Predictors of Outcome in Prostate Cancer

Shibu Thomas, Ph.D.

Disclosures:
Employee of Janssen R&D

Epidemiology of prostate cancer (Pca)

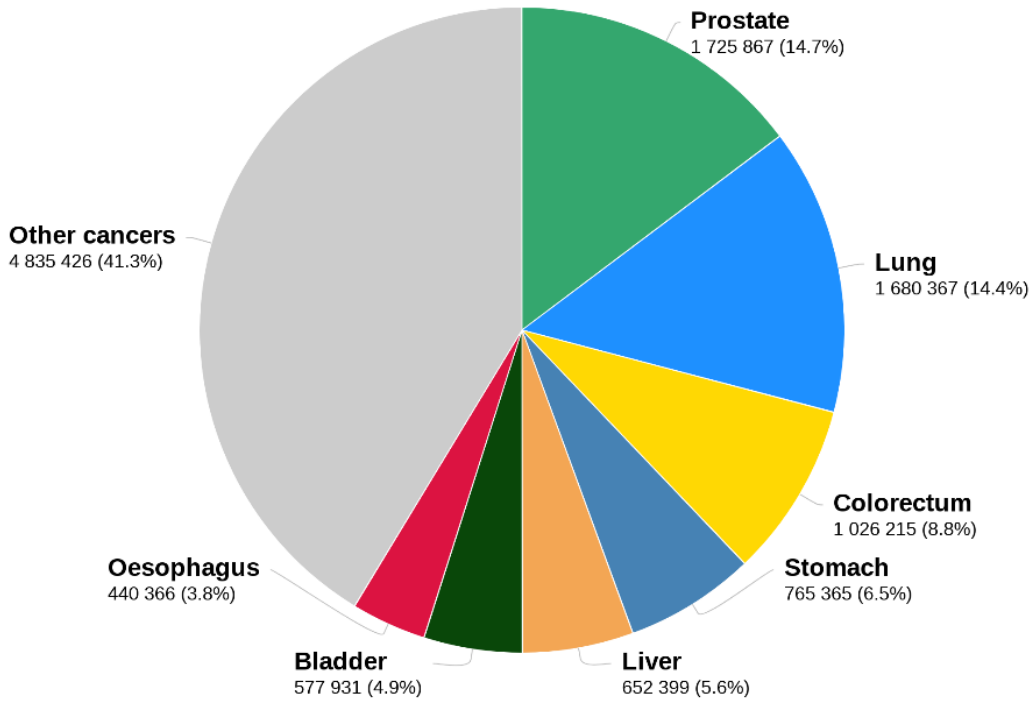
- **Most commonly** diagnosed cancer in men in both the United States and Europe.

- Incidence and mortality due to PCa are associated:
  - with old age
  - family history
  - race (e.g. ~60% more in African-American).

- Prostate cancer was ranked fourth in Europe among the cancers with the best prognosis. **5-year** relative survival was 83%.

- Patients with metastatic prostate cancer have a poor prognosis and median survival is less than 2 years.

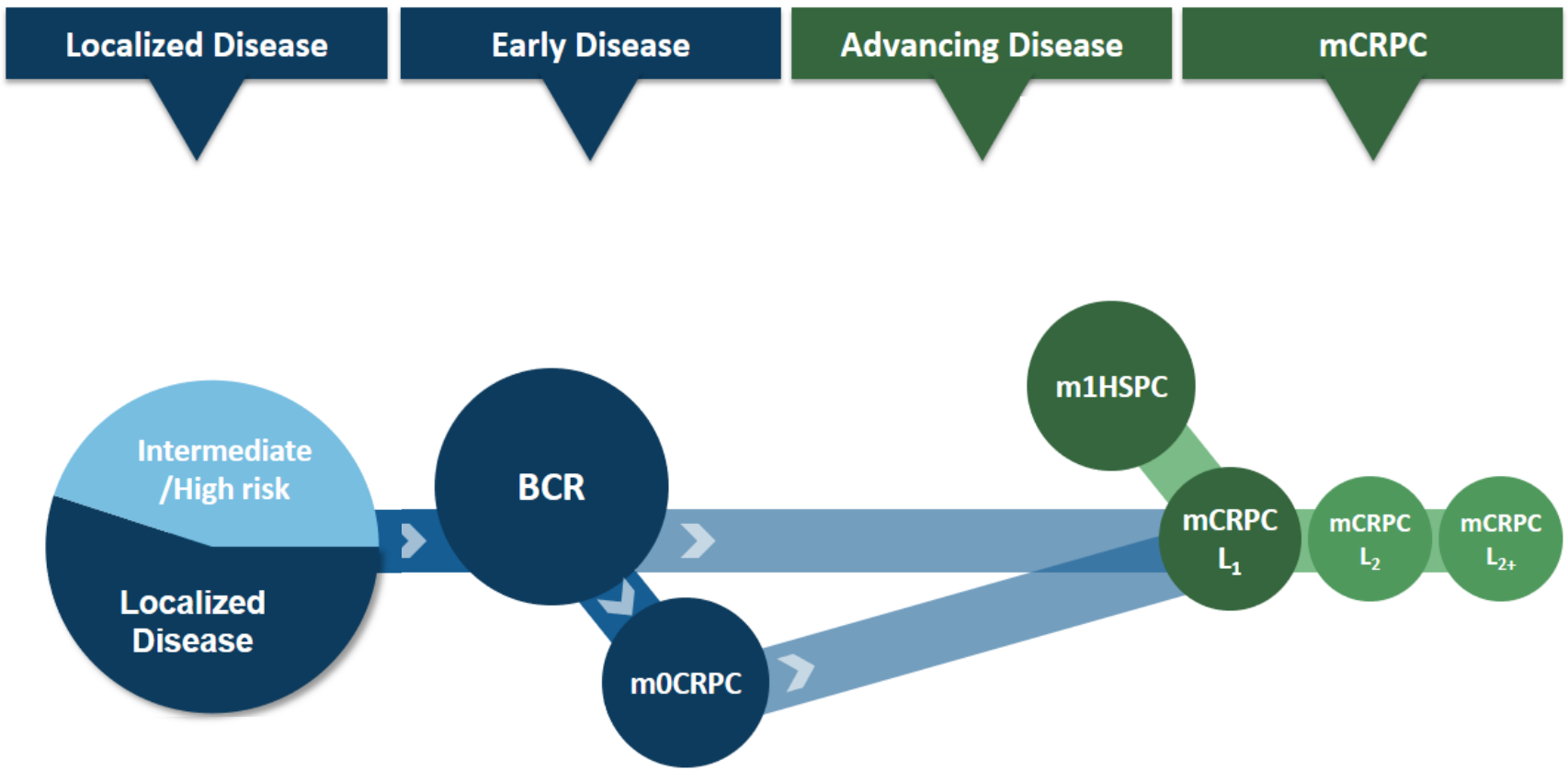
WHO estimated number of new cases in 2018 in Europe (all cancer, males, all ages)



Total : 11 703 936

Merseburger et al 2013 *Oncologist*

Prostate cancer disease segments



Clinical risk stratification: NCCN & CAPRA nomogram

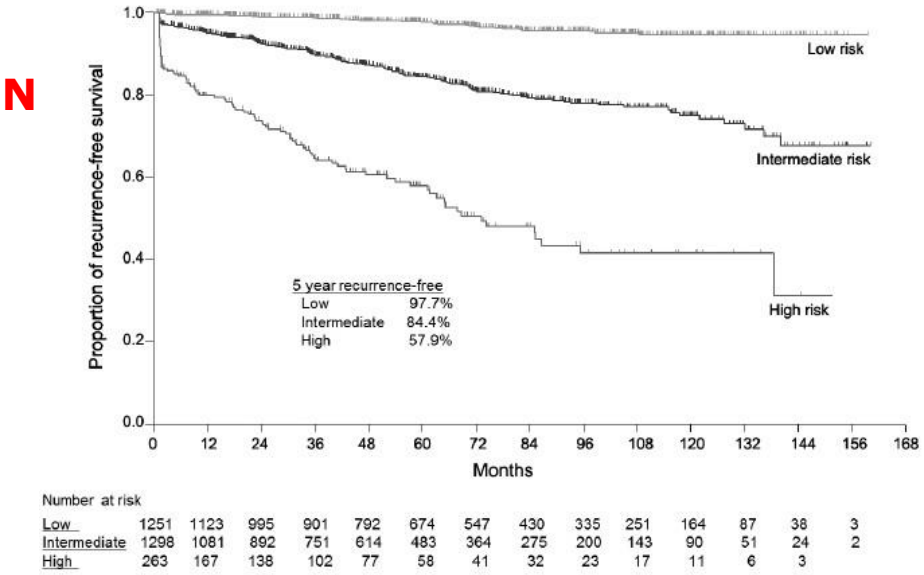
Risk stratification criteria for men with localised prostate cancer					
	PSA (ng/ml)		Gleason score		Clinical stage
Low risk	< 10	and	≤ 6	and	T1–T2a
Intermediate risk	10–20	or	7	or	T2b–T2c
High risk	> 20	or	8–10	or	T3–T4

National Comprehensive Cancer Network (NCCN)

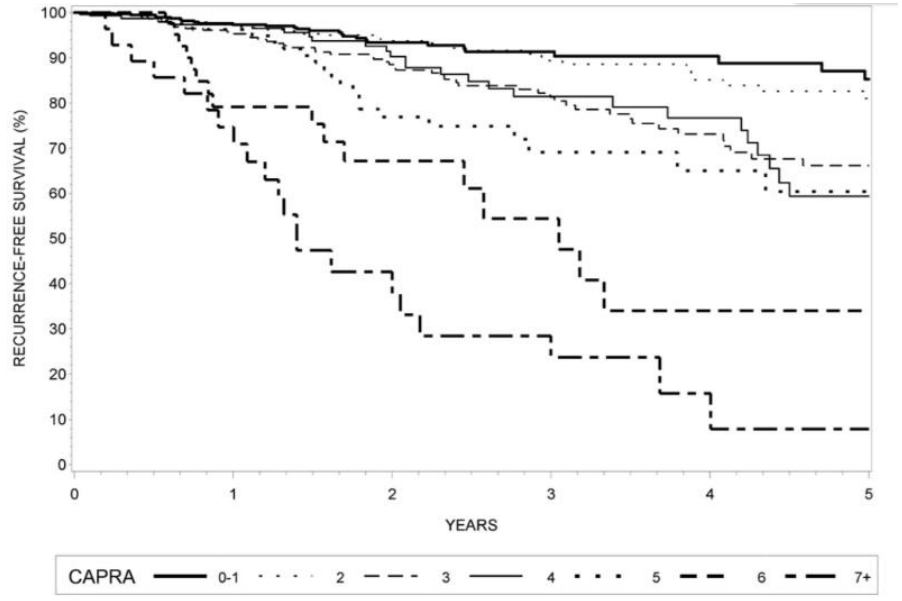
1. CAPRA score system added two risk factors "age at diagnosis" and "percentage of biopsy cores involved with cancer" to NCCN

2. Both NCCN and CAPRA risk stratification strategies are associated with recurrence-free survival of prostate cancer patients.

NCCN



CAPRA



Survival curves for 5-year recurrence-free survival among patients with each UCSF-CAPRA score

Clinical risk stratification: AUA & EAU nomogram

AUA nomogram

TABLE 3: Risk Stratification for Localized Prostate Cancer	
Very Low Risk	PSA <10 ng/ml AND Grade Group 1 AND clinical stage T1-T2a AND <34% of biopsy cores positive AND no core with >50% involved, AND PSA density <0.15 ng/ml/cc
Low Risk	PSA <10 ng/ml AND Grade Group 1 AND clinical stage T1-T2a
Intermediate Risk	PSA 10-<20 ng/ml OR Grade Group 2-3 OR clinical stage T2b-c • Favorable: Grade Group 1 (with PSA 10-<20) OR Grade Group 2 (with PSA<10) • Unfavorable: Grade Group 2 (with either PSA 10-<20 or clinical stage T2b-c) OR Grade Group 3 (with PSA < 20)
High Risk	PSA ≥20 ng/ml OR Grade Group 4-5 OR clinical stage ≥T3*
*Clinical stage T3 cancer is considered locally advanced and, therefore, outside the scope of this guideline.	

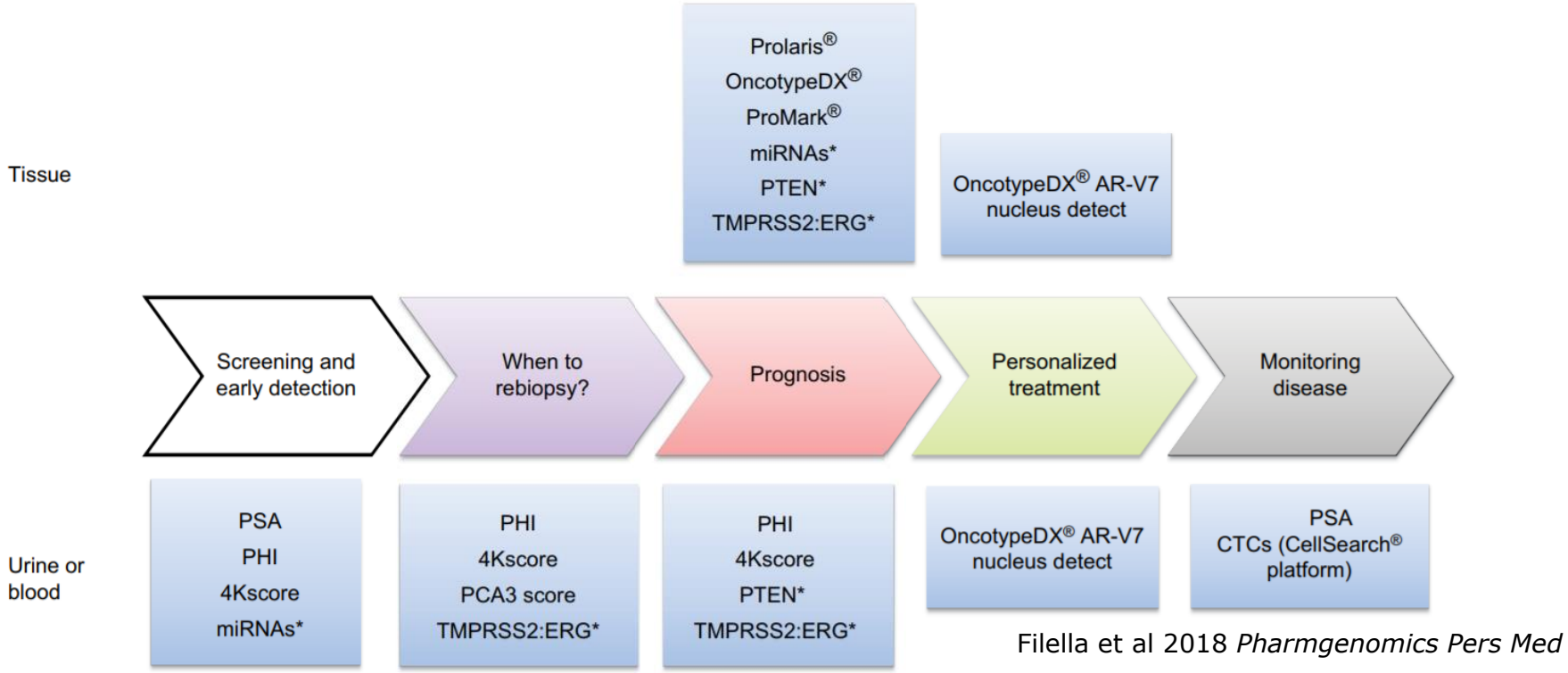
Risk Groups	Gleason	5 year BCR risk free survival
1	3+3	96%
2	3+4	88%
3	4+3	63%
4	4+4	48%
5	4+5, 5+4, 5+5	26%

EAU nomogram

	Low-risk	Intermediate-risk	High-risk	
Definition	PSA < 10 ng / mL and GS < 7 and cT1-2a	PSA 10-20 ng /mL or GS 7 or cT2b	PSA > 20 ng / mL or GS > 7 or cT2c	any PSA any GS cT3-4 or cN+
	Localised			**Locally advanced**

PSA = prostate-specific antigen.

Risk stratification incorporating molecular tests



Filella et al 2018 *Pharmgenomics Pers Med*

- Gleason score is a single independent predictor of aggressive disease
- Can molecular classifier be superior to clinical-pathologic features in predicting aggressive disease?

Molecular tests available

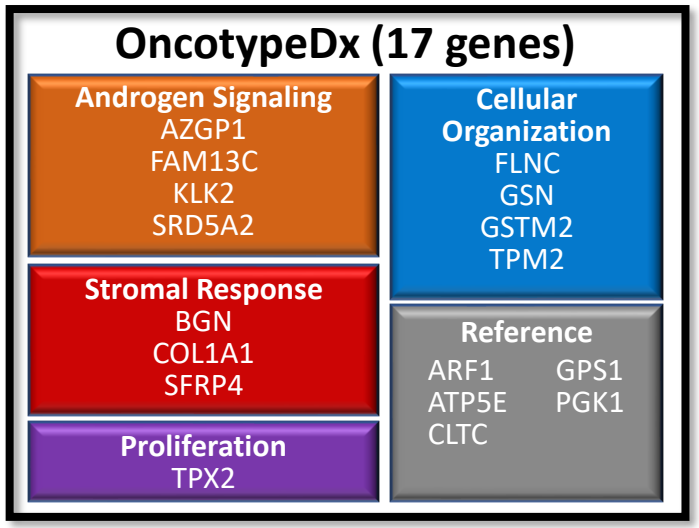
Table 2. Currently available tissue-based tests for prostate cancer

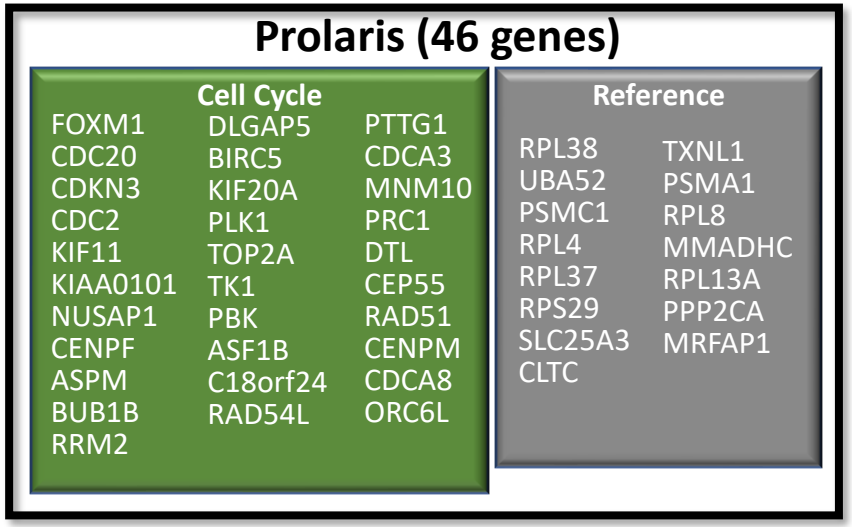
Test	*Platform*	*Molecular basis*	*Marketed use*	*CMS approved use*	*Useful clinical scenario*
Ki-67	IHC	Proliferation	NA	No	Watchful waiting
Prolaris	RT-PCR	Proliferation	Pre and post local Tx decision making	Yes, decision making for surveillance	Watchful waiting
PTEN	IHC/FISH	PTEN	NA	No	Active surveillance
ProMark	Quantitative proteomics	Proteins related to PCa adverse pathology and outcomes	Pre-Tx decision making	No	Active surveillance
OncotypeDX Prostate	RT-PCR	Transcripts related to PCa adverse pathology and outcomes	Pre-Tx decision making	No	Active surveillance
Decipher	RNA MicroArray	Transcripts predictive of PCa metastasis	Post-Tx decision making	Yes, decision making after prostatectomy	Adjuvant radiation

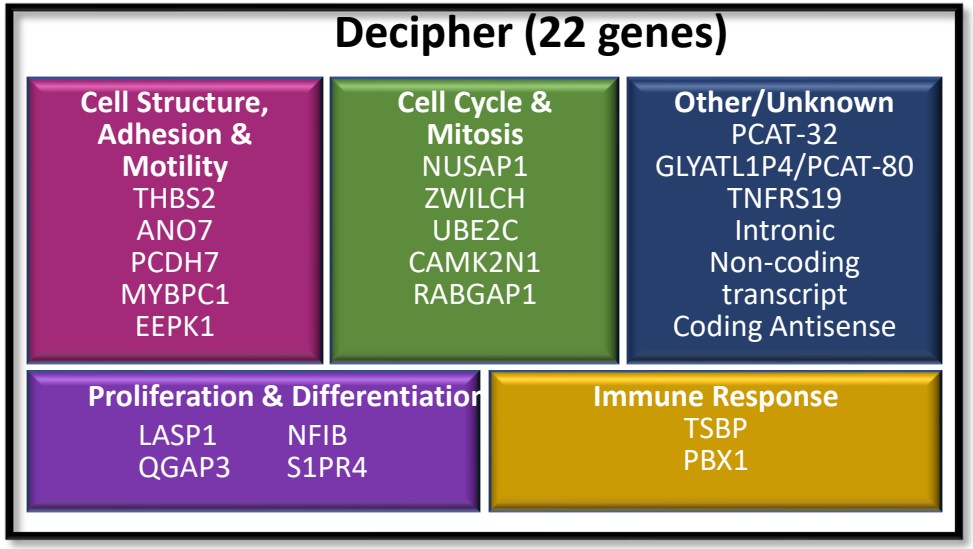
Abbreviations: FISH, fluorescence *in situ* hybridization; IHC, immunohistochemistry; NA, not available.

Ross A.E. et al Pros. Can and Prostatic Diseases 2016

Gene sets of genomic classifiers and its use

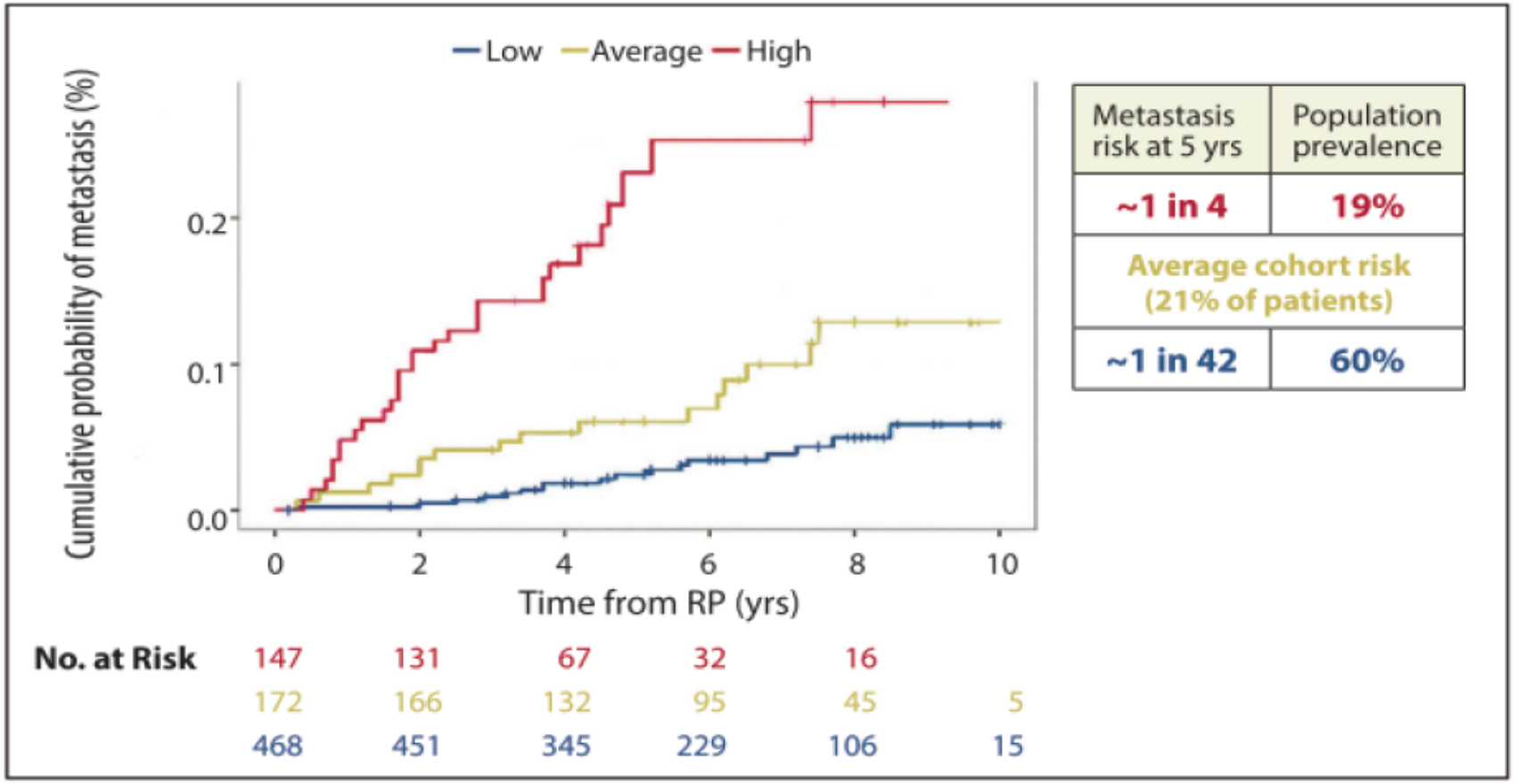






Cuzic J.et al Lancet Onc. 2011
Erho N. et al, PLoS One 2013
Klien et al Eur Urology 2012

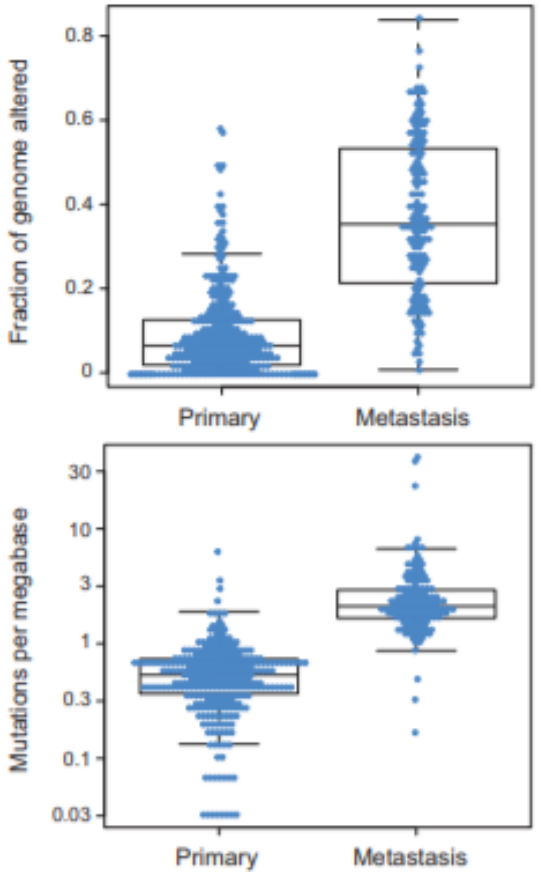
Risk stratification of Pca using Decipher



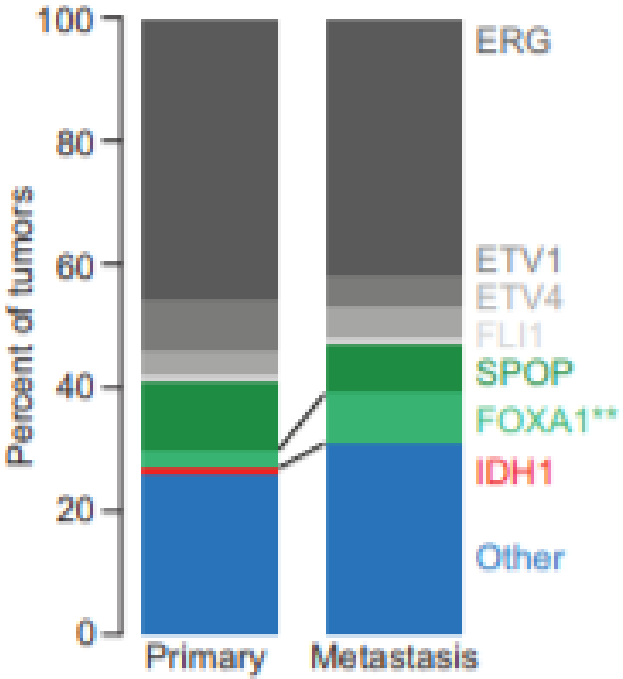
Metastasis risk at 5 yrs	Population prevalence
~1 in 4	19%
Average cohort risk (21% of patients)	
~1 in 42	60%

Adapted from Karnes et al 2013
Crawford D.E. et al Oncology 2015

Molecular subtypes in localized and metastatic PCa



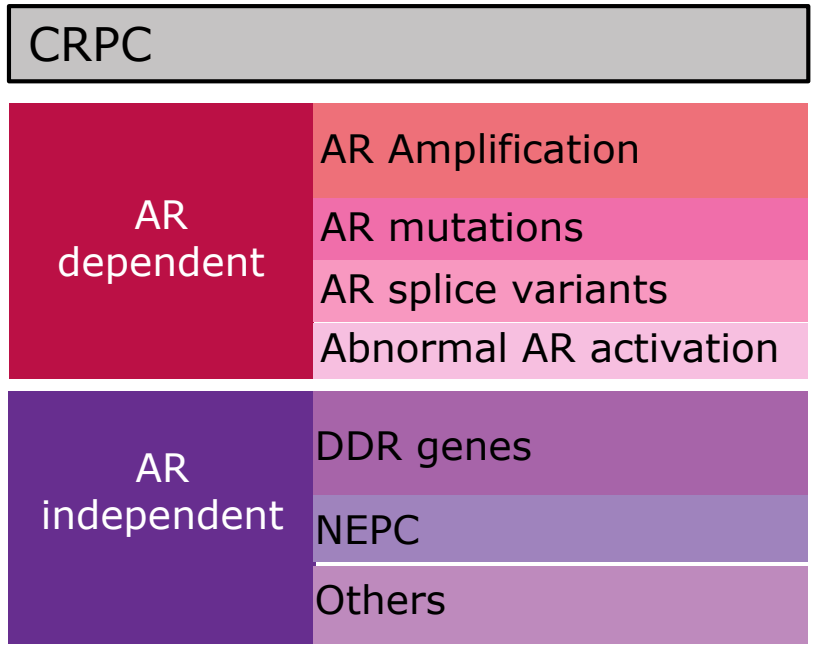
Early, localized PCa		Metastatic PCa
ETS Positive (fusion, OE)	ERG (40-50%)	PTEN (del)
	ETV1 (5-10%)	TP53 (mut)
	ETV4/5 (1-5%)	ATM
ETS Negative (mutations)	SPOP (10-15%)	CHD1 (del)
	FOXA1 (1-5%)	SPINK1 (OE)
	IDH1 (1-5%)	ATM
Others		



Genomic alterations/mutational burden is increased in metastasis compared to localized PCa.

TCGA 2015 *Cell*
Arora et al 2018 *Curr Oncol*

Molecular drivers enriched in CRPC



Arora et al 2018 *Curr Oncol*

Reported AR-targeted therapy resistance mechanisms:

Primary:
AR-mediated: ARv7; AR amp, AR^{F877L}

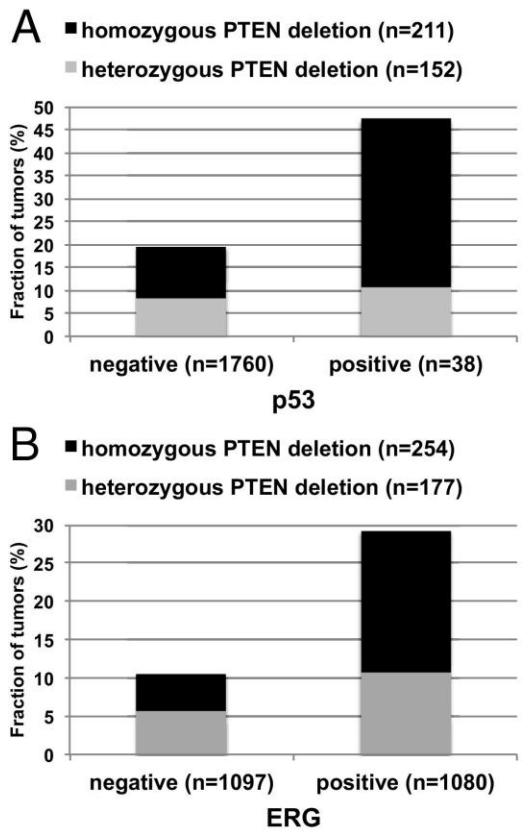
non-AR-mediated: GR, TP53, RB1, MYC, MET

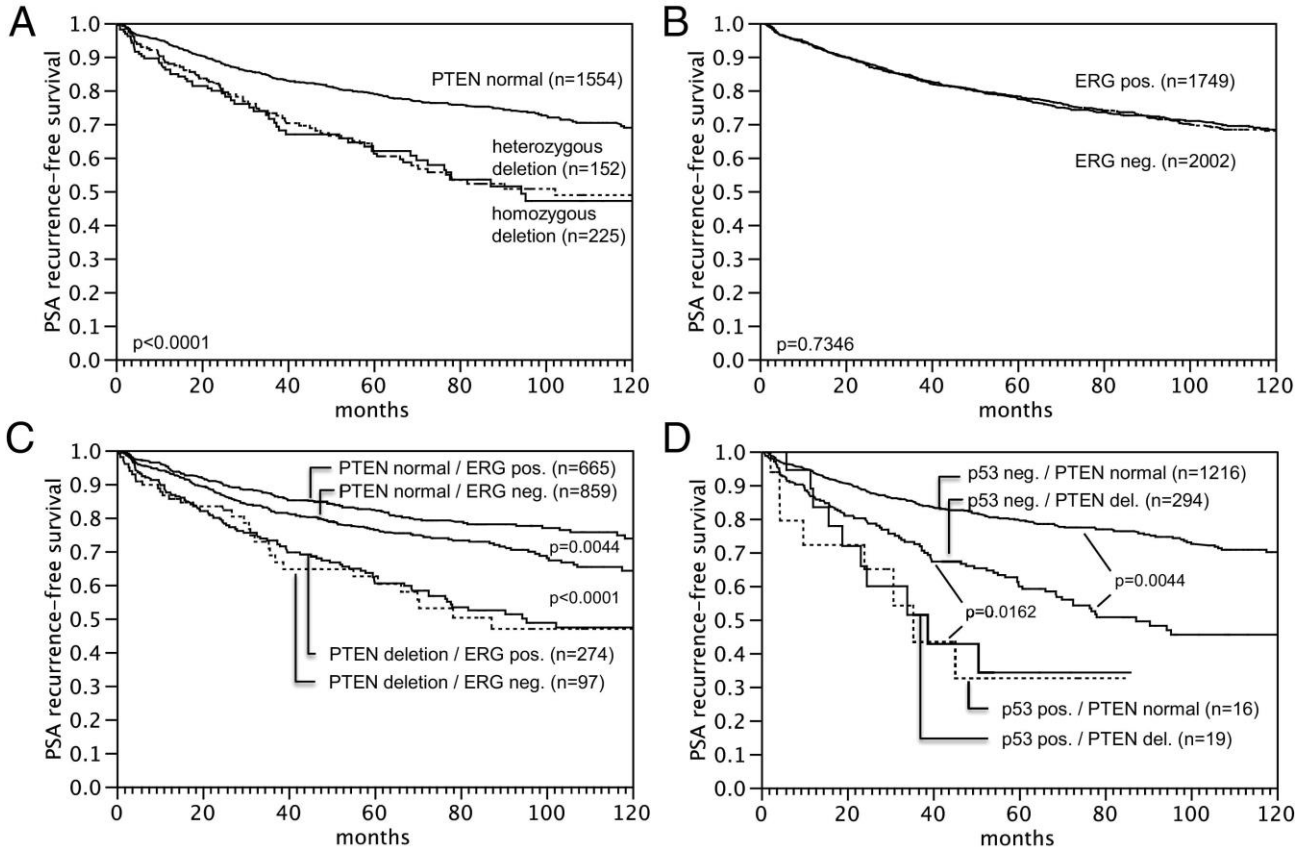
Acquired:
Increased testosterone levels, ARv7, AR amp, AR^{F877L}

Molecular Prognostic Markers in PCa

Prognostic marker	type	Frequency		Prognosis Statistics	References
Basal & Luminal (CD49)		Primary	Luminal 54% Basal 46%	❖ 10-year DMFS freedom as whole: Luminal (0.68); Basal (0.67), p=0.29	Zhao et al., JAMA Oncol 2017 Zhang et al. Nat Commun 2016
		mCRPC	Basal enriched	❖ 61 mCRPC subjects were analyzed (SU2C/PCF)	Simth et al., PNAS 2015
Basal & luminal (PAM50)	Prognostic Predictive Resistance	Primary	LumA 33% LumB 33% Basal 34%	❖ 10-year DMFS freedom as whole: LumA (0.73); LumB (0.53); Basal (0.73) ❖ 10-year DMFS freedom comparing ADT: LumB: ADT (33%) vs no ADT (55%); non–Lum B: ADT (37) vs no ADT (21%)	Zhao et al., JAMA Oncol 2017
		mCRPC	LumA 43% LumB 14% Basal 43%	❖ Median OS for LumA, LumB, and Basal pts was 20.6 months, 9.5 months, and 10.4 months, respectively (p=0.04) ❖ Drug Response Signatures analyses revealed with LumA and LumB pts more sensitive to docetaxel while basal pts are more sensitive to platinums and etoposide (p<0.00001).	Kim et al., ASCO 2018
PTEN Mutations/Loss	Prognostic	Primary	17%	❖ 56 out of 333 primary tumors carry the genetic alterations (TCGA)	TCGA Research Network, Cell 2015
		mCRPC	40%	❖ 61 out of 150 mCRPC tumors carry the genetic alterations (SU2C/PCF)	Robinson et al., Cell 2015
PIK3CA mutations & CNV, TSC1&2 mutation and TSC1&2 CNVs	Prognostic	Primary	2%	❖ 7 out of 333 primary tumors carry the genetic alterations (TCGA)	TCGA Research Network, Cell 2015
		mCRPC	5%	❖ 8 out of 150 mCRPC tumors carry the genetic alterations (SU2C/PCF)	Robinson et al., Cell 2015

PTEN and ERG status associated with PCa progression





Korhn A. et al, Eur. Urol 2012

Molecular Prognostic Markers in PCa

Prognostic marker	type	Frequency		Prognosis Statistics	References
Neuro-endocrine (histopathology)	Resistance		1-4%	❖ 25 out of 635 (4%) tumors were NEPC by histopathology, 70 gene expression signature doesn't add much to IHC	Beltran et al Can Discovery 2011, Epstein J., AJP 2014
Neuroendocrine-like (Tp53 and Rb loss)	Resistance	Primary	5%	❖ Small cell-like histological features were observed in 5-20% primary PCa	Rubin et al., ASCO 2015
		mCRPC	40%	❖ TP53 and RB1-null tumors acquire resistance under ARi selection pressure, expression is 5% in primary, 40% in mCRPC, and 75% in NEPC.	Mu et al. Science 2017
AR & NE double negative (DNPC) (histopathology)	Resistance	mCRPC (1998-2011, no Enza Abi)	5.4 %	❖ 3 out of 56 mCRPC subjects were negative for both AR and NE biomarkers, while 88.4% and 6.3% are AR and NE biomarkers positive.	Bluemn et al., Cancer Cell 2017
		mCRPC (2012-2016, Enaz Abi used)	23.3%	❖ 7 out of 30 mCRPC subjects were negative for both AR and NE biomarkers, while 63.3% and 13.3% are AR and NE biomarkers positive.	Bluemn et al., Cancer Cell 2017
PARP-DDR (BRCA1, BRCA2, FANCA, ATM, PALB2, CHEK2, BRIP1, HDAC2	Predictive	Primary	19%	❖ 62 out of 333 primary tumors carry the genetic alterations (TCGA)	TCGA Research Network, Cell 2015
		mCRPC	23%	❖ 34 out of 150 mCRPC subjects carry the genetic alterations (SU2C/PCF)	Robinson et al., Cell 2015
			33%	❖ 16 out of 49 mCRPC subjects were positive for the biomarkers. 14/16 (88%) of those patients enrolled responded to Olaparib.	Mateo et al., NEJM 2015

Conclusion

- Genomic alterations/mutational burden is increased in metastasis compared
- Genomic selection adds prognostic value on top of the clinical features across clinical risk groups.
- Combining clinical and molecular risk stratification would facilitate the development of precision medicine for improved clinical outcomes.