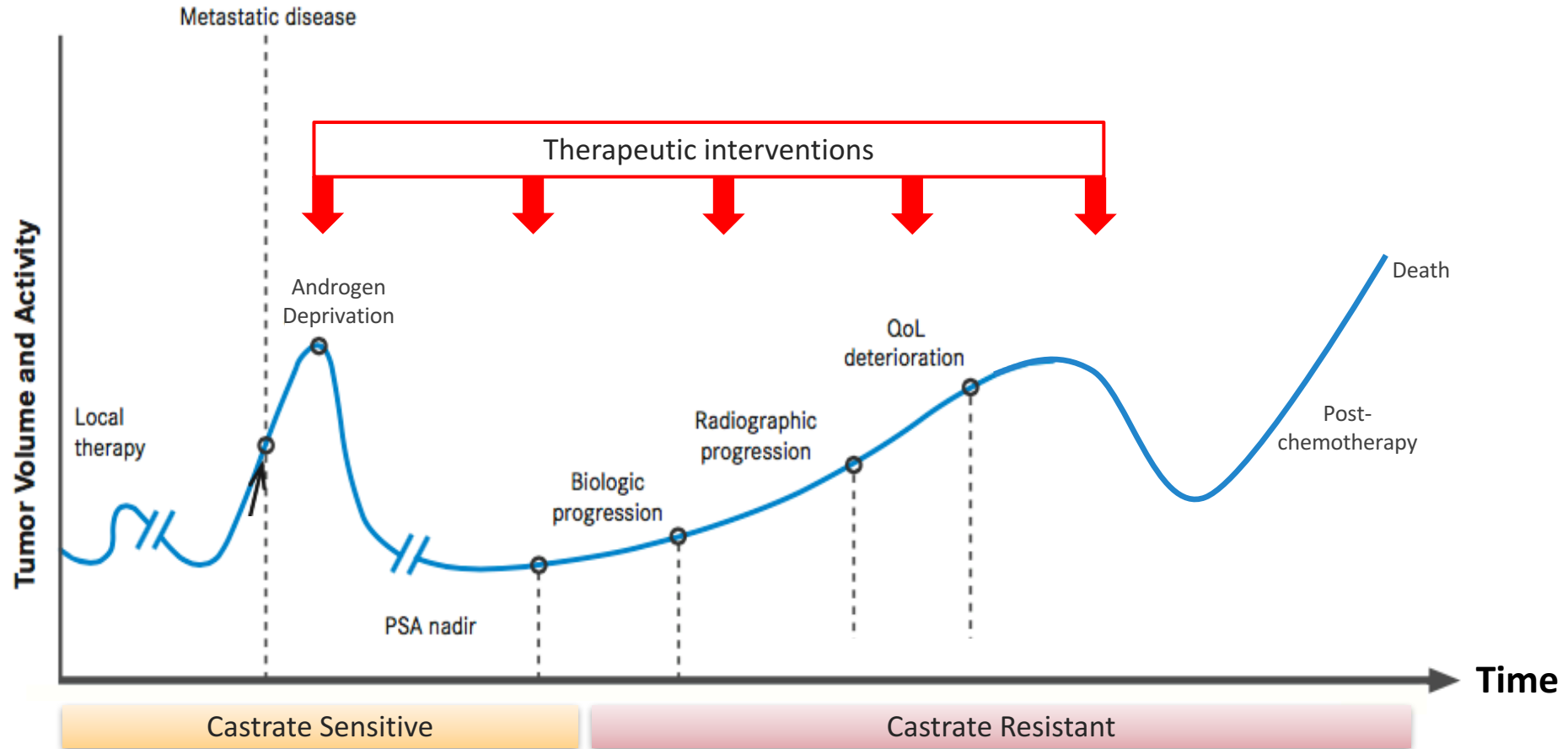


Prostate cancer incidence

- Most common detected cancer in men
- In Europe, **410.000** new diagnoses each year
- In Belgium, **8.000** new cases each year

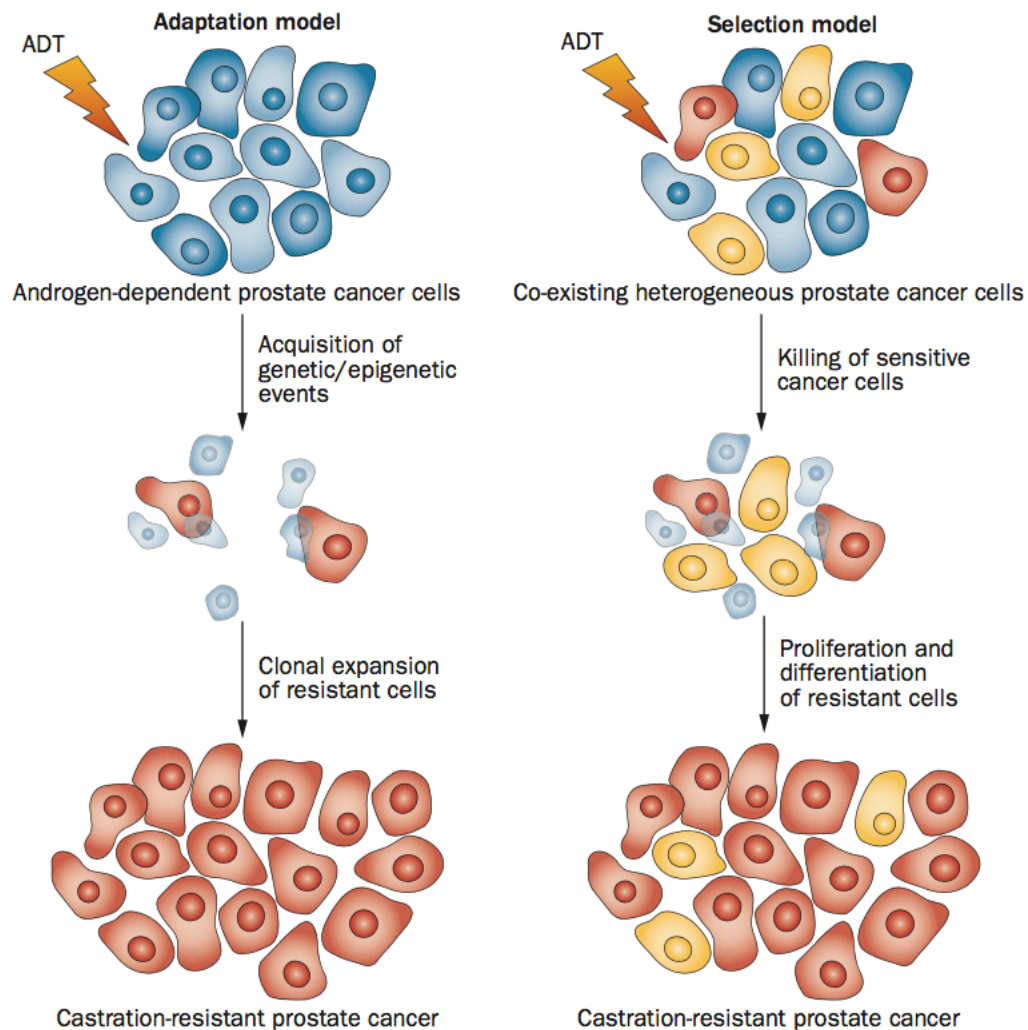


Castration-resistant prostate cancer - disease progression despite castration



Castration-resistant prostate cancer

- models to describe the onset of CRPC



Liquid Biopsy in Castration-resistant prostate cancer – definition of the problem

- ca. 15-20% of prostate cancer diagnosis will developed castration-resistant disease
- Advanced prostate cancer is a heterogeneous disease, both between and within patients
 - Many therapeutics, different therapy regimens
 - A large fraction of patients demonstrates intrinsic resistance
 - Expensive treatment cost



There is a need for predictive biomarkers for treatment response

Liquid Biopsy in Castration-resistant prostate cancer – definition of the problem

How should we tackle this problem?

Which context?

What predictive treatment
biomarkers are there?

How do we measure these?

Liquid Biopsy in Castration-resistant prostate cancer - define the context



Liquid Biopsy in Castration-resistant prostate cancer – definition of the problem

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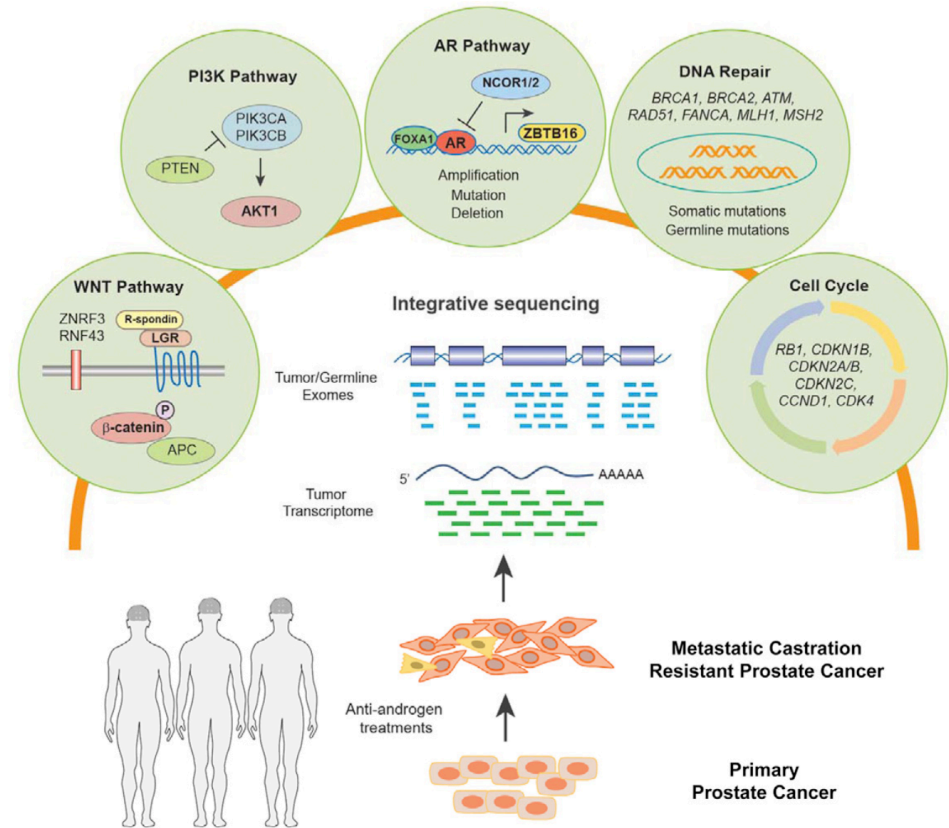
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Liquid Biopsy in Castration-resistant prostate cancer

- Predictive biomarkers from profiling studies

- Drivers of advanced prostate cancer
 - n = 150, WES
- Segregation of different subtypes of advanced PCa using molecular pathways
 - Mutation rate: Localized vs Advanced
 - ~1 mut/Mb vs 4.4 mut/Mb
 - 4/150 (3%) hypermutated
 - 89% of mCRPC patients have clinically actionable aberration
 - AR pathway: 71.3%
 - AMP (~50%), mutation (20%)
 - WNT pathway: 18%
 - APC+CTNNB1: 13%
 - PI3K pathway: 49%
 - PTEN: 41%
 - PI3K: 17%
 - DNA repair: 22.7%
 - Dominated by BRCA2/ATM
 - Cell Cycle: 21%



Liquid Biopsy in Castration-resistant prostate cancer

– Predictive biomarkers from profiling studies

Biomarker	Therapy	Example
Variants of the Androgen Receptor	ARS inhibitors	Abiraterone acetate Enzalutamide
Genomic defects in DNA repair genes	PARP inhibitors	Olaparib
	Platinum-based CT	Cisplatin/Carboplatin
Microsatellite instability/Mismatch repair-deficiency	Immune checkpoint inhibitors	Nivolumab Pembrolizumab

Liquid Biopsy in Castration-resistant prostate cancer

- definition of the problem

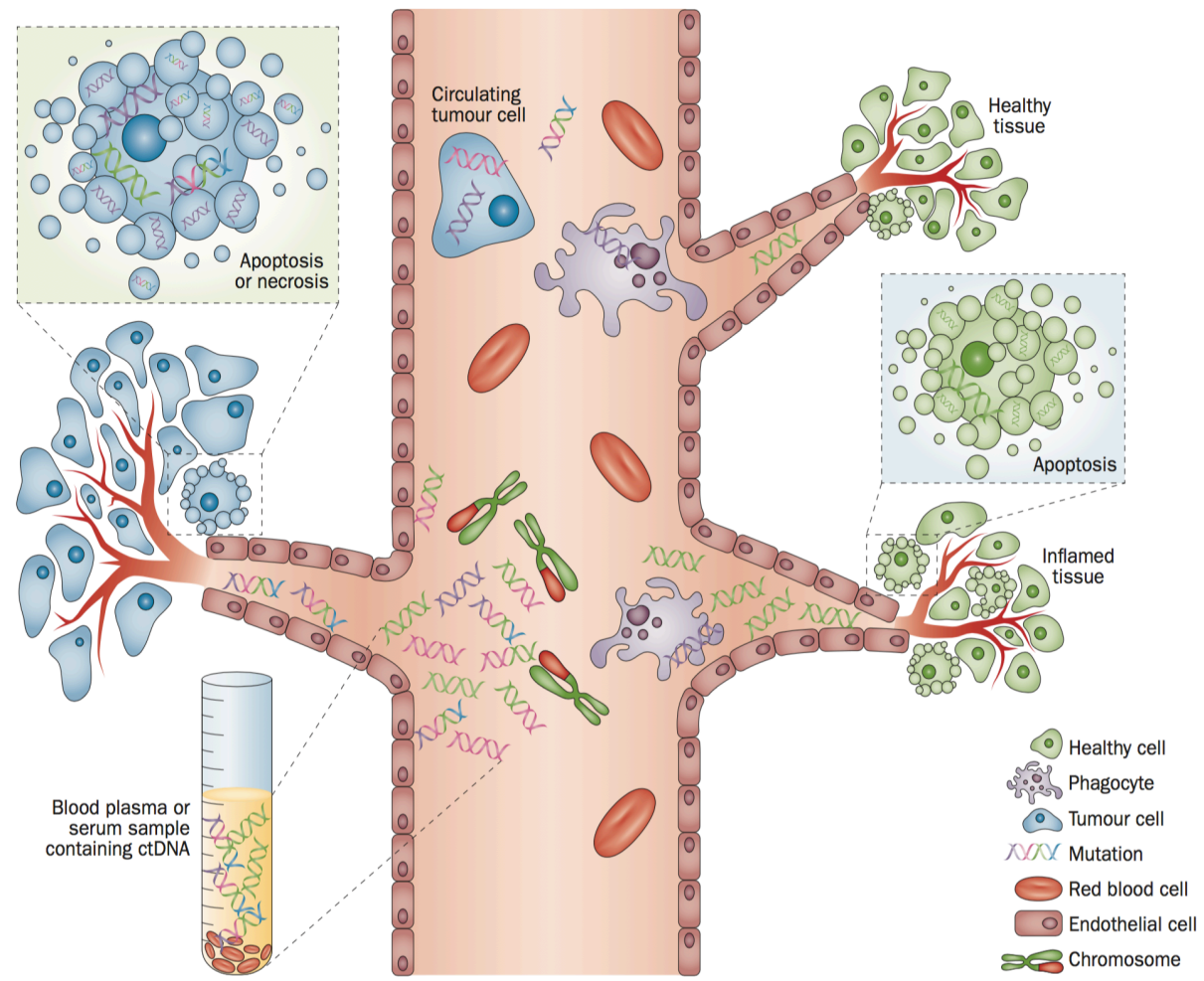
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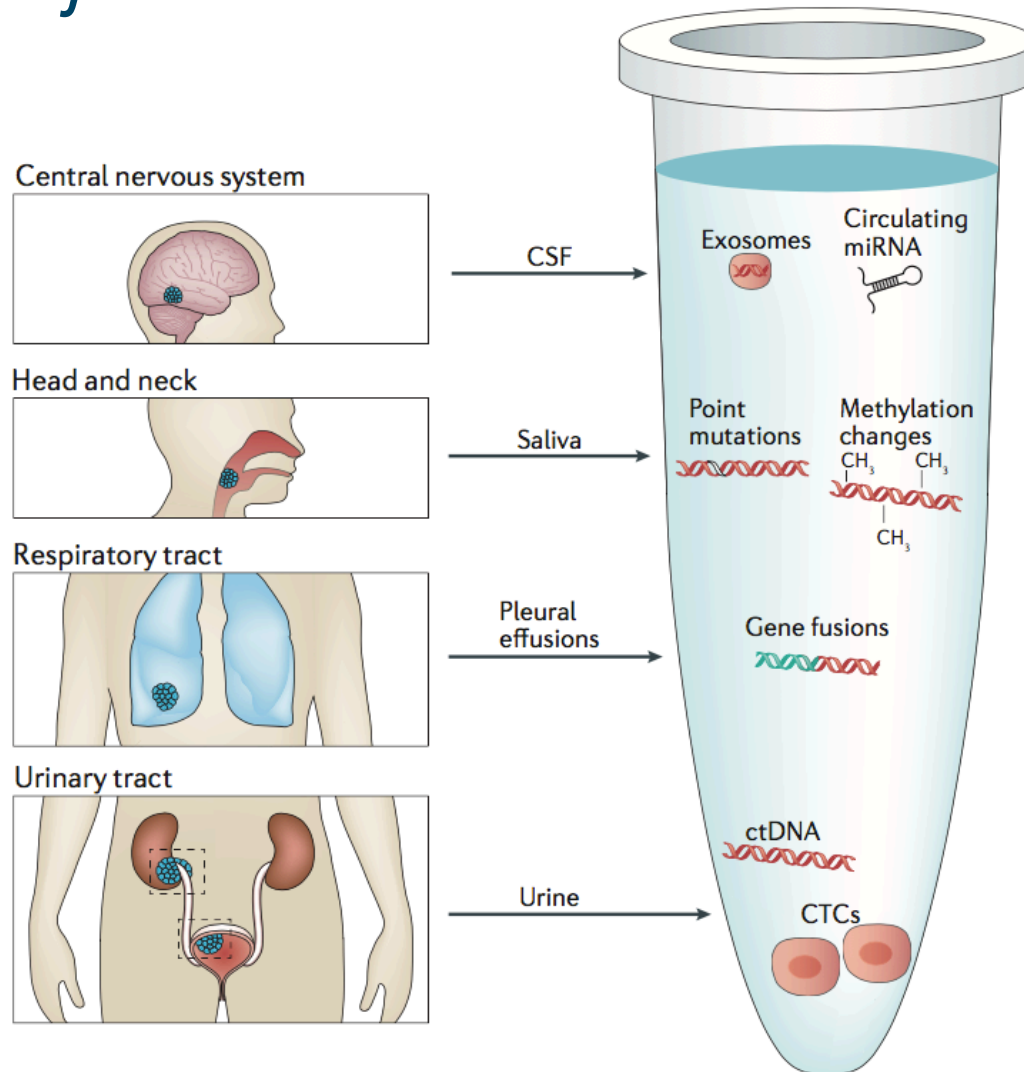
Liquid Biopsy in Castration-resistant prostate cancer - in blood



Crowley et al, Nature Reviews, 2013

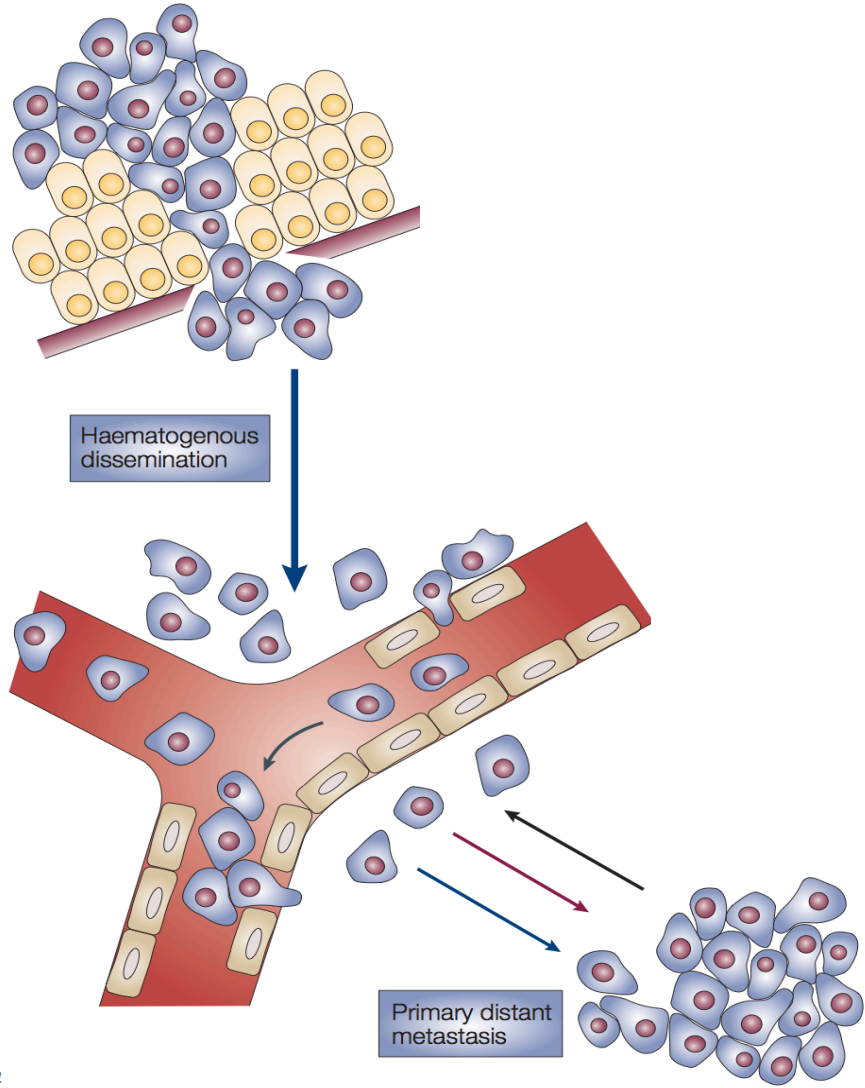


Liquid Biopsy in Castration-resistant prostate cancer - in other body fluids



Liquid Biopsy in Castration-resistant prostate cancer

- Circulating tumor cells

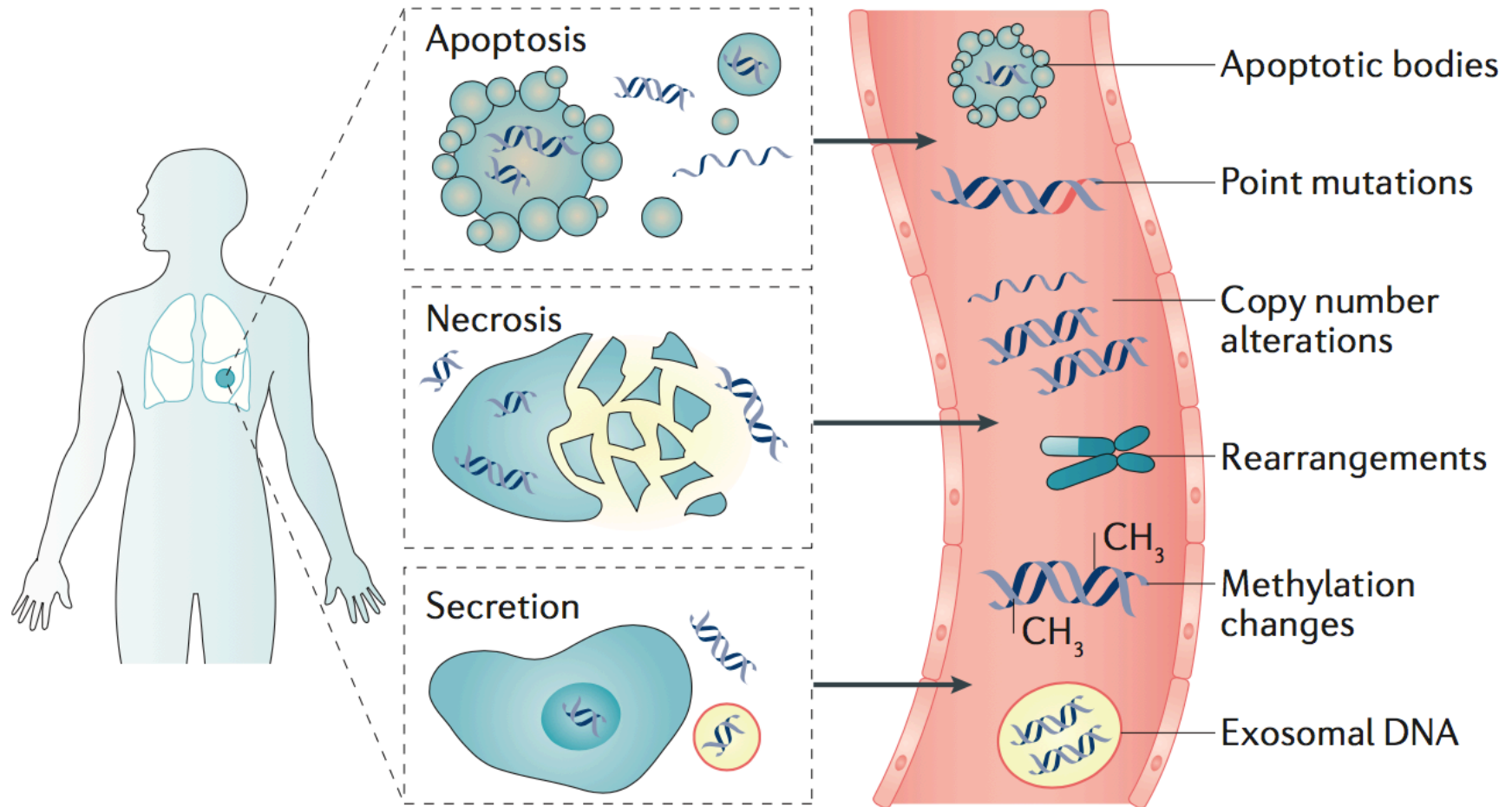


Pantel, K. & Brakenhoff, R. H. *Nature Reviews Cancer*, 2004

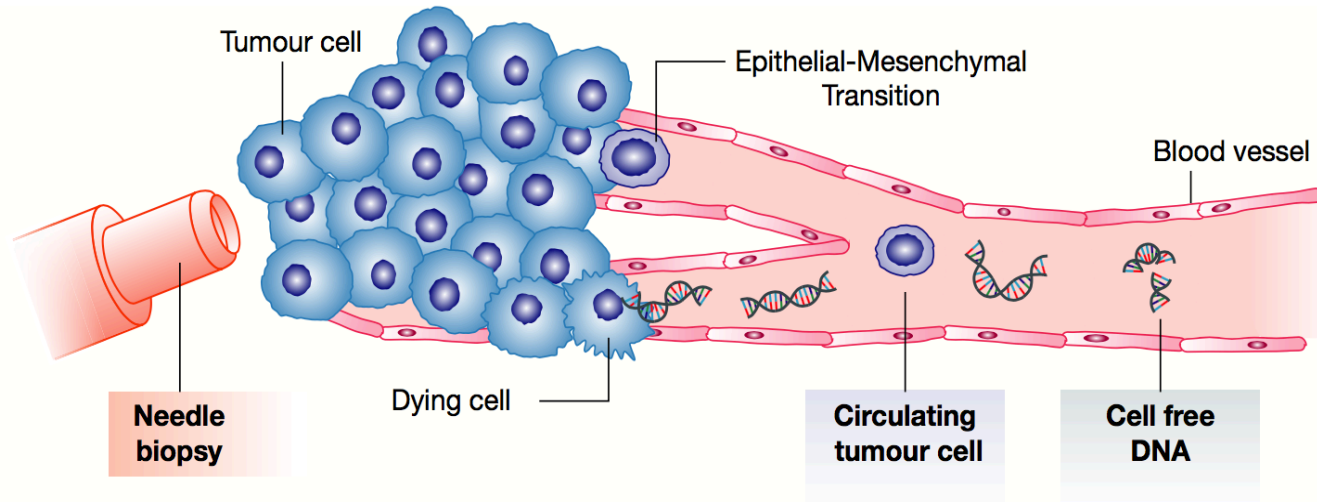


Liquid Biopsy in Castration-resistant prostate cancer

- Circulating cell-free DNA

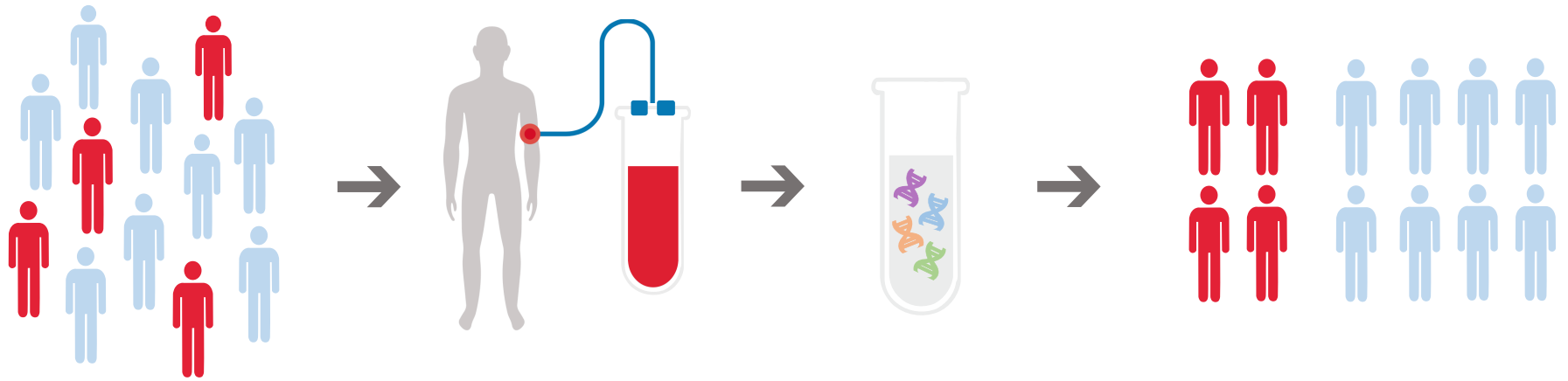


Liquid Biopsy in Castration-resistant prostate cancer - Circulating cell-free DNA



	Biopsy	CTC	cfDNA
Invasive	+	-	-
All patients eligible	-	+	+
Instrumentation required	+	+	-
WGA required	-	+	+/-
RNA profiling	+	+	-
Research applicability	+++	++	+
Repetitive Biomarker applicability	-	++	+++

Liquid Biopsy in Castration-resistant prostate cancer - A practical example



Liquid Biopsy in Castration-resistant prostate cancer – A practical example

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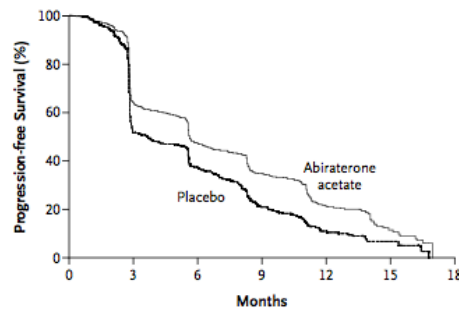
How do we measure these?

Liquid Biopsy in Castration-resistant prostate cancer

- Define the context

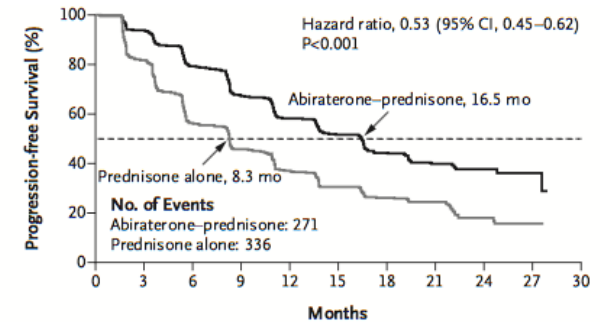


CT-pretreated

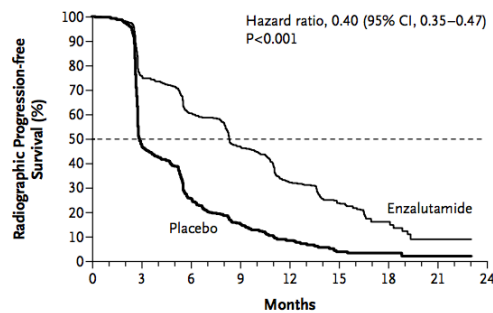


No. at Risk	0	3	6	9	12	15	18
Abiraterone acetate	797	490	352	202	76	14	0
Placebo	398	193	129	64	22	4	0

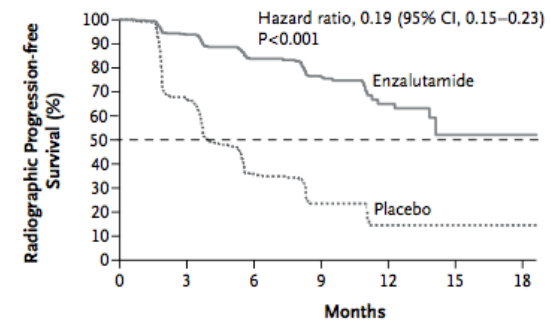
CT-naive



No. at Risk	0	3	6	9	12	15	18	21	24	27	30
Abiraterone-prednisone	546	485	389	311	240	195	155	85	38	9	0
Prednisone alone	542	406	244	177	133	100	80	37	14	1	0



No. at Risk	0	3	6	9	12	15	18	21	24
Enzalutamide	800	583	447	287	140	58	13	1	0
Placebo	399	176	86	46	20	7	3	0	0



No. at Risk	0	3	6	9	12	15	18
Enzalutamide	832	514	256	128	34	5	1
Placebo	801	305	79	20	5	0	0

de Bono, J. S. et al. *The new England Journal of Medicine* 364, 1995–2005 (2011).
 Scher, H. I. et al. *New England Journal of Medicine* 367, 1187–1197 (2012).
 Beer, T. M. et al. *New England Journal of Medicine* 371, 424–433 (2014).
 Ryan, C. J. et al. *New England Journal of Medicine* 368, 138–148 (2013).



Liquid Biopsy in Castration-resistant prostate cancer – A practical example

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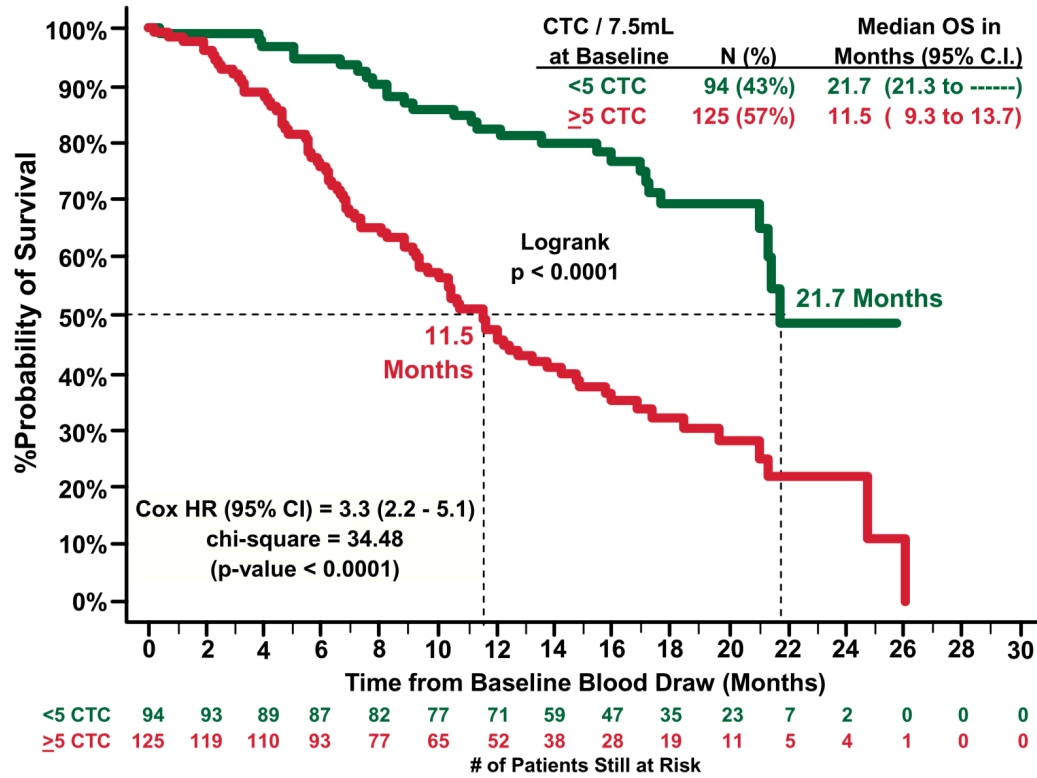
How do we measure these?

Liquid Biopsy in Castration-resistant prostate cancer

- Define the biomarkers

Enumeration of Circulating tumor cells

- Strong, independent predictor of overall and progression-free survival in metastatic prostate cancer.

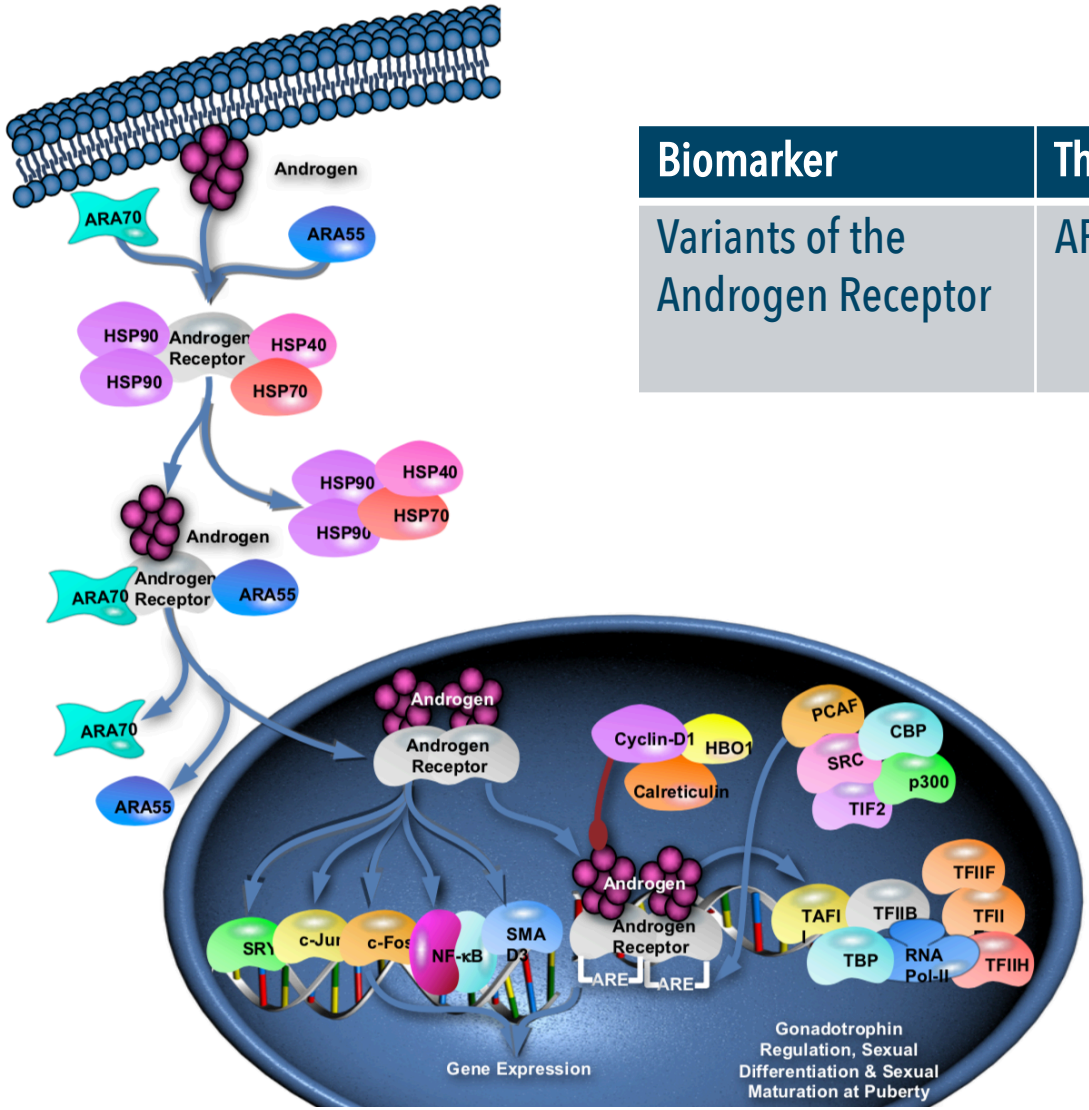


de Bono JS, Scher HI, Montgomery RB, et al. Clin Cancer Res. 2008;14(19):6302-6309.



Liquid Biopsy in Castration-resistant prostate cancer

- Define the biomarkers

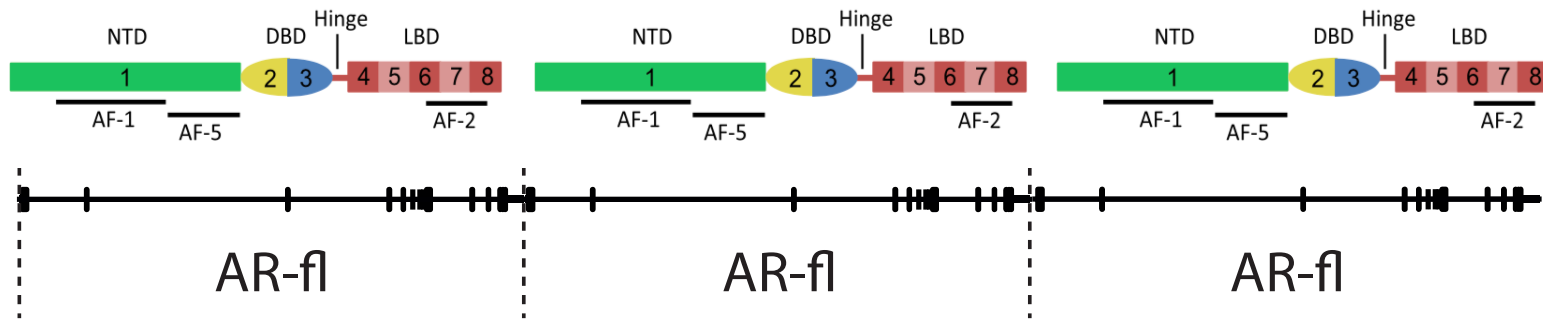


Biomarker	Therapy	Example
Variants of the Androgen Receptor	ARS inhibitors	Abiraterone acetate Enzalutamide



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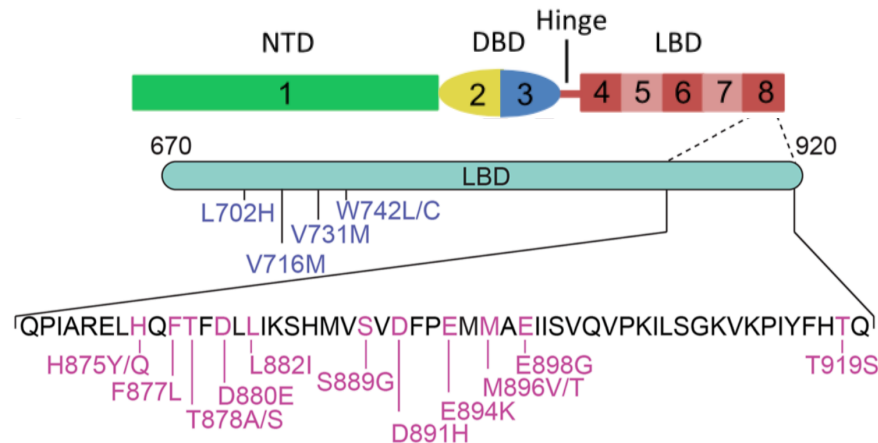
- Define the biomarkers: Androgen Receptor Variation



1. 30-50% have an amplification
2. 10-15% have mutations
3. 30-40% express splice variants
4. 20-30% have genomic structural rearrangements

Liquid Biopsy in Castration-resistant prostate cancer

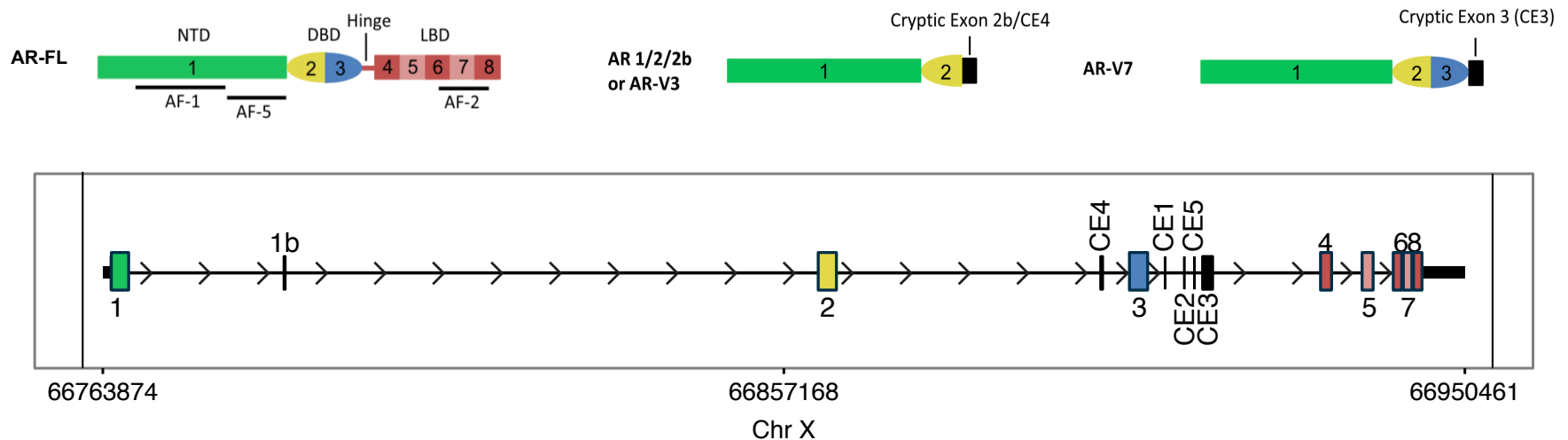
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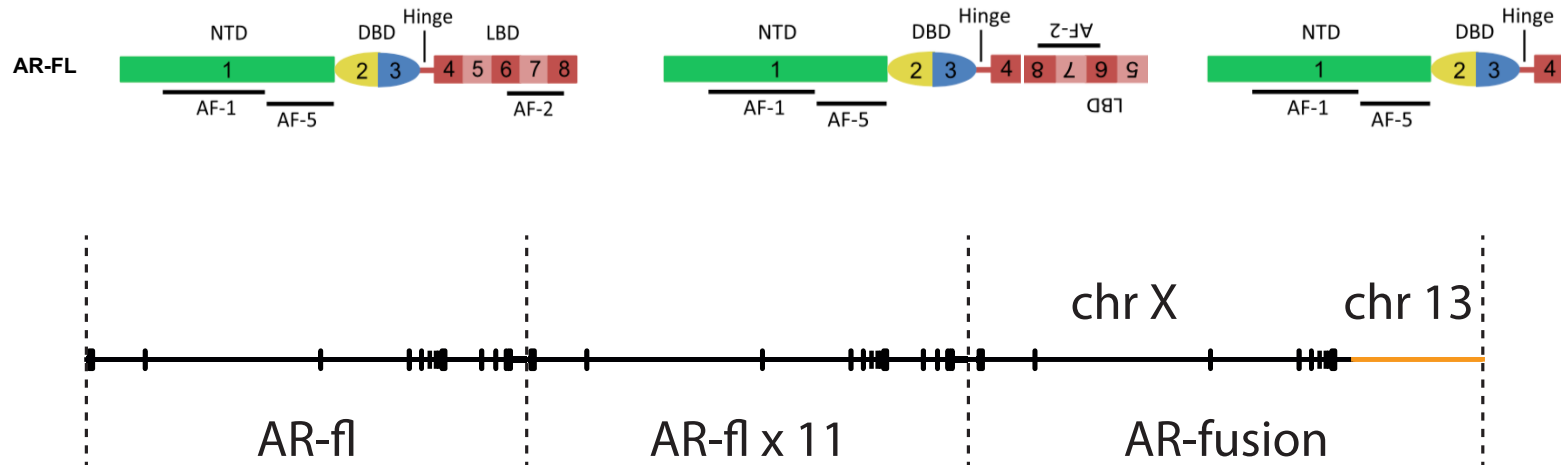
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Liquid Biopsy in Castration-resistant prostate cancer

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Liquid Biopsy in Castration-resistant prostate cancer – A practical example

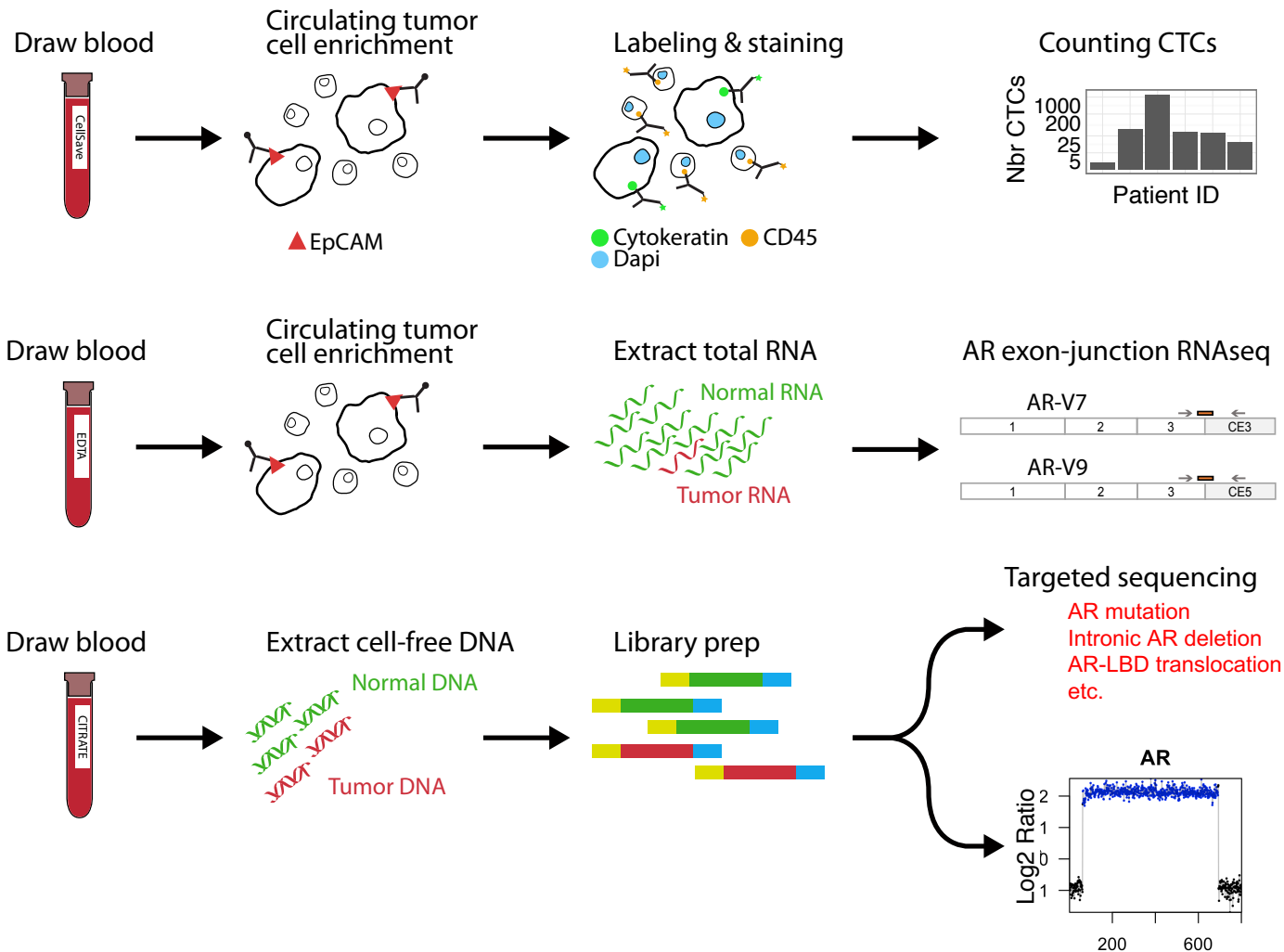
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Liquid Biopsy in Castration-resistant prostate cancer - Development of a workflow



Liquid Biopsy in Castration-resistant prostate cancer – Does the workflow work?



Platinum Priority – Prostate Cancer

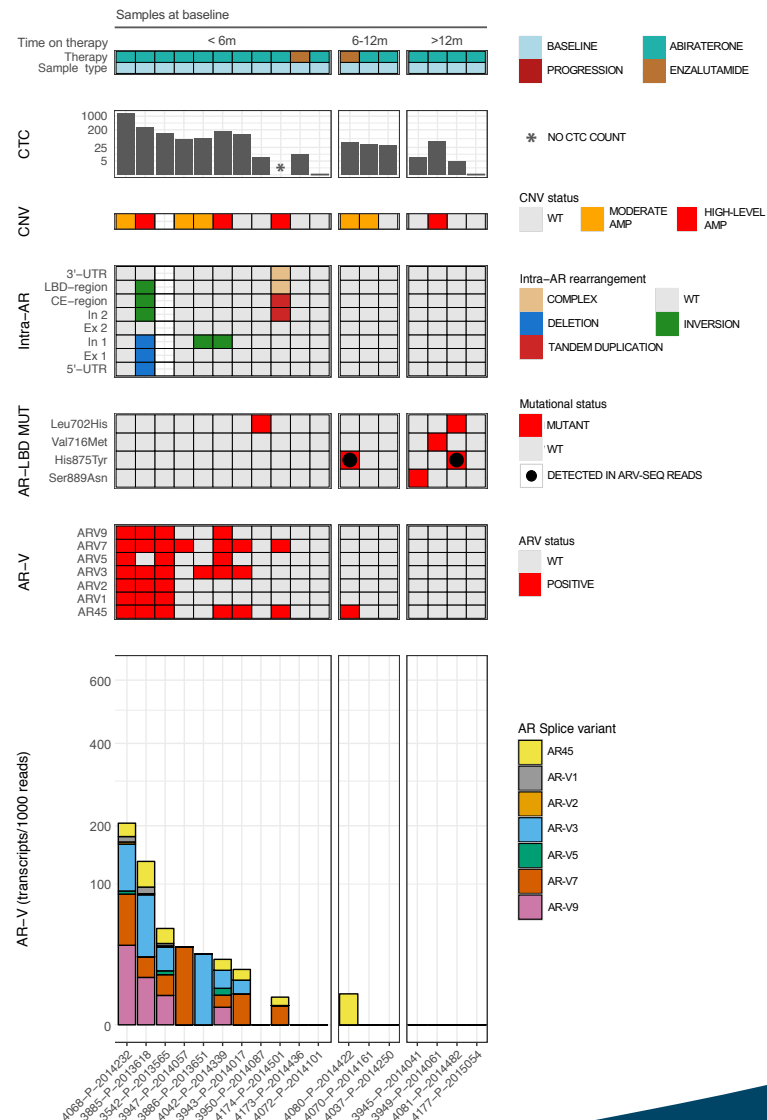
Editorial by Joaquin Mateo, Adam Sharp and Johann S. de Bono on pp. 201–204 of this issue

Comprehensive Profiling of the Androgen Receptor in Liquid Biopsies from Castration-resistant Prostate Cancer Reveals Novel Intra-AR Structural Variation and Splice Variant Expression Patterns

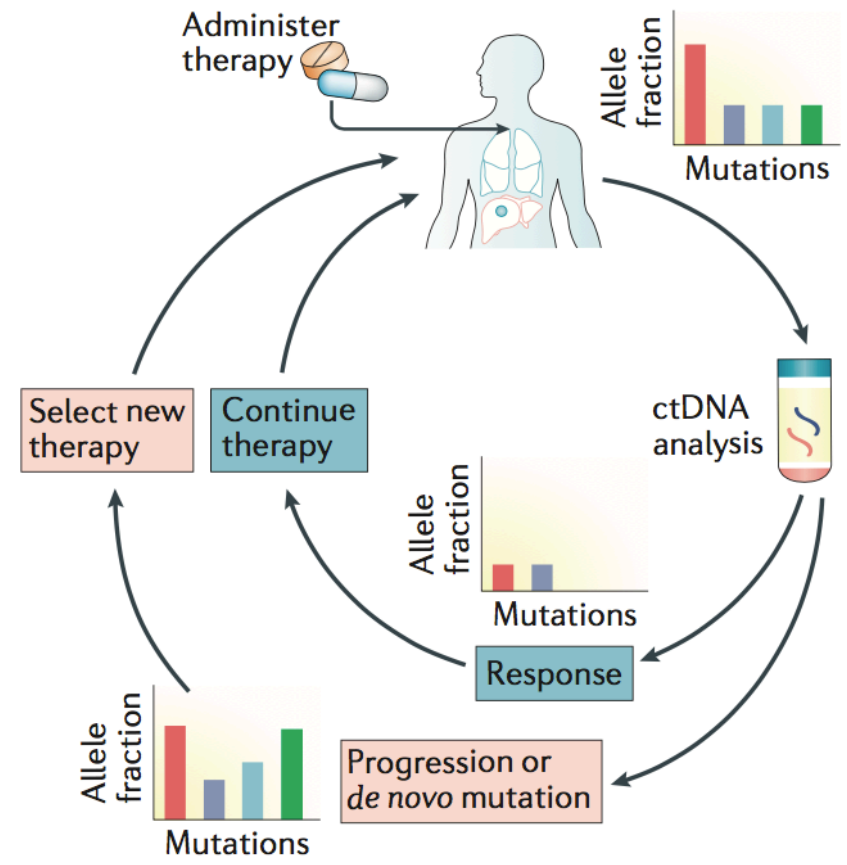
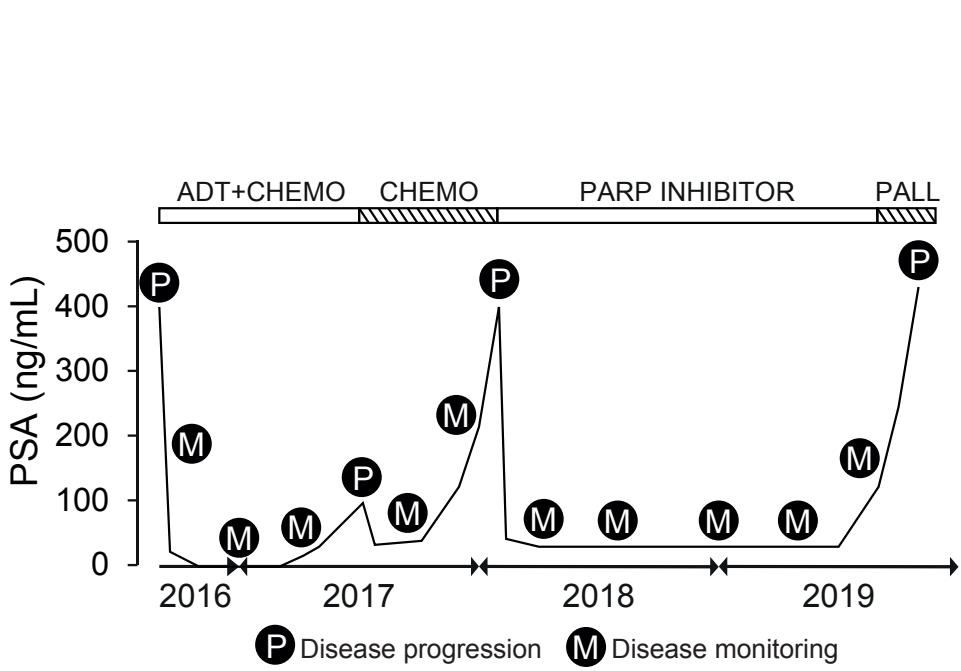
Bram De Laere^a, Pieter-Jan van Dam^a, Tom Whittington^b, Markus Mayrhofer^b, Emanuela Henao Diaz^c, Gert Van den Eynden^d, Jean Vandebroek^e, Jurgen Del-Favero^f, Steven Van Laere^a, Luc Dirix^{a,e,1}, Henrik Grönberg^{b,1}, Johan Lindberg^{c,1,*}

^a Centre for Oncological Research, University of Antwerp, Antwerp, Belgium; ^b Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; ^c Department of Medical Epidemiology and Biostatistics, Science for Life Laboratory, Karolinska Institutet, Stockholm, Sweden; ^d Department of Pathology, GZA Hospitals Sint-Augustinus, Antwerp, Belgium; ^e Department of Oncology, GZA Hospitals Sint-Augustinus, Antwerp, Belgium; ^f Multiplicom N.V., Niel, Belgium

- Liquid biopsies was used for profiling AR in 30 patients with CRPC
- 18 samples at baseline
- 83% patients carried an AR-perturbation
- 50% harbored intra-AR structural variation where 2/3 had multiple variants
- 14/15 intra-AR positive patients expressed splice variants



Liquid Biopsy in Castration-resistant prostate cancer - Future perspectives



Wan et al, Nature Reviews, 2017



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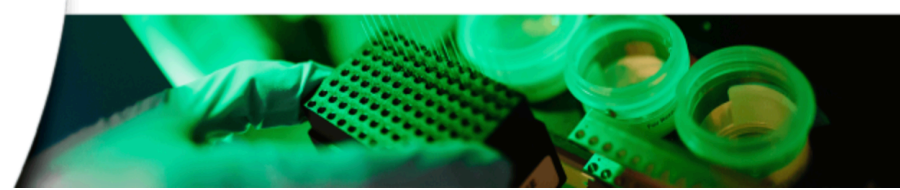
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Thank you for your attention



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tegen Kanker

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