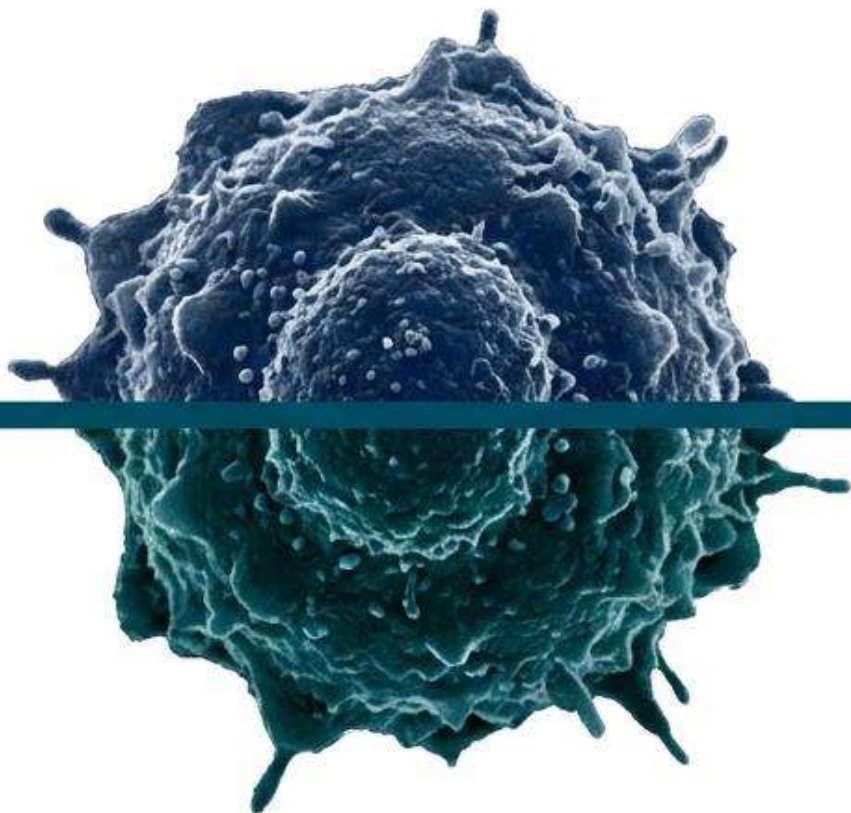




Can We Identify Lethal Prostate Cancer?

*Towards Integrating Clinical
and Molecular Approaches*

Bram De Laere, PhD

Introduction to lethal prostate cancer

- **Epidemiology:** Prostate cancer remains the most commonly detected cancer in men
- Not all prostate cancers are lethal; **identifying aggressive subtypes** is crucial for timely intervention

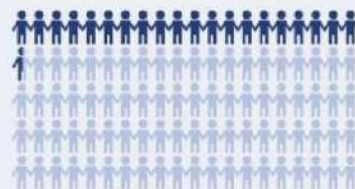


Belgian Cancer Registry

Key facts

- Most common cancer in males
- **12,535** new diagnoses in 2024
- **1,485** deaths due to prostate cancer in 2023
- 10-year net survival of **97.0%**

Lifetime risk (0-84 years)



20.6 in 100 males

12,535

Incidence (2024)

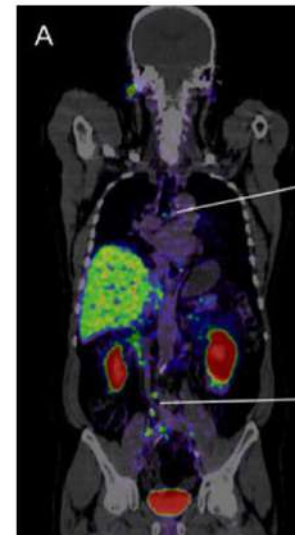
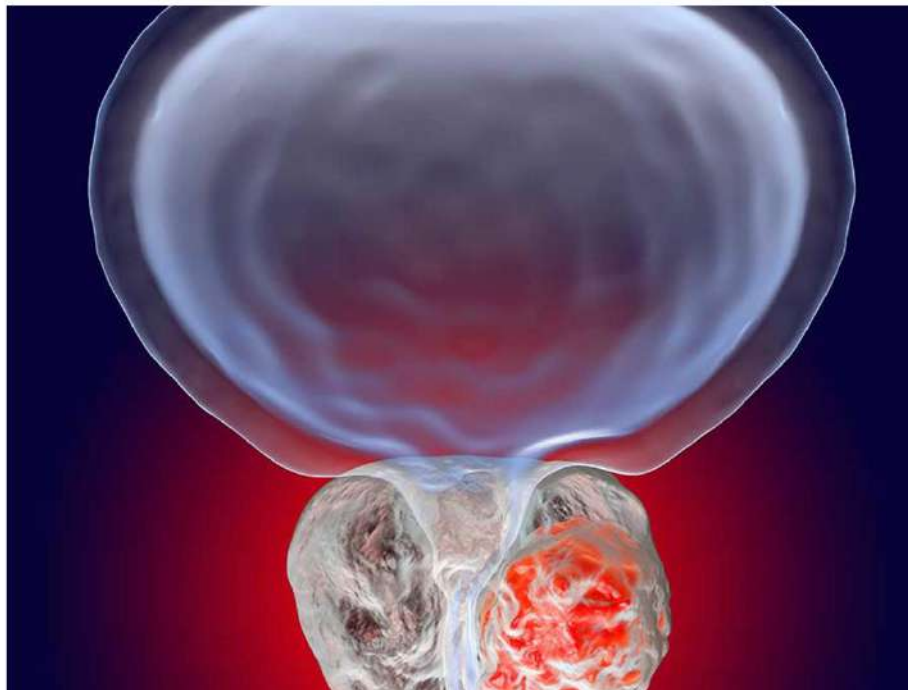
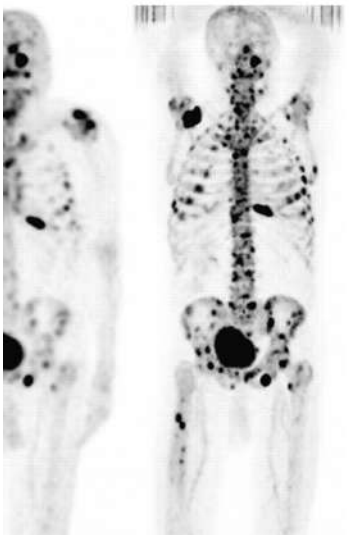
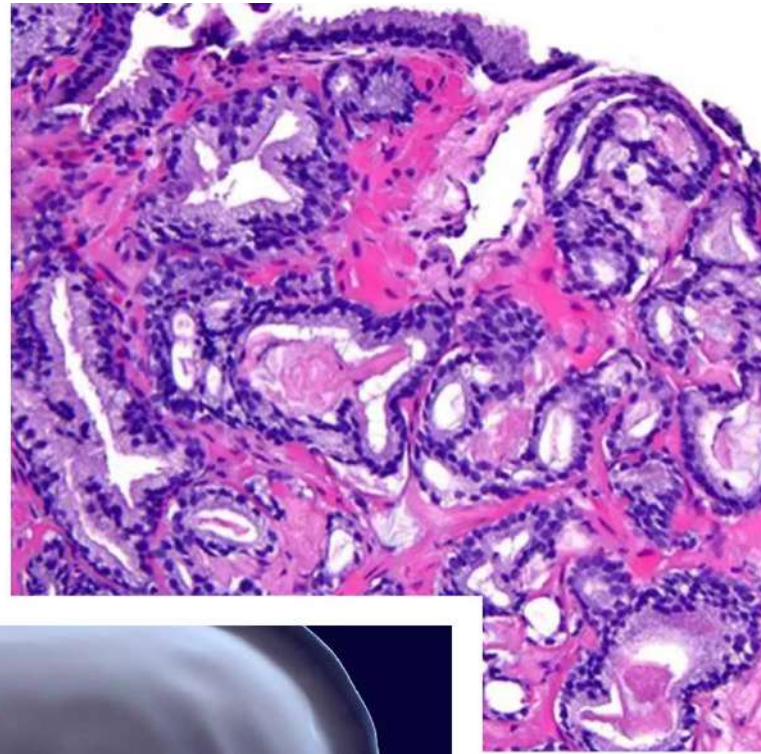
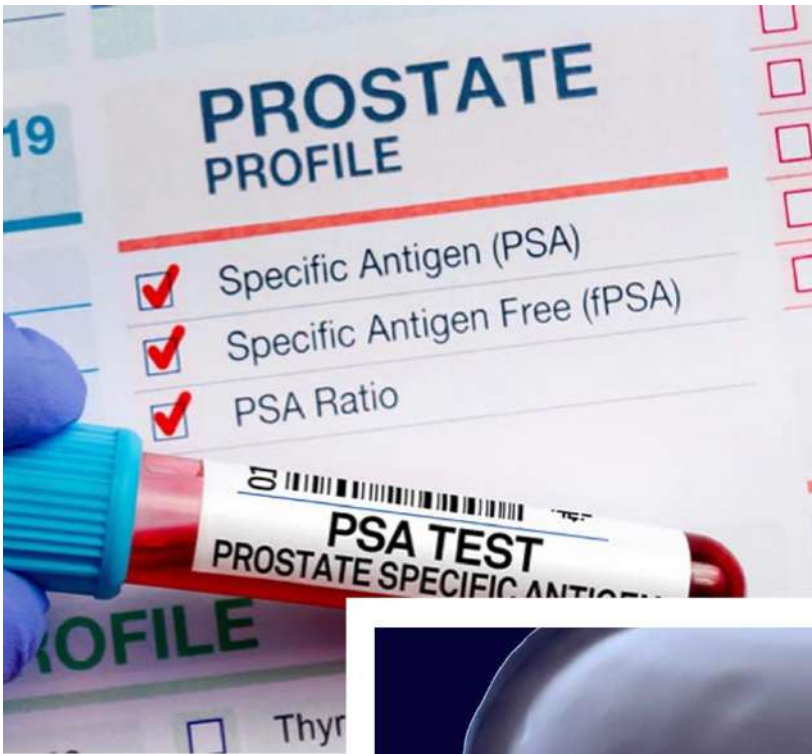
Can we identify
lethal prostate
cancer?



1,485

Mortality* (2023)

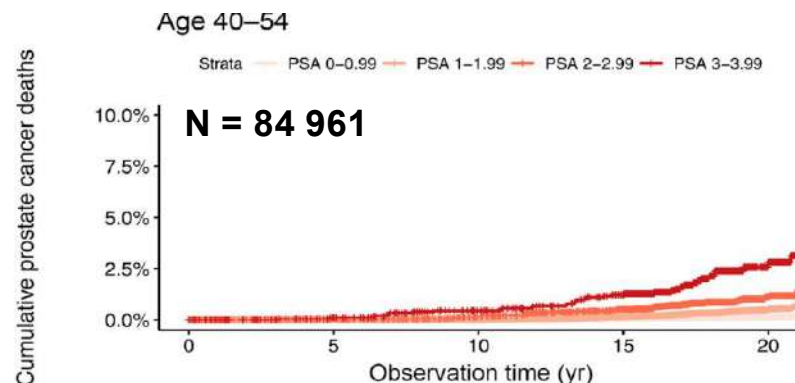
Clinical characteristics



Clinical characteristics of lethal prostate cancer

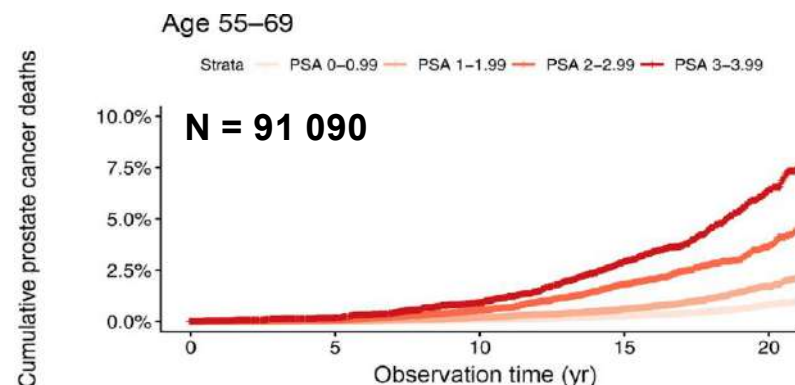
- **Prostate Specific Antigen (PSA)**

- Baseline PSA is an important, though imperfect marker
- PSA can be used to stratify a man's risk of dying from prostate cancer within the next 15–20 yr



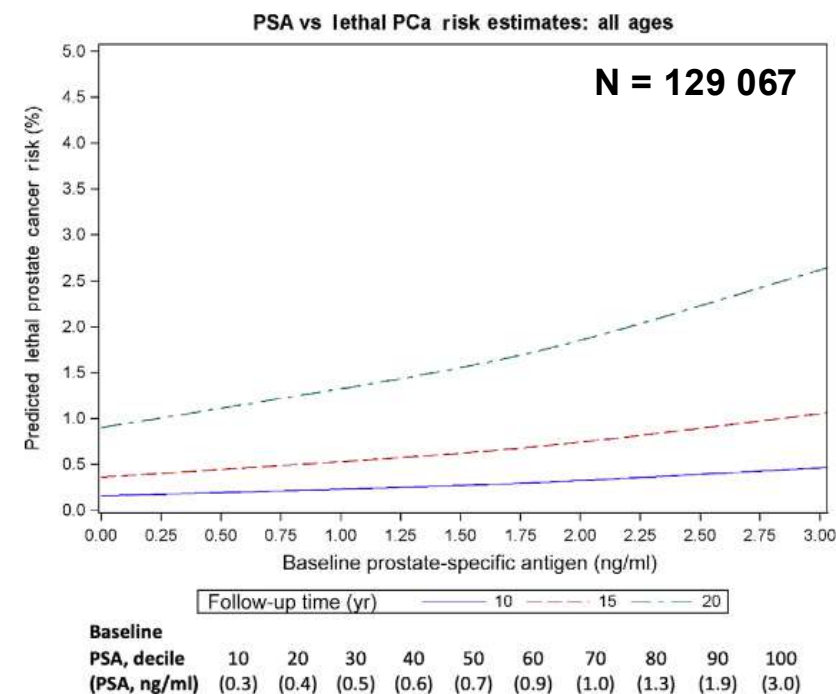
Number at risk

PSA 0–0.99	53 386	52 077	50 850	48 957	12 191
PSA 1–1.99	24 429	23 882	23 292	22 349	5953
PSA 2–2.99	5302	5172	5042	4826	1238
PSA 3–3.99	1844	1784	1720	1637	407



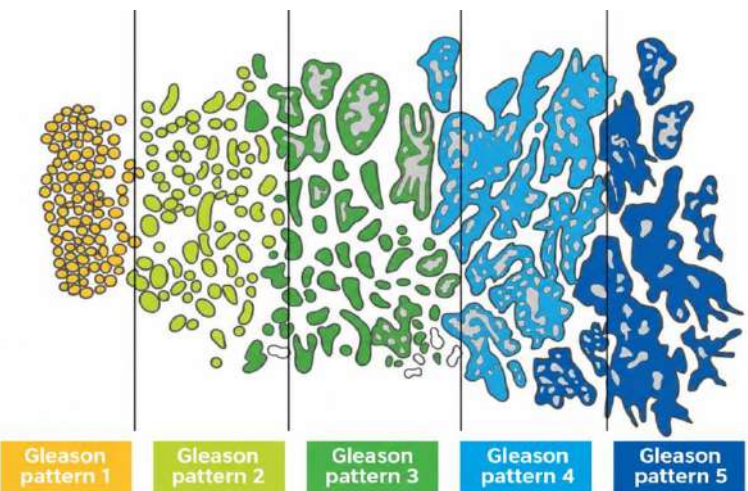
Number at risk

PSA 0–0.99	38 486	35 341	32 385	28 621	4896
PSA 1–1.99	31 045	28 853	26 550	23 305	4258
PSA 2–2.99	14 058	13 038	11 922	10 426	1945
PSA 3–3.99	7501	6975	6328	5426	976

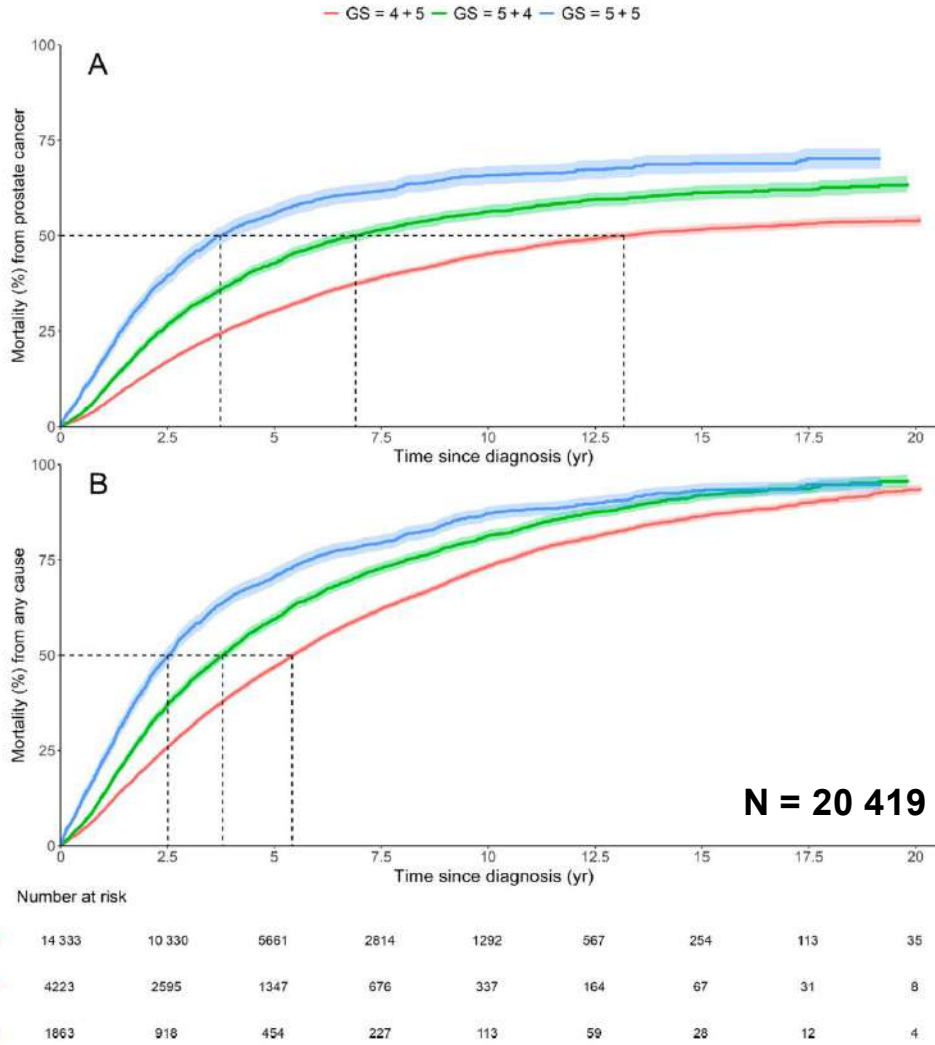
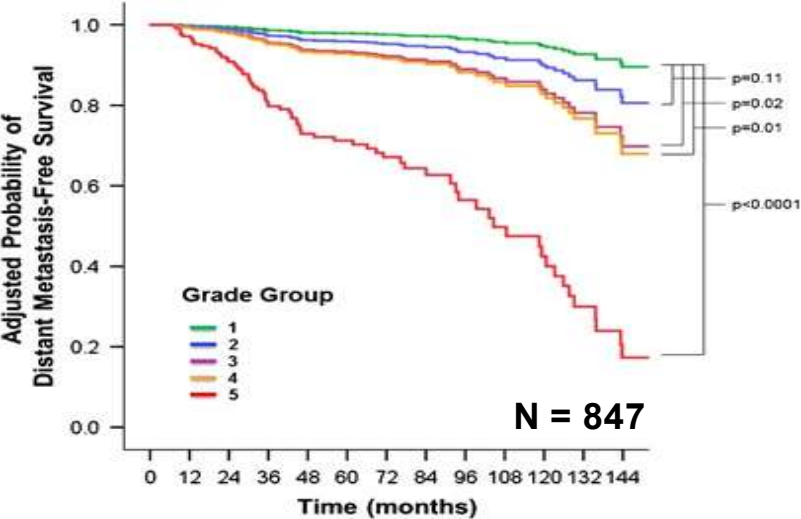


Clinical characteristics of lethal prostate cancer

- Differentiation Grade by Gleason/ISUP Score:**
 - Poorly differentiated tumors are more lethal.
 - Traditional Gleason may provide more accurate prognostic information

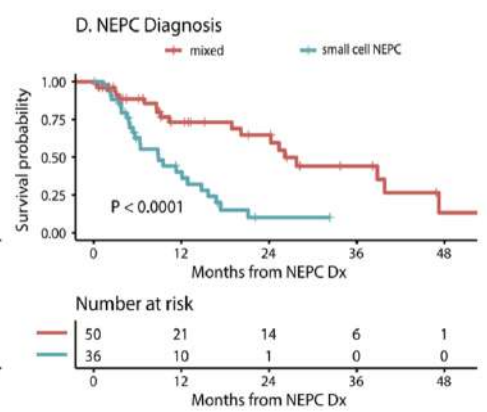
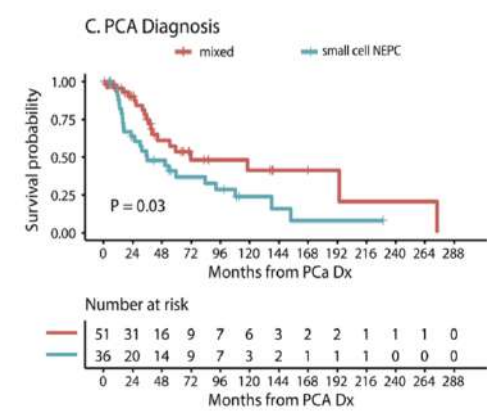
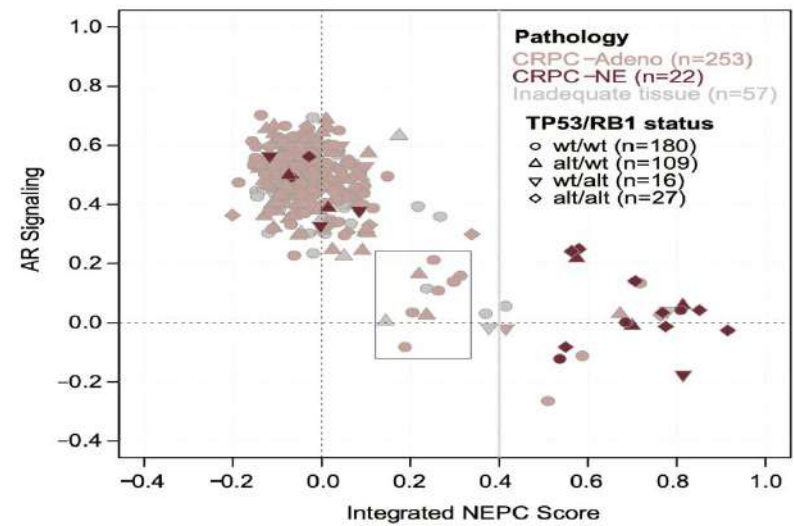
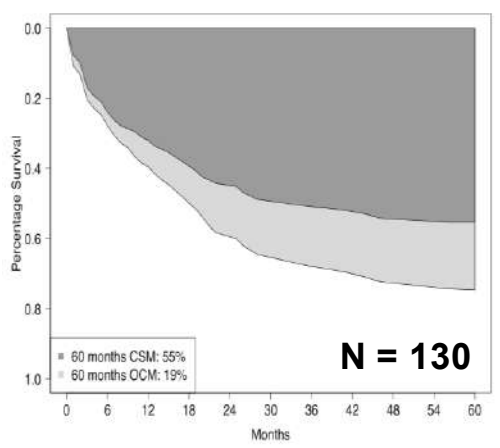
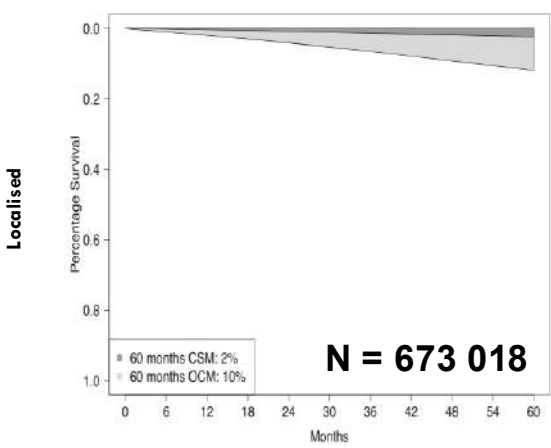
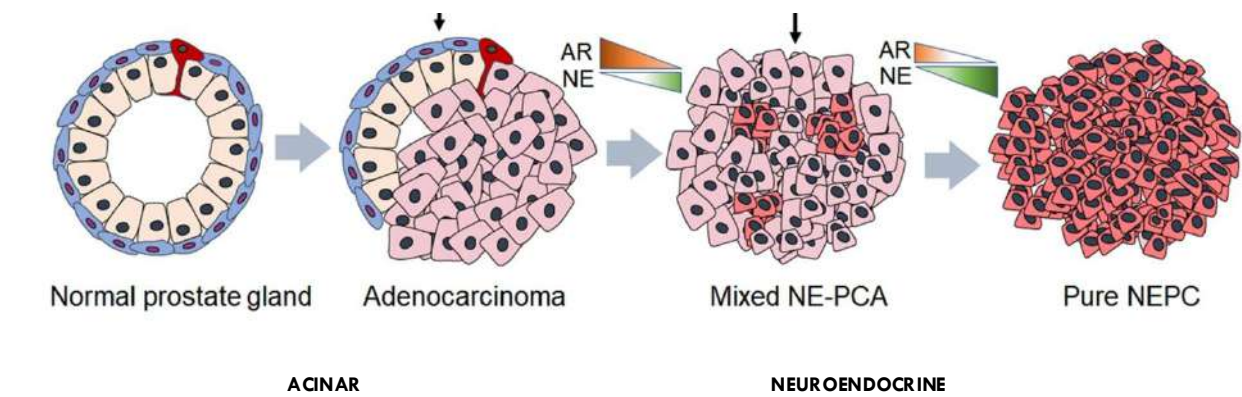


Grade group	Gleason score	Gleason pattern
1	≤6	≤3+3
2	7	3+4
3	7	4+3
4	8	4+4, 3+5, 5+3
5	9 or 10	4+5, 5+4, or 5+5



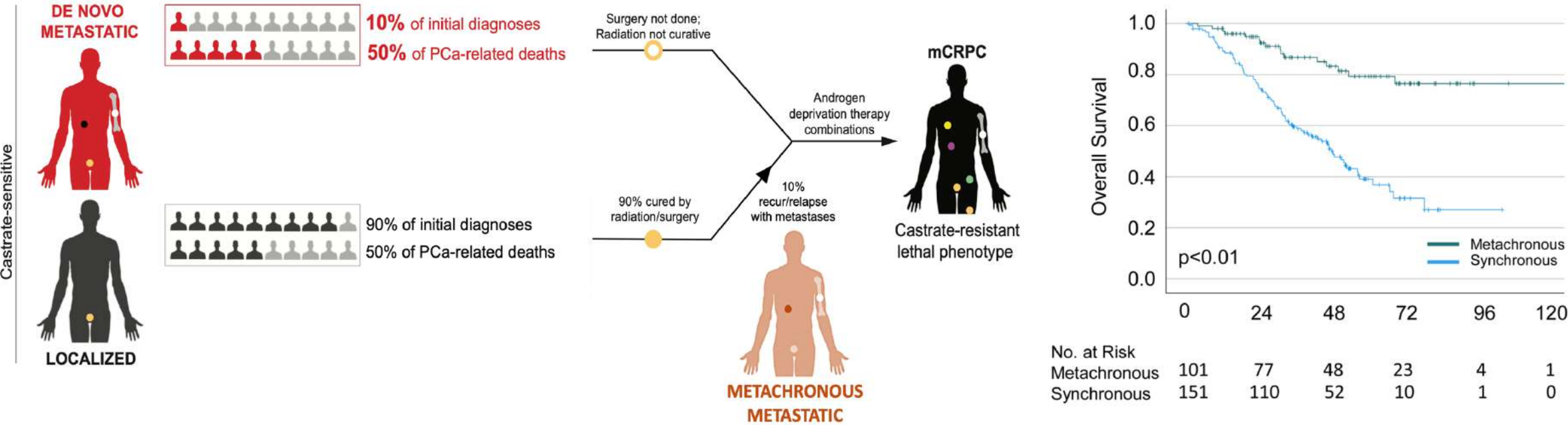
Clinical characteristics of lethal prostate cancer

- Aggressive histological subtypes
 - NEPC/SC



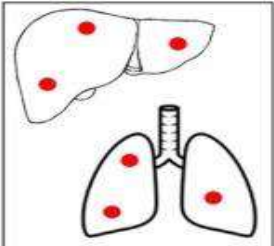
Clinical characteristics of lethal prostate cancer

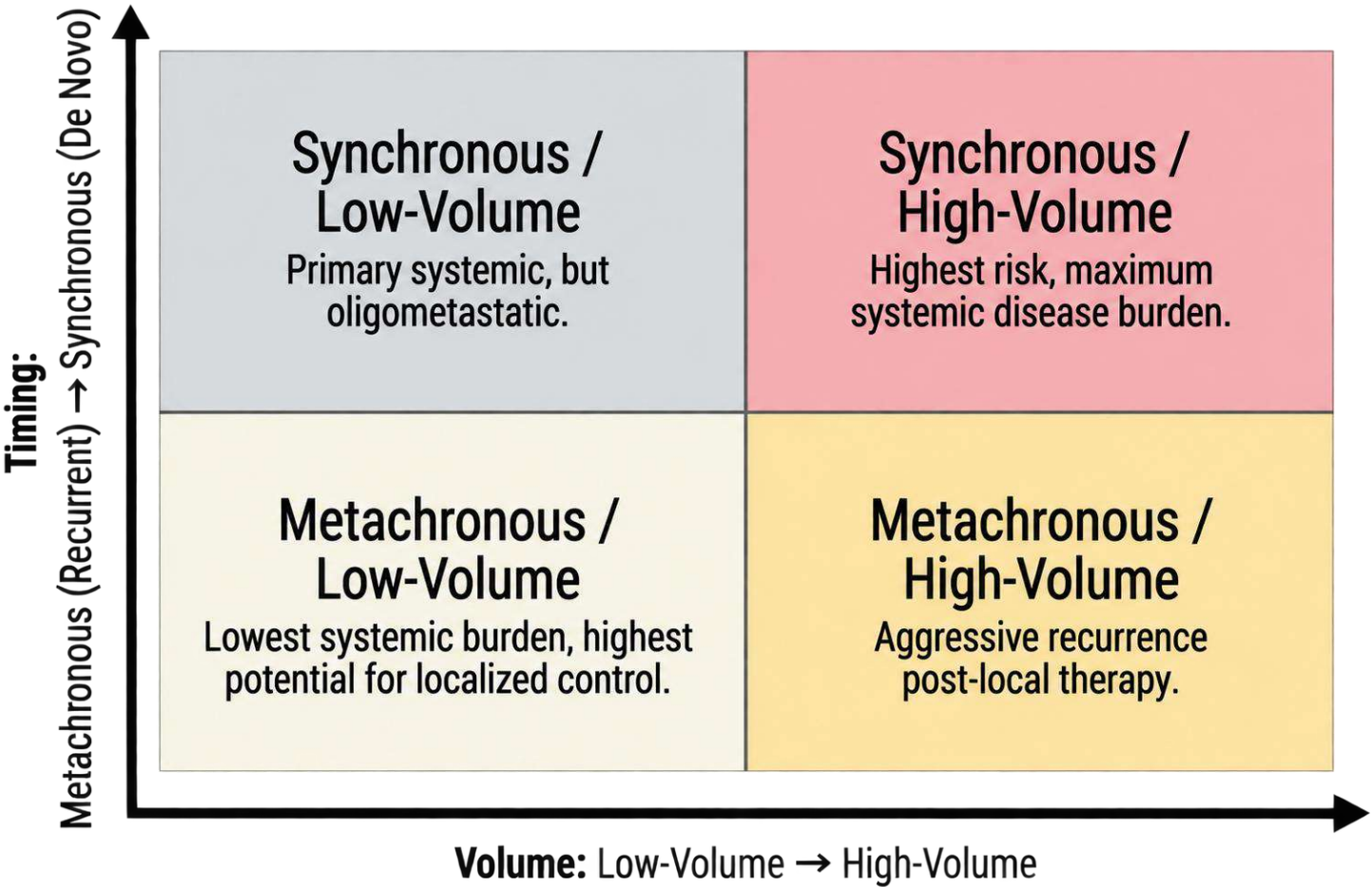
- Timing of M1 disease



Clinical characteristics of lethal prostate cancer

- **Timing of M1 disease**
 - metachronous vs synchronous (de novo)
- **Volume of disease**
 - Low vs high volume

High	Low
≥4 Bone metastasis including ≥1 outside vertebral column or pelvis and/or visceral metastasis  4 or more bone mets (with at least one outside the pelvis/column)	Not high  Visceral mets



Clinical characteristics of lethal prostate cancer

- **Timing of M1 disease**
 - metachronous vs
synchronous (de novo)
- **Volume of disease**
 - Low vs high volume

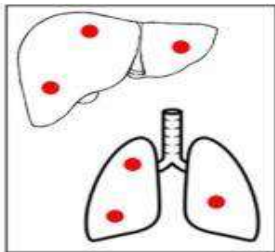
High	Low
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≥4 Bone metastasis including ≥1 outside vertebral column or pelvis and/or visceral metastasis

Not high

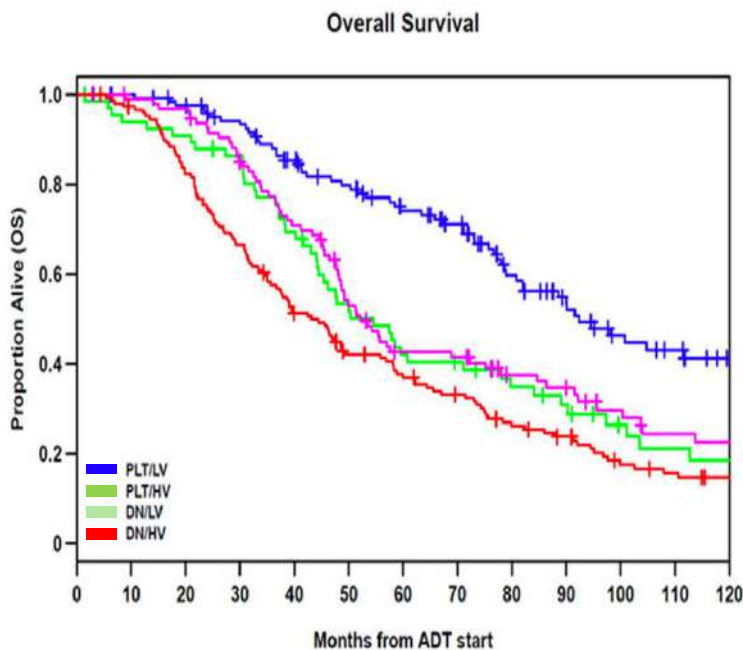


4 or more bone mets
(with at least one outside the pelvis/column)

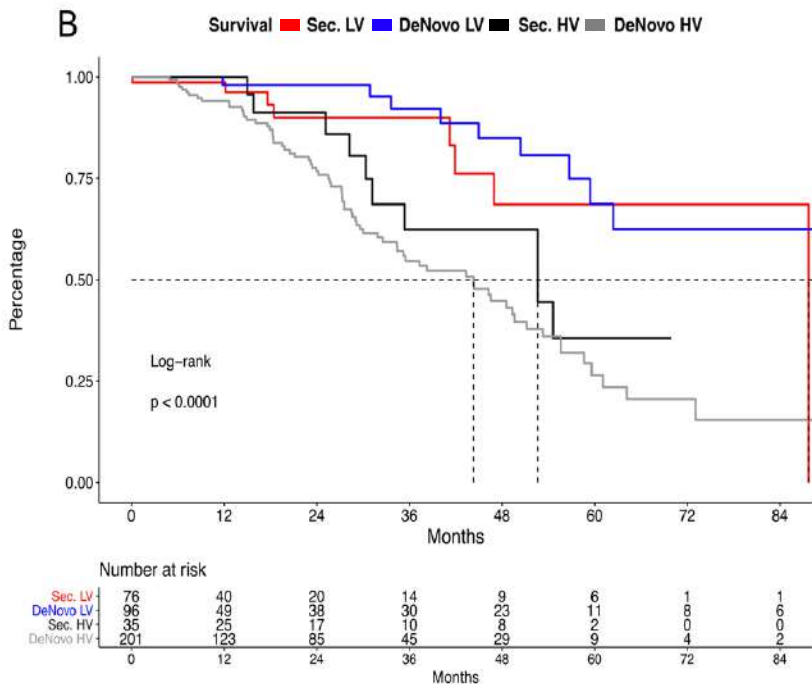


Visceral mets

ADT monotherapy

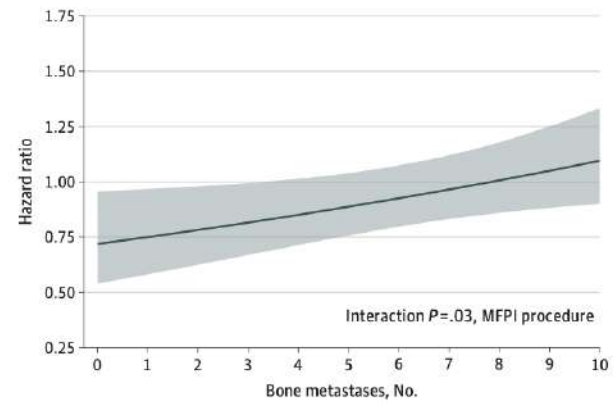


ADT + ARPI or docetaxel

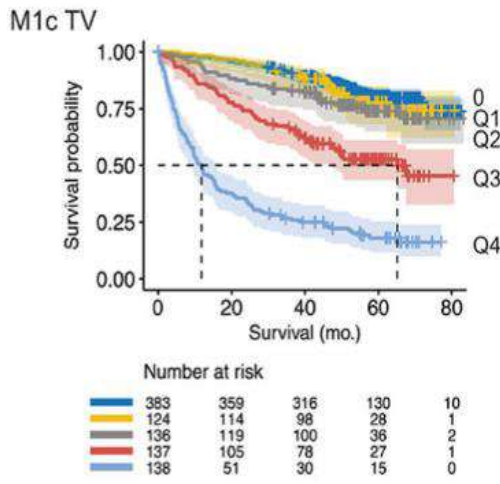
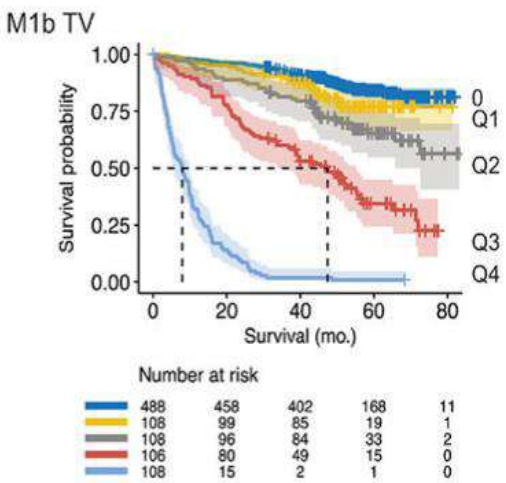
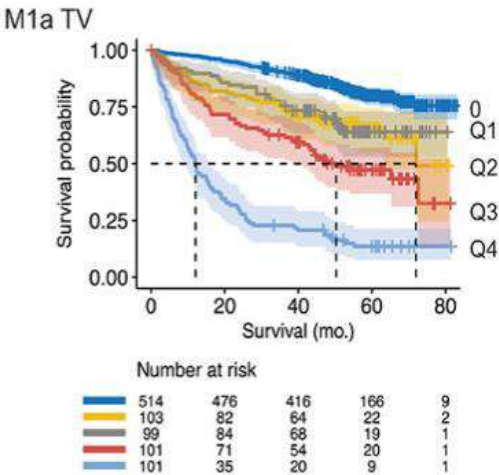
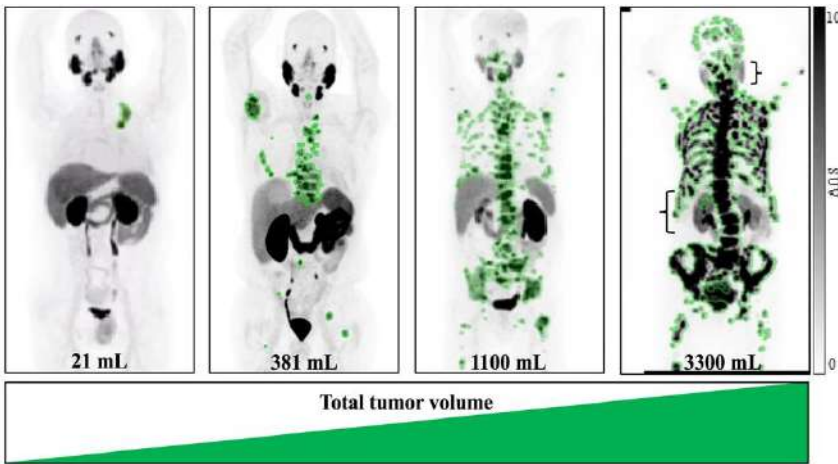


Clinical characteristics of lethal prostate cancer

- Beyond categorised volume of disease
 - Volume of disease is a continuous variable
 - CI
 - PSMA-PET/CT

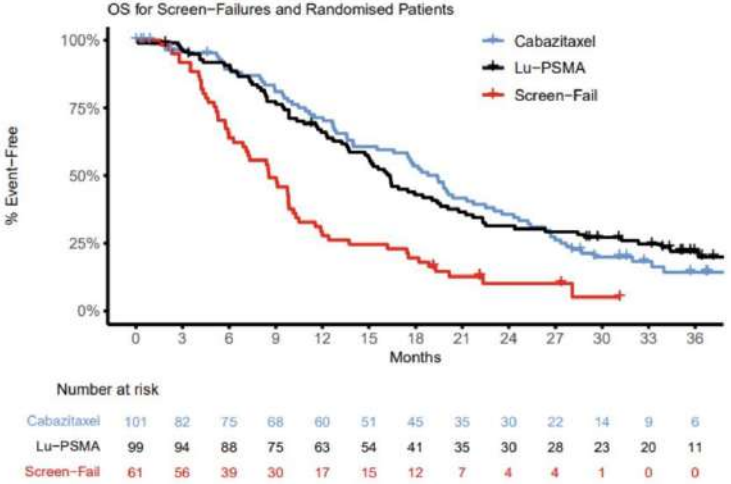
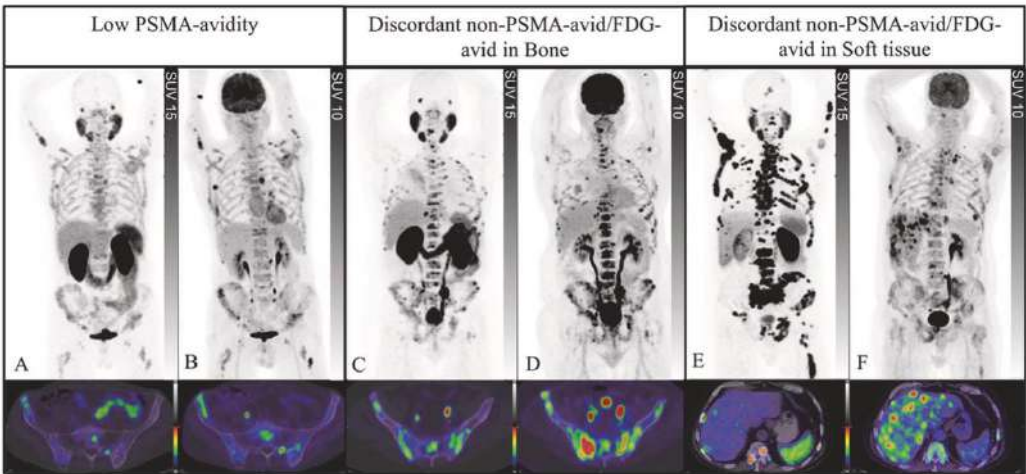
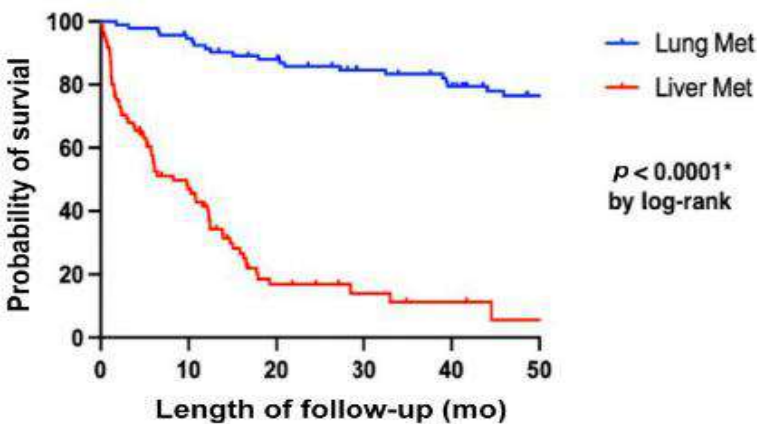
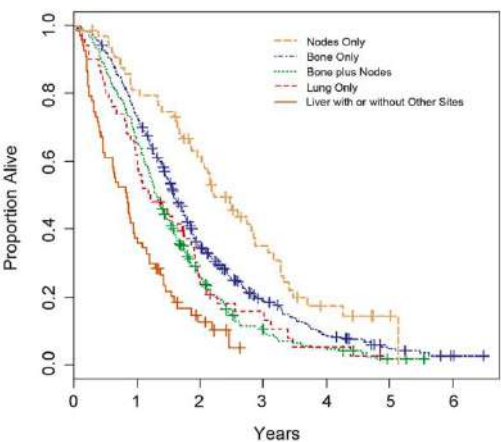


	Patients		Hazard ratio (95% CI)	p value
Tumour volume				
Per 1 L increase	1098		3.64 (3.25-4.07)	<0.0001
Tumour SUV _{mean}				
Per 1 unit increase	1100		1.04 (1.03-1.05)	<0.0001
Total tumour lesion count (T+N+M; reference: 0-5)				
6-20	137		5.00 (3.80-6.59)	<0.0001
>20	185		15.80 (12.41-20.12)	<0.0001



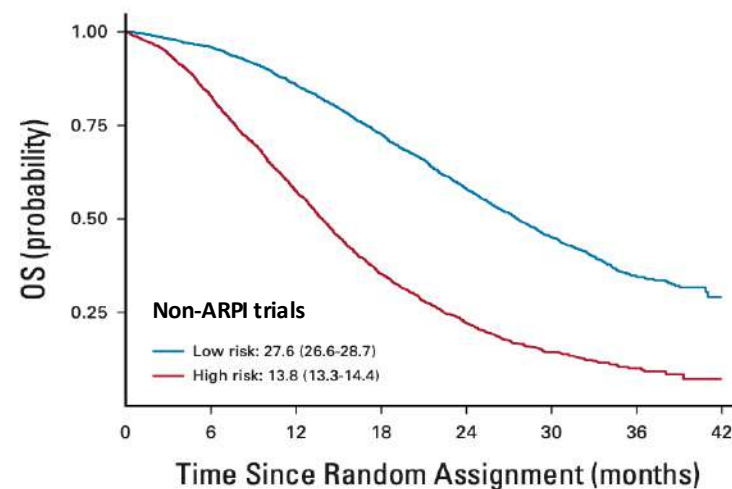
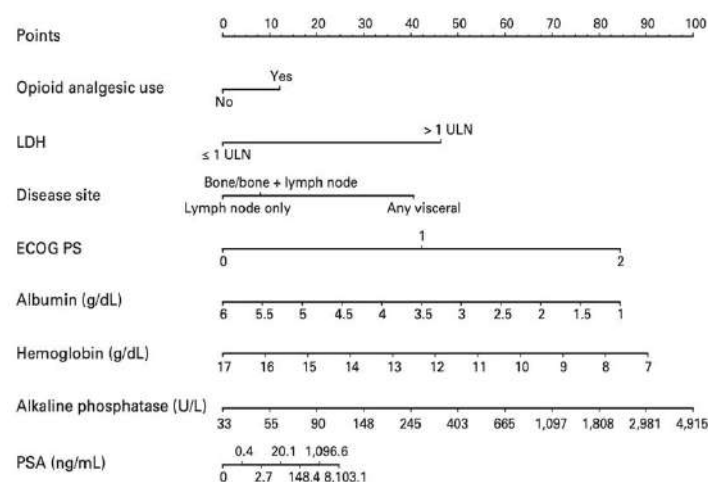
Clinical characteristics of lethal prostate cancer

- Beyond categorised volume of disease**
 - Pattern of metastatic spread matters
 - Site of visceral involvement dictates outcome
 - Tracer uptake discordance or low PSMA expression

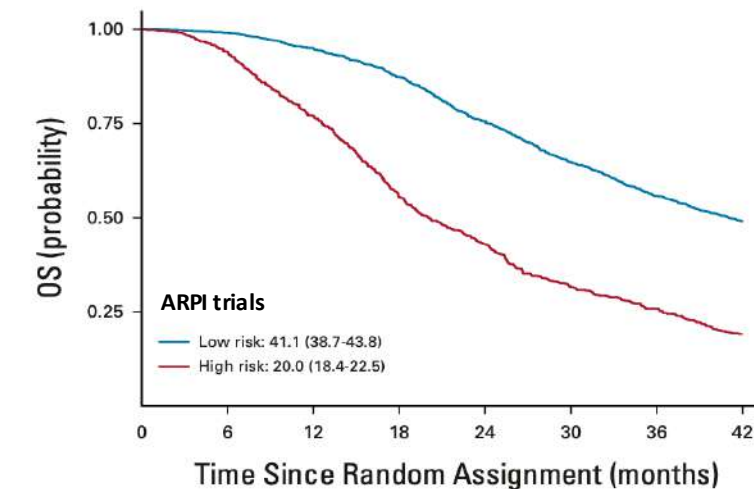


Clinical characteristics of lethal prostate cancer

- Bringing the variables together
 - Nomograms can predict overall survival probability



No. at risk:	0	6	12	18	24	30	36	42
Low risk	3,218	2,878	2,347	1,735	1,090	487	152	11
High risk	2,274	1,697	1,017	516	243	97	26	1

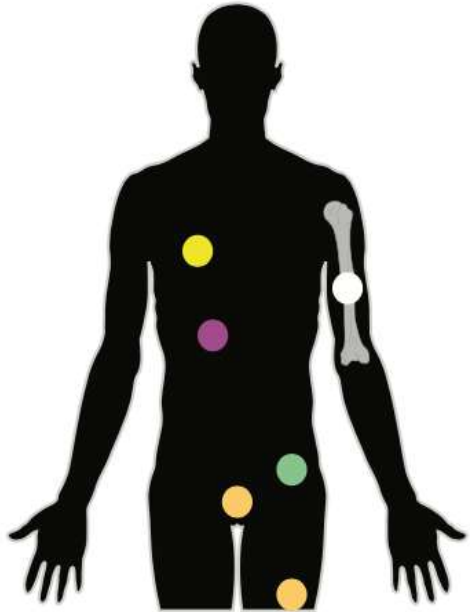


No. at risk:	0	6	12	18	24	30	36	42
Low risk	1,597	1,550	1,467	1,337	1,151	970	823	712
High risk	597	532	428	304	231	167	135	100

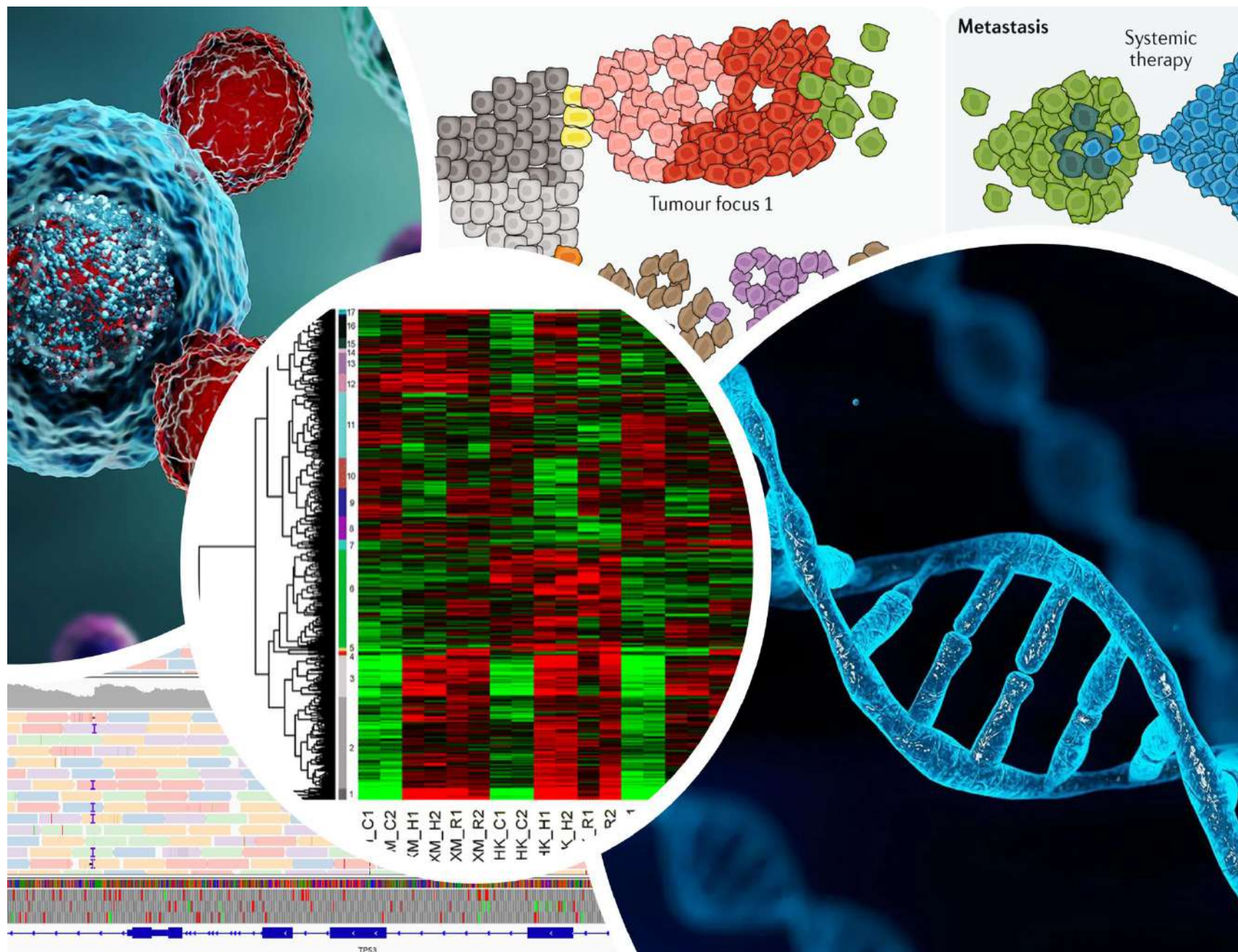
Clinical characteristics of lethal prostate cancer

Clinical characteristics

- Baseline **PSA** vs follow-up time can infer the risk of lethal prostate cancer
- **Differentiation** grade and group within a grade
- Aggressive **histology** and state of transition
- **Timing** of M1 disease
- **Volume** of tumour burden
- M1 **patterns** and site of visceral involvement
- Tracer **uptake** and/or **metabolic** staging
- Clinical **prognostic models** can identify patient populations with differing survival outcomes

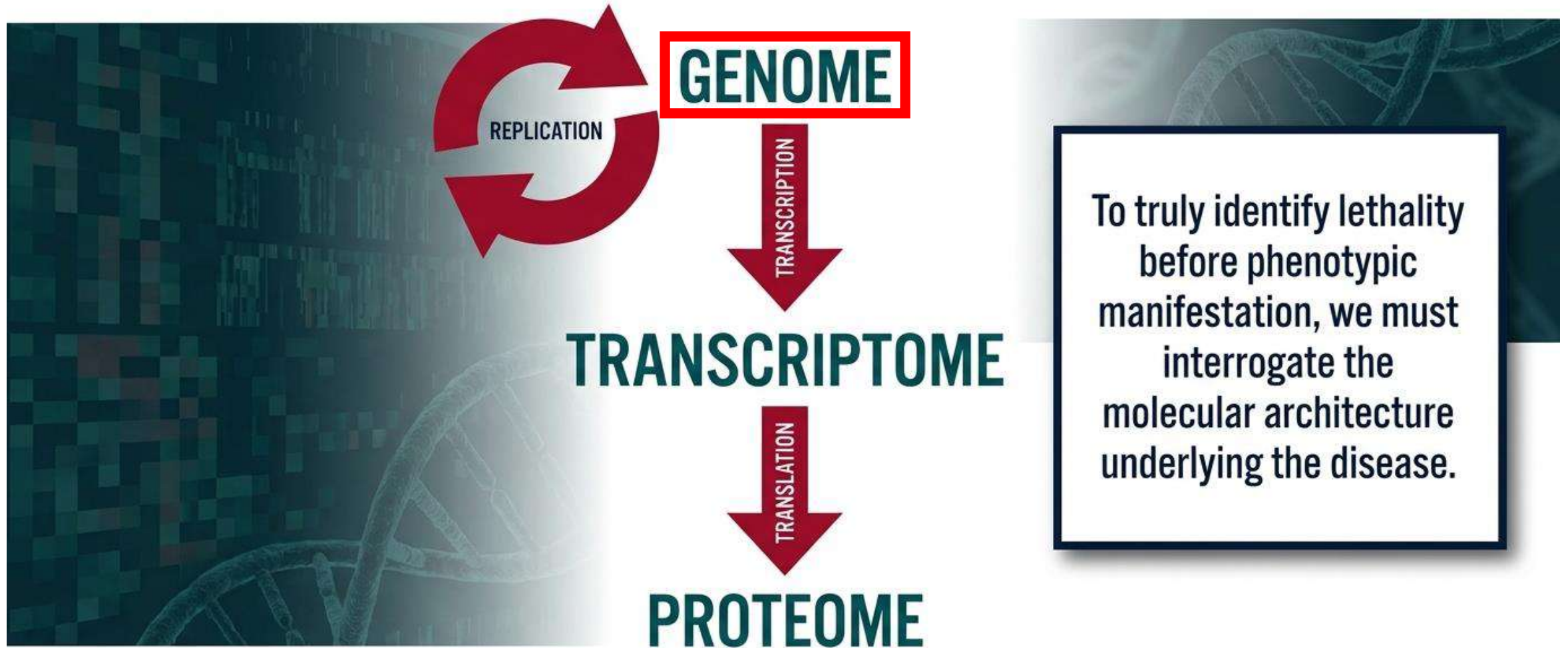


Lethal
Prostate
Cancer



Molecular characteristics

Molecular characteristics of lethal prostate cancer

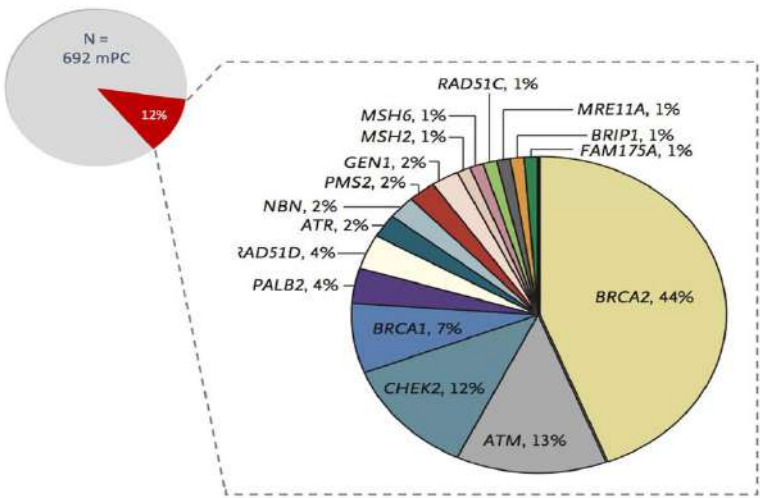


Genomic characteristics of lethal prostate cancer

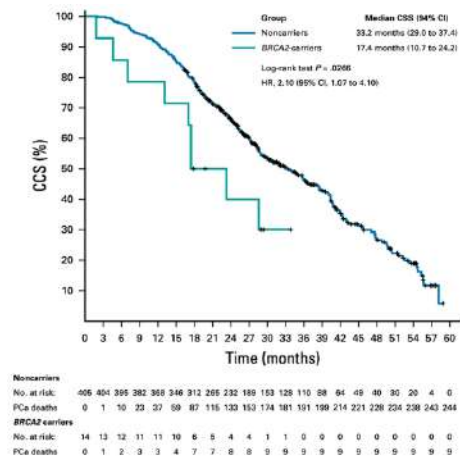
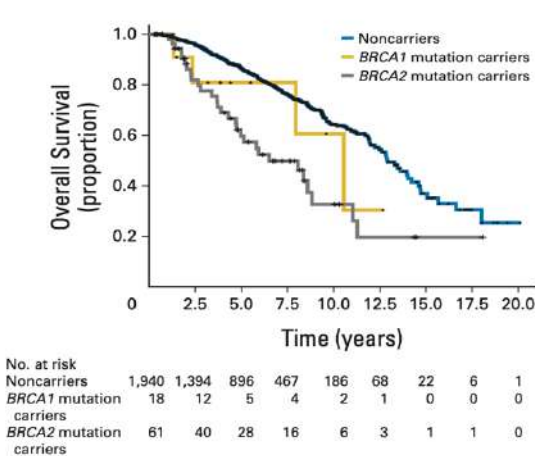
- Hereditary Burden**

- Inherited predispositions such as HBOC and Lynch Syndrome increase the risk and marks an inferior prognosis in prostate cancer

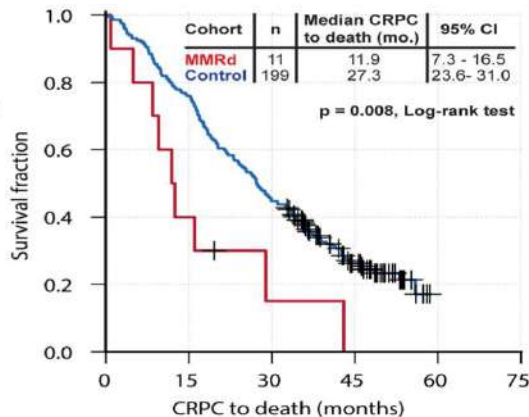
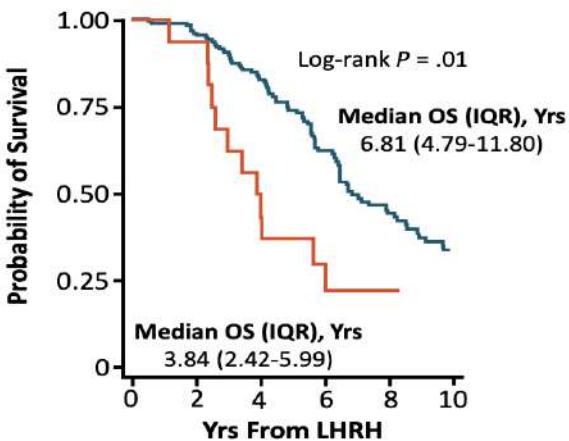
	BRCA1	BRCA2	CHEK2	ATM	HOXB13	MLH1	MSH2	MSH6
PROSTATE	↑	20 - 60%	↑	↑	20 - 60%	↑	20 - 60%	↑
FEMALE BREAST	60 - 80%	60 - 80%	30%	30%				
MALE BREAST	1%	7%	<1%	<1%				
OVARIAN	40%	20%				10 - 15%	10 - 15%	10 - 15%
COLORECTAL			↑	↑		40 - 70%	40 - 70%	10 - 20%
ENDOMETRIUM	↑					30 - 60%	30 - 60%	30 - 60%
PANCREATIC	↑	7%		↑		↑	↑	↑
URINARY TRACT						10 - 15%	25 - 30%	5 - 10%



HRD (BRCA1/2)

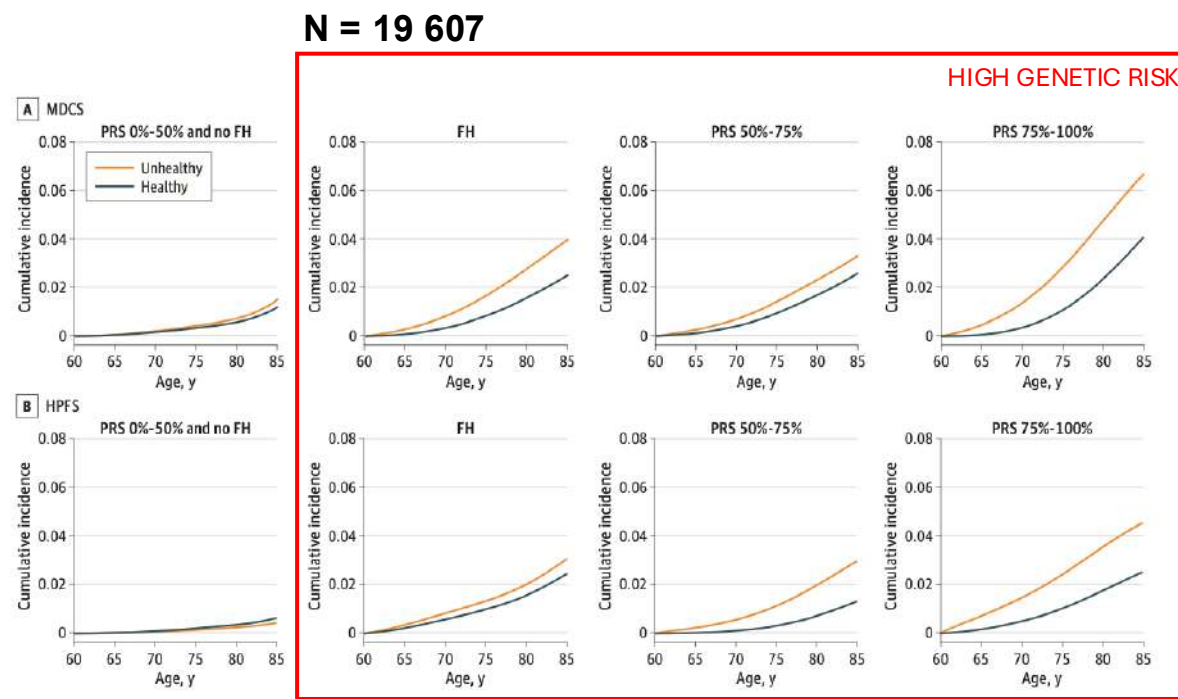
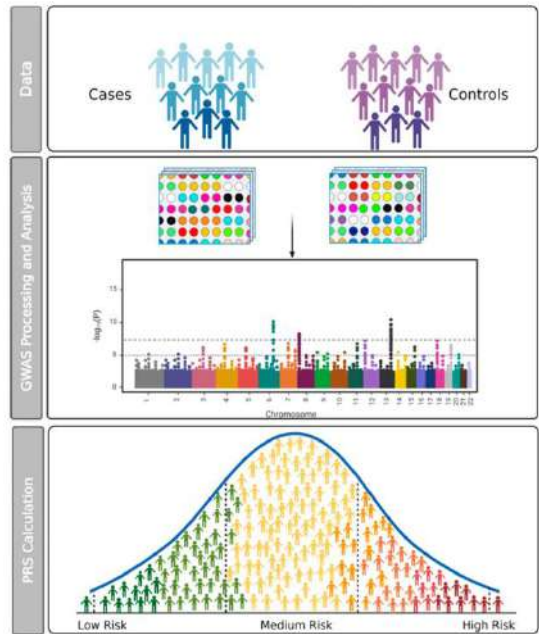
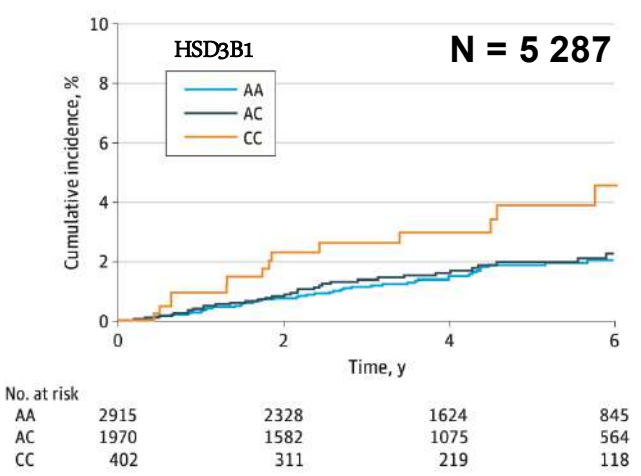


dMMR



Genomic characteristics of lethal prostate cancer

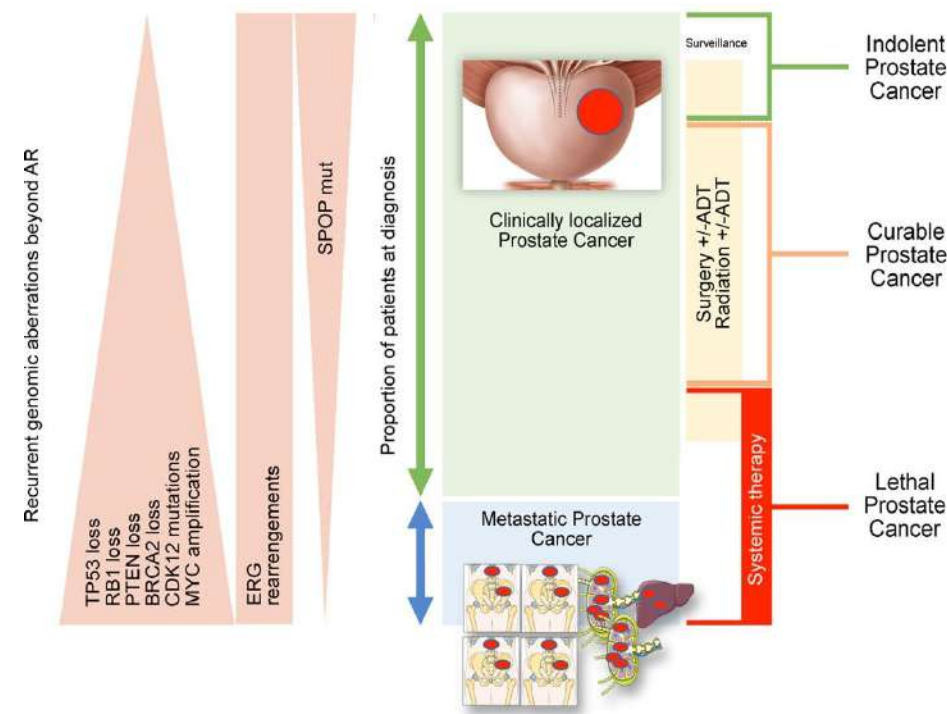
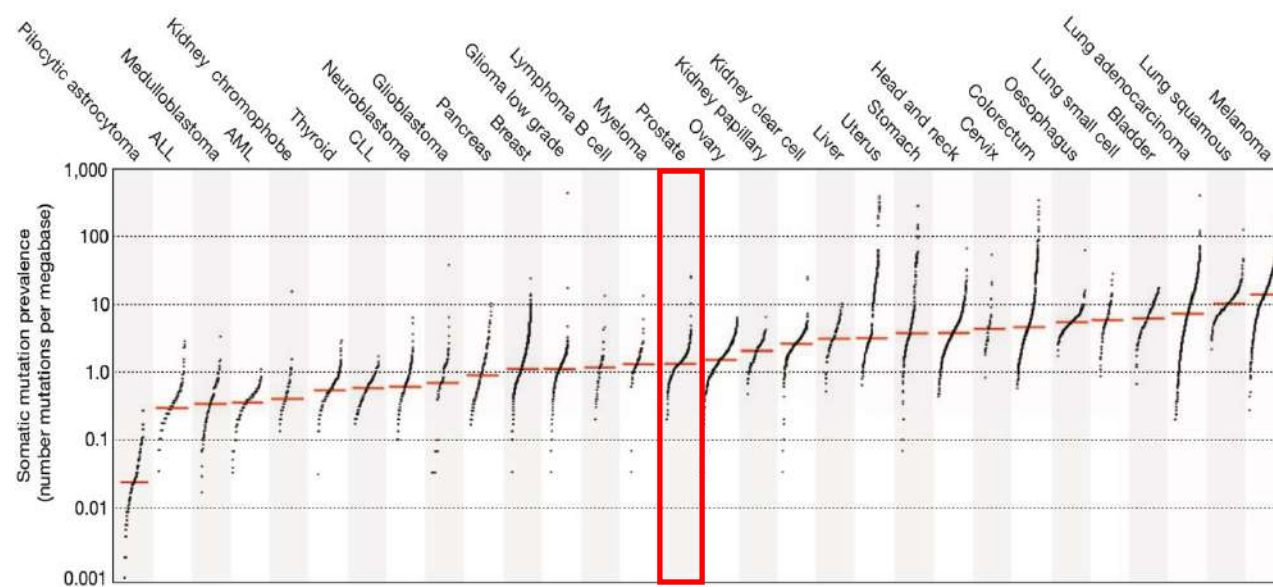
- **Common germline variants and Polygenic Risk Scores (PRS)**
 - *HSD3B1* genotype is associated with outcome
 - Polygenic risk scores use multiple single nucleotide polymorphisms (SNPs) to estimate an individual's genetic risk for prostate cancer death



Genomic characteristics of lethal prostate cancer

- **Somatic burden**

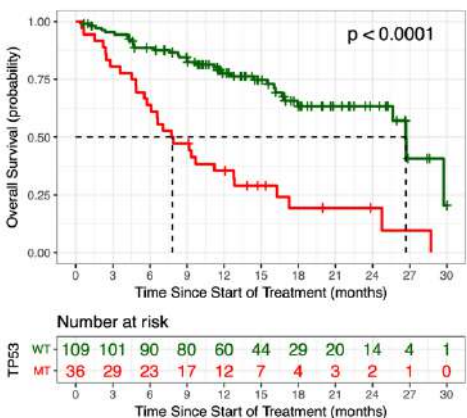
- Relatively low somatic mutation rate
- More genomic instability (GIS)
- Most classes of alterations are more frequent in advanced disease



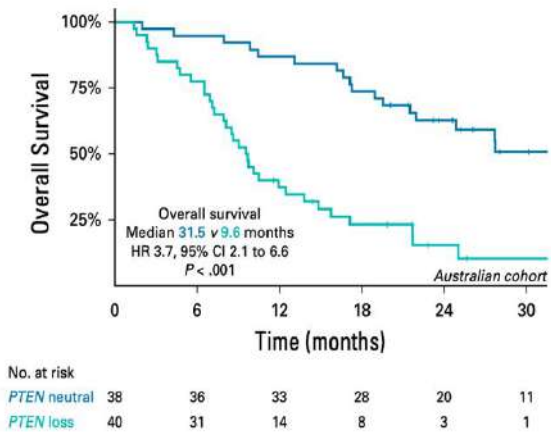
Genomic characteristics of lethal prostate cancer

- Somatic burden
- Tumor Suppressor
 - Alterations in PTEN, TP53, and RB1, among others, define prognosis
 - Compound events in Ts genes

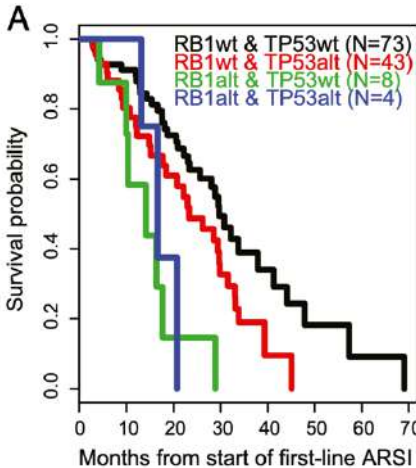
TP53



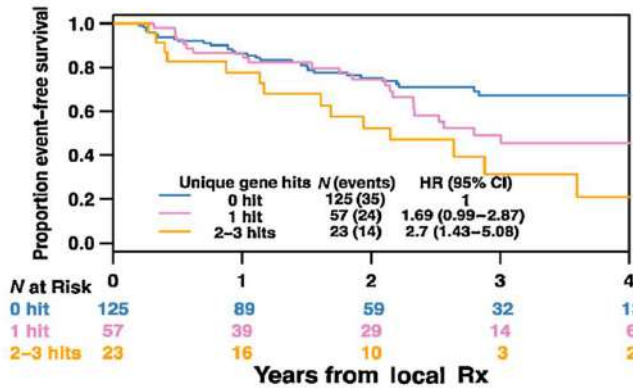
PTEN



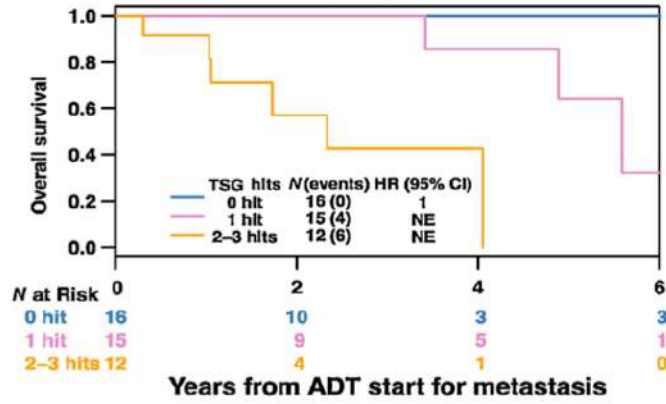
RB1/TP53



Localized CSPC
unique gene hits

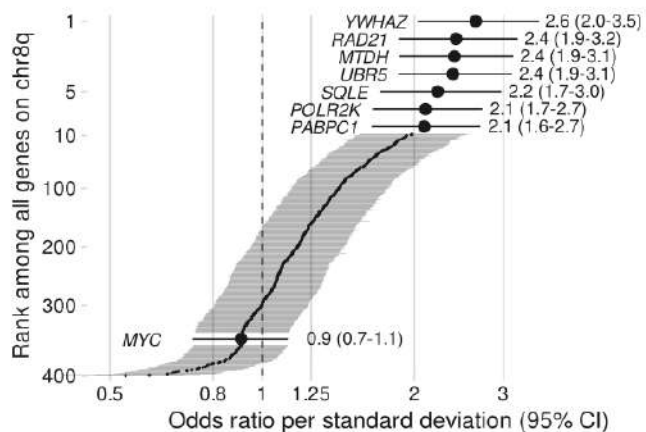
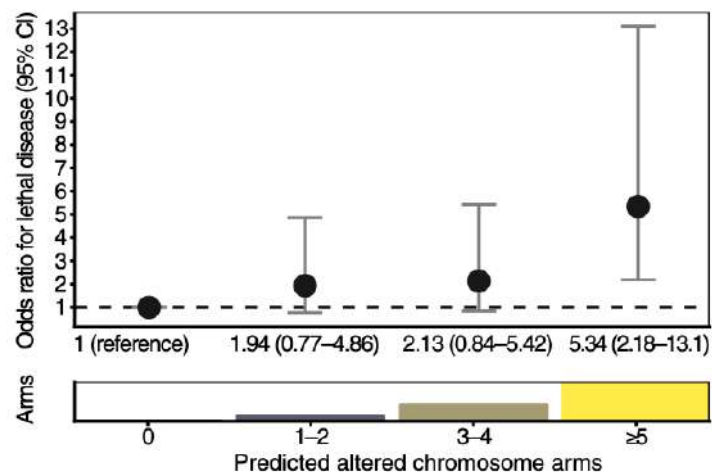
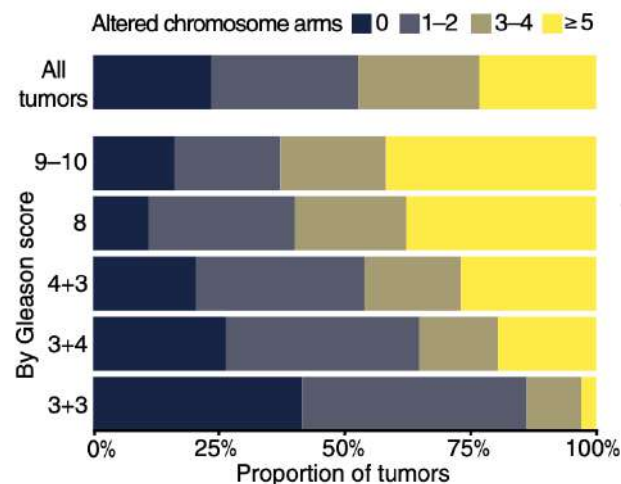
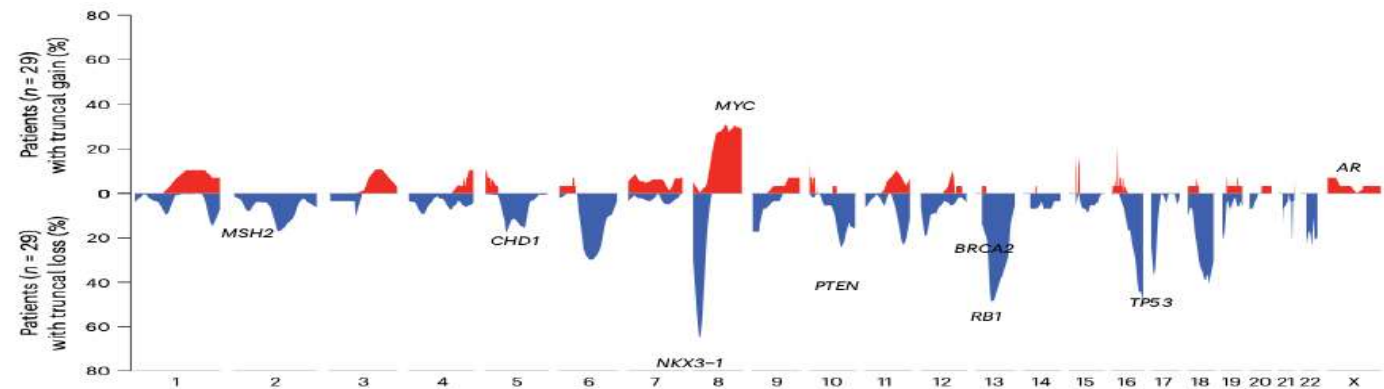


Metastatic CSPC
unique gene hits



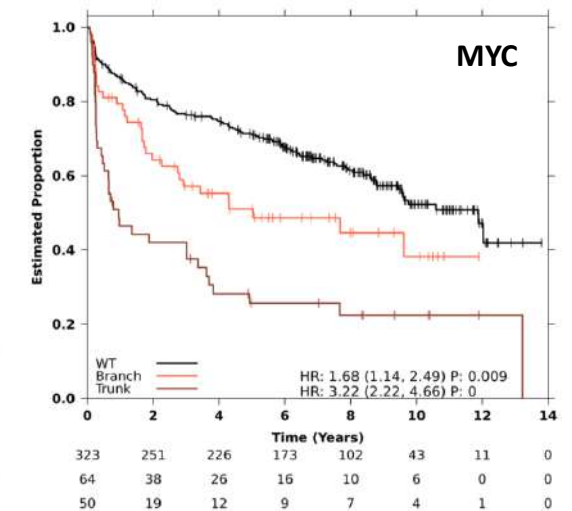
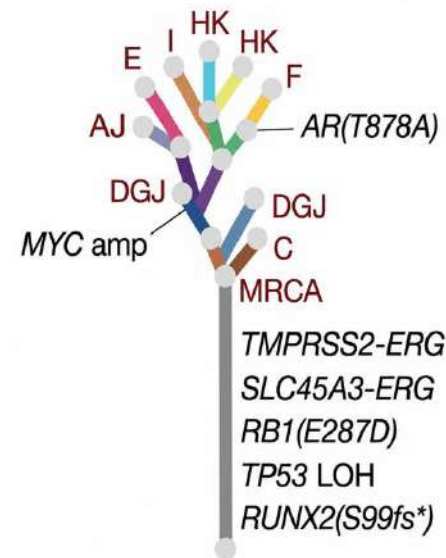
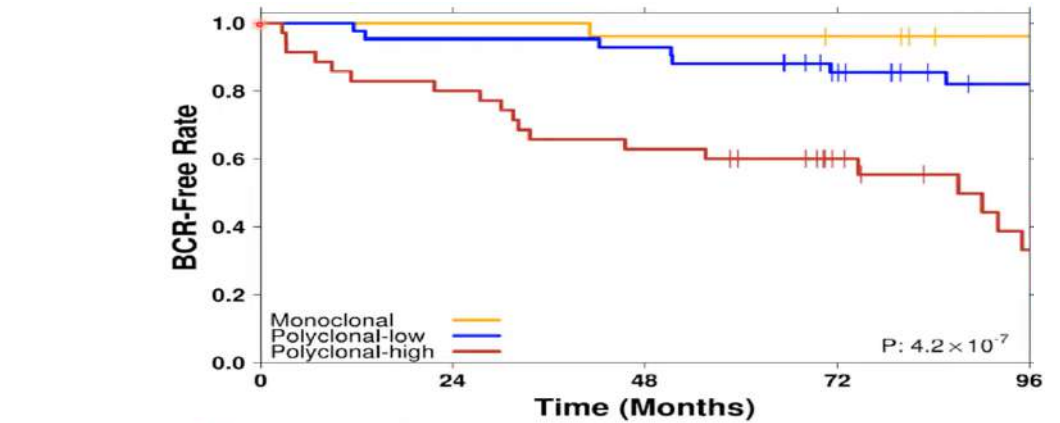
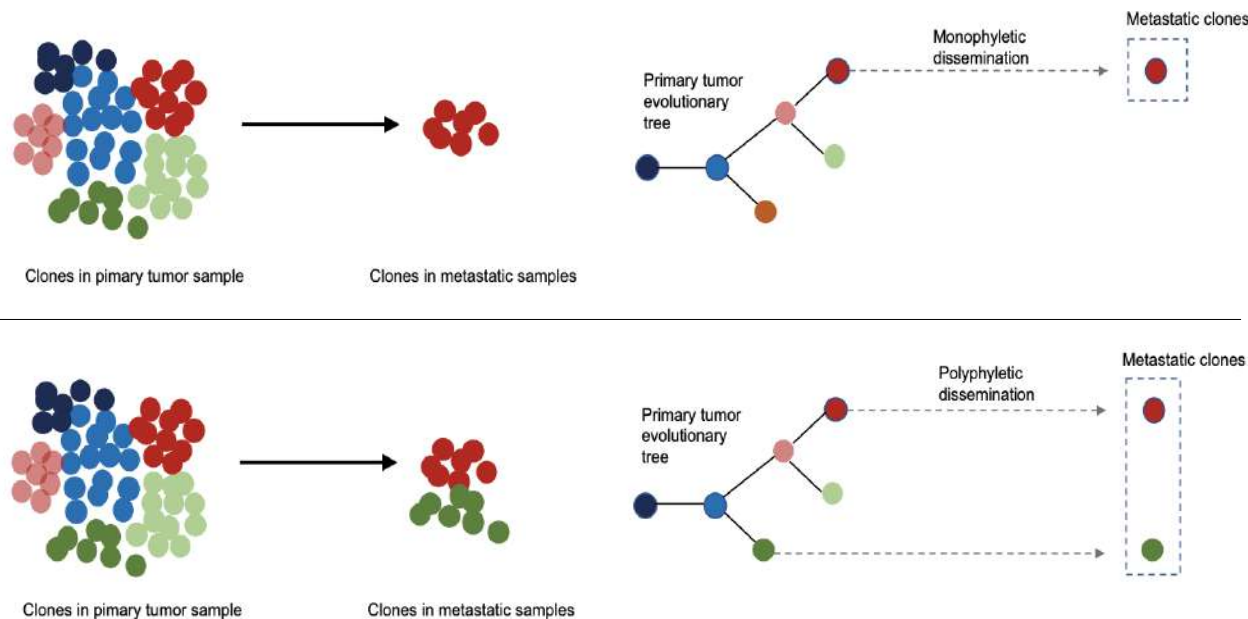
Genomic characteristics of lethal prostate cancer

- **Somatic burden**
 - **Genomic Instability , CNA architecture or aneuploidy**
 - A high genomic instability score (GIS) and aneuploidy are drivers of aggressive, rapidly progressing disease

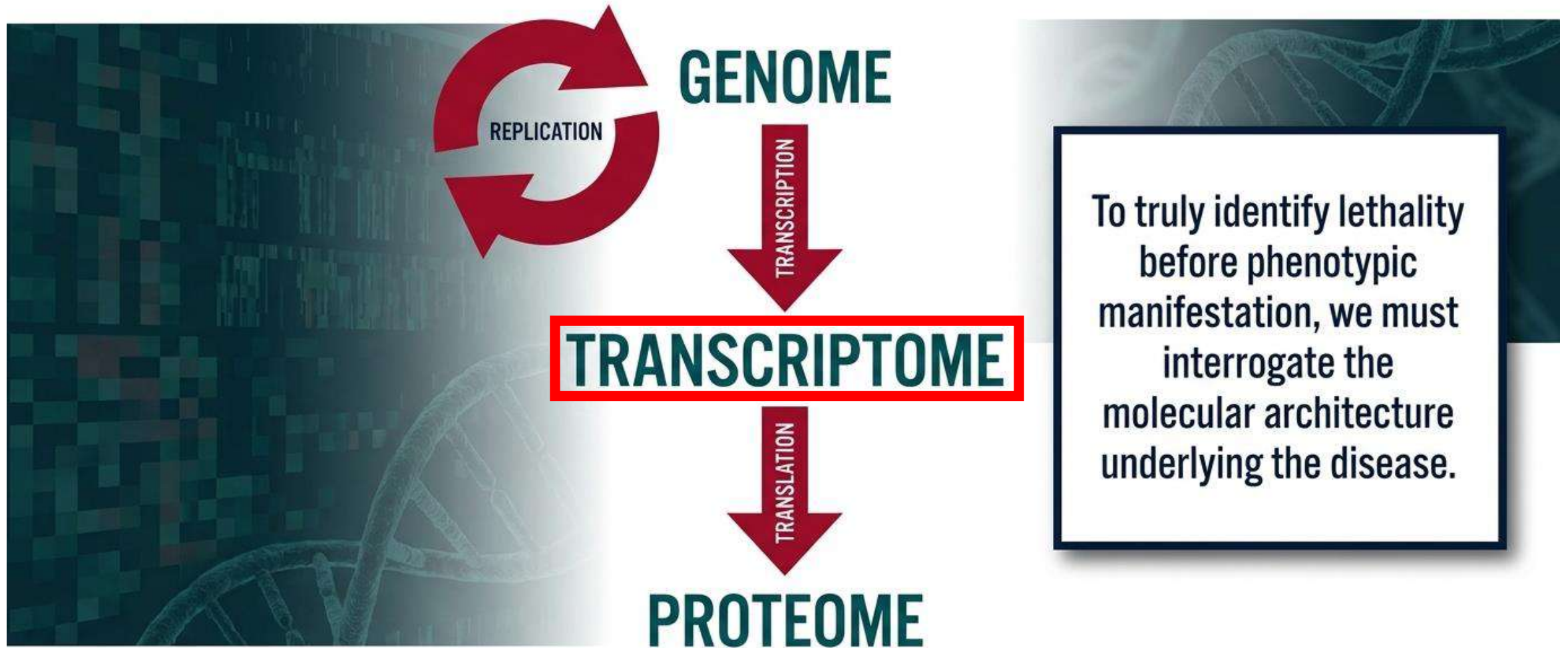


Genomic characteristics of lethal prostate cancer

- **Somatic burden**
 - **Genetic phylogeny, metastatic seeding and timing of the mutations**
 - Mono- versus polyclonality
 - When a mutation occurs matters
 - Trunk vs branch
 - Polyclonal and earlier events have a larger effect size



Molecular characteristics of lethal prostate cancer

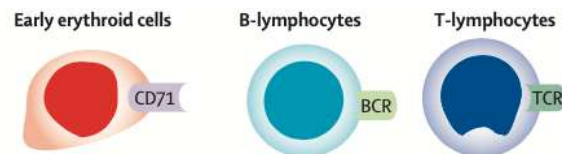


Transcriptomic characteristics of lethal prostate cancer

- Immunological burden

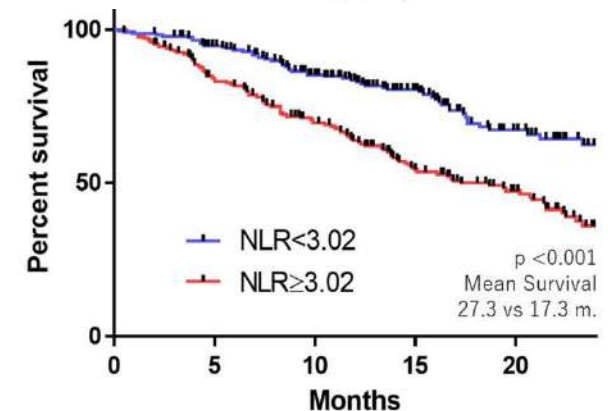
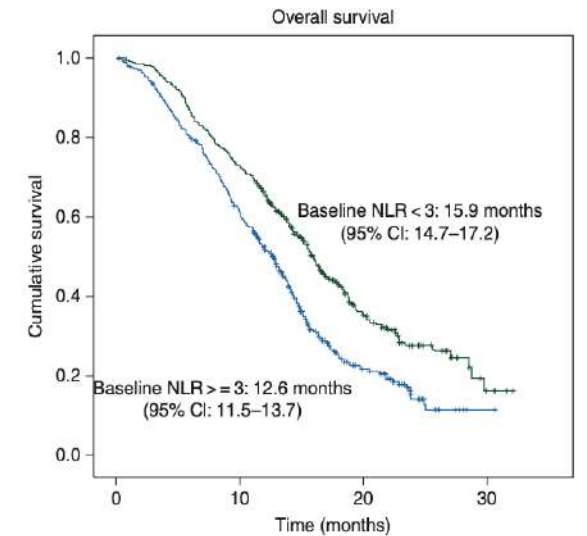
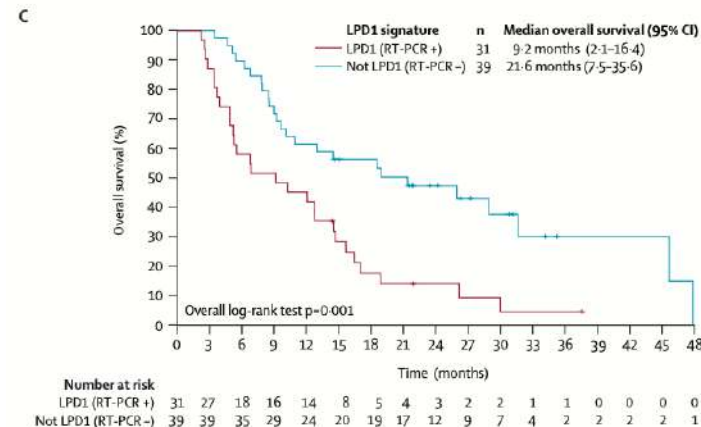
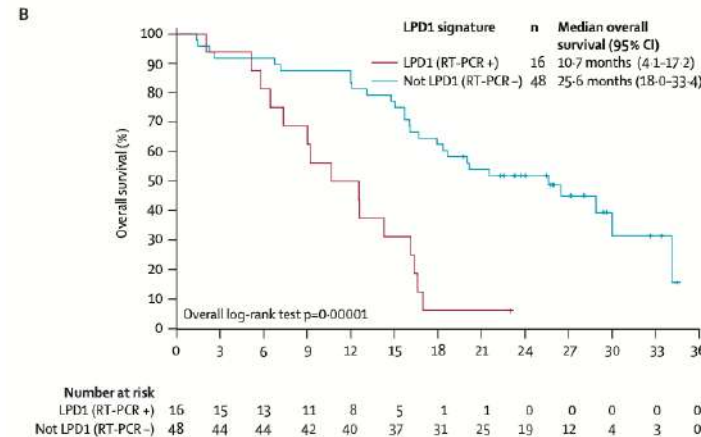
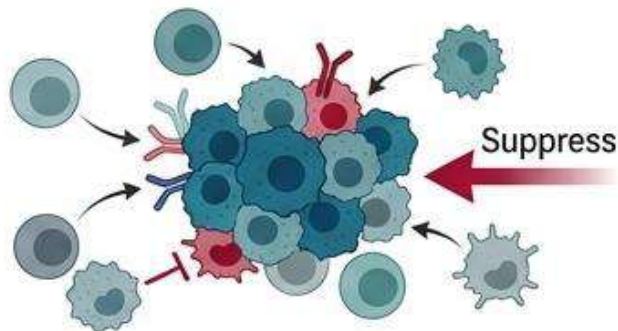
- Blood mRNA expression signatures

- The TME, assessed by a myeloid transcript signature acts as a immunosuppressive driver and is associated with poor outcome
 - High NLR



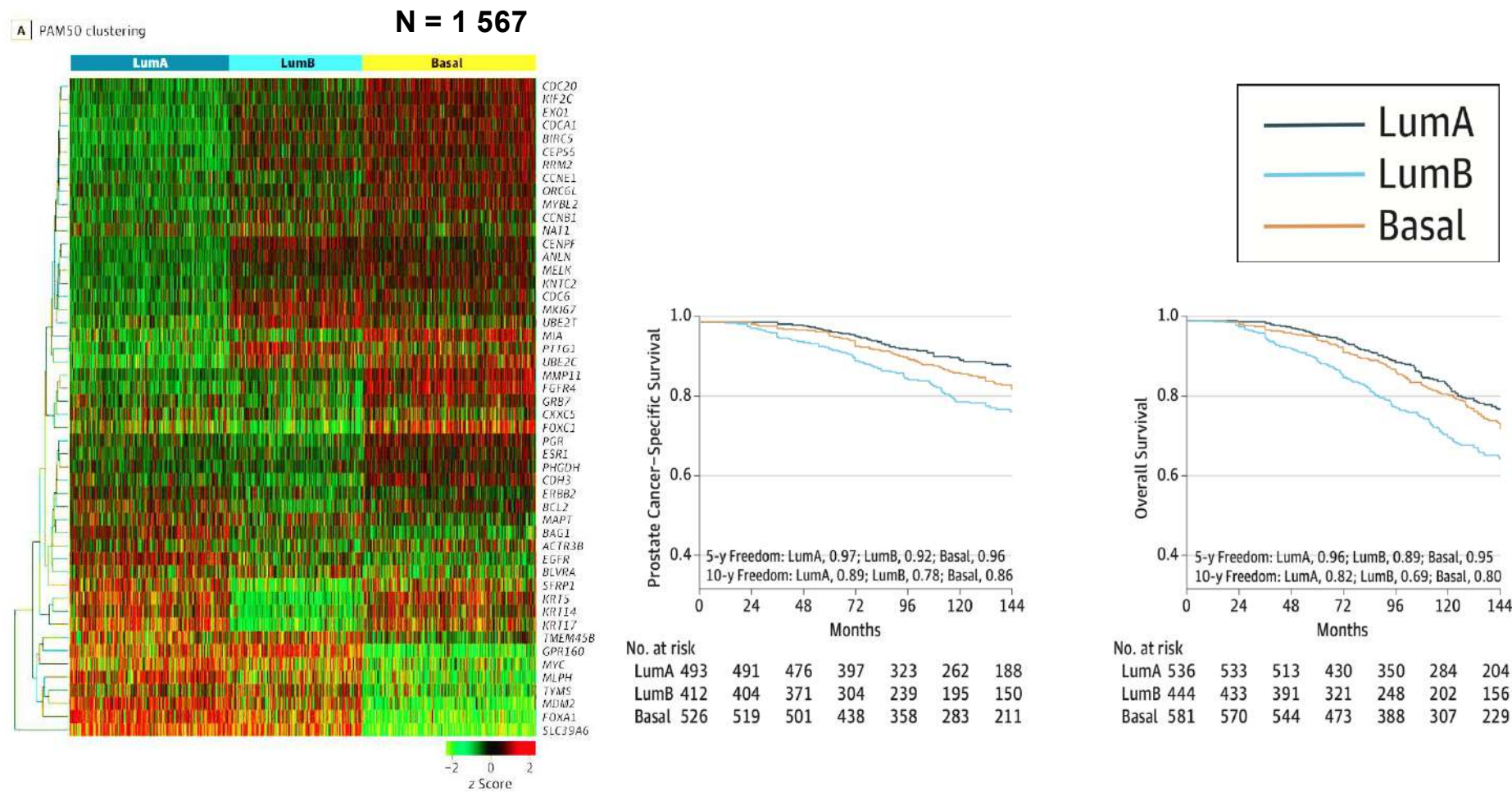
Top significant genes or canonical pathways related to each cell type in LPD profiles

LPD1	↑RHAG	↑SNCA	↑TMEM56	↓EBF1	↓iCOS-iCOSL signalling in T-helper cells ↓Role of NFAT regulation of the immune response ↓CD28 signalling in T-helper cells
	↑CA1	↑HEMGN	↑OSBP2	↓FCRL5	
	↑HEPACAM2	↑SOX6	↑RHD	↓MS4A1	
				↓FCRLA	
				↓ABC4	

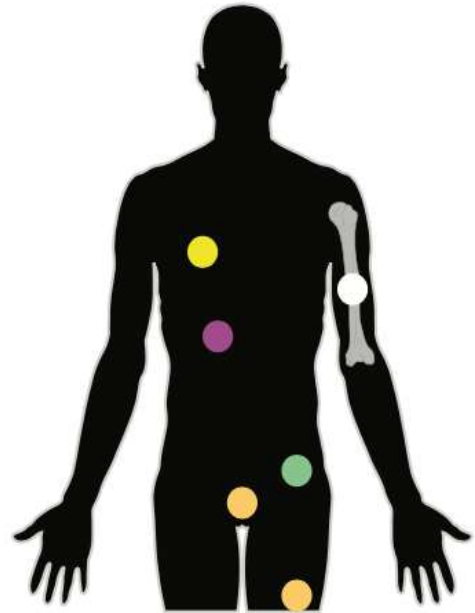


Transcriptomic characteristics of lethal prostate cancer

- Somatic burden
 - PAM50
 - gene expression profiling allows for the identification of clinically relevant molecular subtypes of prostate cancer



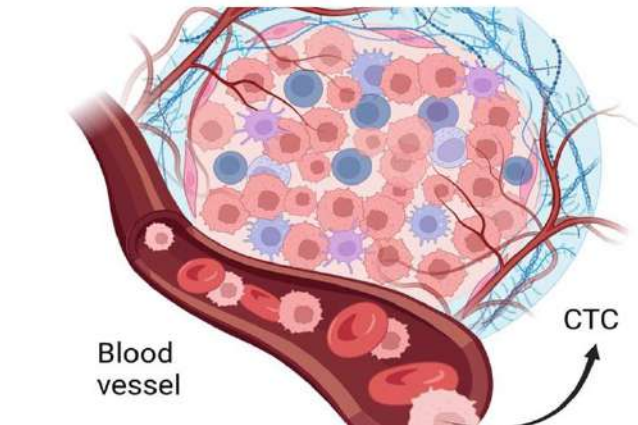
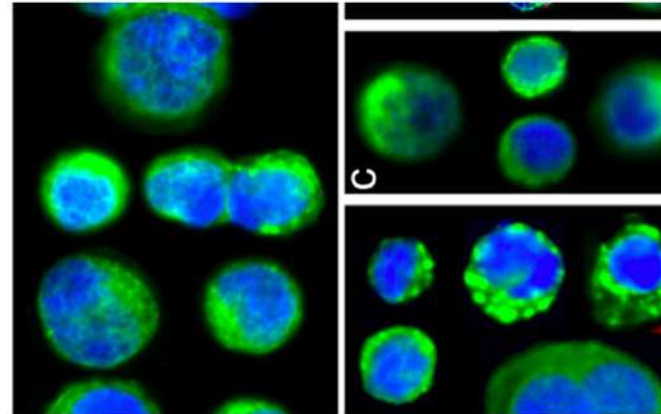
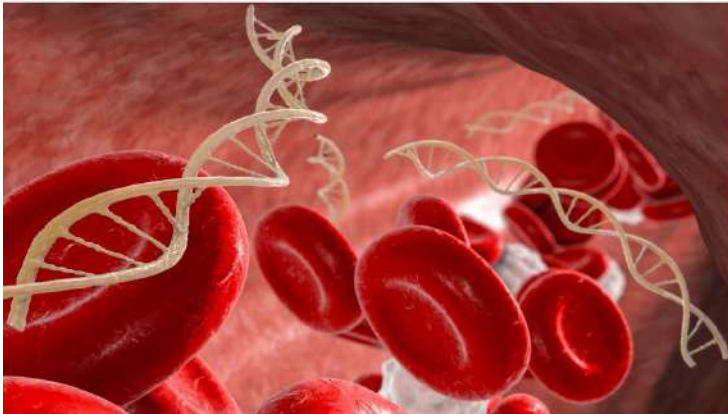
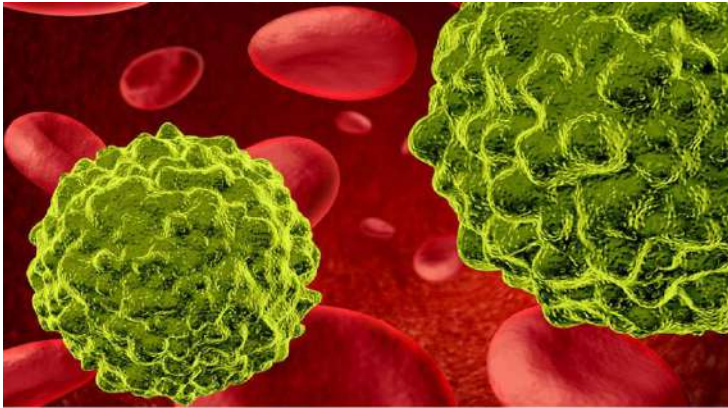
Molecular characteristics of lethal prostate cancer



Lethal
Prostate
Cancer

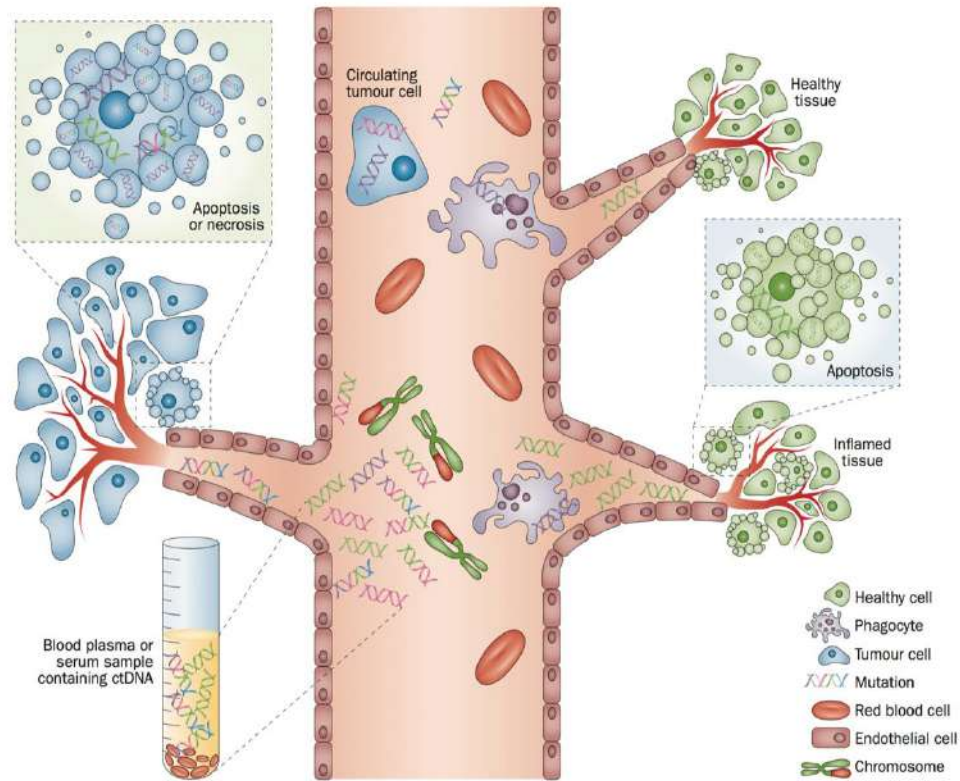
Molecular characteristics

- **Genomically** prostate cancer can be characterised by a **low mutational burden**, but **large GIS and structural variation burden** which increases with advanced disease
- **Inherited common and rare predispositions or PRS** allow to infer prostate cancer risk and identify patients with an inferior prognosis
- Mutation **timing, phylogeny**, and type of **seeding** affects outcome
- The TME, as assessed by **myeloid transcript signatures** in whole blood or increased **NLRs**, can be immunosuppressive and associated with poor outcome
- Prostate cancer **subtypes** (e.g. LumB or NEPC) by **gene expression profiling** identifies poor prognosis subgroup



Circulating tumour burden

Circulating tumour burden vs lethality



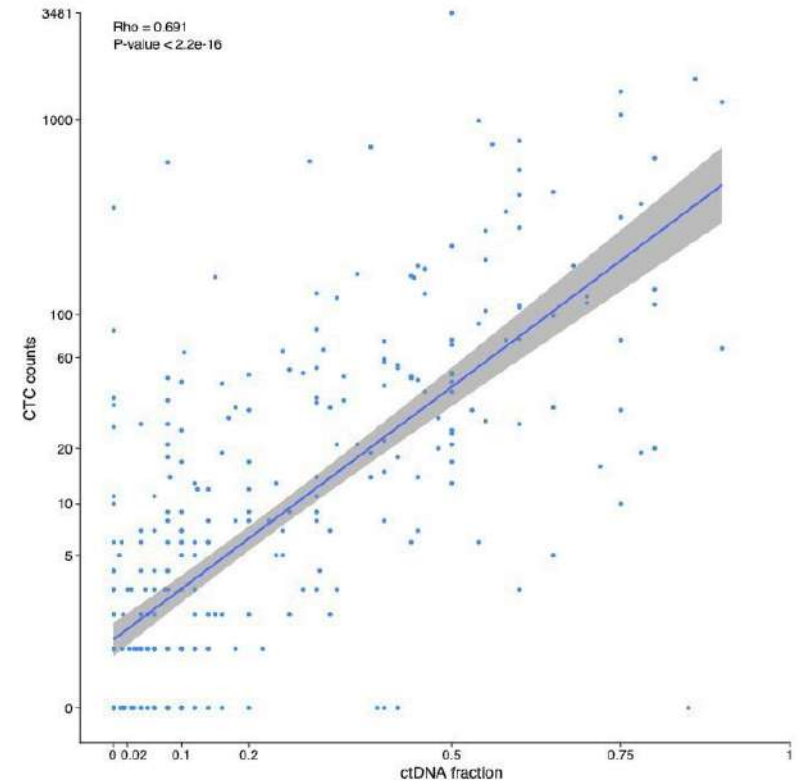
CTC



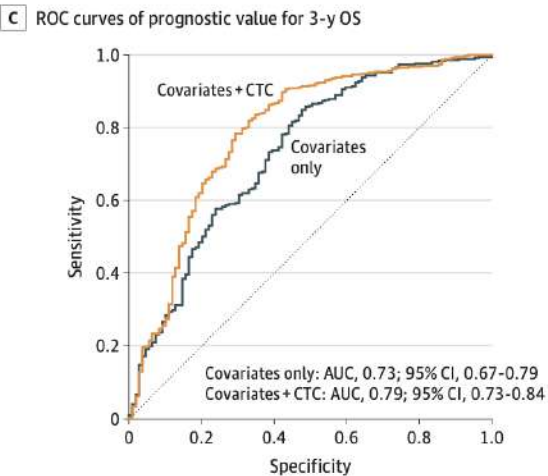
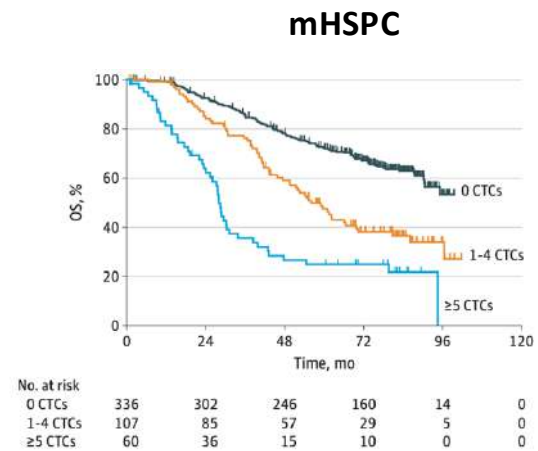
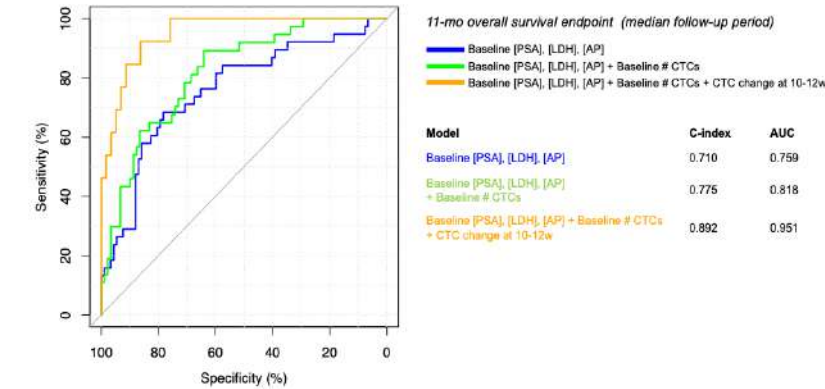
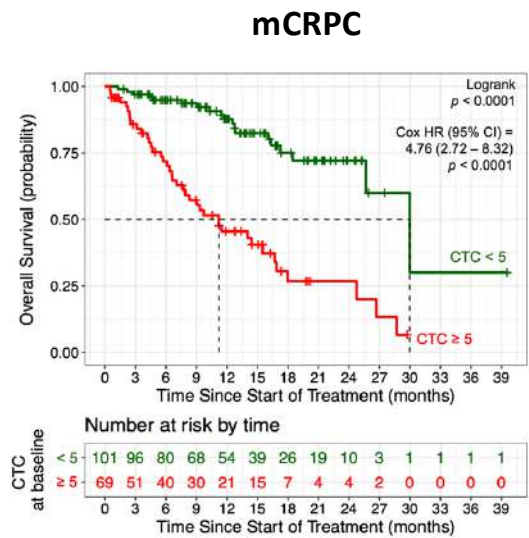
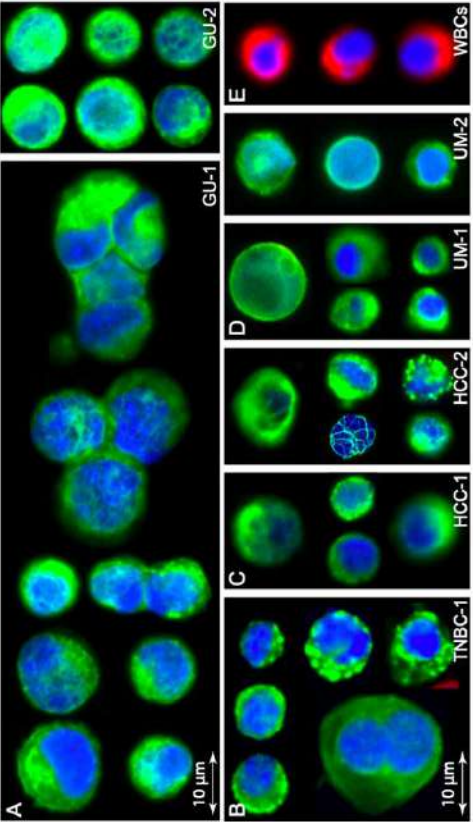
VS



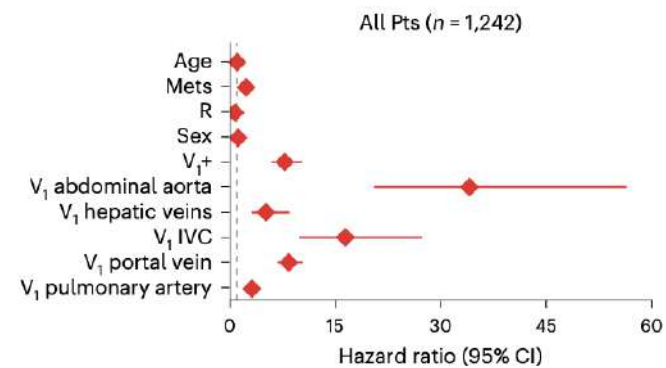
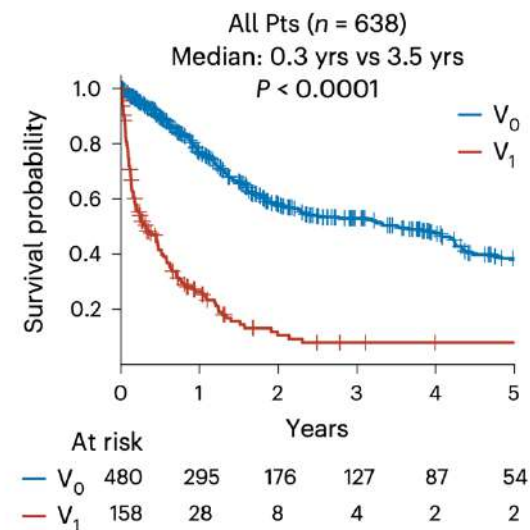
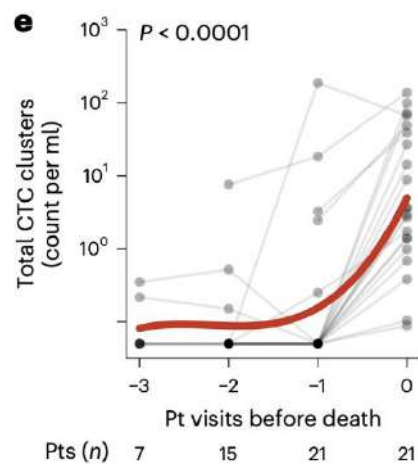
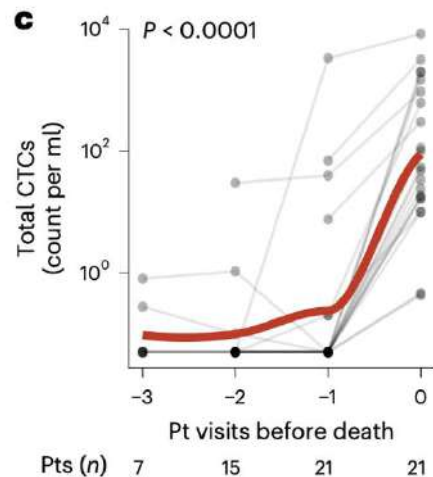
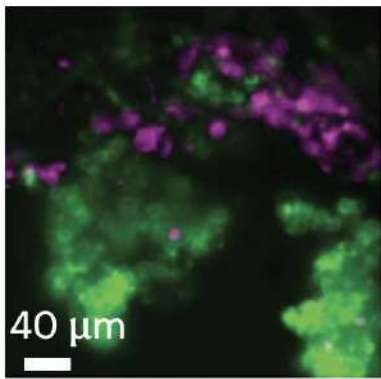
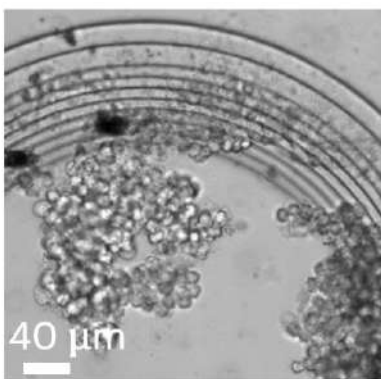
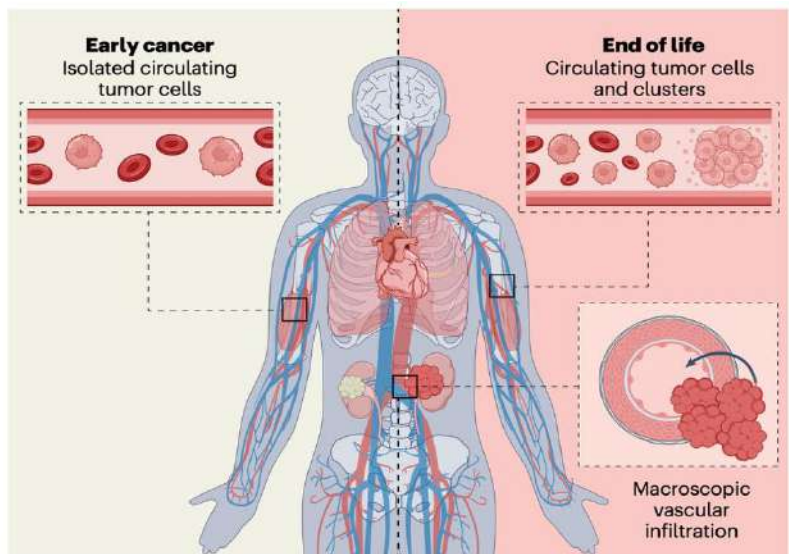
ctDNA



Circulating tumour burden vs lethality

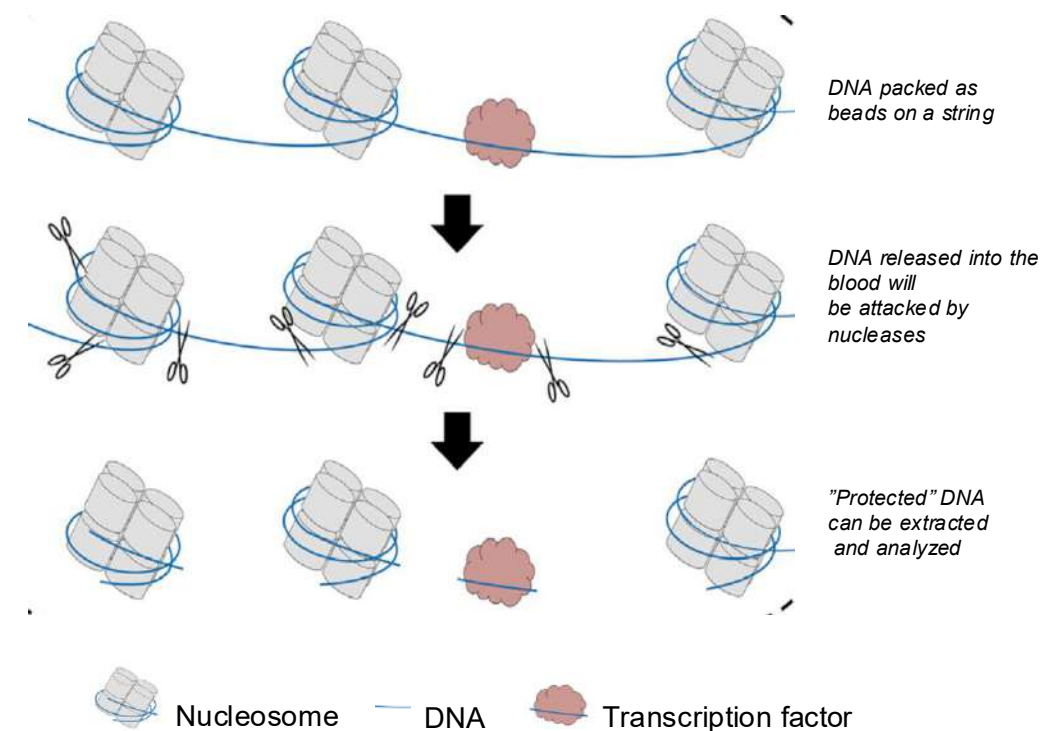
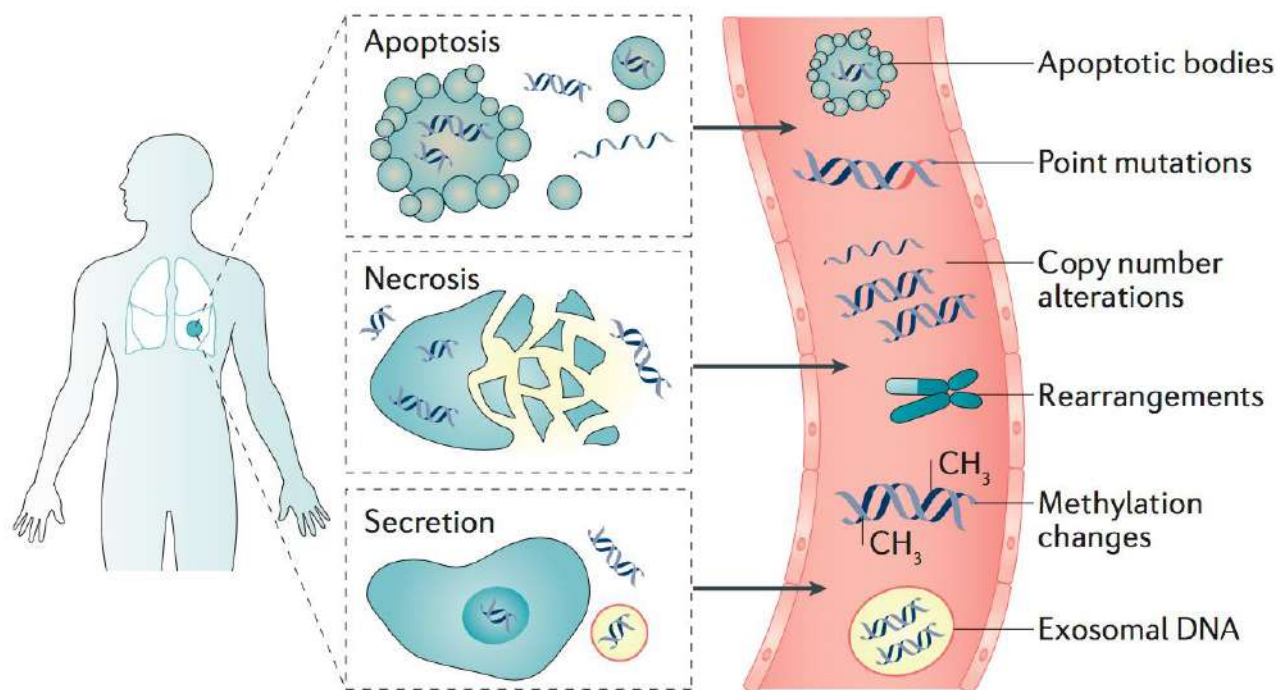


Circulating tumour burden vs lethality



Circulating tumour burden vs lethality

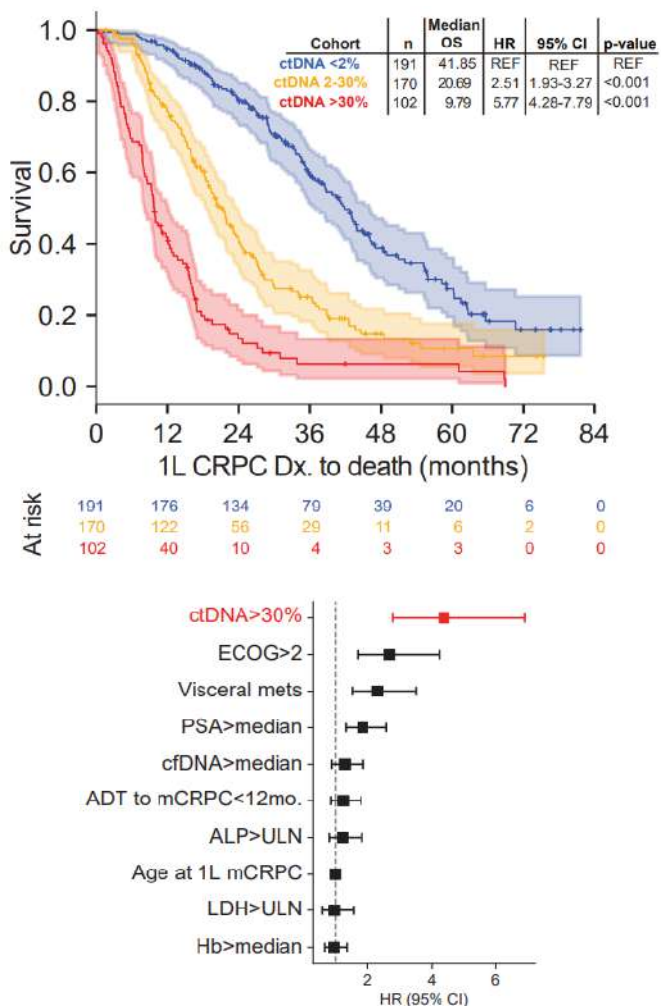
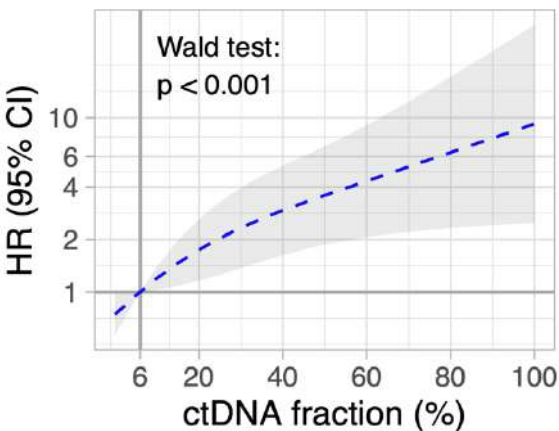
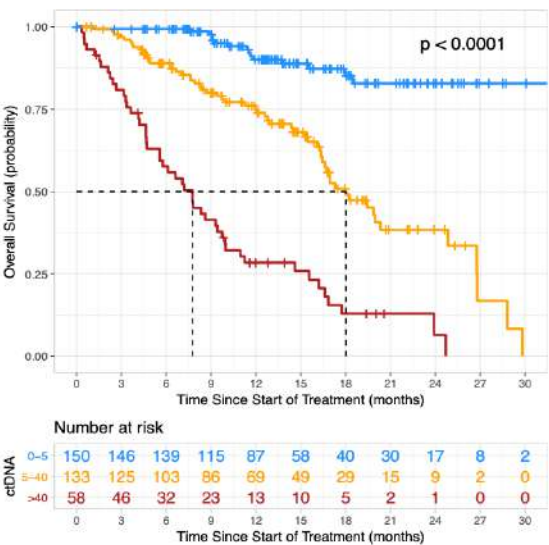
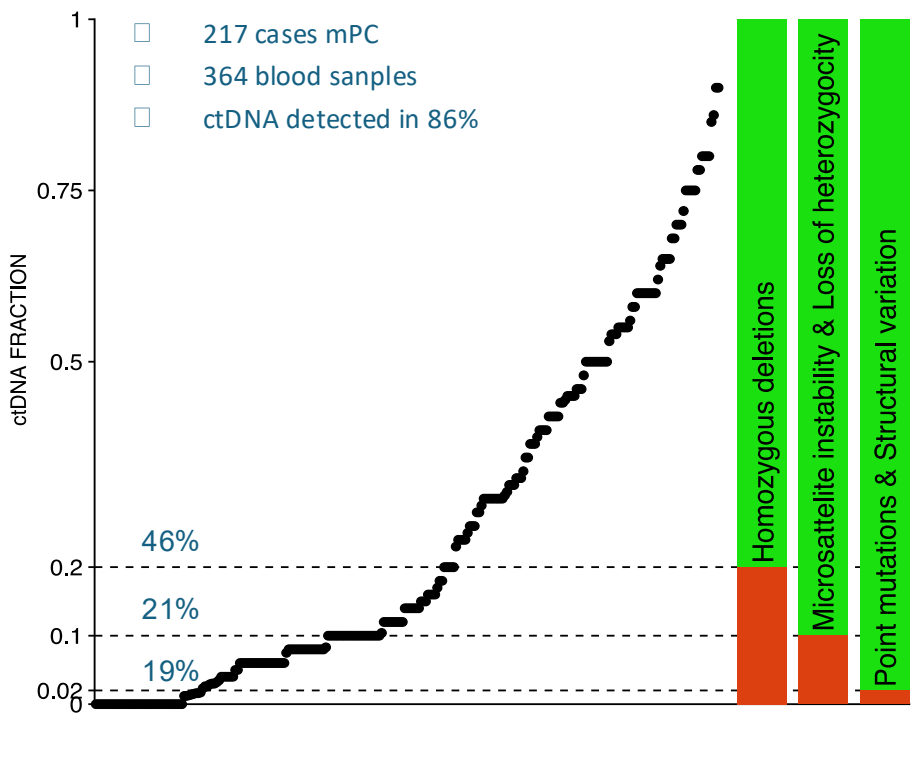
- cfDNA originate (mostly) from apoptotic cells



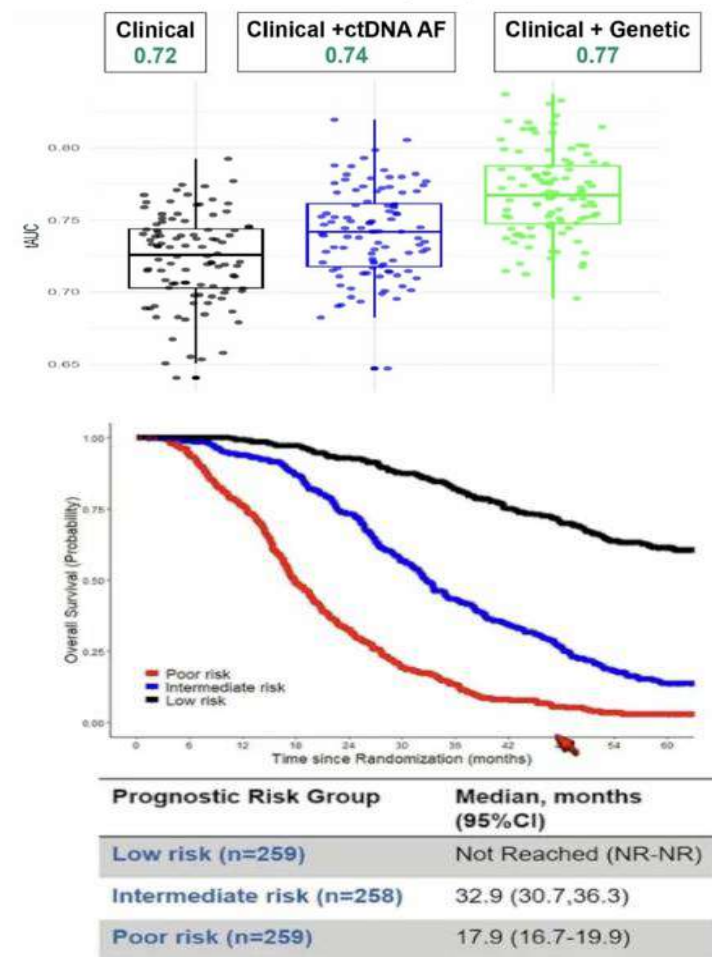
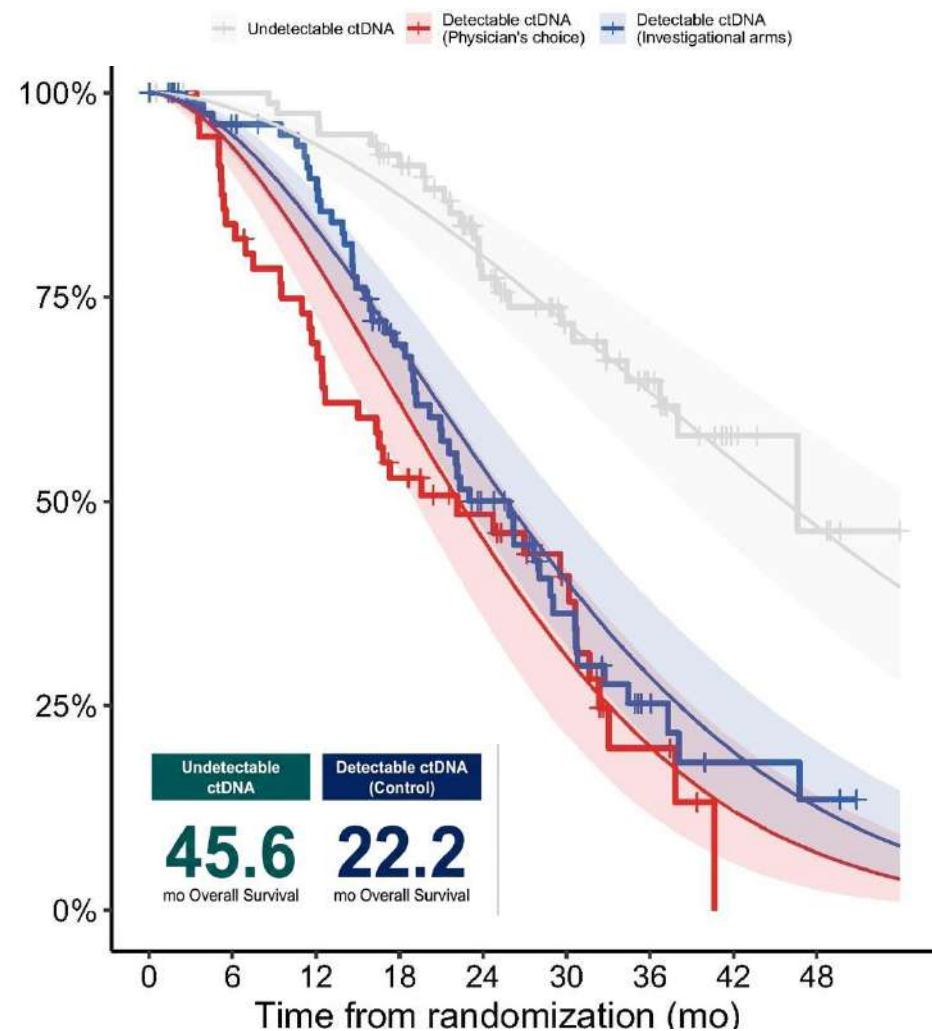
Circulating tumour burden vs lethality

Quantitative analysis

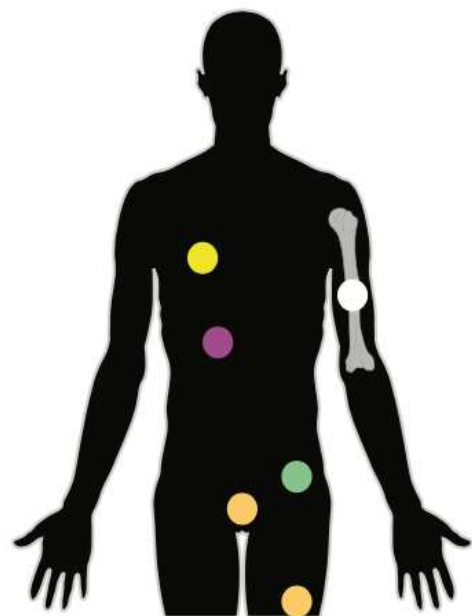
- ctDNA-fraction (ctDNA%) is strongly associated with prognosis



Circulating tumour burden vs lethality



Circulating tumour burden and lethal prostate cancer

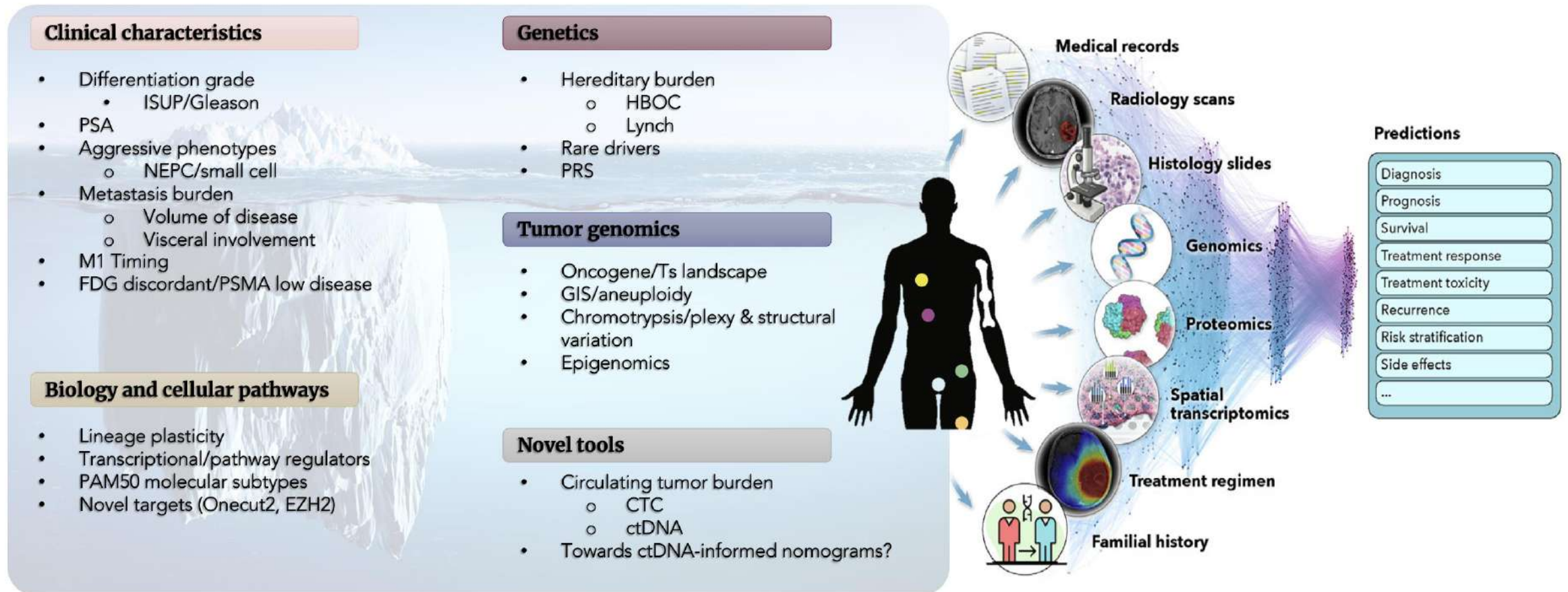


Lethal
Prostate
Cancer

Circulating tumour burden characteristics

- Circulating tumour burden can be quantified by means of **CTC enumeration** or estimation of the **circulating tumour DNA fraction** post cfDNA sequencing
- CTC and ctDNA are strong **prognostic variables**
- **ctDNA undetectability** is associated with superior prognosis
- An **inverse linear relationship** exists between ctDNA fraction and survival time
- Combining **ctDNA information** with clinical characteristics **improves prognostic models**

Conclusion | Can we identify lethal prostate cancer?





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