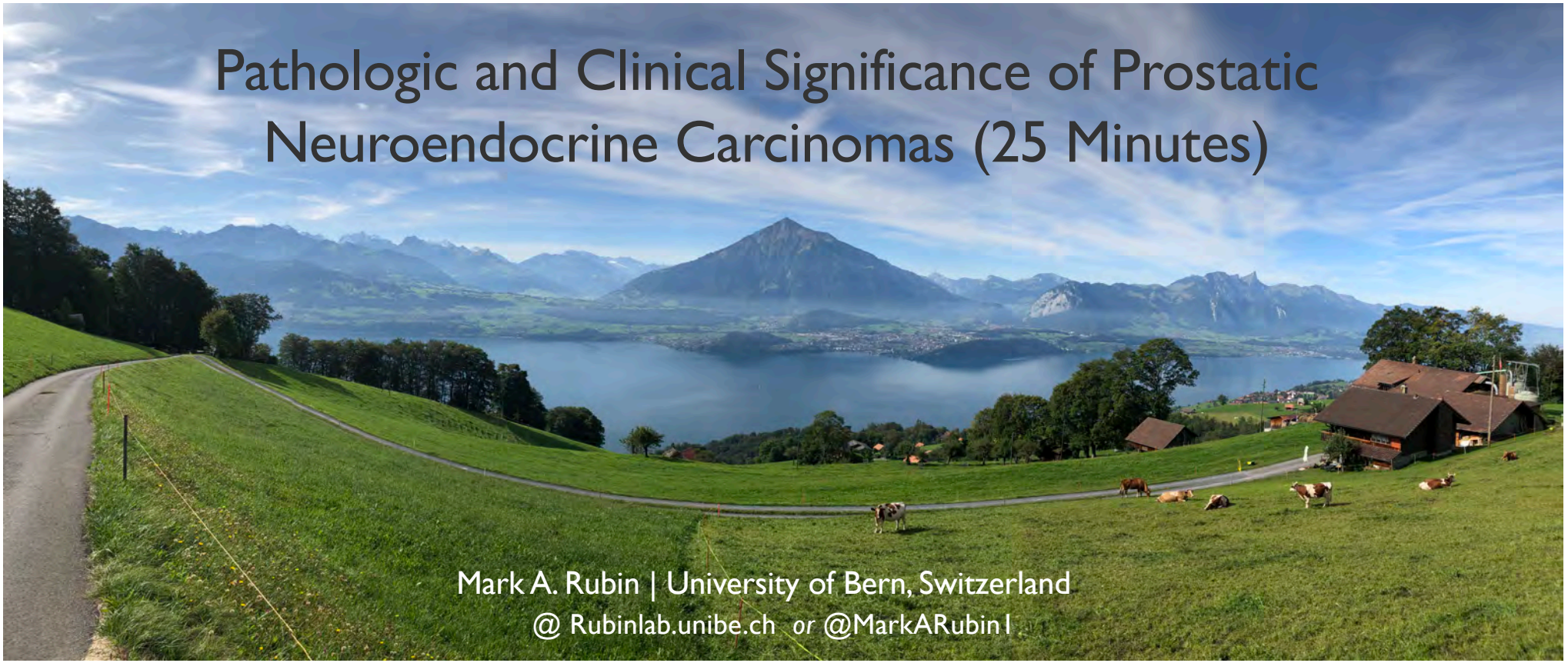
UNIVERSITÄT BERN

Bern Center FOR PRECISION MEDICINE

1994 25 2019 DEPARTMENT FOR BIOMEDICAL RESEARCH

Pathologic and Clinical Significance of Prostatic Neuroendocrine Carcinomas (25 Minutes)



Mark A. Rubin | University of Bern, Switzerland
@ Rubinlab.unibe.ch *or* @MarkARubin1

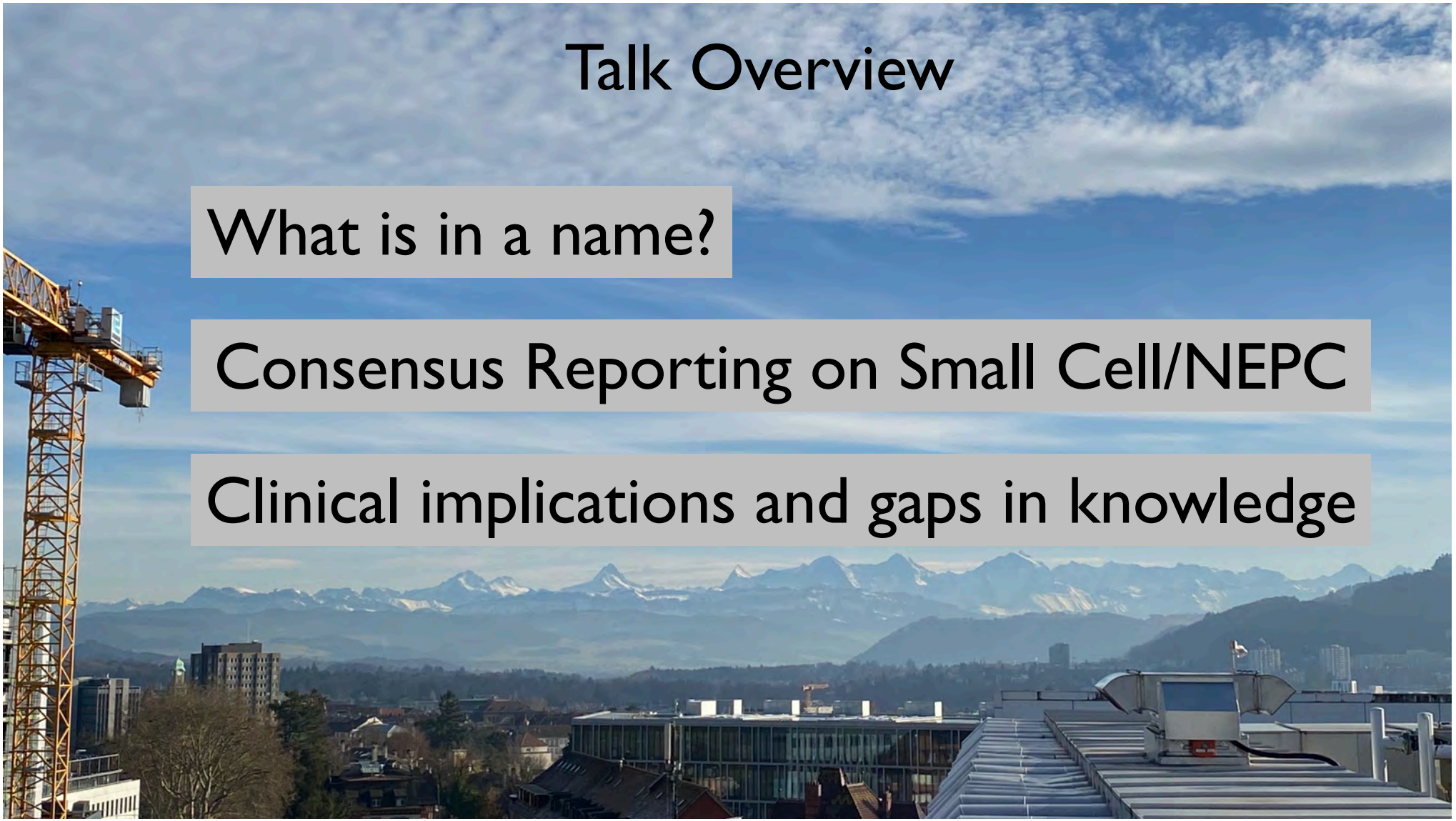
Disclosures

FUNDING:
NCI, EDRN, PCF, SU2C/PCF, Starr Cancer Consortium, DOD, SNF, Krebsliga, SPHN, Sanofi-Aventis, Millennium Pharma, Eli-Lilly and Janssen

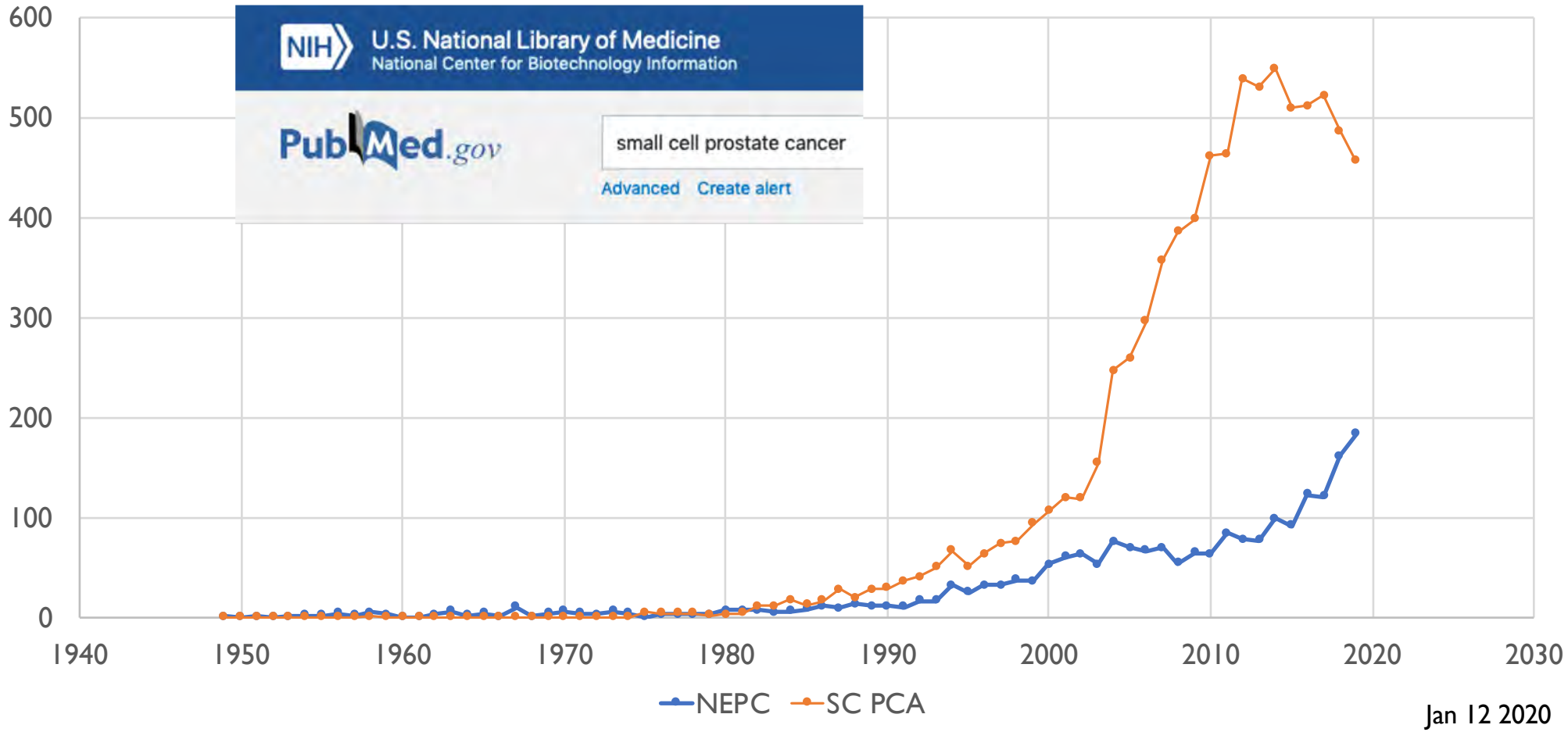
PATENTS:
Listed as co-inventor on patents in the diagnostic and treatment fields for ETS fusions (Harvard/Michigan), EZh2 (Michigan), SPOP (Cornell) and AURKA / NMYC (Cornell)

Scientific Board of Advisors:
Neogenomics Labs, inc. and LynxDx , inc.


9:00 PM
Los Angeles
6:00 AM
Bern (CH)


Talk Overview
What is in a name?
Consensus Reporting on Small Cell/NEPC
Clinical implications and gaps in knowledge

What is in a name?
PUBMED Search from 1949-2019 (60 Years)



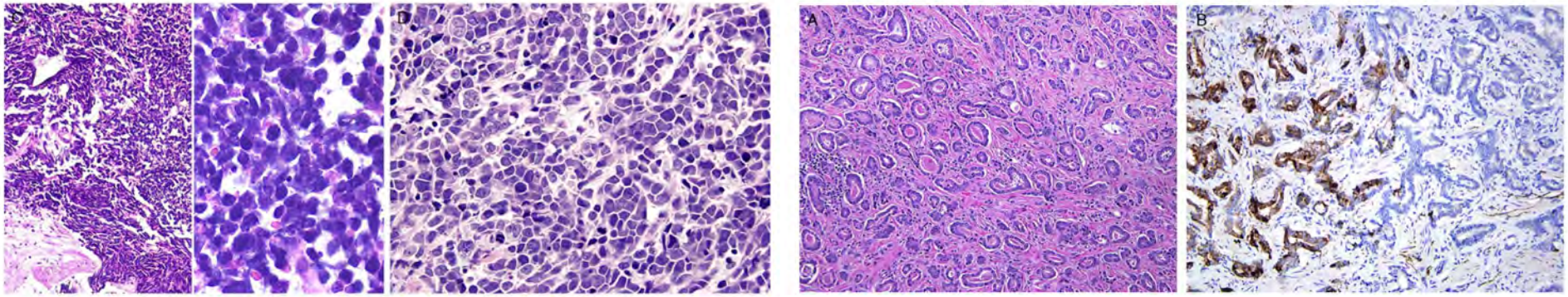
Jan 12 2020

Terminology is a **major** problem

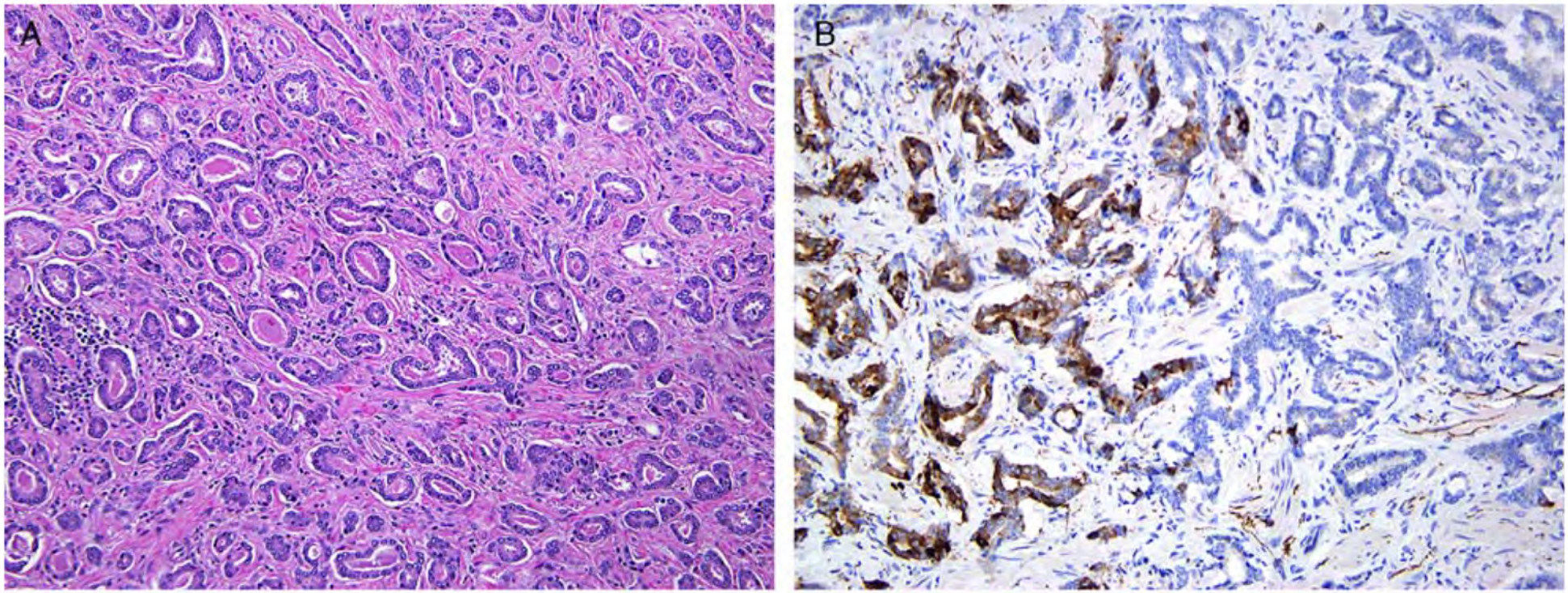
Small Cell Carcinoma vs Neuroendocrine PC (NEPC)

Morphology

Molecular testing & morphology

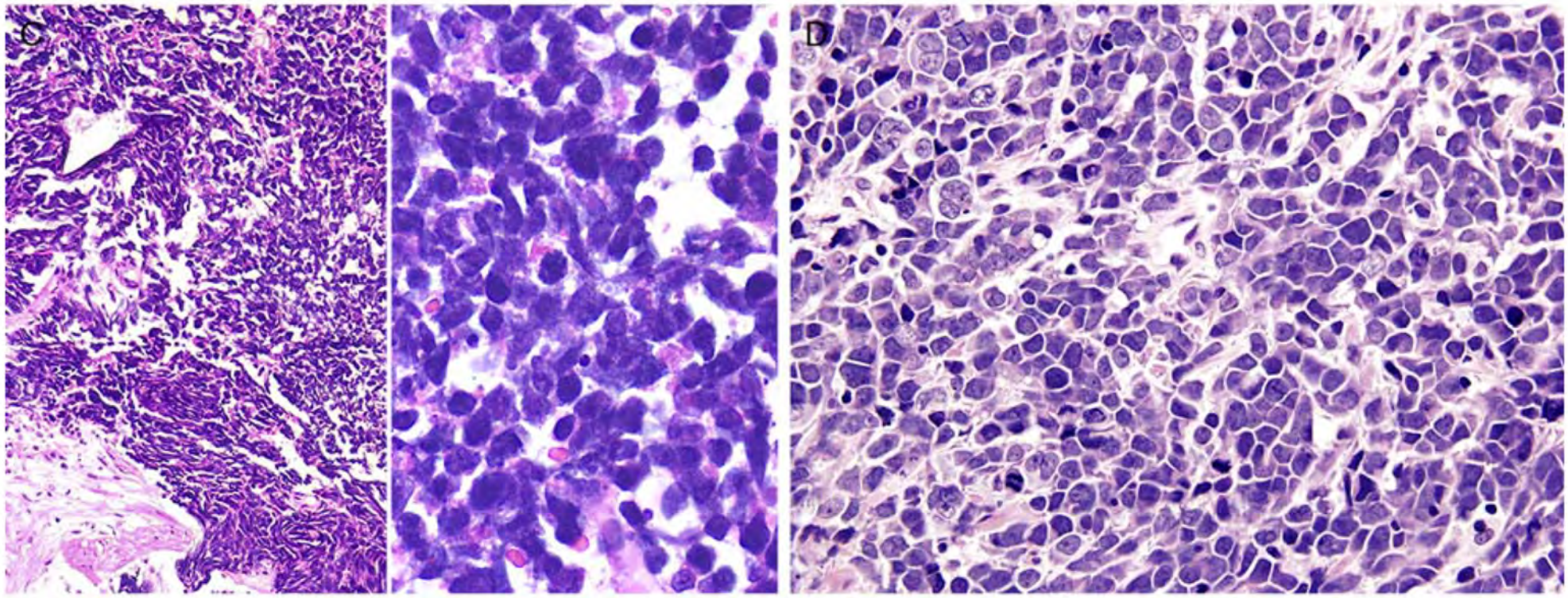


Should we follow immunohistochemistry for neuroendocrine markers?



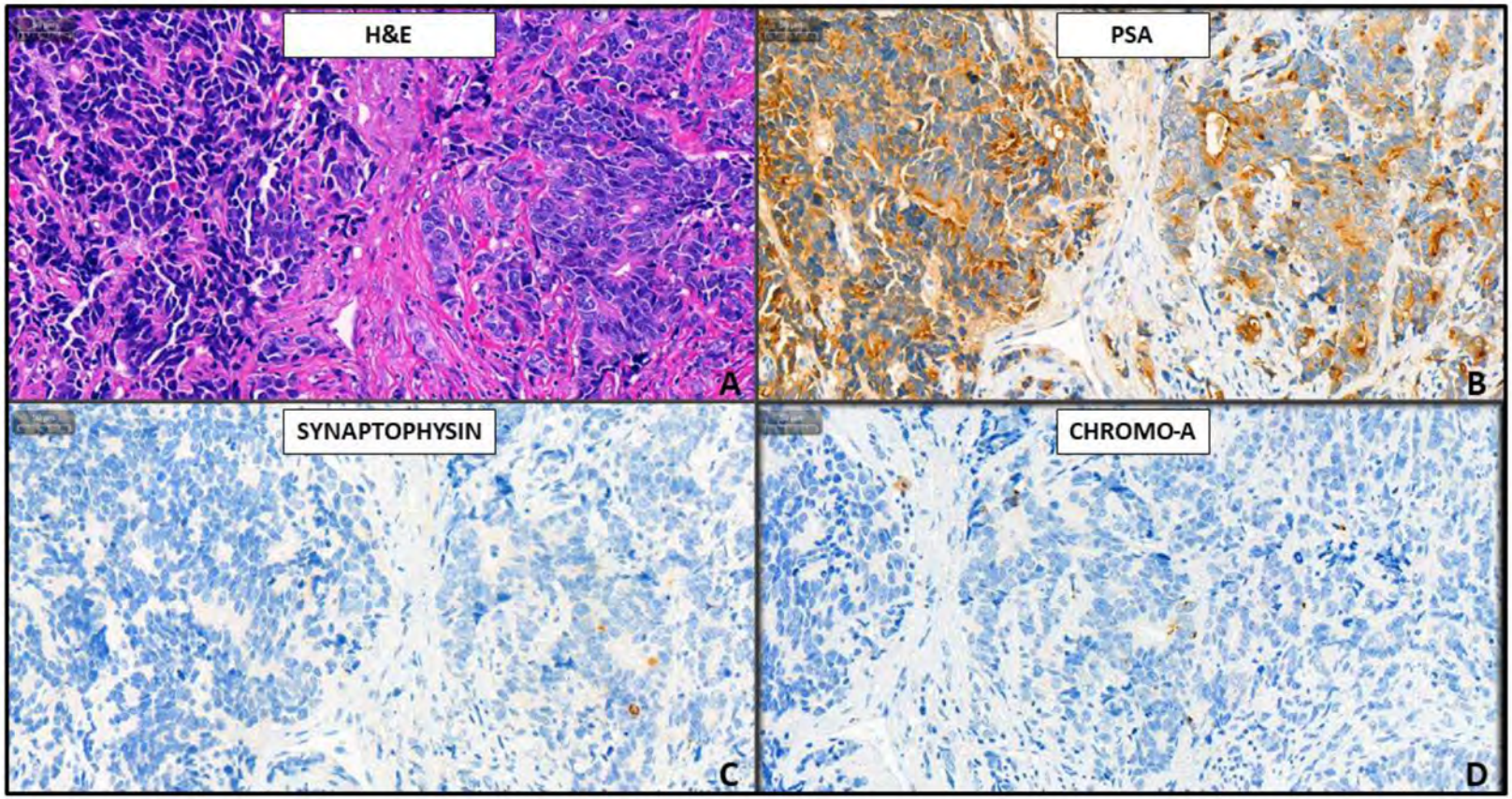
Report from ISUP Consultation Conference: Mol. Path Subgroup
Lotan et al., AJSP 2020 (in press)

Should we only follow morphology?



Report from ISUP Consultation Conference: Mol. Path Subgroup
Lotan et al., AJSP 2020 (in press)

What does morphology mean when neuroendocrine IHC is negative?



Report from ISUP Consultation Conference: Mol. Path Subgroup
Lotan et al., AJSP 2020 (in press)

Part 1: Localized Prostate Cancer

1) This is what we see most often (99.9%) in daily practice.

2) Major questions for us is cancer versus no-cancer and then Gleason score, stage, and margin status.

3) Rarely do we order IHC for neuroendocrine markers but more often we get asked to review cases when they are ordered.

4) What would a urologist do differently if we did find neuroendocrine features?

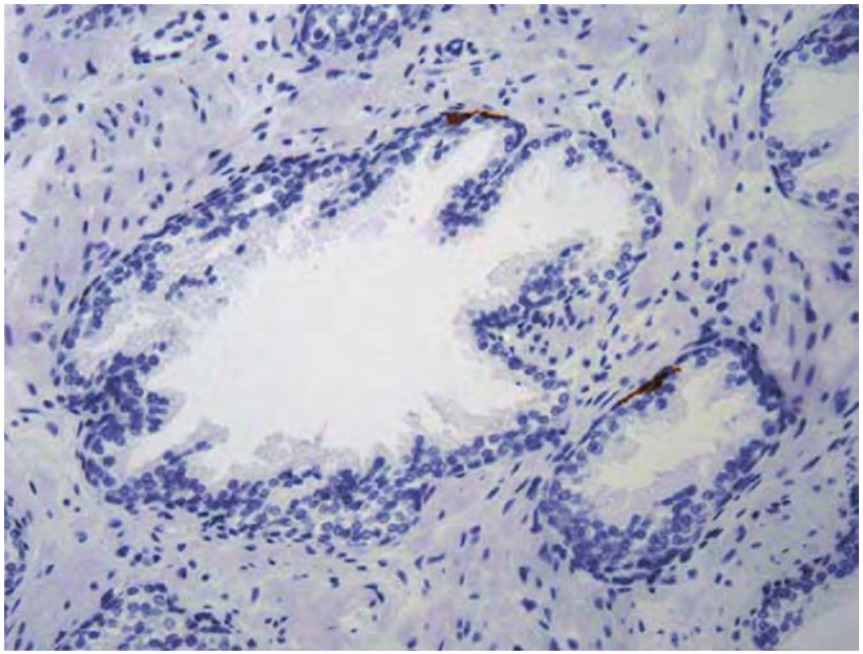
5) What would a urologist do if we identified a small cell cancer?

MODERN PATHOLOGY (2018) 31, S122–S132
© 2018 USCAP, Inc All rights reserved 0893-3952/18 $32.00

Neuroendocrine tumors of the prostate

Samson W Fine

Based on his Prostate Cancer Long Course Talk 2017



-Neuroendocrine (NE) cells present in the prostate

-Widely scattered throughout normal prostatic glands (part of APUD system)

-NE cells can be detected by chromogranin

-In localized prostate cancer, NE positive cells **NOT** independently associated with worse clinical outcome (despite some early studies suggesting this)

Samson Fine, Modern Pathology (2018) 31, S122-S132

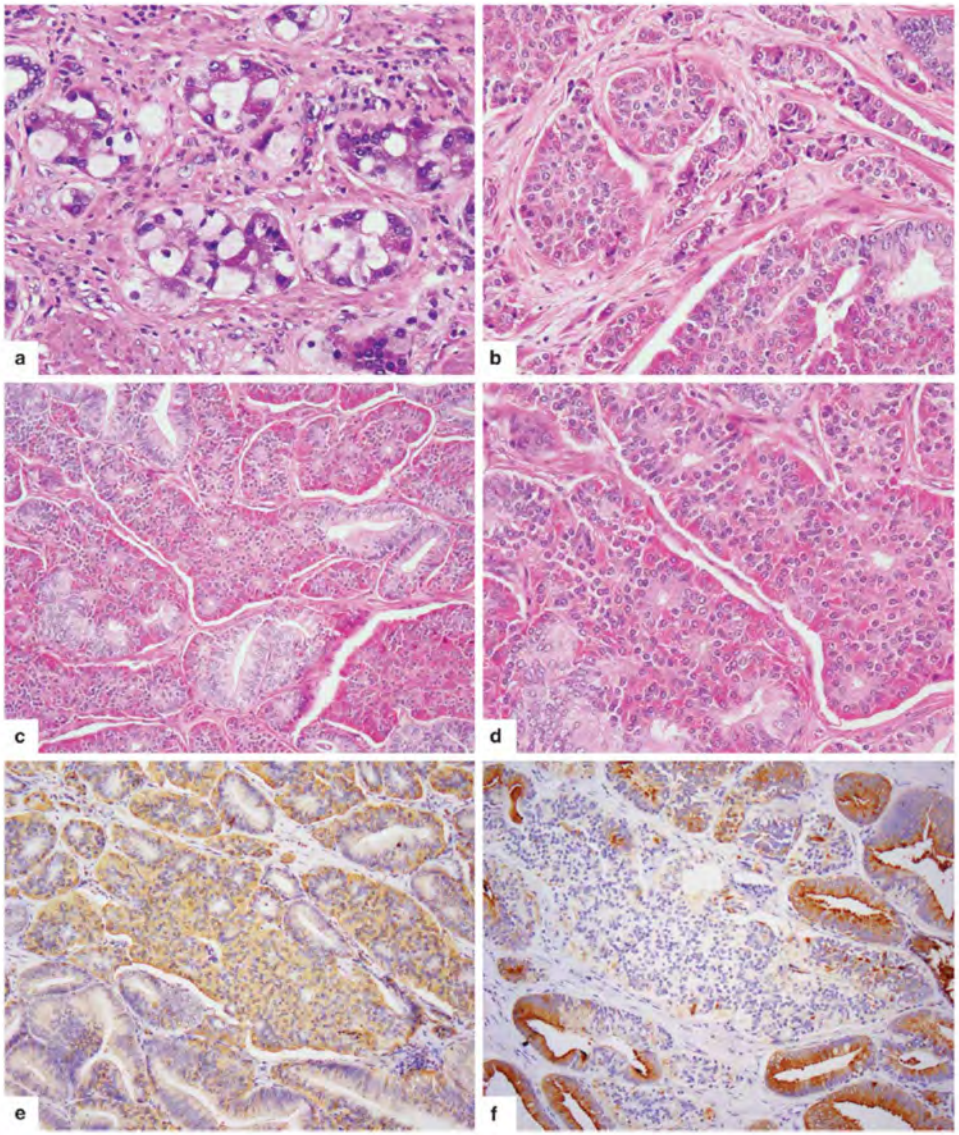
When it is not adenocarcinoma…

Table 1 Existing Classifications of prostate cancer with neuroendocrine differentiation

Prostate Cancer Foundation working committee proposed classification	*2016 World Health Organization genitourinary tumor classification*
Usual prostate adenocarcinoma with NE differentiation	NE cells in usual prostate cancer
Adenocarcinoma with Paneth cell NE differentiation	Adenocarcinoma with Paneth cell-like NE differentiation
Carcinoid tumor	Well-differentiated NE tumor (carcinoid)
Small cell carcinoma	Small cell NE carcinoma
LCNEC	Large cell NE carcinoma
Mixed (small or large cell) NE carcinoma-acinar adenocarcinoma	

Abbreviations: LCNEC, large cell neuroendocrine carcinoma; NE, neuroendocrine.

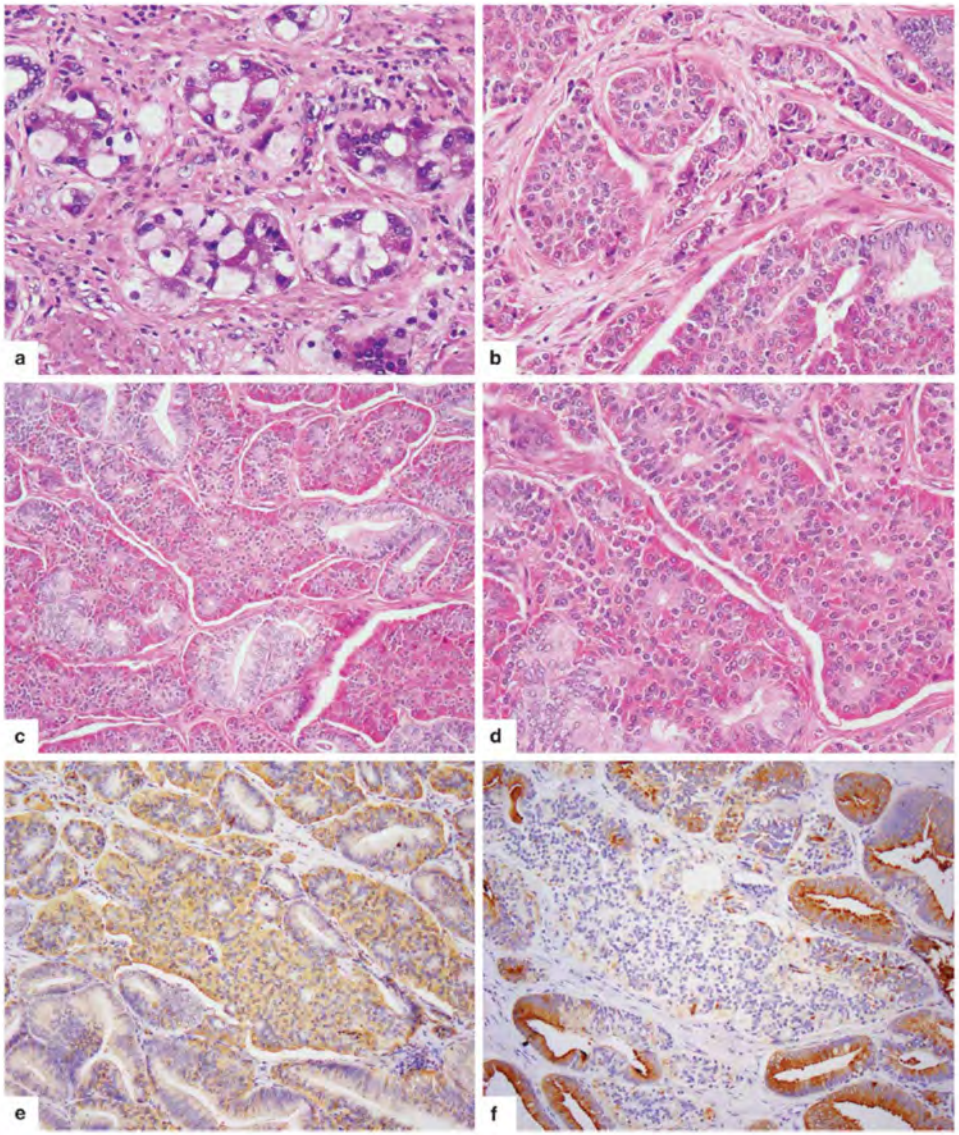
Samson Fine, Modern Pathology (2018) 31, S122-S132



Paneth cell-like changes with adendocarcinoma

Chromogranin but only weak PSA protein expression

Samson Fine, Modern Pathology (2018) 31, S122-S132



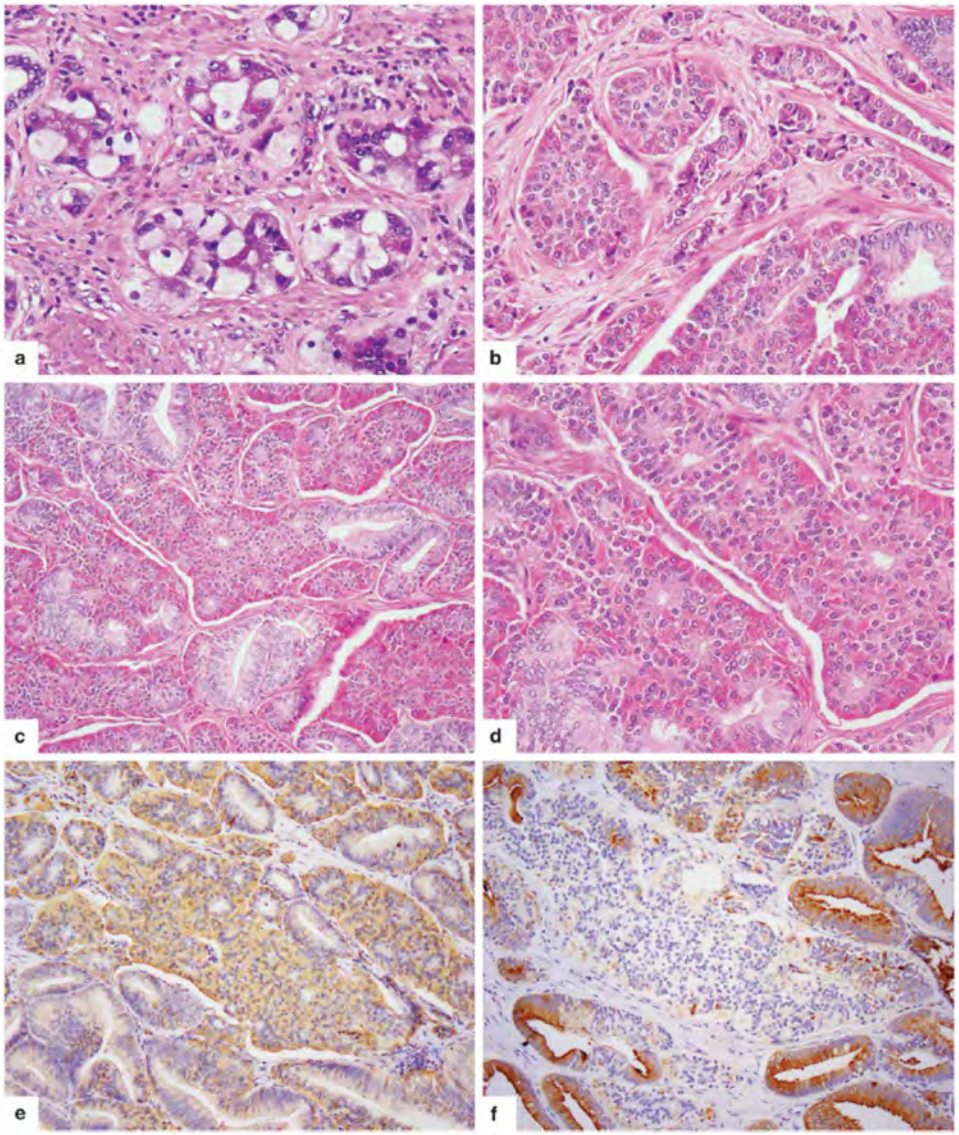
Paneth cell-like changes with adendocarcinoma

Question: How should these areas be graded?

A. Gleason pattern 3
B. Gleason pattern 5
C. Don't grade this area

Audience Response System (ARS) Question

Samson Fine, Modern Pathology (2018) 31, S122-S132



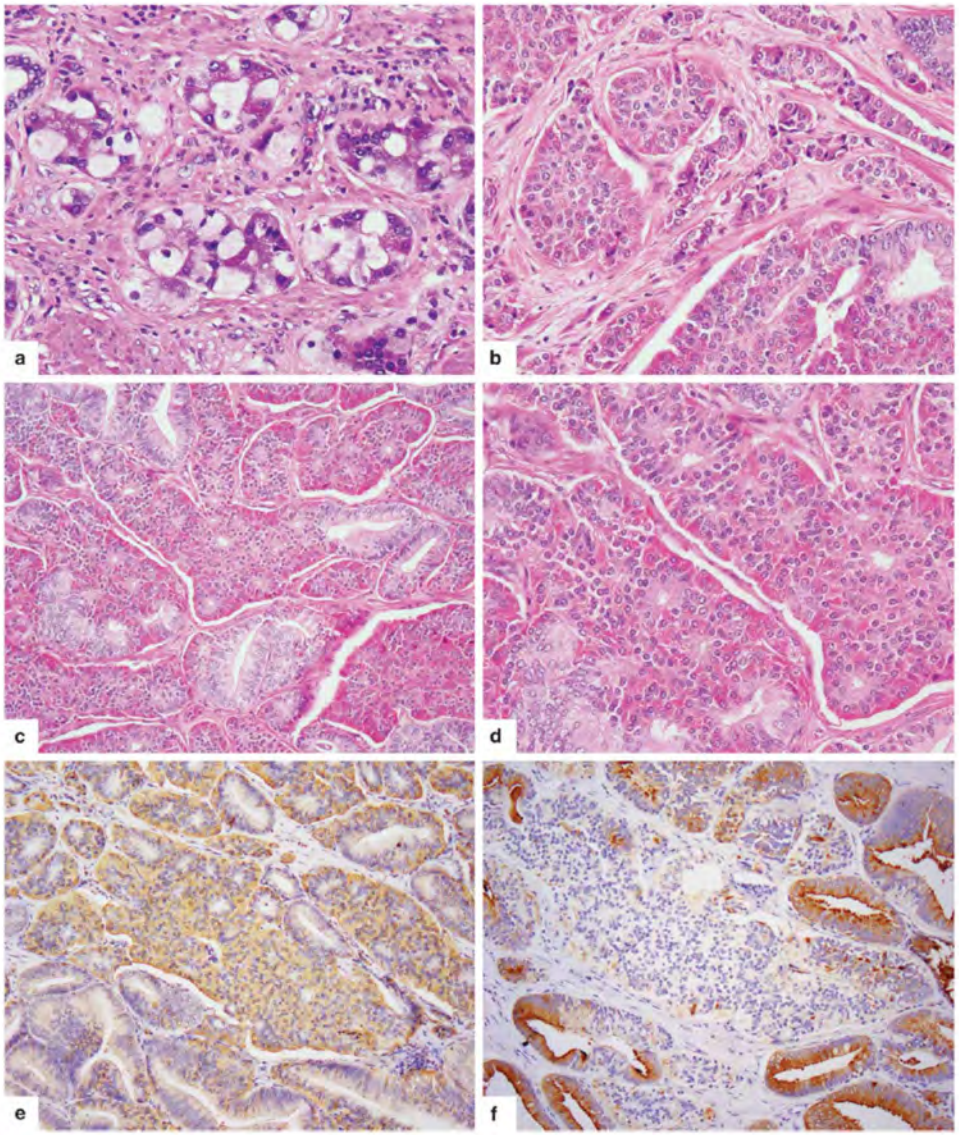
Paneth cell-like changes with adendocarcinoma

Question: How should these areas be graded?

A. Gleason pattern 3
B. Gleason pattern 5
C. Don't grade this area

Audience Response System (ARS) Question

Samson Fine, Modern Pathology (2018) 31, S122-S132



Paneth cell-like changes with adendocarcinoma

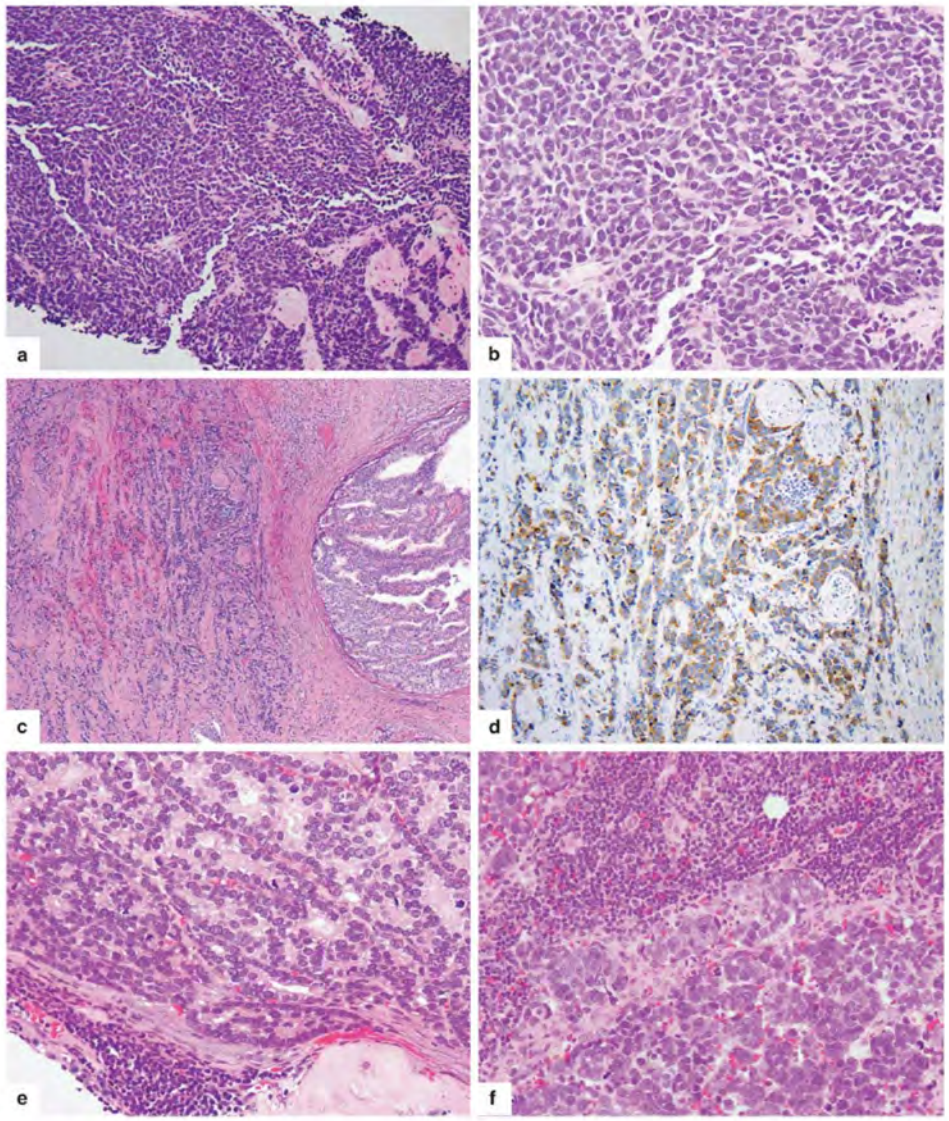
"may present a diagnostic dilemma, as grading them based on architecture would likely result in assigning Gleason pattern 5 (Figure b). Follow-up in small series, however, has suggested that these cases do not manifest clinical progression commensurate with a high-grade diagnosis and have outcome dependent on standard grading (in the non-Paneth cell-like areas) and staging parameters. It is suggested that only the conventional carcinoma be graded, to avoid inaccurate upgrading, and a notation made regarding this finding." –S. Fine, Mod Path 2018

Tamas EF, Epstein JI. Prognostic significance of Paneth cell-like neuroendocrine differentiation in adenocarcinoma of the prostate. Am J Surg Pathol 2006;30: 980–985.

So JS, Gordetsky J, Epstein JI. Variant of prostatic adenocarcinoma with Paneth cell-like neuroendocrine differentiation readily misdiagnosed as Gleason pattern 5. Hum Pathol 2014;45:2388–2393.

Audience Response System (ARS) Question

Samson Fine, Modern Pathology (2018) 31, S122-S132



Small cell carcinoma isolated or with adendocarcinoma is infrequently* seen on prostate needle biopsy or prostatectomy

**Frequency may be related to the selection of patients for definitive therapy. There is increasing use of definitive surgery for men with oligometastatic disease. These frequency of small cell cancer could be expected to be higher in this population*

Samson Fine, Modern Pathology (2018) 31, S122-S132

RESEARCH ARTICLE Open Access

Gene expression signatures of neuroendocrine prostate cancer and primary small cell prostatic carcinoma

Harrison K. Tsai[1,4*], Jonathan Lehrer[2], Mohammed Alshalalfa[2], Nicholas Erho[2], Elai Davicioni[2] and Tamara L. Lotan[1,3]

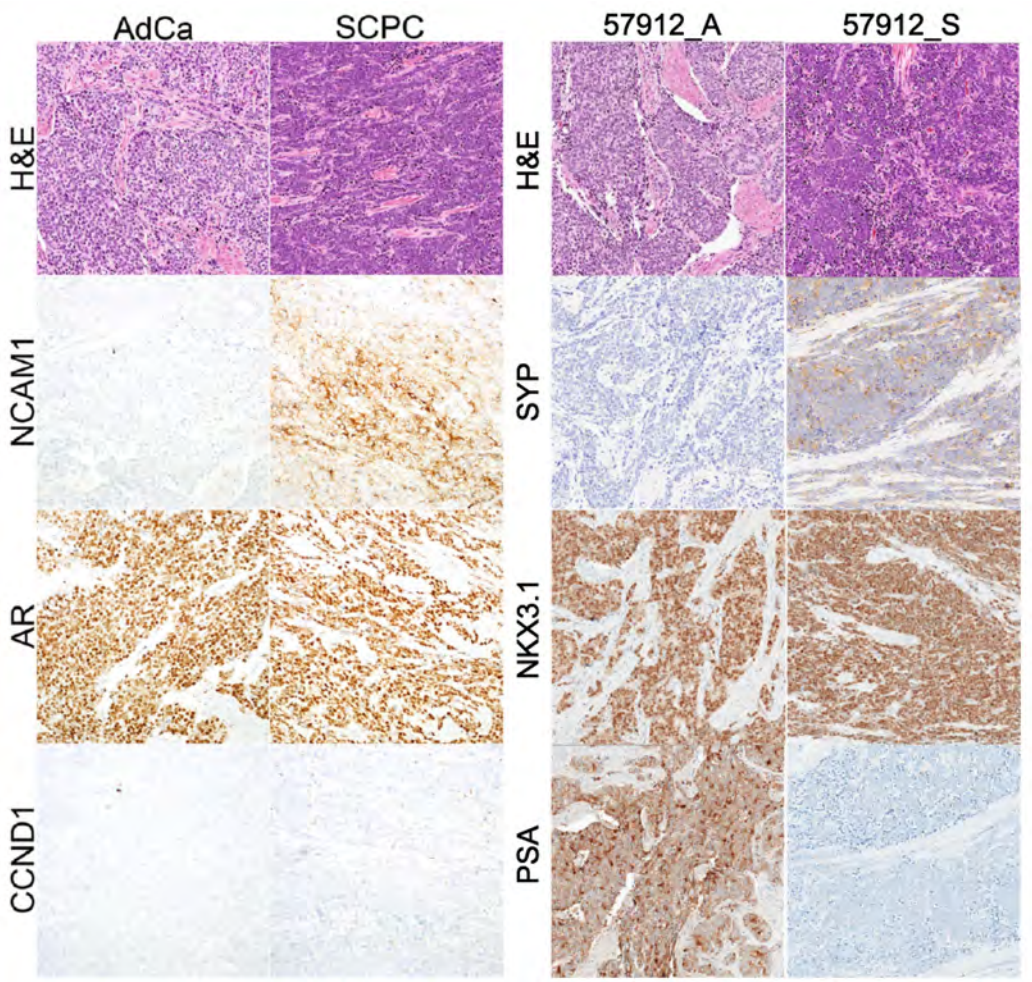
IHC for NE or Small Cell PCa

Synaptophysin

NCAM1/CD56

Chromogranin A

CCND1/Cyclin D1



Tsai et al. BMC Cancer (2017) 17:759

Audience Response System (ARS) Question

Which IHC markers are always useful for NE or Small Cell PCa?

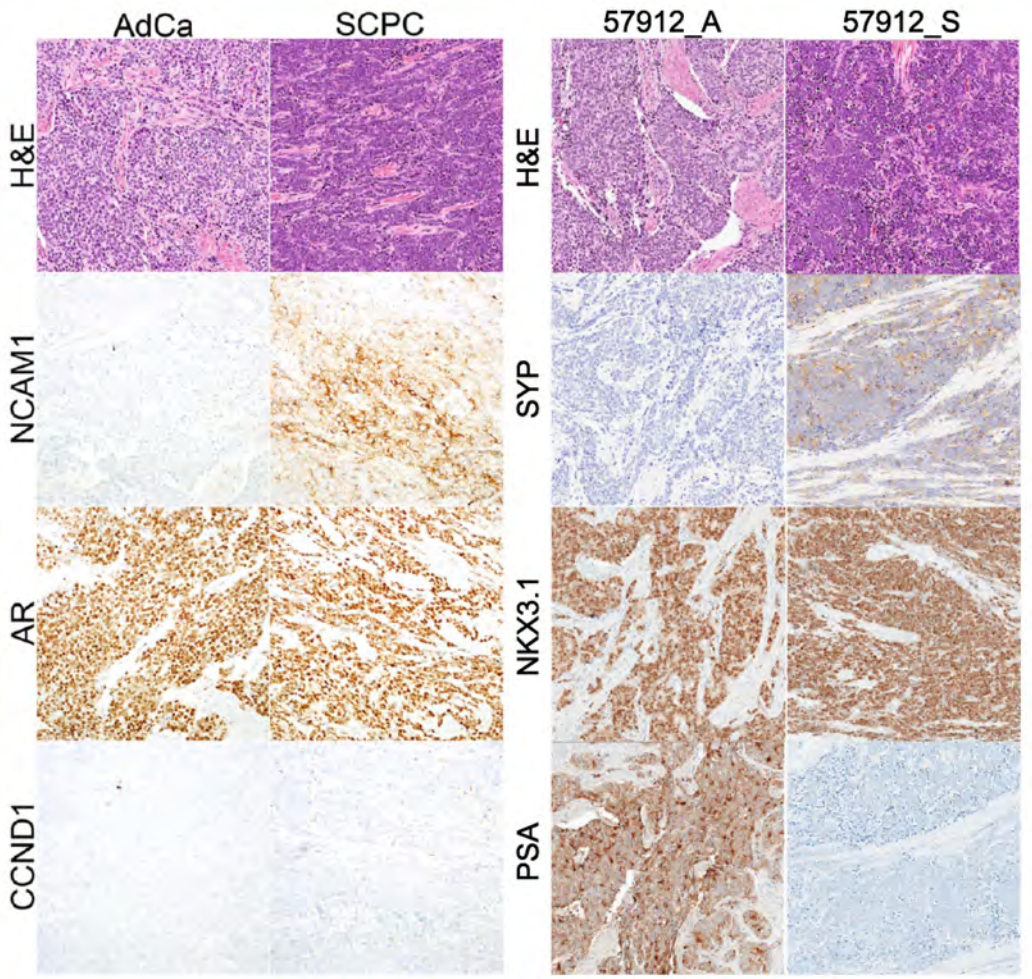
A. Synaptophysin

B. NCAM1/CD56

C. Chromogranin A

D. CCND1/Cyclin D1

E. **None**

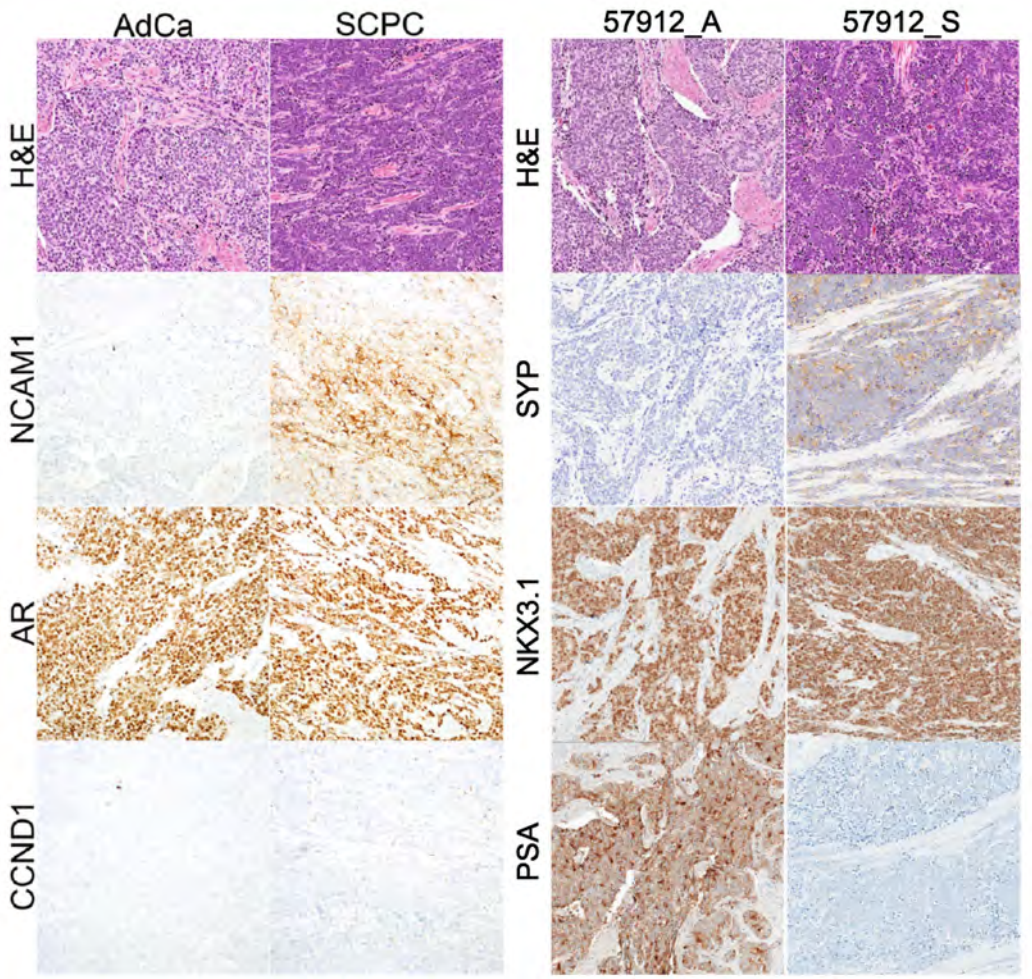


Tsai et al. BMC Cancer (2017) 17:759

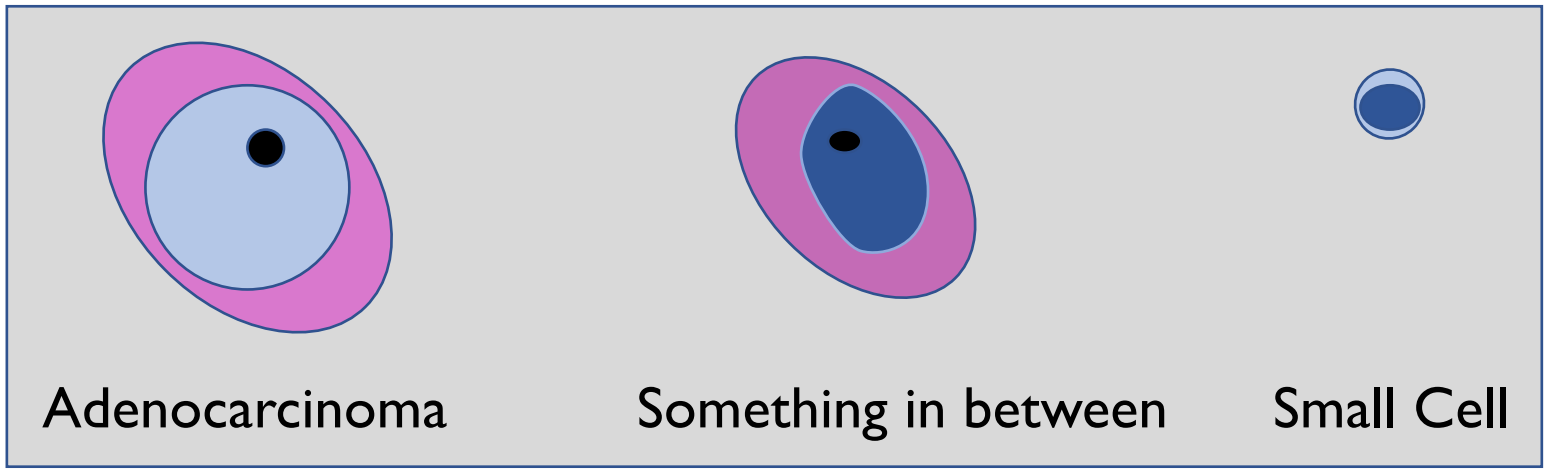
Audience Response System (ARS) Question

Which IHC markers are always useful for NE or Small Cell PCa?

As we can see in this study, sometimes on 2 of 3 IHC NE markers are positive. Prior studies have also shown heterogeneity in expression between tumors.



Tsai et al. BMC Cancer (2017) 17:759



Microscopy

IHC

IHC

IHC

Chromogranin
Synaptophysin
NPE
CD56/NCAM1

Neuroendocrine

No Maybe No

Do you need to perform IHC?

Part 1: Localized Prostate Cancer

1) This is what we see most often (99.9%) in daily practice.

2) Major questions for us is cancer versus no-cancer and then Gleason score, stage, and margin status.

3) Rarely do we order IHC for neuroendocrine markers but more often we get asked to review cases when they are ordered.

4) What would a urologist do differently if we did find neuroendocrine features?

5) What would a urologist do if we identified a small cell cancer?

Part 2: Advanced Prostate Cancer

1) May be seen more often as oncologist perform metastatic biopsies (e.g., indication for PARPi and MSI-Immunotherapy)

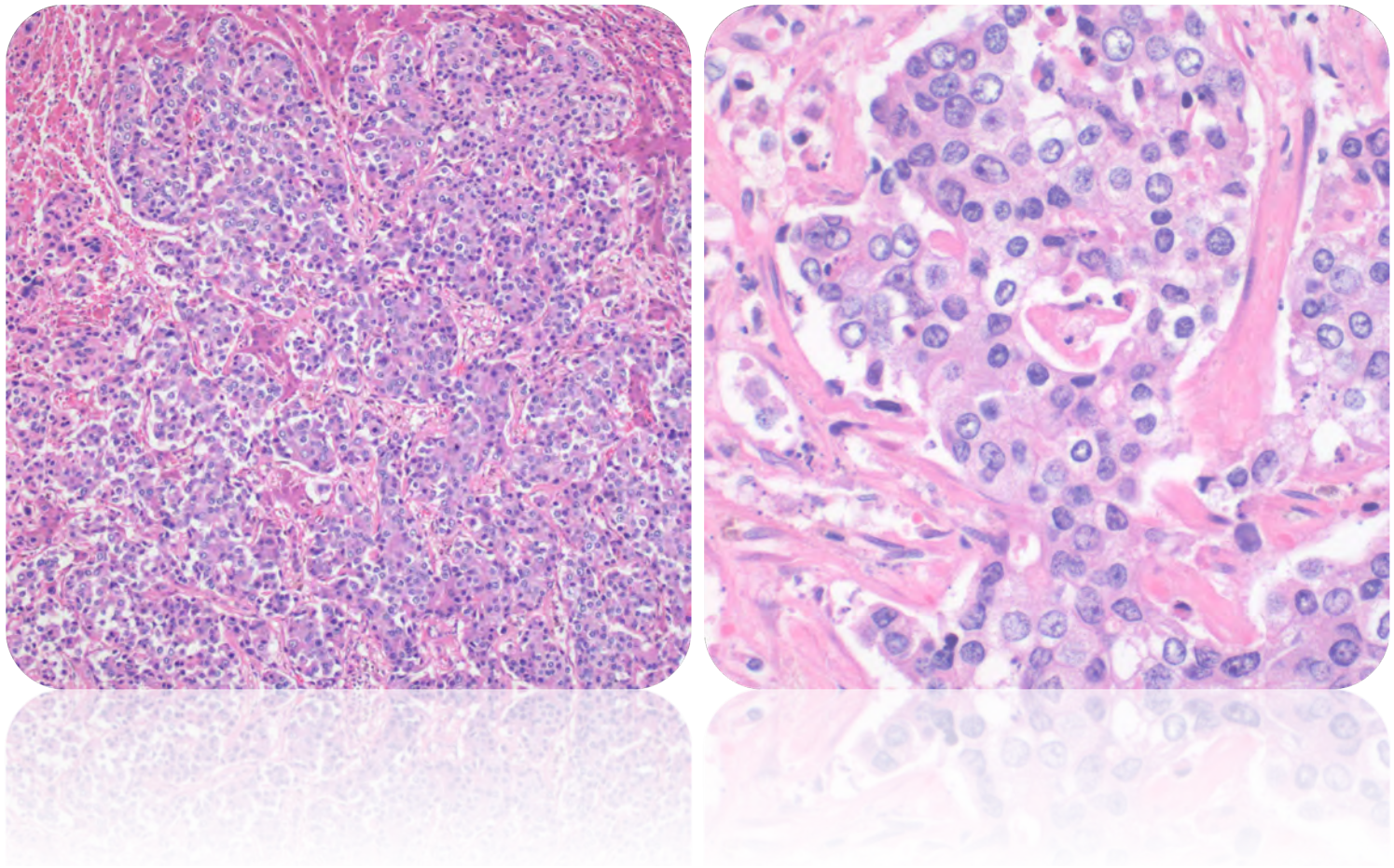
2) Major question is cancer versus no cancer

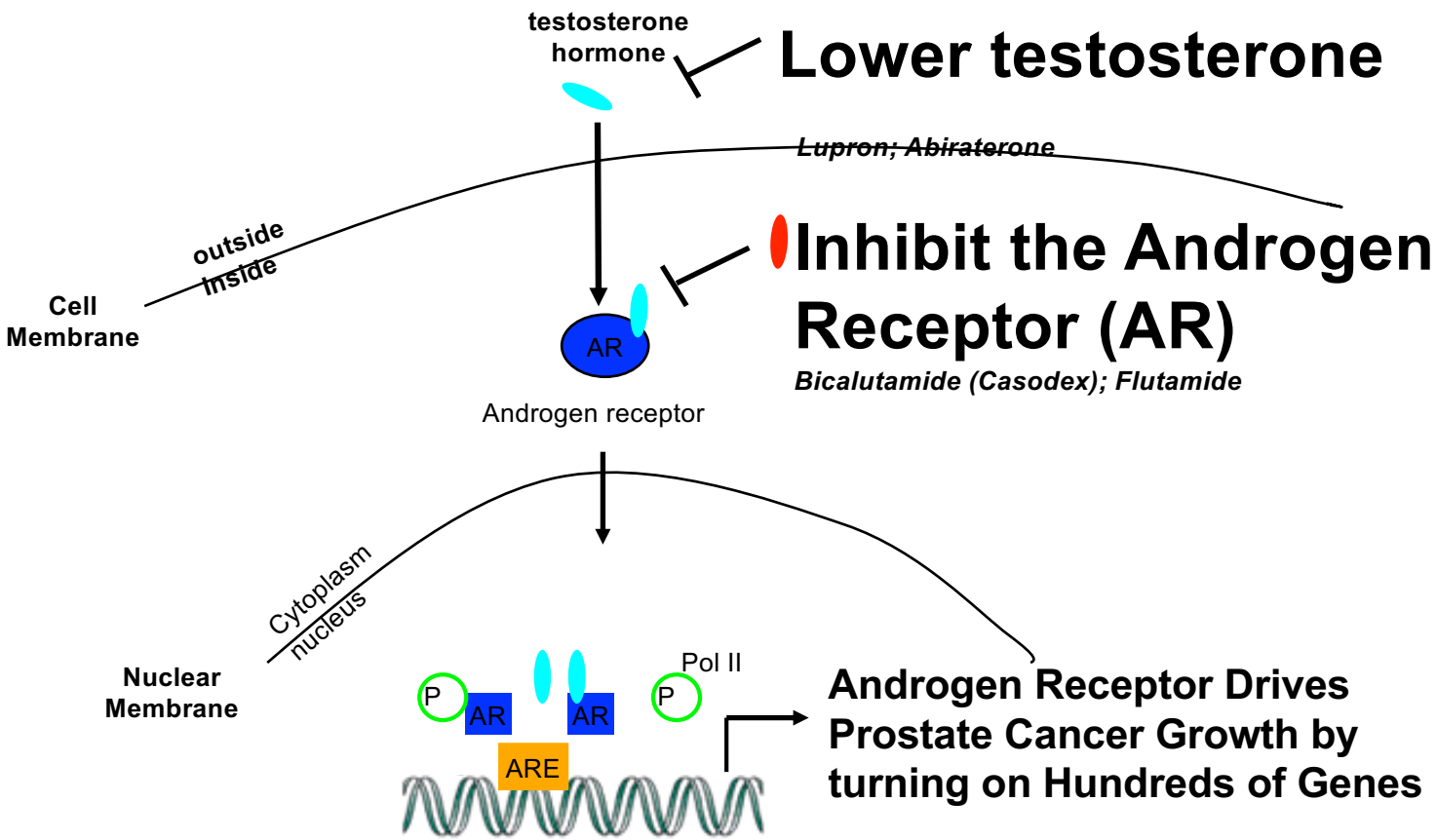
3) Classification and "grading" of treated cancer unclear

4) What would a urologist/oncologist do differently if we did find neuroendocrine features?

5) What would a urologist/oncologist do if we identified a small cell cancer?

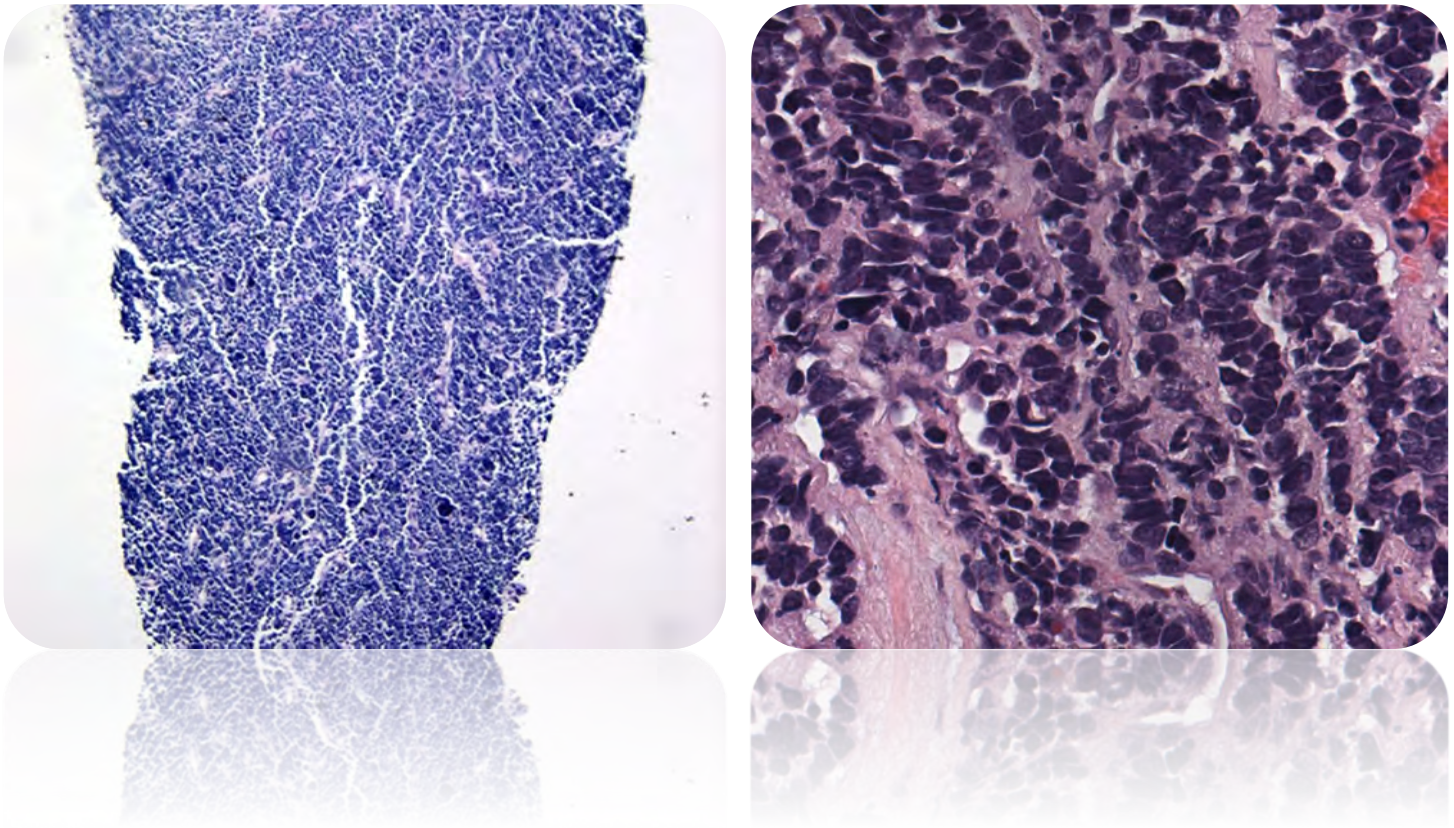
Diagnosis: Prostate Cancer, adenocarcinoma



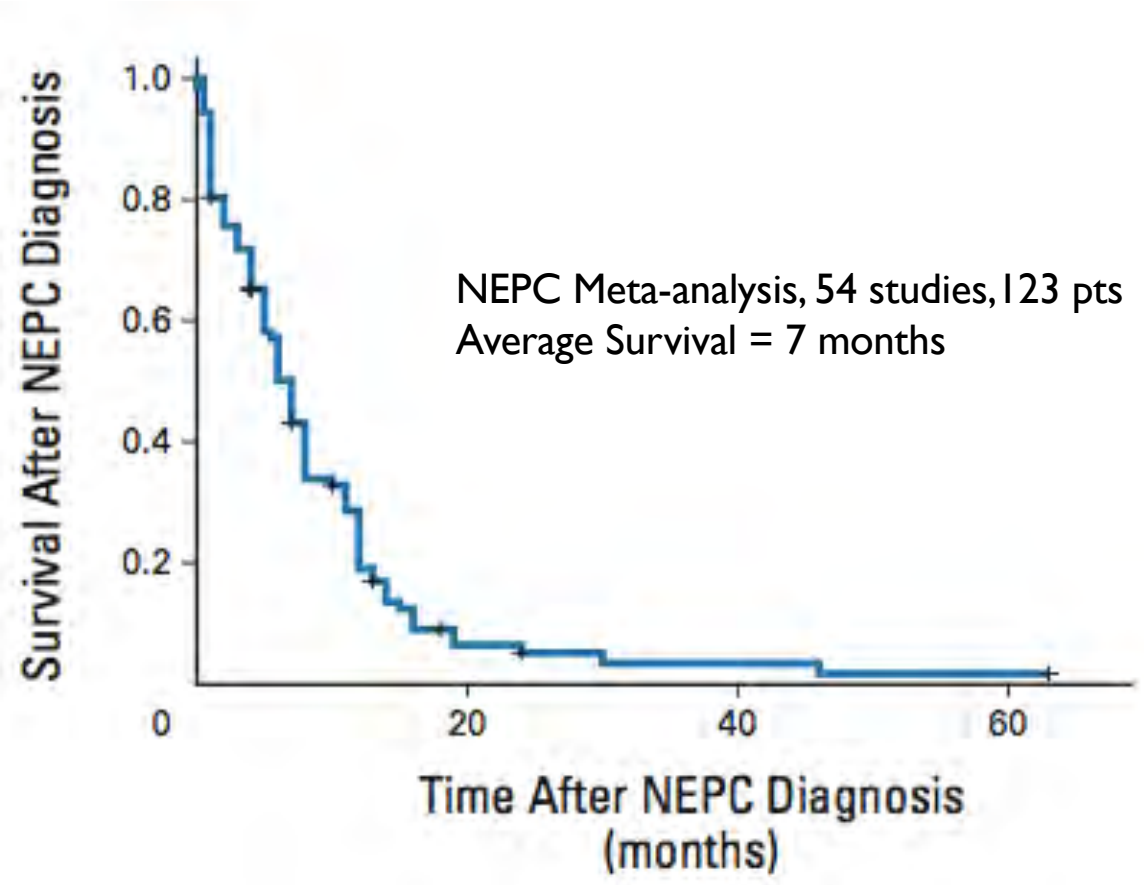


Modified from C. Sawyer

Diagnosis: Small Cell/Neuroendocrine Prostate Cancer



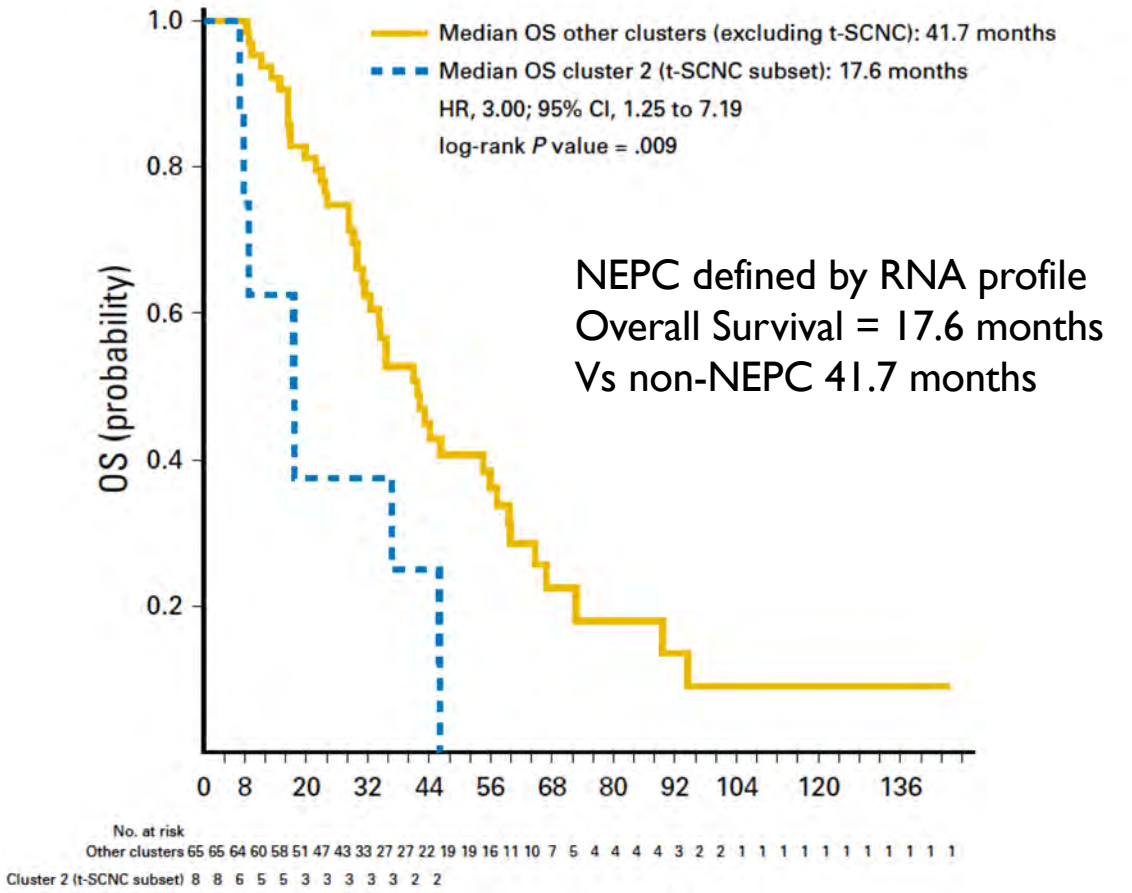
Neuroendocrine Prostate Cancer: Poor Outcome



NEPC Meta-analysis, 54 studies, 123 pts
Average Survival = 7 months

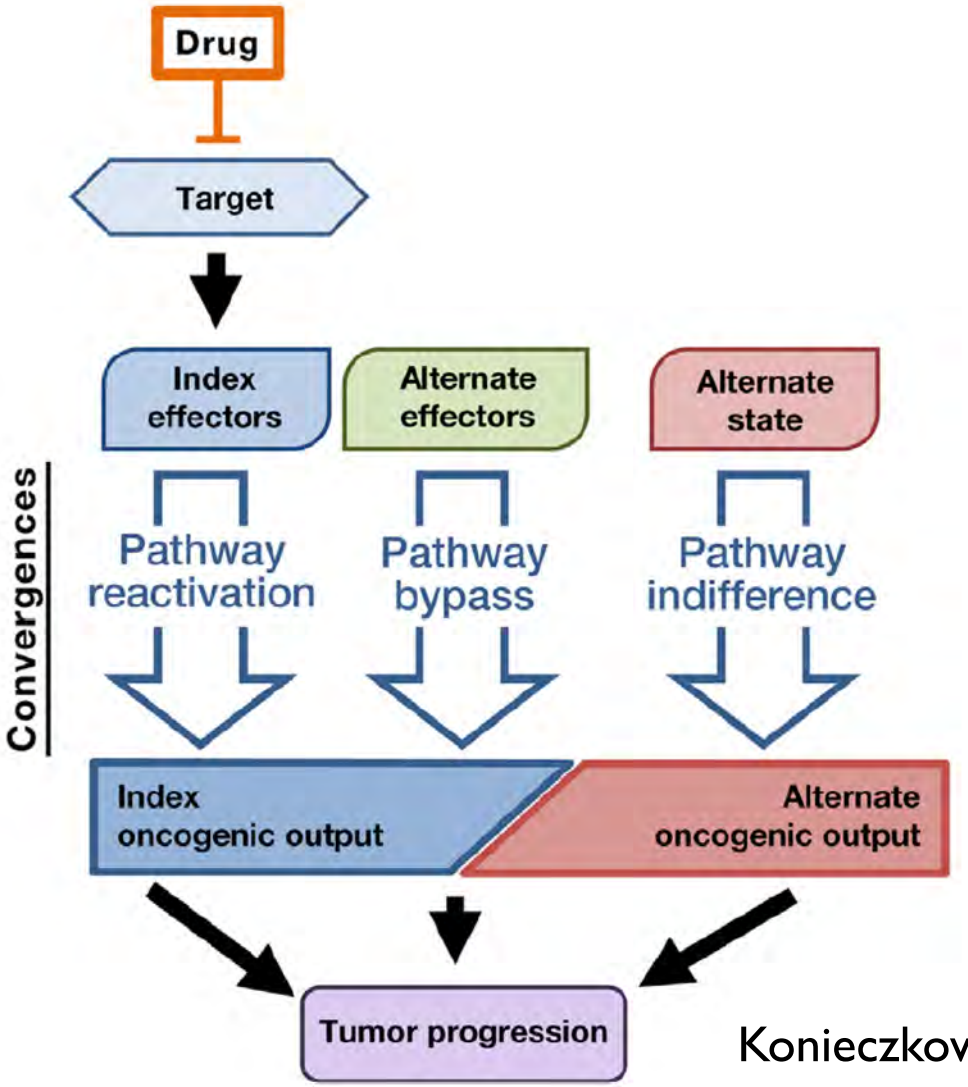
Wang et al, *JCO* Sept 2014

Neuroendocrine Prostate Cancer: Poor Outcome



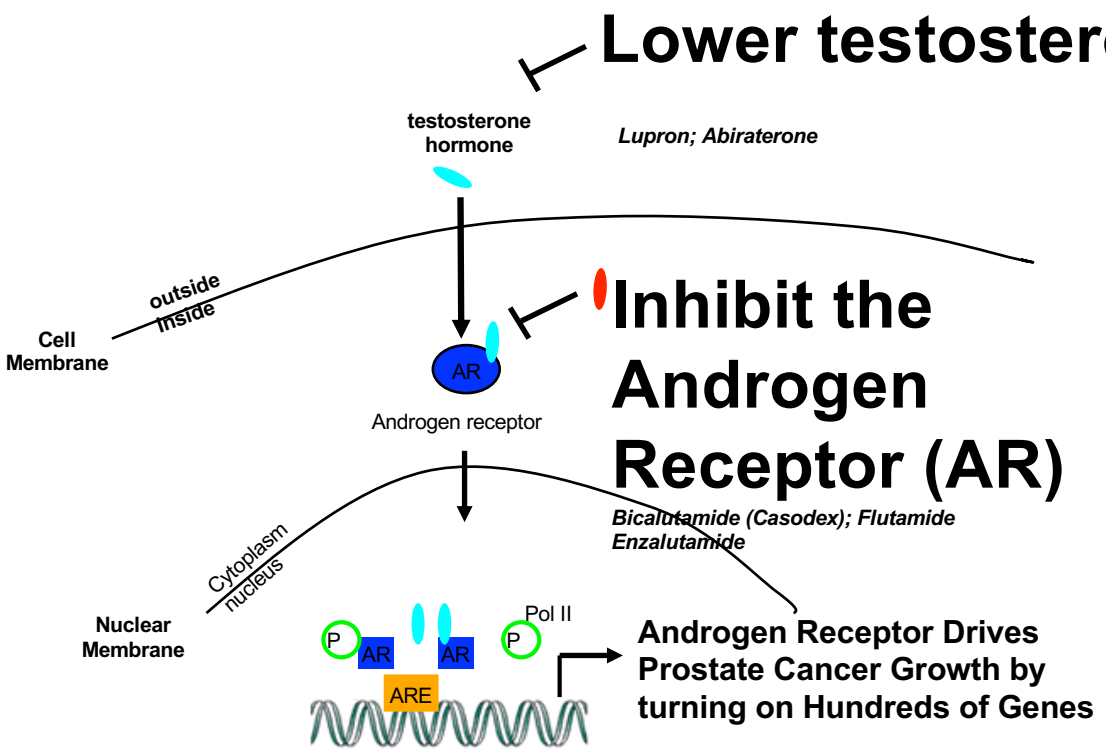
NEPC defined by RNA profile
Overall Survival = 17.6 months
Vs non-NEPC 41.7 months

Aggarwal et al., J Clin Oncol 36:2492-2503

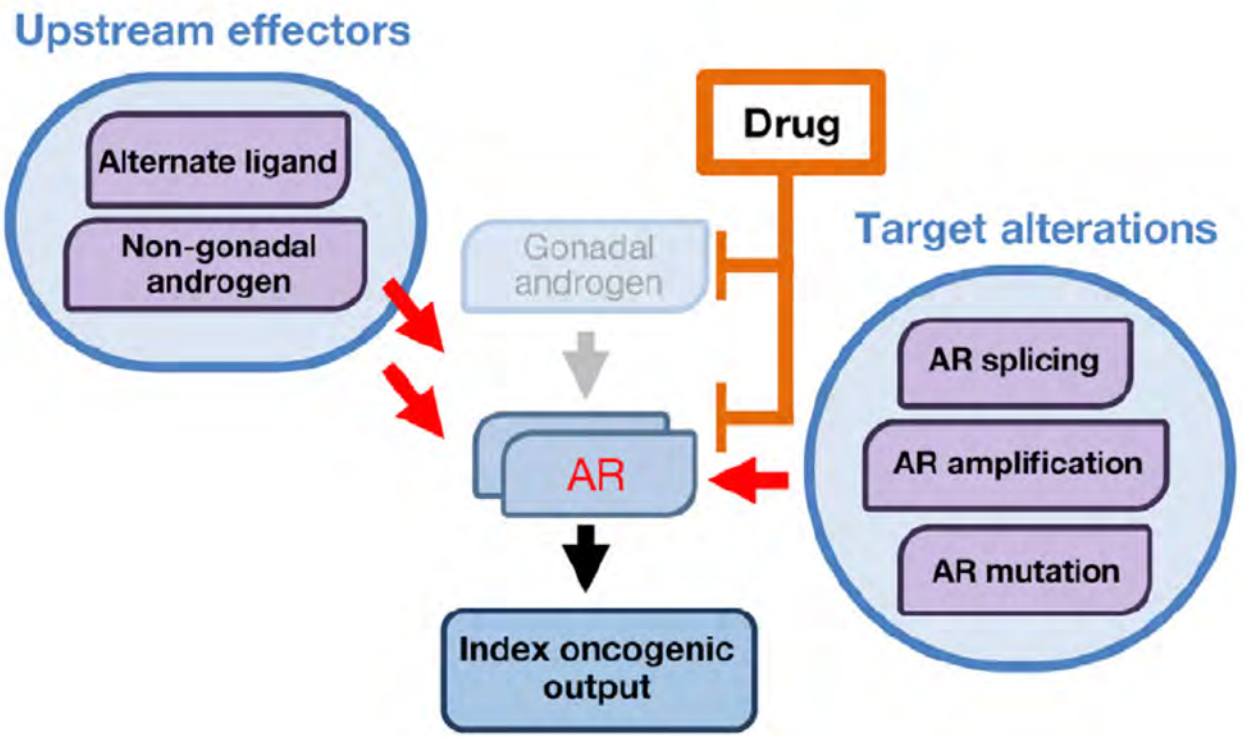


Konieczkowski et al, Cancer Cell 2018

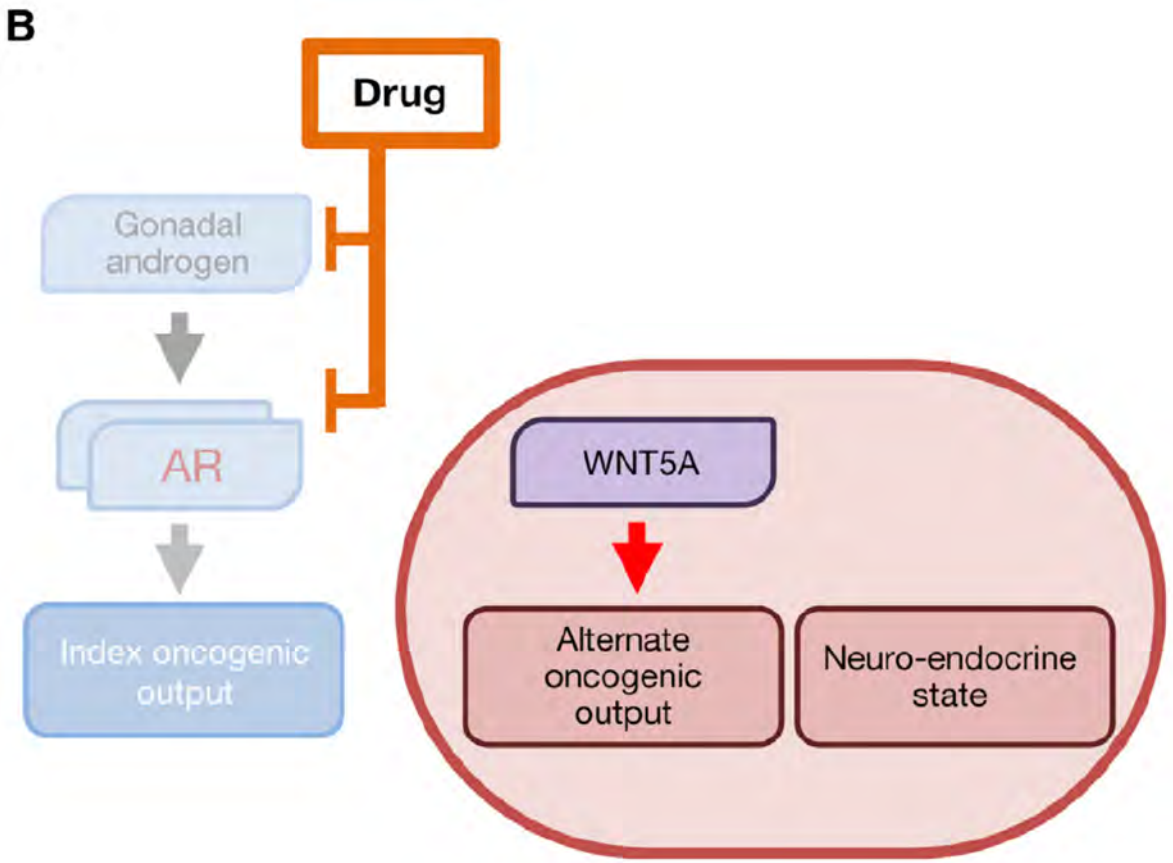
Androgen receptor signaling inhibitors (ARSi) major therapy



Modified from C. Sawyer



Konieczkowski et al, Cancer Cell 2018



Konieczkowski et al, Cancer Cell 2018

The Chameleon Effect

The chameleon responds to the local **environment** and changes **cell type** and **sub-structure** to evade attack

[2]

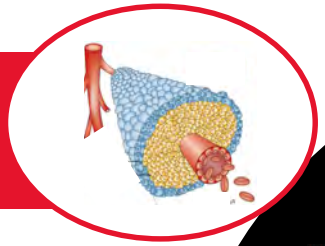
The Chameleon Effect

…..we argue resistant **cancers do the same**……..

[3]

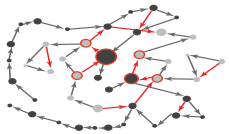
....Four Factors

Tumour microenvironment



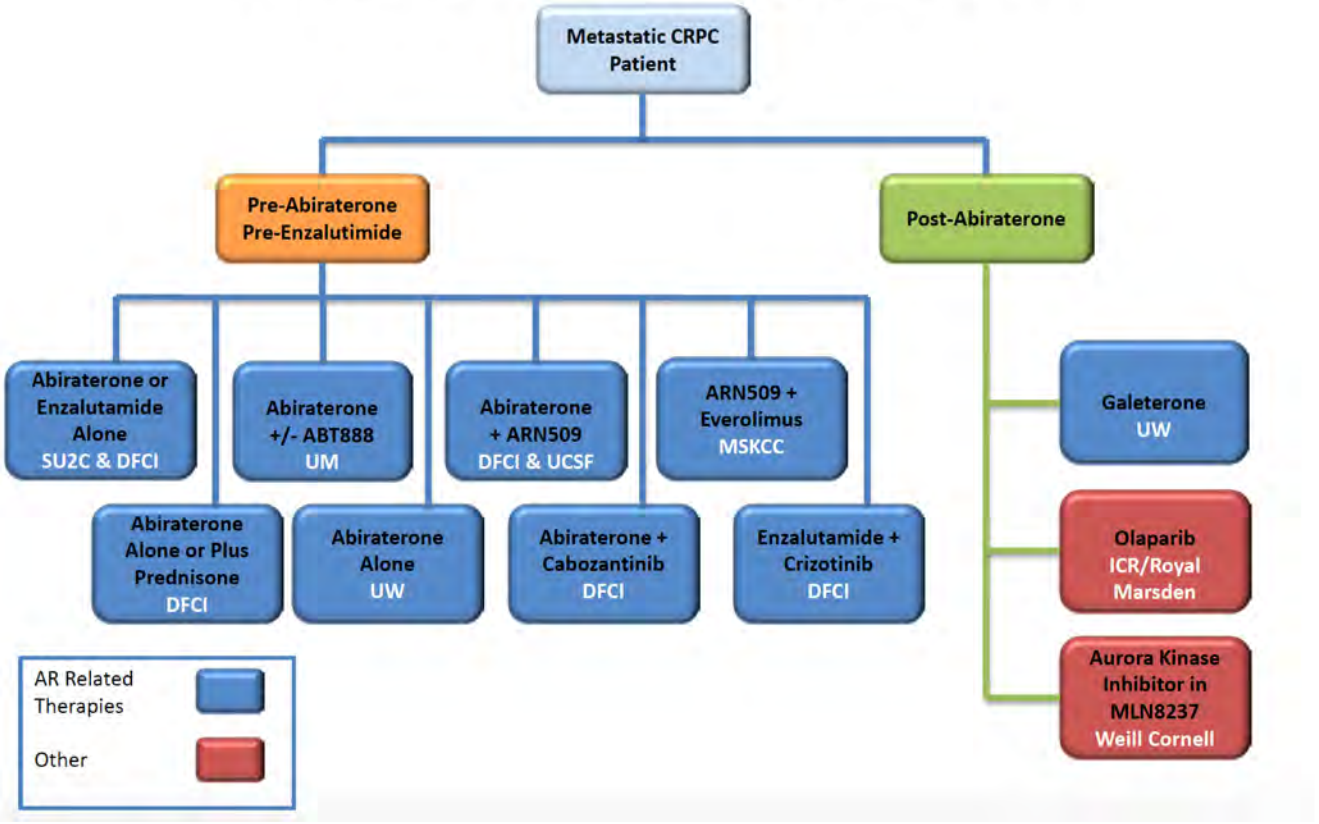
Cell-chromatin landscape and Epigenetics

DNA – Variant's Sub-structure



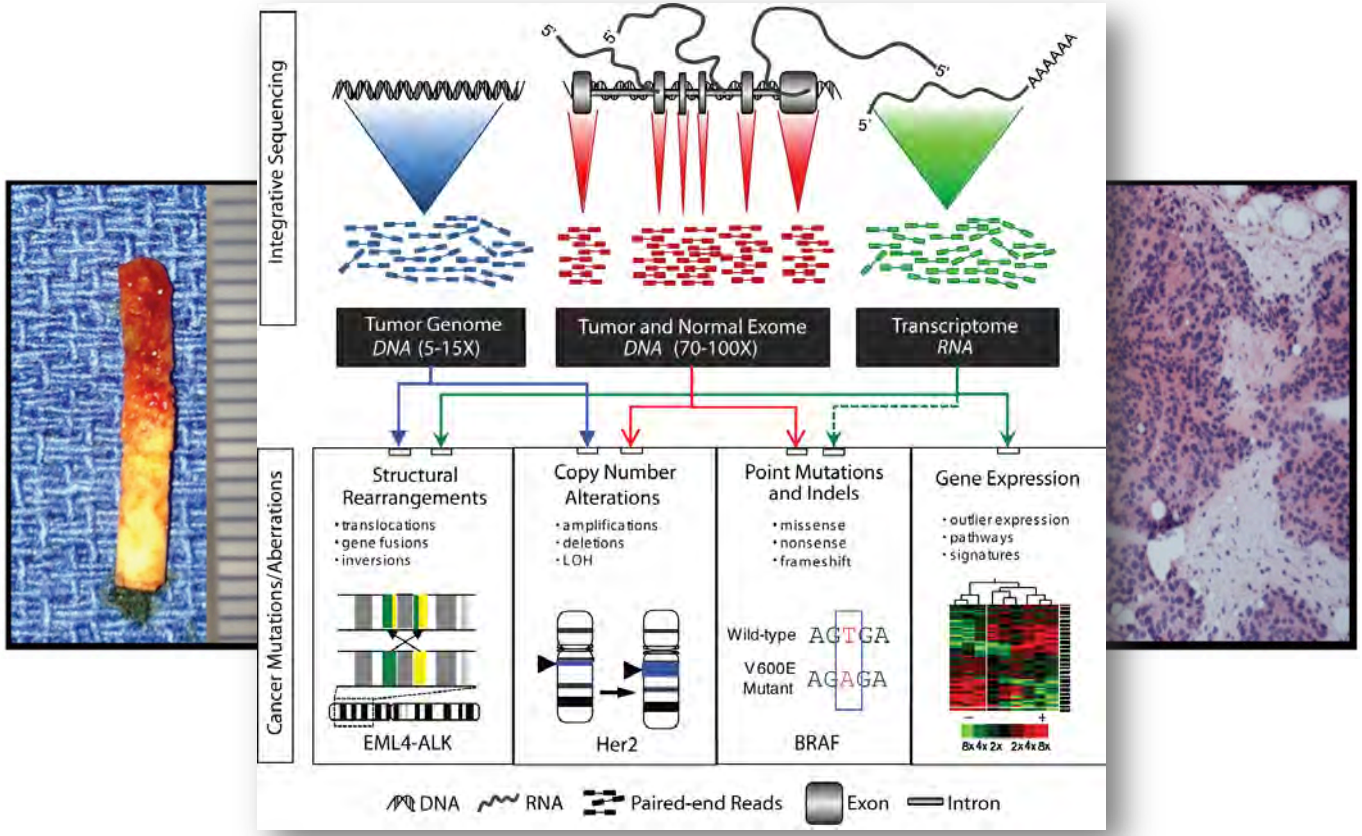
….and the escape from cancer therapy over TIME… [4]

The SU2C-PCF CRPC 500



Leveraging Existing Clinical Trials

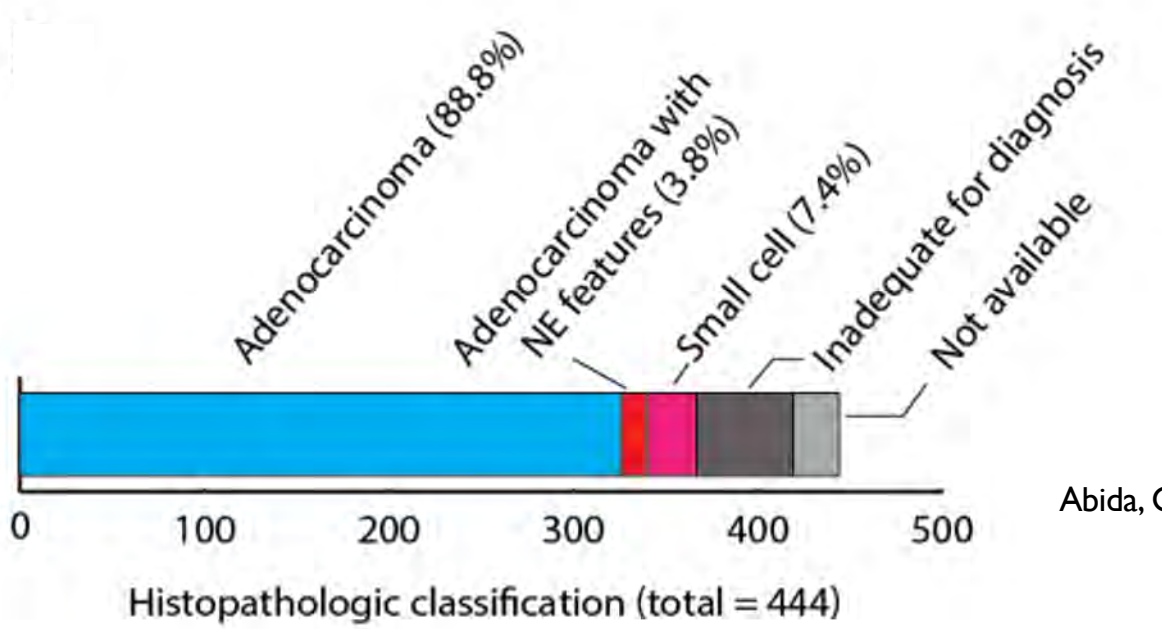
Processing metastatic samples for pathology, RNAseq and WES



SU2C/PCF., Cell 2015

Phenotype / Genotype Correlations: New Pathology

11% mCRPC have some neuroendocrine features

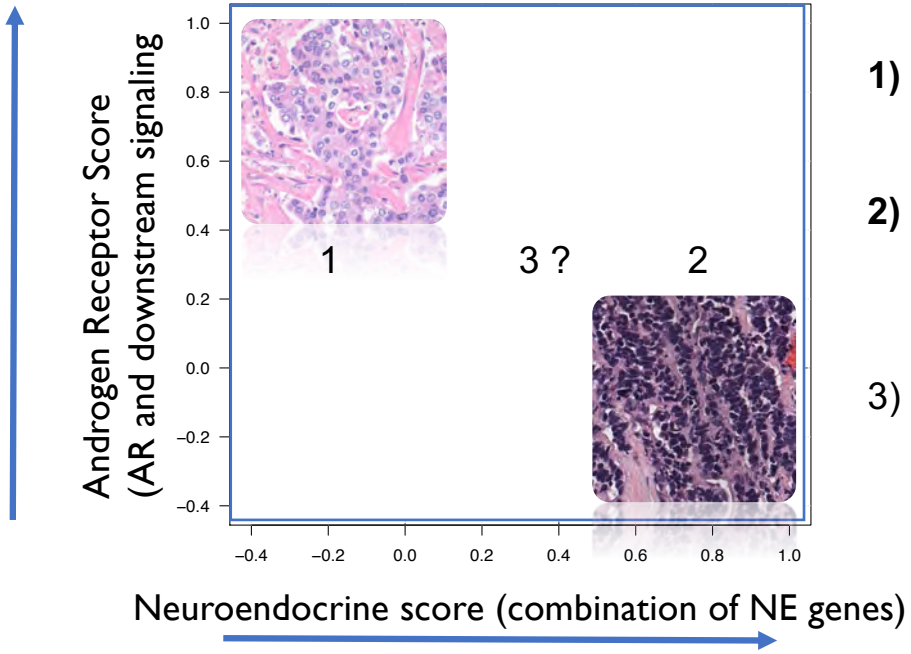


Abida, Cyrta, et al., PNAS 2019

17% mCRPC have some neuroendocrine features

Aggarwal et al., J Clin Oncol 36:2492-2503

Phenotype / Genotype Correlations: New Pathology

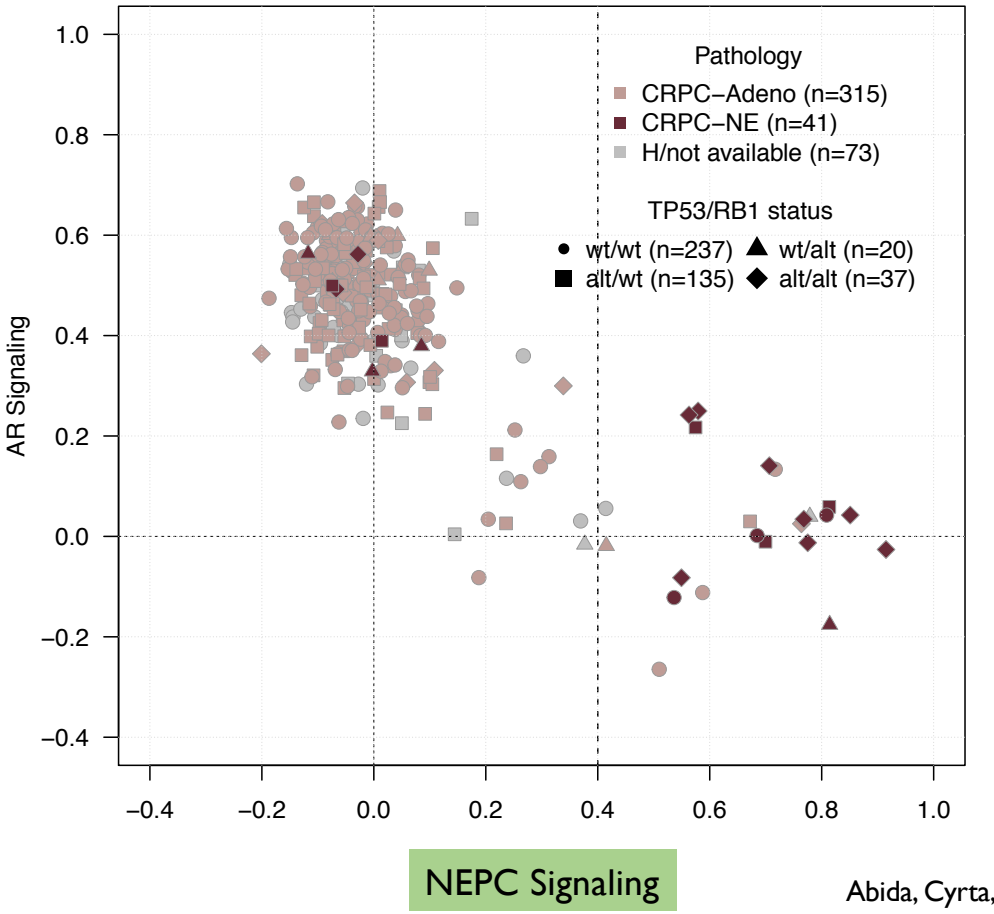


1) **High AR and low NE** signaling associated with adenocarcinoma
2) **High NE and low AR** signaling associated with neuroendocrine prostate cancer
3) Other States? What do they look like and how might they clinically respond to ARSi

Expected Results Comparing AR and NE Signaling in Advanced Prostate Cancer

Phenotype / Genotype Correlations: New Pathology

AR Signaling

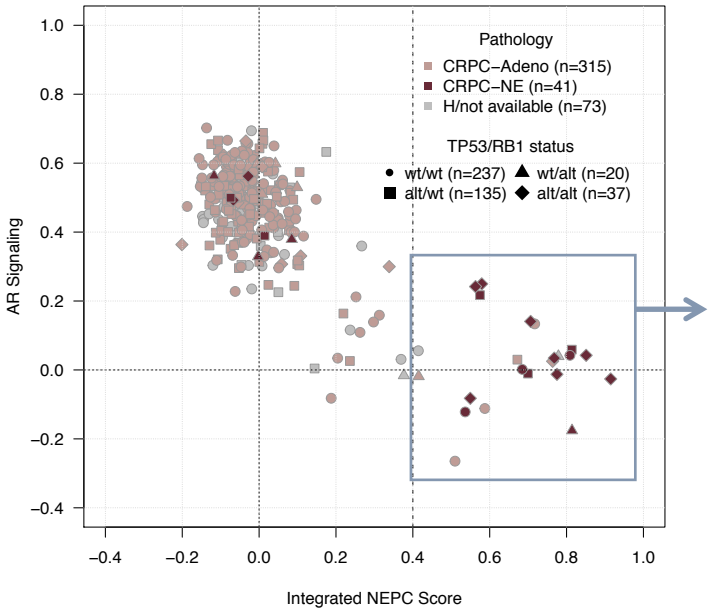


NEPC Signaling

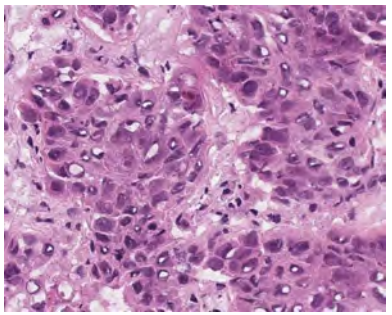
Abida, Cyrta, et al., PNAS 2019

Phenotype / Genotype Correlations: New Pathology

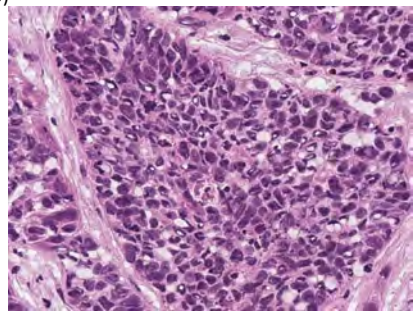
AR Signaling



NEPC Signaling

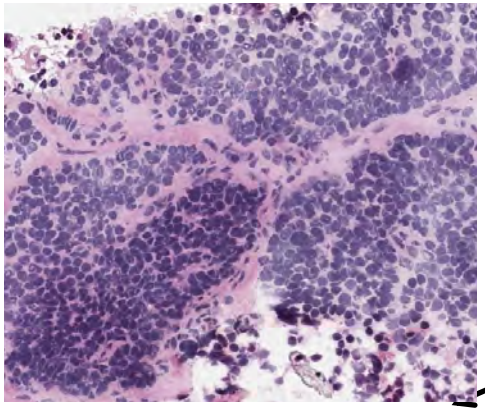


1. Cases with a high NEPC score, but with CRPC-Adeno pathology
(n=6)

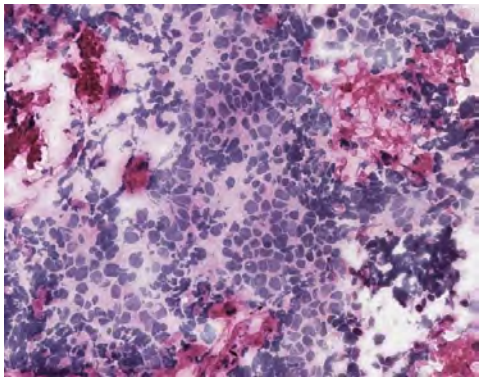


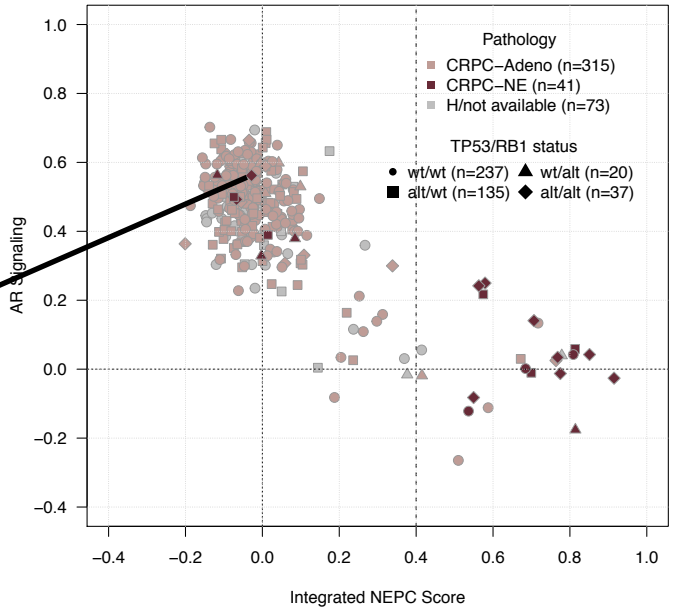
Abida, Cyrta, et al., PNAS 2019

Phenotype / Genotype Correlations: New Pathology



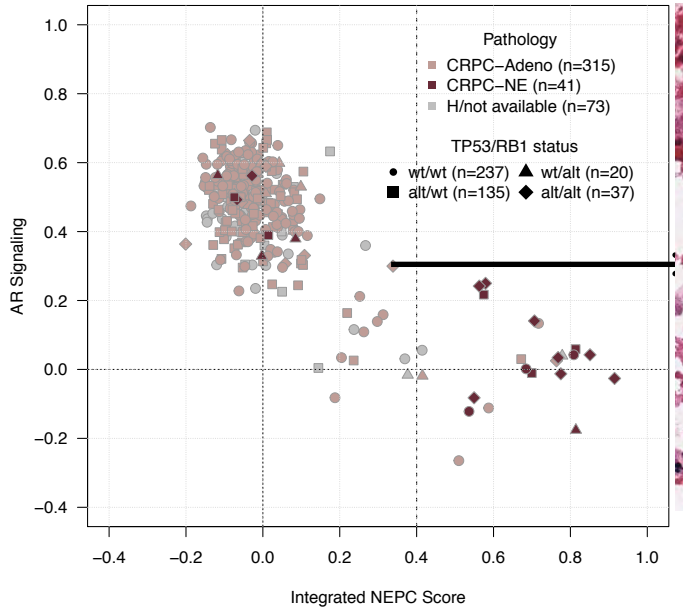
Case : 06115121-T-A-1
Site : LN
NEPC score: -0,03, AR score: 0,56, alt/alt

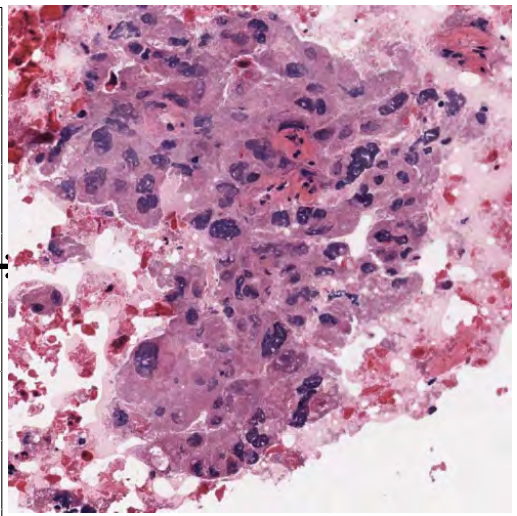




Abida, Cyrta, et al., PNAS 2019

Phenotype / Genotype Correlations: New Pathology



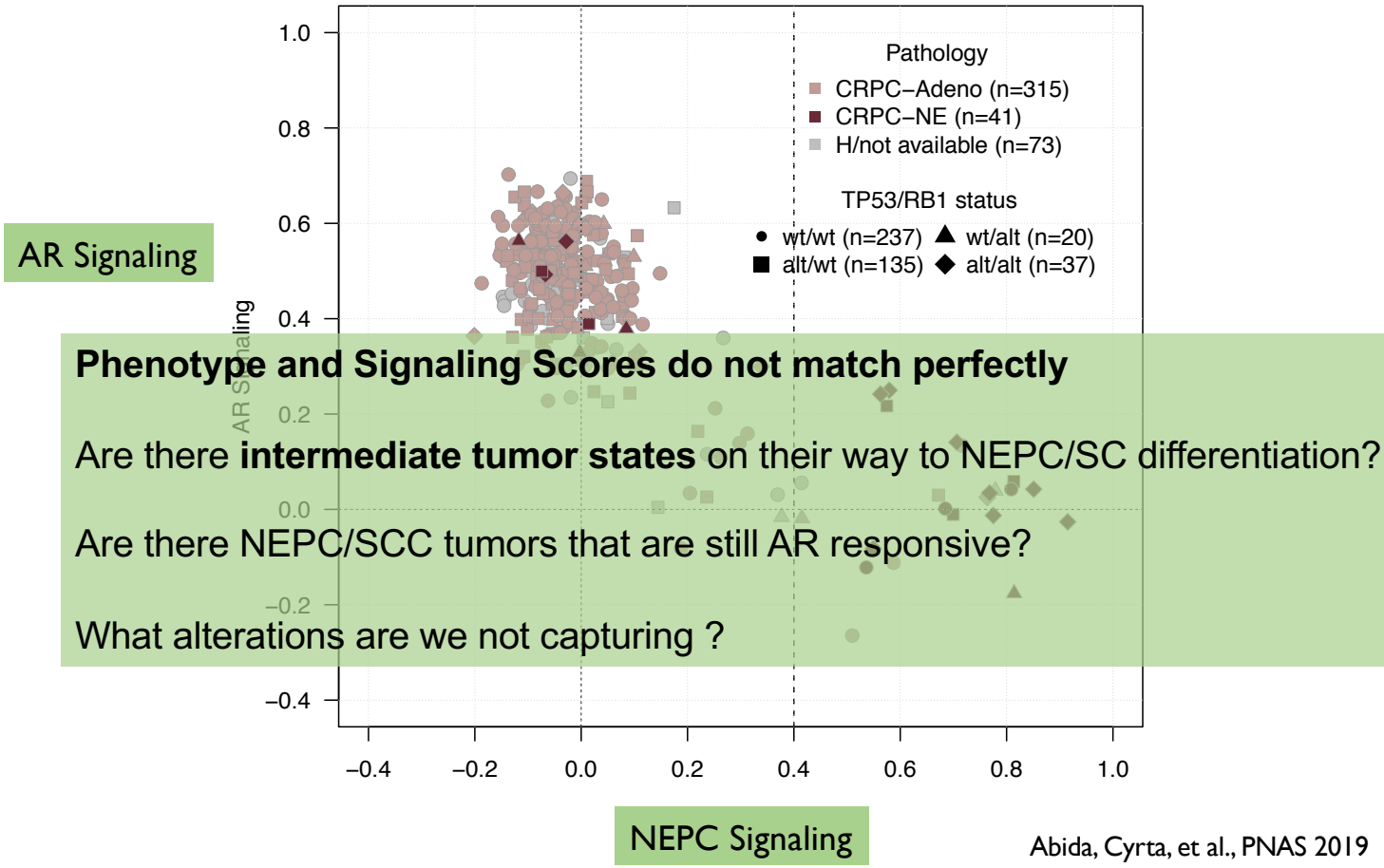


Case : 06115392-T-B-1
Site : LN
NEPC score: 0,34
AR score: 0,3
alt/alt

Pleomorphic nuclei-poorly diff adeno, mut TD53 and RB1

Abida, Cyrta, et al., PNAS 2019

Phenotype / Genotype Correlations: New Pathology



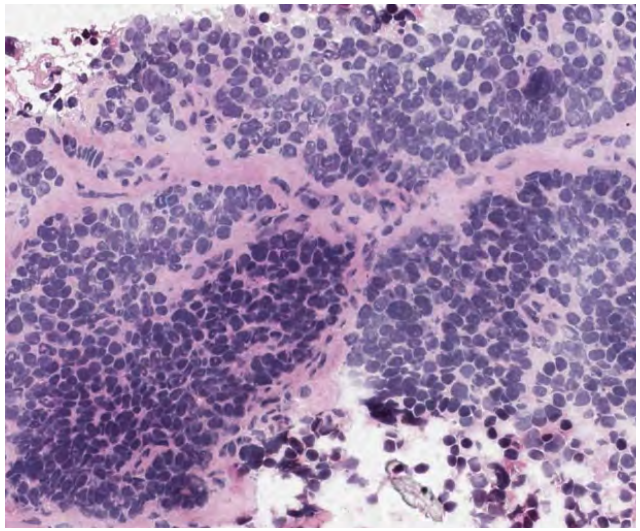
Phenotype and Signaling Scores do not match perfectly

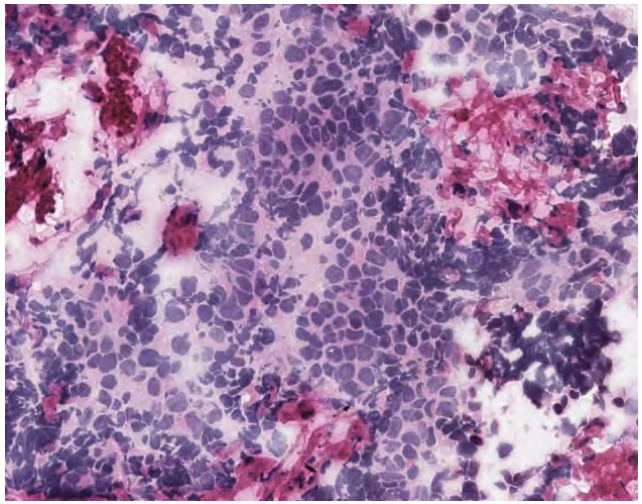
Are there **intermediate tumor states** on their way to NEPC/SC differentiation?

Are there NEPC/SCC tumors that are still AR responsive?

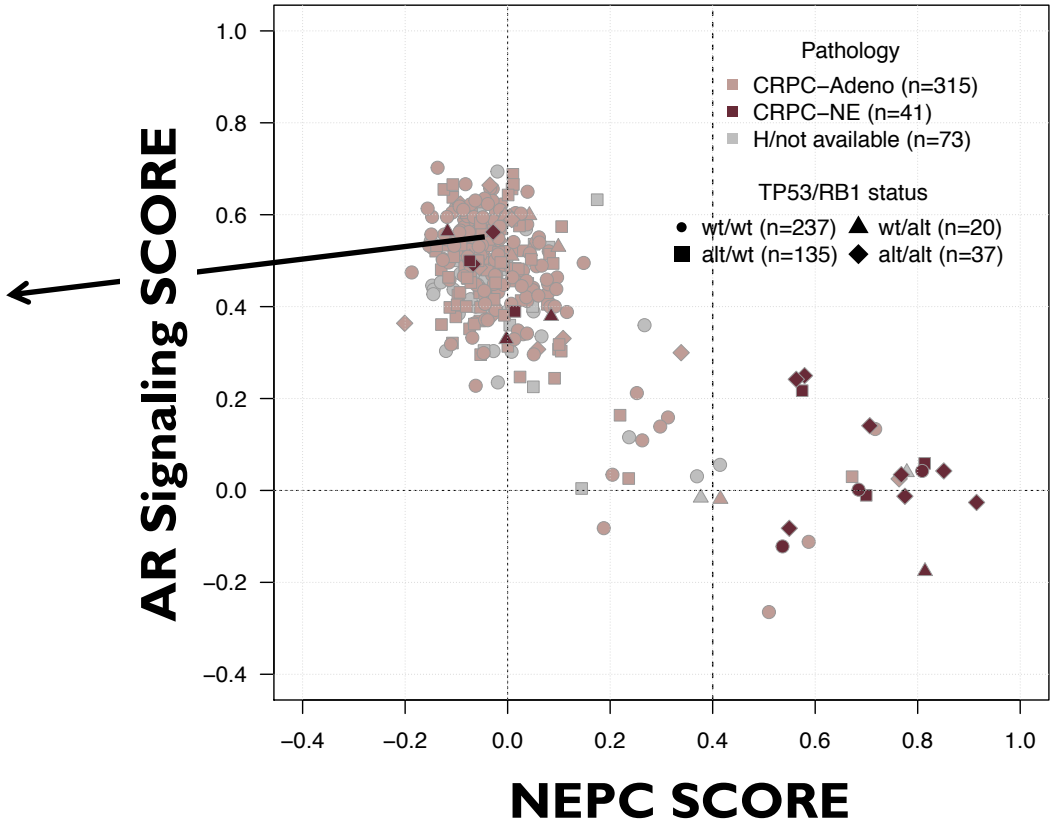
What alterations are we not capturing ?

Abida, Cyrta, et al., PNAS 2019



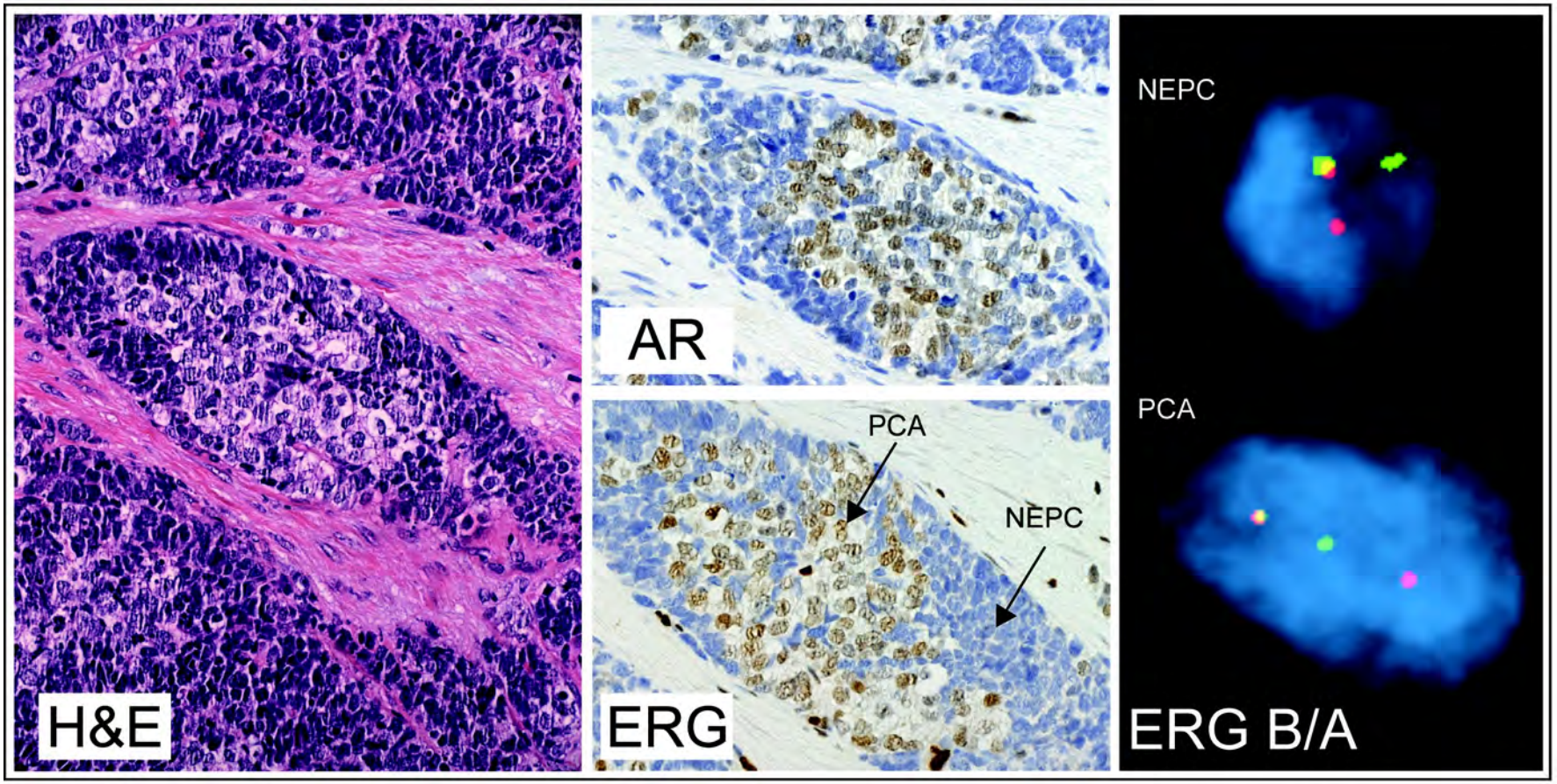


Small cell morphology, but low NEPC score, high AR, and mut TD53 and RB1



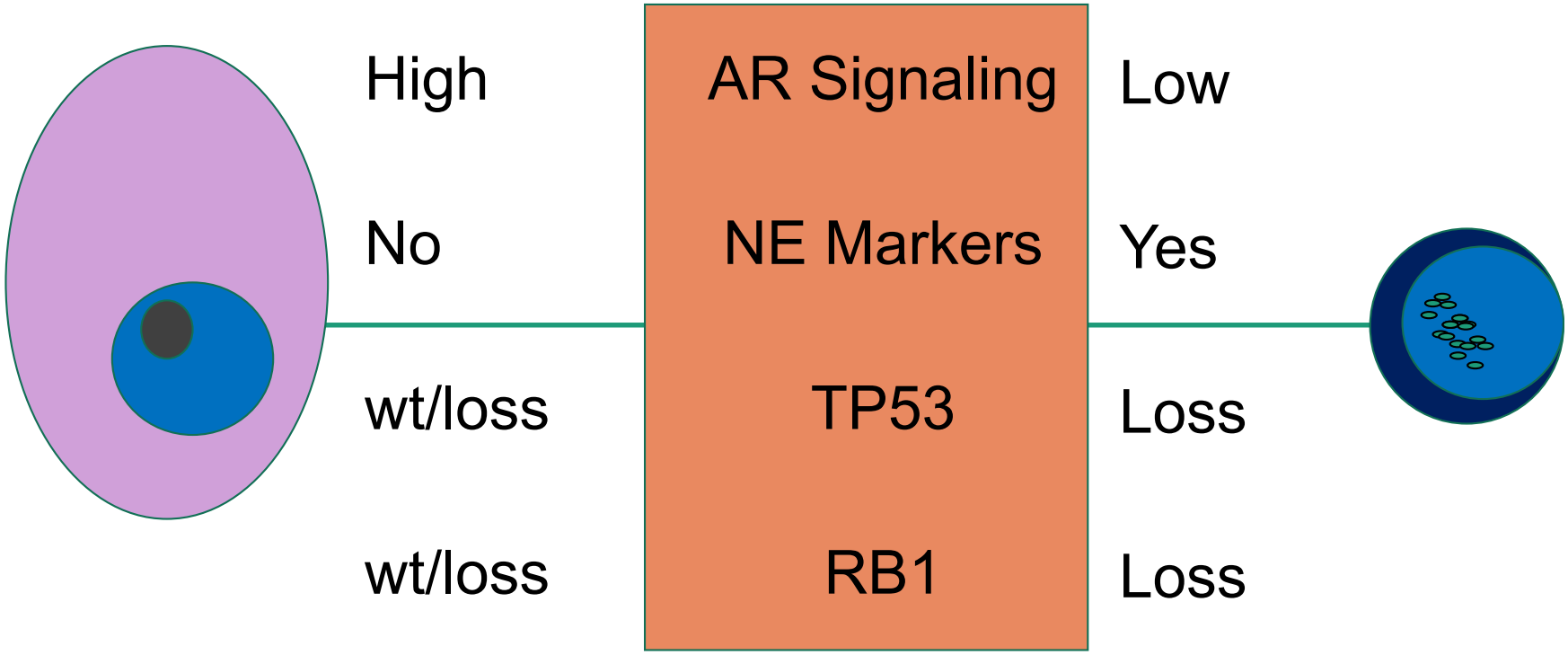
Abida et al, PNAS 2019

Topographic proximity: Adeno and NEPC



Beltran et al, Cancer Discovery 2011

Characteristics that help define NEPC



M.A. Rubin lecture copyright 2018

EGFR Mutations in Small-Cell Lung Cancers in Patients Who Have Never Smoked

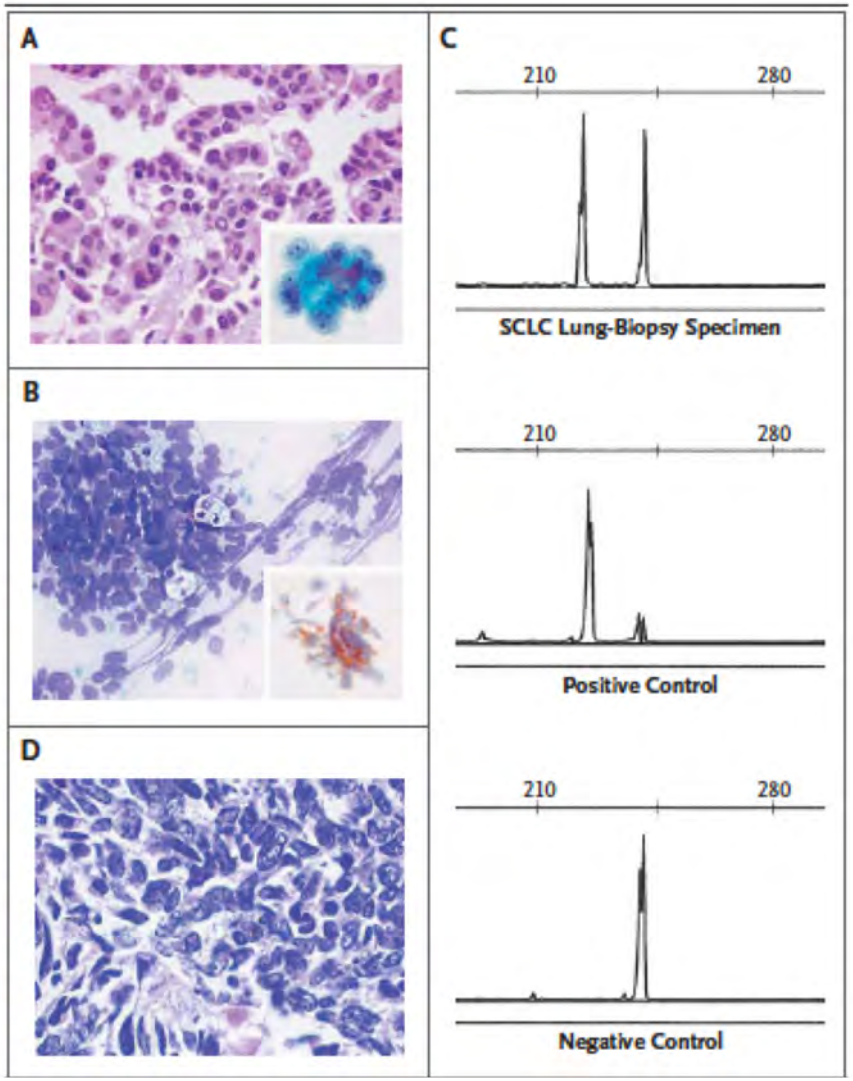
TO THE EDITOR: Mutations in the epidermal growth factor receptor gene (*EGFR*) occur in 10 to 20 percent of non–small-cell lung cancers, specifically adenocarcinomas, and are associated with the response to EGFR tyrosine kinase inhibitors (erlotinib and gefitinib).[1] However, the results of screening of small-cell lung cancers for *EGFR* mutations have been negative.[2] Thus, small-cell lung cancers are not routinely tested for *EGFR* mutations, nor have they been systematically evaluated for responsiveness to EGFR tyrosine kinase inhibitors.

A 45-year-old woman who had never smoked and who had masses in the right lung, pleura,

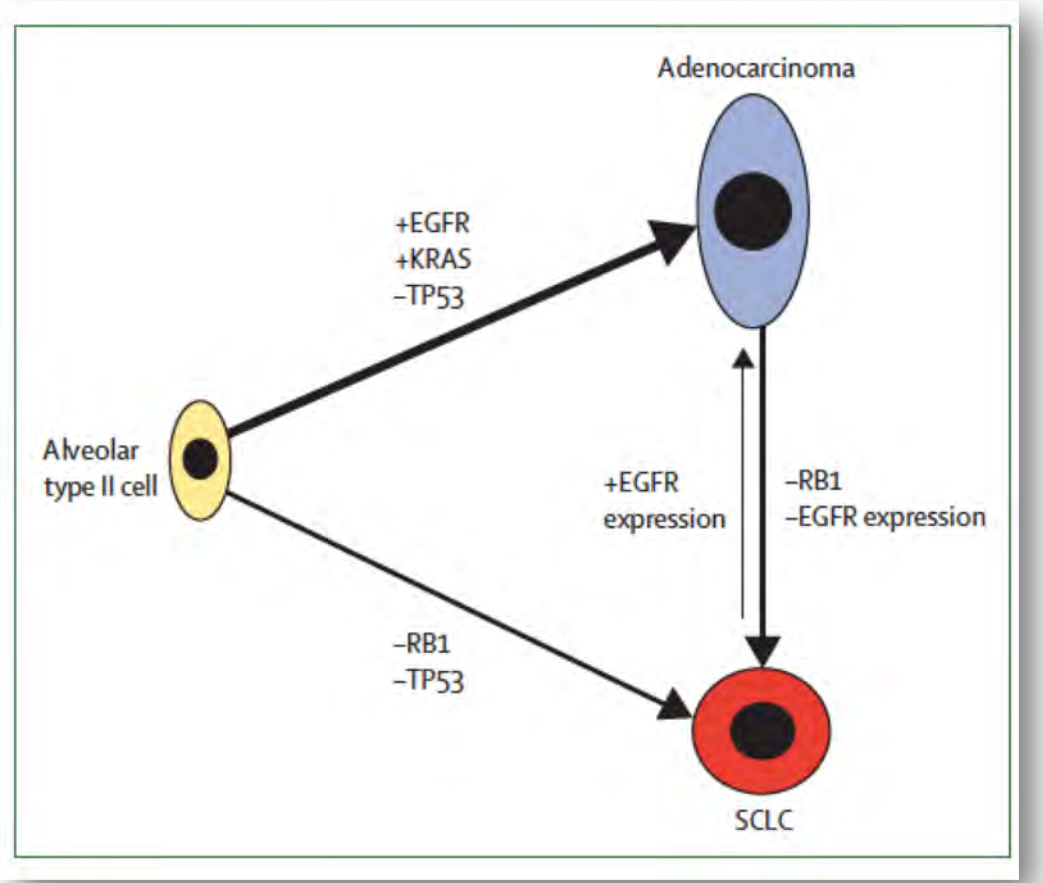
N ENGL J MED 355;2 WWW.NEJM.ORG JULY 13, 2006

Maureen F. Zakowski, M.D.
Marc Ladanyi, M.D.
Mark G. Kris, M.D.
Memorial Sloan-Kettering Cancer Center, New York, NY 10021

for the Memorial Sloan-Kettering Cancer Center Lung Cancer OncoGenome Group



Not only prostate cancer, seen in lung cancer

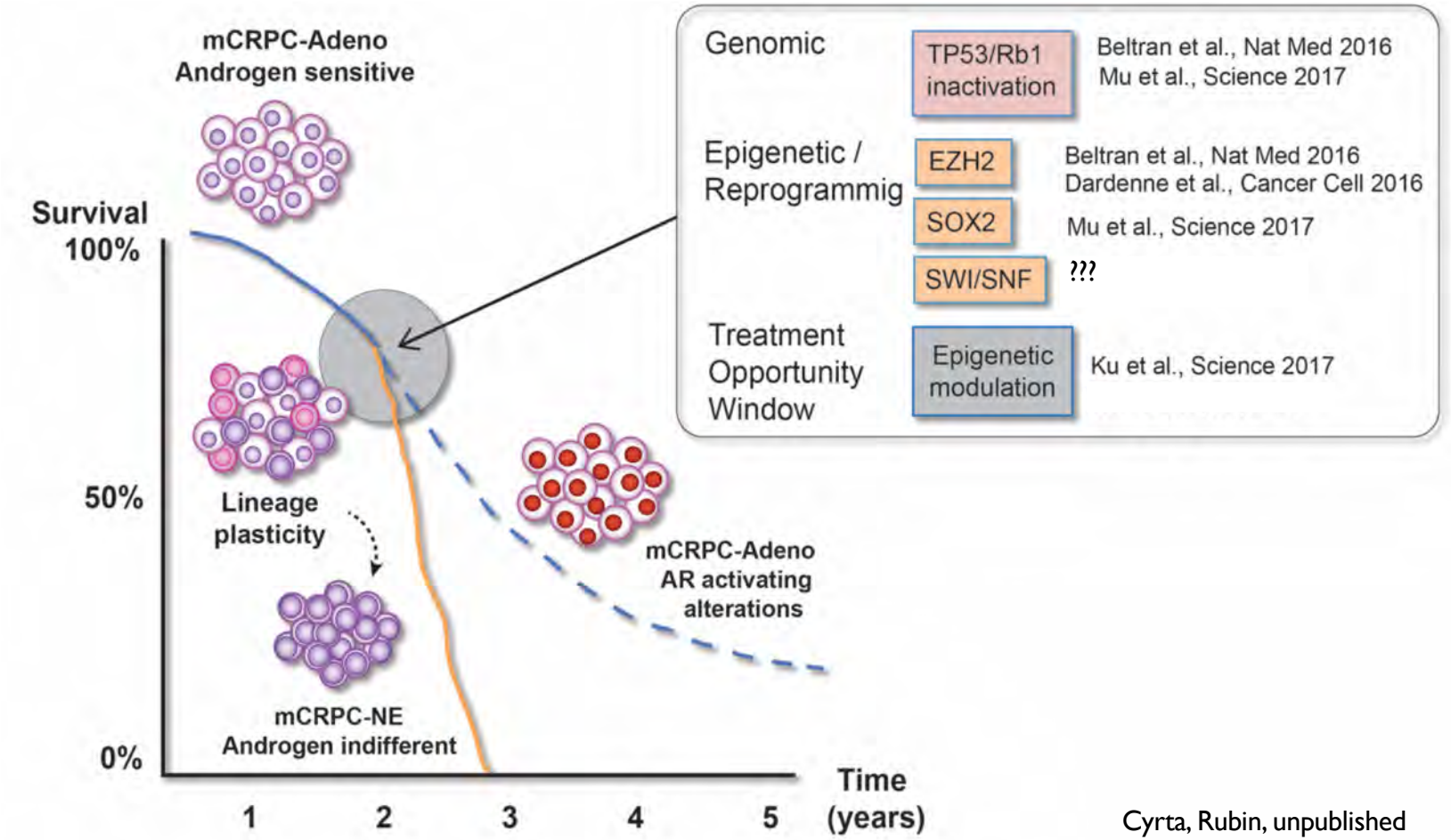


Review of Case Studies

Either Small Cell arises
from different cell of origin or
emerges after specific genomic
alterations (TP53 and RB1 loss)

J. Engelman, Lancet Oncology 2015

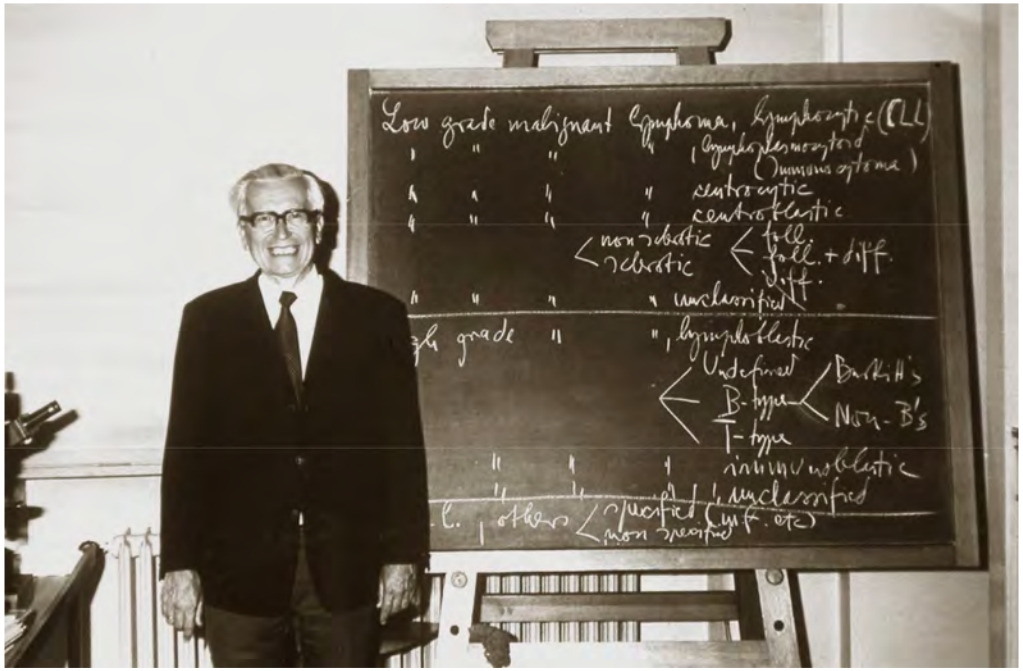
Neuroendocrine prostate cancer (NEPC) and lineage plasticity



Cyrta, Rubin, unpublished

What do we call this thing?

Prof. Lennert presenting the Kiel Classification



Diffuse large B-cell lymphoma variants

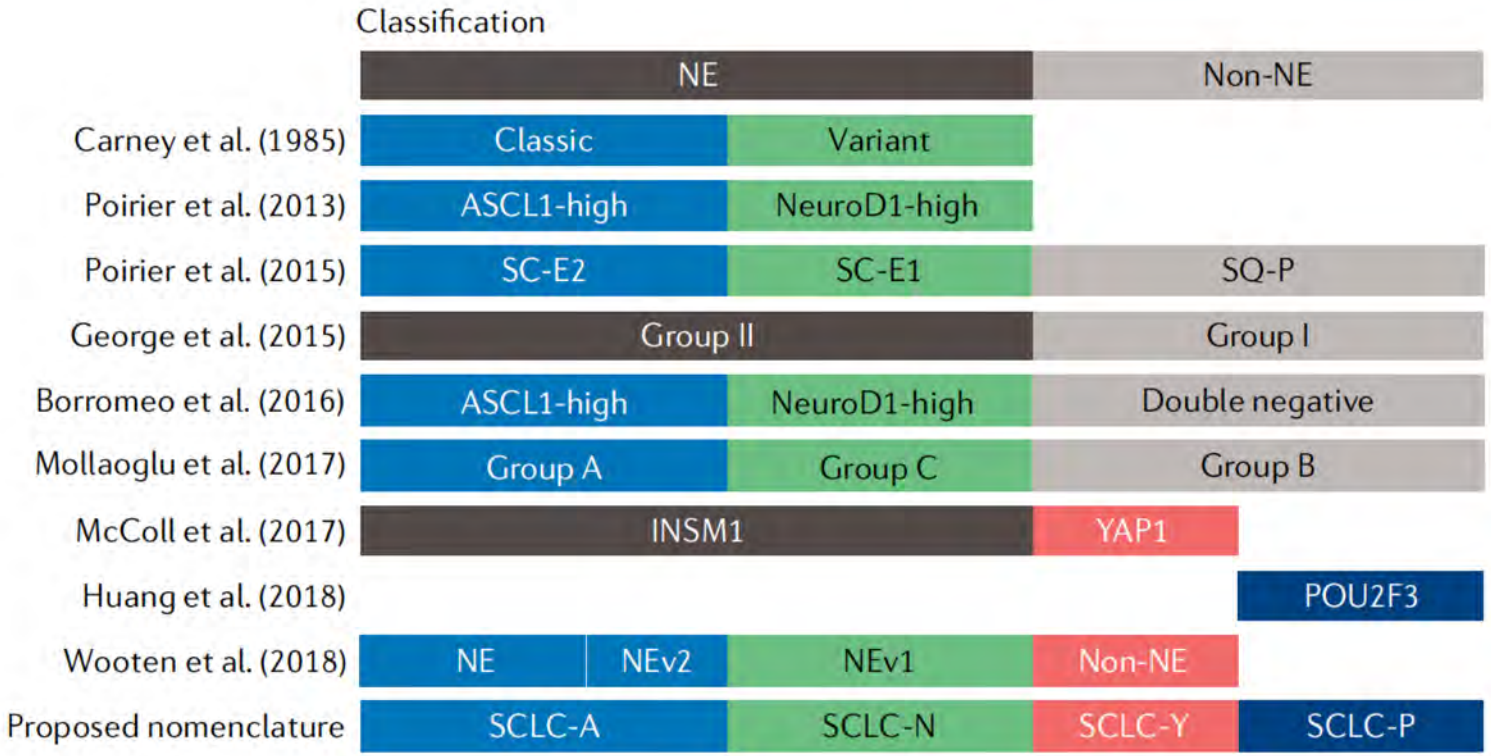
Table 1 Specific variants of diffuse large B-cell lymphoma recognised in the current World Health Organization classification

Distinctive morphology or immunophenotype
T-cell/histiocyte-rich large B-cell lymphoma
ALK+ large B-cell lymphoma
Plasmablastic lymphoma
Intravascular large B-cell lymphoma
Large B-cell lymphoma with *IRF4* rearrangement
Distinctive clinical issues
Primary mediastinal large B-cell lymphoma
Primary cutaneous diffuse large B-cell lymphoma, leg type
Primary diffuse large B-cell lymphoma of the central nervous system
Diffuse large B-cell lymphoma associated with chronic inflammation
Lymphomatoid granulomatosis
Primary effusion lymphoma
Viral driven
EBV-positive diffuse large B-cell lymphoma, not otherwise specified
HHV8-positive diffuse large B-cell lymphoma

Sukswai et al., Pathology (January 2020) 52(1), pp. 53–67

What do we call this thing?

Approach to classifying small cell lung cancer (SCLC)



Rudin et al, Nature Reviews Cancer, volume 19 | MAY 2019 | 289

Part 2: Advanced Prostate Cancer

1) May be seen more often as oncologist perform metastatic biopsies (e.g., indication for PARPi and MSI-Immunotherapy)

2) **Major question is cancer versus no cancer**

3) **Classification and "grading" of treated cancer unclear**

4) What would a urologist/oncologist do differently if we did find neuroendocrine features?

5) What would a urologist/oncologist do if we identified a small cell cancer?

Possible diagnoses for advanced cancer:

1) Metastatic, adenocarcinoma
2) Metastatic, adenocarcinoma with NE differentiation
3) Metastatic, small cell cancer (prostate or not?)
4) Metastatic, mixed adeno and small cell carcinoma

Note: *Important to confirm site of origin. This may be obvious because of the clinical setting but may also requiring considering a secondary or alternative diagnosis (e.g., lung cancer or bladder cancer).*

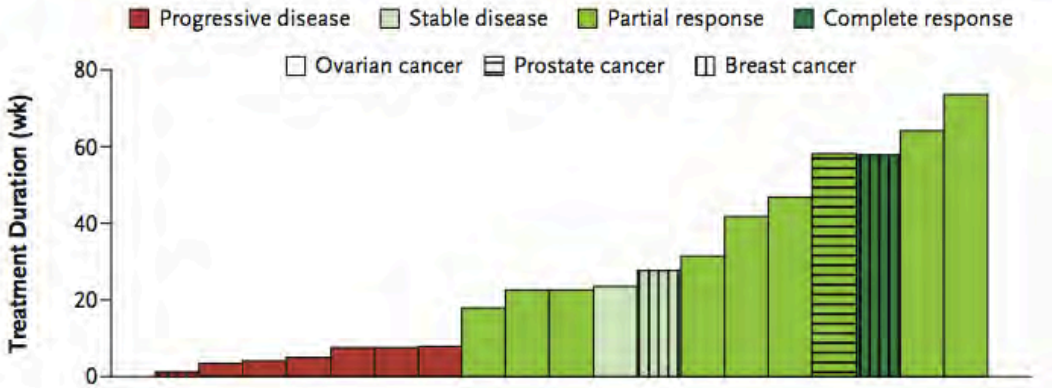
Major message: *Clinical decision making should focus on a constellation of clinical, laboratory, pathology and molecular features. The presence of small cell and or NE features should not exclude androgen deprivation therapy and/or second generation ARSi*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 9, 2009 VOL. 361 NO. 2

Inhibition of Poly(ADP-Ribose) Polymerase in Tumors from *BRCA* Mutation Carriers

Peter C. Fong, M.D., David S. Boss, M.Sc., Timothy A. Yap, M.D., Andrew Tutt, M.D., Ph.D., Peijun Wu, Ph.D., Marja Mergui-Roelvink, M.D., Peter Mortimer, Ph.D., Helen Swaisland, B.Sc., Alan Lau, Ph.D., Mark J. O'Connor, Ph.D., Alan Ashworth, Ph.D., James Carmichael, M.D., Stan B. Kaye, M.D., Jan H.M. Schellens, M.D., Ph.D., and Johann S. de Bono, M.D., Ph.D.



M.A.Rubin Copyright

19 BRCA mutated

Audience Response System (ARS) Question

Genomic testing for advanced prostate cancer may be important in determining a change in therapy for …

A. Men with BRCA1/2 or ATM mutations

B. Mismatch repair

C. Both

Report from ISUP Consultation Conference: Mol. Path Subgroup
Lotan et al., AJSP 2020 (in press)

Audience Response System (ARS) Question

Genomic testing for advanced prostate cancer may be important in determining a change in therapy for …

A. Men with BRCA1/2 or ATM mutations

B. Mismatch repair

C. Both

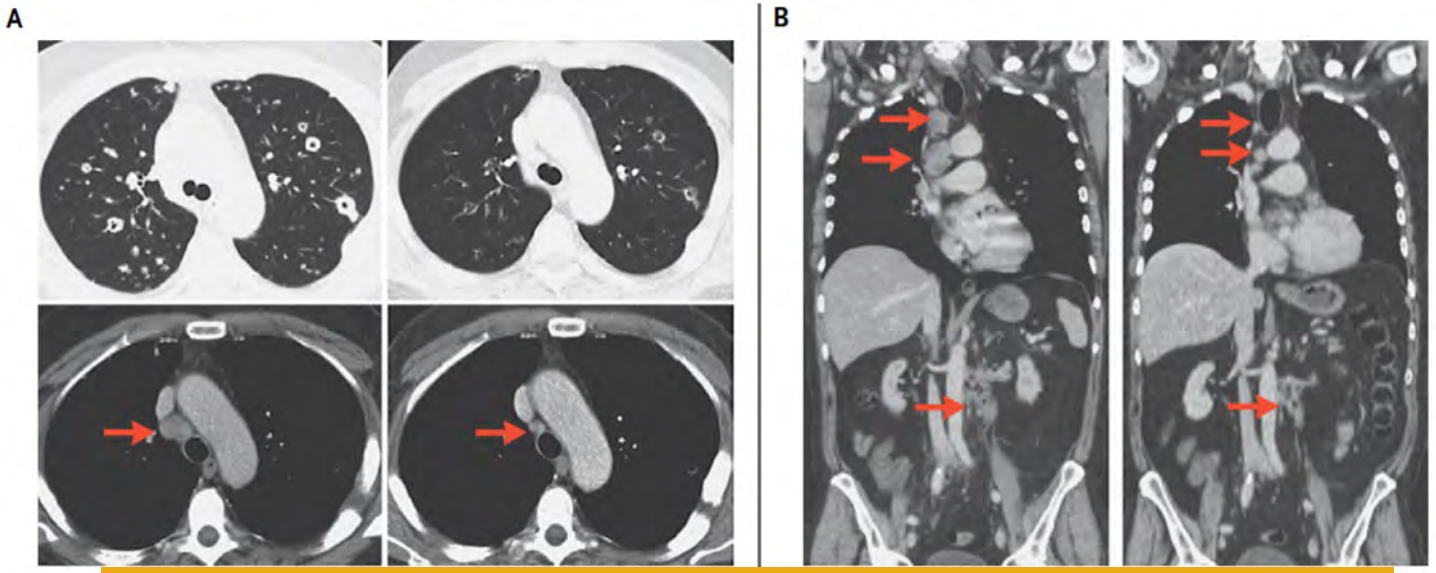
Report from ISUP Consultation Conference: Mol. Path Subgroup
Lotan et al., AJSP 2020 (in press)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 29, 2015 VOL. 373 NO. 18

DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

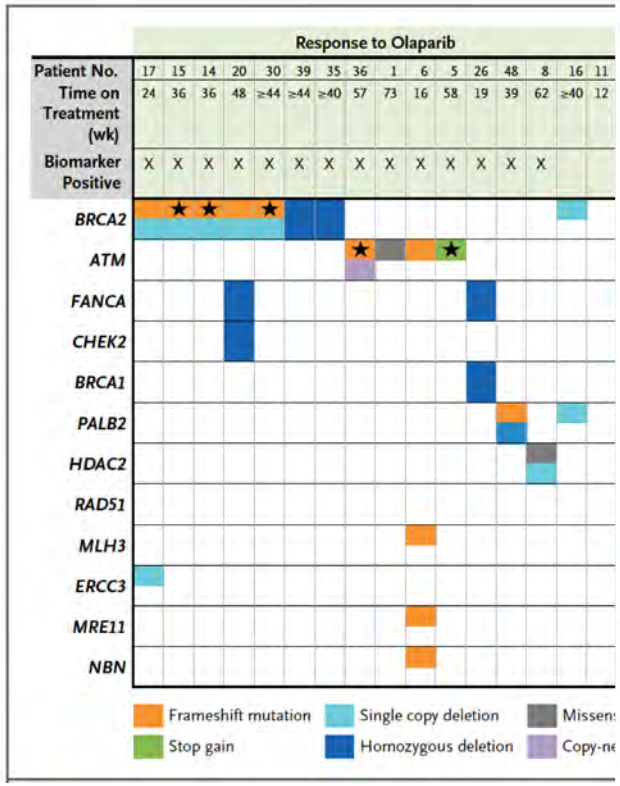
J. Mateo, S. Carreira, S. Sandhu, S. Miranda, H. Mossop, R. Perez-Lopez, D. Nava Rodrigues, D. Robinson, A. Omlin, N. Tunariu, G. Boysen, N. Porta, P. Flohr, A. Gillman, I. Figueiredo, C. Paulding, G. Seed, S. Jain, C. Ralph, A. Protheroe, S. Hussain, R. Jones, T. Elliott, U. McGovern, D. Bianchini, J. Goodall, Z. Zafeiriou, C.T. Williamson, R. Ferraldeschi, R. Riisnaes, B. Ebbs, G. Fowler, D. Roda, W. Yuan, Y.-M. Wu, X. Cao, R. Brough, H. Pemberton, R. A'Hern, A. Swain, L.P. Kunju, R. Eeles, G. Attard, C.J. Lord, A. Ashworth, M.A. Rubin, K.E. Knudsen, F.Y. Feng, A.M. Chinnaiyan, E. Hall, and J.S. de Bono

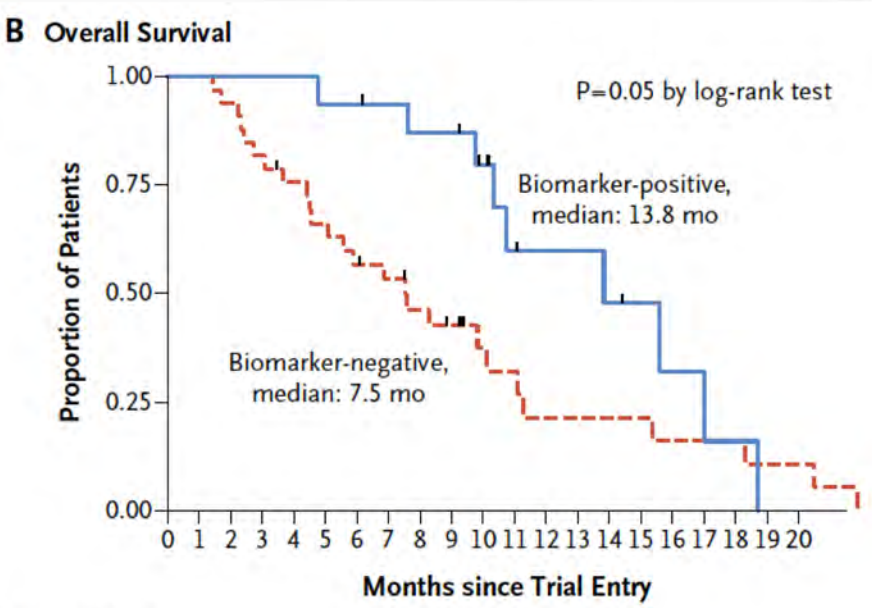


TOPARP Trial shows 30% Long Term Responders

M.A.Rubin Copyright

NEJM, Oct 29 2015





No. at Risk

Biomarker-negative	33	33	31	27	24	21	18	16	13	11	7	6	4	4	4	4	3	3	3	2	2
Biomarker-positive	16	16	16	16	16	15	15	14	13	13	10	6	5	5	4	3	2	2	1	0	0

No. of Events

Biomarker-negative	0	2	4	2	3	3	1	2	1	1	1	2	0	0	0	1	0	0	1	0	–
Biomarker-positive	0	0	0	0	1	0	0	1	0	1	2	0	0	1	0	1	0	2	0	0	–

M.A.Rubin Copyright

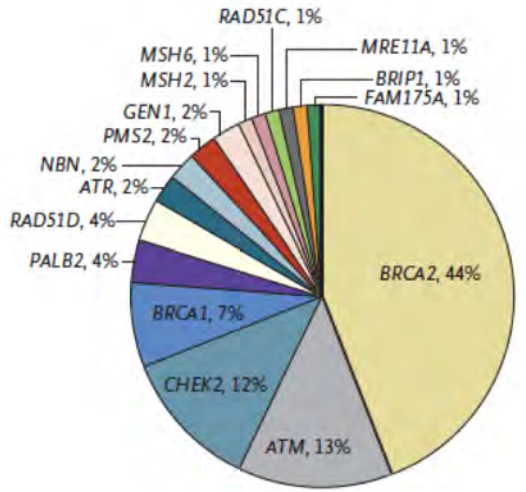
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

Table 2. Germline Mutations in Metastatic Cases as Compared with the General Population and Primary Cases.

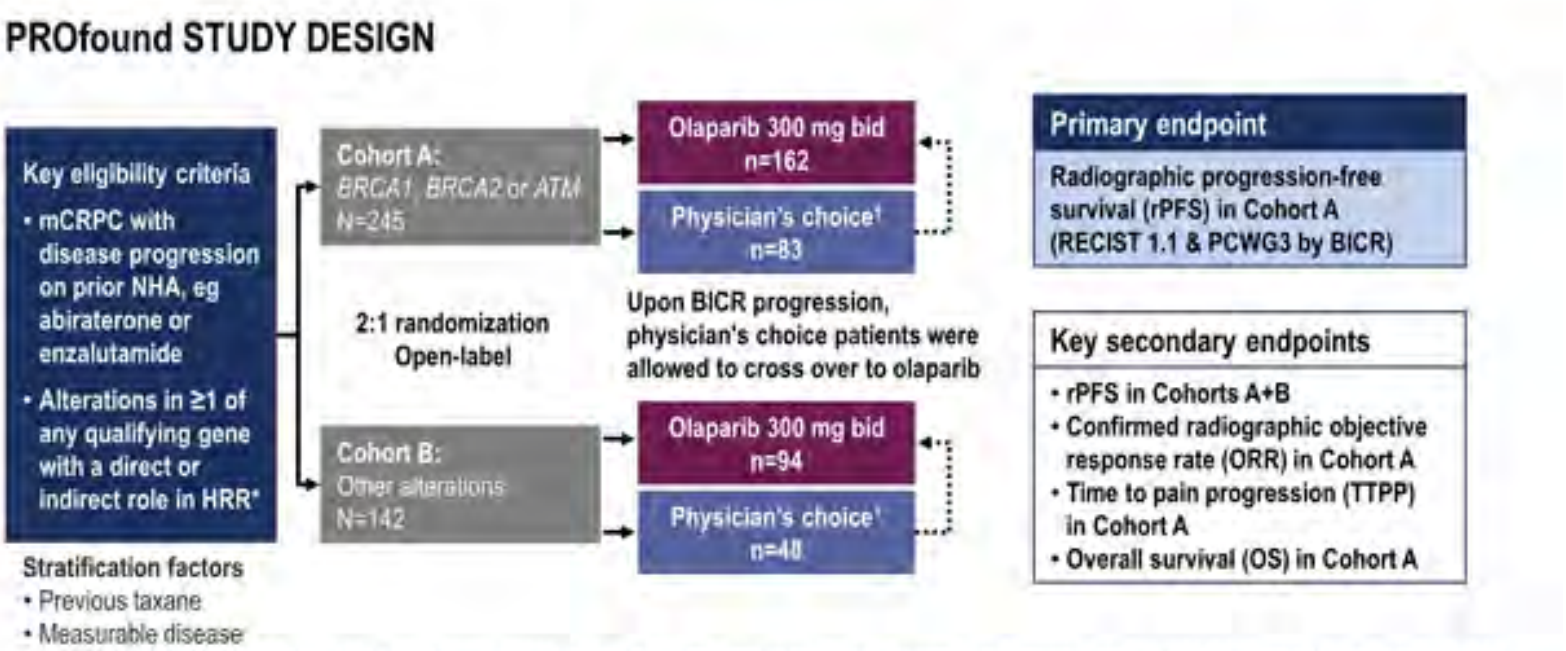
Gene	Metastatic Prostate Cancer (N=692)*	Exome Aggregation Consortium (N=53,105)†	TCGA Cohort with Primary Prostate Cancer (N=499)	Metastatic Prostate Cancer vs. Exome Aggregation Consortium		Metastatic Prostate Cancer vs. TCGA Cohort	
	No. of Mutations (% of Men)			Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
ATM	11 (1.59)	133 (0.25)	5 (1.00)	6.3 (3.2–11.3)	<0.001	1.6 (0.8–2.8)	0.12
ATR	2 (0.29)	43 (0.08)	0	3.6 (0.4–12.8)	0.11	—	—
BAP1‡	0	1	0	—	—	—	—
BARD1‡	0	38 (0.07)	1 (0.20)	—	—	—	—
BRCA1	6 (0.87)	104 (0.22)	3 (0.60)	3.9 (1.4–8.5)	0.005	1.4 (0.5–3.1)	0.32
BRCA2	37 (5.35)	153 (0.29)	1 (0.20)	18.6 (13.2–25.3)	<0.001	26.7 (18.9–36.4)	<0.001
BRIP1‡	1 (0.18)	100 (0.19)	1 (0.20)	0.9 (0.02–5.3)	1.0	0.9 (0.0–4.9)	1.0
CHEK2‡	10 (1.87)	314 (0.61)	2 (0.40)	3.1 (1.5–5.6)	0.002	4.7 (2.2–8.5)	<0.001
FAM175A‡	1 (0.18)	52 (0.10)	0	1.8 (0.05–10.1)	0.42	—	—
GEN1‡	2 (0.46)	42 (0.08)	0	5.8 (0.7–20.8)	0.048	—	—
MLH1	0	11 (0.02)	0	—	—	—	—
MRE11A	1 (0.14)	36 (0.07)	1 (0.20)	2.1 (0.1–11.8)	0.38	0.7 (0.0–4.0)	1.0
MSH2	1 (0.14)	23 (0.04)	1 (0.20)	3.3 (0.1–18.5)	0.26	0.7 (0.0–4.0)	1.0
MSH6	1 (0.14)	41 (0.08)	1 (0.20)	1.9 (0.05–10.4)	0.41	0.7 (0.0–4.0)	1.0
NBN	2 (0.29)	61 (0.11)	1 (0.20)	2.5 (0.3–9.1)	0.19	1.4 (0.2–5.2)	0.40
PALB2	3 (0.43)	65 (0.12)	2 (0.40)	3.5 (0.7–10.3)	0.05	1.1 (0.2–3.1)	0.76
PMS2	2 (0.29)	56 (0.11)	1 (0.20)	2.7 (0.3–9.8)	0.17	1.4 (0.2–5.2)	0.40
RAD51C	1 (0.14)	59 (0.11)	2 (0.40)	1.3 (0.03–7.2)	0.54	0.4 (0.0–2.0)	0.54
RAD51D	3 (0.43)	40 (0.08)	1 (0.20)	5.7 (1.2–16.7)	0.02	2.2 (0.4–6.3)	0.16
XRCC2	0	23 (0.04)	0	—	—	—	—



Selected *DNA repair germline mutations from targeted panel and WES reveal 10-20% frequency* (Pritchard and Nelson, 2016)

M.A.Rubin Copyright

ESMO 2019: PROfound: Phase 3 Study of Olaparib vs. Enzalutamide or Abiraterone for Metastatic Castration-Resistant Prostate Cancer with Homologous Recombination Repair Gene Alterations



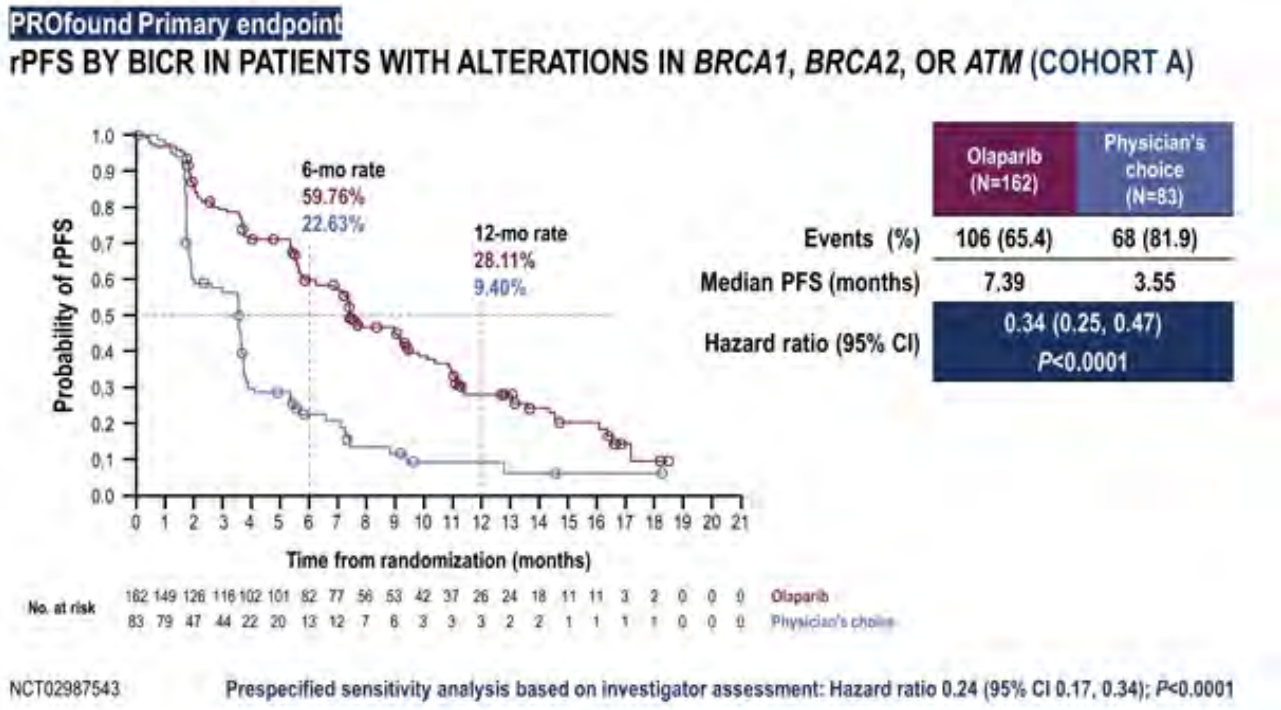
*An investigational Clinical Trial Assay, based on the FoundationOne CDx next-generation sequencing test, and developed in partnership with Foundation Medicine Inc, was used to prospectively select patients harboring alterations in the following genes in their tumor tissue: *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* or *RAD54L*

†Physician's choice of either enzalutamide (160 mg qd) or abiraterone (1000 mg qd plus prednisone [5 mg bid])

BICR, blinded independent central review; PCWG3, Prostate Cancer Working Group 3; RECIST, Response Evaluation Criteria in Solid Tumors

NCT02987543

ESMO 2019: PROfound: Phase 3 Study of Olaparib vs. Enzalutamide or Abiraterone for Metastatic Castration-Resistant Prostate Cancer with Homologous Recombination Repair Gene Alterations



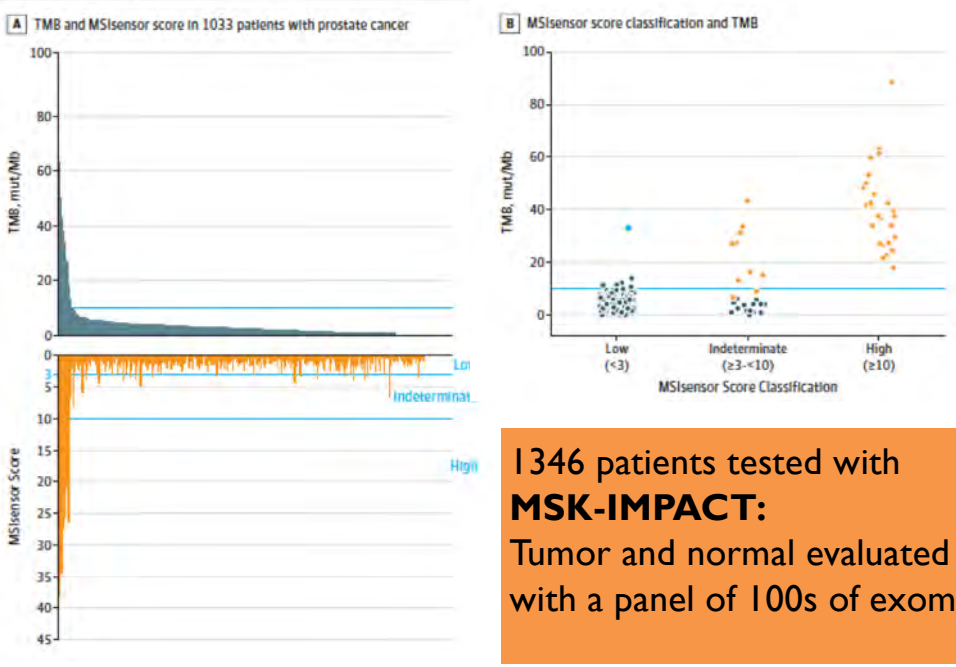
Among the men who underwent screening, 4047 had samples that were tested, among which 2792 (69%) were successfully sequenced and yielded biomarker status. In screened patients, samples were mainly derived from archived tissue (89.9%); most archived samples (79.7%) were from the primary tumour and 10.1% were derived from metastatic tissue.

JAMA Oncology | Original Investigation

Analysis of the Prevalence of Microsatellite Instability in Prostate Cancer and Response to Immune Checkpoint Blockade

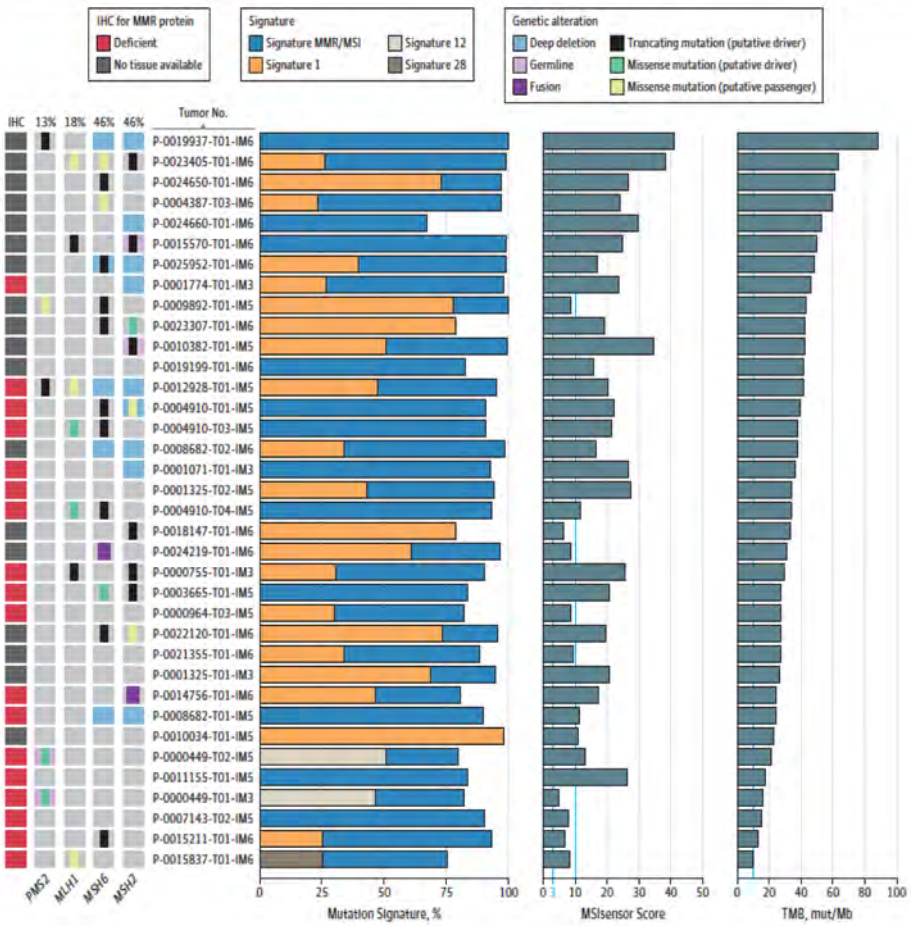
Wassim Abida, MD, PhD; Michael L. Cheng, MD; Joshua Armenia, PhD; Sumit Middha, PhD; Karen A. Autio, MD; Hebert Alberto Vargas, MD; Dana Rathkopf, MD; Michael J. Morris, MD; Daniel C. Danila, MD; Susan F. Slovin, MD, PhD; Emily Carbone, BA; Ethan S. Barnett, MS; Melanie Hullings, BA; Jaclyn F. Hechtman, MD; Ahmet Zehir, PhD; Jinru Shia, MD; Philip Jonsson, PhD; Zsofia K. Stadler, MD; Preethi Srinivasan, BA; Vincent P. Laudone, MD; Victor Reuter, MD; Jedd D. Wolchok, MD, PhD; Nicholas D. Socci, PhD; Barry S. Taylor, PhD; Michael F. Berger, PhD; Philip W. Kantoff, MD; Charles L. Sawyers, MD; Nikolaus Schultz, PhD; David B. Solit, MD; Anuradha Gopalan, MD; Howard I. Scher, MD

Figure 1. Tumor Mutation Burden (TMB) and Microsatellite Instability (MSI) in Prostate Cancer



1346 patients tested with **MSK-IMPACT:**
Tumor and normal evaluated with a panel of 100s of exoms

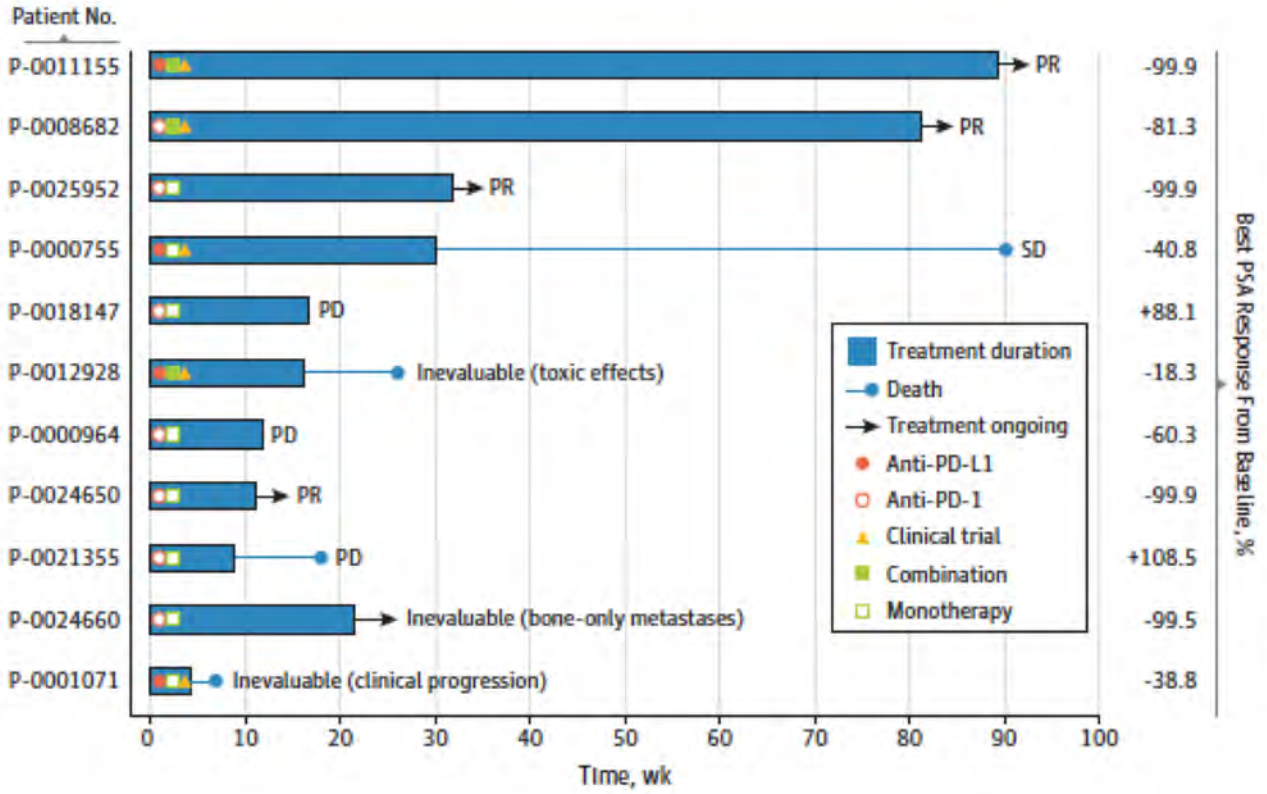
Figure 2. Integrative Analysis of Microsatellite Instability (MSI), Tumor Mutation Burden (TMB), Mutational Signature Decomposition, and Mismatch Repair (MMR) Gene and Protein Status



M.A.Rubin Copyright

JAMA Oncology Published online December 27, 2018

Figure 4. Responses to Immune Checkpoint Blockade in Microsatellite Instability–High and Mismatch Repair Deficient (MSI-H/dMMR) Prostate Cancer



M.A.Rubin Copyright

JAMA Oncology Published online December 27, 2018

Recommendations of the Working Group were the following:

In combination with appropriate genetic counseling, germline panel testing for DNA repair gene alterations should be offered (if clinically indicated) to patients with:

Localized Grade Group ≥4 tumors

Any Grade Group with PSA ≥20

Known metastatic disease

Testing should include:

1) Defective MMR assessment via MMR IHC for MSH2, MSH6, MLH-1, PMS2 with or without MSI testing and/or sequencing of MMR genes (and tumor mutation burden estimate)

AND

2) Defective HR assessment via sequencing for: BRCA1, BRCA2 at a minimum, with ability to detect copy number alterations

Report from ISUP Consultation Conference: Mol. Path Subgroup
Lotan et al., AJSP 2020 (in press)

Part 2: Advanced Prostate Cancer

1) May be seen more often as oncologist perform metastatic biopsies (e.g., indication for PARPi and MSI-Immunotherapy)

2) **Major question is cancer versus no cancer**

3) **Classification and "grading" of treated cancer unclear**

4) What would a urologist/oncologist do differently if we did find neuroendocrine features?

5) What would a urologist/oncologist do if we identified a small cell cancer?

Conclusions: Neuroendocrine Prostate Cancer

1) For clinically **localized** prostate cancer, unless there are clear morphologic neuroendocrine features, immunostaining for neuroendocrine expression (e.g., synaptophysin, chromogranin, or CD56) is **NOT** recommend.

2) Given its clinical implications, the term neuroendocrine differentiation is best reserved for high-grade cancers and not usual-type adenocarcinomas or well-differentiated neuroendocrine tumors.

Report from ISUP Consultation Conference: Mol. Path Subgroup
Lotan et al., AJSP 2020 (in press)

Conclusions: Neuroendocrine Prostate Cancer

3) **Advanced** metastatic CRPC may manifest a range of morphologic features of neuroendocrine differentiation and a combination of molecular evaluation and morphologic features may be required in future definitions of CRPC, guided by biomarker-driven clinical trials.

Report from ISUP Consultation Conference: Mol. Path Subgroup
Lotan et al., AJSP 2020 (in press)


Thanks to ISUP Working Group Members
Tamara L. Lotan
Scott A. Tomlins
Tarek A. Bismar
Colin C. Pritchard
Lukas Bubendorf
All Slides available @ Rubinlab.unibe.ch or @MarkARubin1