Immunohistochemical and Molecular Markers in Prostate Cancer

Glen Kristiansen

Professor and Chairman
Institute of Pathology,
University Hospital Bonn

Topics:

1. Diagnostic IHC
2. Prognostic IHC
3. Prognostic molecular signatures
4. Molecular pathology, targeted therapy and predictive pathology in prostate cancer

Complexity of diagnostic IHC: Lymphoma *vs.* Pca
What is more challenging?

Lymphoma:

BCL-2
CD3
CD4
CD8
CD10
CD15
CD20
CD21
CD23
CD30
CD45
CD79
Cyclin D1
K/L
Mib-1

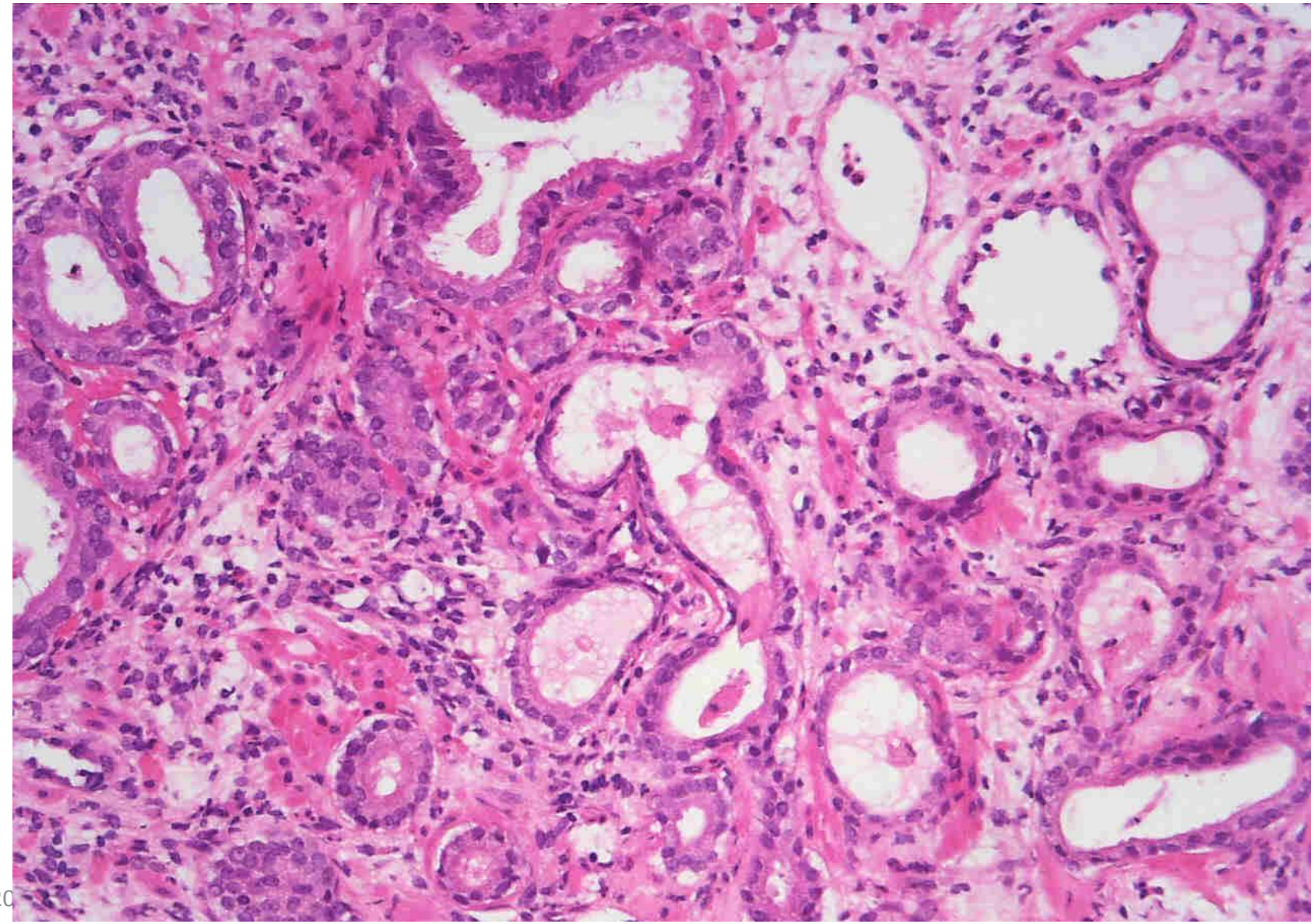
?

Prostate Cancer:

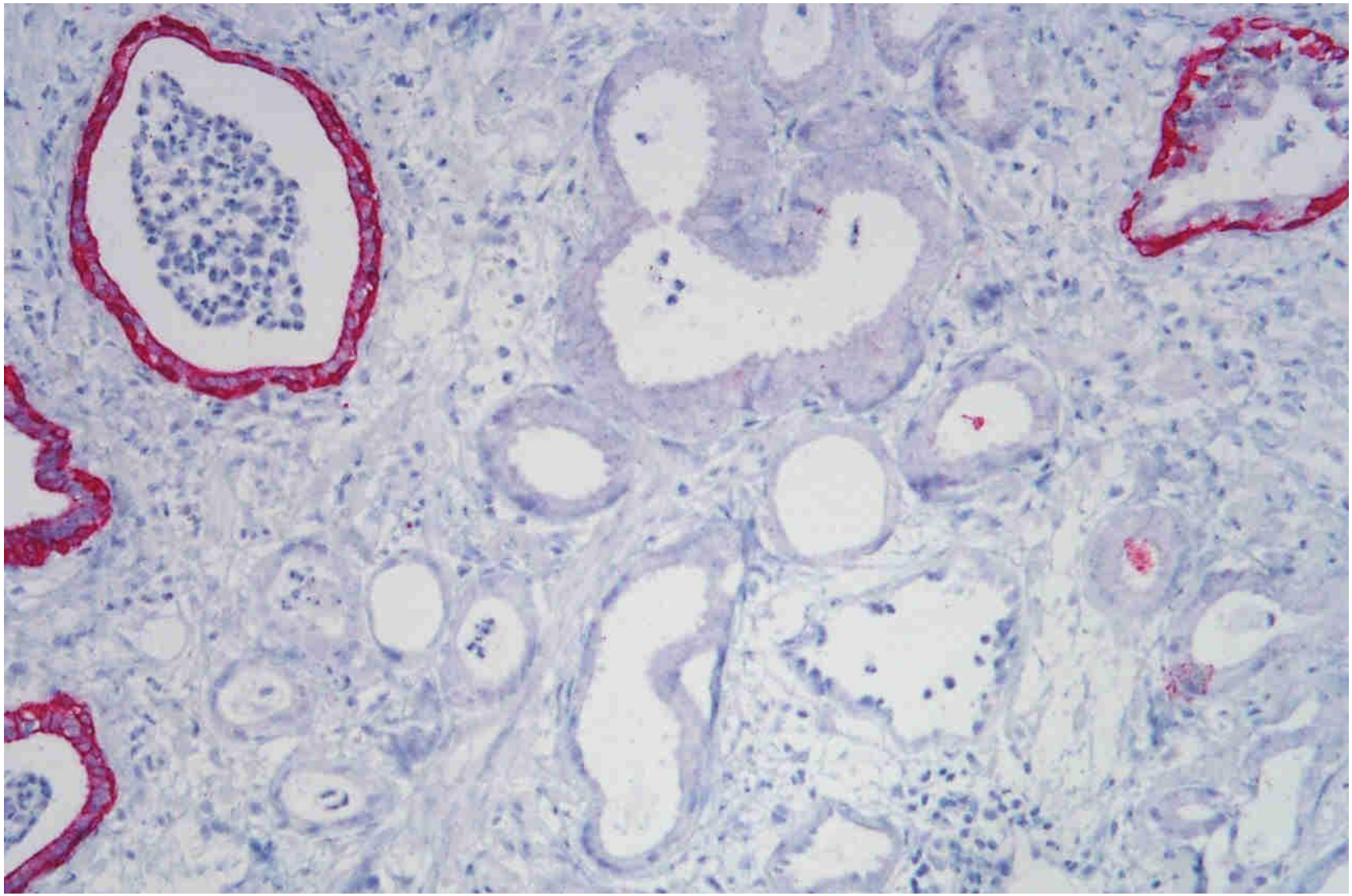
Basal cell markers
AMACR
PSA
Prostein
NKX3.1

The simplicity is misleading,
„Prostate IHC is a mine field."
M. Varma

Typical diagnostic problem:
biopsy: carcinoma *vs.* atrophy/reactive changes?

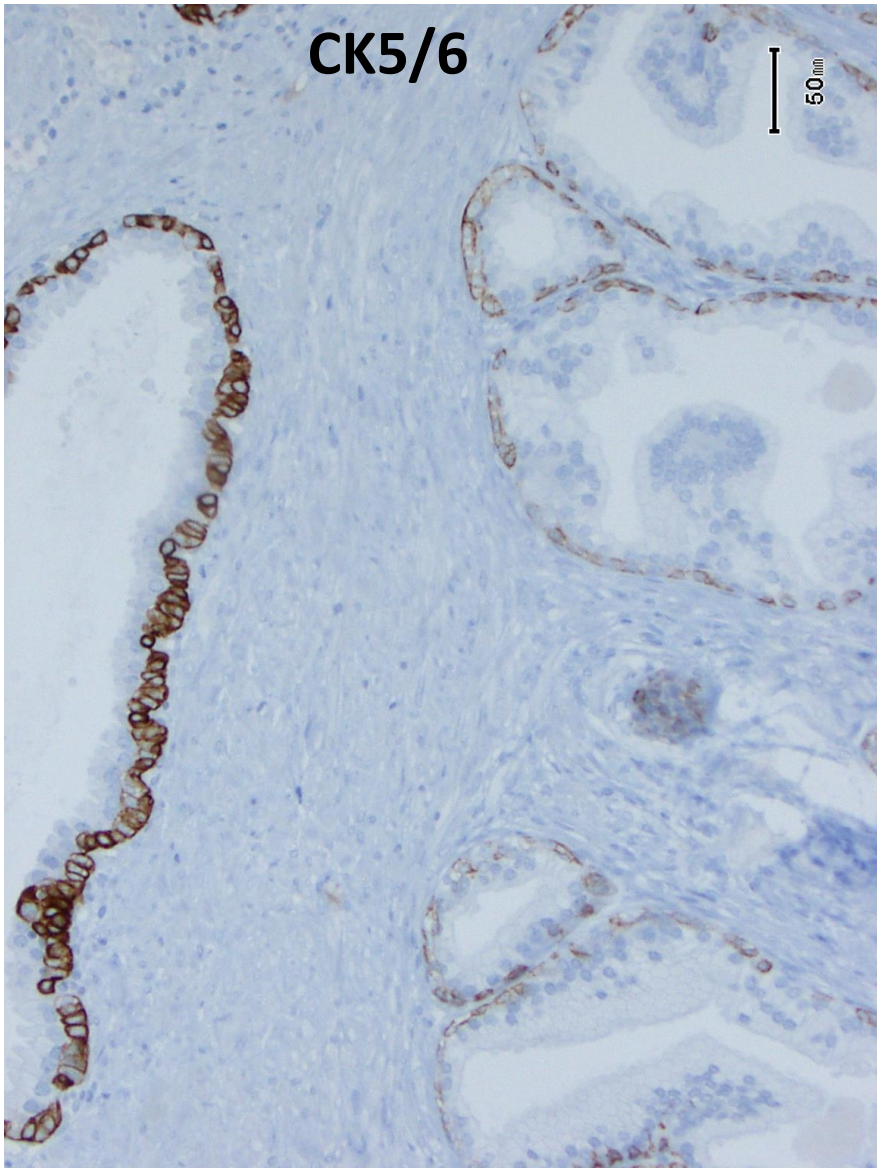


Basal cell marker Immunohistochemistry (CK 5/6):

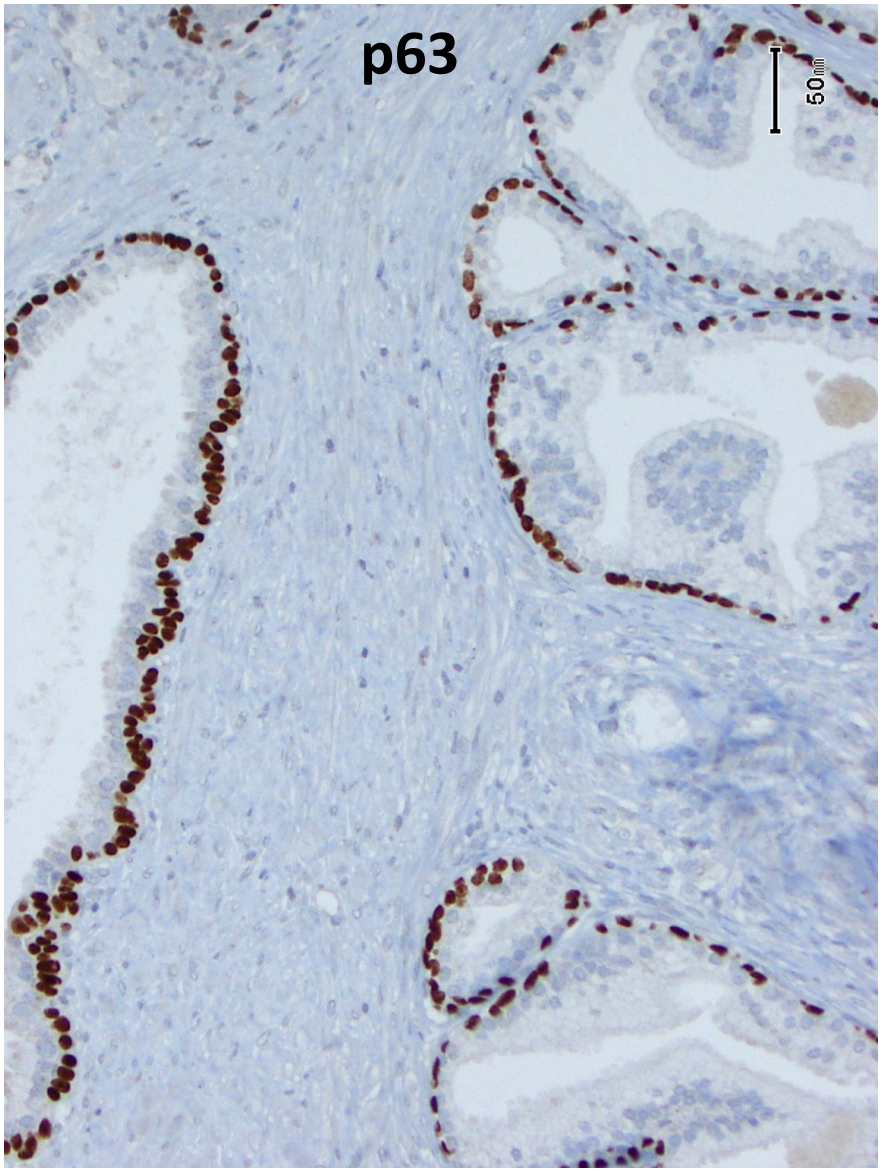


Diagnosis: Adenocarcinoma !

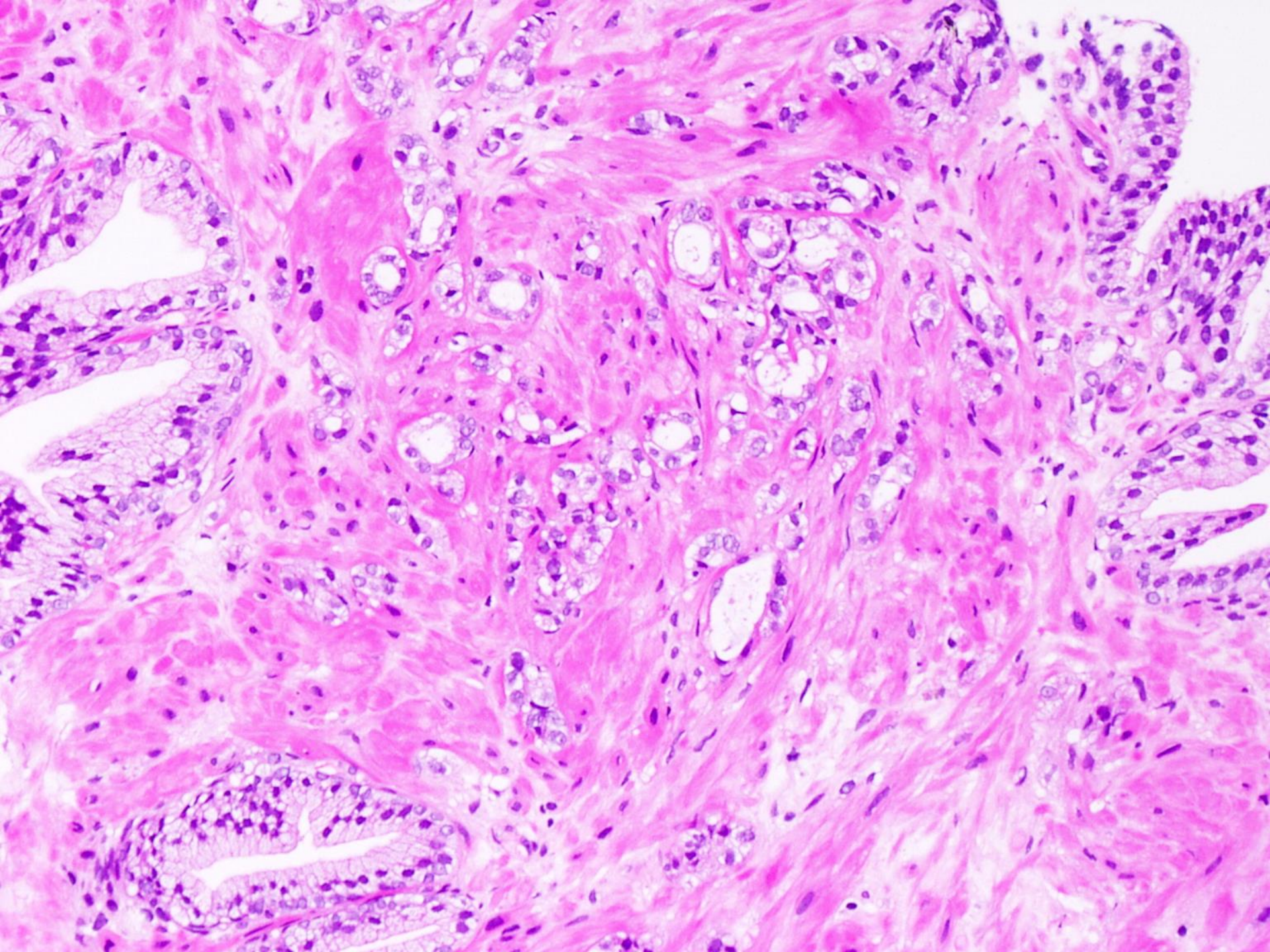
Cytokeratins or p63?

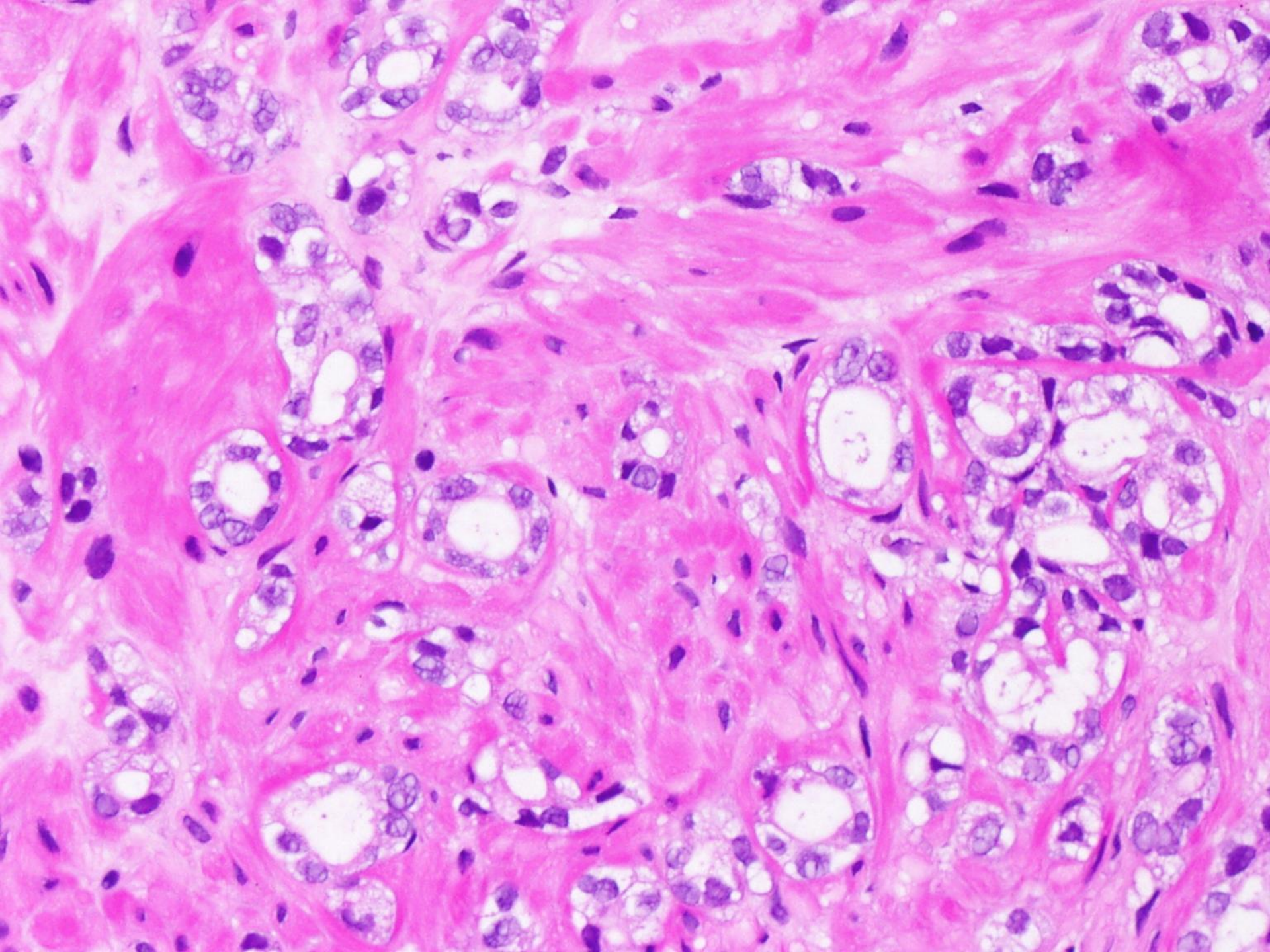


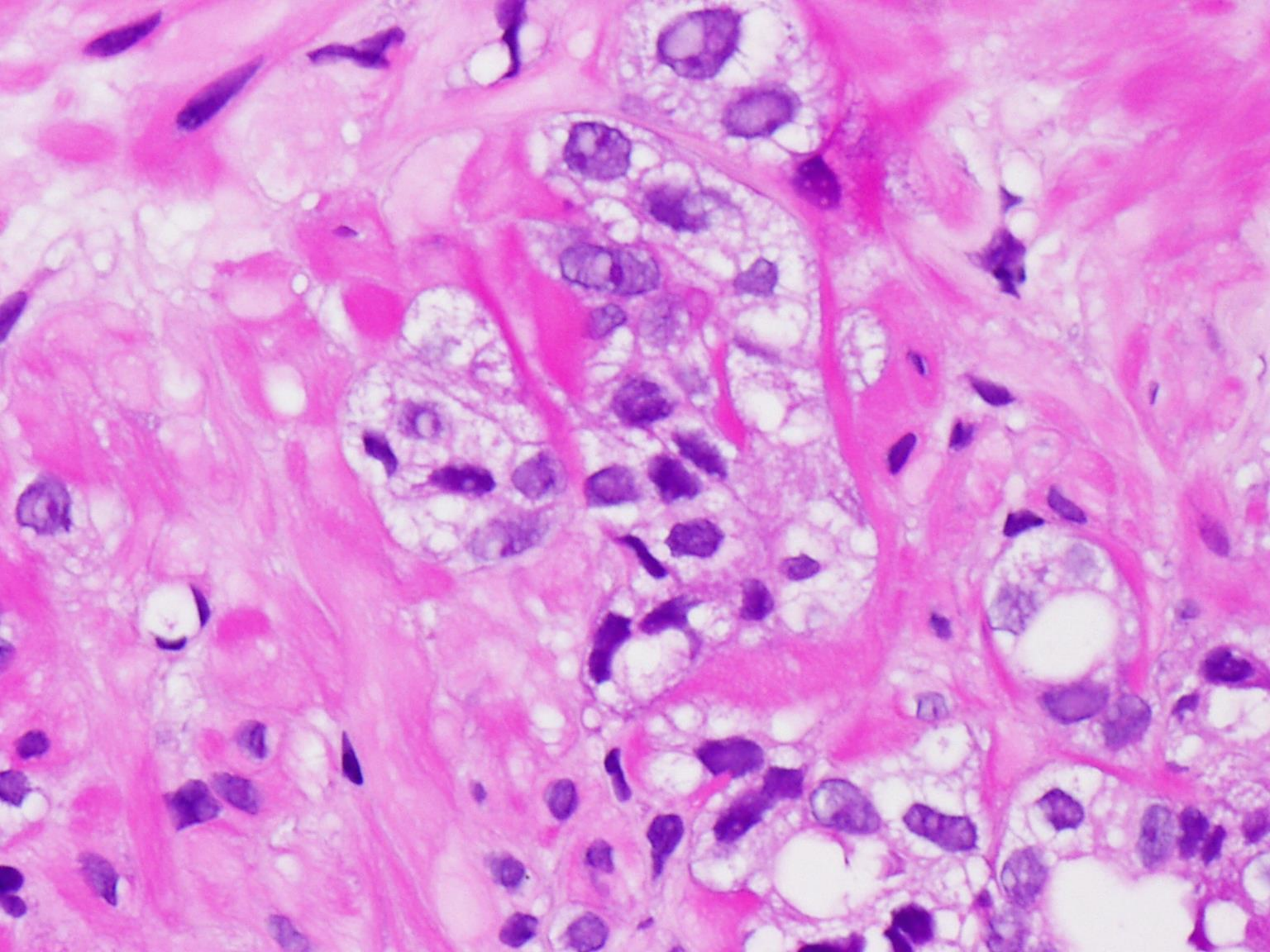
PZ TZ

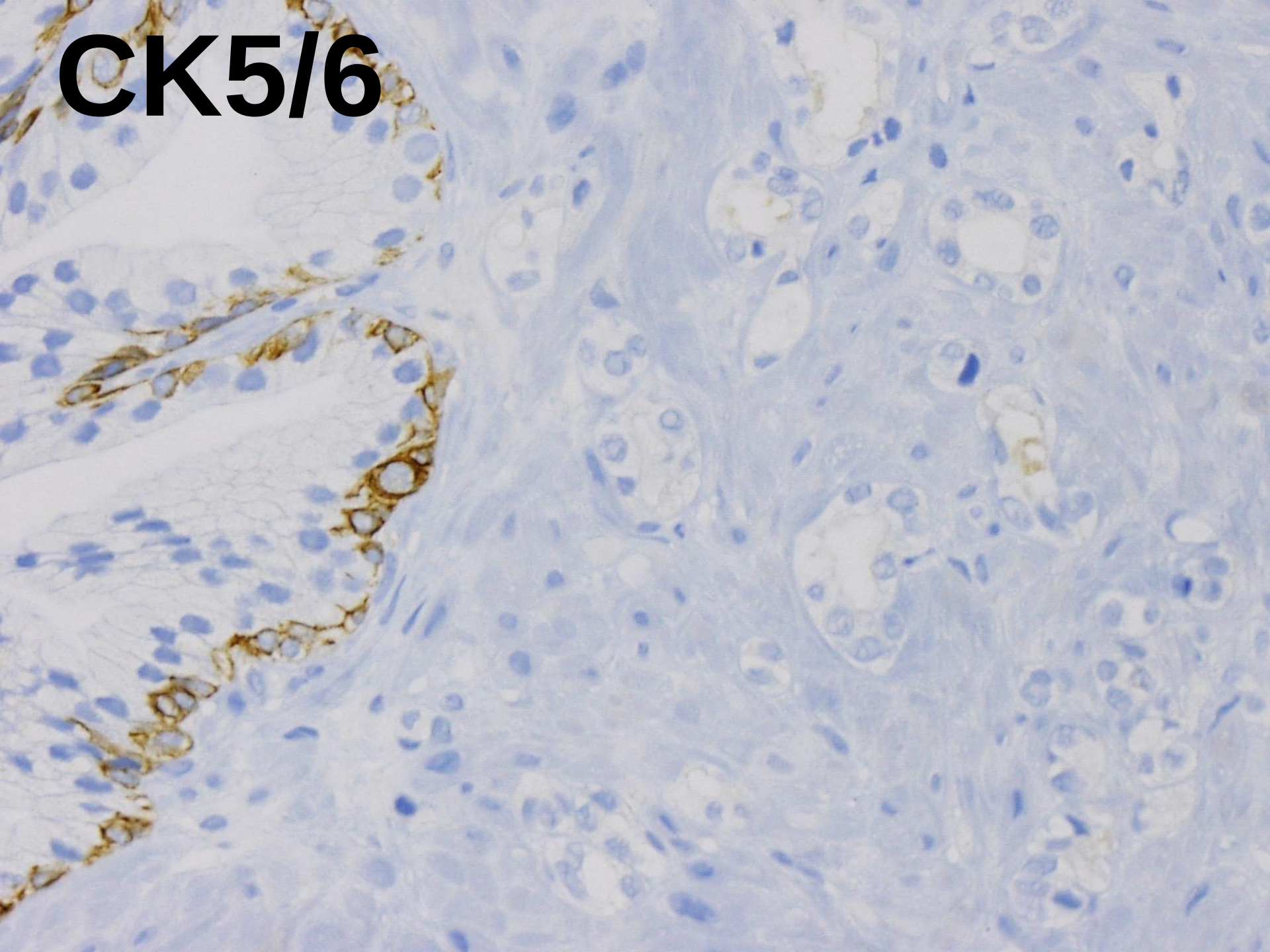


PZ TZ

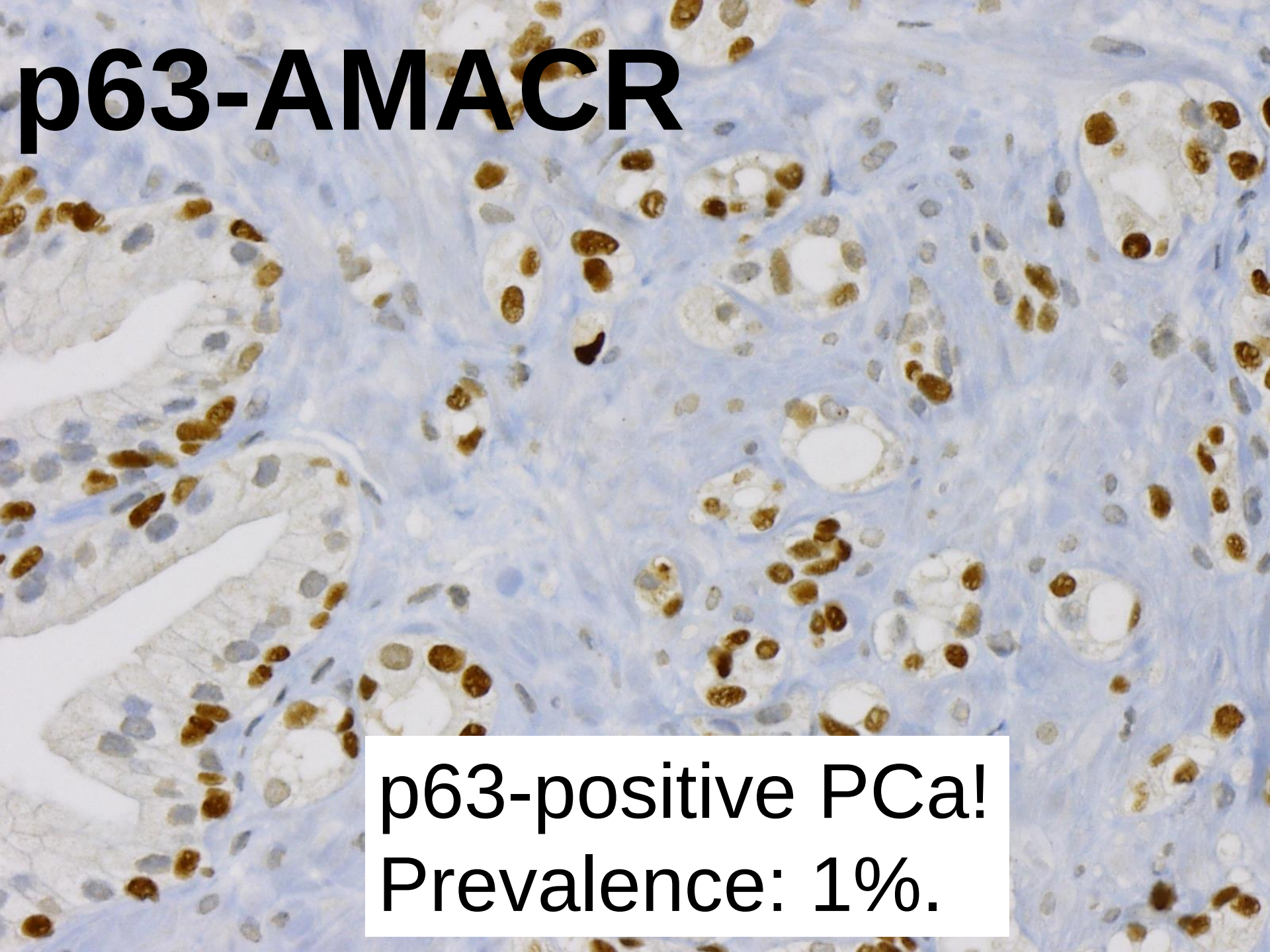







CK5/6

p63-AMACR



p63-positive PCa!
Prevalence: 1%.

Basal cell markers: is p40 the „better“ p63?

MODERN PATHOLOGY (2012) 25, 405–415

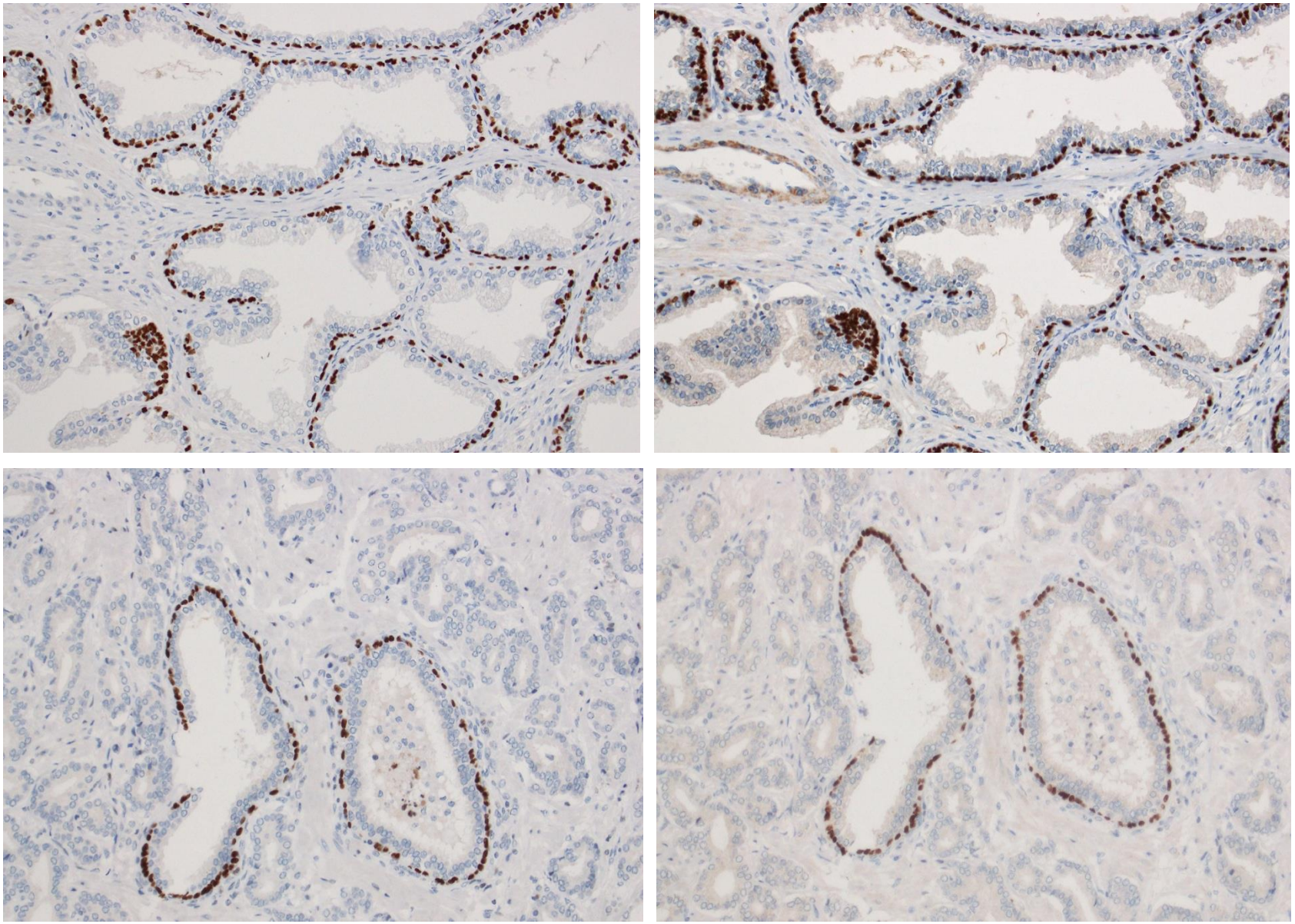
p40 (ΔNp63) is superior to p63 for the diagnosis of pulmonary squamous cell carcinoma

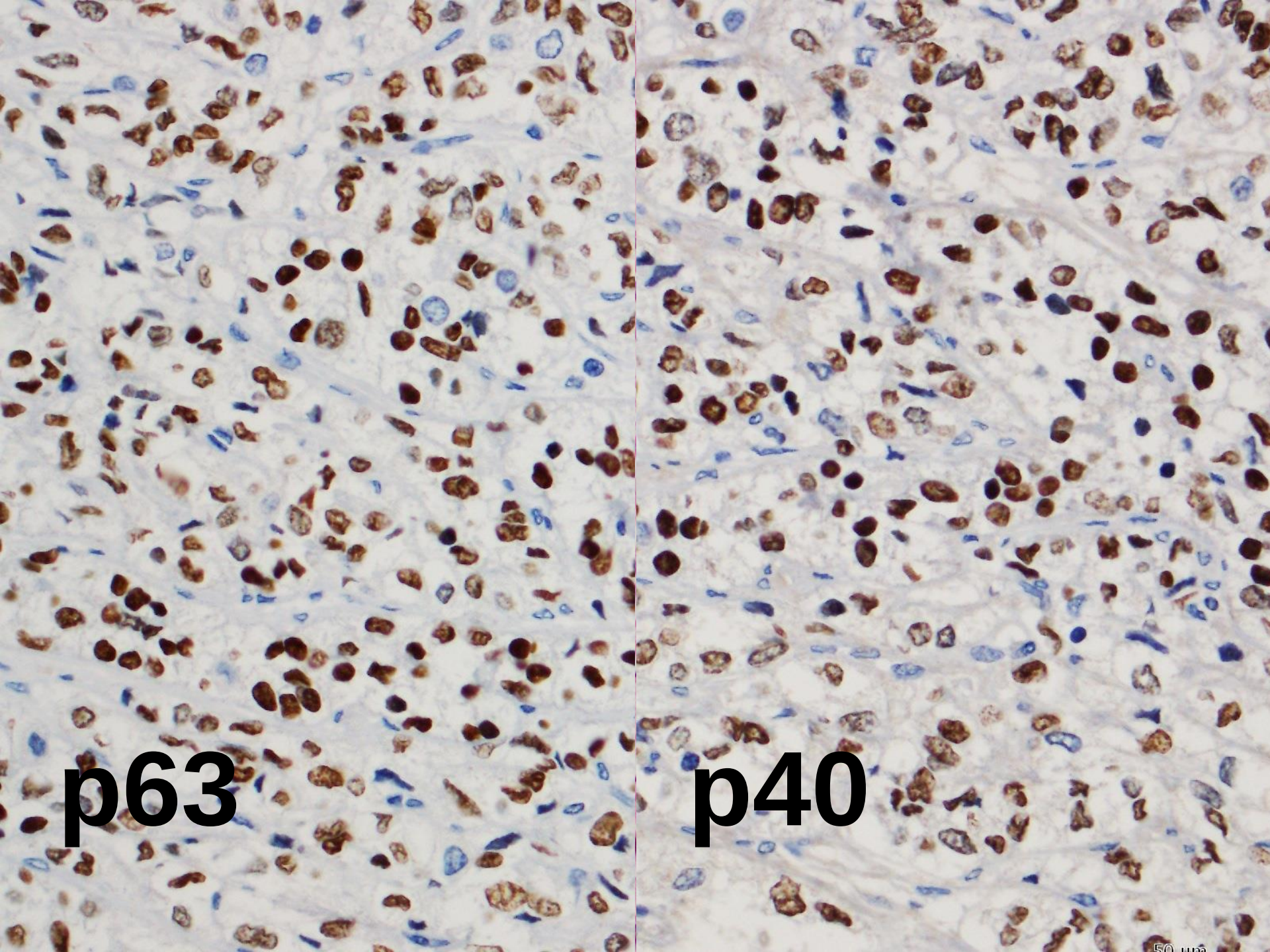
Justin A Bishop[1], Julie Teruya-Feldstein[2], William H Westra[1], Giuseppe Pelosi[3], William D Travis[2] and Natasha Rekhtman[2]

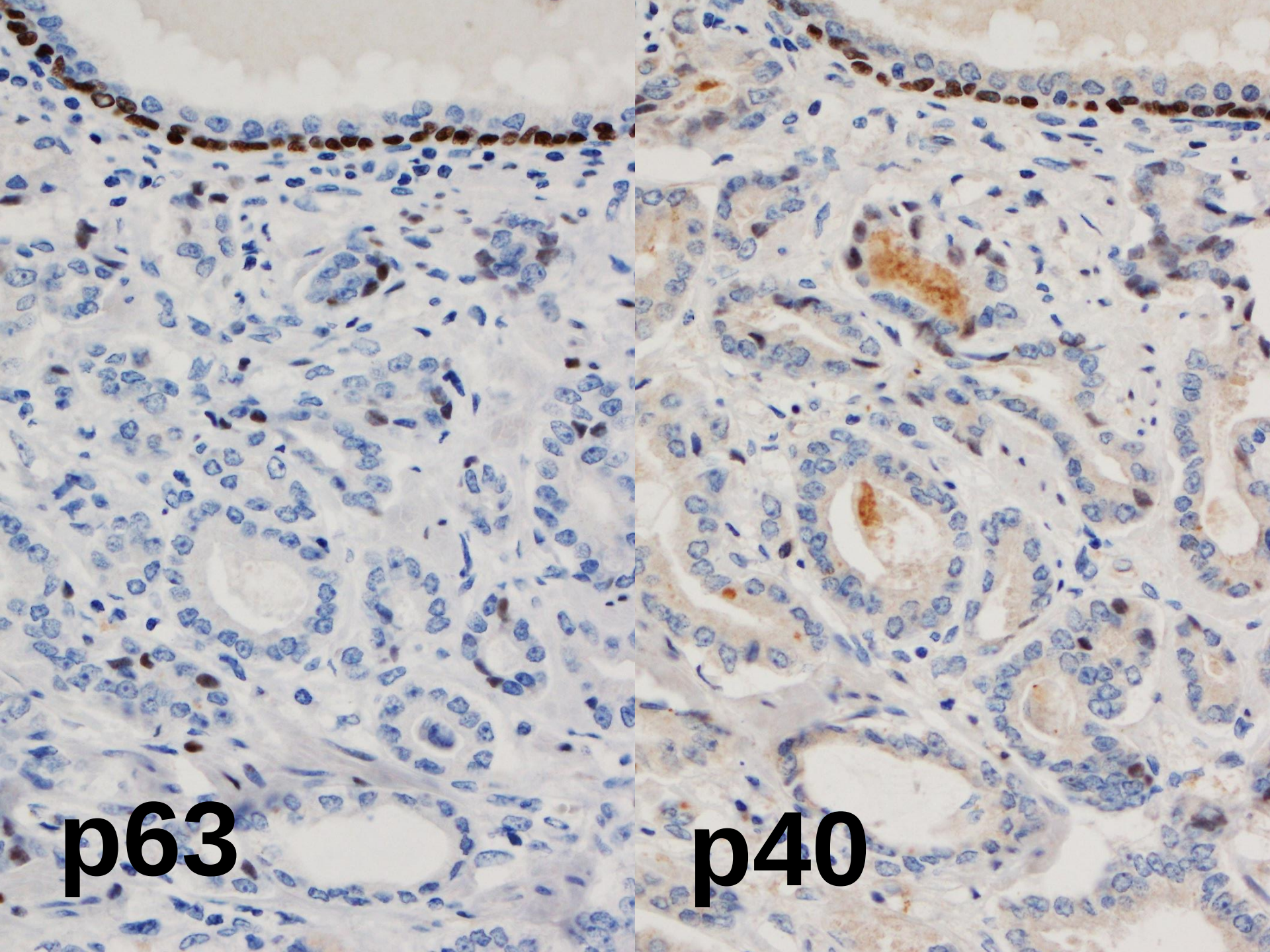
p63 isoform	Antibody reactivity		Simplified protein map and antibody binding sites	Functional role
	p63/4A4	p40		
TAp63	+	-	p63/4A4; TA domain; Core domain	p53-like tumor suppressor
ΔNp63	+	+	p40; p63/4A4; ΔN domain; Core domain	oncogene

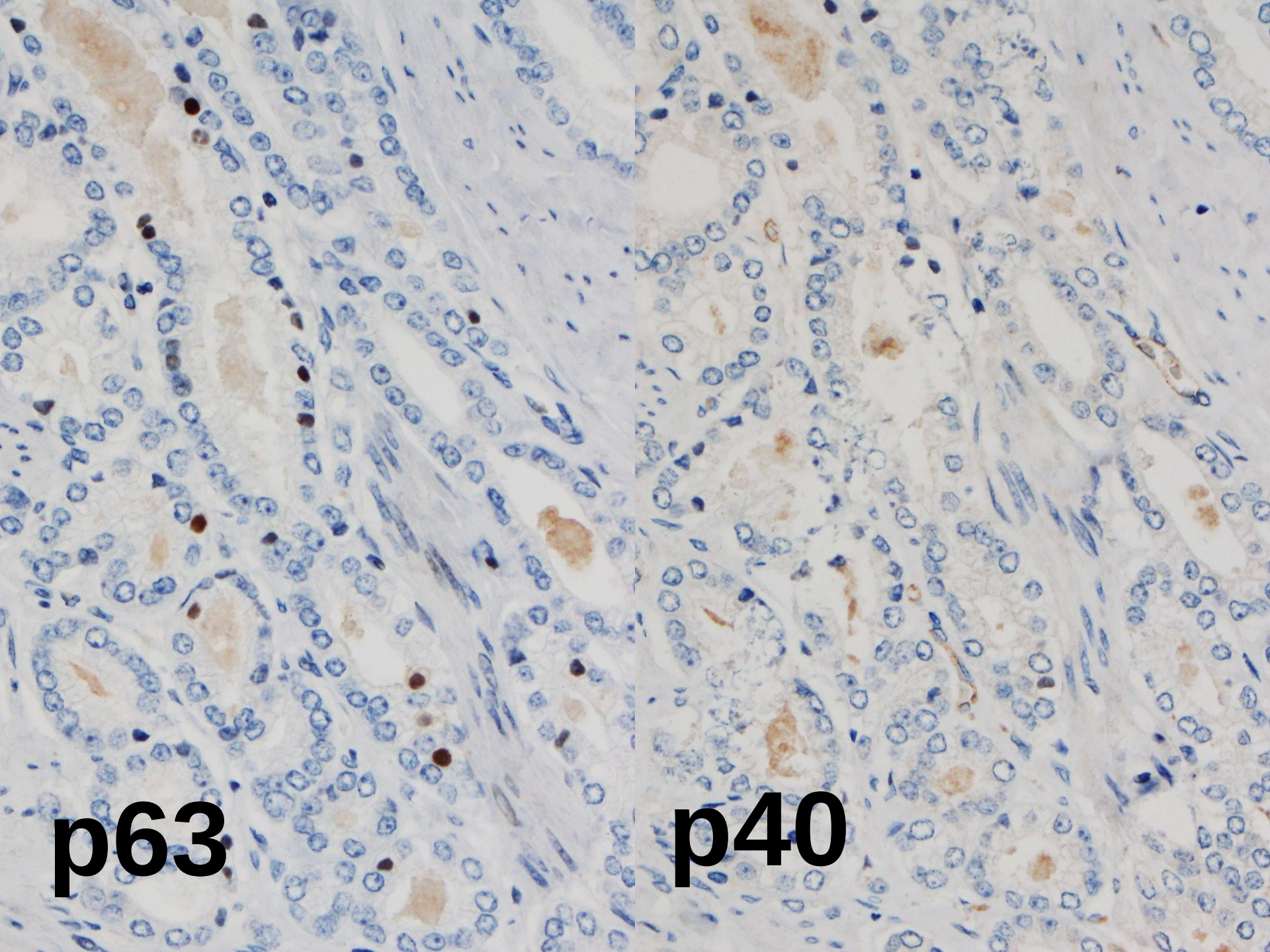
„It has been suggested primarily in laboratory studies that the predominant p63 isoform in basal/progenitor cells is specifically the DN variant, whereas the TA isoform has a wider tissue distribution.“

n=633




p63
p40


p63
p40


p63
p40

Results: Statistics (n=633)

- 98,6% of PCa p40&p63 negative
- 73% totally identical
  - minor differences:
    - 20% p63>p40
    - 7% p40>p63

- p63 positive PCa: 1,4% (!)
- p40 positive PCa: 0,6%.

p40 is slightly superior to p63 as a basal cell marker.

Histopathology. 2013 Jul;63(1):50-6.

ΔNp63 (p40) expression in prostatic adenocarcinoma with diffuse p63 positivity☆

Katsunori Uchida MD[a,b], Hillary Ross MD[b], Tamara Lotan MD, PhD[b], Jean-Christophe Pignon PhD[c], Sabina Signoretti MD[c], Jonathan I. Epstein MD[b], Peter B. Illei MD[b,*]

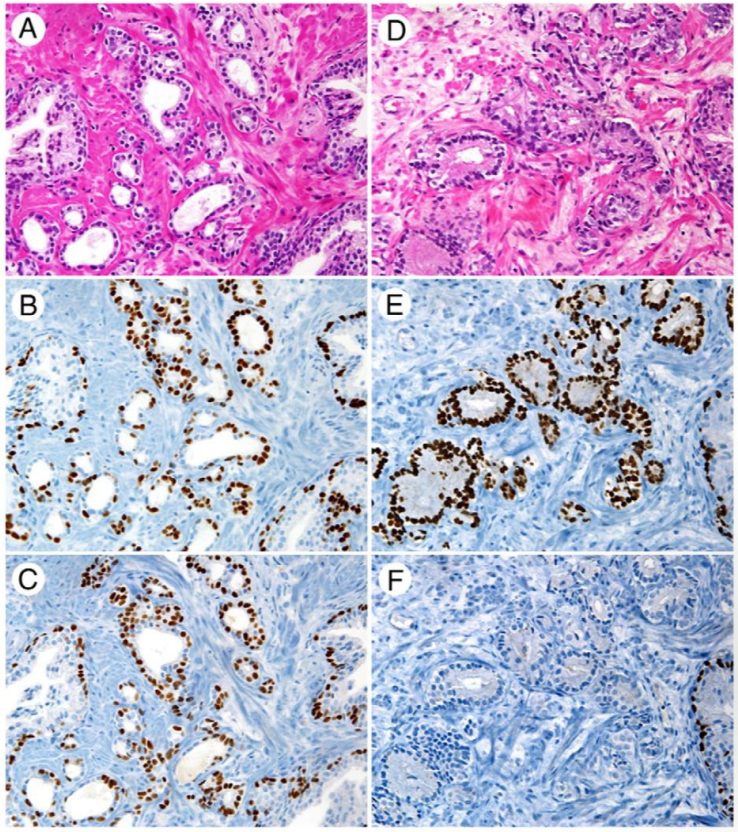
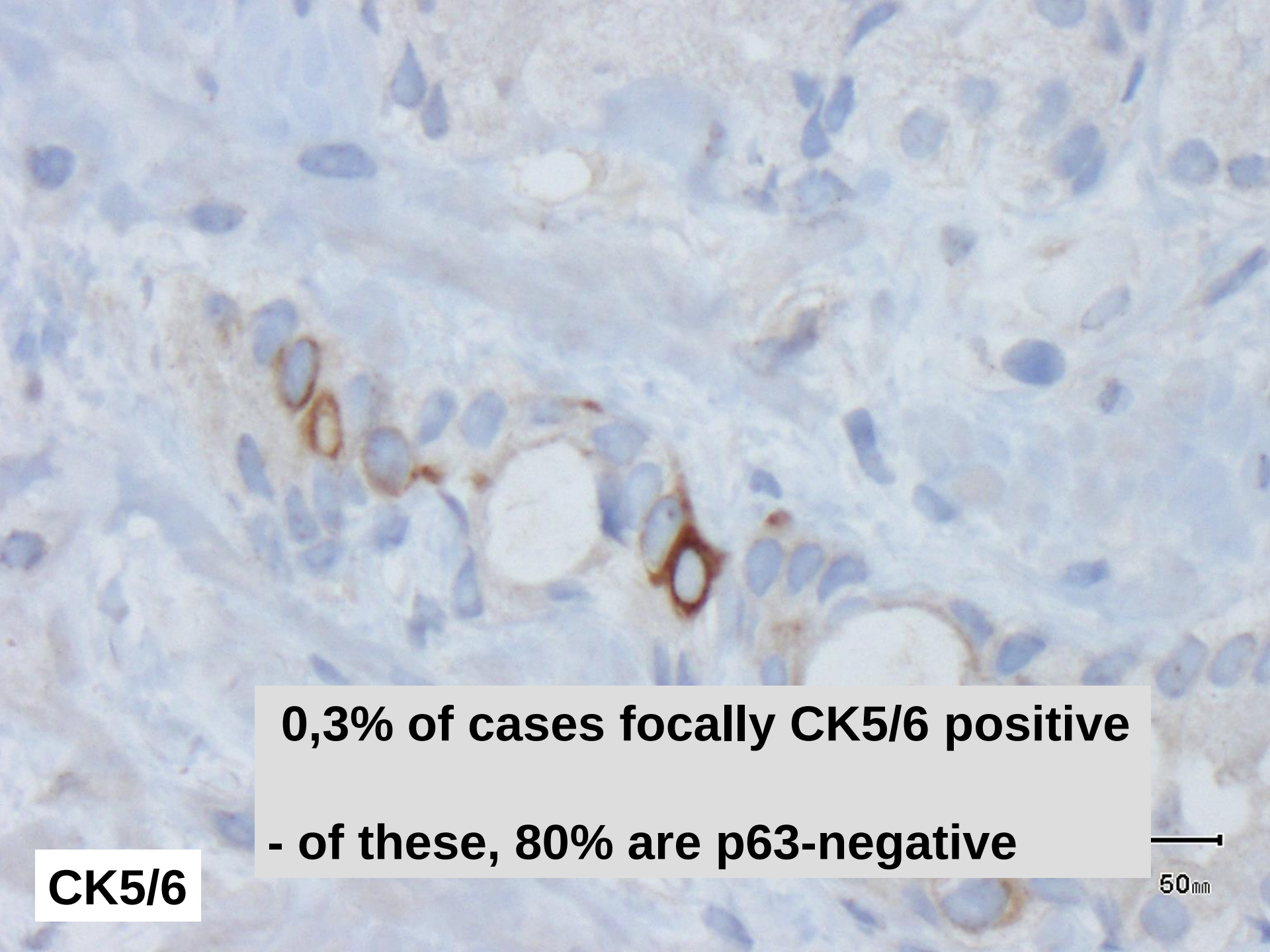


Table p63/p40 staining in 31 cores of prostate adenocarcinoma with aberrant p63 expression, 125 cores of conventional prostate adenocarcinoma, and 157 cores of benign prostatic tissue

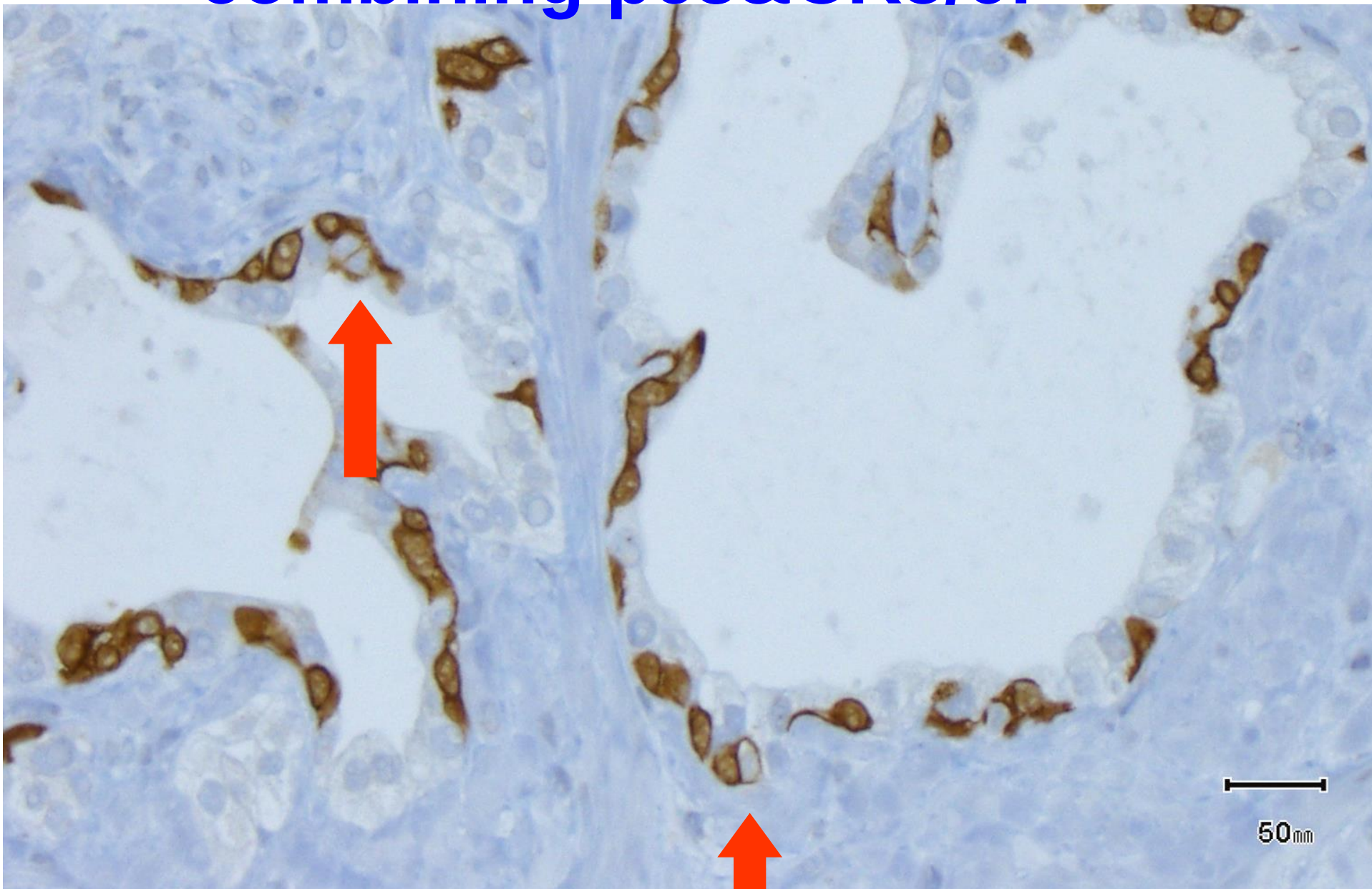
	p63 (clone 4A4)	p40 (polyclonal ΔNp63)
p63 expressing prostate adenocarcinoma	31/31 [a]	29/31 [a]
Conventional prostate adenocarcinoma	0/125 [b]	0/125 [b]
Benign prostate (basal cells)	157/157 [b]	157/157 [b]

„From a diagnostic perspective, the detection of ΔNp63 with use of p40 antibody provides only a slight advantage over the currently in use p63 antibody.“

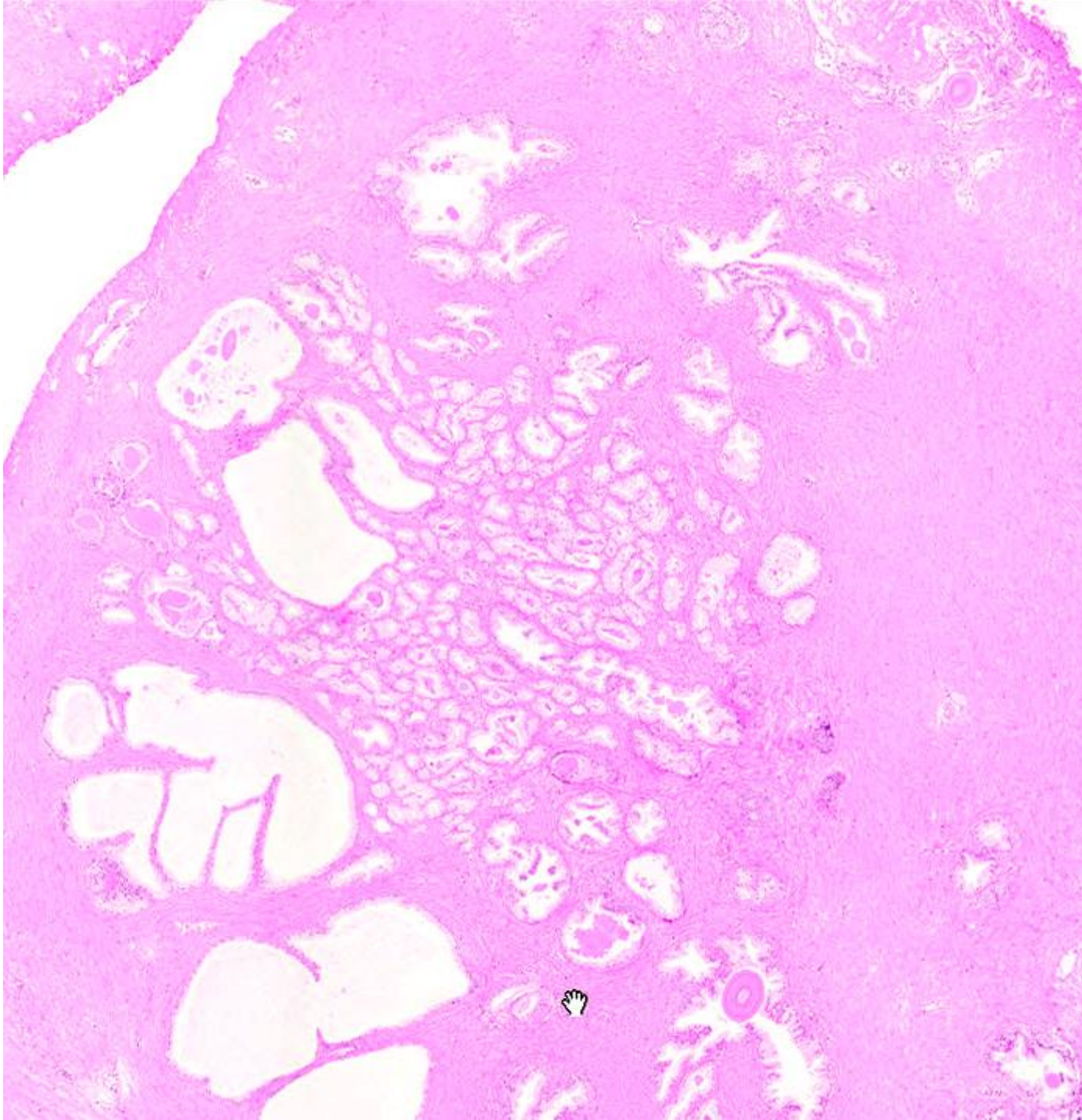
Hum Pathol. 2015 Mar;46(3):384-9.

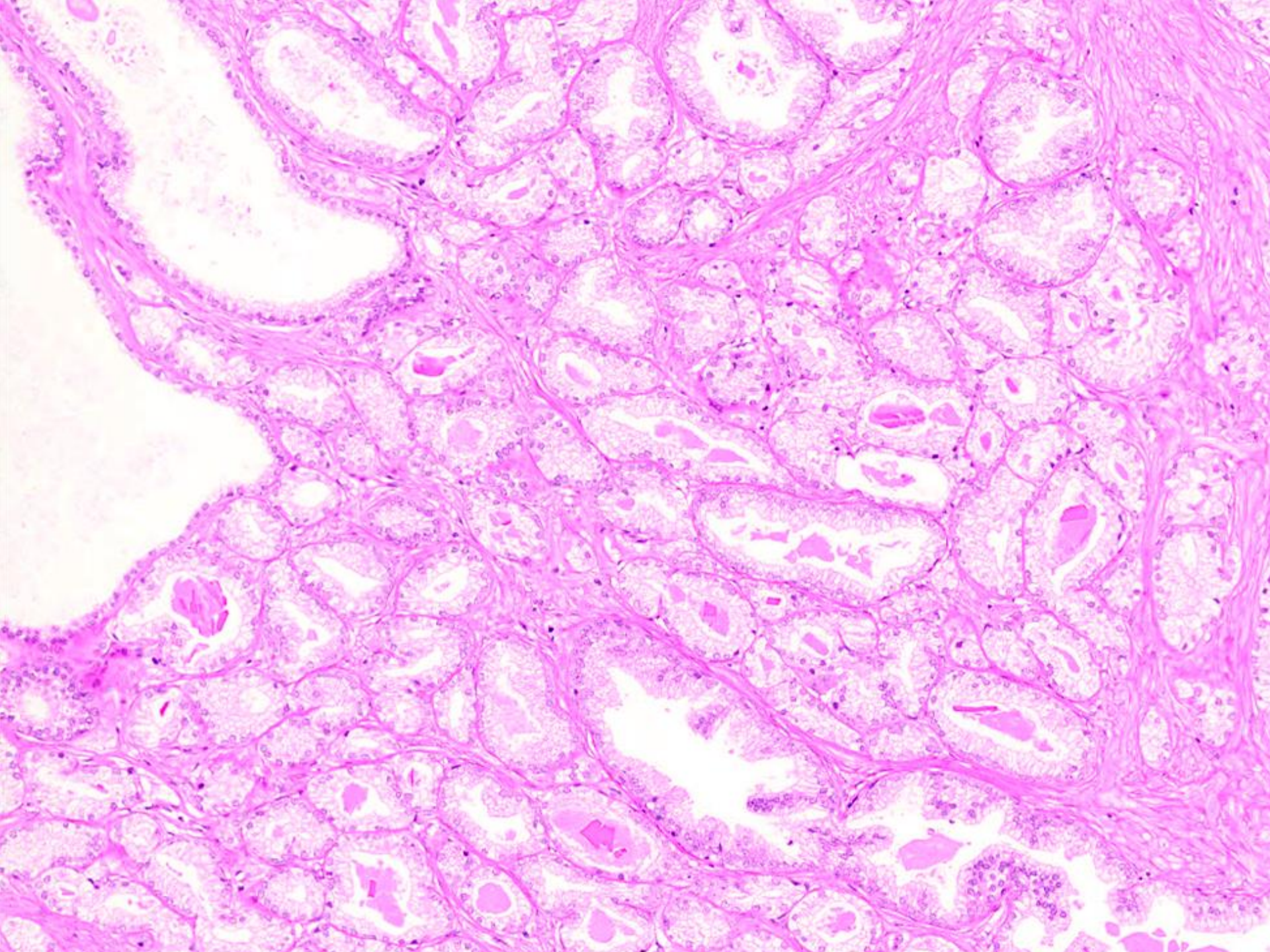

0,3% of cases focally CK5/6 positive
- of these, 80% are p63-negative
CK5/6
50㎛

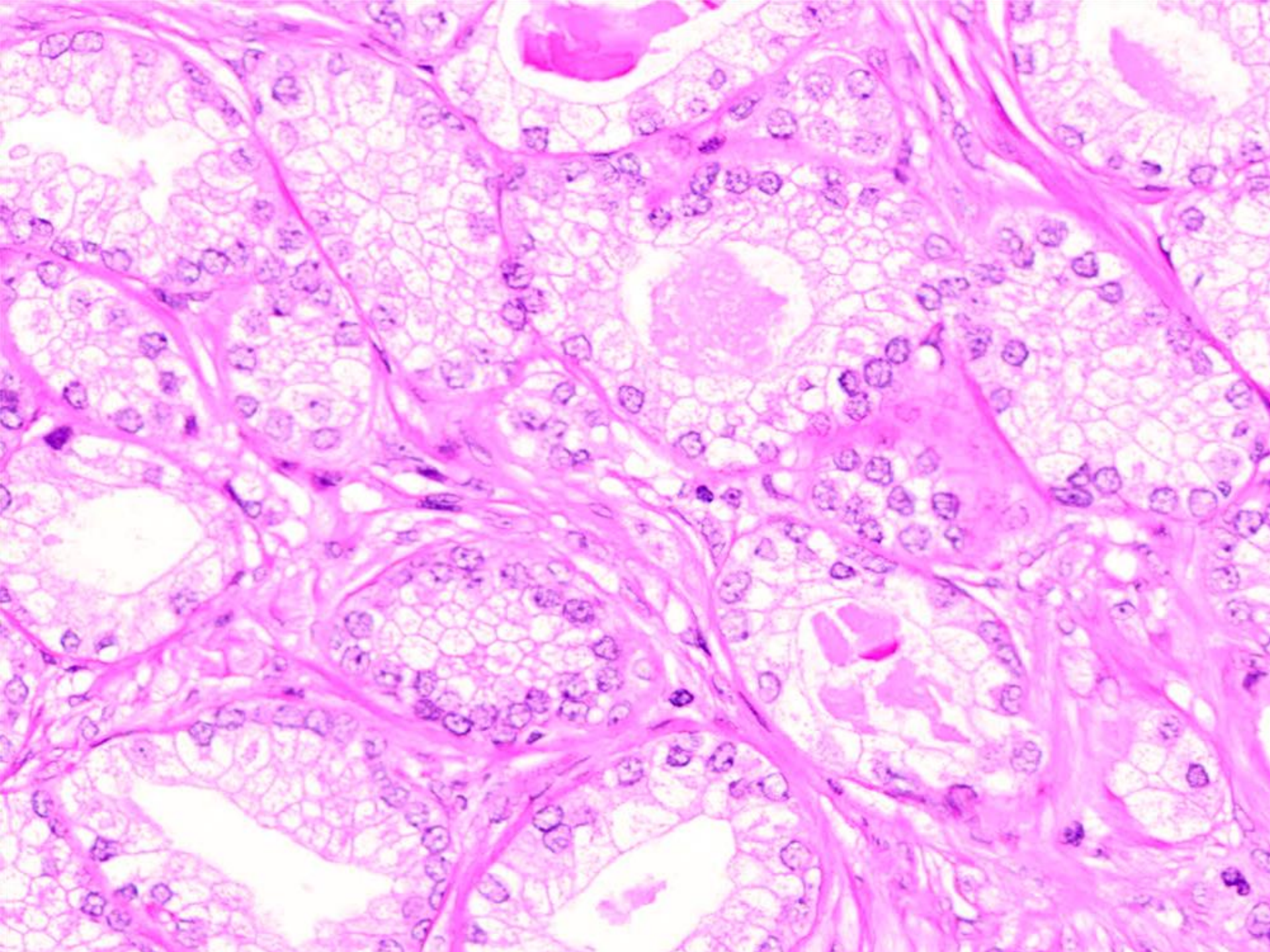
Increased Sensitivity by combining p63&CK5/6:

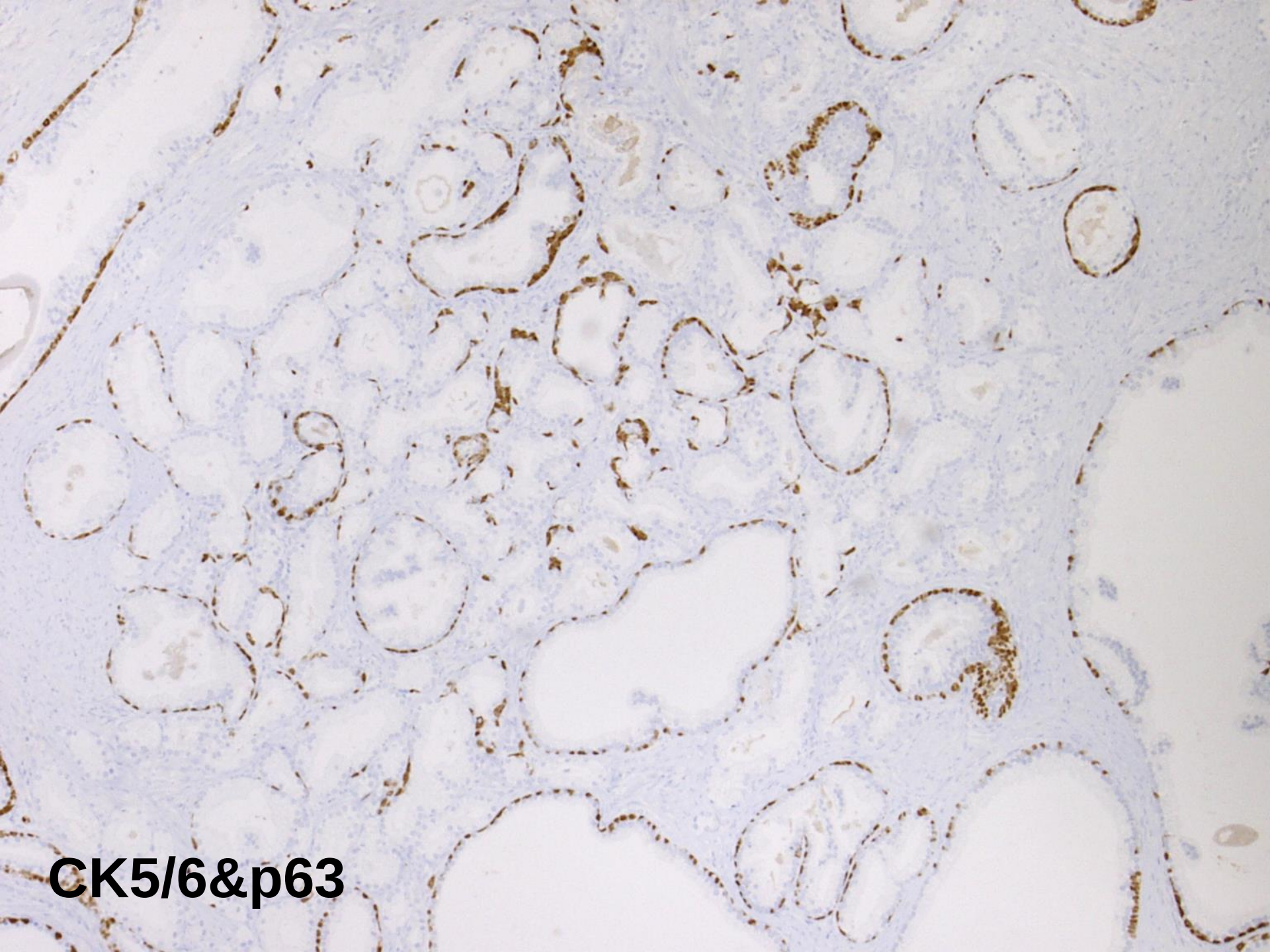


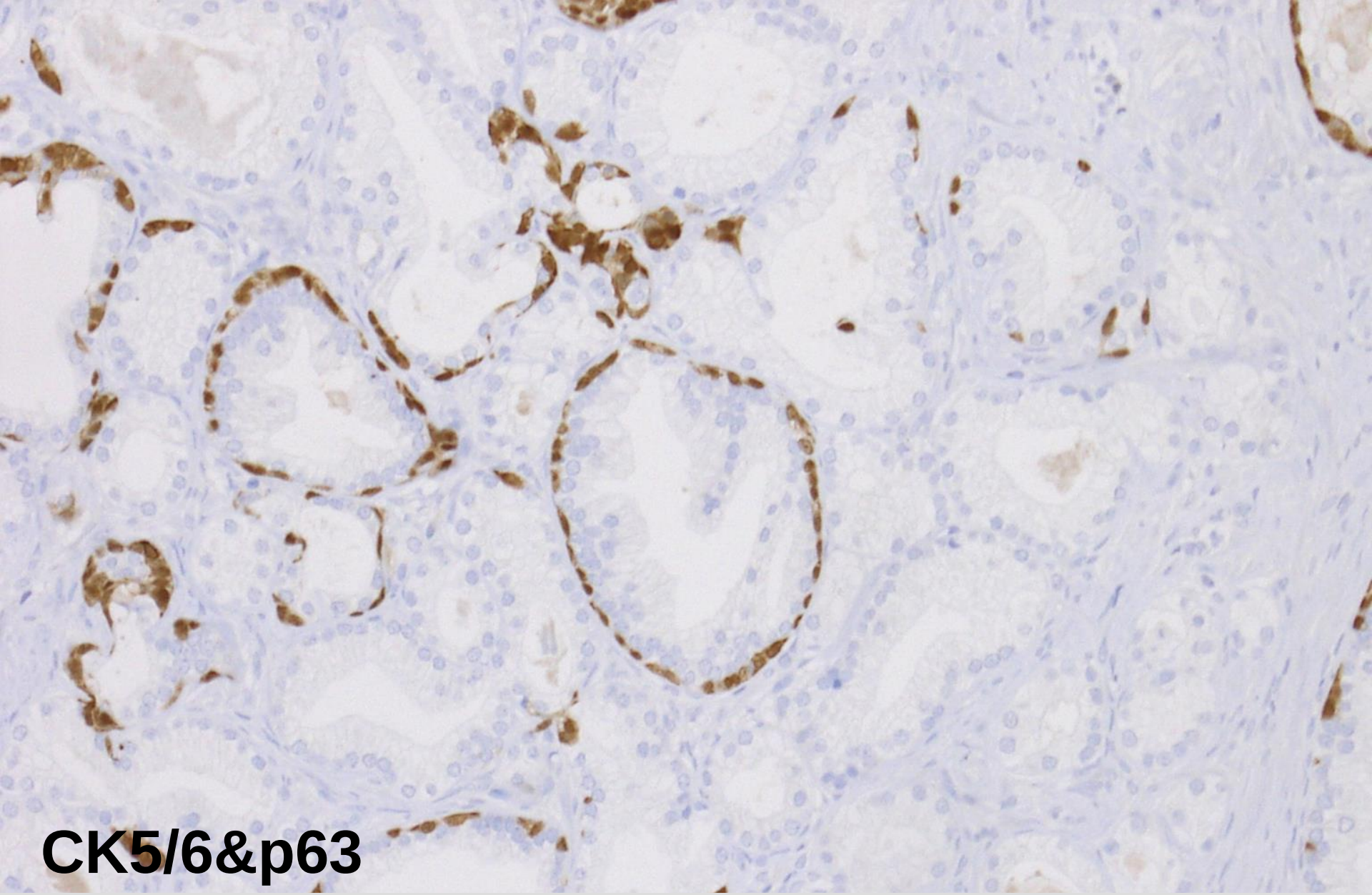
???








CK5/6&p63



Adenosis of the prostate

[CANCER RESEARCH 60, 1677–1682, March 15, 2000]

Identification of Differentially Expressed Genes in Human Prostate Cancer Using Subtraction and Microarray[1]

The American Journal of Surgical Pathology *25(11): 1397–1404, 2001*

P504S

A New Molecular Marker for the Detection of Prostate Carcinoma

[CANCER RESEARCH 62, 2220–2226, April 15, 2002]

Advances in Brief

α-Methylacyl-CoA Racemase: A New Molecular Marker for Prostate Cancer[1]

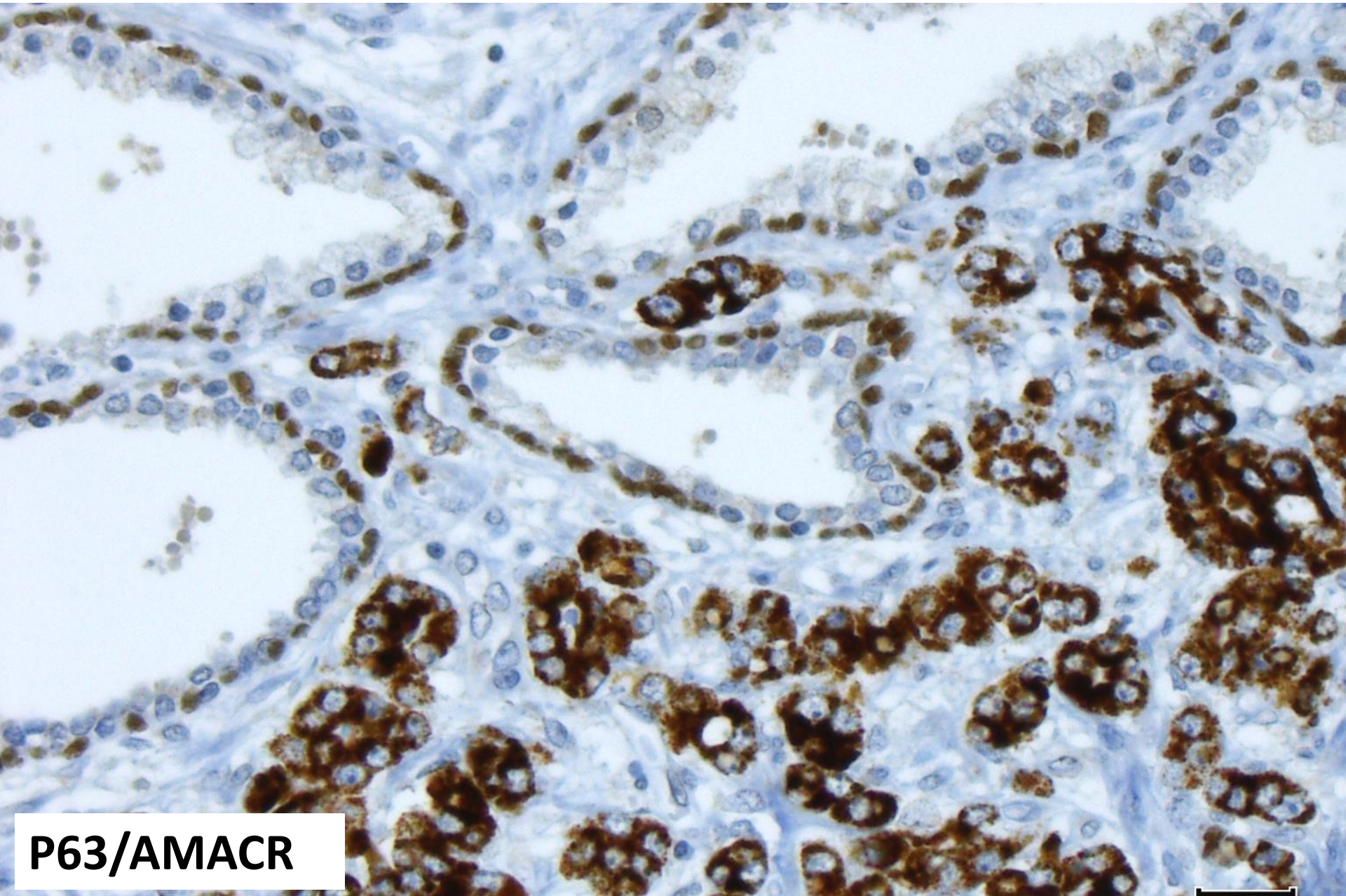
α-Methylacyl Coenzyme A Racemase as a Tissue Biomarker for Prostate Cancer

Mark A. Rubin, MD
Ming Zhou, MD, PhD
Saravana M. Dhanasekaran, PhD
Sooryanarayana Varambally, PhD
Terrence R. Barrette

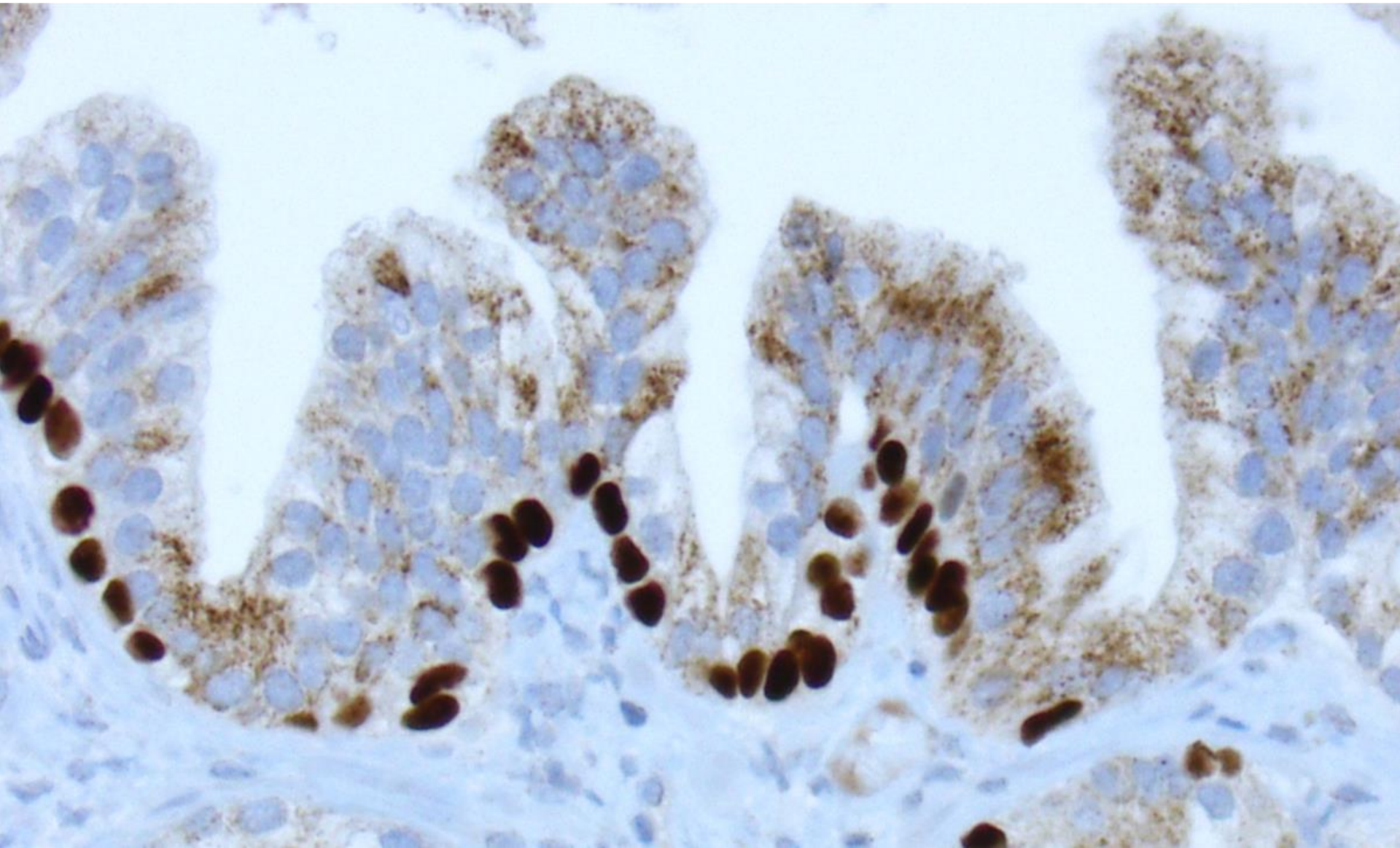
Context Molecular profiling of prostate cancer has led to the identification of candidate biomarkers and regulatory genes. Discoveries from these genome-scale approaches may have applicability in the analysis of diagnostic prostate specimens.

Objectives To determine the expression and clinical utility of α-methylacyl coenzyme A racemase (*AMACR*), a gene identified as being overexpressed in prostate cancer by global profiling strategies.

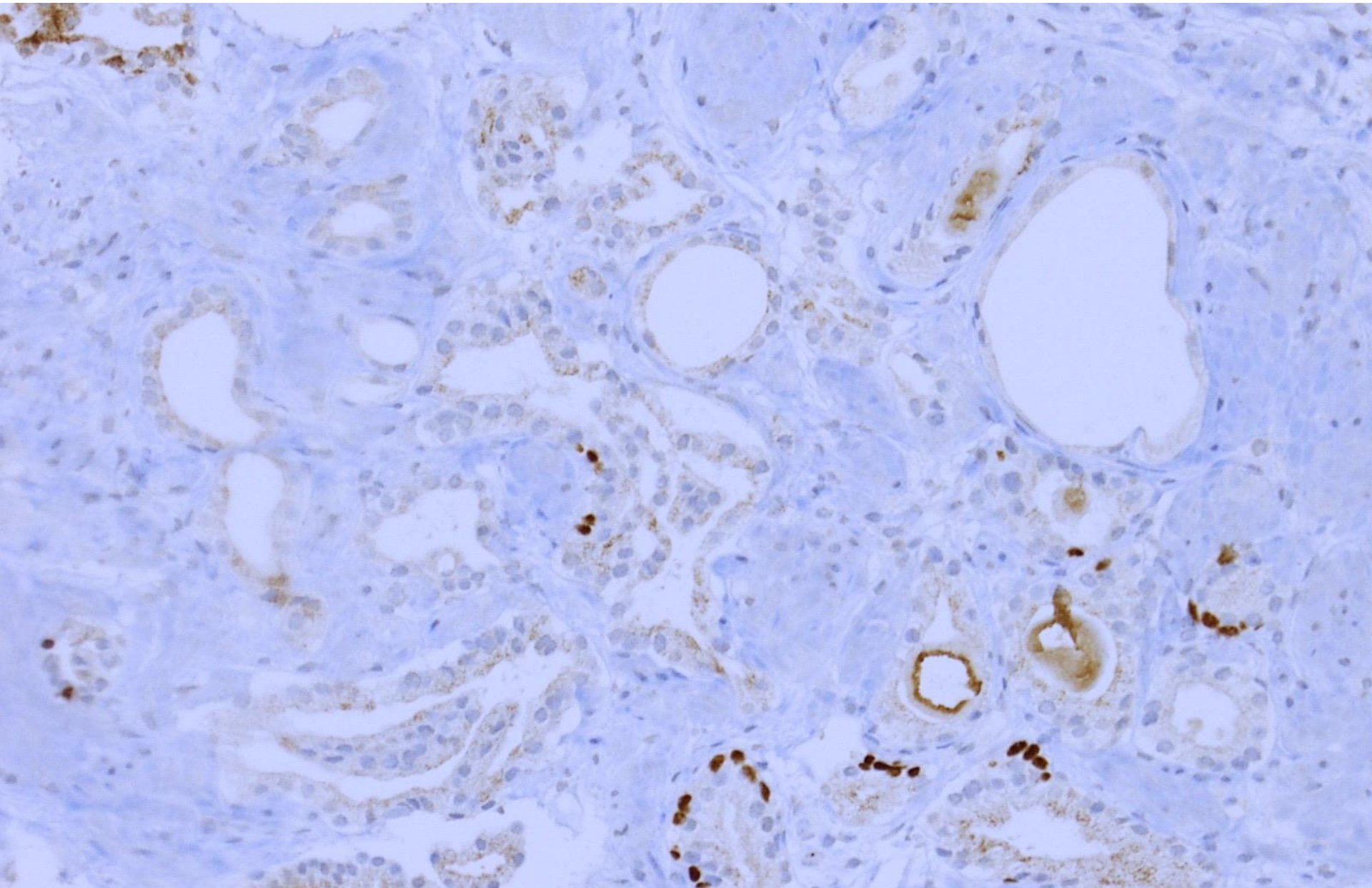
Next Step: Combination of basal cell markers & AMACR

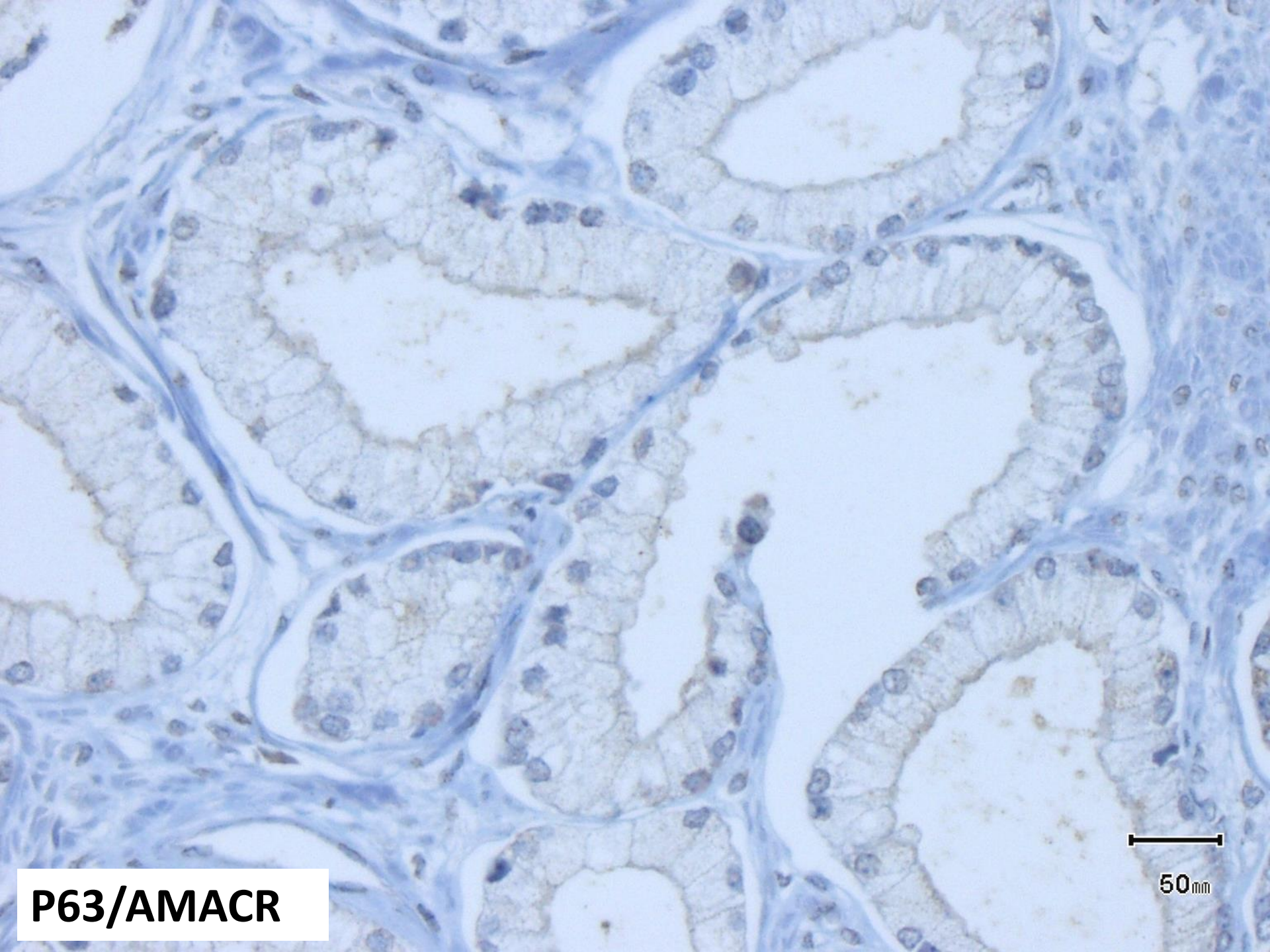


AMACR in benign glands

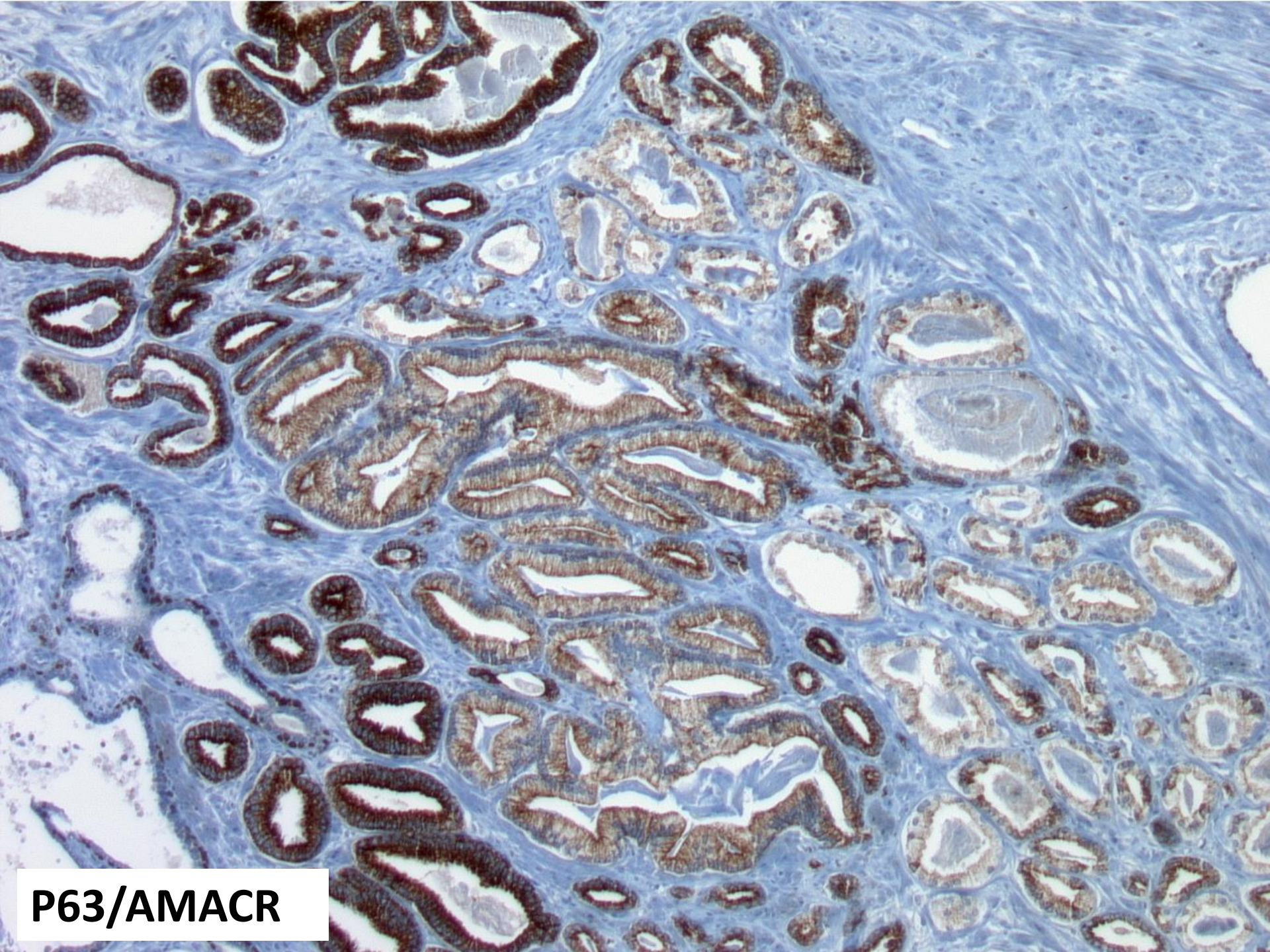


AMACR in Partial Atrophy





P63/AMACR


P63/AMACR

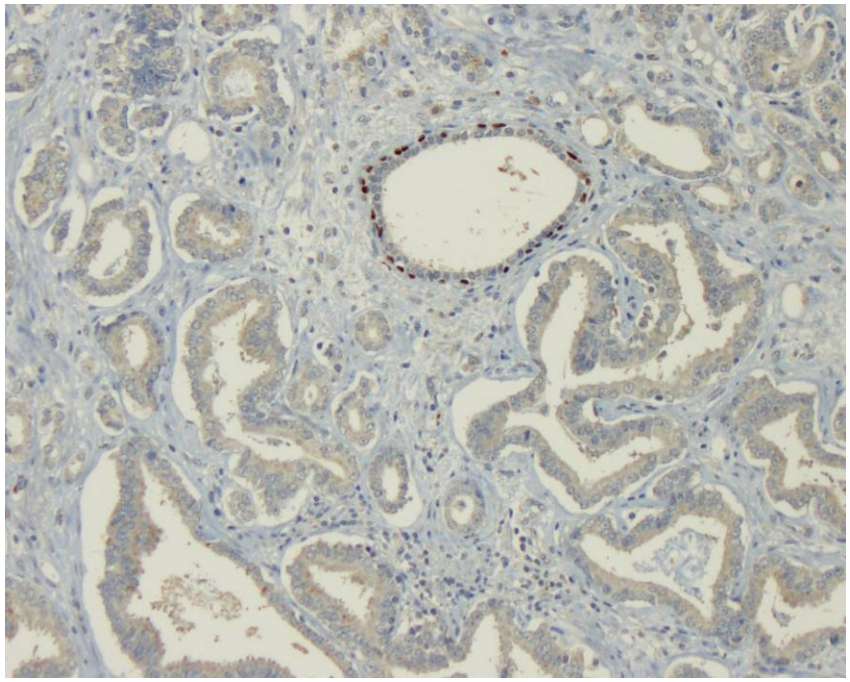
AMACR-Immunoreactivity in Prostate Cancer:

- 95% of cases positive (T>N)
- heterogenous in appr. 50% of cases
- Dependent on fixation and processing

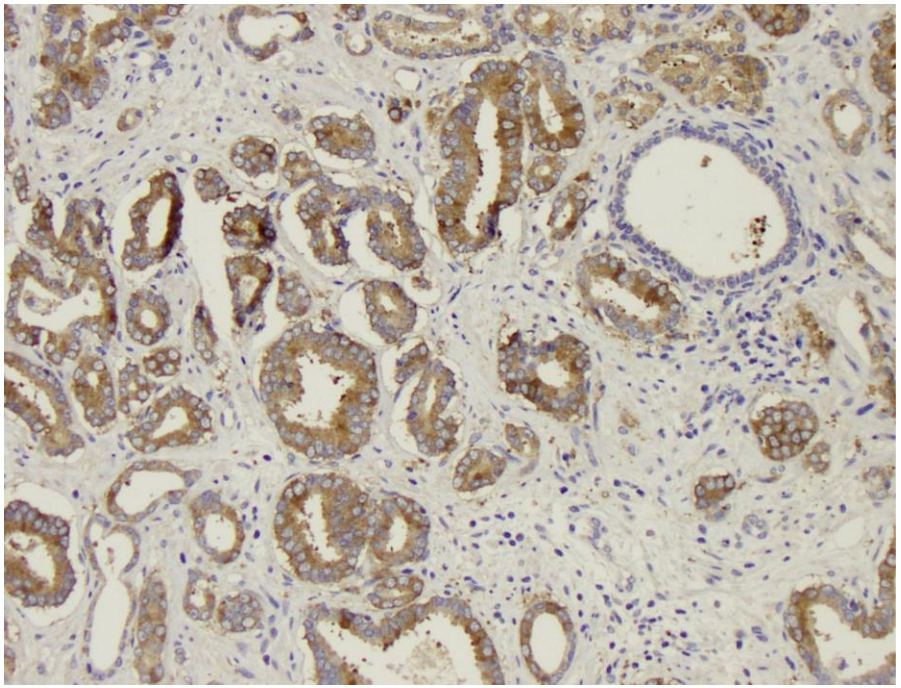
- Important marker in small lesions
- **Pitfall:** nephrogenic adenoma +++
- **Pitfall:** adenosis/partial atrophy in 20%-30% positive (but rarely strong)

Fatty acid synthase (FASN) – alternative positive marker of prostate Cancer

- 93% of cases + (T>N)
- In 91% of AMACR-neg. cases positive

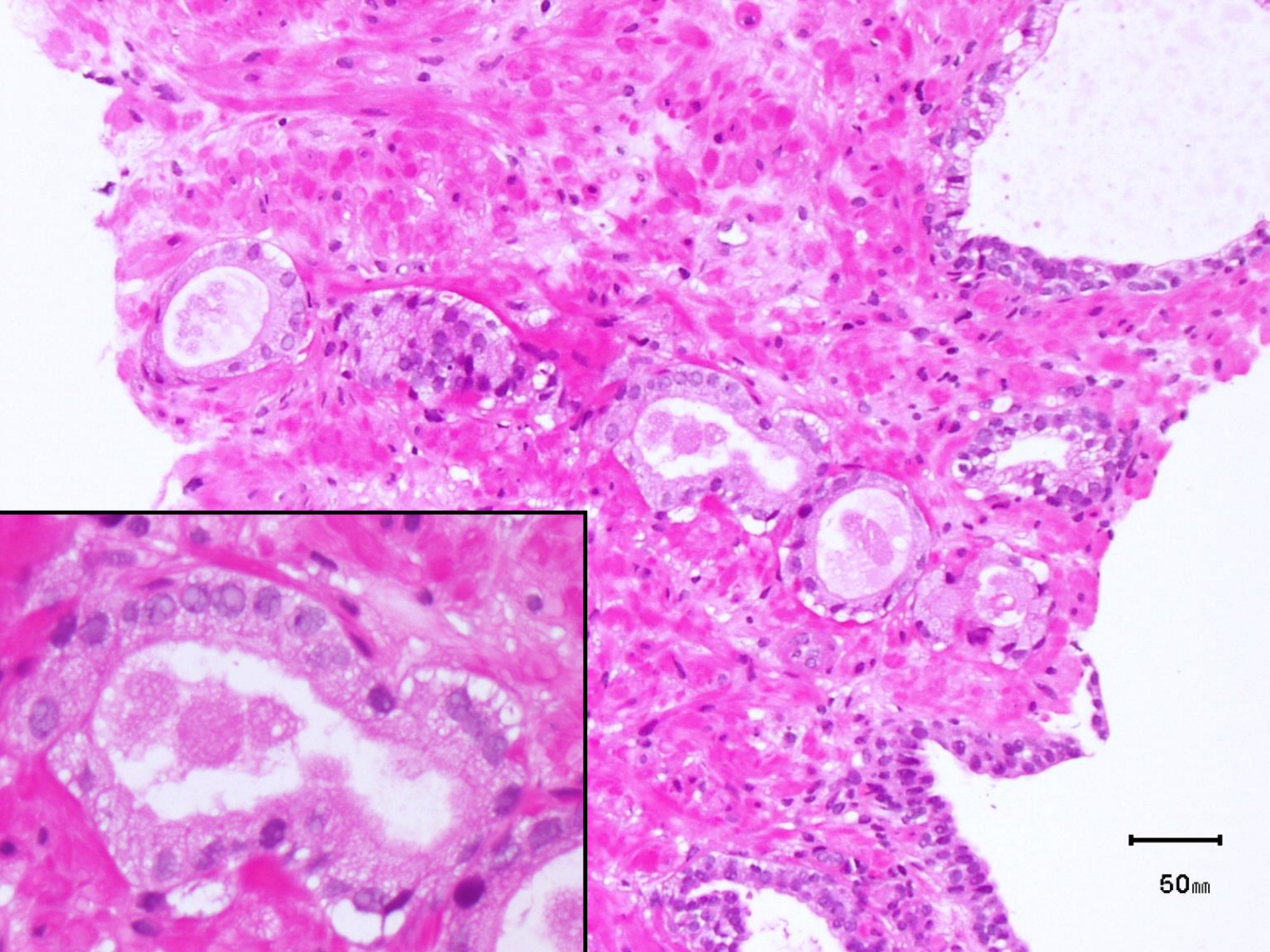


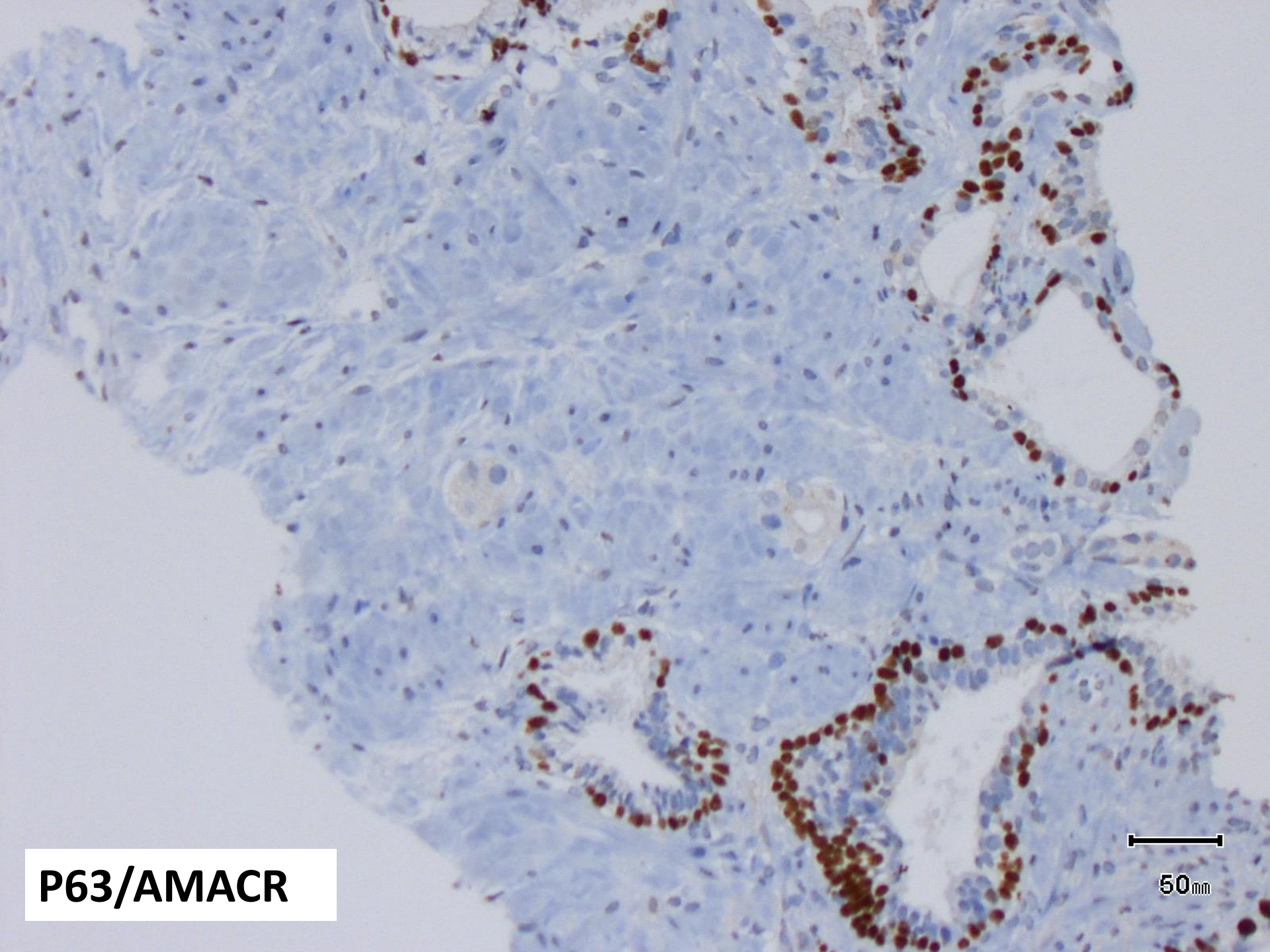
AMACR

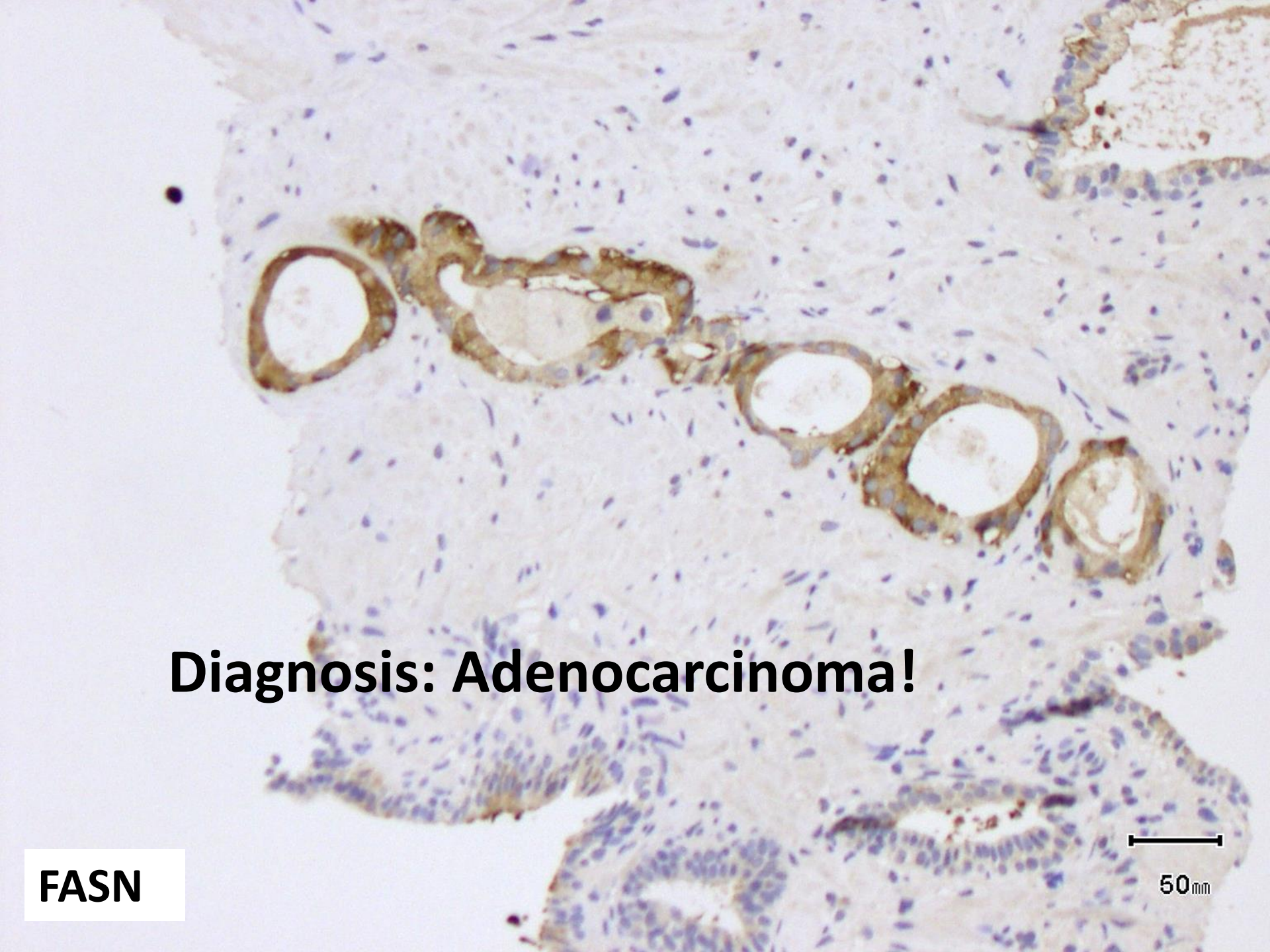


FASN

Tischler *et al.,* Histopathology. 2010 May;56(6):811-5.


50㎜


P63/AMACR
50㎛


Diagnosis: Adenocarcinoma!
FASN
50㎛

FASN is a novel diagnostic Marker of Prostate Cancer

Detection of > 92% of cases

In combination mit p63/AMACR: > 99%

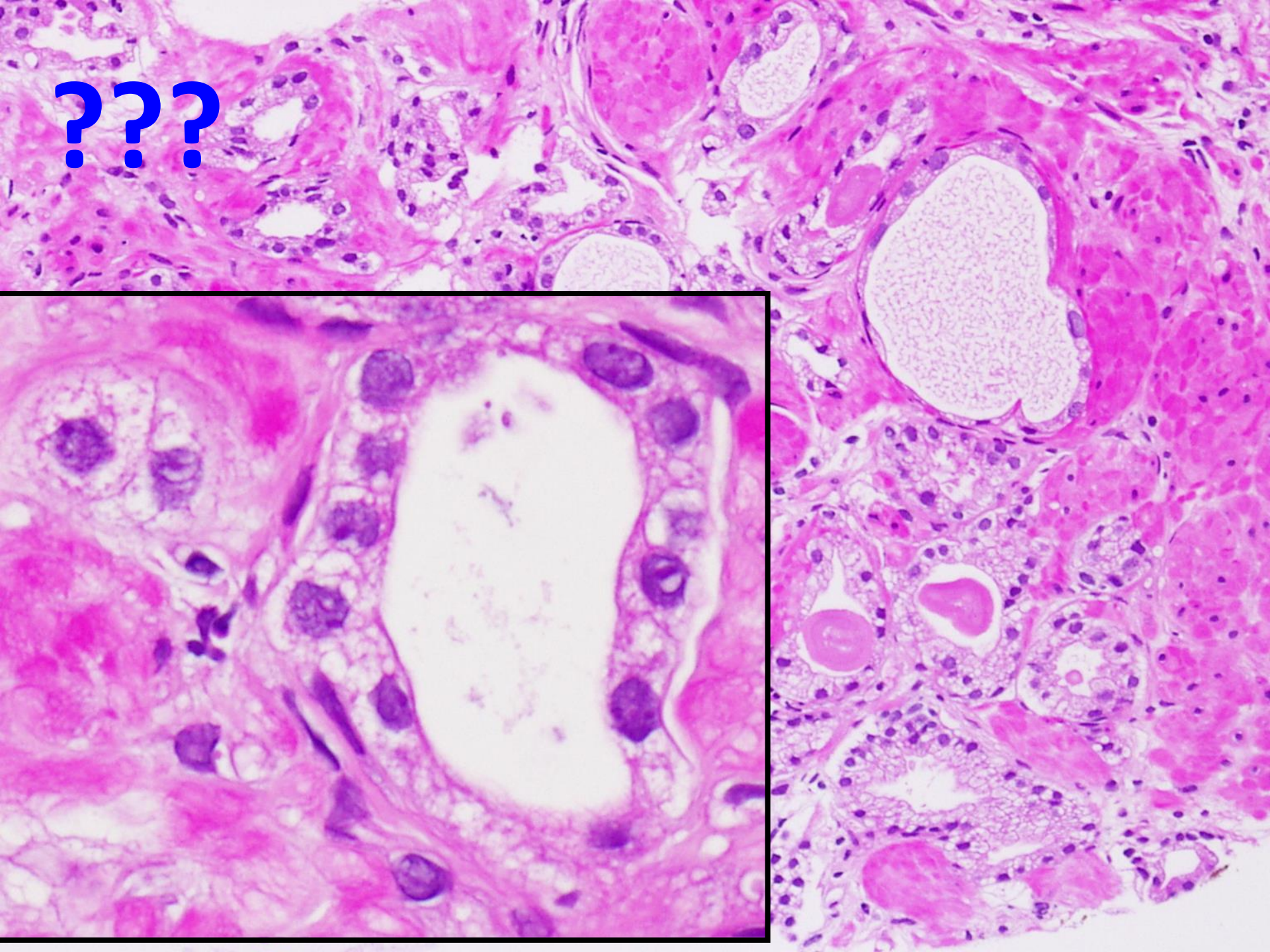
(91% of AMACR-negative case were FASN-positive)

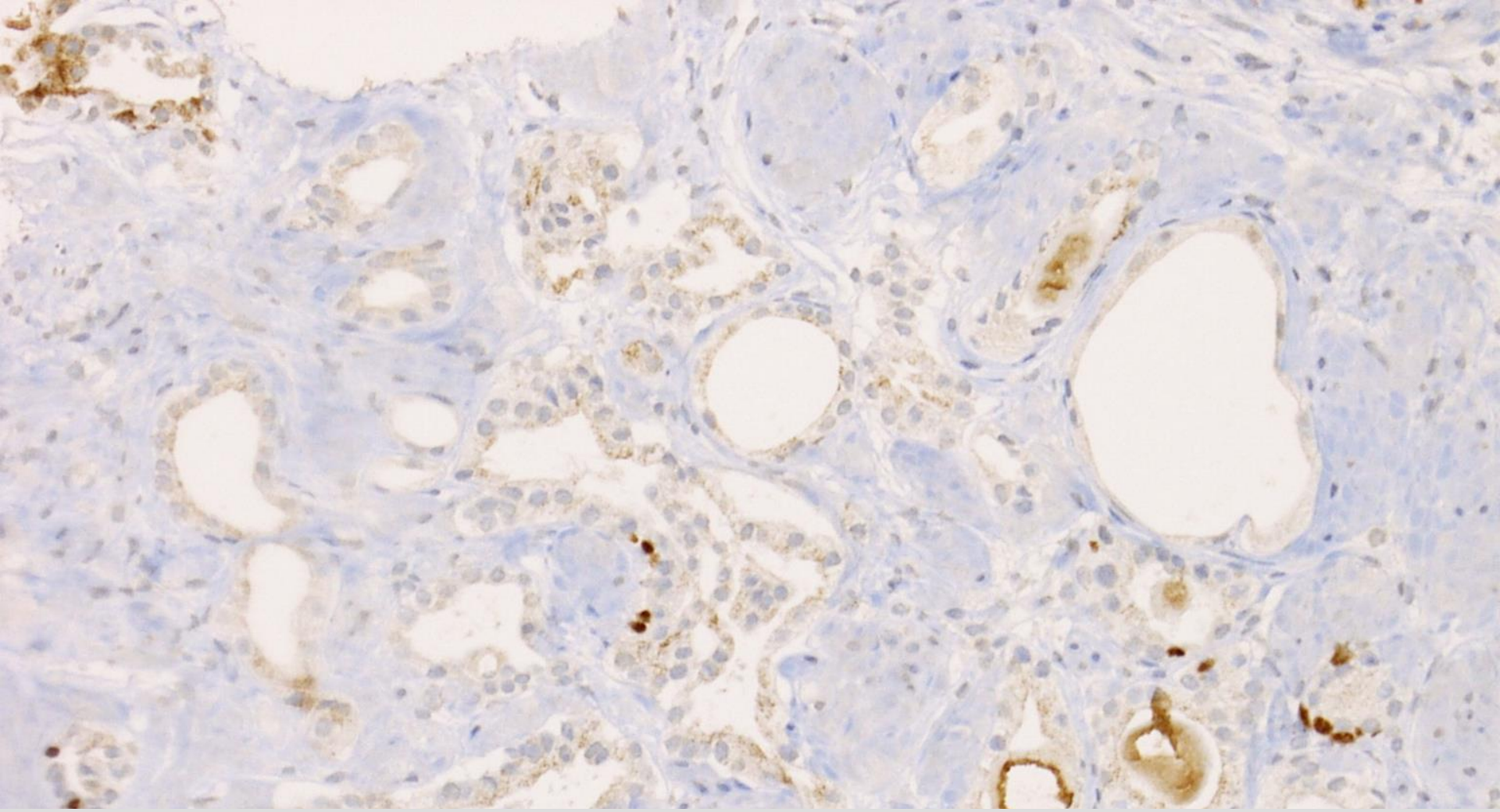
No correlation to pT, Gleason Score

No prognostic value

In routine use at University of Zurich and University of Bonn,

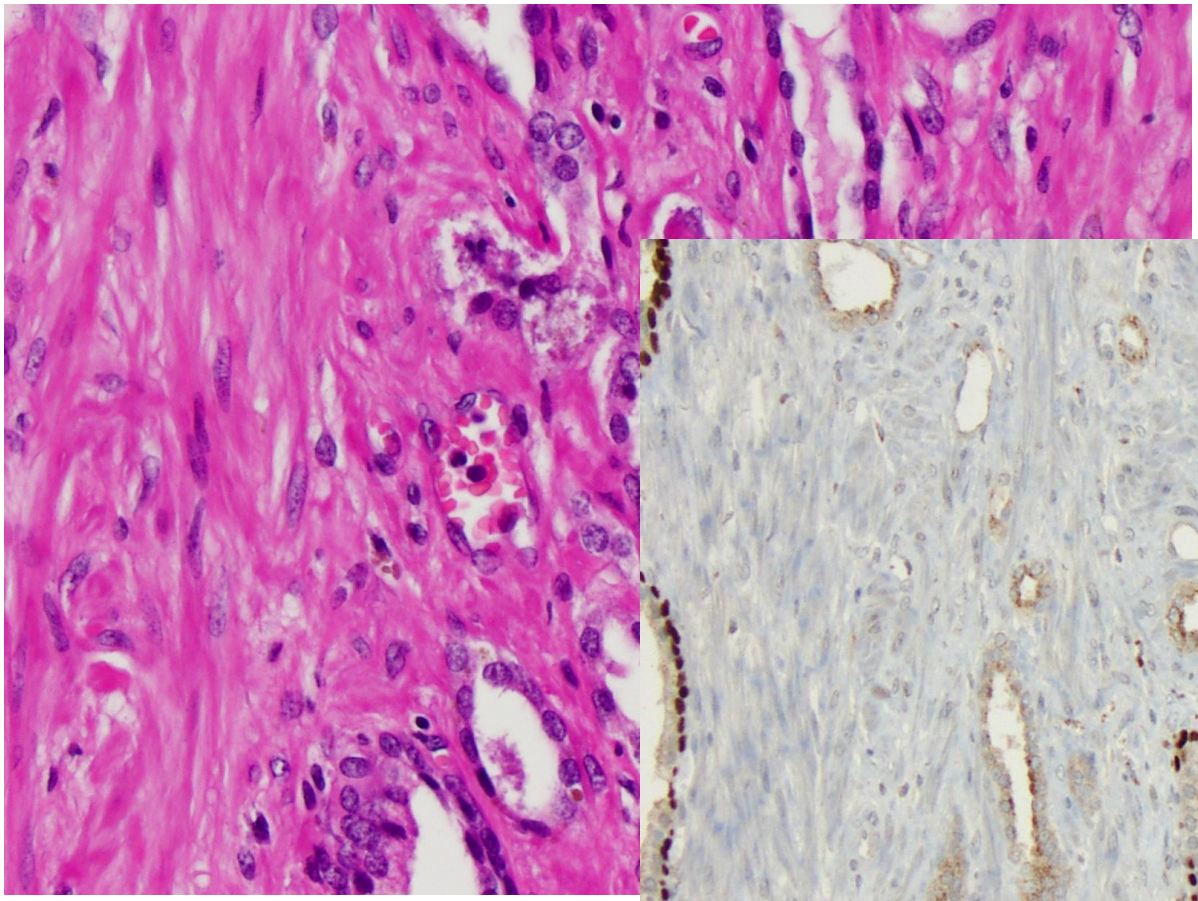
(as second line positive marker)

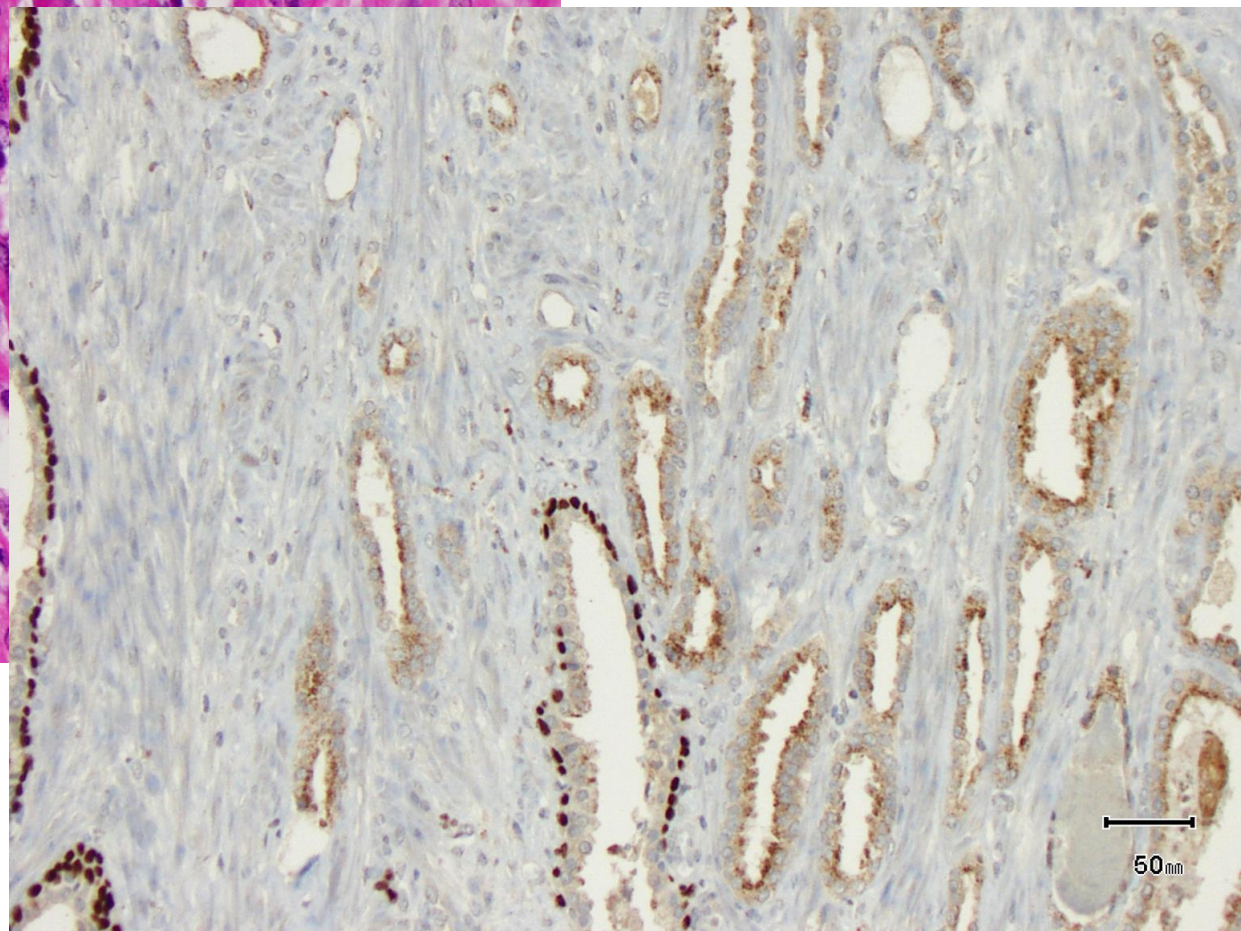


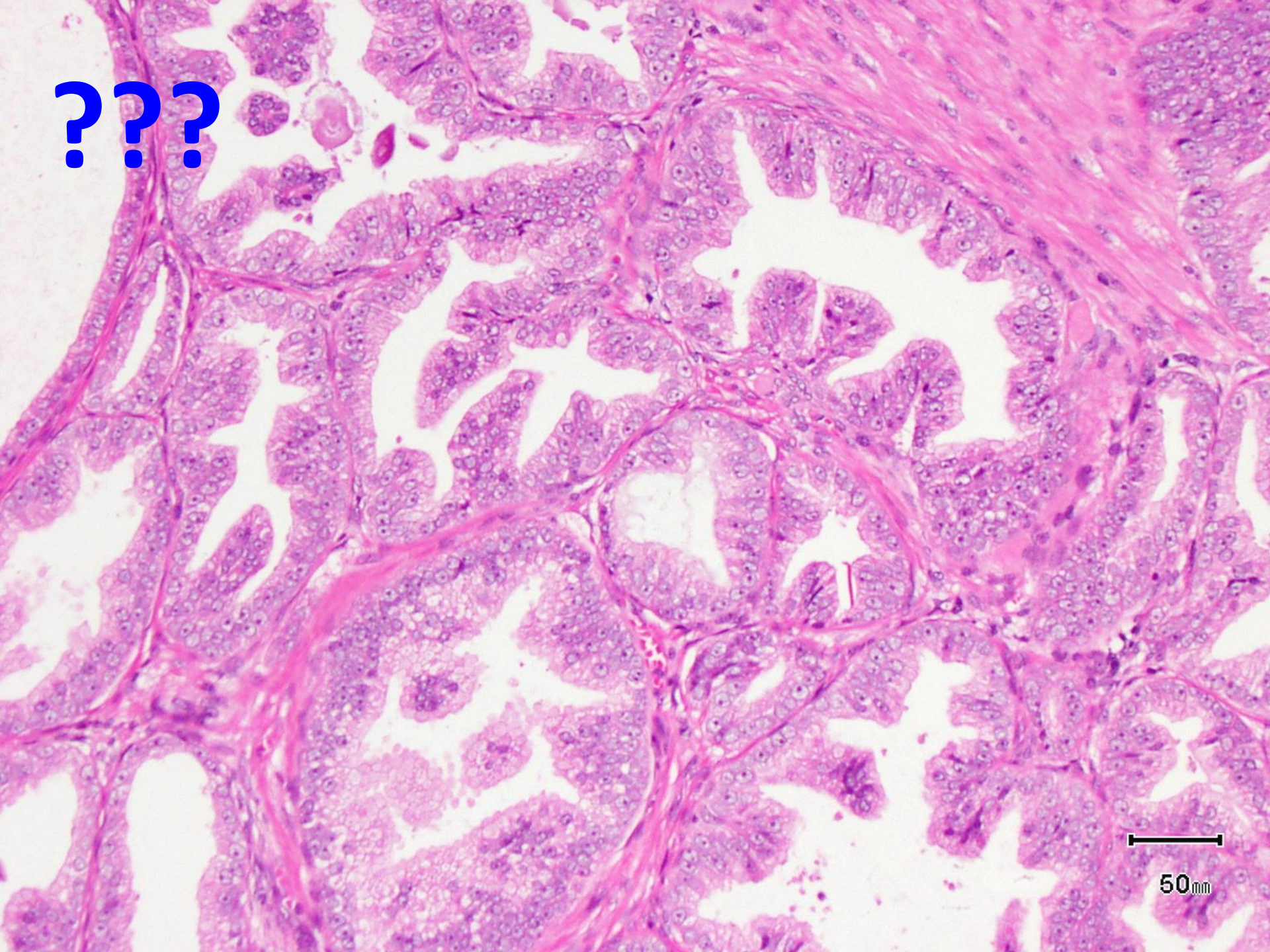


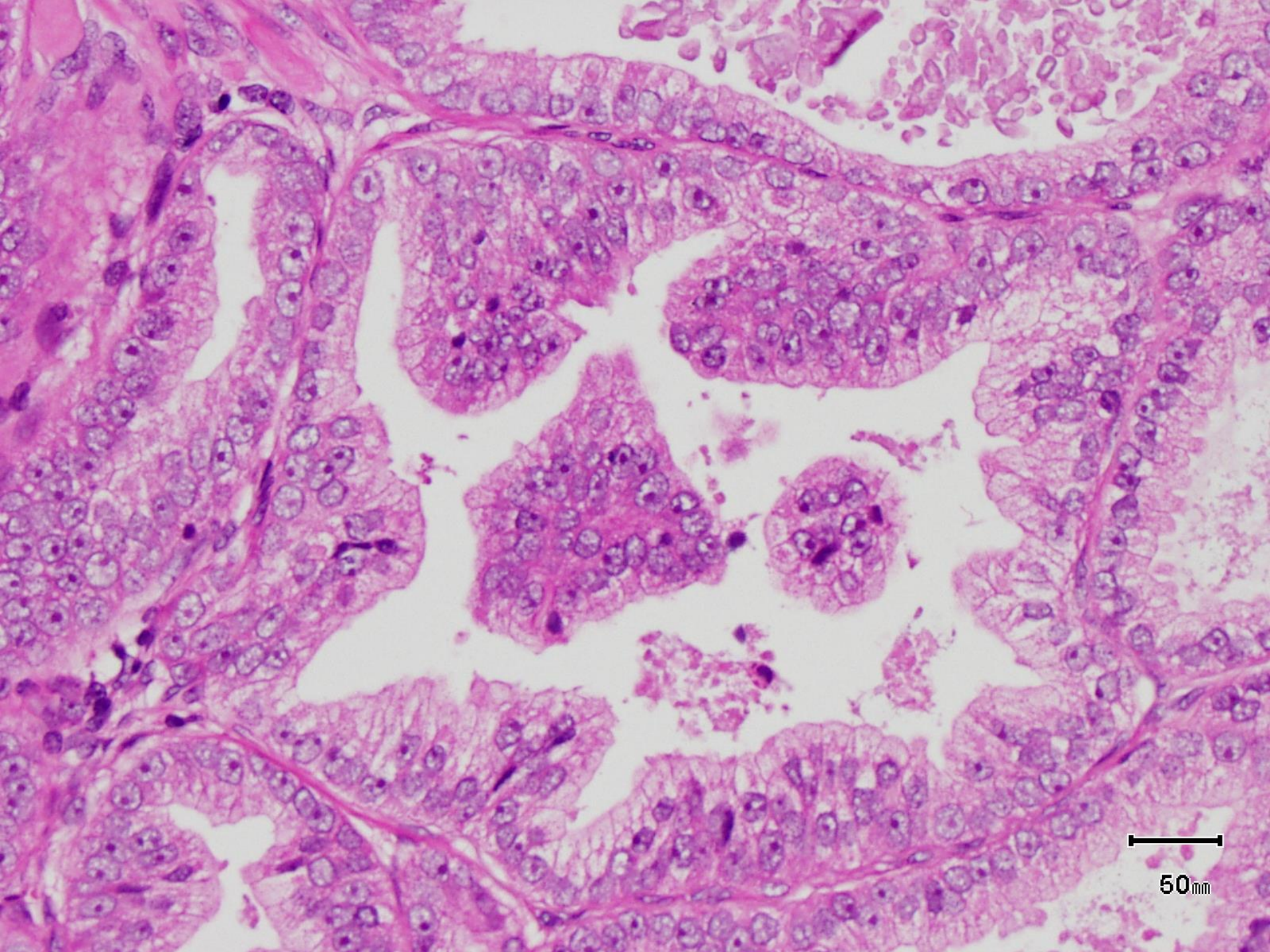
Partial Atrophy:
Atypical immunophenotype
(p63-, AMACR+/-) in up to 30% !!!

Pitfall in Pitfalls: Atrophic Carcinoma

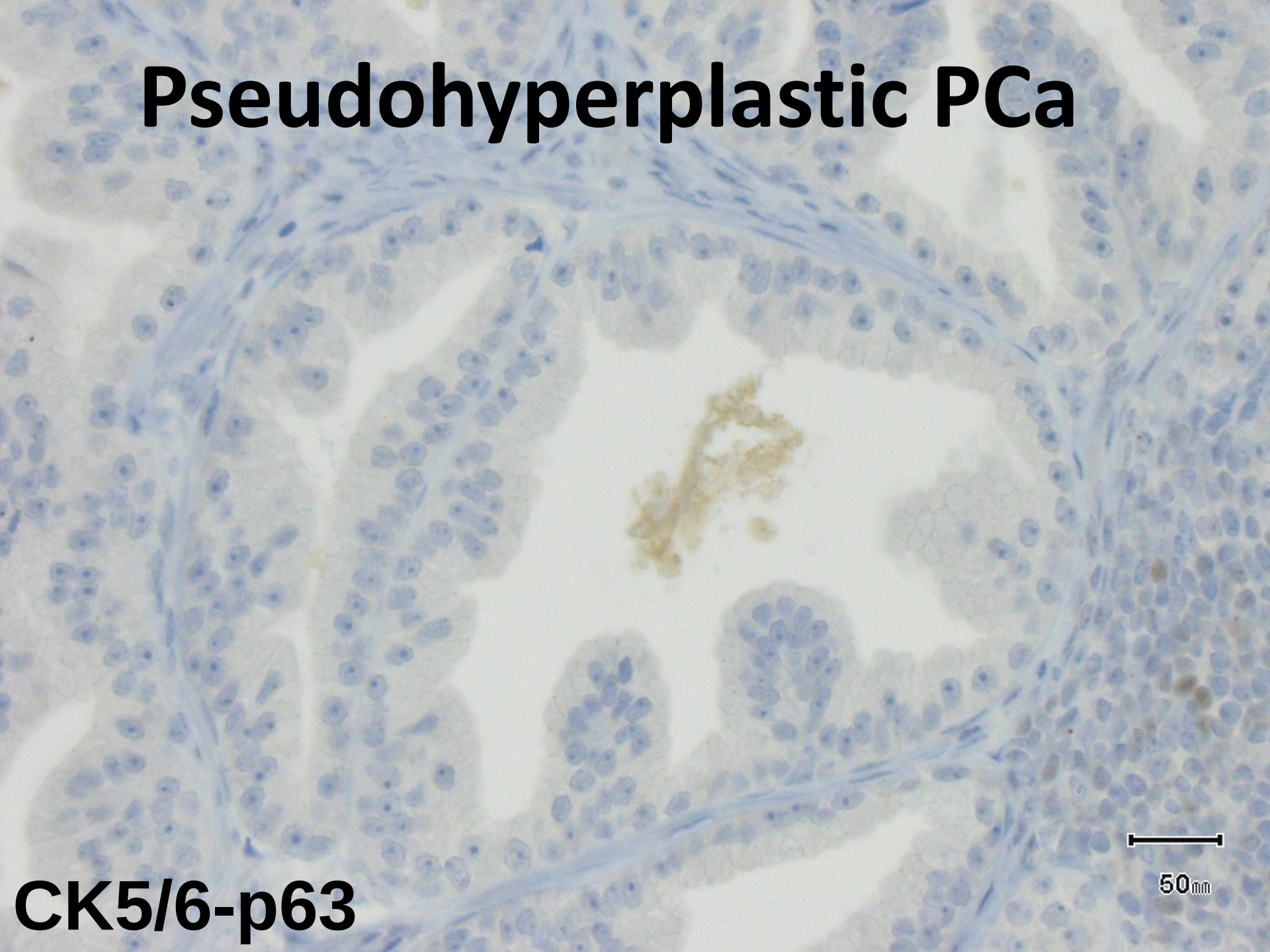





???
50㎛


50㎛

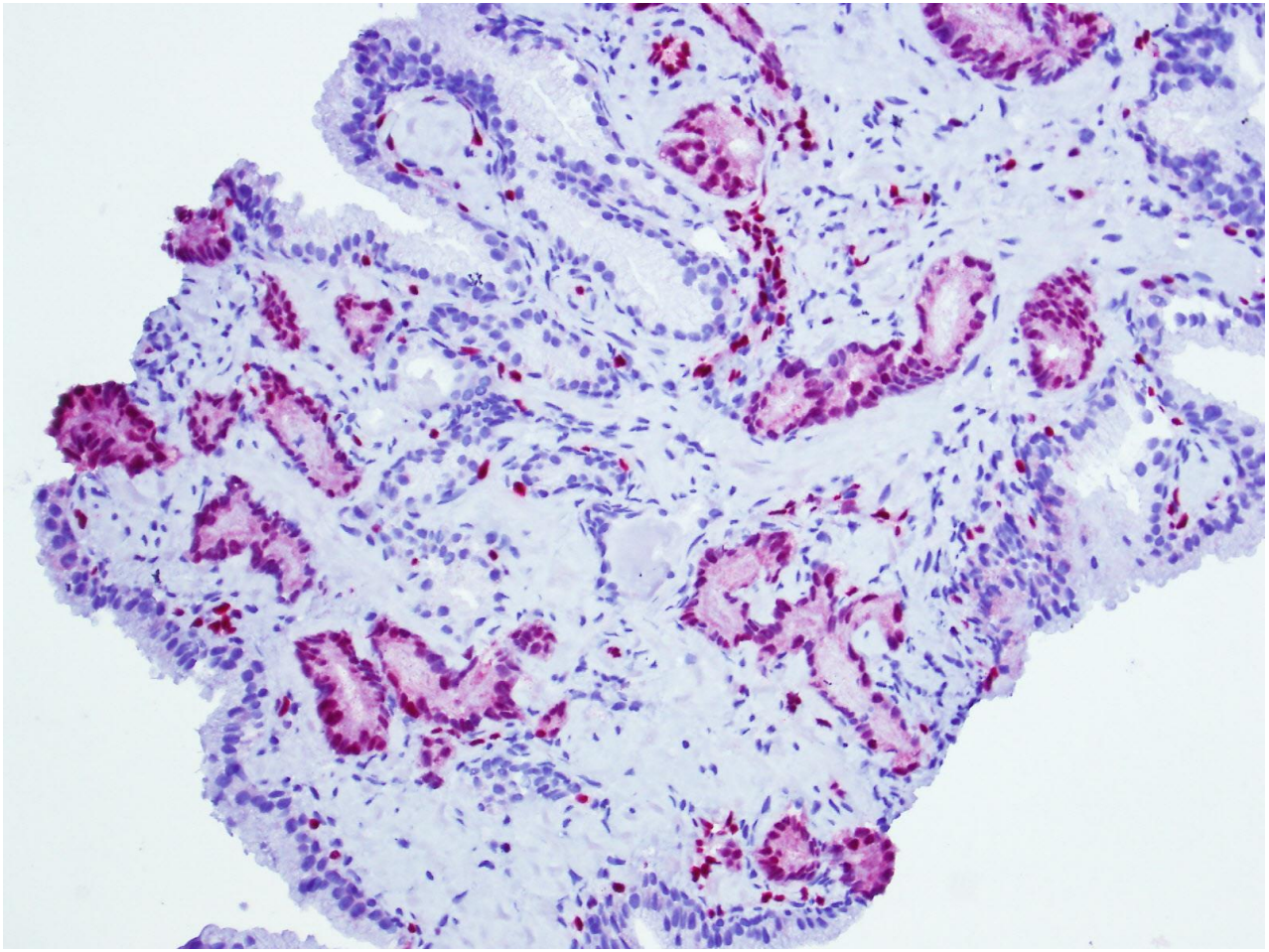
Pseudohyperplastic PCa



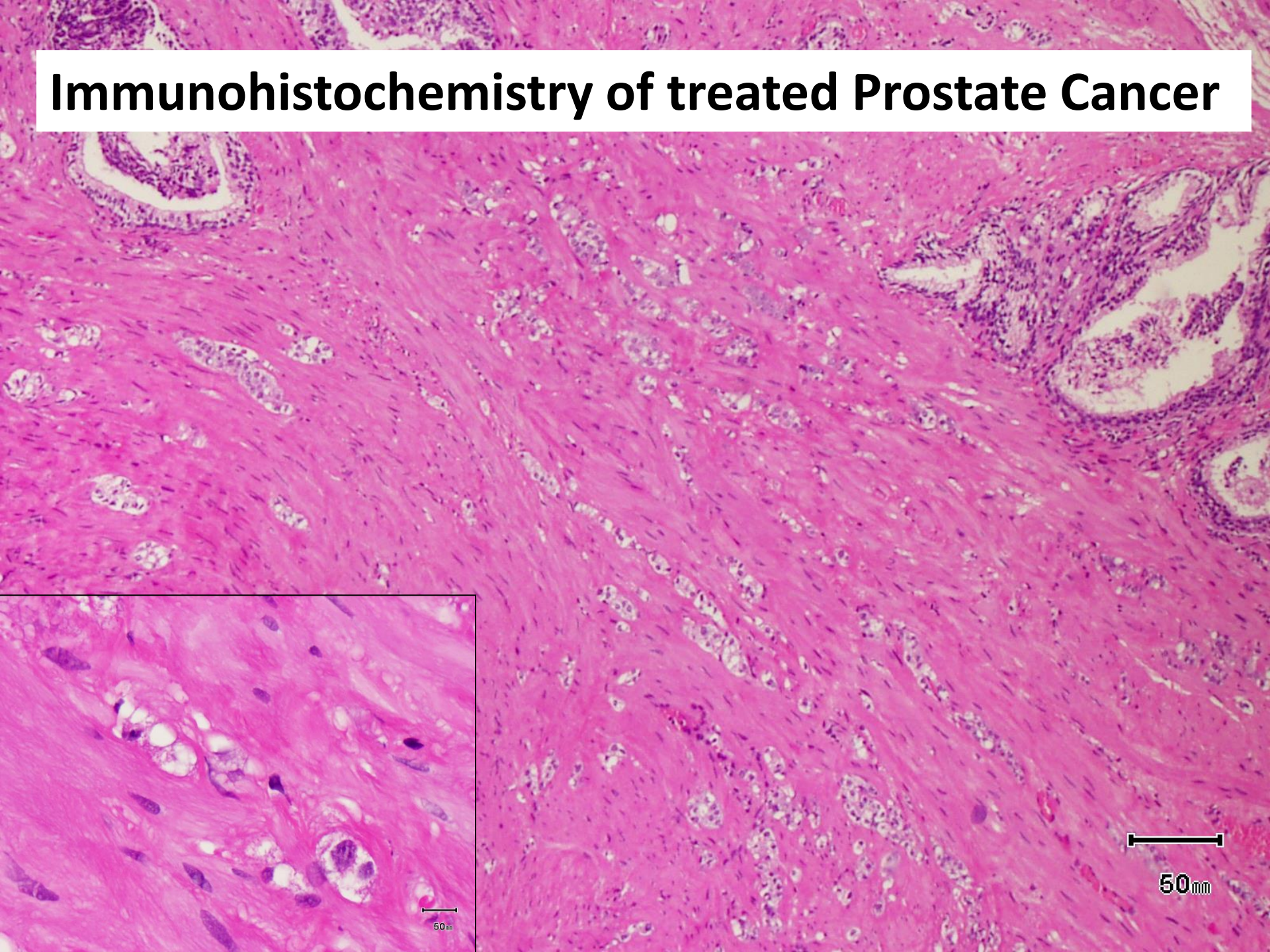
CK5/6-p63

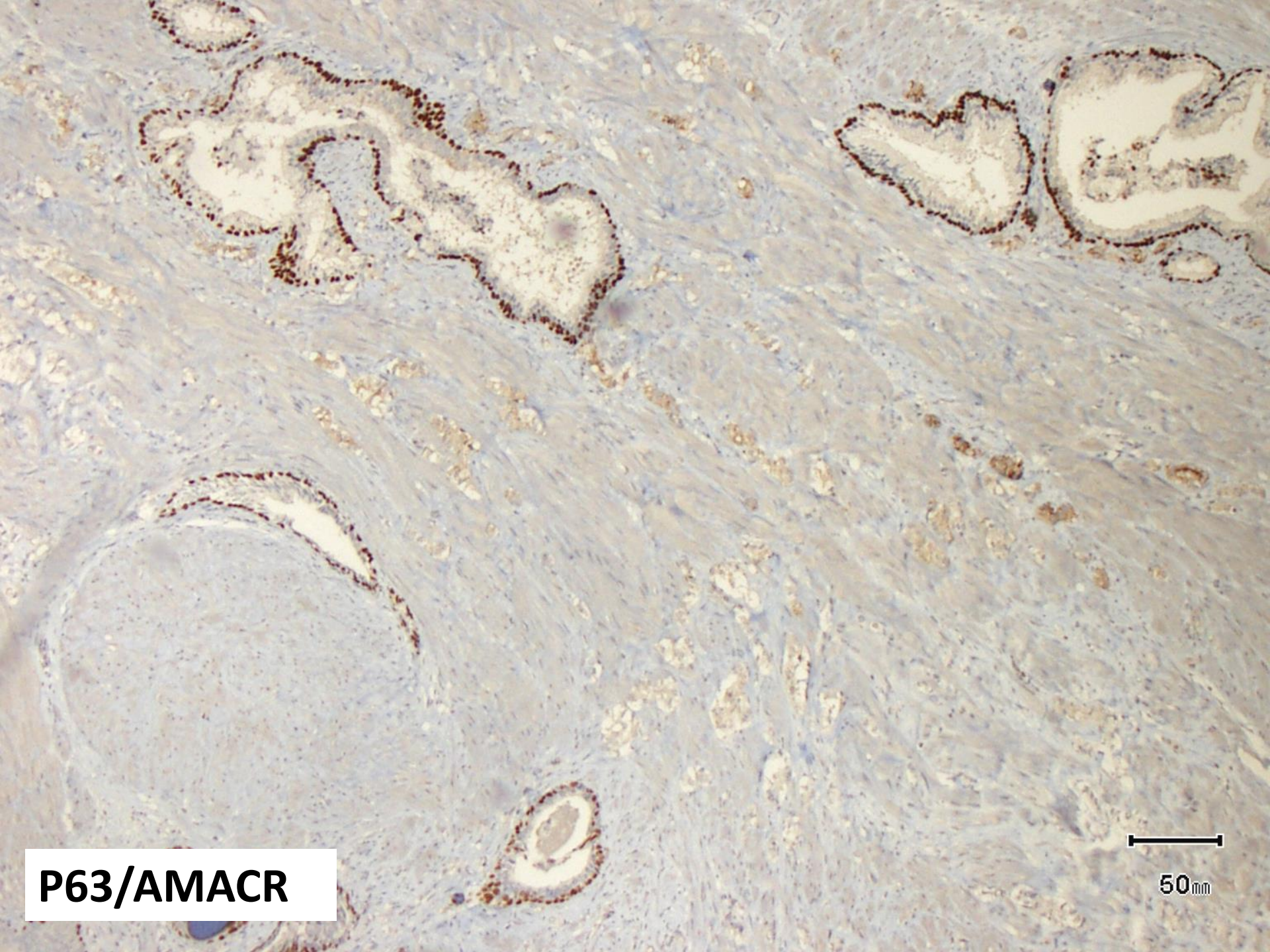
Last resort: ERG

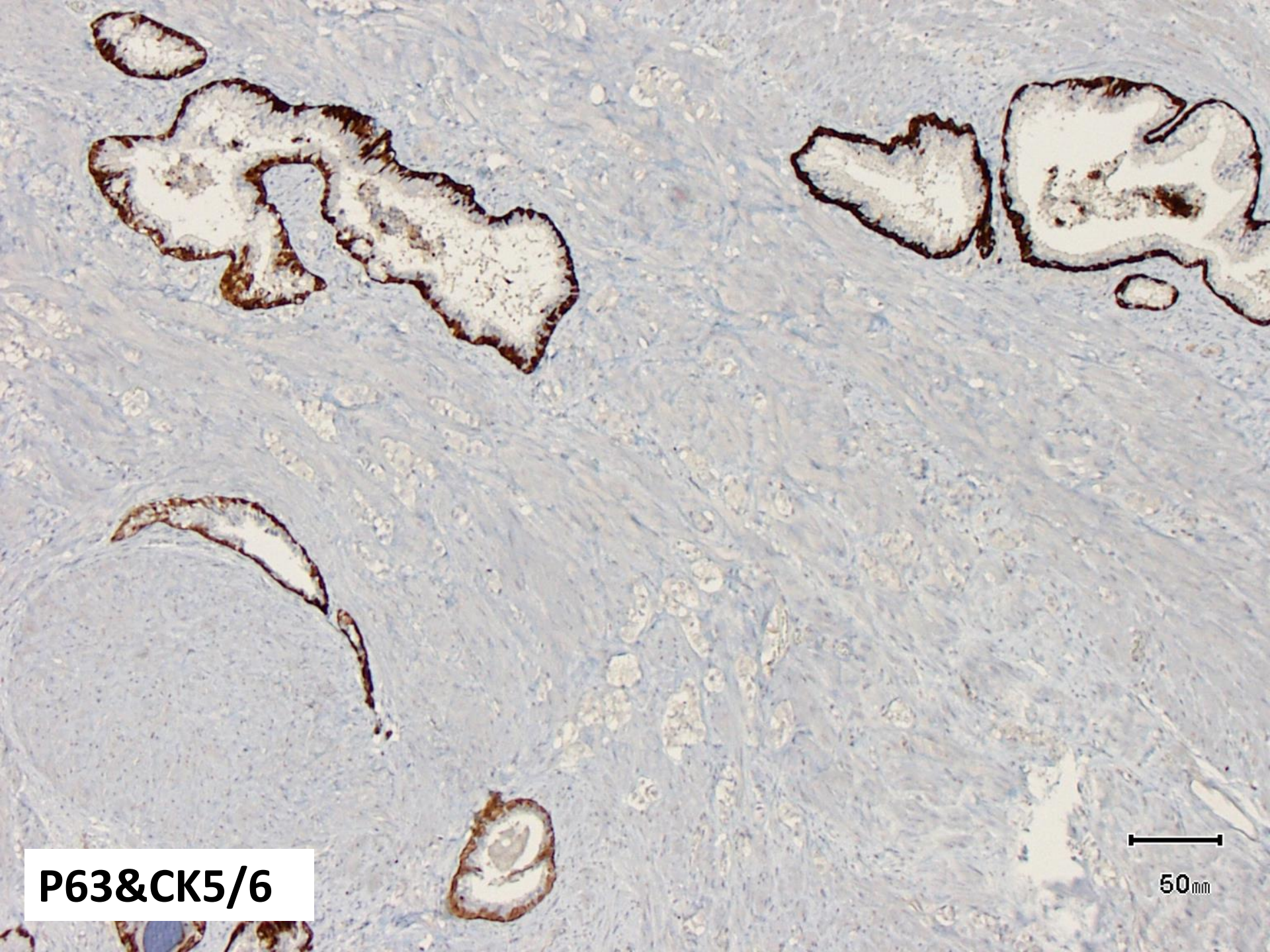
- positive in 50% of PCa

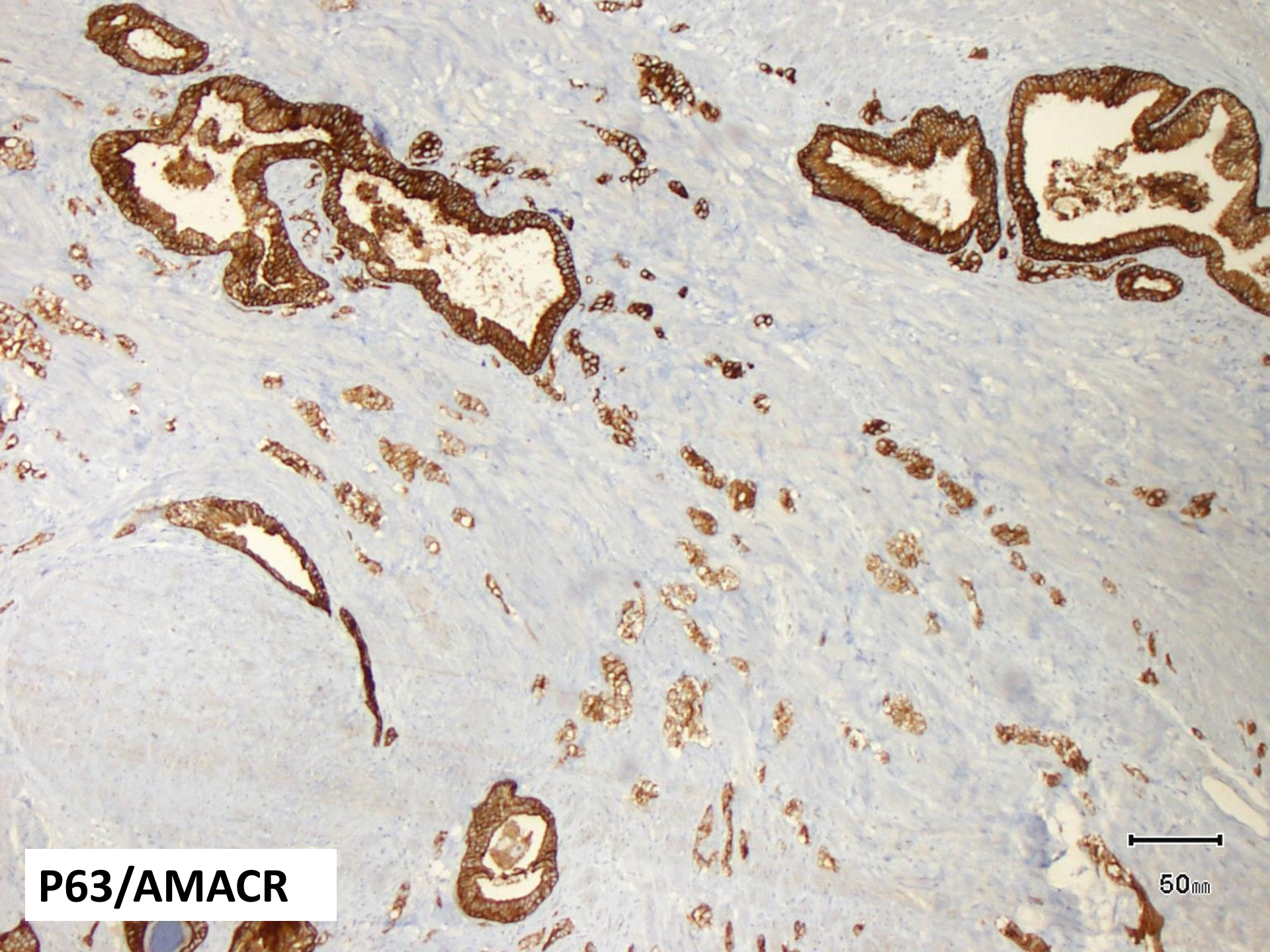


Immunohistochemistry of treated Prostate Cancer




P63/AMACR
50㎛

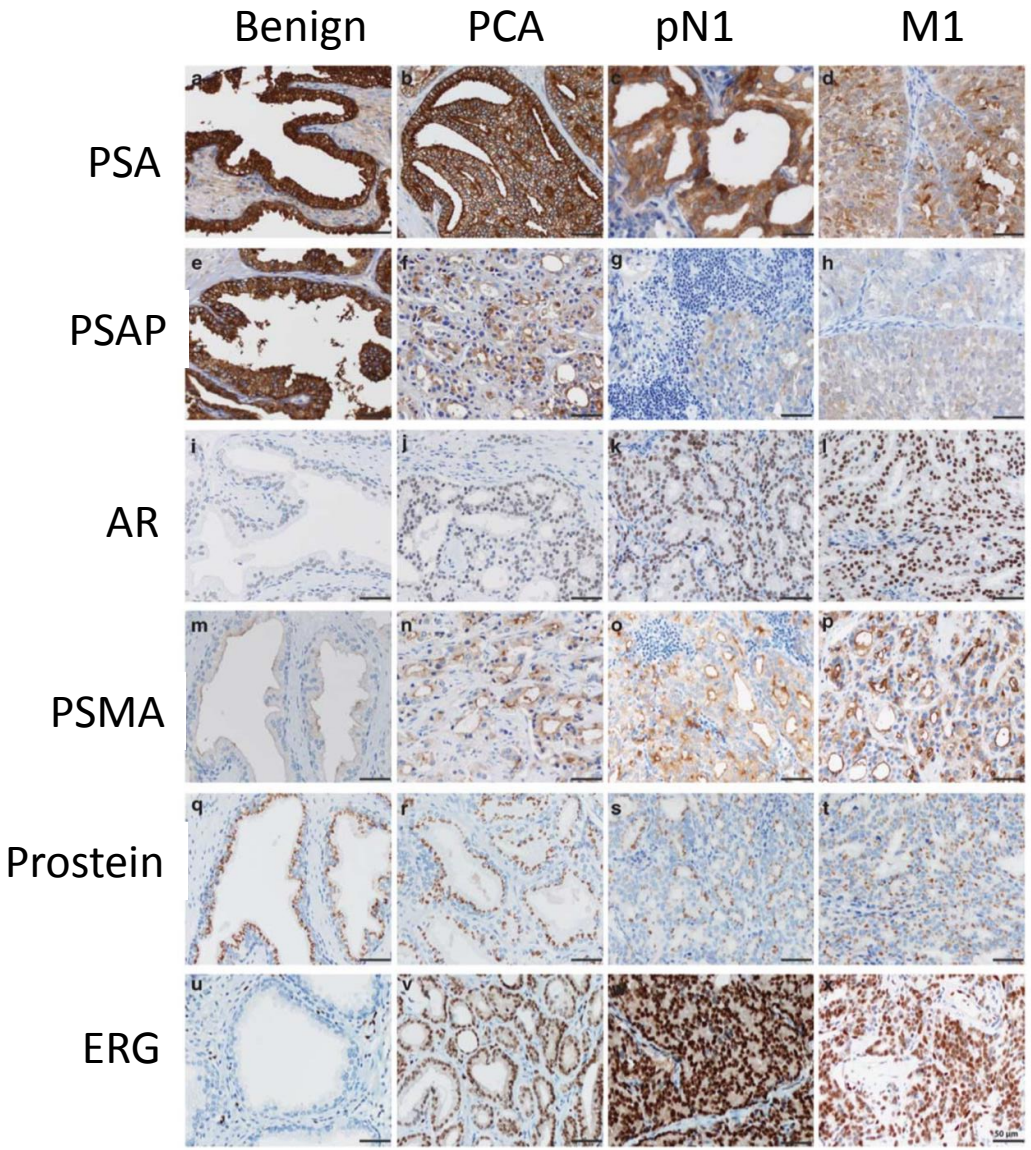

P63&CK5/6
50㎛


P63/AMACR
50㎛

What to look at after ADT/Radiation?

1. Morphology
2. PanCK/PSA
3. p63&CK5/6

Confirmation of Prostatic Origin



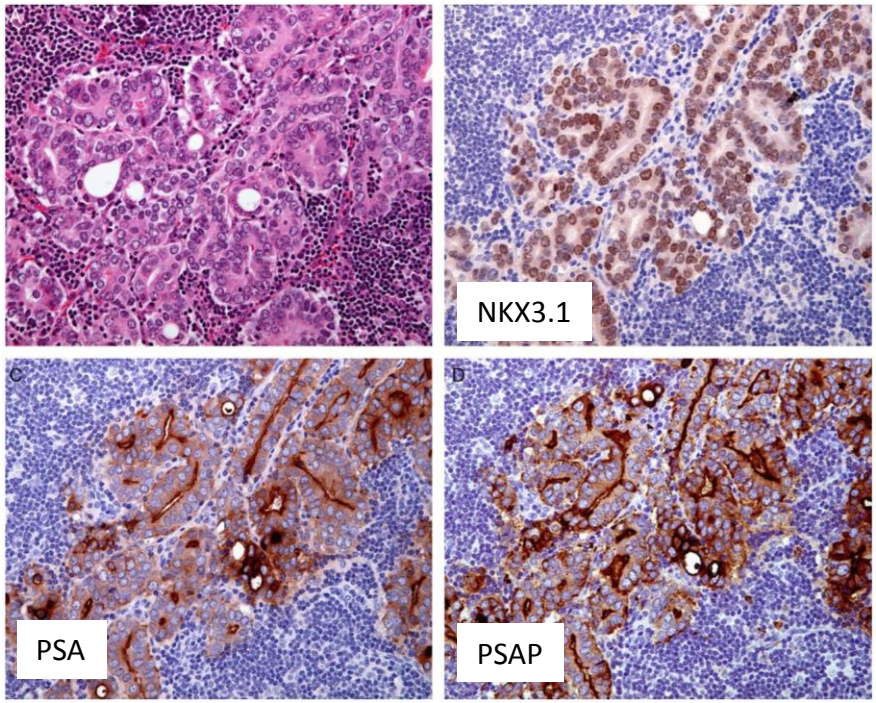
Use a panel!

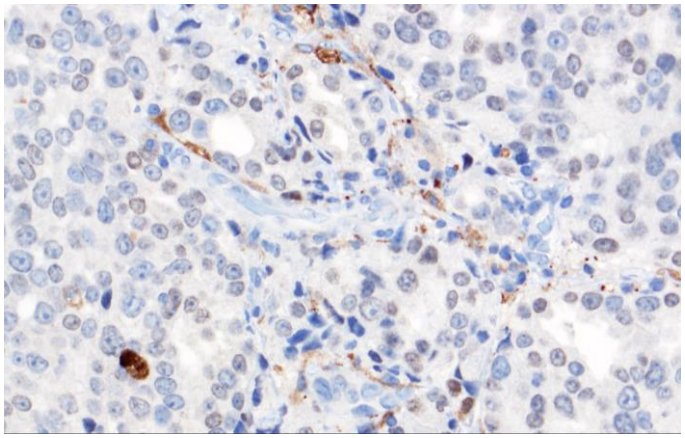
MODERN PATHOLOGY (2015) 28, 138–145

NKX3.1 as a Marker of Prostatic Origin in Metastatic Tumors

Bora Gurel, MD, Tehmina Z. Ali, MD,† Elizabeth A. Montgomery, MD,* Shahnaz Begum, PhD,* Jessica Hicks, BA,* Michael Goggins, MD,*‡ Charles G. Eberhart, MD, PhD,*‡ Douglas P. Clark, MD,*‡ Charles J. Bieberich, PhD,§ Jonathan I. Epstein, MD,*‡‖ and Angelo M. De Marzo, MD, PhD*‡‖*

Am J Surg Pathol • Volume 34, Number 8, August 2010





Very good marker, note that staining may be weak or patchy.

TABLE 3. The Average Percentage of Positively Stained Cells and the Calculated Staining Scores of NKX3.1, PSA and PSAP for Normal Prostate, Primary and Metastatic Prostate Carcinoma

	NKX3.1		PSA‘		PSAP	
	% Positive (Range)	Staining Score(SD)	% Positive (Range)	Staining Score(SD)	% Positive (Range)	Staining Score(SD)
Normal Prostate	92.0 (38.3-100)	218.3 (85.22)	965.0 (0-100)	241.7 (76.88)	97.6 (0-100)	287.8 (50.96)
Primary Ca	84.7 (25-100)	179.1 (77.84)	87.3 (10-100)	180.7 (91.36)	98.6 (85-100)	249.2 (64.35)
Lymph Node Met	74.2 (0-100)	155.4 (84.78)	80.1 (0-100)	1743.0 (99.14)	94.4 (0-100)	235.6 (78.24)
Distant Site Met	54.0 (0-88.3)	111.4 (85.36)	30.8 (0-100)	50.8 (92.83)	74.2 (0-100)	162.0 (116.49)
Average	80.5	175.9 (87.83)	83.1	186.0 (101.29)	95.0	248.5 (77.32)

ISUP-Recommendation: PCA vs. Urothelial Ca

TABLE 2. Prostate Antibodies Used in the Differential Diagnosis of PCa Versus Urothelial Carcinoma

Antibody	Advantages	Disadvantages
PSA	~85%-90% (+) in GS10	Negative in a subset of high-grade PCa
	Commonly available	Weak nonspecific cytoplasmic (+) lead to false (+)
	Negative in UC	
PSAP	Polyclonal (+) in ~85%-90% GS10	Monoclonal used in many kits lower sensitivity
	Commonly available	
	Negative in UC	
P501S (prostein)	(+) in many PSA (–) PCa	Not as widely used
	Coarse cytoplasmic granules reduce false (+)	
	Negative in UC	
NKX3.1	(+) in many PSA (–) PCa	Not as widely used
	Nuclear stain reduce false (+)	
	Negative in UC	
AR	High sensitivity for PCa	Positive in some UC
AMACR	High sensitivity for PCa	Positive in some UC
PSMA	High sensitivity for PCa	Positive in 14% of UC
CK7/CK20	Negative CK7 favors PCa	Not specific as both can be positive in PCa
	Commonly available	
p63	Less false positive in PCa than UC vs. HMWCK	Only positive in ~2/3 of UC
	Diffuse positive in high grade cancer rules out PCa	Occasional false positive in PCa
	Widely used	
HMWCK	Diffuse positive rules out PCa	Only positive in ~2/3 of UC
	Widely used	Occasional false-positive cells in PCa

TABLE 3. Urothelial Antibodies Used in the Differential Diagnosis of PCa Versus Urothelial Carcinoma

Antibody	Advantages	Disadvantages
Thrombomodulin	Widely used	Positive in only 63% of high-grade UC
		Focal positive in 5% PCa
Uroplakin	Negative in PCa	Positive in only 60% of high-grade UC
GATA3	Almost always negative in PCa	
	Positive in 80% of high-grade UC	

UC indicates urothelial carcinoma.

Am J Surg Pathol • Volume 38, Number 8, August 2014

How to avoid (prostatic) disasters

Don’t rush. Take your time reading slides. 10X is a fine lens!

Be aware of benign mimickers.

Diagnose ”atypia” or ”suspicious for cancer” when in doubt (>5 minutes)
(…but do not over-use this diagnosis)

Use and interpret IHC with respect and caution. Morphology rules!

Topics:

1. Diagnostic IHC
2. **Prognostic IHC**
3. Prognostic molecular signatures
4. Molecular pathology, targeted therapy and predictive pathology in prostate cancer

Lack of prognostic markers??

NCBI Resources How To Sign in to NCBI

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed | prostate cancer prognosis immunohistochemistry | Search

Create RSS Create alert Advanced Help

Article types
Clinical Trial
Review
Customize ...

Text availability
Abstract
Free full text
Full text

PubMed Commons
Reader comments
Trending articles

Publication dates
5 years
10 years
Custom range...

Species
Humans
Other Animals

Clear all

Show additional filters

Summary 20 per page Sort by Most Recent Send to:

Filters: Manage Filters

Search results

Items: 1 to 20 of 2007

<< First < Prev Page 1 of 101 Next > Last >>

1. Overexpression of Enhancer of zeste homolog 2 (EZH2) characterizes an aggressive subset of **prostate** cancers and predicts patient **prognosis** independently from pre- and postoperatively assessed clinicopathological parameters.
Melling N, Thomsen E, Tsourlakis MC, Kluth M, Hube-Magg C, Minner S, Koop C, Graefen M, Heinzer H, Wittmer C, Sauter G, Wilczak W, Huland H, Simon R, Schlomm T, Steurer S, Krech T.
Carcinogenesis. 2015 Sep 21. pii: bgv137. [Epub ahead of print]
PMID: 26392259
Similar articles

2. Reduced AZGP1 expression is an independent predictor of early PSA recurrence and associated with ERG fusion positive and PTEN deleted **prostate** cancers.
Burdelski C, Kleinhans S, Kluth M, Hube-Magg C, Minner S, Koop C, Graefen M, Heinzer H, Tsourlakis MC, Wilczak W, Marx A, Sauter G, Wittmer C, Huland H, Simon R, Schlomm T, Steurer S.
Int J **Cancer**. 2015 Sep 18. doi: 10.1002/ijc.29860. [Epub ahead of print]
PMID: 26383228
Similar articles

3. Overexpression of BRCA1 or BRCA2 in prostatectomy specimens is predictive of biochemical recurrence after radical prostatectomy.
Kim SH, Park WS, Yun SI, Joo J, Joung JY, Seo HK, Chung J, Lee GK, Lee KH.
Histopathology. 2015 Aug 14. doi: 10.1111/his.12809. [Epub ahead of print]
PMID: 26272590
Similar articles

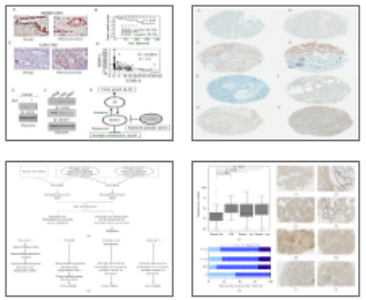
4. Prognostic value of transformer 2β expression in **prostate cancer**.
Diao Y, Wu D, Dai Z, Kang H, Wang Z, Wang X.

New feature
Try the new Display Settings option - **Sort by Relevance**

Results by year

Download CSV

PMC Images search for *prostate cancer prognosis immunohistochemistry*

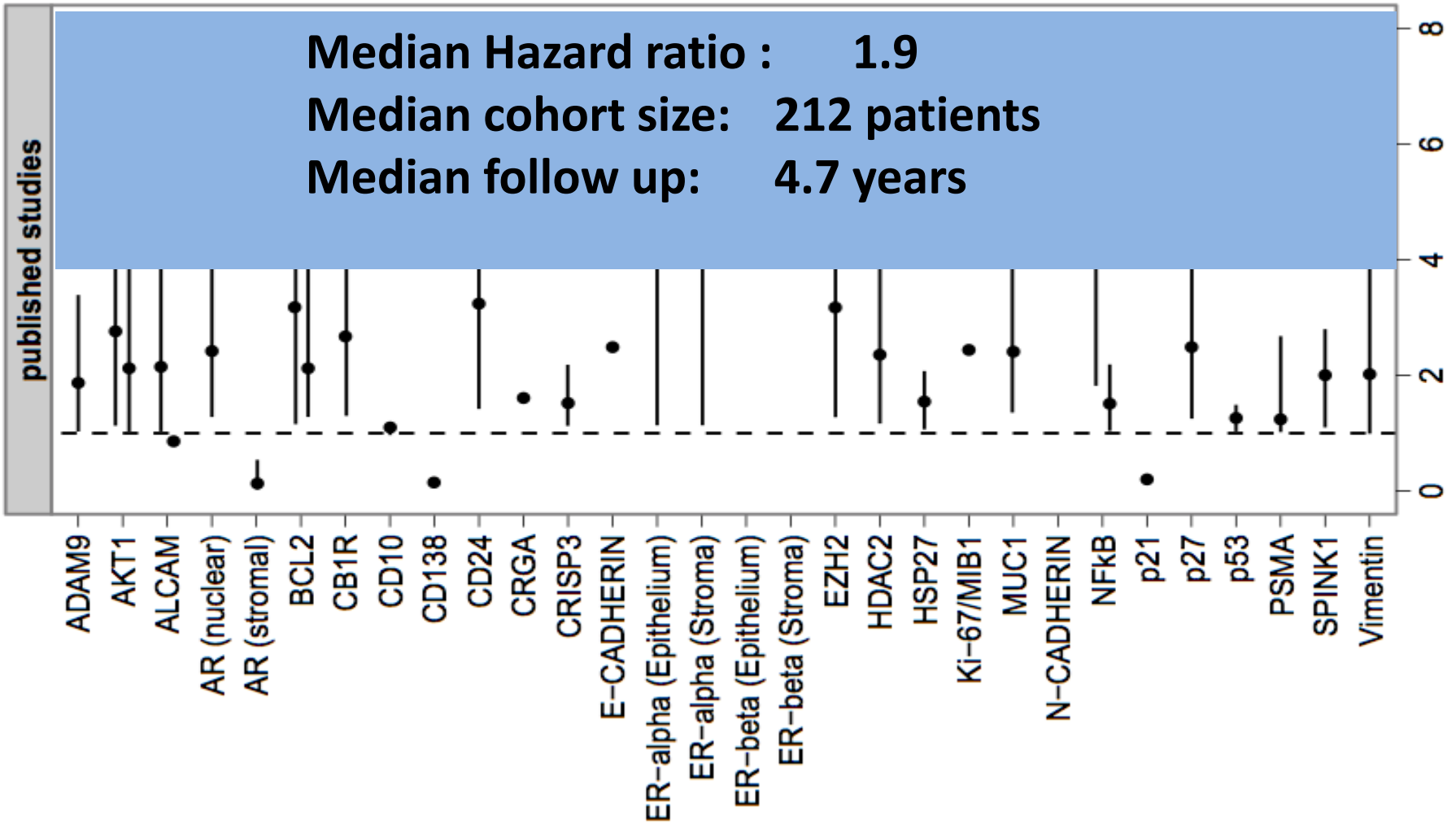


See more (10)...

on average: 10 new prognostic markers per month!

How reproducible are immunohistochemical prognostic markers?

- **Pubmed: identification of 30 independent prognostic markers**



Validating published immunohistochemical prognostic markers:

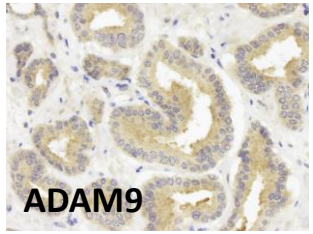
- Validation cohort-
  238 RPE cases (Zurich) on TMAs, 1 core/case

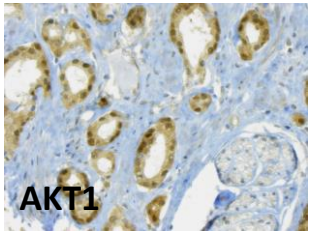
  median follow up: 5.3 years

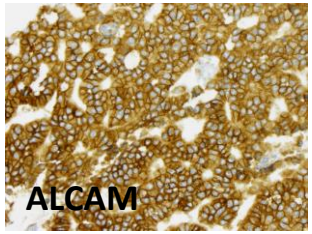
- Automated immunohistochemistry (Ventana/Bond)

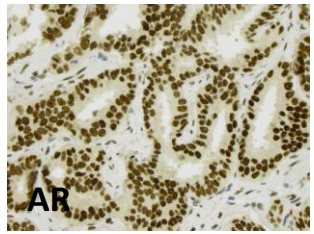
- Supervised reading of slide by a single investigator

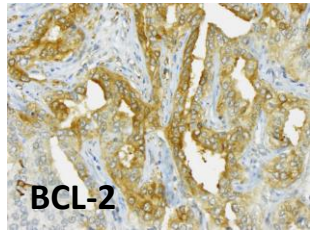
Staining Patterns of evaluated Prognostic Markers

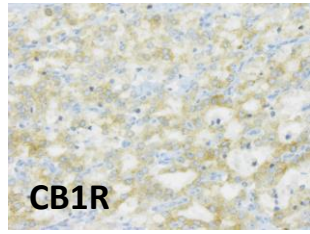


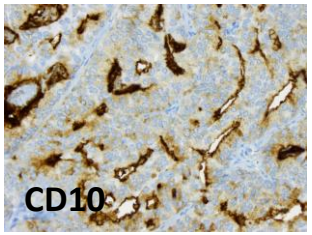


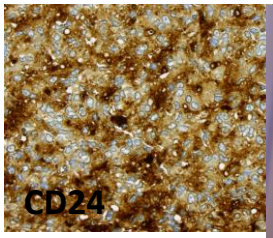


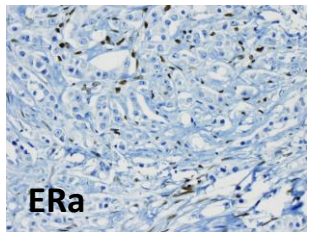


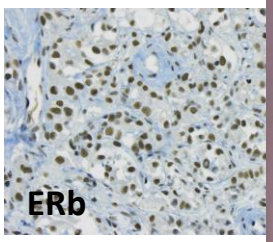


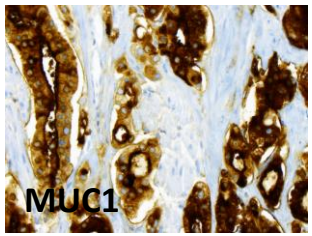


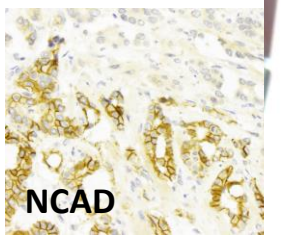


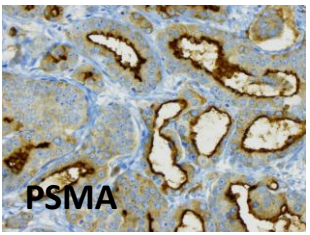


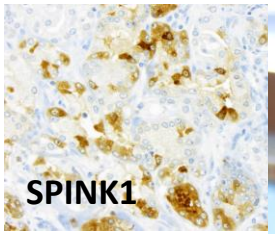


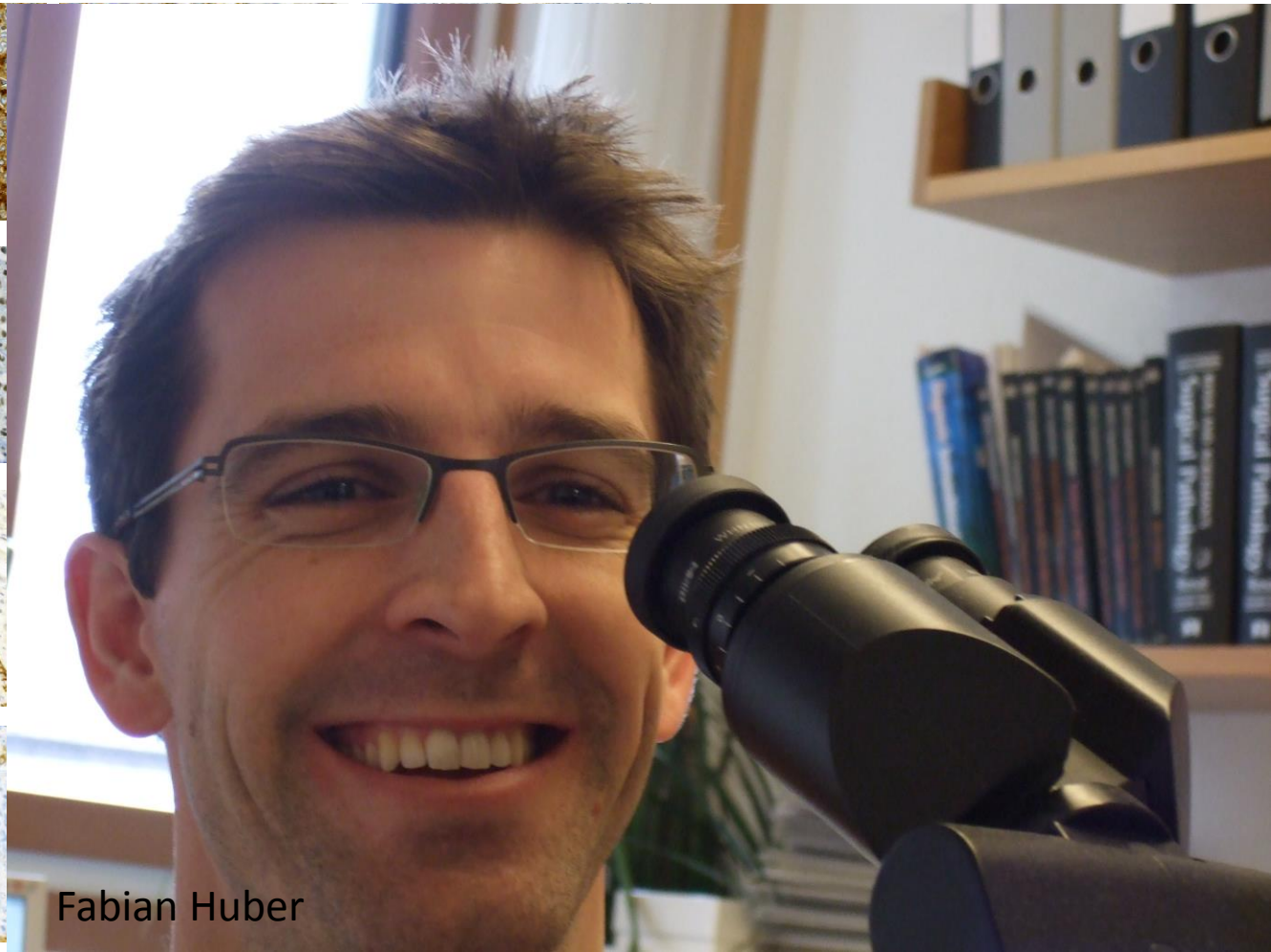




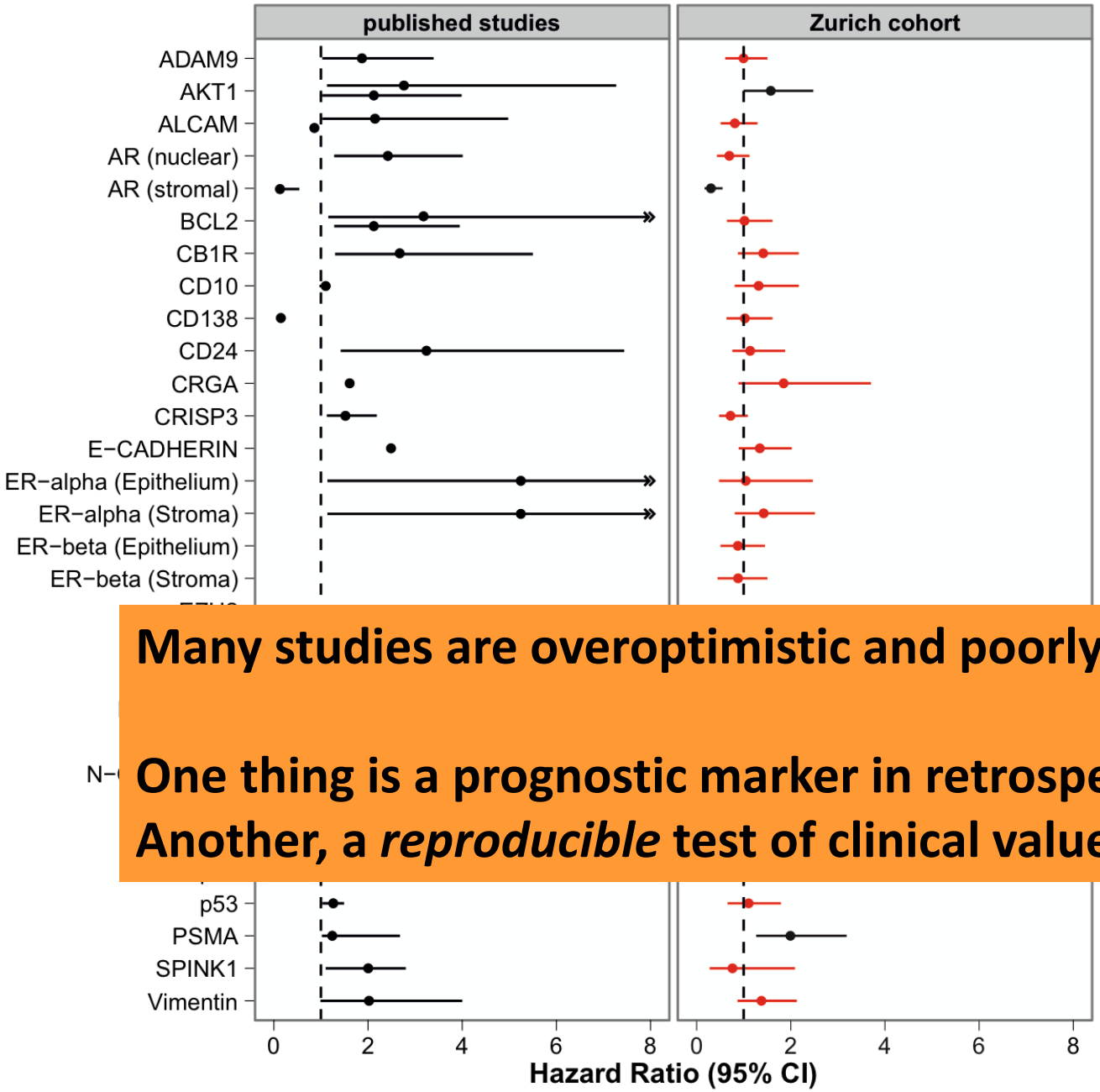








Result: Forrest Plot of prognostic data



red – non significant

black – significant (p<0.05%)

Many studies are overoptimistic and poorly verified.

One thing is a prognostic marker in retrospective study, Another, a *reproducible* test of clinical value!

Br J Cancer 6;112(1):140-8.

Ki-67 is a strong prognostic marker in...

- Watchful waiting cohorts
- Radical prostatectomy cohorts
- Radiation therapy cohorts

Why then is it not used in clinical practise?

Studies endorsing Ki-67 as a Prognostic Marker in PCA:

Author	Year	Cohort Type	Cohort Size	Endpoint	cut-off	p-value (univariate)	p-value (multivariate)	Hazard ratio
Bubendorf	1996	RPE	137	DFS	7.5%	0.02	0.01	2.48
Bettencourt	1996	RPE	180	BCR	26%	<0.001	0.05	3.1
Stattin	1997	WW	125	OS	3%	<0.00005	0.0023	2.51
Bubendorf	1998	Biopsy, mixed Tx	131	OS	7.5%	0.0007	0.0459	
Borre	1998	WW	221	OS	10.3 %	<0.0001	0.0002	1.04 (continuos)
Khoo	1999	RTx	42	BCR	2.4%	0.017	n.s.	
Vis	2000	RPE	92	Clinical progression	10%	0.001	n.s.	
Sebo	2002	RPE	454	BCR		<0.001	0.008	1.64
Cowen	2002	RTx	106	BCR	3.5%	<0.0001	0.003	2.8
Rubin	2002	RPE	88	BCR			0.047	1.49 per 10%
Li	2004	RTx	108	DM	3.5%	0.0005	n.s.	3.77
Pollack	2003	RTX	106	BCR	3.5%	0.0001	0.04	1.17
Pollack	2004	RTx	537	DM	7.1%	0.0003	0.0008	2.39
Rubio	2005	RPE	91	BCR	5%	0.0014	0.006	3.6
Laitinen	2008	RPE	249	BCR	16%	<0.0001	0.013	1.85
Goto	2008	RPE	119	BCR	8.5%	0.04	0.96	
Gunia	2008	RPE	528	BCR	5%	<0.001	0.048	1.62
Zellweger	2008	Biopsy/ RPE	279	BCR	10%	0.0002	<0.05	3.08
Berney	2009	WW	693	OS/DSS	5%	<0.001	0.0012	
Khor	2009	RTX	637	DM	6.3%		0.007	1.63
Miyake	2010	RPE	193	BCR	5%	<0.001	0.029	

Studies endorsing Ki-67 as a Prognostic Marker in PCA:

Author	Year	Cohort Type	Cohort Size	Endpoint	cut-off	p-value (univariate)	p-value (multivariate)	Hazard ratio
Bubendorf	1996	RPE	137	DFS	7.5%	0.02	0.01	2.48
Bettencourt	1996	RPE	180	BCR	26%	<0.001	0.05	3.1
Stattin	1997	WW	125	OS	3%	<0.00005	0.0023	2.51
Bubendorf	1998	Biopsy, mixed Tx	131	OS	7.5%	0.0007	0.0459	
Borre	1998	WW	221	OS	10.3 %	<0.0001	0.0002	1.04 (continuos)
Khoo	1999	RTx	42	BCR	2.4%	0.017	n.s.	
Vis	2000	RPE	92	Clinical progression	10%	0.001	n.s.	
Sebo	2002	RPE	454	BCR		<0.001	0.008	1.64
Cowen	2002	RTx	106	BCR	3.5%	<0.0001	0.003	2.8
Rubin	2002	RPE	88	BCR			0.047	1.49 per 10%
Li	2004	RTx	108	DM	3.5%	0.0005	n.s.	3.77
Pollack	2003	RTX	106	BCR	3.5%	0.0001	0.04	1.17
Pollack	2004	RTx	537	DM	7.1%	0.0003	0.0008	2.39
Rubio	2005	RPE	91	BCR	5%	0.0014	0.006	3.6
Laitinen	2008	RPE	249	BCR	16%	<0.0001	0.013	1.85
Goto	2008	RPE	119	BCR	8.5%	0.04	0.96	
Gunia	2008	RPE	528	BCR	5%	<0.001	0.048	1.62
Zellweger	2008	Biopsy/ RPE	279	BCR	10%	0.0002	<0.05	3.08
Berney	2009	WW	693	OS/DSS	5%	<0.001	0.0012	
Khor	2009	RTX	637	DM	6.3%		0.007	1.63
Miyake	2010	RPE	193	BCR	5%	<0.001	0.029	

Marked Differences:

- Endpoints

Studies endorsing Ki-67 as a Prognostic Marker in PCA:

Author	Year	Cohort Type	Cohort Size	Endpoint	cut-off	p-value (univariate)	p-value (multivariate)	Hazard ratio
Bubendorf	1996	RPE	137	DFS	7.5%	0.02	0.01	2.48
Bettencourt	1996	RPE	180	BCR	26%	<0.001	0.05	3.1
Stattin	1997	WW	125	OS	3%	<0.00005	0.0023	2.51
Bubendorf	1998	Biopsy, mixed Tx	131	OS	7.5%	0.0007	0.0459	
Borre	1998	WW	221	OS	10.3 %	<0.0001	0.0002	1.04 (continuos)
Khoo	1999	RTx	42	BCR	2.4%	0.017	n.s.	
Vis	2000	RPE	92	Clinical progression	10%	0.001	n.s.	
Sebo	2002	RPE	454	BCR		<0.001	0.008	1.64
Cowen	2002	RTx	106	BCR	3.5%	<0.0001	0.003	2.8
Rubin	2002	RPE	88	BCR			0.047	1.49 per 10%
Li	2004	RTx	108	DM	3.5%	0.0005	n.s.	3.77
Pollack	2003	RTX	106	BCR	3.5%	0.0001	0.04	1.17
Pollack	2004	RTx	537	DM	7.1%	0.0003	0.0008	2.39
Rubio	2005	RPE	91	BCR	5%	0.0014	0.006	3.6
Laitinen	2008	RPE	249	BCR	16%	<0.0001	0.013	1.85
Goto	2008	RPE	119	BCR	8.5%	0.04	0.96	
Gunia	2008	RPE	528	BCR	5%	<0.001	0.048	1.62
Zellweger	2008	Biopsy/ RPE	279	BCR	10%	0.0002	<0.05	3.08
Berney	2009	WW	693	OS/DSS	5%	<0.001	0.0012	
Khor	2009	RTX	637	DM	6.3%		0.007	1.63
Miyake	2010	RPE	193	BCR	5%	<0.001	0.029	

Marked Differences:

- Endpoints
- cut-offs

Studies endorsing Ki-67 as a Prognostic Marker in PCA:

Author	Year	Cohort Type	Cohort Size	Endpoint	cut-off	p-value (univariate)	p-value (multivariate)	Hazard ratio
Bubendorf	1996	RPE	137	DFS	7.5%	0.02	0.01	2.48
Bettencourt	1996	RPE	180	BCR	26%	<0.001	0.05	3.1
Stattin	1997	WW	125	OS	3%	<0.00005	0.0023	2.51
Bubendorf	1998	Biopsy, mixed Tx	131	OS	7.5%	0.0007	0.0459	
Borre	1998	WW	221	OS	10.3 %	<0.0001	0.0002	1.04 (continuos)
Khoo	1999	RTx	42	BCR	2.4%	0.017	n.s.	
Vis	2000	RPE	92	Clinical progression	10%	0.001	n.s.	
Sebo	2002	RPE	454	BCR		<0.001	0.008	1.64
Cowen	2002	RTx	106	BCR	3.5%	<0.0001	0.003	2.8
Rubin	2002	RPE	88	BCR			0.047	1.49 per 10%
Li	2004	RTx	108	DM	3.5%	0.0005	n.s.	3.77
Pollack	2003	RTX	106	BCR	3.5%	0.0001	0.04	1.17
Pollack	2004	RTx	537	DM	7.1%	0.0003	0.0008	2.39
Rubio	2005	RPE	91	BCR	5%	0.0014	0.006	3.6
Laitinen	2008	RPE	249	BCR	16%	<0.0001	0.013	1.85
Goto	2008	RPE	119	BCR	8.5%	0.04	0.96	
Gunia	2008	RPE	528	BCR	5%	<0.001	0.048	1.62
Zellweger	2008	Biopsy/ RPE	279	BCR	10%	0.0002	<0.05	3.08
Berney	2009	WW	693	OS/DSS	5%	<0.001	0.0012	
Khor	2009	RTX	637	DM	6.3%		0.007	1.63
Miyake	2010	RPE	193	BCR	5%	<0.001	0.029	

Marked Differences:

- Endpoints
- cut-offs
- multivariate Models

Publication/deposition of original data sets would enable a true post-publicatory peer review and better comparison of studies!

Ki-67: How can we standardize the staining?

Pre-analytics:
- time to fixation
- time in fixative, temperature
- fixative (additives?)
- embedding
- storage conditions

Analytics:
- sectioning
- Antibody (clone Mib-1?)
- IHC-protocol: HIER? Detection?

Interlaboratory variability of Ki67-labelling index in breast cancer tissue microarrays

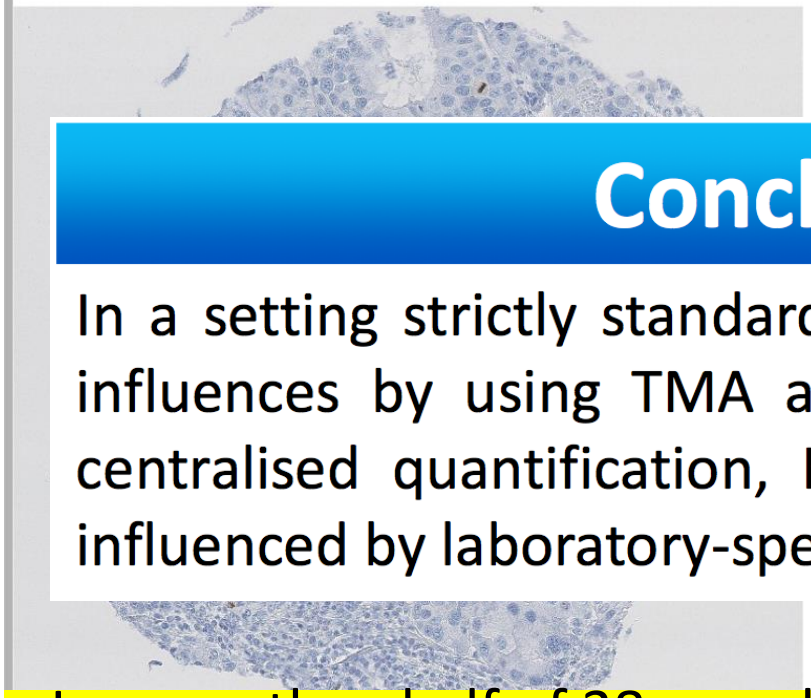
Cornelia M Focke[1,19], Doreen Gläser[1,19], Kai Finsterbusch[1,19], Horst Bürger[2,19], Eberhard Korsching[3], Karl-Heinz Berghäuser[4,19], Reinhard Bollmann[5,19], Gabor Cserni[6,20], Paul J van Diest[7,20], Bernd Hinrichs[8,19], Ulrich Lang[9,19], Johann Lorenzen[10,19], Nikolaj Minew[11,19], Maria Mlynek-Kersjes[12,19], Farid Moinfar[13], Jens Packeisen[14,19], Peter Regitnig[13,20], Angelika Reiner-Concin[15,20] Detlef Rothacker[16,19], Meinald Schultz[17,19], Zsuzsanna Varga[18,20], Thomas Decker[1,19,20,21,22]

1 Department of Pathology, Dietrich Bonhoeffer Medical Center, Neubrandenburg, Germany; 2 Institute of Pathology, Paderborn, Germany; 3 Institute of Bioinformatics, University of Münster, Münster, Germany; 4 Institute of Pathology, Thüringen-Hospital Georgius Agricola, Saalfeld, Germany; 5 Joint Practice for Pathology, Bonn, Germany; 6 Department of Pathology, University of Kecskemét, Hungary; 7 Department of Pathology, University Medical Center Utrecht, Utrecht, The Netherlands; 8 Medical Care Center for Pathology and Cytology, Köln, Germany; 9 Department of Pathology, Medical Center Herford, Germany; 10 Department of Pathology, Medical Center Dortmund, Germany; 11 Joint Practice for Pathology, Eisenhüttenstadt, Germany; 12 Practice for Pathology, Moers, Germany; 13 Department of Pathology, University of Graz, Austria; 14 Joint Practice for Pathology, Osnabrück, Germany; 15 Department of Pathology, Donauspital Wien, Austria; 16 Joint Practice for Pathology, Schwerin, Germany; 17 Joint Practice for Pathology and Cytology, Stendal, Germany; 18 Department of Pathology, University of Zürich, Switzerland; 19 German Breast Screening Pathology Initiative; 20 European Working Group in Breast Screening Pathology; 21 Reference Center Mammography, University of Münster, Germany; 22 Reference Center Mammography Berlin, Germany

Sample 752

Min: 0% **Max:** 29,08%

Median ± SD: 6,13% ± 8,6

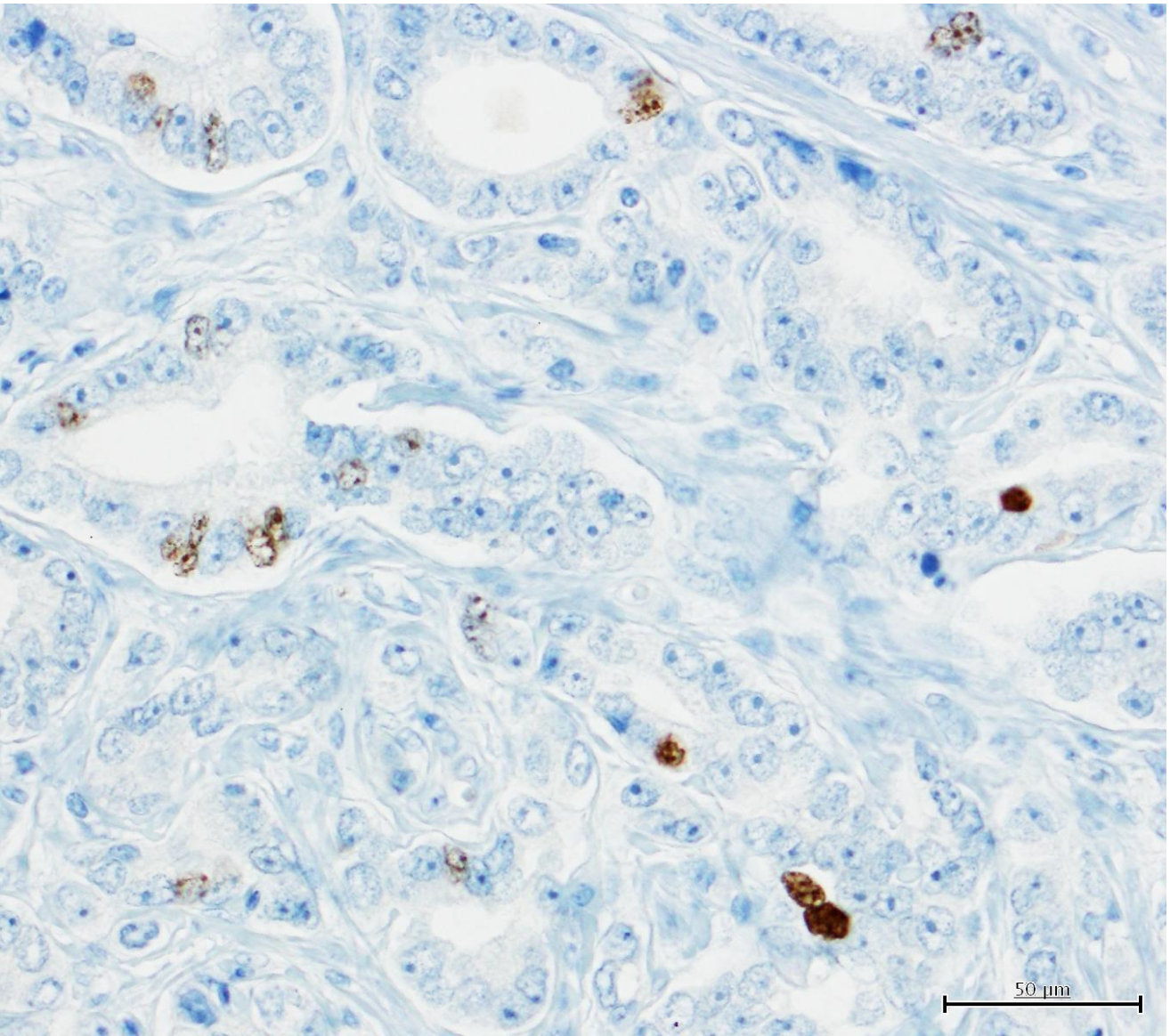


Conclusion

In a setting strictly standardised in terms of preanalytic influences by using TMA and postanalytic variance by centralised quantification, Ki67-LI seems to be heavily influenced by laboratory-specific analytic variables.

„In more than half of 38 samples we did find a Ki-67-LI variation of more than 25%.“

Ki-67: How can we standardize Subjectivity?



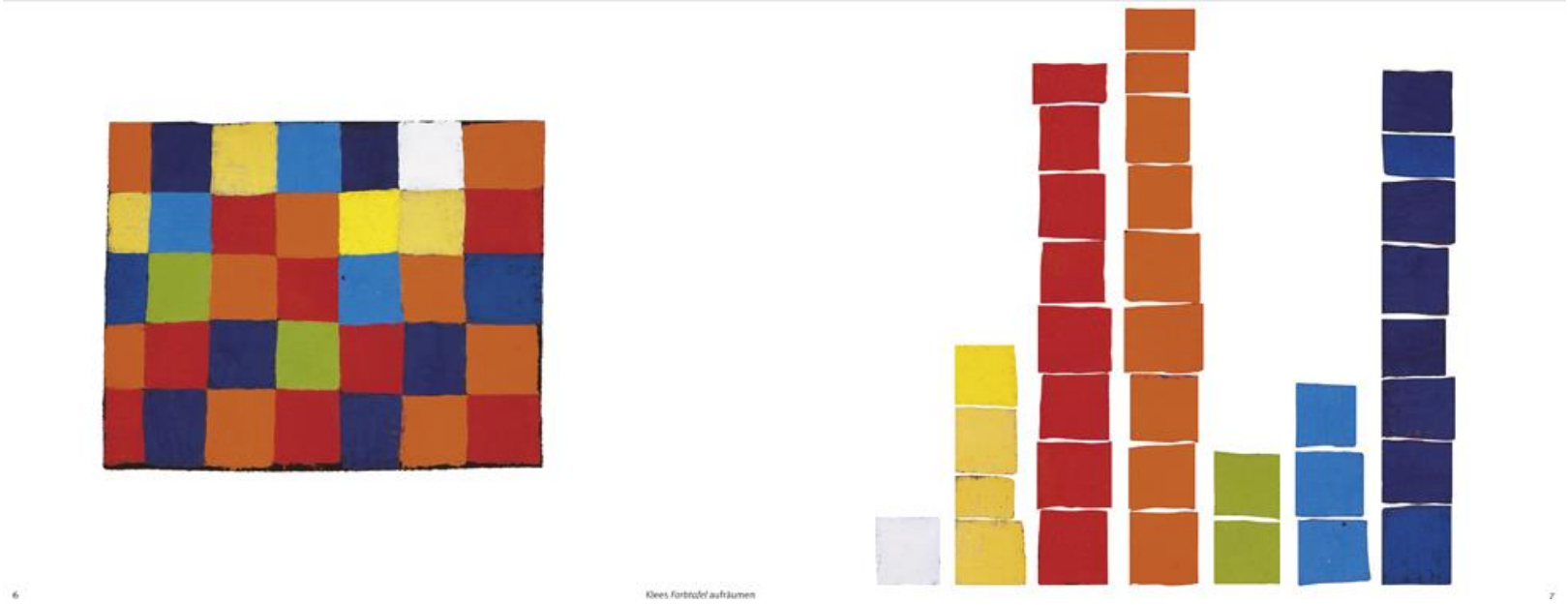
4% ?

8% ??

16% ???

The histopathological diagnosis is not a laboratory test, but individual medical art.

-> How do you standardize Artists??



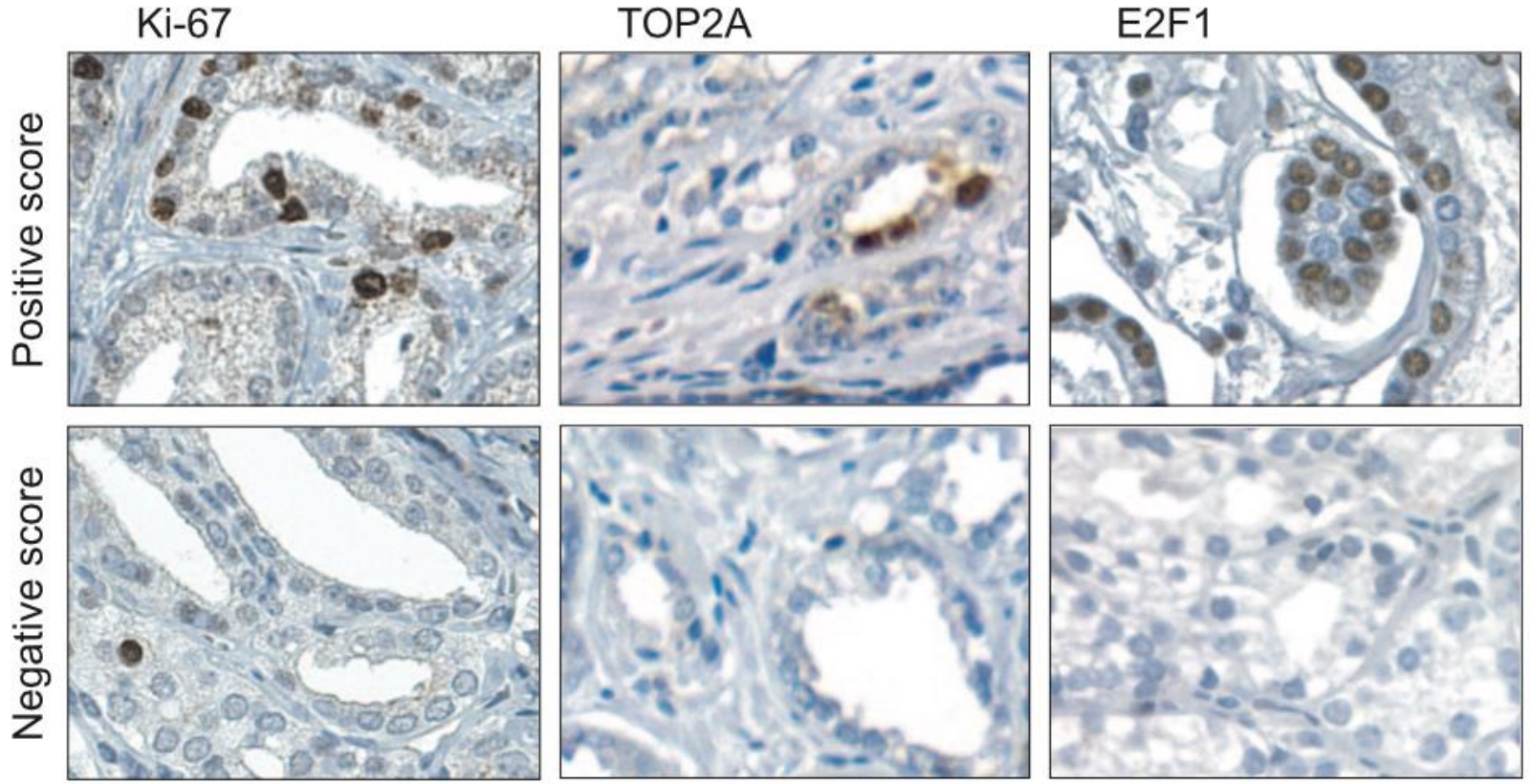
What can we do to make prognostic IHC more reliable?

- Combine Markers with similar biological function (to increase redundancy!)

- (combining markers with divergent functions may increase variability and thus reduce robustness of a test)

A Tri-Marker Proliferation Index Predicts Biochemical Recurrence after Surgery for Prostate Cancer

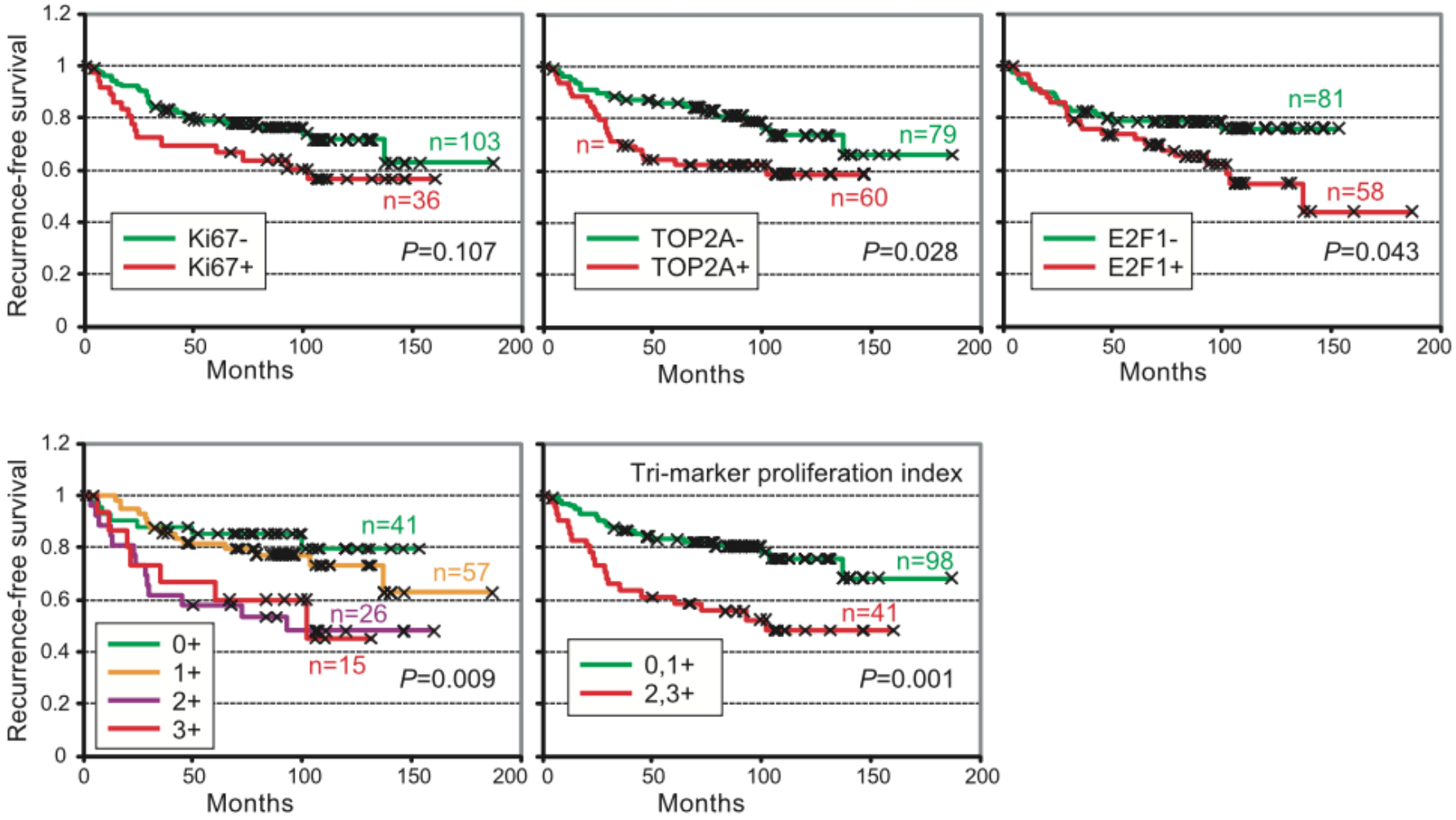
Sameer Malhotra[1☯], Jacques Lapointe[2☯], Keyan Salari[3,4☯], John P. Higgins[3], Michelle Ferrari[1], Kelli Montgomery[3], Matt van de Rijn[3], James D. Brooks[1¶*], Jonathan R. Pollack[3¶*]



PLoS ONE 6(5): e20293. doi:10.1371/journal.pone.0020293

A Tri-Marker Proliferation Index Predicts Biochemical Recurrence after Surgery for Prostate Cancer

Sameer Malhotra[1☯], Jacques Lapointe[2☯], Keyan Salari[3,4☯], John P. Higgins[3], Michelle Ferrari[1], Kelli Montgomery[3], Matt van de Rijn[3], James D. Brooks[1¶*], Jonathan R. Pollack[3¶*]



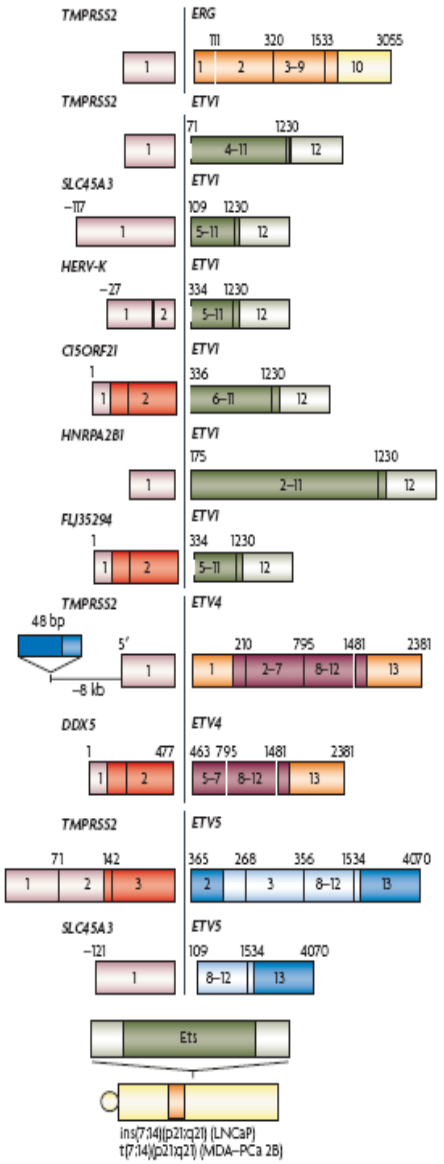
PLoS ONE 6(5): e20293. doi:10.1371/journal.pone.0020293

What can we do to make prognostic IHC more reliable?

- Use markers that **do not need cut off values**, e.g. alteration specific markers

ETS-Gene-Fusions

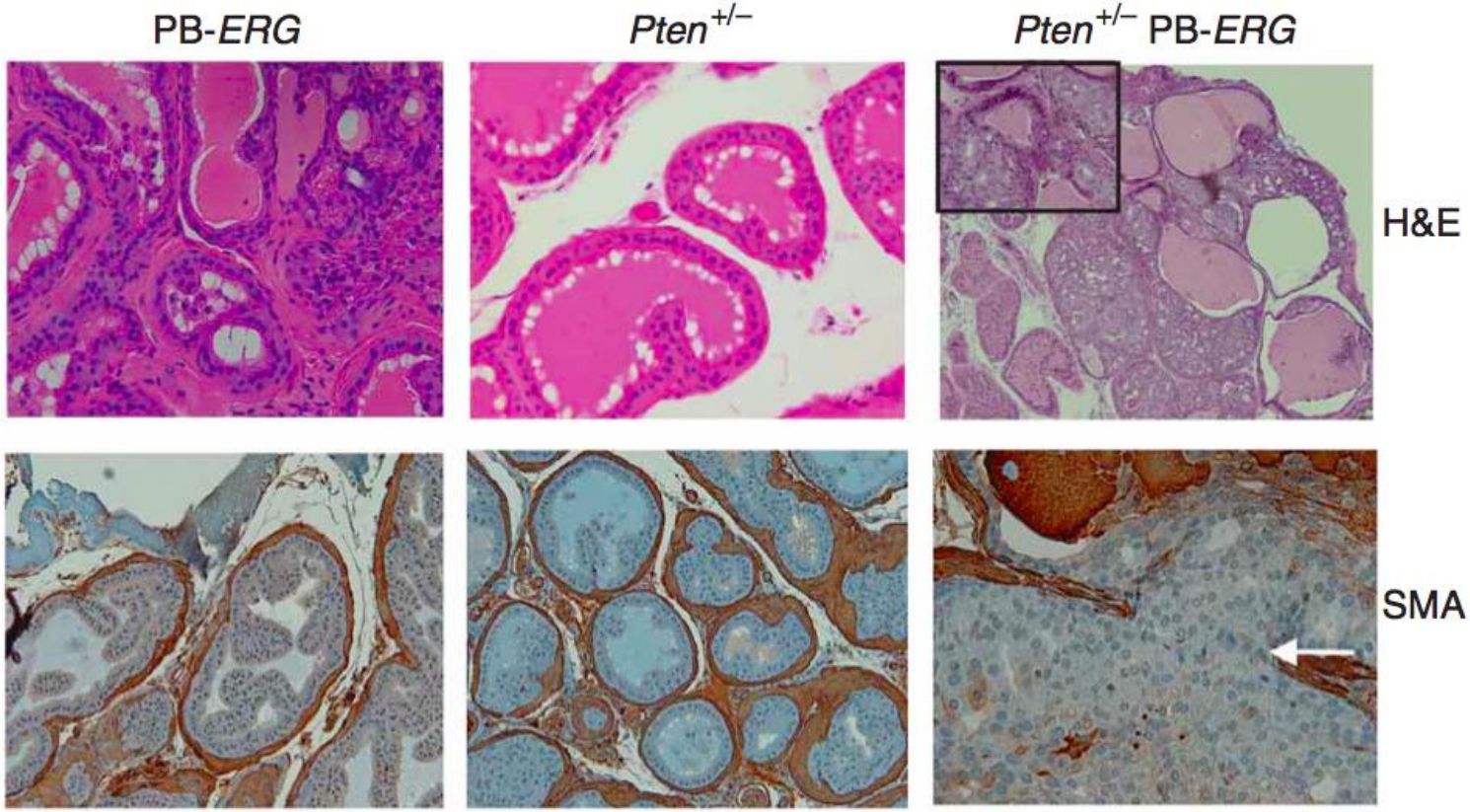
- Recurrent gene fusions of androgen-regulated genes with ETS genes
- TMPRSS2-ERG most common
- >10 different 5‘ partners
- Other 3‘ partners are ETV1,-4,-5, FLi1
- found in 30-80% of Pca
- Mechanistic evidence of importance for tumorigenesis (with AR/PTEN)



Aberrant ERG expression cooperates with loss of PTEN to promote cancer progression in the prostate

Brett S Carver[1,2], Jennifer Tran[1], Anuradha Gopalan[3], Zhenbang Chen[1,4], Safa Shaikh[2], Arkaitz Carracedo[1,4], Andrea Alimonti[1,4], Caterina Nardella[1,4], Shohreh Varmeh[1,4], Peter T Scardino[2], Carlos Cordon-Cardo[5], William Gerald[3] & Pier Paolo Pandolfi[1,3,4]

NATURE GENETICS VOLUME 41 | NUMBER 5 | MAY 2009



By 6 months of age, Pten+/-; PB-ERG **mice** showed multifocal prostatic adenocarcinoma with complete penetrance.

Overview of T2-ERG Studies:

Prognostic value	Author	Year	Cohort	Size	Endpoint
Neg.	Dimichelis	2007	WW/TURP	111	death
Neg.	Attard	2008	WW/TURP	445	death
Neg.	Nam	2007	RPE	165	BCF
Pos.	Saramäki	2008	RPE	150	BCF
Pos.	Winnes	2007	RPE	50	BCF
None.	Lapointe	2007	RPE	54	BCF
None.	Furusato	2008	RPE	45	BCF
None.	Fitzgerald	2008	RPE	214	death
None.	Egueva	2010	RPE	540	BCF
None.	Minner	2011	RPE	2805	BCF
None.	Pettersson	2012	RPE	1180	Death/BCF
None.	Hoogland	2012	RPE	481	Death/BCF
None.	Krohn	2012	RPE	3751	BCF

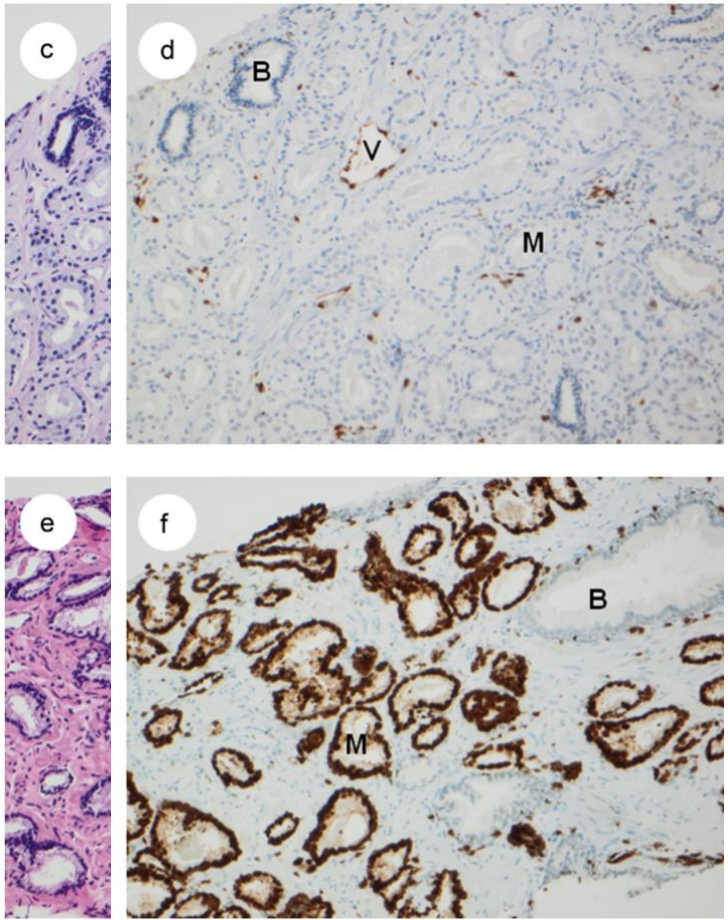
- **Prognostic value in untreated patients**
- **No predictive marker for RPE patients**

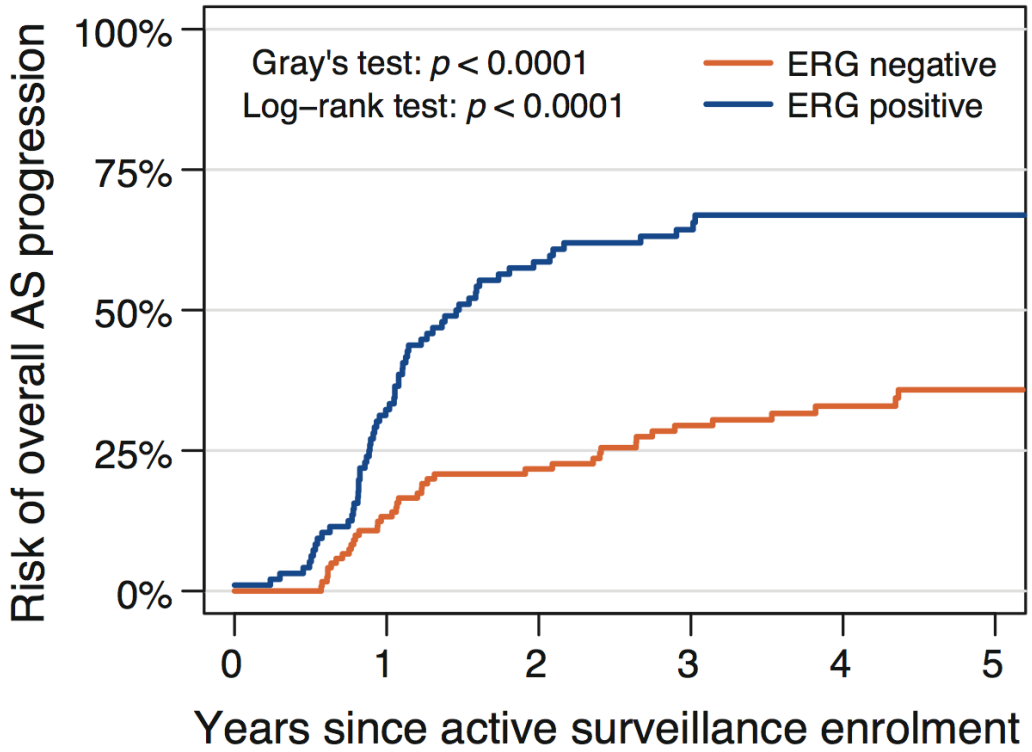
ERG Protein Expression in Diagnostic Specimens Is Associated with Increased Risk of Progression During Active Surveillance for Prostate Cancer

EUROPEAN UROLOGY 66 (2014) 851–860

Kasper Drimer Berg[a,*], *Ben Vainer*[b], *Frederik Birkebæk Thomsen*[a], *M. Andreas Røder*[a], *Thomas Alexander Gerds*[c], *Birgitte Grønkær Toft*[b], *Klaus Brasso*[a], *Peter Iversen*[a]

[a] *Copenhagen Prostate Cancer Center, Department of Urology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark;* [b] *Department of Pathology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark;* [c] *Department of Biostatistics, University of Copenhagen, Copenhagen, Denmark*



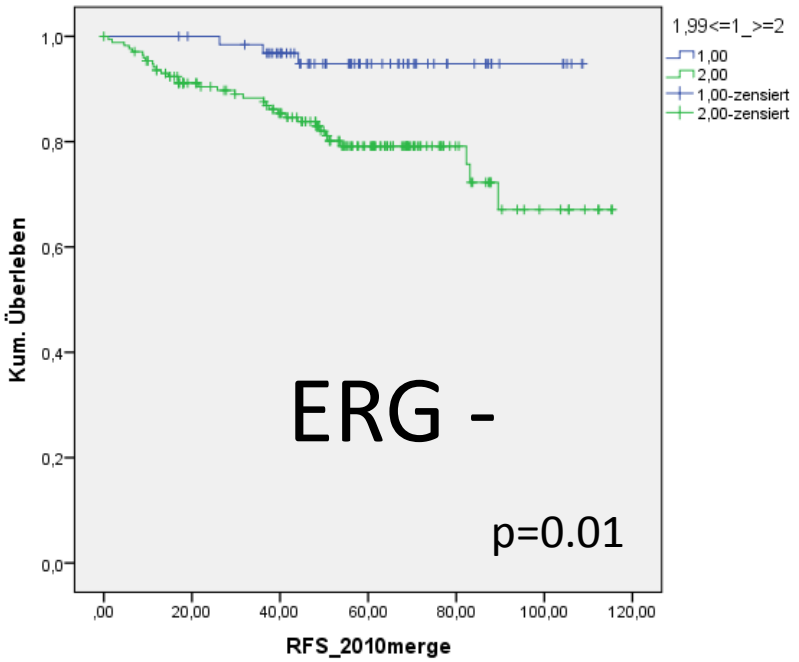


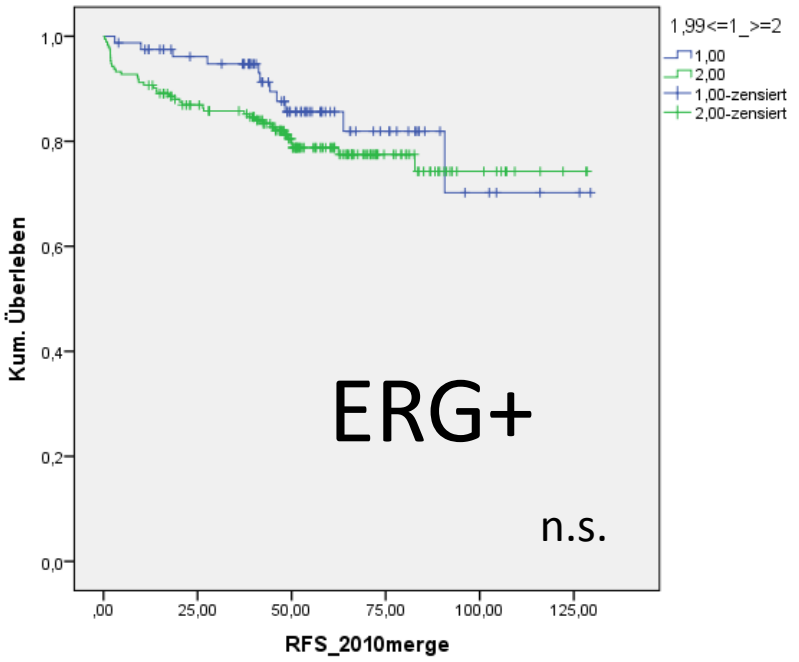
No. at risk	121	103	72	51	27	14
	96	64	35	18	11	6

What can we do to make prognostic IHC more reliable?

- Identify relevant molecular subgroups of Pca

Prognostic value of Ki-67 in PCa:





Ki-67 is only prognostic in ERG- Pca!

Pathology. 2015 Dec;47(7):629-636.

What can we do to make prognostic IHC more reliable?

- Leave IHC behind: e.g. MALDI-proteomics

- MALDI resolution is still worse than IHC, but has advantages: better quantitation, easily multiplexing of multiple markers

MALDI Imaging Identifies Prognostic Seven-Protein Signature of Novel Tissue Markers in Intestinal-Type Gastric Cancer

Benjamin Balluff,*† Sandra Rauser,*
Stephan Meding,* Mareike Elsner,*
Cedrik Schöne,* Annette Feuchtinger,*
Christoph Schuhmacher,‡ Alexander Novotny,‡
Uta Jütting,§ Giuseppina Maccarrone,¶
Hakan Sarioglu,‖ Marius Ueffing,‖
Herbert Braselmann,** Horst Zitzelsberger,**
Roland M. Schmid,† Heinz Höfler,*††
Matthias P. Ebert,‡‡ and Axel Walch*

The American Journal of Pathology, Vol. 179, No. 6, December 2011

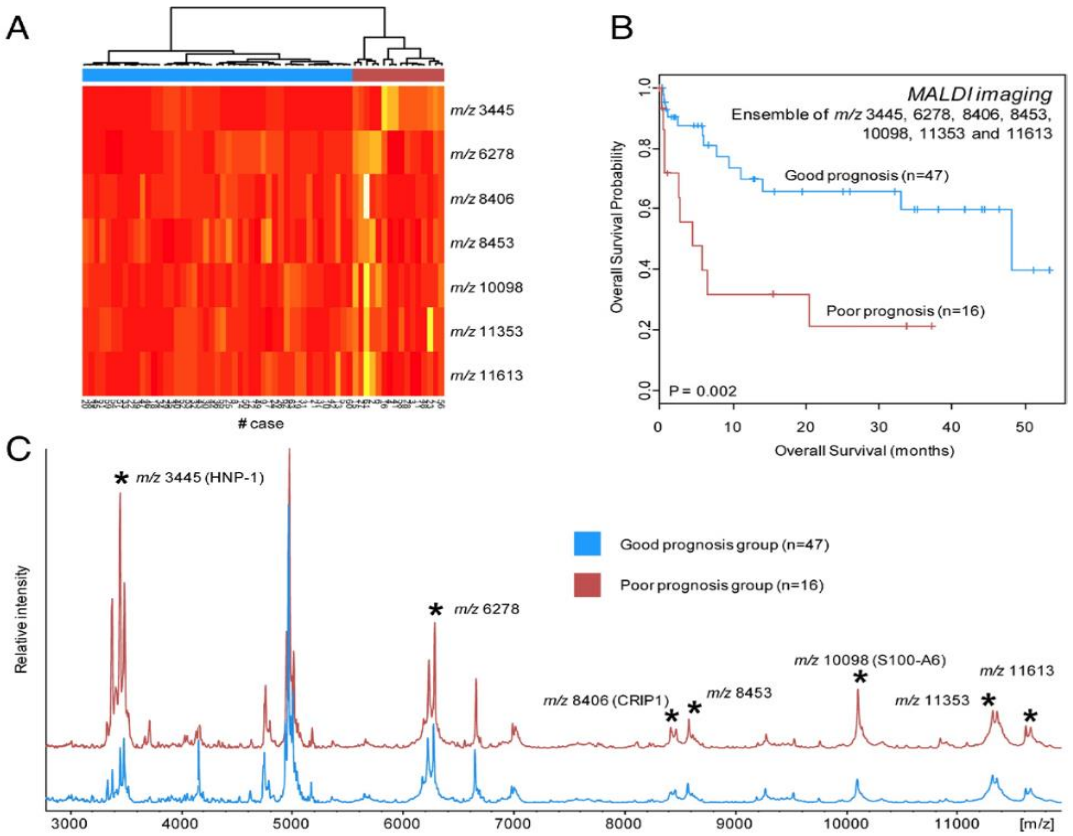


Figure 4. The prognostic power of a combined pattern was investigated by clustering all patients according to the seven protein signals (**A**, **C**). The main two branches of the tree were found to represent a good (blue) and a poor prognosis group (red) (**B**). Moreover, this pattern predicts patient outcome independently of major clinicopathological parameters (Table 2).

Topics:

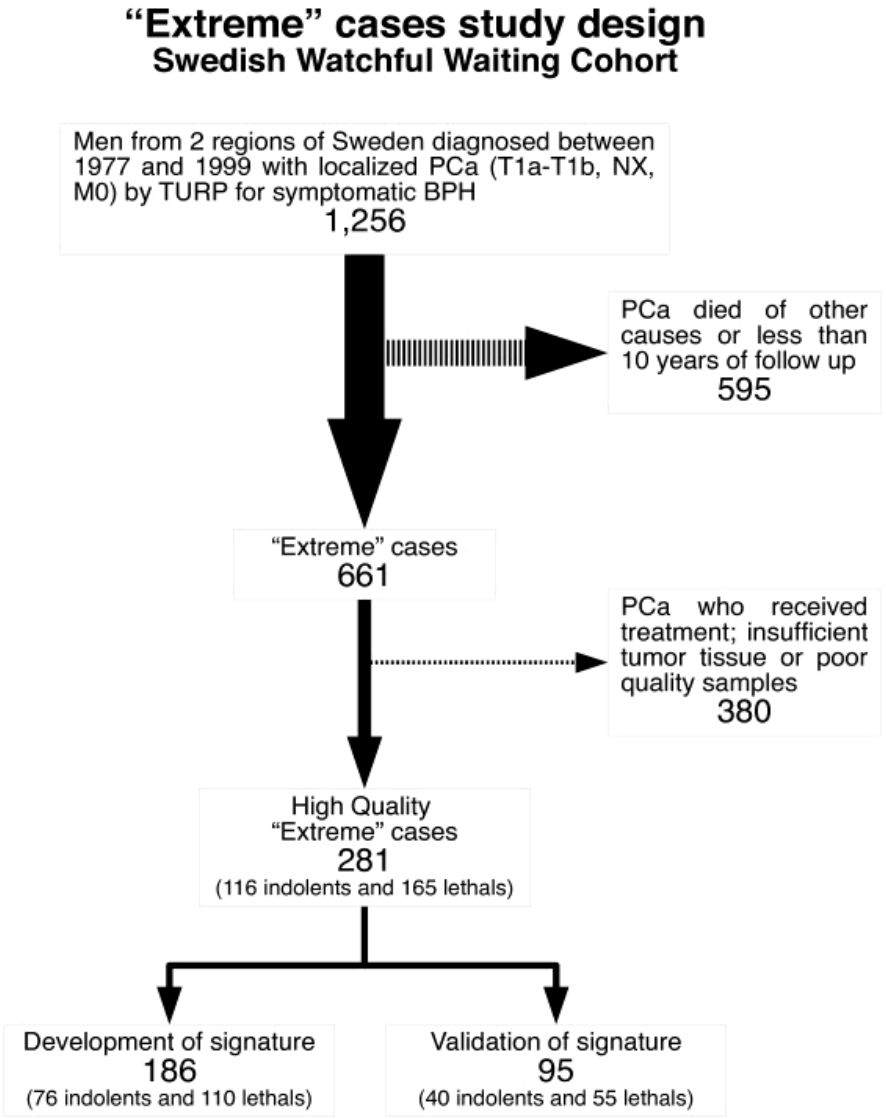
1. Diagnostic IHC
2. Prognostic IHC
3. **Prognostic molecular signatures**
4. Targeted therapy and predictive pathology in prostate cancer

Superior Prognostication by mRNA Signatures?

Aim:
Identification of Signatures for *lethal* and *indolent* PCA

Method:
RNA Profiling
6100 selected genes

Training/Test set design



Sboner *et al. BMC Medical Genomics* 2010 **3**:8 doi:10.1186/1755-8794-3-8

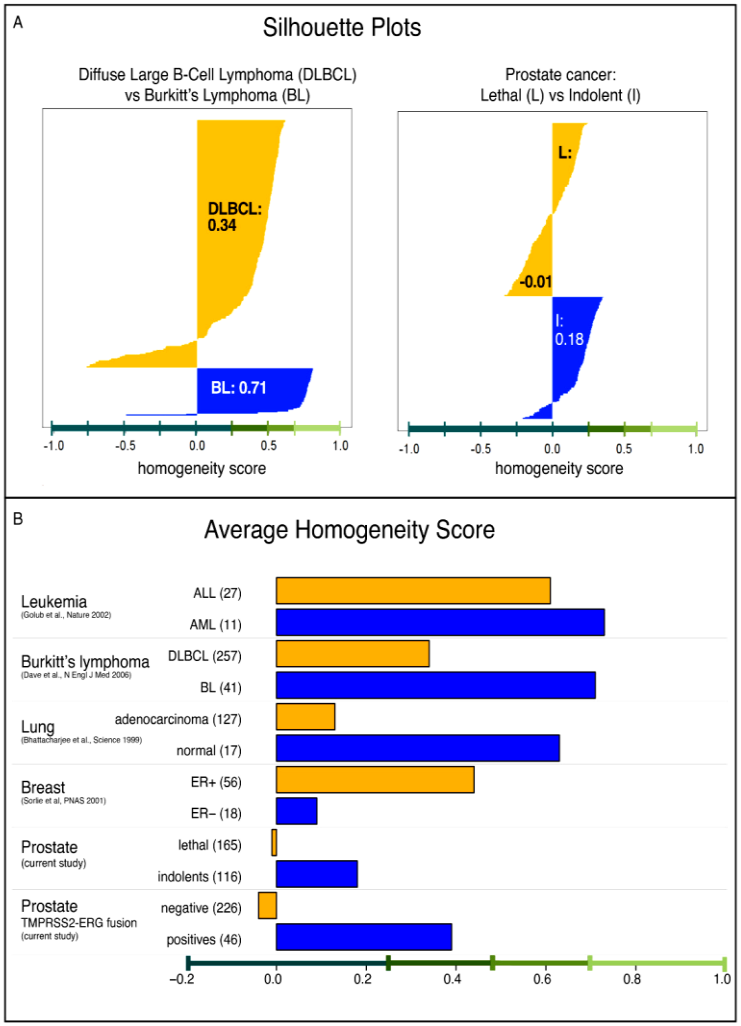
Superior Prognostication by mRNA Signatures?

Results:

1) No molecular signature outperformed clinical parameters.

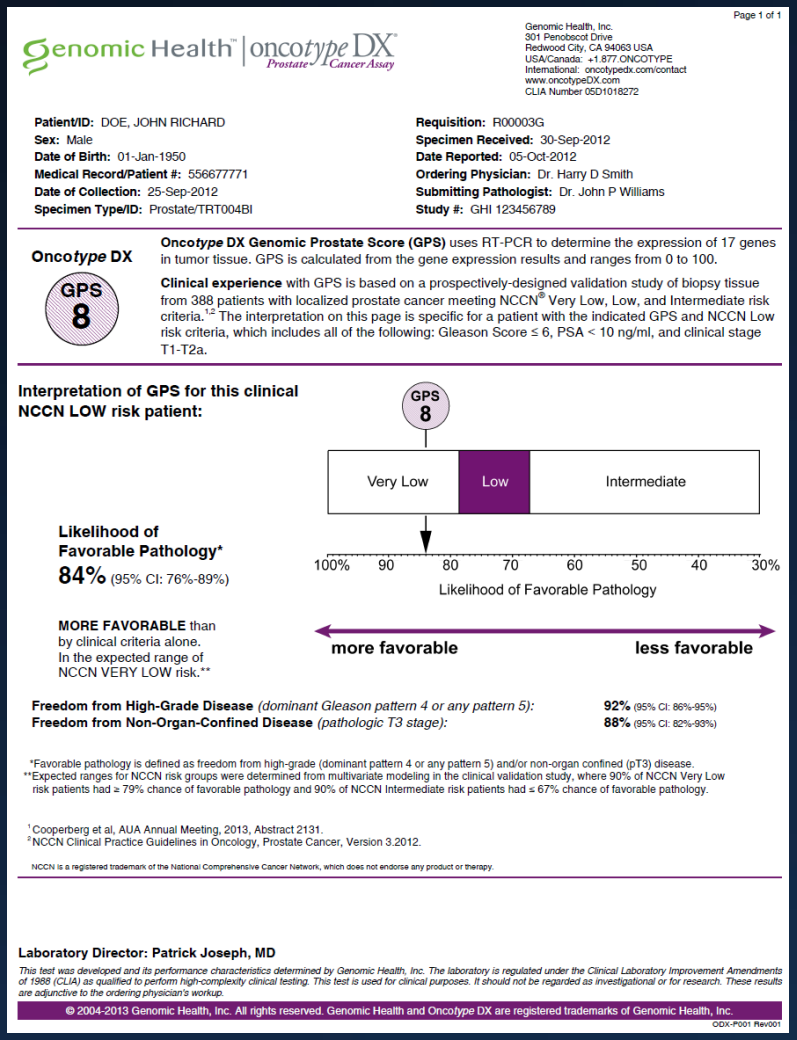
2) Gleason score strongest clinical parameter.

3) Tumoral heterogeneity appears as a major bias.



Sboner *et al. BMC Medical Genomics* 2010 **3**:8 doi:10.1186/1755-8794-3-8

The Oncotype DX® Prostate Cancer Assay



Page 1 of 1

Genomic Health | oncotype DX Prostate Cancer Assay

Genomic Health, Inc.
301 Penobscot Drive
Redwood City, CA 94063 USA
USA/Canada: +1.877.ONCOTYPE
International: oncotypedx.com/contact
www.oncotypeDX.com
CLIA Number 05D1018272

Patient/ID: DOE, JOHN RICHARD
Sex: Male
Date of Birth: 01-Jan-1950
Medical Record/Patient #: 556677771
Date of Collection: 25-Sep-2012
Specimen Type/ID: Prostate/TRT004BI

Requisition: R00003G
Specimen Received: 30-Sep-2012
Date Reported: 05-Oct-2012
Ordering Physician: Dr. Harry D Smith
Submitting Pathologist: Dr. John P Williams
Study #: GHI 123456789

Oncotype DX
GPS 8

Oncotype DX Genomic Prostate Score (GPS) uses RT-PCR to determine the expression of 17 genes in tumor tissue. GPS is calculated from the gene expression results and ranges from 0 to 100.

Clinical experience with GPS is based on a prospectively-designed validation study of biopsy tissue from 388 patients with localized prostate cancer meeting NCCN® Very Low, Low, and Intermediate risk criteria.[1,2] The interpretation on this page is specific for a patient with the indicated GPS and NCCN Low risk criteria, which includes all of the following: Gleason Score ≤ 6, PSA < 10 ng/ml, and clinical stage T1-T2a.

Interpretation of GPS for this clinical NCCN LOW risk patient:

GPS 8

Very Low | Low | Intermediate

100% 90 80 70 60 50 40 30%

Likelihood of Favorable Pathology

Likelihood of Favorable Pathology*
84% (95% CI: 76%-89%)

MORE FAVORABLE than by clinical criteria alone. In the expected range of NCCN VERY LOW risk.**

more favorable ← → less favorable

Freedom from High-Grade Disease *(dominant Gleason pattern 4 or any pattern 5):* **92%** (95% CI: 86%-95%)
Freedom from Non-Organ-Confined Disease *(pathologic T3 stage):* **88%** (95% CI: 82%-93%)

*Favorable pathology is defined as freedom from high-grade (dominant pattern 4 or any pattern 5) and/or non-organ confined (pT3) disease.
**Expected ranges for NCCN risk groups were determined from multivariate modeling in the clinical validation study, where 90% of NCCN Very Low risk patients had ≥ 79% chance of favorable pathology and 90% of NCCN Intermediate risk patients had ≥ 67% chance of favorable pathology.

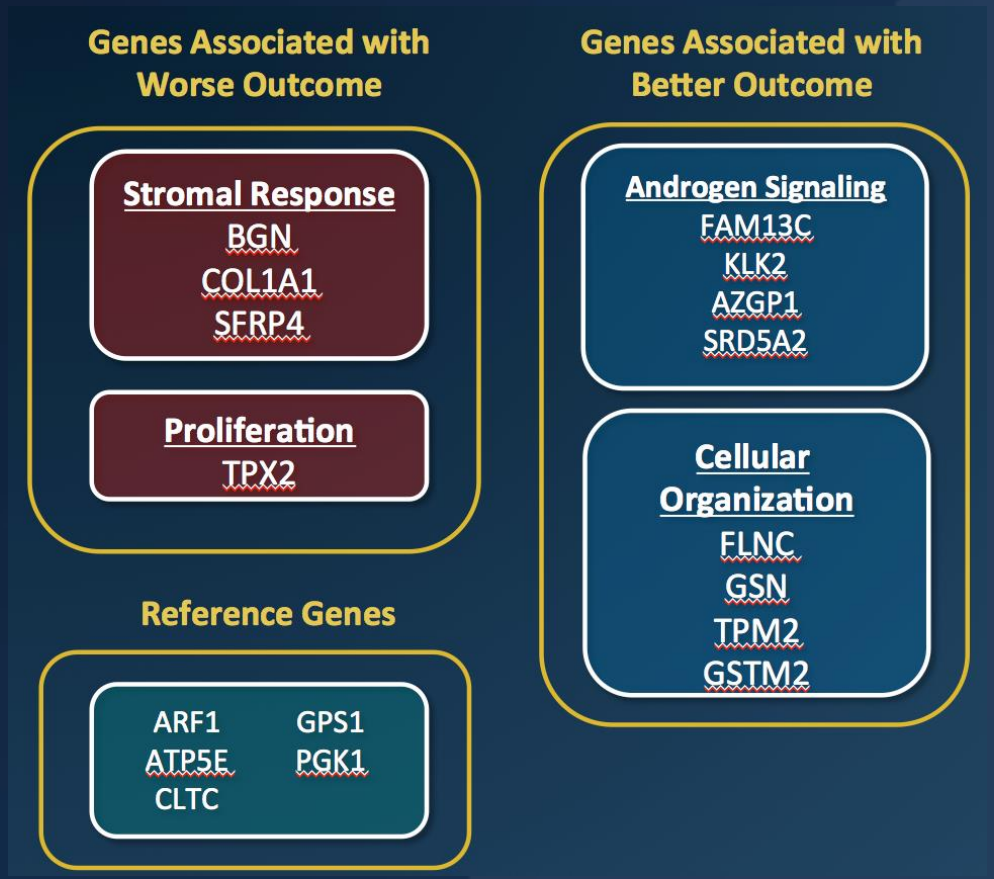
[1] Cooperberg et al, AUA Annual Meeting, 2013, Abstract 2131.
[2] NCCN Clinical Practice Guidelines in Oncology, Prostate Cancer, Version 3.2012.

NCCN is a registered trademark of the National Comprehensive Cancer Network, which does not endorse any product or therapy.

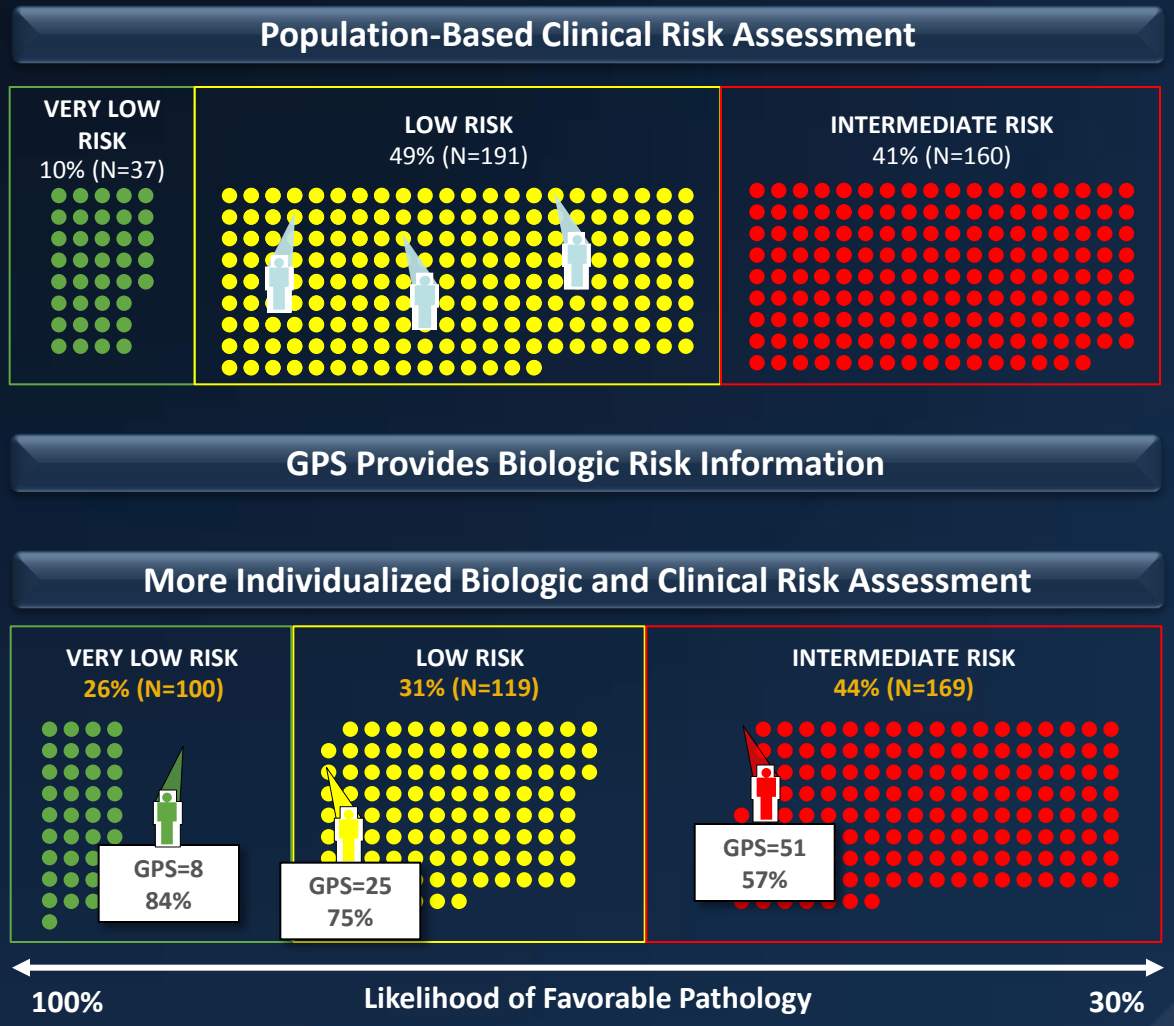
Laboratory Director: Patrick Joseph, MD

This test was developed and its performance characteristics determined by Genomic Health, Inc. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. These results are adjunctive to the ordering physician's workup.

ODX-P001 Rev001



Combining Biologic & Clinical Information Refines Risk Stratification for Individual Patients



UCSF Validation Study

NCCN Risk Classification

- [illegible]
- 10% very Low-risk
- [illegible]
- [illegible]
- [illegible] pathology consistent with Low and intermediate risk disease

Cooperberg et al, AUA 2013

Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study

Lancet Oncol 2011; 12: 245–55

Jack Cuzick, Gregory P Swanson*, Gabrielle Fisher, Arthur R Brothman, Daniel M Berney, Julia E Reid, David Mesher, V O Speights, Elzbieta Stankiewicz, Christopher S Foster, Henrik Møller, Peter Scardino, Jorja D Warren, Jimmy Park, Adib Younus, Darl D Flake II, Susanne Wagner, Alexander Gutin, Jerry S Lanchbury, Steven Stone, on behalf of the Transatlantic Prostate Group*

- mRNA Signature of 31 Cell Cycle Progression (CCP) genes, 21 housekeepers
- low density array profiling

„The final signature consisted of 31 CCP genes (FOXM1, CDC20, CDKN3, CDC2, KIF11, KIAA0101, NUSAP1, CENPF, ASPM, BUB1B, RRM2, DLGAP5, BIRC5, KIF20A, PLK1, TOP2A, TK1, PBK, ASF1B, C18orf24, RAD54L, PTTG1, CDCA3, MCM10, PRC1, DTL, CEP55, RAD51, CENPM, CDCA8, and ORC6L).

These highly correlated genes were used to provide a robust and highly reproducible measurement of cell proliferation and were not intended to capture information related to other factors (eg, invasive potential).“

Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study

Lancet Oncol 2011; 12: 245–55

Jack Cuzick, Gregory P Swanson*, Gabrielle Fisher, Arthur R Brothman, Daniel M Berney, Julia E Reid, David Mesher, V O Speights, Elzbieta Stankiewicz, Christopher S Foster, Henrik Møller, Peter Scardino, Jorja D Warren, Jimmy Park, Adib Younus, Darl D Flake II, Susanne Wagner, Alexander Gutin, Jerry S Lanchbury, Steven Stone, on behalf of the Transatlantic Prostate Group*

RPE

	Final model			
	N	Hazard ratio (95% CI)	χ^2 (1 df)	p value
CCP score*	353	1·74 (1·39–2·17)	21·65	$3·3\times10^{-6}$
log(1+baseline PSA)	353	2·24 (1·71–2·93)	33·47	$7·2\times10^{-9}$
Gleason score (radical prost				
<7	230	1·00	..	..
7	108	1·35 (0·92–2·00)	7·57†	$5·9\times10^{-3}$
>7	15	2·69 (1·43–5·08)	..	..
Pathological T stage	353	1·32 (1·12–1·56)	10·30	$1·3\times10^{-3}$
Pathological grade	..	..	..	..
Positive surgical margins	353	1·89 (1·23–2·91)	8·61	$3·3\times10^{-3}$

TURP

	Final model			
	N	Hazard ratio (95% CI)	χ^2 (1 df)	p value
CCP score*	337	2·57 (1·93 to 3·43)	42·2	$8·2\times10^{-11}$
Gleason score				
<7	172	1·00	..	..
7	73	2·45 (1·09 to 5·48)	5·4†	0·02
>7	92	2·72 (1·22 to 6·08)	..	..
log(1+PSA) (ng/mL)	337	1·84 (1·46 to 2·32)	29·3	$6·2\times10^{-8}$
log(1+[10×Ki67]) (%)	..	..	..	..
Cancer extent (%)‡	..	..	..	..

df=degrees of freedom. CCP 5·4, and 7·1 in the univariate analysis, multivariate analysis, and final model, respectivel were 9·4, 5·4, and 7·2, respectively). ‡Hazard ratio for 10% increase in cancer extent.

Table 2: **Summary of stat**

Prognostic Value of the Cell Cycle Progression Score in Patients with Prostate Cancer: A Systematic Review and Meta-analysis

Silvia Sommariva [a,*], *Rosanna Tarricone* [a,b], *Massimo Lazzeri* [c], *Walter Ricciardi* [d], *Francesco Montorsi* [c]

Eur Urol (2015), http://dx.doi.org/10.1016/j.eururo.2014.11.038

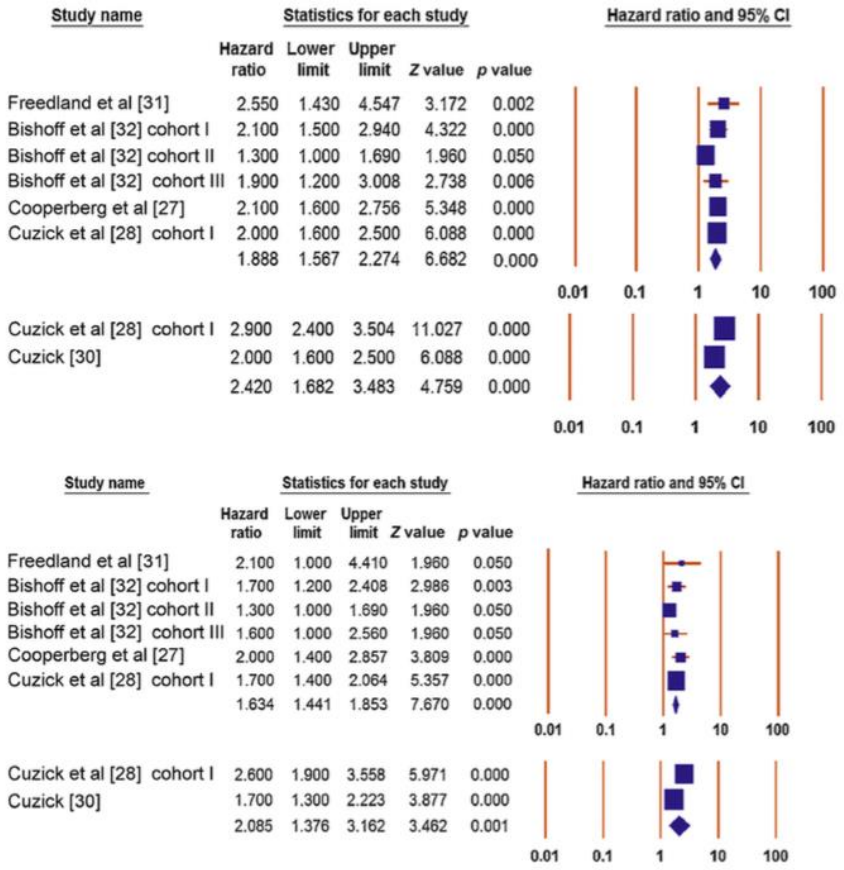


Fig. 2 – Meta-analysis of univariate and ivariate models by endpoint biochemical recurrence (BCR) [27,28,30,31] and disease-specific mortality (DSM) [28,33]): random-effects model. CI = confidence interval.

The pooled hazard ratio for biochemical recurrence per 1-unit increase in the CCP score was 1.88 in a univariate model and 1.63 in a multivariate model.

Four studies showed that CCP testing can impact the decisions of physicians regarding treatment, and potentially lead to a decrease in surgical interventions for low-risk patients.

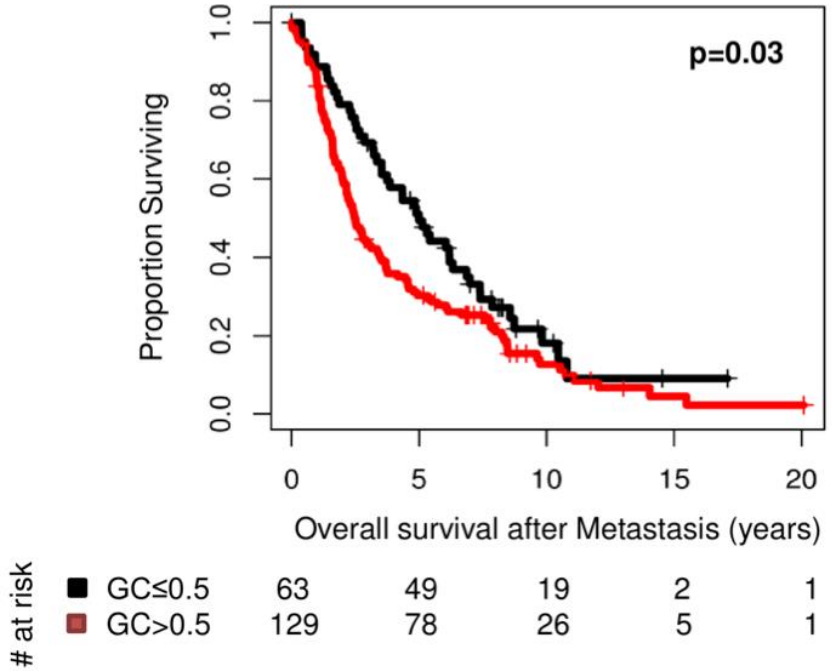
OPEN ACCESS Freely available online

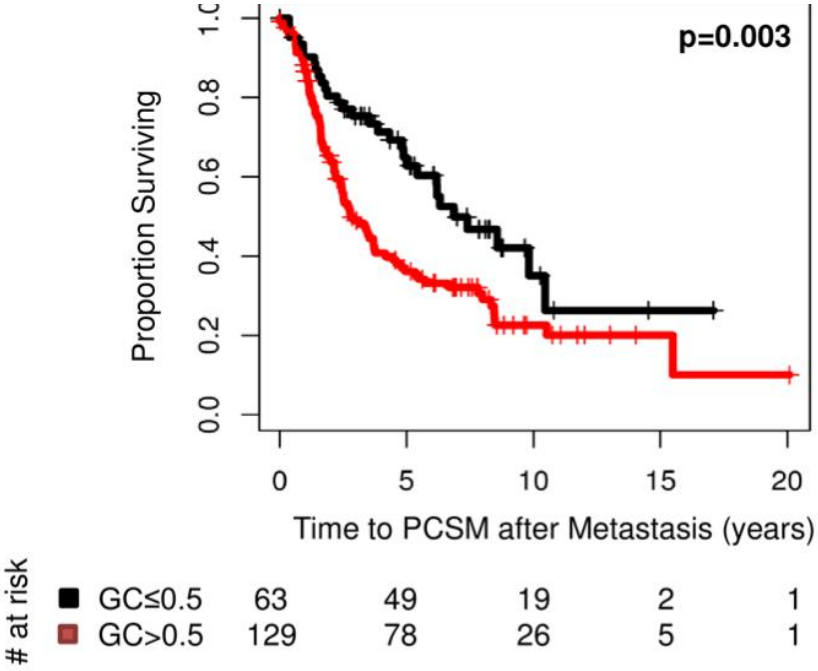
PLOS ONE

Discovery and Validation of a Prostate Cancer Genomic Classifier that Predicts Early Metastasis Following Radical Prostatectomy

Nicholas Erho[1☯], Anamaria Crisan[1☯], Ismael A. Vergara[1], Anirban P. Mitra[2], Mercedeh Ghadessi[1], Christine Buerki[1], Eric J. Bergstralh[3], Thomas Kollmeyer[4], Stephanie Fink[4], Zaid Haddad[1], Benedikt Zimmermann[1], Thomas Sierocinski[1], Karla V. Ballman[3], Timothy J. Triche[1,2], Peter C. Black[5], R. Jeffrey Karnes[6], George Klee[4], Elai Davicioni[1¶], Robert B. Jenkins[4¶*]

RPE Cohort, n=545, training/test set, GeneChips (Affymetrix), 22 markers





Molecular Prognostic Tests

	Prolaris	Oncotype DX prostate cancer Assay	Decipher	....
Provider	Myriad Genetics	Genomic Health	Genomic Dx	
Type of Assay	Proliferation Signature, 31 CCP genes	17 genes covering proliferation, desmoplasia, androgen signalling, controls	22 genes including ncRNA	
Technique	LDA-qPCR	qPCR	qPCR	
Central Lab	yes/(no)	yes	yes	
Indication	Post RPE, WW, RTx, Bx/RPE	Bx, low risk patients	Post RPE	
Prospectively validated in AS cohort	no	no	no	

...but how do we deal with differences?

OPEN ACCESS Freely available online

PLOS ONE

Comparison of EndoPredict and Oncotype DX Test Results in Hormone Receptor Positive Invasive Breast Cancer

Zsuzsanna Varga[1]*, Peter Sinn[2], Florian Fritzsche[3], Arthur von Hochstetter[3], Aurelia Noske[1], Peter Schraml[1], Christoph Tausch[4], Andreas Trojan[4], Holger Moch[1]

1 Institute of Surgical Pathology, University Hospital Zurich, Zurich, Switzerland, **2** Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany, **3** Pathology Institute Enge, Zurich, Switzerland, **4** Breast Cancer Center Seefeld, Zurich, Switzerland

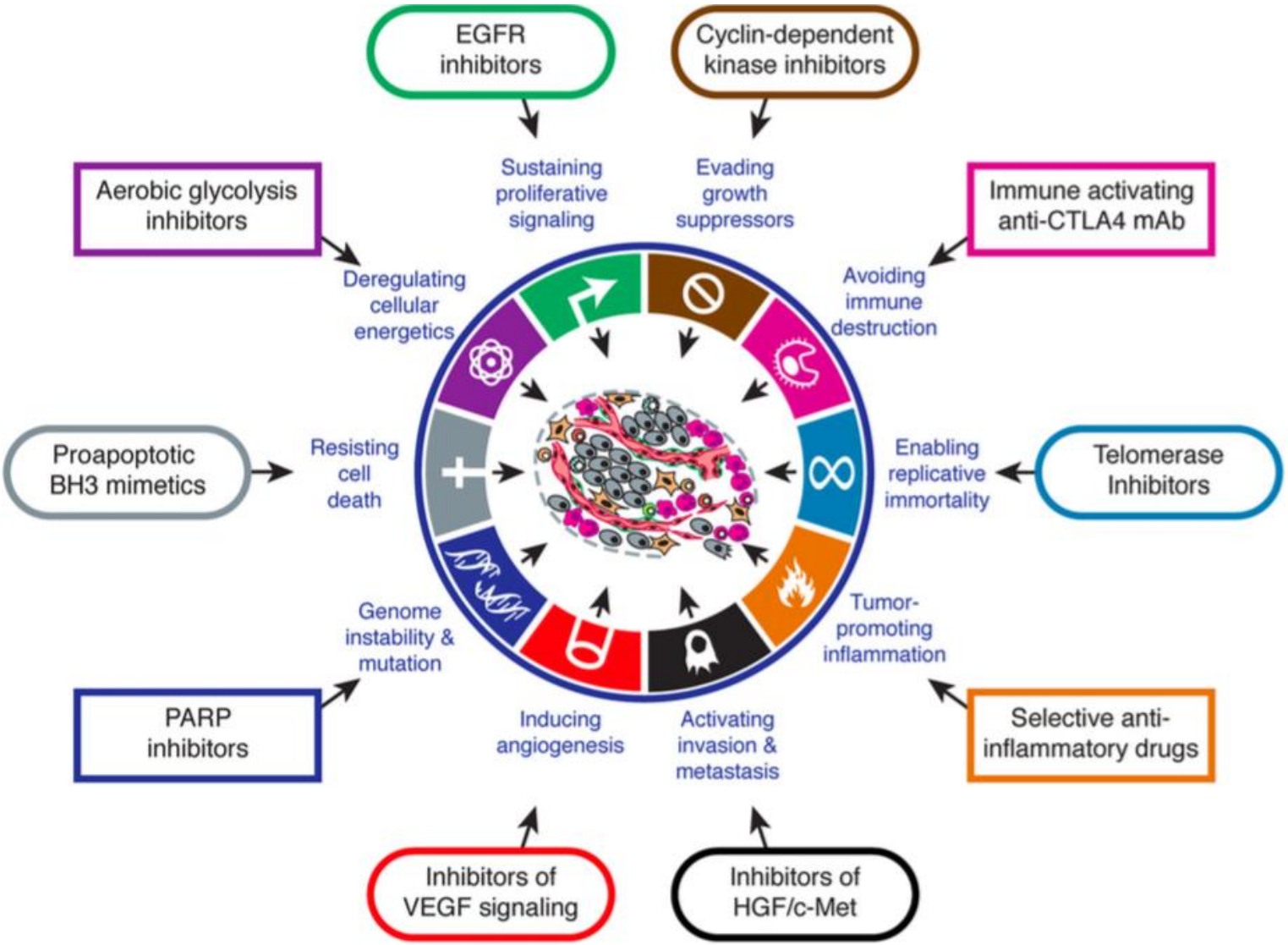
Table 3. Comparison of EP score and Recurrence score (RS). RS in two tiered system: low vs. intermediate+high risk.

n = 34		Recurrence score (RS) (two tiered)	
		Low risk	**High+Intermediate risk**
EP score	Low risk	9 (26%)	2 (6%)
	High risk	6 (18%)	17 (50%)

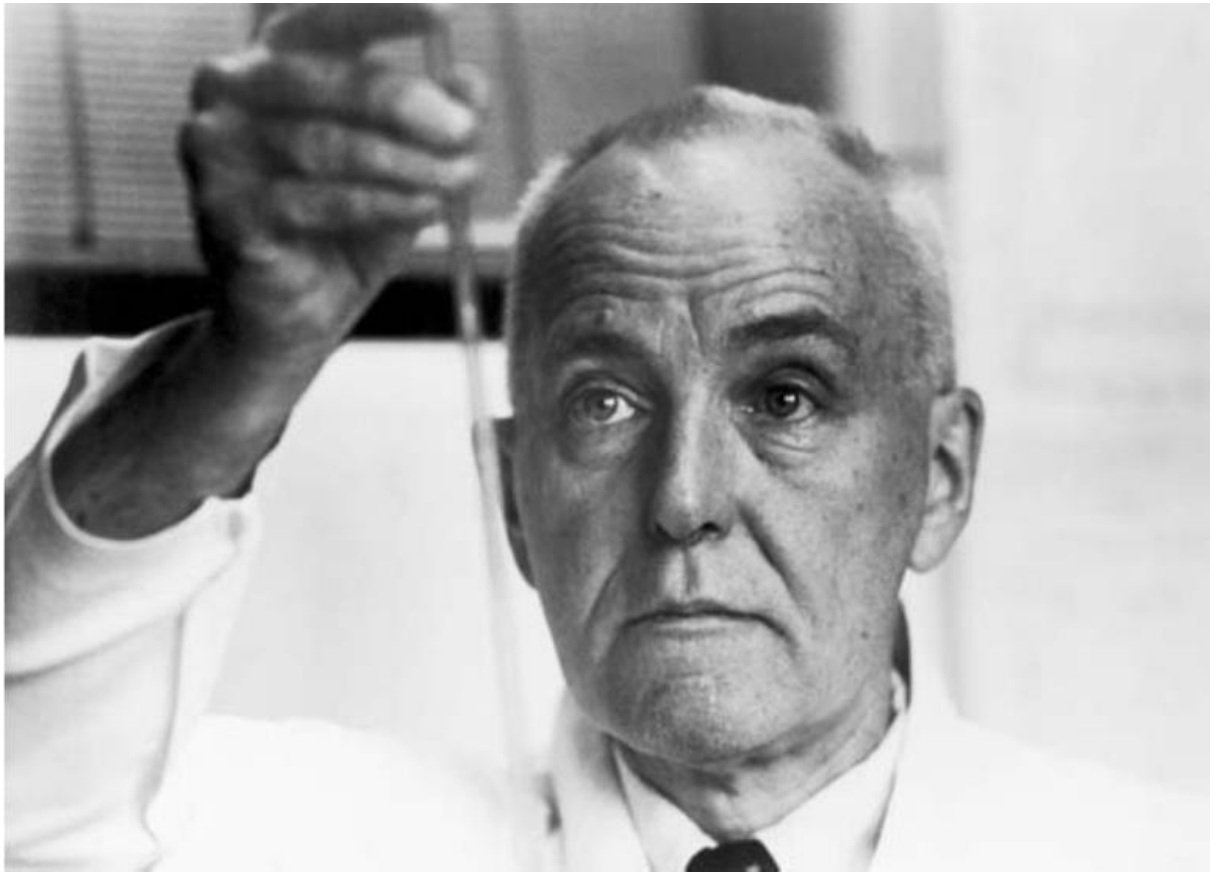
Topics:

1. Diagnostic IHC
2. Prognostic IHC
3. Prognostic molecular signatures
4. **Molecular pathology, targeted therapy and predictive pathology in prostate cancer**

2011 Hallmarks of Cancer: new Targets



Charles Hugins: Father of of ADT



C. Huggins, R.E. Stevens Jr., C.V. Hodges.
Studies on prostate cancer. I. The effect of castration, of oestrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Arch Surg. 1941;43:209*

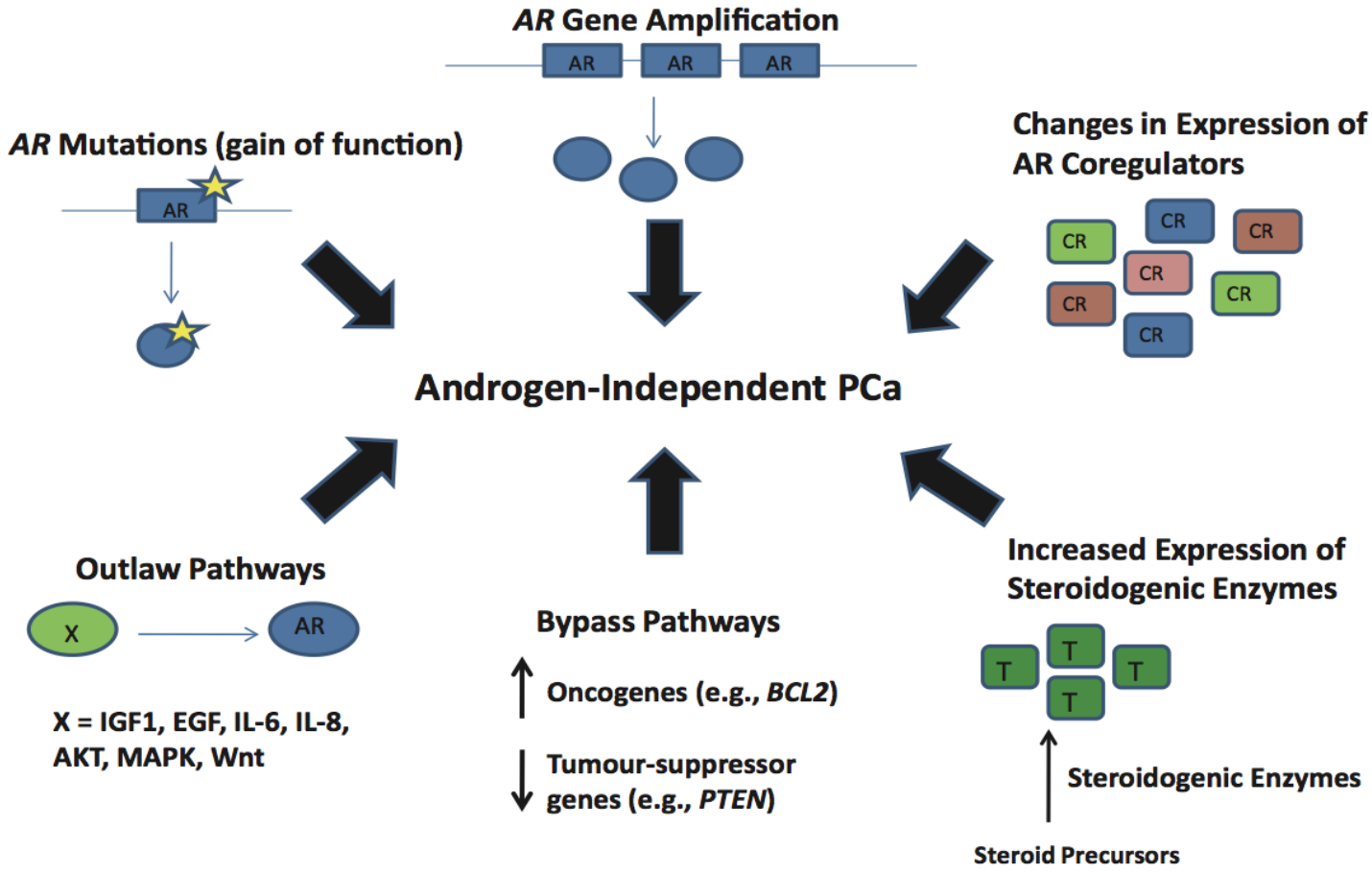


Fig. 3. Mechanisms of androgen independence in prostate cancers.

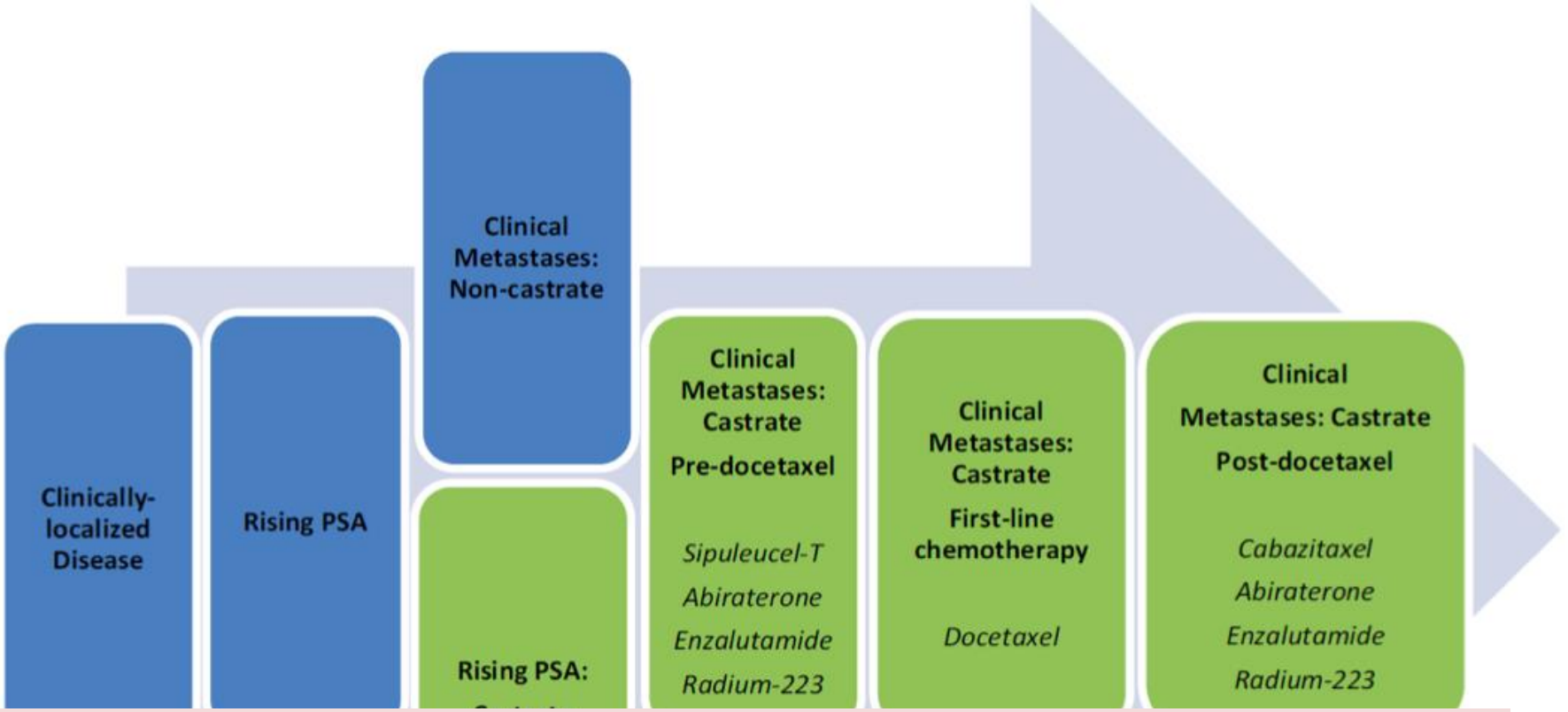
AIPC can arise through many cellular changes. The AR-signaling pathway is by far the most commonly studied pathway in the context of AIPC. This pathway has been shown to be aberrantly regulated at various levels, including gene amplifications, mutations, and changes in AR coregulators or steroidogenic enzymes. The AR protein has also been shown to be activated in a ligand-independent manner via outlaw pathways by a number of different proteins. Various AR-independent bypass mechanisms/pathways have also been implicated in the development of AIPC. PCa, prostate cancer; CR, coregulator; T, testosterone; *BCL2*, B-cell CLL/lymphoma 2; *PTEN*, phosphatase and tensin homolog.

Saraon et al., Clin Chem. 2011 Oct;57(10):1366-75.

New compounds and mode of action

- **Arbiraterone** – CYP17 inhibitor (inhibiting AR signalling)
- **Enzalutamide** – anti-androgen (inhibiting AR signalling)
- **Sipuleucel-T** – Immunotherapy (fortified dendritic cells)
- **Ipilimumab** – targeting CTLA-4
- **Radium-223** – Radionulide to target bone mets
- **Carbazitaxel** – Conventional chemoTx

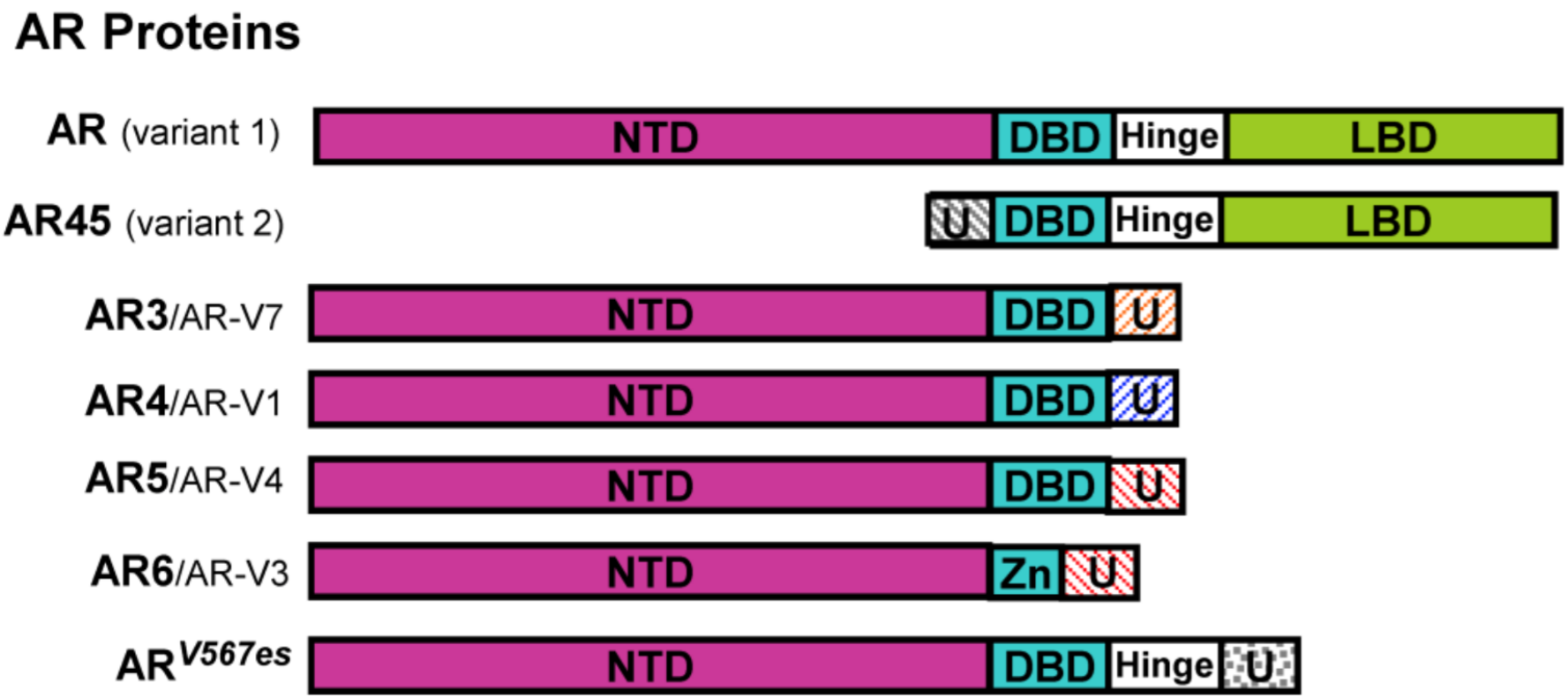
Treatment strategies for CRPC



1) New *predictive markers* for response to new drugs are needed

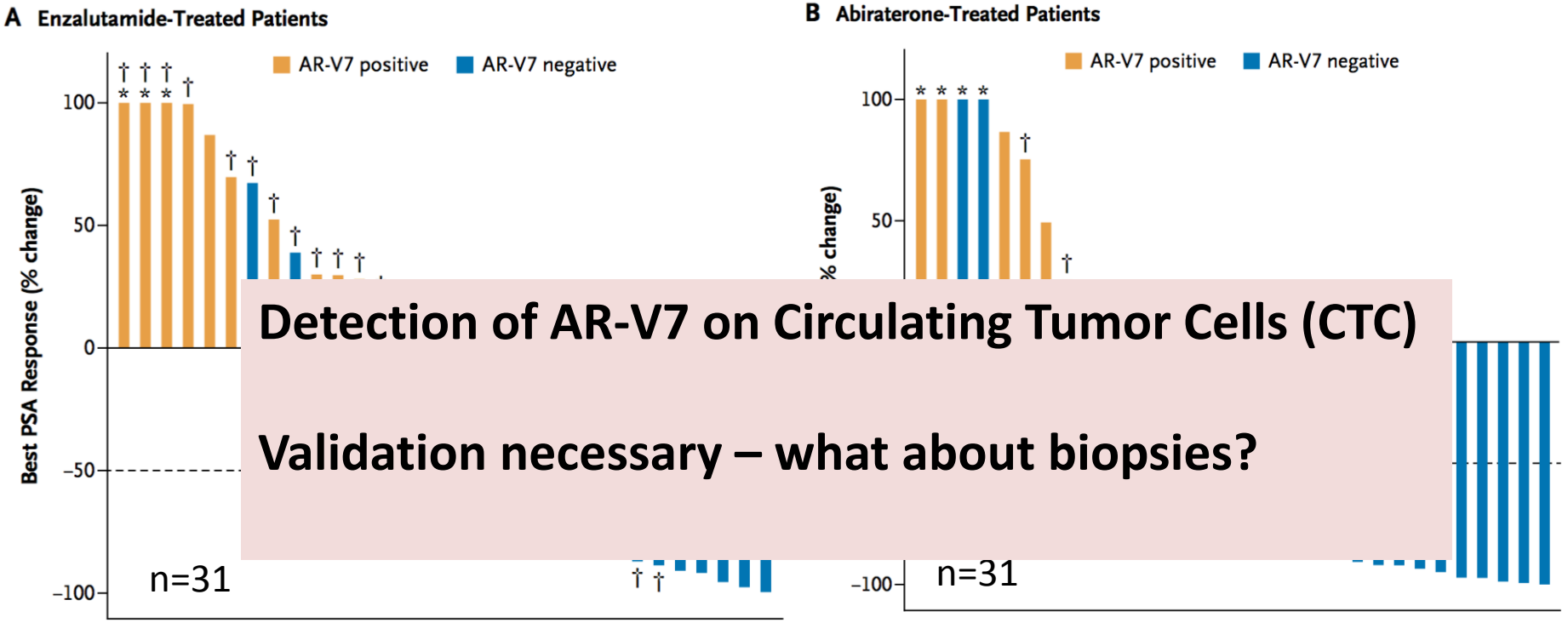
2) Re-biopsies at progressed disease stages may become important

Androgen Receptor Variants:



AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer

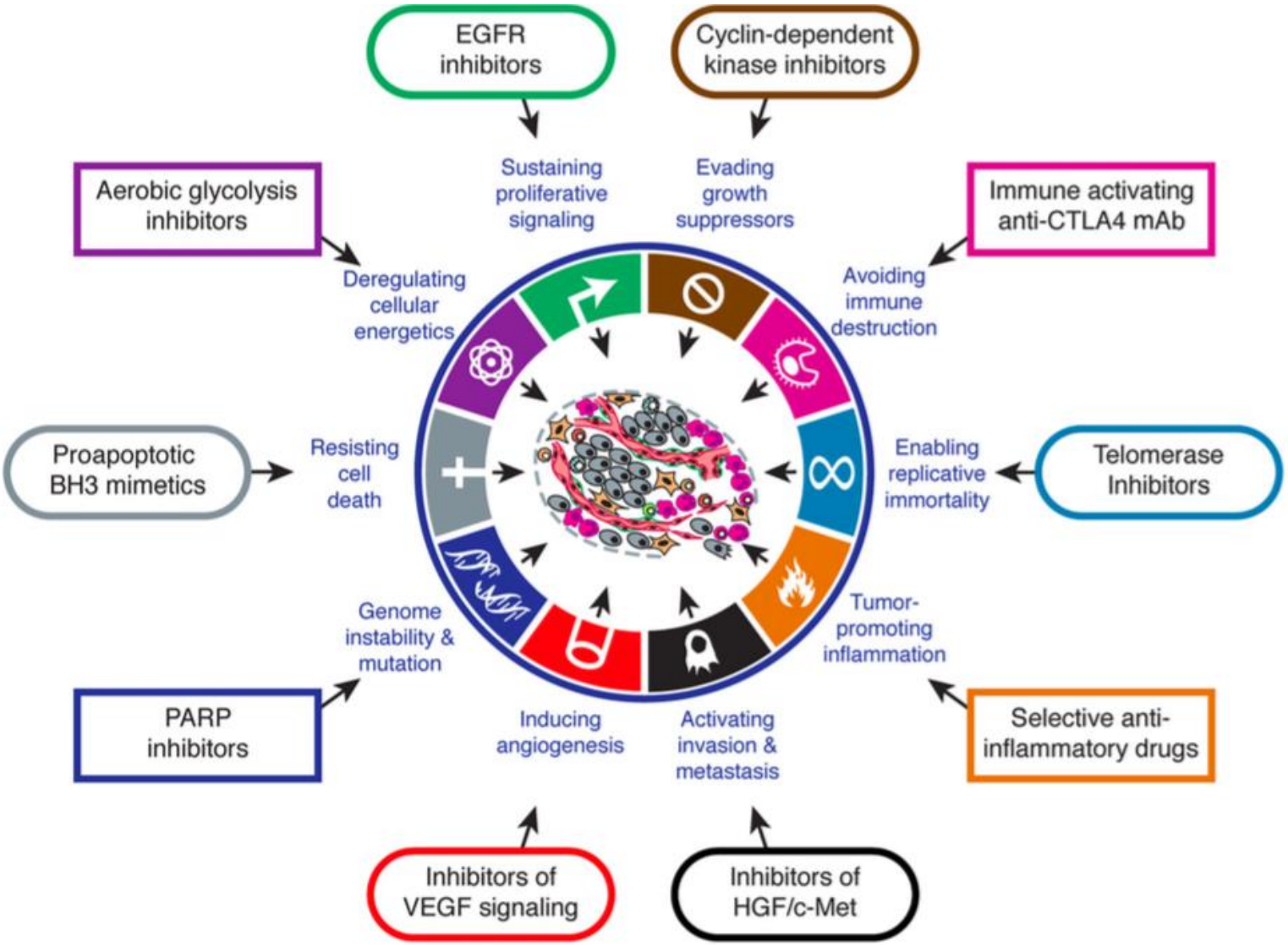
Emmanuel S. Antonarakis, M.D., Changxue Lu, Ph.D., Hao Wang, Ph.D., Brandon Luber, Sc.M., Mary Nakazawa, M.H.S., Jeffrey C. Roeser, B.S., Yan Chen, Ph.D., Tabrez A. Mohammad, Ph.D., Yidong Chen, Ph.D., Helen L. Fedor, B.S., Tamara L. Lotan, M.D., Qizhi Zheng, M.D., Angelo M. De Marzo, M.D., Ph.D., John T. Isaacs, Ph.D., William B. Isaacs, Ph.D., Rosa Nadal, M.D., Channing J. Paller, M.D., Samuel R. Denmeade, M.D., Michael A. Carducci, M.D., Mario A. Eisenberger, M.D., and Jun Luo, Ph.D.

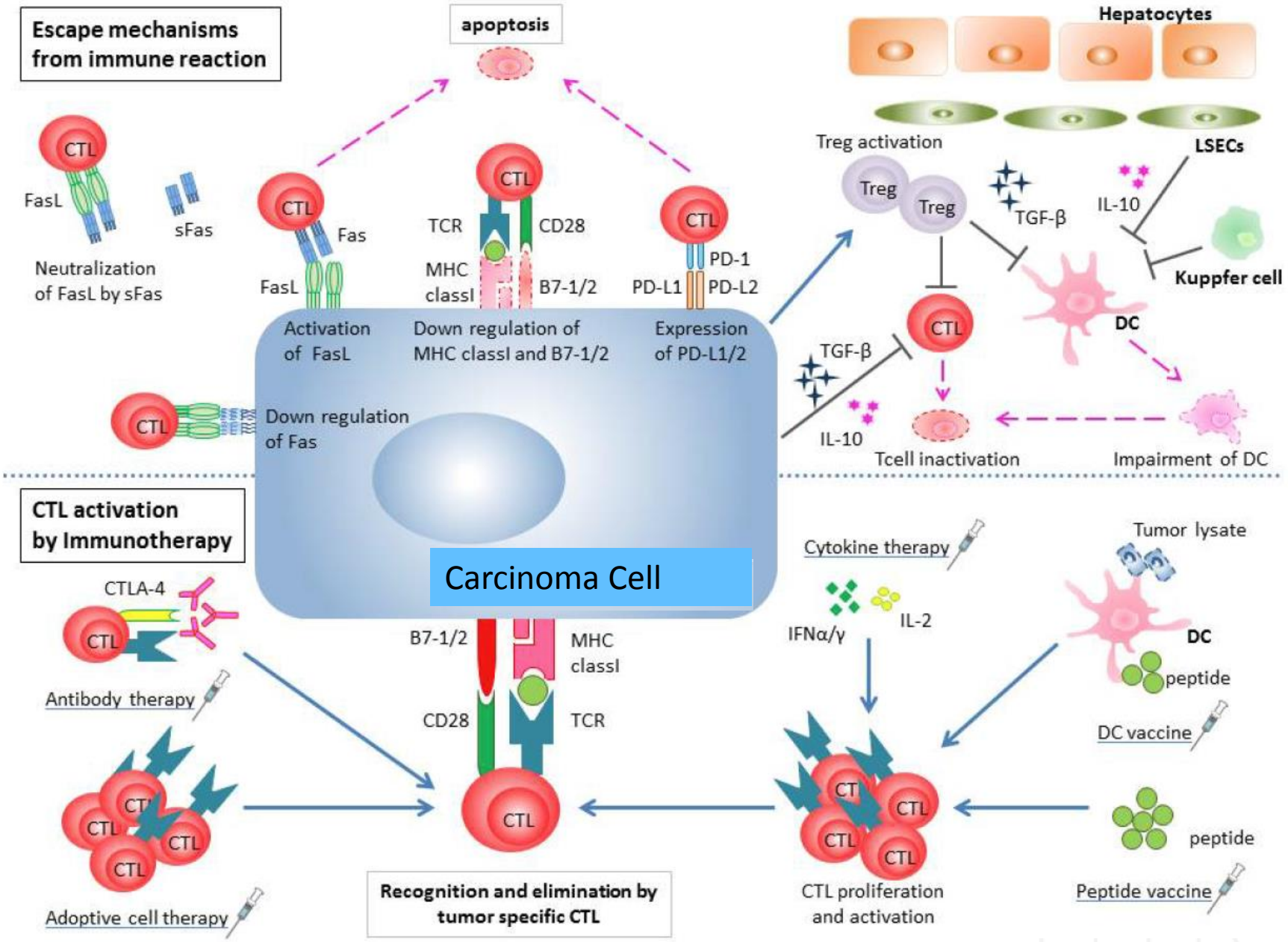


Detection of AR-V7 on Circulating Tumor Cells (CTC)

Validation necessary – what about biopsies?

2011 Hallmarks of Cancer: new Targets





http://dx.doi.org/10.5772/54594

Immunotherapy: PD1- Tumour-Interaction

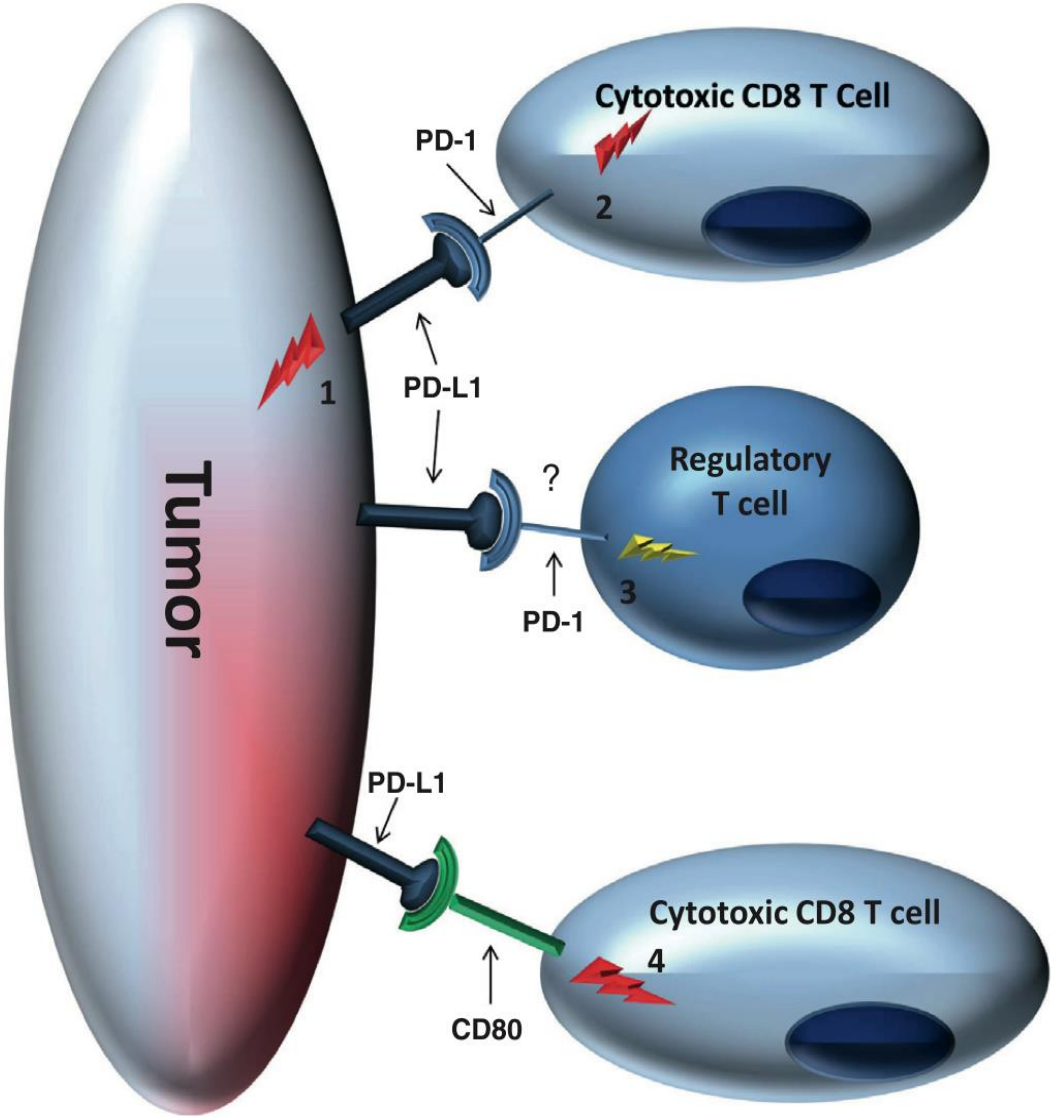


Figure 2. Mechanisms of PD-L1 driven tumor evasion of immune attack.

N Engl J Med 2012;366:2455-65.

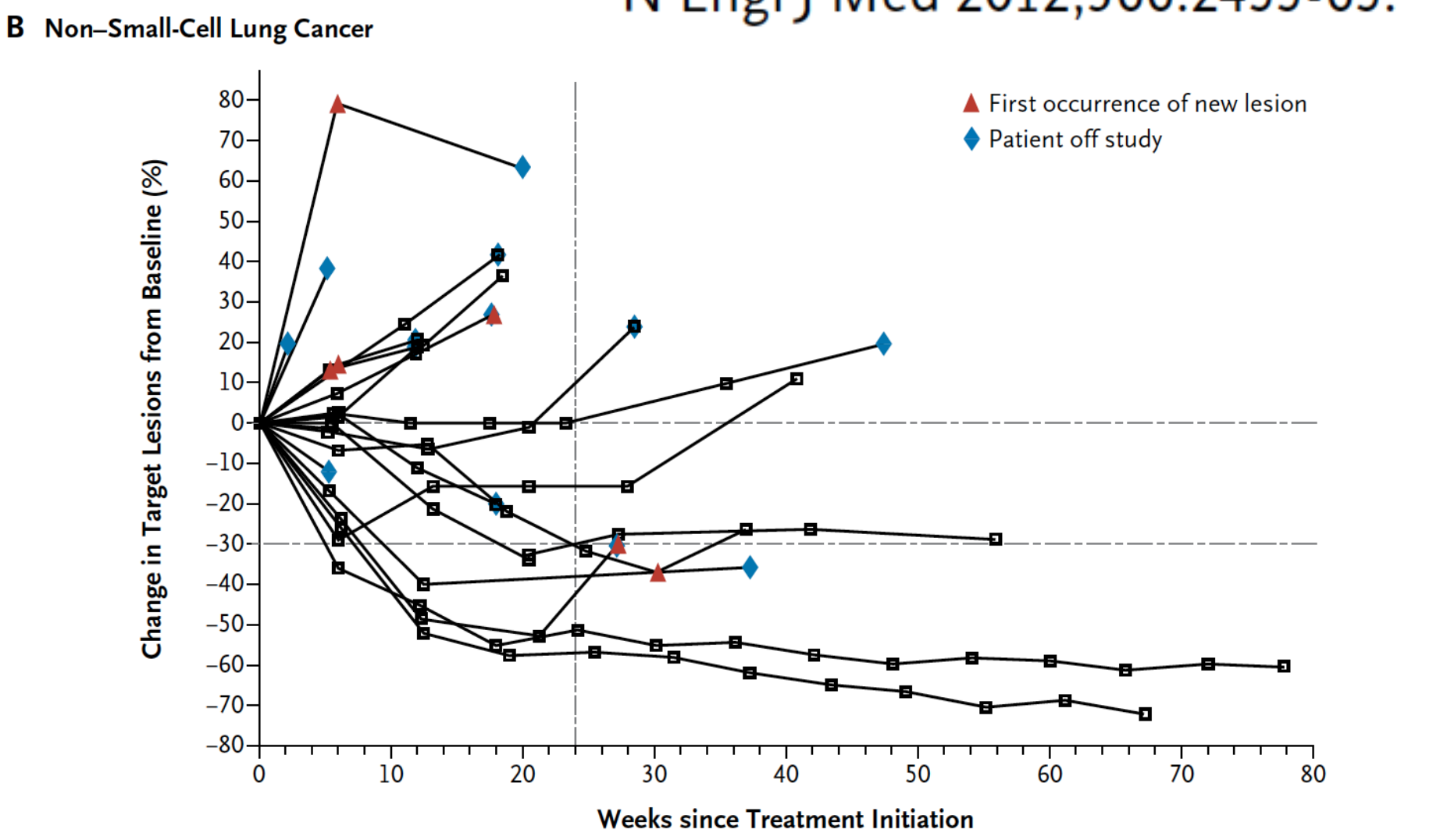


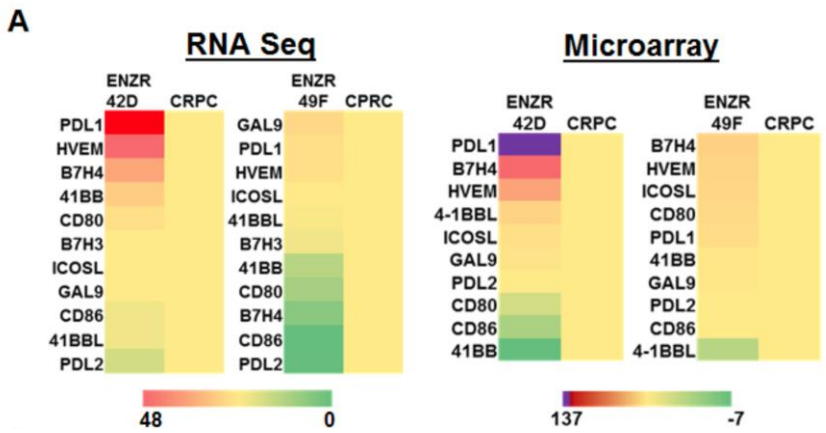
Figure 1. Activity of Anti–PD-L1 Antibody in Patients with Advanced Melanoma and Non–Small-Cell Lung Cancer.

Shown is the tumor burden (assessed as the longest linear dimension) over time in patients with melanoma (Panel A) and non–small-cell lung cancer (Panel B) who received 10 mg of anti–PD-L1 antibody per kilogram of body weight.

PD-L1 is highly expressed in Enzalutamide resistant prostate cancer

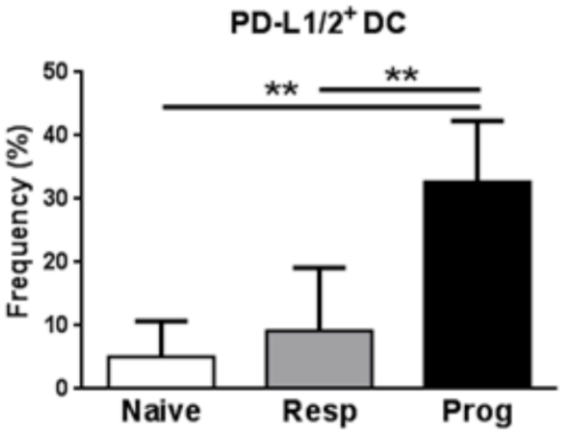
Jennifer L. Bishop[1], Alexander Sio[1], Arkhjamil Angeles[1], Morgan E. Roberts[2], Arun A. Azad[3], Kim N. Chi[3] and Amina Zoubeidi[1,4]

[1] Vancouver Prostate Centre, Vancouver, BC, Canada



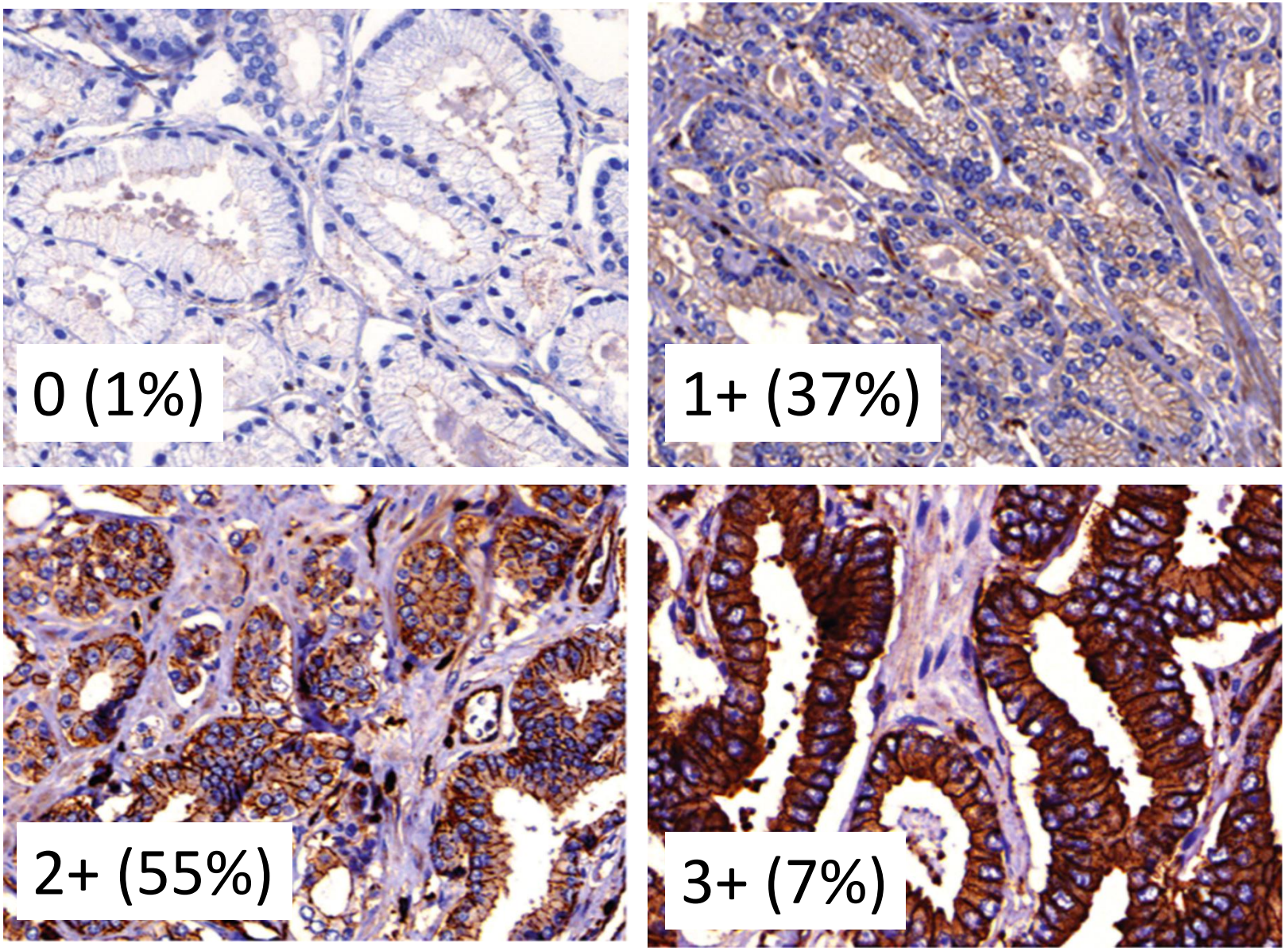
Higher PD-L1 Levels in ENZA-resistant Prostate cancer cells

Patients with disease progression Have higher PD-L-levels on DCs



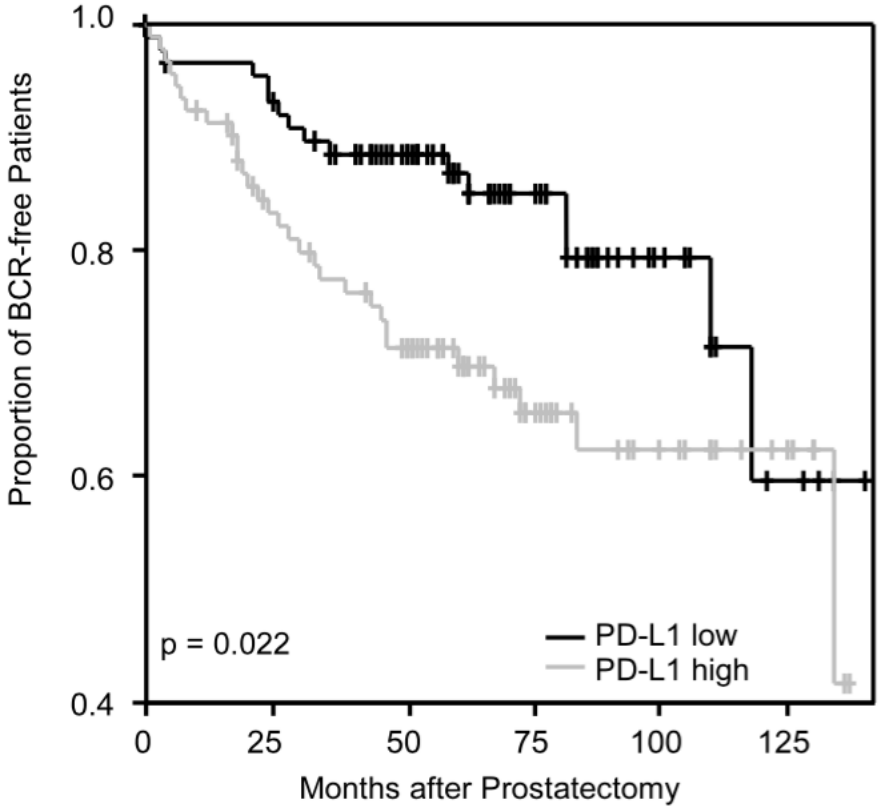
Oncotarget. 2015 Jan 1;6(1):234-42.

PD-L1 Expression in PCa

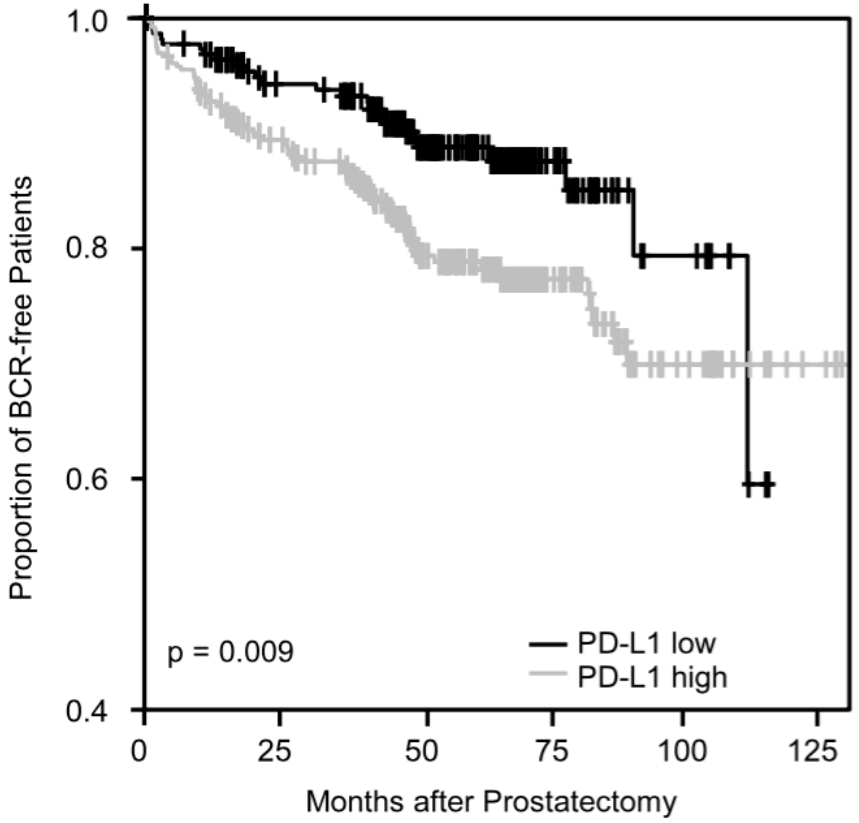


Prognostic value of PD-L1:

Training cohort (n=209)



Test cohort (n=611)

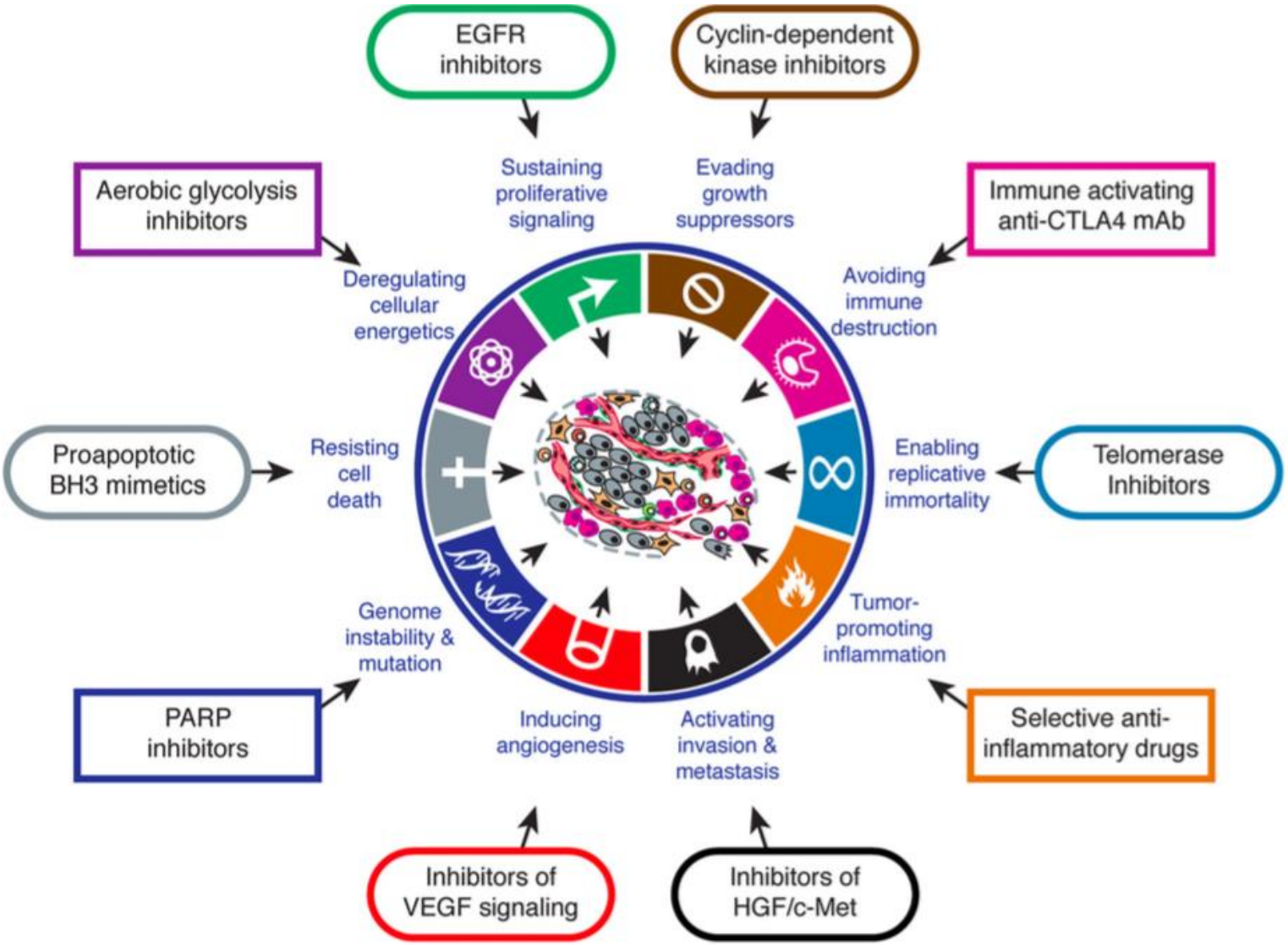


Clin Cancer Res. 2015 Nov 16

PD-L1 in Pca – Open Questions

- is PD-L1 prognostic in WW/AS cohorts?
- is PD-L1 expressed in CRPC?
- may this be therapeutically useful ?
- ...is this marker predictive for PD1/PD-L1 Tx?

2011 Hallmarks of Cancer: new Targets

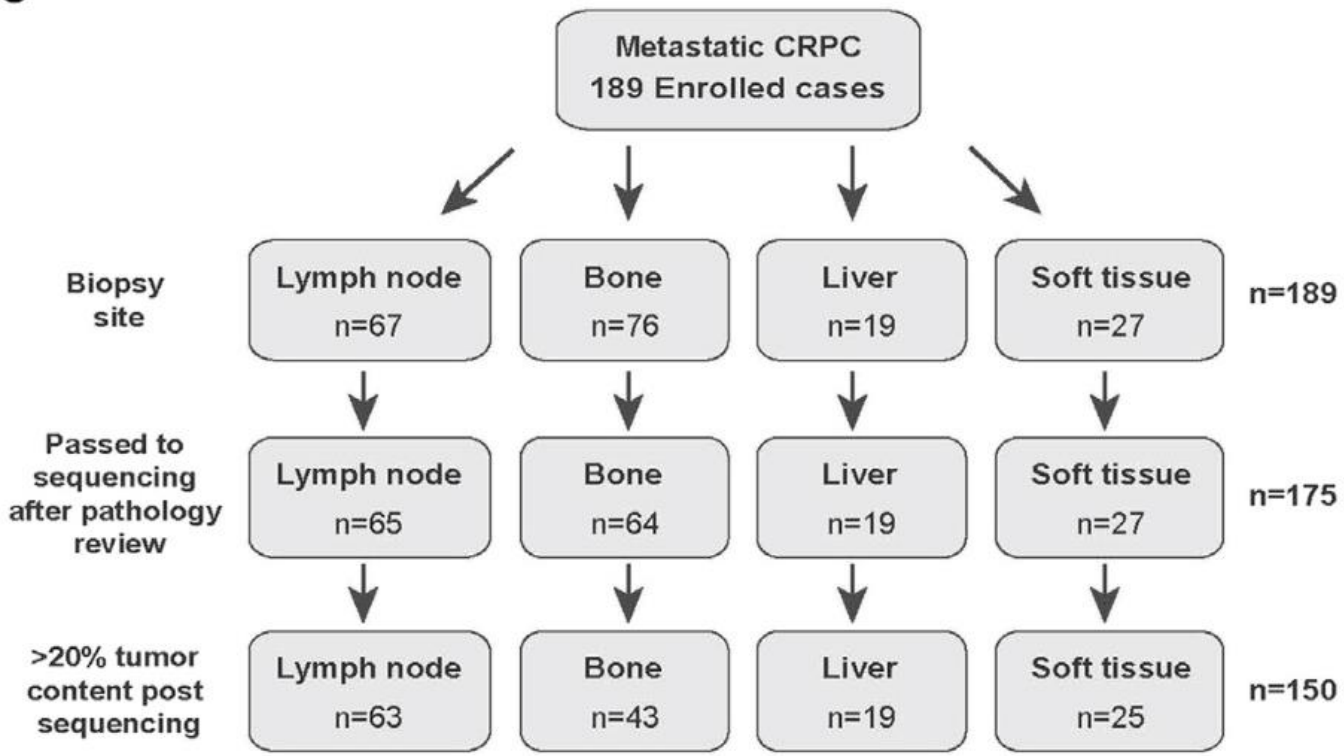


Integrative Clinical Genomics of Advanced Prostate Cancer

Cell *161*, 1215–1228, May 21, 2015

Dan Robinson,[1,2,43] Eliezer M. Van Allen,[3,4,43] Yi-Mi Wu,[1,2] Nikolaus Schultz,[5,40] Robert J. Lonigro,[1] Juan-Miguel Mosquera,[6,7,8,38] Bruce Montgomery,[9,10] Mary-Ellen Taplin,[3] Colin C. Pritchard,[26] Gerhardt Attard,[11,12] Himisha Beltran,[7,8,13,38] Wassim Abida,[14,20] Robert K. Bradley,[9] Jake Vinson,[15] Xuhong Cao,[1,42] Pankaj Vats,[1] Lakshmi P. Kunju,[1,2,17] Maha Hussain,[16,17,18] Felix Y. Feng,[1,17,19] Scott A. Tomlins,[1,2,17,18] Kathleen A. Cooney,[16,17,18] David C. Smith,[16,17,18] Christine Brennan,[1] Javed Siddiqui,[1] Rohit Mehra,[1,2] Yu Chen,[13,14,20] Dana E. Rathkopf,[13,20] Michael J. Morris,[13,20] Stephen B. Solomon,[21] Jeremy C. Durack,[21] Victor E. Reuter,[22] Anuradha Gopalan,[22] Jianjiong Gao,[40] Massimo Loda,[3,4,23,39] Rosina T. Lis,[3,23] Michaela Bowden,[3,23,39] Stephen P. Balk,[24] Glenn Gaviola,[25] Carrie Sougnez,[4] Manaswi Gupta,[4] Evan Y. Yu,[10] Elahe A. Mostaghel,[9,10] Heather H. Cheng,[9,10] Hyojeong Mulcahy,[27] Lawrence D. True,[28] Stephen R. Plymate,[10] Heidi Dvinge,[9] Roberta Ferraldeschi,[11,12] Penny Flohr,[11,12] Susana Miranda,[11,12] Zafeiris Zafeiriou,[11,12] Nina Tunariu,[11,12] Joaquin Mateo,[11,12] Raquel Perez-Lopez,[11,12] Francesca Demichelis,[7,29] Brian D. Robinson,[6,7,8,38] Marc Schiffman,[7,31,38] David M. Nanus,[7,8,13,38] Scott T. Tagawa,[7,8,13,38] Alexandros Sigaras,[7,30,32] Kenneth W. Eng,[7,30,32] Olivier Elemento,[30] Andrea Sboner,[6,7,30,38] Elisabeth I. Heath,[33,34] Howard I. Scher,[13,20] Kenneth J. Pienta,[35] Philip Kantoff,[3,44] Johann S. de Bono,[11,12,44] Mark A. Rubin,[6,7,8,38,44] Peter S. Nelson,[10,36,37,38,44] Levi A. Garraway,[3,4,44] Charles L. Sawyers,[14,41,44,*] and Arul M. Chinnaiyan[1,2,17,18,42,44,*]

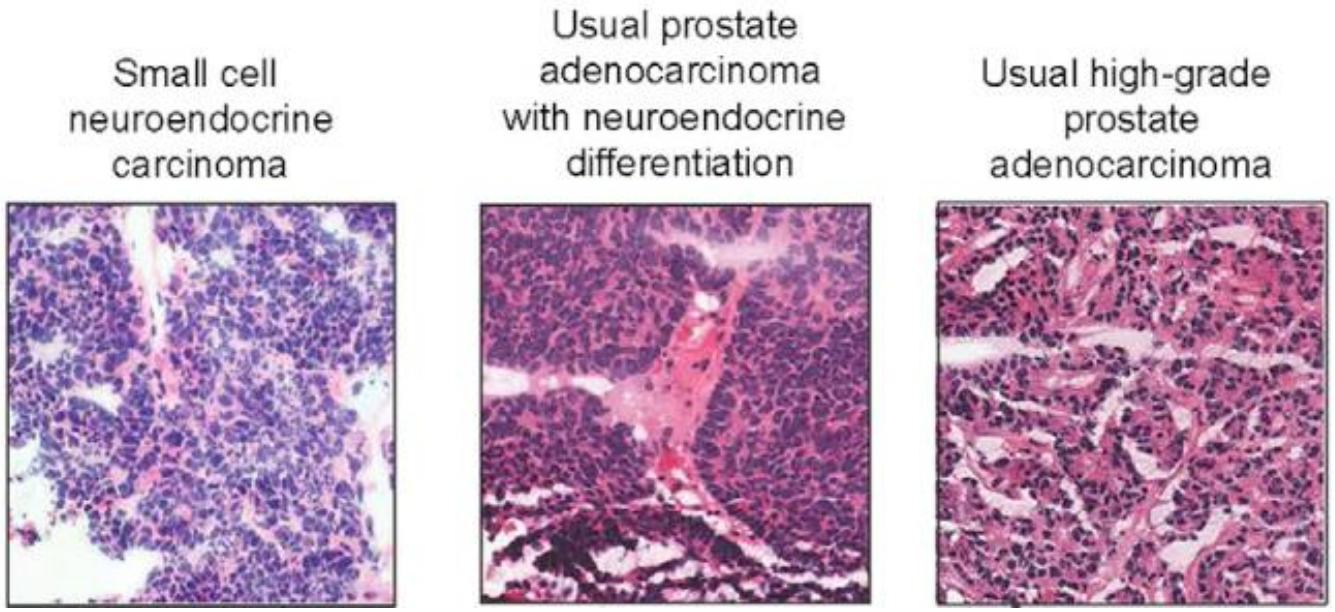
C



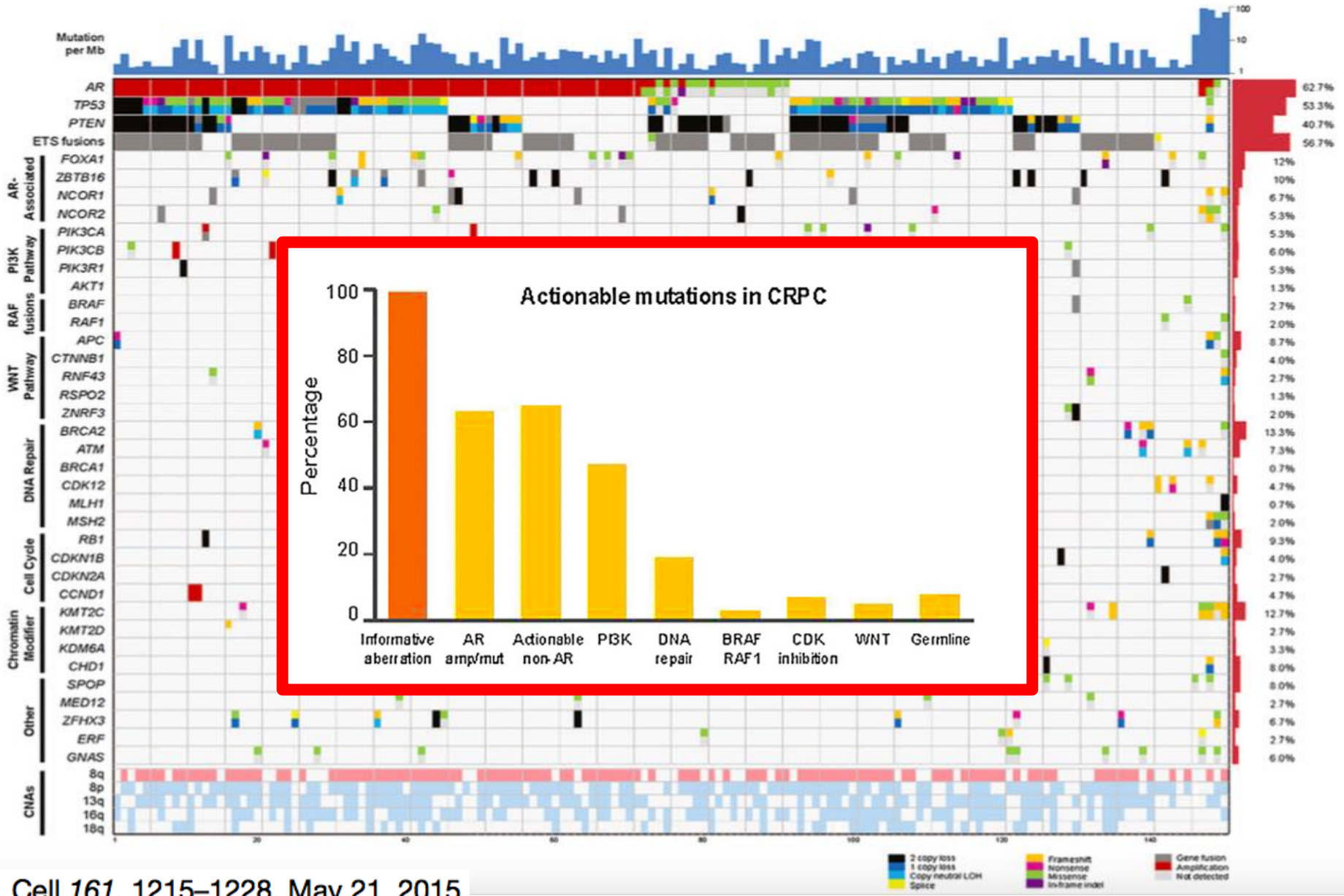
Integrative Clinical Genomics of Advanced Prostate Cancer

Cell *161*, 1215–1228, May 21, 2015

Dan Robinson,[1,2,43] Eliezer M. Van Allen,[3,4,43] Yi-Mi Wu,[1,2] Nikolaus Schultz,[5,40] Robert J. Lonigro,[1] Juan-Miguel Mosquera,[6,7,8,38] Bruce Montgomery,[9,10] Mary-Ellen Taplin,[3] Colin C. Pritchard,[26] Gerhardt Attard,[11,12] Himisha Beltran,[7,8,13,38] Wassim Abida,[14,20] Robert K. Bradley,[9] Jake Vinson,[15] Xuhong Cao,[1,42] Pankaj Vats,[1] Lakshmi P. Kunju,[1,2,17] Maha Hussain,[16,17,18] Felix Y. Feng,[1,17,19] Scott A. Tomlins,[1,2,17,18] Kathleen A. Cooney,[16,17,18] David C. Smith,[16,17,18] Christine Brennan,[1] Javed Siddiqui,[1] Rohit Mehra,[1,2] Yu Chen,[13,14,20] Dana E. Rathkopf,[13,20] Michael J. Morris,[13,20] Stephen B. Solomon,[21] Jeremy C. Durack,[21] Victor E. Reuter,[22] Anuradha Gopalan,[22] Jianjiong Gao,[40] Massimo Loda,[3,4,23,39] Rosina T. Lis,[3,23] Michaela Bowden,[3,23,39] Stephen P. Balk,[24] Glenn Gaviola,[25] Carrie Sougnez,[4] Manaswi Gupta,[4] Evan Y. Yu,[10] Elahe A. Mostaghel,[9,10] Heather H. Cheng,[9,10] Hyojeong Mulcahy,[27] Lawrence D. True,[28] Stephen R. Plymate,[10] Heidi Dvinge,[9] Roberta Ferraldeschi,[11,12] Penny Flohr,[11,12] Susana Miranda,[11,12] Zafeiris Zafeiriou,[11,12] Nina Tunariu,[11,12] Joaquin Mateo,[11,12] Raquel Perez-Lopez,[11,12] Francesca Demichelis,[7,29] Brian D. Robinson,[6,7,8,38] Marc Schiffman,[7,31,38] David M. Nanus,[7,8,13,38] Scott T. Tagawa,[7,8,13,38] Alexandros Sigaras,[7,30,32] Kenneth W. Eng,[7,30,32] Olivier Elemento,[30] Andrea Sboner,[6,7,30,38] Elisabeth I. Heath,[33,34] Howard I. Scher,[13,20] Kenneth J. Pienta,[35] Philip Kantoff,[3,44] Johann S. de Bono,[11,12,44] Mark A. Rubin,[6,7,8,38,44] Peter S. Nelson,[10,36,37,38,44] Levi A. Garraway,[3,4,44] Charles L. Sawyers,[14,41,44,*] and Arul M. Chinnaiyan[1,2,17,18,42,44,*]

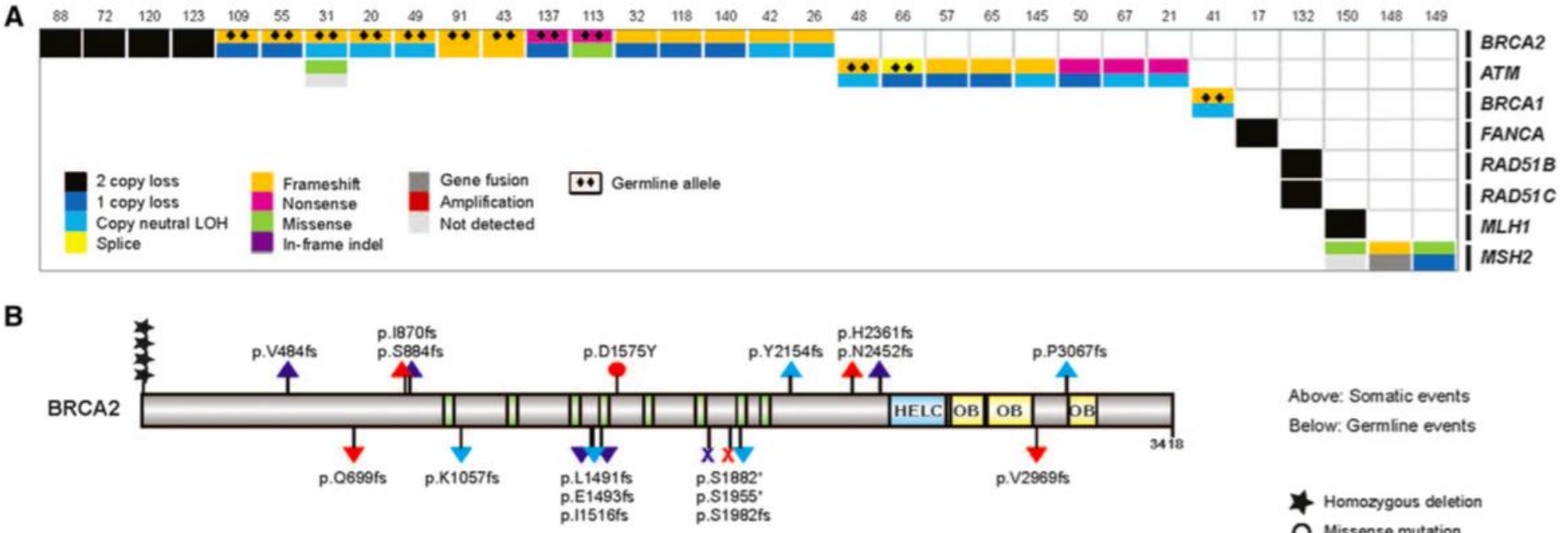


Overview of Molecular Alterations in CRPC



Cell *161*, 1215–1228, May 21, 2015

Overview of Molecular Alterations in CRPC



Additionally, biallelic inactivation of *BRCA2*, *BRCA1*, or *ATM* was observed in nearly 20% of affected individuals. Previous work in other cancer types suggests that these affected individuals may benefit from PARP inhibitors (Fong et al., 2009;

Cell *161*, 1215–1228, May 21, 2015

The NEW ENGLAND JOURNAL of MEDICINE

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

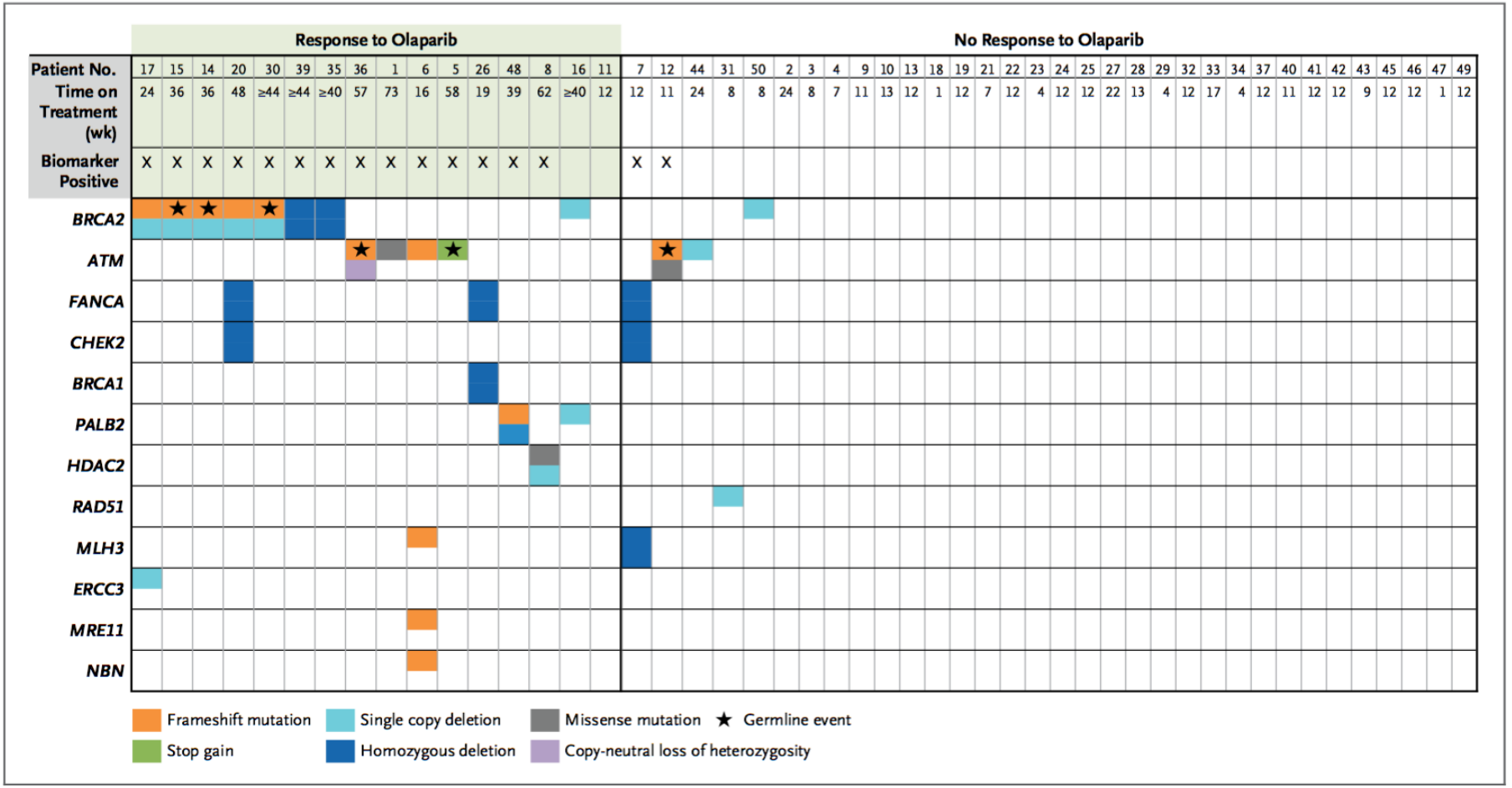
DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

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

50 metastic CRPC cases, post Docetaxel (+Abi/Enza)

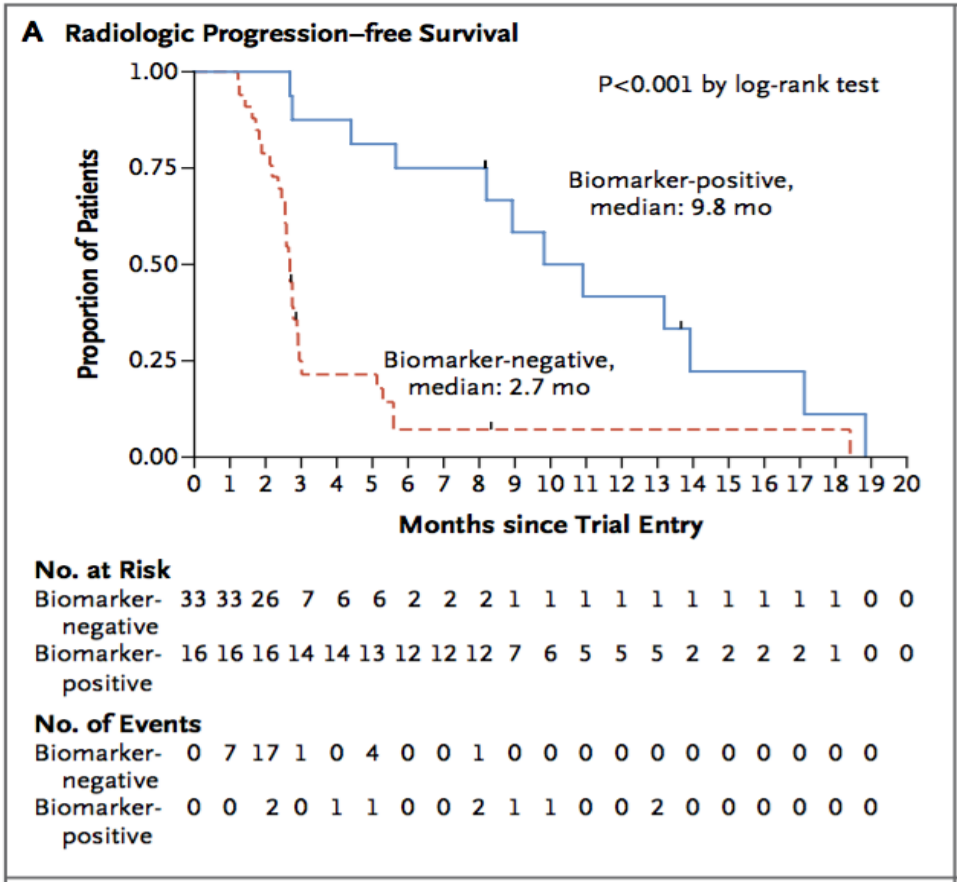
phase 2 trial: olaparib tablets, 400 mg bd.

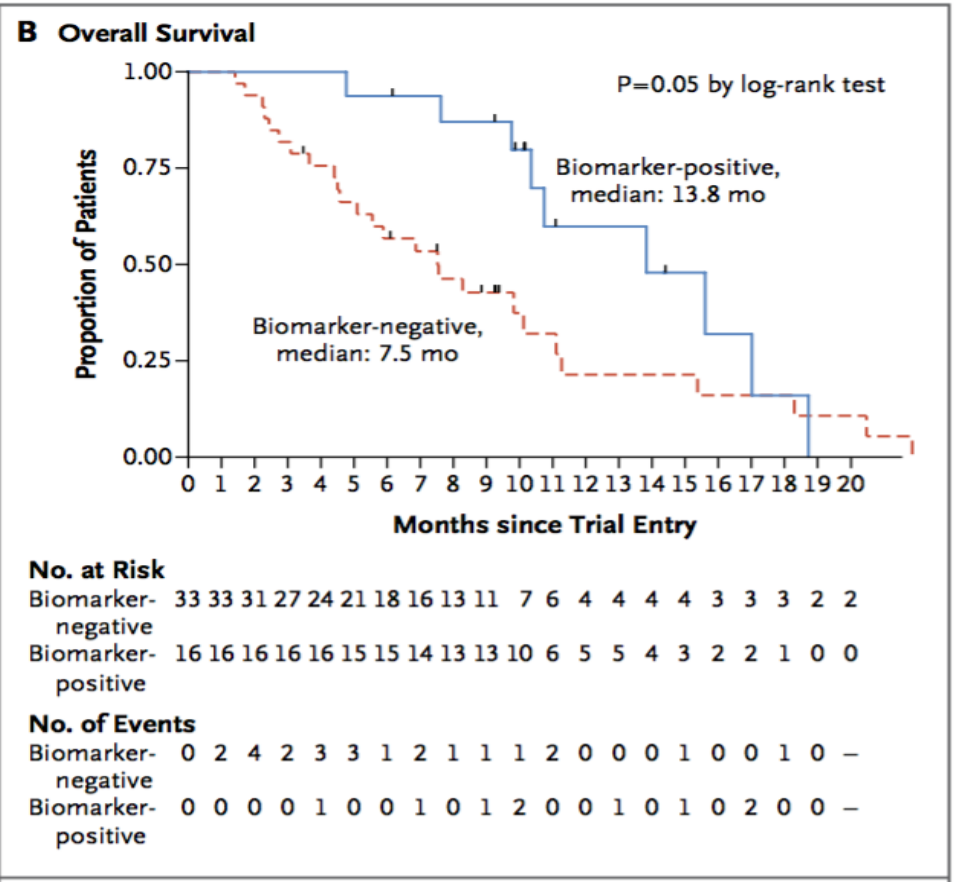
Whole-exome sequencing of fresh- frozen tumor-biopsies



N ENGL J MED 373;18 NEJM.ORG OCTOBER 29, 2015

88% of DNA-repair deficient CRPC responded to Olaparib!



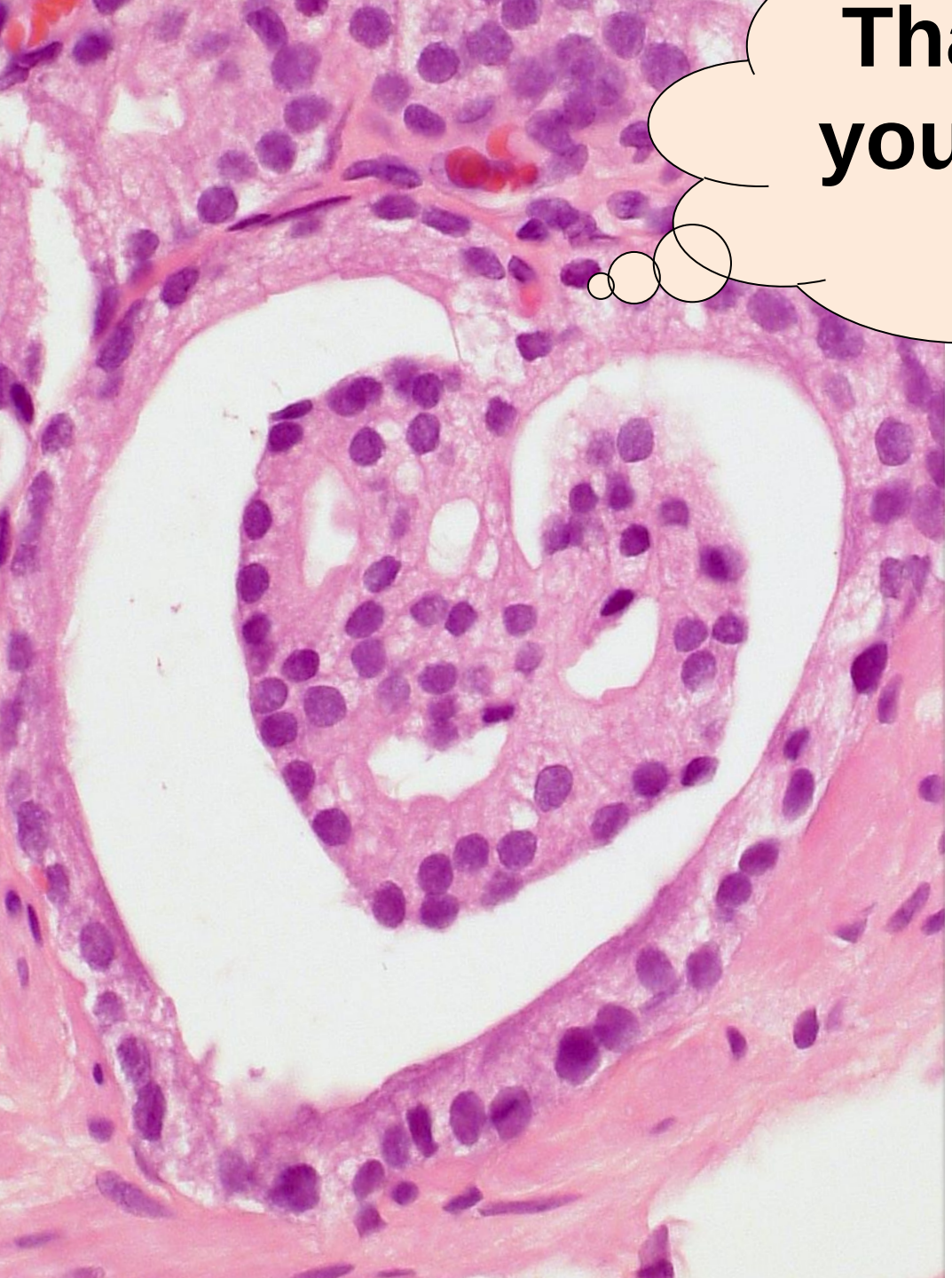


„In conclusion, we report that PARP inhibition has antitumor activity in sporadic cases of metastatic, castration-resistant prostate cancer and that these responses are associated with DNA- repair defects in tumor cells that can be identified through next-generation sequencing assays.“

Final Summary

- The molecular evolution of late stage prostate cancer is still incompletely understood. AR signalling remains relevant in CRPC
- At present, we cannot foresee the mechanism of androgen independence in a given case.
- (Tumor heterogeneity of metastatic Pca is obvious but not addressed)
- Immunotherapy may become relevant
- **Targeted therapy/predictive pathology for CRPC is beginning (DNArepair/Olaparib, ARV7-Enza/Abi, etc.)**

- Liquid biopsy develops: friend of foe of surgical pathology?



Thank you for your attention!