The unknown primary tumour: IHC for diagnostic use

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Department of Pathology

Aalborg University Hospital

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 heriditary 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

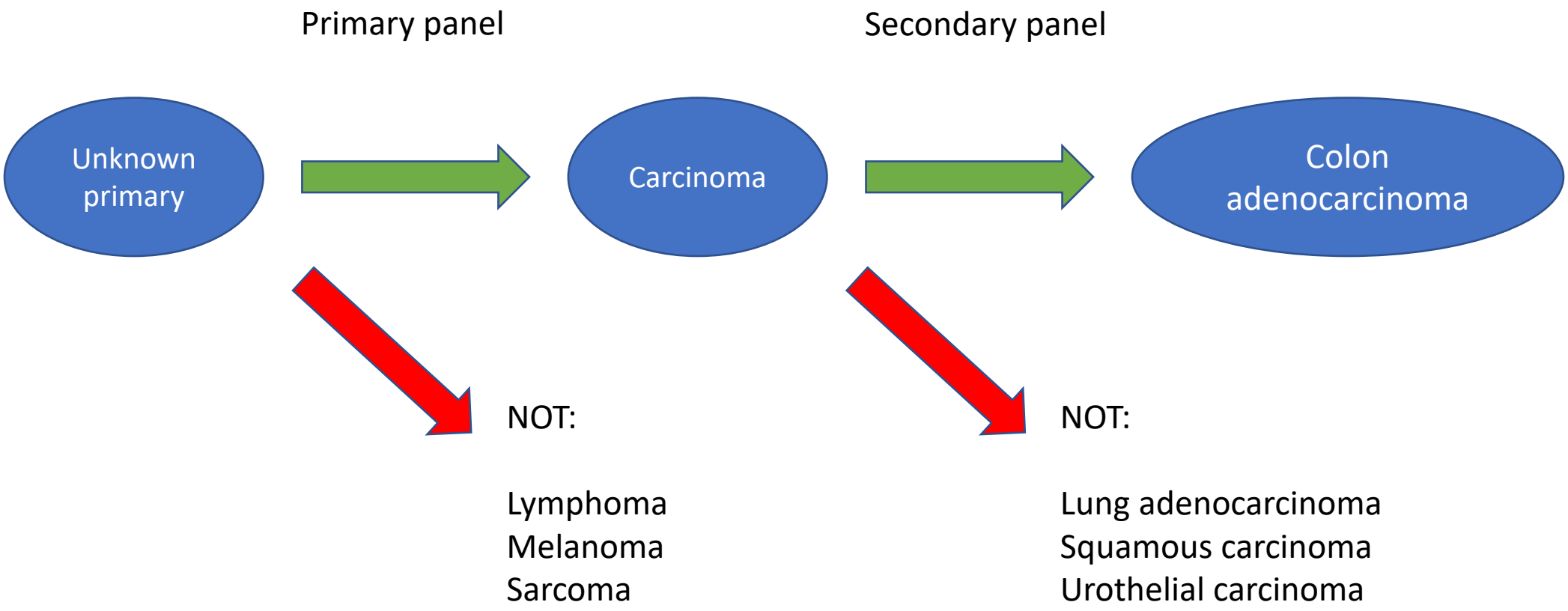
Selection of IHC antibodies for diagnostic algorithm



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

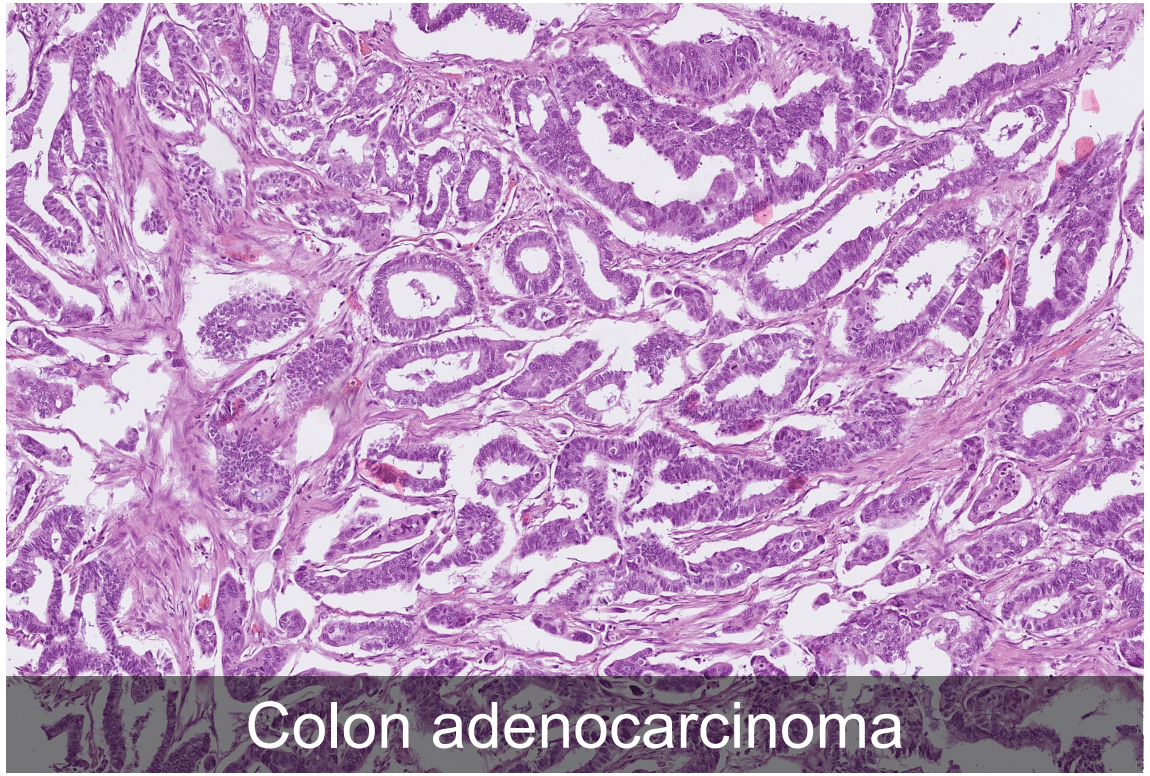
IHC panels for unknown primary tumour



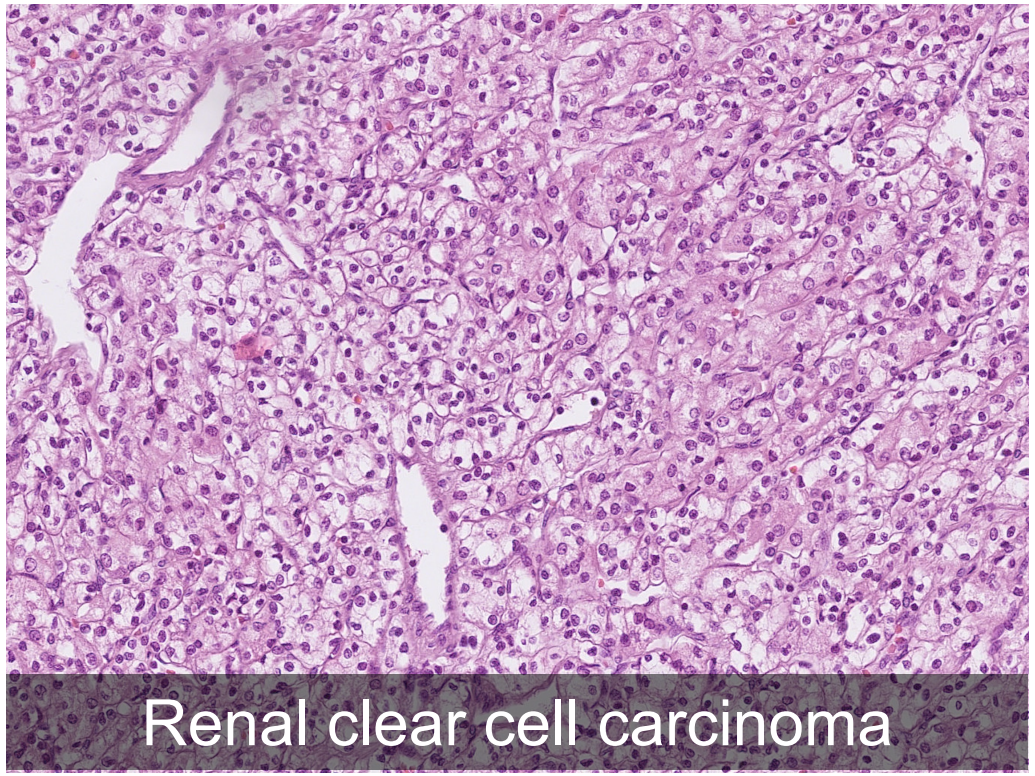
IHC classification of unkown primary tumour

- 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?!

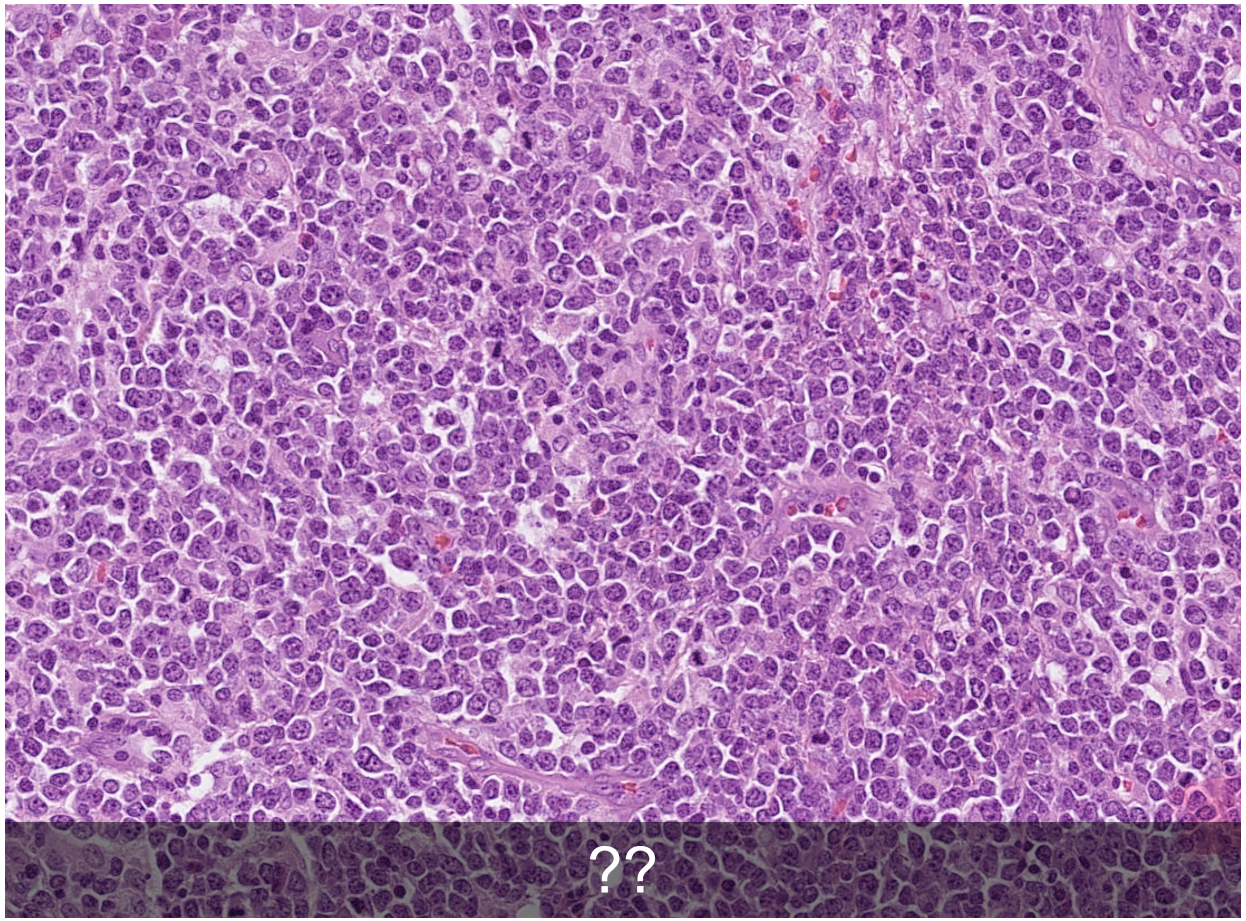


Colon adenocarcinoma



Renal clear cell carcinoma

Undifferentiated cases





Primary panel

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

Neoplasms	CD45	Pan cytokeratin	S100	Vimentin
Haematopoietic / lymphoid	(+)	(-)	(-)	(+)
Epithelial	-	(+)	-/+	-/+
Mesothelial	-	+	-	+
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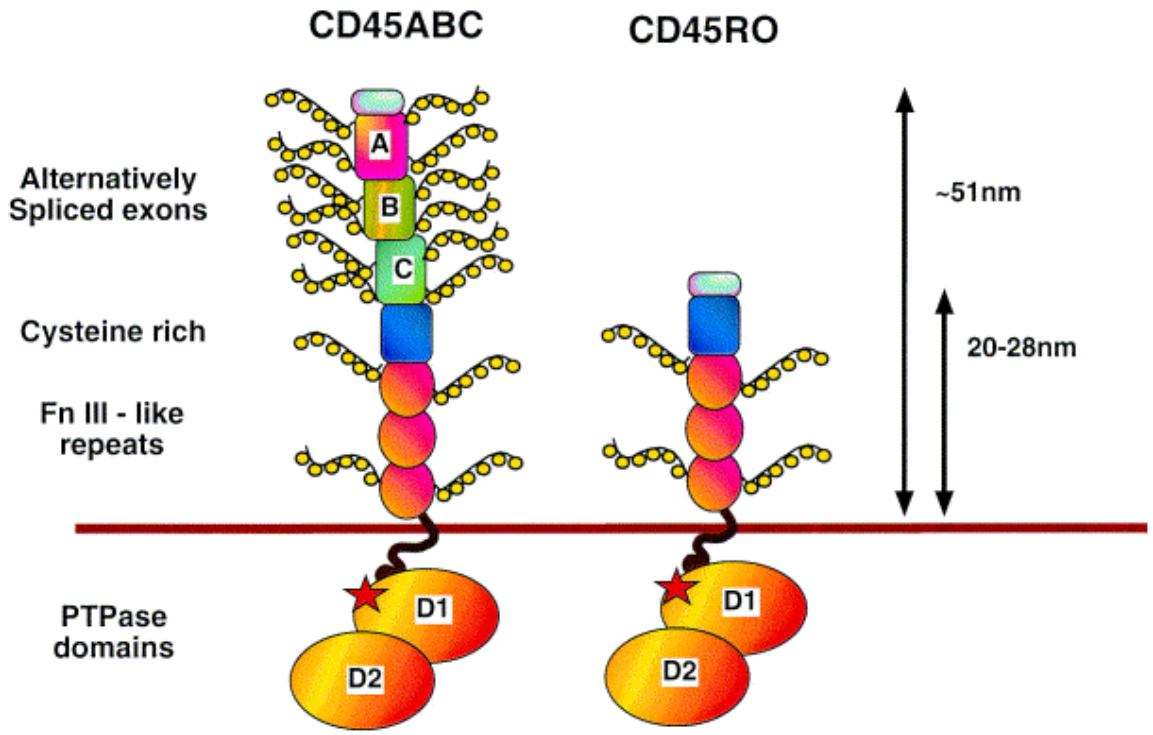
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CD45 – Leucocyte common antigen

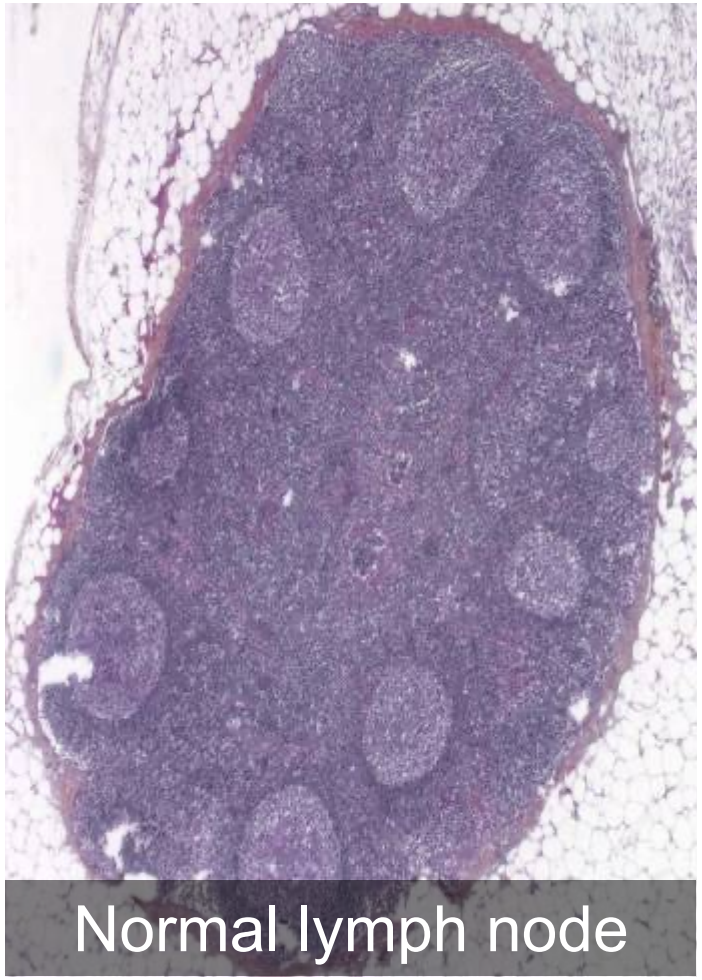
- Protein tyrosin phosphatase, receptor type C (PTPRC)
- Important regulator of T- and B-cell antigen receptor signaling
- Expressed on all hematopoietic cells
- Exception: Plasma cells, erythrocytes and megakaryocytes

CD45 - isoforms

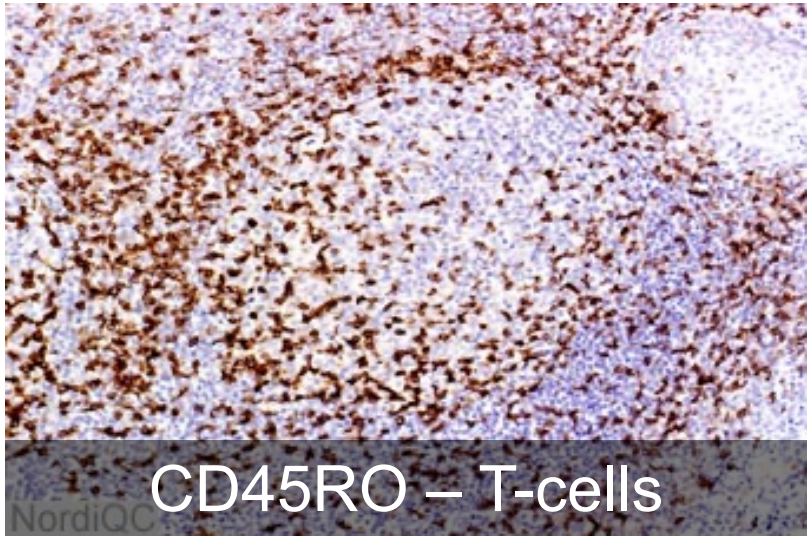
- Alternatively spliced variance in extracellular components
- 5 isoforms: ABC, AB, AC, B, 0
- Isoforms expressed on different subsets of lymphocytes
- Naïve T-cells: CD45RA, CD45RB
- Activated T-cells: CD45R0
- B-cells: CD45ABC, CD45RA



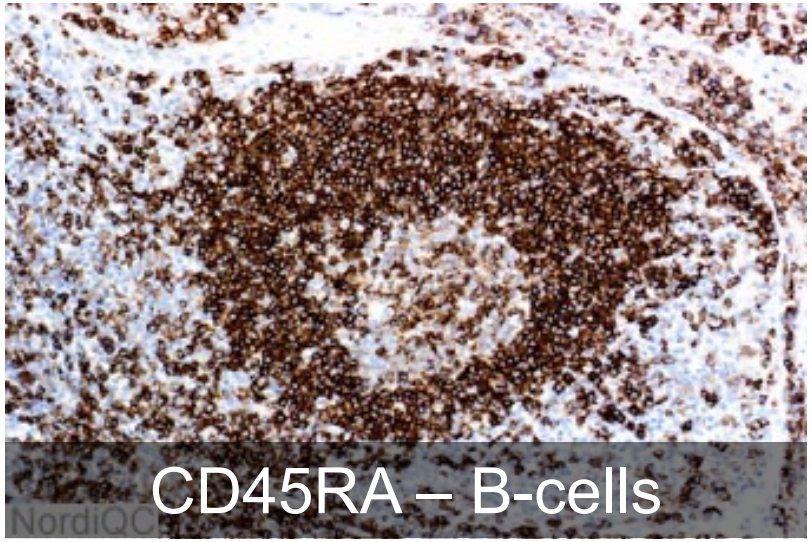
CD45 - isoforms



Normal lymph node

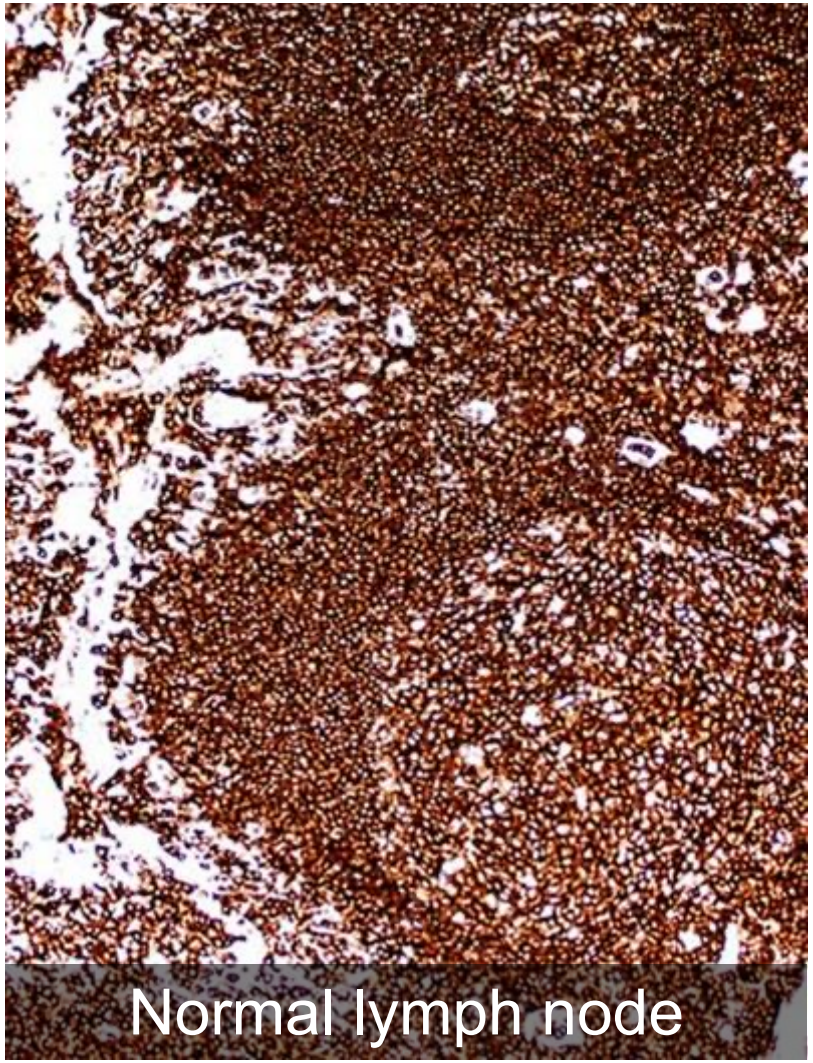


CD45RO – T-cells

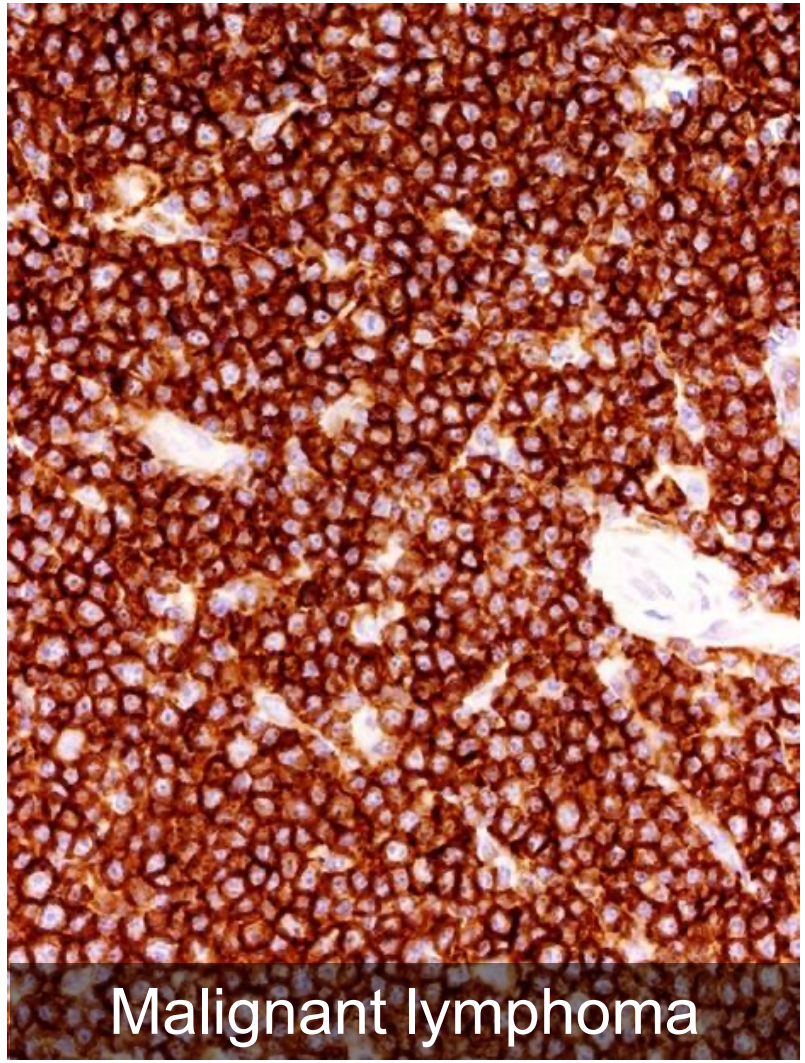


CD45RA – B-cells

CD45

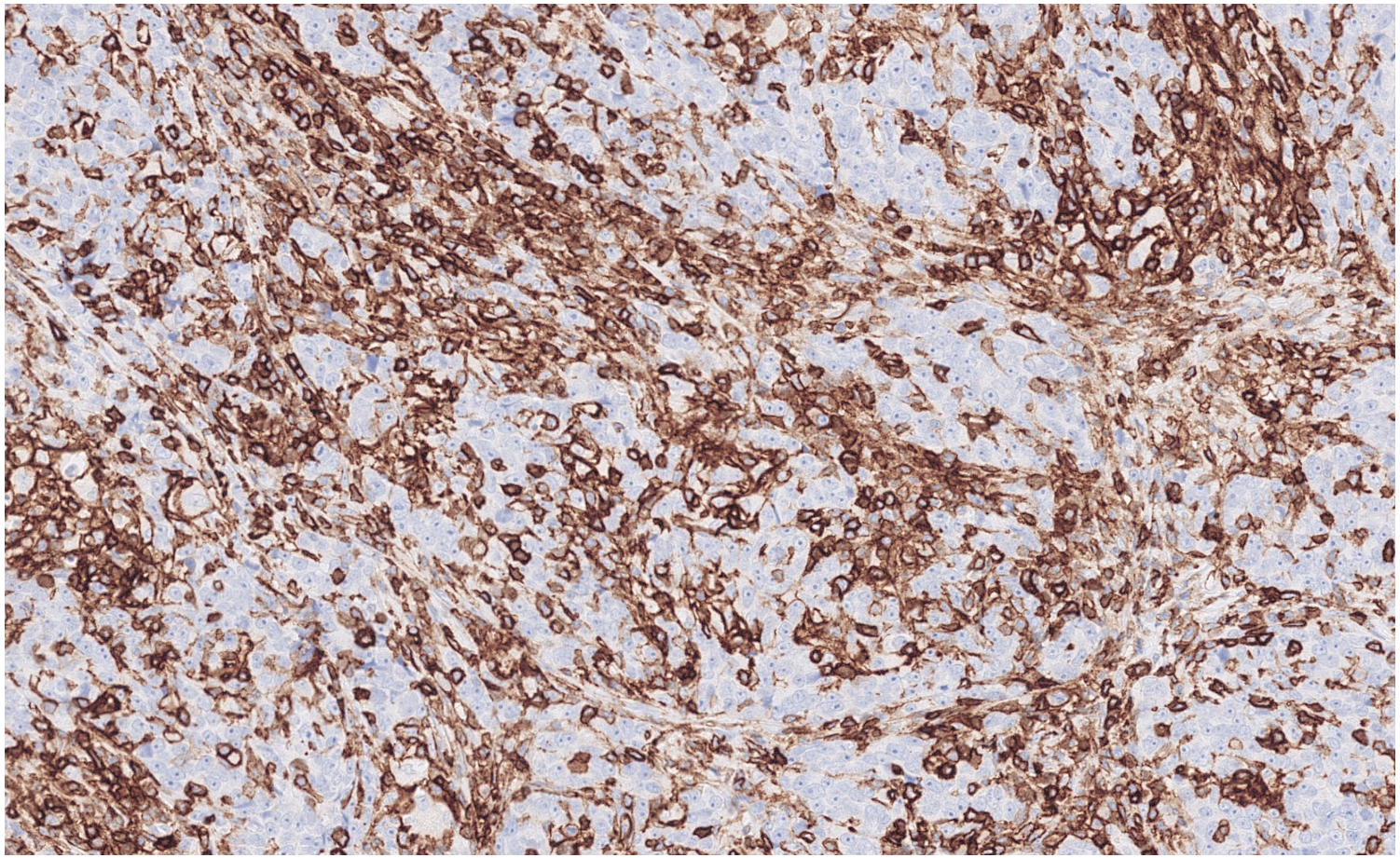


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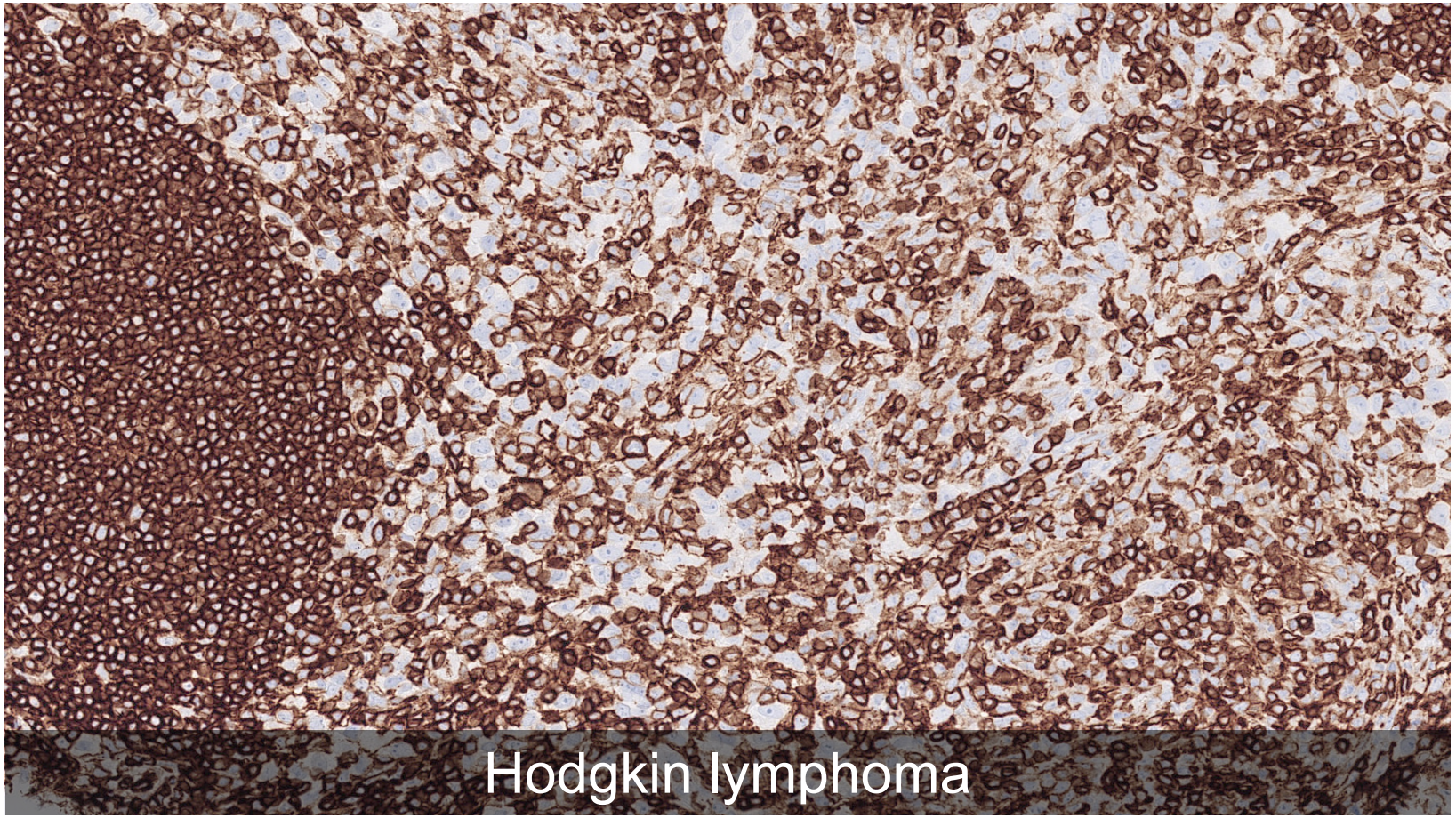


Malignant lymphoma

CD45 – positive carcinoma?



CD45 – negative in some lymphomas



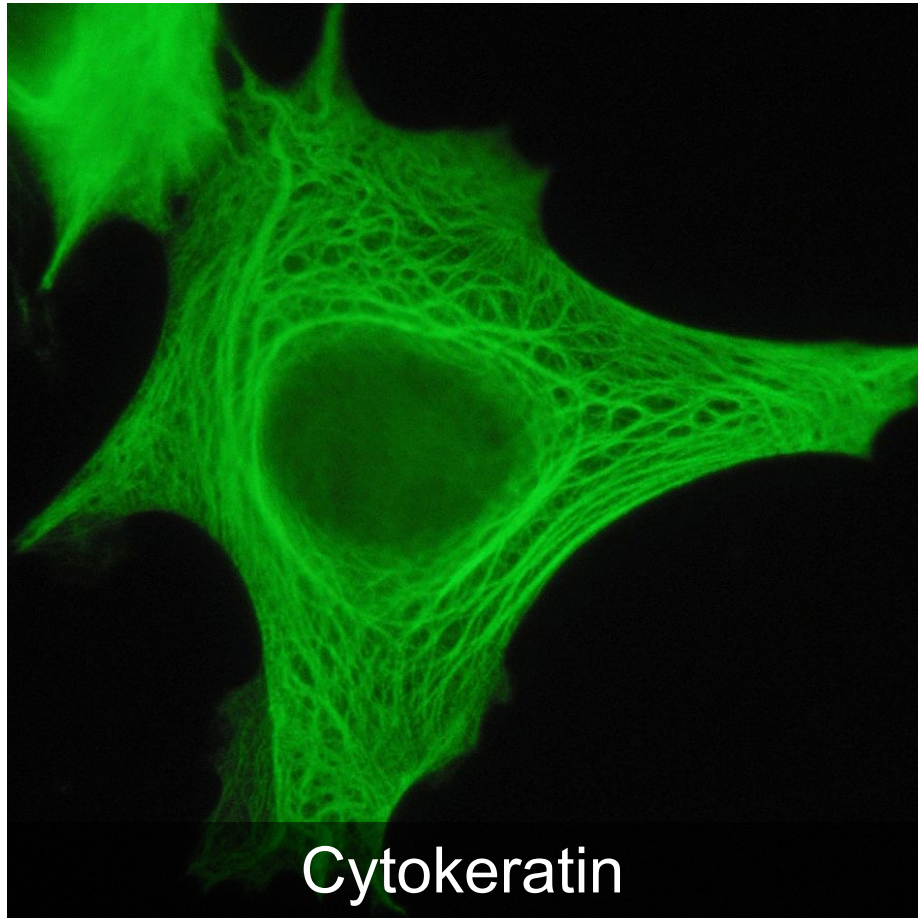
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Pan cytokeratin

- 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) Acidic (A, class I)	1 10	4	13	**5**	14	17	**19**	**7**	**20**	**8** 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	-	-	-	-	-	-	+	(++)	-	++

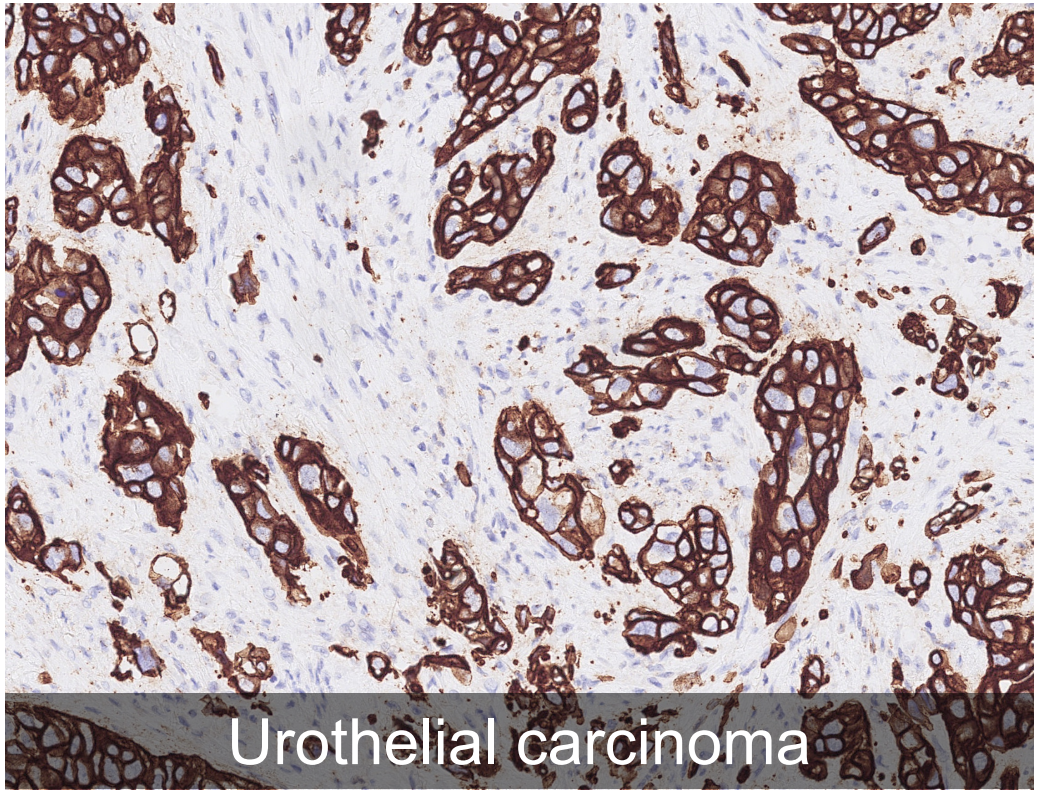
Courtesy of Professor M. Vyberg

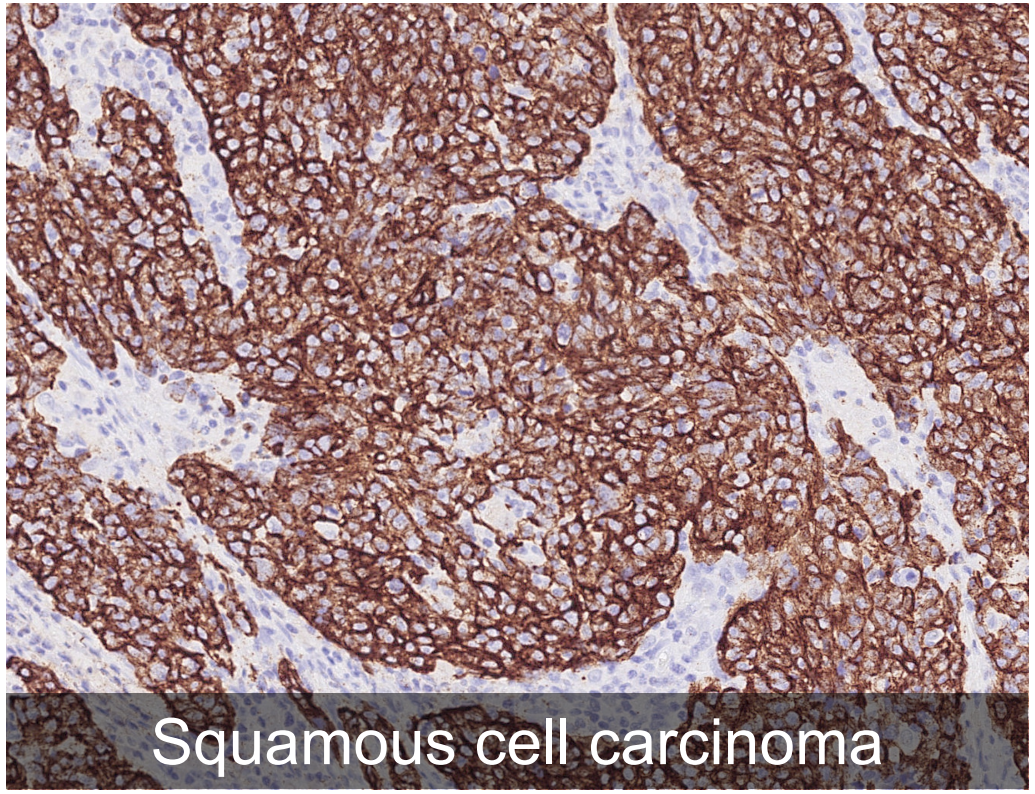
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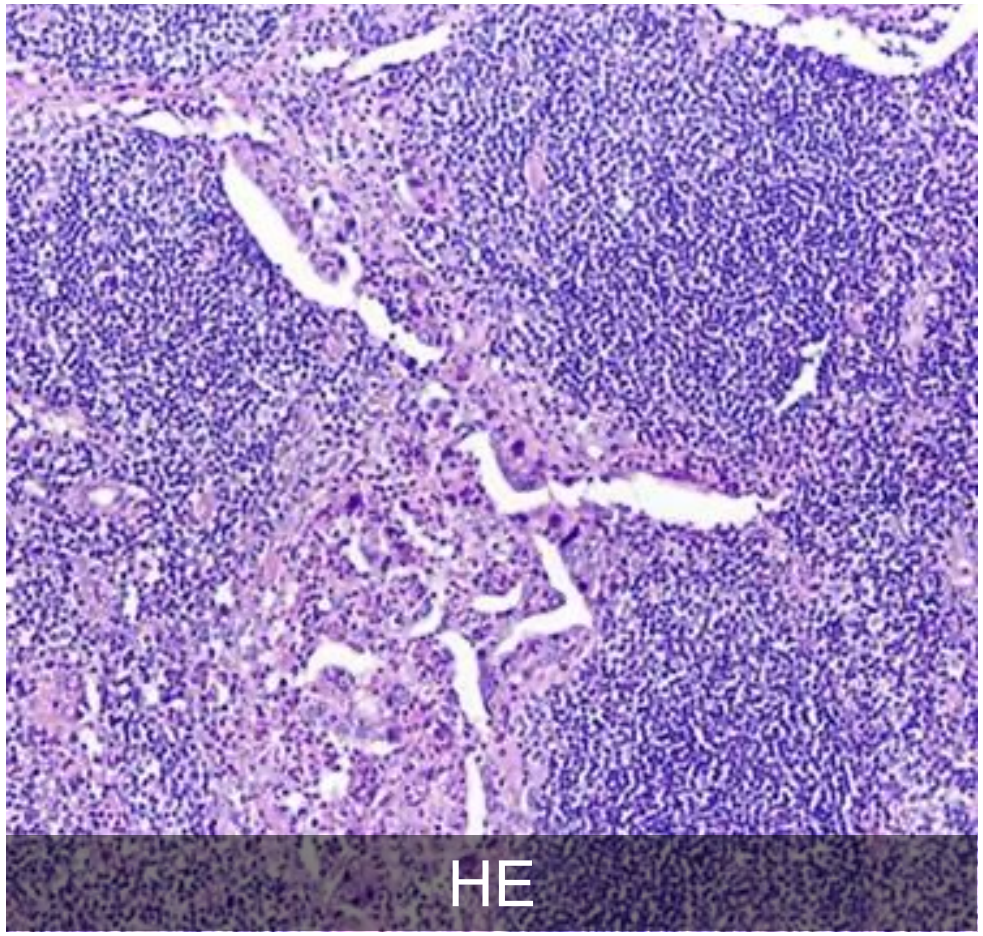
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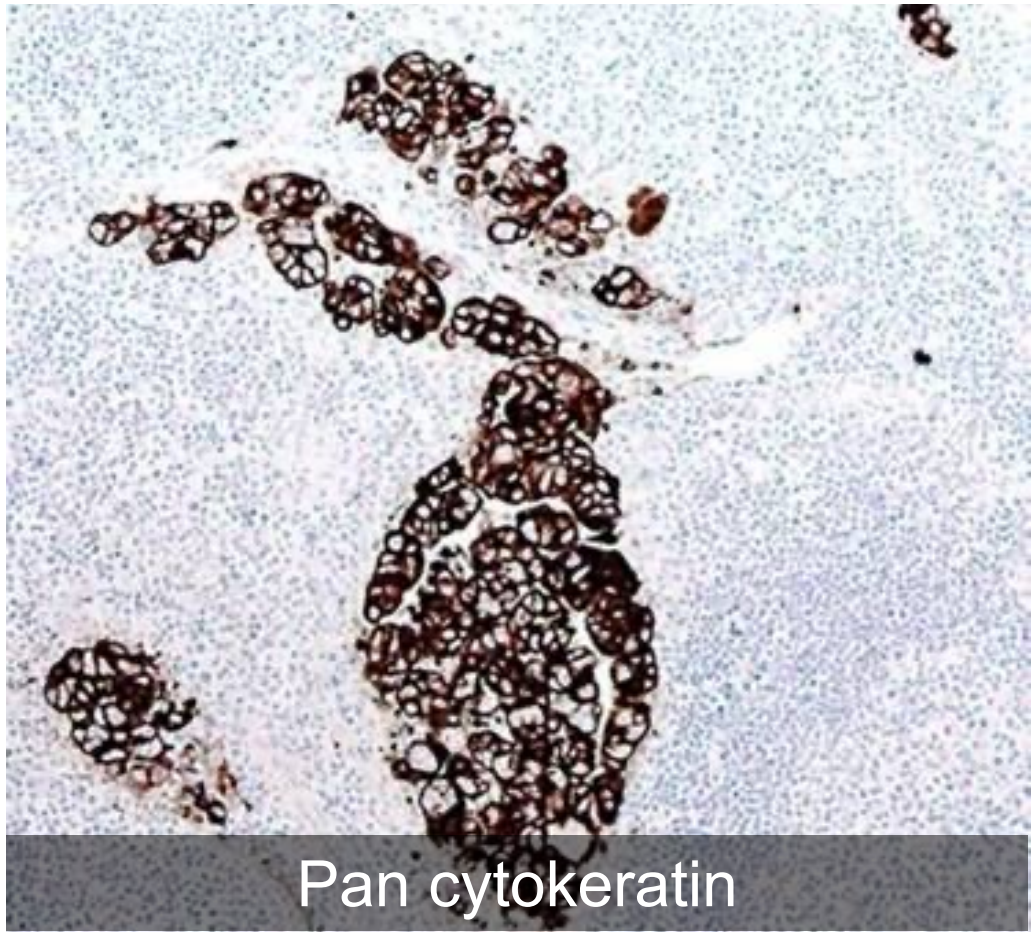
Pan cytokeratin



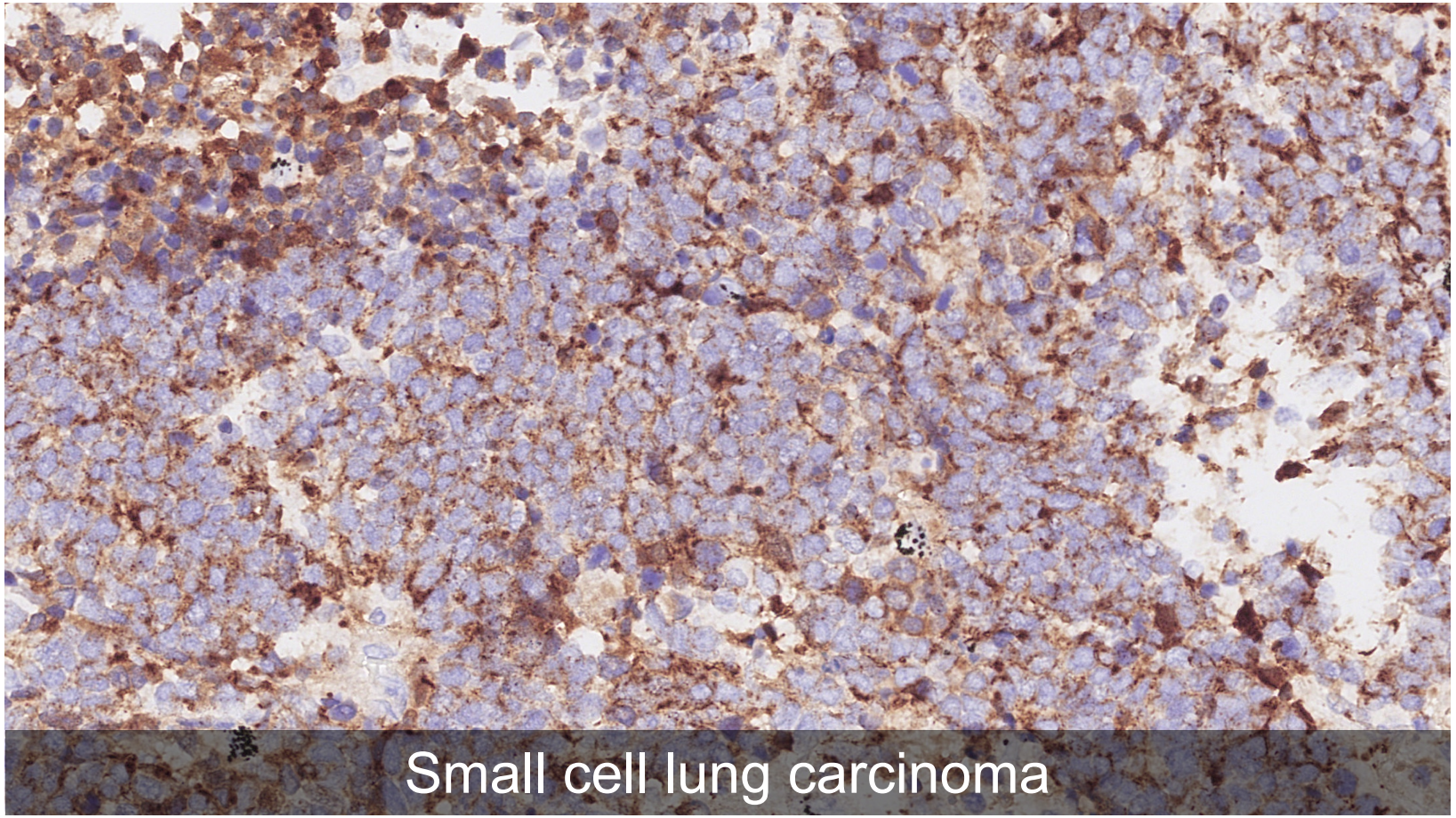


Pan cytokeratin - micrometasis





Pancytokeratin

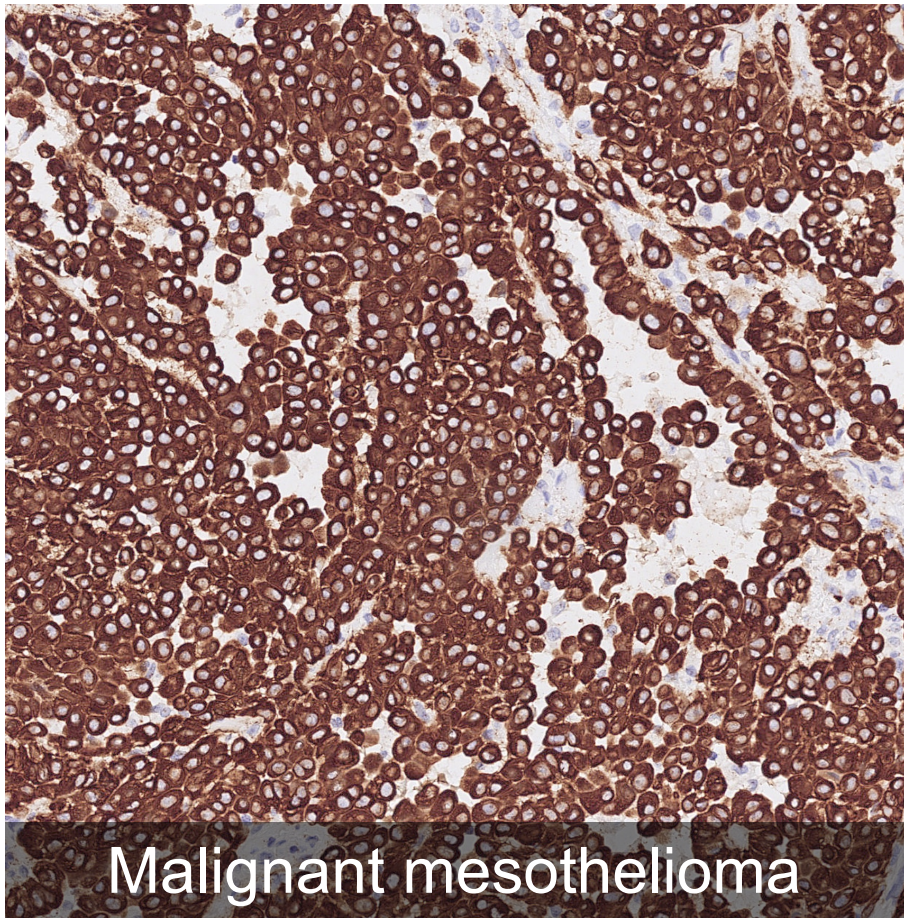


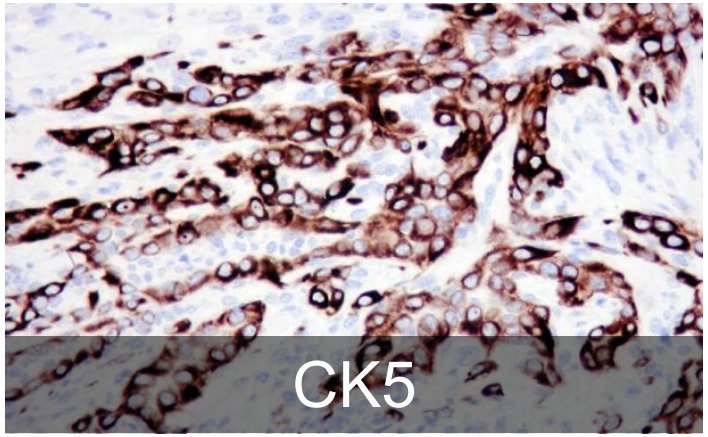
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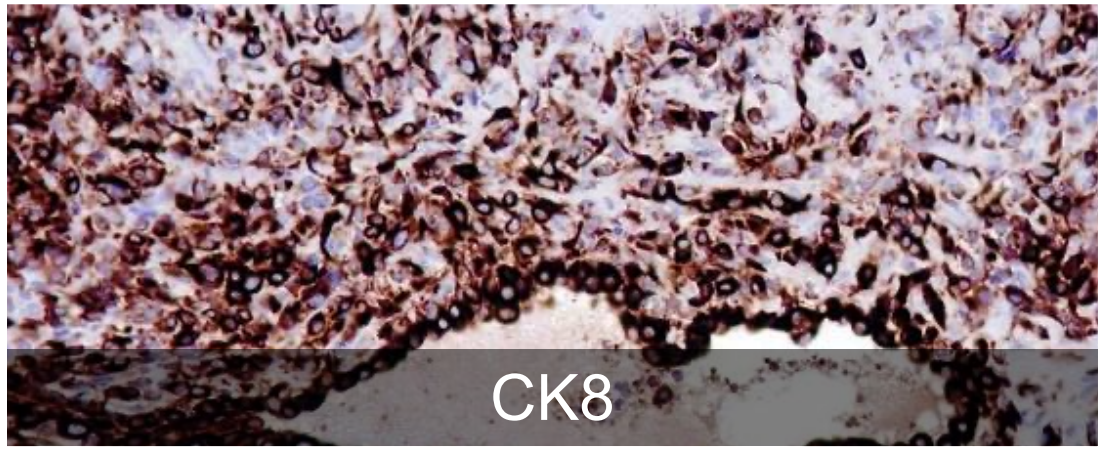
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Pan cytokeratin - mesothelioma





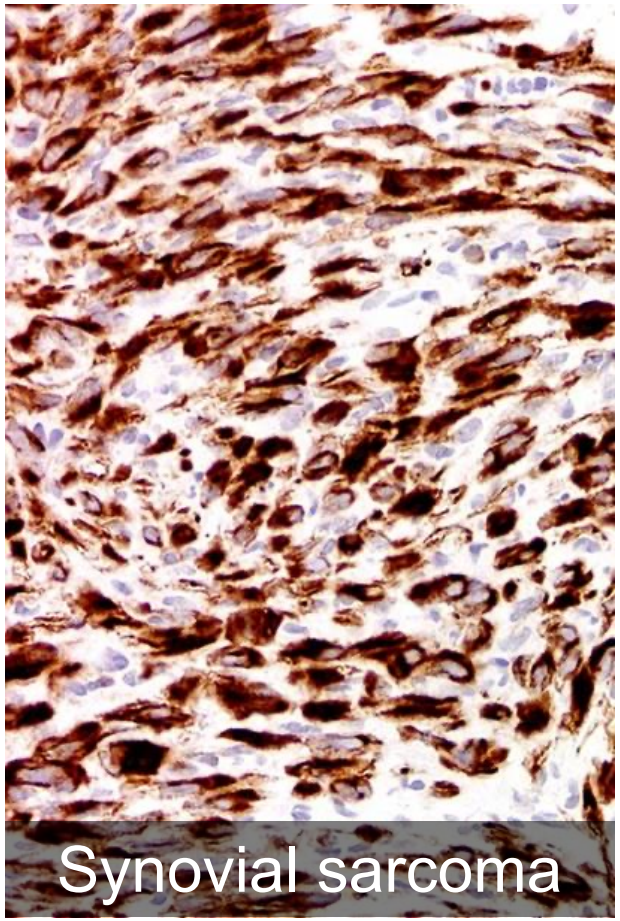


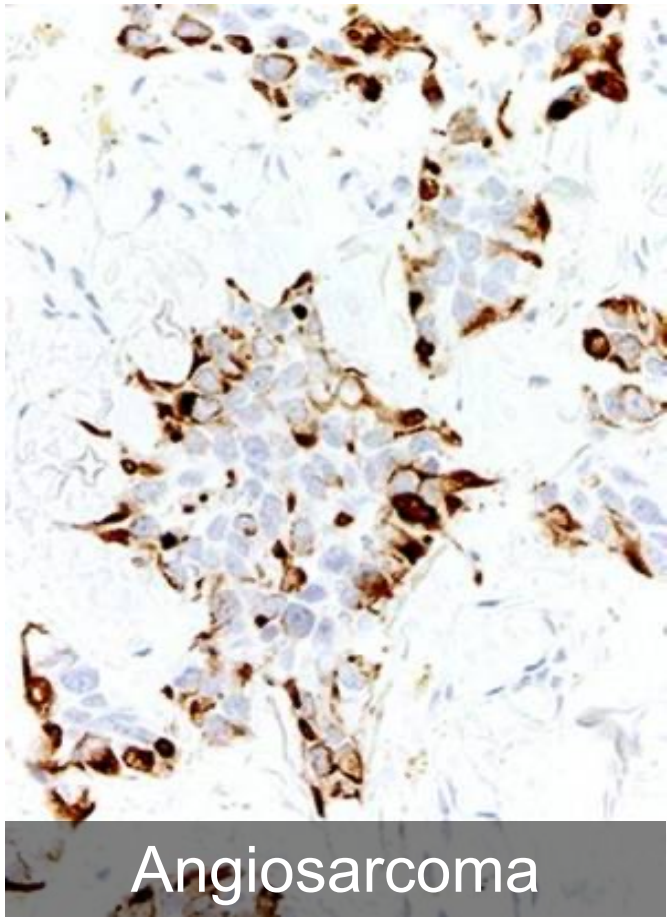
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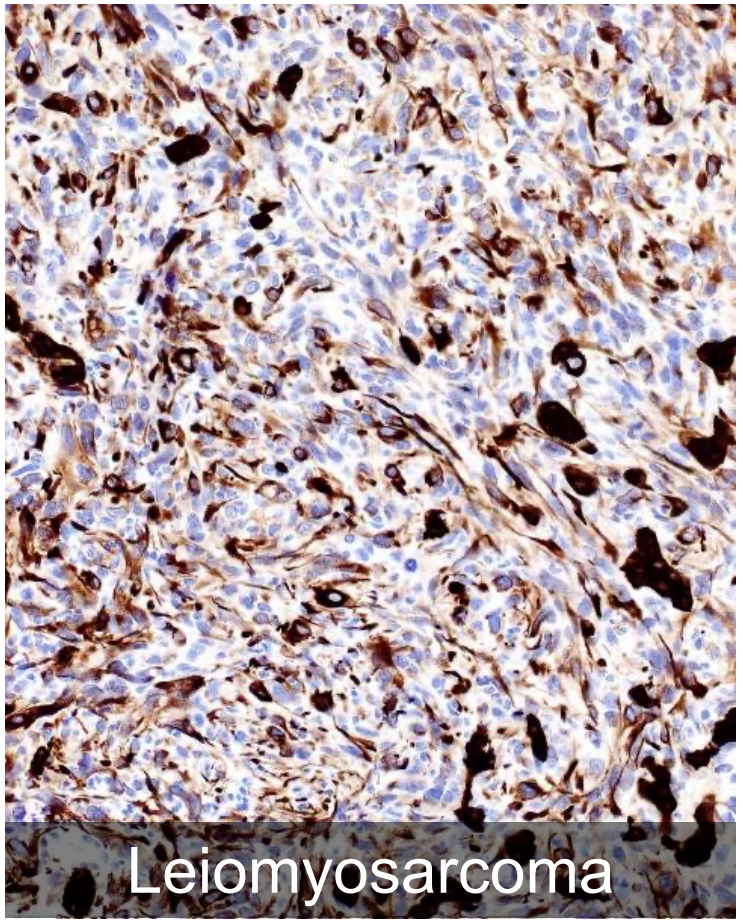
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Pan cytokeratin – mesenchymal neoplasias


Synovial sarcoma


Angiosarcoma


Leiomyosarcoma

NordiQC

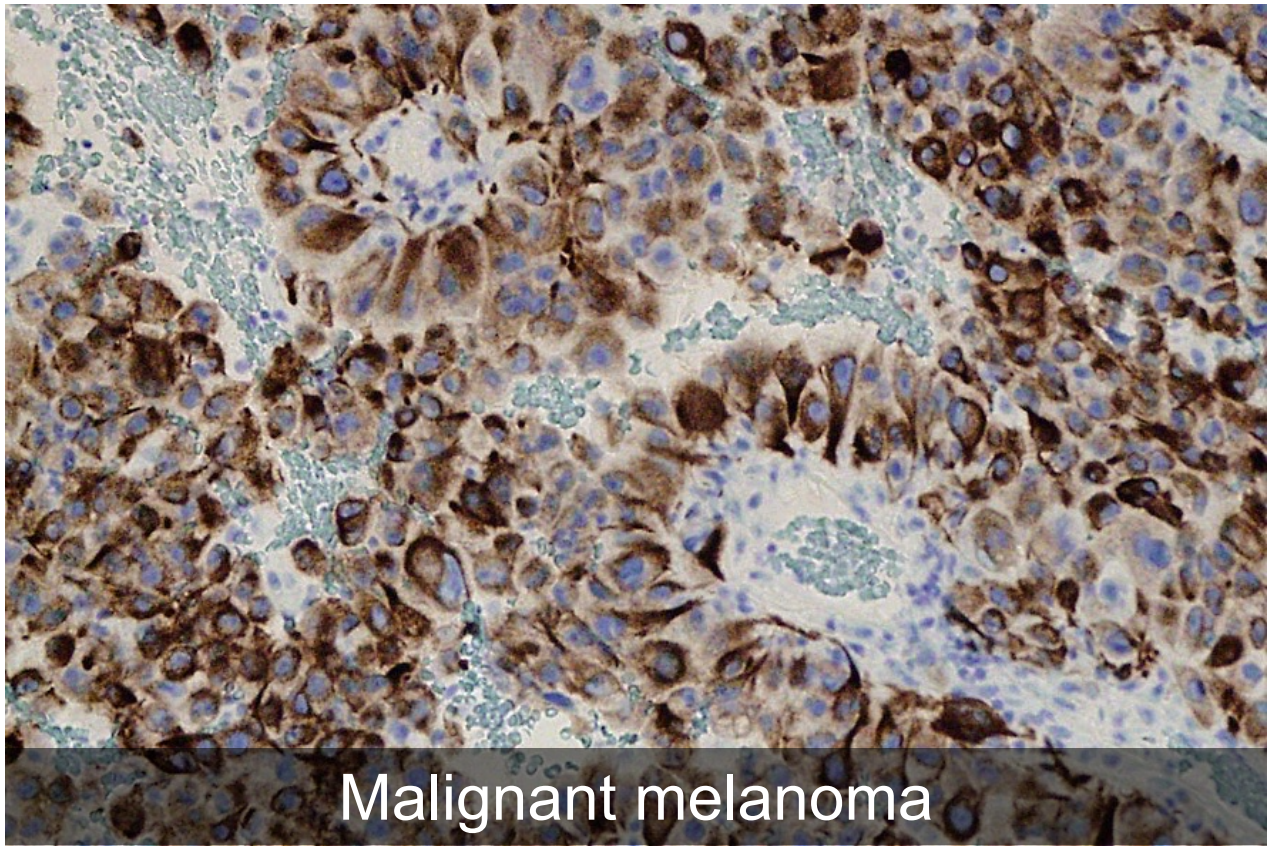
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Pan cytokeratin - melanoma

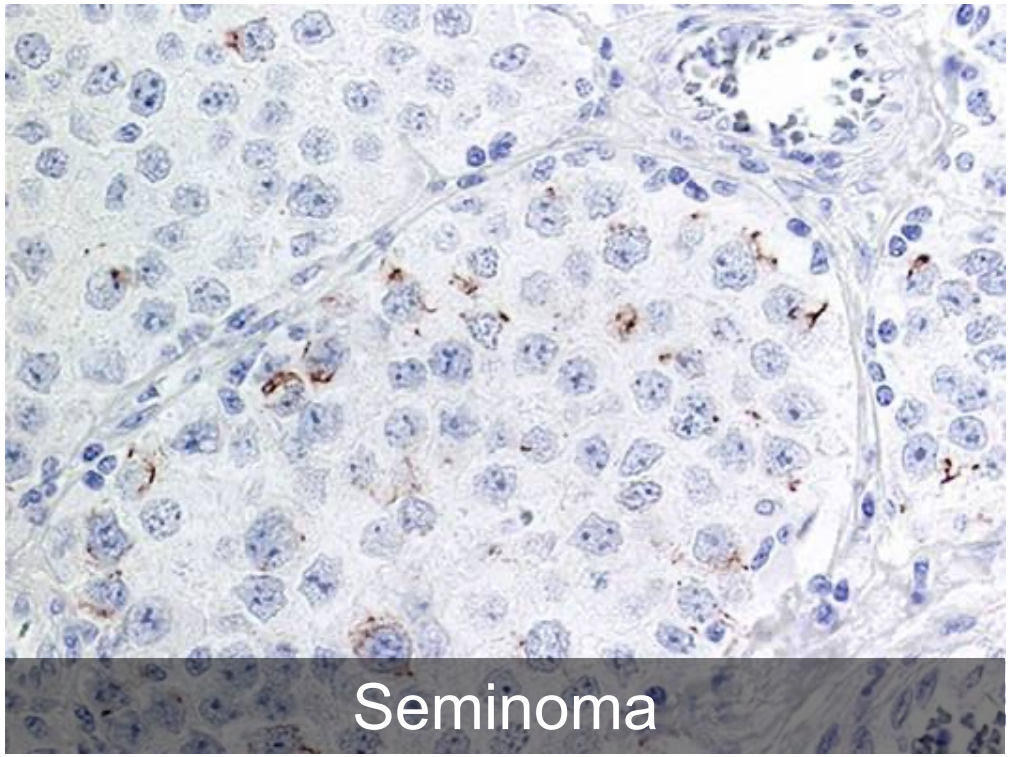


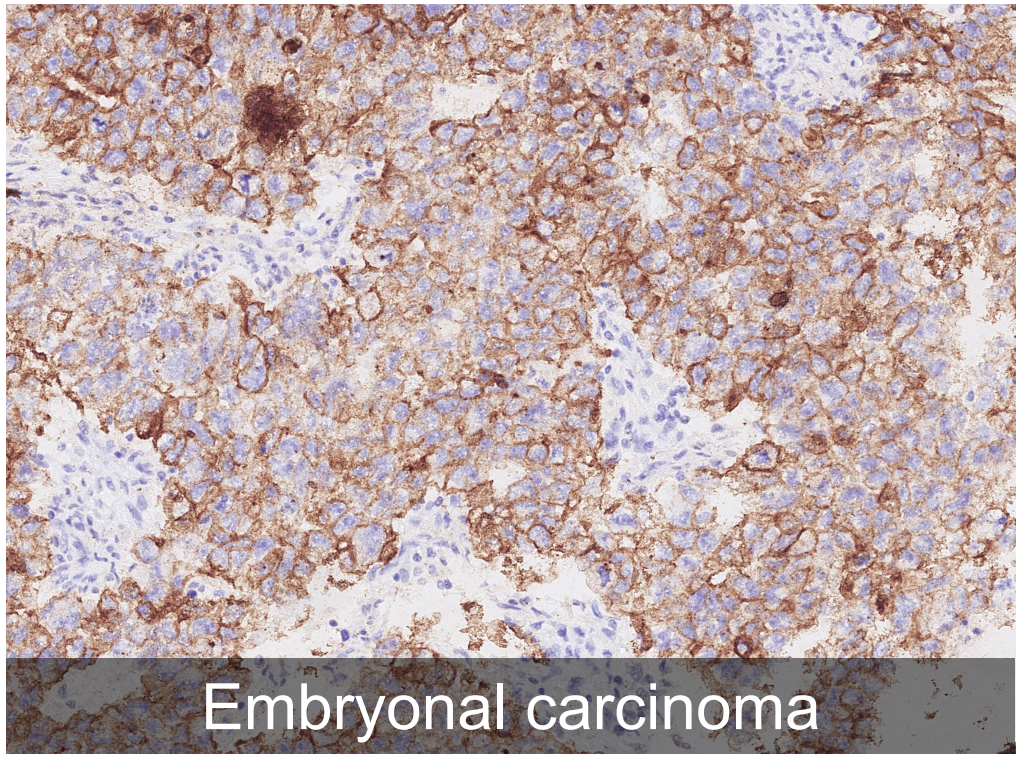
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Pan cytokeratin – germ cell neoplasia


Seminoma


Embryonal carcinoma

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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)

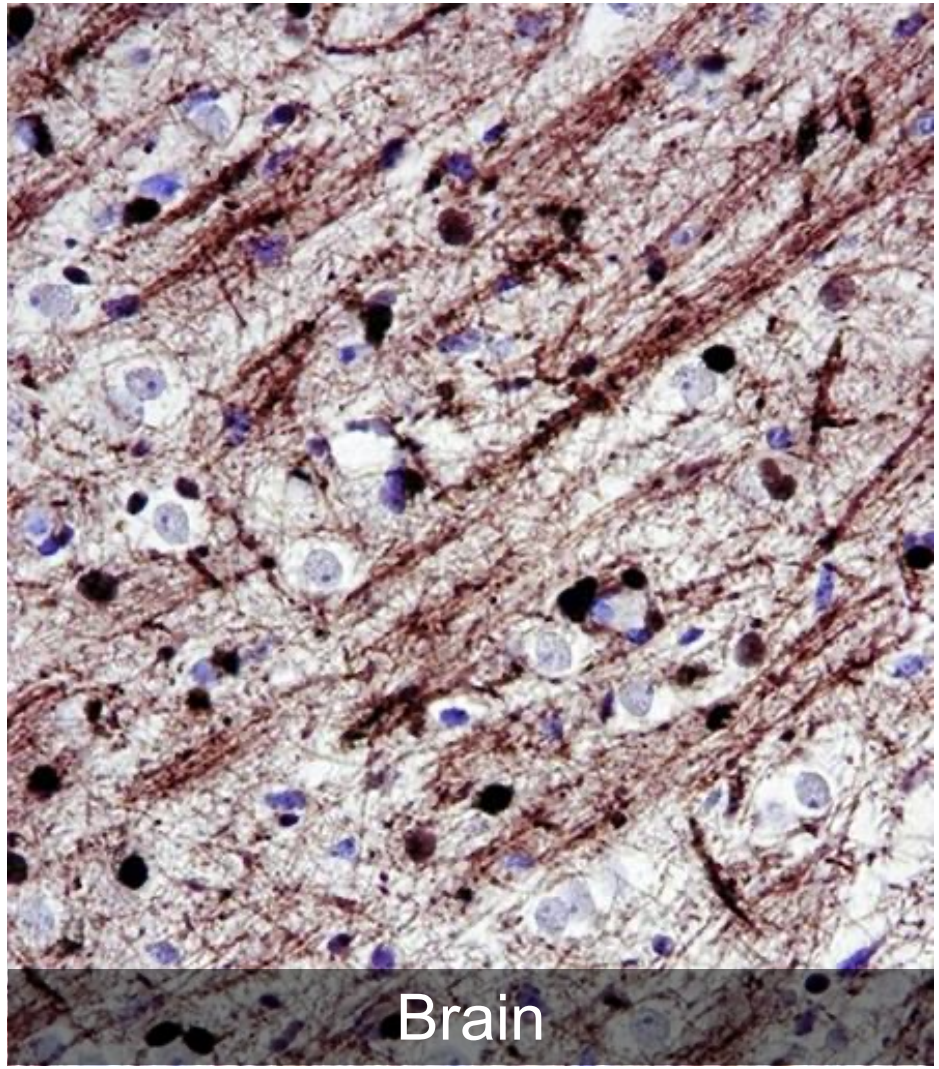
- S100B expressed in
  - Glial cells in brain
  - Melanocytes
  - Fat cells
  - Langerhans cell
  - Myoepithelial cells

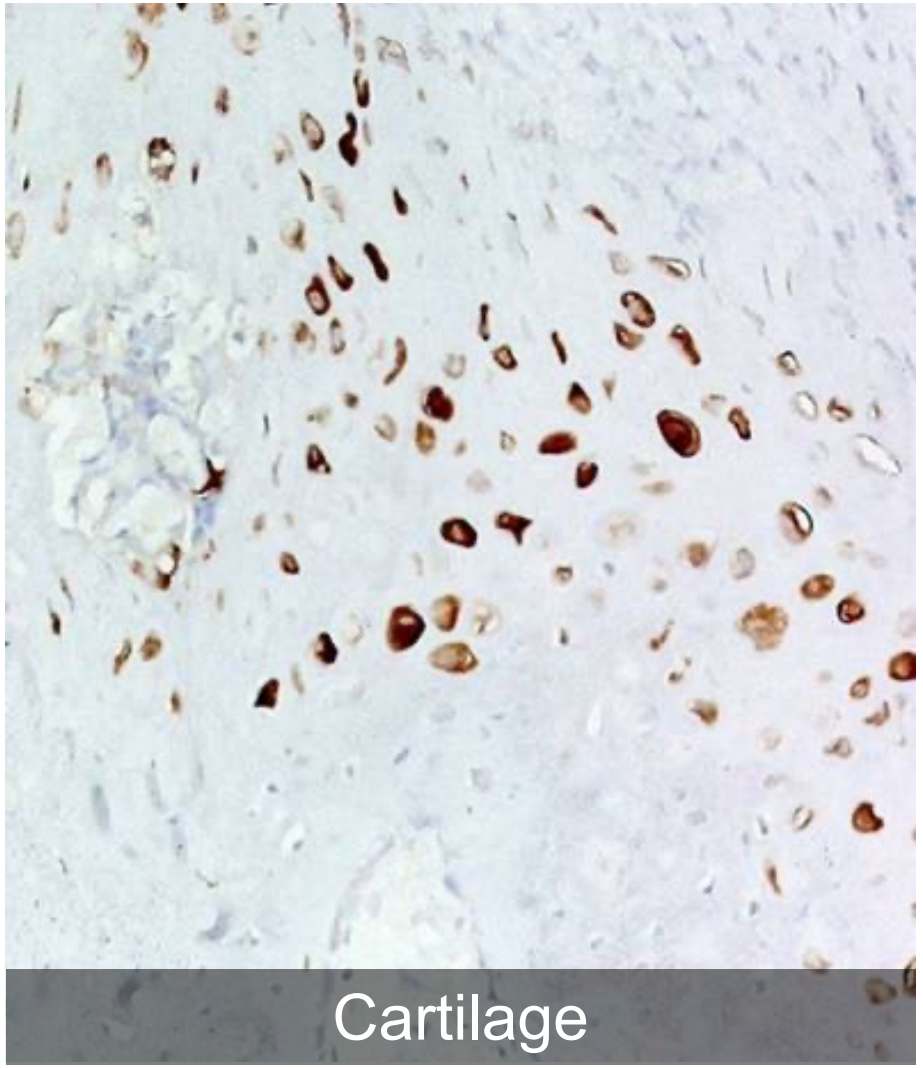
S100

- Expressed in malignant melanoma

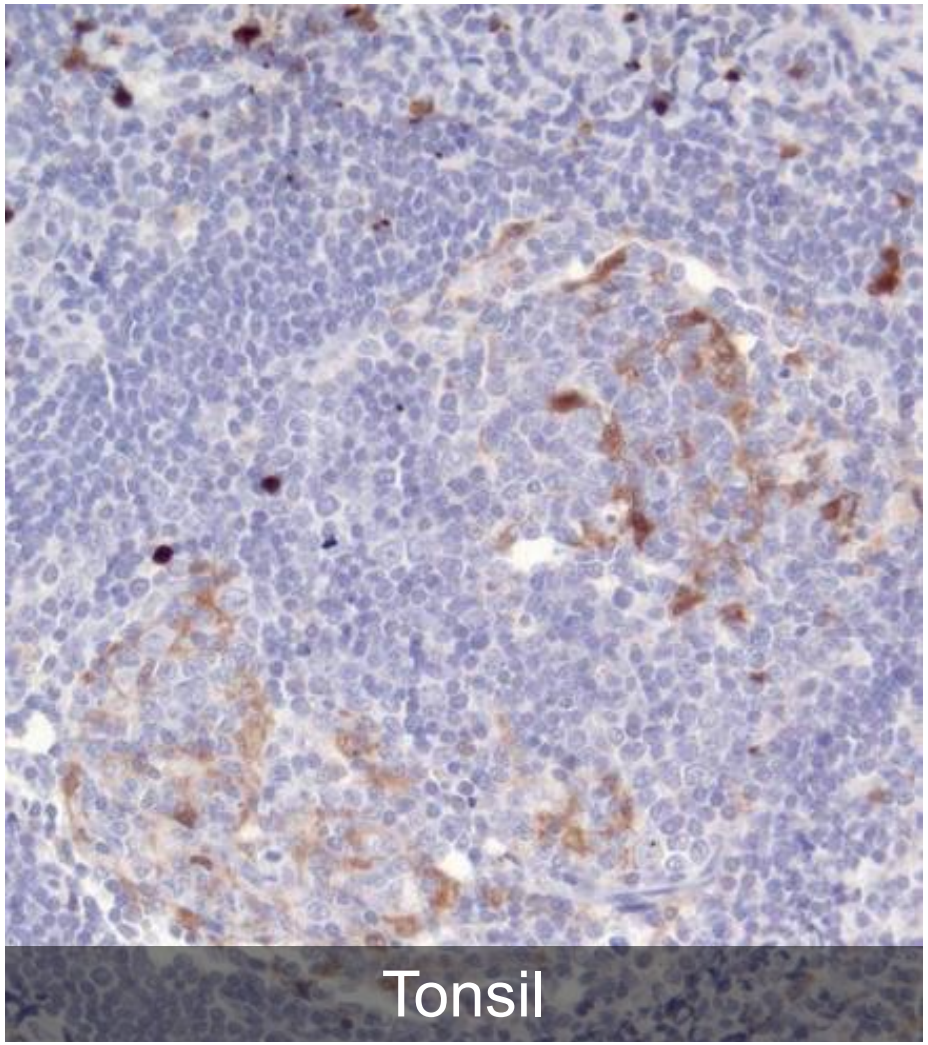
- Also seen in
  - Schwannomas
  - Neurofibromas
  - Chondromas
  - Liposarcomas

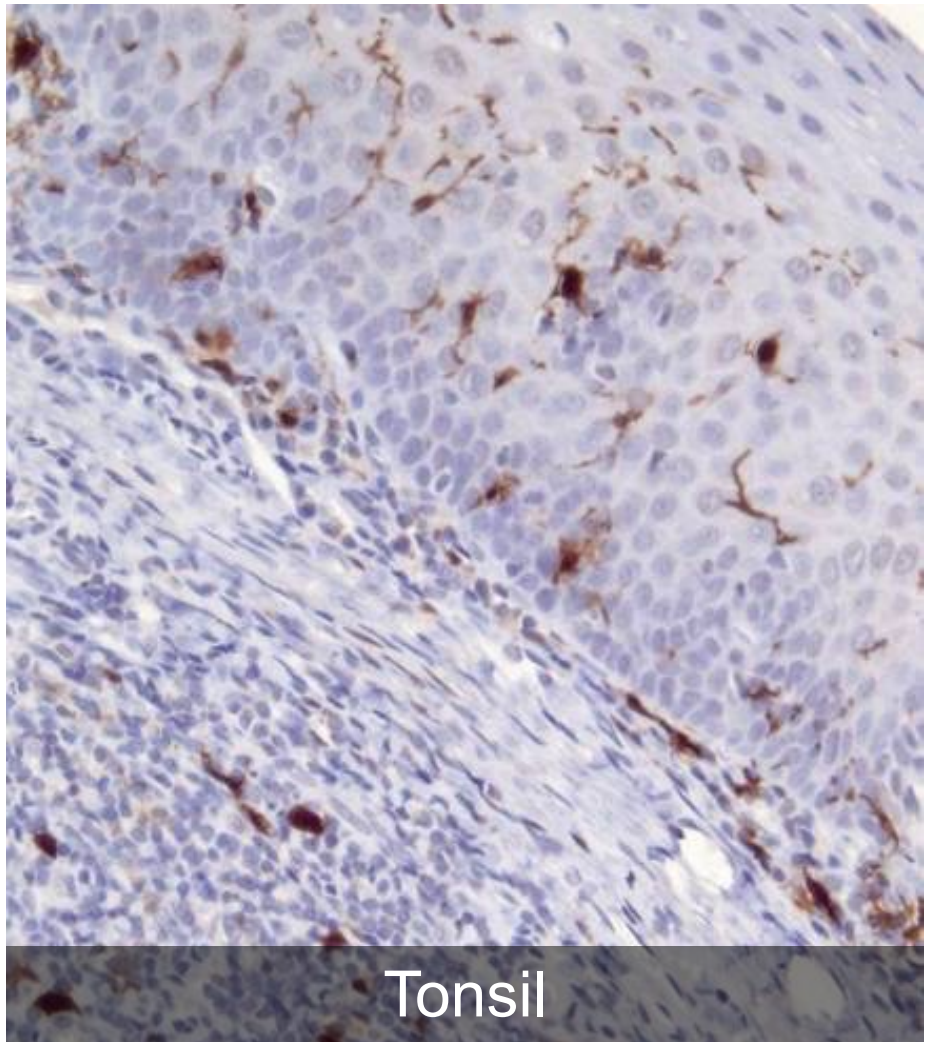
S100



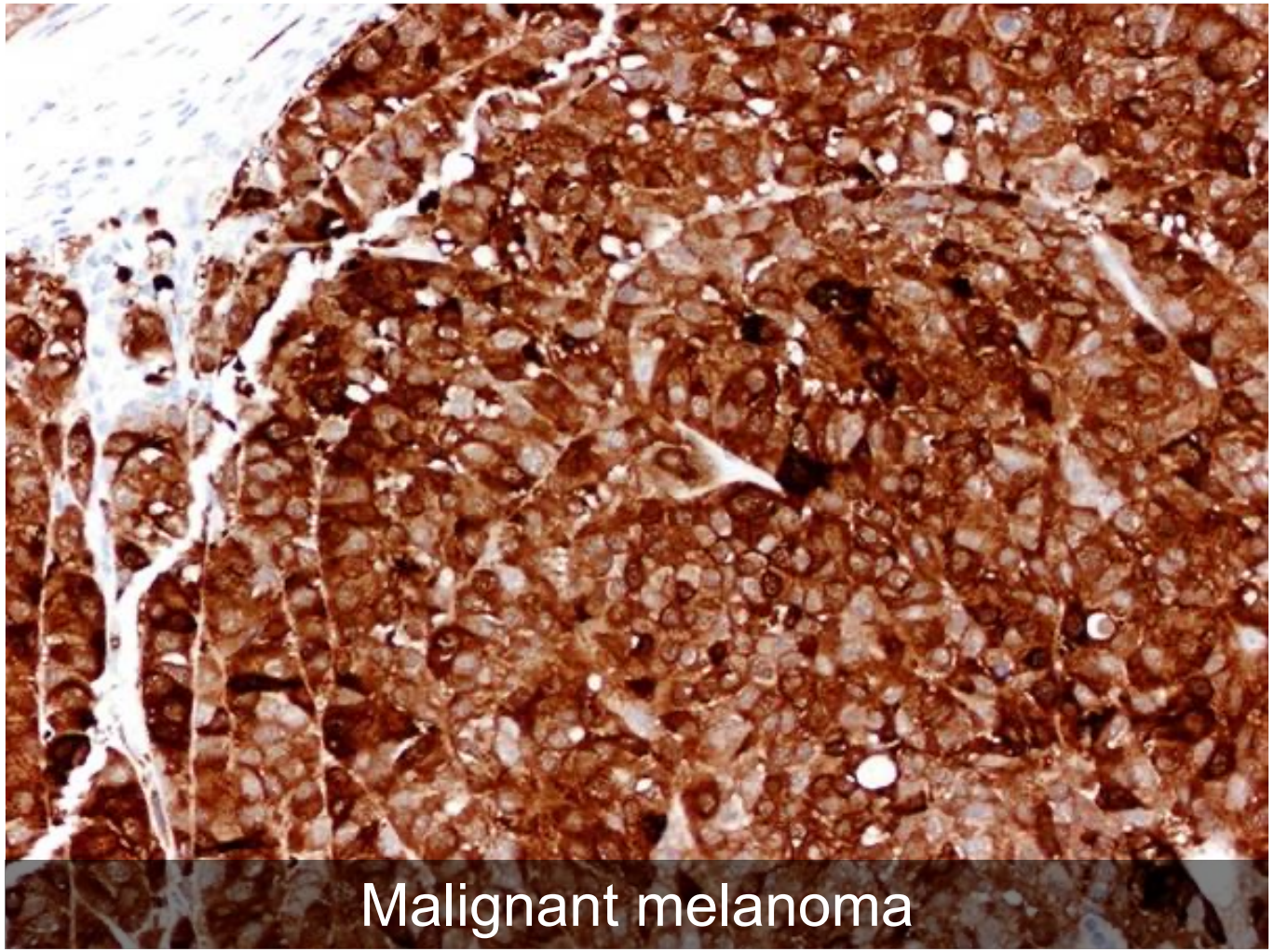


S100





S100



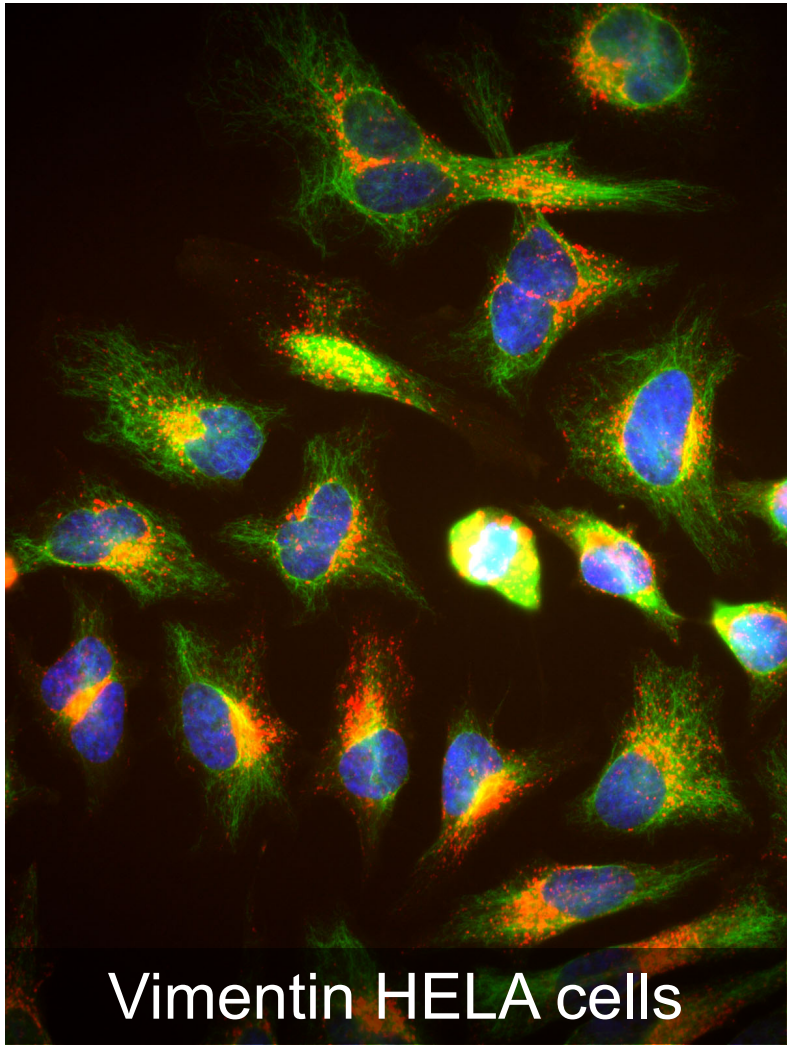
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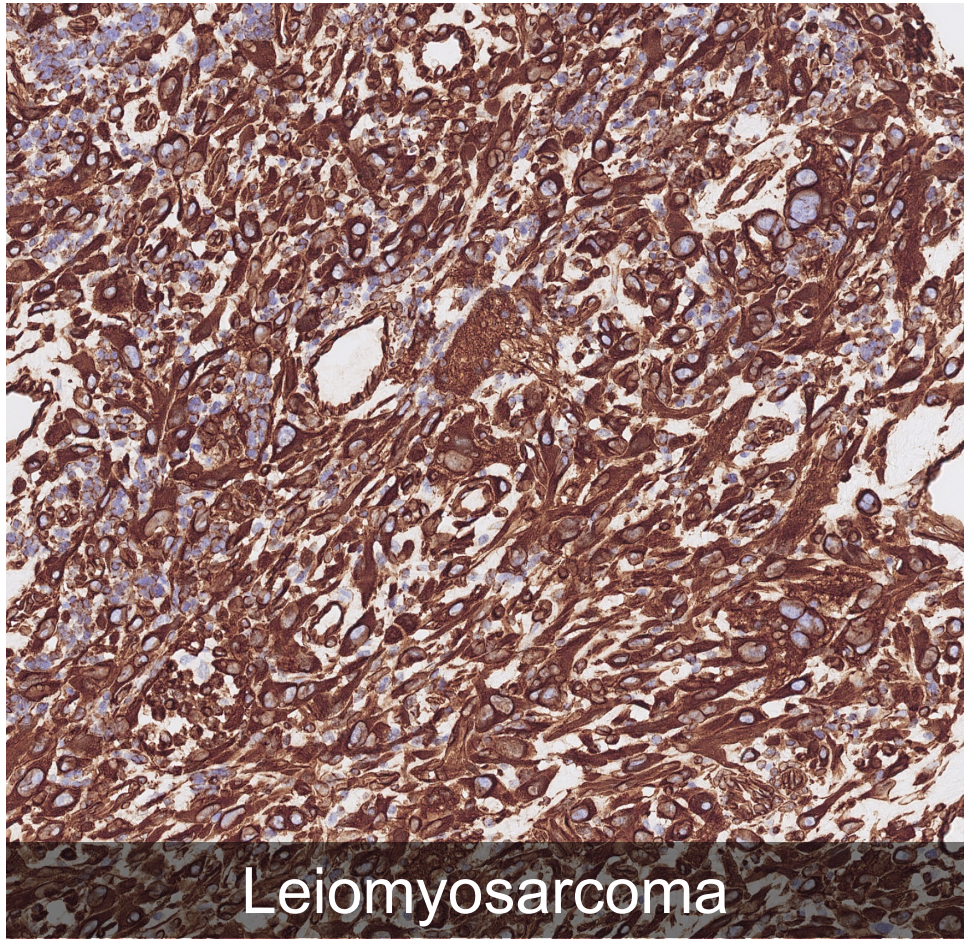
Vimentin

- 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

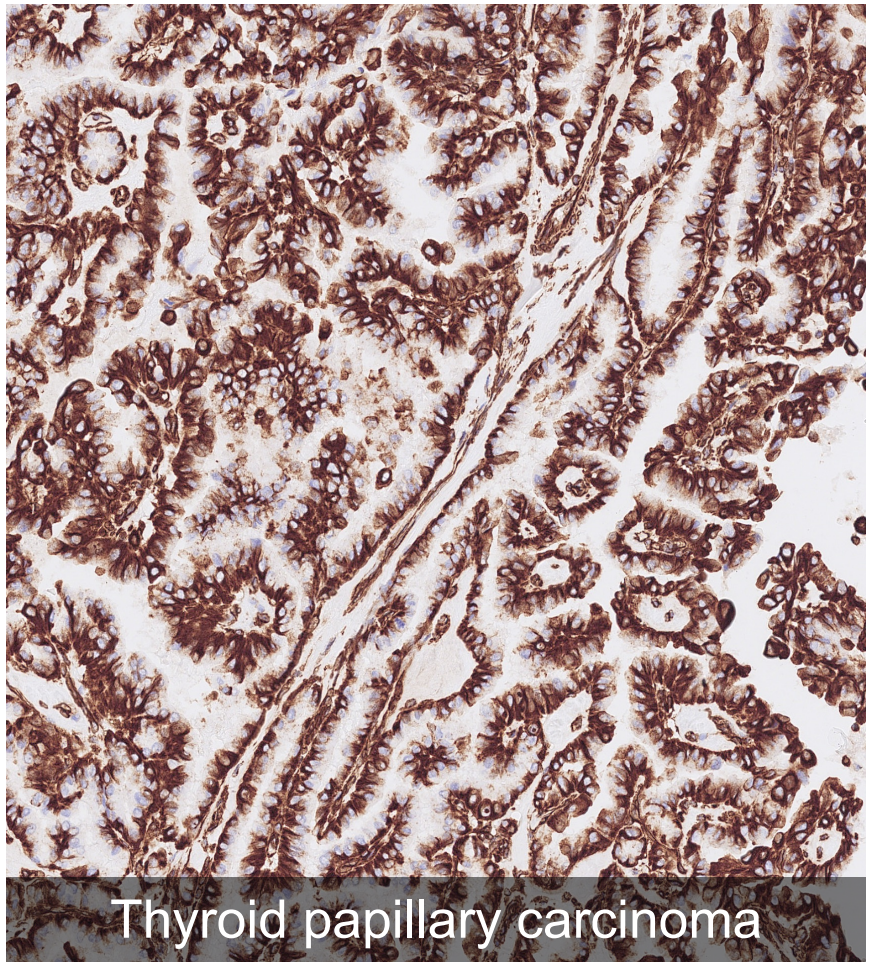


Vimentin – stromal tumours

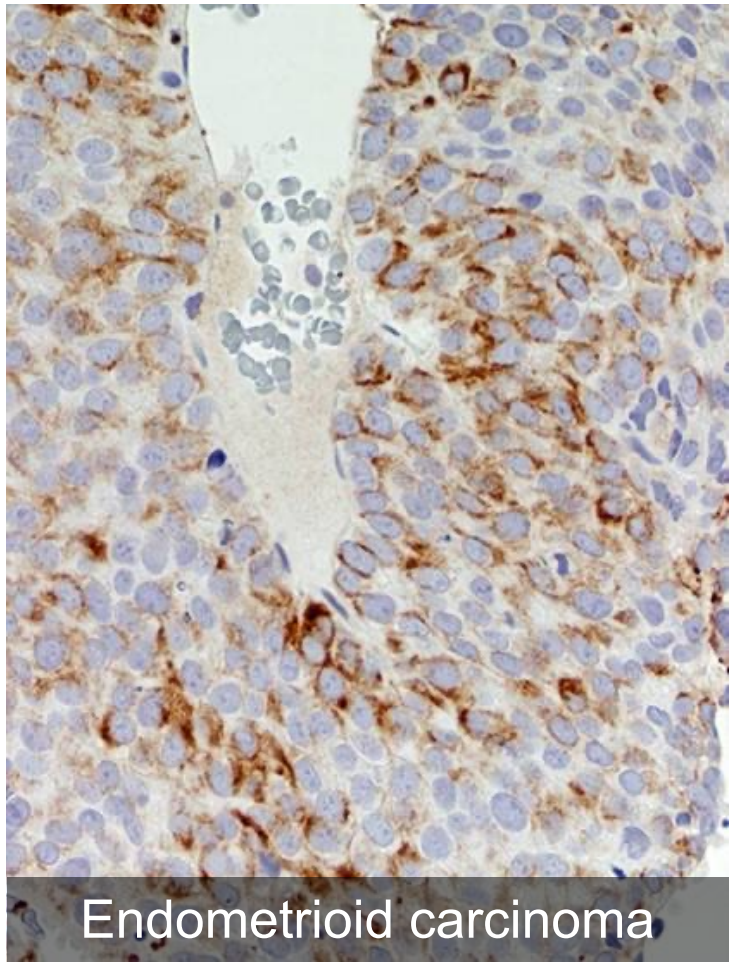




Vimentin - carcinomas

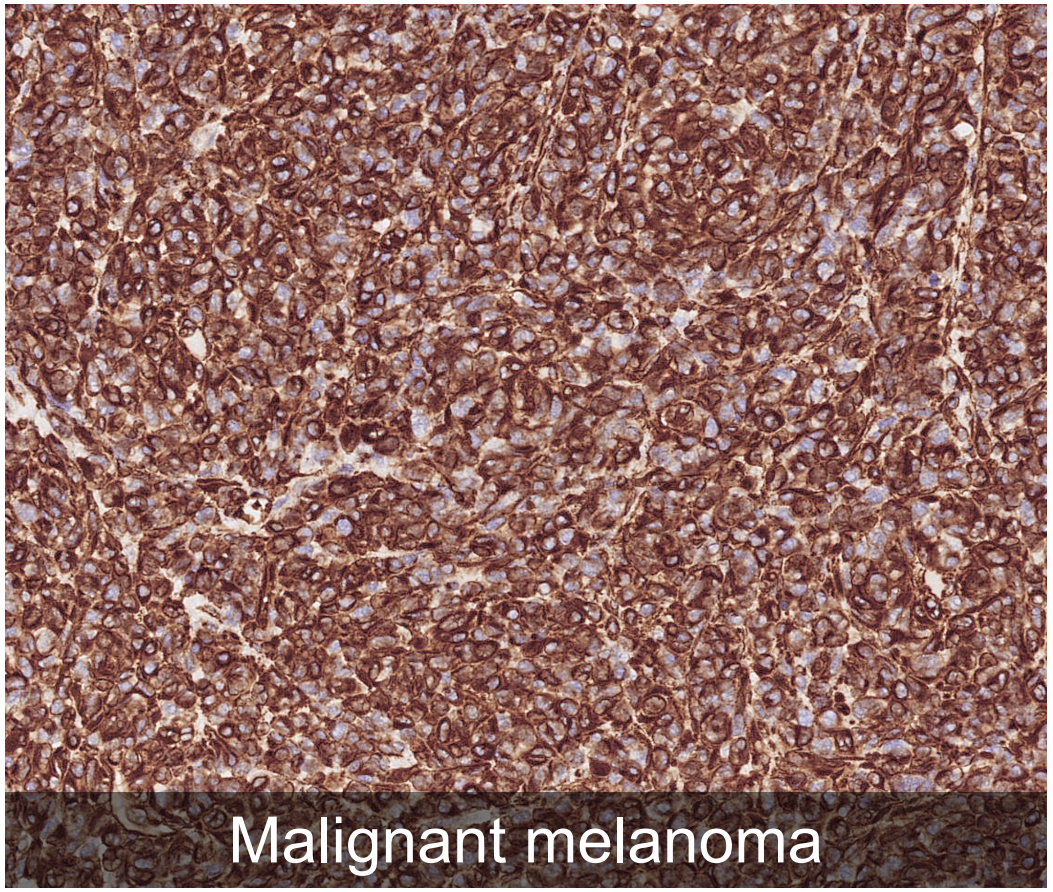


Thyroid papillary carcinoma

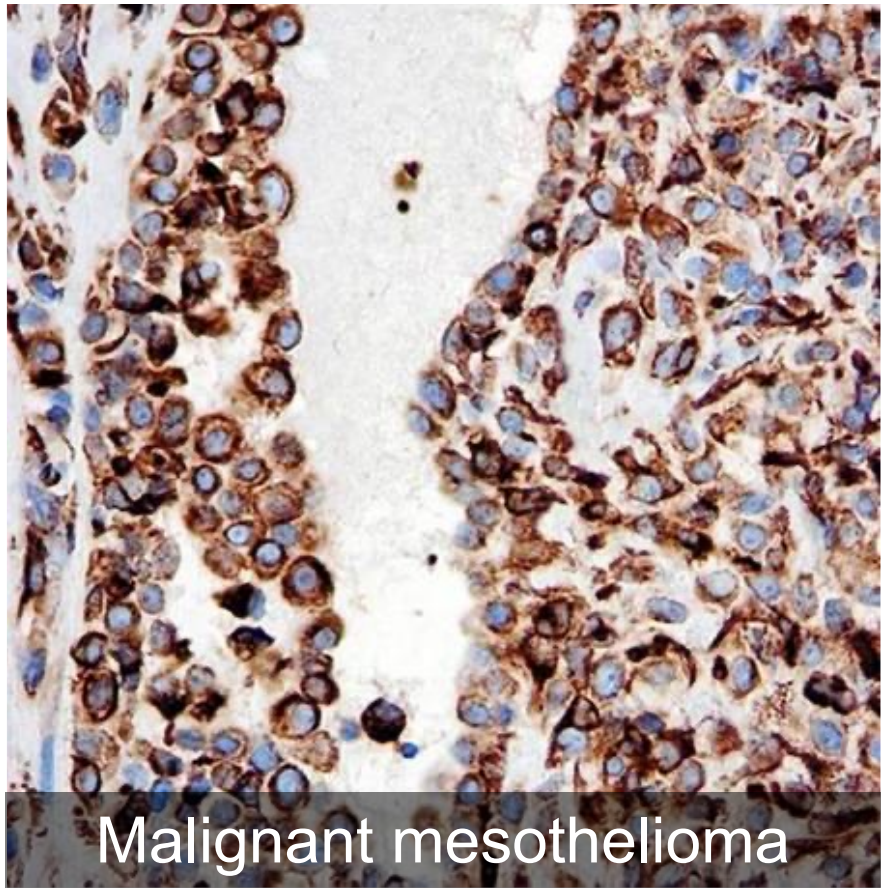


Endometrioid carcinoma

Vimentin – other neoplasia



Malignant melanoma



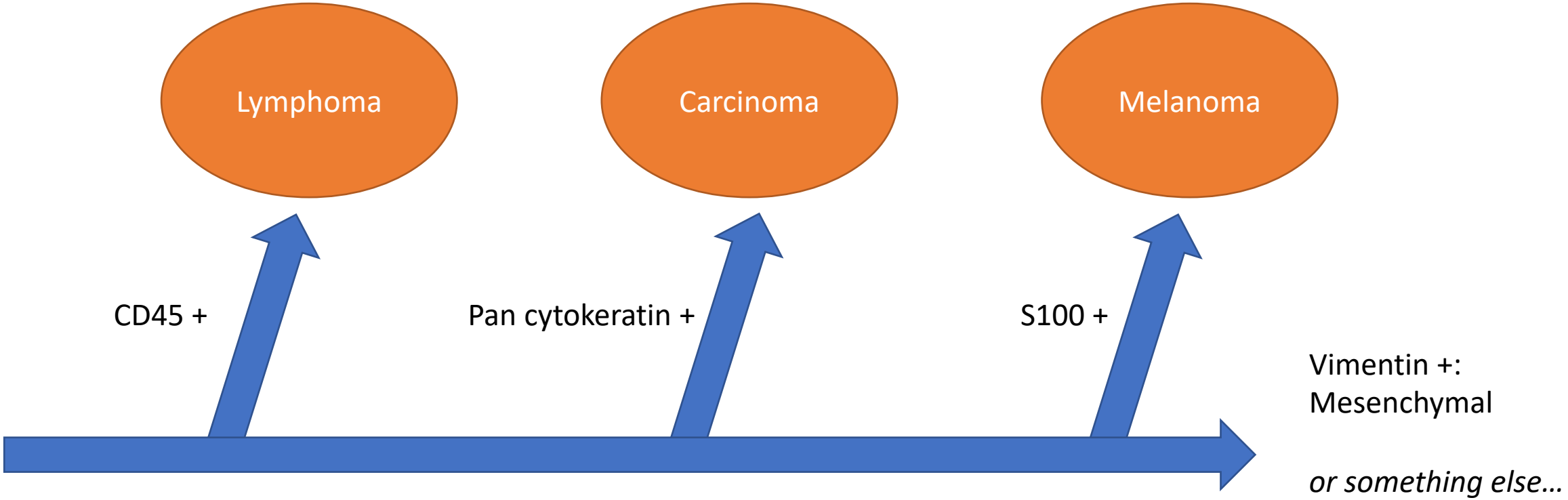
Malignant mesothelioma

Primary panel

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

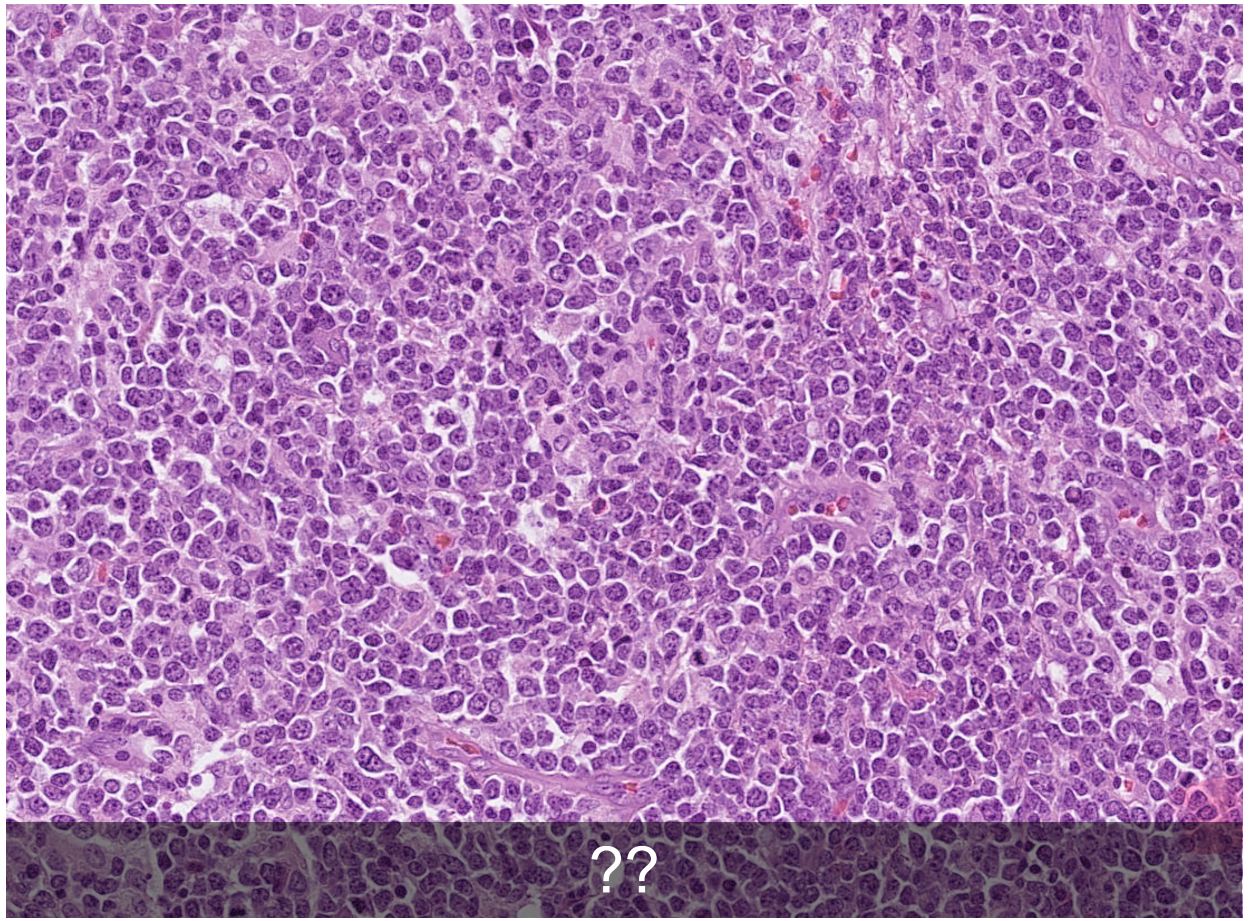
Neoplasms	CD45	Pan cytokeratin	S100	Vimentin
Haematopoietic / lymphoid	(+)	(-)	(-)	(+)
Epithelial	-	(+)	-/+	-/+
Mesothelial	-	+	-	+
Mesenchymal	-	(-)	(-)	+
Melanoma	-	(-)	+	+
Germ cell	-	-/+	-/+	+

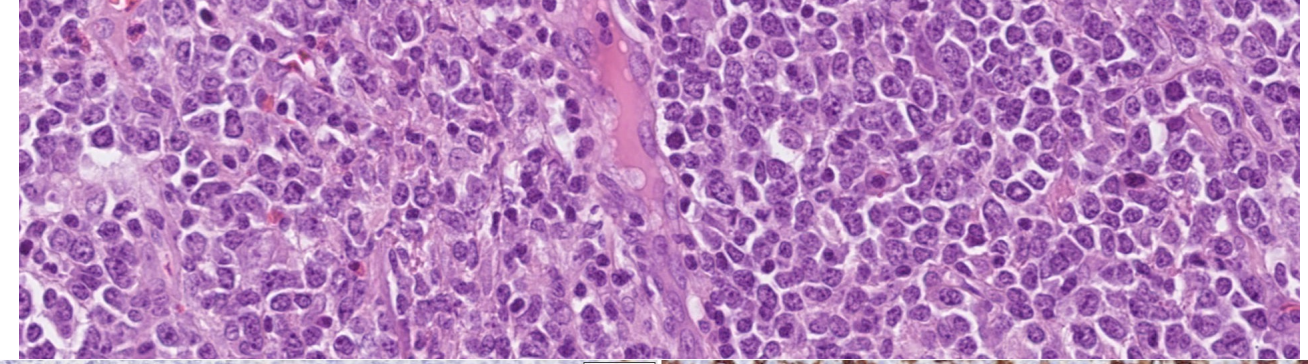
Primary panel in action

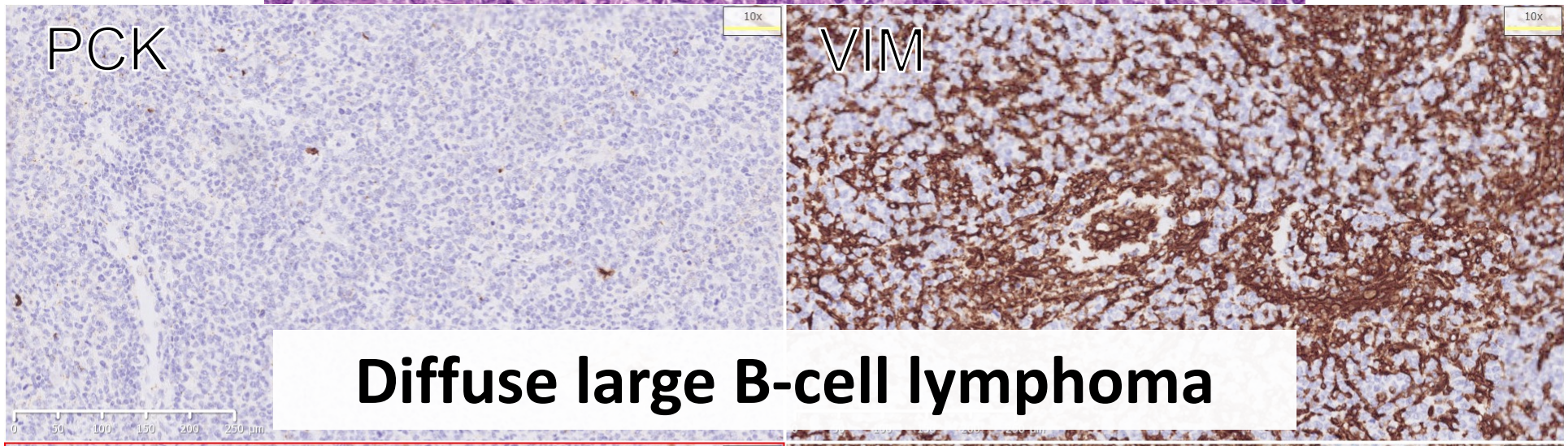


Undifferentiated cases

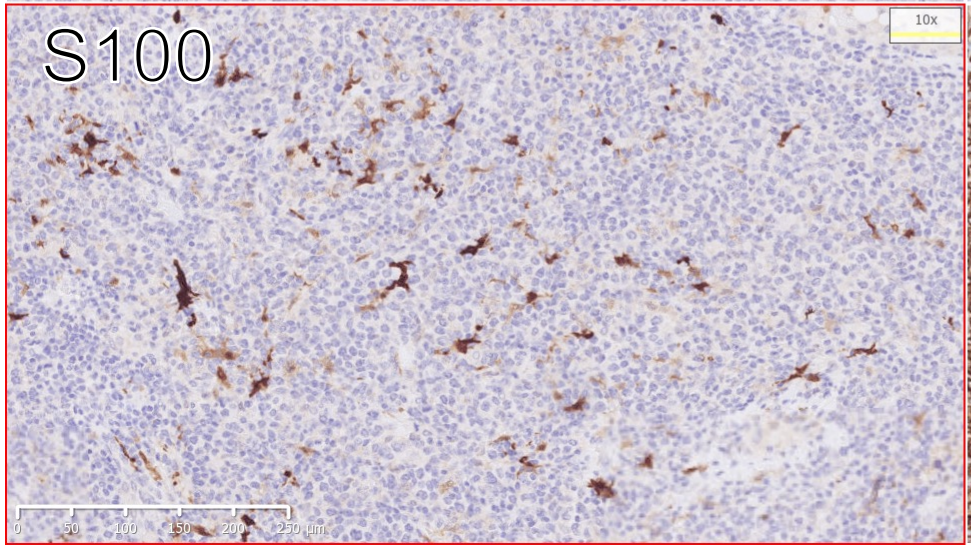
- 56 year old female
- History of smoking
- Heavy drinker
- Previous cancer
  - Cervix squamous
- Enlarged lymph node on neck

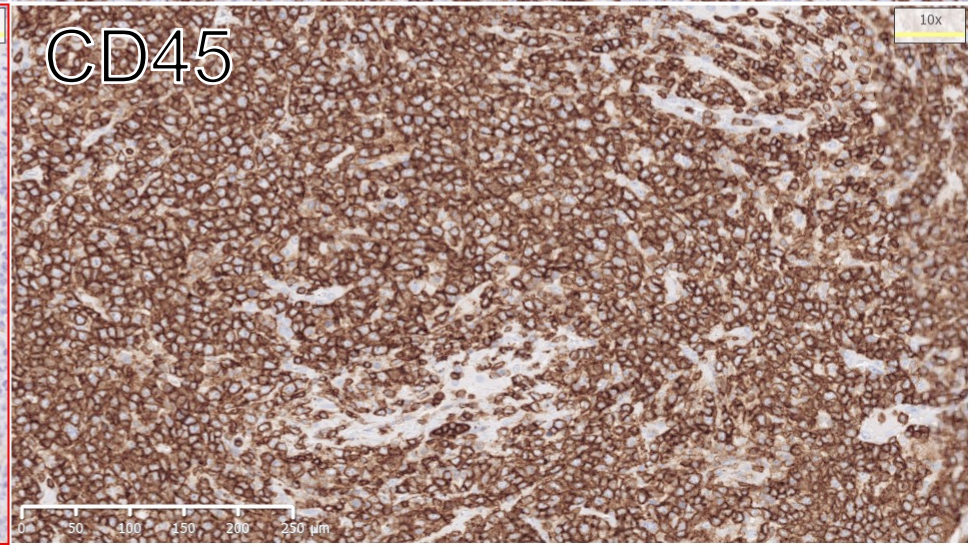






Diffuse large B-cell lymphoma

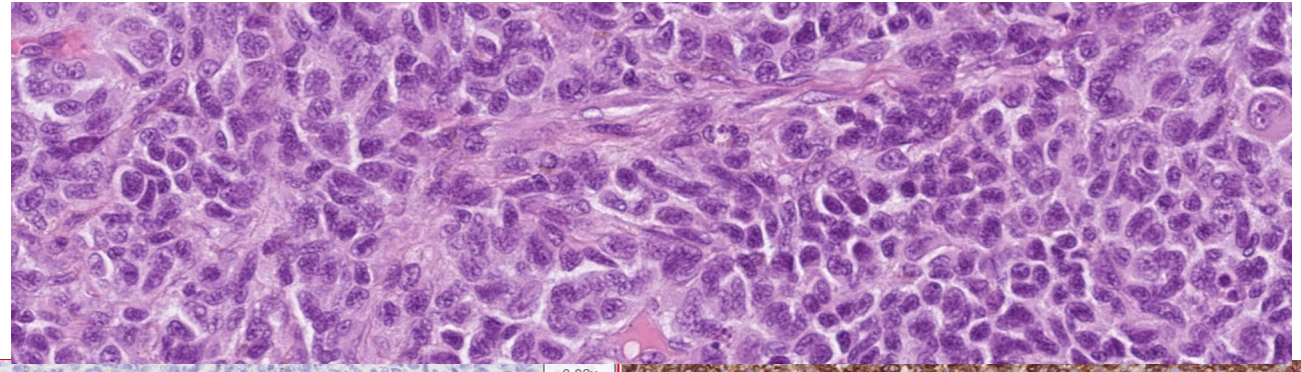


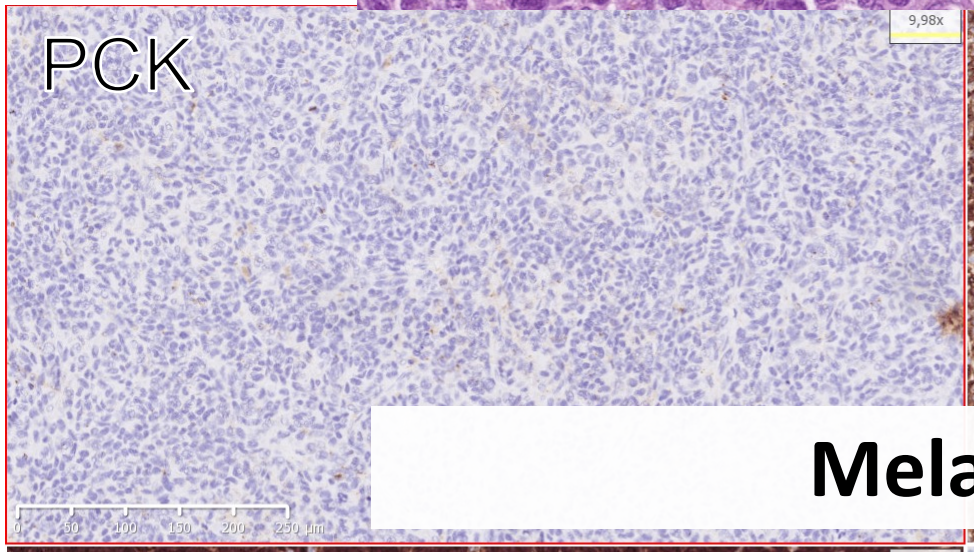


Undifferentiated cases

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

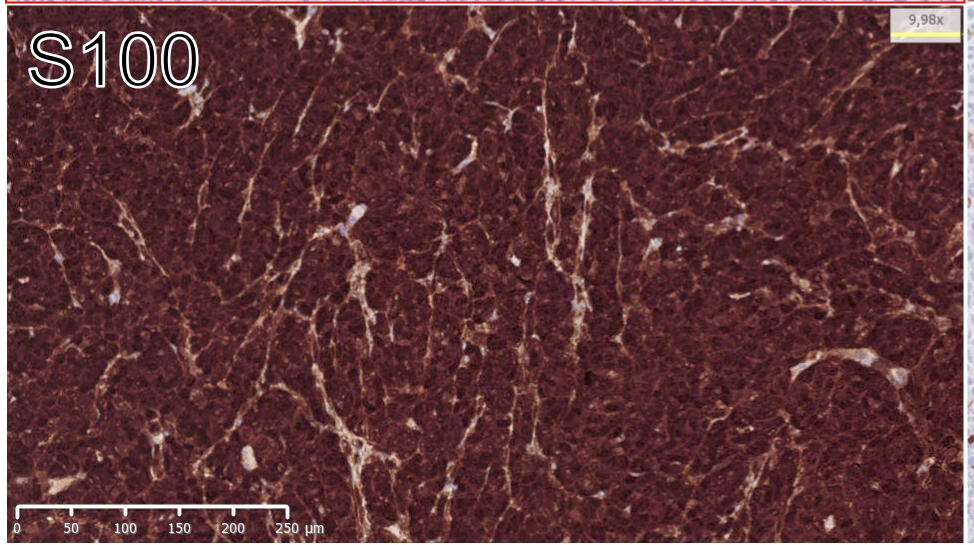


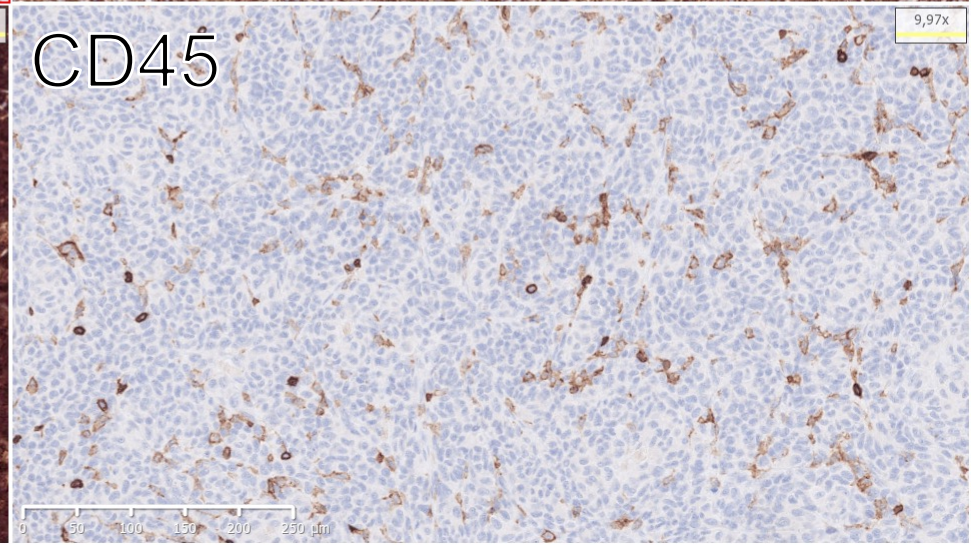



PCK
9,98x
0 50 100 150 200 250 µm


VIM
9,98x

Melanoma


S100
9,98x
0 50 100 150 200 250 µm


CD45
9,97x
0 50 100 150 200 250 µm

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

Neutral/Basic (B, class II) Acidic (A, class I)	1 10	4	13	**5**	14	17	**19**	**7**	**20**	**8** 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	-	-	-	-	-	-	+	(++)	-	++

Courtesy of Professor M. Vyberg

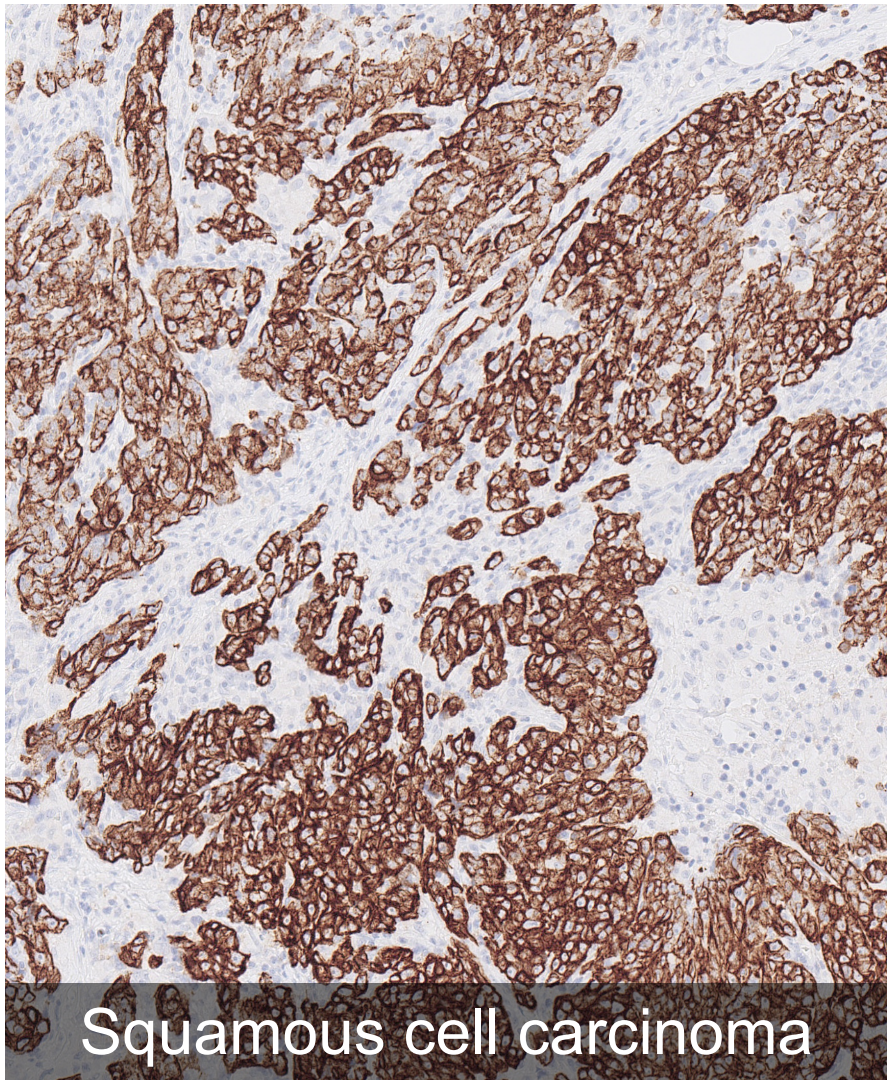
Neutral/Basic (B, class II) Acidic (A, class I)	1 10	4	13	5	14	17	19	7	20	8 18
Squamous cell carcinoma	(+)	+	+	++	++	(+)	(+)	(+)	-	(+)
Urothelial cell tumour	-	+	+	+	+	+	++	++	++	++
Malignant mesothelioma	-	-	-	++	++	+	++	+	-	++
Adenocarcinoma: complex epithelia (bronch., breast, prost.)	-	-	-	(+)	(+)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

NordiQC

Courtesy of Professor M. Vyberg

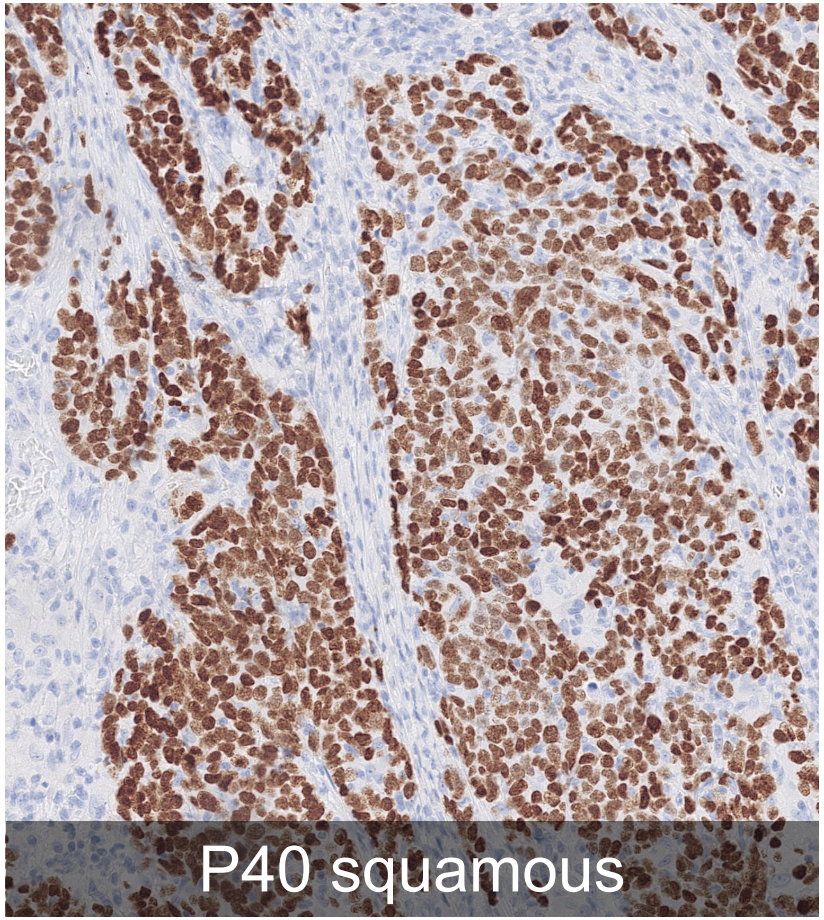
CK5

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

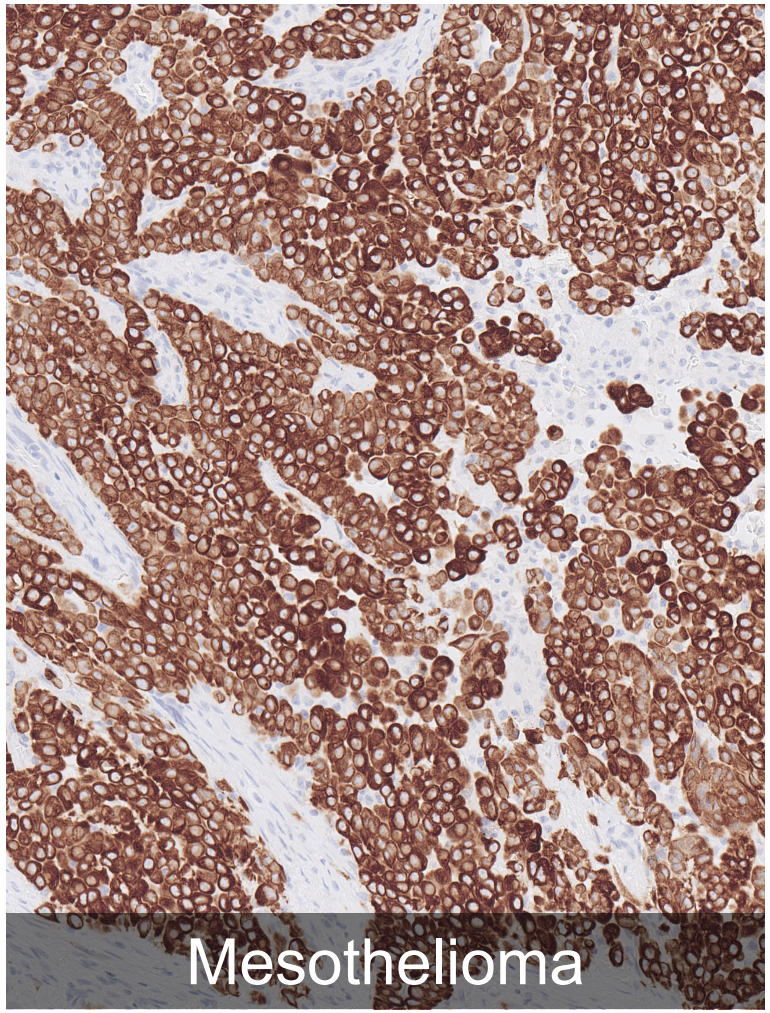


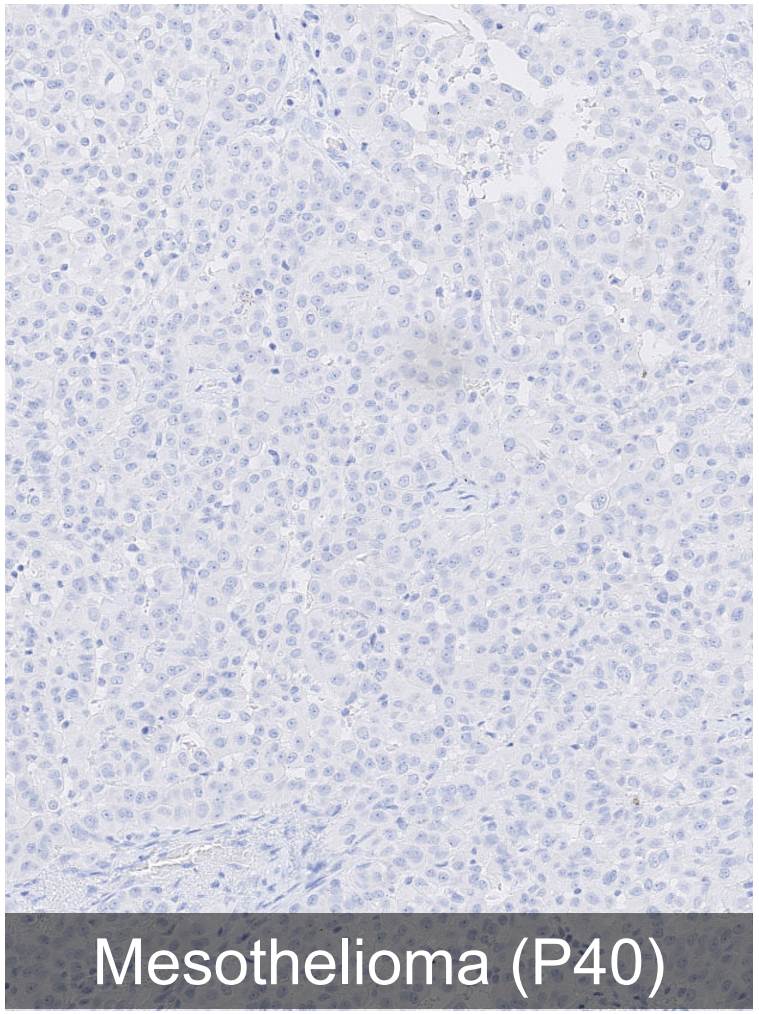
Confirm squamous cell carcinoma

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

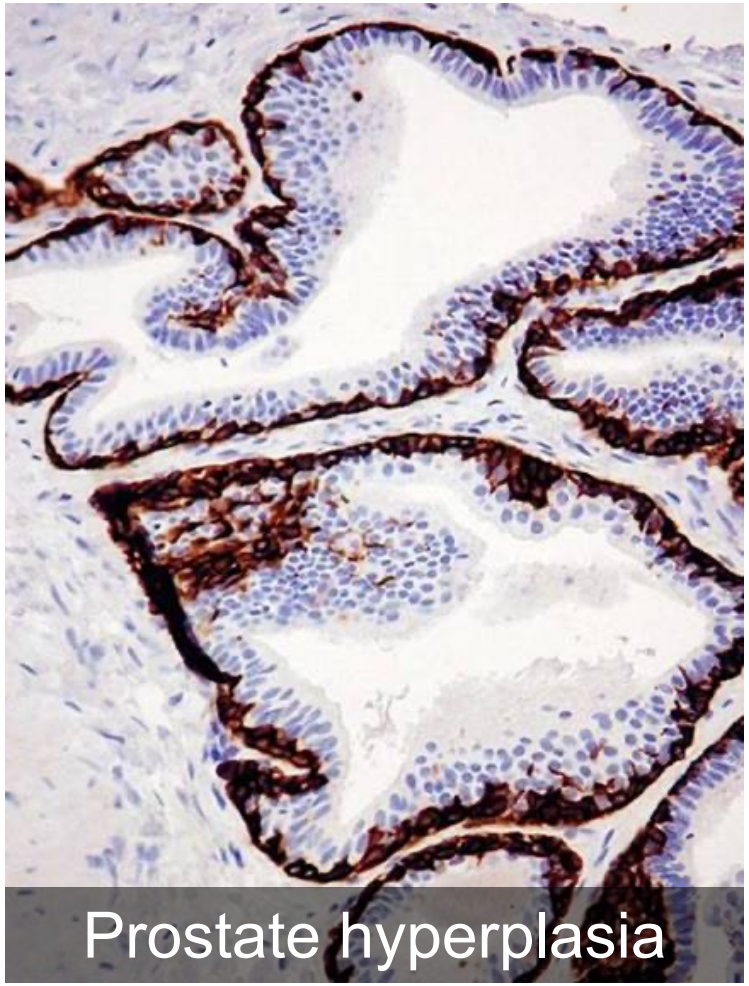


CK5 in mesothelioma

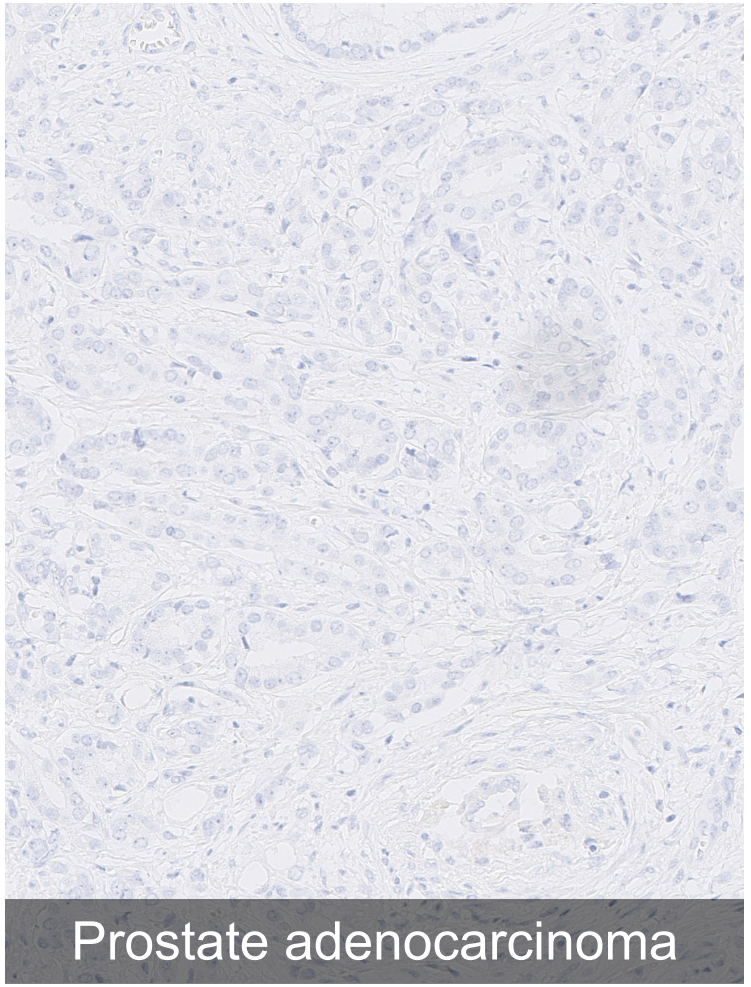




CK5 – other uses



Prostate hyperplasia

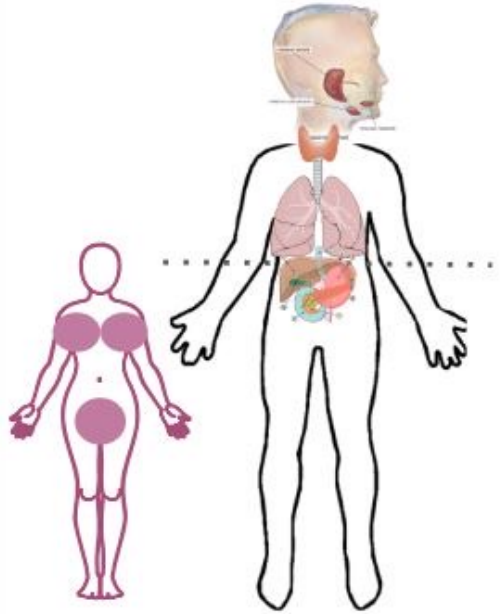


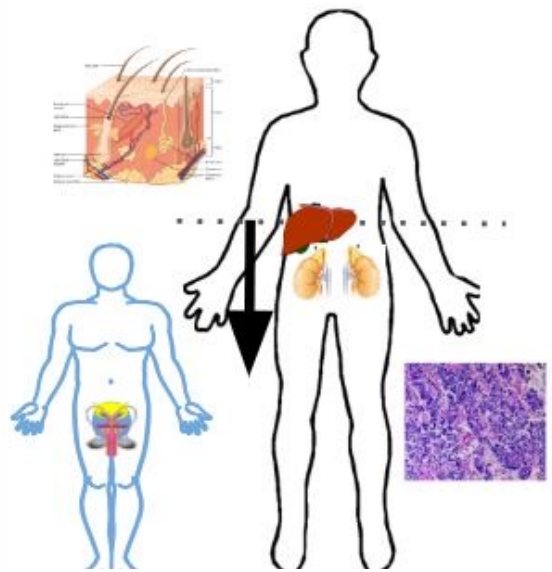
Prostate adenocarcinoma

Neutral/Basic (B, class II) Acidic (A, class I)	1 10	4	13	5	14	17	19	7	20	8 18
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	-	-	-	-	-	-	+	++	-	++

NordiQC

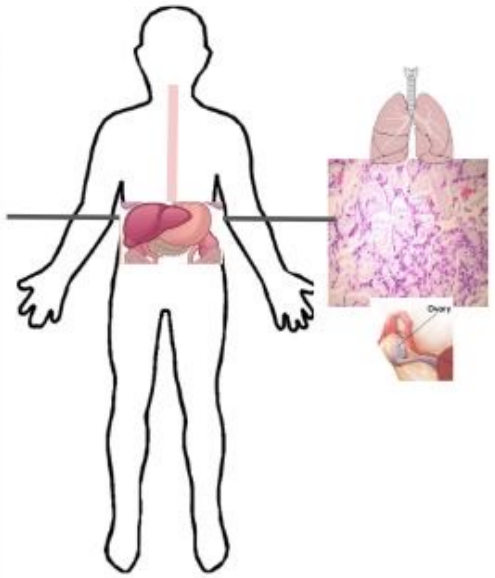
Courtesy of Professor M. Vyberg

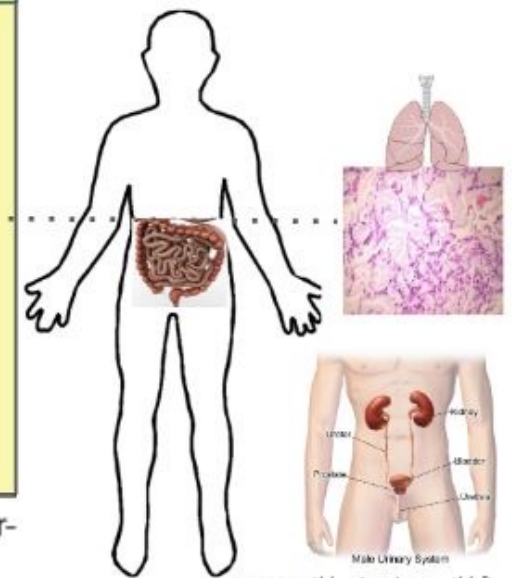




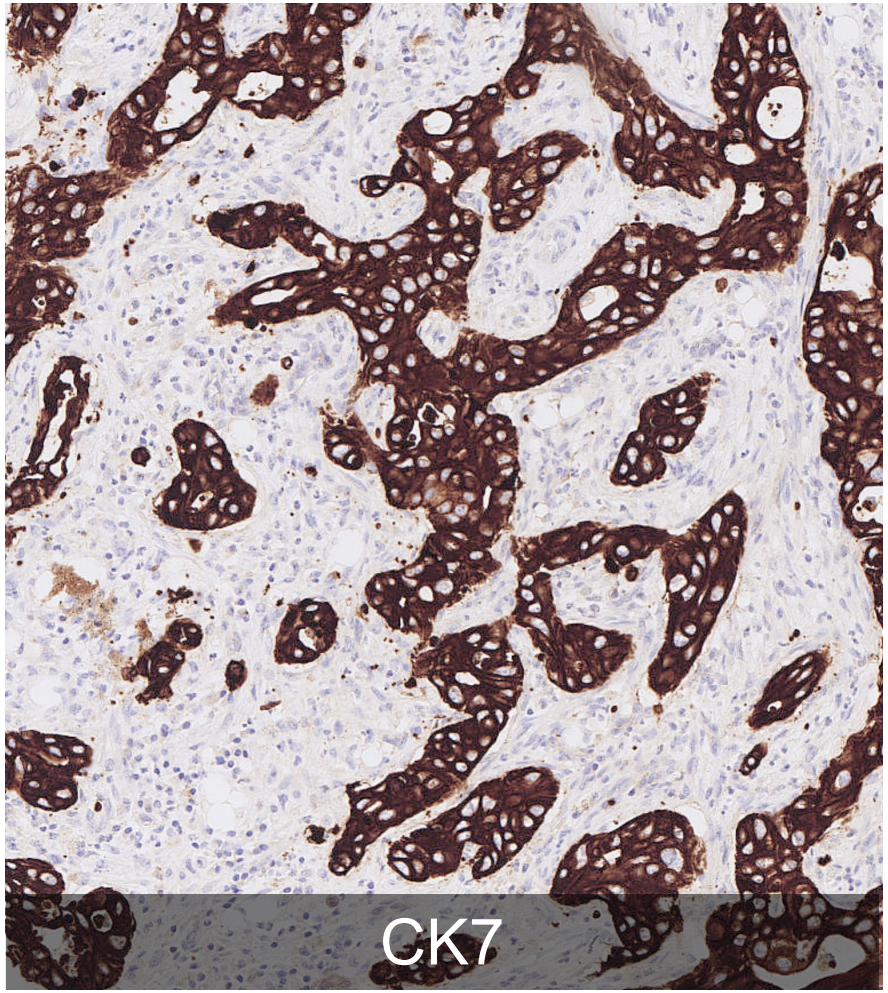
	CK20−	CK20+
CK7+	• Lung • Breast • Upper GI ADC • Pancreatic/biliary ADC • Endometrial/ endocervical ADC • Thyroid • Thymic CA • Salivary gland duct CA • Hepatocellular CA, fibrolamellar type • Ovarian serous CA • Anal duct CA • Mesothelioma	• Urothelial CA • Esophagus ADC • Gastric ADC • Small bowel ADC • Mucinous ADC of lung • Ovarian mucinous CA • Pancreaticobiliary ADC • Cholangiocarcinoma
CK7−	• Hepatocellular CA • Clear cell renal cell carcinoma • Adrenal cortical CA • Prostate ADC • Small cell carcinoma • Squamous cell CA • Germ cell tumors • Neuroendocrine neoplasm • Medullary CA of the colon	• Colorectal ADC • Small bowel ADC • Bladder ADC • Merkel cell carcinoma • Appendiceal ADC • Mucinous ADC of lung • Papillary renal cell carcinoma, type II

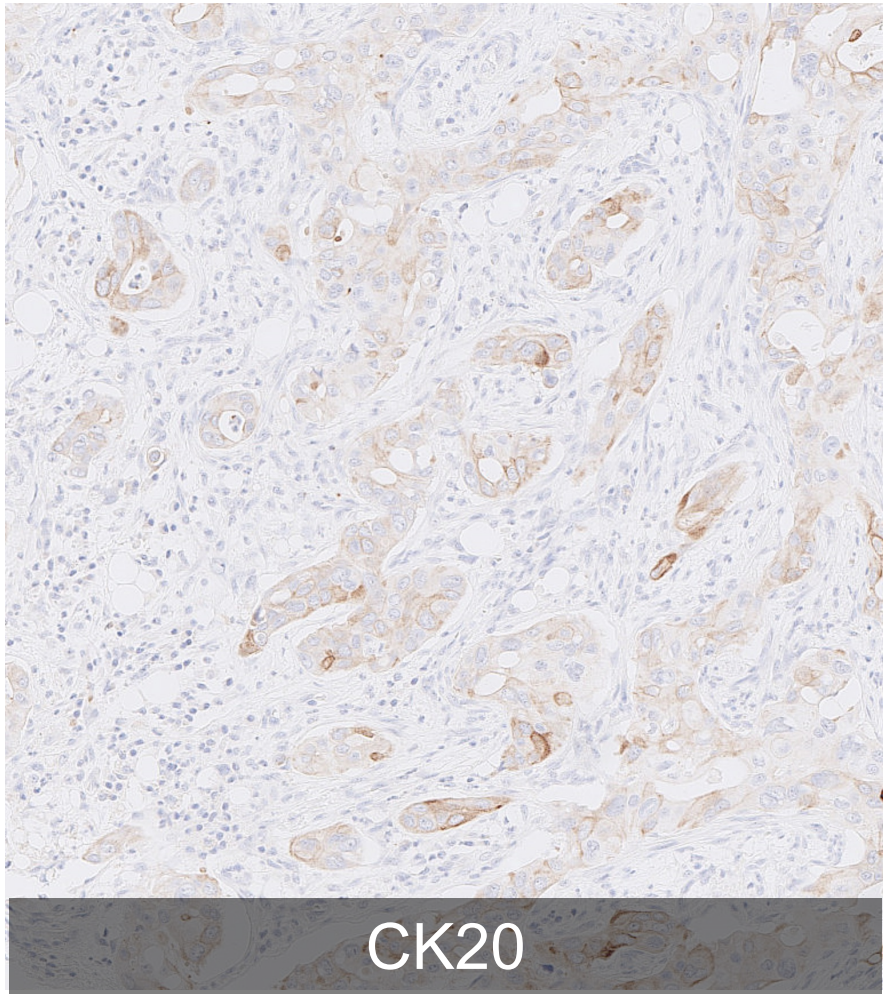
Abbreviations: ADC, adenocarcinoma; CA, carcinoma; CK, cytokeratin; GI, gastrointestinal.



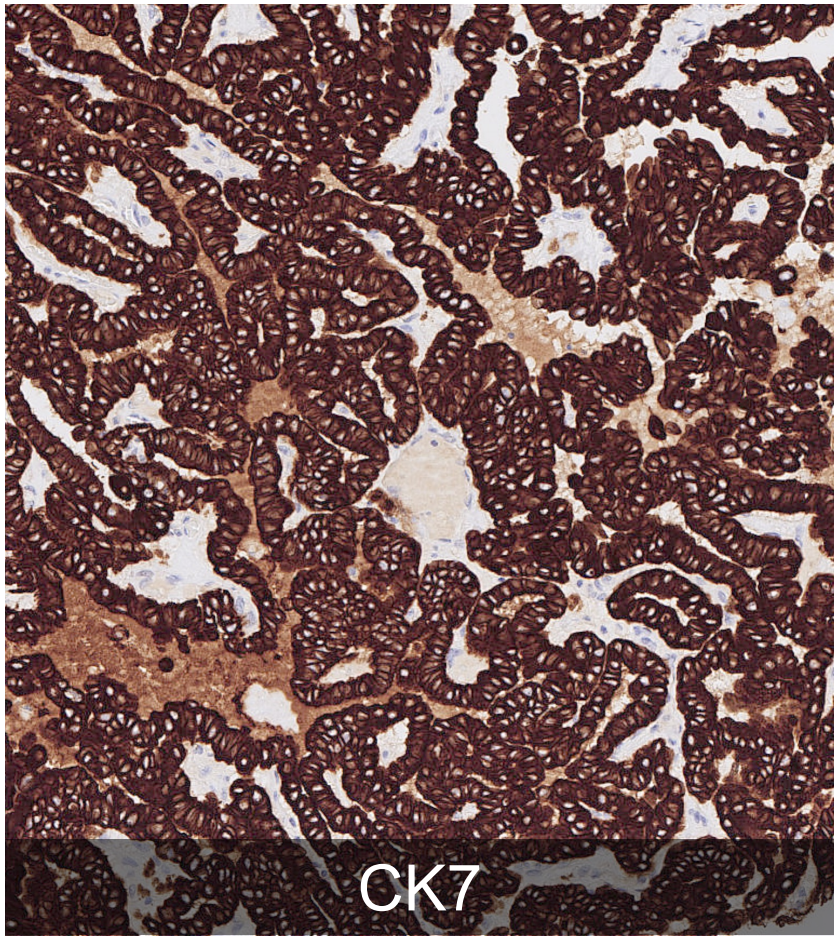


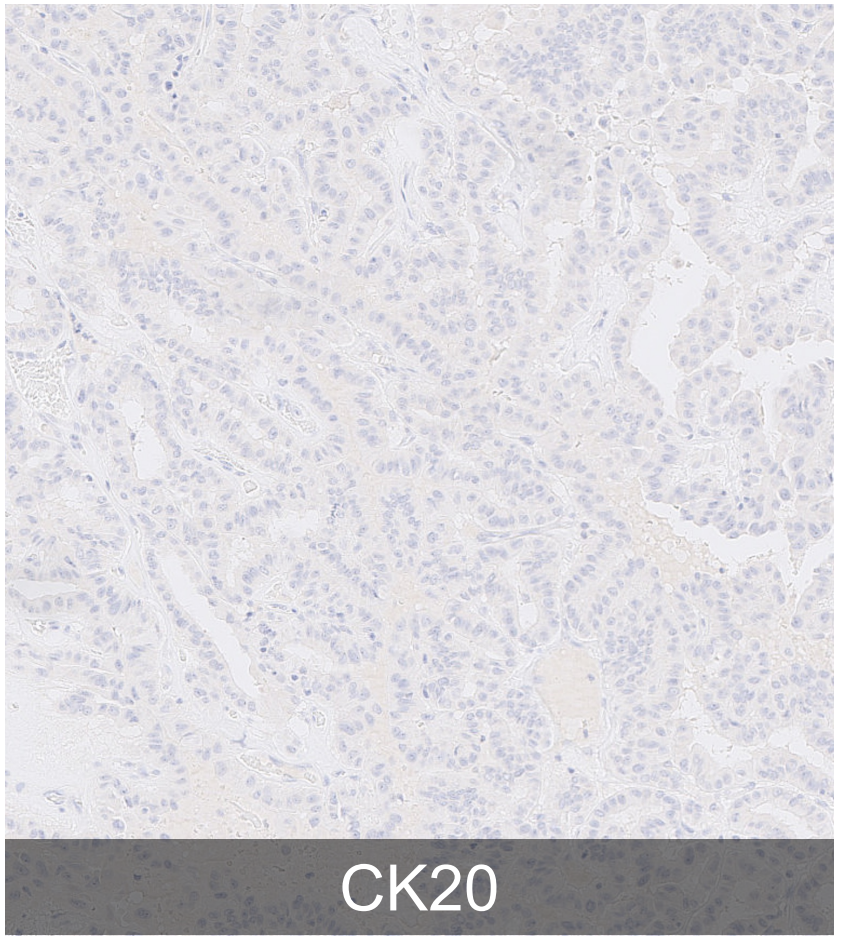
Pancreas adenocarcinoma



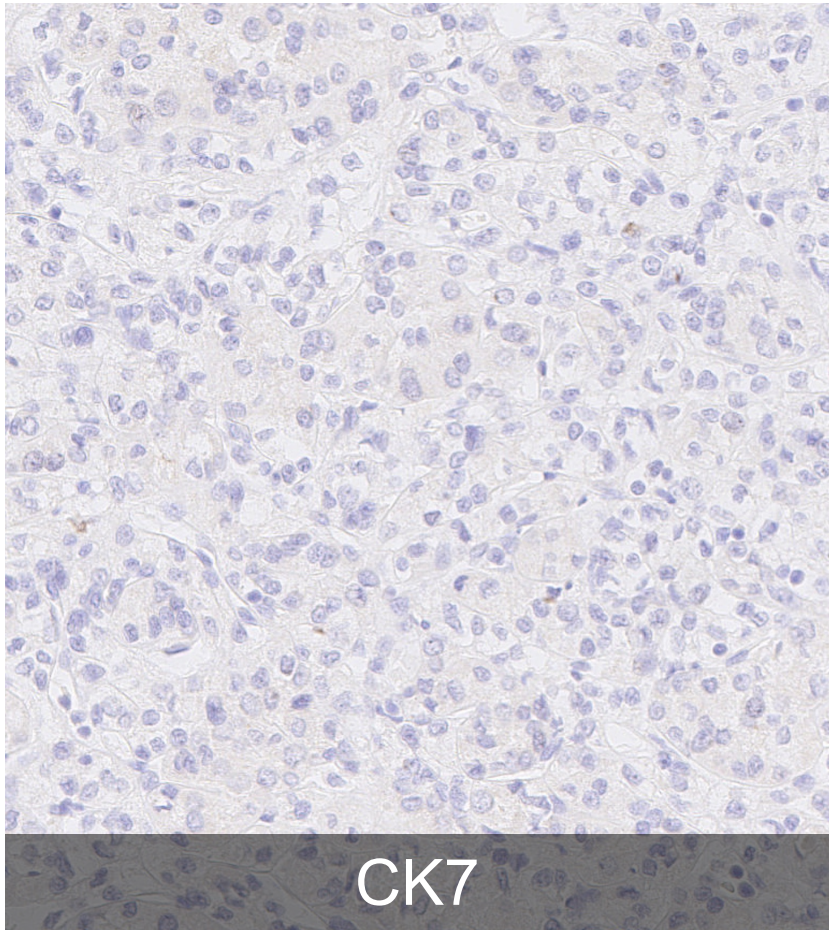


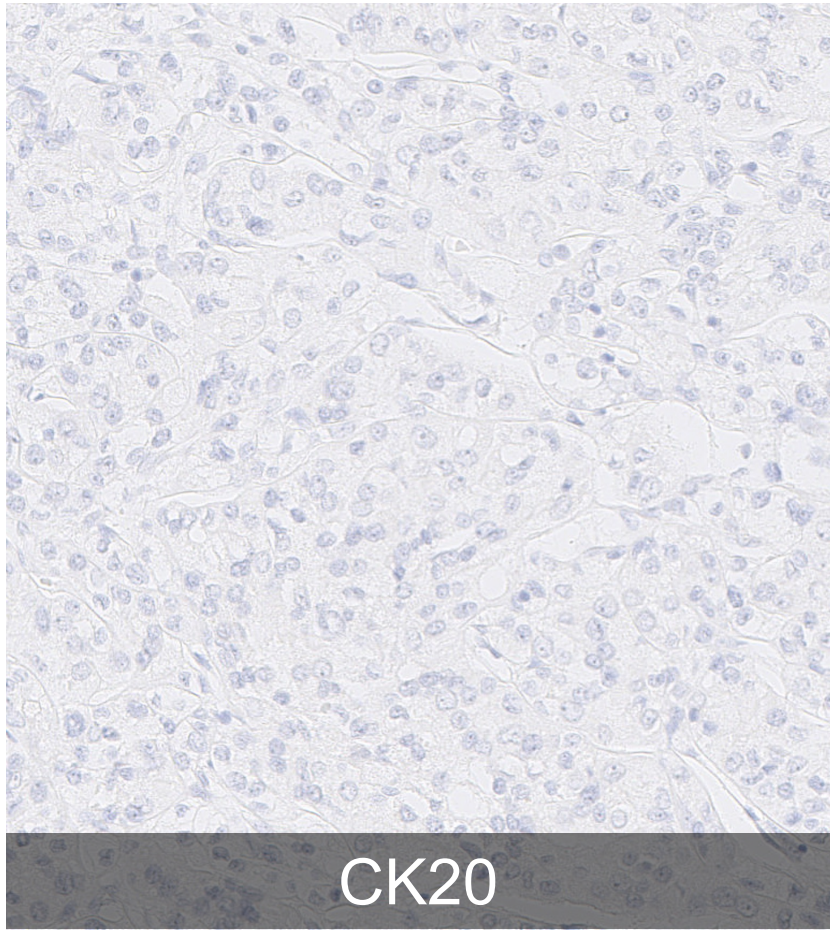
Thyroid carcinoma





Renal clear cell carcinoma





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
Mammaglobin
GCDP-15

Lung:
TTF
Napsin

Gastrointestinal:
CDX2
Cadherin 17
SATB2

Kidney:
PAX8

Prostate:
NKX3.1

Bladder:
GATA3
Uroplakin II

Melanoma:
SOX10
MLA

Mesothelioma:
Calretinin
Podoplanin

Germ cell:
OCT3/4
CD30
SALL4

Neuroendocrine:
SYP
CGA
INSM1

Female genitals:
PAX8
WT1
ER

Pancreas:
SMAD4
Gata3

Thyroid:
TTF
PAX8

NordiQC

Tissue “specific” markers

Breast:
Gata3
Estrogen receptor
Mammaglobin
GCDP-15

Lung:
TTF
Napsin

Gastrointestinal:
CDX2
Cadherin 17
SATB2

Kidney:
PAX8

Prostate:
NKX3.1

Bladder:
GATA3
Uroplakin II

Germ cell:
OCT3/4
CD30
SALL4

Melanoma:
SOX10
MLA

Mesothelioma:
Calretinin
Podoplanin

Neuroendocrine:
SYP
CGA
INSM1

Thyroid:
TTF
PAX8

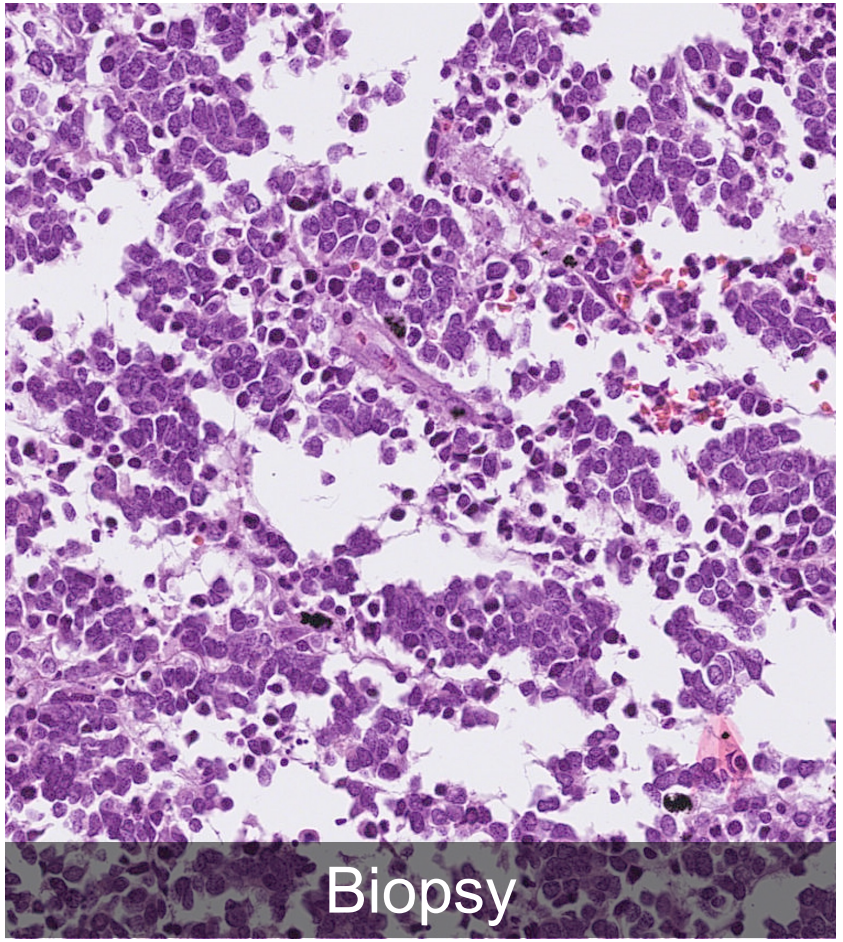
Female genitals:
PAX8
WT1
ER

Pancreas:
SMAD4
Gata3

NordiQC

Case

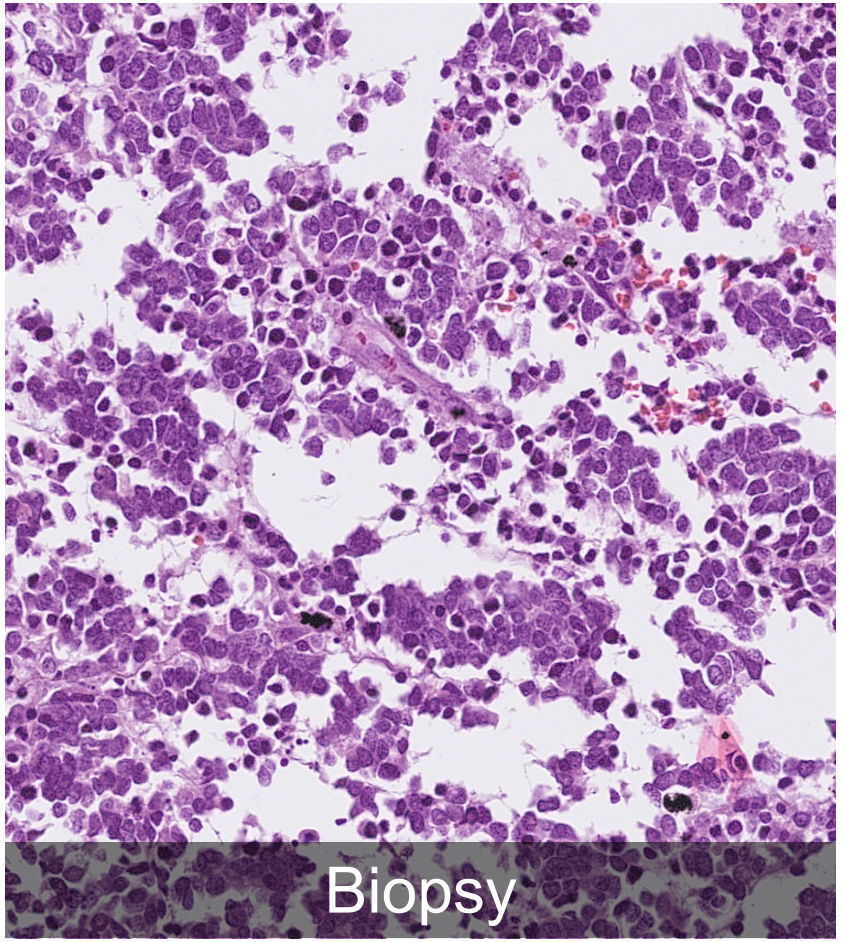
- 67 y.o. female
- Heavy smoker
- Several tumours in both lungs
- Pleural plaques and exposed to asbestos
- Large lymph nodes in mediastinum
- Previous ovarian serous carcinoma



Case

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

CD45	Pan cytokeratin	S100	Vimentin
Negative	Positive	Negative	Negative



NordiQC

Tissue specific markers

Breast:
Gata3
Estrogen receptor
Mammaglobin
GCDP-15

Lung:
TTF
Napsin

Gastrointestinal:
CDX2
Cadherin 17
SATB2

Kidney:
PAX8

Prostate:
NKX3.1

Bladder:
GATA3
Uroplakin II

Melanoma:
SOX10
MLA

Mesothelioma:
Calretinin
Podoplanin

Germ cell:
OCT3/4
CD30
SALL4

Neuroendocrine:
SYP
CGA
INSM1

Female genitals:
PAX8
WT1
ER

Pancreas:
SMAD4
Gata3

Thyroid:
TTF
PAX8

NordiQC

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

Lung	
TTF	Positive
Napsin	Negative

Neuroendocrine:
SYP
CGA
INSM1

Neuroendocrine	
SYP	Positive
CGA	Positive
INSM1	Positive

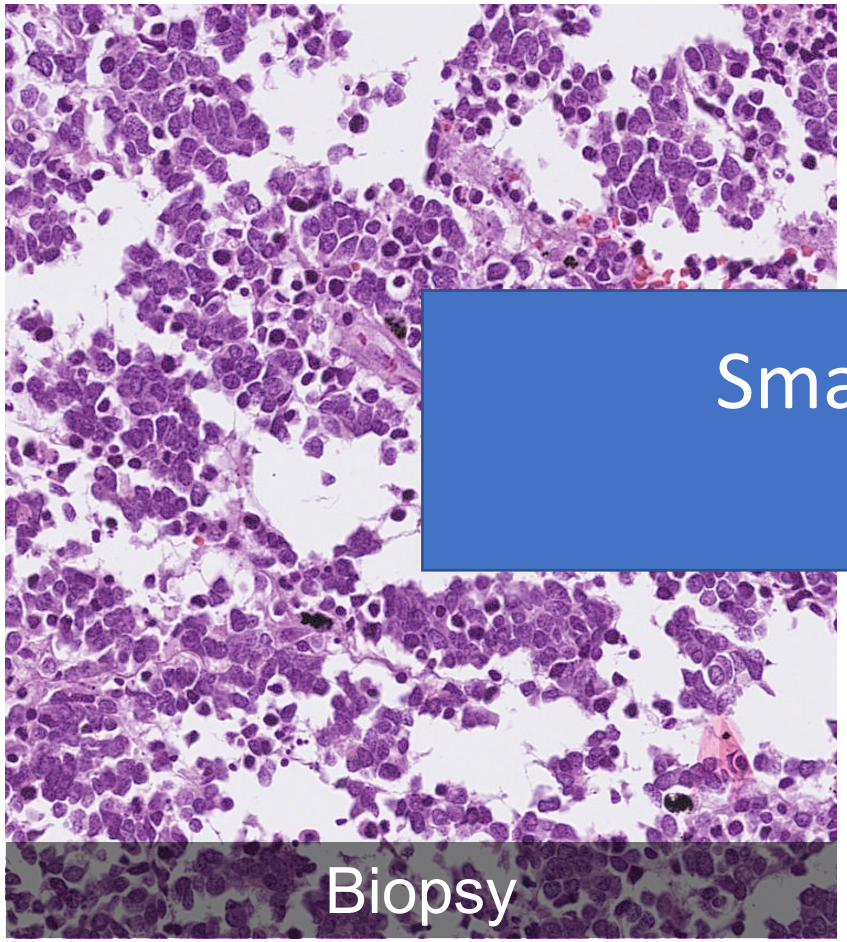
Female genitals:
PAX8
WT1
ER

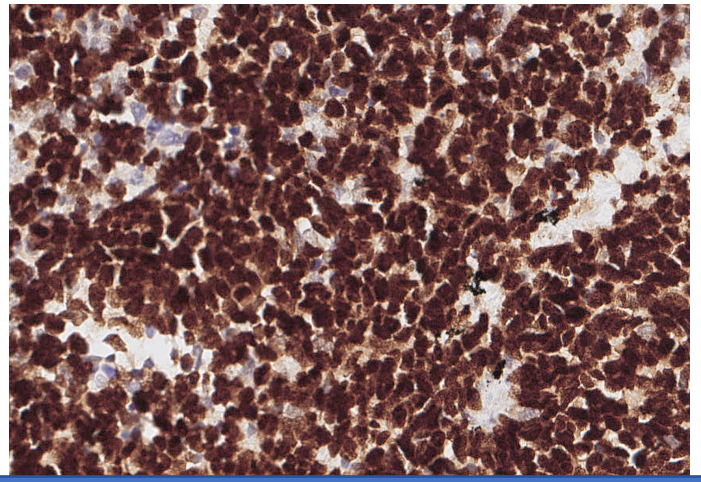
Female genitals	
PAX8	Negative
WT1	Negative
ER	Negative

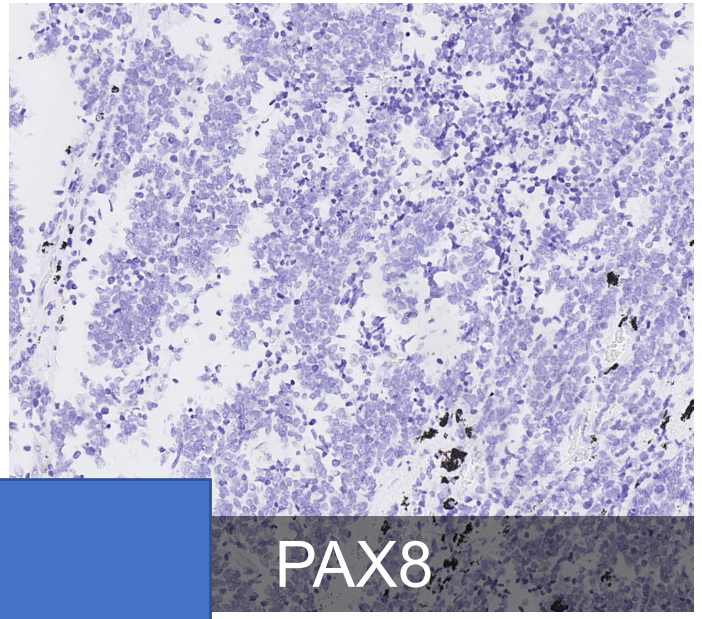
Mesothelioma:
Calretinin
Podoplanin

Mesothelioma	
Calretinin	Negative
Podoplanin	Negative

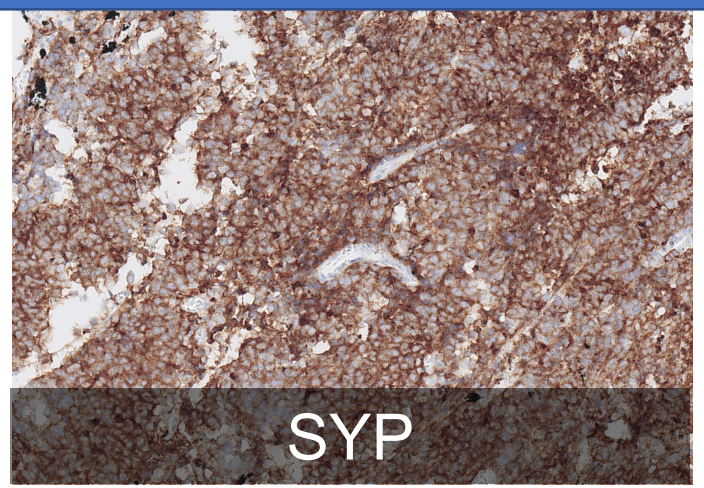
Case

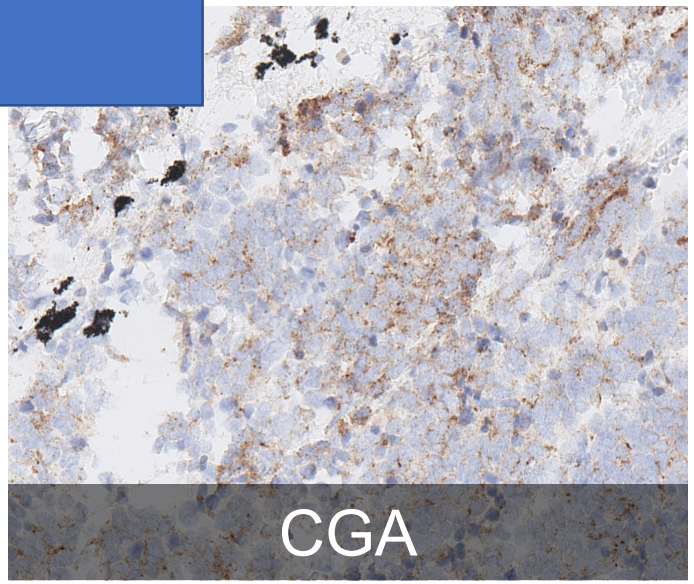






Small cell lung carcinoma
(neuroendocrine)





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 Protein correlate of molecular genetic event
Islet 1	Pancreatic origin of well-differentiated neuroendocrine tumor	Lineage-restricted transcription factor
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; *BCOR*-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.

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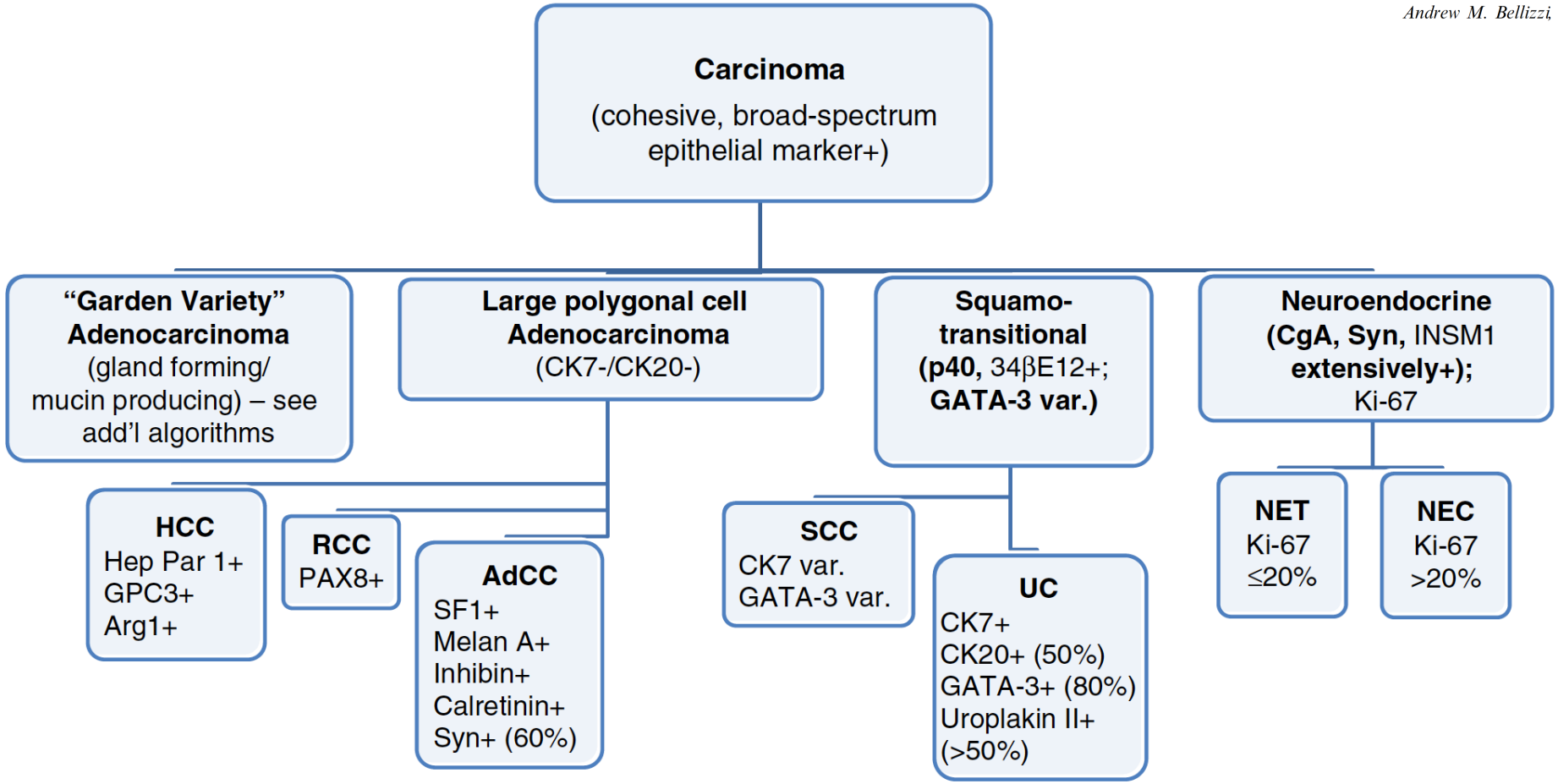


FIGURE 1. Algorithmic approach to diagnosis of four carcinoma types. AdCC indicates adrenal cortical carcinoma; Arg1, arginase-1; CgA, chromogranin A; GPC3, glypican-3; HCC, hepatocellular carcinoma; NEC, poorly differentiated neuroendocrine carcinoma; NET, well-differentiated neuroendocrine tumor; RCC,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

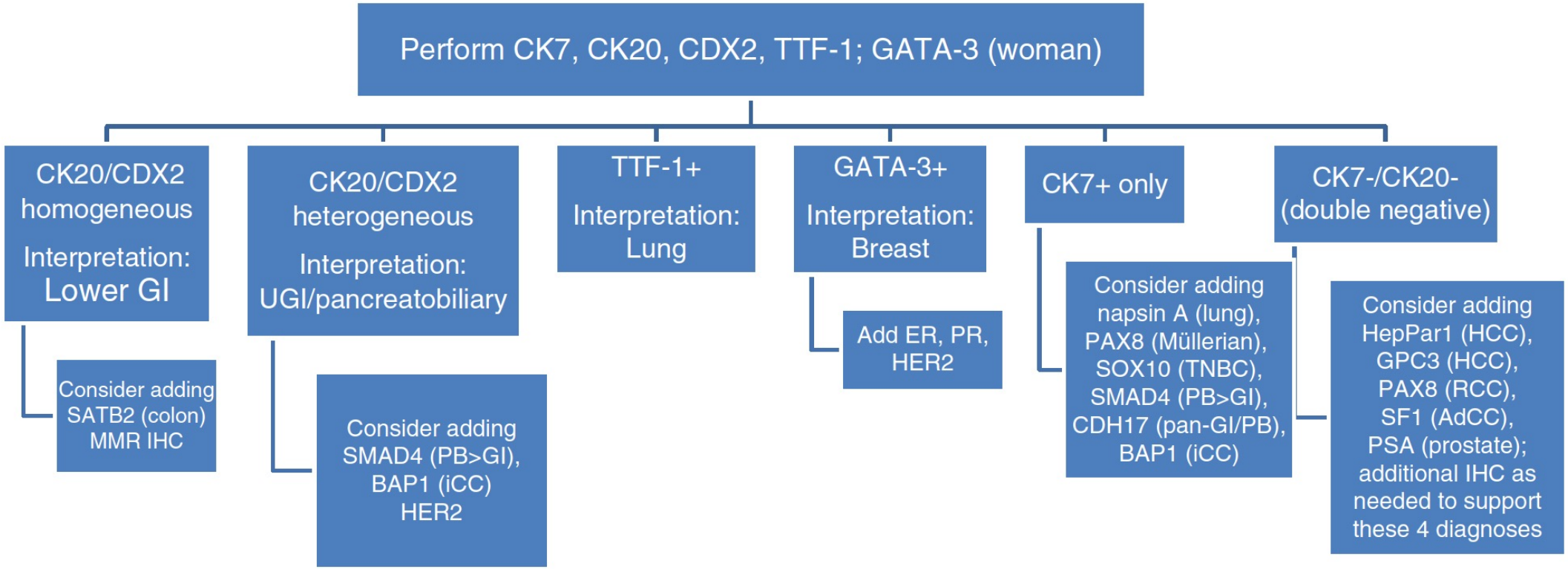


FIGURE 2. Immunohistochemical algorithm for "garden variety" adenocarcinoma in the liver. AdCC indicates adrenal cortical carcinoma; ER, estrogen receptor; GI, gastrointestinal; GPC3, glypican-3; HCC, hepatocellular carcinoma; iCC, intrahepatic cholangiocarcinoma; IHC, immunohistochemistry; PB, pancreatobiliary; 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!

