Workshop in Diagnostic Immunohistochemistry
Aalborg University Hospital, 29 Sept. - October 1 2021

Immunohistochemcal classification of

Lung cancer,

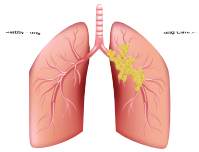
diagnosis and prediction.

Region Syddanmark
Sygehus Lillebælt

Henrik Hager

Dept. of Clinical Pathology
Vejle Hospital

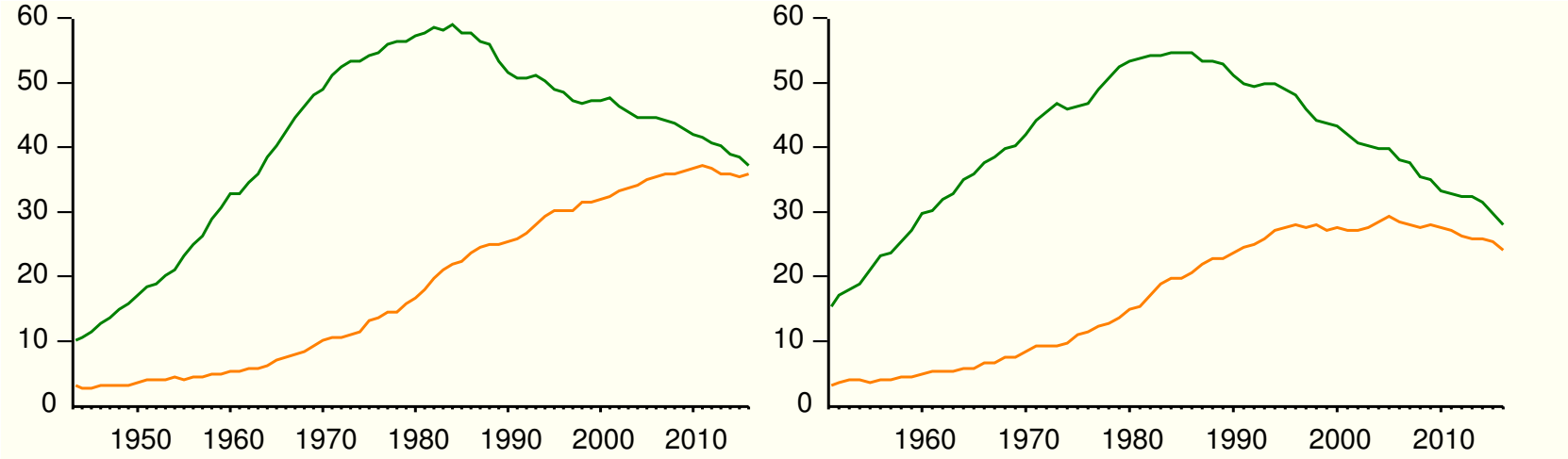
NordiQC



Lung cancer Age's standardized

Incidence new cases/100.000

Mortality Death/100.000



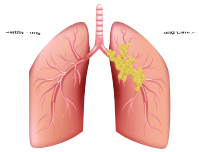
Females

Males

NORDCAN, Association of the Nordic Cancer Registries

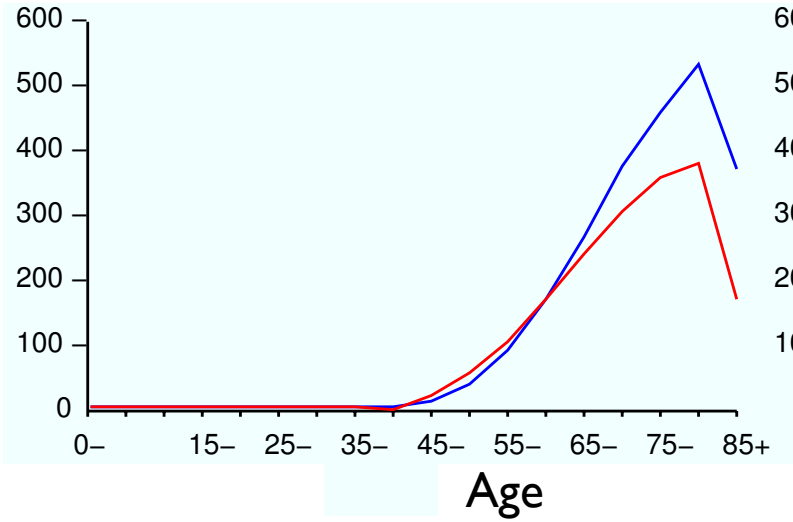
25.3.2019

NordiQC

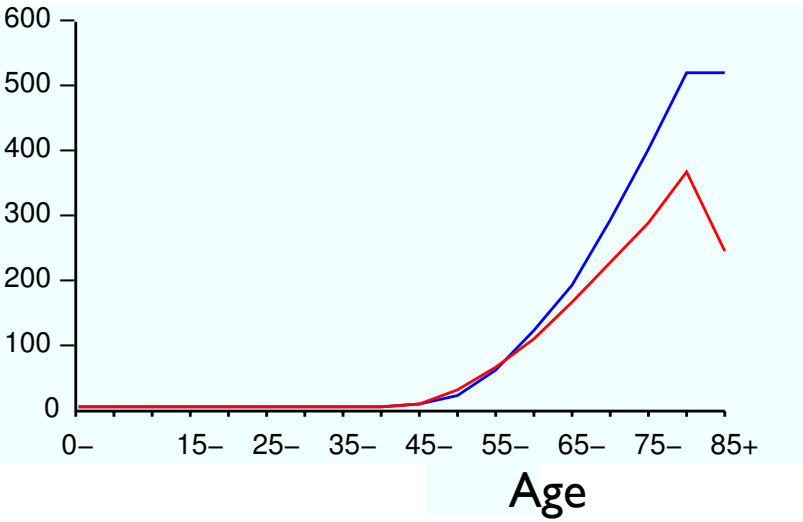


Lung cancer

New cases/100.000 / age interval



Deaths/100.00 / age interval



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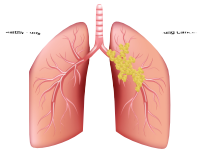
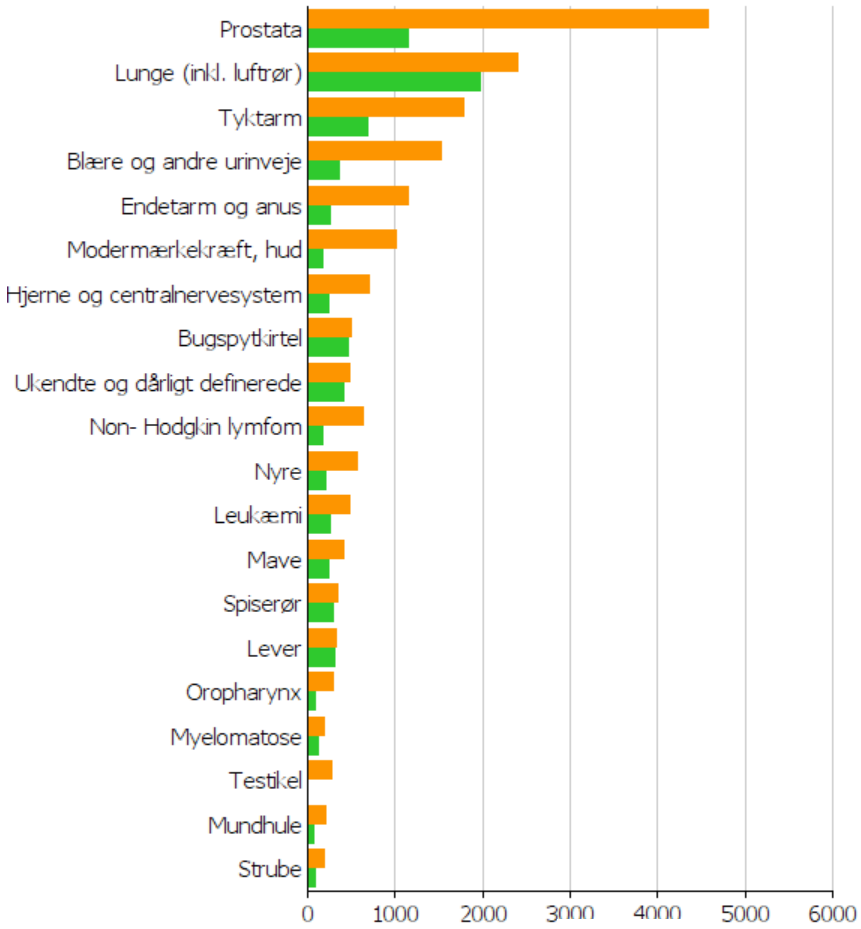
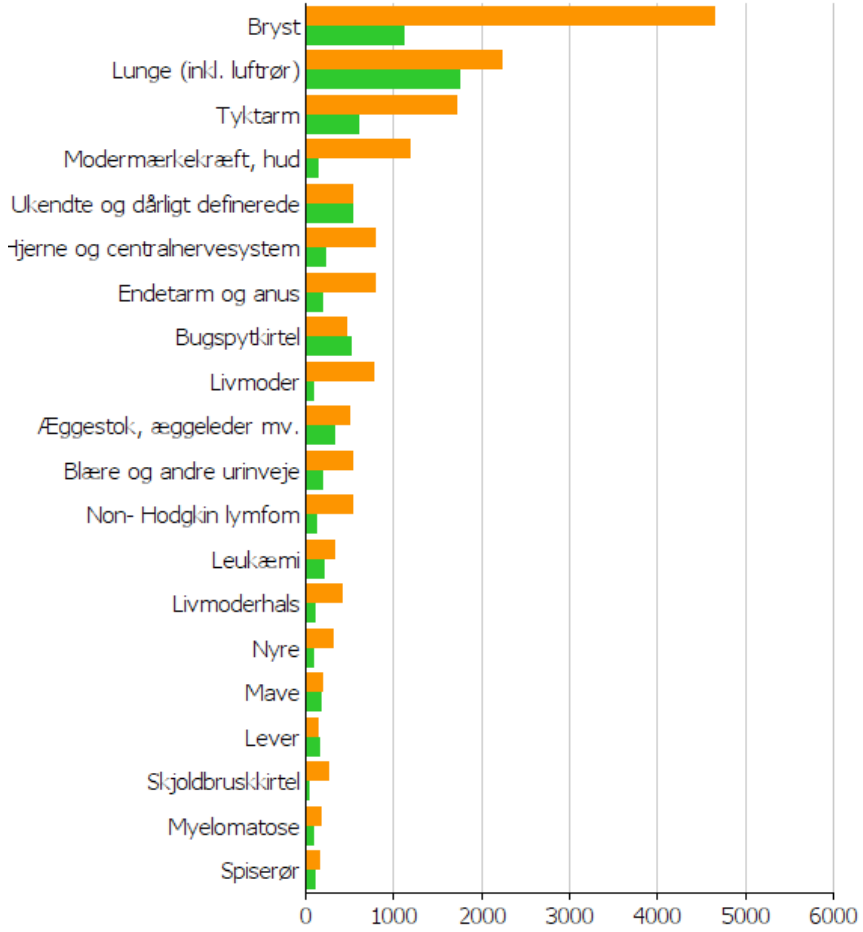


Males



Females



Incidence, new cases / 100.000

Mortality, number of death / 100.000

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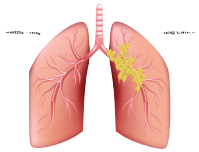
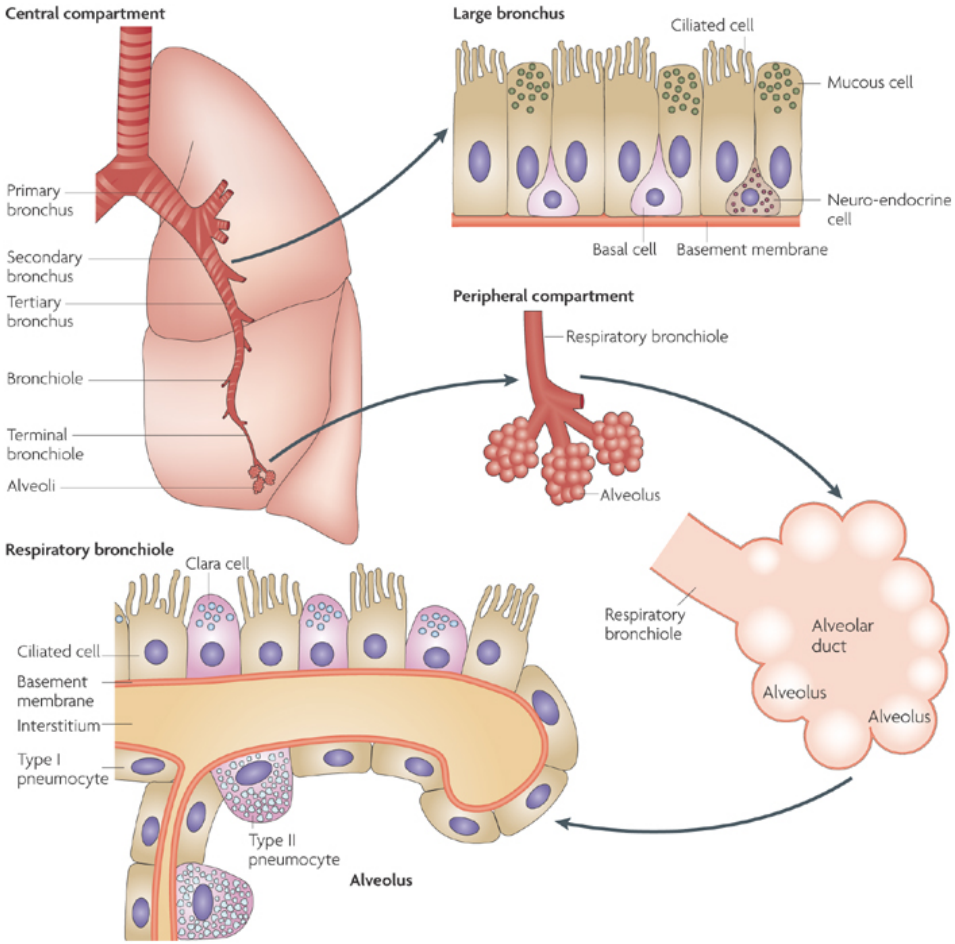


Lung Carcinoma



Lung carcinoma derives from stem cells in the lung epithelium

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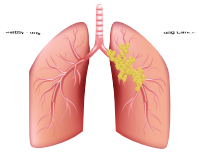

malignant epithelial tumors (carcinomas)

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
PEComatous tumors[e]	
Lymphangioleiomyomatosis	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 *EWSR1–CREB1* 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	

[a]The 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.
[b]The classification is modified from the previous WHO classification[3] taking into account changes in our understanding of these lesions.
[c]This table is reproduced from the 2015 WHO Classification by Travis et al.[1]
[d]These new codes were approved by the International Agency on Cancer Research/WHO Committee for ICDO.
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LCNEC, large cell neuroendocrine carcinoma, WHO, World Health Organization; ICDO International Classification of Diseases for Oncology.

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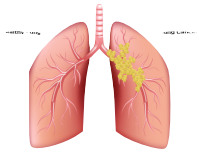

Adenocarcinoma (45%)
Squamous carcinoma (18%)
Large cell neuroendocrine carcinoma (1%)
Small cell carcinoma (12%)

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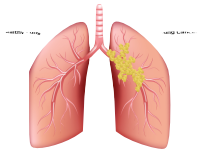
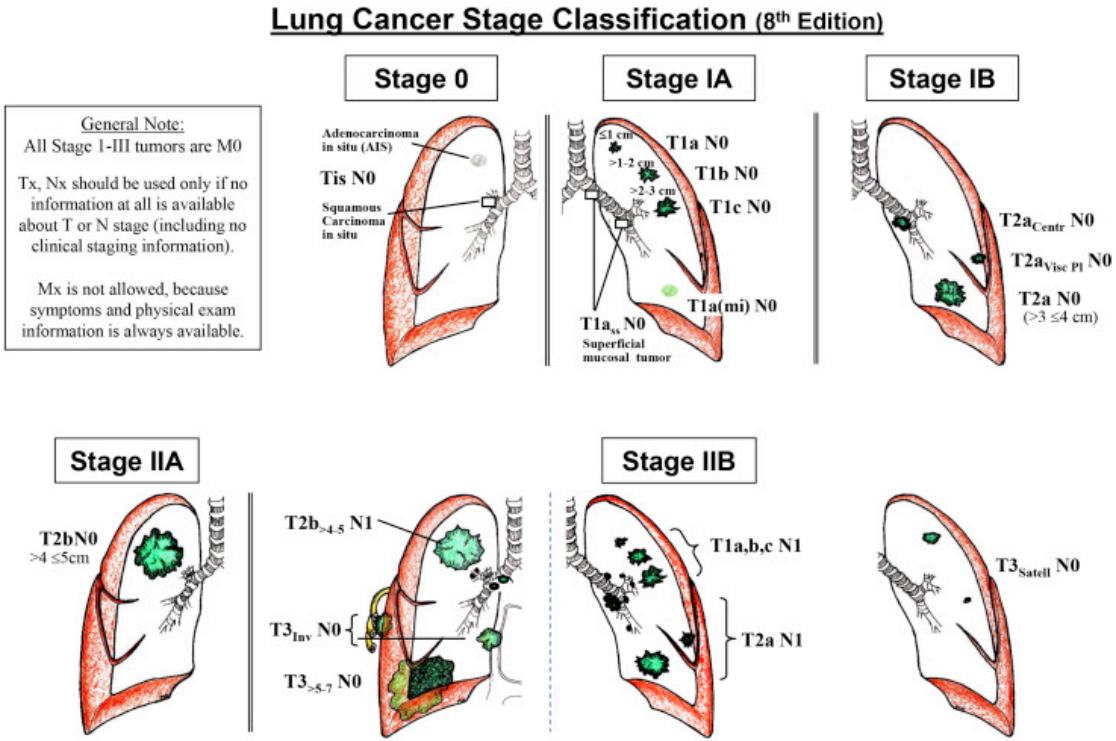
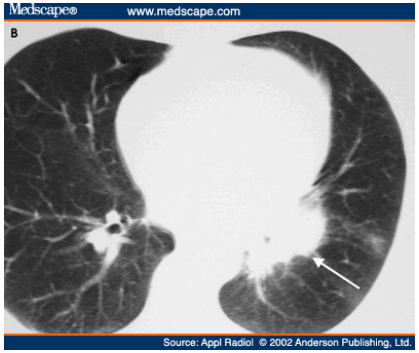


Diagnostic sampling

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





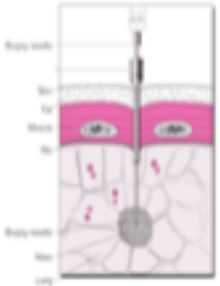
Central tumor

Periferal tumor

Tumor Diagnosis

Bronchial brushing,
Bronchial lavage,
Tissue Biopsi

Fine- or
Course needle
biopsi



Tumor type

Diagnosis of metastases

EBUS
EUS

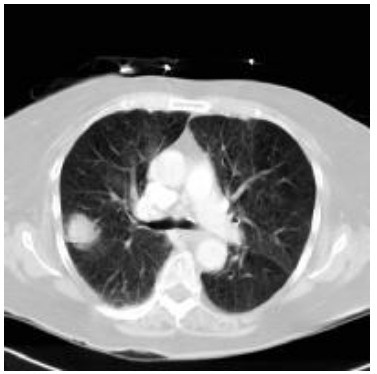
N

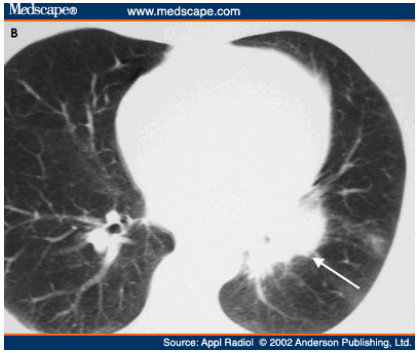
M

Fine- or courseneedle biopsi
from metastasis suspekte
areas (found by CT eller PET scan)

Not operabel

Operabel





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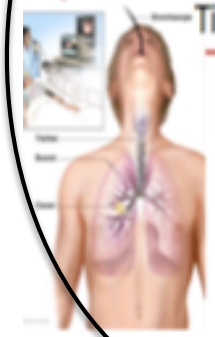

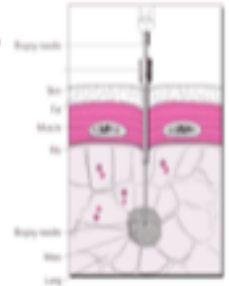

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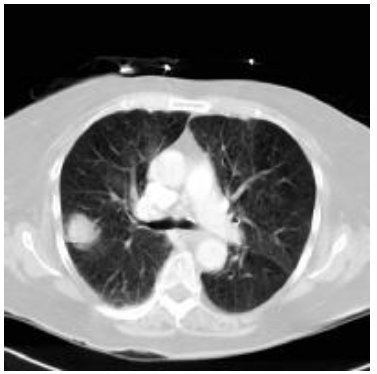

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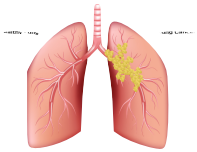
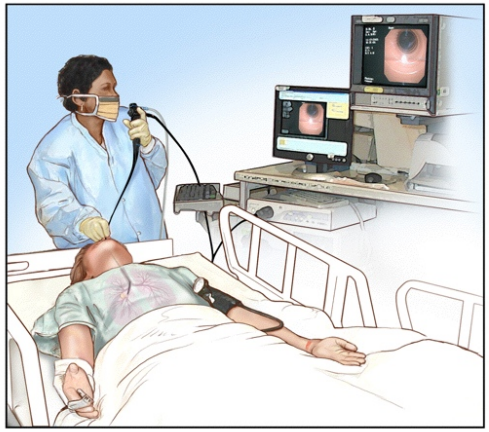




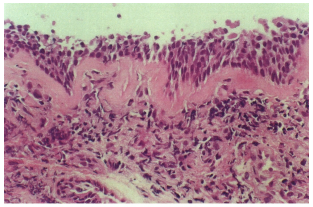
Bronkialwash

*Brushbiopsy**

EBUS **

*EUS**

Biopsy §



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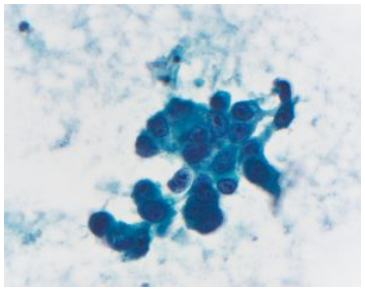

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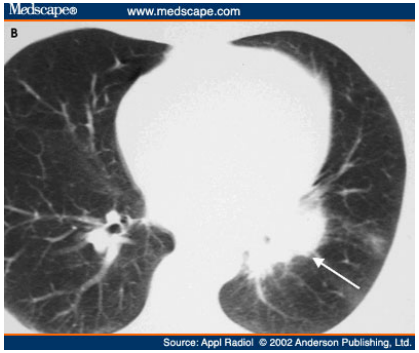

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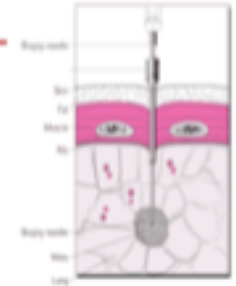
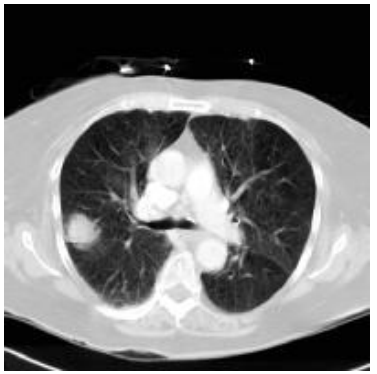


Tumor type



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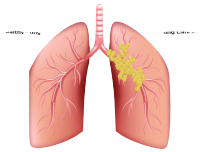

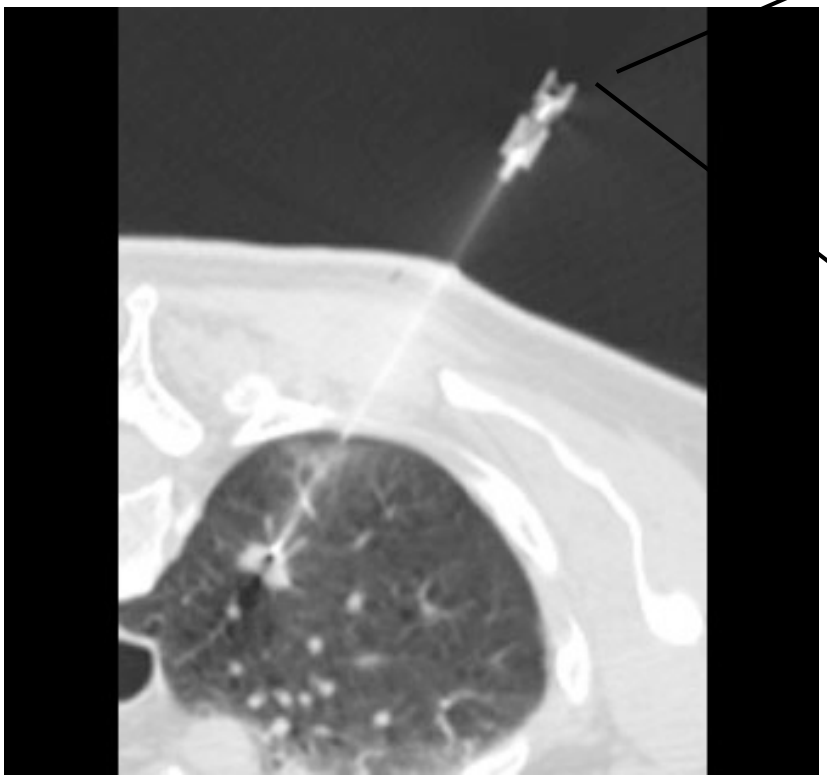

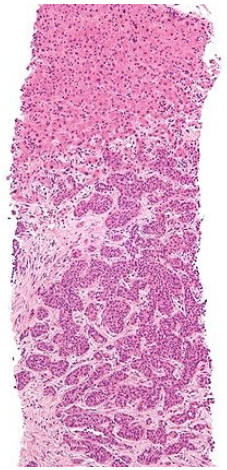

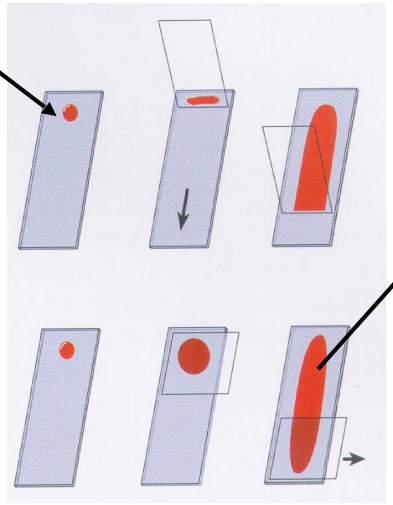

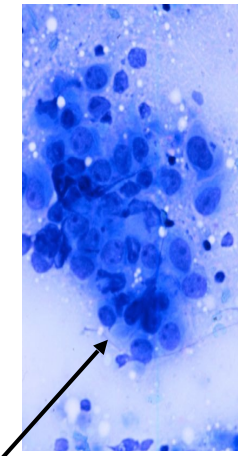

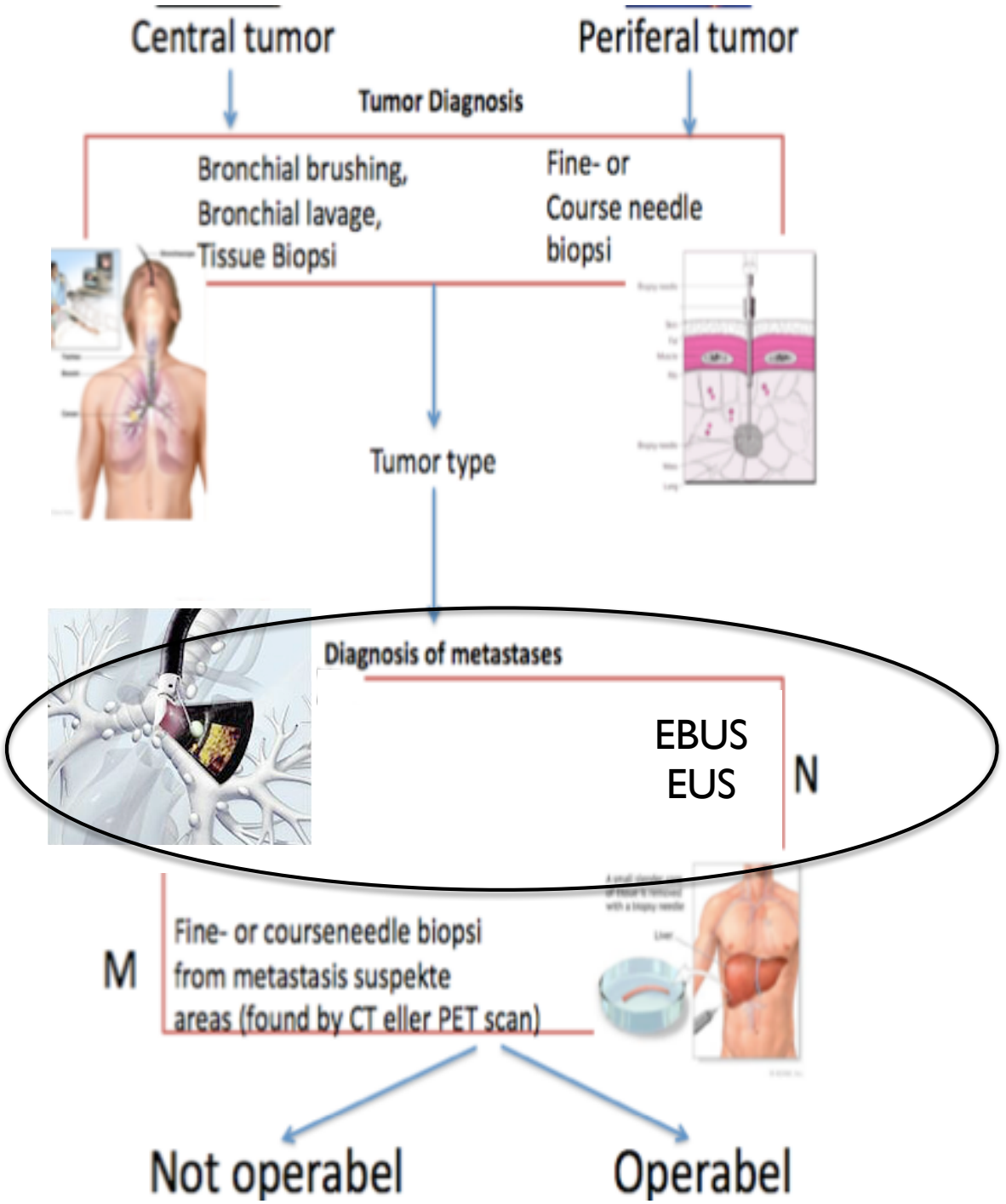
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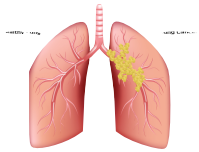
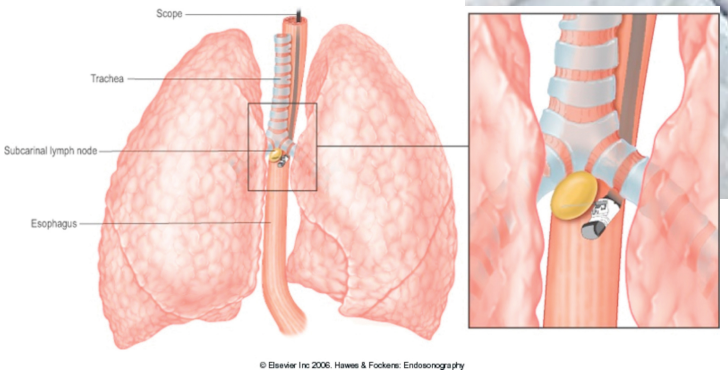
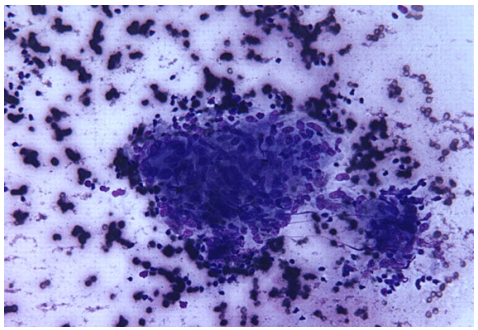
Operabel

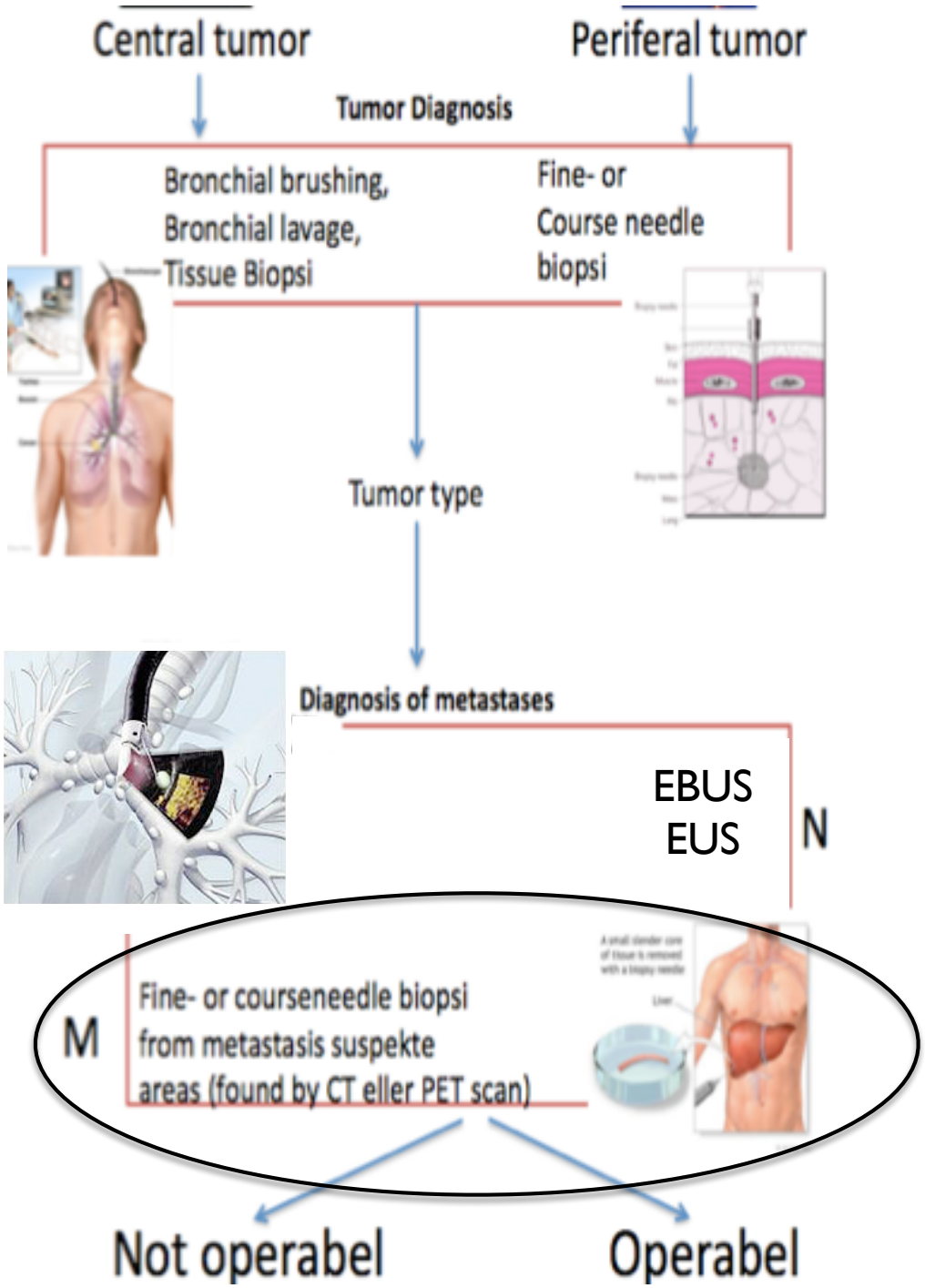
NordiQC



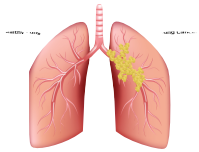
EBUS, EUS



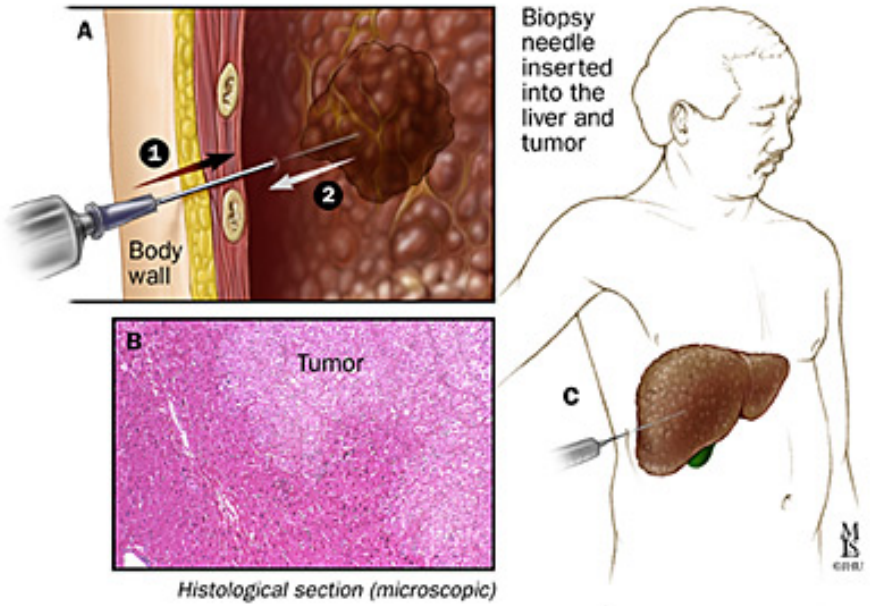



Central tumor
Periferal tumor
Tumor Diagnosis
Bronchial brushing,
Bronchial lavage,
Tissue Biopsi
Fine- or
Course needle
biopsi
Tumor type
Diagnosis of metastases
EBUS
EUS
N
M
Fine- or courseneedle biopsi
from metastasis suspekte
areas (found by CT eller PET scan)
Not operabel
Operabel

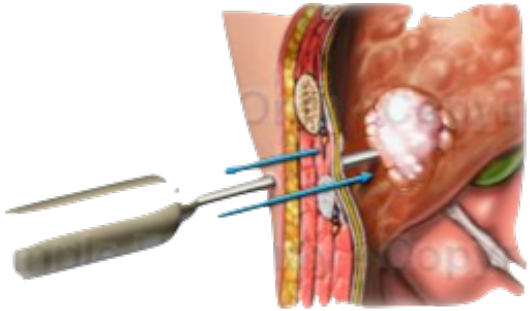
NordiQC

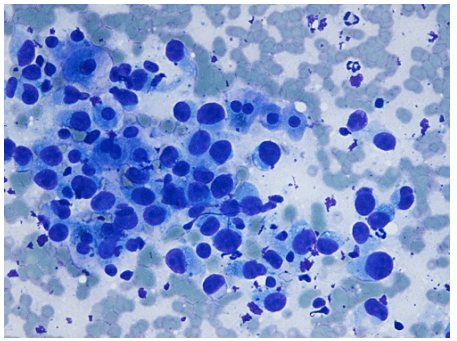


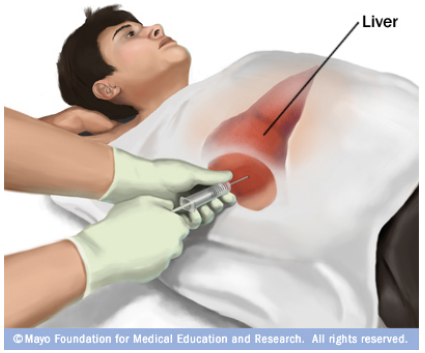
Coarse needle biopsy



Fine needle biopsy







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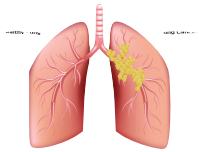
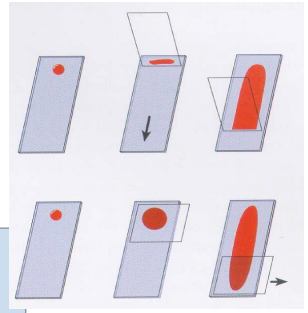


Patoanatomical specimen

Histology

Cytologi



Fixation
Dehydration
Parafinembedding
Microtomy

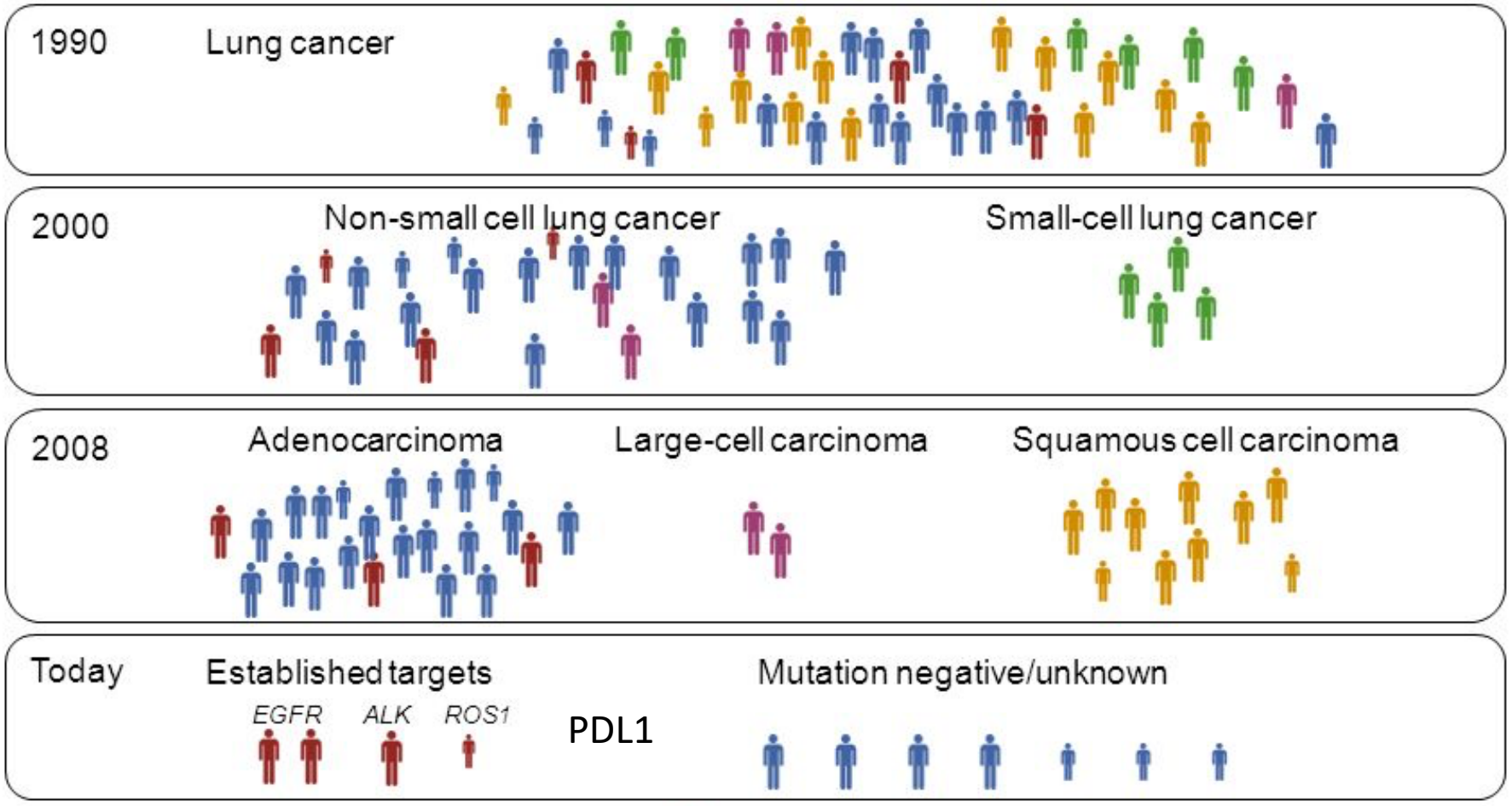
Præparation

Smear preparation

Visualization

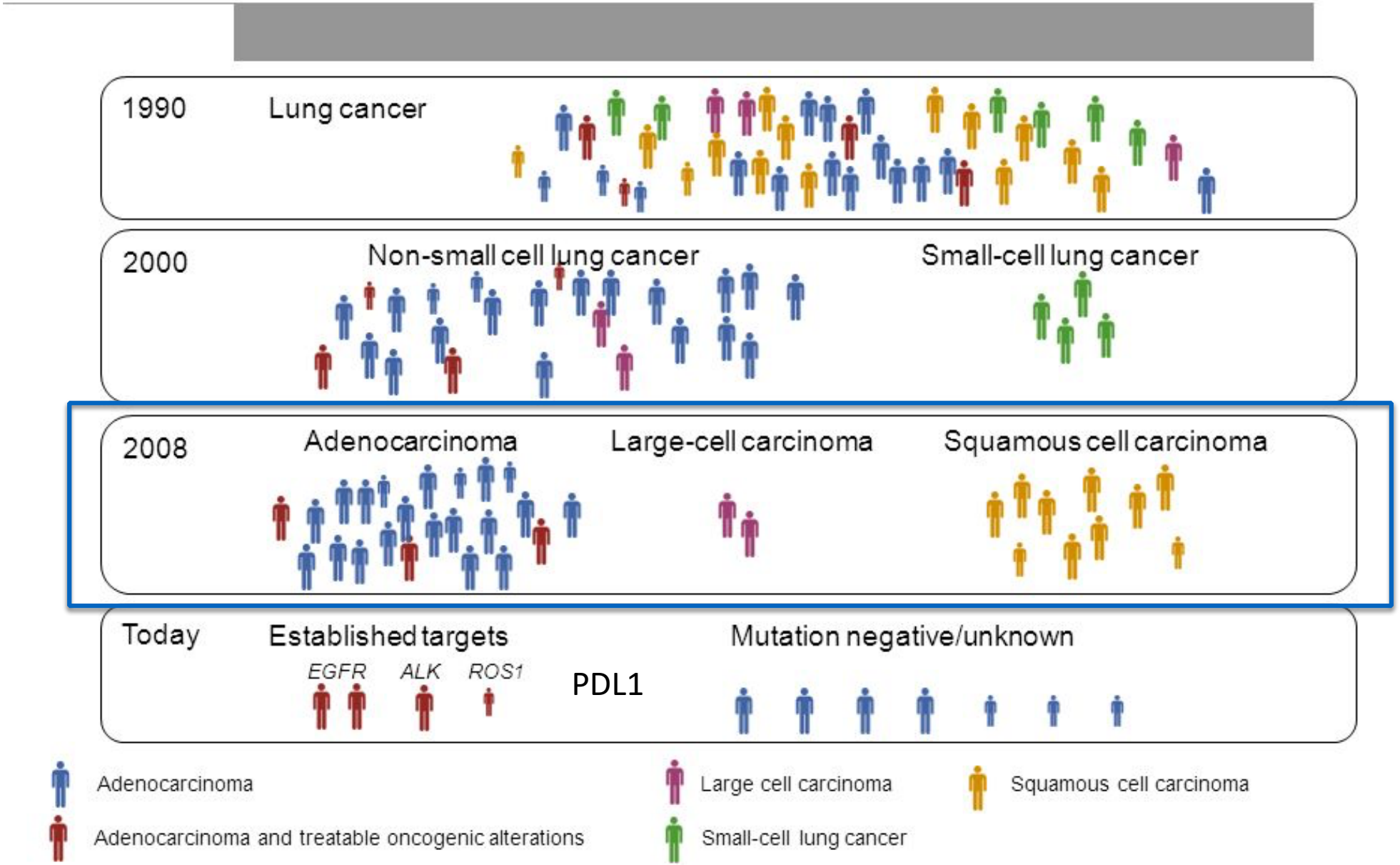
(Staining)

Patient selection in lung cancer: Evolution over time



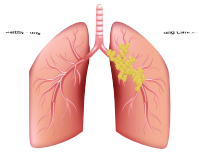
Adapted from Reck M, et al. Lancet 2013;382:709–19

Patient selection in lung cancer: Evolution over time

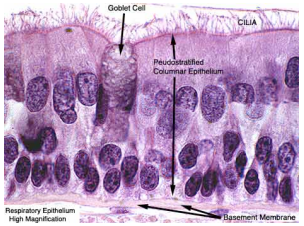


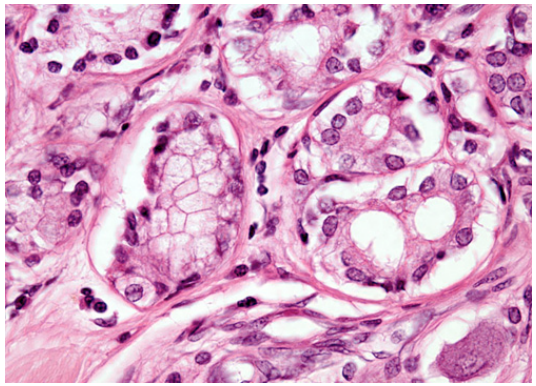
Adapted from Reck M, et al. Lancet 2013;382:709–19

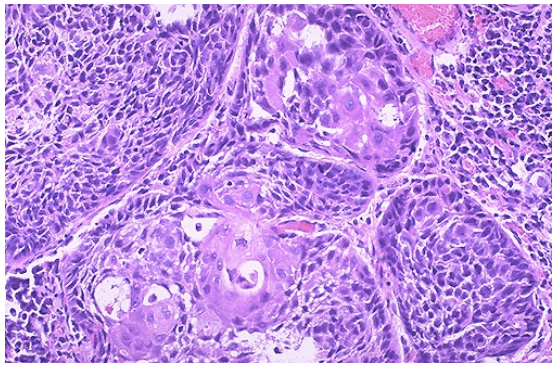
NordiQC

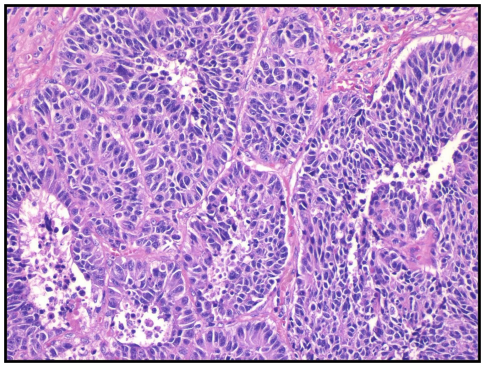


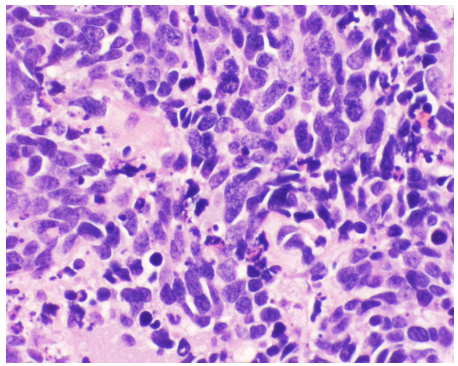
Morphology











Adenocarcinoma

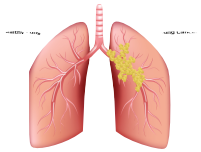
Squamous carcinoma

Large cell neuroendocrine carc.

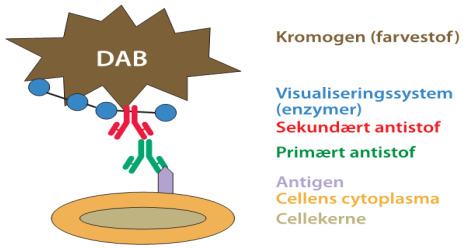
Small cell carcinoma

Non Small Cell Lung Carcinoma (NSCLC)

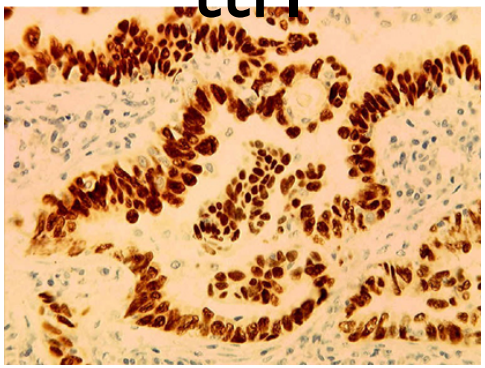
NordiQC



Immunohistochemistry

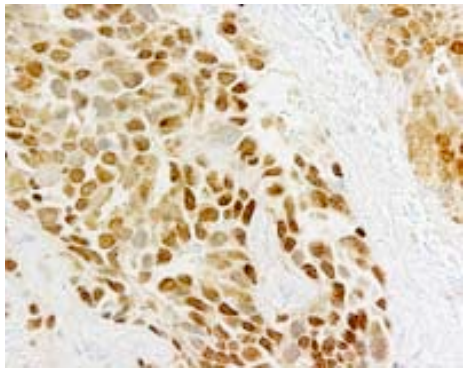


ttf1



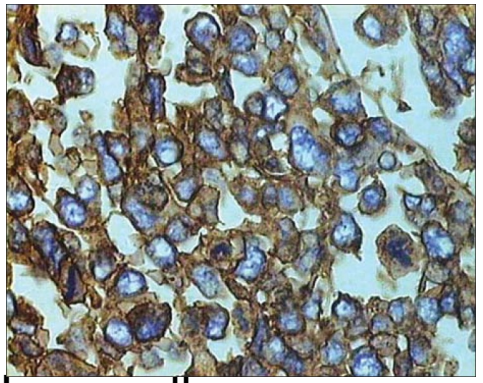
Adenocarcinoma

p63



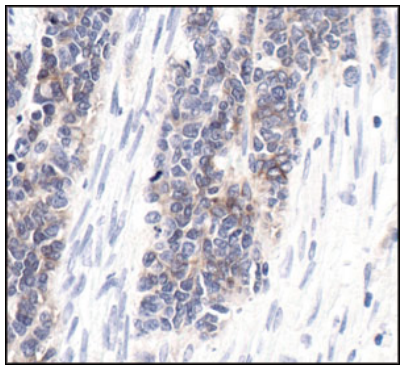
Squamous carcinoma

cd56



Large cell neuroendocrine carc

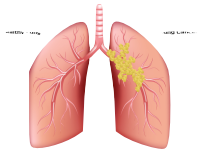
cd56



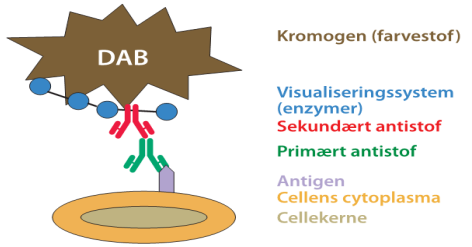
Small cell carcinoma

Neuroendocrine carc.

NordiQC



Immunohistochemistry



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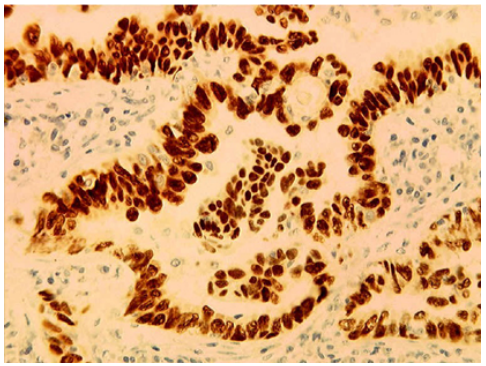
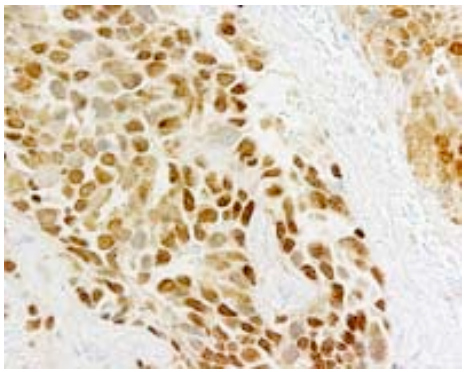


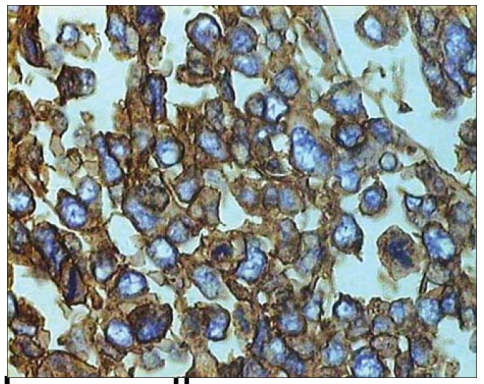
Adenocarcinoma

p63



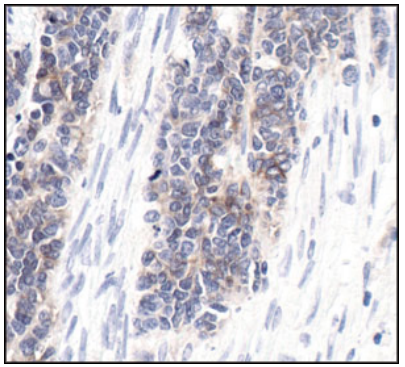
Squamous carcinoma

cd56



Large cell neuroendocrine carc

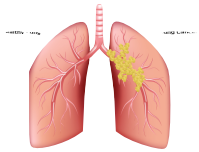
cd56



Small cell carcinoma

Non Small Cell Lung Carcinoma (NSCLC)

NordiQC



Algorithm modified from

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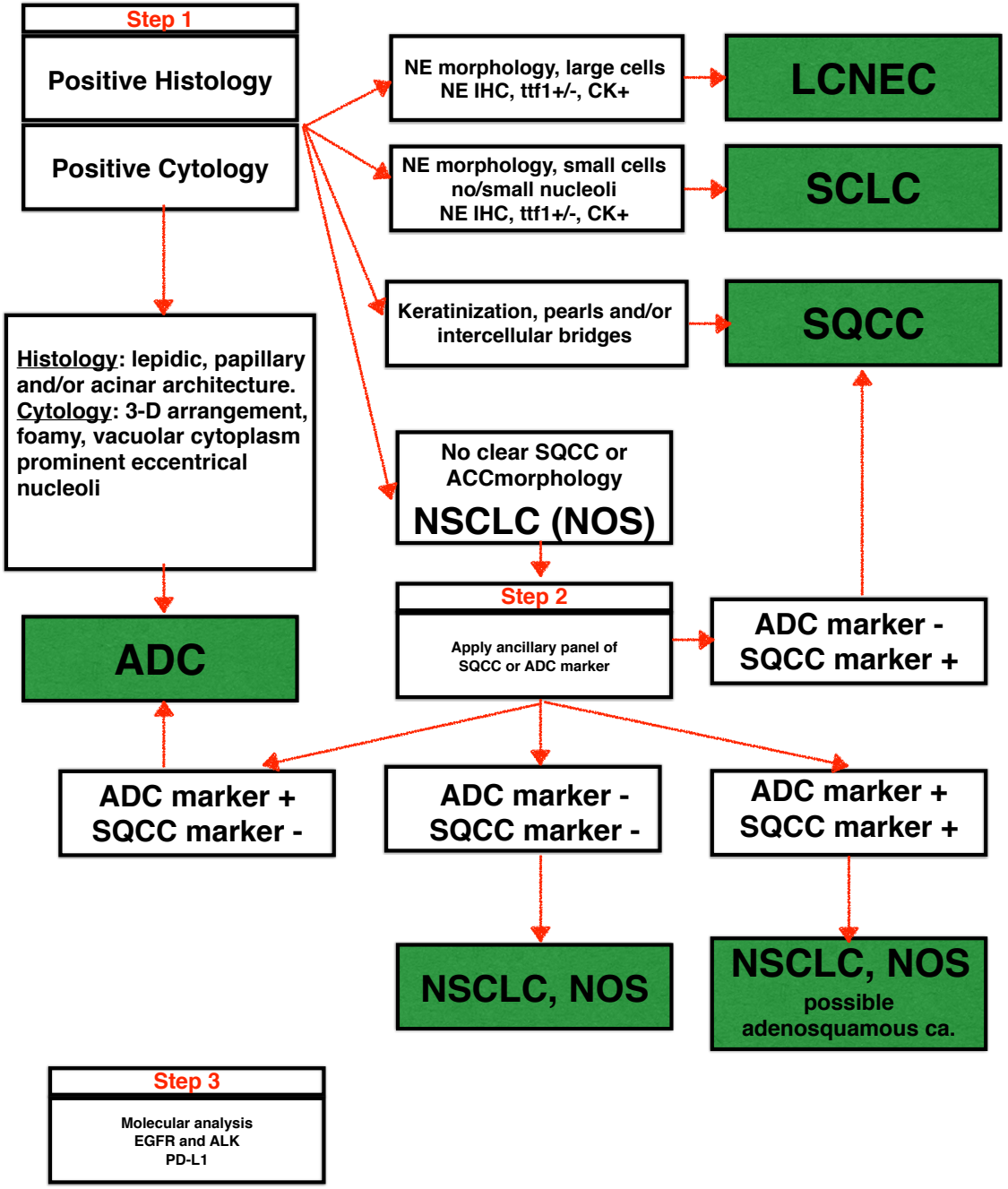

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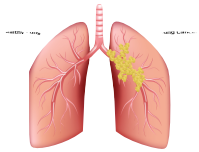

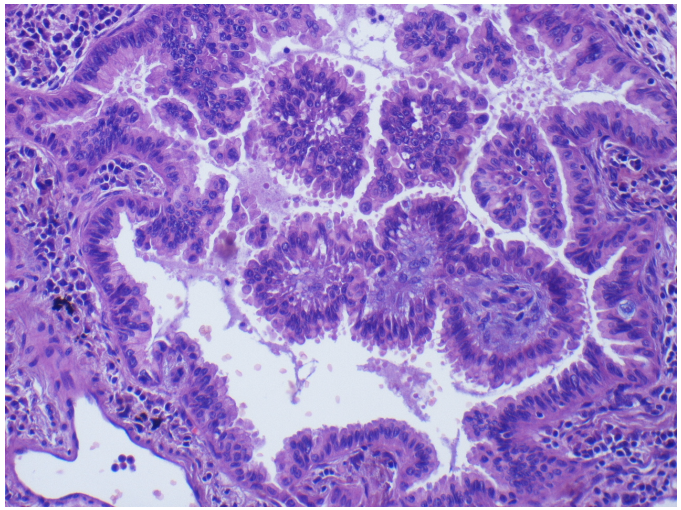

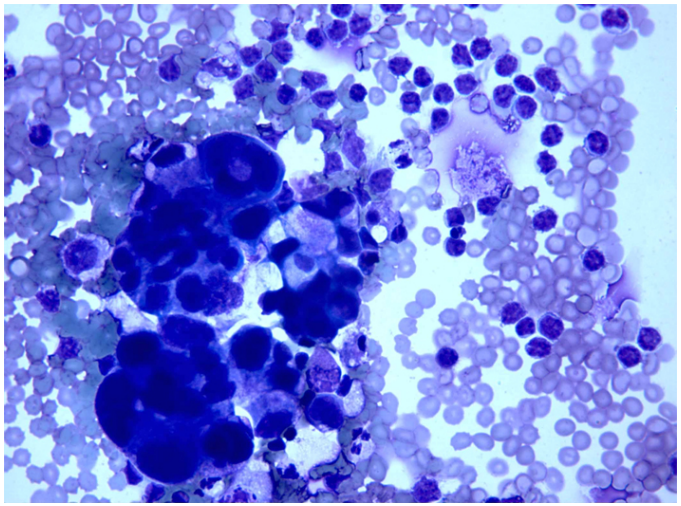

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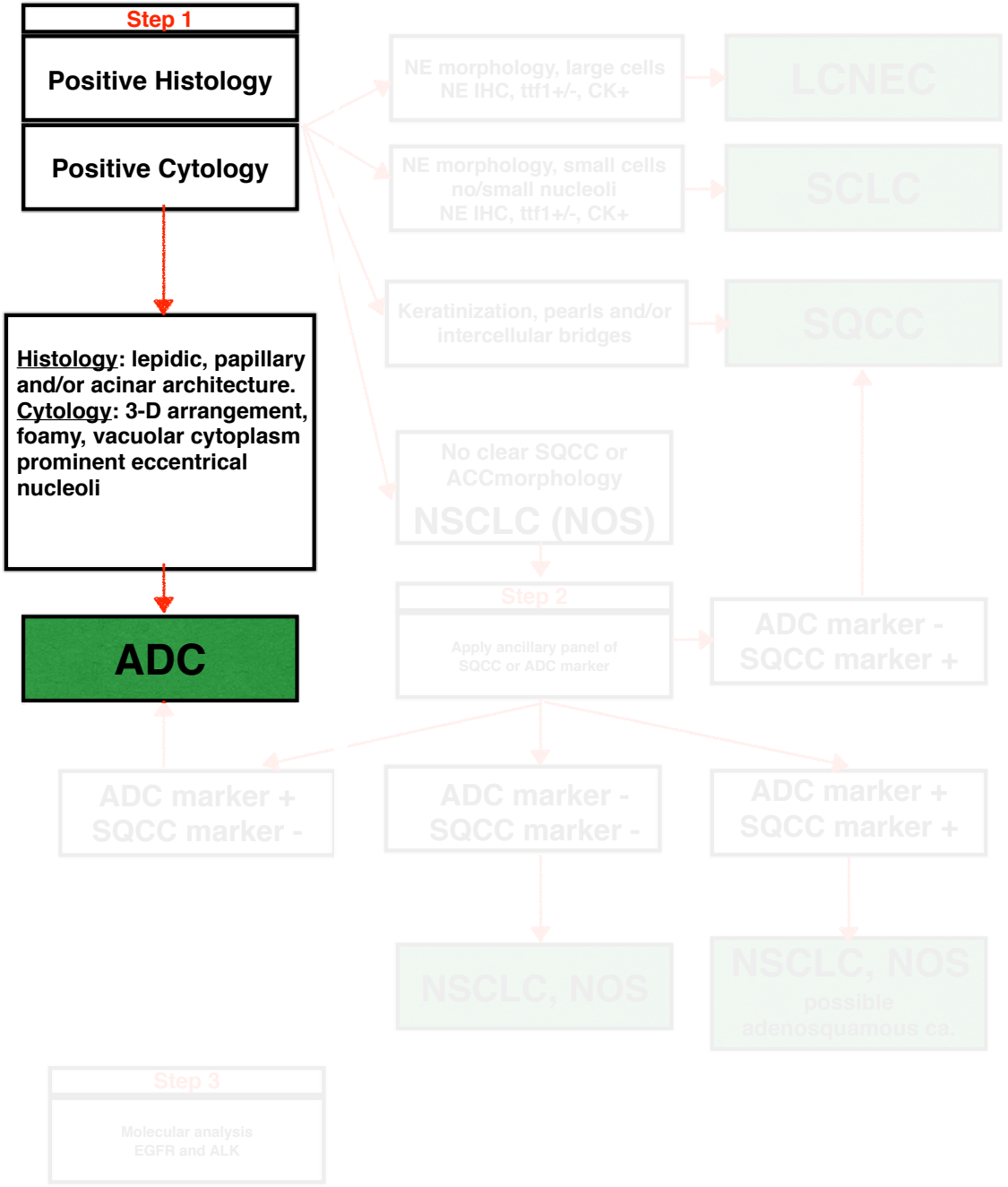

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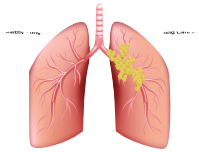

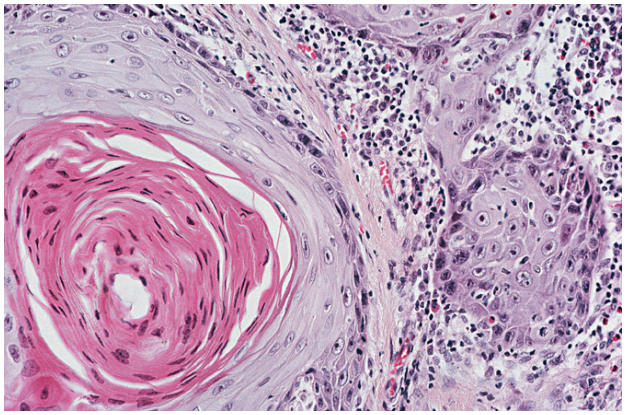

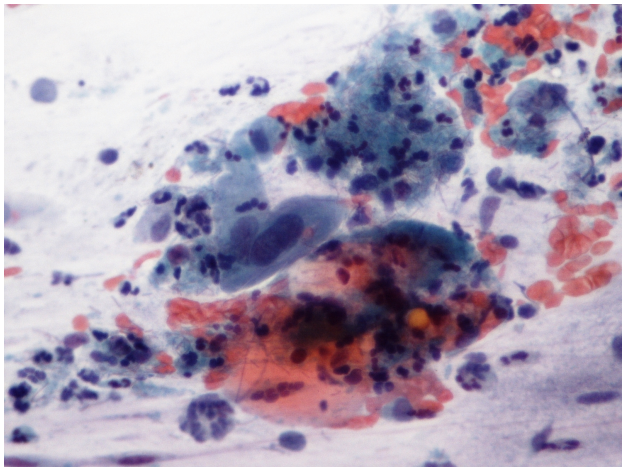

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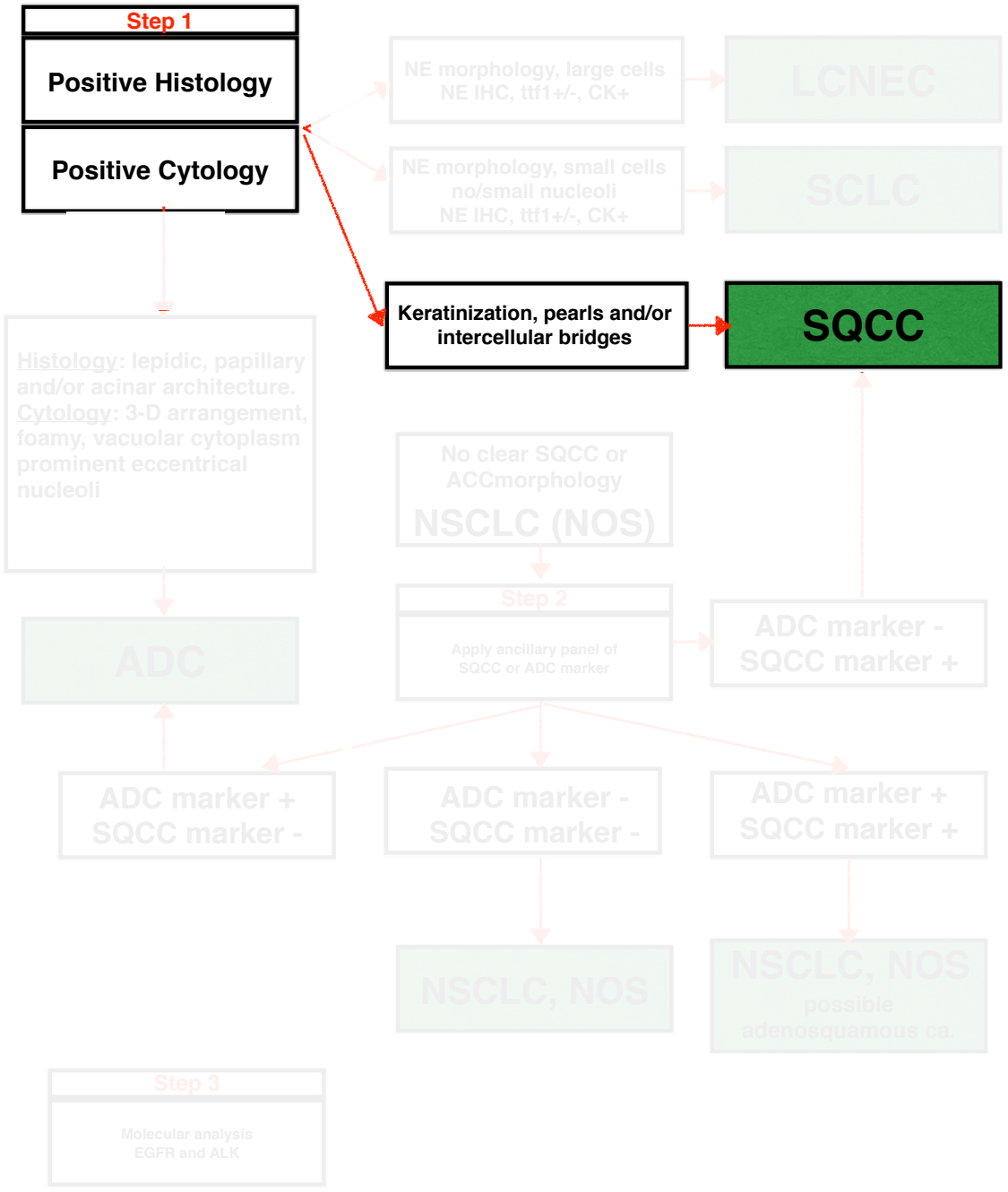

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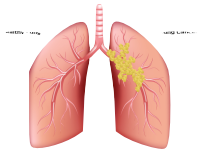

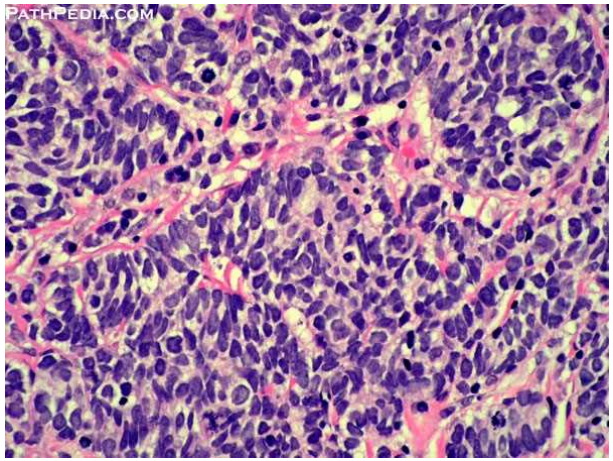

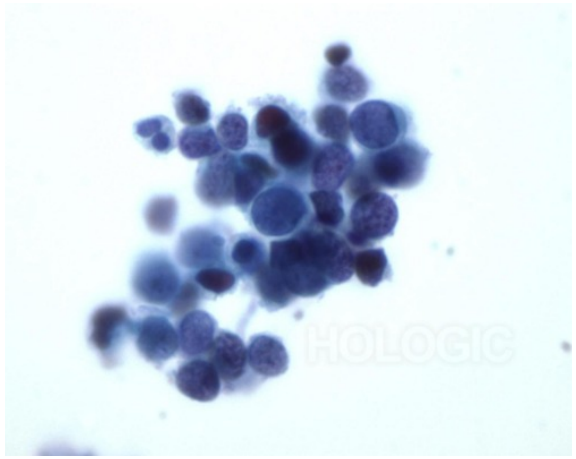

Step 1

Positive Histology

Positive Cytology

NE morphology, large cells
NE IHC, ttf1+/-, CK+

LCNEC

NE morphology, small cells
no/small nucleoli
NE IHC, ttf1+/-, CK+

SCLC

Keratinization, pearls and/or intercellular bridges

SQCC

Histology: lepidic, papillary and/or acinar architecture.
Cytology: 3-D arrangement, foamy, vacuolar cytoplasm prominent eccentrical nucleoli

No clear SQCC or ACCmorphology

NSCLC (NOS)

Step 2

Apply ancillary panel of SQCC or ADC marker

ADC marker - SQCC marker +

ADC

ADC marker + SQCC marker -

ADC marker - SQCC marker -

ADC marker + SQCC marker +

NSCLC, NOS

NSCLC, NOS
possible adenosquamous ca.

Step 3

Molecular analysis
EGFR and ALK

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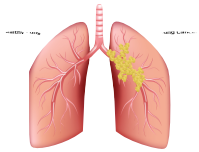
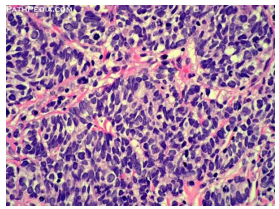
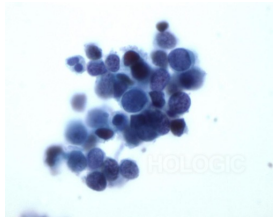
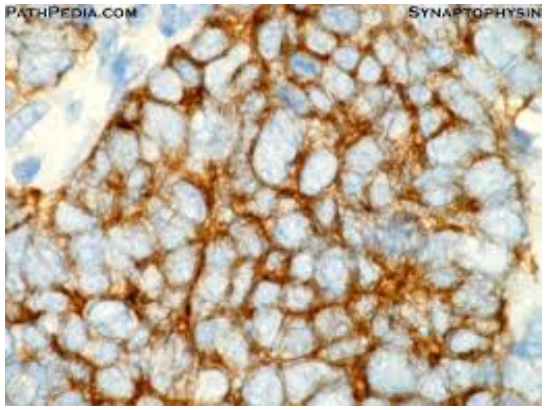
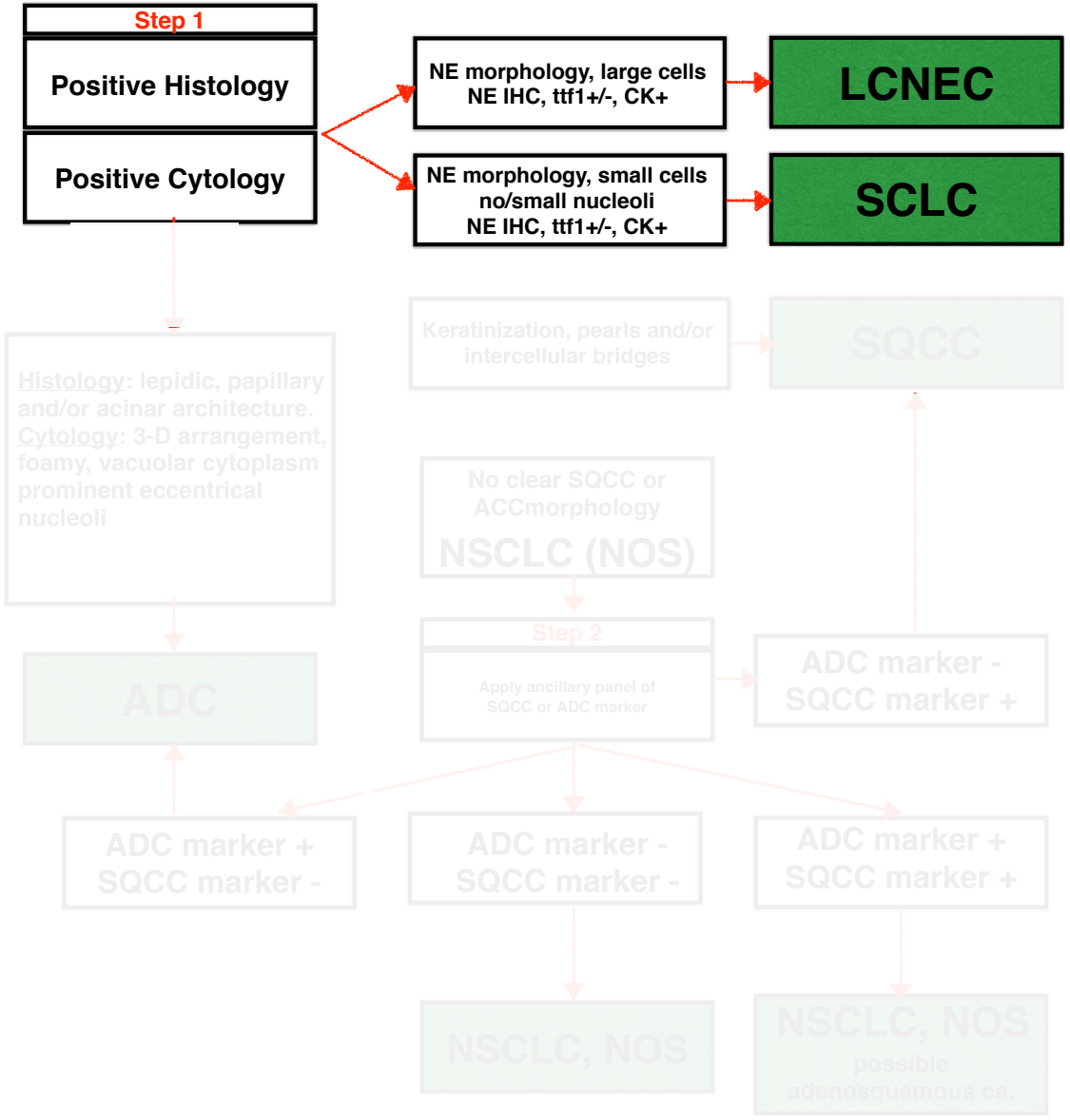






CD56





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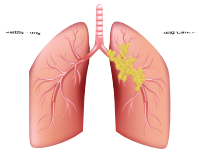
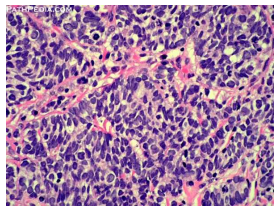
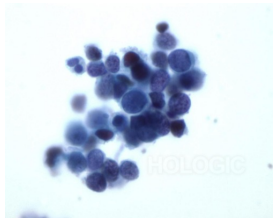
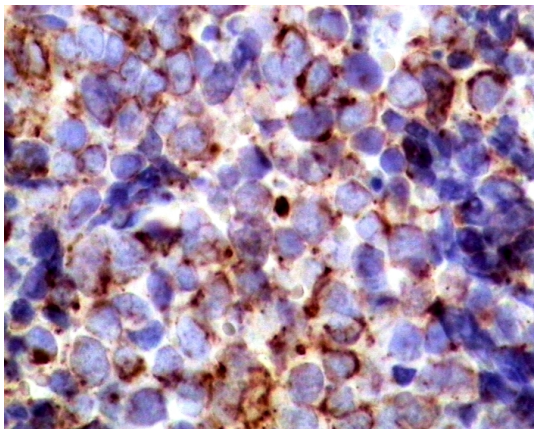
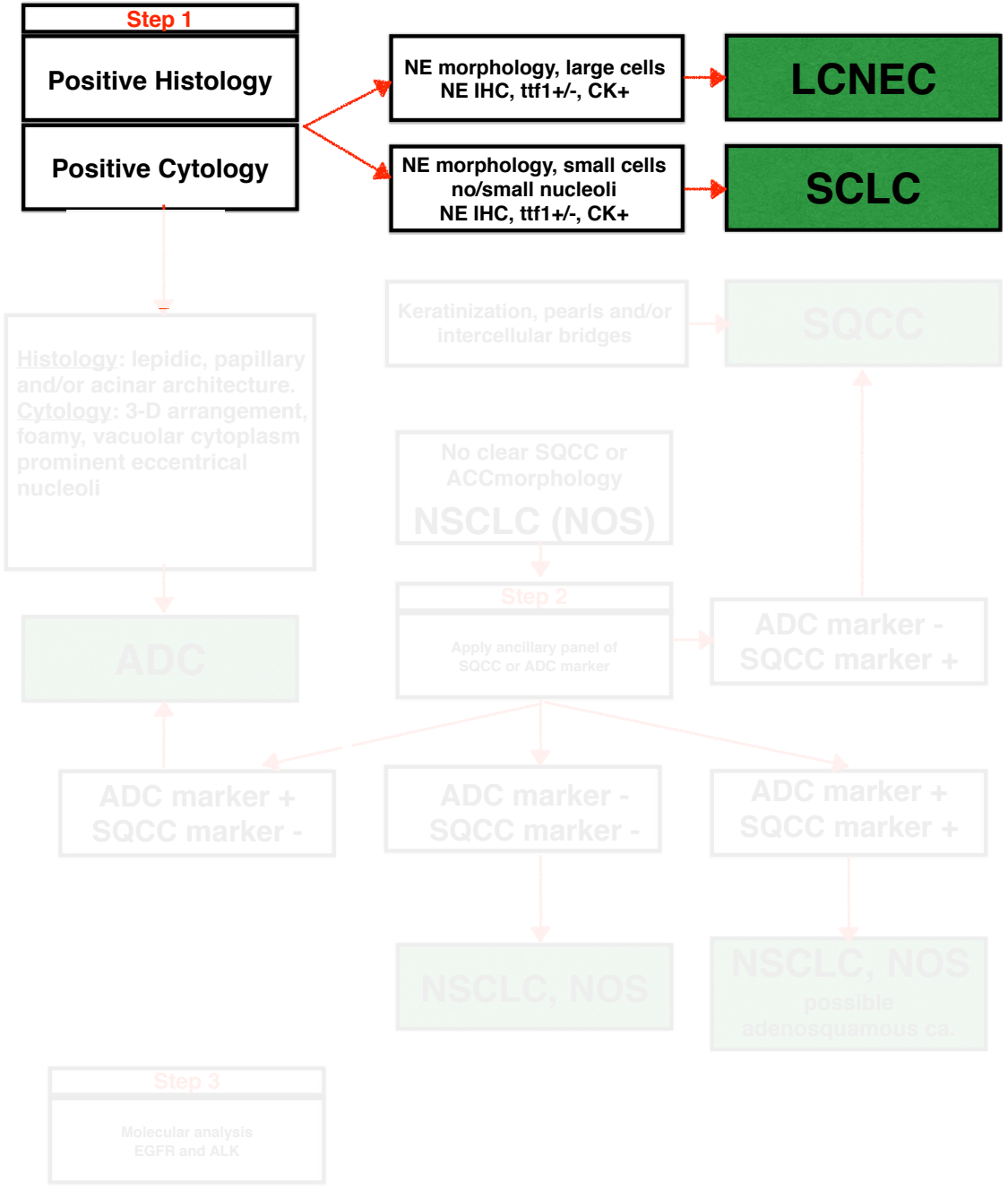






Chromogranin A





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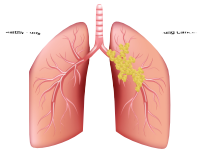
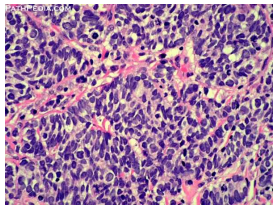
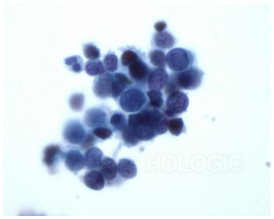
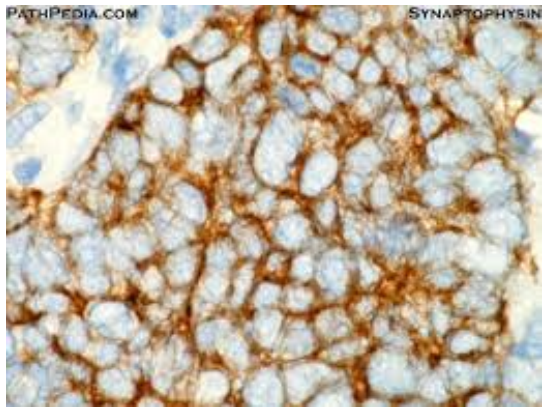
NordiQC

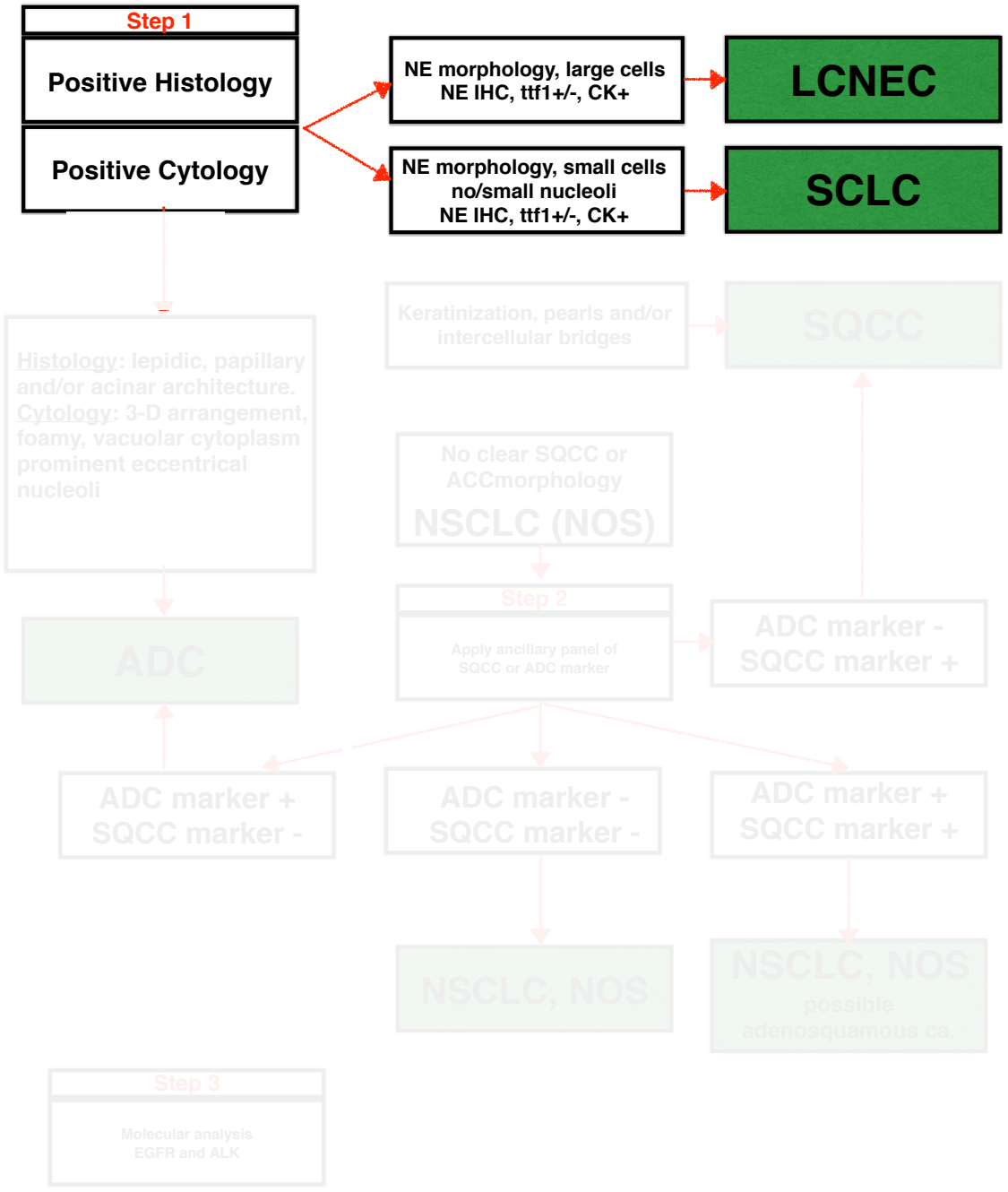






Synaptophysin





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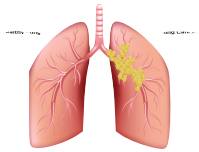
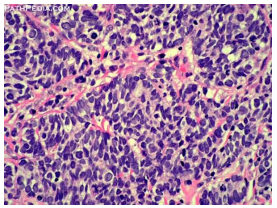
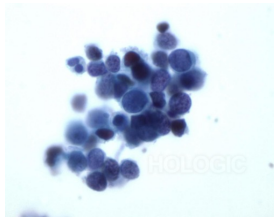
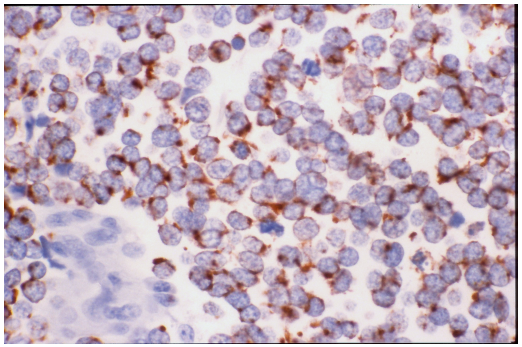
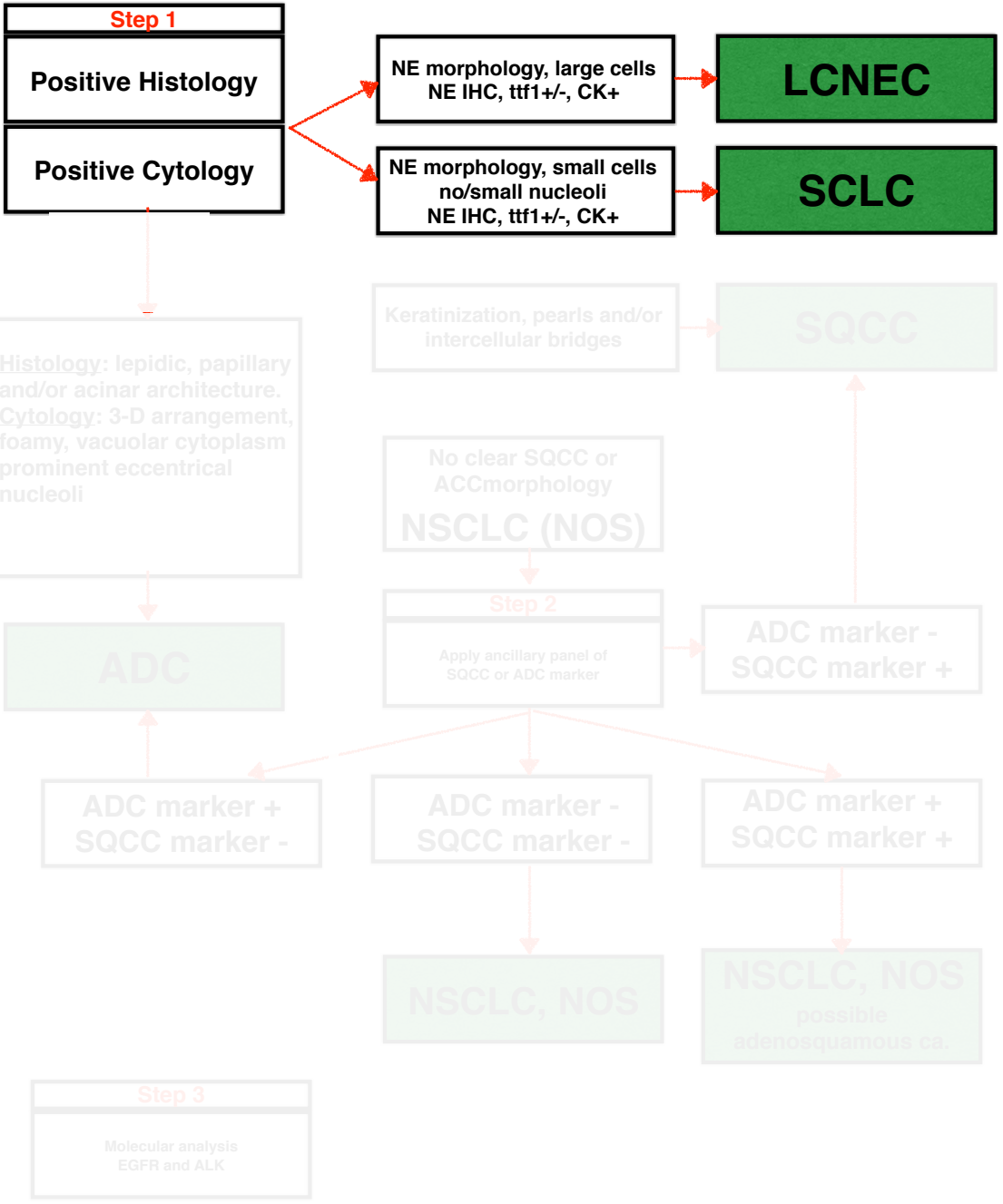






Cytokeratin





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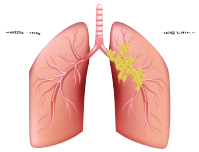
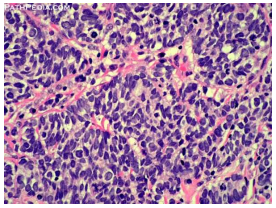
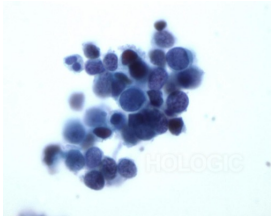
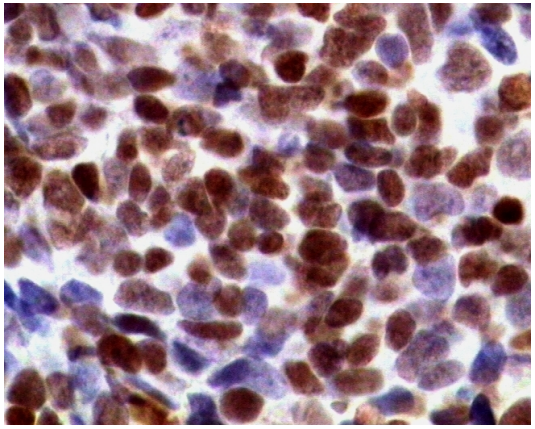
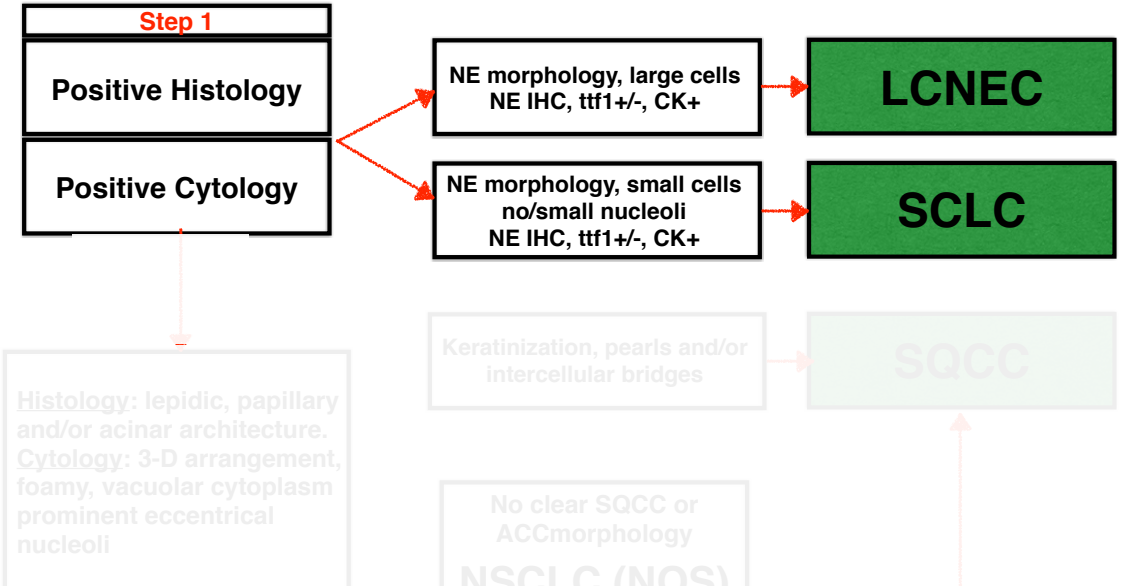






ttf l





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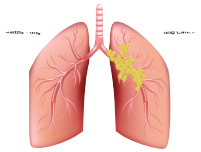
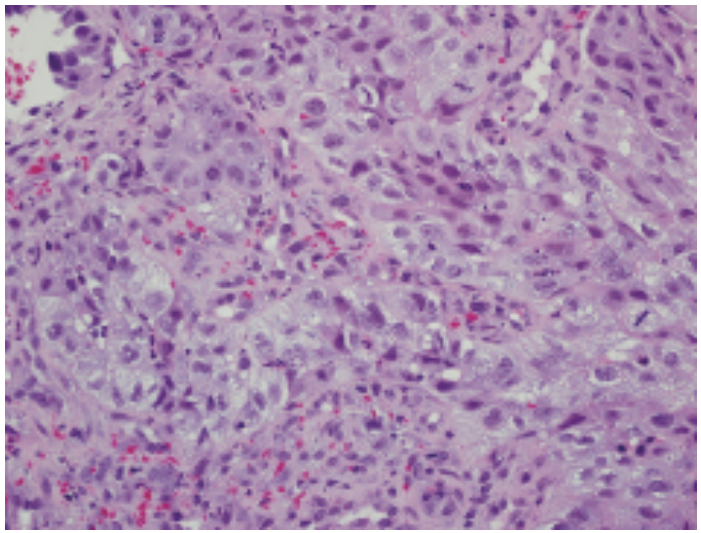




Step 1

Positive Histology

Positive Cytology

NE morphology, large cells
NE IHC, ttf1+/-, CK+ → LCNEC

NE morphology, small cells
no/small nucleoli
NE IHC, ttf1+/-, CK+ → SCLC

Keratinization, pearls and/or
intercellular bridges → SQCC

Histology: lepidic, papillary and/or acinar architecture.
Cytology: 3-D arrangement, foamy, vacuolar cytoplasm prominent eccentrical nucleoli → ADC

No clear SQCC or ACCmorphology

NSCLC (NOS)

Step 2

Apply ancillary panel of SQCC or ADC marker

ADC marker - SQCC marker +

ADC marker + SQCC marker -

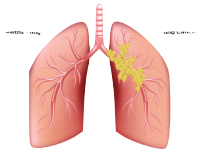
ADC marker - SQCC marker - → NSCLC, NOS

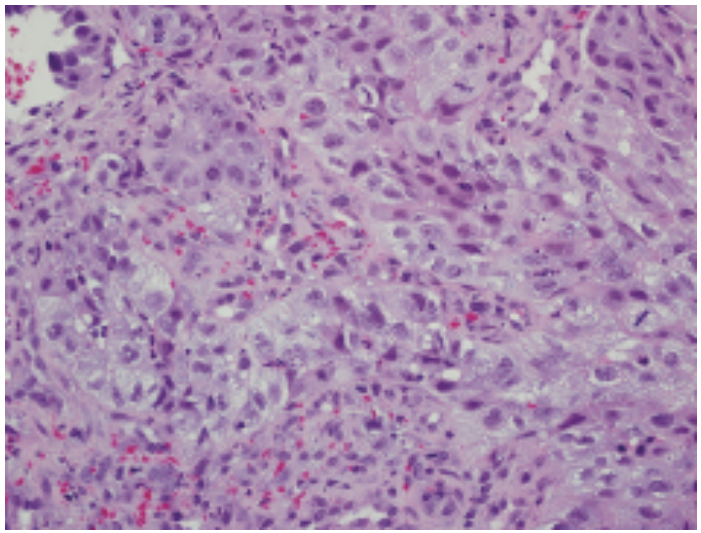
ADC marker + SQCC marker + → NSCLC, NOS
possible adenosquamous ca.

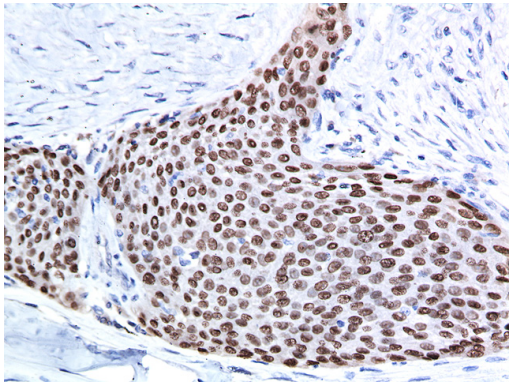
Step 3

Molecular analysis
EGFR and ALK

NordiQC

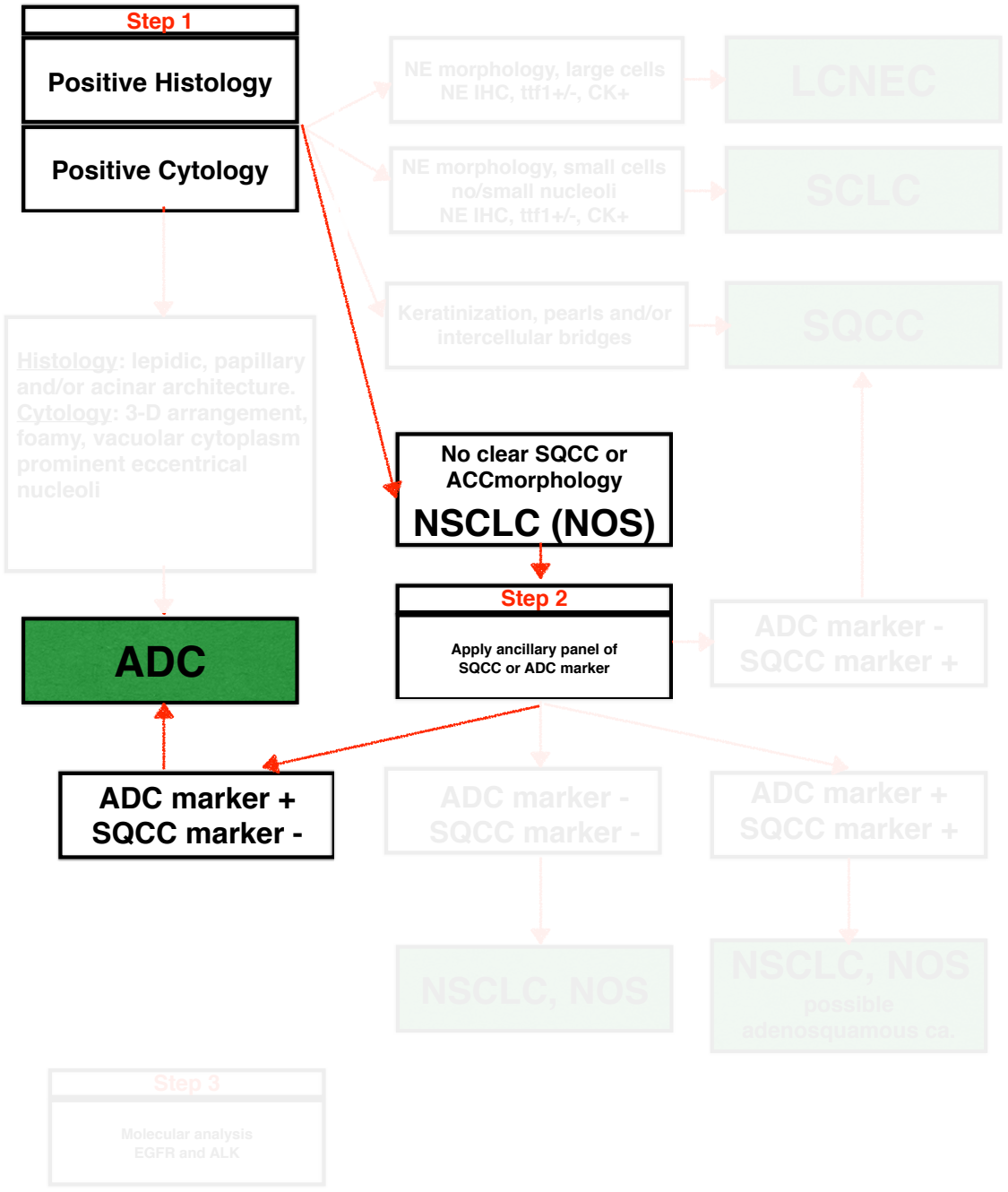






ttf1 +

(+Cytokeratin 7)



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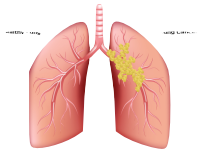
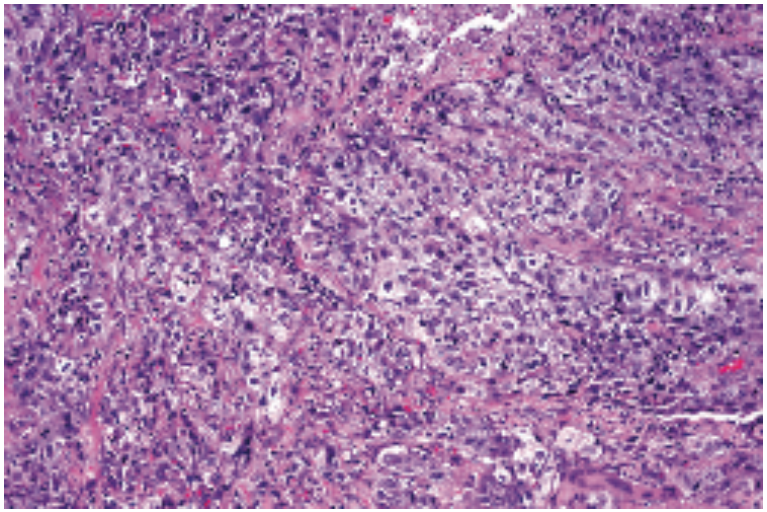
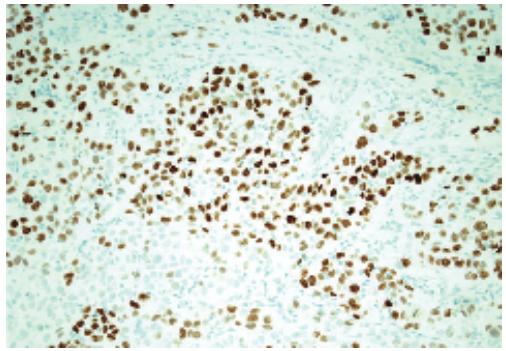
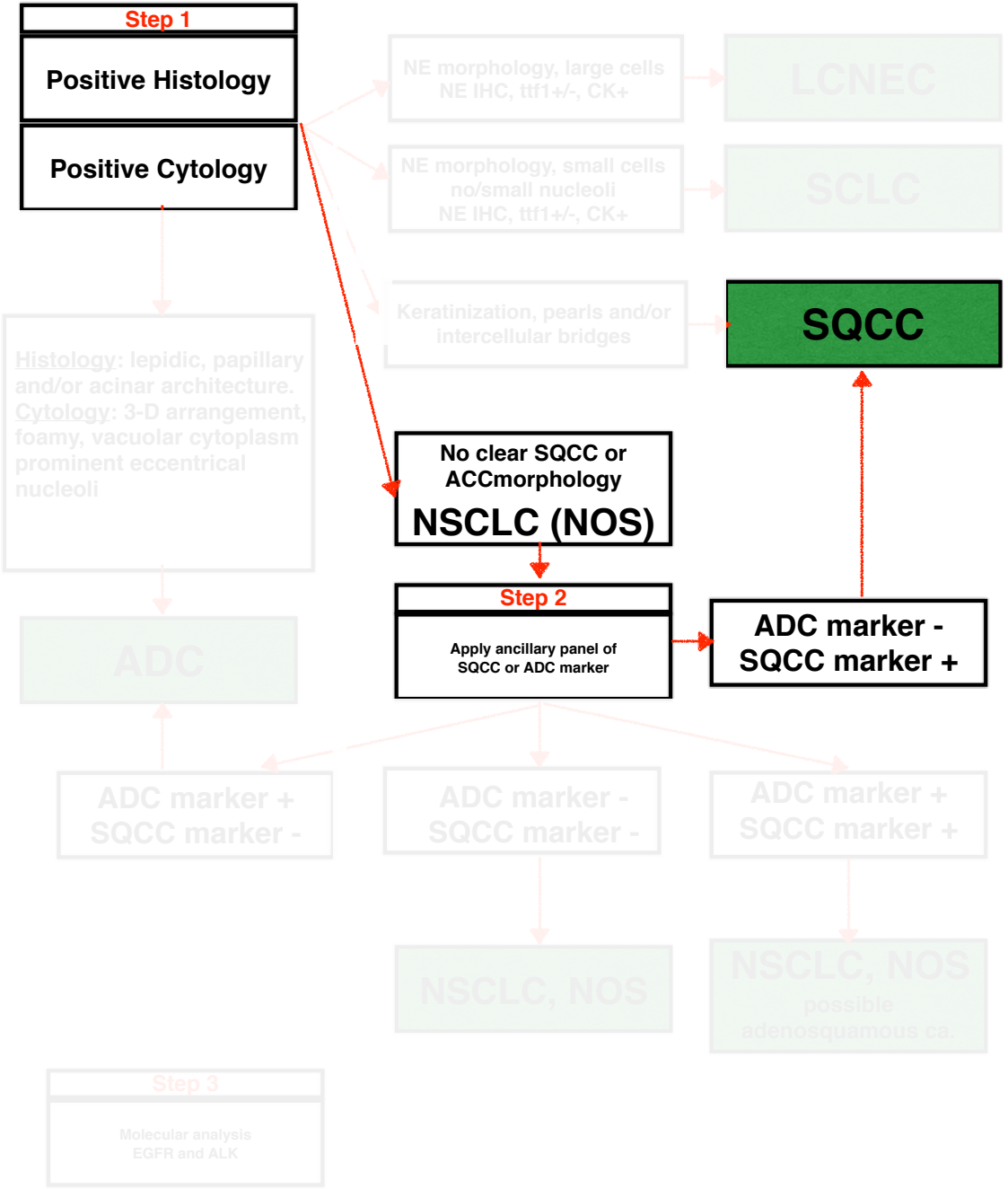






P63+ (+Cytokeratin 5/6)



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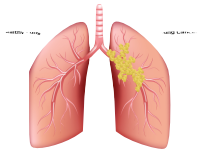
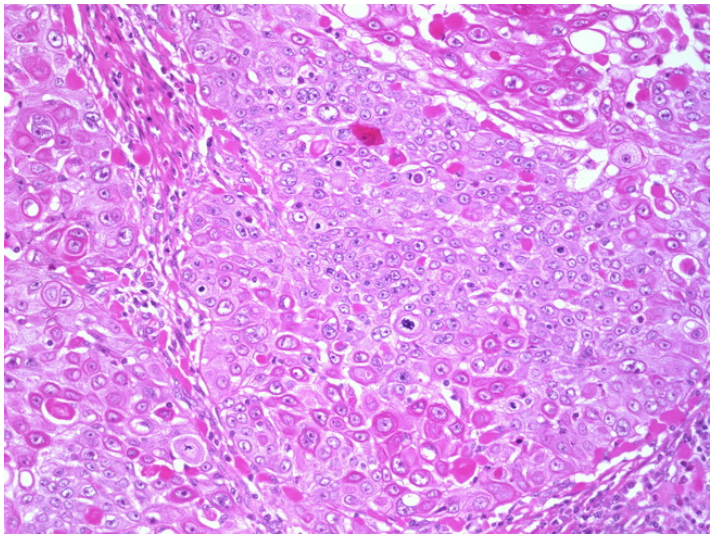
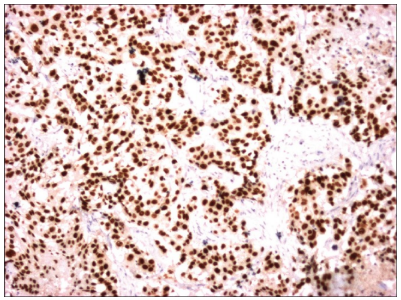
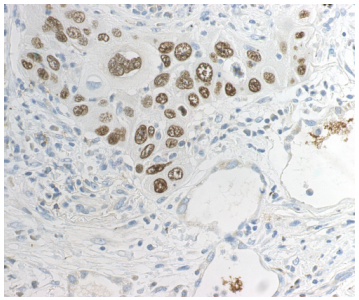


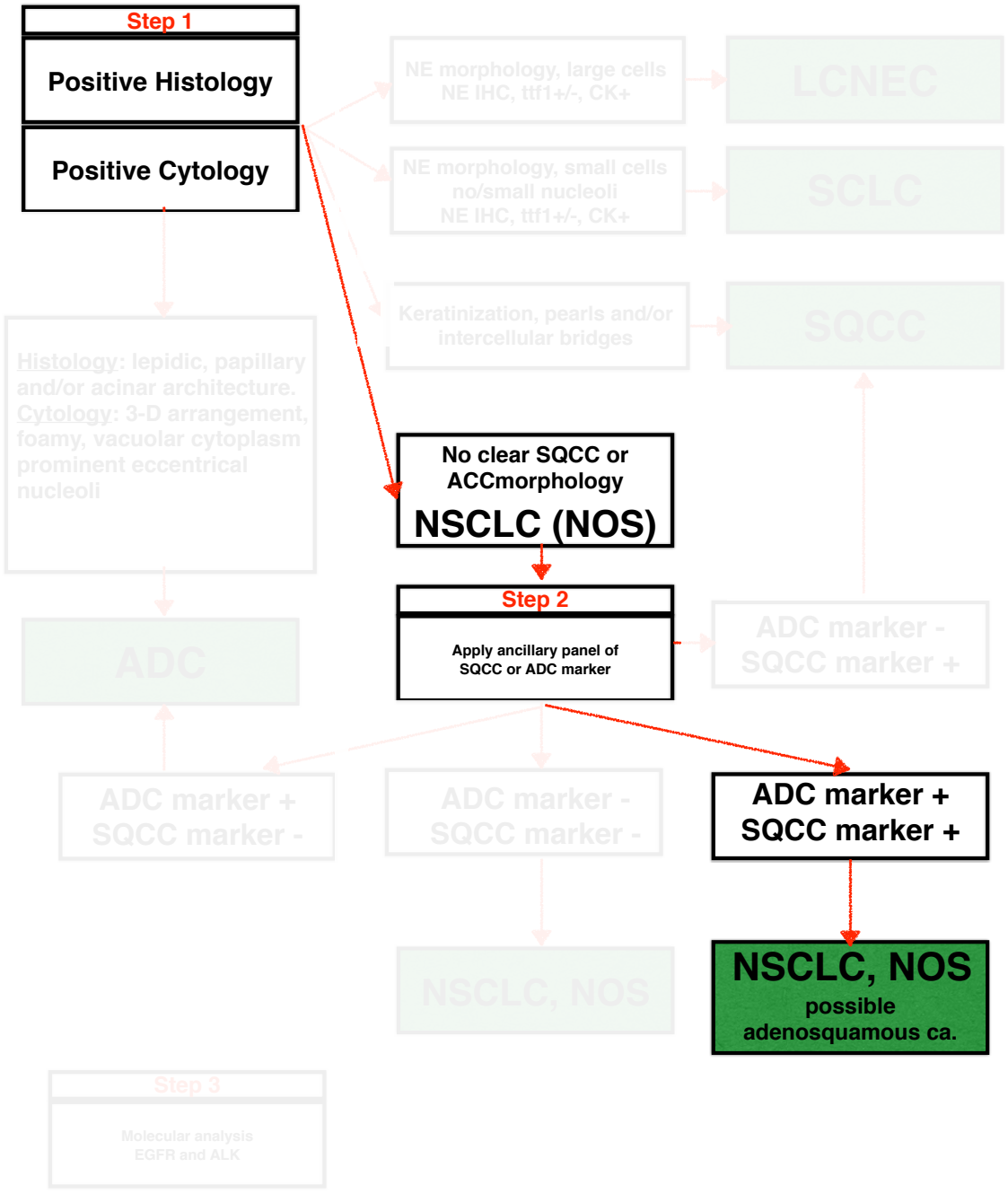




ttf1+



P63+



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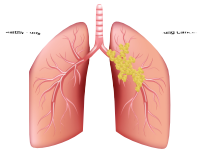
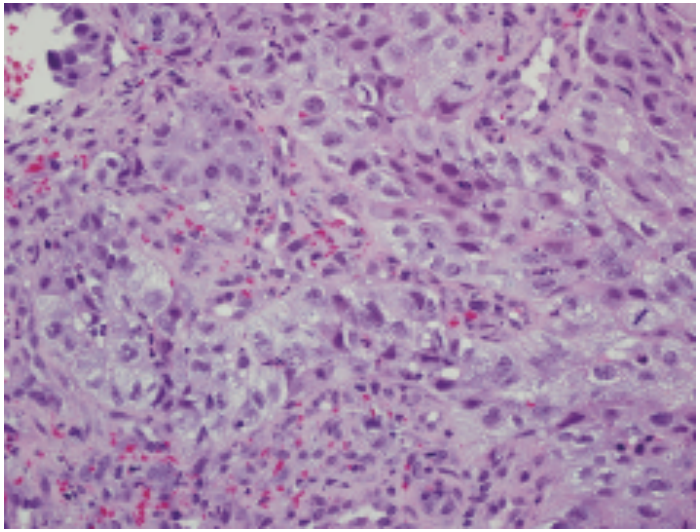




CK7

ttf1

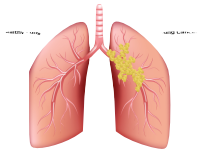
Napsin

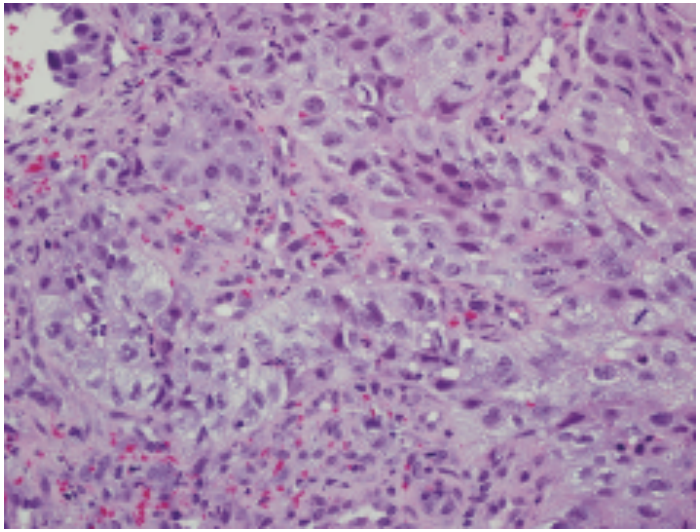
CK5/6

P63

Adenocarcinoma

NordiQC





CK7

ttf1

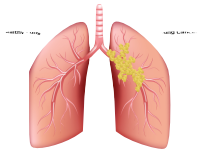
Napsin

CK5/6

P63

Squamous carcinoma

NordiQC



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

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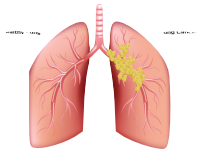
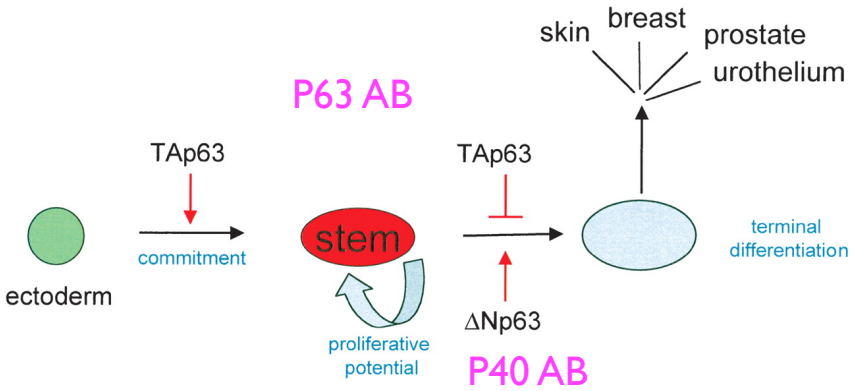


Problems:

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



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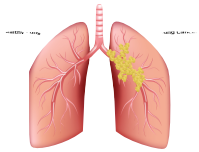

Table 2. Sensitivity, specificity, PPV and NPV of markers used in this study [% (positive/total stained)]

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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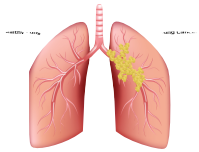
Original Article

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

Wei Zhao, Hui Wang, Yan Peng, Bo Tian, Lei Peng, Da-Chuan Zhang

NordiQC



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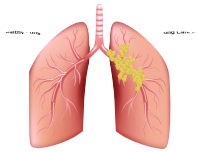
Original Article

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

Wei Zhao, Hui Wang, Yan Peng, Bo Tian, Lei Peng, Da-Chuan Zhang

NordiQC



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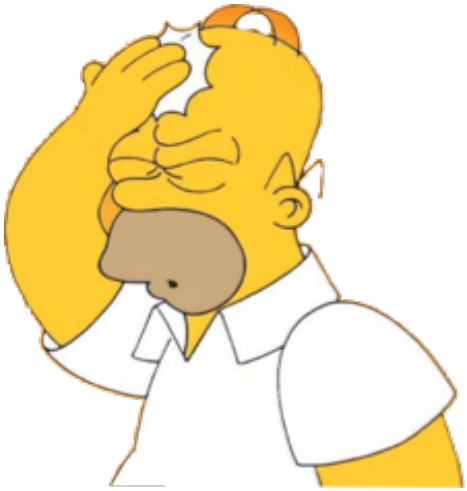

Differential diagnosis between primary and metastatic carcinoma

Other (adeno) carcinomas are positive for ttf1

NordiQC

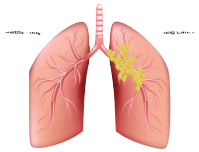

Table 1

Summary of immunohistochemistry results.

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

NS: not significant

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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.

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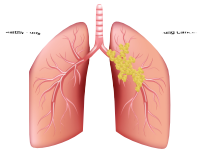
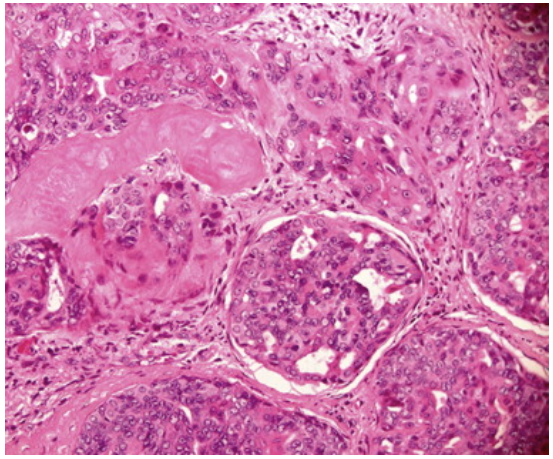
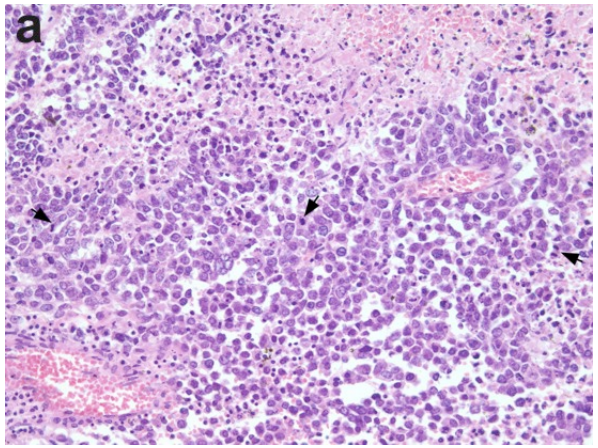


Diagnosis of metastasis to the lung





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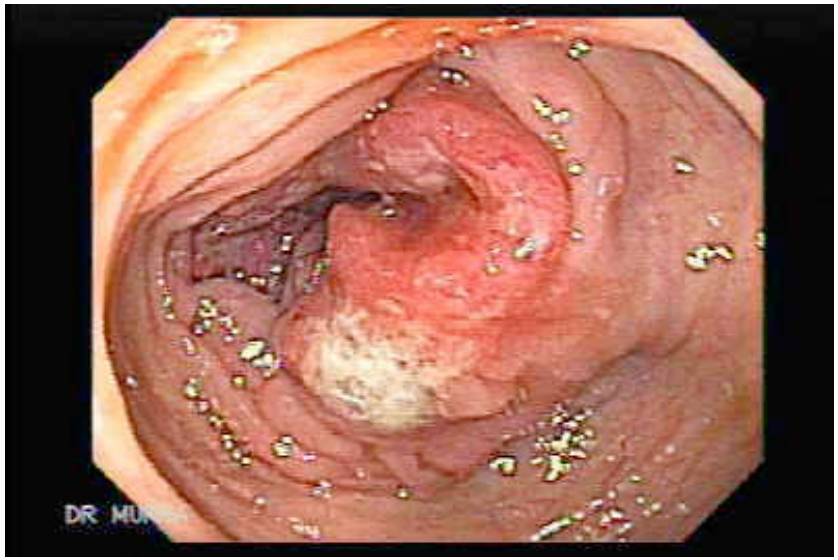
CK7
ttf1
CK20 ←
cdx2 ←
SATB2 ←
NKX3.1
CK5/6
P63
CD10
PAX8
WT1
GATA3

Colon



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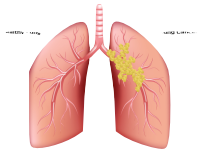
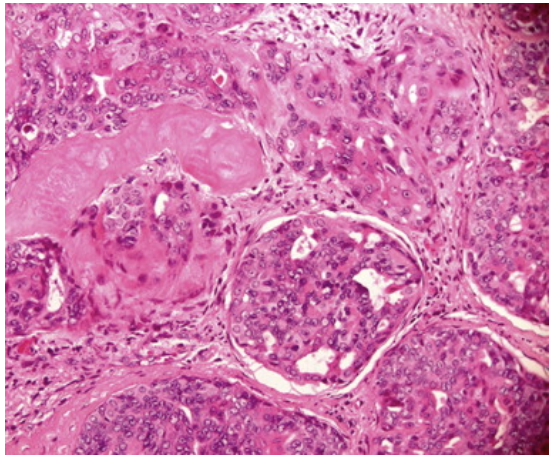
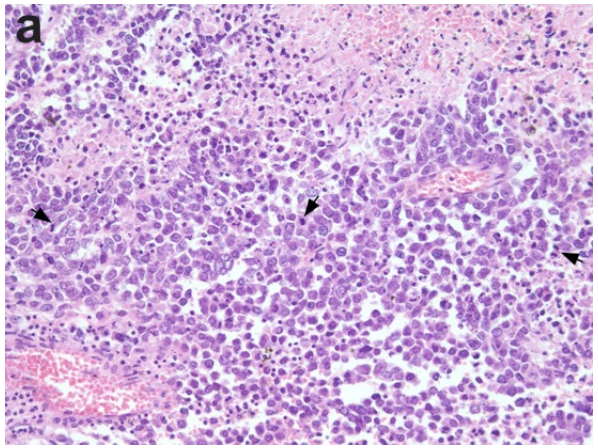


Diagnosis of metastasis to the lung





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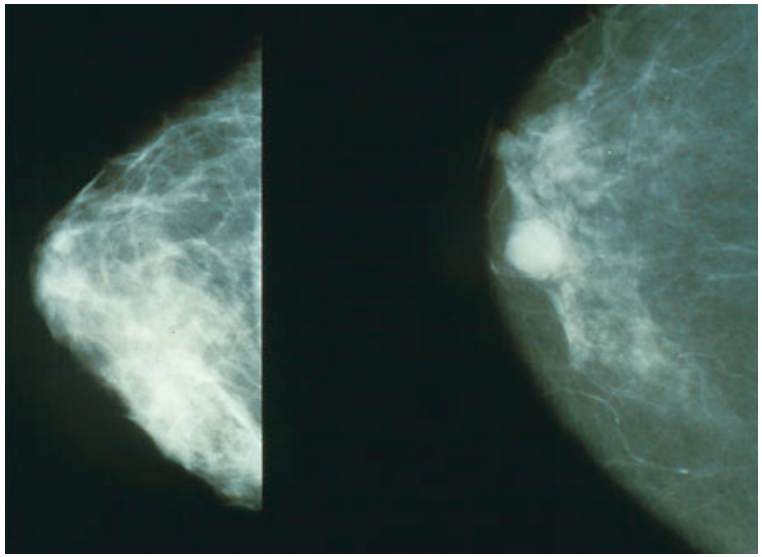
WT1
GATA3 ←

Mamma



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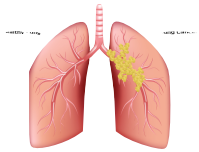
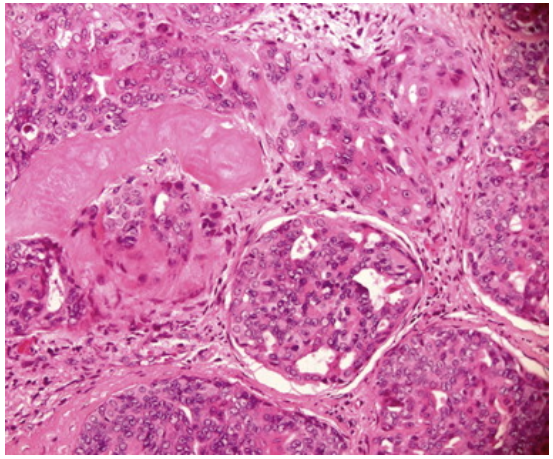
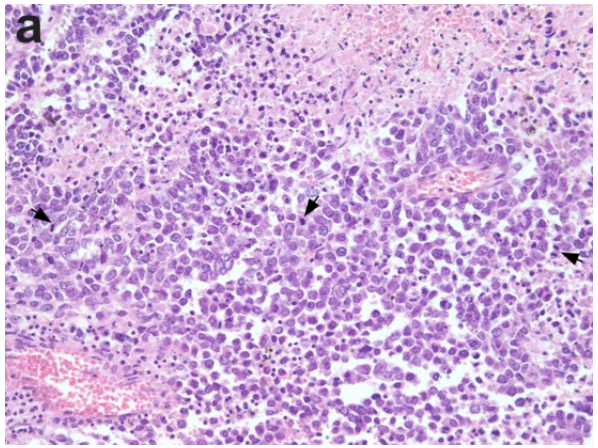


Diagnosis of metastasis to the lung





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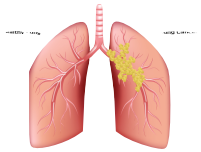
GATA3

Upper GI

NordiQC



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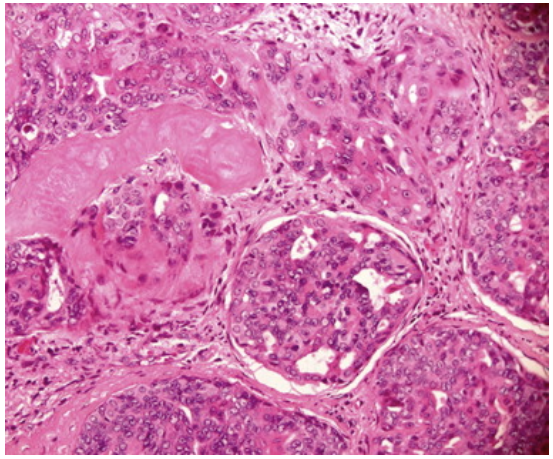

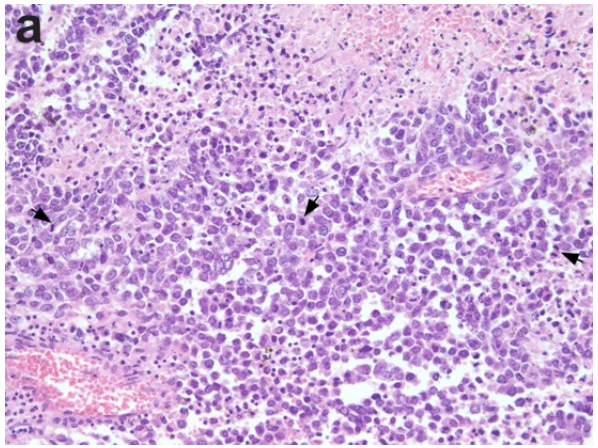

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P63 ←
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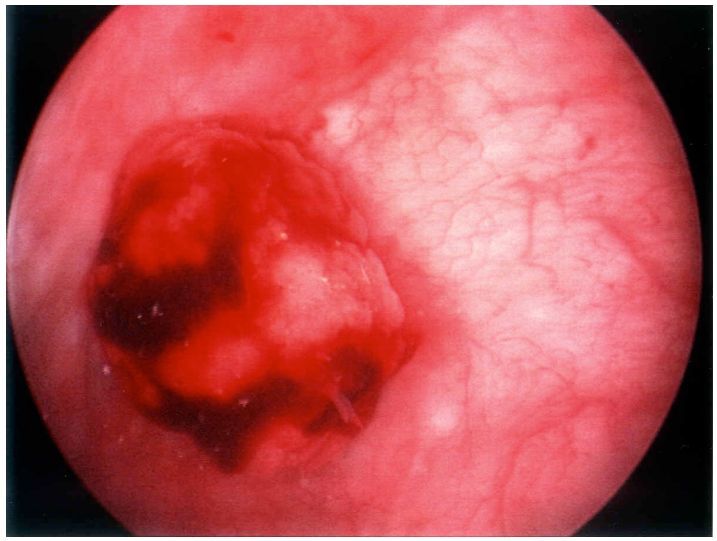
PAX8
WT1
GATA3 ←

Urothelial carcinoma



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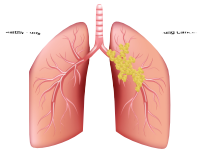
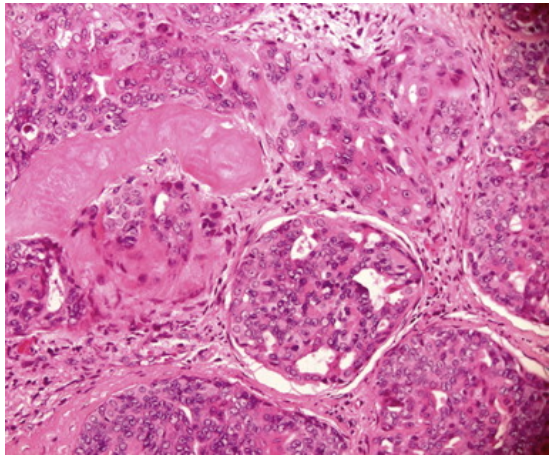
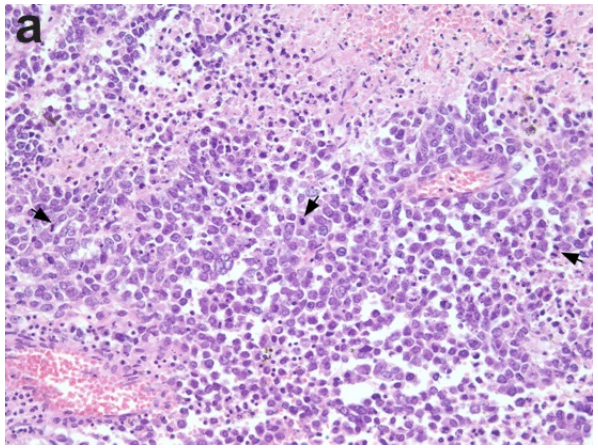


Diagnosis of metastasis to the lung





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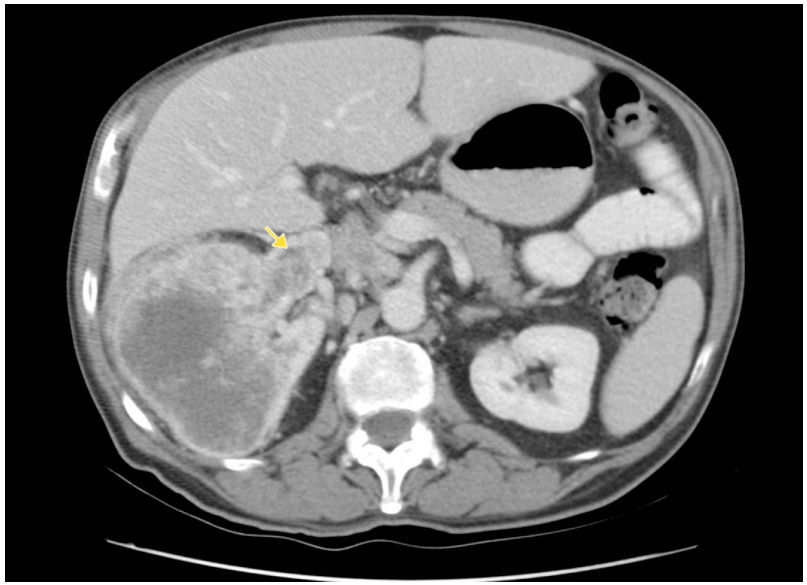
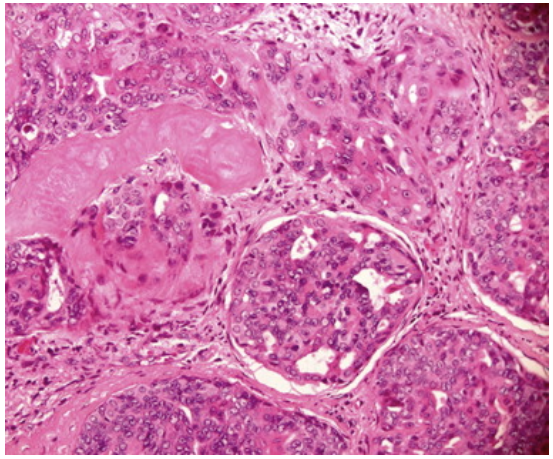
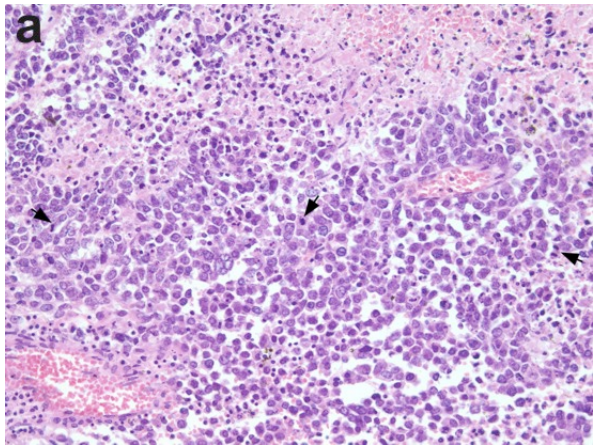
CD10 ←
PAX8 ←
WT1
GATA3

Renal cell carcinoma



Diagnosis of metastasis to the lung





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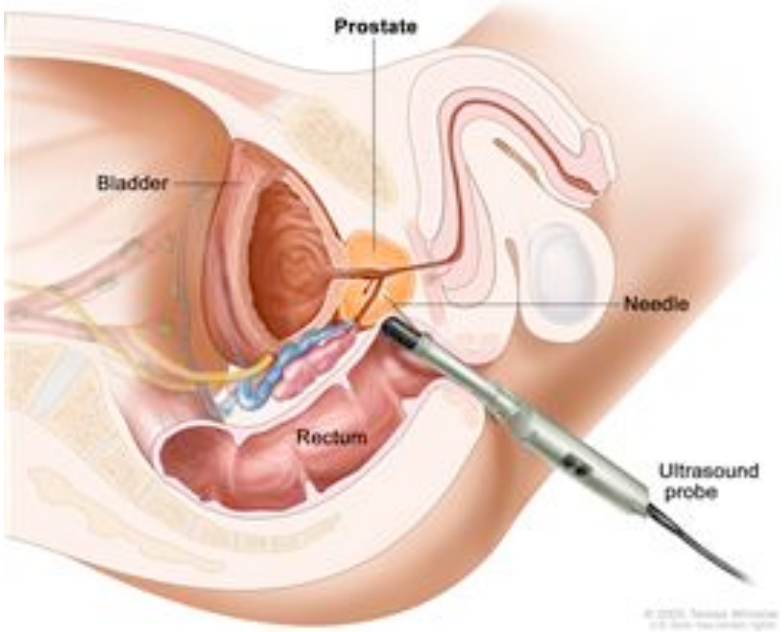
PAX8
WT1
GATA3

Prostate



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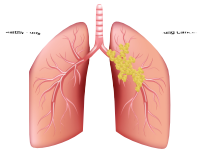

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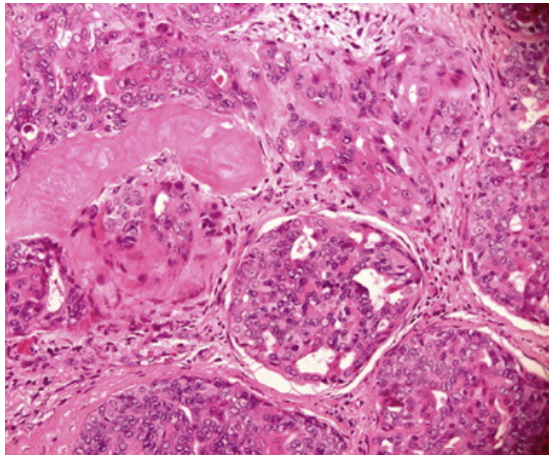

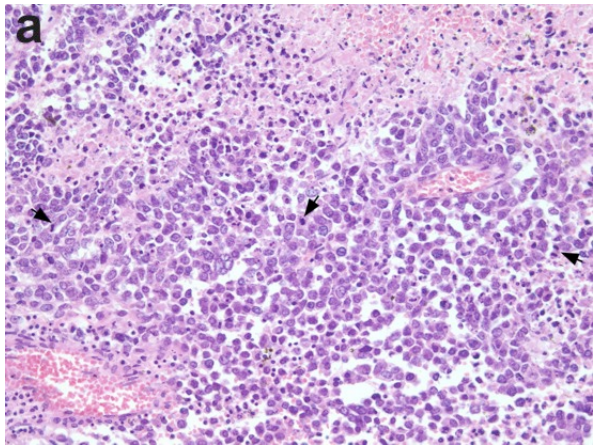

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ttf1
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cdx2
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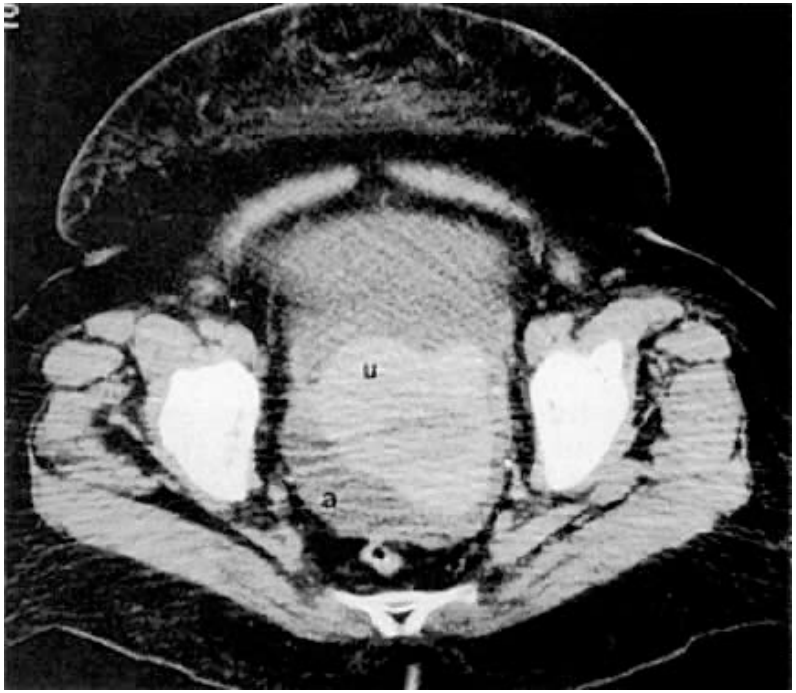
CK5/6
P63
CD10
PAX8 ←
WT1 ←
GATA3

Endometrial cancer



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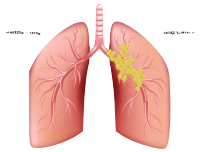

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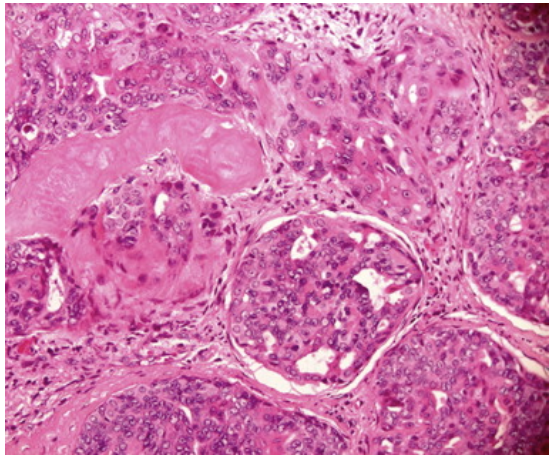

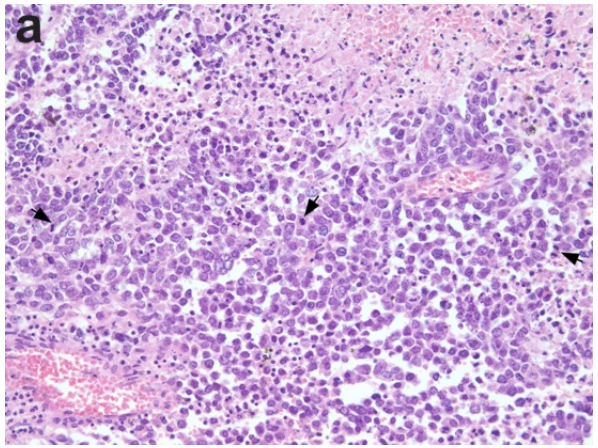

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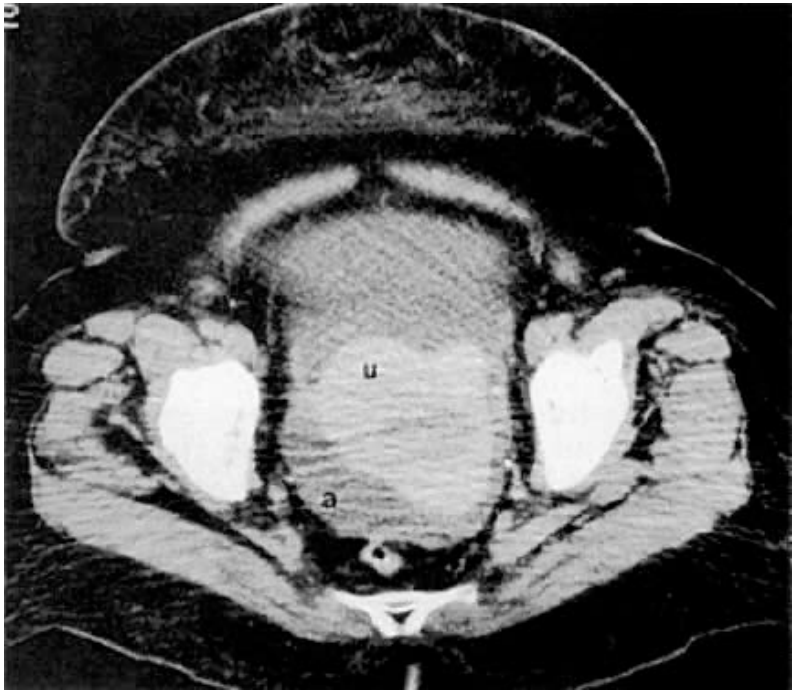
GATA3

Ovarian cancer



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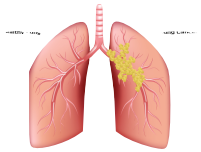
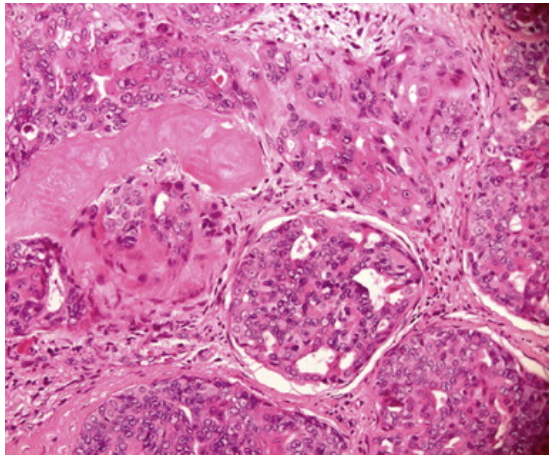
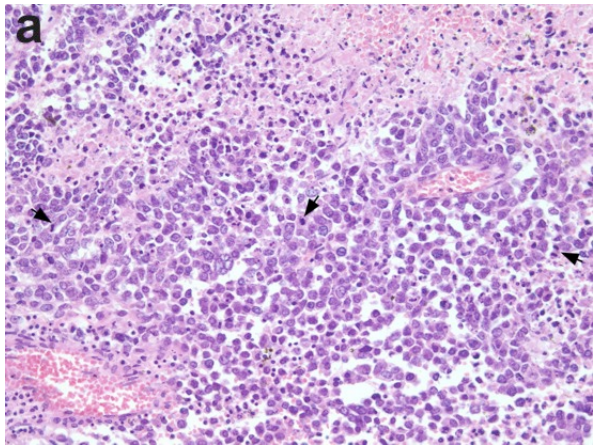


Diagnosis of metastasis to the lung





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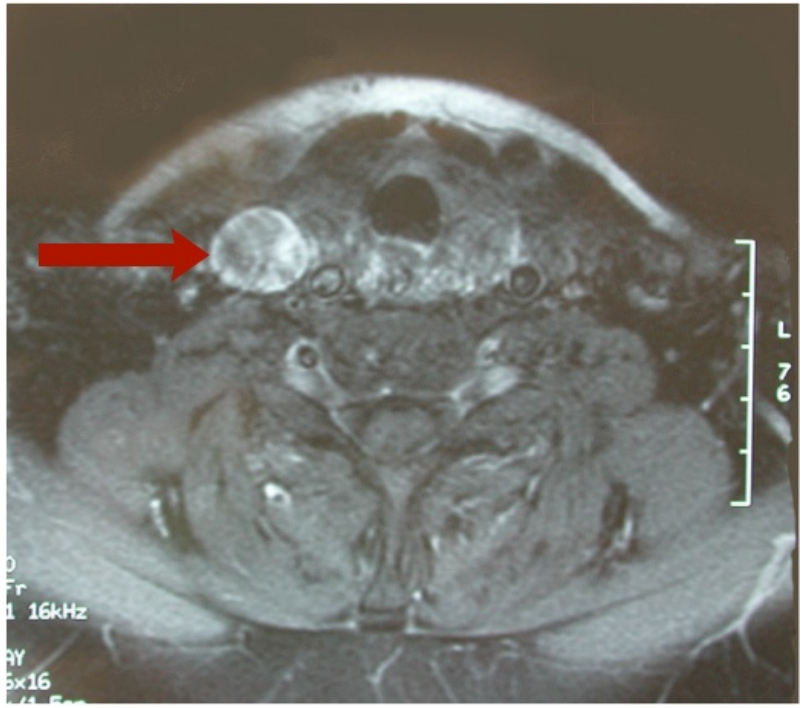
Thyroid cancer



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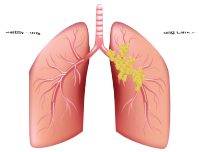
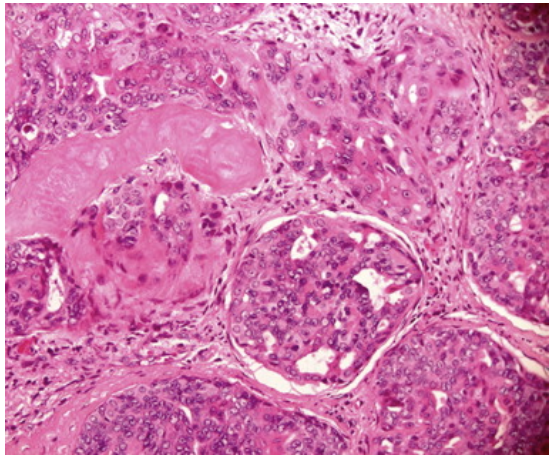
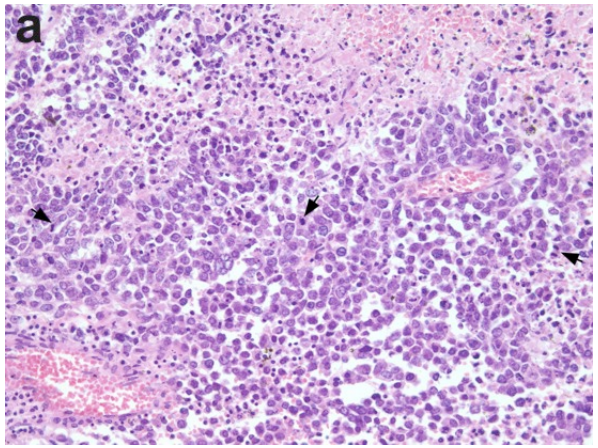


Mesothelioma





Calretinin

WT1

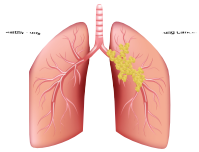
D2-40

CK7

Vim

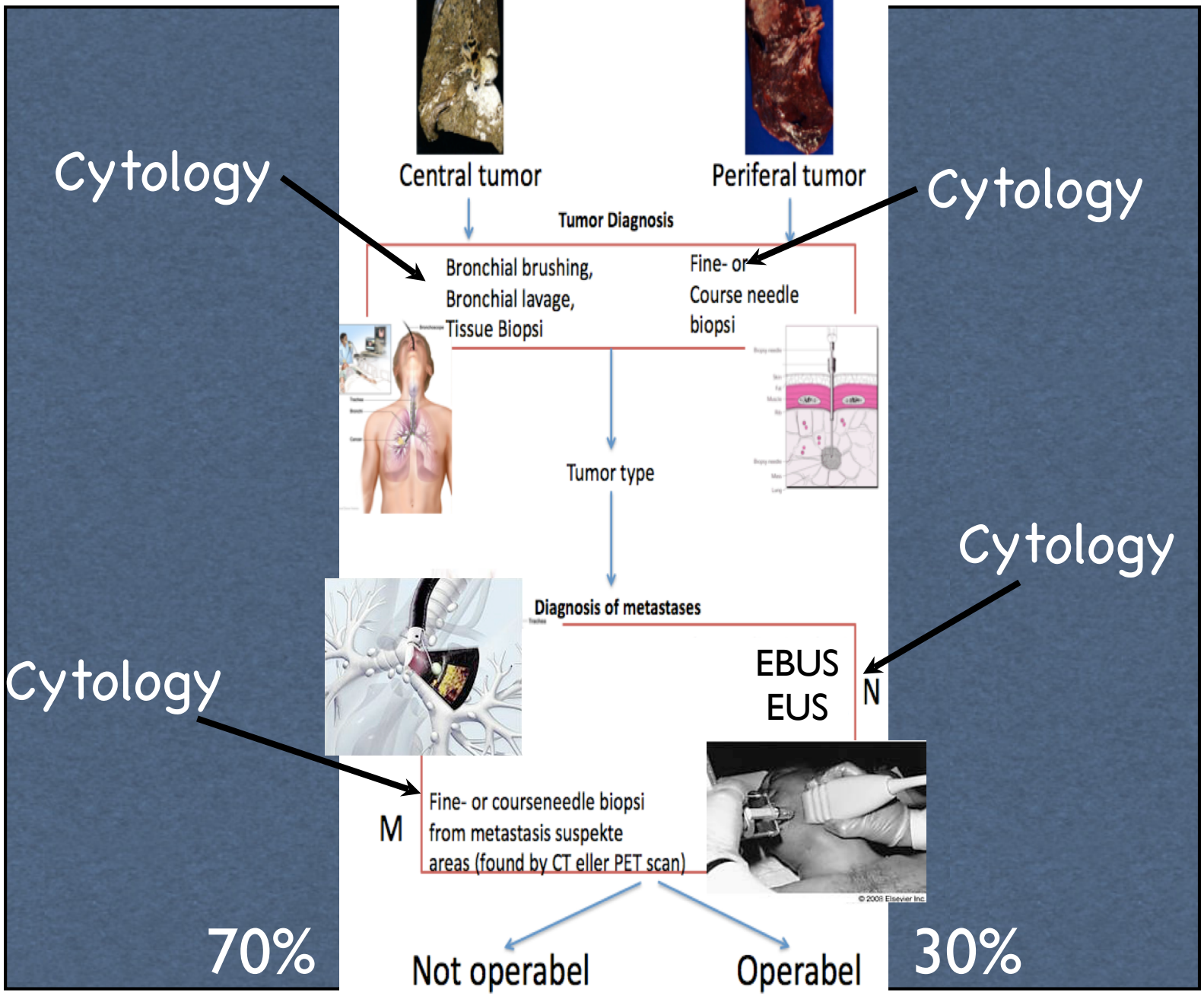
CK5/6

NordiQC



The **M**ulti**D**isciplinary **T**eamconference

MDT


Cytology
Central tumor
Periferal tumor
Cytology
Tumor Diagnosis
Bronchial brushing,
Bronchial lavage,
Tissue Biopsi
Fine- or
Course needle
biopsi
Tumor type
Cytology
Diagnosis of metastases
EBUS
EUS
N
Cytology
M
Fine- or courseneedle biopsi
from metastasis suspekte
areas (found by CT eller PET scan)
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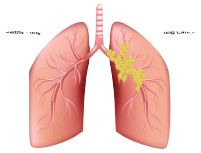
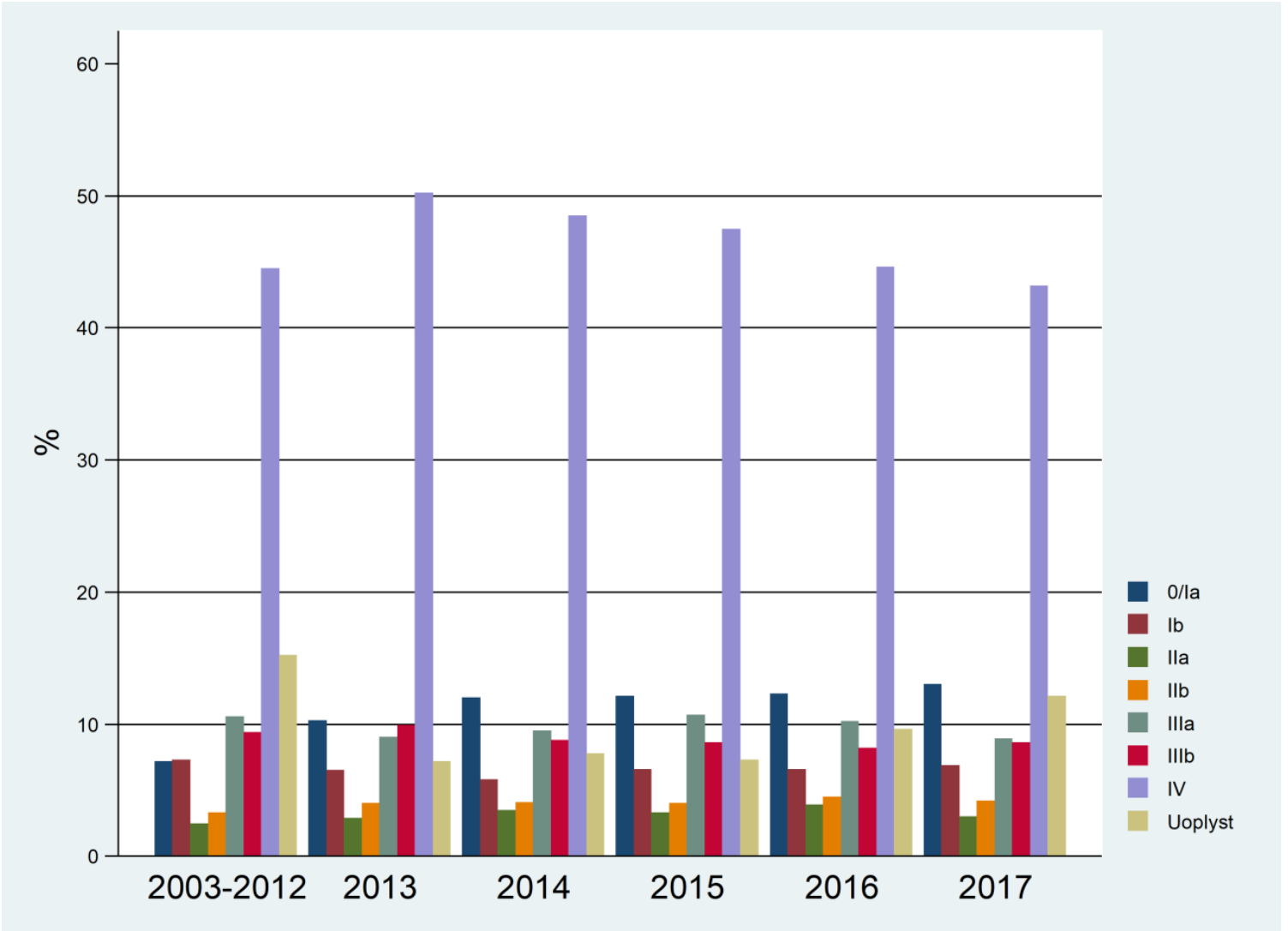
70%
Not operabel
Operabel
30%

NordiQC





Stage at diagnosis

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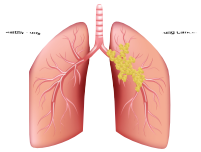
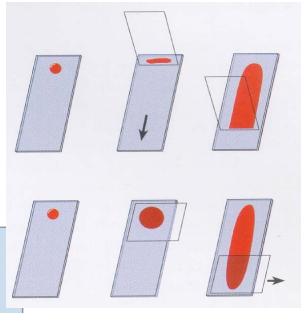


Patoanatomical specimen

Cytology



Histology

Fixation
Dehydration
Parafinembedding
Microtomy

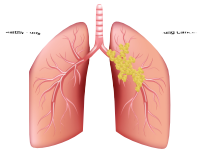
Præparation

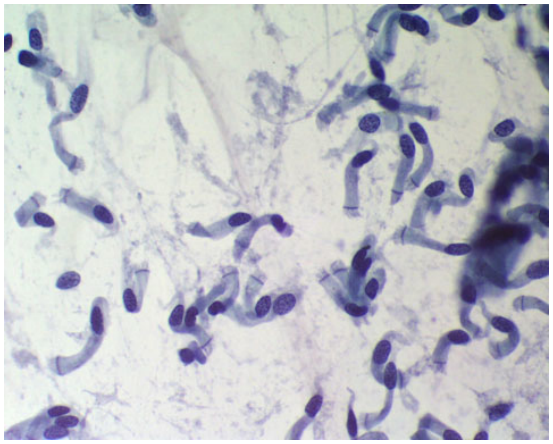
Smear preparation

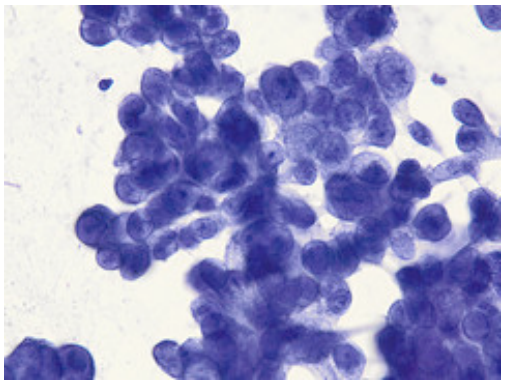
Visualization

(Staining)

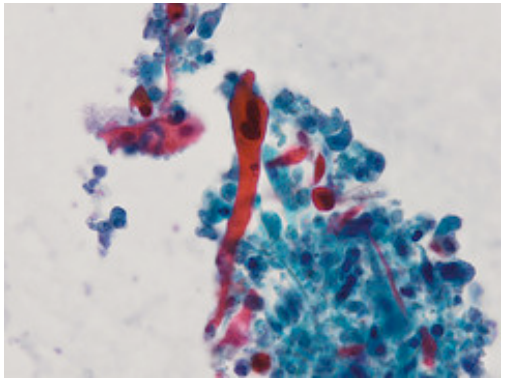
NordiQC



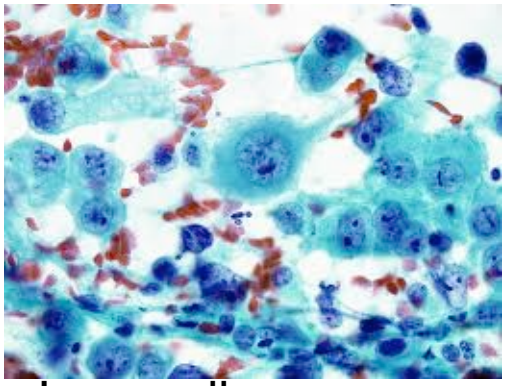




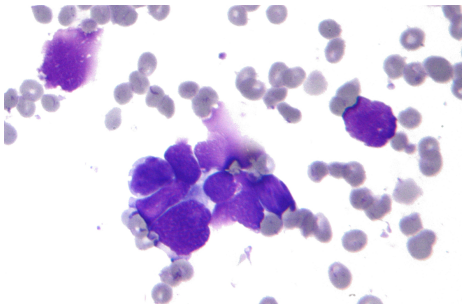
Adenocarcinoma



Squamous carcinoma



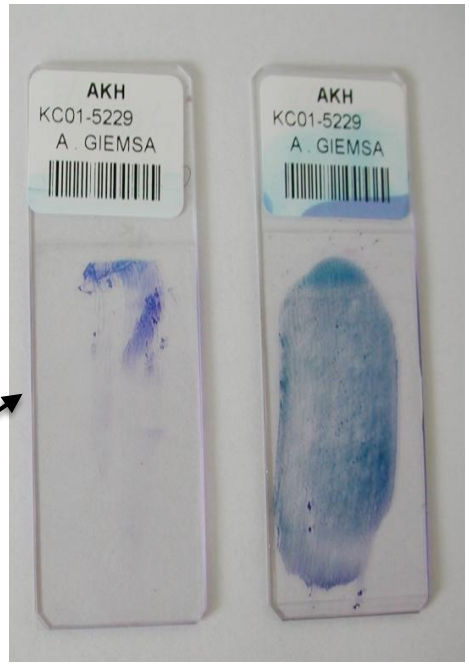
Large cell neuroendocrine carc.

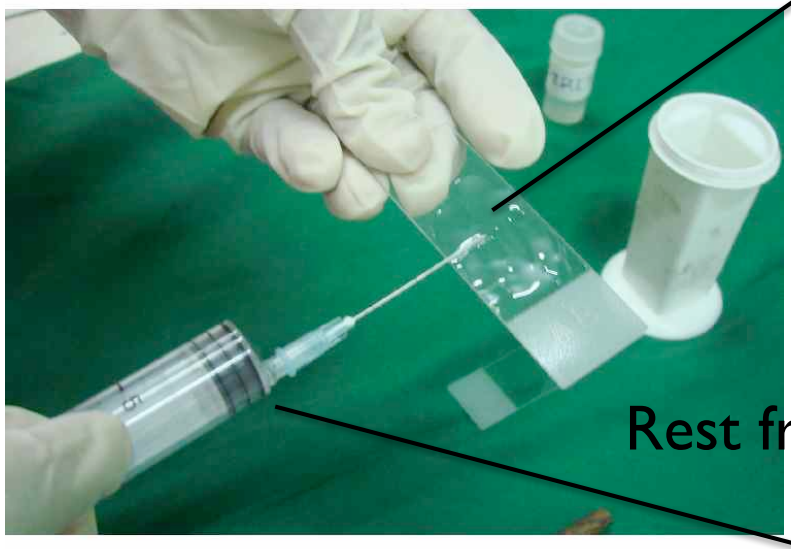


Small cell carcinoma

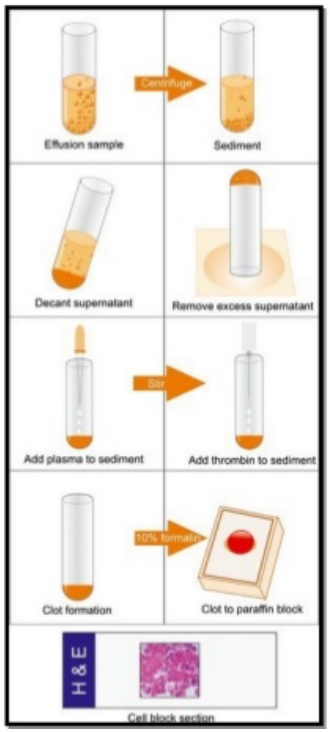
Non Small Cell Lung Carcinoma (NSCLC)

Cytology





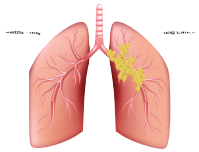
Rest from the needle



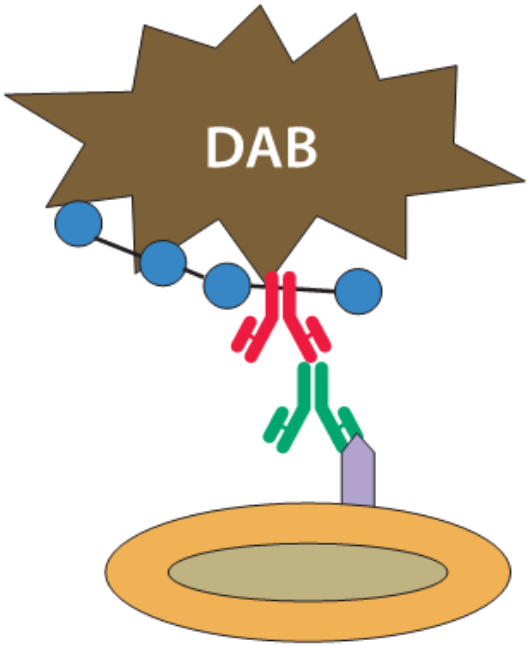
Cellblock

Immunocytologi

NordiQC



Cytology



Kromogen (farvestof)

Visualiseringssystem (enzymer)

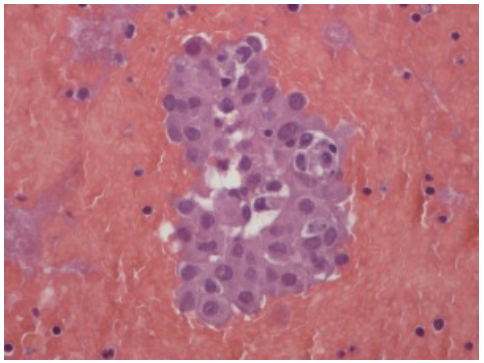
Sekundært antistof

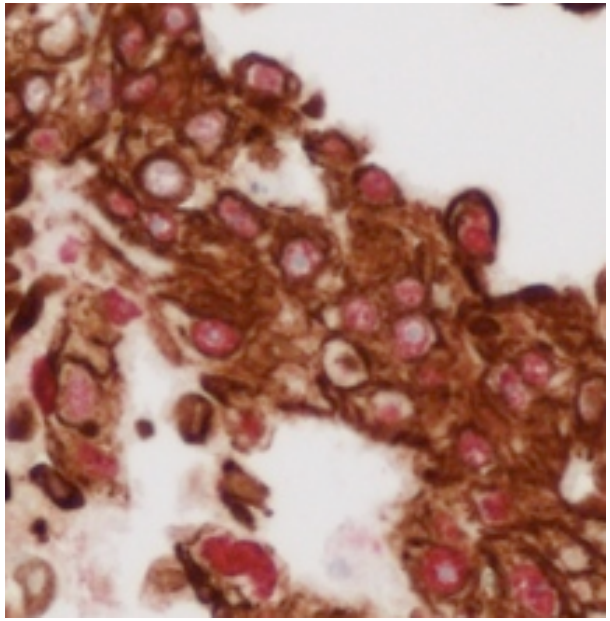
Primært antistof

Antigen

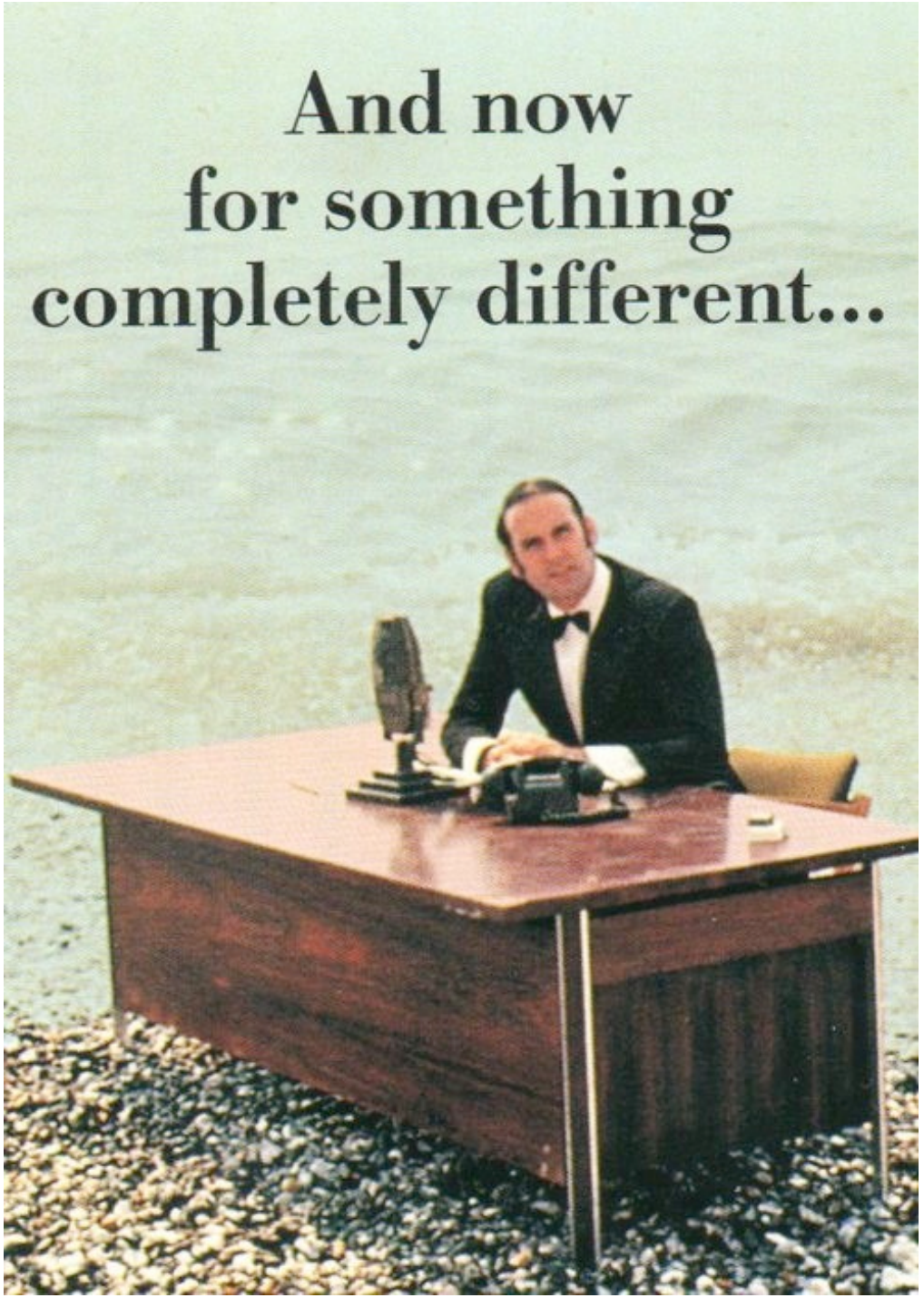
Cellens cytoplasma

Cellekerne

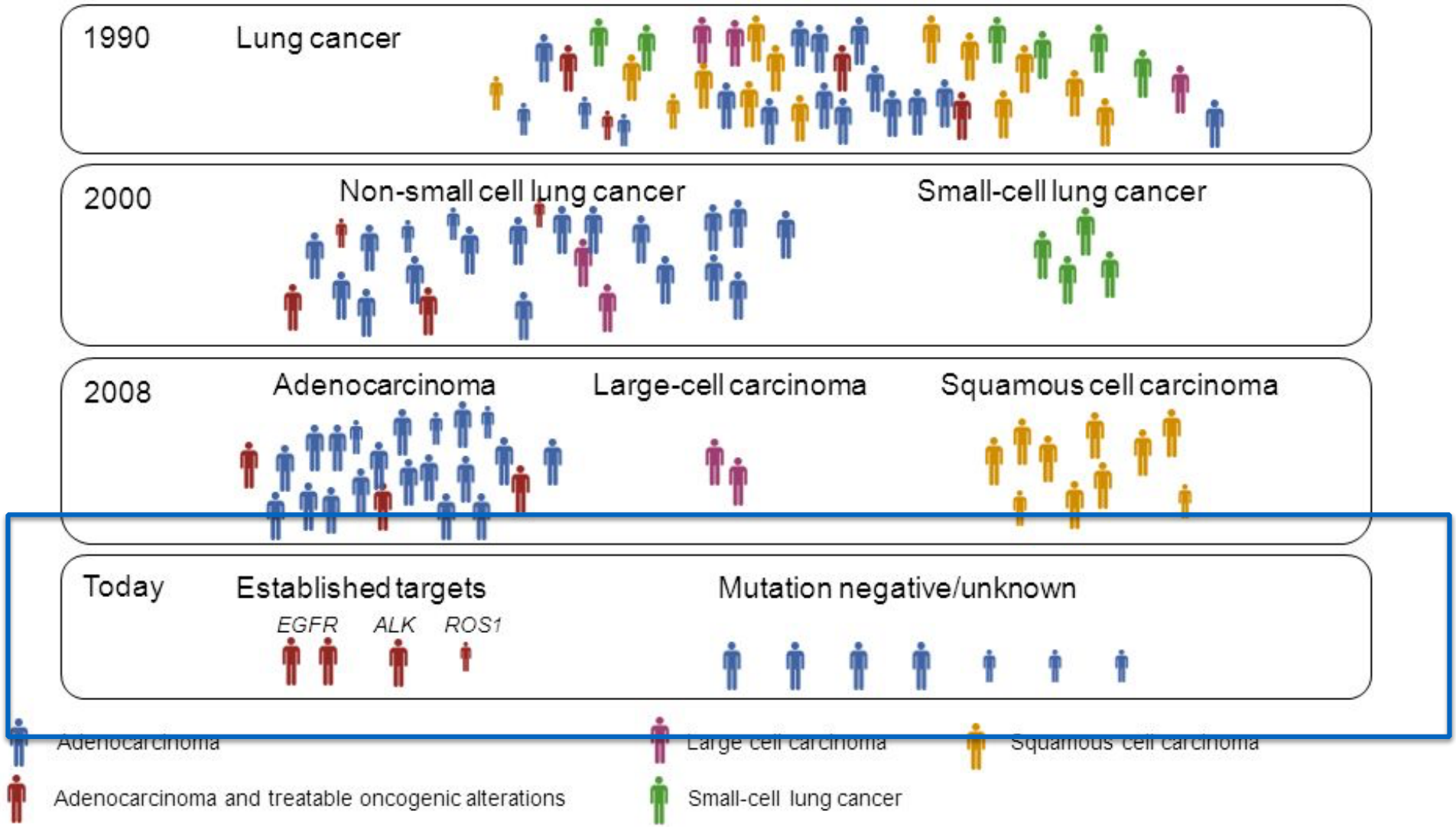




ttf1-CK7

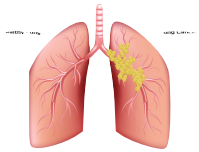

And now
for something
completely different...

Patient selection in lung cancer: Evolution over time



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

NordiQC



Step 1

Positive Histology

Positive Cytology

NE morphology, large cells
NE IHC, ttf1+/-, CK+

LCNEC

NE morphology, small cells
no/small nucleoli
NE IHC, ttf1+/-, CK+

SCLC

Keratinization, pearls and/or intercellular bridges

SQCC

Histology: lepidic, papillary and/or acinar architecture.
Cytology: 3-D arrangement, foamy, vacuolar cytoplasm prominent eccentrical nucleoli

No clear SQCC or ACCmorphology

NSCLC (NOS)

Step 2

Apply ancillary panel of SQCC or ADC marker

ADC

ADC marker +
SQCC marker -

ADC marker -
SQCC marker -

ADC marker +
SQCC marker +

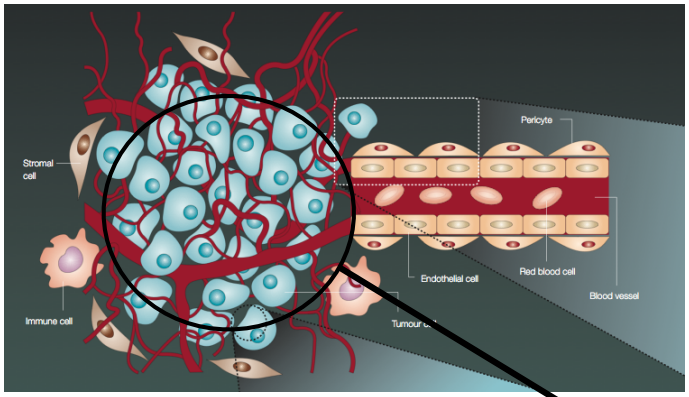
NSCLC, NOS

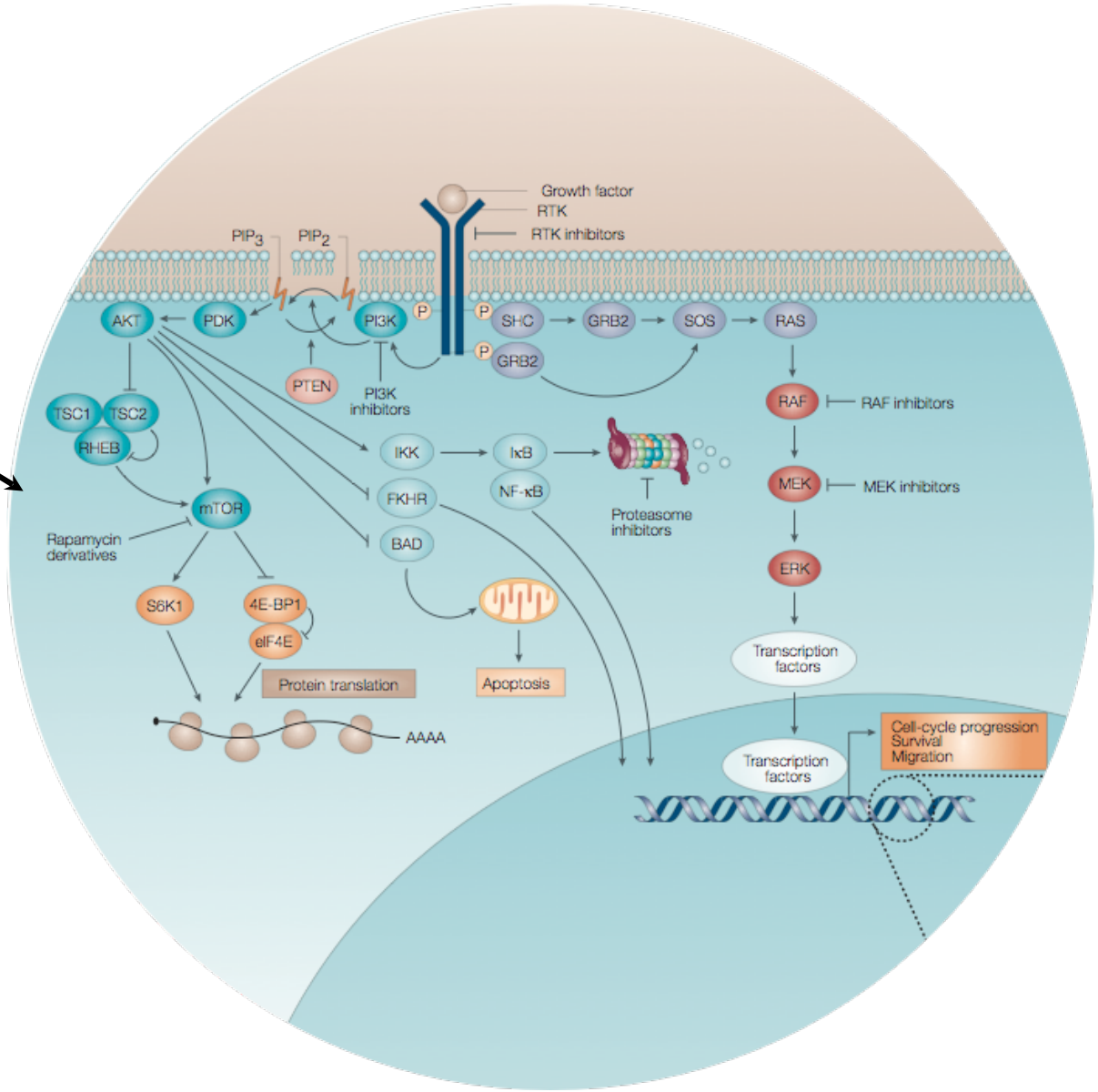
NSCLC, NOS
possible adenosquamous ca.

Step 3

Molecular analysis
EGFR and ALK

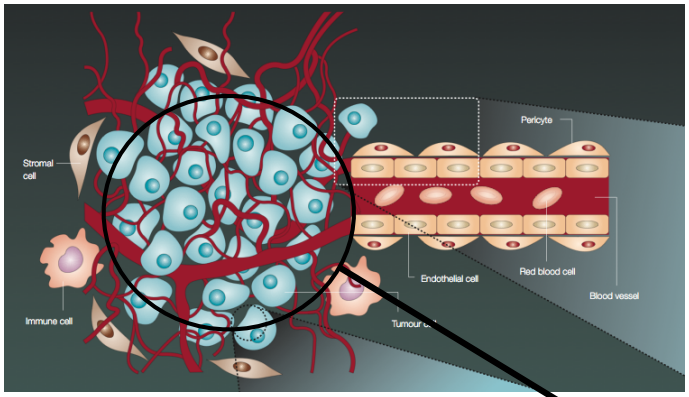
NordiQC

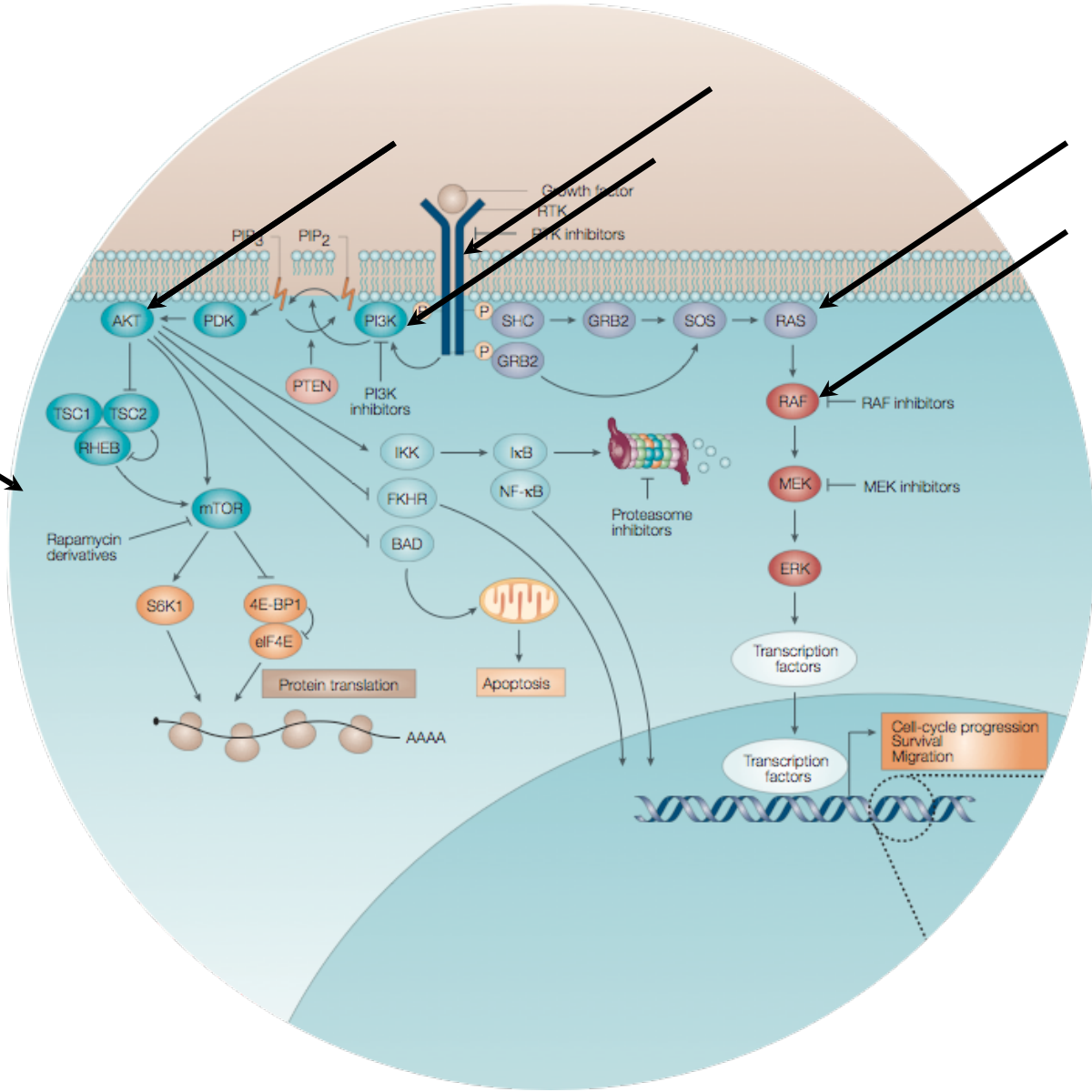




Pathways of cancer

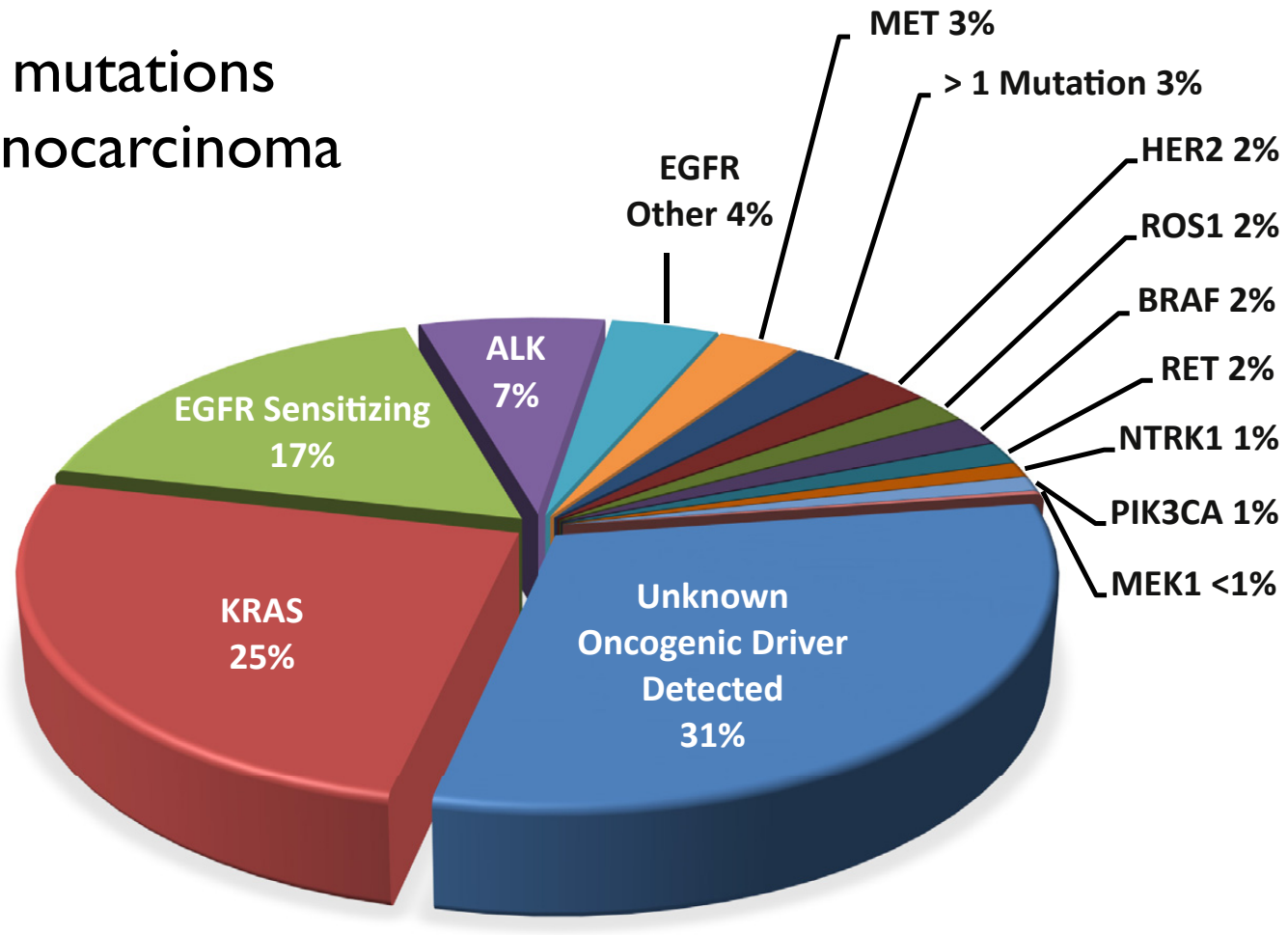
NordiQC





oncogenes

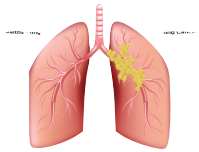
Driver mutations
Lung Adenocarcinoma



STATE OF THE ART: CONCISE REVIEW

Scientific Advances in Lung Cancer 2015

Journal of Thoracic Oncology Vol. 11 No. 5: 613-638



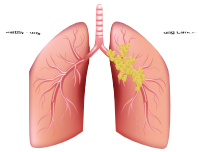
Danish Lung Cancer Group (DLCG)

KLINISKE RETNINGSLINJER | KRÆFT

Lungecancer – Patologi

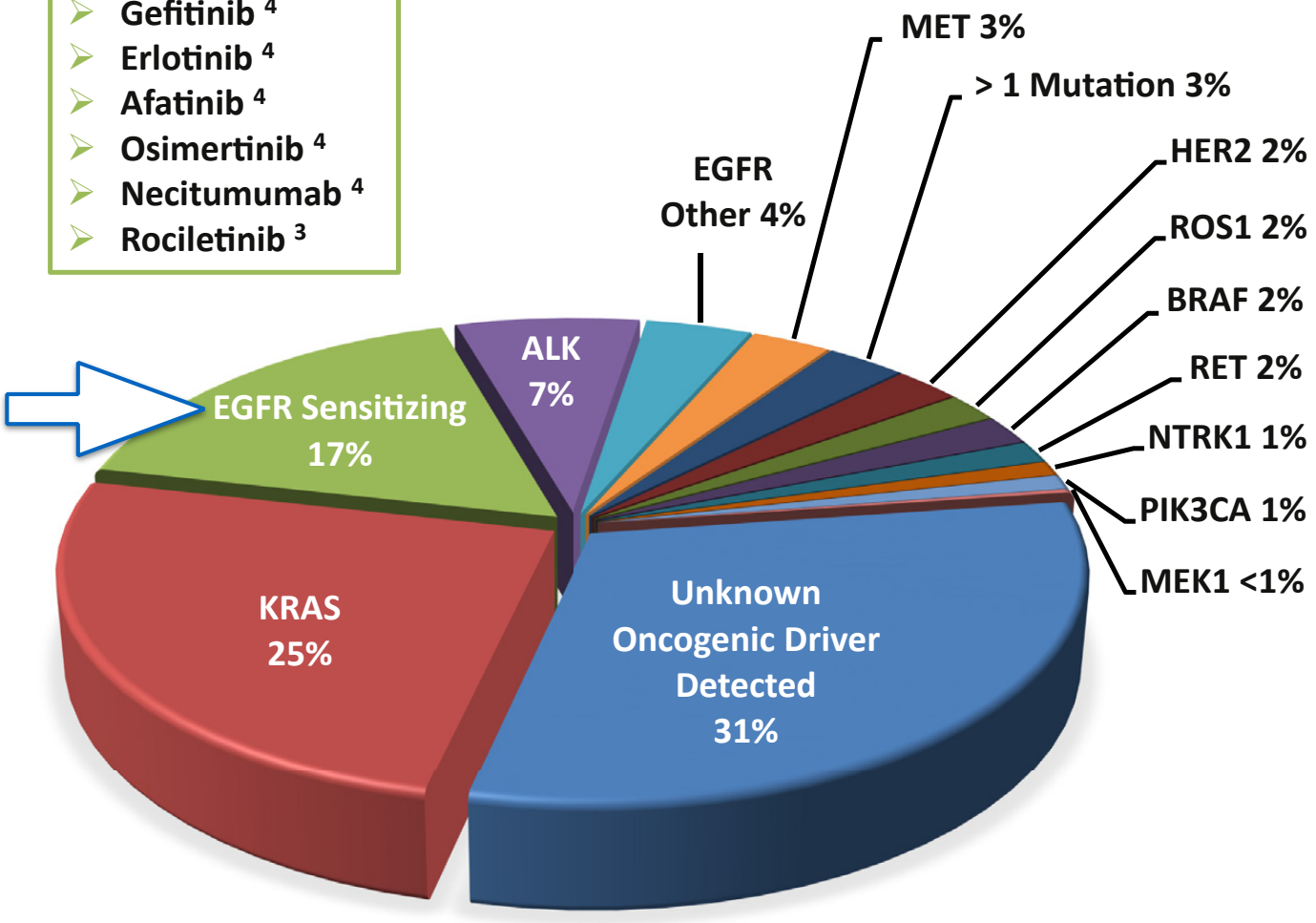
46. **Reflextest af de obligatoriske markører bør foretages ved den primære diagnostik af nedenstående grupper. (A)**
    - **EGFR, ALK, ROS1: adenokarcinomer + ikke-småcellede karcinomer, hvor typen ikke sikkert kan afgøres**
    - **PD-L1: alle ikke-småcellede karcinomer**

NordiQC

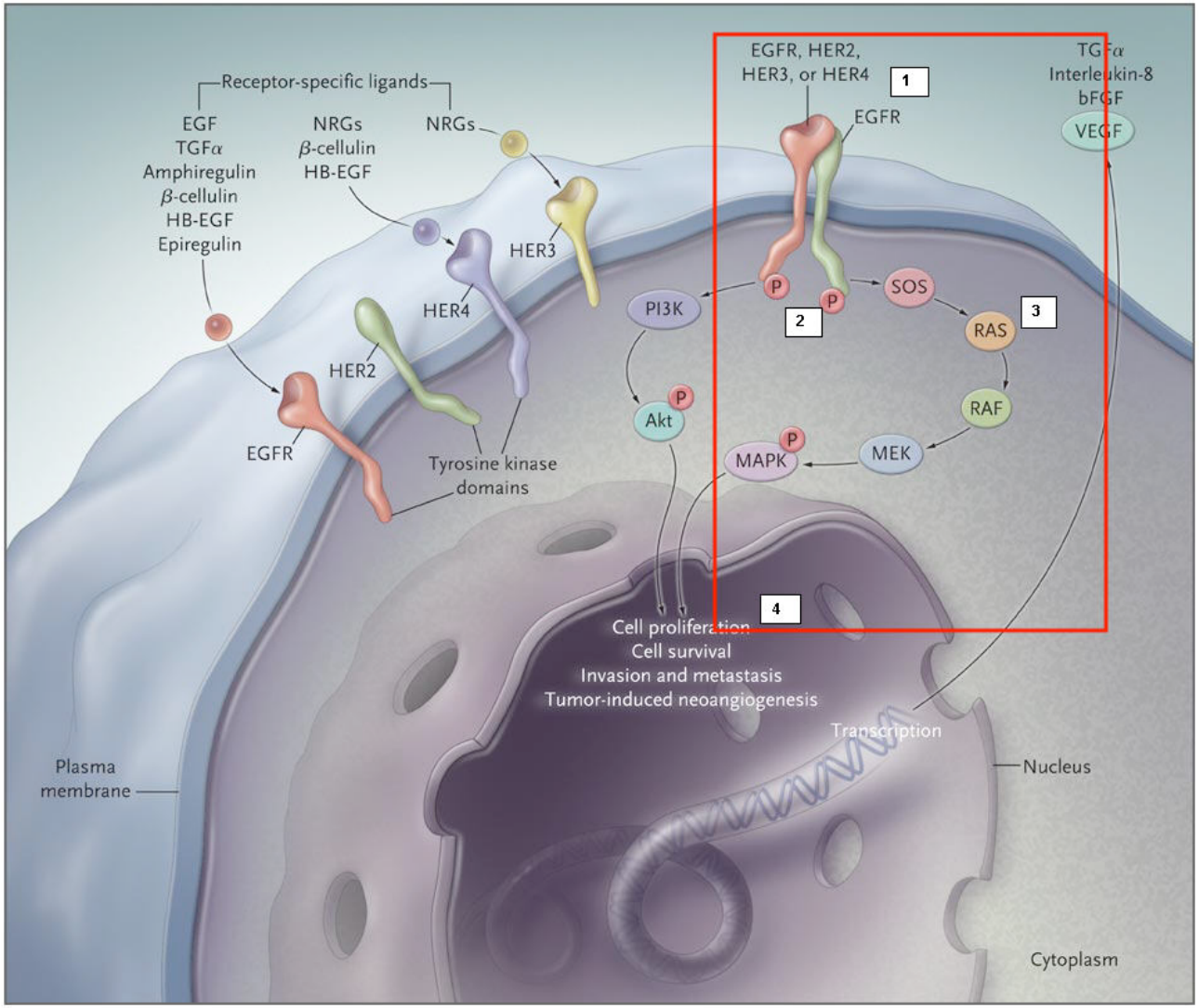


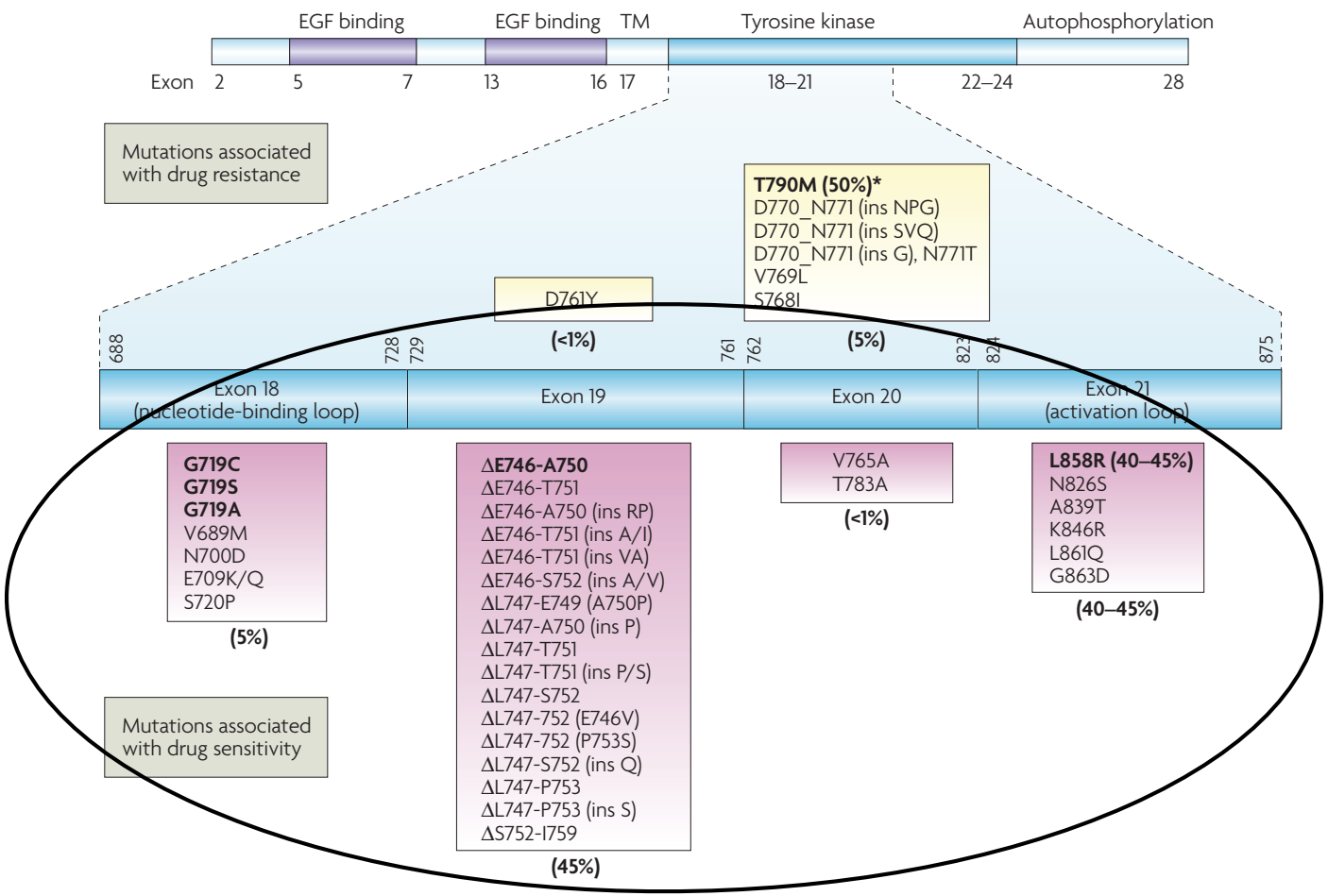
EGFR Sensitizing

- Gefitinib [4]
- Erlotinib [4]
- Afatinib [4]
- Osimertinib [4]
- Necitumumab [4]
- Rociletinib [3]



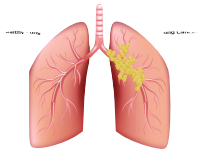
EGFR

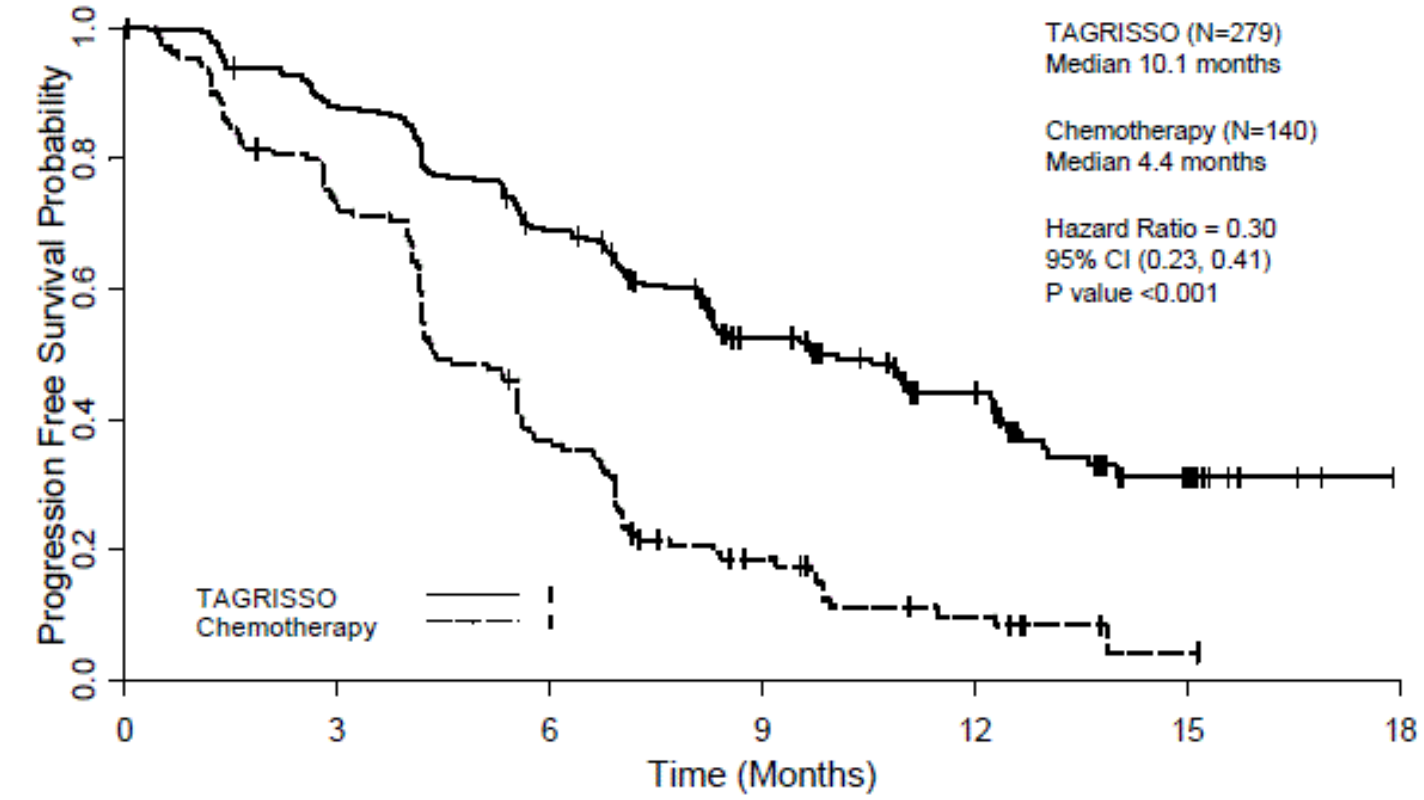

Receptor-specific ligands
EGF
TGFα
Amphiregulin
β-cellulin
HB-EGF
Epiregulin
NRGs
β-cellulin
HB-EGF
NRGs
HER3
HER4
HER2
EGFR
Tyrosine kinase domains
EGFR, HER2, HER3, or HER4
1
EGFR
TGFα
Interleukin-8
bFGF
VEGF
P
P
2
PI3K
SOS
3
RAS
RAF
MEK
P
MAPK
P
Akt
4
Cell proliferation
Cell survival
Invasion and metastasis
Tumor-induced neoangiogenesis
Transcription
Nucleus
Plasma membrane
Cytoplasm



autoactivates EGFR

NordiQC





Number at risk

TAGRISSO						
279	240	162	88	50	13	0
Chemotherapy						
140	93	44	17	7	1	0

Tick marks represent censored observations

Contents lists available at ScienceDirect

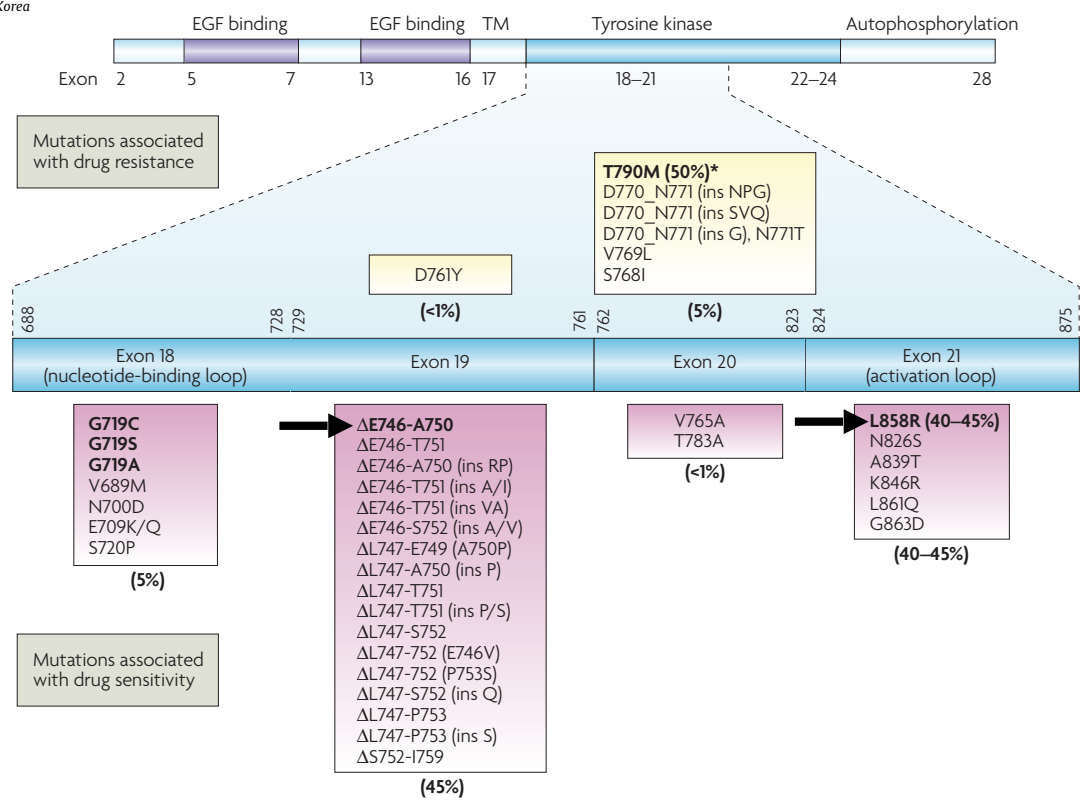
Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

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



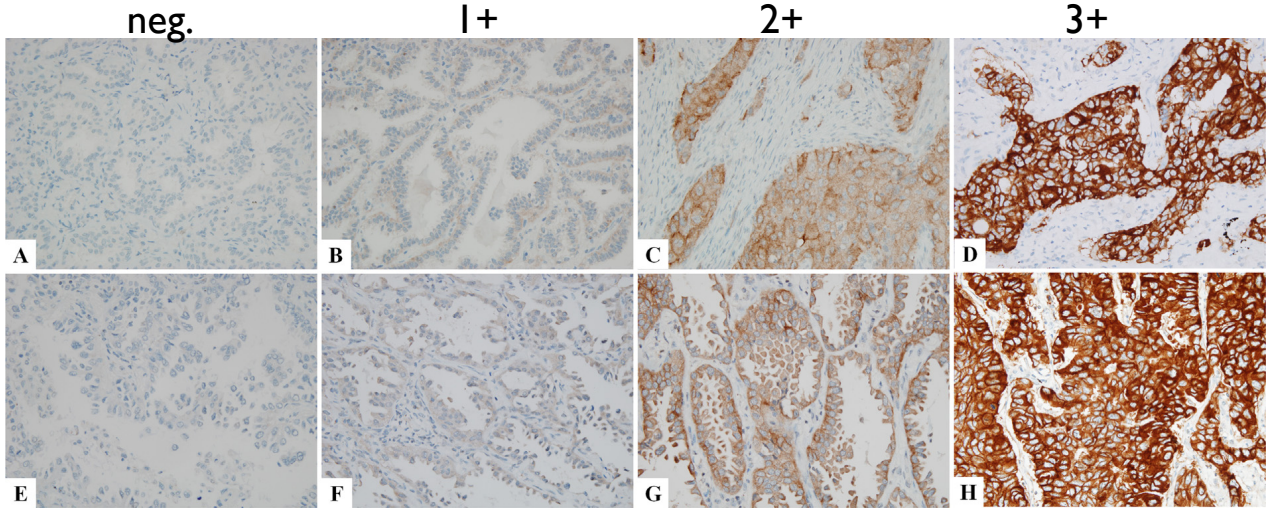


Table 2
Diagnostic power of mutation-specific antibodies comparing with *EGFR* mutational status.

Mutation-specific antibodies	*EGFR* 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%
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.

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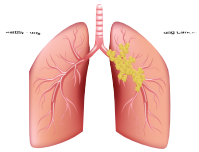
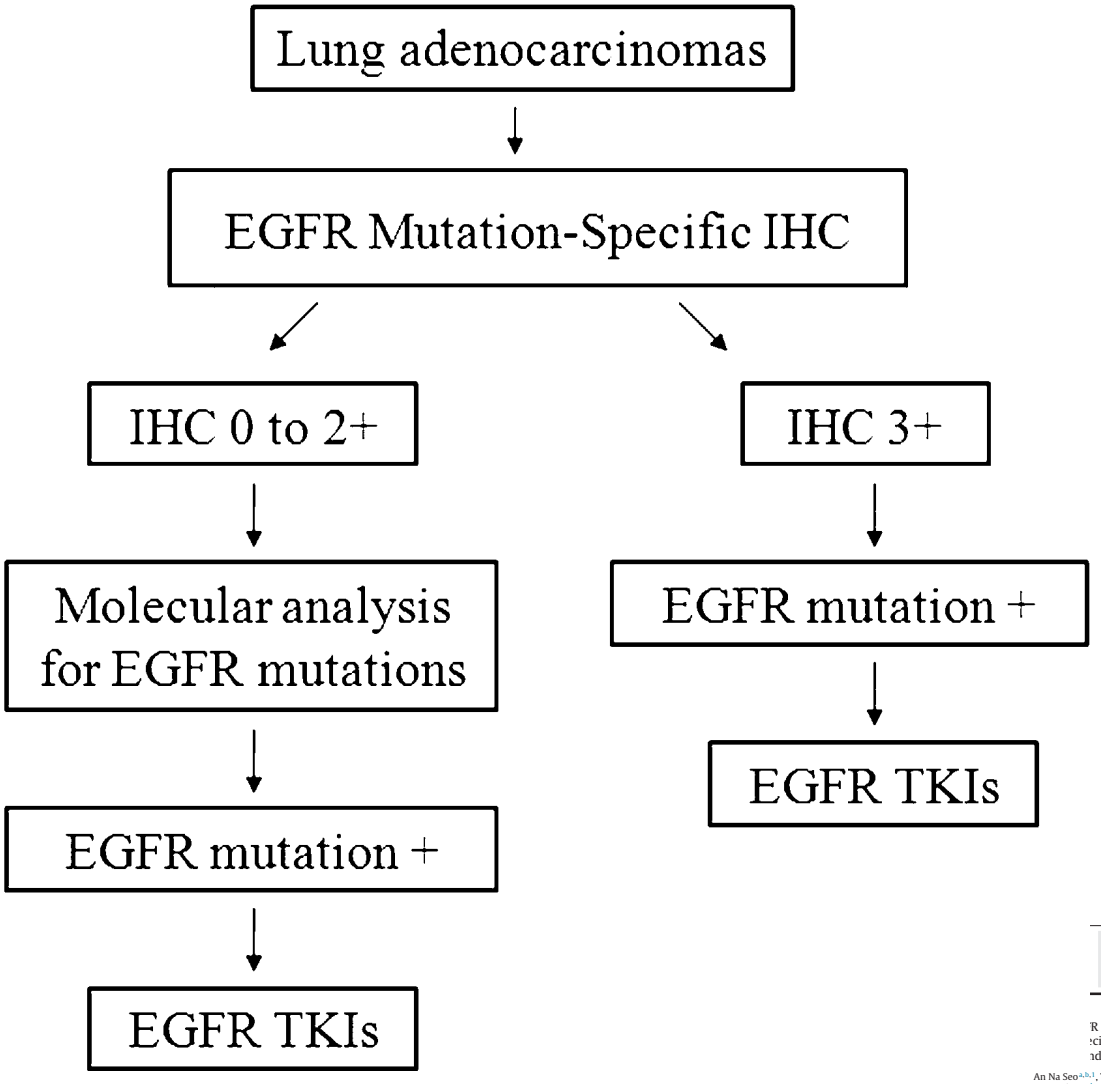
NordiQC



Algorithm



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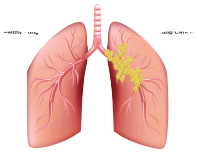
NordiQC



DNA(template)

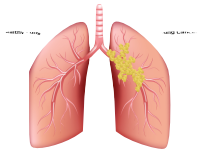
PCR

Analysis

DNA-purification

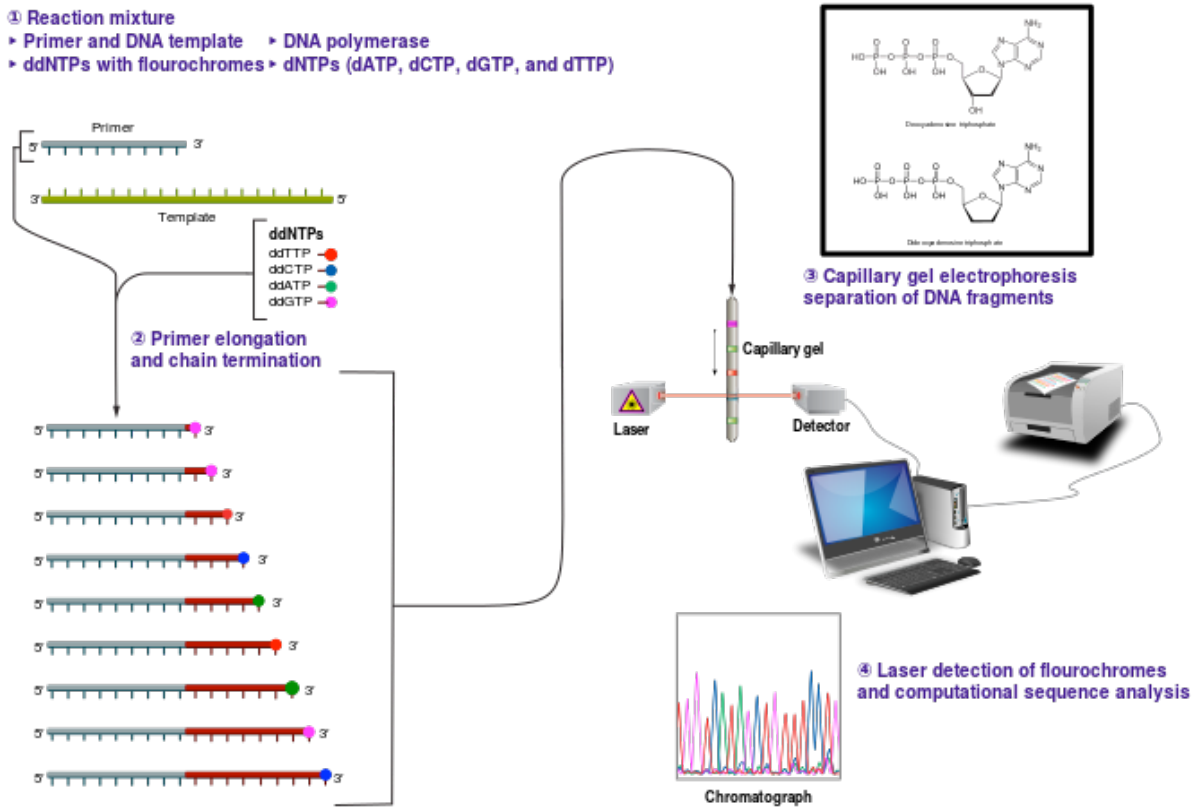
Tissue section

NordiQC

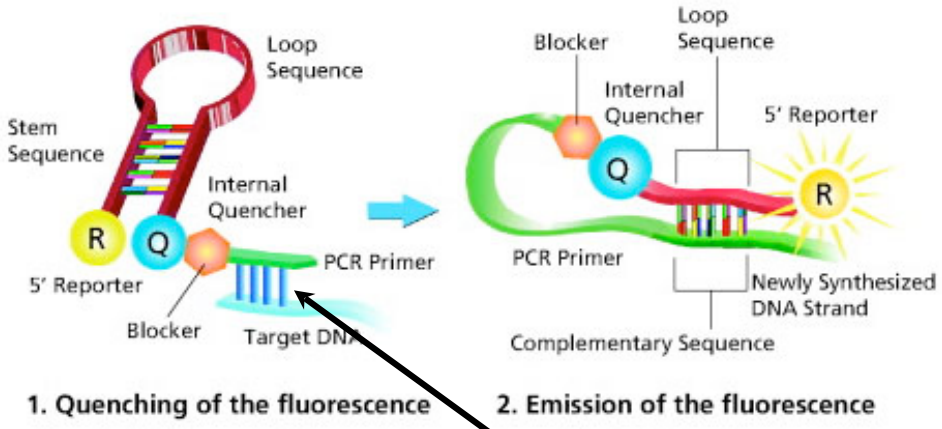


Sequencing

Analysis



PCR bassed test



mutationspecific primer

Scientific Advances in Lung Cancer 2015

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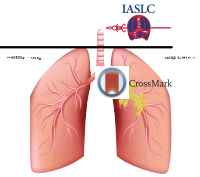

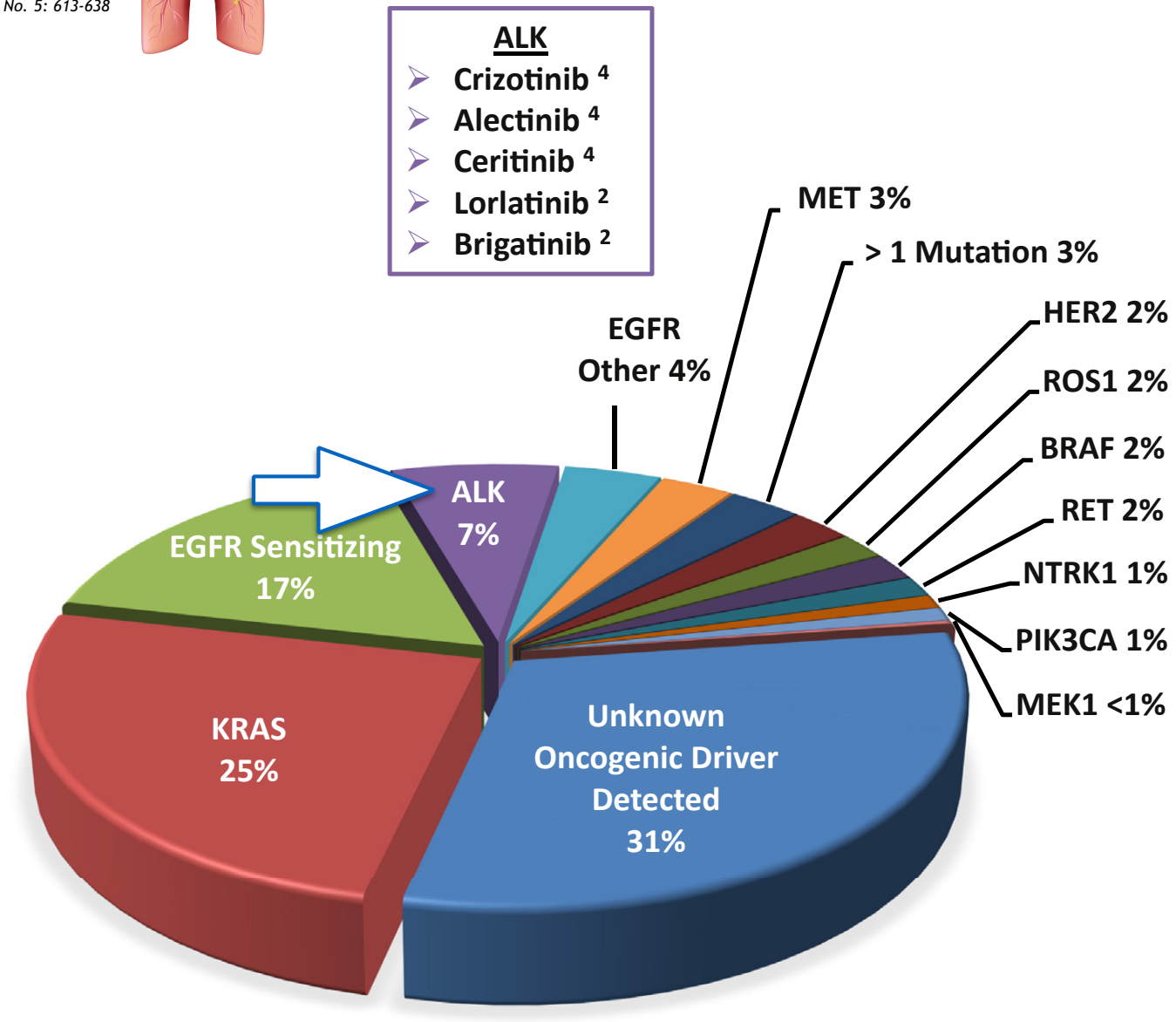

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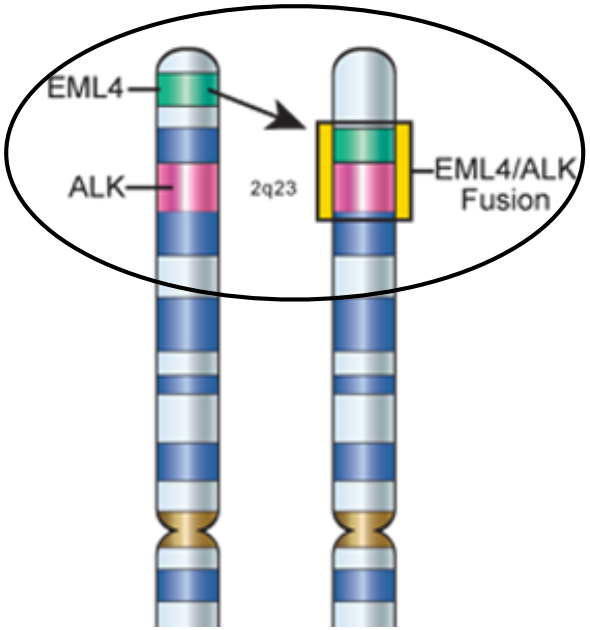
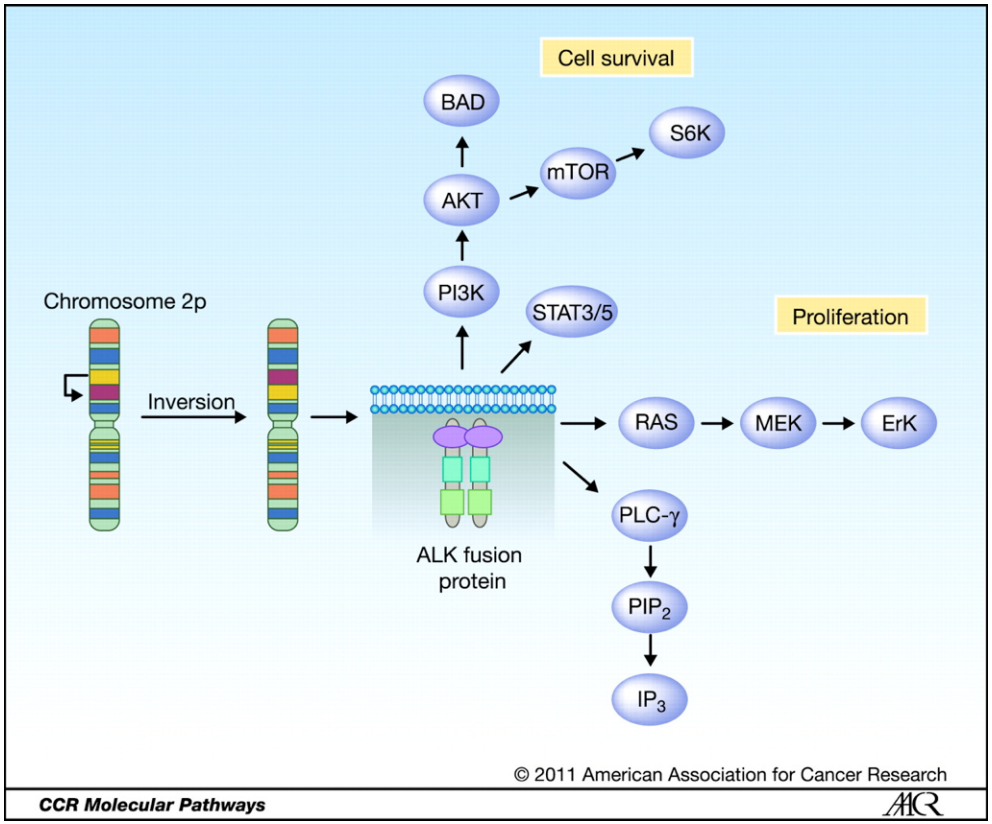
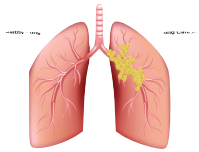
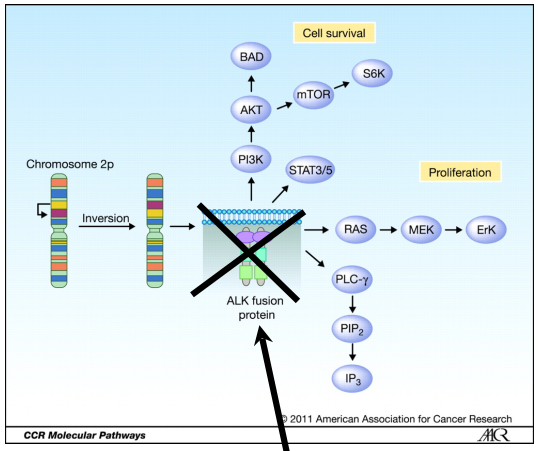
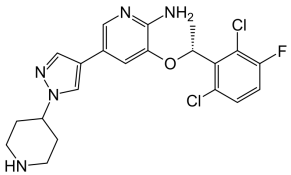

EML4
ALK
2q23
EML4/ALK
Fusion


Cell survival
BAD
S6K
mTOR
AKT
PI3K
STAT3/5
Proliferation
Chromosome 2p
Inversion
RAS
MEK
ErK
PLC-γ
PIP2
IP3
ALK fusion protein
© 2011 American Association for Cancer Research
CCR Molecular Pathways
AACR

NordiQC







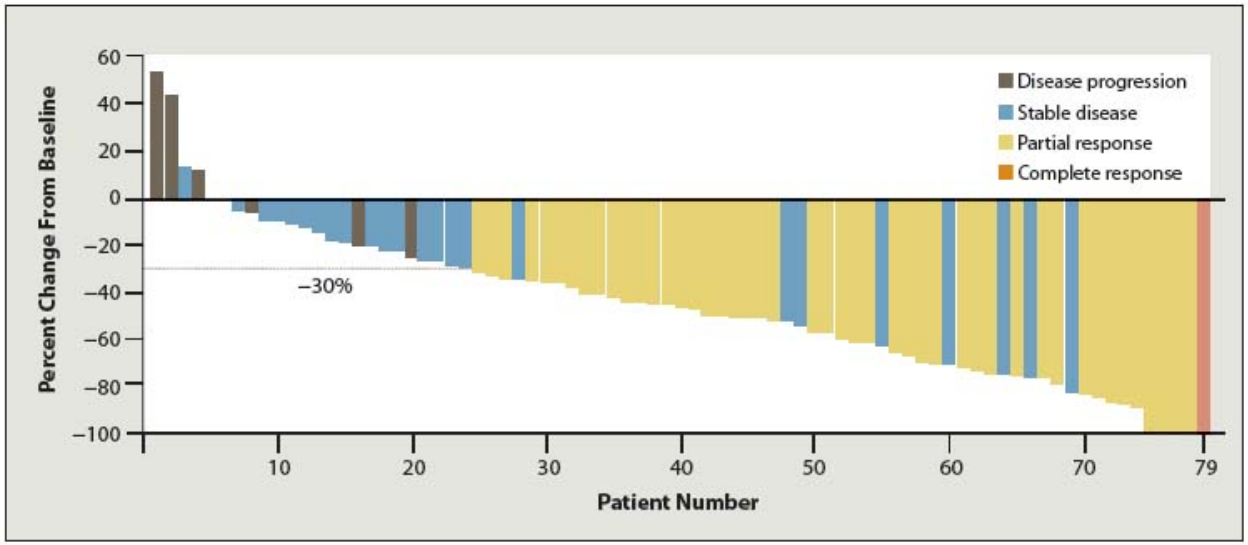
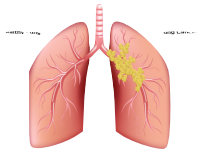
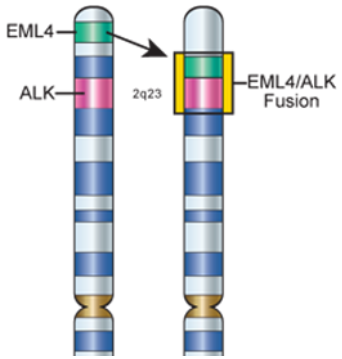


Figure 2: Waterfall plot showing response to crizotinib in patients with *EML4-ALK* NSCLC. Percent change in tumor burden relative to pretreatment baseline is represented. (Reproduced with permission from Kwak et al. N Engl J Med. 2010;363:1693-1703. Copyright © 2010, Massachusetts Medical Society.)

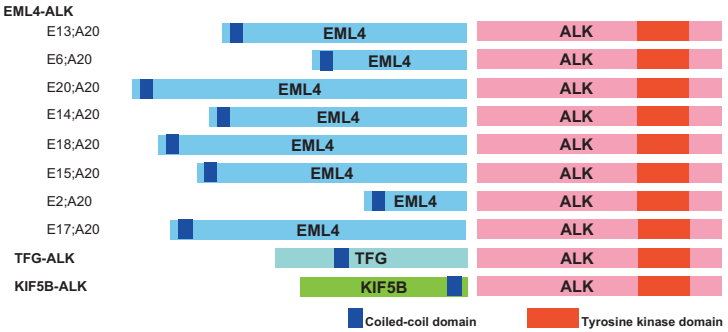
NordiQC



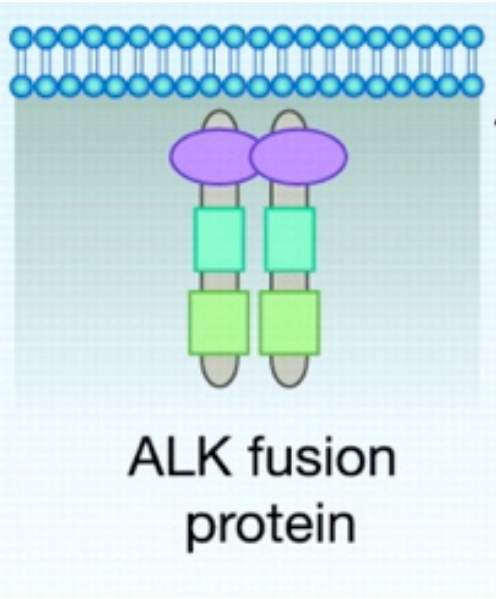
Detection of chromosomal changes



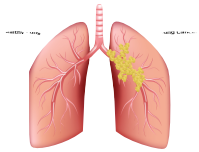
Detection of fusion RNA



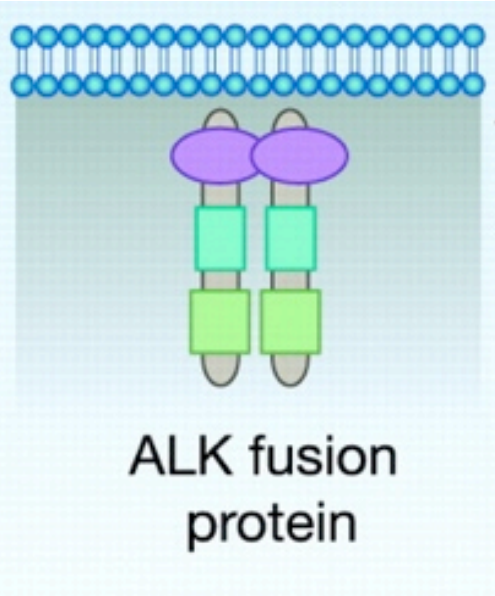
Detection of fusion protein



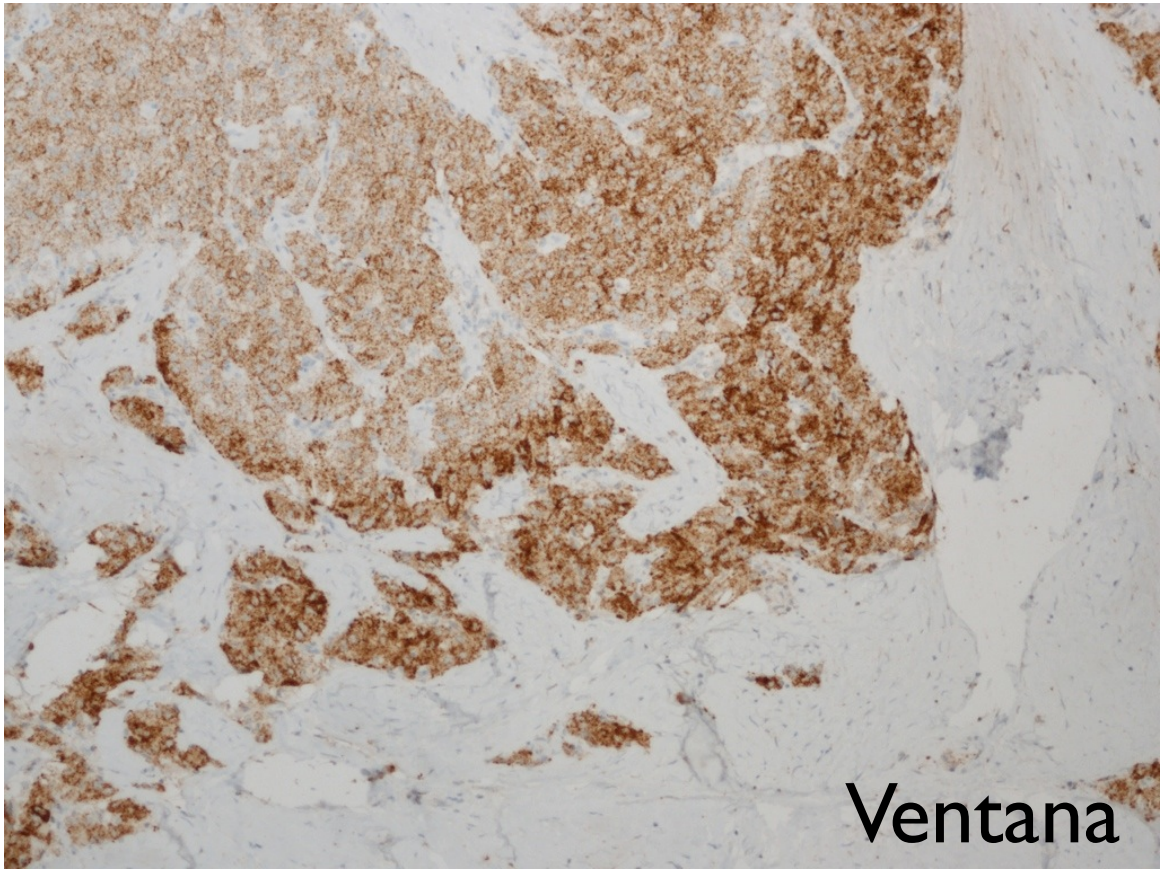
NordiQC



Detection of fusion protein

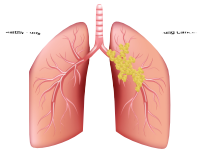


Immunohistochemistry

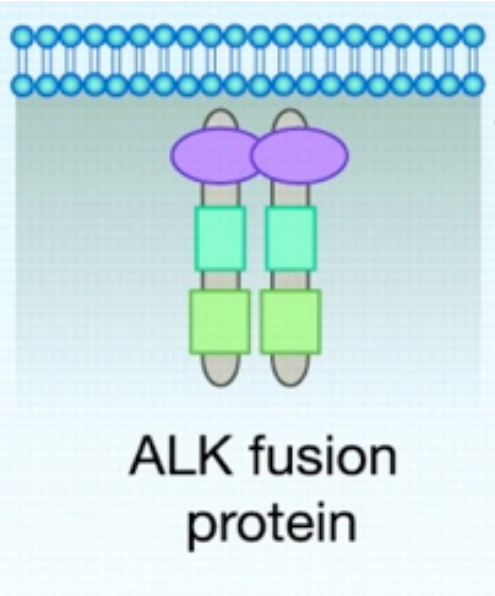


Detects ALK independent of fusion partner

NordiQC



Detection of fusion protein

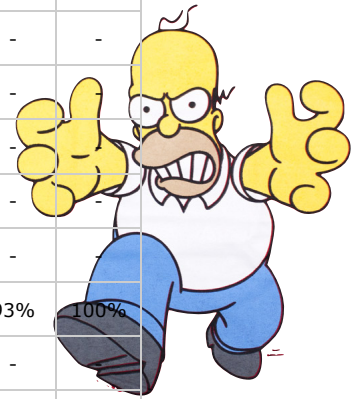


Immunohistochemistry

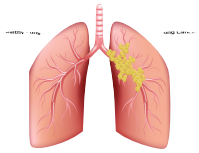
Table 1. **Antibodies and assessment marks for lu-ALK, run 51**

Concentrated antibodies	n	Vendor	Optimal	Good	Borderline	Poor	Suff.[1]	Suff. OPS[2]
mAb clone **5A4**	43 1 1 1 1	Leica/Novocastra Abcam Biocare Monosan ThermoFisher	1	15	24	7	34%	22%
mAb clone **ALK1**	2 1	Dako Cell Marque	0	0	0	3	-	-
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 790-4796**[3]	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)

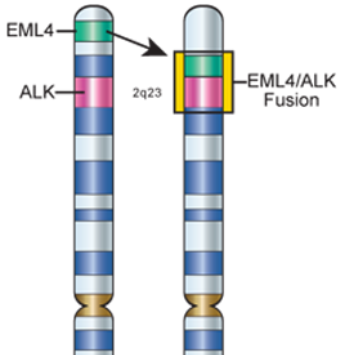


NordiQC

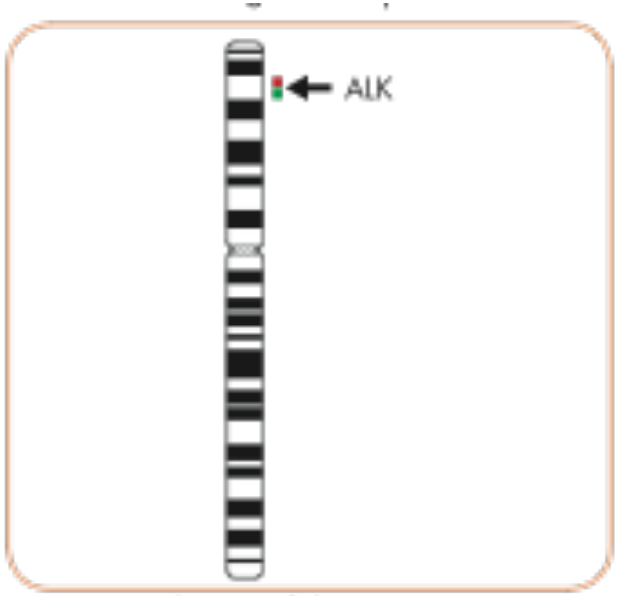


Detection of chromosomal changes

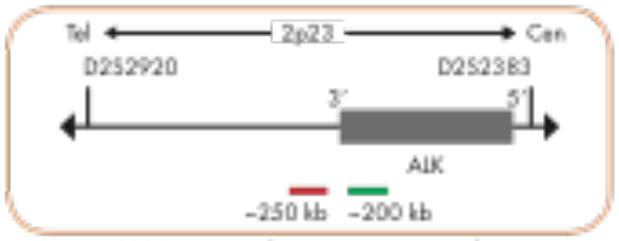
F(C)ISH



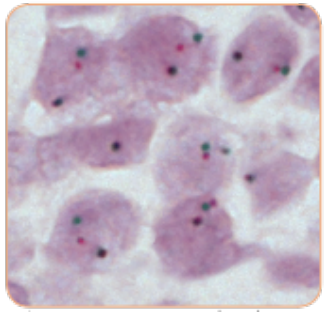
ZYTOVISION
Molecular diagnostics simplified

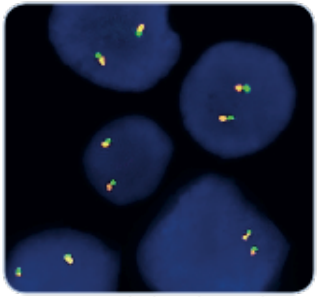


Ideogram of chromosome 2 indicating the hybridization locations.

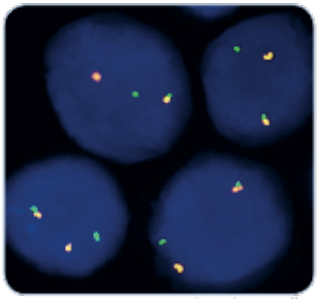


SPEC ALK Probe map (not to scale).

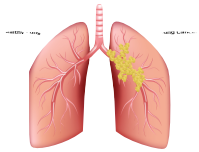




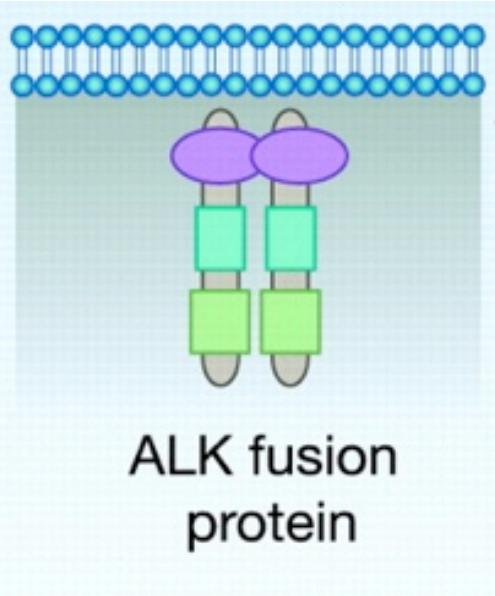
SPEC ALK Dual Color Break Apart Probe hybridized to normal interphase cells as indicated by two orange/green fusion signals per nucleus.



NordiQC



Detection of fusion protein



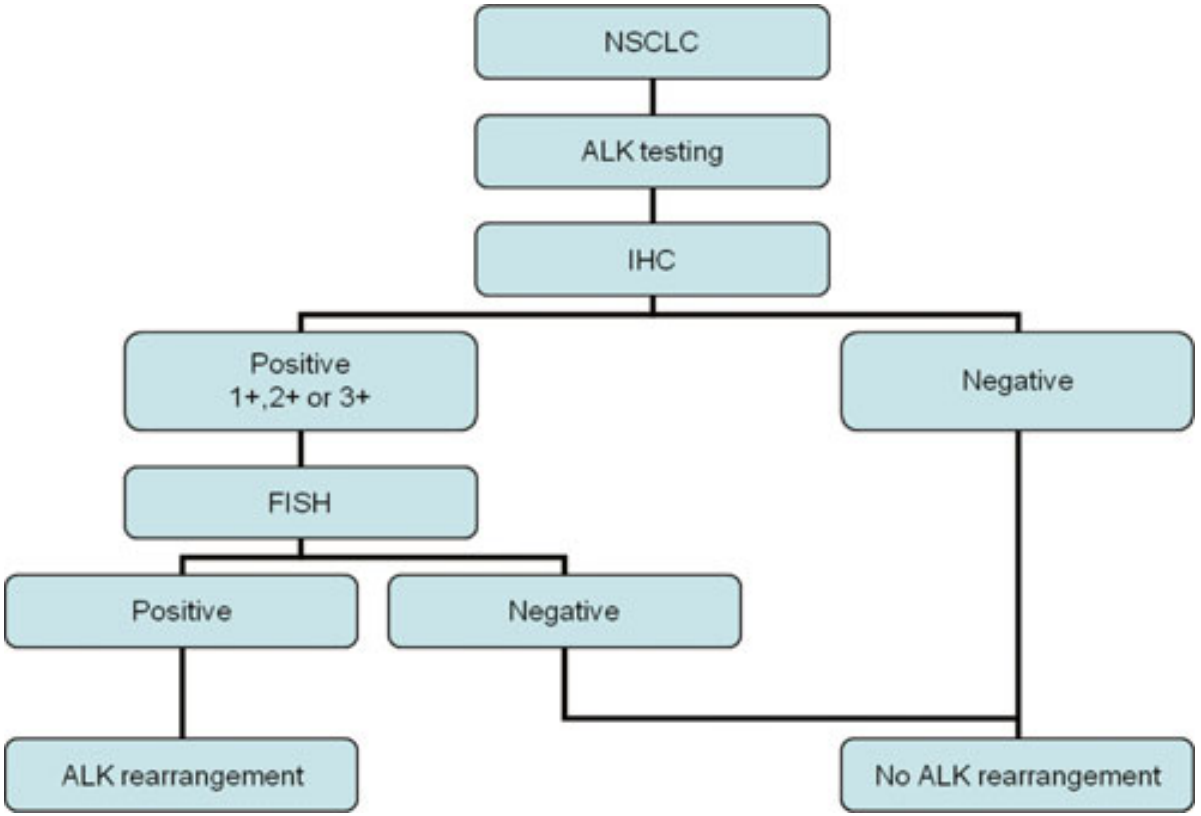
Virchows Arch (2012) 461:245–257
DOI 10.1007/s00428-012-1281-4

REVIEW AND PERSPECTIVES

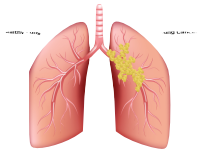
EML4-ALK testing in non-small cell carcinomas of the lung: a review with recommendations

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

Algorithm



NordiQC



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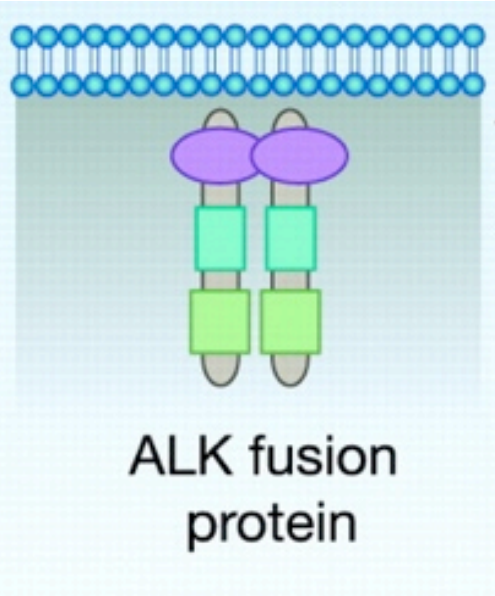
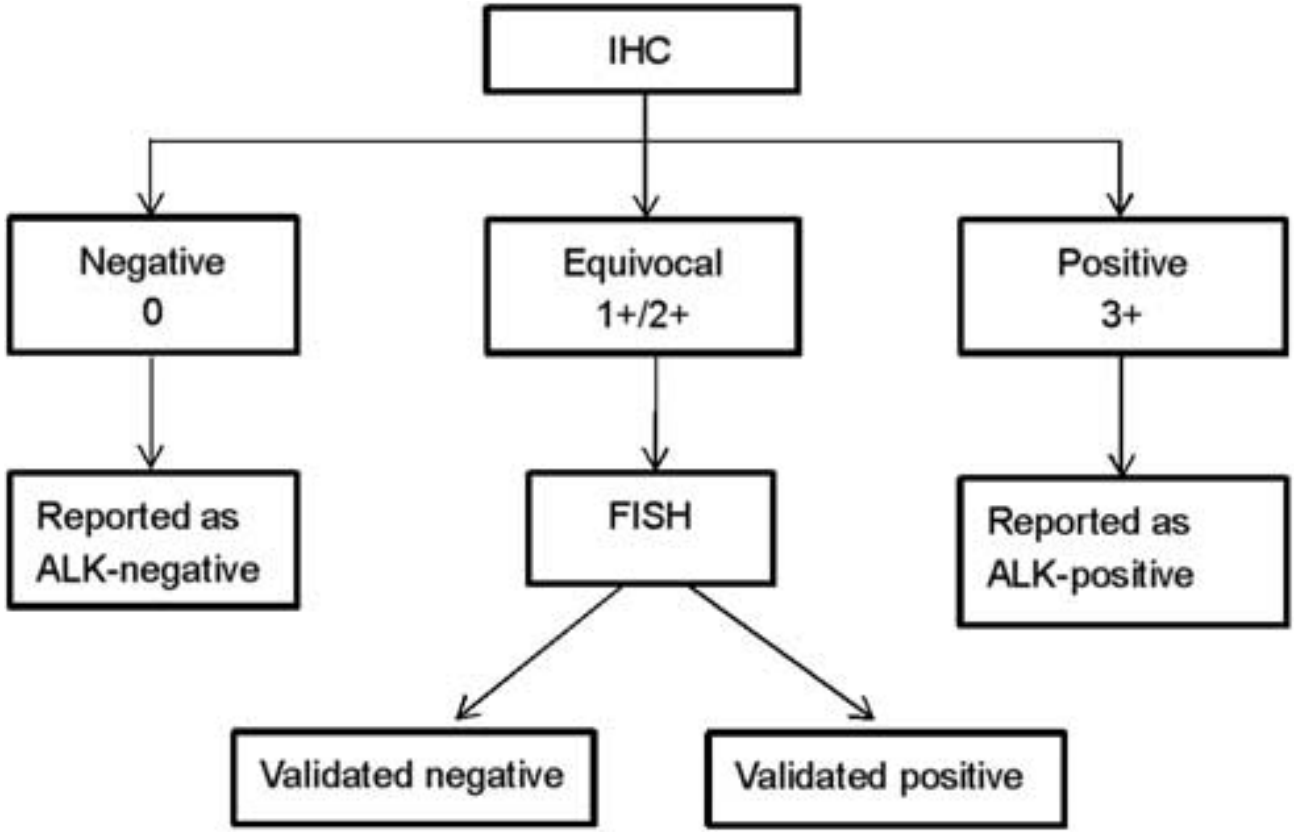


Algorithm



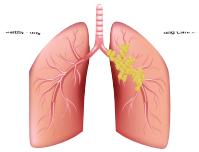
Improving Selection Criteria for *ALK* Inhibitor Therapy in Non–Small Cell Lung Cancer

A Pooled-Data Analysis on Diagnostic Operating Characteristics of Immunohistochemistry

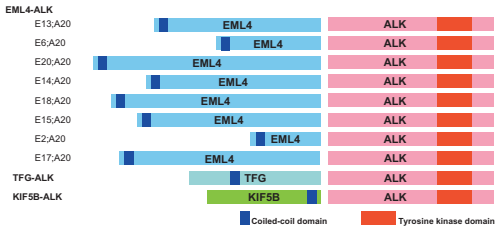
Long Jiang, MD, PhD,† Haihong Yang, MD, PhD,‡ Ping He, MD, PhD,§ Wenhua Liang, MD, PhD,‡ Jianrong Zhang, MD,*† Jingpei Li, MD,*† Yang Liu, MD,*† and Jianxing He, MD, PhD, FACS*†*

(*Am J Surg Pathol* 2016;40:697–703)

NordiQC

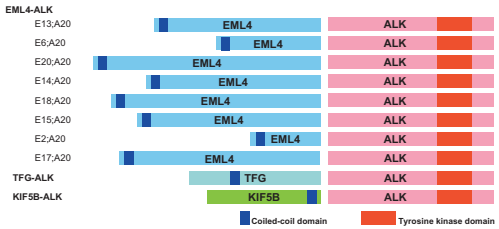


Detection of fusion RNA

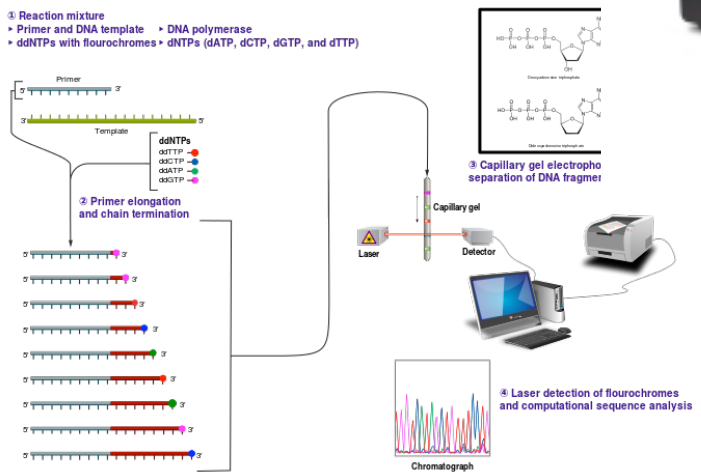


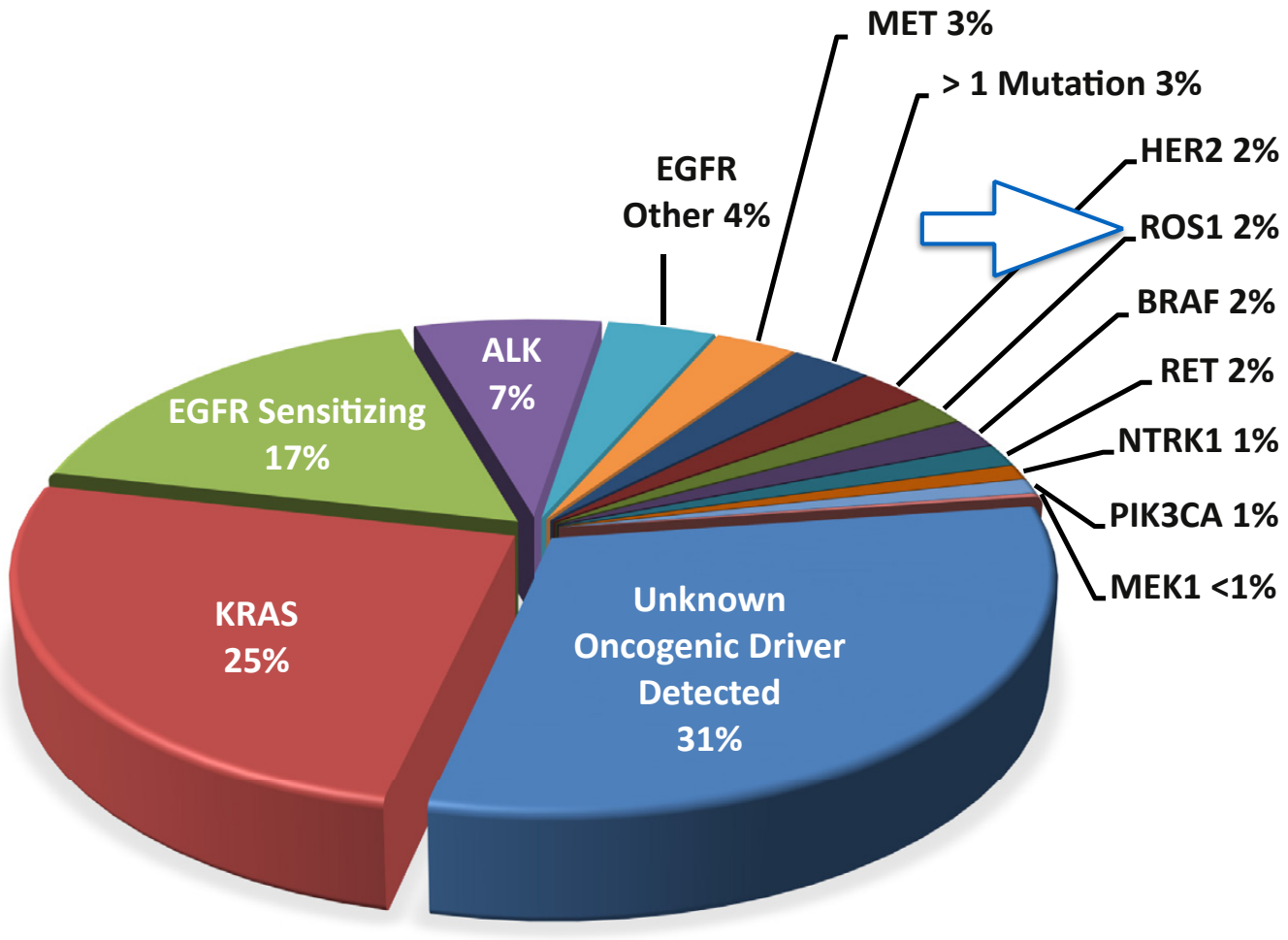
RT PCR based test

Detection of fusion RNA



RNA Sequencing based test

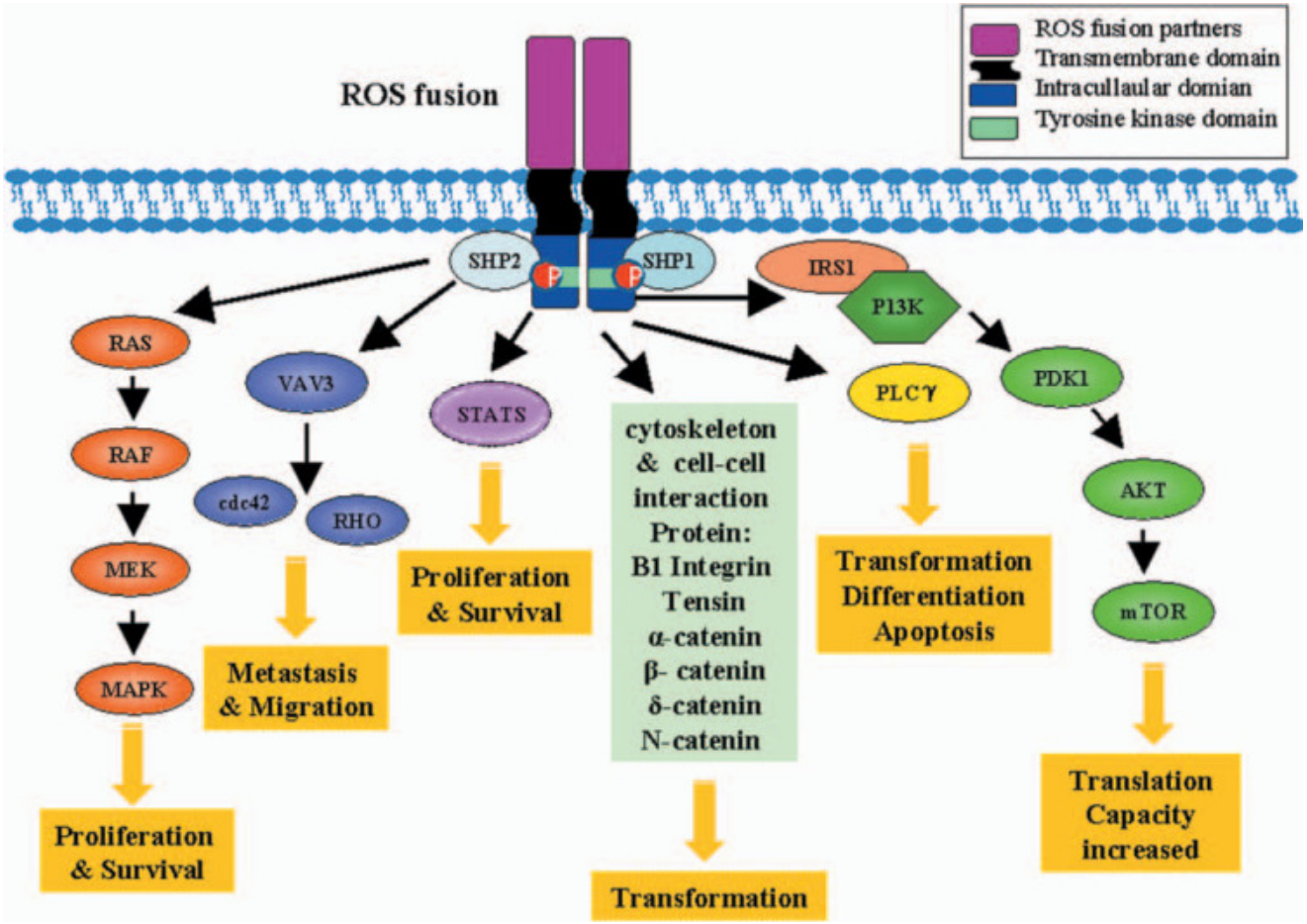




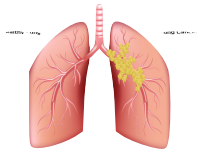
ROS1

- Crizotinib [4]
- Cabozantinib [2]
- Ceritinib [2]
- Lorlatinib [2]
- DS-6051b [1]

NordiQC

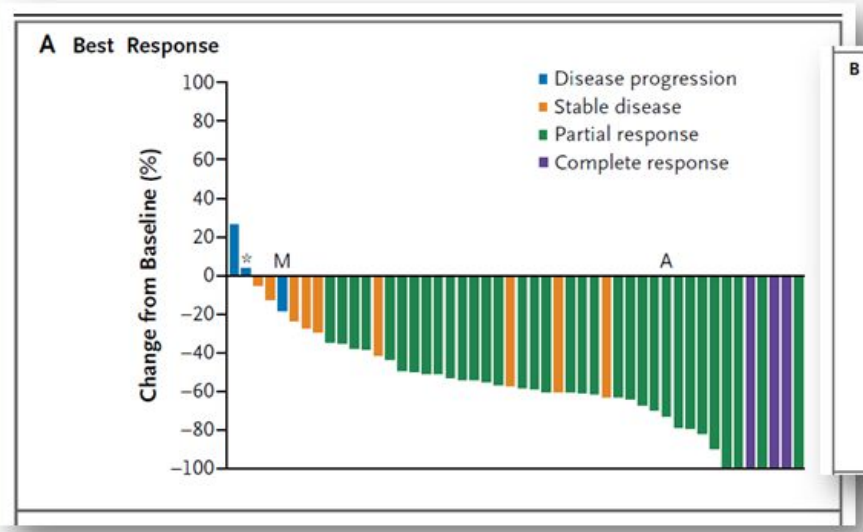

ROS fusion
ROS fusion partners
Transmembrane domain
Intracullaular domian
Tyrosine kinase domain
SHP2
SHP1
IRS1
P13K
RAS
RAF
MEK
MAPK
VAV3
cdc42
RHO
STATS
PLCγ
PDK1
AKT
mTOR
cytoskeleton & cell-cell interaction Protein:
B1 Integrin
Tensin
α-catenin
β- catenin
δ-catenin
N-catenin
Proliferation & Survival
Metastasis & Migration
Proliferation & Survival
Transformation
Differentiation
Apoptosis
Translation Capacity increased
Transformation

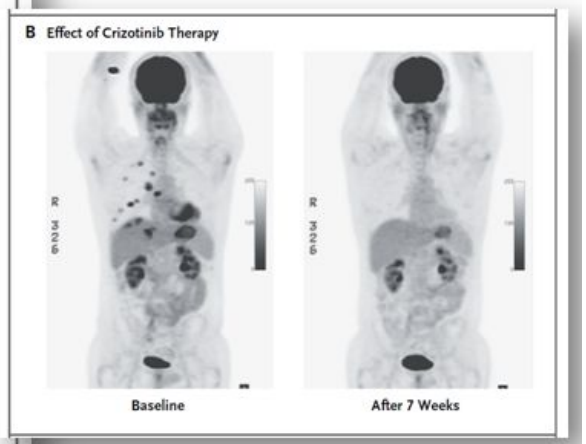
NordiQC



UNIVERSITY OF TORINO – DEPARTMENT OF ONCOLOGY

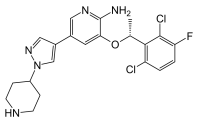
Tumor responses to crizotinib in ROS1-rearranged NSCLC



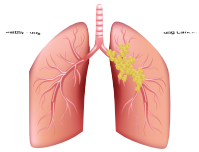


Overall response rate 72% (6% CR, 66% PR).
Median time to response 7.9 weeks (range, 4.3 - 32.0)

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



NordiQC



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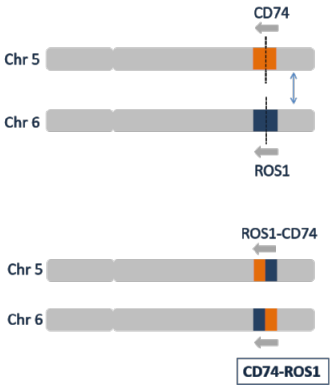
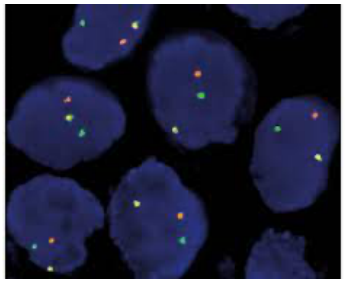
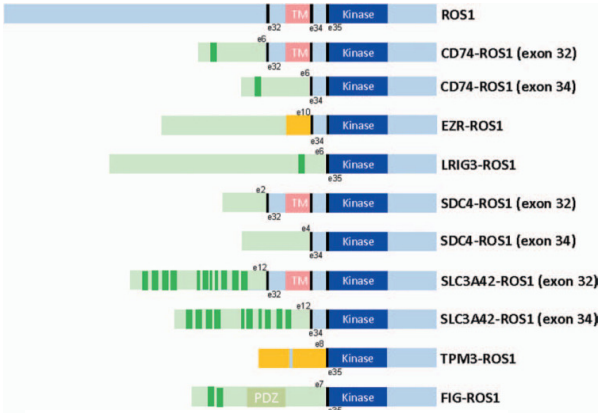
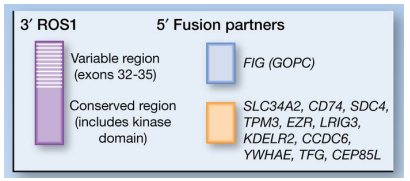


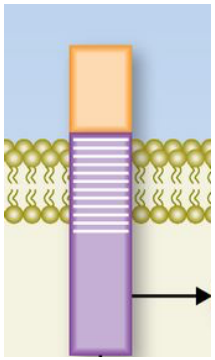


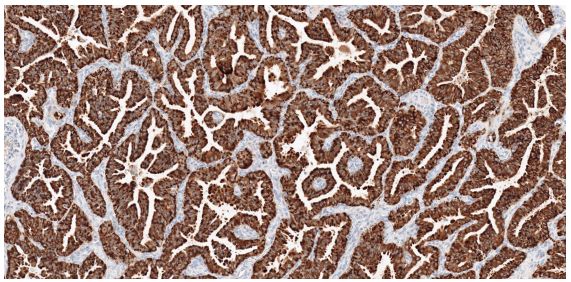
Detection of fusion RNA



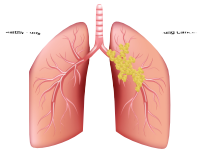
Detection of fusion protein







NordiQC



Next generation seq.

Possible, probable or definite adenocarcinoma

Reflex decision by pathologist

Molecular testing

Bespoke decision by MDT

Patient is never or long-time ex-smoker (MDT discussion or pre-emptive request)

Other lung carcinoma e.g. squamous, small cell

FFPE

Quality
Tumor cell %

DNA workflow

DNA purification → Library prep. → Sequencing → Variant calling (Bioinformatics)

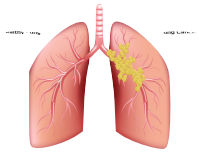
EGFR

RNA workflow

RNA purification → Library prep. → Sequencing → Variant calling (Bioinformatics)

ALK, ROS1

NordiQC

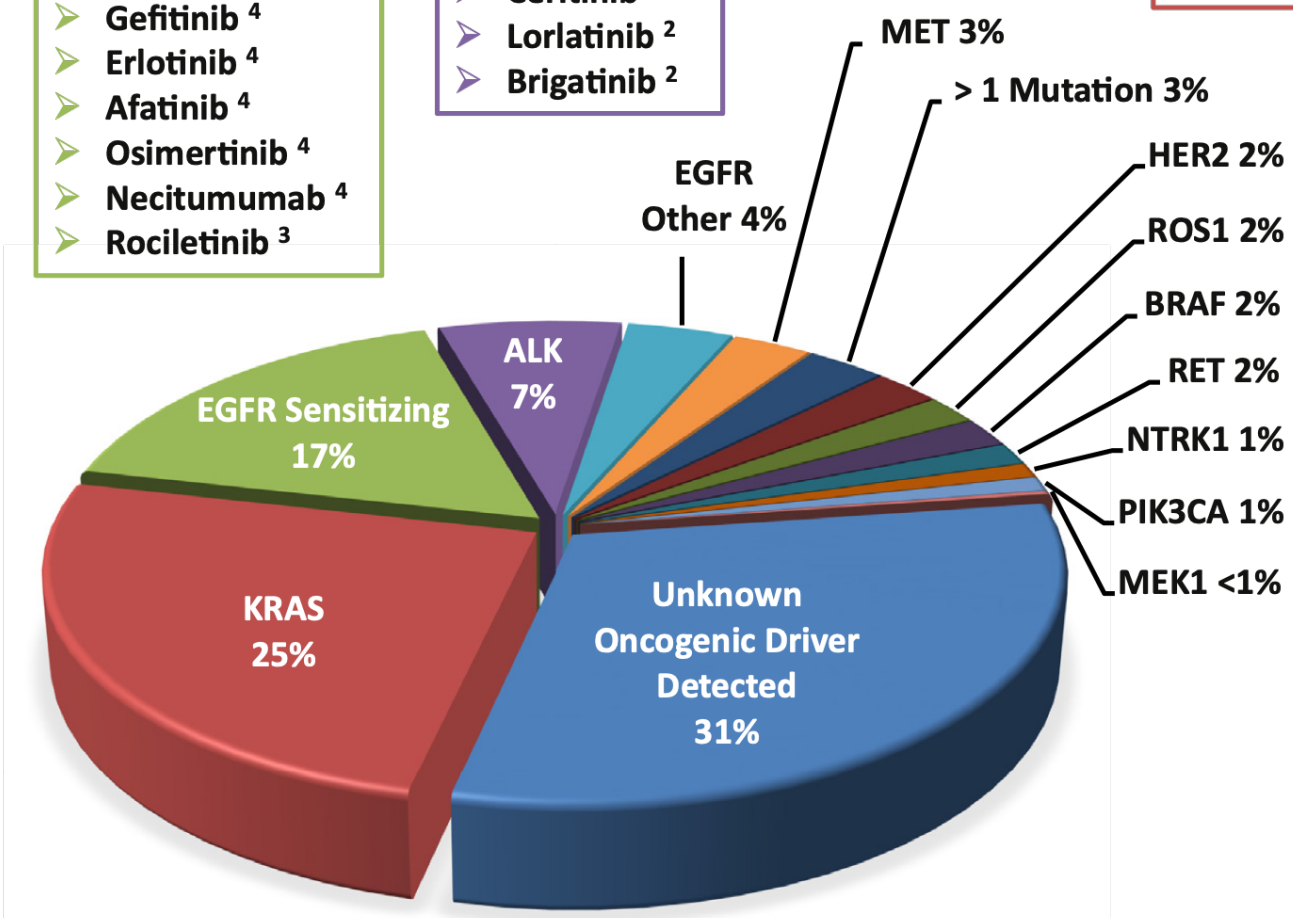


ALK
- Crizotinib [4]
- Alectinib [4]
- Ceritinib [4]
- Lorlatinib [2]
- Brigatinib [2]

MET
- Crizotinib [2]
- Cabozantinib [2]

HER2
- Trastuzumab emtansine [2]
- Afatinib [2]
- Dacomitinib [2]

EGFR Sensitizing
- Gefitinib [4]
- Erlotinib [4]
- Afatinib [4]
- Osimertinib [4]
- Necitumumab [4]
- Rociletinib [3]



ROS1
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- Cabozantinib [2]
- Ceritinib [2]
- Lorlatinib [2]
- DS-6051b [1]

BRAF
- Vemurafenib [2]
- Dabrafenib [2]

RET
- Cabozantinib [2]
- Alectinib [2]
- Apatinib [2]
- Vandetanib [2]
- Ponatinib [2]
- Lenvatinib [2]

NTRK1
- Entrectinib [2]
- LOXO-101 [2]
- Cabozantinib [2]
- DS-6051b [1]

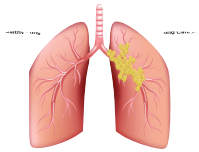
Key

1 - Phase I
2 - Phase II
3 -Phase III
4 - Approved

MEK1
- Trametinib [2]
- Selumetinib [3]
- Cobimetinib [1]

PIK3CA
- LY3023414 [2]
- PQR 309 [1]

NordiQC



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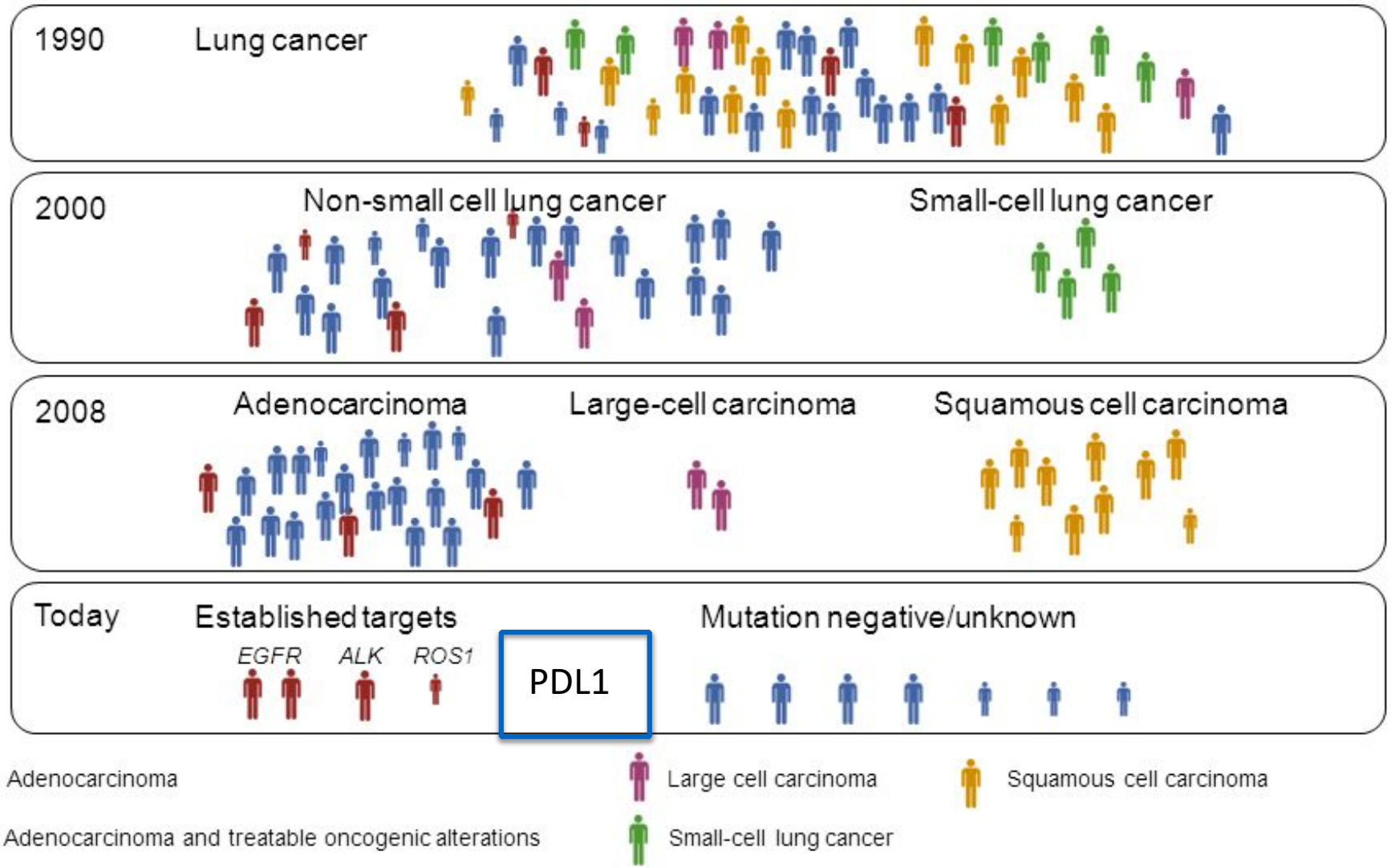
RNA purification | Sequencing | Library prep. | Variant calling (Bioinformatics)

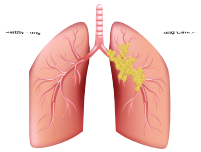
Comprehensive Result

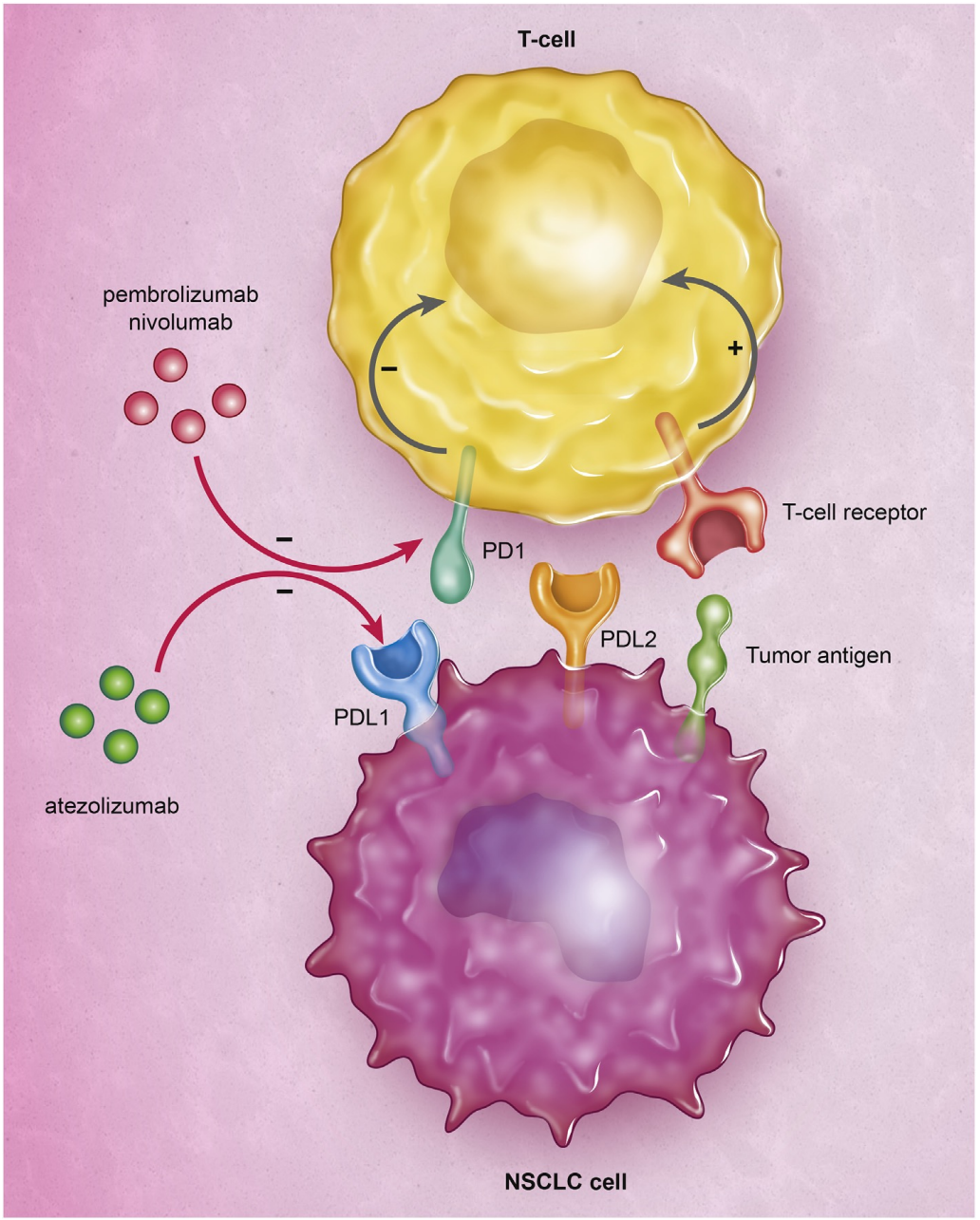
Patient selection in lung cancer: Evolution over time



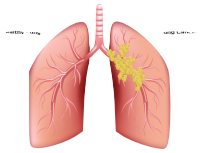
Adapted from Reck M, et al. Lancet 2013;382:709–19

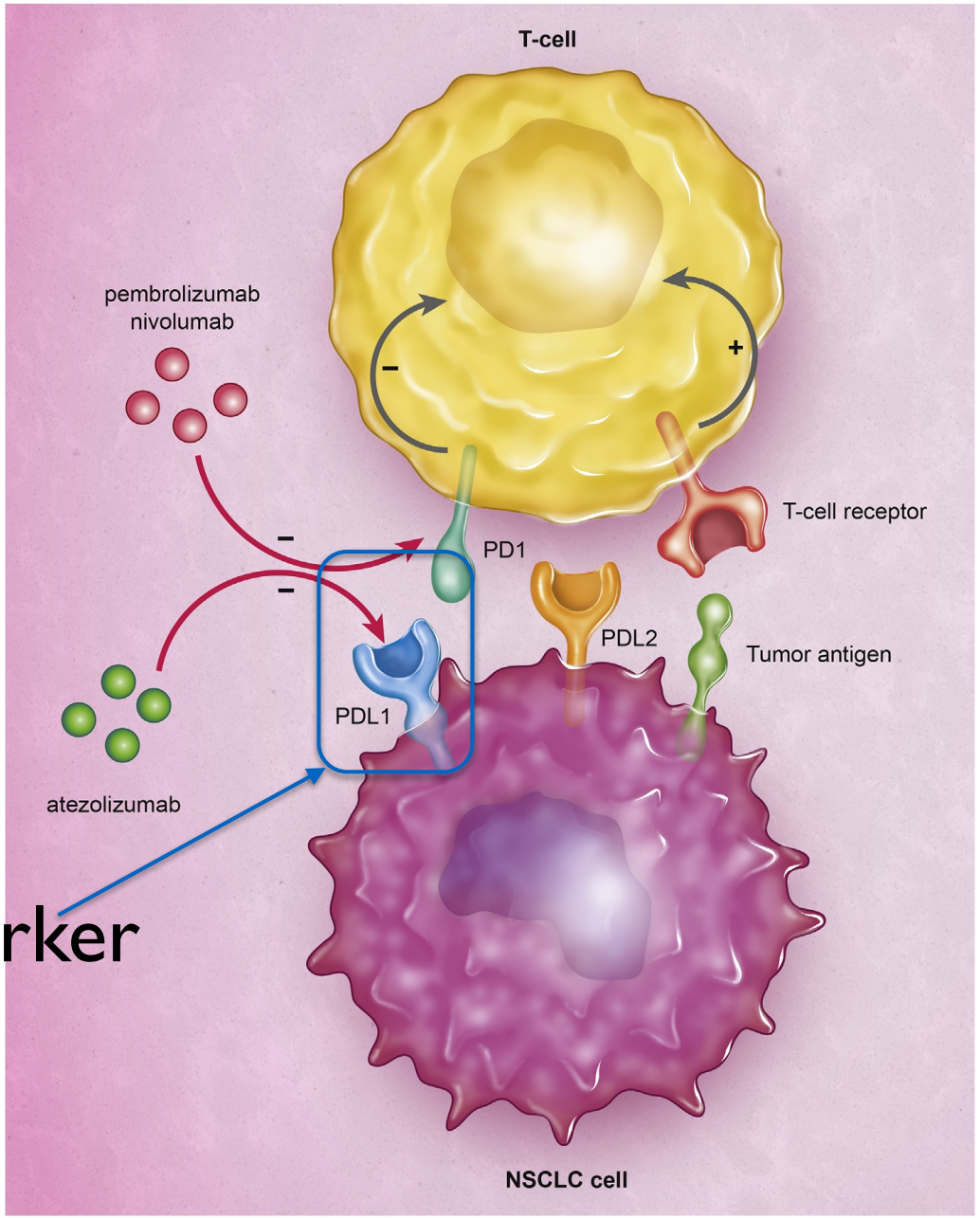
NordiQC




T-cell
pembrolizumab
nivolumab
−
+
T-cell receptor
PD1
−
PDL2
Tumor antigen
PDL1
atezolizumab
NSCLC cell

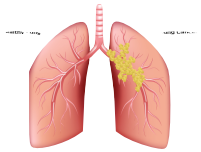
NordiQC

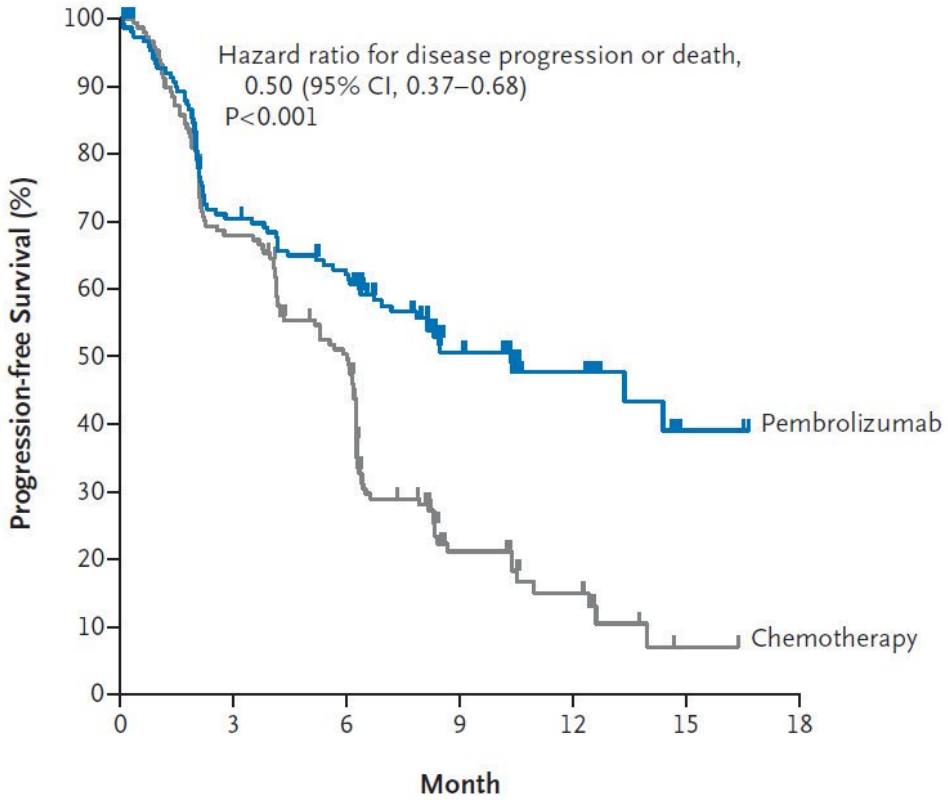




Predictive marker

NordiQC





No. at Risk

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

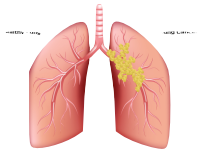
The NEW ENGLAND JOURNAL of MEDICINE

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

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

Martin Reck, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D., Andrew G. Robinson, M.D., Rina Hui, M.B., B.S., Ph.D., Tibor Csőszi, 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*

NordiQC



Step 1

Positive Histology

Positive Cytology

NE morphology, large cells
NE IHC, ttf1+/-, CK+

LCNEC

NE morphology, small cells
no/small nucleoli
NE IHC, ttf1+/-, CK+

SCLC

Keratinization, pearls and/or intercellular bridges

SQCC

Histology: lepidic, papillary and/or acinar architecture.
Cytology: 3-D arrangement, foamy, vacuolar cytoplasm prominent eccentrical nucleoli

ADC

No clear SQCC or ACCmorphology

NSCLC (NOS)

Step 2

Apply ancillary panel of SQCC or ADC marker

ADC marker +
SQCC marker -

ADC marker -
SQCC marker -

ADC marker +
SQCC marker +

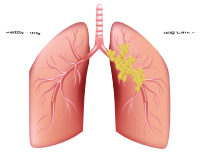
NSCLC, NOS

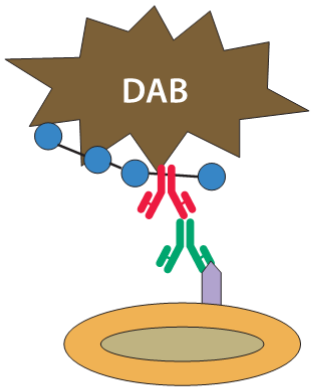
NSCLC, NOS
possible adenosquamous ca.

Step 3

PD-L1 testing

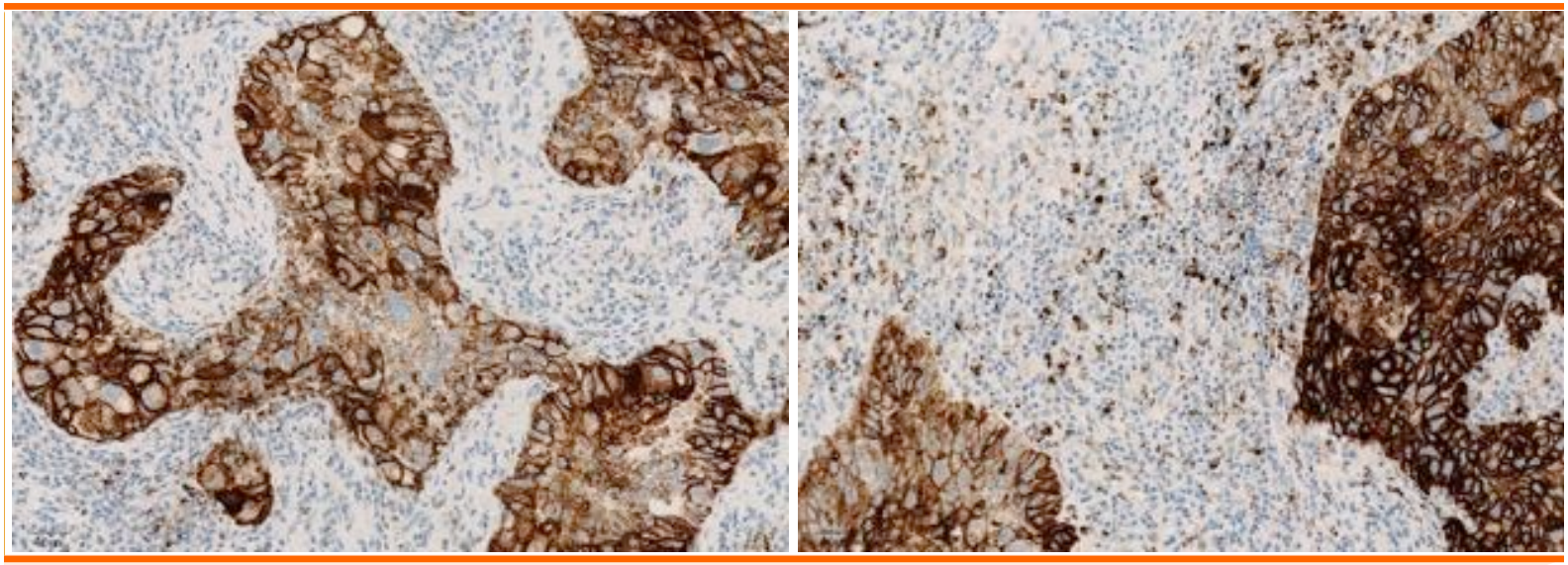
NordiQC



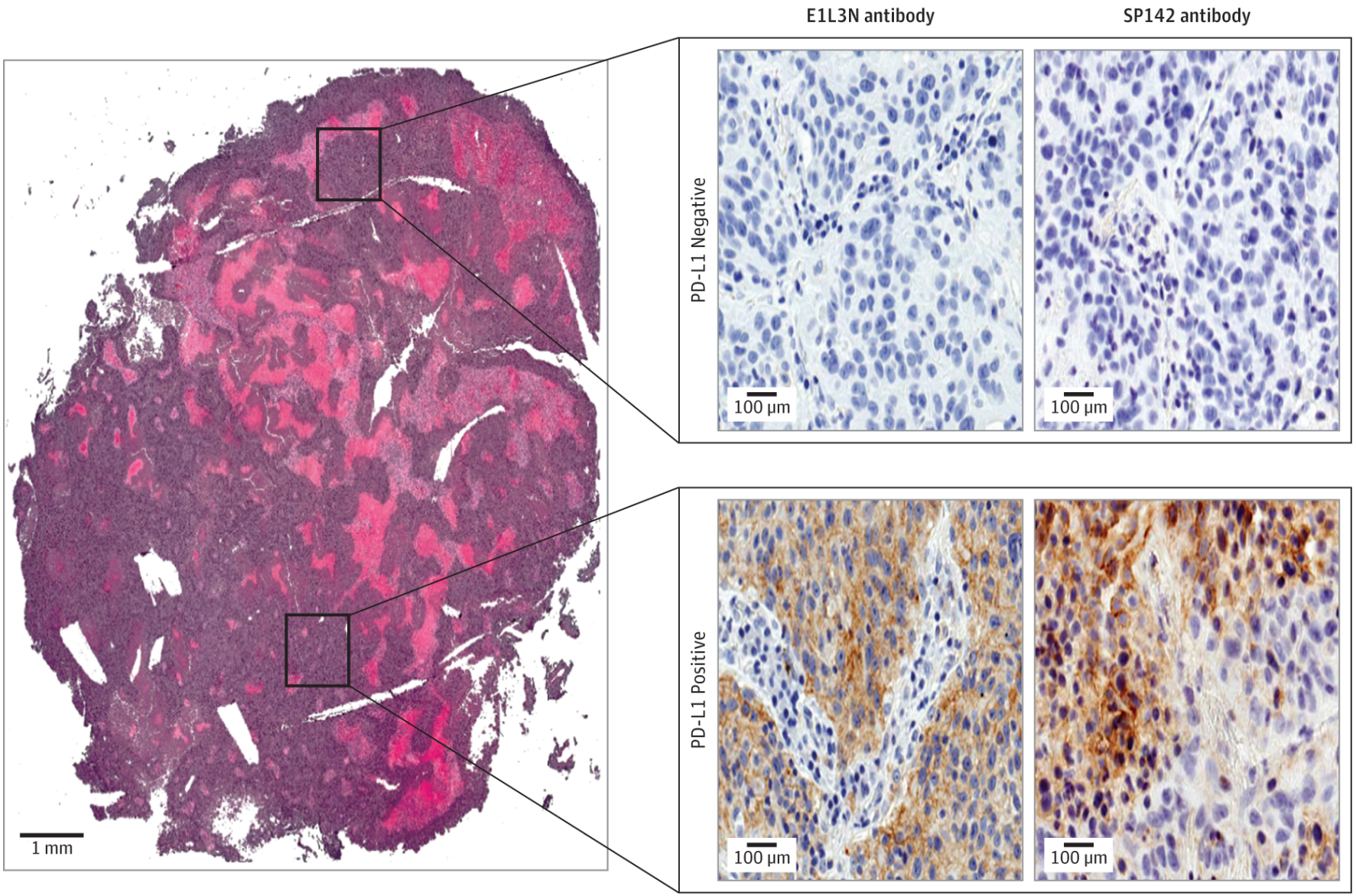


Tumor cells (TCs)

Tumor and immune cells (TCs and ICs)



Immunhistological staining for PDL1


E1L3N antibody
SP142 antibody
PD-L1 Negative
PD-L1 Positive
1 mm
100 µm
100 µm
100 µm
100 µm

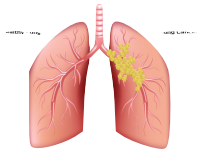


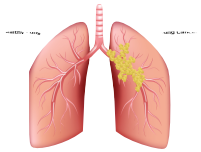
Table 1
Results of randomised phase III trials of immune checkpoint inhibitors (ICIs) for advanced non-small-cell lung cancer (NSCLC).

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.

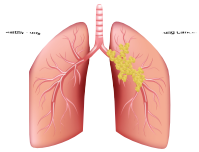
[a] Cutoff at 1% was used for inclusion, but cutoff at 5% was used for PFS (primary end-point), OS and ORR (secondary end-points).

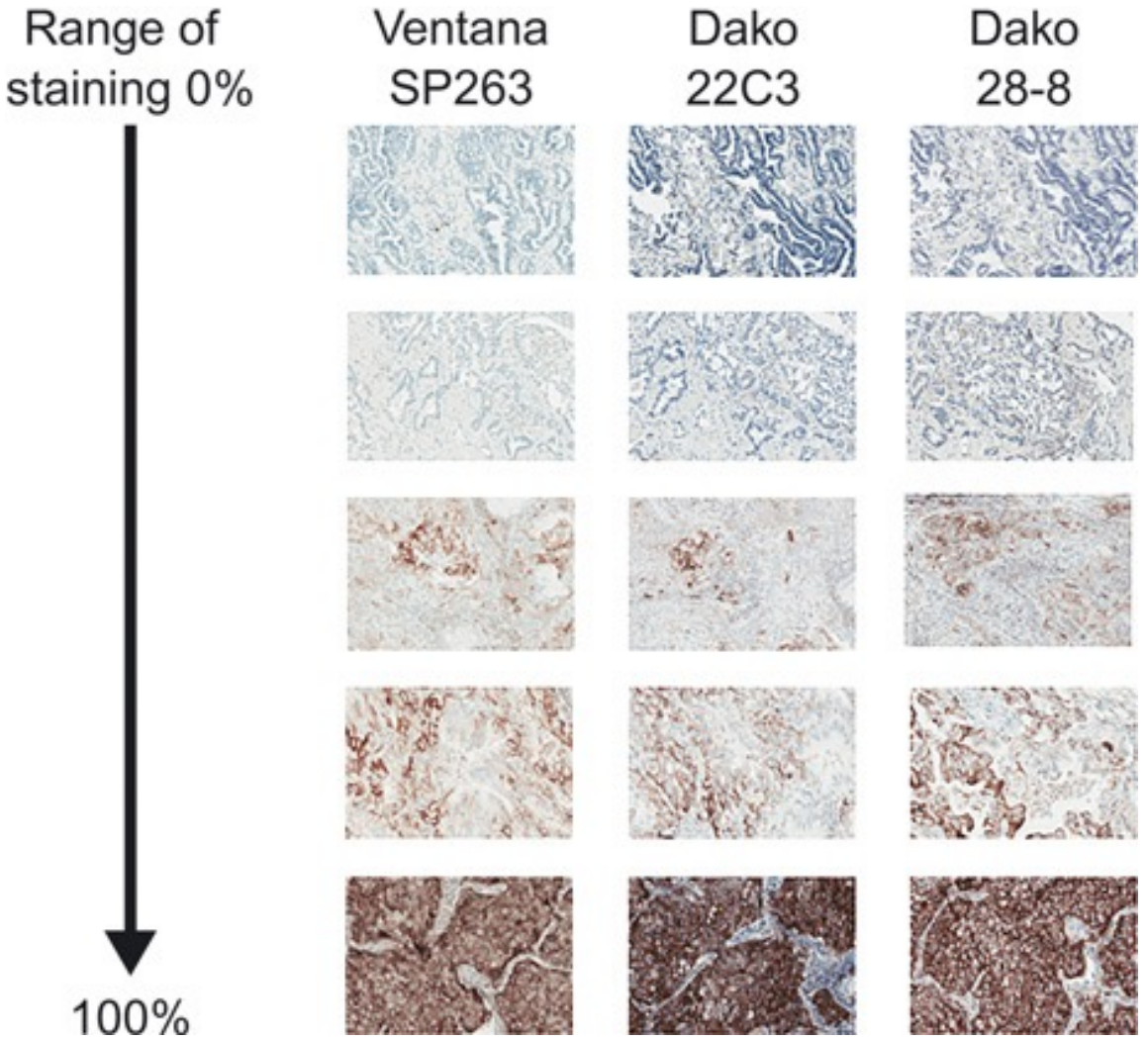
[b] Results for pembrolizumab 10 mg/kg.



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

NordiQC





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

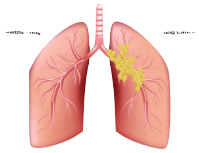
Cancer Therapy: Clinical

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. Ratcliffe[1], Alan Sharpe[2], Anita Midha[1], Craig Barker[2], Marietta Scott[2], Paul Scorer[2], Hytham Al-Masri[3], Marlon C. Rebelatto[4], and Jill Walker[2]

NordiQC



Cytology

Central tumor

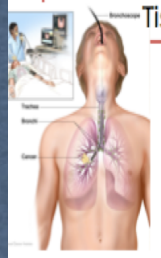
Periferal tumor

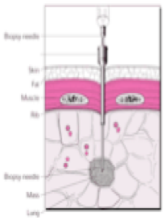
Cytology

Tumor Diagnosis

Bronchial brushing,
Bronchial lavage,
Tissue Biopsi

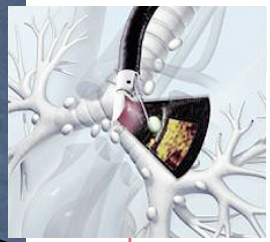
Fine- or
Course needle
biopsi





Tumor type

Cytology



Diagnosis of metastases

EBUS
EUS N

Cytology

M

Fine- or courseneedle biopsi
from metastasis suspekte
areas (found by CT eller PET scan)

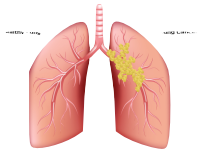
80%

Not operabel

Operabel

20%

NordiQC



Research Article

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

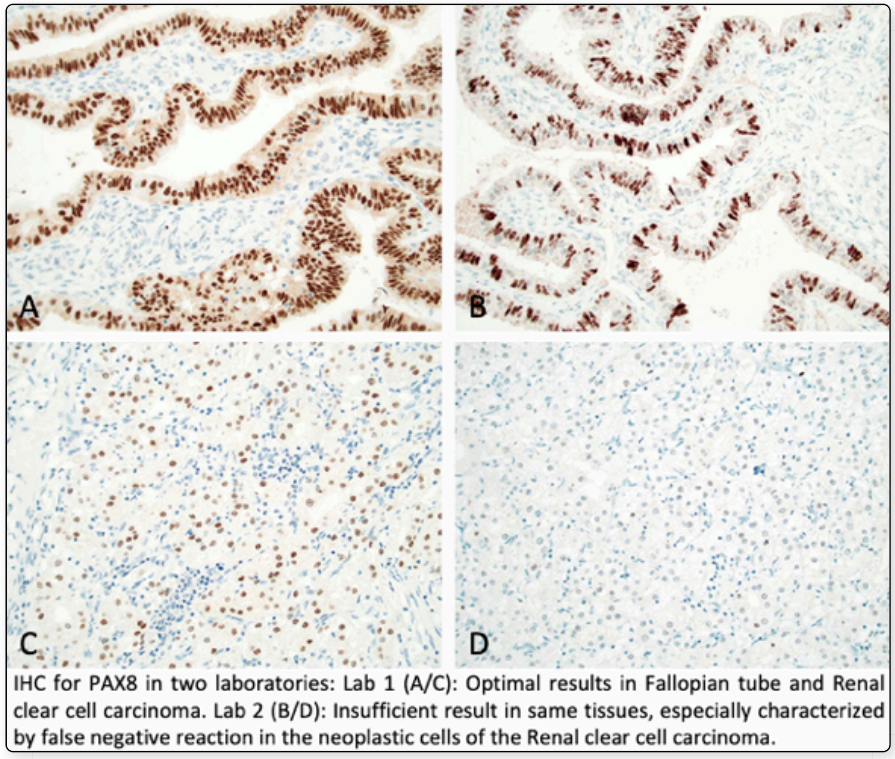
Birgit G. Skov, MD, DrMedSci and Torsten Skov, MD, PhD†*

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

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

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

Values are represented as percent, 95% CI.
CI indicates confidence interval; IHC, immunohistochemistry; PD-L1, programmed cell death ligand-1.



IHC for PAX8 in two laboratories: Lab 1 (A/C): Optimal results in Fallopian tube and Renal clear cell carcinoma. Lab 2 (B/D): Insufficient result in same tissues, especially characterized by false negative reaction in the neoplastic cells of the Renal clear cell carcinoma.

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

NordiQC

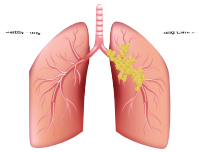
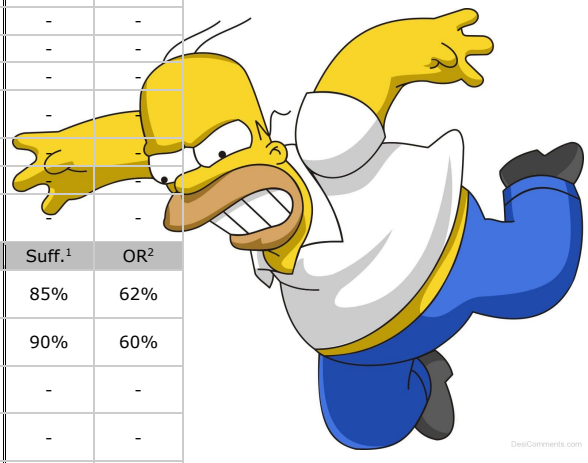
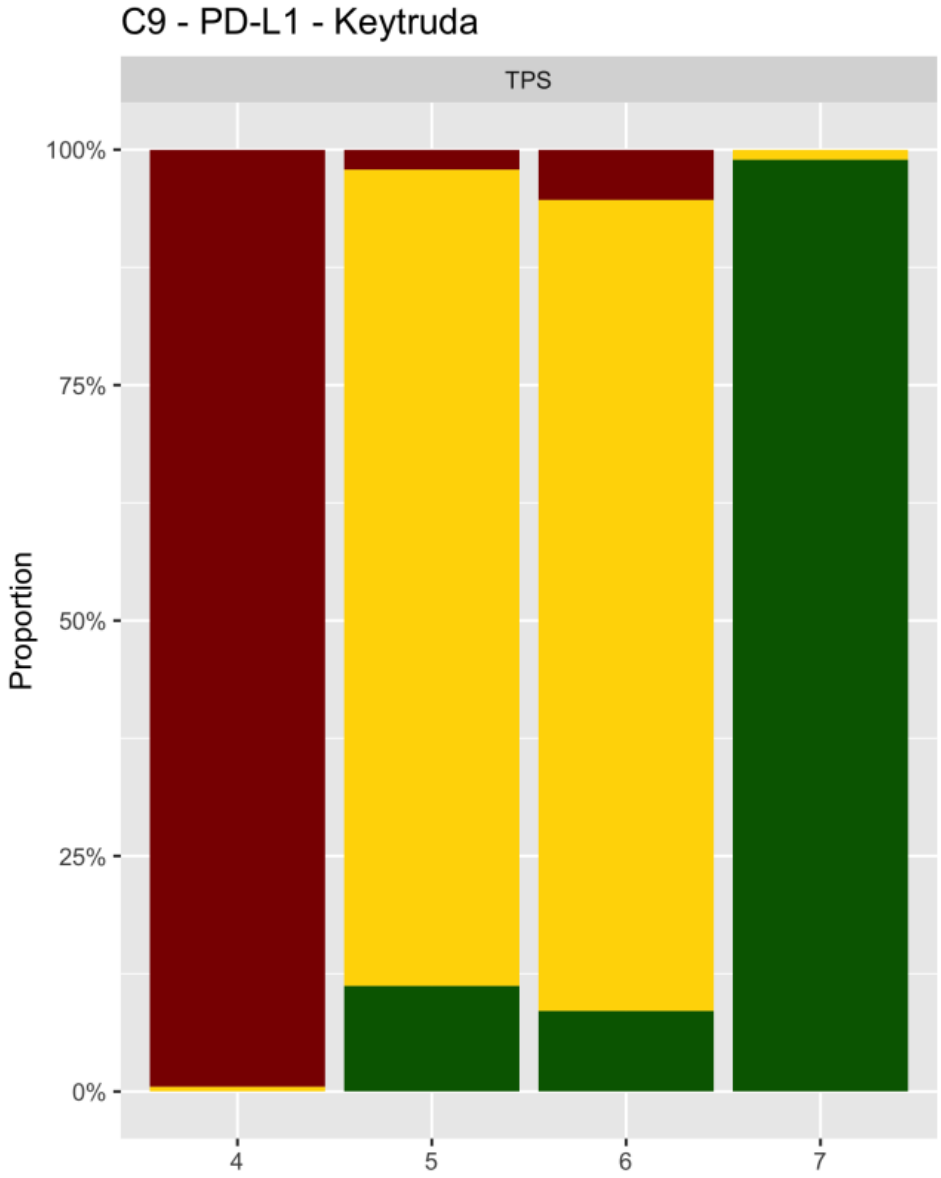


Table 2. **Assessment marks for IHC assays and antibodies run C9, PD-L1 TPS/CPS (KEYTRUDA®)**

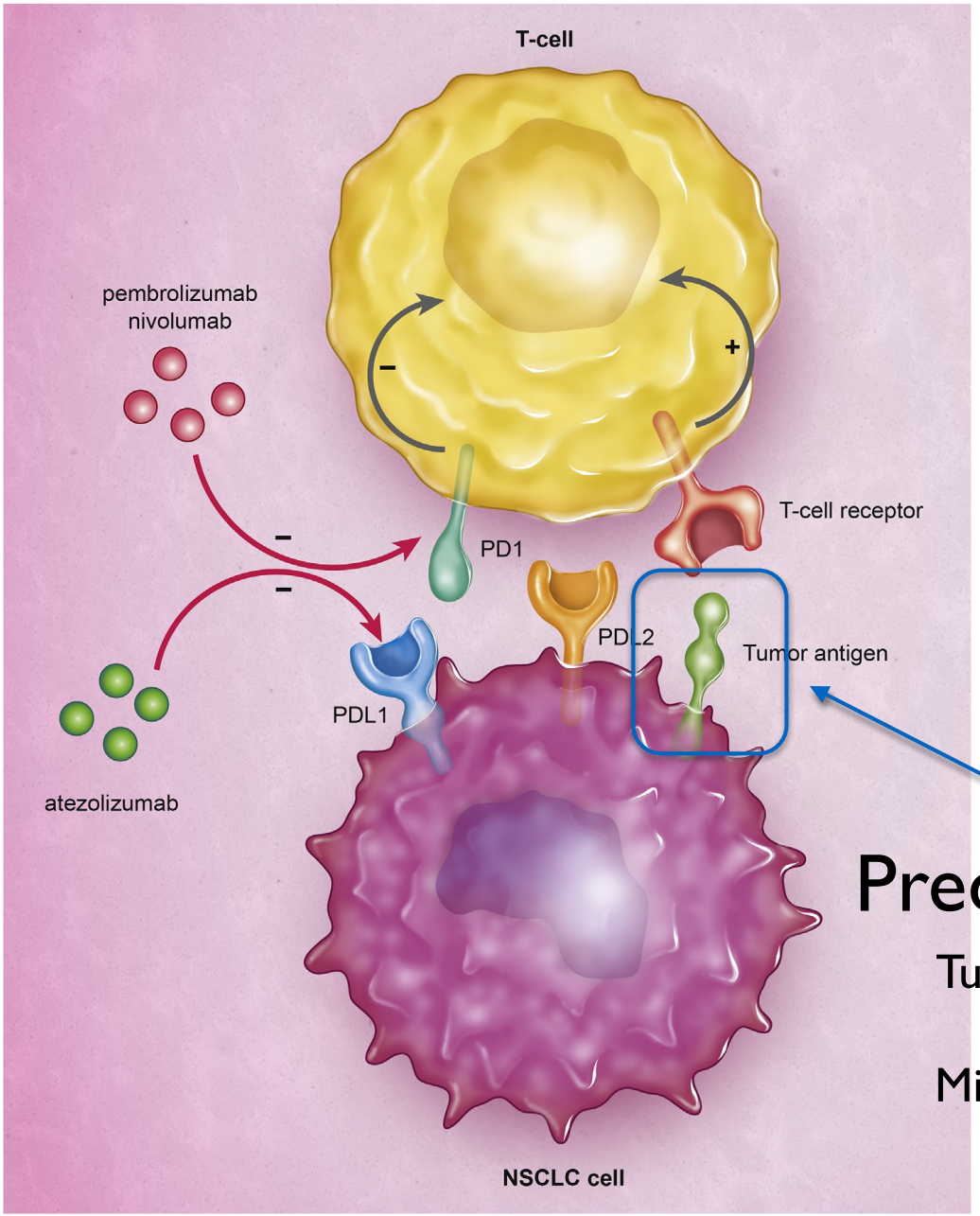
CE-IVD / FDA approved PD-L1 assays	n	Vendor	Optimal	Good	Borderline	Poor	Suff.[1]	OR[2]
rmAb clone SP263, **741-4905 (VRPS)[3]**	42	Ventana/Roche	29	9	4	-	91%	69%
rmAb clone SP263, **741-4905 (LPMS)[4]**	2	Ventana/Roche	-	-	1	1	-	-
rmAb clone SP263, **740-4907 (VRPS)[3]**	13	Ventana/Roche	8	4	1	-	92%	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 1	Biocare Zytomed Systems	3	1	-	-	-	-
rmAb clone **QR1**	1	Biocyc	-	-	1	-	-	-
rmAb clone **SP142**	1	Abcam	-	1	-	-	-	-
rmAb clone **ZR3**	1 1	Zeta Corporation Zytomed systems	-	-	2	-	-	-
Ready-To-Use antibodies[6]	n	Vendor	Optimal	Good	Borderline	Poor	Suff.[1]	OR[2]
rmAb clone SP263, **790-4905[6] (VRPS)[3]**	13	Ventana/Roche	8	3	1	1	85%	62%
rmAb clone SP263, **790-4905[6] (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%	82%	

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.





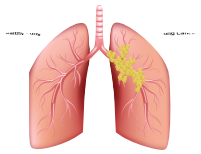
Graph 1. **NordiQC PD-L1 run C9: Tumour Proportion scores (TPS) in NSCLCs (core no. 4-7)**

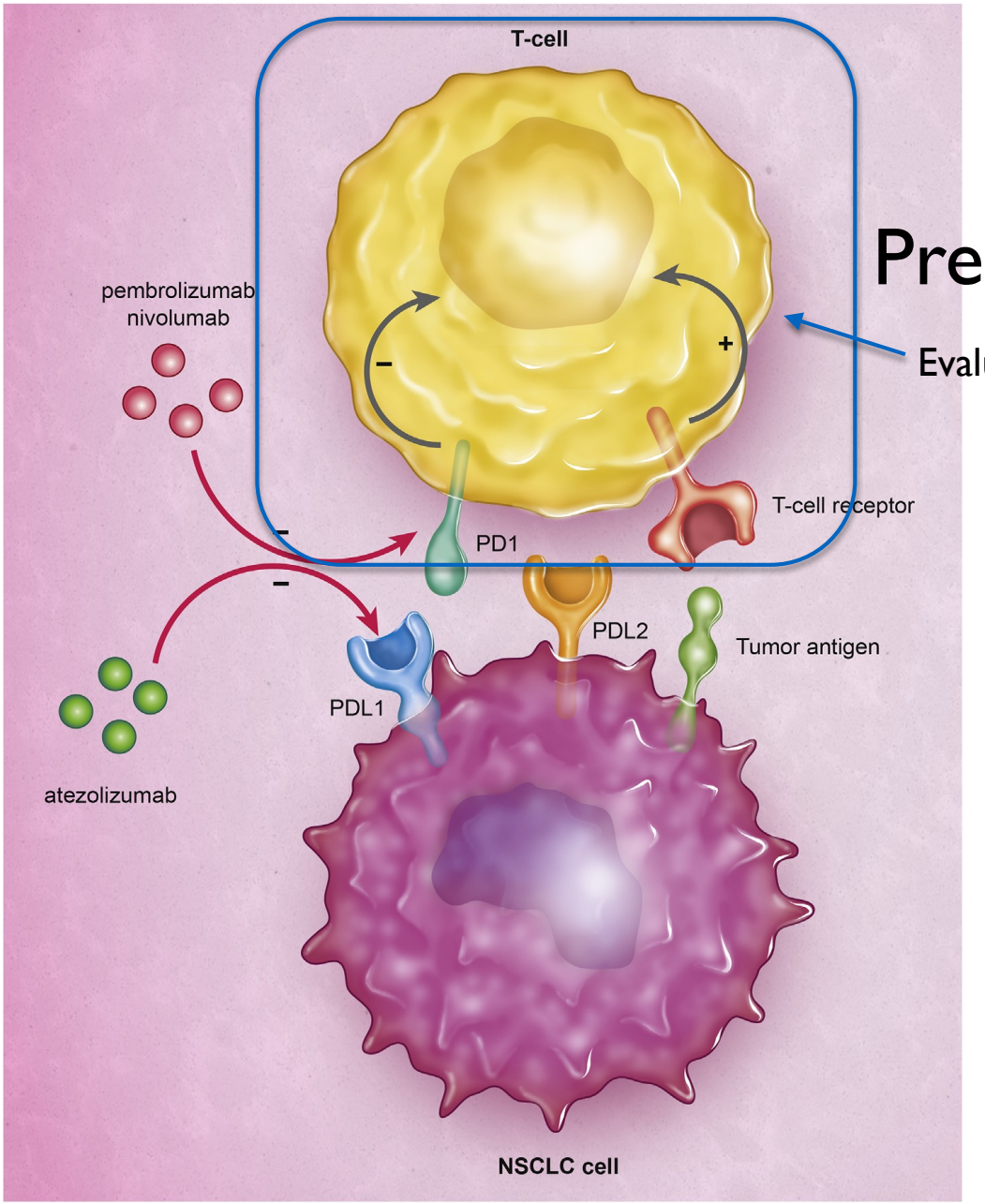


Future:

Predictive marker

Tumor Mutational Burden
TMB
Micro Satellite Instability
MSI



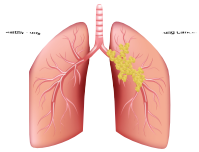


Future:

Predictive marker

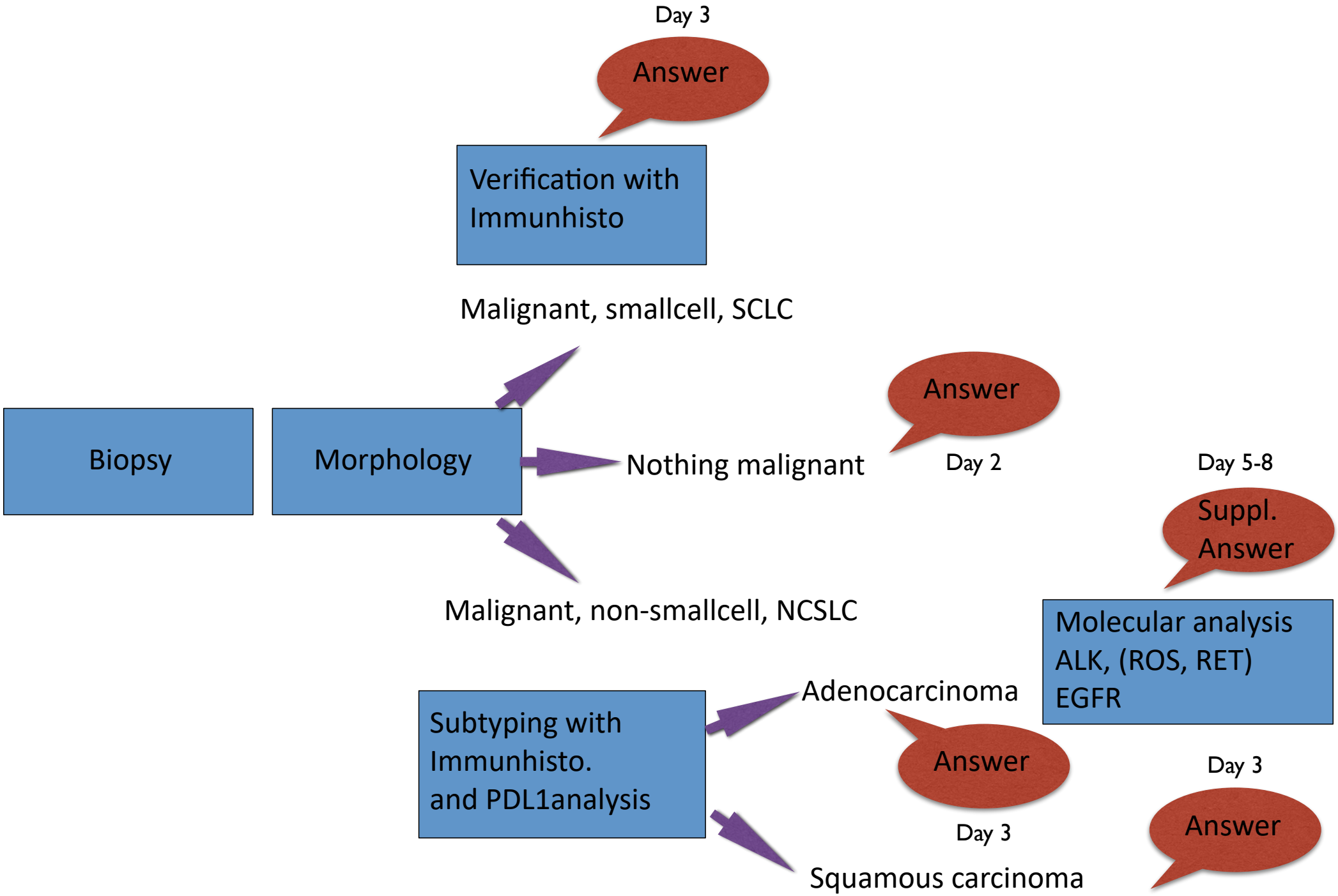
Evaluation of immune respons

NordiQC

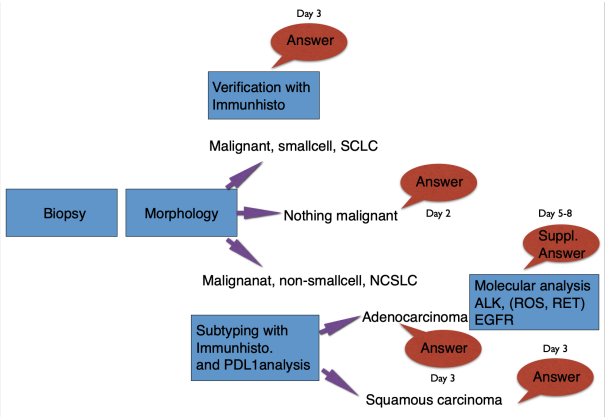


The Diagnostic algorithm

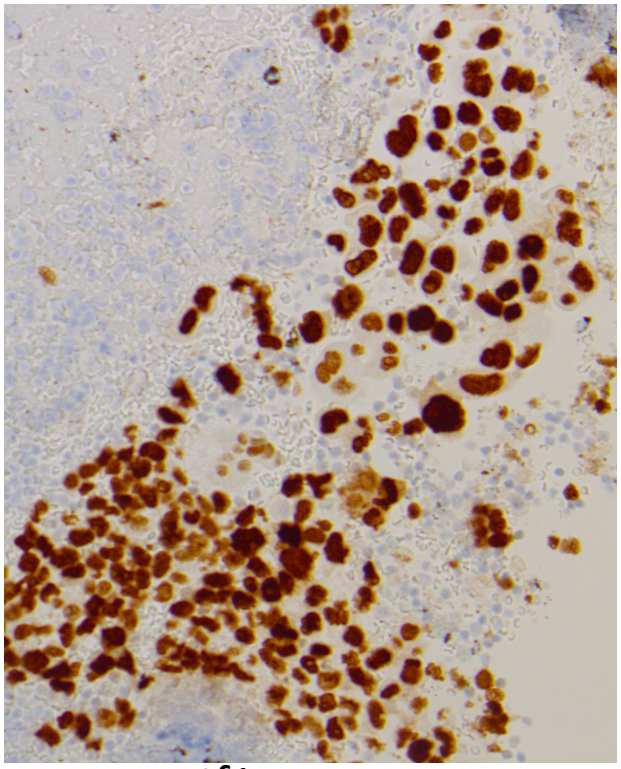
The Diagnostic algorithm



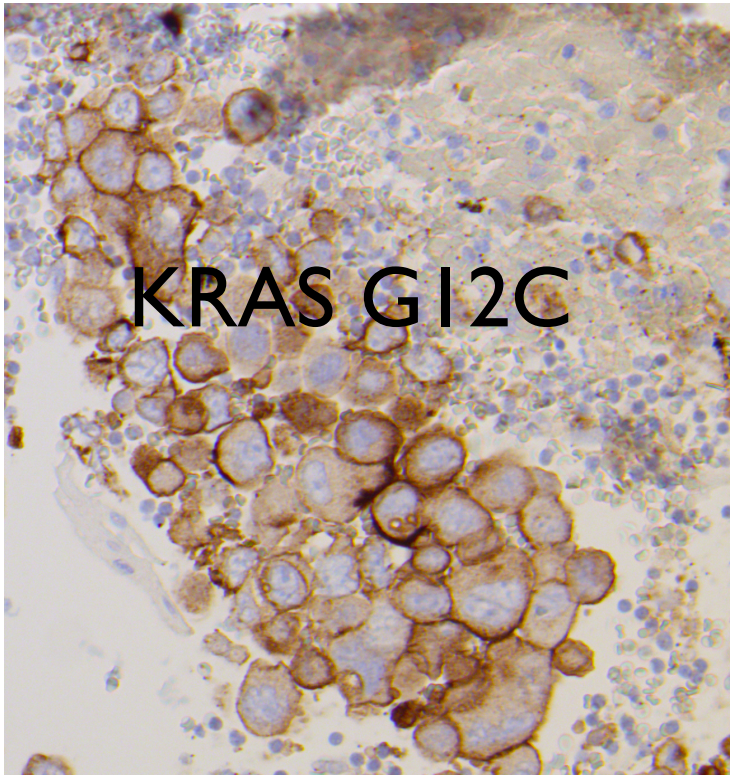
The Diagnostic algorithm



Pleura effusion Cell Block



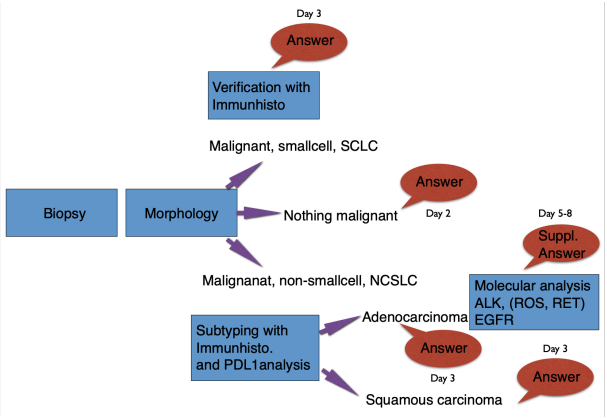
ttf1, CK7+



PD-L1 (22C3)

2. line TKI

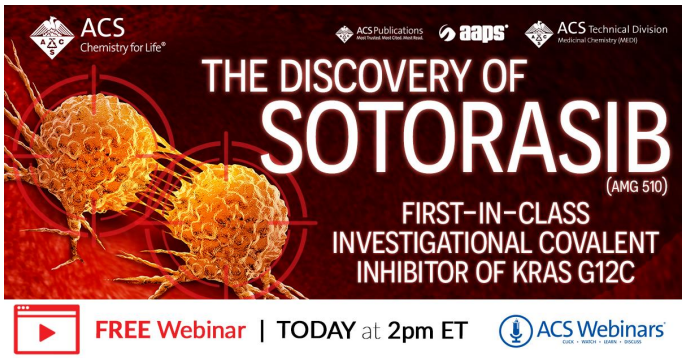
The Diagnostic algorithm



Pleura effusion Cell Block

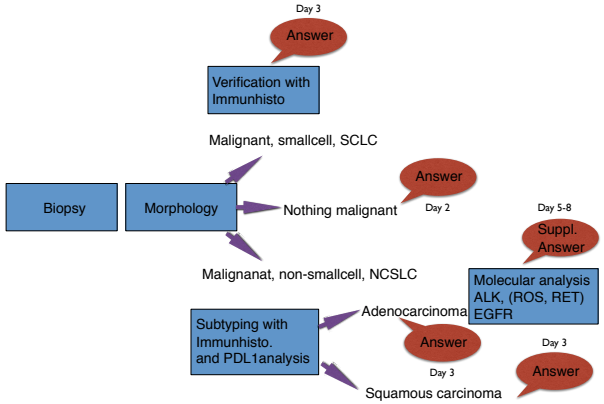
Mutation analysis

KRAS G12C

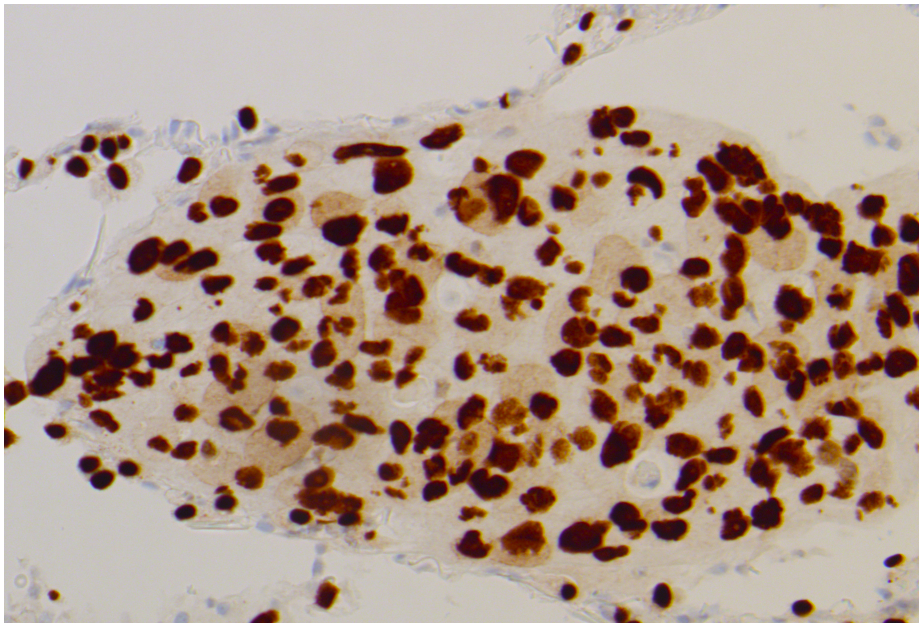


2. line TKI

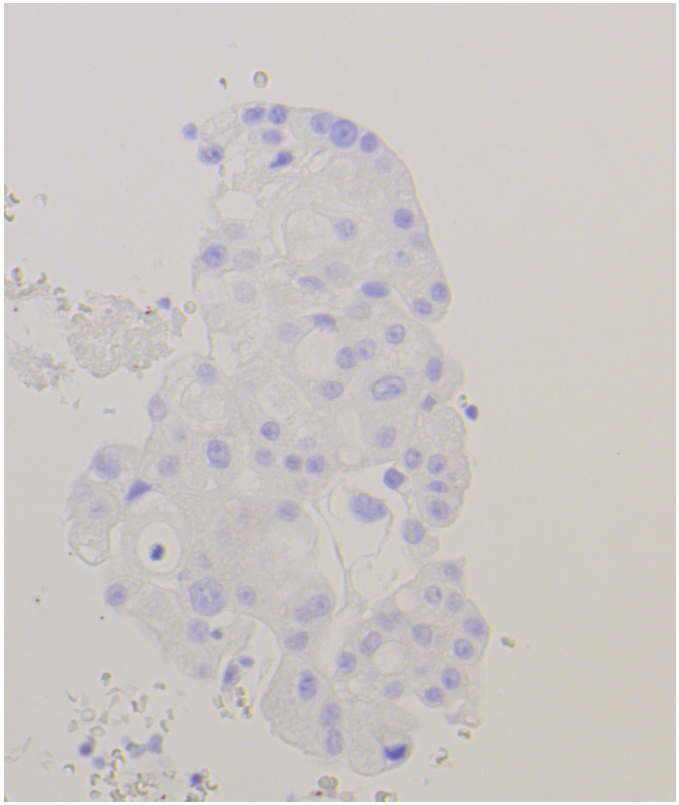
The Diagnostic algorithm



EBUS CellBlock

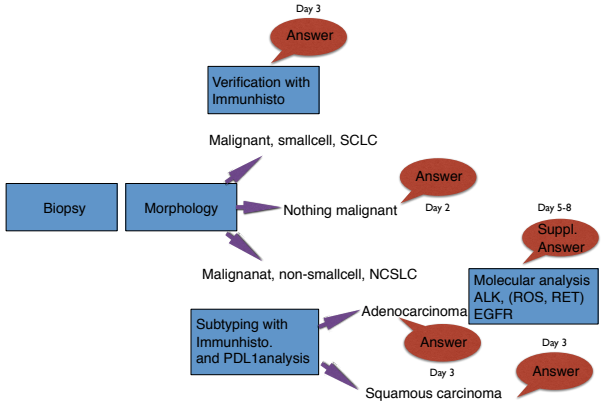


CK5/6, CK7 and P40+

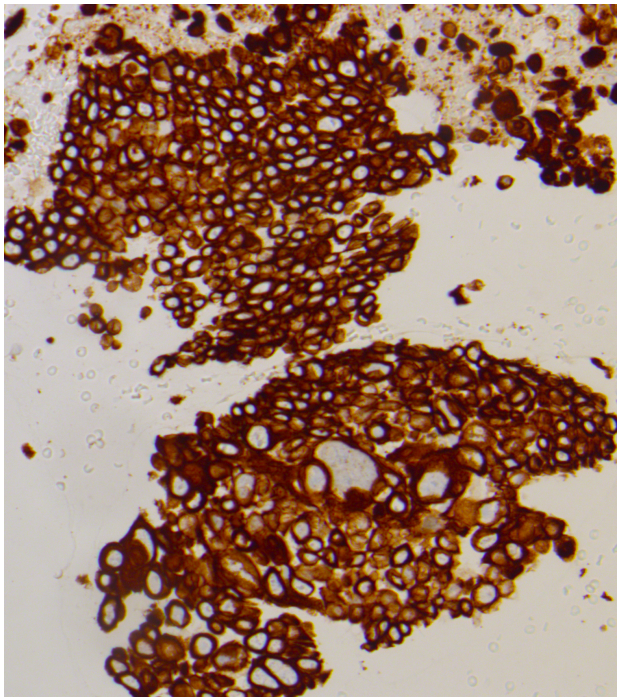


PD-L1 (22C3)

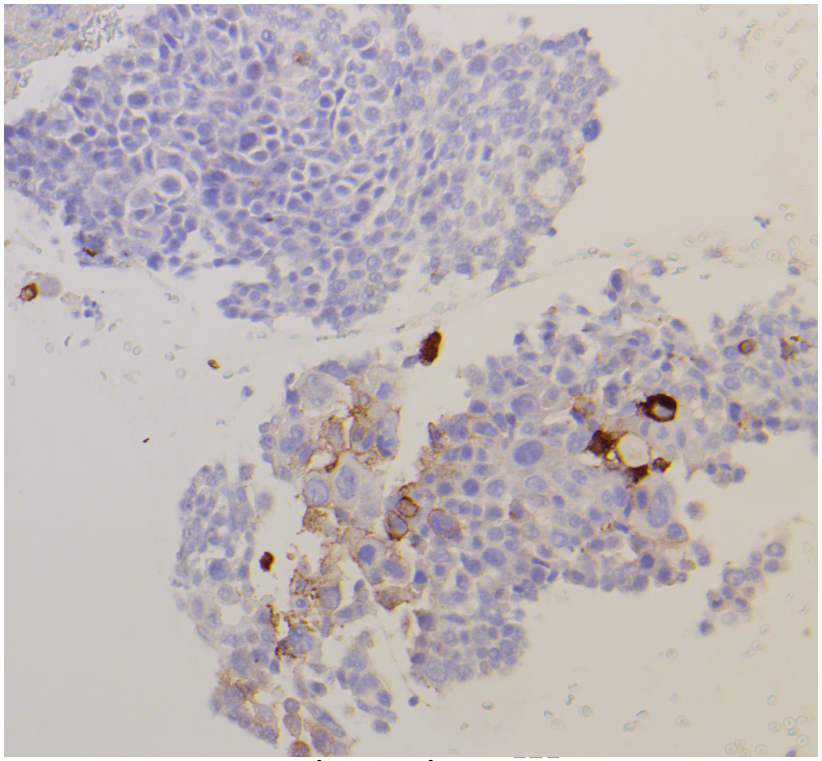
The Diagnostic algorithm



EBUS Cell Block

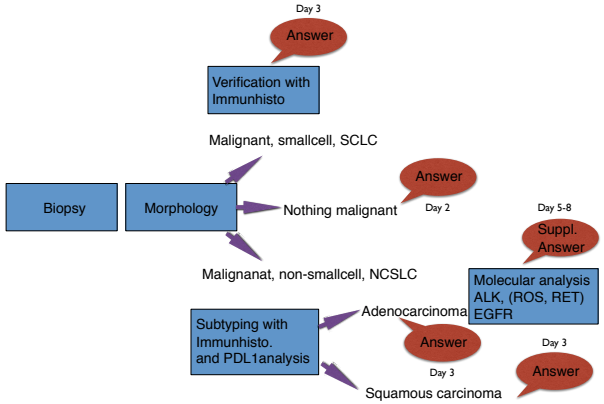


CK5/6 and P40+

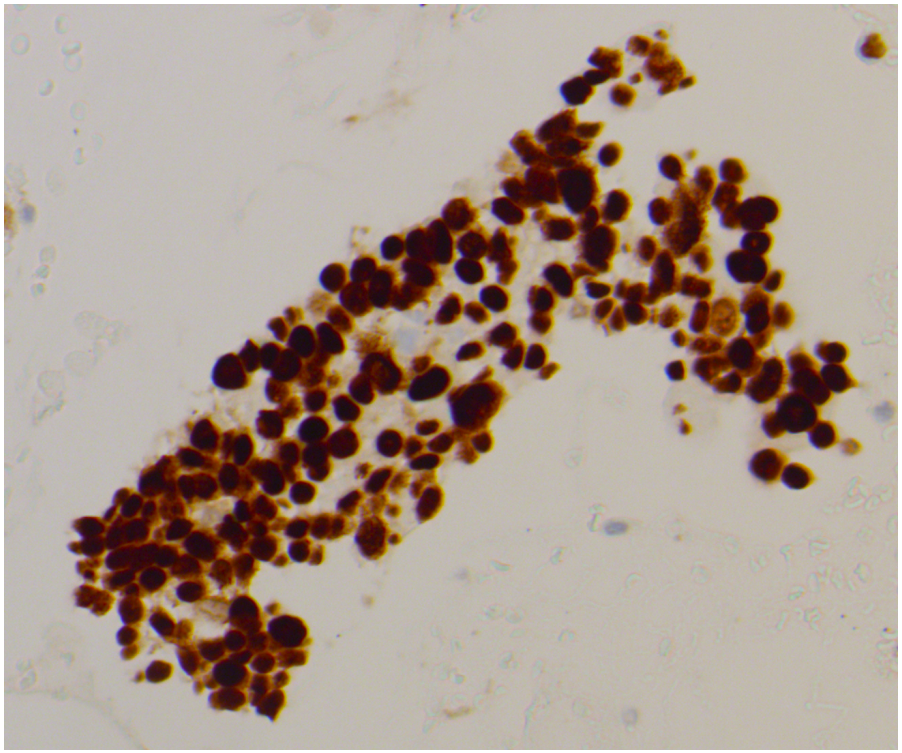


PD-L1 (22C3)

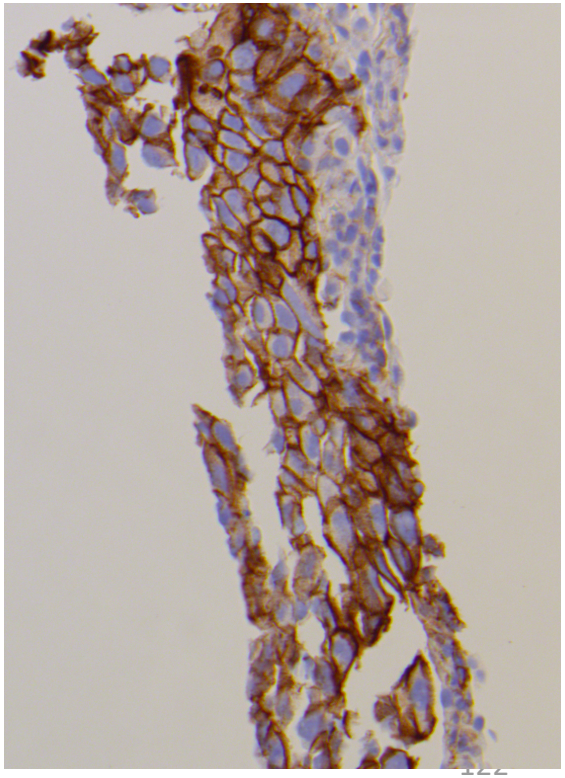
The Diagnostic algorithm



Coarse needle biopsy

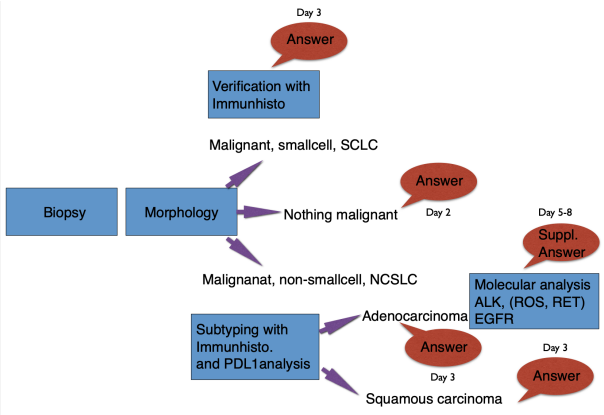


ttf1 and CK7+



PDL1 (22C3)

The Diagnostic algorithm



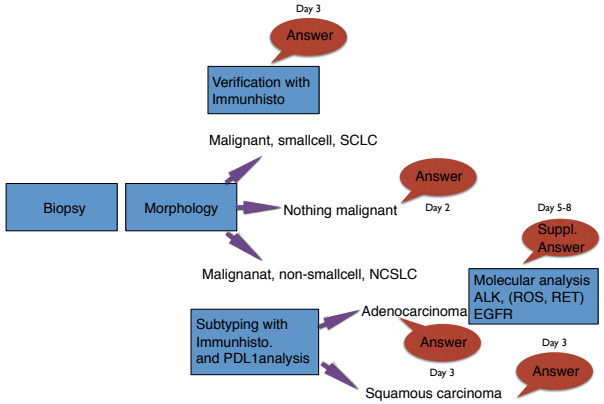
Coarse needle biopsy

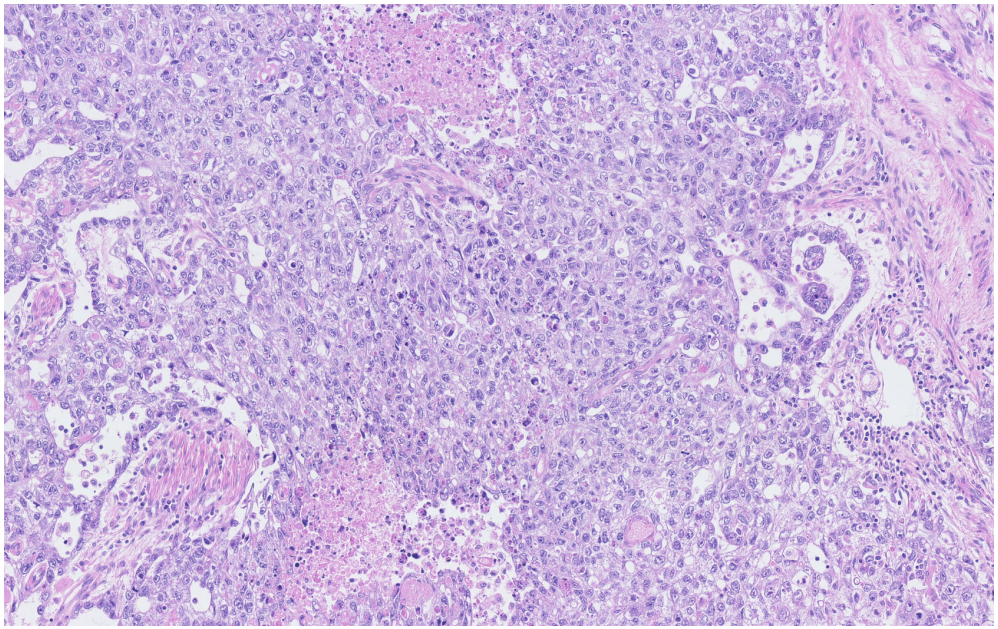
Mutation analysis

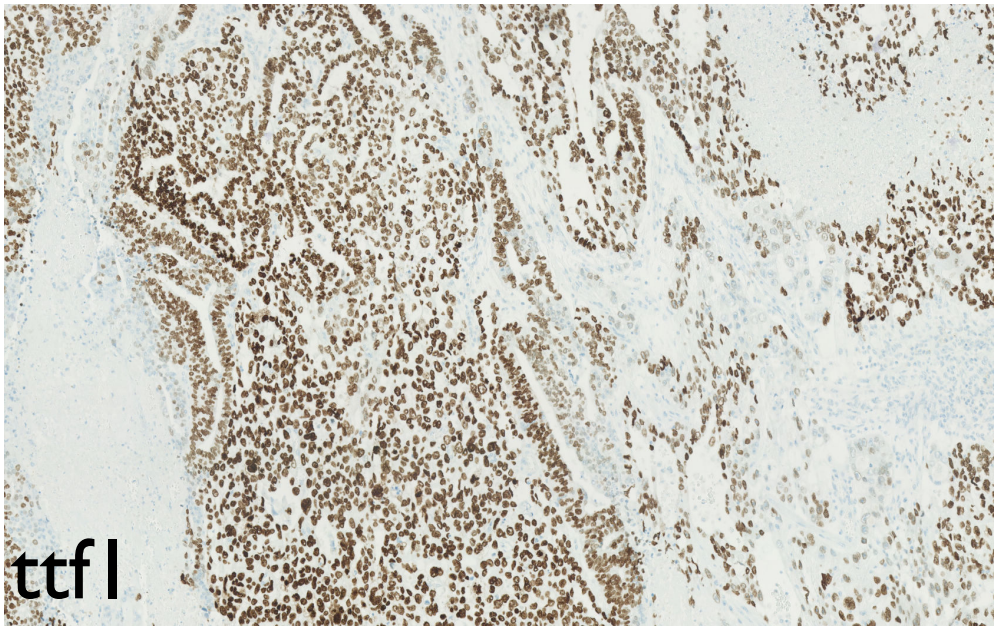
EGFR exon 19 del

1. line TKI

The Diagnostic algorithm



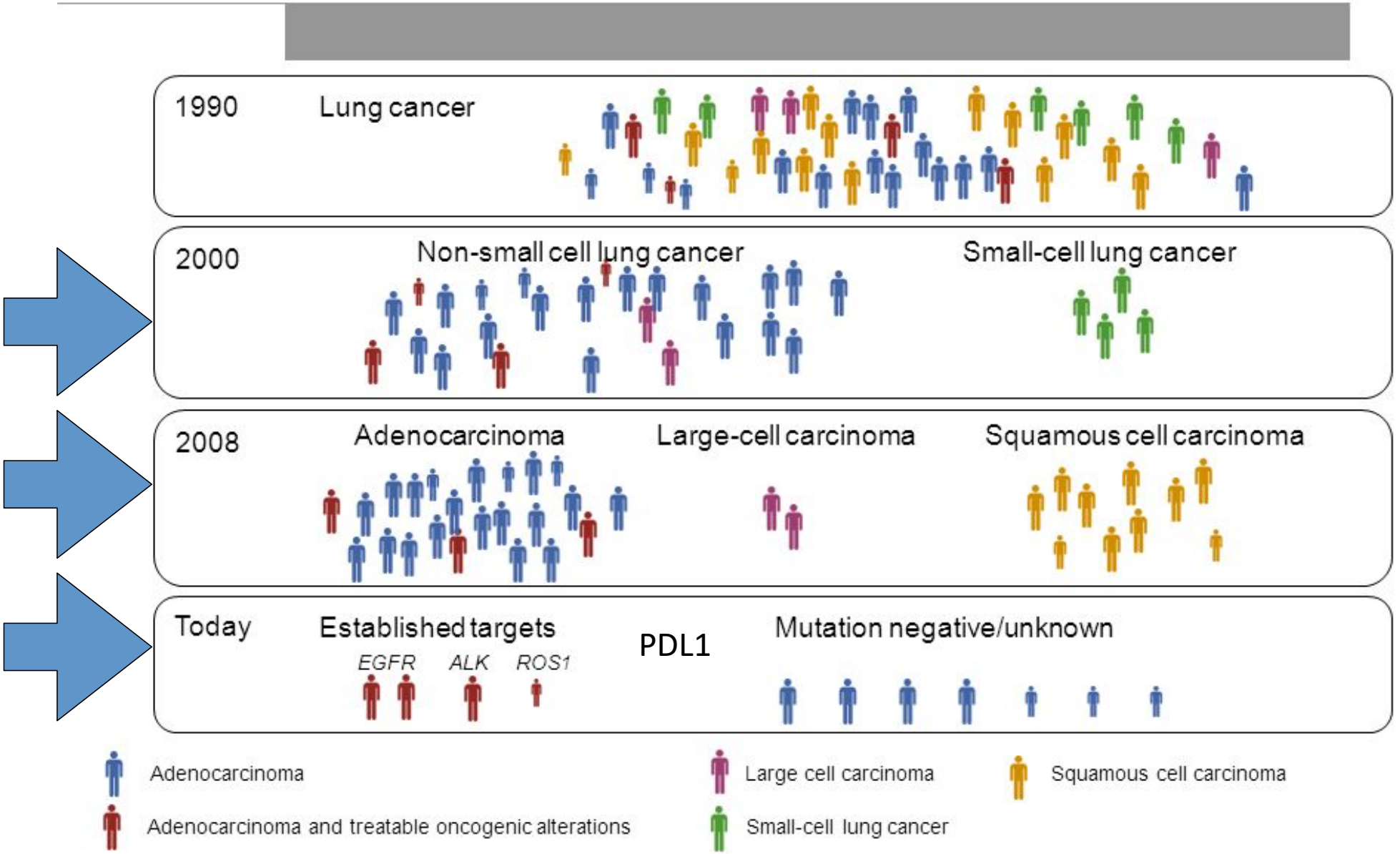




Large tumor intra uterine

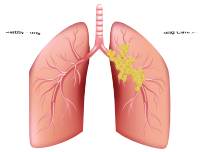
Endometrial cancer (yolk sac tumor)

Patient selection in lung cancer: Evolution over time

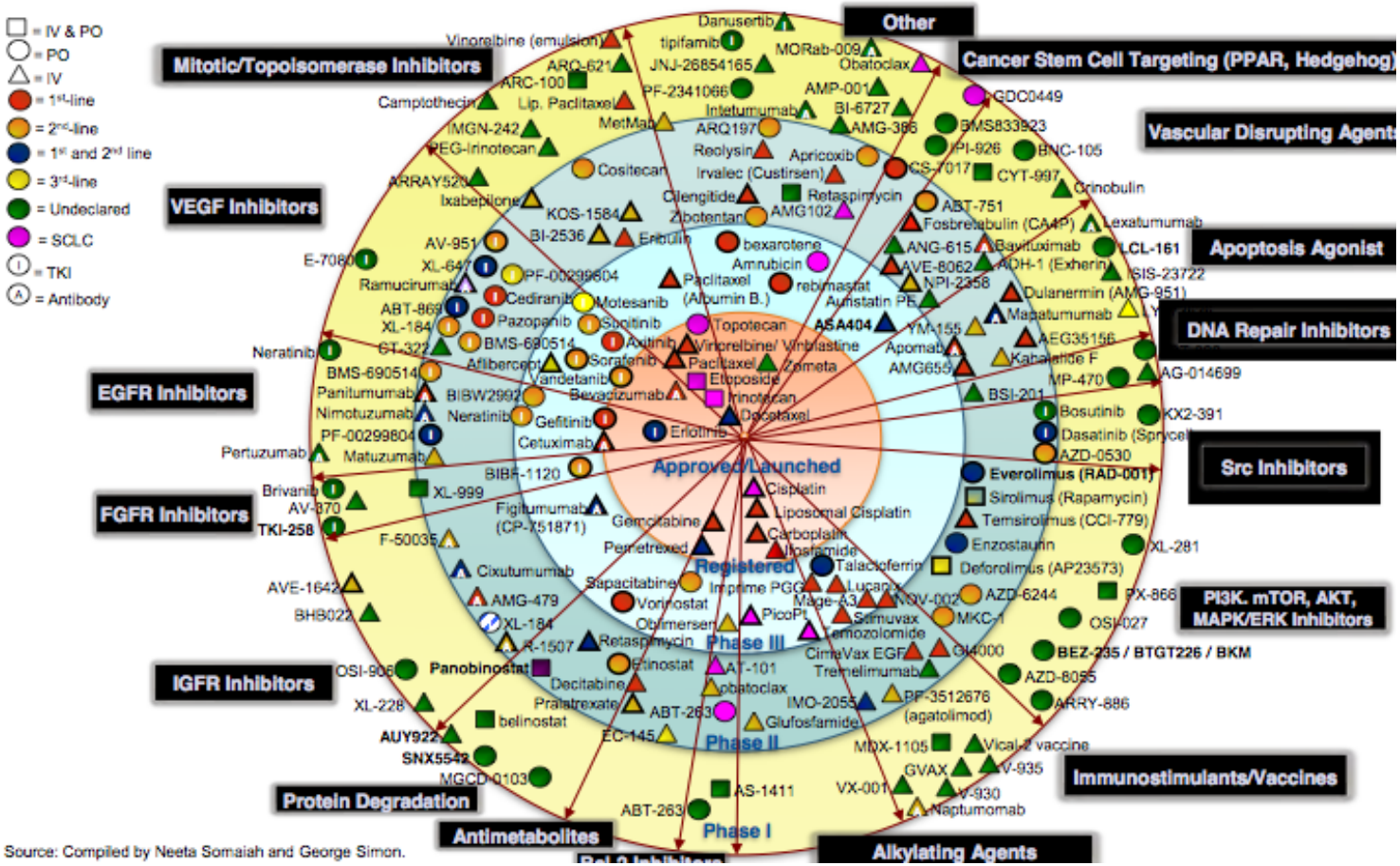


Adapted from Reck M, et al. Lancet 2013;382:709–19

NordIQC



Lung cancer research landscape – MoA group and phase



Source: Compiled by Neeta Somaiah and George Simon.

Future