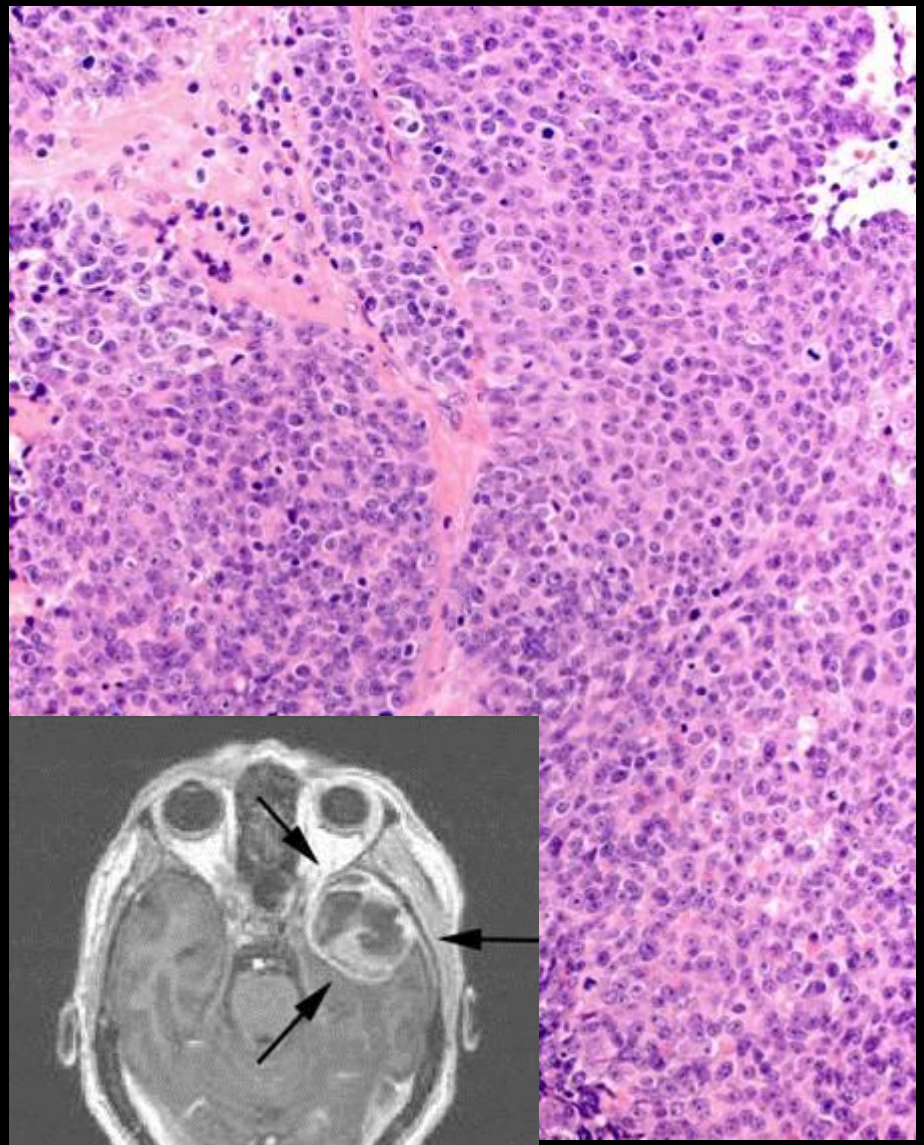
NordiQC
Workshop in Diagnostic Immunohistochemistry
Aalborg University Hospital, September 19th – 21st 2016

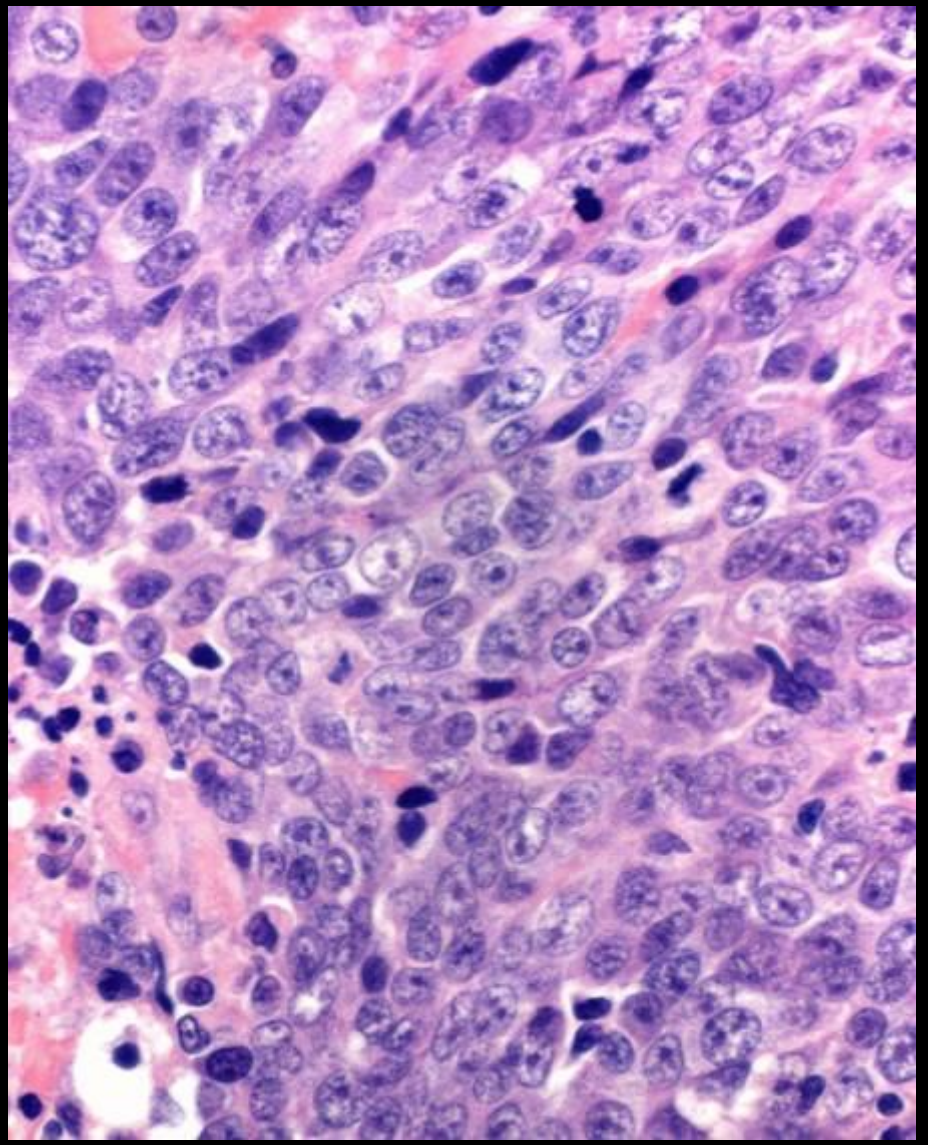
Immunohistochemical classification of the unknown primary tumour (UPT)

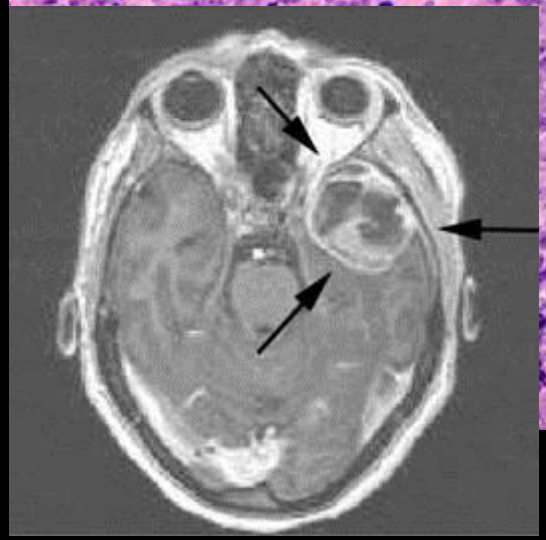
Part I

Prof. Mogens Vyberg
NordiQC
Institute of Pathology
Aalborg, Denmark

Tumours of unknown origin: Histology

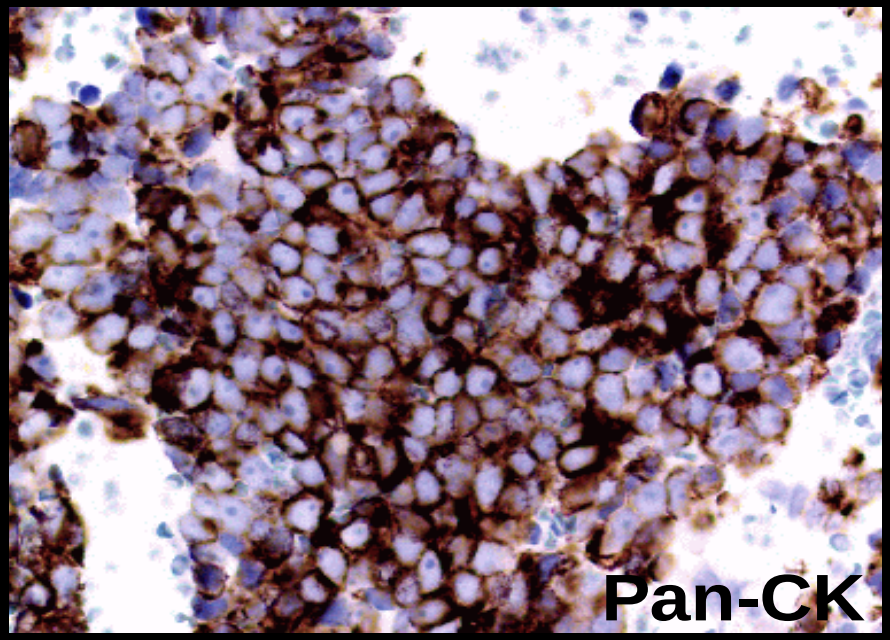


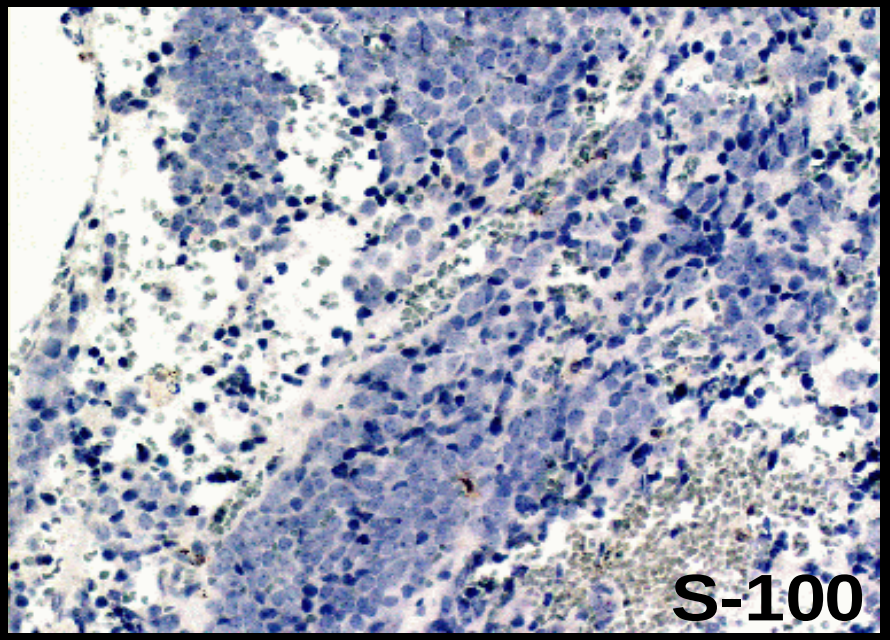


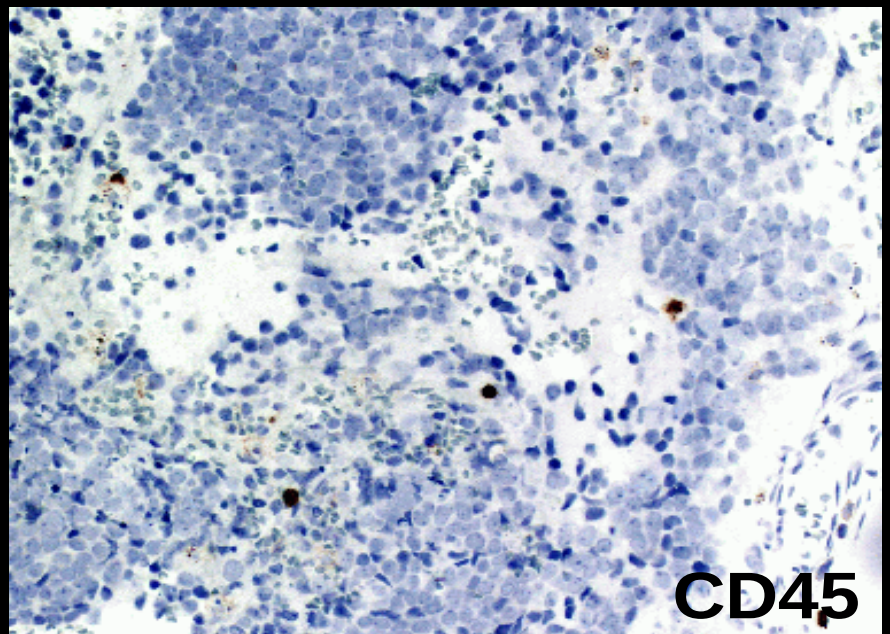


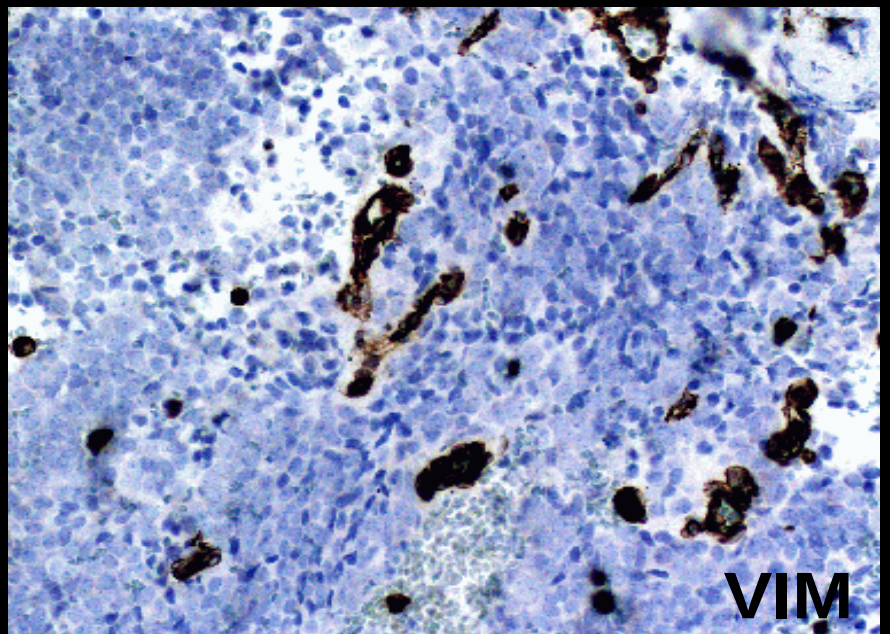
Brain tumour - biopsy

Tumours of unknown origin: Immunohistochemistry









IHC classification of the Unknown Primary Tumour

UPT: A tumour appearing in metastatic setting without a histologically proven primary tumour.

UPT pose an increasing challenge for the pathologist - due to the progress in surgical and oncological treatment possibilities.

IHC classification of the Unknown Primary Tumour

New, relatively specific antibodies give the pathologist more and better diagnostic tools.

But the diagnostic work also become more complex in terms of planning, optimization of protocols, interpretation of reaction patterns and error trapping.

IHC classification of the Unknown Primary Tumour

10 - 15% of cancers remain UPTs

+ ??% uncertain if primary or metastatic

- liver, lung, bone, lymph nodes, brain, peritoneum . . .

- ‘Undifferentiated’ neoplasms (5-10%)

  - carcinomas, sarcomas, melanomas, germ cell tumours

  - malignant lymphomas

- Adenocarcinomas (80-90%)

  - lung, breast, prostate, colorectum, ovary, pancreas …

- Squamous cell carcinomas (5-10%)

  - lung, esophagus, uterine cervix …

IHC classification of the Unknown Primary Tumour

Differences in prognosis

Differences in treatment regimes

- malignant lymphomas
- carcinomas (breast, prostate, ovary . . .)
- sarcomas (GIST, synovial sarcoma . . .)
- germ cell tumours

Pathology tests cost effective

Pathology tests save patient discomfort

The patient's 'right to know'

The risk of hereditary cancer

IHC classification of the Unknown Primary Tumour

- Most likely diagnoses
- Relevant differential diagnoses

↓

- Optimal selection of antibodies for a diagnostic algorithm
  - Primary and secondary antibody panels
  - Turn-around-time
  - Laboratory expenses

IHC classification of the Unknown Primary Tumour

Pathologist

- knowledge, acceptance, skill

Tumour material

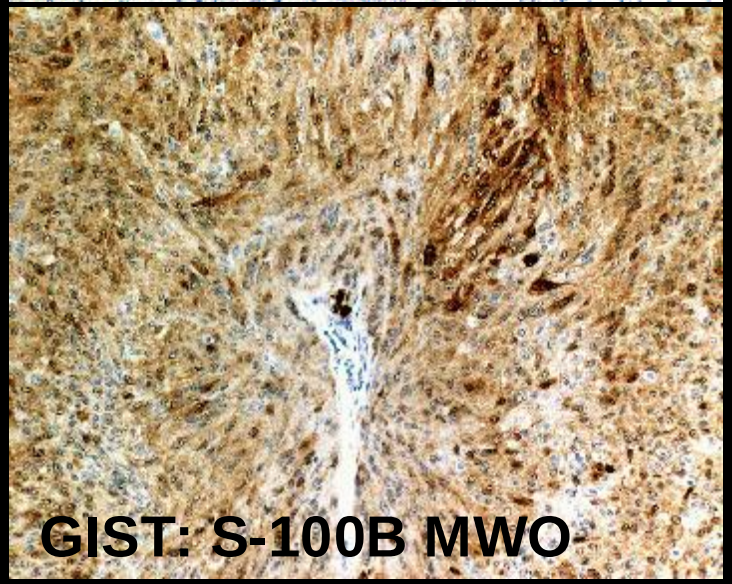
- diagnostic markers

Antibodies available

- applic. in diagnostic algorithms

Methods

- protocol:
  sensitivity, specificity, reliability
- interpretation:
  cut-off level for positivity
  clinical relevance



IHC classification of the Unknown Primary Tumour

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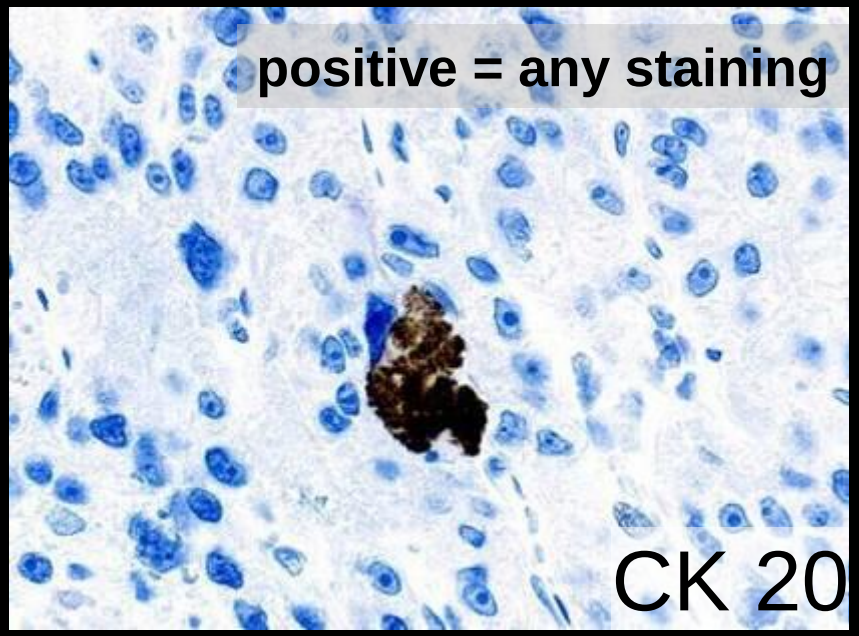
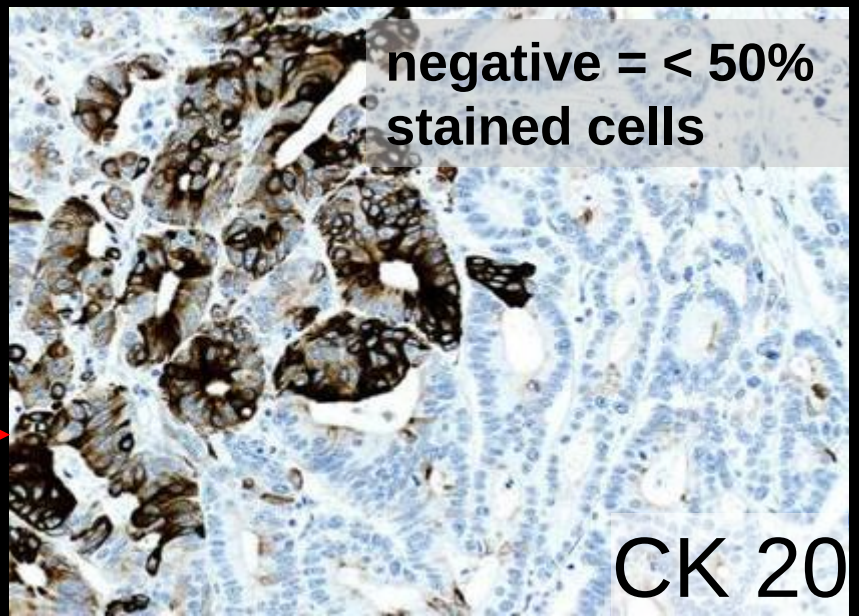
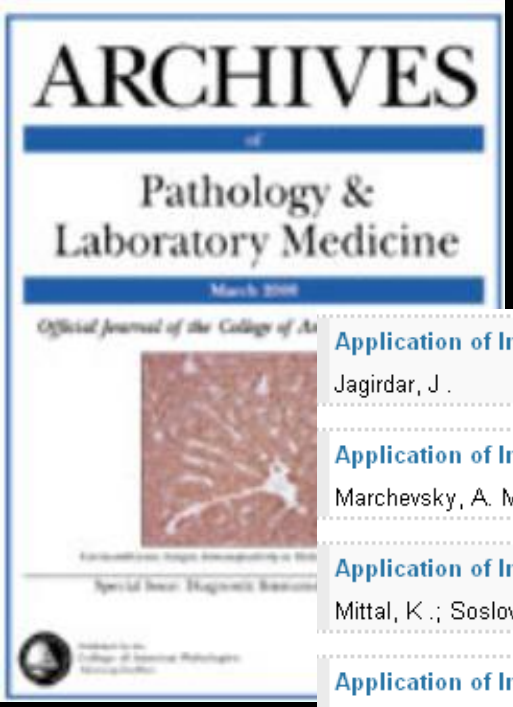






March 2008

Application of Immunohistochemistry to the Diagnosis of Primary and Metastatic Carcinoma to the Lung

Jagirdar, J .

Application of Immunohistochemistry to the Diagnosis of Malignant Mesothelioma

Marchevsky, A. M .

Application of Immunohistochemistry to Gynecologic Pathology

Mittal, K .; Soslow, R .; McCluggage, W. G .

Application of Immunohistochemistry to Infections

Eyzaguirre, E .; Haque, A. K .

Application of Immunohistochemistry to the Genitourinary System (Prostate, Urinary Bladder, Testis, and Kidney)

Hammerich, K. H .; Ayala, G. A .; Wheeler, T. M .

Application of Immunohistochemistry in the Diagnosis of Non-Hodgkin and Hodgkin Lymphoma

Higgins, R. A .; Blankenship, J. E .; Kinney, M. C .

Acute Leukemia Immunohistochemistry: A Systemic Diagnostic Approach

Olsen, R. J .; Chang, C.-C .; Herrick, J. L .; Zu, Y .; Ehsan, A .

Application of Immunohistochemistry to Soft Tissue Neoplasms

Heim-Hall, J .; Yohe, S. L .

Application of Immunohistochemistry to Liver and Gastrointestinal Neoplasms: Liver, Stomach, Colon, and Pancreas

Geller, S. A .; Dhall, D .; Alsabeh, R .

The Differential Diagnosis of Central Nervous System Tumors: A Critical Examination of Some Recent Immunohistochemical Applications

Edgar, M. A .; Rosenblum, M. K .

MPP 19

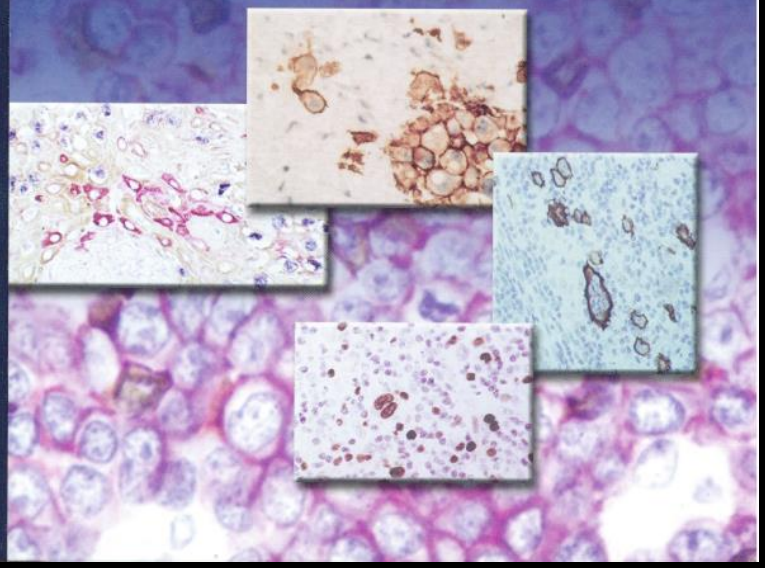
Clive R. Taylor
Richard J. Cote

Immunomicroscopy

A Diagnostic Tool for the Surgical Pathologist

MAJOR PROBLEMS IN PATHOLOGY

THIRD EDITION



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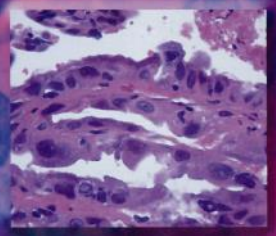

Diagnostic Immunohistochemistry

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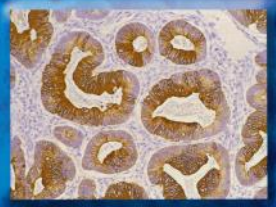

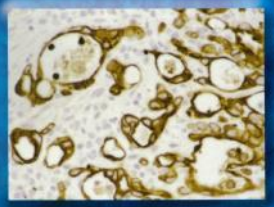

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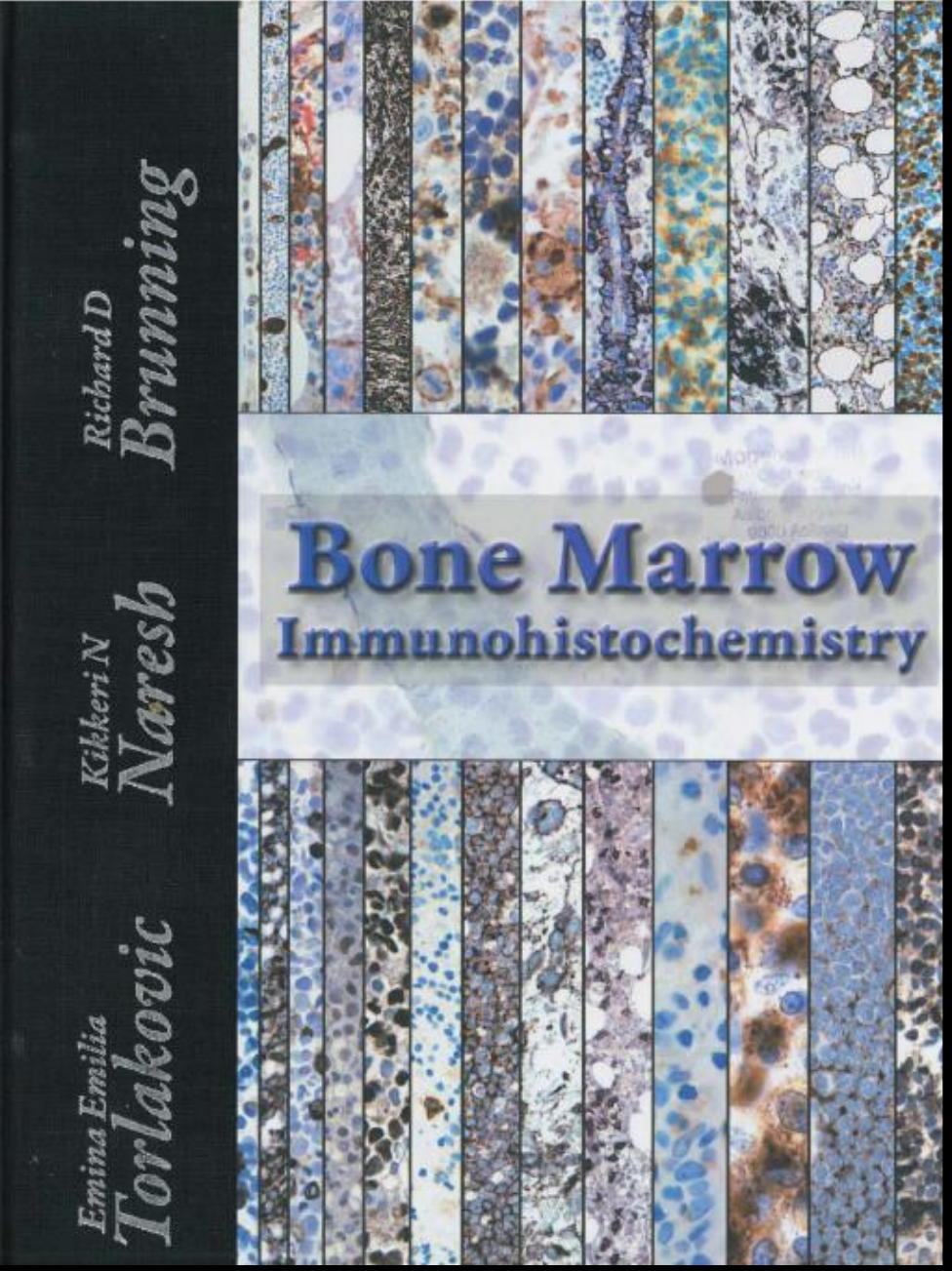
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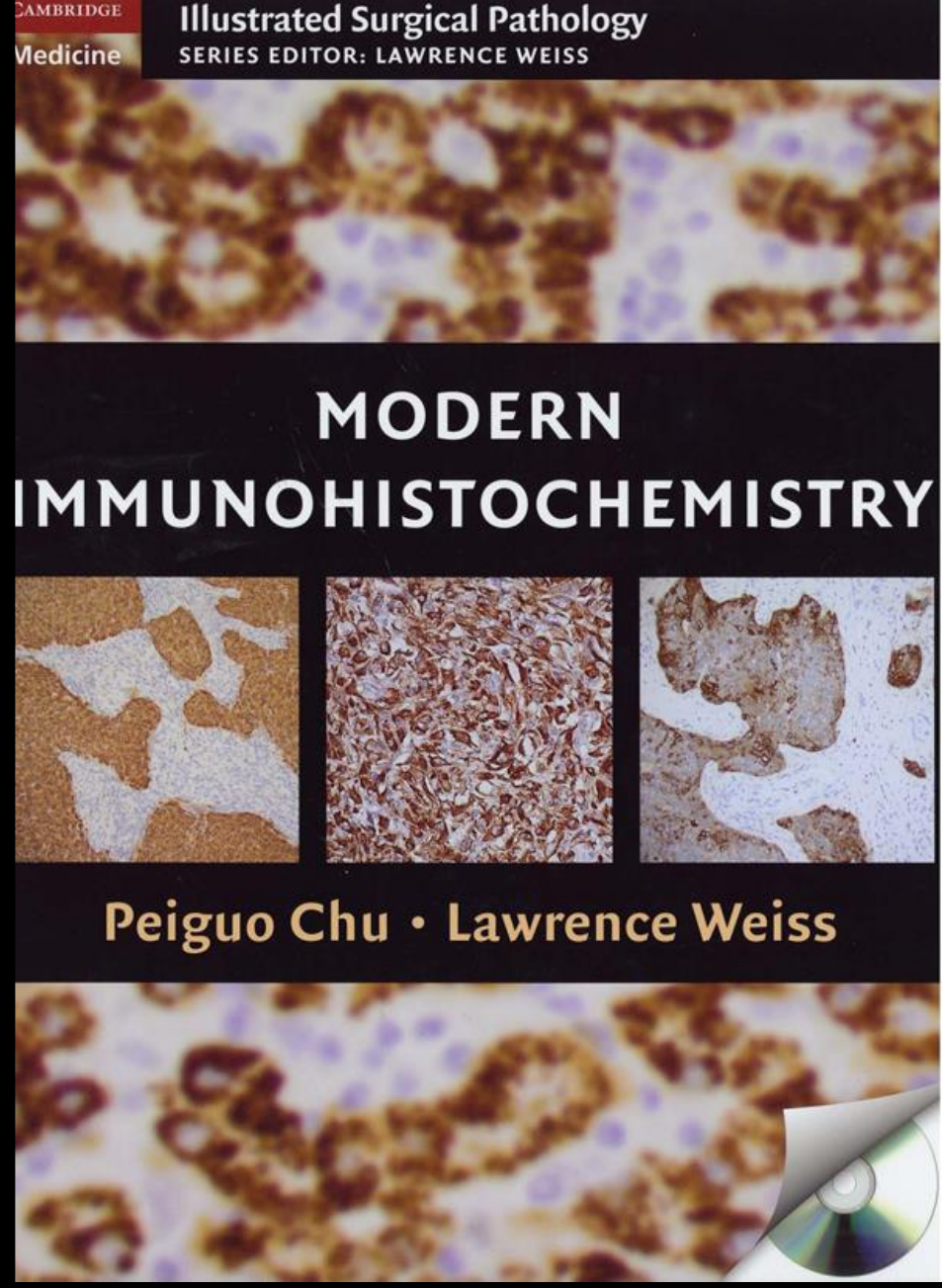
Kikkeri N Naresh
Richard D Brunning
Bone Marrow
Immunohistochemistry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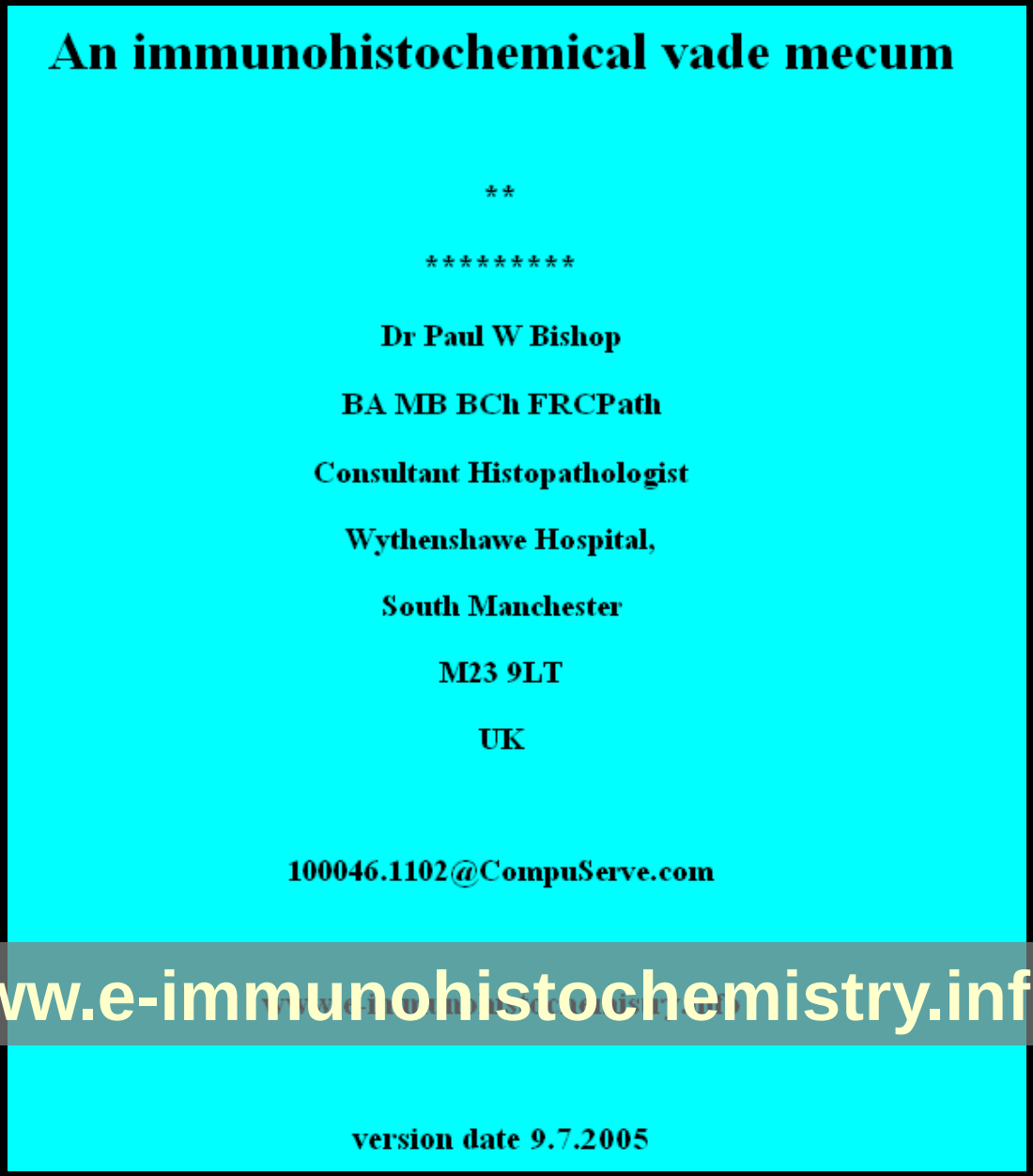
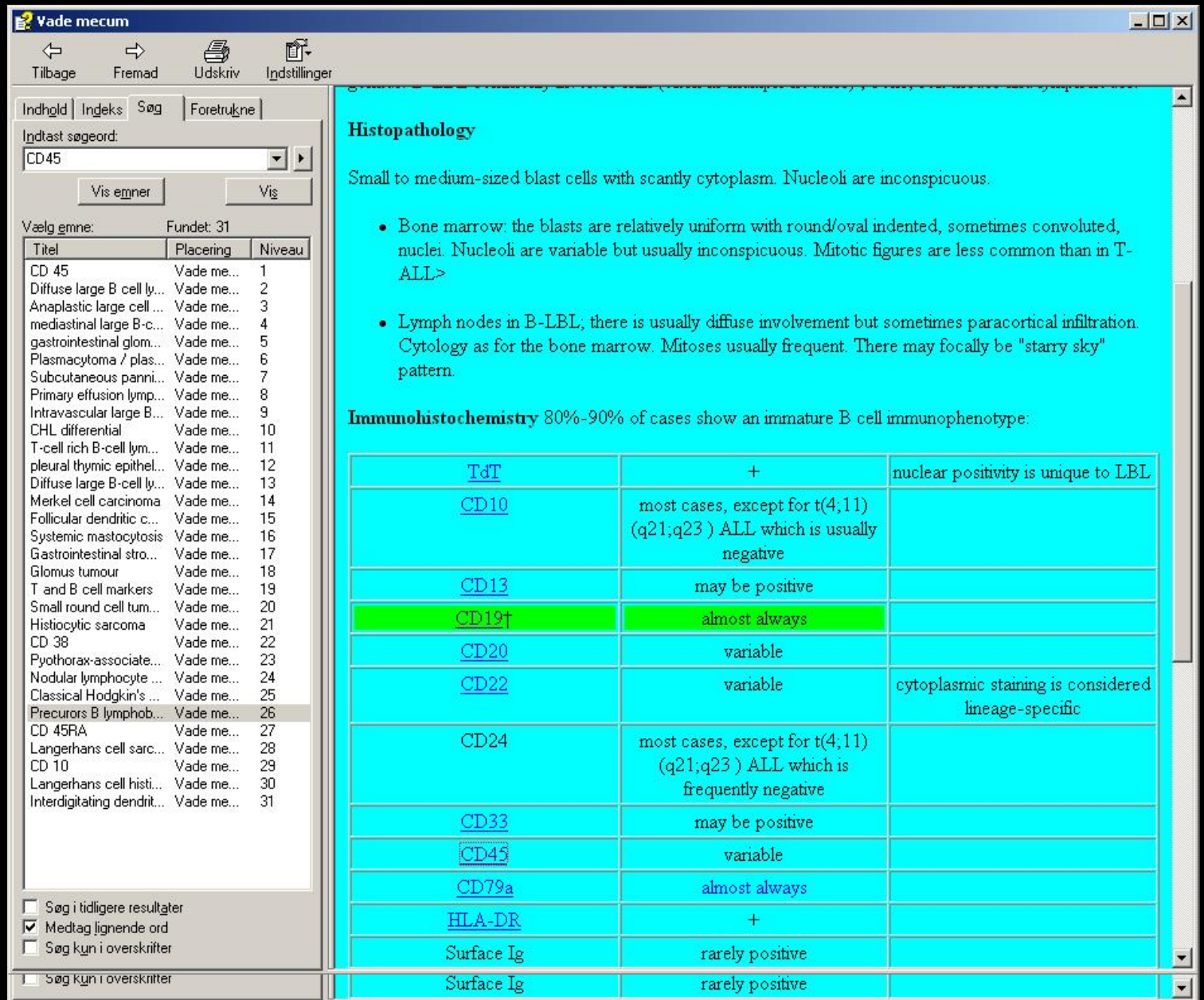
Planning diagnostic immunohistochemistry



www.e-immunohistochemistry.info

Planning diagnostic immunohistochemistry



Planning diagnostic immunohistochemistry

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CD Markers

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Navigational links to CD markers

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CD 100-247

Primary references

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American Journal of Surgical Pathology **(AJSP)**, Jan 2001-Feb 2003
Archives of Pathology and Lab Medicine **(Archives)**, Jan 2002-Feb 2003
Human Pathology **(Hum Path)**, Jan 2002-Dec 2002

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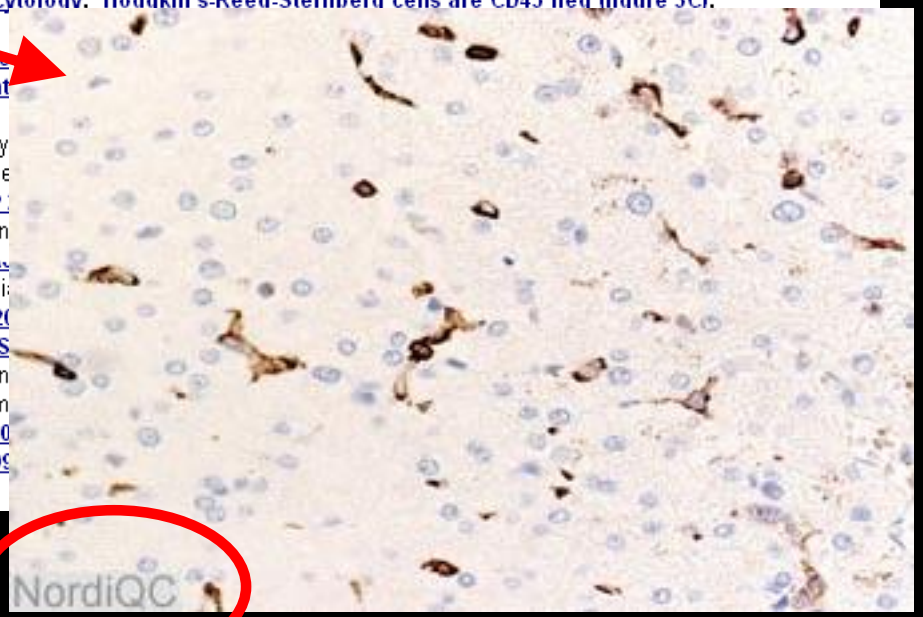
CD Markers CD1 to CD49

CD45

top

Also called leukocyte common antigen (LCA),
An essential regulator of T and B cell antigen re
The target of immunosuppressive antibody treat
Major component of glycocalyx
Negative regulator of IgE class switch recombination (J Biol Chem 2002;277:28830)
Mutations with loss of CD45 cause severe combined immunodeficiency - autosomal recessive, T cell negative, B cell positive, NK cell positive (OMIM 608971); patients have a defect in function or B and T cell development, lymphopenia, and deficiency in humoral and cell-mediated immunity.
77C to G mutation may increase intensity of T cell receptor signaling (J Immunol 2006;176:931), and cause some cases of systemic sclerosis (Genes Immun 2003;4:168), multiple sclerosis (controversial, Nat Genet 2000;26:495) and autoimmune hepatitis (Genes Immun 2003;4:79)
Loss of CD45 activity in lymphocytes of elderly may cause T cell dysfunction in elderly (Mech Ageing Dev 2003;124:191)
Necrotic lymphomas are still CD45+, but necrotic carcinomas may also be CD45+ (AJCP 1998;110:641)
Different subsets of hematopoietic cells express different CD45 isoforms due to variable exon splicing, which can change in response to cytokines:
CD45RA - naive/resting T cells, medullary thymocytes
CD45RO - memory/activated T cells, cortical thymocytes
Uses: confirm presence of inflammatory cells, including intestinal intraepithelial lymphocytes (Archives 2002;126:897); confirm hematopoietic nature of tumors; classify lymphomas and leukemias (AJCP 1998;110:797)
Micro images: *normal* - liver with CD45+ Kupffer cells and lymphocytes; small intestine with CD45+ intraepithelial lymphocytes; splenic lymphocytes; thymus; tonsil
lymphoma - B cell lymphoma-unusual CD45 negative case (figure B); CLL; #2 - urine cytology; Hodgkin's-Reed-Sternberg cells are CD45 neg (figure 3C); intravascular (figure 4); primary bone lymphoma (figure 1b)
other - lymphoepithelioma-like carcinoma #1 of stomach (CD45+ lymphocytes); #2 of
Flow cytometry images: transient myeloproliferative disorder with erythroid differentiat
Virtual slides: diffuse large B cell lymphoma
Positive staining (normal): hematopoietic cells (including monocytes, macrophages / histiocy
platelets and megakaryocytes; dendritic cells, fibrocytes (J Immunol 1998;160:419), thymus (me
Positive staining (disease): AML (AJCP 1998;109:211), anaplastic large cell lymphoma (AJCP
(+) lineage-negative malignancies (AJSP 2005;29:1274), dendrocytoma (AJSP 1990;14:867), gian
1993;17:1011), histiocytic sarcoma (AJSP 1998;22:1386), inflammatory pseudotumors (some, A
lymphocyte predominant Hodgkin's lymphoma (AJSP 1994;18:526), osteoclasts in osteoclast gi
(variable, Blood Cells Mol Dis 2004;32:293), post-transplant lymphoproliferative disorders (AJCP 2
effusion lymphoma (AJCP 1996;105:221, AJSP 2004;28:1401), reticulohistiocytoma (variable, AJS
Candida albicans yeast forms (AJCP 2000;113:59); rarely carcinomas (undifferentiated / neuroen
Negative staining (although infiltrating leukocytes are CD45+): red blood cells and their im
carcinomas may be CD45+, AJCP 1998;110:641), follicular dendritic cell sarcoma (AJCP 1995;10
9%, AJCP 2004;121:482), Reed-Sternberg cells in classic Hodgkin's lymphoma (Am J Pathol 19
References: OMIM 151460



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Build Dx Panel | Build Ab Panel | Analyze Results

Enter a search phrase to select a Diagnosis Group (and repeat for a 2 or 3 Dx Group search), set Sensitivity and Minimum Refs, then click Build Panel button.

meso | View All

- **Adenoca CK07 positive CK20 Negative**
  Mesothelioma, NOS
- **Mesothelioma, All**
  Mesothelioma, Biphasic; Proliferation, Mesothelial, NOS; Mesothelioma, Sarcomatoid; Mesothelioma, NOS; Mesothelioma, Epithelioid
- **Mesothelioma, benign proliferations**
  Proliferation, Mesothelial, NOS
- **Mesothelioma, lymphohistiocytoid**

Selected Dxs:

none selected

Set Sensitivity: 1 2 3

Set Minimum Refs: All > 1 > 5

Build Panel

Open Cases

Start date	Case Description

View Panel | Analyze Results | Delete

Diagnosis Group and Antibody Education

Enter a Diagnosis Group or Antibody search phrase and select the desired item.

Learn About a Diagnosis Group:

Learn About an Antibody:

News:

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Ask an Expert | Meta-analysis

Dx Panel for Mesoth...

Antibody					
G-GCS-H					
EPO					
CK 19					
CK 18					
C-MET					
AMAD-2					
AE1					
PKK1					
CAM 5.2					
35BH11					
H-CALDESMON					
AE1_AE3					
KERATIN-PAN					
CK 05					
CD44H					
MESOTHELIN					
CA 15-3	89%	19	76 - 100		1
PODOPLANIN	85%	503			6
CALRETININ	85%	1,345	83 - 87		31
CK 05_06	83%	646	80 - 86		18
34BE12	82%	82	73 - 90		3
N-CADHERIN	81%	242	76 - 86		6

References For CALRETININ: Close X

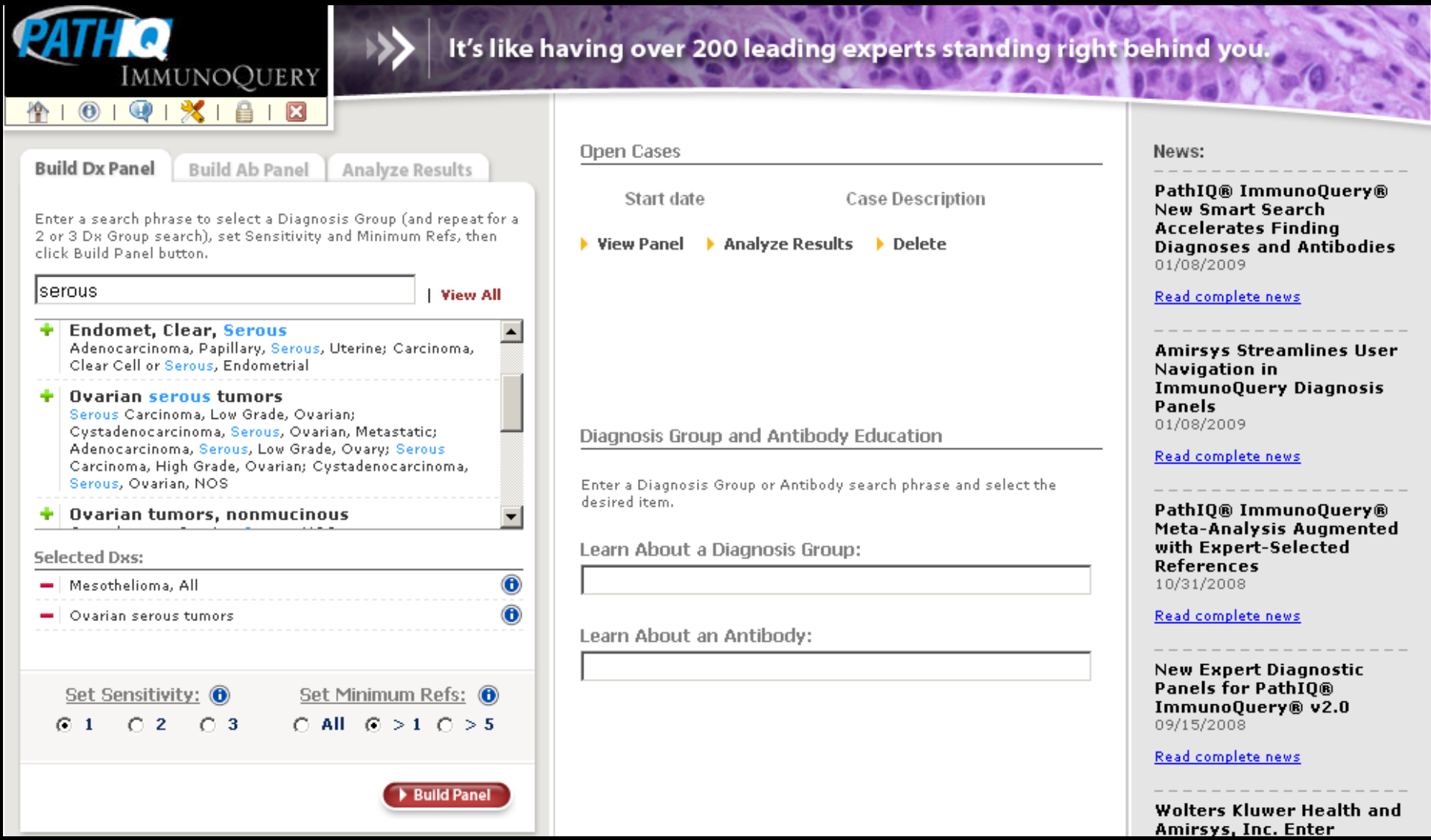
Articles Sorted by relevance: 31

Year Published: 2008
Author(s): Lyons-Boudreaux V, Mody DR, Zhai J, Coffey D
Article: Cytologic malignancy versus benignancy: how useful are the "newer" markers in body fluid cytology?
Publication: ARCH PATHOL LAB MED. 132:23-28

Year Published: 2006
Author(s): BARNETSON,R.J. , BURNETT,R.A. , DOWNIE,I. , HARPER,C.M. , ROBERTS,F.
Article: IMMUNOHSTIOCHEMICAL ANALYSIS OF PERITONEAL MESOTHELIOMA AND PRIMARY AND SECONDARY SEROUS CARCINOMA OF THE PERITONEUM. ANTIBODIES TO ESTROGEN AND PROGESTERONE RECEPTORS ARE USEFUL.
Publication: AM J CLIN PATHOL. 125 :67-76

Year Published: 2006
Author(s): WINSTANLEY,A.M. , LANDON,G. , BERNEY,D. , MINHAS,S. , FISHER,C. , PARKINSON,M.C.
Article: THE IMMUNOHISTOCHEMICAL PROFILE OF MALIGNANT MESOTHELIOMAS OF THE TUNICA VAGINALIS. A STUDY OF 20 CASES.
Publication: AM J SURG PATHOL. 30 :1-6

Year Published: 2003
Author(s): LUGLI,A. , FORSTER,Y. , HAAS,P. , NOCITO,A. , BUCHER,C. , BISSIG,H. , MIRLACHER,M. , STORZ,M. , MIHATSCH,M.J. , SAUTER,G.
Article: CALRETININ EXPRESSION IN HUMAN NORMAL AND NEOPLASTIC TISSUES: A TISSUE MICROARRAY ANALYSIS ON 5233 TISSUE SAMPLES.
Publication: HUM PATHOL. 34 :994-1000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Build Ab Panel
Analyze Results
Enter a search phrase to select a Diagnosis Group (and repeat for a 2 or 3 Dx Group search), set Sensitivity and Minimum Refs, then click Build Panel button.
serous
View All
Endomet, Clear, Serous
Adenocarcinoma, Papillary, Serous, Uterine; Carcinoma, Clear Cell or Serous, Endometrial
Ovarian serous tumors
Serous Carcinoma, Low Grade, Ovarian; Cystadenocarcinoma, Serous, Ovarian, Metastatic; Adenocarcinoma, Serous, Low Grade, Ovary; Serous Carcinoma, High Grade, Ovarian; Cystadenocarcinoma, Serous, Ovarian, NOS
Ovarian tumors, nonmucinous
Selected Dxs:
Mesothelioma, All
Ovarian serous tumors
Set Sensitivity:
1 2 3
Set Minimum Refs:
All > 1 > 5
Build Panel
Open Cases
Start date
Case Description
View Panel
Analyze Results
Delete
Diagnosis Group and Antibody Education
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Wolters Kluwer Health and Amirsys, Inc. Enter

	Mesothelioma, All			Ovarian Serous Tumors		
	Positive	Cases	vs2	Positive	Cases	vs1
ERP NUCLEAR	0%	71		95%	63	
H-CALDESMON	97%	70		5%	40	
MOC-31	8%	404		98%	62	
BER-EP4	10%	1,421		97%	99	
S-100 CYTOPLASMIC/NUCLEAR	5%	208		73%	52	
TAG-72	5%	1,545		73%	85	
LEWIS-Y	8%	266		73%	45	
E-CADHERIN MEMBRANE/CYTOPLASMIC	35%	265		100%	20	
CALRETININ Nucleus/Cytoplasm	85%	1,345		22%	232	
CA 19-9 CYTOPLASMIC	1%	152		64%	85	
PRP NUCLEAR	0%	22		62%	63	
THROMBOMOD CYTOPLASMIC	65%	1,039		5%	108	
PODOPLANIN MEMBRANE/CYTOPLASMIC	85%	503		28%	111	

	Mesothelioma, All			Ovarian Serous Tumors		
	Positive	Cases	vs2	Positive	Cases	vs1
CK 05 CYTOPLASMIC	92%	48		57%	14	
RCC	21%	193		0%	22	
HBME-1 CYTOPLASMIC/MEMBRANE	79%	687		100%	16	
N-CADHERIN	81%	242		100%	20	
MESOTHELIN CYTOPLASMIC/MEMBRANE	89%	253		99%	70	
CK 20 CYTOPLASMIC	3%	90		11%	98	
KERATIN-PAN CYTOPLASMIC	94%	1,071		100%	3	
MELAN-A103 CYTOPLASMIC	0%	4		6%	16	
INHIBIN cytoplasm	0%	1		4%	23	
AE1 AE3	96%	197		100%	20	
CEA-P	3%	1,066		1%	142	
CEA-M CYTOPLASMIC	2%	1,125		0%	64	
CDX-2 NUCLEAR	0%	65		1%	228	

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Enter a search phrase to select an Antibody (and repeat for a 2 or 3 Antibody search), then click Build Panel button.

kera | View All

- **KERATIN-HMW**
  KERATIN-HMW
- **KERATIN-LMW**
  KERATIN-LMW
- **KERATIN-PAN**
  KERATIN-PAN

Selected Abs:

- VIMENTIN
- KERATIN-PAN

Build Panel

PATHIQ IMMUNOQUERY

Discrete Diagnosis (15)	VIMENTIN			KERATIN-PAN			# of Refs
	Pos	Positive	Cases	Pos	Positive	Cases	
Ewing's Sarcoma, Atypical		44%	9		0%	5	2
Carcinoma, Small Cell, Breast		44%	9		0%	2	2
Medulloblastoma, NOS		42%	57		0%	53	2
Pheochromocytoma, NOS		40%	63		16%	116	4
Stromal Sarcoma, Low Grade		38%	8		0%	6	2
Askin Tumor		37%	19		0%	14	2
Seminoma, Testes		30%	96		21%	170	6
Clear Cell Tumor Of Lung		29%	17		0%	32	5
Alveolar Soft Part Sarcoma		25%	4		0%	3	4
Leiomyoma, Epithelioid		20%	5		15%	13	2
Neuroblastoma, Olfactory		8%	13		8%	38	4
Thymic Carcinoma, Spindle Cell		0%	10		0%	10	1
Solitary Fibrous Tumor, Malignant		0%	1		0%	1	1
Seminoma, Spermatocytic		0%	7		0%	3	2
Sarcoma, Perivascular Epithelioid Cell		0%	4		0%	4	1

HUMAN PROTEIN ATLAS

The human protein atlas shows expression and localization of proteins in a large variety of normal human tissues, cancer cells and cell lines with the aid of immunohistochemistry (IHC) images.

Enter search: search

Advanced search

Or choose a chromosome:

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 X Y

OTHER

Version: **3.1** Atlas updated: **2008-02-15** (release history)
Atlas content: **3014** antibodies and **2,940,744** images.

Knut och Alice Wallenbergs Stiftelse

The HPR project is funded by the Knut & Alice Wallenberg foundation. The atlas is part of the HUPO Human Antibody Initiative (HAI).

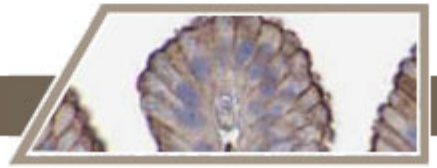
2008-02-15
An update to the Human Protein Atlas has been released. The new version (3.1) displays more tissue information, more cell images has been added, some celltypes has got corrected names. See release history for full details.

2007-10-09
A new feature with immunofluorescent (IF) images generated with confocal microscopy has been added. At present, the subcellular localization for 769 antibodies in three human cell lines are shown.

2007-10-09
A new feature has been added to allow the possibility to search for proteins with specific expression patterns in normal and/or cancer tissues.

KTH VETENSKAP OCH KONST

UPPSALA UNIVERSITET



Advanced Search

Search for proteins expressed in

cytokeratin

Add free search | Add tissue search | Clear search

search

Search Results

Search results for advanced query : **20 hits** (genes)

Choose, if available:
- an Antibody ID to view the annotation data
- a link button to open a new window with Ensembl/NCBI/Uniprot info

#	Gene name	Description	Chr	Links	Antibody ID	Validation
1	Cytokeratin (HMW)	No description			CAB000033	N/A
2	Cytokeratin AE1/AE3	No description			CAB000025	N/A
3	Cytokeratin MNF116	No description			CAB000026	N/A
4	KRT1	Keratin, type II cytoskeletal 1 (Cytokeratin-1) (CK-1) (Keratin-1) (K1) (67 kDa cytokeratin) (Hair alpha protein).	12:q13.13	U N E	CAB002153	N/A
5	KRT10	Keratin, type I cytoskeletal 10 (Cytokeratin-10) (CK-10) (Keratin-10) (K10).	17:q21.2	U N E	CAB000132	N/A
6	KRT13	Keratin, type I cytoskeletal 13 (Cytokeratin-13) (CK-13) (Keratin-13) (K13).	17:q21.2	U E	CAB000133	N/A
7	KRT14	Keratin, type I cytoskeletal 14 (Cytokeratin-14) (CK-14) (Keratin-14) (K14).	17:q21.2	U N E	CAB000134	N/A
8	KRT15	Keratin, type I cytoskeletal 15 (Cytokeratin-15) (CK-15) (Keratin-15) (K15).	17:q21.2	U N E	CAB000135	N/A
9	KRT16	Keratin, type I cytoskeletal 16 (Cytokeratin-16) (CK-16) (Keratin-16) (K16).	17:q21.2	U N E	CAB000136	N/A
10	KRT17	Keratin, type I cytoskeletal 17 (Cytokeratin-17) (CK-17) (Keratin-17) (K17) (39.1).	17:q21.2	U N E	CAB000029 HPA000452 HPA000453 HPA000539	N/A High High High
11	KRT18	Keratin, type I cytoskeletal 18 (Cytokeratin-18) (CK-18) (Keratin-18) (K18).	12:q13.13	U N E	CAB000008 CAB000030 HPA001605	N/A N/A Medium
12	KRT19	Keratin, type I cytoskeletal 19 (Cytokeratin-19) (CK-19) (Keratin-19) (K19).	17:q21.2	U N E	CAB000031 HPA002465	N/A High
13	KRT2	Keratin, type II cytoskeletal 2 epidermal	12:q13.13	U N E	HPA006200	Medium

Search

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 X Y OTHER

search

Show search results:

1 to 20

help for this page

CAB000025 expression profiles. Validation score: N/A

Gene data

Description: **N/A**
Chromosome: **N/A**
EnsEMBL ID: **N/A**

Normal Tissues - IHC

alph. sort order

Adrenal gland	cortical cells	**Lymph node**	lymphoid cells outside reaction centra
Appendix	glandular cells		reaction center cells
	lymphoid cells	**Nasopharynx**	respiratory epithelial cells
Bone marrow	bone marrow poietic cells	**Oral mucosa**	squamous epithelial cells
Breast	glandular cells	**Ovary**	follicle cells
Bronchus	respiratory epithelial cells		ovarian stromal cells
Cerebellum	cells in granular layer	**Pancreas**	exocrine glandular cells
	cells in molecular layer		islet cells
	purkinje cells	**Parathyroid gland**	glandular cells
Cerebral cortex	glial cells	**Placenta**	decidual cells
	neuronal cells		trophoblastic cells
Cervix, uterine	glandular cells	**Prostate**	glandular cells
	squamous epithelial cells	**Rectum**	glandular cells
Colon	glandular cells	**Salivary gland**	glandular cells
Corpus, uterine 1	cells in endometrial stroma	**Seminal vesicle**	glandular cells
	glandular cells	**Skeletal muscle**	myocytes
Corpus, uterine 2	cells in endometrial stroma	**Skin**	adnexal cells
	glandular cells		epidermal cells
Duodenum	glandular cells	**Small intestine**	glandular cells
Epididymis	glandular cells	**Smooth muscle**	smooth muscle cells
Esophagus	squamous epithelial cells	**Soft tissue 1**	mesenchymal cells
Fallopian tube	glandular cells	**Soft tissue 2**	mesenchymal cells
Gall bladder	glandular cells	**Spleen**	cells in red pulp
Heart muscle	myocytes		cells in white pulp
Hippocampus	glial cells	**Stomach 1**	glandular cells
	neuronal cells	**Stomach 2**	glandular cells
Kidney	cells in glomeruli	**Testis**	cells in seminiferus ducts
	cells in tubules		leydig cells
Lateral ventricle	glial cells	**Thyroid gland**	glandular cells
	neuronal cells	**Tonsil**	lymphoid cells outside reaction centra
Liver	bile duct cells		reaction center cells
	hepatocytes		squamous epithelial cells
Lung	alveolar cells	**Urinary bladder**	urothelial cells
	macrophages	**Vagina**	squamous epithelial cells
		Vulva/anal skin	squamous epithelial cells

Navigation

Home
Search result
CAB000025
Expression profiles
Normal tissues
Cancer tissues
Cells IHC
Antibody info

Search

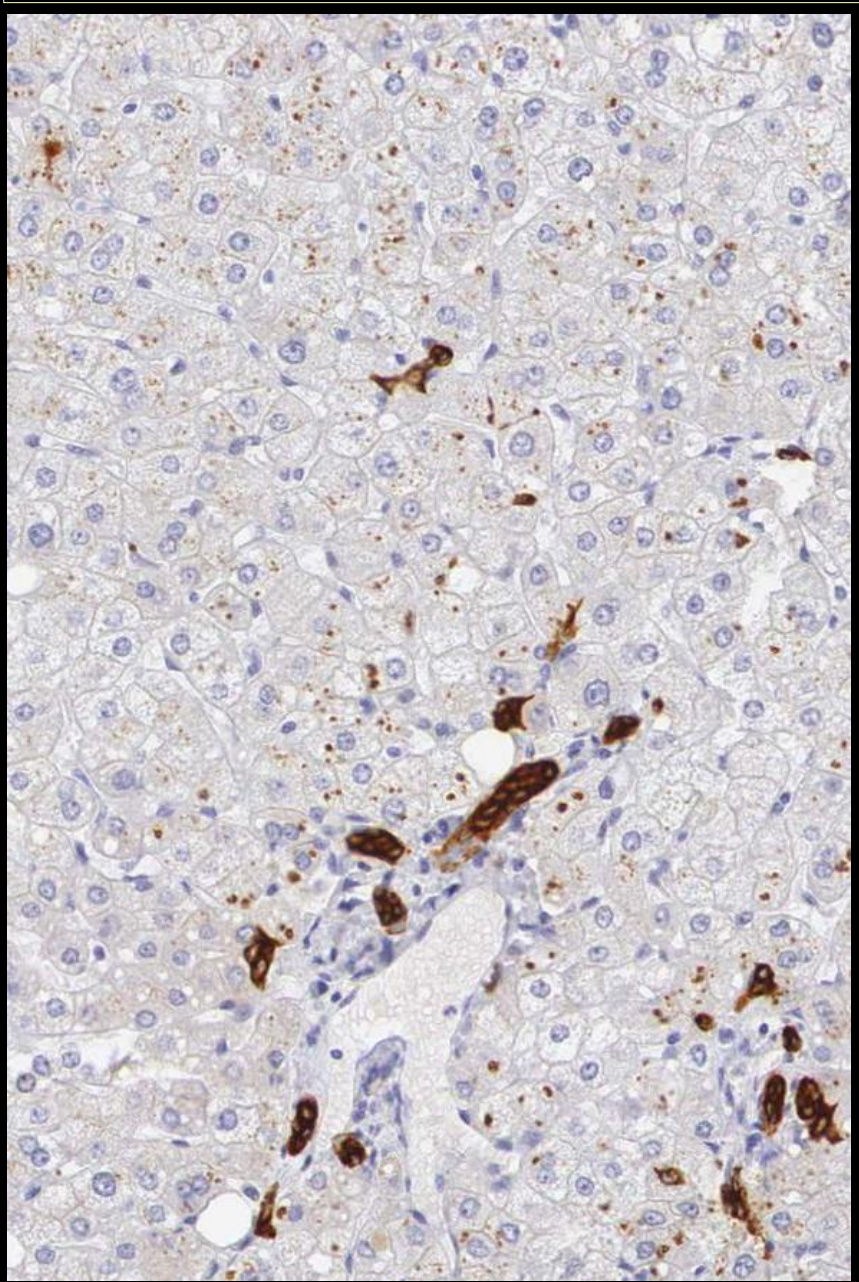
search

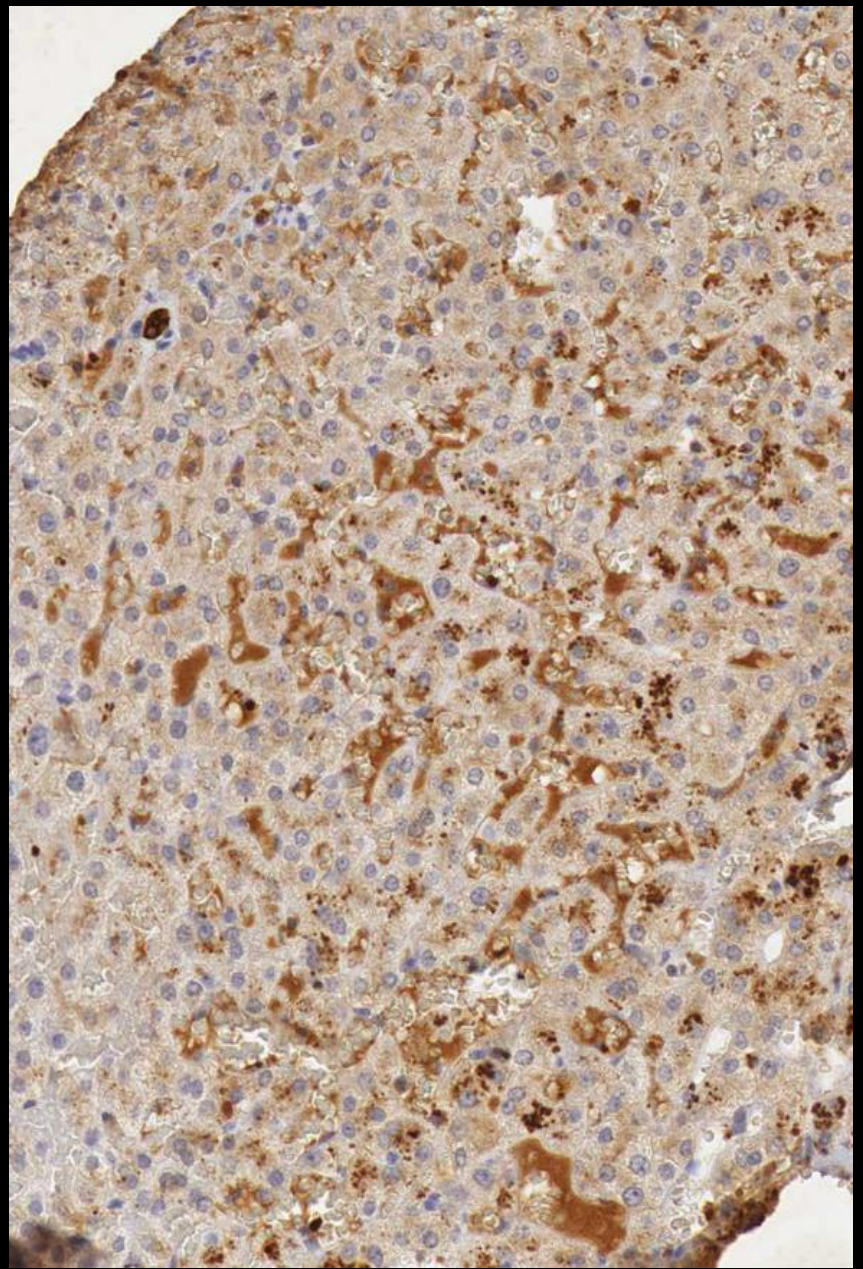
Protein expression

- Strong
- Moderate
- Weak
- Negative
- Not representative

help for this page

Human protein Atlas – AE1/AE3

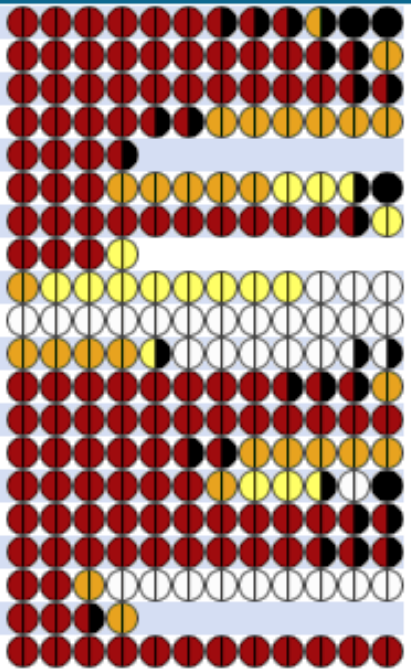




alph. sort order

Cancer Tissues - IHC

- Breast cancer
- Cervical cancer
- Colorectal cancer
- Endometrial cancer
- Head & neck cancer
- Liver cancer
- Lung cancer
- Malignant carcinoid
- Malignant glioma
- Malignant lymphoma
- Malignant melanoma
- Ovarian cancer
- Pancreatic cancer
- Prostate cancer
- Renal cancer
- Skin cancer
- Stomach cancer
- Testis cancer
- Thyroid cancer
- Urothelial cancer



Cell lines - IHC

Myeloid

- HEL
- HL-60
- HMC-1
- K-562
- NB-4
- THP-1
- U-937

Lymphoid

- Daudi
- HDLM-2
- Karpas-707
- KM3
- LP-1
- MOLT-4
- RPMI-8226
- U-266/70
- U-266/84
- U-698

Abdominal

- CACO-2
- CAPAN-2
- Hep-G2

Breast, female reproductive system

- AN3-CA
- EFO-21
- HeLa
- MCF-7
- SiHa
- SK-BR-3

Urinary, male reproductive system

- NTERA-2
- PC-3
- RT-4

Skin

- A-431
- HaCaT
- SK-MEL-30

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Poorly differentiated cancer from an unknown primary site

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Michael E Ross, MD

Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Jul 2013. | **This topic last updated:** jan 3, 2013.

INTRODUCTION — Cancer of unknown primary site (CUP) is a relatively common clinical entity, with about 4 to 5 percent having an apparent primary at presentation [1]. Within this category, tumors from many primary sites with varying biology a of unknown primary site are adenocarcinomas, and can be recognized by routine histologic examination. However, 20 to 25 differentiated, and cannot be precisely characterized by histologic examination. About 80 percent of these poorly differentiat carcinoma, and are termed "poorly differentiated carcinoma" after initial pathologic examination. In the remainder, histologic diagnosis of "poorly differentiated neoplasm", signifying the inability to distinguish between carcinoma, melanoma, lymphom tumor.

As accurate a diagnosis as possible is essential since the therapy for various tumors can be quite different and may be cur diagnostic approach to poorly differentiated cancers of unknown primary site will be reviewed here, along with the prognostic

Other relevant topics include:

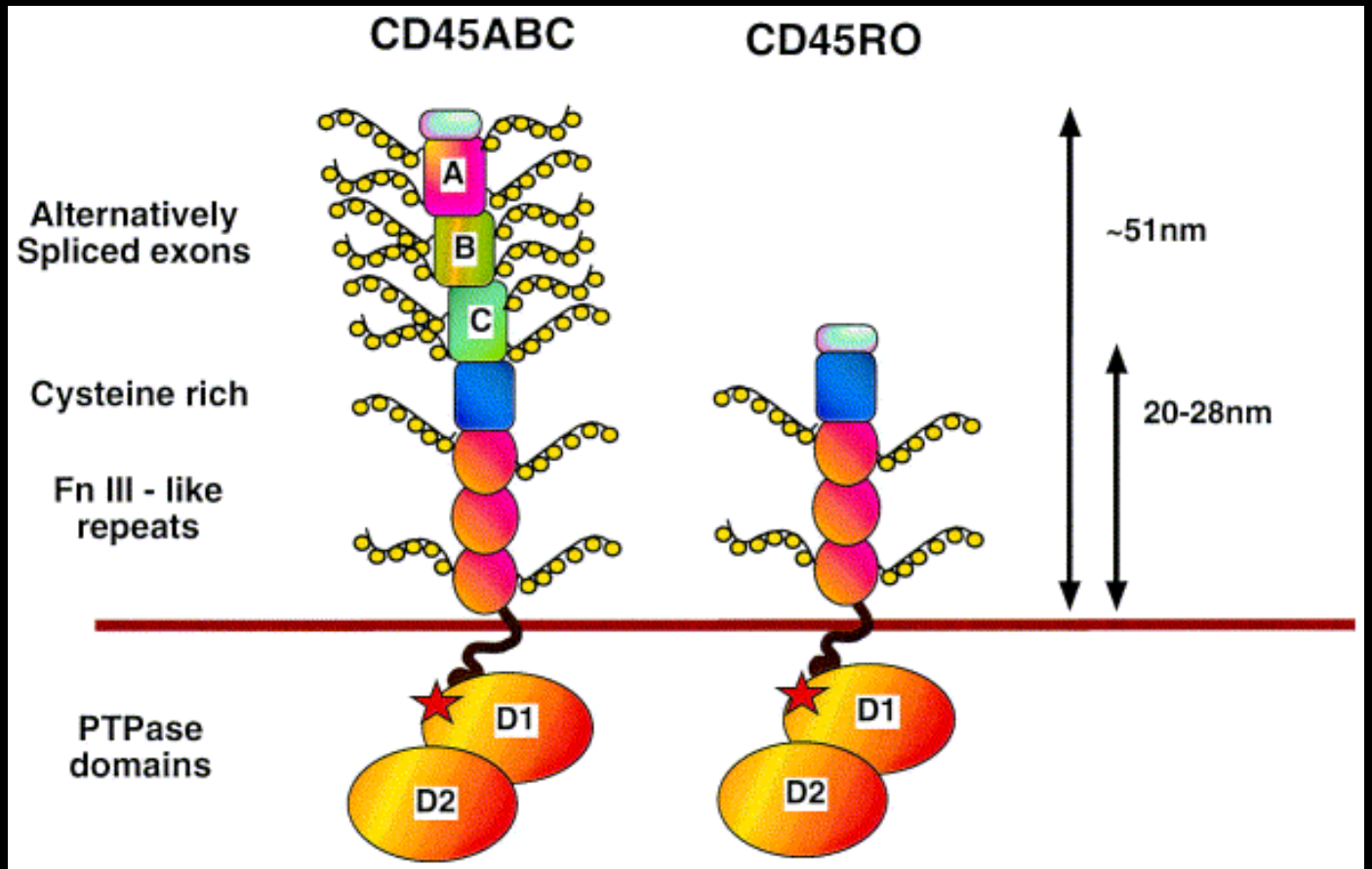
- (See "Overview of the classification and management of cancers of unknown primary site".)
- (See "Adenocarcinoma of unknown primary site".)
- (See "Squamous cell carcinoma of unknown primary site".)
- (See "Head and neck squamous cell carcinoma of unknown primary".)
- (See "Neuroendocrine cancer of unknown primary site".)
- (See "Axillary node metastases with occult primary breast cancer".)

Primary panel for the unknown primary tumour

”Real”	CD45	CK	S-100	VIM
Haemato-lymphoid neoplasms	+/(-)	-/(+)	-/(+)	+/(-)
Epithelial neoplasms	-	+/(-)	-/+	-/+
Mesothelial neoplasms	-	+	-	+
Mesenchymal and neuronal neoplasms	-	-/(+)	-/+	+
Non-neuronal neuroepithelial neoplasms	-	-/(+)	+	+
Germ cell neoplasms	-	-/+	-/+	+

CD45 - Leucocyte common antigen (LCA)

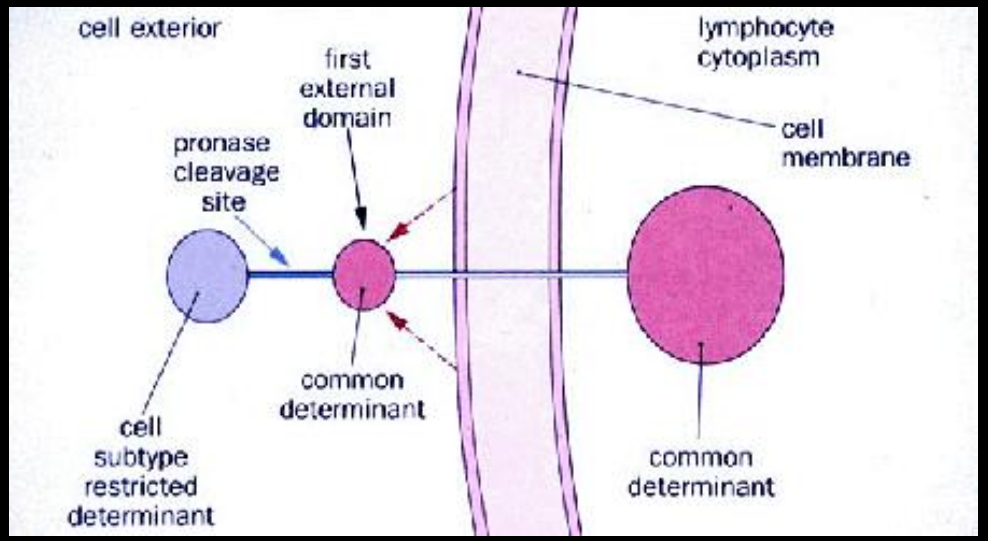
- Transmembrane protein tyrosin phospatase essential for haematopoietic signal transduction and cell activation
- Membrane associated component: 5 isotypes
- Intracellular component: one common type



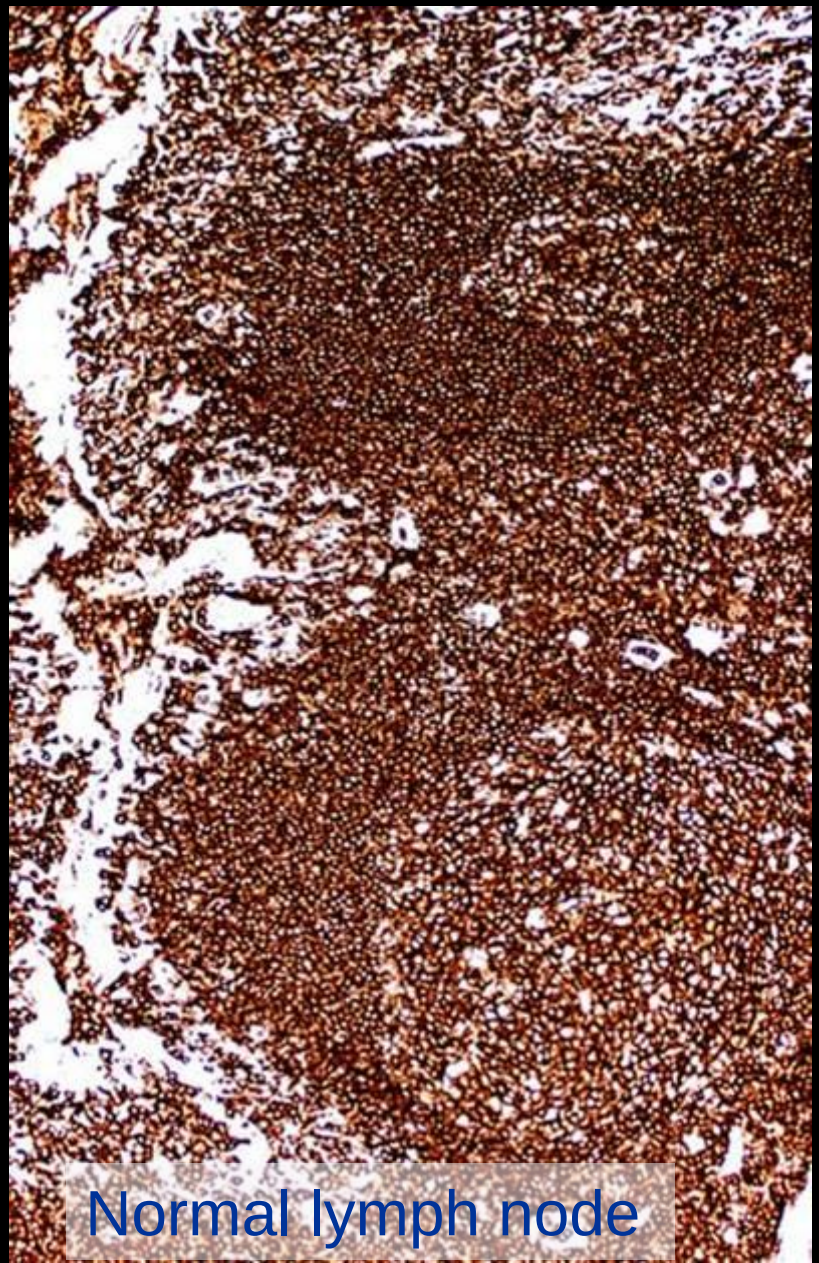
CD45 - Leucocyte common antigen (LCA)

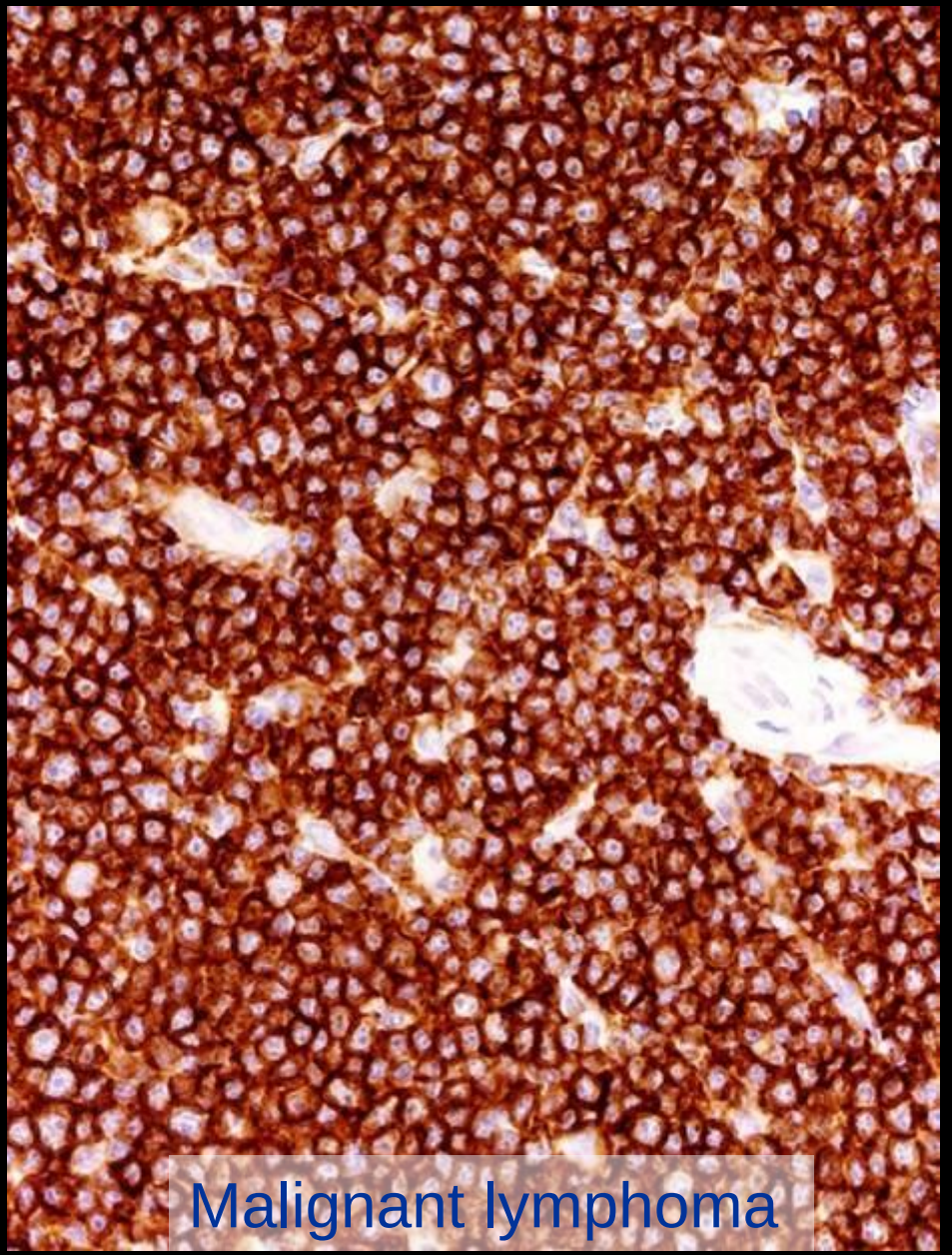
- Transmembrane protein tyrosin phospatase essential for haematopoietic signal transduction and cell activation
- Membrane associated component: 5 isotypes
- Intracellular component: one common type

- Large majority of haematolymphoid cells
- Lost in maturing erythocytes, megakaryocytes and plasmacells
- ”Never” found in non-haematolymphoid cells



CD45 - Leucocyte common antigen (LCA)



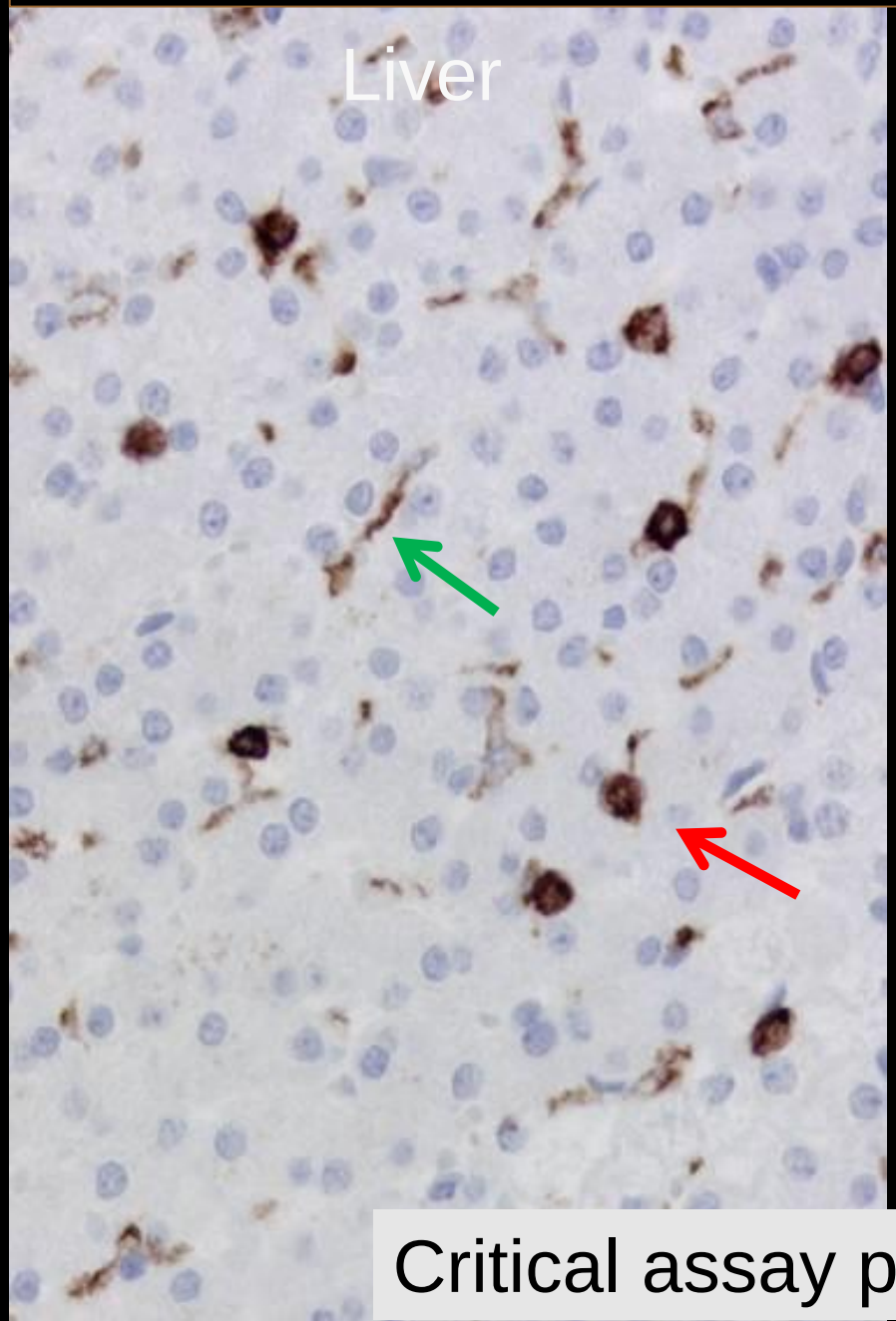


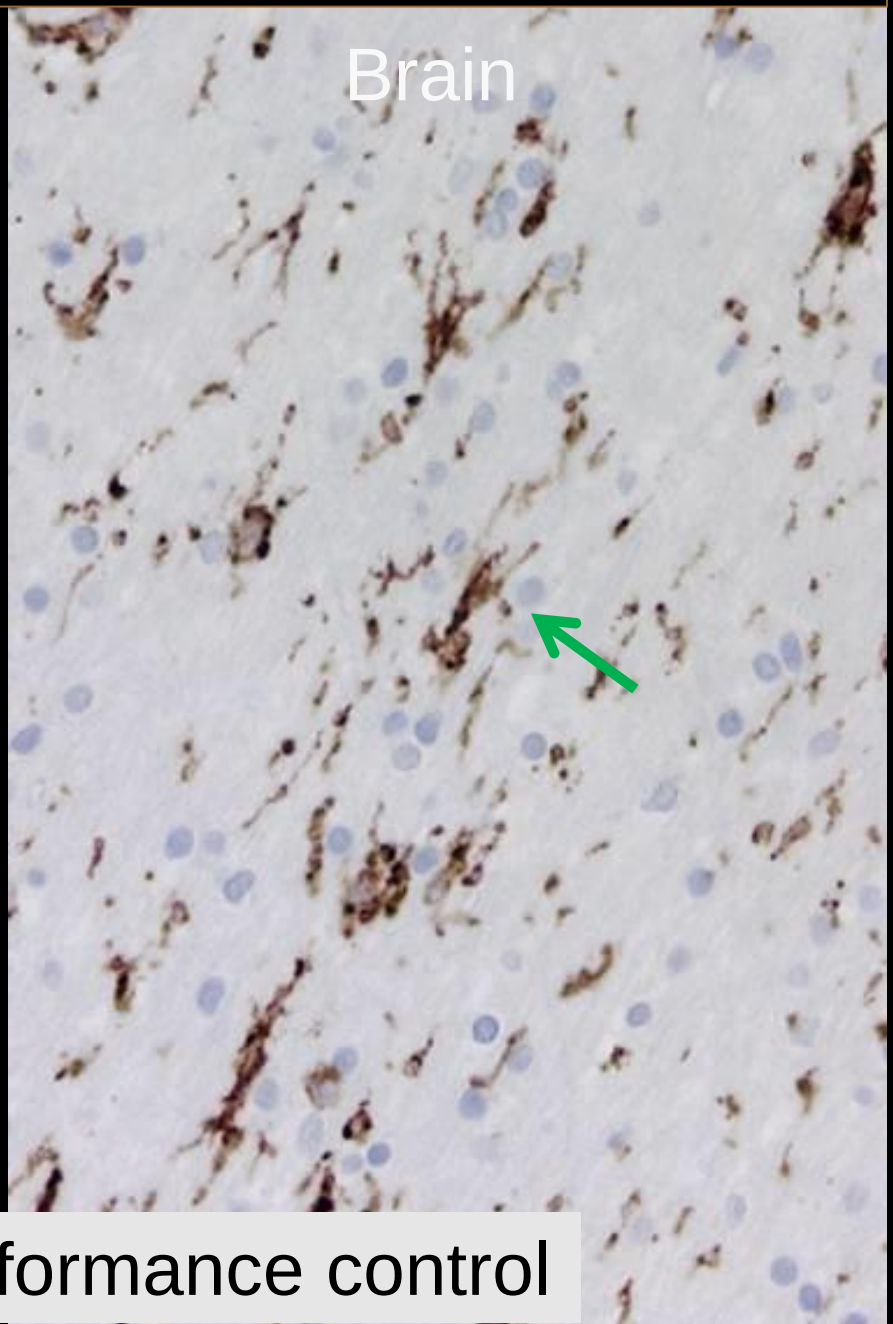
CD45 - Leucocyte common antigen (LCA)

- **More than 90% of lymphomas are positive**

- Negative on:
  - some Acute Lymphoblastic Leukaemia/LBL
  - plasma cell malignancies
  - HR-S cells in classic Hodgkin Lymphoma
  - some Anaplastic Large Cell Lymphoma (ALCL)
  - ALK+ Large B-Cell Lymphoma
- Exceptionally positive in non haematol. tumours ?

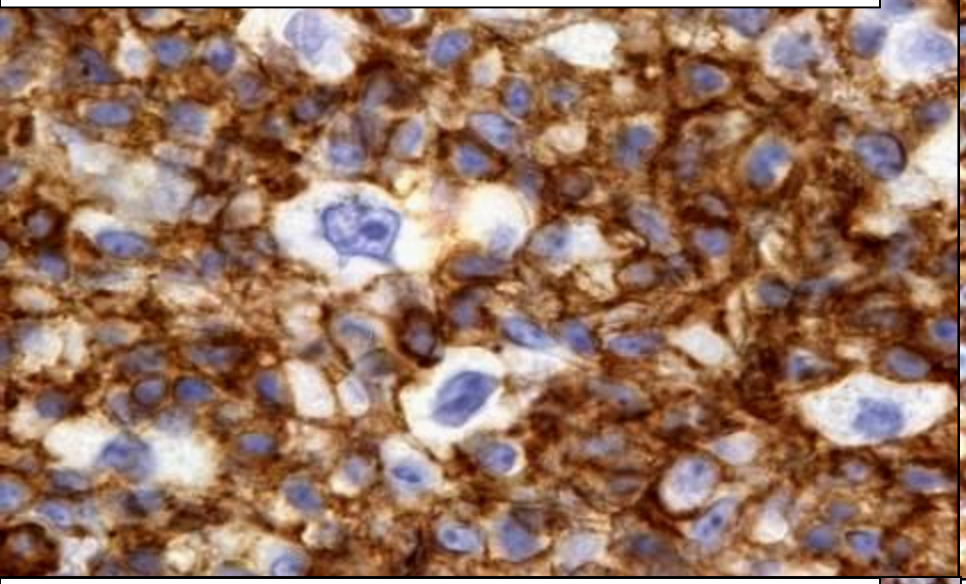
CD45 - Leucocyte common antigen (LCA)



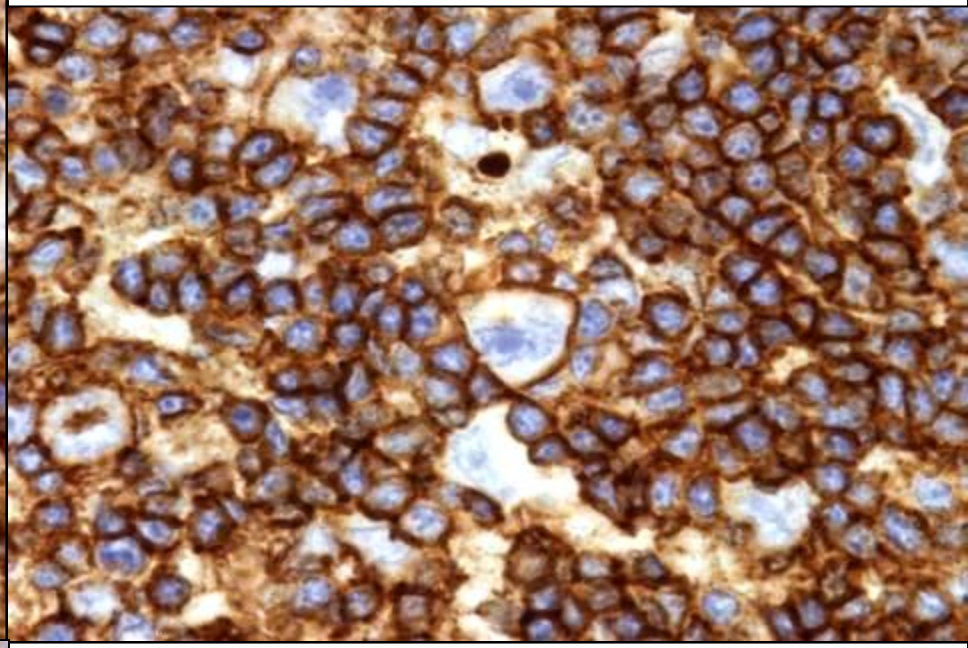


Critical assay performance control

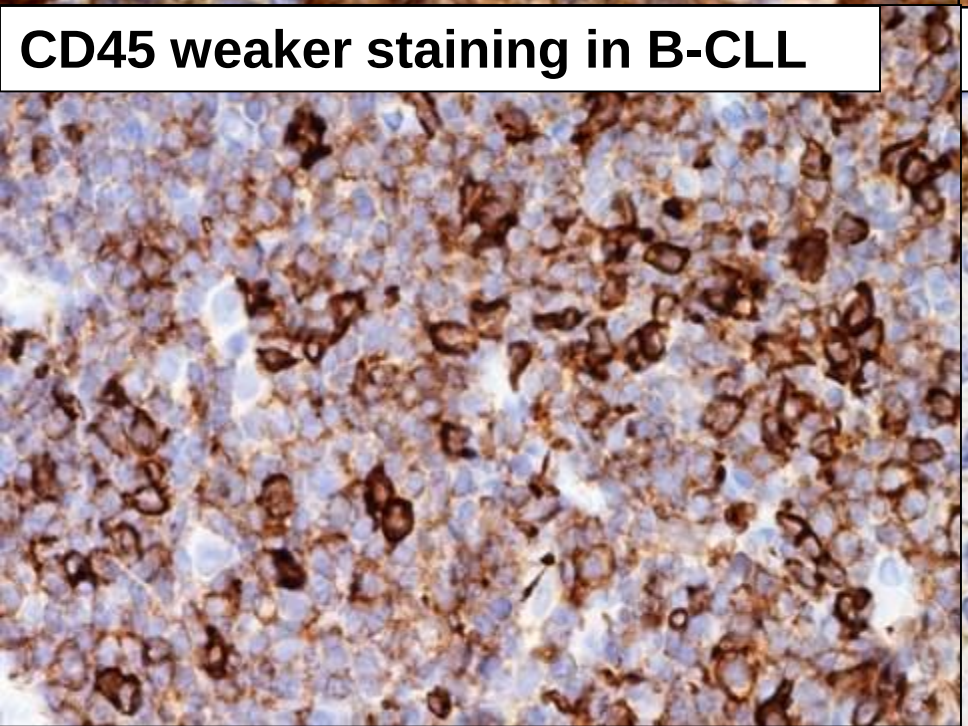
CD45 negative HRS cells in classic Hodgkin Lymphoma



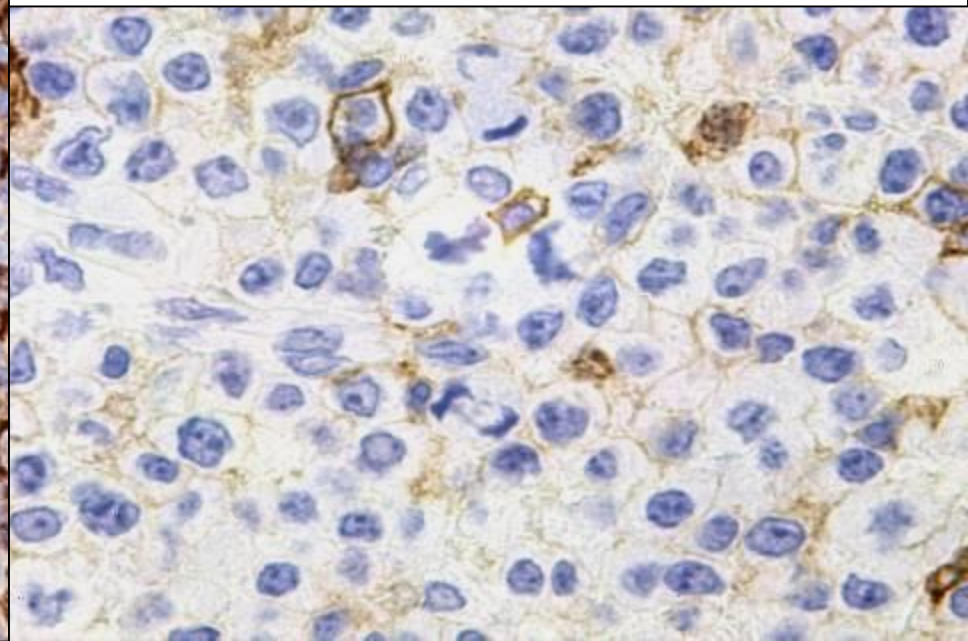
CD45 positive LH cells in NLPHL



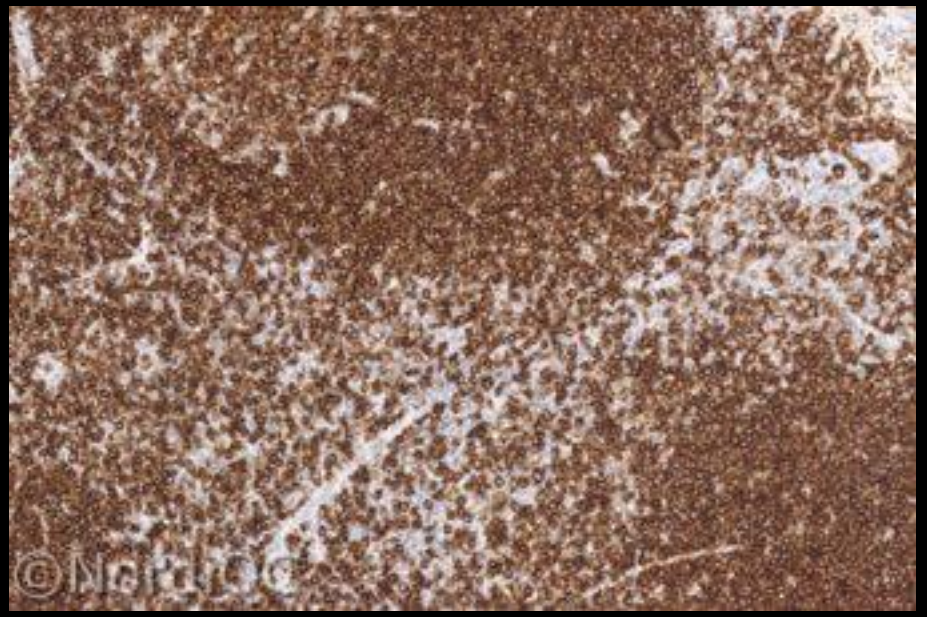
CD45 weaker staining in B-CLL



CD45 weak reactivity in ALCL

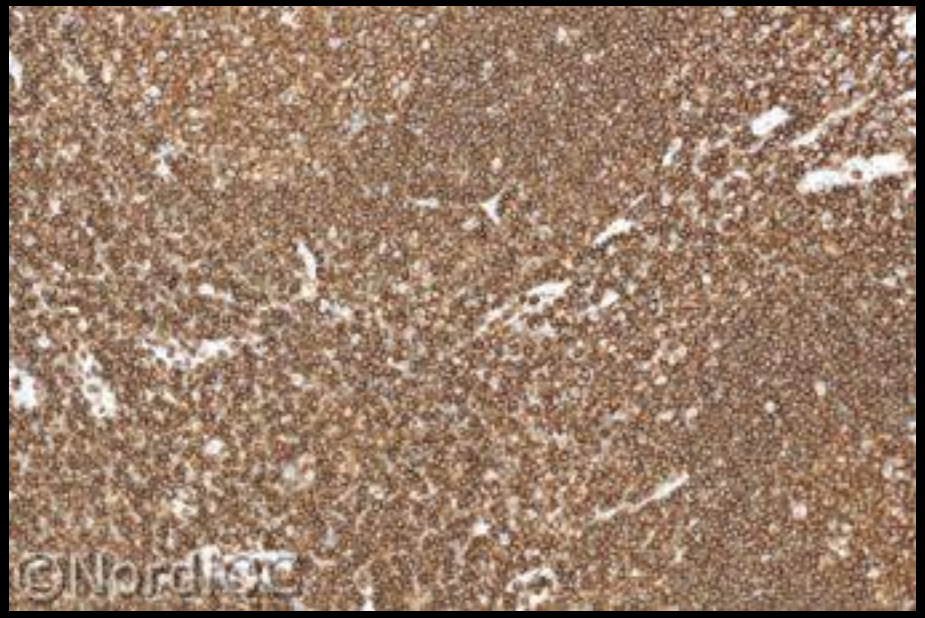


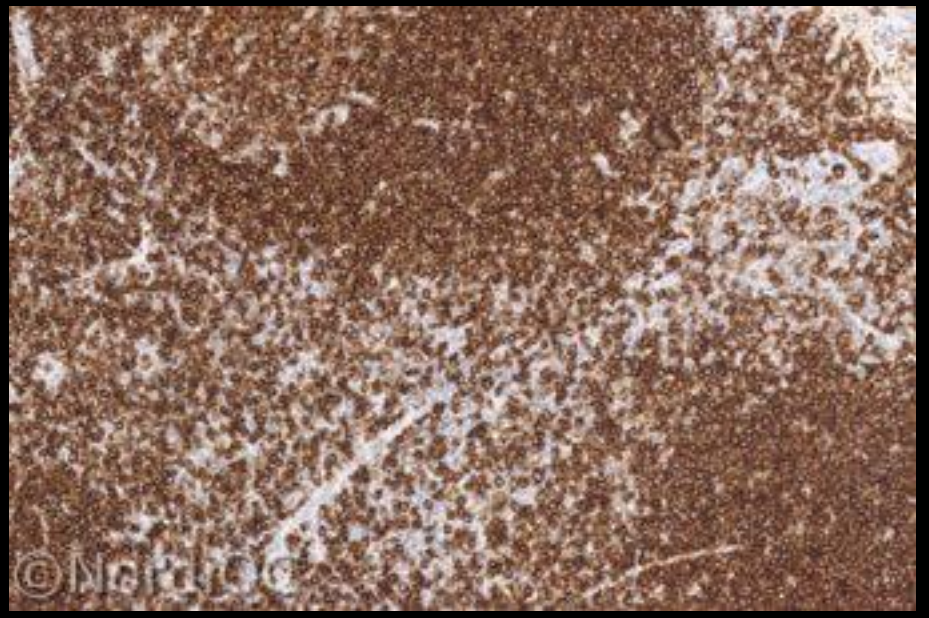
CD45 – NordiQC run 37 2013

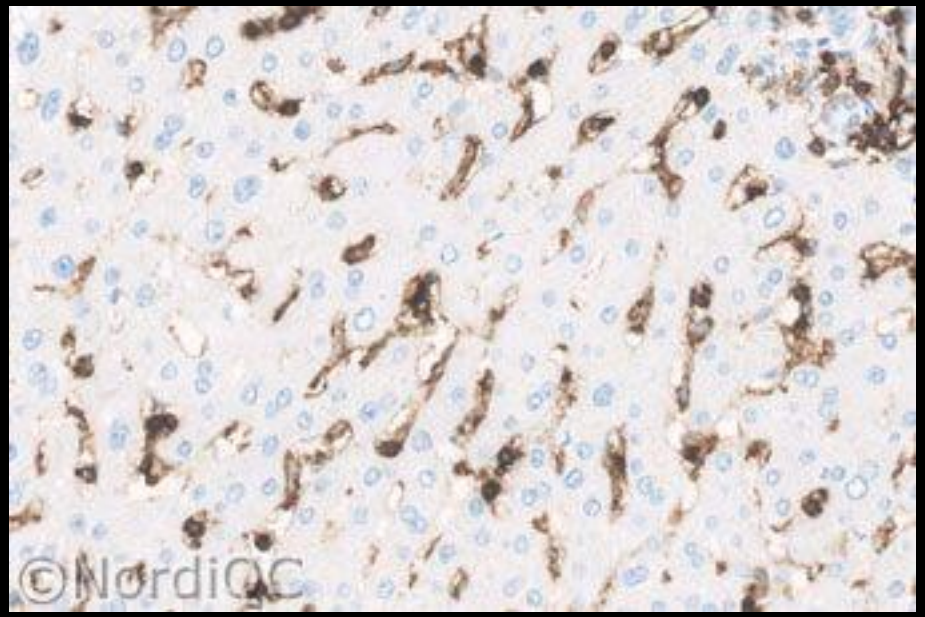


Which is best?

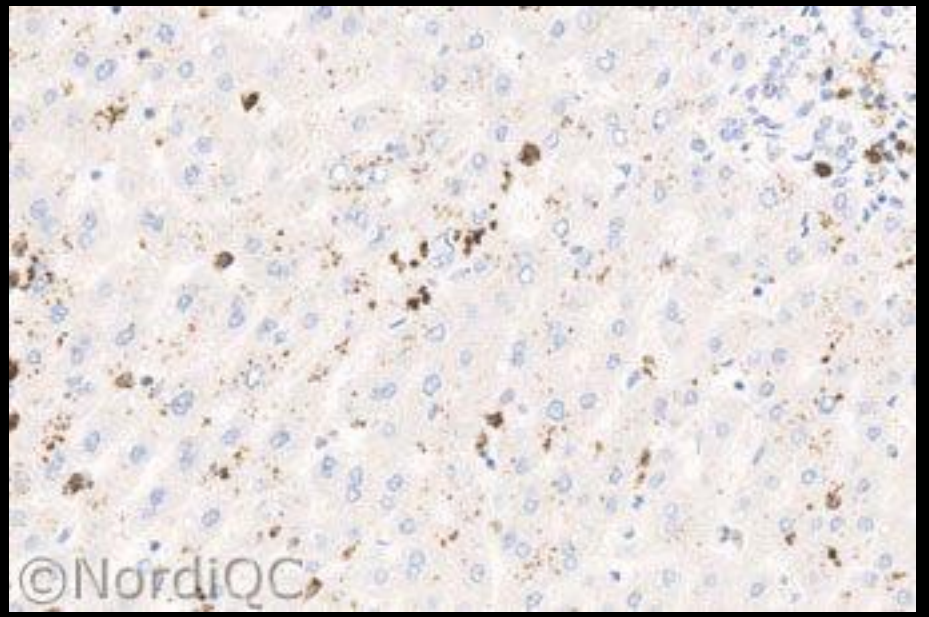
CD45 – NordiQC run 37 2013







Optimal



Insufficient

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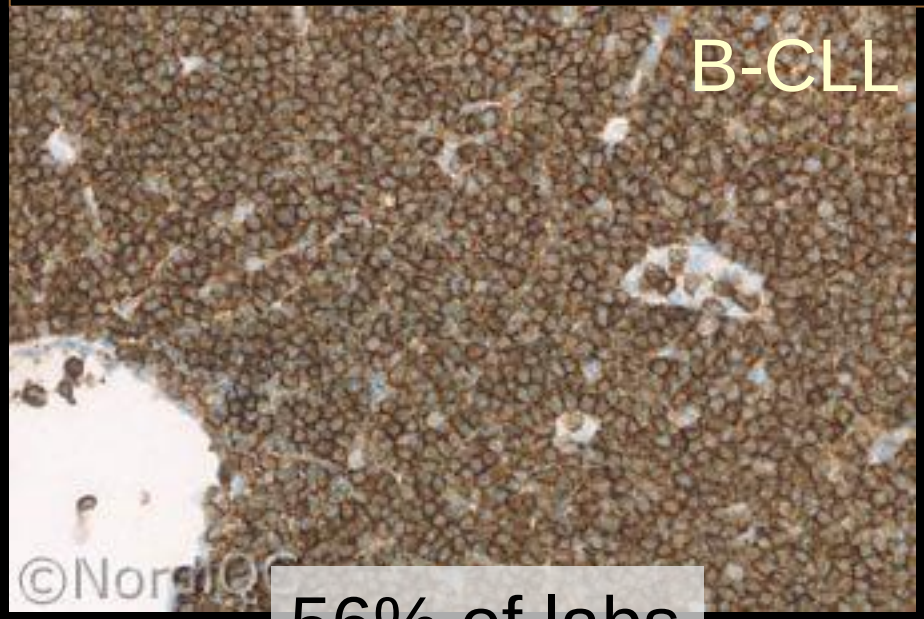
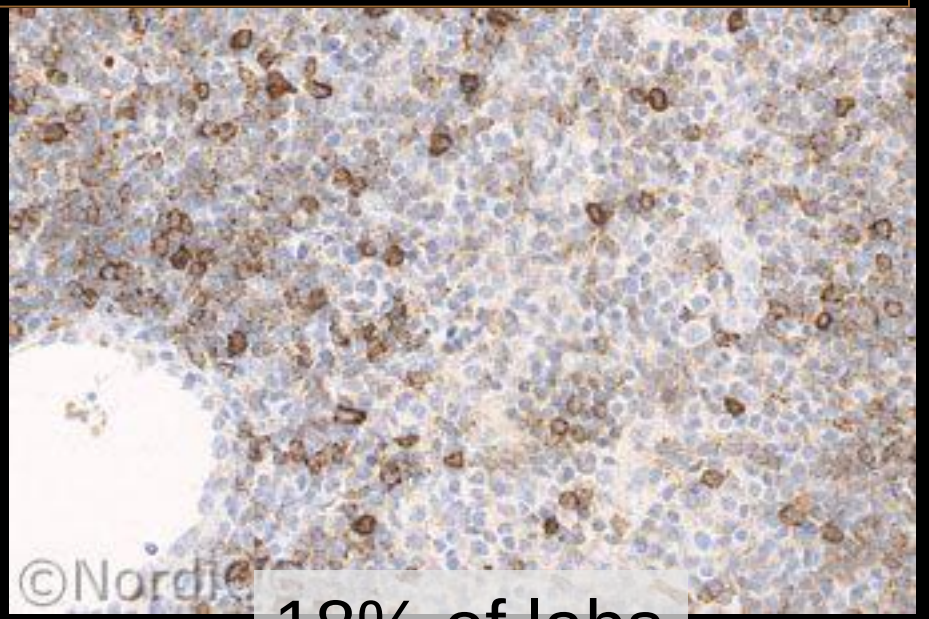
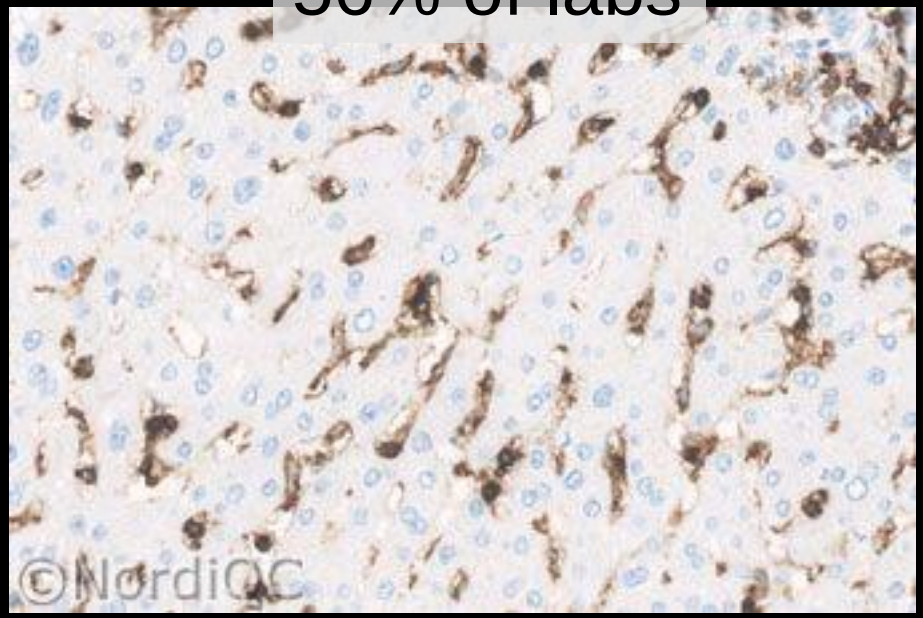
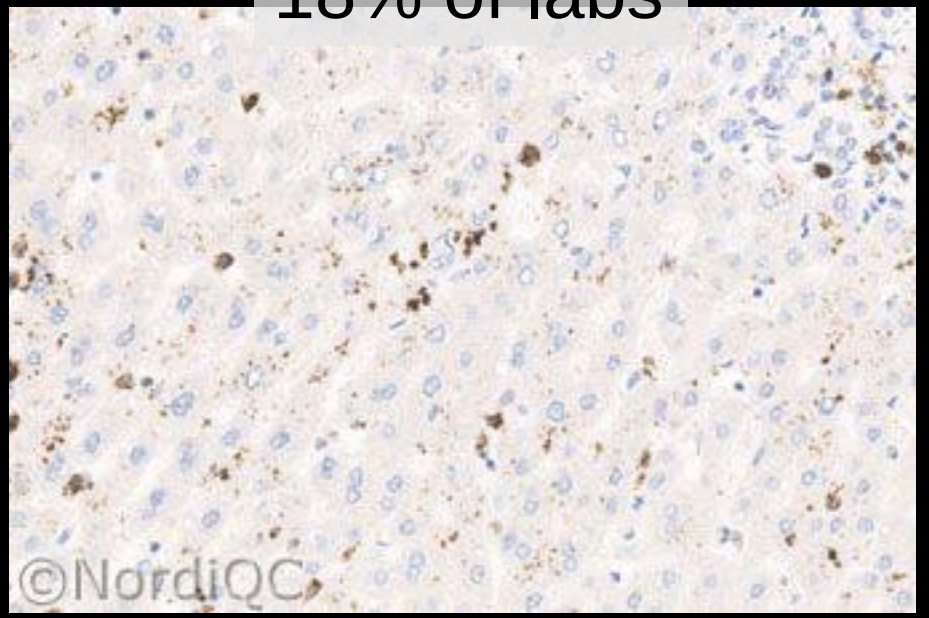




56% of labs

18% of labs



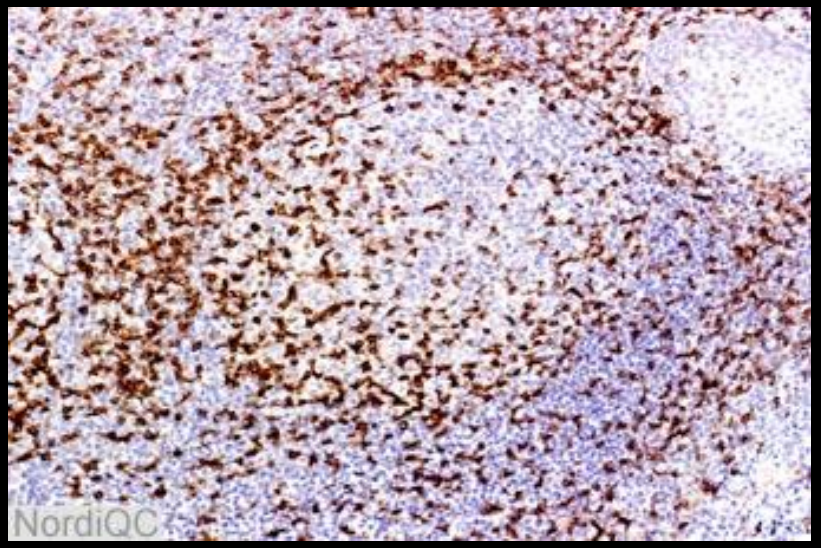


Optimal

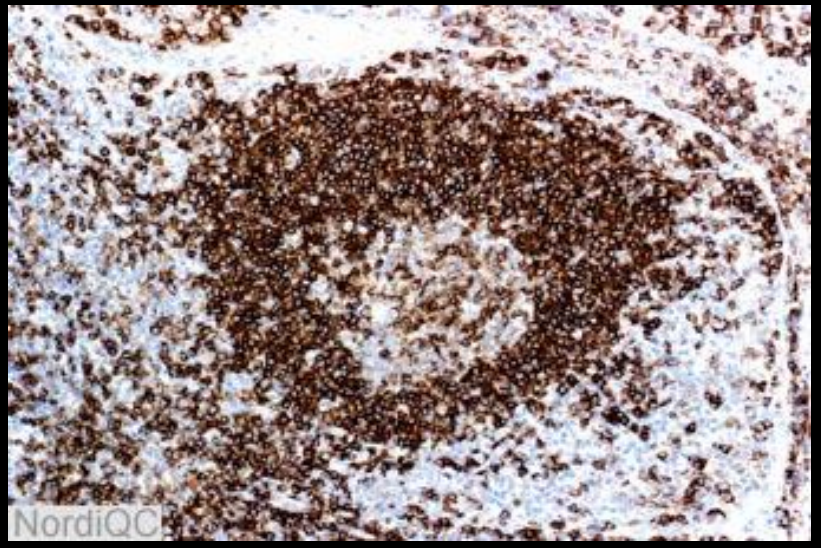
Insufficient

CD45 - Leucocyte common antigen (LCA)

Lymph node/Tonsil



- CD45 RO ~ T-cells



- CD45 RA ~ B-cells

CD45 - Leucocyte common antigen (LCA)

Cytokeratin-Positive, CD45-Negative Primary Centroblastic Lymphoma of the Adrenal Gland

A Potential for a Diagnostic Pitfall

Ludvik R. Donner, MD, PhD; Frank E. Mott, MD; Isaac Tafur, MD

● We report a case of cytokeratin-positive, CD45-negative primary polymorphic centroblastic lymphoma of the adrenal gland. Additional immunostaining, which demonstrated positivity for CD20 and κ light chain, as well as detection of the monoclonal rearrangement of the immunoglobulin heavy chain gene, helped to establish the diagnosis of lymphoma and to rule out an initially favored diagnosis of poorly differentiated carcinoma.

(*Arch Pathol Lab Med.* 2001;125:1104–1106)

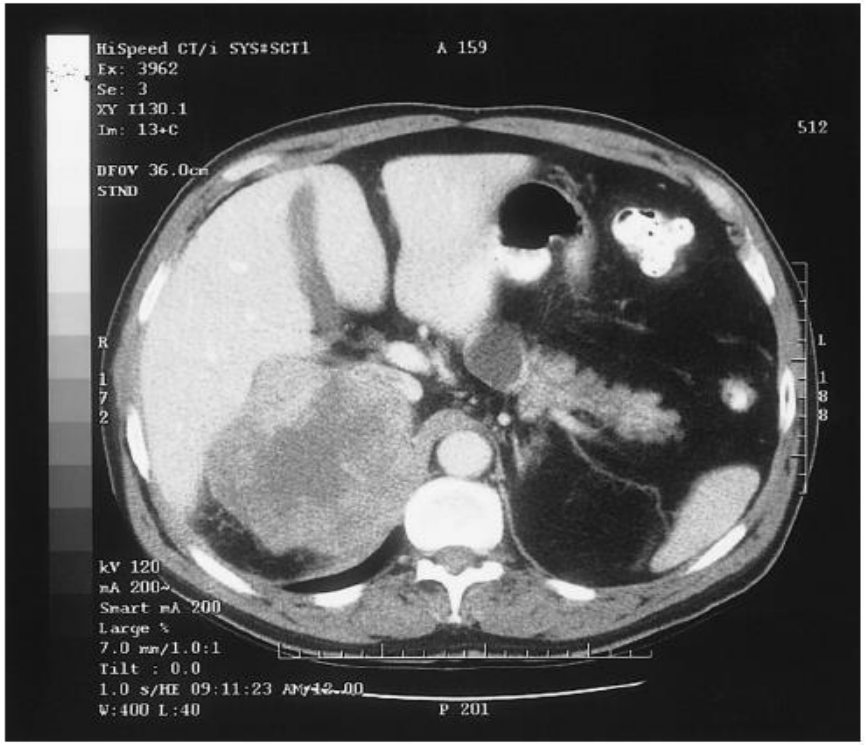


Figure 1. *Computed tomography of a large right suprarenal mass involving the liver.*

CD45 - Leucocyte common antigen (LCA)

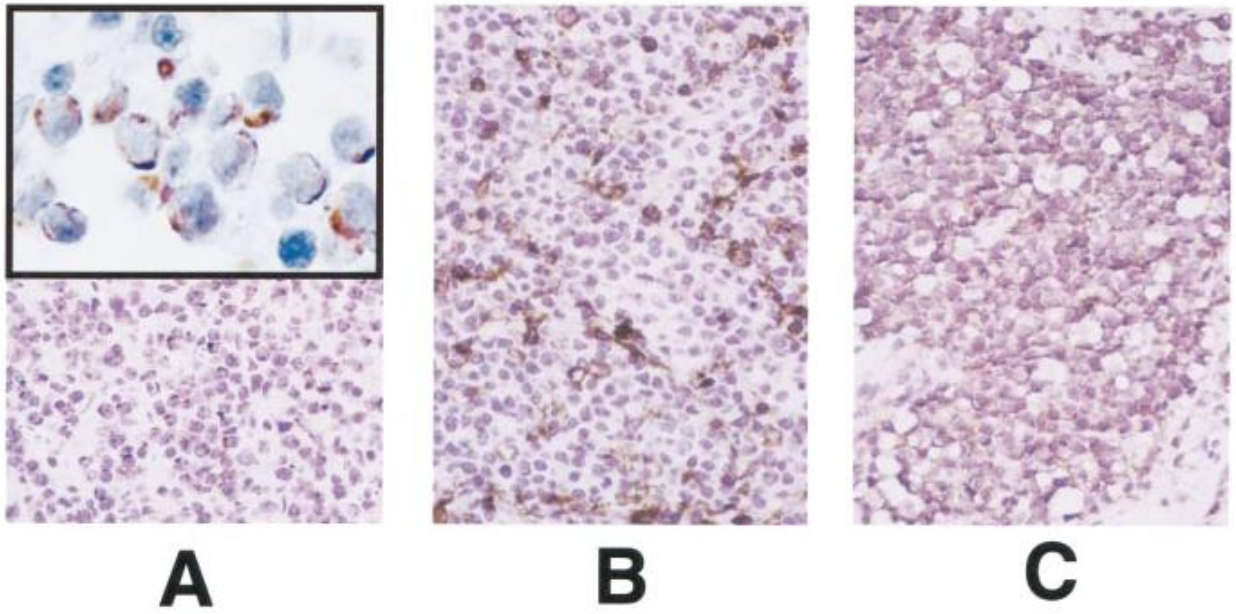


Figure 3. *Note immunoreactivity of the lymphoma cells for cytokeratin (A) and CD20 (C) but not CD45 (B) (original magnification ×100, inset ×250).*

Molecular Biologic Findings

Monoclonal rearrangement of the immunoglobulin heavy chain gene was identified by polymerase chain reaction (data not shown).

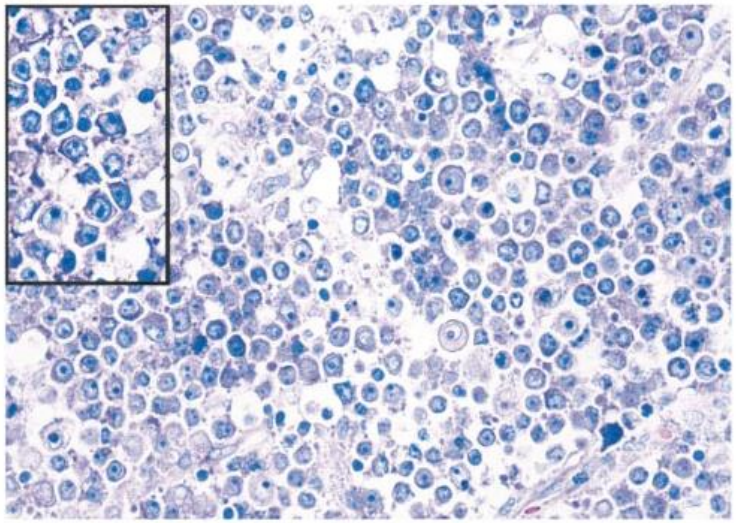


Figure 2. *Light microscopic appearance of the tumor (Giemsa stain, original magnification ×100, inset ×250).*

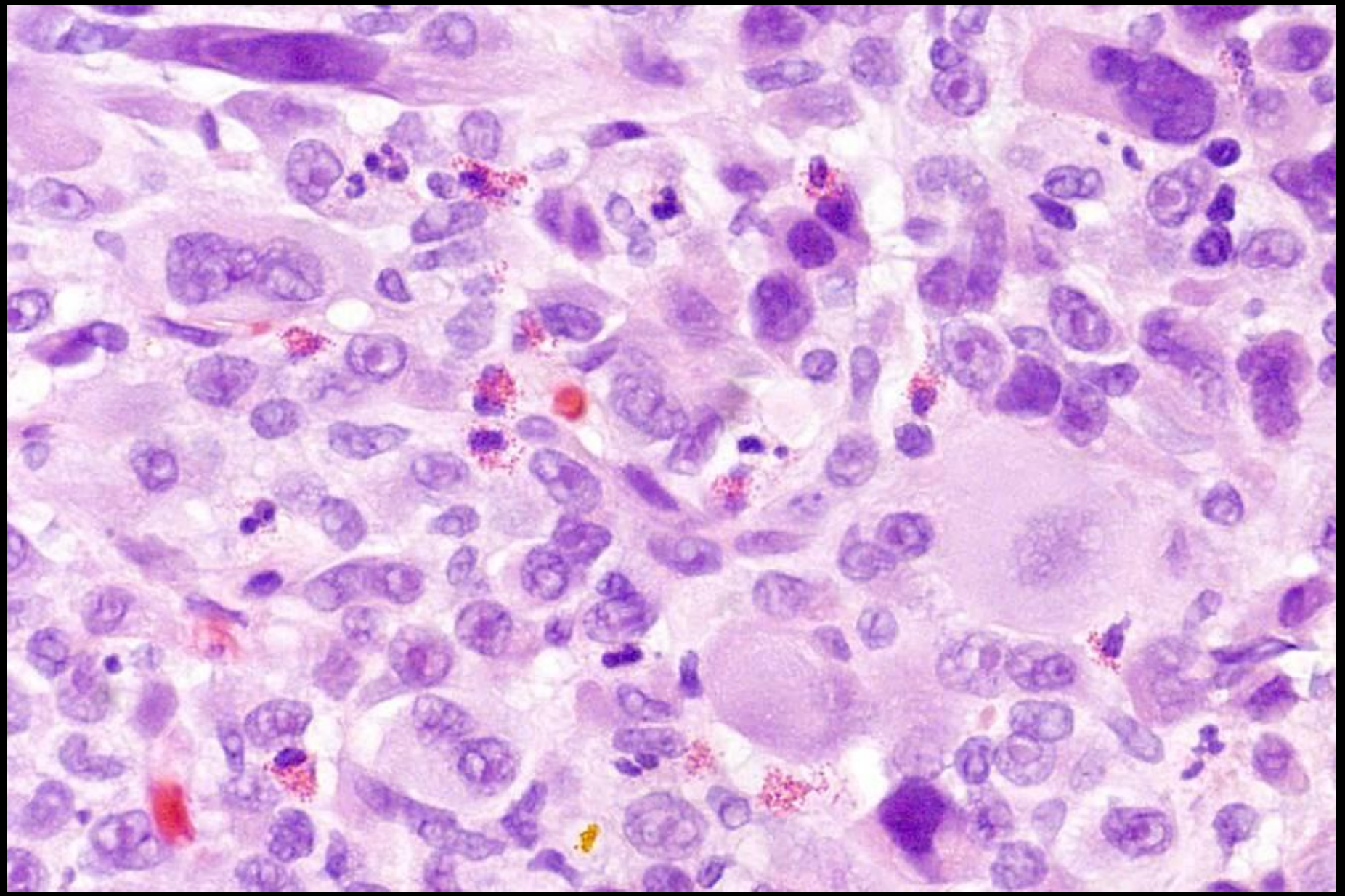
CD45 - Leucocyte common antigen (LCA)

MATERIALS AND METHODS

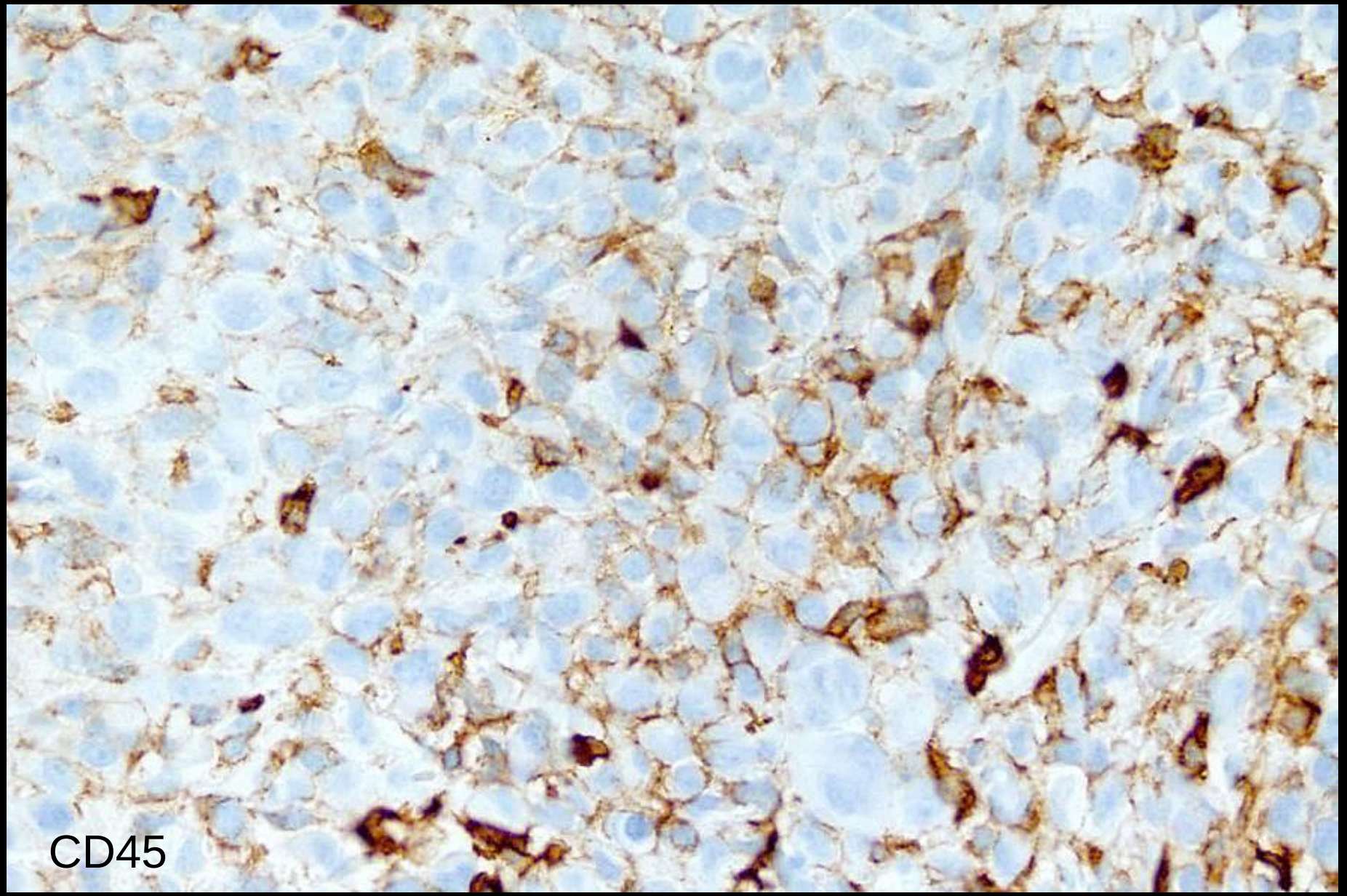
We performed immunohistochemical stains for cytokeratin (AE1/AE3. Cell Marque. Austin. Tex: CAM5.2. Becton Dickinson. San Jose, Calif; cytokeratins 5/6, Zymed, San Francisco, Calif; cytokeratin 7, Dako Corporation, Carpinteria, Calif; cytokeratin 20, Dako; 34βE12, Enzo, New York, NY), CD3, CD20, CD30, CD45RO, CD68, κ light chain, λ light chain, myeloperoxidase, epithelial membrane antigen, neuron-specific enolase, synaptophysin, S100 protein, HMB-45 (Dako), and chromogranin A (Cell Marque) on a TechMate 500 with a ChemMate Secondary Detection Kit–Peroxidase/DAB (Ventana Medical Systems, Tucson, Ariz). The histologic sections were pretreated by steaming in citrate buffer solution (Target Retrieval Solution, Dako) for 30 minutes at 99°C.

The monoclonal antibodies AE1/AE3 (working concentration, 0.4 μg of protein/mL) were applied for 25 minutes at room temperature. The immunostaining was repeated twice, each time with identical results.

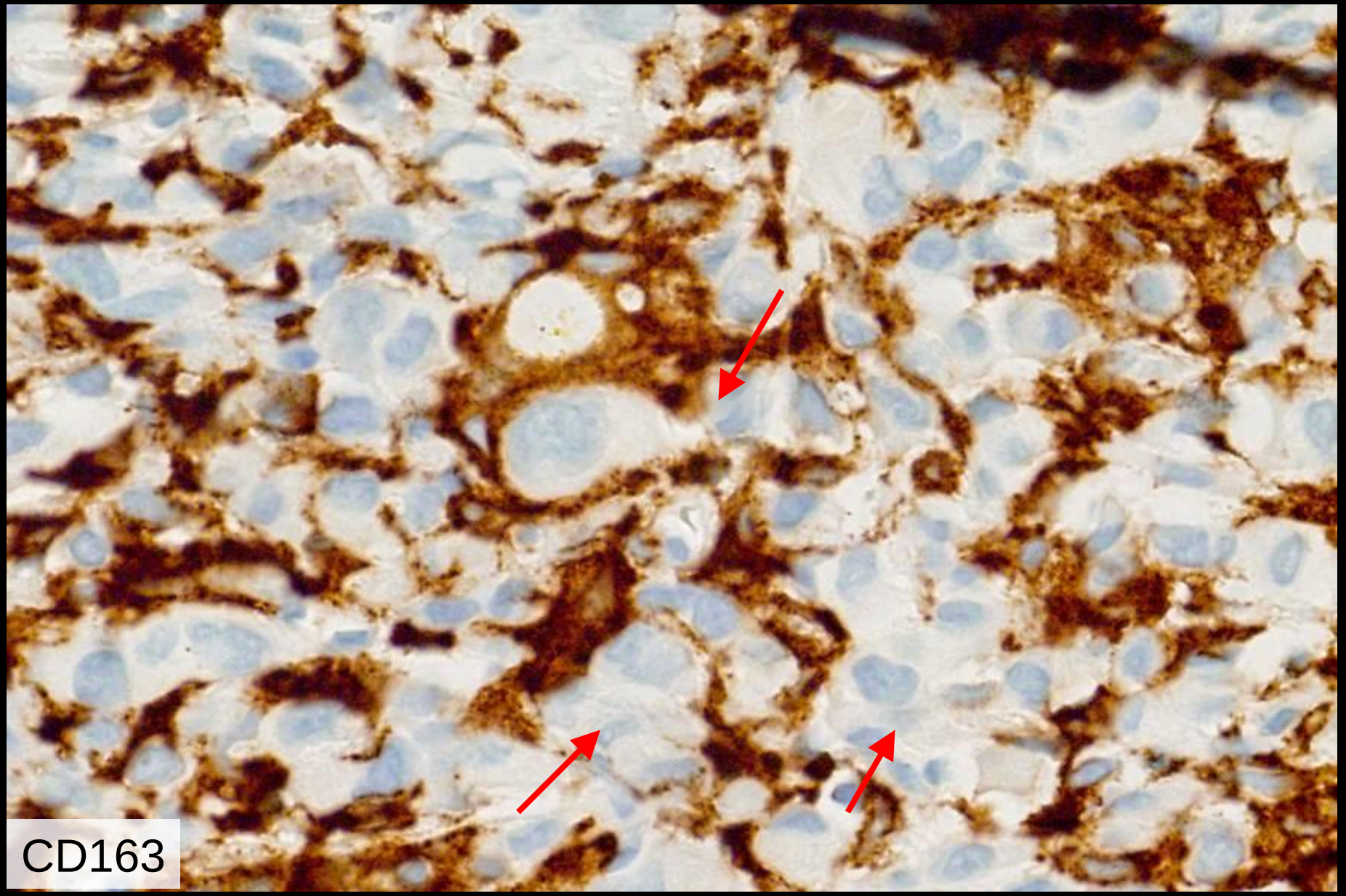
Pancreas tumour



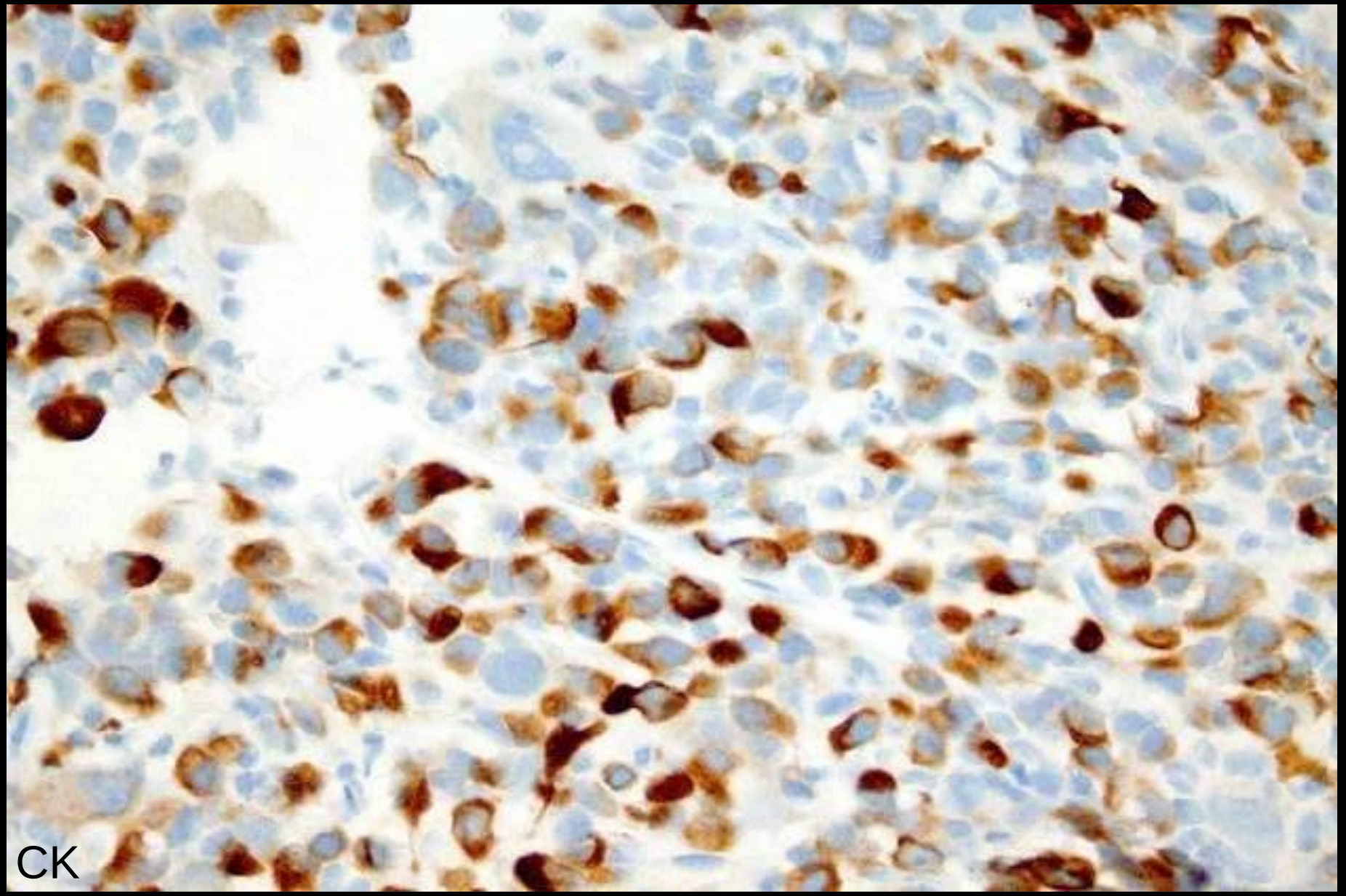
Pancreas tumour



Pancreas tumour



Pancreas tumour: undifferentiated carcinoma



Primary panel for the unknown primary tumour

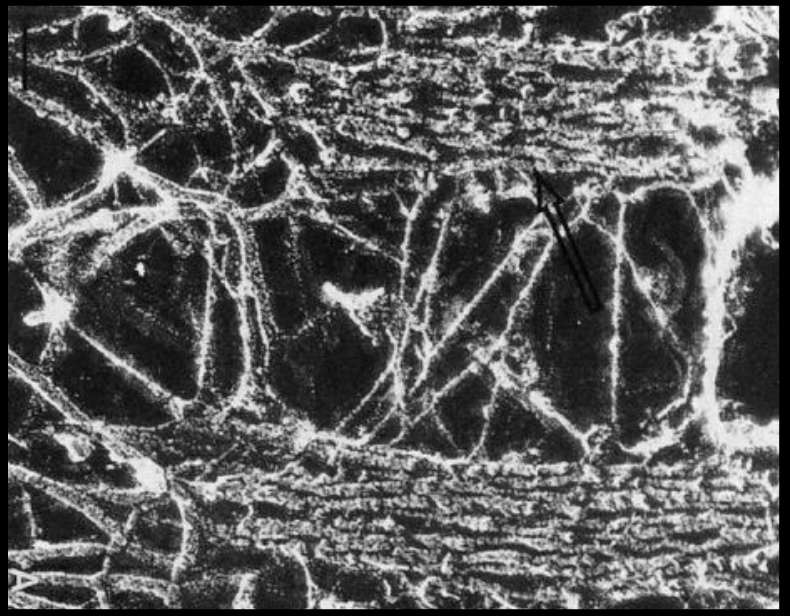
	CD45	CK	S-100	VIM
Haemato-lymphoid neoplasms	+/(-)	-/(+)	-/(+)	+/(-)
Epithelial neoplasms	-	+/(-)	-/+	-/+
Mesothelial neoplasms	-	+	-	+
Mesenchymal and neuronal neoplasms	-	-/(+)	-/+	+
Non-neuronal neuroepithelial neoplasms	-	-/(+)	+	+
Germ cell neoplasms	-	-/+	-/+	+

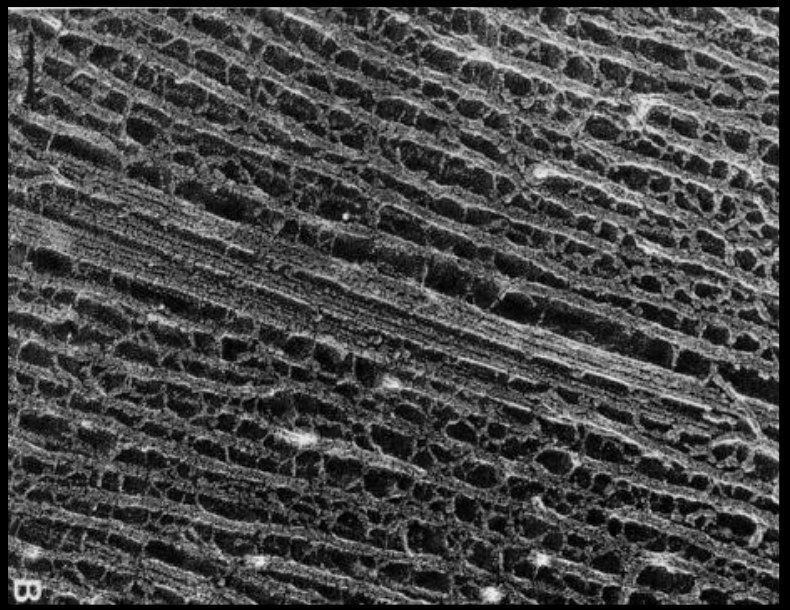
Cellular filaments

Microfilaments: (6 nm)

Intermediate filaments (7- 11 nm)

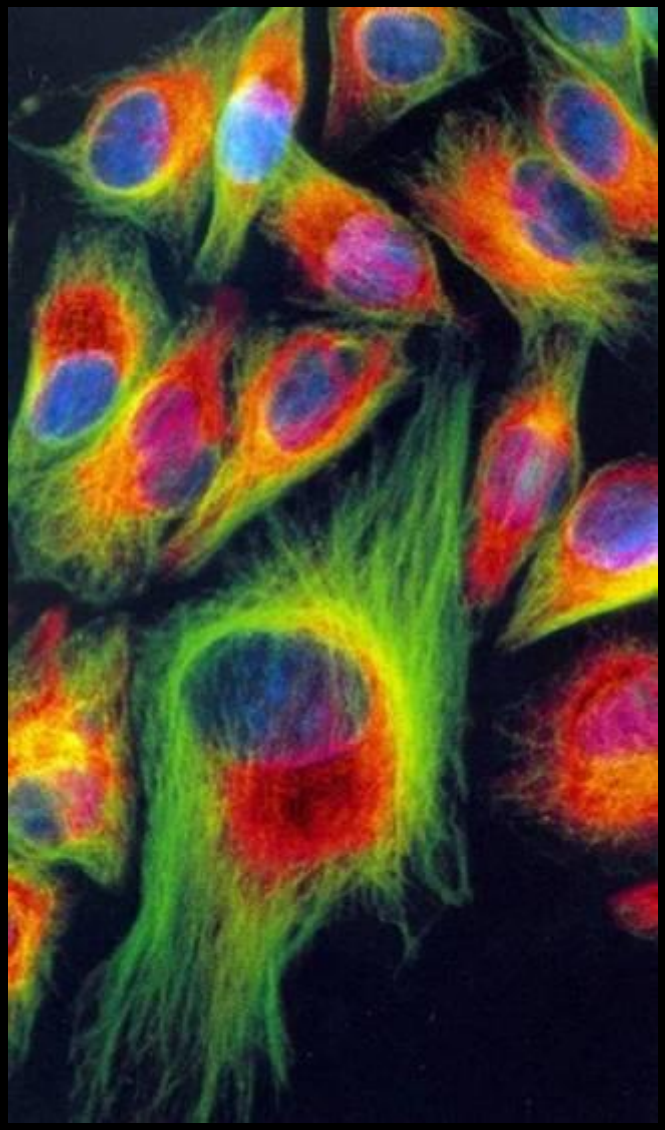
Microtubuli (23 nm)



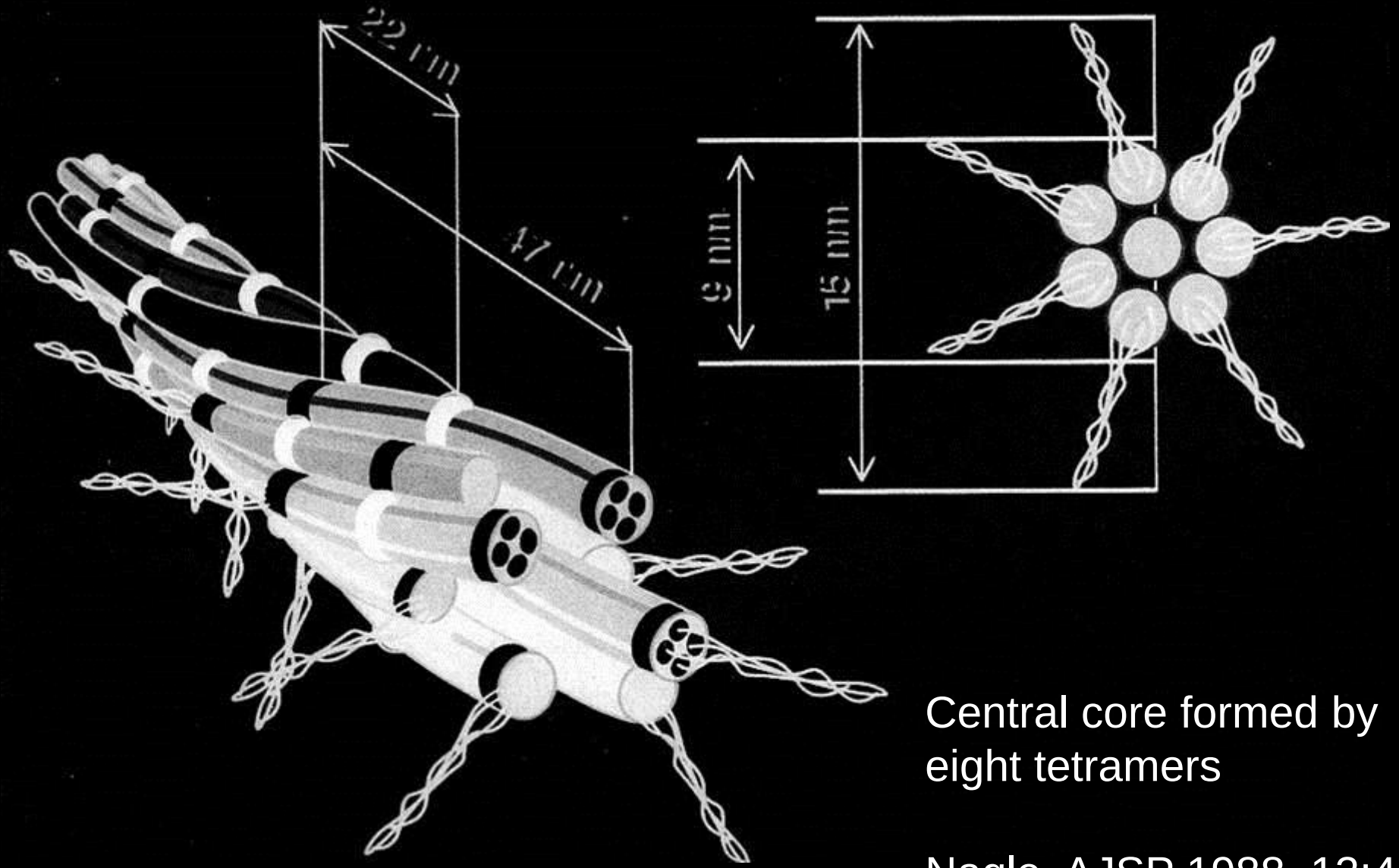


Intermediate filaments

- Group of mainly cytoplasmic filaments 7 – 11 nm in diameter
- Part of the cytoskeleton in virtually all cells, creating as meshwork and connecting nuclear membrane with cell membrane
- Often associated with microfilaments (6 nm) and microtubules (23 nm)
- Important for mechanical strength and cellular functions



Intermediate filaments – tetrameric units

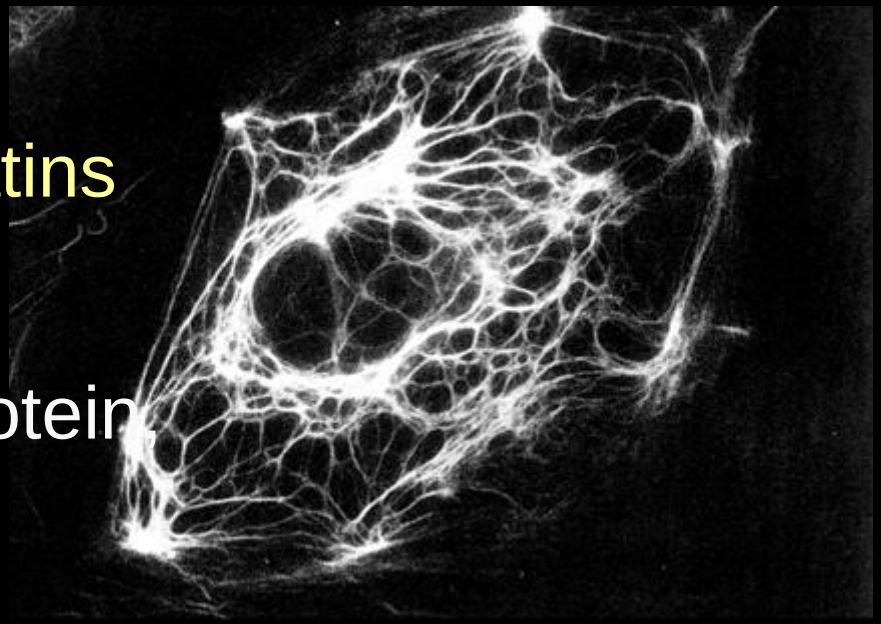


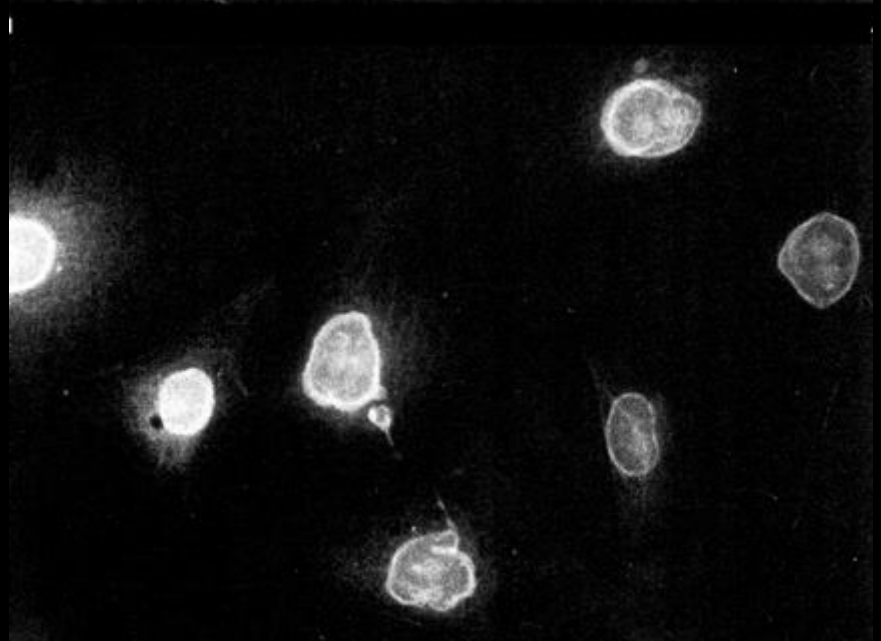
Central core formed by eight tetramers

Nagle, AJSP 1988, 12:4

Intermediate filaments - 5 classes

- **I** acidic cytokeratins
- **II** basic-neutral cytokeratins
- III vimentin, desmin,
- glial fibrillary acidic protein
- peripherin
- IV neurofilament protein,
- α-internexin, nestin
- V lamins





Cytokeratins as tonofilaments

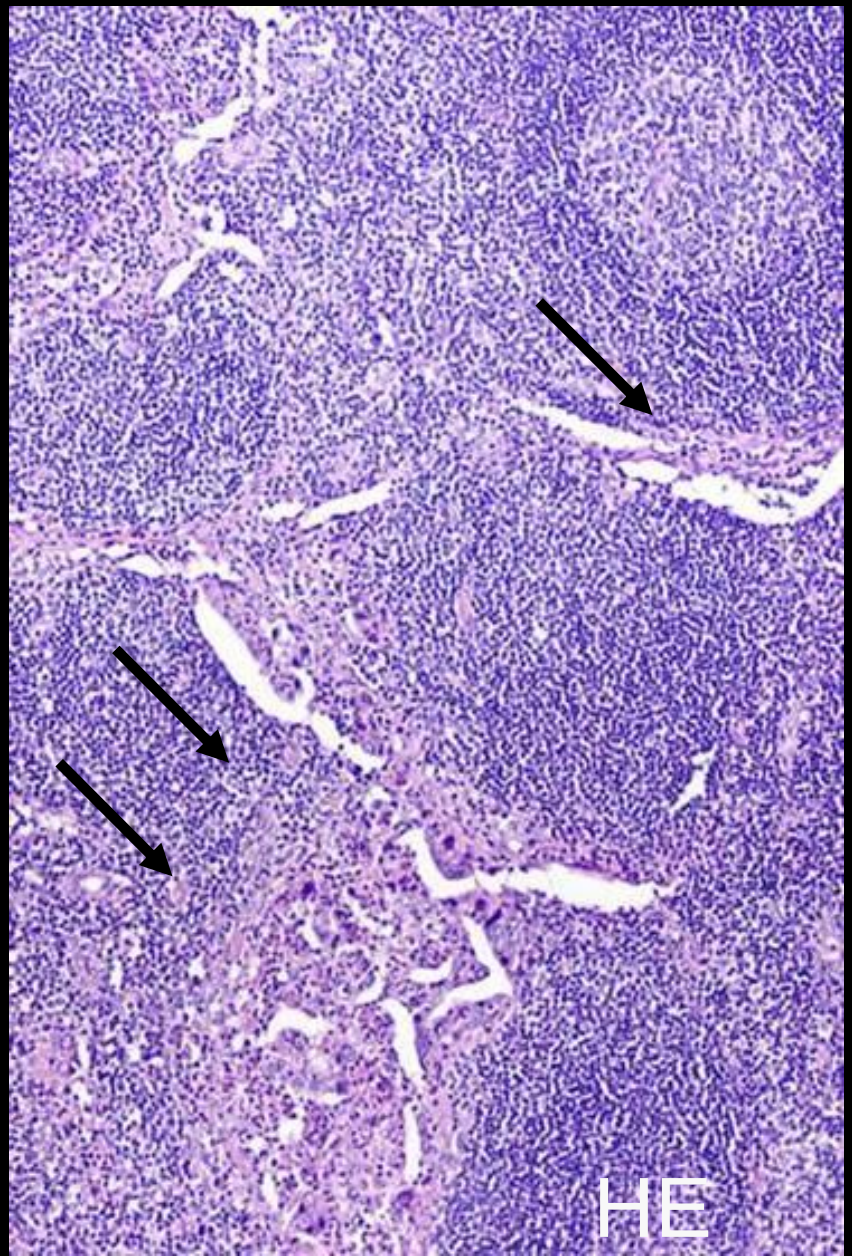
Cytokeratin intermediate filaments attached to desmosomes

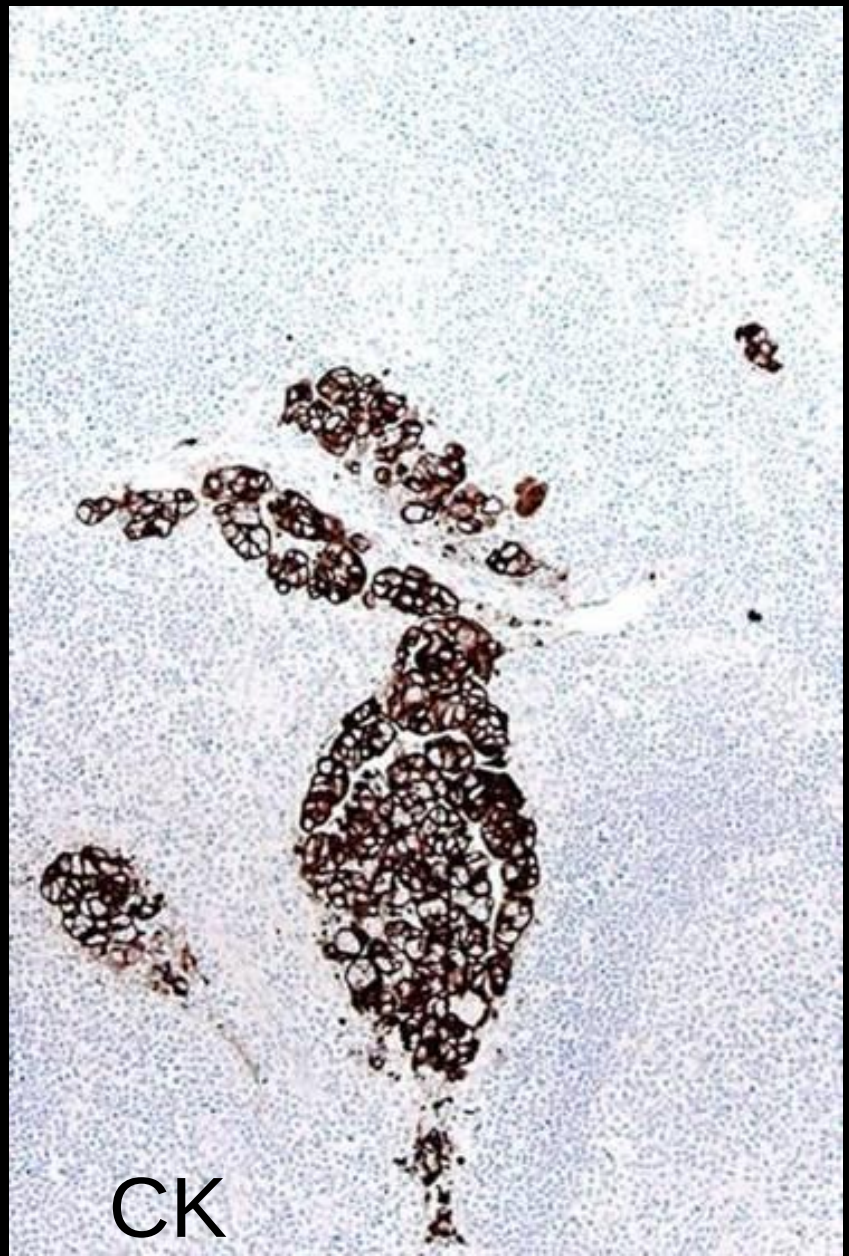
Drochmans et al.
J Cell Biol. 1978, 79:427

Cytokeratins in diagnostic pathology

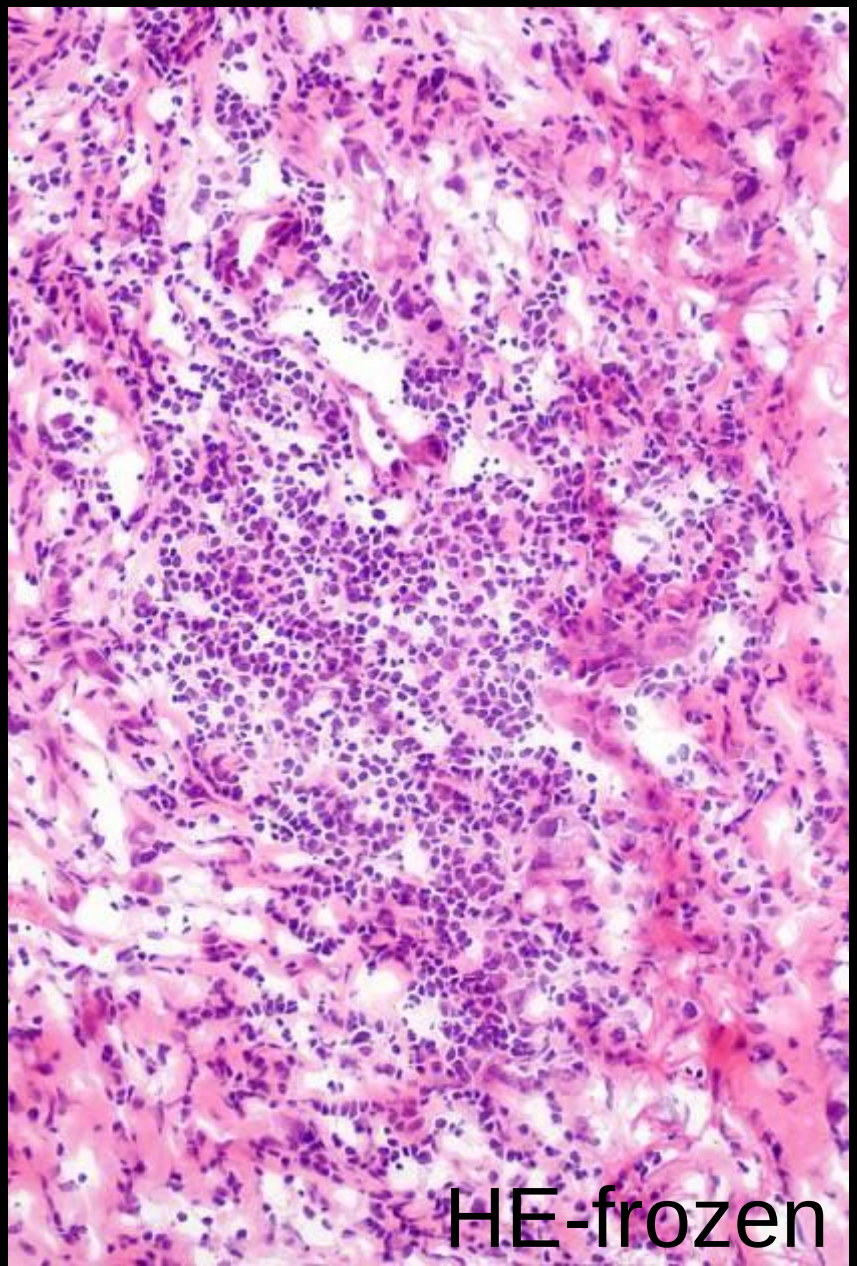
- Cytokeratins (CKs) belong to the most fundamental markers of epithelial differentiation
- CKs comprise a large family of subtypes. Different cell types express different patterns of CK subtypes
- Cancers generally express CK patterns that at least in part represent the pattern of the putative cell of origin
- Metastases express CK patterns fairly concordant with those of the primary tumours

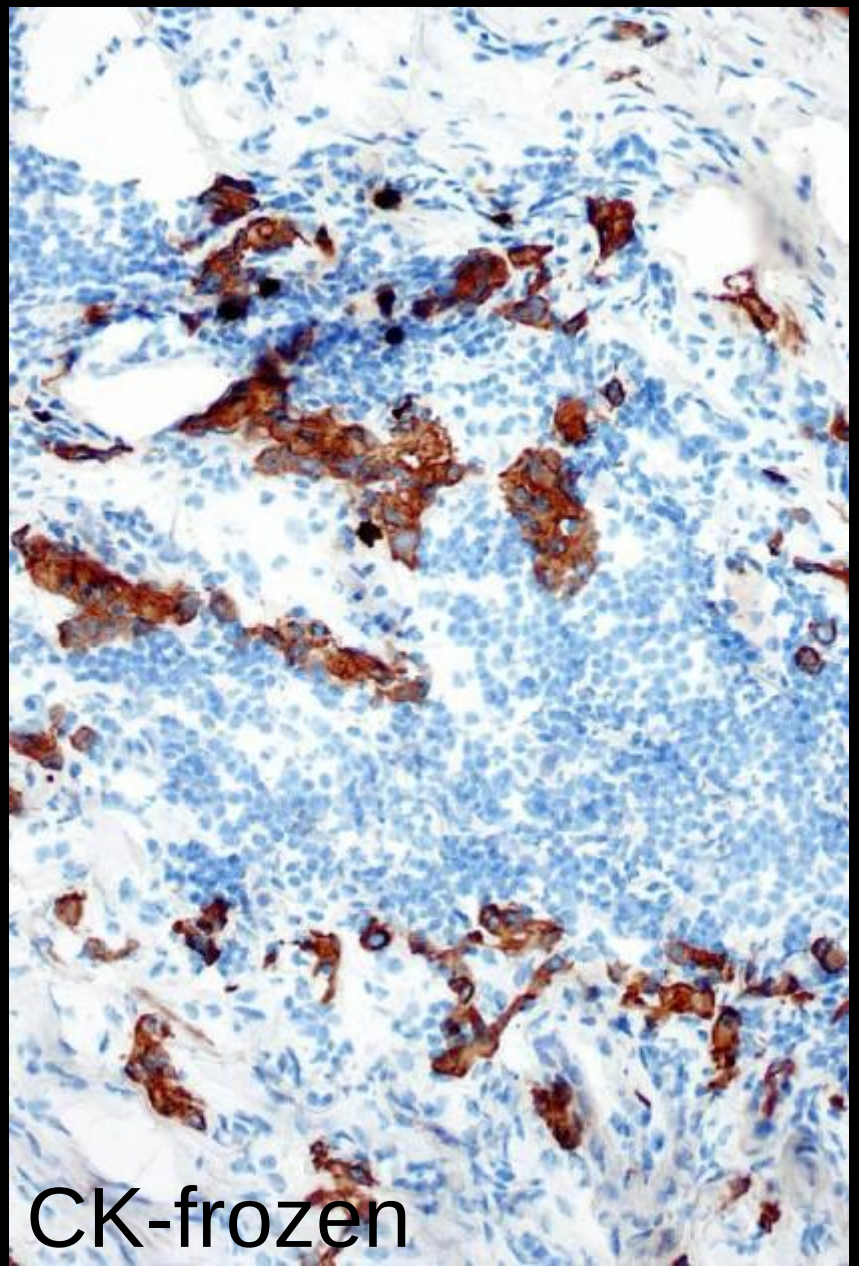
Micrometastases identified by cytokeratin



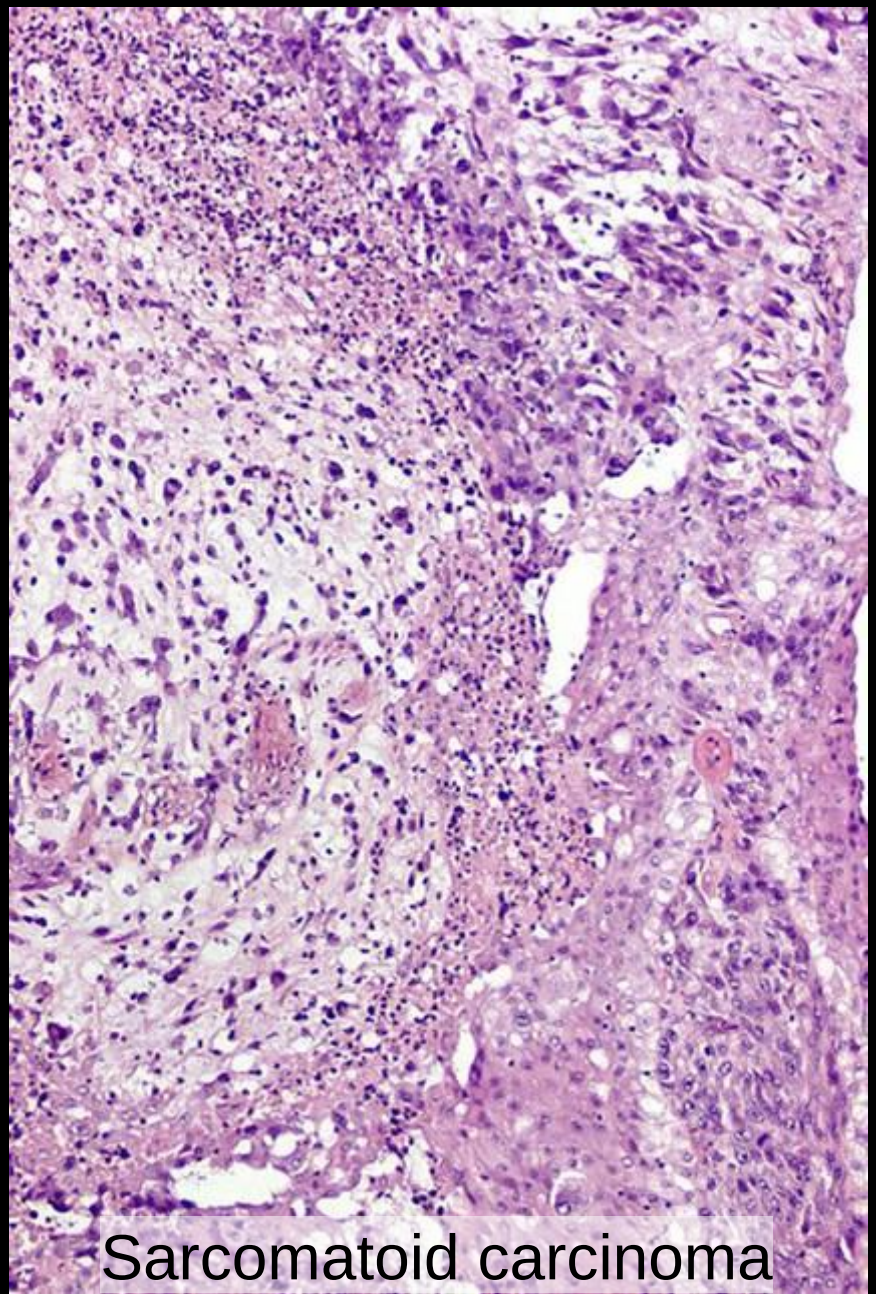


Carcinoma in frosen section identified by cytokeratin

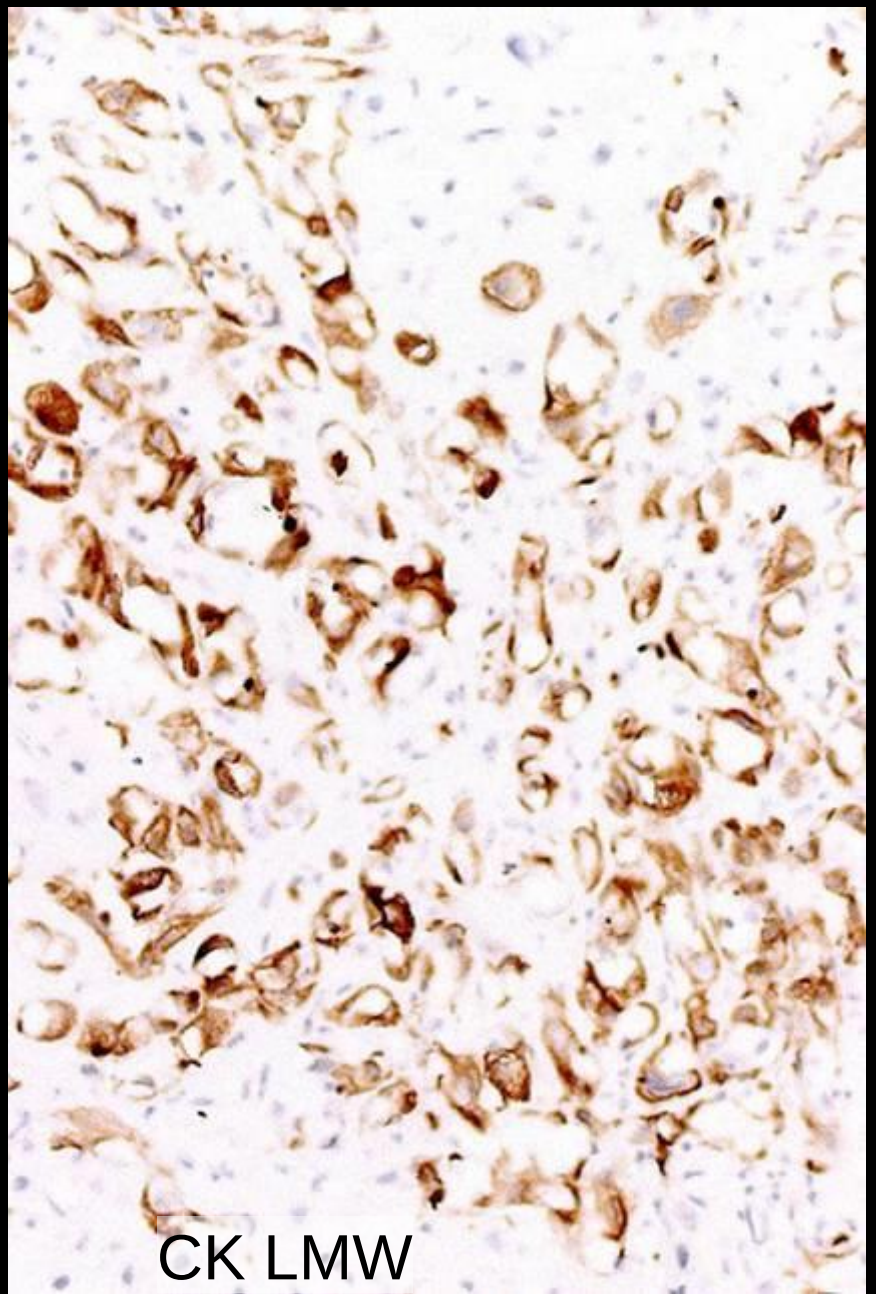




Cytokeratins in carcinomas with aberrant growth patterns



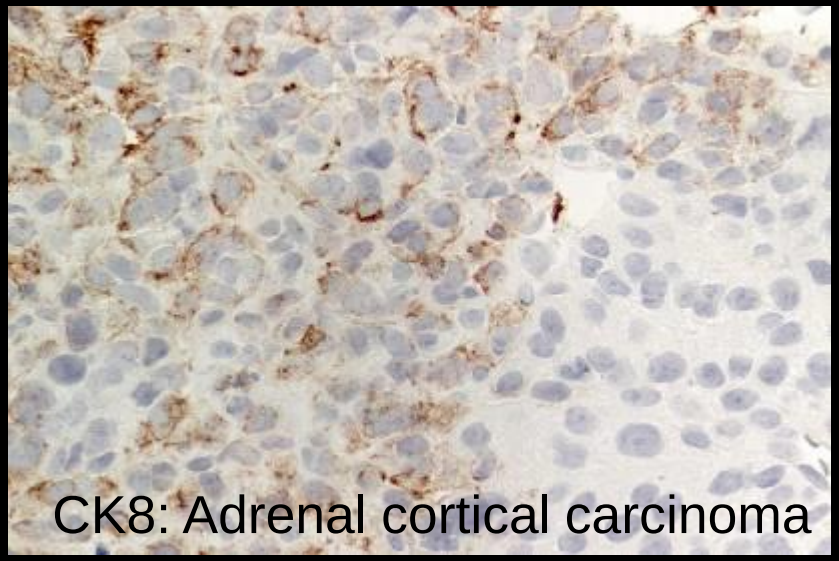
Sarcomatoid carcinoma



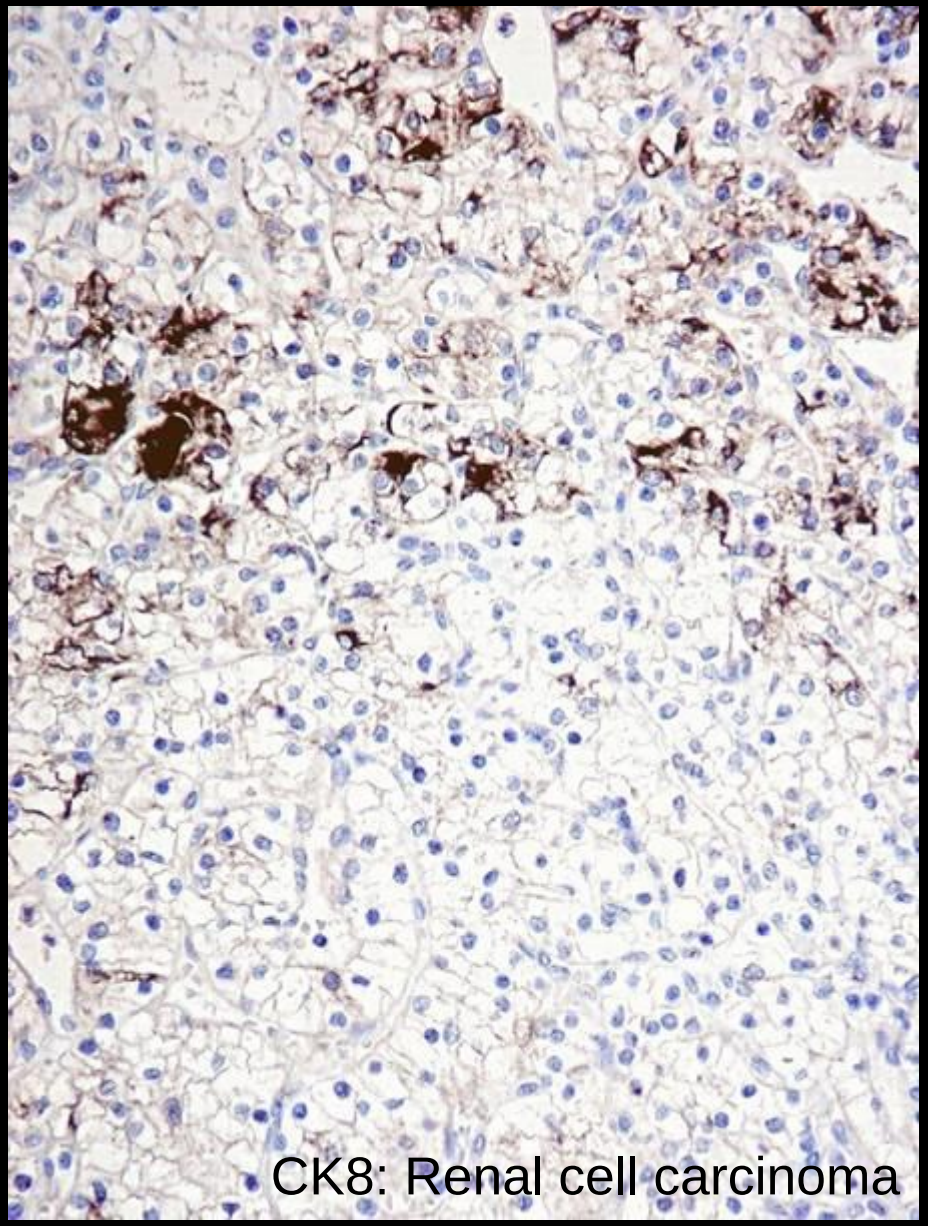
CK LMW

Low molecular weight cytokeratins in carcinomas

- Carcinomas “always” LMW-CK-positive, except some cases of
  - Renal cell carcinoma
  - Adrenal cortical carcinoma
  - Small cell carcinoma



CK8: Adrenal cortical carcinoma

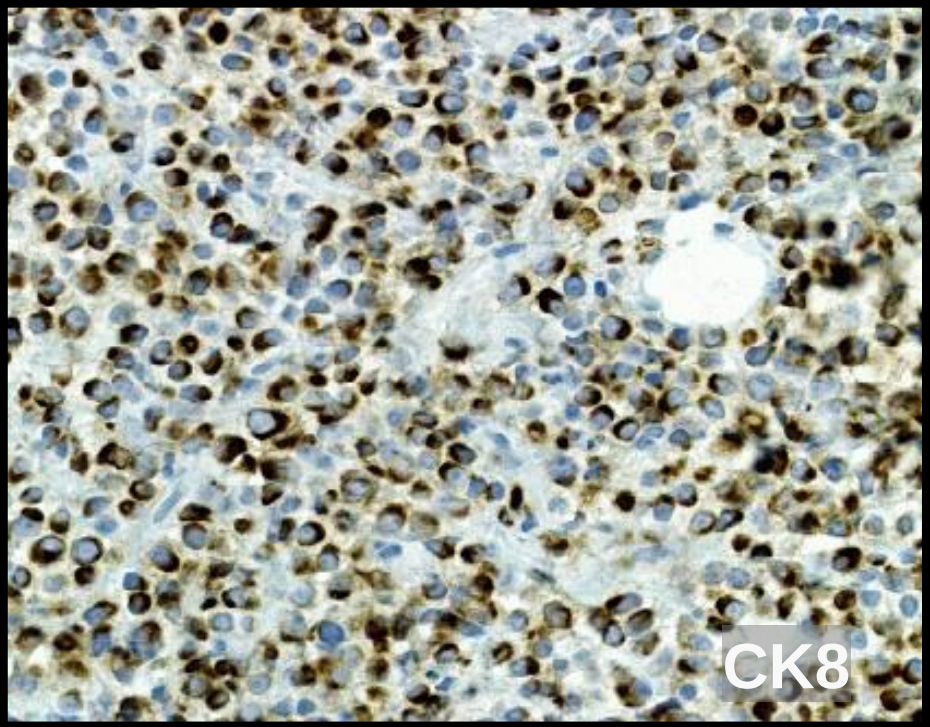


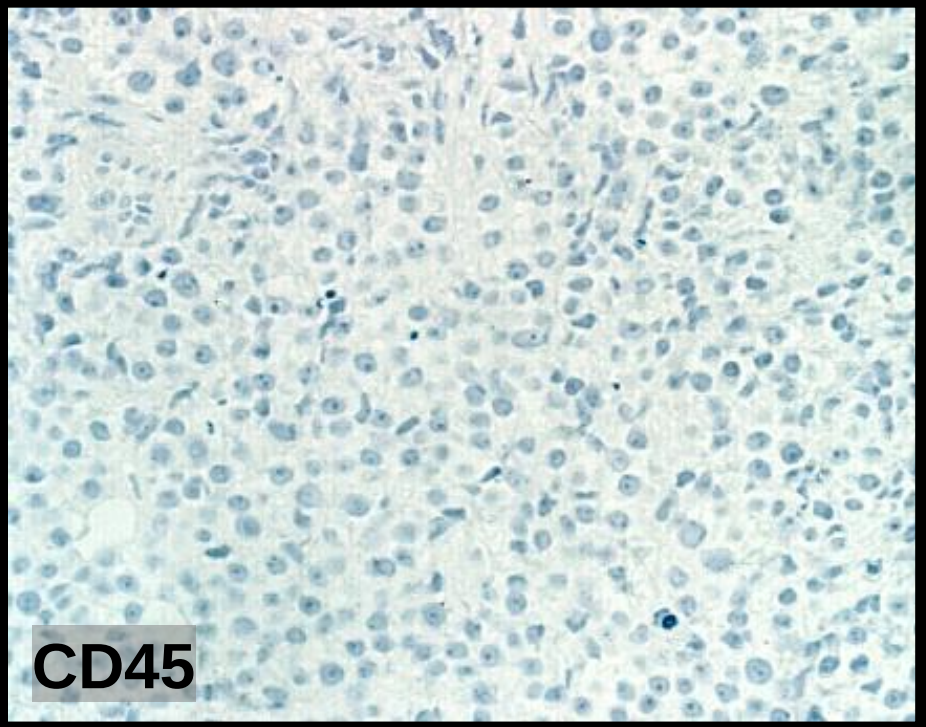
CK8: Renal cell carcinoma

Primary panel for the unknown primary tumour

	CD45	CK	S-100	VIM
Haemato-lymphoid neoplasms	+/(-)	-/(+)	-/(+)	+/(-)
Epithelial neoplasms	-	+/(-)	-/+	-/+
Mesothelial neoplasms	-	+	-	+
Mesenchymal and neuronal neoplasms	-	-/(+)	-/+	+
Non-neuronal neuroepithelial neoplasms	-	-/(+)	+	+
Germ cell neoplasms	-	-/+	-/+	+

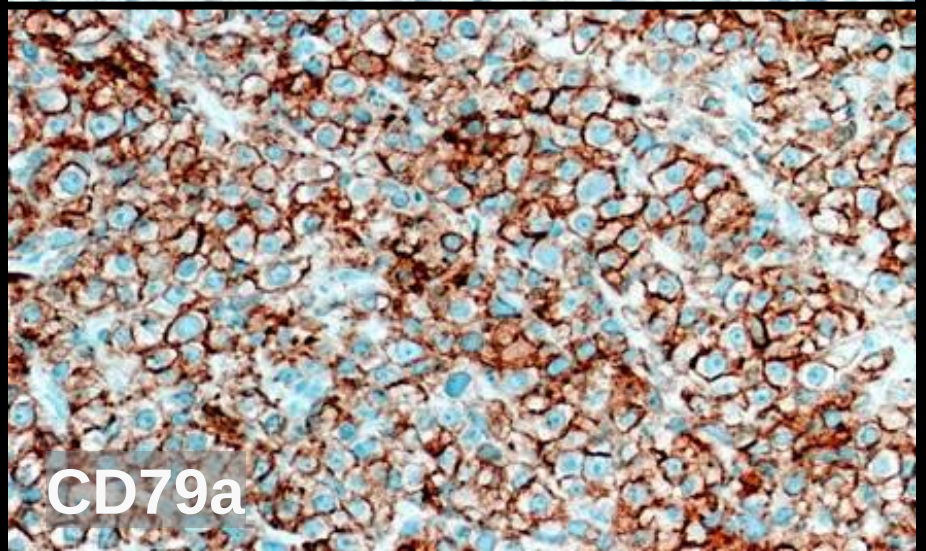
Cytokeratins in non-epithelial tumours





♀ 42 y, tumour infiltrating retroperitoneum

Malignant lymphoma !



Primary panel for the unknown primary tumour

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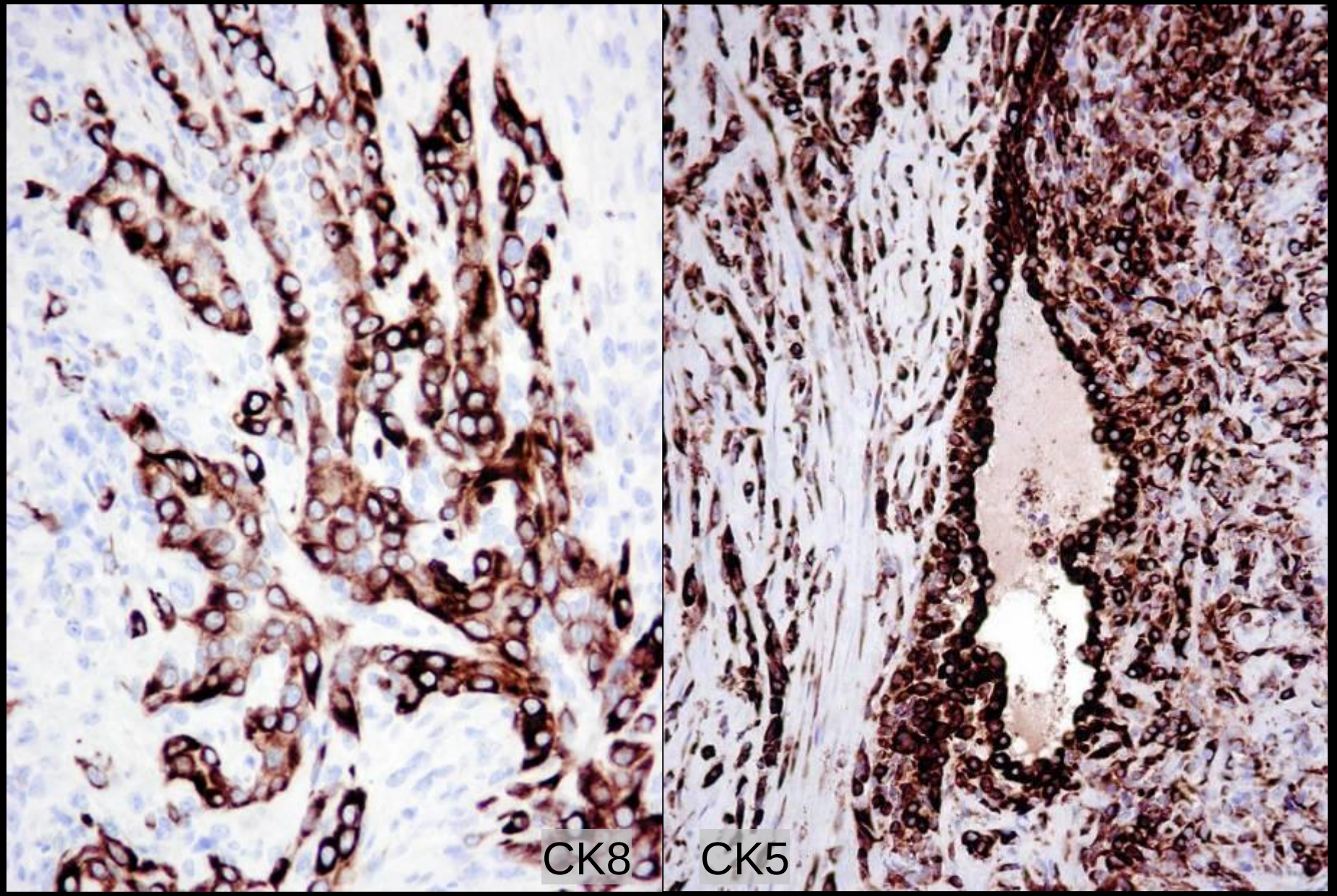
Haemato-lymphoid neoplasms	+/(-)	-/(+)	-/(+)	+/(-)
Epithelial neoplasms	-	+/(-)	-/+	-/+
Mesothelial neoplasms	-	+	-	+
Mesenchymal and neuronal neoplasms	-	-/(+)	-/+	+
Non-neuronal neuroepithelial neoplasms	-	-/(+)	+	+
Germ cell neoplasms	-	-/+	-/+	+

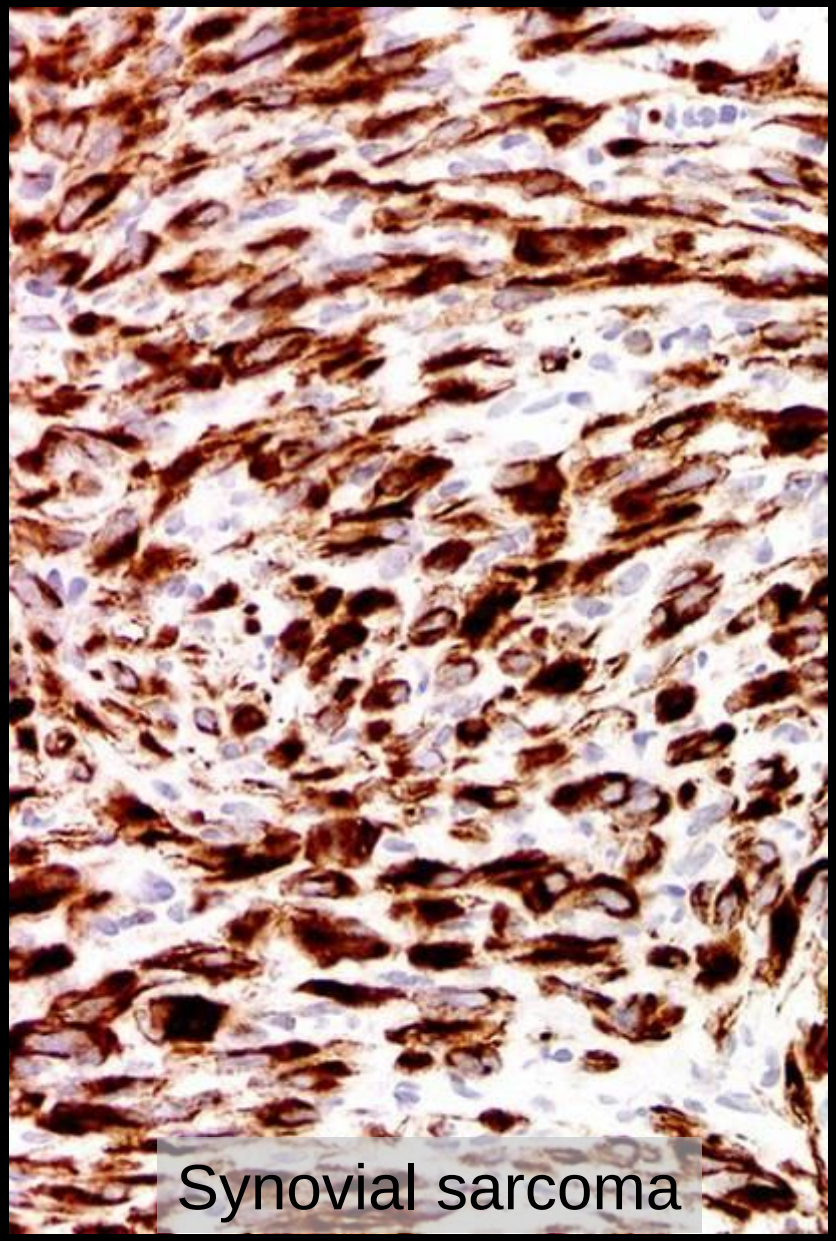
Cytokeratins in malignant mesothelioma



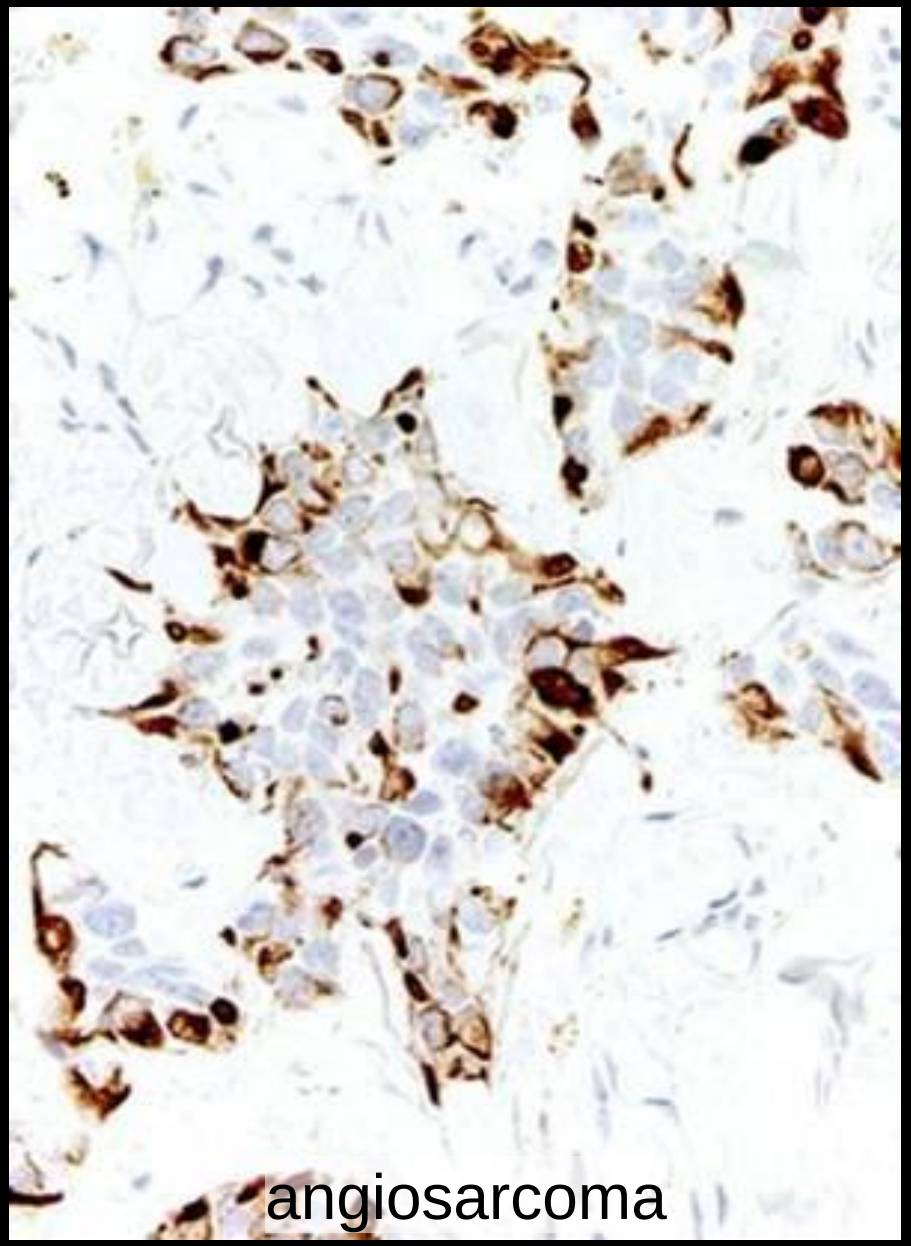
Primary panel for the unknown primary tumour

	CD45	CK	S-100	VIM
Haemato-lymphoid neoplasms	+/(-)	-/(+)	-/(+)	+/(-)
Epithelial neoplasms	-	+/(-)	-/+	-/+
Mesothelial neoplasms	-	+	-	+
Mesenchymal and neuronal neoplasms	-	-/(+)	-/+	+
Non-neuronal neuroepithelial neoplasms	-	-/(+)	+	+
Germ cell neoplasms	-	-/+	-/+	+

Cytokeratins in sarcomas

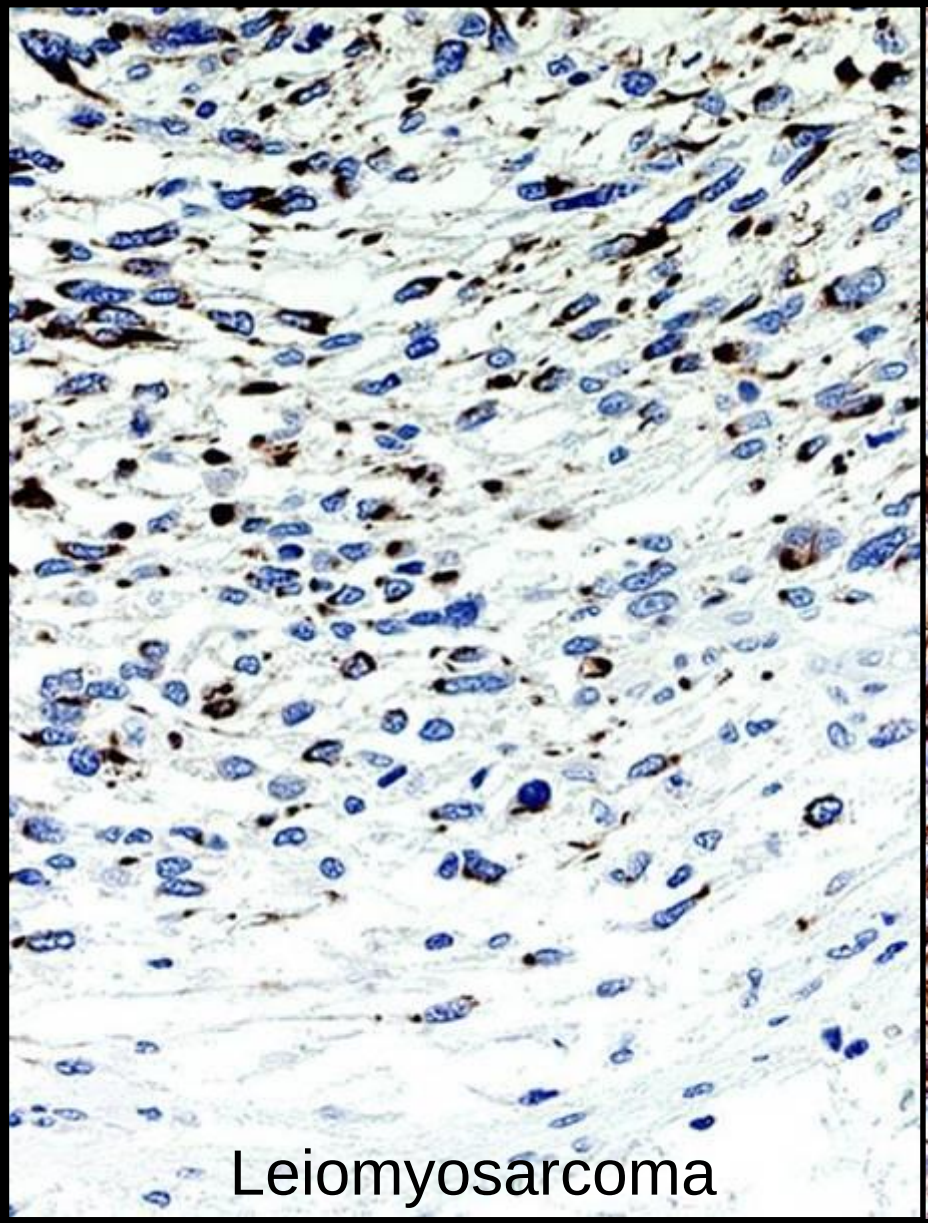


Synovial sarcoma

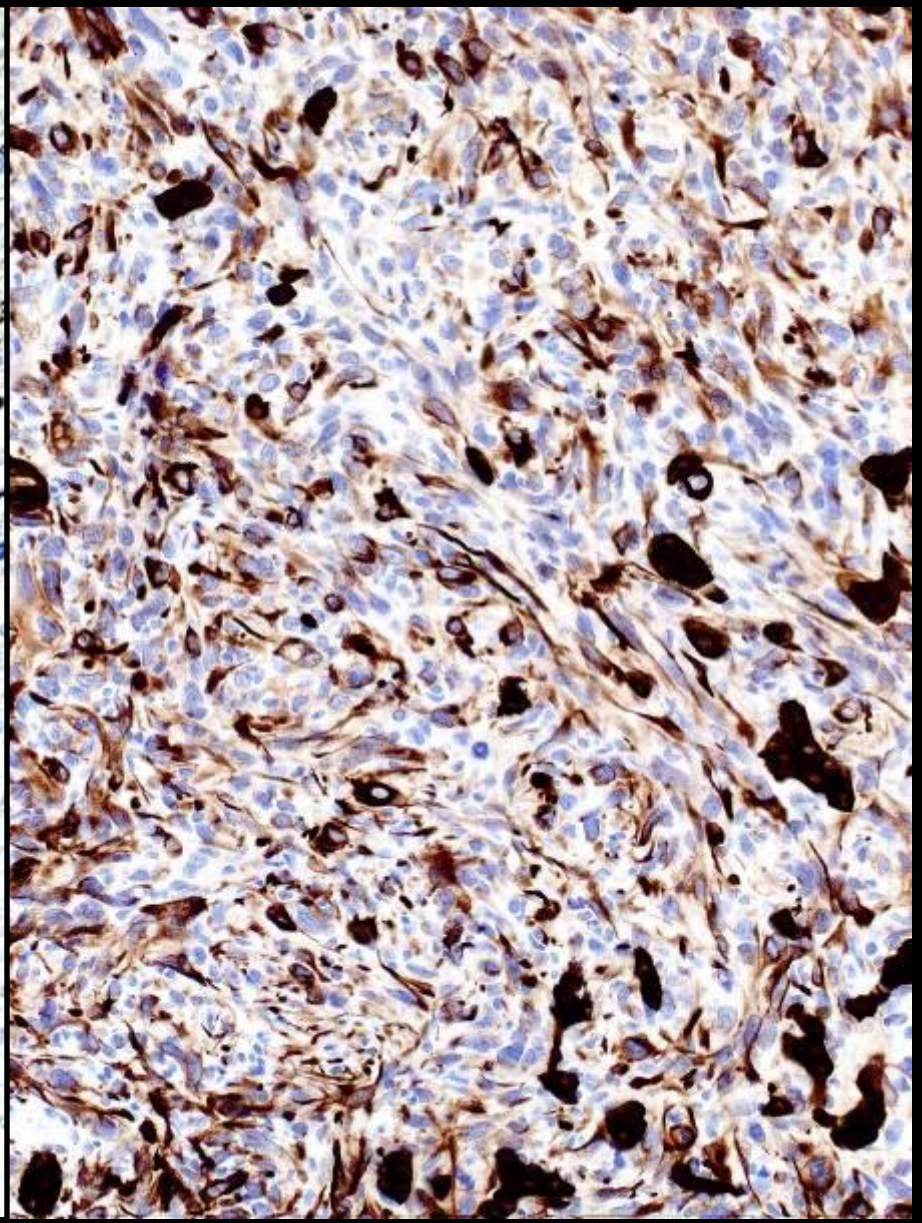


angiosarcoma

Cytokeratins in non-epithelial tumours



Leiomyosarcoma



Primary panel for the unknown primary tumour

	CD45	CK	S-100	VIM
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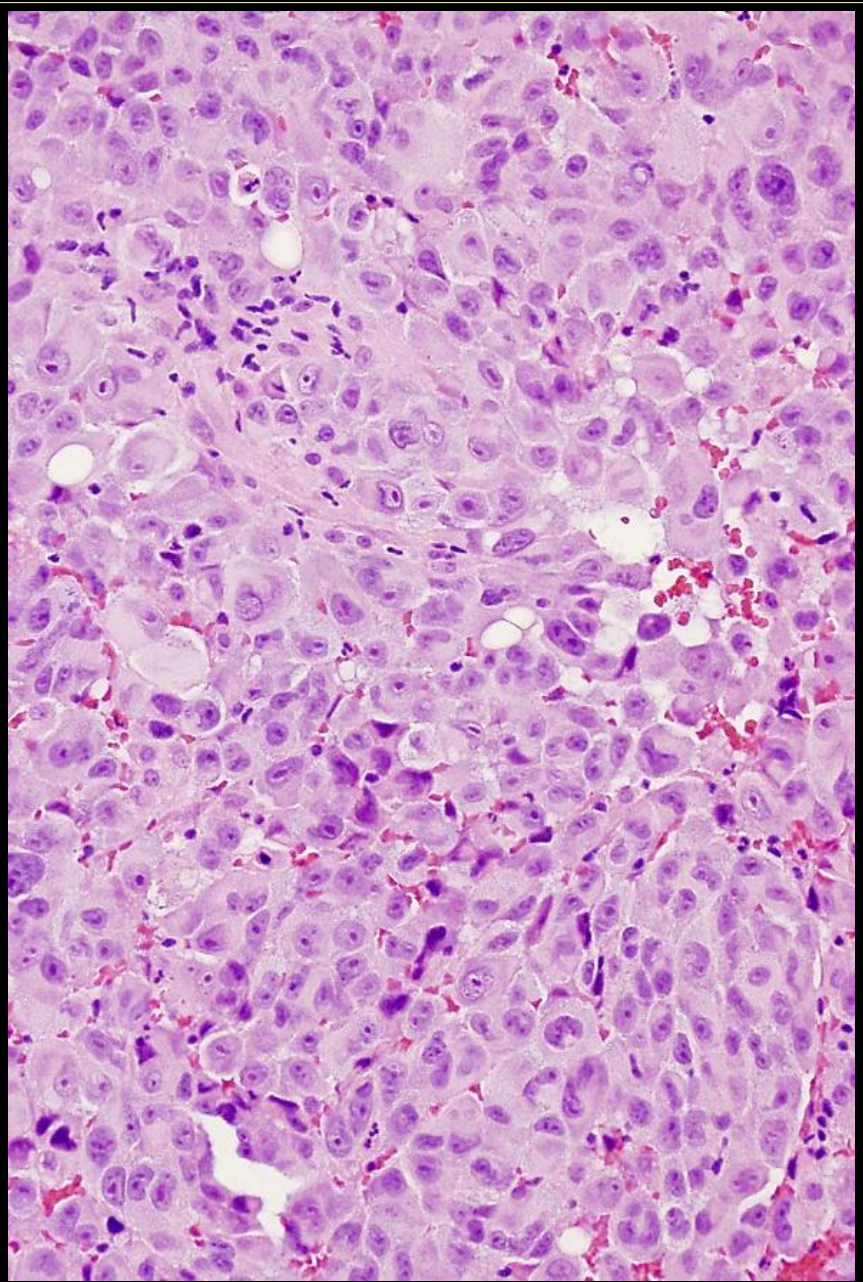
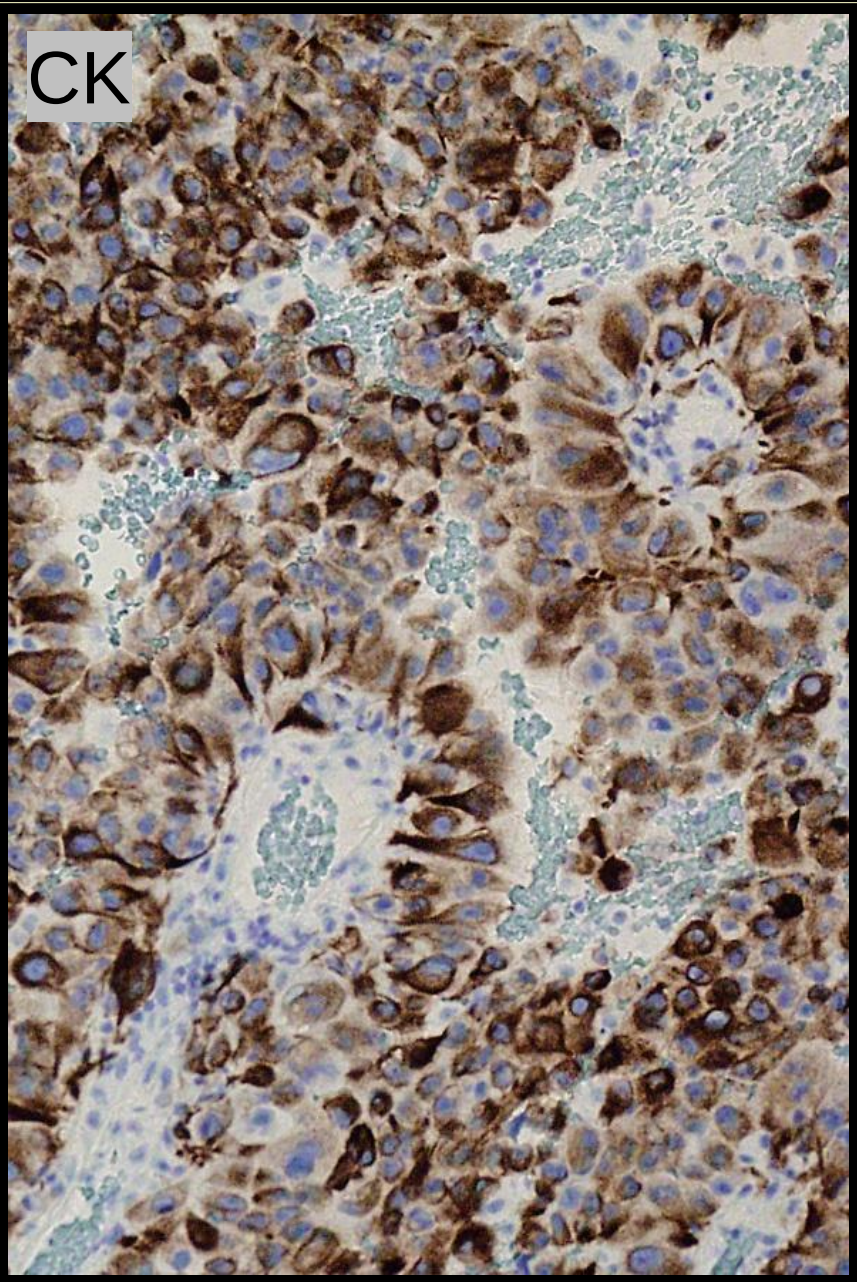
Epithelial neoplasms	-	+/(-)	-/+	-/+
Mesothelial neoplasms	-	+	-	+
Mesenchymal and neuronal neoplasms	-	-/(+)	-/+	+
Non-neuronal neuroepithelial neoplasms	-	-/(+)	+	+
Germ cell neoplasms	-	-/+	-/+	+

Cytokeratins in malignant melanoma





Primary panel for the unknown primary tumour

	CD45	CK	S-100	VIM
Haemato-lymphoid neoplasms	+/(-)	-/(+)	-/(+)	+/(-)
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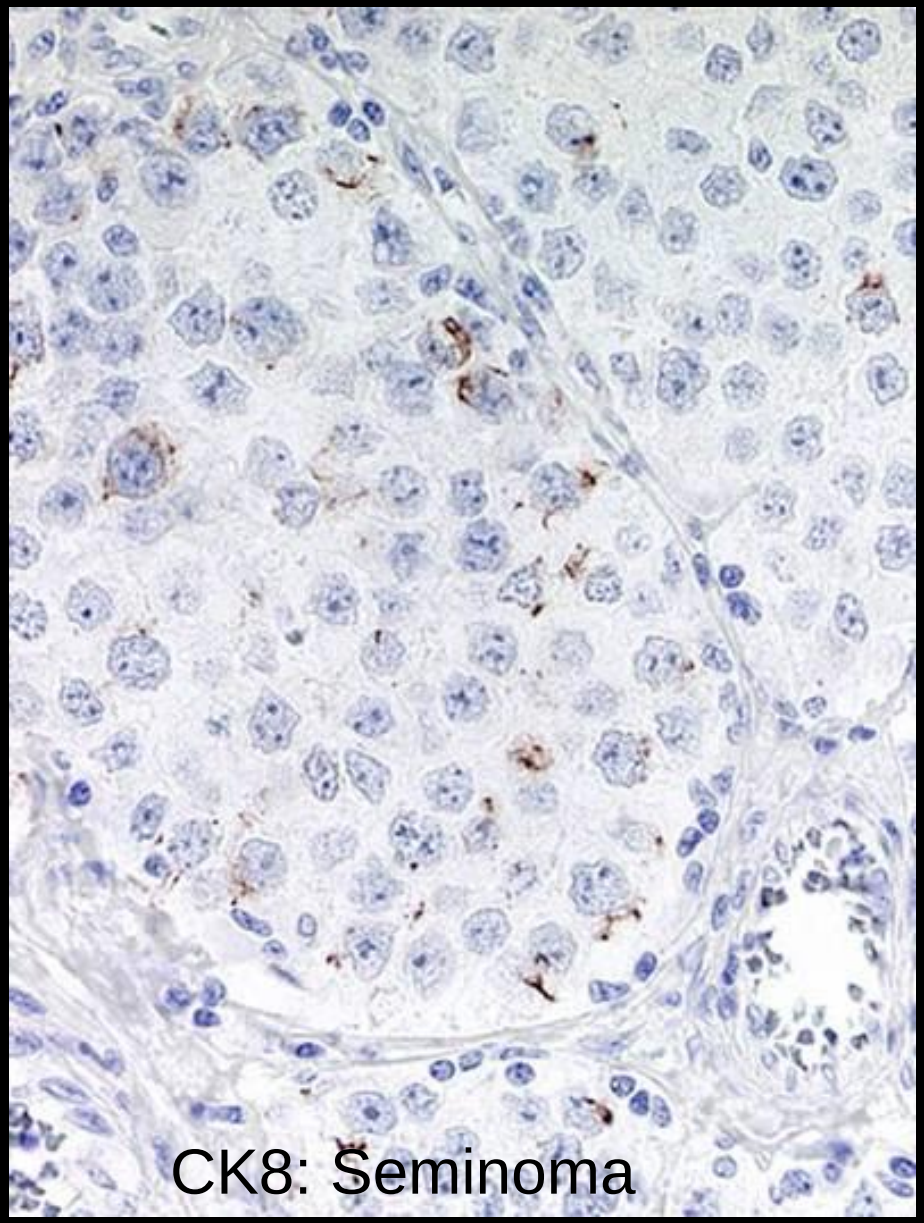
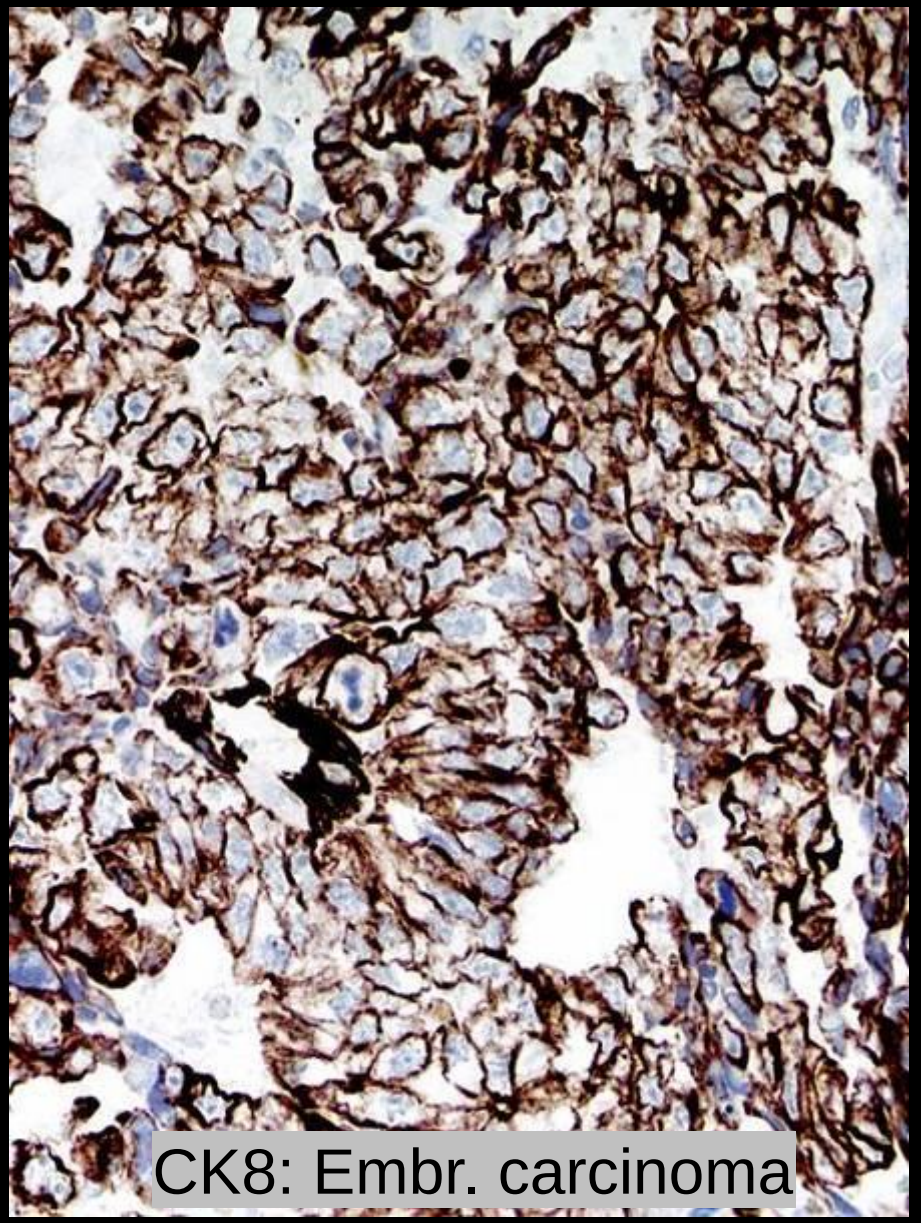
Mesothelial neoplasms	-	+	-	+
Mesenchymal and neuronal neoplasms	-	-/(+)	-/+	+
Non-neuronal neuroepithelial neoplasms	-	-/(+)	+	+
Germ cell neoplasms	-	-/+	-/+	+

Cytokeratins in germ cell tumours

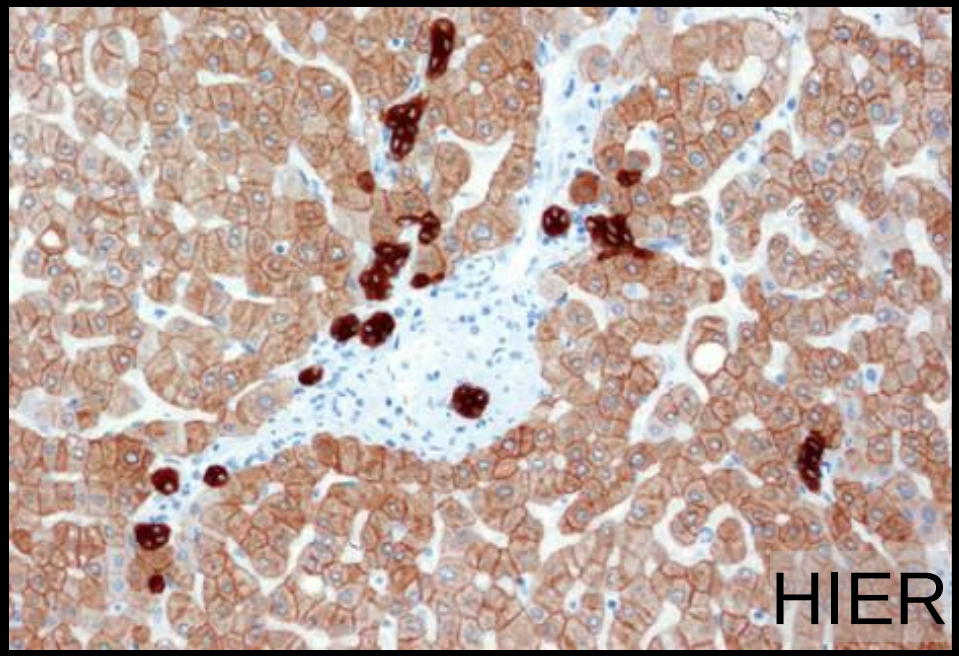


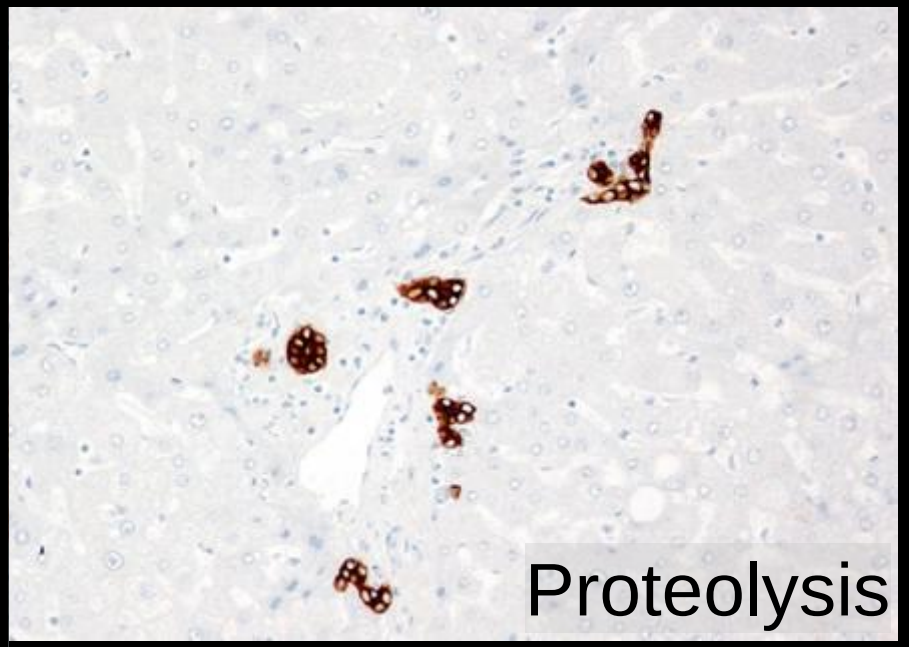
CK8: Seminoma



CK8: Embr. carcinoma

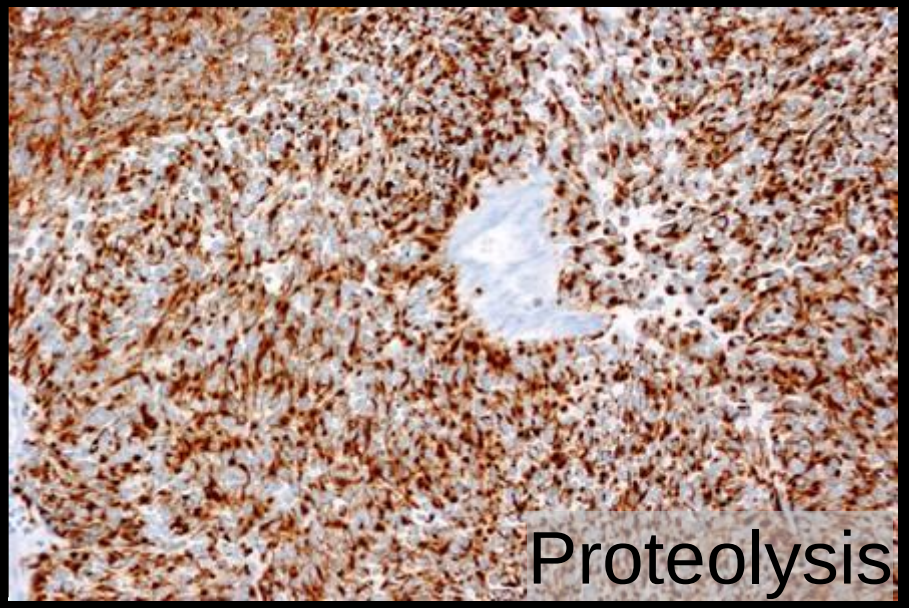
Cytokeratins: retrieval causing false negativity



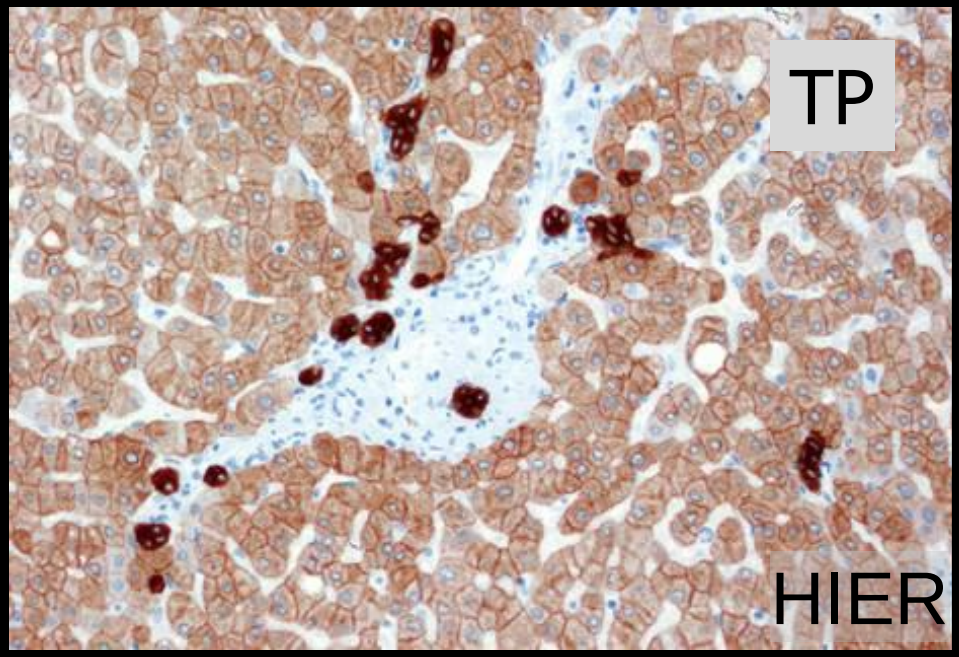


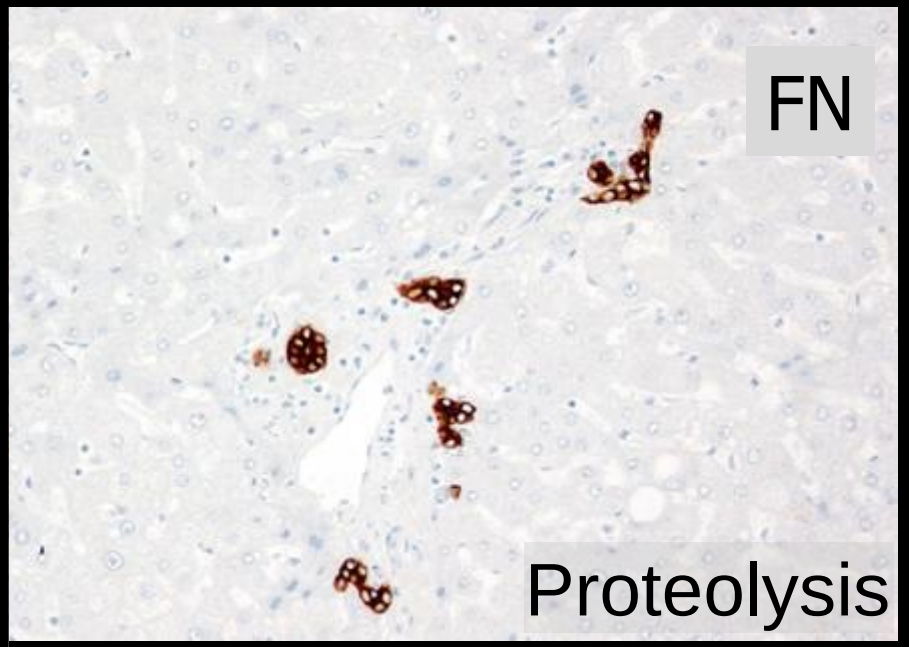
- AE1 detects CK8 after HIER onl
- AE1 does not detect CK18
- AE3 does not detect CK8/CK18

SCLC

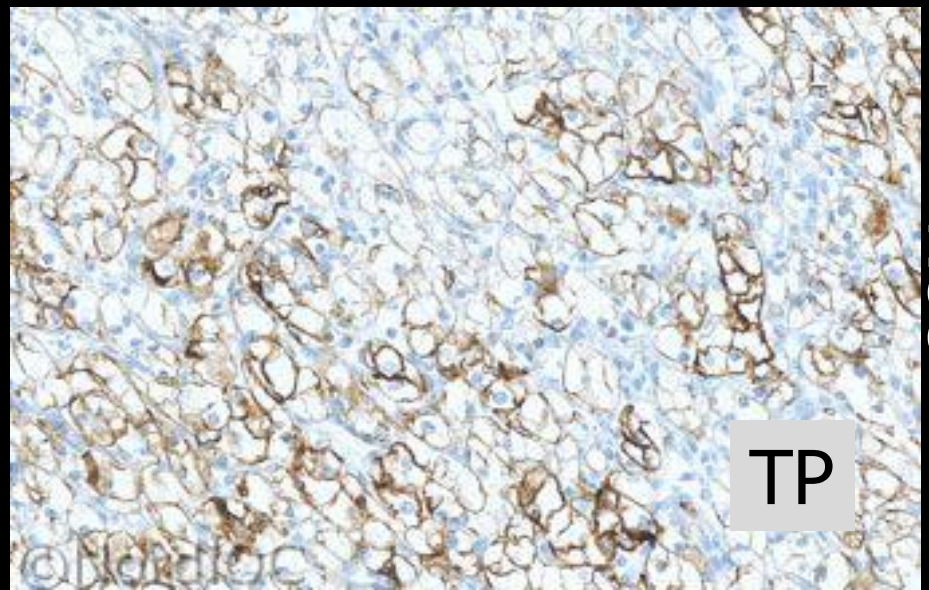


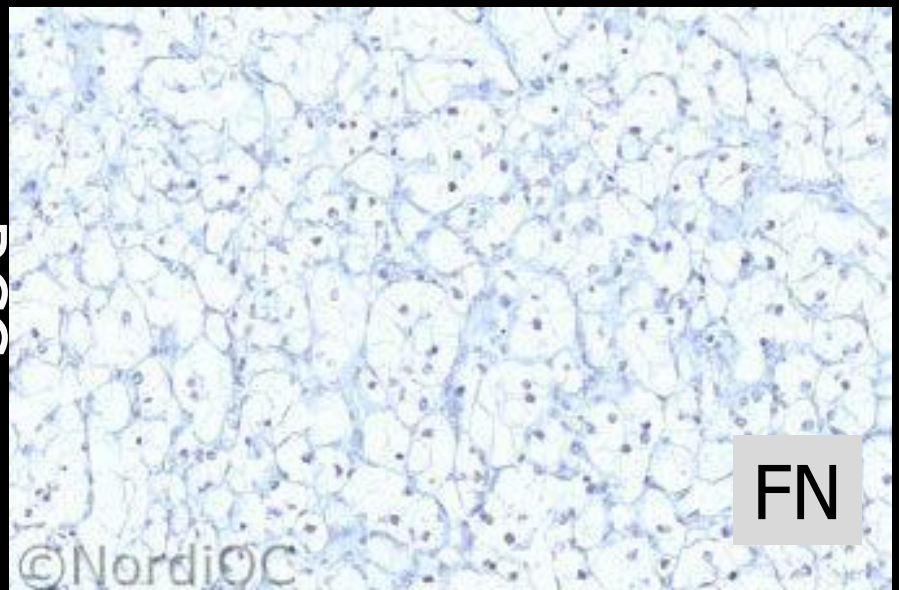
Cytokeratins: retrieval causing false negativity





RCC





Primary panel for the unknown primary tumour

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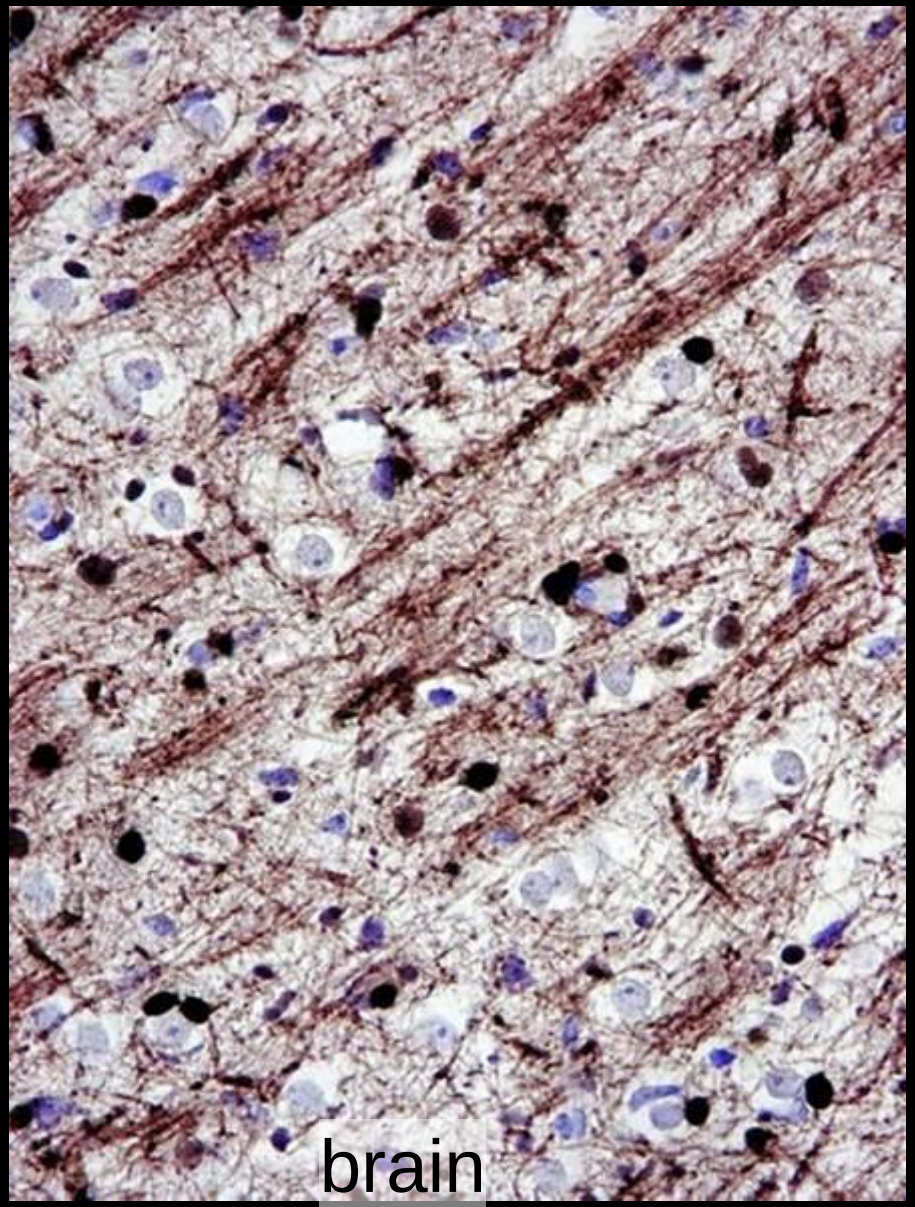
Mesenchymal and neuronal neoplasms	-	-/(+)	-/+	+
Non-neuronal neuroepithelial neoplasms	-	-/(+)	+	+
Germ cell neoplasms	-	-/+	-/+	+

S-100 protein

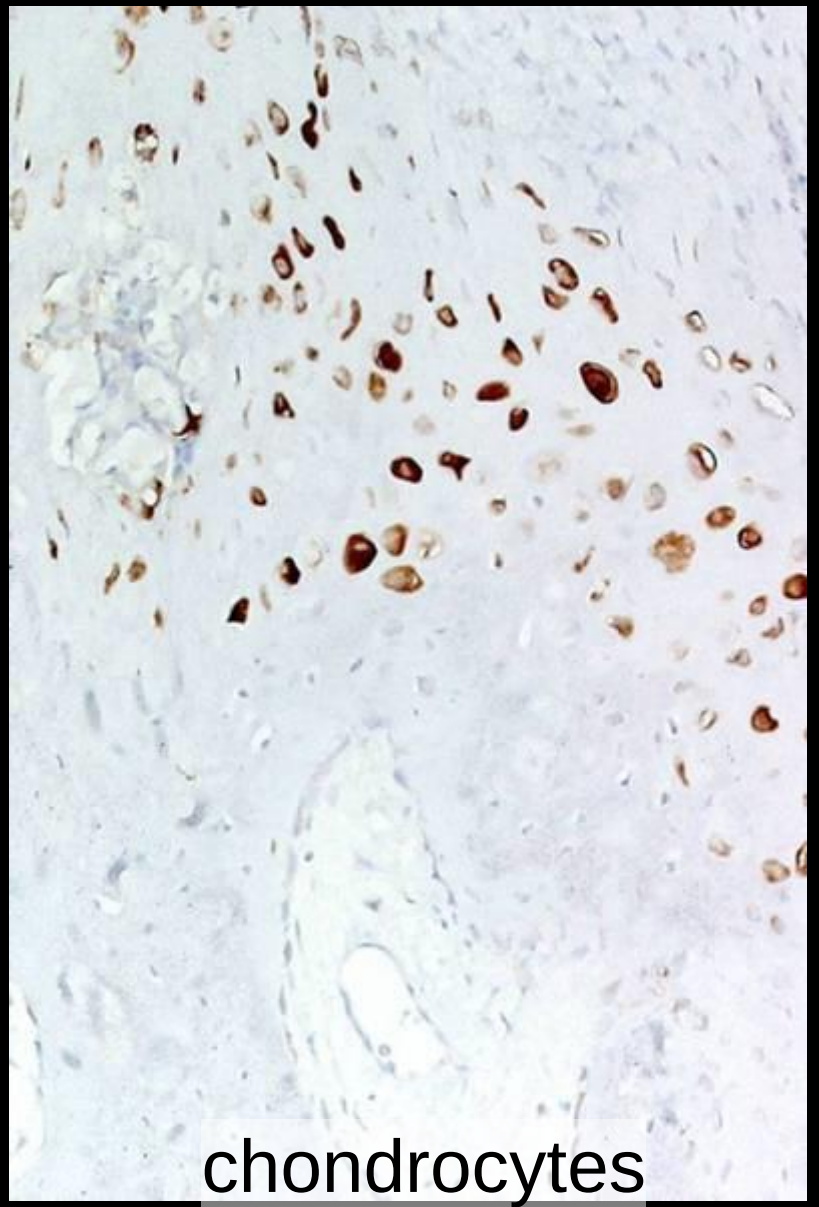
- Family of acid calcium binding proteins 9/13 kDa
- Located in nuclei, cytoplasm and cell membranes
- At least 10 α-chains and one β-chain creating homo- and heterodimers

- S-100 β-chain mainly found in
  - Melanocytes
  - Glial cells
  - Langerhans' cells / interdigitating reticulum cells
  - Fat cells
  - Myoepithelial cells
- Polyclonal antibodies primarily detects the β-chain

S-100 protein

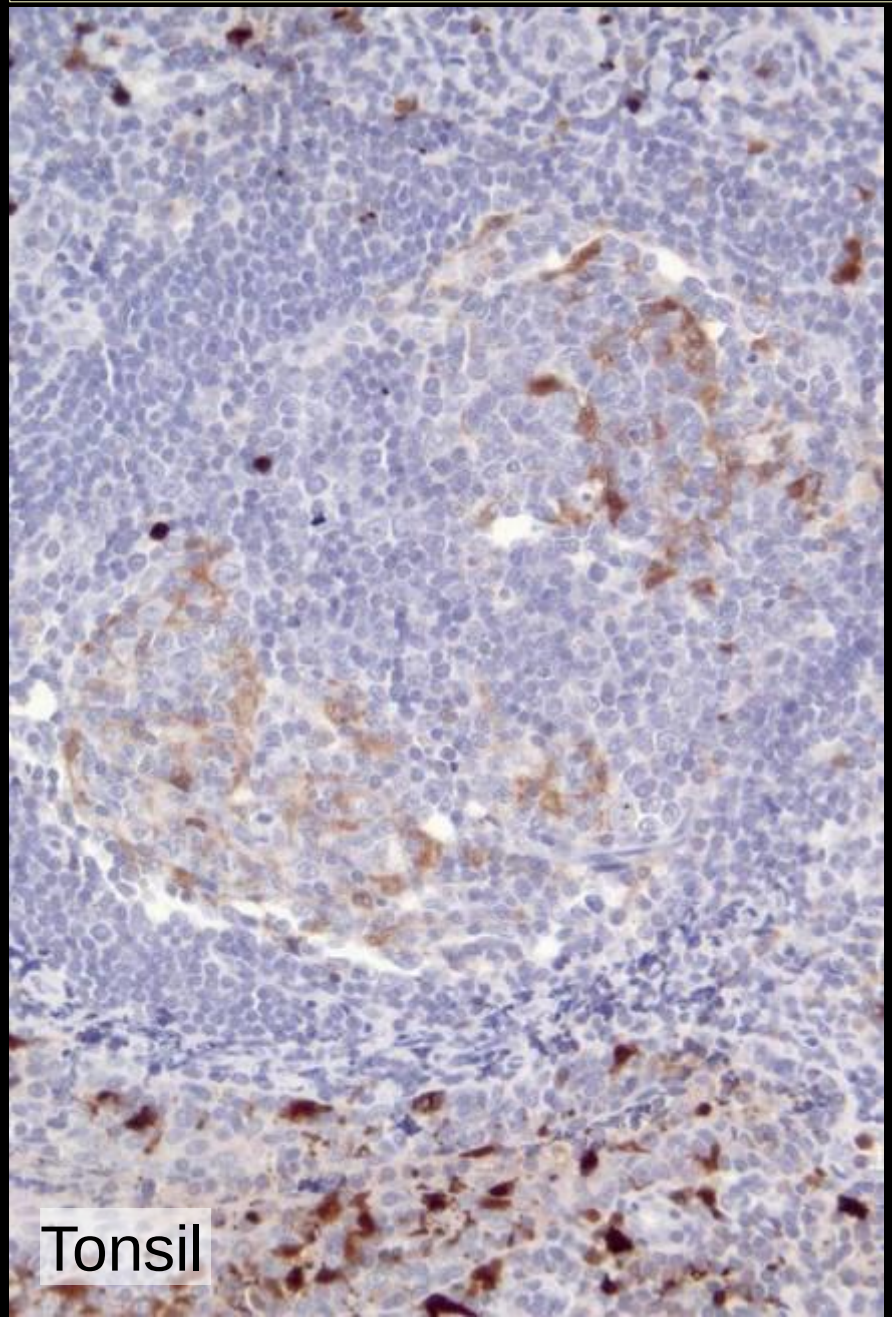


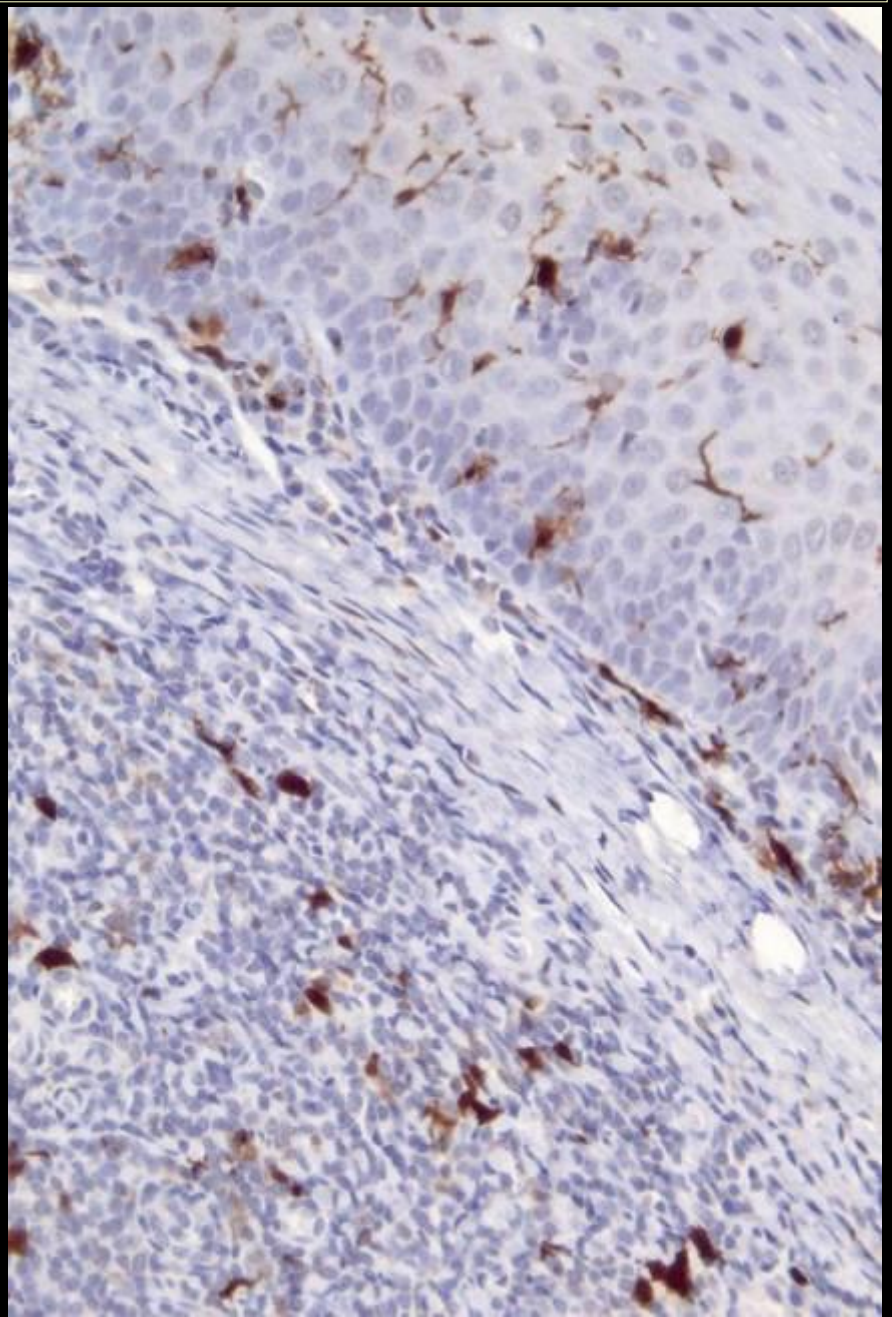
brain



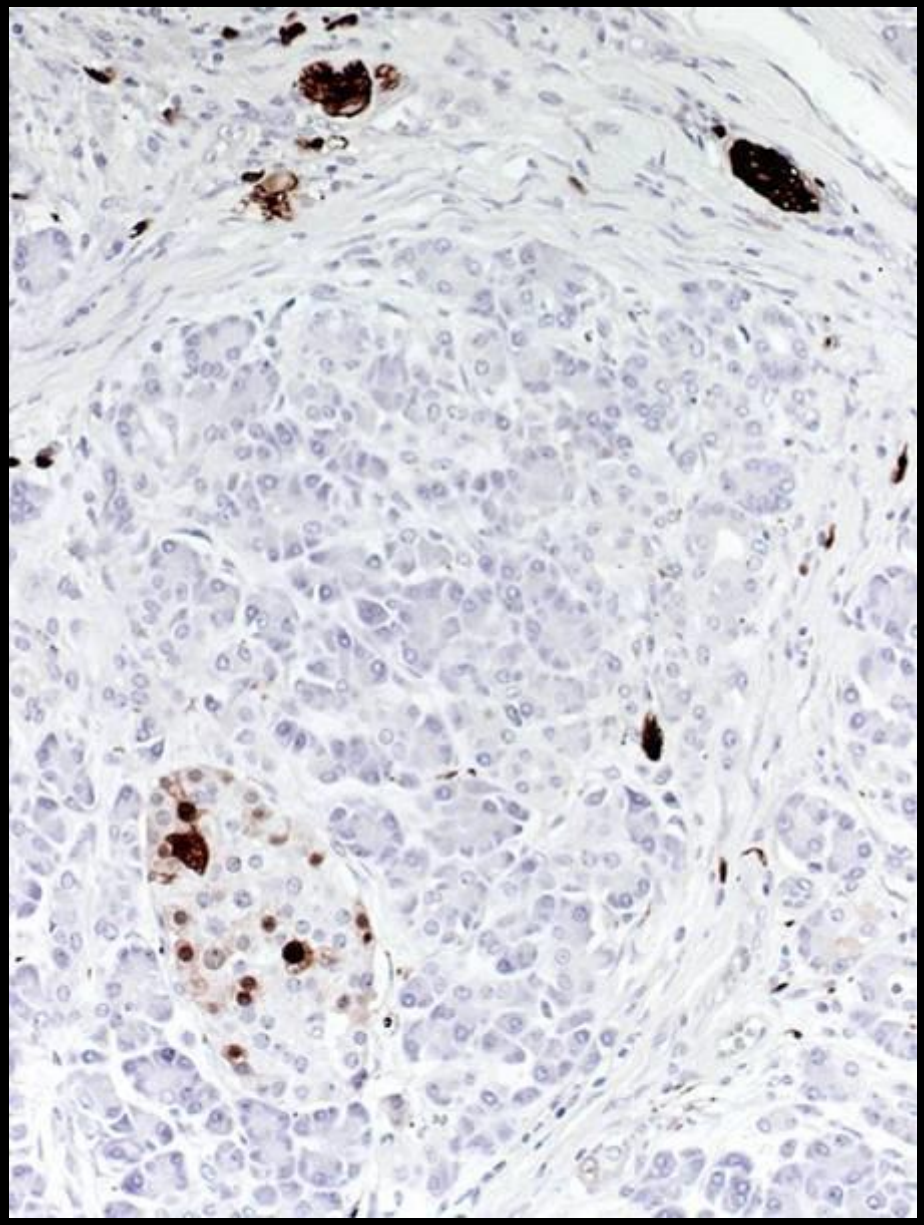
chondrocytes

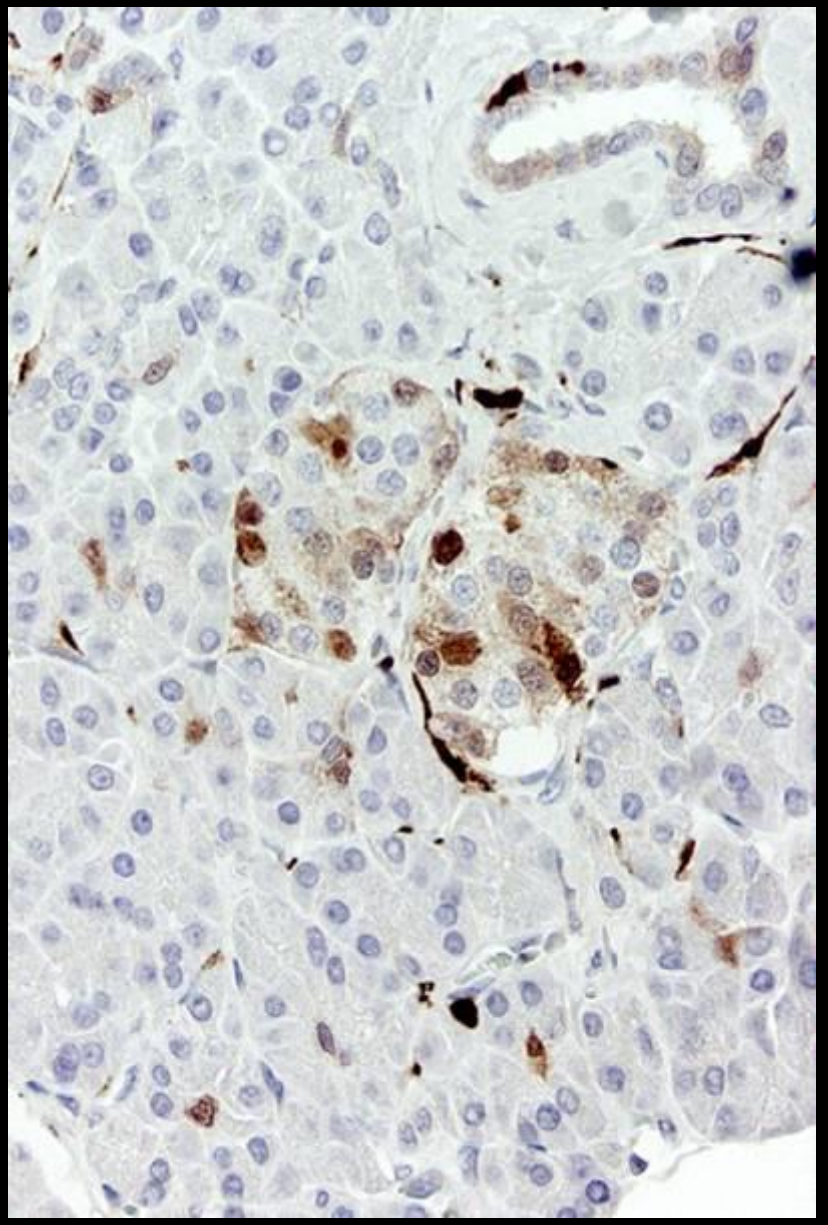
S-100 protein



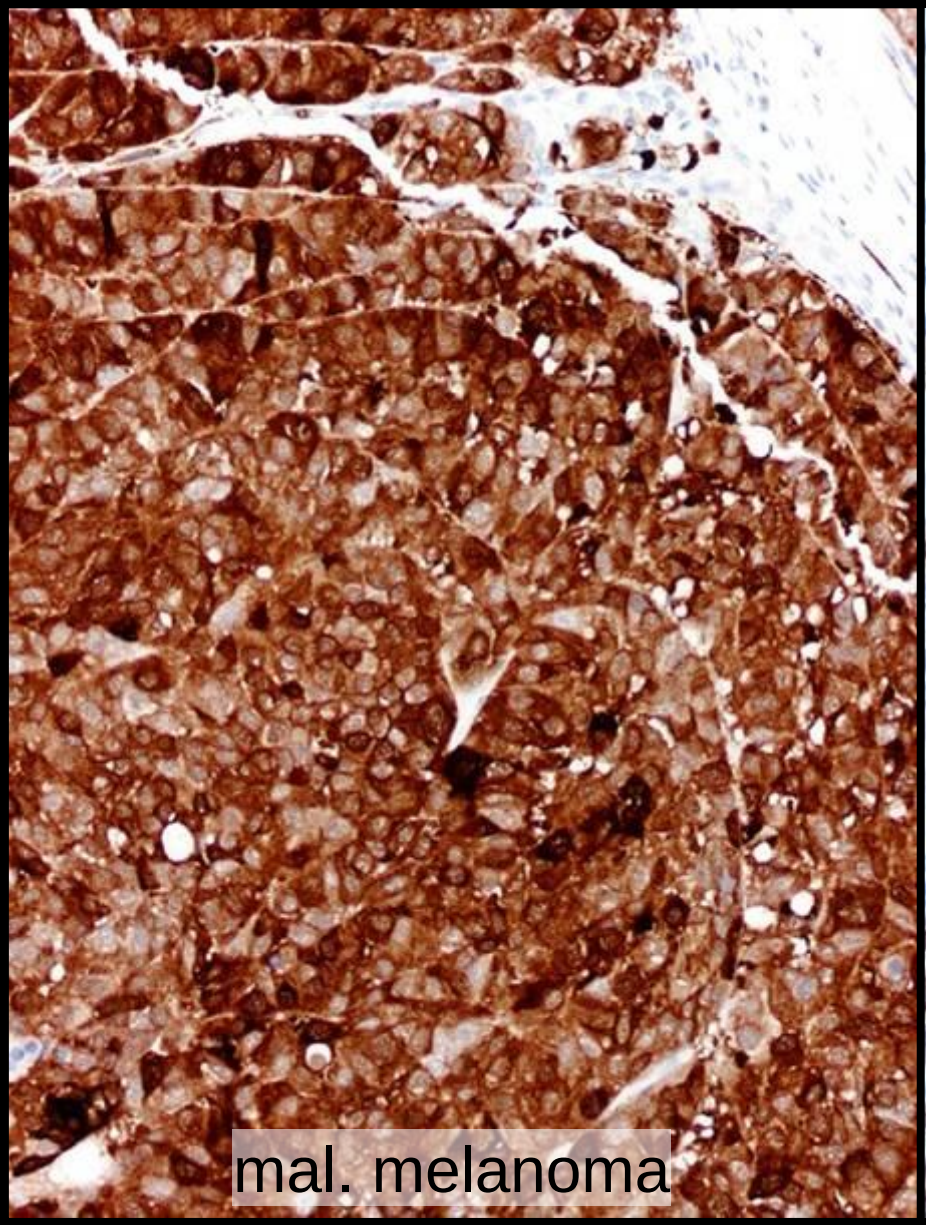


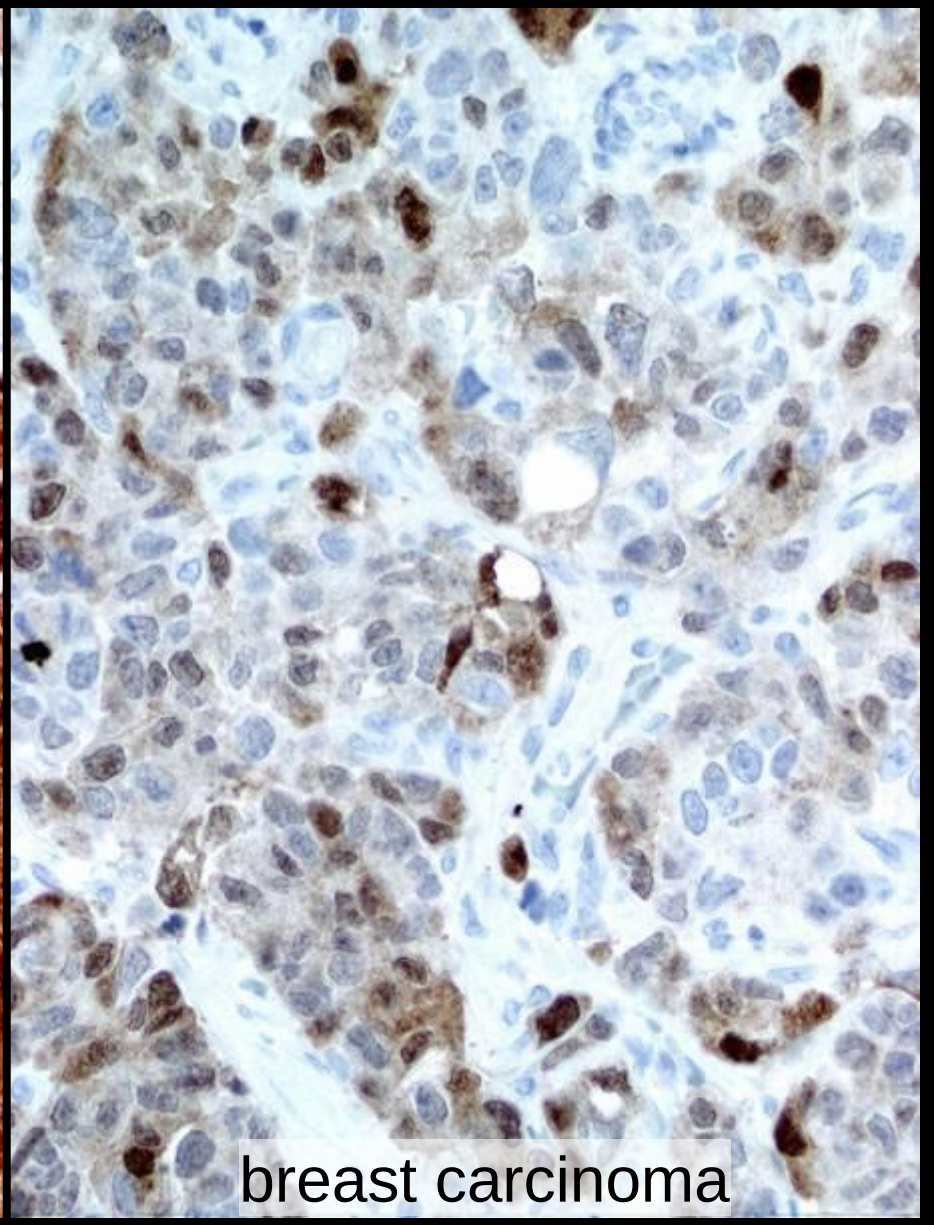
S-100 protein – pancreas





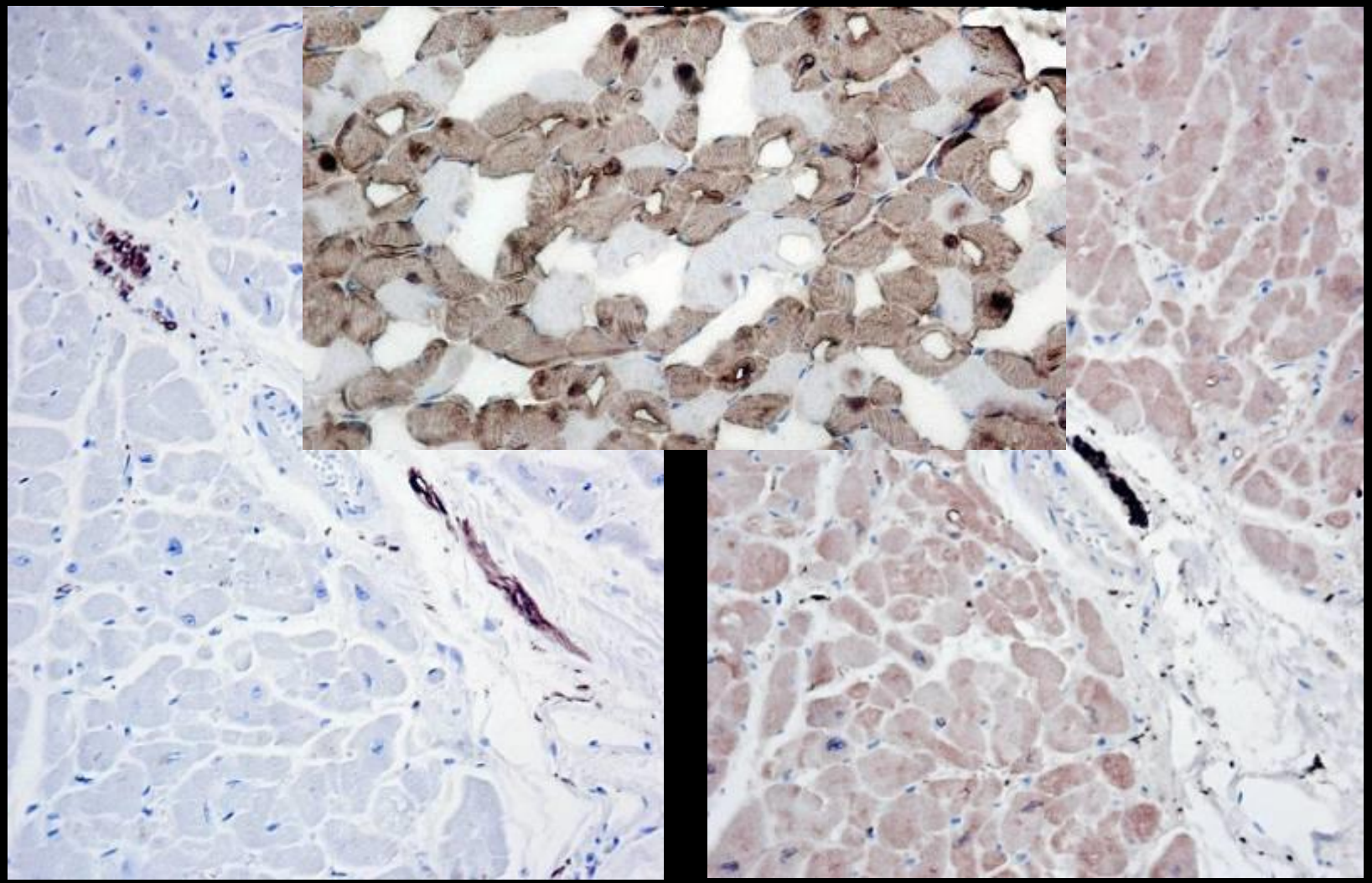
S-100 in malignant tumours





S-100 protein

To HIER or not..



Proteolytic

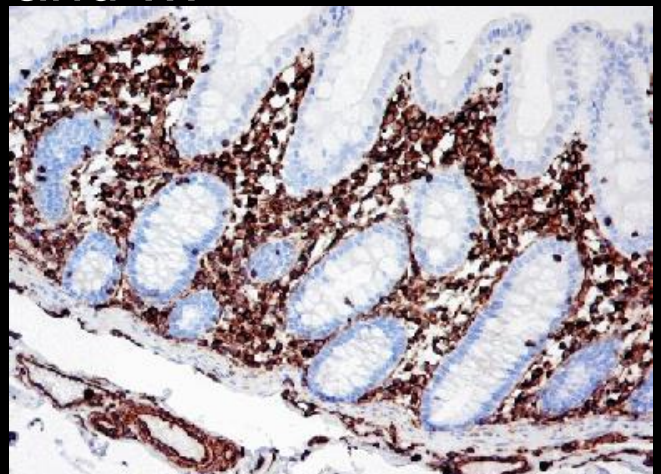
HIER

Primary panel for the unknown primary tumour

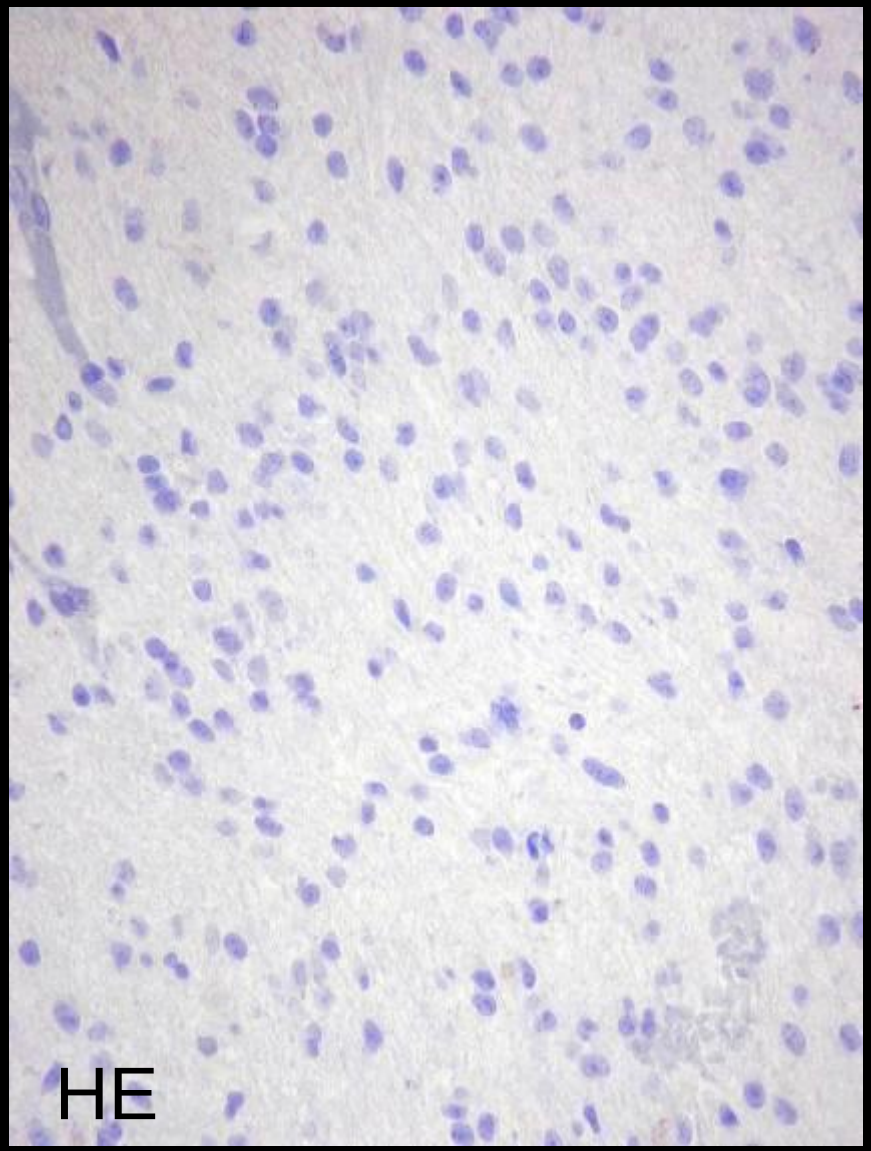
”Real”	CD45	CK	S-100	VIM
Haemato-lymphoid neoplasms	+/(-)	-/(+)	-/(+)	+/(-)
Epithelial neoplasms	-	+/(-)	-/+	-/+
Mesothelial neoplasms	-	+	-	+
Mesenchymal and neuronal neoplasms	-	-/(+)	-/+	+
Non-neuronal neuroepithelial neoplasms	-	-/(+)	+	+
Germ cell neoplasms	-	-/+	-/+	+

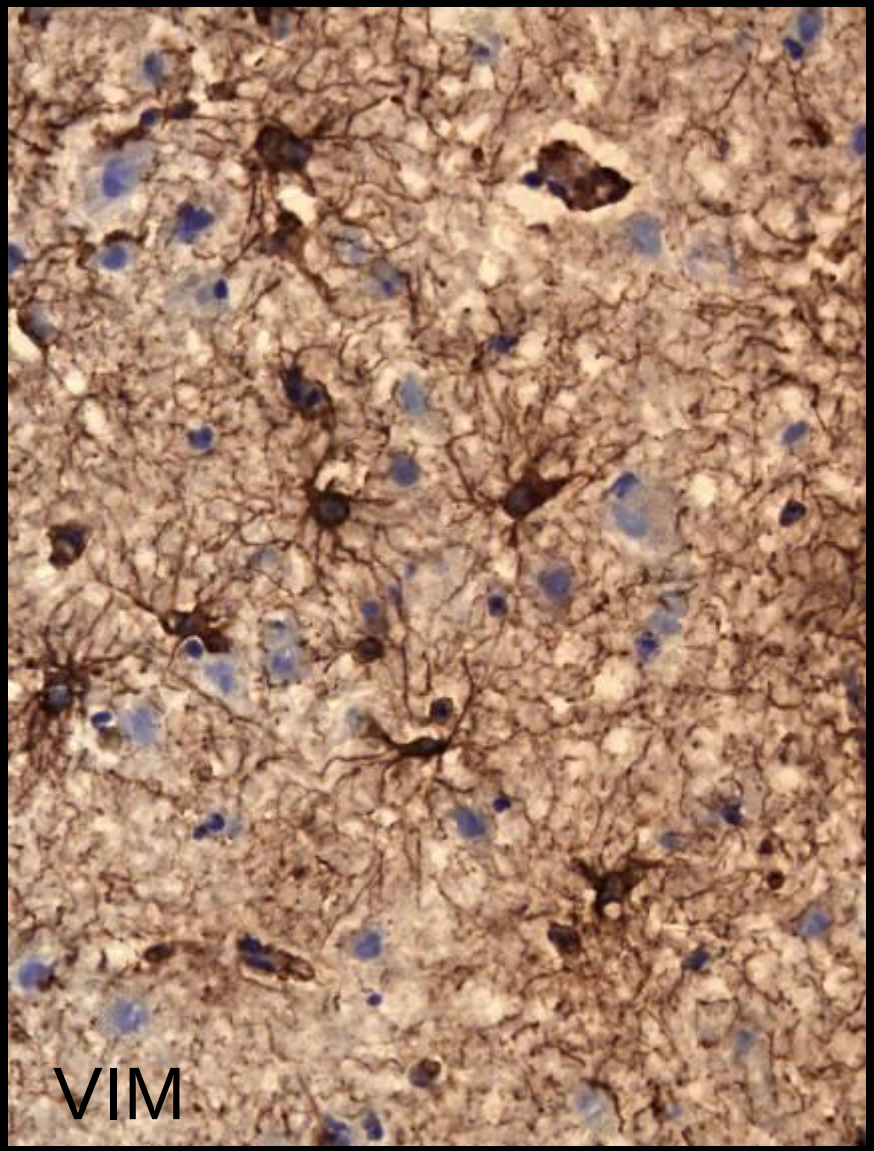
Vimentin

- Cytoplasmic intermediate filament, 57 kDa
- Present in all mesenchymal cells
- Present in early stages of all cells, replaced by other intermediate filaments in most non-mesenchymal cells
- Coexpressed with cytokeratin in some epithelia
  - Endometrium, renal tubules, thyroid gland …
- Coexpressed with cytokeratin in some non-epithelial cells
  - Mesothelium



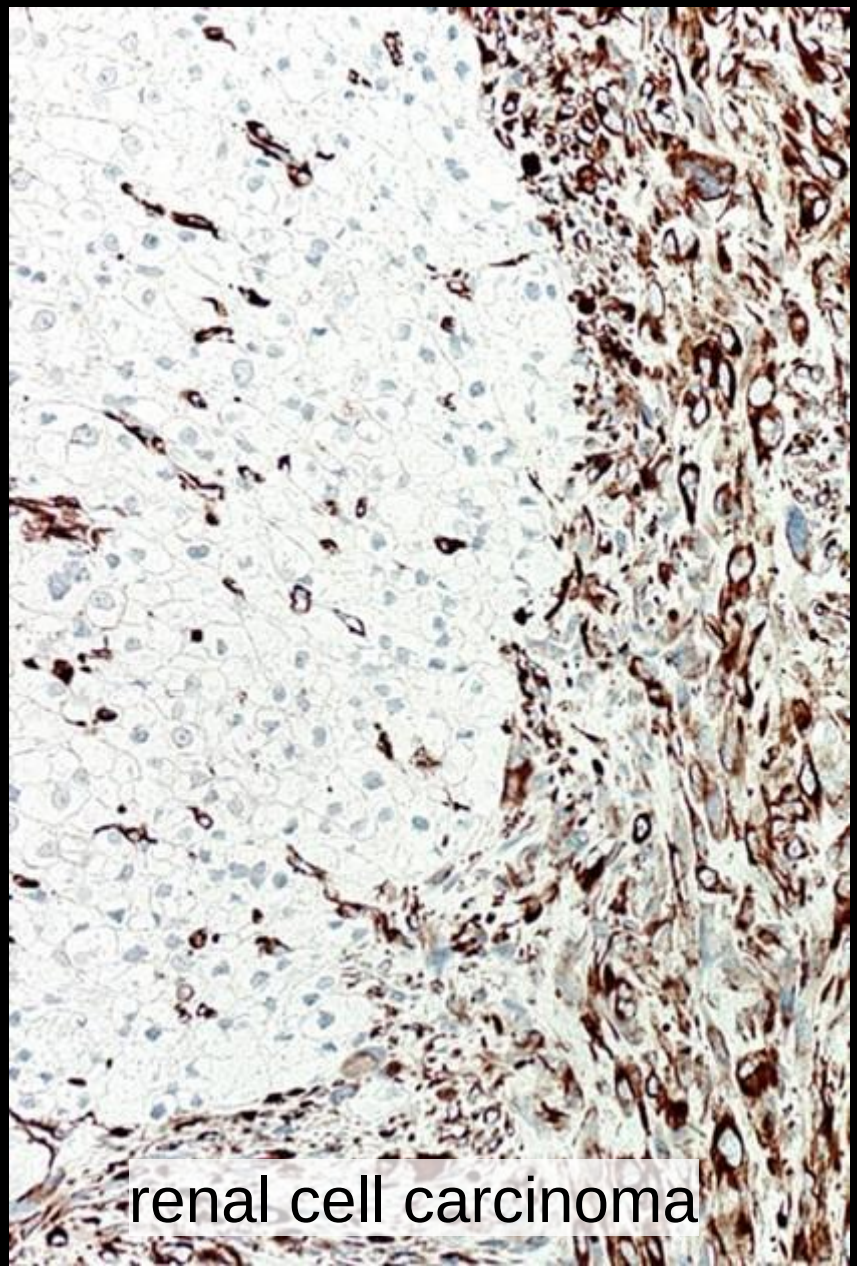
Vimentin in normal tissue



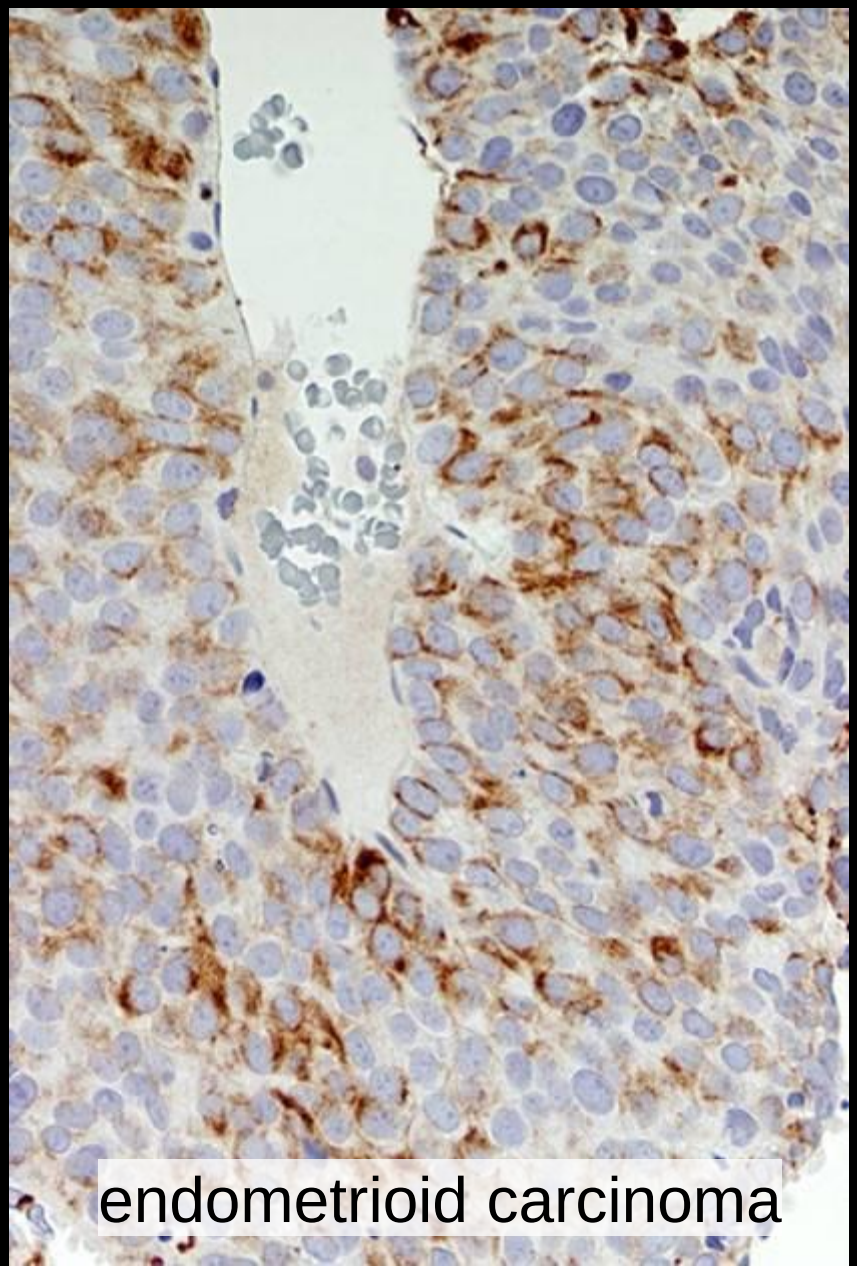


Normal brain

Vimentin in carcinomas

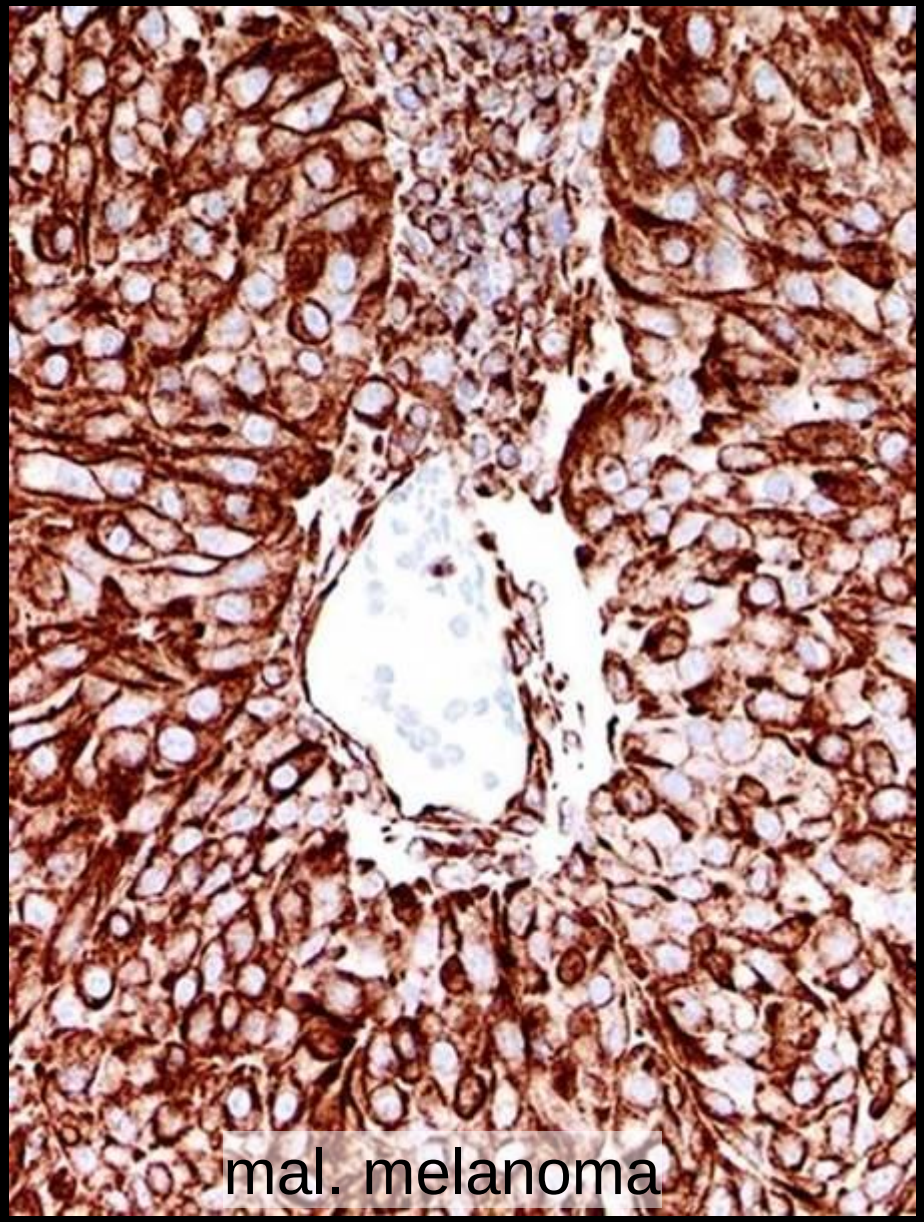


renal cell carcinoma

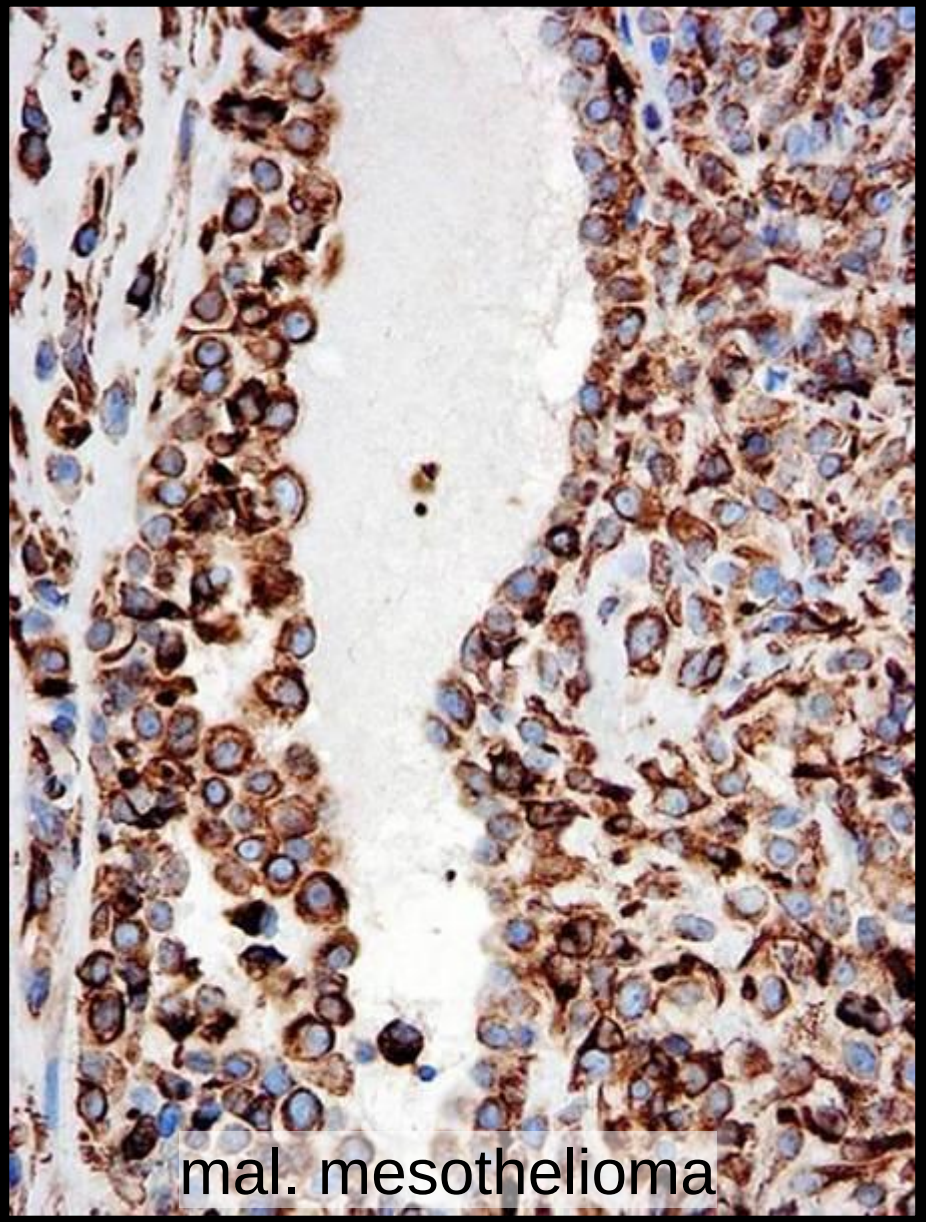


endometrioid carcinoma

Vimentin in non-epithelial tumours



mal. melanoma



mal. mesothelioma

Secondary panels for **carcinoma** identification/subclassification

- **Cytokeratin subtypes**
- Oncofetal proteins
- Transcription factors
- Neuroendocrine proteins
- Hormone receptors
- Secretory proteins
- Cell adhesion molecules
- . . .

- ”Breast markers”
- ”Lung markers”
- ”GI-markers”
- ”Fem.gen.tract markers”
- ”Urinary tract markers”
- Prostate markers
- Squamous cell markers
- ”Mesothelial markers”
- NE cell markers
- ”Liver markers”
- ”Adrenal cortical markers”
- Germinal cell markers