

Can we identify lethal prostate cancer?

Towards integrating Clinical and Molecular Approaches

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bmuc.be/bmuc2025



**12th Belgian Multidisciplinary
Meeting on Urological Cancers**

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
- **12,699** new diagnoses in 2022
- **1,495** deaths due to prostate cancer in 2021
- 10-year net survival of **97.2%**

Lifetime risk (0-84 years)



21.3 in 100 males



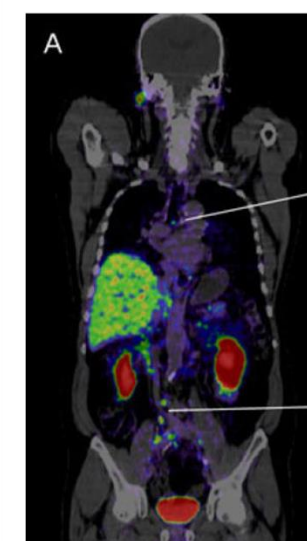
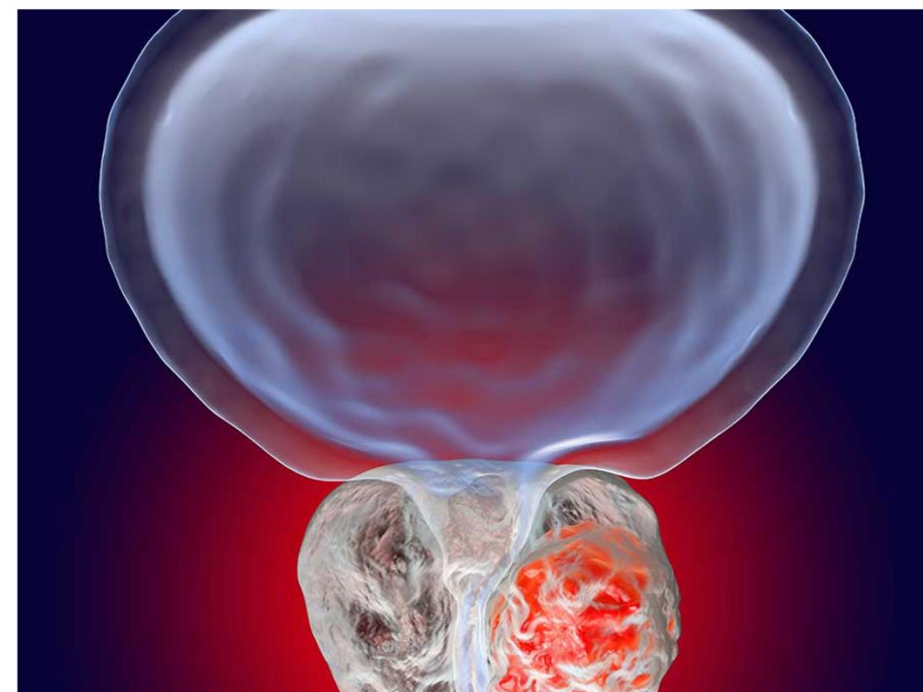
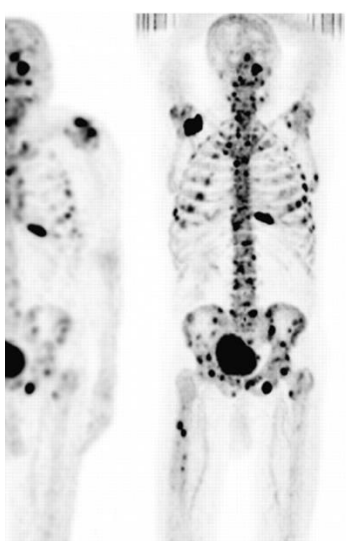
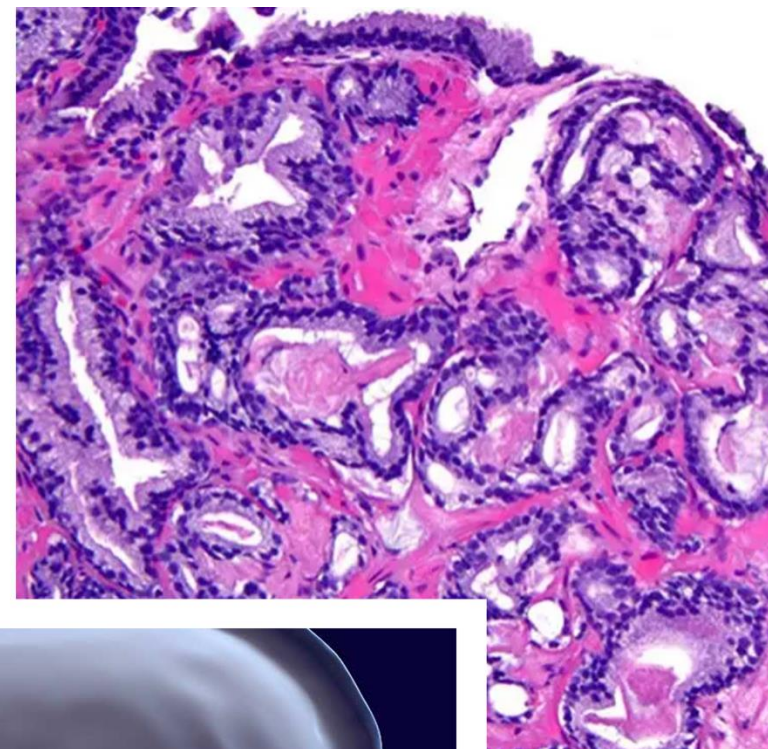
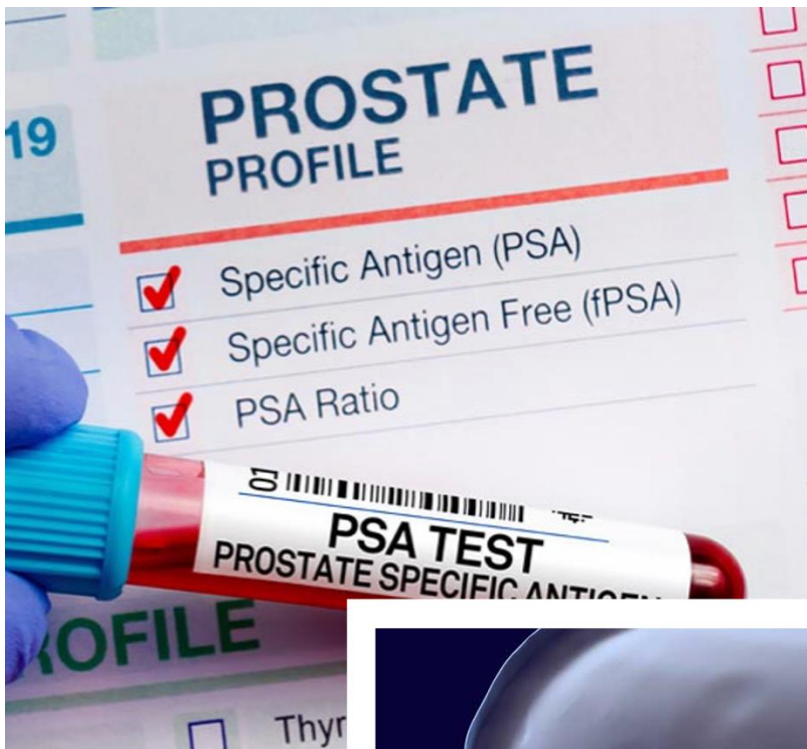
Incidence (2022)

Can we identify
lethal prostate
cancer?



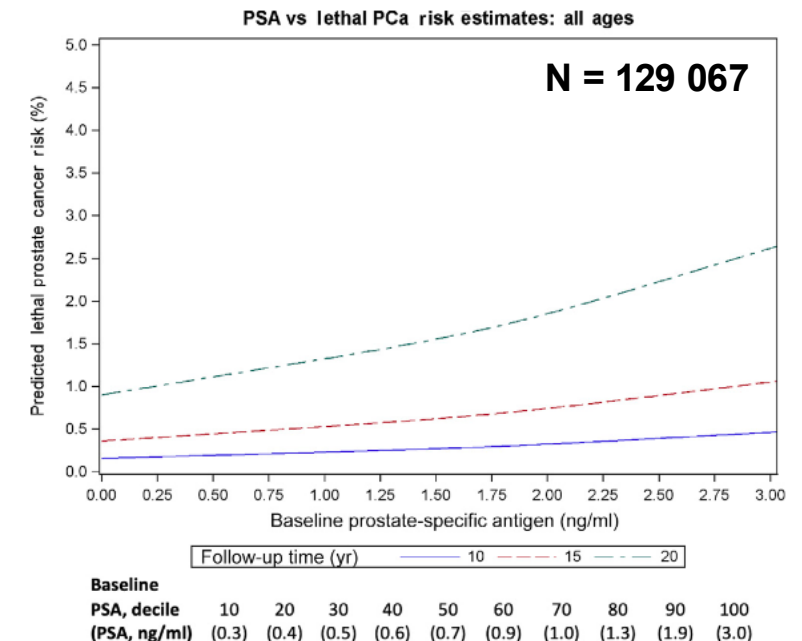
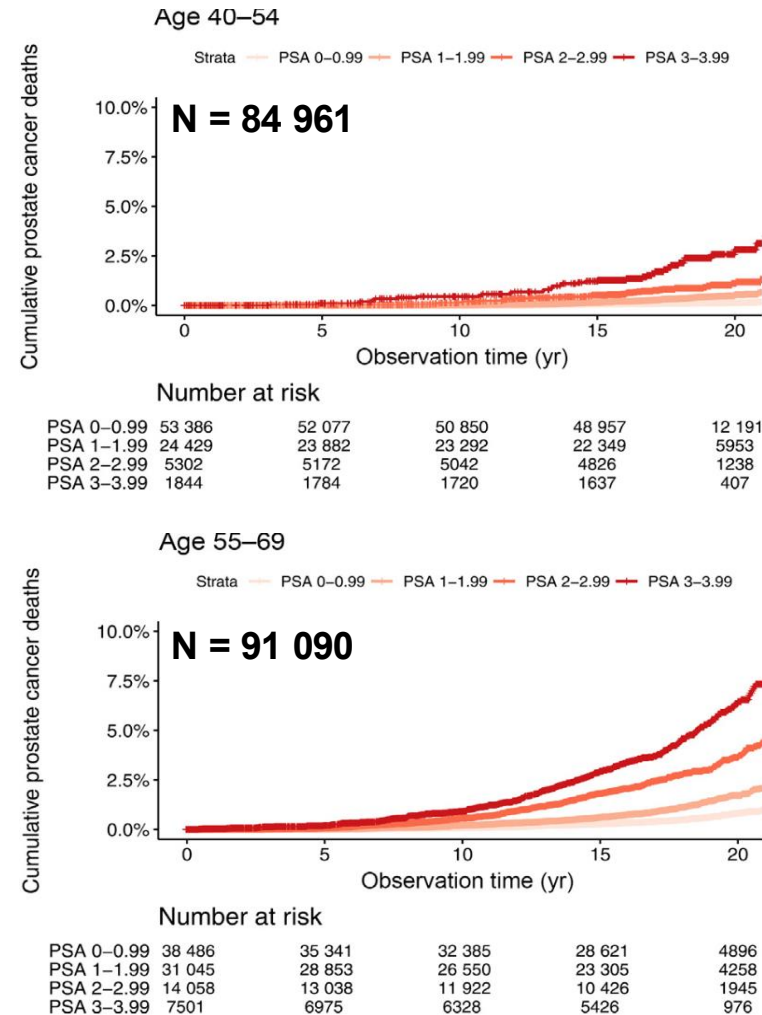
Mortality* (2021)

Clinical characteristics



Clinical characteristics of lethal prostate cancer

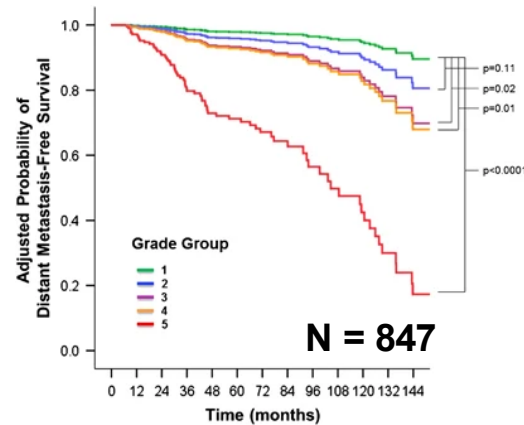
- Prostate Specific Antigen (PSA)
 - Baseline PSA is an important, though imperfect marker and can be used to stratify a man's risk of dying from prostate cancer within the next 15–20 yr



Clinical characteristics of lethal prostate cancer

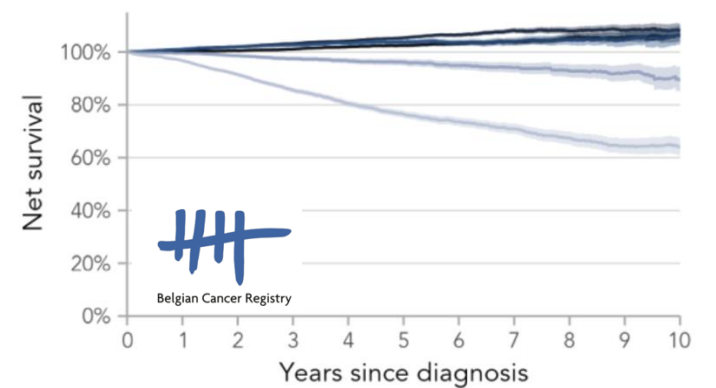
- **Differentiation Grade by Gleason/ISUP Score:**
 - Poorly differentiated tumors are more lethal.
 - Traditional Gleason may provide more accurate prognostic information

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

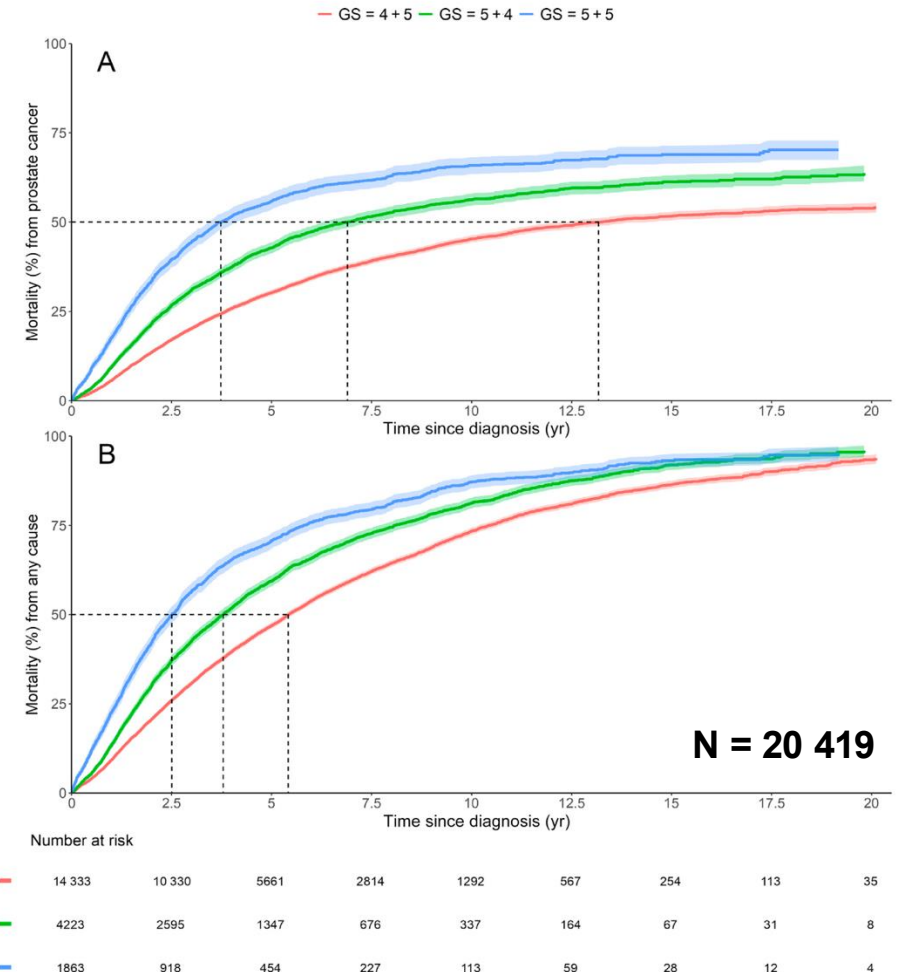


Number at risk	0	12	24	36	48	60	72	84	96	108	120	132	144
1	287	223	180	100	52	28	4						
2	254	177	129	81	48	29	7						
3	140	96	66	42	17	10	3						
4	95	66	47	34	13	6	2						
5	91	39	18	9	3	2	1						

Net survival by Histopathological Grade Group, 2013-2022

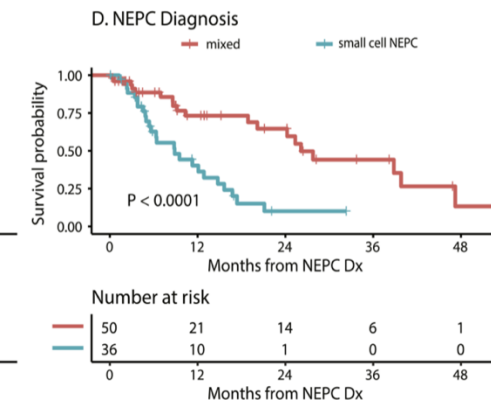
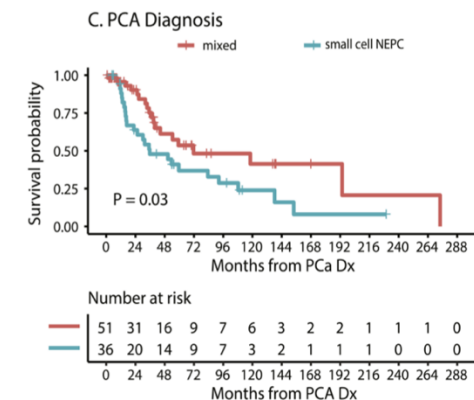
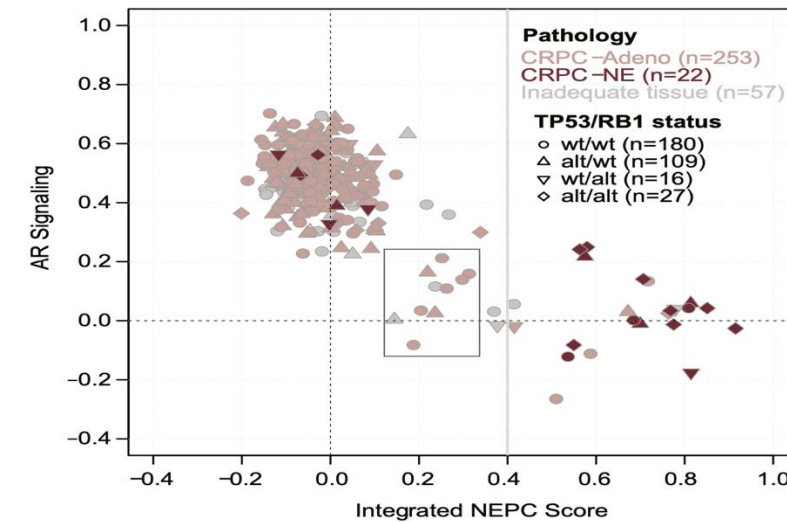
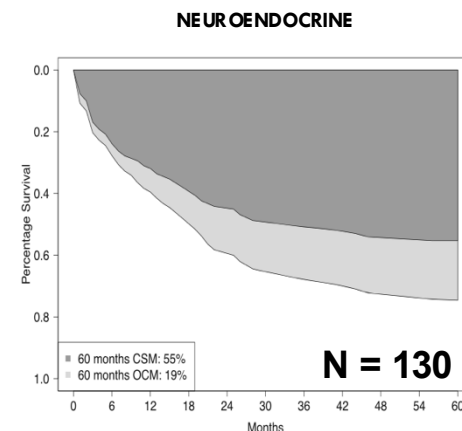
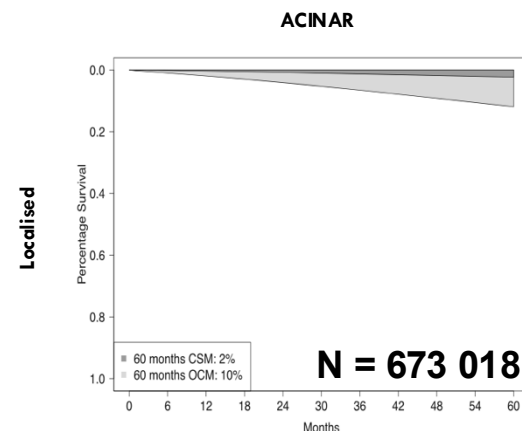
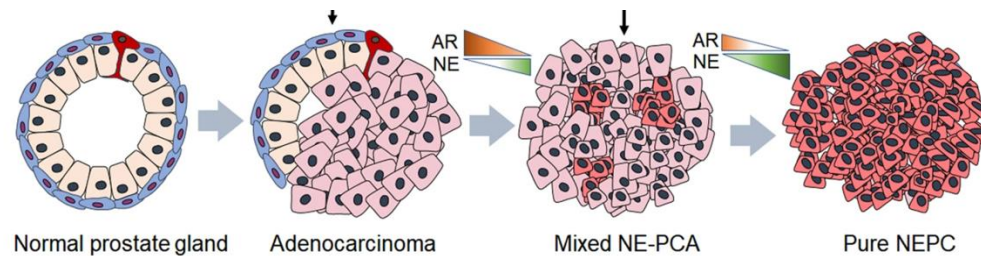


Histopathological Grade Group: I II III IV V



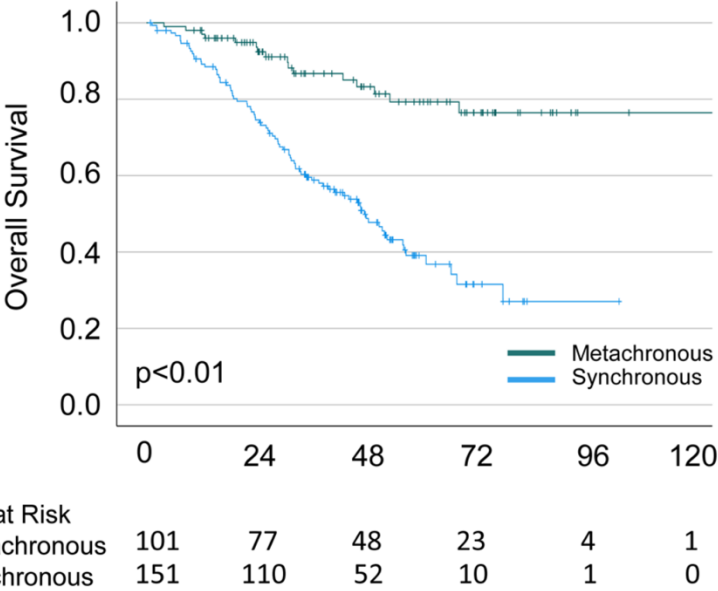
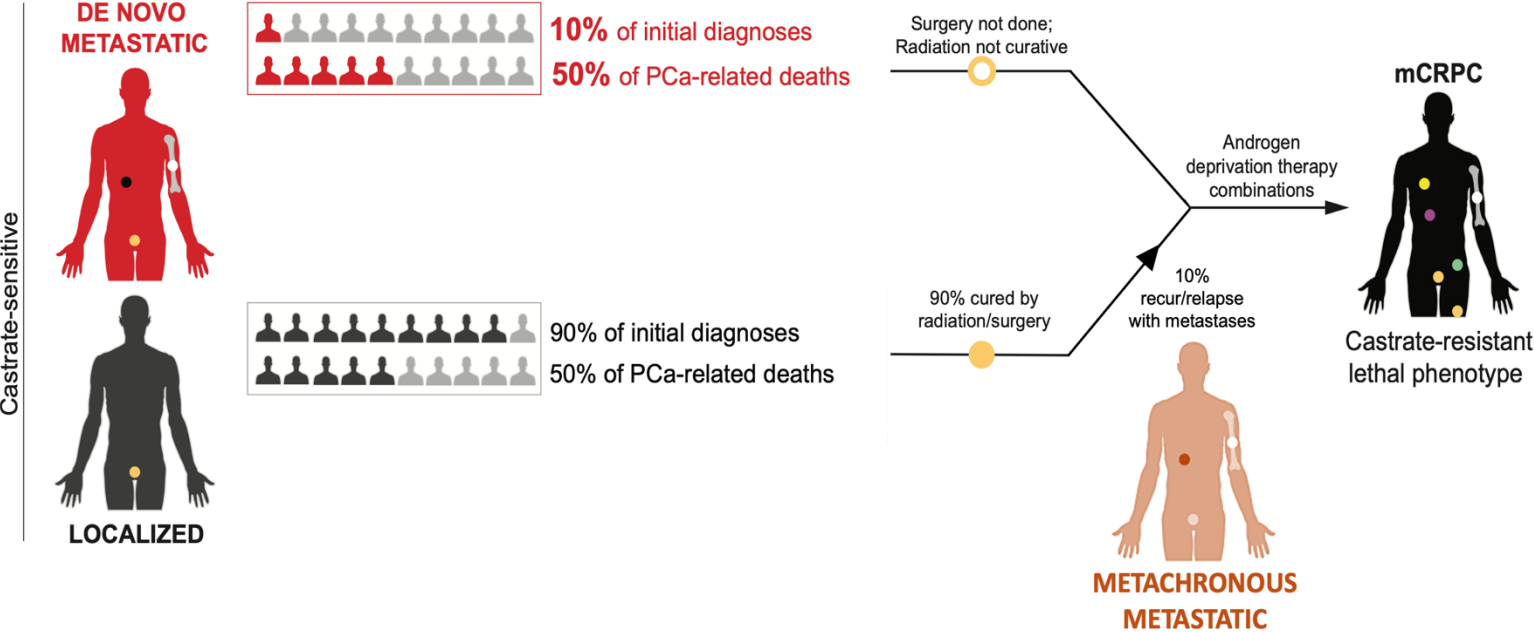
Clinical characteristics of lethal prostate cancer

- Aggressive histological subtypes
 - NEPC/SC



Clinical characteristics of lethal prostate cancer

- Timing of M1 disease



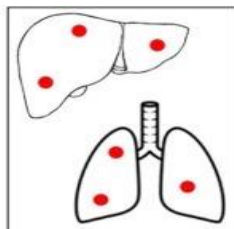
Clinical characteristics of lethal prostate cancer

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

High	Low
≥4 Bone metastasis including ≥1 outside vertebral column or pelvis and/or visceral metastasis	Not high

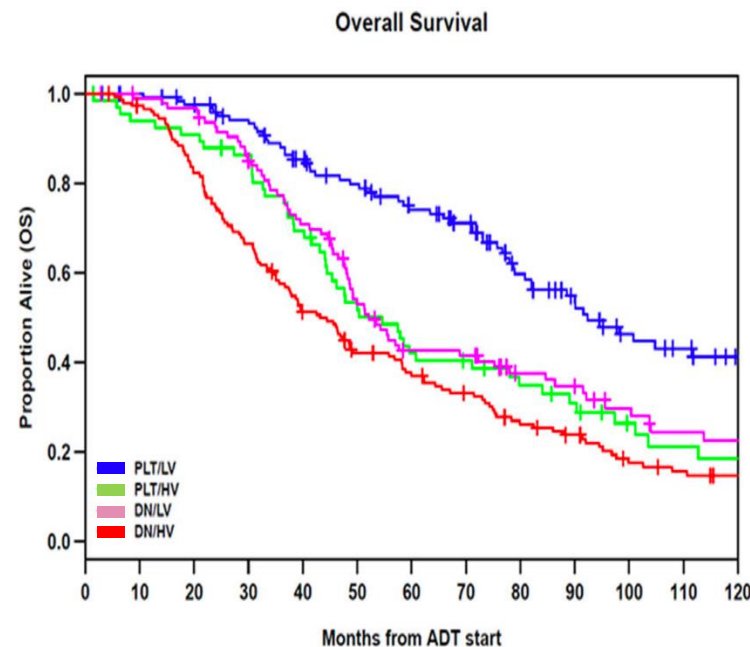


4 or more bone mets
(with at least one outside
the pelvis/column)

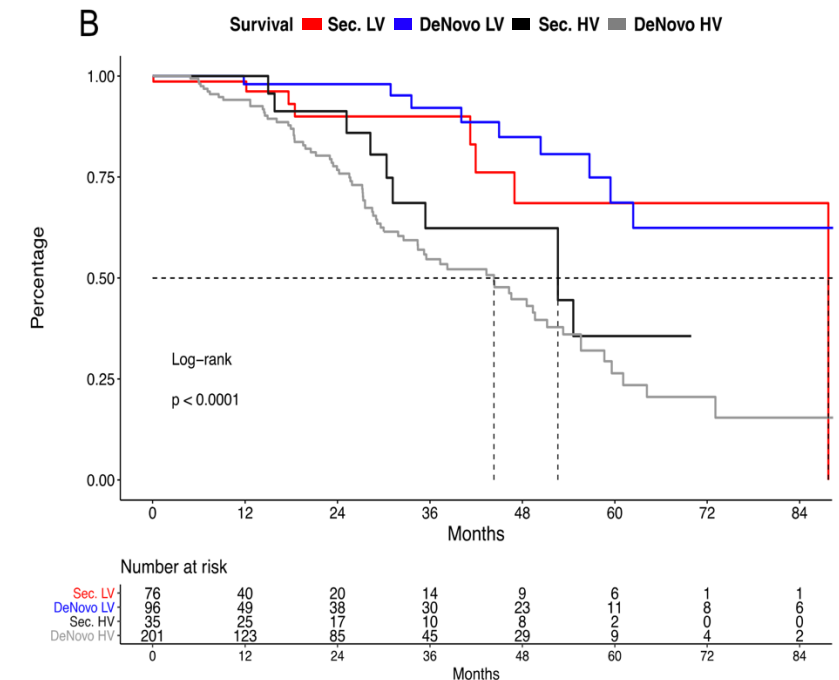


Visceral mets

ADT monotherapy

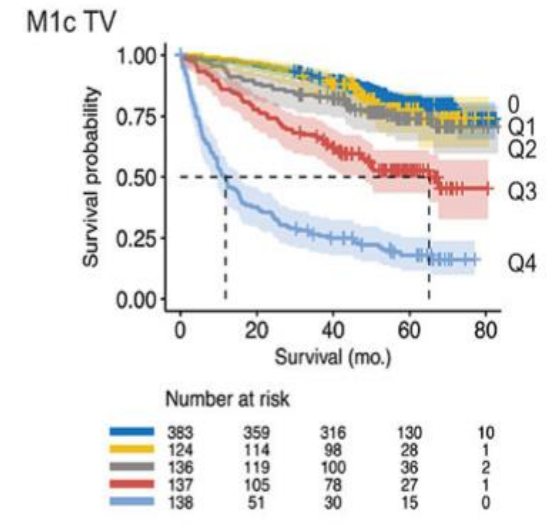
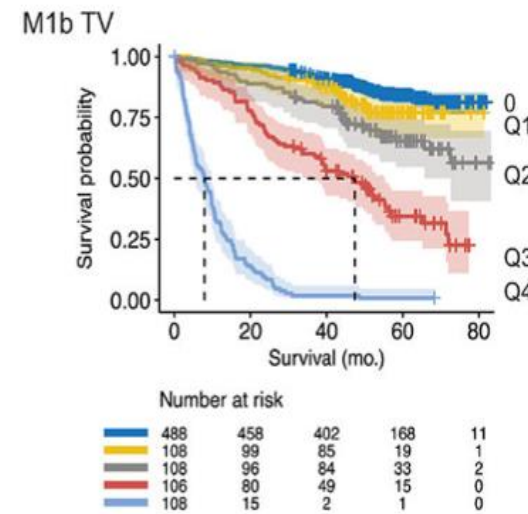
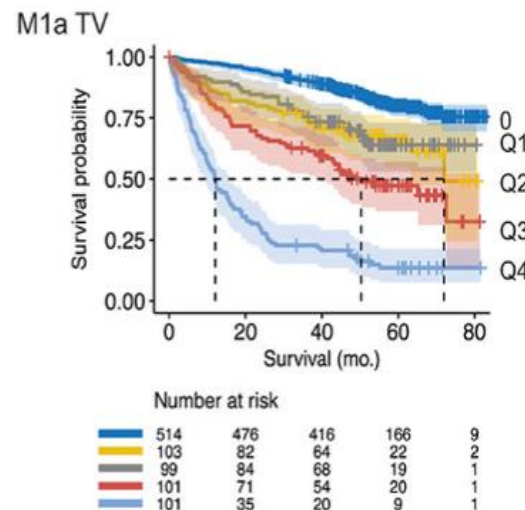
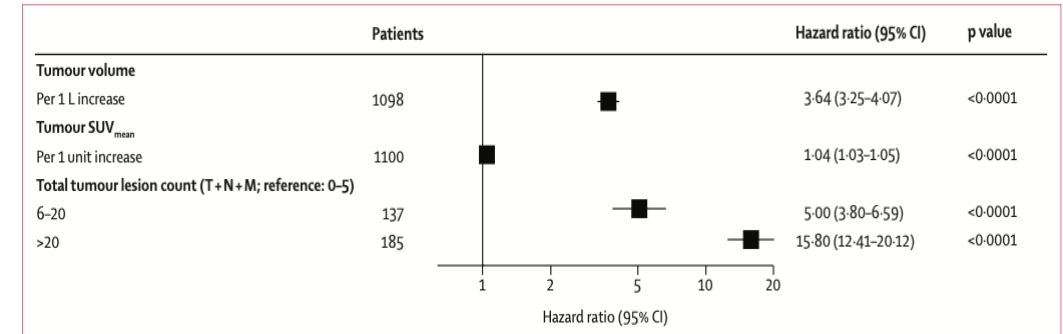
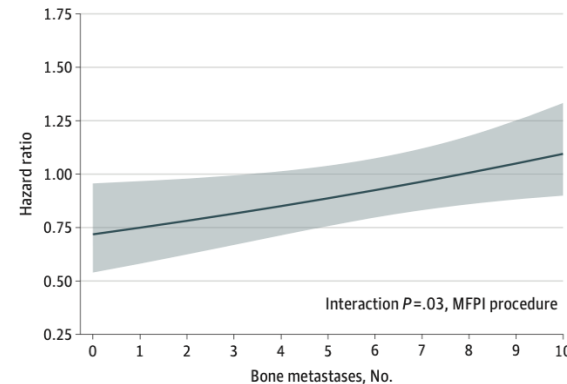


ADT + ARPI or docetaxel



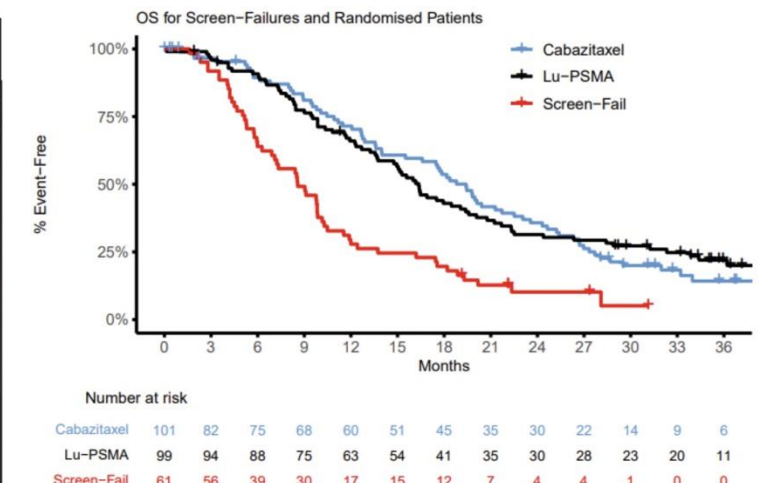
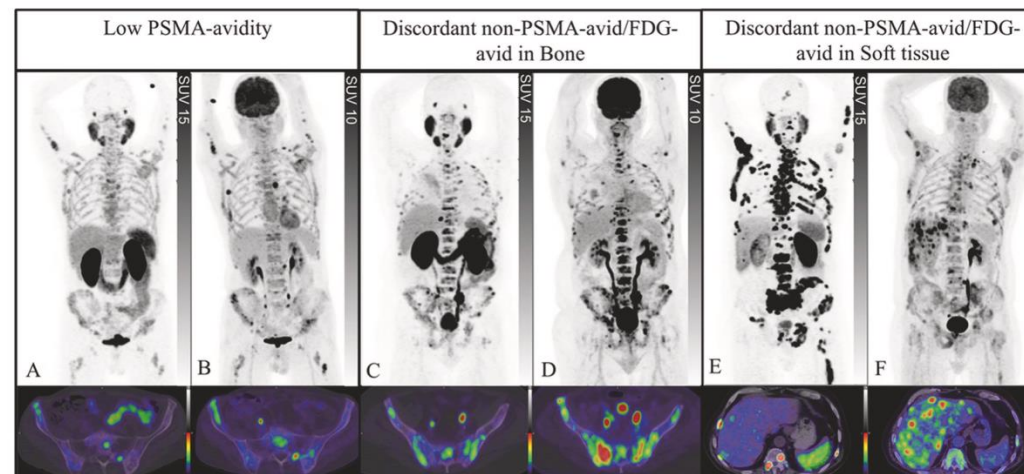
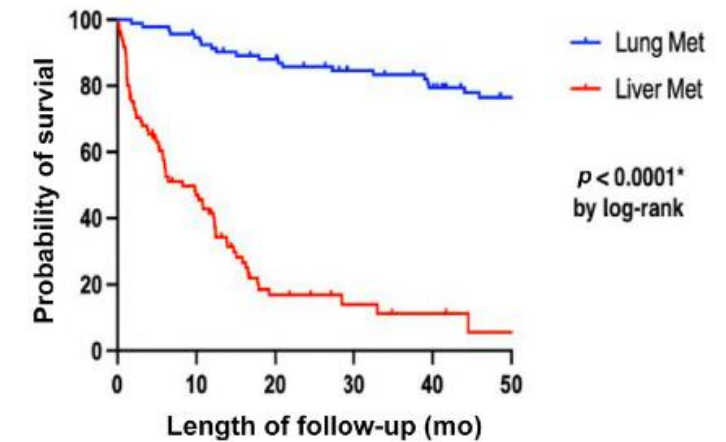
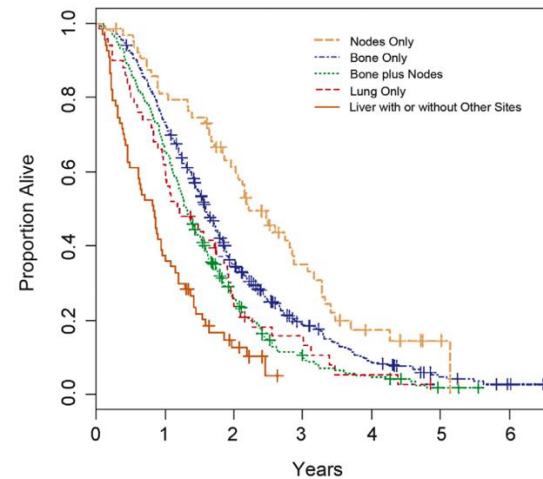
Clinical characteristics of lethal prostate cancer

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



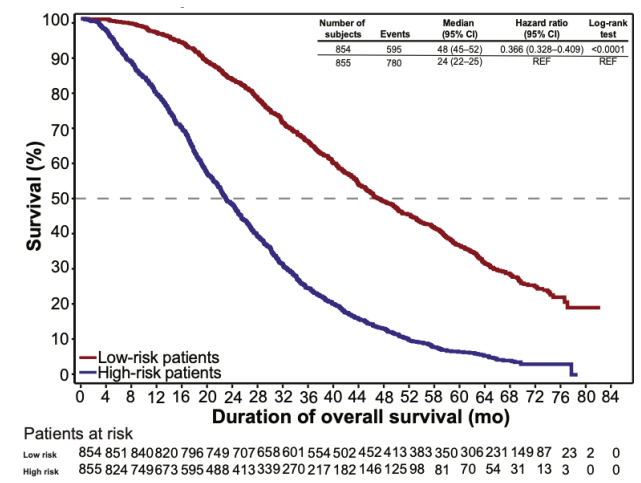
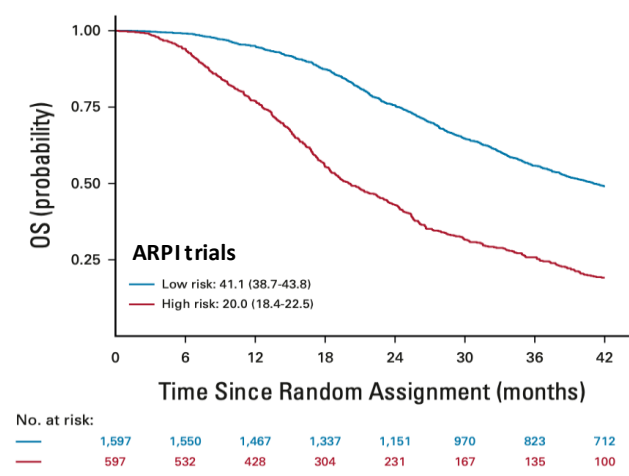
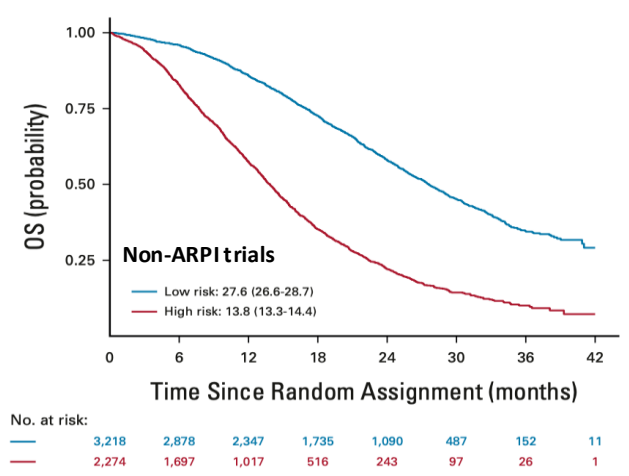
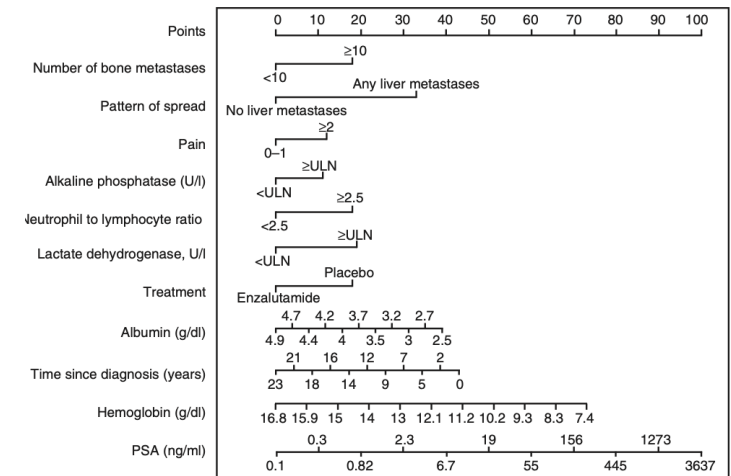
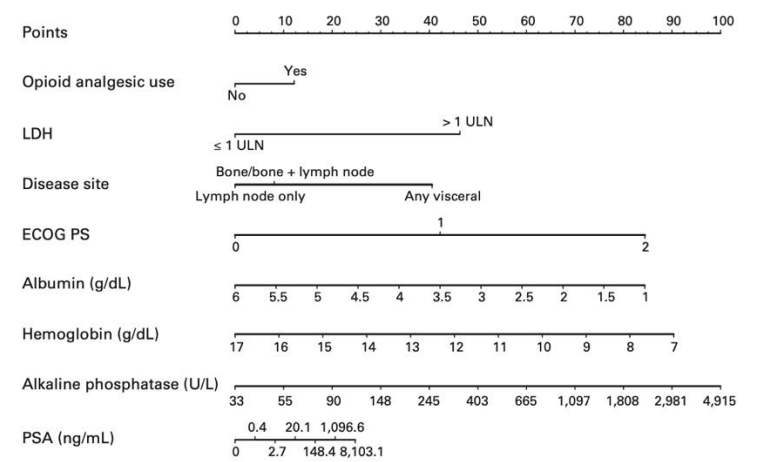
Clinical characteristics of lethal prostate cancer

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

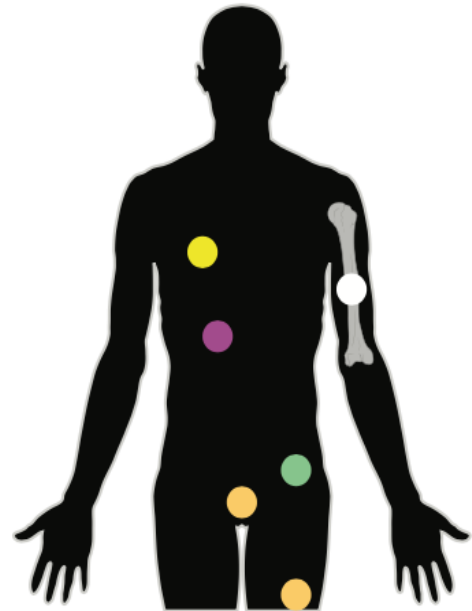


Clinical characteristics of lethal prostate cancer

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



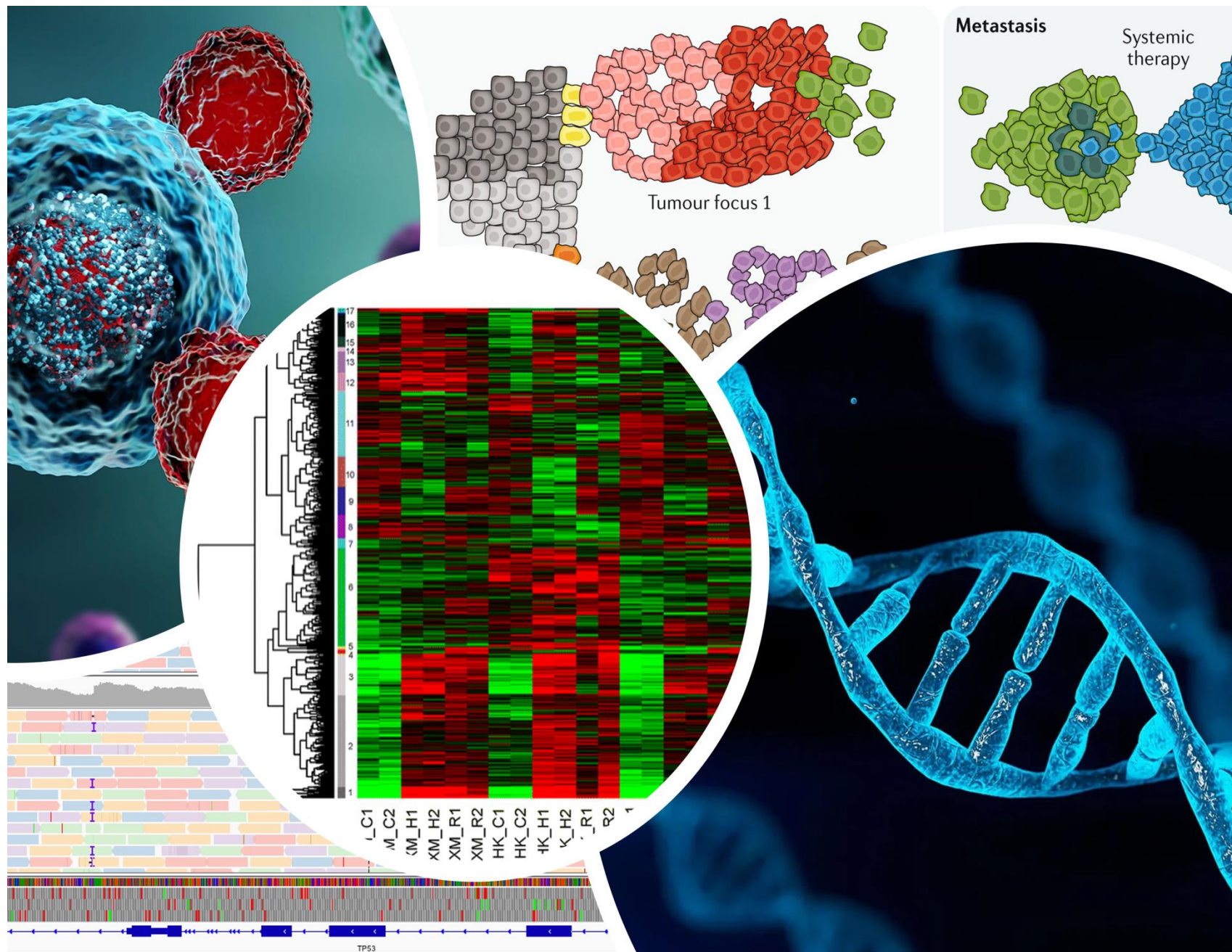
Clinical characteristics of lethal prostate cancer



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



Molecular characteristics

Molecular characteristics of lethal prostate cancer

Central Dogma of Molecular Biology

by
FRANCIS CRICK
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The central dogma of molecular biology deals with the detailed residue-by-residue transfer of sequential information. It states that such information cannot be transferred from protein to either protein or nucleic acid.

NATURE VOL. 227 AUGUST 8 1970

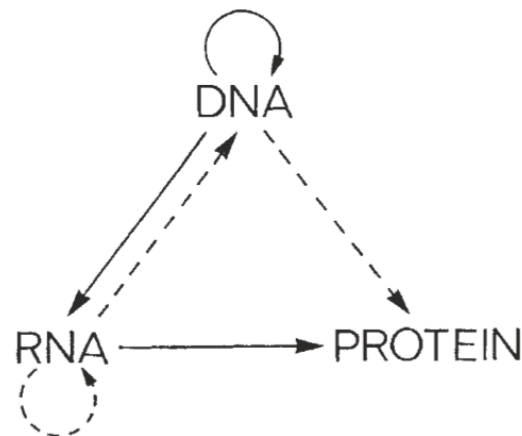
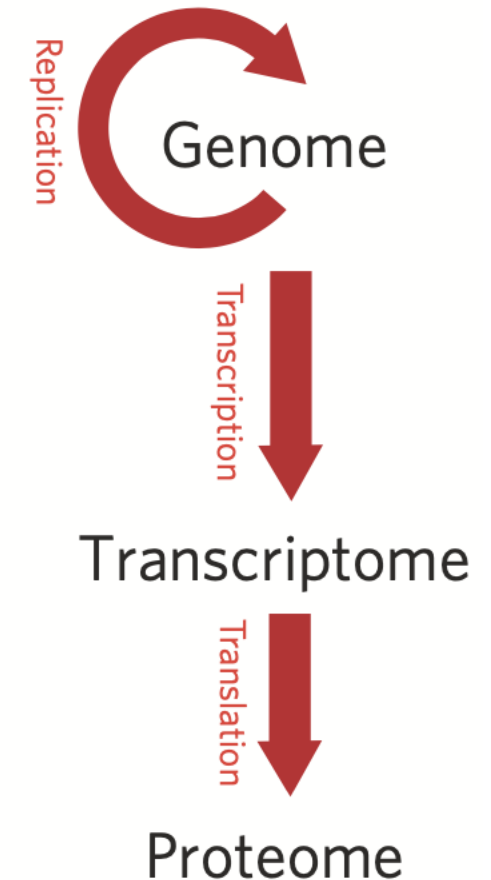


Fig. 3. A tentative classification for the present day. Solid arrows show general transfers; dotted arrows show special transfers. Again, the absent arrows are the undetected transfers specified by the central dogma.



Genomic characteristics of lethal prostate cancer

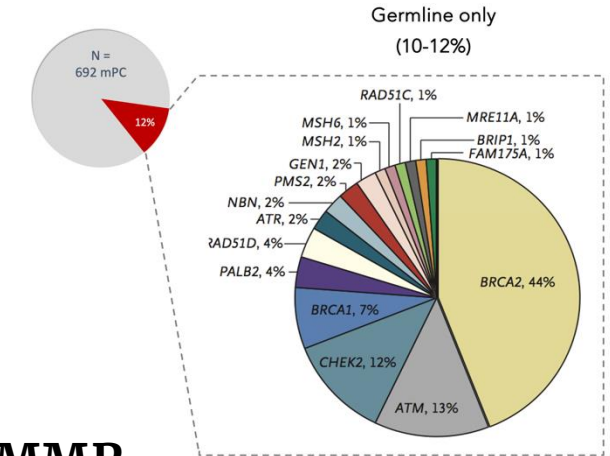
• Hereditary Burden

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

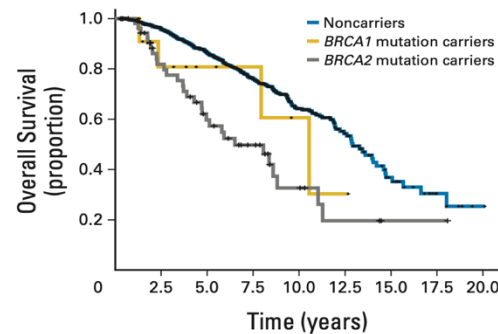
Table 1: Cancer risks in germline carriers

Cancer Risk	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%

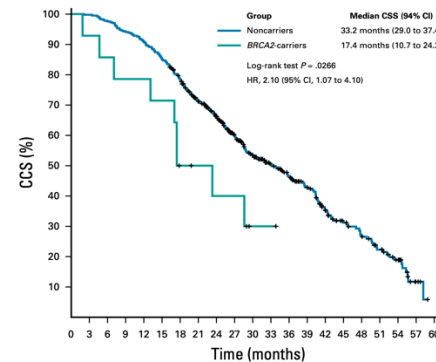
↑ = moderate increased risk (RR/OR between 1.8 – 3.75)



HRD (BRCA1/2)

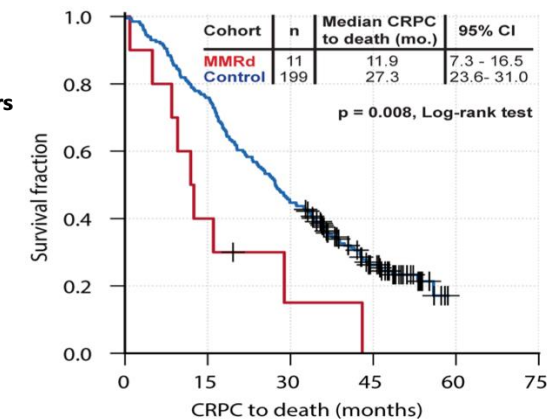
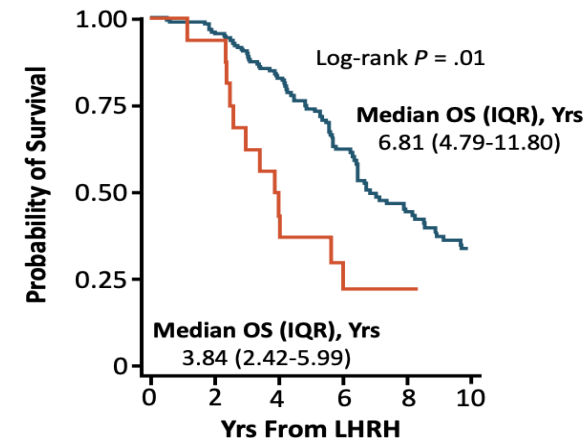


No. at risk	1,940	1,394	896	467	186	68	22	6	1
Noncarriers	1,940	1,394	896	467	186	68	22	6	1
BRCA1 mutation carriers	18	12	5	4	2	1	0	0	0
BRCA2 mutation carriers	61	40	28	16	6	3	1	1	0



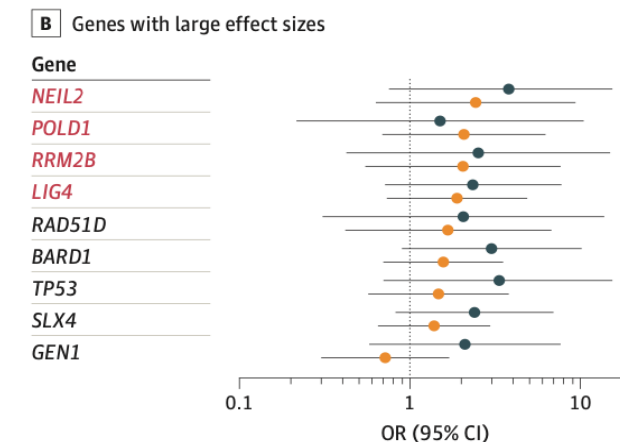
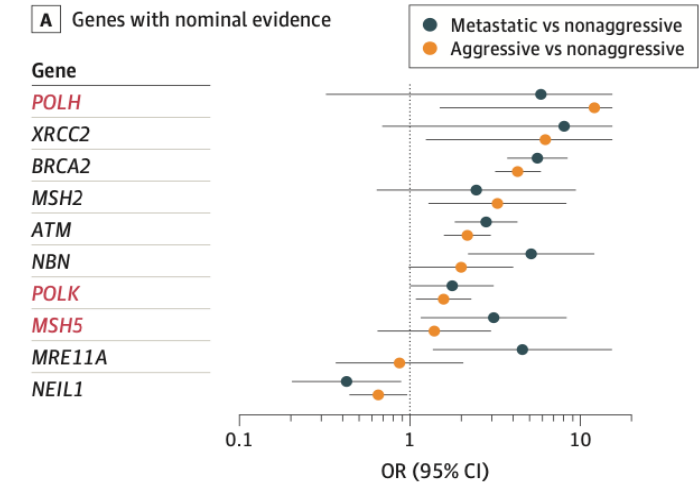
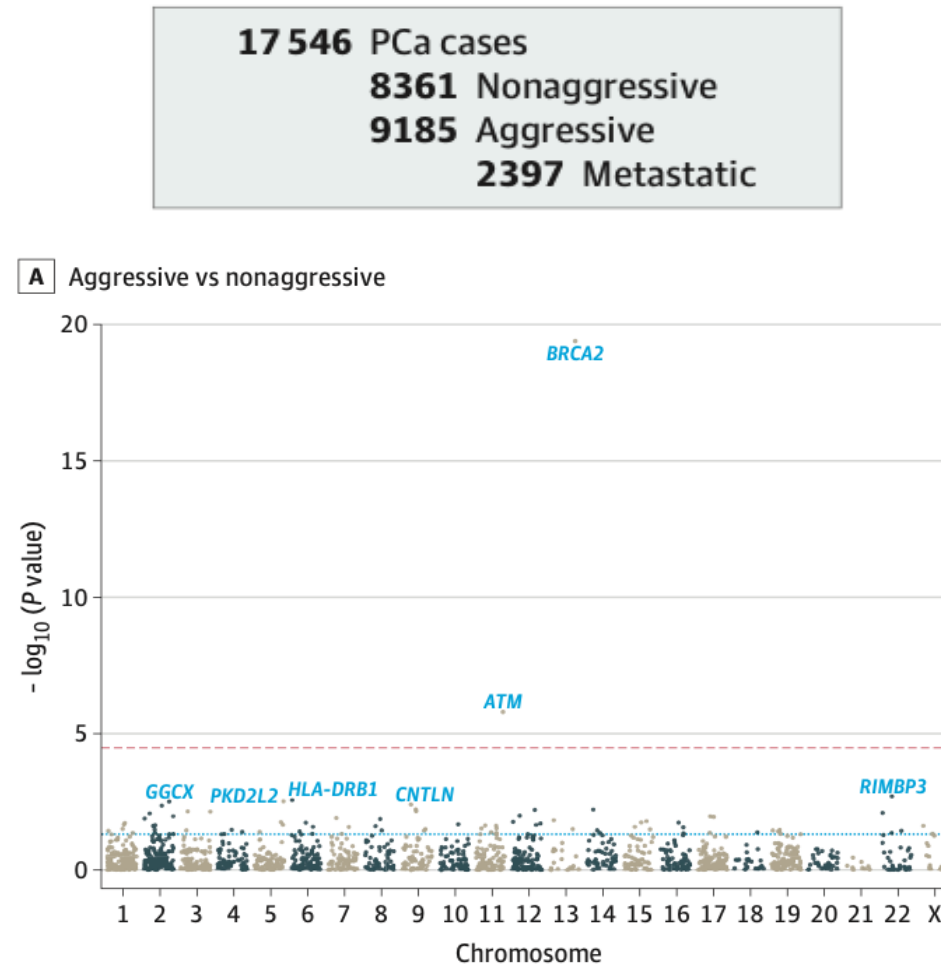
No. at risk	405	404	395	382	368	346	312	285	232	189	153	128	110	88	64	49	40	30	20	4	0
Noncarriers	405	404	395	382	368	346	312	285	232	189	153	128	110	88	64	49	40	30	20	4	0
BRCA1 mutation carriers	18	12	5	4	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
BRCA2 mutation carriers	61	40	28	16	6	3	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0

dMMR



Genomic characteristics of lethal prostate cancer

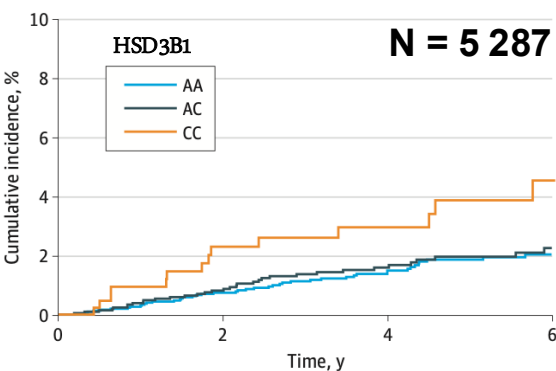
- **Hereditary Burden**
 - Rare Genetic Drivers can be associated with aggressive disease



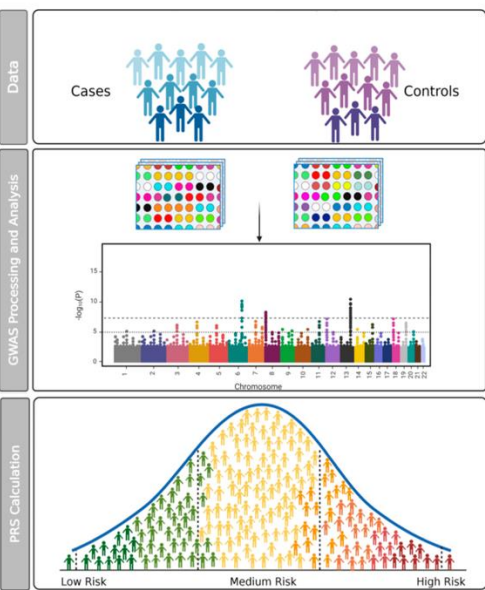
Genomic characteristics of lethal prostate cancer

- Common germline variants and Polygenic Risk Scores (PRS)

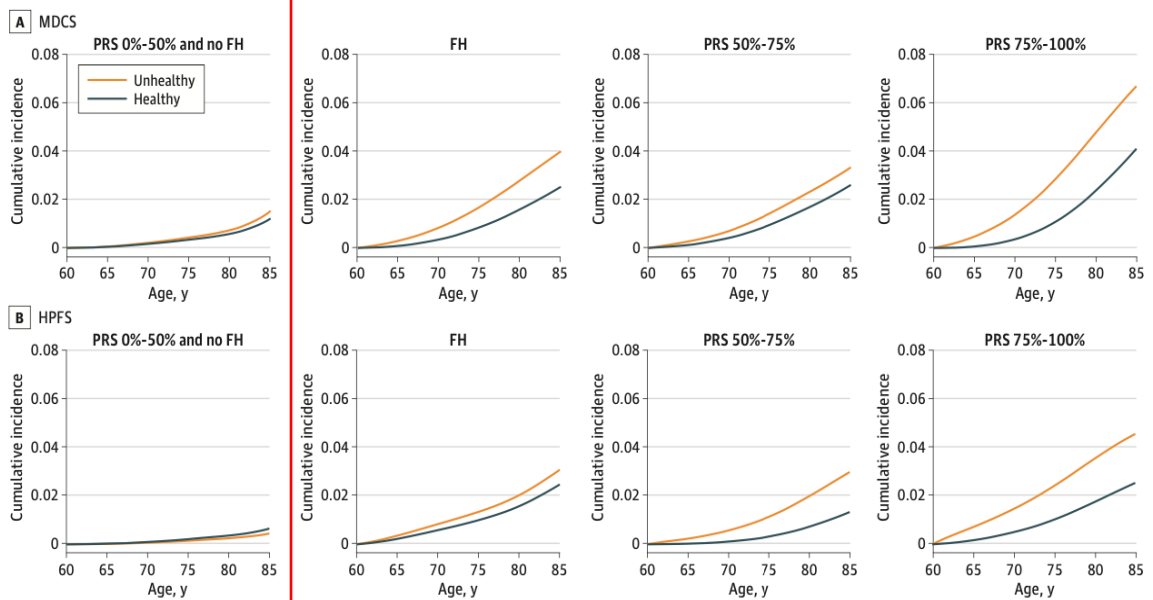
- HSD3B1* genotype is associated with outcome
- Polygenic risk scores (PRSs) use multiple single nucleotide polymorphisms (SNPs) to estimate an individual's genetic risk for prostate cancer death



No. at risk				
AA	2915	2328	1624	845
AC	1970	1582	1075	564
CC	402	311	219	118



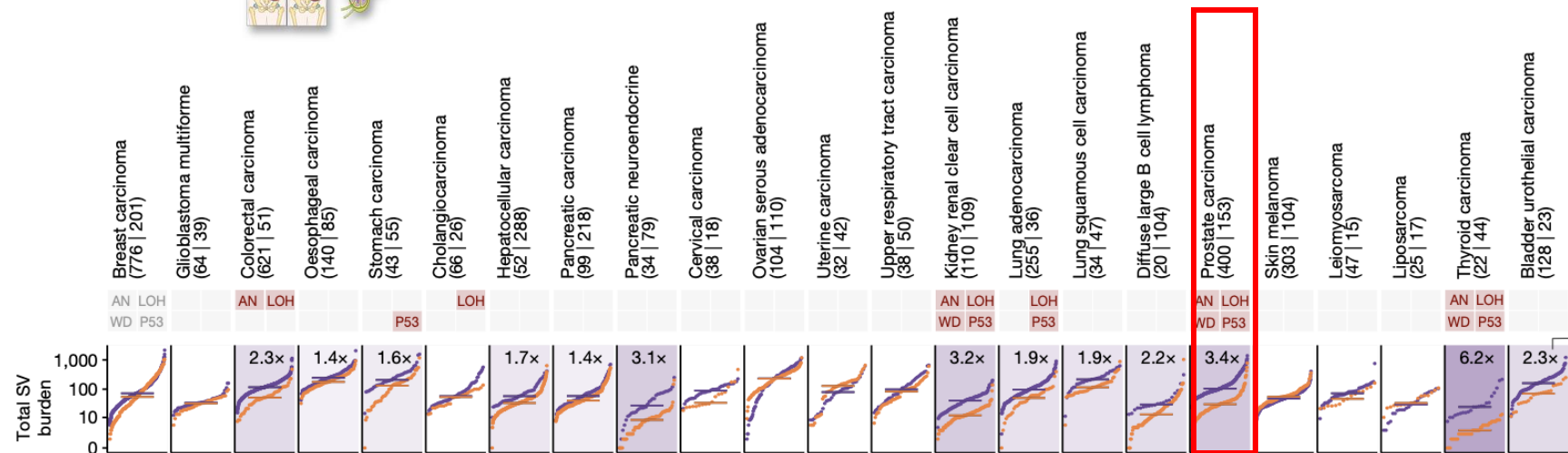
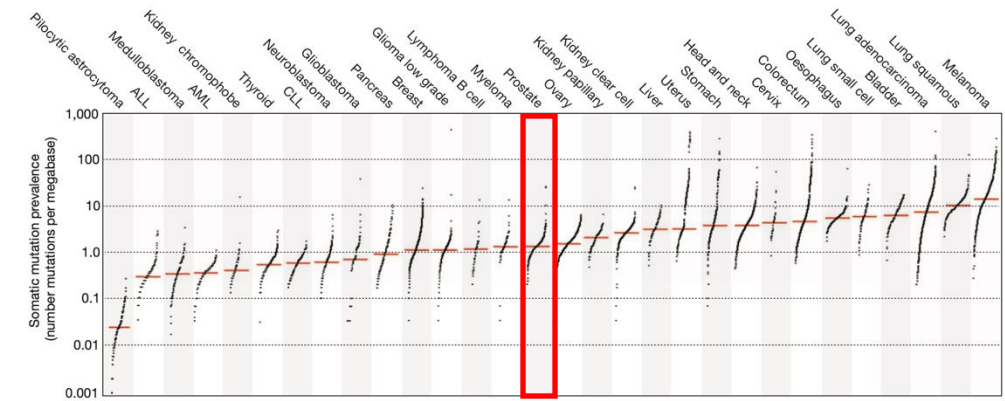
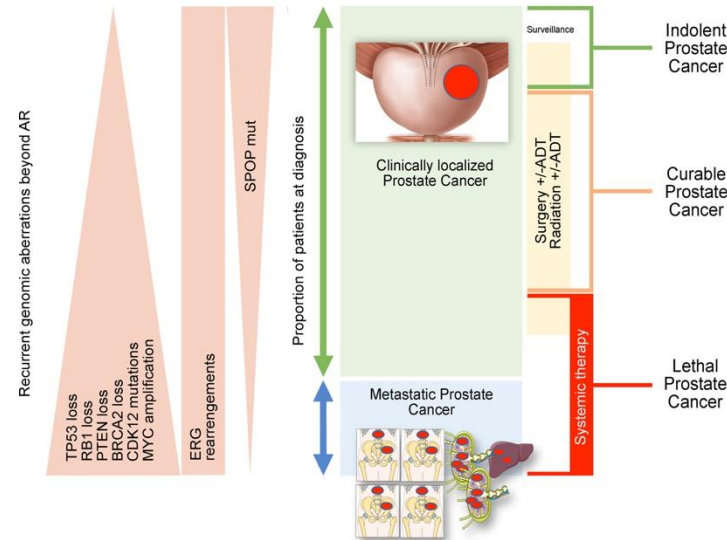
N = 19 607



Genetic or lifestyle group	All PCa deaths		Early PCa deaths		Late PCa deaths	
	Events/PY	HR (95% CI) ^a	Events/PY	HR (95% CI) ^a	Events/PY	HR (95% CI) ^a
PRS^b						
0%-50%	122/313 414	1 [Reference]	26/194 533	1 [Reference]	96/118 837	1 [Reference]
50%-100%	322/296 471	2.87 (2.32-3.54)	81/188 659	3.19 (2.03-5.01)	241/107 792	2.77 (2.18-3.51)
Family history of cancer^b						
No	241/422 111	1 [Reference]	47/263 167	1 [Reference]	194/158 900	1 [Reference]
Yes	203/187 775	1.33 (1.10-1.61)	60/120 026	2.10 (1.42-3.10)	143/67 728	1.15 (0.92-1.43)
Combined genetic risk^c						
Lower: PRS 0%-50% and no family history	71/221 560	1 [Reference]	13/137 090	1 [Reference]	58/84 441	1 [Reference]
Higher: PRS 50%-100% or family history	373/388 326	2.48 (1.92-3.20)	94/246 101	3.26 (1.82-5.84)	279/142 188	2.26 (1.70-3.01)

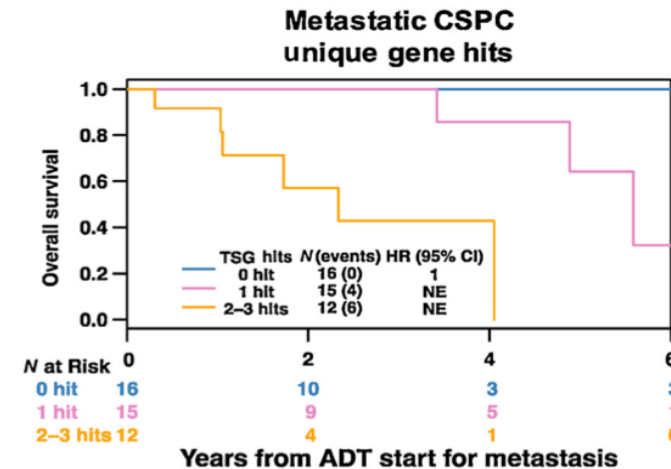
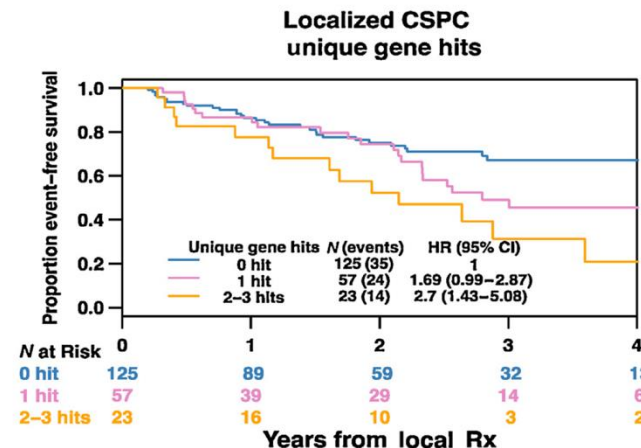
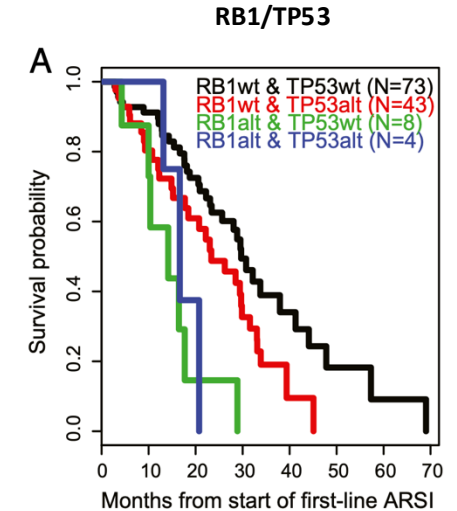
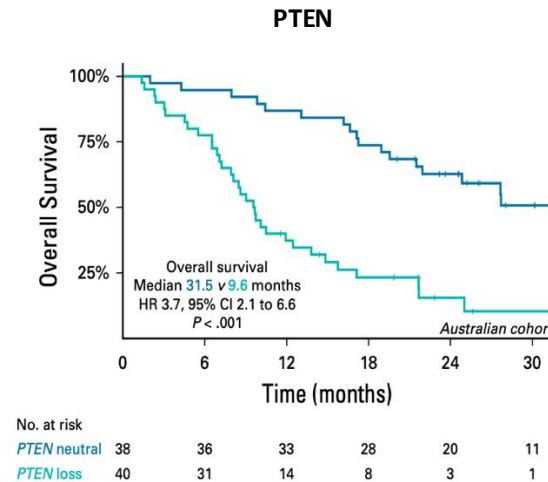
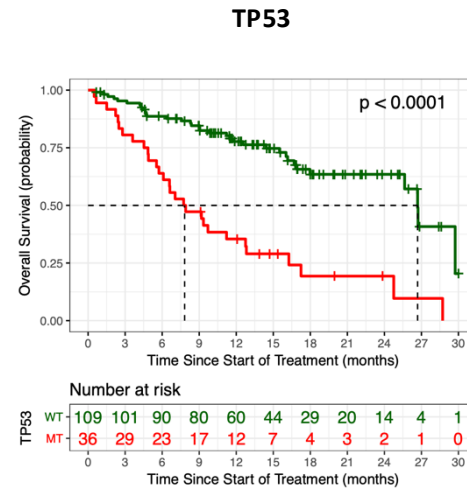
Genomic characteristics of lethal prostate cancer

- **Somatic burden**
 - Relatively low somatic mutation rate
 - More genomic instability (GIS)
 - Frequent copy number alterations and structural rearrangements
 - Most classes of alterations are more frequent in advanced disease



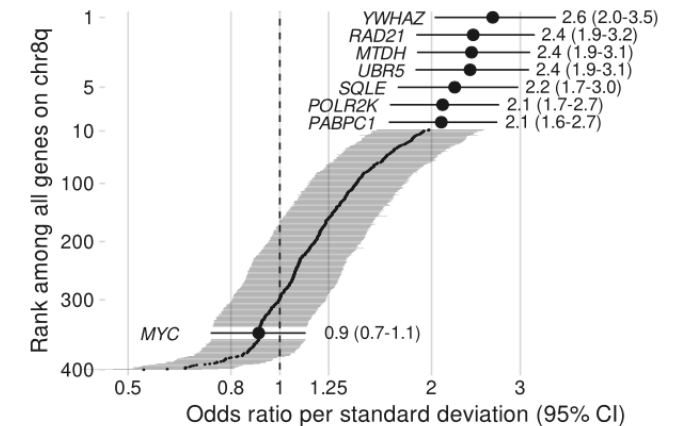
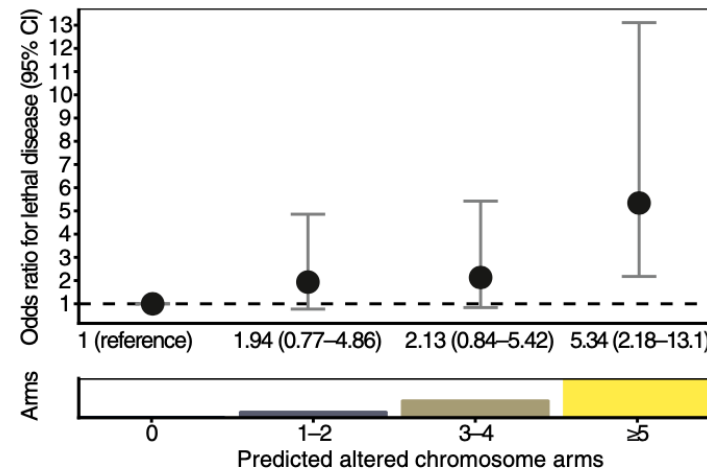
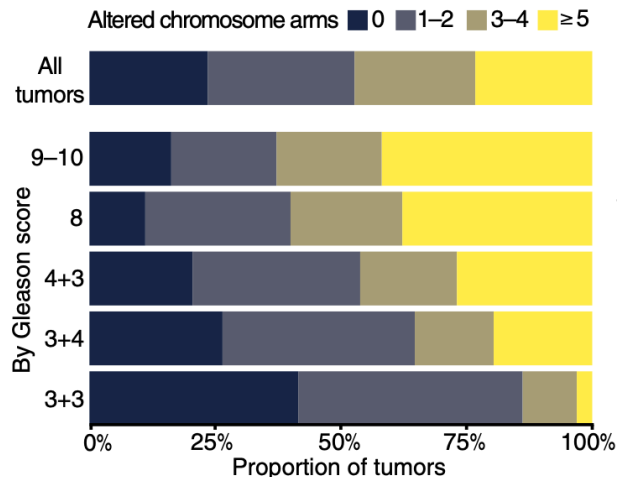
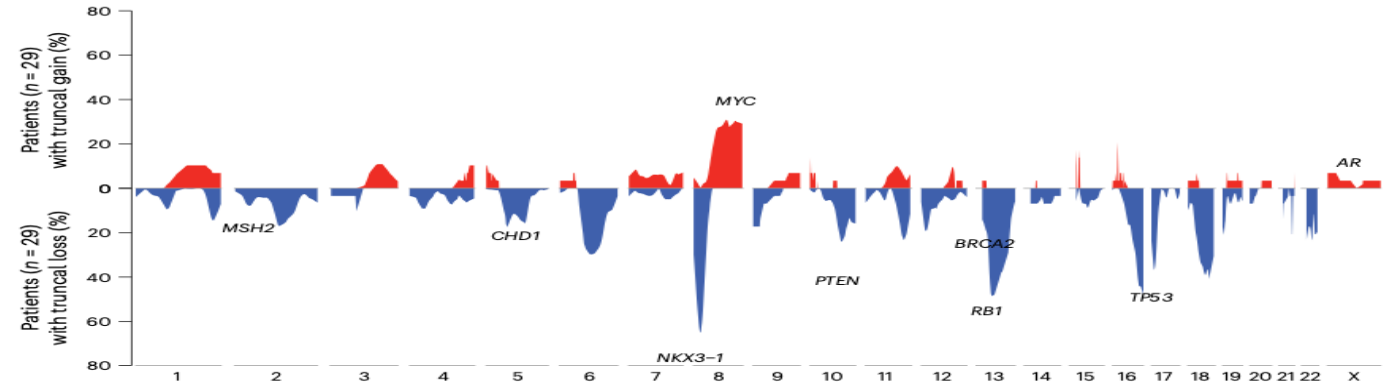
Genomic characteristics of lethal prostate cancer

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



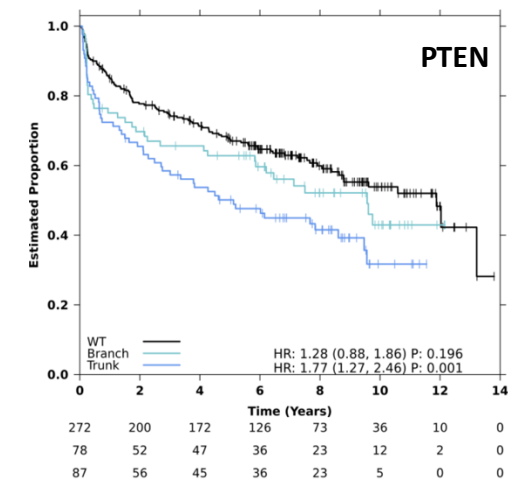
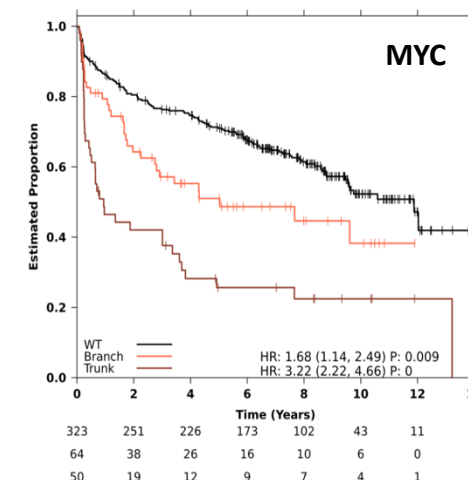
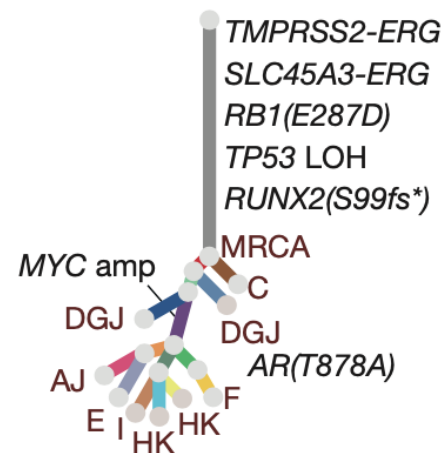
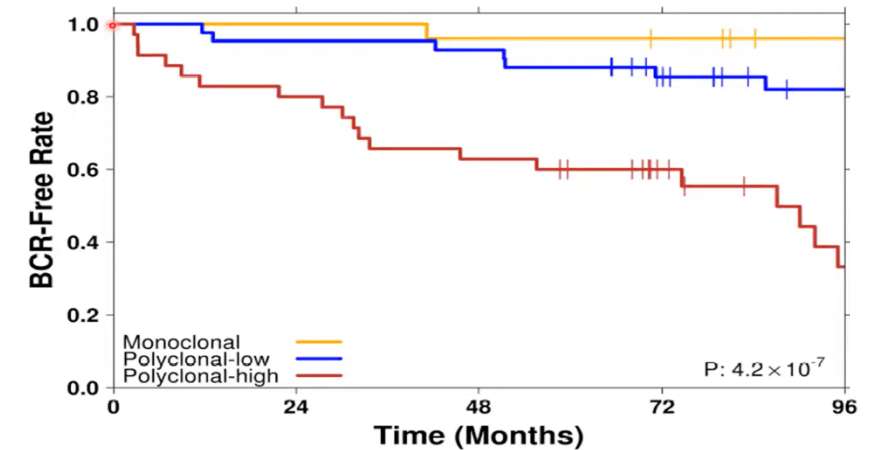
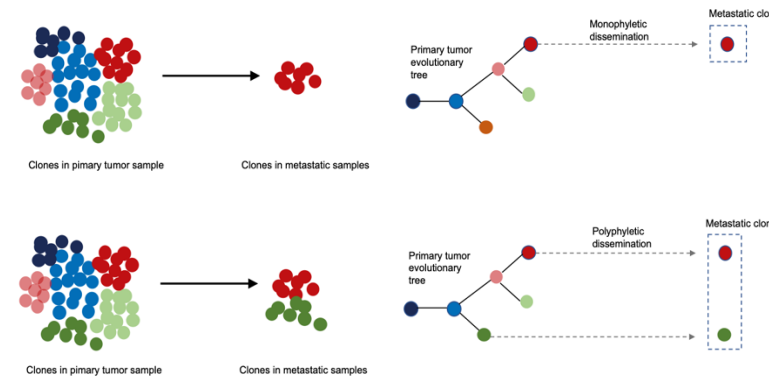
Genomic characteristics of lethal prostate cancer

- 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 vs polyclonality
 - When a mutation occurs matters
 - Trunk vs branch
- Evolutionary behavior determines the impact of a mutation on patient outcome
 - Polyclonal and earlier events have a larger effect size



Molecular characteristics of lethal prostate cancer

Central Dogma of Molecular Biology

by
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The central dogma of molecular biology deals with the detailed residue-by-residue transfer of sequential information. It states that such information cannot be transferred from protein to either protein or nucleic acid.

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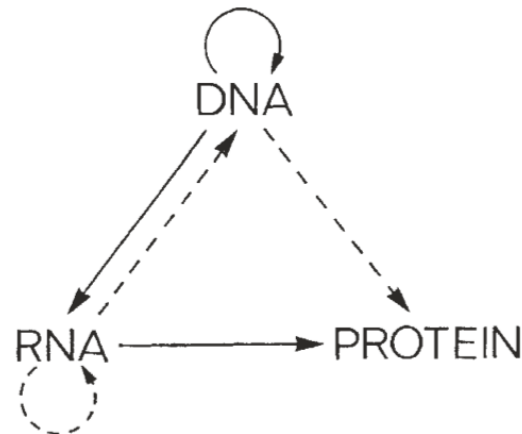
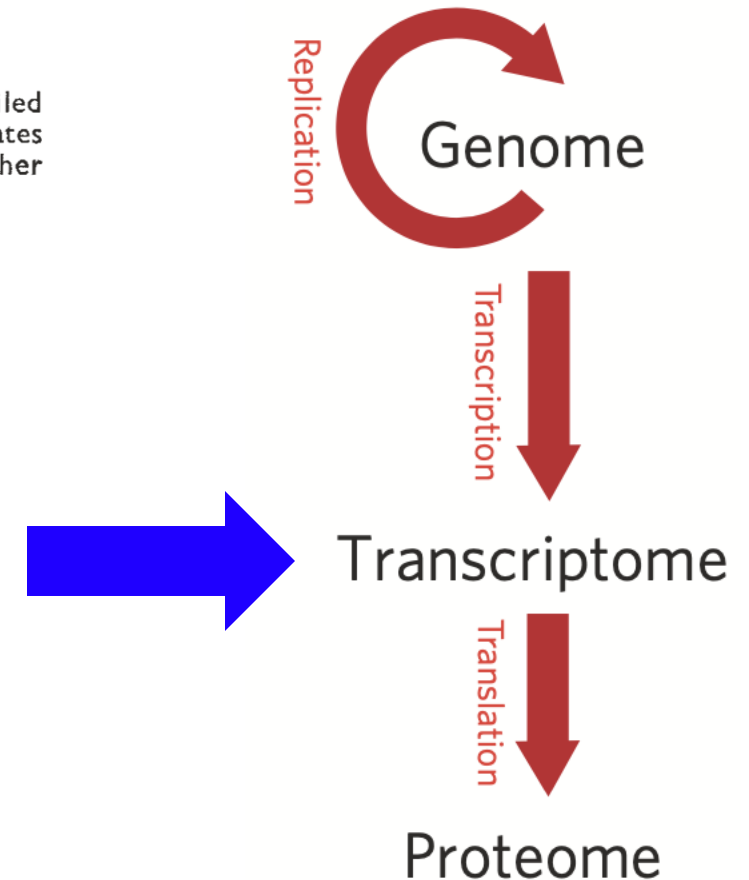
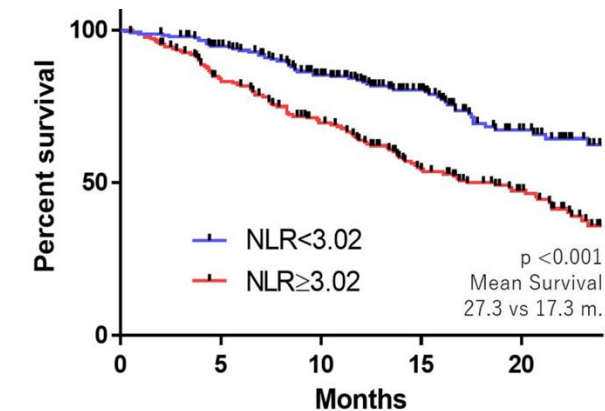
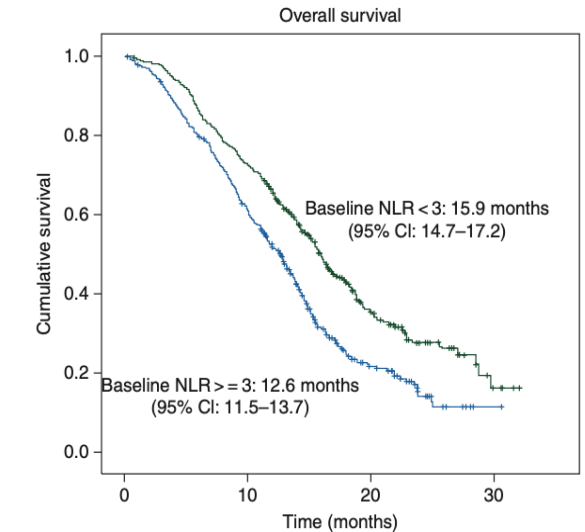
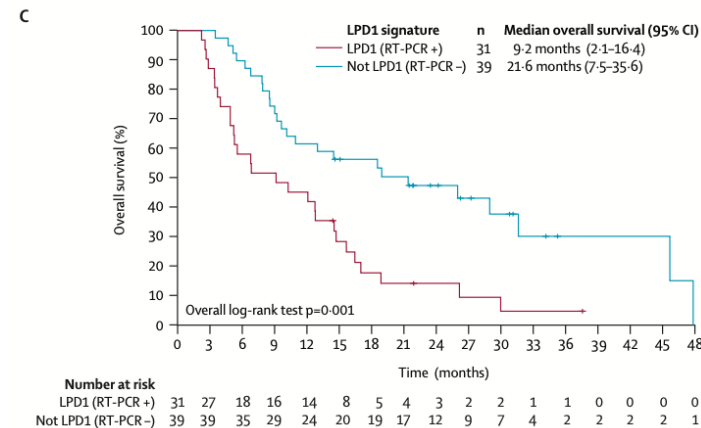
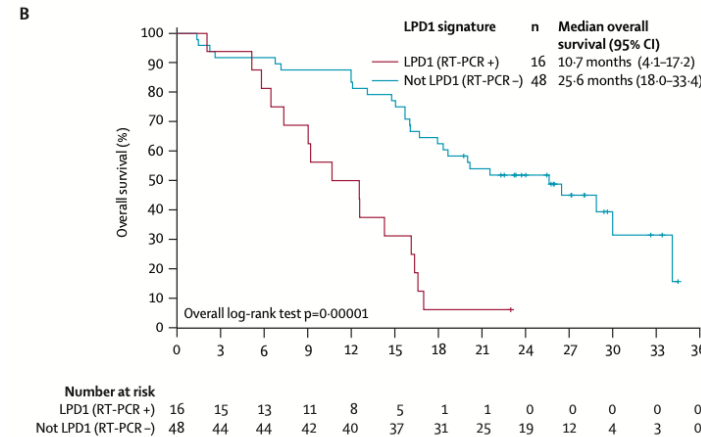
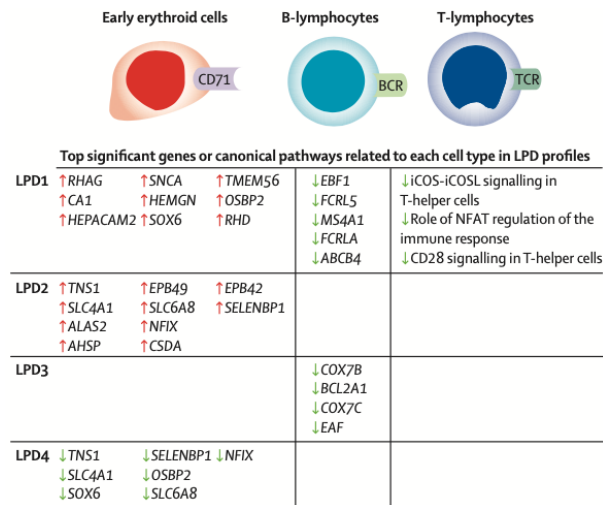


Fig. 3. A tentative classification for the present day. Solid arrows show general transfers; dotted arrows show special transfers. Again, the absent arrows are the undetected transfers specified by the central dogma.



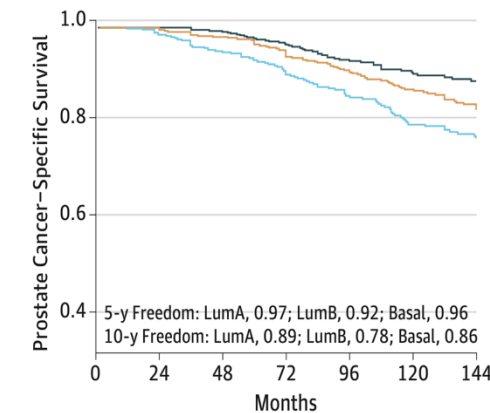
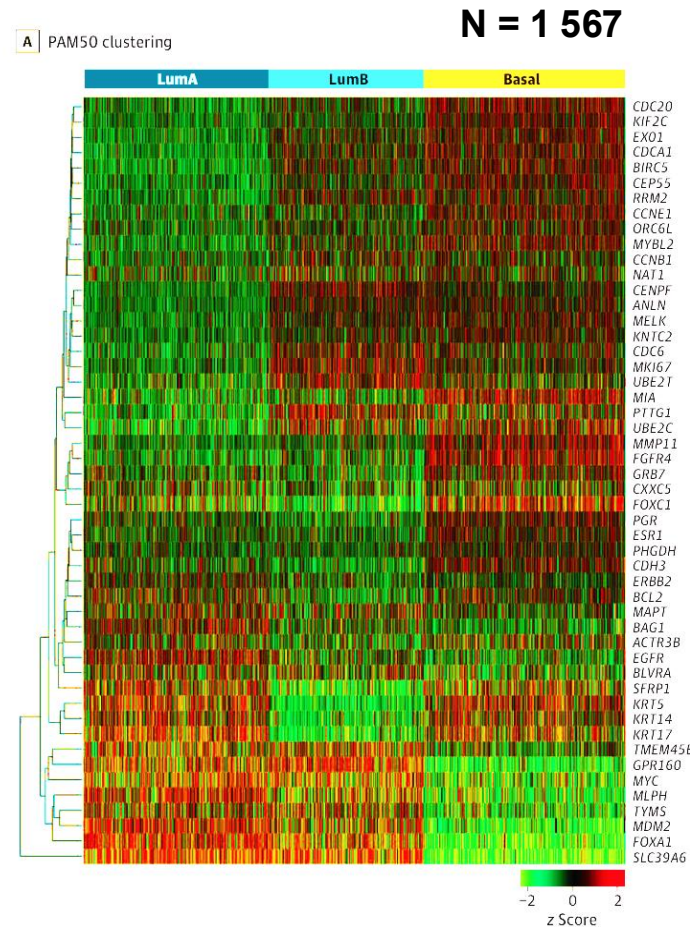
Transcriptomic characteristics of lethal prostate cancer

- Immunological burden
 - Blood mRNA expression signatures
 - a myeloid transcript signature associated with poor outcome
 - High NLR

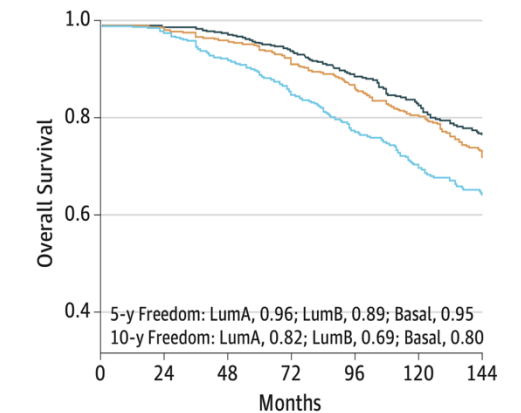


Transcriptomic characteristics of lethal prostate cancer

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

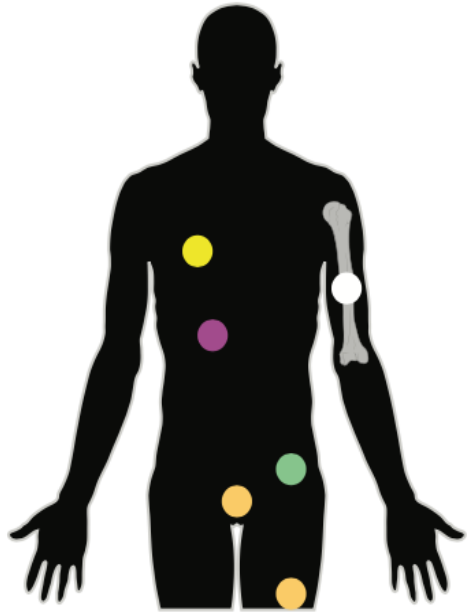


No. at risk							
LumA	493	491	476	397	323	262	188
LumB	412	404	371	304	239	195	150
Basal	526	519	501	438	358	283	211



No. at risk							
LumA	536	533	513	430	350	284	204
LumB	444	433	391	321	248	202	156
Basal	581	570	544	473	388	307	229

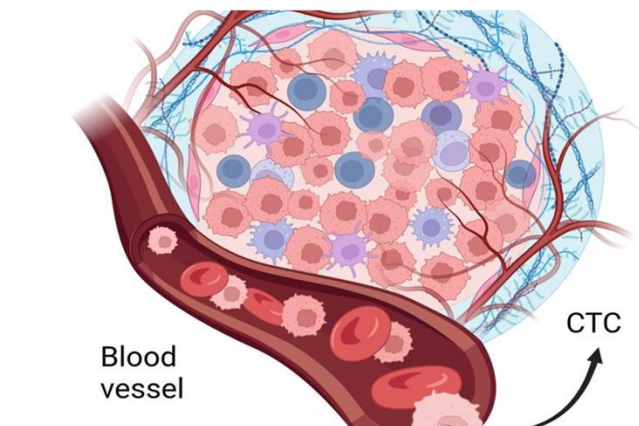
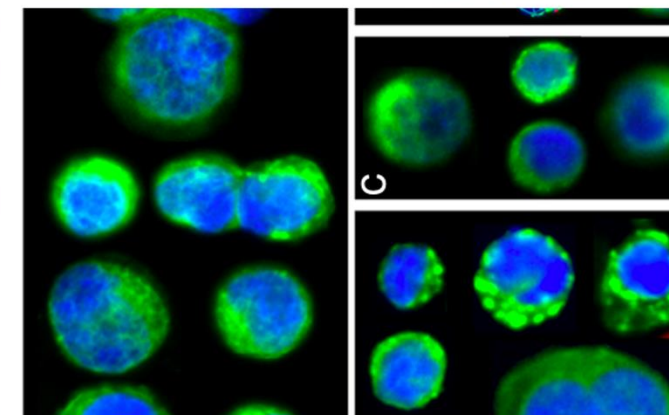
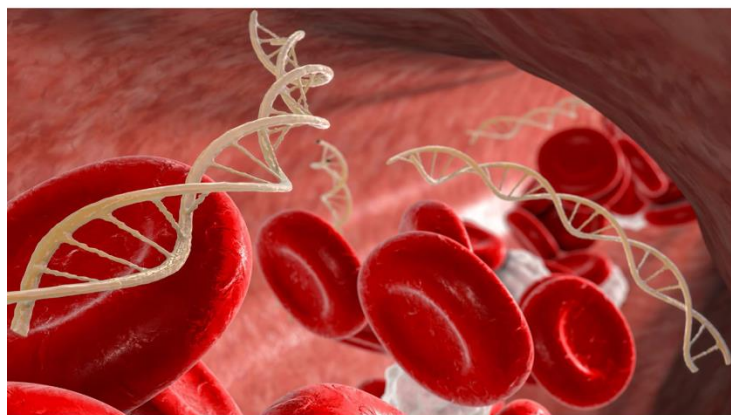
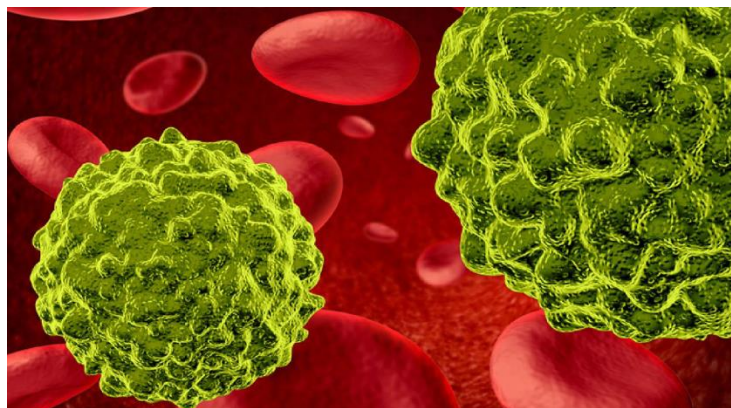
Molecular characteristics of lethal prostate cancer



Lethal
Prostate
Cancer

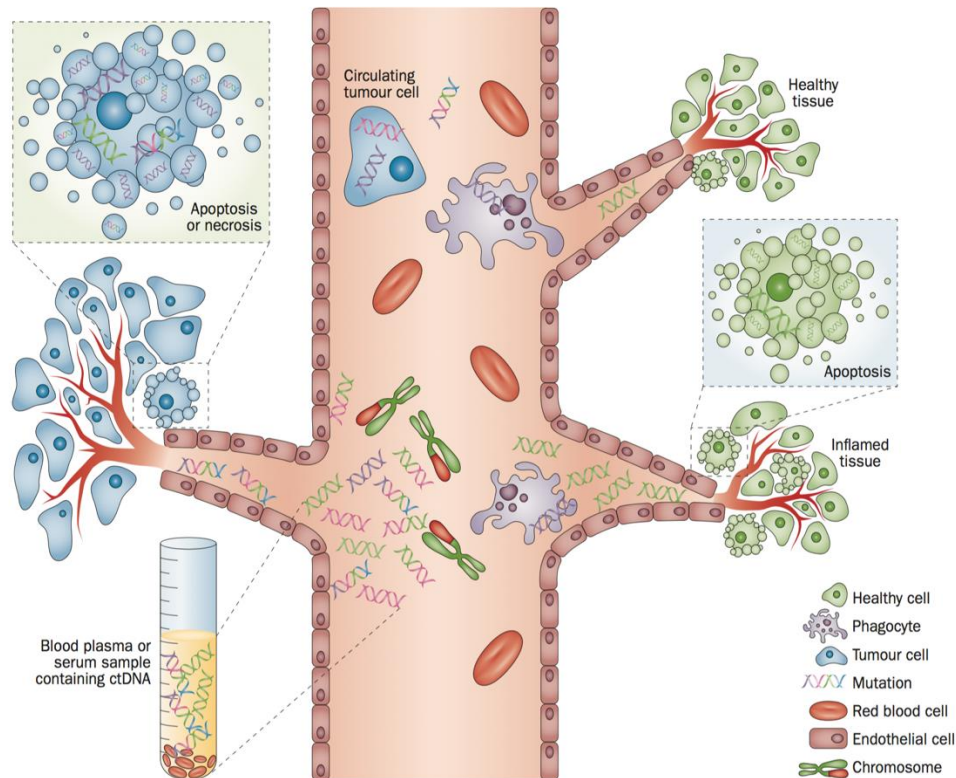
Molecular characteristics

- 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



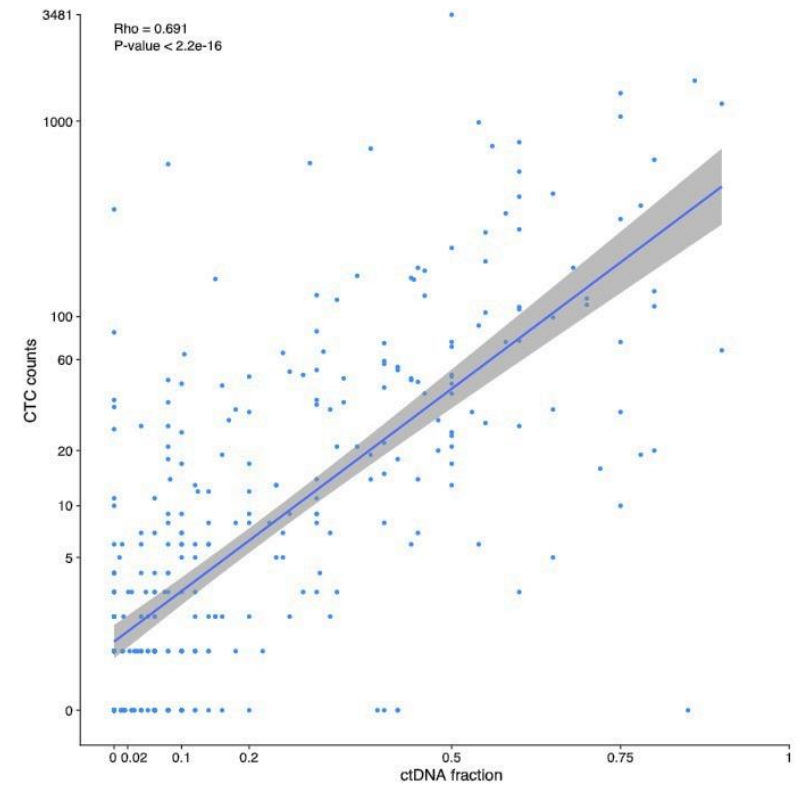
CTC



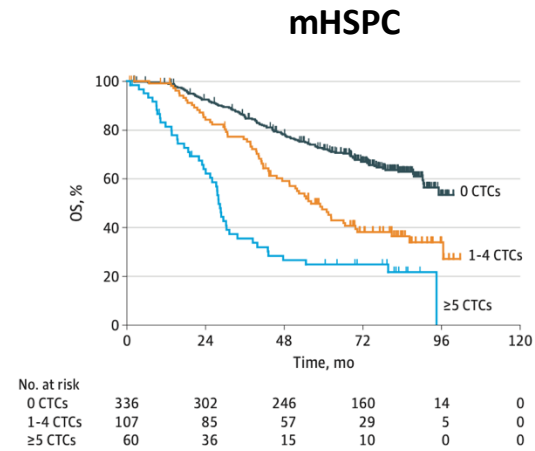
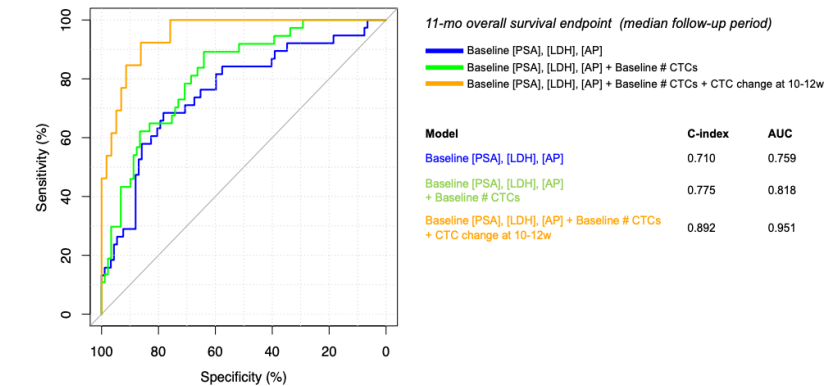
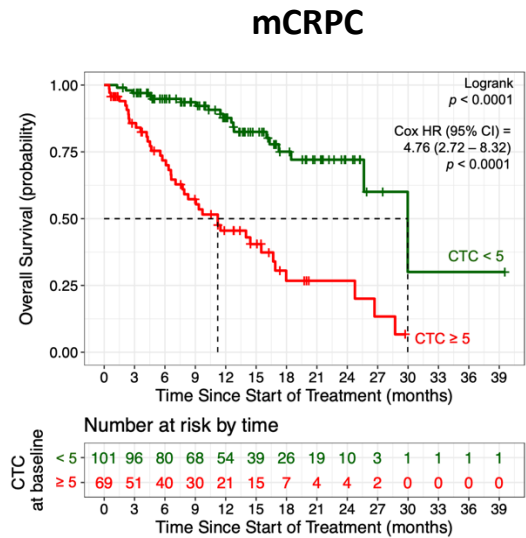
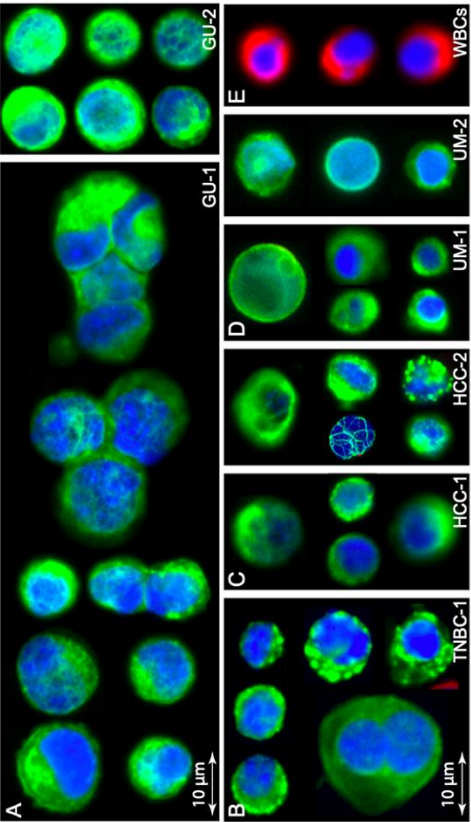
VS



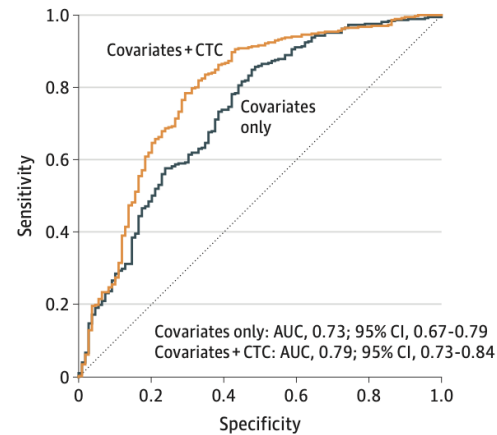
ctDNA



Circulating tumour burden vs lethality

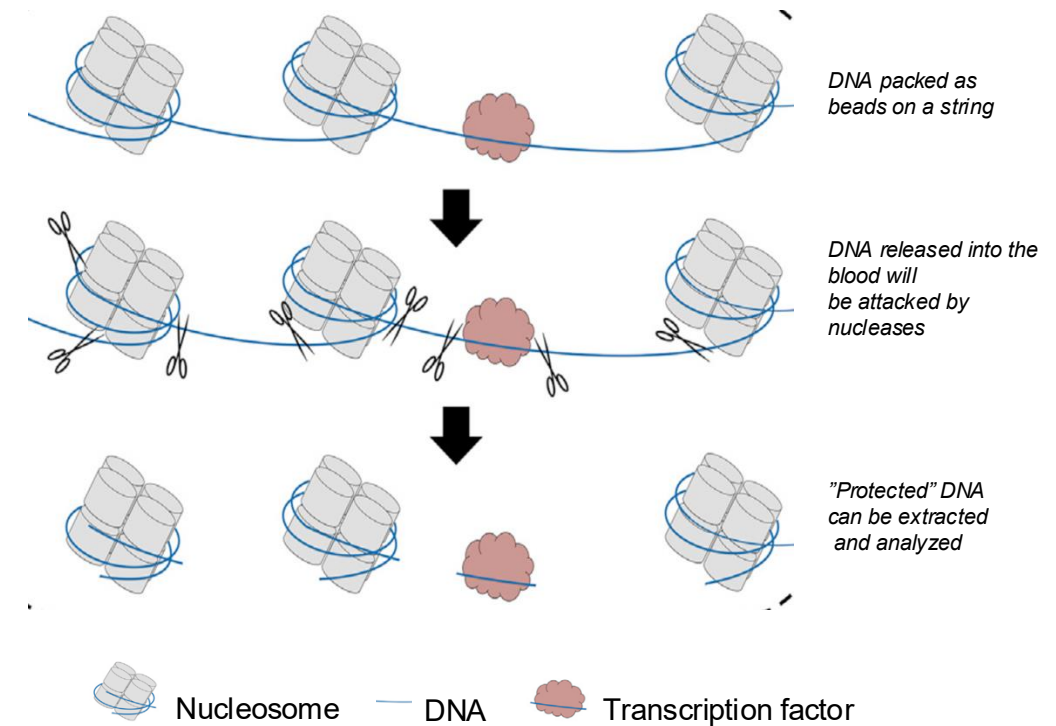
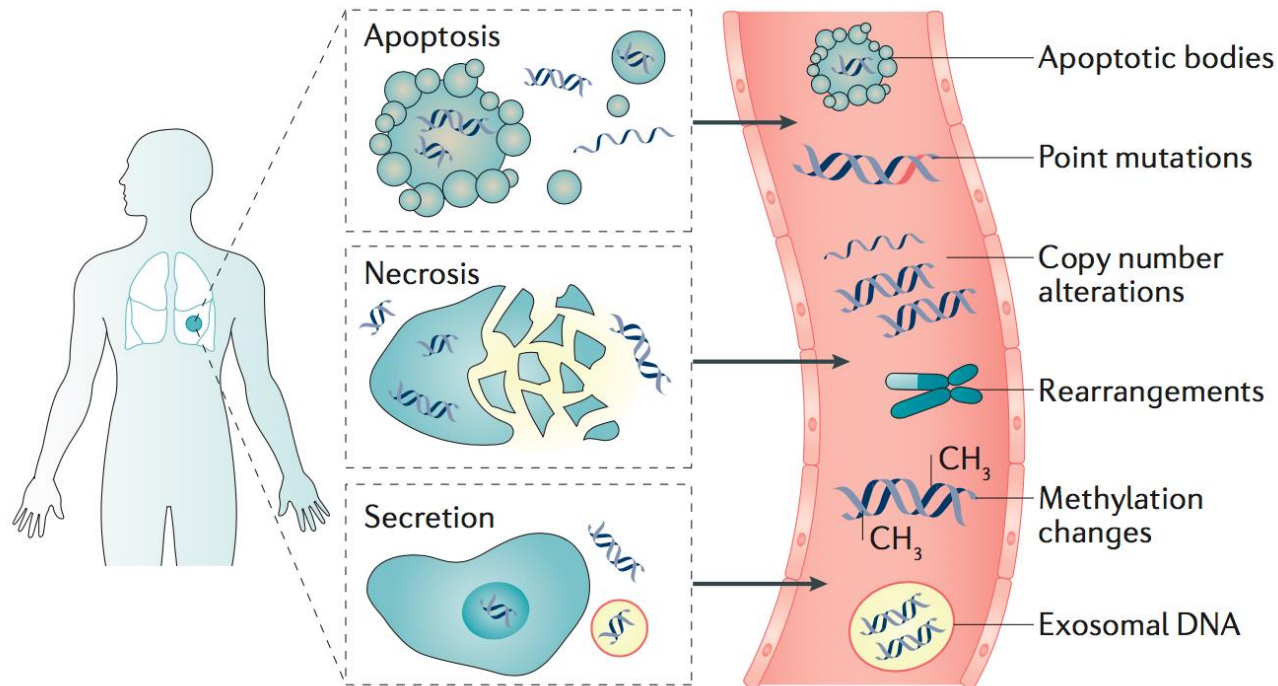


C ROC curves of prognostic value for 3-y OS



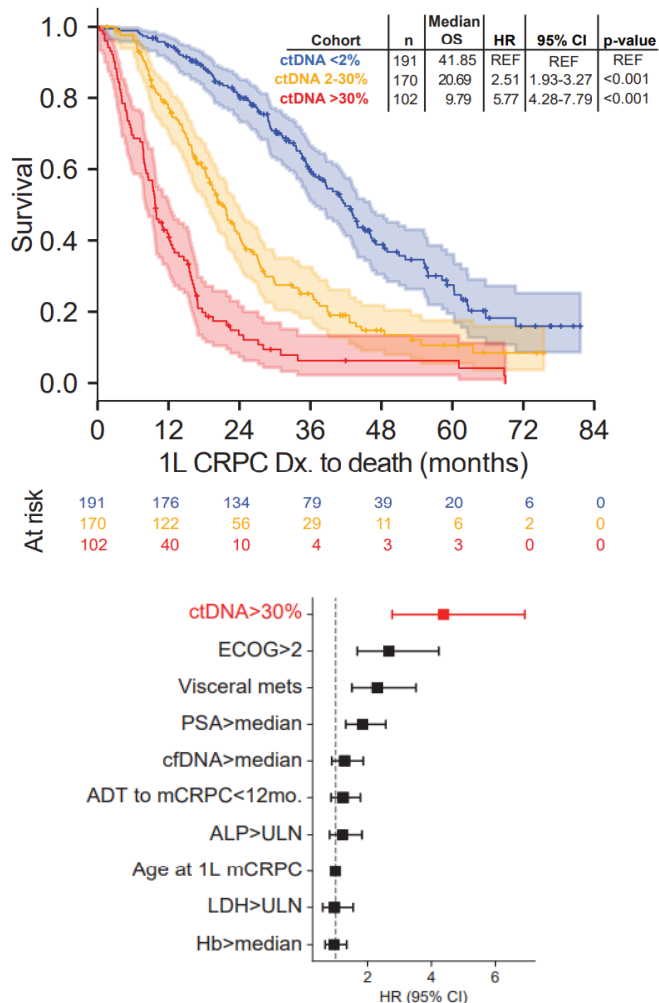
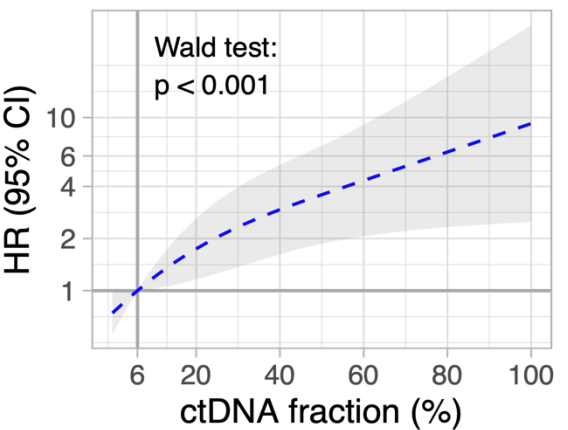
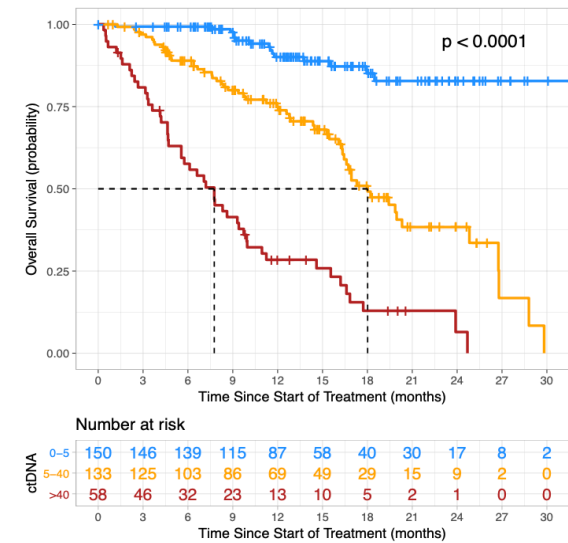
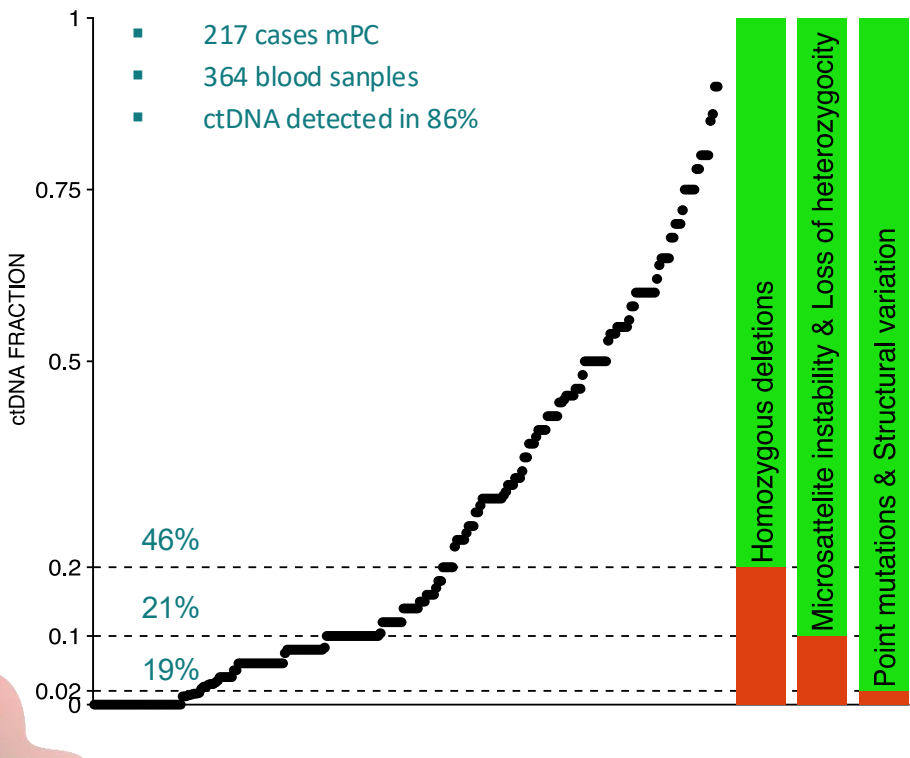
Circulating tumour burden vs lethality

- cfDNA originate (mostly) from apoptotic cells

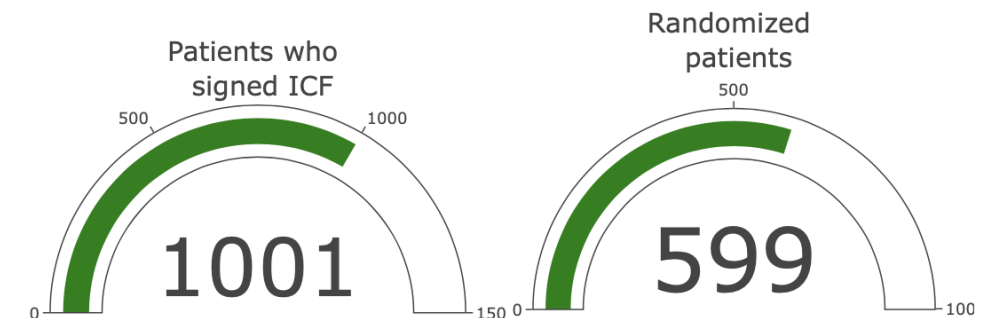
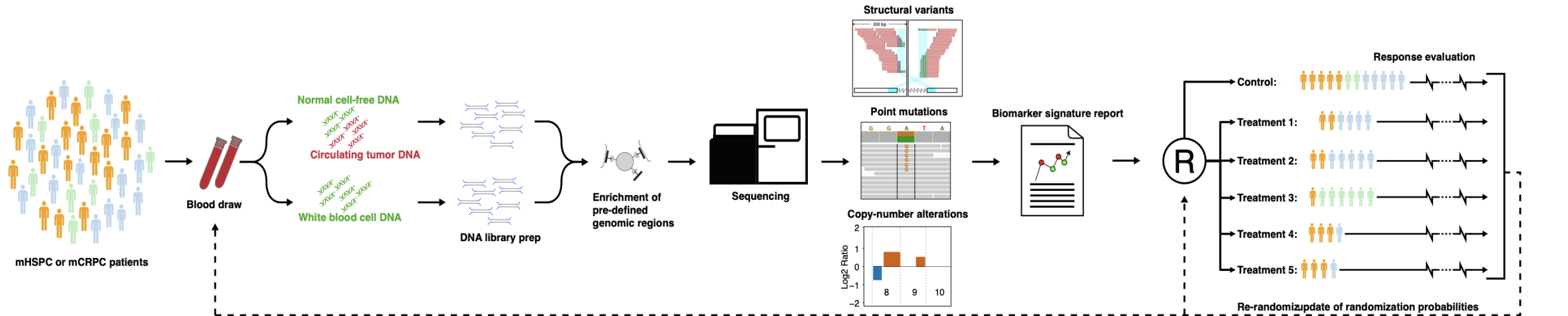


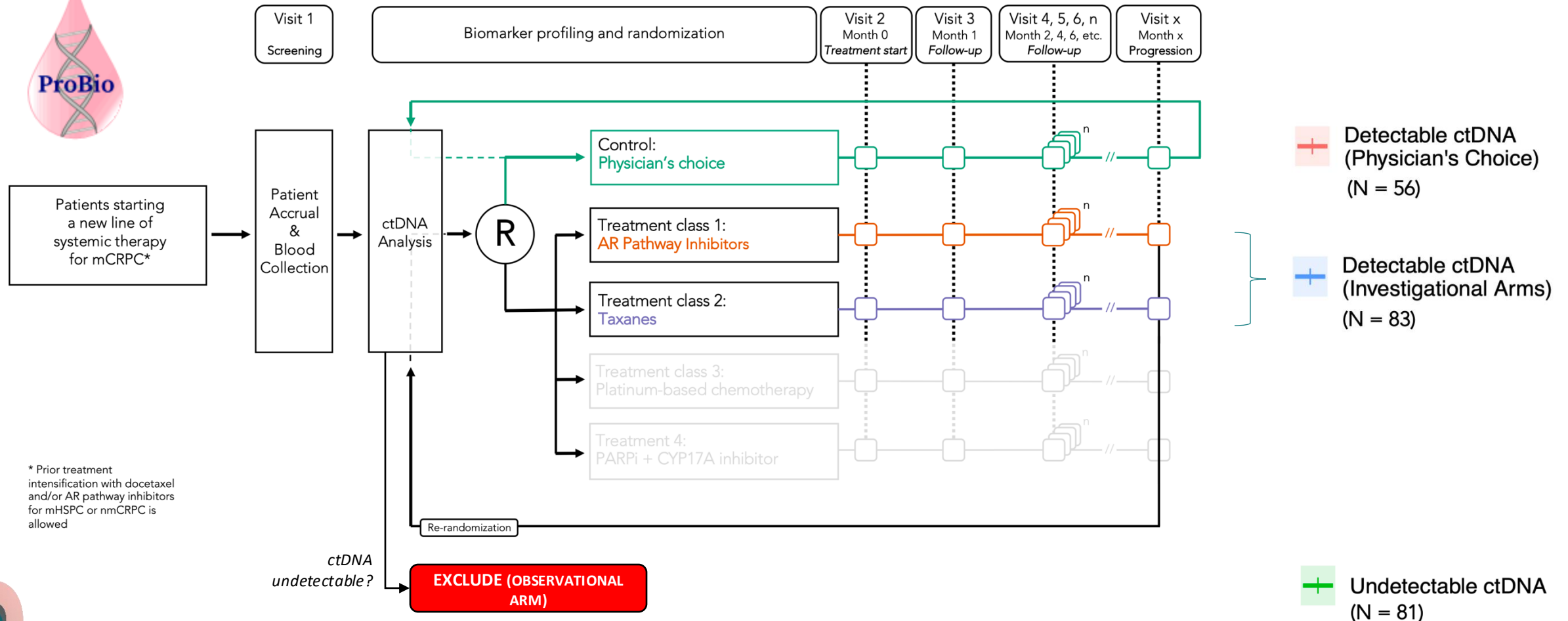
Circulating tumour burden vs lethality

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

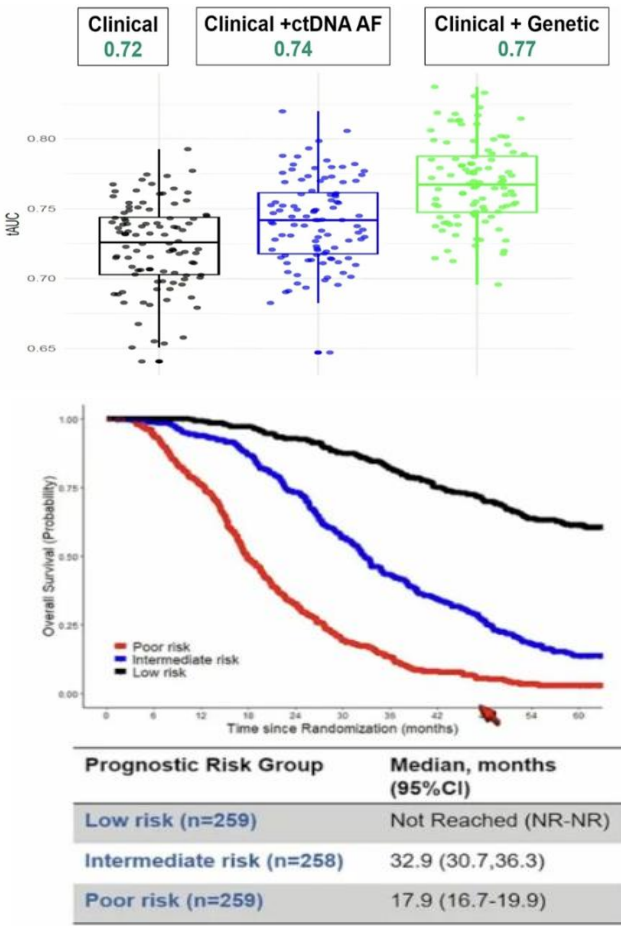
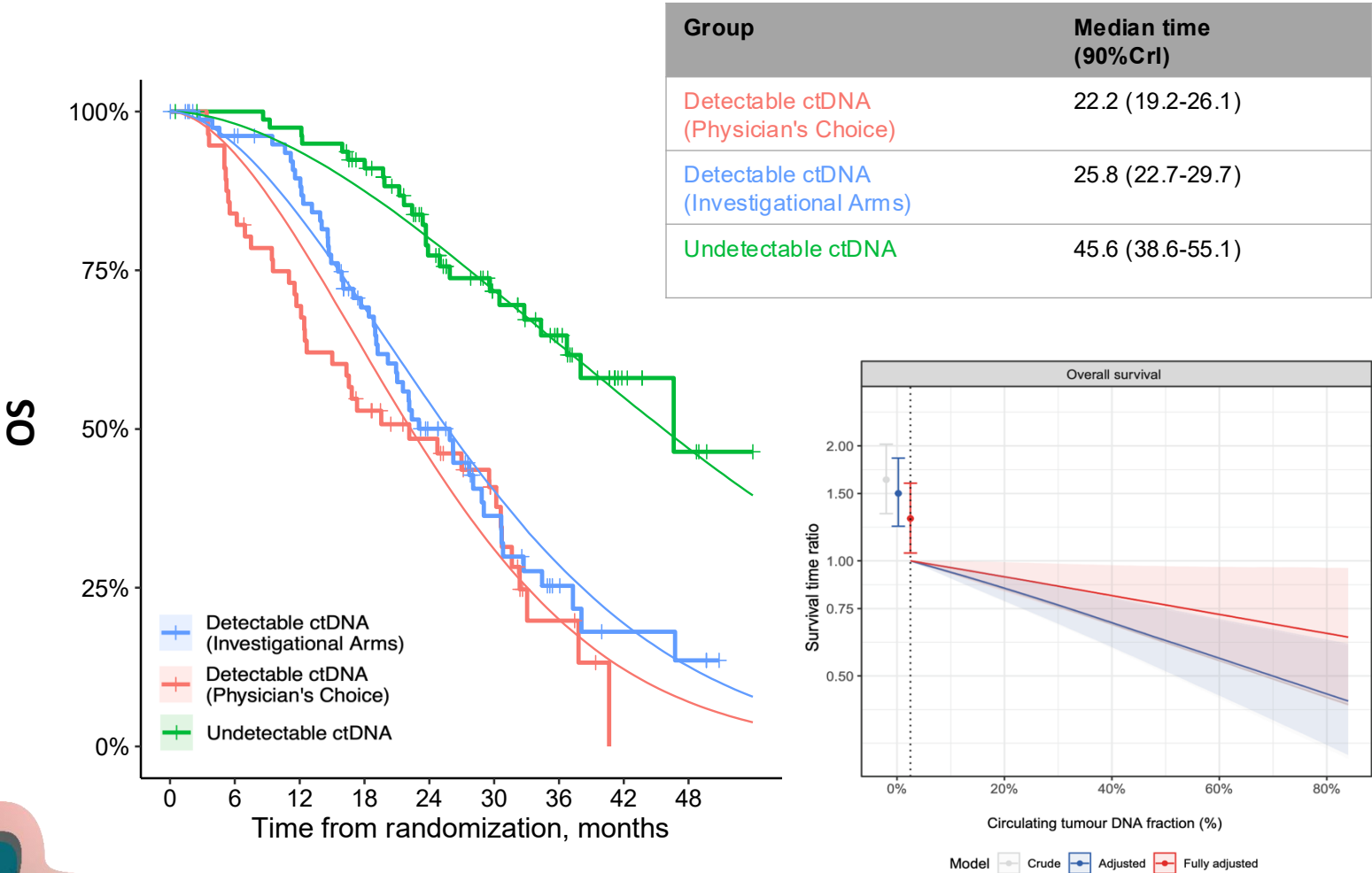


Circulating tumour burden vs lethality

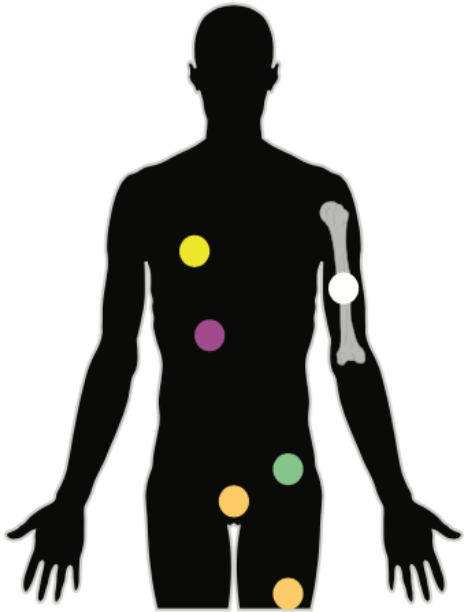




Circulating tumour burden vs lethality



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?

Clinical characteristics

- Differentiation grade
 - ISUP/Gleason
- PSA
- Aggressive phenotypes
 - NEPC/small cell
- Metastasis burden
 - Volume of disease
 - Visceral involvement
- M1 Timing
- FDG discordant/PSMA low disease

Biology and cellular pathways

- Lineage plasticity
- Transcriptional/pathway regulators
- PAM50 molecular subtypes
- Novel targets (Onecut2, EZH2)

Genetics

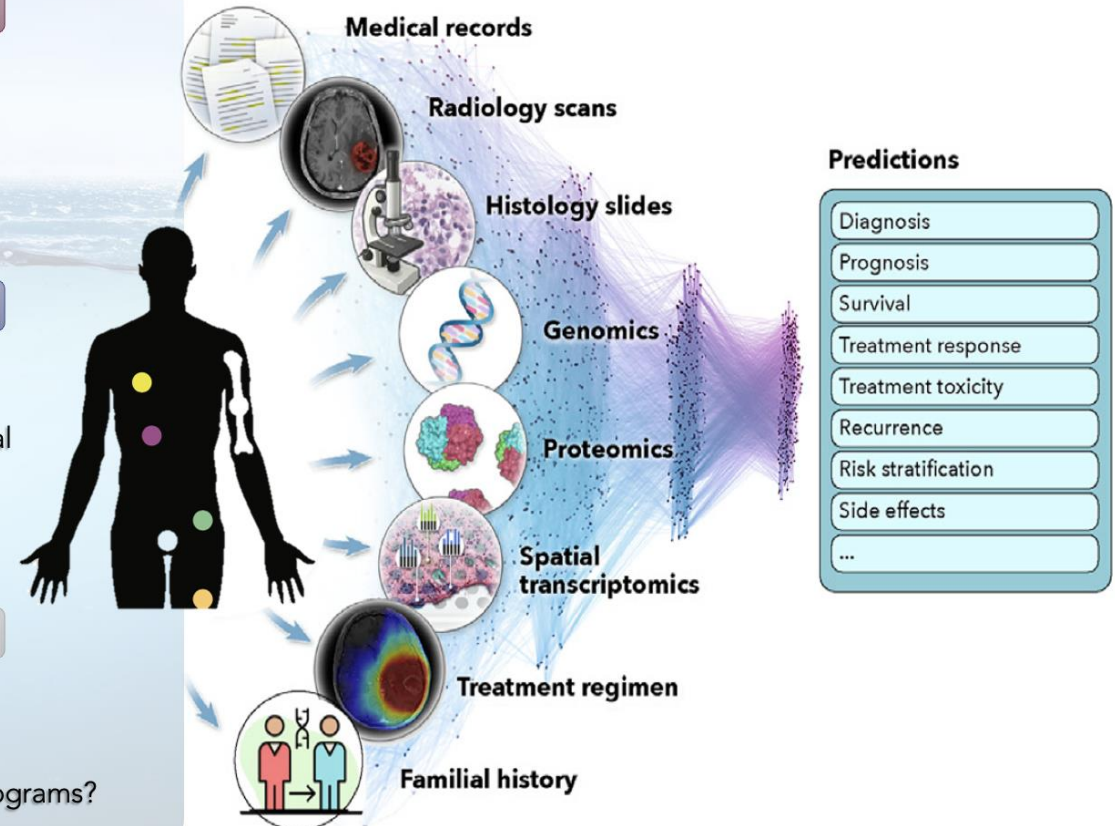
- Hereditary burden
 - HBOC
 - Lynch
- Rare drivers
- PRS

Tumor genomics

- Oncogene/Ts landscape
- GIS/aneuploidy
- Chromotrypsis/plexy & structural variation
- Epigenomics

Novel tools

- Circulating tumor burden
 - CTC
 - ctDNA
- Towards ctDNA-informed nomograms?



Acknowledgments



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