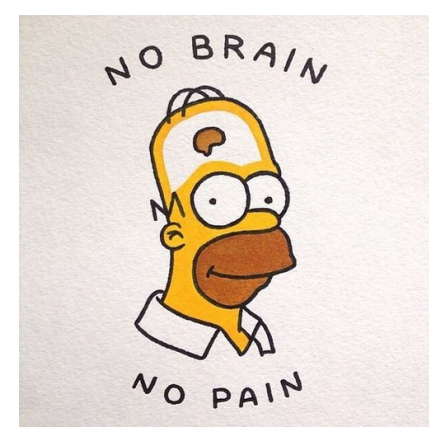




Henrik Hager

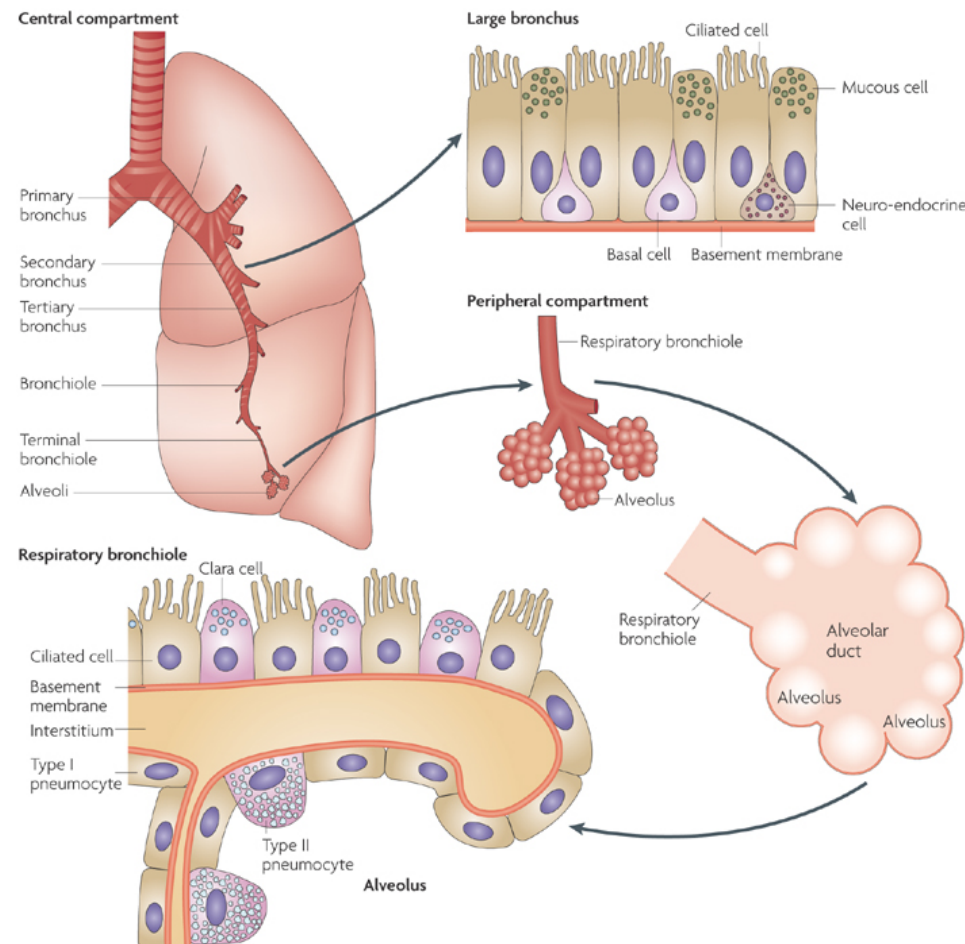
Dept. of Clinical Pathology
Vejle Hospital



Lung Carcinoma



Lung Carcinoma



Lung carcinoma derives from stem cells
in the lung epithelium

Lung Carcinoma



TABLE 1. 2015 WHO Classification of Lung Tumors^{a,b,c}

Histologic Type and Subtypes	ICDO Code
Epithelial tumors	
Adenocarcinoma	8140/3
Lepidic adenocarcinoma ^a	8250/3 ^d
Acinar adenocarcinoma	8551/3 ^d
Papillary adenocarcinoma	8260/3
Micropapillary adenocarcinoma ^a	8265/3
Solid adenocarcinoma	8230/3
Invasive mucinous adenocarcinoma ^a	8253/3 ^d
Mixed invasive mucinous and nonmucinous adenocarcinoma	8254/3 ^d
Colloid adenocarcinoma	8480/3
Fetal adenocarcinoma	8333/3
Enteric adenocarcinoma ^a	8144/3
Minimally invasive adenocarcinoma ^a	
Nonmucinous	8256/3 ^d
Mucinous	8257/3 ^d
Preinvasive lesions	
Atypical adenomatous hyperplasia	8250/0 ^d
Adenocarcinoma in situ ^a	
Nonmucinous	8250/2 ^d
Mucinous	8253/2 ^d
Squamous cell carcinoma	8070/3
Keratinizing squamous cell carcinoma ^a	8071/3
Nonkeratinizing squamous cell carcinoma ^a	8072/3
Basaloid squamous cell carcinoma ^a	8083/3
Preinvasive lesion	
Squamous cell carcinoma in situ	8070/2
Neuroendocrine tumors	
Small cell carcinoma	8041/3
Combined small cell carcinoma	8045/3
Large cell neuroendocrine carcinoma	8013/3
Combined large cell neuroendocrine carcinoma	8013/3
Carcinoid tumors	
Typical carcinoid tumor	8240/3
Atypical carcinoid tumor	8249/3
Preinvasive lesion	
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia	8040/0 ^d
Large cell carcinoma	8012/3
Adenosquamous carcinoma	8560/3
Sarcomatoid carcinomas	
Pleomorphic carcinoma	8022/3
Spindle cell carcinoma	8032/3
Giant cell carcinoma	8031/3
Carcinosarcoma	8980/3
Pulmonary blastoma	8972/3
Other and Unclassified carcinomas	
Lymphoepithelioma-like carcinoma	8082/3
NUT carcinoma ^a	8023/3 ^d
Salivary gland-type tumors	
Mucoepidermoid carcinoma	8430/3
Adenoid cystic carcinoma	8200/3
Epithelial-myoepithelial carcinoma	8562/3
Pleomorphic adenoma	8940/0

(Continued)

TABLE 1. (Continued)

Histologic Type and Subtypes	ICDO Code
Papillomas	
Squamous cell papilloma	8052/0
Exophytic	8052/0
Inverted	8053/0
Glandular papilloma	8260/0
Mixed squamous and glandular papilloma	8560/0
Adenomas	
Sclerosing pneumocytoma ^a	8832/0
Alveolar adenoma	8251/0
Papillary adenoma	8260/0
Mucinous cystadenoma	8470/0
Mucous gland adenoma	8480/0
Mesenchymal tumors	
Pulmonary hamartoma	8992/0 ^d
Chondroma	9220/0
PEComatous tumors ^a	
Lymphangioliomyomatosis	9174/1
PEComa, benign ^a	8714/0
Clear cell tumor	8005/0
PEComa, malignant ^a	8714/3
Congenital peribronchial myofibroblastic tumor	8827/1
Diffuse pulmonary lymphangiomatosis	
Inflammatory myofibroblastic tumor	8825/1
Epithelioid hemangioendothelioma	9133/3
Pleuropulmonary blastoma	8973/3
Synovial sarcoma	9040/3
Pulmonary artery intimal sarcoma	9137/3
Pulmonary myxoid sarcoma with <i>EWSR1-CREB1</i> translocation ^a	8842/3 ^d
Myoepithelial tumors ^a	
Myoepithelioma	8982/0
Myoepithelial carcinoma	8982/3
Lymphohistiocytic tumors	
Extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT lymphoma)	9699/3
Diffuse large cell lymphoma	9680/3
Lymphomatoid granulomatosis	9766/1
Intravascular large B cell lymphoma ^a	9712/3
Pulmonary Langerhans cell histiocytosis	9751/1
Erdheim-Chester disease	9750/1
Tumors of ectopic origin	
Germ cell tumors	
Teratoma, mature	9080/0
Teratoma, immature	9080/1
Intrapulmonary thymoma	8580/3
Melanoma	8270/3
Meningioma, NOS	9530/0

^aThe morphology codes are from the ICDO.^b Behavior is coded /0 for benign tumors, /1 for unspecified, borderline or uncertain behavior, /2 for carcinoma in situ and grade III intraepithelial neoplasia, and /3 for malignant tumors.

^cThe classification is modified from the previous WHO classification¹ taking into account changes in our understanding of these lesions.

^dThis table is reproduced from the 2015 WHO Classification by Travis et al.¹

^eThese new codes were approved by the International Agency on Cancer Research/WHO Committee for ICDO.

^fNew terms changed or entities added since 2004 WHO Classification.³

LCNEC, large cell neuroendocrine carcinoma, WHO, World Health Organization; ICDO International Classification of Diseases for Oncology.

Lung Carcinoma

malignant epithelial tumors
(carcinomas)

TABLE 1. 2015 WHO Classification of Lung Tumors^{a,b,c}

Histologic Type and Subtypes	ICDO Code
Epithelial tumors	
Adenocarcinoma	8140/3
Lepidic adenocarcinoma ^a	8250/3 ^d
Acinar adenocarcinoma	8551/3 ^d
Papillary adenocarcinoma	8260/3
Micropapillary adenocarcinoma ^a	8265/3
Solid adenocarcinoma	8230/3
Invasive mucinous adenocarcinoma ^a	8253/3 ^d
Mixed invasive mucinous and nonmucinous adenocarcinoma	8254/3 ^d
Colloid adenocarcinoma	8480/3
Fetal adenocarcinoma	8333/3
Enteric adenocarcinoma ^a	8144/3
Minimally invasive adenocarcinoma ^a	
Nonmucinous	8256/3 ^d
Mucinous	8257/3 ^d
Preinvasive lesions	
Atypical adenomatous hyperplasia	8250/0 ^d
Adenocarcinoma in situ ^a	
Nonmucinous	8250/2 ^d
Mucinous	8253/2 ^d
Squamous cell carcinoma	8070/3
Keratinizing squamous cell carcinoma ^a	8071/3
Nonkeratinizing squamous cell carcinoma ^a	8072/3
Basaloid squamous cell carcinoma ^a	8083/3
Preinvasive lesion	
Squamous cell carcinoma in situ	8070/2
Neuroendocrine tumors	
Small cell carcinoma	8041/3
Combined small cell carcinoma	8045/3
Large cell neuroendocrine carcinoma	8013/3
Combined large cell neuroendocrine carcinoma	8013/3
Carcinoid tumors	
Typical carcinoid tumor	8240/3
Atypical carcinoid tumor	8249/3
Preinvasive lesion	
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia	8040/0 ^d
Large cell carcinoma	8012/3
Adenosquamous carcinoma	8560/3
Sarcomatoid carcinomas	
Pleomorphic carcinoma	8022/3
Spindle cell carcinoma	8032/3
Giant cell carcinoma	8031/3
Carcinosarcoma	8980/3
Pulmonary blastoma	8972/3
Other and Unclassified carcinomas	
Lymphoepithelioma-like carcinoma	8082/3
NUT carcinoma ^a	8023/3 ^d
Salivary gland-type tumors	
Mucoepidermoid carcinoma	8430/3
Adenoid cystic carcinoma	8200/3
Epithelial-myoepithelial carcinoma	8562/3
Pleomorphic adenoma	8940/0

(Continued)

TABLE 1. (Continued)

Histologic Type and Subtypes	ICDO Code
Papillomas	
Squamous cell papilloma	8052/0
Exophytic	8052/0
Inverted	8053/0
Glandular papilloma	8260/0
Mixed squamous and glandular papilloma	8560/0
Adenomas	
Sclerosing pneumocytoma ^a	8832/0
Alveolar adenoma	8251/0
Papillary adenoma	8260/0
Mucinous cystadenoma	8470/0
Mucous gland adenoma	8480/0
Mesenchymal tumors	
Pulmonary hamartoma	8992/0 ^d
Chondroma	9220/0
PEComatous tumors ^a	
Lymphangioliomyomatosis	9174/1
PEComa, benign ^a	8714/0
Clear cell tumor	8005/0
PEComa, malignant ^a	8714/3
Congenital peribronchial myofibroblastic tumor	8827/1
Diffuse pulmonary lymphangiomatosis	
Inflammatory myofibroblastic tumor	8825/1
Epithelioid hemangioendothelioma	9133/3
Pleuropulmonary blastoma	8973/3
Synovial sarcoma	9040/3
Pulmonary artery intimal sarcoma	9137/3
Pulmonary myxoid sarcoma with <i>EWSR1-CREB1</i> translocation ^a	8842/3 ^d
Myoepithelial tumors ^a	
Myoepithelioma	8982/0
Myoepithelial carcinoma	8982/3
Lymphohistiocytic tumors	
Extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT lymphoma)	9699/3
Diffuse large cell lymphoma	9680/3
Lymphomatoid granulomatosis	9766/1
Intravascular large B cell lymphoma ^a	9712/3
Pulmonary Langerhans cell histiocytosis	9751/1
Erdheim-Chester disease	9750/1
Tumors of ectopic origin	
Germ cell tumors	
Teratoma, mature	9080/0
Teratoma, immature	9080/1
Intrapulmonary thymoma	8580/3
Melanoma	8270/3
Meningioma, NOS	9530/0

^aThe morphology codes are from the ICDO.^b Behavior is coded /0 for benign tumors, /1 for unspecified, borderline or uncertain behavior, /2 for carcinoma in situ and grade III intraepithelial neoplasia, and /3 for malignant tumors.

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Lung Carcinoma

- Adenocarcinoma
- Squamous carcinoma
- Large cell neuroendocrine carcinoma
- Small cell carcinoma

TABLE 1. 2015 WHO Classification of Lung Tumors^{a,b,c}

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Micropapillary adenocarcinoma ^a	8265/3
Solid adenocarcinoma	8230/3
Invasive mucinous adenocarcinoma ^a	8253/3 ^d
Mixed invasive mucinous and nonmucinous adenocarcinoma	8254/3 ^d
Colloid adenocarcinoma	8480/3
Fetal adenocarcinoma	8333/3
Enteric adenocarcinoma ^a	8144/3
Minimally invasive adenocarcinoma ^a	
Nonmucinous	8256/3 ^d
Mucinous	8257/3 ^d
Preinvasive lesions	
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Nonkeratinizing squamous cell carcinoma ^a	8072/3
Basaloid squamous cell carcinoma ^a	8083/3
Preinvasive lesion	
Squamous cell carcinoma in situ	8070/2
Neuroendocrine tumors	
Small cell carcinoma	8041/3
Combined small cell carcinoma	8045/3
Large cell neuroendocrine carcinoma	8013/3
Combined large cell neuroendocrine carcinoma	8013/3
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Pulmonary blastoma	8972/3
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NUT carcinoma ^a	8023/3 ^d
Salivary gland-type tumors	
Mucoepidermoid carcinoma	8430/3
Adenoid cystic carcinoma	8200/3
Epithelial-myoepithelial carcinoma	8562/3
Pleomorphic adenoma	8940/0

(Continued)

TABLE 1. (Continued)

Histologic Type and Subtypes	ICDO Code
Papillomas	
Squamous cell papilloma	8052/0
Exophytic	8052/0
Inverted	8053/0
Glandular papilloma	8260/0
Mixed squamous and glandular papilloma	8560/0
Adenomas	
Sclerosing pneumocytoma ^a	8832/0
Alveolar adenoma	8251/0
Papillary adenoma	8260/0
Mucinous cystadenoma	8470/0
Mucous gland adenoma	8480/0
Mesenchymal tumors	
Pulmonary hamartoma	8992/0 ^d
Chondroma	9220/0
PEComatous tumors^e	
Lymphangioliomyomatosis	9174/1
PEComa, benign ^f	8714/0
Clear cell tumor	8005/0
PEComa, malignant ^f	8714/3
Congenital peribronchial myofibroblastic tumor	8827/1
Diffuse pulmonary lymphangiomatosis	
Inflammatory myofibroblastic tumor	8825/1
Epithelioid hemangioendothelioma	9133/3
Pleuropulmonary blastoma	8973/3
Synovial sarcoma	9040/3
Pulmonary artery intimal sarcoma	9137/3
Pulmonary myxoid sarcoma with <i>EWSR1-CREB1</i> translocation ^g	8842/3 ^d
Myoepithelial tumors^h	
Myoepithelioma	8982/0
Myoepithelial carcinoma	8982/3
Lymphohistiocytic tumors	
Extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT lymphoma)	9699/3
Diffuse large cell lymphoma	9680/3
Lymphomatoid granulomatosis	9766/1
Intravascular large B cell lymphoma ^a	9712/3
Pulmonary Langerhans cell histiocytosis	9751/1
Erdheim-Chester disease	9750/1
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Germ cell tumors	
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Teratoma, immature	9080/1
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Lung Carcinoma

Patologitype	2016
Småcellet karcinom	12,4
Storcellet neuroendokrint karcinom	0,8
Ikke småcellet karcinom	10,1
Planocellulært karcinom	18,4
Adenokarcinom	44,8
Storcellet karcinom	0,0
Adenoskvamøst karcinom	0,3
Neuroendokrin tumor	0,7
Karcinoid tumor	1,6
Anden malign primær lungecancer (NOS)	3,9
Blandingstumor	1,7
Ingen patologi	5,4
Antal udredte	4.706

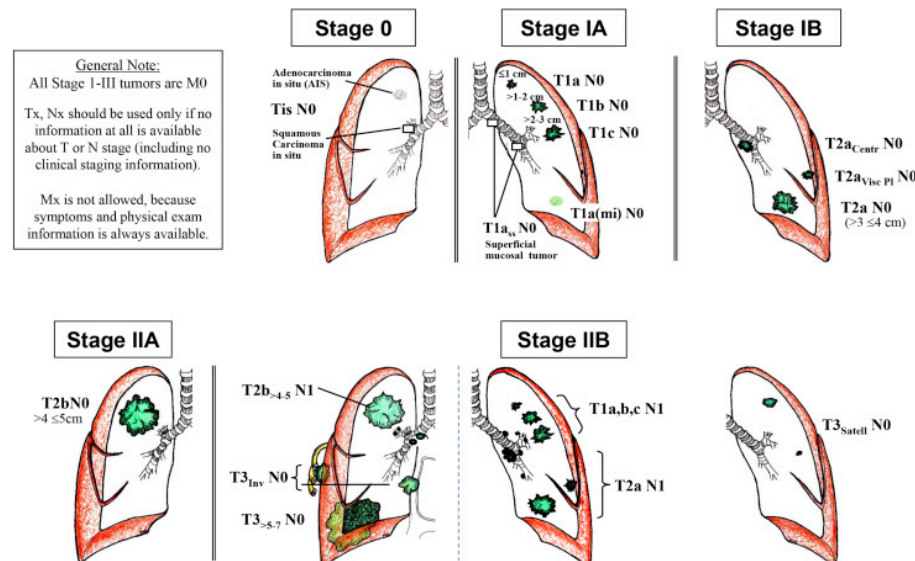
- Adenocarcinoma
- Squamous carcinoma
- Large cell neuroendocrine carcinoma
- Small cell carcinoma

Lung Carcinoma

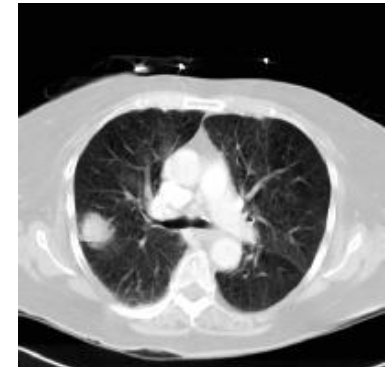
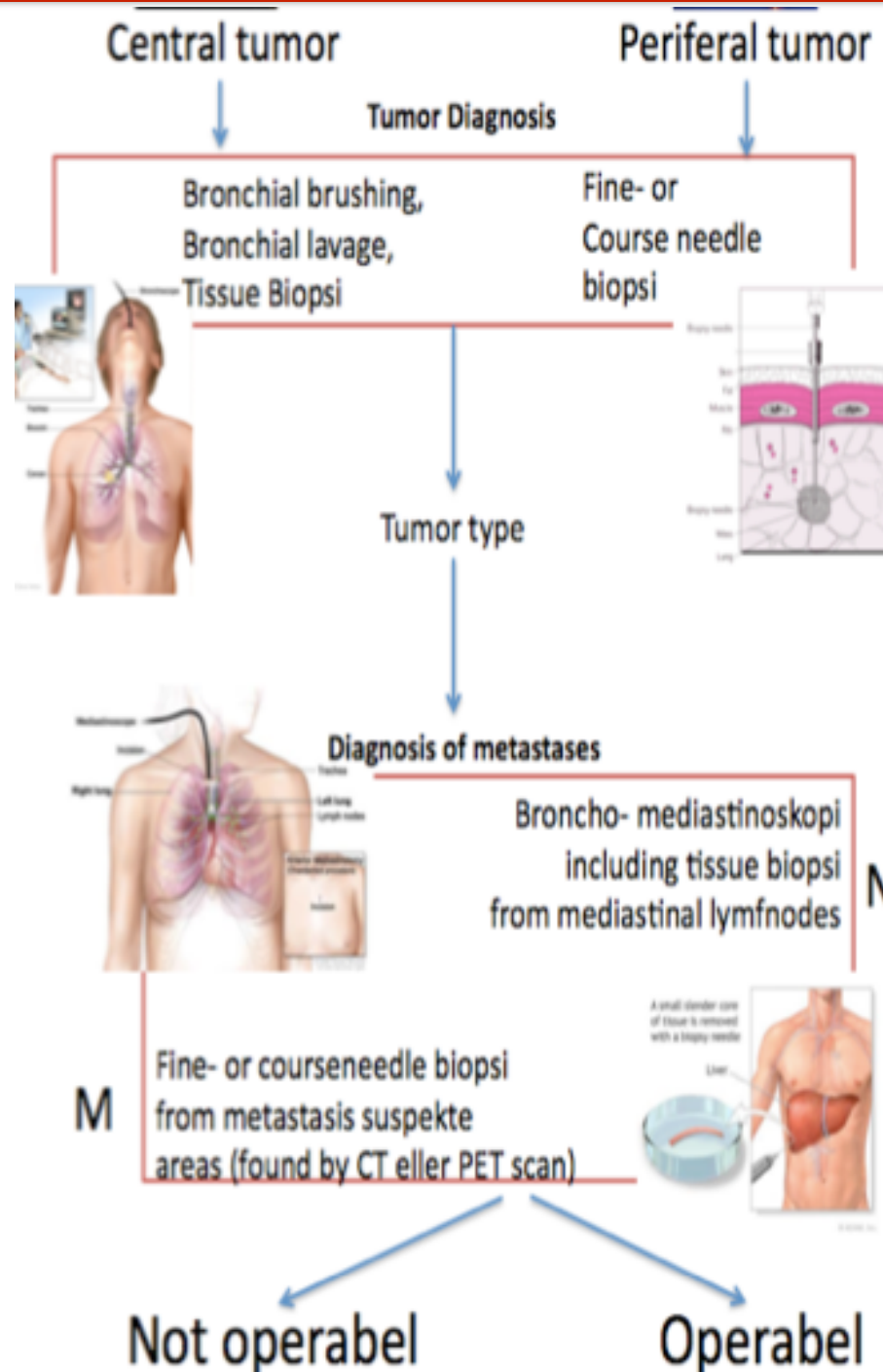
Diagnostic sampling

1. Diagnosis
2. Tumor, Node, Metastasis (TNM)

Lung Cancer Stage Classification (8th Edition)



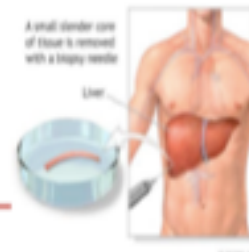
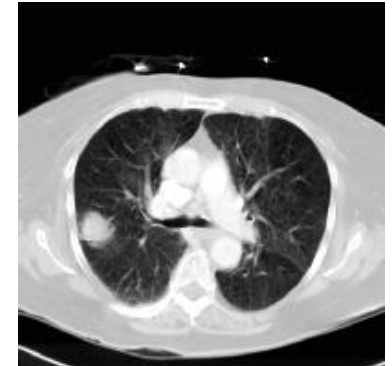
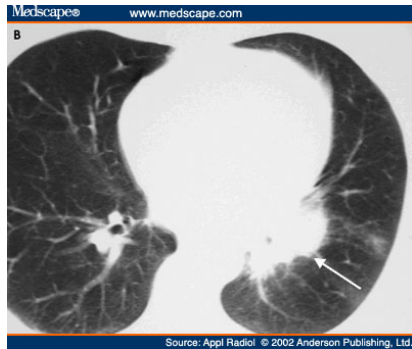
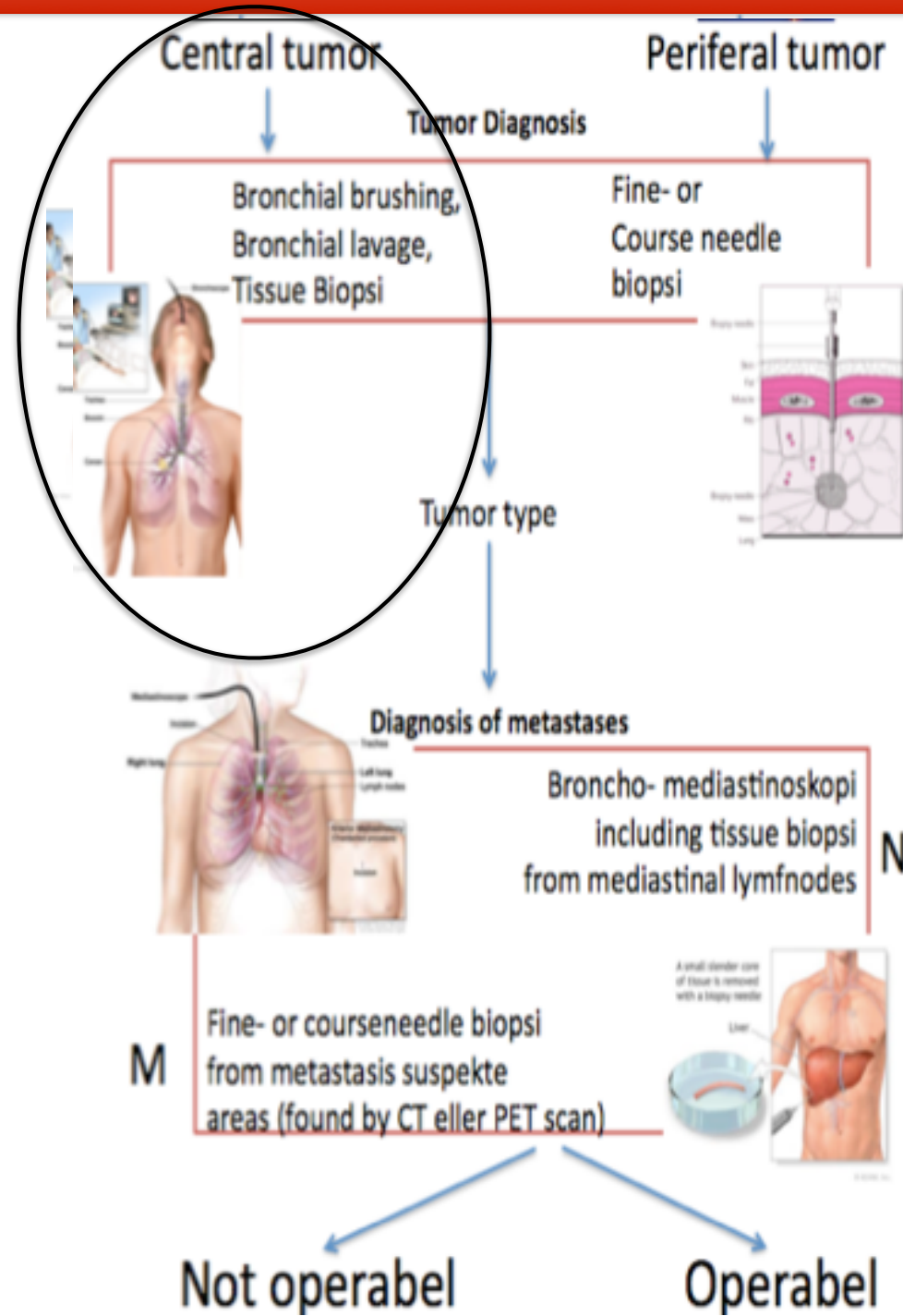
Patoanatomiske analyser i forhold til lungecancerudredning.

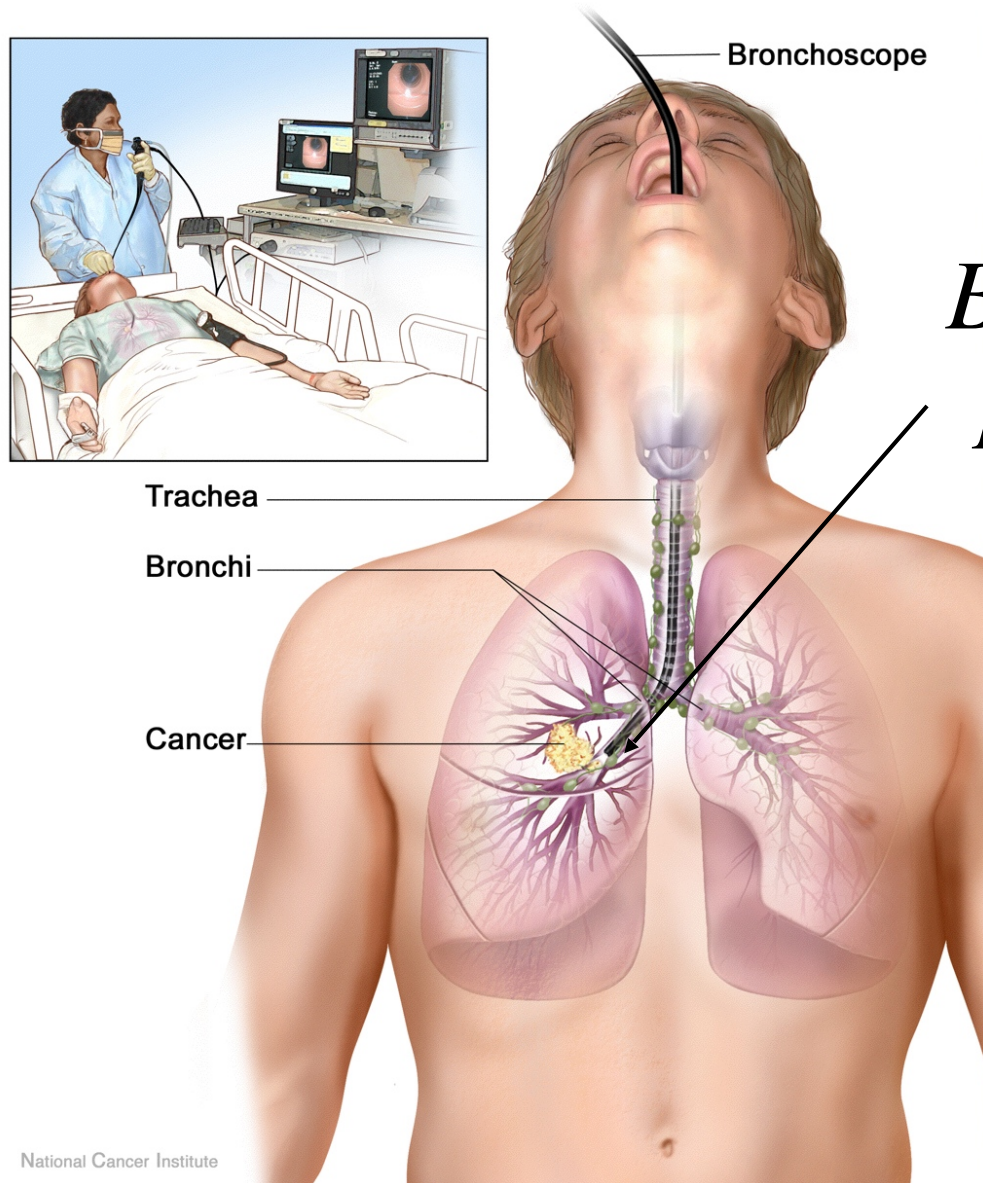


M

N

Patoanatomiske analyser i forhold til lungecancerudredning.





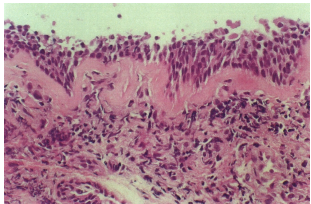
*Bronkialwash**

*Brushbiopsy**

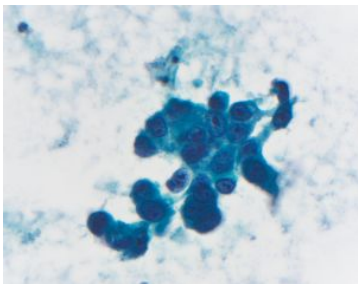
*EBUS**

*EUS**

Biopsy §

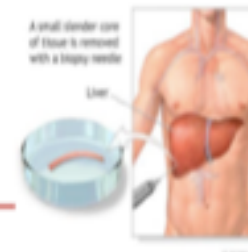
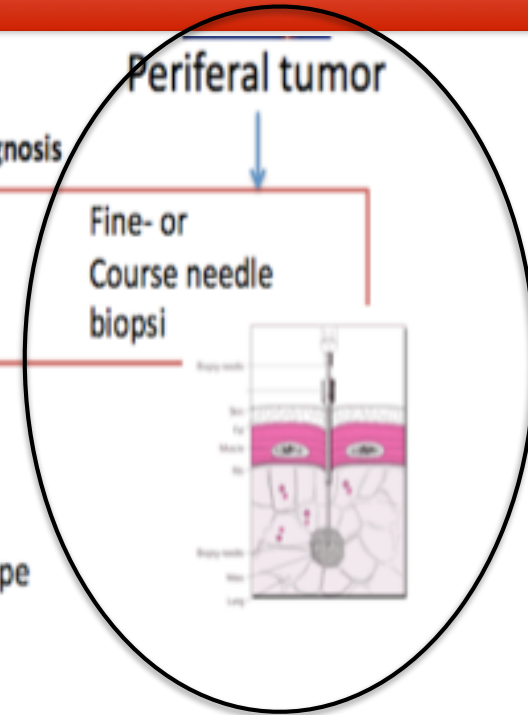
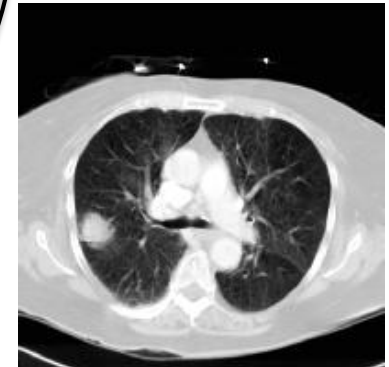
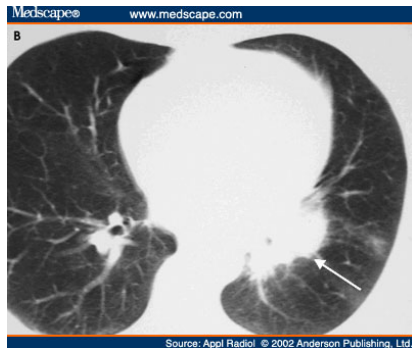
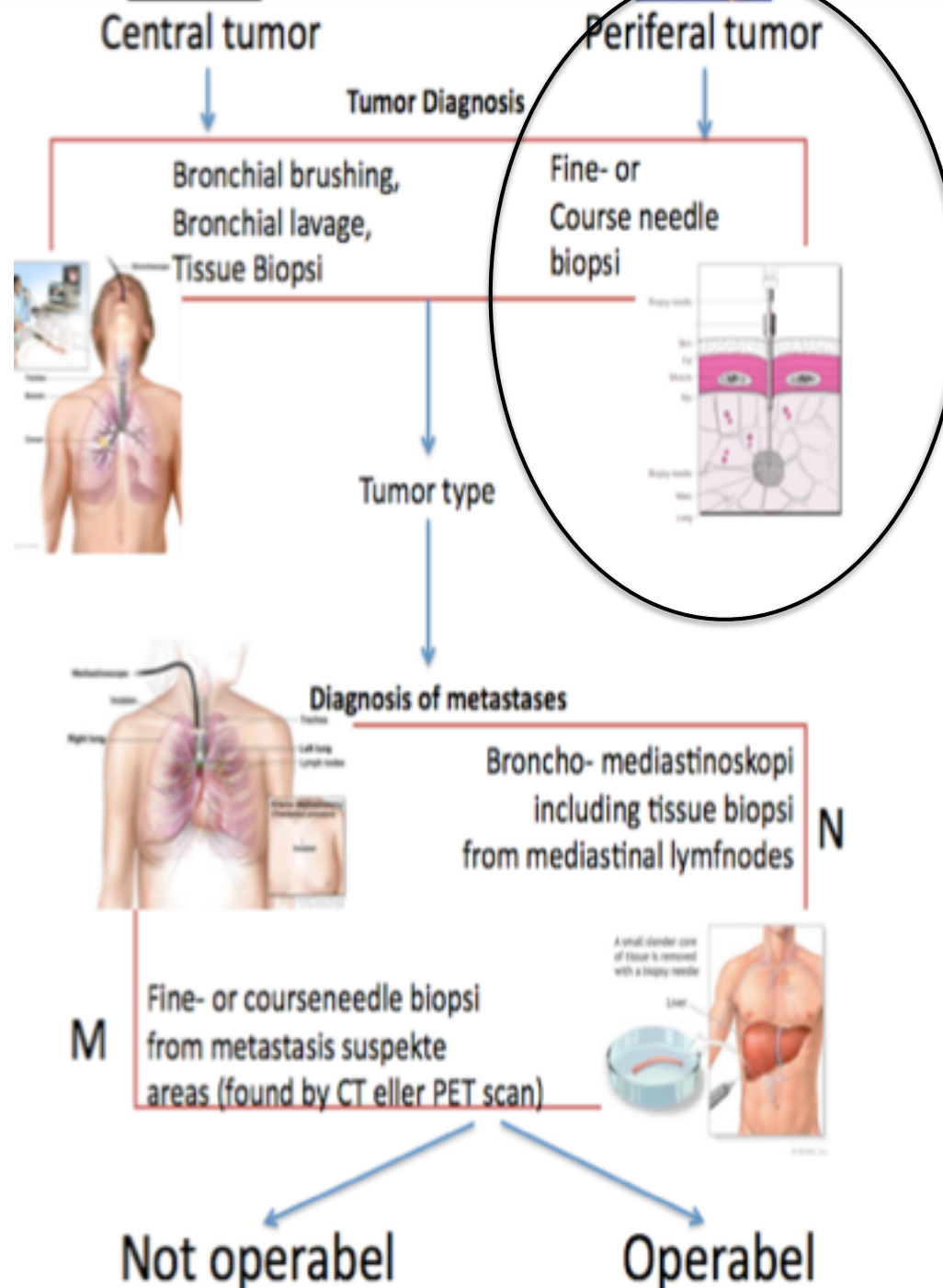


§

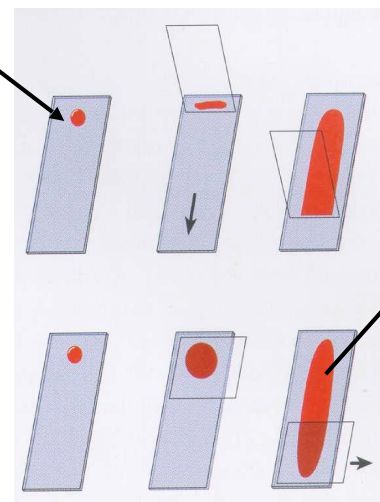
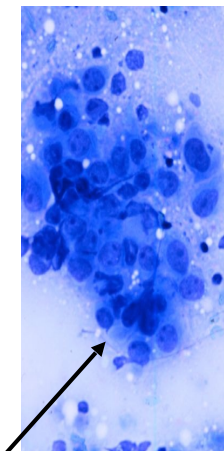
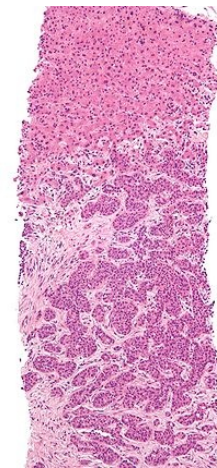
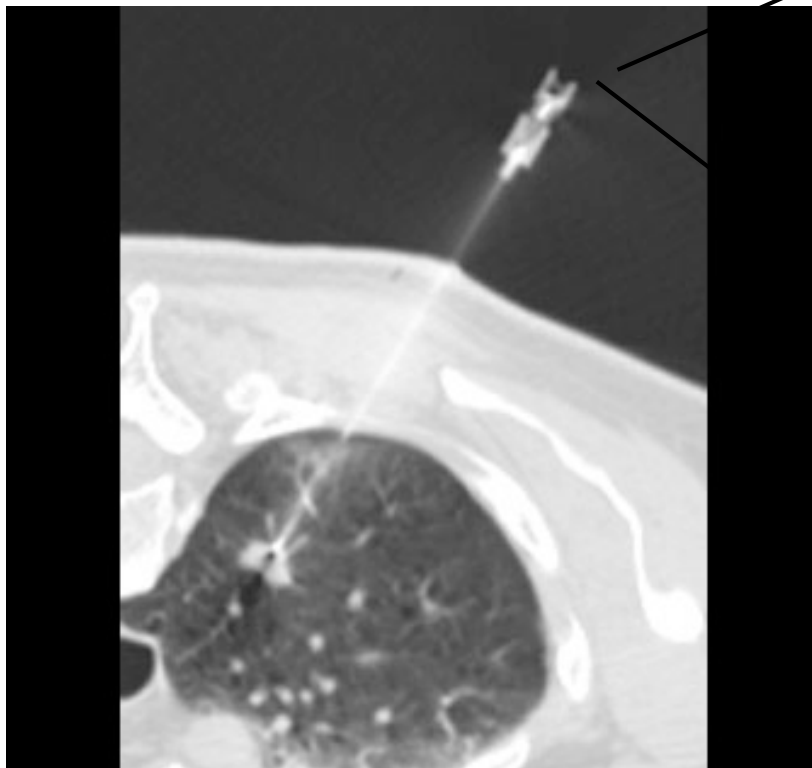


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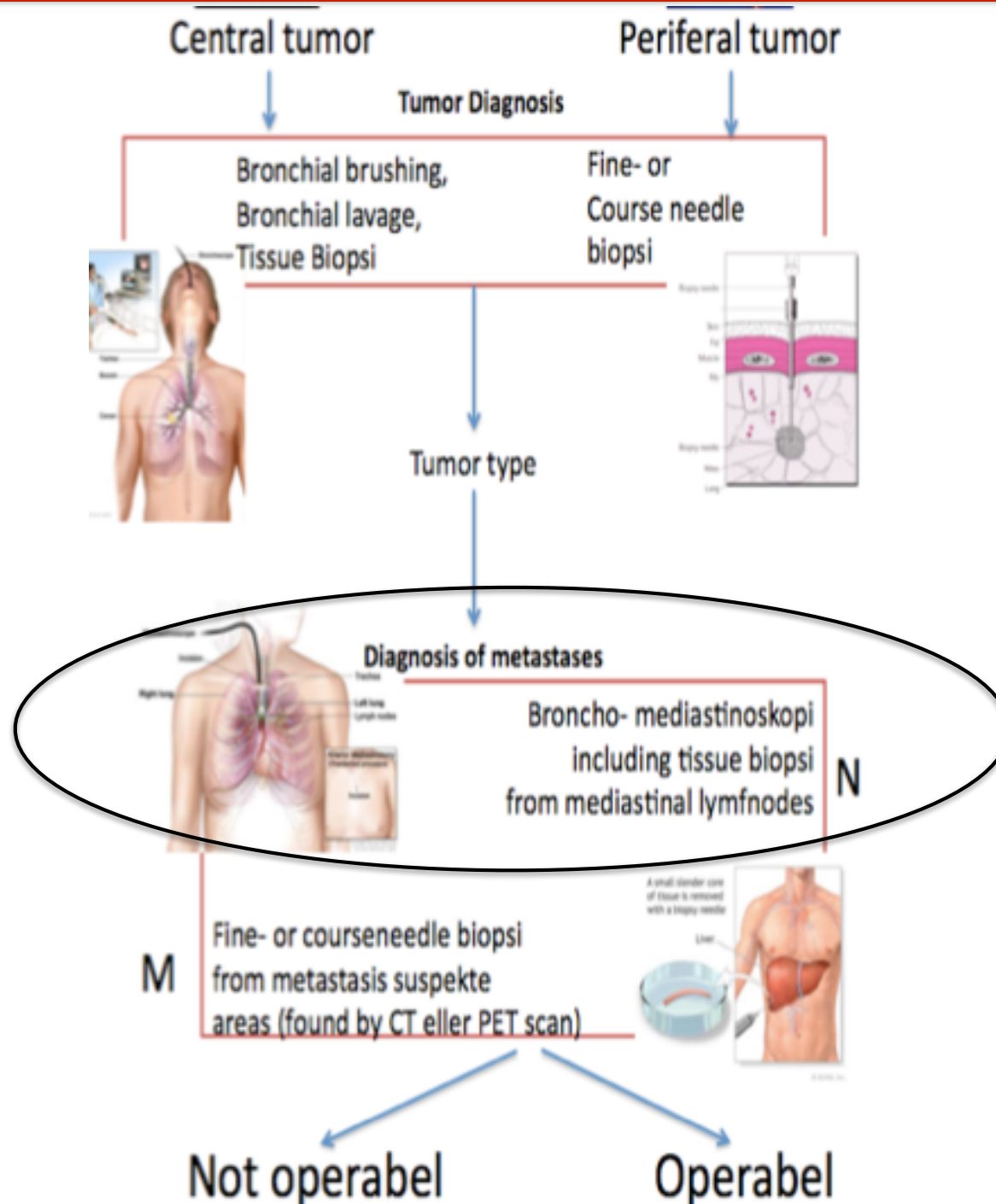
Patoanatomiske analyser i forhold til lungecancerudredning.



Patoanatomiske analyser i forhold til lungecancerudredning.

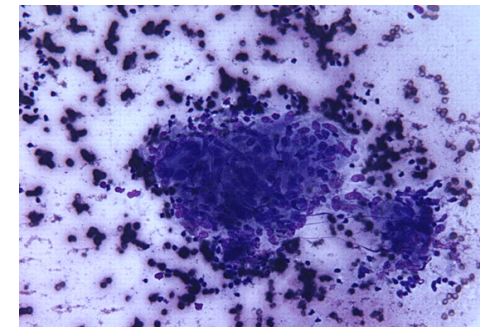
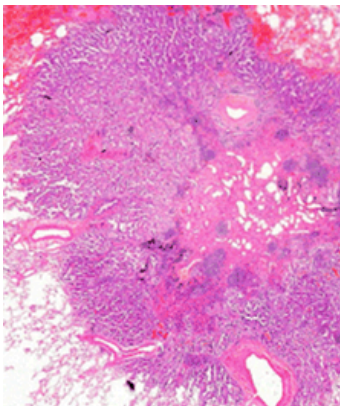
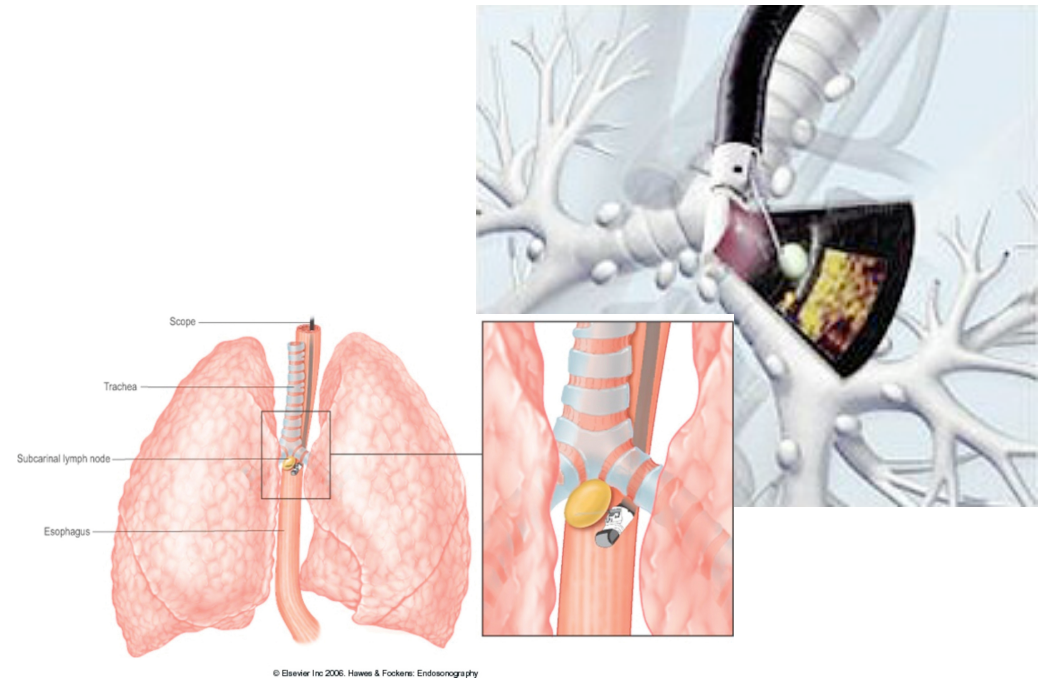
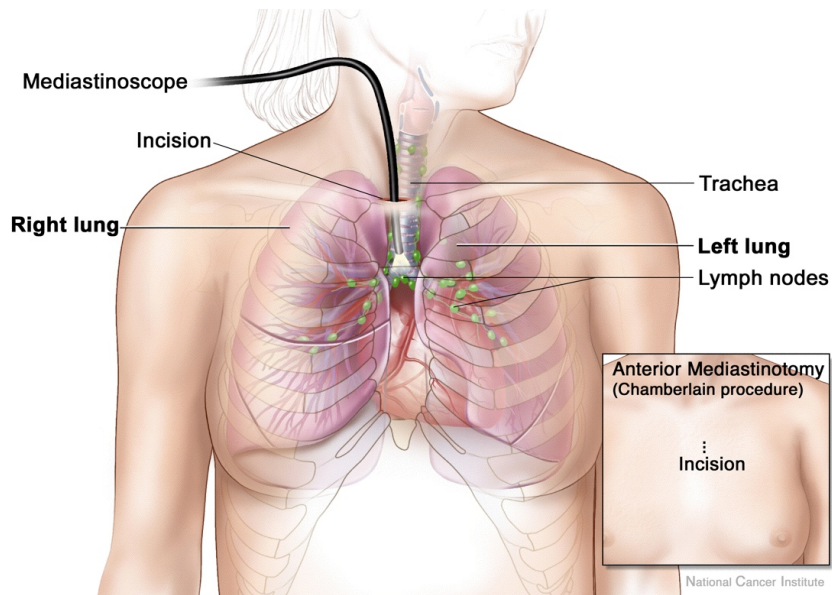


Patoanatomiske analyser i forhold til lungecancerudredning.

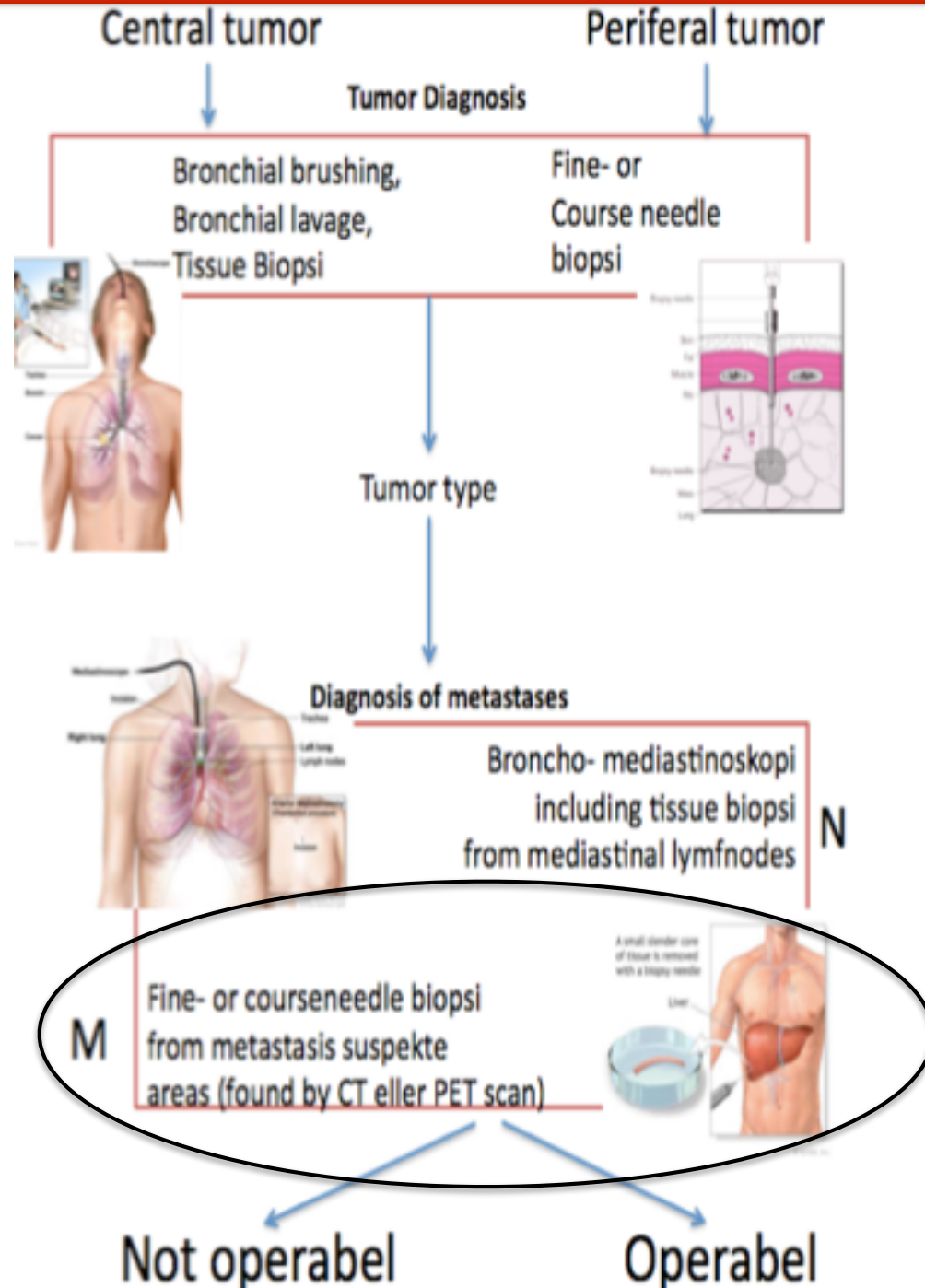


EBUS, EUS

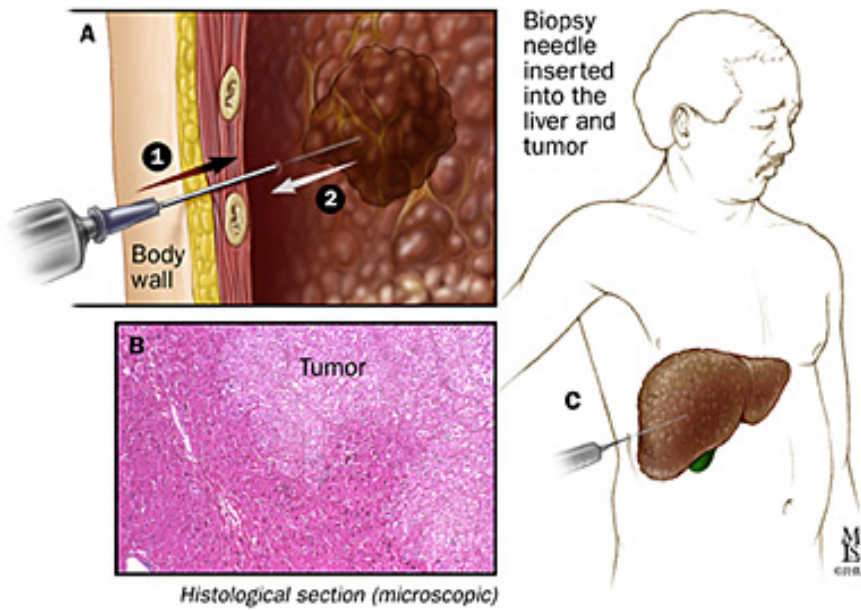
Mediastinoscopy



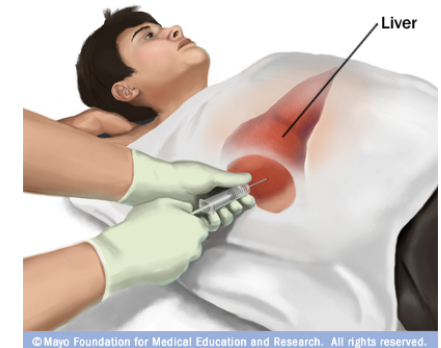
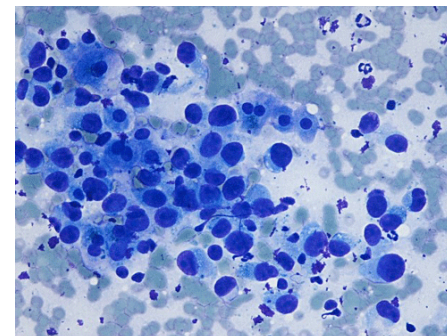
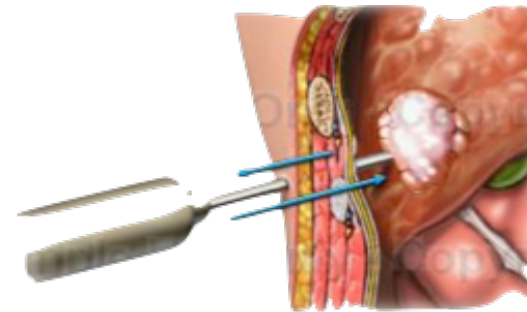
Patoanatomiske analyser i forhold til lungecancerudredning.



Coarse needle biopsy



Fine needle biopsy



Patoanatomical specimen

Histology

Cytologi



Fixation

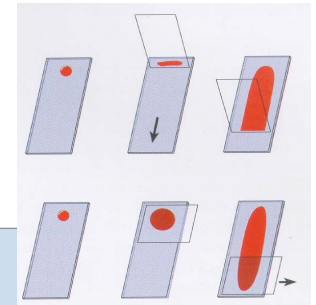
Dehydration

Parafinembedding

Microtomy

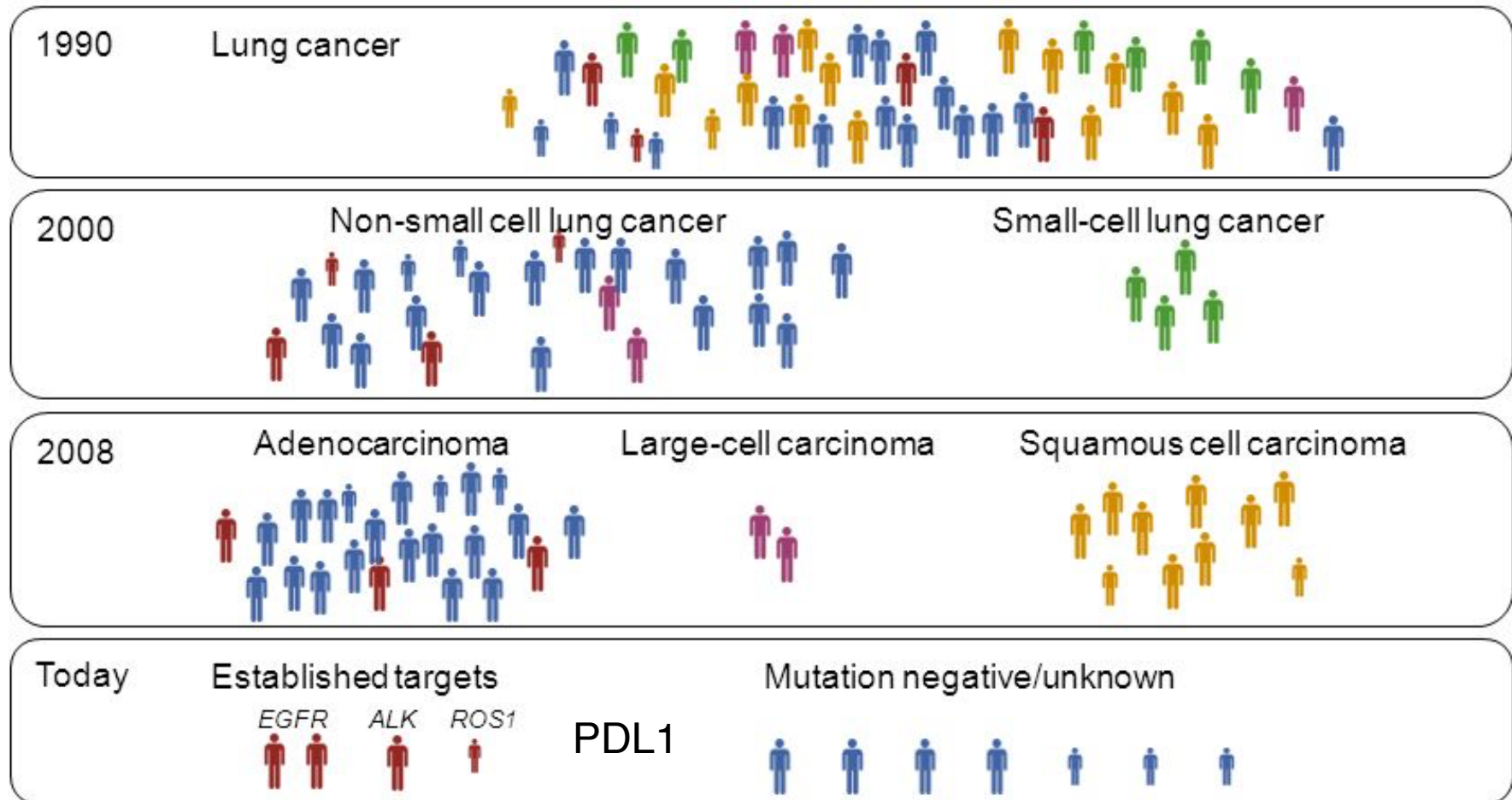
Præparation

Smear preparation

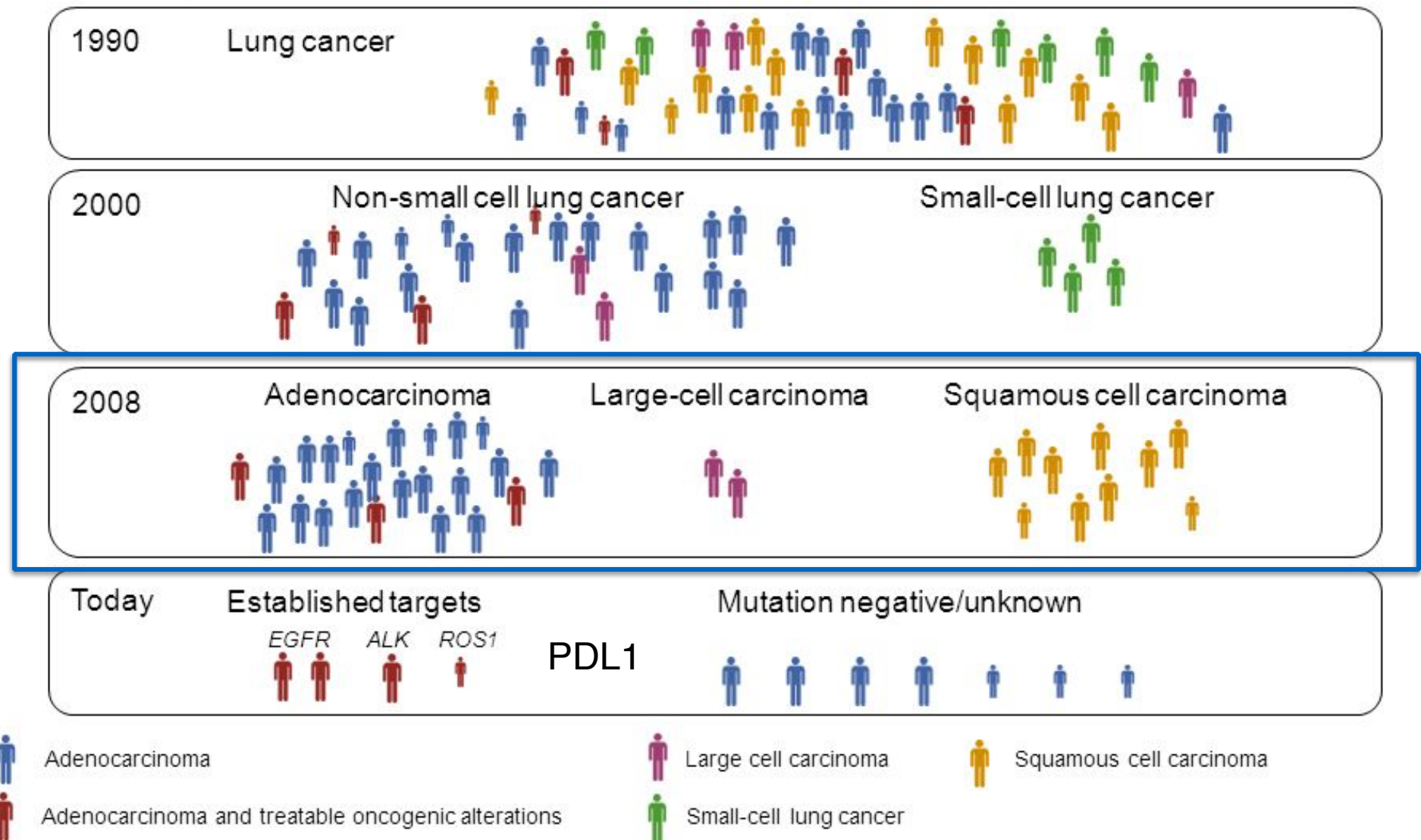


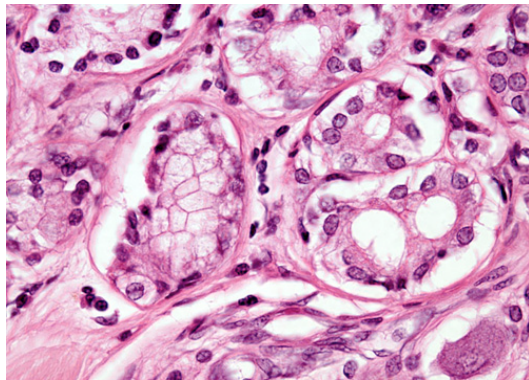
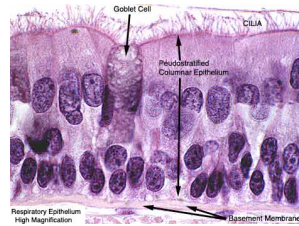
Visualization (Staining)

Patient selection in lung cancer: Evolution over time

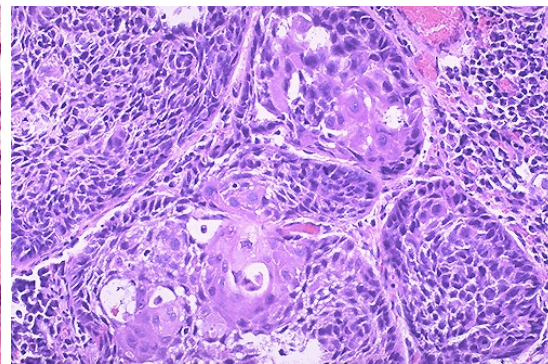


Patient selection in lung cancer: Evolution over time

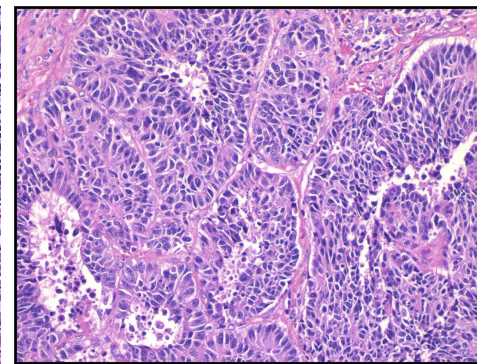




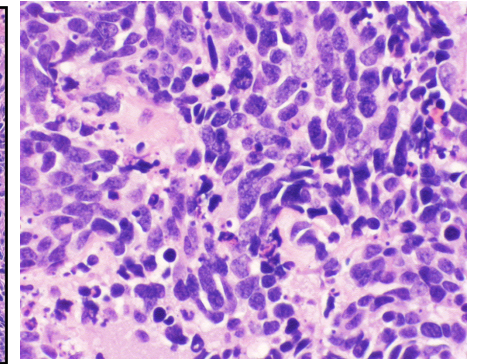
Adenocarcinoma



Squamous carcinoma



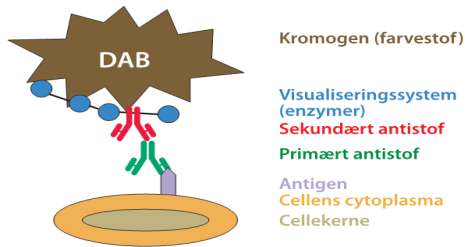
Large cell
neuroendocrine carc.



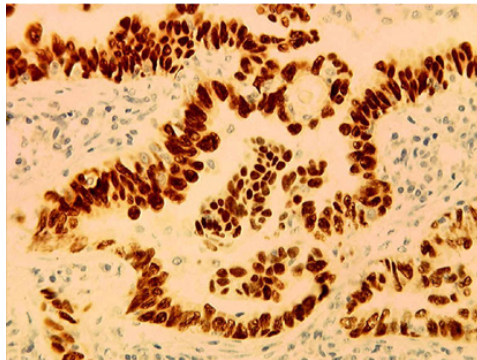
Small cell carcinoma



Non Small Cell Lung Carcinoma (NSCLC)

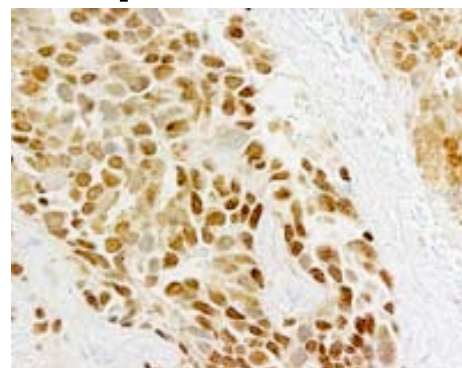


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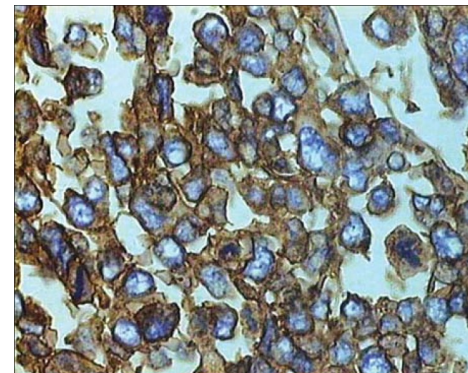
Adenocarcinoma

p63



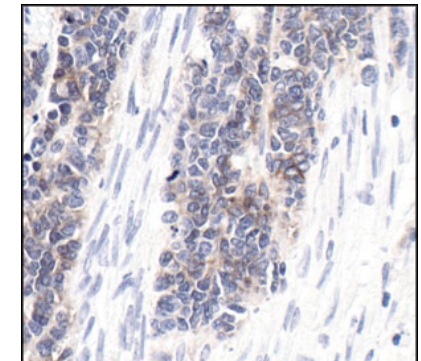
Squamous carcinoma

cd56



Large cell
neuroendocrine carc

cd56



Small cell carcinoma

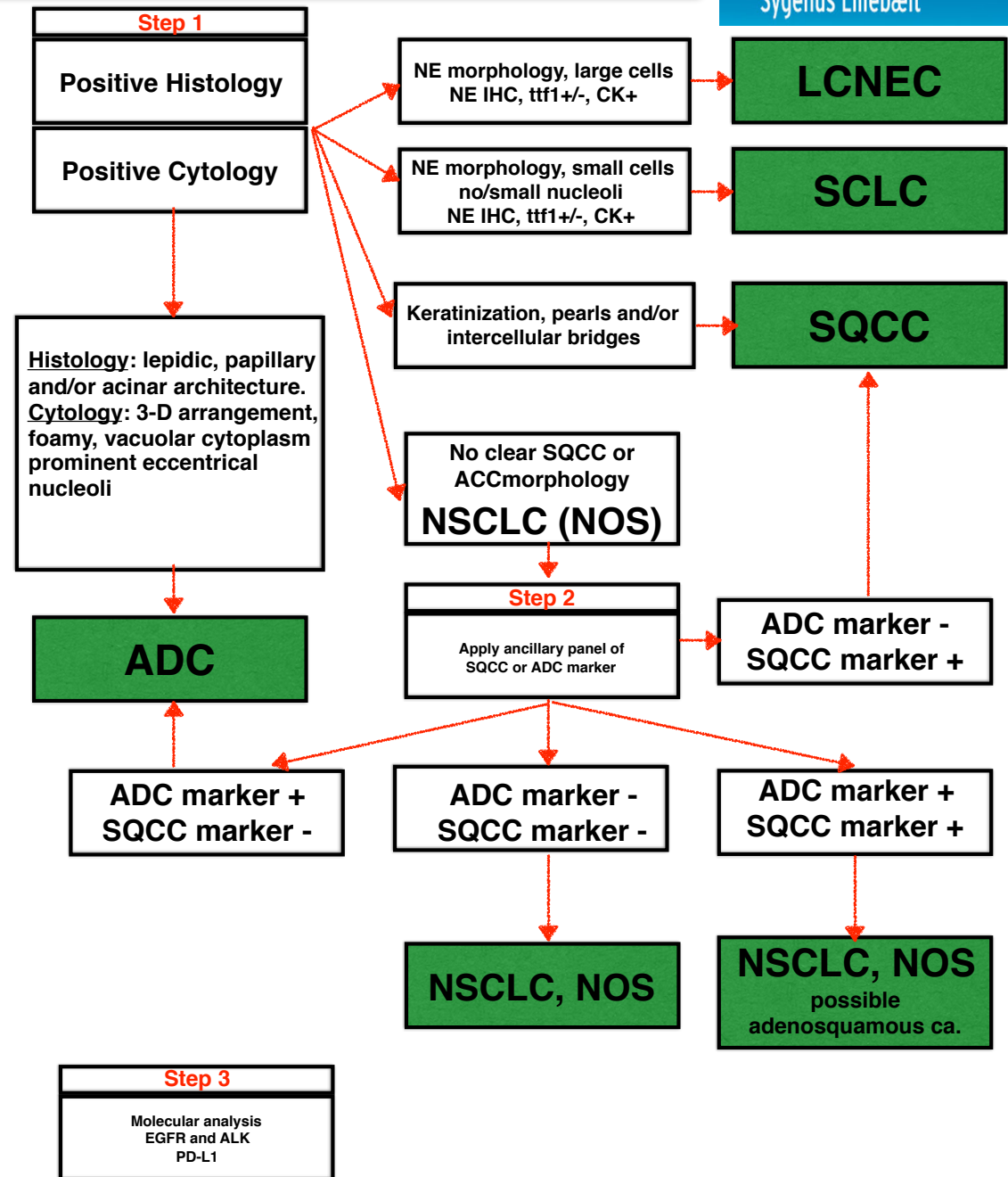
Non Small Cell Lung Carcinoma (NSCLC)

Patoanatomiske analyser i forhold til lungecancerudredning.

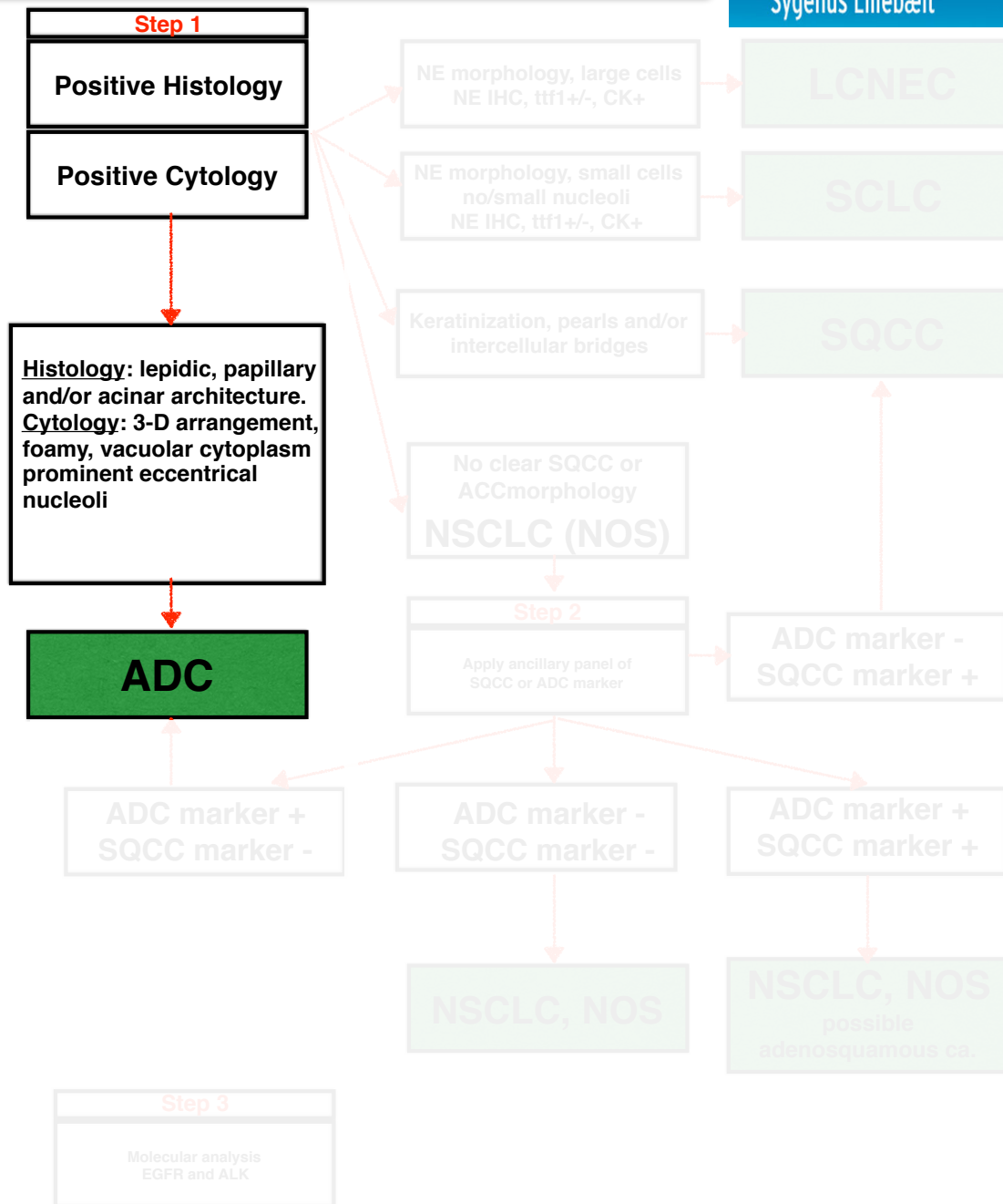
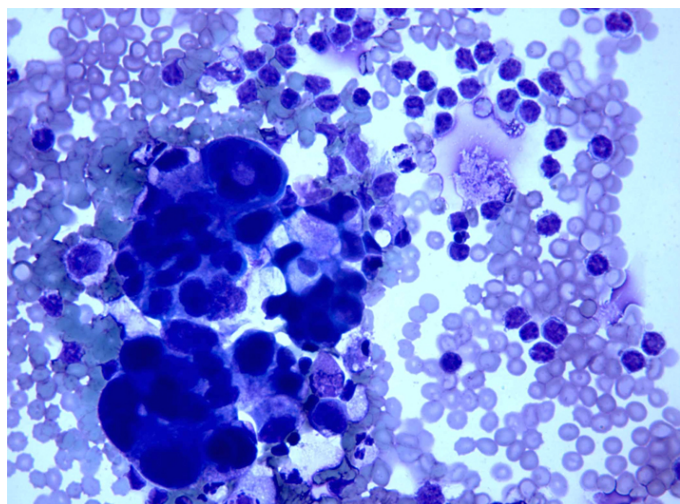
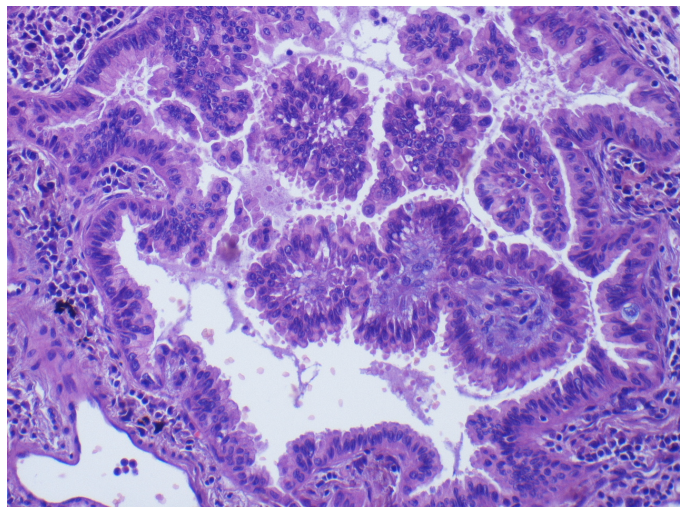
Algorithm modified from

Diagnosis of Lung Cancer in Small Biopsies and Cytology
Implications of the 2011 International Association for the Study of Lung Cancer/
American Thoracic Society/European Respiratory Society Classification

*William D. Travis, MD; Elisabeth Brambilla, MD; Masayuki Noguchi, MD; Andrew C. Nicholson, DM; Kim Csisinger, MD;
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Erik Thunnissen, MD; Ming Tsao, MD*



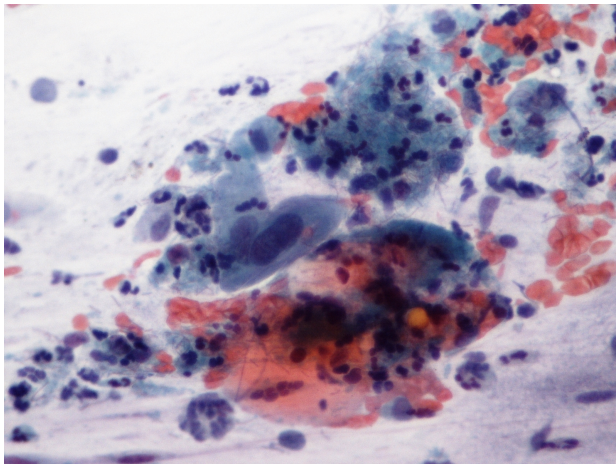
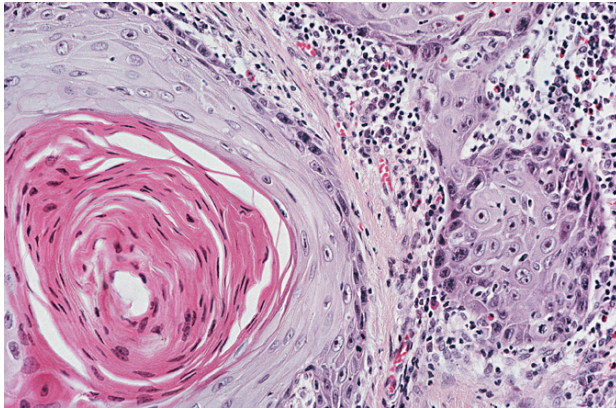
Patoanatomiske analyser i forhold til lungecancerudredning.



Diagnosis of Lung Cancer in Small Biopsies and Cytology Implications of the 2011 International Association for the Study of Lung Cancer/ American Thoracic Society/European Respiratory Society Classification

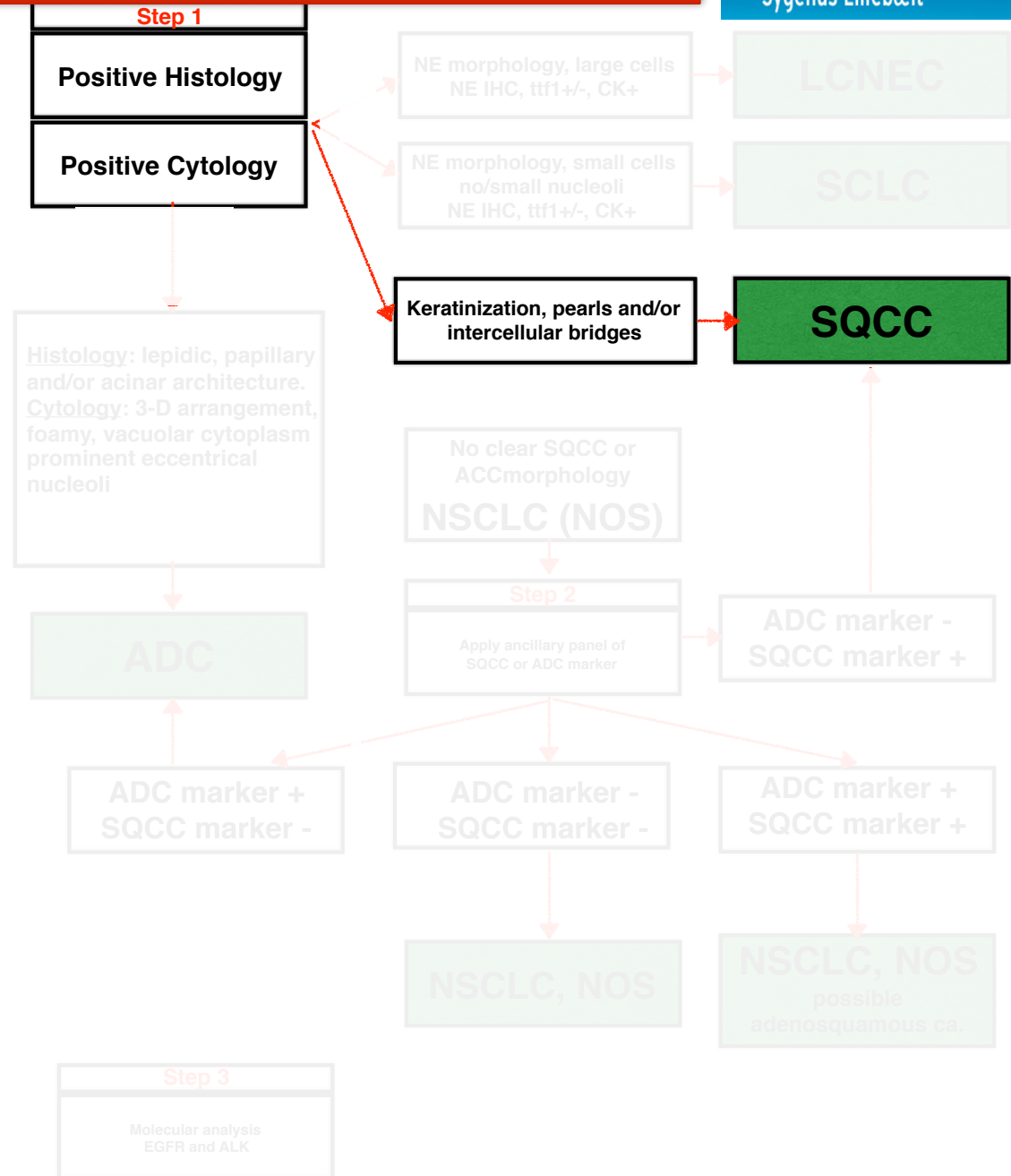
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Patoanatomiske analyser i forhold til lungecancerudredning.

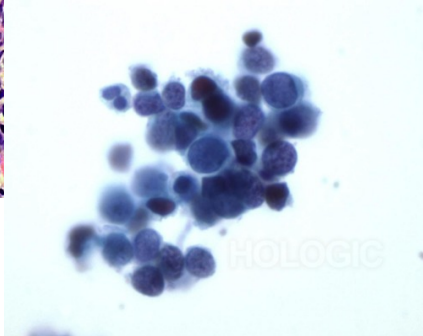
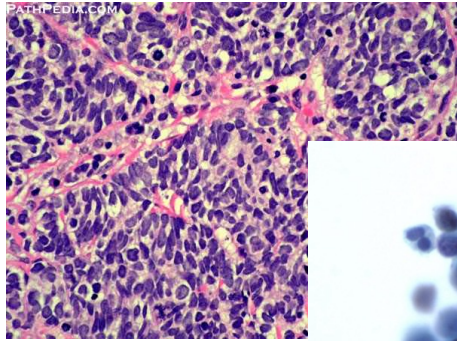


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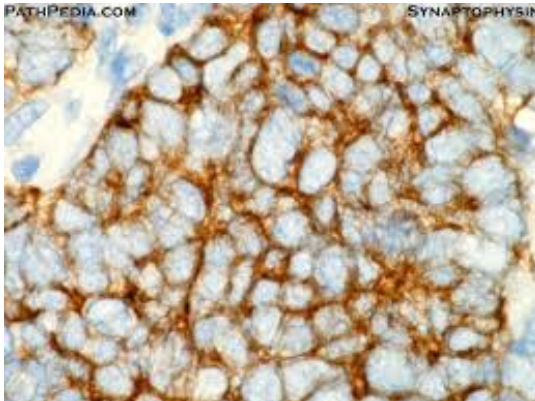
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Patoanatomiske analyser i forhold til lungecancerudredning.

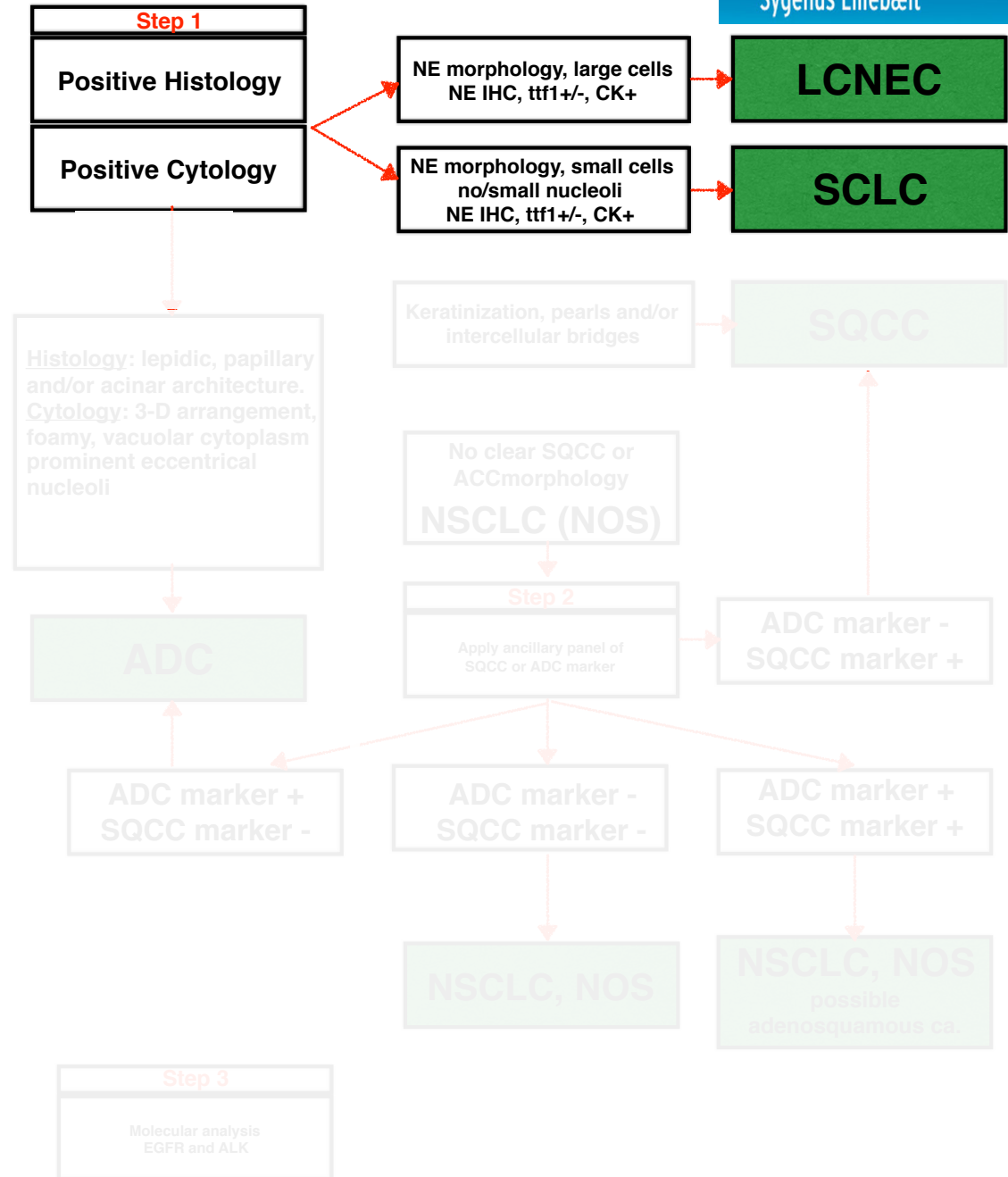


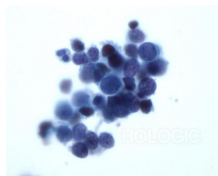
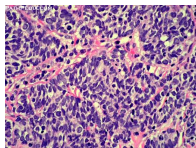
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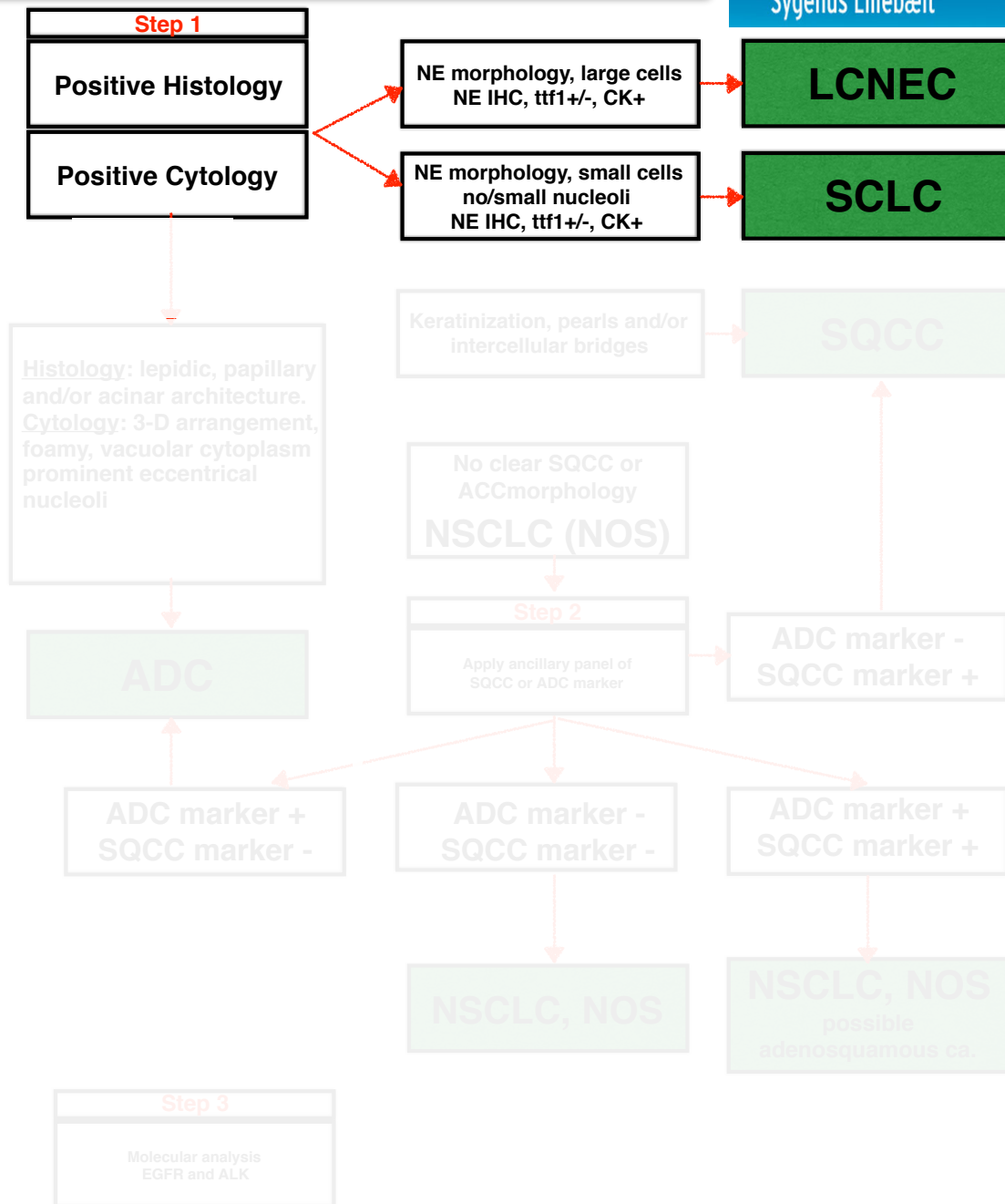
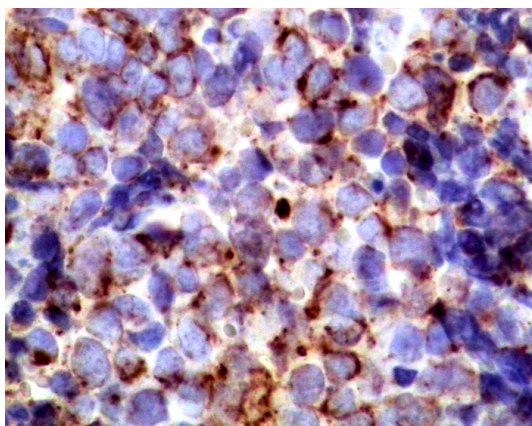
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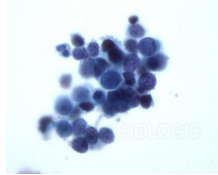
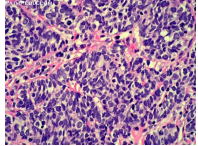
Chromogranin A



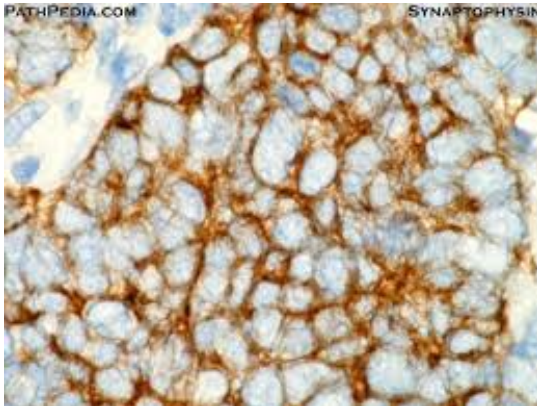
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Patoanatomiske analyser i forhold til lungecancerudredning.

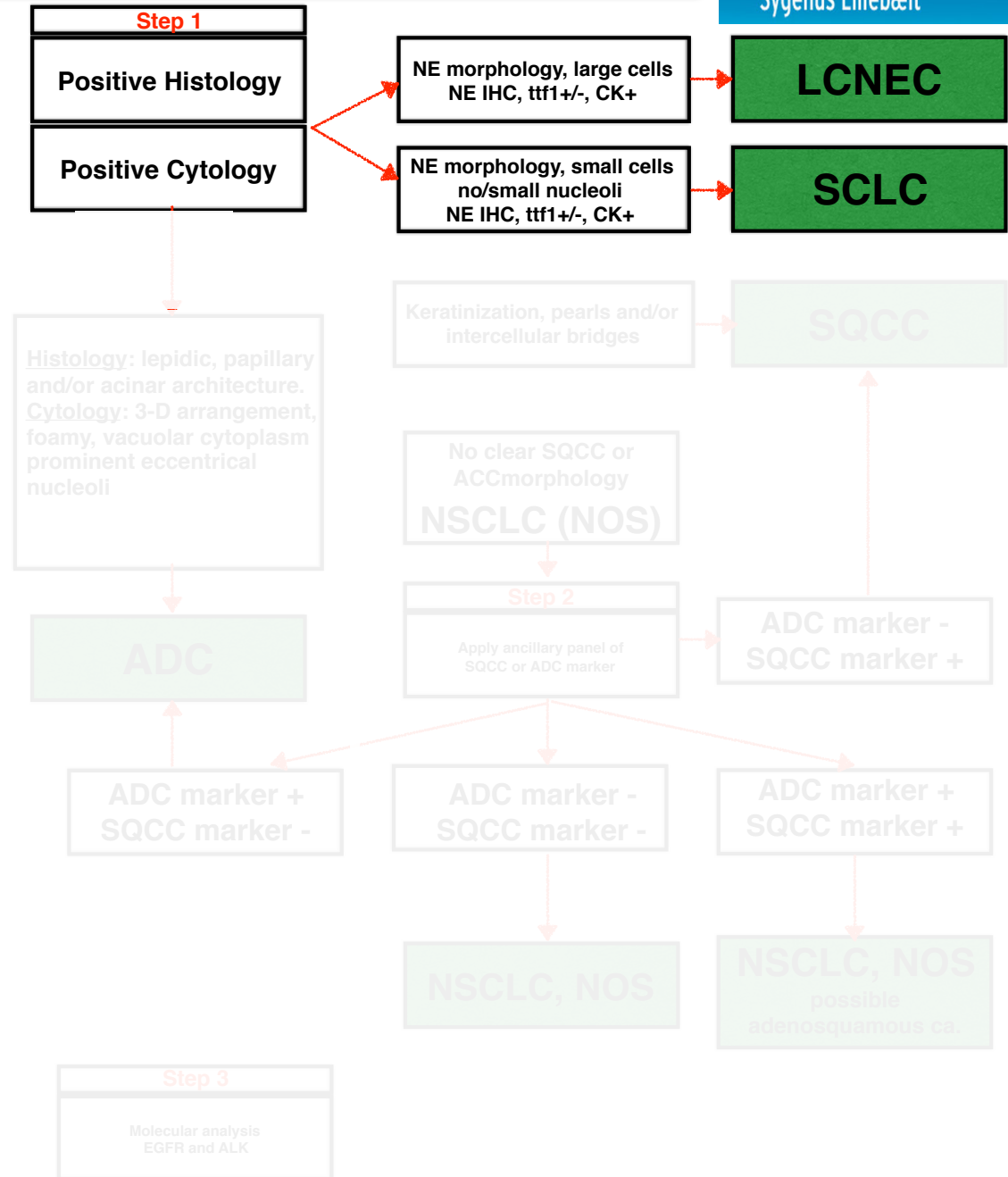


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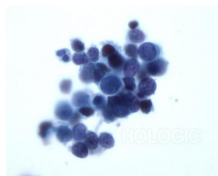
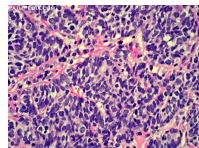


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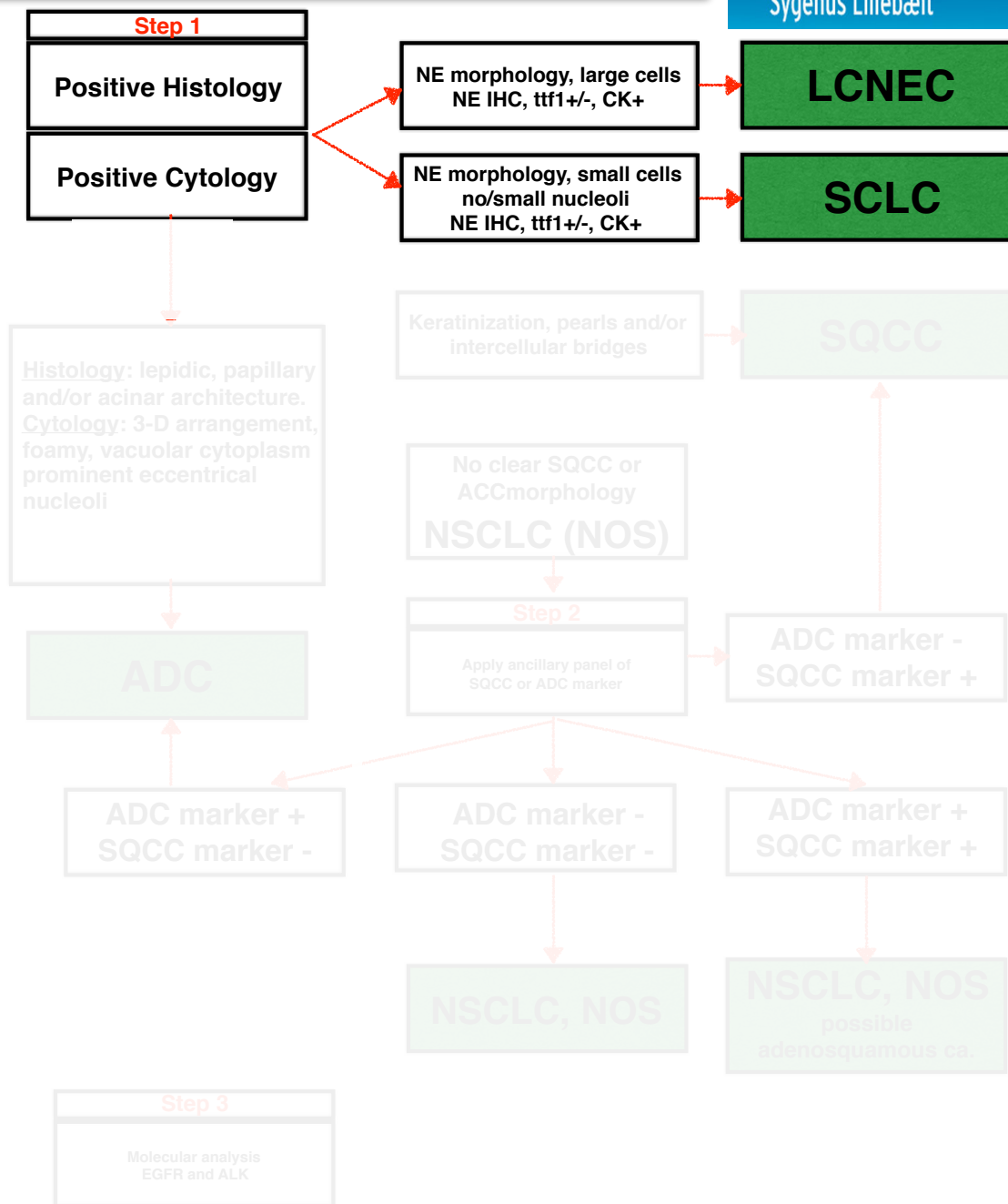
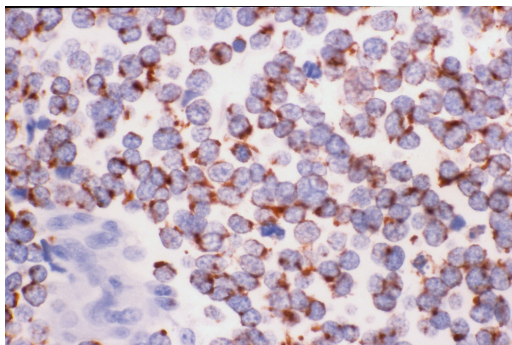
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Patoanatomiske analyser i forhold til lungecancerudredning.



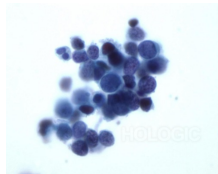
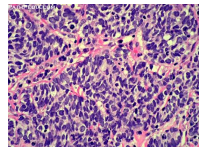
Cytokeratin



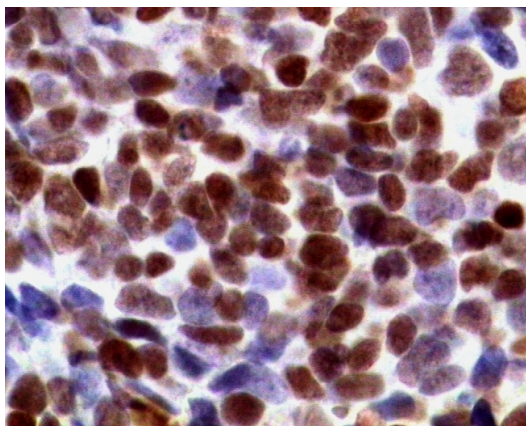
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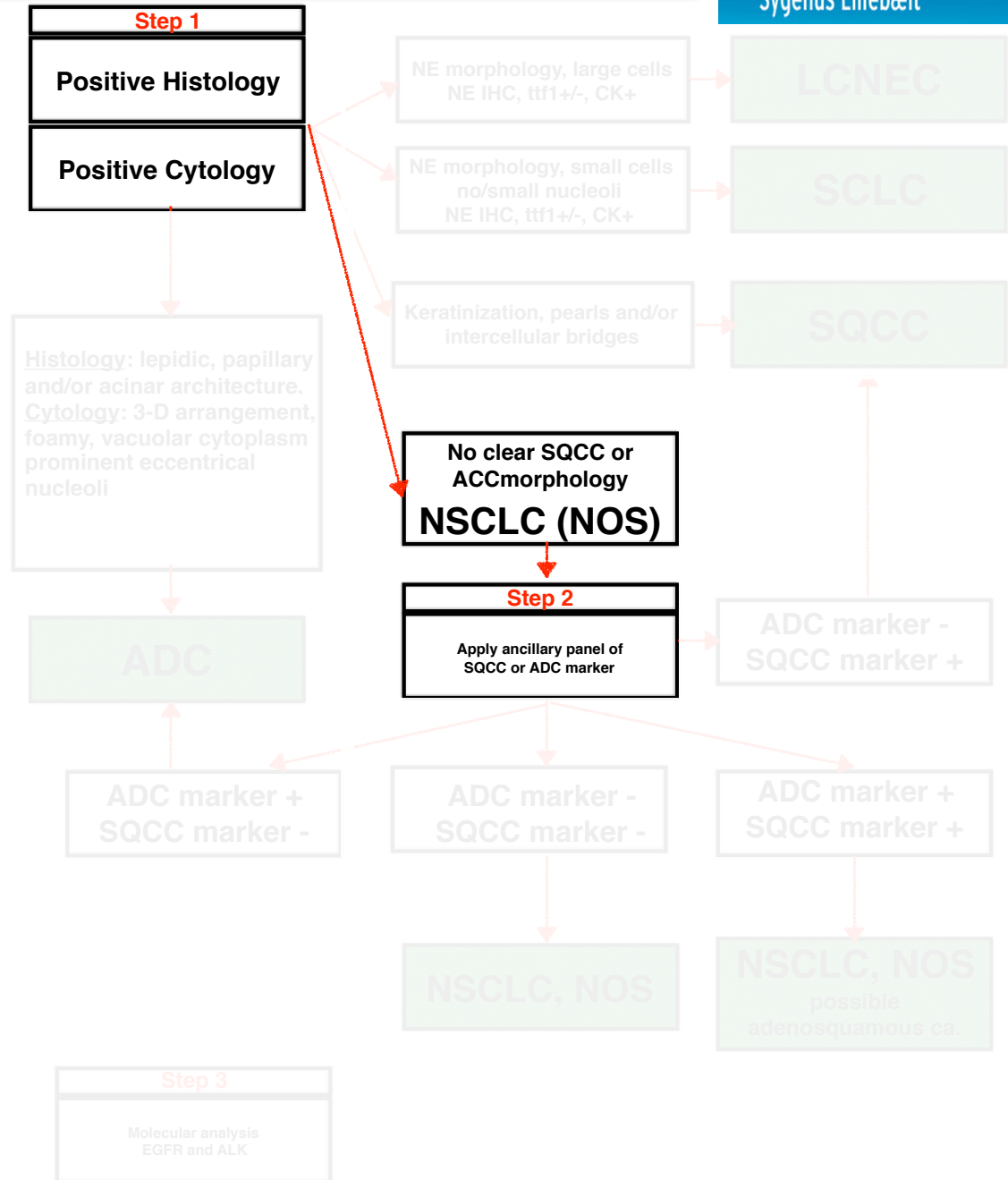
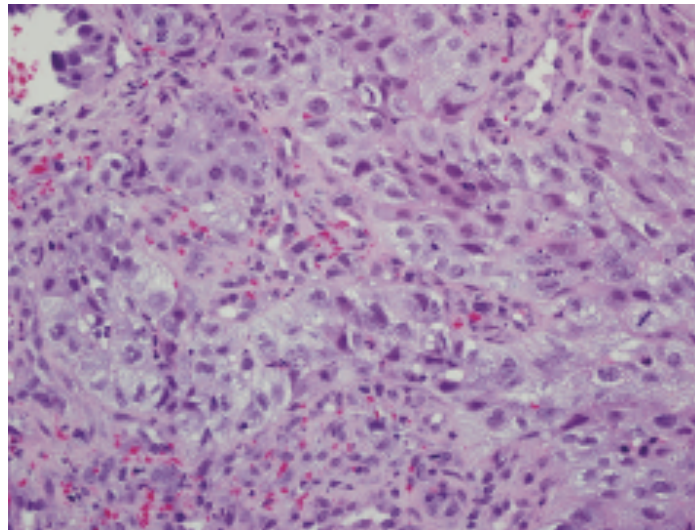
ttf1



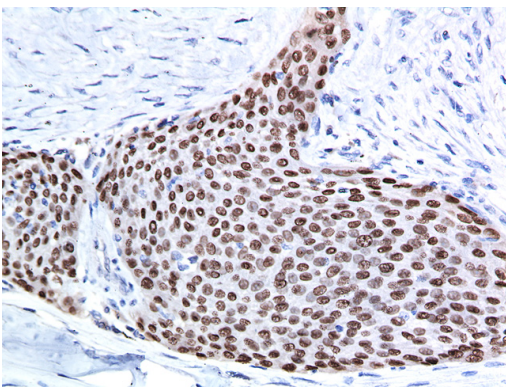
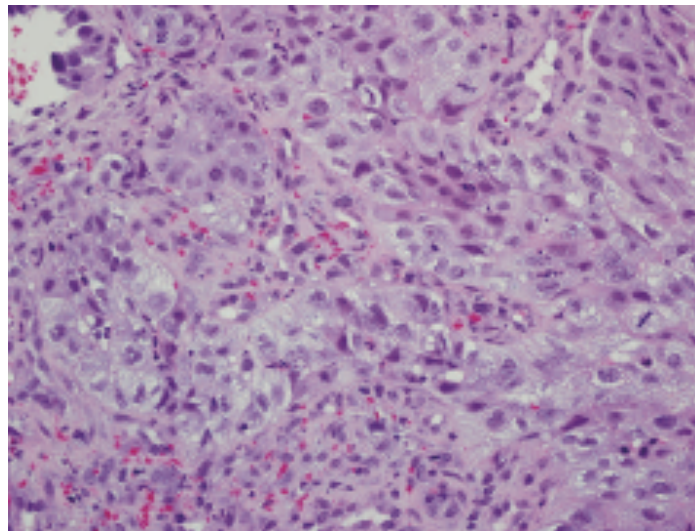
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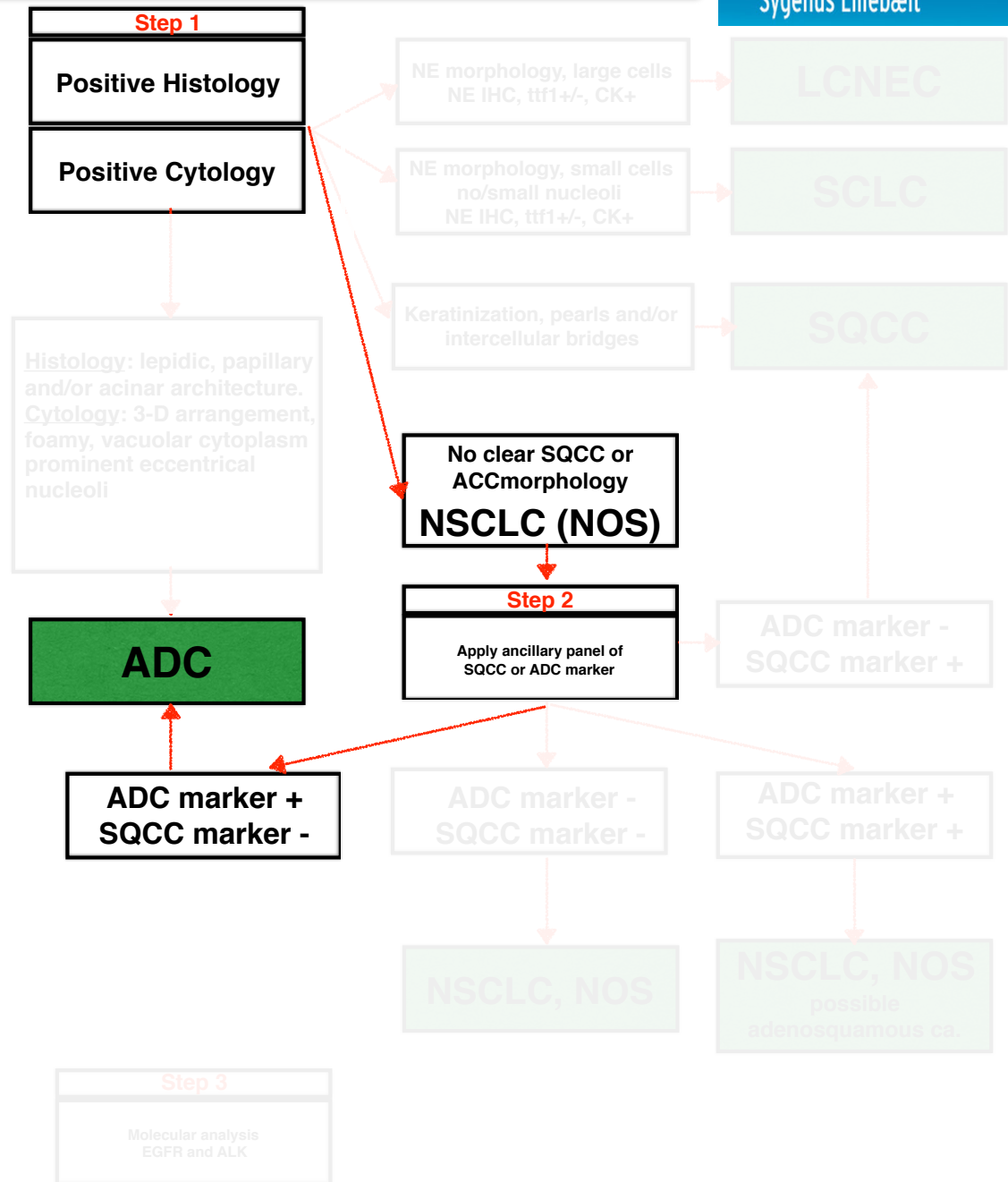


Patoanatomiske analyser i forhold til lungecancerudredning.

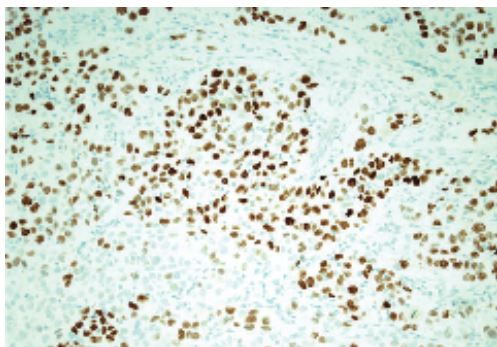
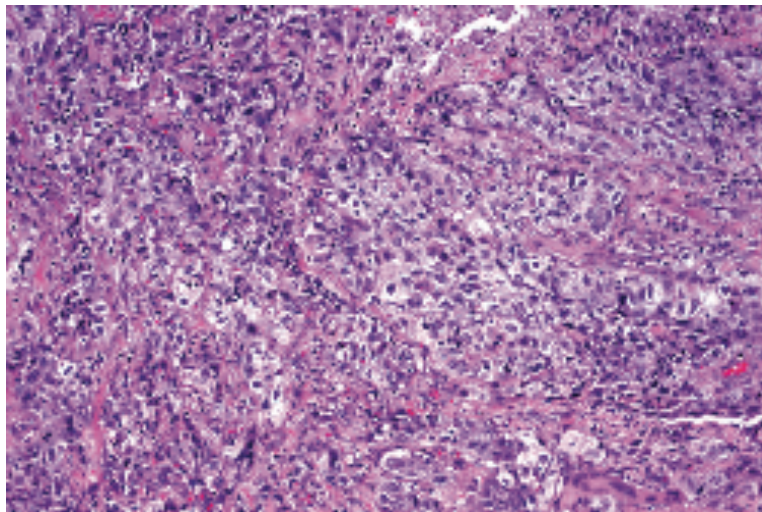


ttf1 +

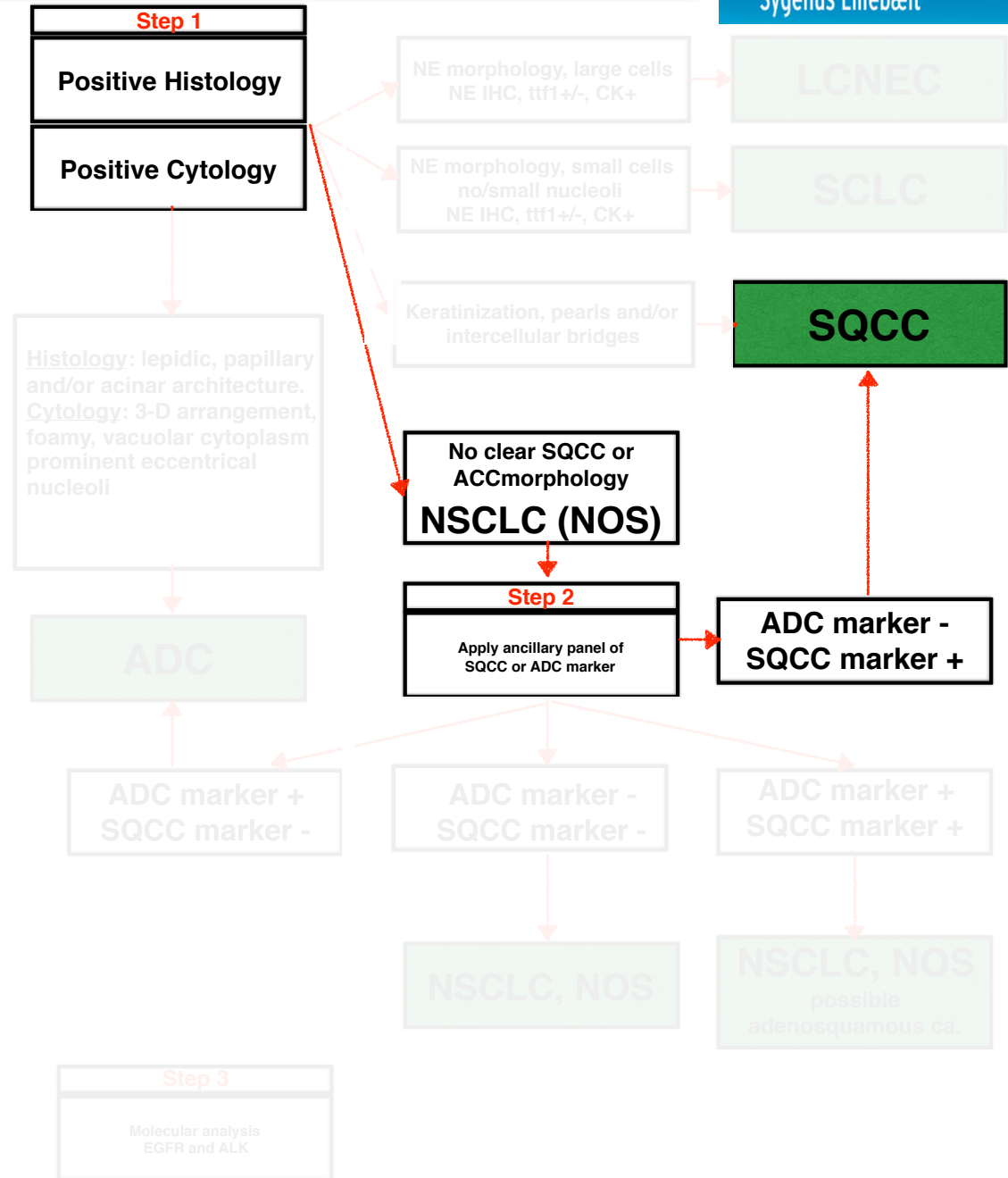
(+Cytokeratin 7)



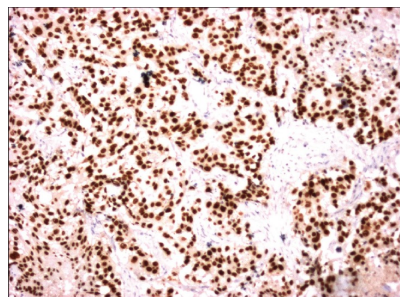
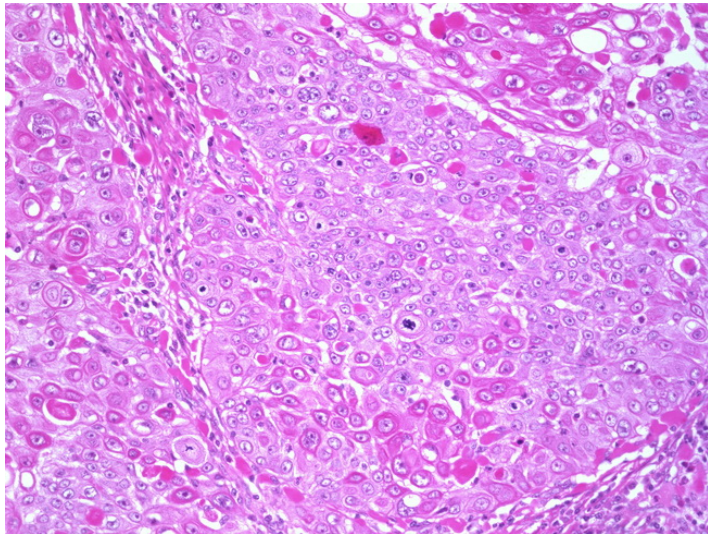
Patoanatomiske analyser i forhold til lungecancerudredning.



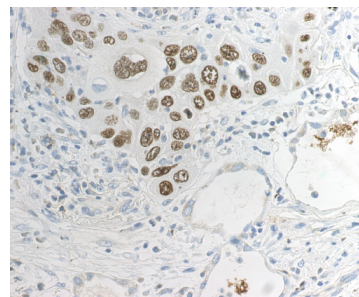
P63+ (+Cytokeratin 5/6)



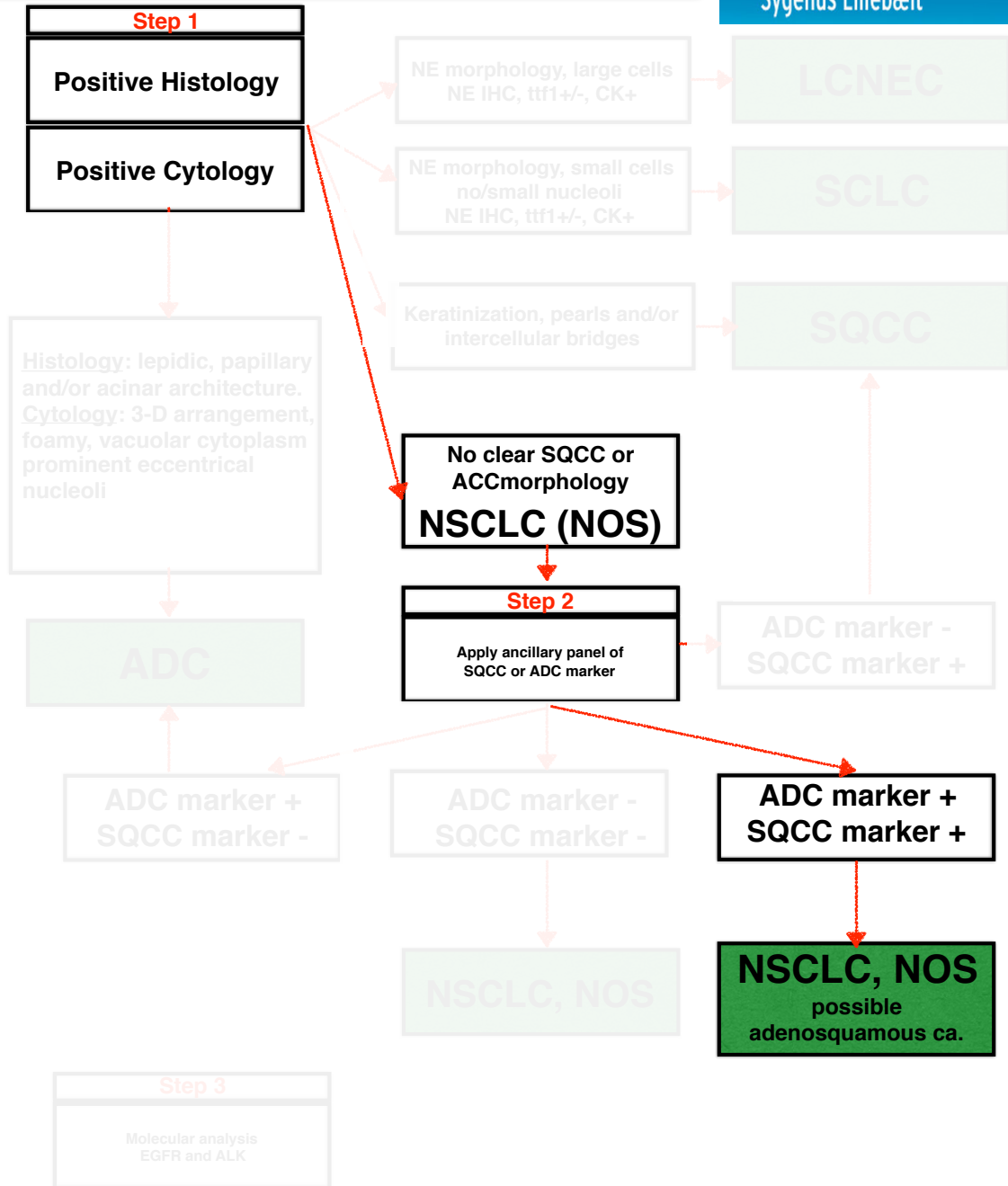
Patoanatomiske analyser i forhold til lungecancerudredning.



ttf1 +



P63+



CK7

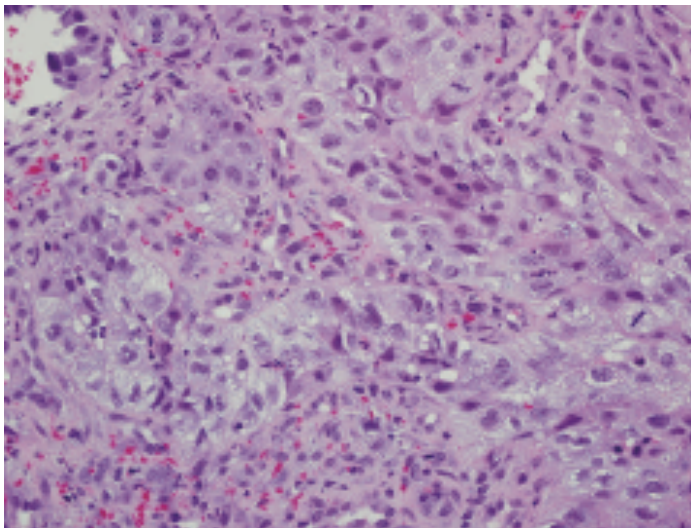
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Adenocarcinoma

Napsin

CK5/6

P63



CK7

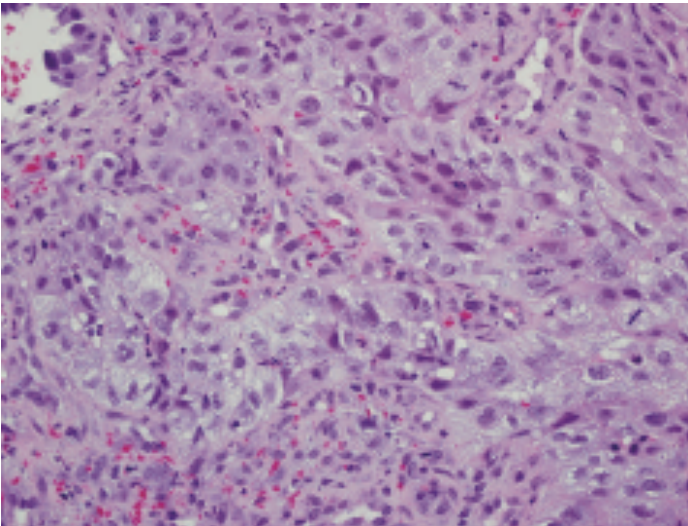
ttf1

Napsin

CK5/6

P63

Squamous
carcinoma



Problems:

Adenocarcinoma can be P63+



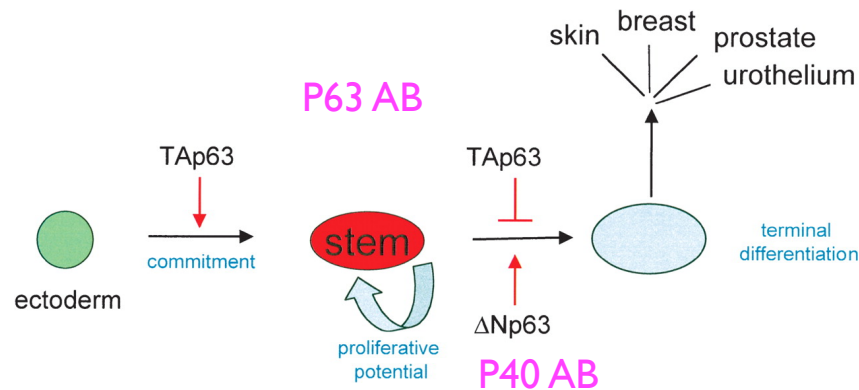
p40 is the Best Marker for Diagnosing Pulmonary Squamous Cell Carcinoma: Comparison With p63, Cytokeratin 5/6, Desmocollin-3, and Sox2

Takahiro Tatsunori, MD,*† Koji Tsuta, MD, PhD,* Kyohei Masai, MD,* Tomoaki Kinno, MD,* Tomoko Taniyama, MD,* Akihiko Yoshida, MD, PhD,* Kenji Suzuki, MD, PhD,† and Hitoshi Tsuda, MD, PhD*

Problems:

Adenocarcinoma can be P63+

Marker	Total	No. Cases (%) Immunoreactivity		Mean Staining Score (0-300)	
		Negative	Positive		
SQC	p40	158	5 (3.2)	153 (96.8)	169
	p63	154	4 (2.6)	150 (97.4)	237
Non-SQC	p40	418	405 (96.9)	13 (3.1)	1.3
	p63	419	305 (72.8)	114 (27.2)	16.9



p40 is the Best Marker for Diagnosing Pulmonary Squamous Cell Carcinoma: Comparison With p63, Cytokeratin 5/6, Desmocollin-3, and Sox2

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Tomoko Taniyama, MD,* Akihiko Yoshida, MD, PhD,* Kenji Suzuki, MD, PhD,†
and Hitoshi Tsuda, MD, PhD*

Table 2. Sensitivity, specificity, PPV and NPV of markers used in this study [% (positive/total stained)]

Marker	Subtype	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ΔNp63	SCC	100 (16/16)	100 (32/32)	100 (16/16)	100 (32/32)
p63	SCC	100 (16/16)	88 (28/32)	80 (16/20)	100 (28/28)
CK5/6	SCC	81 (13/16)	100 (32/32)	100 (13/13)	91 (32/35)
34βE12	SCC	94 (15/16)	47 (15/32)	47 (15/32)	94 (15/16)
TTF1	AC	80 (20/25)	87 (20/23)	87 (20/23)	80 (20/25)
Napsin A	AC	64 (16/25)	100 (23/23)	100 (16/16)	72 (23/32)
CK7	AC	100 (25/25)	35 (8/23)	63 (25/40)	100 (8/8)
CK8/18	AC	100 (25/25)	35 (8/23)	63 (25/40)	100 (8/8)

Sensitivity = TP/TP+FN; Specificity = TN/TN+FP; Positive predictive value (PPV) = TP/TP+FP; Negative predictive value (NPV) = TN/TN+FN. FN indicates false negatives; FP, false positives; TN, true negatives; TP, true positives.

Table 2. Sensitivity, specificity, PPV and NPV of markers used in this study [% (positive/total stained)]

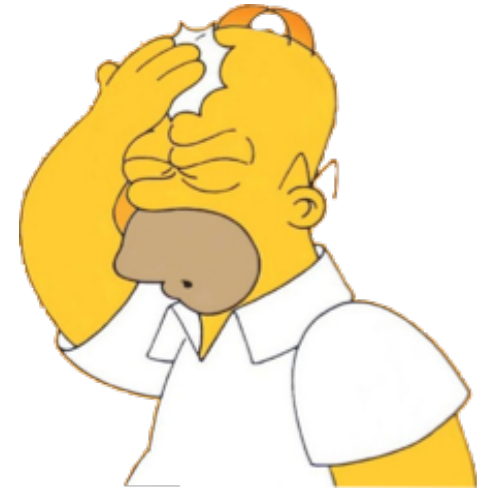
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Table 3. Algorithm for subtyping of poorly-differentiated non-small cell lung carcinomas according to immunohistochemical staining in lung biopsies

Δ Np63	CK5/6	TTF1	Napsin A	Diagnosis
+	+	-	-	Squamous cell carcinoma
+	-	-	-	Squamous cell carcinoma
-	-	+	+	Adenocarcinoma
-	-	+	-	Adenocarcinoma
-	-	-	-	Poorly-differentiated non-small cell carcinoma

Problems:



Differential diagnosis between primary and metastatic carcinoma

Other (adeno) carcinomas are positive for ttf1

Table 1

Summary of immunohistochemistry results.

	Total cases	SPT24	8G7G3/1	P
Lung	374			
<i>Adenocarcinoma</i>	185	134 (72.4%)	121 (65.4%)	0.08
<i>Large Cell</i>	47	22(46.8%)	17(36.2%)	0.201
<i>Carcinoid</i>	23	14(60.8%)	4(17.4%)	0.003
<i>Squamous Cell</i>	97	14(16.8%)	1(1.0%)	0.003
<i>Unclassified</i>	22	10(45.5%)	7(31.8%)	0.26
Bladder	98	5 (5.1%)	5 (5.1%)	NS
Colon	120	3 (2.5%)	3 (2.5%)	NS
Prostate	160	2(1.2%)	2(1.2%)	NS
Stomach	110	1(0.9%)	1(0.9%)	NS
Salivary Gland	56	1(1.8%)	1(1.8%)	NS
Squamous cell carcinoma of head and neck	38	0(0%)	0(0%)	NS
Pancreatic adenocarcinomas	110	0(0%)	0(0%)	NS
Breast	34	0(0%)	0(0%)	NS

NS: not significant



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Appl Immunohistochem Mol Morphol. Author manuscript; available in PMC 2011 March 1.

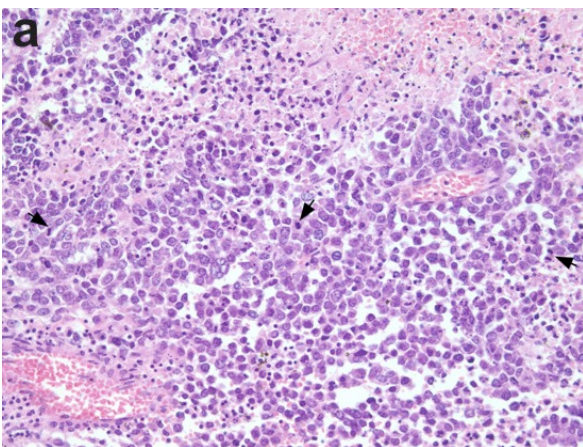
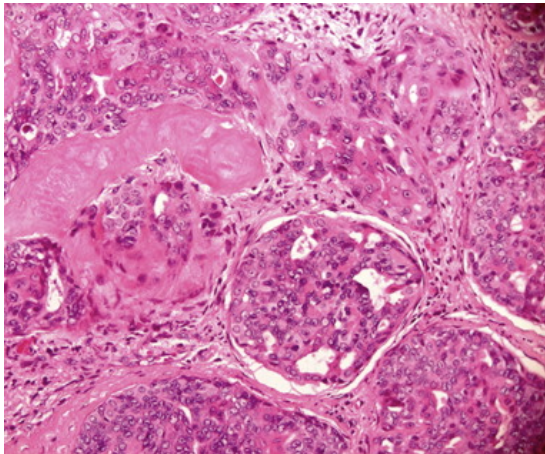
Published in final edited form as:

Appl Immunohistochem Mol Morphol. 2010 March ; 18(2): 142–149. doi:10.1097/PAI.0b013e3181bd4e7.

Comparison of thyroid transcription factor-1 expression by two monoclonal antibodies in pulmonary and non-pulmonary primary tumors

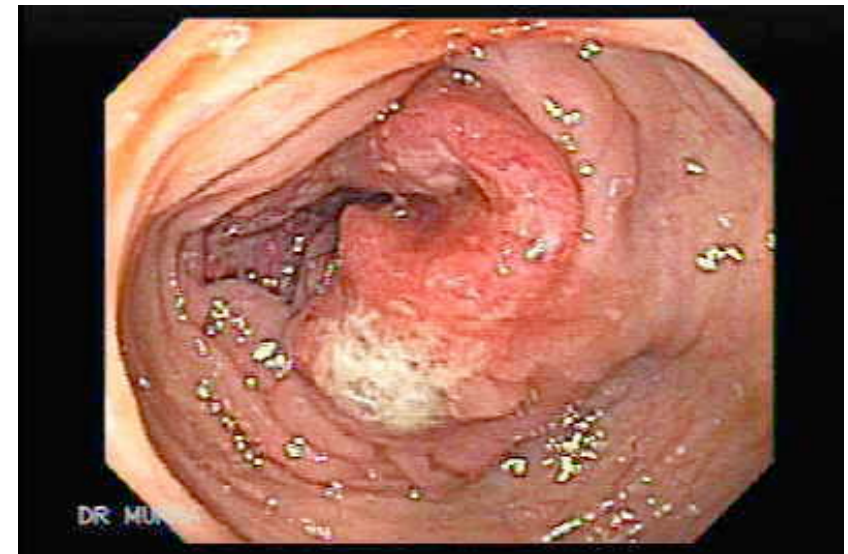
Andres Matoso, Kamaljeet Singh, Rafik Jacob, Wesley O. Greaves, Rosemarie Tavares, Lelia Noble, Murray B. Resnick, Ronald A. DeLellis, and Li J. Wang
Department of Pathology and Laboratory Medicine, Rhode Island Hospital and Brown Medical School, Providence, RI.

Diagnosis of metastasis to the lung

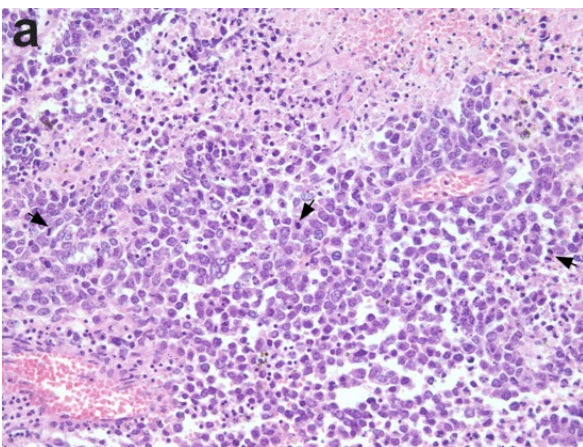
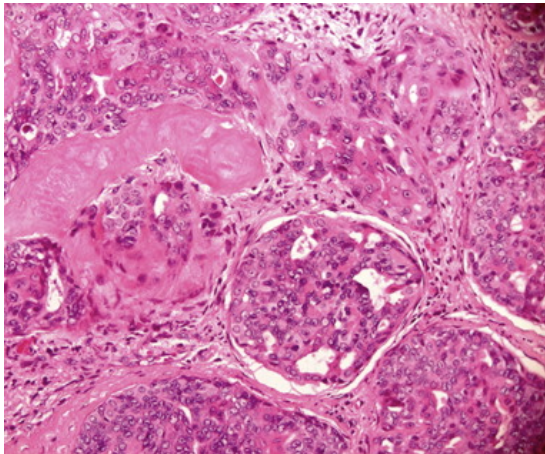


KI1 ←
CK7
ttf1
Napsin
CK20 ←
cdx2 ←
ER
GCDFP15
PSA
Vim
CK5/6
P63
CD10
RCC
Ca125
PAX8
WT1
GATA3

Colon

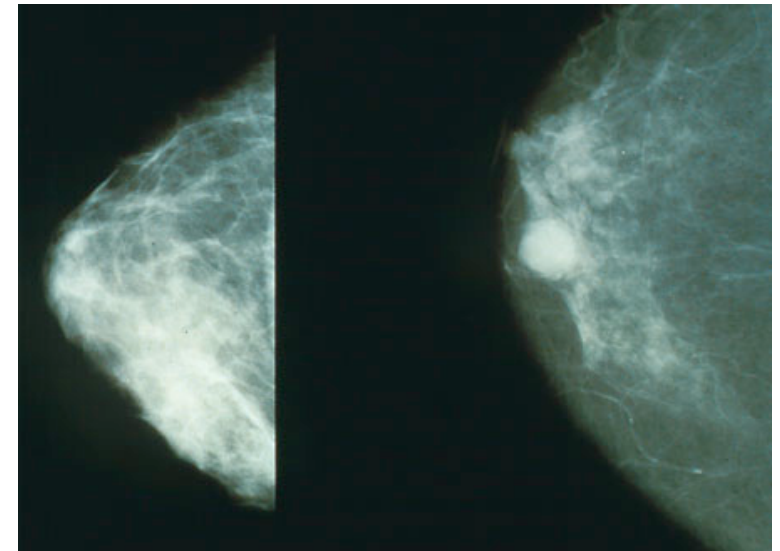


Diagnosis of metastasis to the lung

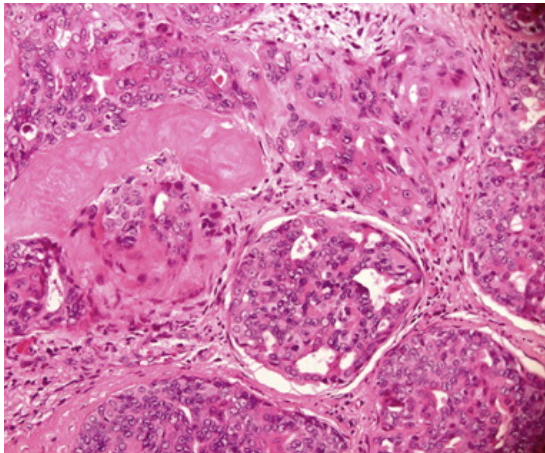


- KI1 ←
- CK7 ←
- ttf1
- Napsin
- CK20
- cdx2
- ER ←
- GCDFP15 ←
- PSA
- Vim
- CK5/6
- P63
- CD10
- RCC
- Ca125
- PAX8
- WT1
- GATA3 ←

Mamma

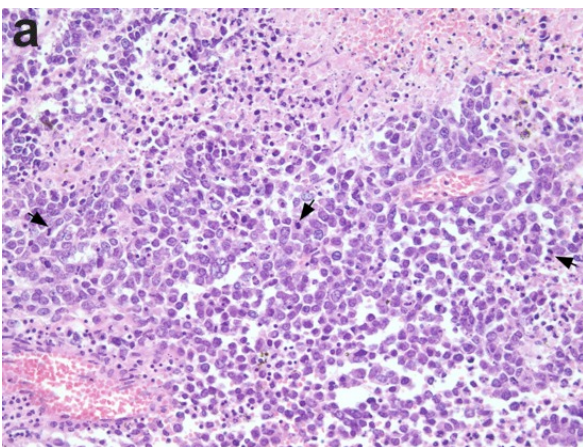


Diagnosis of metastasis to the lung

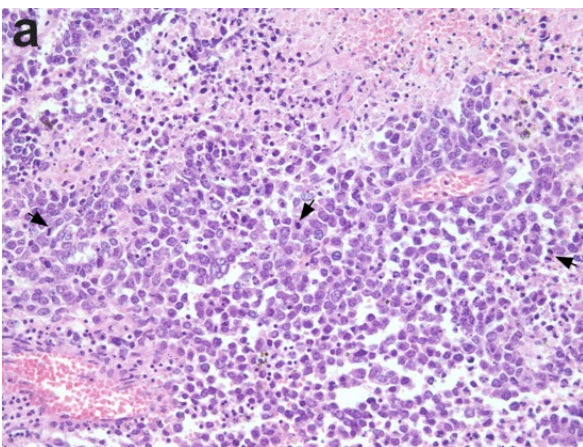
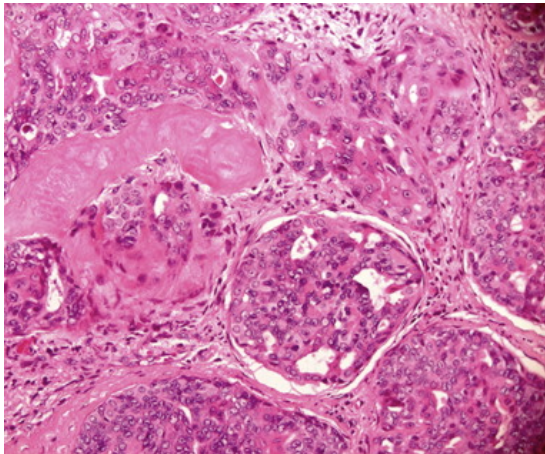


KI1 ←
CK7 ←
ttf1
Napsin
CK20 ←
cdx2
ER
GCDFP15
PSA
Vim
CK5/6
P63
CD10
RCC
Ca125
PAX8
WT1
GATA3

Upper GI

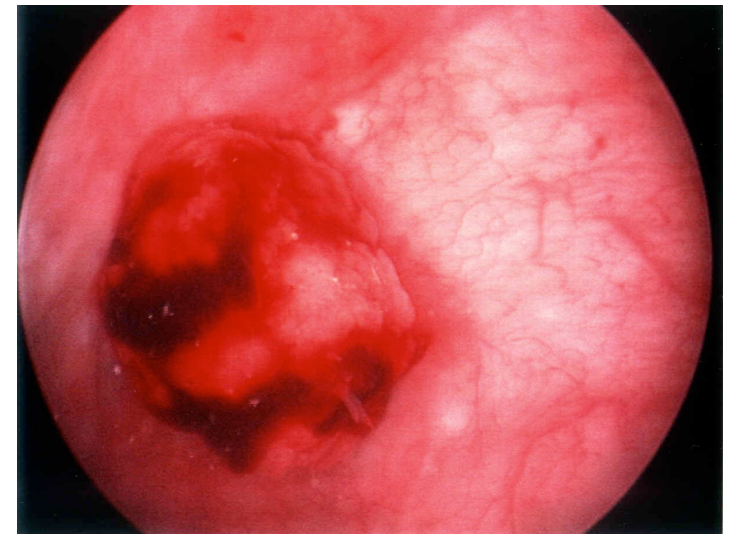


Diagnosis of metastasis to the lung

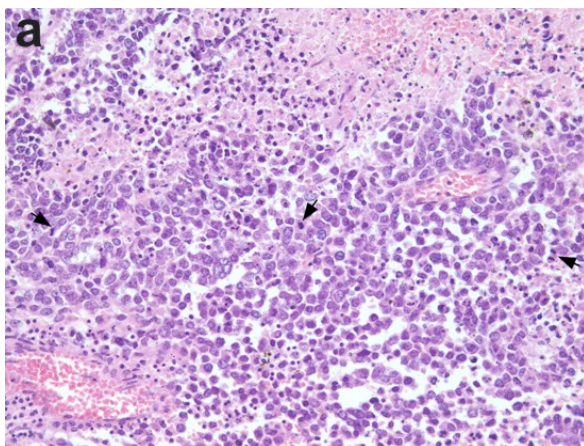
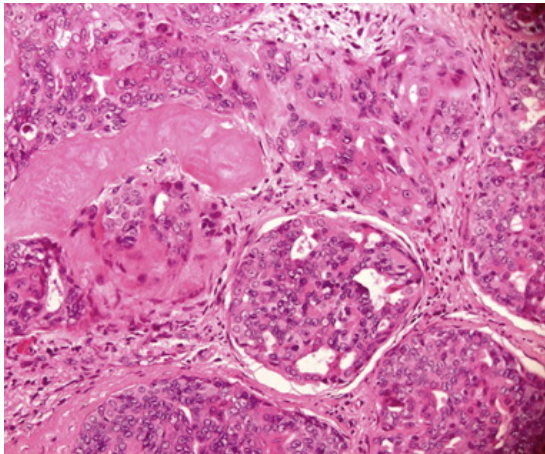


- KI1 ←
- CK7 ←
- ttf1
- Napsin
- CK20 ←
- cdx2
- ER
- GCDFP15
- PSA
- Vim
- CK5/6 ←
- P63 ←
- CD10
- RCC
- Ca125
- PAX8
- WT1
- GATA3 ←

Urothelial carcinoma

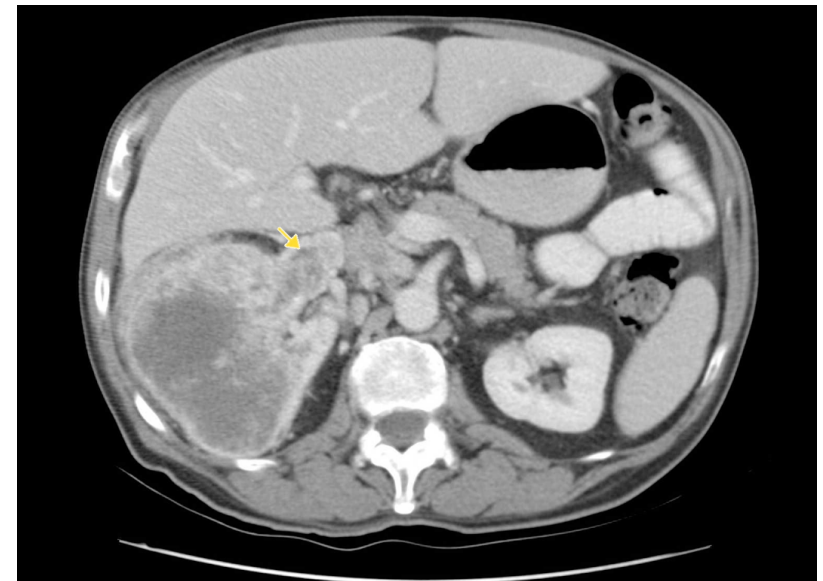


Diagnosis of metastasis to the lung

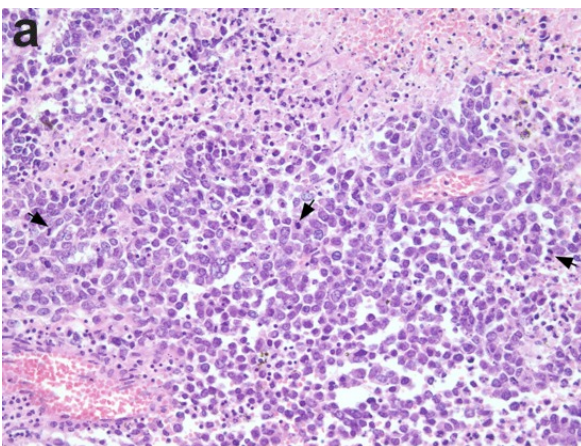
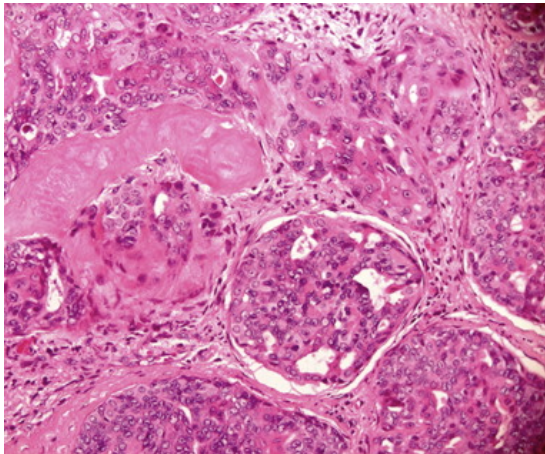


KI1 ←
CK7
ttf1
Napsin
CK20
cdx2
ER
GCDFFP15
PSA
Vim ←
CK5/6
P63
CD10 ←
RCC ←
Ca125
PAX8 ←
WT1
GATA3

Renal cell carcinoma



Diagnosis of metastasis to the lung



KI1 ←

CK7

ttf1

Napsin

CK20

cdx2

ER

GCDFP15

PSA ←

Vim

CK5/6

P63

CD10

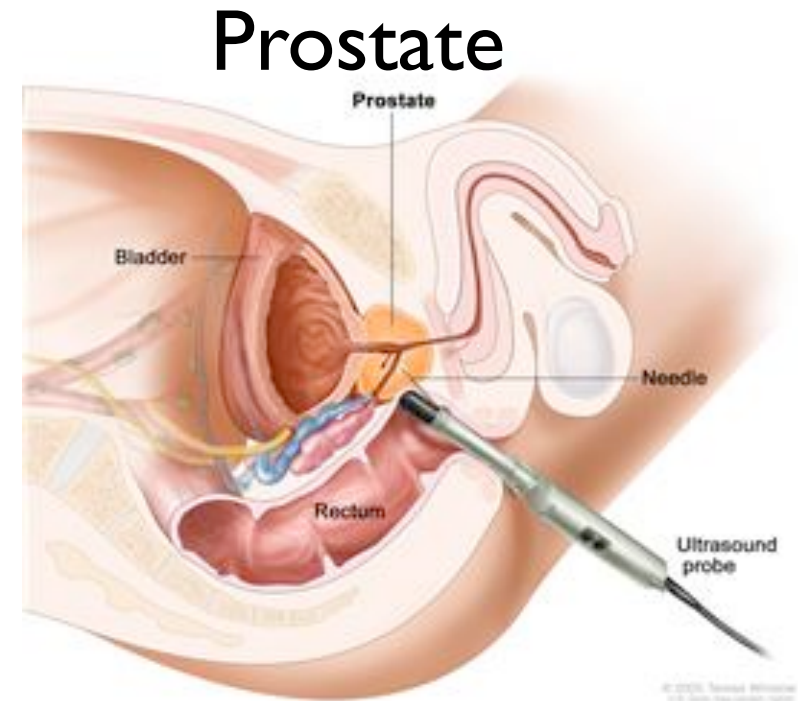
RCC

Ca125

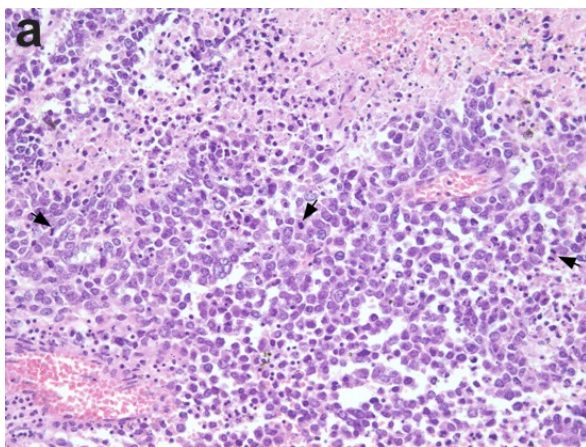
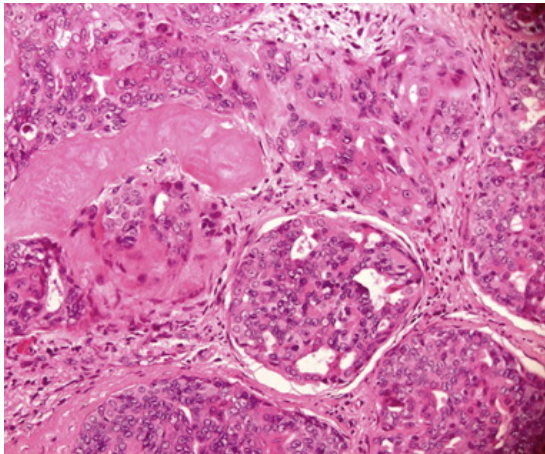
PAX8

WT1

GATA3



Diagnosis of metastasis to the lung



KI1 ←

CK7

ttf1

Napsin

CK20

cdx2

ER ←

GCDFP15

PSA

Vim ←

CK5/6

P63

CD10

RCC

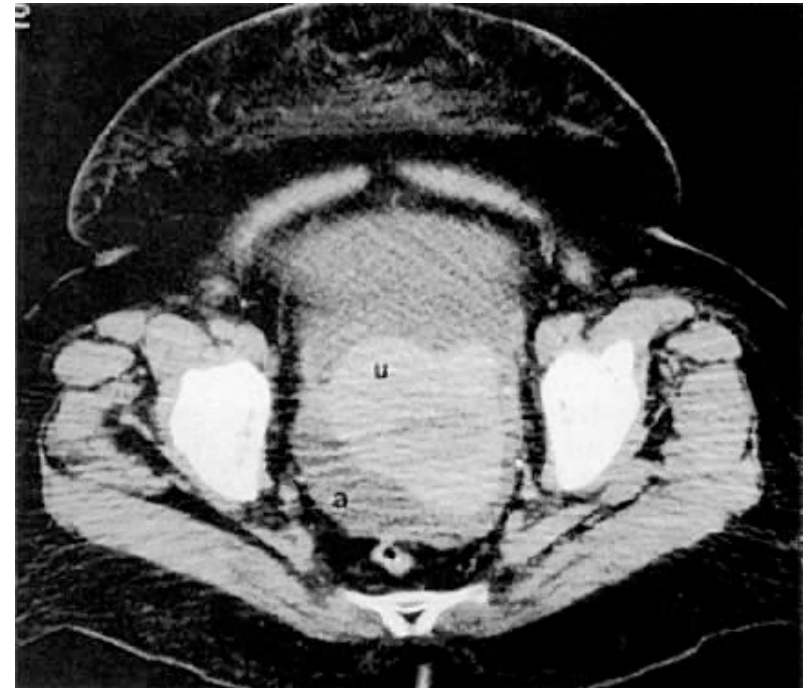
Ca125

PAX8 ←

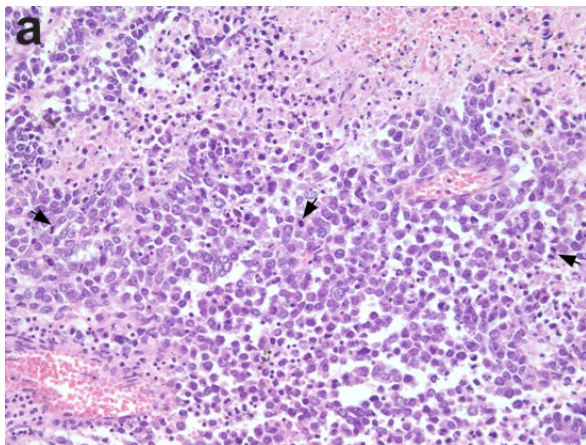
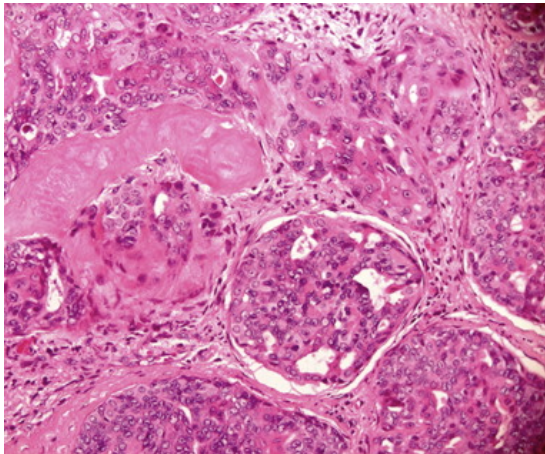
WT1

GATA3

Endometrial cancer

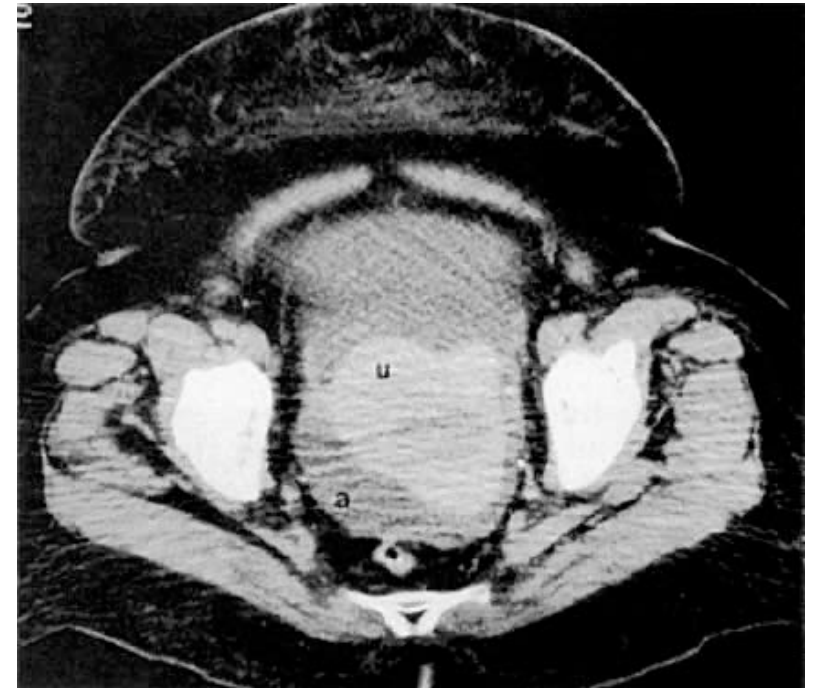


Diagnosis of metastasis to the lung

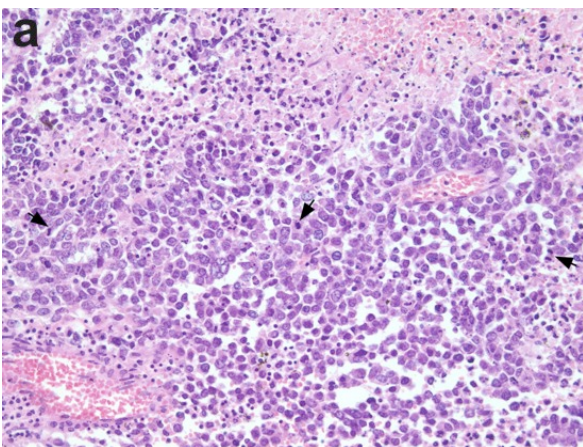
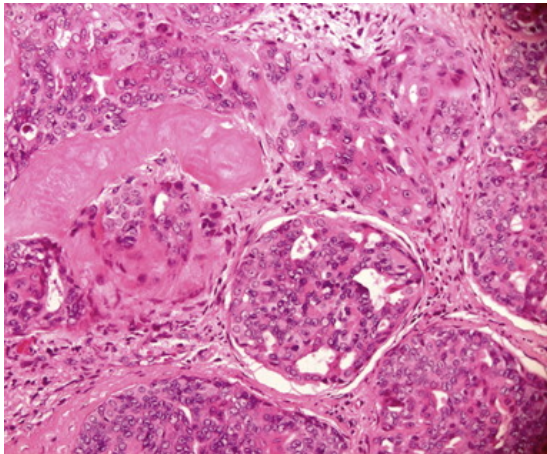


KI1 ←
CK7
ttf1
Napsin
CK20
cdx2
ER ←
GCDFP15
PSA
Vim
CK5/6
P63
CD10
RCC
Ca125 ←
PAX8
WT1 ←
GATA3

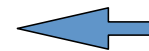
Ovarian cancer



Diagnosis of direct invasion of mesothelioma



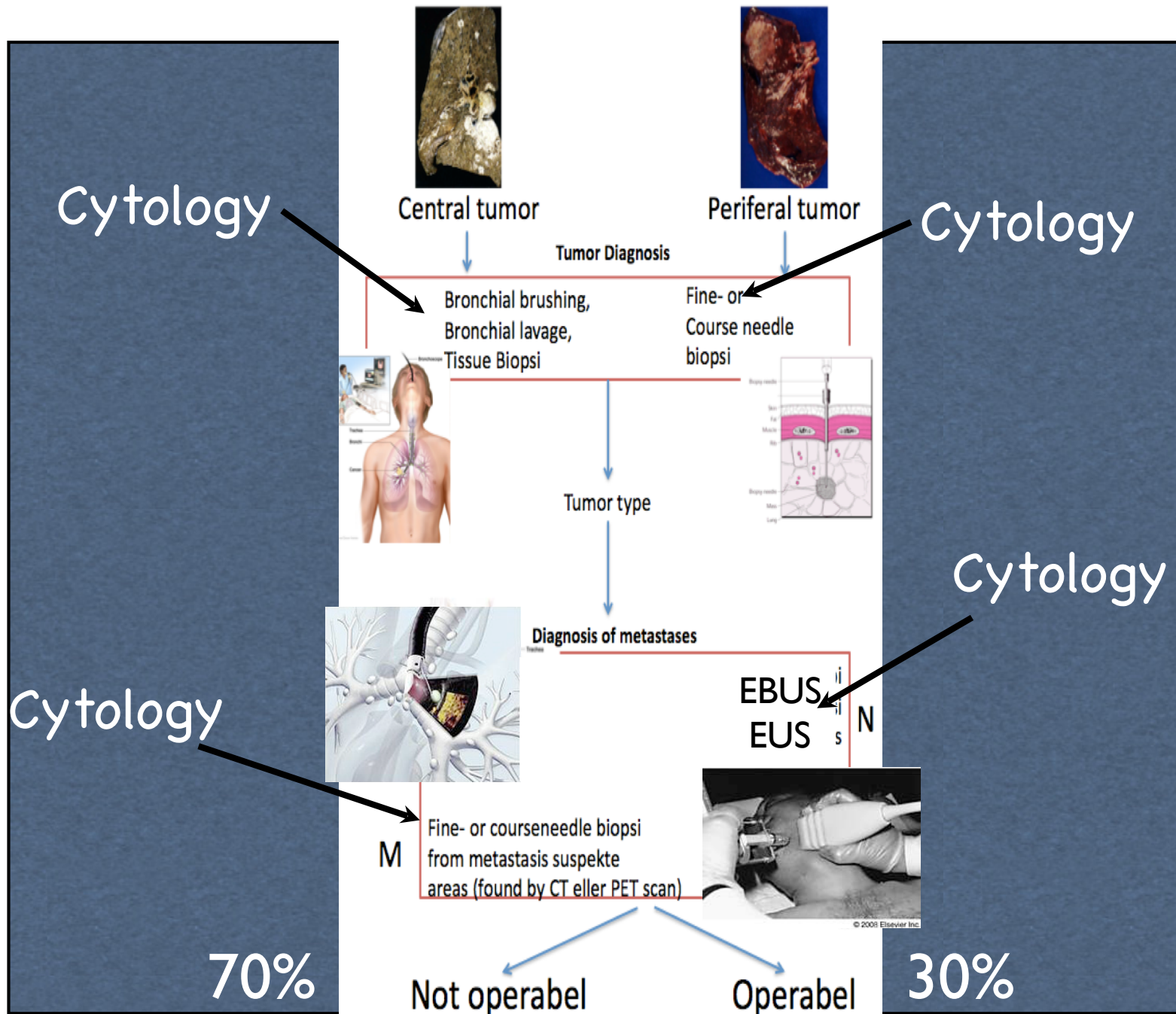
Calretinin
WT1
D2-40
CK7
Vim
CK5/6



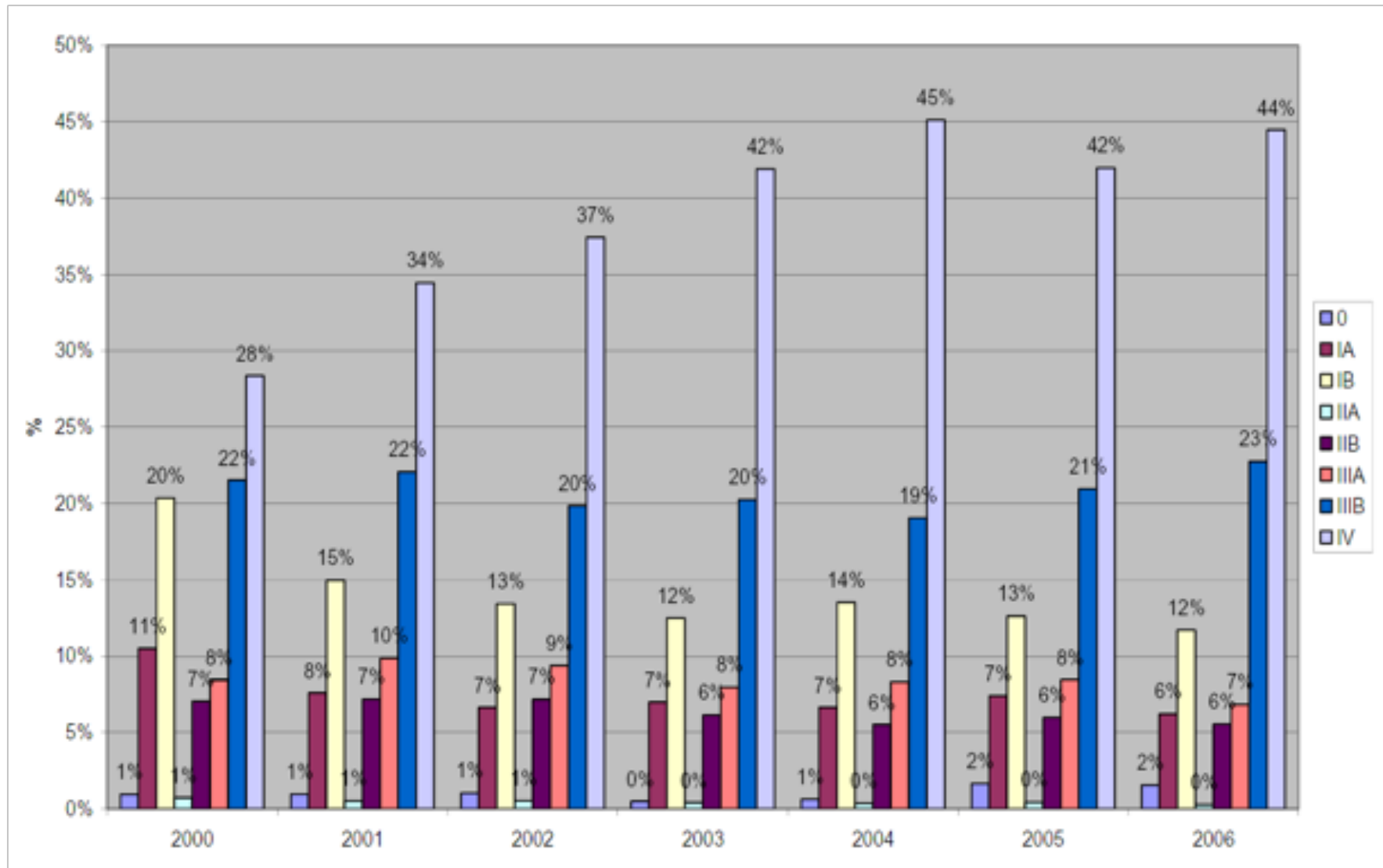
The **MultiDisciplinary** Teamconference



Patoanatomiske analyser i forhold til lungecancerudredning.



Patoanatomiske analyser i forhold til lungecancerudredning.



Stage at diagnosis

Patoanatomical specimen

Cytology

Histology



Fixation

Dehydration

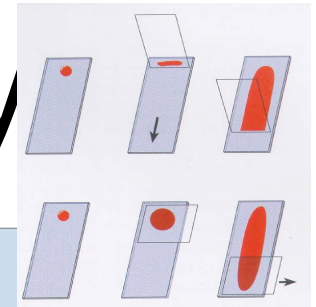
Parafinembedding

Microtomy

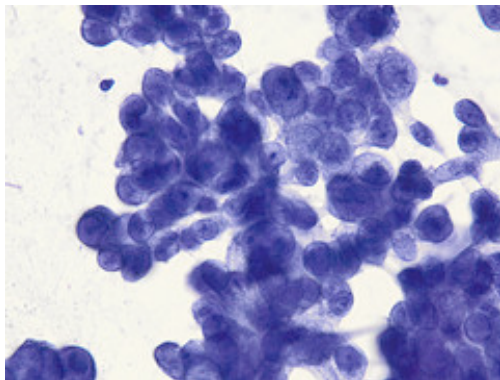
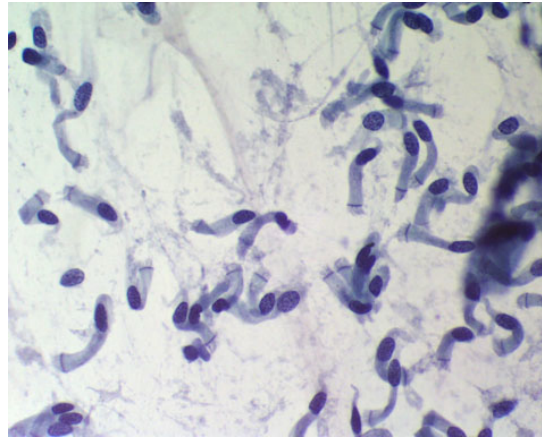


Præparation

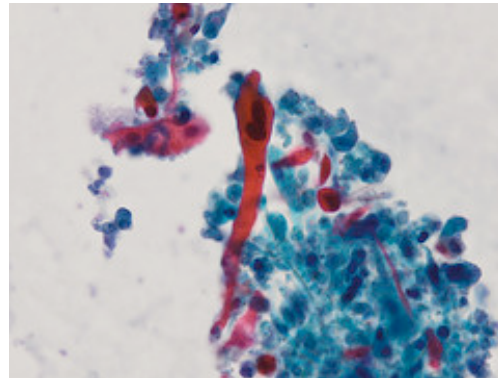
Smear preparation



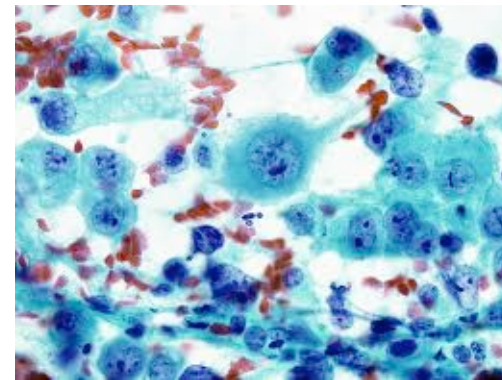
Visualization (Staining)



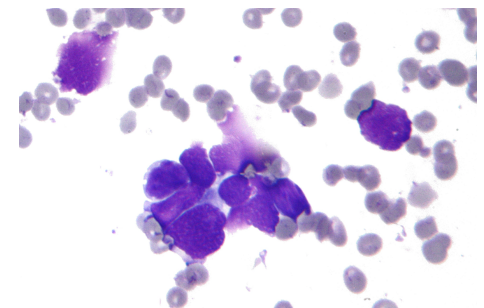
Adenocarcinoma



Squamous carcinoma



Large cell carcinoma



Small cell carcinoma



Non Small Cell Lung Carcinoma
(NSCLC)

Cytology



Morfologi

Thinprep
morfologi



Cellblock
Immunocytologi ←

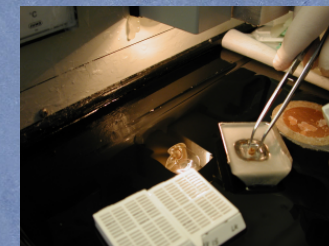
Cytology



Cellblock Immuncytologi



1. Centrifuger materialet 10 min. ved 3000 omdr./min.
2. Hæld supernatanten fra.
3. Tilsæt 3 dråber humant plasma.
4. Opslem, med pipetten, forsigtigt bundfaldet i plasmaen.
5. Tilsæt 2 dråber thrombin. Dannes der ikke et koagel indenfor 1 minut; tilsæt 1 dråbe BT.
6. Tilsæt 4% neutralt bufferet formaldehyd.
7. Åben en gazepose, træk den over reagensglasset.
8. Hæld koaglet i gazeposen.
9. Læg posen i en kapsel med mikroskopi-nummeret.
10. Dryp et par dråber hæmatein på koaglet.
11. Læg kapslen i en bøtte med 4% neutralt buffet formaldehyd.



Dannelse af koagel

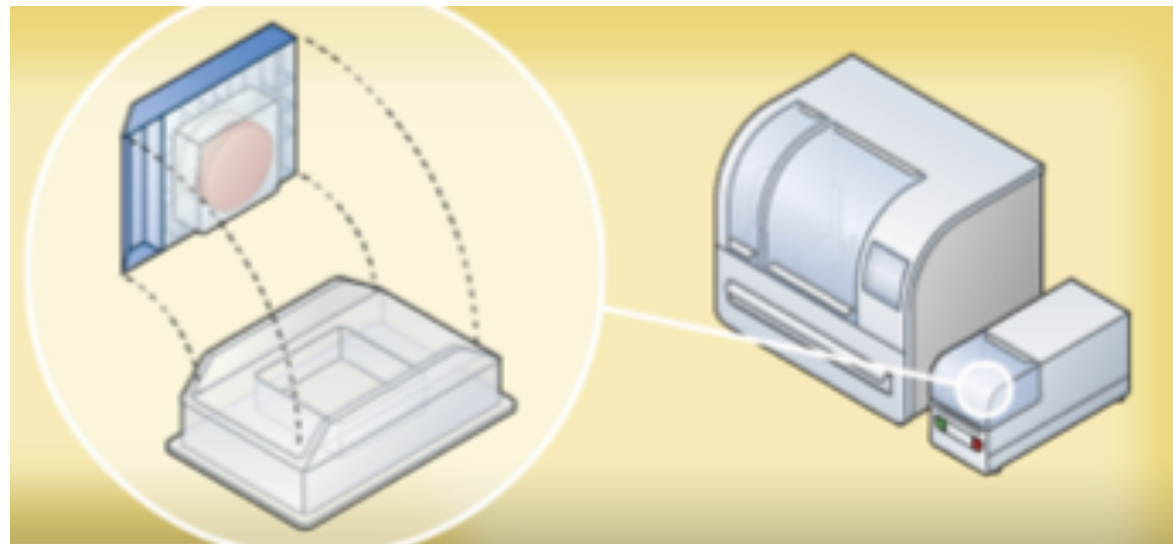
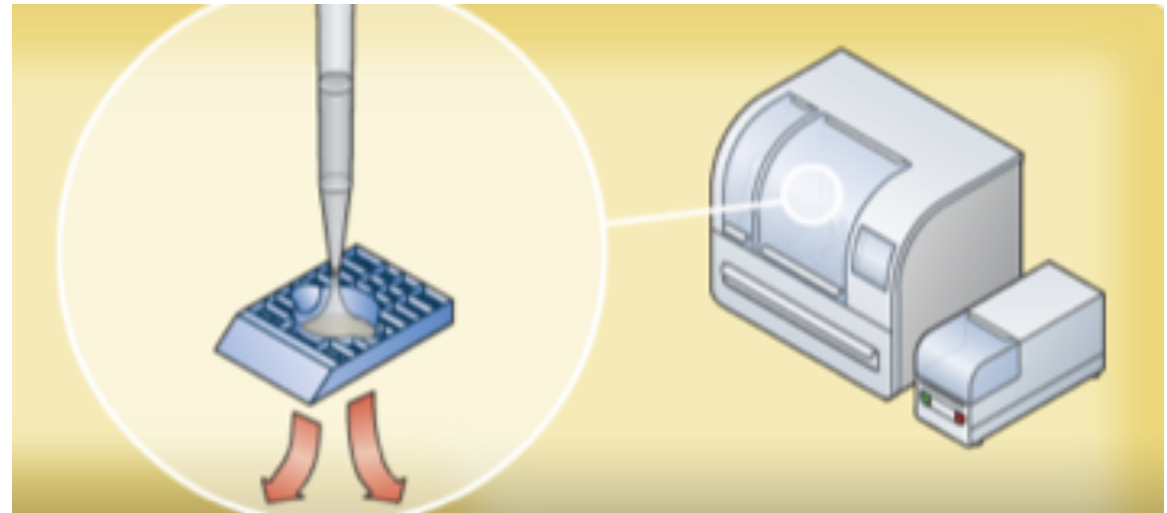
Til Parafin

Indstøbning

Cytology



Cellblock
Immuncytologi



Cytology

Improved capture

- Vacuum-assisted filtration
- Captures available cells, maximizing cellularity even from small/scanty samples
- Built on ThinPrep® technology

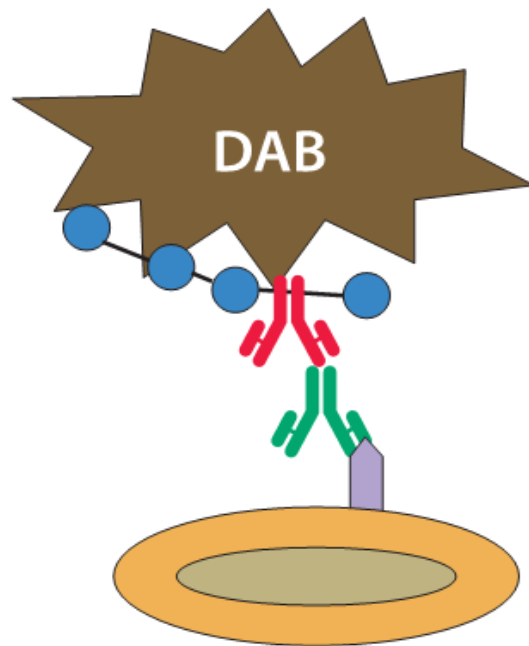
Improved presentation

- Helps maintain crisp, clear cellular architecture
- Creates concentrations of cells within the block
- Reviews of cytology and cell block simultaneously
- Supports easier and more productive pathology review

Improved consistency

- High-quality blocks
- Fully automated with minimal operator dependency
- Less cross-contamination risk
- Consistently rapid processing time (45 minutes or less)

Cytology



Kromogen (farvestof)

Visualiseringsystem
(enzymer)

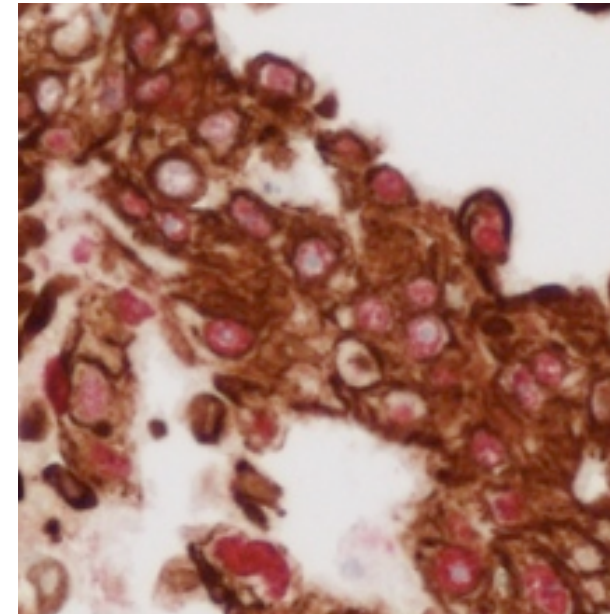
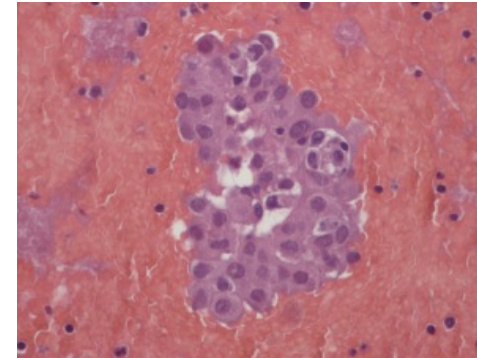
Sekundært antistof

Primært antistof

Antigen

Cellens cytoplasma

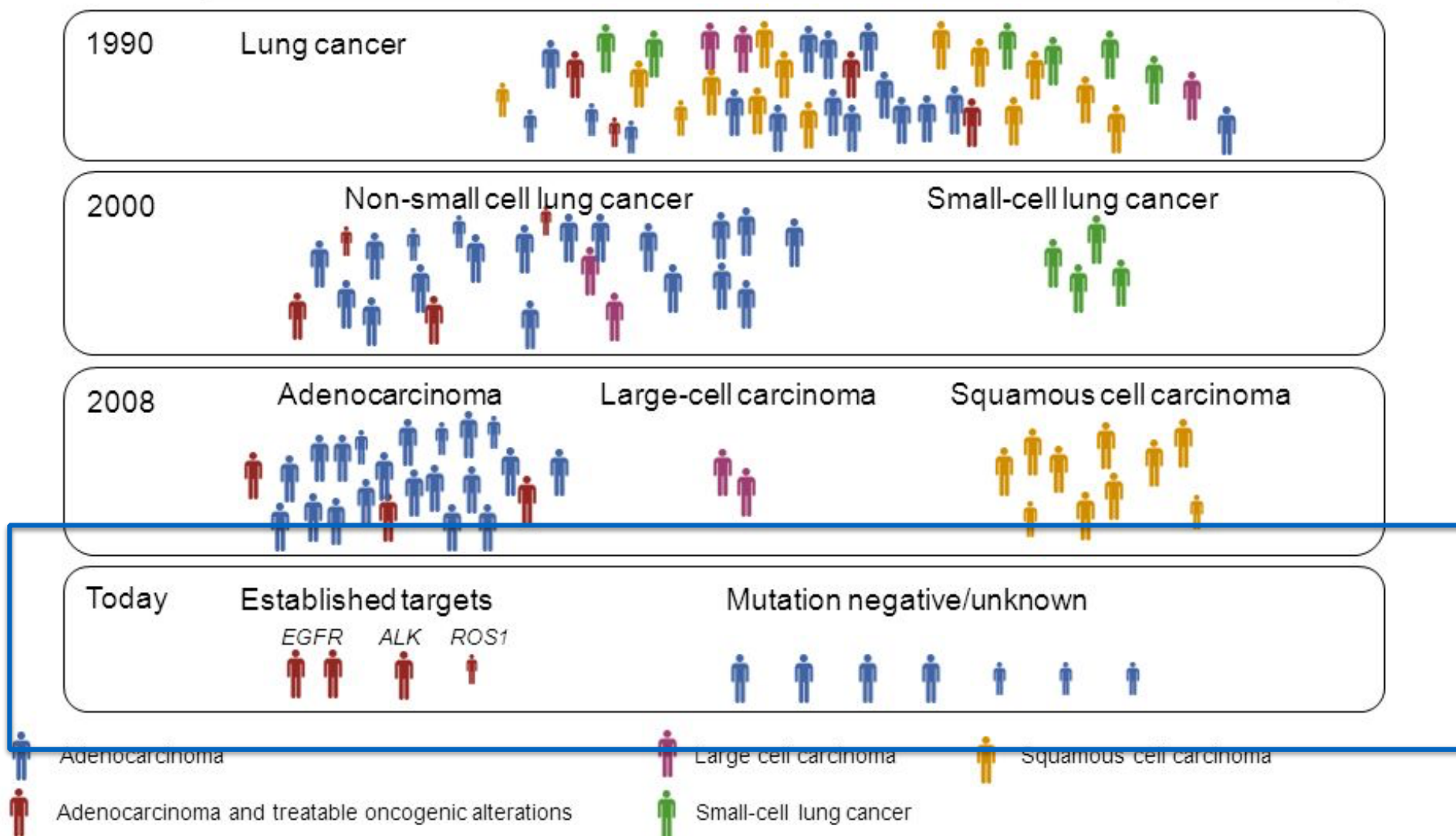
Cellekerne



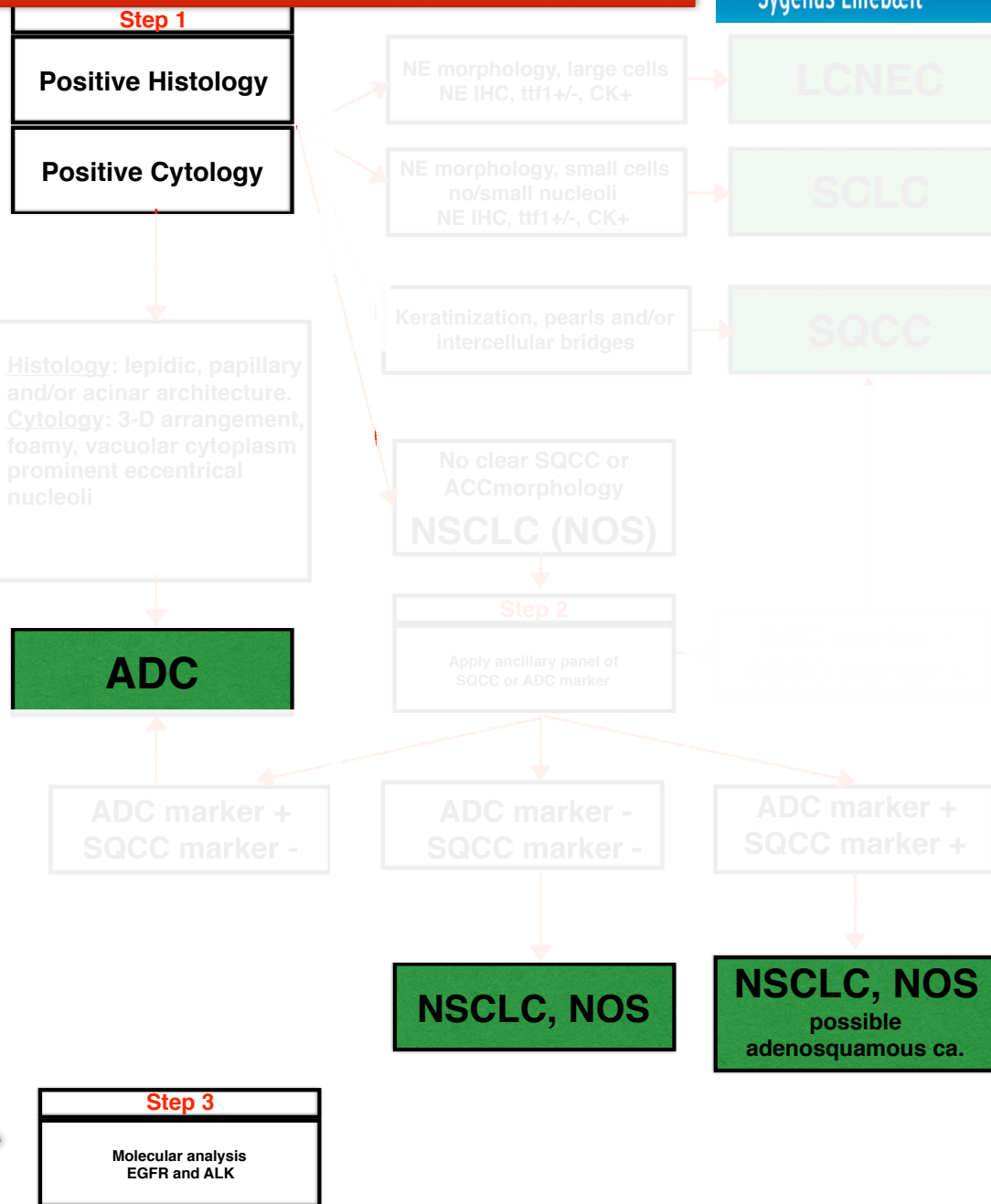
And now
for something
completely different...



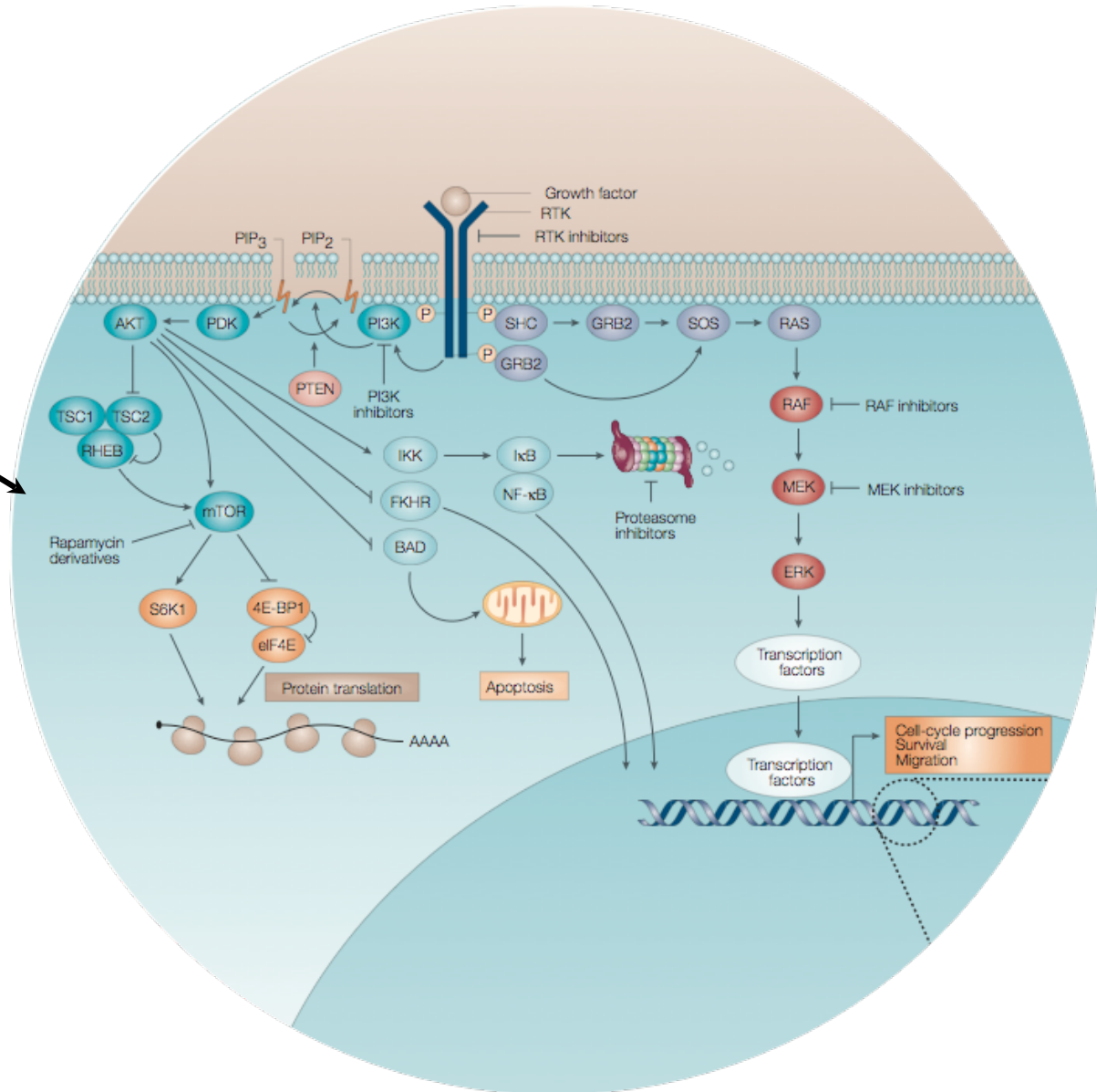
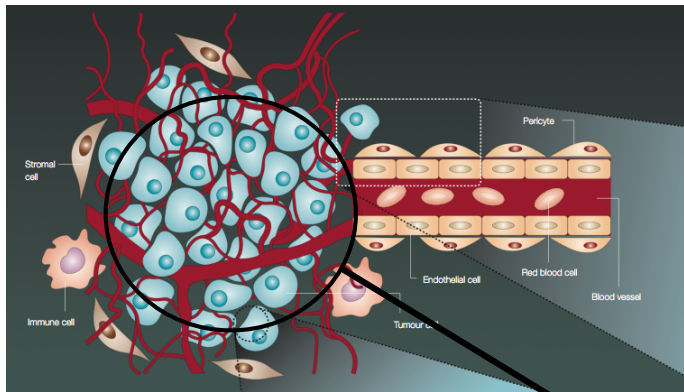
Patient selection in lung cancer: Evolution over time



Patoanatomiske analyser i forhold til lungecancerudredning.

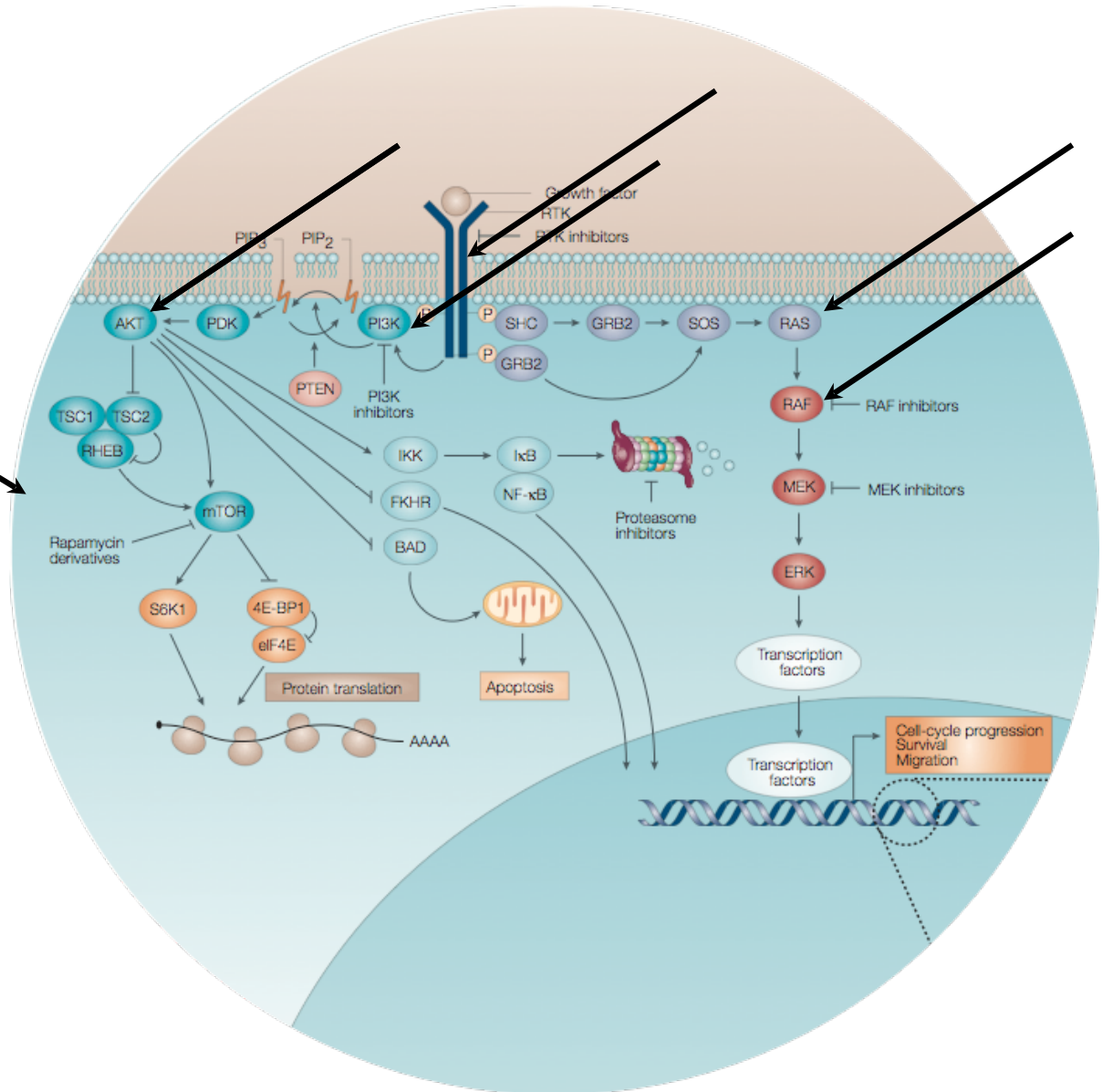
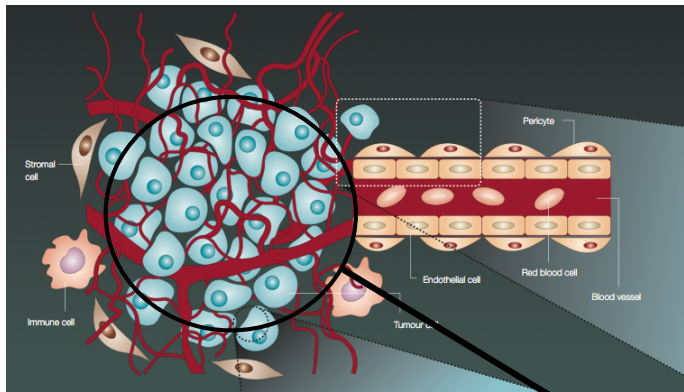


Patoanatomiske analyser i forhold til lungecancerudredning.



Pathways of cancer

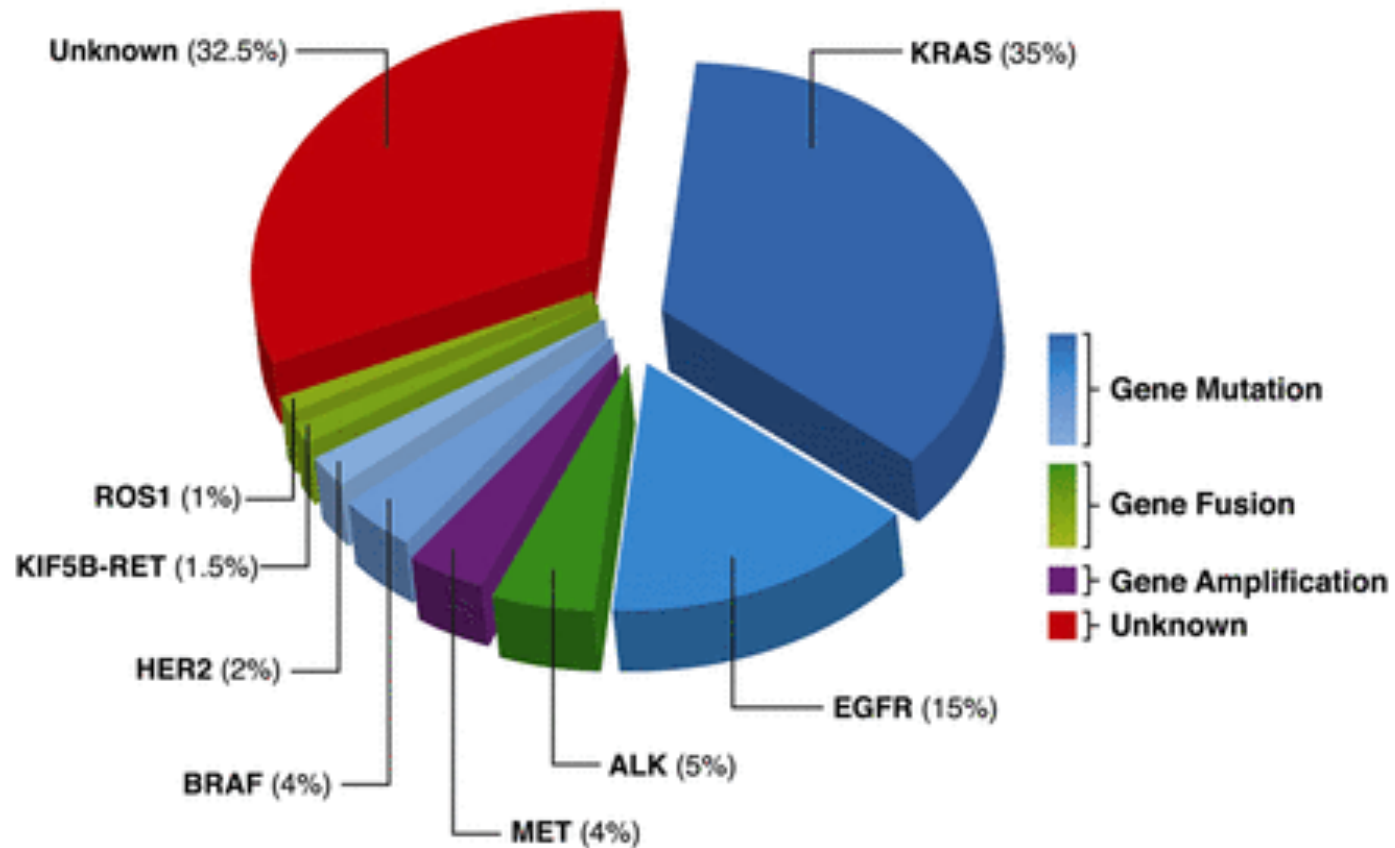
Patoanatomiske analyser i forhold til lungecancerudredning.



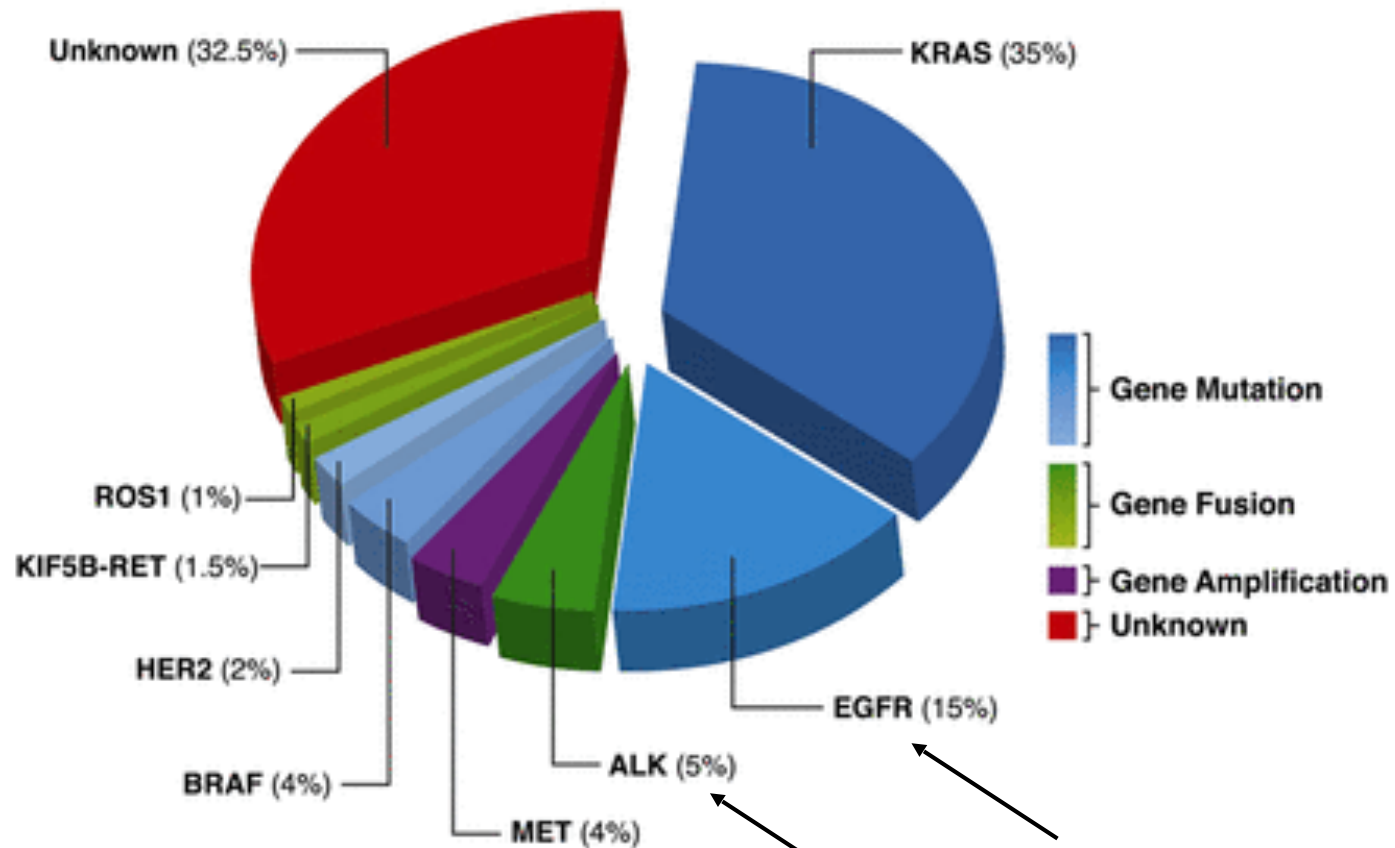
oncogenes



Oncogene 'drivers' in Adenocarcinoma

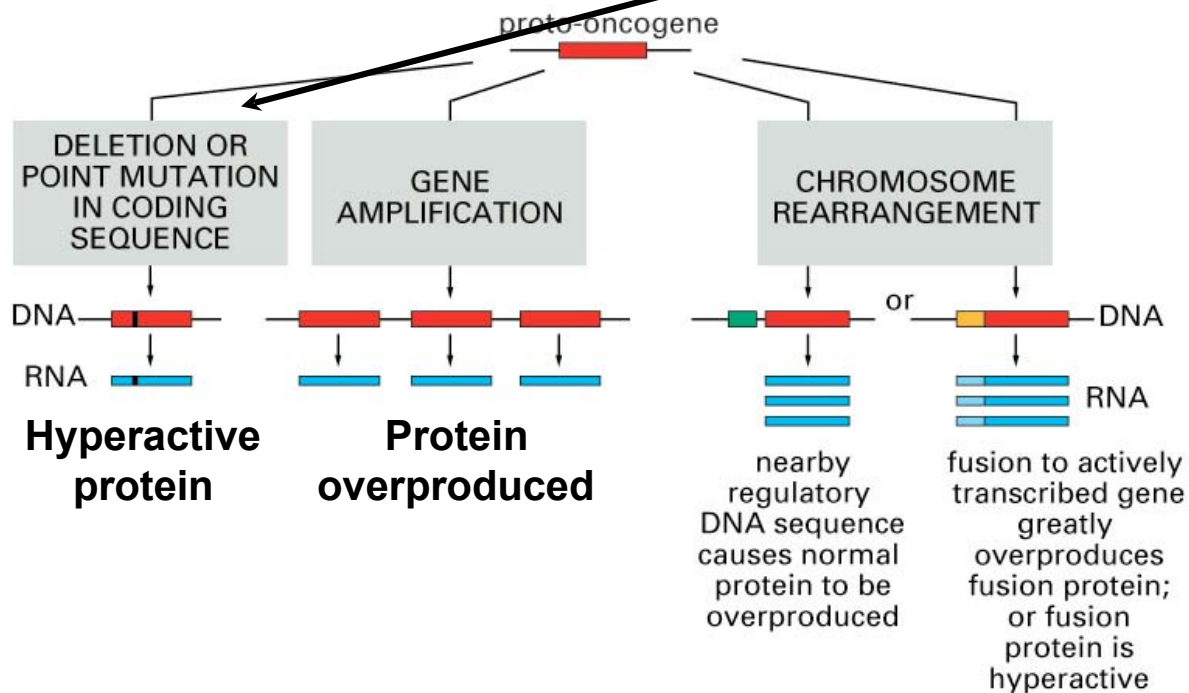
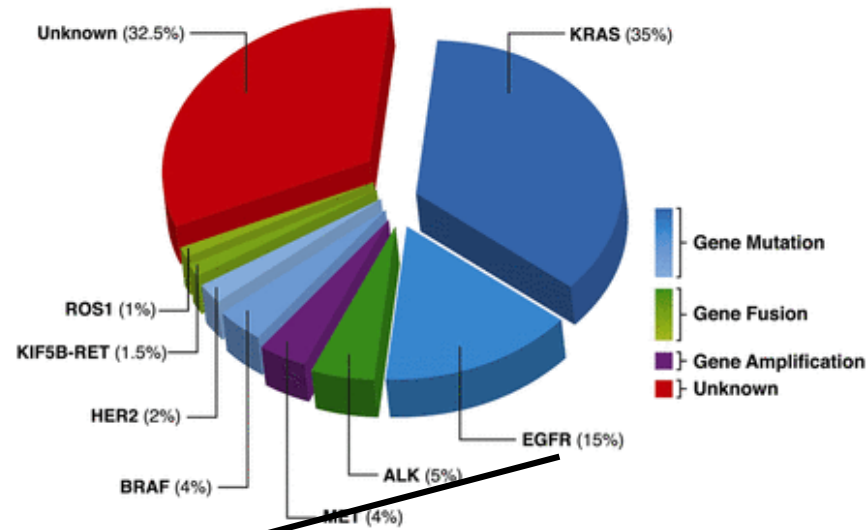


Oncogene 'drivers' in Adenocarcinoma

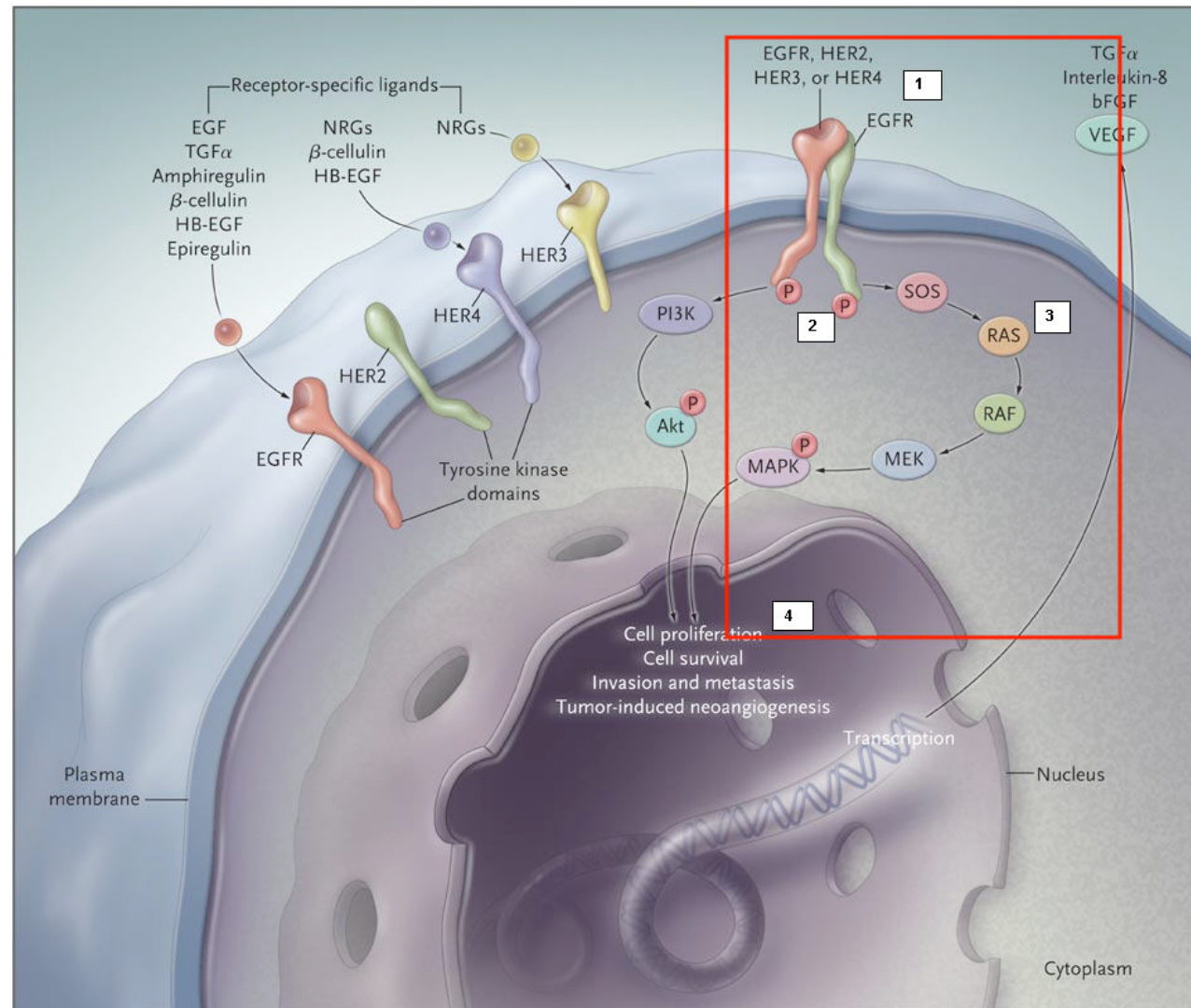
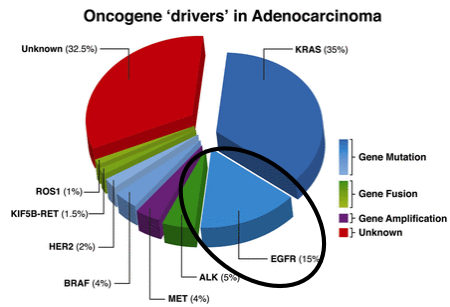


Predictive marker

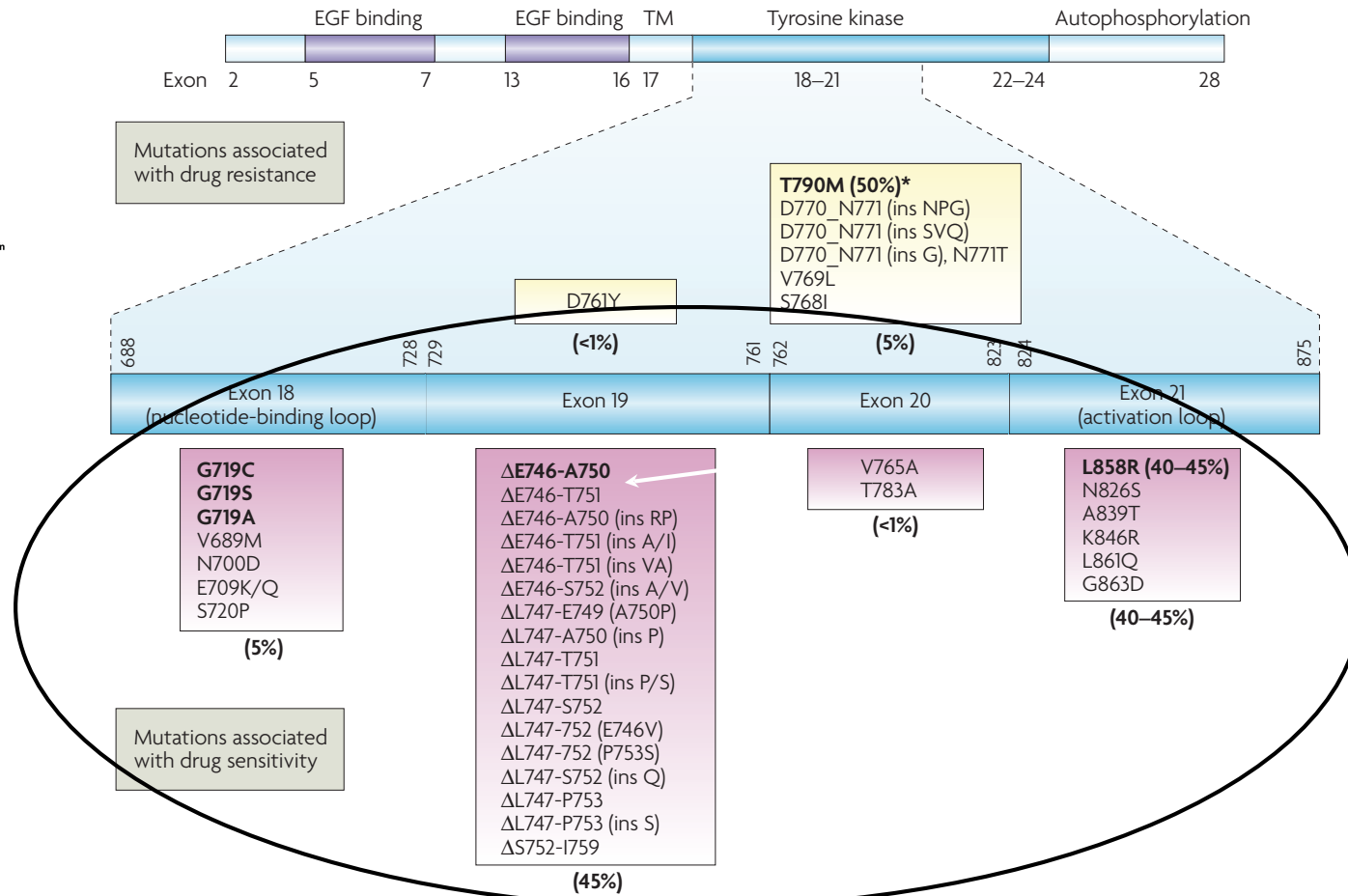
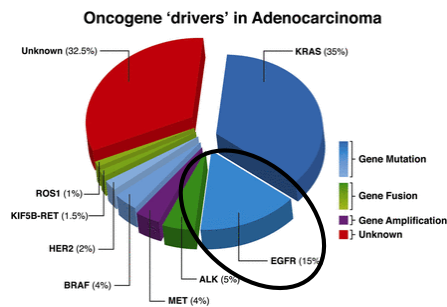
Oncogene 'drivers' in Adenocarcinoma



EGFR

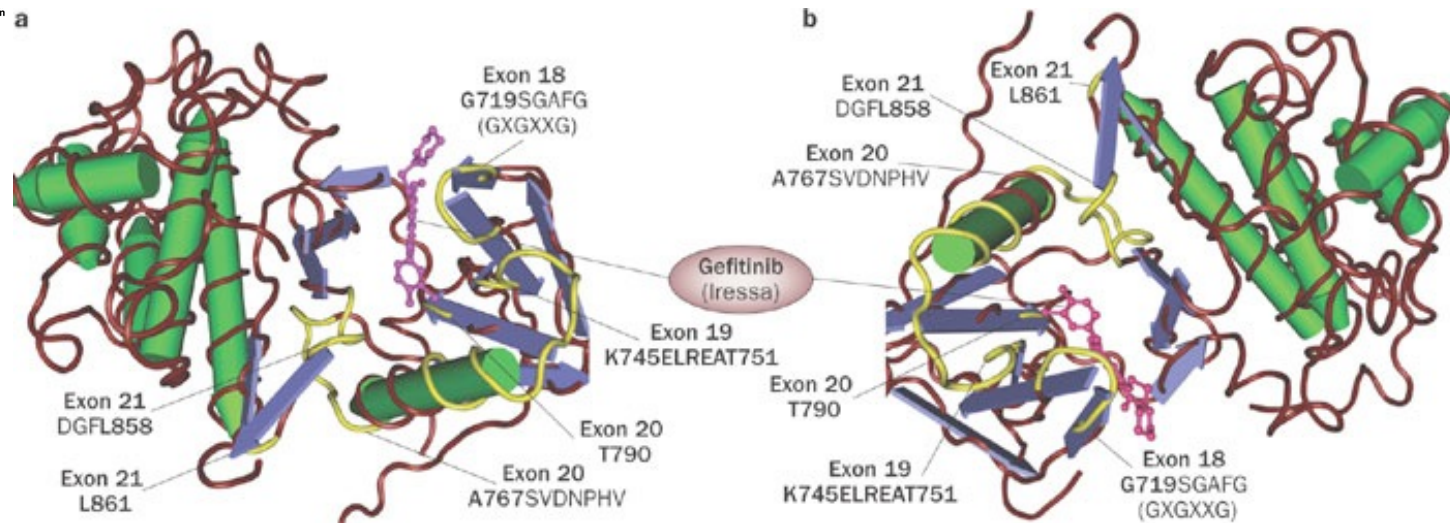
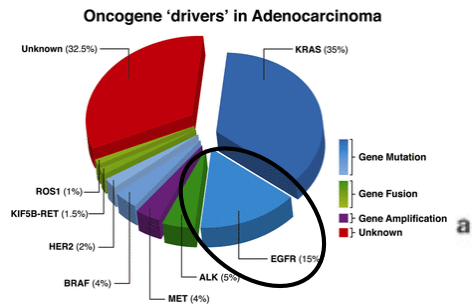


EGFR

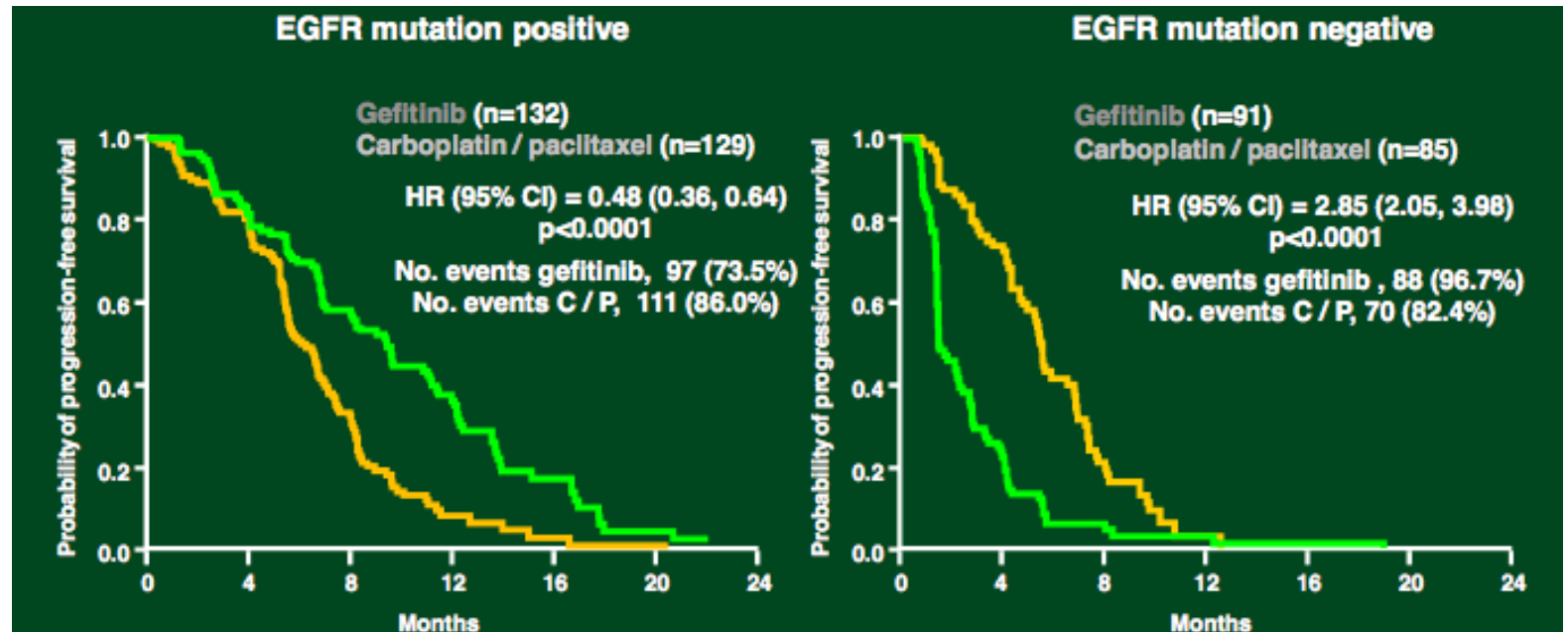
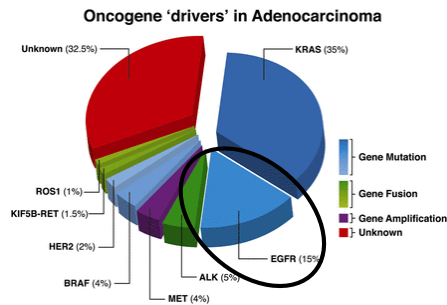


autoactivates EGFR

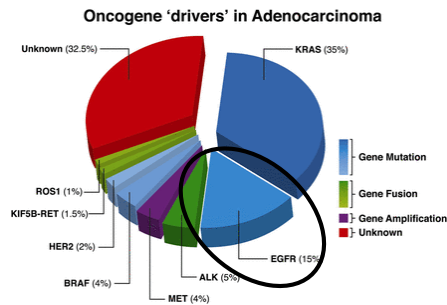
EGFR



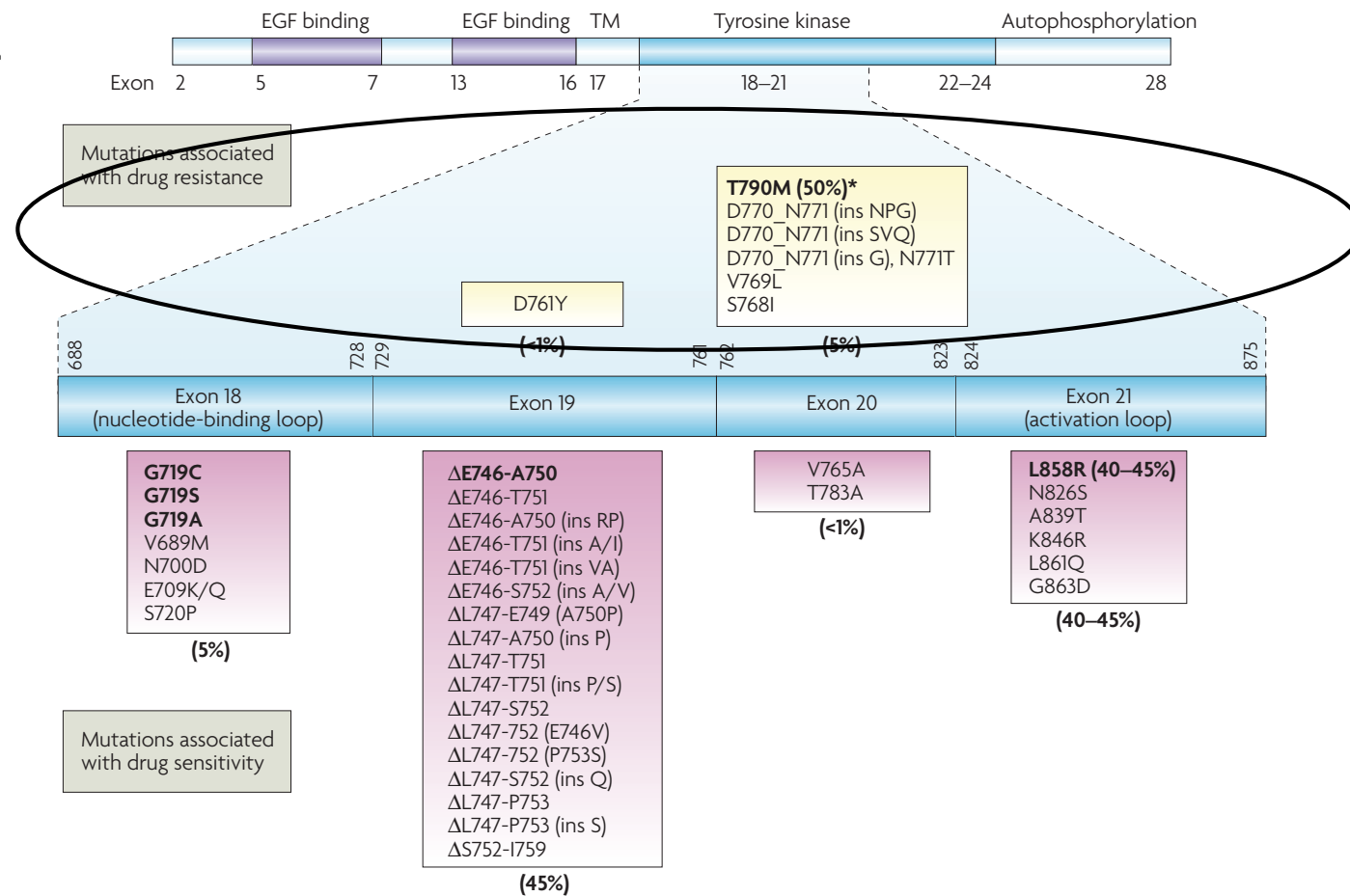
EGFR



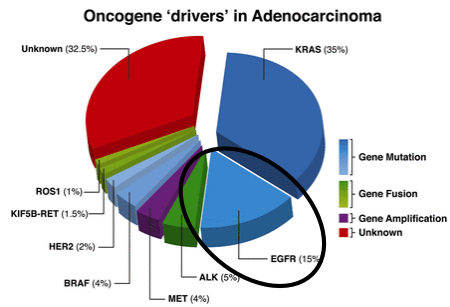
EGFR



Resistens



EGFR



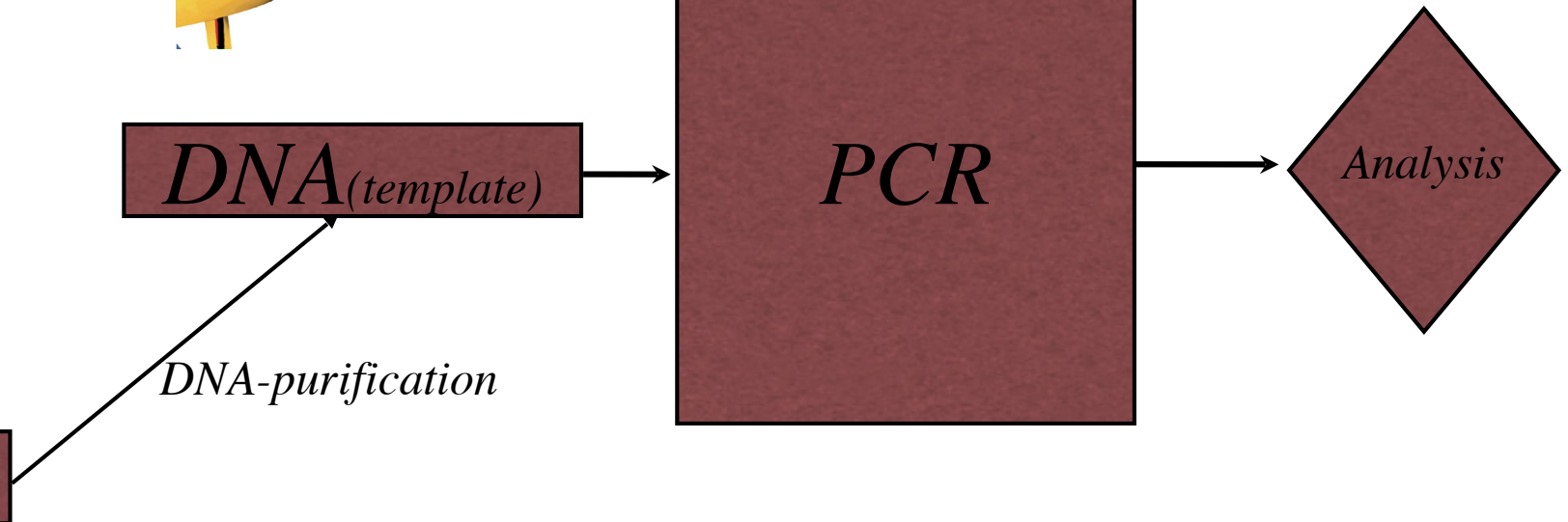
DNA(*template*)

DNA-purification

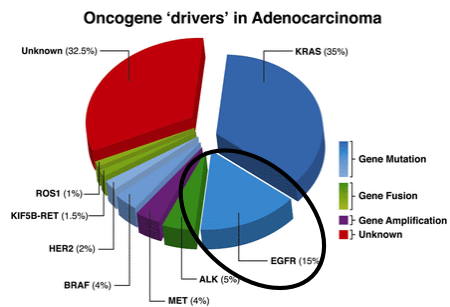
PCR

Analysis

Tissue section

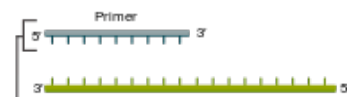


EGFR

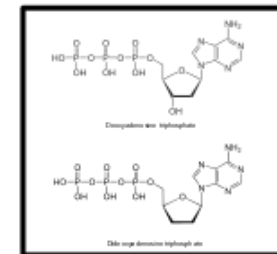
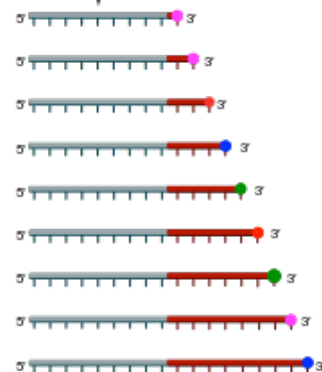


Sequencing

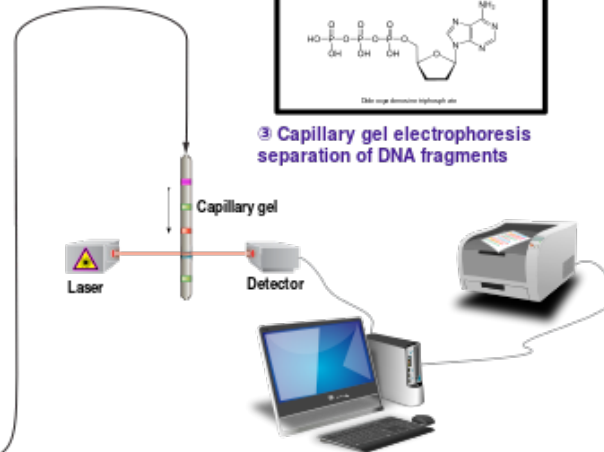
- Reaction mixture
 - Primer and DNA template
 - DNA polymerase
 - ddNTPs with flouochromes
 - dNTPs (dATP, dCTP, dGTP, and dTTP)



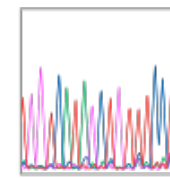
- Primer elongation and chain termination



- Capillary gel electrophoresis separation of DNA fragments



- Laser detection of flouochromes and computational sequence analysis

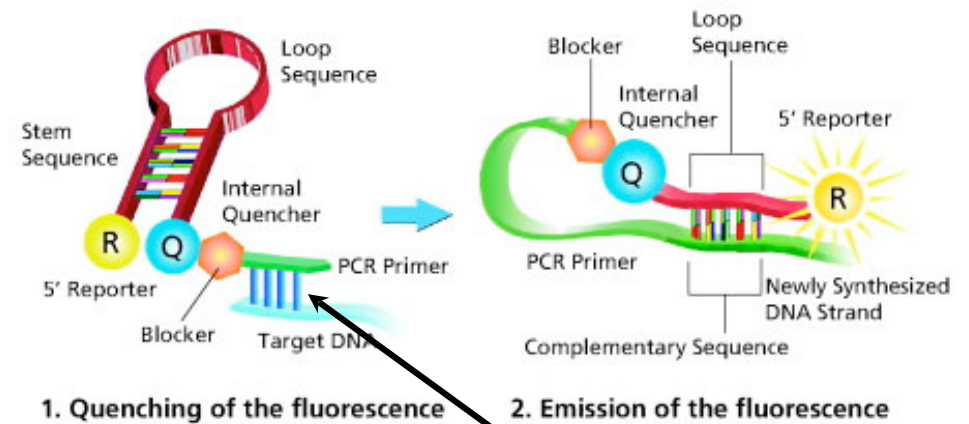
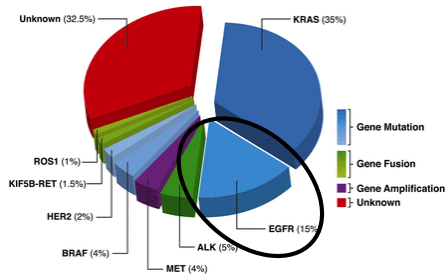


Chromatograph



EGFR

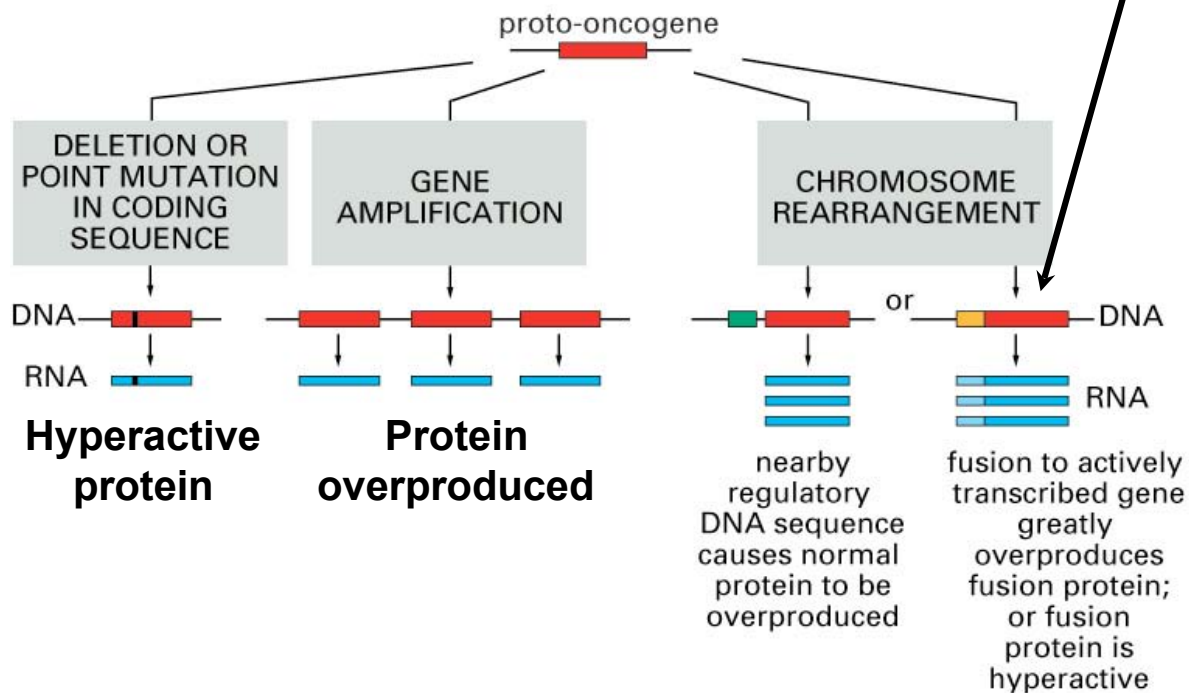
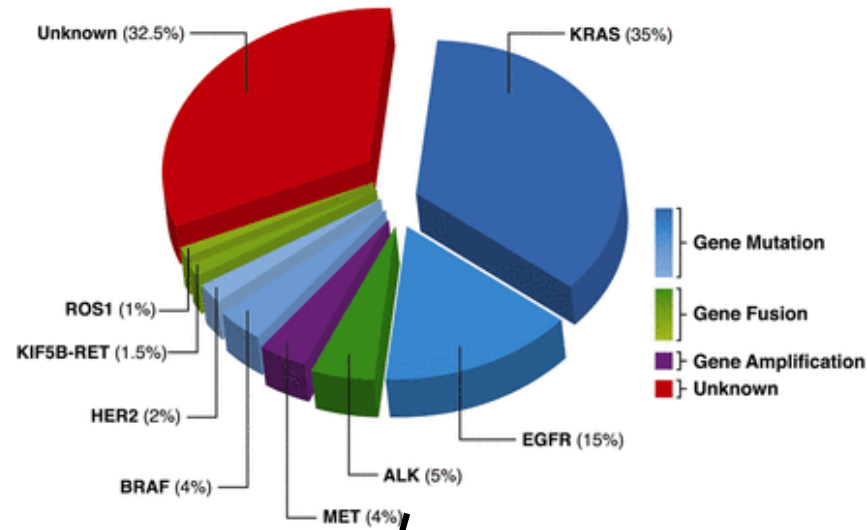
Oncogene 'drivers' in Adenocarcinoma



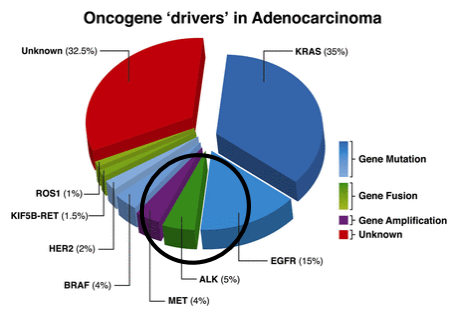
mutationspecific primer



Oncogene 'drivers' in Adenocarcinoma



ALK



EML4-ALK

E13;A20



E6;A20



E20;A20



E14;A20



E18;A20



E15;A20



E2;A20



E17;A20



TFG-ALK



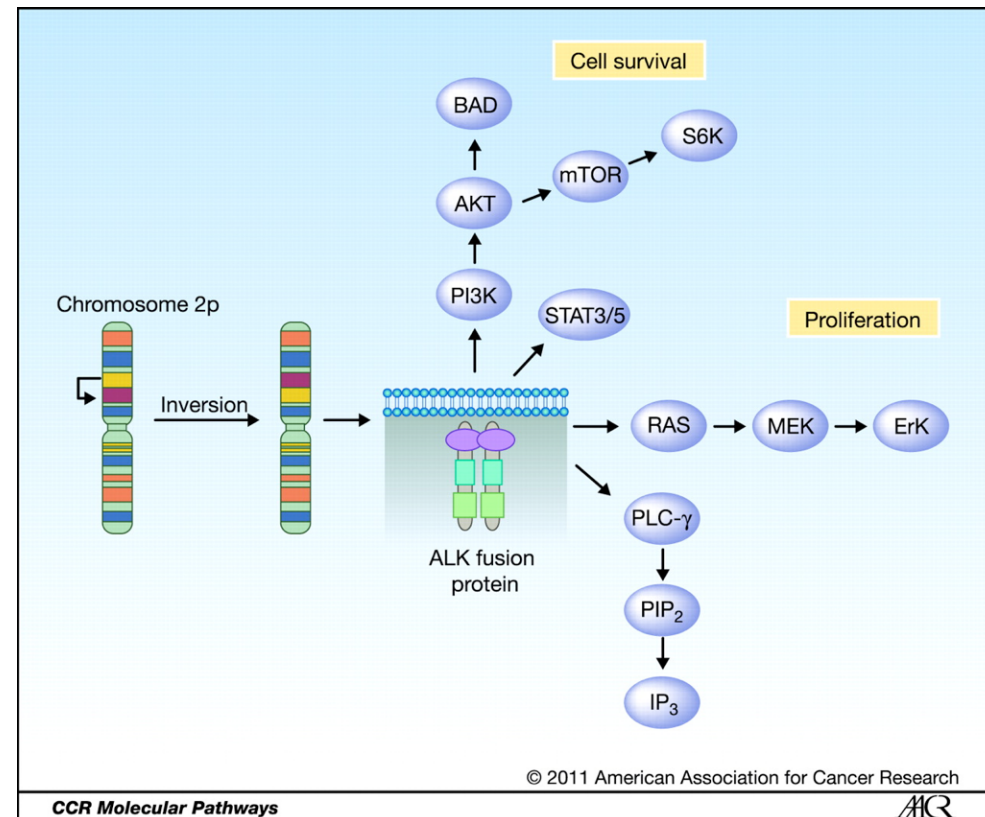
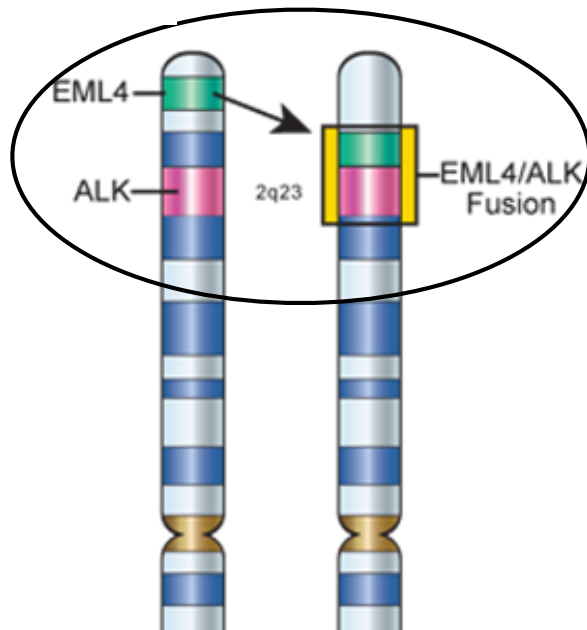
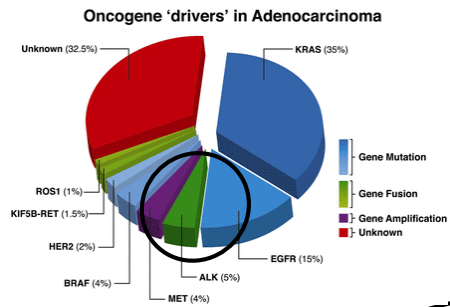
KIF5B-ALK



■ Coiled-coil domain

■ Tyrosine kinase domain

ALK



ALK

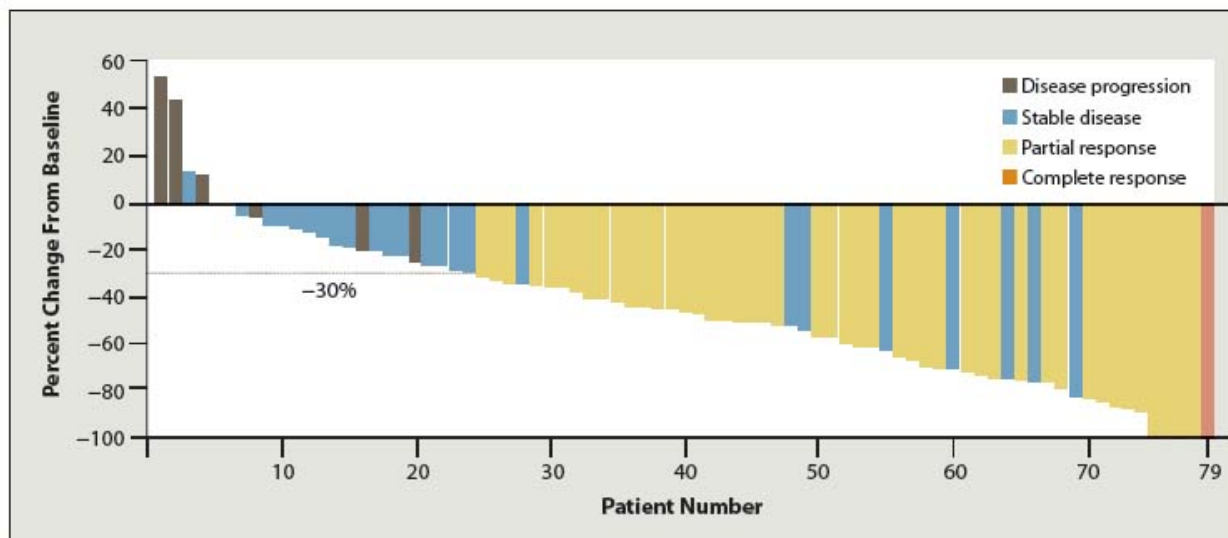
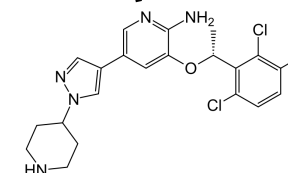
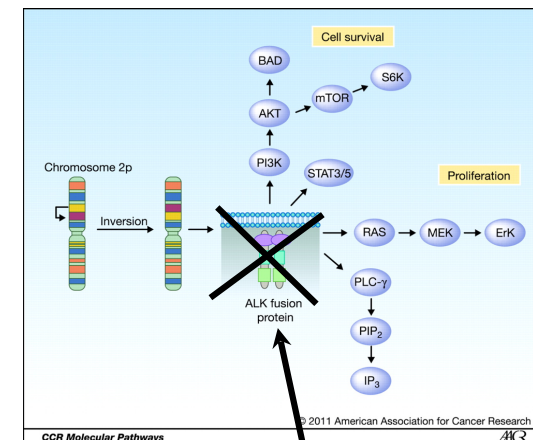
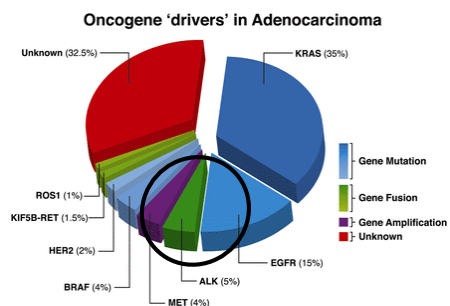
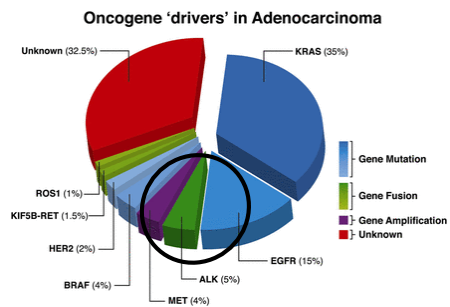


Figure 2: Waterfall plot showing response to crizotinib in patients with *EML4-ALK* NSCLC. Percent change in tumor burden relative to pretreatment baseline is represented. (Reproduced with permission from Kwak et al. *N Engl J Med.* 2010;363:1693-1703. Copyright © 2010, Massachusetts Medical Society.)

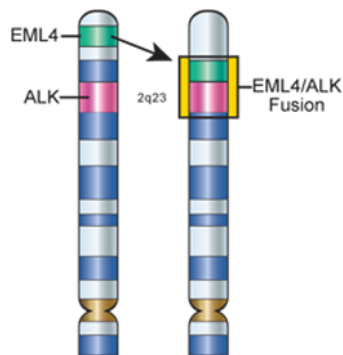


Detection of fusion protein

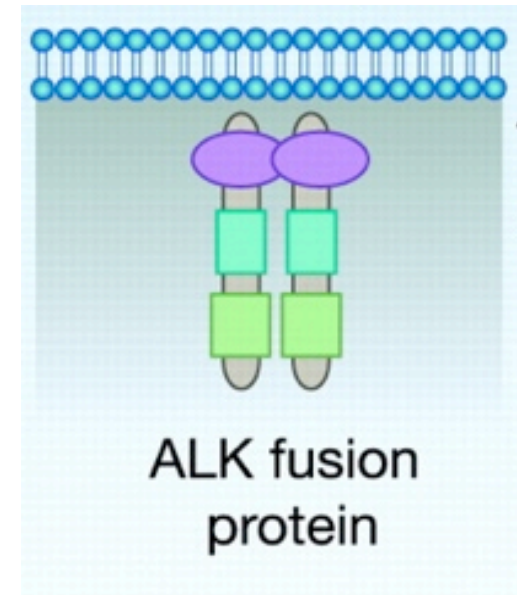
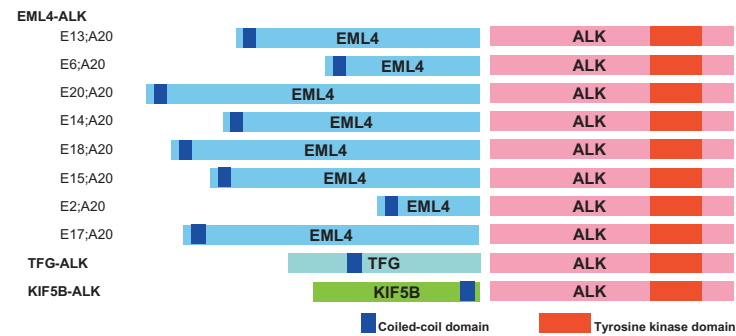
ALK



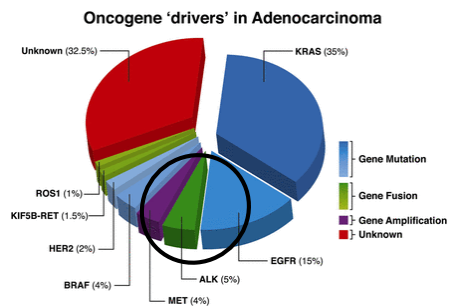
Detection of chromosomal changes



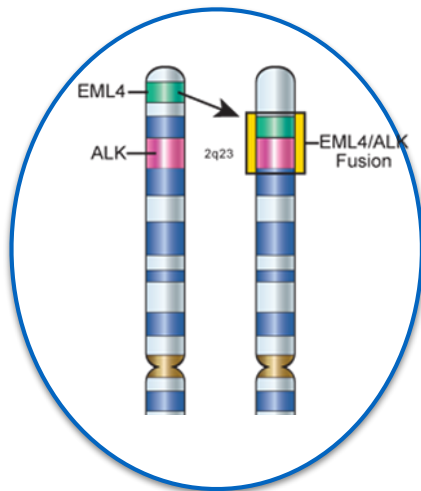
Detection of fusion RNA



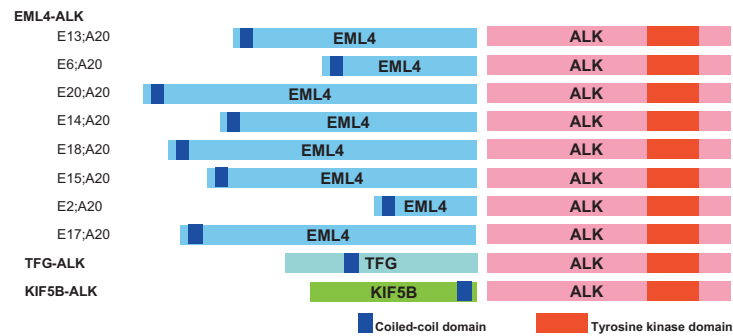
ALK



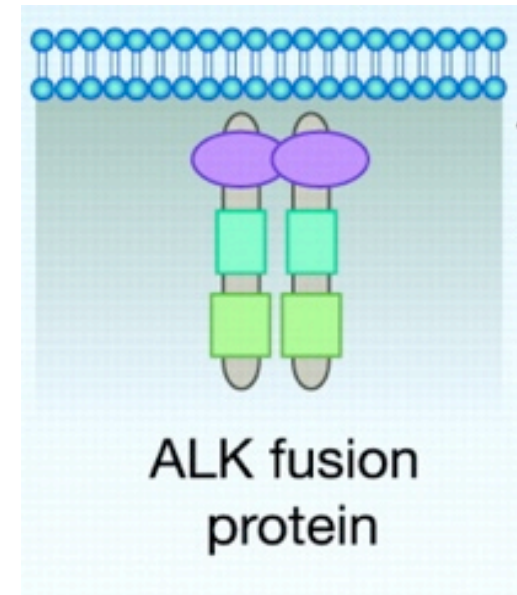
Detection of chromosomal changes



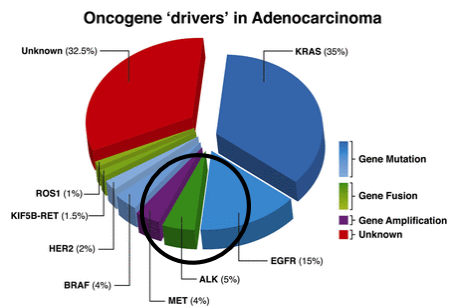
Detection of fusion RNA



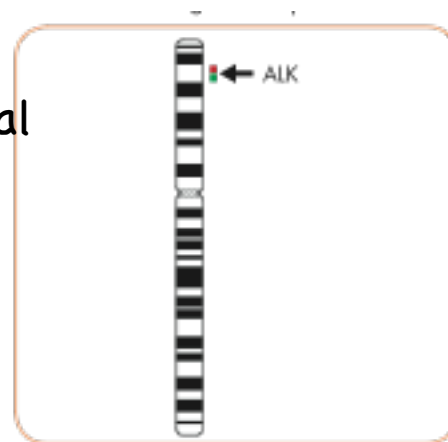
Detection of fusion protein



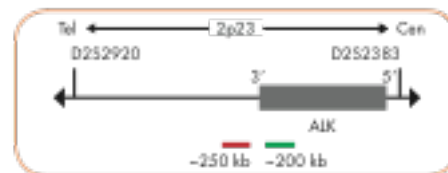
ALK



Detection of chromosomal changes

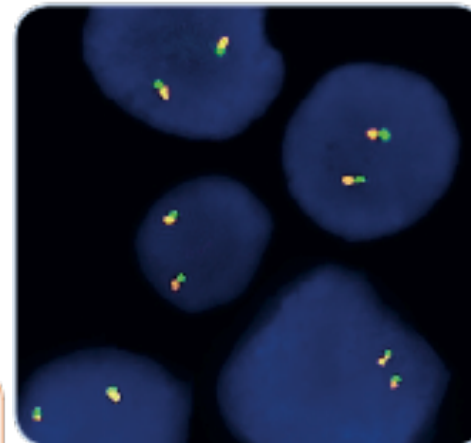


Ideogram of chromosome 2 indicating the hybridization locations.

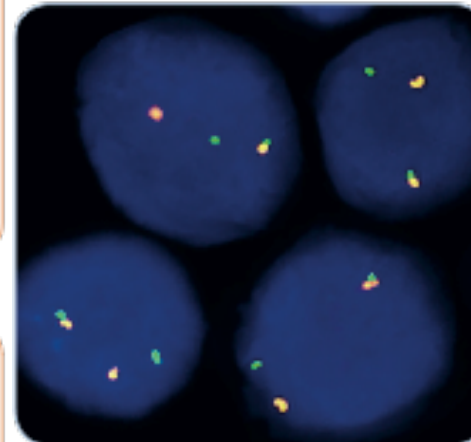


SPEC ALK Probe map (not to scale).

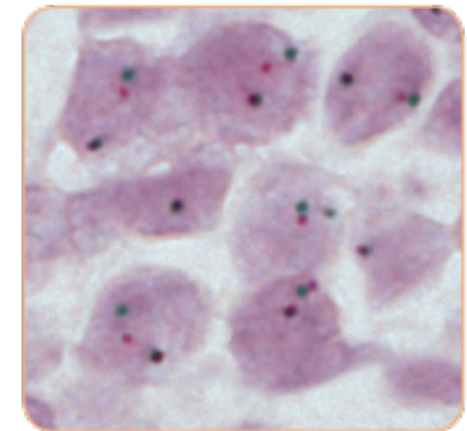
Inversion probe



SPEC ALK Dual Color Break Apart Probe hybridized to normal interphase cells as indicated by two orange/green fusion signals per nucleus.

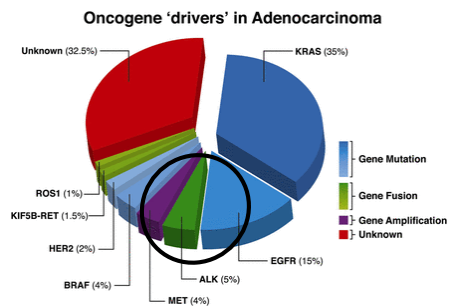


ZYTOVISION
Molecular diagnostics simplified

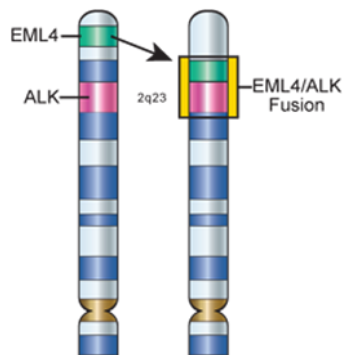


Detection of fusion protein

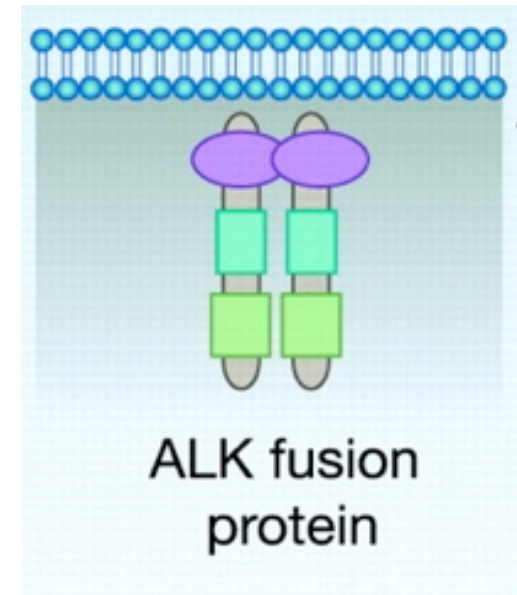
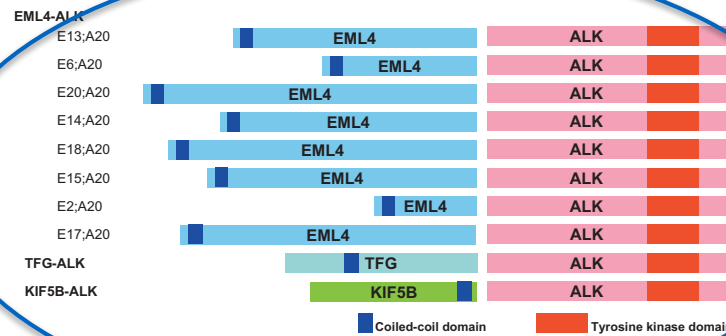
ALK



Detection of chromosomal changes



Detection of fusion RNA



Detection of fusion RNA

Different variants of EML4-ALK and non-EML4 fusion partners

10 different primers

EML4-ALK



TFG-ALK

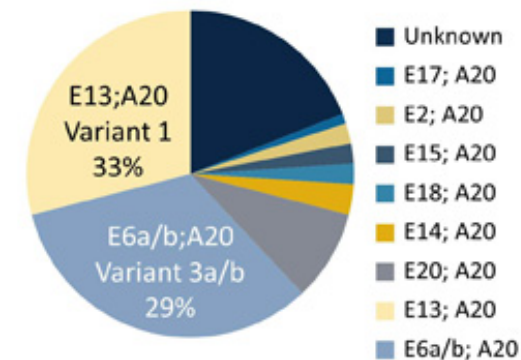


KIF5B-ALK



Coiled-coil domain

Tyrosine kinase domain

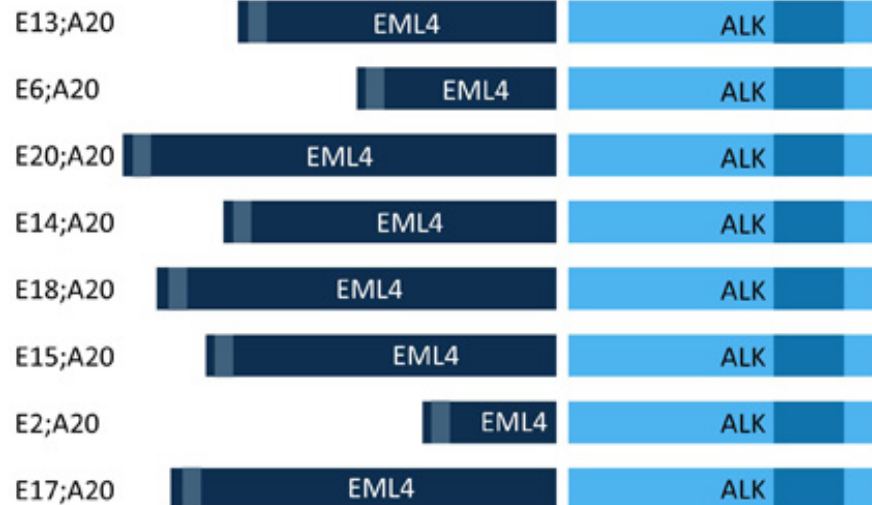


Detection of fusion RNA

Different variants of EML4-ALK and non-EML4 fusion partners

3 different primers

EML4-ALK



TFG-ALK

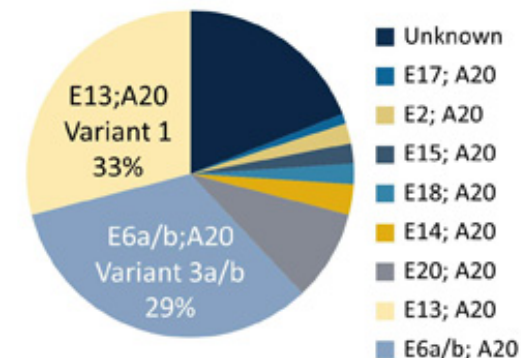


KIF5B-ALK

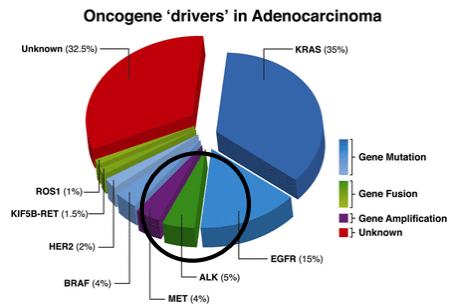


Coiled-coil domain

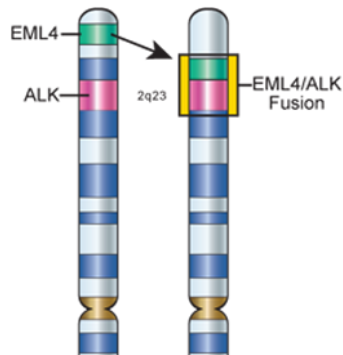
Tyrosine kinase domain



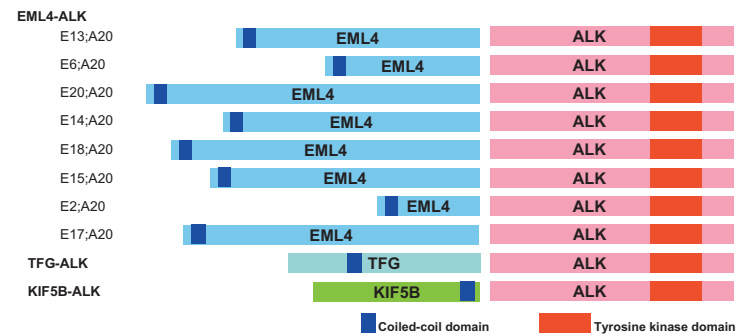
ALK



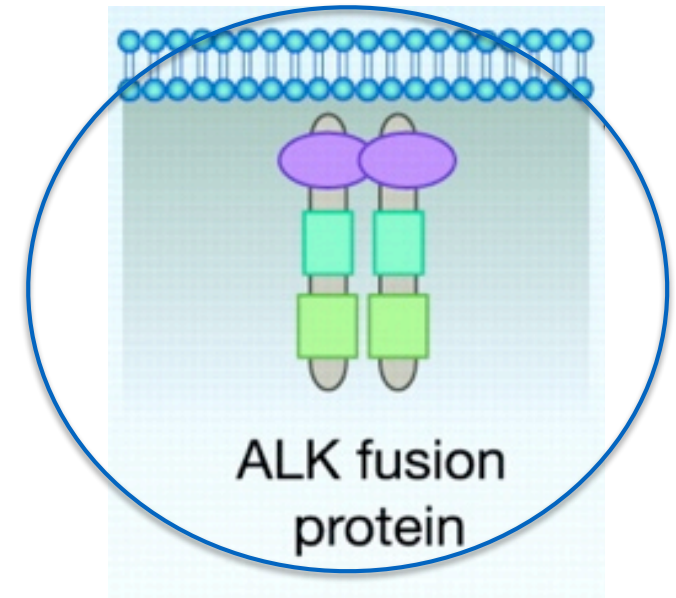
Detection of chromosomal changes



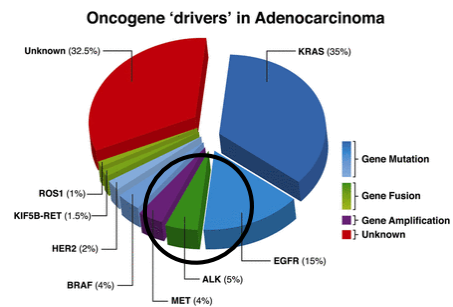
Detection of fusion RNA



Detection of fusion protein

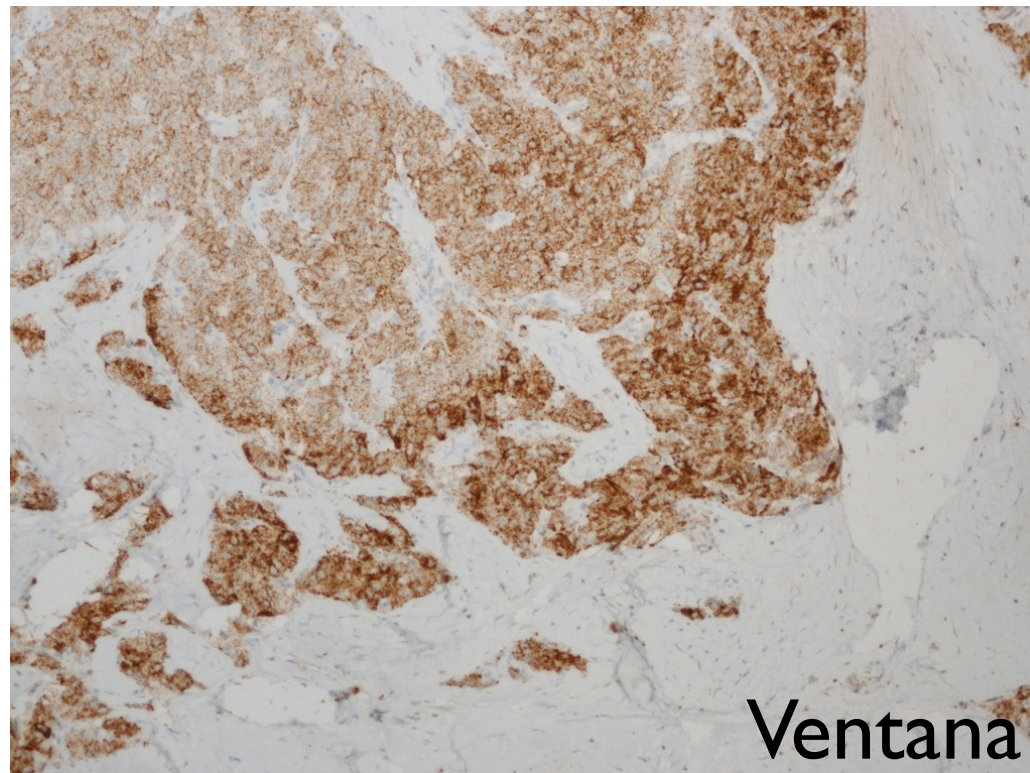


ALK



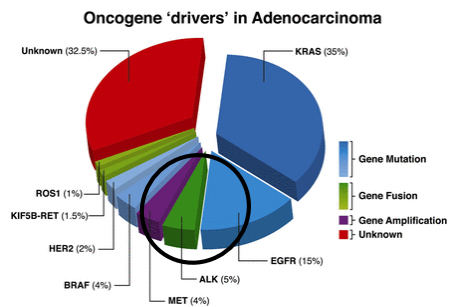
Immunohistolochemistry

Detects ALK independent of fusion partner



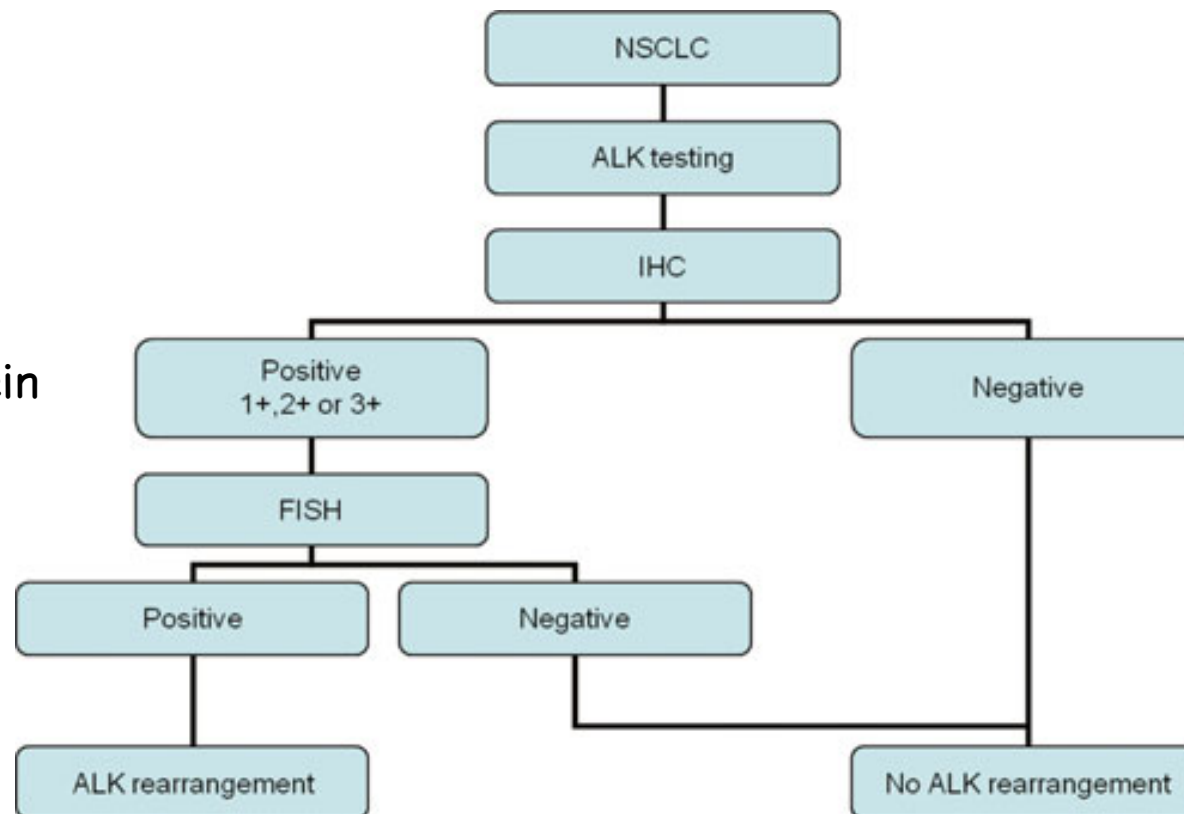
Detection of fusion protein

ALK



Detection of fusion protein

Algorithm

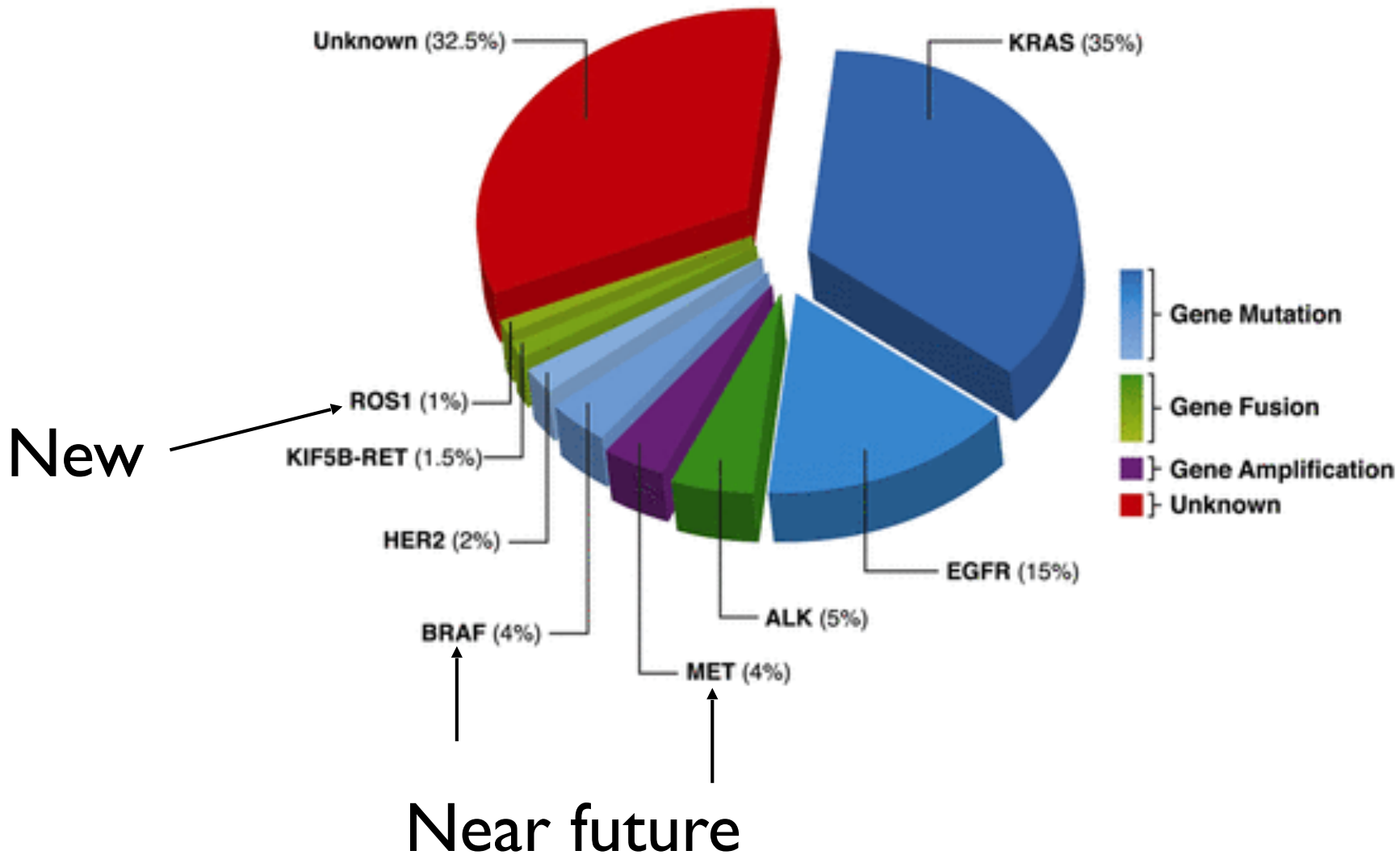


Virchows Arch (2015) 463:245–257
DOI 10.1007/s00428-012-1261-4
REVIEW AND PERSPECTIVES

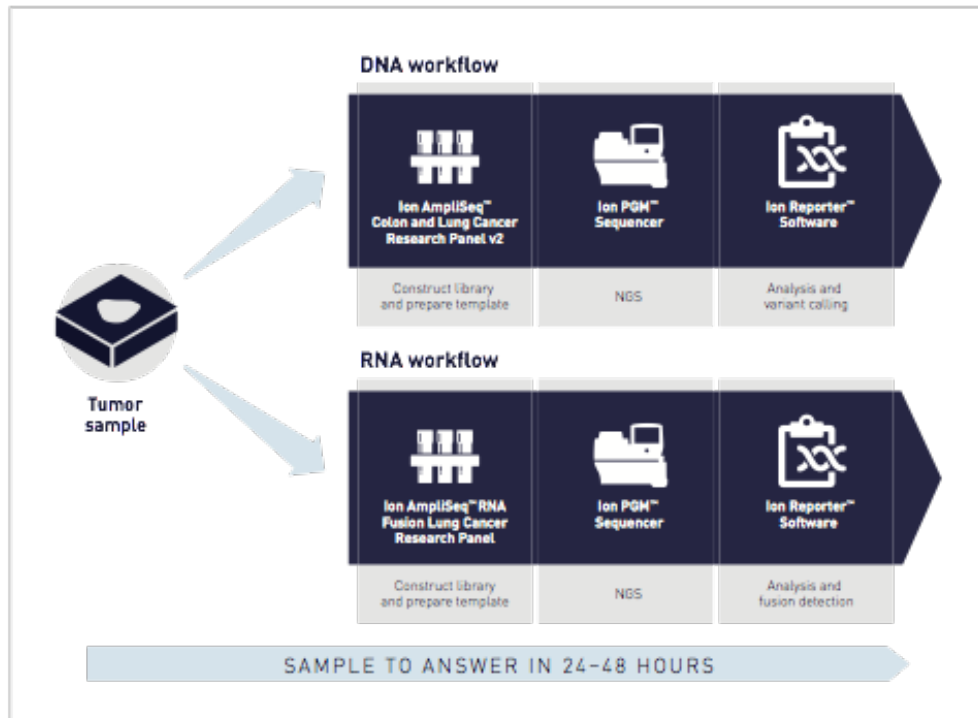
EML4-ALK testing in non-small cell carcinomas of the lung: a review with recommendations

Erk Thunnissen · Lukas Scheiderer · Manfred Bittel · Göran Elmberger · Keith Kerr · Fernando Lopez-Rios · Halger Moch · Wiesława Olczak · Patrick Parada · Frédéric Pèneau-Laura · Giulio Rossi

Oncogene 'drivers' in Adenocarcinoma



Patoanatomiske analyser i forhold til lungecancerudredning.



KRAS, EGFR, BRAF, PIK3CA, AKT1, ERBB2, PTEN, NRAS, STK11, MAP2K1, ALK, DDR2, CTNNB1, MET, TP53, SMAD4, FBX7, FGFR3, NOTCH1, ERBB4, FGFR1, FGFR2

ALK, RET, ROS1, and NTRK1 fusion transcripts, in addition to targets designed to detect 5' and 3' ALK gene expression

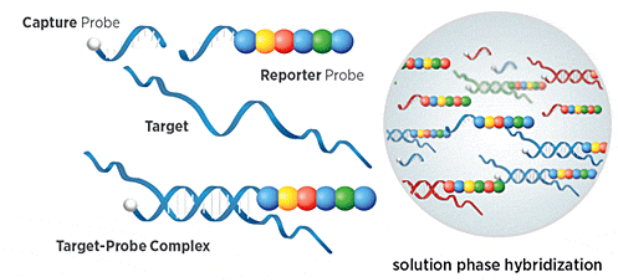
Next generation seq.



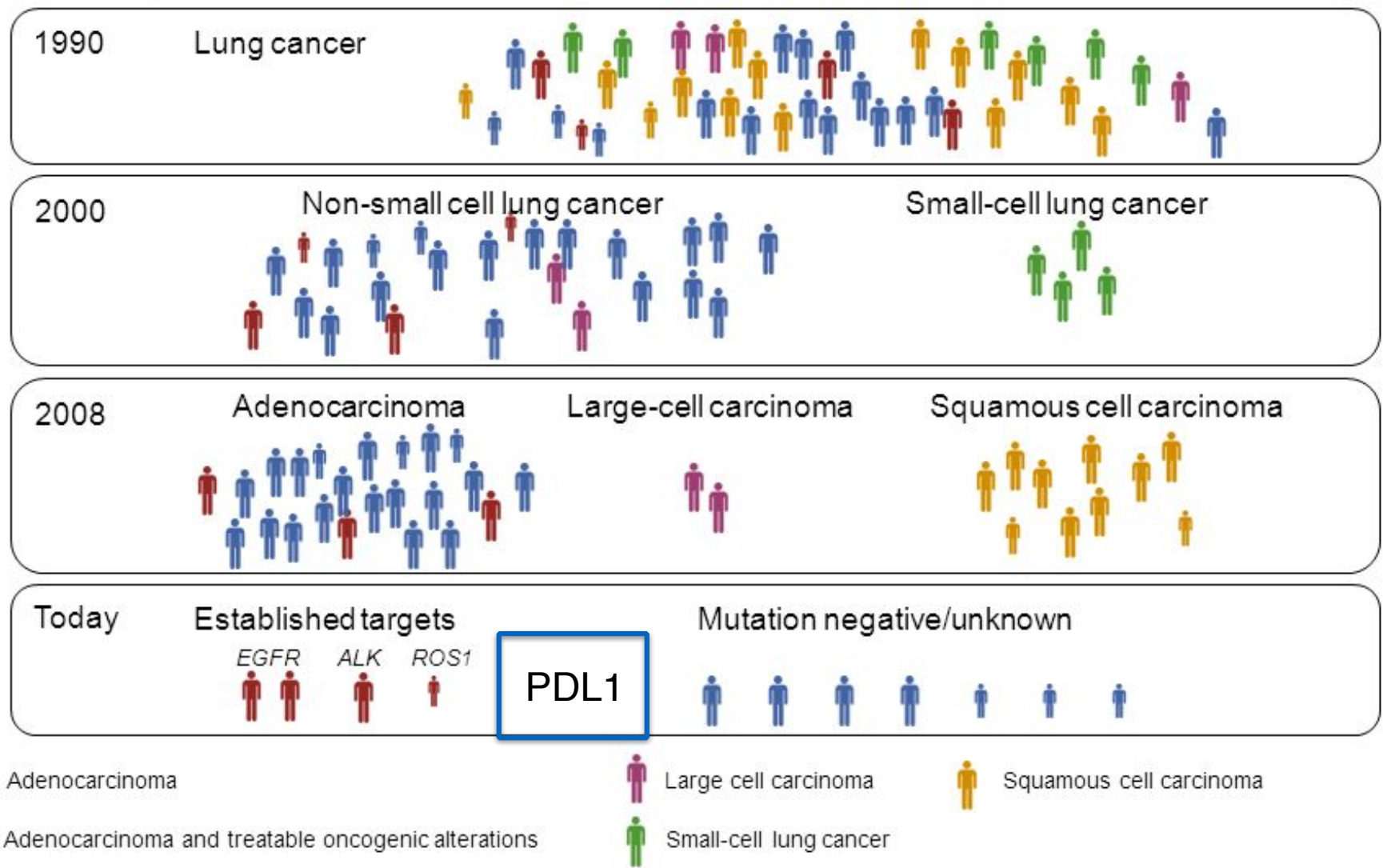
Patoanatomiske analyser i forhold til lungecancerudredning.



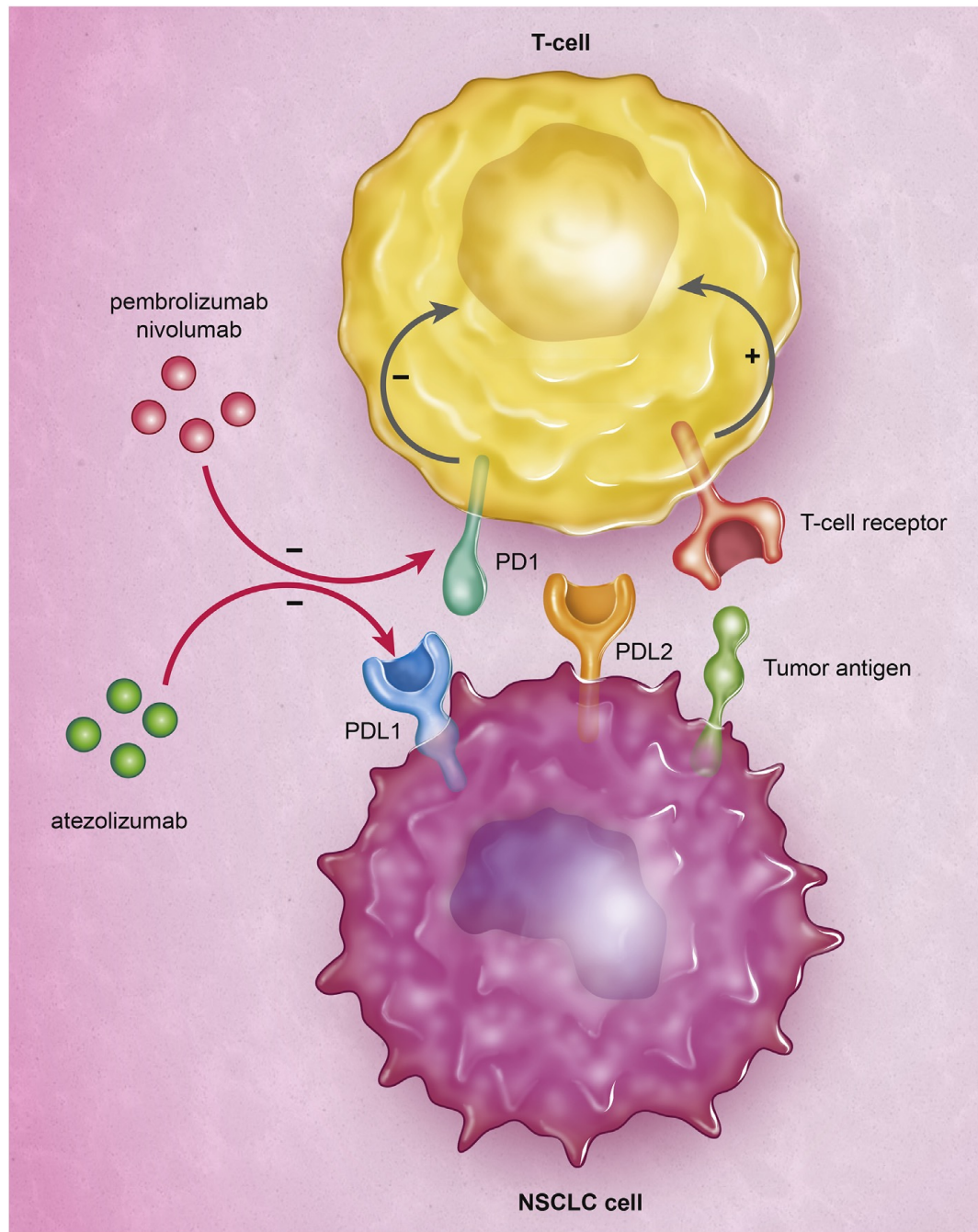
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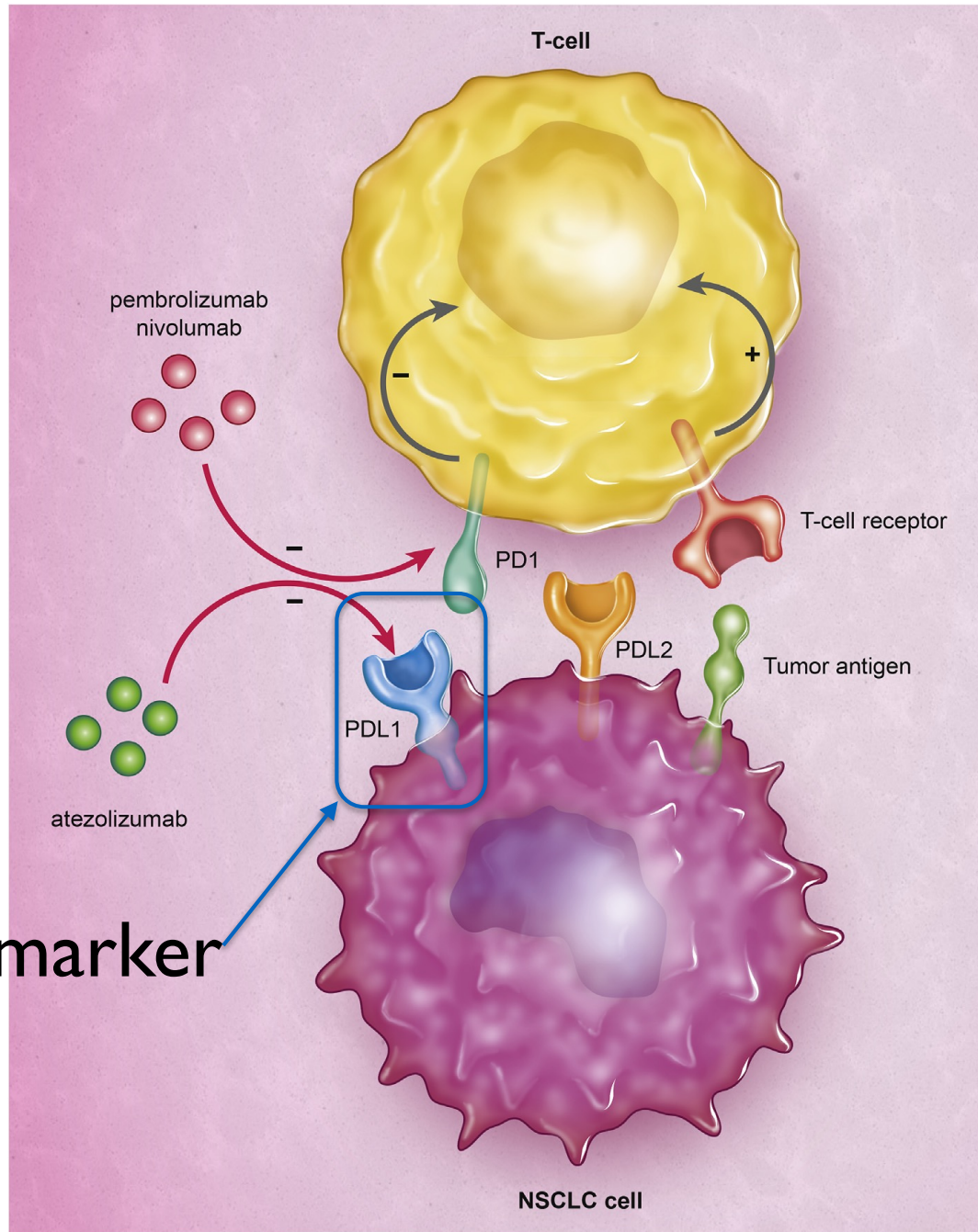


Patient selection in lung cancer: Evolution over time



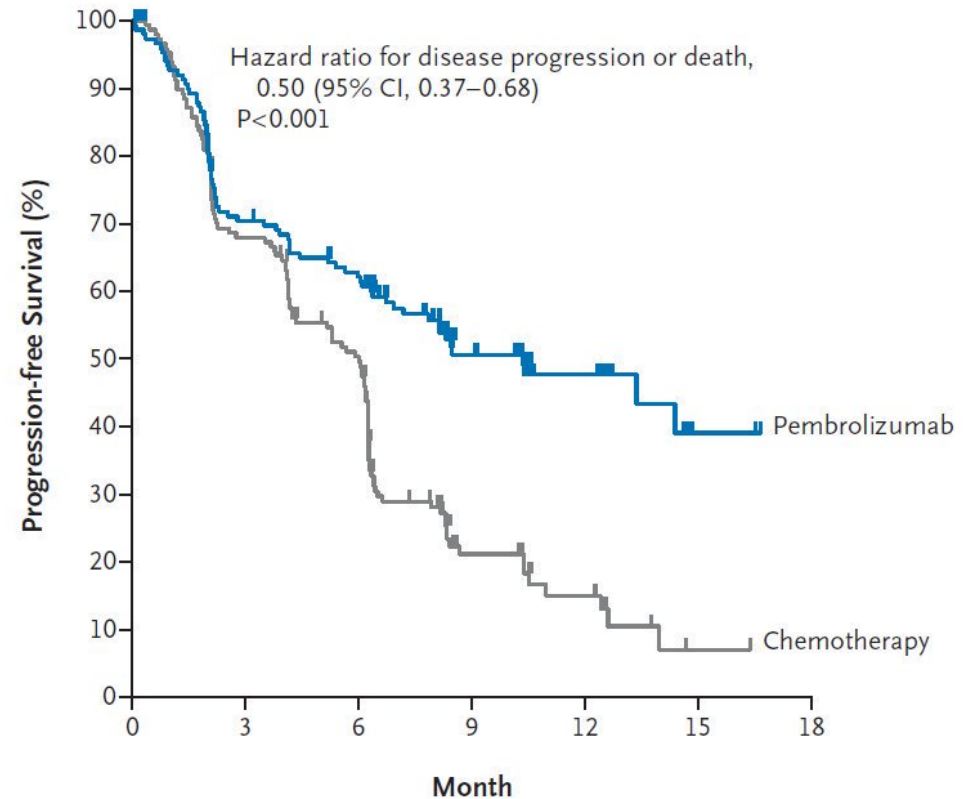
Patoanatomiske analyser i forhold til lungecancerudredning.





Predictive marker

Patoanatomiske analyser i forhold til lungecancerudredning.



No. at Risk	0	3	6	9	12	15	18
Pembrolizumab	154	104	89	44	22	3	1
Chemotherapy	151	99	70	18	9	1	0

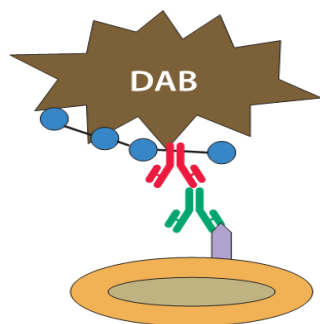
The **NEW ENGLAND**
JOURNAL of *MEDICINE*

ESTABLISHED IN 1812 NOVEMBER 10, 2016 VOL. 375 NO. 19

Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer

Martin Reck, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D., Andrew G. Robinson, M.D., Rina Hui, M.B., B.S., Ph.D., Tibor Cs6szi, M.D., Andrea F6l6p, M.D., Maya Gottfried, M.D., Nir Peled, M.D., Ph.D., Ali Tafreshi, M.D., Sinead Cuffe, M.D., Mary O'Brien, M.D., Surman Rao, M.D., Katsuyuki Hotta, M.D., Ph.D., Melanie A. Leiby, Ph.D., Gregory M. Lubiniecki, M.D., Yue Shentu, Ph.D., Reshma Rangwala, M.D., Ph.D., and Julie R. Brahmer, M.D., for the KEYNOTE-024 Investigators*

Patoanatomiske analyser i forhold til lungecancerudredning.



Kromogen (farvestof)

Visualiseringssystem (enzymer)

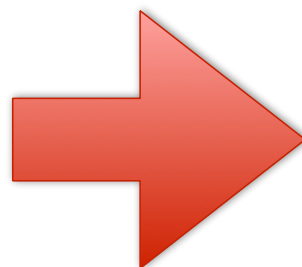
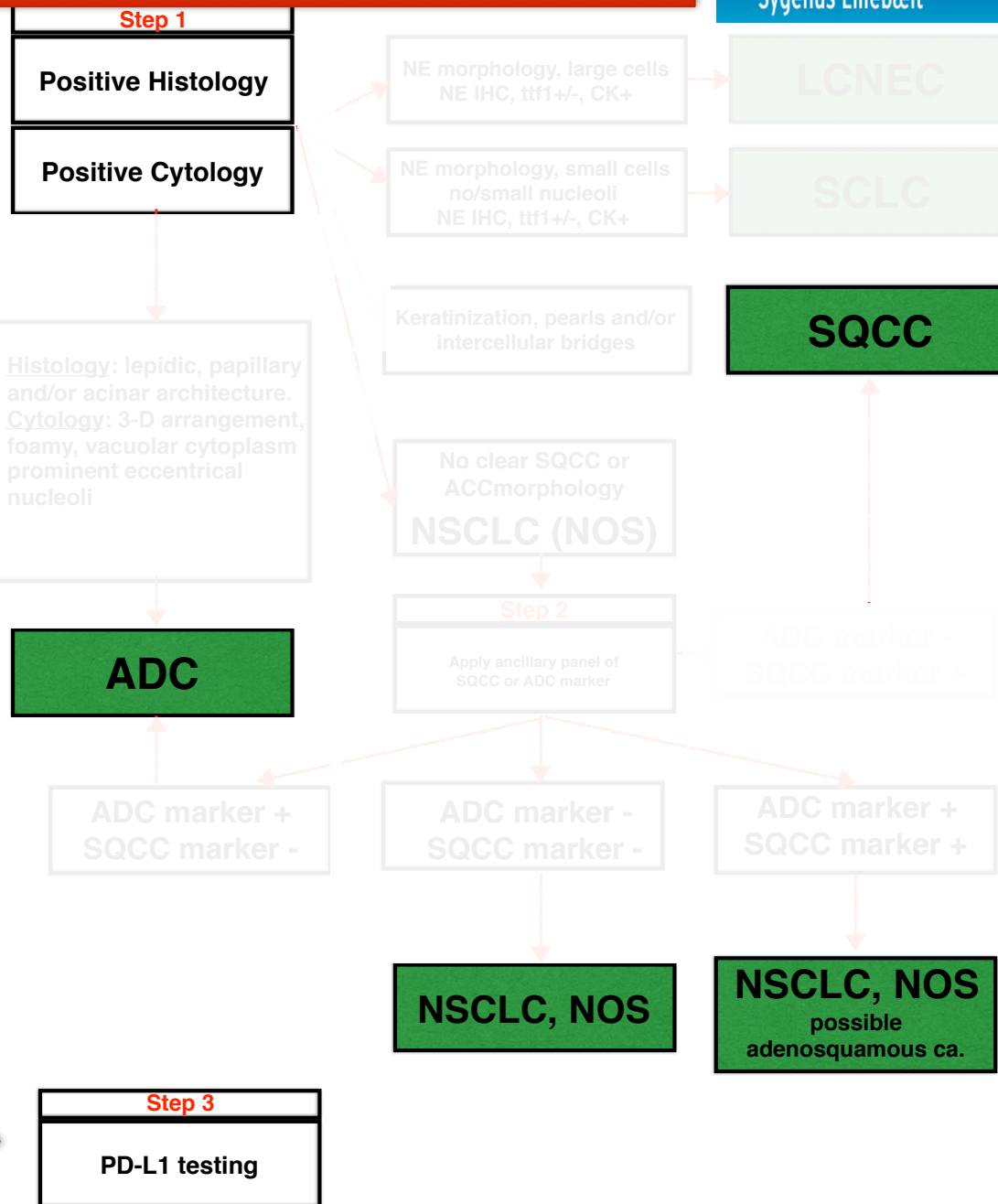
Sekundært antistof

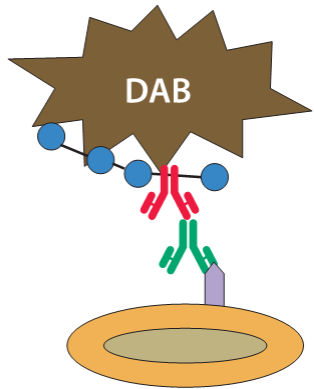
Primært antistof

Antigen

Cellens cytoplasma

Cellekerne





Kromogen (farvestof)

Visualiseringssystem
(enzymer)

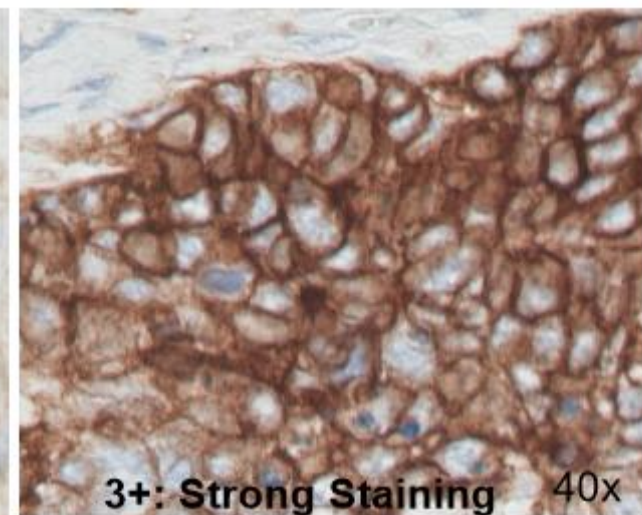
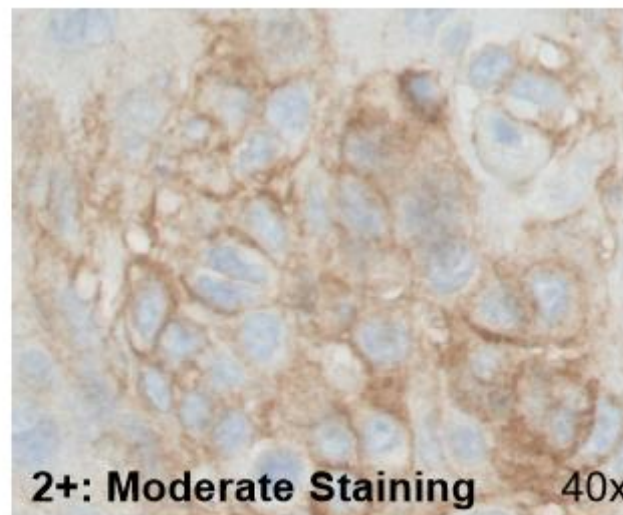
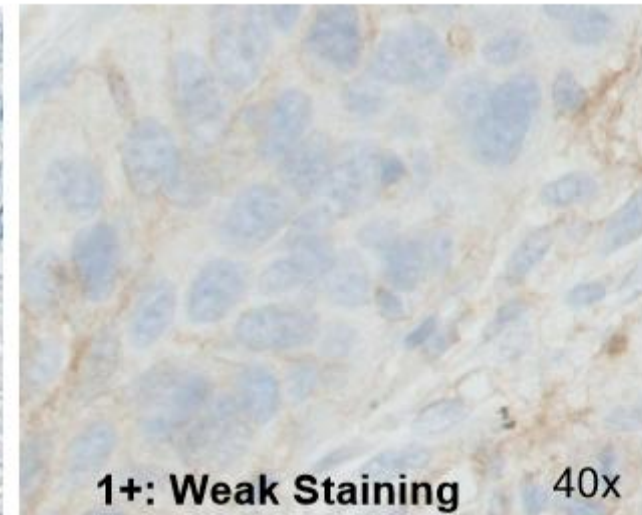
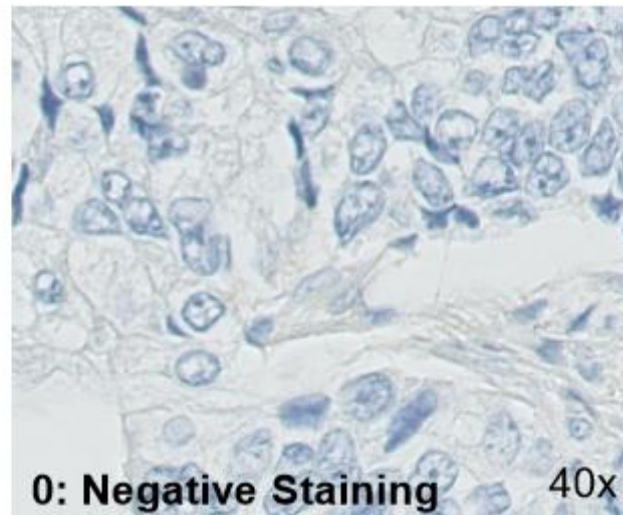
Sekundært antistof

Primært antistof

Antigen

Cellens cytoplasma

Cellekerne



Patoanatomiske analyser i forhold til lungecancerudredning.

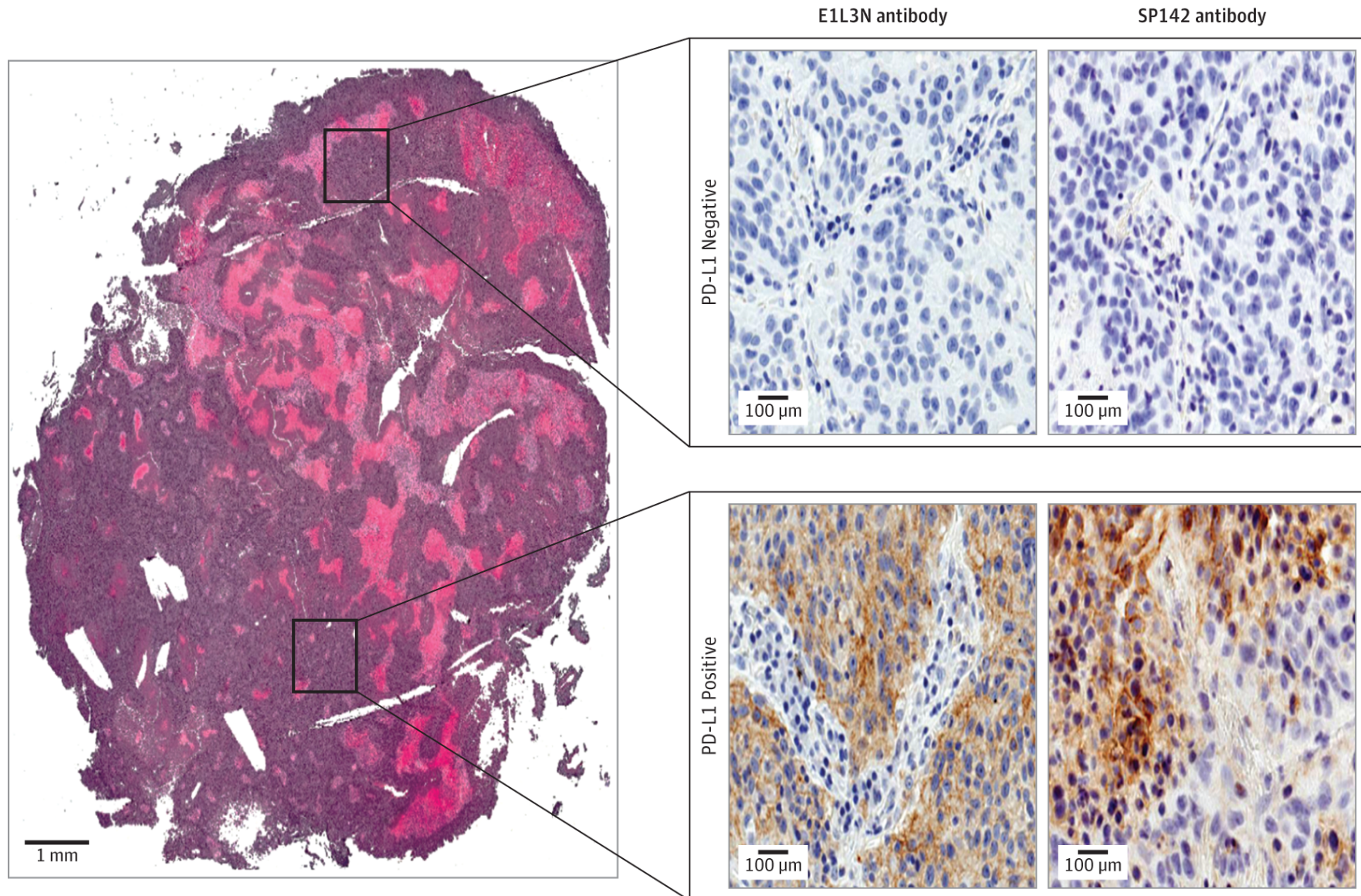


Table 1

Results of randomised phase III trials of immune checkpoint inhibitors (ICIs) for advanced non-small-cell lung cancer (NSCLC).

Line of treatment	Drug	Trial	PDL1 selection	ORR	PFS (months)		OS (months)	
					Median	HR	Median	HR
L1	Pembrolizumab	Keynote-024	≥50%	45%	10.4	0.50	NR	0.60
	Nivolumab	Checkmate-026	≥5% ^a	26%	4.2	1.15	14.4	1.02
L2 and beyond	Pembrolizumab ^b	Keynote-010	≥1%	18%	4	0.79	12.7	0.61
	Pembrolizumab ^b	Keynote-010	≥50%	29%	5.2	0.59	17.3	0.50
	Nivolumab	Checkmate-017	No	20%	3.5	0.62	9.2	0.59
	Nivolumab	Checkmate-57	No	19%	2.3	0.92	12.2	0.73
	Atezolizumab	OAK	No	14%	2.8	0.95	13.8	0.73

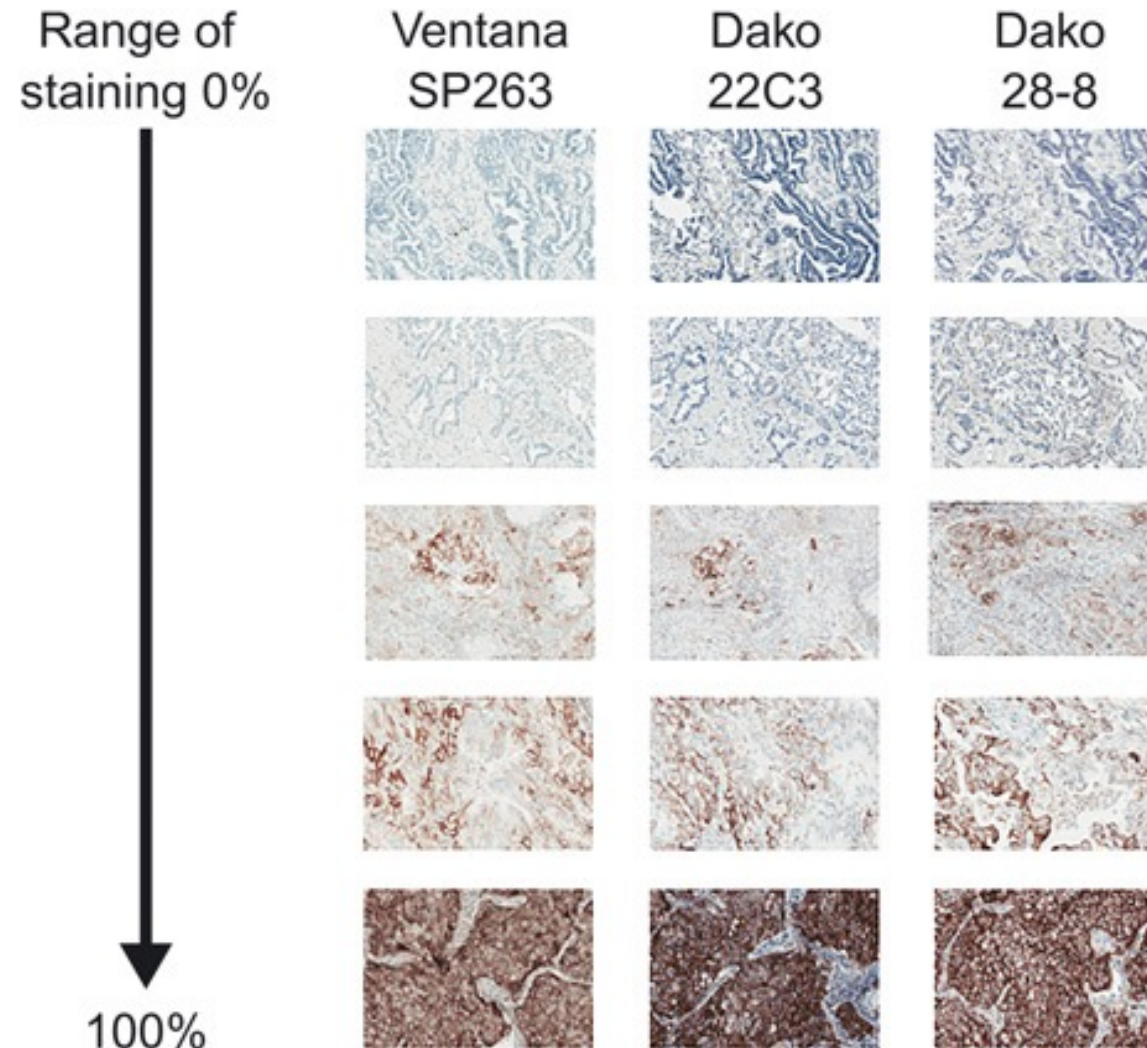
Abbreviations: ORR, overall response rate; PDL1, programmed death-ligand 1; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; L1, first-line; L2, second-line.

^a Cutoff at 1% was used for inclusion, but cutoff at 5% was used for PFS (primary end-point), OS and ORR (secondary end-points).

^b Results for pembrolizumab 10 mg/kg.

Patoanatomiske analyser i forhold til lungecancerudredning.

Test	Ventana SP263 (1)	Dako 22C3 (2)	Dako 28-8 (3)	Ventana SP142 (4)
Developed as companion diagnostic	Durvalumab (AstraZeneca/	Pembrolizumab (Merck Sharp & Dohme)	Nivolumab (Bristol-Myers Squibb)	Atezolizumab (Genentech)
Instrument	VENTANA BenchMark ULTRA	Dako Autostainer Link 48	Dako Autostainer Link 48	VENTANA BenchMark ULTRA
PD-L1 antibody	Clone SP263 (rabbit monoclonal)	Clone 22C3 (mouse monoclonal)	Clone 28-8 (rabbit monoclonal)	Clone SP142 (rabbit monoclonal)
Compartment	Tumor cell membrane	Tumor cell membrane	Tumor cell membrane	Tumor cells and tumor-infiltrating immune cells
Cut-off(s) for high PD-L1	≥25% of tumor cells (5)	≥1%; ≥50% of tumor cells (6)	≥1%; ≥5%; ≥10% of tumor cells (7)	≥50% of tumor cells or ≥10% of tumor area



Published OnlineFirst January 10, 2017; DOI: 10.1158/1078-0432.CCR-16-2375

Cancer Therapy: Clinical

Clinical
Cancer
Research

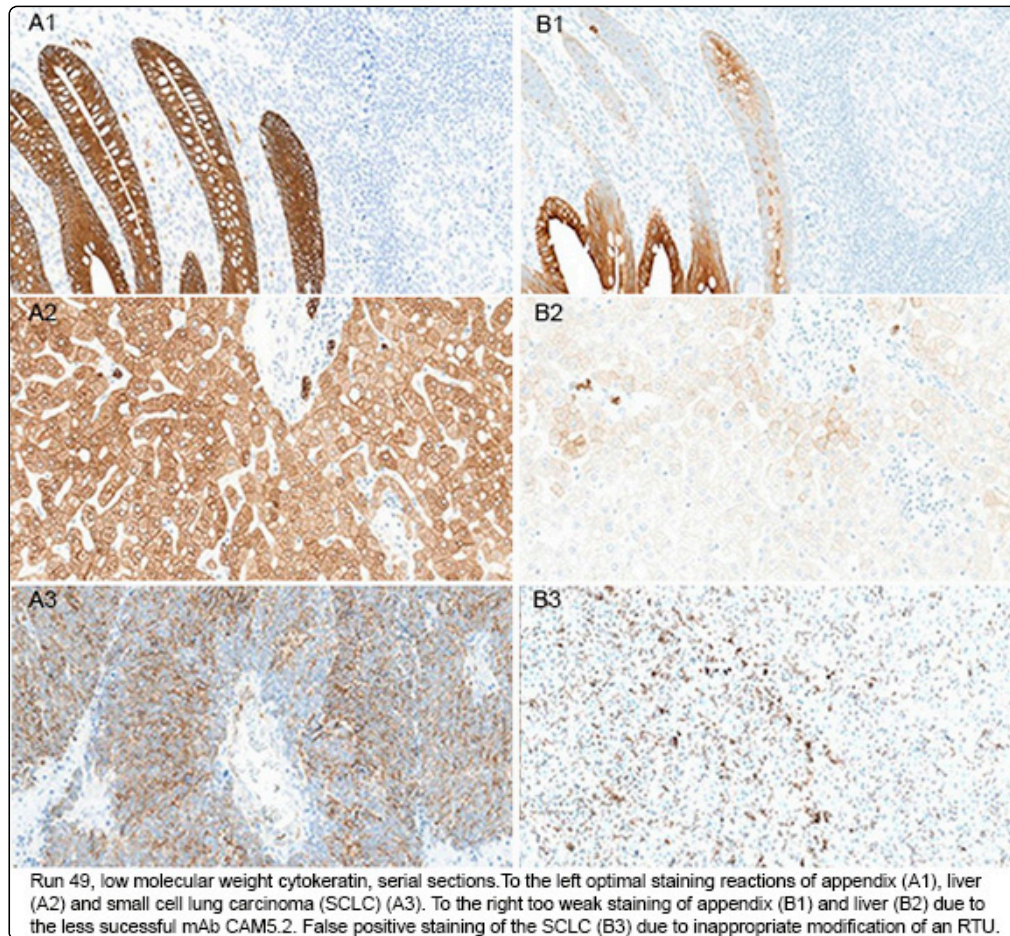
Agreement between Programmed Cell Death Ligand-1 Diagnostic Assays across Multiple Protein Expression Cutoffs in Non-Small Cell Lung Cancer

Marianne J. Ratcliffe¹, Alan Sharpe², Anita Midha¹, Craig Barker², Marietta Scott², Paul Scorer², Hytham Al-Masri³, Marlon C. Rebelatto⁴, and Jill Walker²



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Results - module 49, B23, H11 & C1 available

Events

[3rd NordiQC Conference on Applied Immunohistochemistry](#)
6-9 Jun 2017: Aalborg, Denmark

[1st Copenhagen Surgical Pathology Update 2017](#)
19-17 Jun 2017: Copenhagen, Denmark

[NordiQC Workshop in Diagnostic Immunohistochemistry](#)
20-22 Sep 2017: Aalborg, DK

[4th Diagnostic Immunohistochemistry for Pathologists](#)
18-20 Oct 2017: Krakow, Poland

Important dates

[Run 50](#)
Publication of results
10 Jul 2017

Questions

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Lung Cancer

Diagnosis and prediction

Table 1. **Assessment marks for IHC assays and antibodies run C1, PD-L1 IHC**

CE-IVD / FDA approved PD-L1 assays	n	Vendor	Optimal	Good	Borderline	Poor	Suff. ¹	Suff. OPS ²
22C3 pharmDX, SK006	12	Dako/Agilent	10	1	0	1	92%	92%
22C3 pharmDX, SK006 ⁴	2	Dako/Agilent	0	0	1	1	-	-
28-8 pharmDX, SK005	7	Dako/Agilent	3	3	1	0	86%	86%
SP263, 790-4905	16	Ventana/Roche	9	2	2	3	69%	77%
SP142, 740-4859	1	Ventana/Roche	0	0	0	1	-	-
Antibodies³ for laboratory developed PD-L1 assays, conc. antibody	n	Vendor	Optimal	Good	Borderline	Poor	Suff. ¹	Suff. OPS ²
mAb clone 22C3	13	Dako/Agilent	1	1	4	7	15%	-
mAb clone E1L3N	8	Cell Signaling	1	1	1	5	25%	-
mAb CAL10	1	Biocare	0	0	1	0	-	-
rmAb clone 28-8	6	Abcam	0	1	1	4	17%	-
rmAb clone ZR3	1	Zeta Corporation	1	0	0	0	-	-
Antibodies for laboratory developed PD-L1 assays, RTU	n	Vendor	Optimal	Good	Borderline	Poor	Suff. ¹	Suff. OPS ²
rmAb clone SP142	1	Spring Biosystems	0	0	0	1	-	-
Total	68		25	9	11	23	-	-
Proportion			37%	13%	16%	34%	50%	-

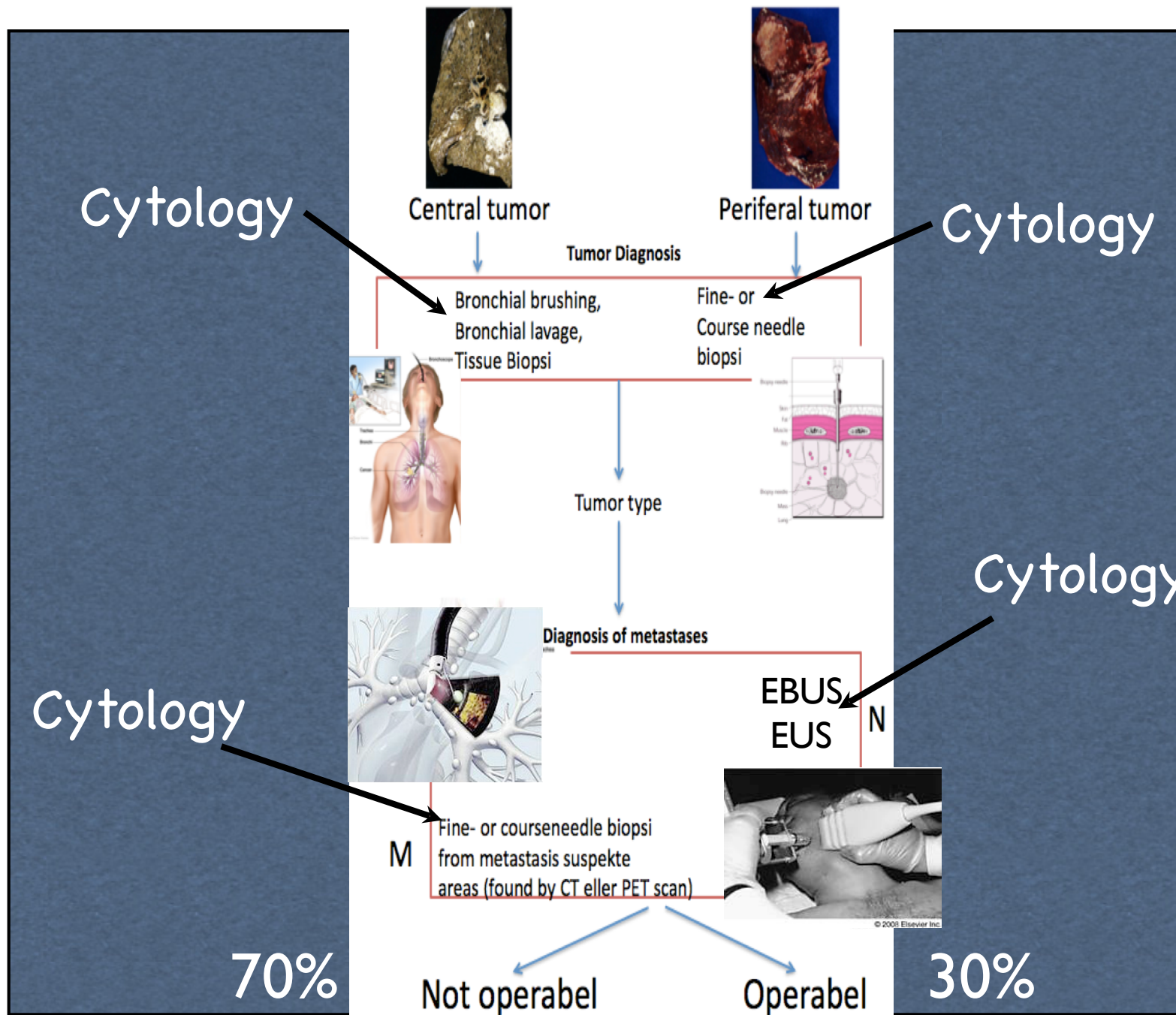
1) Proportion of sufficient stains (optimal or good).

2) Proportion of sufficient stains with optimal protocol settings only, see below.

3) mAb: mouse monoclonal antibody, rmAb: rabbit monoclonal antibody.

4) RTU system developed for the Agilent/Dako`s semi-automated systems (Autostainer Link48) but used by laboratories on different platforms (Ventana Benchmark and Dako Omnis).

Patoanatomiske analyser i forhold til lungecancerudredning.



RESEARCH ARTICLE

Paired Comparison of PD-L1 Expression on Cytologic and Histologic Specimens From Malignancies in the Lung Assessed With PD-L1 IHC 28-8pharmDx and PD-L1 IHC 22C3pharmDx

Birgit G. Skov, MD, DrMedSci and Torsten Skov, MD, PhD†*

Conclusion: PD-L1 assessment is feasible on cytologic material with the tested assays using cutoffs for positivity similar to those used on histologic material.

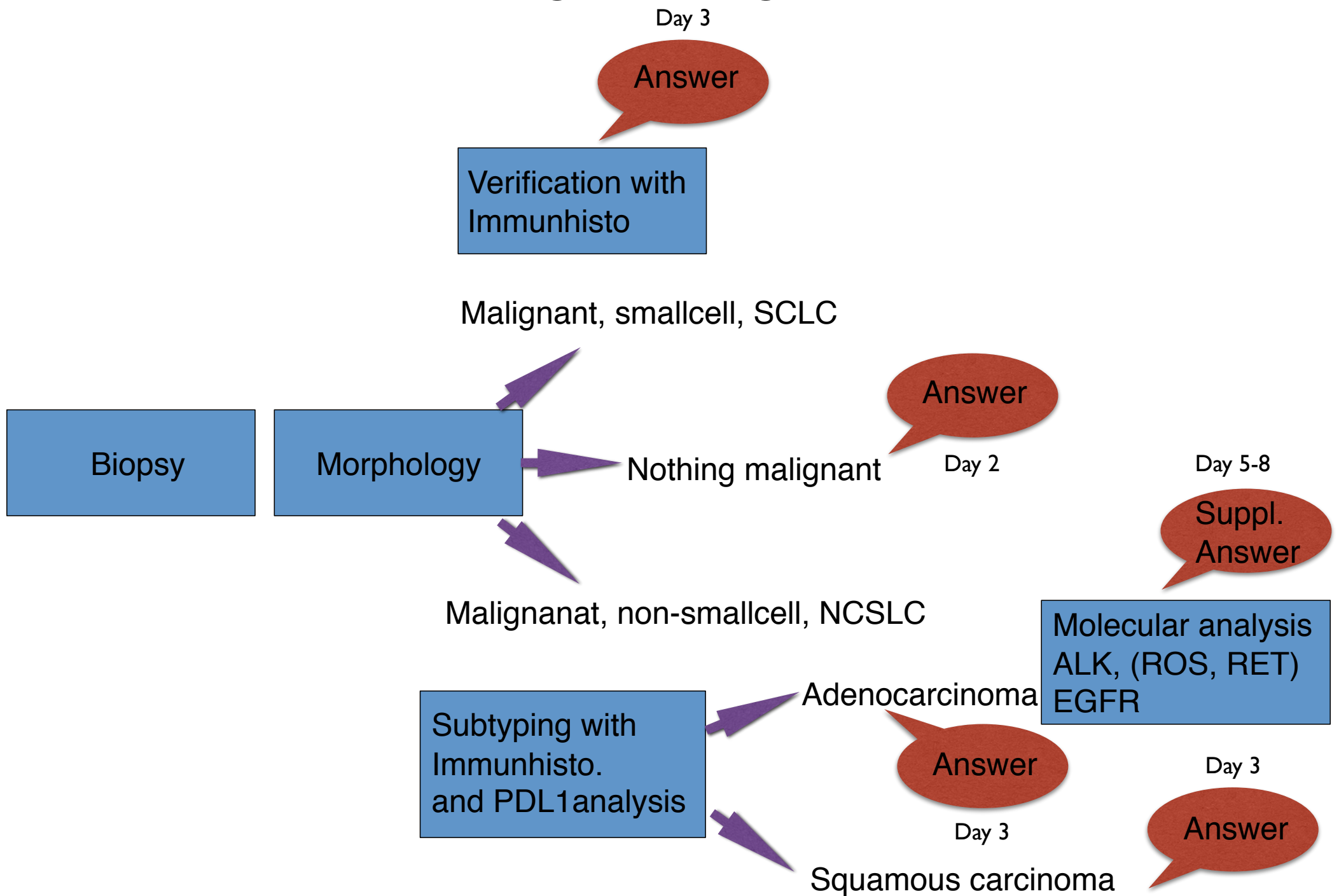
TABLE 3. IHC Staining Outcome in Cytology Samples Compared With Histologic Samples by Agreement Statistics for Different Thresholds of PD-L1 Positivity

	Cutoff \geq 1% Positive Cells		Cutoff \geq 50% Positive Cells
PD-L1 IHC 22C3pharmDx			
Overall agreement	85 (76-91)		94 (87-98)
Positive percent agreement	80 (70-87)		100 (96-100)
Negative percent agreement	89 (81-94)		93 (86-97)
	Cutoff \geq 1% positive cells	Cutoff \geq 5% positive cells	Cutoff \geq 10 % positive cells
PD-L1 IHC 28-8 pharmDx			
Overall agreement	87 (79-93)	95 (89-98)	90 (81-94)
Positive percent agreement	81 (72-88)	91 (83-95)	79 (70-87)
Negative percent agreement	93 (86-97)	98 (93-100)	95 (88-98)

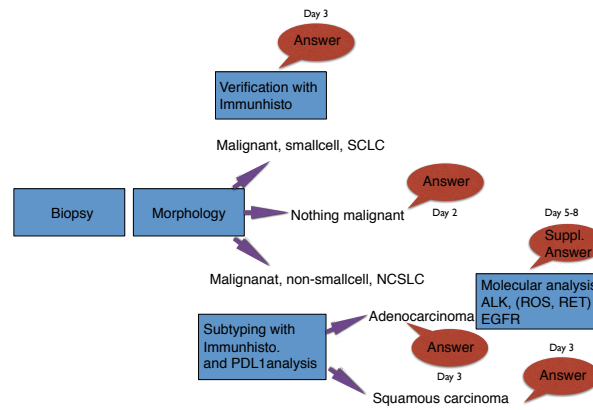
Values are represented as percent, 95% CI.

CI indicates confidence interval; IHC, immunohistochemistry; PD-L1, programmed cell death ligand-1.

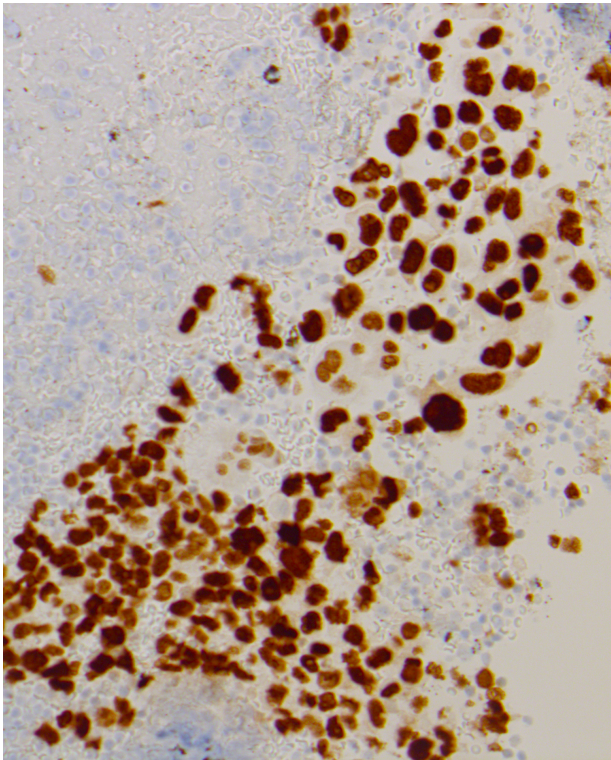
The Diagnostic algorithm



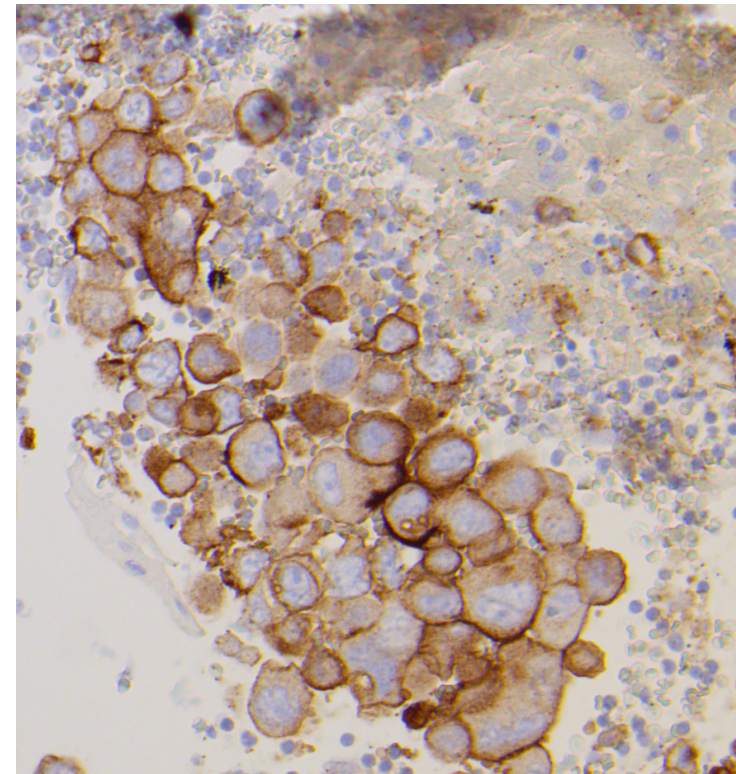
The Diagnostic algorithm



Pleura effusion Cell Block

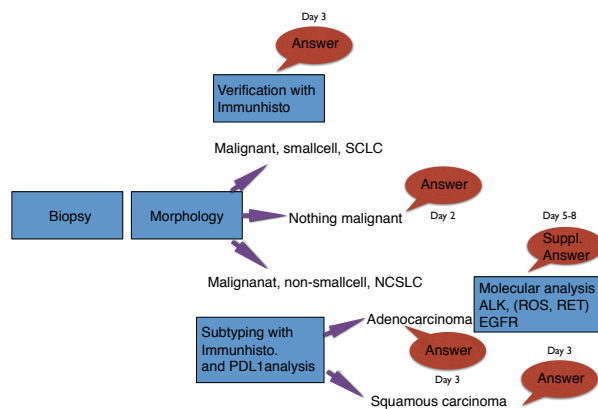


ttf1, CK7+

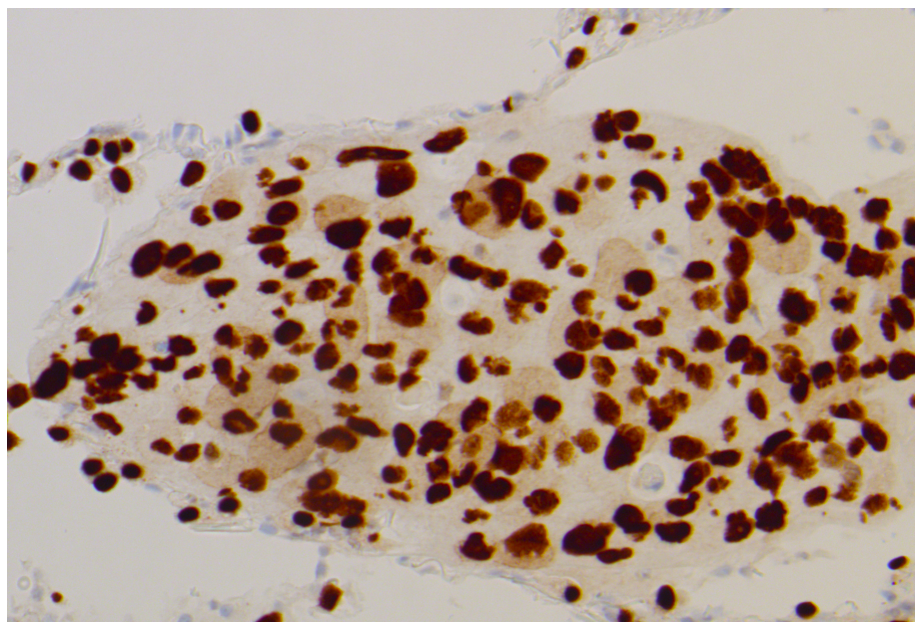


PD-L1 (22C3) 110

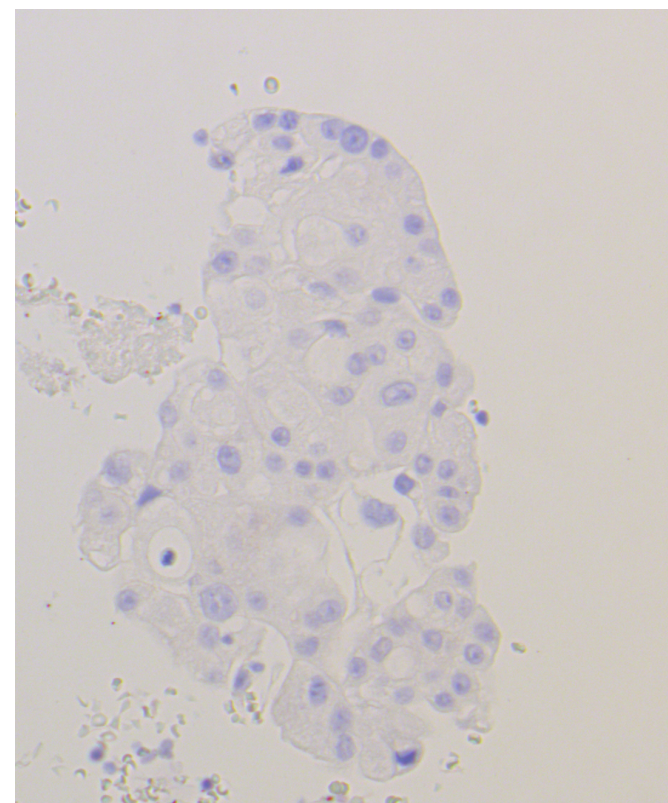
The Diagnostic algorithm



EBUS CellBlock

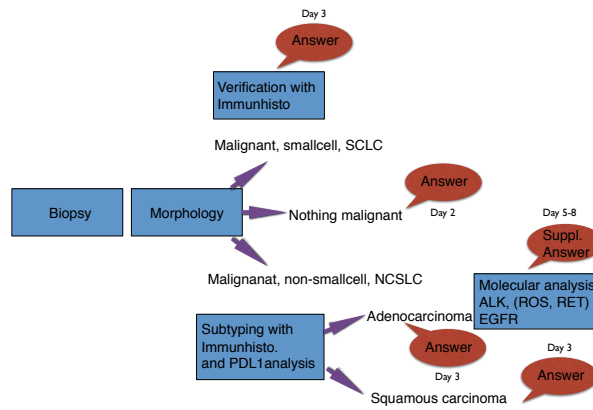


CK5/6, CK7 and P40+

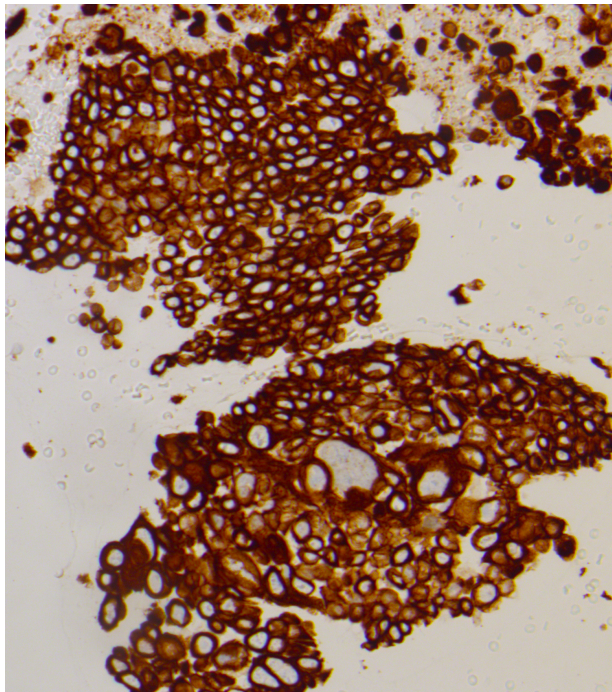


PD-L1 (22C3)

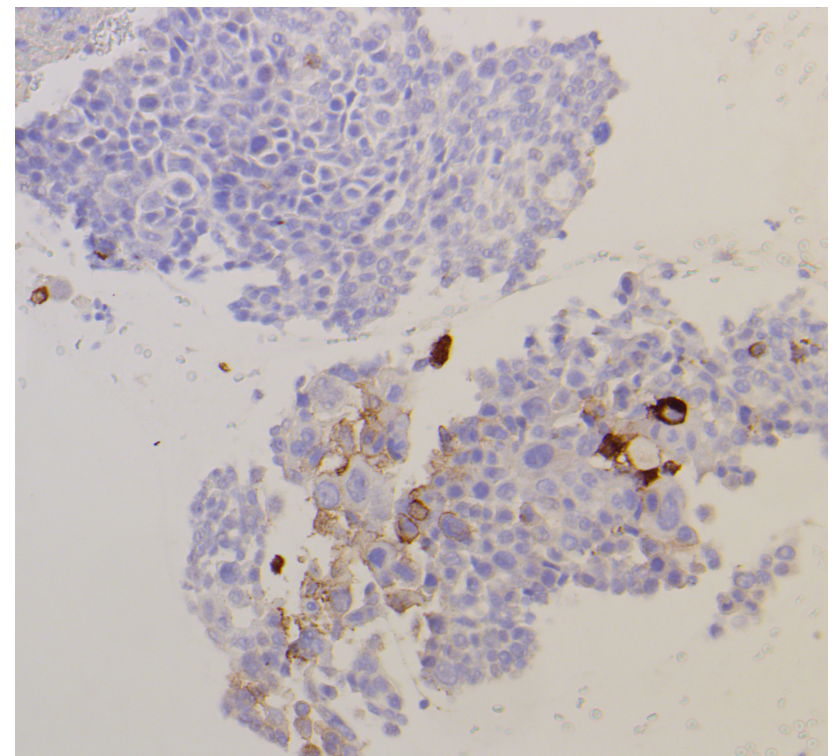
The Diagnostic algorithm



EBUS Cell Block

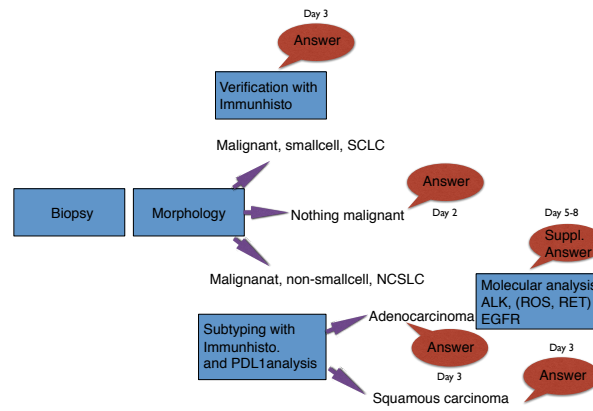


CK5/6 and P40+

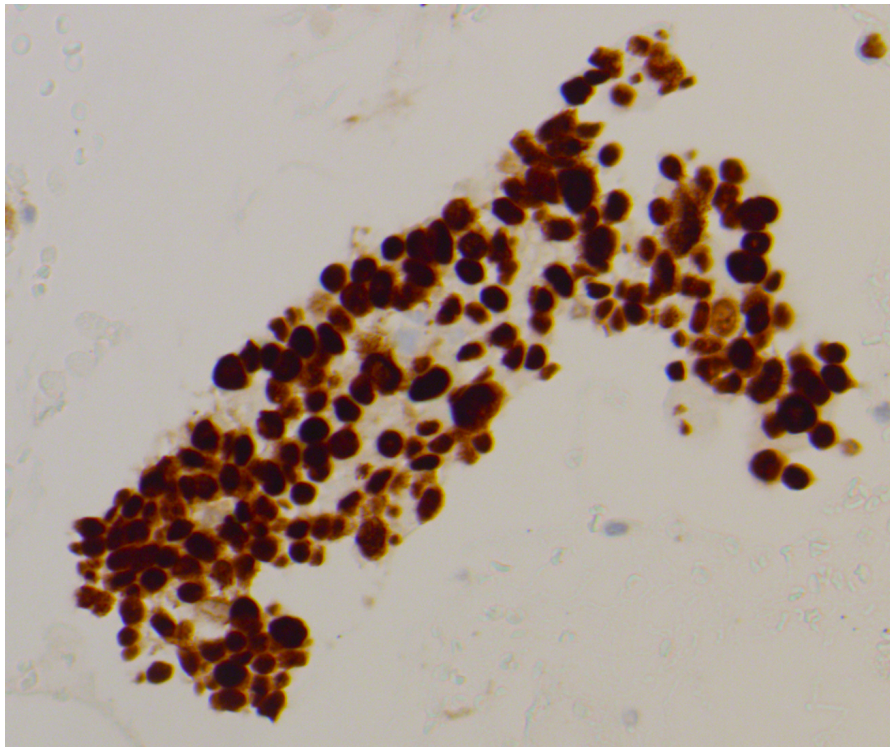


PD-L1 (22C3)

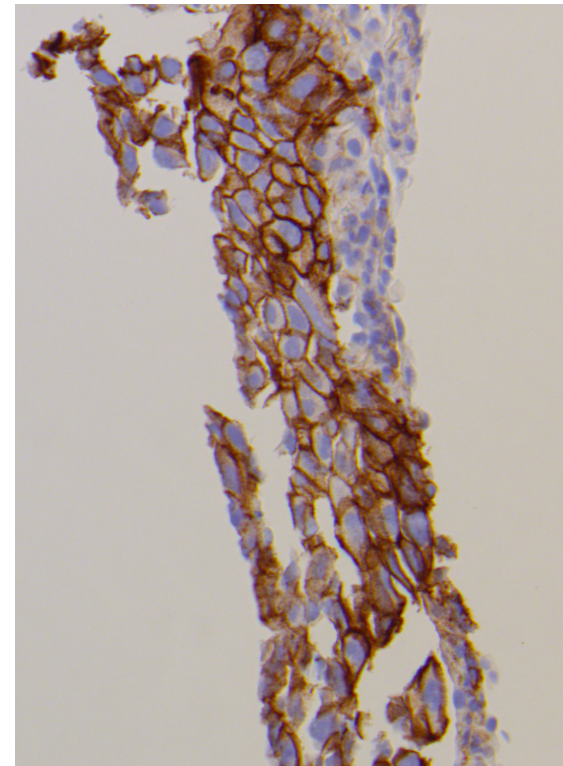
The Diagnostic algorithm



Coarse needle biopsy

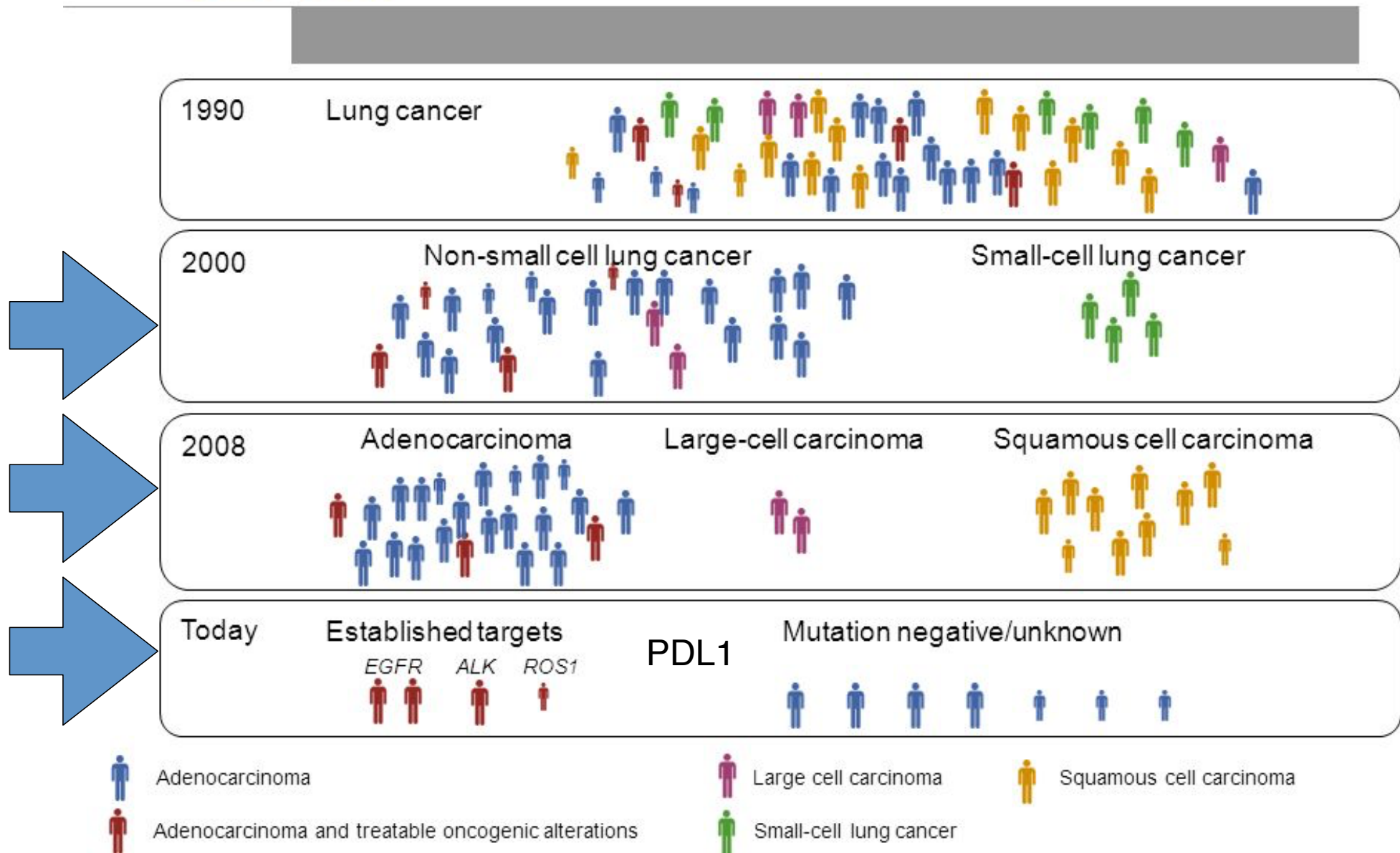


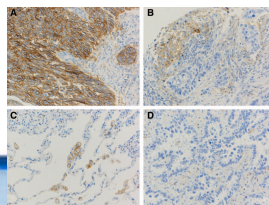
ttf1 and CK7+



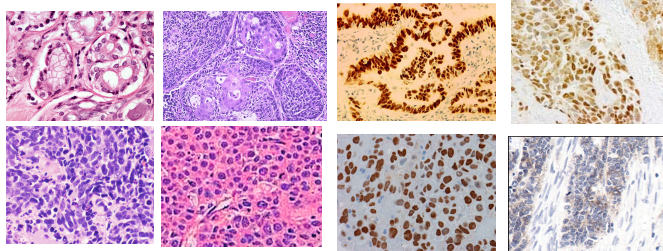
PDL1 (22C3)

Patient selection in lung cancer: Evolution over time



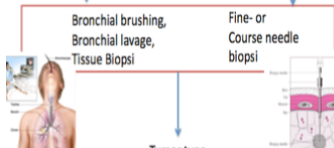


ALK, RET, ROS1, and NTRK1 fusion transcripts, in addition to targets designed to detect 5' and 3' ALK gene expression
KRAS, EGFR, BRAF, PIK3CA, AKT1, ERBB2, PTEN, NRAS, STK11, MAP2K1, ALK, DDR2, CTNNB1, MET, TP53, SMAD4, FBX7, FGFR3, NOTCH1, ERBB4, FGFR1, FGFR2



Central tumor Periferal tumor

Tumor Diagnosis



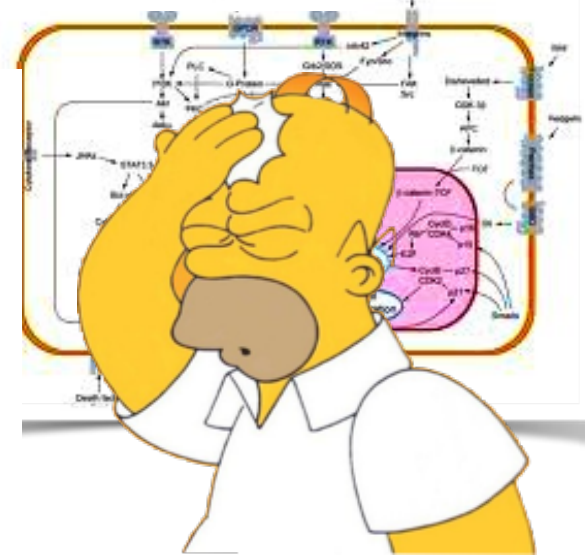
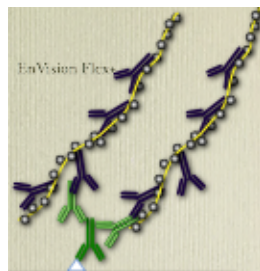
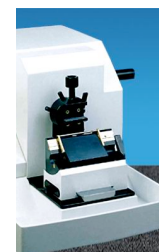
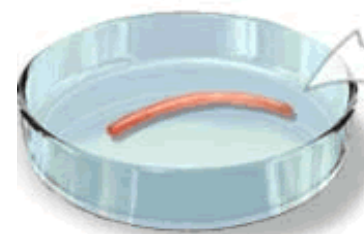
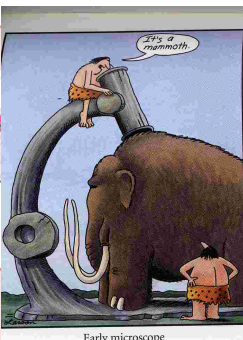
Tumor type

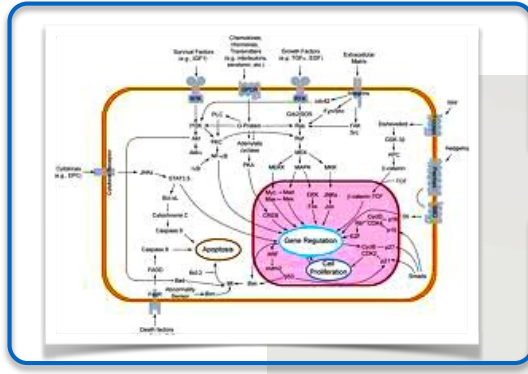
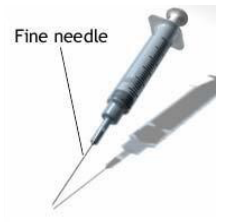
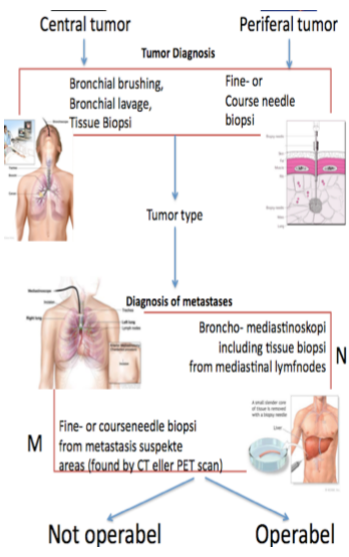
Analysis of metastases

Broncho-mediastinoskopi including tissue biopsy from mediastinal lymphnodes

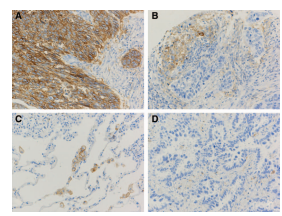
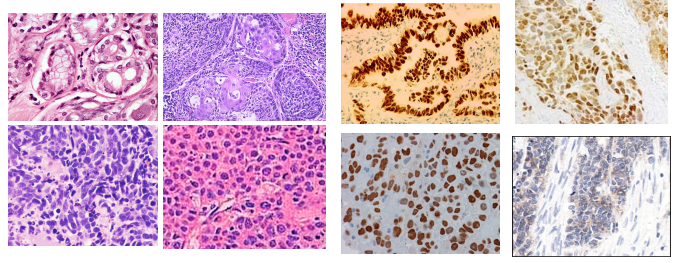
Genetic analysis (e.g. PCR, FISH, NGS, or PET scan)

Operative





Diagnosis | **Prediction**



ALK, RET, ROS1, and NTRK1 fusion transcripts, in addition to targets designed to detect 5' and 3' ALK gene expression
 KRAS, EGFR, BRAF, PIK3CA, AKT1, ERBB2, PTEN, NRAS, STK11, MAP2K1, ALK, DDR2, CTNNB1, MET, TP53, SMAD4, FBX7, FGFR3, NOTCH1, ERBB4, FGFR1, FGFR2



The end