

Early microscope

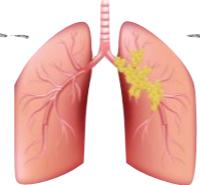
**Immunohistochemical classification of
Lung cancer,
diagnosis and prediction.**



A short
introduction



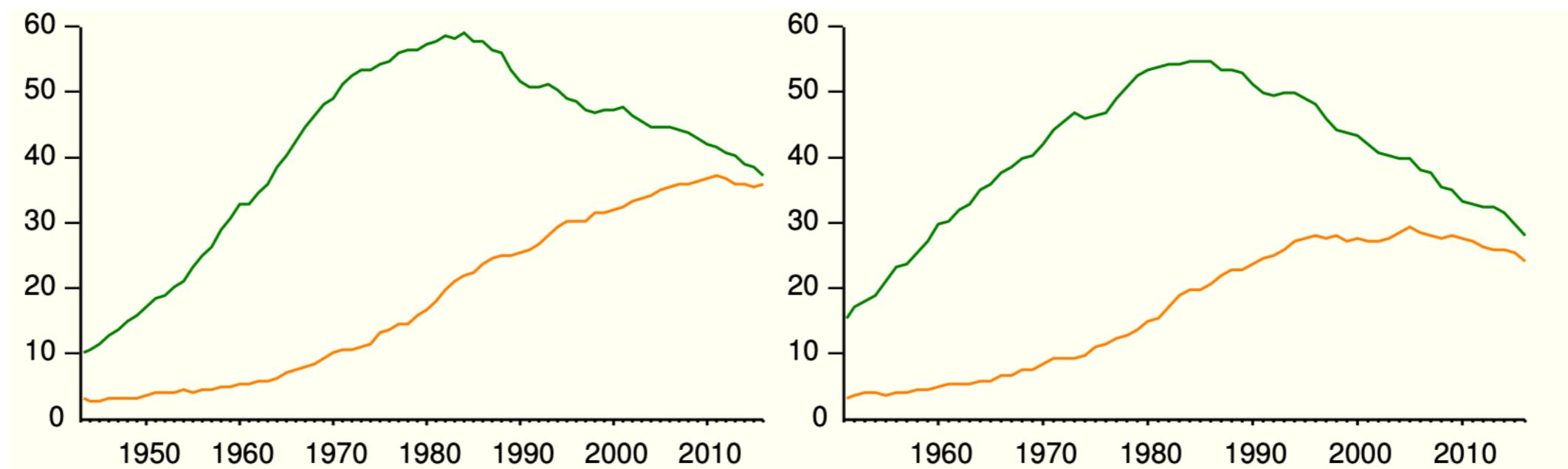
Henrik Hager
Dept. of Pathology
Aarhus Universityhospital



Lung cancer Age's standardized

Incidence new cases/100.000

Mortality Death/100.000



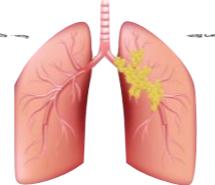
Females

Males

NORDCAN, Association of the Nordic Cancer Registries

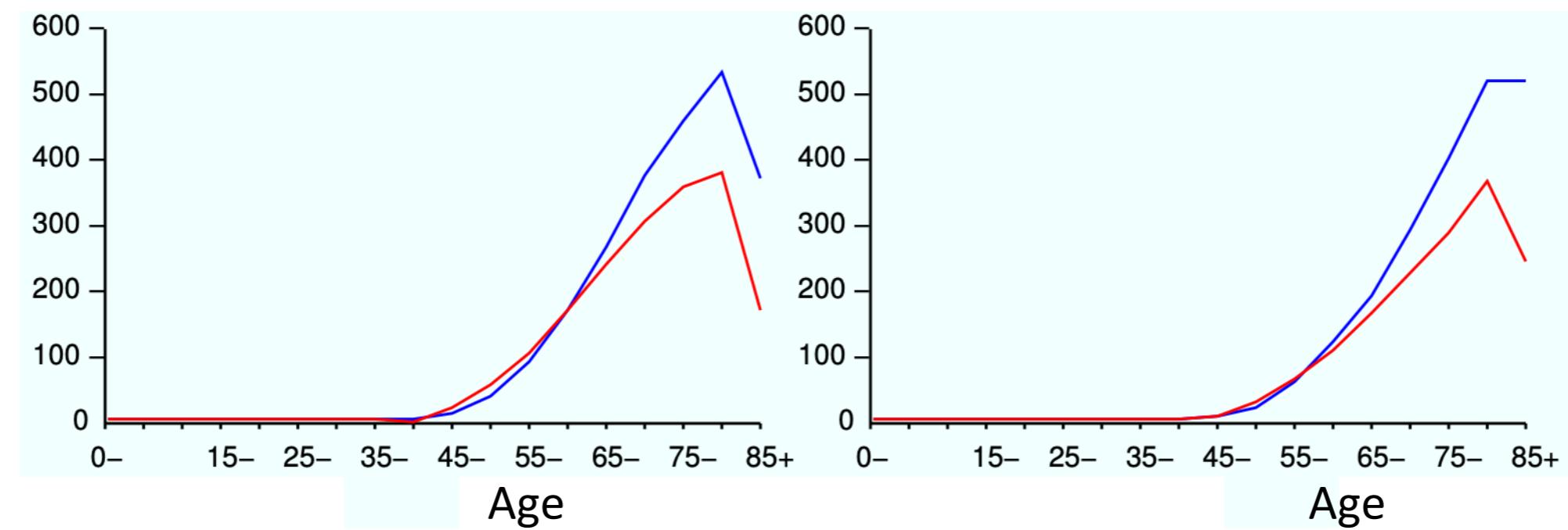
25.3.2019





Lung cancer

New cases/100.000 / age interval Deaths/100.00 / age interval



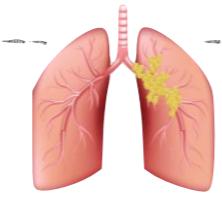
Females —

Males —

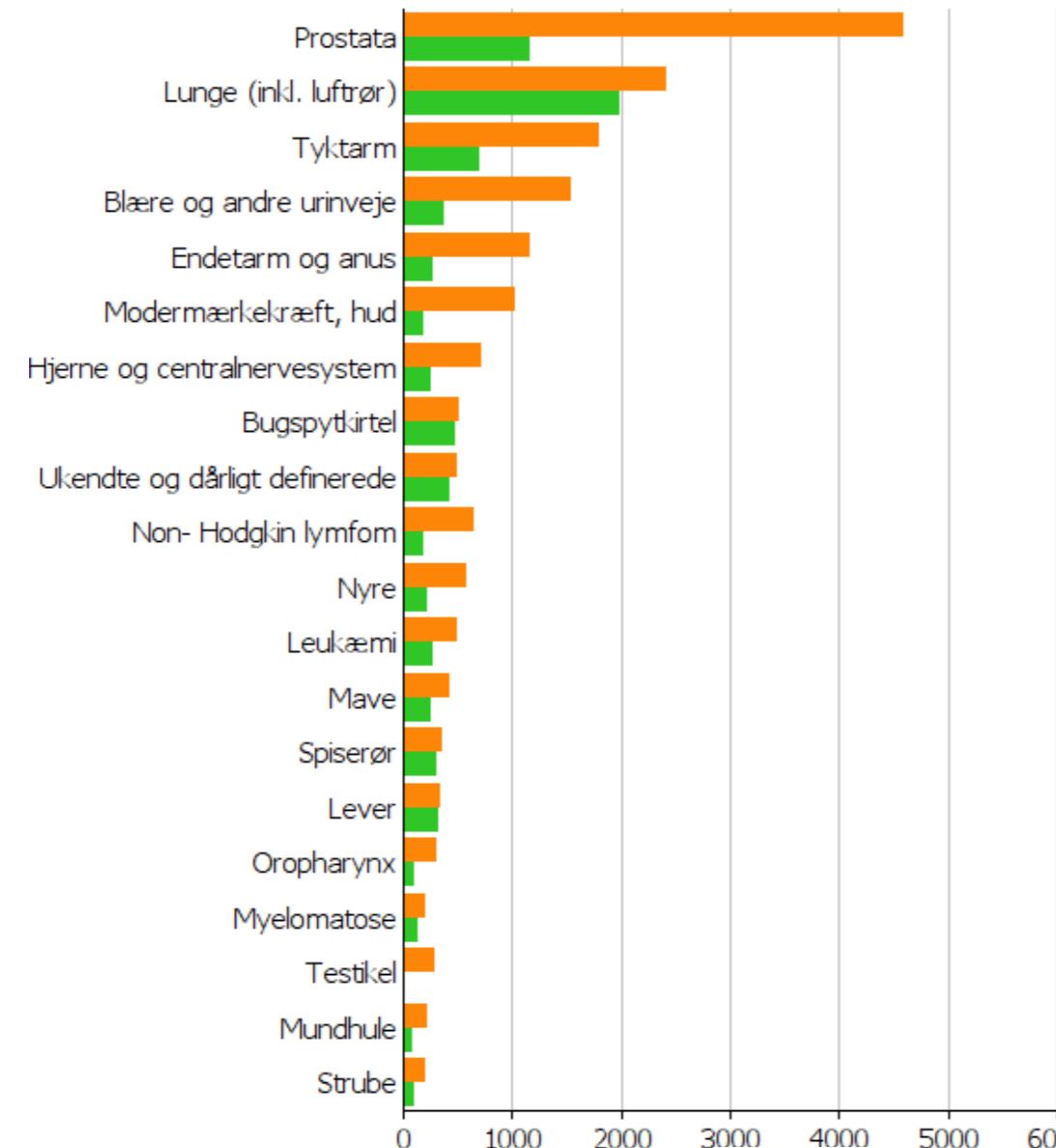
NORDCAN, Association of the Nordic Cancer Registries

25.3.2019

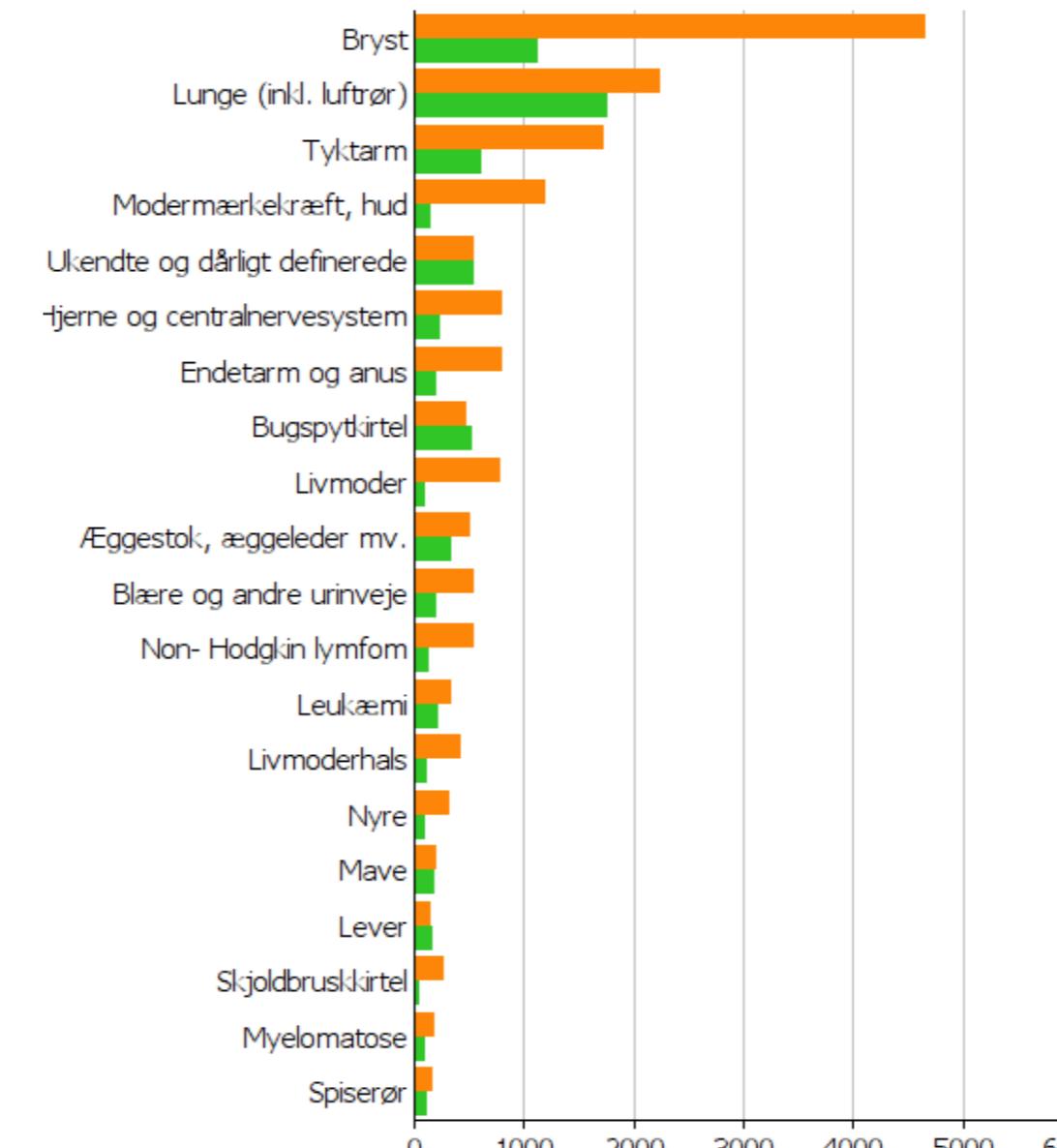




Males

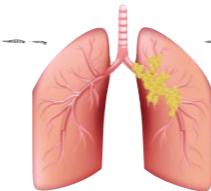


Females

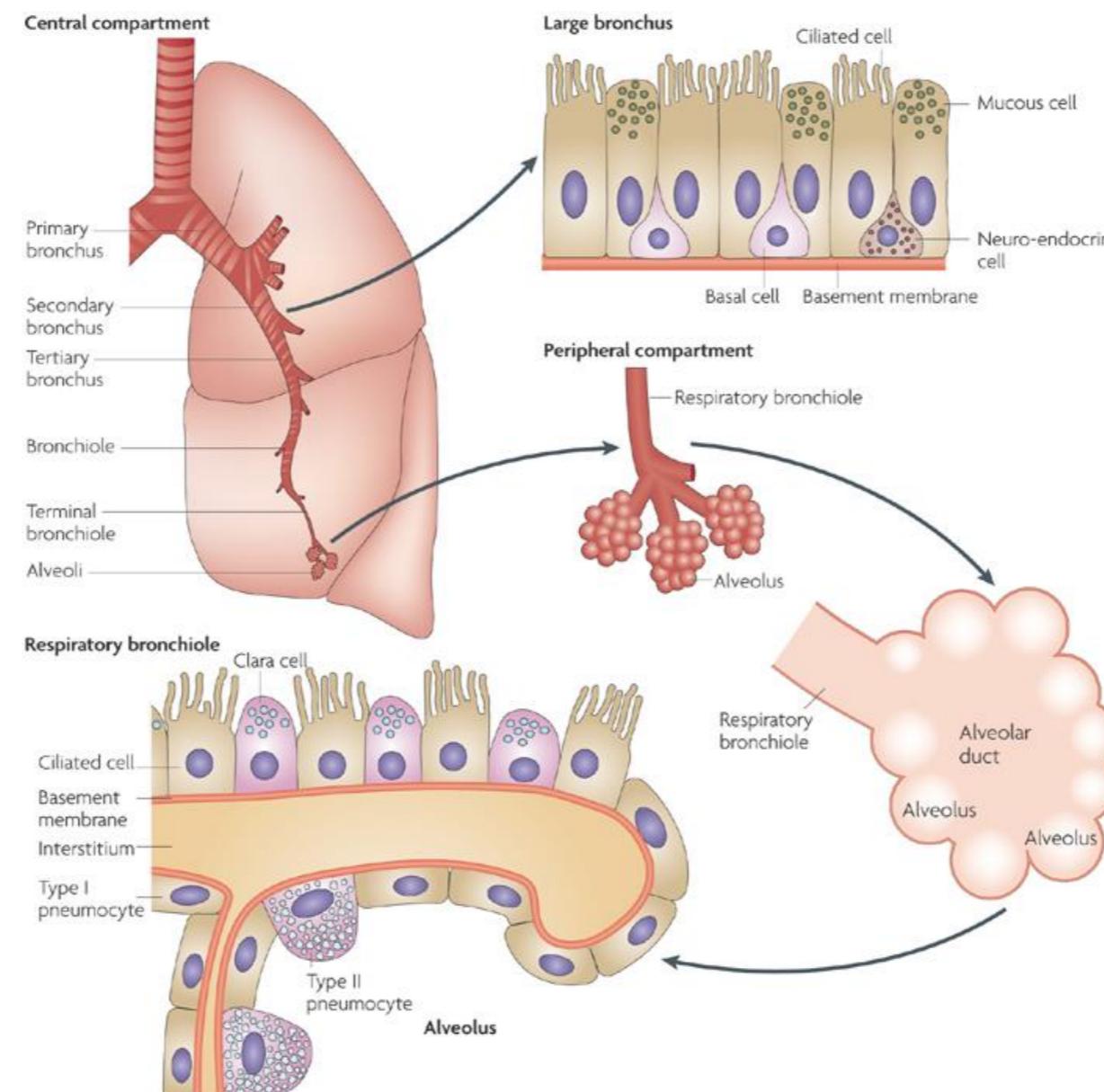


 Incidence, new cases / 100.000

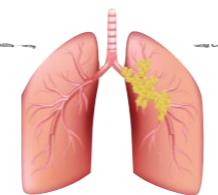
 Mortality, number of death / 100.000



Lung Carcinoma



Lung carcinoma derives from stem cells
in the lung epithelium



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 ^e	8250/3 ^d
Acinar adenocarcinoma	8551/3 ^d
Papillary adenocarcinoma	8260/3
Micropapillary adenocarcinoma ^e	8265/3
Solid adenocarcinoma	8230/3
Invasive mucinous adenocarcinoma ^e	8253/3 ^d
Mixed invasive mucinous and nonmucinous adenocarcinoma	8254/3 ^d
Colloid adenocarcinoma	8480/3
Fetal adenocarcinoma	8333/3
Enteric adenocarcinoma ^e	8144/3
Minimally invasive adenocarcinoma ^e	
Nonmucinous	8256/3 ^d
Mucinous	8257/3 ^d
Preinvasive lesions	
Atypical adenomatous hyperplasia	8250/0 ^d
Adenocarcinoma in situ ^e	
Nonmucinous	8250/2 ^d
Mucinous	8253/2 ^d
Squamous cell carcinoma	8070/3
Keratinizing squamous cell carcinoma ^e	8071/3
Nonkeratinizing squamous cell carcinoma ^e	8072/3
Basaloid squamous cell carcinoma ^e	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 ^e	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 ^e	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
PEComatos tumors ^e	
Lymphangiomyomatosis	9174/1
PEComa, benign ^e	8714/0
Clear cell tumor	8005/0
PEComa, malignant ^e	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 ^e	8842/3 ^d
Myoepithelial tumors ^e	
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 ^e	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
Metastatic tumors	

^aThe morphology codes are from the ICDO.² 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.

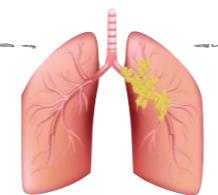
^bThe classification is modified from the previous WHO classification³ taking into account changes in our understanding of these lesions.

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

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

^eNew 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.



Adenocarcinoma (45%)

Squamous carcinoma (18%)

Large cell neuroendocrine carcinoma (1%)

Small cell carcinoma (12%)

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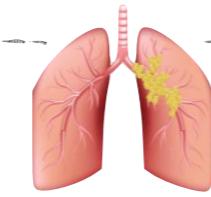
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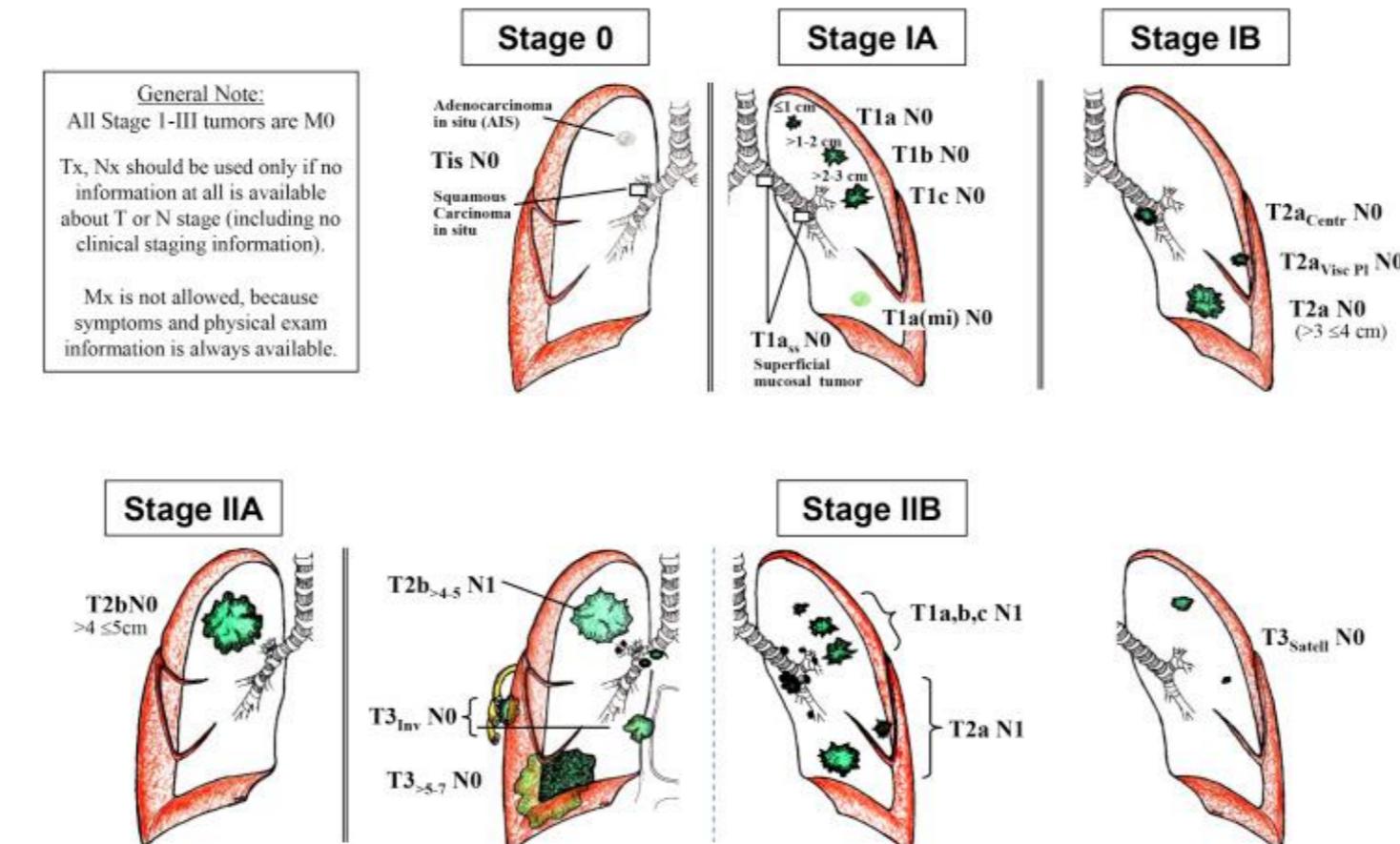
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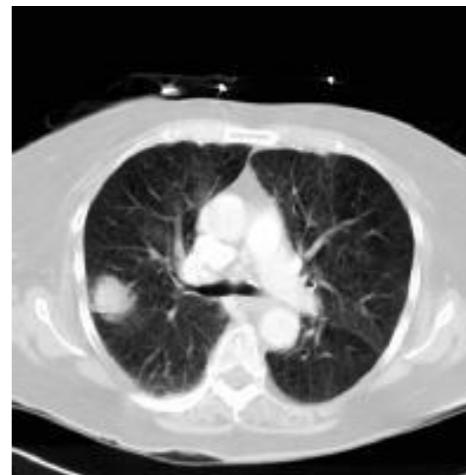
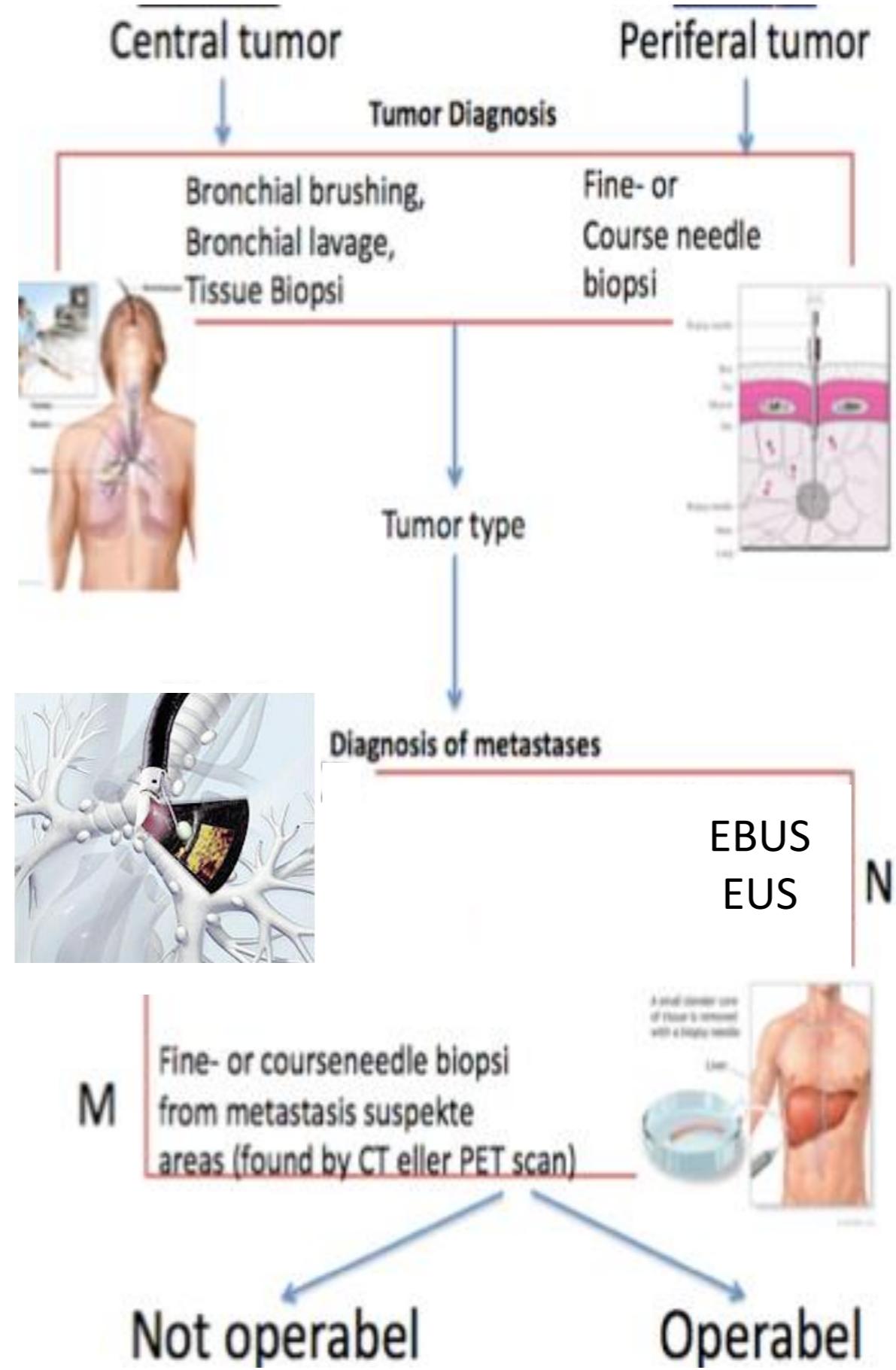
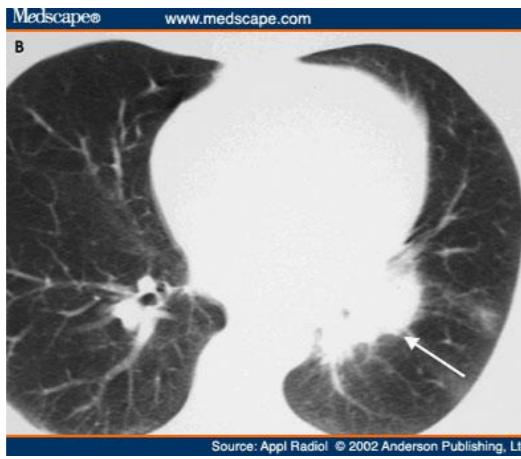


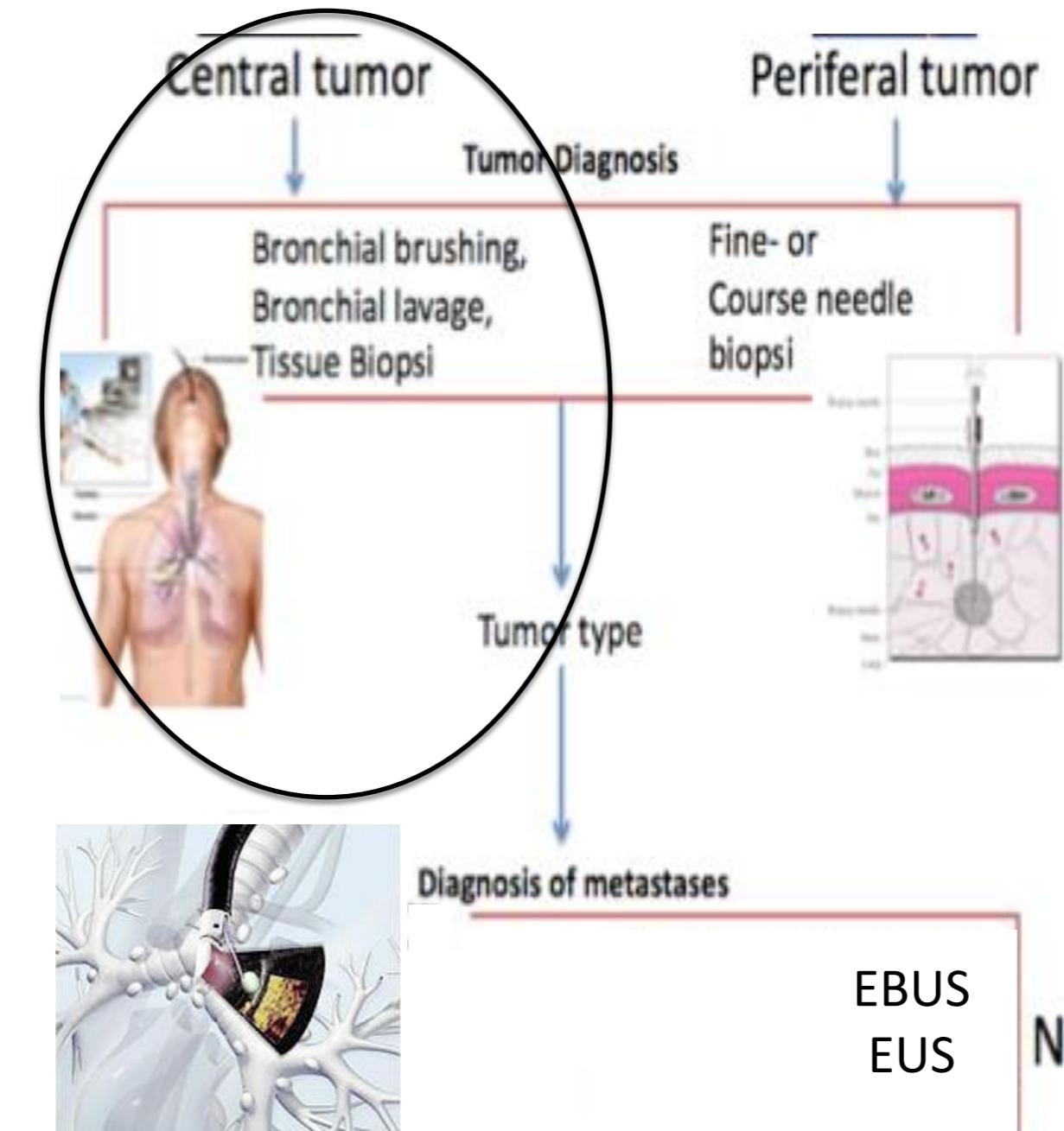
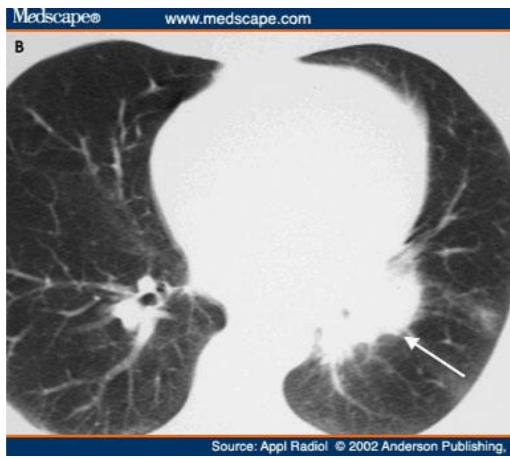
Diagnostic sampling

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

Lung Cancer Stage Classification (8th Edition)

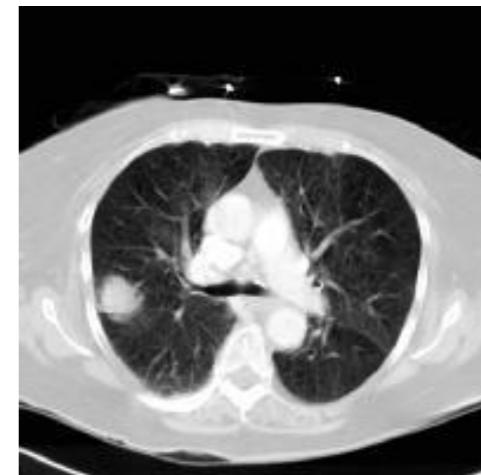


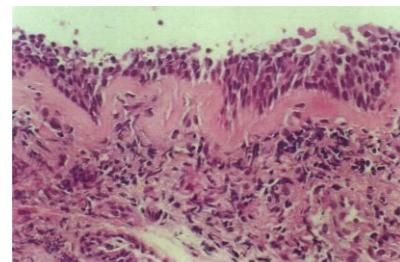
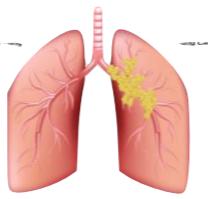




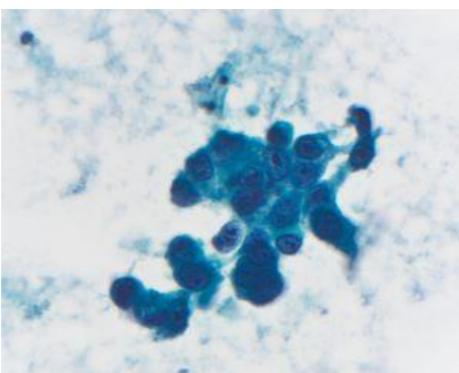
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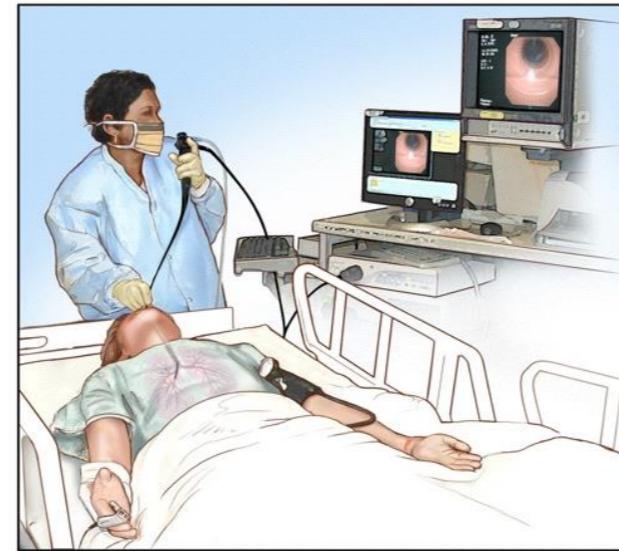




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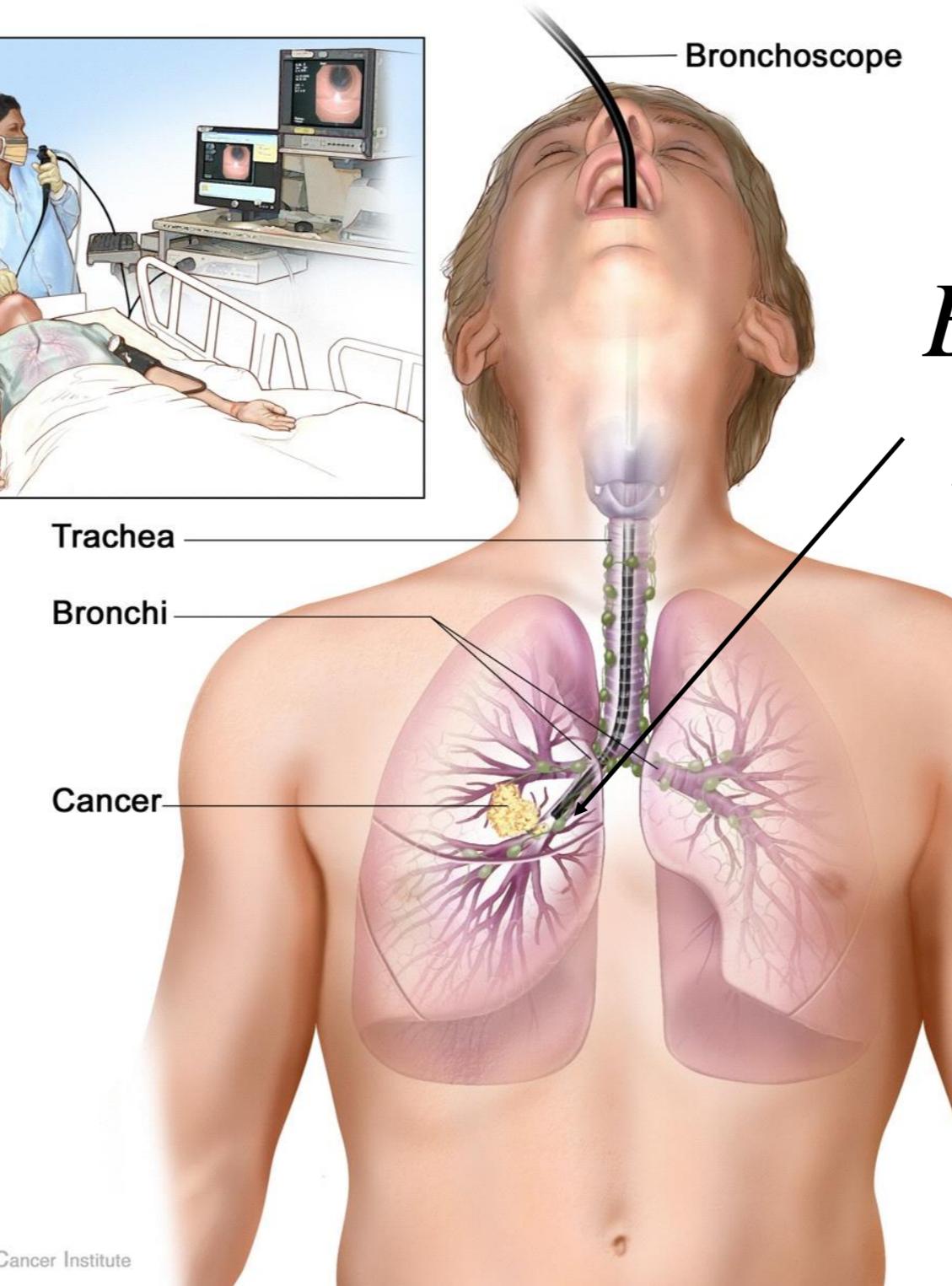
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Trachea

Bronchi

Cancer



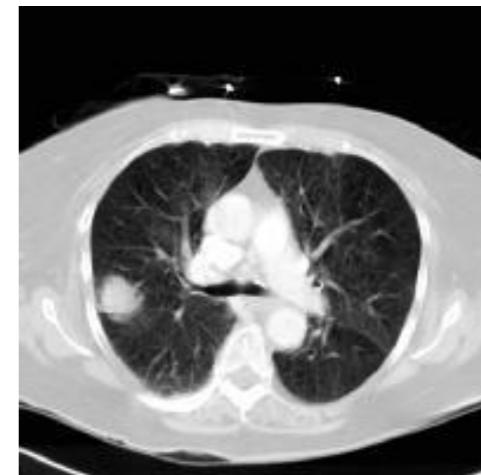
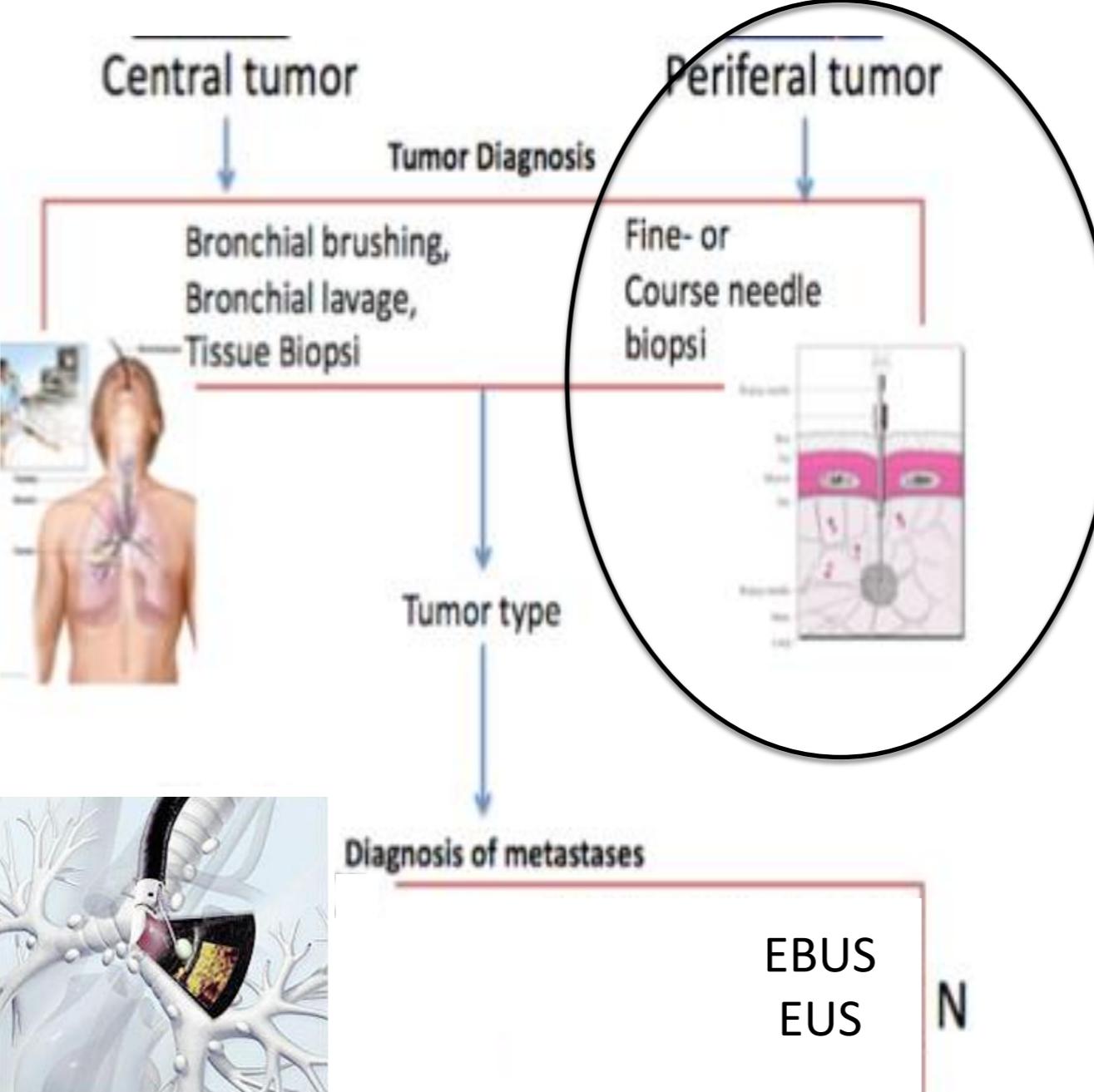
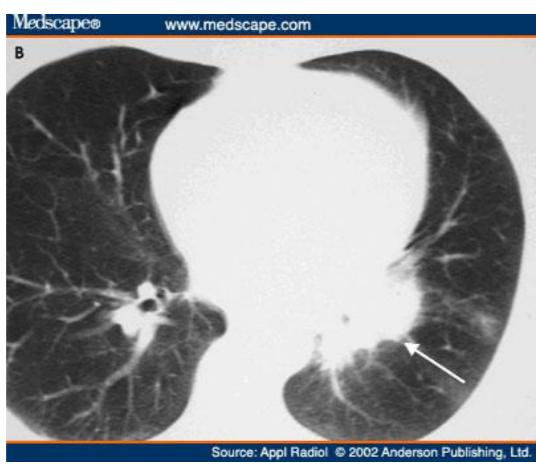
National Cancer Institute

Bronkialwash
*Brushbiopsy**

EBUS * *

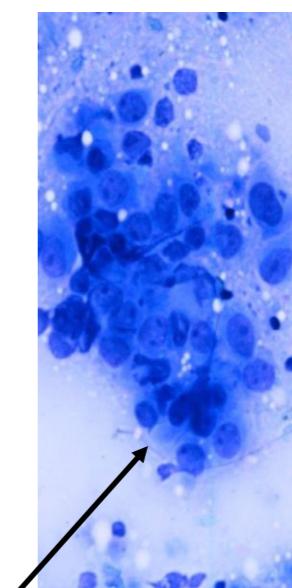
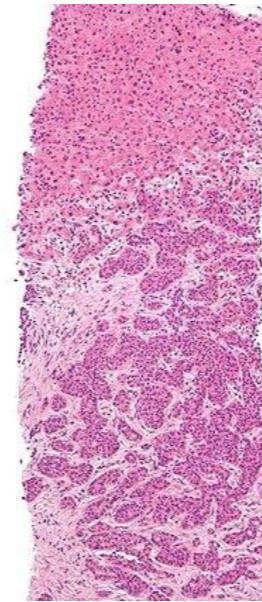
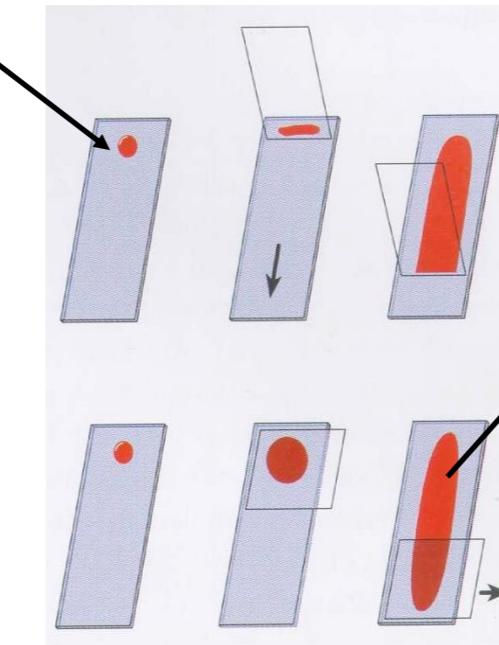
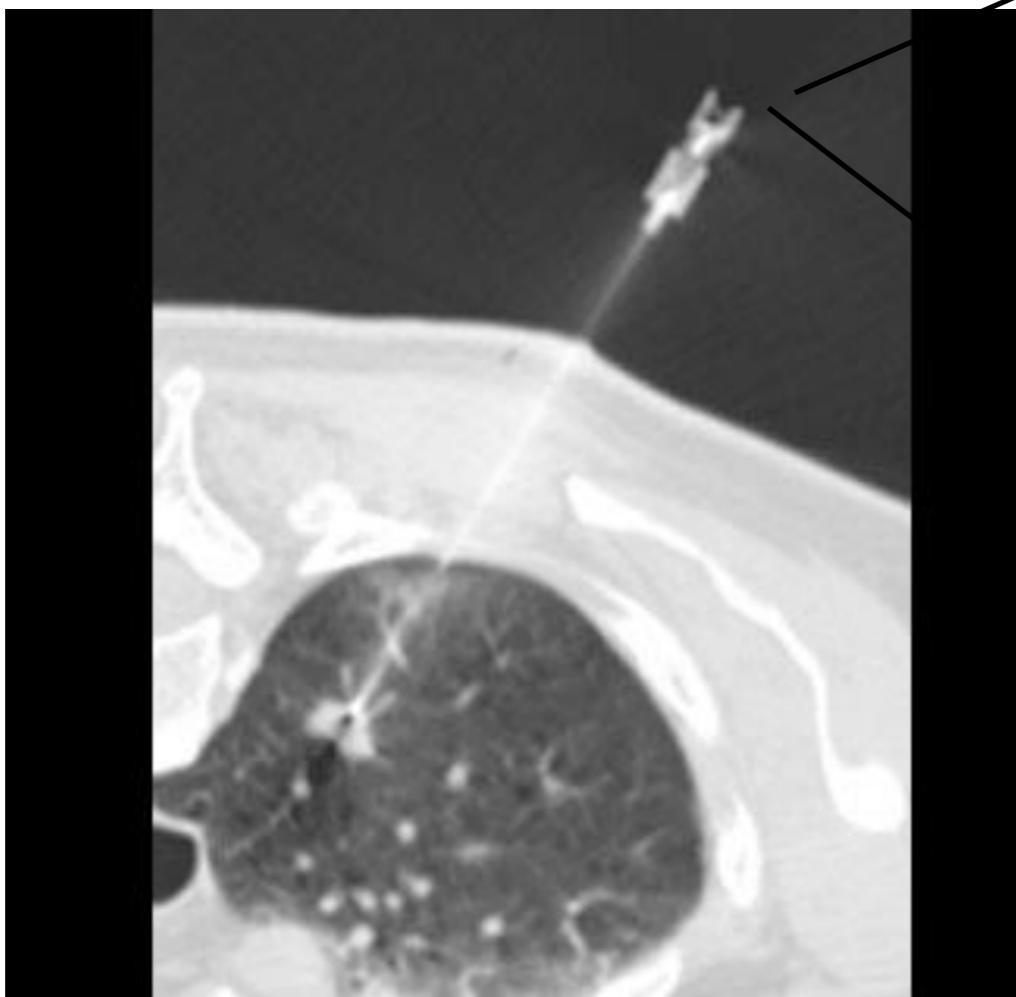
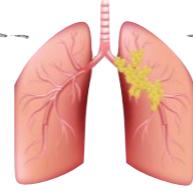
EUS *

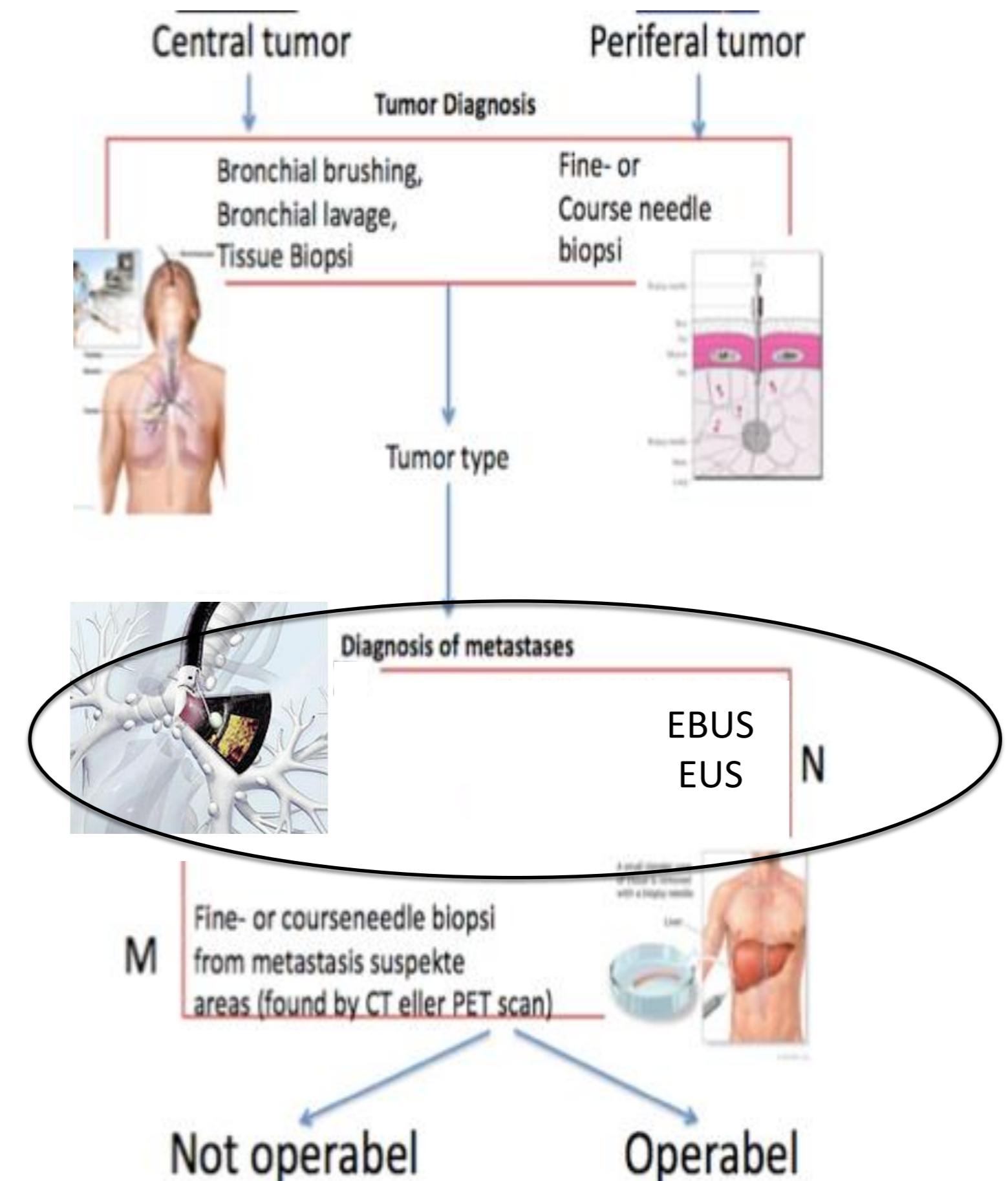
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Biopsy

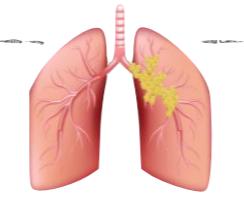


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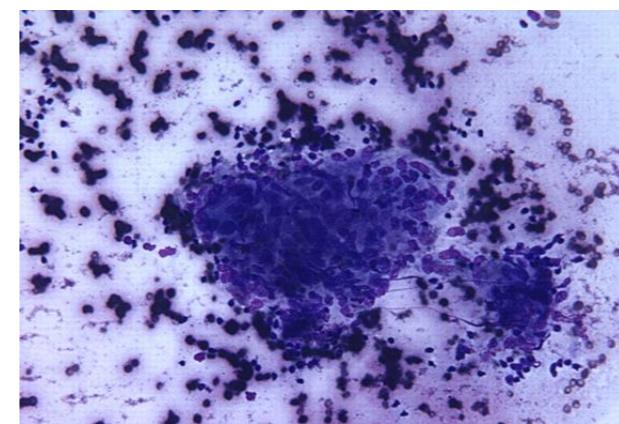
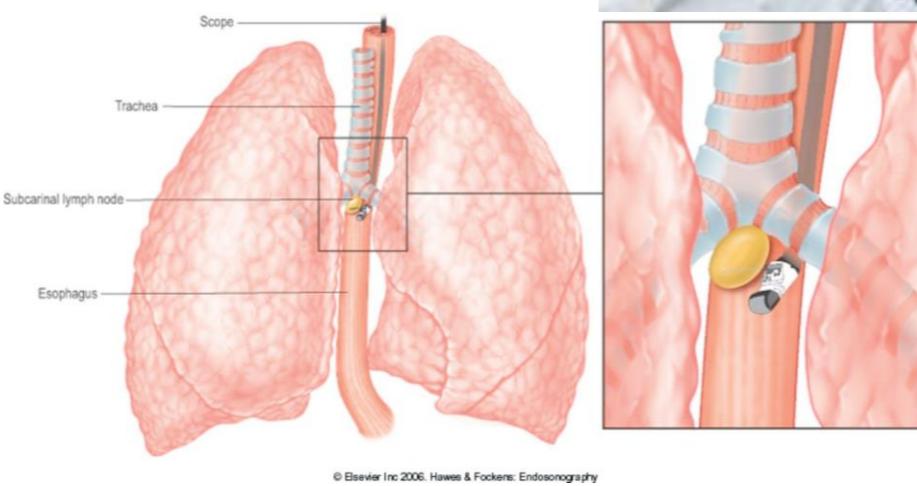
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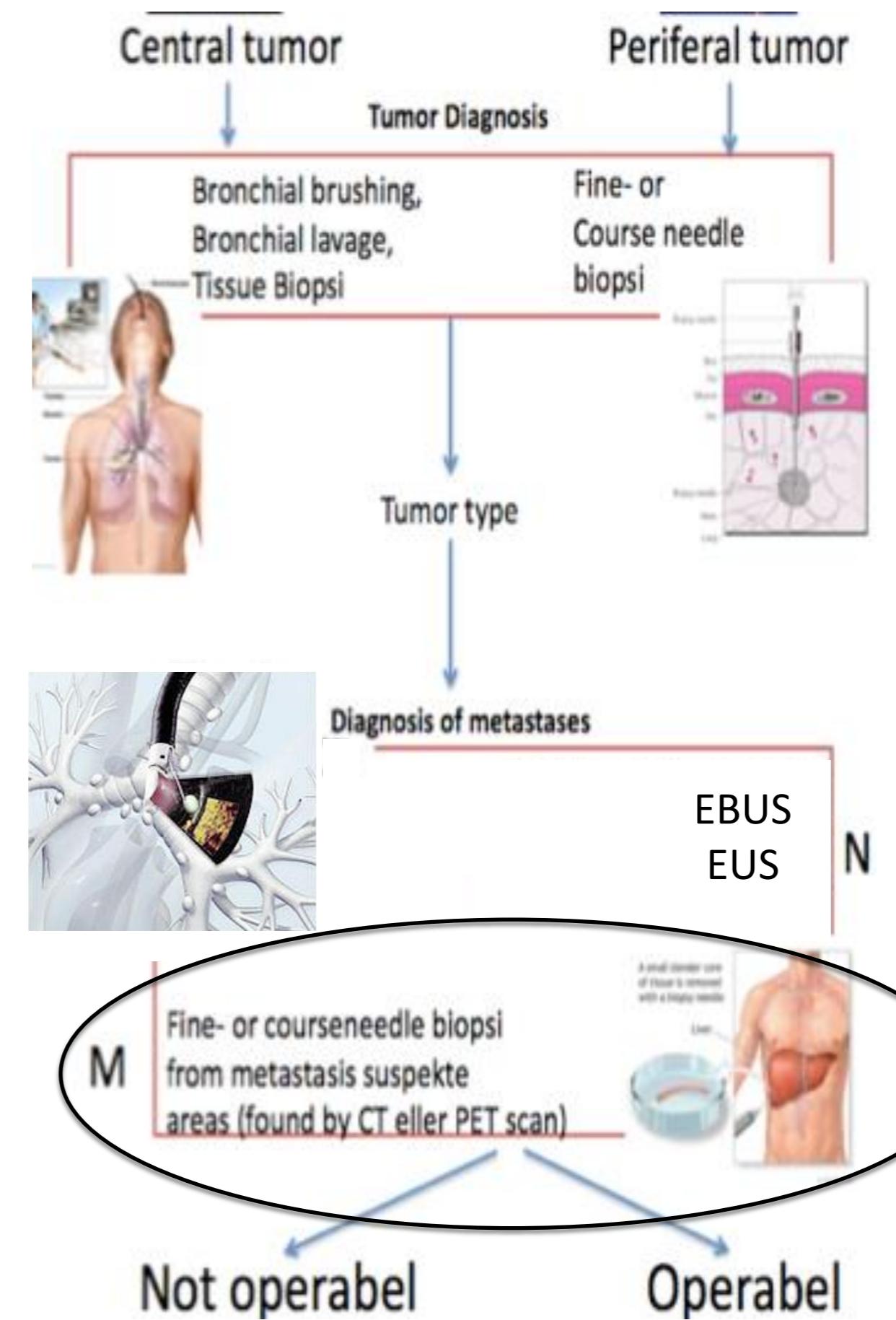


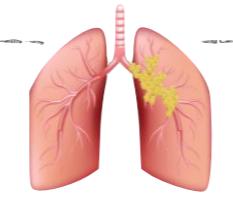




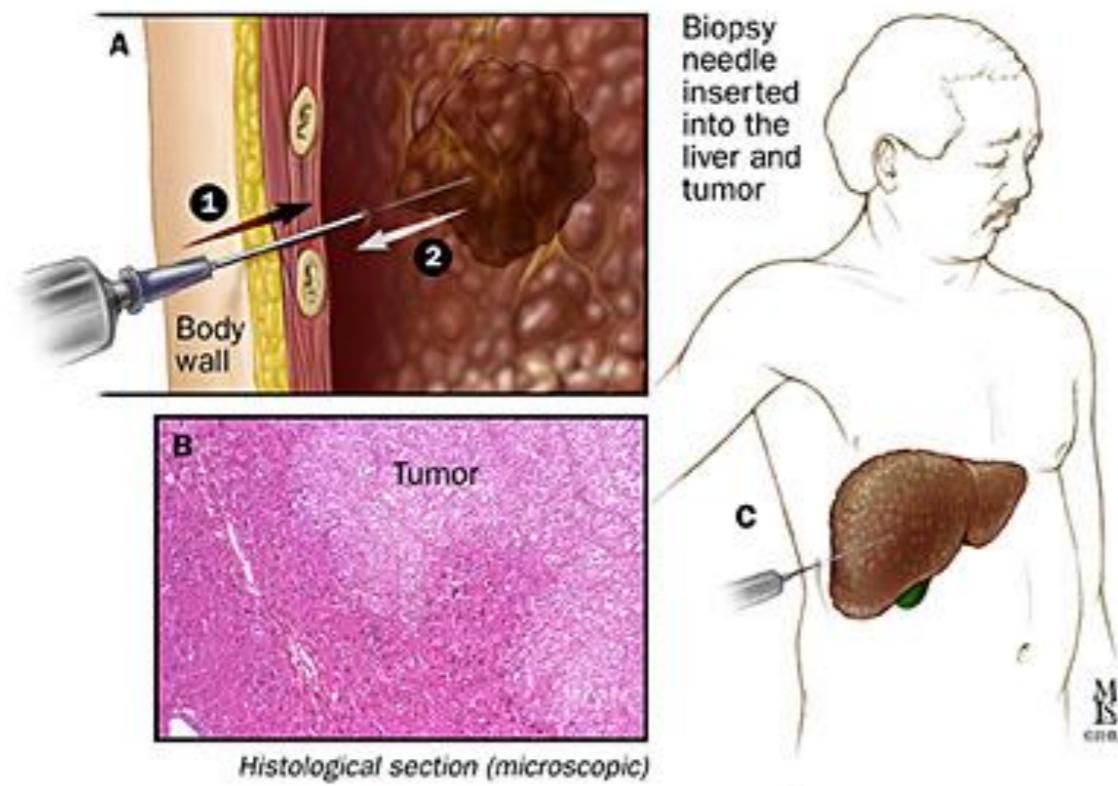
EBUS, EUS



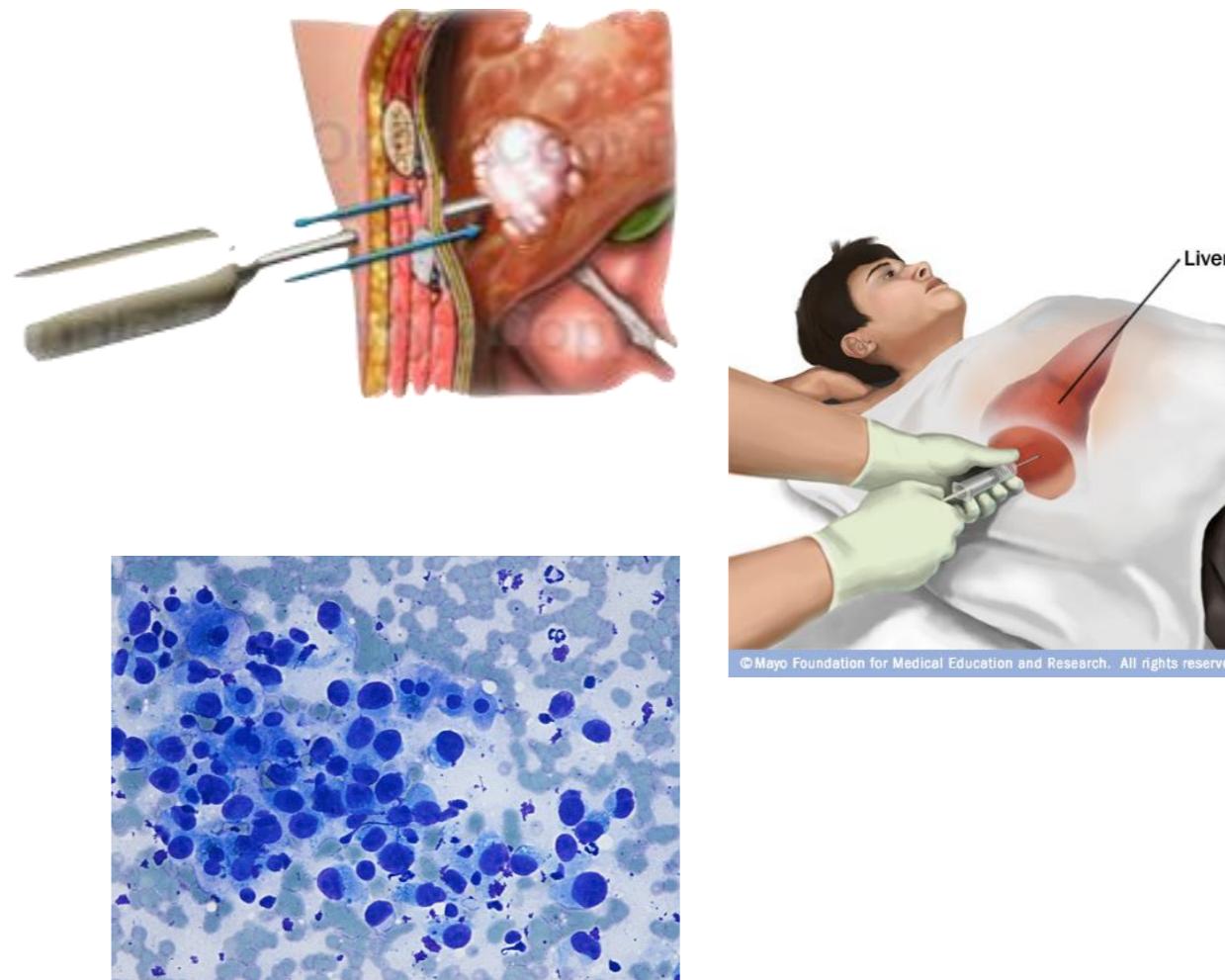


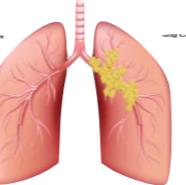


Coarse needle biopsy



Fine needle biopsy





Patoanatomical specimen

Histology

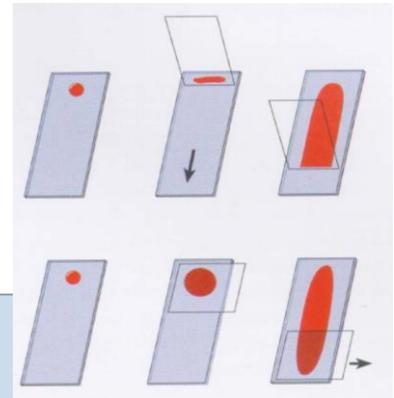


Fixation
Dehydration
Parafinembedding
Microtomy

Præparation



Cytologi



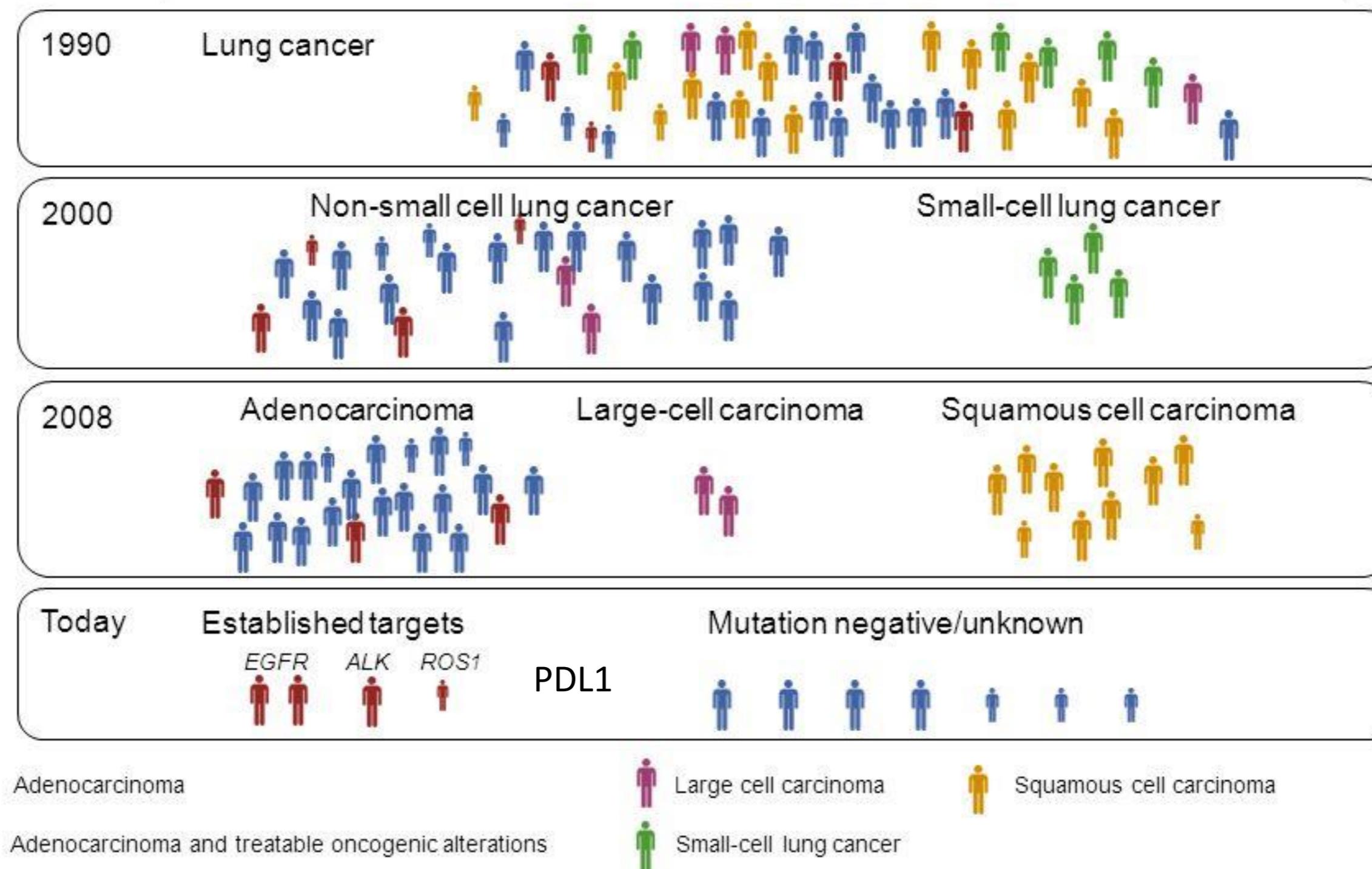
Smear preparation



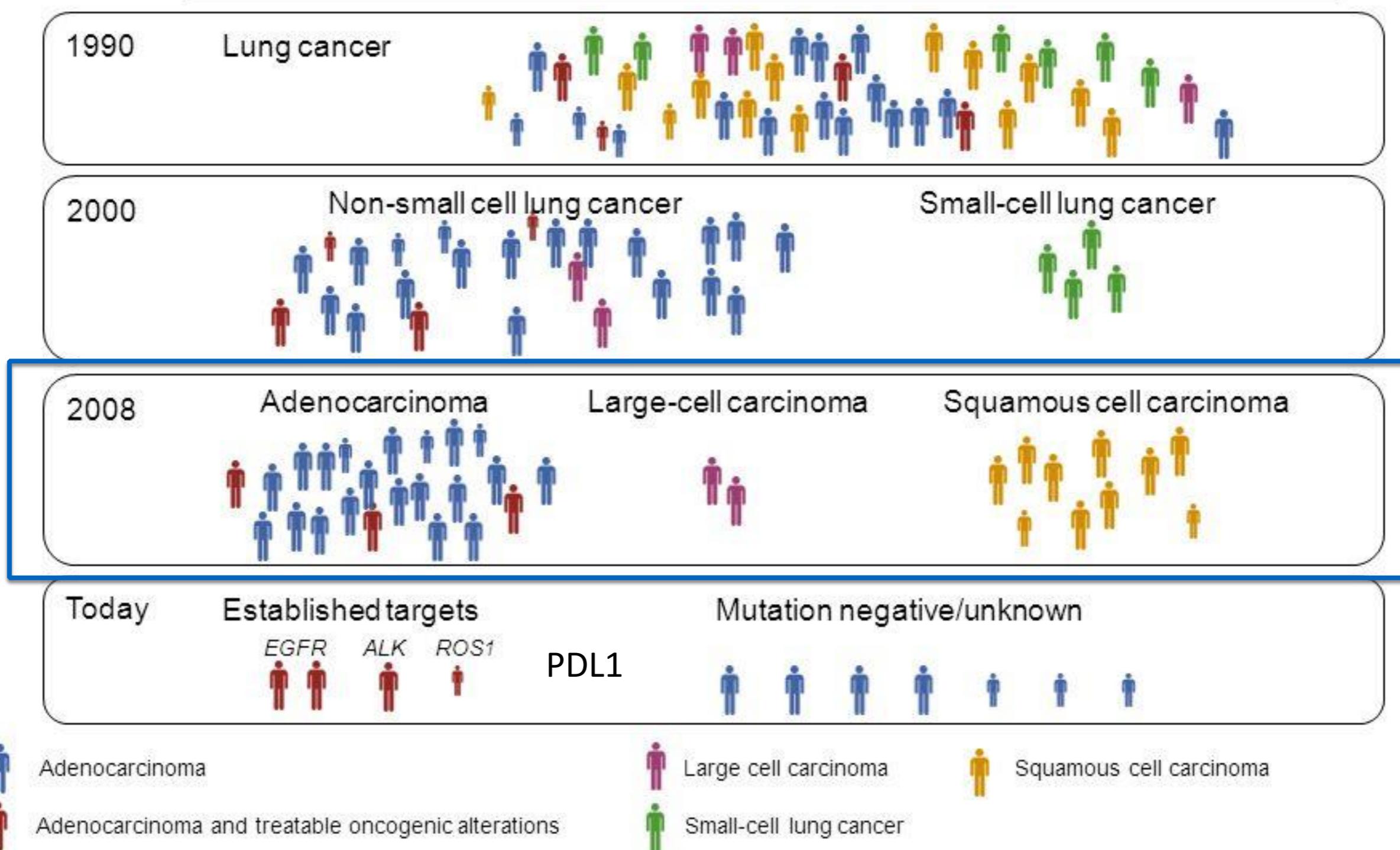
Visualization

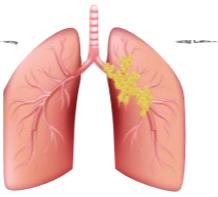
(Staining)

Patient selection in lung cancer: Evolution over time

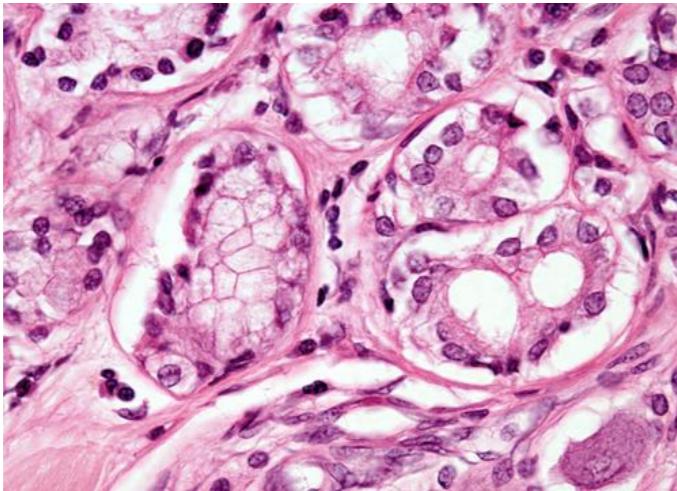
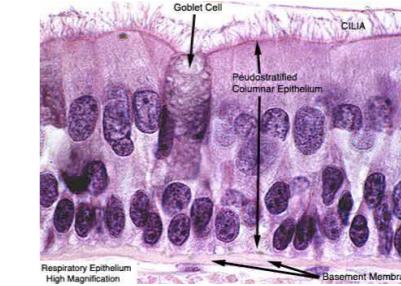


Patient selection in lung cancer: Evolution over time

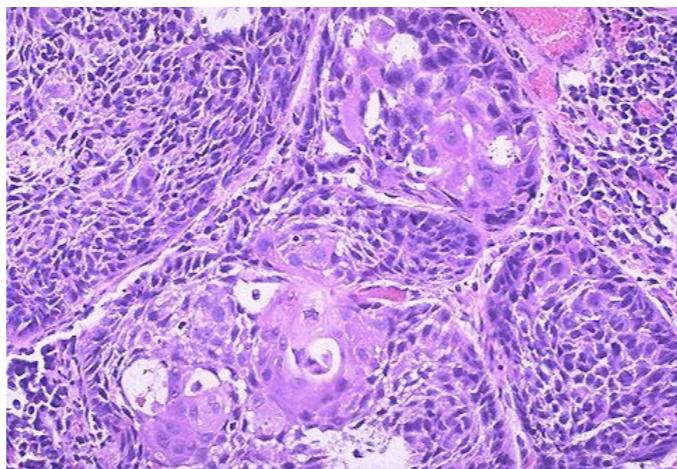




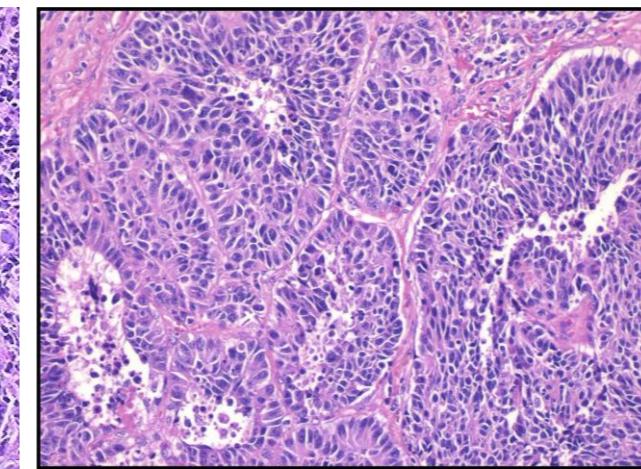
Morphology



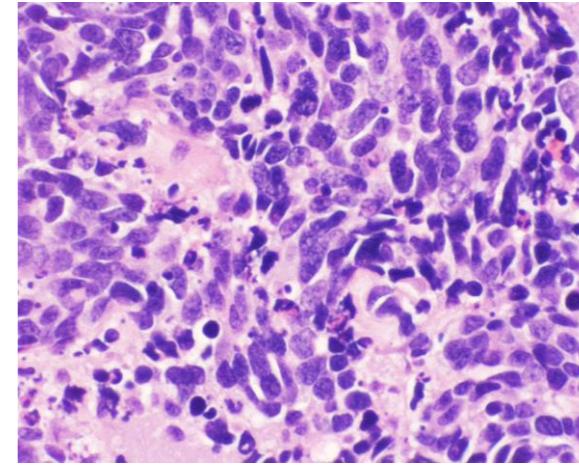
Adenocarcinoma



Squamous carcinoma



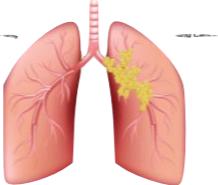
Large cell
neuroendocrine carc.



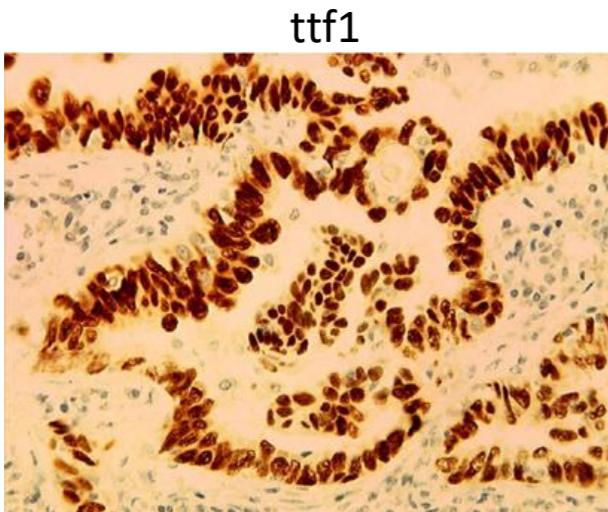
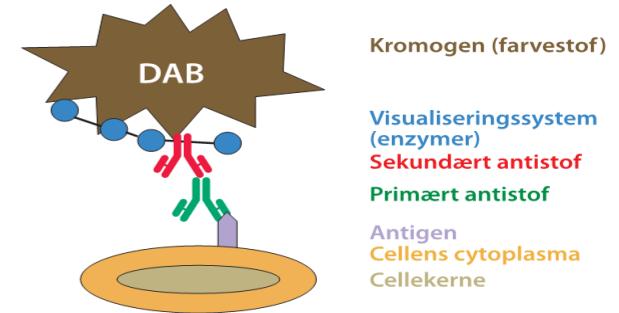
Small cell carcinoma

← →

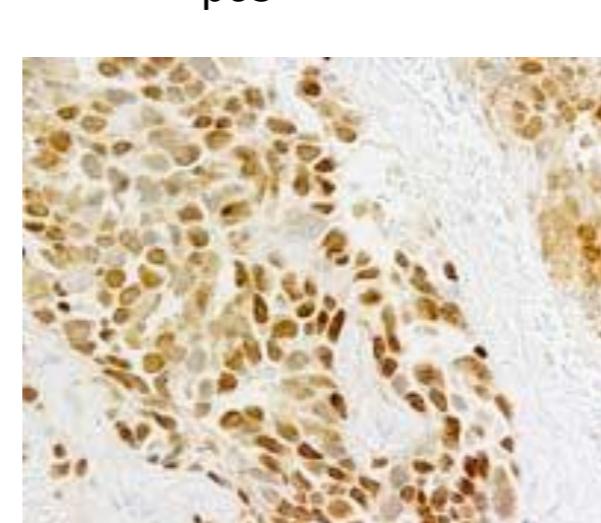
Non Small Cell Lung Carcinoma (NSCLC)



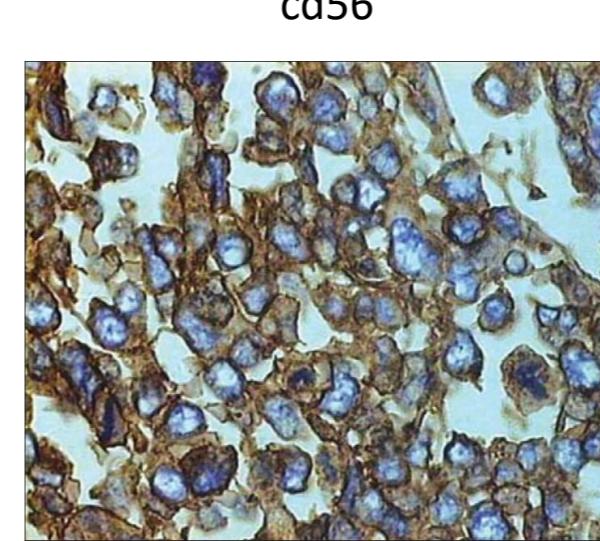
Immunohistochemistry



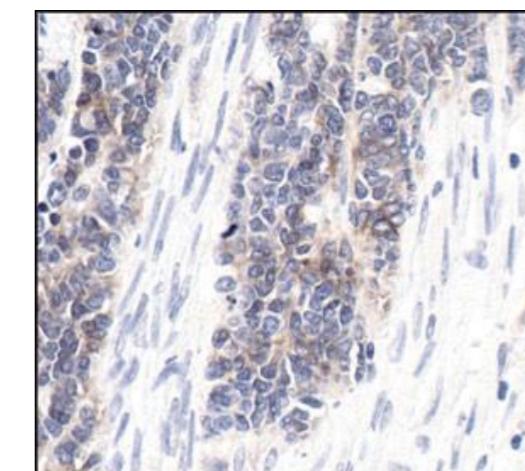
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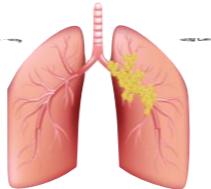


Large cell
neuroendocrine carc

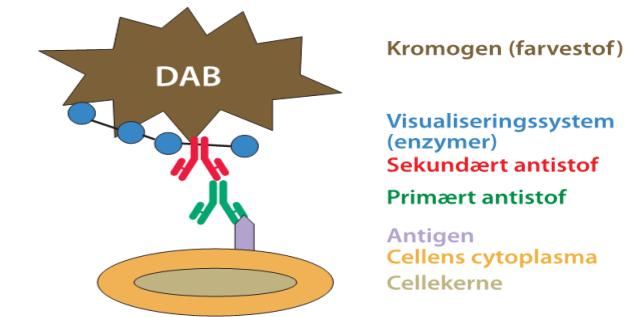


Small cell carcinoma

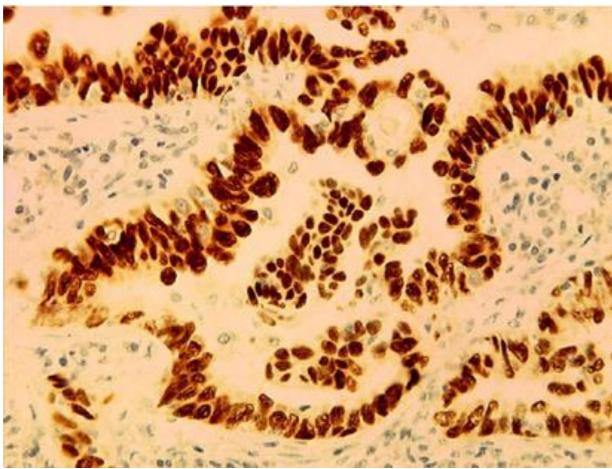
← Neuroendocrine carc.



Immunohistochemistry

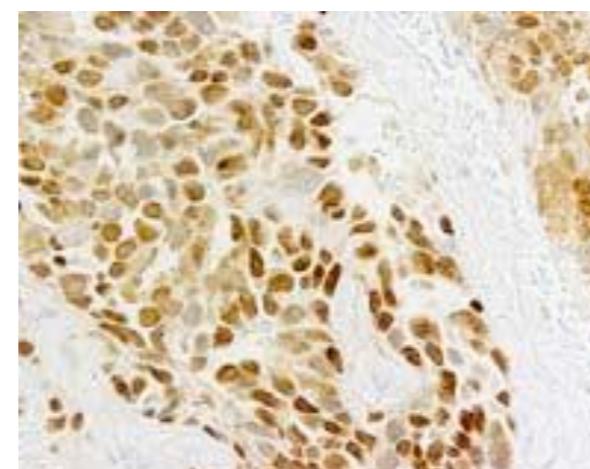


ttf1



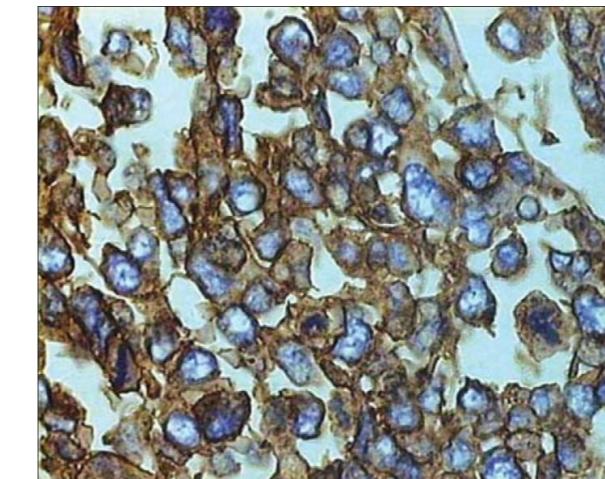
Adenocarcinoma

p63



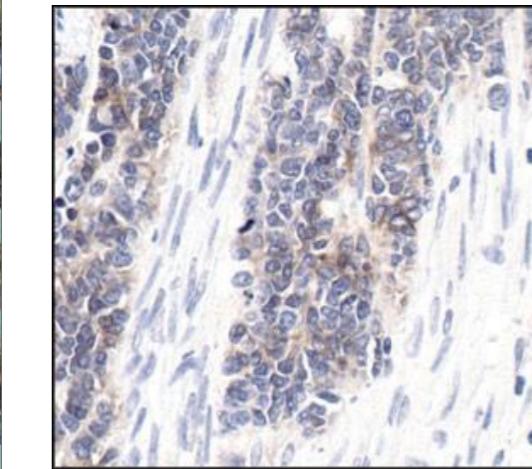
Squamous carcinoma

cd56



Large cell
neuroendocrine carc

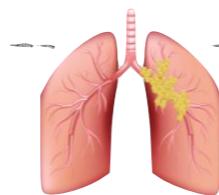
cd56



Small cell carcinoma

↔

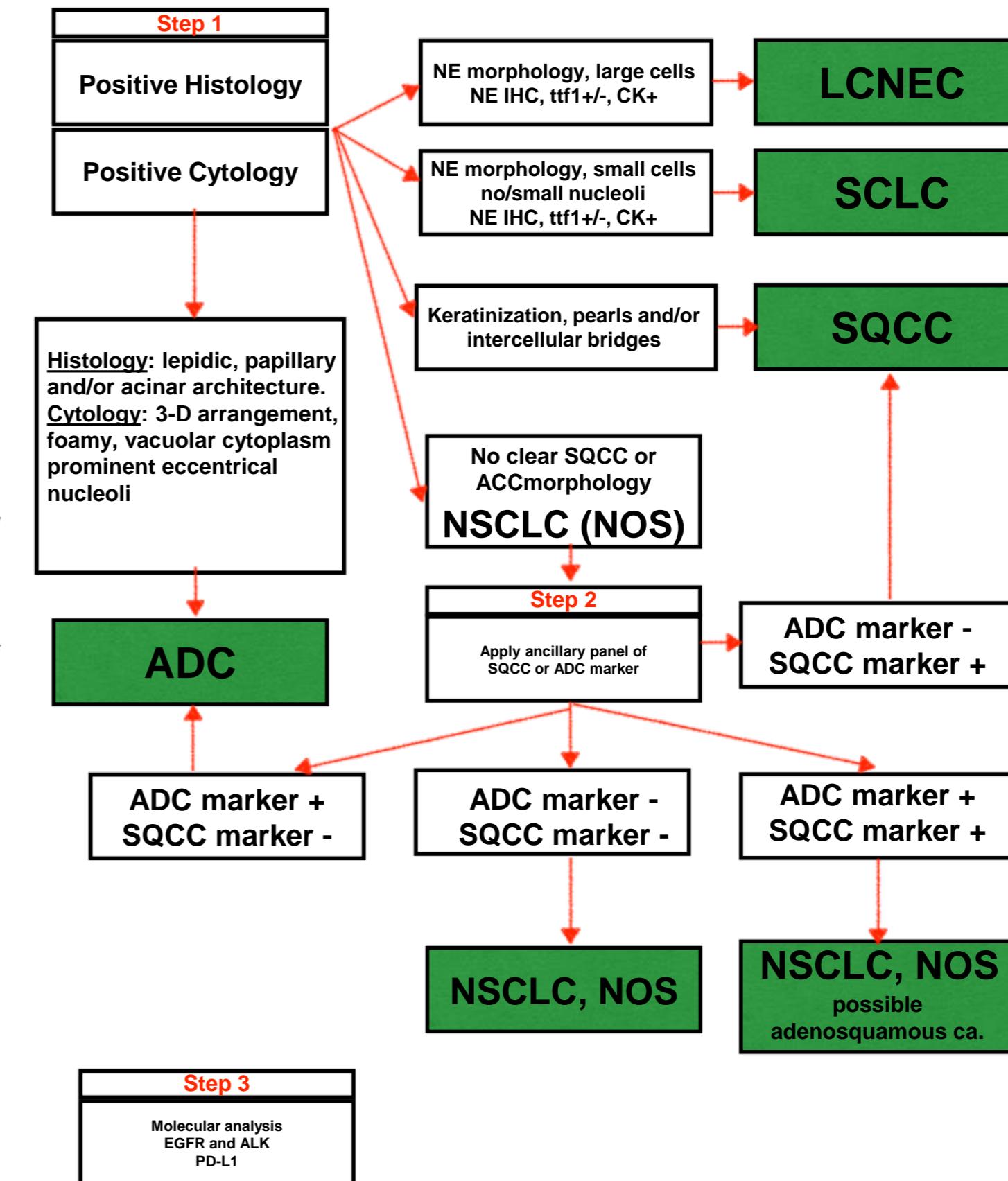
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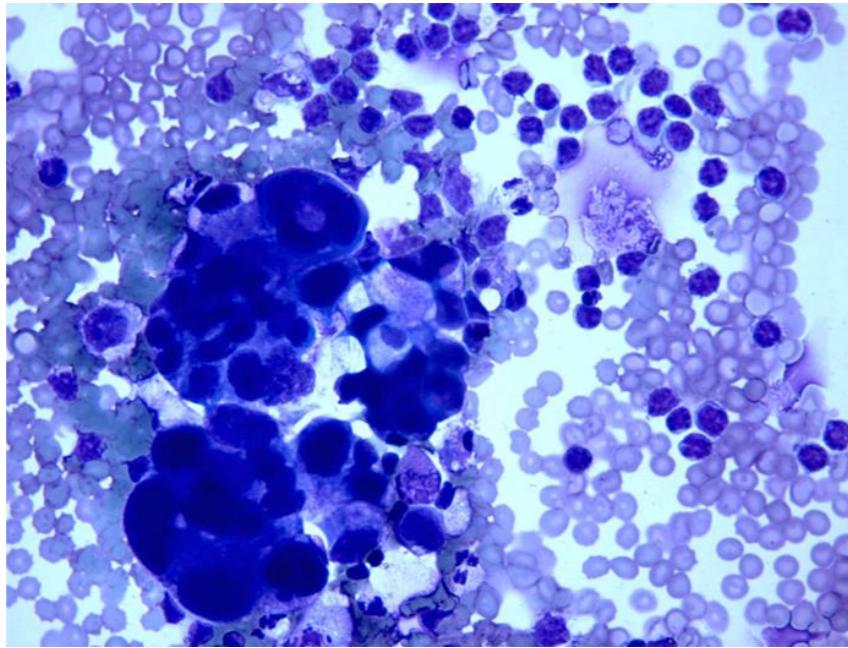
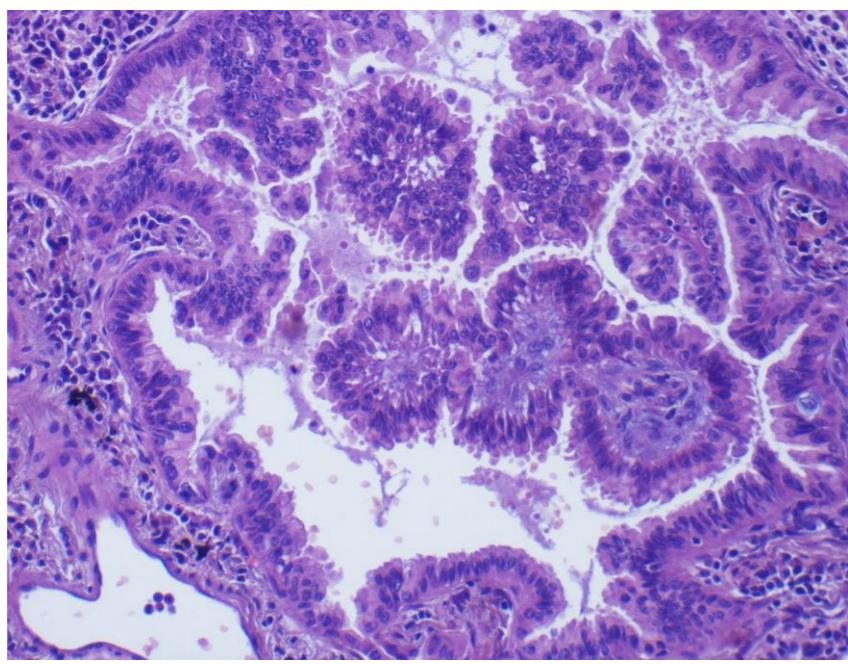
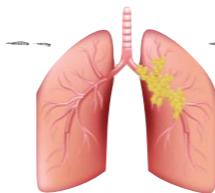


Algorithm modified from

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

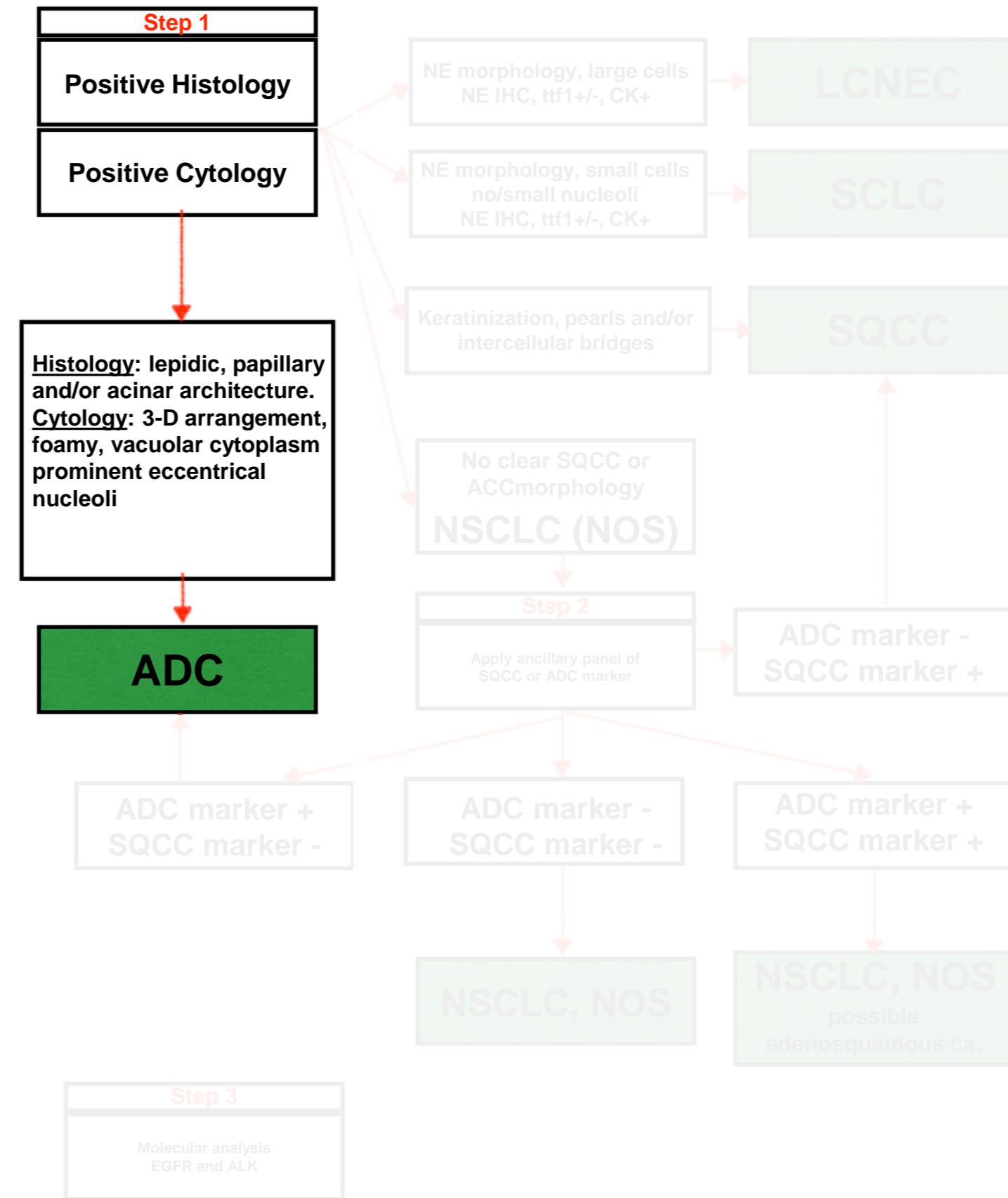
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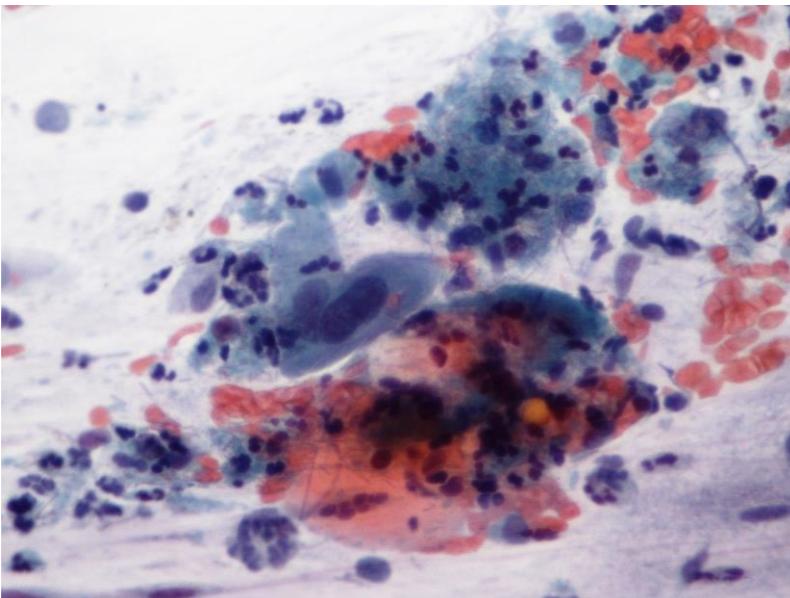
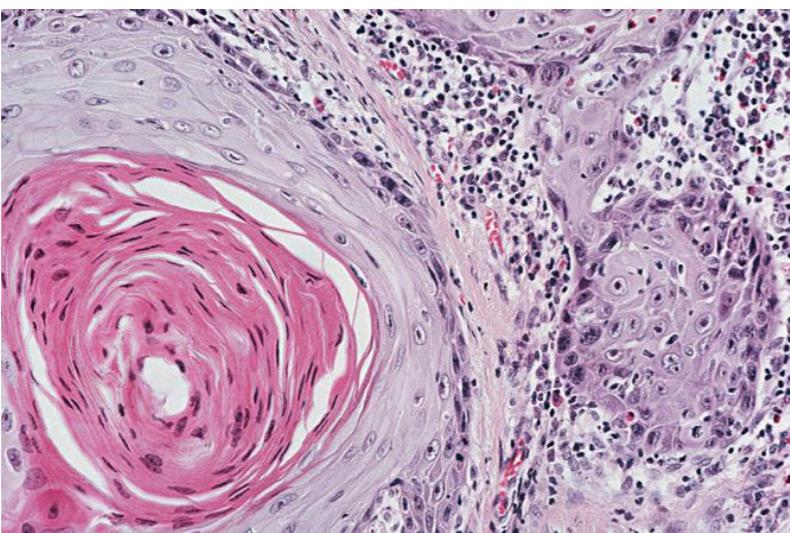




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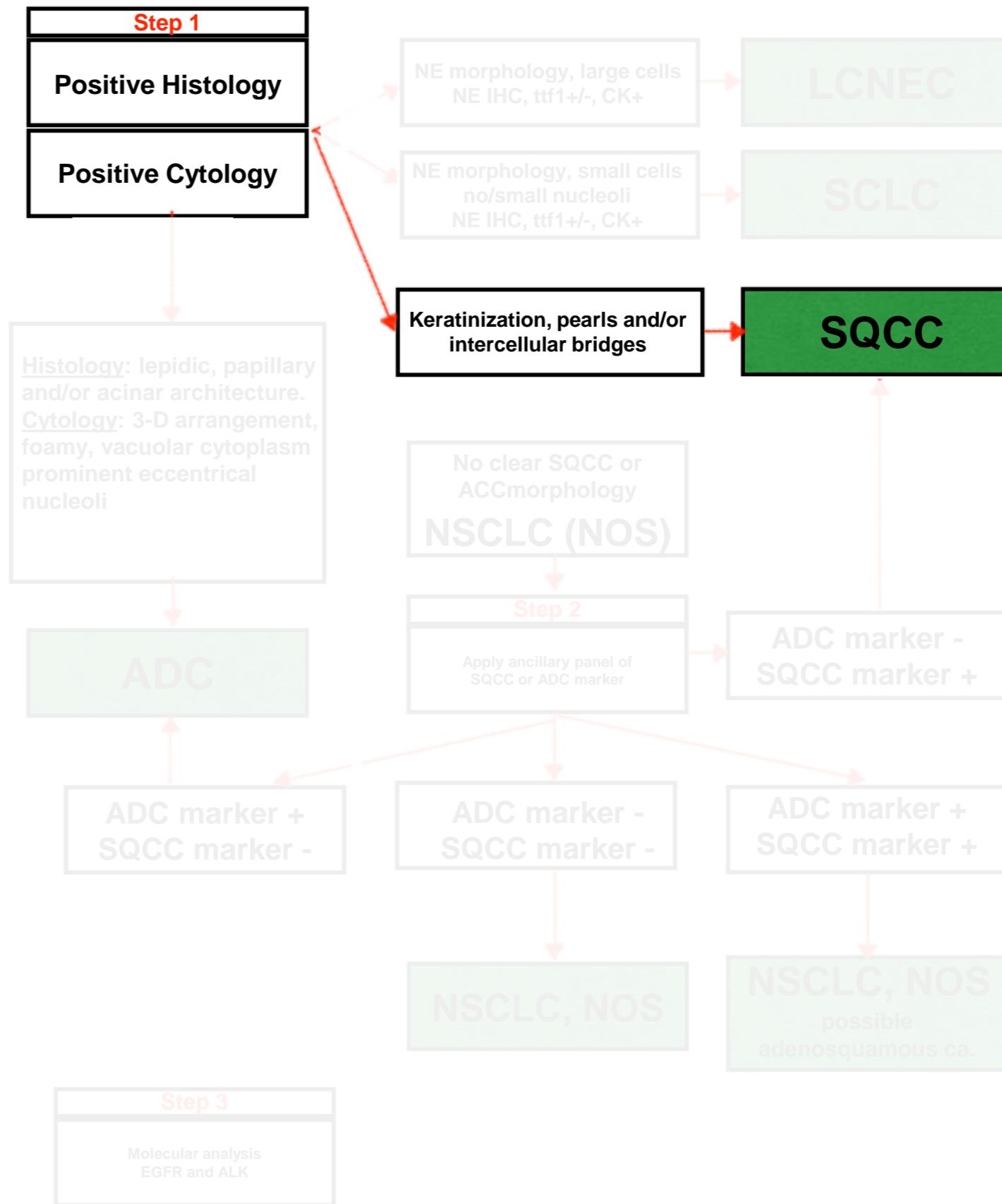
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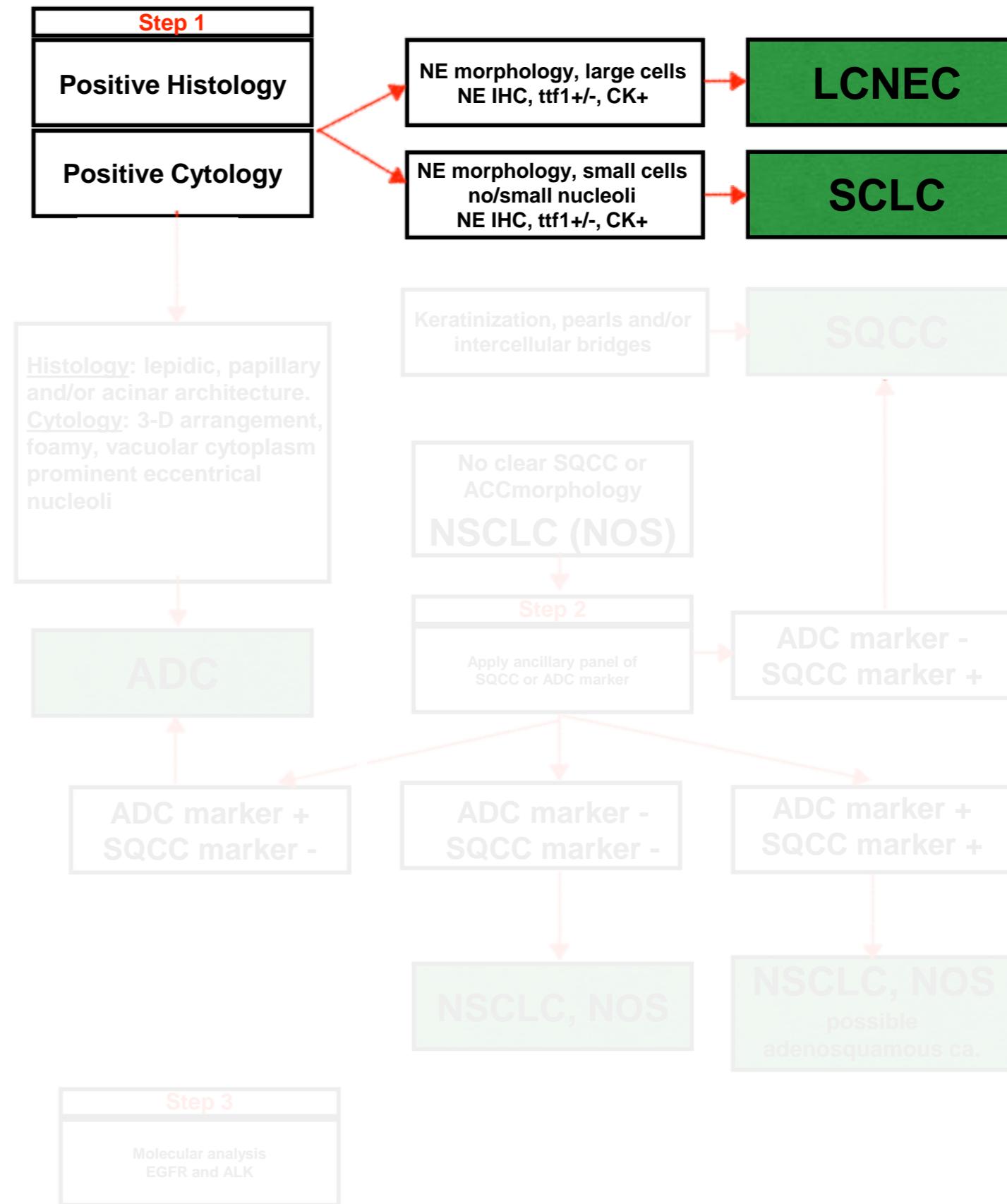
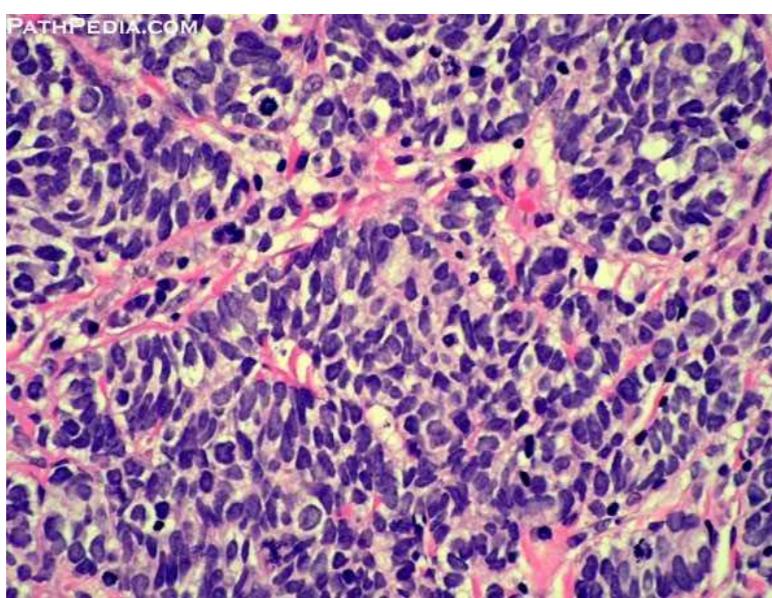
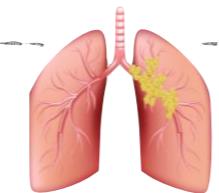




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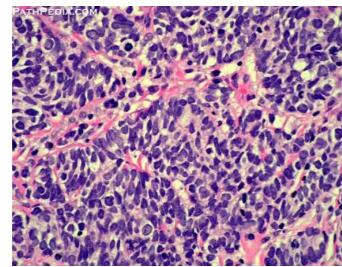
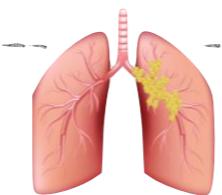




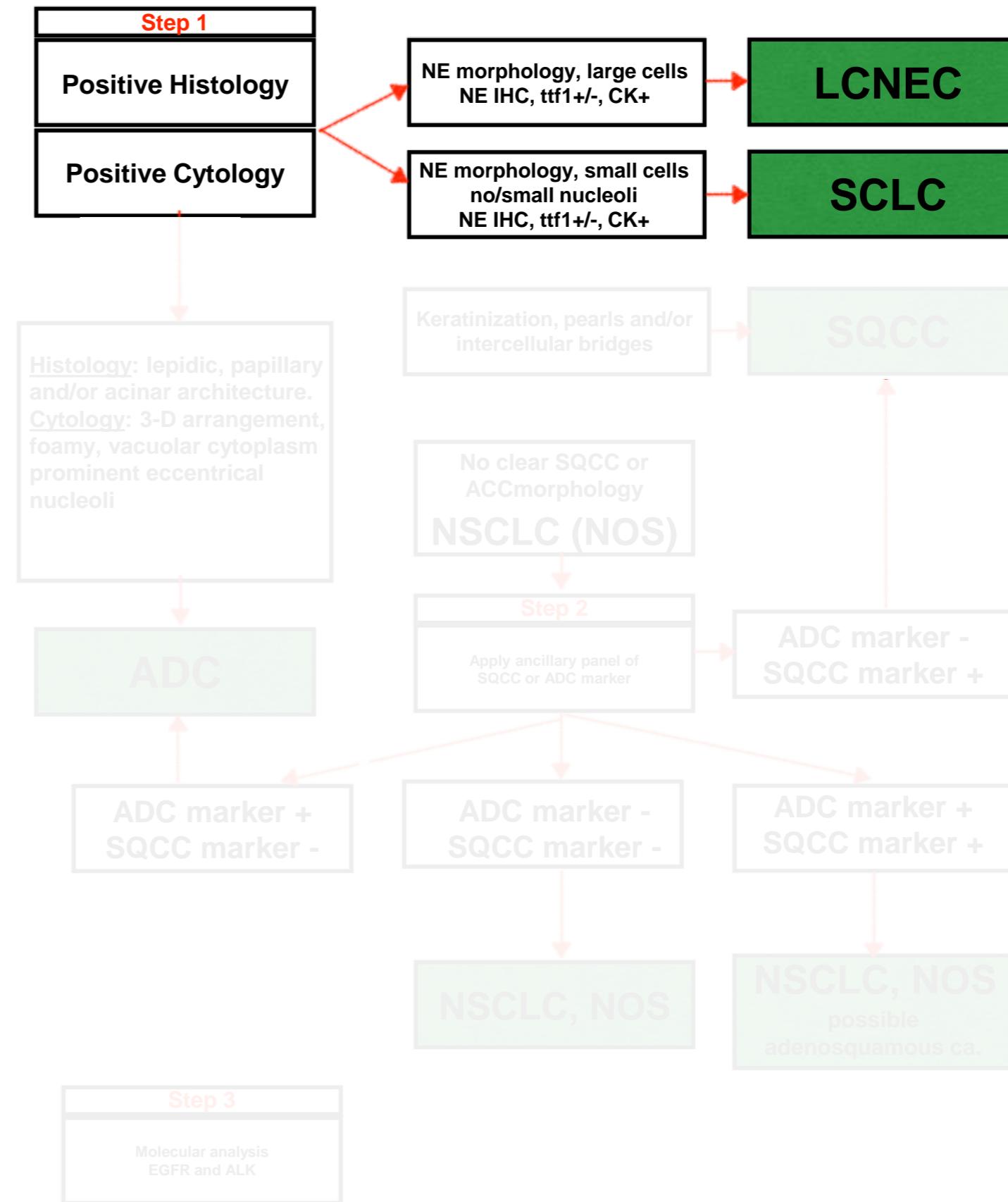
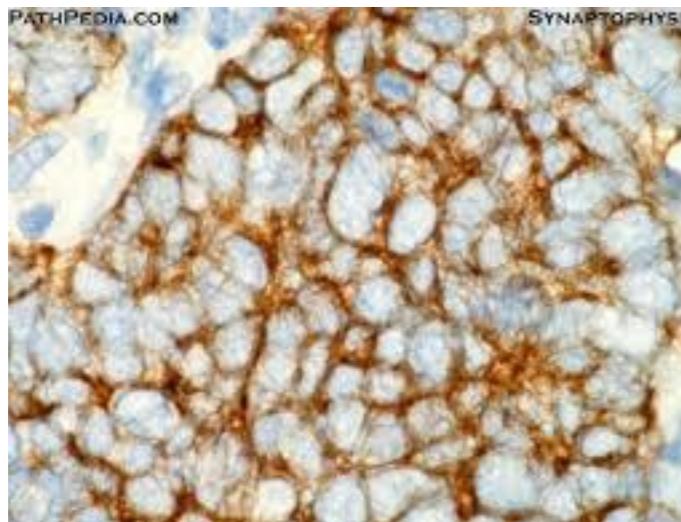
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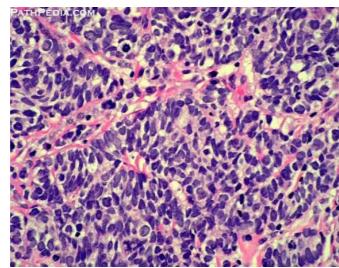
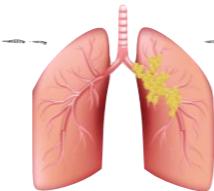
CD56



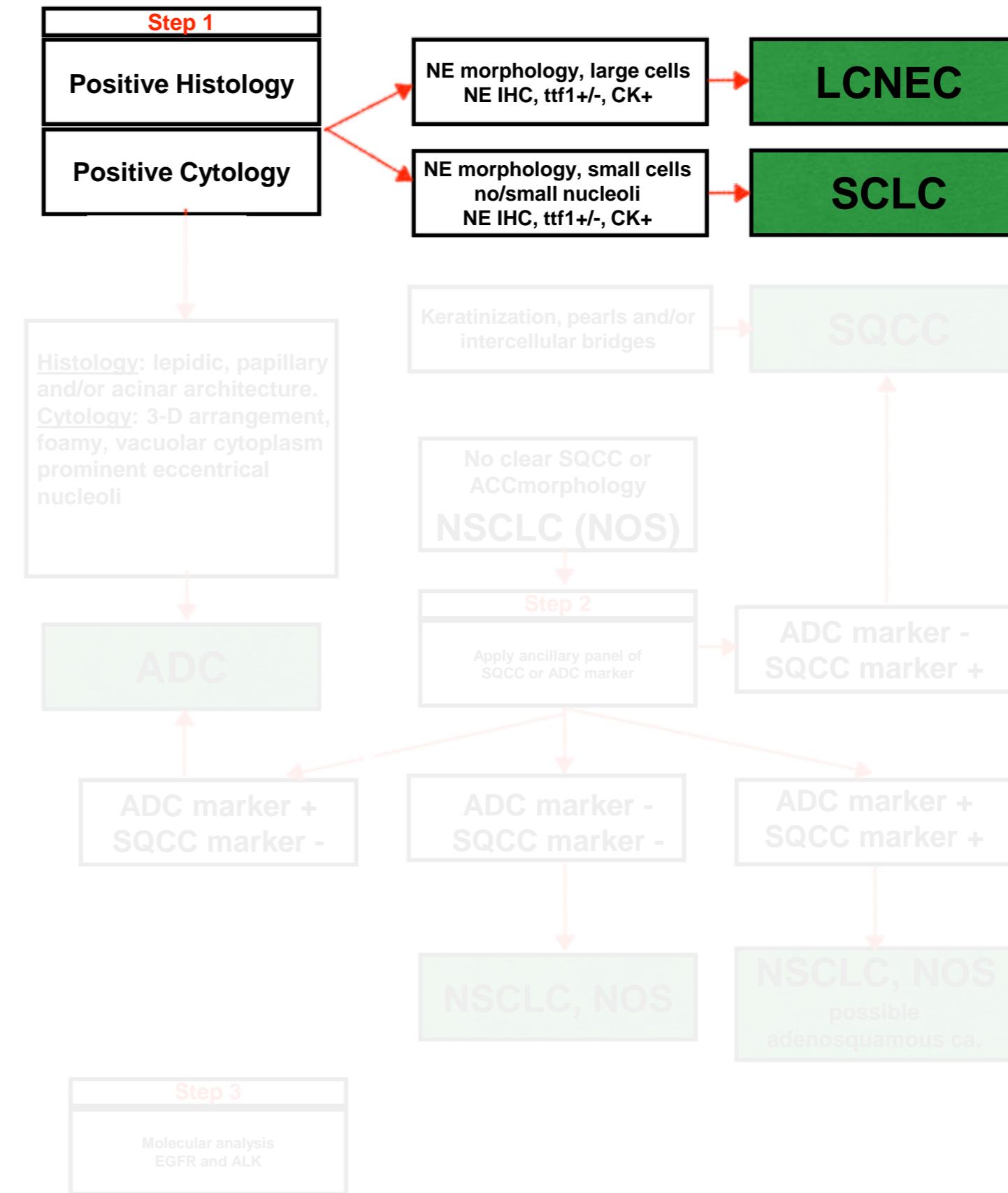
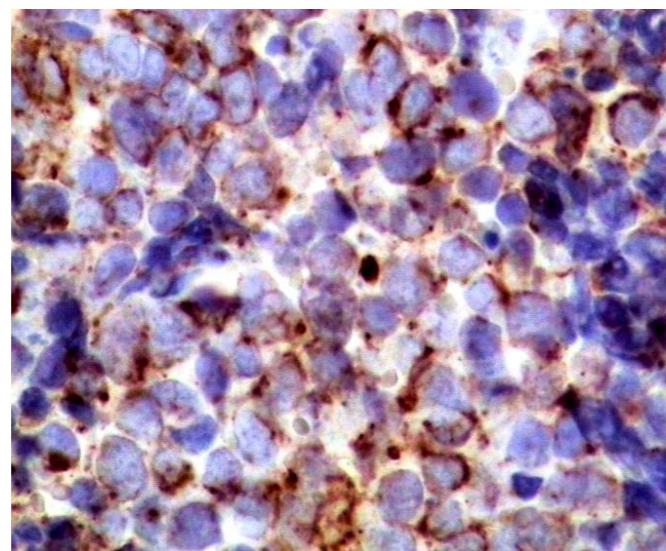
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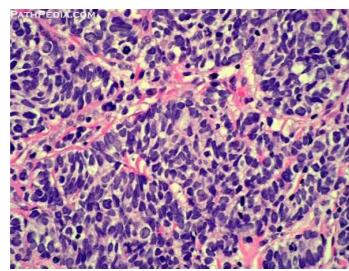
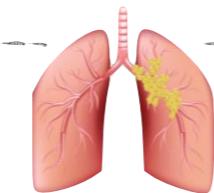
Chromogranin A



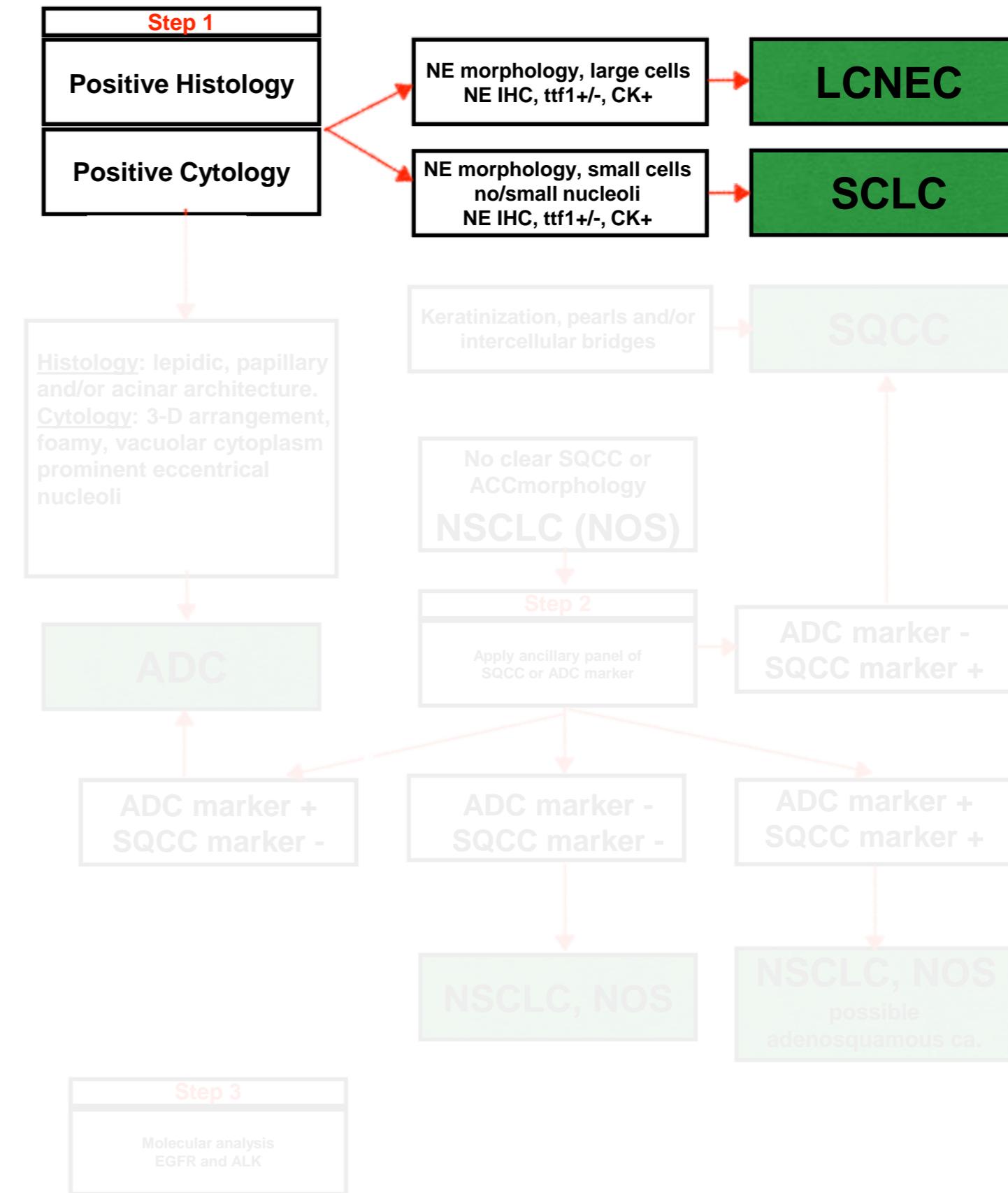
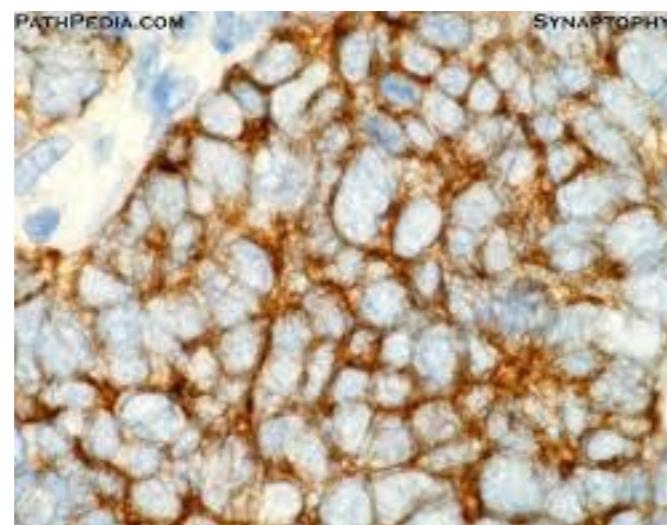
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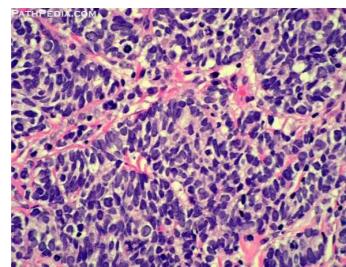
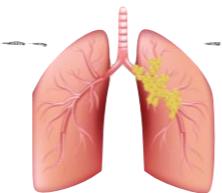
Synaptophysin



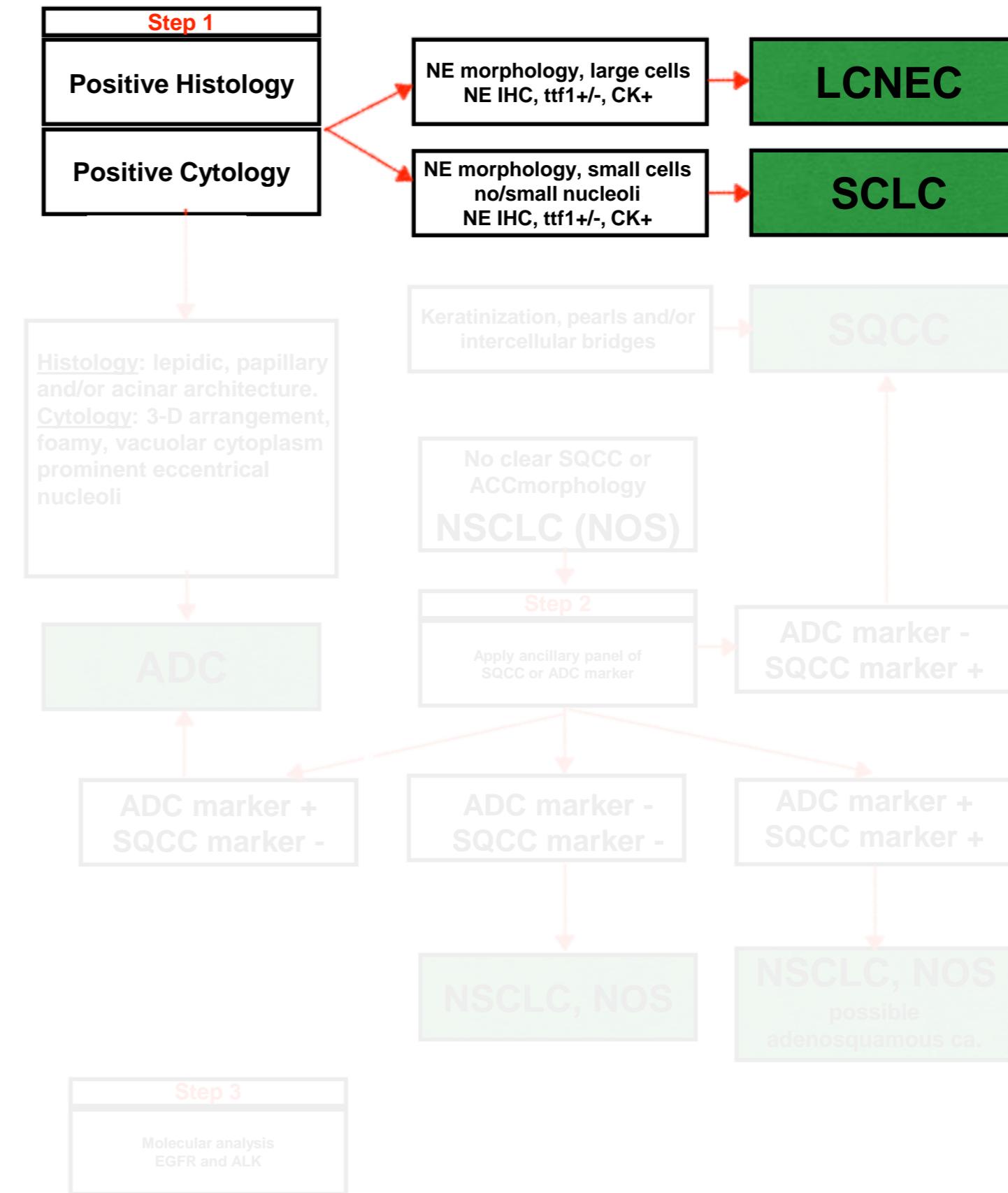
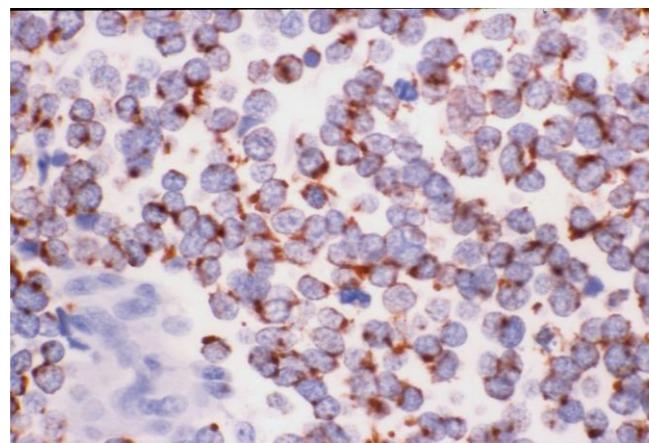
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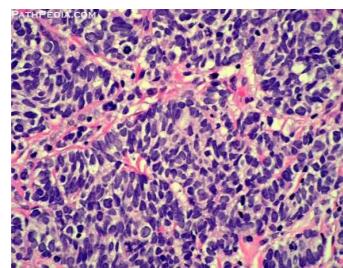
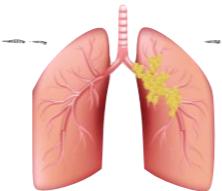
Cytokeratin



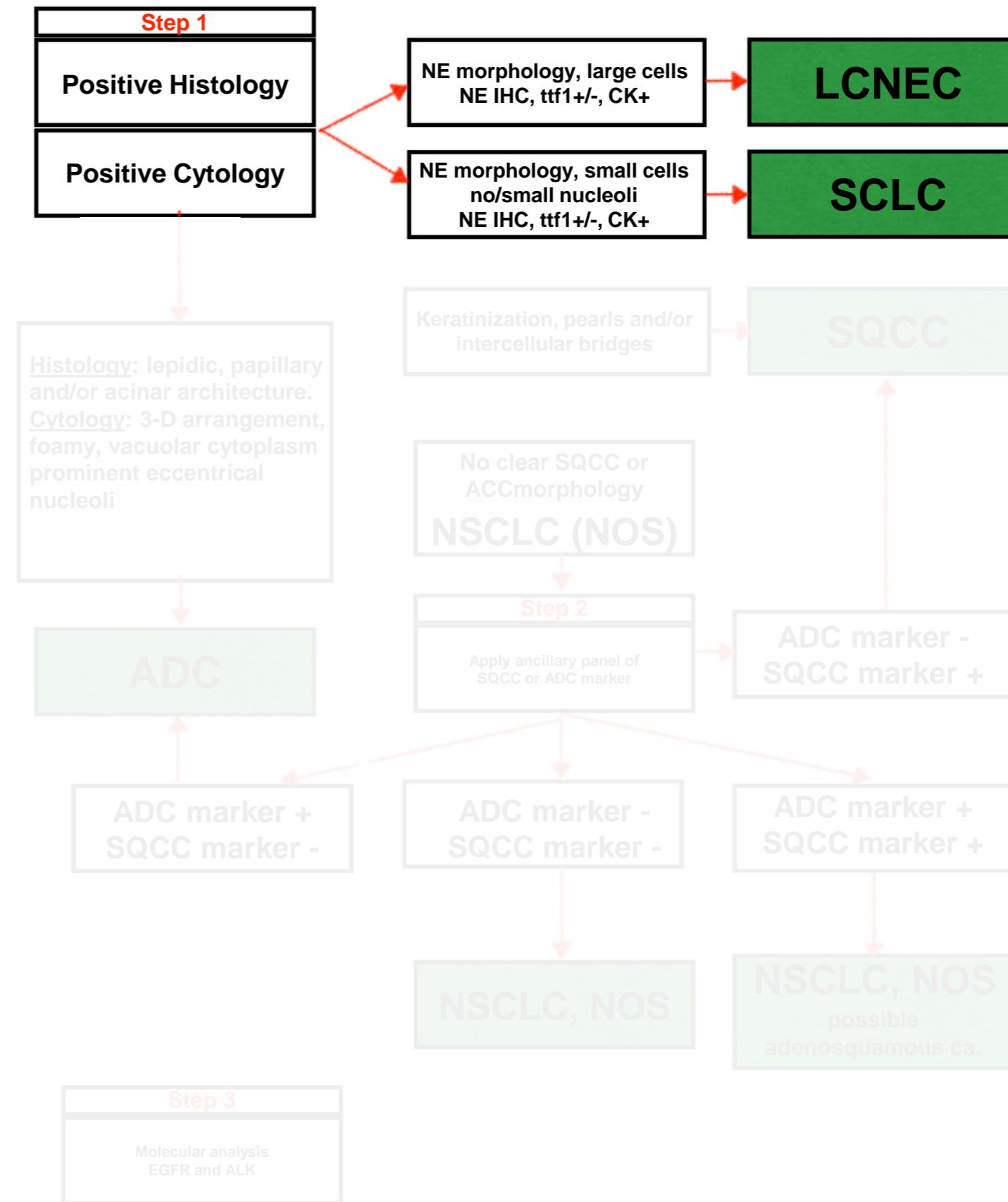
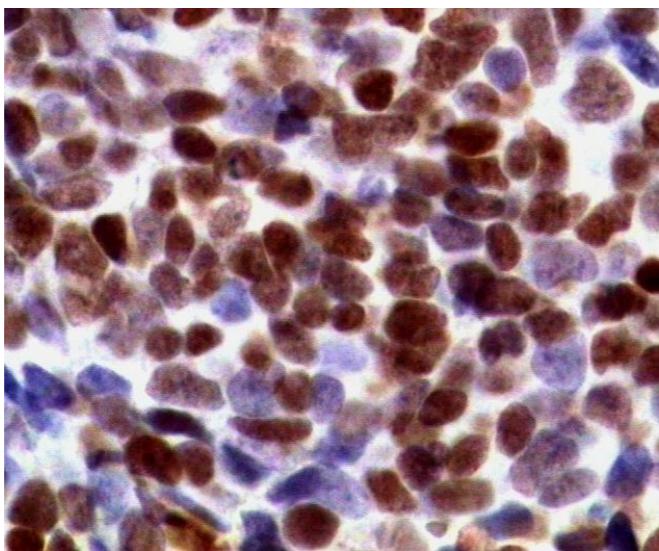
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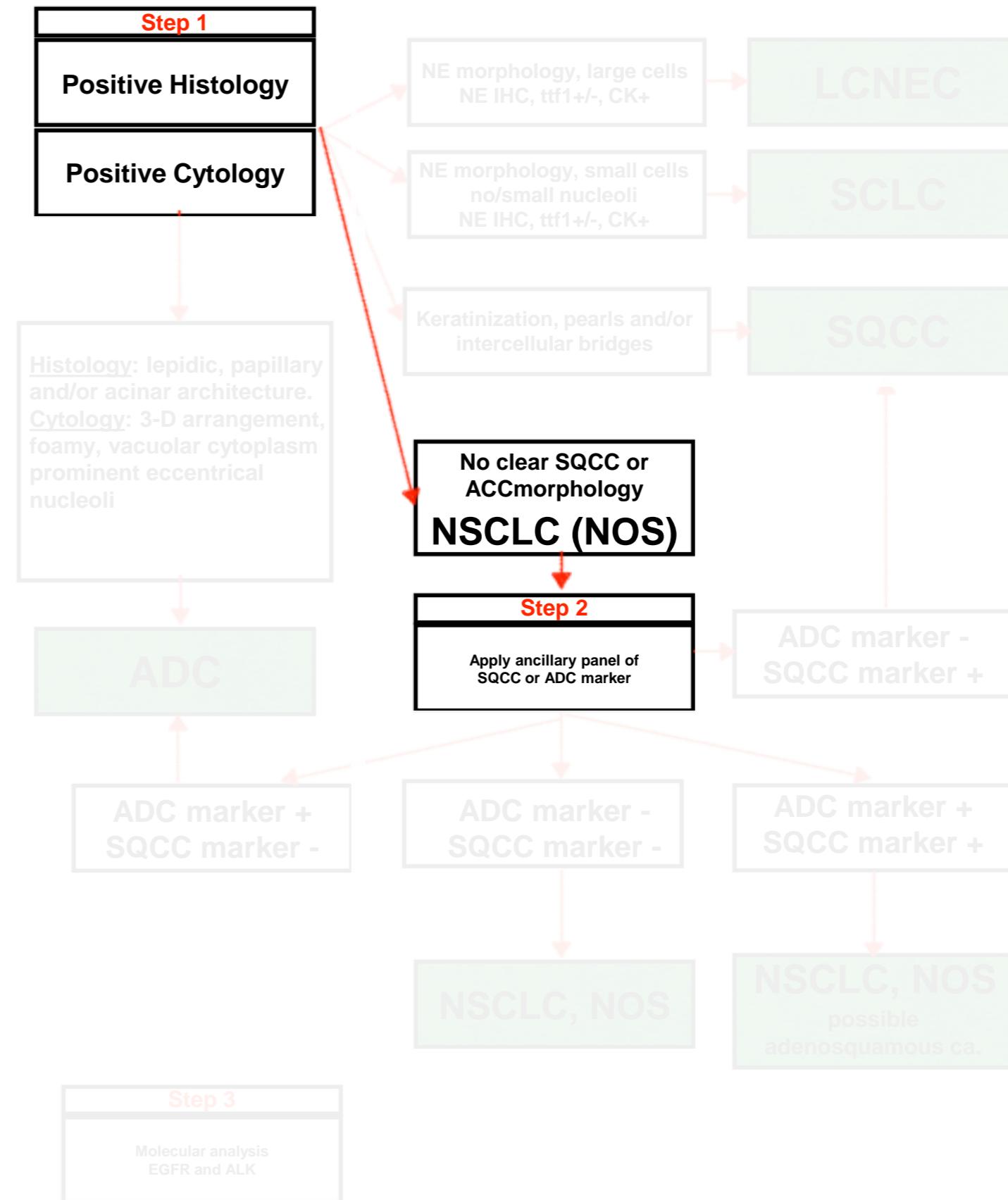
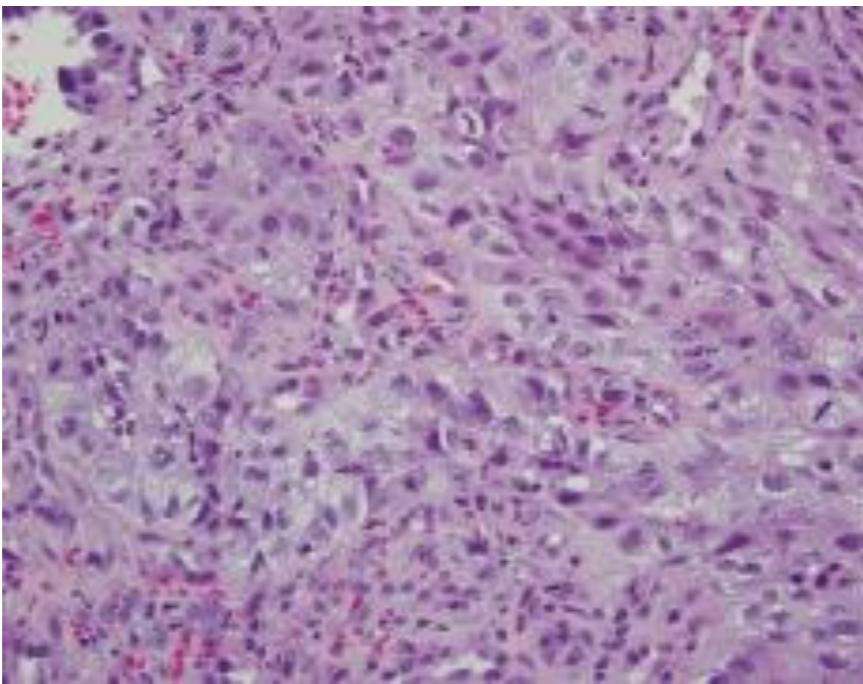
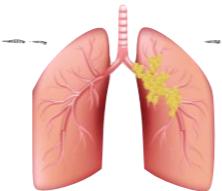
ttf1

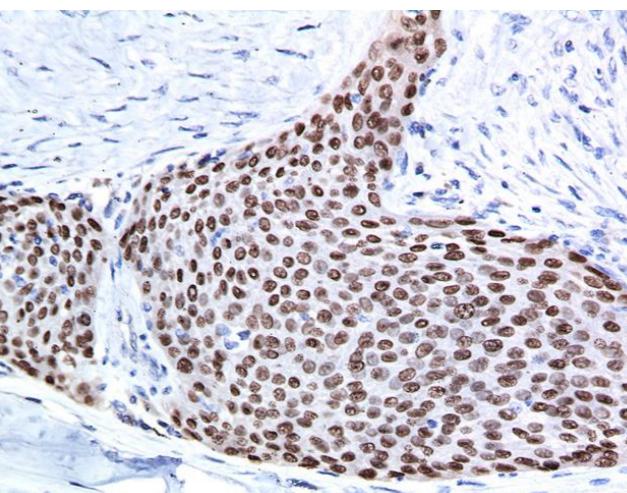
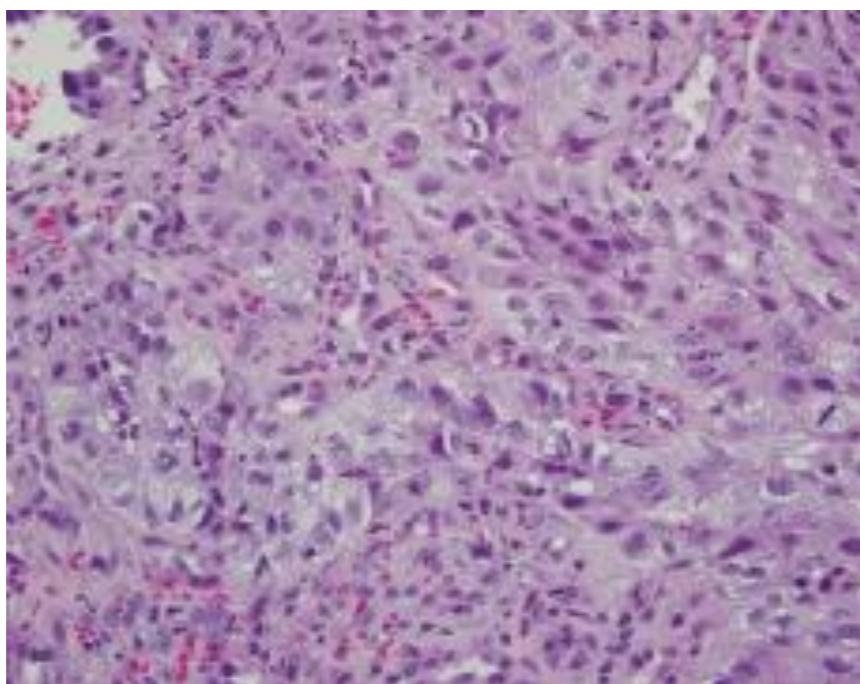
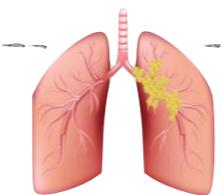


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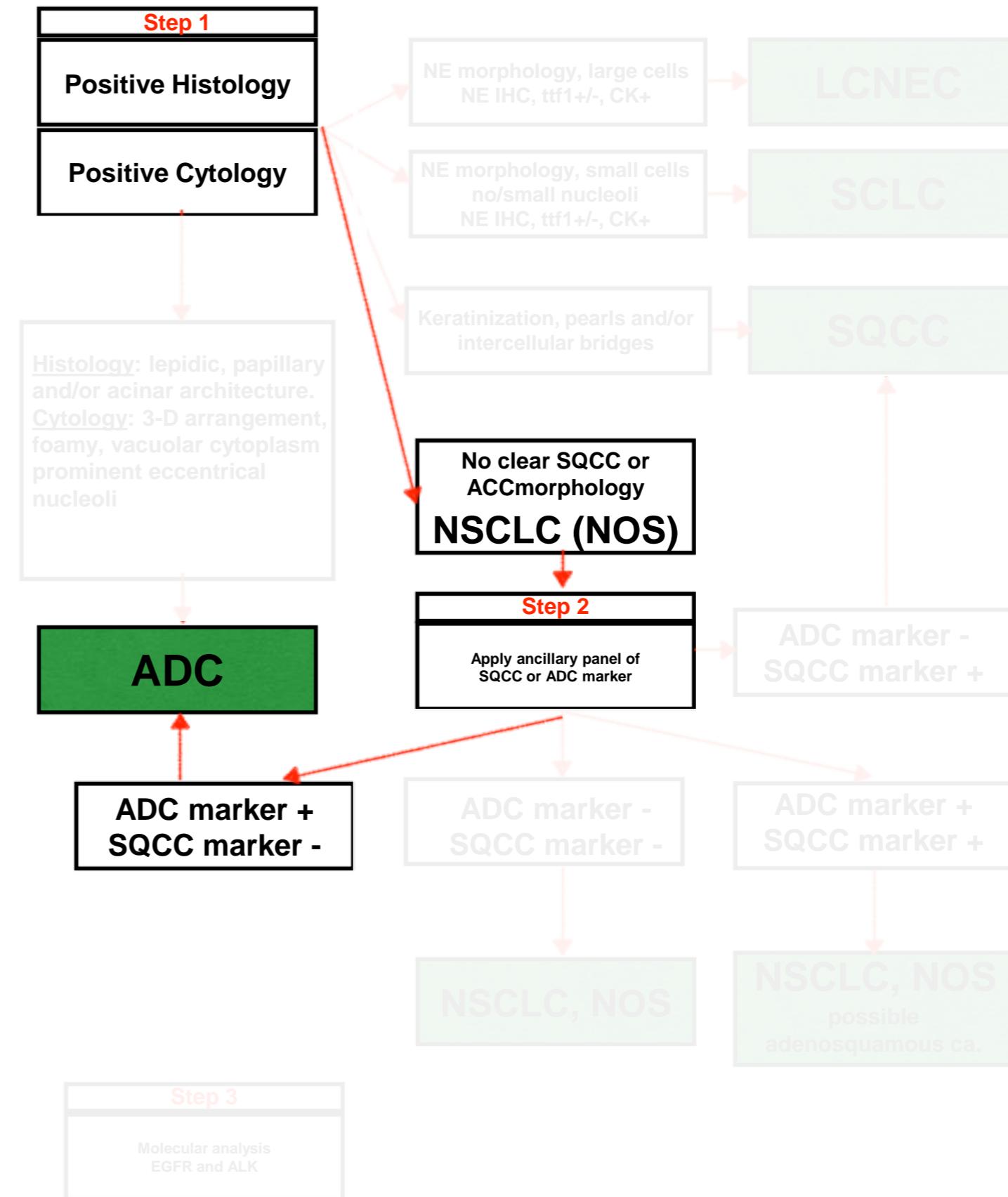
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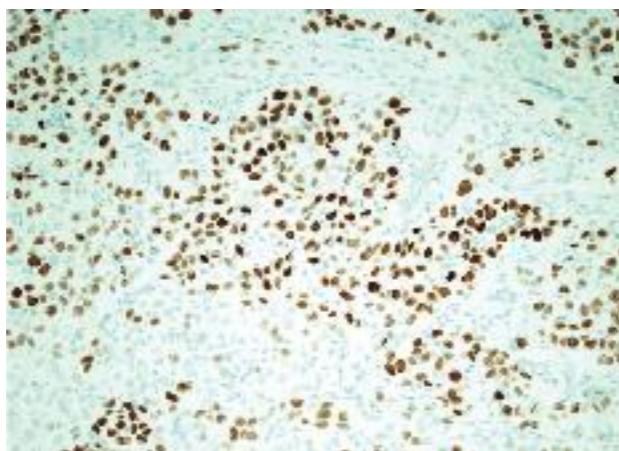
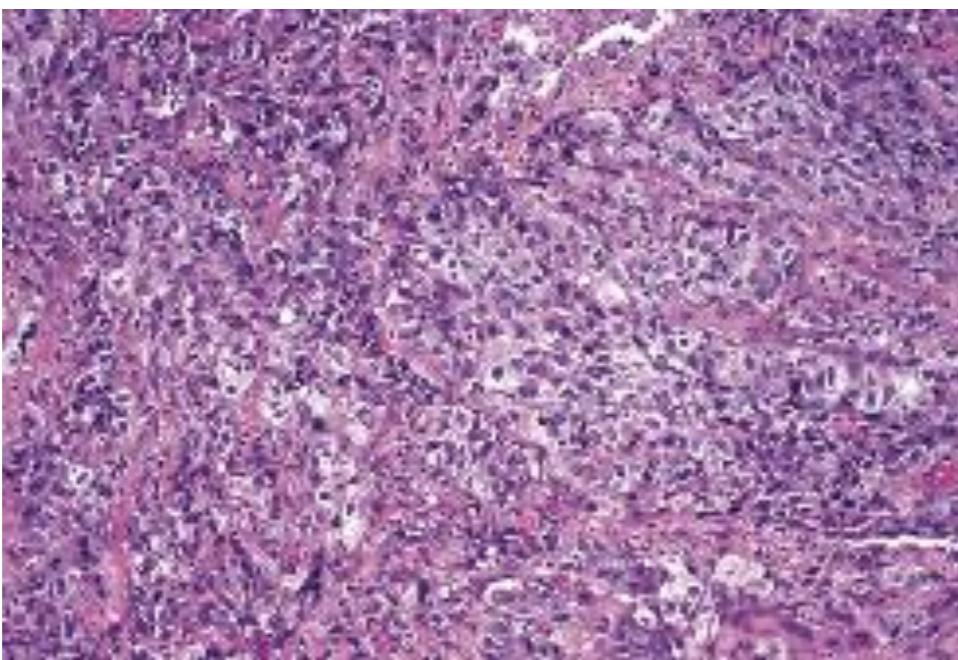
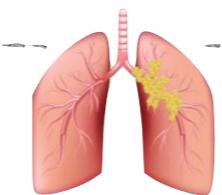




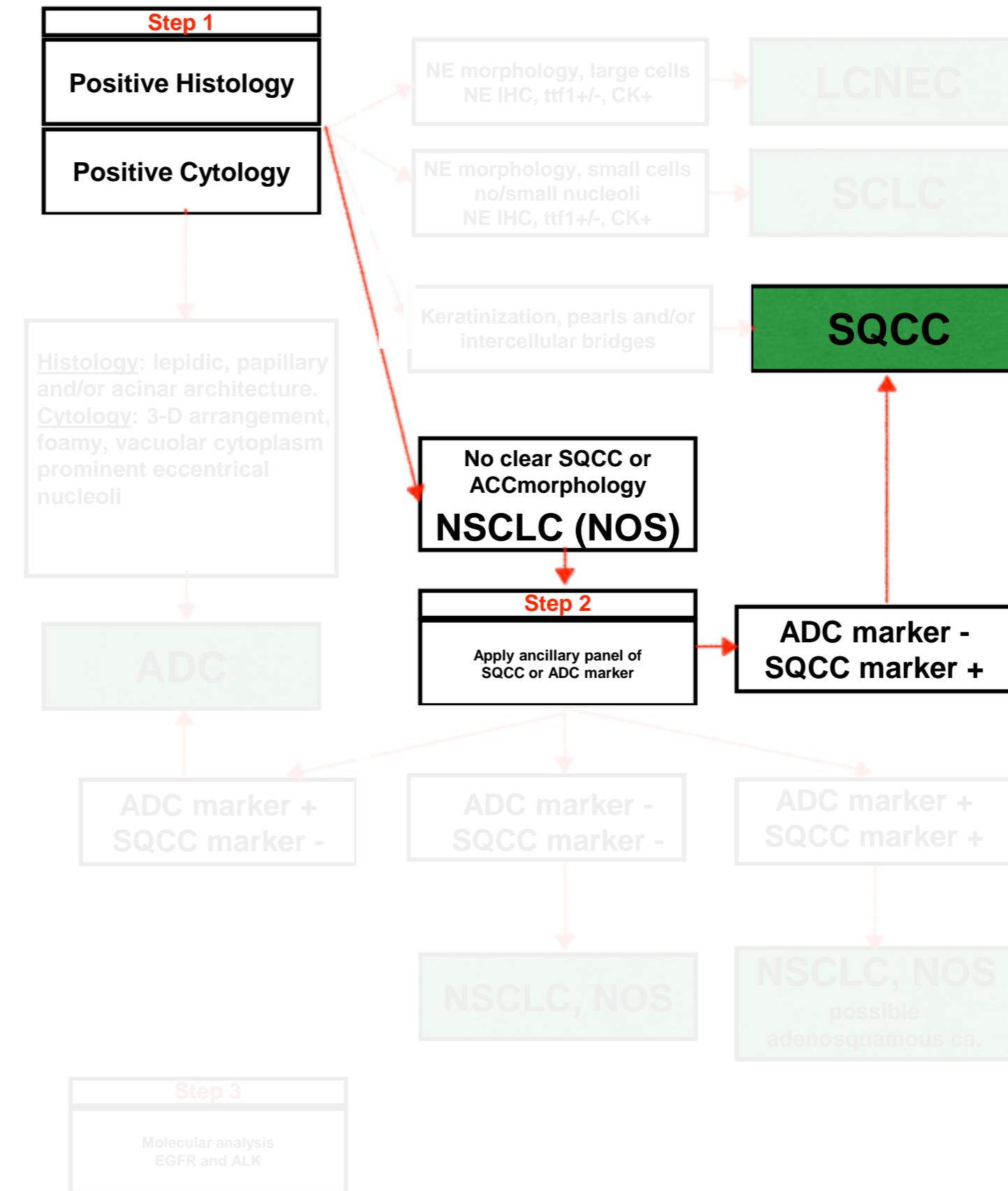
ttf1+

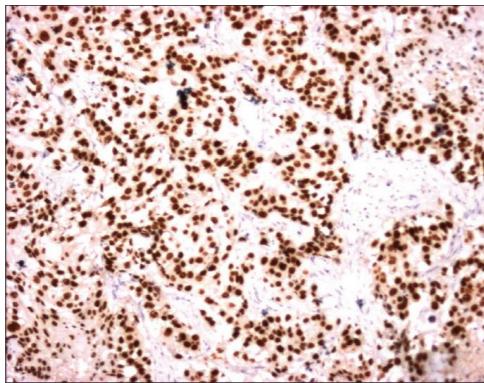
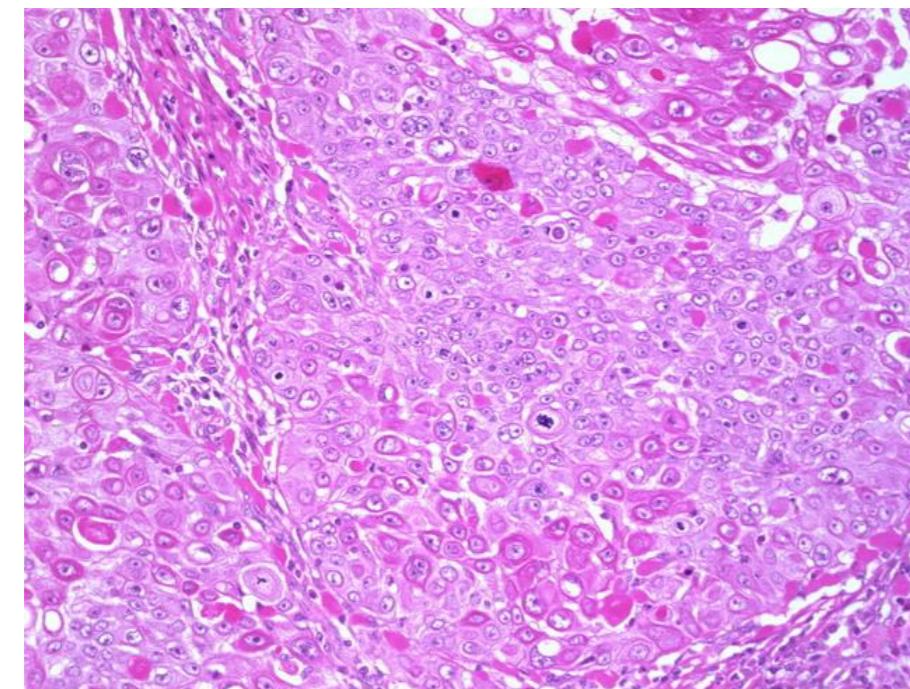
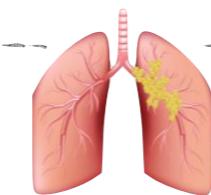
(+Cytokeratin 7)



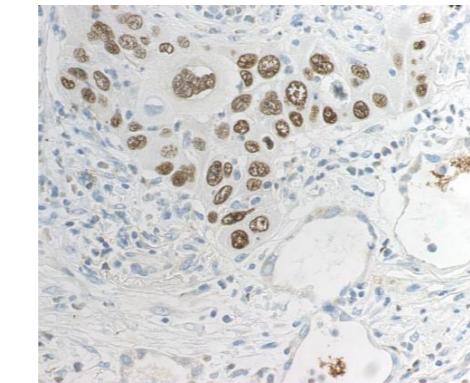


P63+ (+Cytokeratin 5/6)

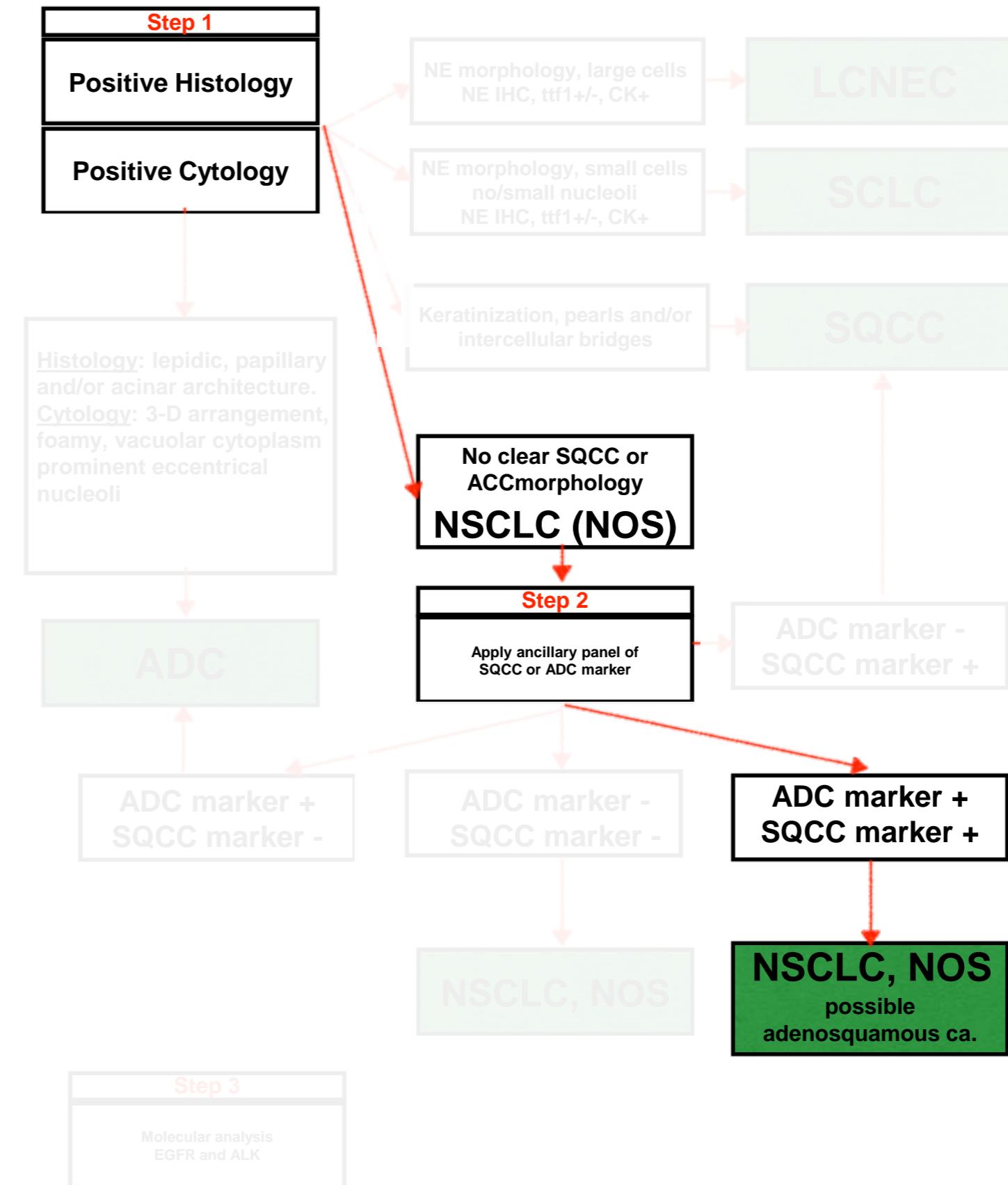


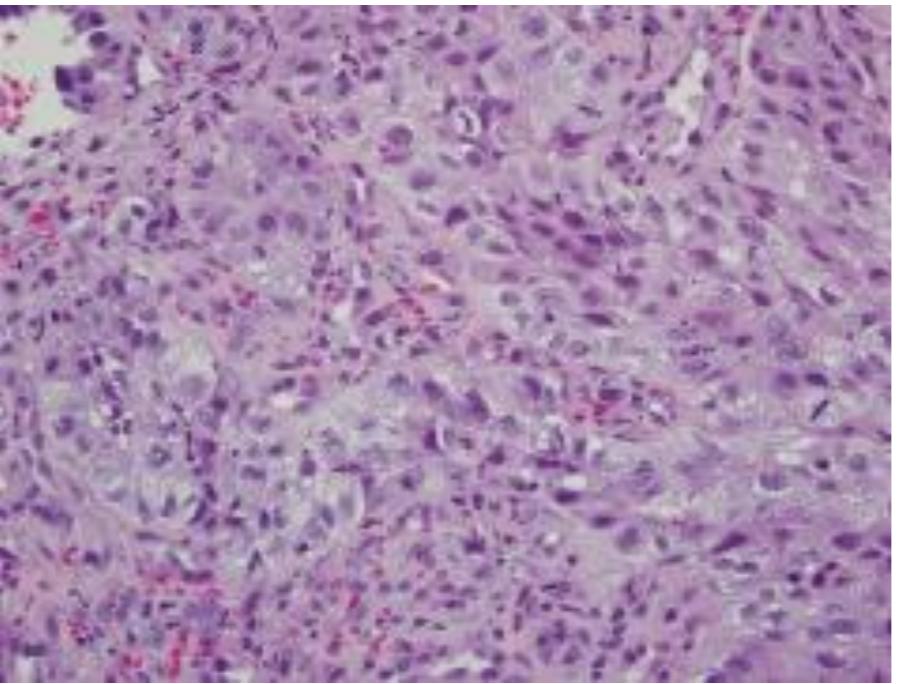
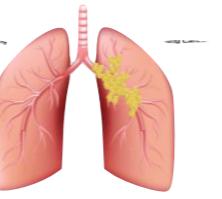


ttf1+



P63+





CK7

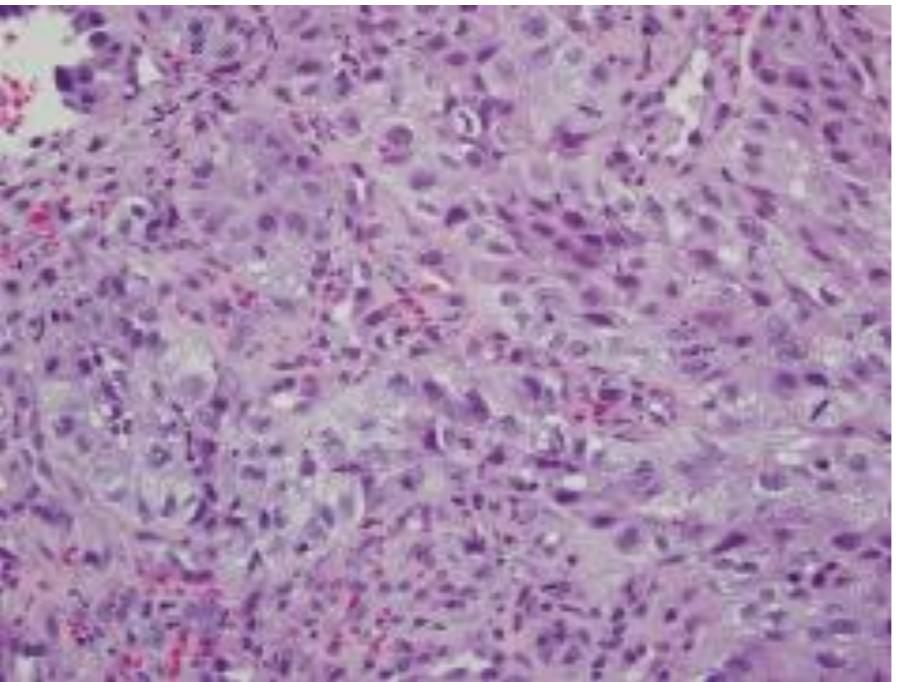
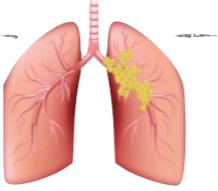
ttf1

Napsin

CK5/6

Adenocarcinoma

P63



CK7

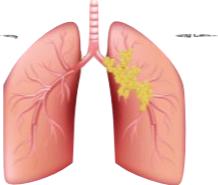
ttf1

Napsin

CK5/6

P63

Squamous
carcinoma



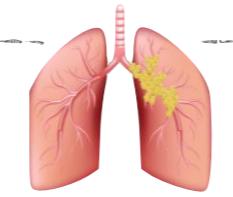
Problems:

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

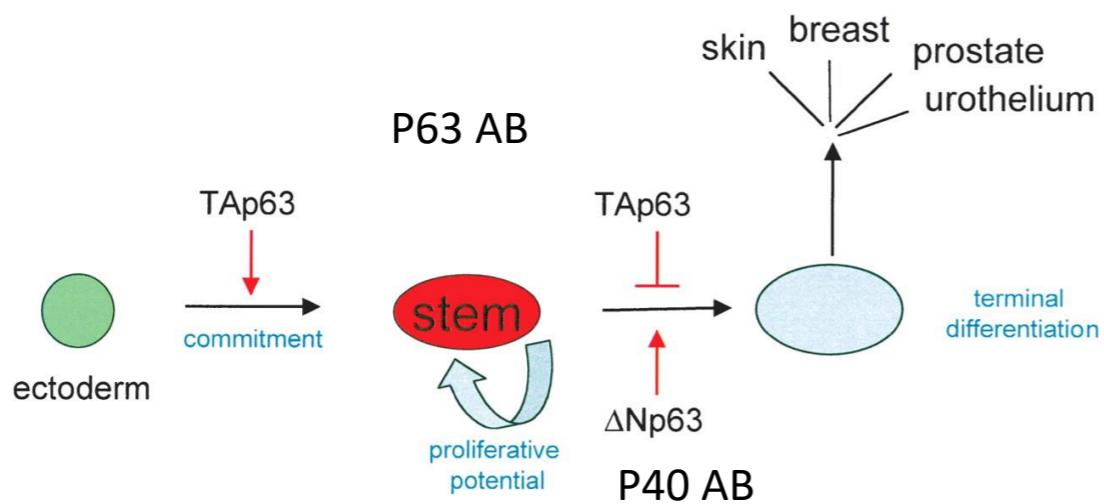
Takahiro Tatsumori, MD,*† Koji Tsuta, MD, PhD,* Kyohei Masai, MD,* Tomoaki Kinno, MD,*
Tomoko Taniyama, MD,* Akihiko Yoshida, MD, PhD,* Kenji Suzuki, MD, PhD,†
and Hitoshi Tsuda, MD, PhD*



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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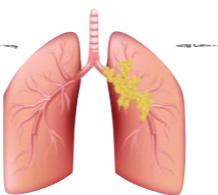


Table 2. Sensitivity, specificity, PPV and NPV of markers used in this study [% (positive/total stained)]

Marker	Subtype	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ΔNp63(p40)	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.

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Original Article
ΔNp63, CK5/6, TTF-1 and napsin A, a reliable panel to subtype non-small cell lung cancer in biopsy specimens

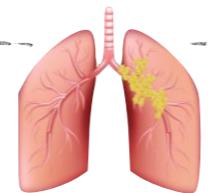


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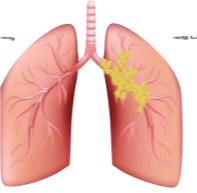
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ΔNp63(p40)	SCC	100 (16/16)	100 (32/32)	100 (16/16)	100 (32/32)
p63	SCC	100 (16/16)	88 (28/32)	80 (16/20)	100 (28/28)
CK5/6	SCC	81 (13/16)	100 (32/32)	100 (13/13)	91 (32/35)
34βE12	SCC	94 (15/16)	47 (15/32)	47 (15/32)	94 (15/16)
TTF1	AC	80 (20/25)	87 (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.

Int J Clin Exp Pathol 2014;7(7):4247-4253
www.ijcep.com /ISSN:1936-2625/IJCEP0000624

Original Article

ΔNp63, CK5/6, TTF-1 and napsin A, a reliable panel to subtype non-small cell lung cancer in biopsy specimens

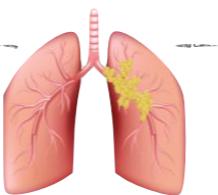


Problems:



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

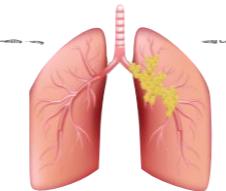
NS: not significant


NIH Public Access
Author Manuscript
Appl Immunohistochem Mol Morphol. Author manuscript; available in PMC 2011 March 1.

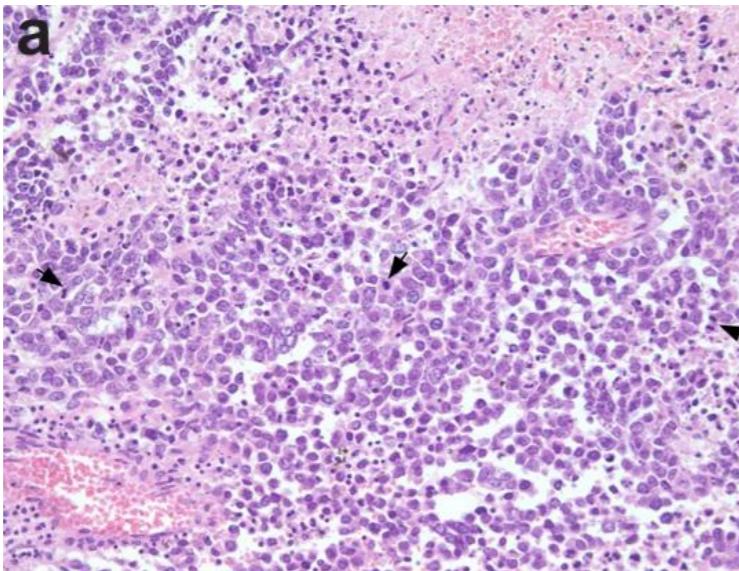
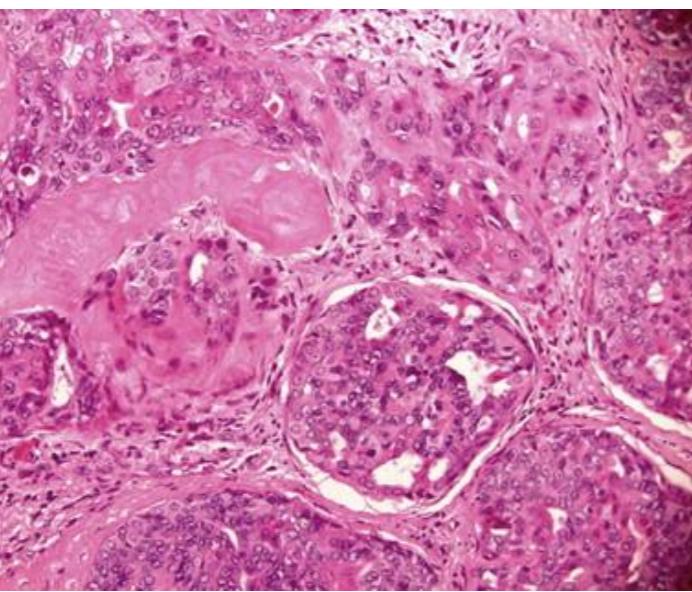
Published in final edited form as:
Appl Immunohistochem Mol Morphol. 2010 March ; 18(2): 142–149. doi:10.1097/PAI.0b013e3181bd4e7.

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.



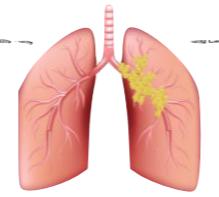
Diagnosis of metastasis
to the lung



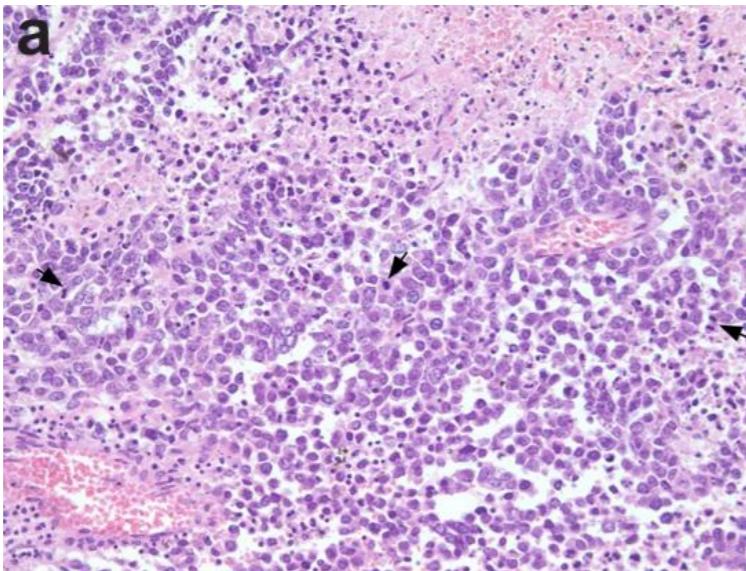
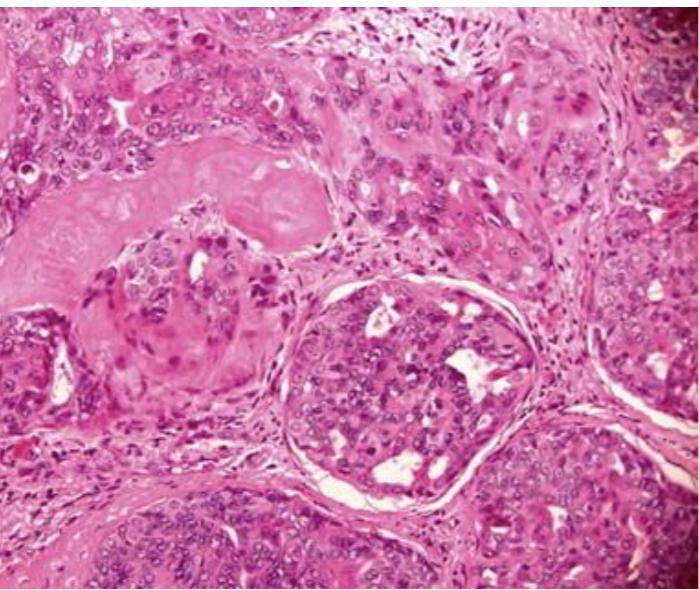
AE1/AE3 ←
CK7
ttf1
CK20 ←
cdx2 ←
SATB2 ←
NKX3.1
CK5/6
P63
CD10
PAX8
WT1
GATA3

Colon





Diagnosis of metastasis
to the lung



AE1/AE3

CK7

ttf1

CK20

cdx2

SATB2

NKX3.1

CK5/6

P63

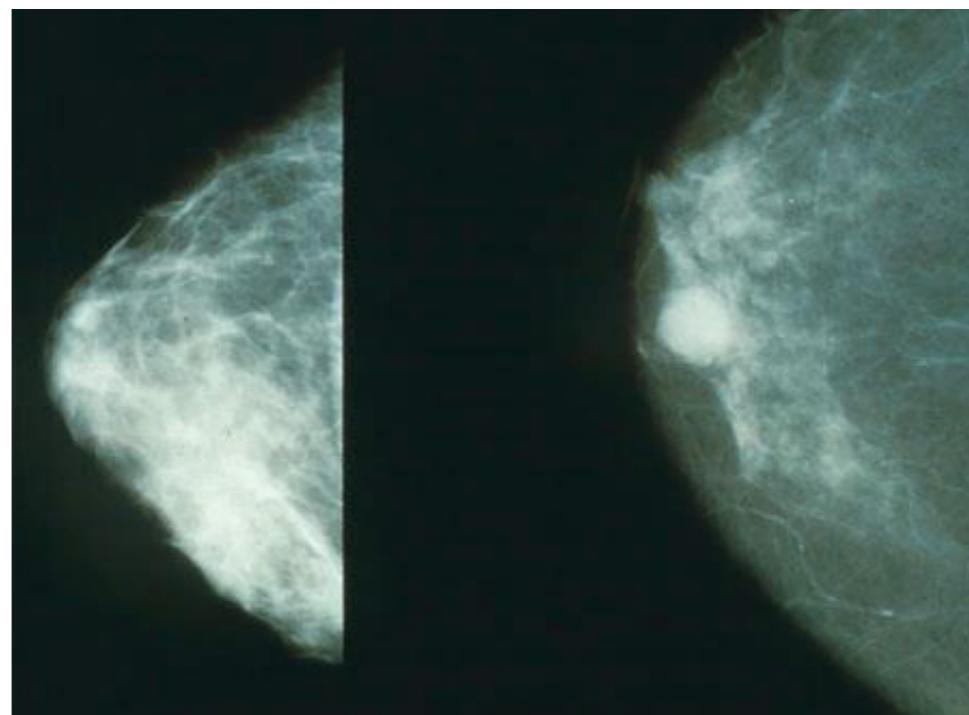
CD10

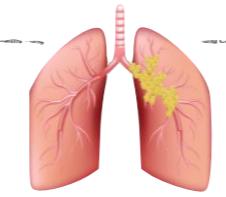
PAX8

WT1

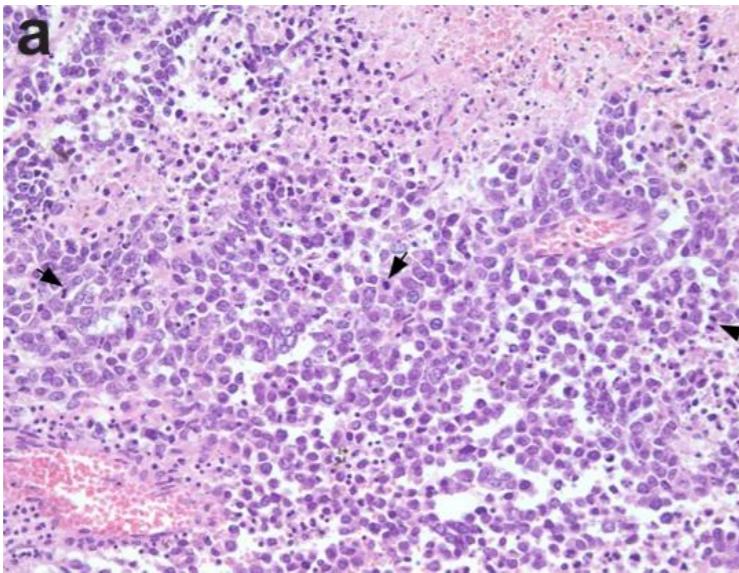
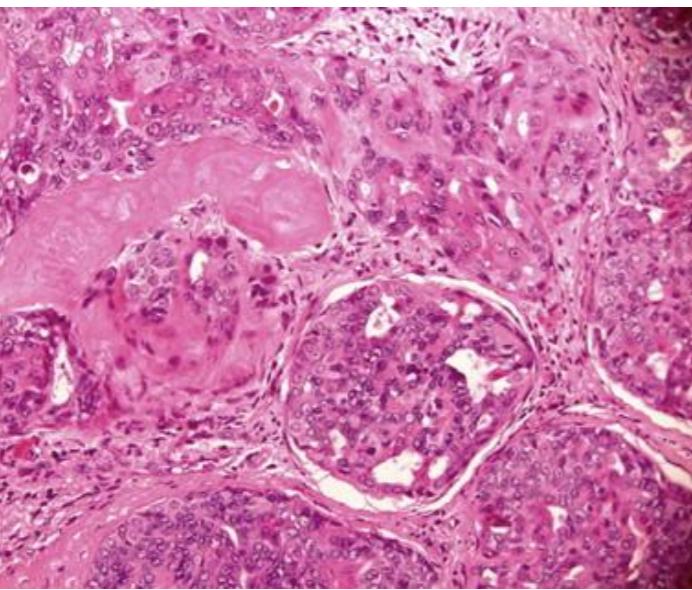
GATA3

Mamma





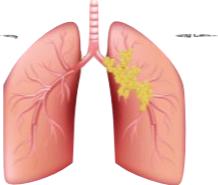
Diagnosis of metastasis
to the lung



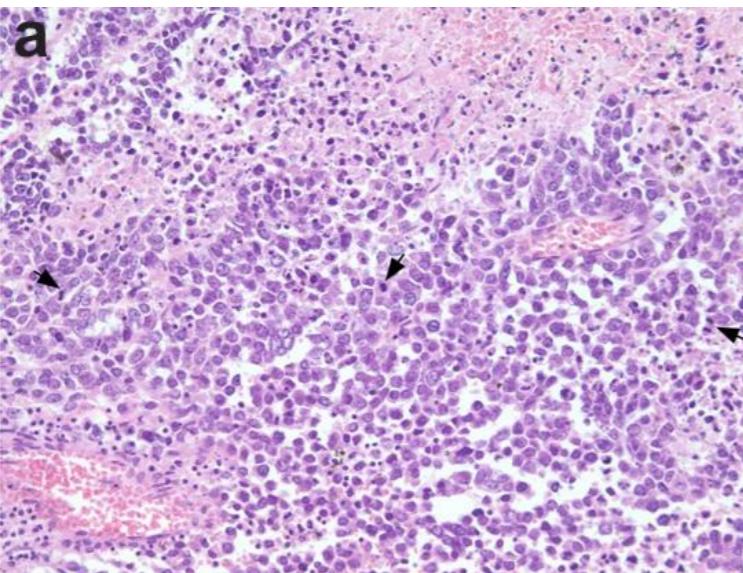
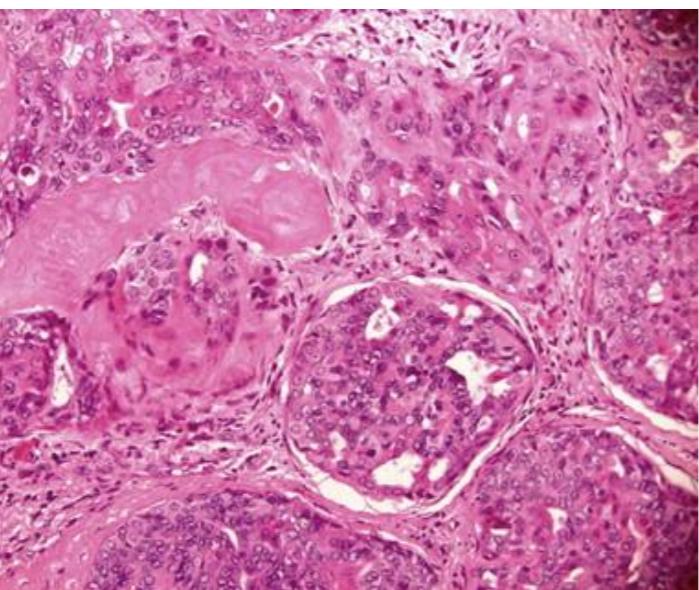
AE1/AE3
CK7
ttf1
CK20
cdx2
SATB2
NKX3.1
CK5/6
P63
CD10
PAX8
WT1
GATA3

Upper GI





Diagnosis of metastasis
to the lung



AE1/AE3 ←

CK7 ←

ttf1

CK20 ←

cdx2

SATB2

NKX3.1

CK5/6 ←

P63 ←

CD10

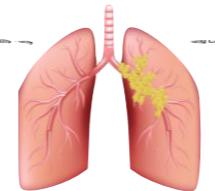
PAX8

WT1

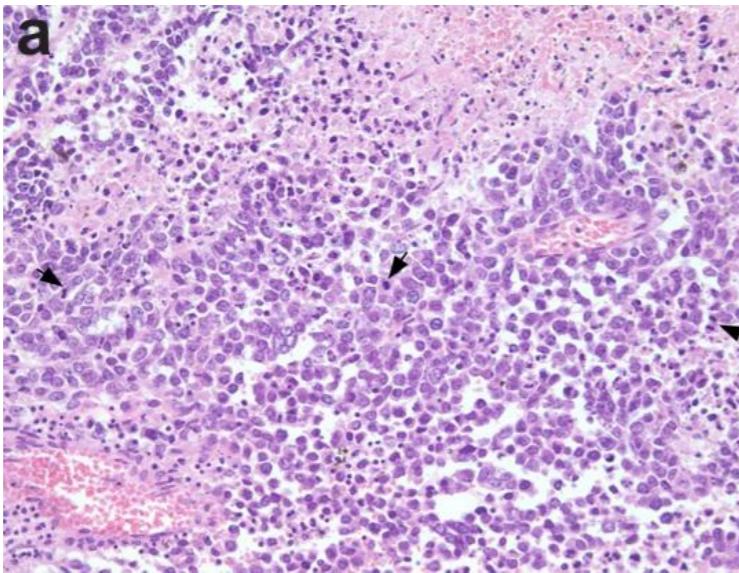
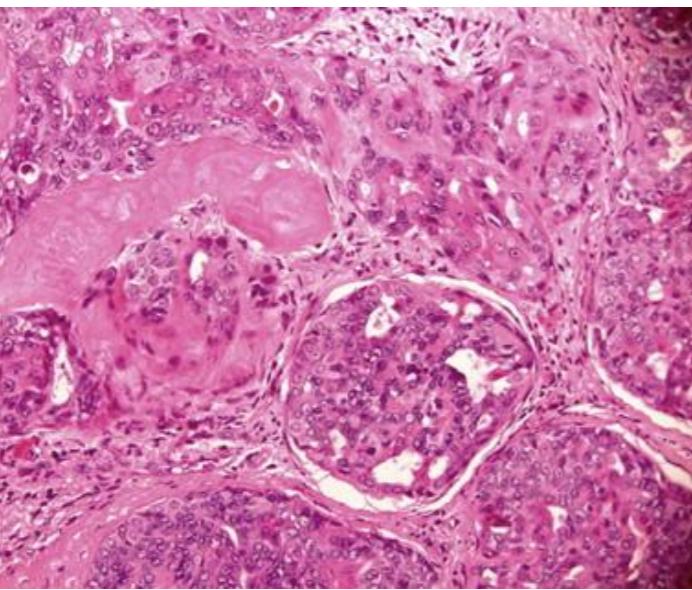
GATA3 ←

Urothelial carcinoma





Diagnosis of metastasis
to the lung



AE1/AE3 ←

CK7

ttf1

CK20

cdx2

SATB2

NKX3.1

CK5/6

P63

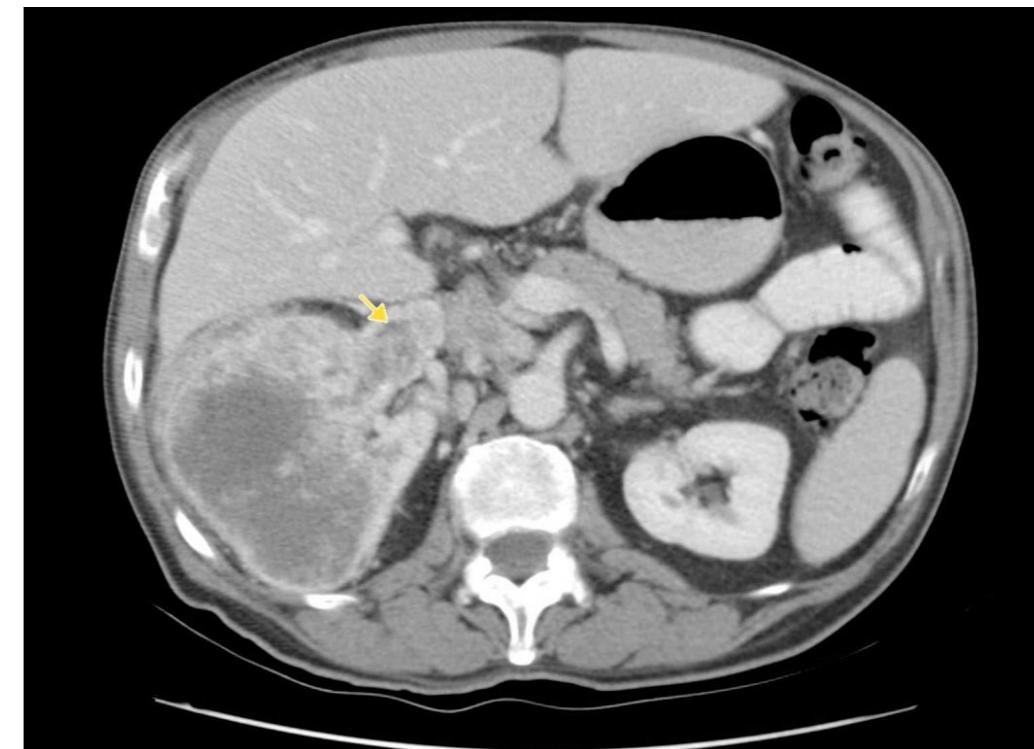
CD10 ←

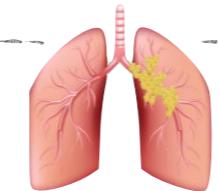
PAX8 ←

WT1

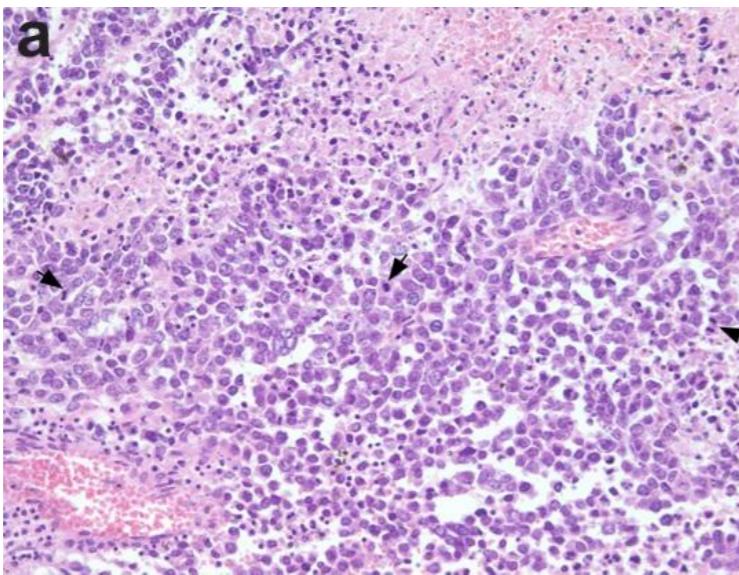
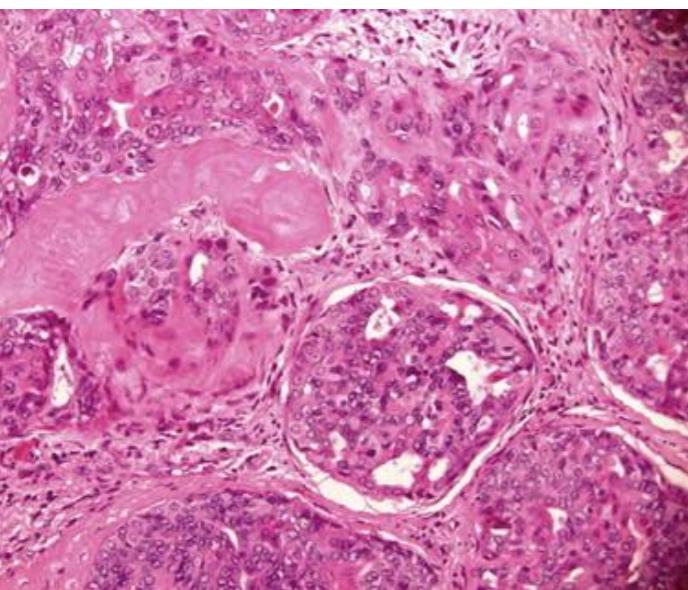
GATA3

Renal cell carcinoma





Diagnosis of metastasis
to the lung



AE1/AE3

CK7

ttf1

CK20

cdx2

SATB2

NKX3.1

CK5/6

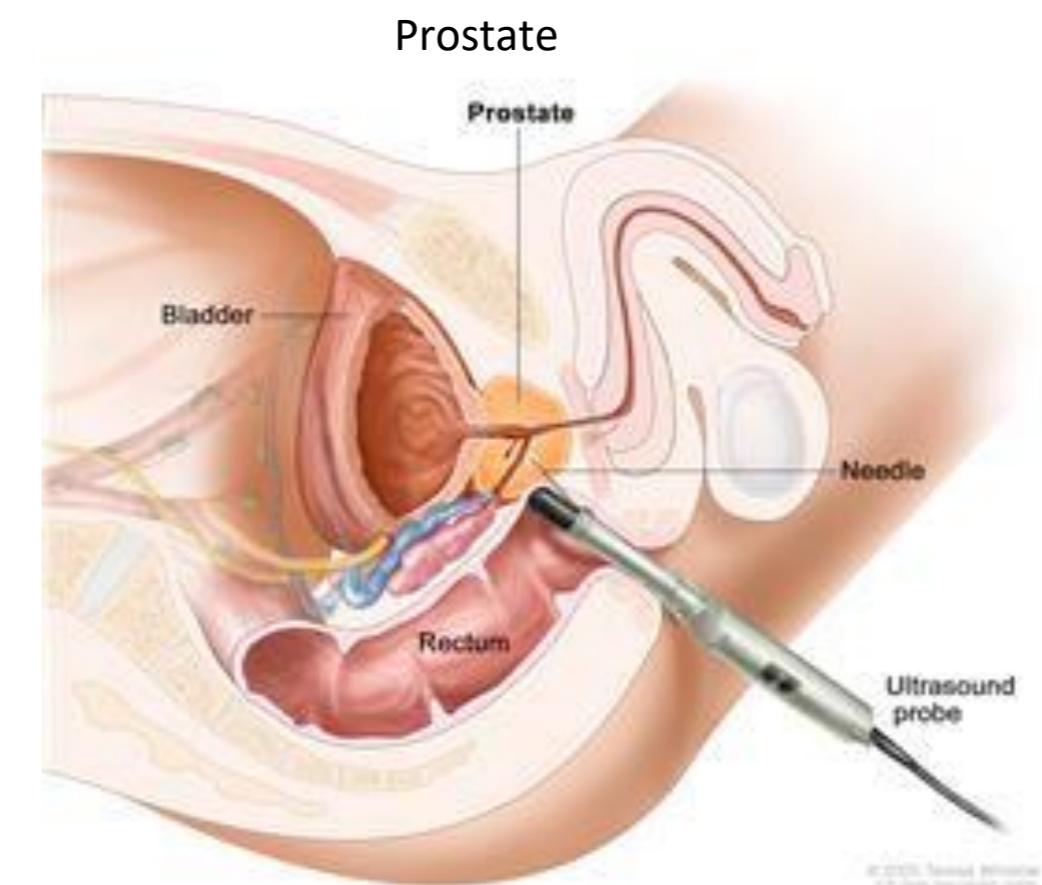
P63

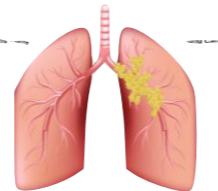
CD10

PAX8

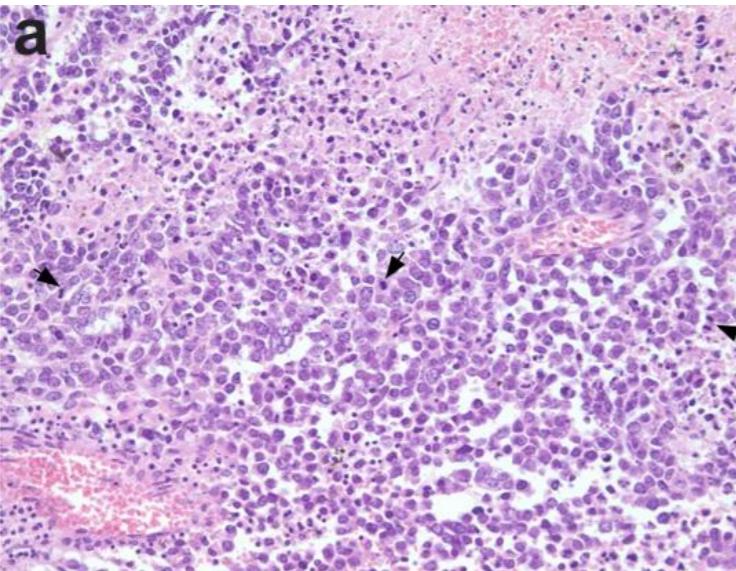
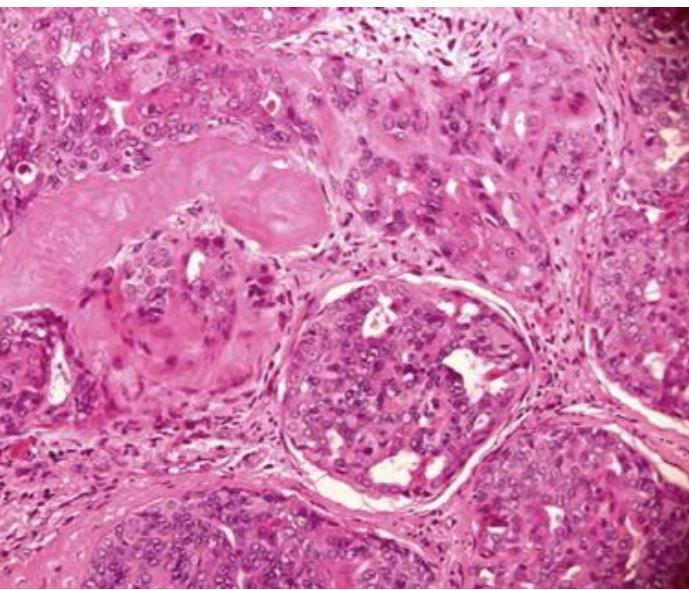
WT1

GATA3





Diagnosis of metastasis
to the lung



AE1/AE3

CK7

ttf1

CK20

cdx2

SATB2

NKX3.1

CK5/6

P63

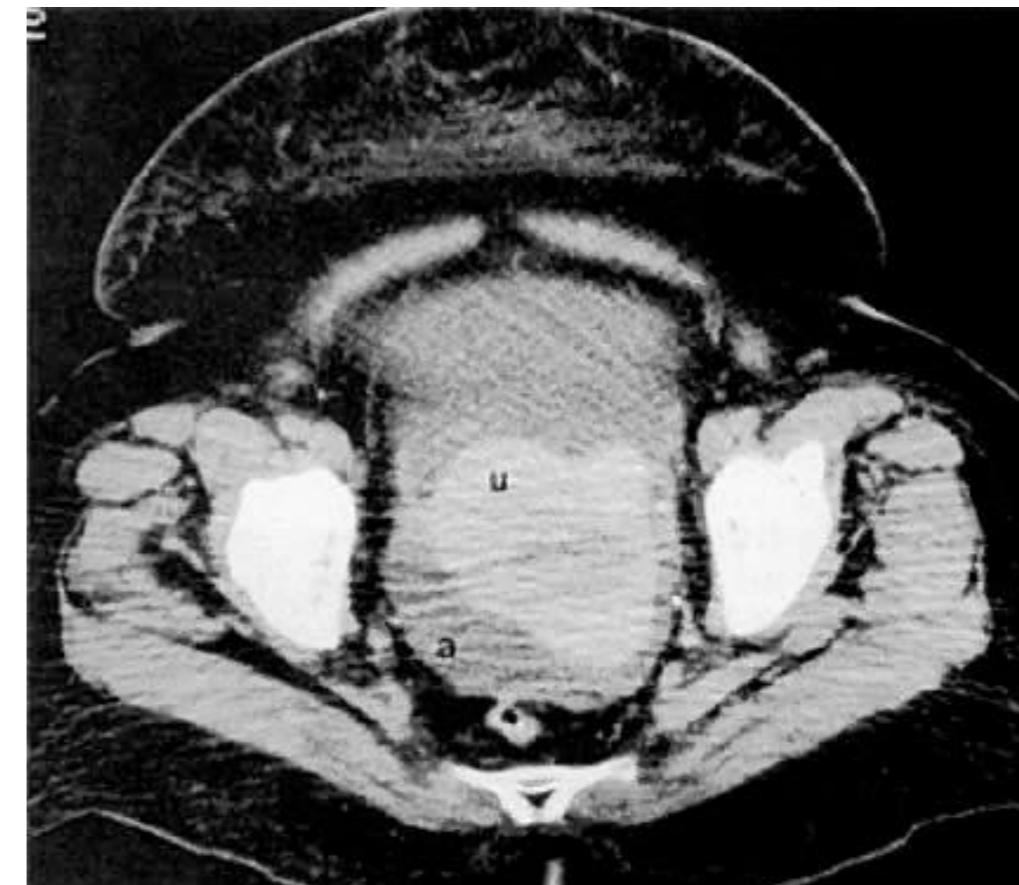
CD10

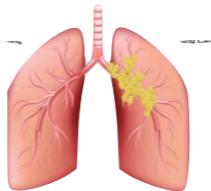
PAX8

WT1

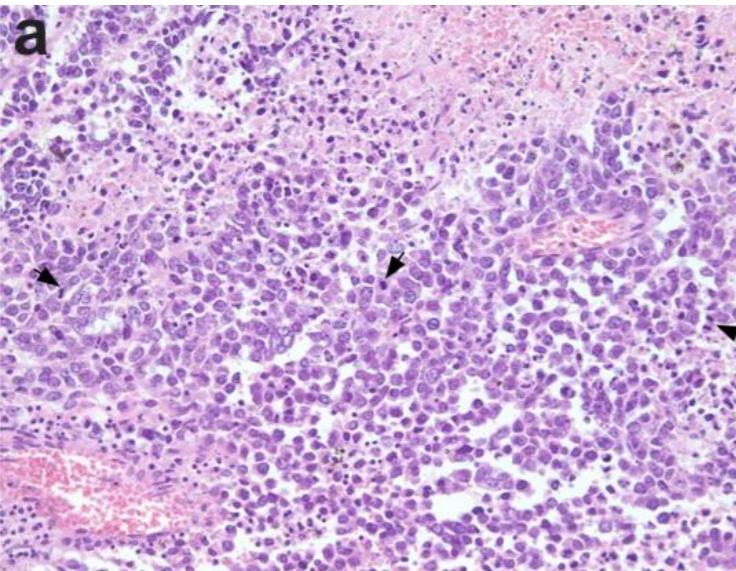
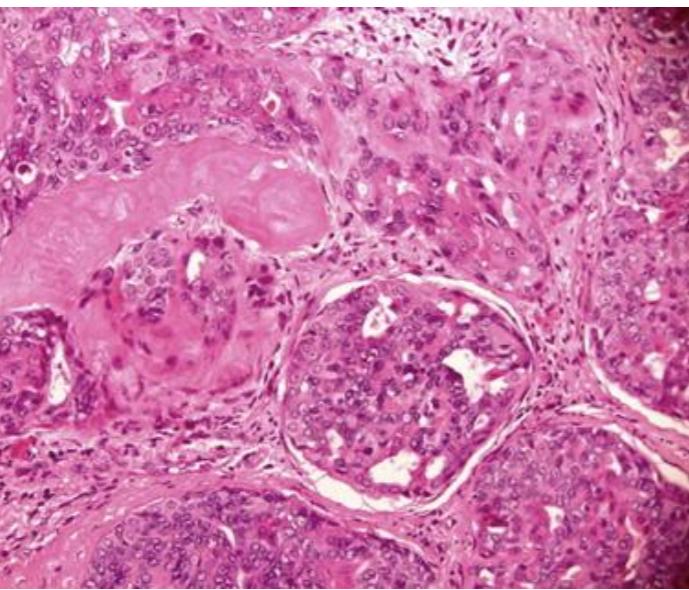
GATA3

Endometrial cancer





Diagnosis of metastasis
to the lung



AE1/AE3
CK7

ttf1

CK20

cdx2

SATB2

NKX3.1

CK5/6

P63

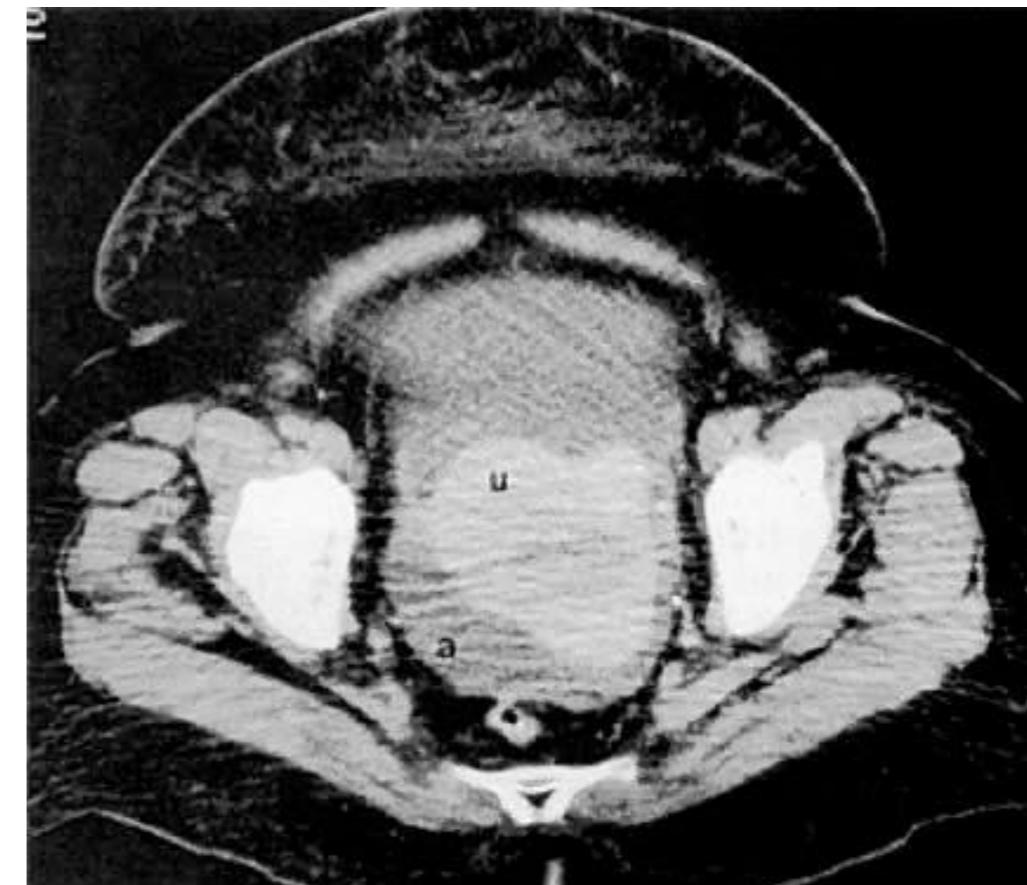
CD10

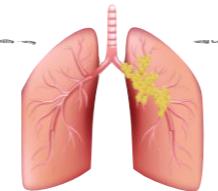
PAX8

WT1

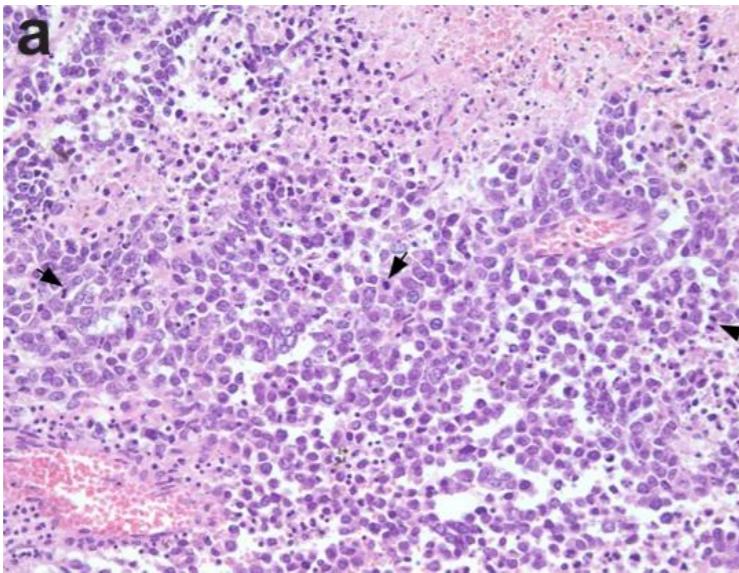
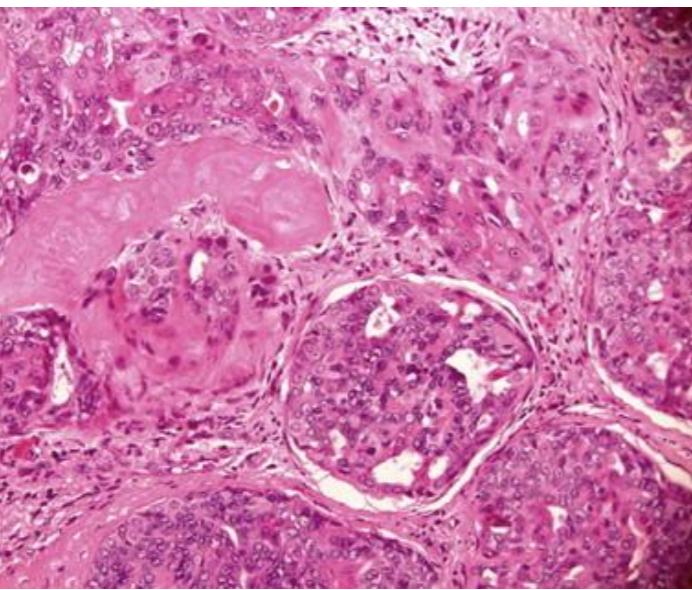
GATA3

Ovarian cancer



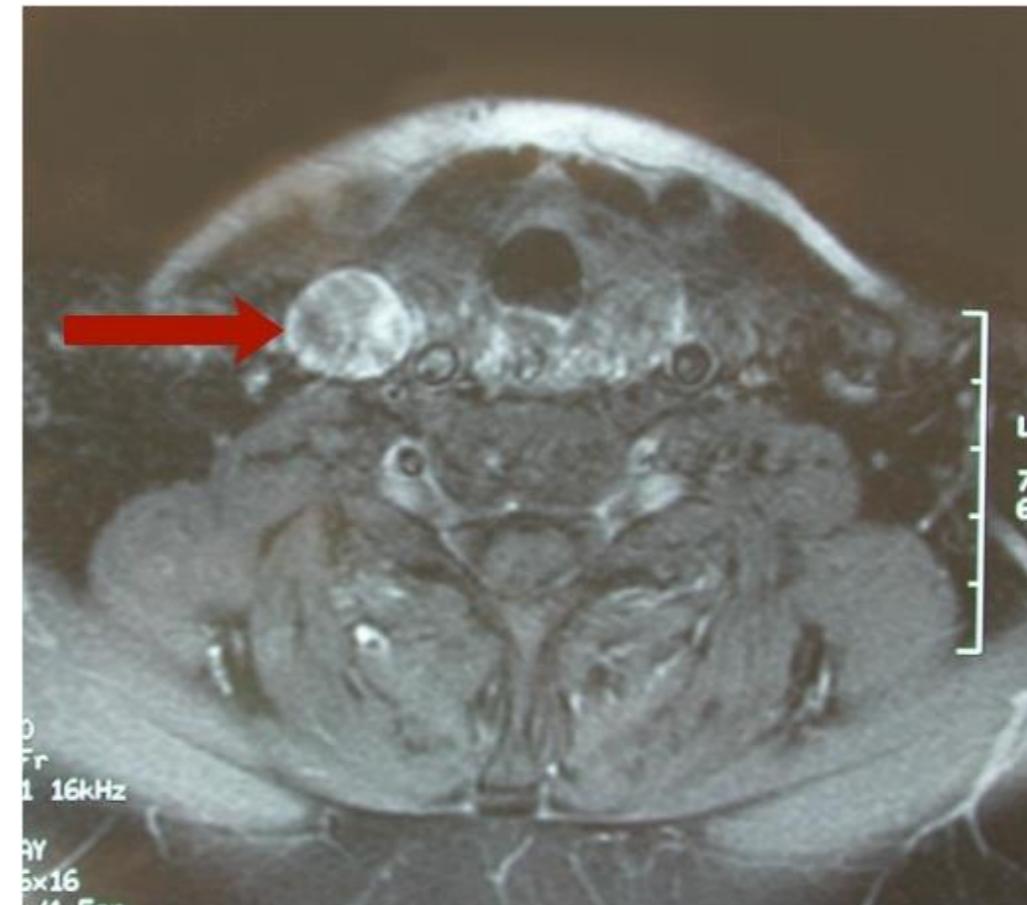


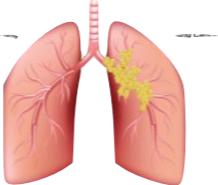
Diagnosis of metastasis
to the lung



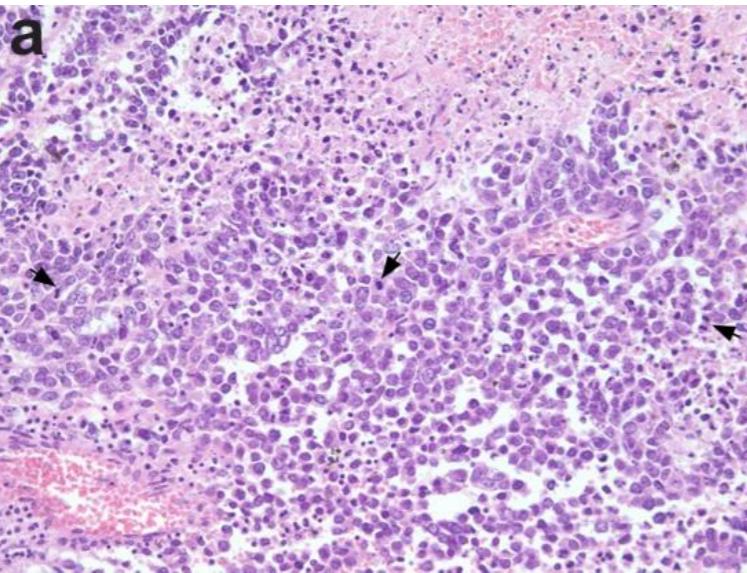
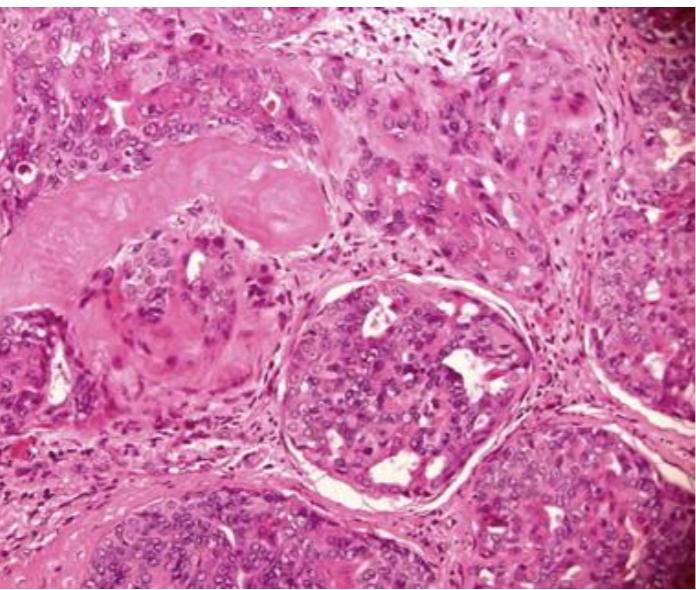
AE1/AE3 ←
CK7 ←
ttf1 ←
CK20
cdx2
SATB2
NKX3.1
CK5/6
P63
CD10 ←
PAX8
WT1
GATA3

Thyroid cancer





Mesothelioma



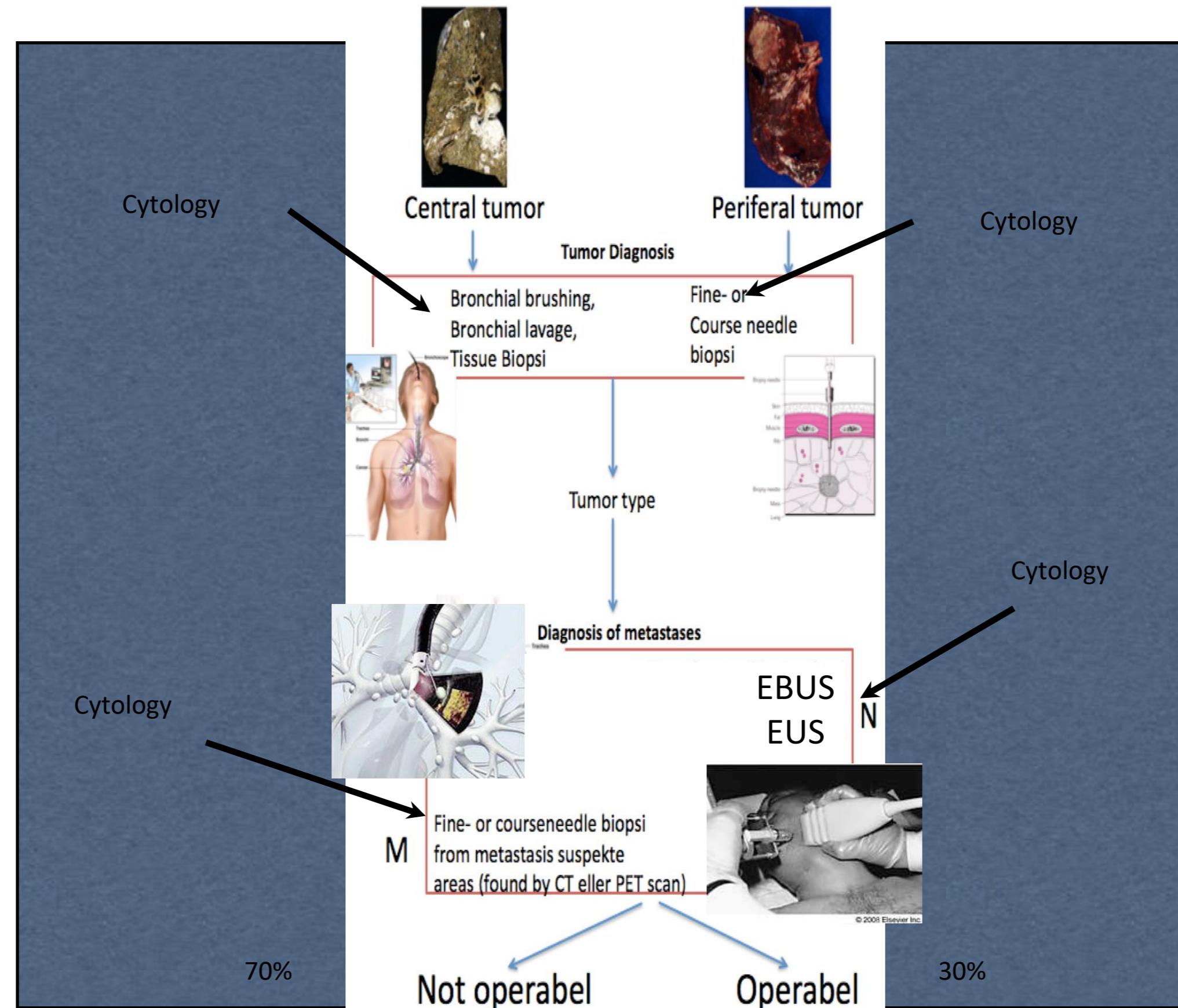
Calretinin
WT1
D2-40
CK7
Vim
CK5/6

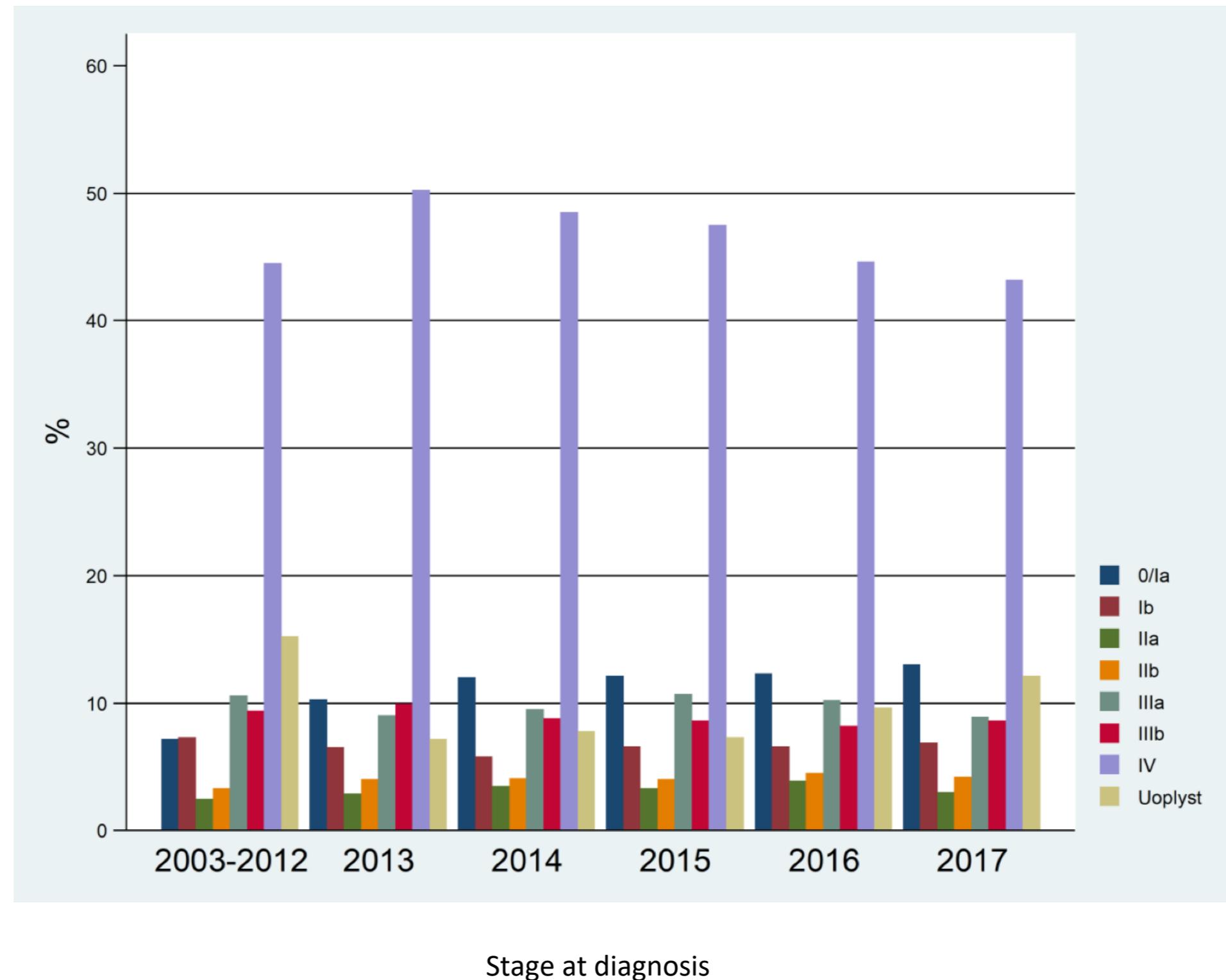
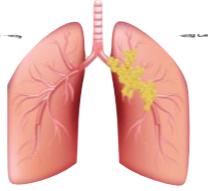


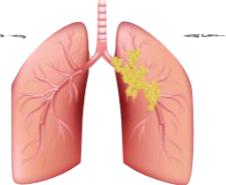


The MultiDisciplinary Teamconference MDT









Pathological specimen



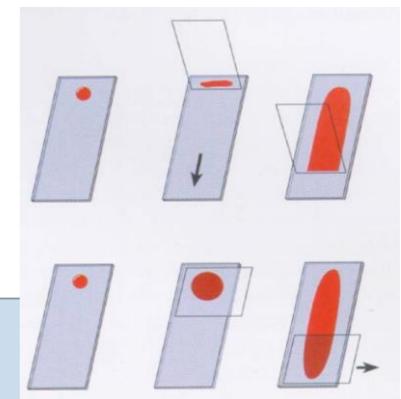
Histology



Fixation
Dehydration
Paraffinembedding
Microtomy

Preparation

Cytology

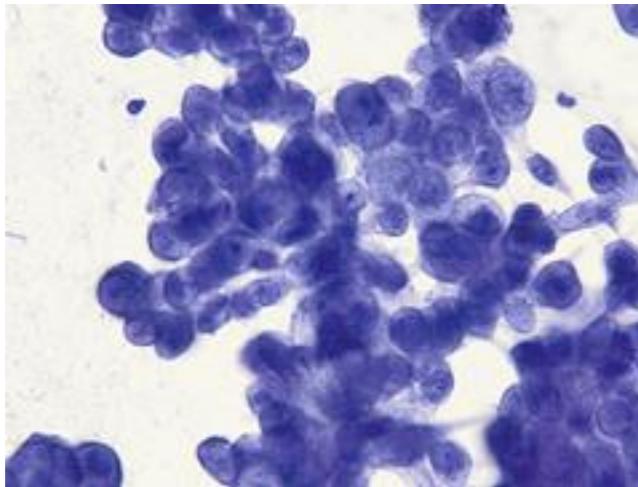
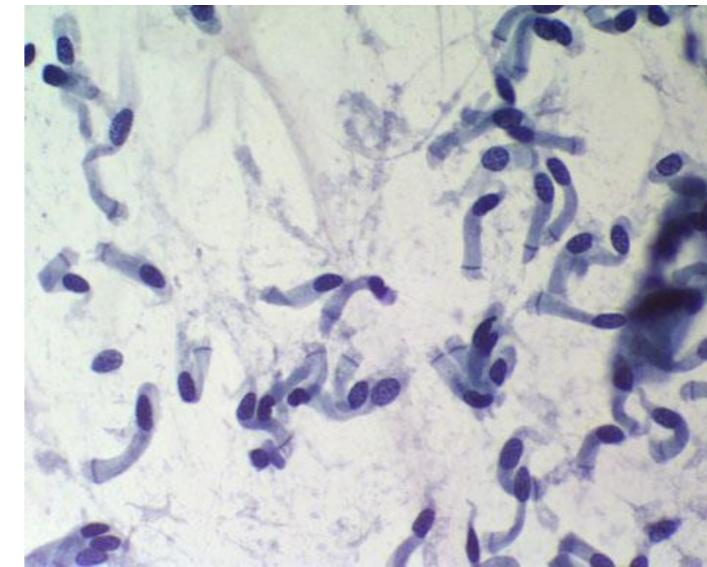
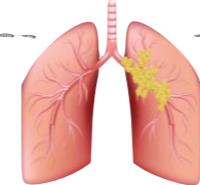


Smear preparation

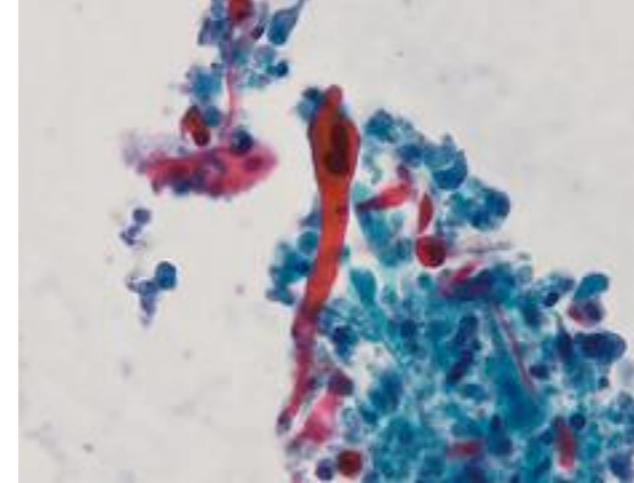


Visualization

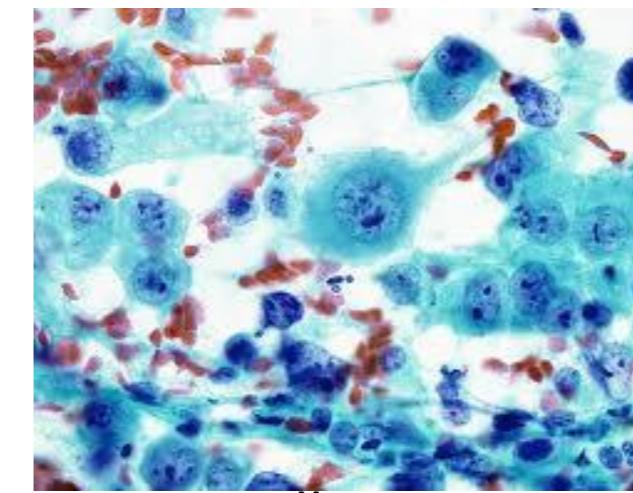
(Staining)



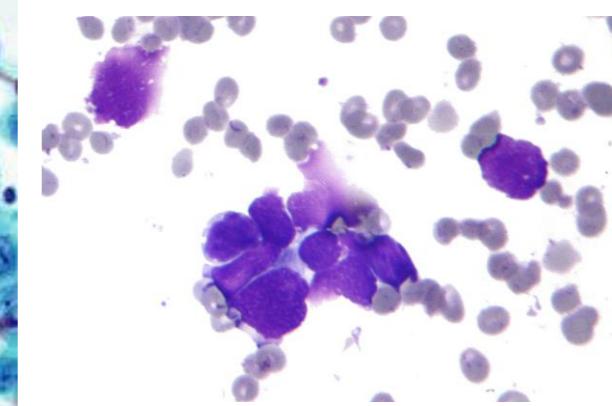
Adenocarcinoma



Squamous carcinoma



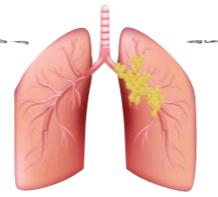
Large cell
neuroendocrine carc.



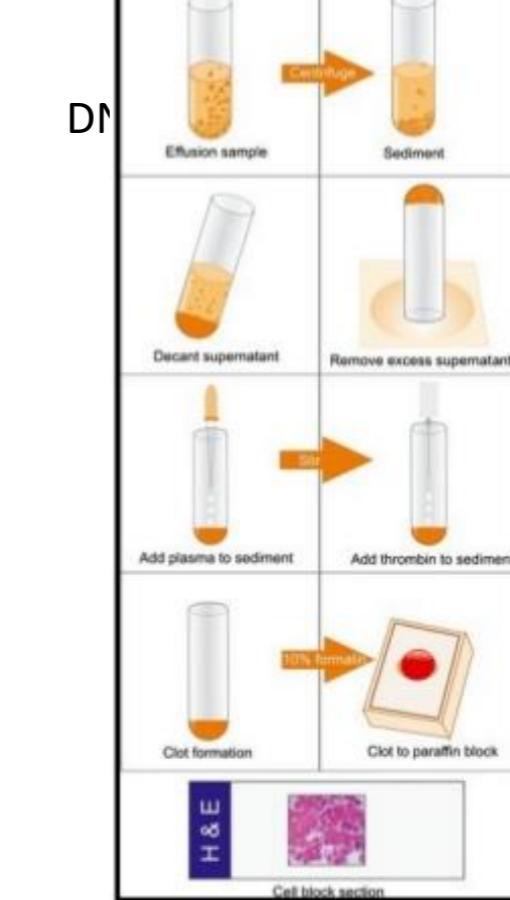
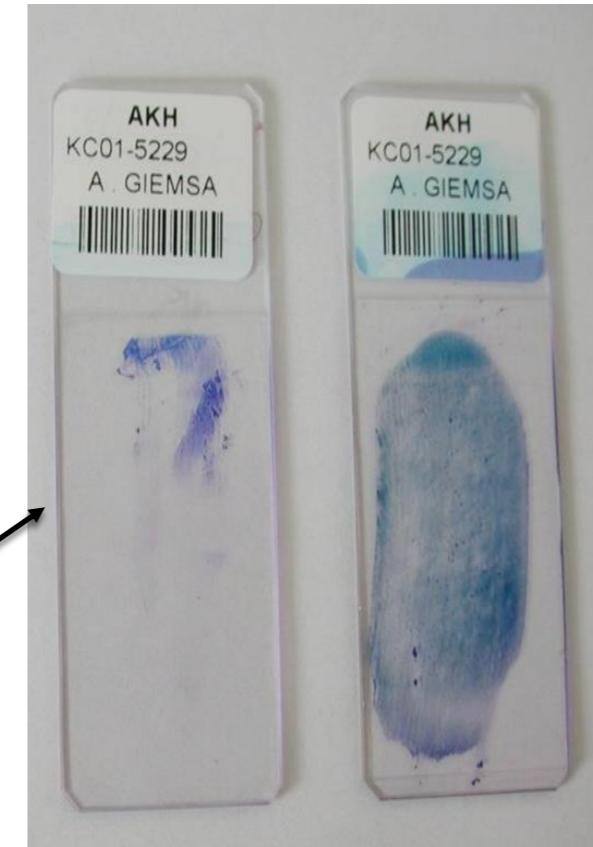
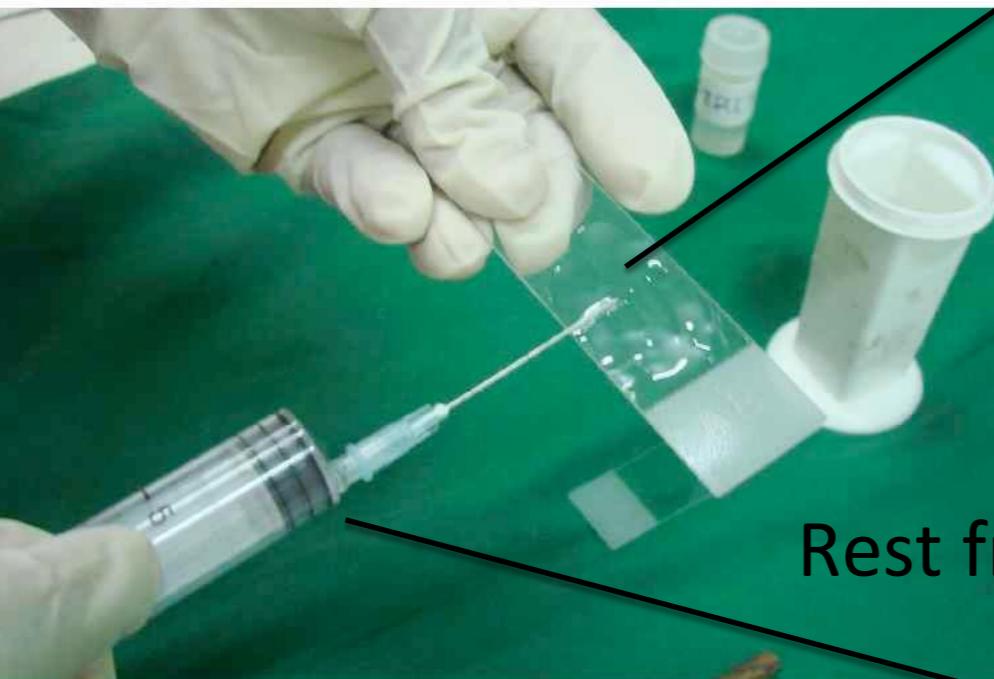
Small cell carcinoma

← →

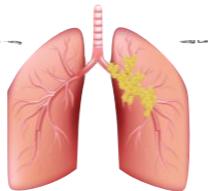
Non Small Cell Lung Carcinoma (NSCLC)



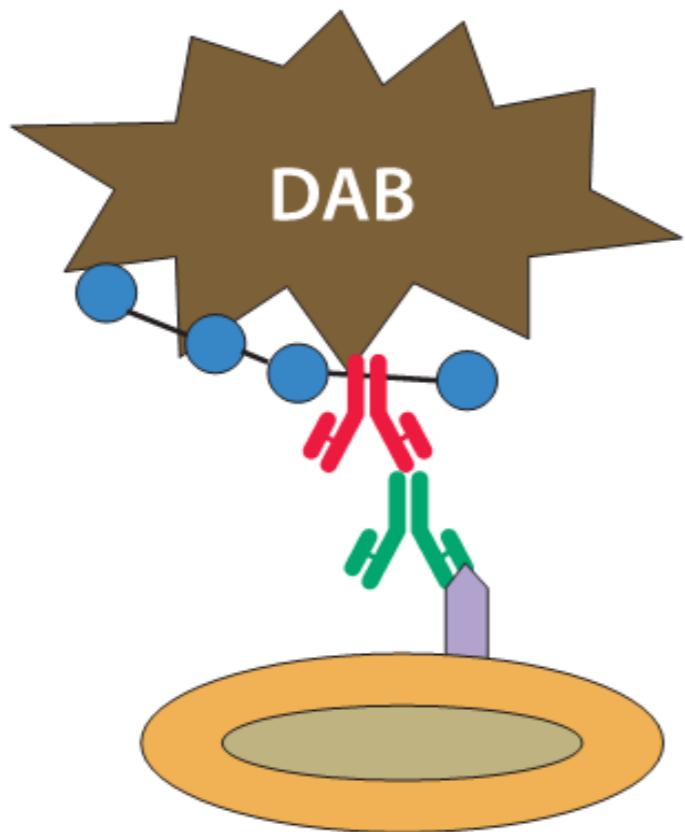
Cytology



Cellblock
Immunocytologi



Cytology



Kromogen (farvestof)

Visualiseringssystem
(enzymer)

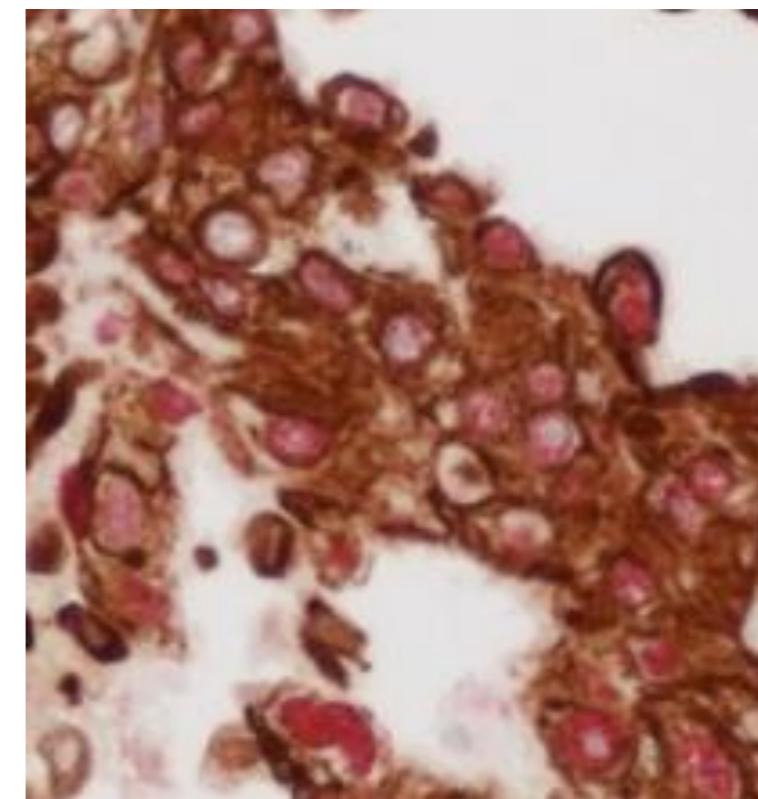
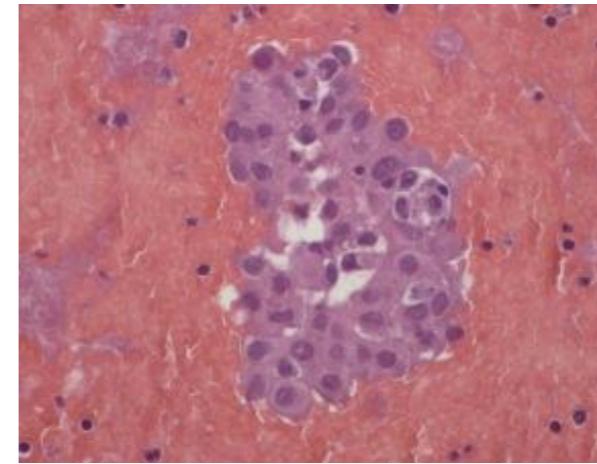
Sekundært antistof

Primært antistof

Antigen

Cellens cytoplasma

Cellekerne

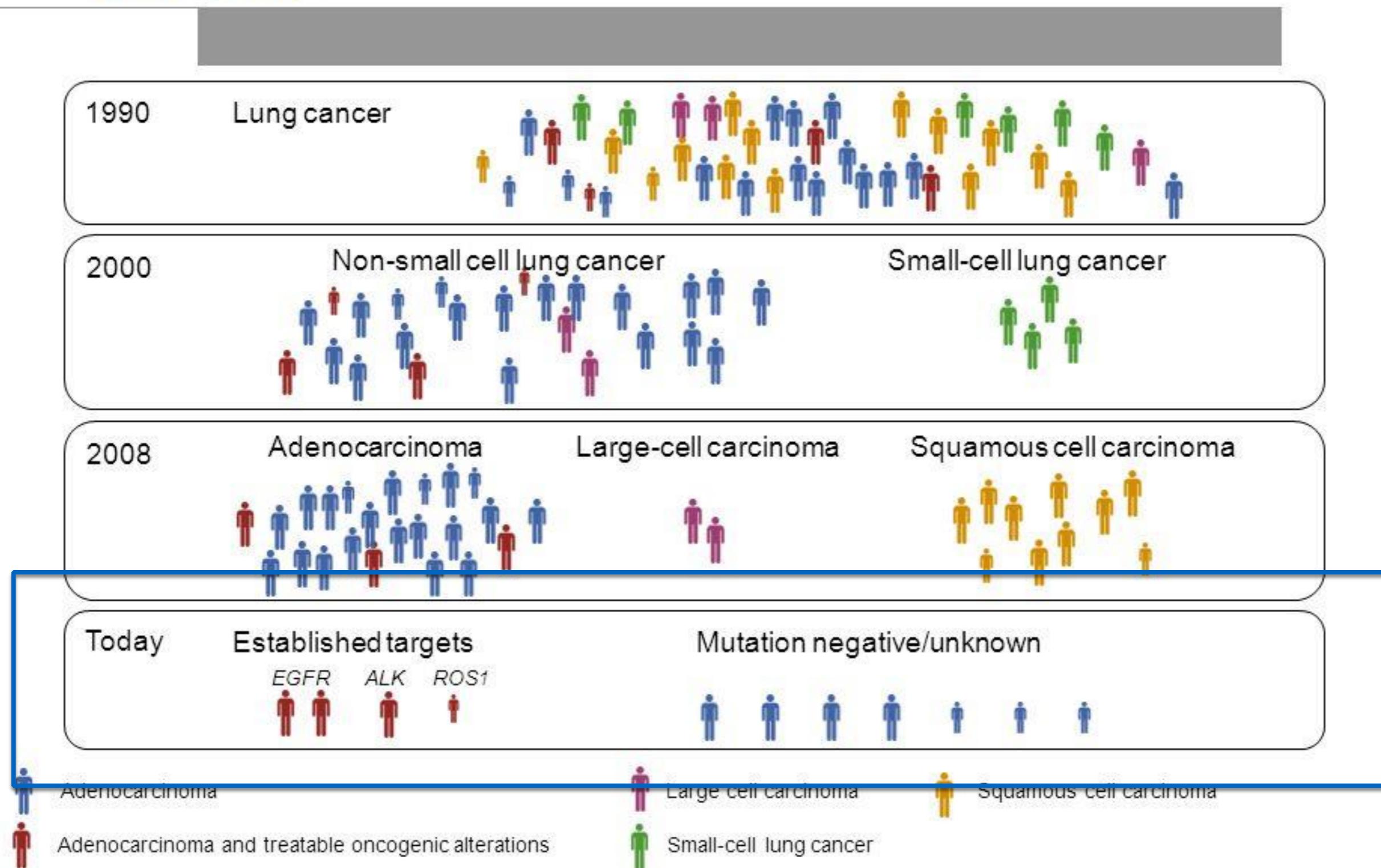


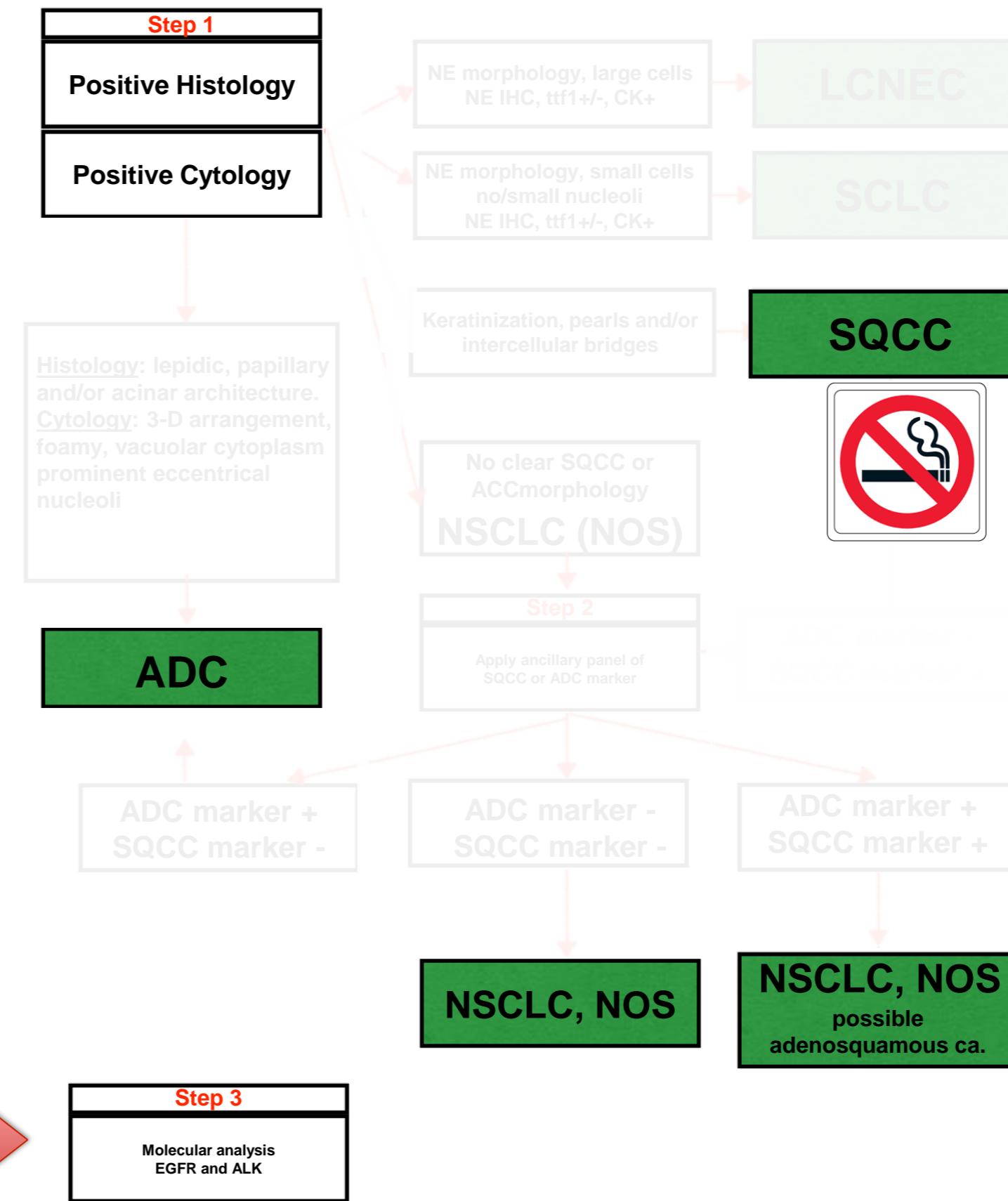
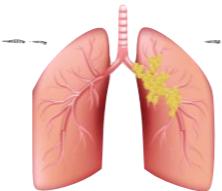
ttf1-CK7

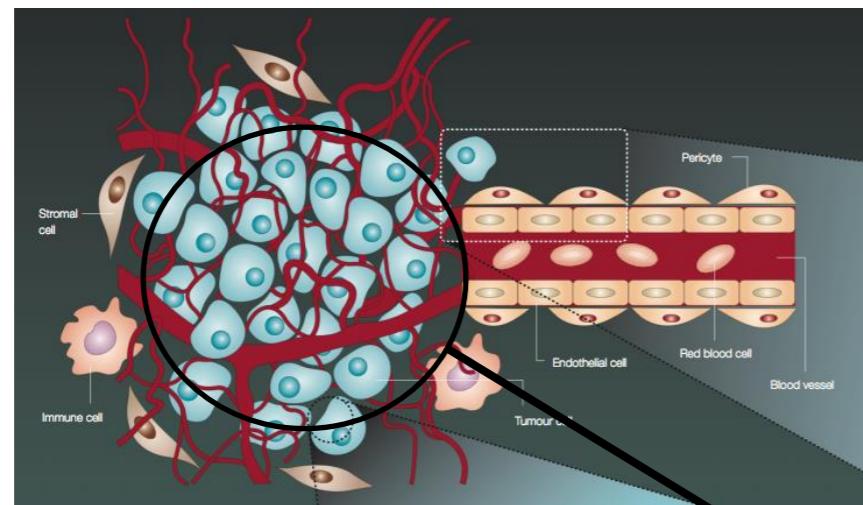
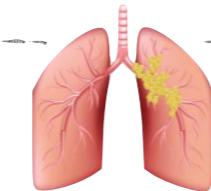
**And now
for something
completely different...**



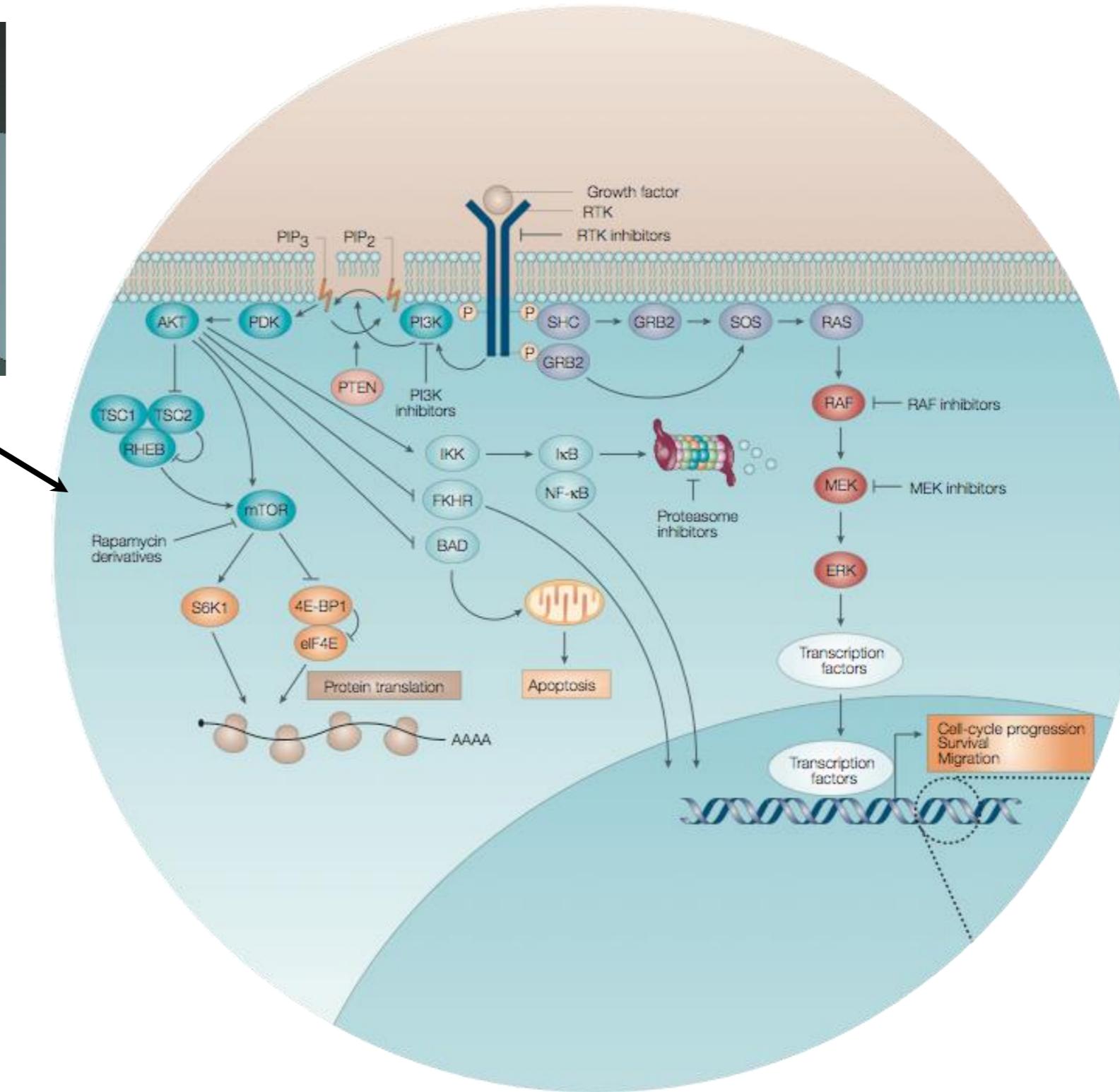
Patient selection in lung cancer: Evolution over time

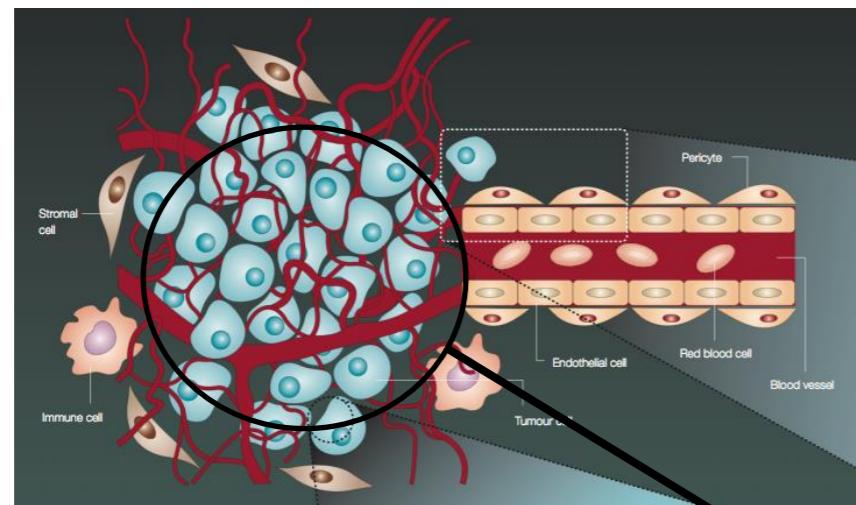
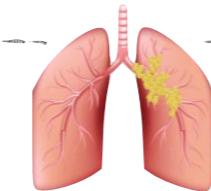




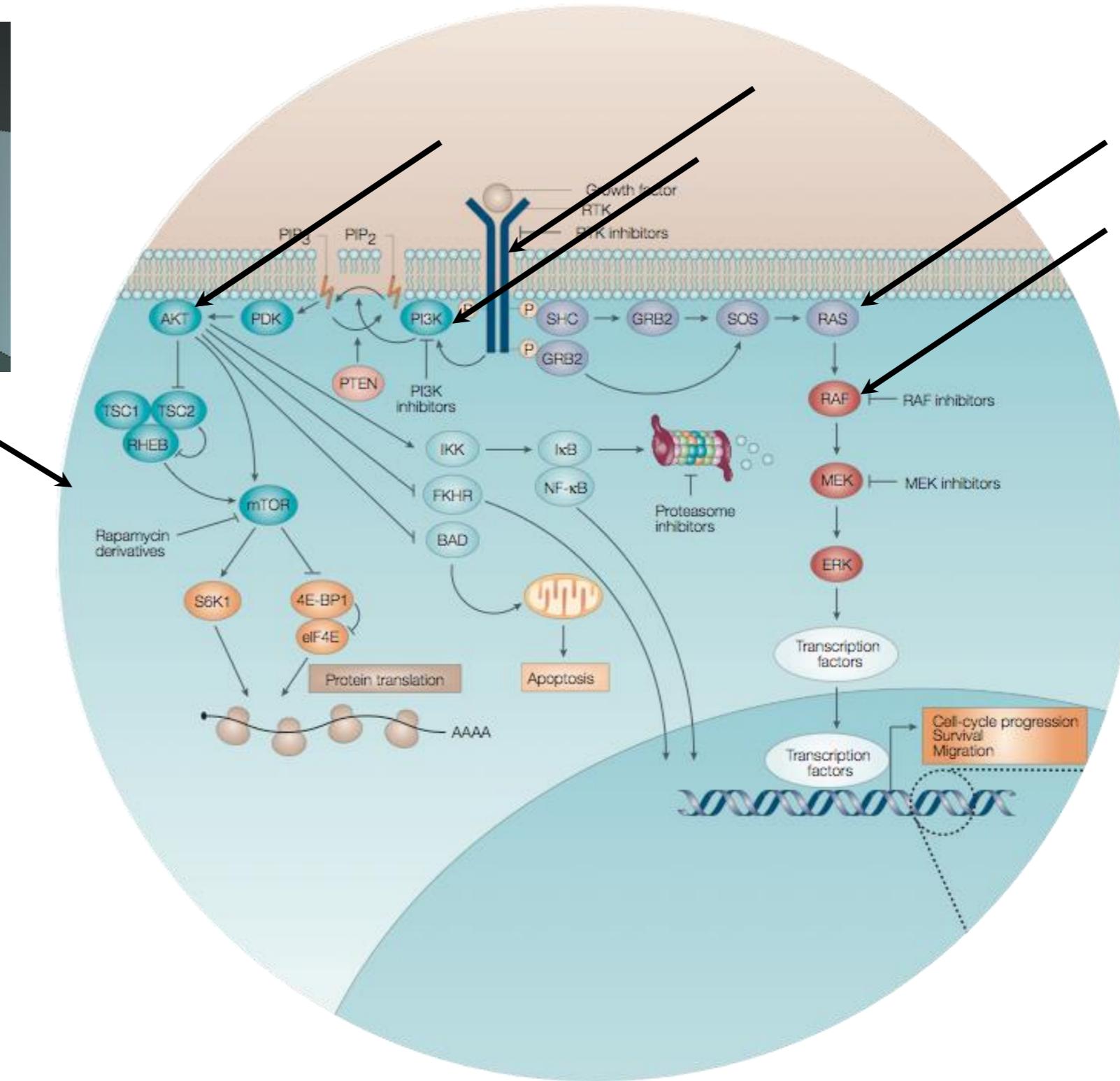


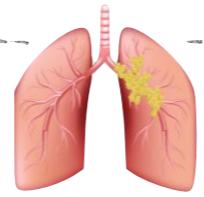
Pathways of cancer



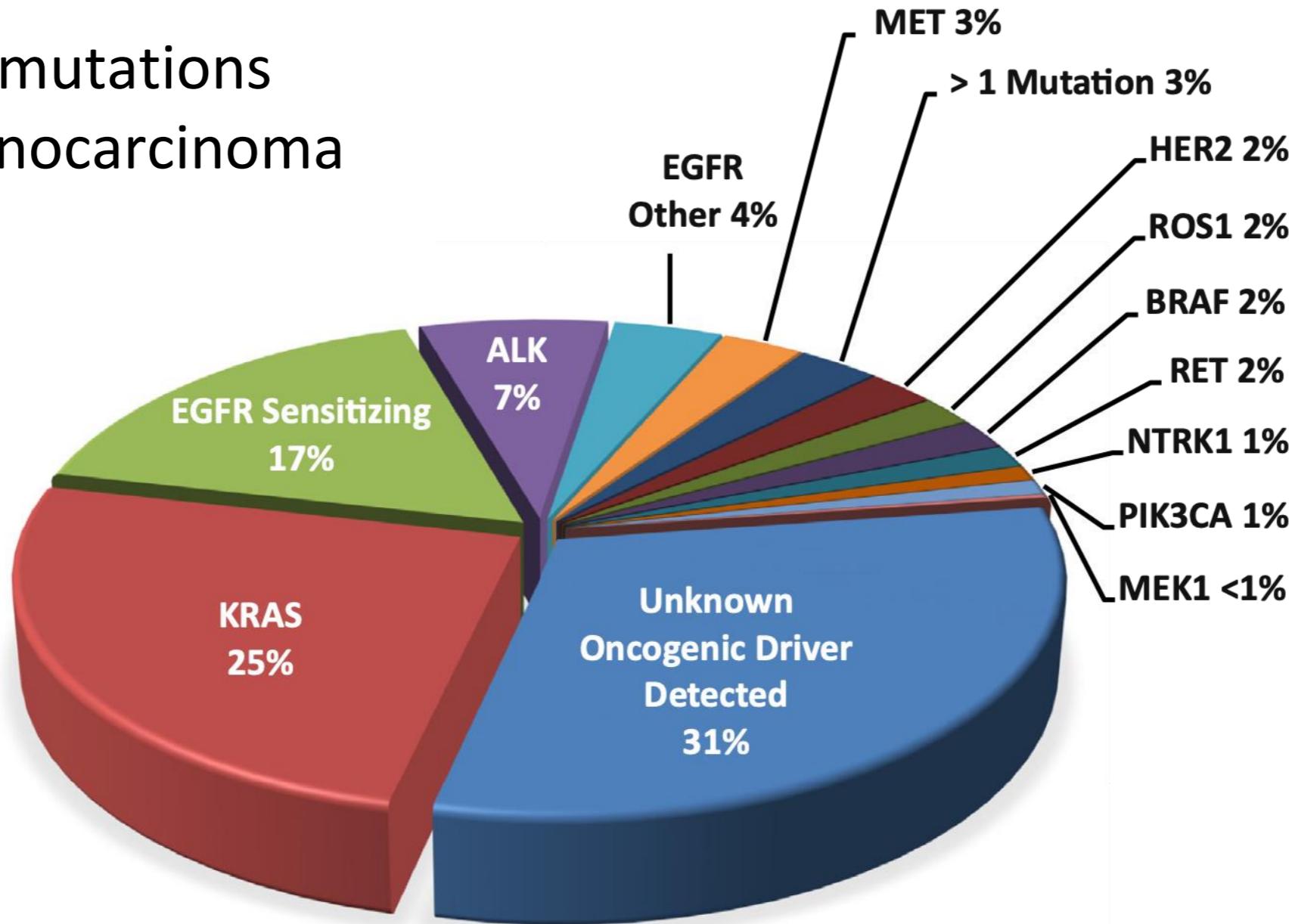


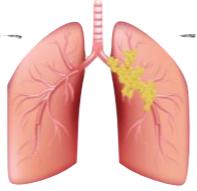
oncogenes



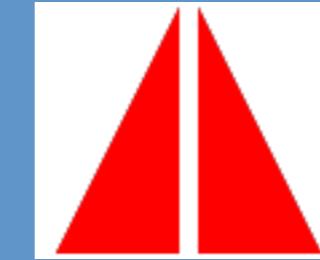


Driver mutations Lung Adenocarcinoma





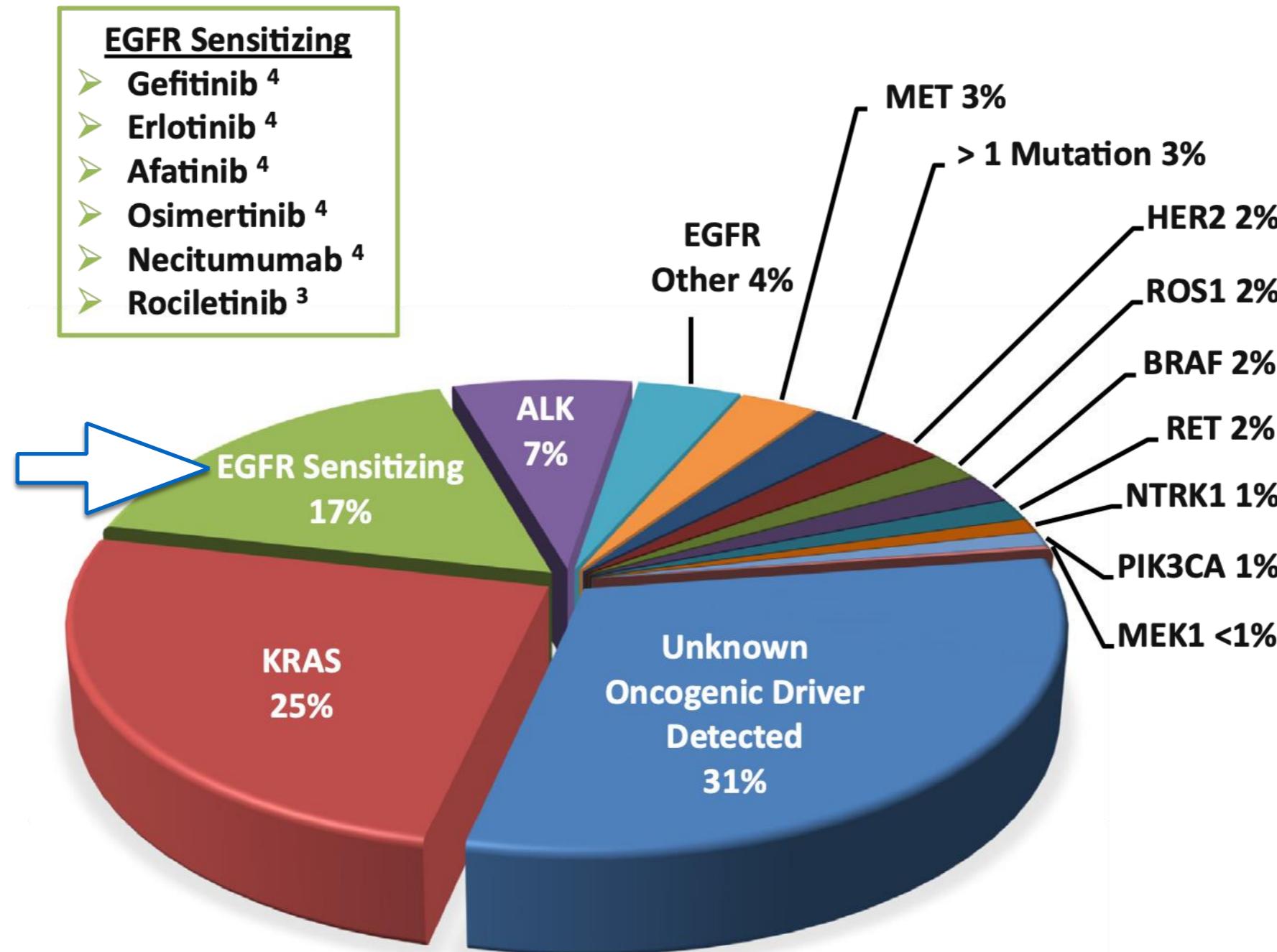
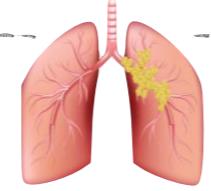
Danish Lung Cancer Group (DLCG)

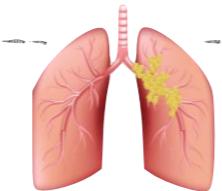


Lungecancer – Patologi

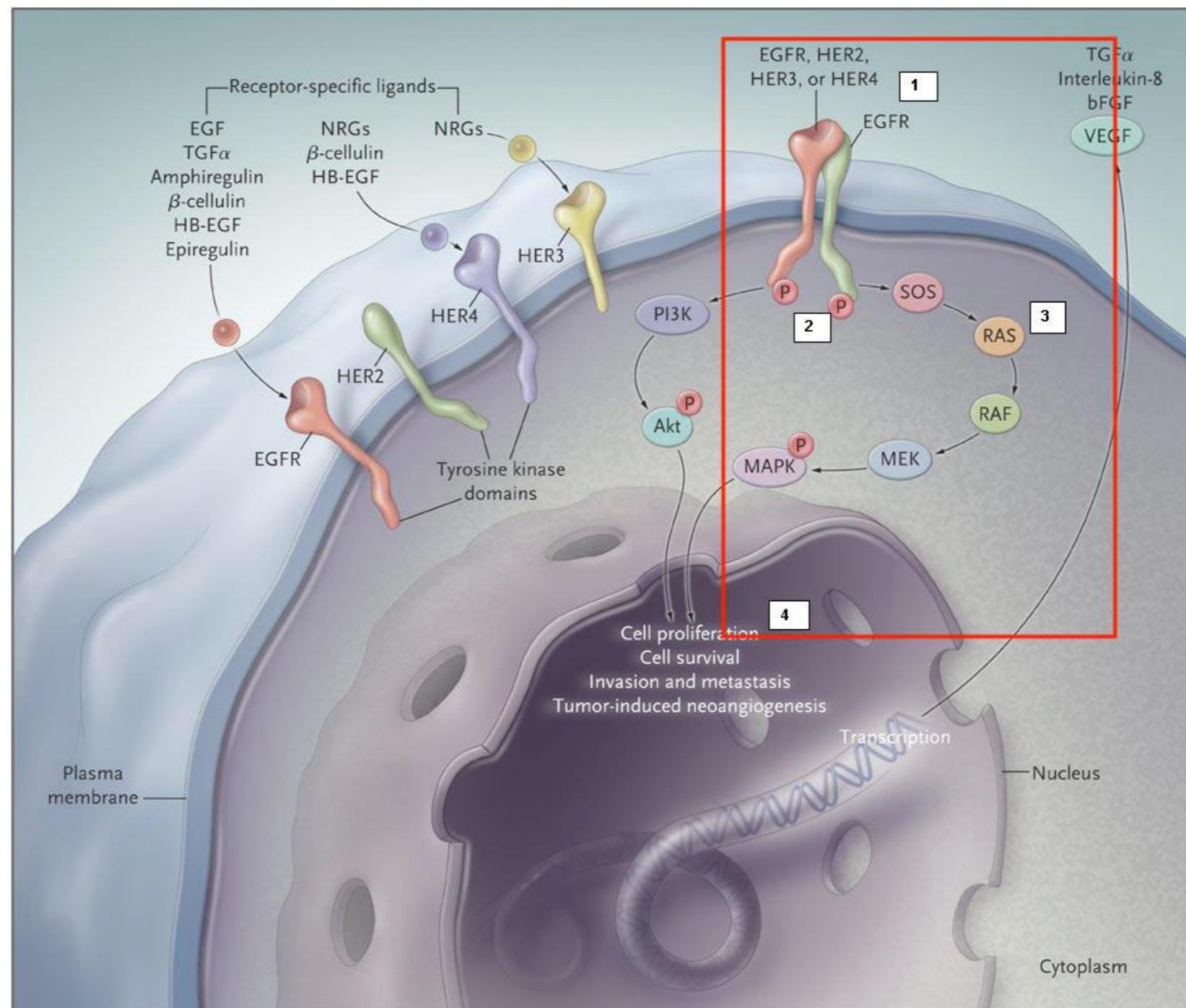
46. Reflextest af de obligatoriske markører bør foretages ved den primære diagnostik af nedenstående grupper. (A)

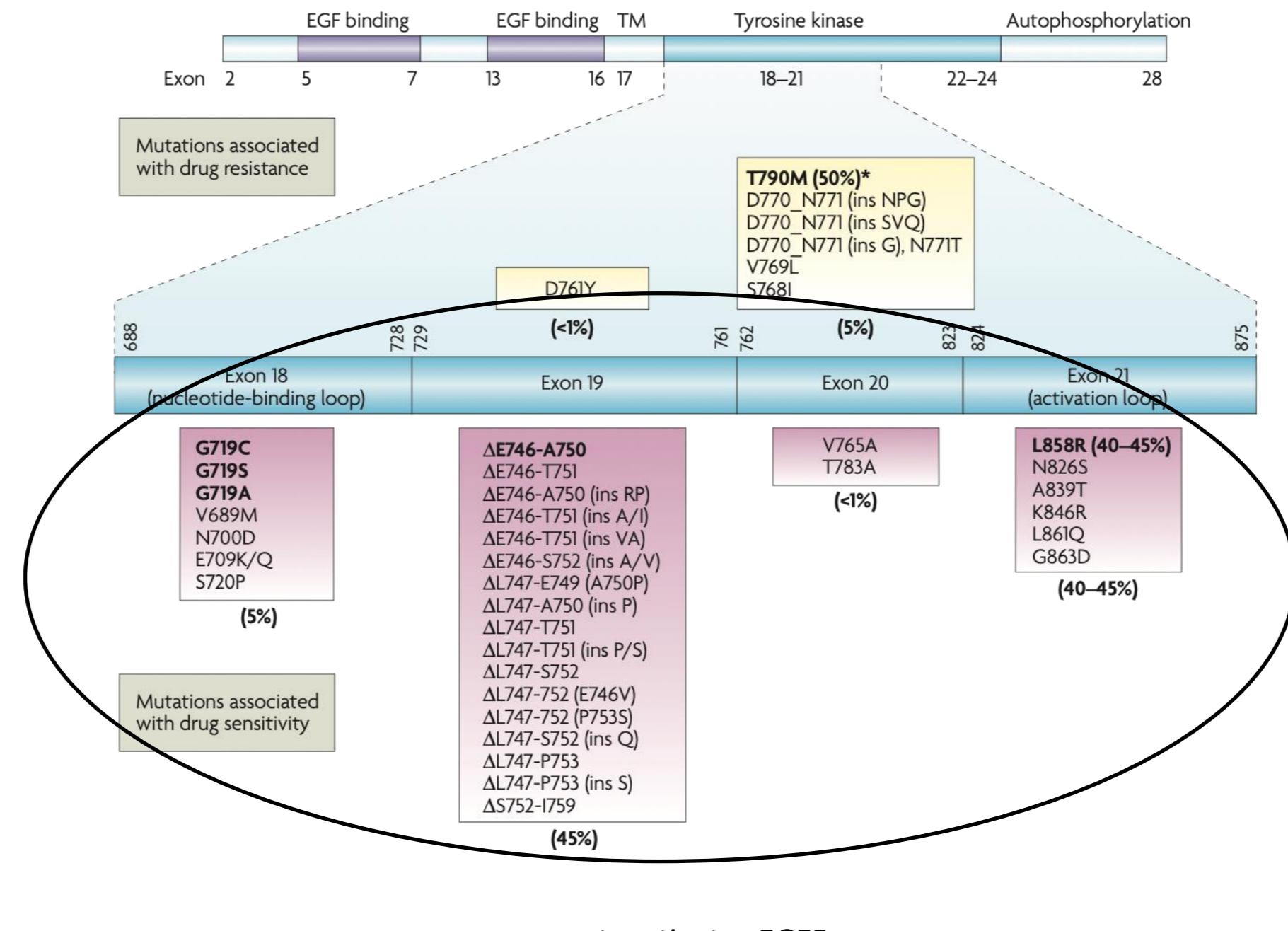
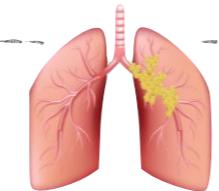
- EGFR, ALK, ROS1: adenokarcinomer + ikke-småcellede kancer, hvor typen ikke sikkert kan afgøres
- PD-L1: alle ikke-småcellede kancer

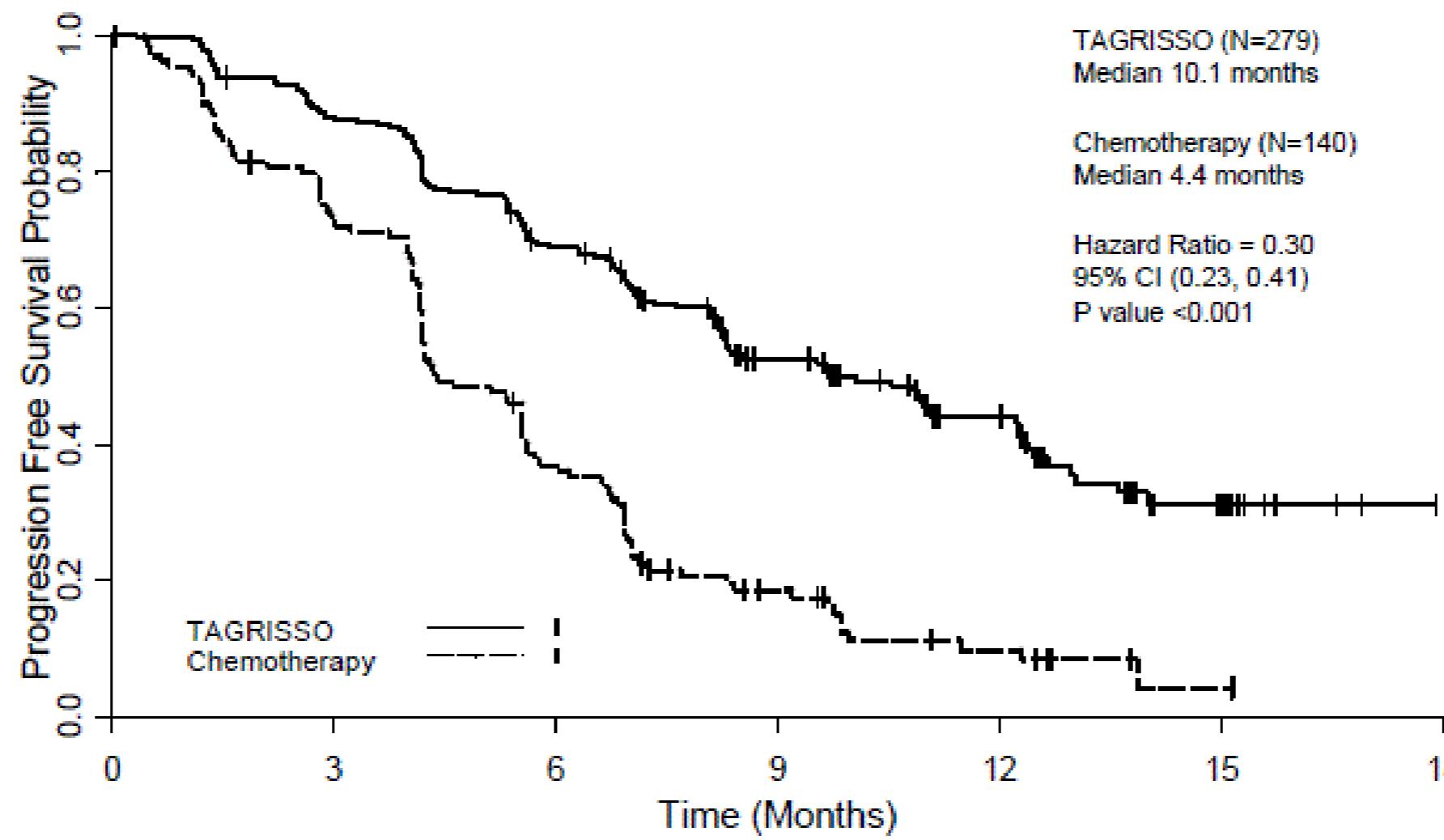
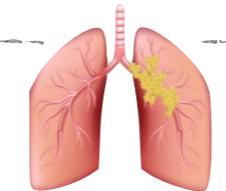




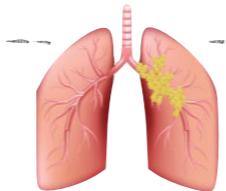
EGFR







Tick marks represent censored observations



Novel EGFR mutation-specific antibodies for lung adenocarcinoma:
 Highly specific but not sensitive detection of an E746_A750 deletion in
 exon 19 and an L858R mutation in exon 21 by immunohistochemistry



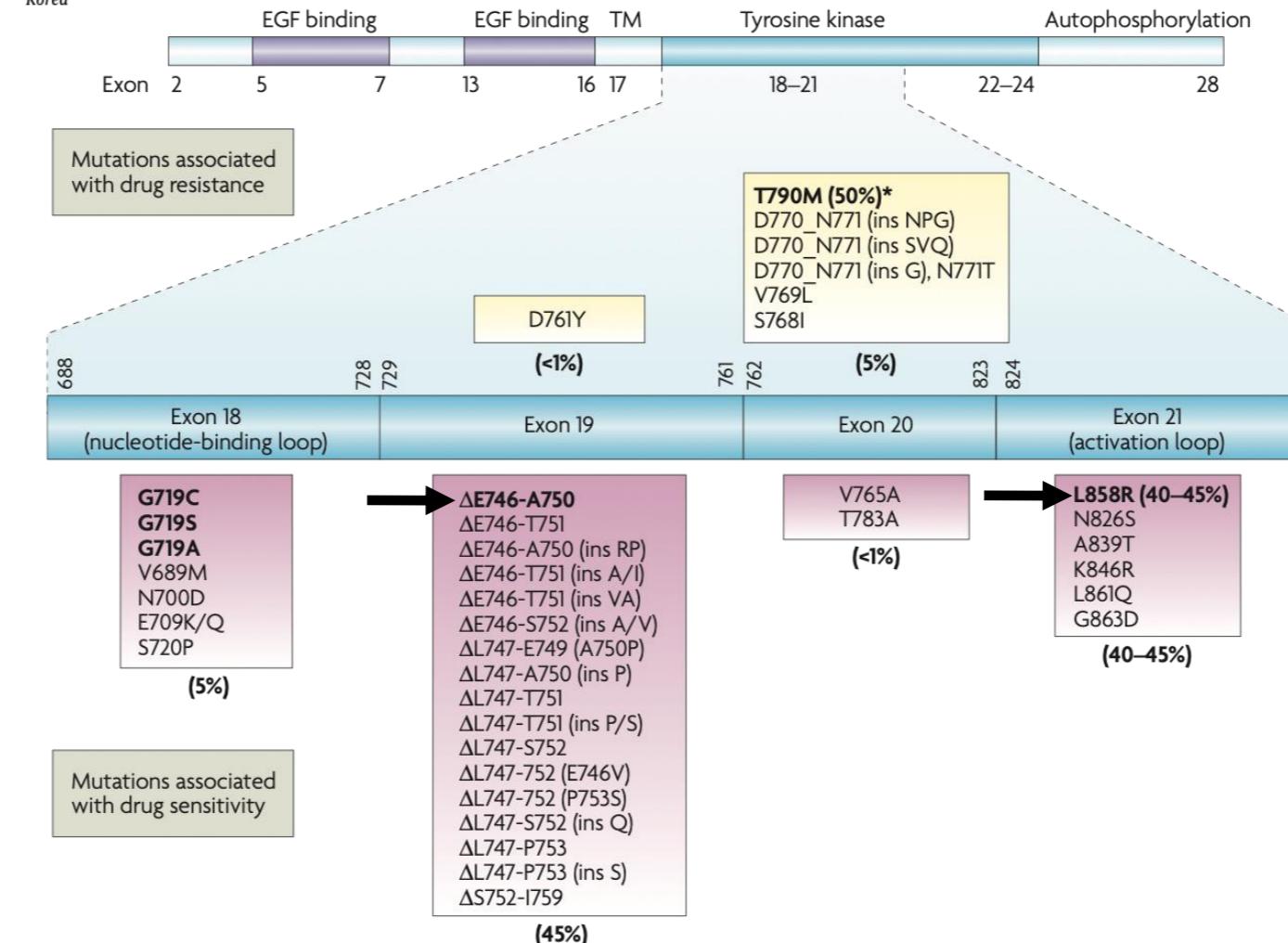
An Na Seo ^{a,b,1}, Tae-In Park ^{b,1}, Yan Jin ^{a,c}, Ping-Li Sun ^{a,c}, Hyojin Kim ^{a,c},
 Hyun Chang ^d, Jin-Haeng Chung ^{a,c,*}

^a Department of Pathology, Seoul National University Bundang Hospital, 300 Gumi-dong, Bundang-gu, Seongnam-si, Gyeonggi 463-707, Republic of Korea

^b Department of Pathology, Kyungpook National University College of Medicine, 680 Gukchaebosang-ro, Jung-gu, Daegu 700-842, Republic of Korea

^c Department of Pathology, Seoul National University College of Medicine, 103 Daehak-ro, Jongno-gu, Seoul 110-799, Republic of Korea

^d Department of Internal Medicine, Seoul National University Bundang Hospital, 300 Gumi-dong, Bundang-gu, Seongnam-si, Gyeonggi 463-707, Republic of Korea



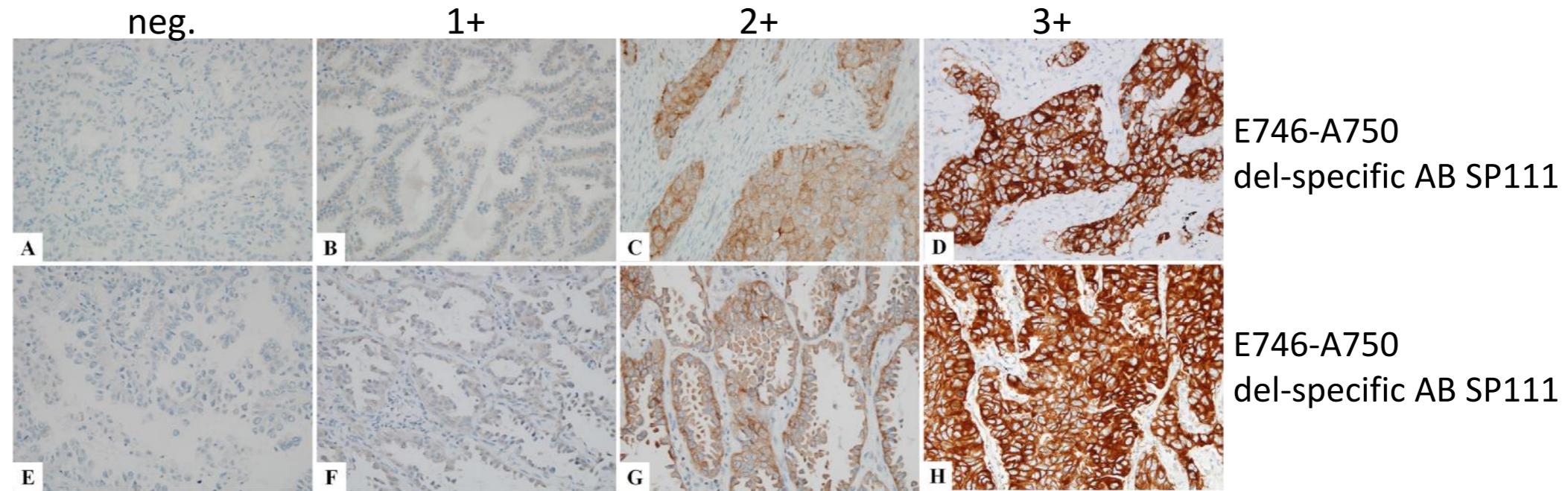
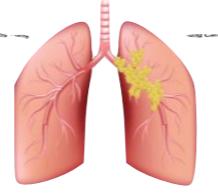
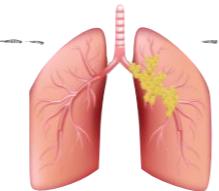


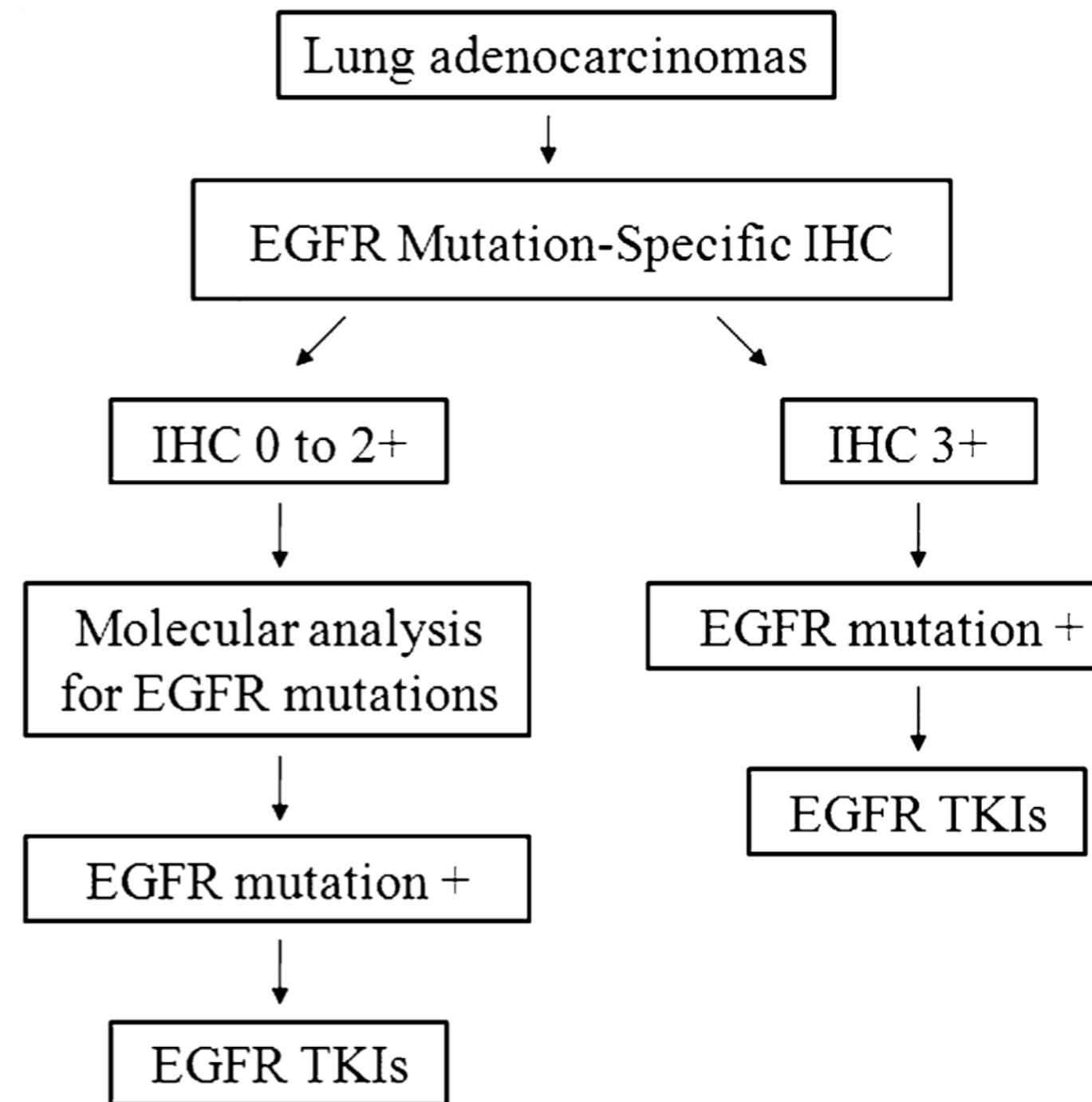
Table 2
Diagnostic power of mutation-specific antibodies comparing with *EGFR* mutational status.

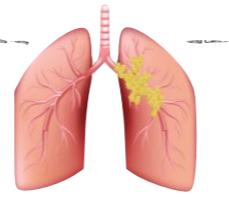
Mutation-specific antibodies	<i>EGFR</i> mutations	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Anti-EGFR E746.A750 del	E746.A750 deletion				
	≥Score 1 as positive	94.1%	96.1%	80.0%	99.0%
	≥Score 2 as positive	70.6%	99.0%	92.3%	95.3%
	≥Score 3 as positive	29.4%	100.0%	100.0%	89.6%
	All deletions in exon 19				
	≥Score 1 as positive	54.8%	96.6%	85.0%	86.0%
	≥Score 2 as positive	40.3%	99.4%	96.2%	82.7%
	≥Score 3 as positive	16.1%	100.0%	100.0%	77.4%
	L858R				
Anti-EGFR L858R	L858R				
	≥Score 1 as positive	93.5%	50.0%	30.7%	97.0%
	≥Score 2 as positive	80.4%	89.7%	64.9%	95.1%
	≥Score 3 as positive	41.3%	100.0%	100.0%	87.8%

Abbreviations: PPV, positive predictive value; NPV, negative predictive value.

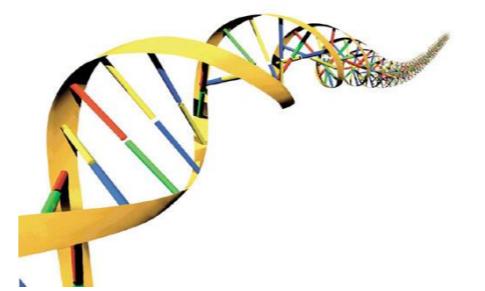


Algorithm





Tissue section



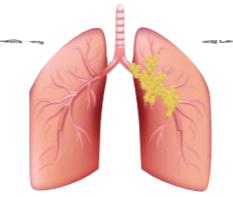
DNA(*template*)

DNA-purification

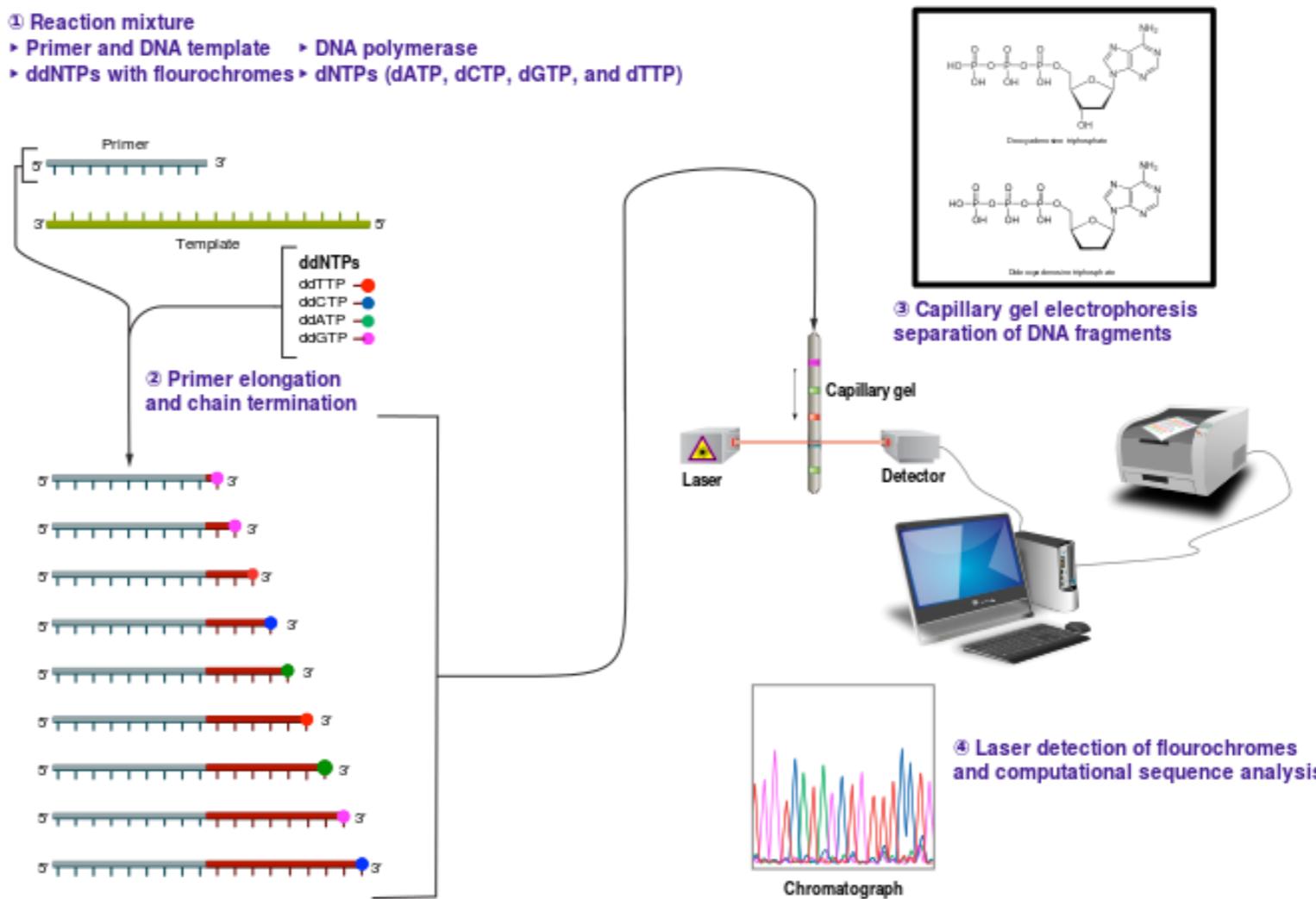
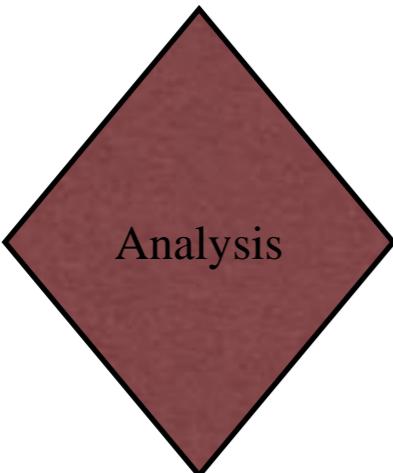


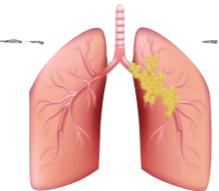
PCR

Analysis

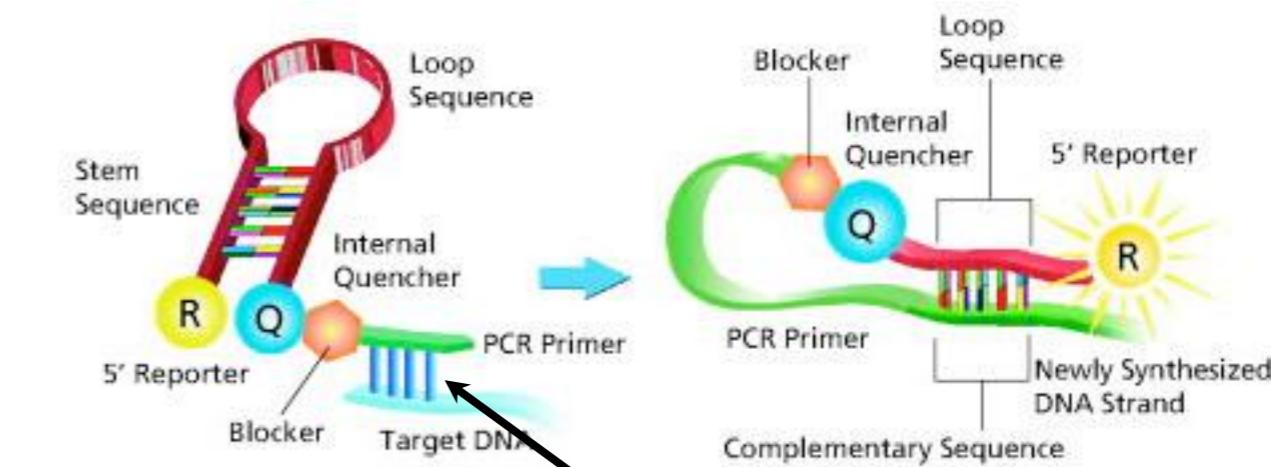


Sequencing





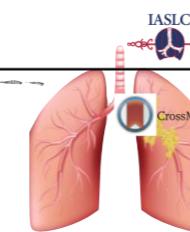
PCR based test



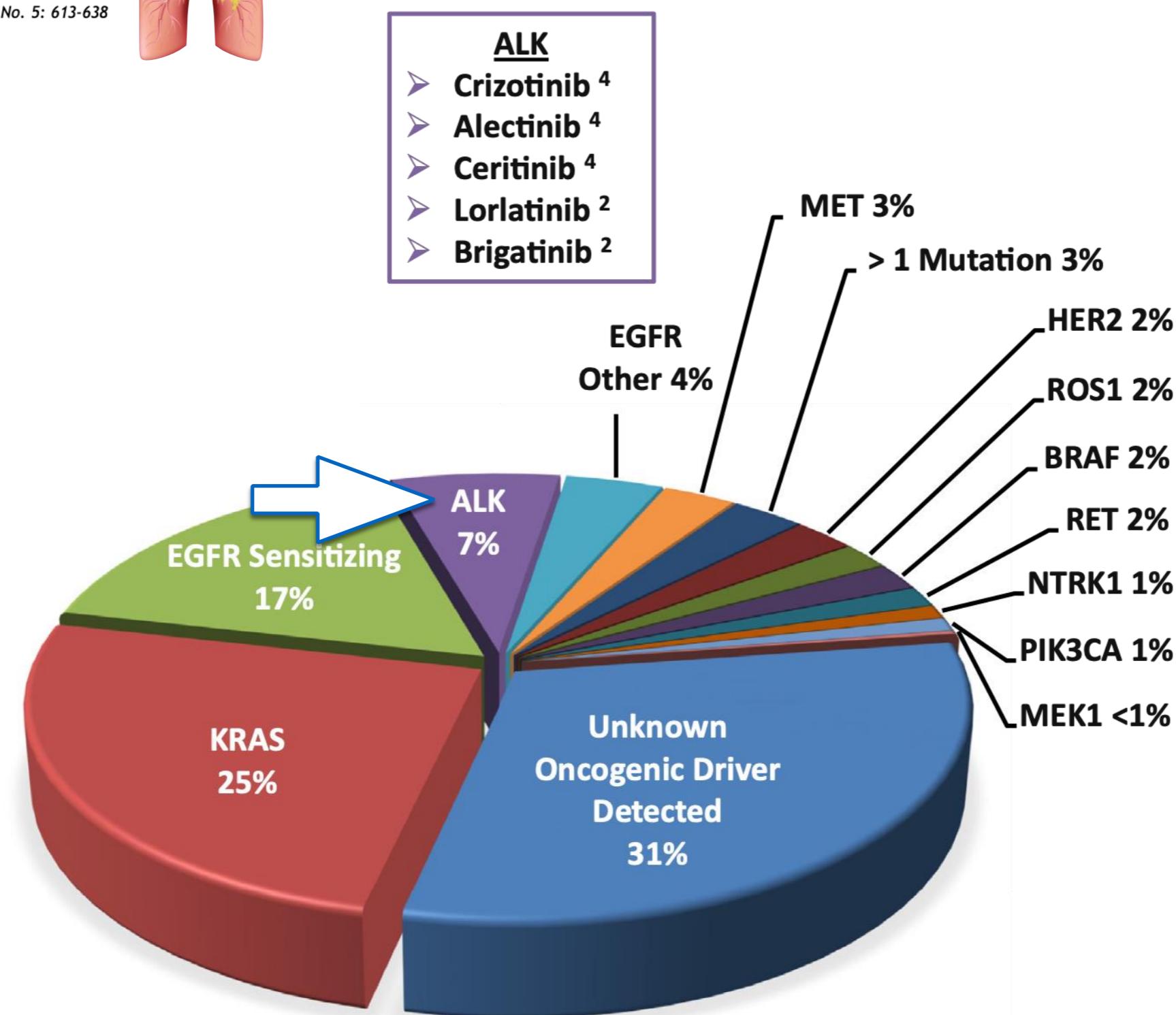
1. Quenching of the fluorescence

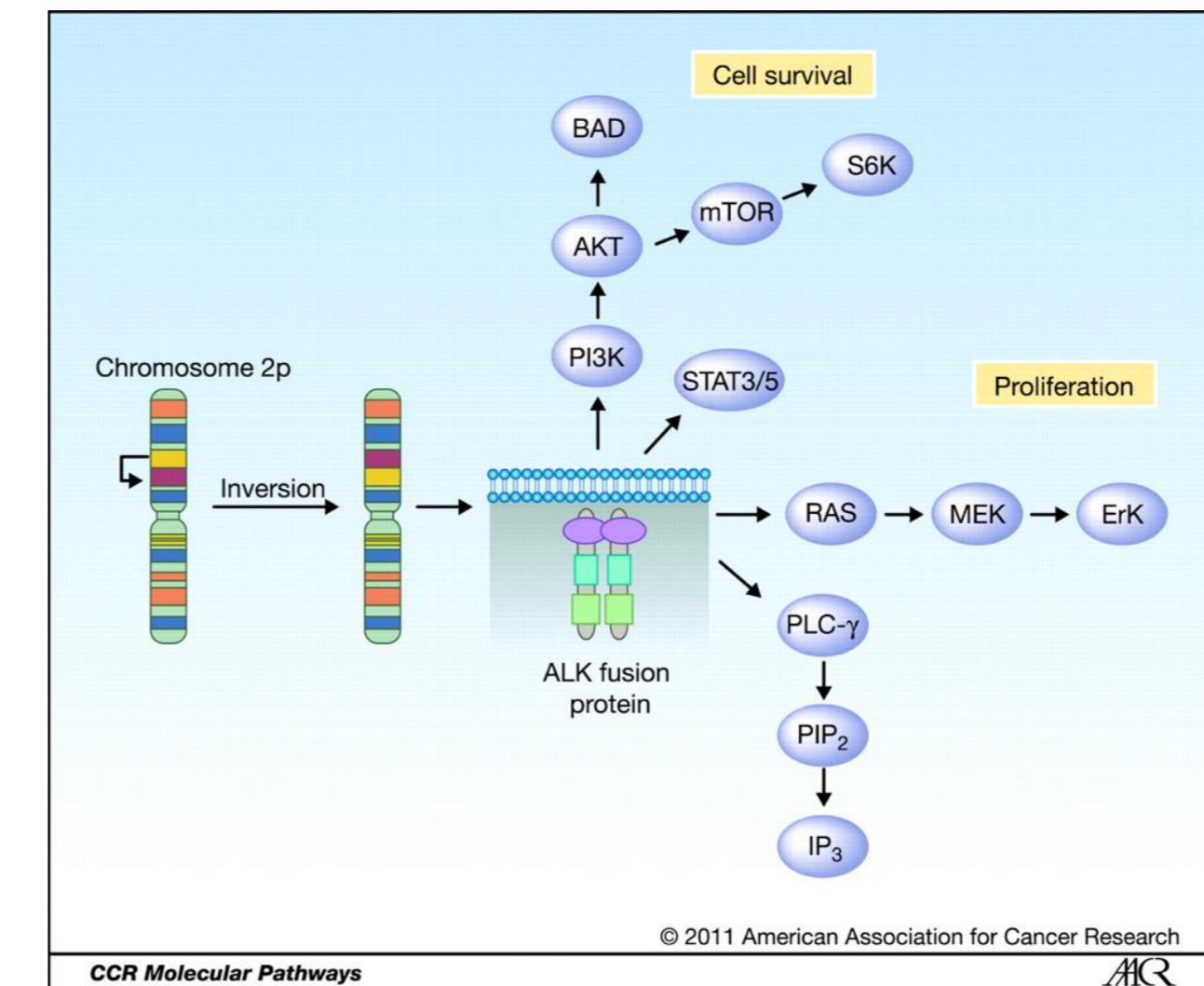
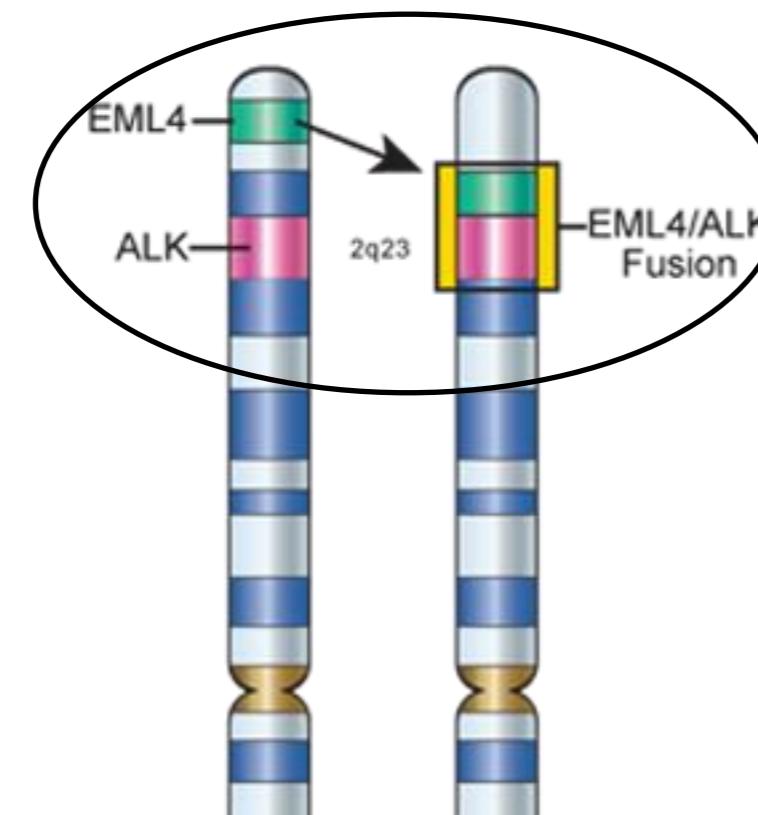
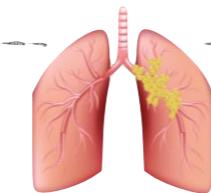
2. Emission of the fluorescence

mutationspecific primer



CrossMark





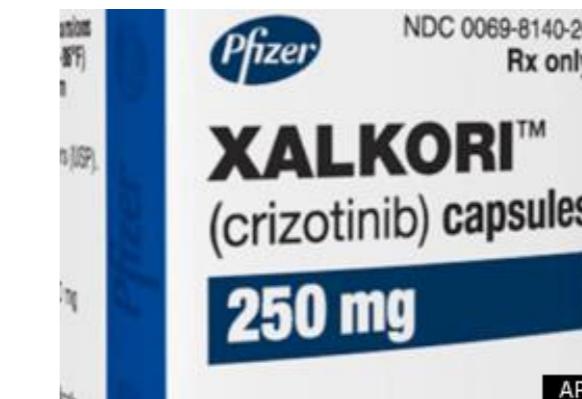
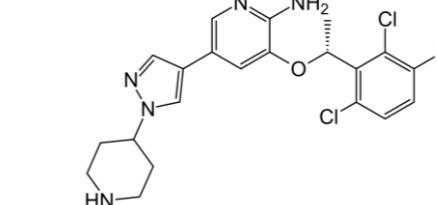
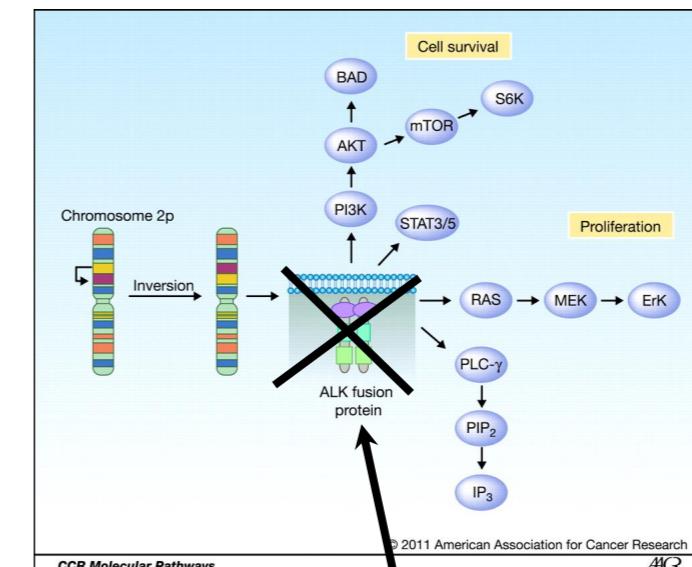
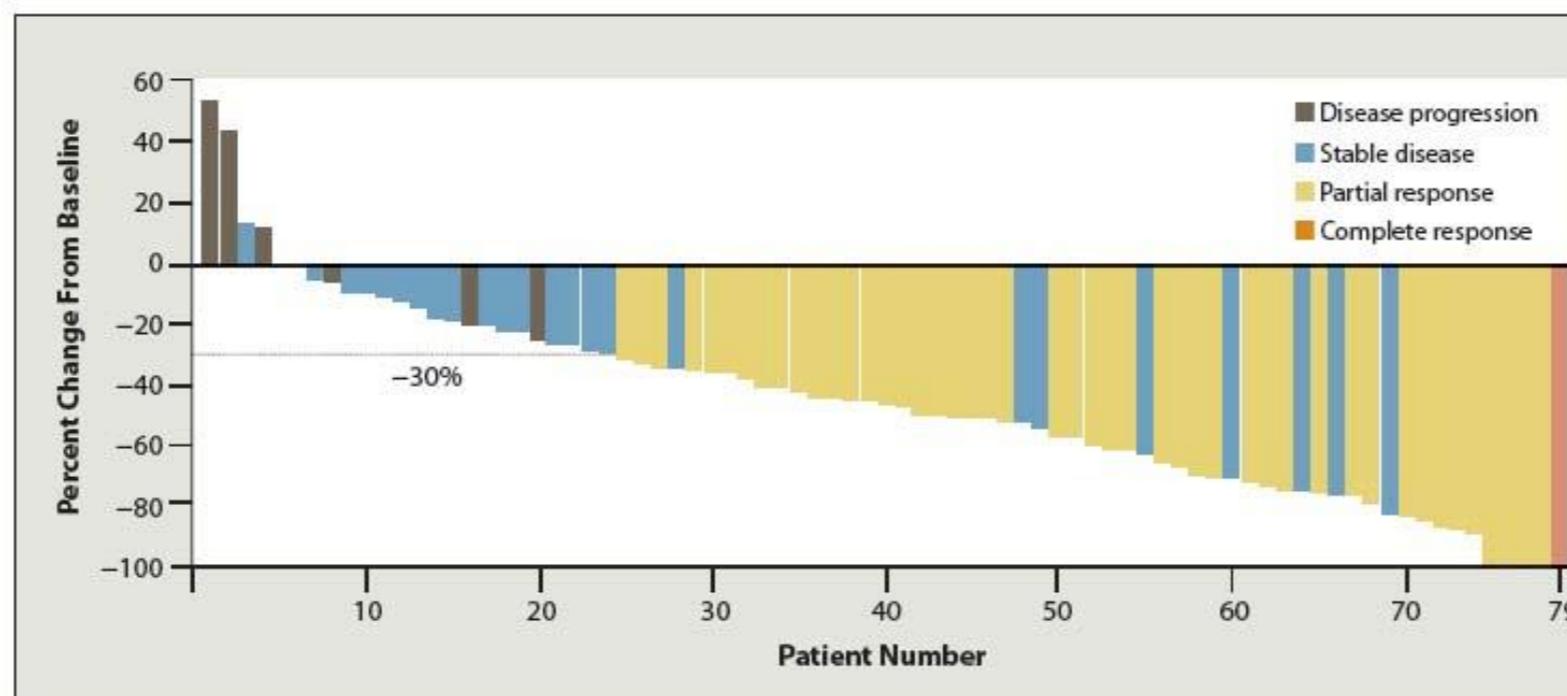
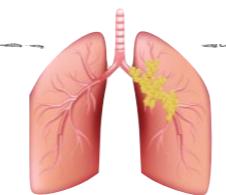
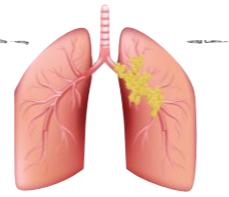
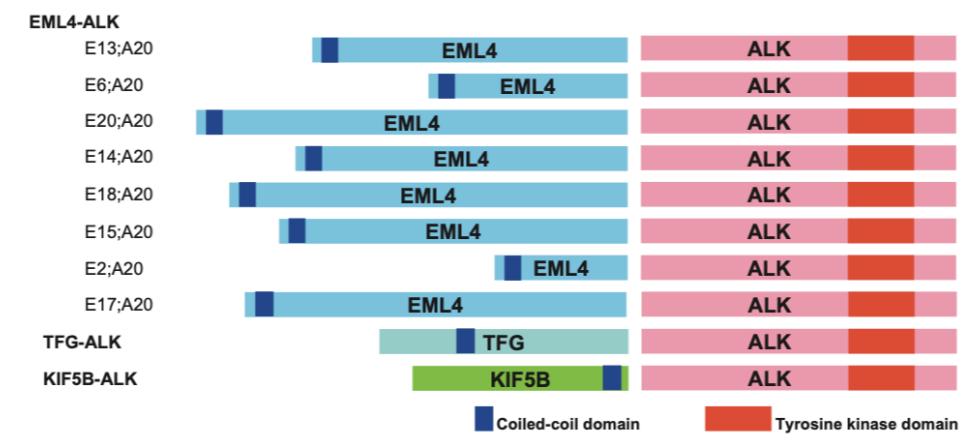
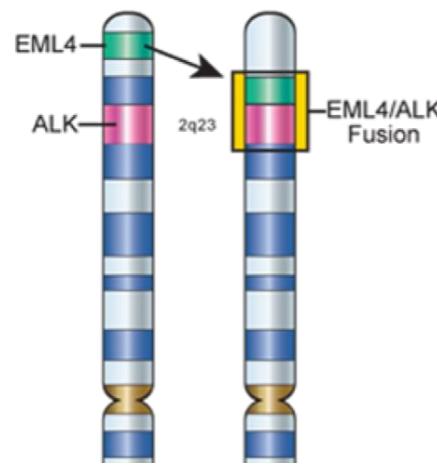


Figure 2: Waterfall plot showing response to crizotinib in patients with EML4-ALK NSCLC. Percent change in tumor burden relative to pretreatment baseline is represented. (Reproduced with permission from Kwak et al. N Engl J Med. 2010;363:1693-1703. Copyright © 2010, Massachusetts Medical Society.)

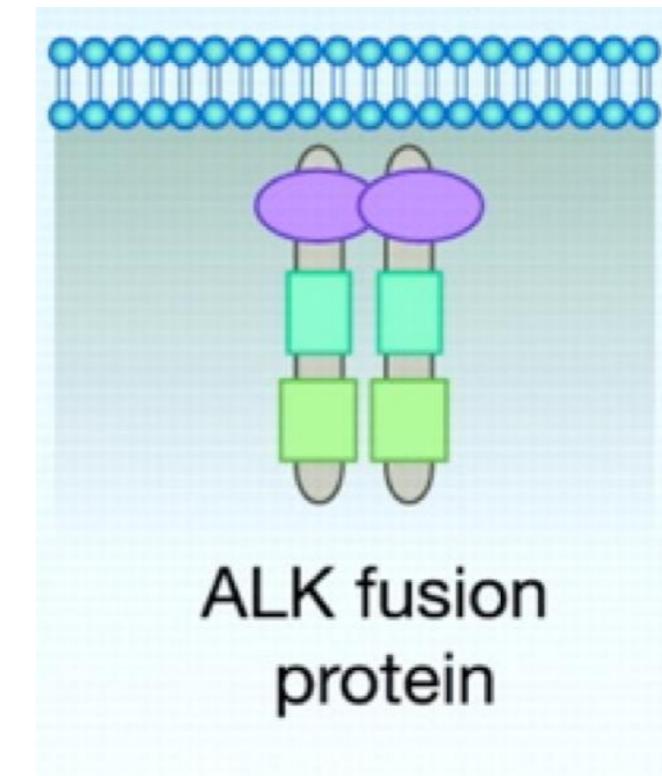


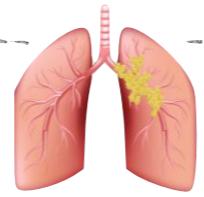
Detection of chromosomal changes



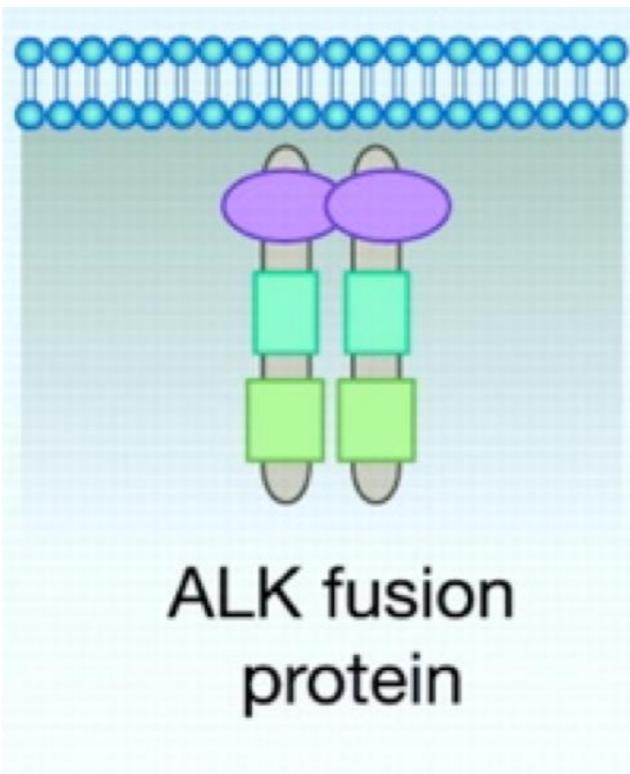
Detection of fusion RNA

Detection of fusion protein

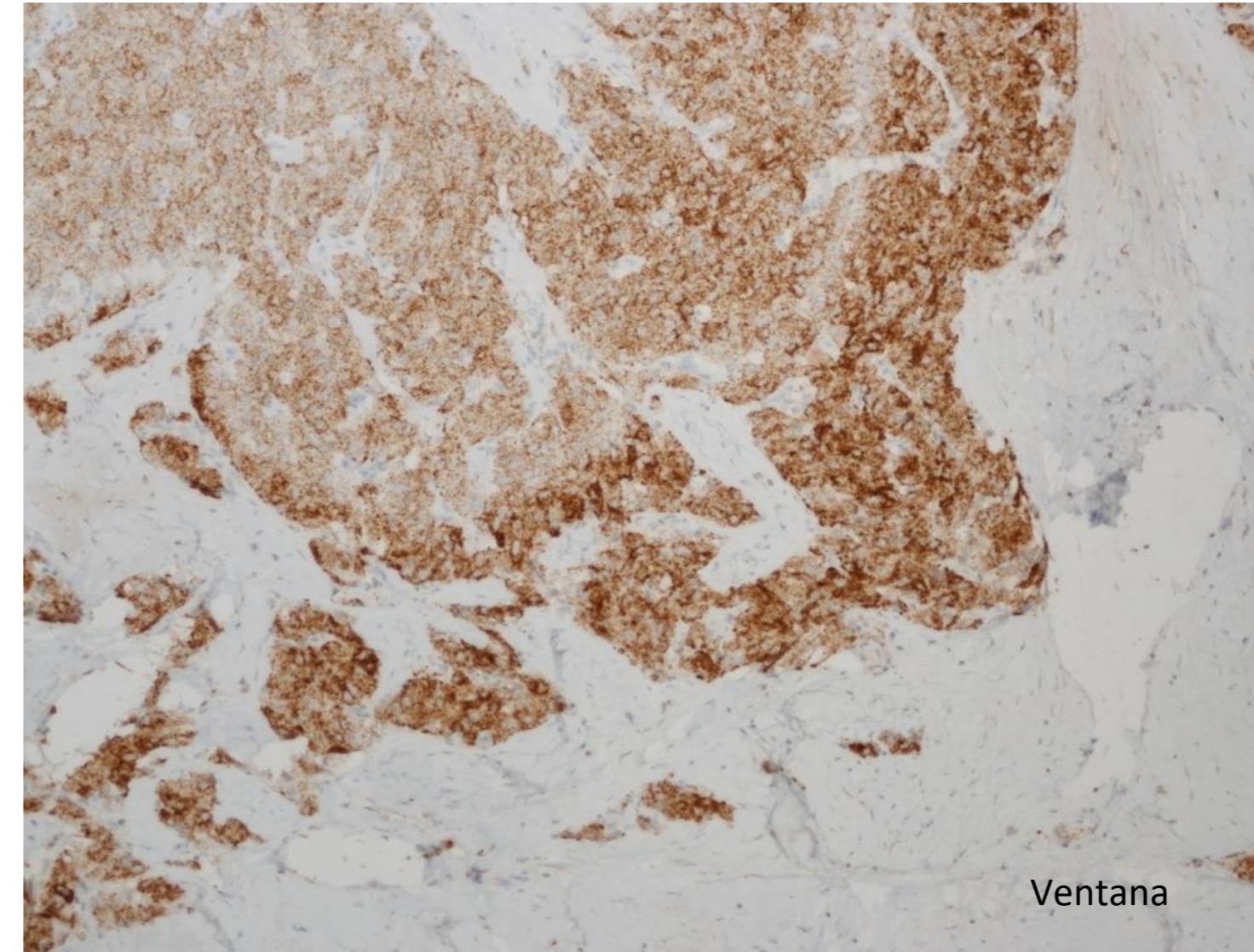




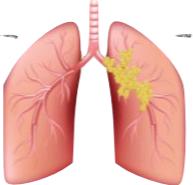
Detection of fusion protein



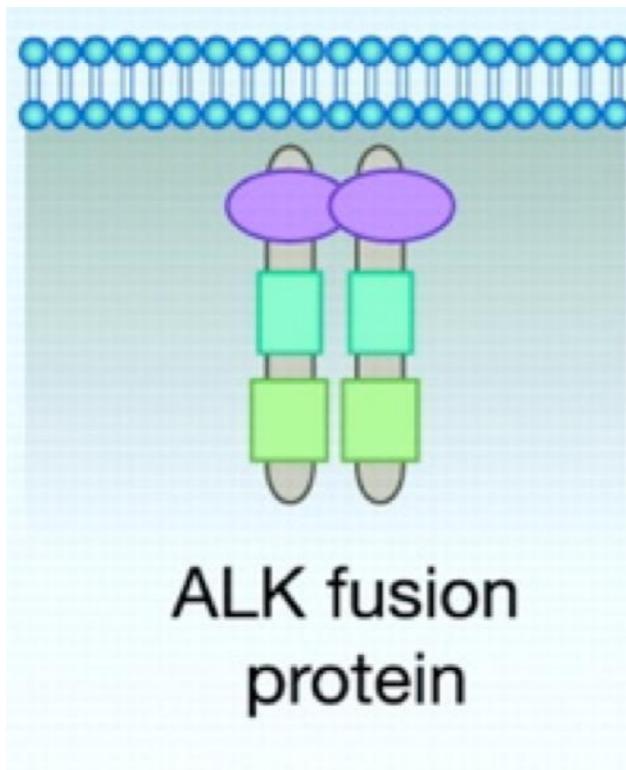
Immunohistochemistry



Detects ALK independent of fusion partner



Detection of fusion protein

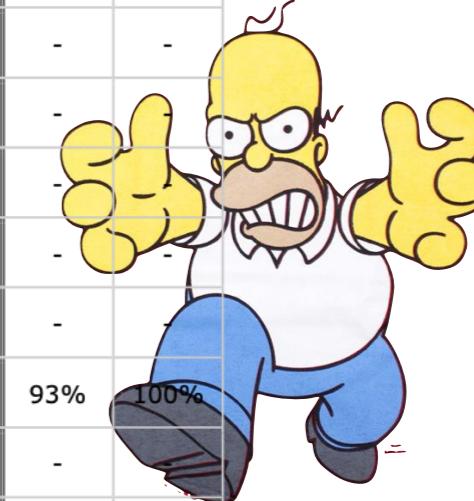


RT-PCR

Immunohistochemistry

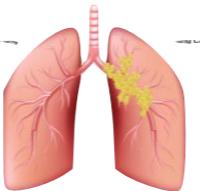
Table 1. Antibodies and assessment marks for lu-ALK, run 51

Concentrated antibodies	n	Vendor	Optimal	Good	Borderline	Poor	Suff. ¹	Suff. OPS ²
mAb clone 5A4	43	Leica/Novocastra						
	1	Abcam	1	15	24	7	34%	22%
	1	Biocare						
	1	Monosan						
	1	ThermoFisher						
mAb clone ALK1	2	Dako	0	0	0	3	-	-
	1	Cell Marque						
rmAb clone D5F3	23	Cell Signaling	6	12	3	2	78%	94%
mAb clone OTI1A4	13	ORIGENE	10	3	0	0	100%	100%
Ready-To-Use antibodies								
mAb clone 5A4 PA0306	6	Leica/Novocatra	0	0	6	0	-	-
mAb clone 5A4 MAB-0281	1	Maixin	0	0	1	0	-	-
mAb 5A4 MAD-001720QD	1	Master Diagnostica	0	0	1	0	-	-
mAb clone 5A4 MS-1104-R7	1	ThermoFisher	0	1	0	0	-	-
mAb ALK1 IR641	9	Dako	0	0	1	8	-	
mAb clone ALK1 GA641	4	Dako	0	0	0	4	-	
mAb clone ALK1 790/800-2918	7	Ventana	0	0	2	5	-	
rmAb clone SP8 AN770	1	BioGenex	0	0	0	1	-	
rmAb clone D5F3 790-4796	70	Ventana	53	12	4	1	93%	100%
rmAb clone D5F3 790-4796³	2	Ventana	1	0	1	0	-	
mAb clone OTI1A4 8344-C010	1	Sakura Finetek	1	0	0	0	-	-
Total	189		72	43	43	31	-	
Proportion			38%	23%	23%	16%	61%	



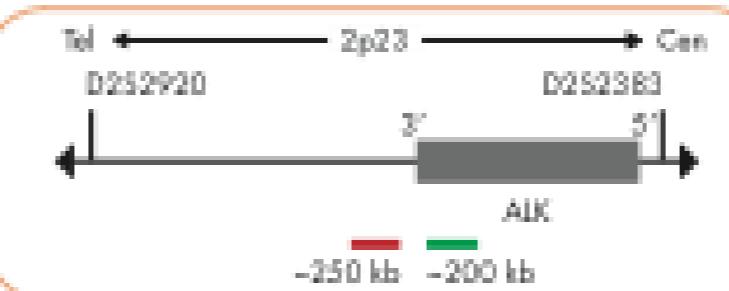
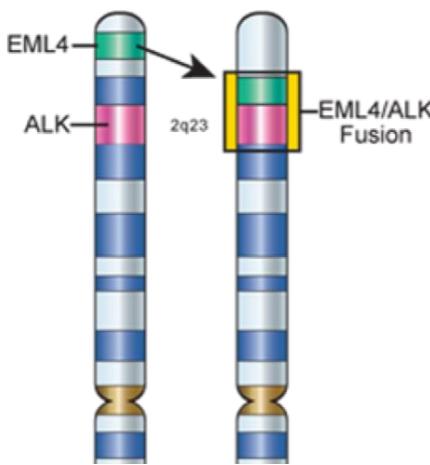
1) Proportion of sufficient stains (optimal or good).

2) Proportion of sufficient stains with optimal protocol settings only, see below. . 3) RTU system developed for the Ventana BenchMark systems (Ultra/XT) but used by laboratories on different platforms (e.g Dako Autostainer)

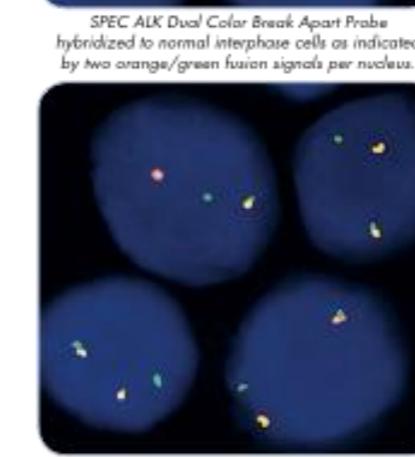
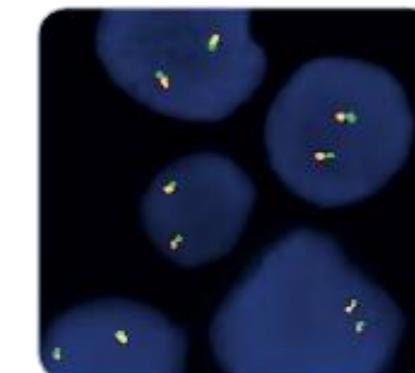
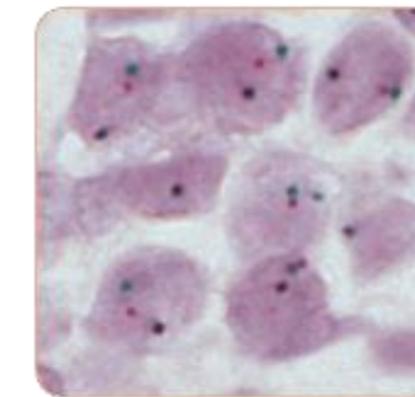


Detection of chromosomal changes

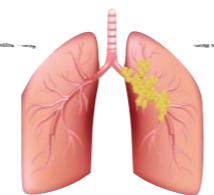
F(C)ISH



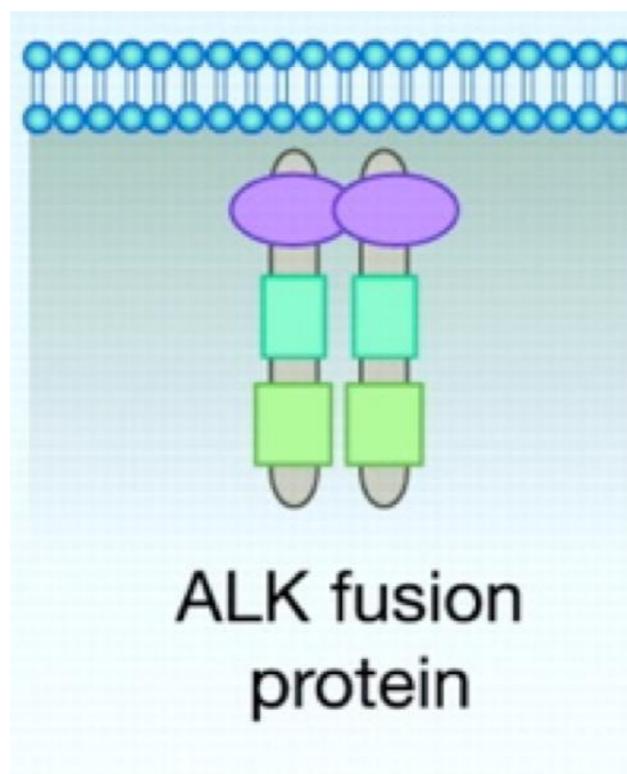
SPEC ALK Probe map (not to scale).



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



Detection of fusion protein



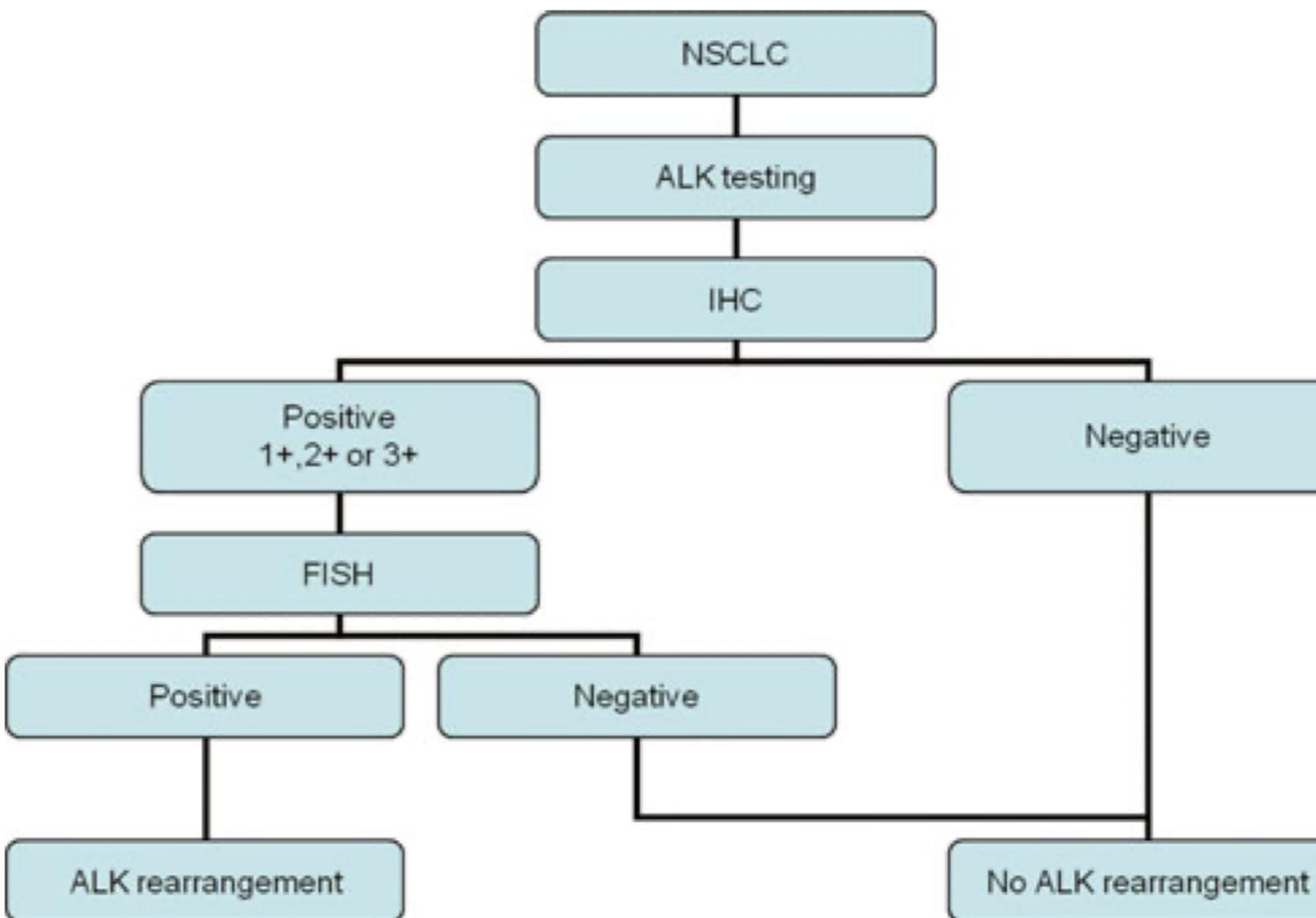
Virchows Arch (2012) 461:245–257
DOI 10.1007/s00428-012-1281-4

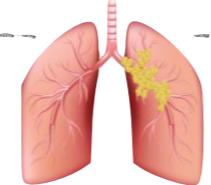
REVIEW AND PERSPECTIVES

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

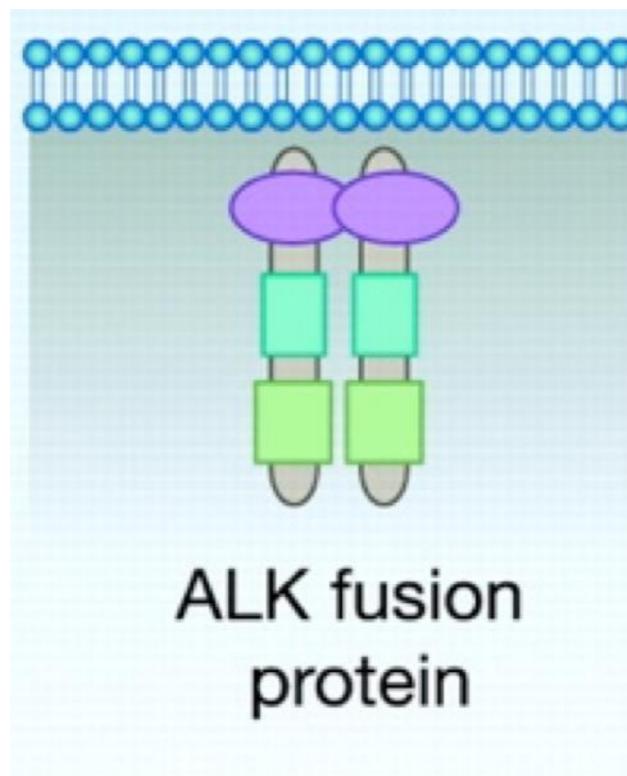
Erik Thunnissen · Lukas Bubendorf · Manfred Dietel ·
Göran Elmberger · Keith Kerr · Fernando Lopez-Rios ·
Holger Moch · Włodzimierz Olszewski ·
Patrick Pauwels · Frédérique Penault-Llorca ·
Giulio Rossi

Algorithm



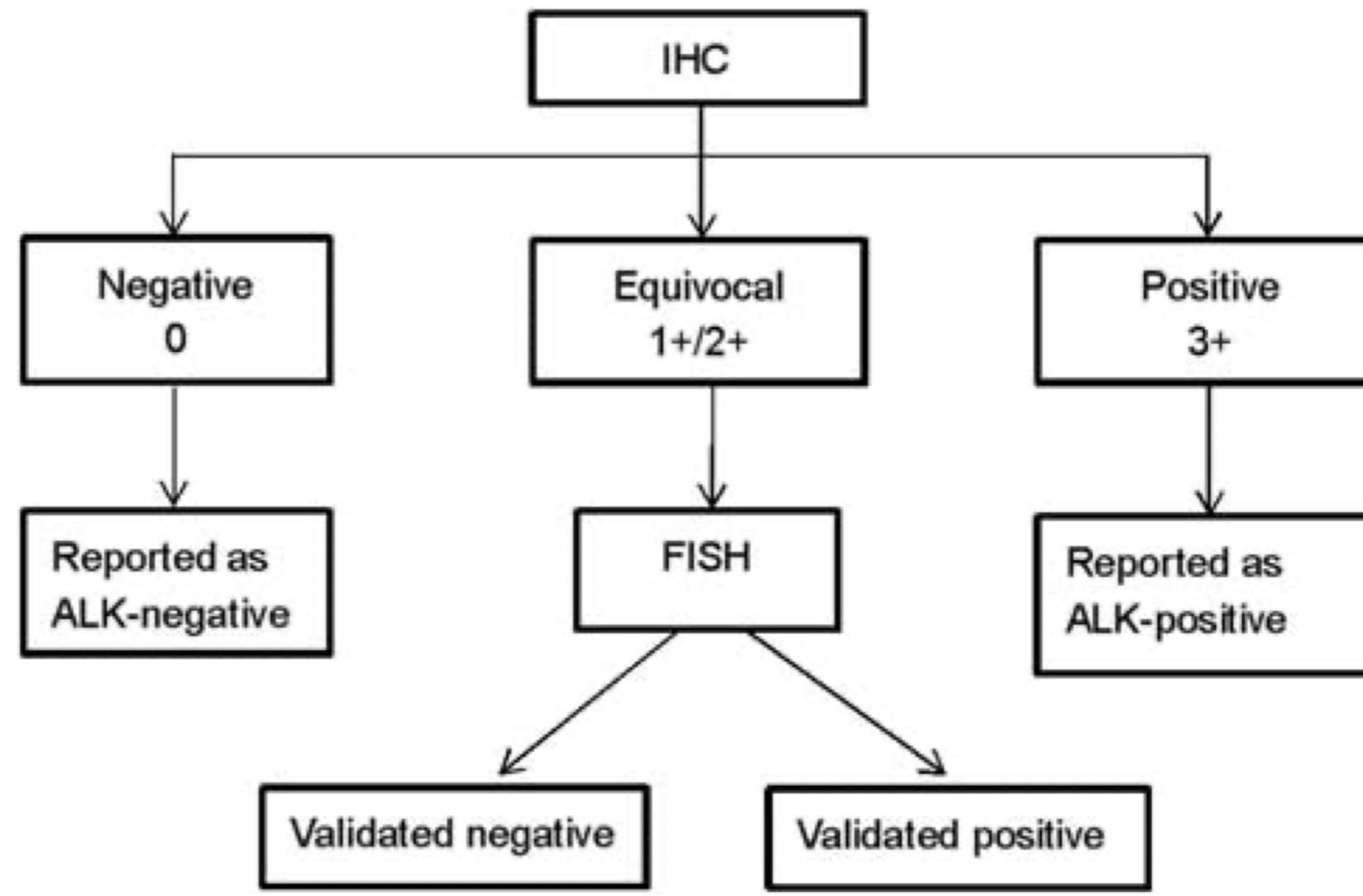


Detection of fusion protein



RT-PCR

Algorithm

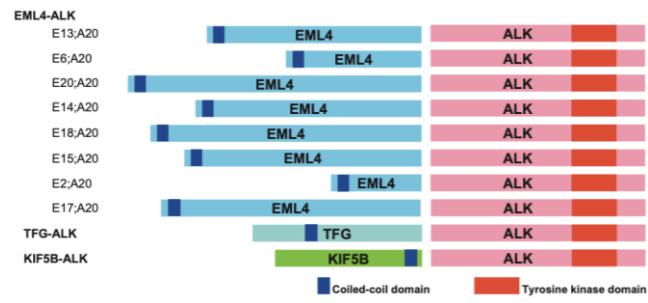


Improving Selection Criteria for ALK Inhibitor Therapy in Non-Small Cell Lung Cancer
A Pooled-Data Analysis on Diagnostic Operating Characteristics of Immunohistochemistry

Long Jiang, MD, PhD,*† Haihong Yang, MD, PhD,‡ Ping He, MD, PhD,§ Wenhua Liang, MD, PhD,‡
Jianrong Zhang, MD,*† Jingpei Li, MD,*† Yang Liu, MD,*† and Jianxing He, MD, PhD, FACS*†

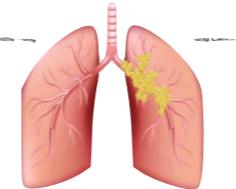


Detection of fusion RNA



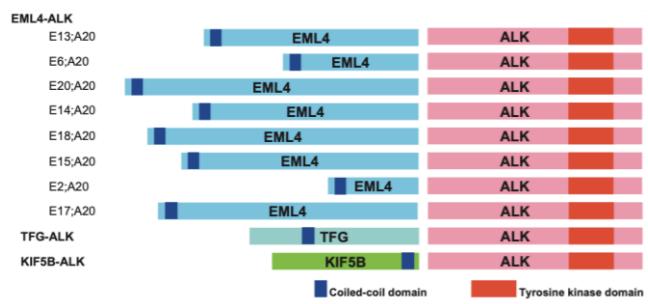
RT PCR based test



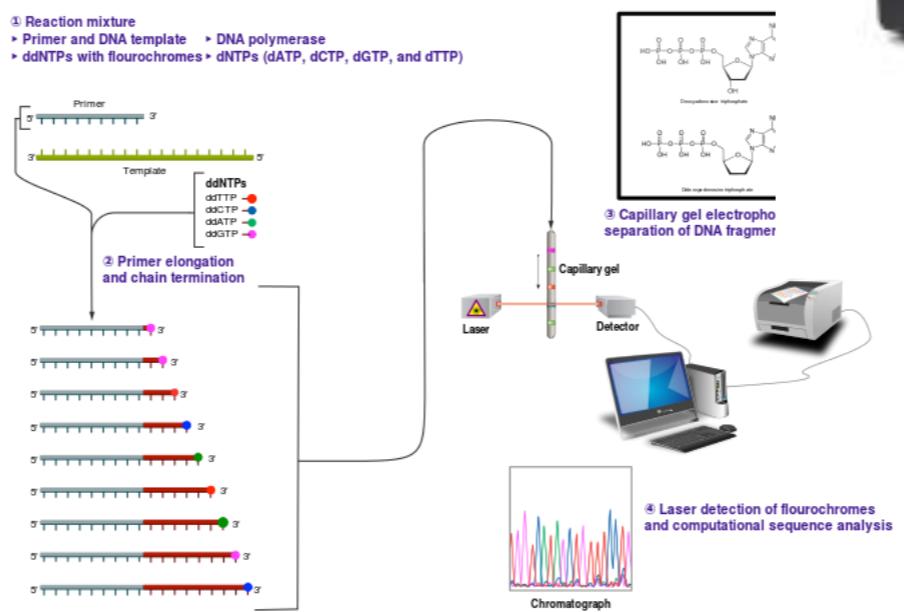


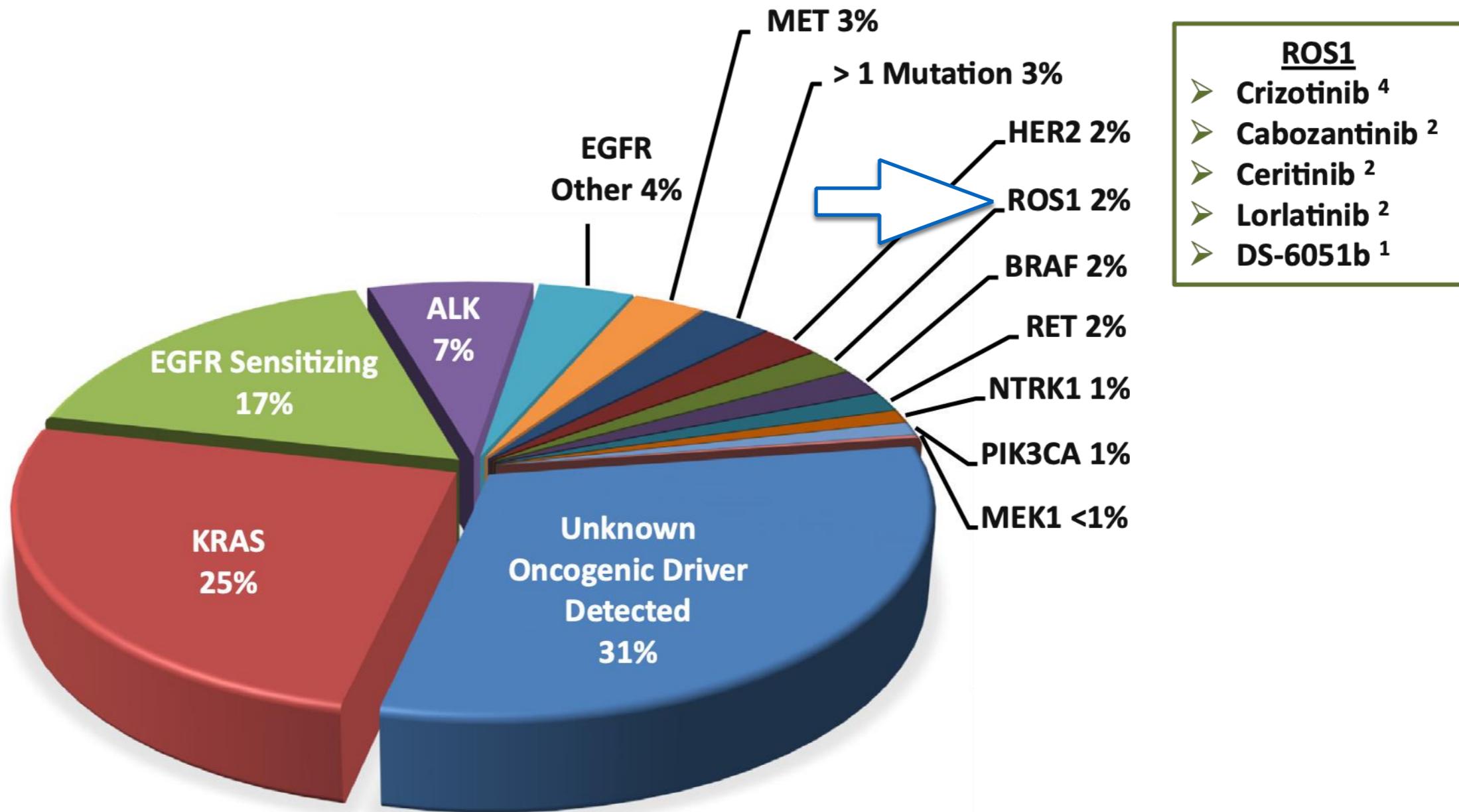
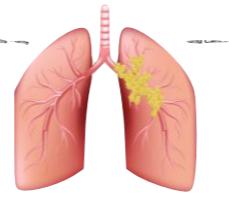
RNA Sequencing based test

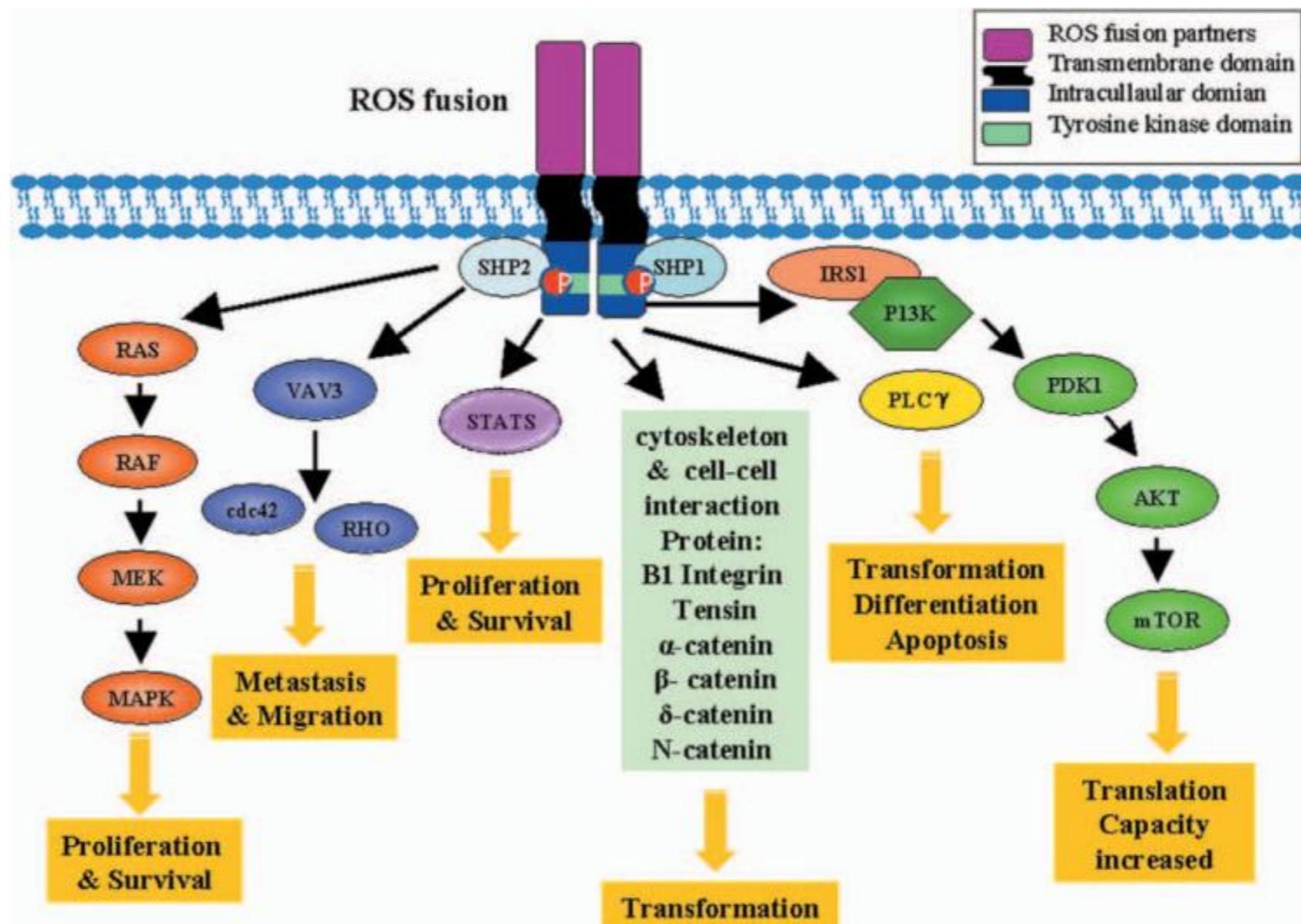
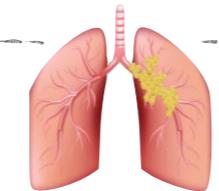
Detection of fusion RNA

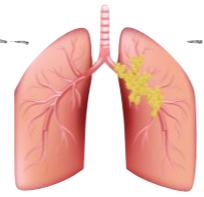


RNA Sequencing based test

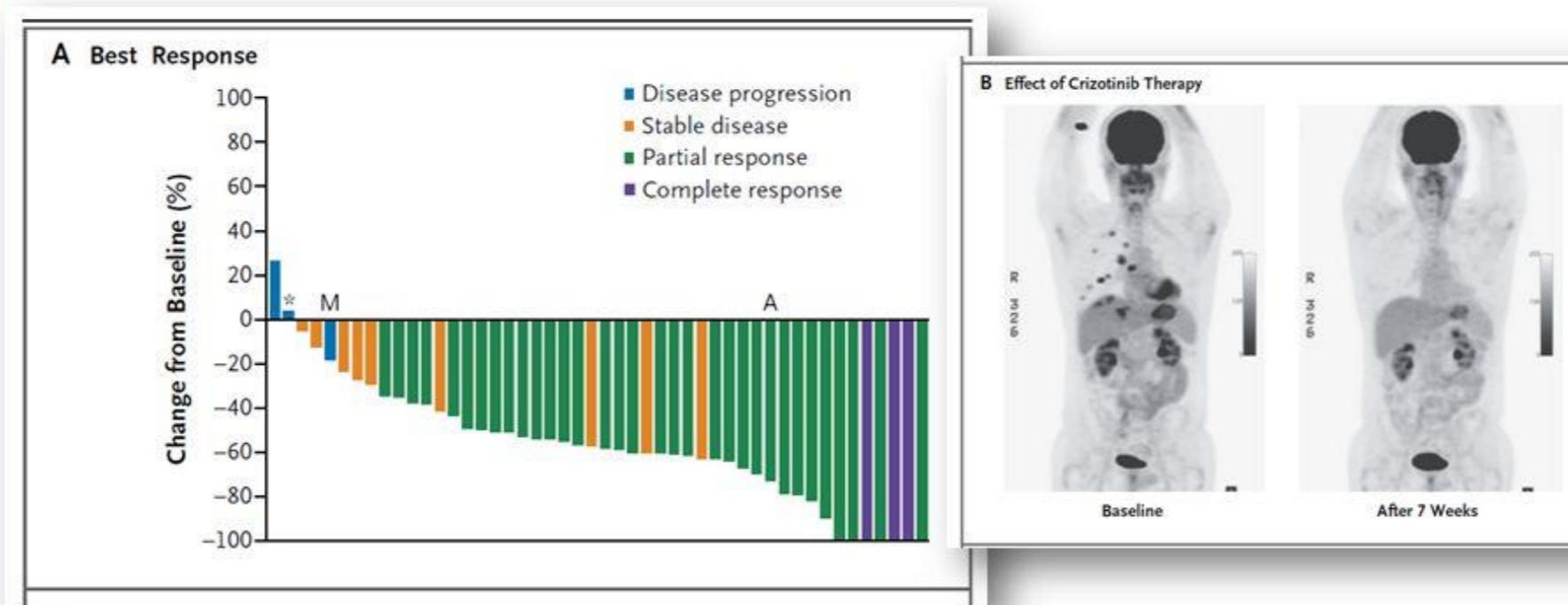






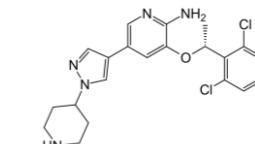


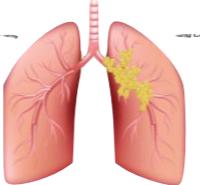
Tumor responses to crizotinib in ROS1-rearranged NSCLC



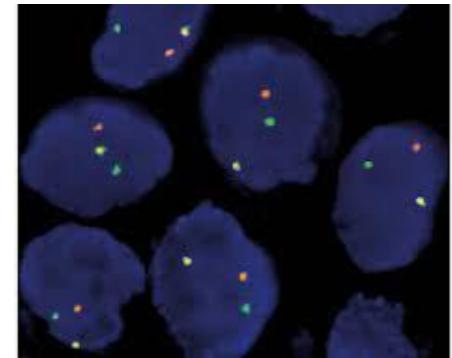
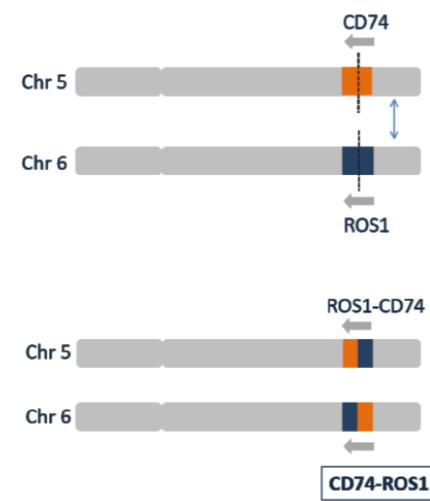
Overall response rate 72% (6% CR, 66% PR).
Median time to response 7.9 weeks (range, 4.3 - 32.0)

Shaw AT et al, N Engl J Med 2014;371:1963-71.

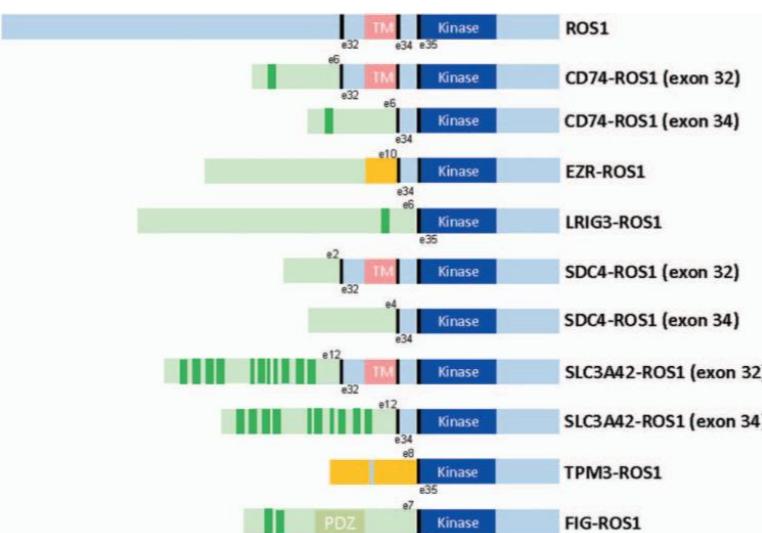




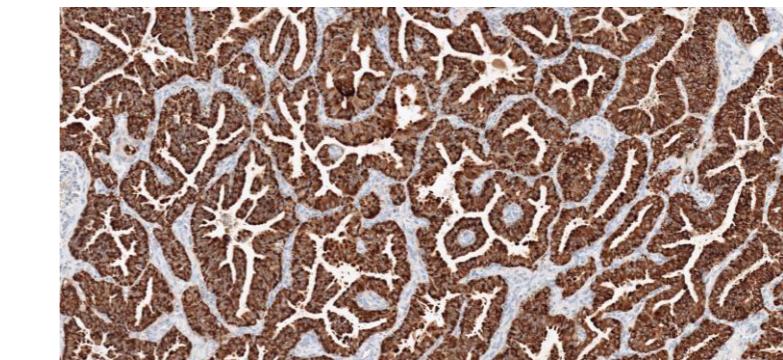
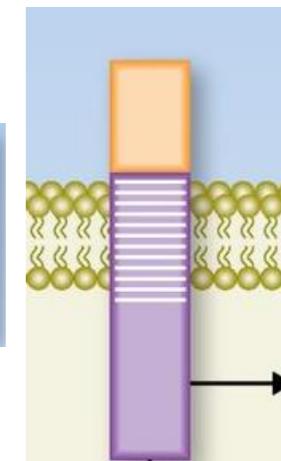
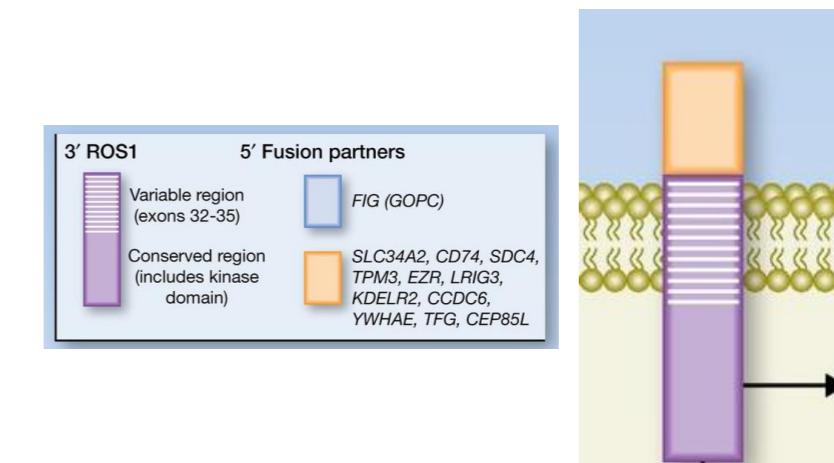
Detection of chromosomal changes

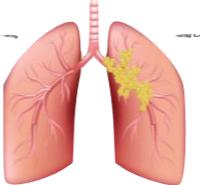


Detection of fusion RNA

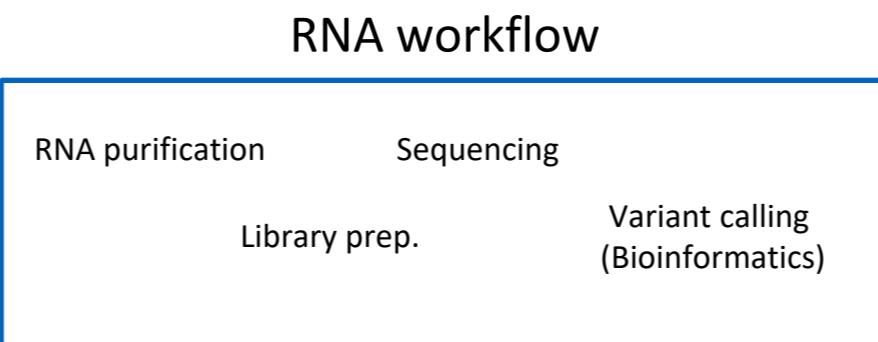
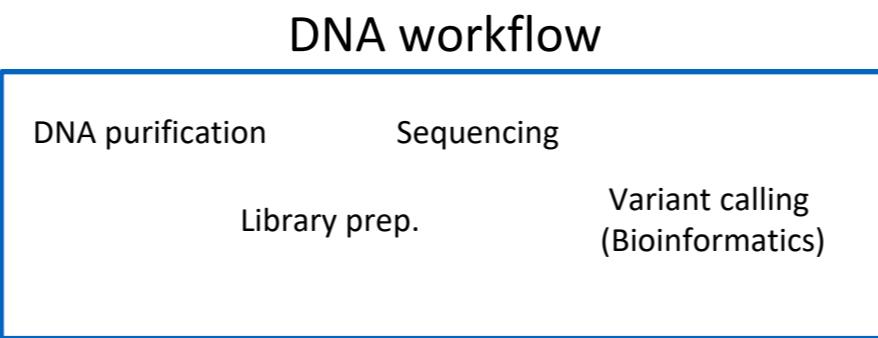
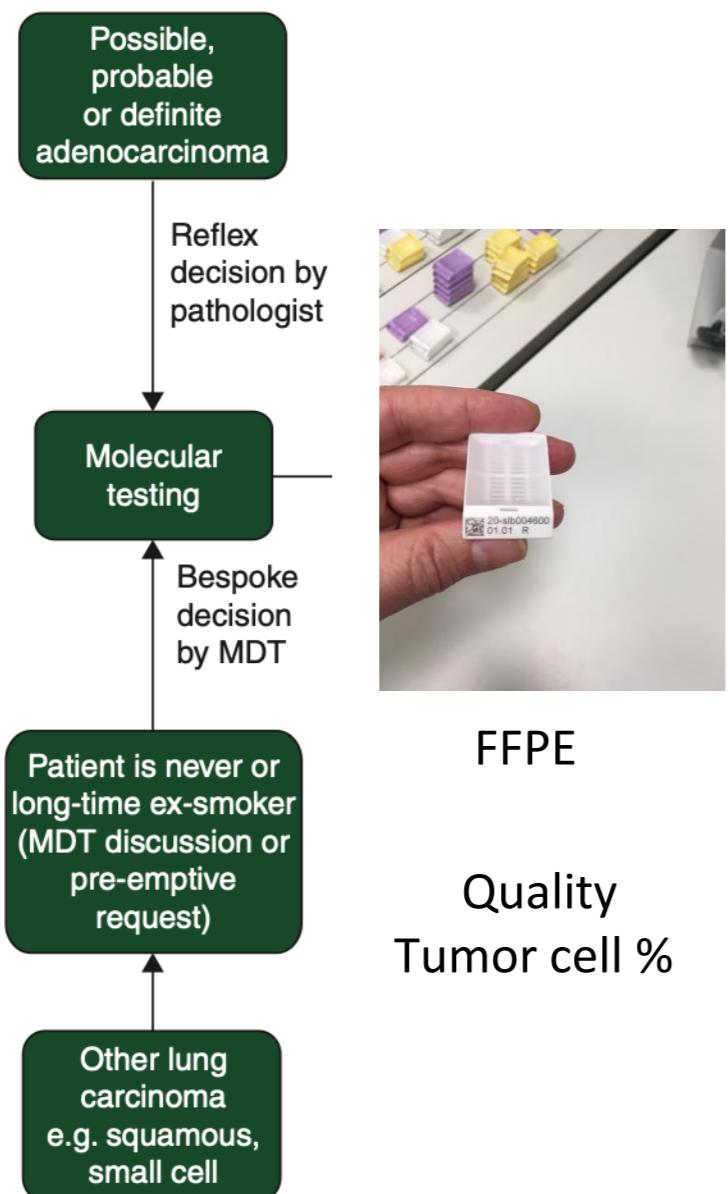


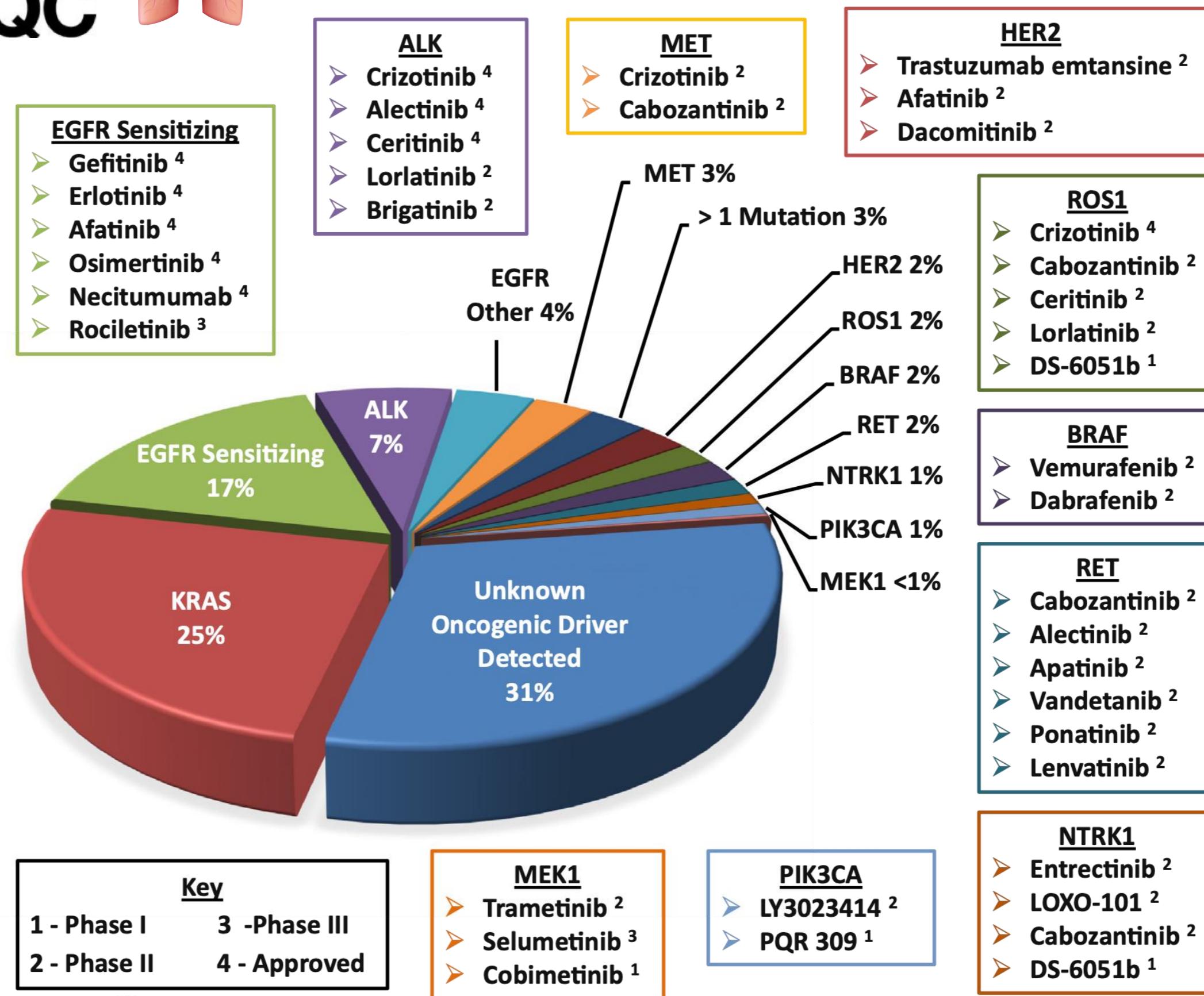
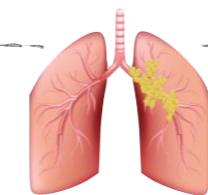
Detection of fusion protein

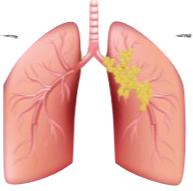




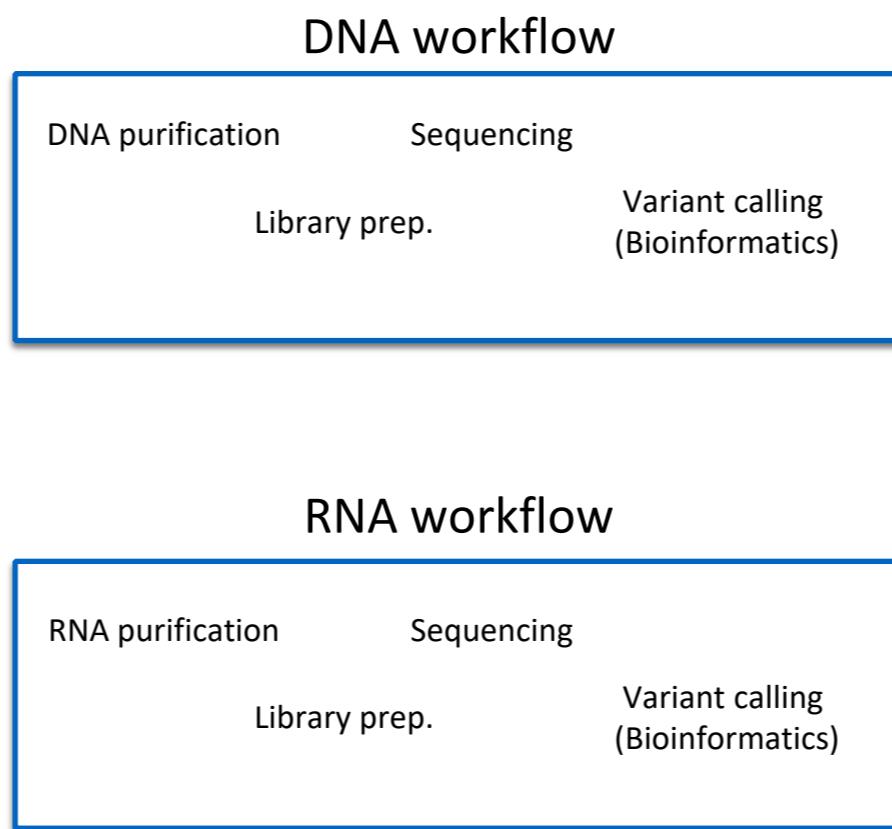
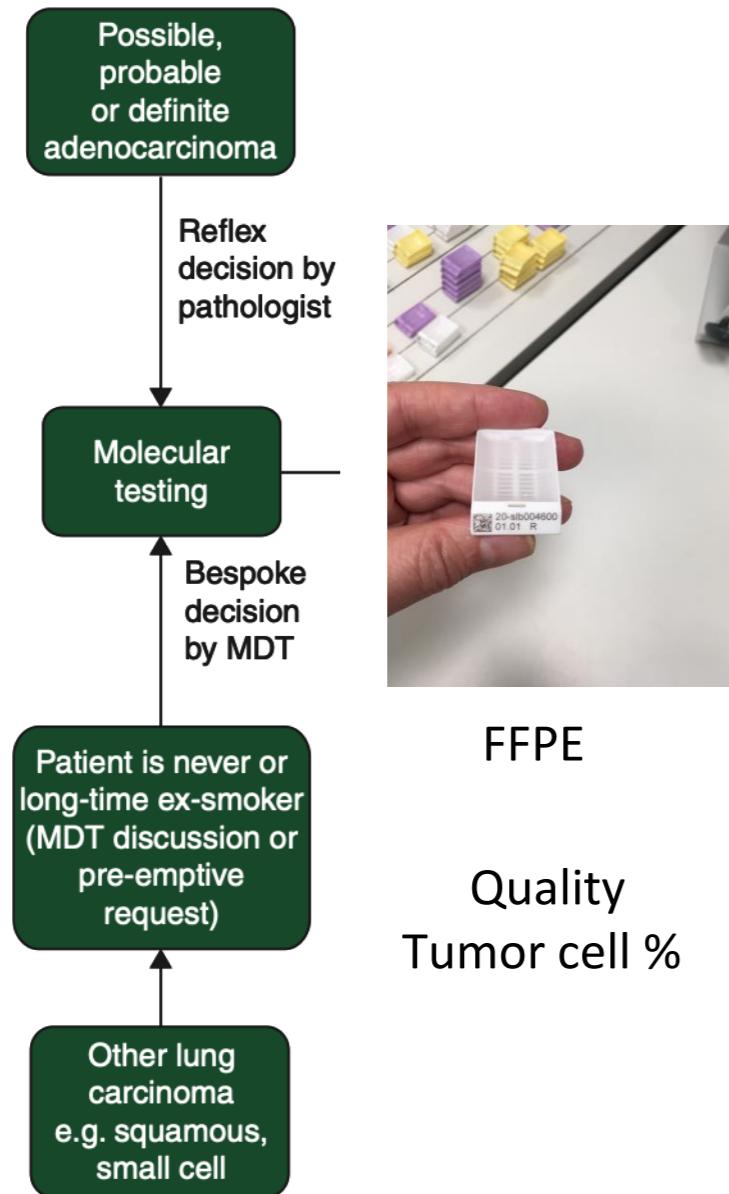
Next generation seq.







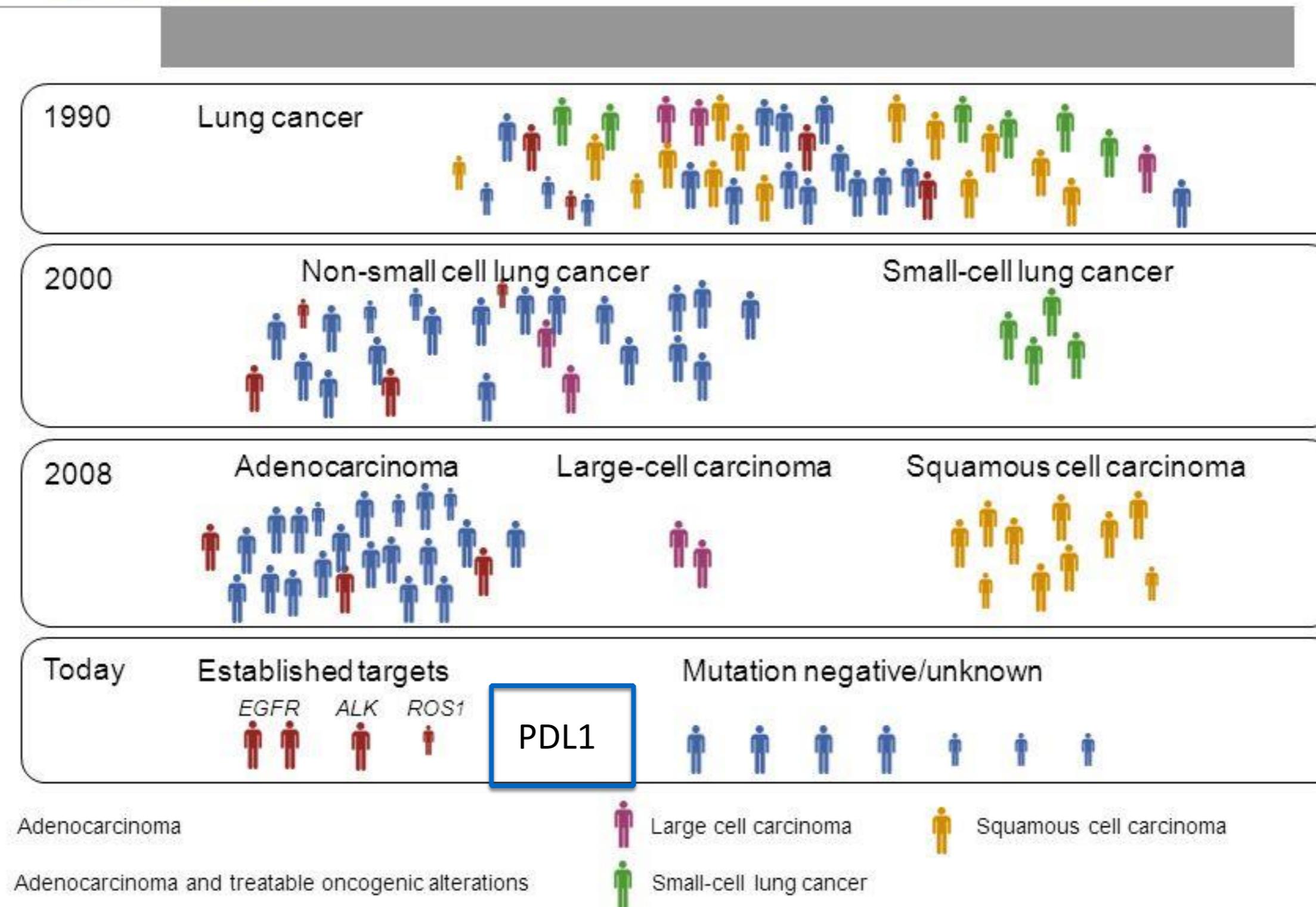
Next generation seq.

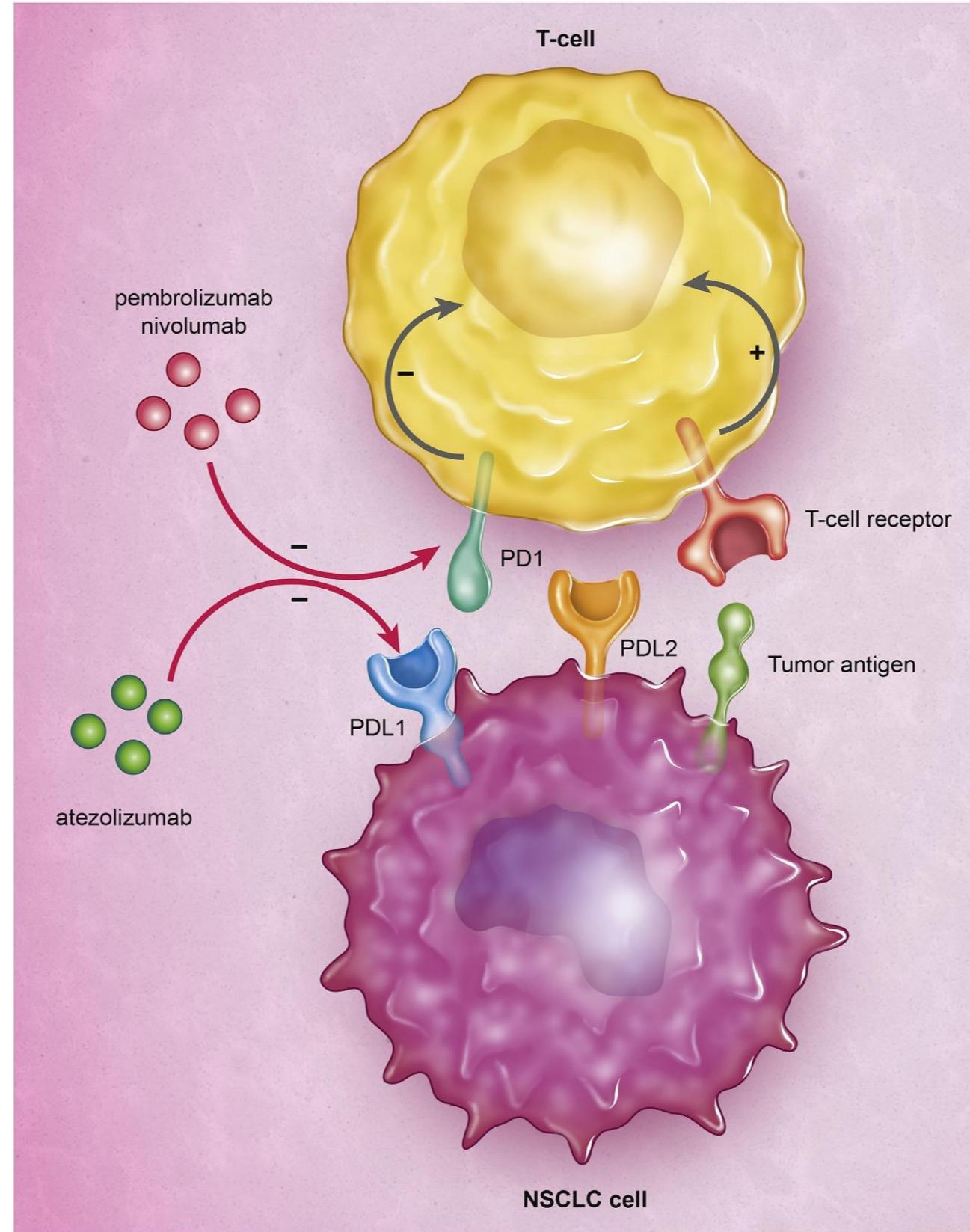
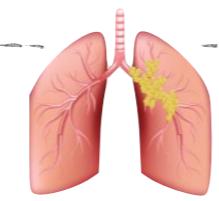


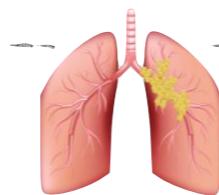
Comprehensive Result



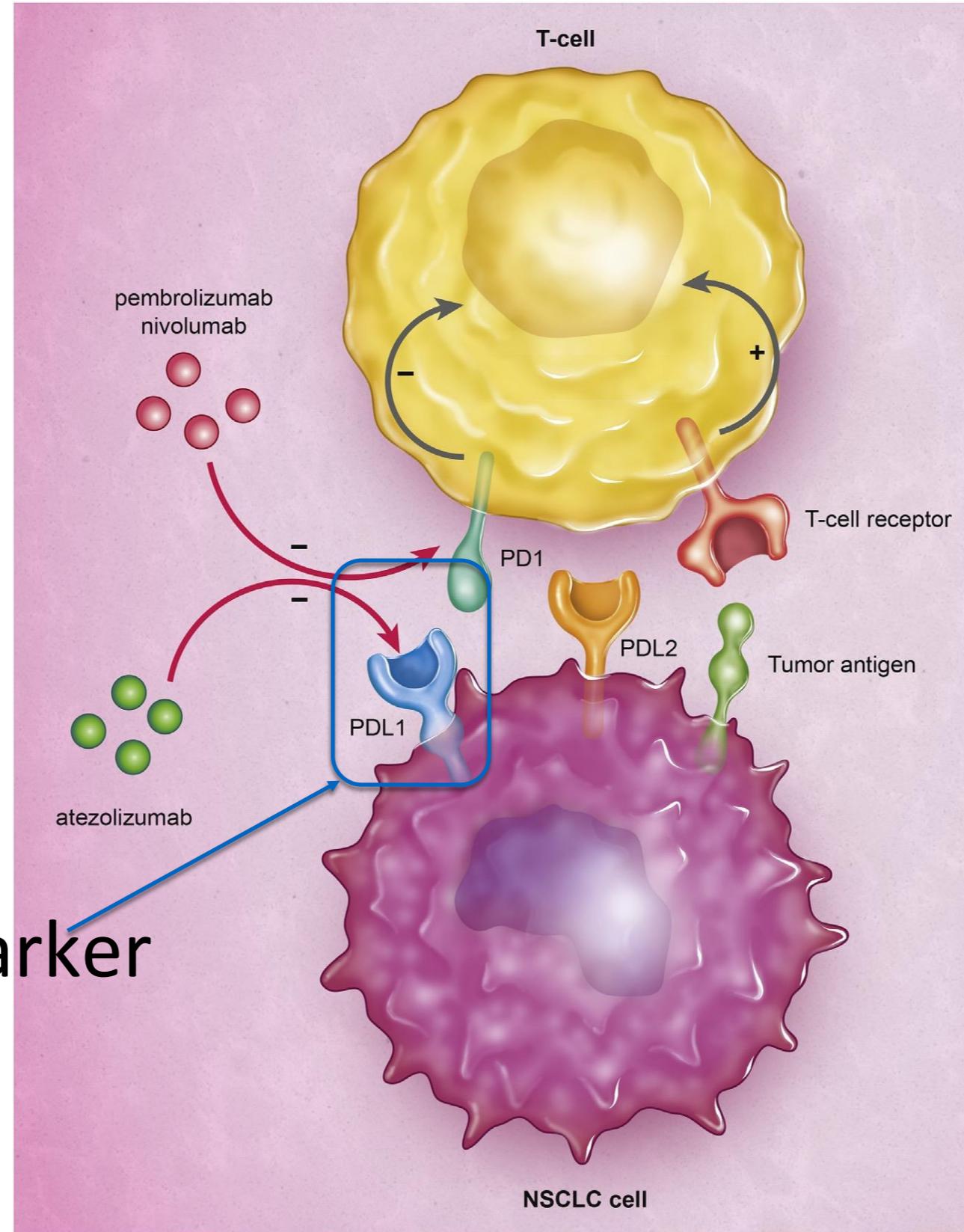
Patient selection in lung cancer: Evolution over time







Predictive marker





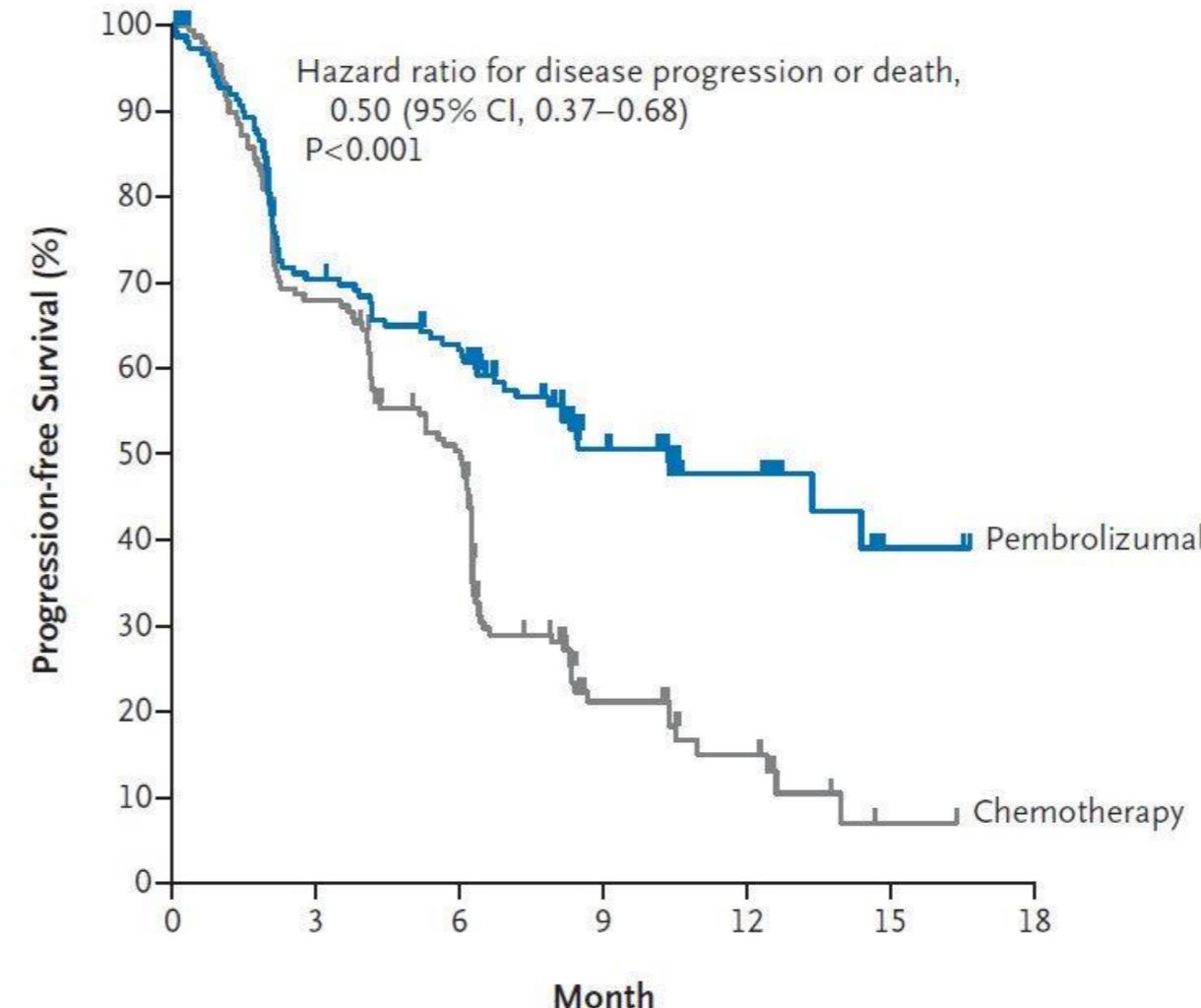
ESTABLISHED IN 1812

NOVEMBER 10, 2016

VOL. 375 NO. 19

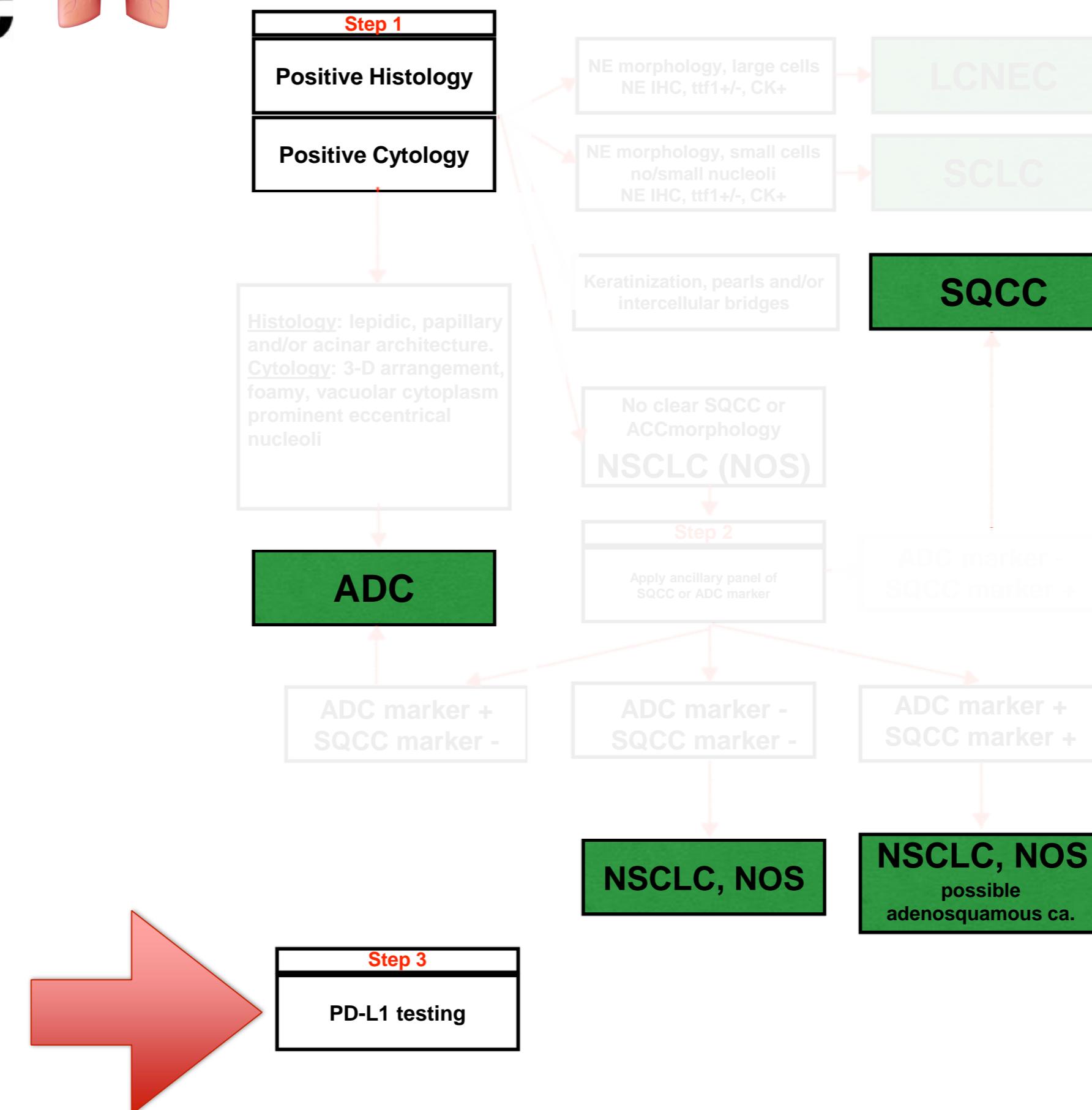
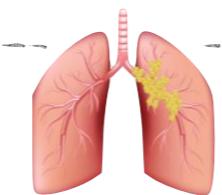
Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer

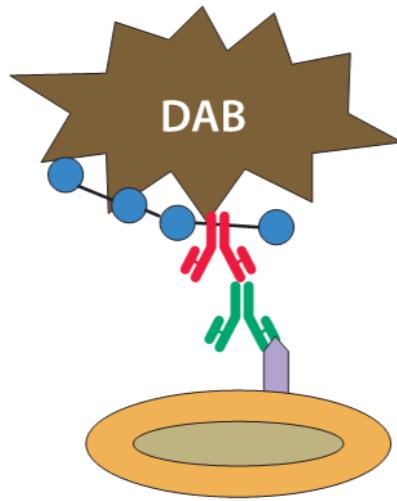
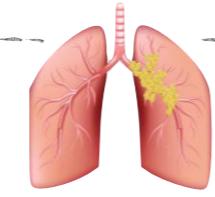
Martin Reck, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D., Andrew G. Robinson, M.D., Rina Hui, M.B., B.S., Ph.D., Tibor Csőszsi, M.D., Andrea Fülöp, M.D., Maya Gottfried, M.D., Nir Peled, M.D., Ph.D., Ali Tafreshi, M.D., Sinead Cuffe, M.D., Mary O'Brien, M.D., Suman Rao, M.D., Katsuyuki Hotta, M.D., Ph.D., 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*



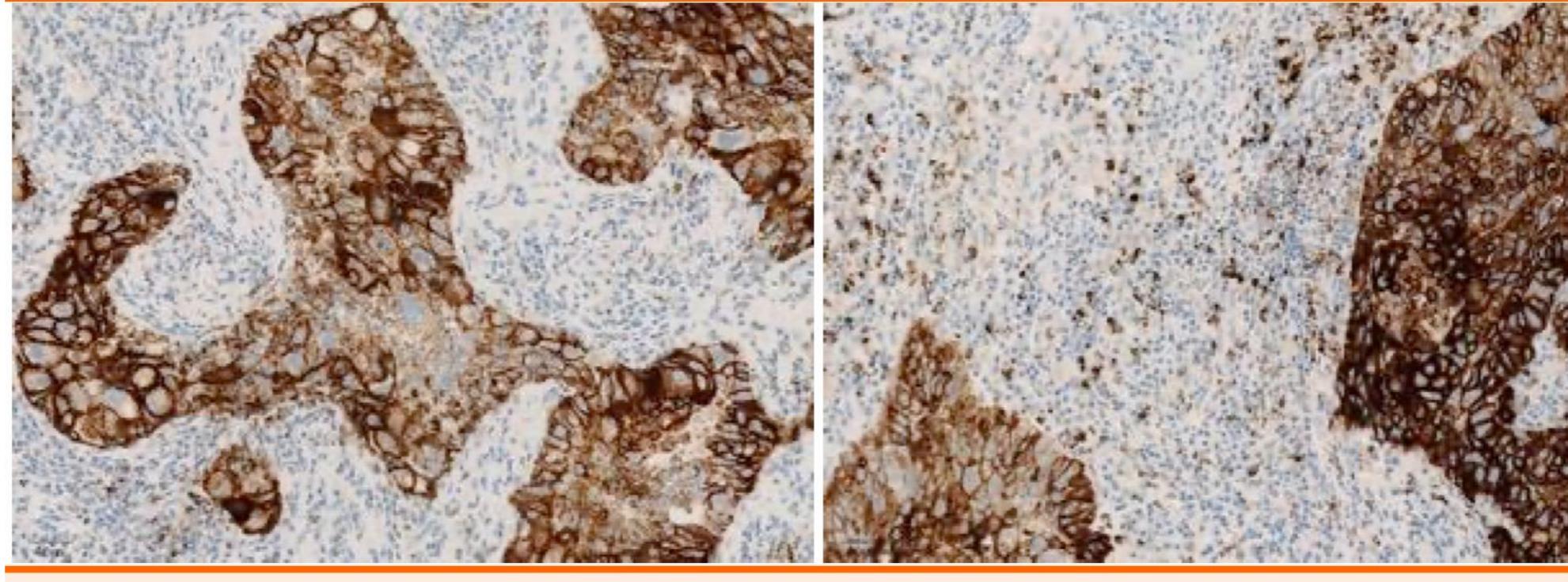
No. at Risk

	154	104	89	44	22	3	1
Pembrolizumab	154	104	89	44	22	3	1
Chemotherapy	151	99	70	18	9	1	0





**Tumor cells
(TCs)**



**Tumor and immune cells
(TCs and ICs)**

Immunhistological staining for PDL1

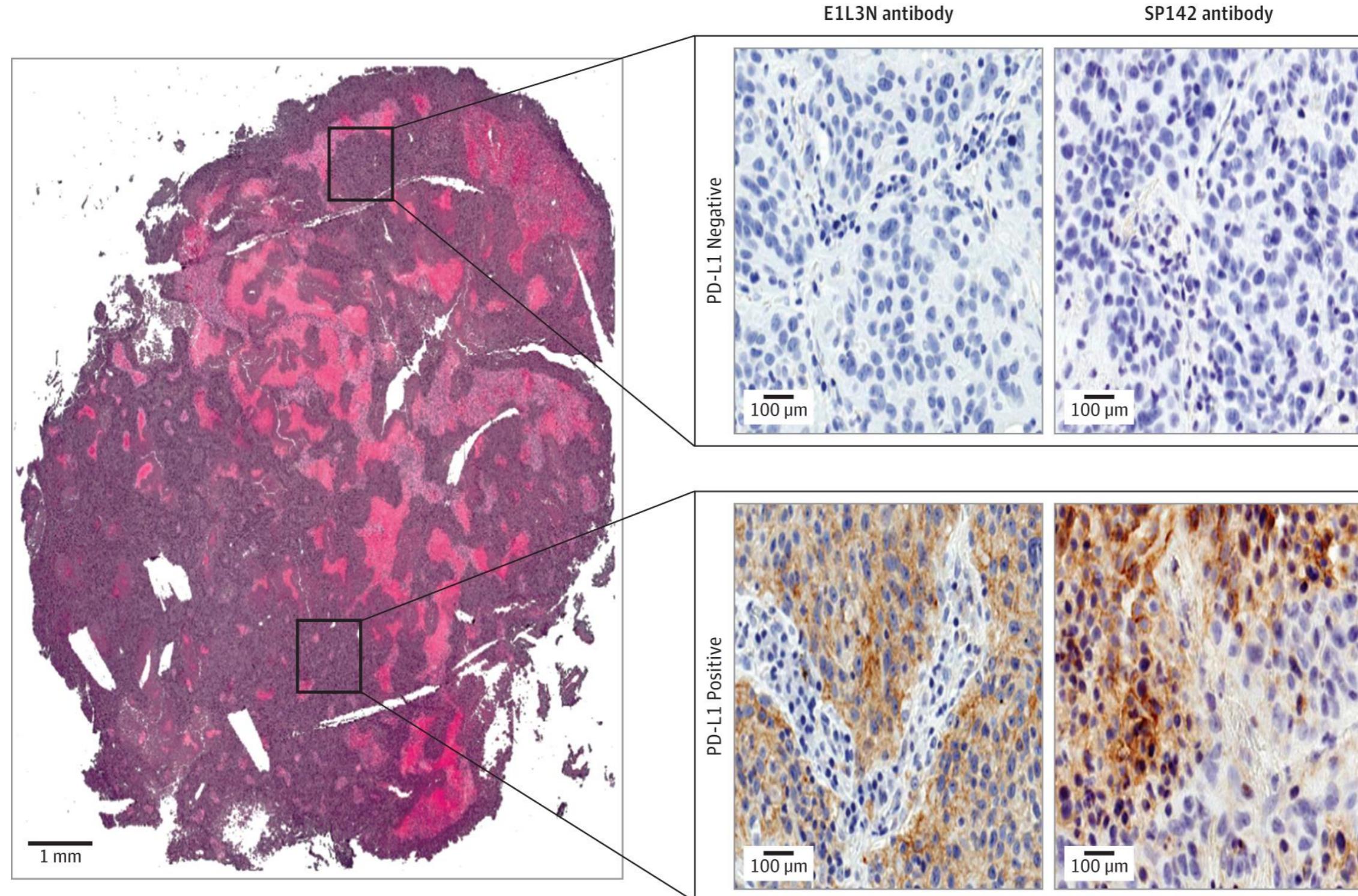
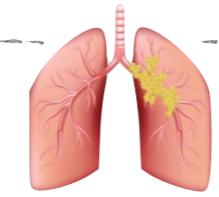


Table 1

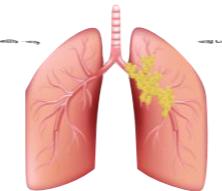
Results of randomised phase III trials of immune checkpoint inhibitors (ICIs) for advanced non-small-cell lung cancer (NSCLC).

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

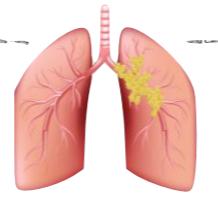
Abbreviations: ORR, overall response rate; PDL1, programmed death-ligand 1; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; L1, first-line; L2, second-line.

^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.



Test	Ventana SP263 (1)	Dako 22C3 (2)	Dako 28-8 (3)	Ventana SP142 (4)
Developed as companion diagnostic assay for:	Durvalumab (AstraZeneca/ MedImmune)	Pembrolizumab (Merck Sharp & Dohme)	Nivolumab [SEP](Bristol-Myers Squibb)	Atezolizumab [SEP](Genentech)
Instrument	VENTANA BenchMark ULTRA	Dako Autostainer Link 48	Dako Autostainer [SEP]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 [SEP]high PD-L1 expression	≥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 with immune cells (if <50% of tumor cells) (8)

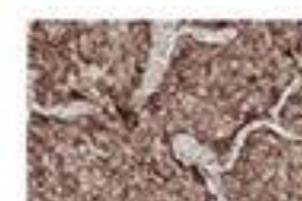
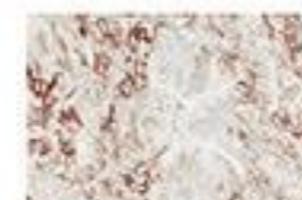


Range of staining 0%

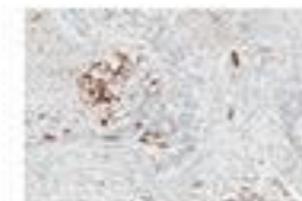


100%

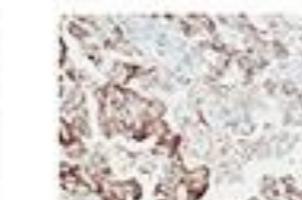
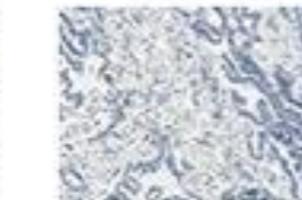
Ventana
SP263



Dako
22C3



Dako
28-8



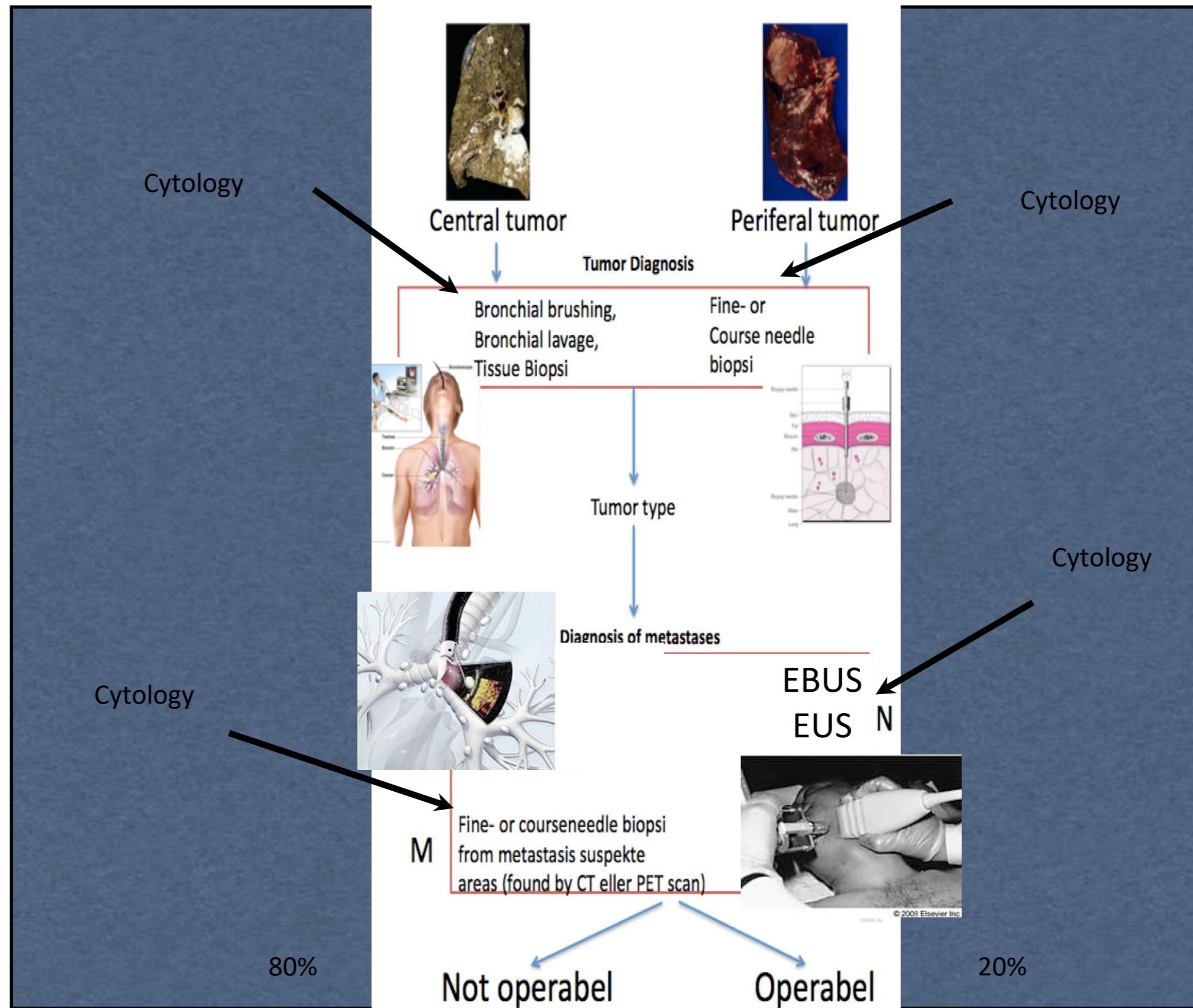
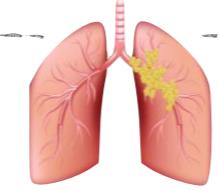
Published OnlineFirst January 10, 2017; DOI: 10.1158/1078-0432.CCR-16-2375

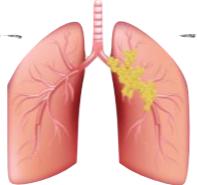
Cancer Therapy: Clinical

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





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†

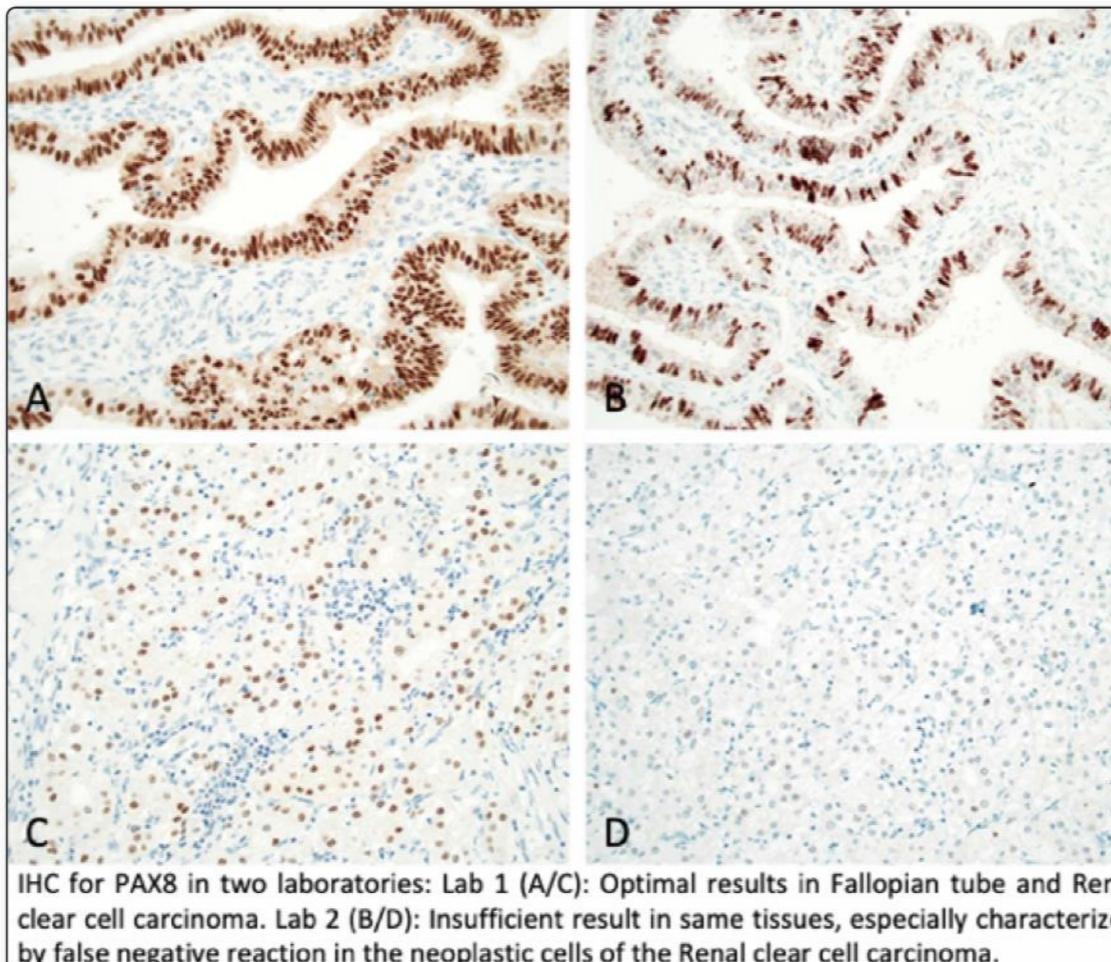
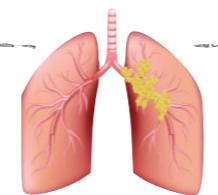
Conclusion: PD-L1 assessment is feasible on cytologic material with the tested assays using cutoffs for positivity similar to those used on histologic material.

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

Values are represented as percent, 95% CI.

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



Results - Run 56, C5

9-Jul-2019

The results for the runs 56 and C5 are now available on the website. Individual results can be seen after logging in.

[All news](#)

Events

[NordiQC Workshop in Diagnostic Immunohistochemistry](#)
2-4 Oct 2019: Aalborg, DK

[6th Academy of Diagnostic Immunohistochemistry](#)
9-11 Oct 2019: Krakow, Poland

[4th NordiQC Conference on Applied Immunohistochemistry](#)
2-5 Jun 2020: Aalborg, Denmark

Important dates

[Run 57, B28, H16, C6](#)
Protocol submission deadline
4 Sep 2019
Slide circulation
10 Sep 2019
Slide return deadline
11 Oct 2019
Publication of results
6 Dec 2019

Questions

Check out our [FAQ](#) (Frequently asked questions) or [contact us](#)

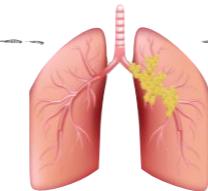


Table 2. Assessment marks for IHC assays and antibodies run C9, PD-L1 TPS/CPS (KEYTRUDA®)

CE-IVD / FDA approved PD-L1 assays	n	Vendor	Optimal	Good	Borderline	Poor	Suff. ¹	OR ²
rmAb clone SP263, 741-4905 (VRPS)³	42	Ventana/Roche	29	9	4	-	91%	69%
rmAb clone SP263, 741-4905 (LMPs)⁴	2	Ventana/Roche	-	-	1	1	-	-
rmAb clone SP263, 740-4907 (VRPS)³	13	Ventana/Roche	8	4	1	-	92%	62%
rmAb clone SP142, 740-4859 (VRPS)³	1	Ventana/Roche	-	-	-	1	-	-
mAb clone 22C3 pharmDX, SK006 (VRPS)³	23	Dako/Agilent	5	14	4	-	83%	22%
mAb clone 22C3 pharmDX, SK006 (LMPs)⁴	9	Dako/Agilent	2	3	2	2	56%	22%
mAb clone 22C3 pharmDX, GE006 (VRPS)³	21	Dako/Agilent	17	4	-	-	100%	81%
mAb clone 22C3 pharmDX, GE006 (LMPs)⁴	7	Dako/Agilent	2	3	2	-	71%	29%
rmAb clone 28-8 pharmDX, SK005 (VRPS)³	2	Dako/Agilent	2	-	-	-	-	-
Antibodies ⁵ for laboratory developed PD-L1 assays, concentrated antibodies	n	Vendor	Optimal	Good	Borderline	Poor	Suff. ¹	OR ²
mAb clone 22C3	38	Dako/Agilent	10	21	5	2	82%	26%
mAb clone E1L3N	4	Cell Signaling	-	1	3	-	-	-
rmAb clone 28-8	1	Abcam	-	1	-	-	-	-
rmAb clone BSR90	1	Nordic Biosite	-	1	-	-	-	-
rmAb CAL10	3	Biocare	3	1	-	-	-	-
	1	Zytomed Systems						
rmAb clone QR1	1	Biocyc	-	-	1	-	-	-
rmAb clone SP142	1	Abcam	-	1	-	-	-	-
rmAb clone ZR3	1	Zeta Corporation	-	-	2	-	-	-
	1	Zytomed systems						
Ready-To-Use antibodies ⁶	n	Vendor	Optimal	Good	Borderline	Poor	Suff. ¹	OR ²
rmAb clone SP263, 790-4905⁶ (VRPS)³	13	Ventana/Roche	8	3	1	1	85%	62%
rmAb clone SP263, 790-4905⁶ (LMPs)⁴	20	Ventana/Roche	12	6	1	1	90%	60%
mAb 405-9A11 PDM572	1	Diagnostic Biosystems	-	-	1	-	-	-
mAb IHC441 IHC441-7	1	GenomeMe	-	-	1	-	-	-
rmAb clone 73-10, PA0832 (VRPS)³	1	Leica Biosystems	-	1	-	-	-	-
rmAb clone MX070C, MAB-0854	2	Maixin	2	-	-	-	-	-
rmAb clone ZR3 GT228002	1	Gene Tech	-	-	1	-	-	-
Total	211		100	73	30	8		
Proportion			47%	35%	14%	4%	32%	

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

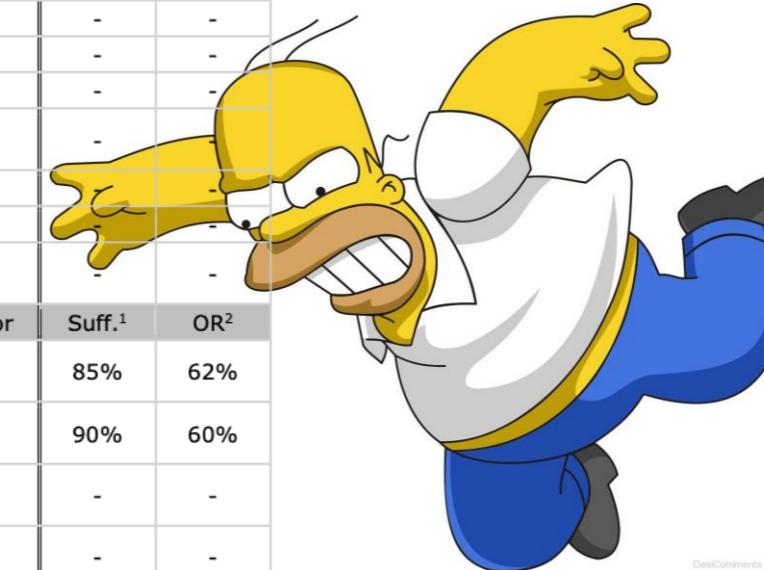
2) Proportion of optimal results.

3) Vendor recommended protocol settings – RTU product used in compliance to protocol settings, platform and package insert.

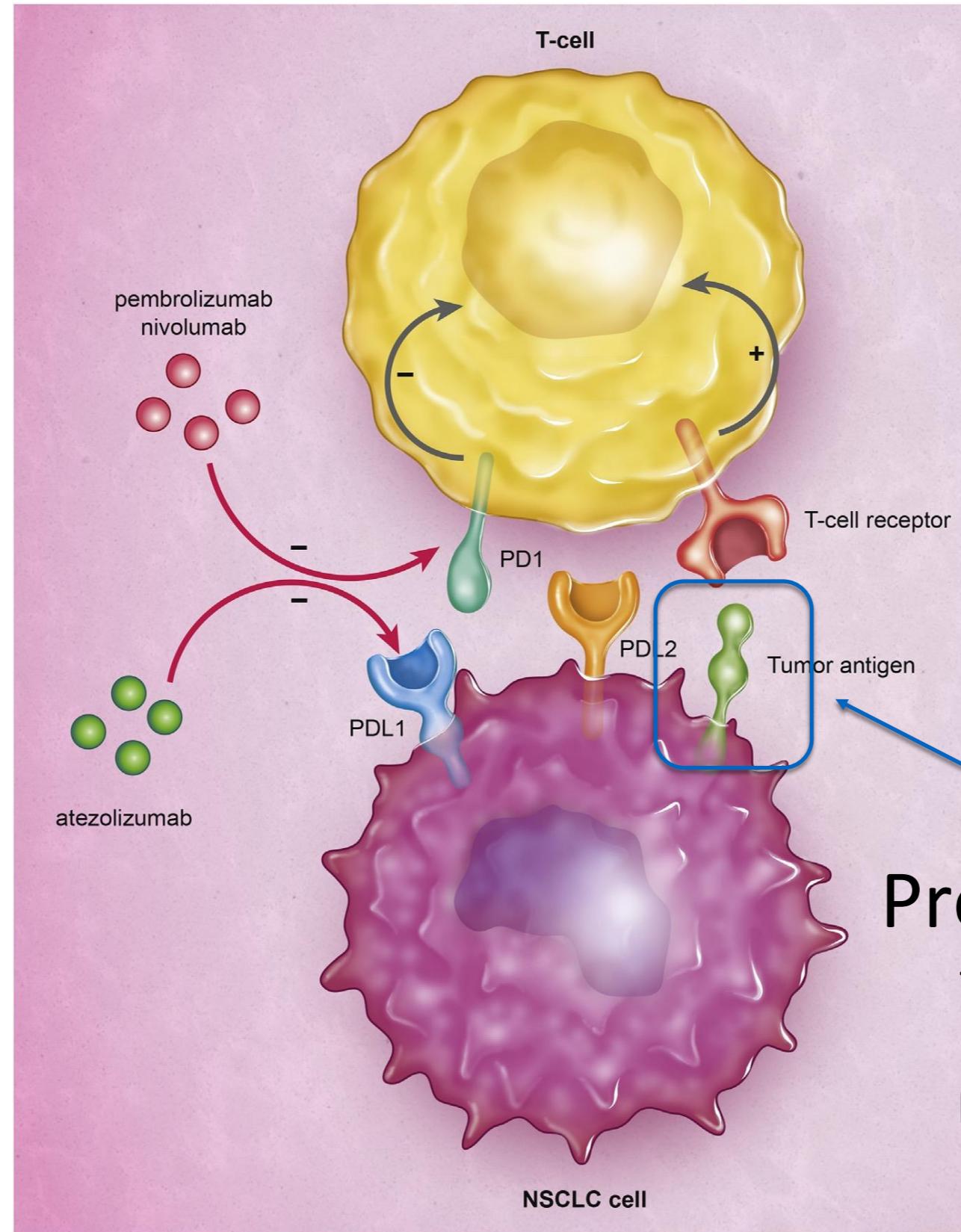
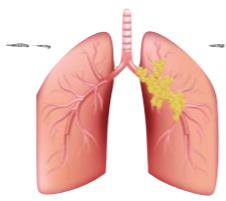
4) Laboratory modified protocol settings for a RTU product applied either on the vendor recommended platform(s) or other platforms.

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

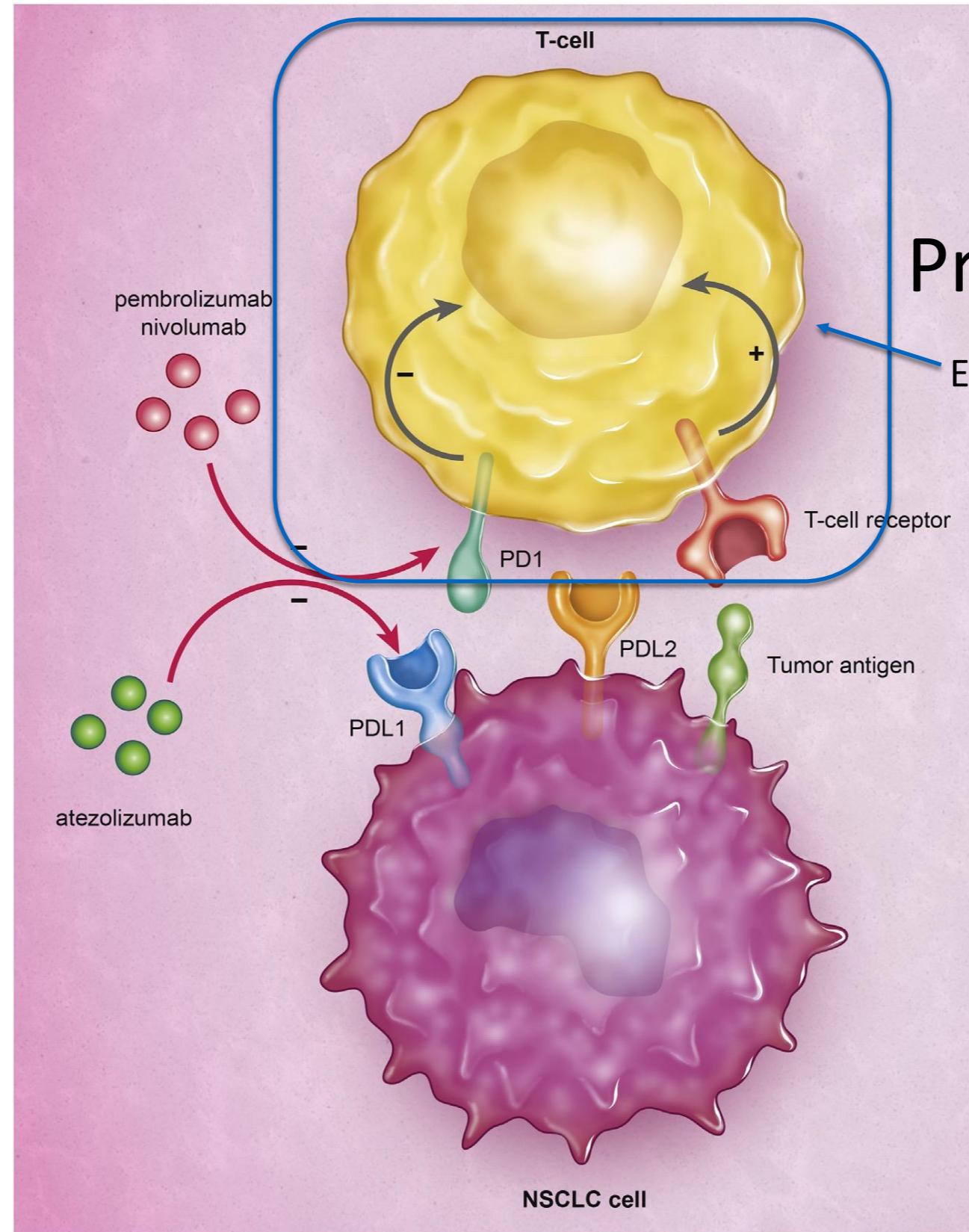
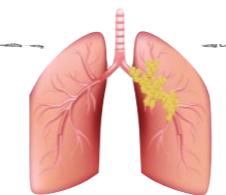
6) Ready-To-Use antibodies without predictive claim.



DensComments.com



Future:
Predictive marker
Tumor Mutational Burden
TMB
Micro Satellite Instability
MSI



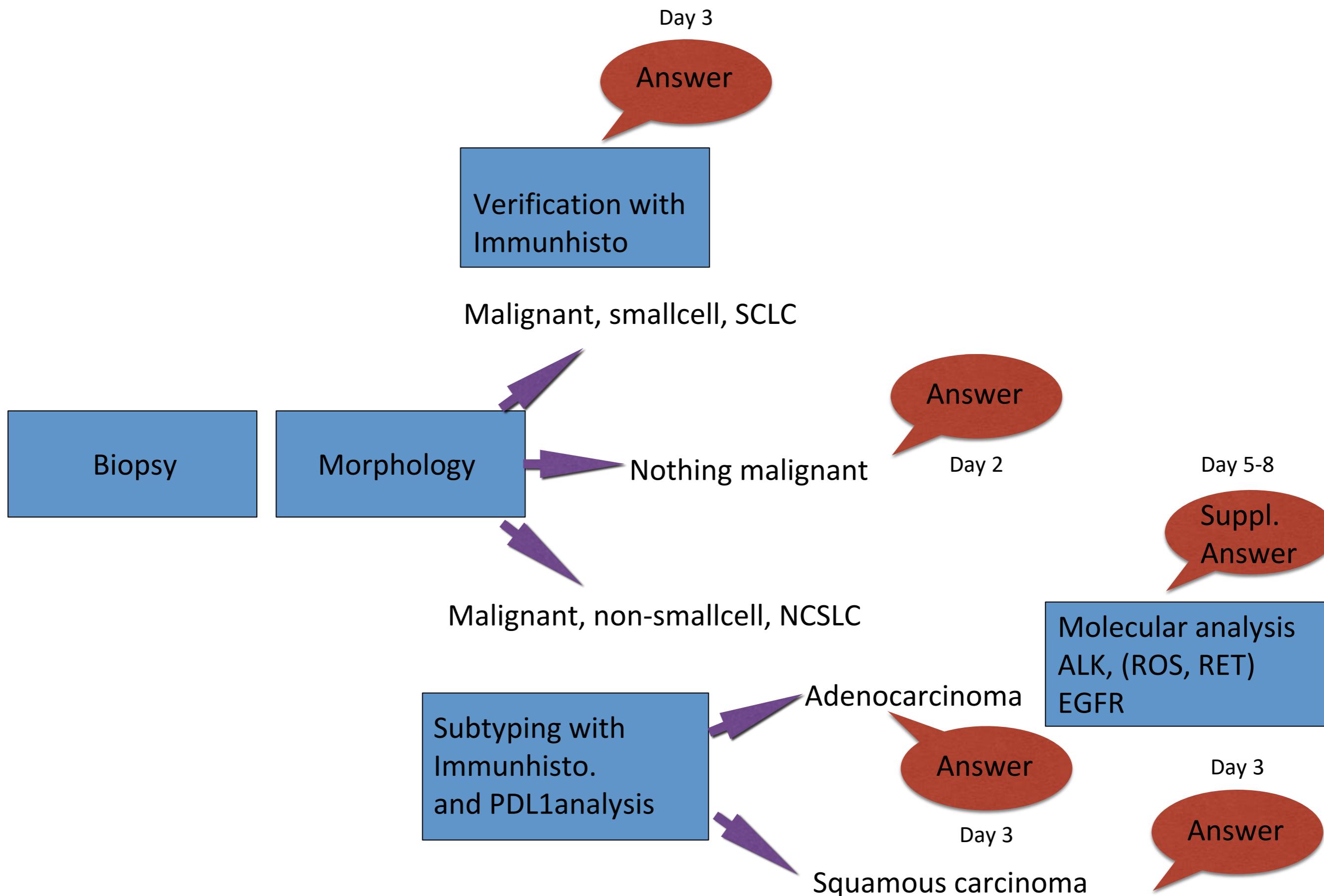
Future:
Predictive marker

Evaluation of immune responses

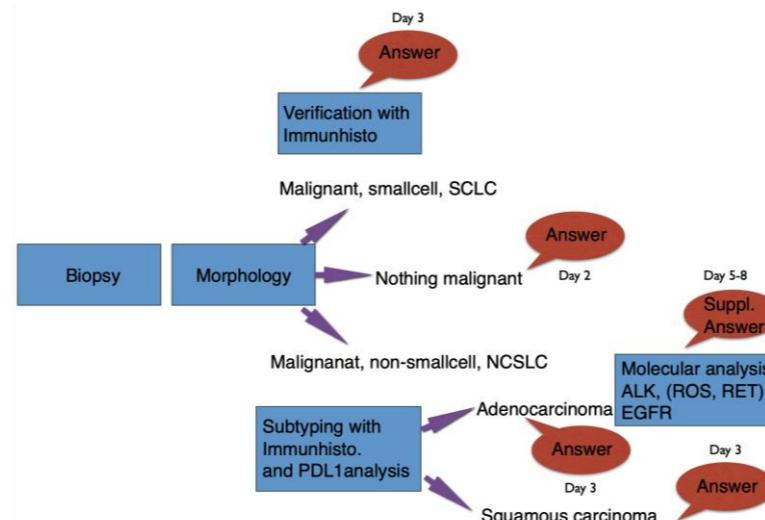


The Diagnostic algorithm

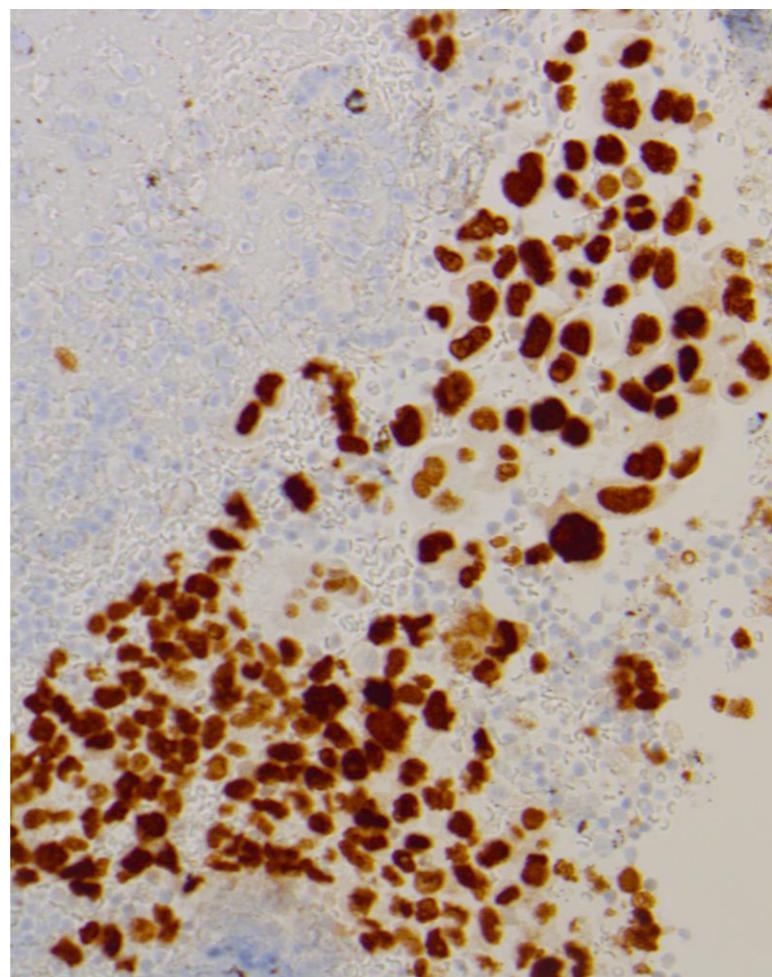
The Diagnostic algorithm



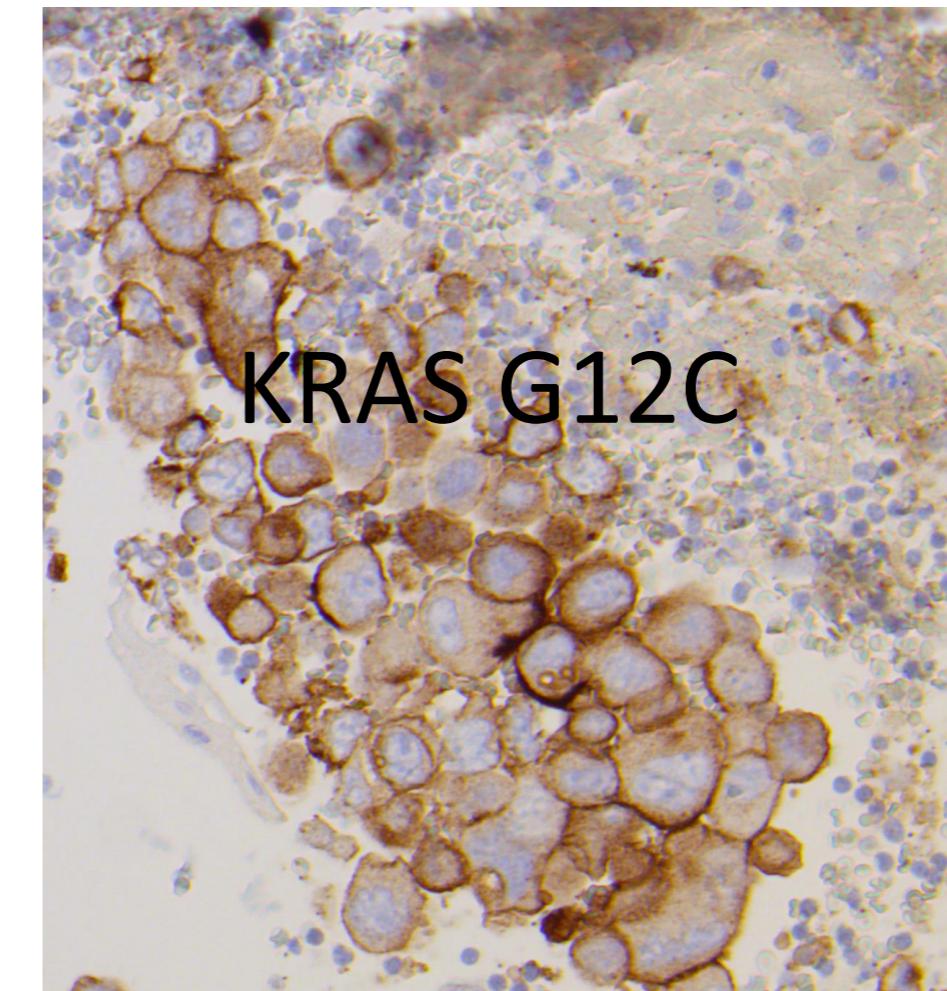
The Diagnostic algorithm



Pleura effusion Cell Block

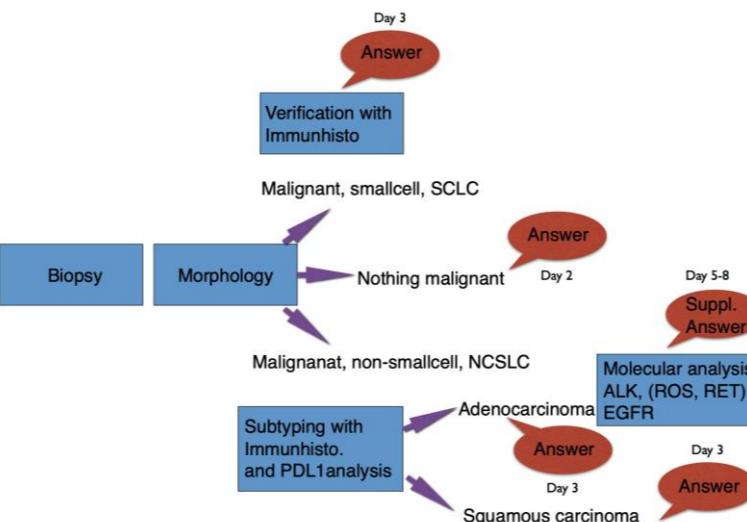


ttf1, CK7+



KRAS G12C
PD-L1(22C3)

The Diagnostic algorithm



Pleura effusion Cell Block

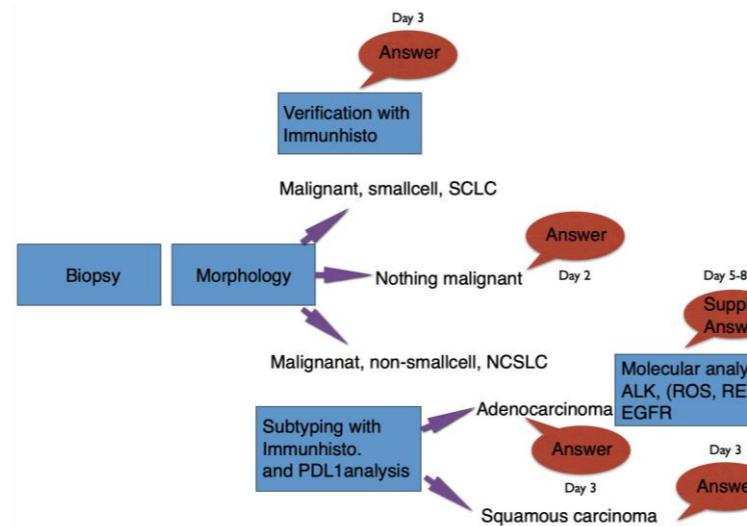
Mutation analysis

KRAS G12C

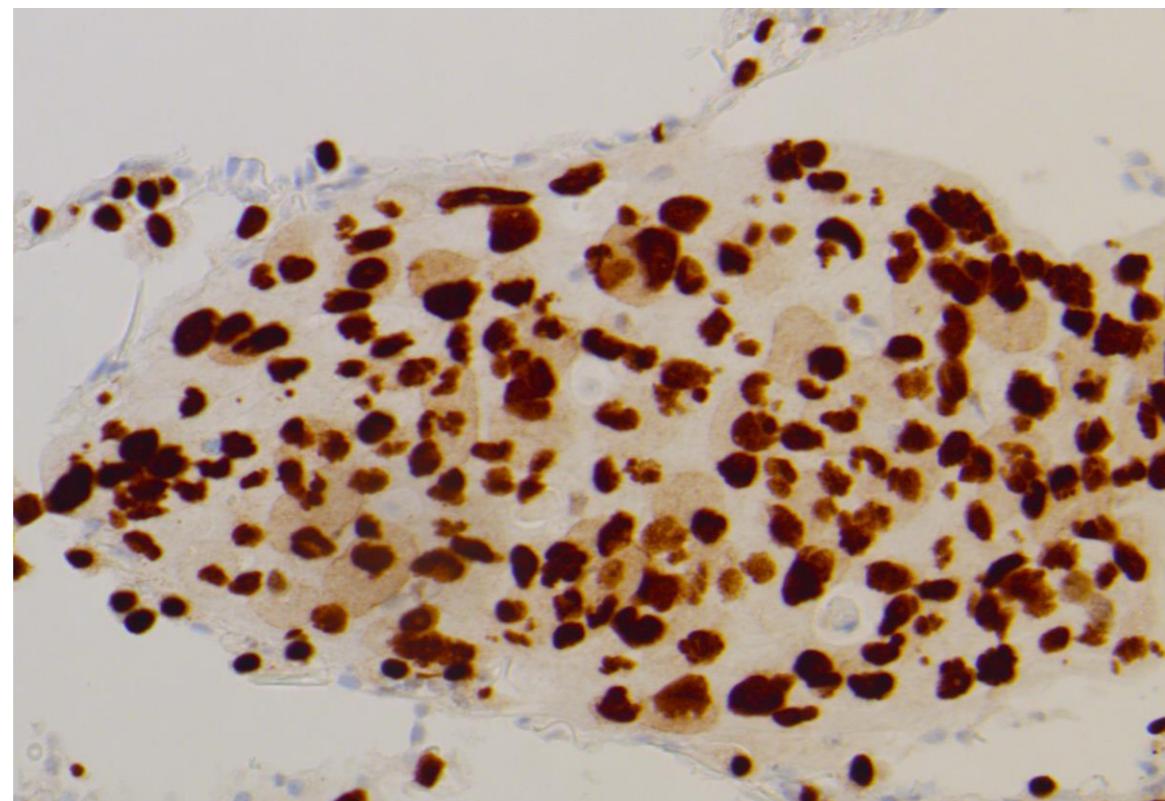


2. line TKI

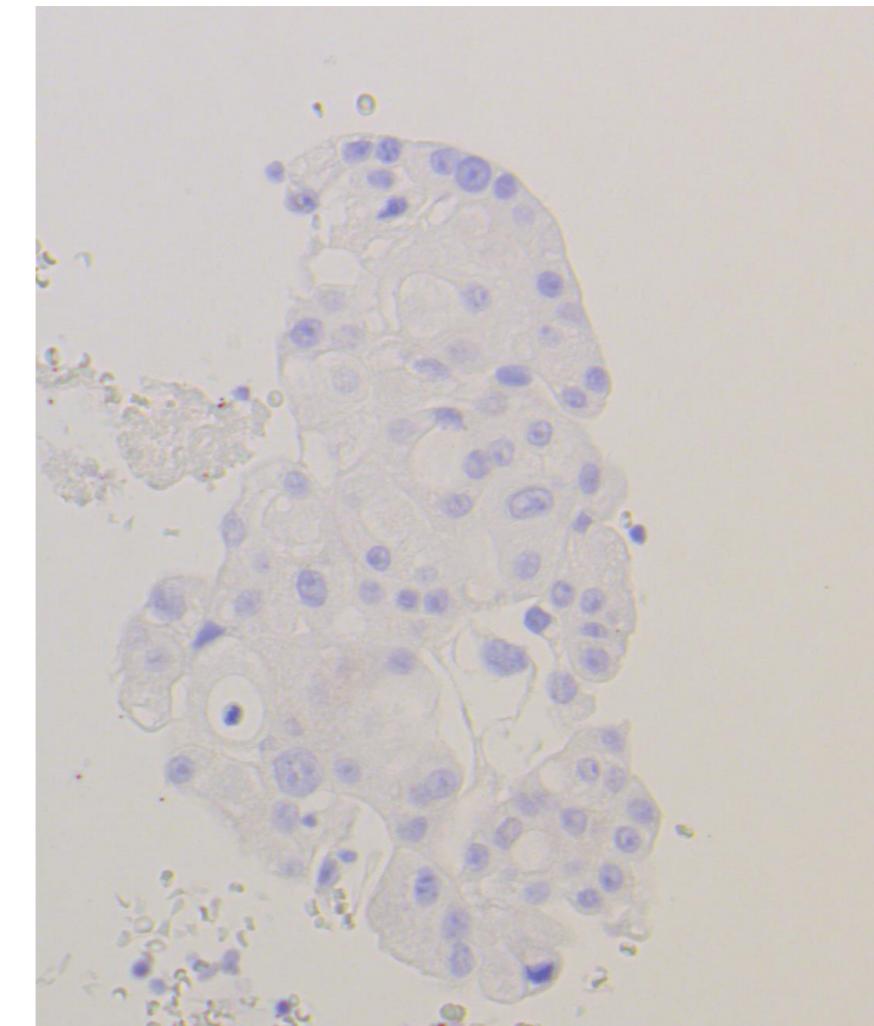
The Diagnostic algorithm



EBUS CellBlock

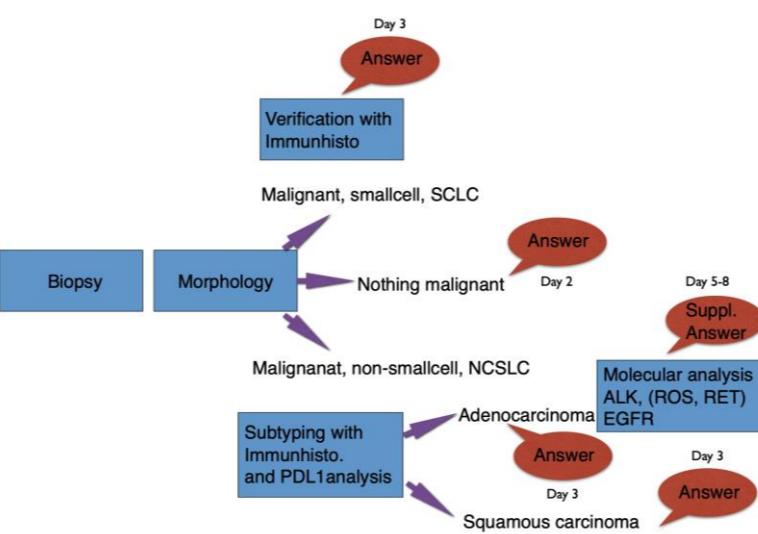


CK5/6, CK7 and P40+

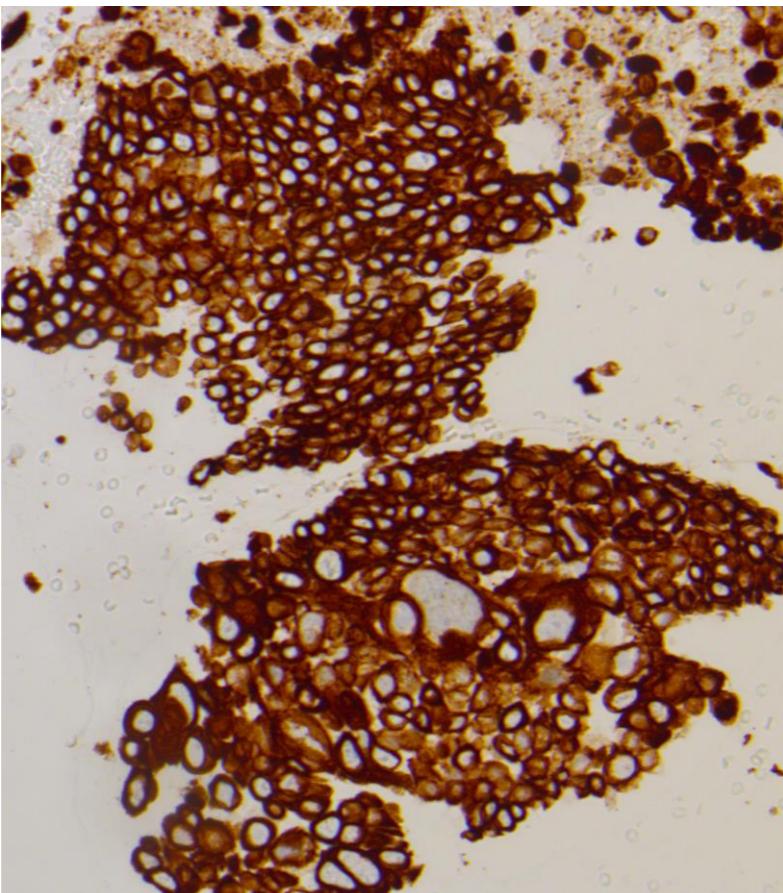


PD-L1 (22C3)

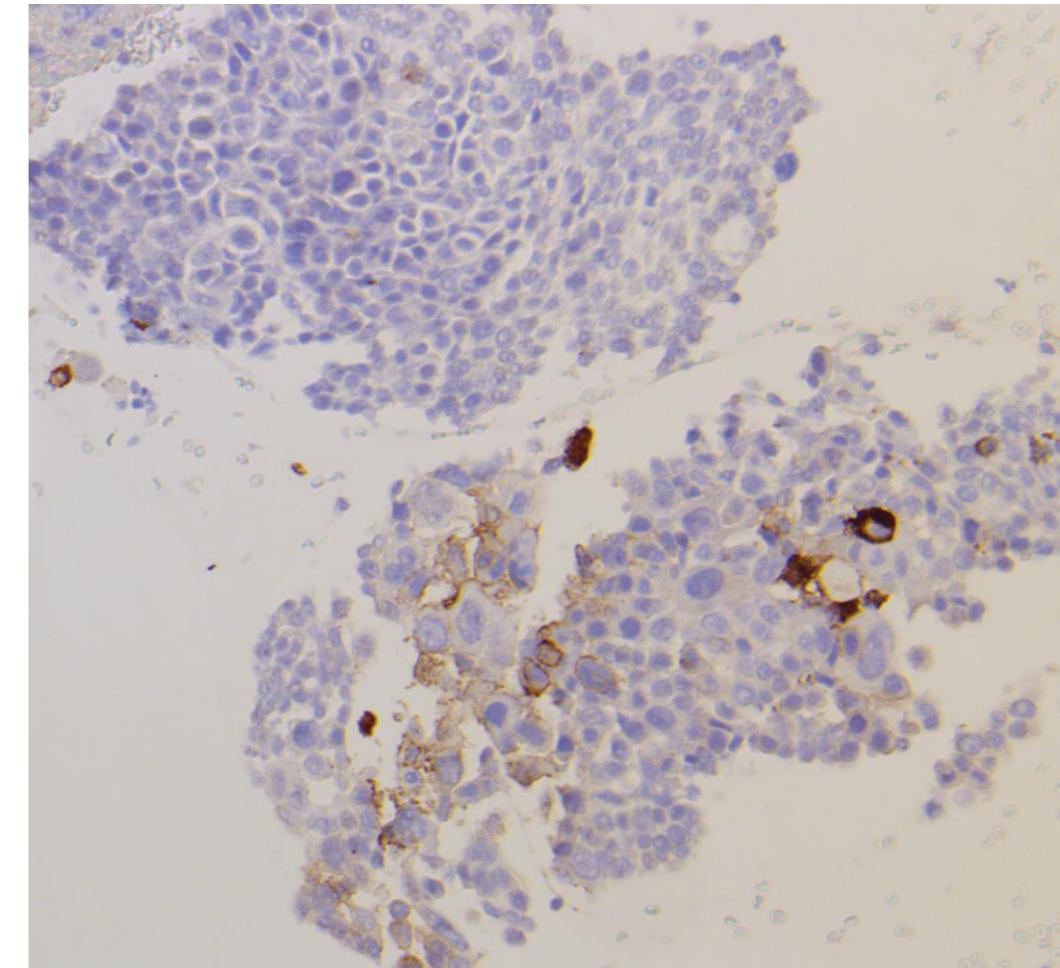
The Diagnostic algorithm



EBUS Cell Block

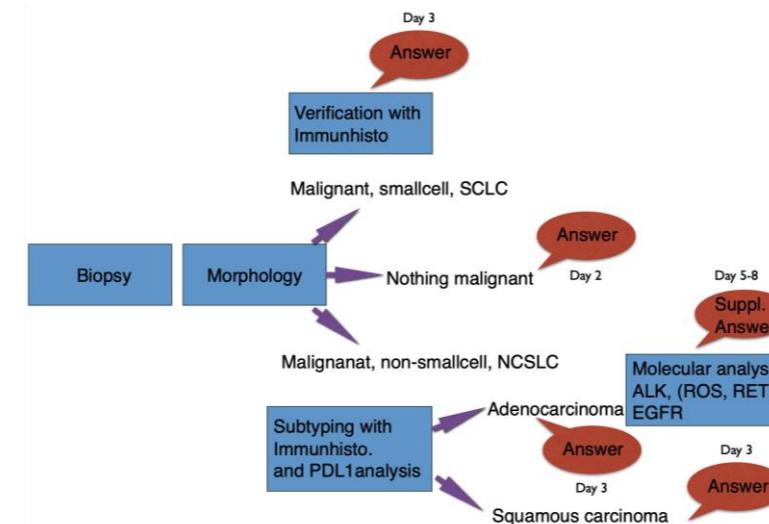


CK5/6 and P40+

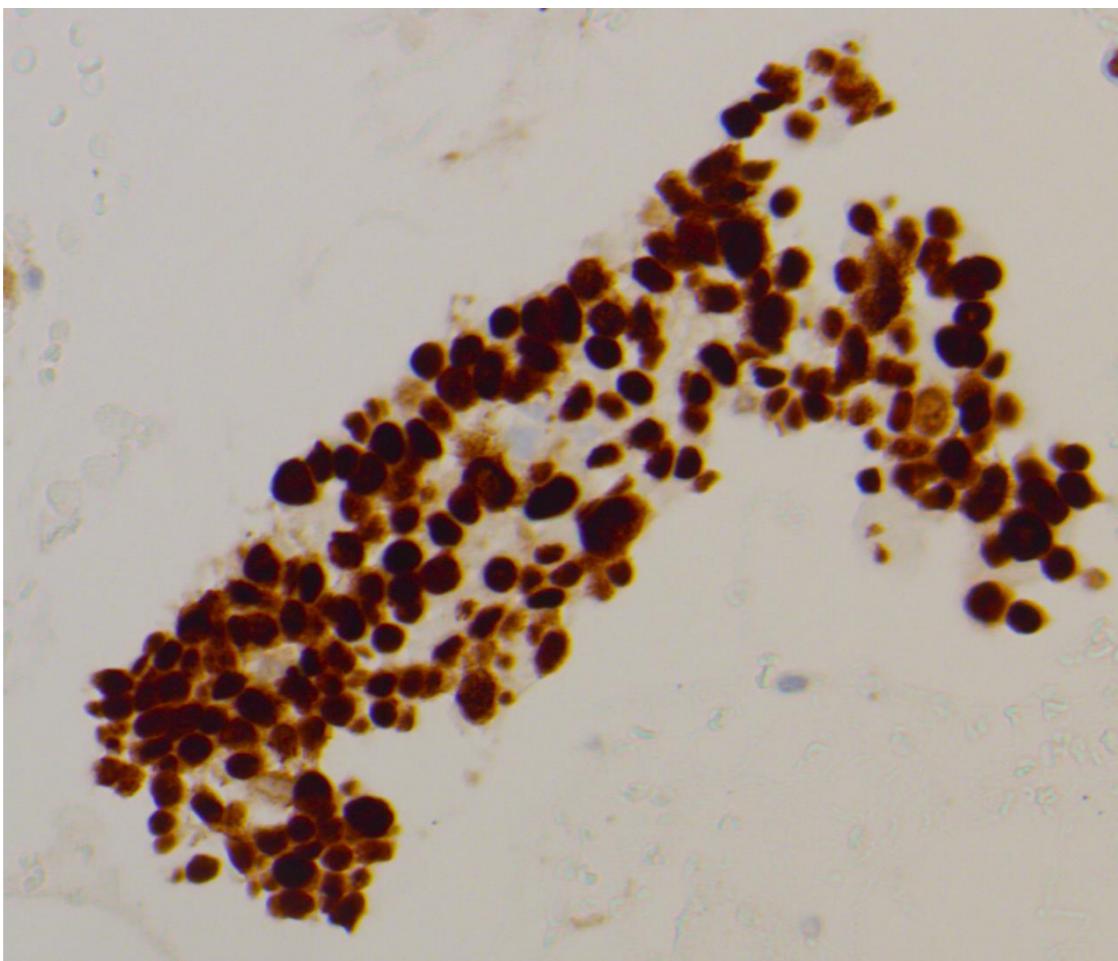


PD-L1 (22C3)

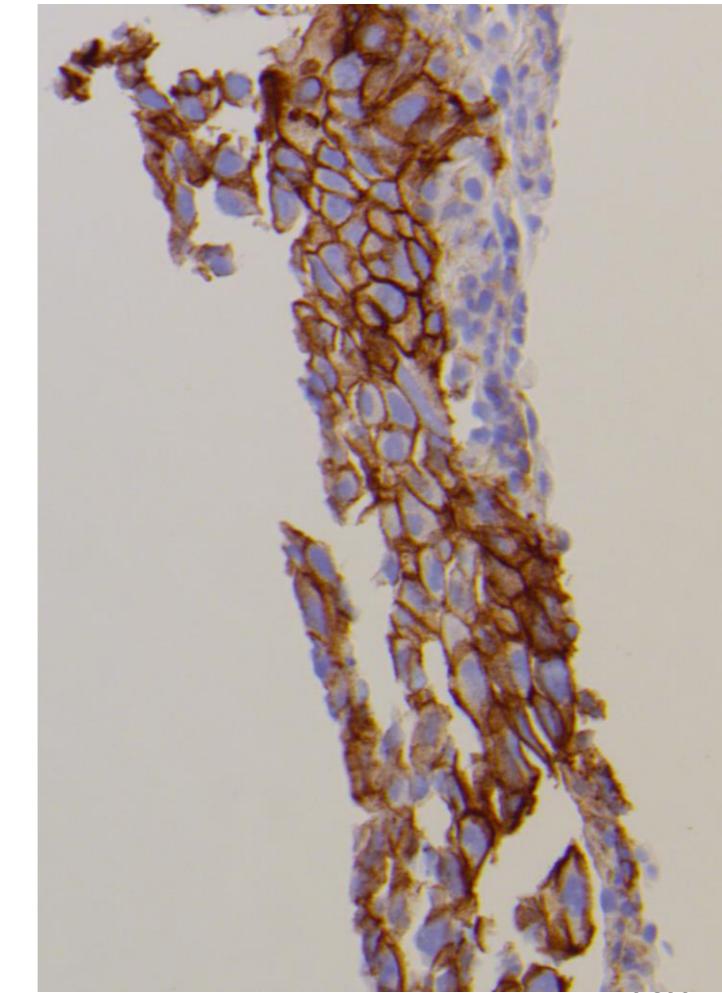
The Diagnostic algorithm



Coarse needle biopsy

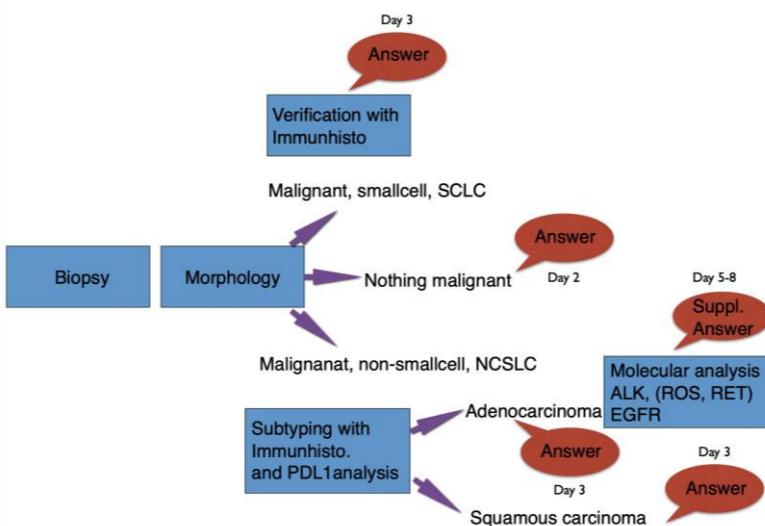


ttf1 and CK7+



PDL1 (22C3)

The Diagnostic algorithm



Coarse needle biopsy

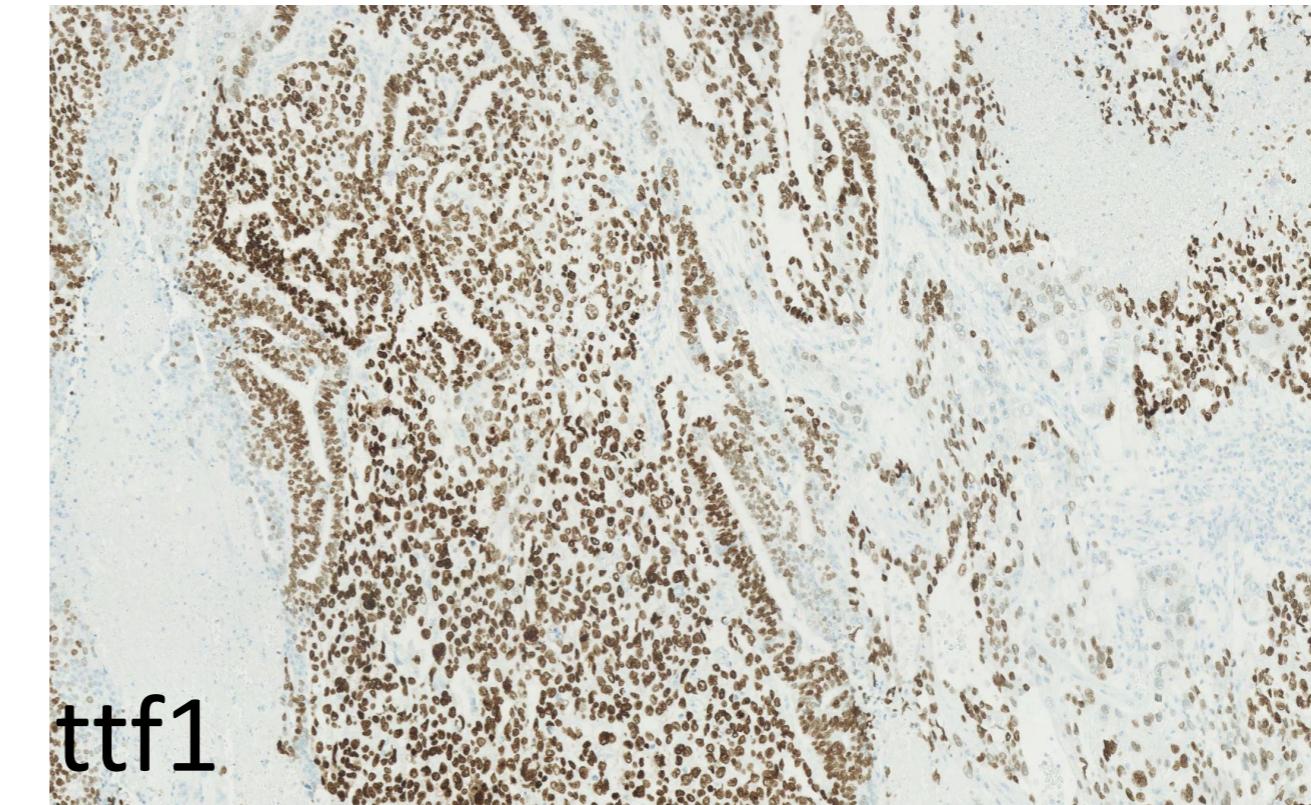
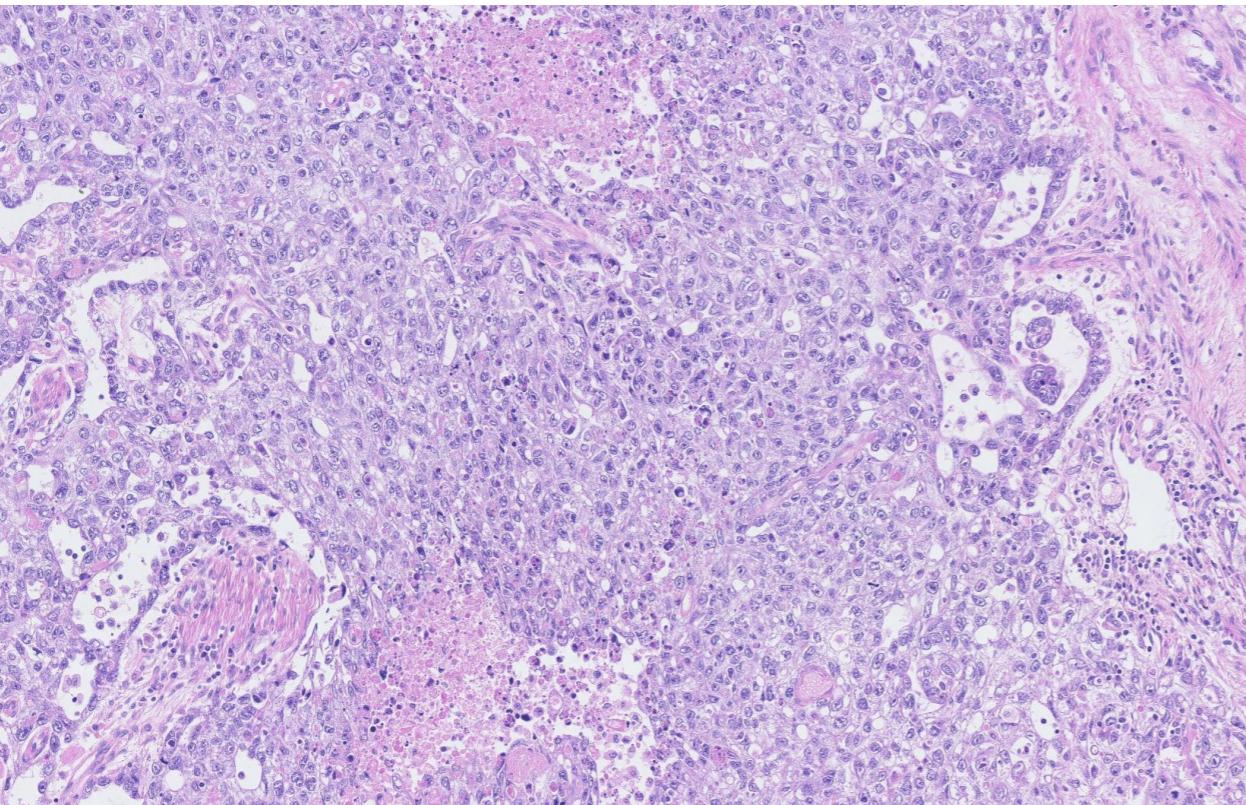
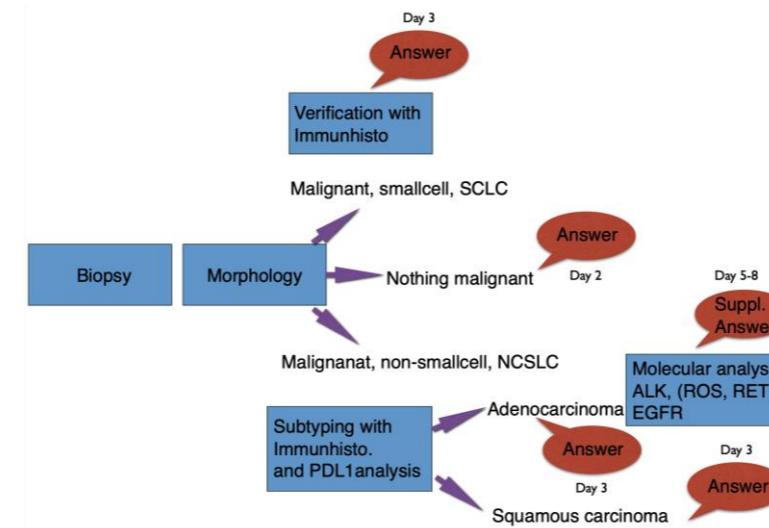
Mutation analysis

EGFR exon 19 del



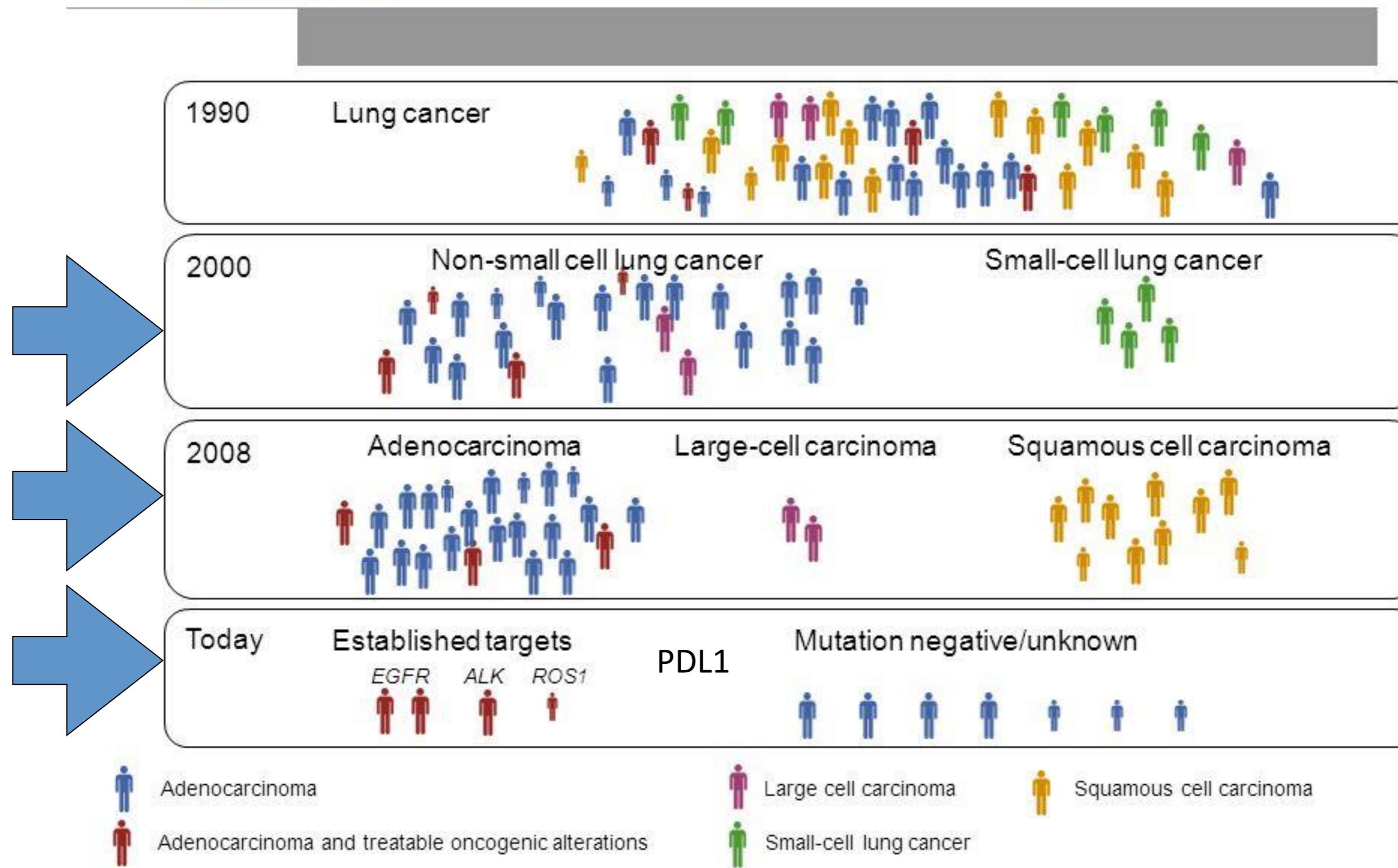
1. line TKI

The Diagnostic algorithm

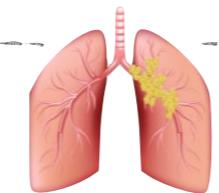


Large tumor intra uterine
Endometrial cancer (yolk sac tumor)

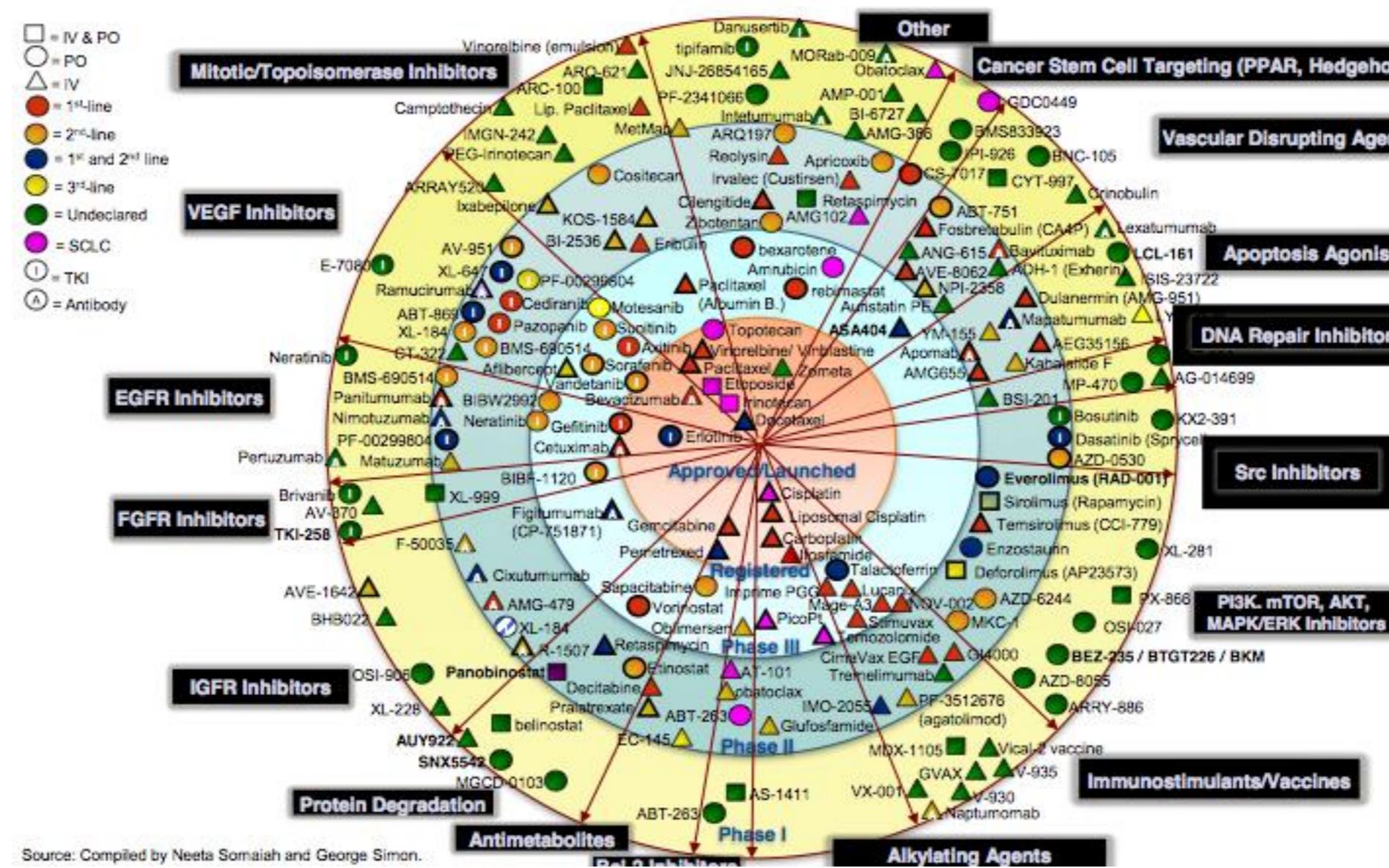
Patient selection in lung cancer: Evolution over time

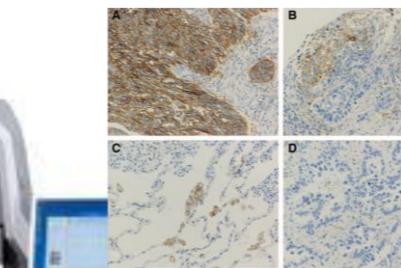


Adapted from Reck M, et al. Lancet 2013;382:709–19

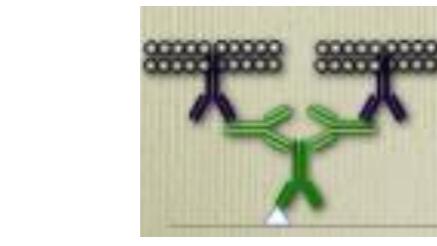
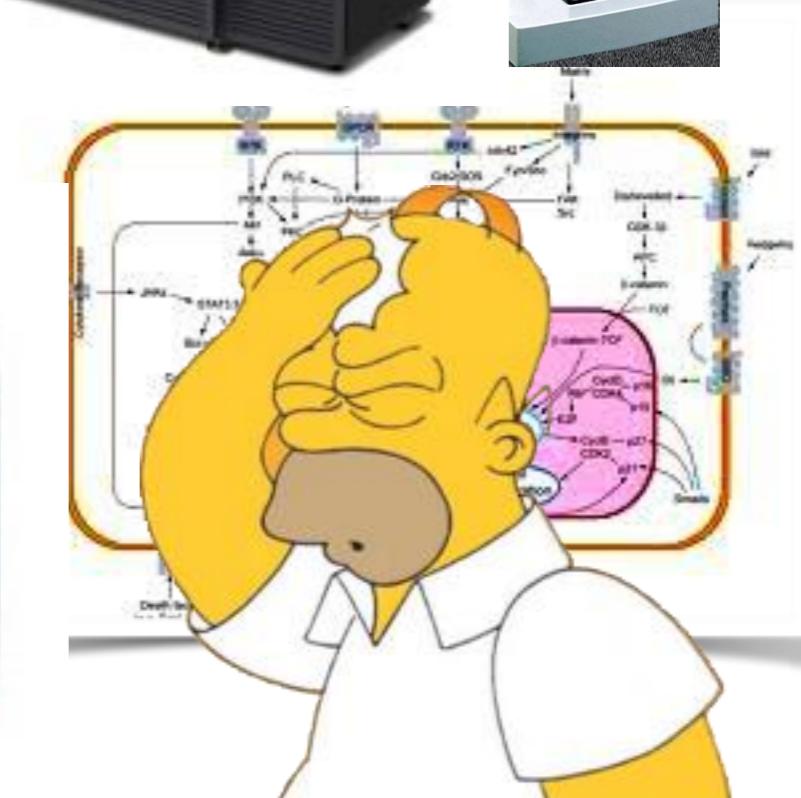
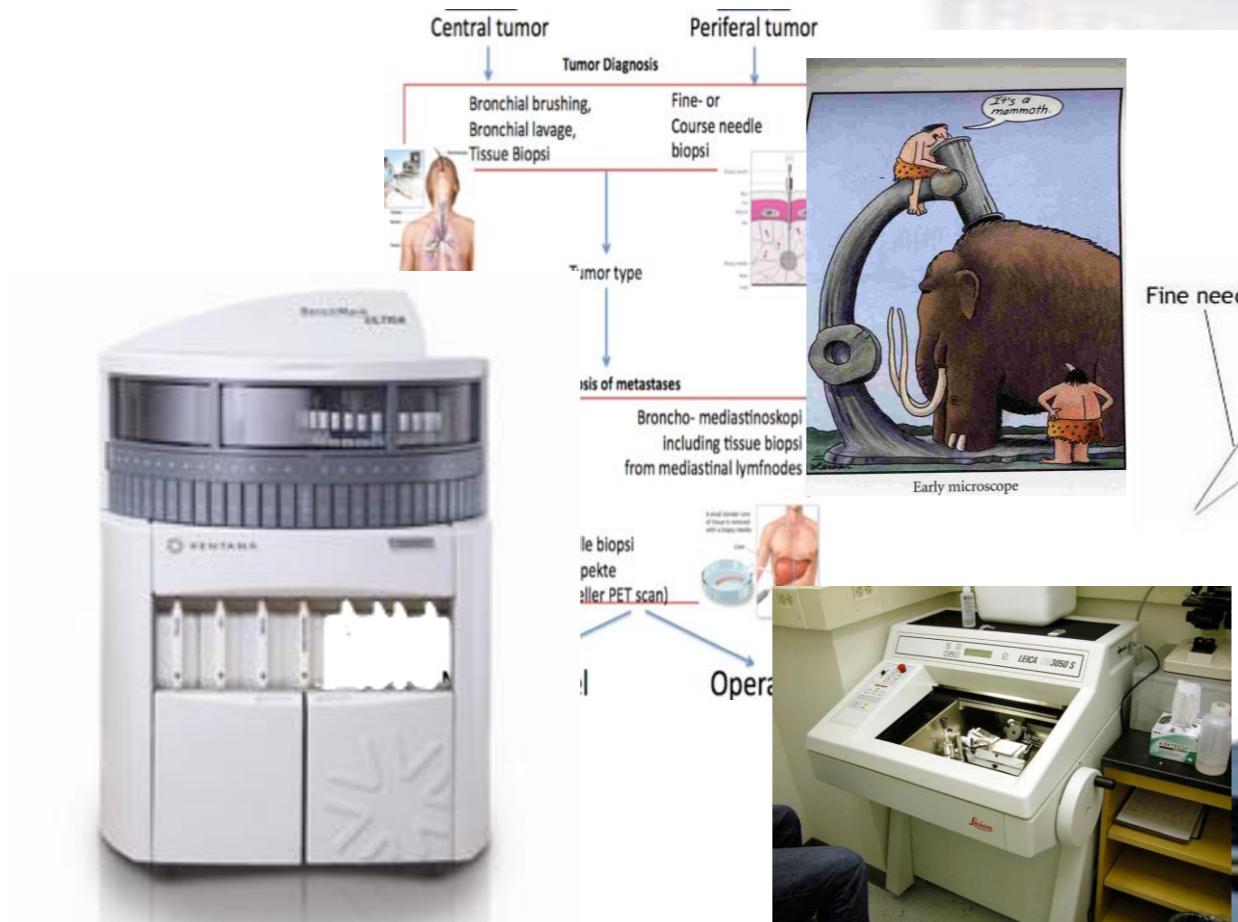
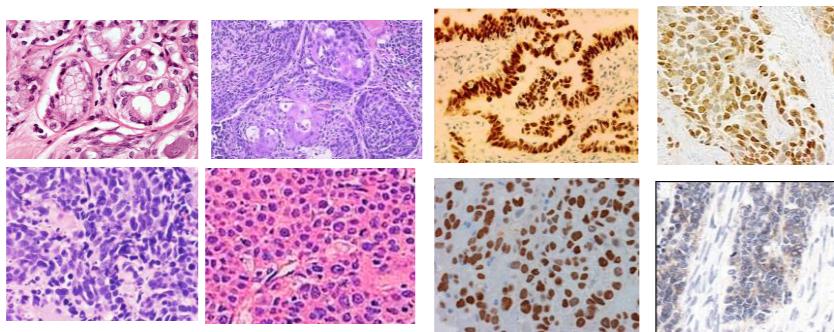


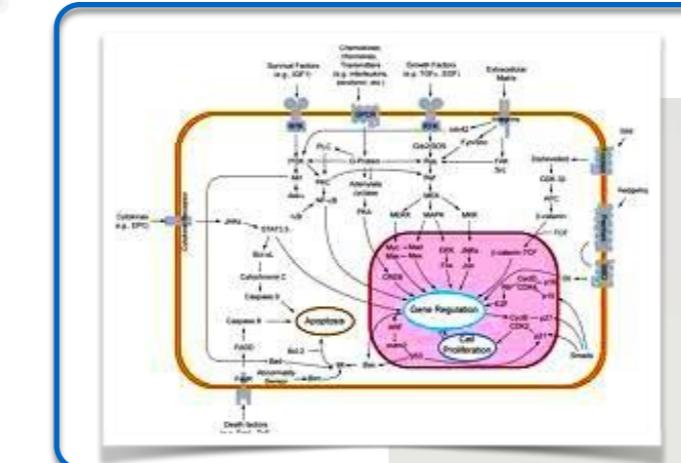
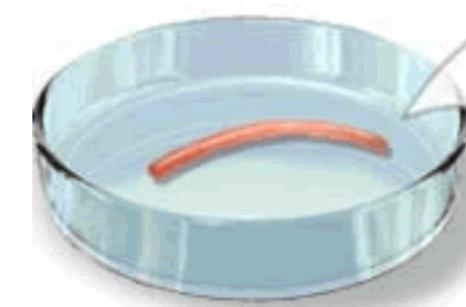
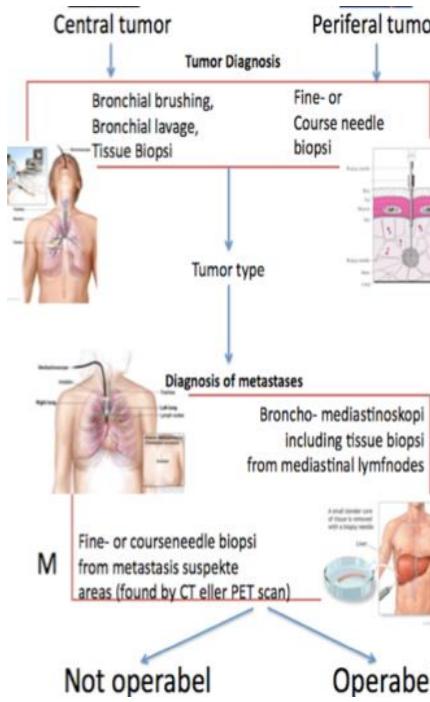
Lung cancer research landscape – MoA group and phase





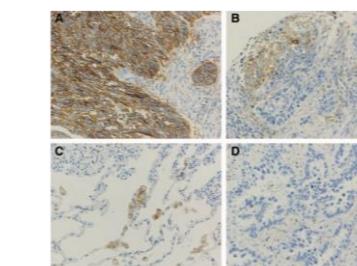
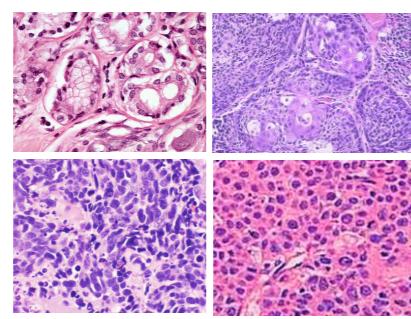
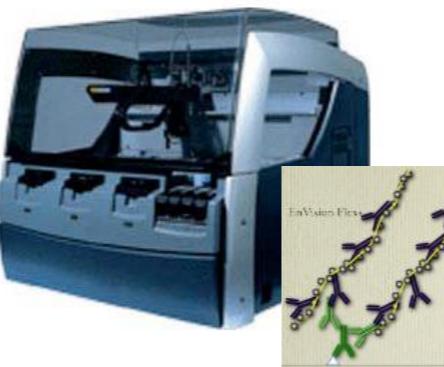
ALK, RET, ROS1, and NTRK1 fusion transcripts, in addition to targets designed to detect 5' and 3' ALK gene expression
KRAS, EGFR, BRAF, PIK3CA, AKT1, ERBB2, PTEN, NRAS, STK11, MAP2K1, ALK, DDR2, CTNNB1, MET, TP53, SMAD4, FBX7, FGFR3, NOTCH1, ERBB4, FGFR1, FGFR2



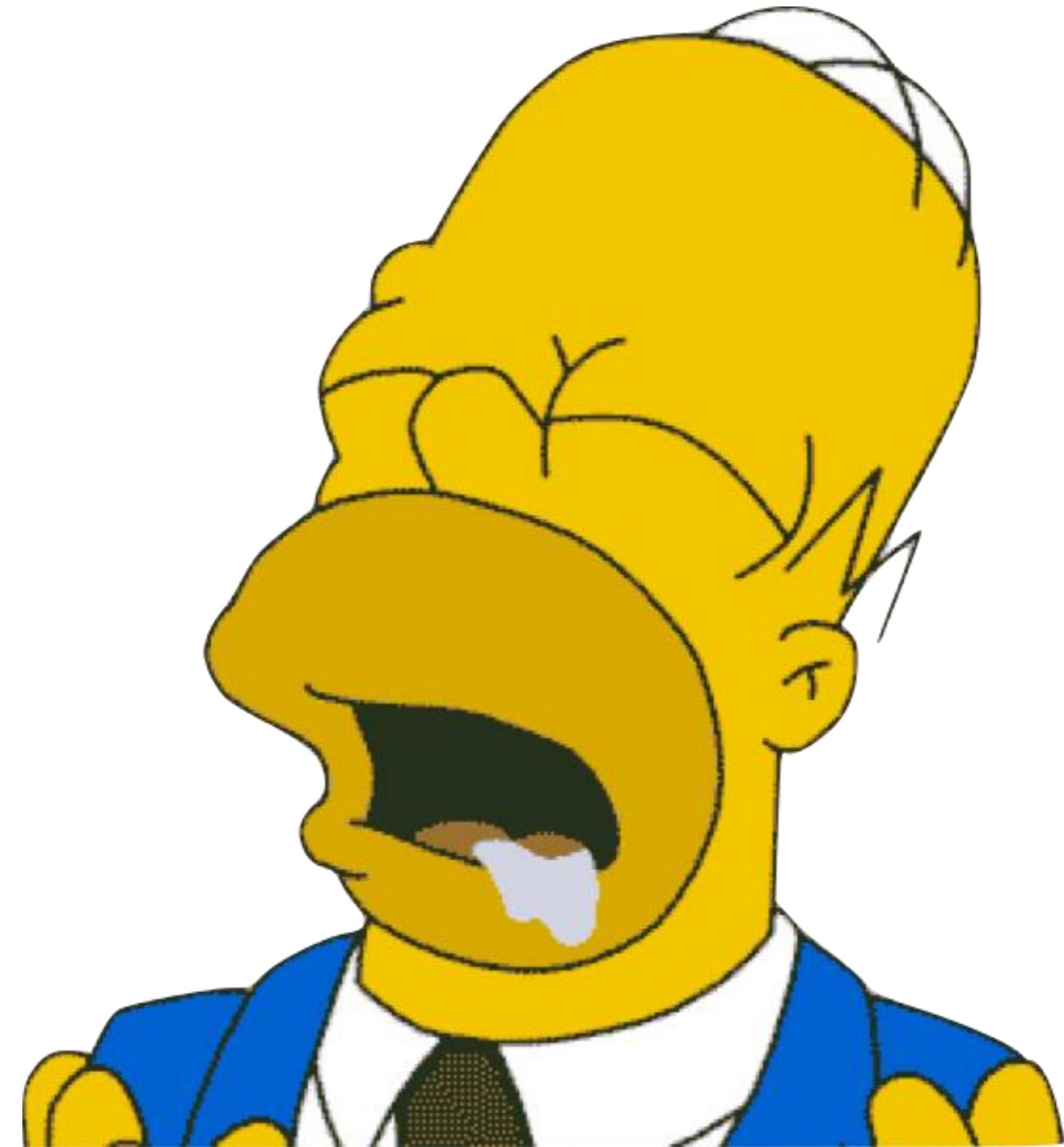


Diagnosis

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