FACULTY OF MEDICINE | UNIVERSITY OF CALGARY

Update on Prostate Cancer with emphasis on Diagnosis, Prognosis and Therapeutic Targeting

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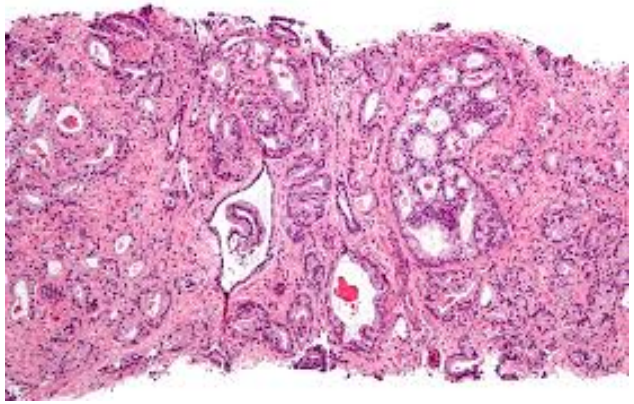
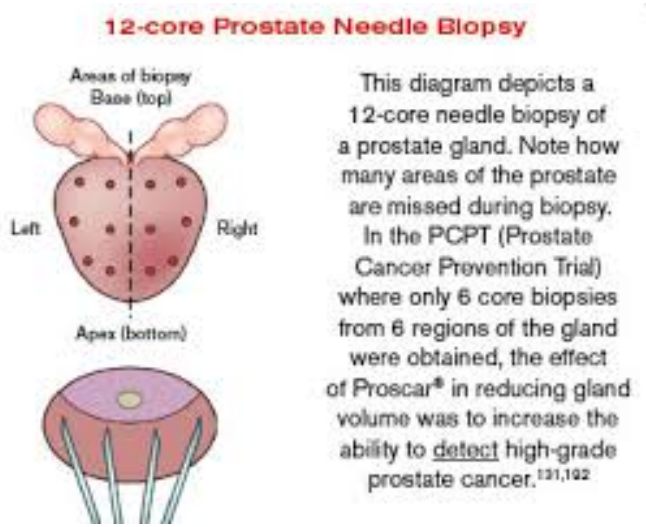
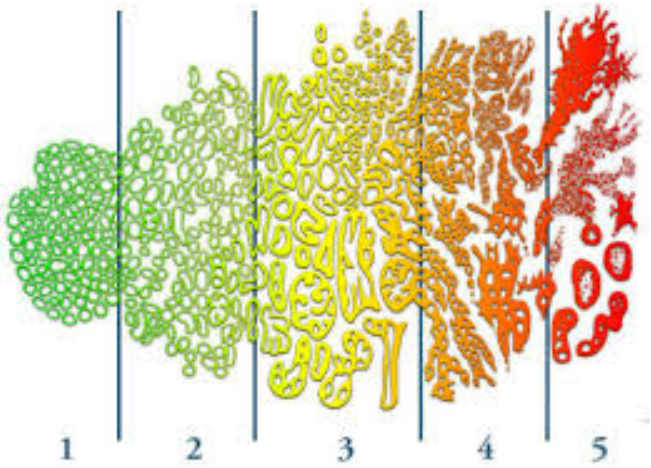
Role as Surgical Pathologist







Prostate Cancer

- One of the common cancers affecting men in western world
- PSA remains a major screening tool and the most widely used serum biomarker
- PSA is not ideal as it overlaps between BPH and PCA (est 15% of men with PSA<2.5 will have PCA)

Current treatment Options

- Surgery
- Radiotherapy
- Active surveillance
- Hormone and Chemotherapy (advanced CRPC)
- Specific targeted therapy for more rapid disease

Serum PSA

- This should be carried out with DRE and consultation with urology to assess for various risk factors
- Absolute value is important, but also PSA doubling time and potentially PSA density

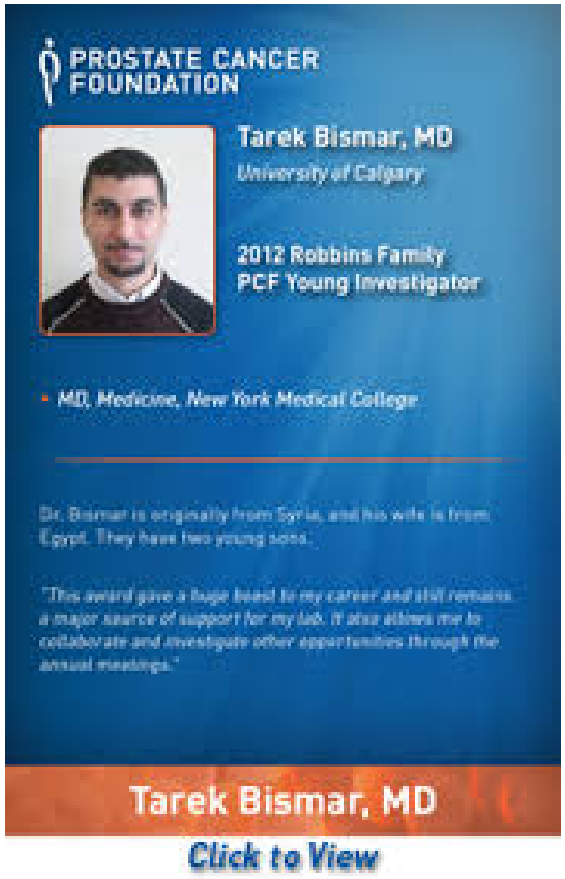
Active Surveillance

- Patients with low/low intermediate risk can be managed with such programs
  - GS6/ 3+4 with 3 or less positive cores and PSA < 10
  - 10-30% of such patients may exist AS programs due to disease progression or patient's anxiety
  - ERG and PTEN suggested to have a role in predicting progression *(Current Prostate Centre Study)*

2nd Line drugs for Advanced PCA

- Current new hormonal drugs are being developed and used such as enzu, abi, +/- Docetaxol and new research to investigate patients responsive/ resistant to such drugs are being conducted
- PARPi for DDR somatic and potential germline mutations

Role as Scientist



- *Develop molecular signatures for aggressive and indolent PCA that can be implemented clinically to aid in better decision making for patients*

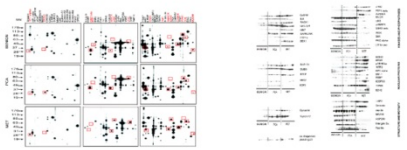
Tissue Based and blood Based Signatures

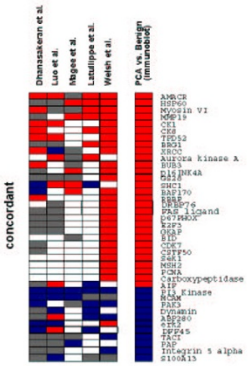
- Decipher
- PCA Oncotype DX
- Cell cycle signature
- TMPRSS2-ERG/PCA3 (urine)
- Potential tissue based (*ERG, PTEN* in AS)
- Our own HDDA10 gene signature for AS and for predicting neuroendocrine differentiation post XRT/HR therapy *(projects at the Prostate Centre Calgary)*

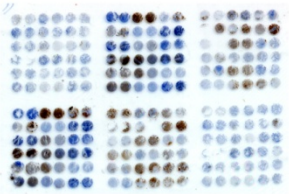
Bioinformatics

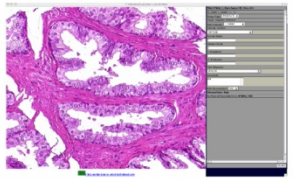
Prostate Cancer

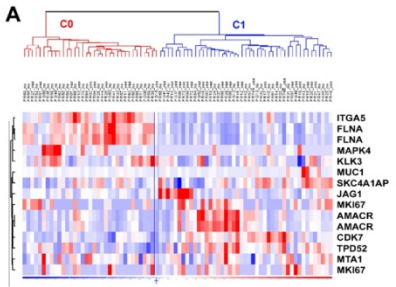
Proteomic Screen

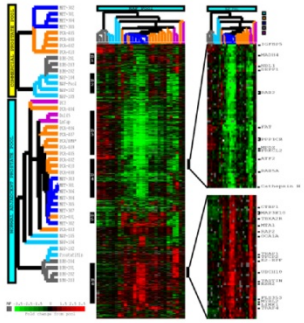


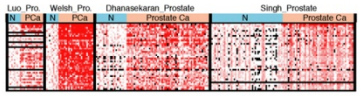


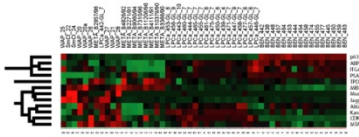


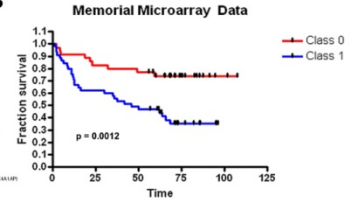












Prostate Samples | cDNA Expression Array Analysis | Oncomine | TMA | cDNA Outcomes

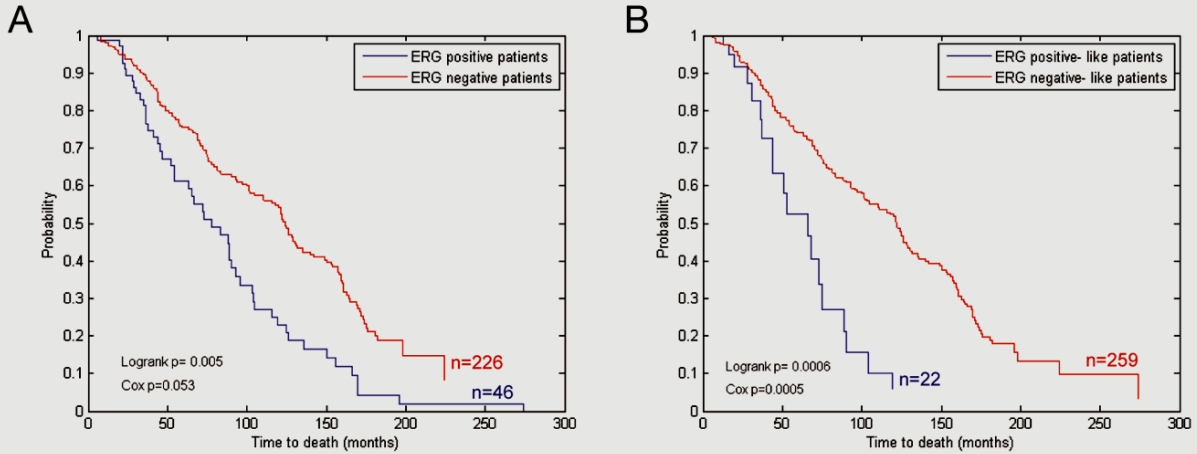
Resources | Discovery | Meta Analysis | Testing | Validation

Neoplasia 2006 Jan;8(1):59-68

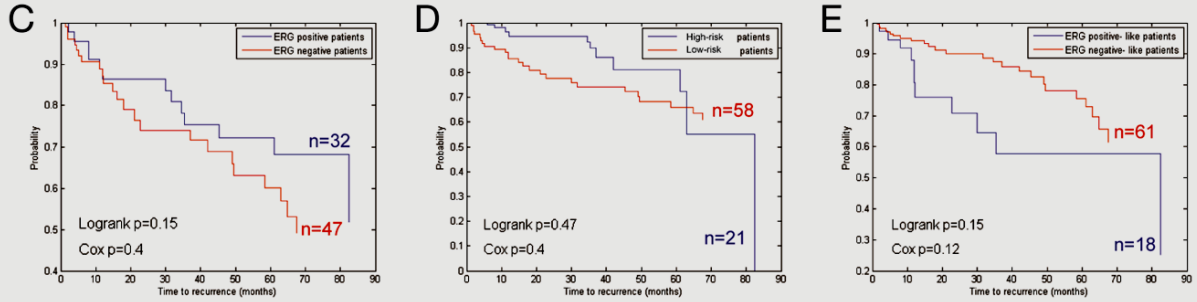
Validation of 10-Gene molecular signature in PCA patients

UC Active surveillance eligible cohorts

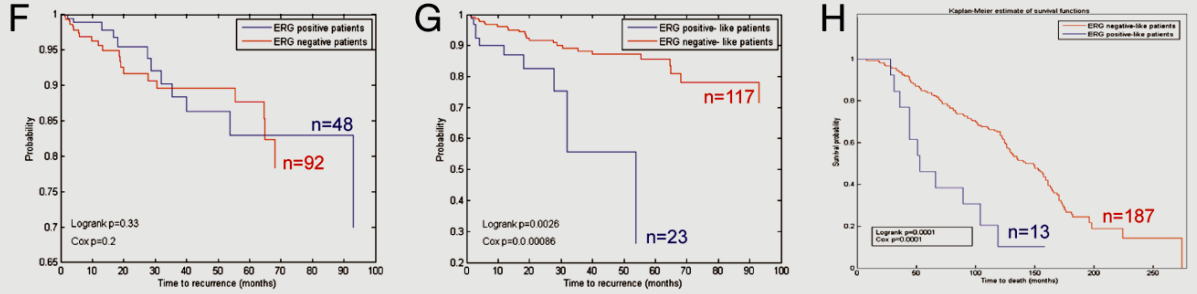
Figure 3



Swedish Prostate Cancer Cohort



Glinsky Prostate Cancer Cohort



Taylor Prostate Cancer Cohort

Gleason Score 6&7 Patients
(Swedish PCA Cohort)

Swedish Cohort

	Group	Number of Samples		HR (95%CI)	p-value/Cox value
GS 7 Patients	GS 7 alone	GS 7(3+4)	GS 7(4+3)	2.23 (1.5-3.5)	$2x10^{-4}/2.4x10^{-4}$
		79	38		
	GS 7 + ERG	GS 7(3+4) AND ERG0	GS 7(4+3) OR ERG1	1.8 (1.4-2.5)	$9x10^{-4}/5.6x10^{-5}$
		61	44		
	GS 7 + ERG-like	GS 7(3+4) AND ERG0-like	GS 7(4+3) OR ERG1-like	2.52 (1.6-3.4)	$3x10^{-5}/6.2x10^{-6}$
		72	45		
GS 6+7 Patients	GS 6+7 alone	GS 6 +GS 7(3+4)	GS 7(4+3)	3 (2-4.5)	$<10^{-7}/5.3x10^{-8}$
		162	38		
	GS 6+7 + ERG	GS 6 +GS 7(3+4) AND ERG0	GS 7(4+3) OR ERG1	1.5 (1.2-2)	$<10^{-5}/5x10^{-5}$
		136	46		
	GS 6+7 + ERG-like	GS 6 +GS 7(3+4) AND ERG0-like	GS 7(4+3) OR ERG1-like	3.2 (2.1-4.1)	$<10^{-10}/7.5x10^{-11}$
		153	45		

Intraductal adenocarcinoma (IDC-P)

- ***Typically associated with invasive cancer (95%): high grade (GS≥8 in ≈ 50%), high stage***
  - *Rare cases of RPs with IDC-P only or IDC-P with GS 6 adenocarcinoma have been described*

- ***Significance***
  - ***Intraductal spread*** *of adjacent high-grade carcinoma 'regular IDC-P'*
  - ***Precursor lesion*** *distinct from HGPIN without an adjacent invasive component 'precursor IDC-P'*

- *Independent predictor of BCR and survival even in intermediate- and high- risk pca (Prostate 2014;74:680-687, Arch Pathol Lab Med 2013;137: 610-617, Eur J Cancer 2012;48:1318-1325)*

- *Independent predictor of early BCR in patients undergoing radiation therapy (Eur J Cancer 2012; 48 (9): 1318-1325)*

- *Prognostic in patients presenting with distant metastases as initial presentation (Mod Pathol 2016; 29 (2): 166-173)*

Isolated IDC-P Mutational Landscape without concurrent high grade PCA (n=15)

- *By copy number profiling, iIDC-P alterations were similar to those previously described in high-grade invasive PCa (PTEN, RB1, and CHD1 loss; MYC gain).*
- *However, in four cases, targeted sequencing revealed a striking number of activating oncogenic driver mutations in MAPK and PI3K pathway genes, which are extraordinarily rare in conventional PCa.*
- *In addition, pathogenic mutations in DNA repair genes were found in two cases of iIDC-P (BRCA2, CHEK2, CDK12) and other known PCa-associated mutations (FOXA1, SPOP) in two cases*
- *ERG was expressed in 7% (1/15) of the iIDC-P lesions and PTEN was lost in 53% (8/15)*

F Khani, J pathology 2019

Mutational Landscape of IDC-P in absence of invasive high grade PCA

		RP Case Number						
		4	8	11	5	12	9	15
MAPK pathway genes	*BRAF*							
	KRAS							
	MAP2K1							
PI3K pathway genes	*PIK3CA*							
	AKT1							
	PTEN	~					&	
DNA repair genes	*BRCA2*							
	CHEK2				#			
	CDK12				**			
Cell cycle genes	*CDKN2A*						&	
	RB1						~	
	CCND1							
Other altered PCa-related genes	*TP53*							
	FOXA1							
	SPOP							
	CHD1							
	TSC2							
	MYC							^
Chromosome 8 CNAs	8p		~			~		~
Total number of CNAs		15	16	16	35	18	80	191
Percent genome alteration (%)		1.6	4.4	3.6	3.6	6.3	21	11
IHC	PTEN							
	ERG							

	Activating driver mutation (SNV)
	Other SNV
	CN loss
	CN gain
	IHC loss
	Focal IHC loss
**	biallelic mutations
#	homozygous germline mutation
~	Loss of heterozygosity
&	Homozygous CN loss
^	High CN gain

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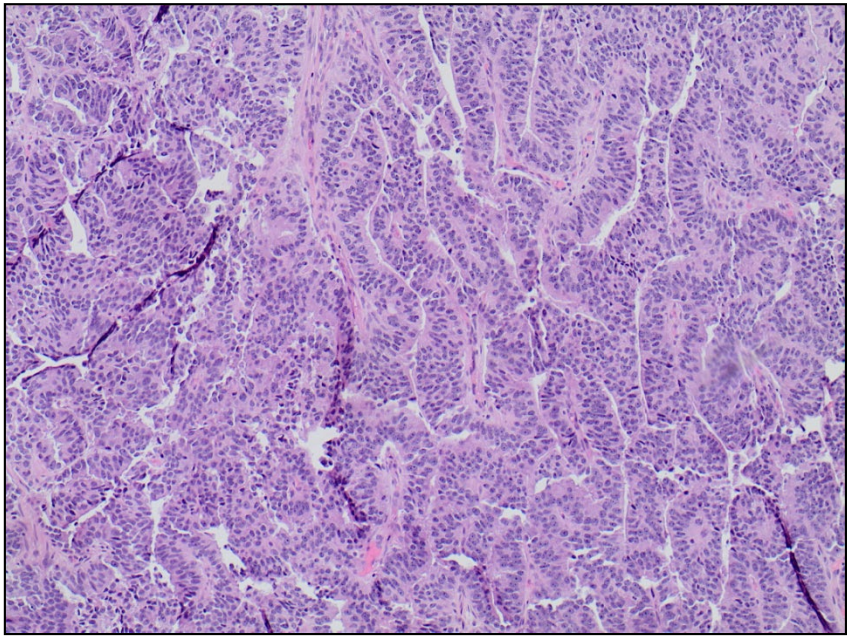
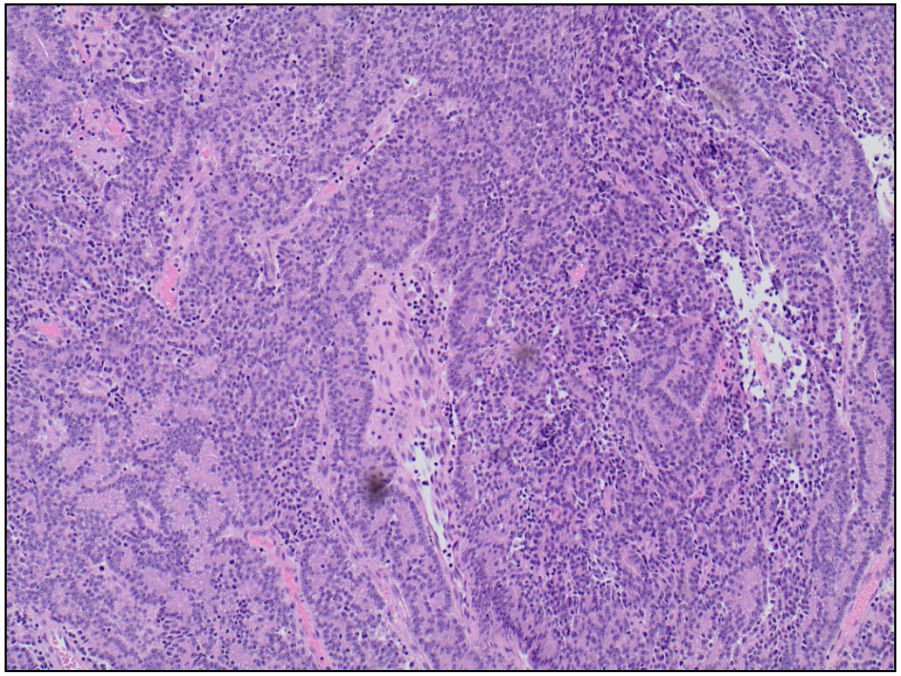
Ductal Type PCA (D-PCA)

- *Rare variant of PCA, estimated that about 3% of PCA exhibit some form of ductal morphology*
- *Characterized by large glands lined by tall, pseudostratified, columnar, neoplastic epithelial cells, typically arranged over fibrovascular cores or cribriform glands and associated with an aggressive clinical course*



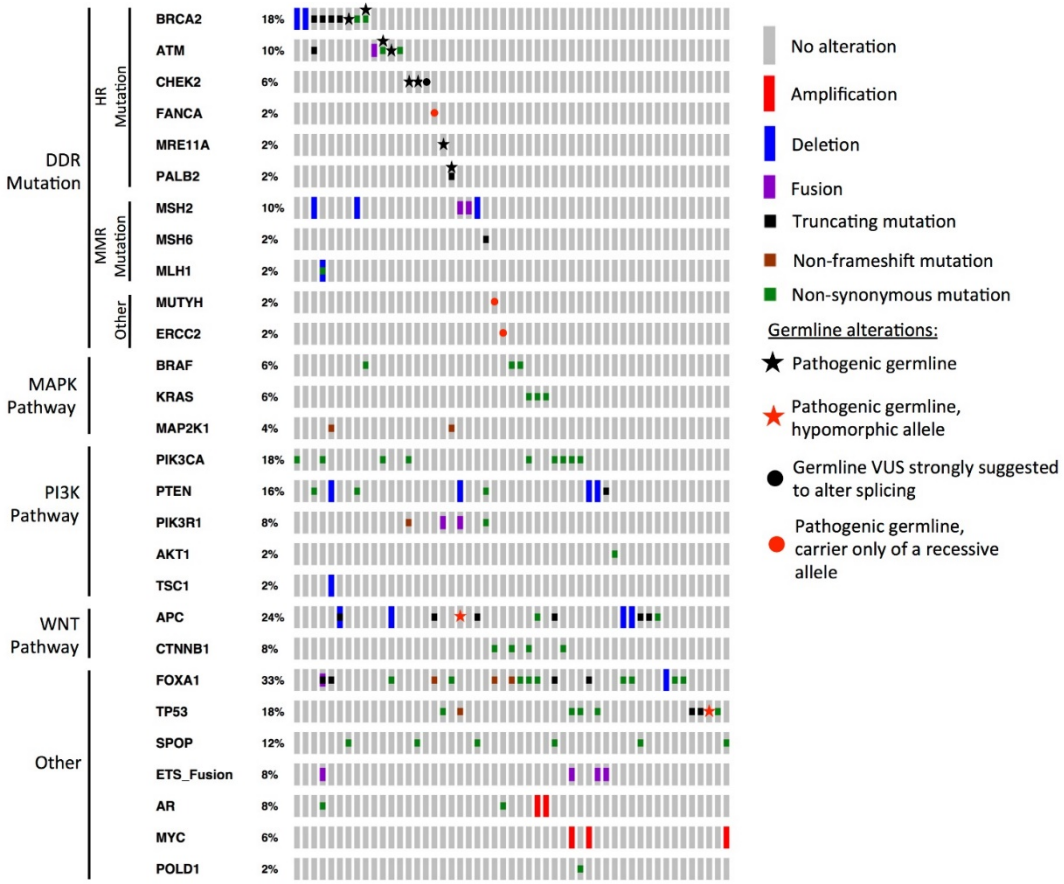
Characterization of Mutational Landscape Ductal PCA



Mutational Landscape of Ductal PCA

- *To characterize mutational landscape of D-PCA, we carried out a study of 51 patients; 57% showed pT3 or higher, 25% were deceased with 43% developing metastasis during follow-up*
- *Overall, our combined cohort of patients with D-PCA demonstrated a high number of recurrent genomic alterations. These included alterations in genes involved in DDR repair (n = 24; 47%), PI3K pathway (n = 19; 37%), WNT-signaling pathway (n = 16; 31%), and MAPK signaling (n = 8; 16%). A large number of patients also had mutations in FOXA1 (n = 17; 33%), TP53 (n = 9; 18%), and SPOP (n = 6; 12%).*

Figure: Landscape of genomic alterations across 51 patients with ductal prostate cancer. Each column represents one patient. Pathogenic mutations were those predicted to either activate oncogenic signaling pathways (e.g. WNT- or PI3K-signaling) or inactivate tumor suppressors (e.g. DDR genes, *TP53*). DDR, DNA damage repair; HR, homologous recombination; MMR, mismatch repair.



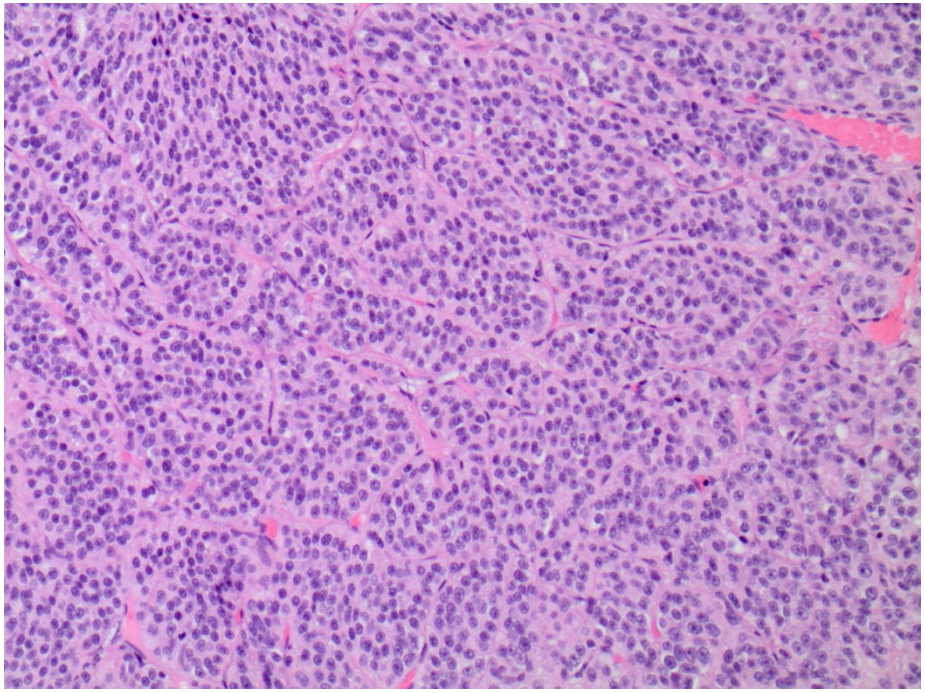
Recurrent DDR mutations in D-PCA

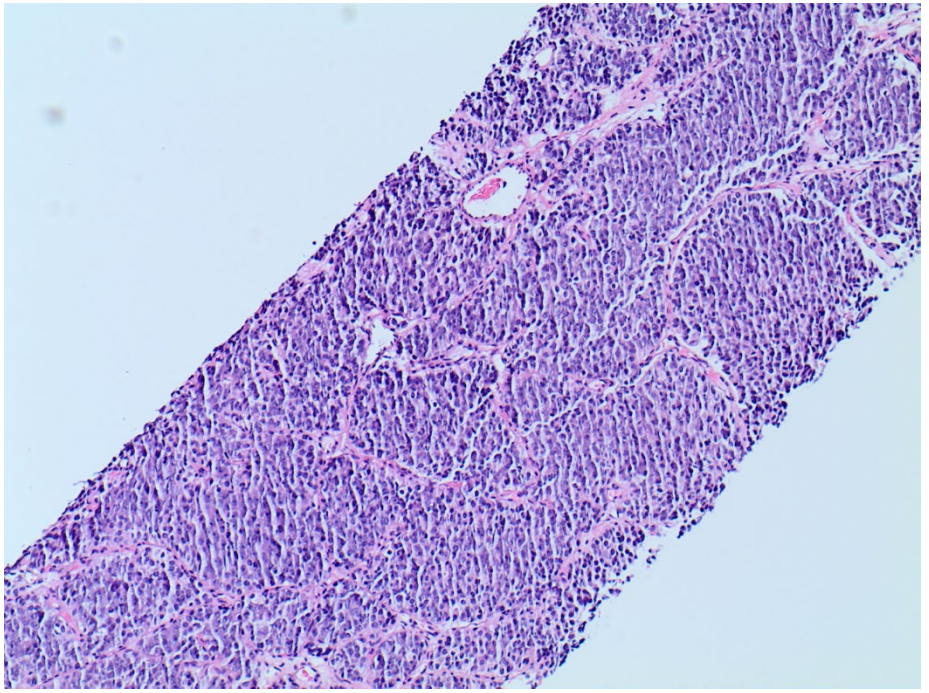
- *49% of patients had at least one alteration in a DDR pathway gene*
- *Overall,14% had evidence of MMR alterations, with 43% showing evidence of hypermutation (ie, ≥ 10 mutation per megabase), consistent with deficient MMR (one patient with monoallelic loss of MSH2 was not hypermutated).*
- *About 30% of patients with MMR alterations also had concurrent secondary mutations in homologous recombination (HR) pathway genes*
- *31% had an HR mutation in the absence of a concurrent MMR mutation.*
- *One patient with a hotspot POLD1 mutation was ultramutated (ie, > 100 mutations per megabase)*
- *(20%) of patients had evidence of a pathogenic autosomal dominant germline*

CDK12 mutations in PCA

- *CDK12 occur in 3-7% of metastatic PCA and is characterized by genomic instability signature*
- *CDK12 mutated cohorts had higher GS at presentation, shorter time to PSA relapse, CRPC and metastasis*
- *CDK12 and HRD cohorts exhibit different clinical characteristics with CDK12 having genomic instability signature vs BRCA2*
- *BRCA2 cohort exhibit large chromosomal deletions with flanking microhomology, CDK12 mutated tumor exhibit tandom duplication leading to high copy number gains of PCA oncogenes (MYC, AR, CCND1).*
- *CDK12 tumors also have novel gene fusion and increased T cell infiltrate suggesting better response to immunotherapy*

Histology of NEPCA



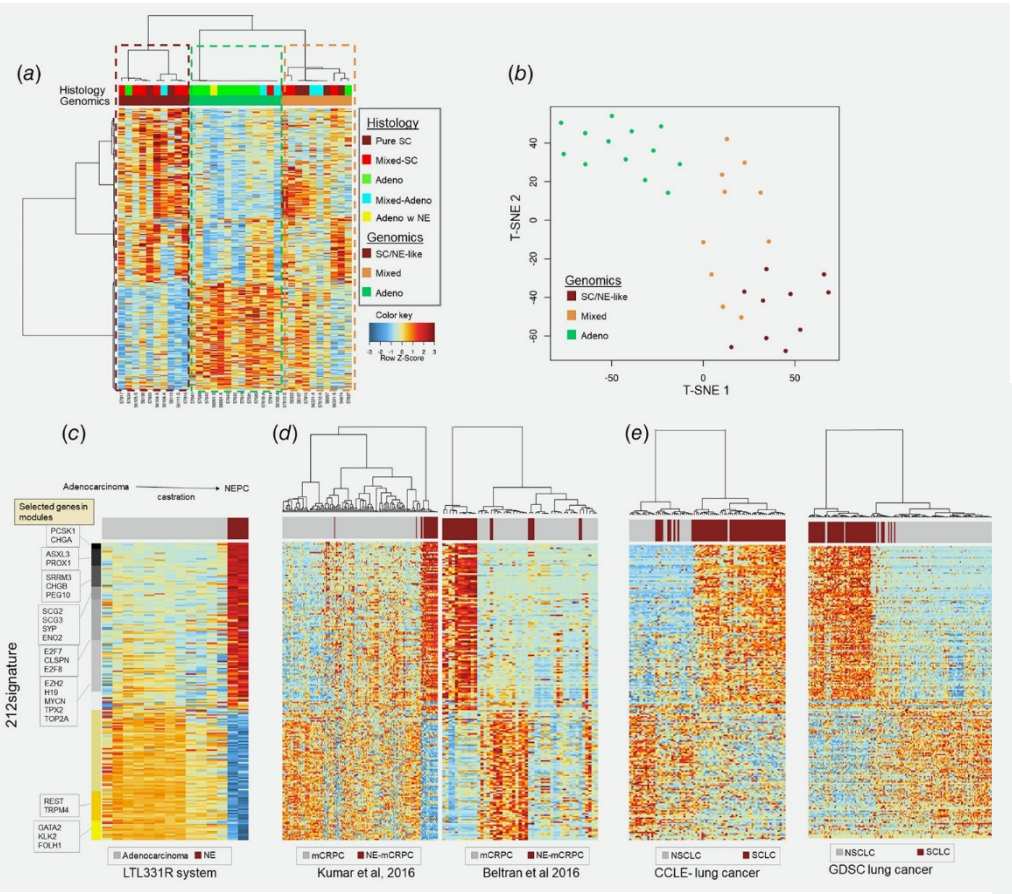


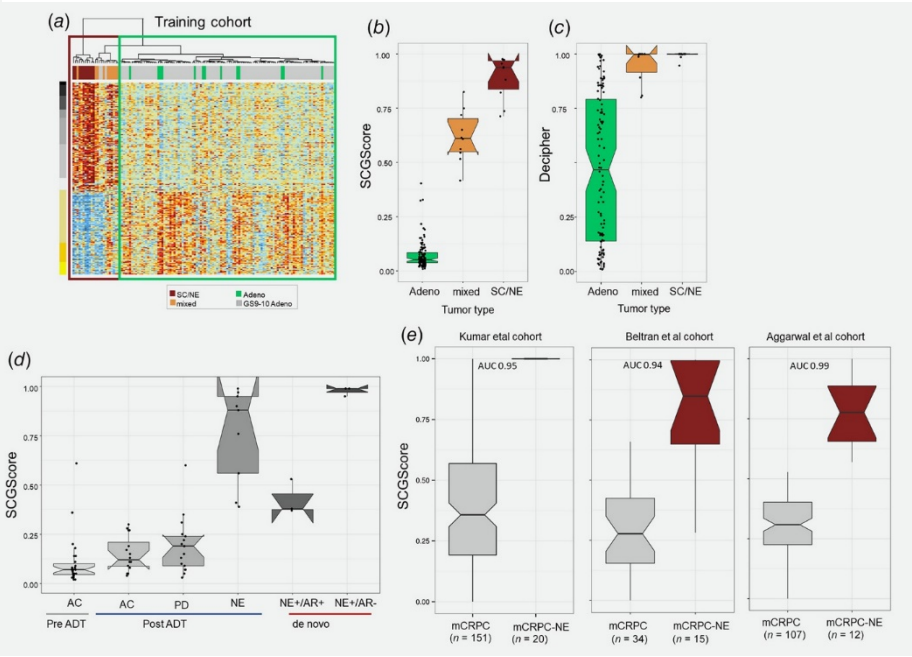
Neuroendocrine PCA

- *De-novo NE-PCA, less than 1%*
- *Therapy induced 20-30%*
- *Wide range of features (small cell, large cell, mixed)*
- *Wide range of IHC profile with some even completely negative for NE-markers*
- *Use of NKX3.1 (commonly mutated in PCA, but mostly one allele that keep protein expression expressed) to differentiate from NE-PCA*
- *AR profile changes post therapy including AR related genes (PSA, PSAP and AR)*
- *Now with the notion of mixed AR-NEPCA, Double negative and NE markers pos NEPCA which are to be characterized for targeted therapy response*

Characterization of transcriptomic signature of primary prostate cancer analogous to prostatic small cell neuroendocrine carcinoma

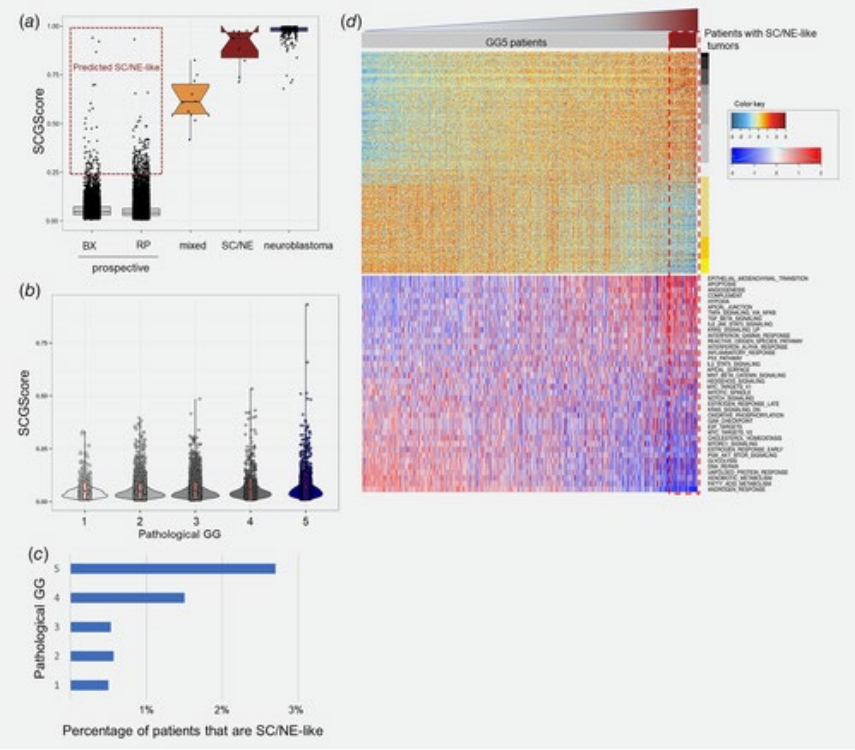
Int J Cancer. 2019 May 24



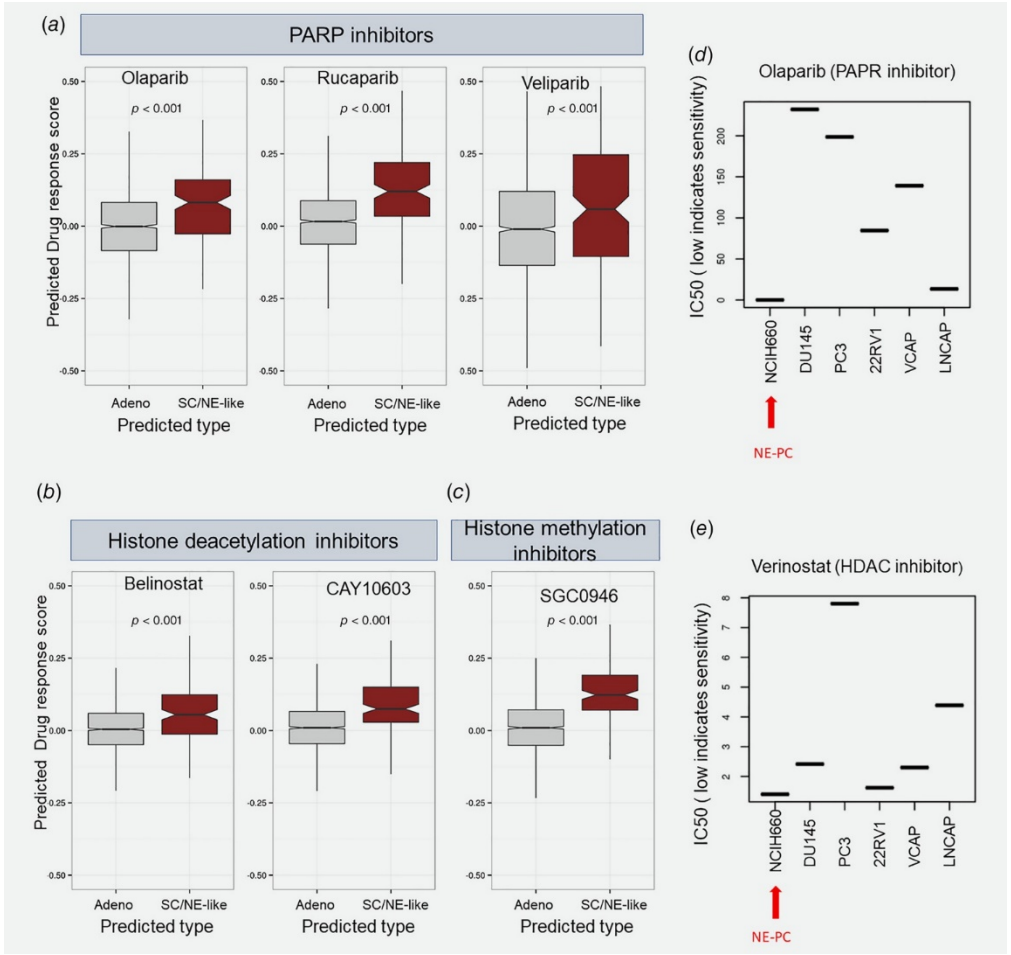


Development of validation of 212 gene signature for NEPCA

Evaluating SCGScore in a large prospective cohort. (*a*) Evaluating the SCGScore in prospective prostate RP ($n = 17{,}967$) and BX ($n = 6{,}697$) and neuroblastoma ($n = 283$) compared to SC/NE tumors. (*b*) SCGScore across pathological GG in RP samples. (*c*) Frequency of predicted SC/NE-like across GG showing higher frequency in GG5. (*d*) Predicted SC/NE-like patients have distinct genomic fingerprint compared to GG5 ($n = 1{,}679$) and distinct pathway activity



Therapeutic implications of SCGScore. SC/NE-like are predicted to be more sensitive to (*a*) PARP inhibitors, (*b*) HDAC inhibitors and (*c*) methylation inhibitors. (*d–e*) NCIH660 (prostatic NE cell line) showed to respond to both PAPR and HDAC inhibitors



Conclusion

- *In AS setting critical points is # of cores, Extent, GS6 or 3+4 minimal, but no cribriform or IDC-P*
- *ERG and PTEN may aid in IDC-P vs HGPIN but morphology remains a key with high suspicious index*
- *D-PCA (as well as IDC-P)is important to be recognized as it signify worse clinical outcome and higher rates of actionable*