

# The unknown primary tumour: IHC for diagnostic use

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# Unknown primary tumour

- Tumour appearing in metastatic setting without a known primary tumour
- Important to correctly classify since tumour type determines surgical and oncological treatment
- Diagnostic approach for unknown primary tumour can be used in most diagnostic settings

# Unknown primary tumour

- Differences in prognosis
- Differences in treatments
  - Lymphomas (malign or “benign”)
  - Carcinomas
  - Germ cell tumours
  - Sarcomas
- Pathology tests can guide diagnostic proces
- Risk of hereditary or occupational cancer

# Unknown primary tumour

Ideally we want to know

- Type of cancer
- Primary or metastasis
- Site of origin



# Immunohistochemical panels !

Based on

- Most likely diagnosis (clinical information, morphology)
- Relevant other diagnosis
- Rare but important diagnosis

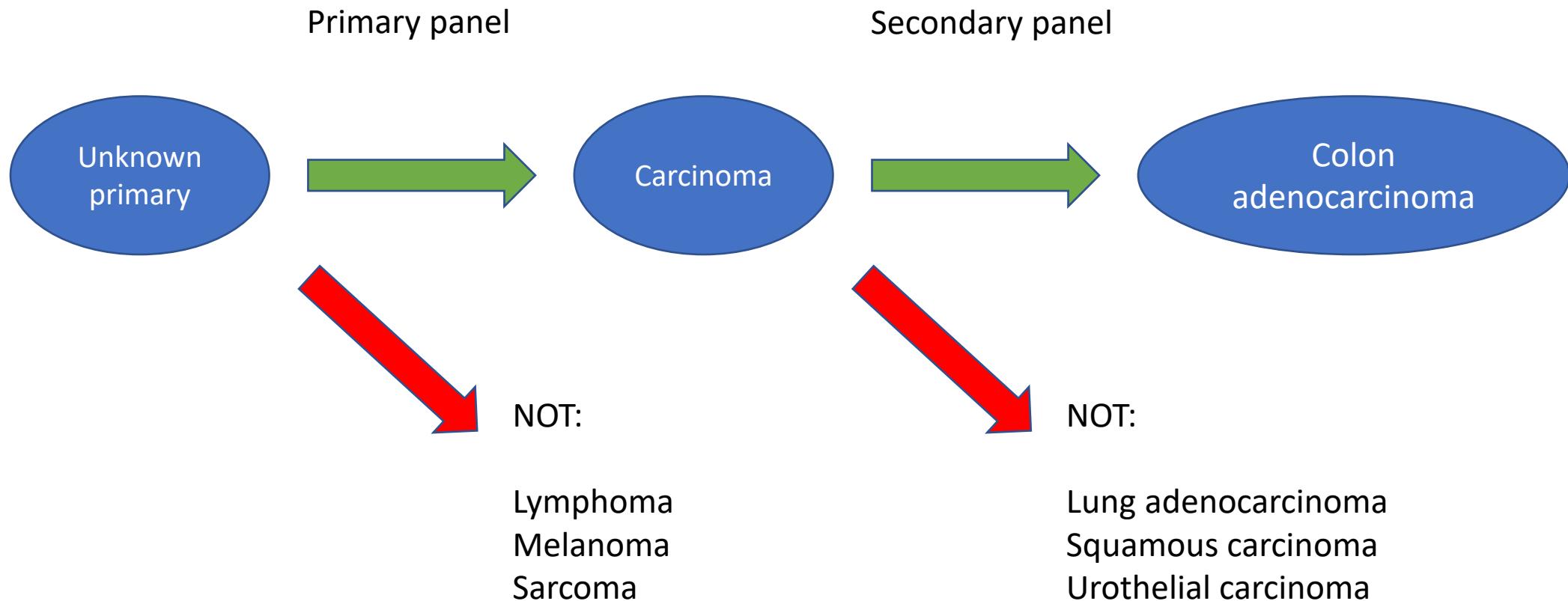
Selection of IHC antibodies for diagnostic algorithm



# IHC panels for unknown primary tumour

- Primary panel
  - Which overall tumour type
- Secondary cytokeratin panel
  - Information on site of origin
- Secondary organ specific panel
  - Confirmation (or rejection) of diagnosis with organ specific marker

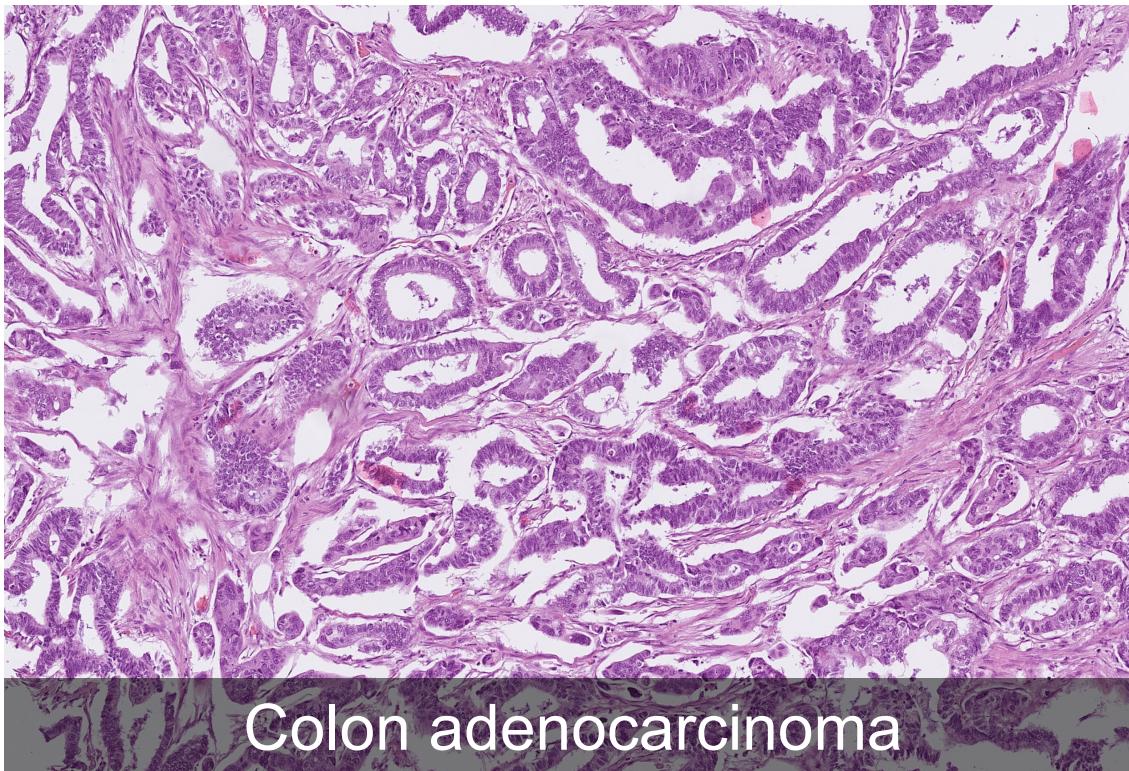
# IHC panels for unknown primary tumour



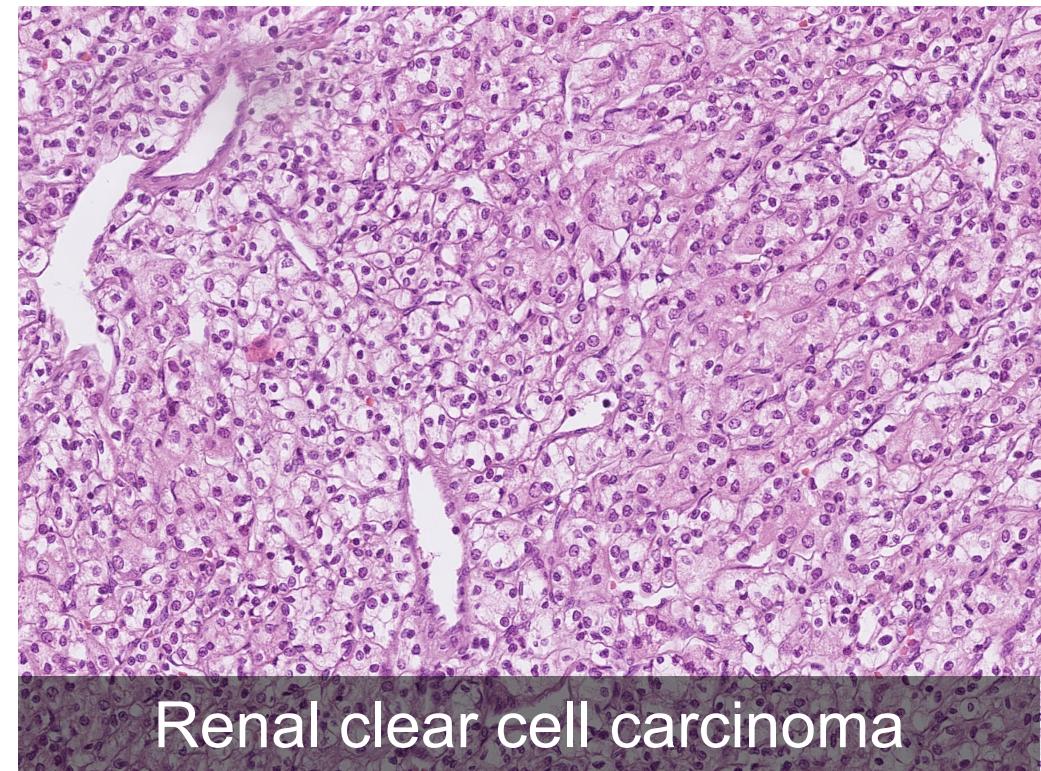
# IHC classification of unknown primary tumour

- Adenocarcinomas (80-90%)
  - Lung, breast, prostate, colon, ovary, pancreas
- Squamous cell carcinoma (5-10%)
  - Lung, esophagus, cervix
- Undifferentiated neoplasms (5-10%)
  - Carcinomas, sarcomas, melanomas, germ cells tumours
  - Lymphomas

# Easy cases – no IHC?!

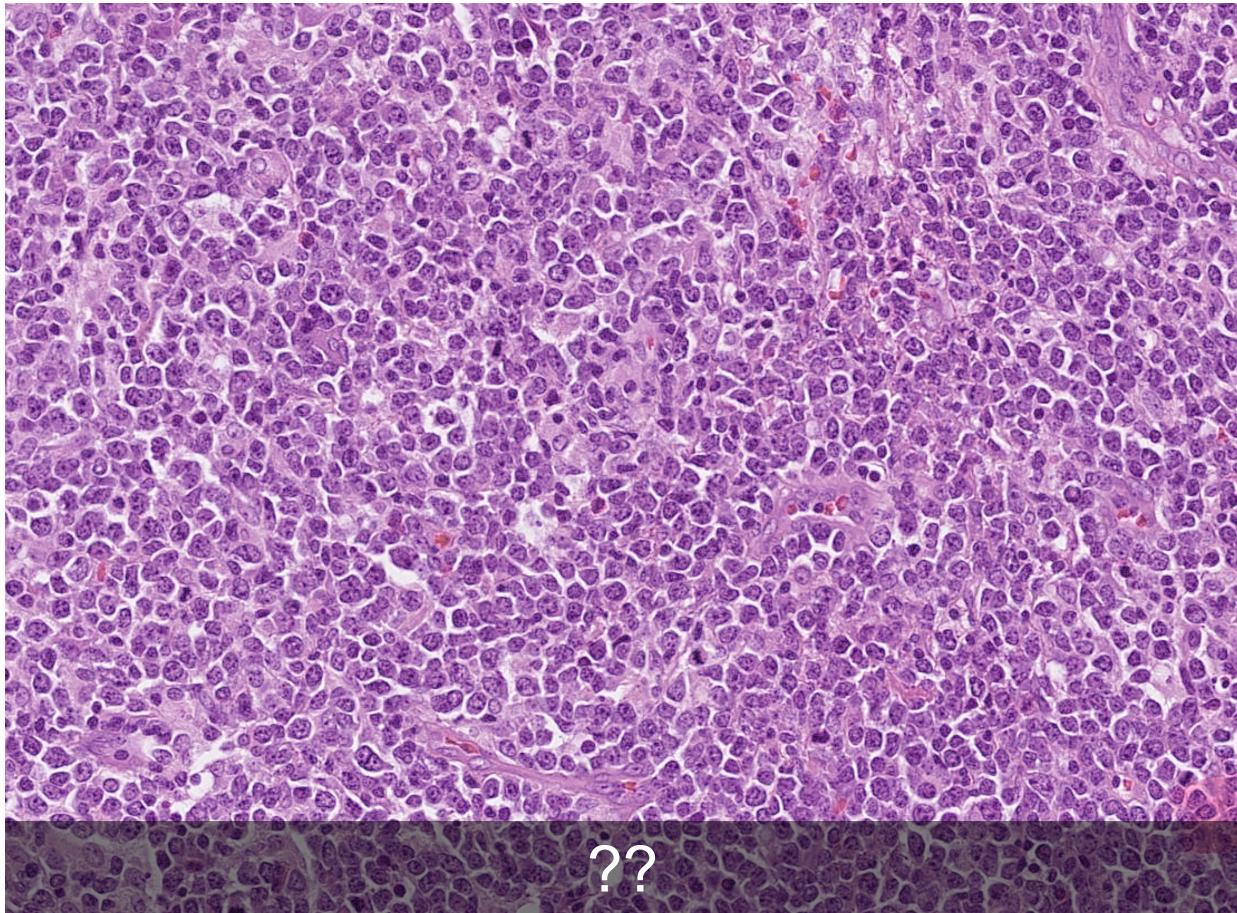


Colon adenocarcinoma



Renal clear cell carcinoma

# Undifferentiated cases



+	~ 100% pos.
(+)	> 90%
+/-	~ 50-90%
-/+	~ 10-50%
(-)	< 10%
-	~ 0%

# Primary panel

Neoplasms	CD45	Pan cytokeratin	S100	Vimentin
Haematopoietic / lymphoid	(+)	(-)	(-)	(+)
Epithelial	-	(+)	-/+	-/+
Mesothelial	-	+	-	+
Mesenchymal	-	(-)	(-)	+
Melanoma	-	(-)	+	+
Germ cell	-	-/+	-/+	+

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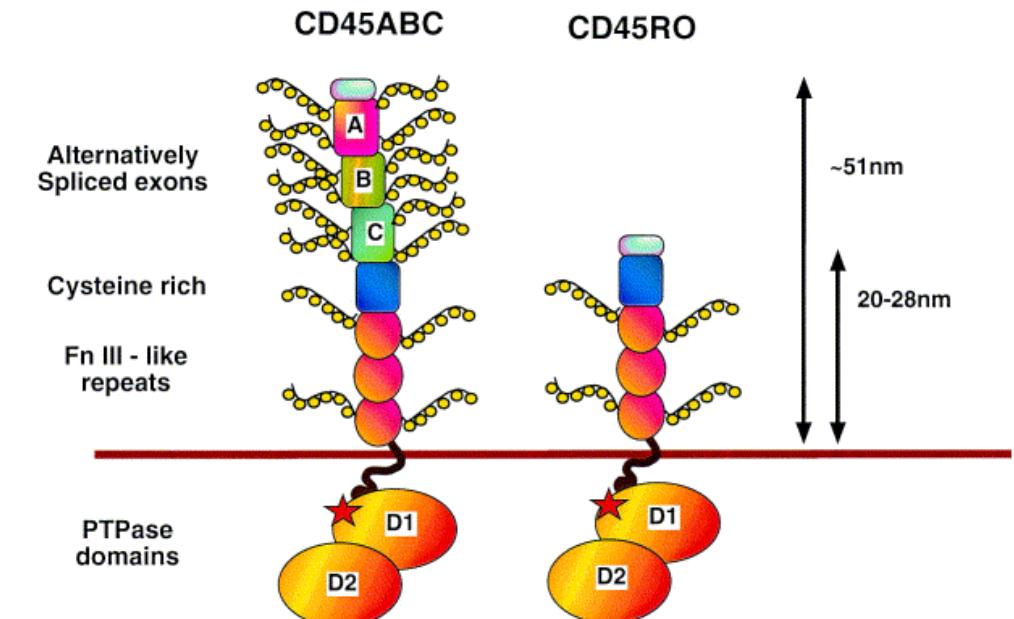
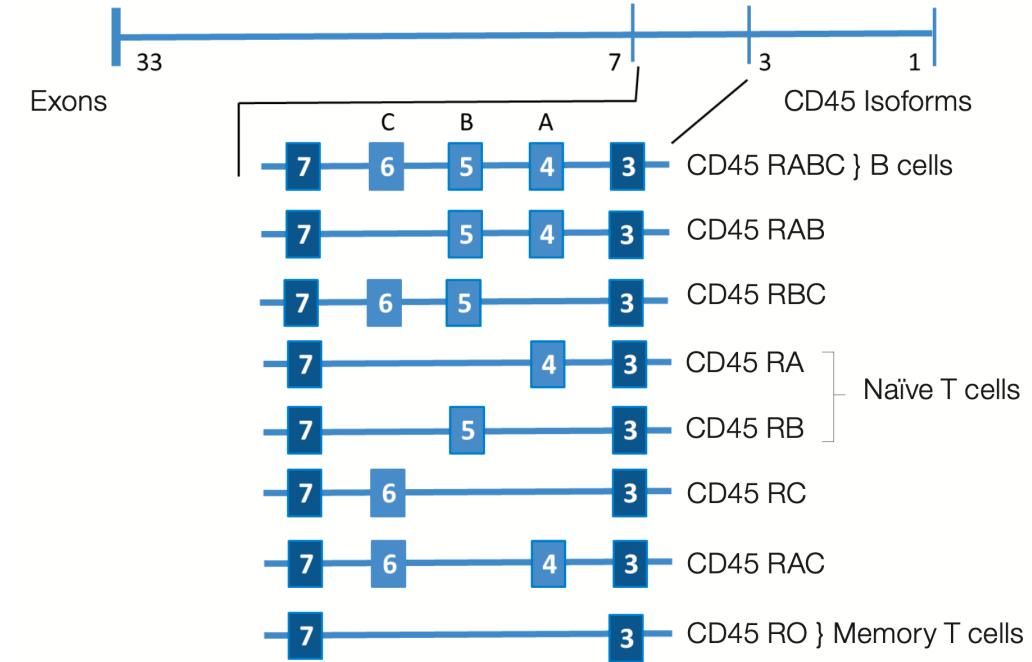
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# CD45 – Leucocyte common antigen

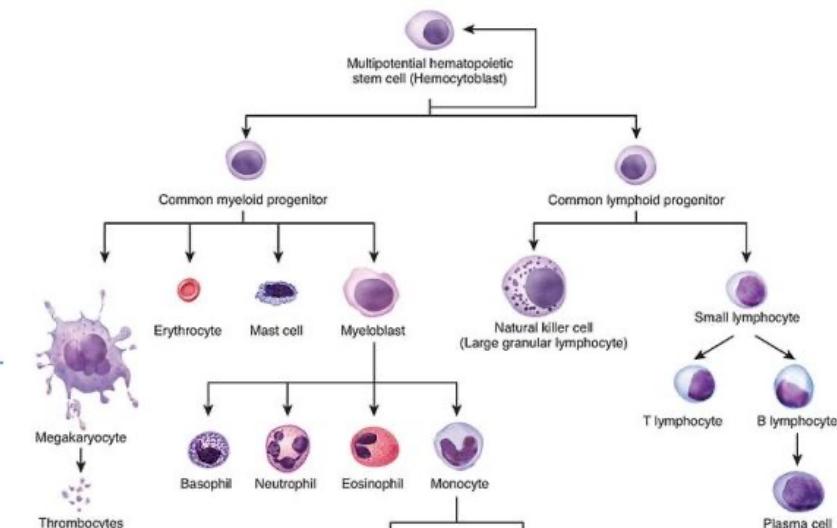
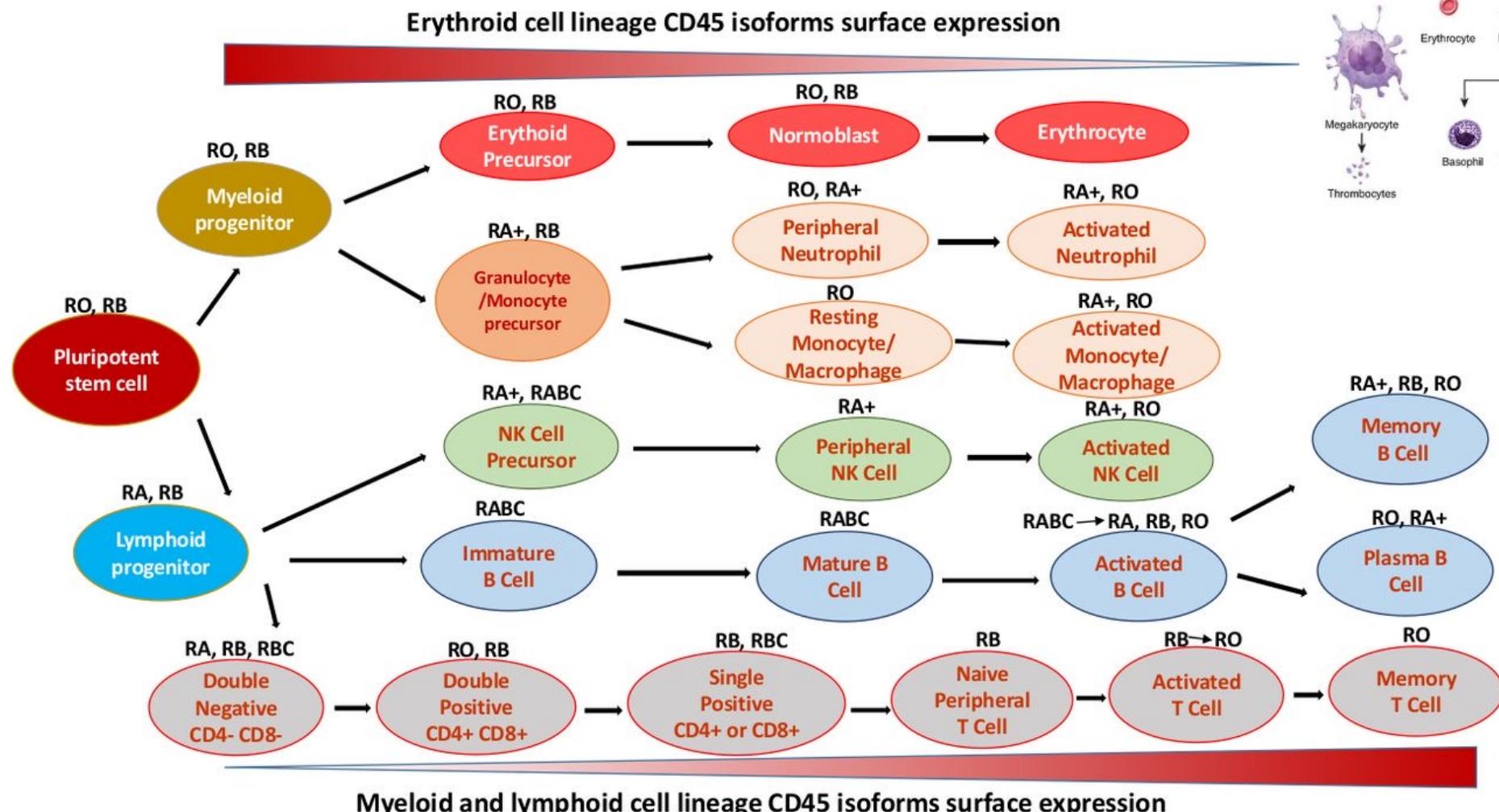
- Protein tyrosin phosphatase, receptor type C (PTPRC)
- Previously called Leucocyte common antigen (LCA)
- Important regulator of T- and B-cell antigen receptor signaling
- Expressed on all hematopoietic cells
- Exception: Plasma cells, erythrocytes and megakaryocytes

# CD45 - isoforms

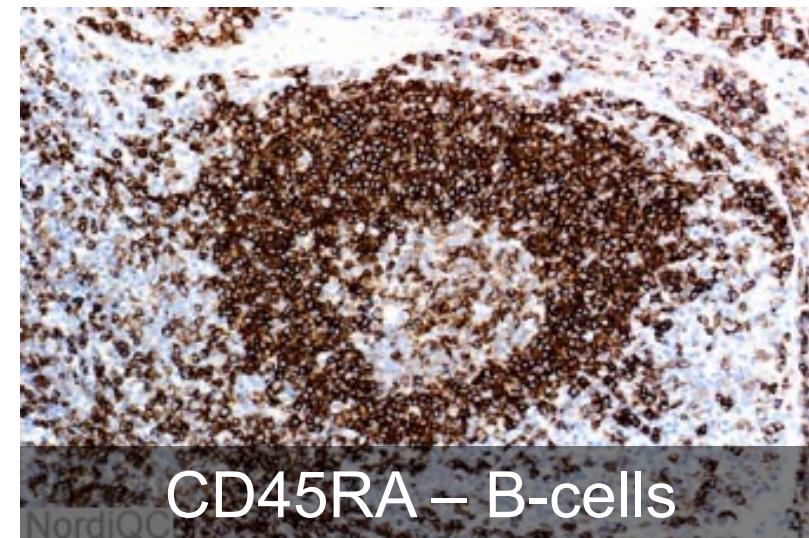
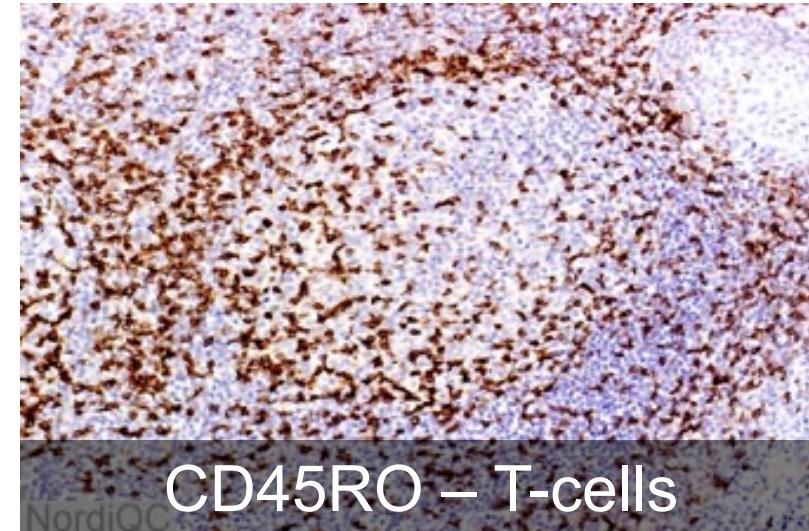
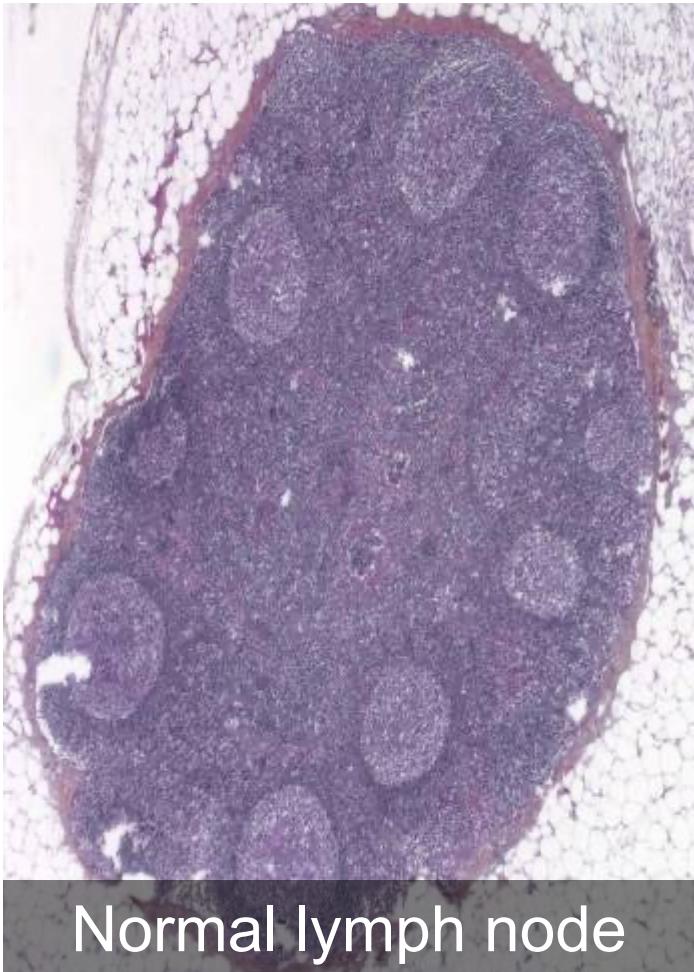
- Alternatively spliced variance in extracellular components
- Six human isoforms identified:
  - RABC, RAB, RBC, RA, RB, RO
- Isoforms expressed on different subsets of lymphocytes



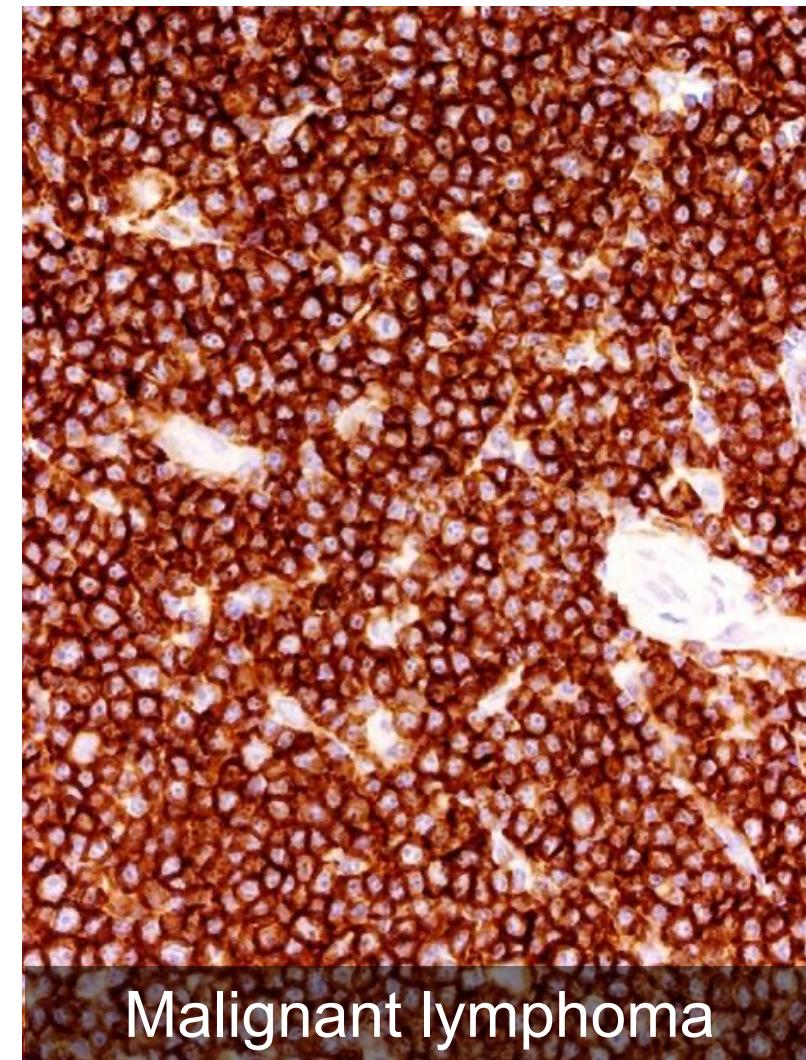
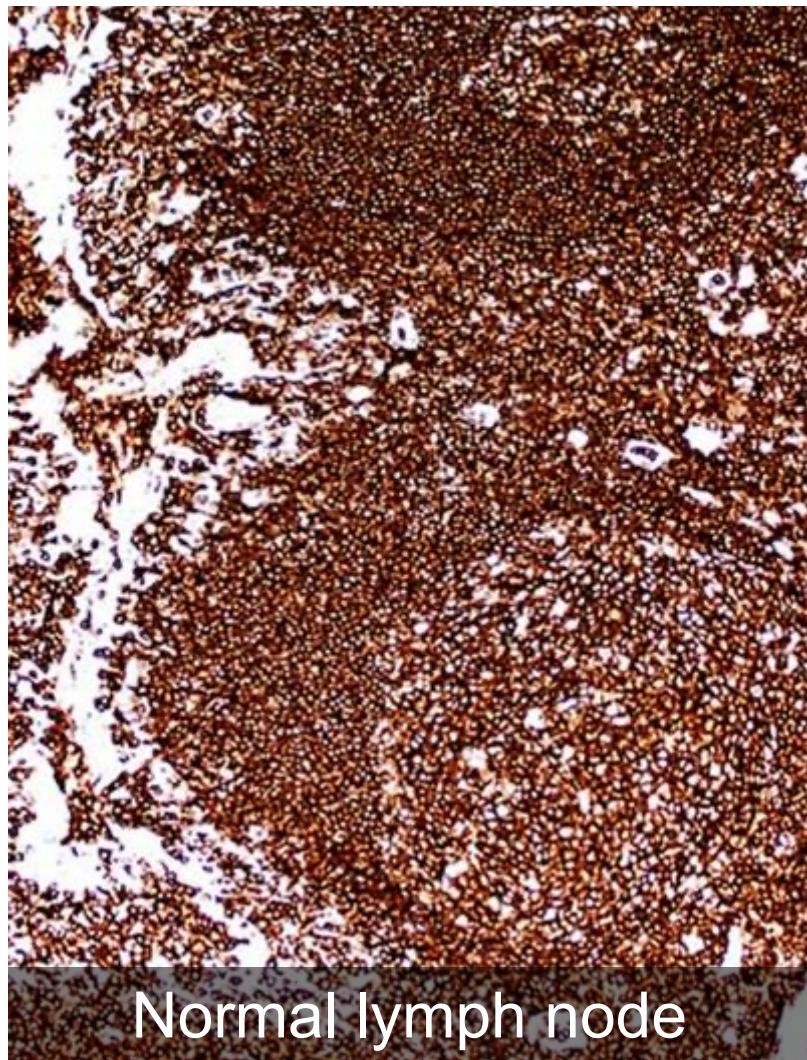
# CD45 - isoforms



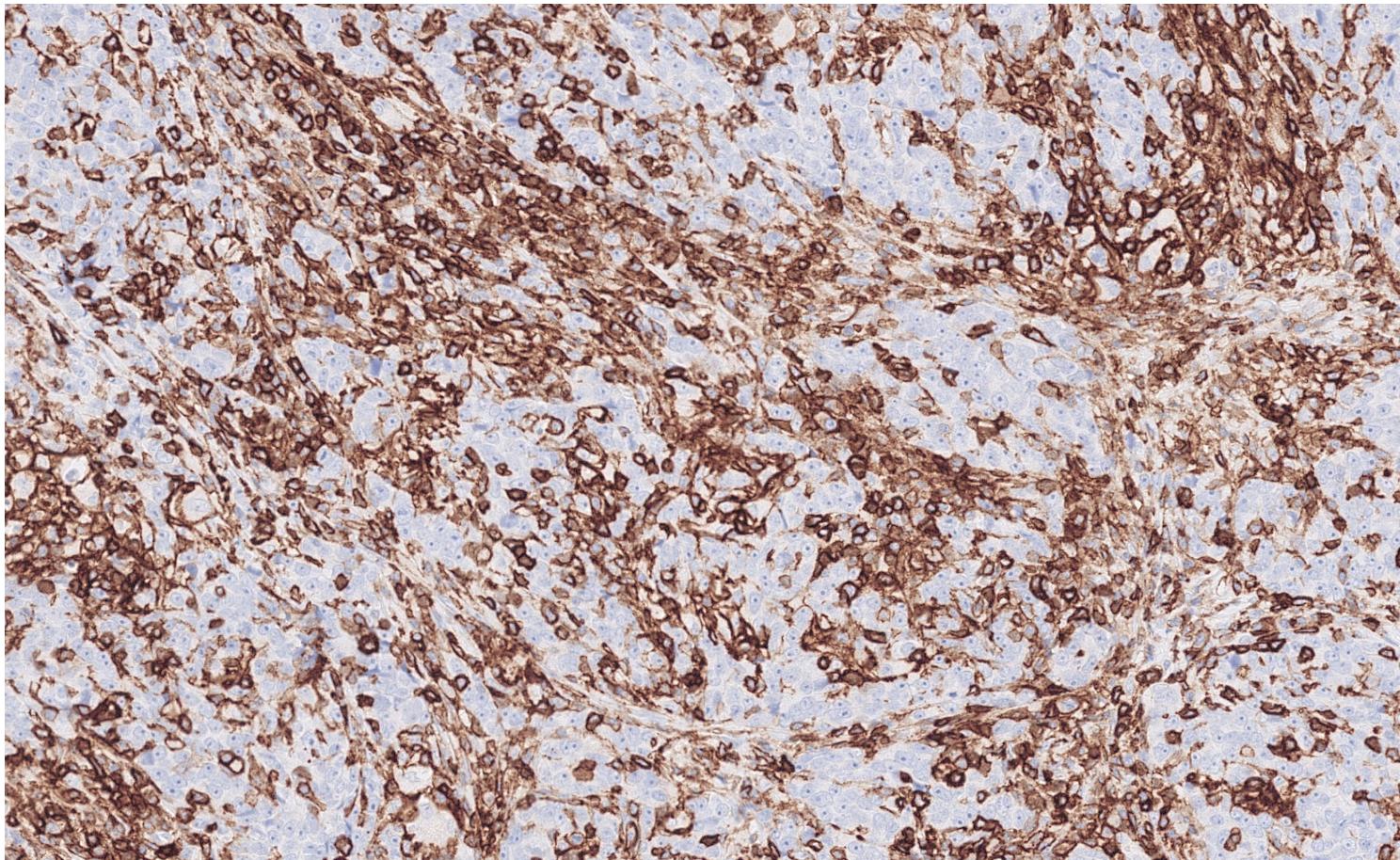
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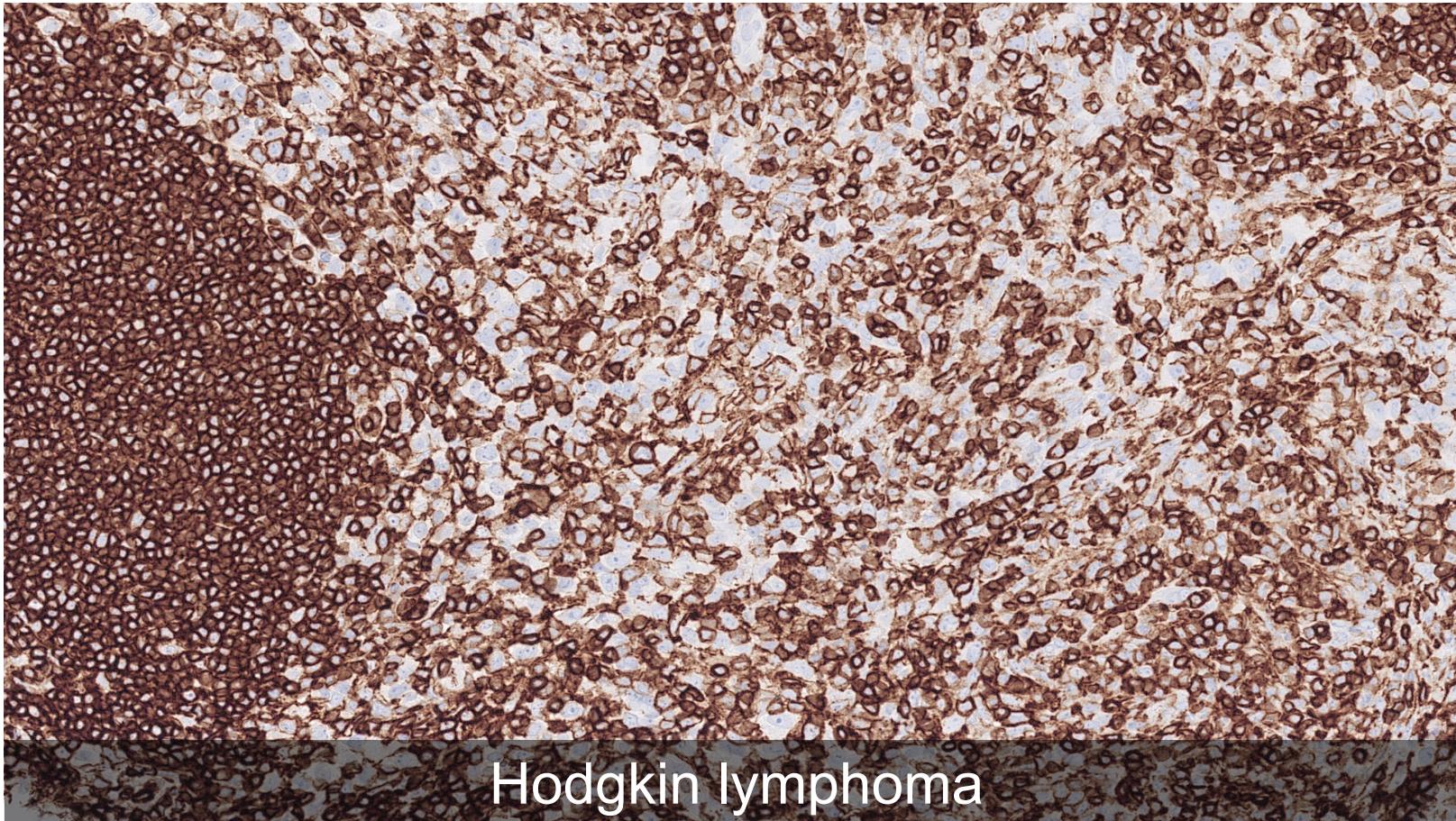
# CD45



# CD45 – positive carcinoma?



# CD45 – negative in some lymphomas



Hodgkin lymphoma

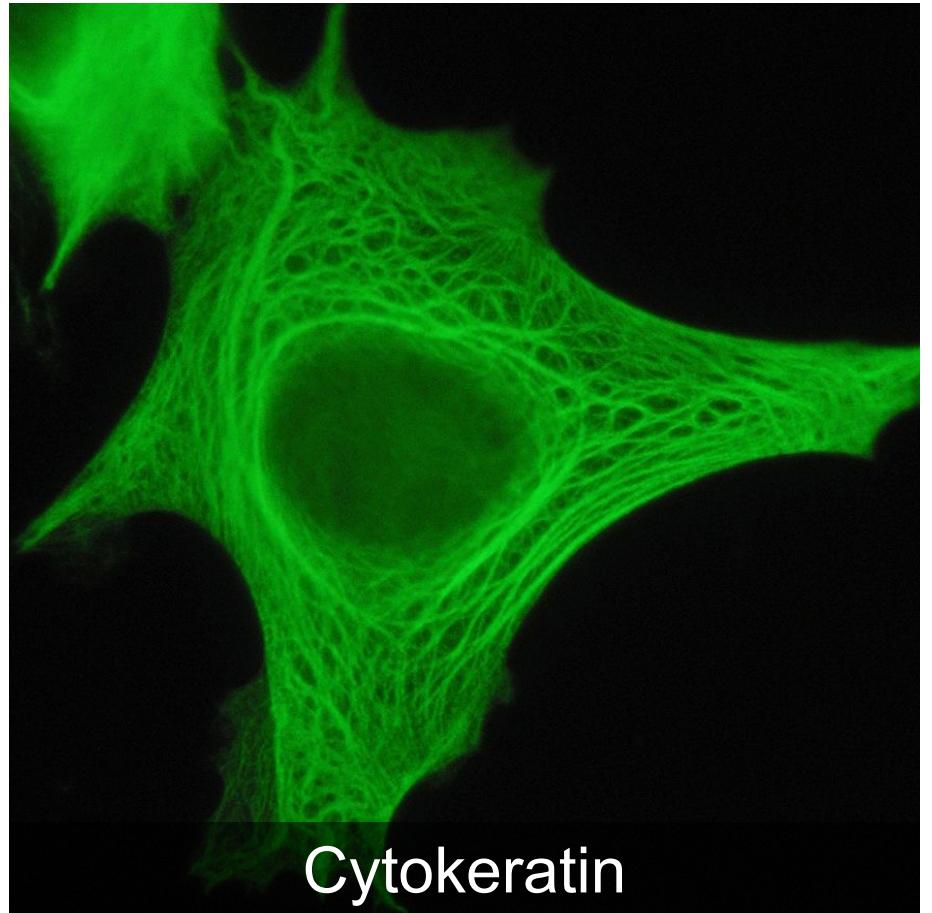
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# Primary panel

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Mesothelial	-	+	-	+
Mesenchymal	-	(-)	(-)	+
Melanoma	-	(-)	+	+
Germ cell	-	-/+	-/+	+

# Pan cytokeratin

- Group of intermediary filaments
- Part of the cytoskeleton in epithelial cells
- Important for mechanical strength of cells and cellular functions
- Many different types:
  - Group I: acidic
  - Group II: basic or neutral
- Paired expression
- Different cytokeratins seen in different tissues



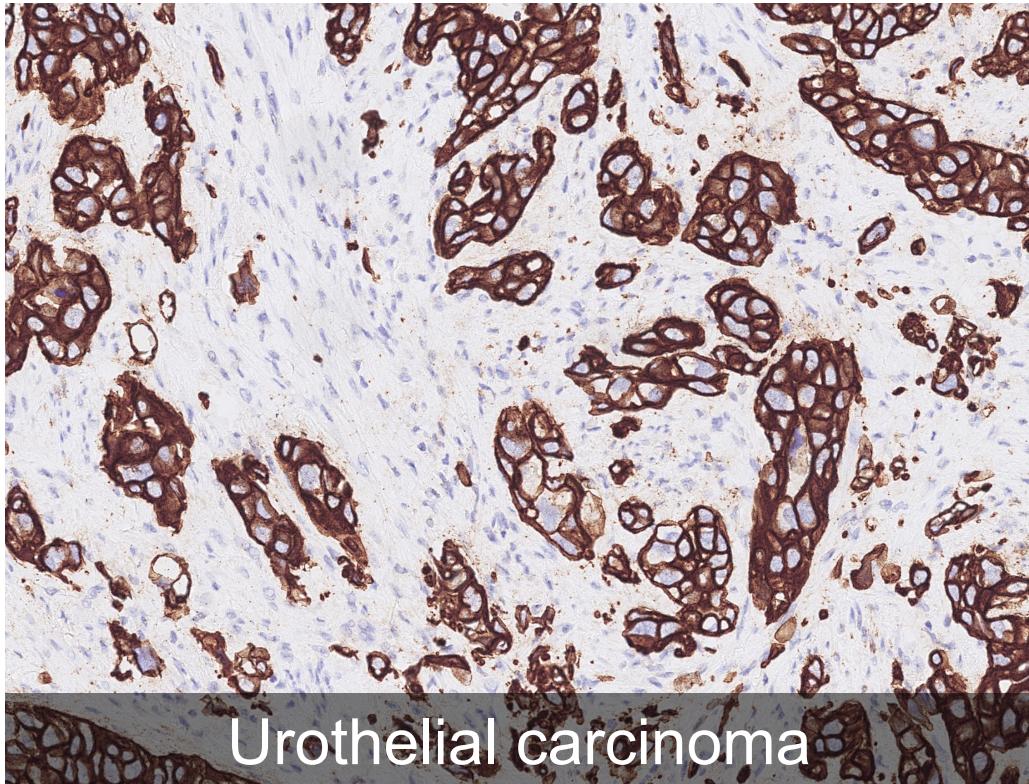
Neutral/Basic (B, class II)	1	4	13	5	14	17	19	7	20	8
Acidic (A, class I)	10									18
Squamous epithelia:										
- suprabasal, keratinizing	+++	-	-	+	++	(+)	-	-	-	-
- suprabasal, non-keratinizing	+	+++	+++	+	++	(+)	-	-	-	-
- basal cells (tonsil, mucosa)	-	-	-	+++	+++	(+)	(++)	(+)	-	(+)
Transit. epith.: superficial cells	-	-	-	-	-	-	+++	+++	++	+++
- intermediary. / basal cells	-	(+)	+++	(+++)	-	(++)	+++	+++	(+)	+++
Mesothelium	-	-	-	++	++	+	+++	+++	-	+++
Bronchus, breast, prost., cerv.:										
- basal/myoepithelial cells	-	-	-	+++	++	+++	++	-	-	-
- luminal cells	-	-	-	+	+	+	+++	+++	-	+++
Biliary/pancr. ducts, lung alv., endometr., renal collect. ducts	-	-	-	-	-	-	+++	+++	-	+++
Stomach (foveola), intestine	-	-	-	-	-	-	+++	(+)	+++	+++
Hepatocytes, pancr. acini, prox. renal tubules	-	-	-	-	-	-	-	-	-	+++
Endocrine cells (Merkel, thyroid)	-	-	-	-	-	-	(+++)	(++)	(+++)	+++
Smooth muscle (vasc., myom.), myofibrobl., sm.ves.endothelia	-	-	-	-	-	-	+	(++)	-	++

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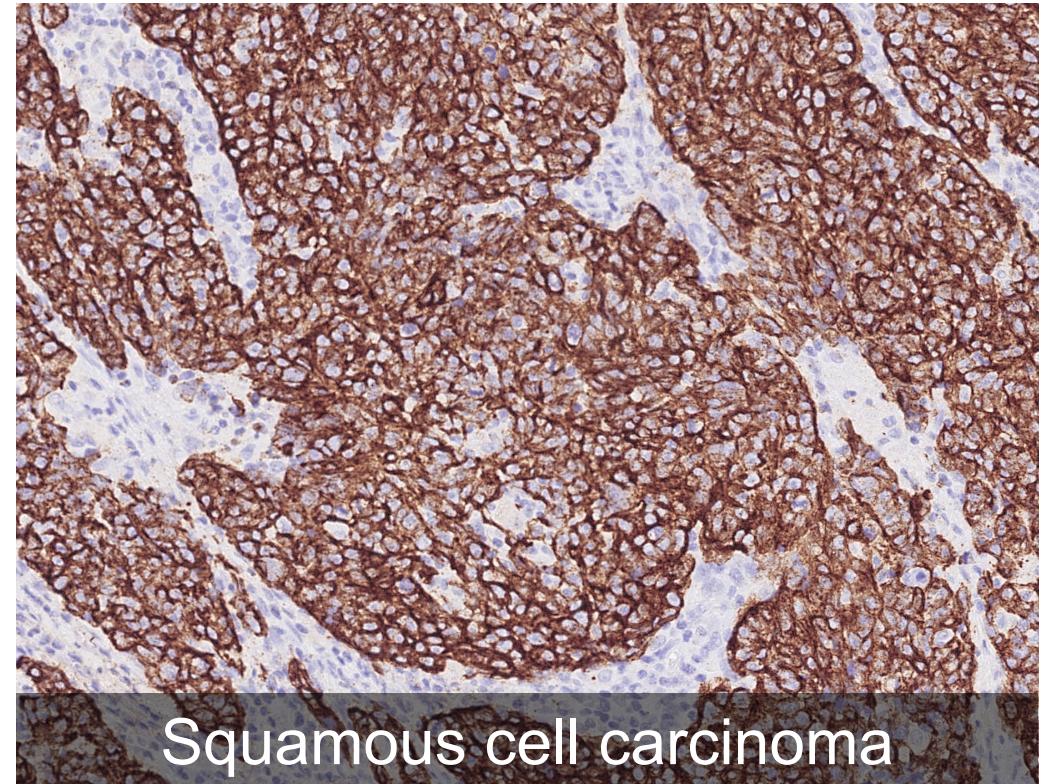
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# Pan cytokeratin

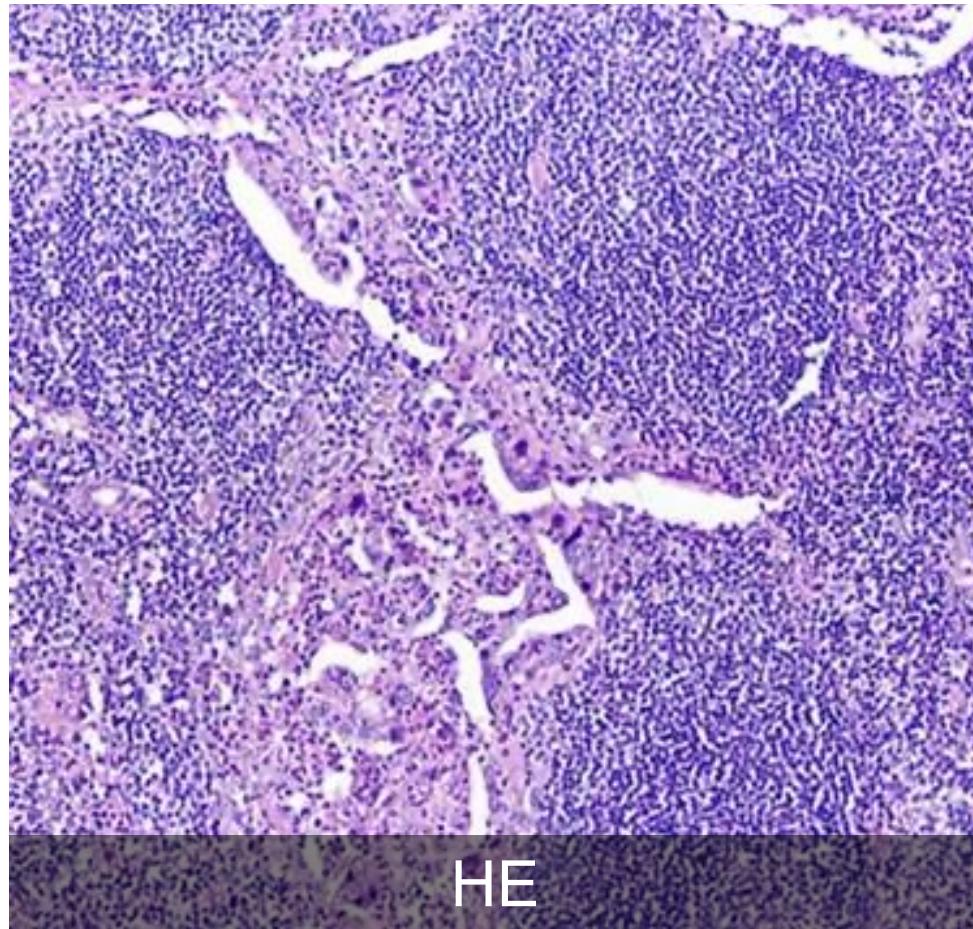


Urothelial carcinoma



Squamous cell carcinoma

# Pan cytokeratin - micrometasis

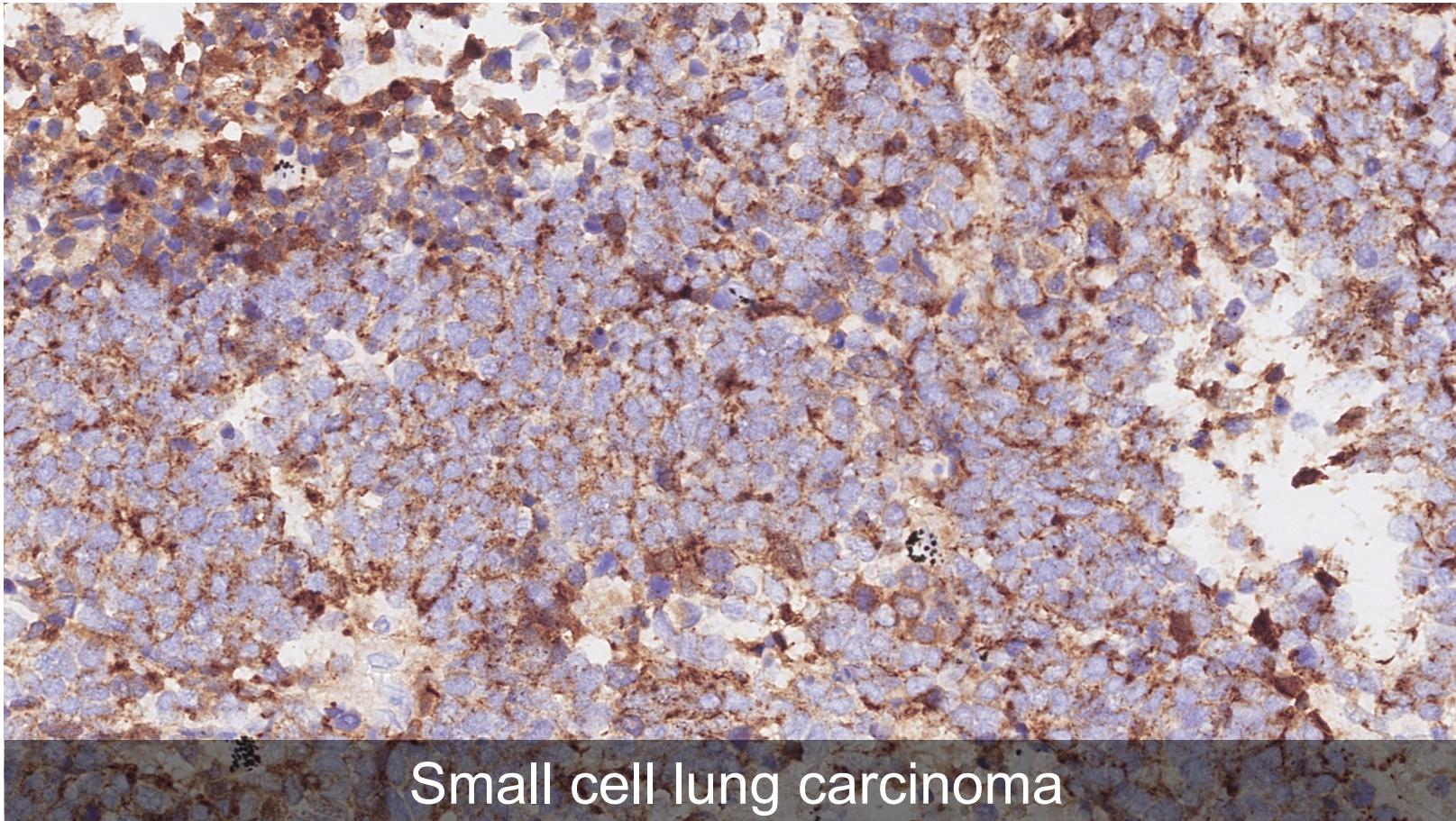


HE



Pan cytokeratin

# Pancytokeratin

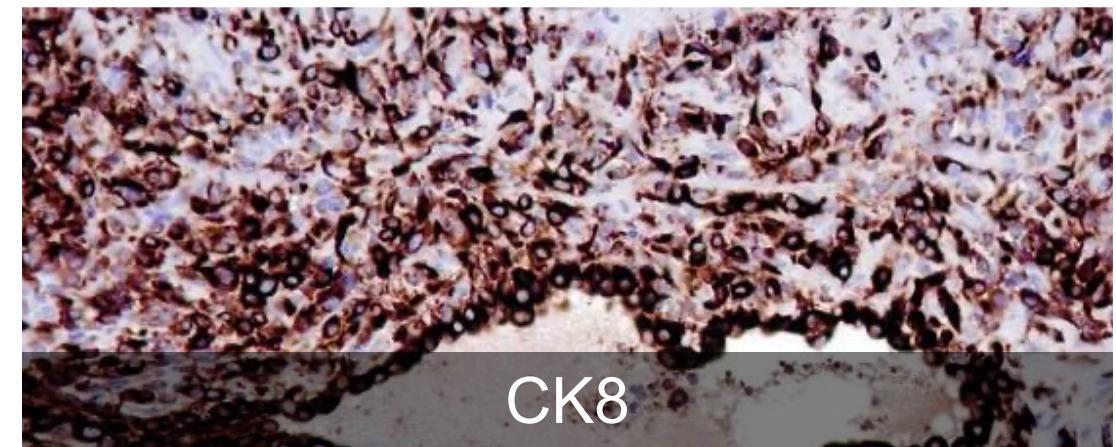
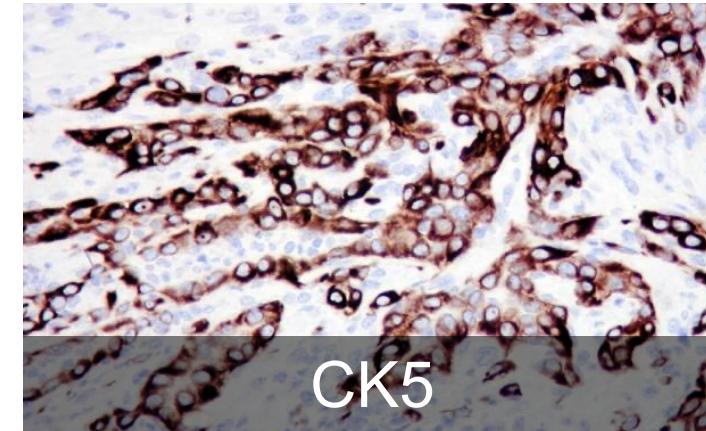
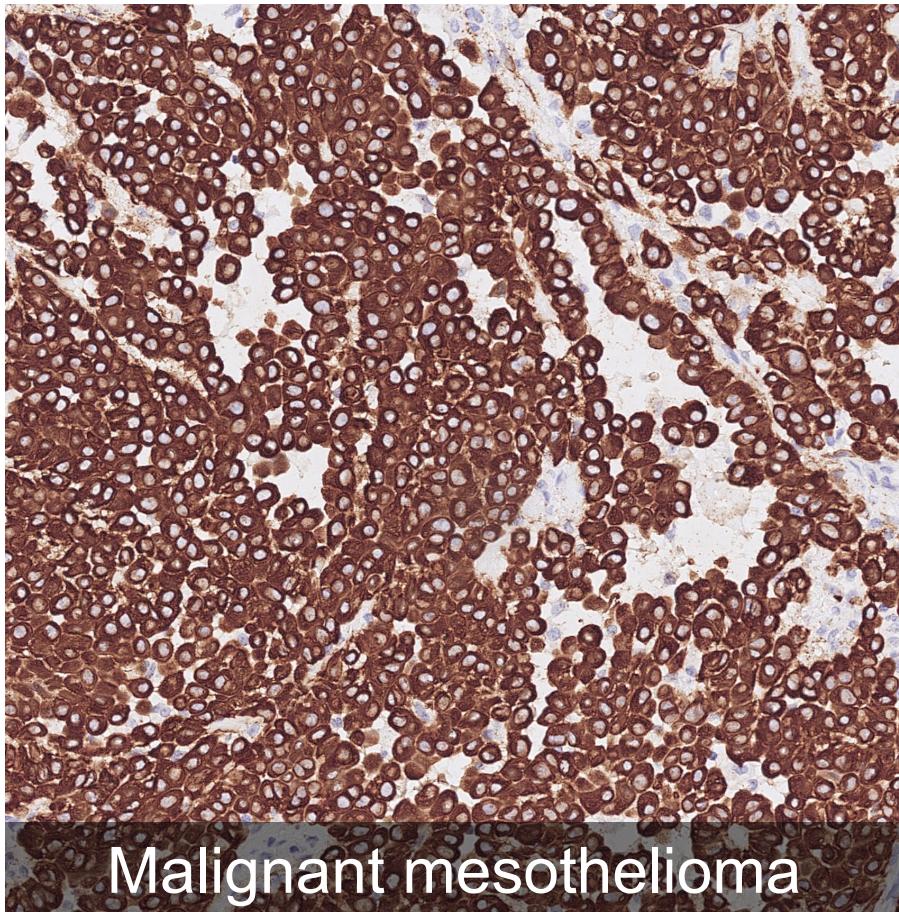


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# Pan cytokeratin - mesothelioma

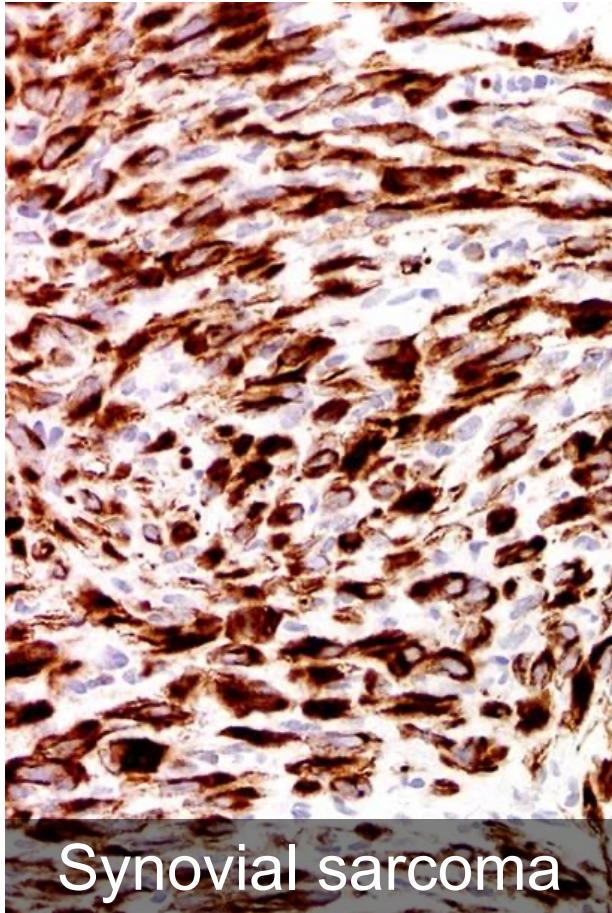


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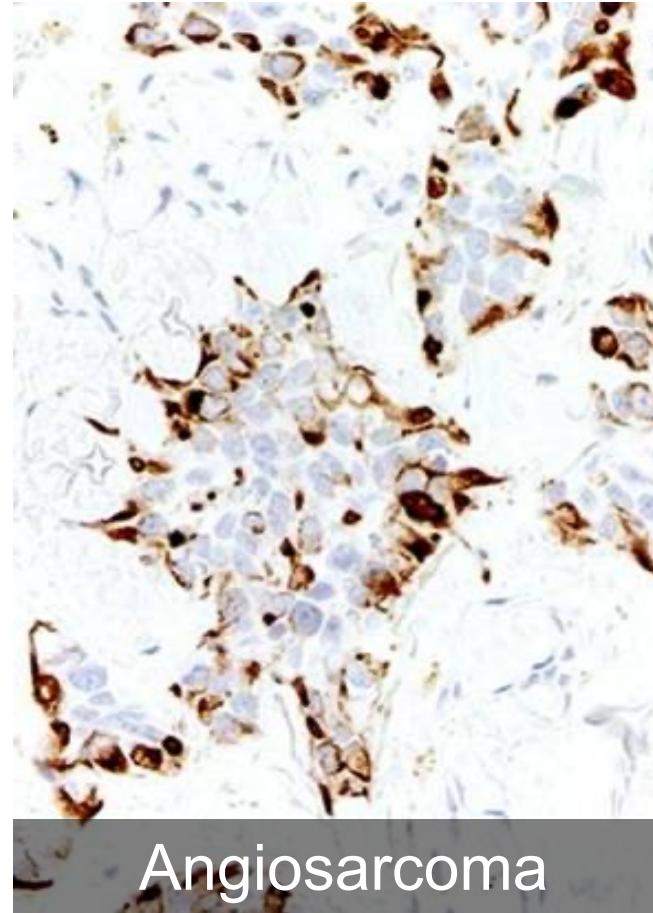
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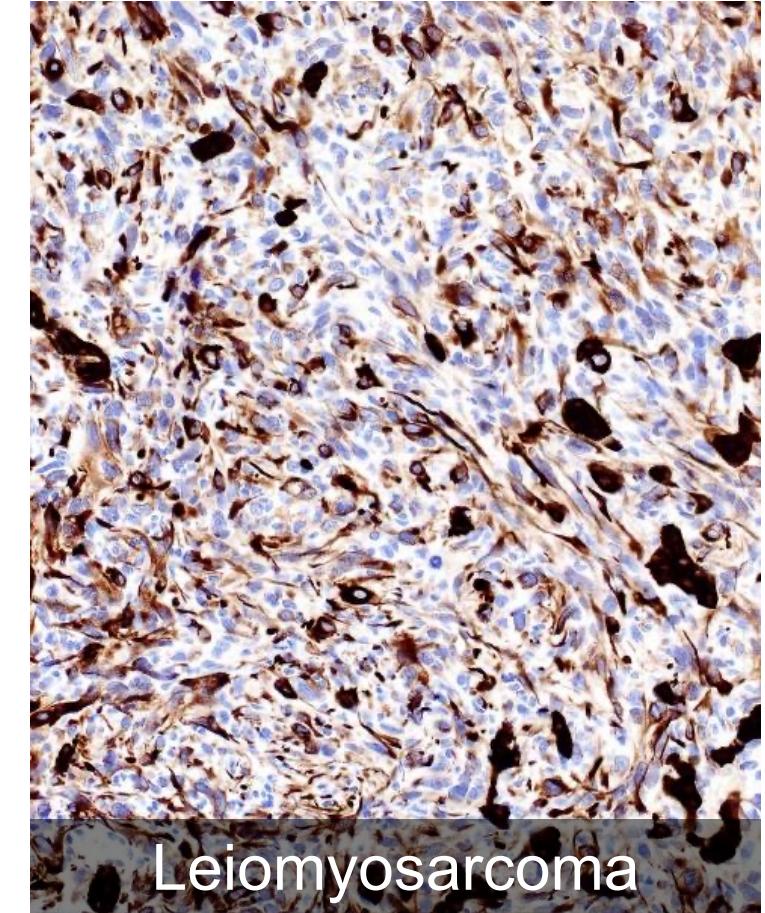
# Pan cytokeratin – mesenchymal neoplasias



Synovial sarcoma



Angiosarcoma



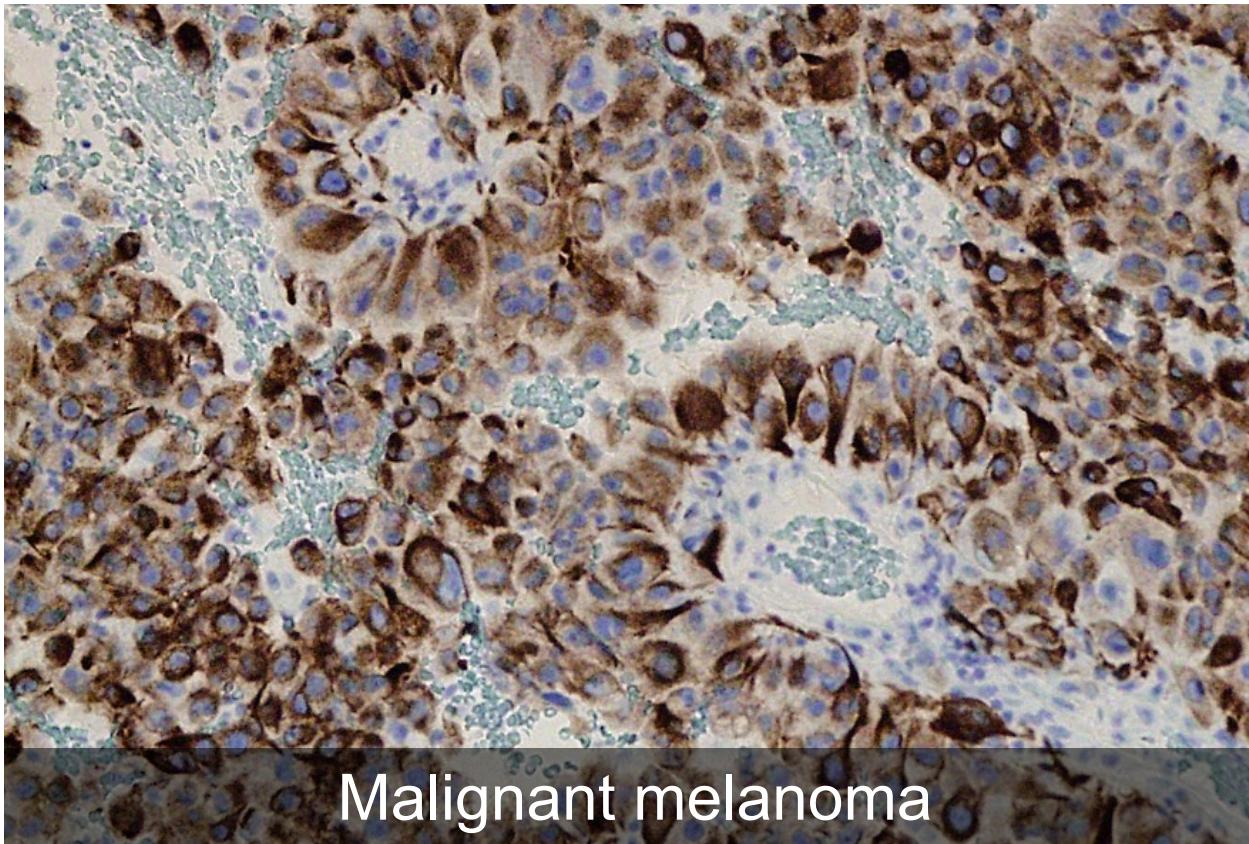
Leiomyosarcoma

+	~ 100% pos.
(+)	> 90%
+/-	~ 50-90%
-/+	~ 10-50%
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# Primary panel

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# Pan cytokeratin - melanoma

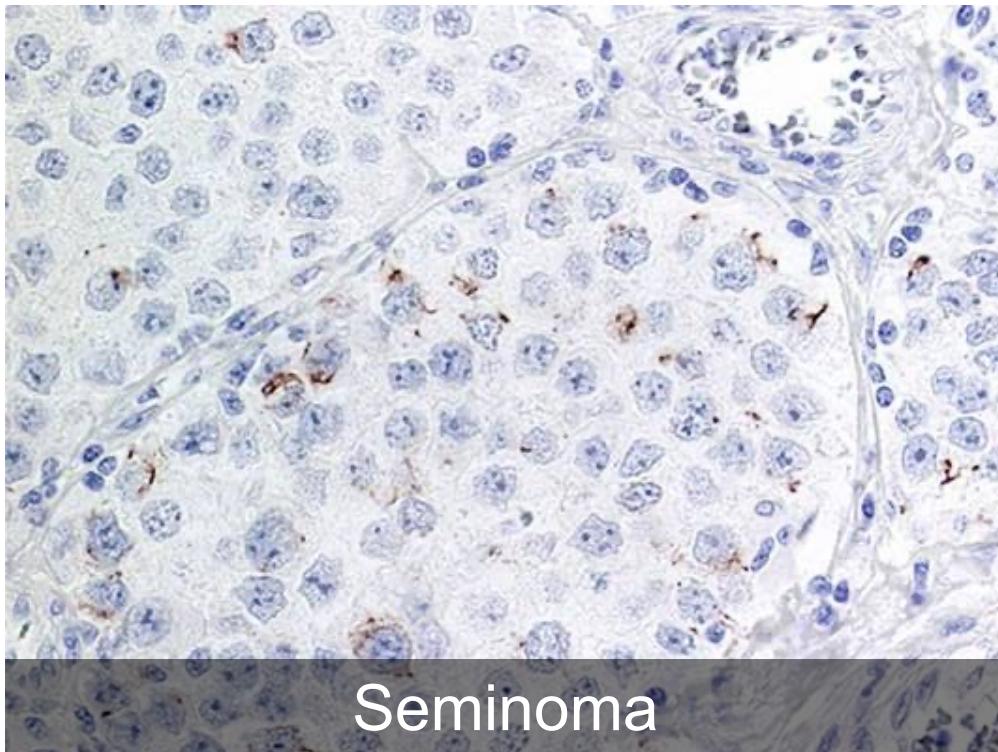


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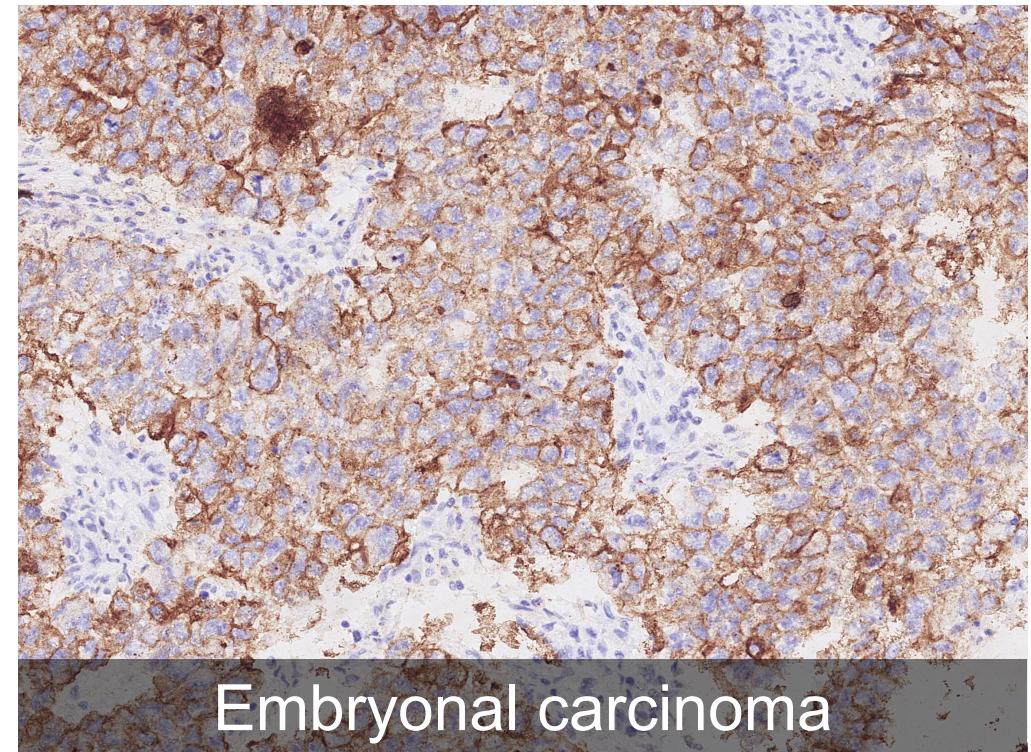
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Melanoma	-	(-)	+	+
Germ cell	-	-/+	-/+	+

# Pan cytokeratin – germ cell neoplasia



Seminoma



Embryonal carcinoma

+	~ 100% pos.
(+)	> 90%
+/-	~ 50-90%
-/+	~ 10-50%
(-)	< 10%
-	~ 0%

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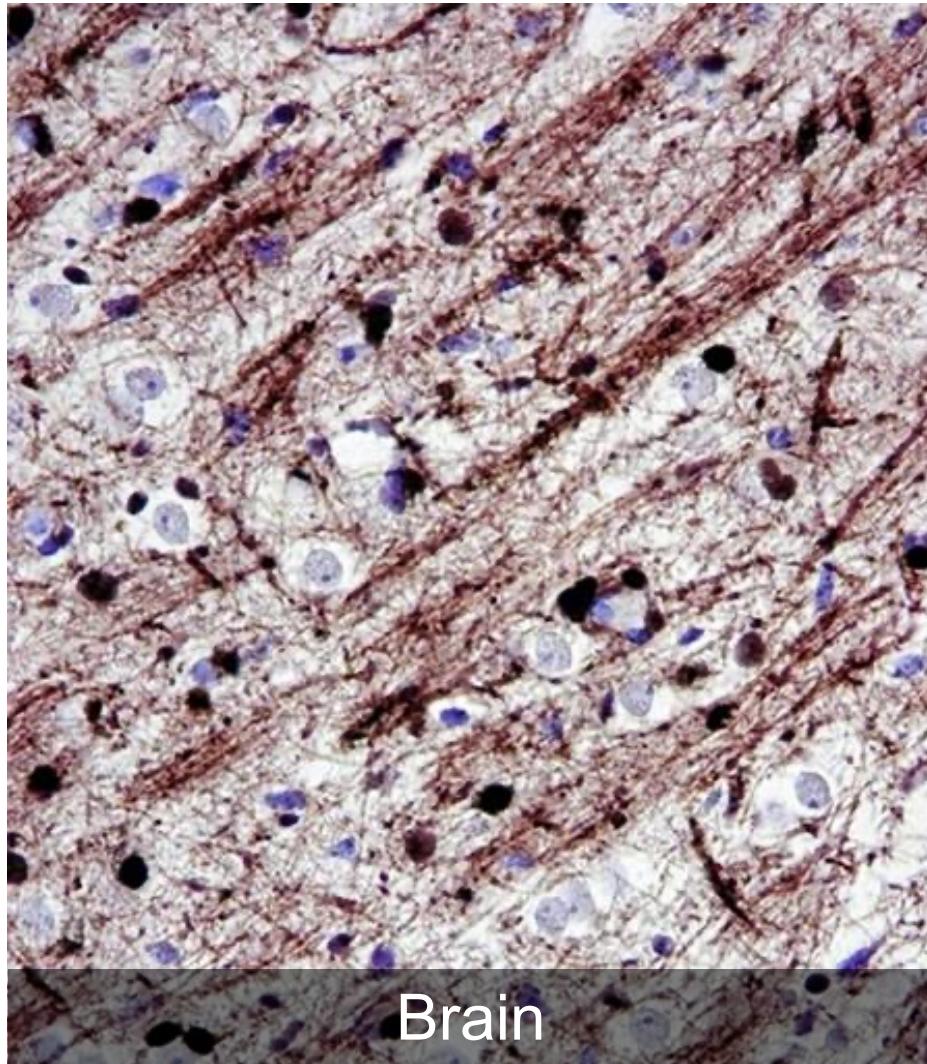
# S100

- Family of low molecular weight calcium binding molecules
- Located in nuclei, cytoplasm and cell membranes
- At least 21 different types exist (S100A1, S100A2... & S100B, S100P)
- S100B expressed in
  - Glial cells in brain
  - Melanocytes
  - Fat cells
  - Langerhans cell
  - Myoepithelial cells

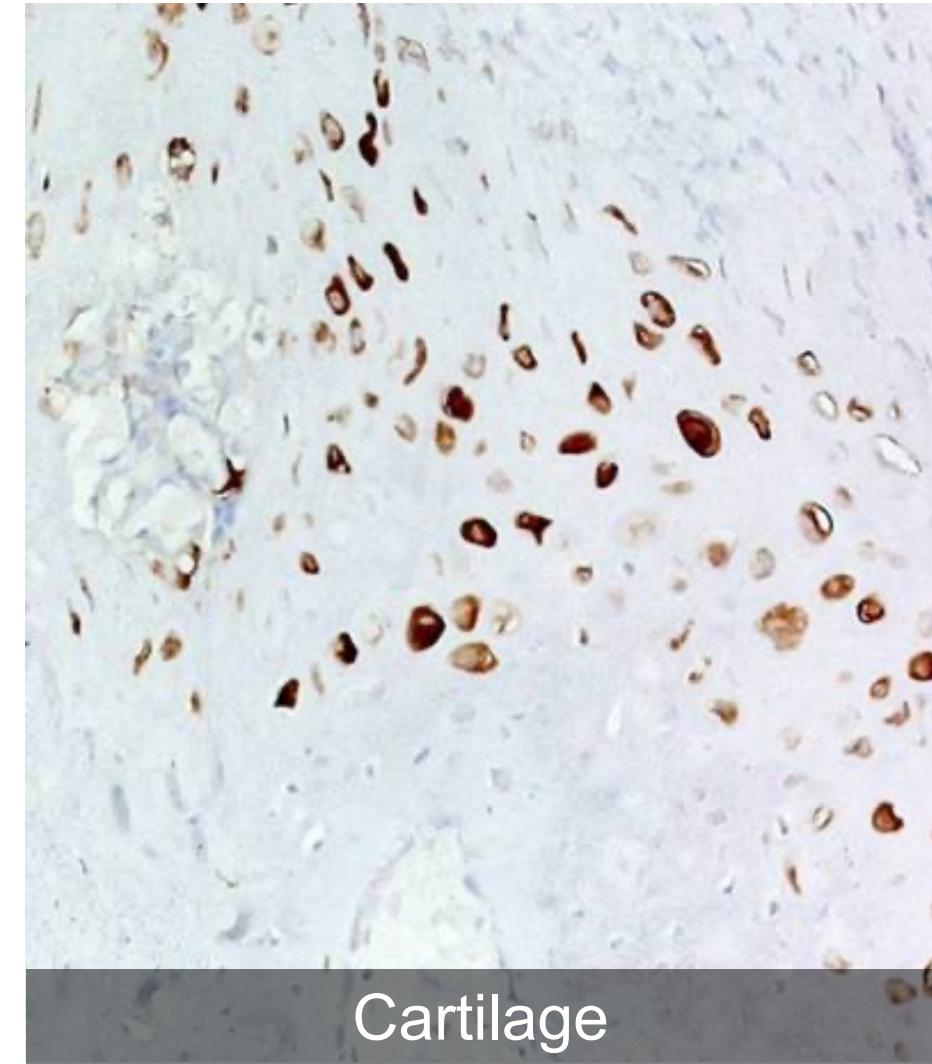
# S100

- Expressed in malignant melanoma
- Also seen in
  - Schwannomas
  - Neurofibromas
  - Chondromas
  - Liposarcomas

S100

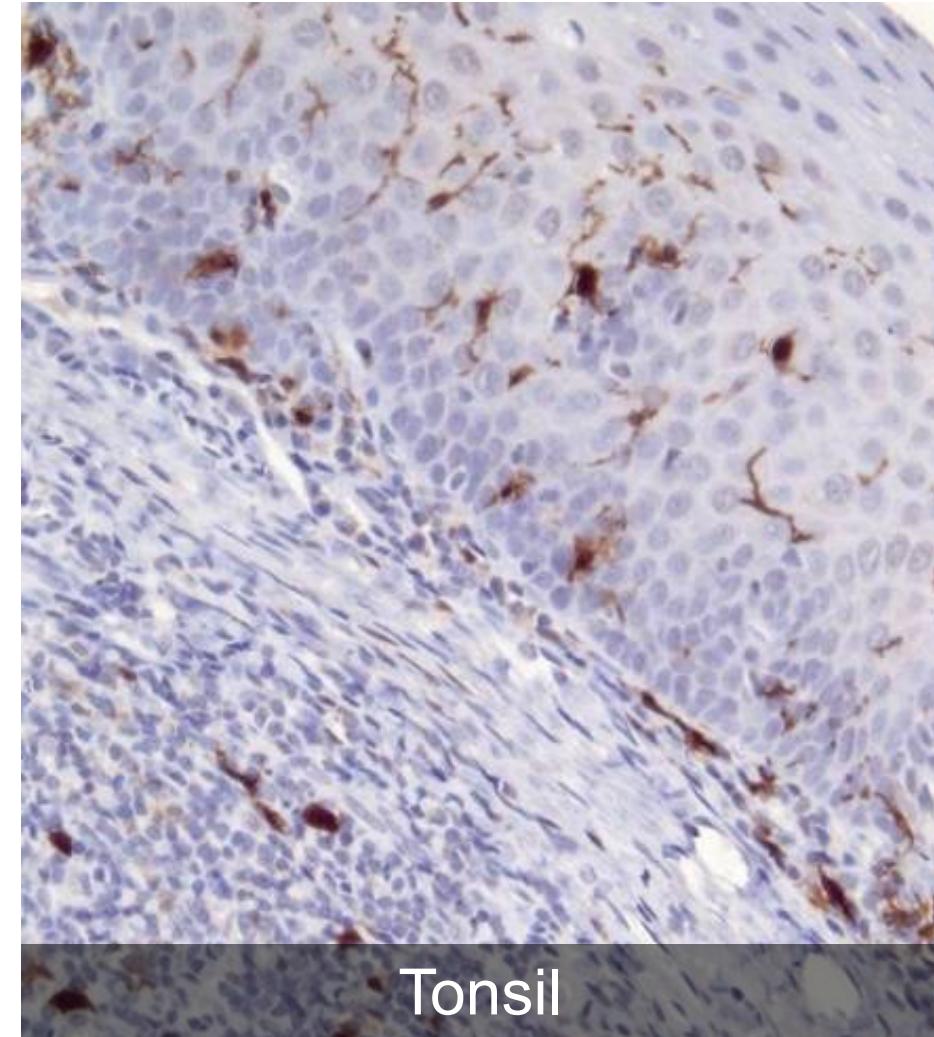
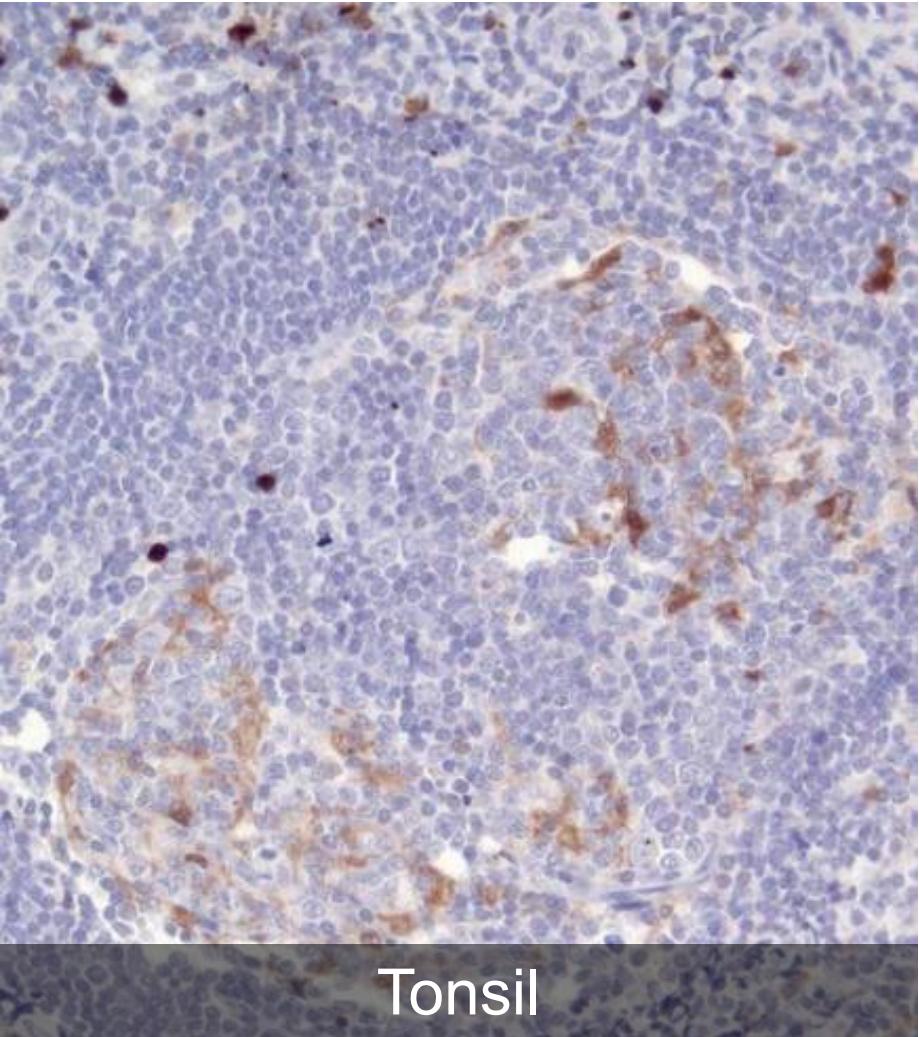


Brain

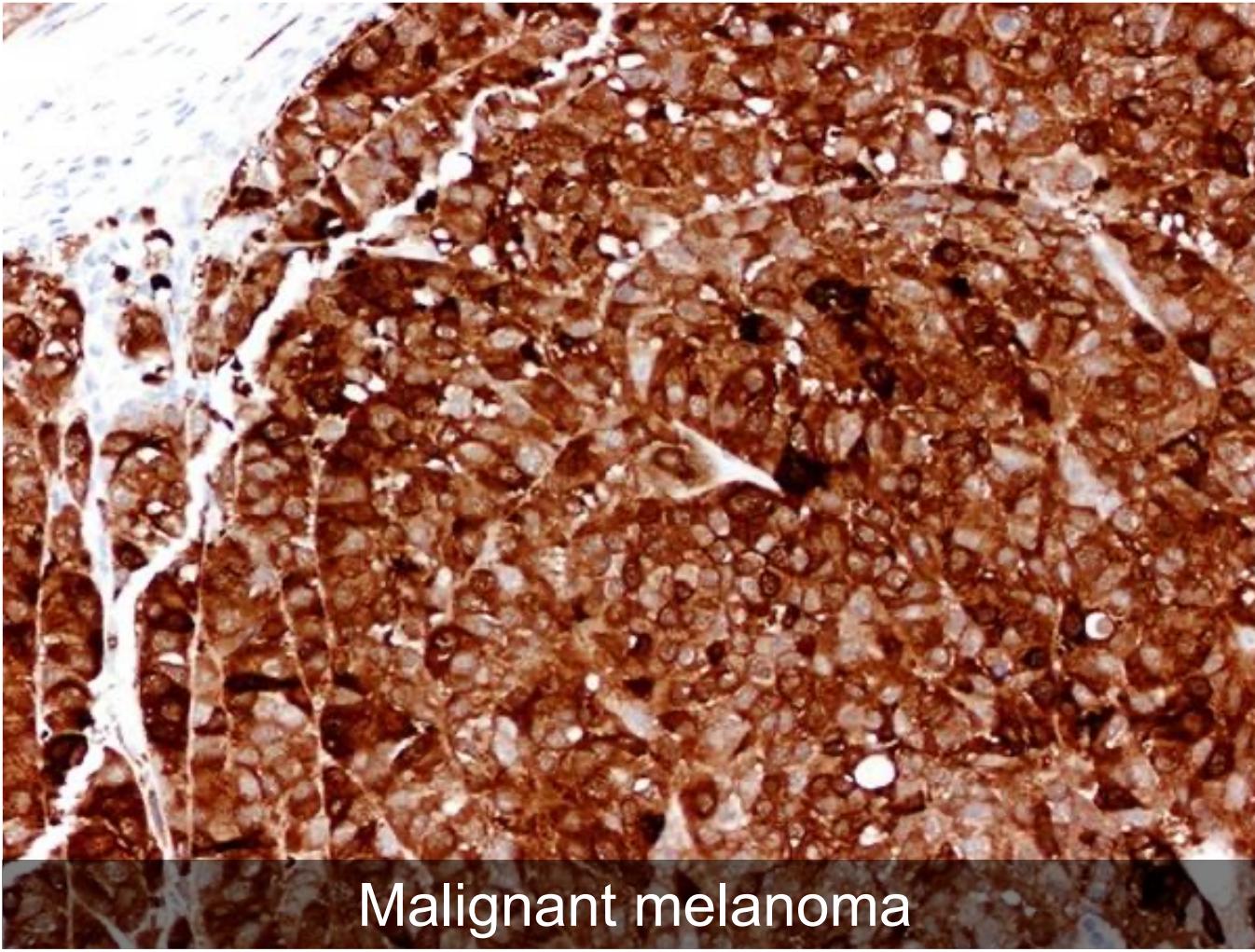


Cartilage

S100



S100



Malignant melanoma

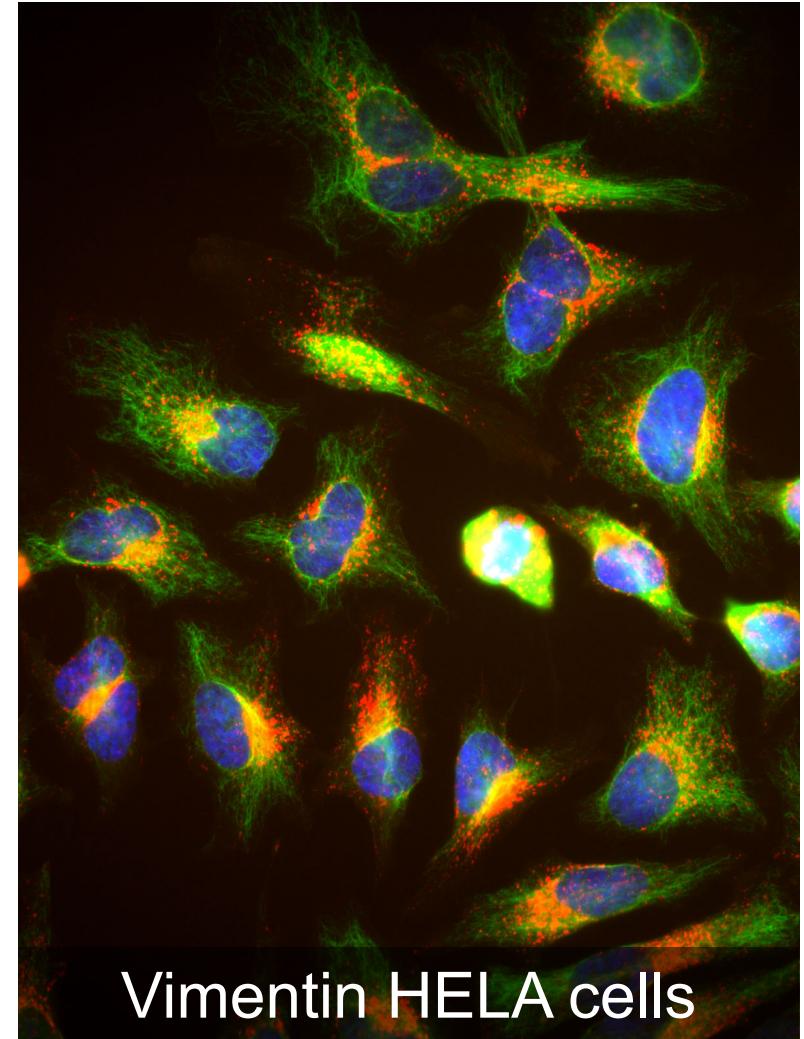
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# Vimentin

- Cytoplasmic intermediate filament
- Cytoskeleton, support and positioning of organelles
- Expressed in all mesenchymal cells
- Co-expressed with cytokeratins in some epithelia
- Co-expressed in mesothelium

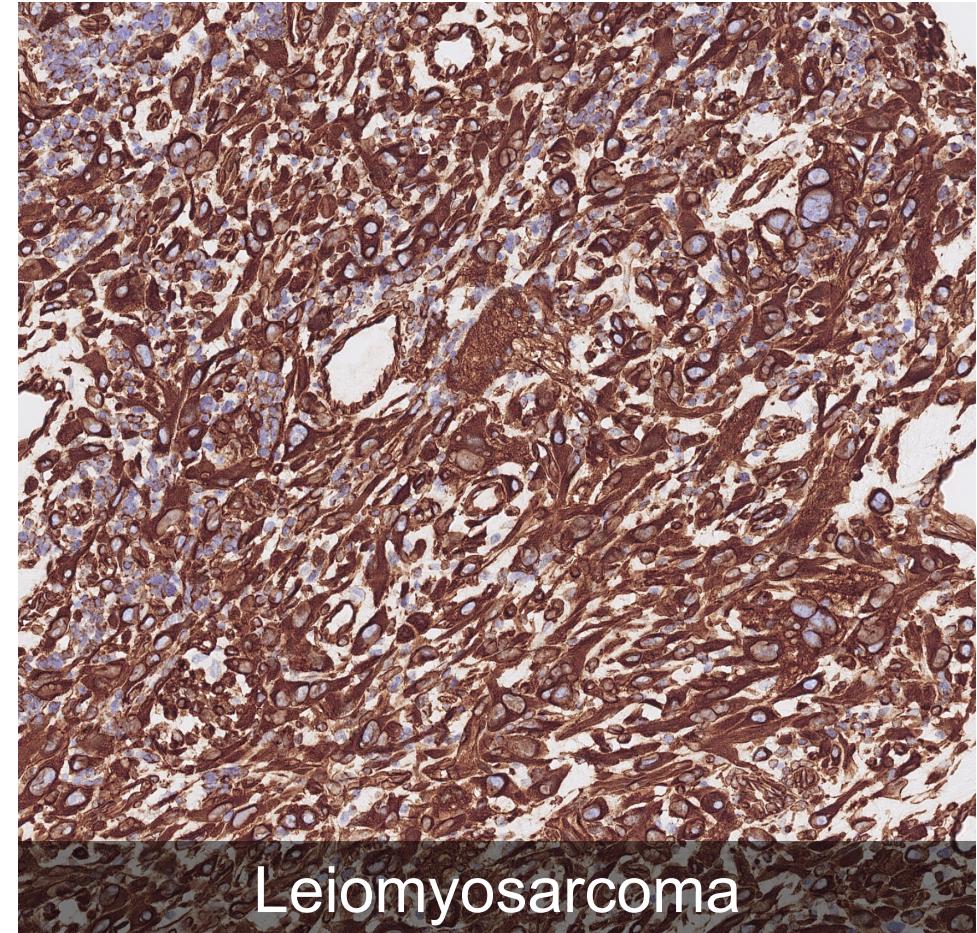


Vimentin HEA cells

# Vimentin – stromal tumours

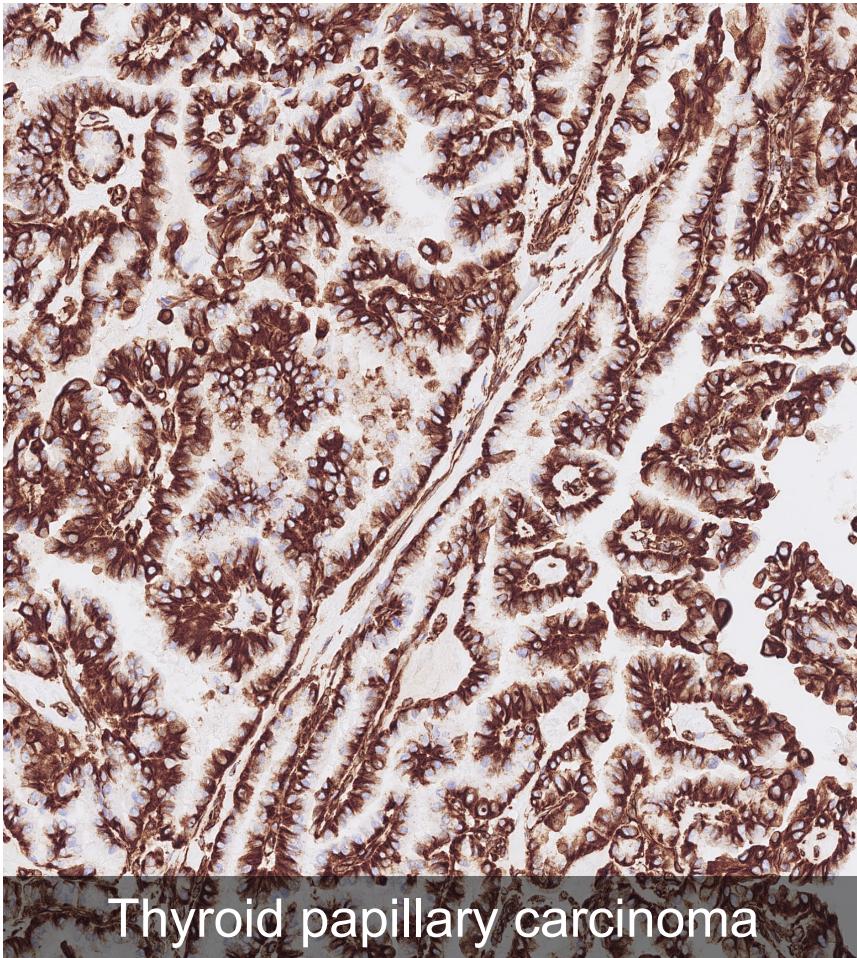


GIST

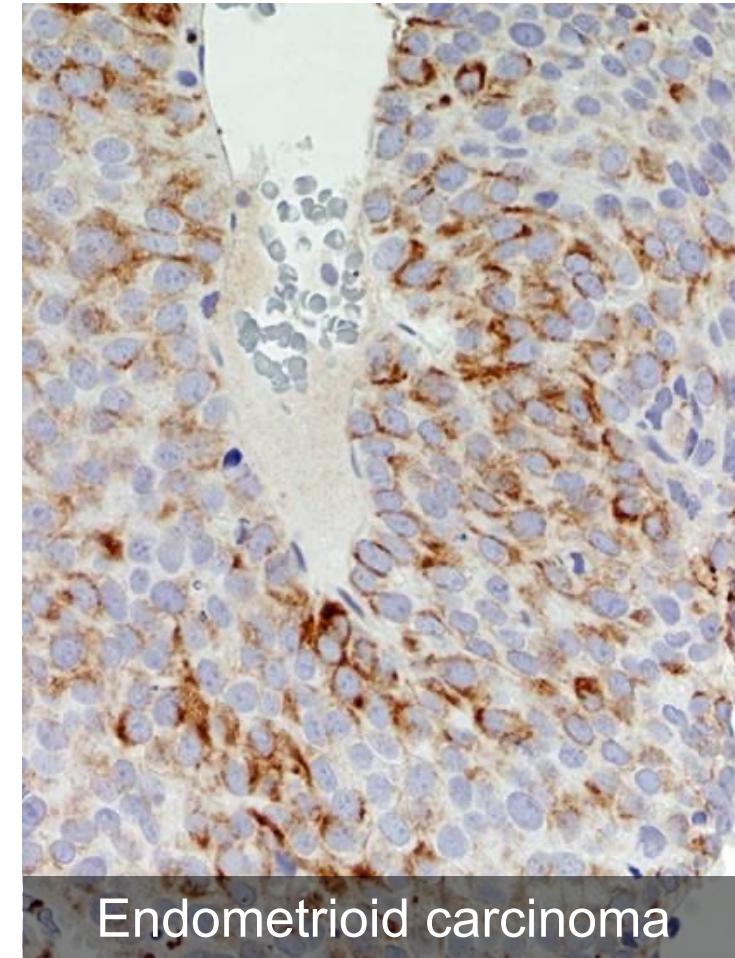


Leiomyosarcoma

# Vimentin - carcinomas

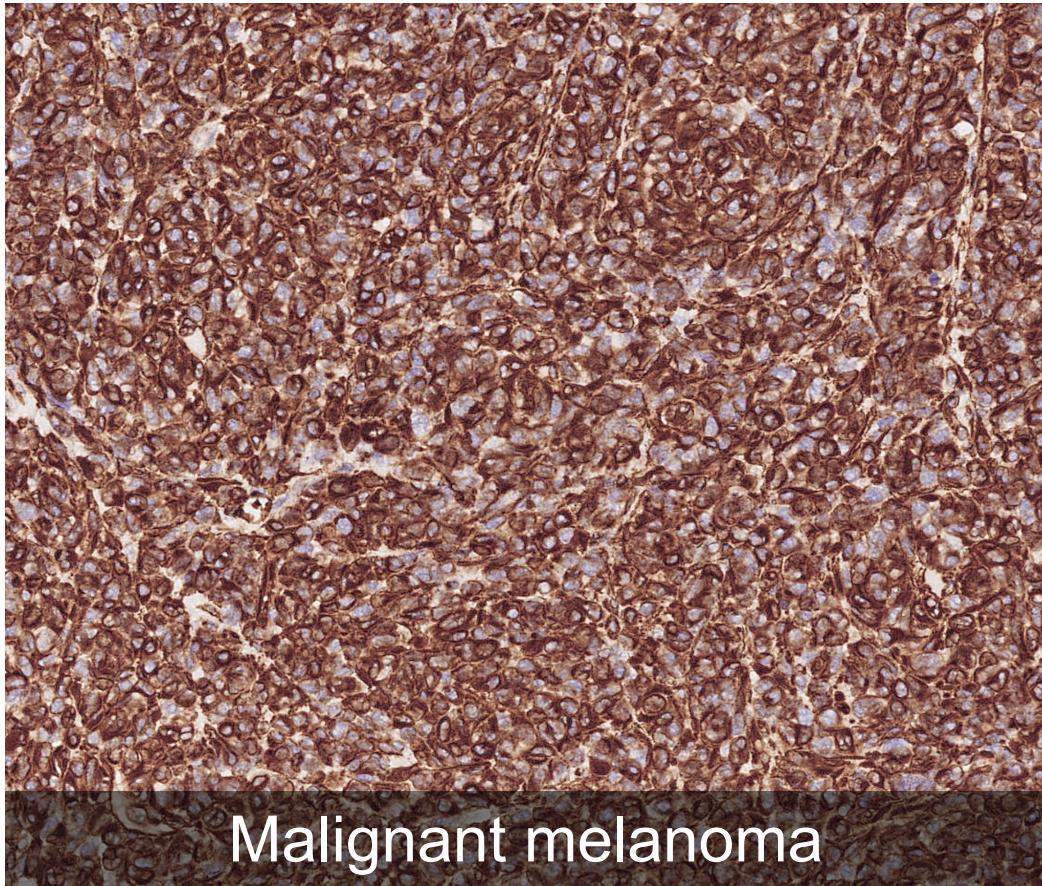


Thyroid papillary carcinoma

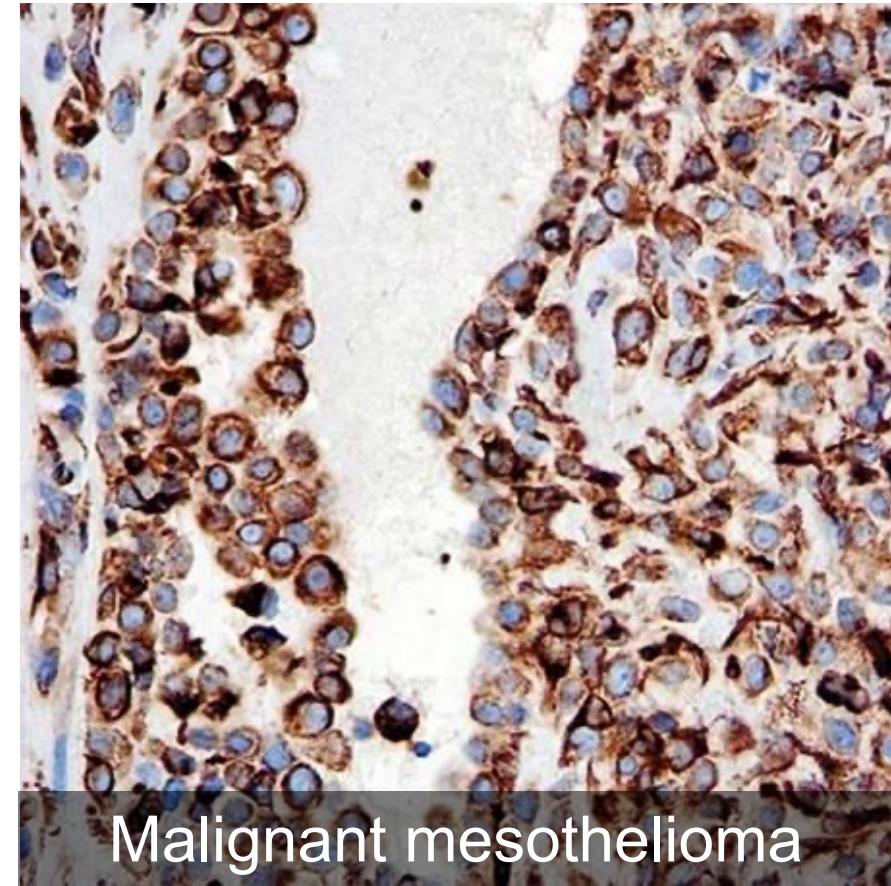


Endometrioid carcinoma

# Vimentin – other neoplasia



Malignant melanoma



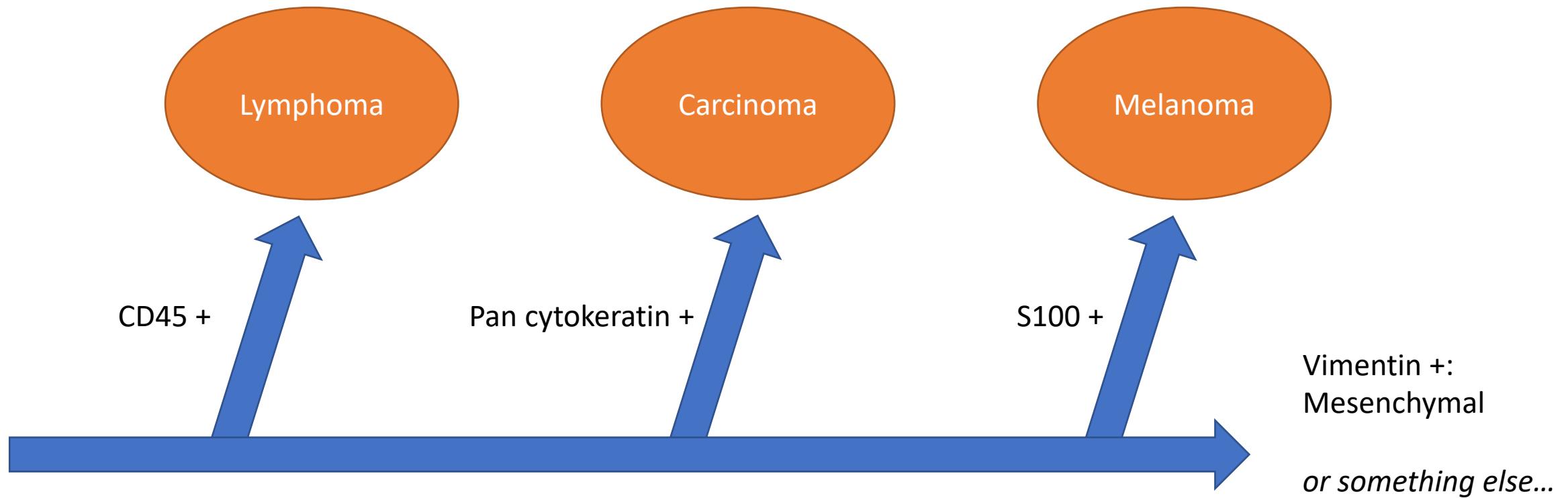
Malignant mesothelioma

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# Primary panel

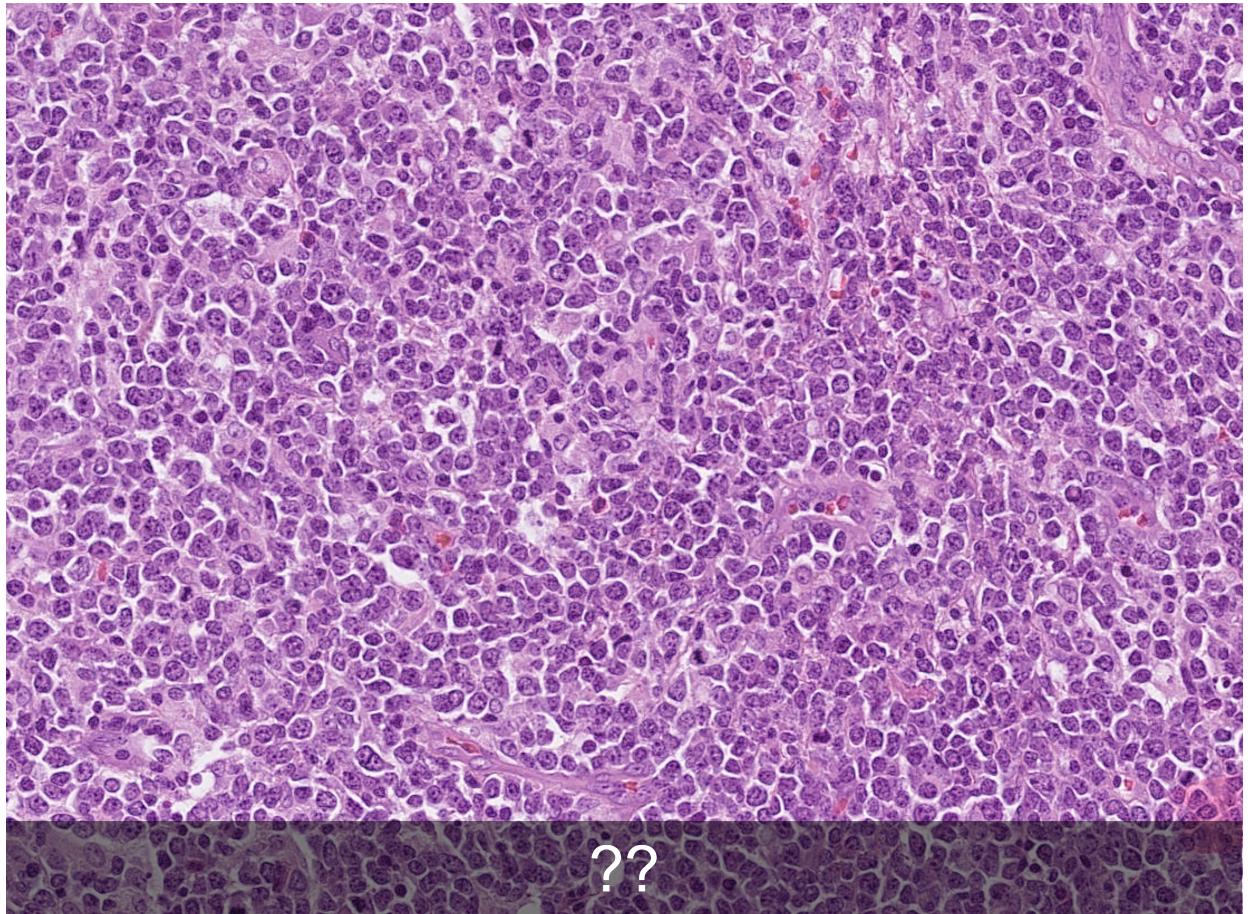
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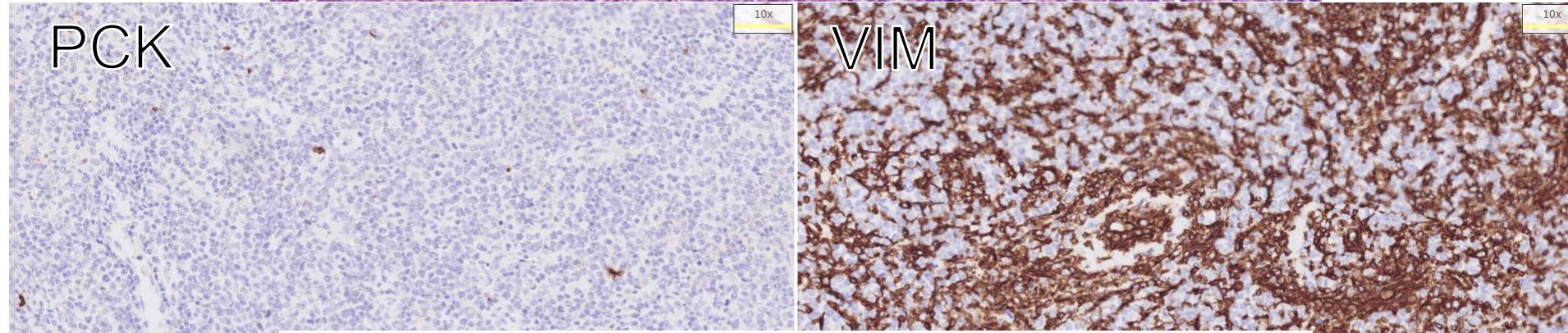
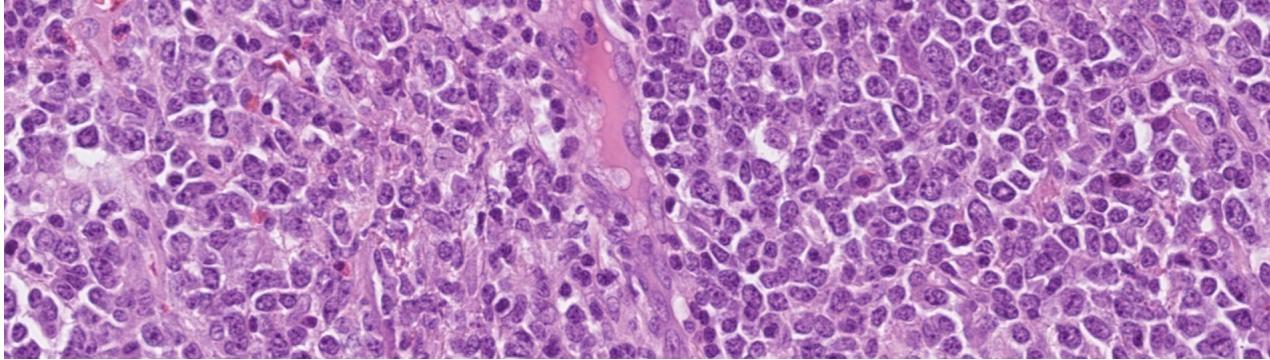
# Primary panel in action



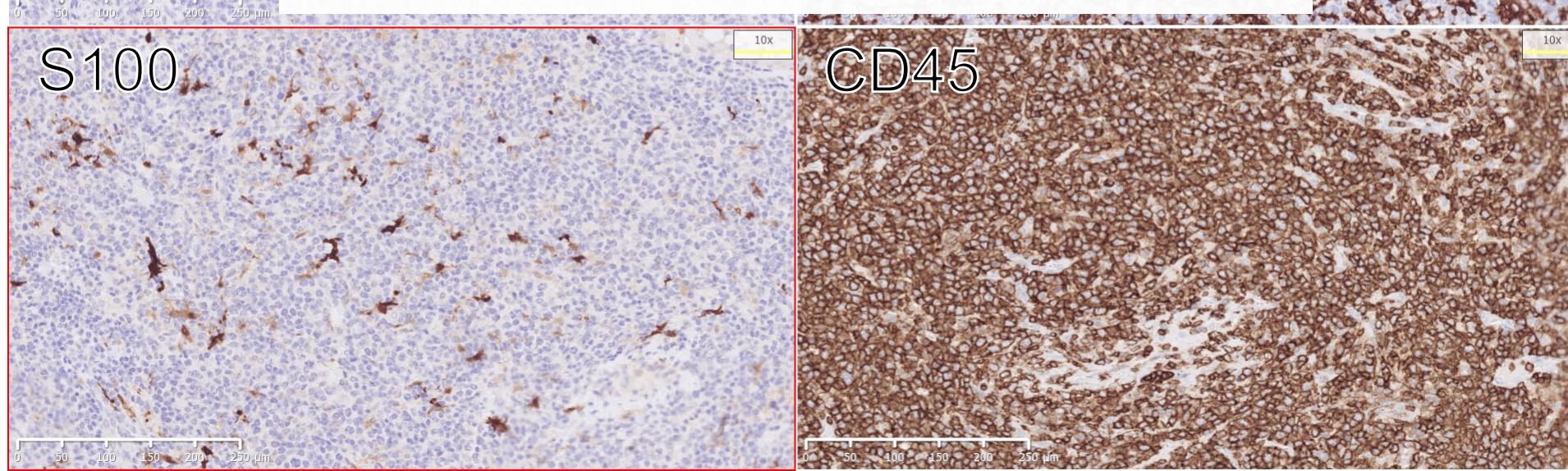
# Undifferentiated cases

- 56 year old female
- History of smoking
- Heavy drinker
- Previous cancer
  - Cervix squamous
- Enlarged lymph node on neck





## Diffuse large B-cell lymphoma

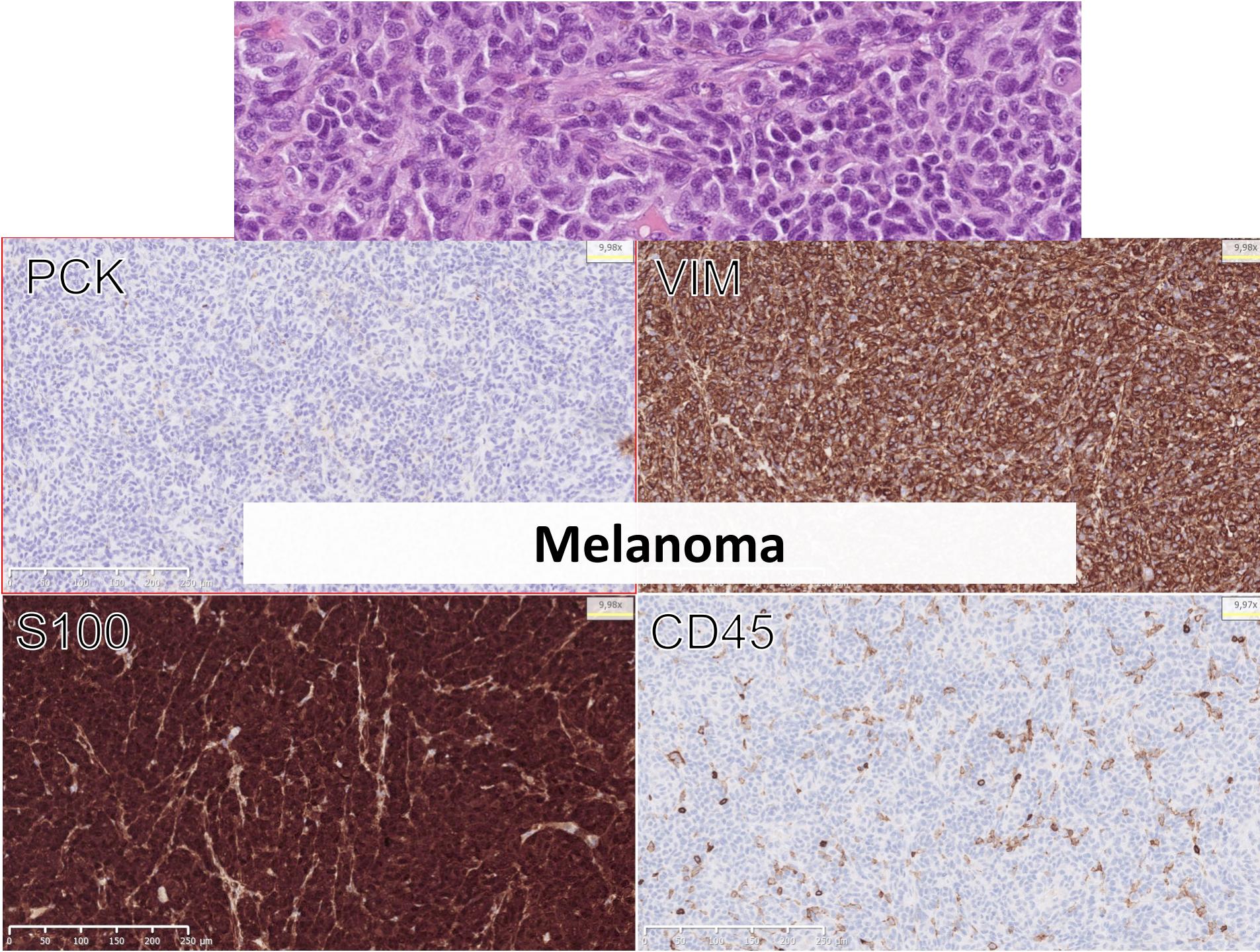


# Undifferentiated cases

- 49 year old male
- History of smoking
- Previous cancer
  - Seminoma of testis
- Enlarged lymph node in groin



??



# IHC panels for unknown primary tumour

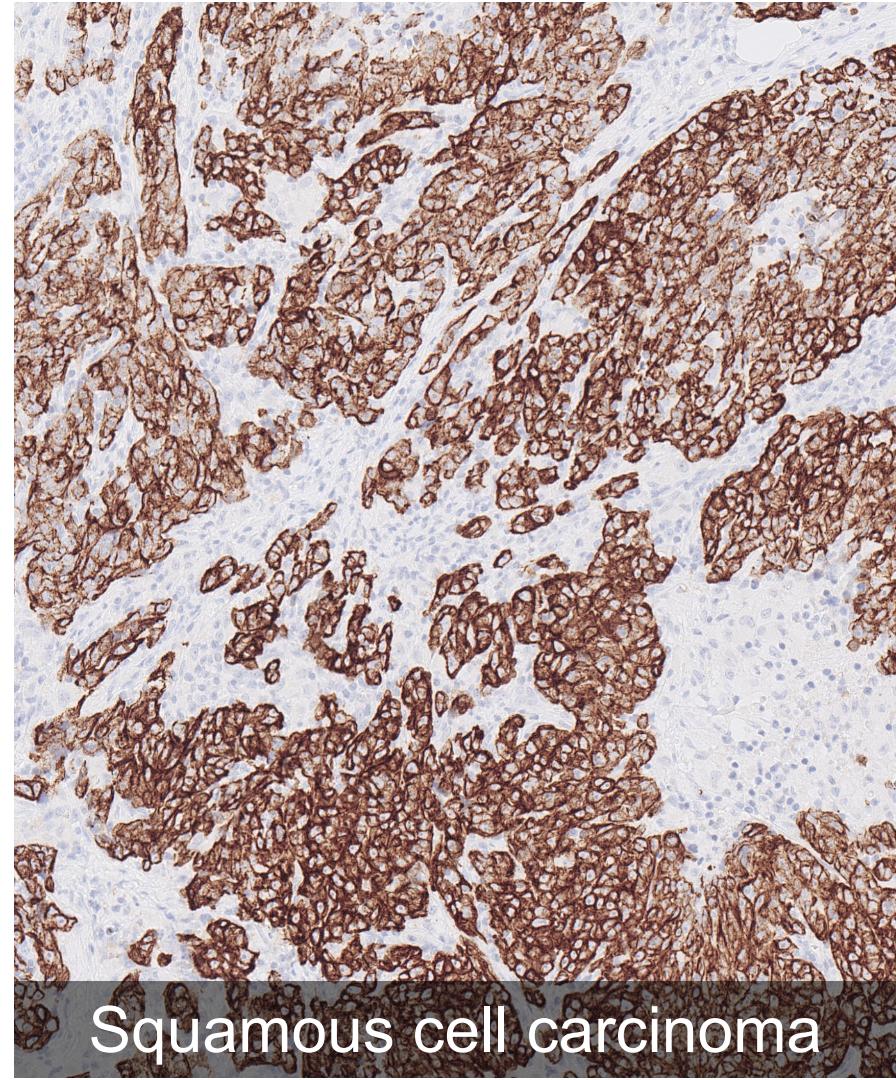
- Primary panel
  - Which overall tumour type
- Secondary cytokeratin panel
  - Information on site of origin
- Secondary organ specific panel
  - Confirmation (or rejection) of diagnosis with organ specific marker

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Squamous epithelia:										
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- suprabasal, non-keratinizing	+	+++	+++	+	++	(+)	-	-	-	-
- basal cells (tonsil, mucosa)	-	-	-	+++	+++	(+)	(++)	(+)	-	(+)
Transit. epith.: superficial cells	-	-	-	-	-	-	+++	+++	++	+++
- intermediary. / basal cells	-	(+)	+++	(+++)	-	(++)	+++	+++	(+)	+++
Mesothelium	-	-	-	++	++	+	+++	+++	-	+++
Bronchus, breast, prost., cerv.:										
- basal/myoepithelial cells	-	-	-	+++	++	+++	++	-	-	-
- luminal cells	-	-	-	+	+	+	+++	+++	-	+++
Biliary/pancr. ducts, lung alv., endometr., renal collect. ducts	-	-	-	-	-	-	+++	+++	-	+++
Stomach (foveola), intestine	-	-	-	-	-	-	+++	(+)	+++	+++
Hepatocytes, pancr. acini, prox. renal tubules	-	-	-	-	-	-	-	-	-	+++
Endocrine cells (Merkel, thyroid)	-	-	-	-	-	-	(+++)	(++)	(+++)	+++
Smooth muscle (vasc., myom.), myofibrobl., sm.ves.endothelia	-	-	-	-	-	-	+	(++)	-	++

Neutral/Basic (B, class II)	1	4	13	5	14	17	19	7	20	8
Acidic (A, class I)	10									18
Squamous cell carcinoma	(+)	+	+	++	++	(+)	(+)	(+)	-	(+)
Urothelial cell tumour	-	+	+	+	+	+	++	++	++	++
Malignant mesothelioma	-	-	-	++	++	+	++	+	-	++
Adenocarcinoma: complex epithelia (bronch., breast, prost.)	-	-	-	(+)	(+)	(+)	++	++	-	++
Adenocarc.: biliary tract, pancr., endom., ovary	-	-	-	(+)	(+)	(+)	++	++	(+)	++
Adenocarc.: stomach	-	-	-	-	-	-	++	+	+	++
Adenocarc.: intestine	-	-	-	-	-	-	++	+	++	++
Hepatocellular carcinoma										
Renal cell carcinoma	-	-	-	-	-	-	-	+	-	++
Endocrine tumours: carcinoids	-	-	-	-	-	-	+	+	-	++
- Merkel cell carcinoma	-	-	-	-	-	-	+	-	++	++
- Thyroid carcinoma	-	-	-	-	-	-	+	++	-	++

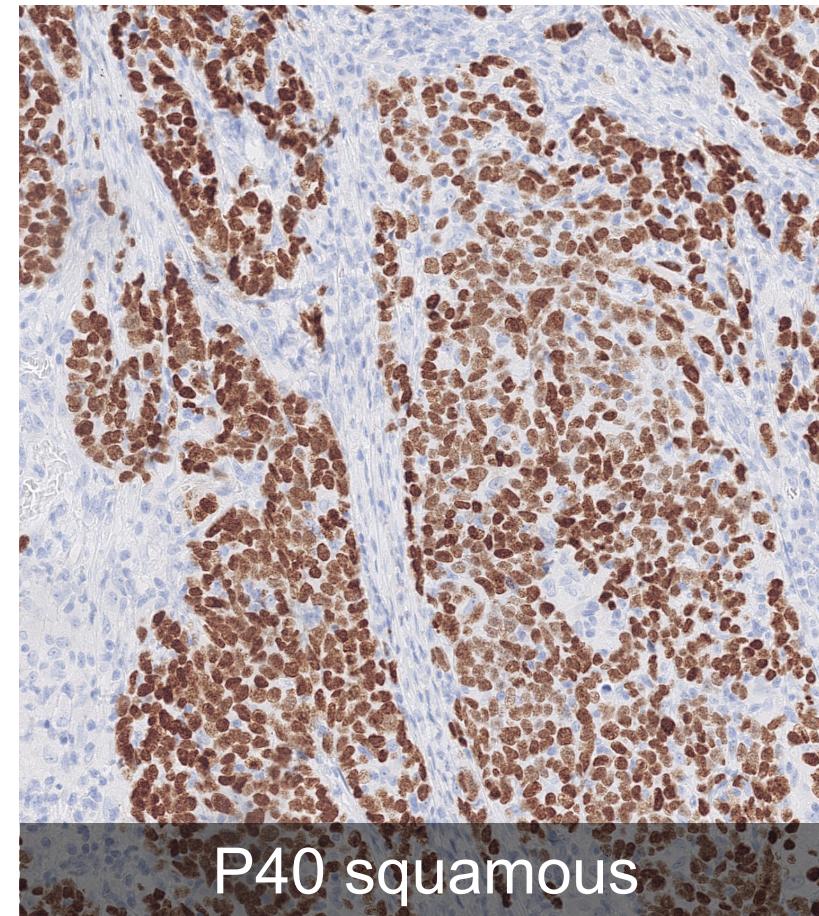
# CK5

- Indicative of squamous differentiation
- Strongly positive in squamous cell carcinoma
- Strongly positive in mesothelioma
- Often focally positive in urothelial carcinoma



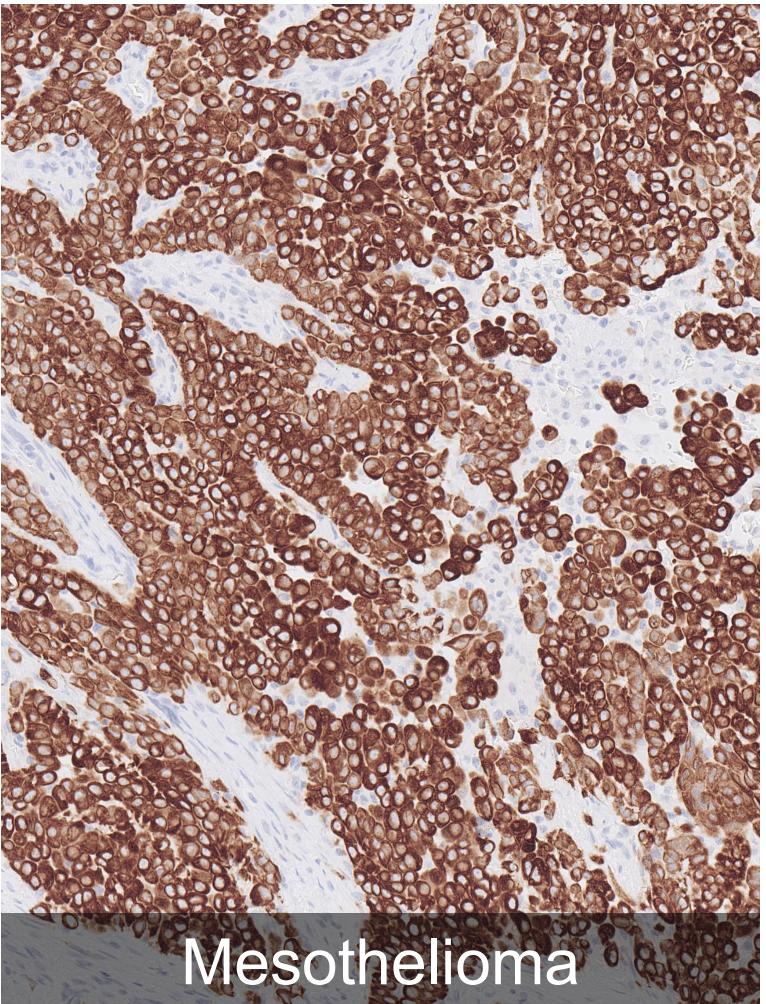
# Confirm squamous cell carcinoma

- Use p40!
- Nuclear transcription factor
- Limited to squamous cell carcinomas (and urothelial carcinomas)

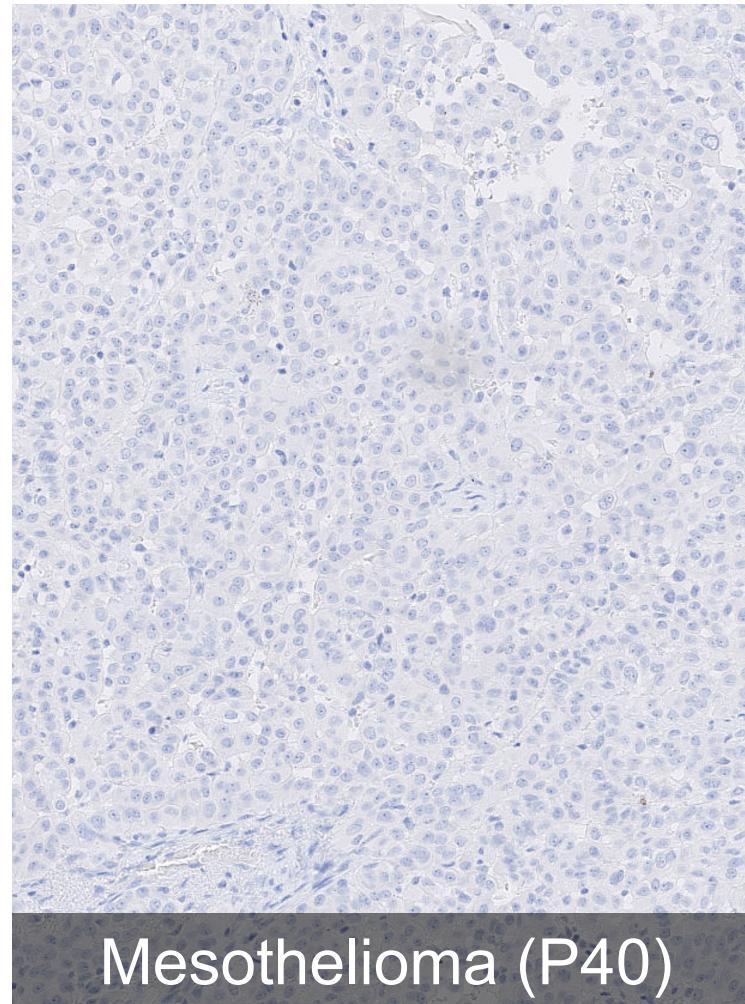


P40 squamous

# CK5 in mesothelioma

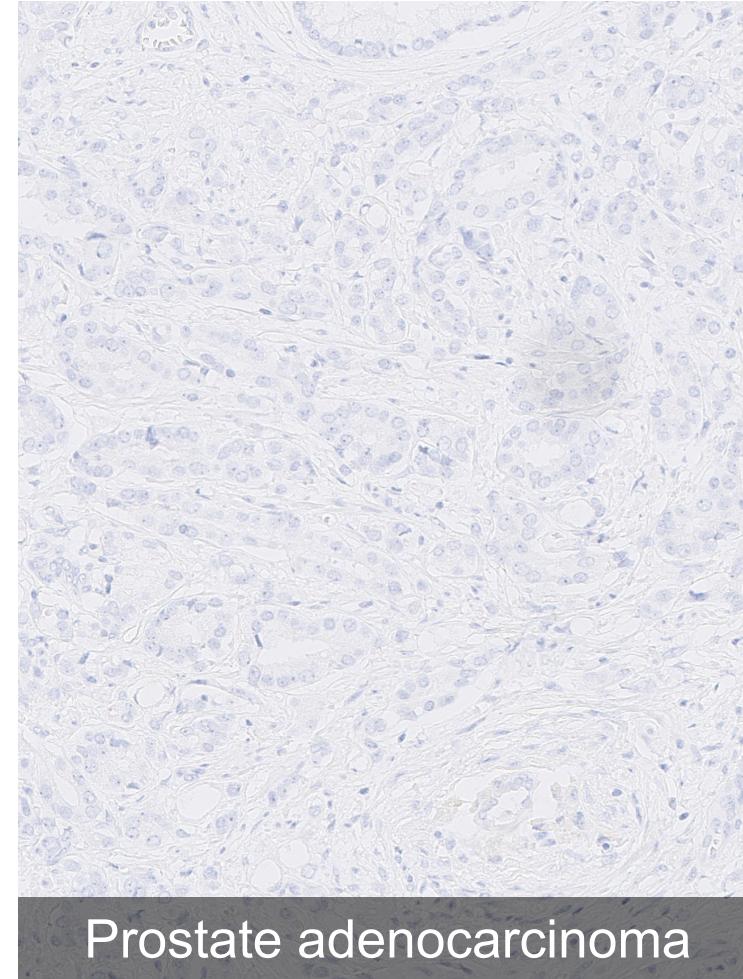
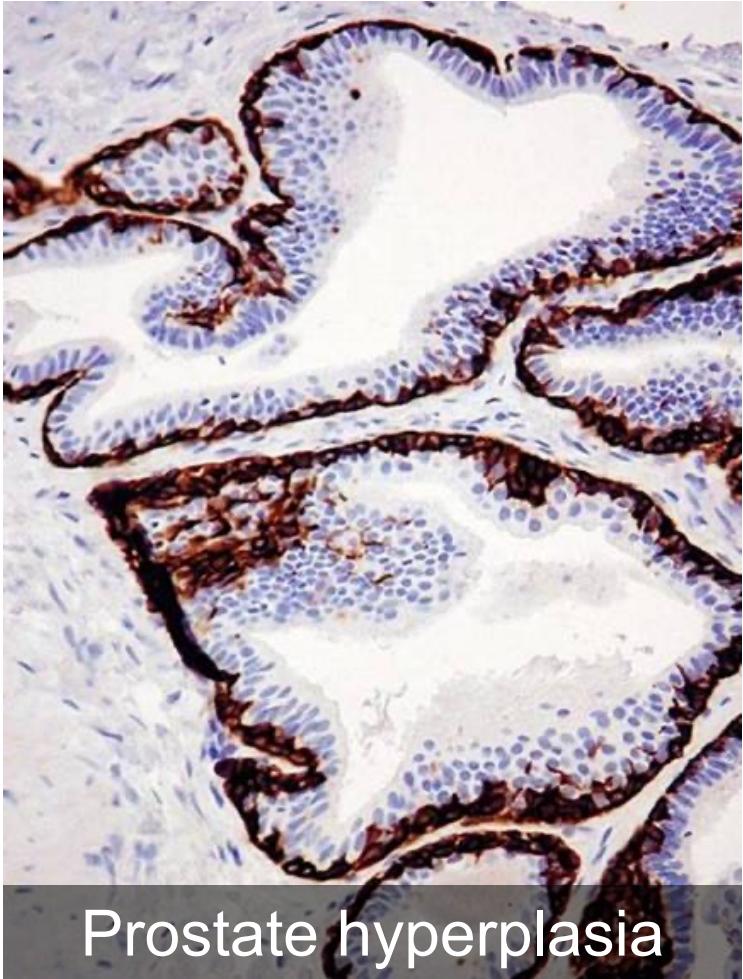


Mesothelioma

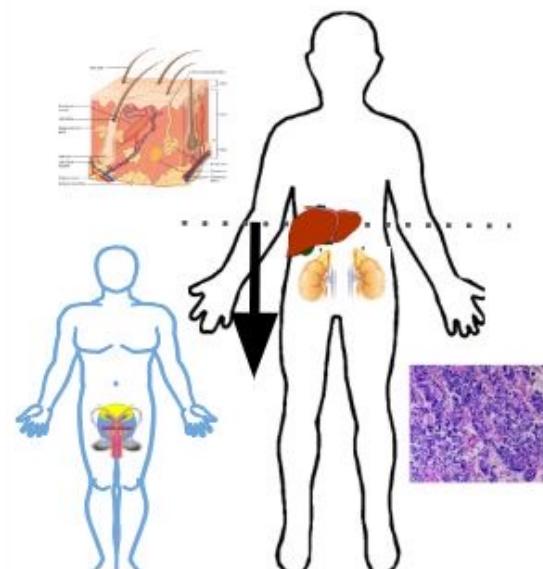
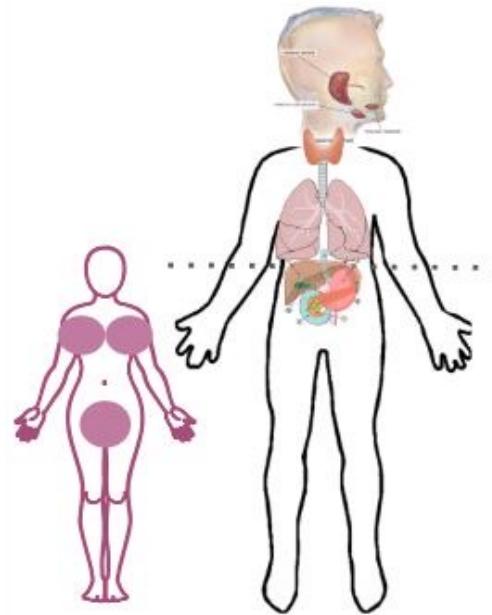


Mesothelioma (P40)

# CK5 – other uses

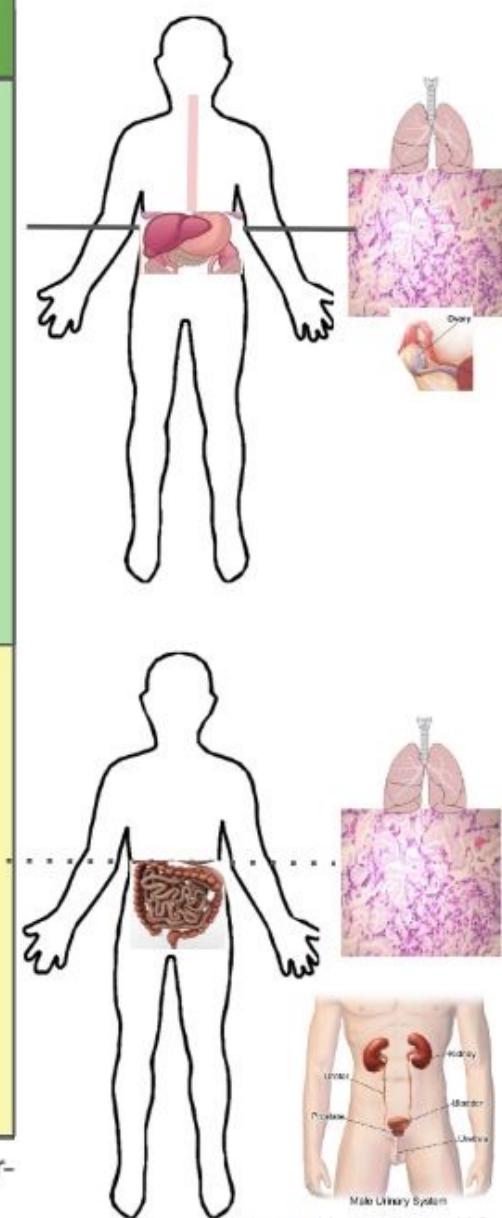


	1	4	13	5	14	17	19	7	20	8	18
Neutral/Basic (B, class II)	10										
Acidic (A, class I)											
Squamous cell carcinoma	(+)	+	+	++	++	(+)	(+)	(+)	-	(+)	
Transitional cell tumour	-	+	+	+	+	+	++	++	++	++	++
Malignant mesothelioma	-	-	-	++	++	+	++	+	-	++	
Adenocarcinoma: complex epithelia (bronch., breast, prost.)	-	-	-	(+)	(+)	(+)	++	++	-	++	
Adenocarc.: biliary tract, pancr., endom., ovary	-	-	-	(+)	(+)	(+)	++	++	(+)	++	
Adenocarc.: stomach	-	-	-	-	-	-	++	+	+	+	++
Adenocarc.: intestine	-	-	-	-	-	-	++	+	++	++	++
Hepatocellular carcinoma											
Renal cell carcinoma	-	-	-	-	-	-	-	+	-	++	
Endocrine tumours: carcinoids	-	-	-	-	-	-	+	+	-	++	
- Merkel cell carcinoma	-	-	-	-	-	-	+	-	++	++	
- Thyroid carcinoma	-	-	-	-	-	-	+	++	-	++	

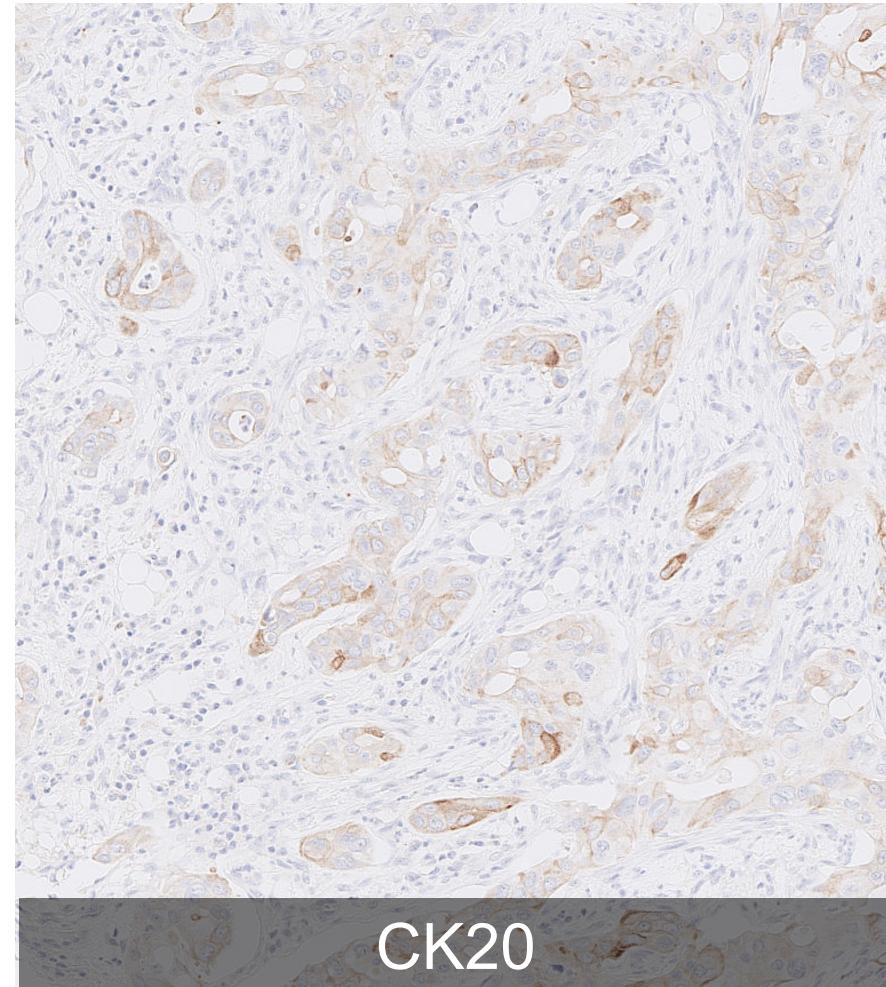
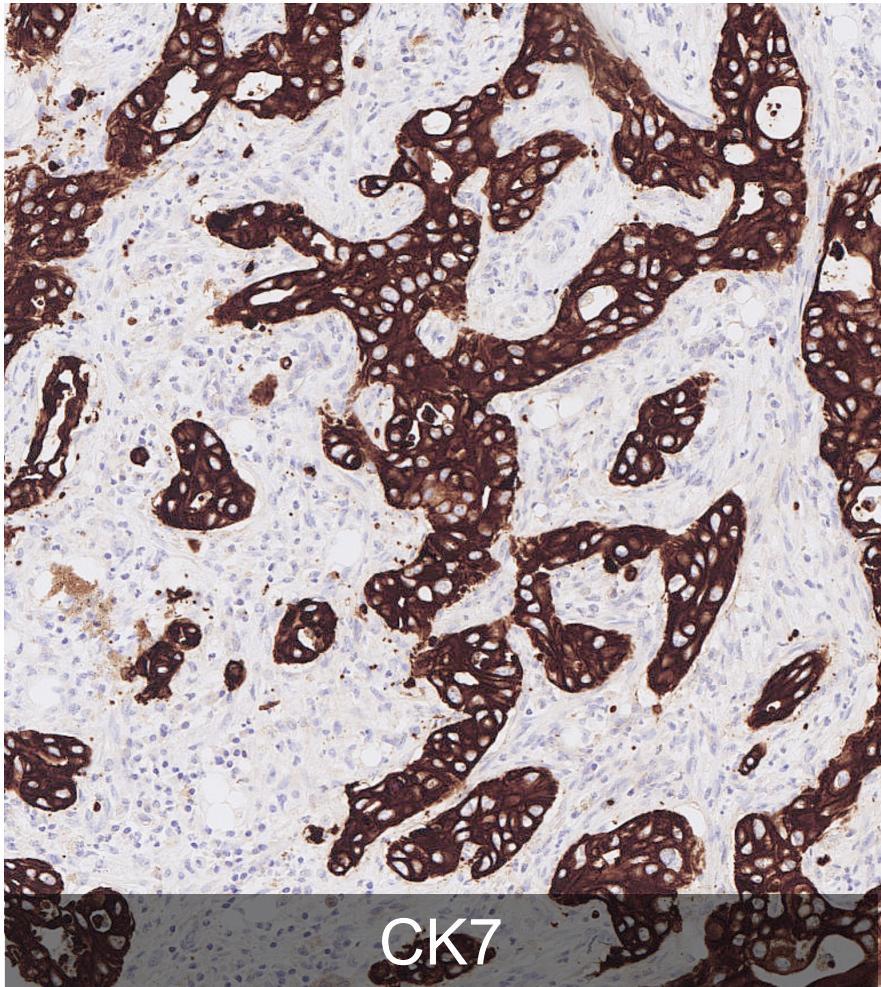


	CK20-	CK20+
CK7+	<ul style="list-style-type: none"> <li>Lung</li> <li>Breast</li> <li>Upper GI ADC</li> <li>Pancreatic/biliary ADC</li> <li>Endometrial/endocervical ADC</li> <li>Thyroid</li> <li>Thymic CA</li> <li>Salivary gland duct CA</li> <li>Hepatocellular CA, fibrolamellar type</li> <li>Ovarian serous CA</li> <li>Anal duct CA</li> <li>Mesothelioma</li> </ul>	<ul style="list-style-type: none"> <li>Urothelial CA</li> <li>Esophagus ADC</li> <li>Gastric ADC</li> <li>Small bowel ADC</li> <li>Mucinous ADC of lung</li> <li>Ovarian mucinous CA</li> <li>Pancreaticobiliary ADC</li> <li>Cholangiocarcinoma</li> </ul>
CK7-	<ul style="list-style-type: none"> <li>Hepatocellular CA</li> <li>Clear cell renal cell carcinoma</li> <li>Adrenal cortical CA</li> <li>Prostate ADC</li> <li>Small cell carcinoma</li> <li>Squamous cell CA</li> <li>Germ cell tumors</li> <li>Neuroendocrine neoplasm</li> <li>Medullary CA of the colon</li> </ul>	<ul style="list-style-type: none"> <li>Colorectal ADC</li> <li>Small bowel ADC</li> <li>Bladder ADC</li> <li>Merkel cell carcinoma</li> <li>Appendiceal ADC</li> <li>Mucinous ADC of lung</li> <li>Papillary renal cell carcinoma, type II</li> </ul>

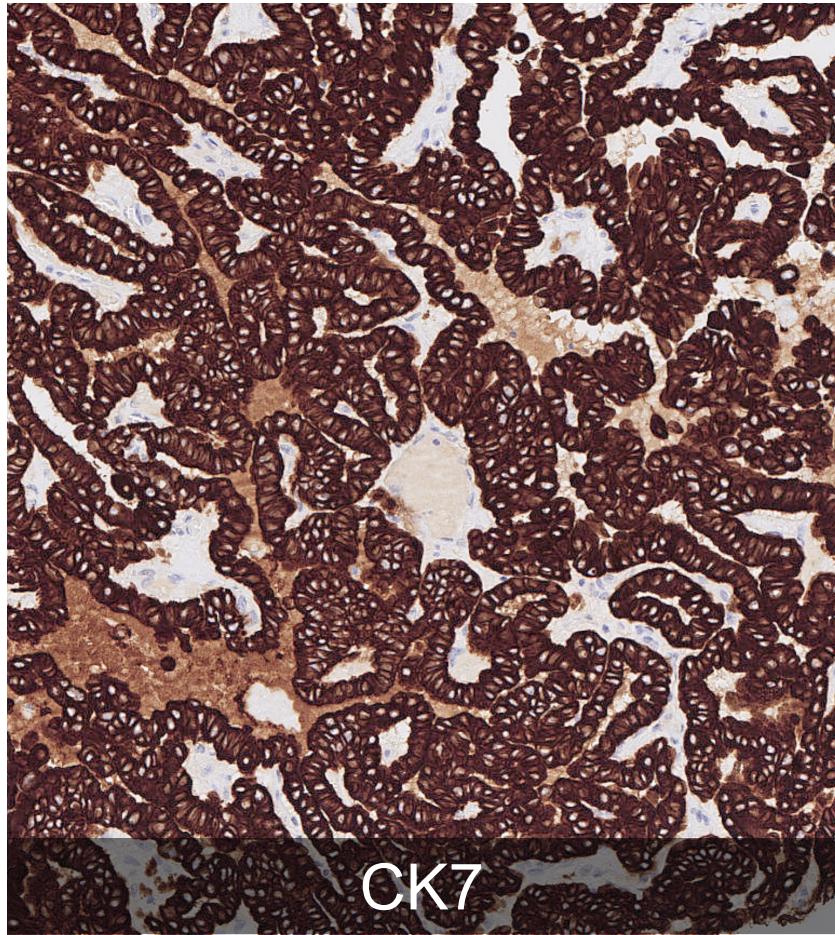
Abbreviations: ADC, adenocarcinoma; CA, carcinoma; CK, cytokeratin; GI, gastrointestinal.



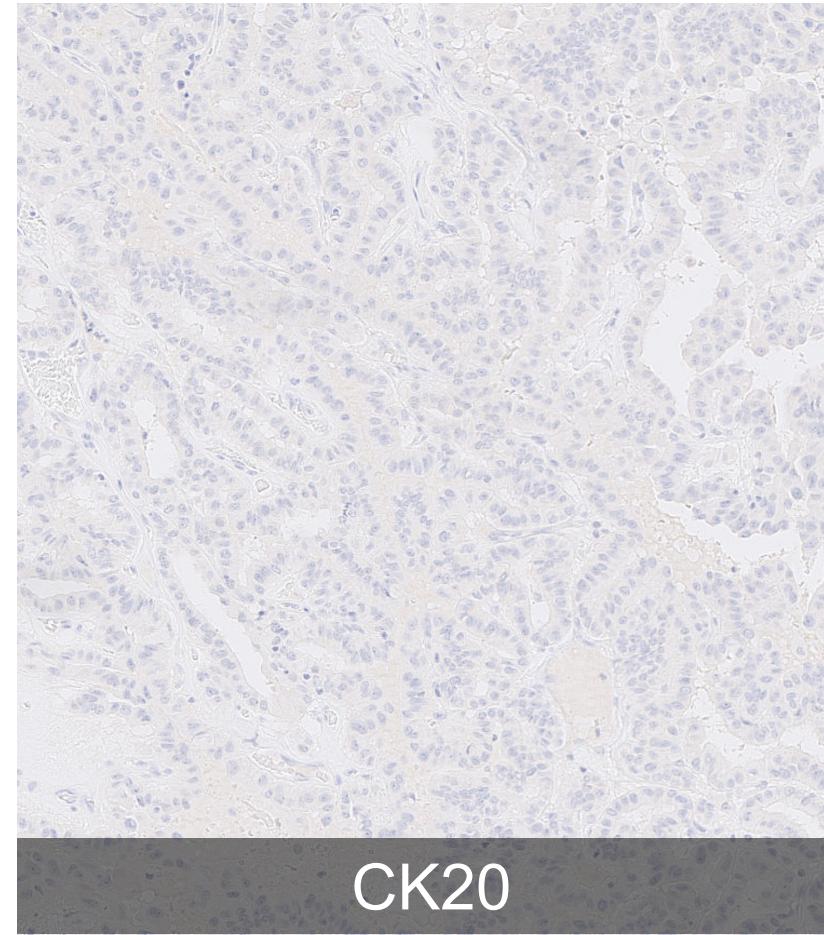
# Pancreas adenocarcinoma



# Thyroid carcinoma

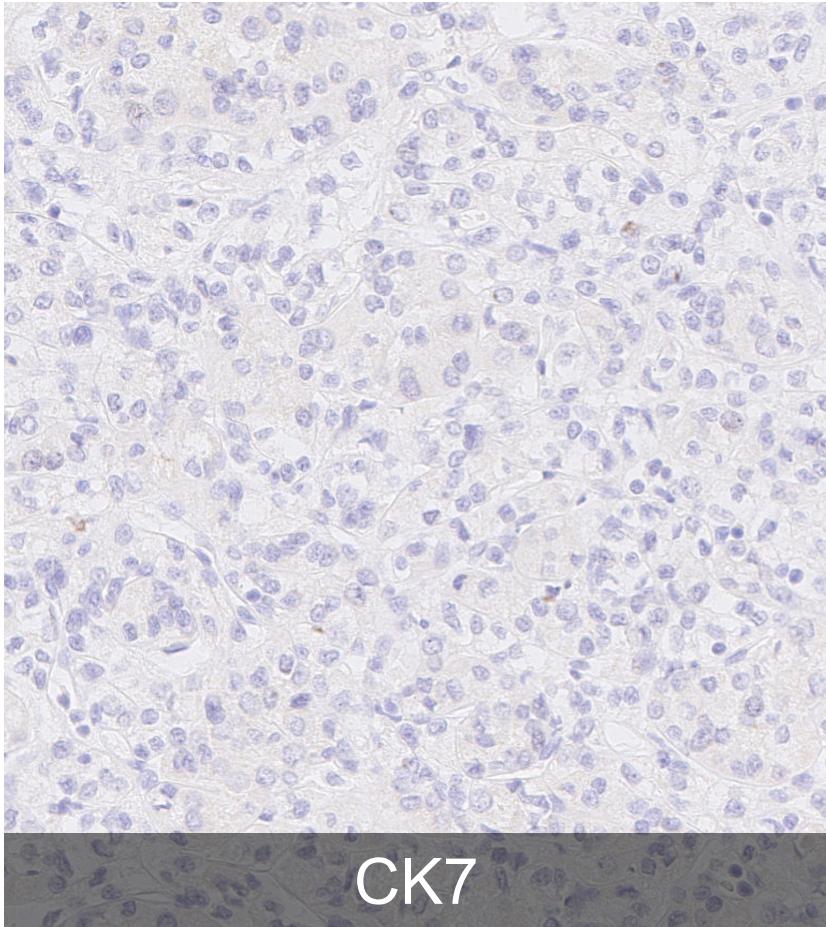


CK7

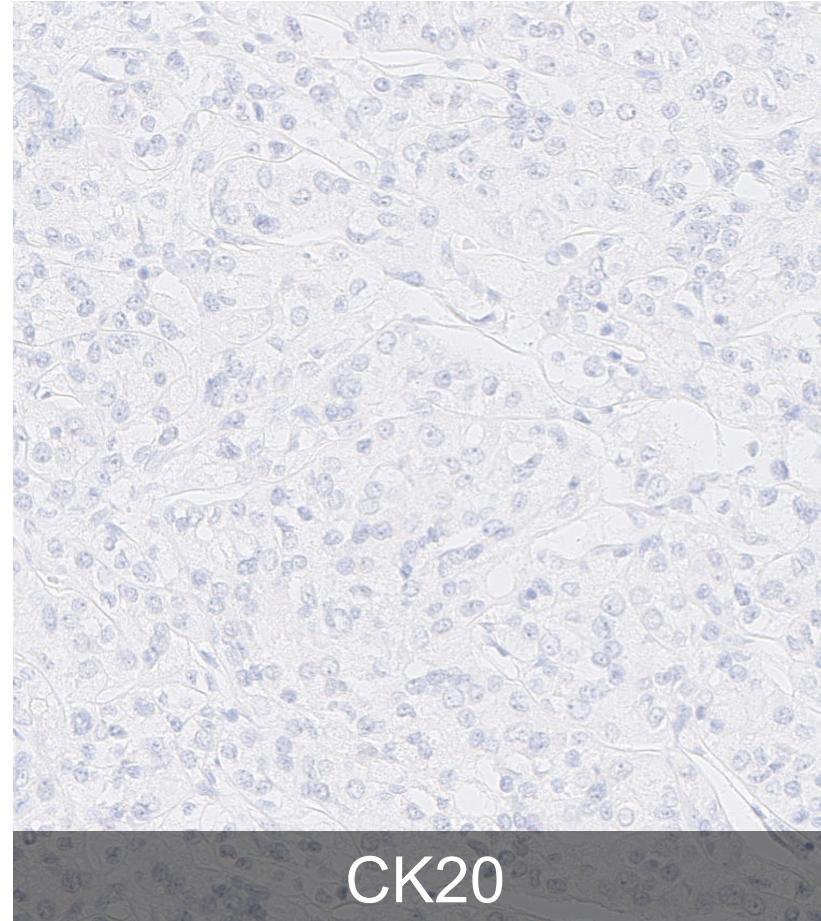


CK20

# Renal clear cell carcinoma



CK7



CK20

# Tissue specific panels

- Large number of somewhat tissue specific markers
- Several markers for each potential diagnosis are optimal
  - Increases chance of correct diagnosis in tumours with aberrant staining
- Should be combined in panels based on each specific case
- Negative stains also contain important information

# Tissue specific markers

## Breast:

Gata3  
Estrogen receptor  
TRPS1  
SOX10

## Lung:

TTF  
Napsin

## Kidney:

PAX8

## Bladder:

GATA3  
Uroplakin II

## Neuroendocrine:

SYP  
CGA  
INSM1

## Germ cell:

OCT3/4  
CD30  
SALL4

## Thyroid:

TTF  
PAX8

## Gastrointestinal:

CDX2  
Cadherin 17  
SATB2

## Melanoma:

SOX10  
MLA

## Mesothelioma:

Calretinin  
Podoplanin

## Pancreas:

SMAD4  
Gata3

# Tissue “specific” markers

Breast:  
Gata3  
Estrogen receptor  
TRPS1  
SOX10

Bladder:  
GATA3  
Uroplakin II

Neuroendocrine:  
SYP  
CGA  
INSM1

Lung:  
TTF  
Napsin

Prostate:  
NKX3.1

Germ cell:  
OCT3/4  
CD30  
SALL4

Thyroid:  
TTF  
PAX8

Gastrointestinal:  
CDX2  
Cadherin 17  
SATB2

Melanoma:  
SOX10  
MLA

Female genitals:  
PAX8  
WT1  
ER

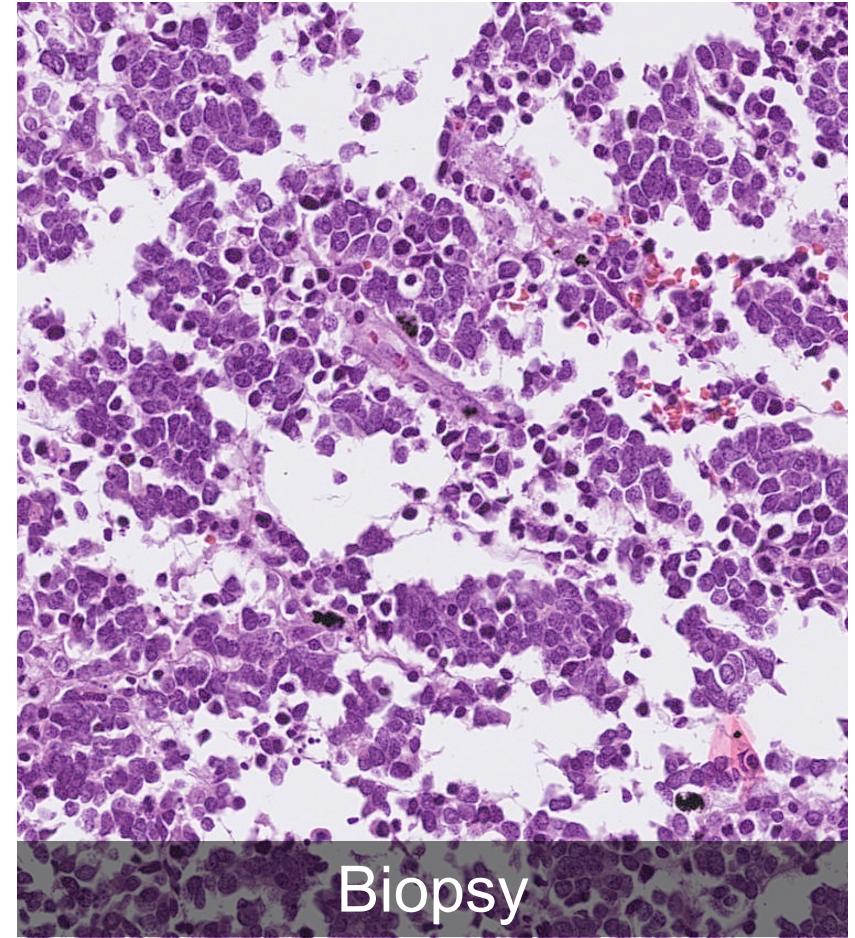
Kidney:  
PAX8

Mesothelioma:  
Calretinin  
Podoplanin

Pancreas:  
SMAD4  
Gata3

# Case

- 67 y.o. female
- Heavy smoker
- Several tumours in both lungs
- Pleural plaques and exposed to asbestos
- Large lymph nodes in mediastinum
- Previous ovarian serous carcinoma

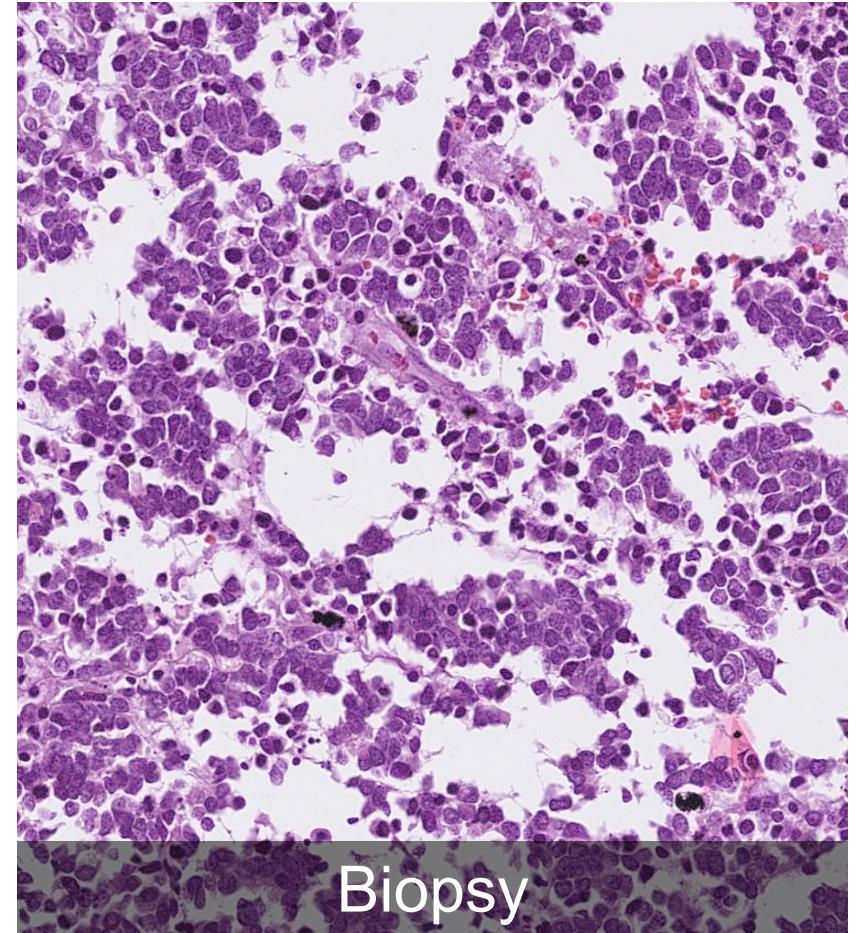


Biopsy

# Case

- Carcinoma
- Lung cancer ?
  - Adeno? Squamous? Small cell (neuroendocrine)?
- Relapse ovarian serous carcinoma ?
- Mesothelioma ?

CD45	Pan cytokeratin	S100	Vimentin
Negative	Positive	Negative	Negative



Biopsy

# Tissue specific markers

## Breast:

Gata3  
Estrogen receptor  
TRPS1  
SOX10

## Lung:

TTF  
Napsin

## Kidney:

PAX8

## Bladder:

GATA3  
Uroplakin II

## Neuroendocrine:

SYP  
CGA  
INSM1

## Germ cell:

OCT3/4  
CD30  
SALL4

## Thyroid:

TTF  
PAX8

## Gastrointestinal:

CDX2  
Cadherin 17  
SATB2

## Melanoma:

SOX10  
MLA

## Mesothelioma:

Calretinin  
Podoplanin

## Pancreas:

SMAD4  
Gata3

# Selected panels

Lung:

TTF

Napsin

Mesothelioma:  
Calretinin  
Podoplanin

Neuroendocrine:

SYP

CGA

INSM1

Female genitals:

PAX8

WT1

ER

# Selected panels

All purpose cytokeratins:  
CK5  
CK7  
CK20

## Cytokeratins

CK5	Negative
CK7	Positive (dots)
CK20	Negative

Lung:  
TTF  
Napsin

Neuroendocrine:  
SYP  
CGA  
INSM1

Female genitals:  
PAX8  
WT1  
ER

Mesothelioma:  
Calretinin  
Podoplanin

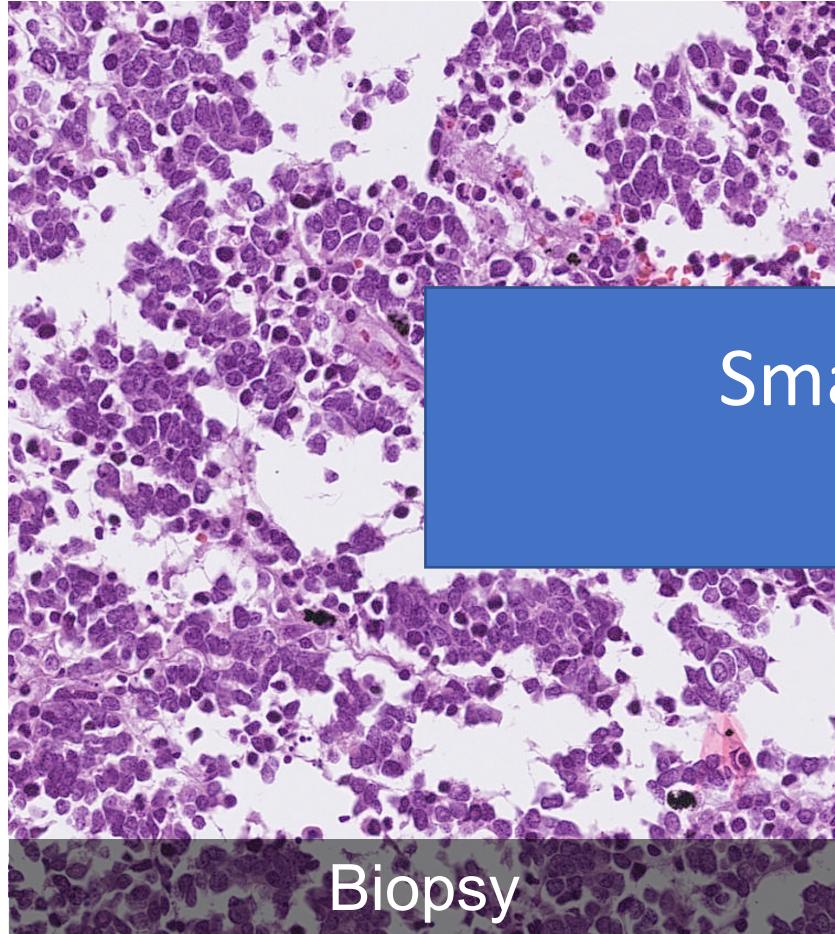
Lung	
TTF	Positive
Napsin	Negative

Neuroendocrine	
SYP	Positive
CGA	Positive
INSM1	Positive

Female genitals	
PAX8	Negative
WT1	Negative
ER	Negative

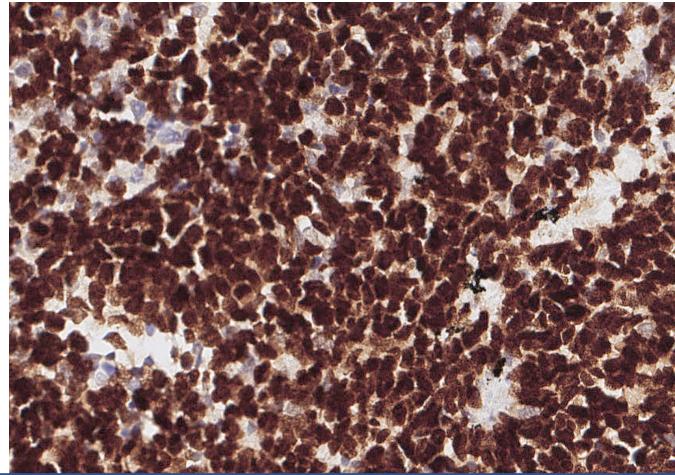
Mesothelioma	
Calretinin	Negative
Podoplanin	Negative

# Case

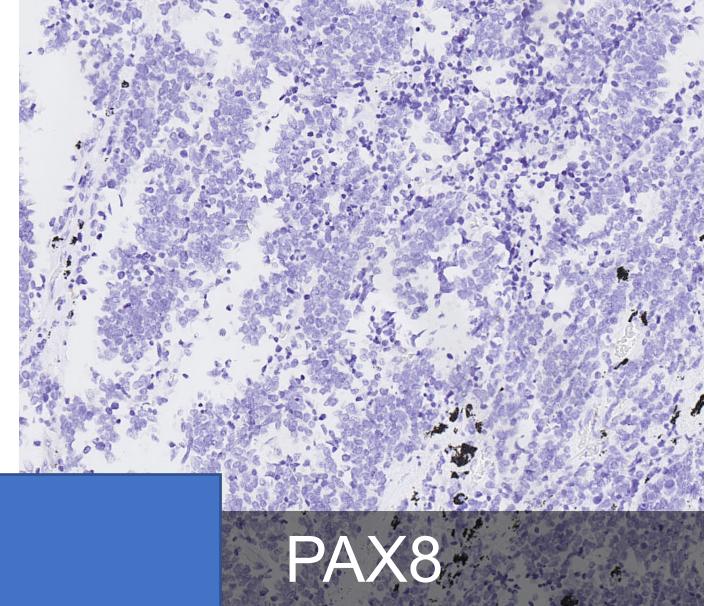


Biopsy

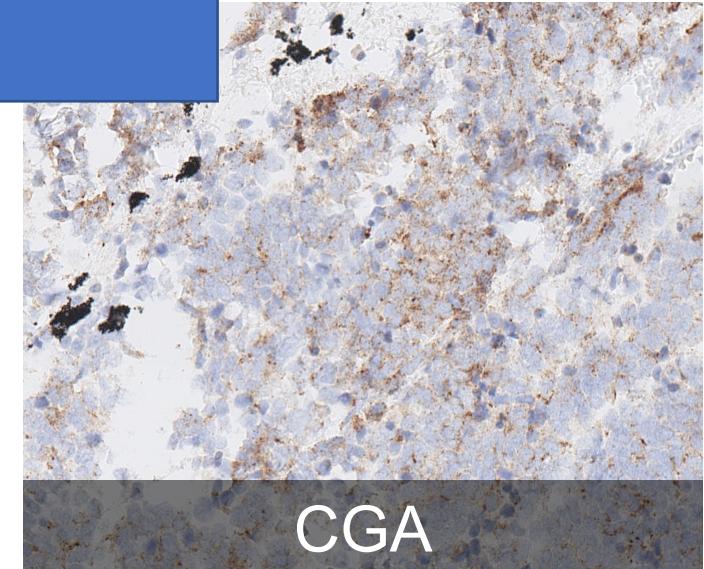
Small cell lung carcinoma  
(neuroendocrine)



SYP



PAX8



CGA

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

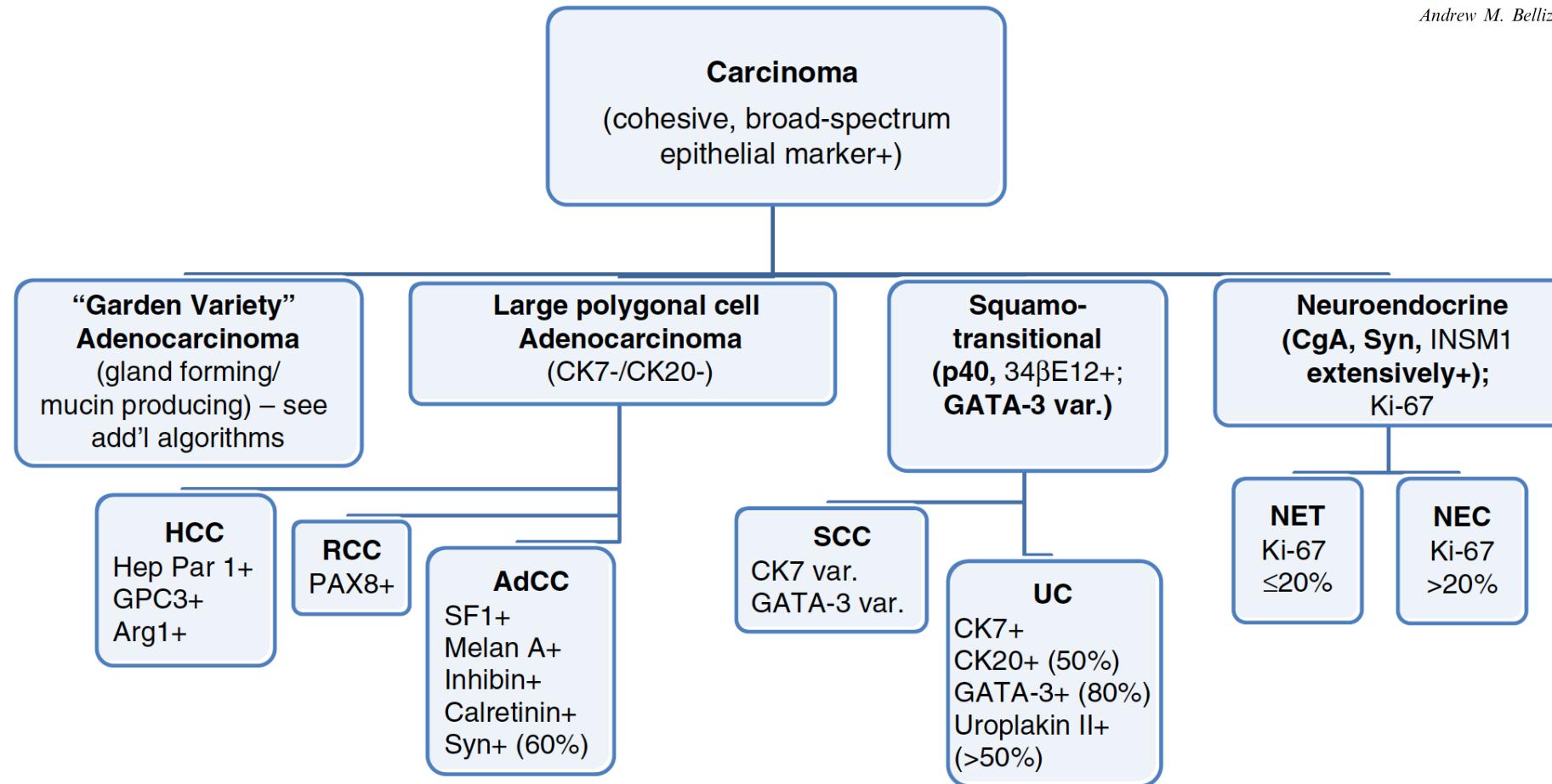
Andrew M. Bellizzi, MD

TABLE 1. Next-generation Immunohistochemical Markers Discussed in This Review

Marker	Useful in Diagnosis of	Next-generation IHC “Qualifications”
PAX8	Müllerian, renal, and thyroid carcinoma; thymic neoplasms (with polyclonal antibody); pancreatic origin of well-differentiated neuroendocrine tumor (with polyclonal antibody)	Lineage-restricted transcription factor
MDM2/ CDK4	Well- and dedifferentiated liposarcoma	Protein correlate of molecular genetic event
GATA-3	Breast and urothelial carcinoma; also expressed by pheochromocytoma/paraganglioma, choriocarcinoma, mesonephric carcinoma, parathyroid tumors, and pituitary gonadotroph and TSH-expressing tumors; often expressed by mesothelioma, chromophobe renal cell carcinoma, and cutaneous epithelial neoplasms; variably expressed by yolk sac tumor	Lineage-restricted transcription factor
ERG	Vascular neoplasms; also expressed by subsets of prostate cancer, Ewing sarcoma, and acute leukemia; antibodies to N-terminus label epithelioid sarcoma	Lineage-restricted transcription factor
Islet 1	Pancreatic origin of well-differentiated neuroendocrine tumor	Protein correlate of molecular genetic event
PAX6	Pancreatic origin of well-differentiated neuroendocrine tumor	Lineage-restricted transcription factor
SALL4	Germ cell neoplasia; also expressed by hepatoid adenocarcinoma; may be frequently expressed by rhabdoid and Wilms tumor; aberrant expression in a significant minority (20%-30%) of serous, gastric, urothelial, and biliary carcinomas	Lineage-restricted transcription factor
SOX10	Melanocytic, nerve sheath, and myoepithelial tumors; also often (60%) expressed by triple-negative breast cancer	Lineage-restricted transcription factor
INI1/ SMARCB1 (loss)	Epithelioid sarcoma; malignant rhabdoid tumors of soft tissue, kidney, and CNS, and medullary carcinoma of kidney; subset of epithelioid MPNST, myoepithelial carcinoma of soft tissue, and extraskeletal myxoid chondrosarcoma	Protein correlate of molecular genetic event
p40	Squamous, urothelial, and myoepithelial tumors; myoepithelial/basal cell marker in breast and prostate	Lineage-restricted transcription factor
ATRX (loss)	Diffuse astrocytoma and pancreatic origin of well-differentiated neuroendocrine tumor	Protein correlate of molecular genetic event
SATB2	Colorectal origin of adenocarcinoma, lower GI origin of well-differentiated neuroendocrine tumor, and possibly cutaneous origin of a poorly differentiated neuroendocrine carcinoma; osteoblastic lineage; <i>BCOR</i> -rearranged sarcoma	Lineage-restricted transcription factor
OTP	Bronchopulmonary origin of well-differentiated neuroendocrine tumor	Lineage-restricted transcription factor; identified through gene expression profiling
Rb protein (loss)	Poorly differentiated neuroendocrine carcinoma; spindle cell/pleomorphic lipoma, cellular angiofibroma, and mammary-type myofibroblastoma	Protein correlate of molecular genetic event
SMAD4 (loss)	Pancreatic origin of adenocarcinoma; also frequently lost in colorectal cancer	Protein correlate of molecular genetic event
BAP1 (loss)	Mesothelioma (especially epithelioid) and intrahepatic cholangiocarcinoma; loss in ocular melanoma and renal cell carcinoma prognostically adverse	Protein correlate of molecular genetic event
SF1	Adrenal cortical and sex cord-stromal neoplasms	Lineage-restricted transcription factor
NKX3.1	Prostate cancer	Lineage-restricted transcription factor
INSM1	Neuroendocrine neoplasms	Lineage-restricted transcription factor

CNS indicates central nervous system; GI, gastrointestinal; IHC, immunohistochemistry; MPNST, malignant peripheral nerve sheath tumor; OTP, orthopedia homeobox; SF1, steroidogenic factor 1.

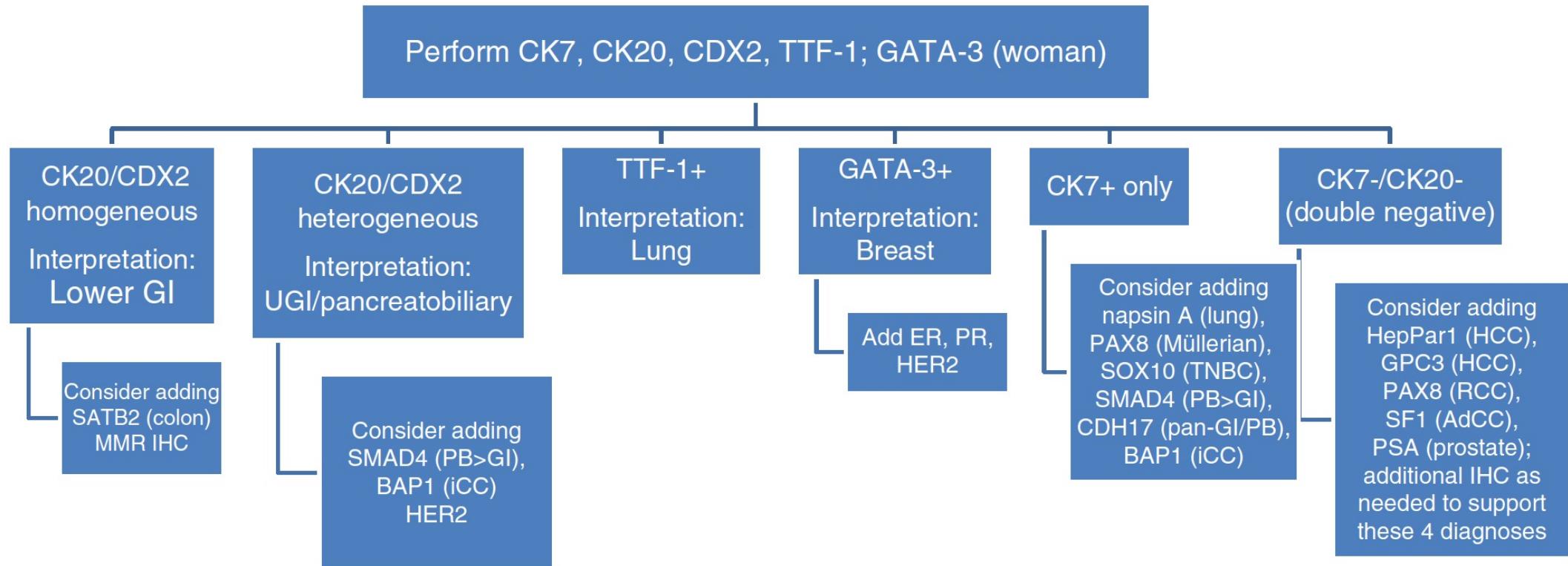
Andrew M. Bellizzi, MD



**FIGURE 1.** Algorithmic approach to diagnosis of four carcinoma types. AdCC indicates adrenal cortical carcinoma; Arg1, arginase-1; CgA, chromogranin A; GPC3, glyican-3; HCC, hepatocellular carcinoma; NEC, poorly differentiated neuroendocrine carcinoma; NET, well-differentiated neuroendocrine tumor; RCC, renal cell carcinoma; SCC, squamous cell carcinoma; Syn, synaptophysin; UC, urothelial carcinoma. Please see this image in color online.

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

Andrew M. Bellizzi, MD



**FIGURE 2.** Immunohistochemical algorithm for “garden variety” adenocarcinoma in the liver. AdCC indicates adrenal cortical carcinoma; ER, estrogen receptor; GI, gastrointestinal; GPC3, glyican-3; HCC, hepatocellular carcinoma; iCC, intrahepatic cholangiocarcinoma; IHC, immunohistochemistry; PB, pancreatobiliary; PR, progesterone receptor; RCC, renal cell carcinoma; TNBC, triple-negative breast cancer; UGI, upper gastrointestinal. Please see this image in color online.

# Thank you for your attention!

