Molecular Pathology: Towards Classification of CRPC

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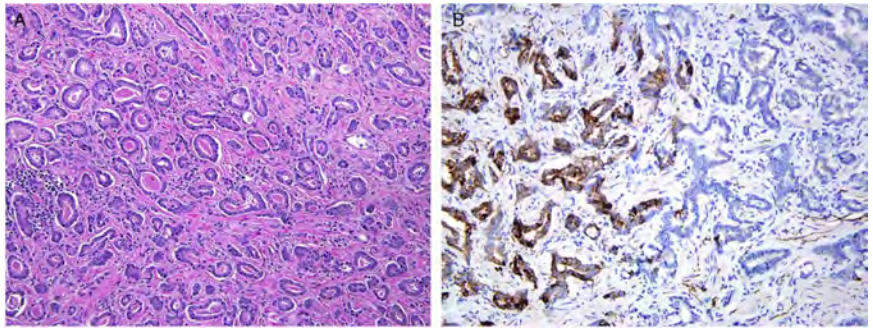
Clinical and Pathology Setting for Neuroendocrine Prostate Cancer

Localized Hormone Naïve Prostate Cancer

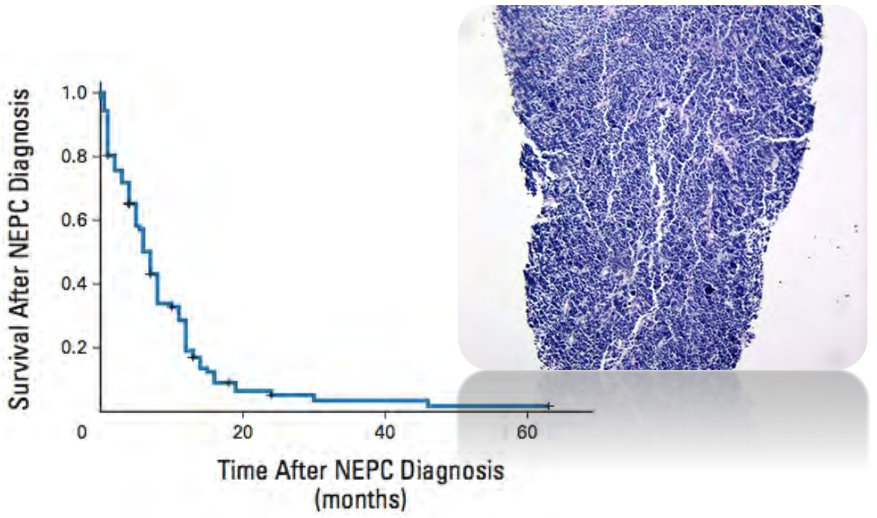
NE cells commonly observed
Some reports suggest more are bad prognostic finding
Clinical implications uncertain and no impact on care



Epstein et al, *AJSP* 2014

Advanced met PCA or CRPC

Observed in 10%+ cases
Diagnosis associated with 7 month med survival
Limited treatment –including PARPi and Platinum



Wang et al, *JCO* Sept 2014

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Pathologist's Role in PCA Diagnosis 2018

	Localized Prostate Cancer	CRPC
Evidence-Based Support	Established standard	Anecdotal
Formal Training	Established and Rigorous	Rare, Informal and based on institutional practices
Major Clinical Role	Diagnosis with Gleason Grade (Bx, RP), Stage (RP), Margin status (RP)	Prostate Cancer versus Other (melanoma, lung, etc.)
Molecular Testing	p63, 34beta E12, AMACR, ERG, CK	CK, PSA, ERG, AR, (others based on Hx)
Experienced Pathologists	100%	1-5%

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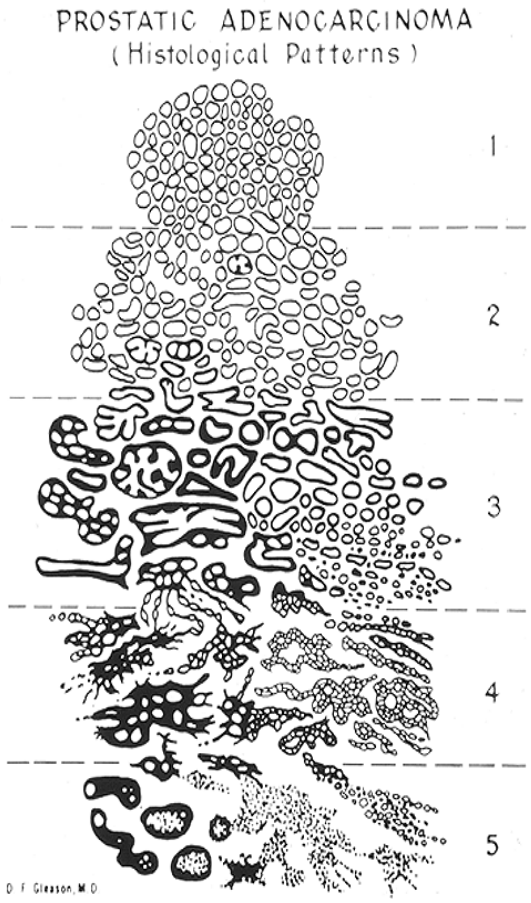
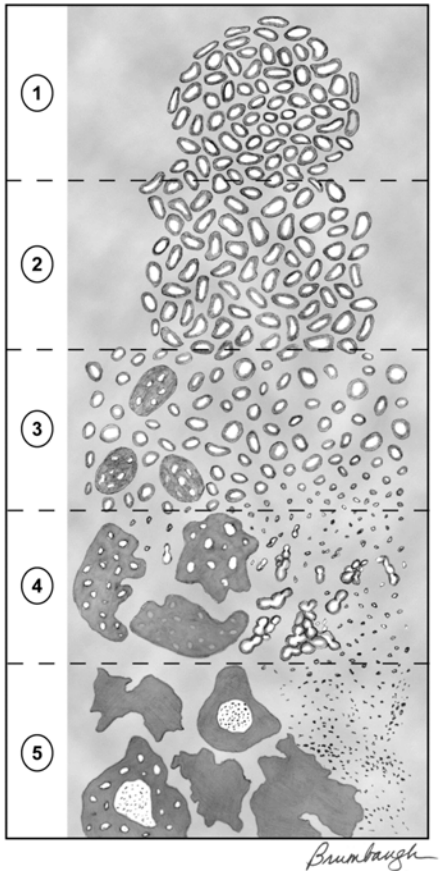
Gleason's role in developing a robust system





-Minnesota Multiphasic Personality Inventory (MMPI)

a standardized psychometric test (1943)

-Evidenced-based research leads to enduring grading system (1960s)

-Through education and formal training it has become highly reproducible

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Towards Classification of CRPC in Motion

Precision Medicine Era

2010

Bx or RP from men on ADT

Autopsies (Hopkins/Mich/UW)

Precision medicine approaches (e.g., UM, SU2C-PCF Studies)

Histology	WES, WGS	cfDNA, CTC
IHC	RNAseq	Mol.Imaging (e.g., PSMA)
Transcriptomics	Epigenetic	
Array CGH	Proteomic	
FISH		

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ORIGINAL ARTICLE

Proposed Morphologic Classification of Prostate Cancer With Neuroendocrine Differentiation

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Based on work from a July 31, 2013, the Prostate Cancer Foundation assembled a working committee on the molecular biology and pathologic classification of neuroendocrine (NE) differentiation in prostate cancer.

AJSP 2014

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TABLE 1. Pathologic Classification of NE Differentiation in Prostate Carcinoma

Usual prostate adenocarcinoma with NE differentiation
Adenocarcinoma with Paneth cell NE differentiation
Carcinoid tumor
Small cell carcinoma
LCNEC
Mixed (small or large cell) NE carcinoma—acinar adenocarcinoma

AJSP 2014

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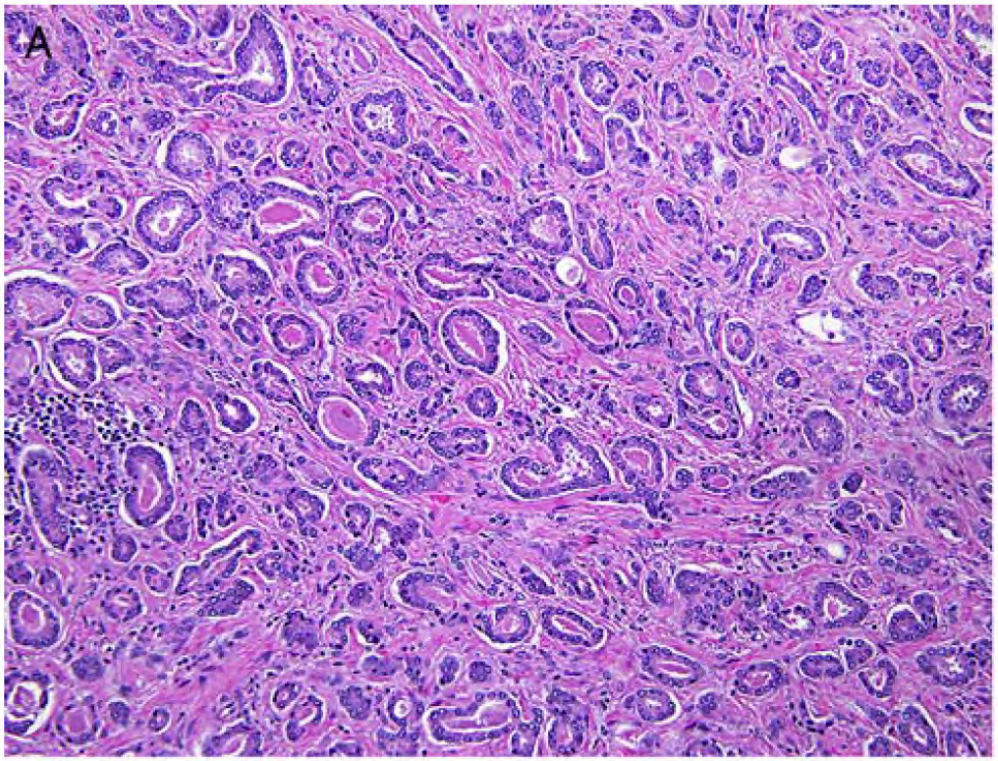

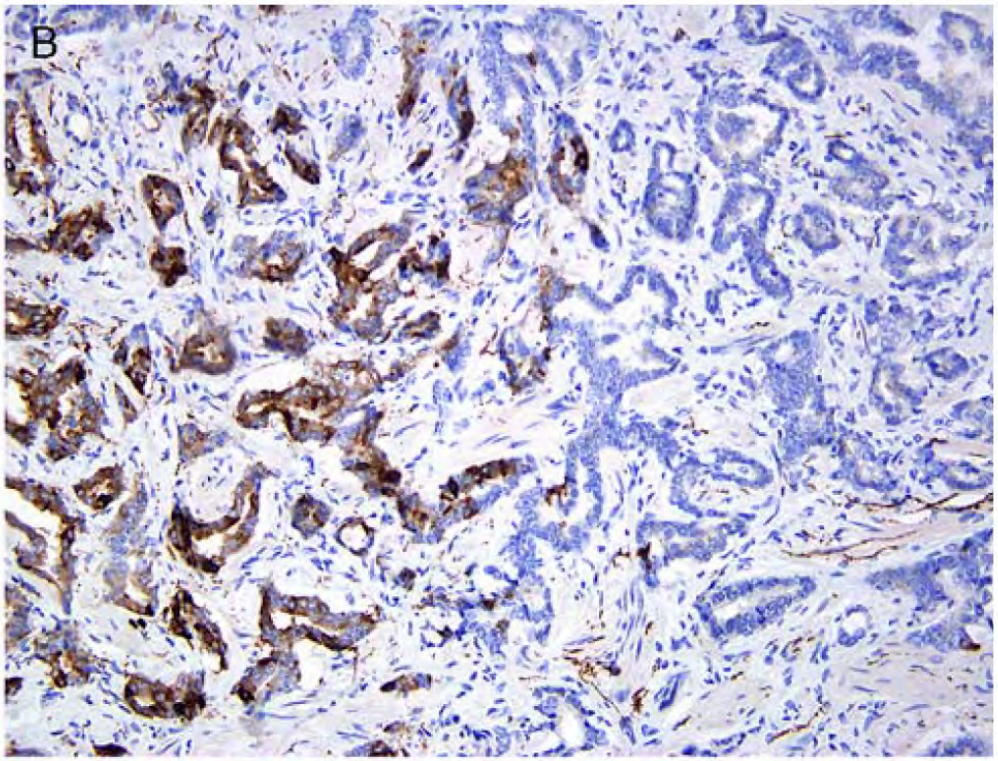

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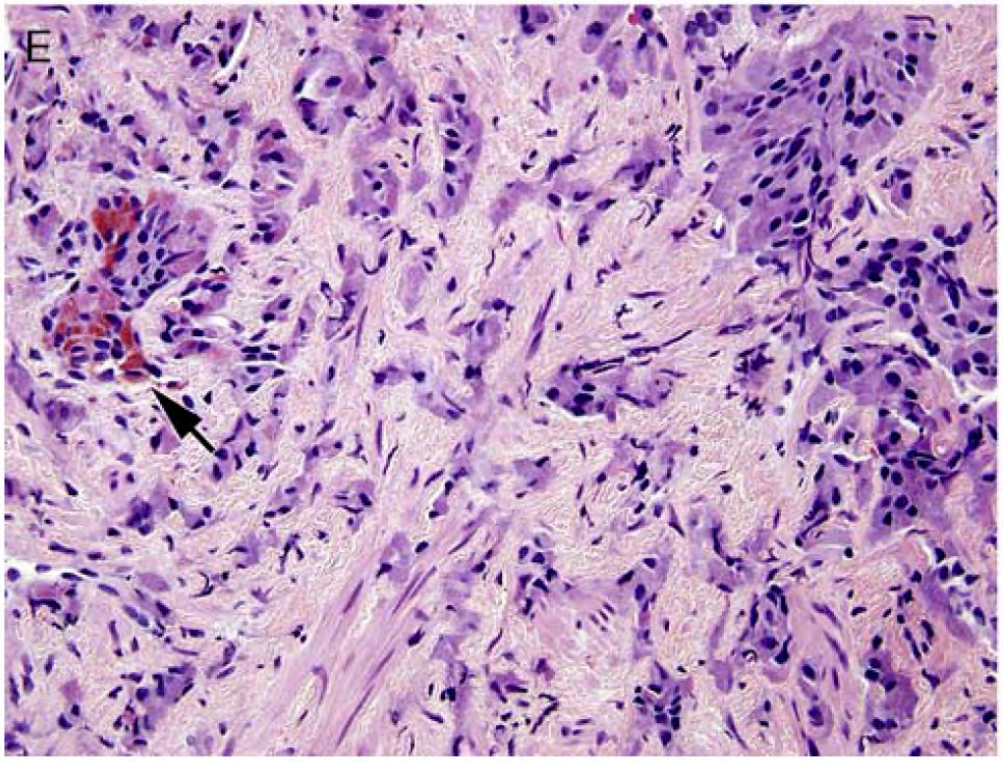

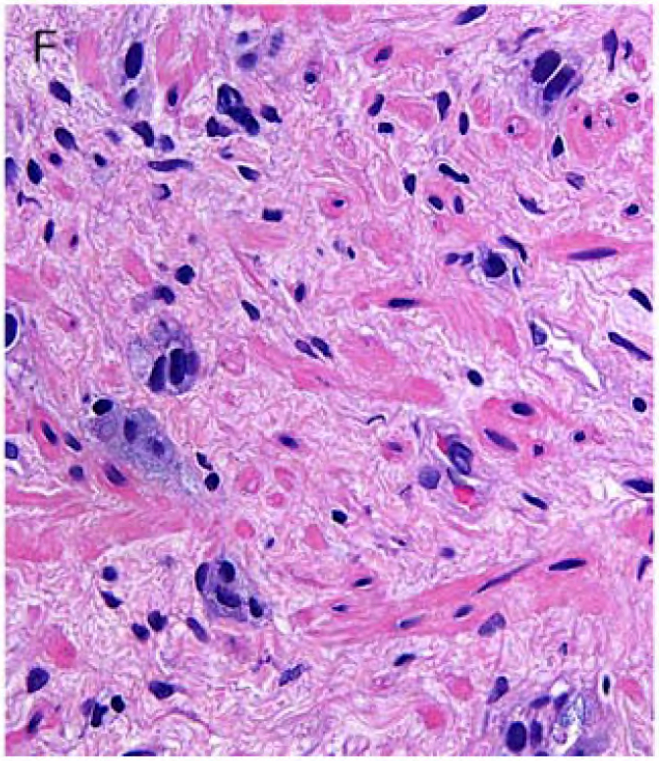

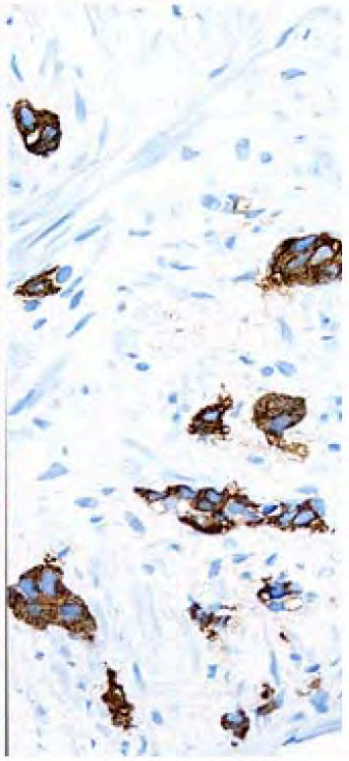

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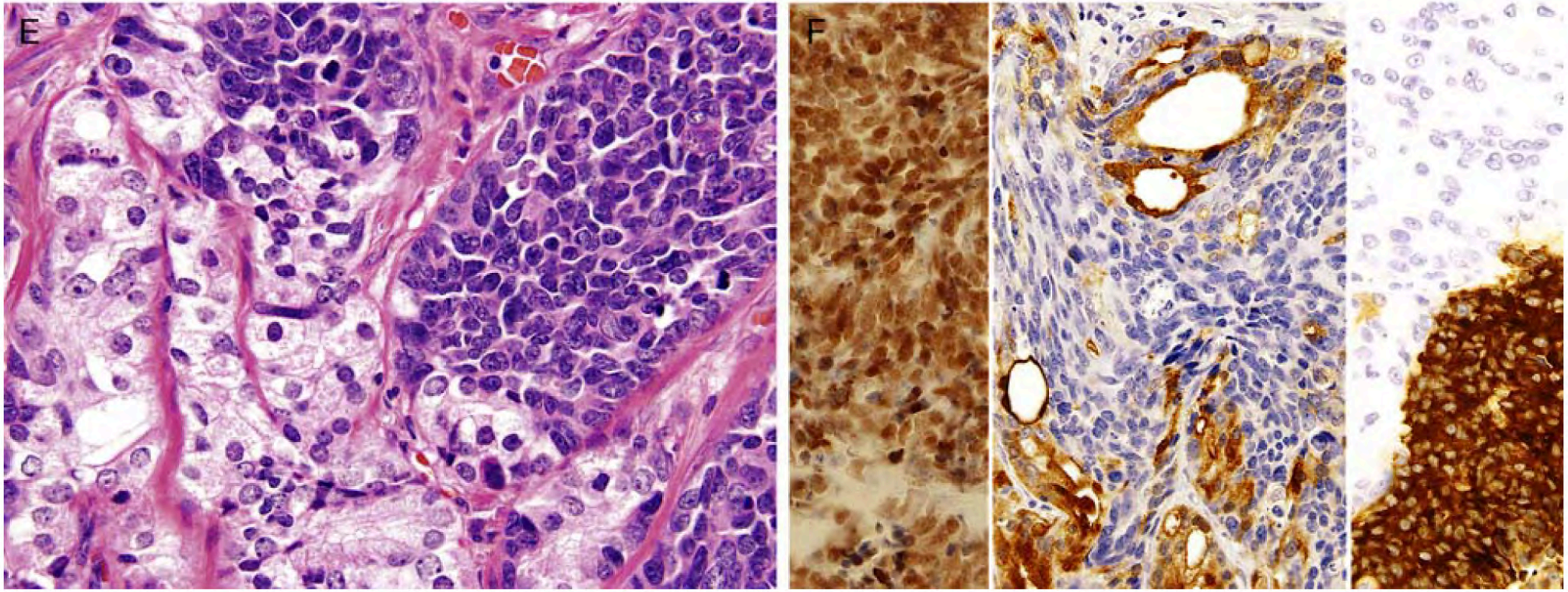

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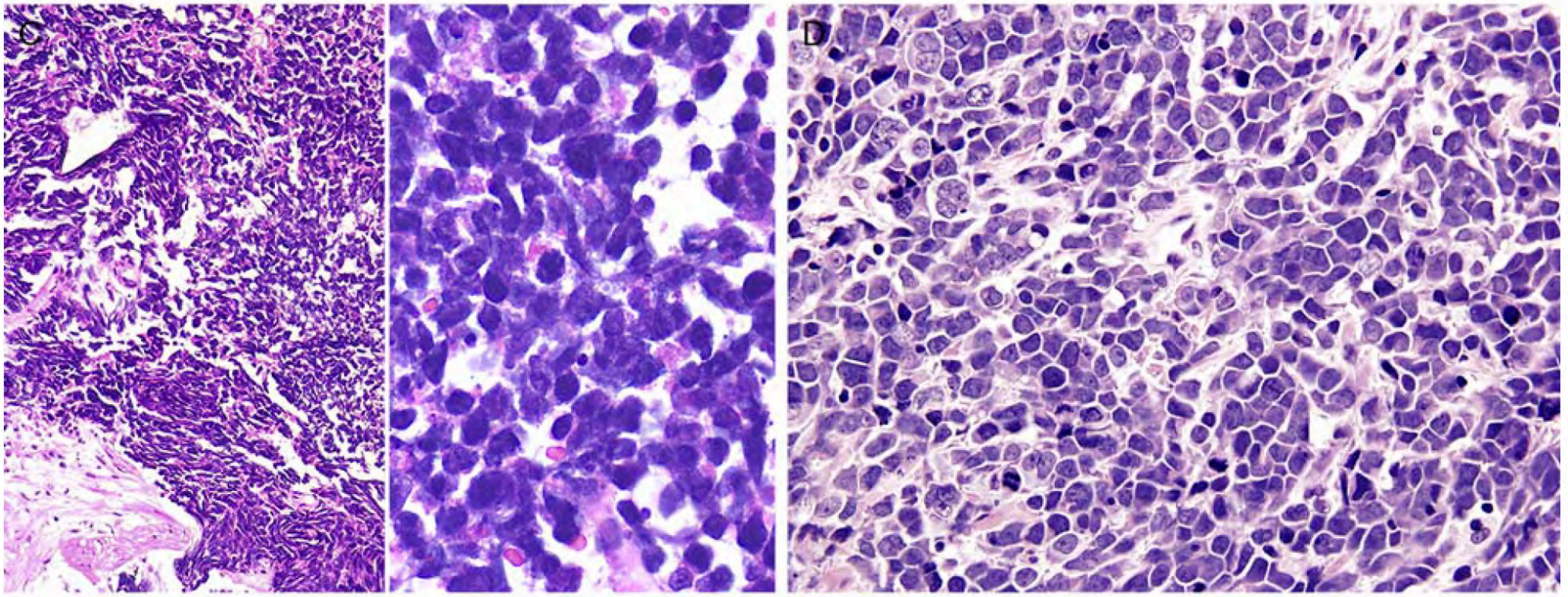

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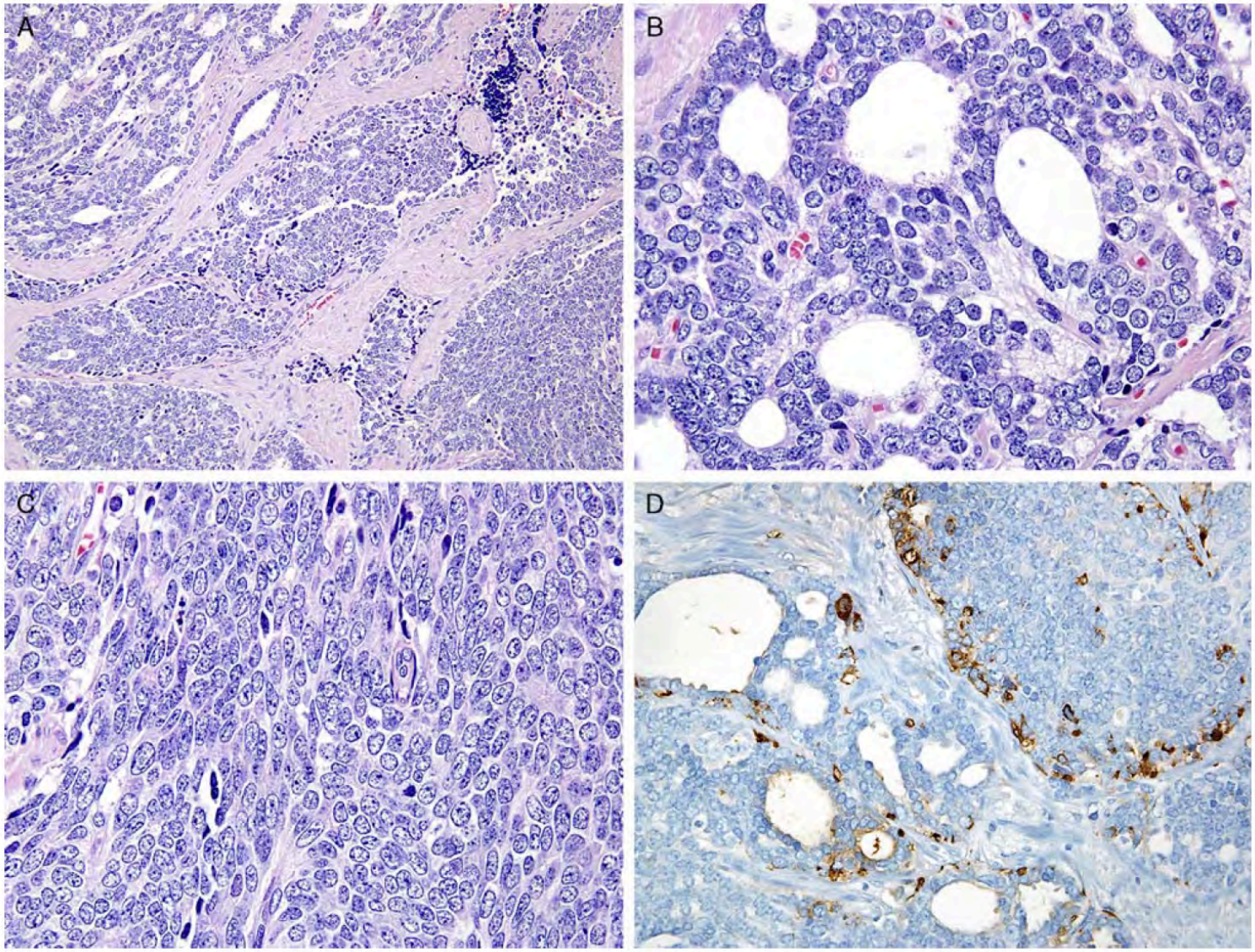
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MODERN PATHOLOGY (2018) 31, S122–S132

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Neuroendocrine tumors of the prostate

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Neuroendocrine (NE) differentiation in tumors of the prostate or in the setting of prostate cancer (PCa) is rare. A survey of these lesions is presented, including usual PCa with focal NE marker-positive cells, Paneth cell-like change, prostatic 'carcinoid', high-grade NE carcinoma, as well as other tumors that do not fit neatly into these categories. The most significant clinical and pathologic features, emerging molecular evidence and the importance of differentiating NE tumors involving the prostate from secondary involvement are highlighted.
Modern Pathology (2018) **31,** S122–S132; doi:10.1038/modpathol.2017.164

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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.

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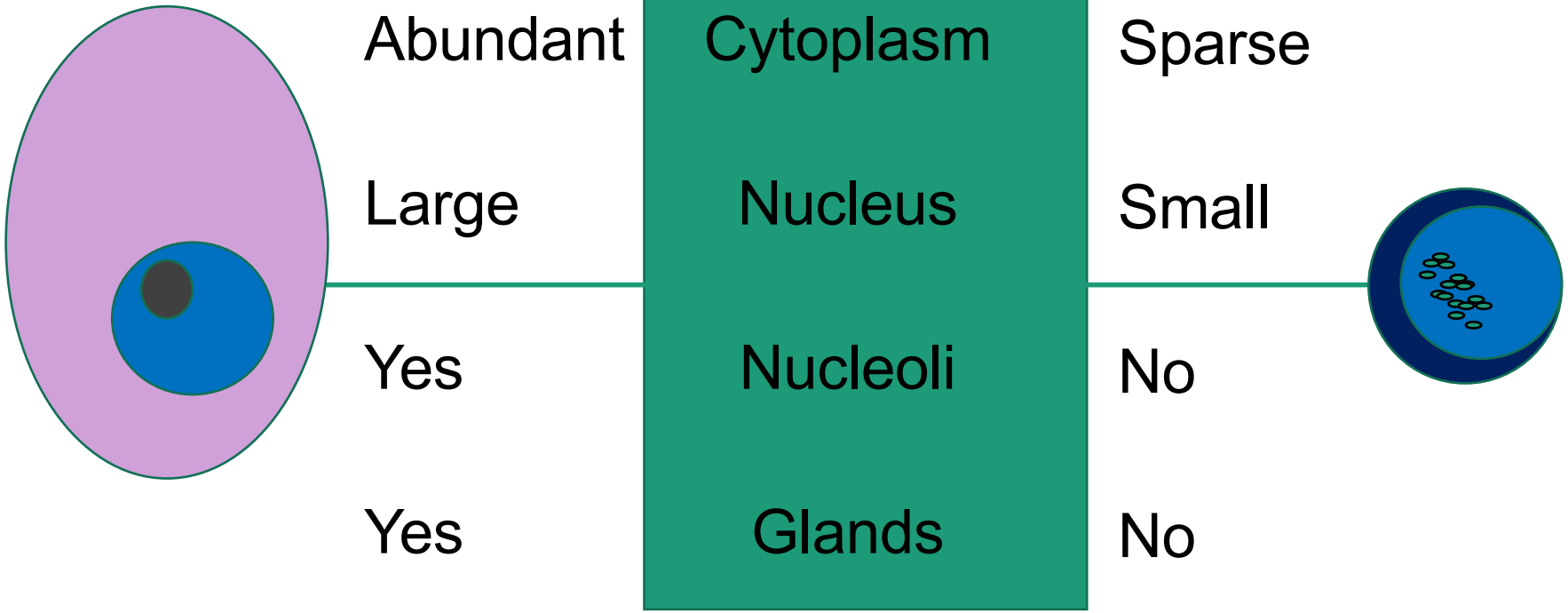
Characteristics that help define NEPC



CRPC (adenocarcinoma)

Small cell/NEPC

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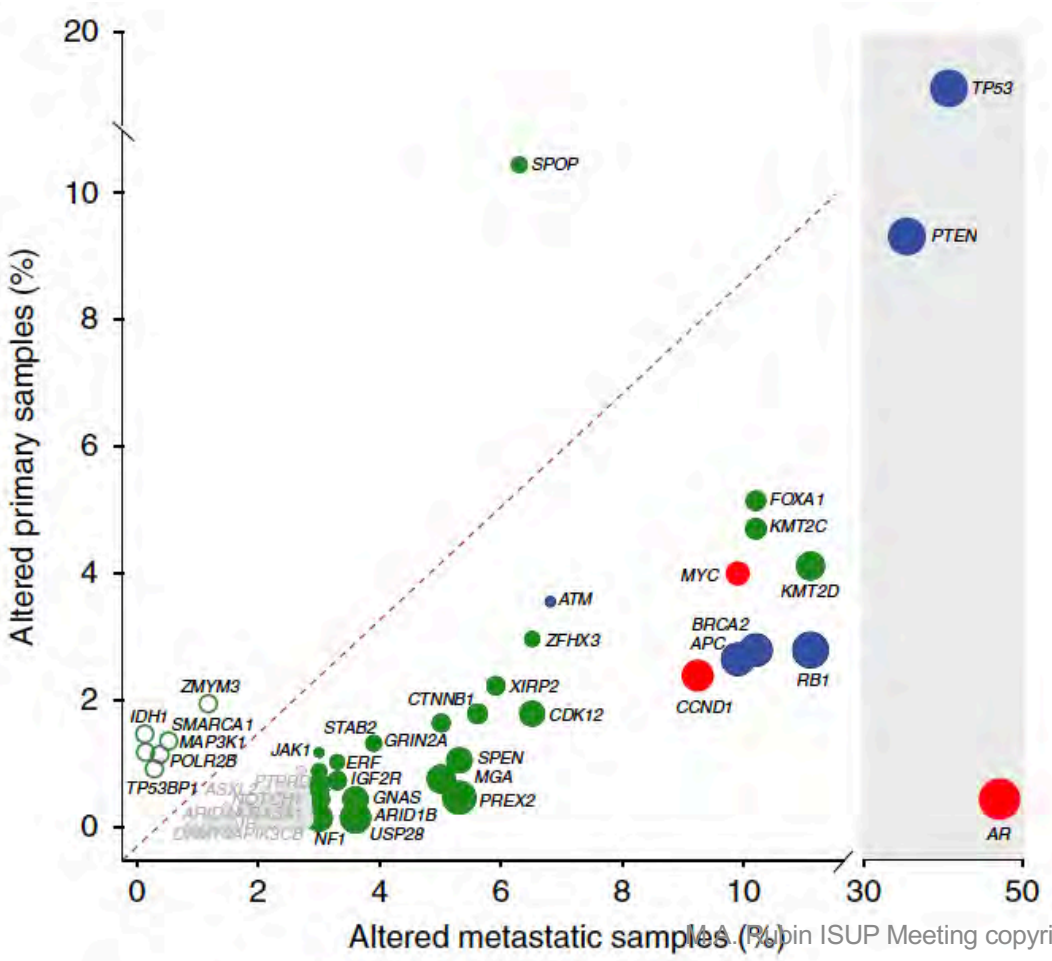
Genomic enrichment and depletion during AR targeted therapy



Enriched after AR Targeted Therapy

AR mutations and amplifications
Myc amplification
PTEN loss
RB1 loss
TP53 loss/mutations
BRCA2 somatic loss

Depleted after AR Targeted Therapy

SPOP mutations

Armenia et al. Nat. Gen. 2018

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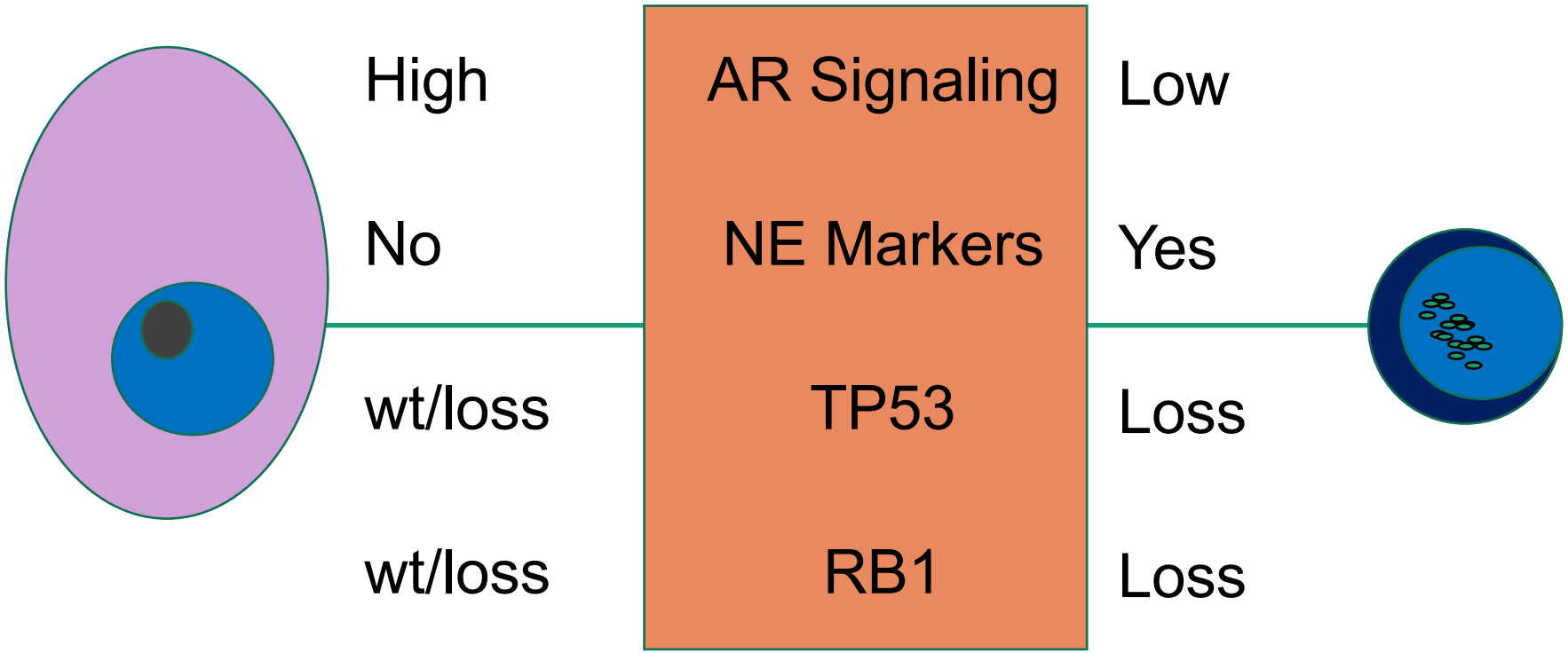
Characteristics that help define NEPC



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Consensus Recommendation Proposal

1) Routine staining for NE expression of localized PCa in the absence of morphologic changes not recommended

2) The term “NE” differentiation best reserved for high-grade cancers (i.e., not carcinoids)

3) Advanced metPCA or CRPC may manifest a range of features that include NE differentiation

4) A combination of molecular evaluation and pathology features may be best approach to classification

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