UNIVERSITY of IOWA HOSPITALS & CLINICS
University of Iowa Health Care

Algorithmic Approach to Define Tumo Type and Assign Site of Origin in Carcinoma of Unknown Primary

Andrew M Bellizzi, M.D.
Department of Pathology
University of Iowa Hospitals and Clinics
andrew-bellizzi@uiowa.edu
@IHC_guy

What I Wanted You to Remember From Last Lecture

- Age, Gender, Anatomic Location
- Primary vs Metastasis
- Screening Markers (Keratin, CD45, SOX10, SALL4)
- Differentiation Markers (everything else)

- Don’t start ordering differentiation markers if you’re unsure about the broad tumor class

Outline

- Clinical Aspects of CUP
- Epidemiology-based approach
- Added value of semiquantitative IHC Stain Assessment
- Core IHC algorithms
  - Carcinoma type
  - CK7/CK20
  - Garden variety adenocarcinoma
  - Surface ovarian vs metastasis
  - Other site specific algorithms
  - SCC vs UC
  - NET SOO
  - NEC SOO
  - NET G3 vs NEC

Clinical Aspects of Carcinoma of Unknown Prim

- Workup
  - H&P, CBC, UA, basic chemistries
  - Chest radiograph
  - CT or MRI of abdomen/pelvis
  - Pelvic exam and mammogram (women)
  - Prostate exam and serum PSA (men)
- Empiric therapy
  - Platinum plus cytotoxic (e.g., taxane, gemcitabine, irinotecan)
- Survival
  - Median: 7-10 months
  - 2-year survival: 20-25%

Estimated Annual Cancer Incidence Stratified by Broad Tumor Class

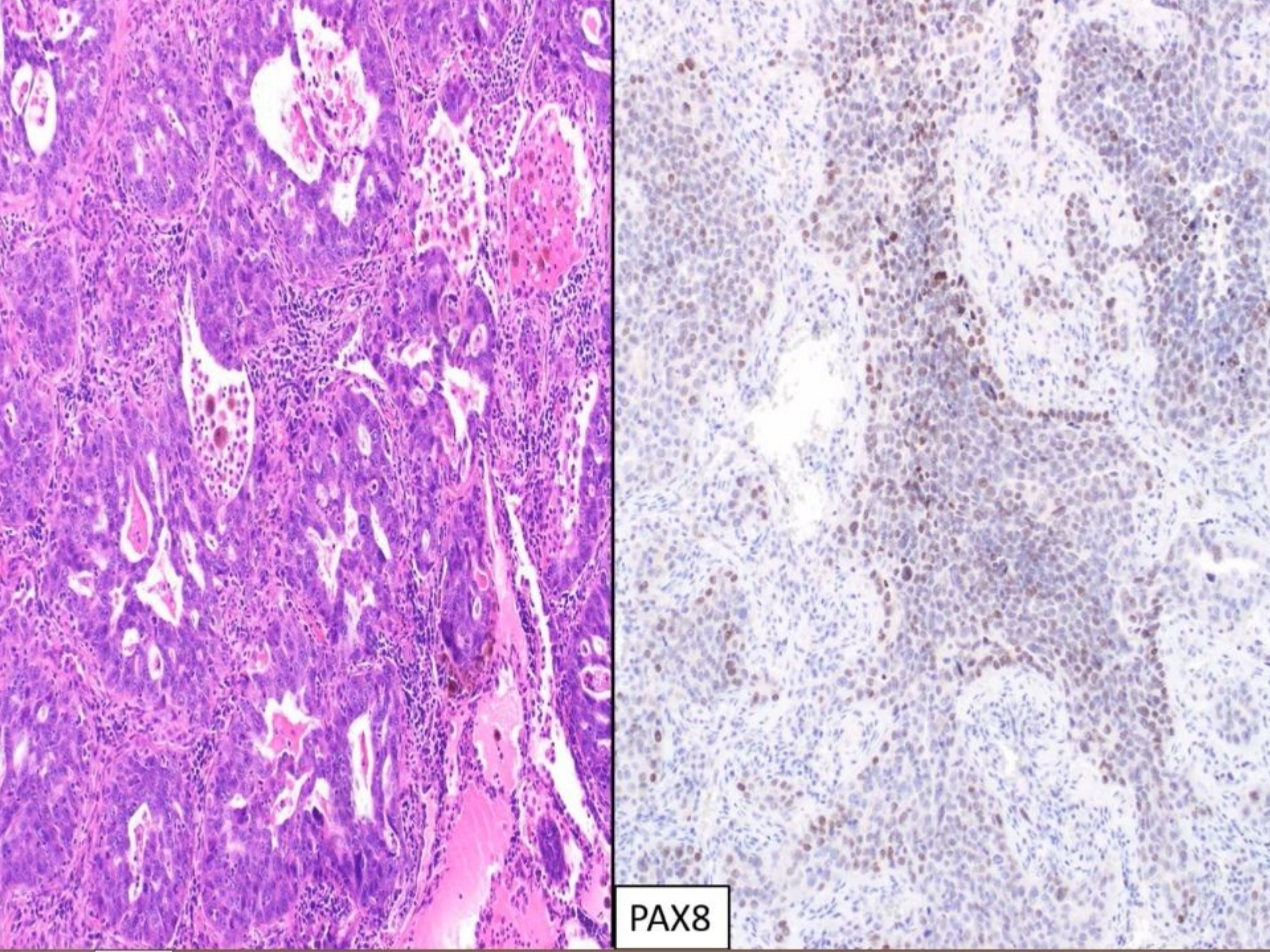
Tumor Type	Estimated Annual Incidence	% of All Incident Cases
Carcinoma	1,335,410	80%
Hematolymphoid	174,250	10%
Melanoma	94,810	6%
Sarcoma	16,490	1%
Germ cell tumor	10,422	0.6%
Mesothelioma	3,300	0.2%
Pheochromocytoma/paraganglioma	2,608	0.2%
Other and unspecified primary sites	31,810	2%

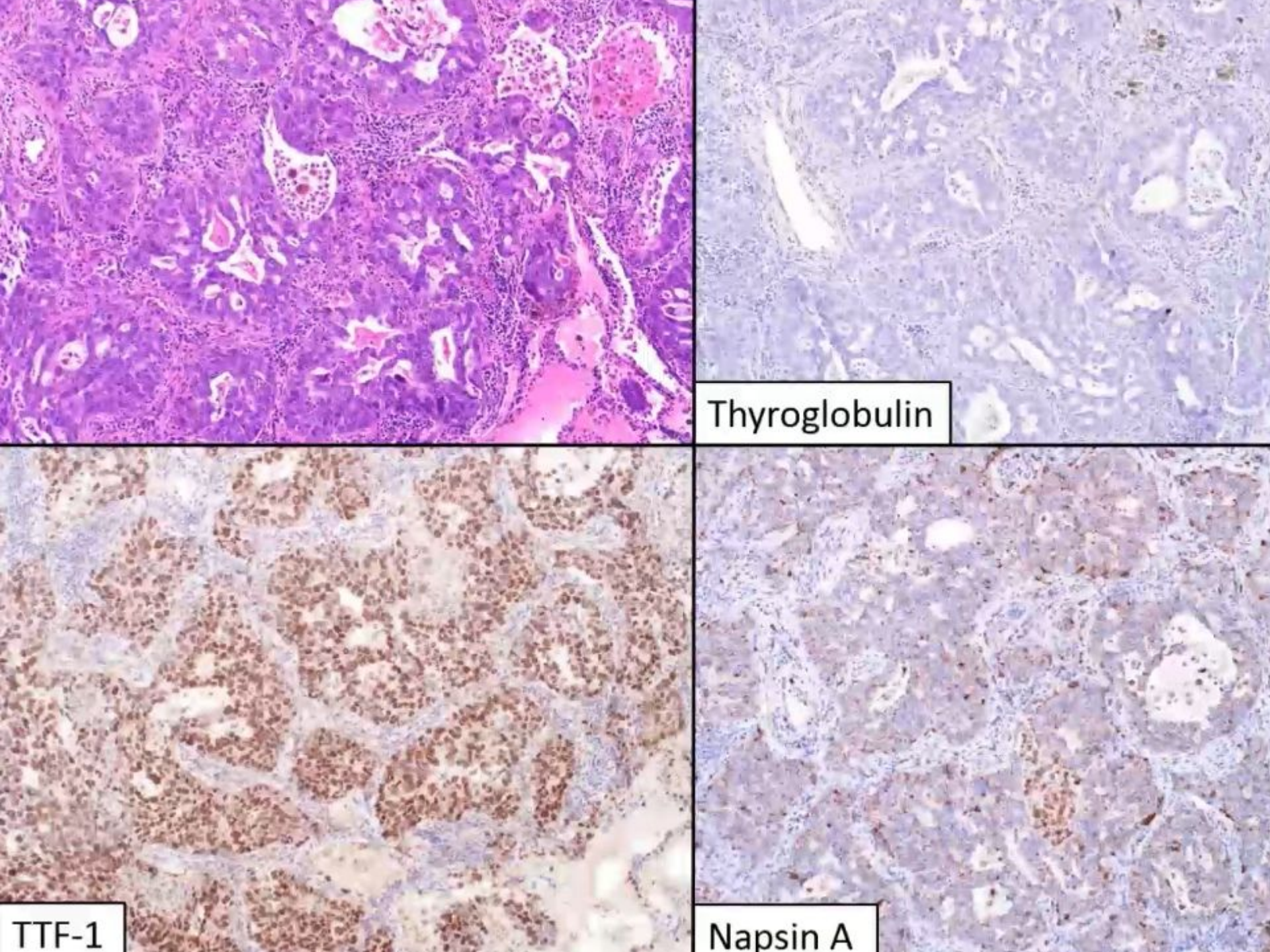
Estimated Annual Adenocarcinoma Incidence Stratified by Site of Origin

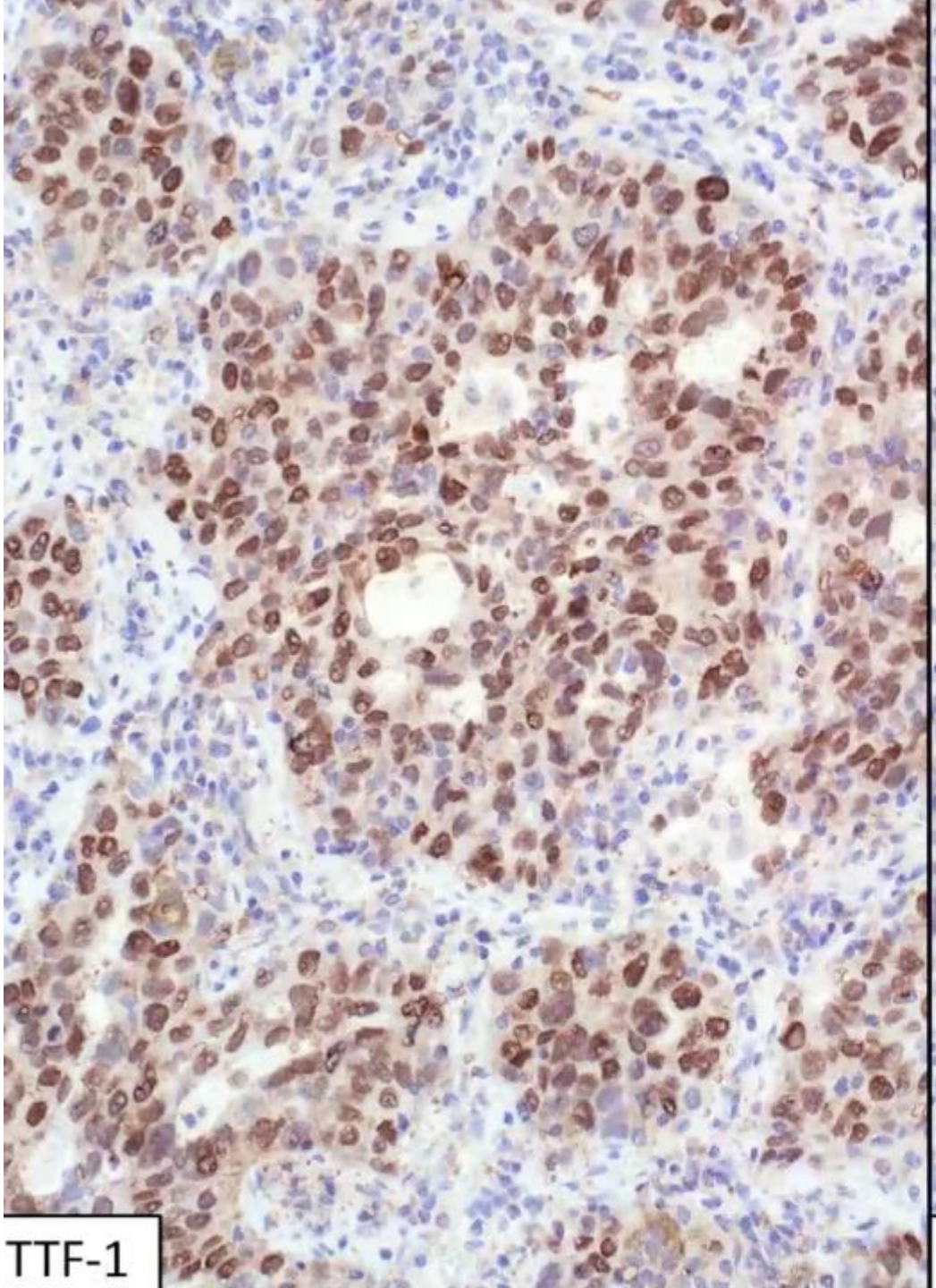
Tumor Type	Estimated Annual Incidence	% of All Incident Cases
Breast	268,670	26%
Prostate	164,690	16%
Colorectum	140,250	13%
Lung	124,036	12%
Müllerian	84,358	8%
Pancreatobiliary	72,331	7%
Kidney	58,806	6%
Thyroid	53,990	5%
Upper GI tract	44,566	4%
Hepatocellular carcinoma	34,747	3%

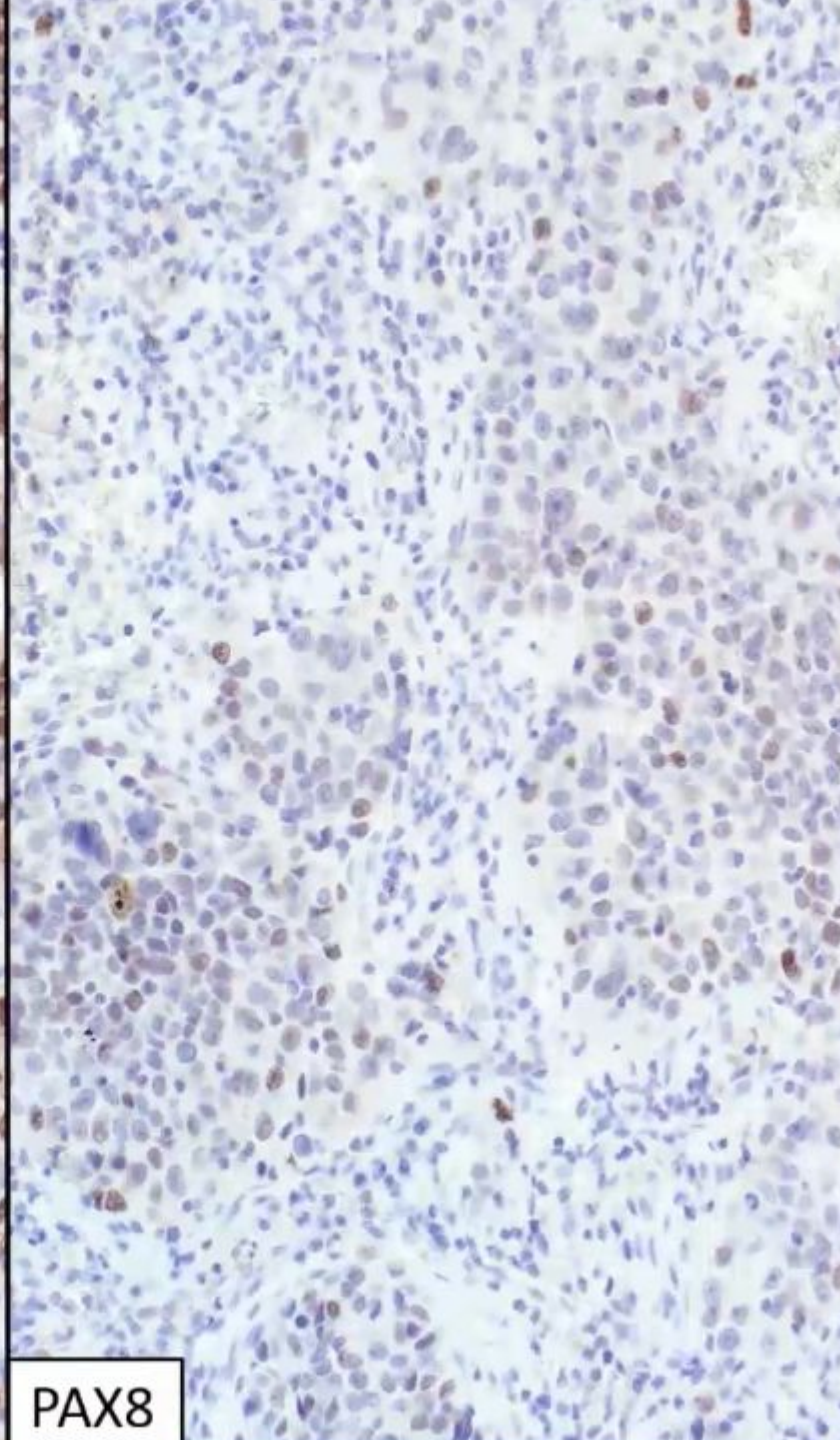
Cancer Epidemiology and Morphology-Based Site of Origin Generator

Most Common Primary Sites in Men (Rank Order)	Morphology	Most Common Primary Sites in Women (Rank Order)	Morphology
Prostate (25%) (AdCA)	Characteristic nuclear features regardless of Gleason grade: monomorphous and prominent nucleoli	Breast (26%) (AdCA)	Variable
Lung (15%) (AdCA, SCC, NEC)	Variable (AdCA)	Lung (14%) (AdCA, SCC, NEC)	Variable (AdCA)
Colorectum (10%) (AdCA)	Characteristic cytoarchitectural features: "tall, dark, and dirty"	Colorectum (10%) (AdCA)	Characteristic cytoarchitectural features: "tall, dark, and dirty"


PAX8


Thyroglobulin
TTF-1
Napsin A

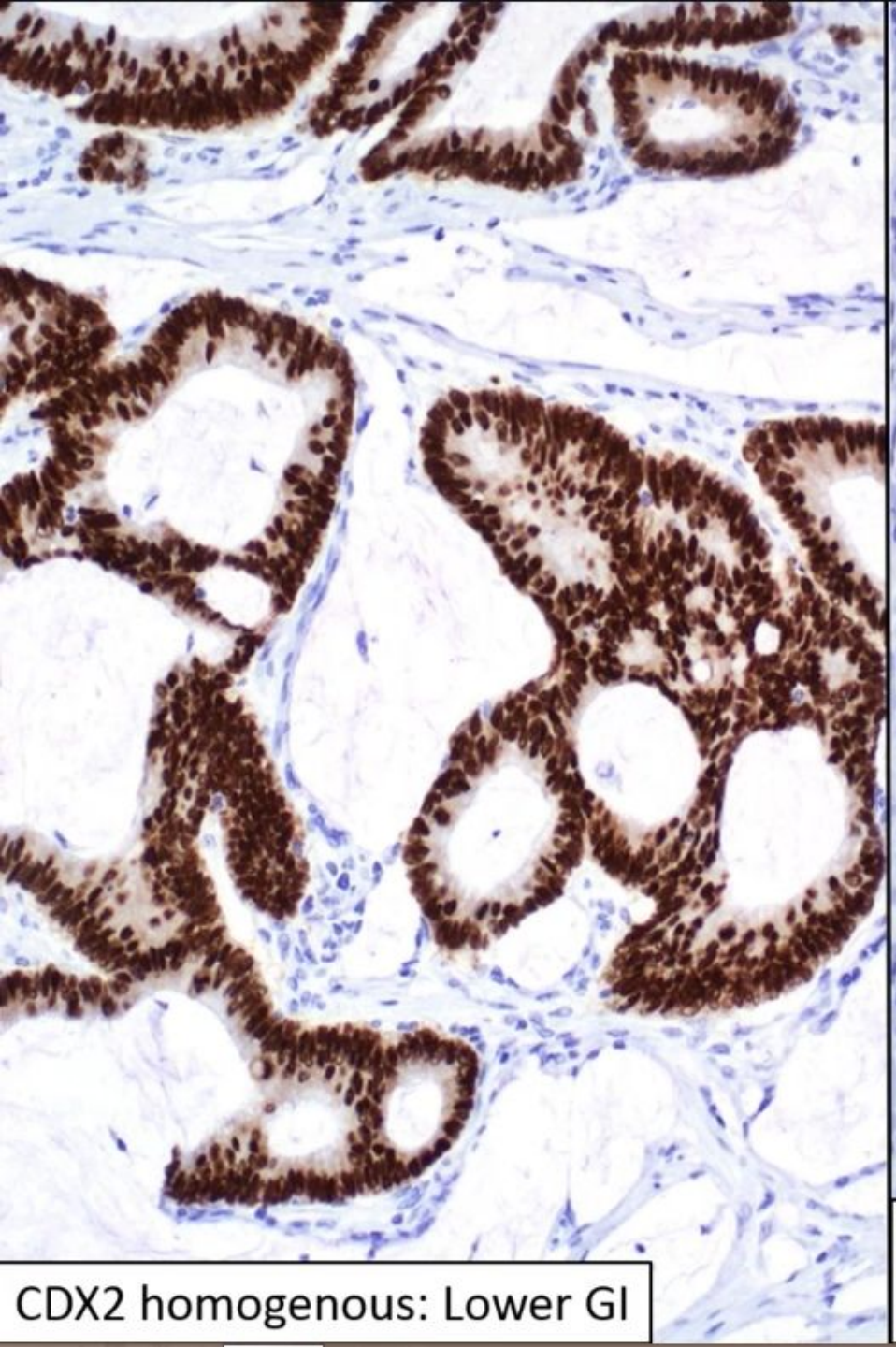

TTF-1


PAX8

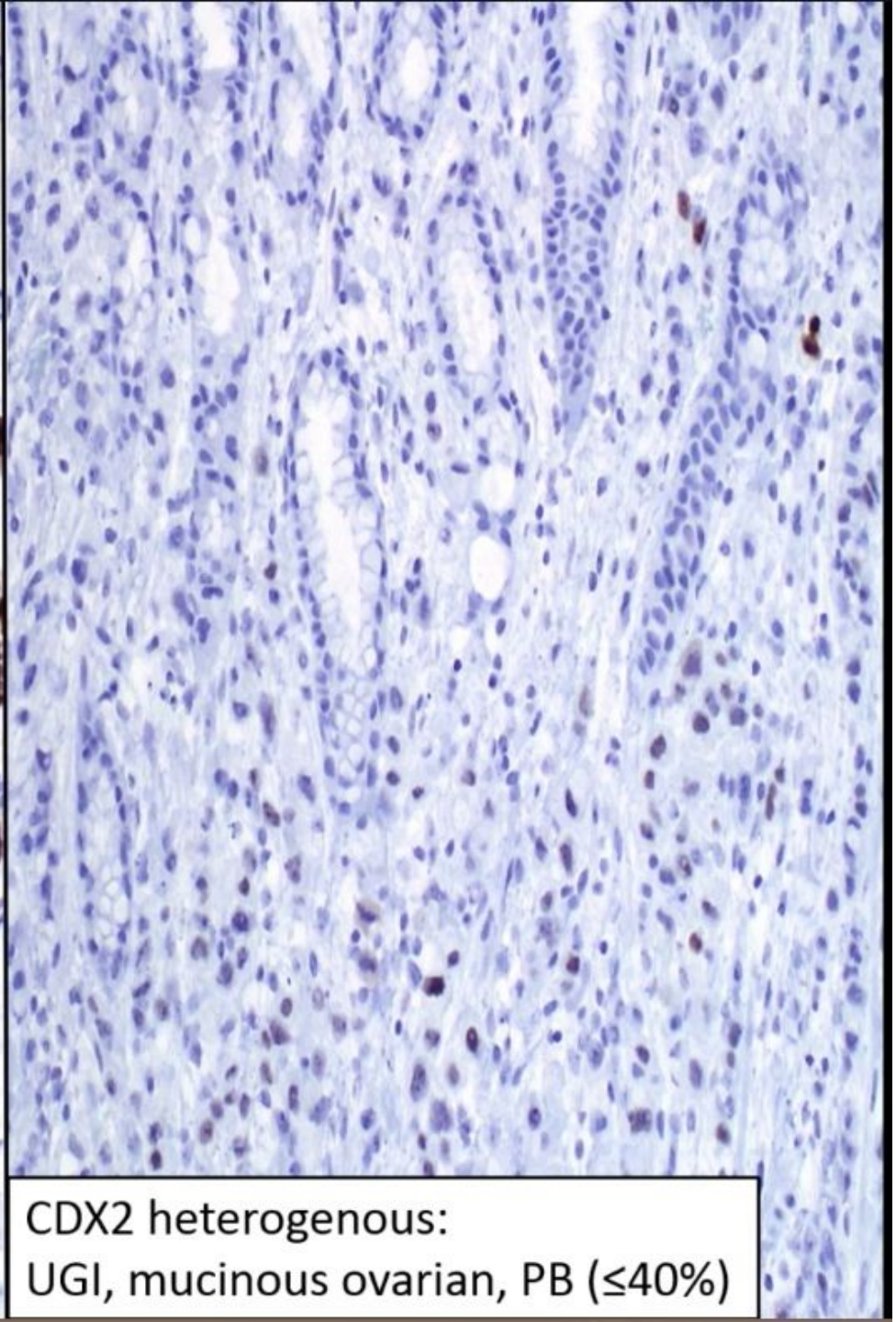
High-Expressing Group (positive in >90% of cases; generally diffuse, strong)
Colorectal adenocarcinoma
Appendiceal adenocarcinoma
Low-grade appendiceal mucinous neoplasm
Midgut well-differentiated neuroendocrine tumor
Moderately High-Expressing Group (positive in >50-90% of cases; weaker and less intense)
Esophageal adenocarcinoma
Gastric adenocarcinoma
Small intestinal adenocarcinoma
Ampullary adenocarcinoma
Mucinous ovarian adenocarcinoma
Intestinal-type sinonasal adenocarcinoma
Urinary bladder adenocarcinoma
Urachal adenocarcinoma
Variably Expressing Group (positive in 10-50% of cases; generally weak, patchy)
Pancreatic adenocarcinoma
Biliary tract adenocarcinoma
Endocervical adenocarcinomas, especially intestinal-type
Ovarian intestinal-type mucinous borderline tumor
Pancreatic well-differentiated neuroendocrine tumor
Rectal well-differentiated neuroendocrine tumor
Poorly differentiated neuroendocrine carcinoma
Yolk sac tumor
Rarely Expressing Group (positive in <10% of cases)
Pulmonary adenocarcinoma

CDX2 Expression in Epithelial Neoplasms

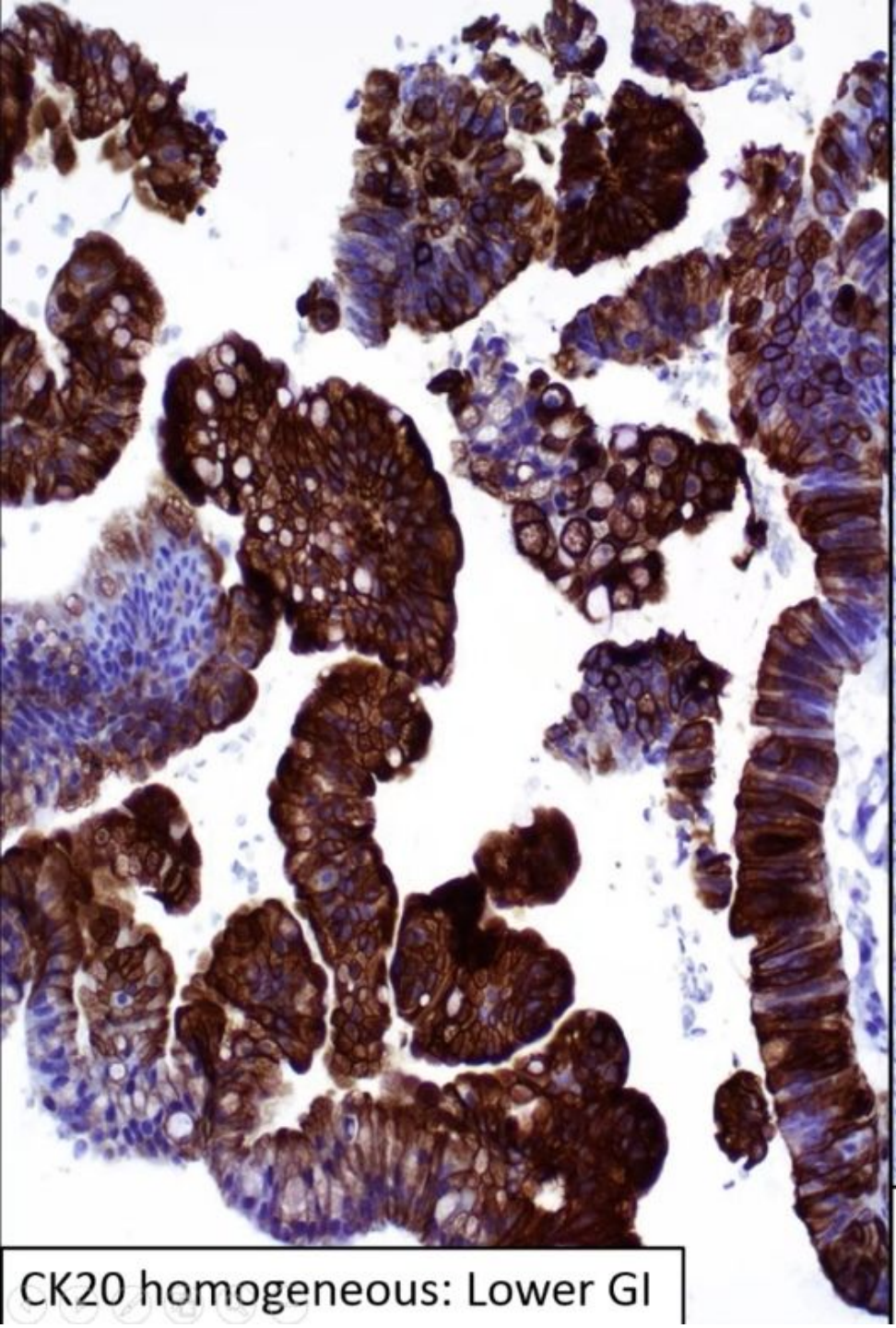
- With TFs there are often high, variably, and rarely expressing groups
- Expression extent and intensity stronger in high-expressing group



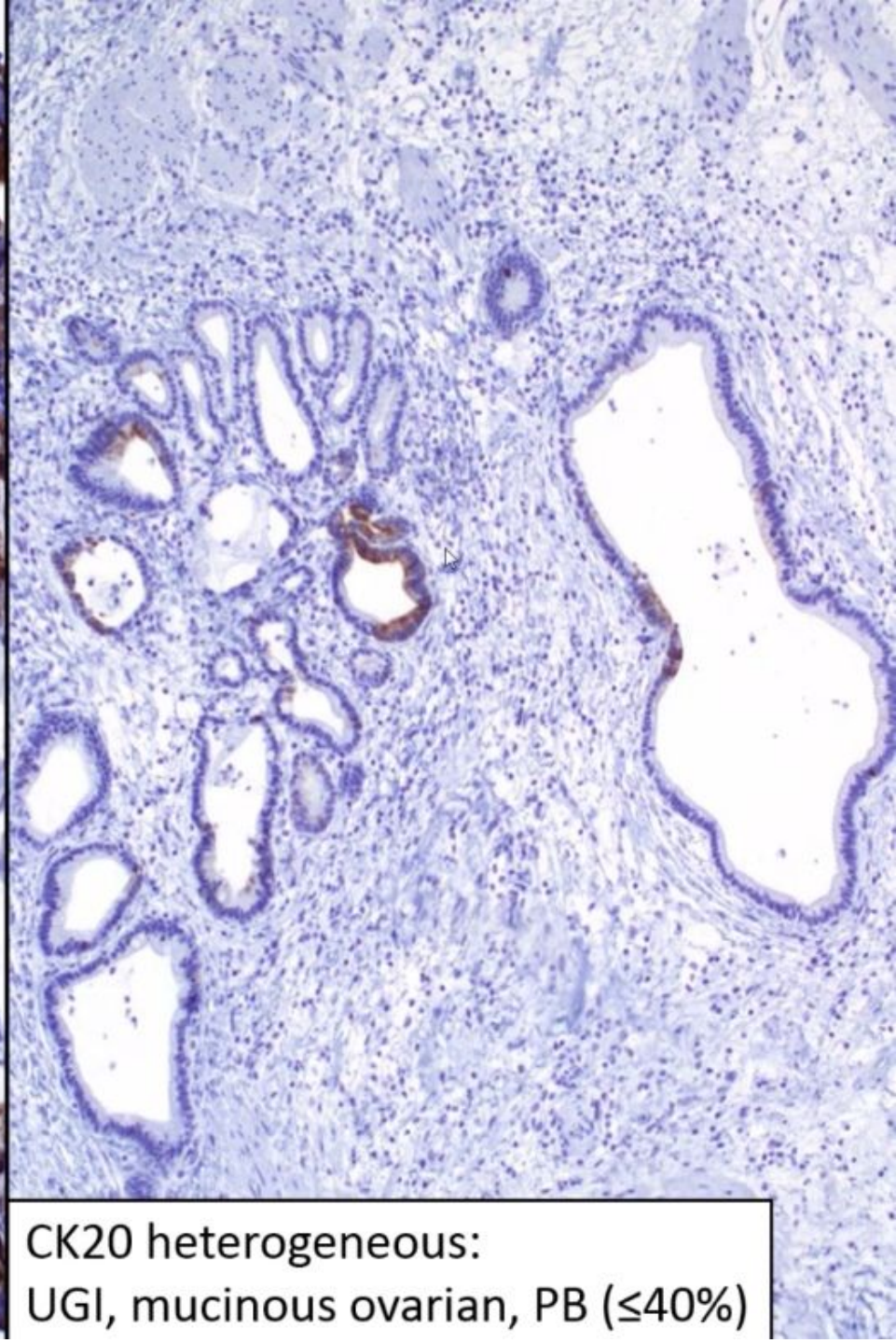
CDX2 homogenous: Lower GI



CDX2 heterogenous:
UGI, mucinous ovarian, PB (≤40%)



CK20 homogeneous: Lower GI

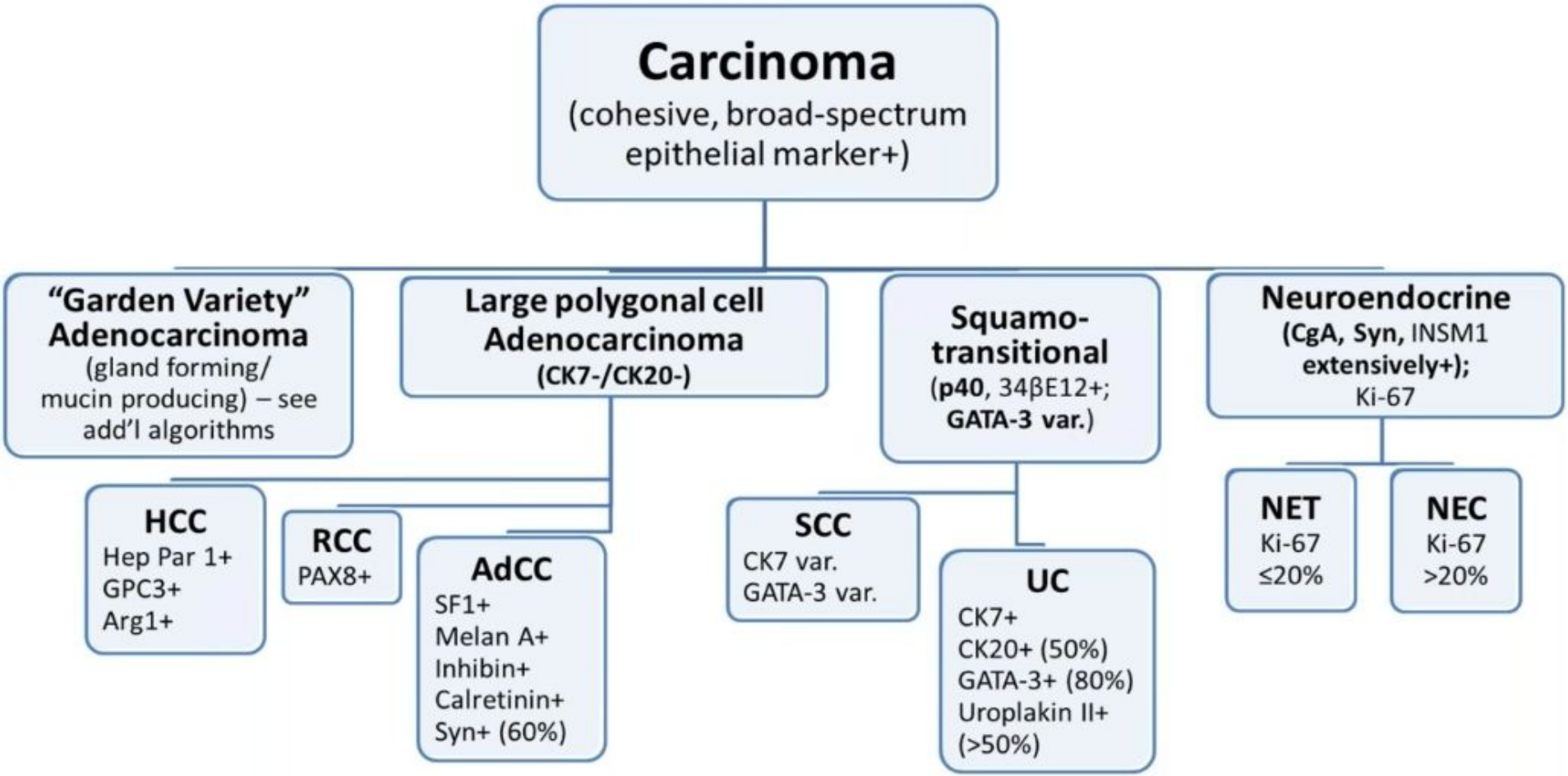


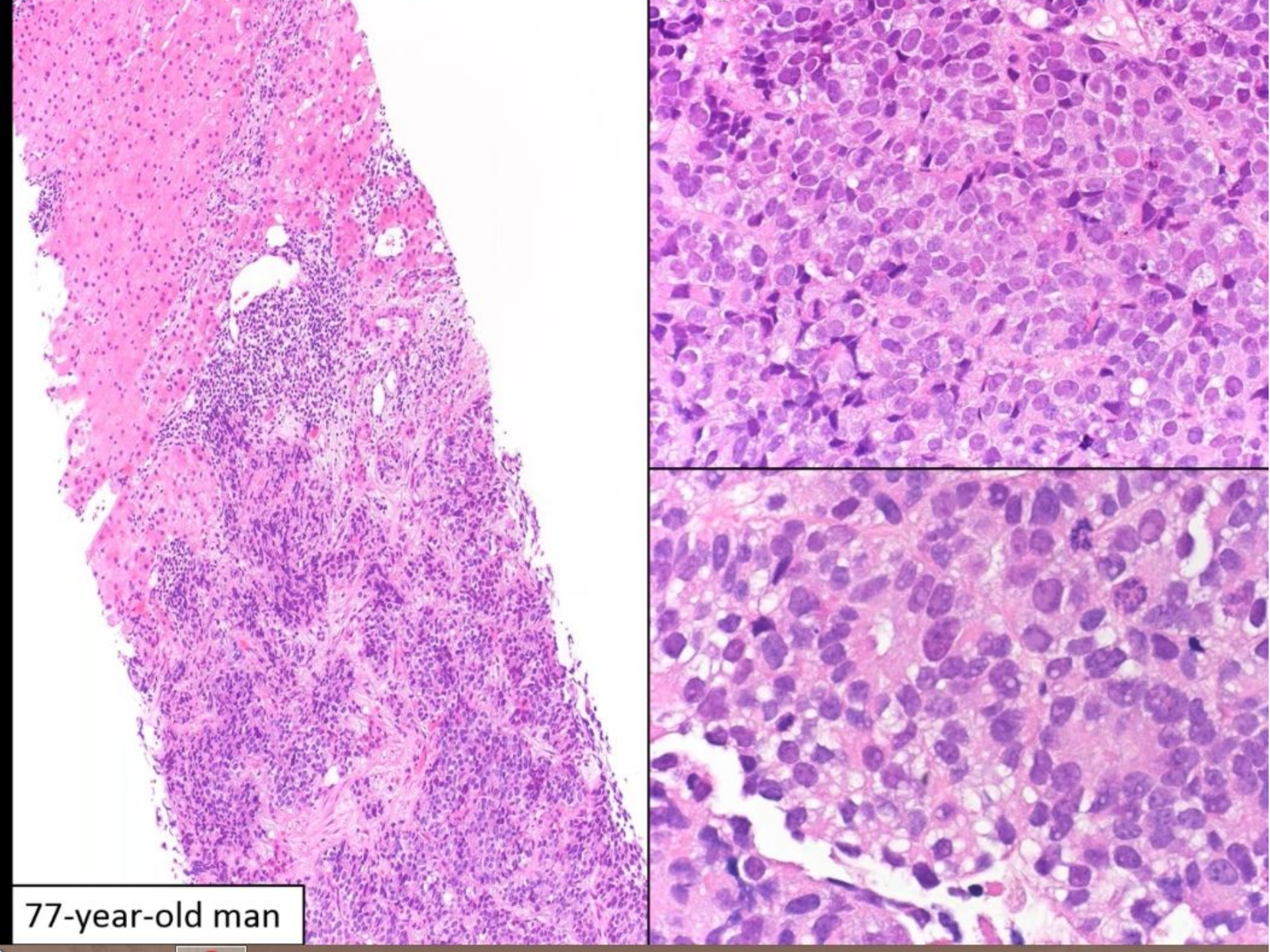
CK20 heterogeneous:
UGI, mucinous ovarian, PB (≤40%)

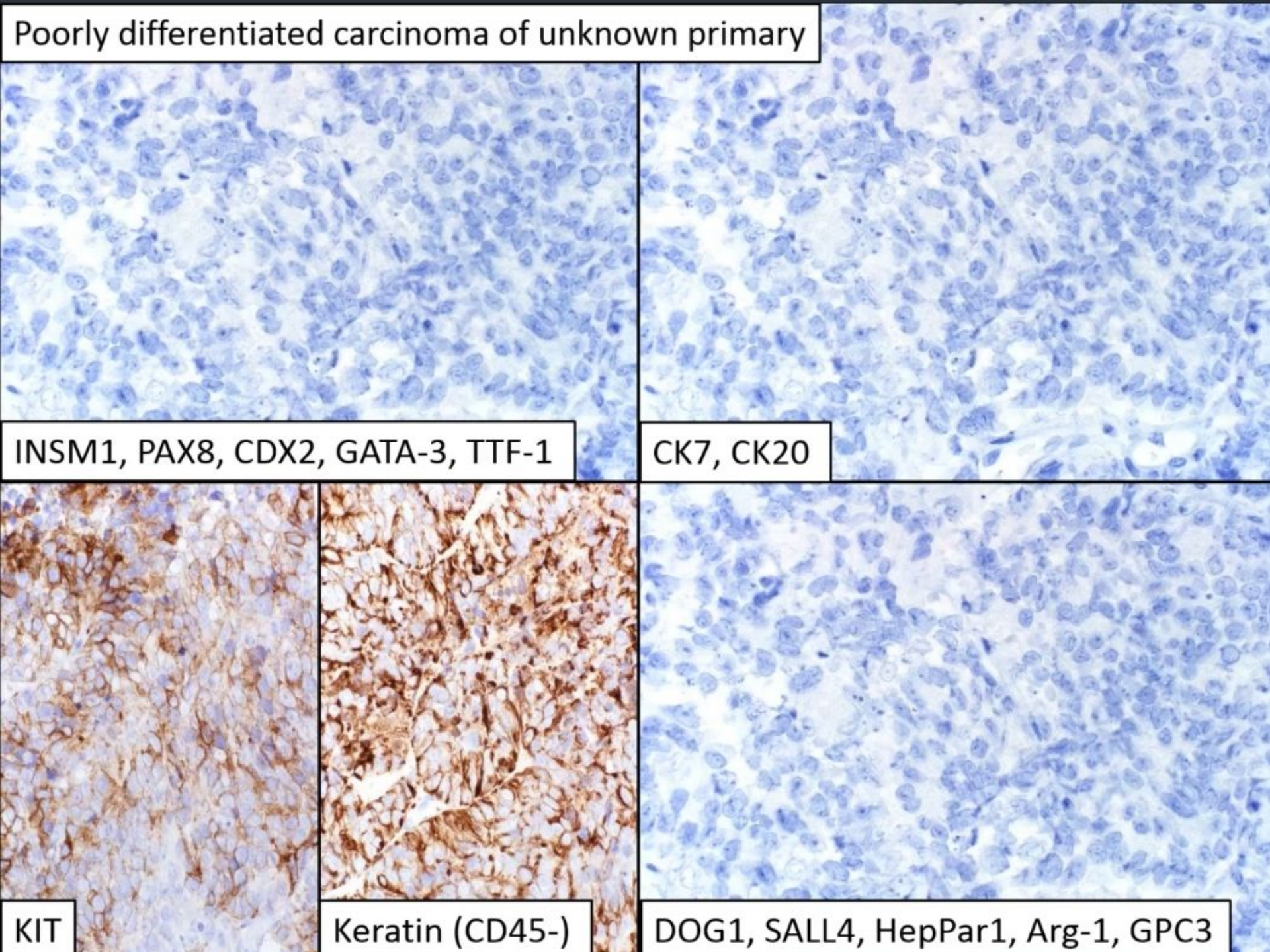
Coordinate Expression of CK7/CK20

Site (tumor)	CK7	CK20
Prostate, hepatocellular carcinoma, renal cell carcinoma, adrenal cortical carcinoma, squamous cell carcinoma, NET, visceral NEC, germ cell tumor (i.e., yolk sac tumor, seminoma)	-	-
Lung, breast, Müllerian, thyroid, bladder, upper GI (UG), pancreatobiliary (PB), mucinous ovarian	+	-
Bladder, UGI, PB, Mucinous Ovarian, occasional colon (especially rectum), occasional lung (especially mucinous)	+	+
Colon, Merkel cell, occasional UGI	-	+

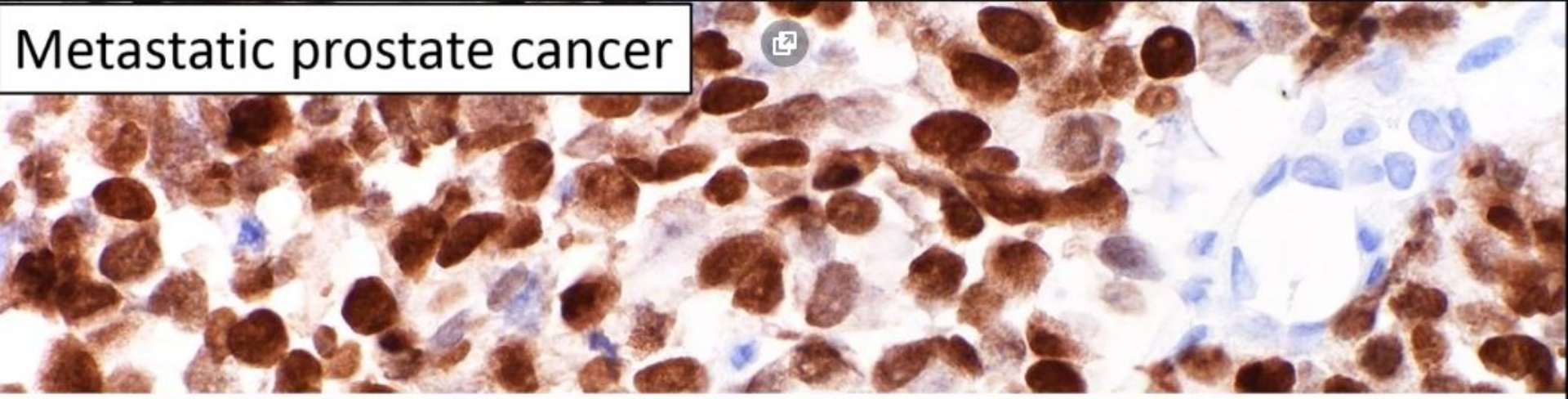
Diagnosis of Carcinoma Type



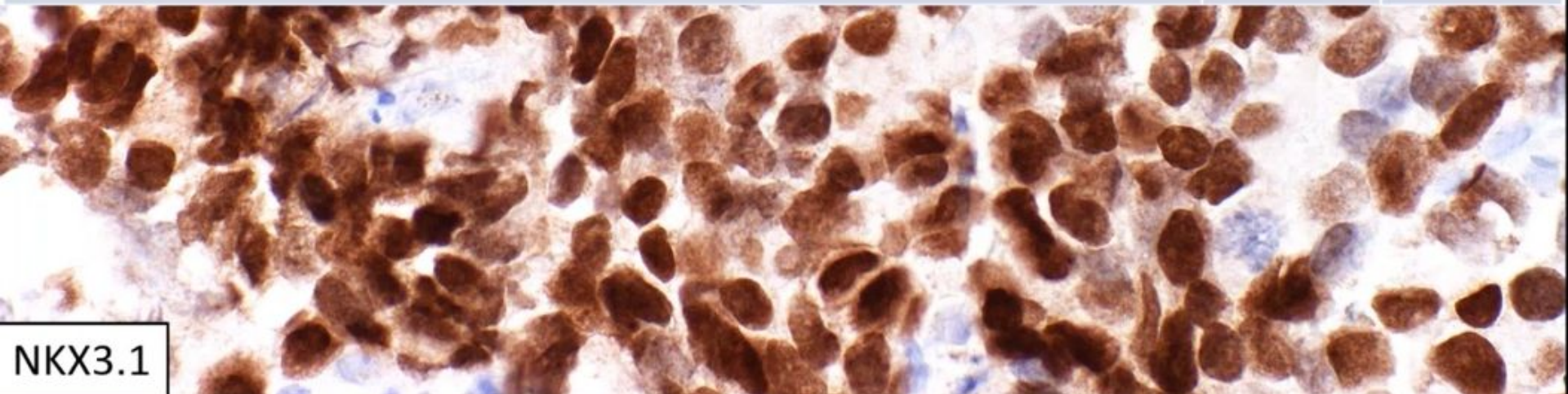

77-year-old man


Poorly differentiated carcinoma of unknown primary
INSM1, PAX8, CDX2, GATA-3, TTF-1
CK7, CK20
KIT
Keratin (CD45-)
DOG1, SALL4, HepPar1, Arg-1, GPC3

Metastatic prostate cancer

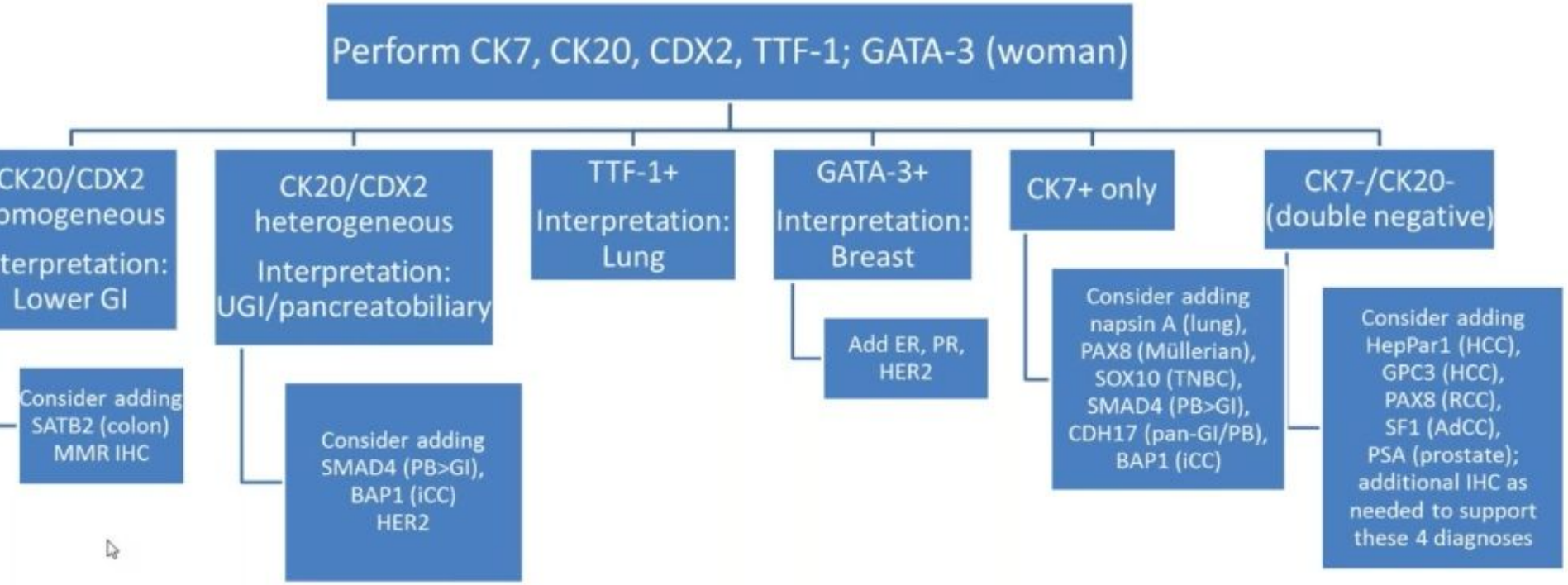


Site (tumor)	CK7	CK20
Prostate, hepatocellular carcinoma, renal cell carcinoma, adrenal cortical carcinoma, squamous cell carcinoma, NET, visceral NEC, germ cell tumor (i.e., yolk sac tumor, seminoma)	-	-



NKX3.1

"Garden Variety" Adenocarcinoma in the Liver

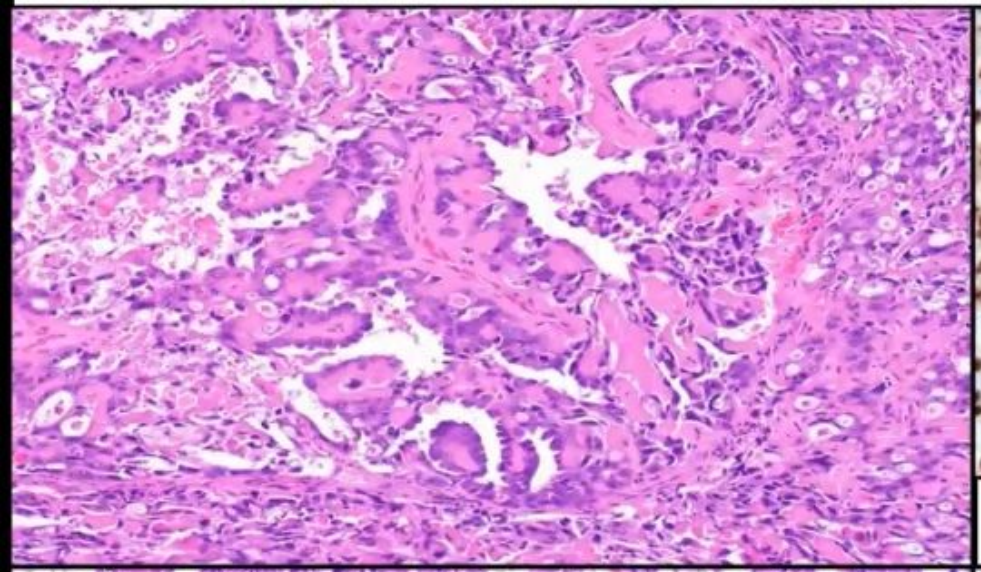


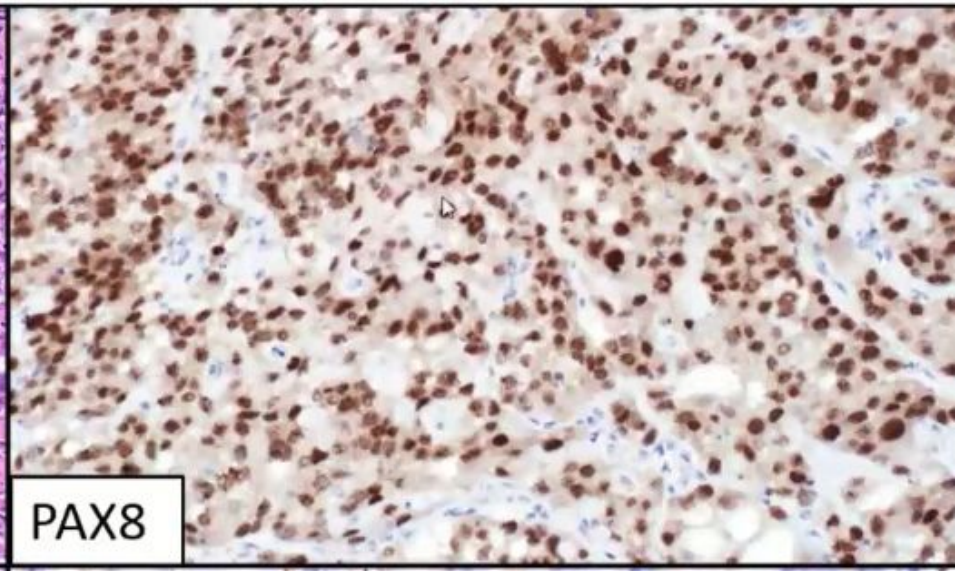
SCC/UC may be CK7+ only or CK7/CK20-; if one of those patterns, reconsider H&E and have low threshold to add p40 and GATA-3

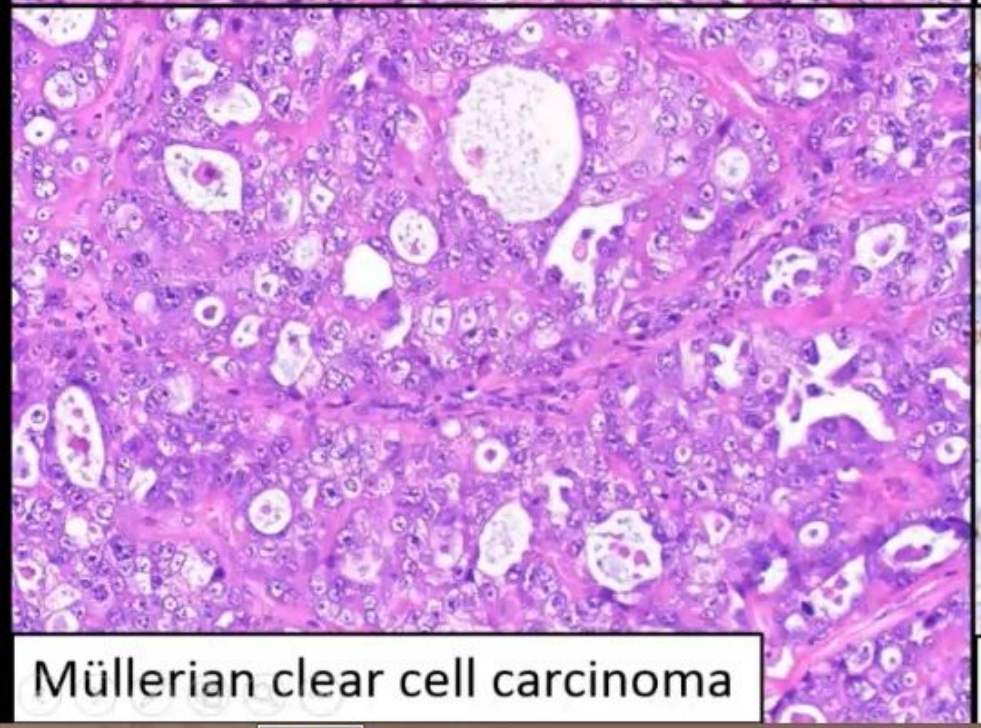
NETs and NECs are often CK7/CK20- and type C NET and LCNEC mimic AdCA; reconsider H&E and have low threshold to add CgA/Syn (or INSM1)

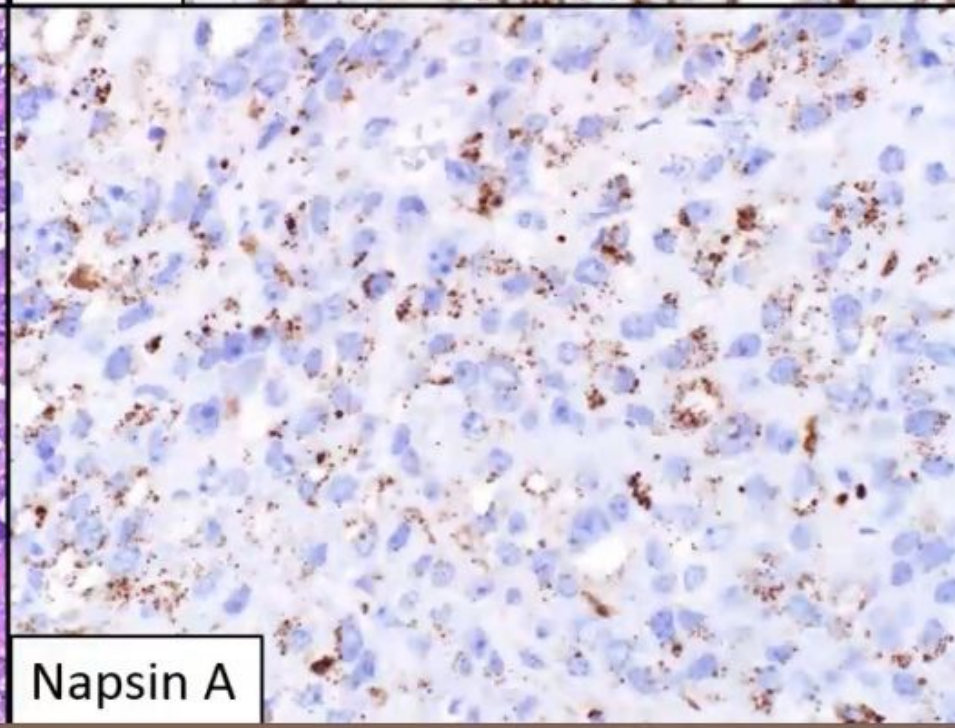
For AdCA in peritoneum, add PAX8 (woman) and consider mesothelioma (calretinin, WT-1, D2-40+; MOC-31-)

On my meta-review of 11 studies and 807 lung AdCAs, TTF-1 and napsin A were identically sensitive (80.3%) and performing both increased sensitivity to 87.2%





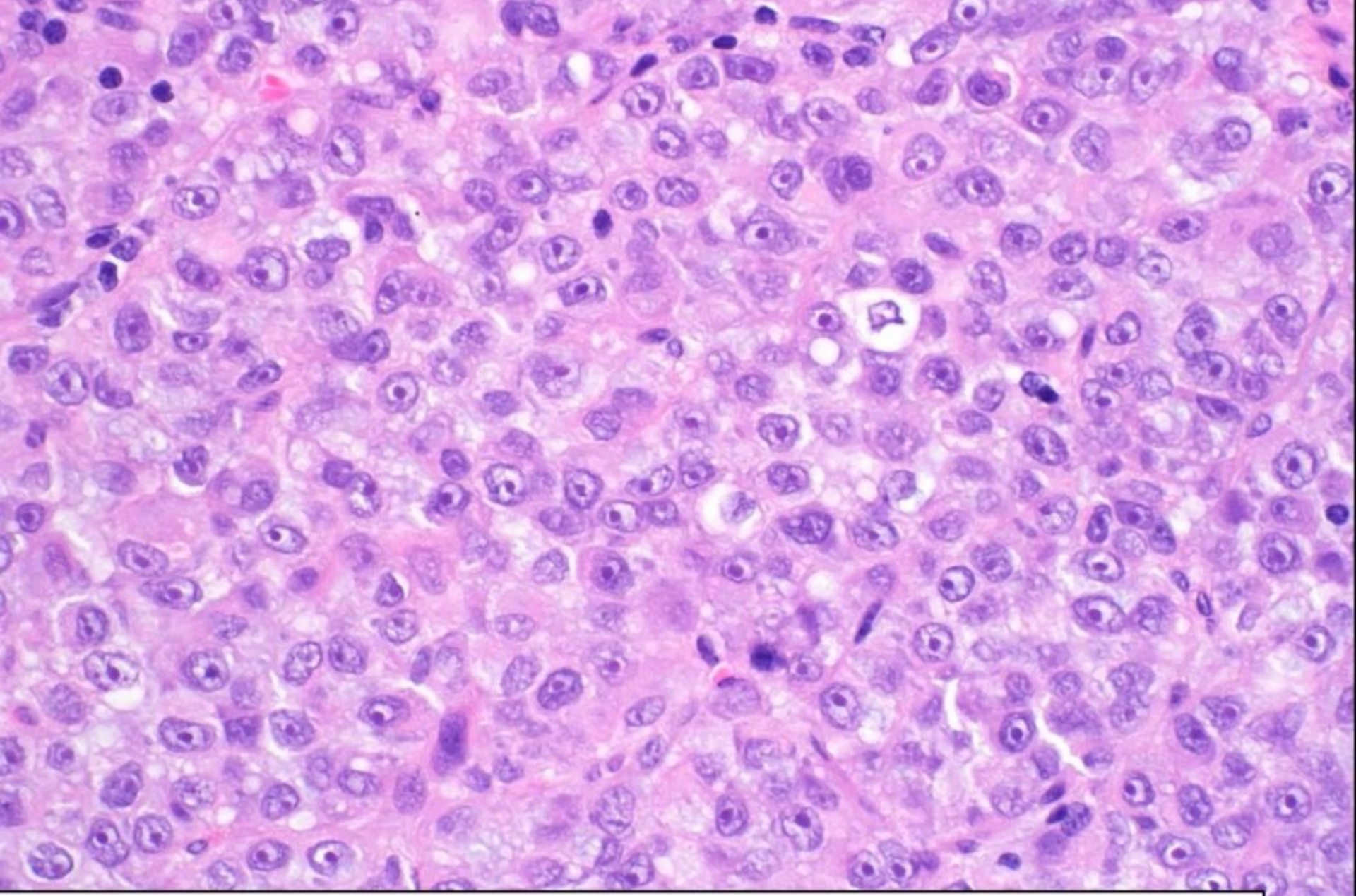




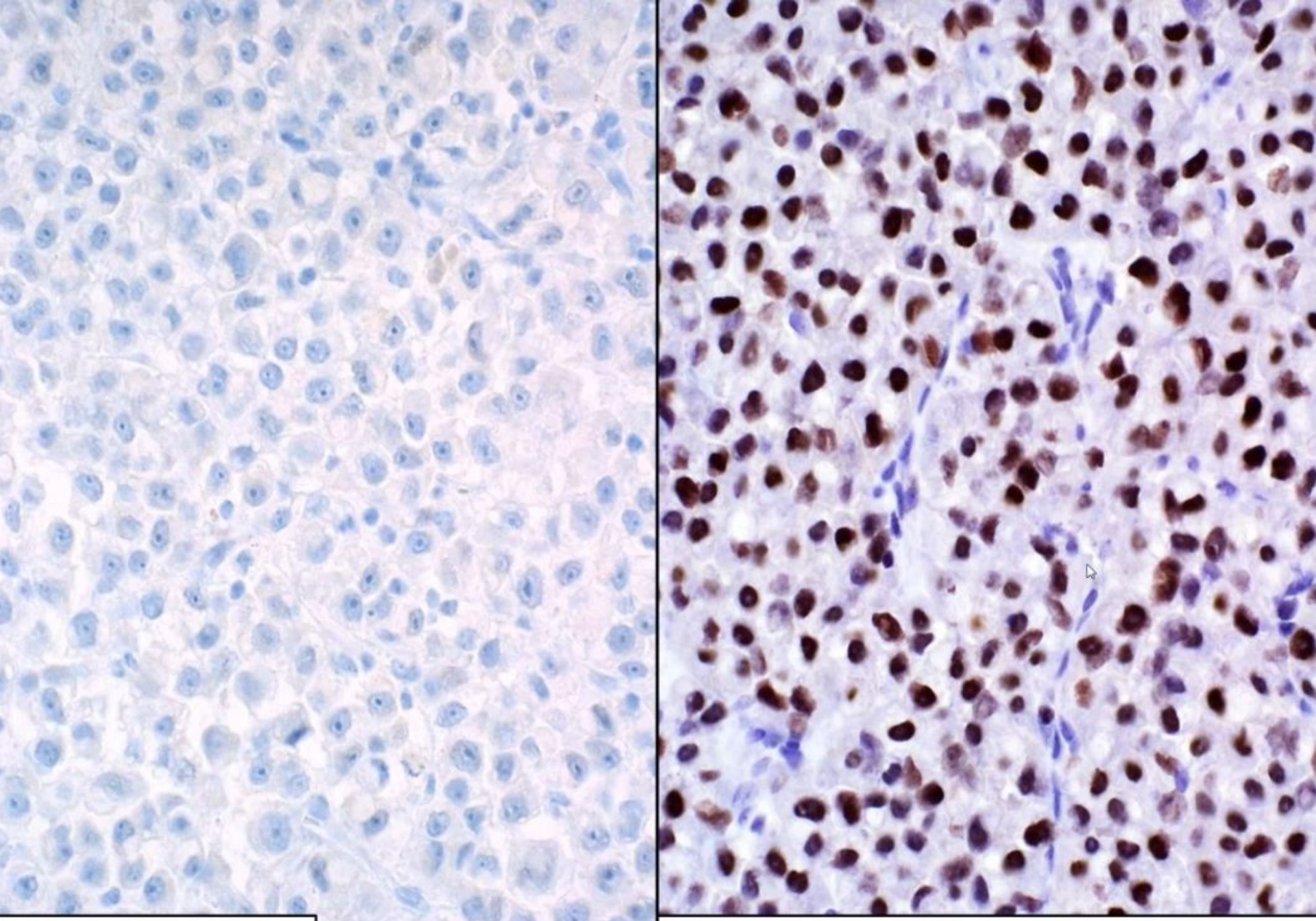
SOX10 expression in breast cancer

Cimino-Matthews	
Luminal A (ER+/HER2-)	0% (0/21)
Luminal B (ER or PR+/HER2+)	14% (1/7)
HER2 (ER and PR-/HER2+)	7% (1/14)
Basal-like (triple-negative; CK5/6 or EGFR+)	69% (22/32)
Unclassified triple-negative (pan-negative)	77% (10/13)
Miettinen	
Ductal	12% (57/486)
Lobular	0% (0/50)

Cimino-Matthews, et al. *Hum Pathol*. 2013 Jun;44(6):959-65



48-year-old woman with a h/o breast cancer 5-years ago p/w widespread metastatic disease; core biopsy of left neck lymph node



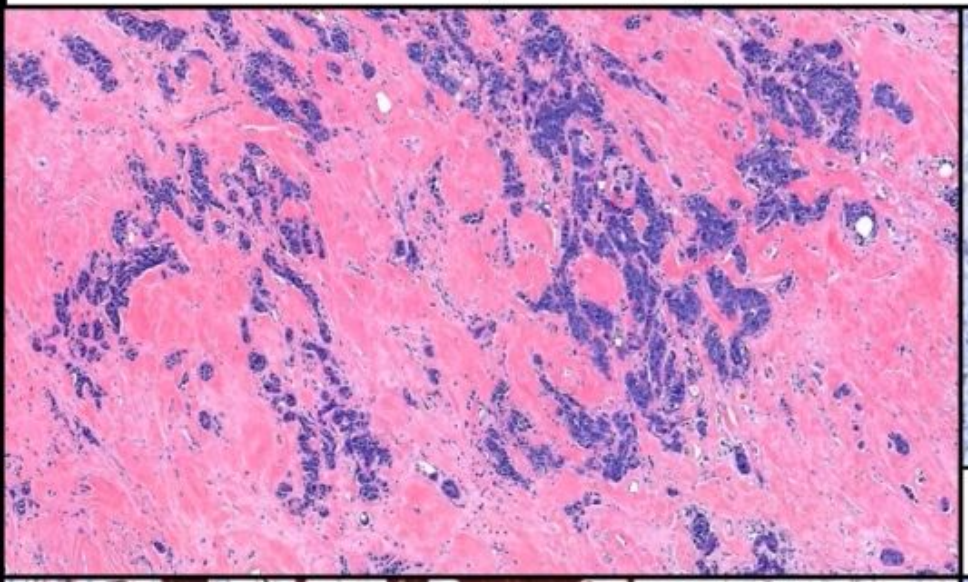
ER, PR, HER2-

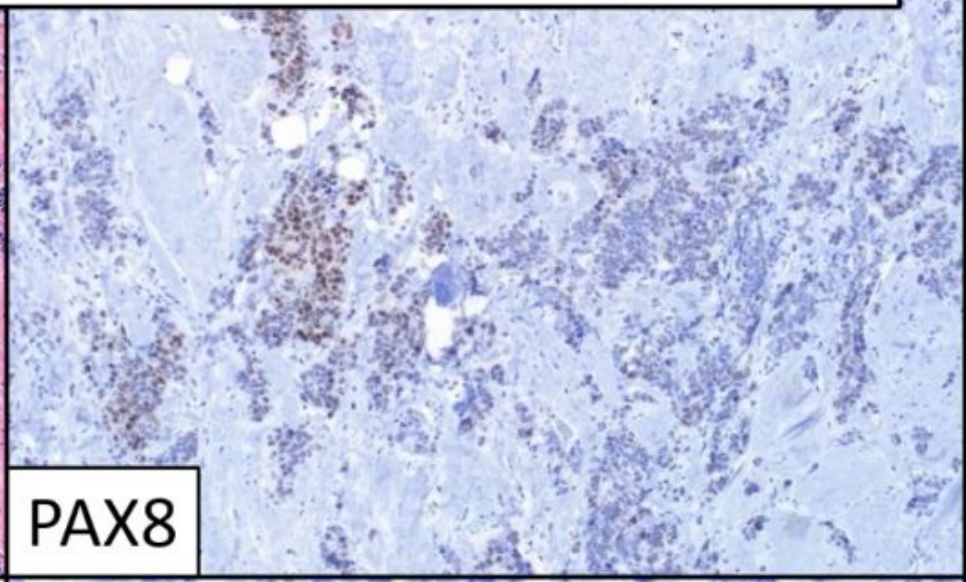
GATA3+; conc: met. breast CA

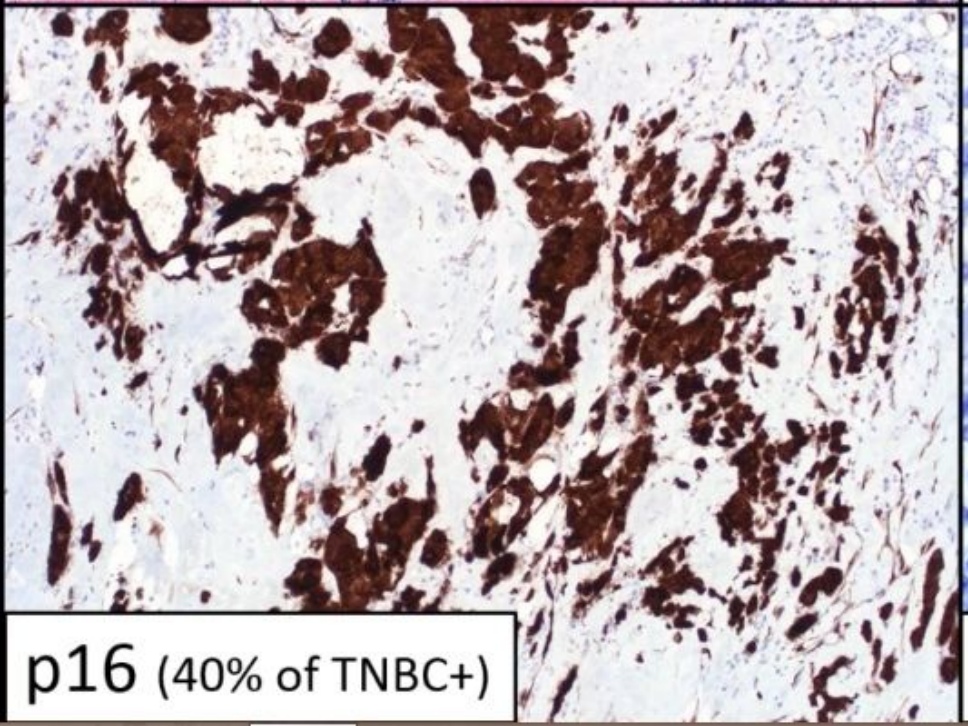
GATA-3 Expression in ER- Breast CA

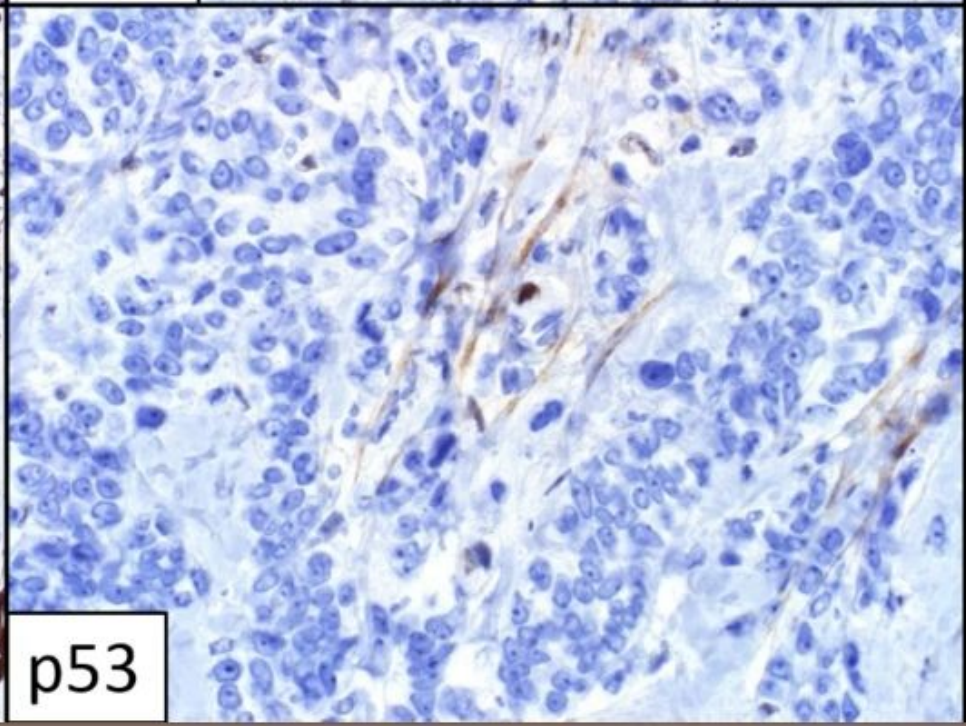
Clone	L50-823 (Biocare)		HG3-31 (Santa Cruz)	
	% Positive	Avg H-score (if positive)	% Positive	Avg H-score (if positive)
ER-Negative (n=196, 192)	**79**	168	**67**	136
ER-Positive (n=23)	100	292	100	292

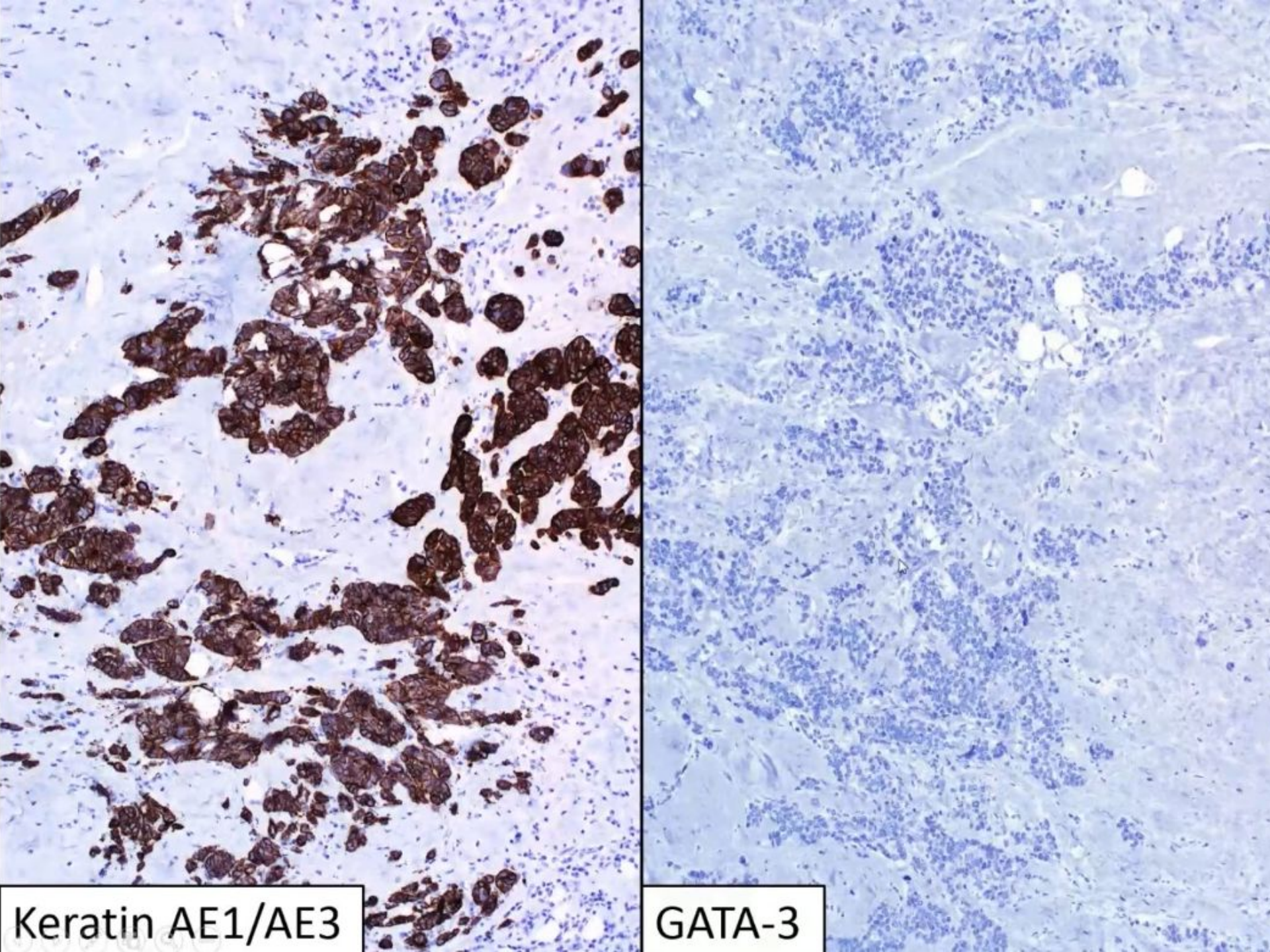
72-year-old woman with a remote history of “medullary carcinoma” also diagnosed with serous cancer 2-years-ago; ?recurrent breast cancer in lumpectomy scar

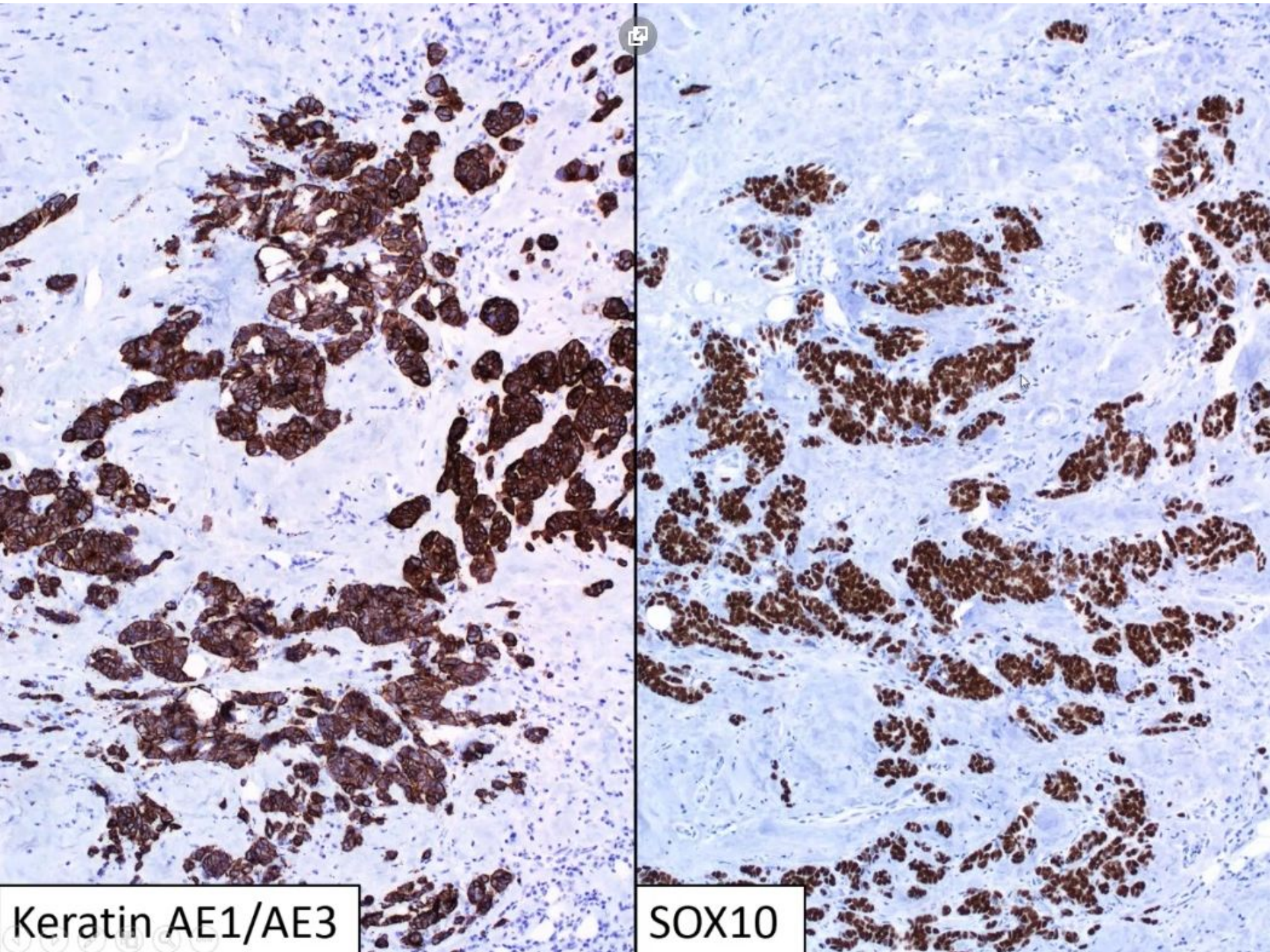


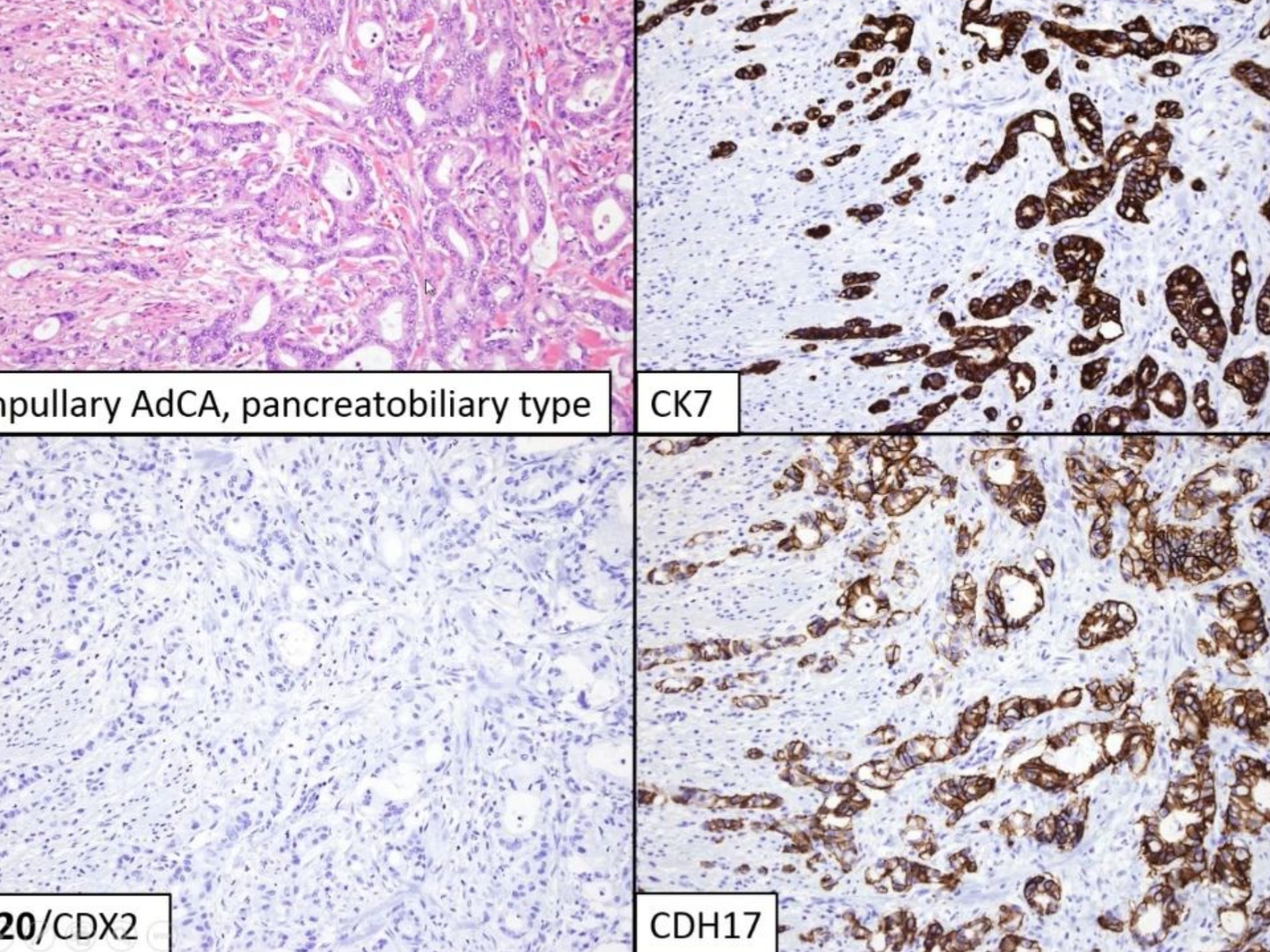






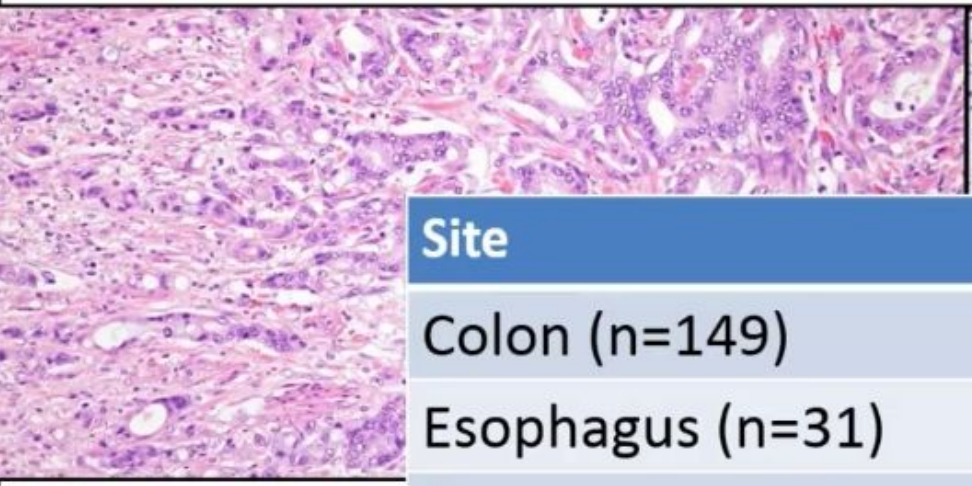

Keratin AE1/AE3
GATA-3


Keratin AE1/AE3
SOX10


npullary AdCA, pancreatobiliary type
CK7
20/CDX2
CDH17

CDH17 May Give CDX2 a Run For its Money as THE pan-GI Marker

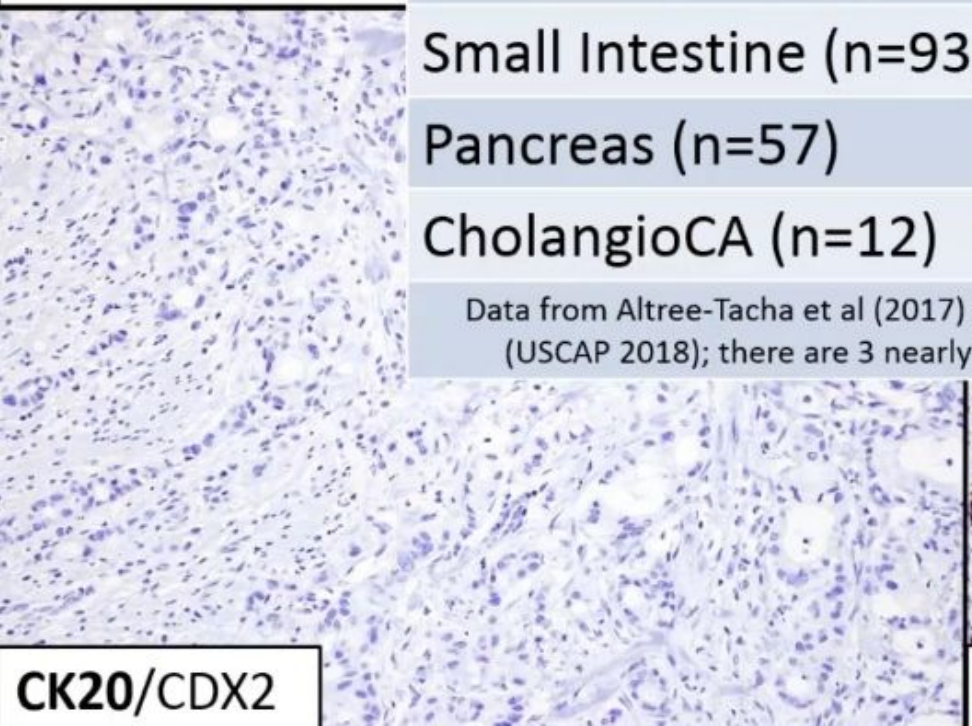
(also expressed by midgut/hindgut NETs, 1° bladder AdCA, and metanephric adenoma)



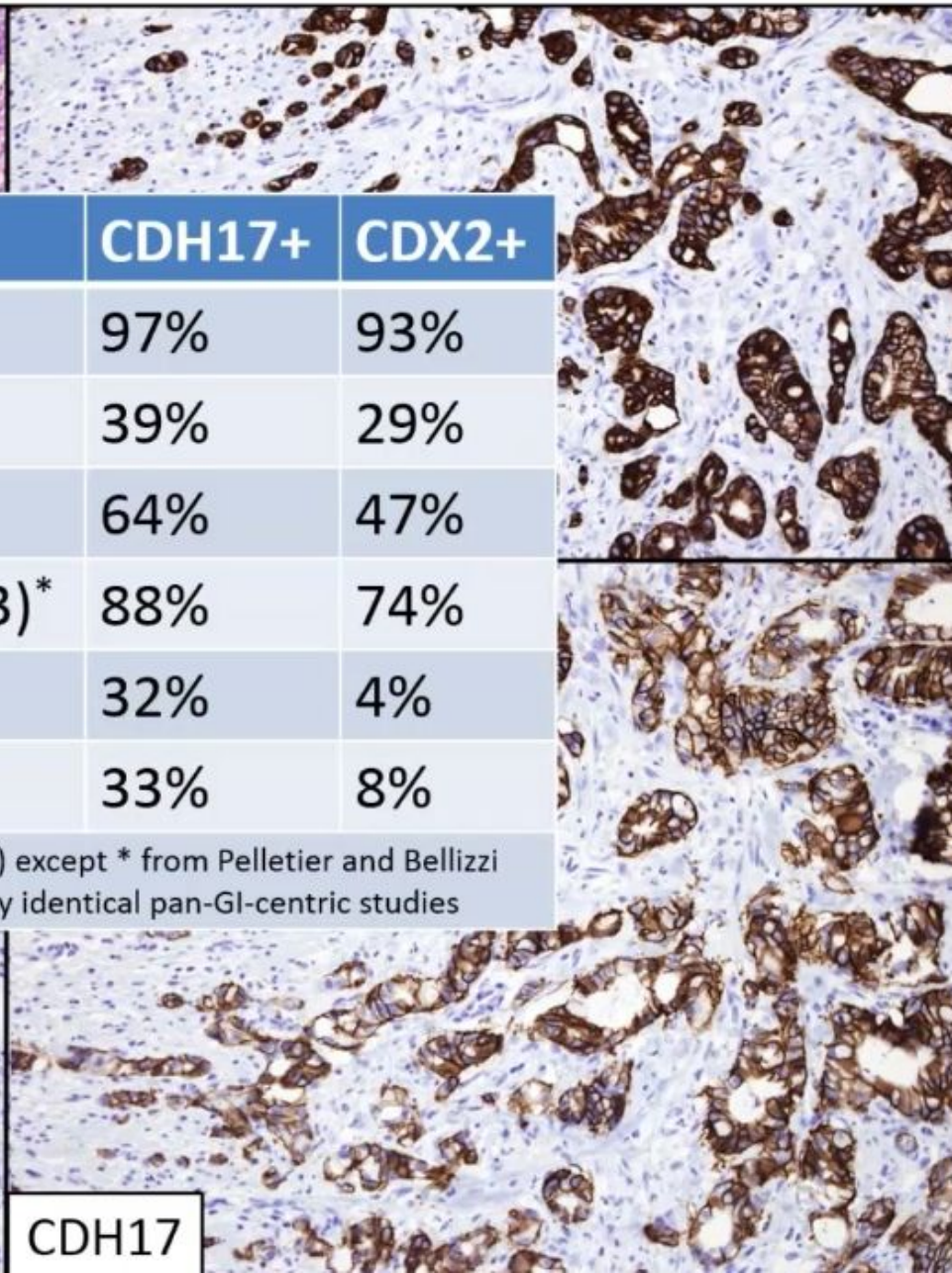
Ampullary AdCA,

Site	CDH17+	CDX2+
Colon (n=149)	97%	93%
Esophagus (n=31)	39%	29%
Stomach (n=175)	64%	47%
Small Intestine (n=93)*	88%	74%
Pancreas (n=57)	32%	4%
CholangioCA (n=12)	33%	8%

Data from Altree-Tacha et al (2017) except * from Pelletier and Bellizzi (USCAP 2018); there are 3 nearly identical pan-GI-centric studies



CK20/CDX2

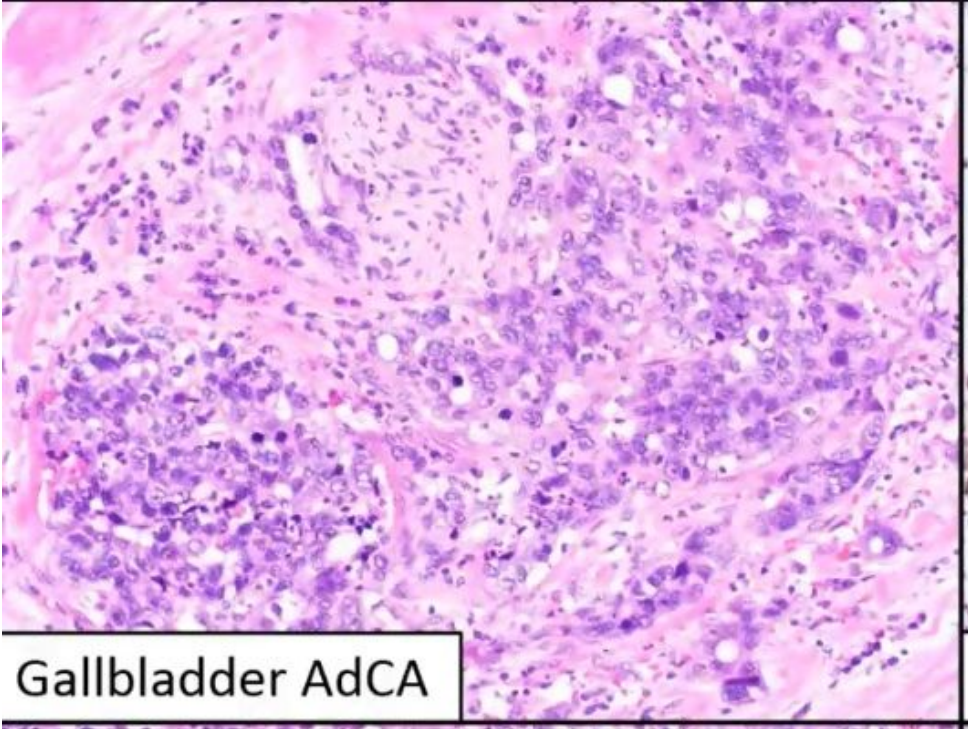


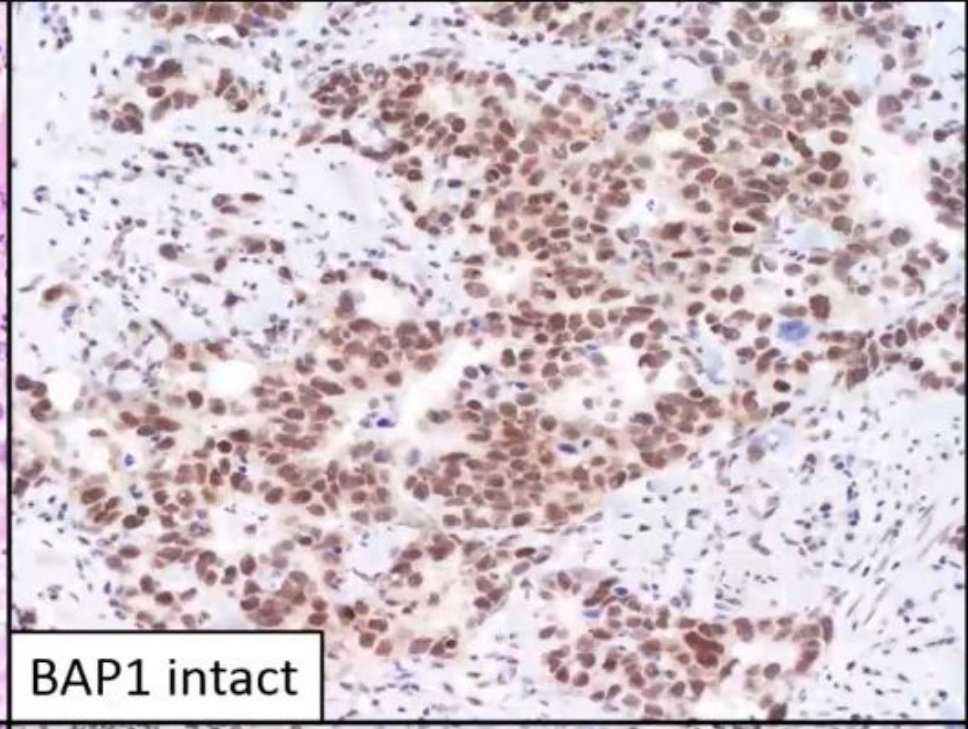
CDH17

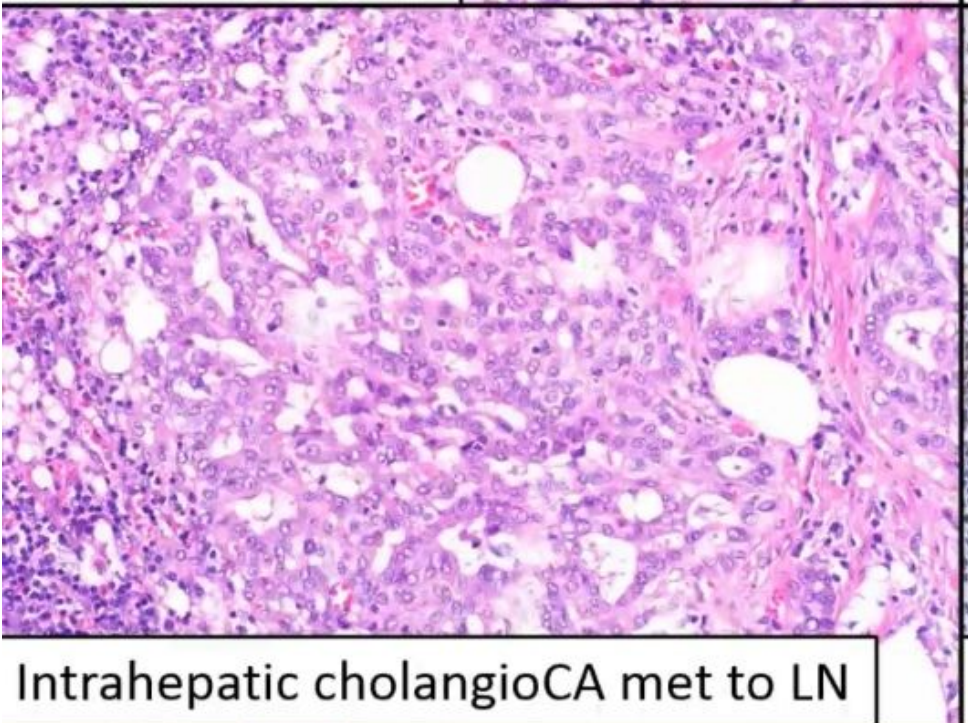
High-Expressing Group (positive in >90% of cases; generally diffuse, strong)
Colorectal adenocarcinoma
Appendiceal adenocarcinoma
Low-grade appendiceal mucinous neoplasm
Midgut well-differentiated neuroendocrine tumor
Moderately High-Expressing Group (positive in >50-90% of cases; weaker and less intense)
Esophageal adenocarcinoma
Gastric adenocarcinoma
Small intestinal adenocarcinoma
Ampullary adenocarcinoma
Mucinous ovarian adenocarcinoma
Intestinal-type sinonasal adenocarcinoma
Urinary bladder adenocarcinoma
Urachal adenocarcinoma
Variably Expressing Group (positive in 10-50% of cases; generally weak, patchy)
Pancreatic adenocarcinoma
Biliary tract adenocarcinoma
Endocervical adenocarcinomas, especially intestinal-type
Ovarian intestinal-type mucinous borderline tumor
Pancreatic well-differentiated neuroendocrine tumor
Rectal well-differentiated neuroendocrine tumor
Poorly differentiated neuroendocrine carcinoma
Yolk sac tumor
Rarely Expressing Group (positive in <10% of cases)
Pulmonary adenocarcinoma
Endometrial adenocarcinoma
Prostatic adenocarcinoma

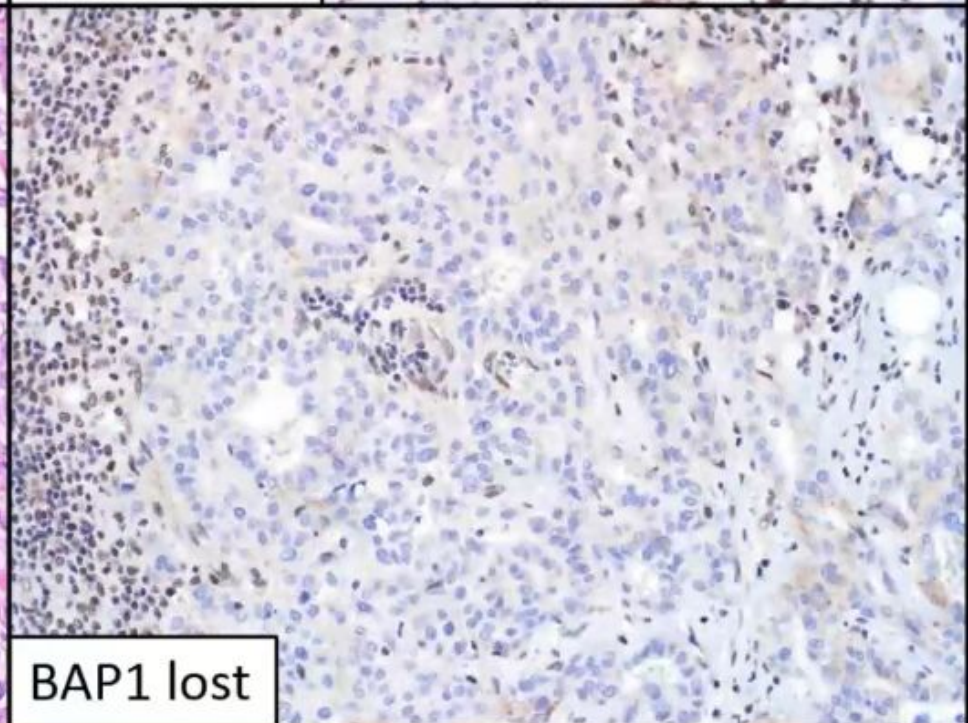
CDX2 Expression in Epithelial Neoplasms

- With TFs there are often high, variably, and rarely expressing groups
- Expression extent and intensity stronger in high-expressing group


Gallbladder AdCA


BAP1 intact


Intrahepatic cholangioCA met to LN


BAP1 lost

BAP1 to support a diagnosis of small duct iCC

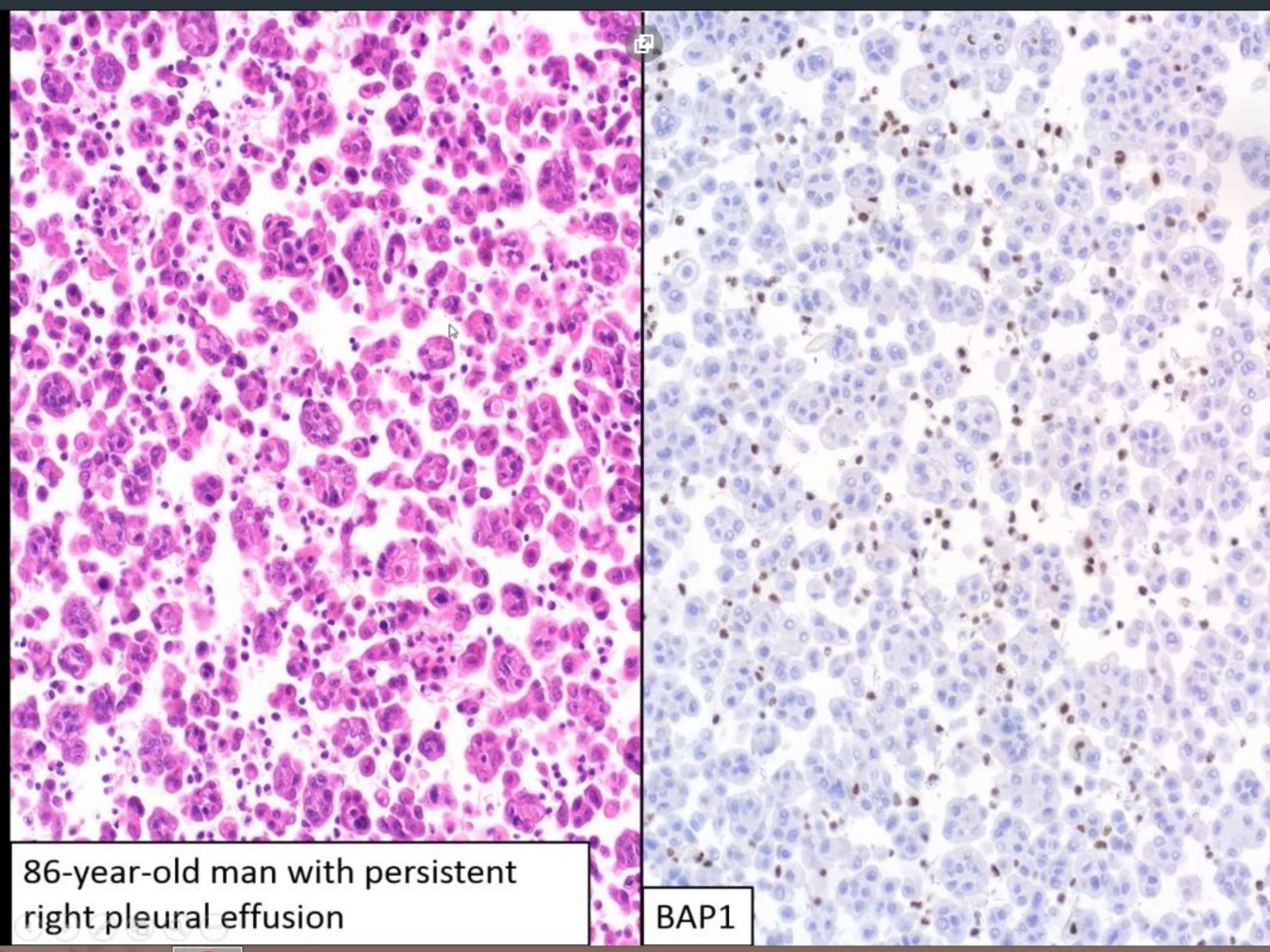
Site	BAP1 loss	SMAD4 loss
Intrahepatic (n=27)	22%	16%
Perihilar (n=8)	13%	43%
Cystic Duct (n=3	0%	33%
Gallbladder (n=46)	7%	37%
Distal (n=12)	0%	60%
Pancreatic (n=77)	3%	37%

Data from Pelletier and Bellizzi (USCAP 2019)

Gallbladder Ac

Intrahepatic cholangioCA met to LN

BAP1 lost


86-year-old man with persistent right pleural effusion
BAP1

SMAD4 Loss to Support the Pancreatic Origin of an Adenocarcinoma

SMAD4 Loss in Adenocarcinoma Stratified by Anatomic Site

Site	Frequency of Loss
Pancreas	58% (19/33)
Appendix	27% (6/22)
Colorectal	17% (86/522)
Cholangiocarcinoma	16% (6/37)
Lung	10% (2/21)
Esophagus	4% (2/53)
Breast	3% (8/266)
Stomach	2% (1/45)
Non-serous ovarian	2% (1/42)
Papillary thyroid	0% (0/20)
Hepatocellular carcinoma	0% (0/12)
High-grade serous ovarian	0% (0/26)
Endometrial	0% (0/122)
Kidney	0% (0/33)

Reference: Ritterhouse L, et al.(290)

SMAD4 Loss in Gastroesophageal AdCA

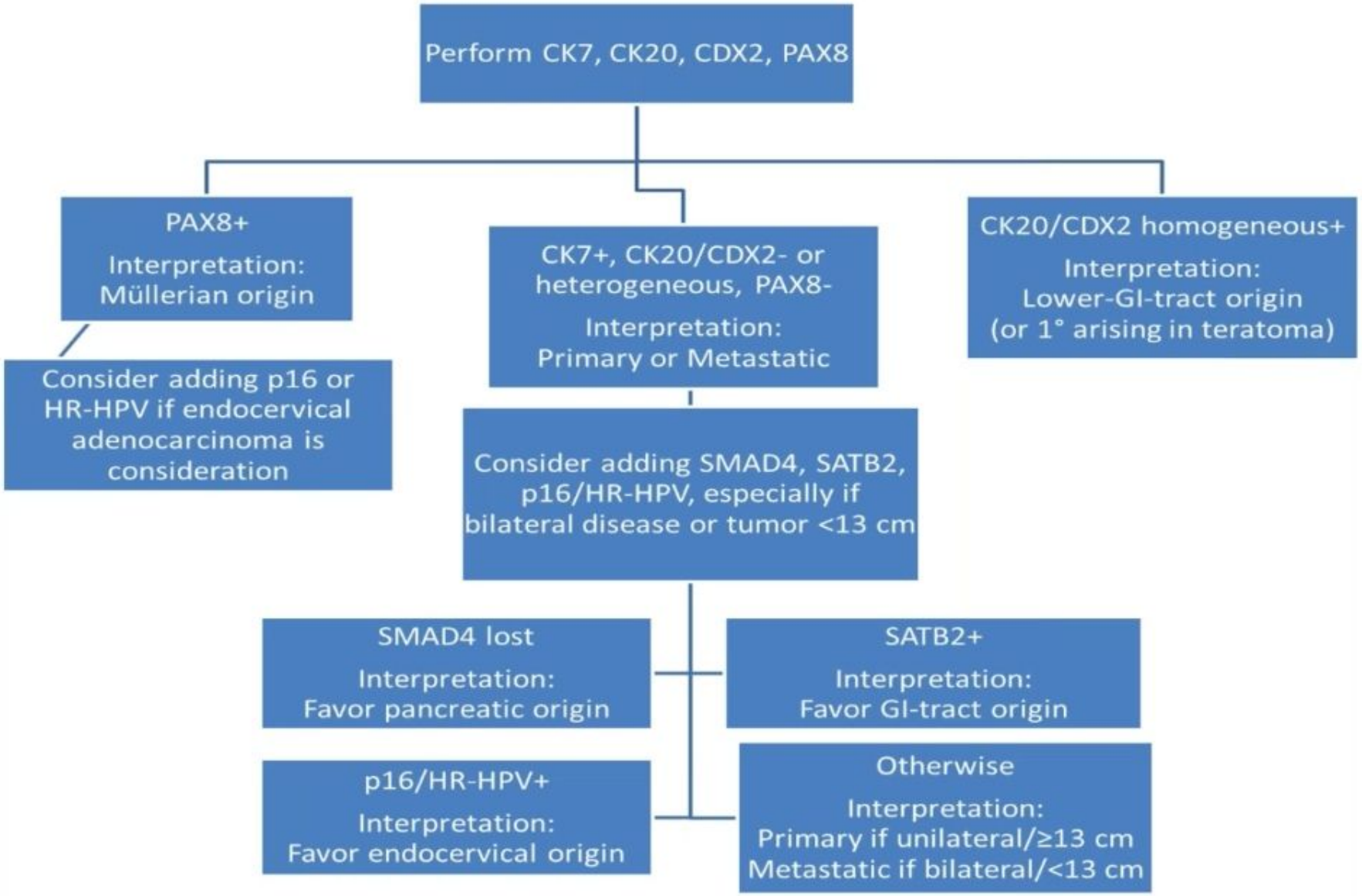
	SMAD4 Loss	TTF-1/Napsin A+	EBV+
Esophagus (n=109)	10%	4%	0%
GEJ (n=68)	7%	1.5%	0%
Stomach (n=72)	4%	6%	4% (n=3
Primary (n=229)	6%		
LN metastasis (n=81)	11%		
Distant metastasis (n=25)	**4%**		
Recurrence (n=4)	0%		

PAX8 vs PAX2 Expression

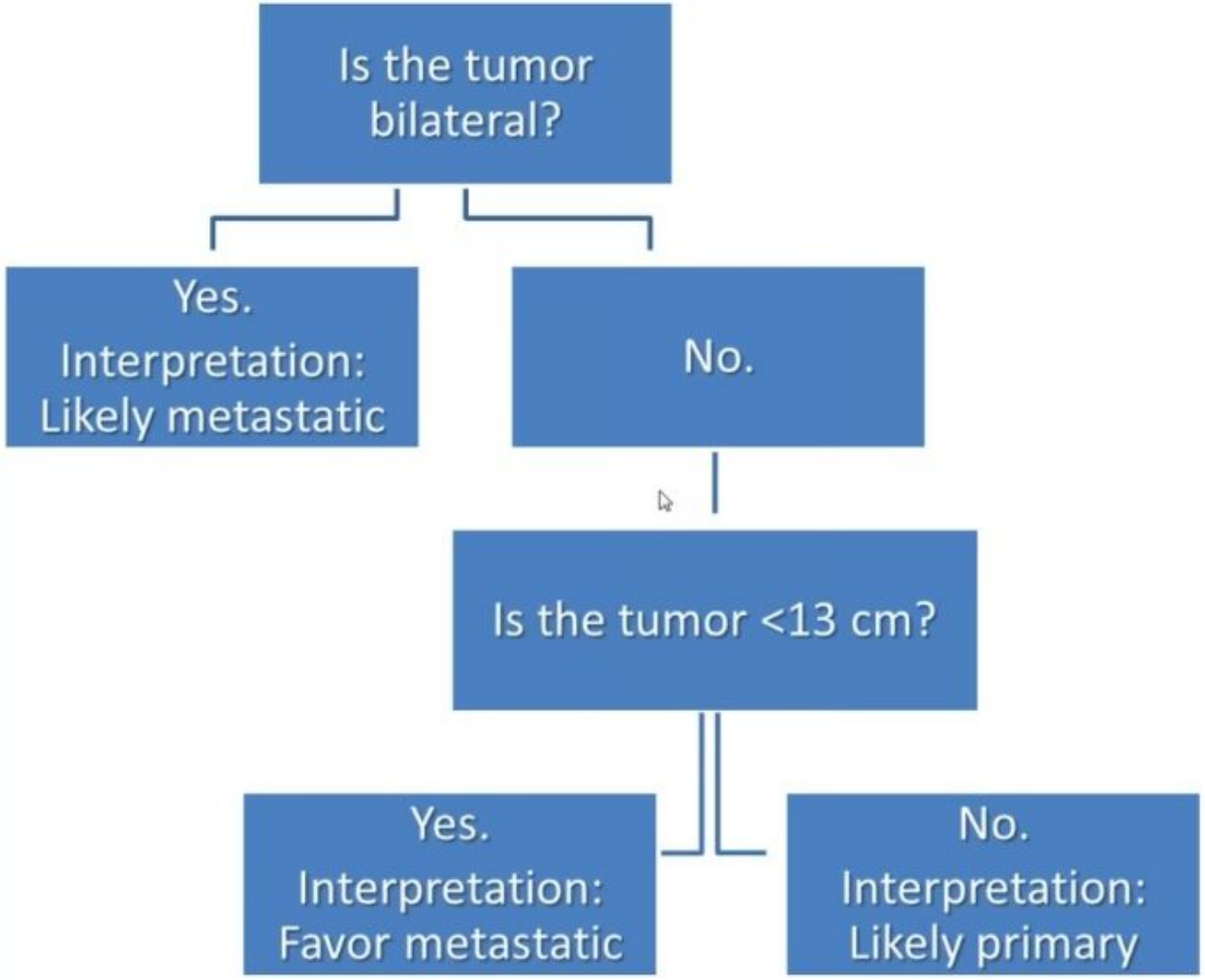
Tumor Type	PAX8 (% Positive)	PAX2 (% Positive)
Clear cell	97	95
Papillary	100	76
Chromophobe	88	56
Collecting duct	71	43
Serous	98	55
Endometrioid	94	25
Clear cell	100	19
Transitional	67	11
Mucinous	29	10
Thyroid	91	0

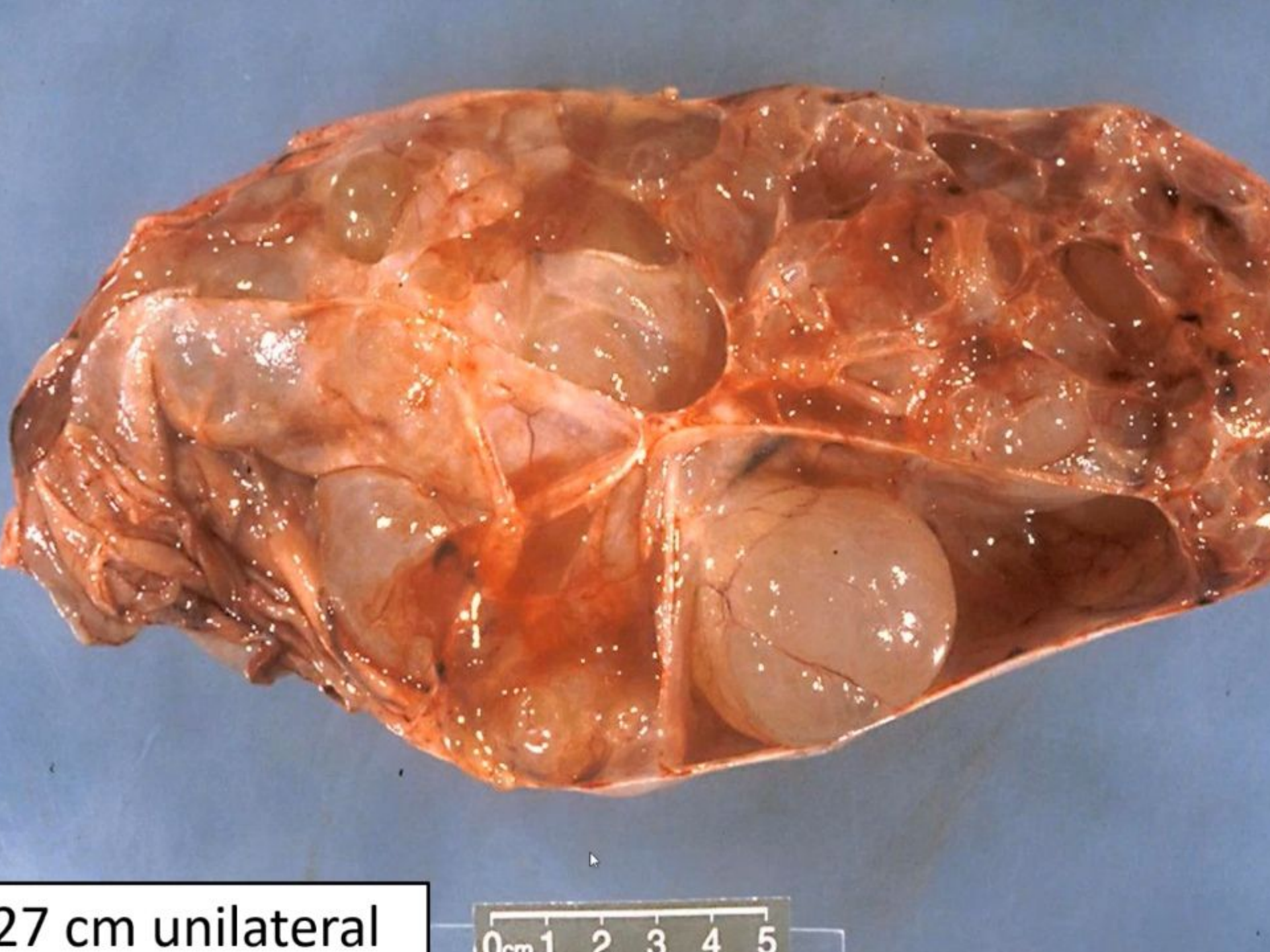
Ozcan A, et al. *Am J Surg Pathol* 2011;35:1837-47.
Ozcan A, et al. *Arch Pathol Lab Med* 2012;136:1541-51.
Laury AR, et al. *Am J Surg Pathol* 2011;35:816-26.

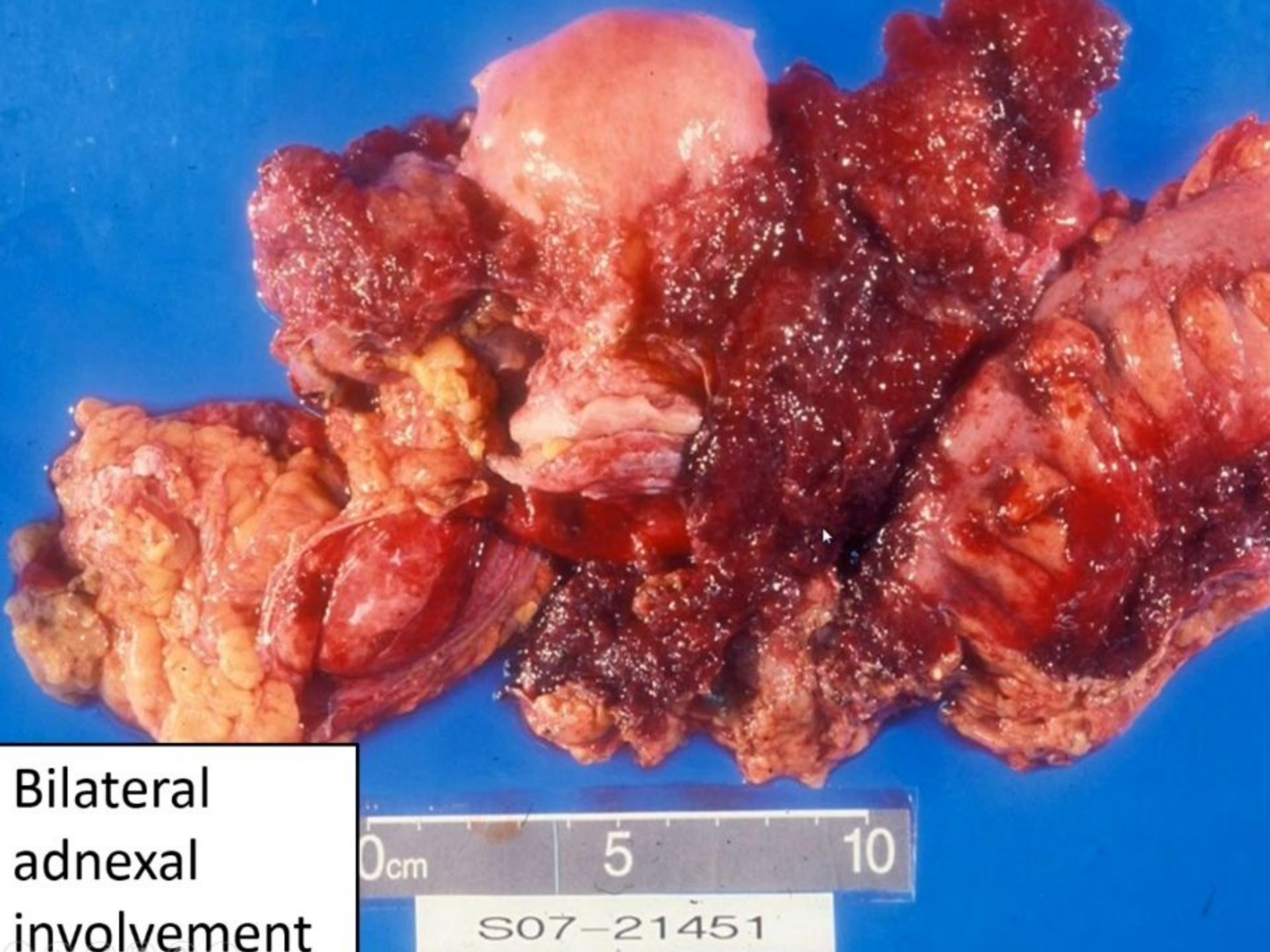
1° Ovarian Surface Epithelial Tumor vs Metastasis



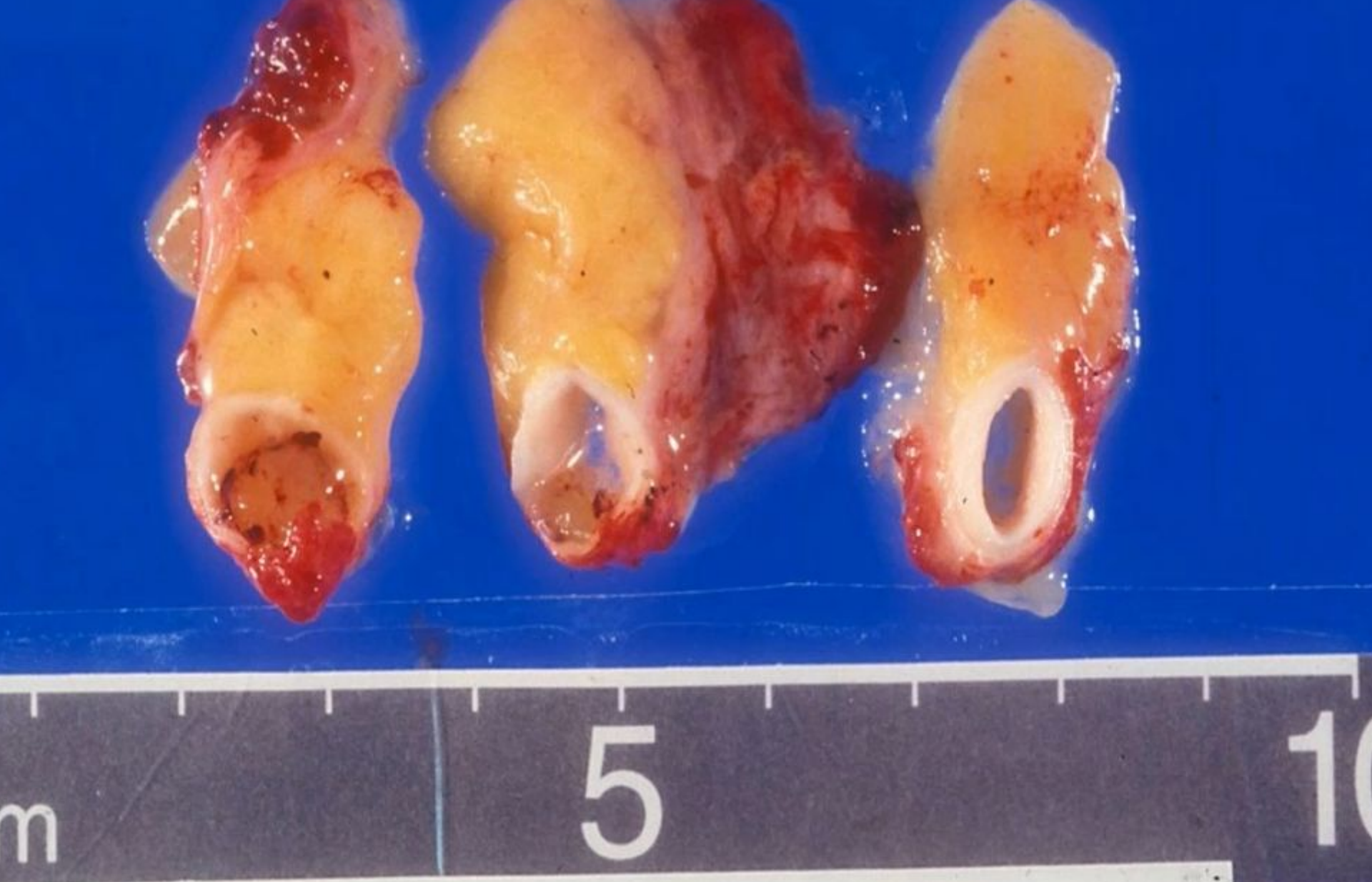
1° Ovarian Surface Epithelial Tumor vs Metastasis



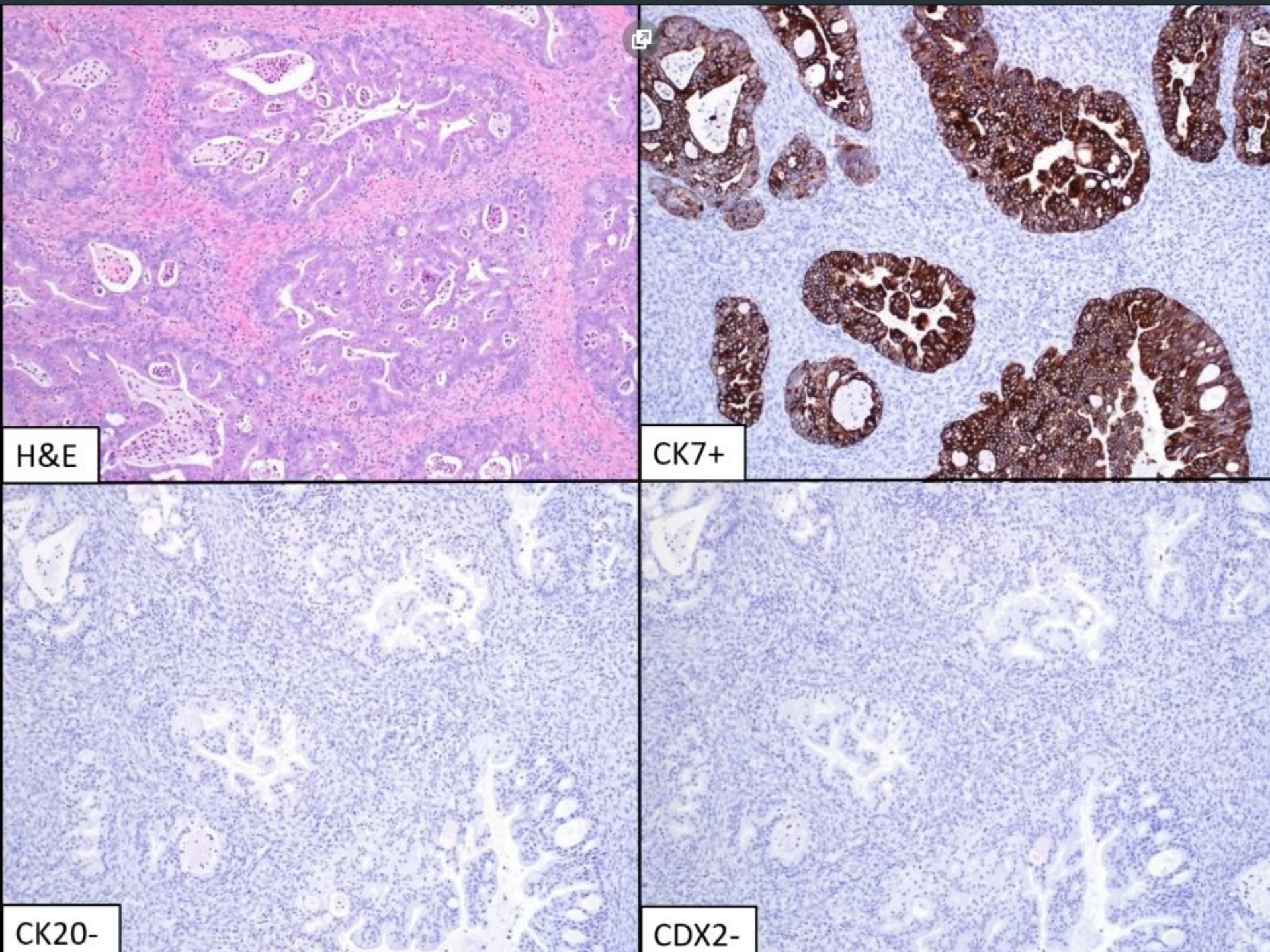

27 cm unilateral
0cm 1 2 3 4 5



Bilateral adnexal involvement



S07-21451


H&E
CK7+
CK20-
CDX2-

Comparison of Immunohistochemistry to a Clinicopathologic Classifier in Diagnosis of Primary Mucinous Ovarian Tumor

Neha Varshney[1,2], Ilham O Farhat[1], and Andrew M Bellizzi[1]

1. University of Iowa Hospitals and Clinics, Iowa City, IA; 2. The University of Arizona Health Sciences, Tucson

Abstract

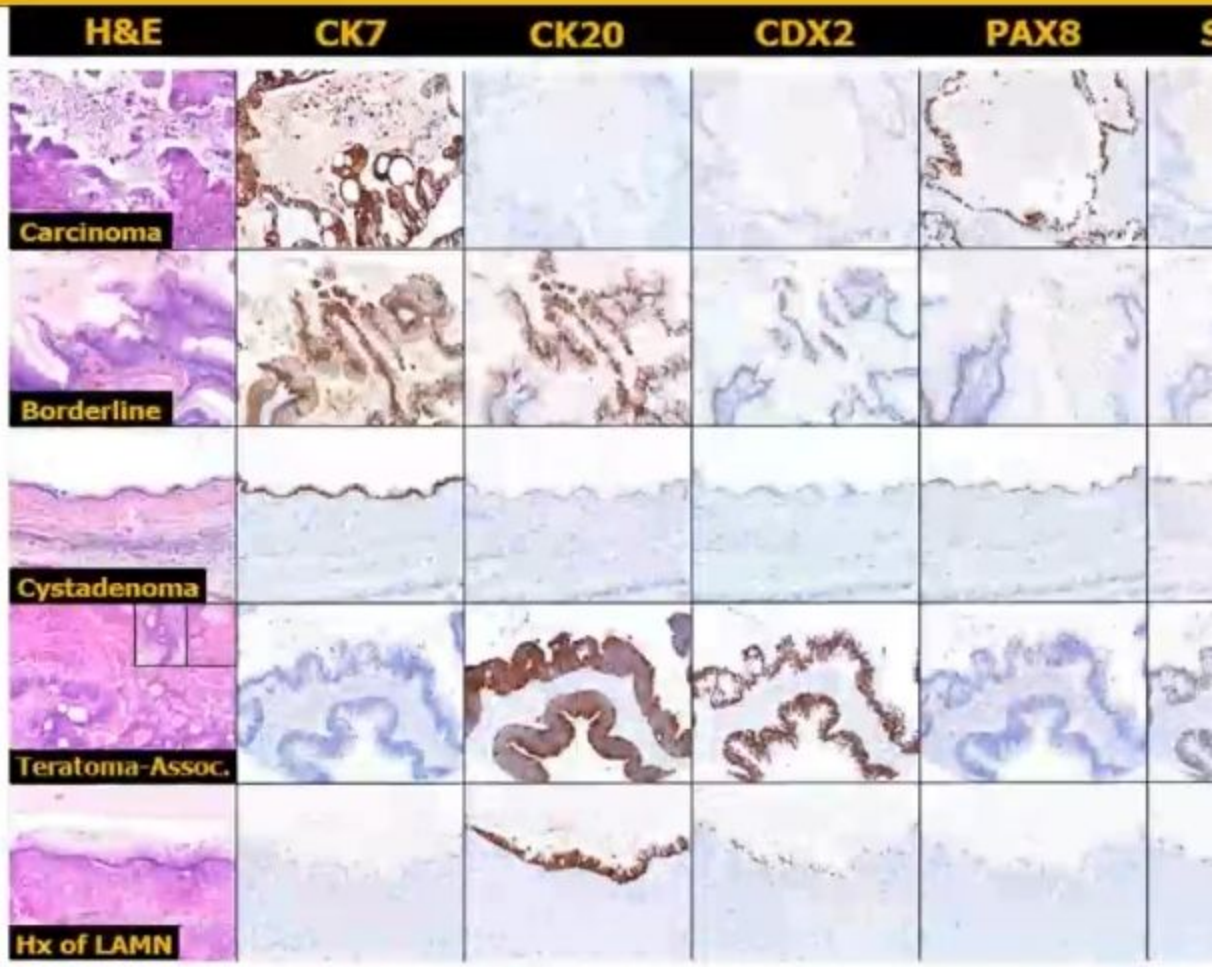
Background: Ovarian involvement by non-Müllerian mucinous epithelial tumors (i.e., low-grade appendiceal mucinous neoplasm or metastatic carcinoma) is frequently mistaken for a primary mucinous ovarian tumor. We routinely employ a clinicopathologic classifier originally published by Yemelyanova (PMID: 18162780) and immunohistochemistry (IHC) in this setting. We undertook this study, at least in part, given availability of a newly validated pan-gastrointestinal marker (CDH17) and monoclonal PAX8 in our laboratory.

Design: IHC for CK7, CK20, CDX2, PAX8 (rabbit monoclonal EP298), SATB2, and CDH17 was performed on tissue microarrays of 101 primary mucinous ovarian tumors (33 carcinomas, 41 borderline tumors, 27 cystadenomas). Markers were assessed for intensity (0-3+) and extent (0-100%) of expression with an H-score calculated (intensity*extent). Patient age, tumor size (cm), and presence of uni- or bilateral tumor was recorded. For the clinicopathologic classifier, bilateral tumors and unilateral tumors <13 cm are designated metastatic; for the IHC classifier, cases with any PAX8-positivity are designated primary, PAX8-negative tumors with CK20 and/or CDX2 H-scores ≥200 are designated metastatic, and all others are deferred.

Results: Detailed data are presented in the Table. CDH17 was frequently, strongly expressed across all three tumor classes (44%; mean/median H-score 164/175); SATB2 was only expressed by 2 tumors (H-scores 230, 300), both of which arose in association with a mature cystic teratoma; somewhat surprisingly, PAX8 was frequently, strongly expressed (73%; mean/median H-score 206/240).

Although the IHC classifier was only marginally more frequently correct than the clinicopathologic classifier (70% vs 62%), it was very rarely incorrect (4%, while it deferred in 26%).

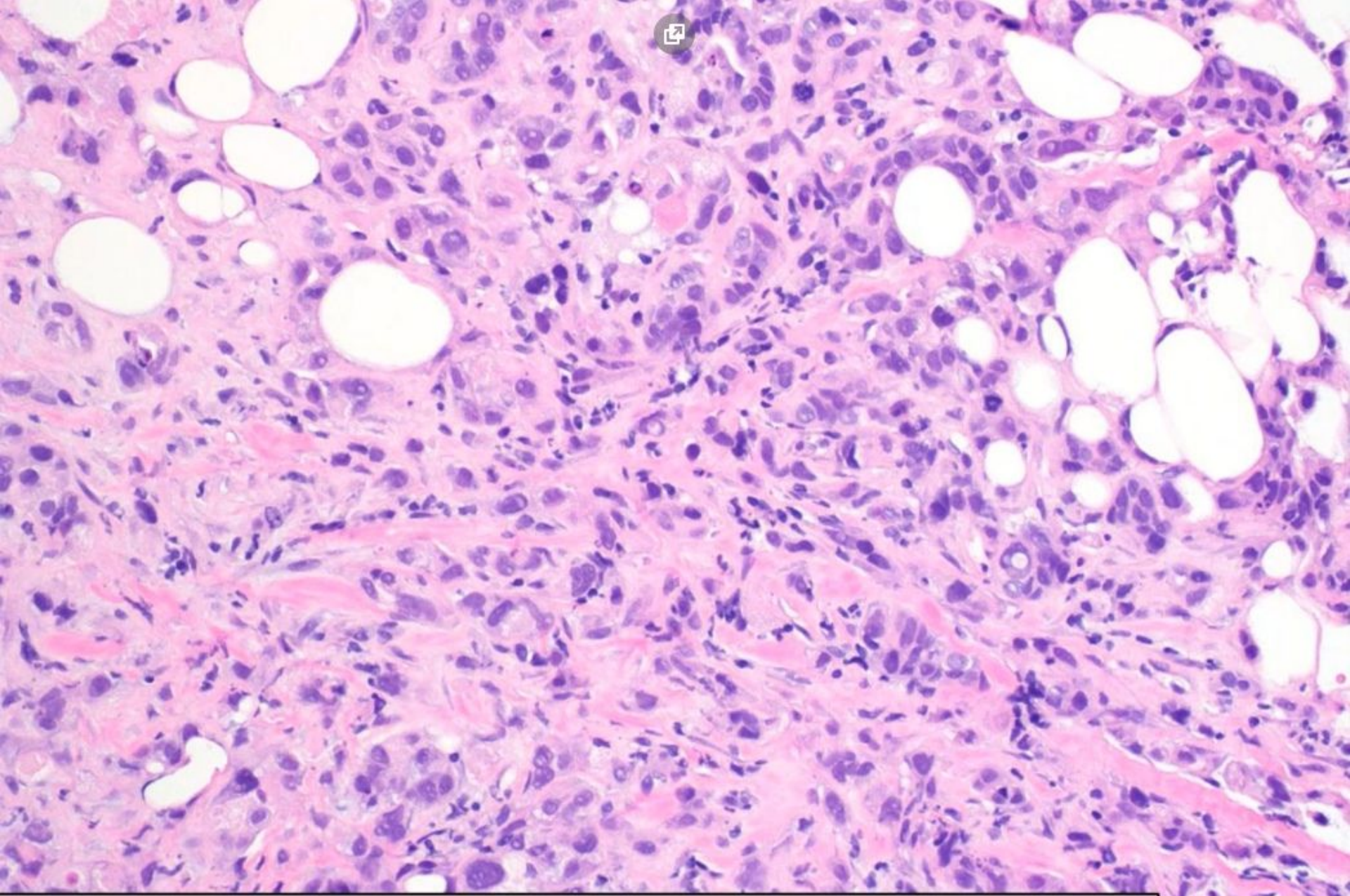
Conclusion: This study affirms our combined clinicopathologic and IHC approach to tumors in the ovary with mucinous histology. Unlike SATB2 (which is only strongly positive in rare primary tumors arising in a teratoma), CDH17 has no value in this setting. Frequent



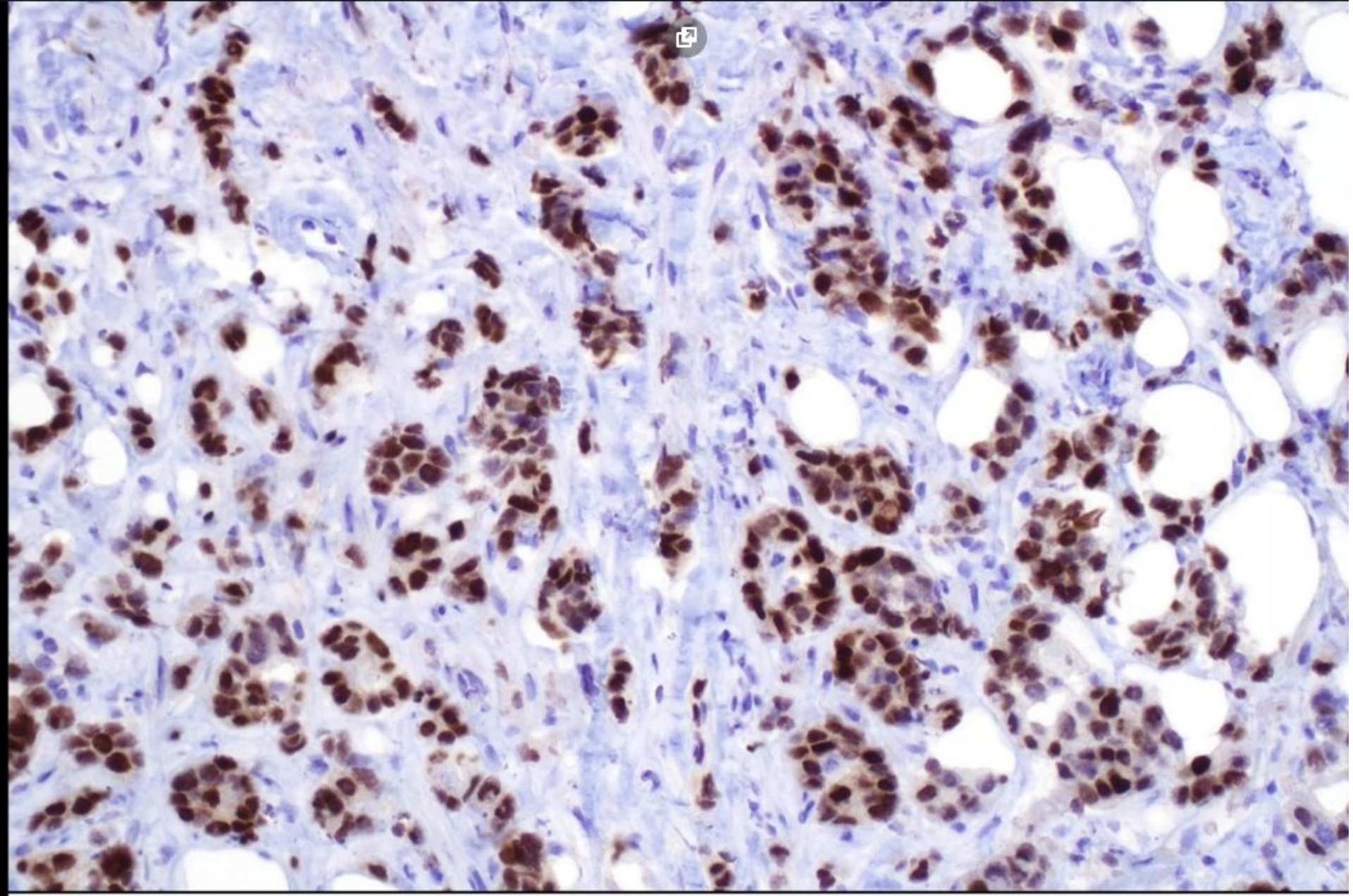
Diagnosis	Age Mean (Median)	Unilateral/ Bilateral	Size (cm) Mean (Median)	CK7 % Positive Mean (Median) H-score	CK20 % Positive Mean (Median) H-score	CDX2 % Positive Mean (Median) H-score	PAX8 % Positive Mean (Median) H-score	CDH17 % Positive Mean (Median) H-score	Clinicopathologic Classifier (Primary/ Metastatic)
Carcinoma	57 (57)	U: 82% B: 18%	19 (17)	97% 215 (265)	48% 77 (60)	39% 51 (15)	75% 202 (260)	52% 168 (175)	P: 64% M: 36%
Borderline	51 (55)	U: 93% B: 7%	19 (20)	97% 238 (245)	51% 103 (65)	35% 88 (49)	85% 196 (200)	49% 159 (175)	P: 71% M: 29%

Regional Differential Diagnosis: 1° vs Metastasis

Site	Additional Considerations
Mediastinum	Lung is principal consideration, regardless of TTF-1 result Thymic neoplasm: pPAX8, p40; KIT, CD5 (latter 2 in thymic carcinoma) Germ cell neoplasm: SALL4 Well- and dedifferentiated liposarcoma: MDM2/CDK4
Pleura	Mesothelioma: calretinin, WT-1, D2-40, CK5/6, BAP1 (loss)
Peritoneum	Müllerian adenocarcinoma: PAX8 Mesothelioma: calretinin, WT-1, D2-40, CK5/6, BAP1 (loss)
Retroperitoneum	Renal cell carcinoma: PAX8 Adrenal cortical carcinoma: SF1, melan A, calretinin, inhibin A, synapto Germ cell tumor: SALL4 Liposarcoma: MDM2/CDK4
Somatic soft tissue	Always consider sarcoma, even if keratin-positive
Bone	Blastic metastasis: prostate (PSA, PrAP, NKX3.1), breast (GATA-3) Lytic metastasis: kidney (PAX8), thyroid (thyroglobulin if TTF-1/PAX8 co-expressing) Mixed metastasis: lung (TTF-1)



61-year-old man with h/o muscle invasive bladder cancer s/p cystectomy presenting with carcinomatosis; peritoneal biopsy



GATA-3, CK7+ (p40, PSA, TTF-1-); p40 is only 80-90% sensitive for UC;
Utility of GATA-3 in p40-negative urothelial carcinoma

GATA-3 Expression in UC vs SCC

	% (n)	Mean H-score
Urothelial Carcinoma	84% (42/50)	228
Squamous Cell Carcinoma:		80
Anus	37% (7/19)	
Cervix	22% (7/32)	
Esophagus	13% (3/24)	
Larynx	0% (0/27)	
Lung	0% (0/31)	
Oral Cavity	0% (0/26)	
Penis	29% (8/28)	
Skin	43% (10/23)	
Vagina	50% (13/26)	
Vulva	23% (6/26)	

Gailey MP, Bellizzi AM. Poster at 2014 USCAP Annual Meeting.

Squamous Cell Carcinoma vs Urothelial Carcinom

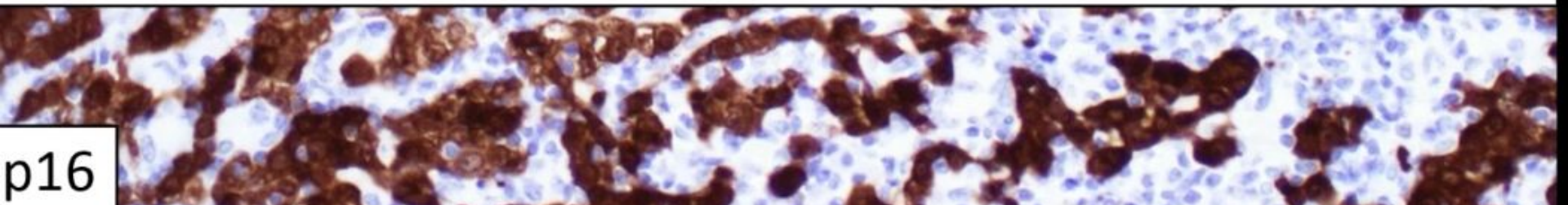
	Squamous Cell Carcinoma	Urothelial Carcinoma
p40	≥95%	85%
34βE12	≥95%	≥95%
CK5/6	≥95%	50%
GATA-3	20%	80%
Uroplakin II	<1%	70%
CK7	30%	≥90%
CK20	<2%	50%
CD44 (loss)	5%	50%

p16-positivity in SCC supports an association with high-risk HPV:

1. Anogenital
2. Oropharyngeal (tonsil, base of tongue)

We routinely test:

1. Oropharyngeal primaries
2. Cervical LN metastases of occult origin (especially cystic ones)



Please Read My Article☺

REVIEW ARTICLE

An Algorithmic Immunohistochemical Approach to Define Tumor Type and Assign Site of Origin

Andrew M. Bellizzi, MD

Abstract: Immunohistochemistry represents an indispensible complement to an epidemiology and morphology-driven approach to tumor diagnosis and site of origin assignment. This review reflects the state of my current practice, based on 15-years' experience in Pathology and a deep-dive into the literature, always striving to be better equipped to answer the age old questions, "What is it, and where is it from?" The tables and figures in this manuscript are the ones I "pull up on the computer" when I am teaching at the microscope and turn to myself when I am (frequently) stuck. This field is so exciting because I firmly believe that, through the application of next-generation immunohistochemistry, we can provide better answers than ever before. Specific topics covered in this review include (1) broad tumor classification and associated screening markers; (2) the role of cancer epidemiology in determining pretest probability; (3) broad-spectrum epithelial markers; (4) nonanatomical expression of broad tumor class screening markers; (5) a morphologic pattern-based approach to poorly to undifferentiated malignant neoplasms; (6) a morphologic and immunohistochemical approach to define 4 main carcinoma types; (7) CK7/CK20 coordinate expression; (8) added value of semiquantitative immunohistochemical stain assessment; algorithmic immunohistochemical approaches to (9) "garden variety" adenocarcinomas presenting in the liver, (10) large polygonal cell adenocarcinomas, (11) the distinction of primary surface ovarian epithelial tumors with mucinous features from metastasis, (12) tumors presenting at alternative anatomic sites, (13) squamous cell carcinoma versus urothelial carcinoma, and neuroendocrine neoplasms, including (14) the distinction of pheochromocytoma/paraganglioma from well-differentiated neuroendocrine tumor, site of origin assignment in (15) well-differentiated neuroendocrine tumor and (16) poorly differentiated neuroendocrine carcinoma, and (17) the distinction of well-differentiated neuroendocrine tumor G3 from poorly differentiated neuroendocrine carcinoma; it concludes with (18) a discussion of diagnostic considerations in the broad-spectrum keratin/CD45/b-100-"triple-negative" neoplasm.

Key Words: immunohistochemistry, tumor classification, carcinoma of unknown primary, site of origin, differential diagnosis

(*Adv Anat Pathol* 2020;00:000–000)

NEXT-GENERATION IMMUNOHISTOCHEMISTRY AND THE PRIMACY OF LINEAGE-RESTRICTED TRANSCRIPTION FACTORS

"Next-generation immunohistochemistry" refers to the mining of the molecular genetic and developmental biology literature to "discover" new immunohistochemical markers, including those identified through gene expression profiling, protein correlates of molecular genetic events, and lineage-restricted transcription factors. While historically our diagnostic armamentarium was geared toward cytoplasmic or membranous differentiation markers, which often demonstrate reduced expression and, thus, reduced sensitivity in poorly differentiated tumors, transcription factors tend to be strongly expressed regardless of differentiation. Table 1 lists the next-generation immunohistochemical markers discussed in this review, associated diagnostic applications, and their "qualifications" as next-generation markers.

There are "immuno-optimists" and "immuno-pessimists." I like to think I am an "immuno-realist." There is no "perfect" immunohistochemical marker, and in most instances a panel of immunohistochemical stains should be applied to adjudicate an epidemiology and morphology-driven differential diagnosis. The "immuno-pessimists" are perfectly fine with an *EWSR1* rearrangement driving Ewing sarcoma, clear cell sarcoma, desmoplastic small round cell tumor, angiomatoid fibrous histiocytoma, extraskeletal myxoid chondrosarcoma, and sclerosing epithelioid fibrosarcoma but have the unrealistic expectation that a single marker, especially a lineage-restricted transcription factor, will have a single diagnostic application. Even an "old school" next-generation marker like TTF-1 is expressed by lung and thyroid (and mesonephric-like adenocarcinoma, by the way).[1,2] Just like that *EWSR1* rearrangement, transcription factors are "allowed" to exert differential effects in a cell-type-specific manner.

A colleague recently remarked "GATA-3 is ruined" when I let her know that it was the best widely available marker to distinguish pheochromocytoma/paraganglioma from well-differentiated neuroendocrine tumor. Expression in this tumor type is not "random," it is predicted by developmental biology, in which GATA-3 participates in a complex transcriptional network to regulate development of the autonomic nervous system.[3,4] Large-scale immunohistochemical surveys of emerging markers not only confirm what we already know, but provide the opportunity to discover additional "tools." For example, when Miettinen and colleagues described SOX10 expression in 12% of 486 invasive ductal carcinomas of breast origin, it was not "aberrant" staining, but rather, a signal demanding an explanation. It turns out that SOX10 expression is restricted to estrogen receptor (ER)-negative breast cancers and that SOX10-positivity is, thus, incredibly useful in the diagnosis of triple-negative breast cancer.

My favorite immunohistochemical markers are oligospecific transcription factors. I refer to them as the "Swiss Army Knives" of immunopathology, capable of "solving" multiple differential diagnoses. GATA-3 is a classic example, and Miettinen *et al*[5] highlighted 9 unique diagnostic contexts in which GATA-3 could be useful! In addition to the familiar ones in which GATA-3 functions as a positive marker of breast and urothelial carcinoma,

From the Department of Pathology, University of Iowa Hospitals and Clinics, University of Iowa Carver College of Medicine, Iowa City, IA.

The authors have no funding or conflicts of interest to disclose.

Reprints: Andrew M. Bellizzi, MD, Department of Pathology, University of Iowa Hospitals and Clinics, University of Iowa Carver College of Medicine, 200 Hawkins Drive, Iowa City, IA 52242 (e-mail: andrew-bellizzi@uiowa.edu).

Please Read My Other Article☺

Human Pathology (2020) 96, 1–11

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

Hans popper society current topic

Immunohistochemistry in the diagnosis and classification of neuroendocrine neoplasms: what can brown do for you?☆

Andrew M Bellizzi MD*

Department of Pathology, University of Iowa Hospitals and Clinics and Carver College of Medicine, Iowa City, IA, USA
University of Iowa Neuroendocrine Cancer Program, University of Iowa Hospitals and Clinics and Holden Comprehensive Cancer Center, Iowa City, IA 52242, USA

Received 6 December 2019; accepted 8 December 2019

Keywords:
Neuroendocrine;
World Health Organization Classification;
Carcinoma of Unknown Primary;
Immunohistochemistry;
Differential Diagnosis;
INSM1;
Ki-67

Summary This review is based on a presentation given at the Hans Popper Hepatopathology Society companion meeting at the 2019 United States and Canadian Academy of Pathology Annual Meeting. It presents updates on the diagnosis and classification of neuroendocrine neoplasms, with an emphasis on the role of immunohistochemistry. Neuroendocrine neoplasms often present in liver biopsies as metastases of occult origin. Specific topics covered include 1. general features of neuroendocrine neoplasms, 2. general neuroendocrine marker immunohistochemistry, with discussion of the emerging marker INSM1, 3. non-small cell carcinoma with (occult) neuroendocrine differentiation, 4. the WHO Classification of neuroendocrine neoplasms, with discussion of the 2019 classification of gastroenteropancreatic neoplasms, 5. use of Ki-67 immunohistochemistry, 6. immunohistochemistry to assign site of origin in neuroendocrine metastasis of occult origin, 7. immunohistochemistry to distinguish well-differentiated neuroendocrine tumor G3 from poorly differentiated neuroendocrine carcinoma, 8. lesions frequently misdiagnosed as well-differentiated neuroendocrine tumor, and 9. required and recommended data elements for biopsies and resections with associated immunohistochemical stains. Next-generation immunohistochemistry, including lineage-restricted transcription factors (e.g., CDX2, islet 1, OTP, SATB2) and protein correlates of molecular genetic events (e.g., p53, Rb), is indispensable for the accurate diagnosis and classification of these neoplasms.

1. General Features of Neuroendocrine Neoplasms

Neuroendocrine neoplasms (NEN) include well-differentiated neuroendocrine tumor (NET), poorly differentiated neuroendocrine carcinoma (NEC), pheochromocytoma (PHEO), and paraganglioma (PARA). All of these are characterized by **general neuroendocrine marker**

☆ Nothing to Disclose: The author of this manuscript has indicated that he has no conflicts of interest that relate to the content of this manuscript.

* Corresponding author at: University of Iowa Hospitals and Clinics, Department of Pathology, 200 Hawkins Drive, Iowa City, IA 52242.
E-mail address: andrew-bellizzi@uiowa.edu.

https://doi.org/10.1016/j.humpath.2019.12.002
0046-8177/© 2019 Elsevier Inc. All rights reserved.

PMID: 31857137