Klinische toepassing van ctDNA voor castratie-resistant prostaatkanker

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Medisch Oncoloog, Radboudumc

15 november 2023

ONCOLOGIE UPDATE 2023

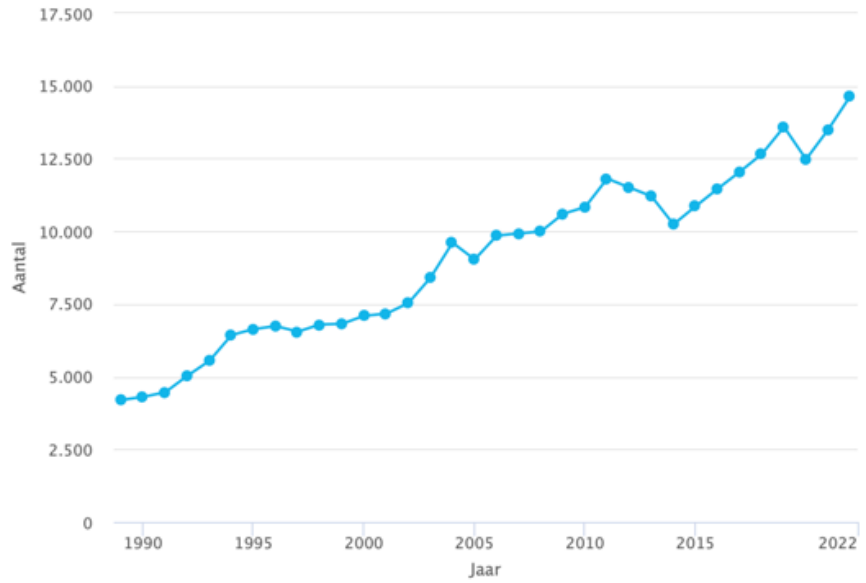
Predictieve diagnostiek voor immuun- en doelgerichte therapie

(Potentiële) belangenverstrengeling	Geen / Zie hieronder
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Bedrijfsnamen
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk …	Astellas, Janssen, Astrazeneca/MSD, Pfizer, BMS, Roche Astrazeneca/MSD, Pfizer, BMS, Janssen, Astellas Geen Geen

Gemetastaseerd prostaatkanker gepaard met slechte prognose

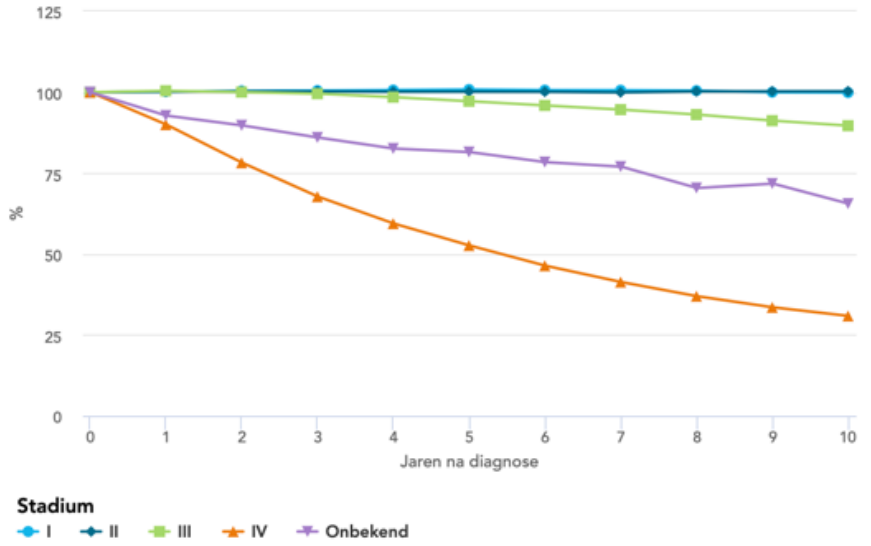
IKNL cijfers 2015-2020

Incidentie per jaar, Aantal
Prostaatkanker
Geslacht: Man | **Leeftijdsgroep:** Totaal | **Regio:** Nederland



2022, 2021: Deze cijfers betreffen voorlopige gegevens.

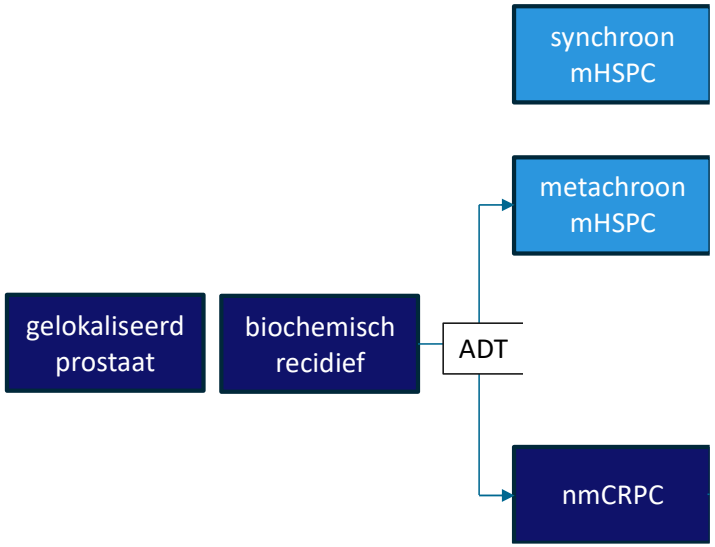
Overleving per jaren na diagnose, Relatieve overleving
Prostaatkanker
Jaar: 2010-2016 (TNM 7e editie) | **Geslacht:** Man | **Leeftijdsgroep:** Totaal

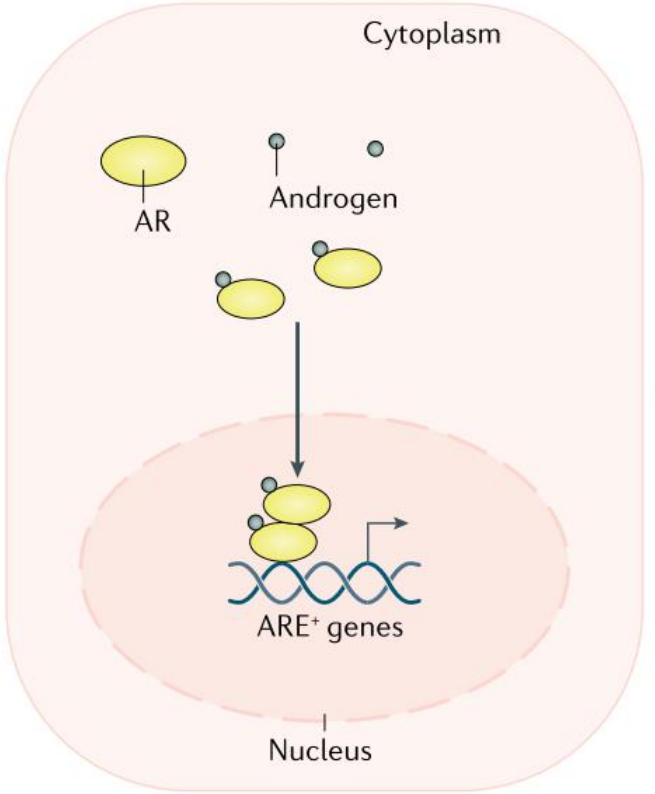


Jaarlijks 13.500 mannen gediagnosticeerd met prostaatkanker

IKNL Prostaatkankercijfers in Nederland (2010-2016).

Behandeling voor gemetastaseerd hormoongevoelig prostaatkanker: androgeen deprivatie





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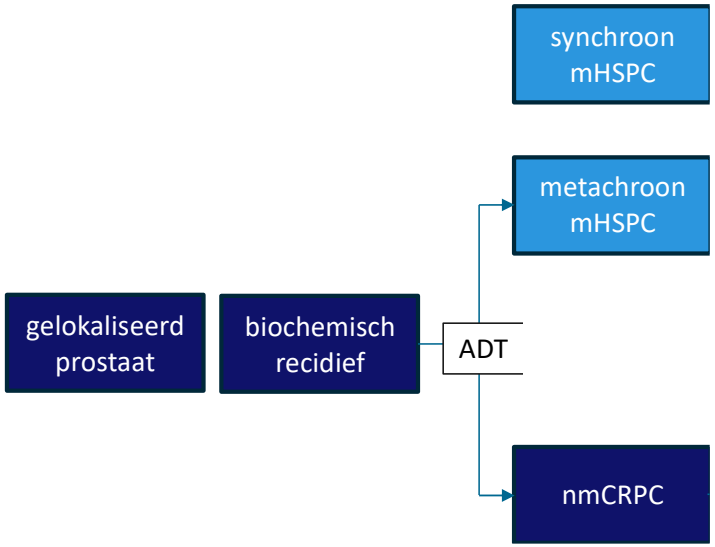


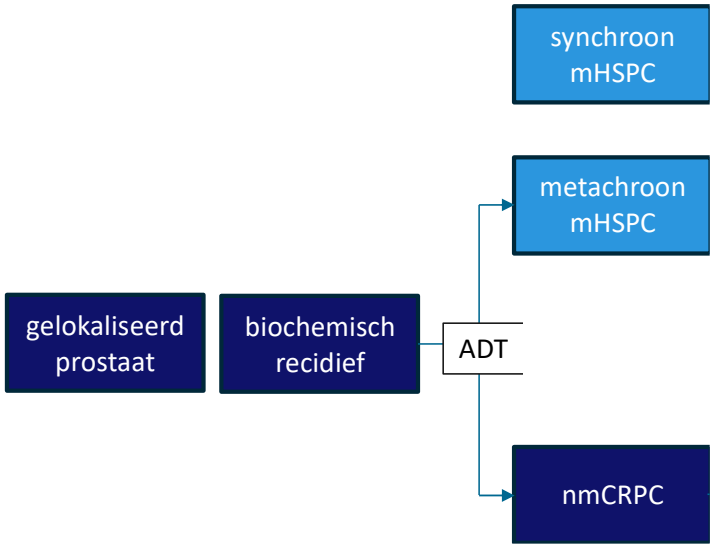
Charles B. Huggins

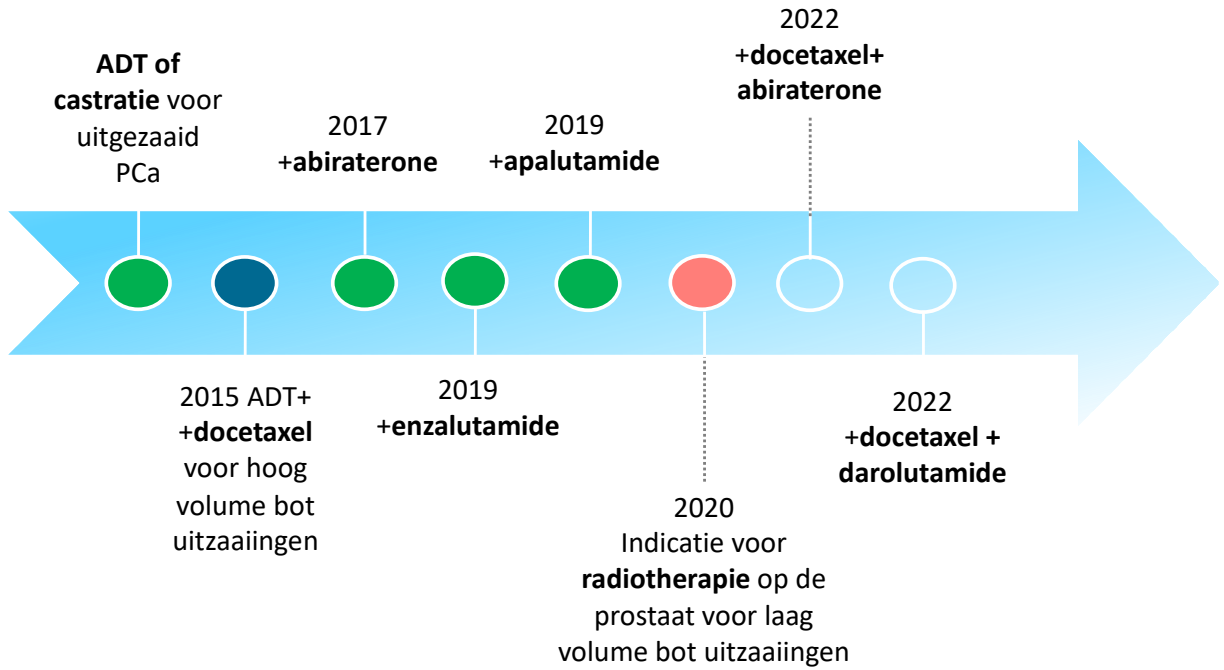
“Despite regressions of great magnitude, it is obvious that there are many failures of endocrine therapy to control the disease”

Nobel Lecture
December 13, 1966

IKNL Prostaatkankercijfers in Nederland (2010-2016).

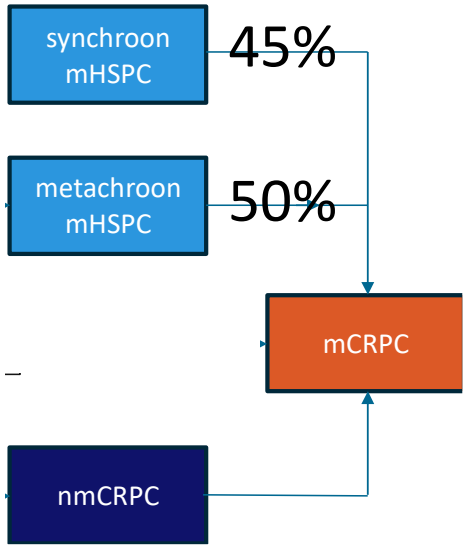
Behandeling voor gemetastaseerd hormoongevoelig prostaatkanker: androgeen deprivatie

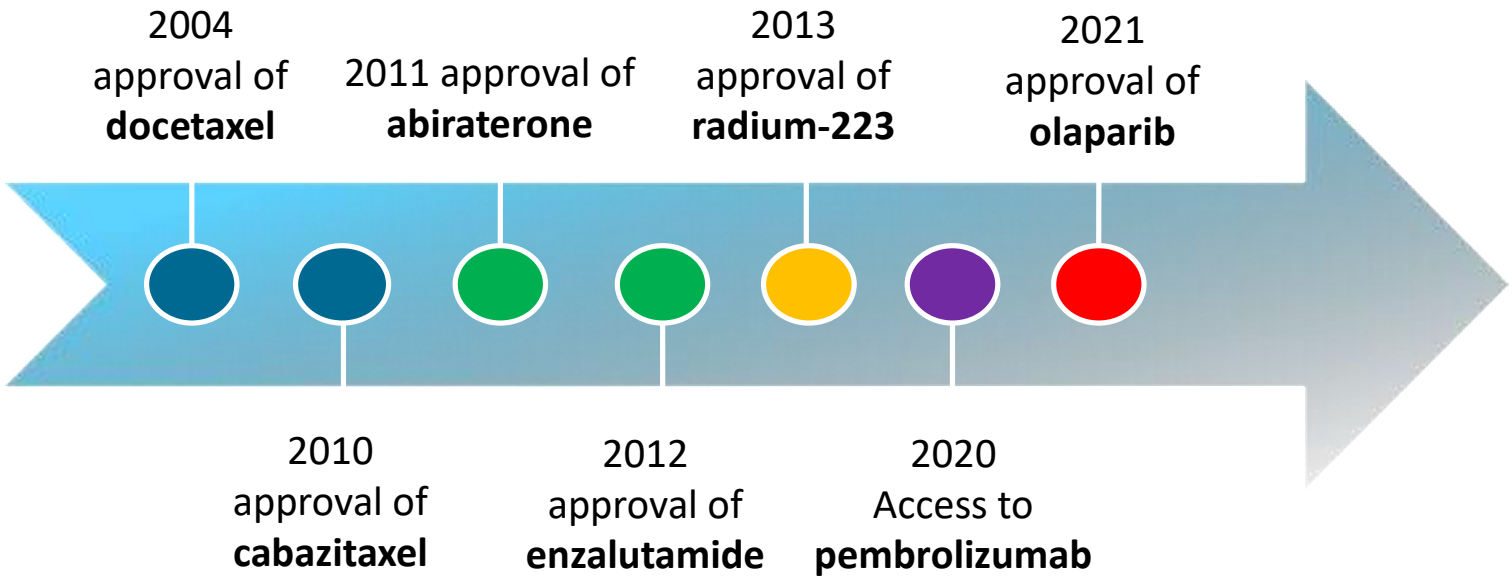




IKNL Prostaatkankercijfers in Nederland (2010-2016).

Behandelopties voor patienten met gemetastaseerd castratie-resistant prostaatkanker (mCRPC)





7 levensverlengende medicijnen

Het mediane aantal behandellijnen in mCRPC is slechts twee !!

Hoe maken we therapeuthische keuzes bij mCRPC?

Performance status
comborbiditeit

Prognostische variabelen

Biomarkers/
genomics/
genetica

(inter)nationale richtlijnen

nvmo

Richtlijnen tumortest – level I evidence

Guideline	
NCCN Guidelines Prostate Cancer V2.2021	'Based on the current evidence, ESMO recommends routine use of NGS on tumour samples in prostate cancers' **BRCA, MSH-H/dMMR**
ESMO	
AUA	
(EAU guidelines)	
APCCC 2019	

Mosele F, et al. Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group. Ann Oncol. 2020.

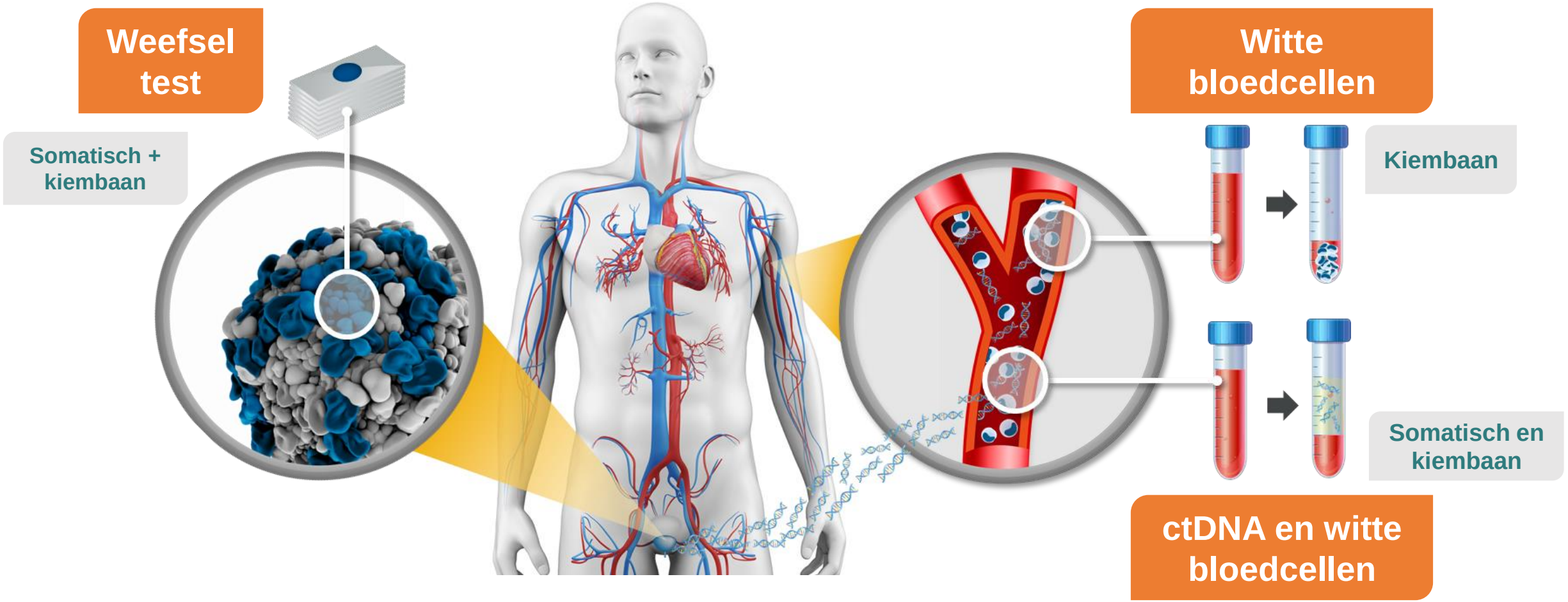
Predictive biomarkers in prostate cancer

Gene	Alteration	Prevalence	ESCAT	ESMO	Expert opinion
BRCA1 *BRCA2*	snv, CNV	10%	Level IA	Yes	Yes (also CNV)
PTEN *AKT* *PIKC3CA*	snv/CNV snv Hotspot	44%	Leven IIA Level IIIA Level IIIA	Yes	Not necessary, nice to have
MSH2 *MSH6* *MLH1* *PMS2*	MSI-H	4%	Level IC	Yes	Yes MSI-H
hTMB	snv	1-2%	Level IIA	No	Yes
PALB2 *ATM* *CDK12* *RAD51B* *RAD51C* *BARD1* *BRIP1*	snv/CNV	15%	Level IIA/IIB	Yes Yes No No No No No	Yes Yes Yes Yes Yes Yes Yes

Prognostic biomarkers in prostate cancer

Gene	Alteration	Prevalence	ESCAT	ESMO	Expert opinion
TP53 *PTEN* *RB1* *(AVPC=2/3 altered)*	snv/CNV	70%	N/A	No, but APCCC yes	Yes
AR *AR enhancer* *AR splice variants* *SPOP*	snv/CNV	55%	N/A	No	Yes

Biomarkers, genomisch- en genetische MD testen



ONCOLOGIE UPDATE 2023

Predictieve diagnostiek voor immuun- en doelgerichte therapie

Eigenschappen van circulerend tumor-DNA

Celvrij DNA (cfDNA)

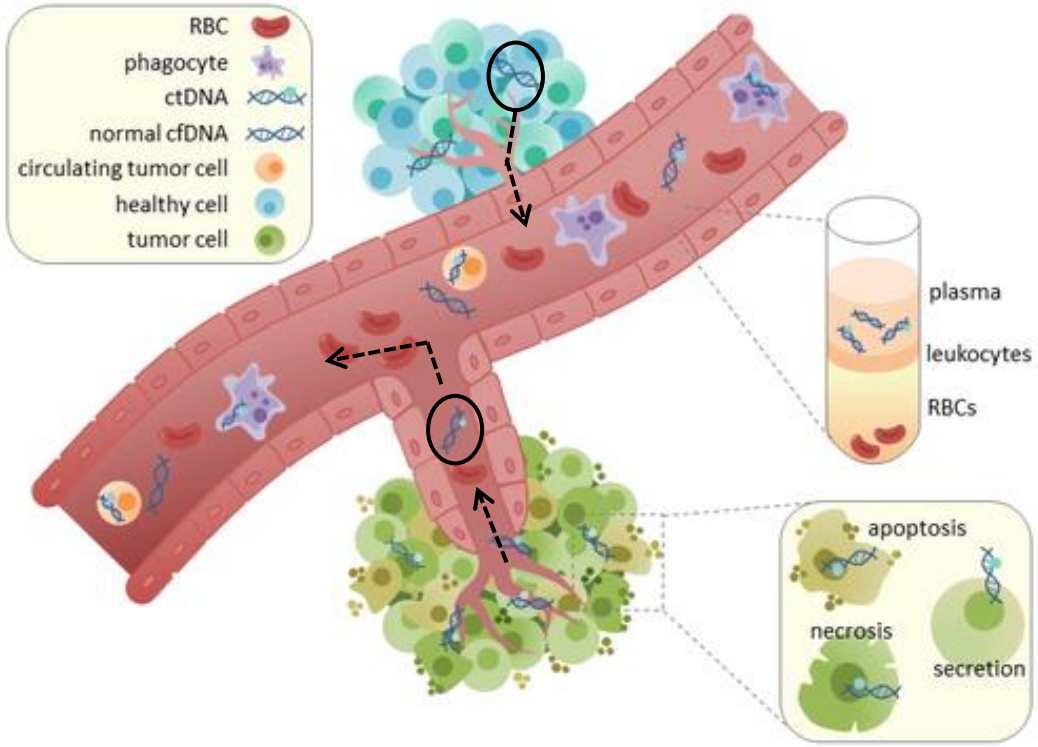
1. Bevat cfDNA (CHiP) + ctDNA

Circulerend tumor DNA (ctDNA)

1. Minimaal invasieve genomische profilering
2. Korte halfwaardetijd (16min – 2,5u)
3. ctDNA-fractie weerspiegelt tumor volume
4. Longitudinale opvolging mogelijk

Witte bloedcellen

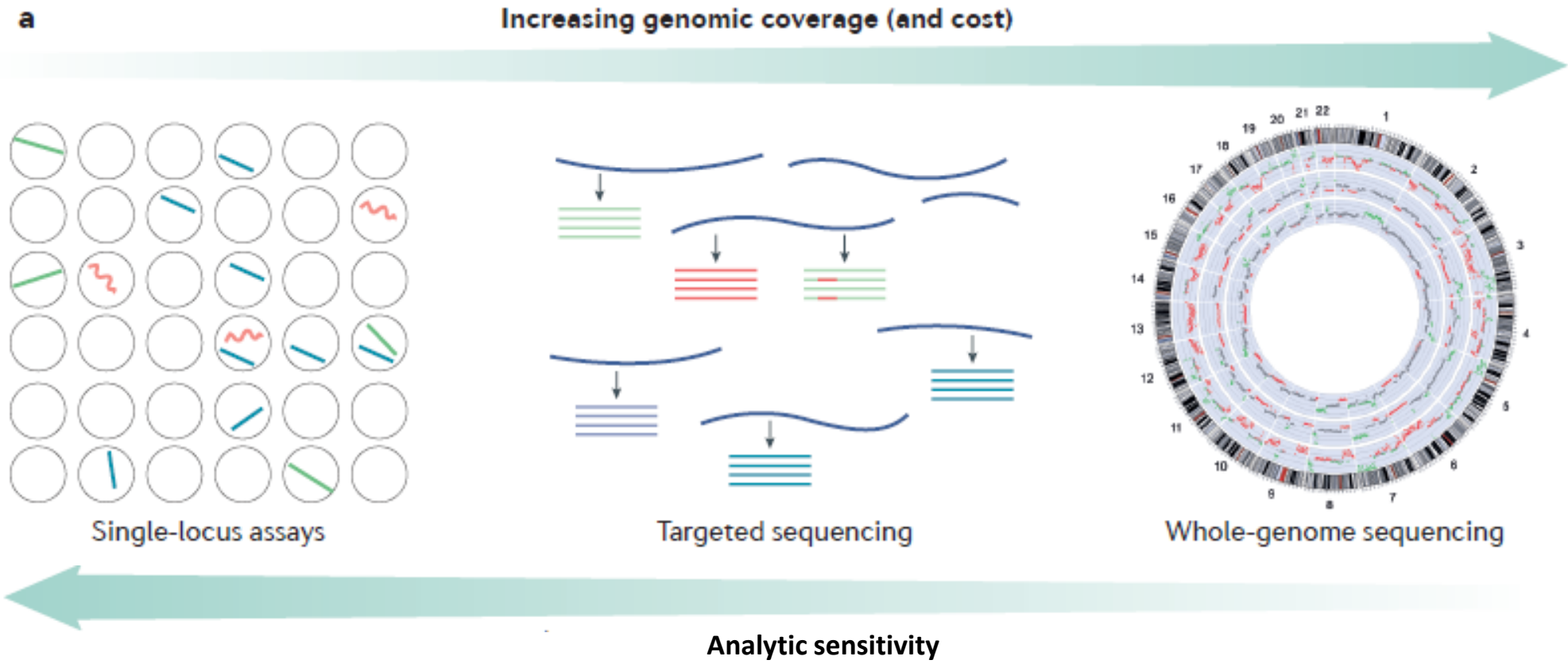
1. CHiP
2. Kiembaan mutaties



ONCOLOGIE UPDATE 2023

Predictieve diagnostiek voor immuun- en doelgerichte therapie

Detectie van ctDNA in cfDNA

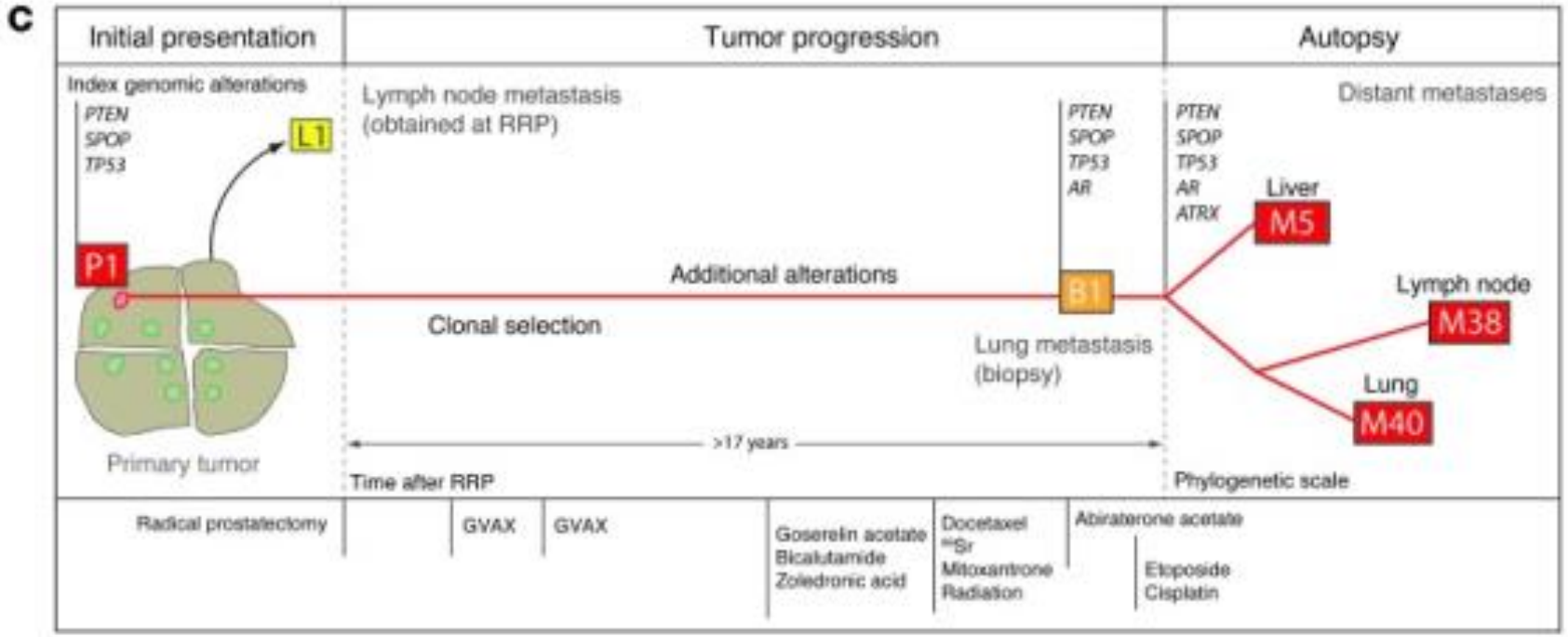


Wan, Nat. Rev. Cancer, 2017

Moet ctDNA de standaard worden voor MD testen in prostaatkanker?

- **Prostaatkanker is een heterogene ziekte**
  - Intra-tumoraal: primaire tumor

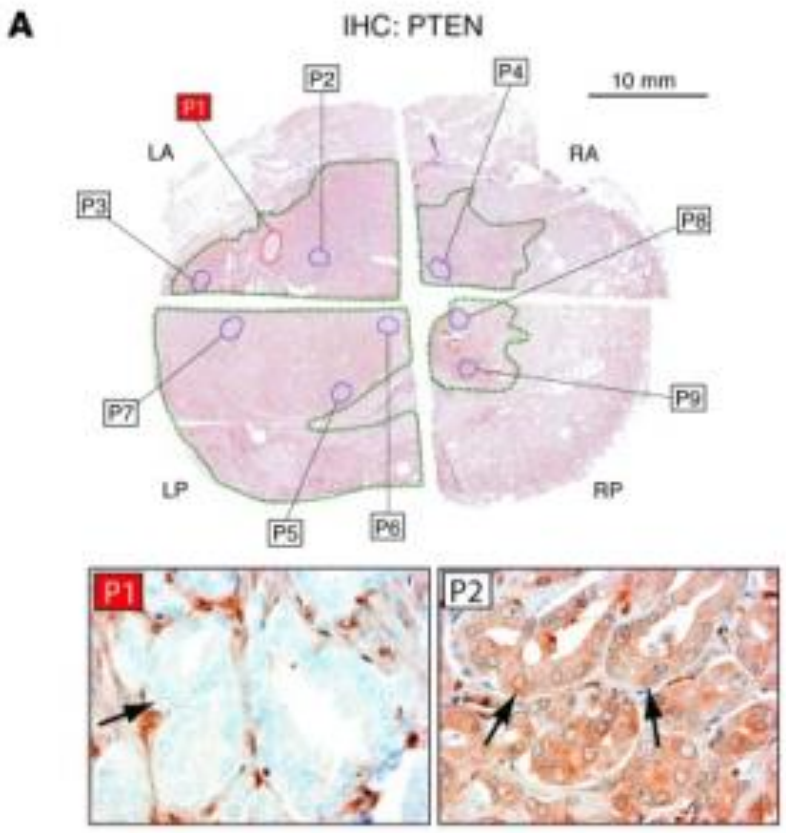
De klonale oorsprong van lethaal PCa

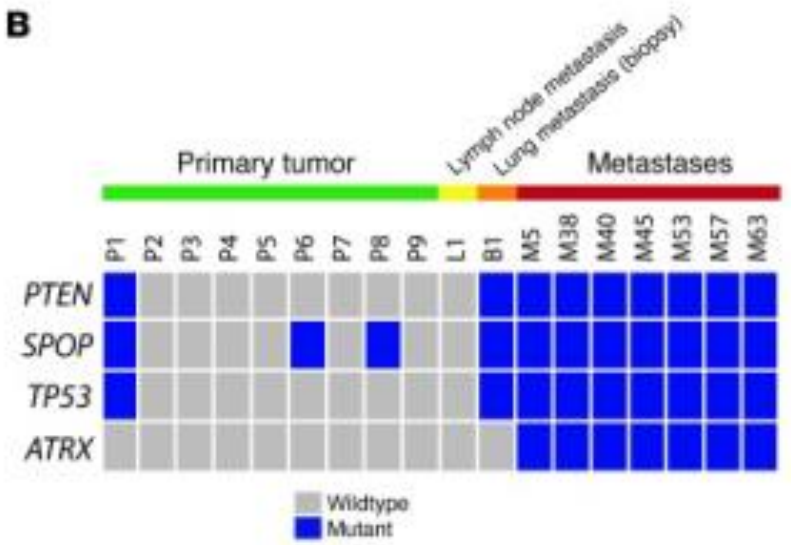


- 47-jarige pt gediagnosticeerd met GG 8 PCa
- Stierf 17 jaar later als gevolg van mCRPC
- Genetische analyse van meta's en primair: lethale kloon ontstond uit een kleine laaggradige focus

Haffner MC et al. J Clin Invest 2013;123: 4918–4922
PCa: prostate cancer; mCRPC: metastatic castration-resistant prostate cancer

De klonale oorsprong van lethaal PCa





- Genetische analyse van meta's en primair: lethale kloon ontstond uit een kleine laaggradige focus
- Kleine focus met mutaties in PTEN en p53
- MD optimal op CRPC biopten of ctDNA

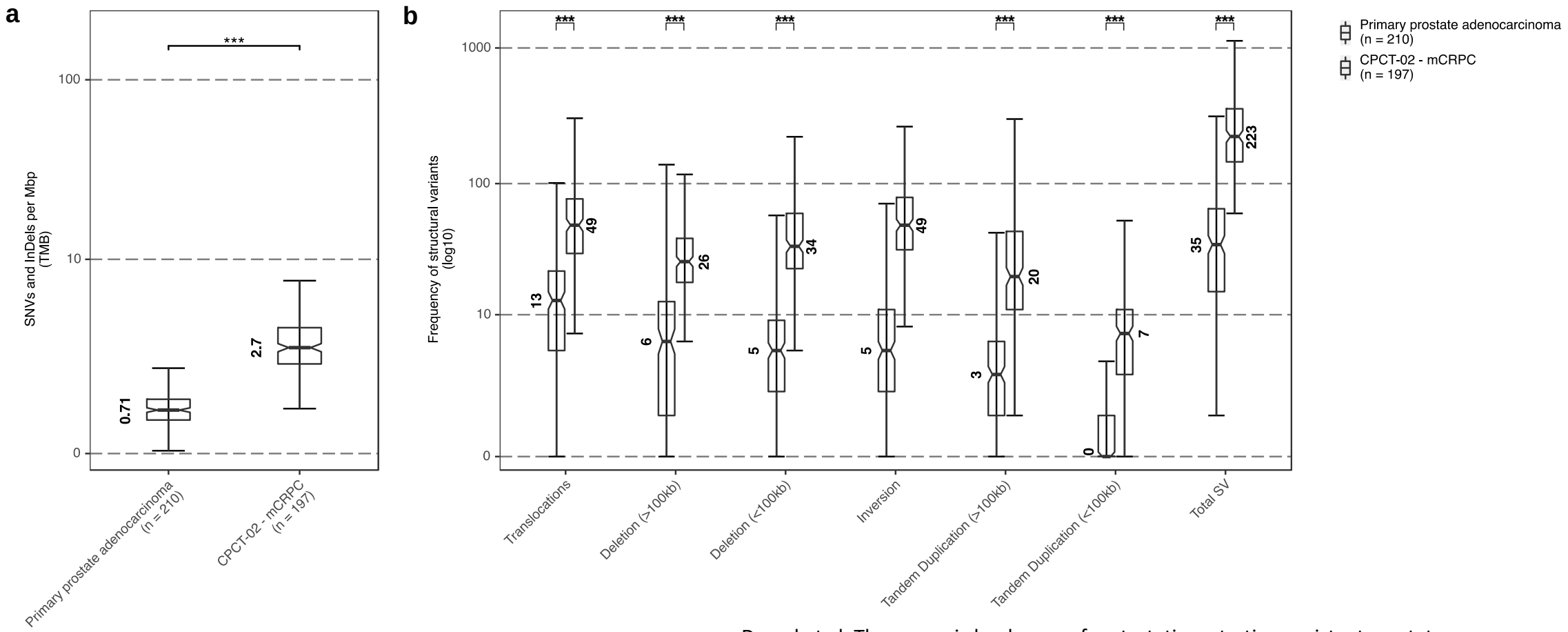
Haffner MC et al. J Clin Invest 2013;123: 4918–4922

PCa: prostate cancer; mCRPC: metastatic castration-resistant prostate cancer

Moet ctDNA de standaard worden voor MD testen in prostaatkanker?

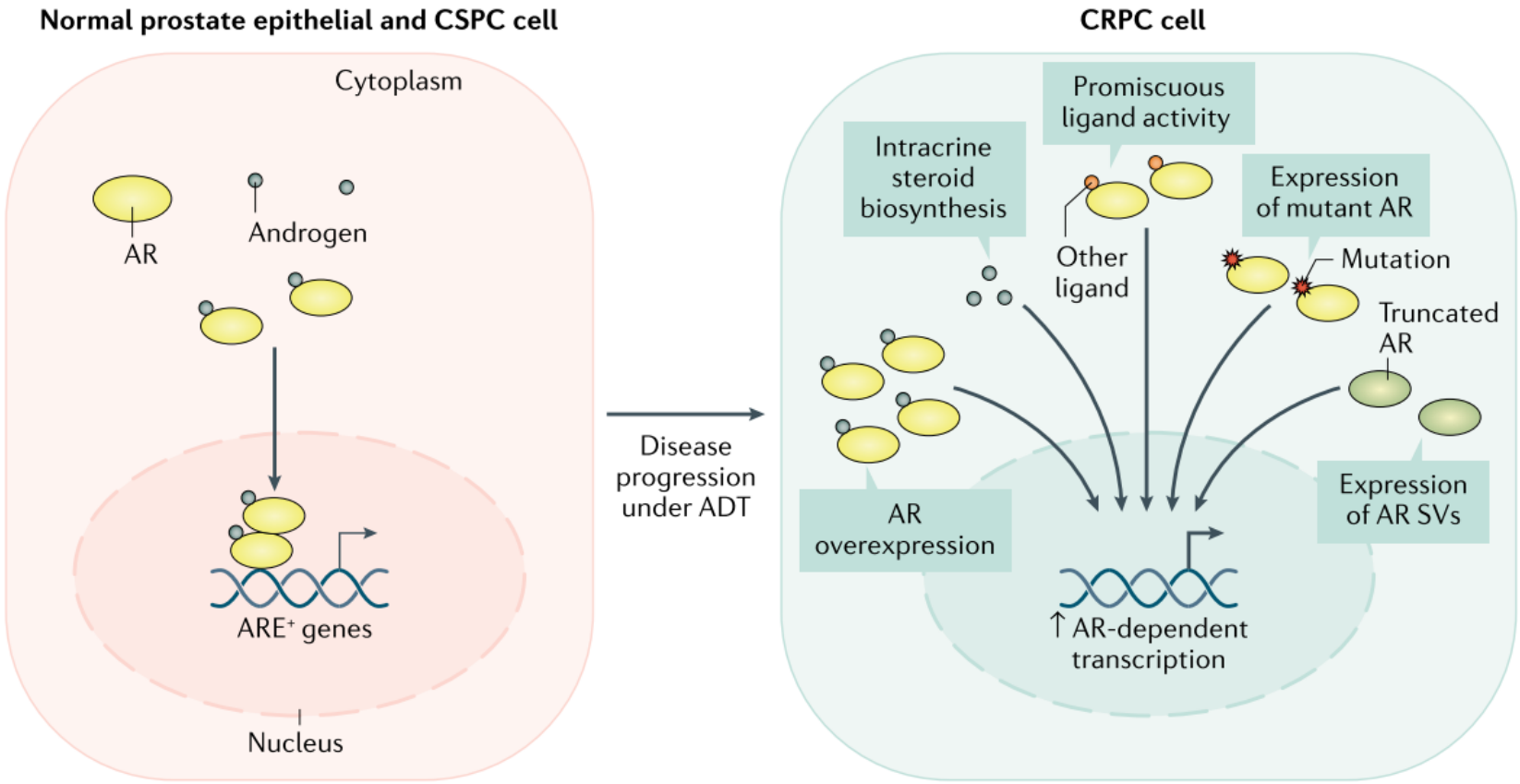
- **Prostaatkanker is een heterogene ziekte**
  - Intra-tumoraal: primaire tumor
  - Temporele veranderingen
    - Van gelokaliseerde tot gemetastaseerde ziekte (ADT resistentie)

Verandering van primair HSPC naar mCRPC



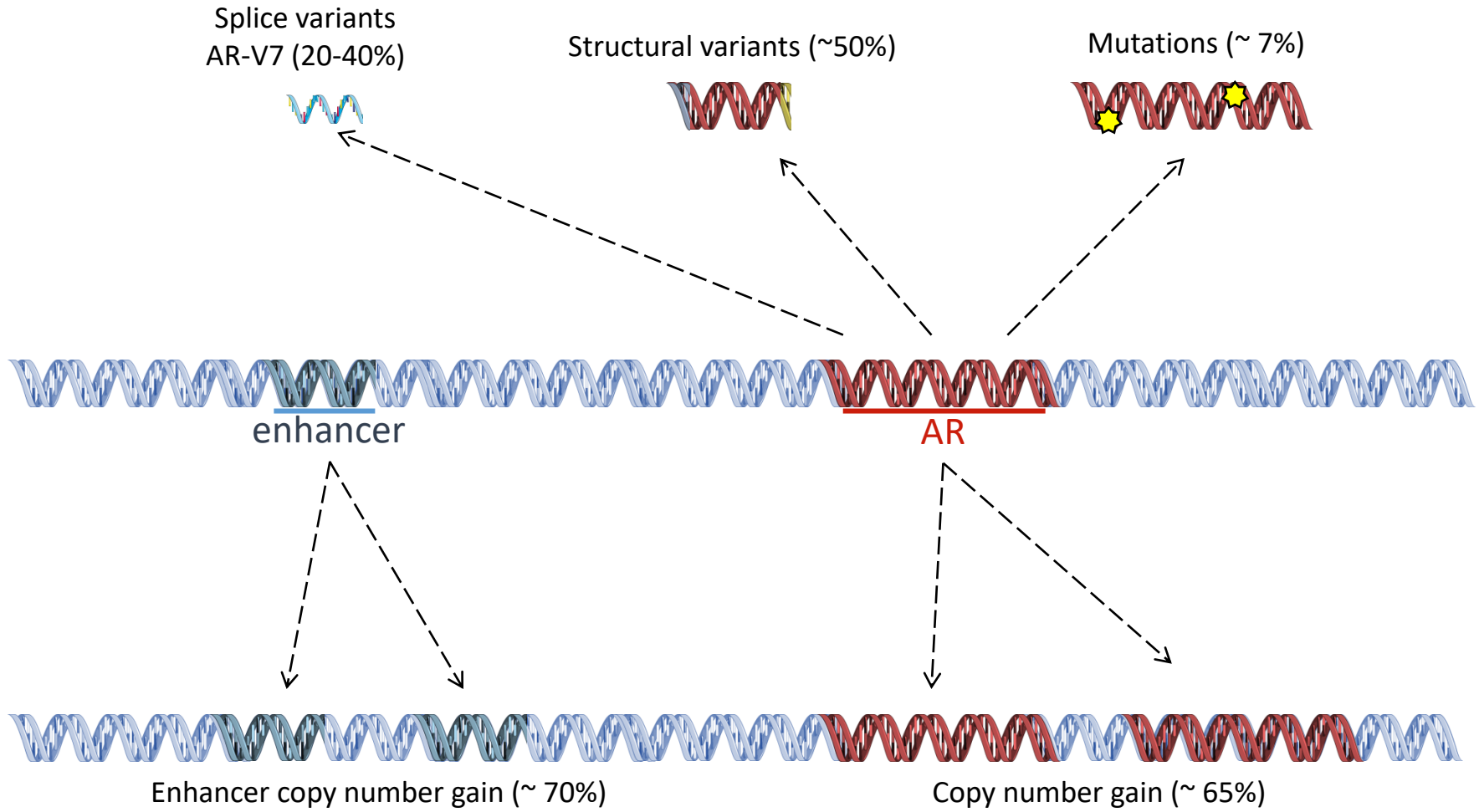
van Dessel et al. The genomic landscape of metastatic castration-resistant prostate cancers reveals multiple distinct genotypes with potential clinical impact. Nat Commun. 2019

mCRPC resistentie mechanismen (in AR)



Rebello RJ, et al. Prostate cancer. Nat Rev Dis Prim. 2021 Dec 4;7(1):9.

mCRPC resistentie mechanismen (in AR)



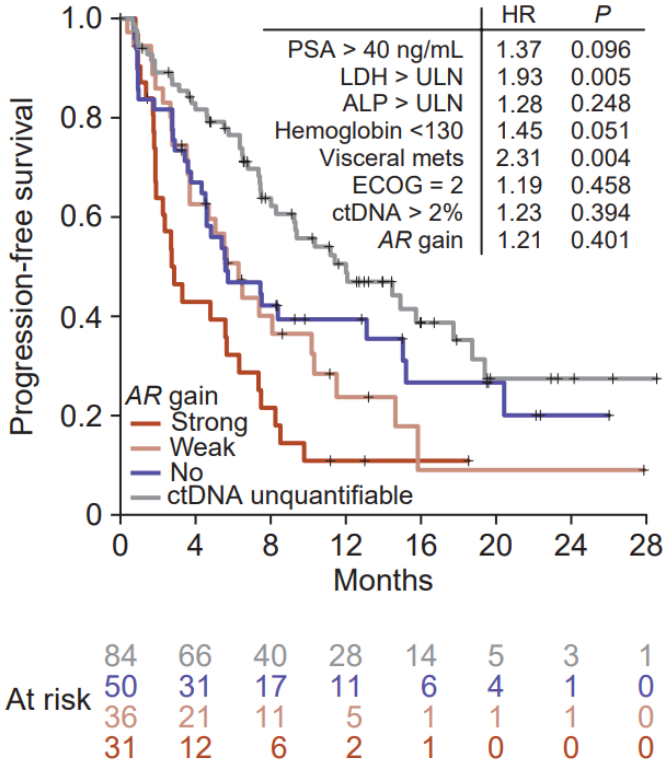
Annala, *et al.* 2018

De Laere, *et al.* 2017

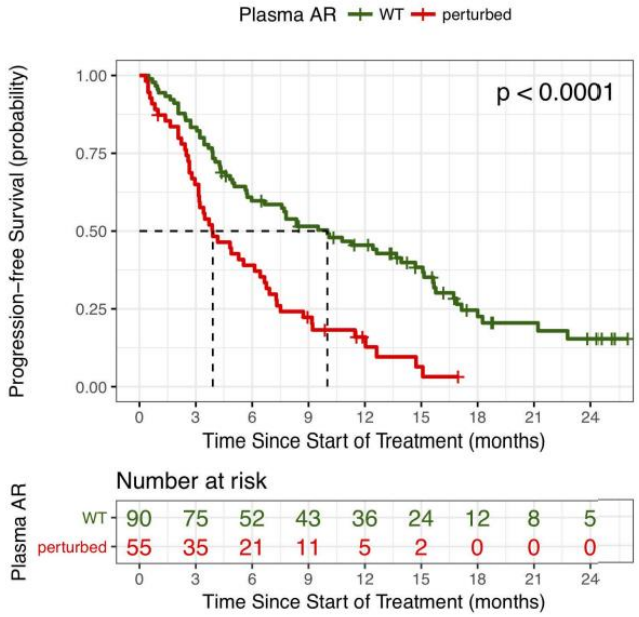
Del Re, *et al.* 2017
Antonarakis, *et al.* 2014
Scher, *et al.* 2018

Annala, *et al.* 2018
Viswanathan, *et al. 2018*

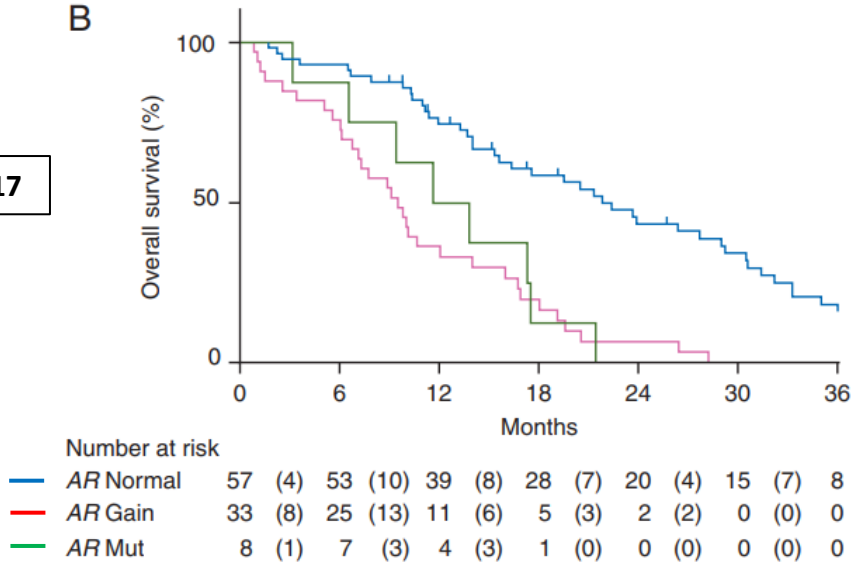
Annala, Cancer Discovery, 2018



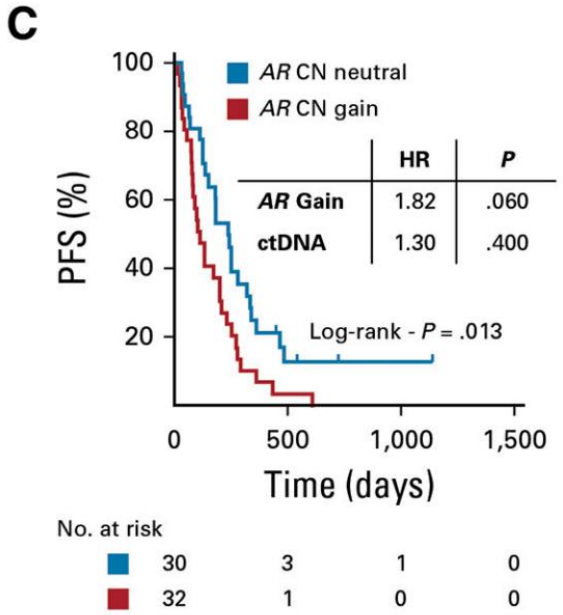
De Laere, CCR, 2018



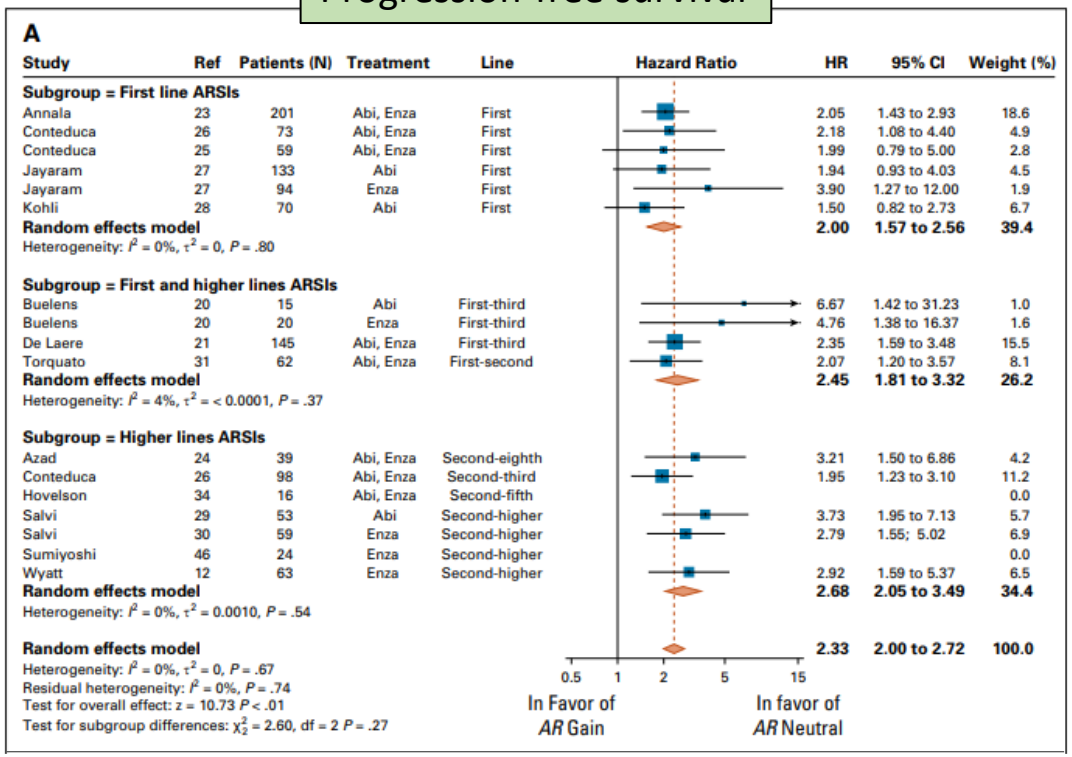
Conteduca, Ann of Onc, 2017



Torquato, JCO PO, 2019



Progression-free survival



A

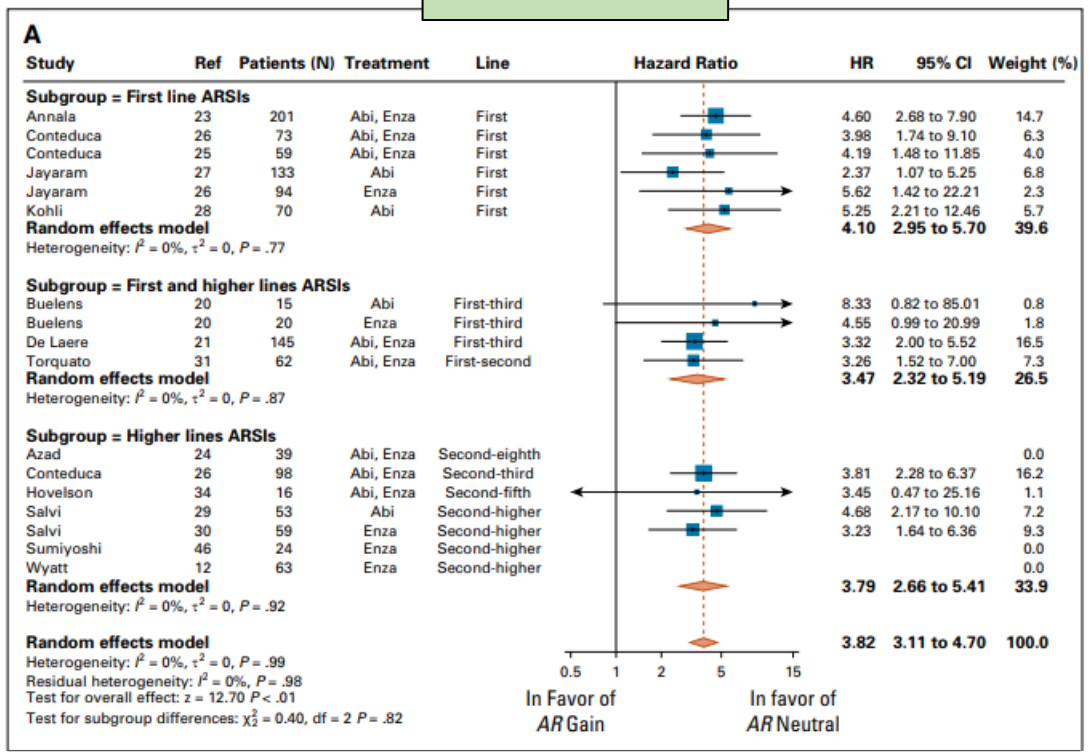
Study	Ref	Patients (N)	Treatment	Line	HR	95% CI	Weight (%)
Subgroup = First line ARSIs							
Annala	23	201	Abi, Enza	First	2.05	1.43 to 2.93	18.6
Conteduca	26	73	Abi, Enza	First	2.18	1.08 to 4.40	4.9
Conteduca	25	59	Abi, Enza	First	1.99	0.79 to 5.00	2.8
Jayaram	27	133	Abi	First	1.94	0.93 to 4.03	4.5
Jayaram	27	94	Enza	First	3.90	1.27 to 12.00	1.9
Kohli	28	70	Abi	First	1.50	0.82 to 2.73	6.7
Random effects model					**2.00**	**1.57 to 2.56**	**39.4**
Heterogeneity: I^2 = 0%, τ^2 = 0, P = .80							
Subgroup = First and higher lines ARSIs							
Buelens	20	15	Abi	First-third	6.67	1.42 to 31.23	1.0
Buelens	20	20	Enza	First-third	4.76	1.38 to 16.37	1.6
De Laere	21	145	Abi, Enza	First-third	2.35	1.59 to 3.48	15.5
Torquato	31	62	Abi, Enza	First-second	2.07	1.20 to 3.57	8.1
Random effects model					**2.45**	**1.81 to 3.32**	**26.2**
Heterogeneity: I^2 = 4%, τ^2 = < 0.0001, P = .37							
Subgroup = Higher lines ARSIs							
Azad	24	39	Abi, Enza	Second-eighth	3.21	1.50 to 6.86	4.2
Conteduca	26	98	Abi, Enza	Second-third	1.95	1.23 to 3.10	11.2
Hovelson	34	16	Abi, Enza	Second-fifth			0.0
Salvi	29	53	Abi	Second-higher	3.73	1.95 to 7.13	5.7
Salvi	30	59	Enza	Second-higher	2.79	1.55; 5.02	6.9
Sumiyoshi	46	24	Enza	Second-higher			0.0
Wyatt	12	63	Enza	Second-higher	2.92	1.59 to 5.37	6.5
Random effects model					**2.68**	**2.05 to 3.49**	**34.4**
Heterogeneity: I^2 = 0%, τ^2 = 0.0010, P = .54							
Random effects model					**2.33**	**2.00 to 2.72**	**100.0**
Heterogeneity: I^2 = 0%, τ^2 = 0, P = .67							
Residual heterogeneity: I^2 = 0%, P = .74							
Test for overall effect: z = 10.73 P < .01							
Test for subgroup differences: χ^2_2 = 2.60, df = 2 P = .27							

Hazard Ratio: 0.5, 1, 2, 5, 15

In Favor of *AR* Gain

In favor of *AR* Neutral

Overall survival



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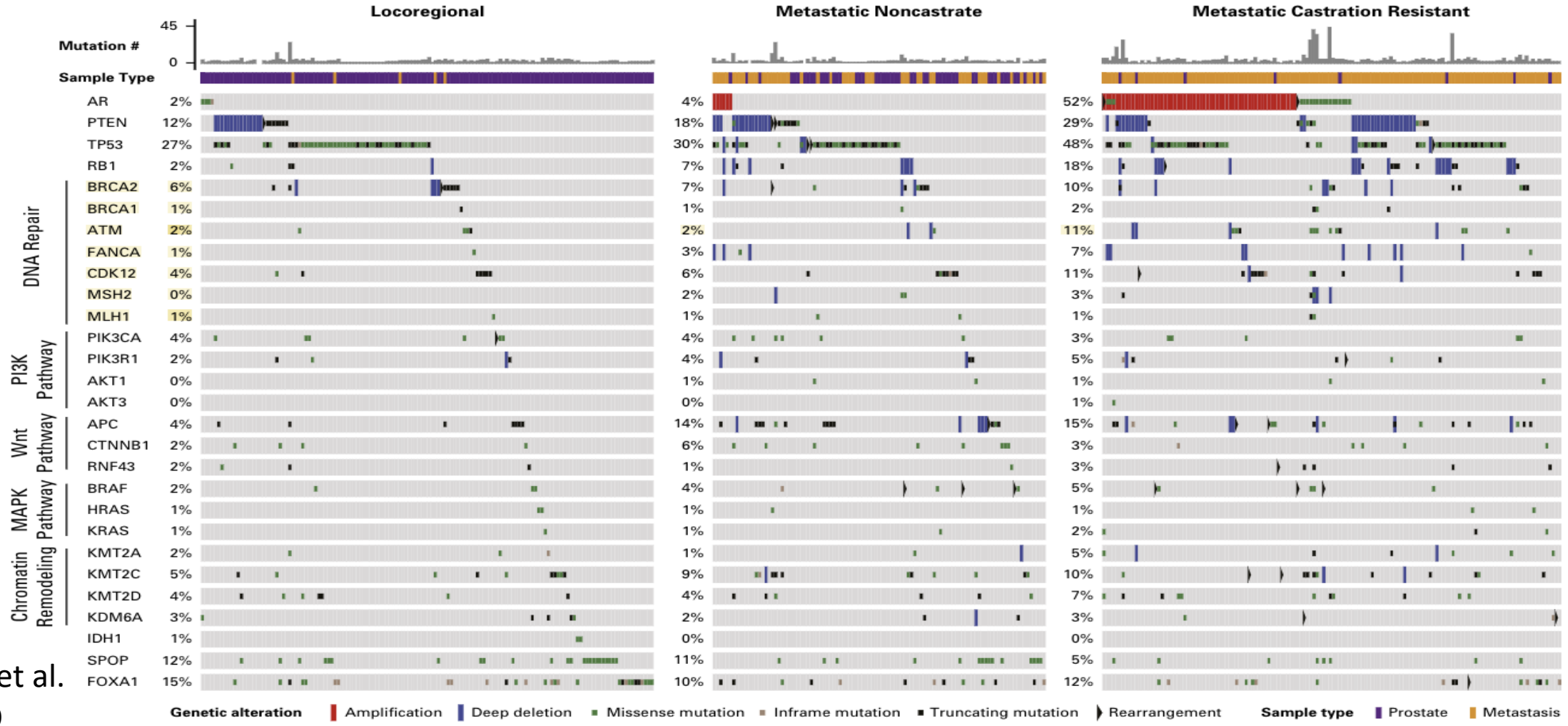
Study	Ref	Patients (N)	Treatment	Line	HR	95% CI	Weight (%)
Subgroup = First line ARSIs							
Annala	23	201	Abi, Enza	First	4.60	2.68 to 7.90	14.7
Conteduca	26	73	Abi, Enza	First	3.98	1.74 to 9.10	6.3
Conteduca	25	59	Abi, Enza	First	4.19	1.48 to 11.85	4.0
Jayaram	27	133	Abi	First	2.37	1.07 to 5.25	6.8
Jayaram	26	94	Enza	First	5.62	1.42 to 22.21	2.3
Kohli	28	70	Abi	First	5.25	2.21 to 12.46	5.7
Random effects model					**4.10**	**2.95 to 5.70**	**39.6**
Heterogeneity: I^2 = 0%, τ^2 = 0, P = .77							
Subgroup = First and higher lines ARSIs							
Buelens	20	15	Abi	First-third	8.33	0.82 to 85.01	0.8
Buelens	20	20	Enza	First-third	4.55	0.99 to 20.99	1.8
De Laere	21	145	Abi, Enza	First-third	3.32	2.00 to 5.52	16.5
Torquato	31	62	Abi, Enza	First-second	3.26	1.52 to 7.00	7.3
Random effects model					**3.47**	**2.32 to 5.19**	**26.5**
Heterogeneity: I^2 = 0%, τ^2 = 0, P = .87							
Subgroup = Higher lines ARSIs							
Azad	24	39	Abi, Enza	Second-eighth			0.0
Conteduca	26	98	Abi, Enza	Second-third	3.81	2.28 to 6.37	16.2
Hovelson	34	16	Abi, Enza	Second-fifth	3.45	0.47 to 25.16	1.1
Salvi	29	53	Abi	Second-higher	4.68	2.17 to 10.10	7.2
Salvi	30	59	Enza	Second-higher	3.23	1.64 to 6.36	9.3
Sumiyoshi	46	24	Enza	Second-higher			0.0
Wyatt	12	63	Enza	Second-higher			0.0
Random effects model					**3.79**	**2.66 to 5.41**	**33.9**
Heterogeneity: I^2 = 0%, τ^2 = 0, P = .92							
Random effects model					**3.82**	**3.11 to 4.70**	**100.0**
Heterogeneity: I^2 = 0%, τ^2 = 0, P = .99							
Residual heterogeneity: I^2 = 0%, P = .98							
Test for overall effect: z = 12.70 P < .01							
Test for subgroup differences: χ^2_2 = 0.40, df = 2 P = .82							

Hazard Ratio: 0.5, 1, 2, 5, 15

In Favor of *AR* Gain

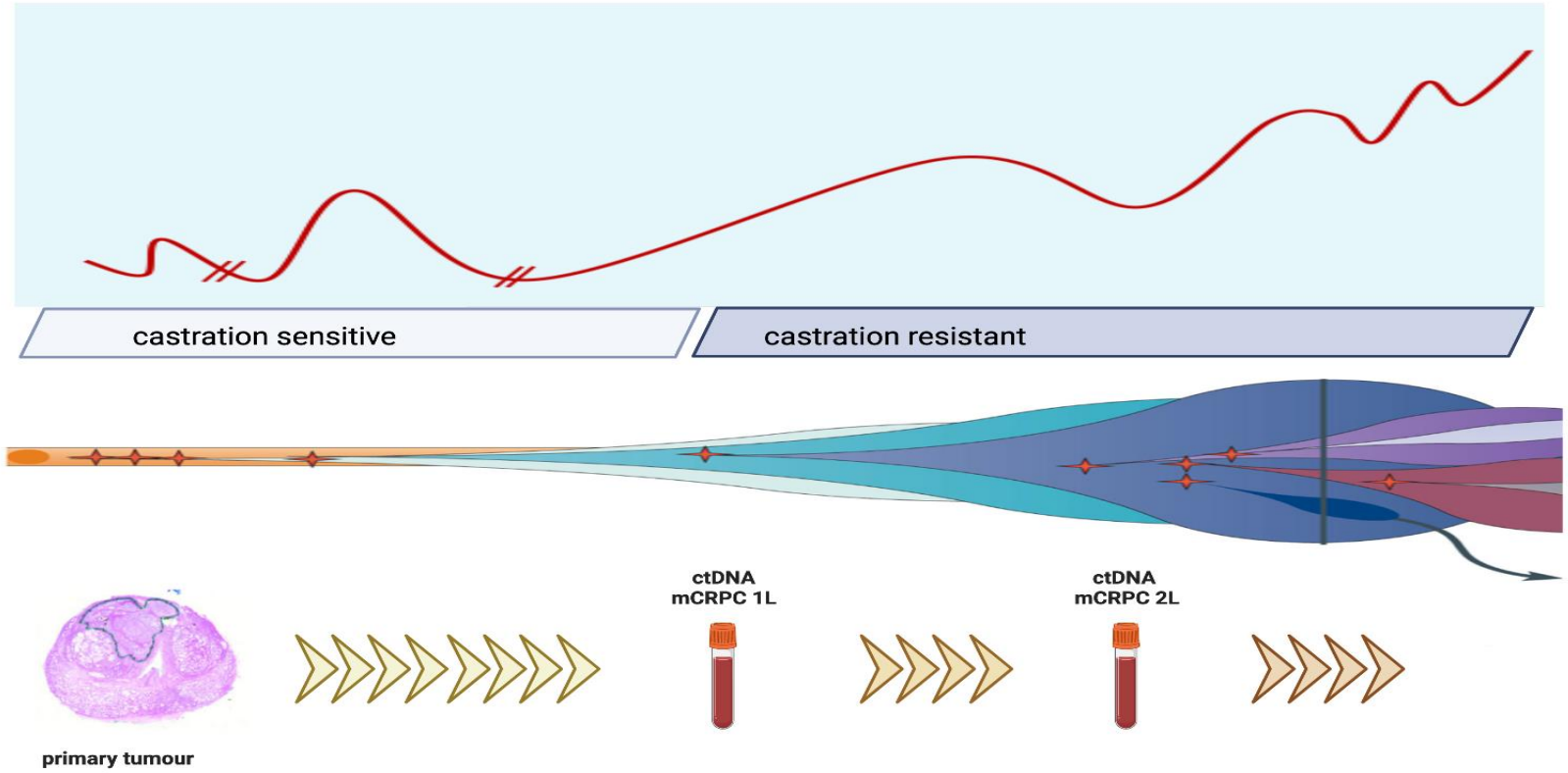
In favor of *AR* Neutral

mCRPC resistentie mechanismen (buiten AR)



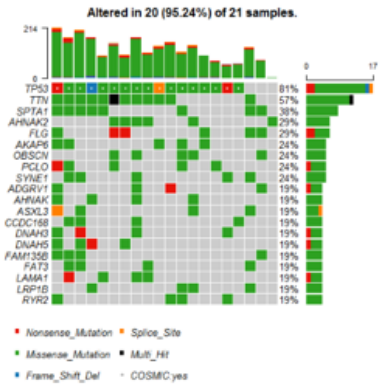
Abida et al. JCP PO

Optimaler inzet precision medicine door gebruik ctDNA in mCRPC

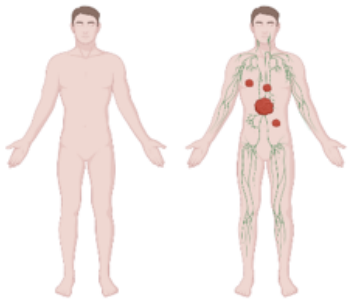


Optimaler inzet precision medicine door gebruik ctDNA in mCRPC

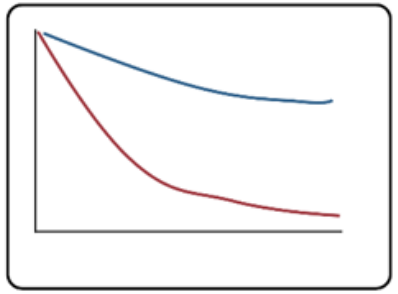
1 **ctDNA profling**
to allow for molecular characterization of PCa



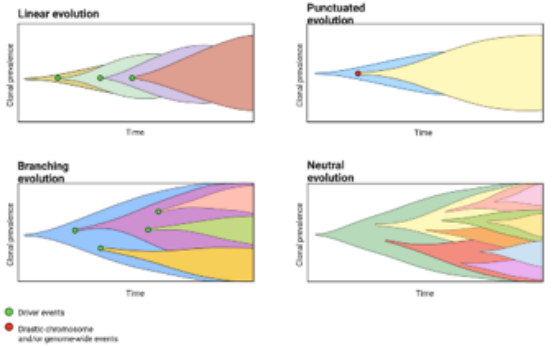
2 **ctDNA quantitation**
as a measure of tumour vo
or minimal residual disease



3 **ctDNA changes**
detectable or undetectable ctDNA during therapy



4 **ctDNA longitudinal for tumor evolution**



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Predictieve diagnostiek voor immuun- en doelgerichte therapie

1. ctDNA profiling

OXFORD

JNCI J Natl Cancer Inst (2018) 110(1): djx118

doi: 10.1093/jnci/djx118
First published online June 29, 2017
Article

ARTICLE

Concordance of Circulating Tumor DNA and Matched Metastatic Tissue Biopsy in Prostate Cancer

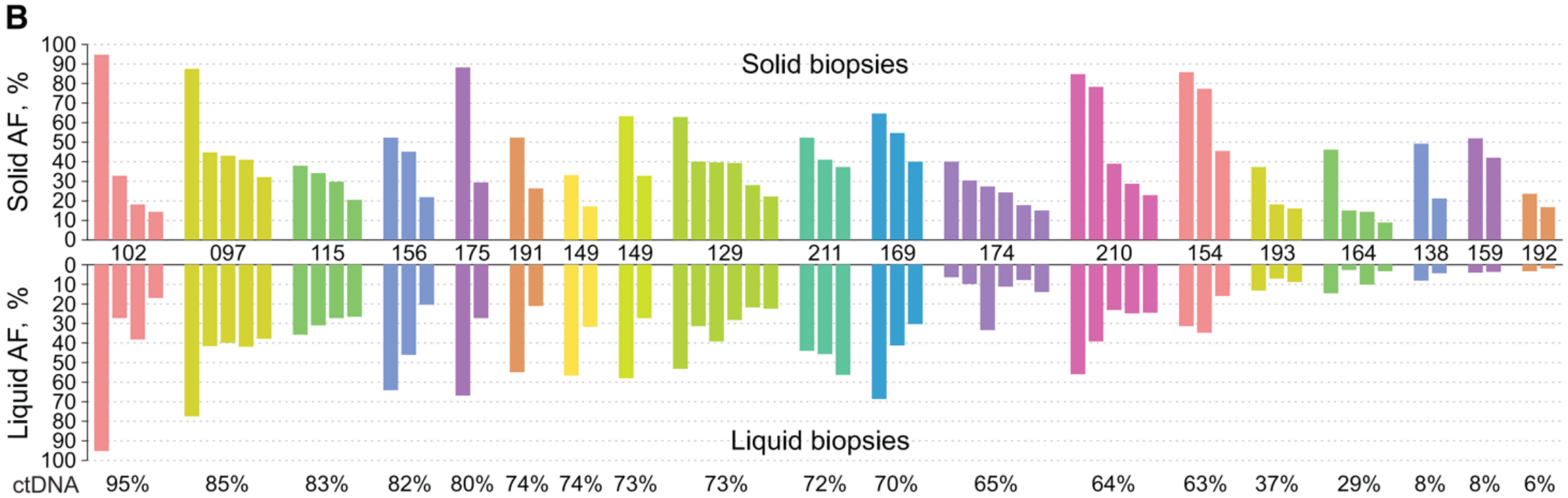
Alexander W. Wyatt*, Matti Annala*, Rahul Aggarwal, Kevin Beja, Felix Feng, Jack Youngren, Adam Foye, Paul Lloyd, Matti Nykter, Tomasz M. Beer, Joshi J. Alumkal, George V. Thomas, Robert E. Reiter, Matthew B. Rettig, Christopher P. Evans, Allen C. Gao, Kim N. Chi†, Eric J. Small†, Martin E. Gleave†

Wyatt et al. JNCI, 2018

ONCOLOGIE UPDATE 2023

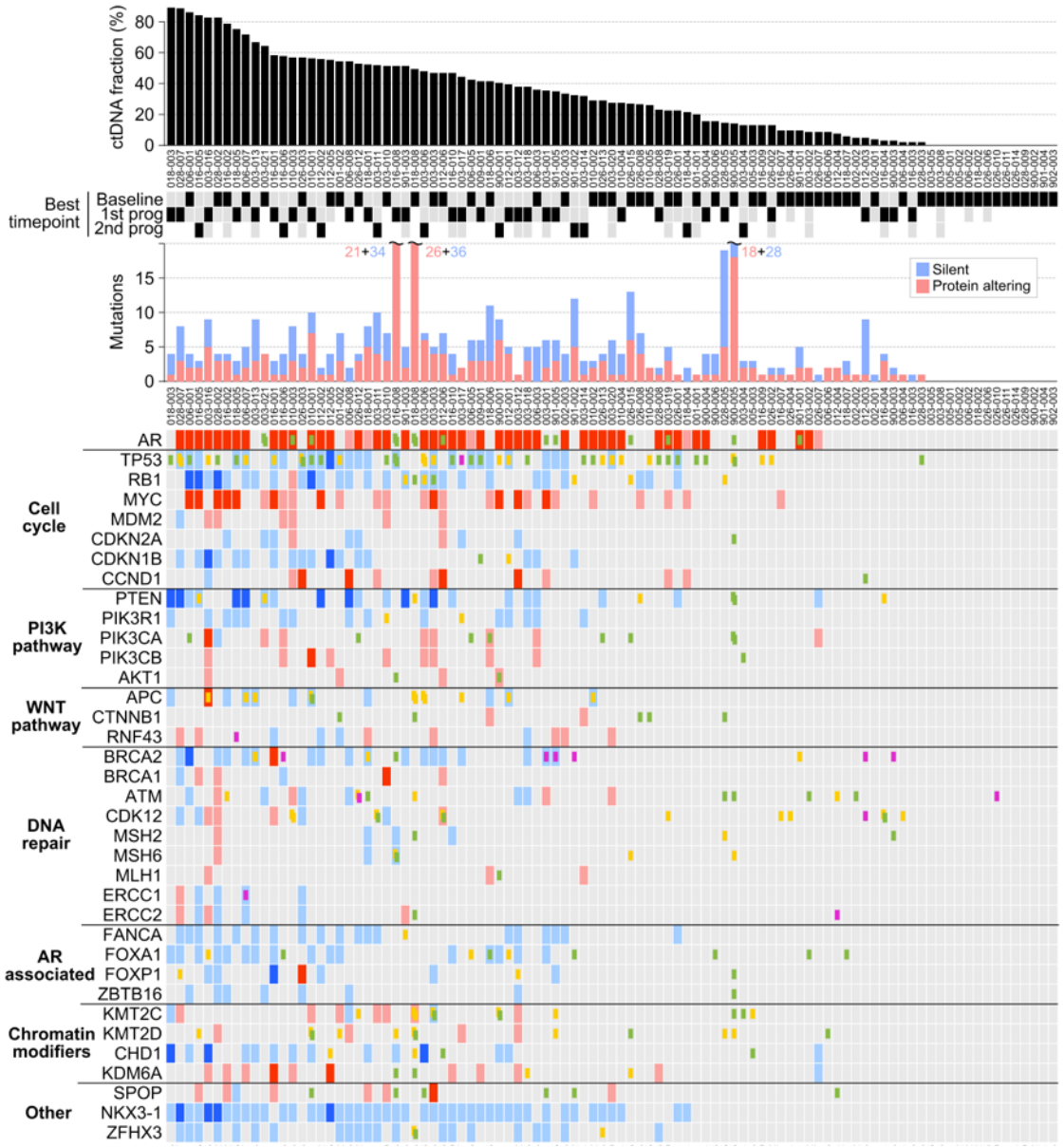
Predictieve diagnostiek voor immuun- en doelgerichte therapie

1. ctDNA profiling: circulating tumour DNA vs liquid



Concordance of mutation calls between solid and liquid biopsies. B) Variant allele frequencies for somatic mutations shared between matched liquid and solid biopsies, showing broad conservation of mutant allele fraction hierarchy. ctDNA fraction for each liquid biopsy is provided at the bottom.

Wyatt et al. JNCI, 2018



1. ctDNA profiling: MD

Mutations and rearrangements
- Missense or in-frame indel
- Truncating
- Germline defect
- Rearrangement

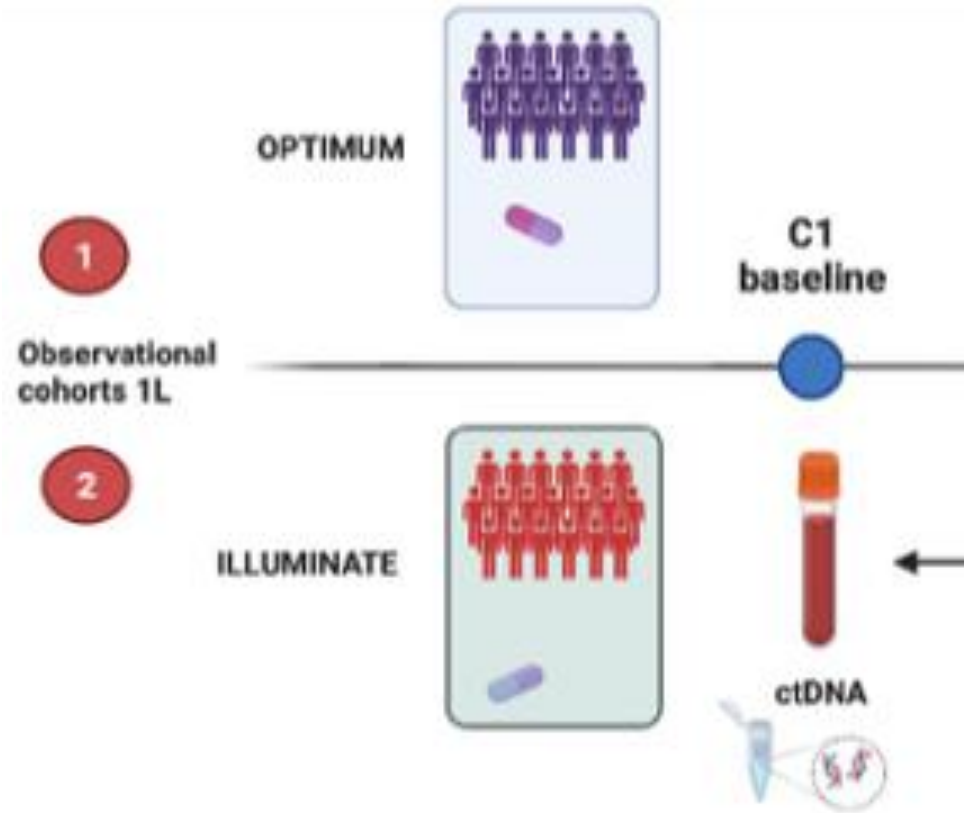
Copy number alterations
- Gain
- Gain (logratio > 0.6)
- Deletion
- Deletion (logratio < -1.0)

Supplemental table 8

76 pt (80%) had een ctDNA content >2%

Annala M, et al. Cabazitaxel versus abiraterone or enzalutamide in poor prognosis metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase II trial. Ann Oncol. 2021

OPTIMUM and ILLUMINATE studies: 1L mCRPC



- All patients recently progressed from CSPC to mCRPC (1L)
- Populations were comparable between trials
- OPTIMUM trial evaluated biomarkers in abiraterone-treated patients
- ILLUMINATE trial evaluated biomarkers in enzalutamide treated patients
- Both drugs show equal progression-free survival (PFS) and overall survival (OS)

Tolmeijer et al. Early on-treatment changes in circulating tumor DNA fraction and response to enzalutamide or abiraterone in metastatic castration-resistant prostate cancer: Unpublished results.

1. ctDNA profiling: methoden

- Single streck cfDNA BCT (9 mL)

- EDTA whole blood sample (6 mL) to address germline variants and somatic variants from white bloods cells (CHiP)

- Deep targeted-sequencing with a custom panel covering the coding regions (and selected introns) of 73 PCa genes
  - Including a genome wide grid capturing common heterozygous germline SNPs

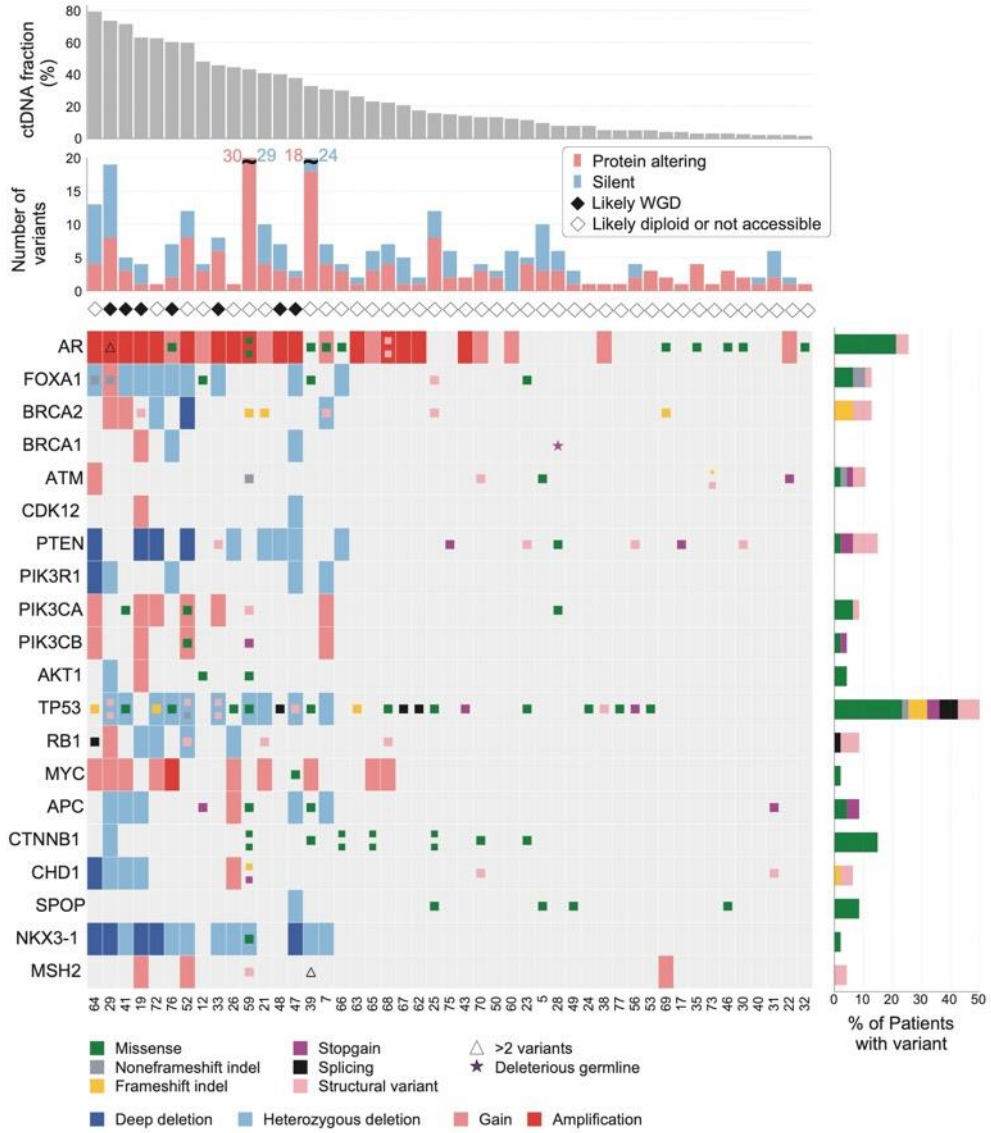
- Sequencing libraries prepared from 10-100ng cfDNA or 100ng of gDNA. Library pools were hybridized to a custom-designed KAPA HyperChoice probe set. Pools sequenced on Illumina machines.

1. ctDNA profiling: methoden

- Somatic mutations calling
  - At least 8 supporting reads and a VAF of at least 0.5%
    - VAF >20x average allel fraction from 83 WBC samples
    - VAF >3x patient specific WBC sample

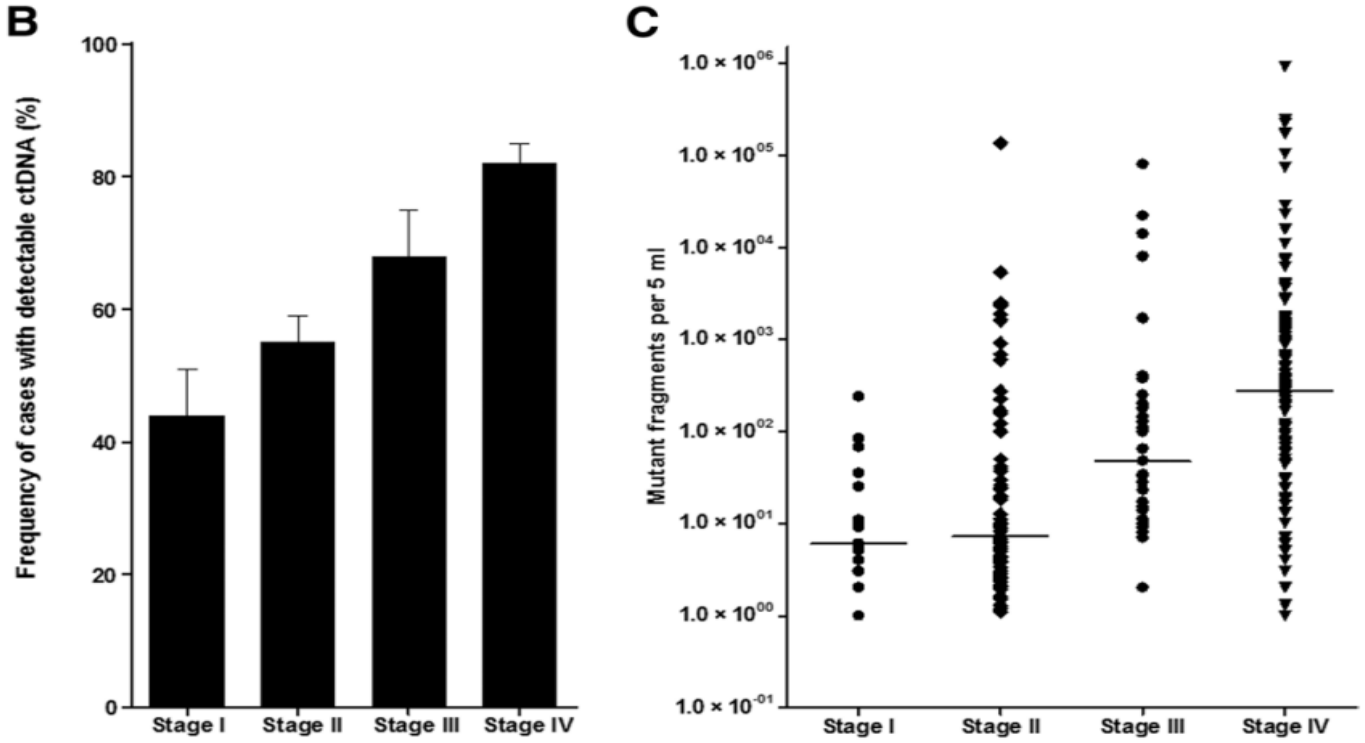
- ctDNA fraction estimation
  - Somatic autosomal mutations - calculated using VAF in non-amplified genes
  - Germline heterozygous SNPs - correcting potential LOH
  - Correcting for statistical outliers by conservative estimation (binomial distribution, with hightest VAF 95% quantile outlier)

1. ctDNA profiling: OPTIMUM en ILLUMINATE

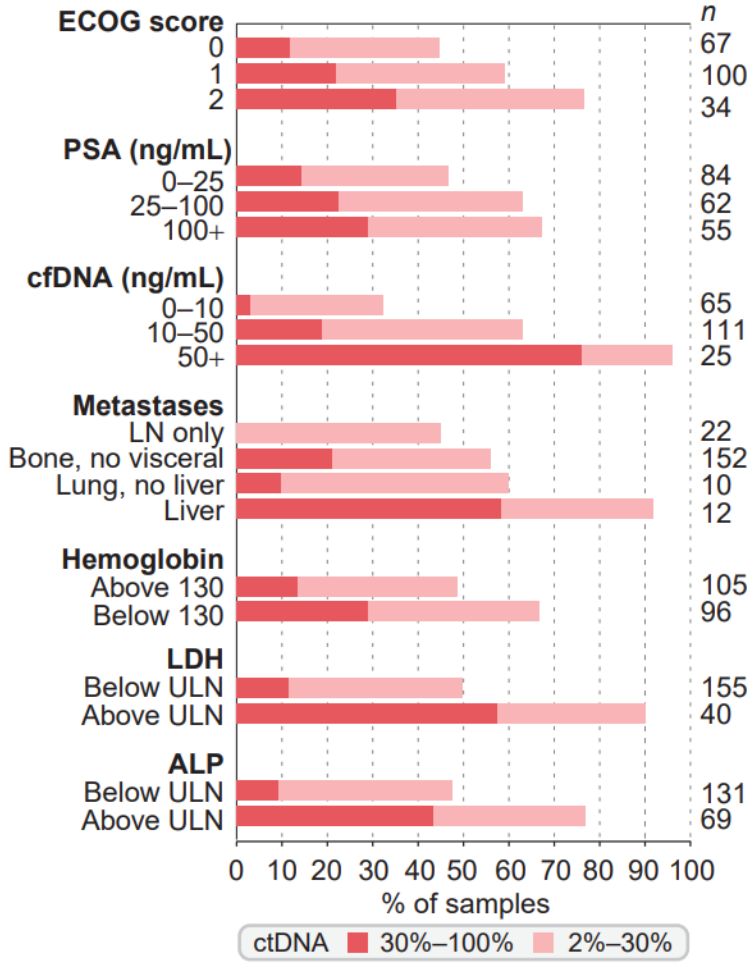


Tolmeijer et al.

2. ctDNA quantificatie: ctDNA% als weerspiegeling van de tumorvolume

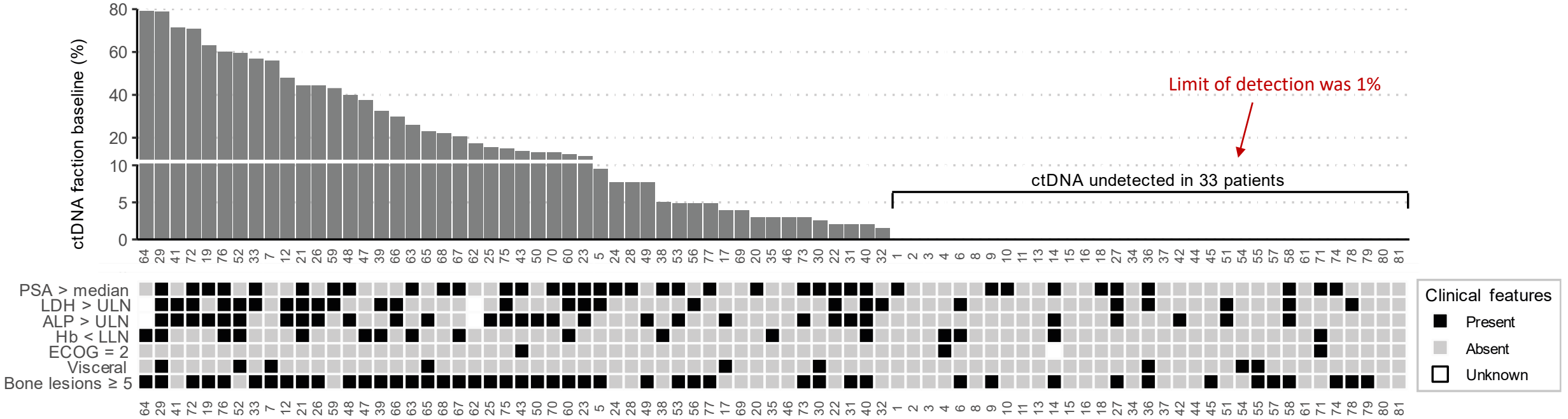


Bettegowda, Sci Transl Med, 2014



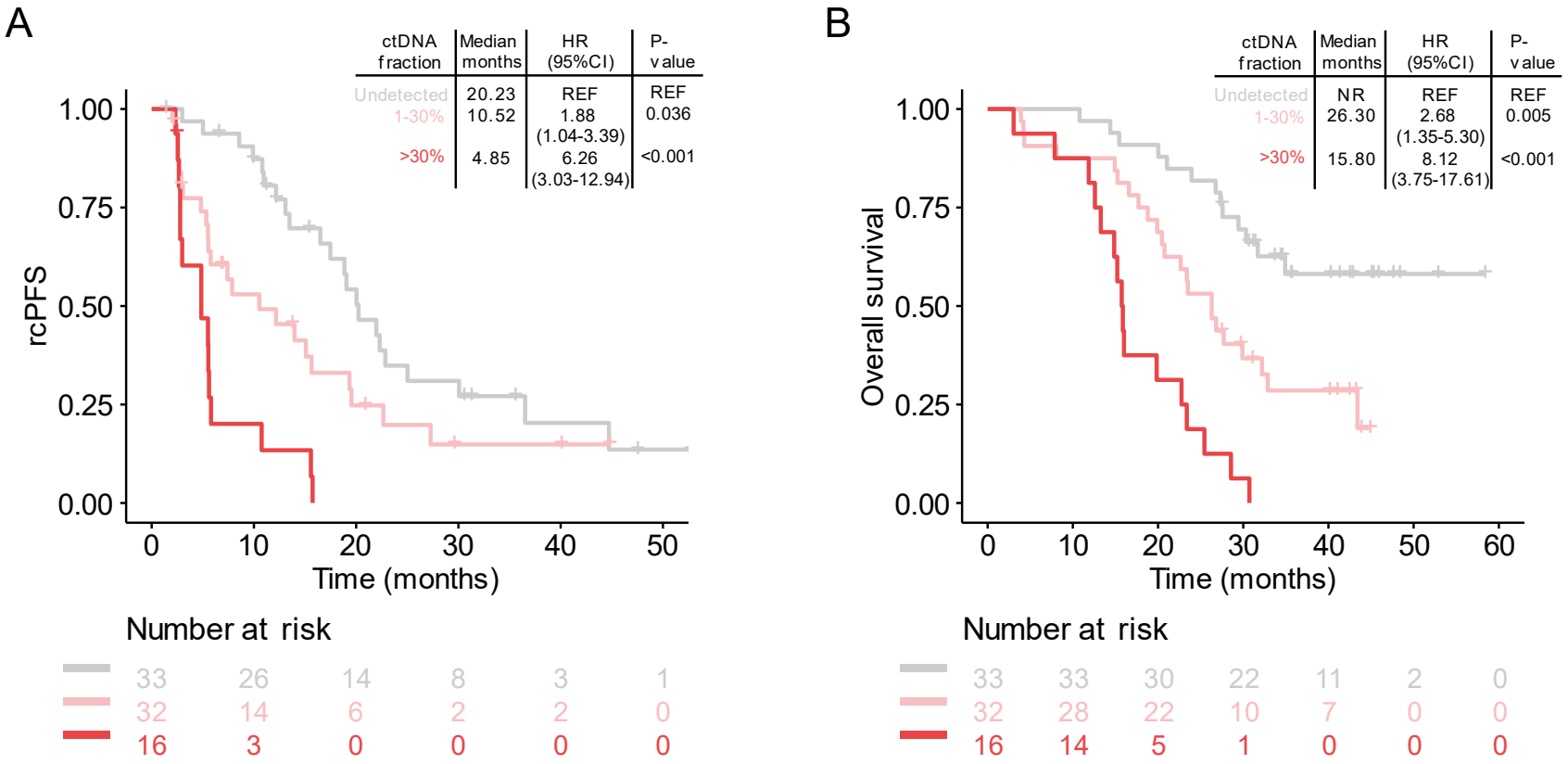
Annala, Cancer Discovery, 2018

2. ctDNA quantificatie: ctDNA% als weerspiegeling van de tumorvolume



Tolmeijer et al, CCR, 2023

2. ctDNA quantificatie: ctDNA as reflection of the tumor burden



Tolmeijer et al. CCR, 2023

2. ctDNA quantificatie: ctDNA% berekening op basis van clinico-pathologische variabelen

Clinical information (all optional)

cfDNA: 35 ng / mL plasma

PSA: 20 ng / mL

LDH: 210 U / L, with lab ULN 150

ALP: 250 U / L, with lab ULN 110

ECOG PS: 0 | 1 | **2** | 3 | 4 | N/A

Liver mets: **Yes** | No | N/A

Lung mets: Yes | **No** | N/A

Node mets: **Yes** | No | N/A

Predict ctDNA%

Predicted plasma ctDNA fraction

44%

for a patient with progressive disease

Probability of having ctDNA > 2%

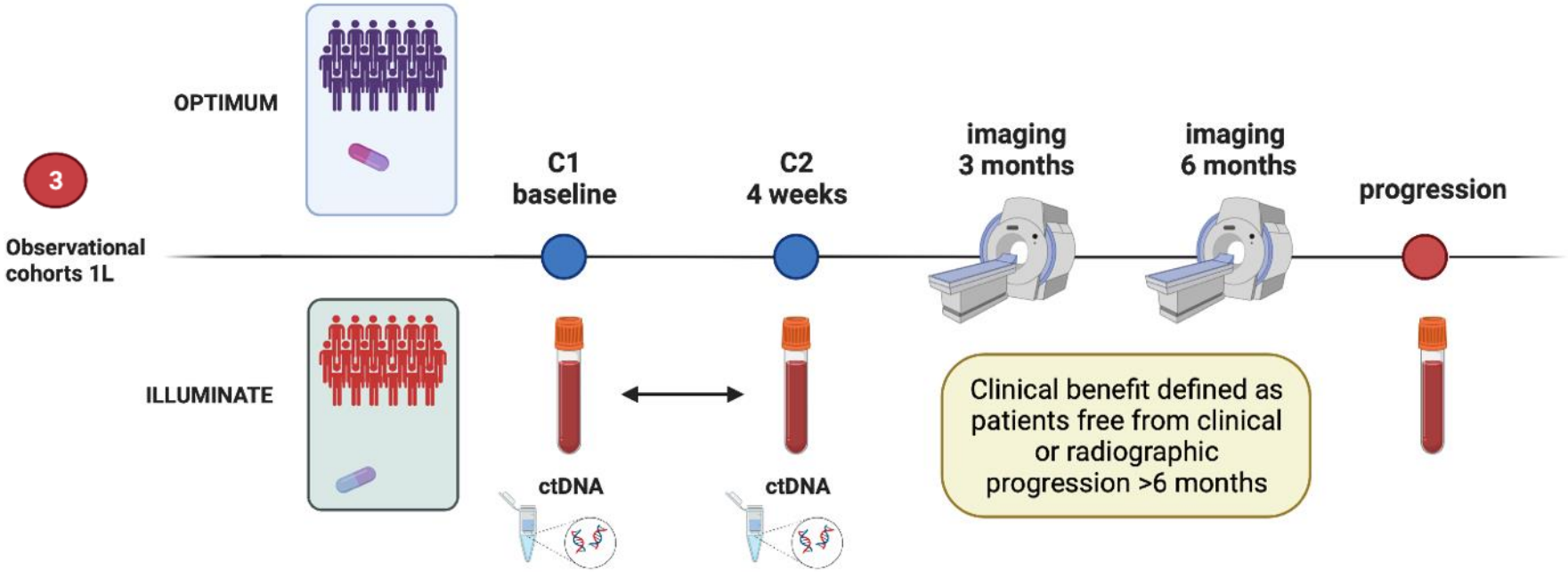
98%

ctDNA.org

ONCOLOGIE UPDATE 2023

Predictieve diagnostiek voor immuun- en doelgerichte therapie

3. ctDNA veranderingen: monitoring van therapie OPTIMUM & ILUMINATE

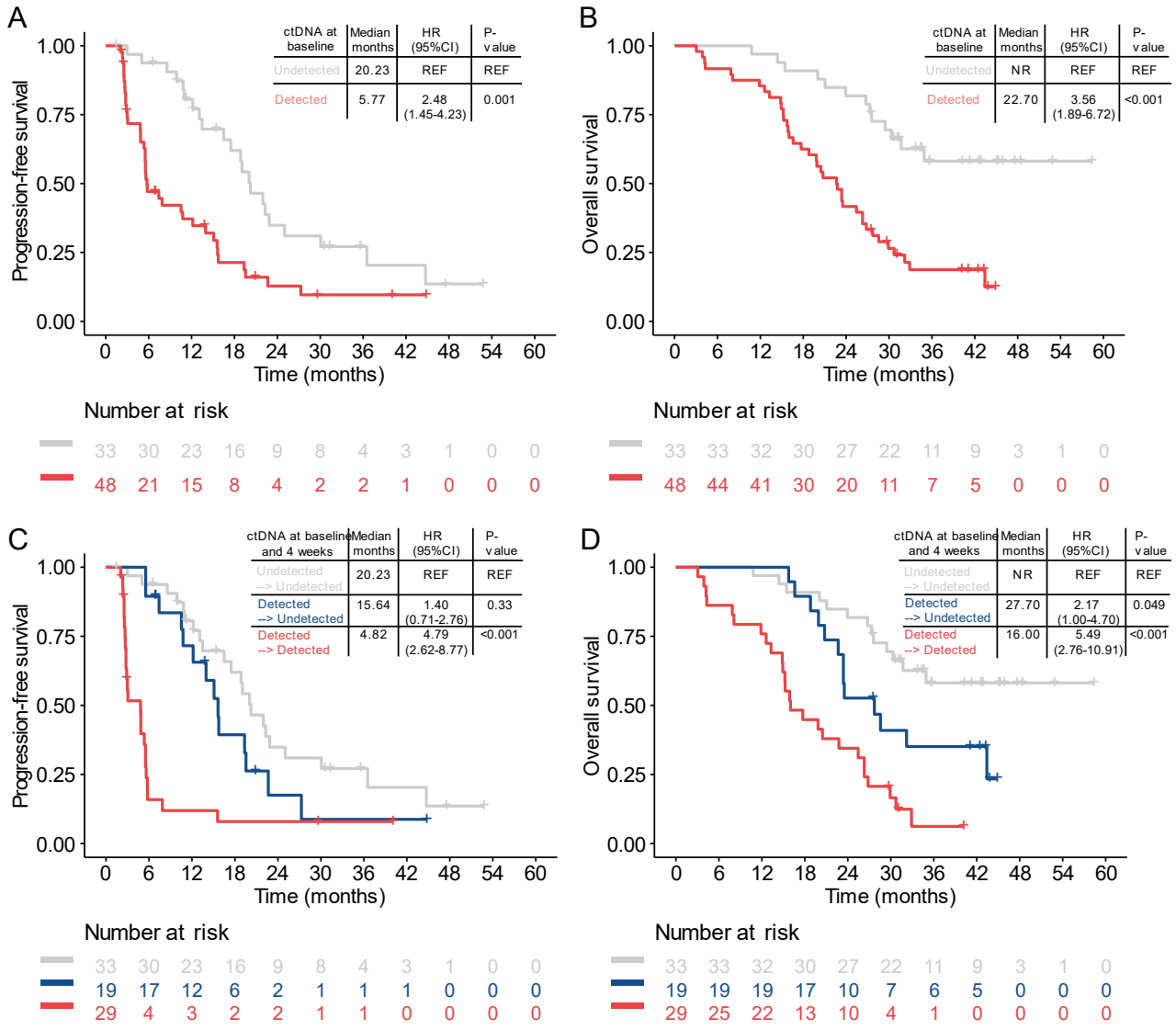


81 patients

ctDNA detection at Vancouver Prostate Centre *(up to 1%)*

Tolmeijer et al. Early on-treatment changes in circulating tumor DNA fraction and response to enzalutamide or abiraterone in metastatic castration-resistant prostate cancer. CCR, 2023.

3. ctDNA veranderingen: monitoring van therapie OPTIMUM & ILUMINATE



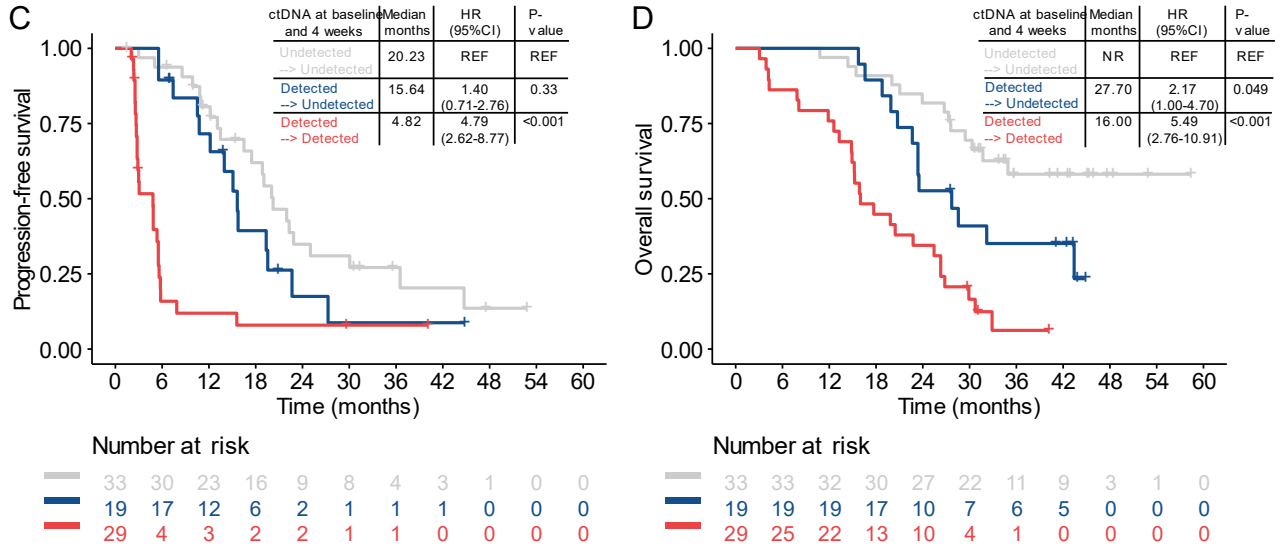
Tolmeijer, CCR 2023

3. ctDNA veranderingen: monitoring van therapie OPTIMUM & ILUMINATE

Multivariate results corrected for baseline ctDNA%, PSA, LDH, ALP

	PFS	
ctDNA% change at 4 weeks	HR (95% CI)	*P*-value
Undetected → Undetected	ref	ref
Detected → Undetected	1.16 (0.57-2.33)	0.681
Detected → Detected	4.98 (2.08-11.93)	**0.000**

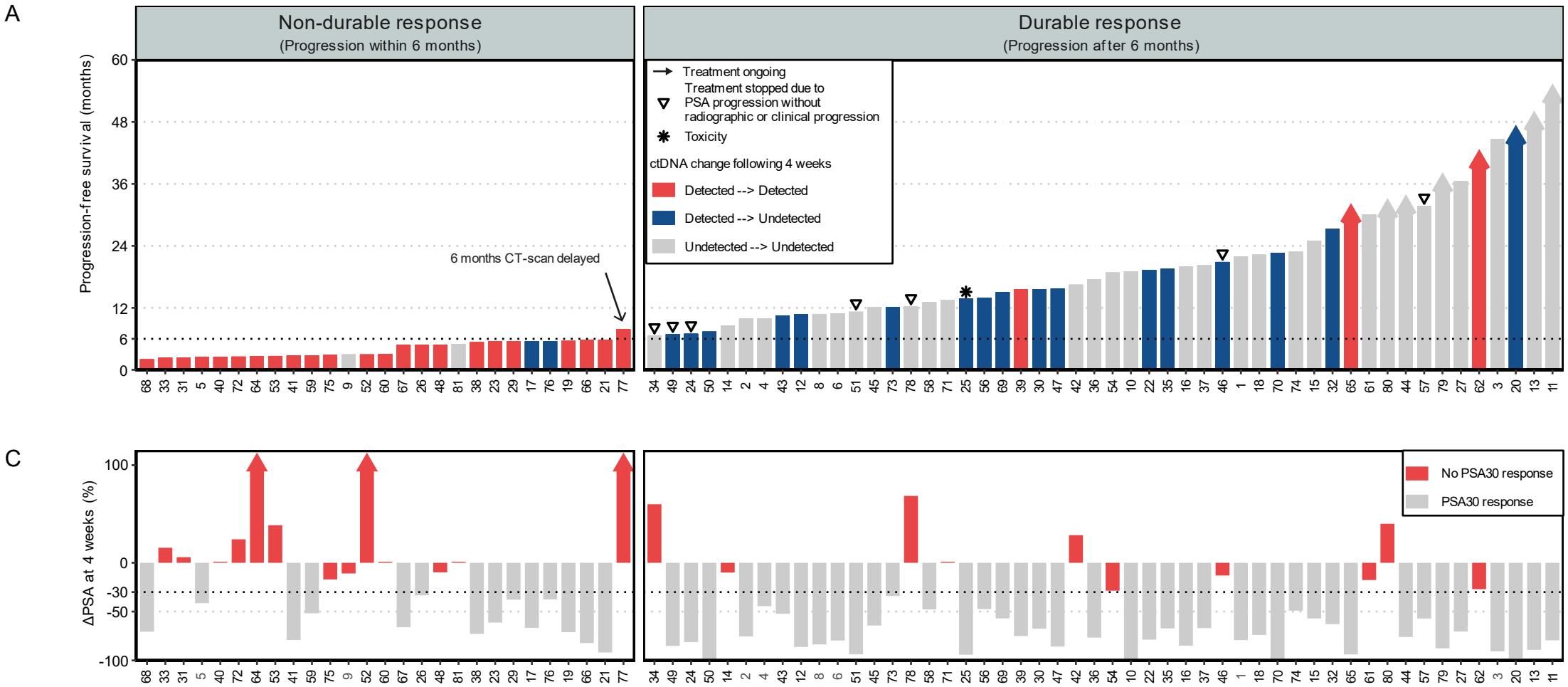
	OS	
ctDNA% change at 4 weeks	HR (95% CI)	*P*-value
Undetected → Undetected	ref	ref
Detected → Undetected	1.82 (0.8-4.12)	0.150
Detected → Detected	3.69 (1.5-9.08)	**0.005**



Tolmeijer, CCR 2023

3. ctDNA veranderingen: kort- vs langdurige respons

PPV = 88%
NPV = 92%



PPV = 57%
NPV = 74%

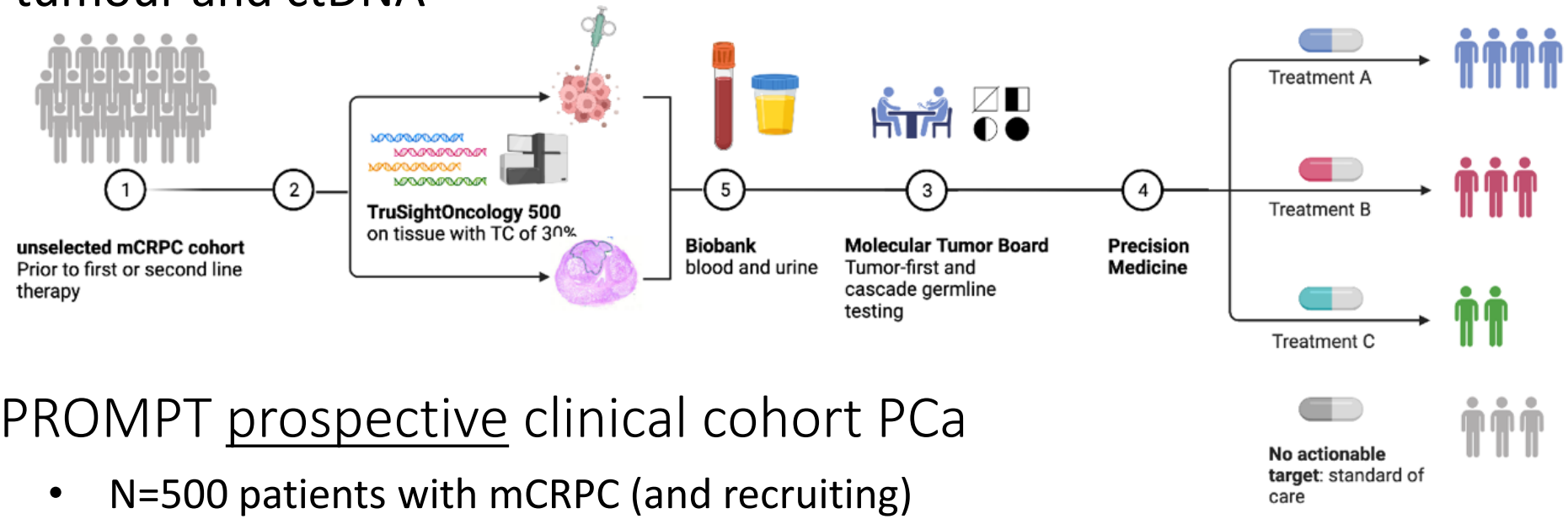
Tolmeijer, CCR 2023

3. ctDNA veranderingen: Still independent prognostic for baseline alterations

			Radiographic and/or clinical progression free survival					Overall survival				
				Univariate analysis		Multivariate analysis			Univariate analysis		Multivariate analysis	
Clinical marker	**Subgroup**	**No. patients**	**Median (months)**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**	**Median (months)**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
ctDNA change following 4 weeks	ND > ND	33	20.23	ref	ref	ref	ref	Not reached	ref	ref	ref	ref
	D > ND	19	15.64	1.4 (0.71-2.75)	0.328	1.35 (0.65-2.8)	0.423	27.70	2.17 (1-4.69)	**0.049**	1.53 (0.66-3.53)	0.323
	D > D	29	4.82	4.79 (2.61-8.77)	**0.000**	4.22 (1.69-10.57)	**0.002**	16.00	5.49 (2.76-10.9)	**0.000**	2.65 (1.06-6.61)	**0.036**
AR gain	Absent	56	16.49	ref	ref	ref	ref	32.89	ref	ref	ref	ref
	Present	25	5.34	2.38 (1.39-4.09)	**0.002**	0.9 (0.44-1.84)	0.779	15.87	3.5 (1.99-6.16)	**0.000**	1.59 (0.81-3.11)	0.176
TP53 alteration	Absent	57	18.85	ref	ref	ref	ref	32.20	ref	ref	ref	ref
	Present	24	5.34	3.03 (1.72-5.32)	**0.000**	1.38 (0.68-2.79)	0.374	15.93	4.26 (2.43-7.48)	**0.000**	2.14 (1.08-4.24)	**0.029**

Current plans on panel validation and screening

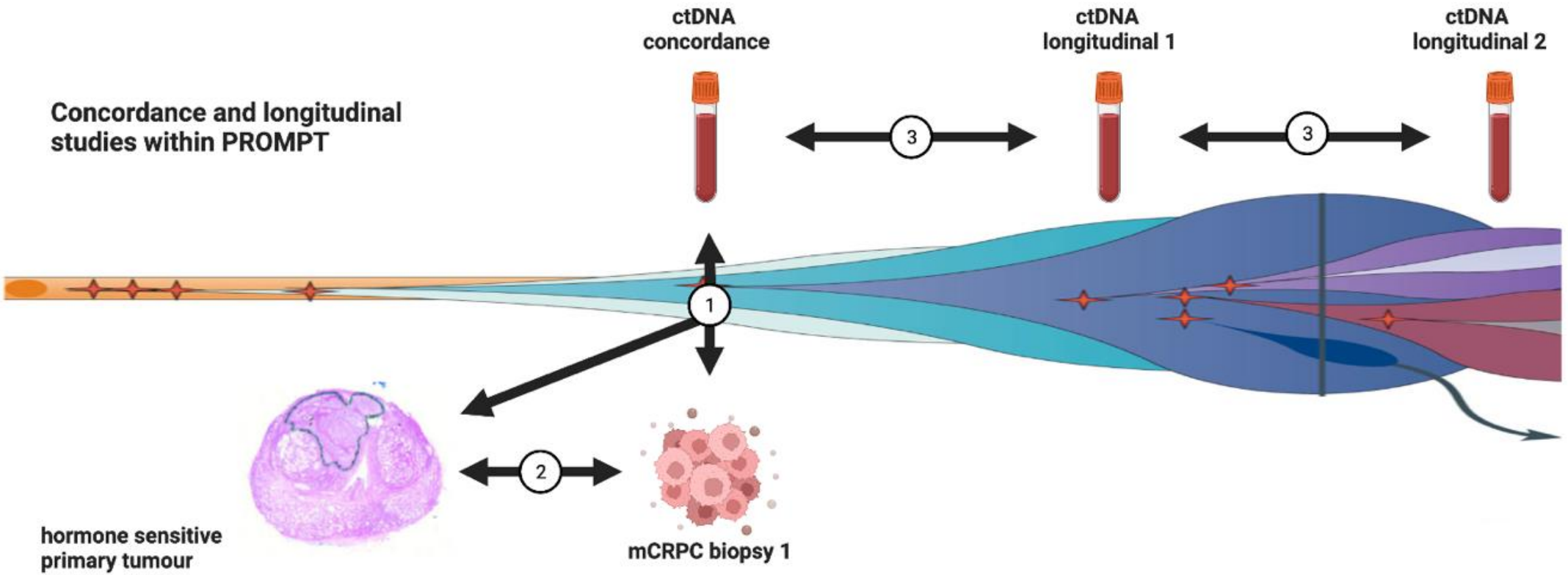
Validating a newly designed targeted panel comprising 53 prostate cancer specific recurrent gene alterations in a new prospective cohort with matched tumour and ctDNA



PROMPT <u>prospective</u> clinical cohort PCa

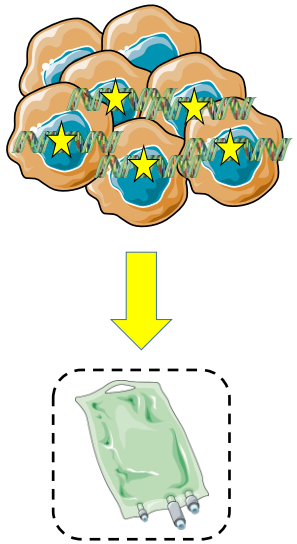
- N=500 patients with mCRPC (and recruiting)
- N=250 have matched fresh biopsies and ctDNA

Current plans on panel validation and screening



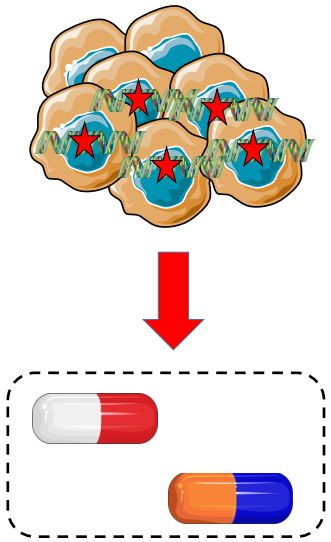
Concordance studies ongoing 2024: oa BRCA1/2 (snv, CNV, signatures) en MMRd en MSI

Current plans for ctDNA treatment selection: 2024



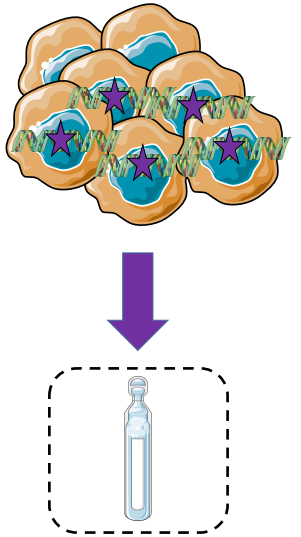
PARP inhibitors

Defect in homologous recombination repair (HRR) genes: BRCA1, BRCA2, possibly others like PALB2



PI3K inhibitors

Activating mutations in PI3K/Akt/mTOR pathway



Immunotherapy

Defect in mismatch repair (MMR) genes: MLH1, MSH2, MSH6, PMS2, or MSI signature

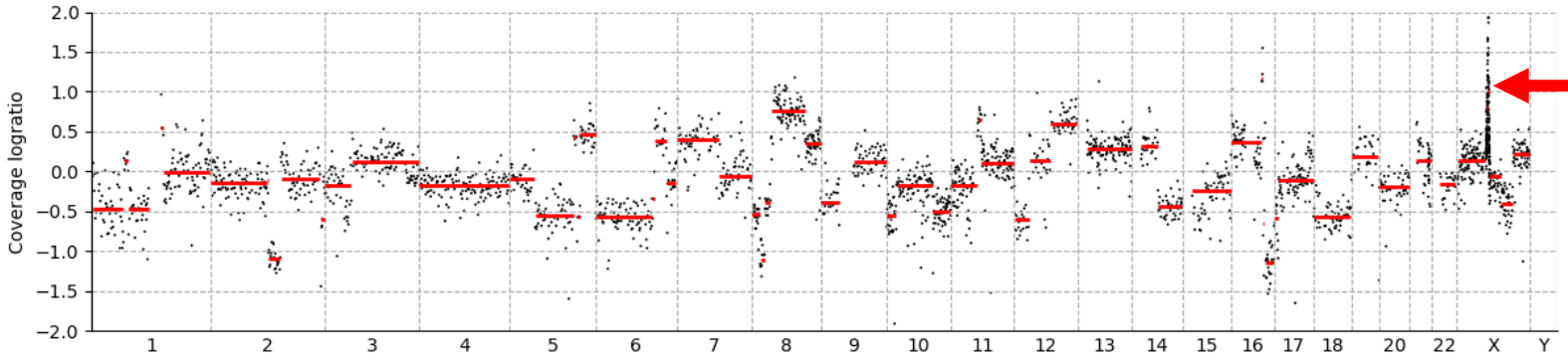
ONCOLOGIE UPDATE 2023

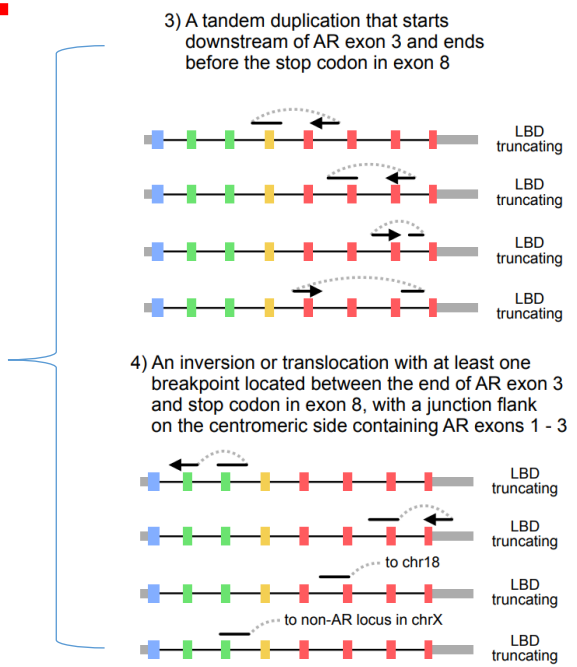
Predictieve diagnostiek voor immuun- en doelgerichte therapie

Current plans for ctDNA treatment selection: 2024

- ctDNA fractional abundance 75%
- High level amplification of AR

WGS





- Ligand binding domain truncating structural variants: 3 intrachromal translocations / 1 tandem duplication
- Other: TP53 biallelic inactivation, no BRCAm/DDRm

Annala M, et al. Ann Oncol. 2021 ; Tolmeijer SH, et al. JCO Precis Oncol 2020

Voor- en nadelen inzet MD op tumor, bloed en ctDNA in mCRPC

	Voordelen	Nadelen
Tumor weefsel	• Detectie van zowel kiembaan- als somatisch mutaties • Weefsel is momenteel de gouden standaard	• Sample kwaliteit en kwantiteit soms onvoldende • Kan genetische heterogeniteit binnen tumor missen • Invasieve methode om sample te verkrijgen, derhalve vaak alleen diagnostisch 'archief' weefsel • Profiel mCRPC ≠ mHSPC ≠ lokaal prostaatkanker
Bloed cellen	• Detectie van kiembaan mutaties • Gemakkelijk te verkrijgen, weinig invasief	• Geen detectie van somatische mutaties • Genetic counselling noodzakelijk via geneticus of mainstreaming
Plasma ctDNA + bloed cellen	• Detectie van zowel kiembaan- als somatisch mutaties • Addresseert tumor heterogeniteit • Gemakkelijk te verkrijgen, weinig invasief • Longitudinaal sampling adresseert tumor evolutie • Additioneel: ctDNA% en veranderingen na therapie	• Momenteel nog niet (breed) beschikbaar • Lagere gevoeligheid dan testen op tumorweefsel (met name CNV) • Custom design panels noodzakelijk en bioinformatica pipeline • ctDNA analyse bloed ≠ gevalideerde kiembaan analyse

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