NordiQC

Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

Region Syddanmark
Sygehus Lillebælt

Henrik Hager

Dept. of Clinical Pathology
Vejle Hospital

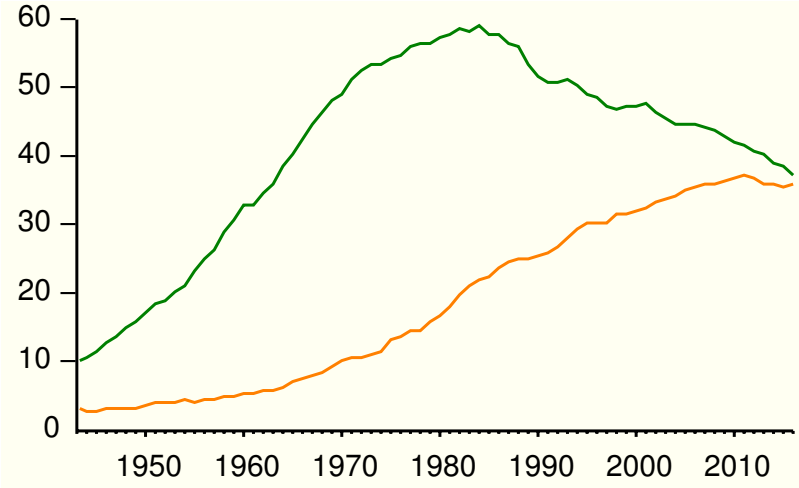
Immunohistochemcal classification of

Lung cancer,

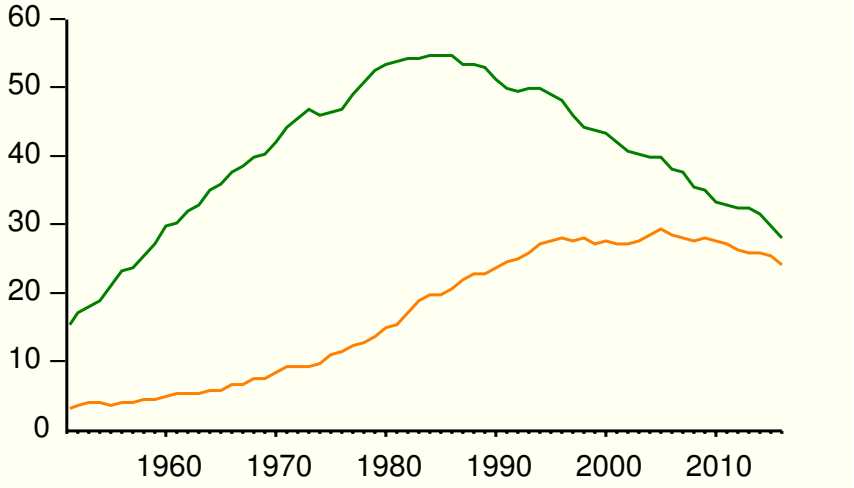
diagnosis and prediction.

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

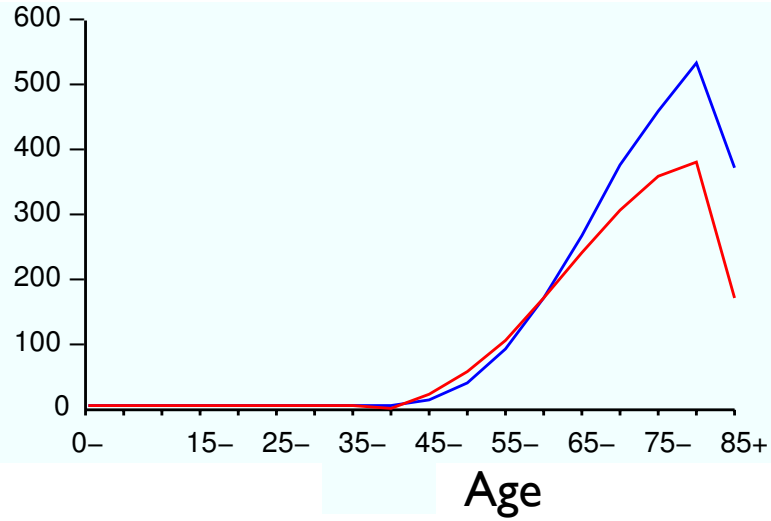
Immunohistochemcal classification of

Lung cancer,

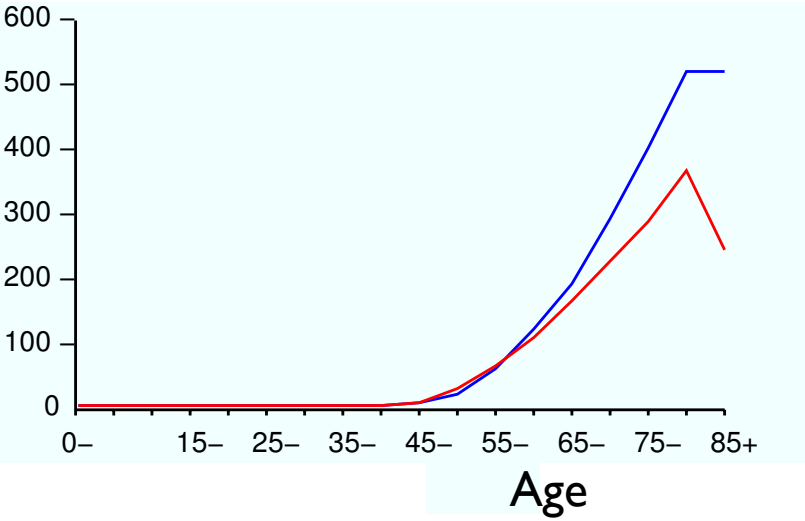
diagnosis and prediction.

Lung cancer

New cases/100.000 / age interval



Deaths/100.00 / age interval



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Males

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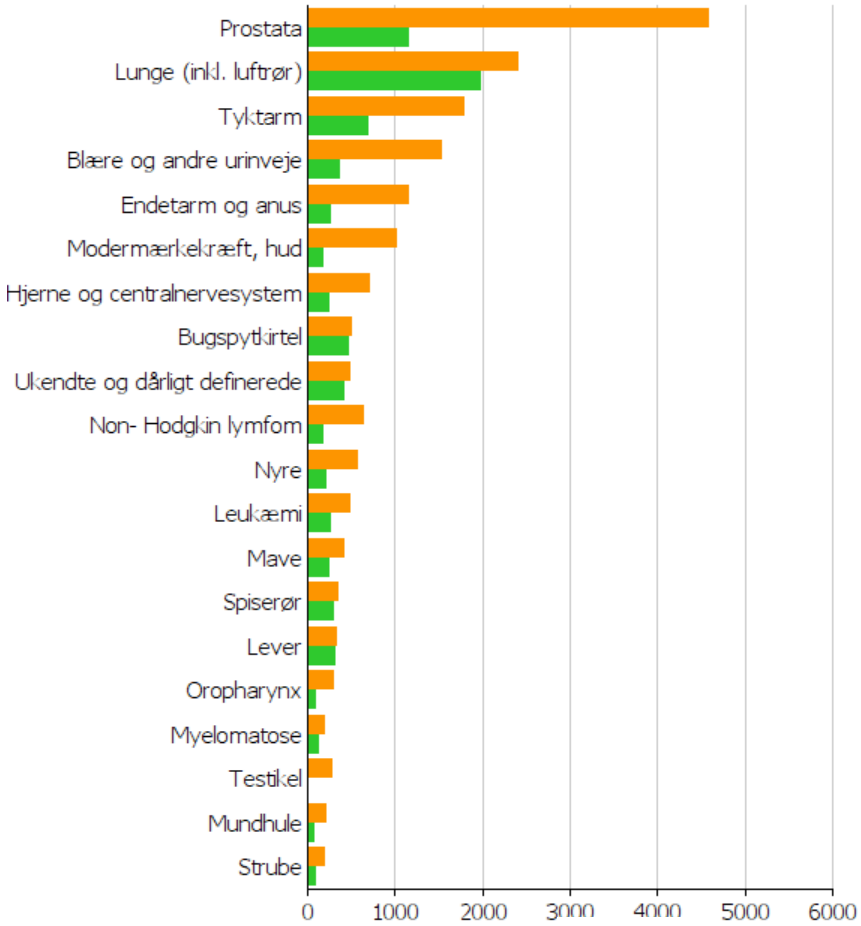
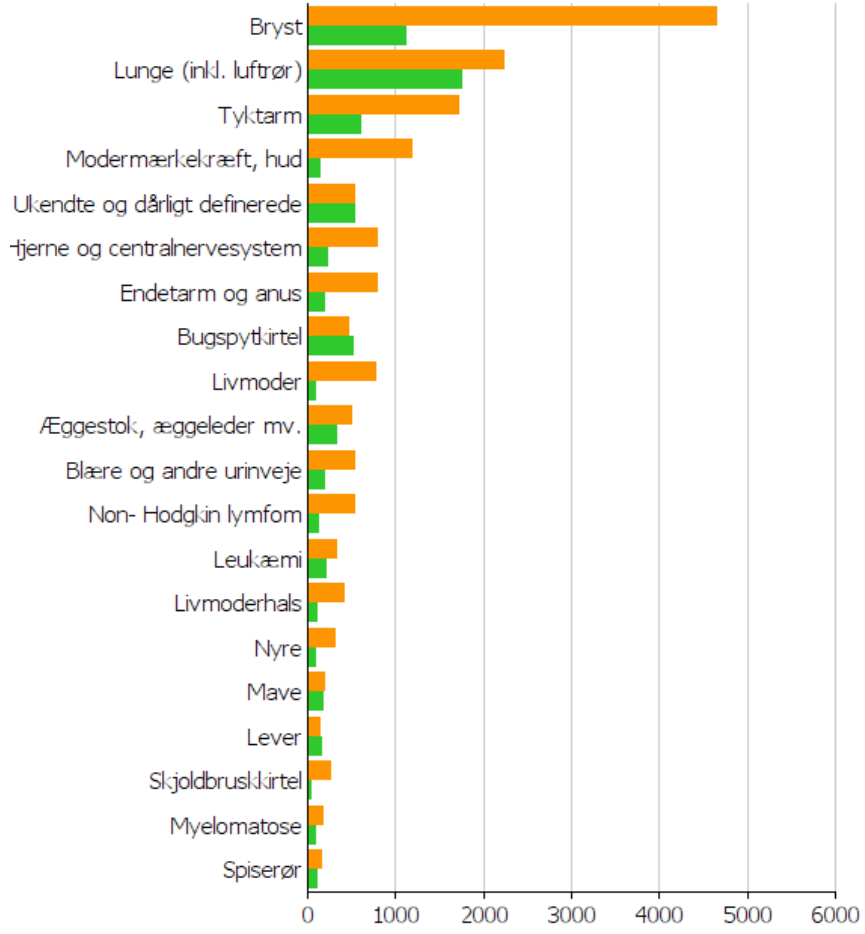
Males



Females



Incidence, new cases / 100.000

Mortality, number of death / 100.000

Immunohistochemcal classification of

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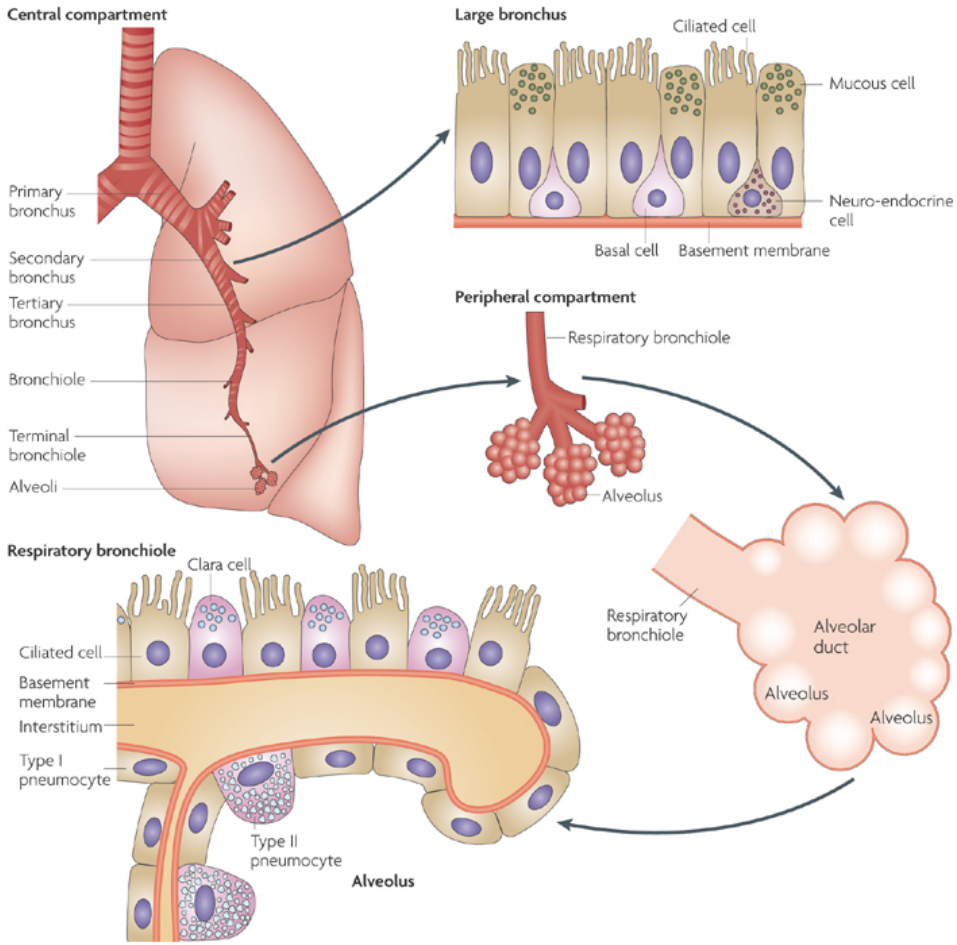
Lung Carcinoma



Lung carcinoma derives from stem cells
in the lung epithelium

Immunohistochemcal classification of

Lung cancer,

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Lung Carcinoma

TABLE 1. 2015 WHO Classification of Lung Tumors[a,b,c]

Histologic Type and Subtypes	ICDO Code
Epithelial tumors	
Adenocarcinoma	8140/3
Lepidic adenocarcinoma[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]

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malignant epithelial tumors
(carcinomas)

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Lung Carcinoma

Adenocarcinoma
Squamous carcinoma
Large cell neuroendocrine carcinoma
Small cell carcinoma

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Immunohistochemcal classification of

Lung cancer,

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Lung Carcinoma

Adenocarcinoma
Squamous carcinoma
Large cell neuroendocrine carcinoma
Small cell carcinoma

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

Dansk Lunge Cancer Gruppe & Dansk Lunge Cancer Register

Immunohistochemcal classification of

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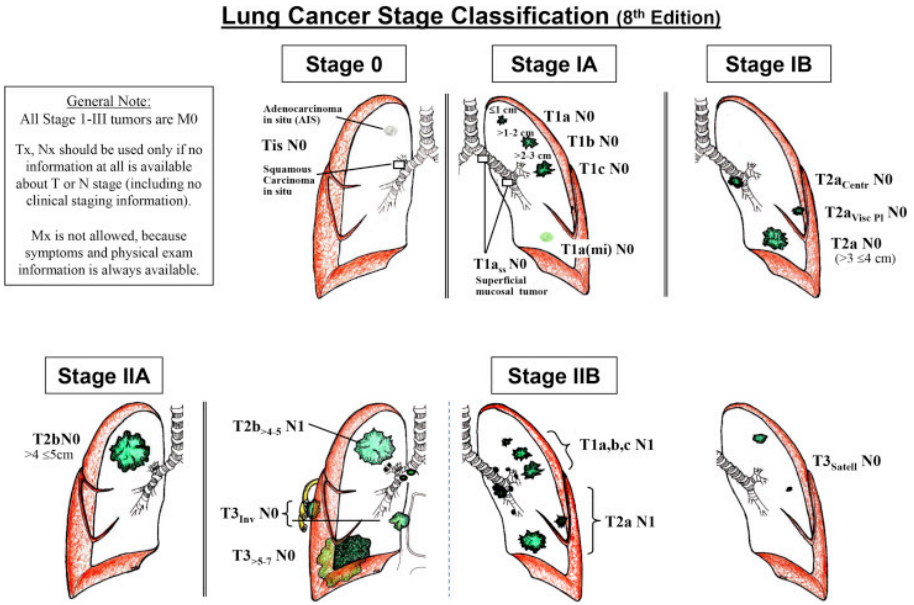
Lung Carcinoma

Diagnostic sampling

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



Immunohistochemcal classification of

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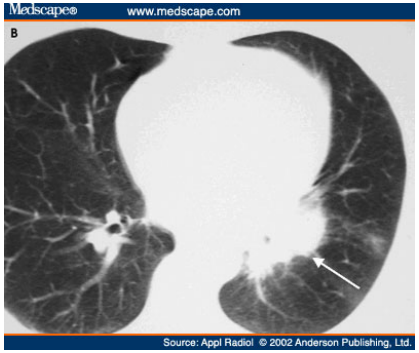
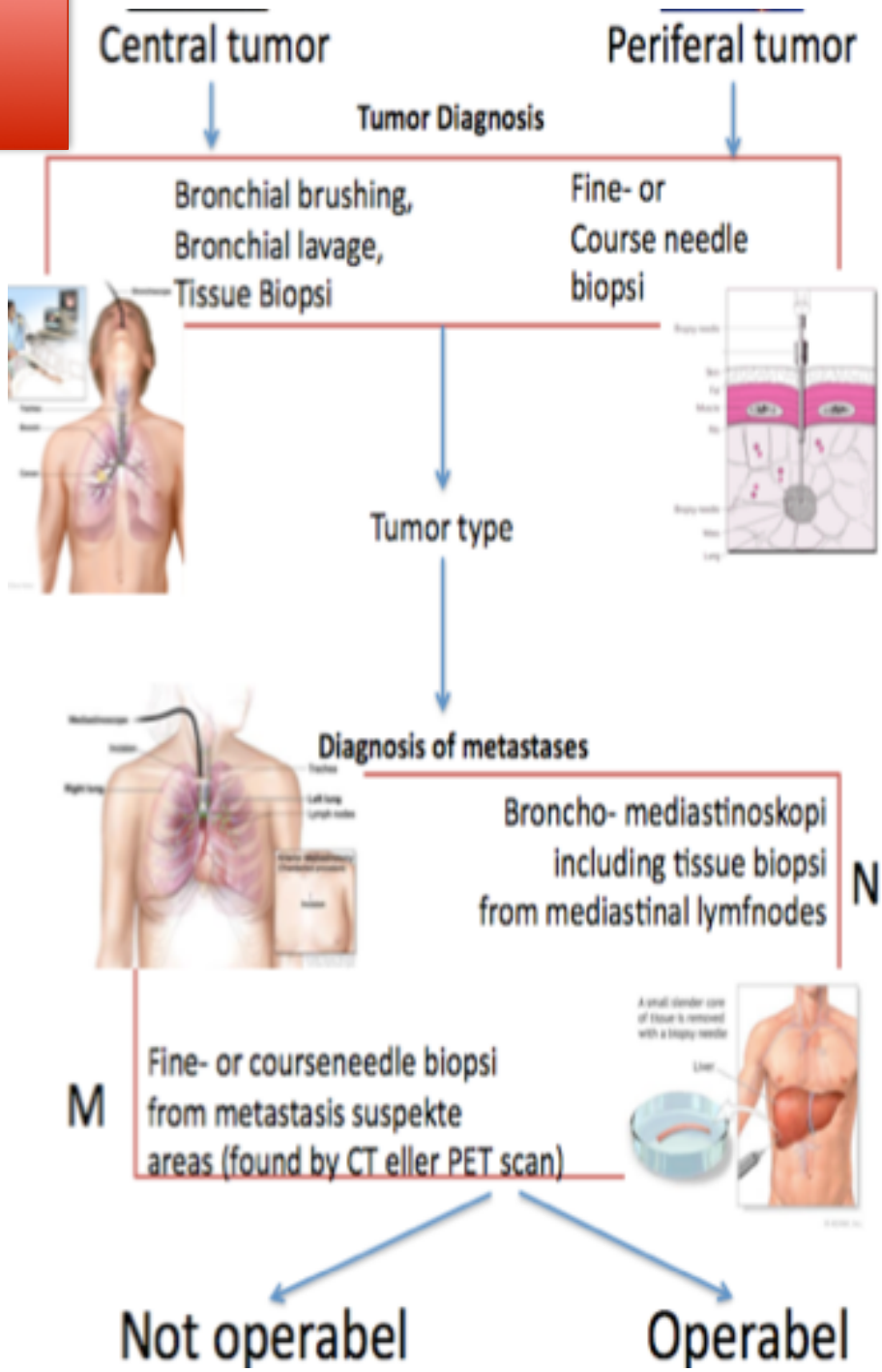
Region Syddanmark
Sygehus Lillebælt





Immunohistochemcal classification of

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Region Syddanmark
Sygehus Lillebælt

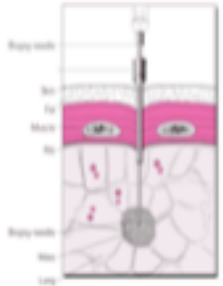
Central tumor

Periferal tumor

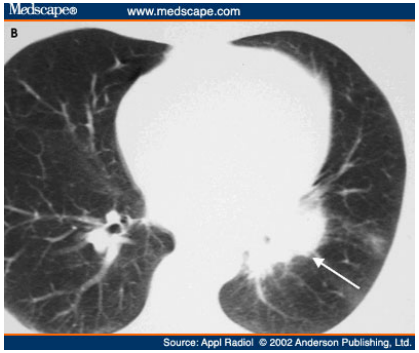
Tumor Diagnosis

Bronchial brushing,
Bronchial lavage,
Tissue Biopsi

Fine- or
Course needle
biopsi



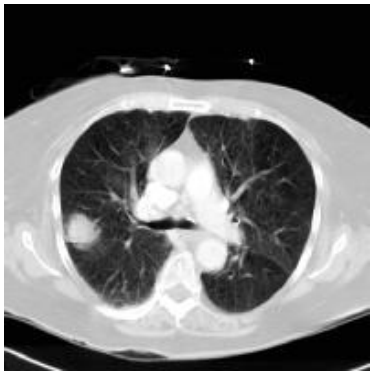
Tumor type



Diagnosis of metastases

EBUS
EUS

N



M

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

Not operabel

Operabel

Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

Central tumor

Periferal tumor

Tumor Diagnosis

Bronchial brushing,
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Fine- or
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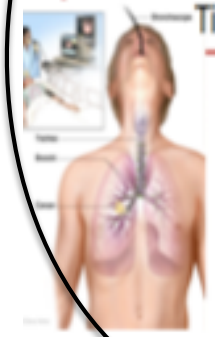
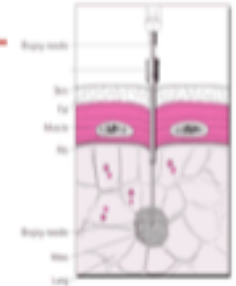
biopsi





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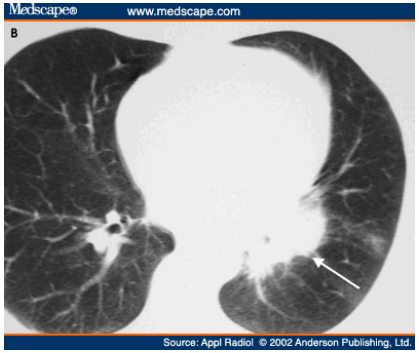


Diagnosis of metastases

EBUS
EUS

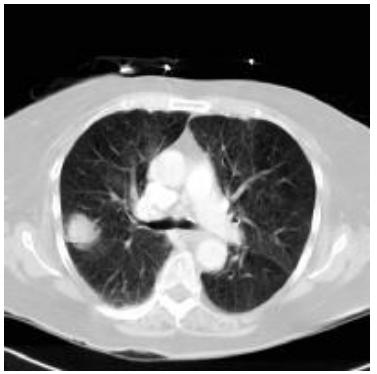
N

M

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

Not operabel

Operabel



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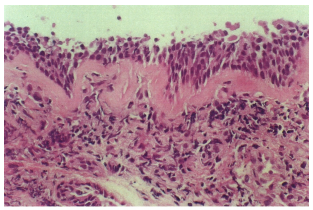

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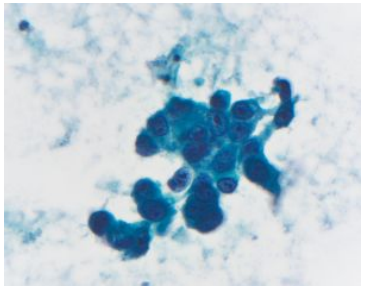

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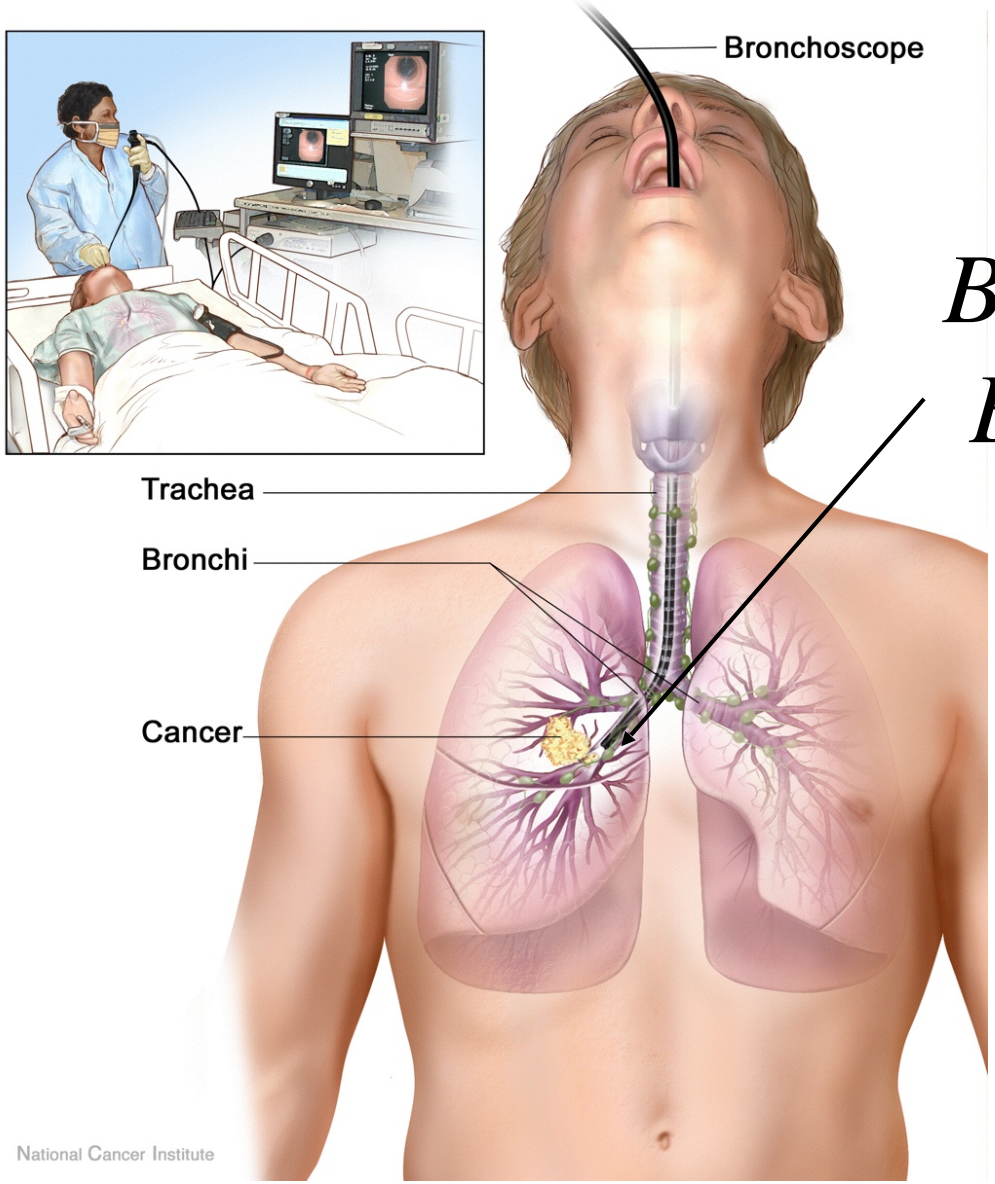

*Bronkialwash**

*Brushbiopsy**

*EBUS**

*EUS**

Biopsy §

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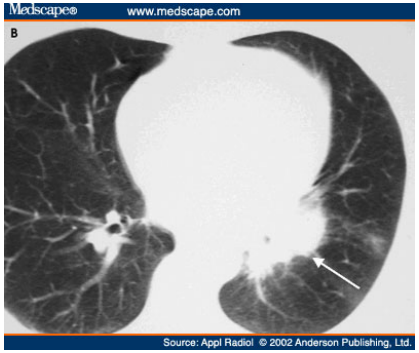
Region Syddanmark
Sygehus Lillebælt



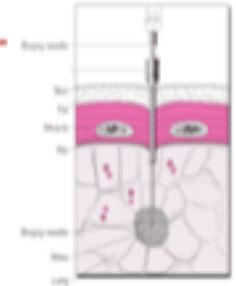
Central tumor

Periferal tumor

Tumor Diagnosis

Bronchial brushing,
Bronchial lavage,
Tissue Biopsi

Fine- or
Course needle
biopsi



Tumor type

Diagnosis of metastases

EBUS
EUS

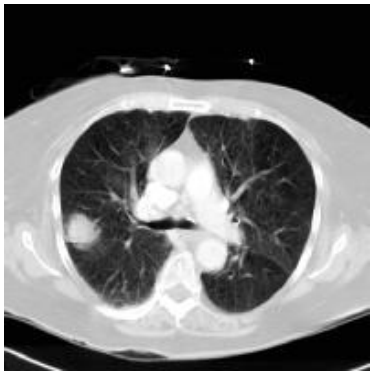
N

M

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

Not operabel

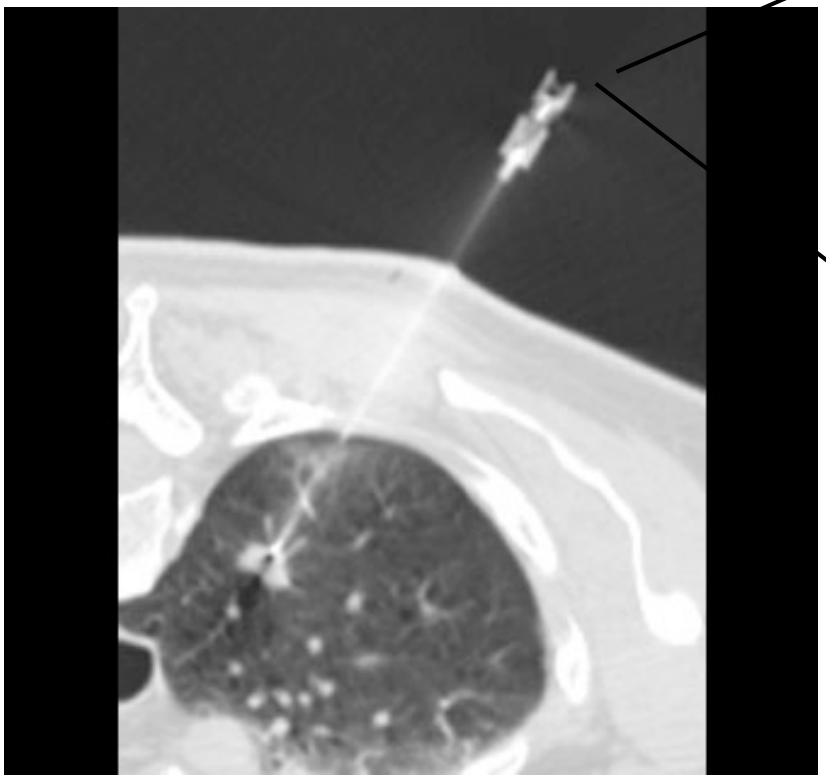
Operabel

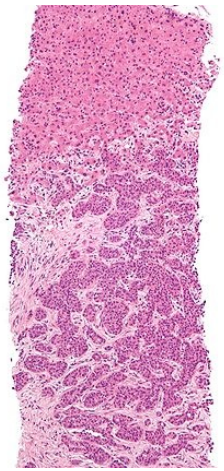


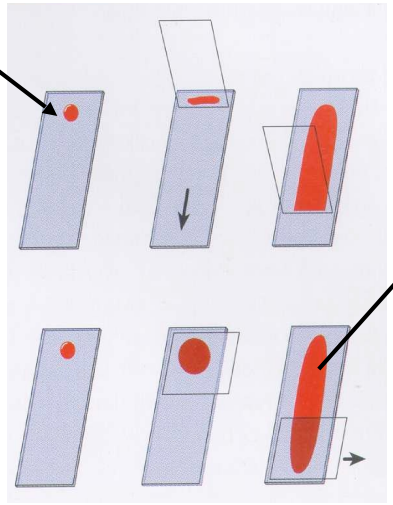
Immunohistochemcal classification of

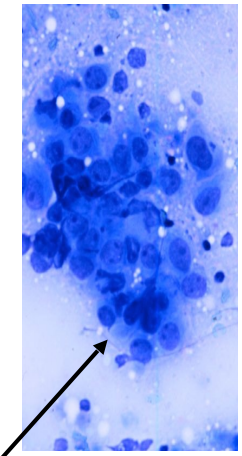
Lung cancer,

diagnosis and prediction.









Immunohistochemcal classification of

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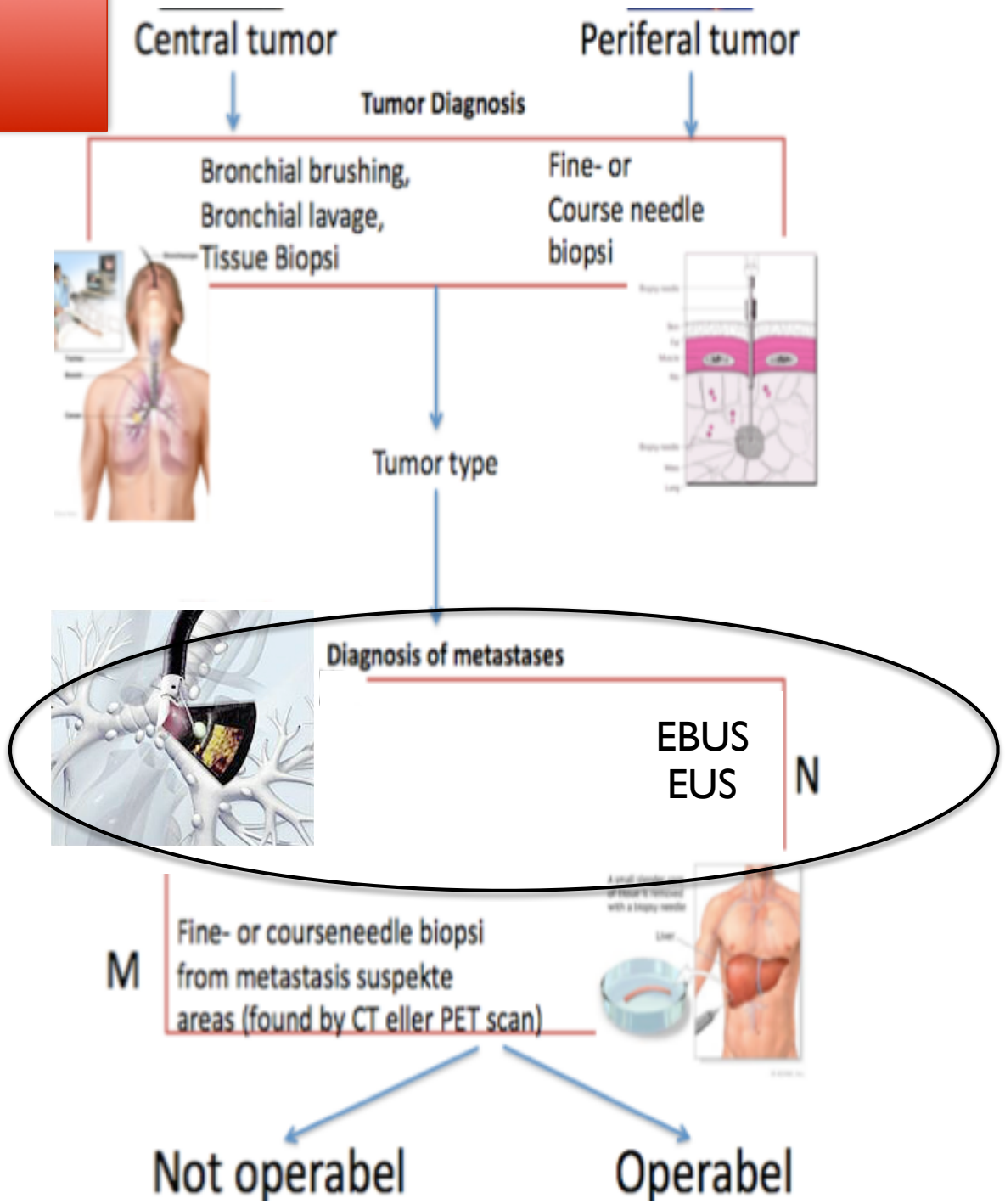
Region Syddanmark
Sygehus Lillebælt



Immunohistochemcal classification of

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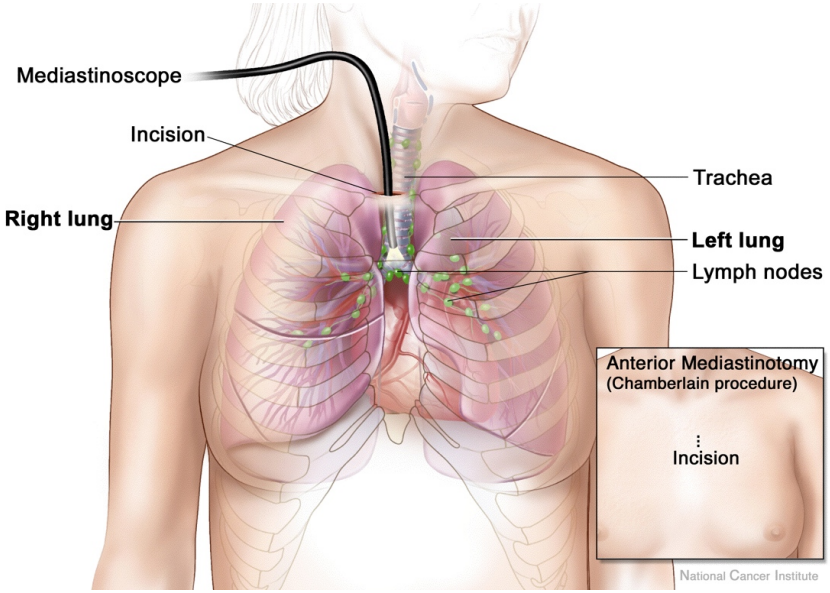
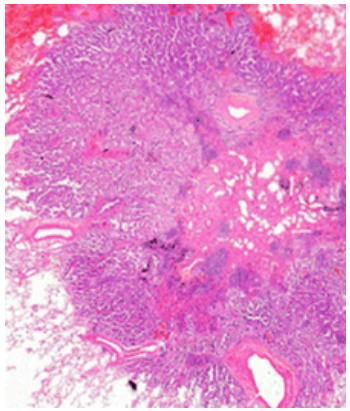
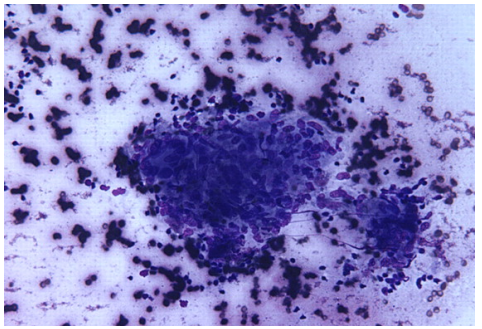
Mediastinoscopy





EBUS, EUS



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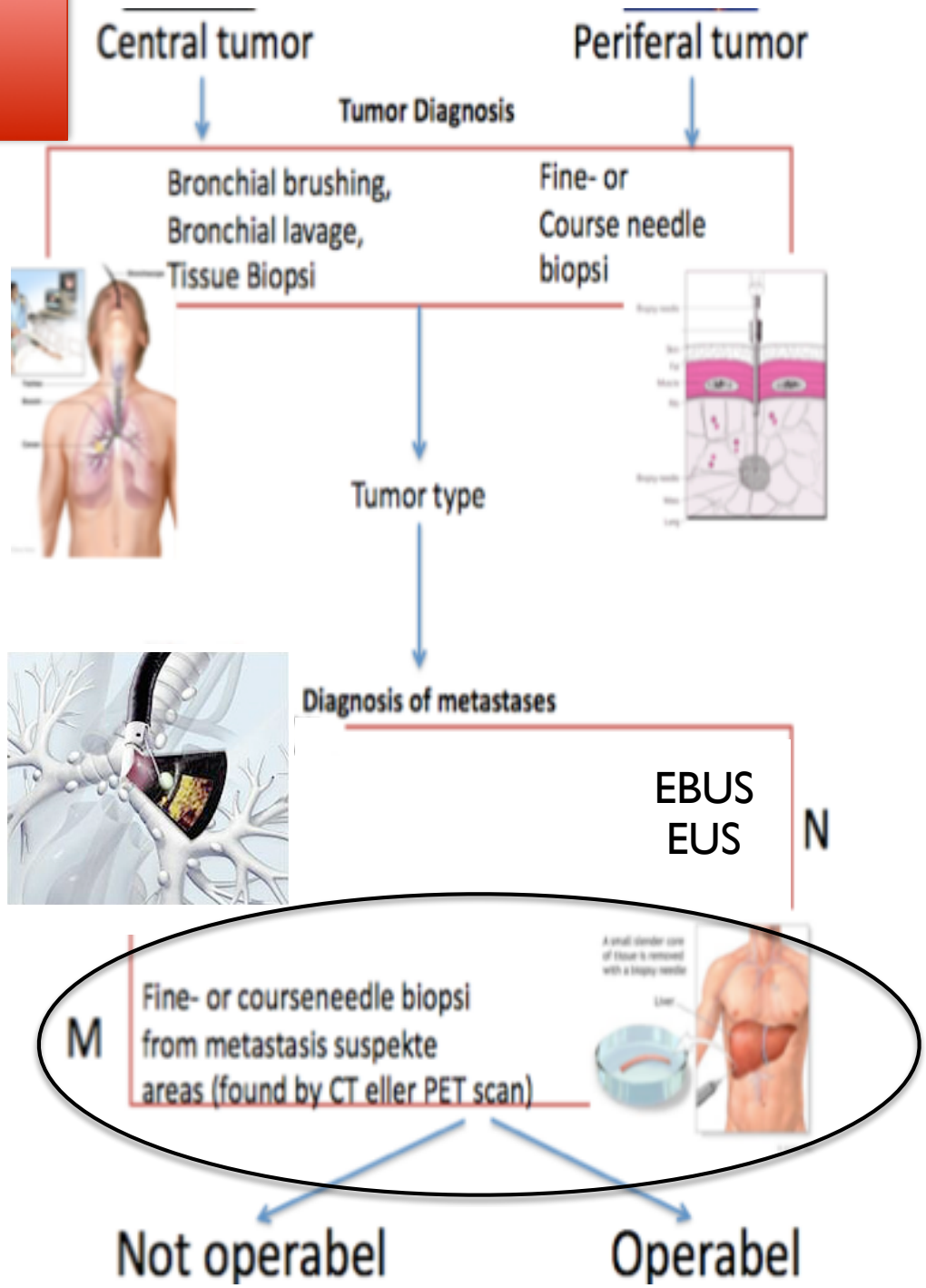

Immunohistochemcal classification of

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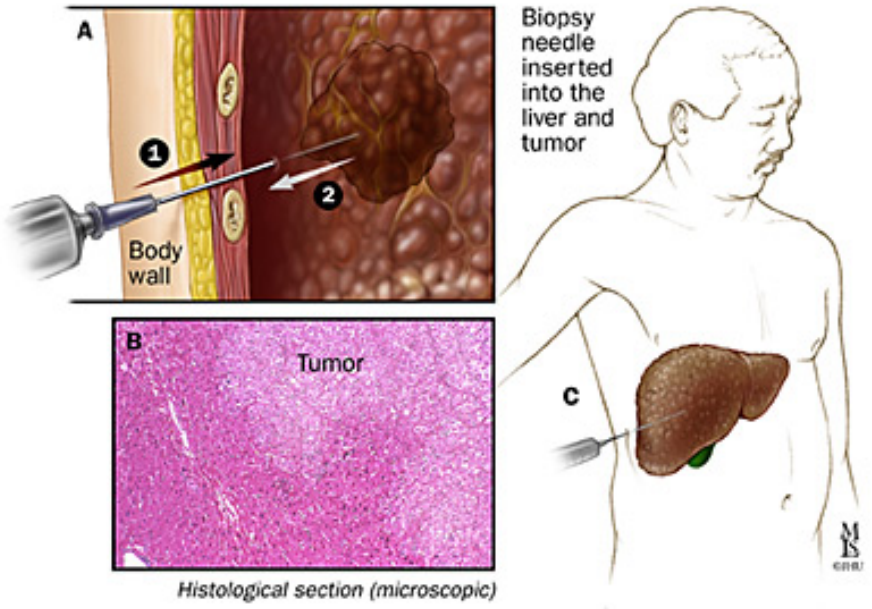
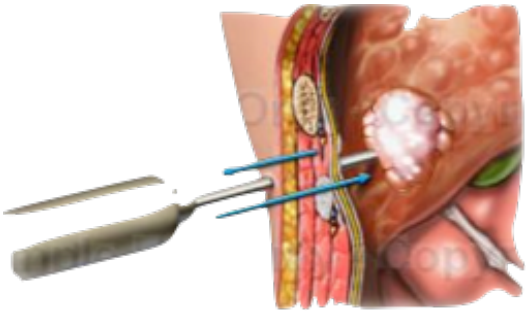
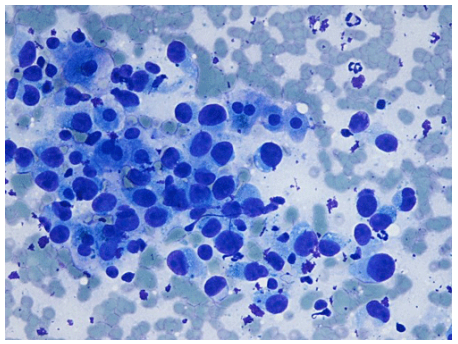
diagnosis and prediction.

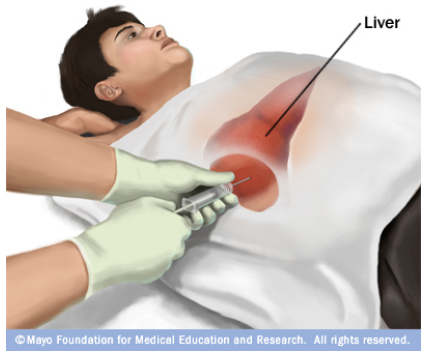
Coarse needle biopsy



Fine needle biopsy







Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

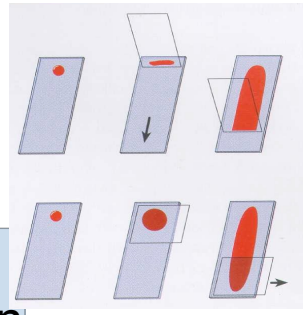
Patoanatomical specimen

Histology

Fixation
Dehydration
Parafinembedding
Microtomy

Præparation

Cytologi

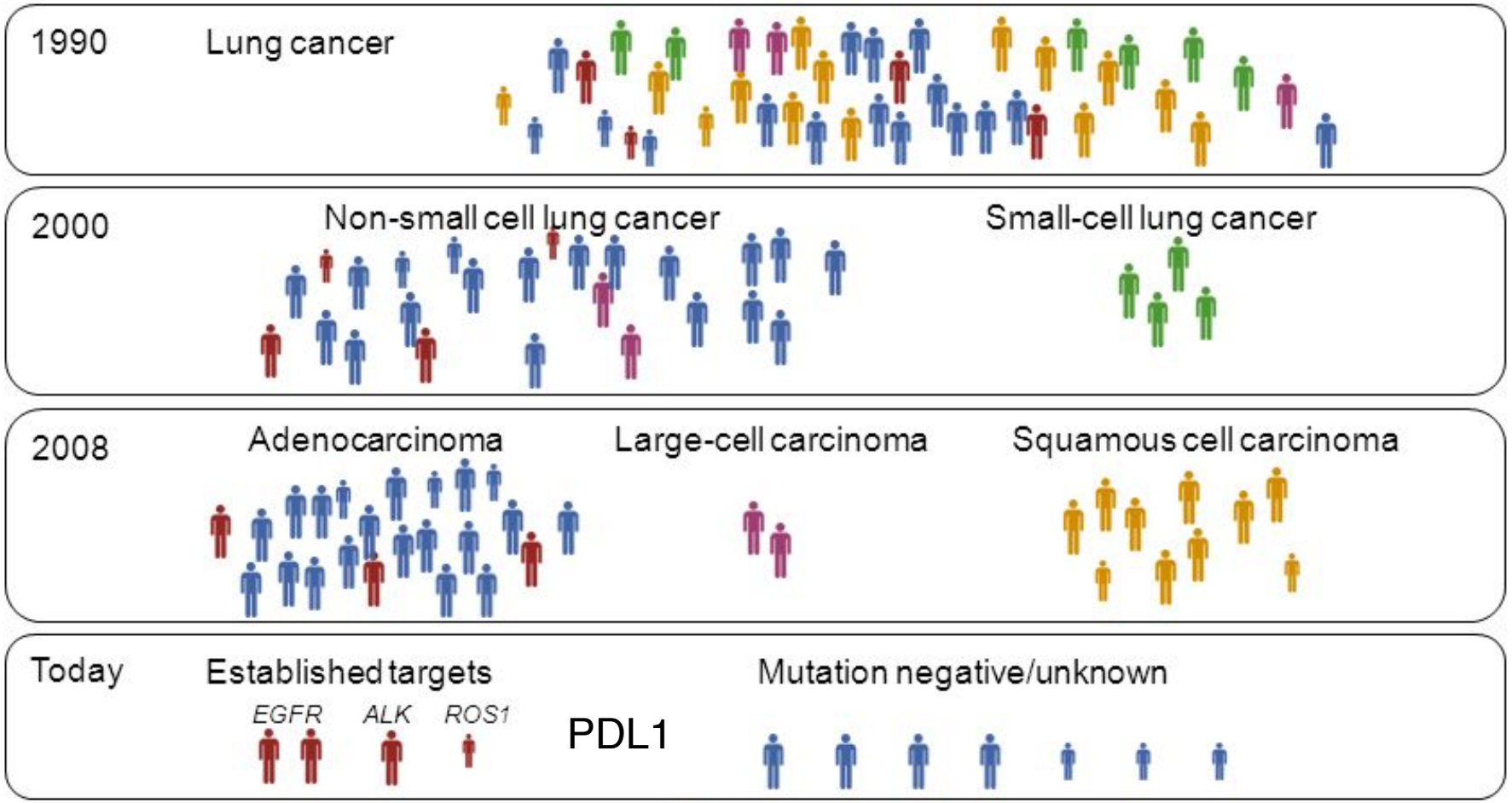


Smear preparation

Visualization

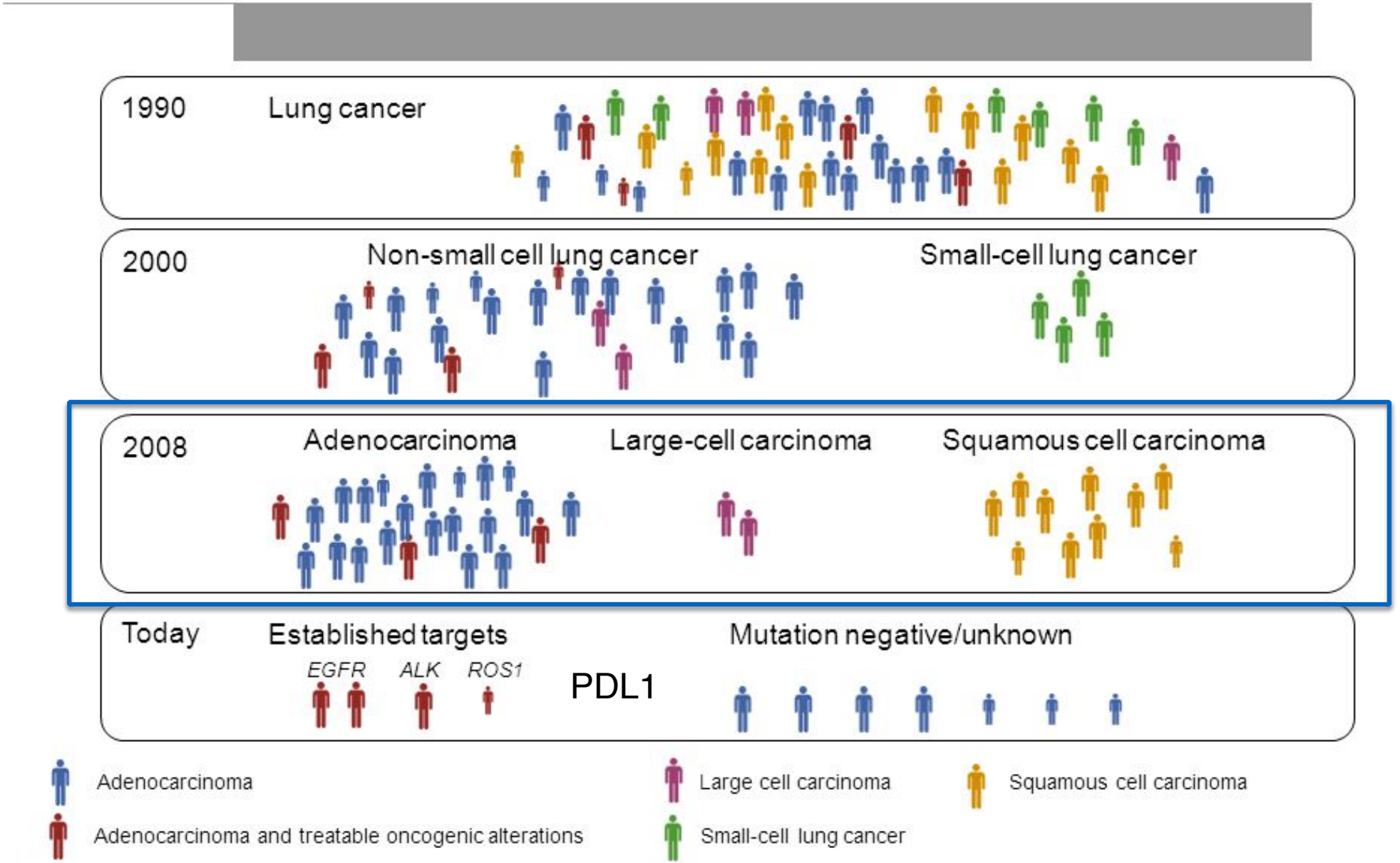
(Staining)

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



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Immunohistochemcal classification of

Lung cancer,

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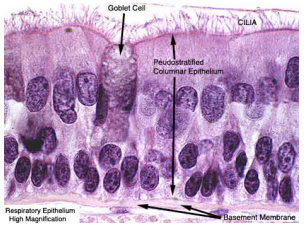
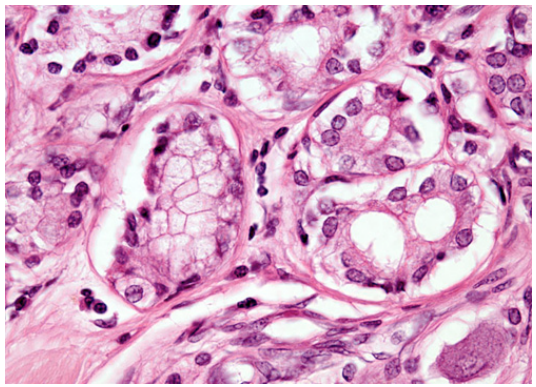
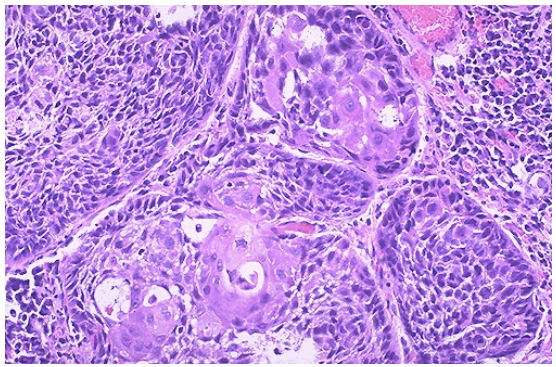
Morphology

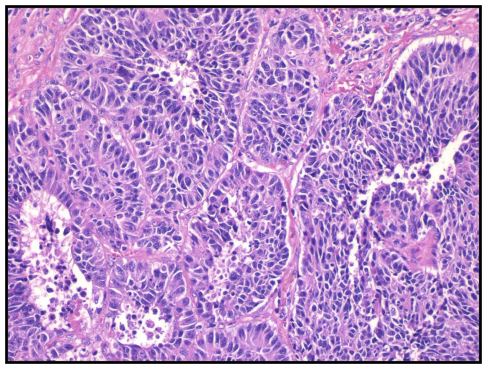




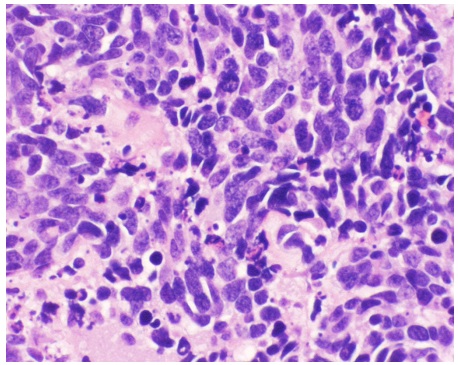
Adenocarcinoma



Squamous carcinoma



Large cell neuroendocrine carc.



Small cell carcinoma

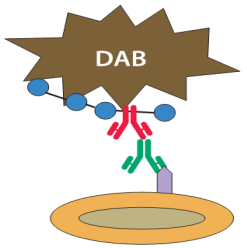
Non Small Cell Lung Carcinoma (NSCLC)

Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

Immunohistochemistry

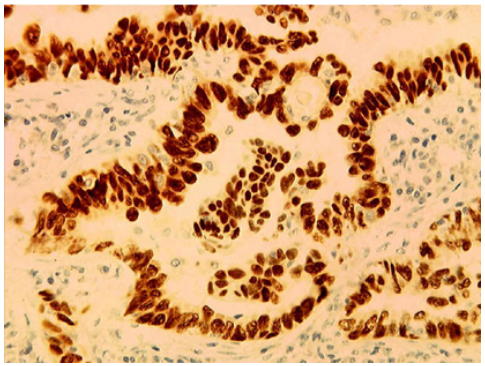


Kromogen (farvestof)

Visualiseringssystem (enzymer)
Sekundært antistof
Primært antistof

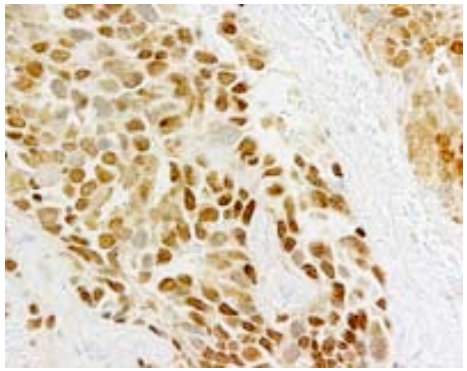
Antigen
Cellens cytoplasma
Cellekerne

ttf1



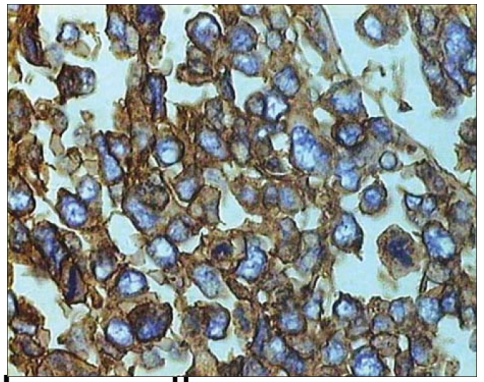
Adenocarcinoma

p63



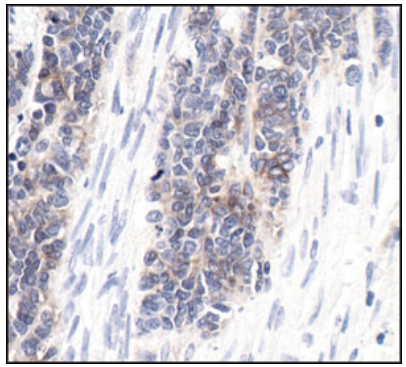
Squamous carcinoma

cd56



Large cell neuroendocrine carc

cd56



Small cell carcinoma

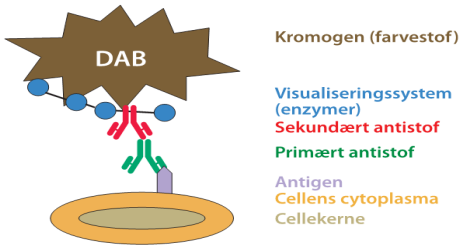
Neuroendocrine carc.

Immunohistochemcal classification of

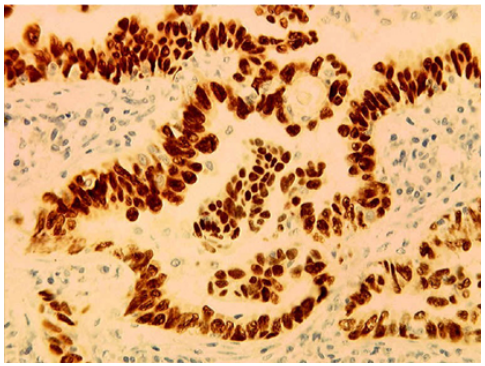
Lung cancer,

diagnosis and prediction.

Immunohistochemistry

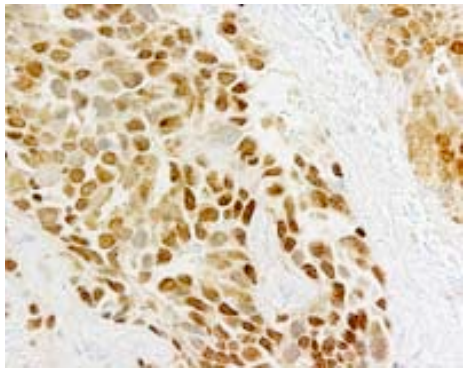


ttf1



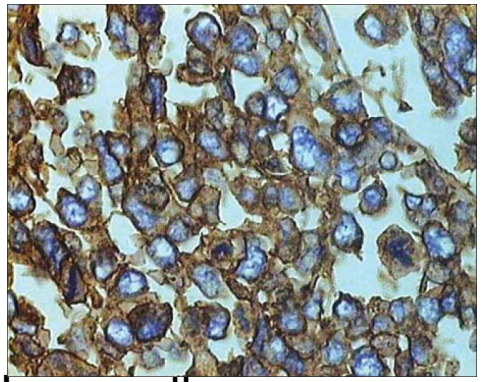
Adenocarcinoma

p63



Squamous carcinoma

cd56



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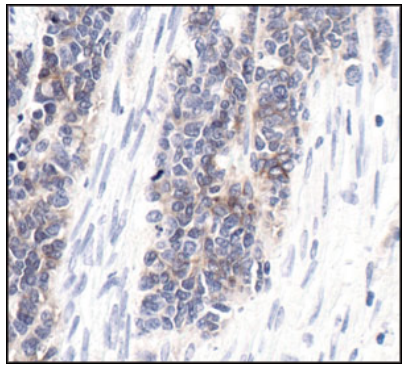

Small cell carcinoma

Non Small Cell Lung Carcinoma (NSCLC)

Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

Algorithm modified from

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Implications of the 2011 International Association for the Study of Lung Cancer/ American Thoracic Society/European Respiratory Society Classification

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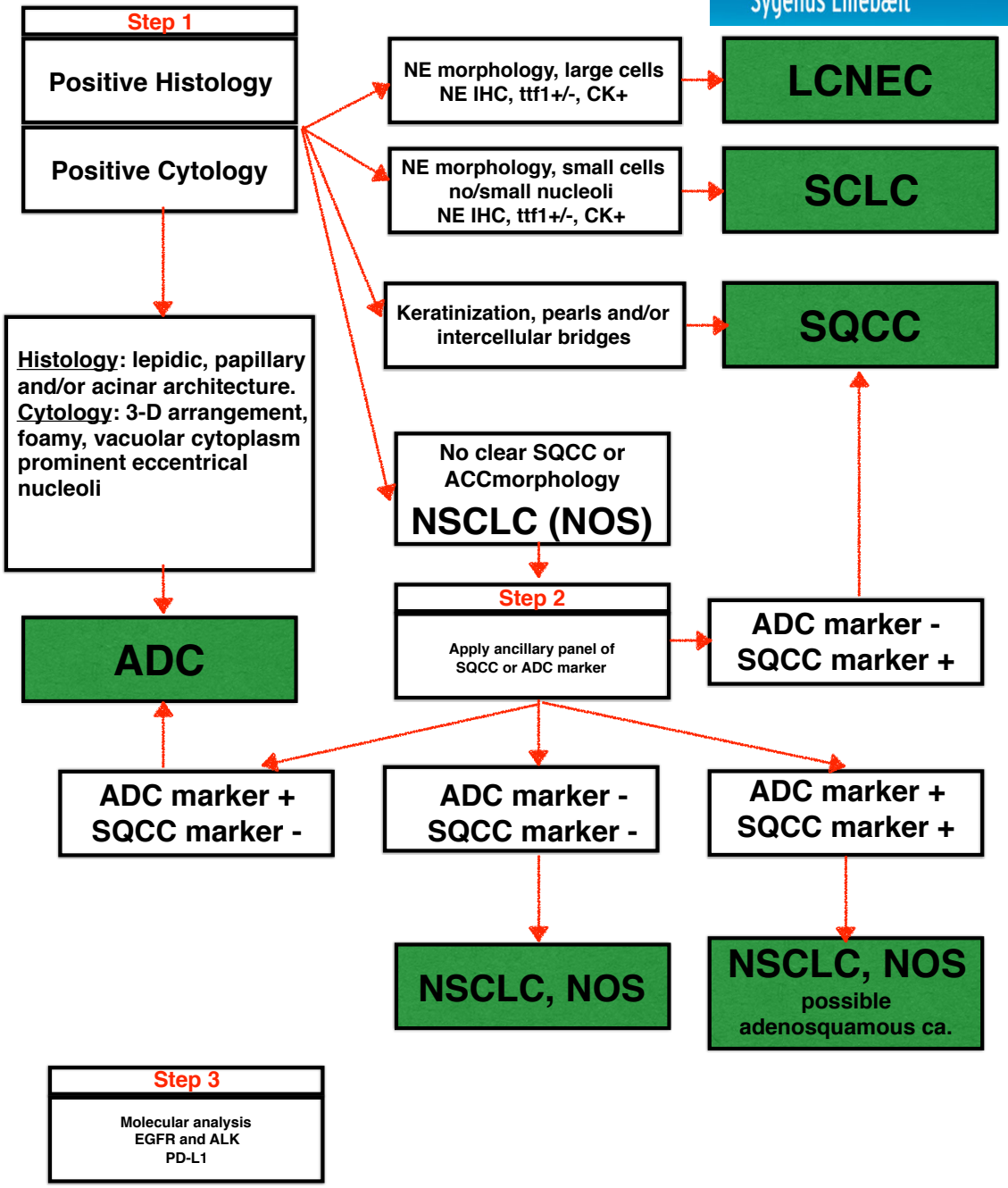
Region Syddanmark
Sygehus Lillebælt



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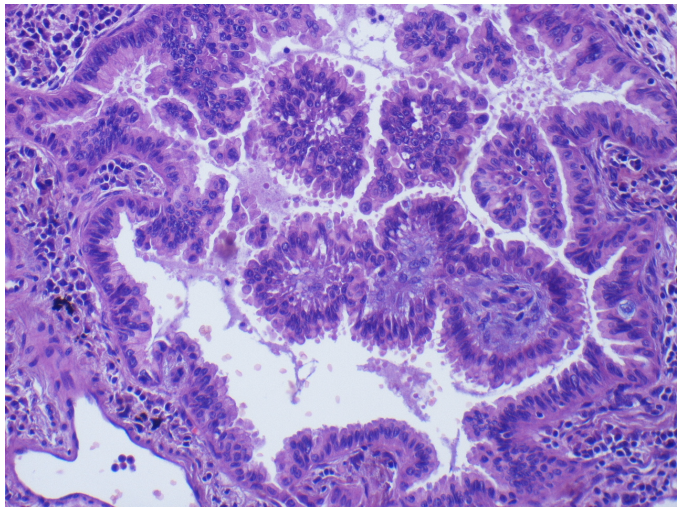

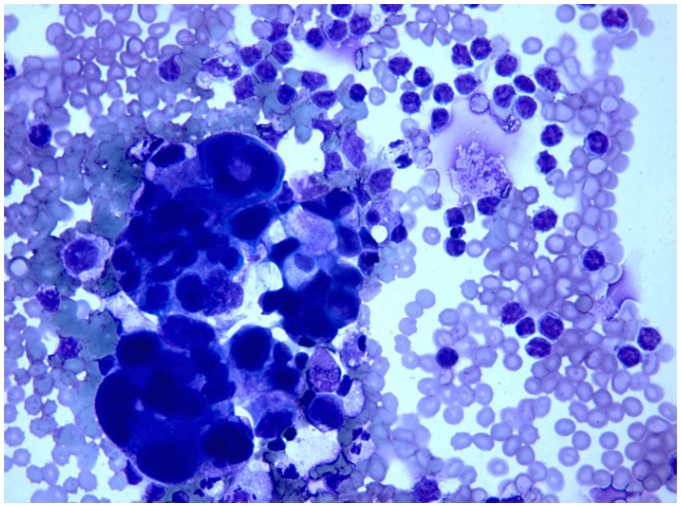

Region Syddanmark
Sygehus Lillebælt

Step 1

Positive Histology

Positive Cytology

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

ADC

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

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 -

ADC marker +
SQCC marker +

NSCLC, NOS

NSCLC, NOS
possible
adenosquamous ca.

Step 3

Molecular analysis
EGFR and ALK

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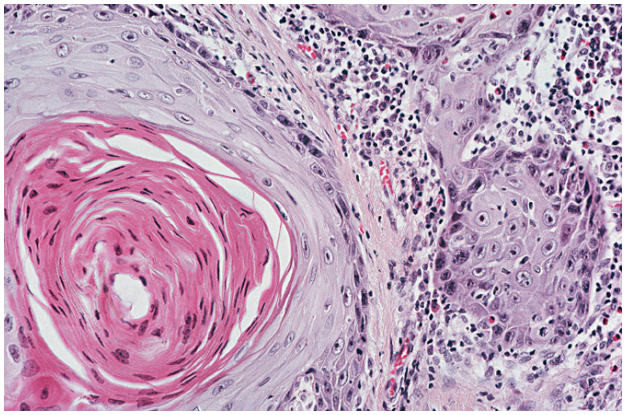

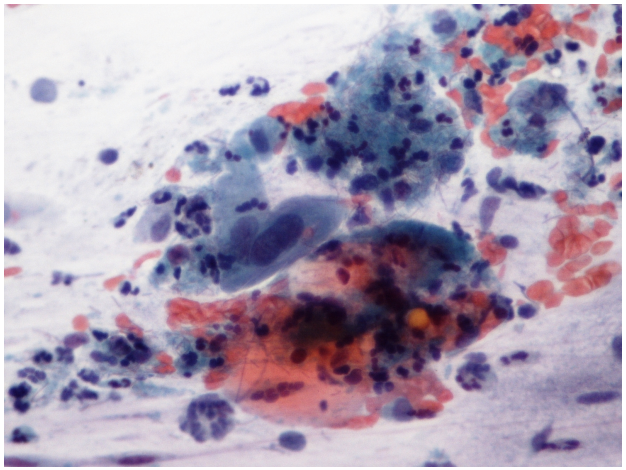

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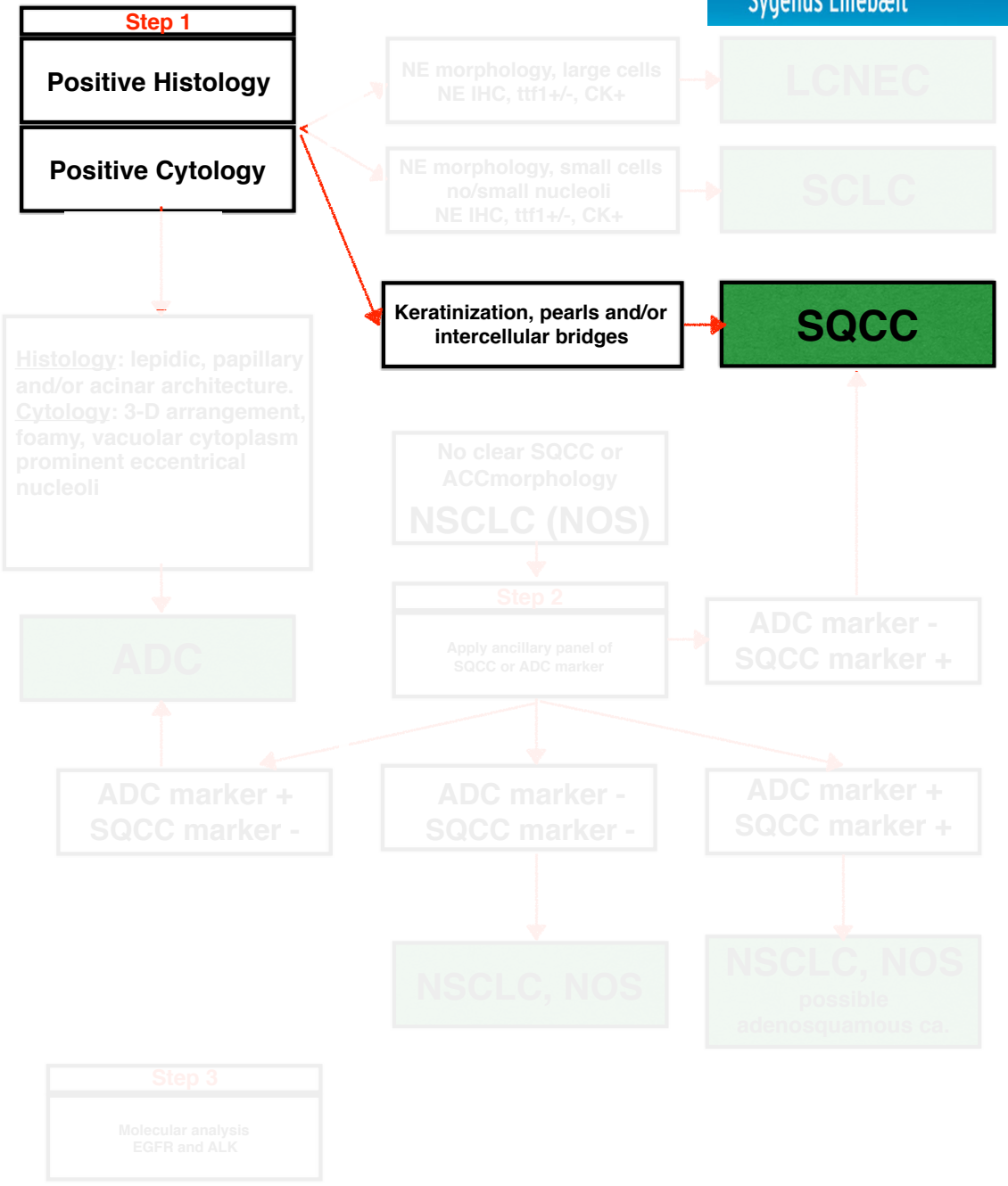

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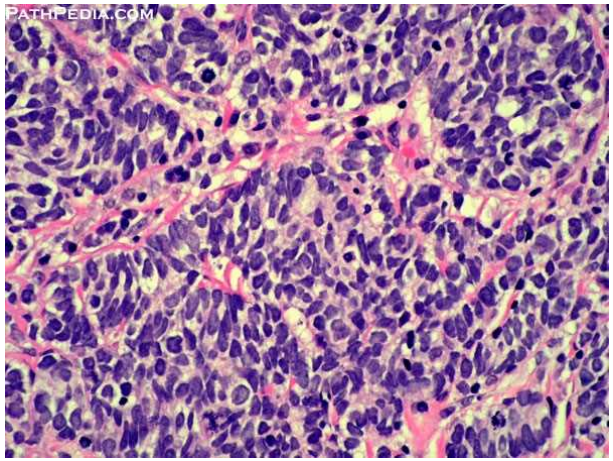

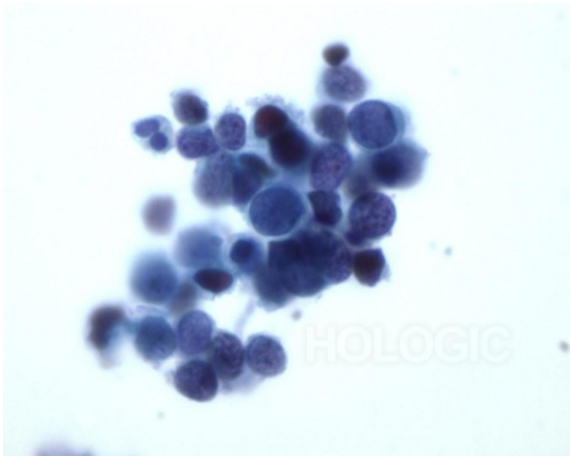

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ADC

ADC marker - SQCC marker +

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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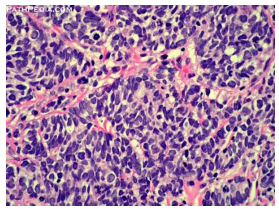
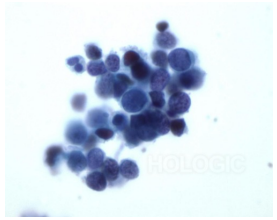
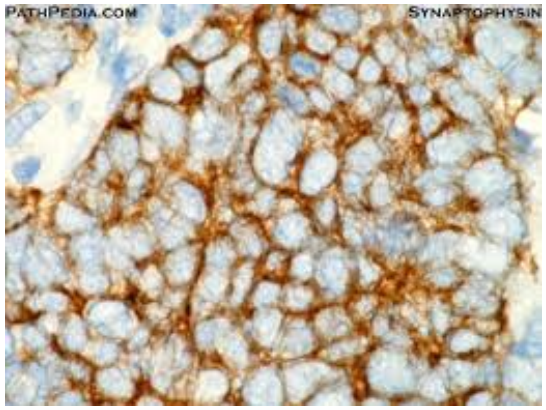
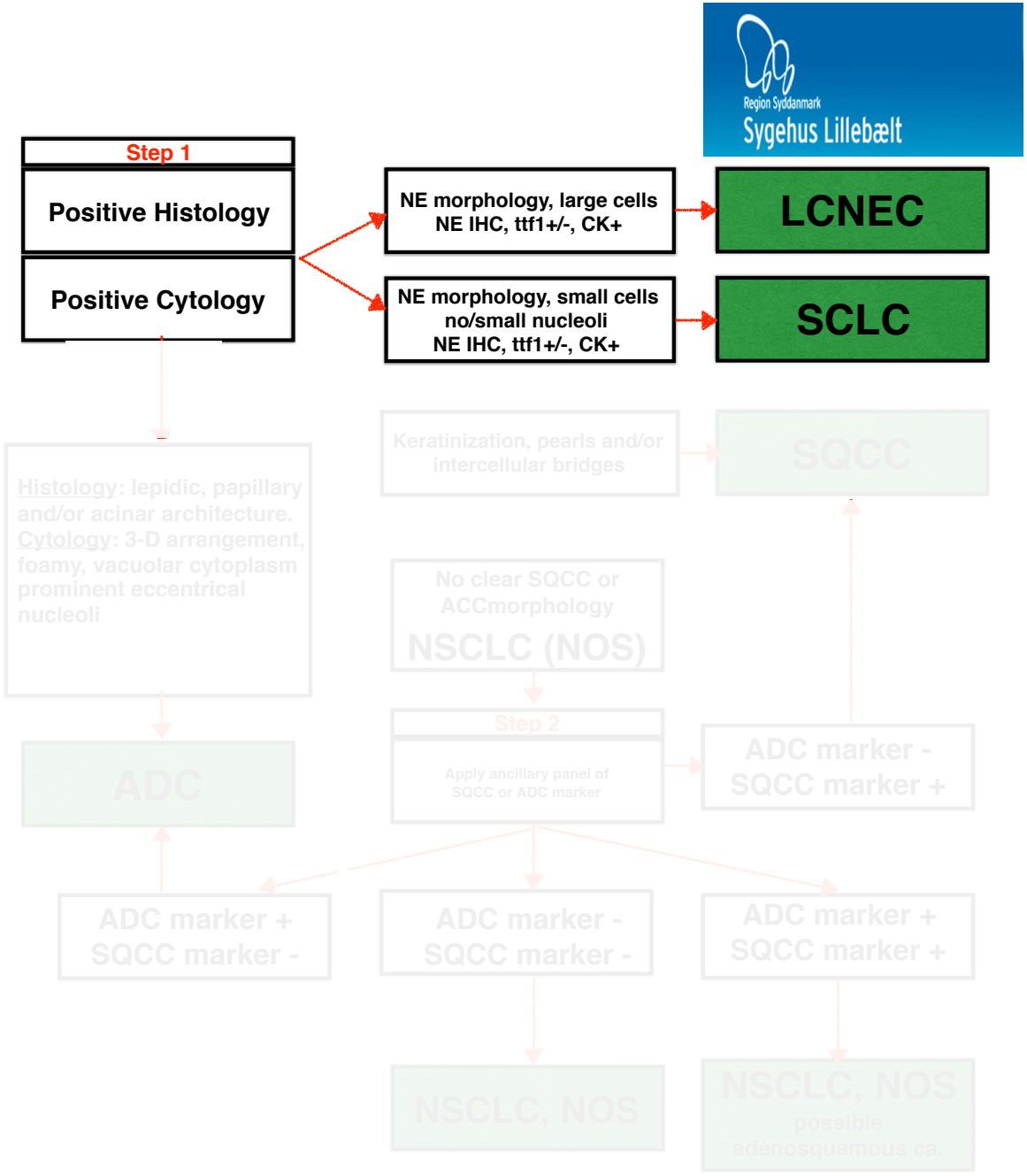




CD56





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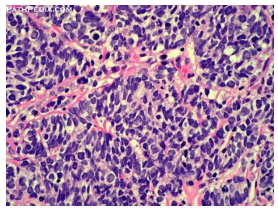
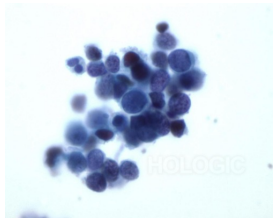
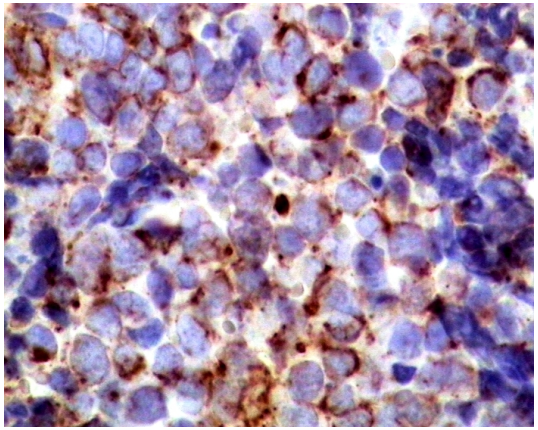
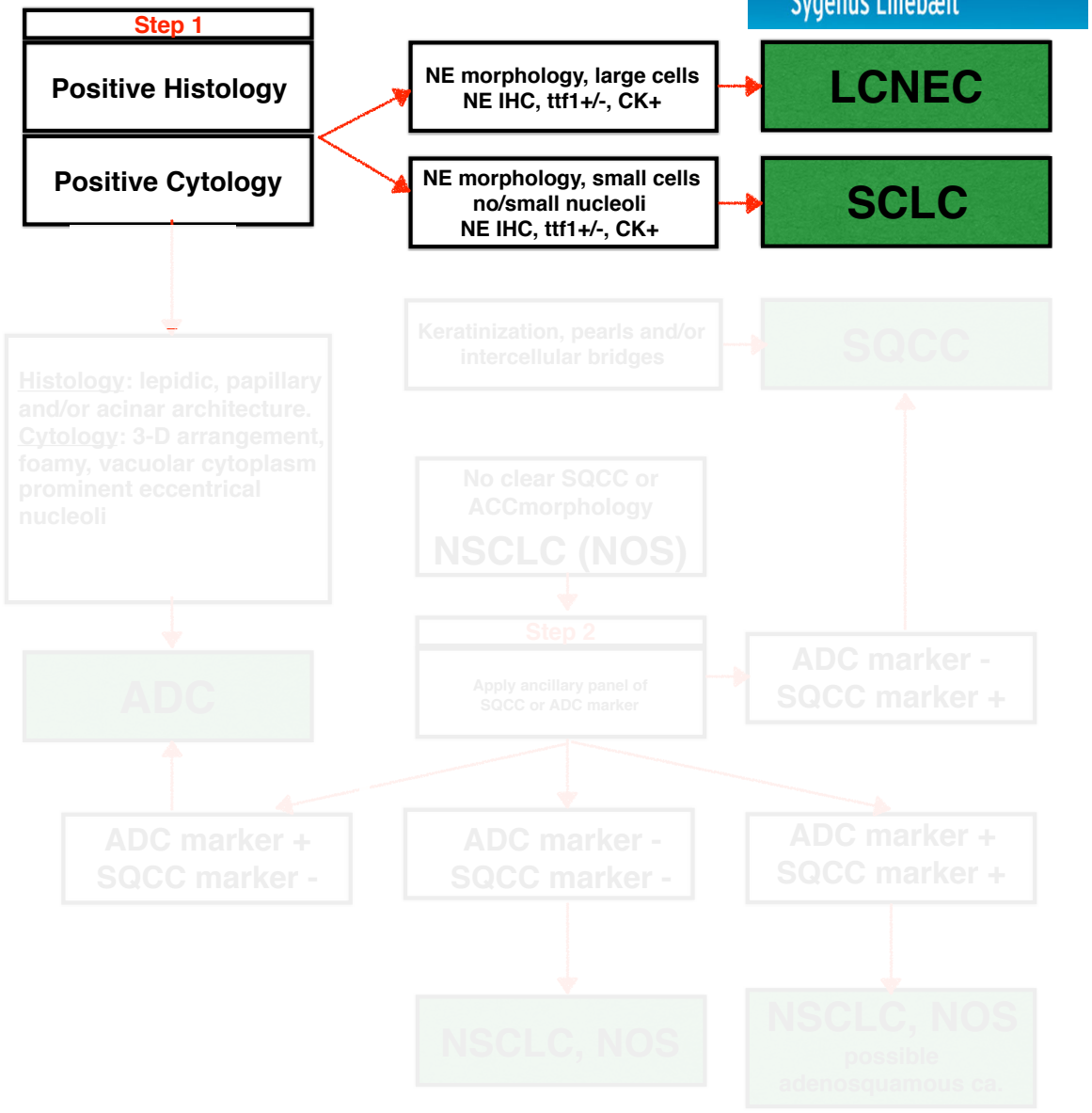




Chromogranin A



Region Syddanmark
Sygehus Lillebælt



Diagnosis of Lung Cancer in Small Biopsies and Cytology

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Immunohistochemcal classification of

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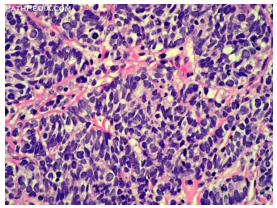
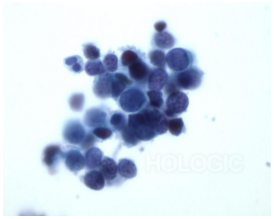
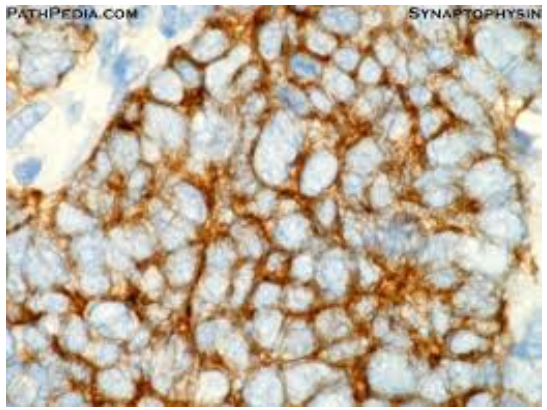
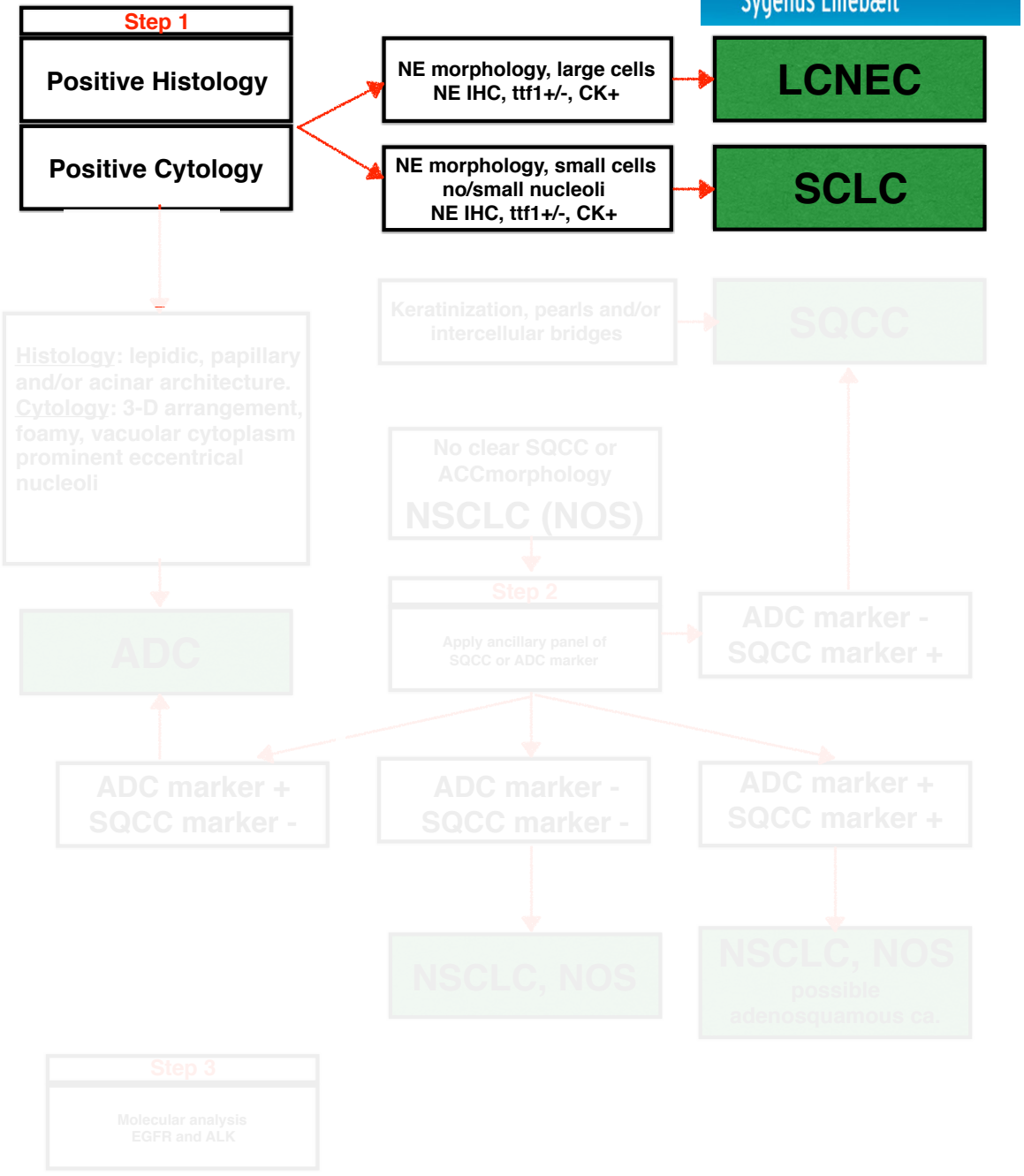




Synaptophysin





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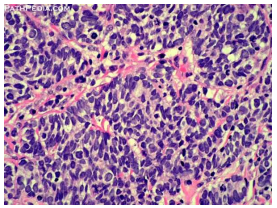
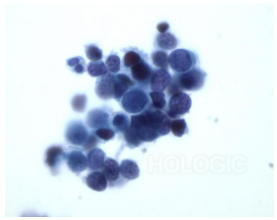
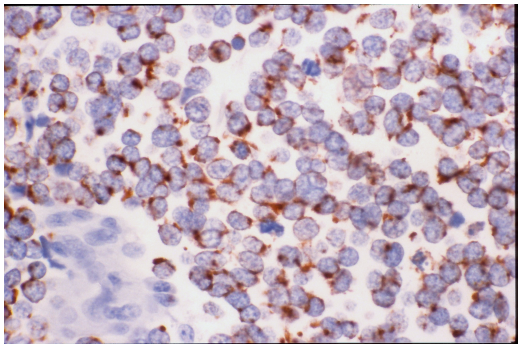
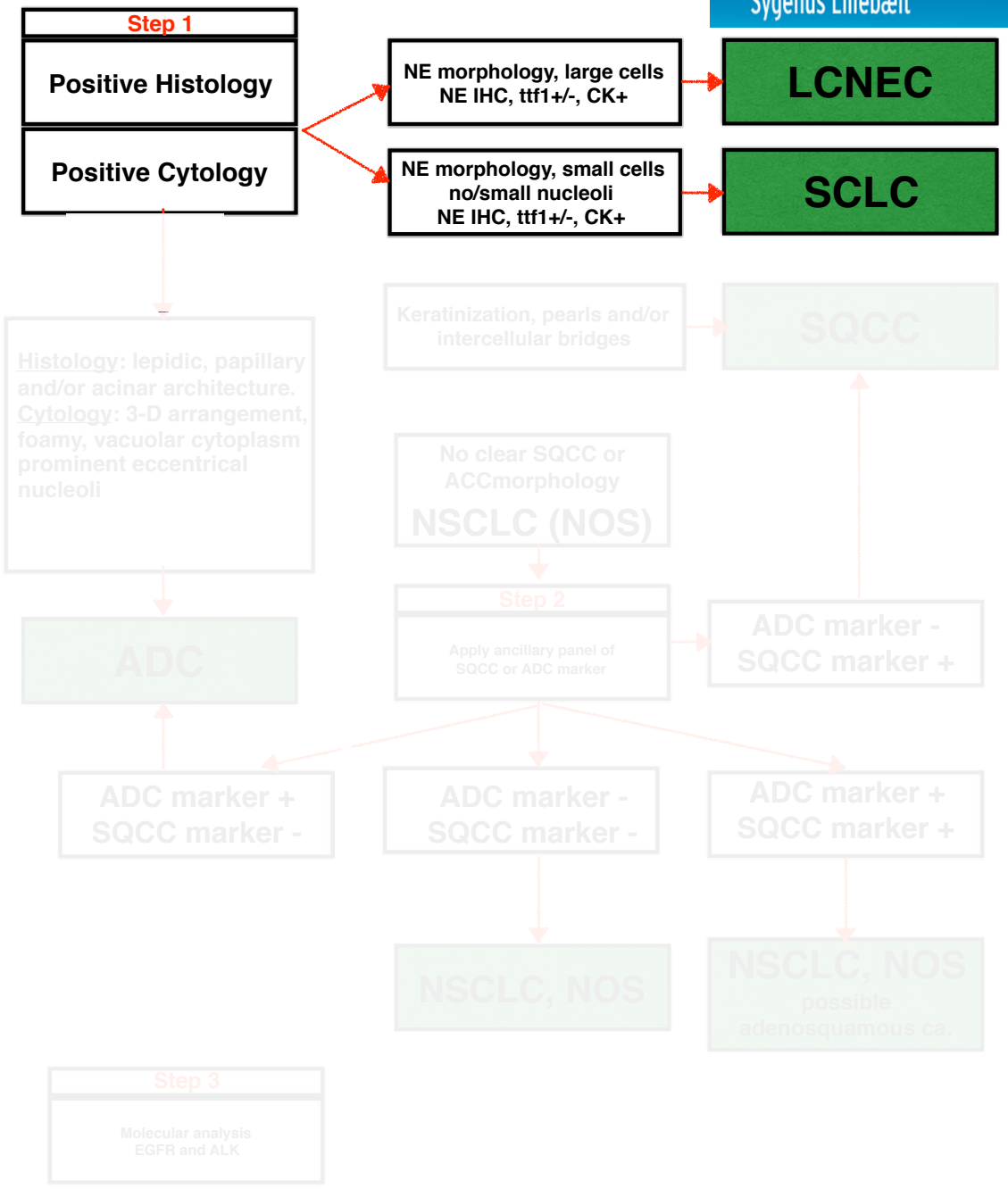




Cytokeratin





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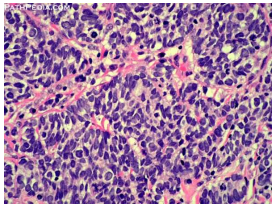
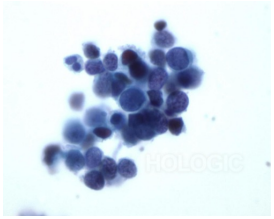
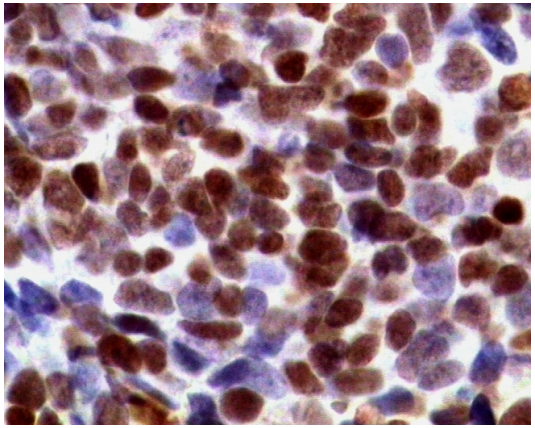




ttf1



Region Syddanmark
Sygehus Lillebælt

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

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

Keratinization, pearls and/or intercellular bridges

SQCC

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 -

ADC marker + SQCC marker +

NSCLC, NOS

NSCLC, NOS
possible adenosquamous ca.

Step 3

Molecular analysis
EGFR and ALK

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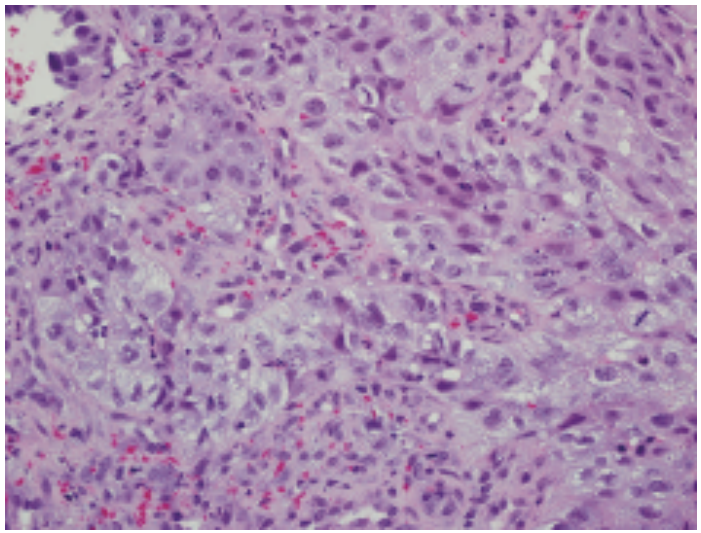

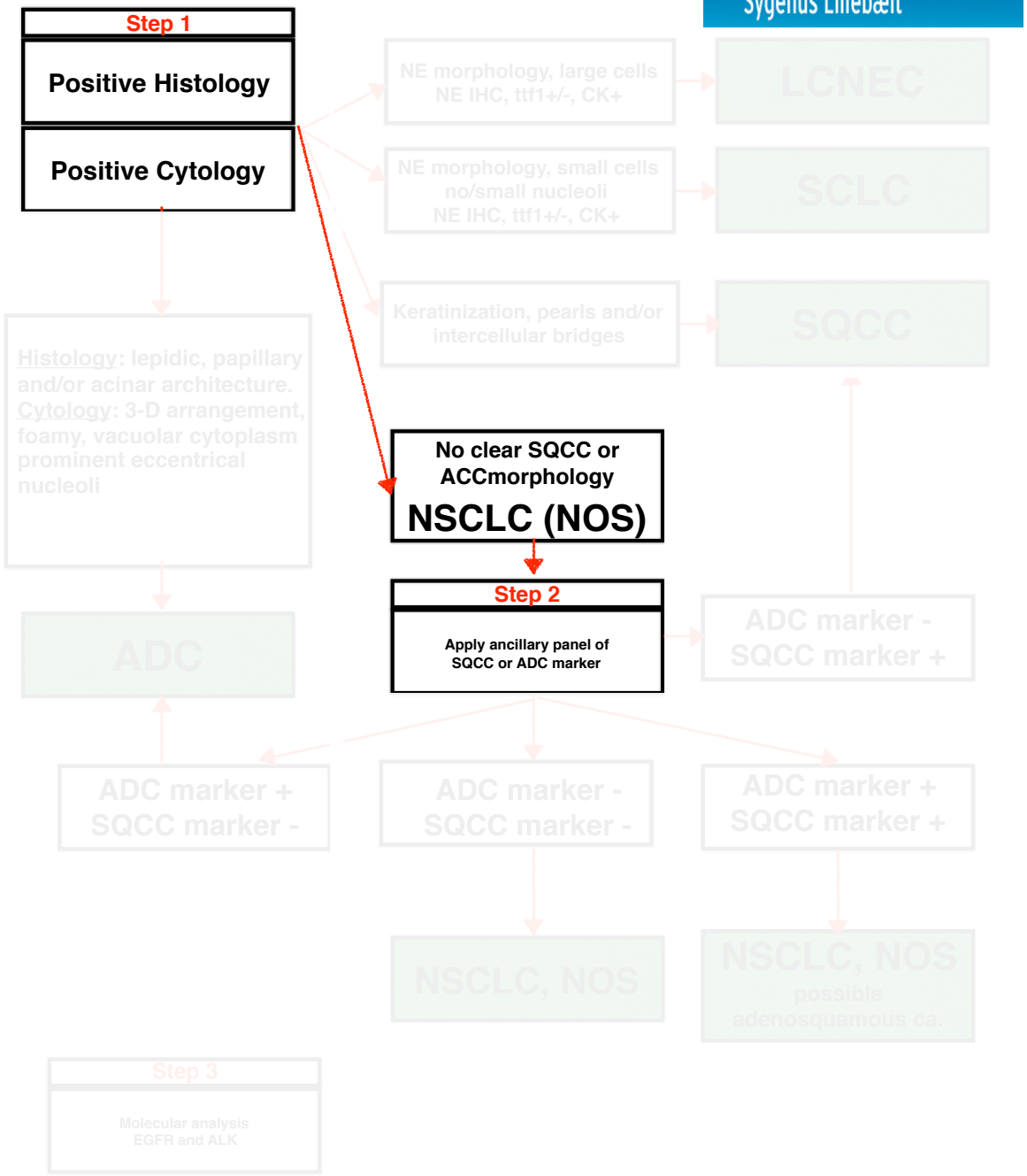

Immunohistochemcal classification of

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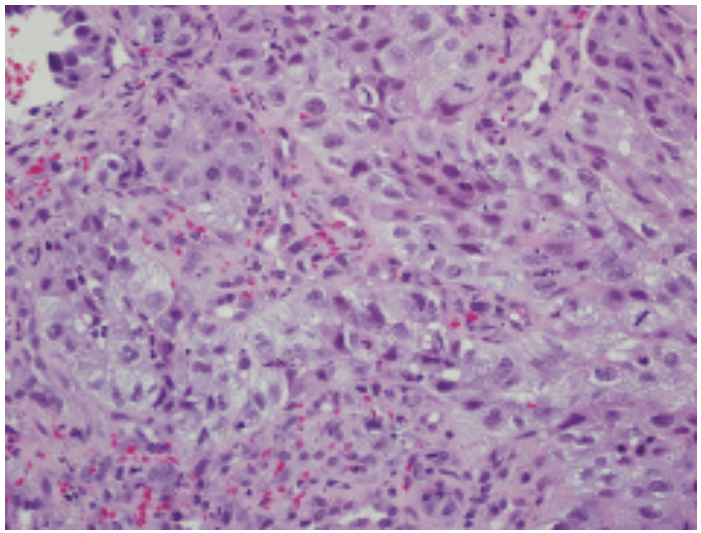
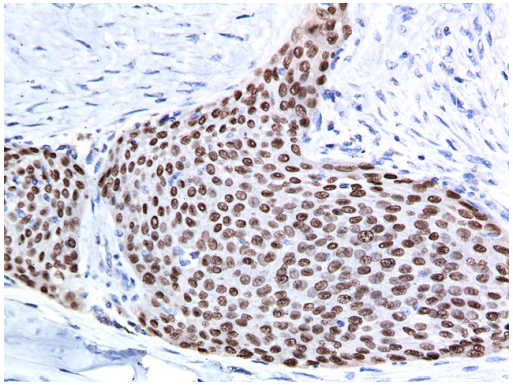
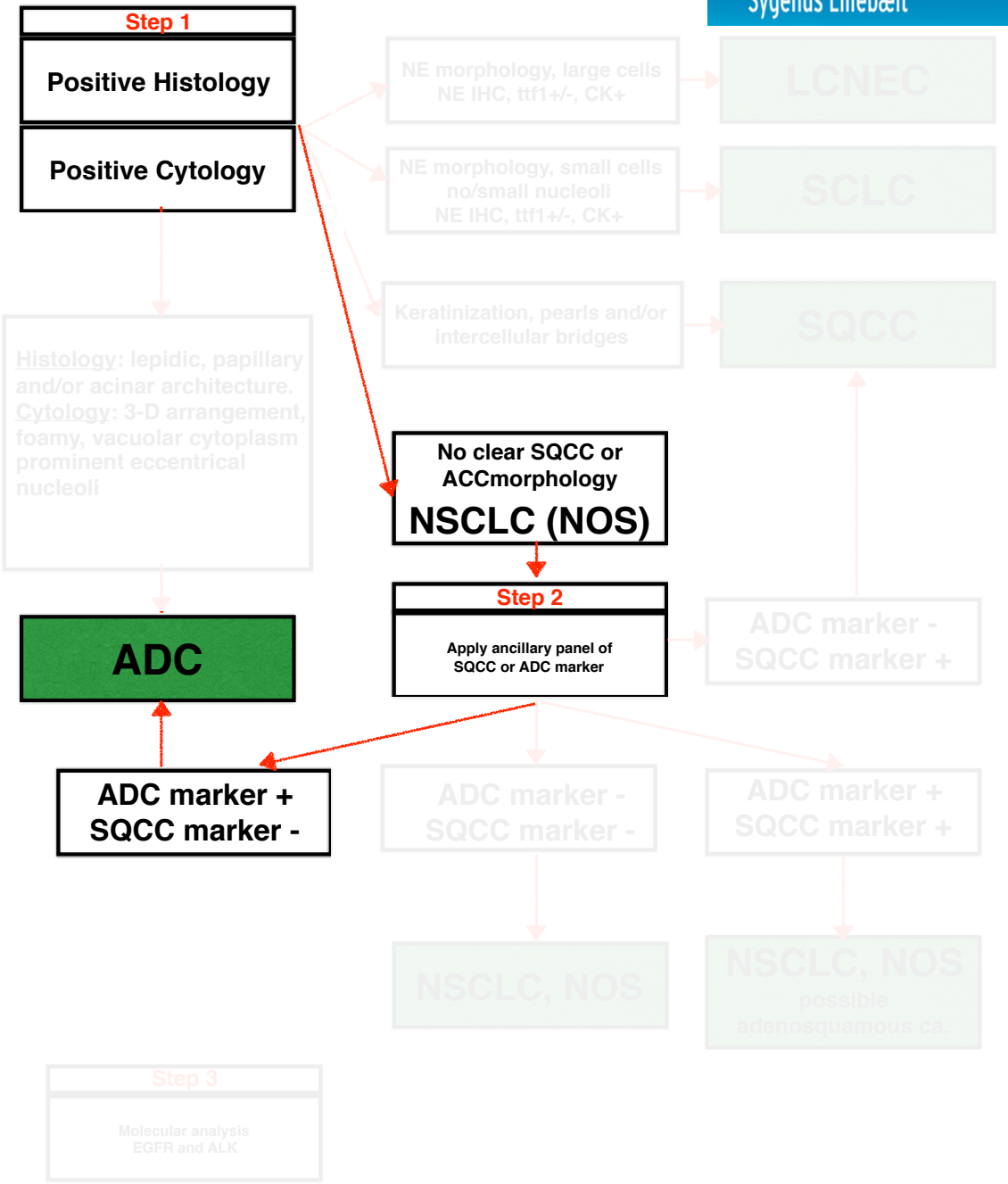




ttf1 +

(+Cytokeratin 7)



Immunohistochemcal classification of

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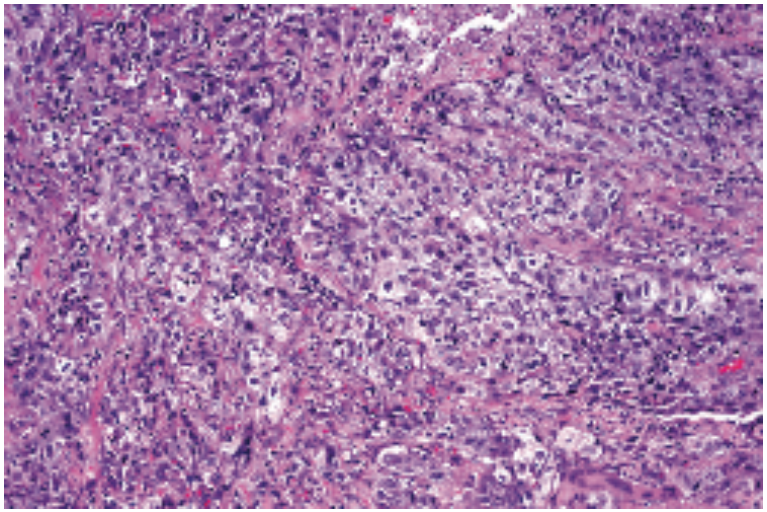
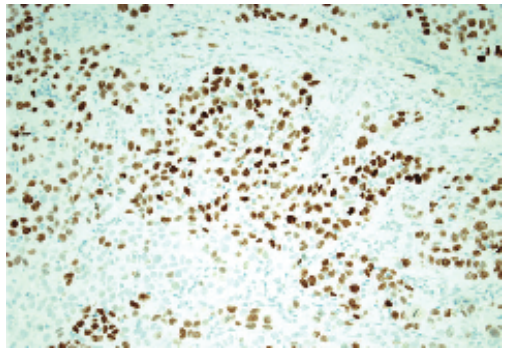
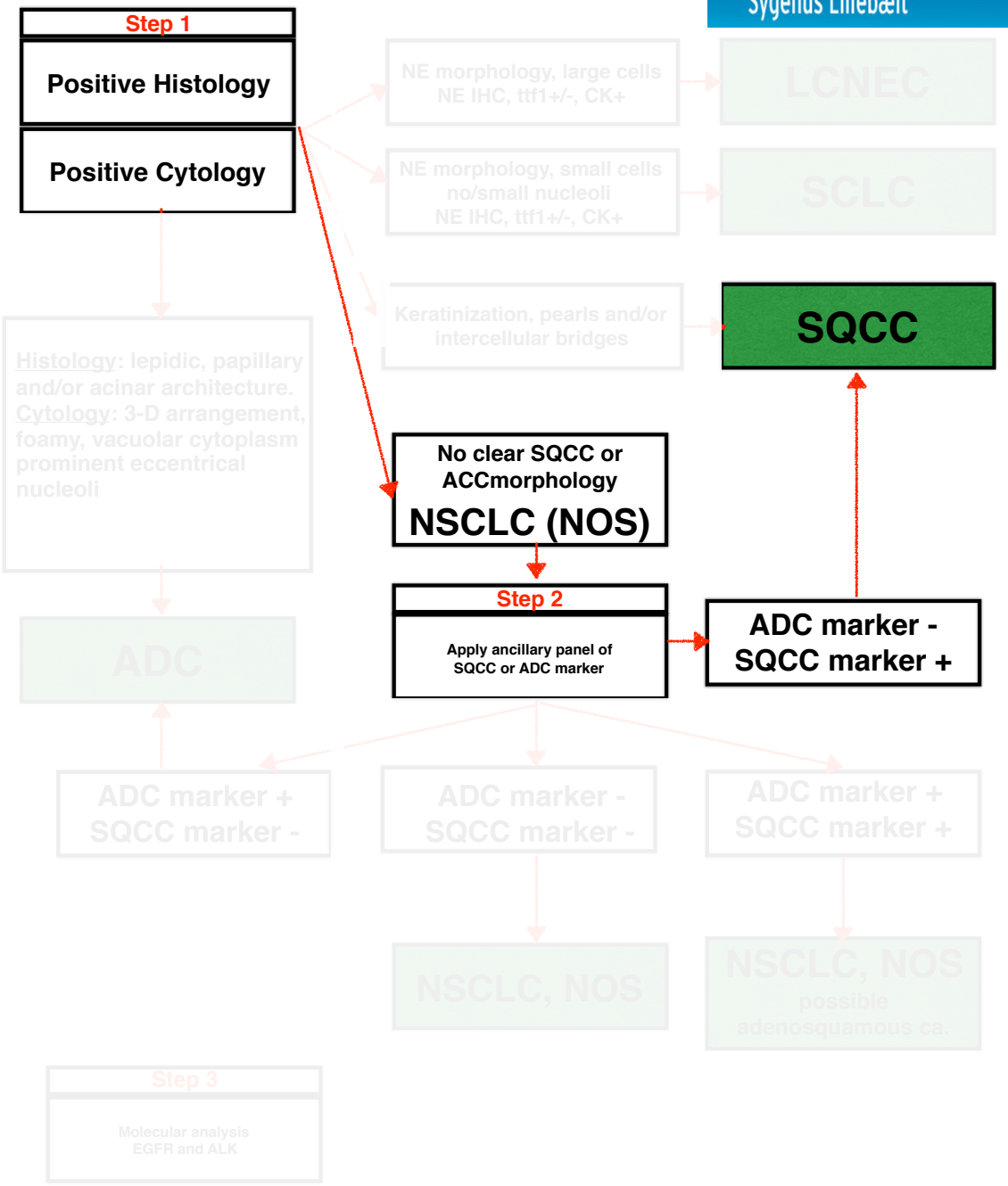




P63+ (+Cytokeratin 5/6)

Region Syddanmark
Sygehus Lillebælt



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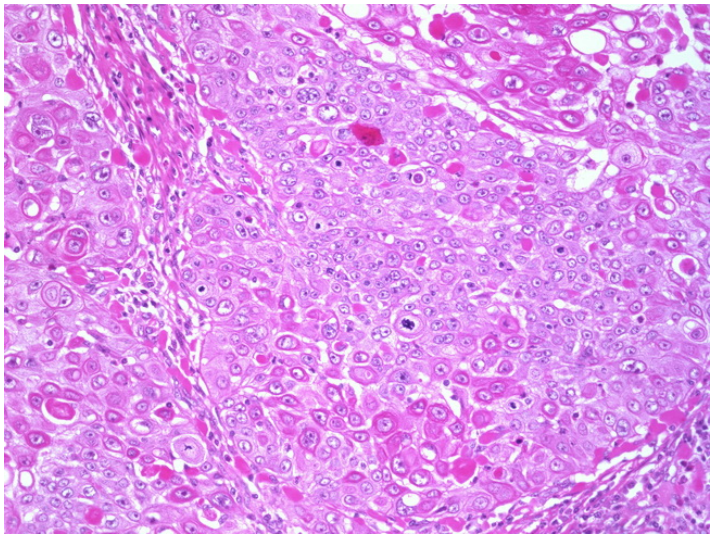
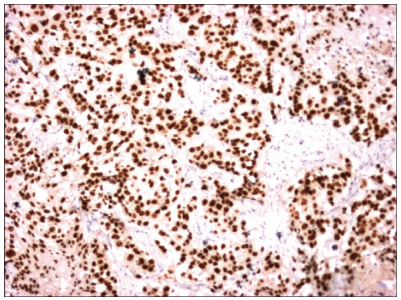
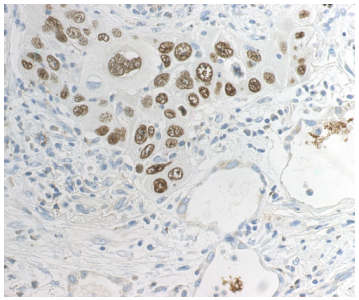




ttf1+



P63+

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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 -

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SQCC marker -

ADC marker +
SQCC marker +

NSCLC, NOS

NSCLC, NOS
possible
adenosquamous ca.

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EGFR and ALK

Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

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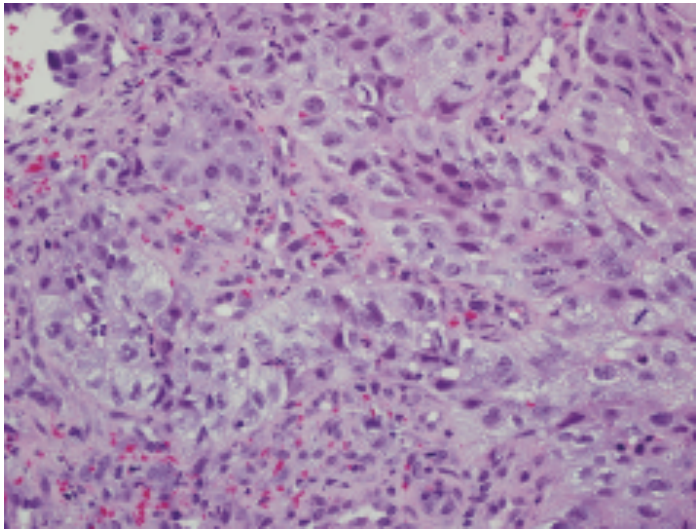
Sygehus Lillebælt



CK7

ttf1

Napsin

CK5/6

P63

Adenocarcinoma

Immunohistochemcal classification of

Lung cancer,

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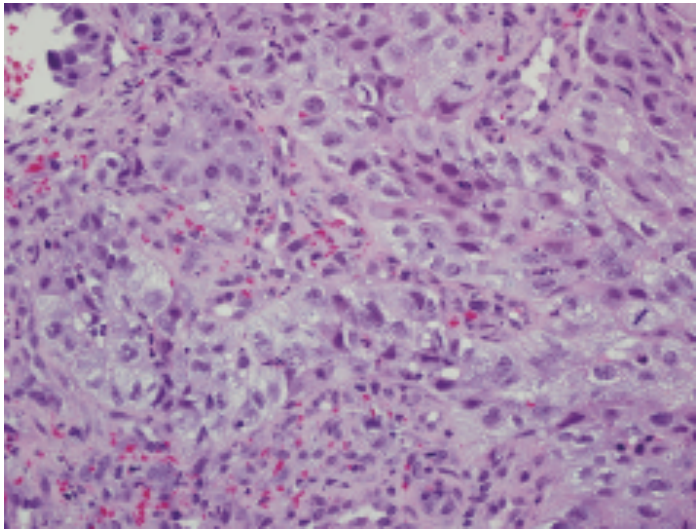
Region Syddanmark
Sygehus Lillebælt



CK7

ttf1

Napsin

CK5/6

P63

Squamous carcinoma

Immunohistochemcal classification of

Lung cancer,

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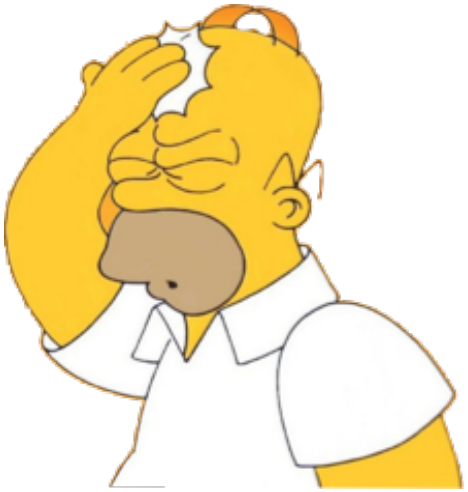
Problems:

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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Immunohistochemcal classification of

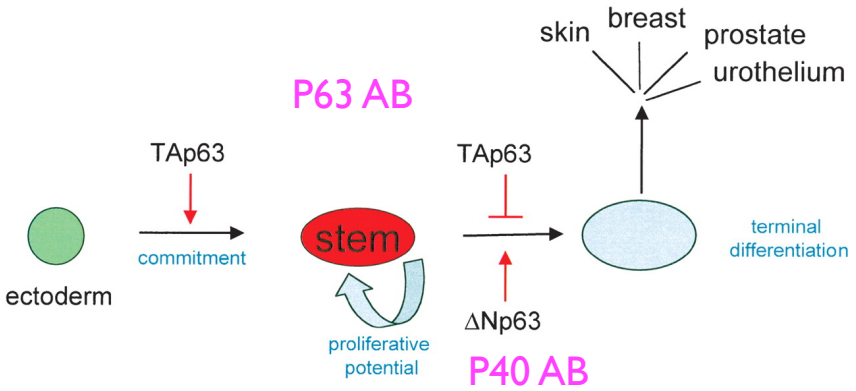
Lung cancer,

diagnosis and prediction.

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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NordiQC

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Region Syddanmark
Sygehus Lillebælt

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.

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

Original Article

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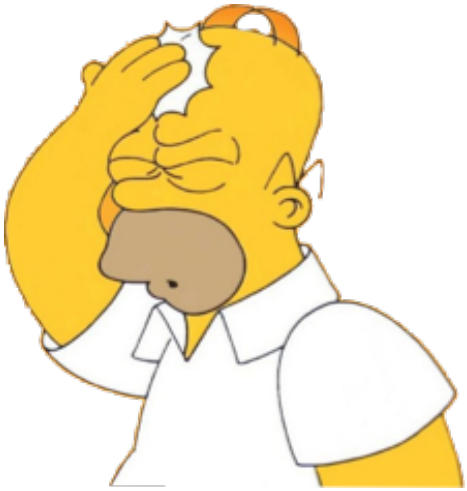

Differential diagnosis between primary and metastatic carcinoma

Other (adeno) carcinomas are positive for ttf1

NordiQC

Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

Region Syddanmark
Sygehus Lillebælt

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

Published in final edited form as:
Appl Immunohistochem Mol Morphol. 2010 March ; 18(2): 142–149. doi:10.1097/PAI.0b013e3181bdf4e7.

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.

Immunohistochemcal classification of

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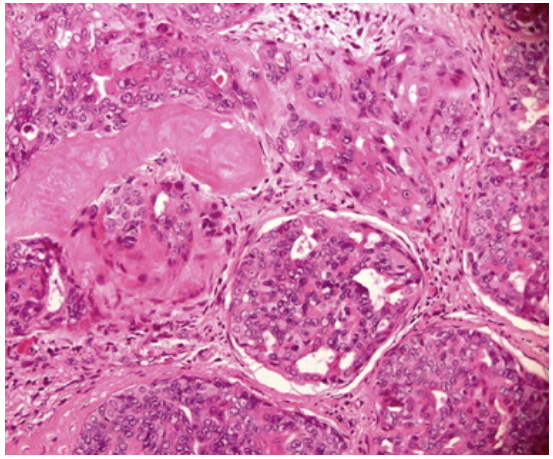
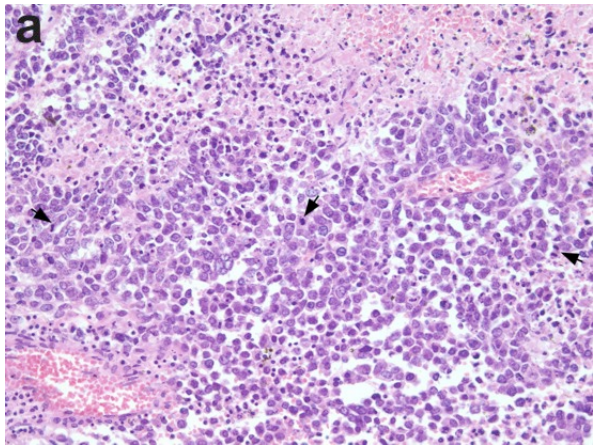
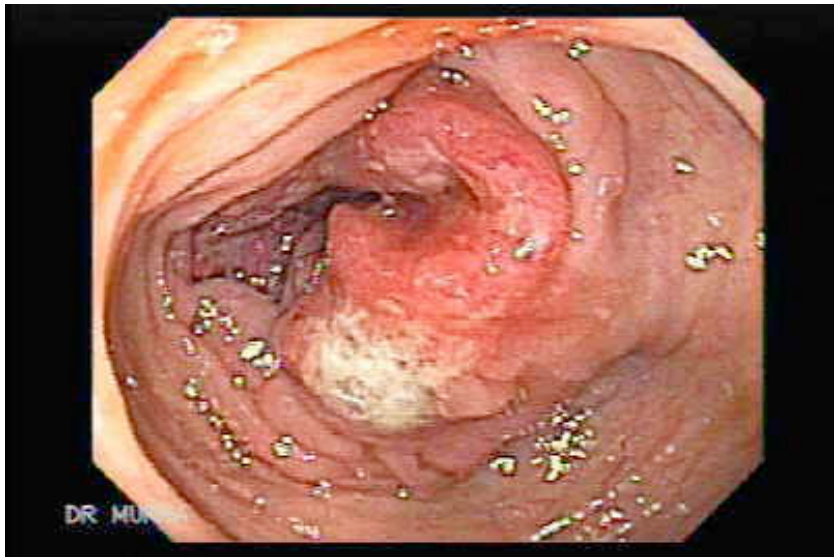
Diagnosis of metastasis to the lung





AE1/AE3 ←
CK7
ttf1
Napsin
CK20 ←
cdx2 ←
ER
GCDFP15
PSA
Vim
CK5/6
P63
CD10
RCC
Ca125
PAX8
WT1
GATA3

Colon

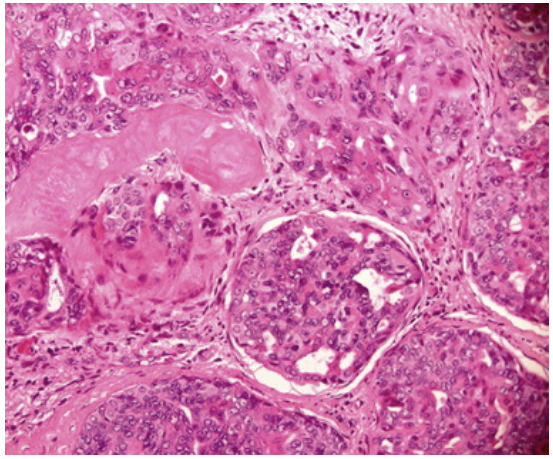


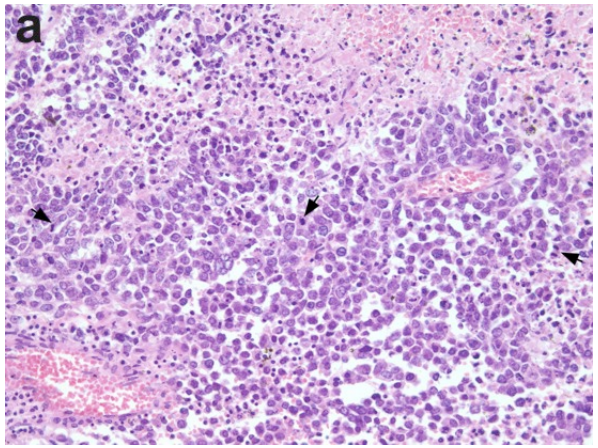
Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

Diagnosis of metastasis to the lung





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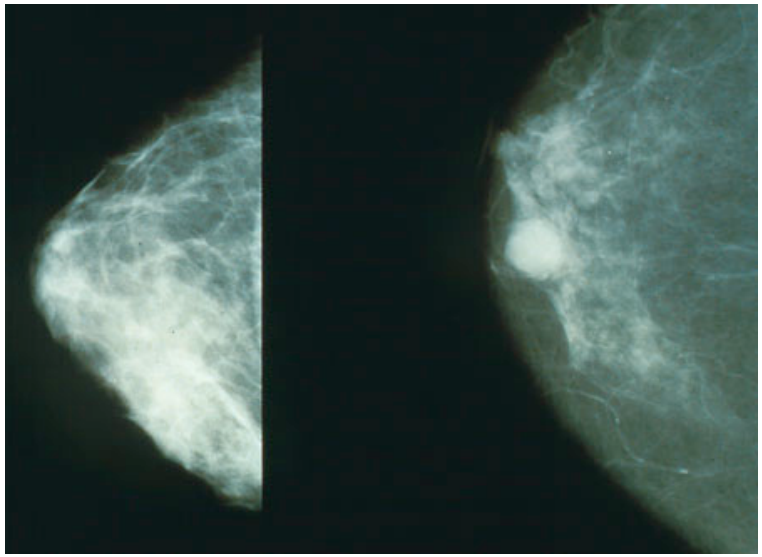
CK7 ←
ttf1
Napsin
CK20
cdx2
ER ←
GCDFP15 ←
PSA
Vim
CK5/6
P63
CD10
RCC
Ca125
PAX8
WT1
GATA3 ←

Mamma



Immunohistochemcal classification of

Lung cancer,

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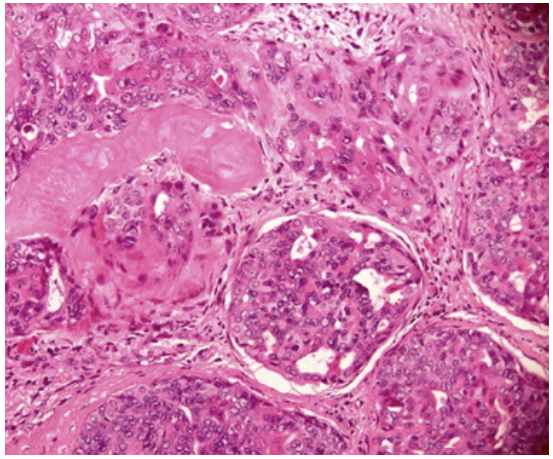
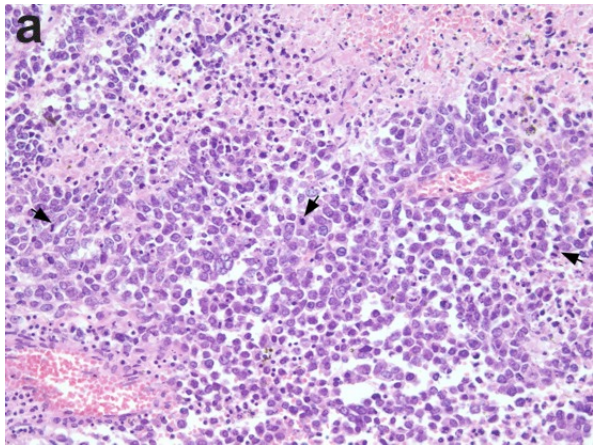
Diagnosis of metastasis to the lung





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CK20 ←
cdx2 ←
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GCDFP15
PSA
Vim
CK5/6
P63
CD10
RCC
Ca125
PAX8
WT1
GATA3

Upper GI

Immunohistochemcal classification of

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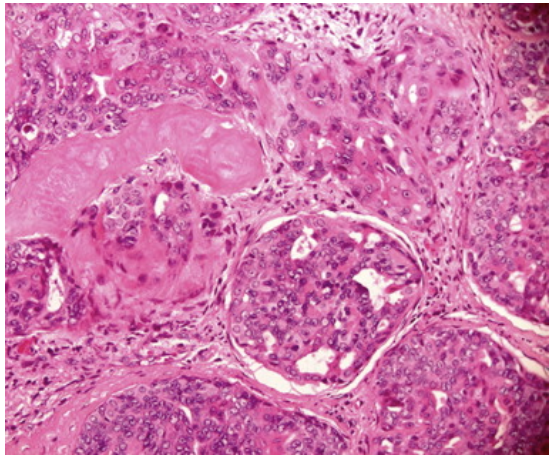

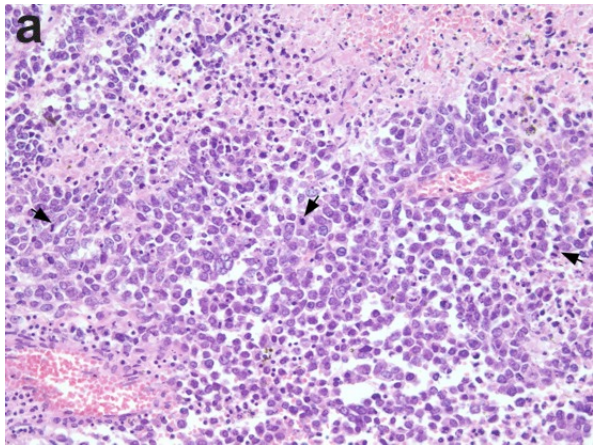

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CK20 ←
cdx2
ER
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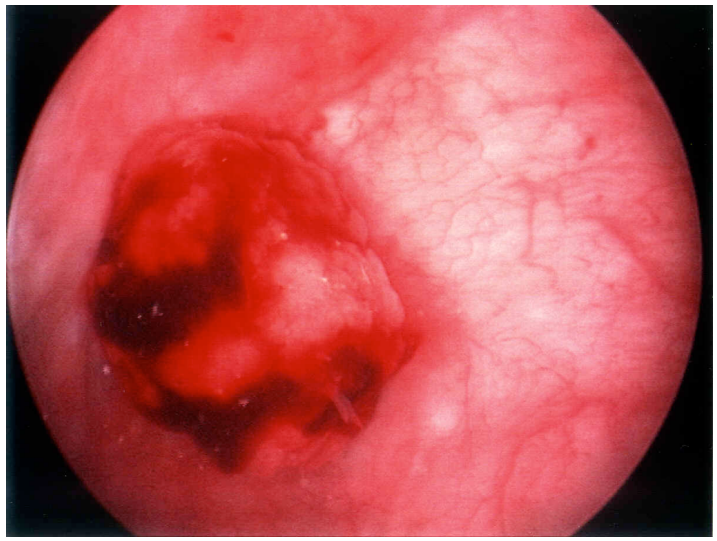
CK5/6 ←
P63 ←
CD10
RCC
Ca125
PAX8
WT1
GATA3 ←

Urothelial carcinoma

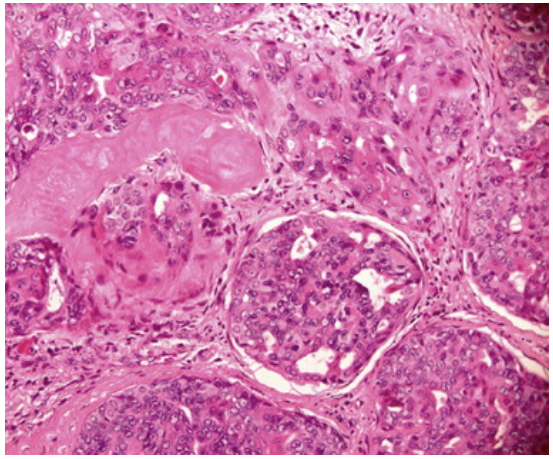


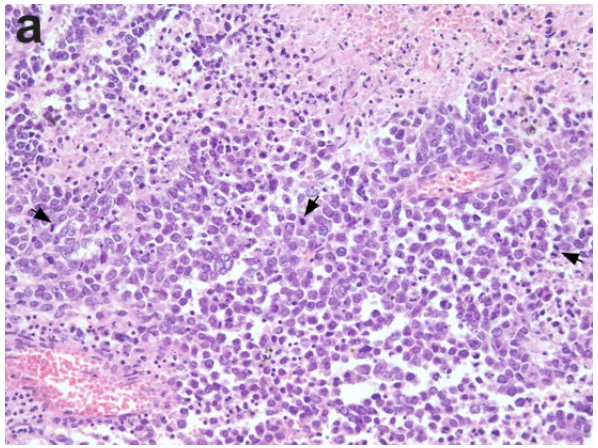
Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

Diagnosis of metastasis to the lung





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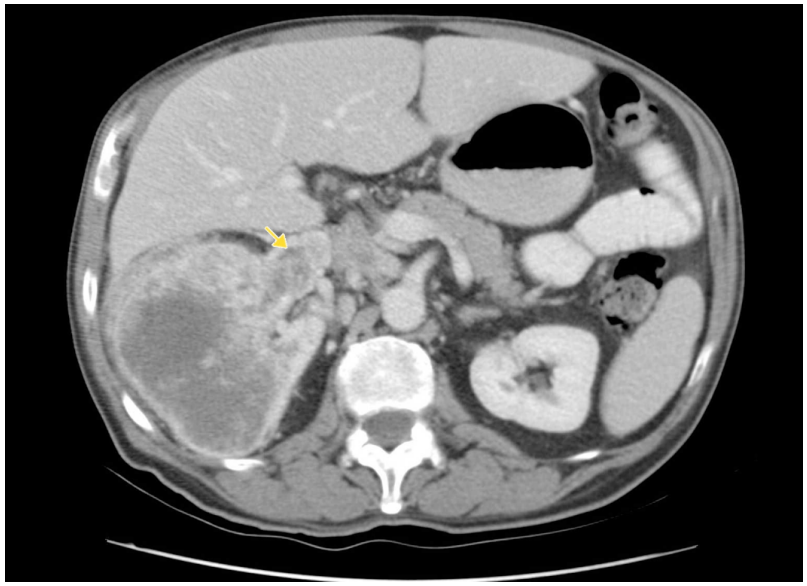
ttf1
Napsin
CK20
cdx2
ER
GCDFP15
PSA
Vim ←
CK5/6
P63
CD10 ←
RCC ←
Ca125
PAX8 ←
WT1
GATA3

Renal cell carcinoma

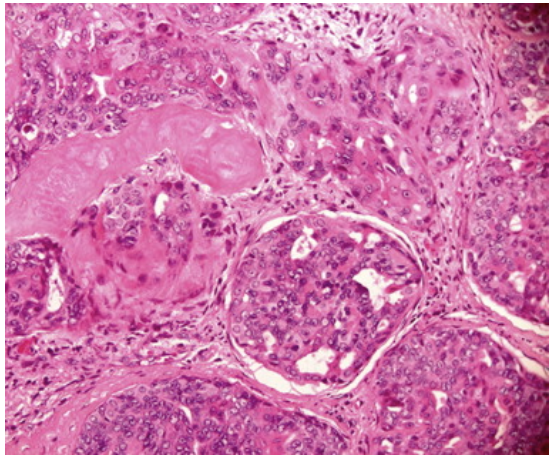


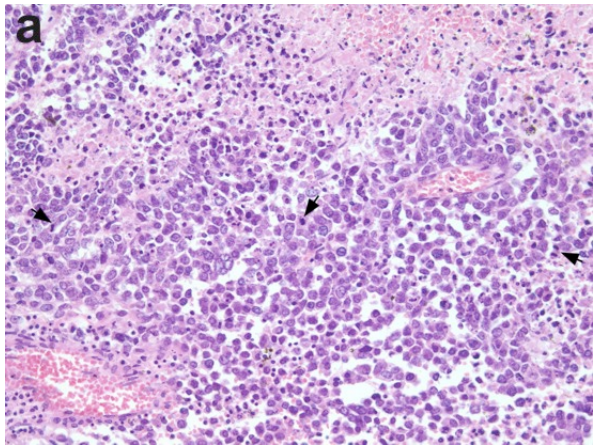
Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

Diagnosis of metastasis to the lung





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Napsin
CK20
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CK5/6
P63
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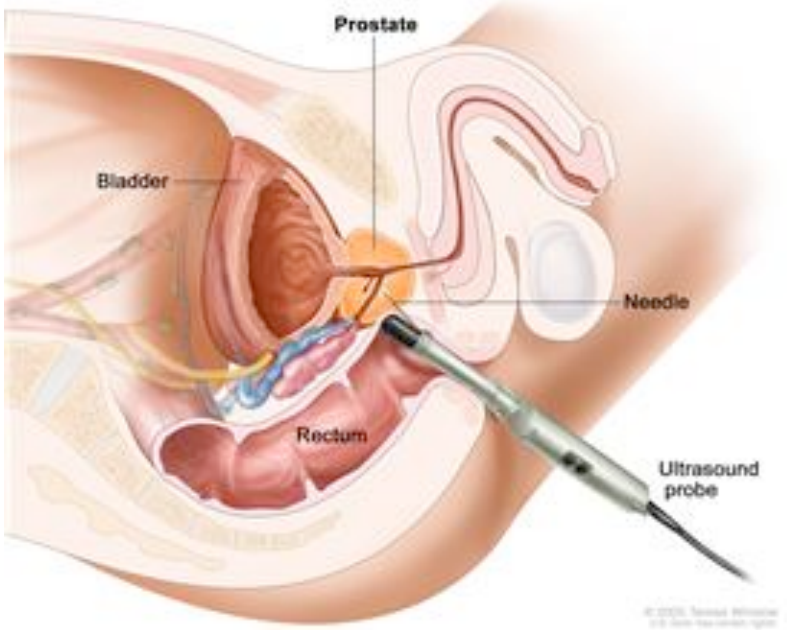
RCC
Ca125
PAX8
WT1
GATA3

Prostate

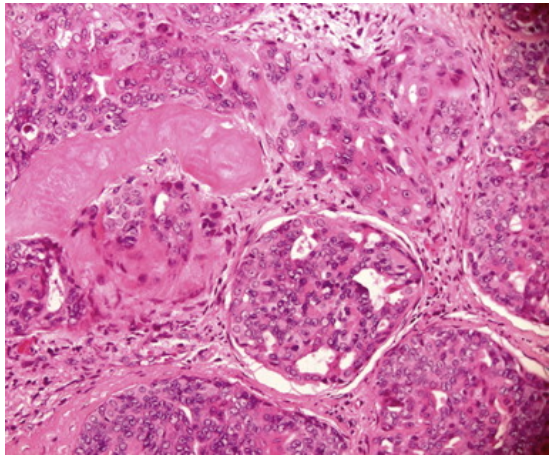


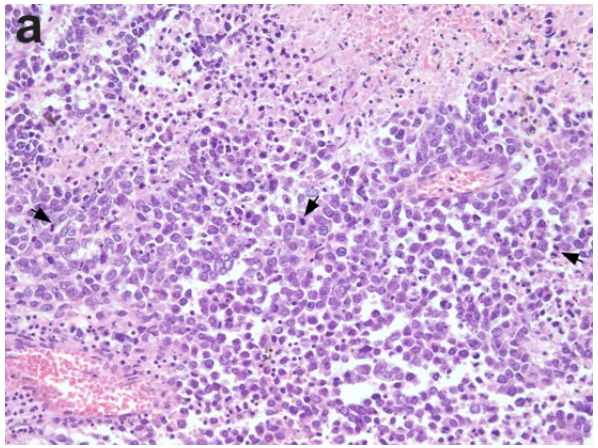
Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

Diagnosis of metastasis to the lung





AE1/AE3 ←
CK7
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cdx2
ER ←
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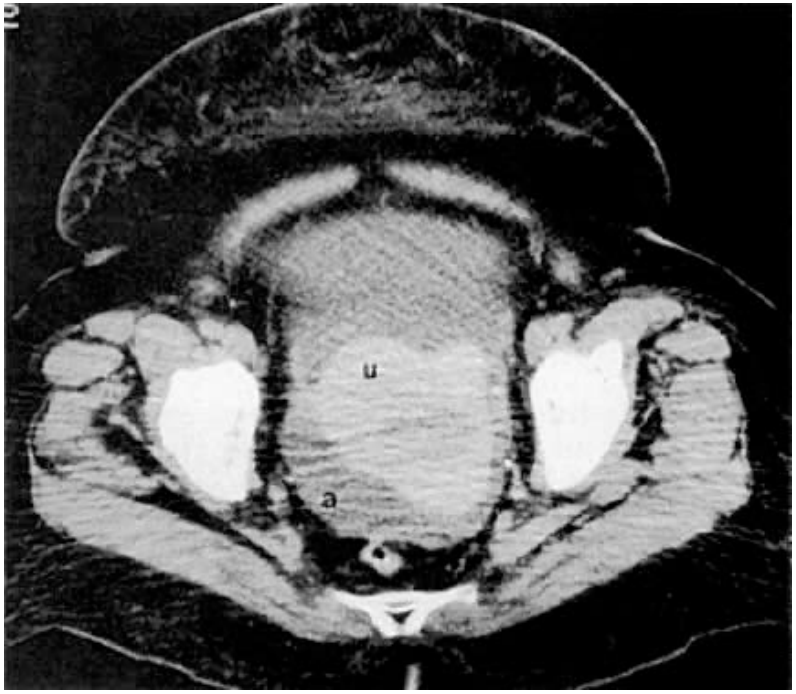
CK5/6
P63
CD10
RCC
Ca125
PAX8 ←
WT1
GATA3

Endometrial cancer

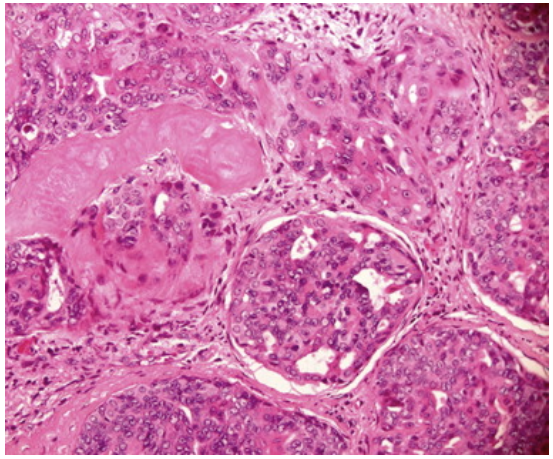


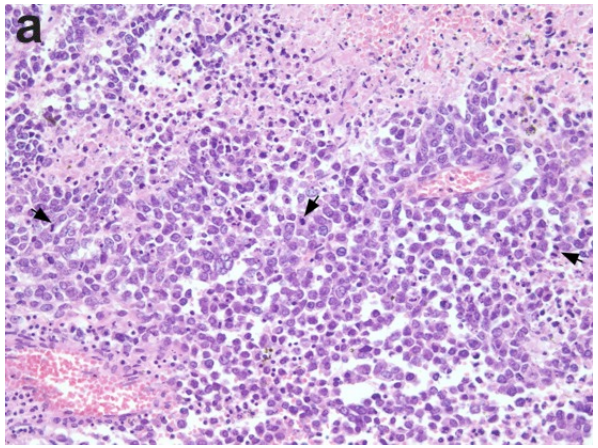
Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

Diagnosis of metastasis to the lung





AE1/AE3 ←
CK7 ←
ttf1
Napsin
CK20
cdx2
ER ←
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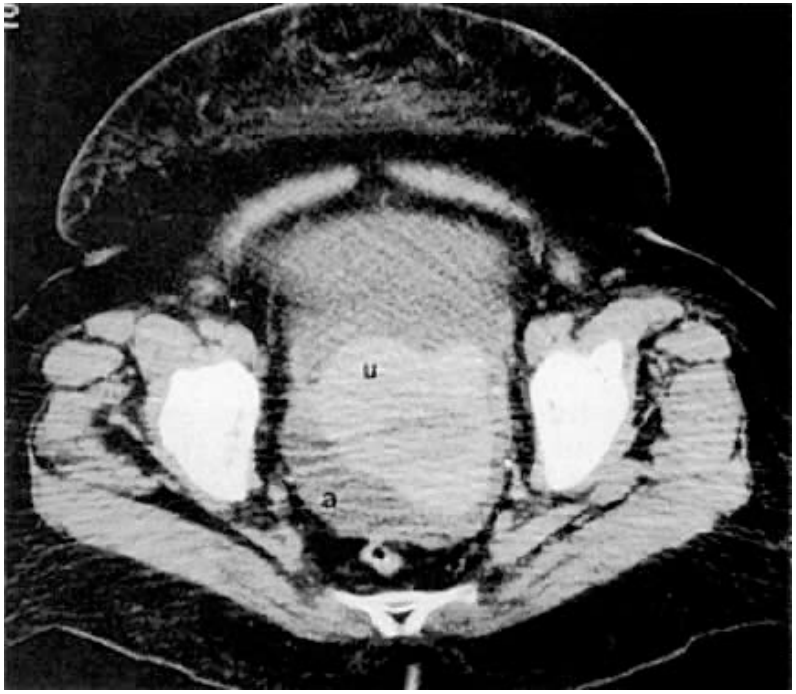
Vim
CK5/6
P63
CD10
RCC
Ca125 ←
PAX8
WT1 ←
GATA3

Ovarian cancer

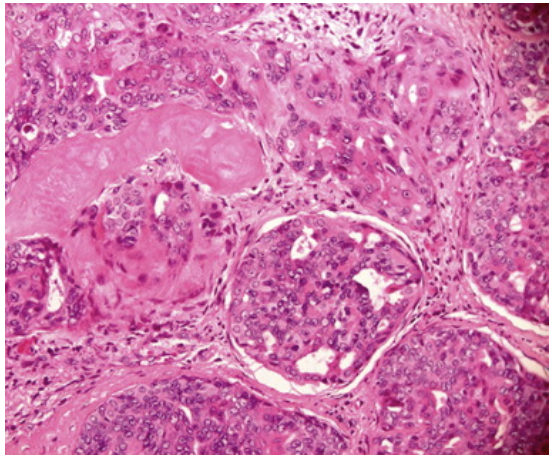


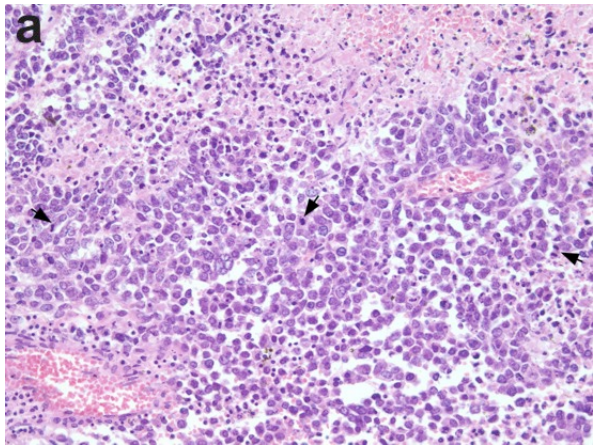
Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

Diagnosis of metastasis to the lung





AE1/AE3 ←
CK7 ←
ttf1 ←
Napsin
CK20
cdx2
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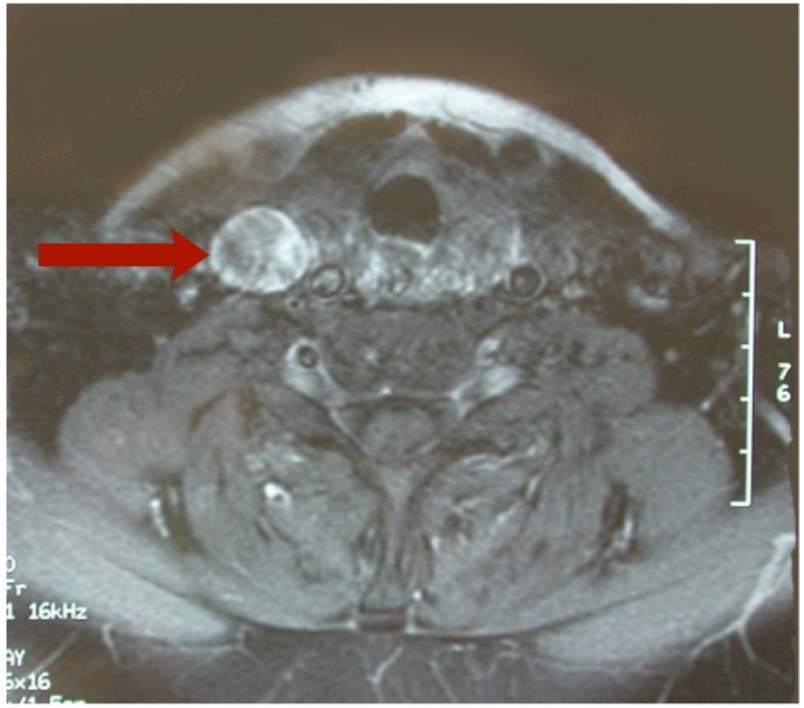
Vim ←
CK5/6
P63
CD10
RCC
Ca125
PAX8 ←
WT1
GATA3

Thyroid cancer

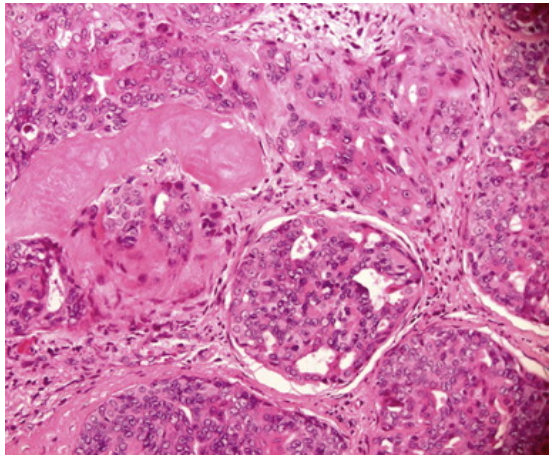


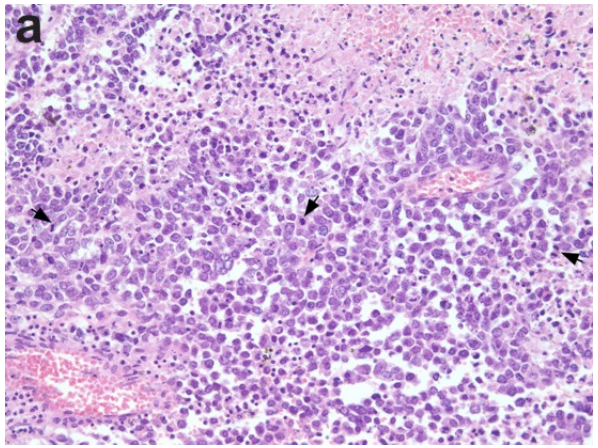
Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

Diagnosis of metastasis to the lung





Calretinin
WT1
D2-40
CK7
Vim
CK5/6

Immunohistochemcal classification of

Lung cancer,

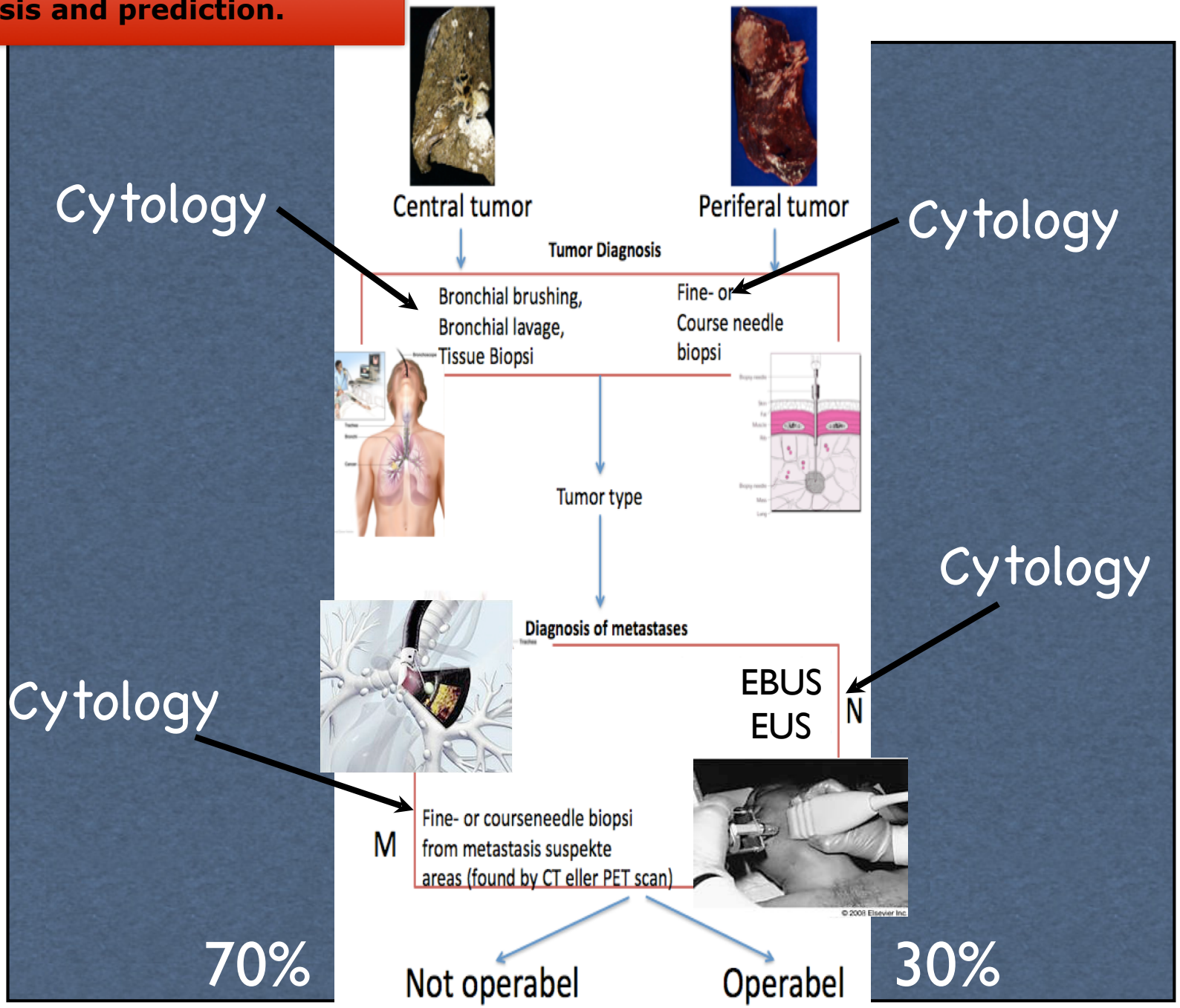
diagnosis and prediction.

The MultiDisciplinary Teamconference MDT

Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.



Immunohistochemcal classification of

Lung cancer,

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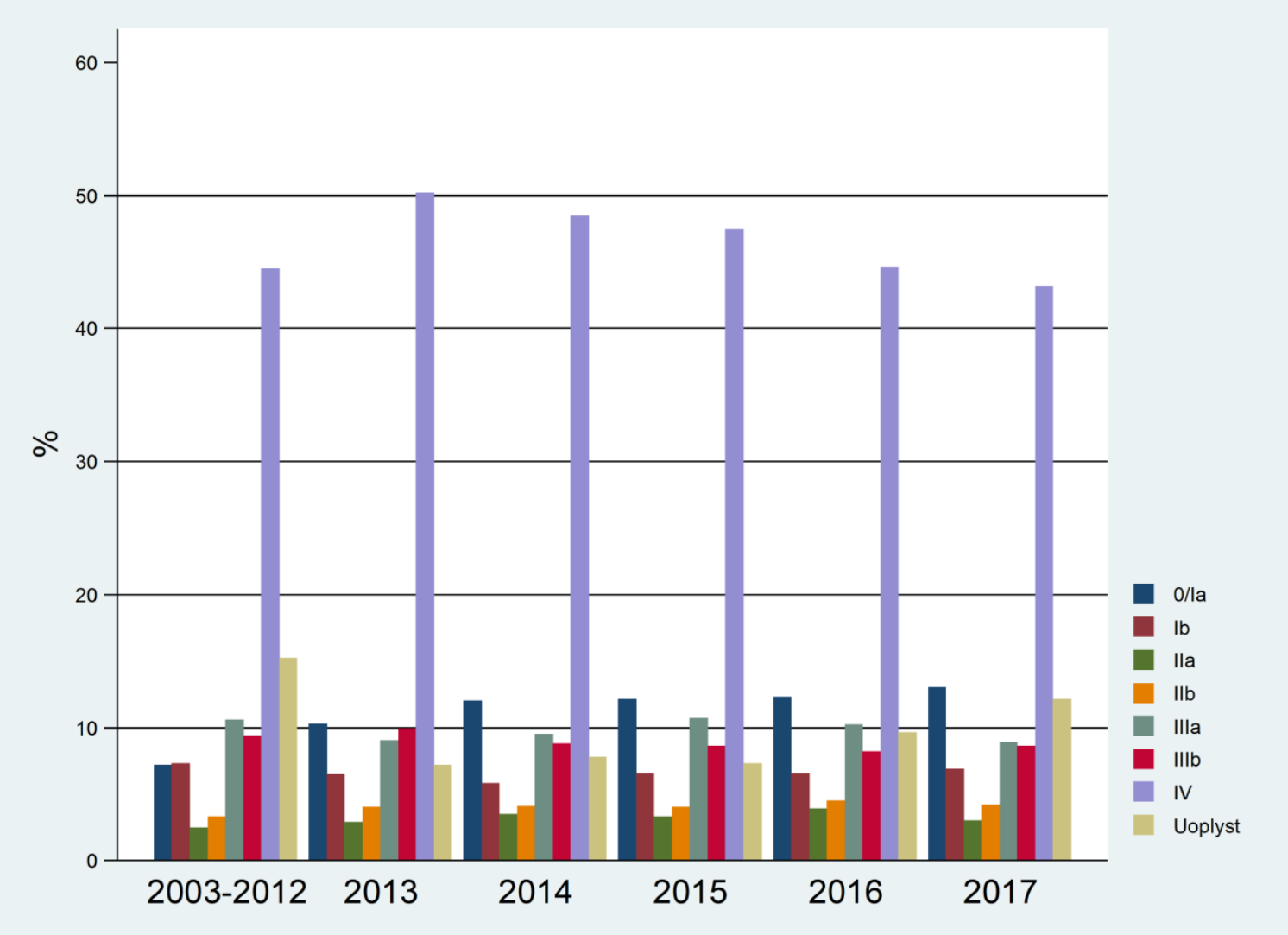


Stage at diagnosis

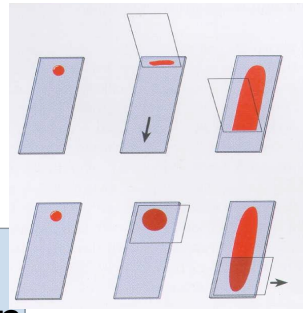
Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

Patoanatomical specimen

Cytology



Histology

Fixation
Dehydration
Parafinembedding
Microtomy

Præparation

Smear preparation

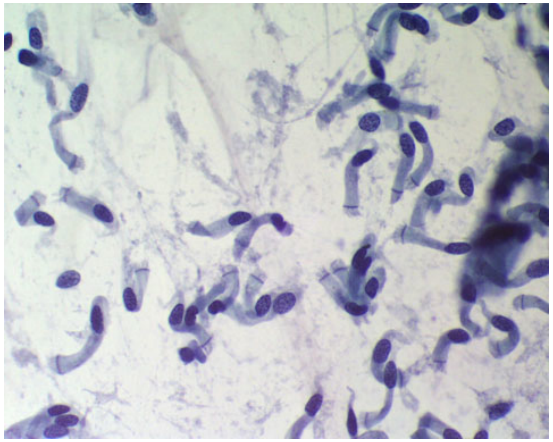
Visualization

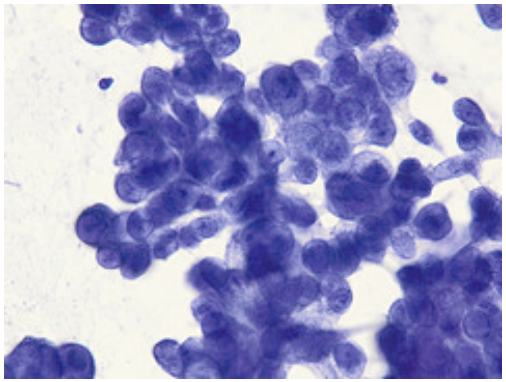
(Staining)

Immunohistochemcal classification of

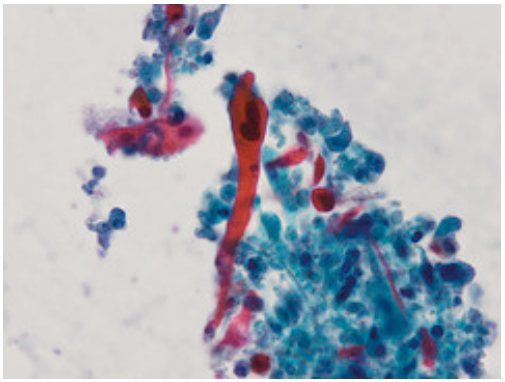
Lung cancer,

diagnosis and prediction.

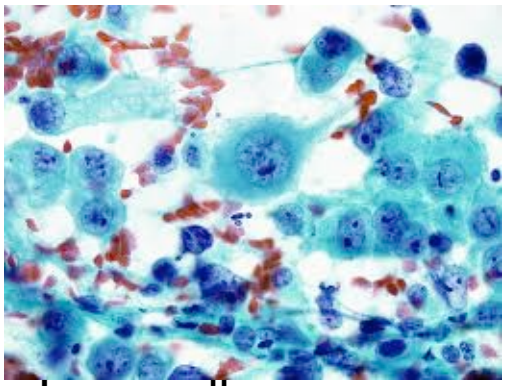




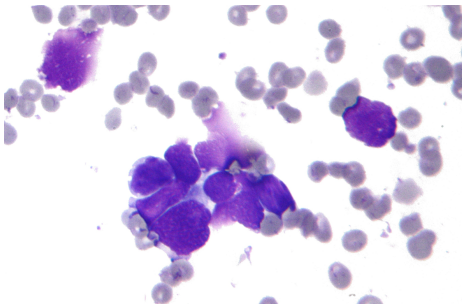
Adenocarcinoma



Squamous carcinoma



Large cell neuroendocrine carc.



Small cell carcinoma

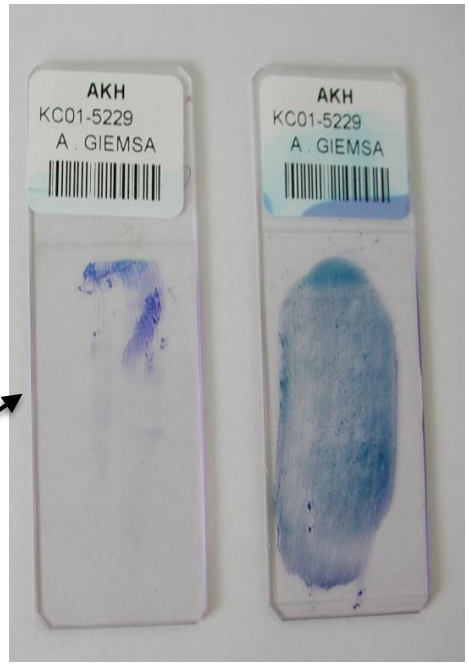
Non Small Cell Lung Carcinoma (NSCLC)

Immunohistochemcal classification of

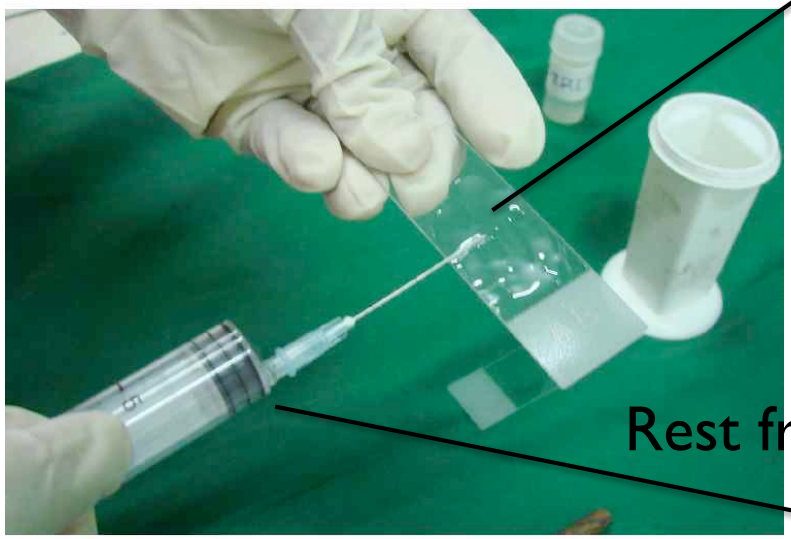
Lung cancer,

diagnosis and prediction.

Cytology



Morfologi



Rest from the needle

Cellblock

Immunocytologi

Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

Cytology

Cellblock

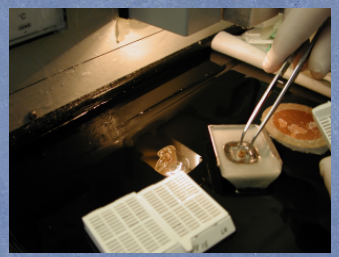
Immuncytologi

Dannelse af koagel

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

Til Parafin

Indstøbning



Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

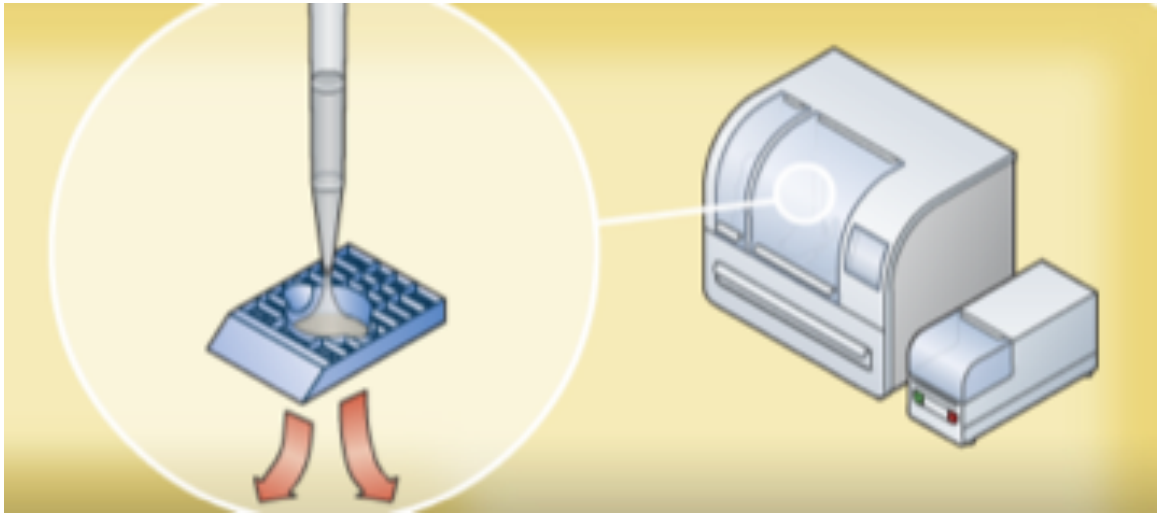
Cytology

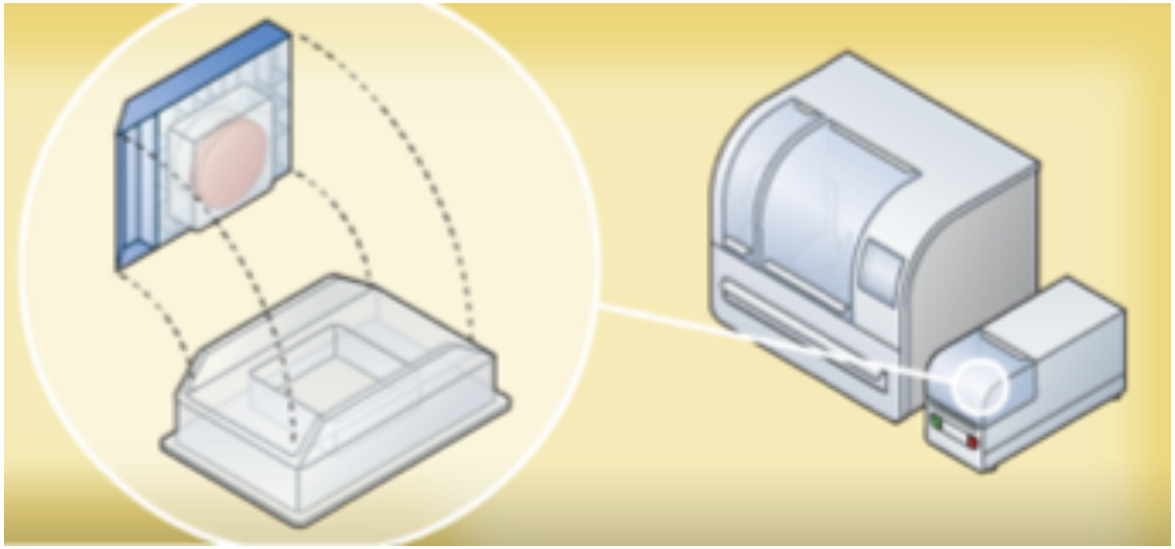
Cellblock

Immuncytologi

cellient™ AUTOMATED CELL BLOCK SYSTEM

HOLOGIC





Immunohistochemcal classification of

Lung cancer,

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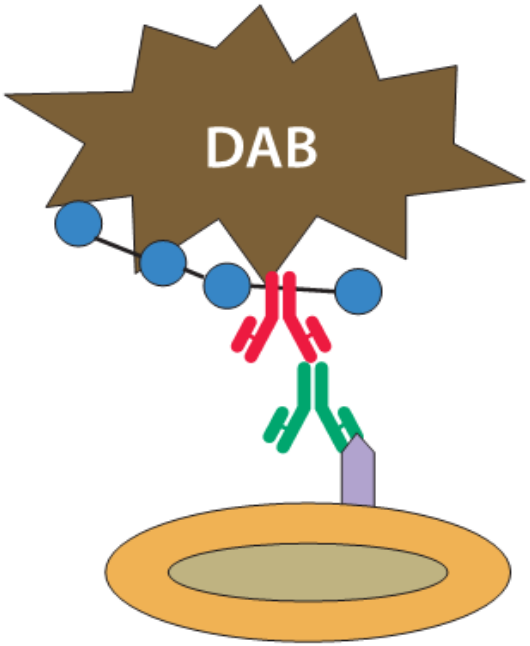
Cytology



Kromogen (farvestof)

Visualiseringssystem (enzymer)

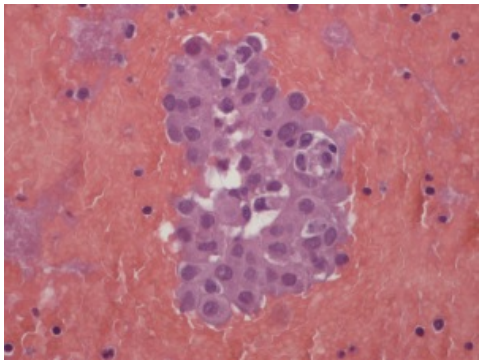
Sekundært antistof

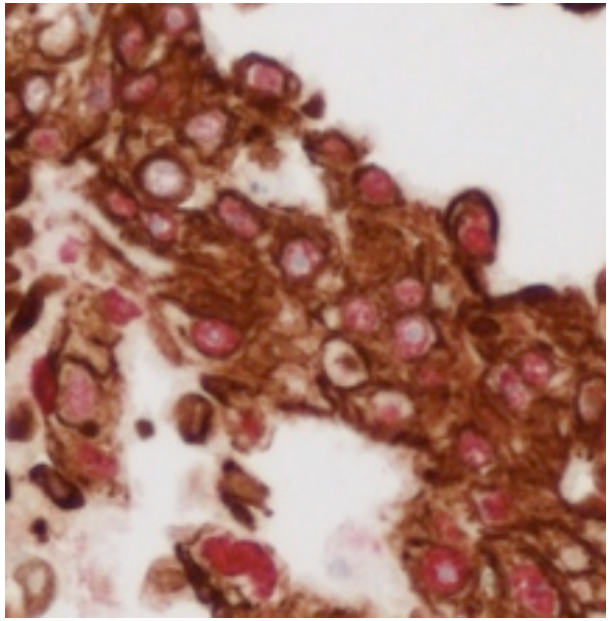
Primært antistof

Antigen

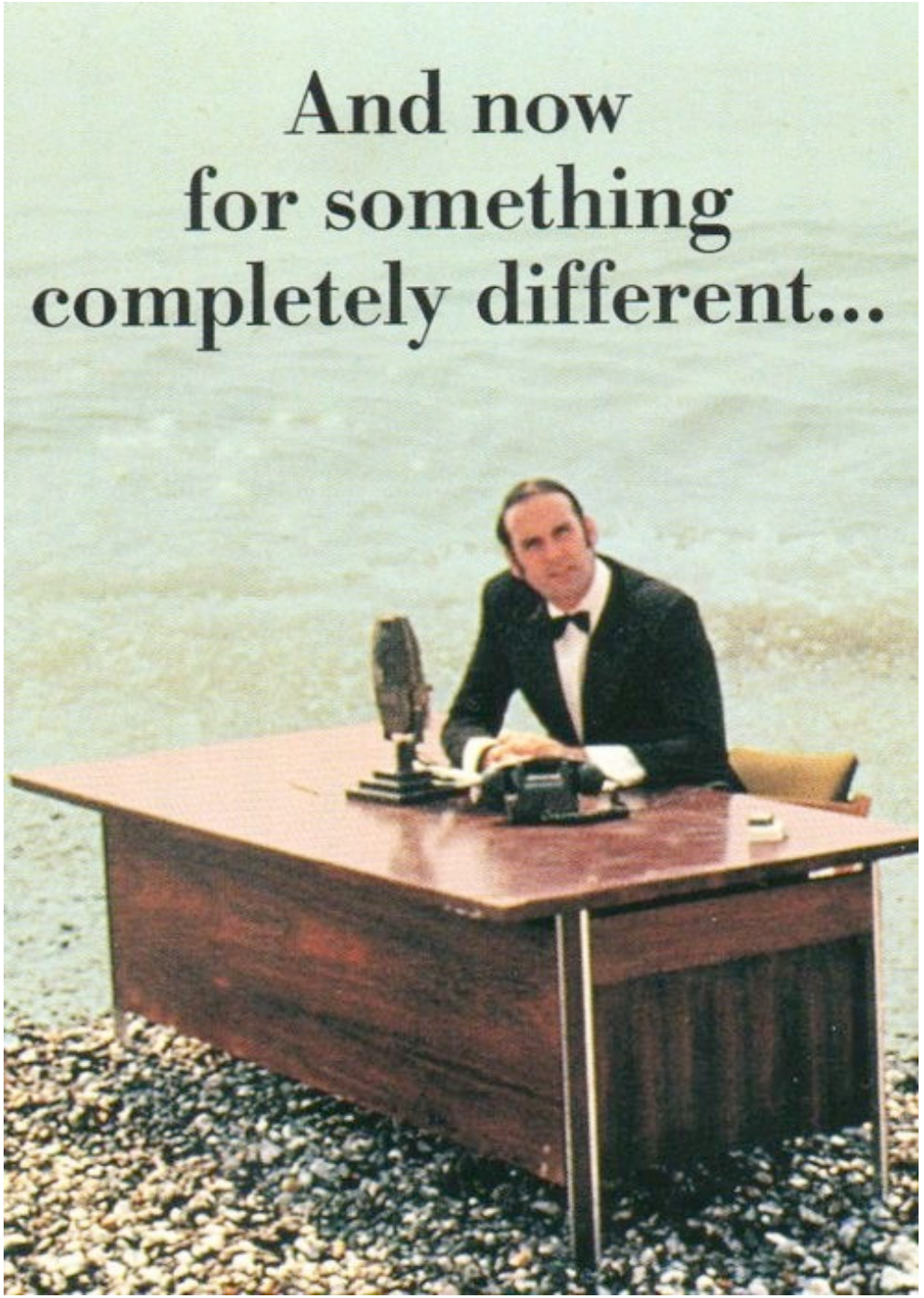
Cellens cytoplasma

Cellekerne

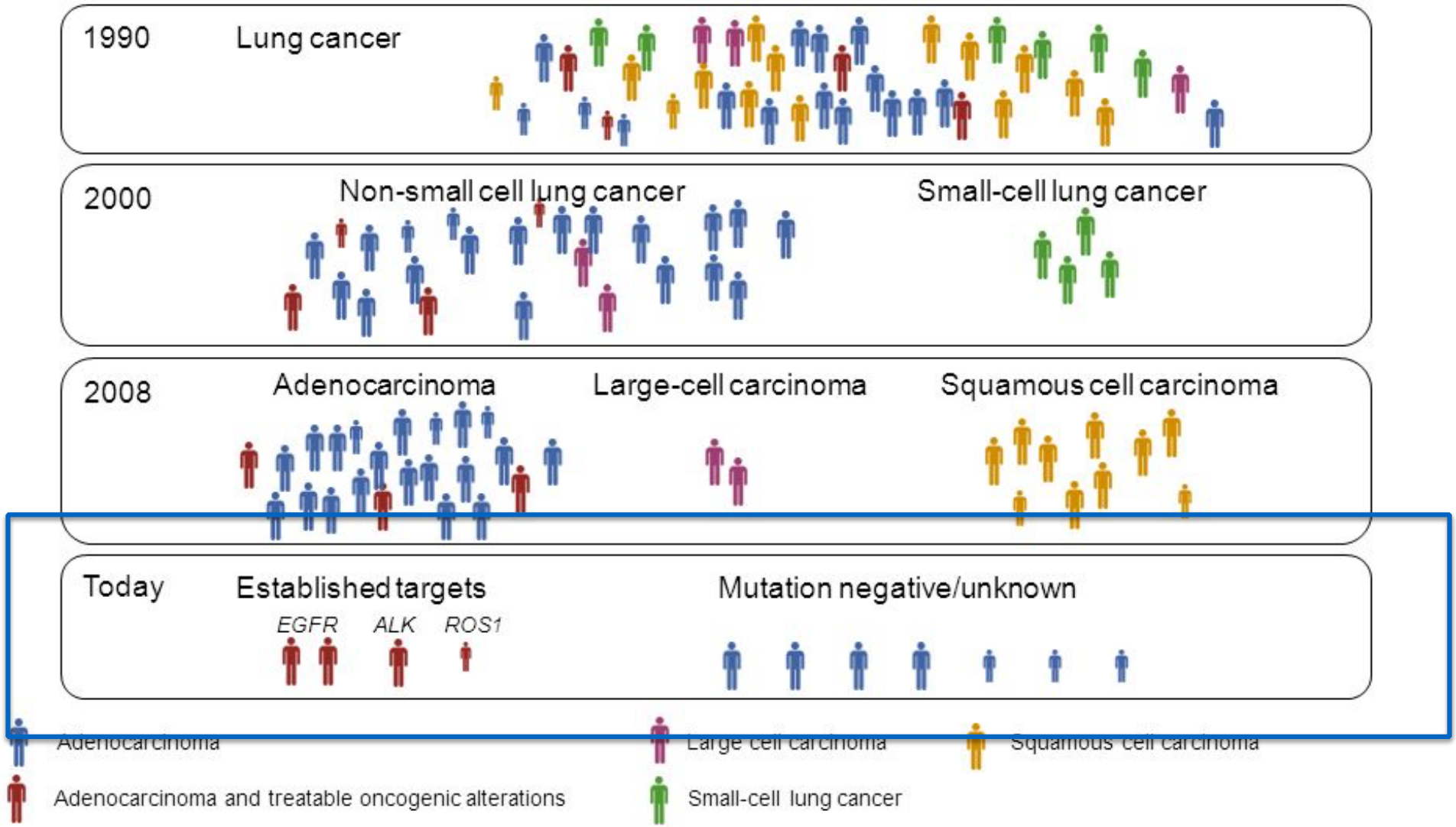




ttf1-CK7


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

Immunohistochemcal classification of

Lung cancer,

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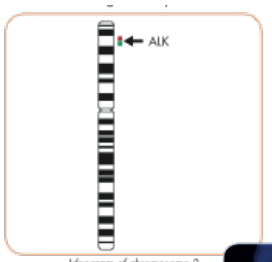
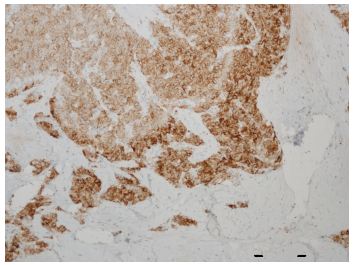
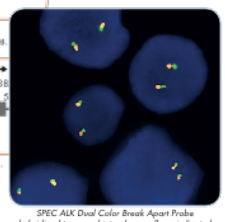
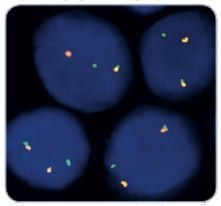
Region Syddanmark
Sygehus Lillebælt









Step 1

Positive Histology

Positive Cytology

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

ADC

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

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.

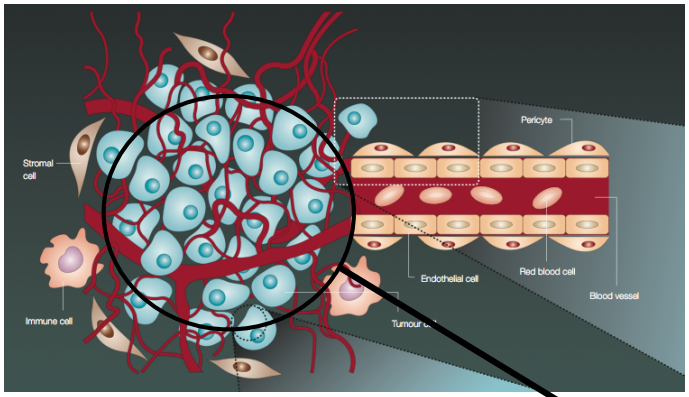
Step 3

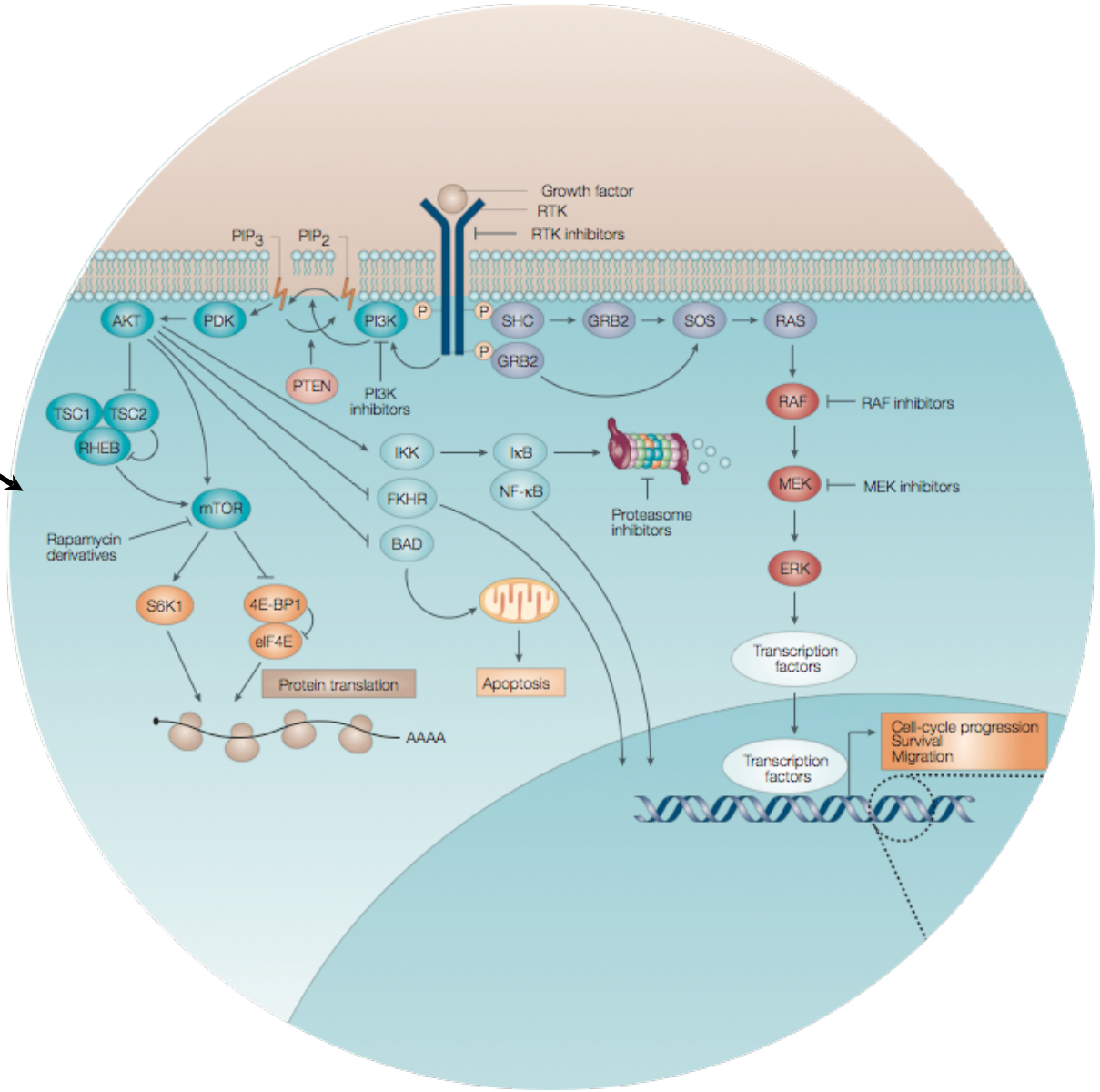
Molecular analysis
EGFR and ALK

Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.



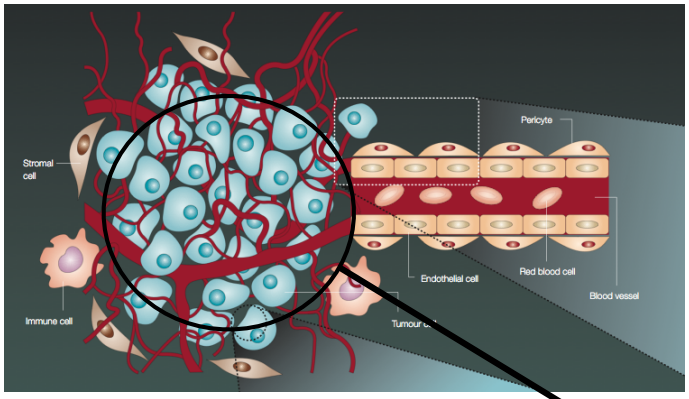


Pathways of cancer

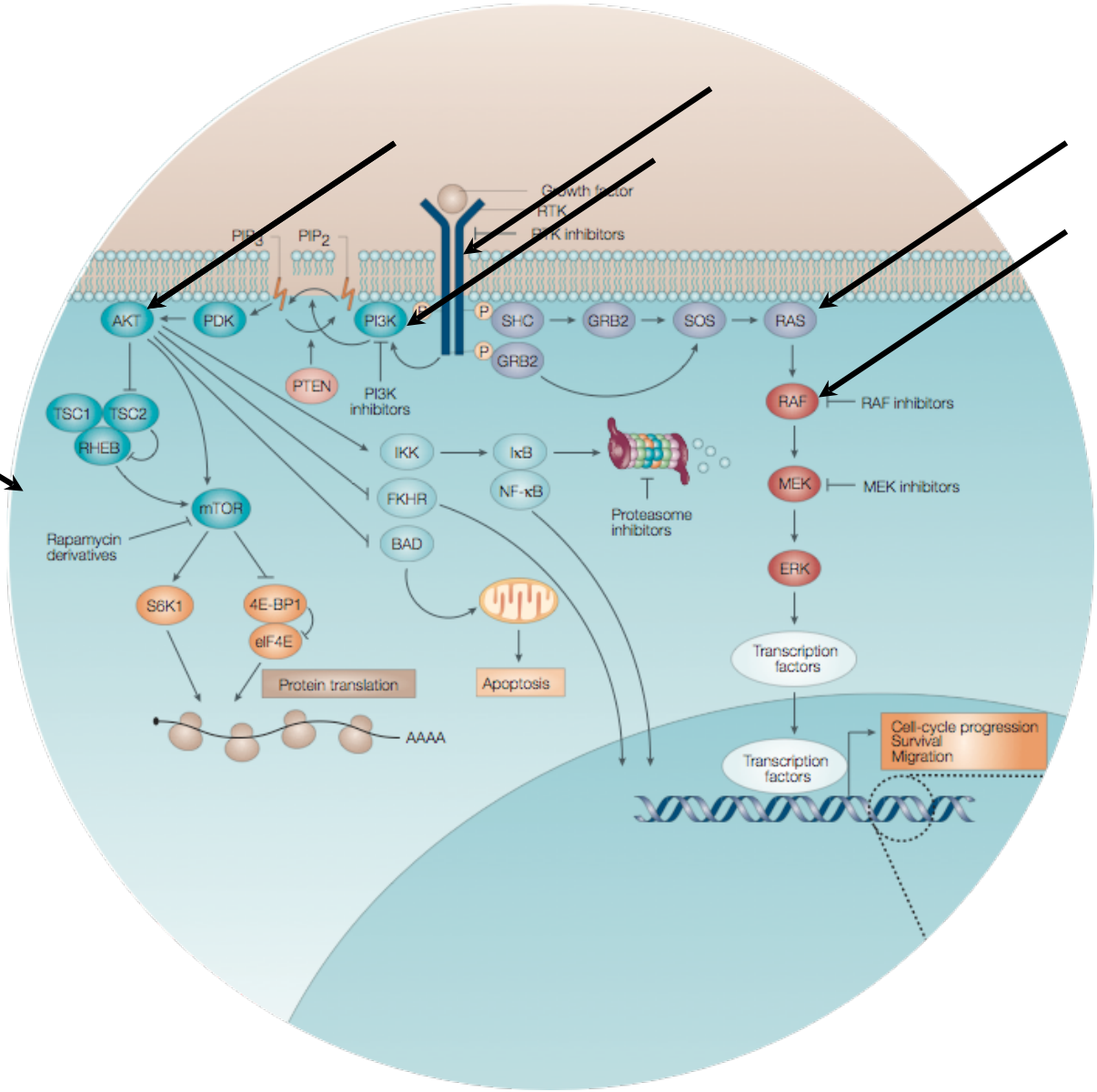
Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.



oncogenes



Immunohistochemcal classification of

Lung cancer,

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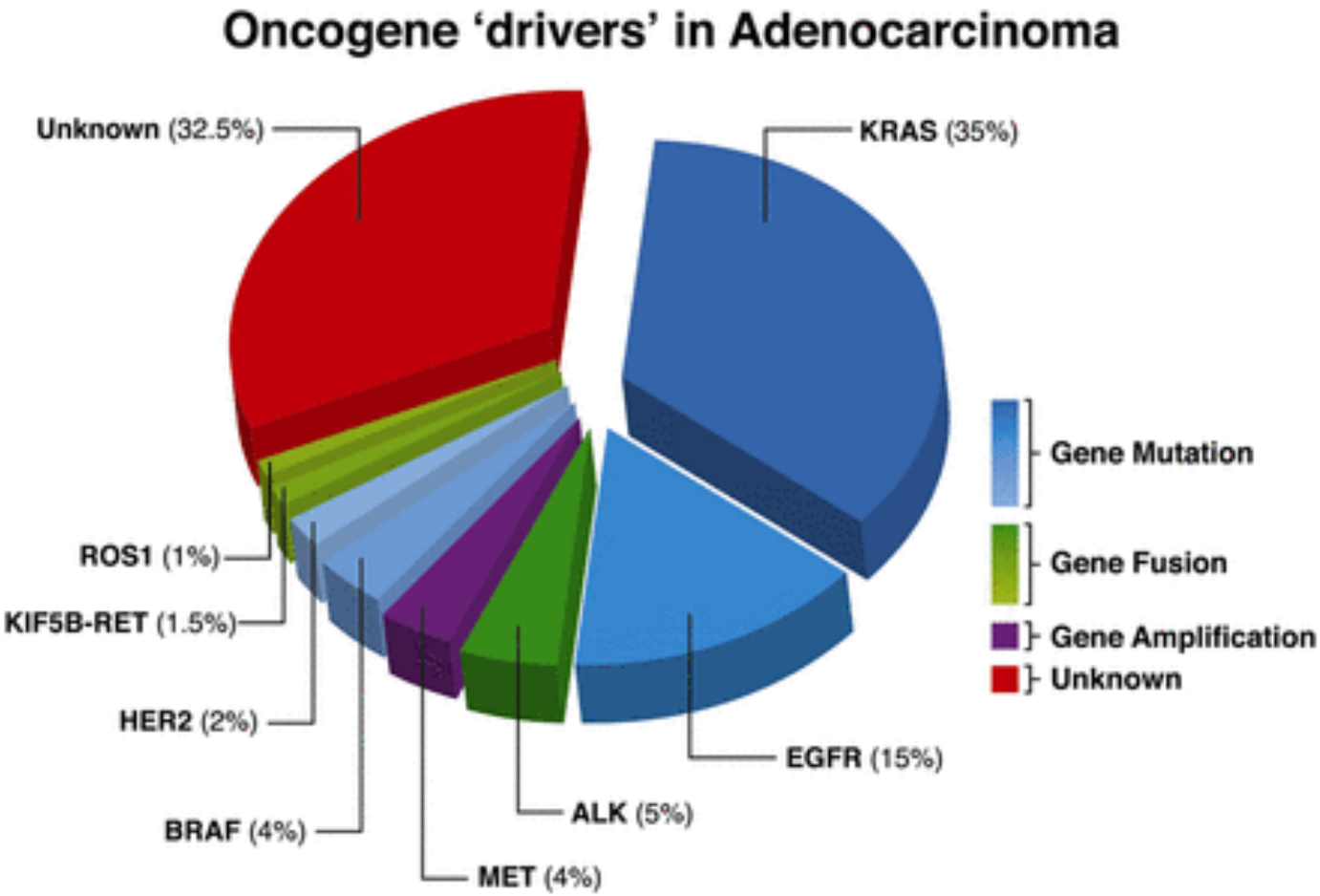

Immunohistochemcal classification of

Lung cancer,

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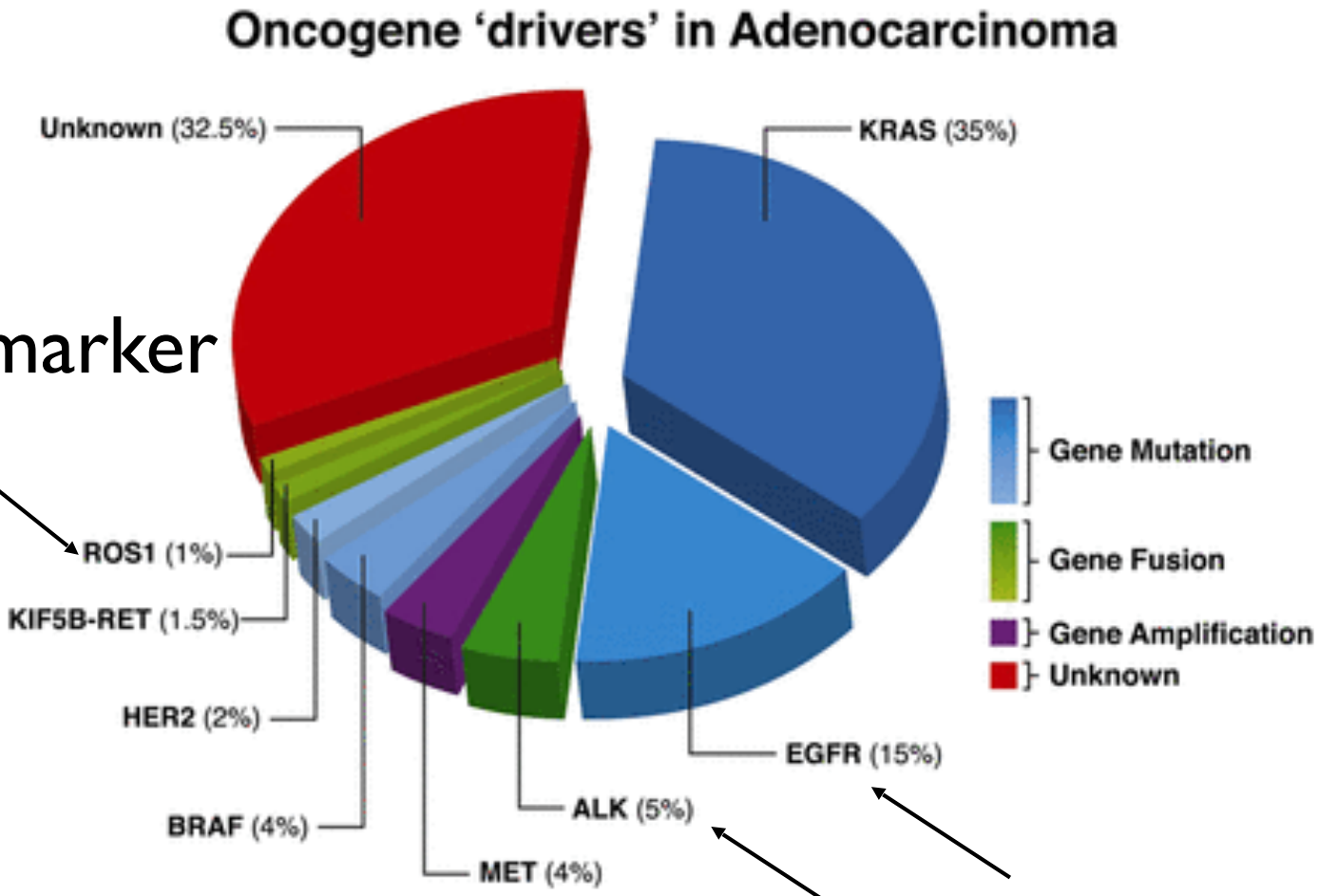
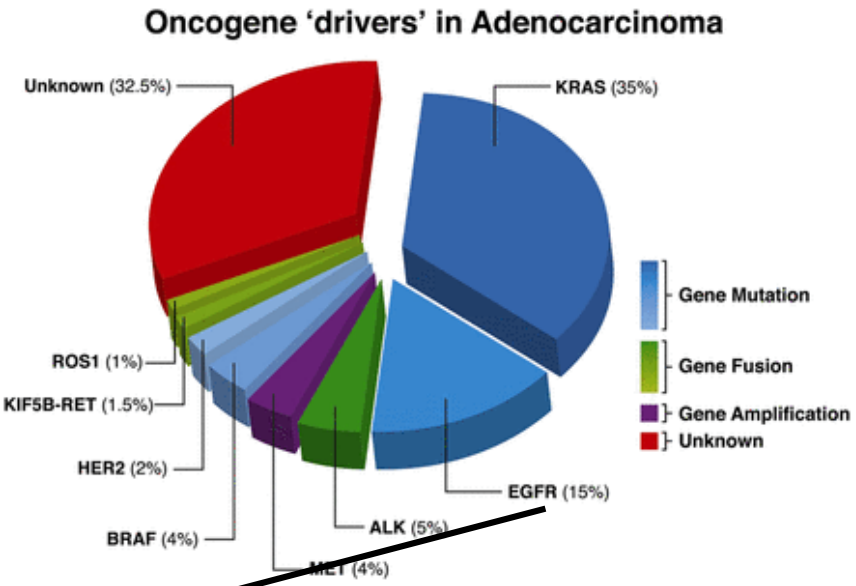
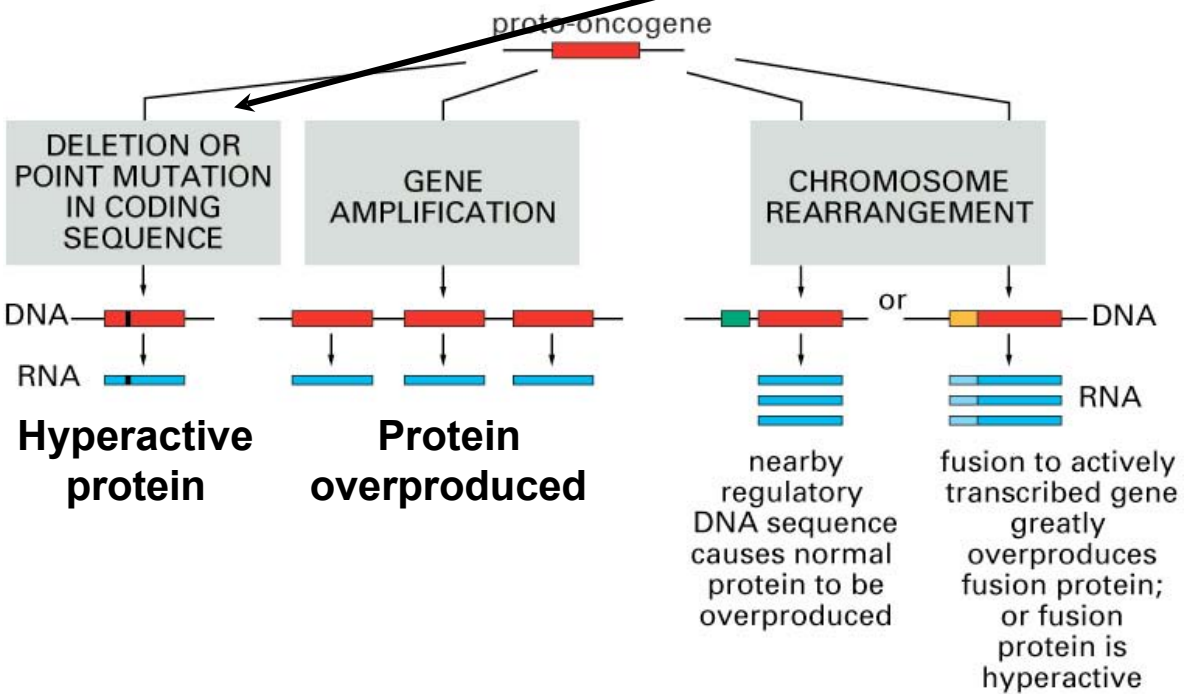


Predictive marker

Predictive marker


Oncogene 'drivers' in Adenocarcinoma
Unknown (32.5%)
KRAS (35%)
ROS1 (1%)
KIF5B-RET (1.5%)
HER2 (2%)
BRAF (4%)
MET (4%)
ALK (5%)
EGFR (15%)
Gene Mutation
Gene Fusion
Gene Amplification
Unknown

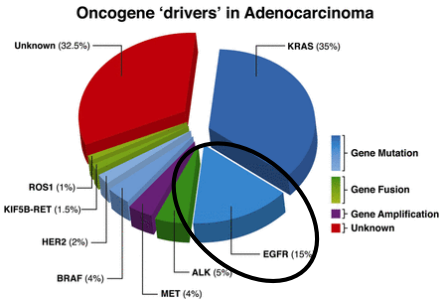

proto-oncogene
DELETION OR POINT MUTATION IN CODING SEQUENCE
GENE AMPLIFICATION
CHROMOSOME REARRANGEMENT
DNA
RNA
or
DNA
RNA
Hyperactive protein
Protein overproduced
nearby regulatory DNA sequence causes normal protein to be overproduced
fusion to actively transcribed gene greatly overproduces fusion protein; or fusion protein is hyperactive

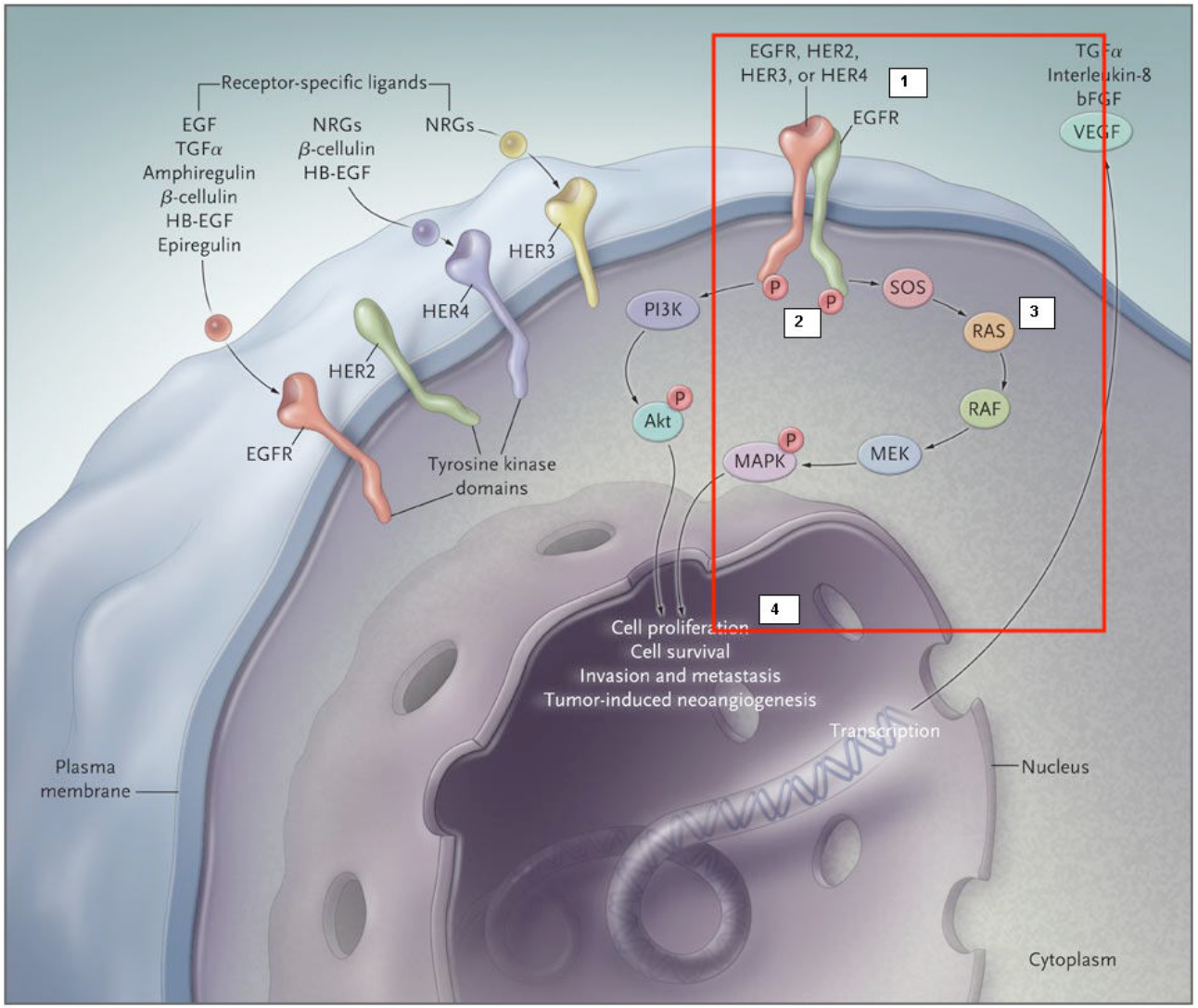
Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

EGFR





Immunohistochemcal classification of

Lung cancer,

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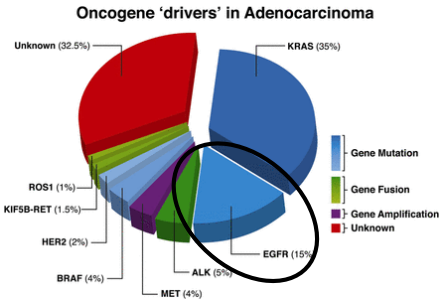
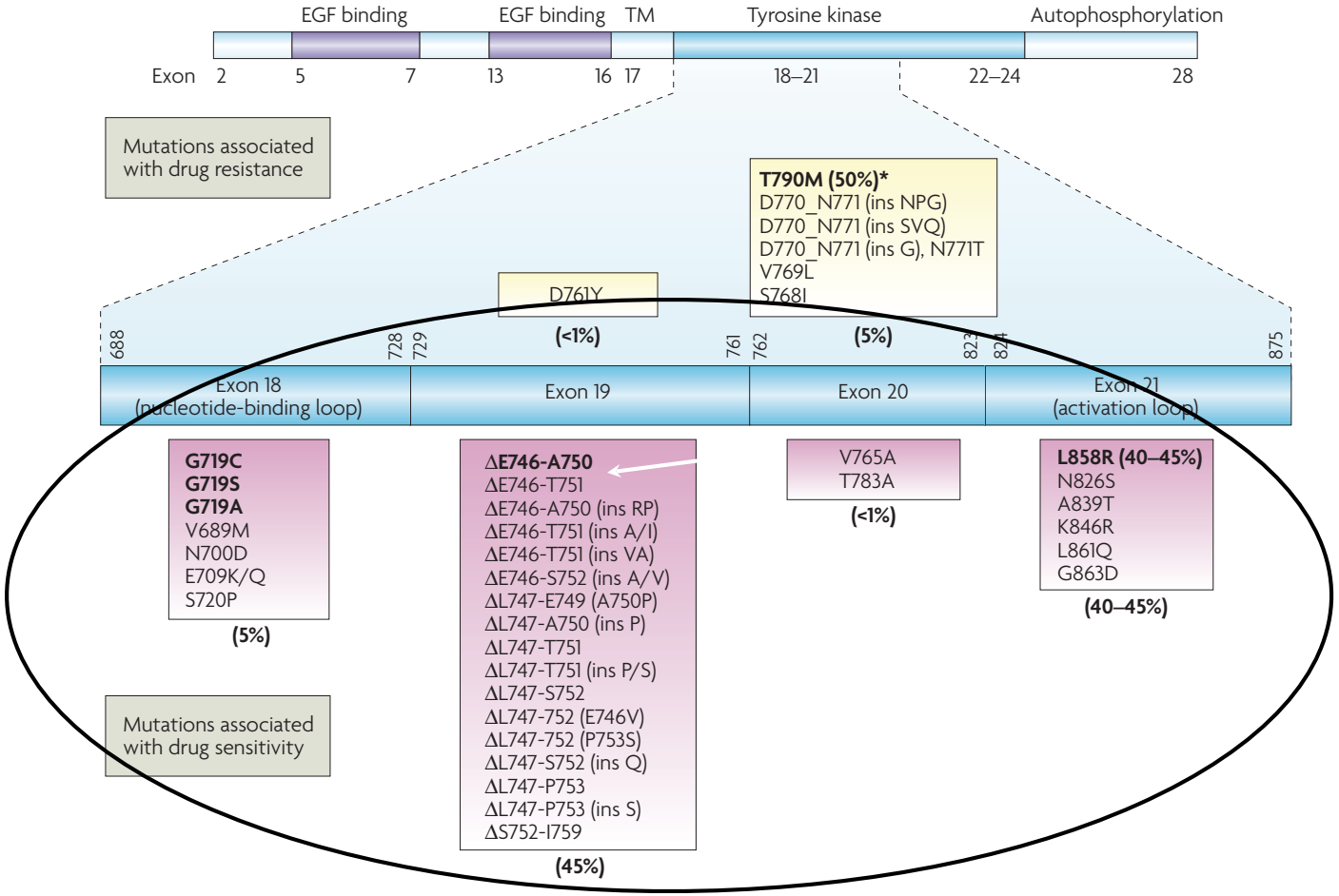
EGFR





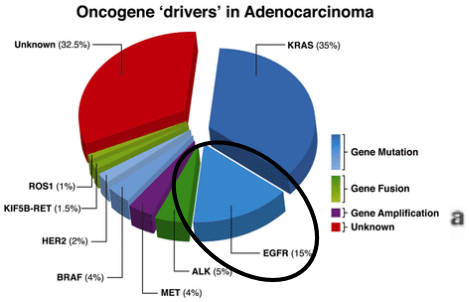
autoactivates EGFR

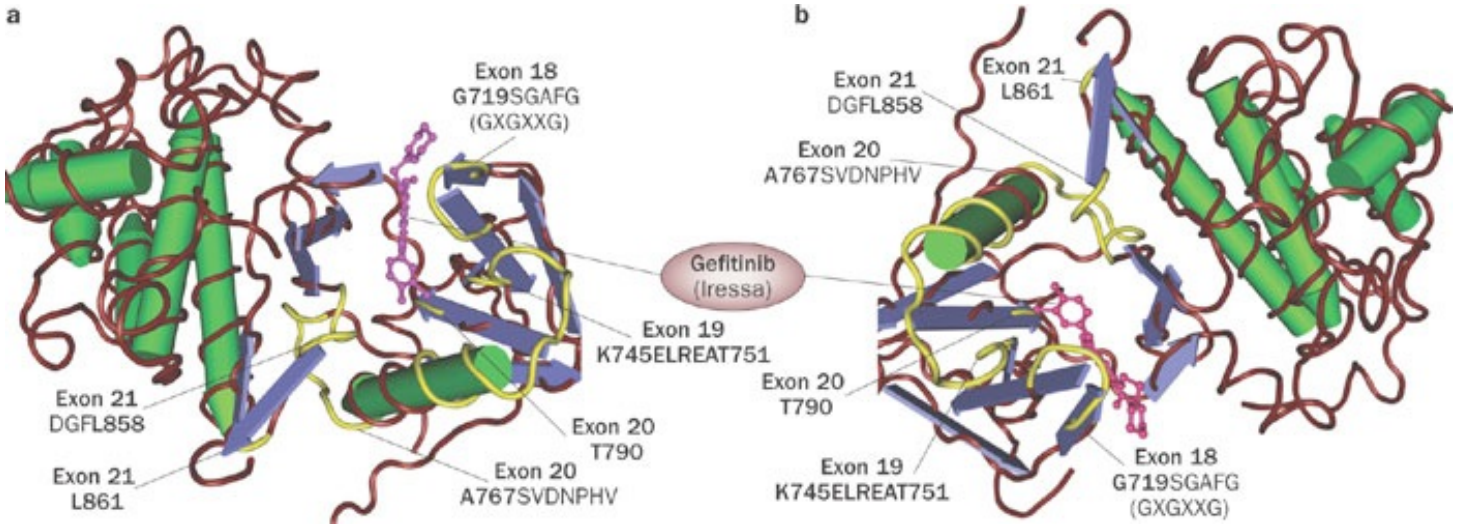
Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

EGFR



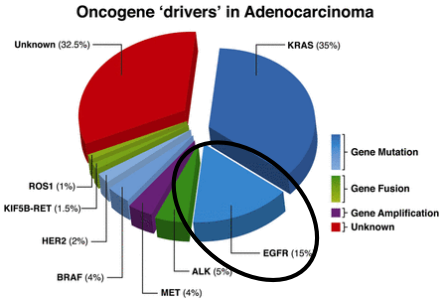


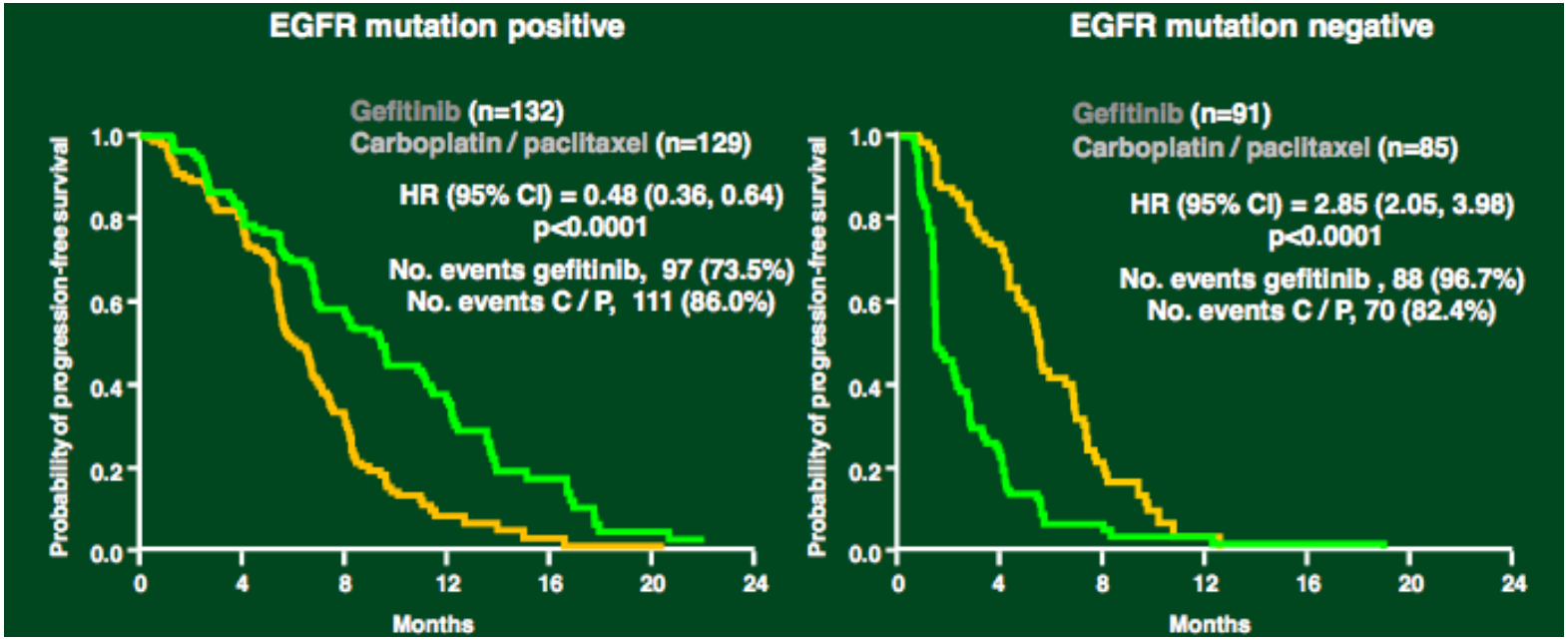
Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

EGFR





Immunohistochemcal classification of

Lung cancer,

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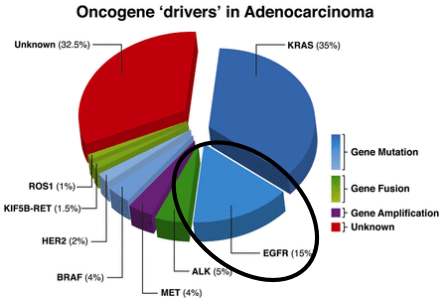
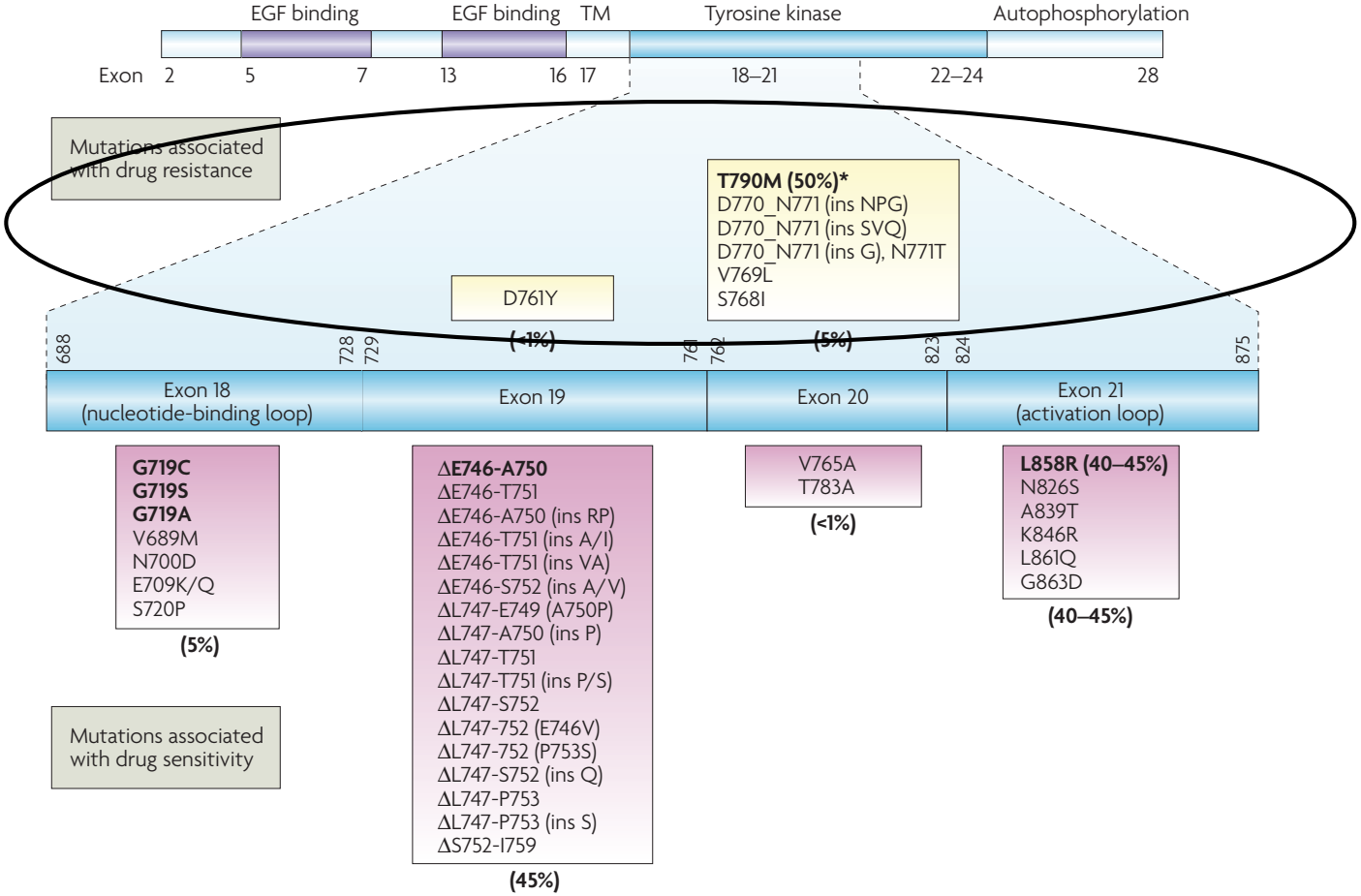
EGFR



Resistens

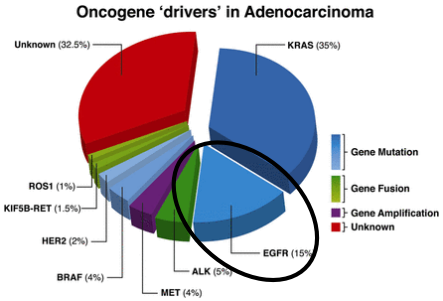


NordiQC

Immunohistochemcal classification of Lung cancer, diagnosis and prediction.

Region Syddanmark
Sygehus Lillebælt

EGFR



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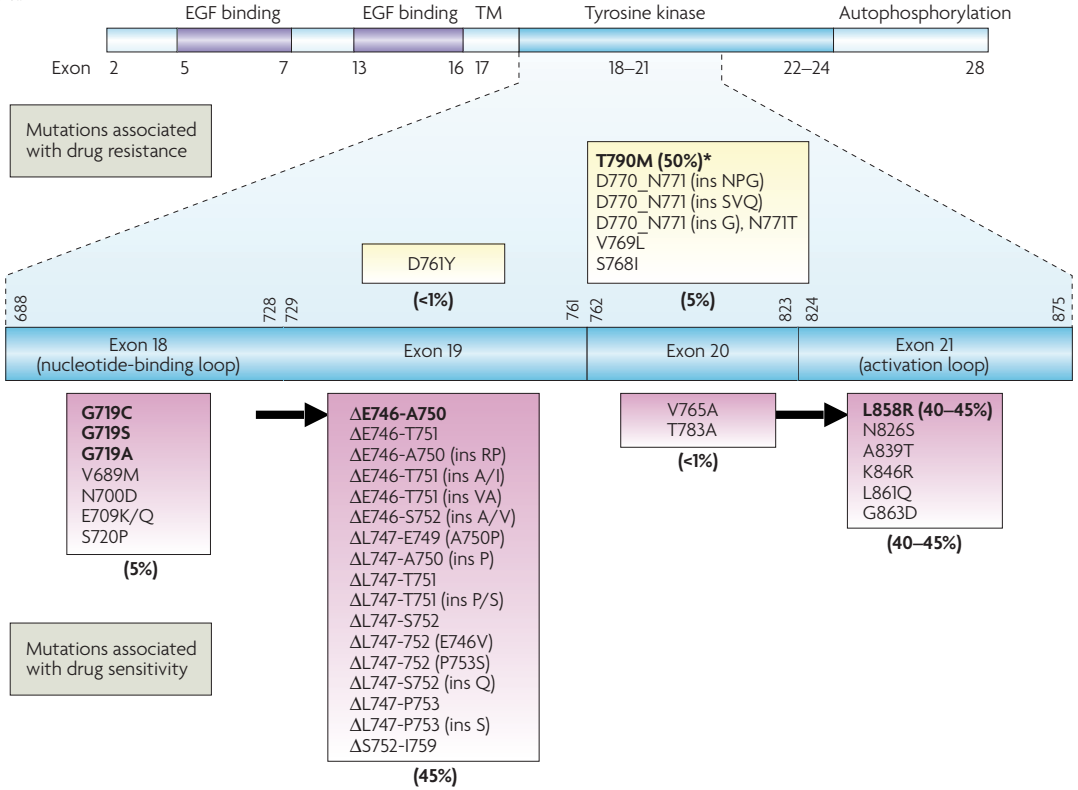
Novel EGFR mutation-specific antibodies for lung adenocarcinoma: Highly specific but not sensitive detection of an E746_A750 deletion in exon 19 and an L858R mutation in exon 21 by immunohistochemistry

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

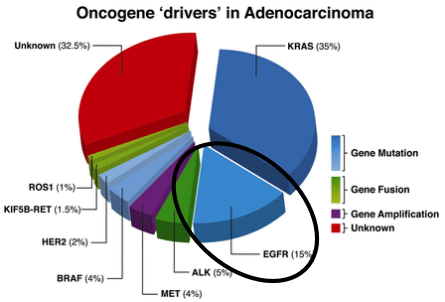


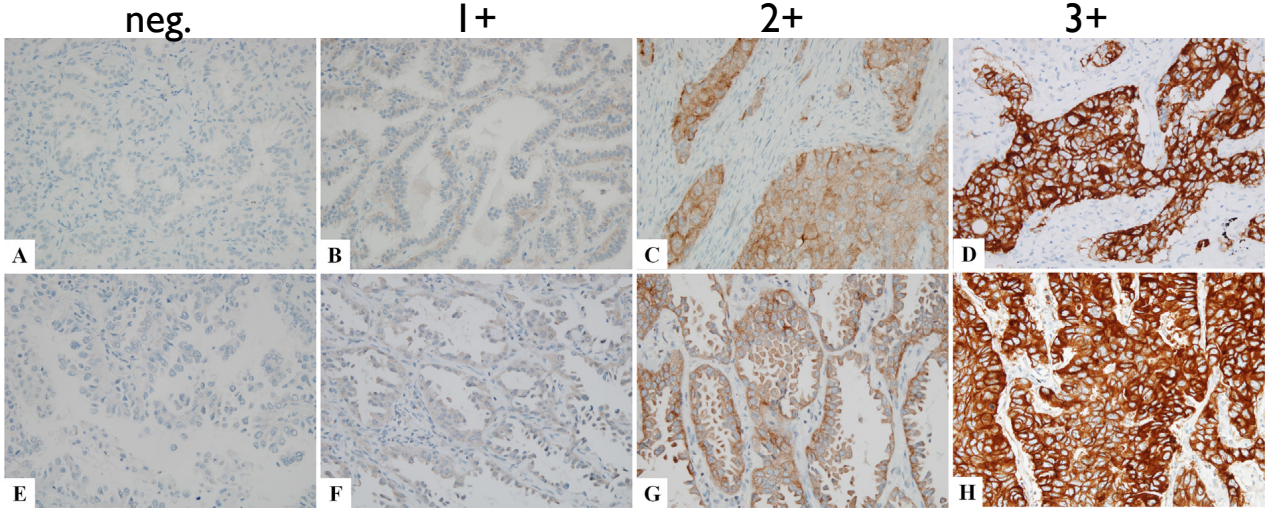
NordiQC

Immunohistochemcal classification of Lung cancer, diagnosis and prediction.

Region Syddanmark
Sygehus Lillebælt

EGFR





E746-A750 del-specific AB SP111

E746-A750 del-specific AB SP111

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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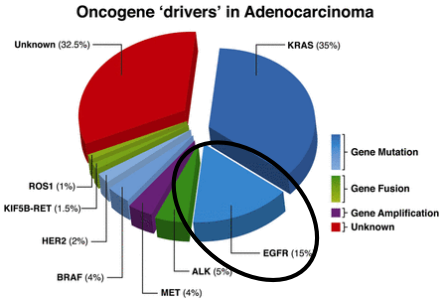
Immunohistochemcal classification of

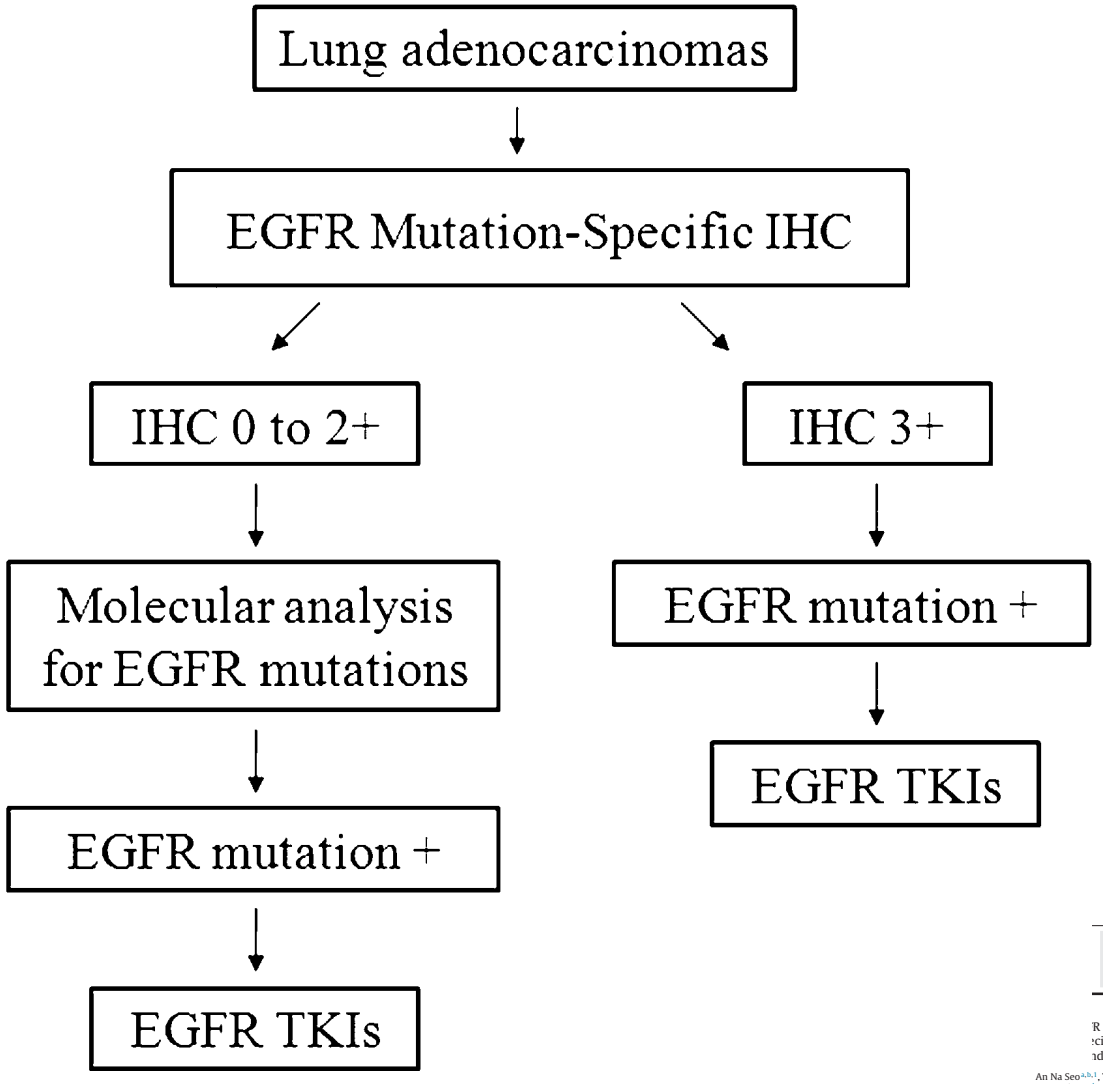
Lung cancer,

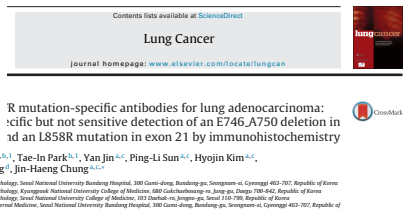
diagnosis and prediction.

EGFR



Algorithm

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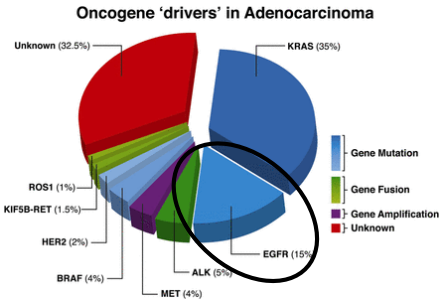
Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

EGFR



DNA(template) → *PCR* → *Analysis*

DNA-purification

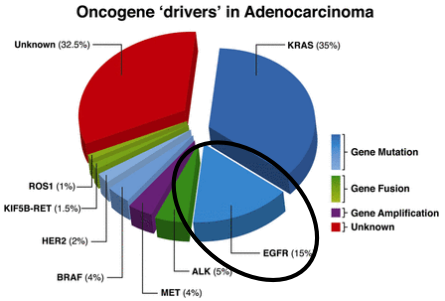
Tissue section

Immunohistochemcal classification of

Lung cancer,

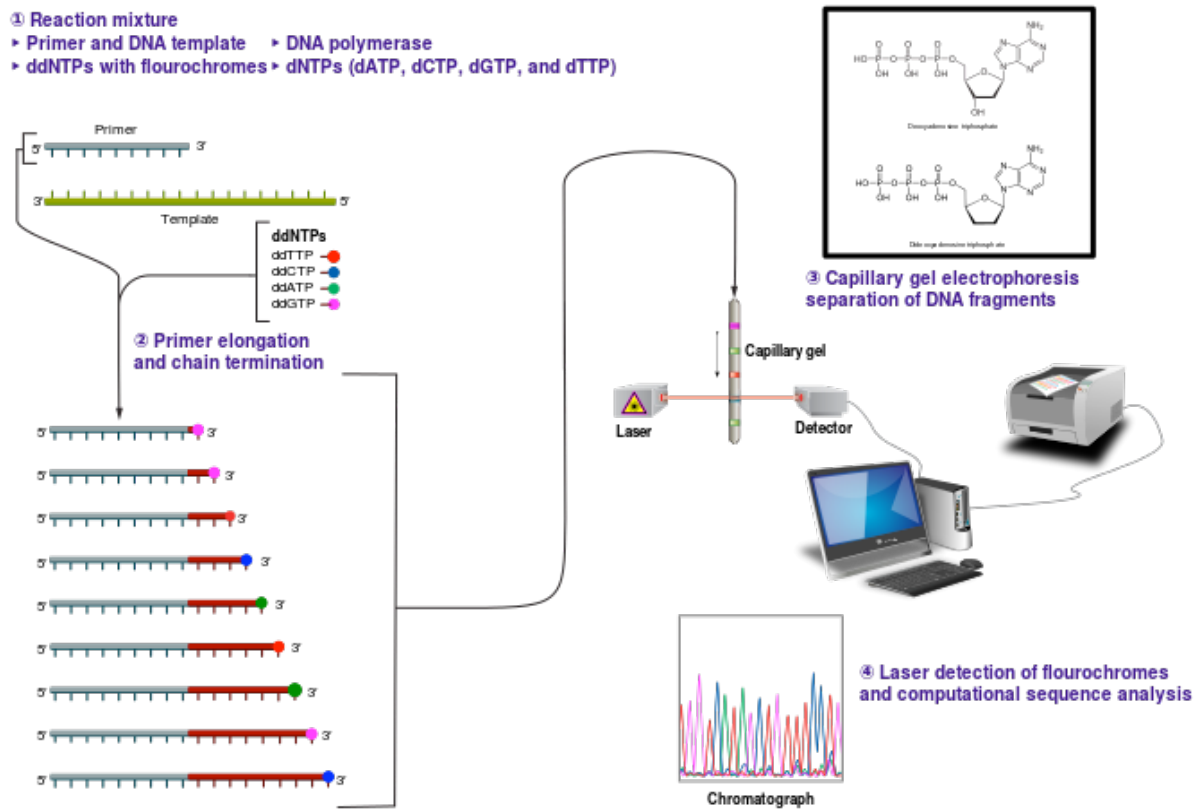
diagnosis and prediction.

EGFR



Analysis

Sequencing



Immunohistochemcal classification of

Lung cancer,

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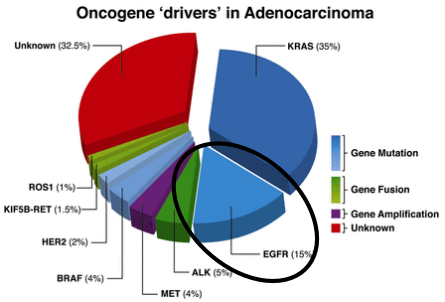
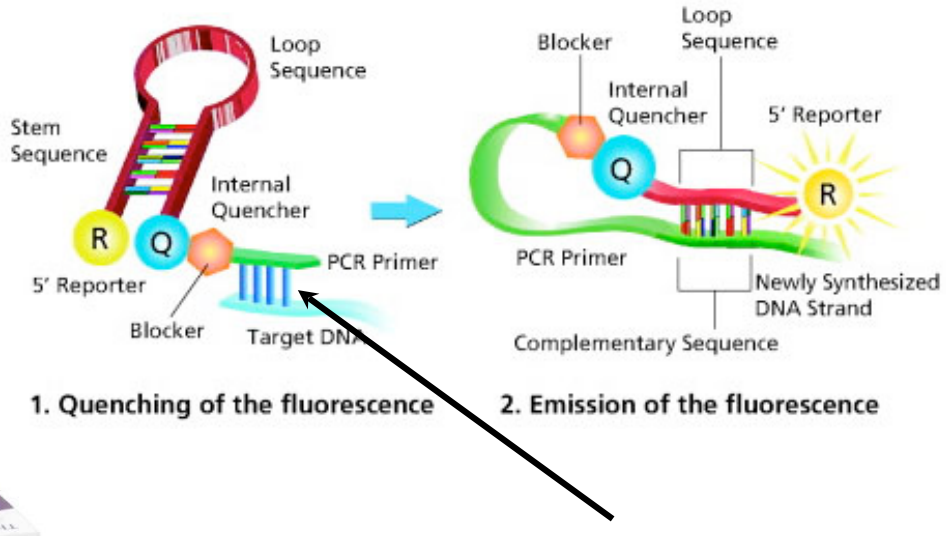
EGFR



PCR bassed test

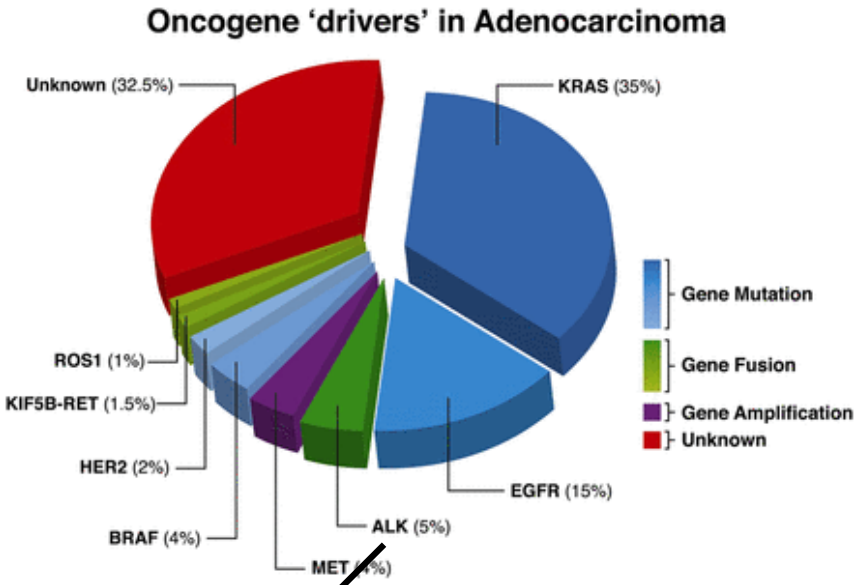


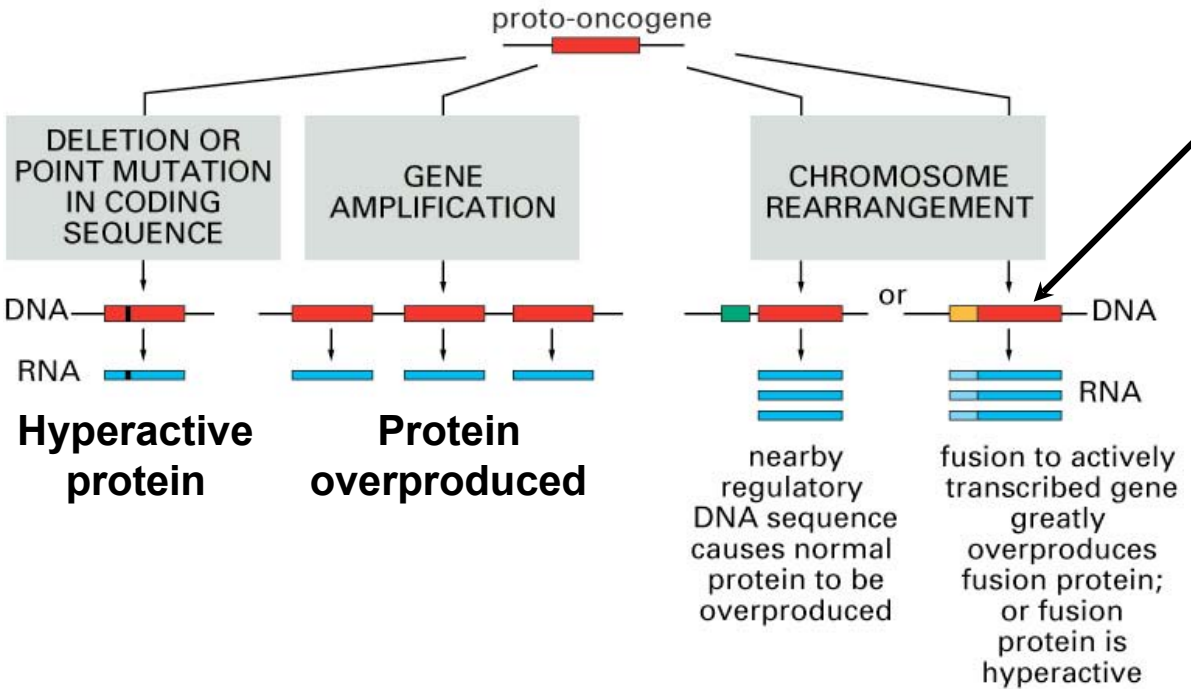
mutationspecific primer

Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.



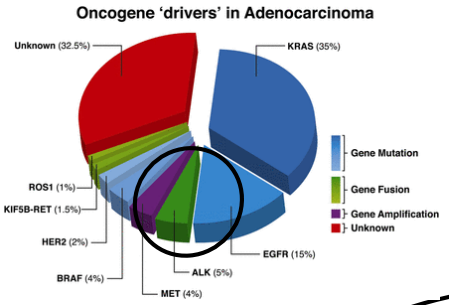


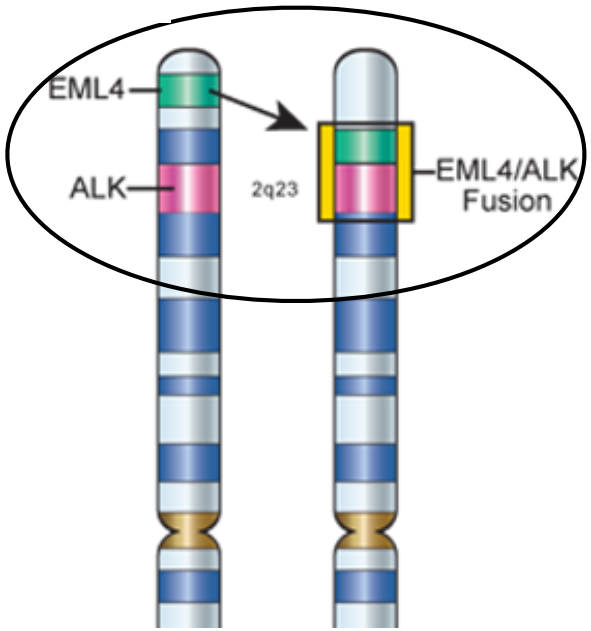
Immunohistochemcal classification of

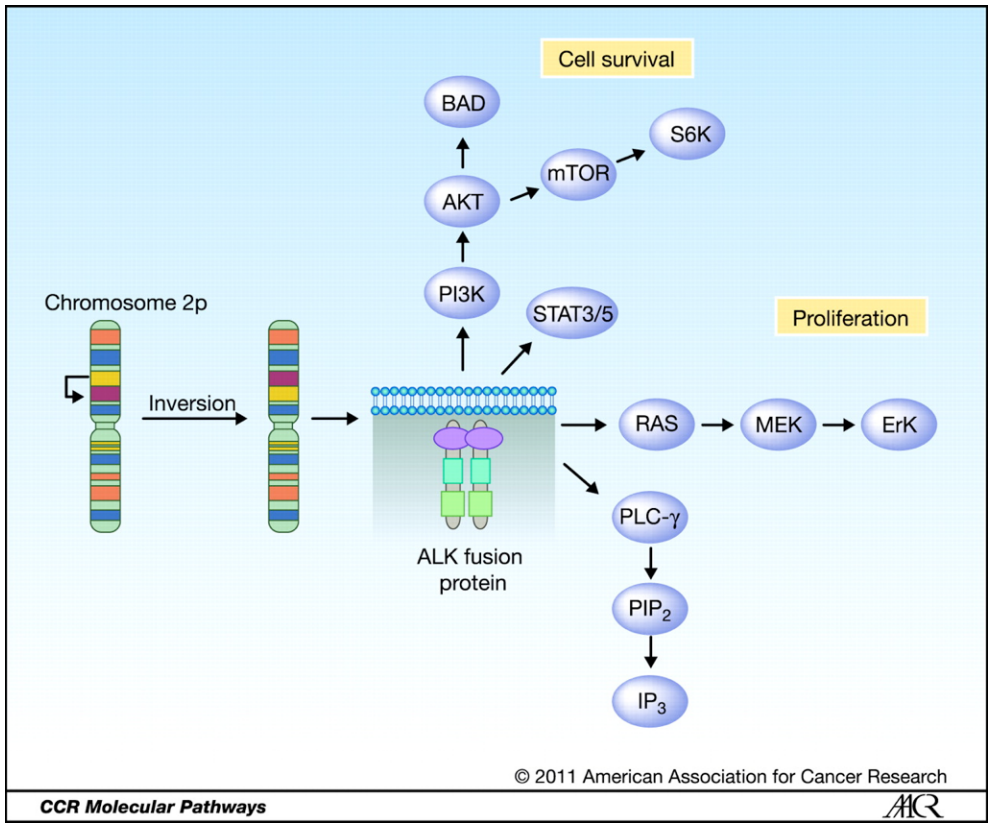
Lung cancer,

diagnosis and prediction.

ALK







Immunohistochemcal classification of

Lung cancer,

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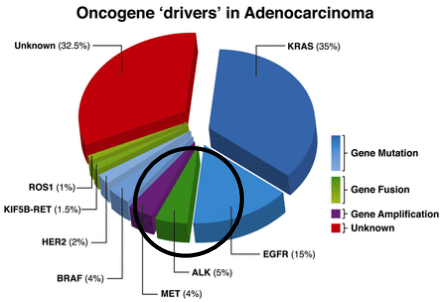
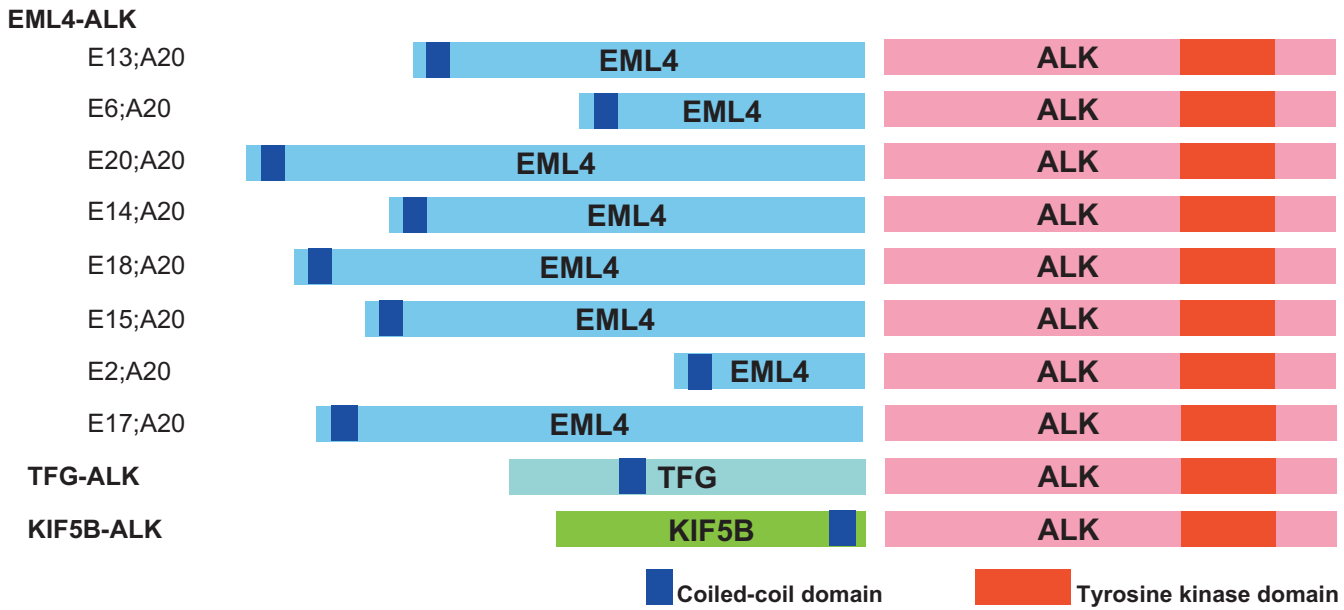
ALK





Immunohistochemcal classification of

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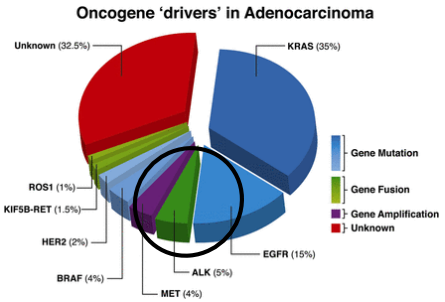

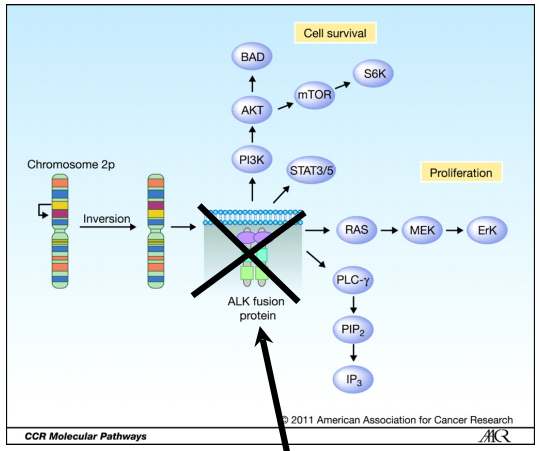

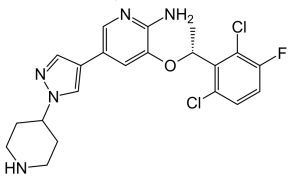

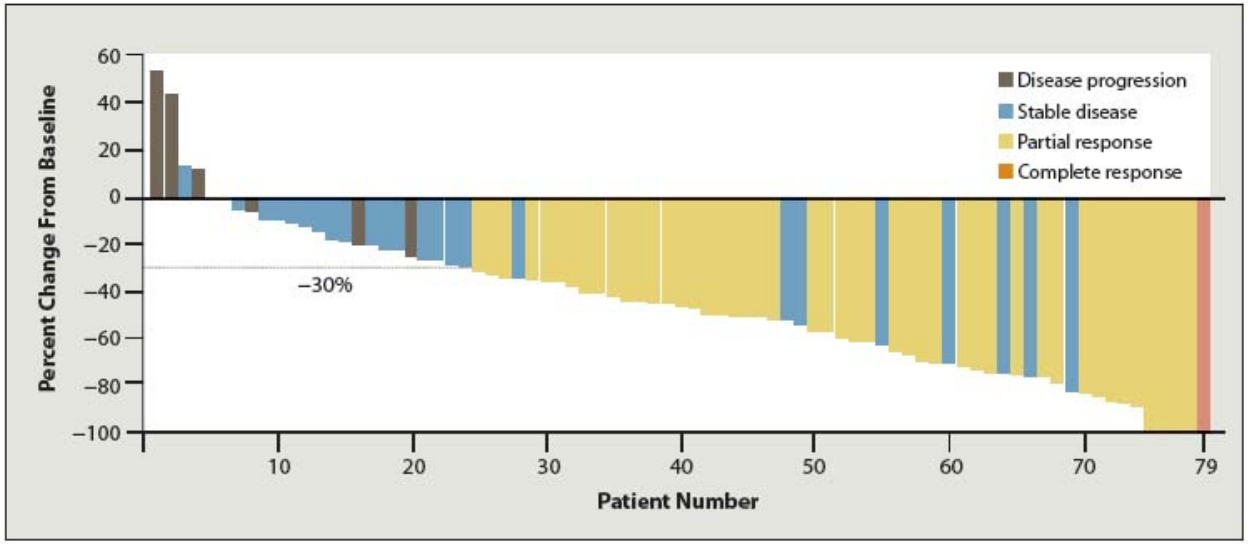

Figure 2: Waterfall plot showing response to crizotinib in patients with *EML4-ALK* NSCLC. Percent change in tumor burden relative to pretreatment baseline is represented. (Reproduced with permission from Kwak et al. N Engl J Med. 2010;363:1693-1703. Copyright © 2010, Massachusetts Medical Society.)

Immunohistochemcal classification of

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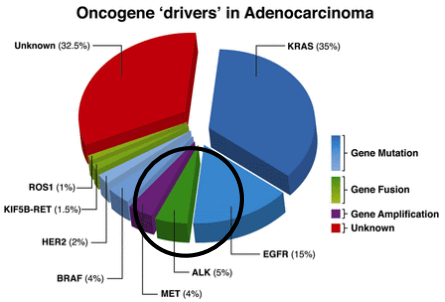
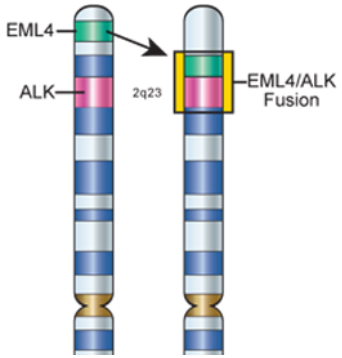
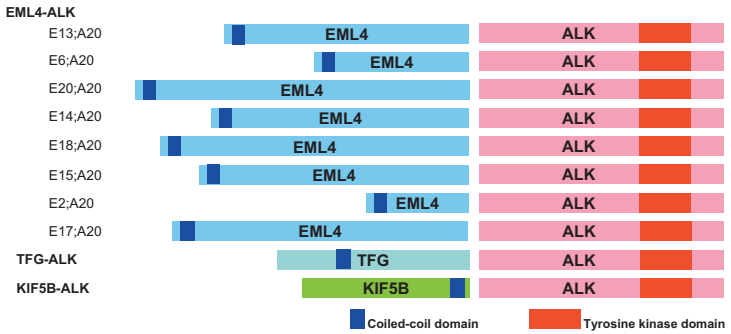
ALK



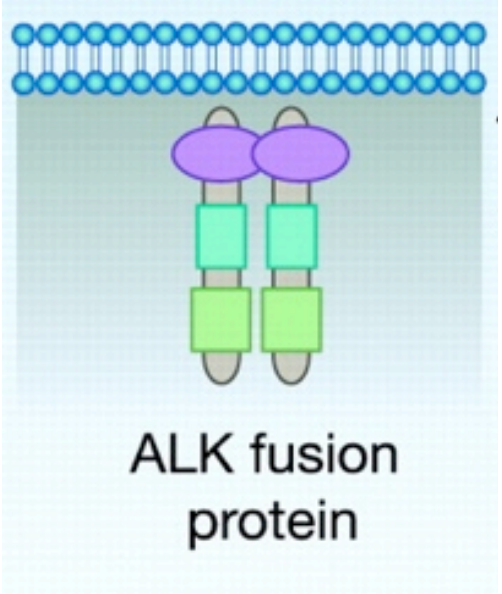
Detection of chromosomal changes



Detection of fusion RNA



Detection of fusion protein



Immunohistochemcal classification of

Lung cancer,

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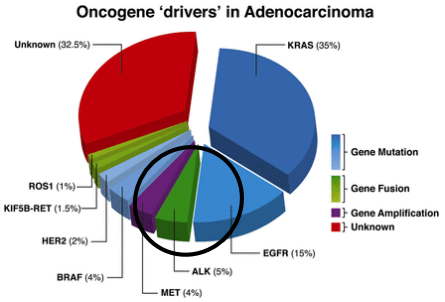
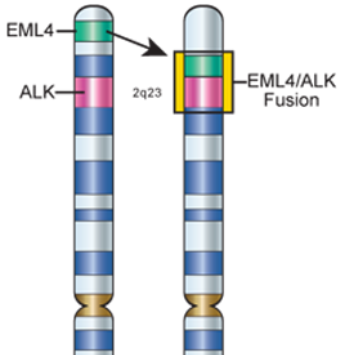
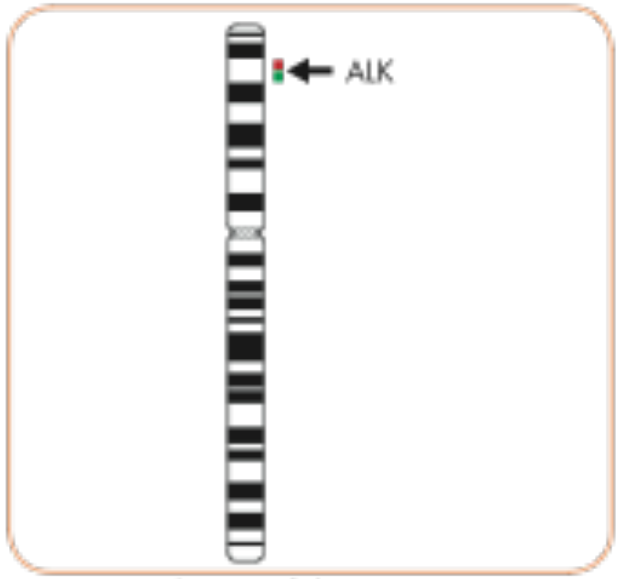


Detection of chromosomal changes

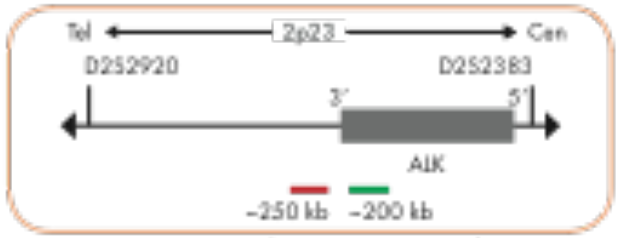


F(C)ISH

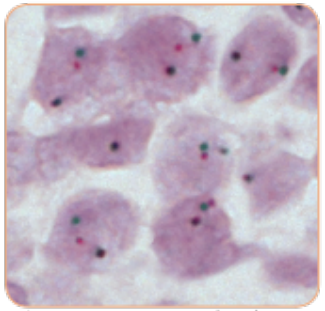
ZYTOVISION
Molecular diagnostics simplified

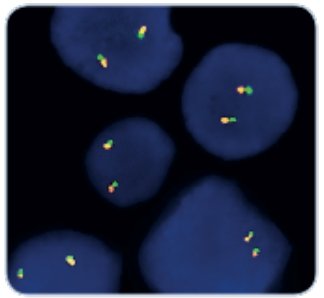


Ideogram of chromosome 2
indicating the hybridization locations.

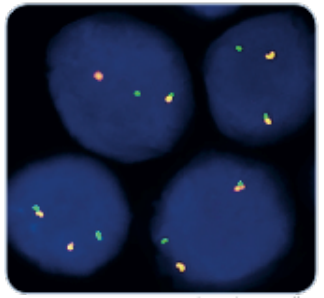


SPEC ALK Probe map (not to scale).





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

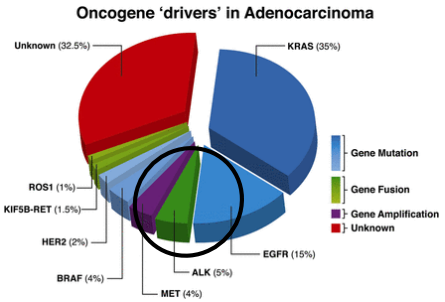


Immunohistochemcal classification of

Lung cancer,

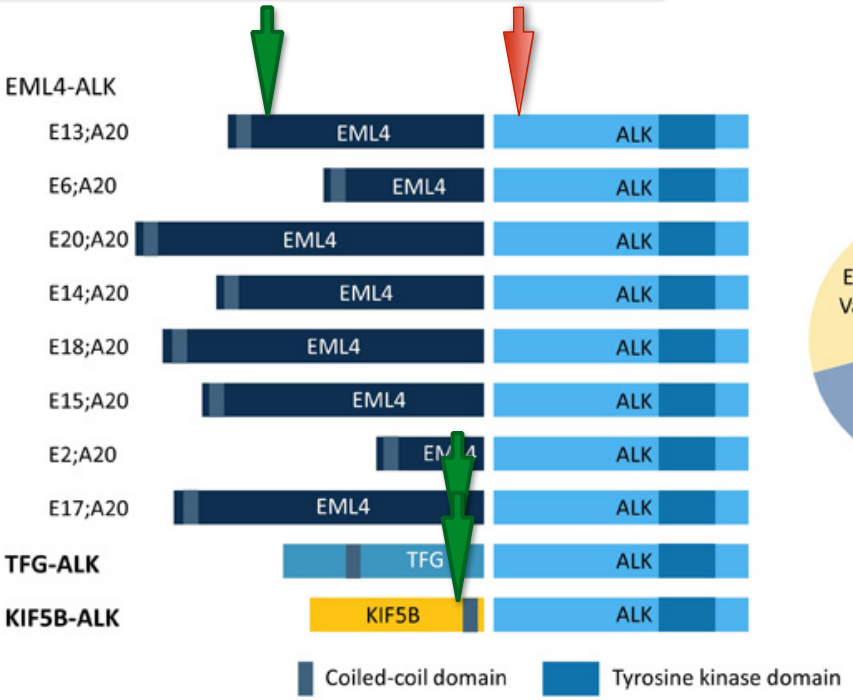
diagnosis and prediction.

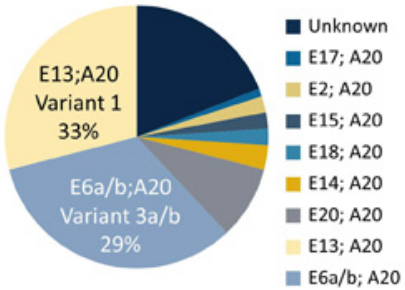
ALK



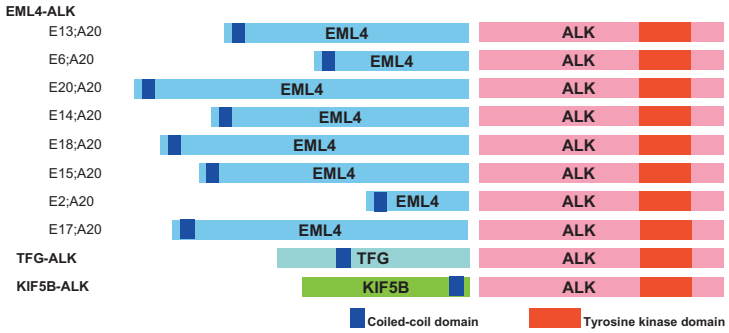
RT-PCR

3 different primers





Detection of fusion RNA



Immunohistochemcal classification of

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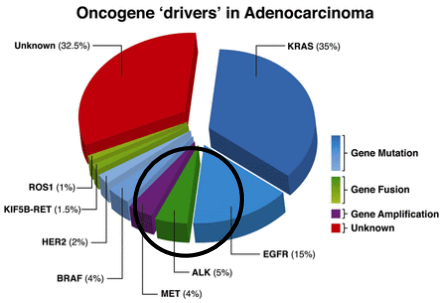
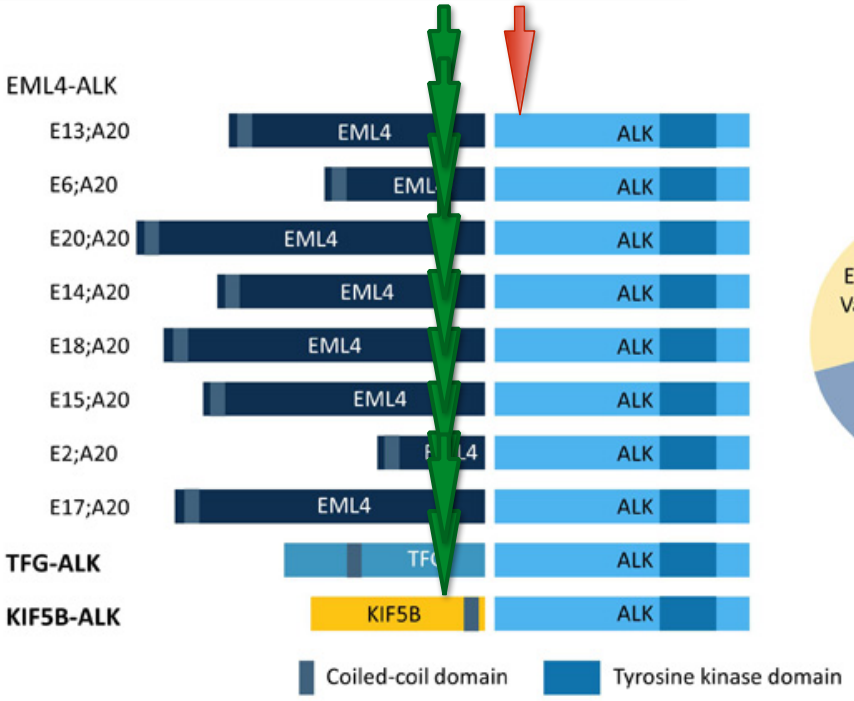
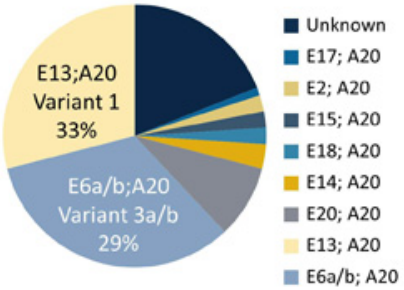


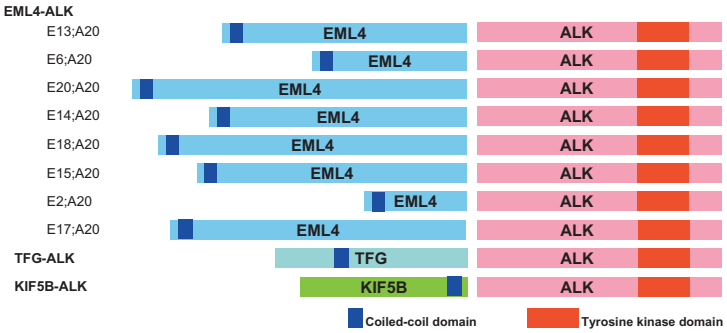
RT-PCR

10 different primers





Detection of fusion RNA



Immunohistochemcal classification of

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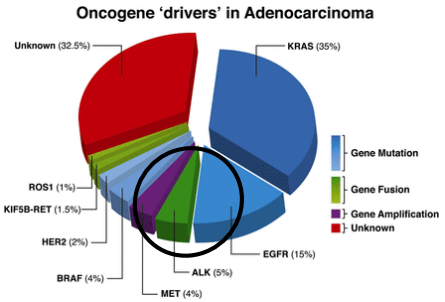
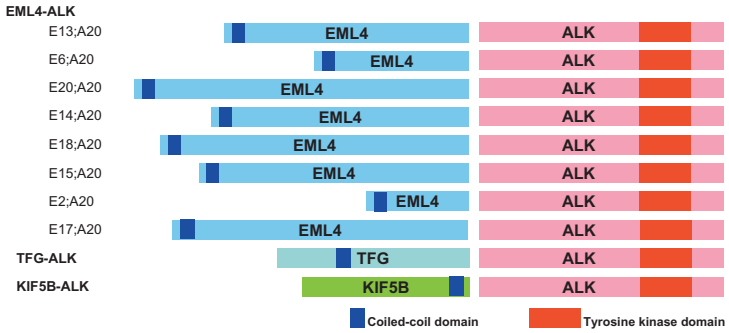
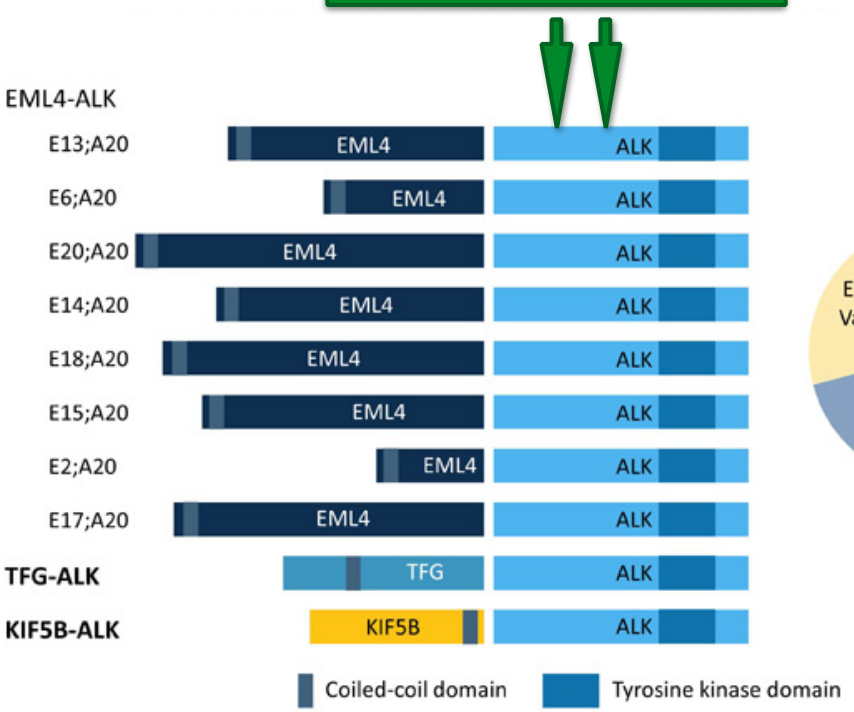
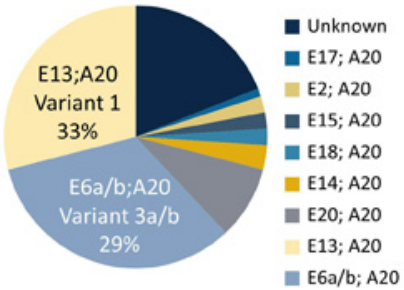


Detection of fusion RNA



1 primer set





Detects ALK independent of fusion partner

Immunohistochemcal classification of

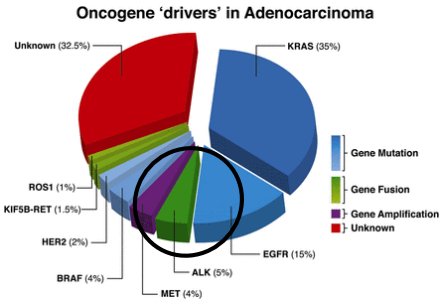
Lung cancer,

diagnosis and prediction.

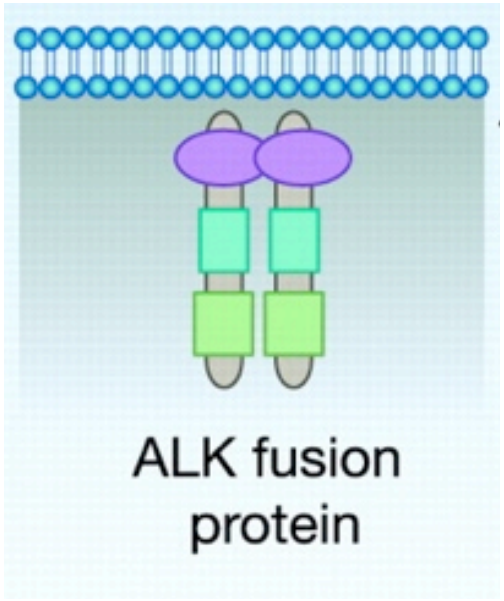
Region Syddanmark
Sygehus Lillebælt

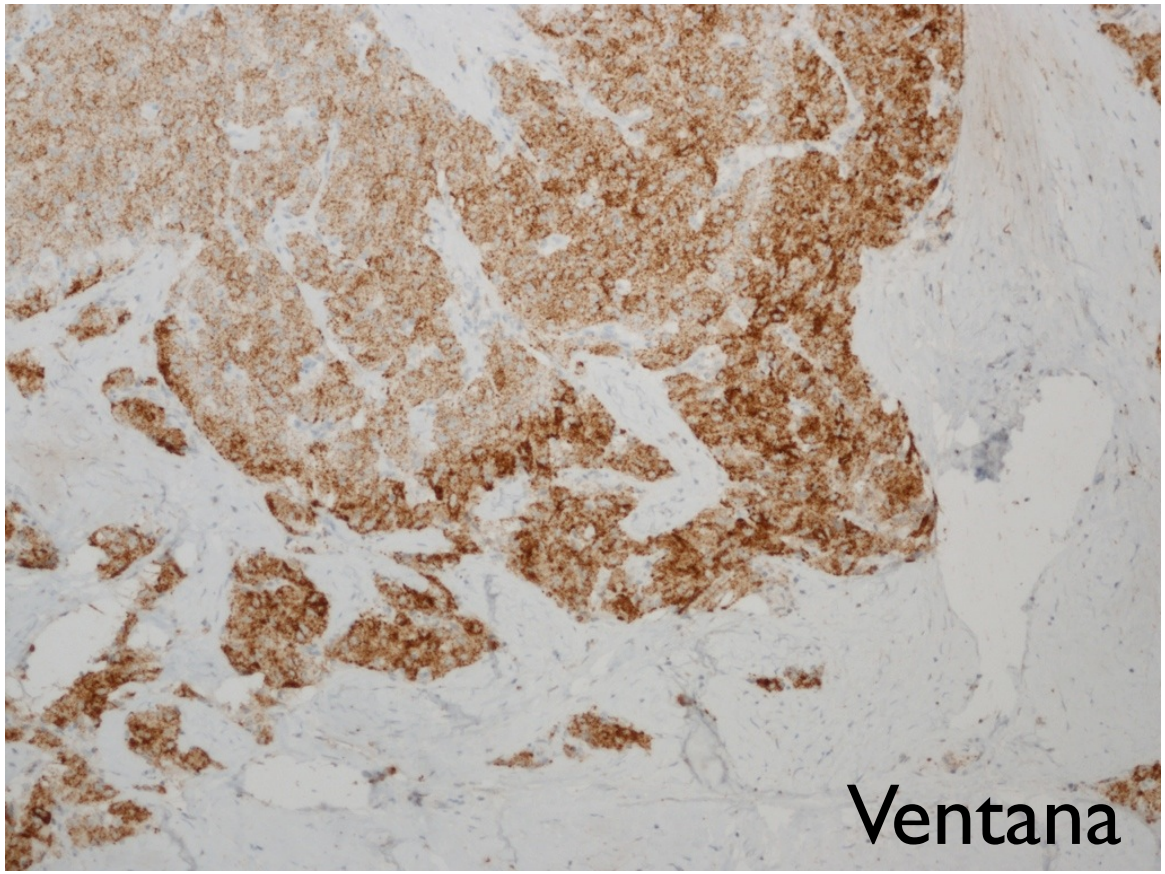
Immunohistochemistry

ALK



Detection of fusion protein





Detects ALK independent of fusion partner

Immunohistochemcal classification of

Lung cancer,

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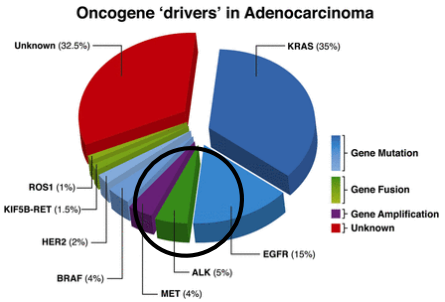
Immunohistochemistry

ALK



Detection of fusion protein

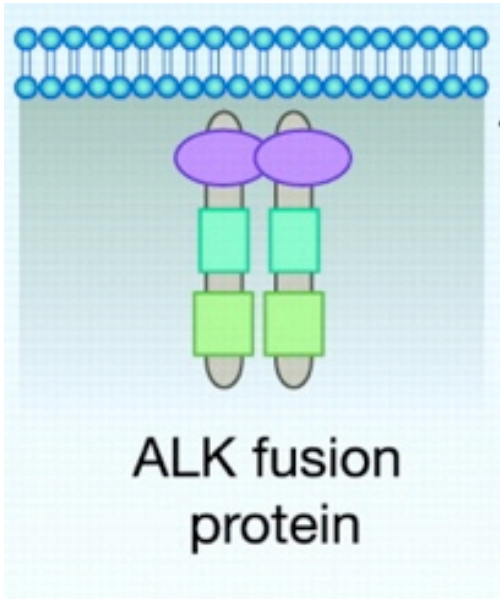
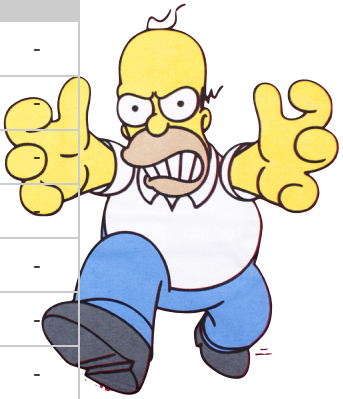


Table 1. **Antibodies and assessment marks for lu-ALK, run 51**

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)

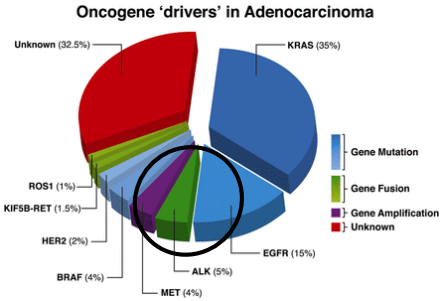


Immunohistochemcal classification of

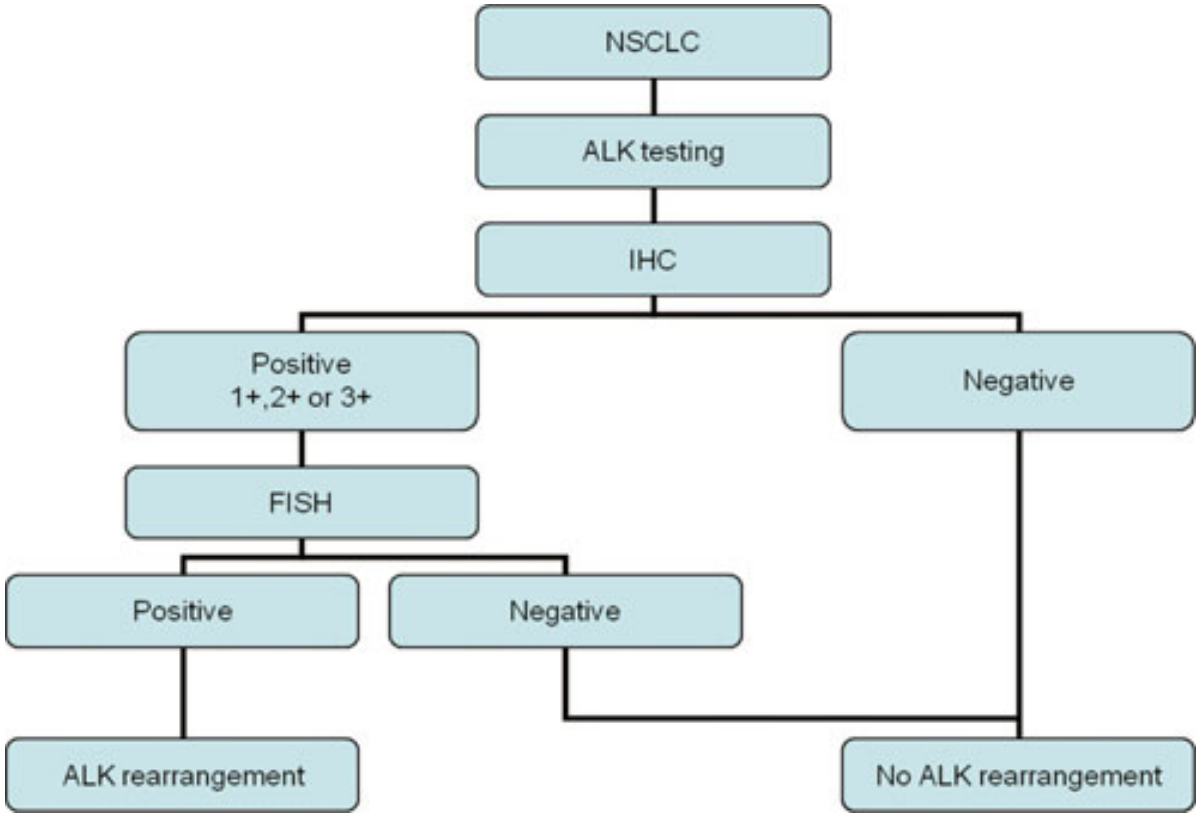
Lung cancer,

diagnosis and prediction.

ALK



Algorithm



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

Immunohistochemcal classification of

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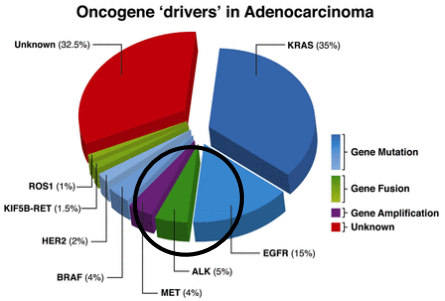
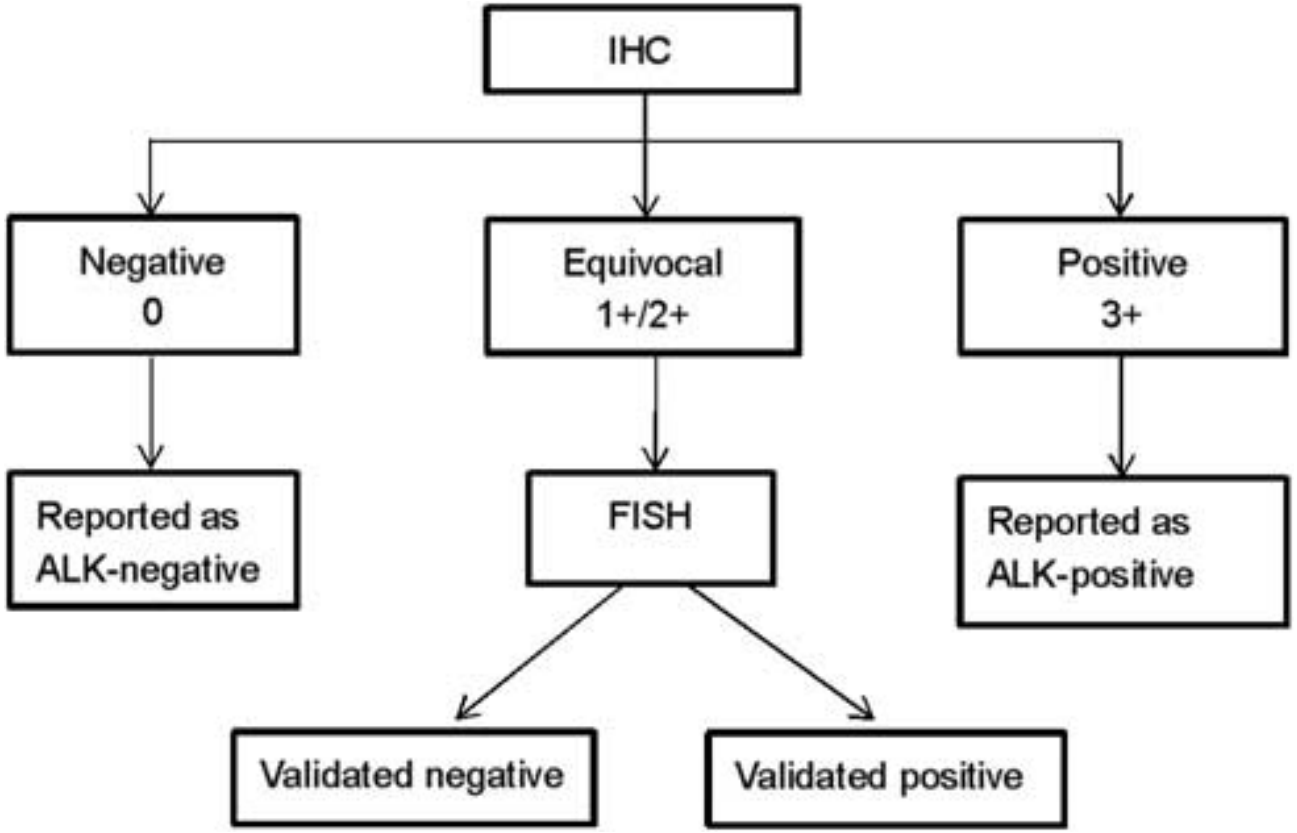
ALK



Detection of fusion protein

Algorithm



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

A Pooled-Data Analysis on Diagnostic Operating Characteristics of Immunohistochemistry

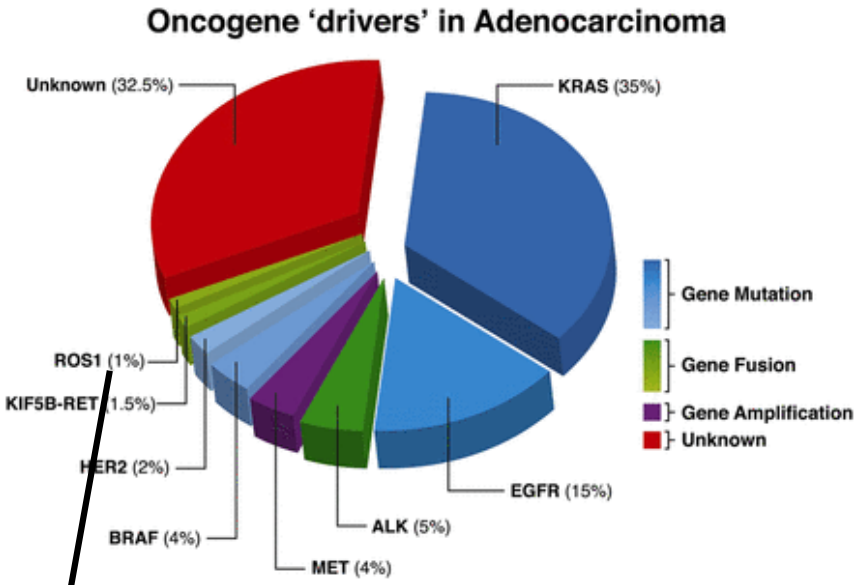
Long Jiang, MD, PhD,† Haihong Yang, MD, PhD,‡ Ping He, MD, PhD,§ Wenhua Liang, MD, PhD,‡ Jianrong Zhang, MD,*† Jingpei Li, MD,*† Yang Liu, MD,*† and Jianxing He, MD, PhD, FACS*†*

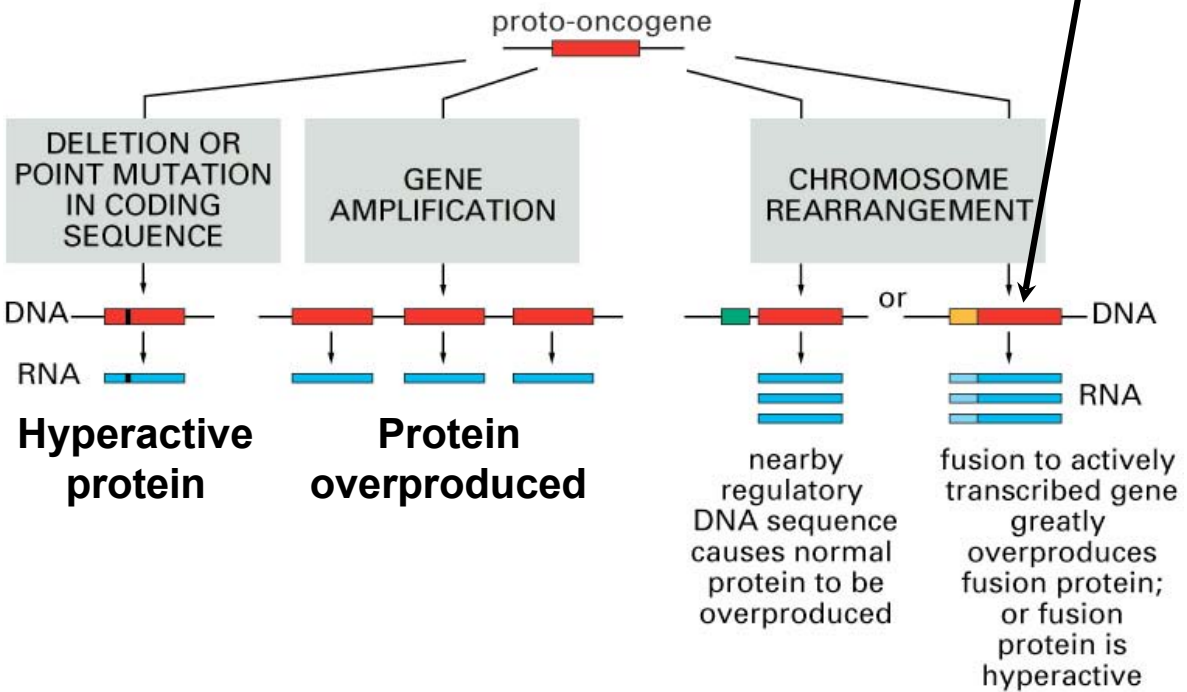
(*Am J Surg Pathol* 2016;40:697–703)

Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.



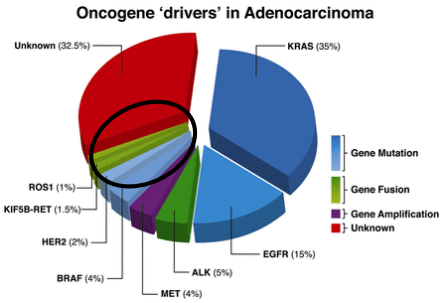


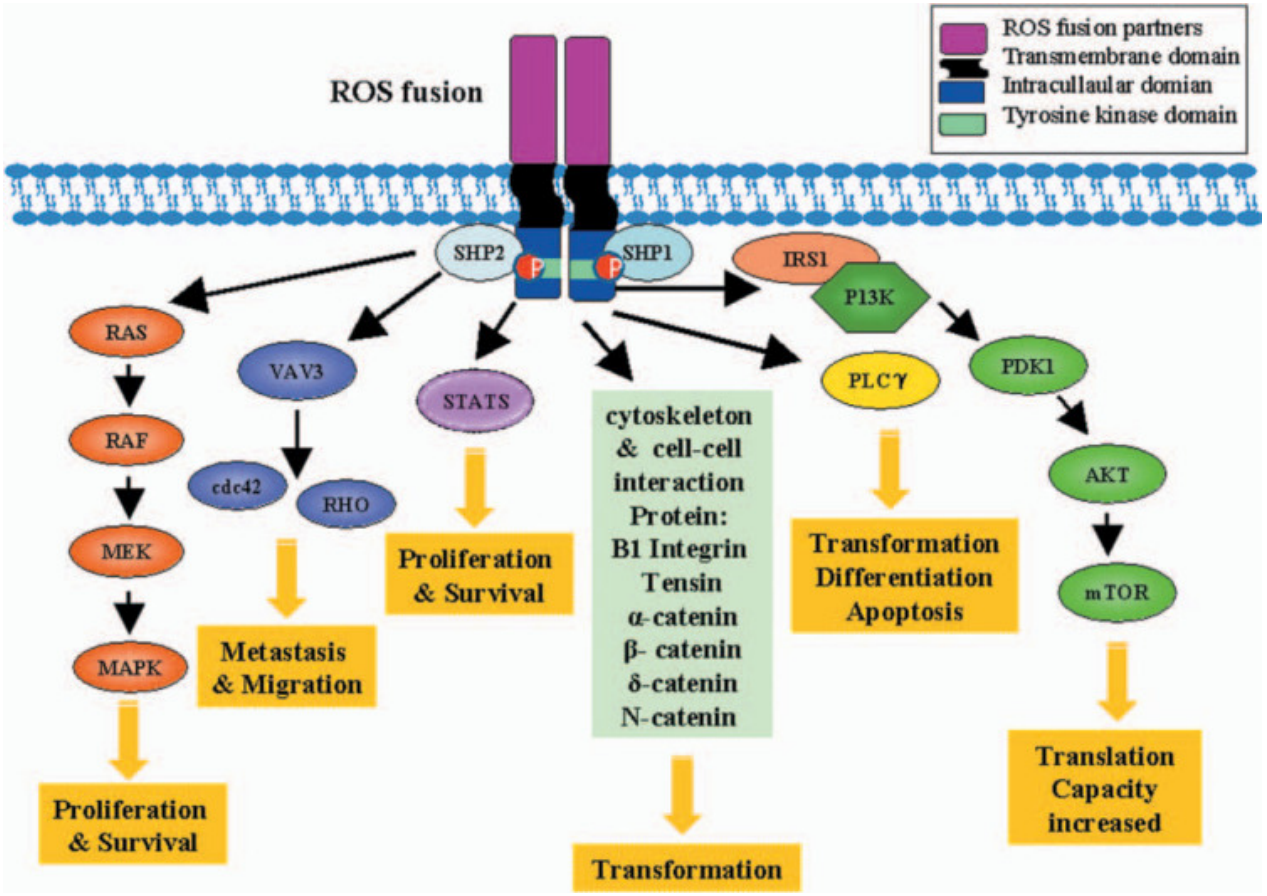
Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

ROS1





Immunohistochemcal classification of

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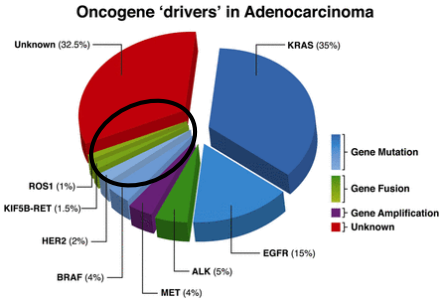
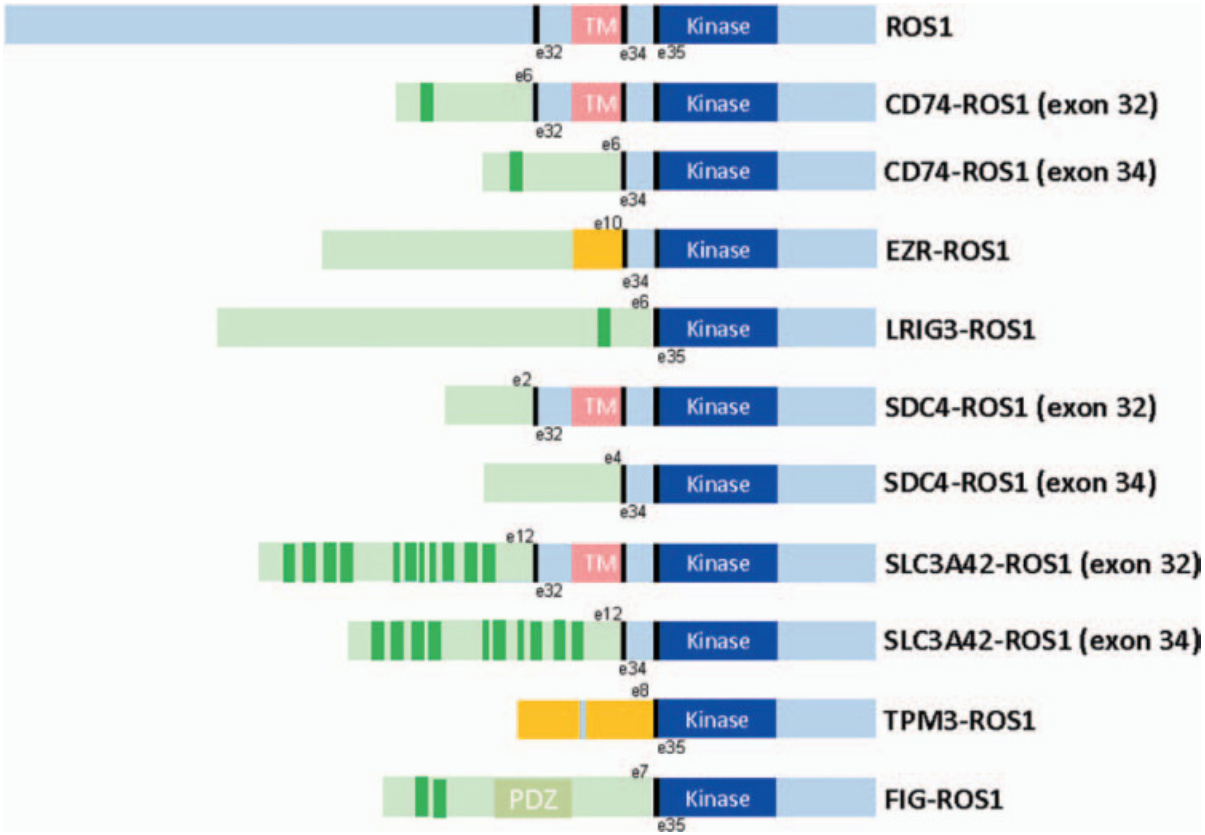
ROS1





Immunohistochemcal classification of

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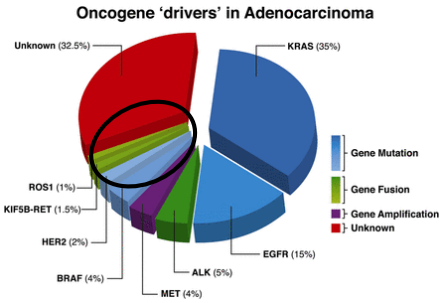
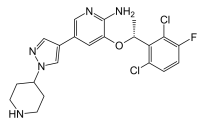
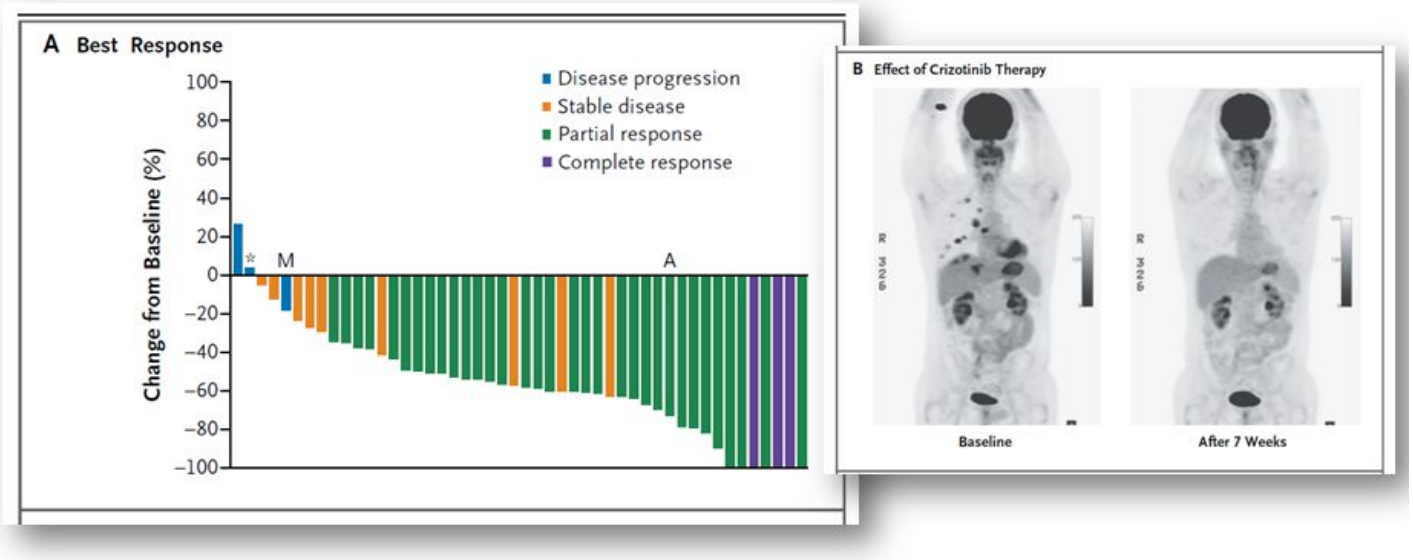
ROS1





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)

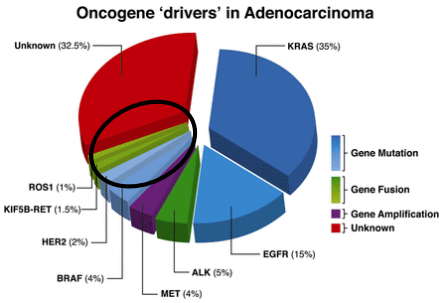
Shaw AT et al, N Engl J Med 2014;371:1963-71.

Immunohistochemcal classification of

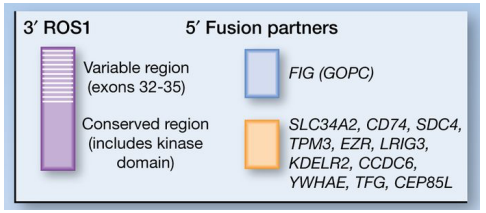
Lung cancer,

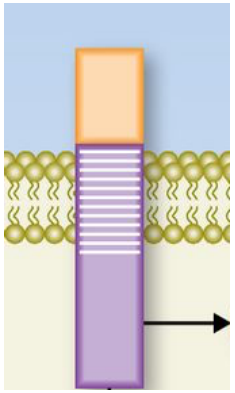
diagnosis and prediction.

ROS1

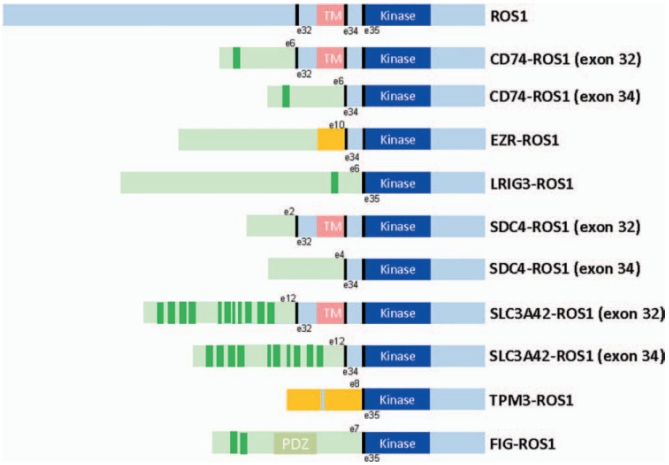


Detection of fusion protein

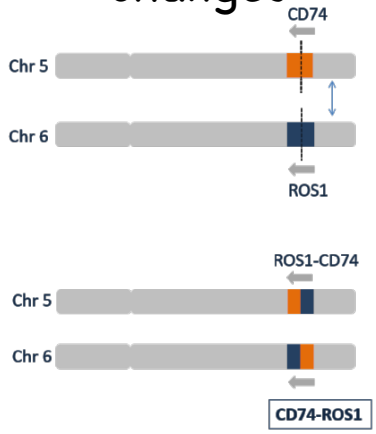




Detection of fusion RNA



Detection of chromosomal changes

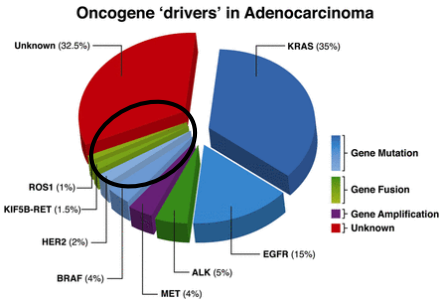


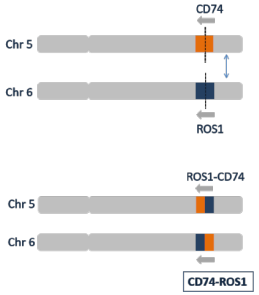
Immunohistochemcal classification of

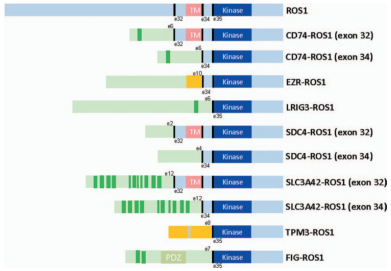
Lung cancer,

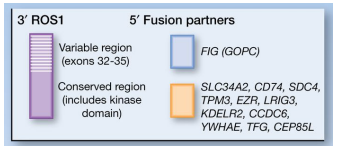
diagnosis and prediction.

ROS1









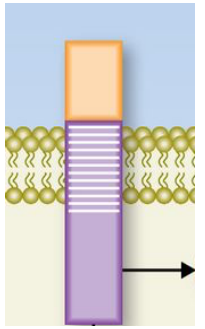


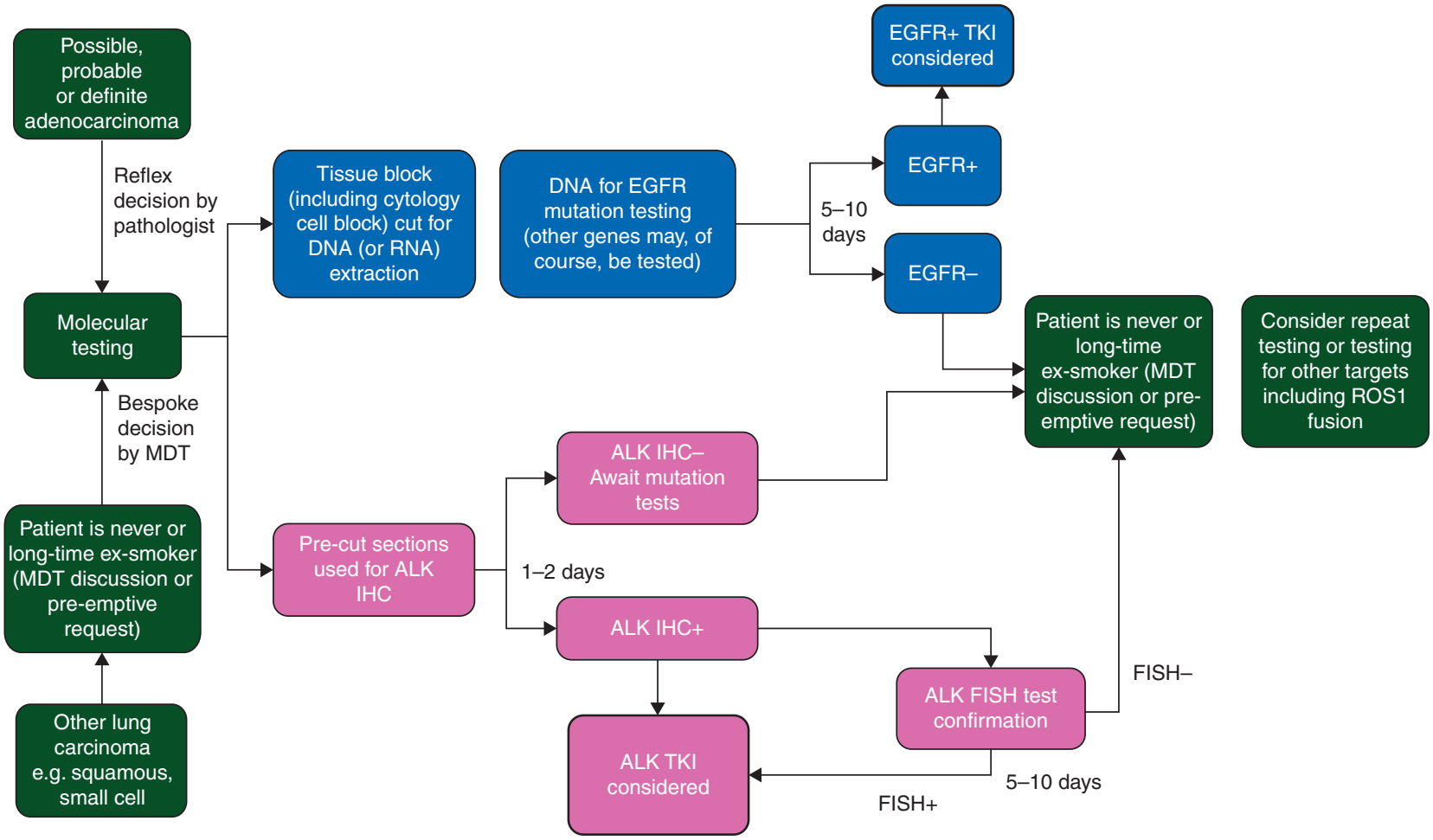
Table 5 Commercially available assays for *ROS1* testing

Method	Manufacturer	Reagent	Regulatory status
FISH	Cytocell	ROS1 Dual Color Break Apart Probe	CE-IVD
	ZytoVision/Zytomed	ZytoLight SPEC ROS1 Dual Color Break Apart Probe	CE-IVD
	Abbott	ROS 1 Break-Apart FISH	RUO
IHC	Cell Signaling Technologies	ROS1 D4D6 rabbit monoclonal antibody	RUO
RT-PCR	AmoyDx	ALK and ROS1 gene fusion detection kit	CE-IVD
NGS	Thermo Fisher	Oncomine Fusion panel (ALK, ROS1, RET and NTRK1)	CE-IVD
	ArcherDx	FusionPlex™ ALK, RET, ROS1 v2 Panel	RUO

NordiQC

Immunohistochemcal classification of Lung cancer, diagnosis and prediction.

Region Syddanmark
Sygehus Lillebælt



Precision medicine in NSCLC and pathology: how does *ALK* fit in the pathway?

K. M. Kerr[1]* & F. López-Ríos[2]

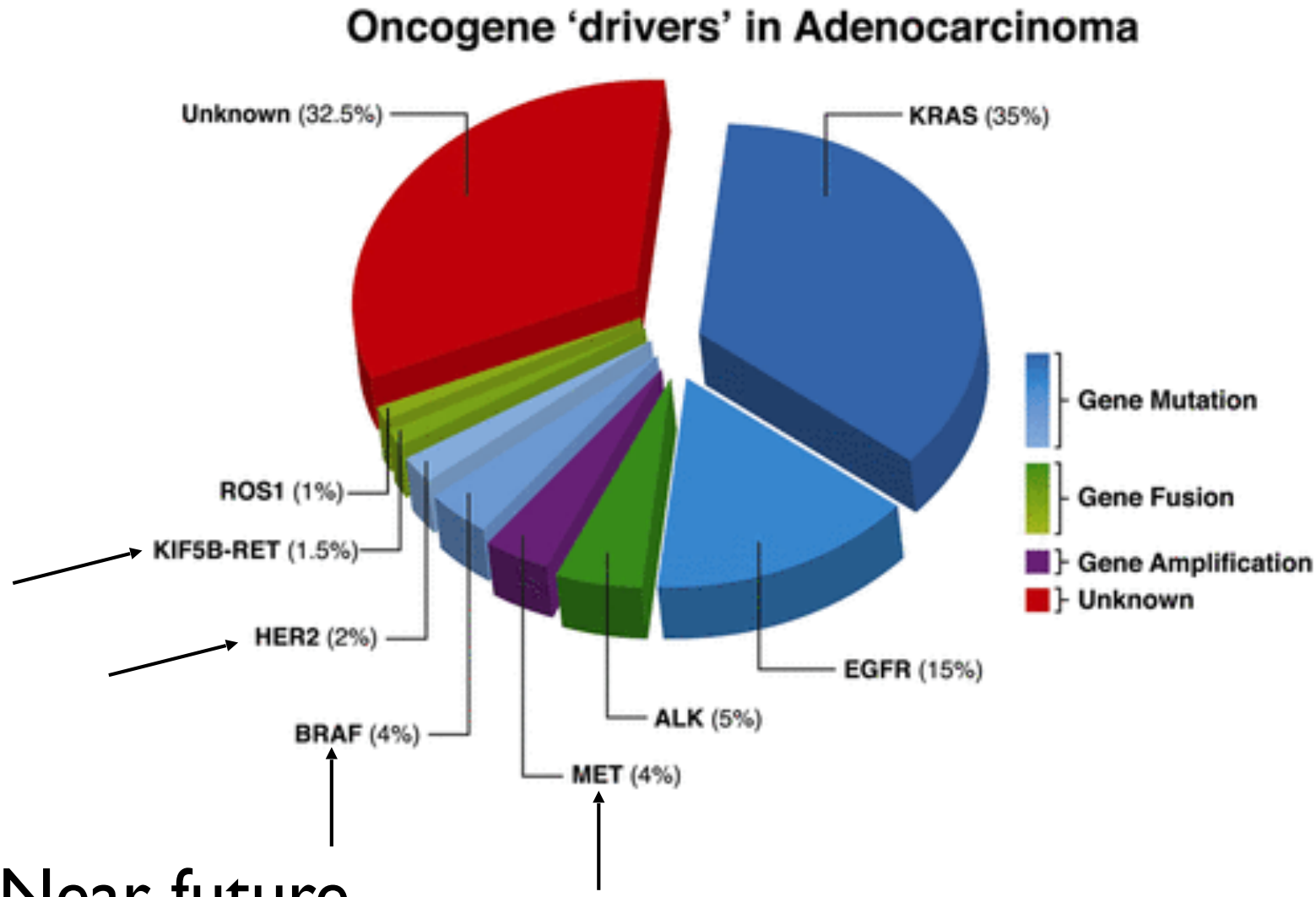
[1]Department of Pathology, Aberdeen University Medical School, Aberdeen Royal Infirmary, Aberdeen, UK; [2]Laboratorio de Dianas Terapéuticas, Hospital Universitario HM Sanchinarro, Madrid, Spain

Annals of Oncology 27 (Supplement 3): iii16–iii24, 2016
doi:10.1093/annonc/mdw302

Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.



Near future

(now ?)

Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

Region Syddanmark
Sygehus Lillebælt

Next generation seq.

Possible, probable or definite adenocarcinoma

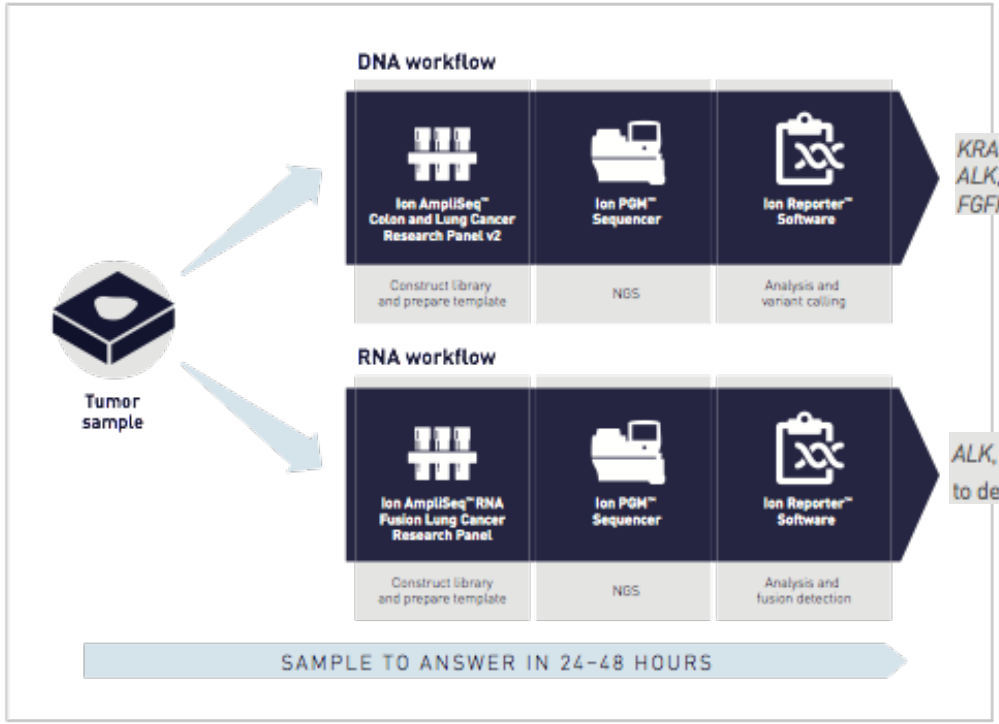
Reflex decision by pathologist

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

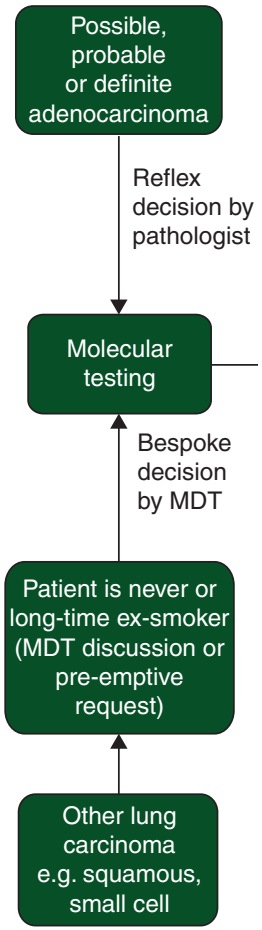


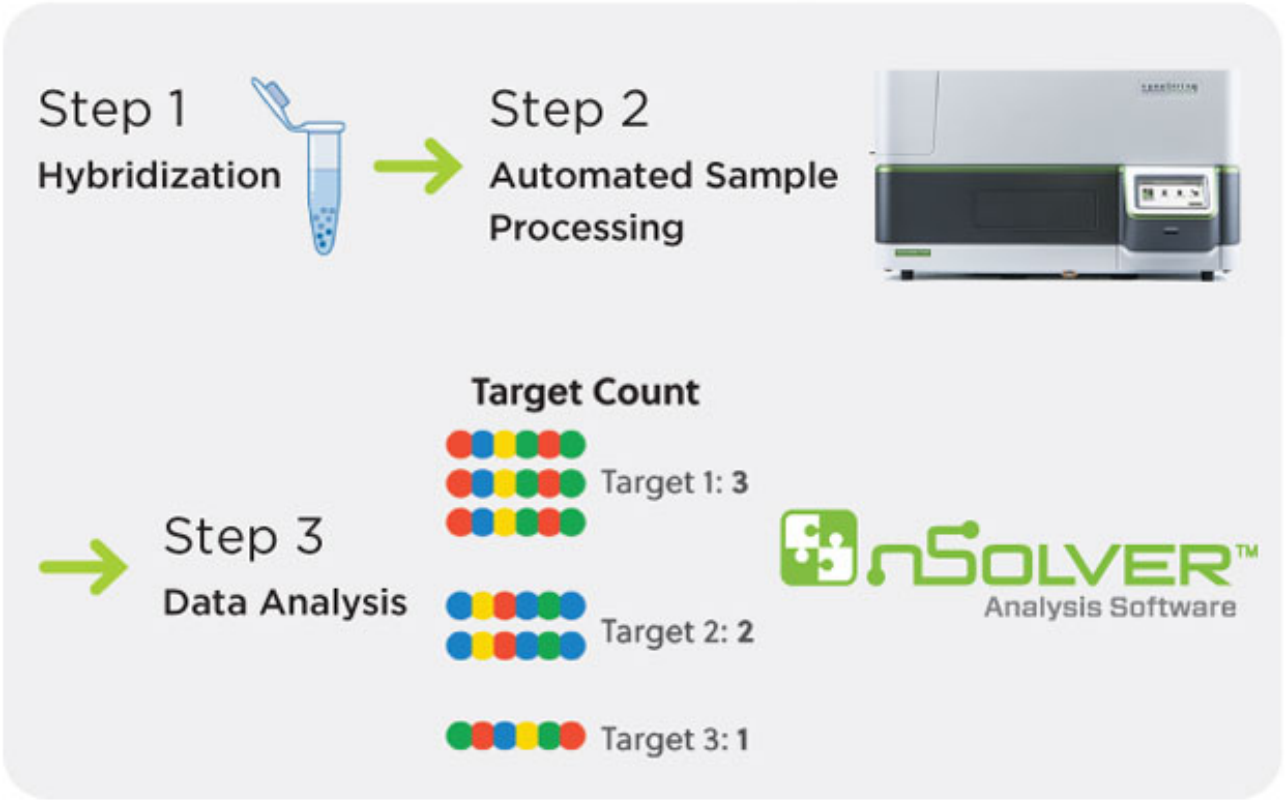
Immunohistochemcal classification of

Lung cancer,

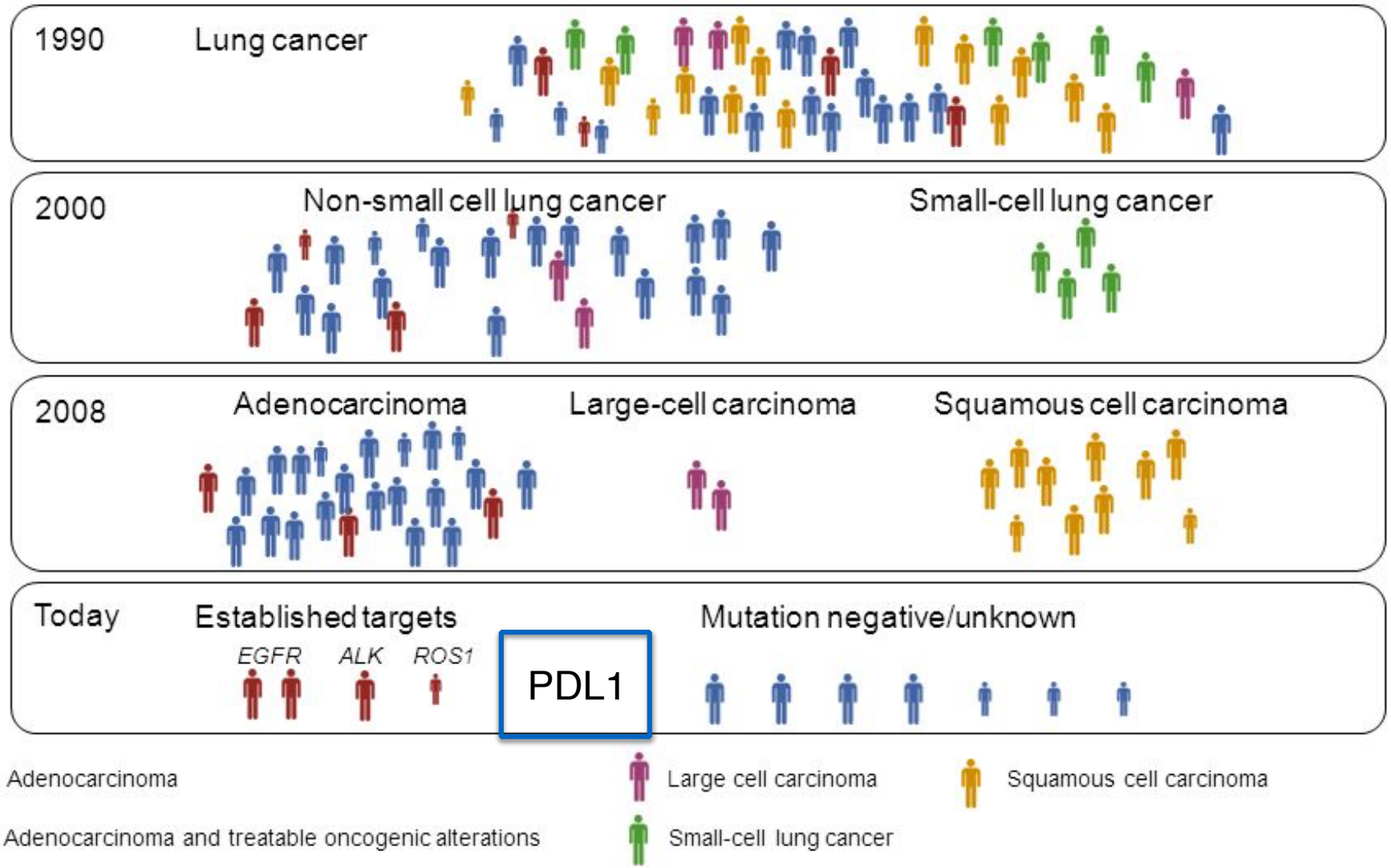
diagnosis and prediction.

NanoString





Patient selection in lung cancer: Evolution over time



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

Immunohistochemcal classification of

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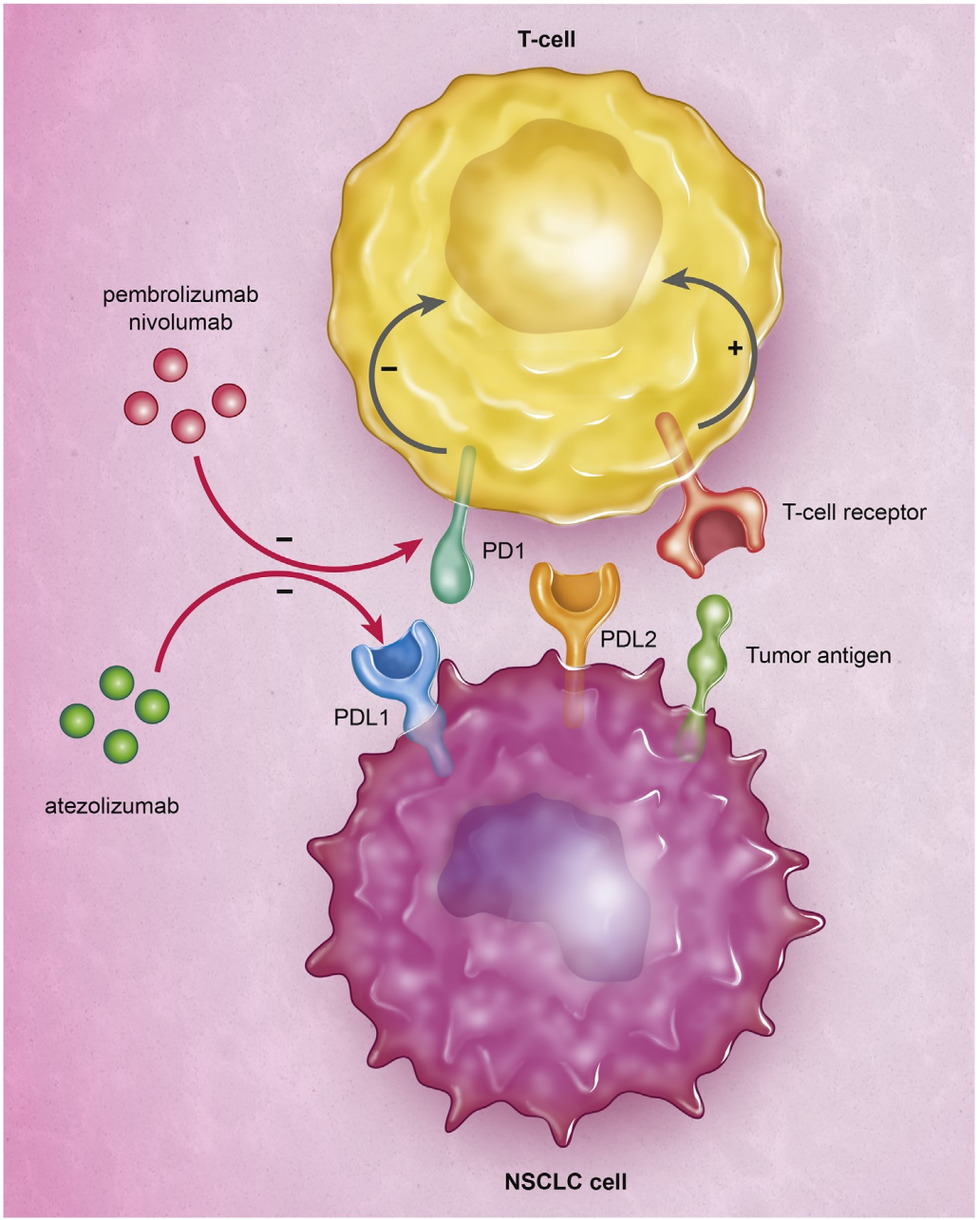

Immunohistochemcal classification of

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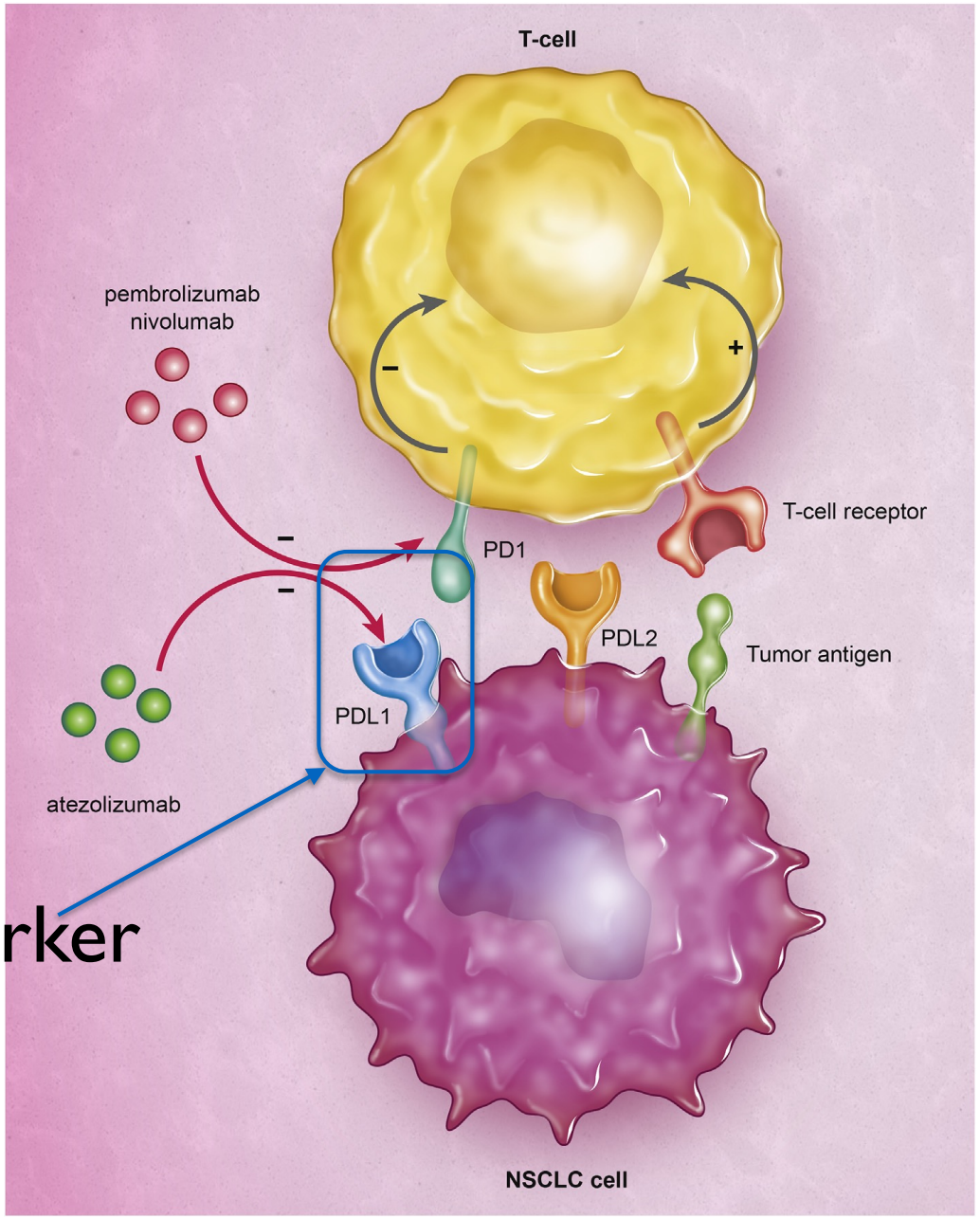
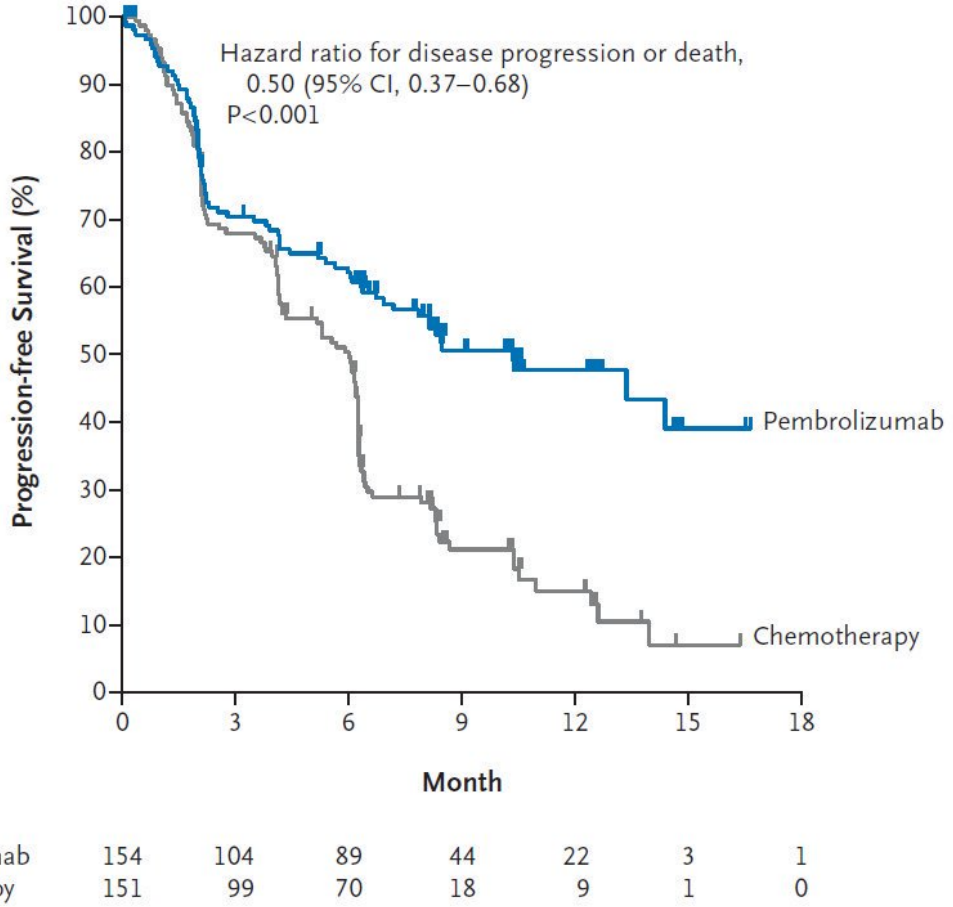


Predictive marker

Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.



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

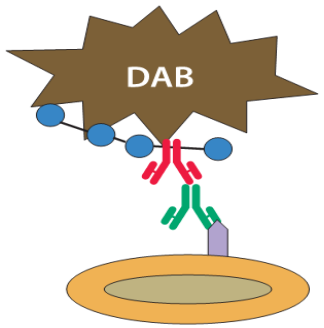
Martin Reck, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D., Andrew G. Robinson, M.D., Rina Hui, M.B., B.S., Ph.D., Tibor Csőszi, M.D., Andrea Fülöp, M.D., Maya Gottfried, M.D., Nir Peled, M.D., Ph.D., Ali Tafreshi, M.D., Sinead Cuffe, M.D., Mary O'Brien, M.D., Suman Rao, M.D., Katsuyuki Hotta, M.D., Ph.D.,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

Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

Region Syddanmark
Sygehus Lillebælt



Kromogen (farvestof)

Visualiseringssystem (enzymer)
Sekundært antistof
Primært antistof

Antigen
Cellens cytoplasma
Cellekerne

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.

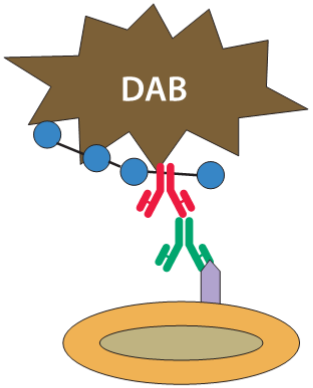
Step 3

PD-L1 testing

Immunohistochemcal classification of

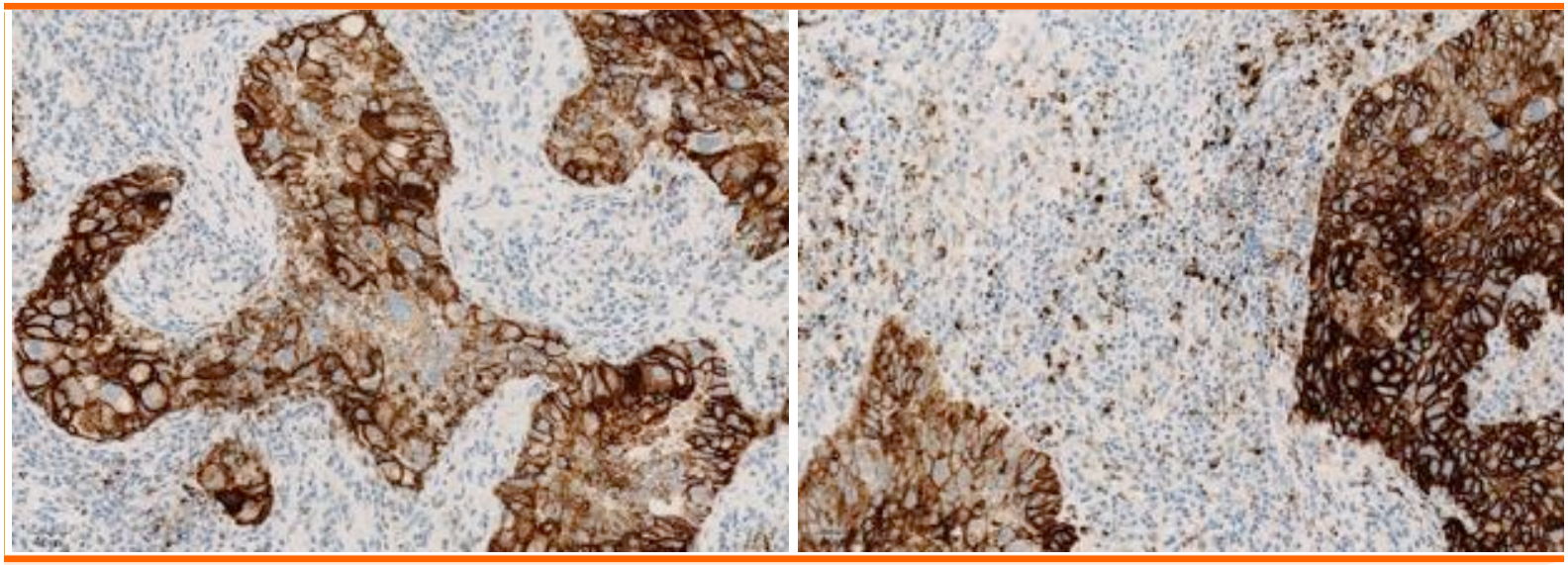
Lung cancer,

diagnosis and prediction.



Kromogen (farvestof)

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



Immunhistological staining for PDL1

Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

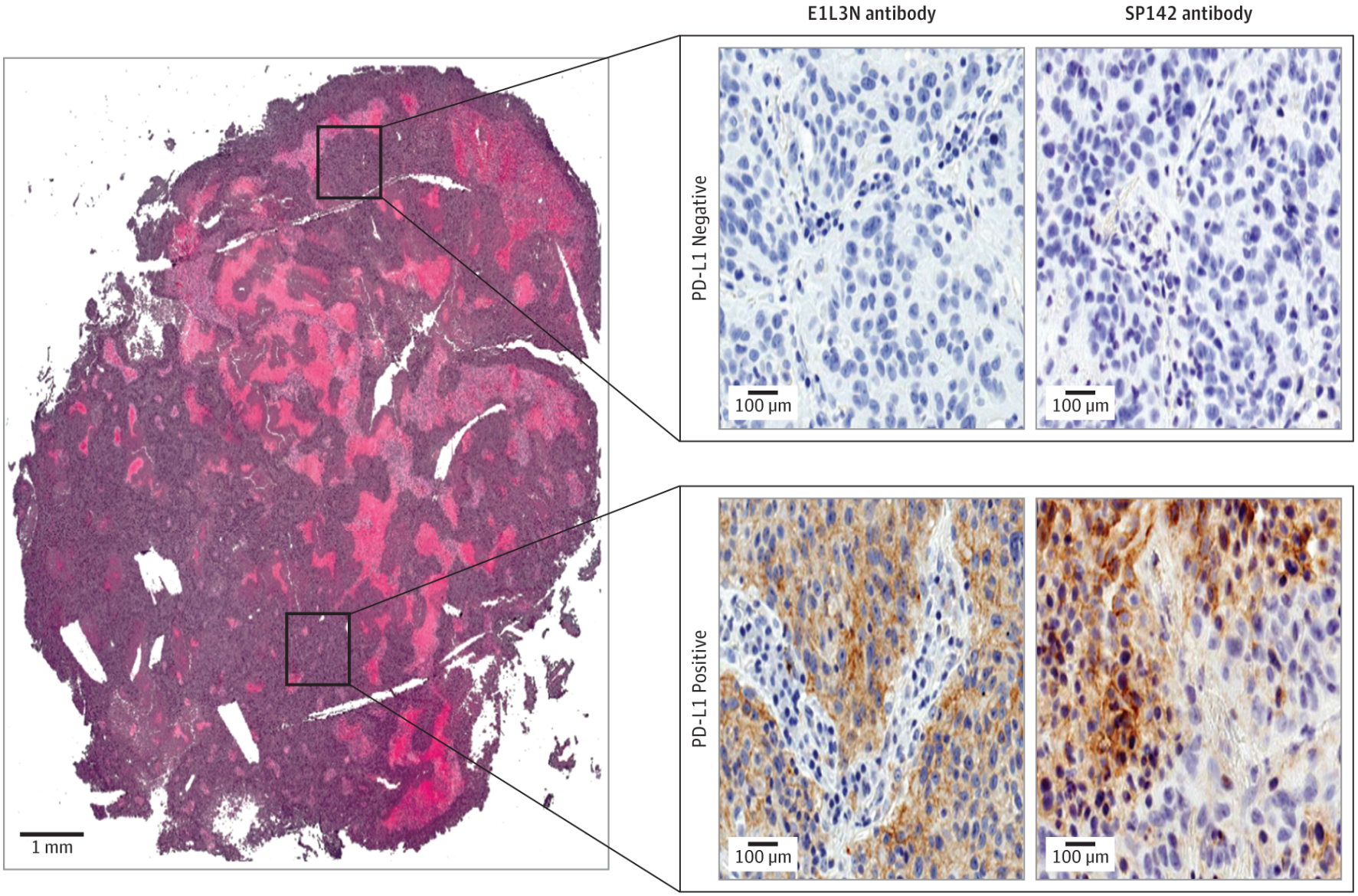


Table 1
Results of randomised phase III trials of immune checkpoint inhibitors (ICIs) for advanced non-small-cell lung cancer (NSCLC).

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.

Immunohistochemcal classification of

Lung cancer,

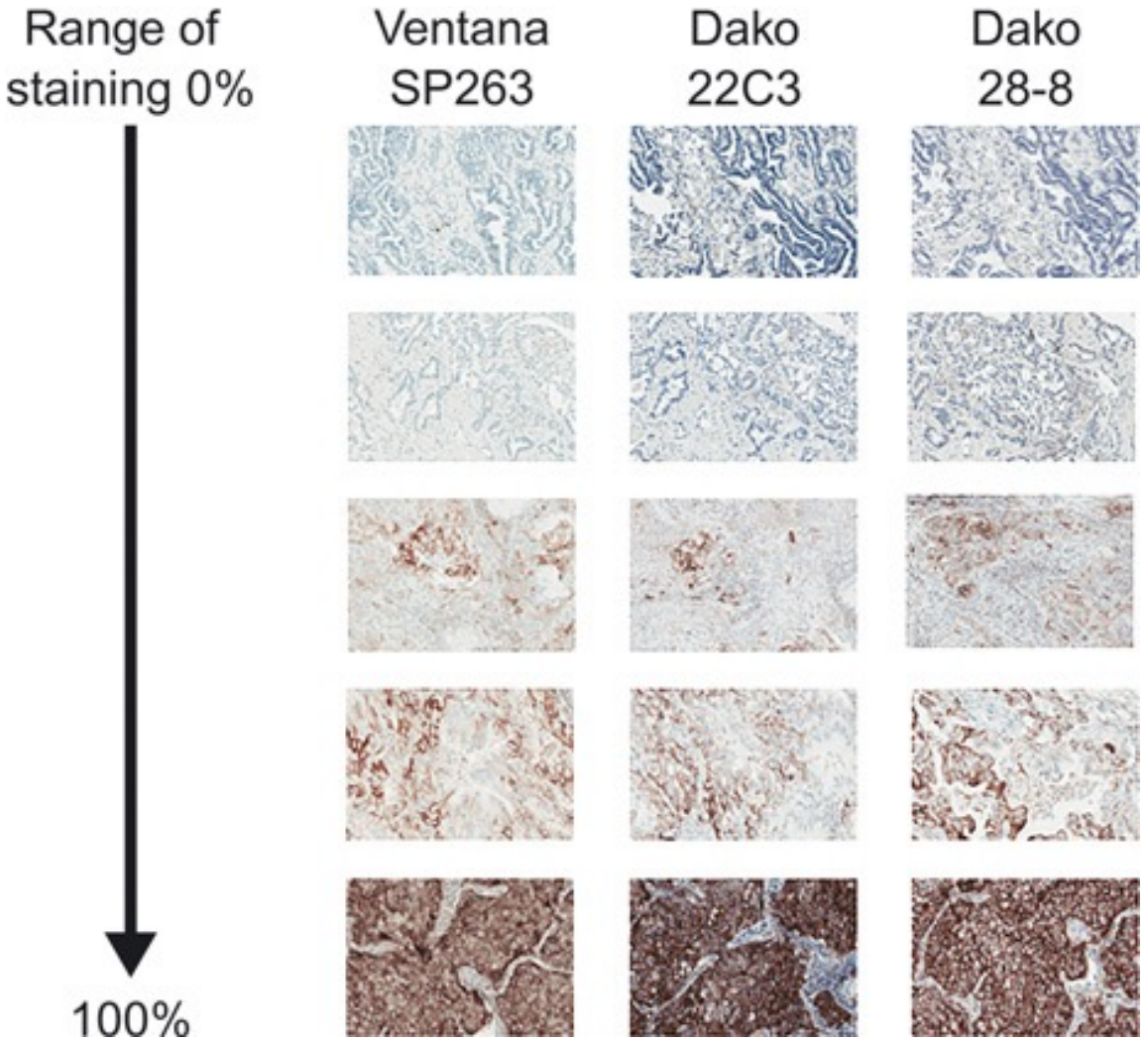
diagnosis and prediction.

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

Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.



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

Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

Region Syddanmark
Sygehus Lillebælt

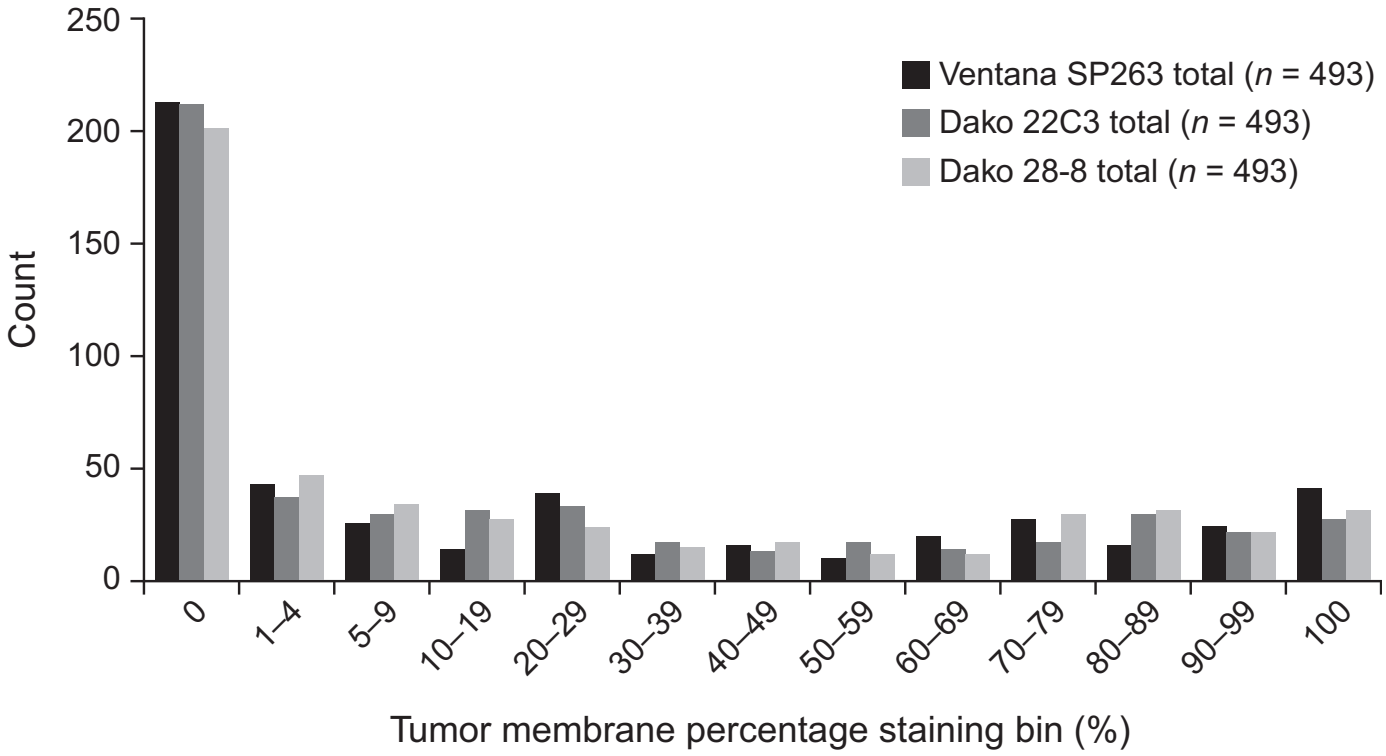


Figure 3.
PD-L1 expression by bins (all samples by assay).

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Immunohistochemcal classification of

Lung cancer,

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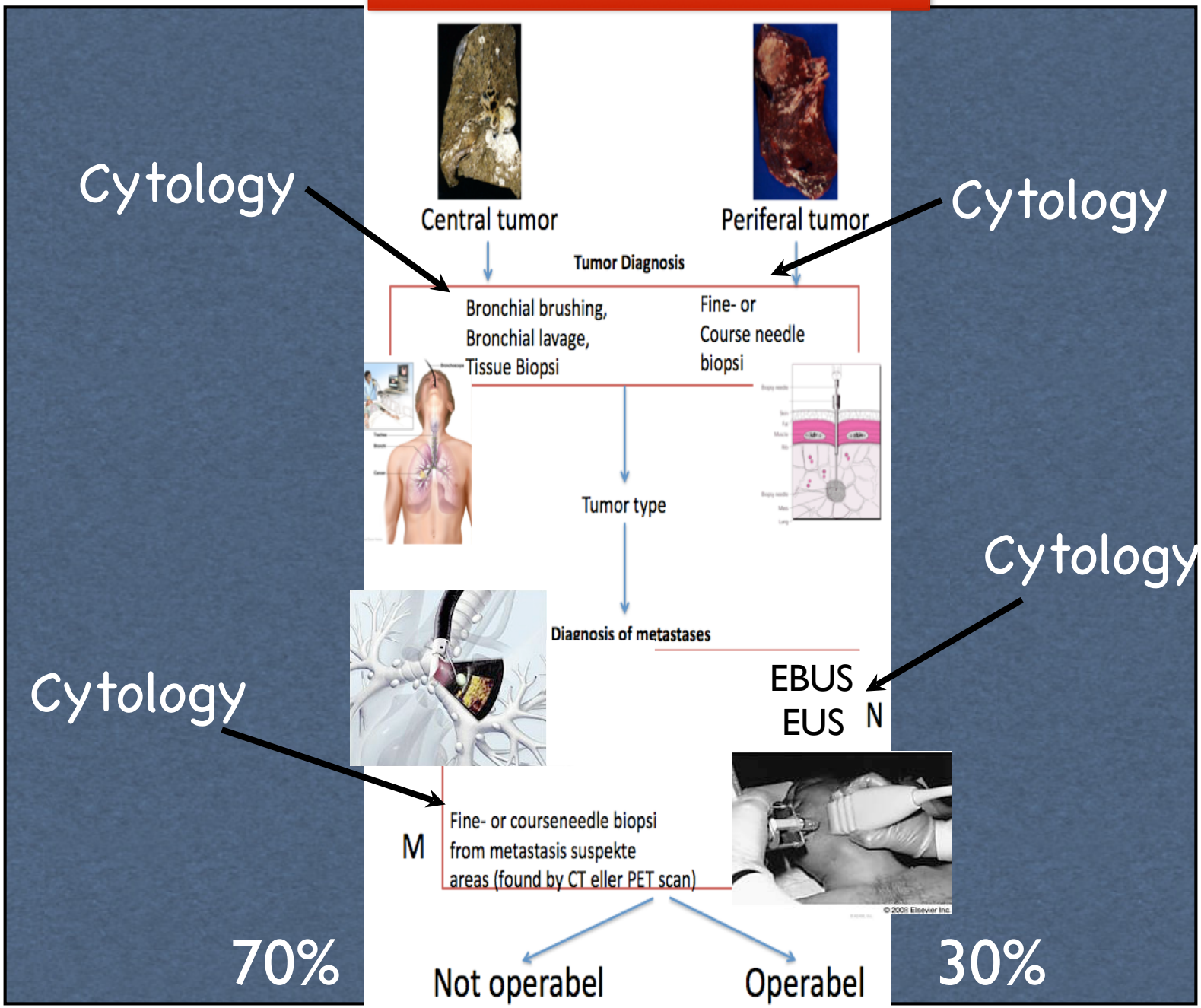


Research Article

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

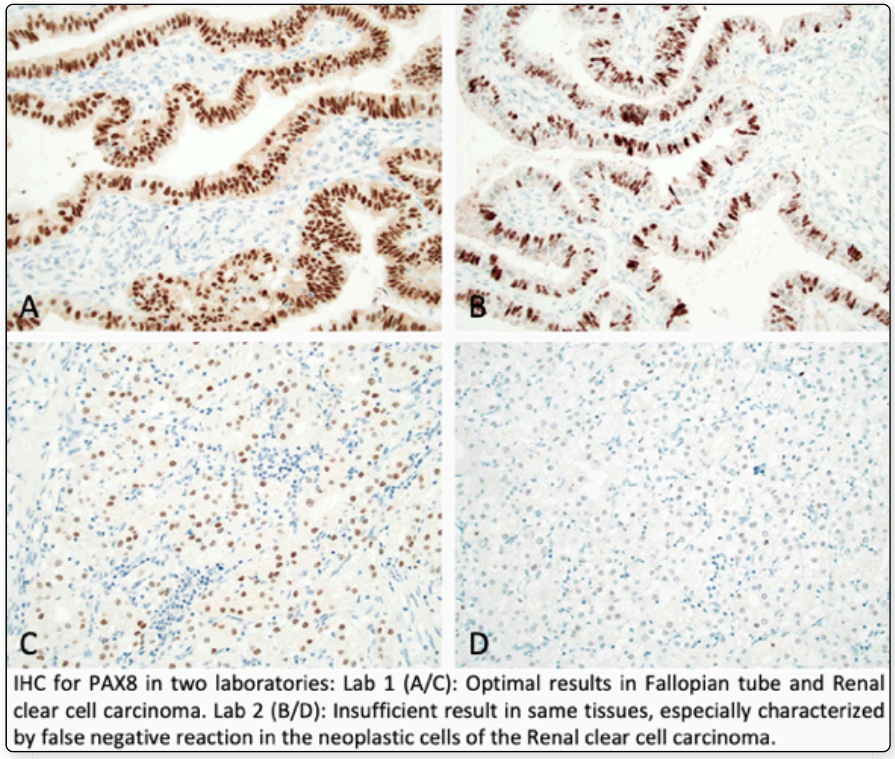
	Cutoff ≥1% Positive Cells		Cutoff ≥50% Positive Cells
PD-L1 IHC 22C3pharmDx			
Overall agreement	85 (76-91)		94 (87-98)
Positive percent agreement	80 (70-87)		100 (96-100)
Negative percent agreement	89 (81-94)		93 (86-97)
	Cutoff ≥1% positive cells	Cutoff ≥5% positive cells	Cutoff ≥10 % positive cells
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.

Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.



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

Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

Assessment Run C5 2019

PD-L1 (lung)

Table 3. **Assessment marks for IHC assays and antibodies run C5, PD-L1 (lung) IHC**

CE-IVD / FDA approved PD-L1 assays	n	Vendor	Optimal	Good	Borderline	Poor	Suff.[1]	Suff. OPS[2]
rmAb clone SP263, **740-4907**[3]	16	Ventana/Roche	12	2	2	-	88%	93%
rmAb clone SP263, **740-4907**[4]	1	Ventana/Roche	-	-	-	1	-	-
rmAb clone SP263, **741-4905**[5]	4	Ventana/Roche	2	2	-	-	-	-
rmAb clone SP263, **790-4905**	48	Ventana/Roche	34	10	4	-	92%	92%
mAb clone 22C3 pharmDX, **SK006**[6]	24	Dako/Agilent	17	5	-	2	92%	92%
mAb clone 22C3 pharmDX, **SK006**[7]	9	Dako/Agilent	2	2	1	4	44%	-
mAb clone 22C3 pharmDX, **GE006**[8]	3	Dako/Agilent	3	-	-	-	-	-
rmAb clone 28-8 pharmDX, **SK005**[9]	3	Dako/Agilent	2	1	-	-	-	-
Antibodies[10] for laboratory developed PD-L1 assays, concentrated antibodies	n	Vendor	Optimal	Good	Borderline	Poor	Suff.[1]	Suff. OPS[2]
mAb clone **22C3**	42	Dako/Agilent	11	20	9	2	74%	74%
mAb clone **E1L3N**	5	Cell Signaling	1	4	-	-	100%	100%
rmAb **CAL10**	3 3	Biocare Zytomed Systems	3	1	-	2	67%	100%
rmAb clone **28-8**	4	Abcam	1	2	-	1	-	-
rmAb clone **ZR3**	1 1 1 1	Cell Marque Zeta Corporation Nordic Biosite Gene Tech	1	-	-	3	-	-
rmAb clone **QR1**	1 1	Quartett Diagomics	1	-	-	1	-	-
rmAb **BSR90**	1	Nordic Biosite	1	-	-	-	-	-
rmAb clone **SP142**	1	Spring Biosystems	-	1	-	-	-	-
Ready-To-Use antibodies	n	Vendor	Optimal	Good	Borderline	Poor	Suff.[1]	Suff. OPS[2]
rmAb CAL10, **API3171**	1	Biocare	-	-	1	-	-	-
rmAb QR1, **2-PR292-13**	1	Biocyc	-	1	-	-	-	-
rmAb clone MXR003, **RMA-0732**	1	Maixin	-	-	-	1	-	-
Total	176		91	51	17	17		
Proportion			51%	29%	10%	10%	80%	

1) Proportion of sufficient staine (optimal or good)

NordiQC

Immunohistochemcal classification of Lung cancer, diagnosis and prediction.

Region Syddanmark
Sygehus Lillebælt

Assessment Run C5 2019
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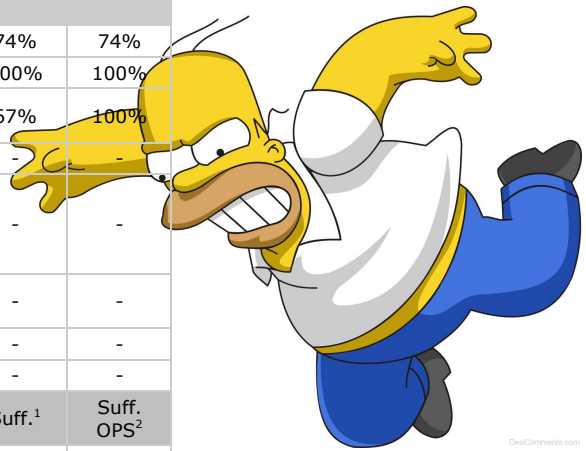


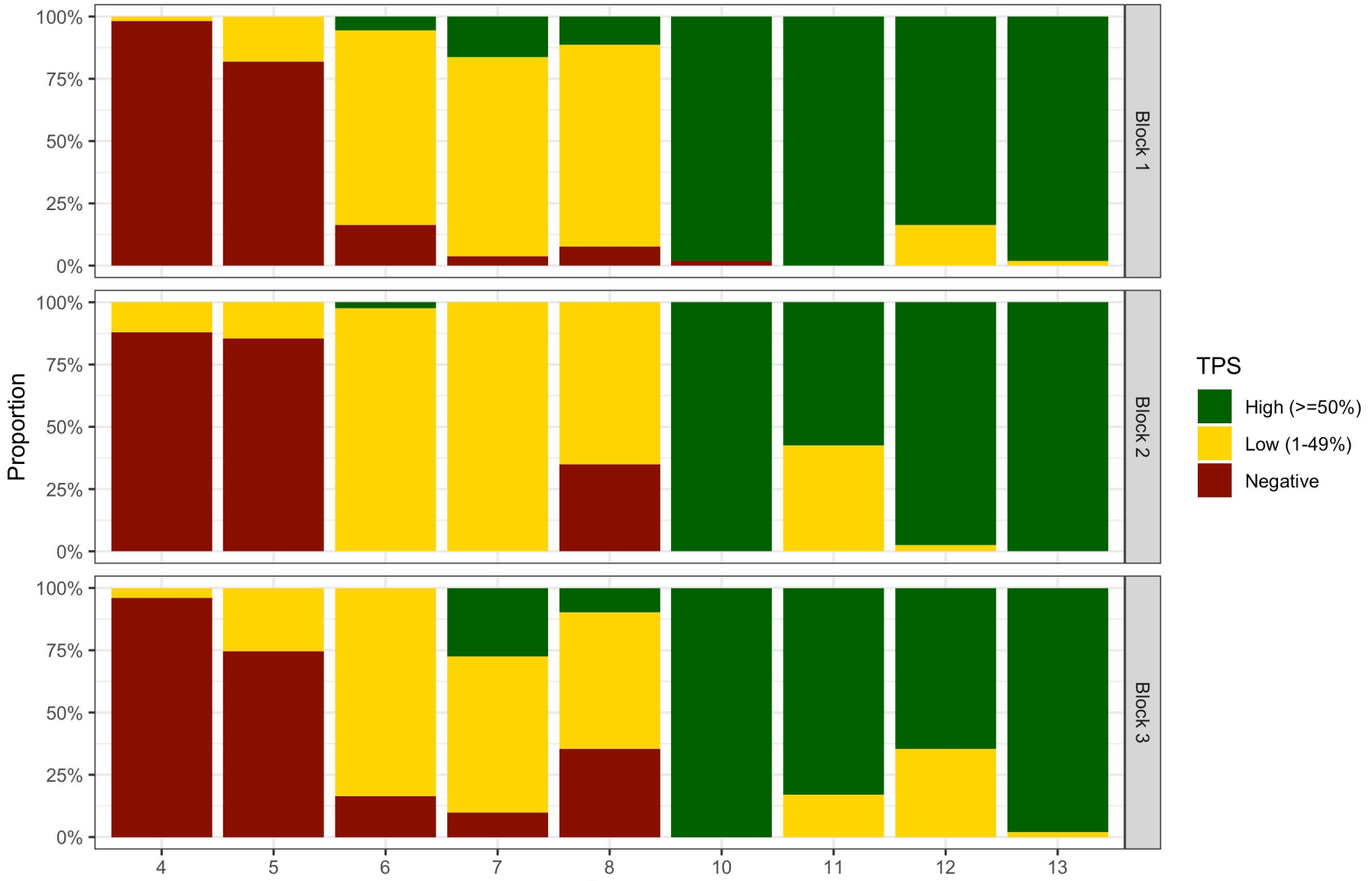
Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

Assessment Run C5 2019

PD-L1 (lung)



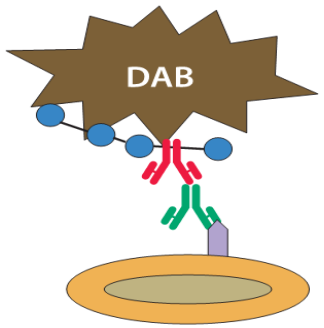
Graph 1. **NordiQC PD-L1 run C5: Tumour proportion scores across tissue core split up by different TMA blocks**

Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

Region Syddanmark
Sygehus Lillebælt



Kromogen (farvestof)

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Sekundært antistof
Primært antistof

Antigen
Cellens cytoplasma
Cellekerne

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Positive Histology

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LCNEC

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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 -
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ADC marker +
SQCC marker +

NSCLC, NOS

NSCLC, NOS
possible adenosquamous ca.

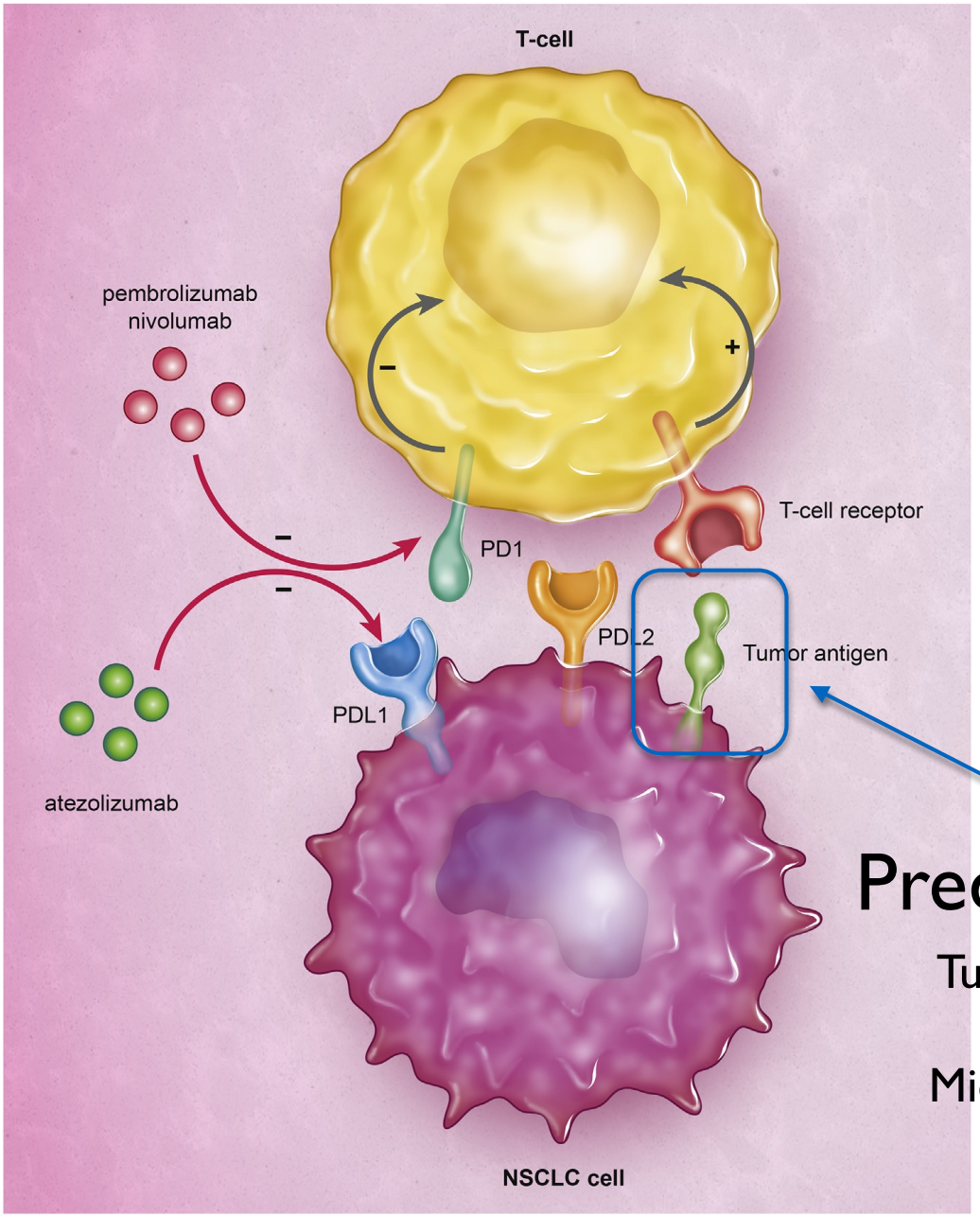
Step 3

PD-L1 testing

Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.



Future:

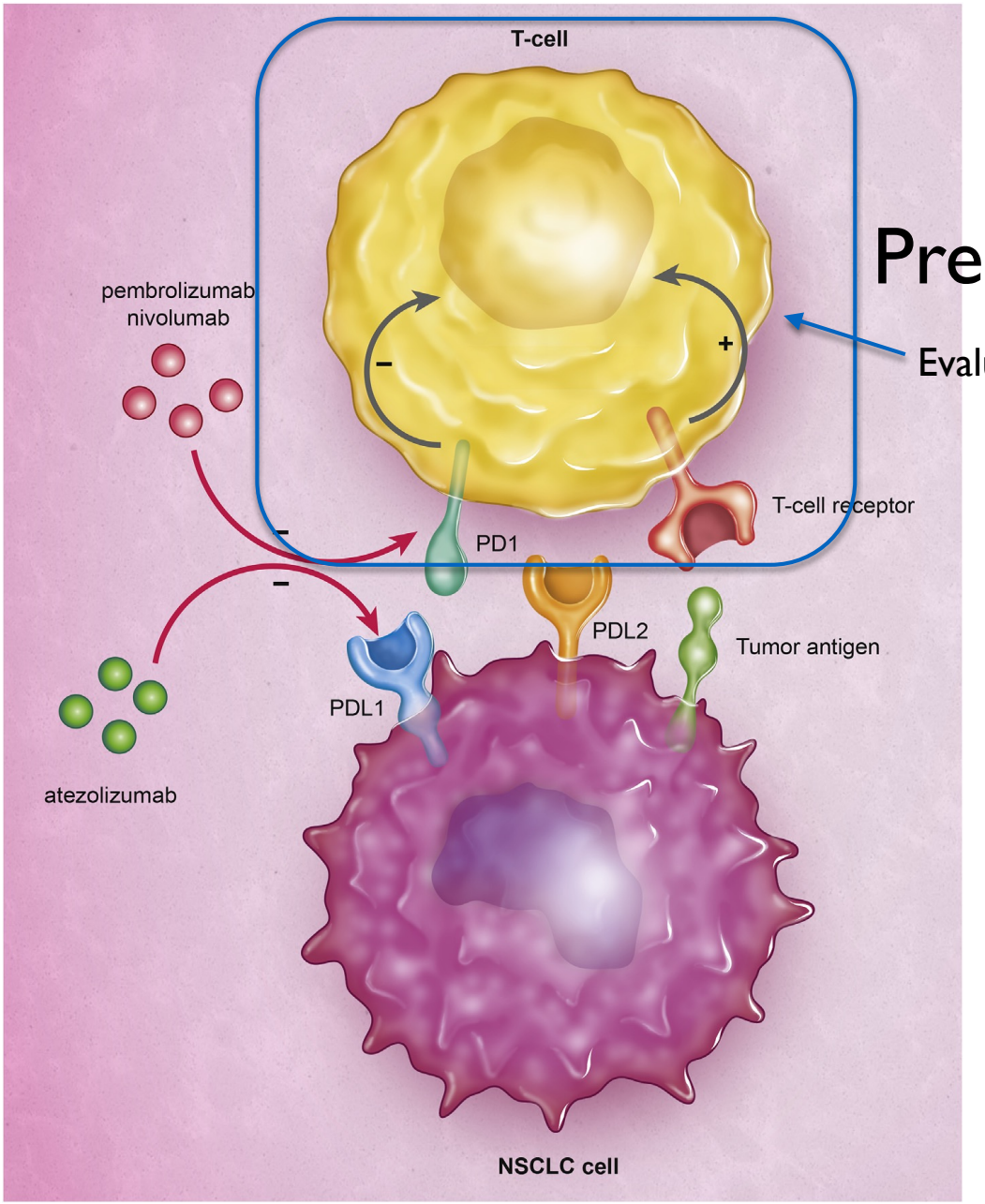
Predictive marker

Tumor Mutational Burden
TMB
Micro Satellite Instability
MSI

Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

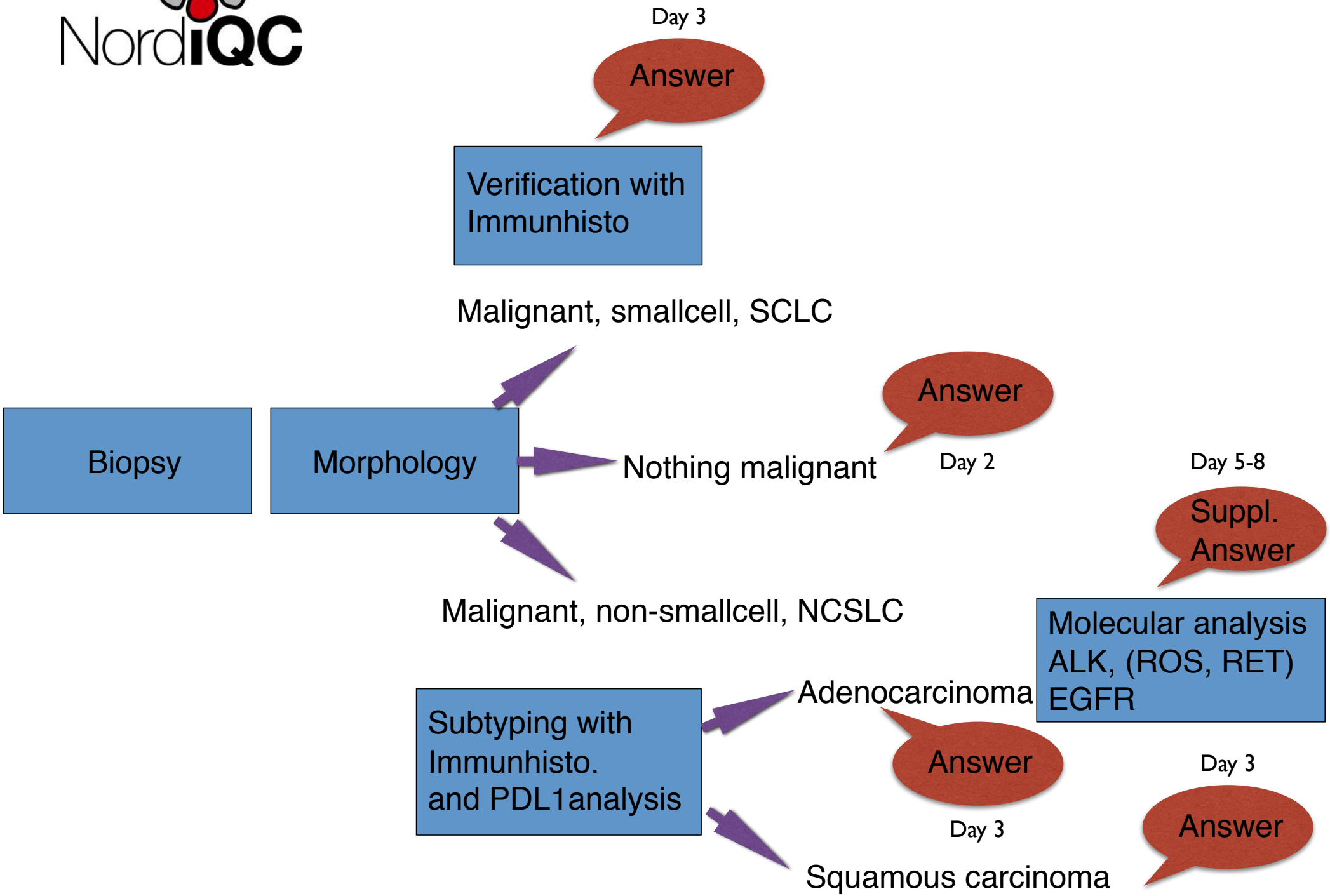


Future:

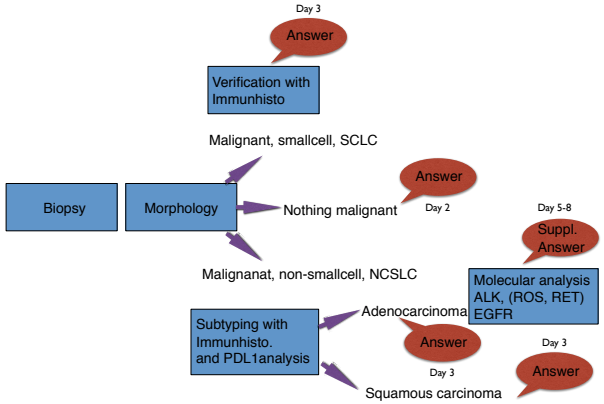
Predictive marker

Evaluation of immune respons

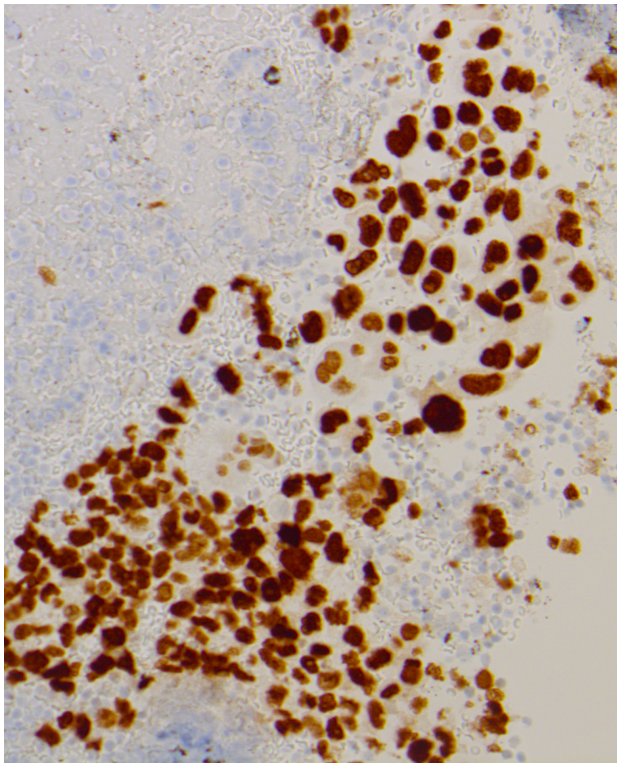
The Diagnostic algorithm



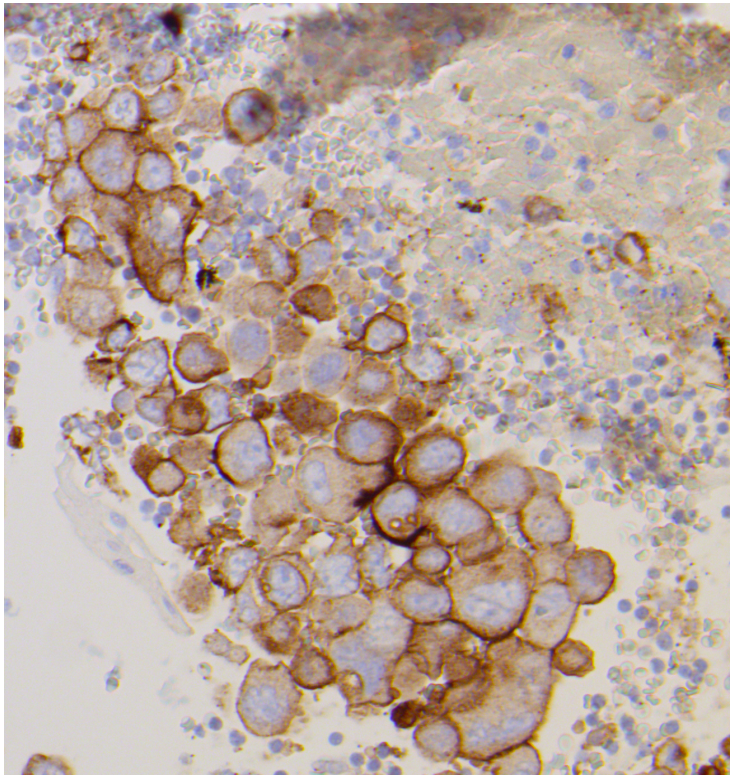
The Diagnostic algorithm



Pleura effusion Cell Block

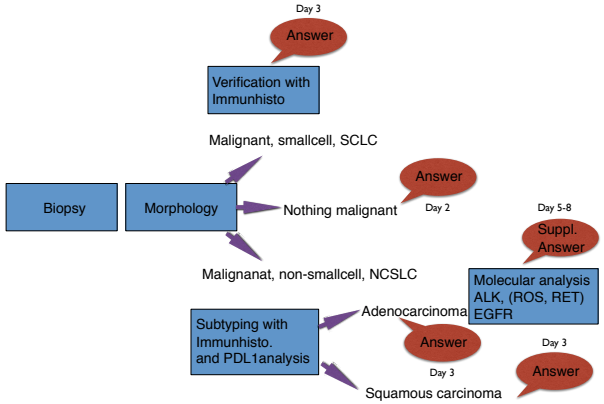


ttf1, CK7+

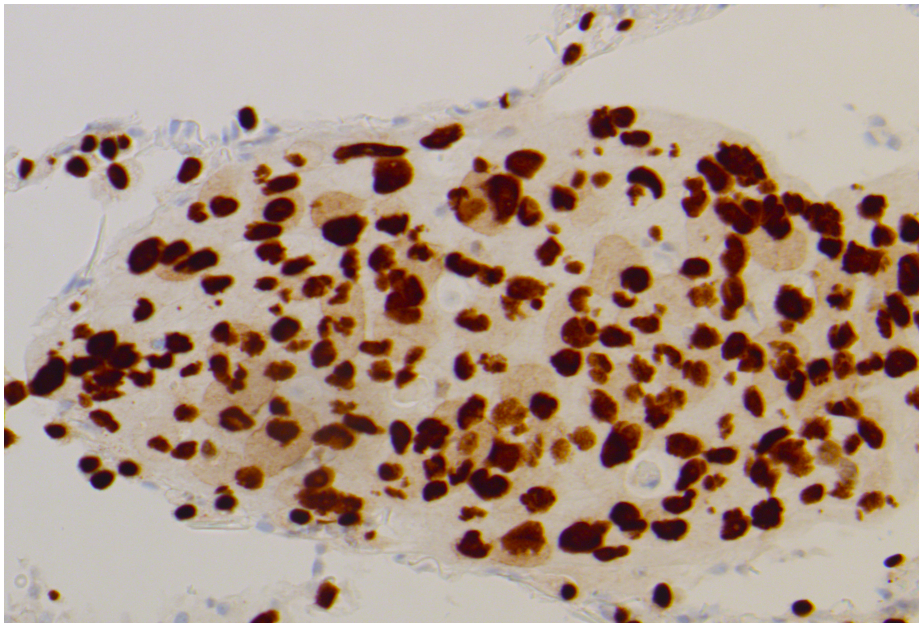


PD-L1 (22C3)

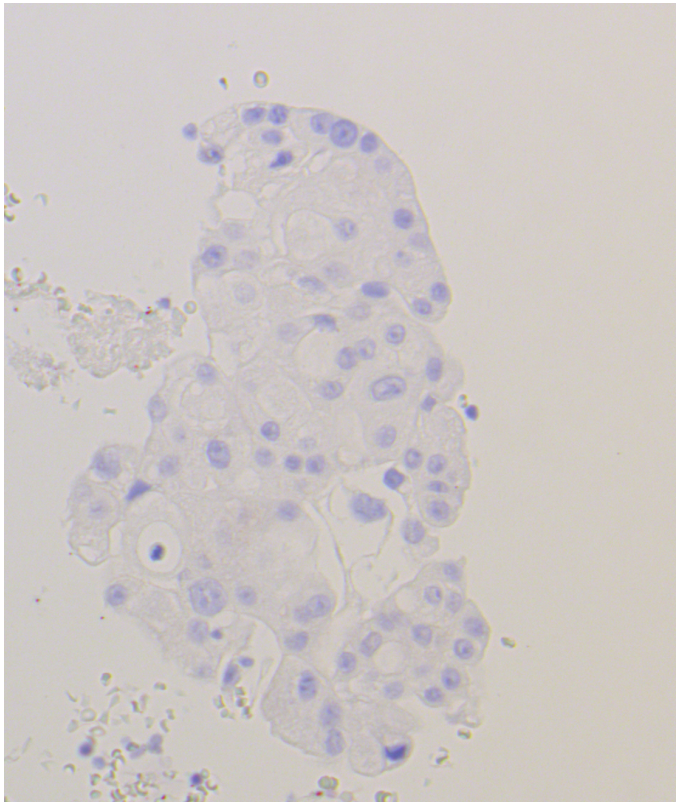
The Diagnostic algorithm



EBUS CellBlock

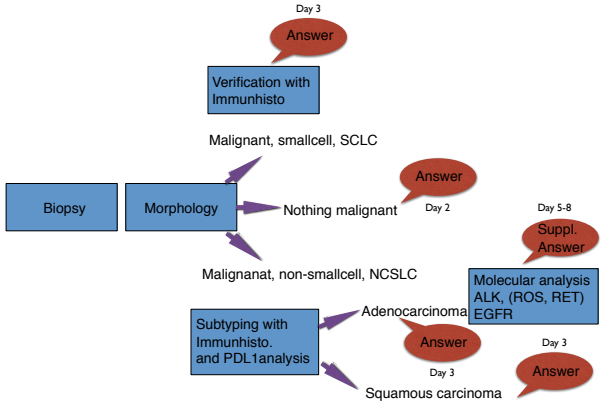


CK5/6, CK7 and P40+

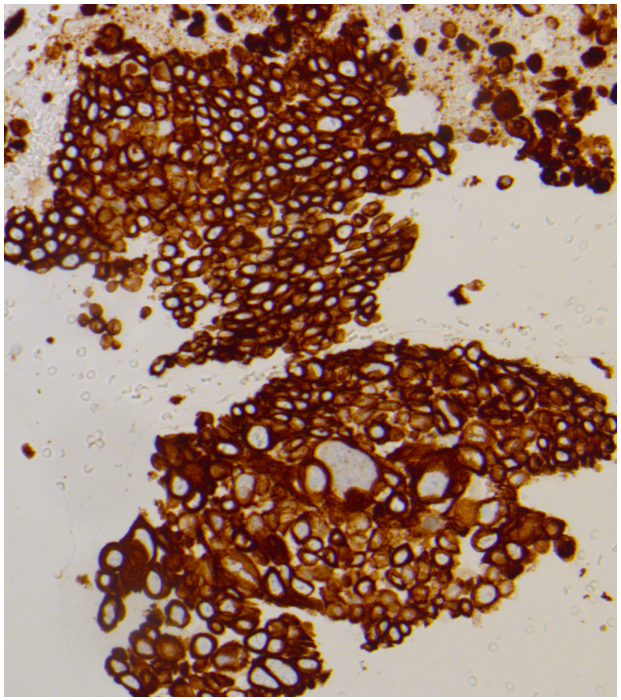


PD-L1 (22C3)

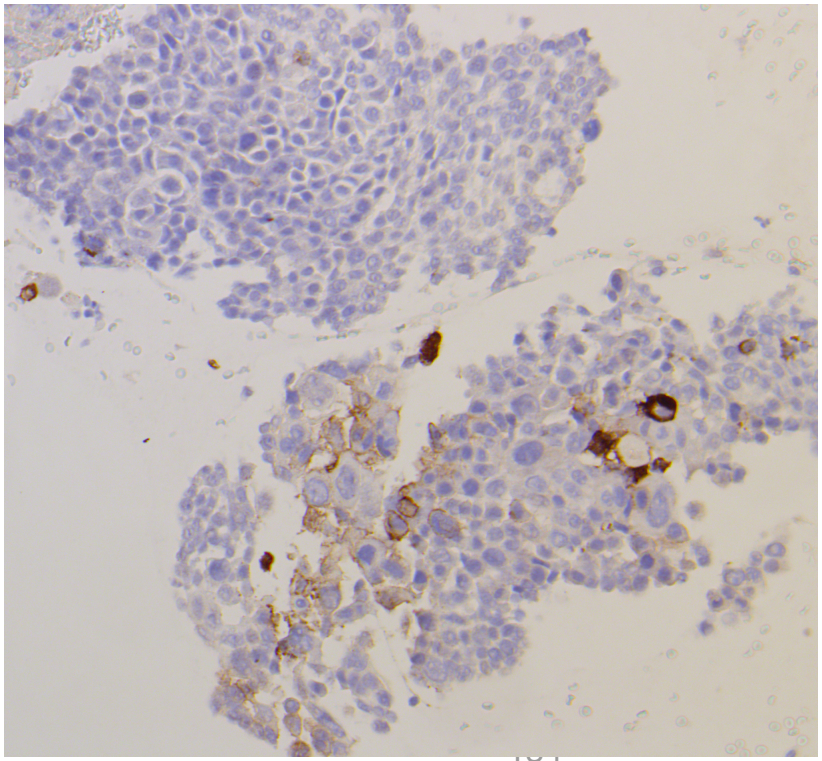
The Diagnostic algorithm



EBUS Cell Block

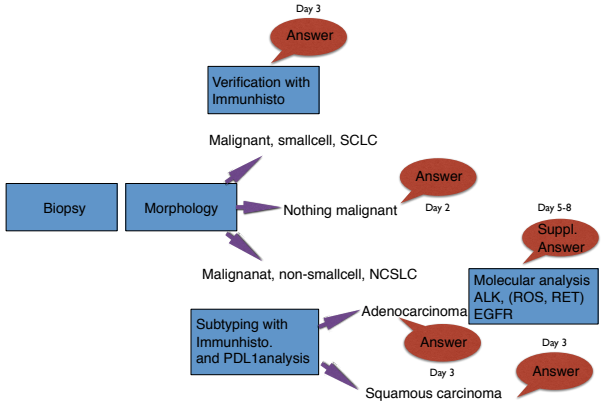


CK5/6 and P40+

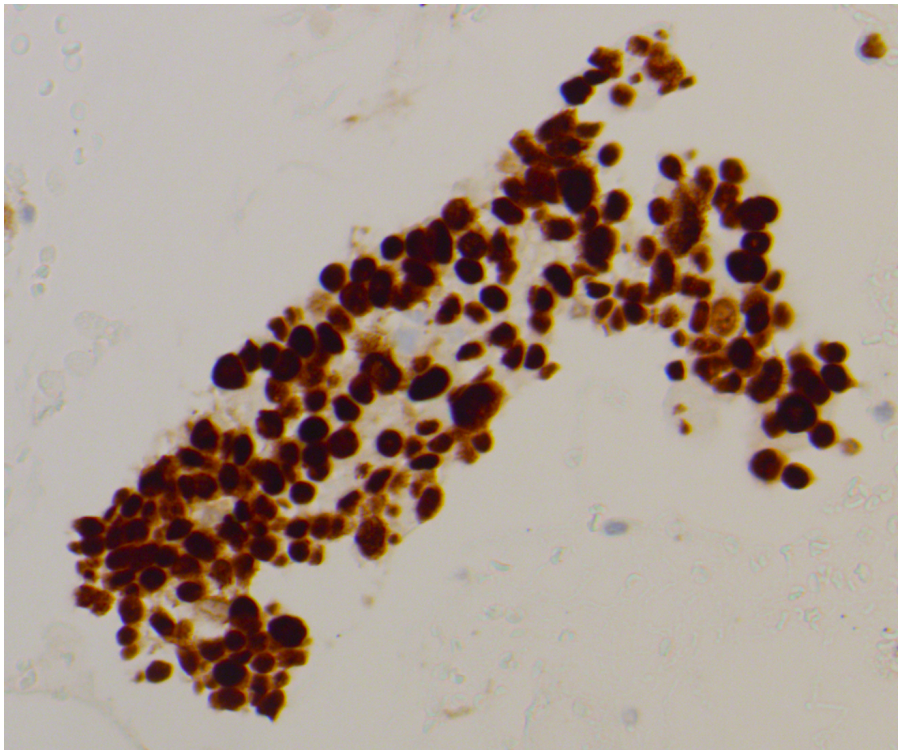


PD-L1 (22C3)

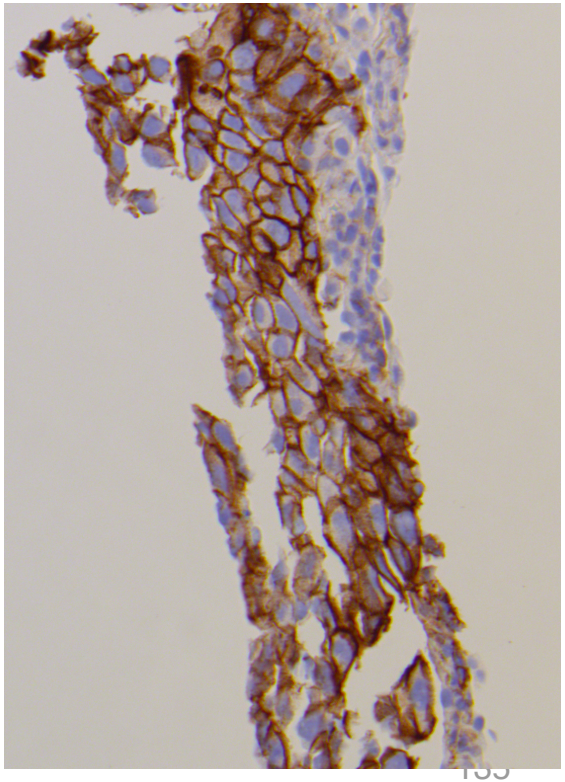
The Diagnostic algorithm



Coarse needle biopsy

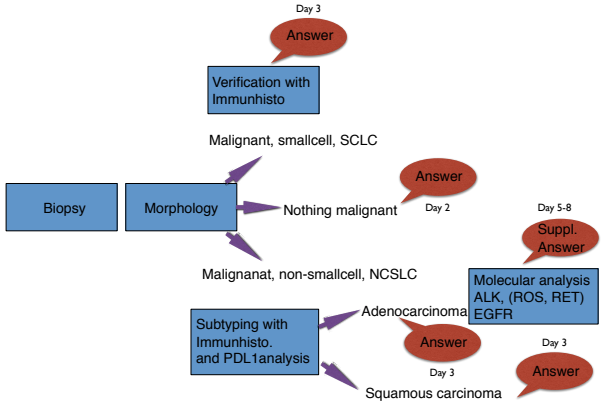


ttf1 and CK7+

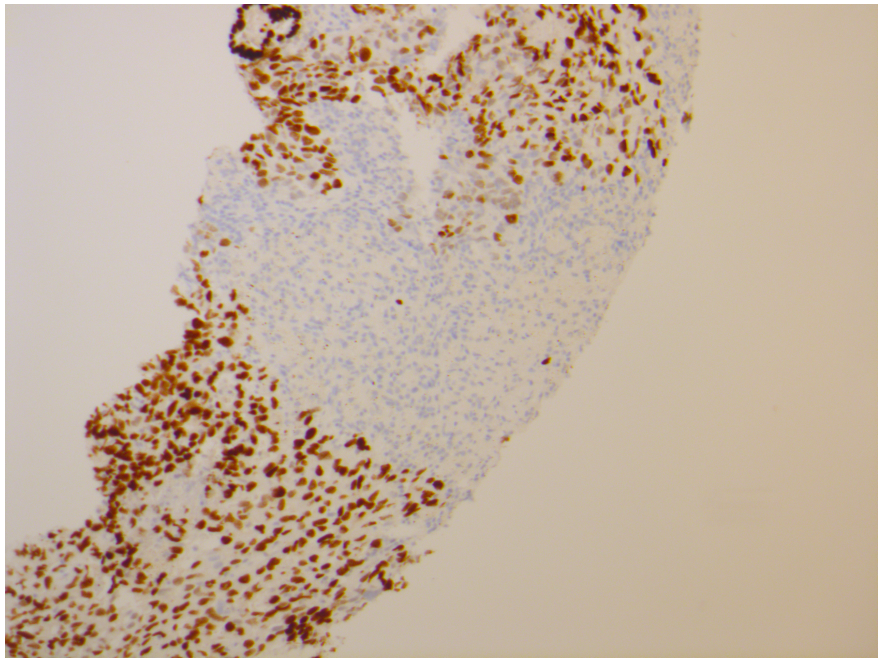


PDL1 (22C3)

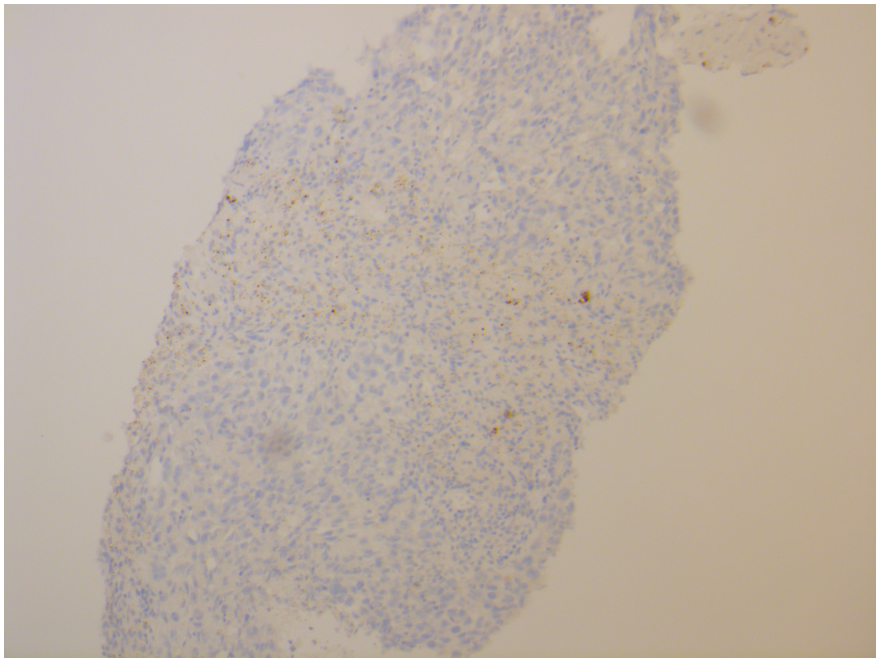
The Diagnostic algorithm



Coarse needle biopsy

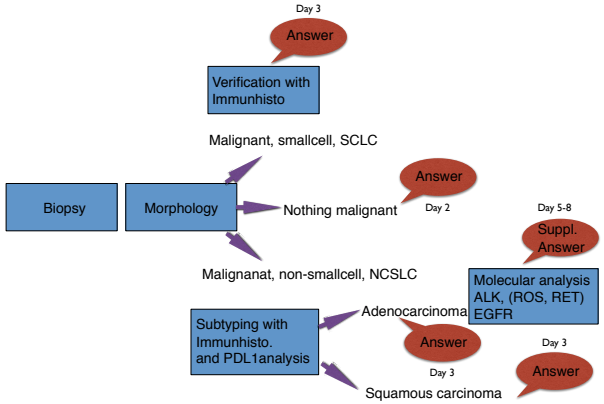


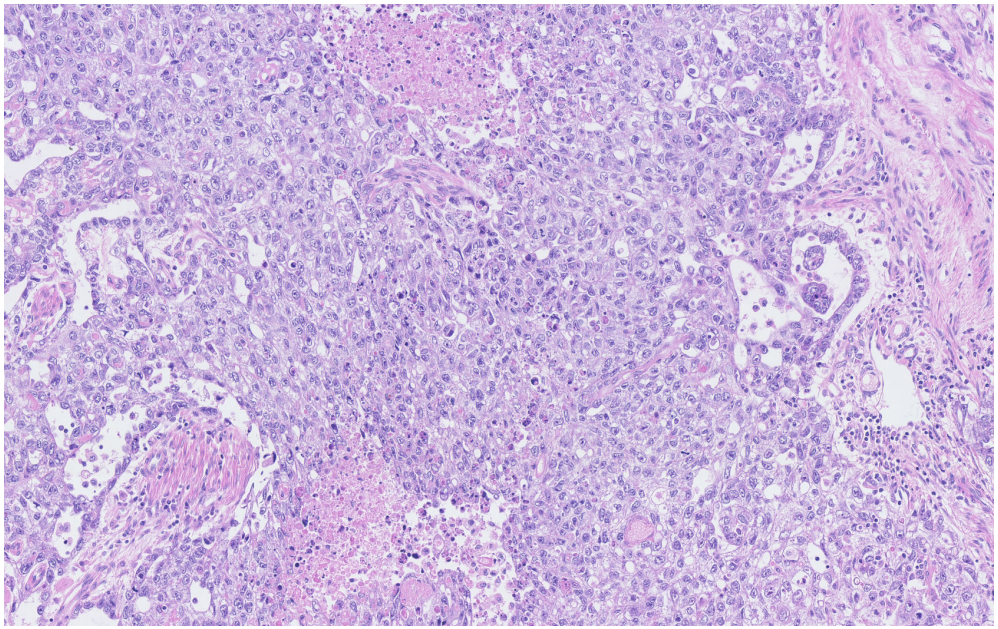
ttf1 and CK7+

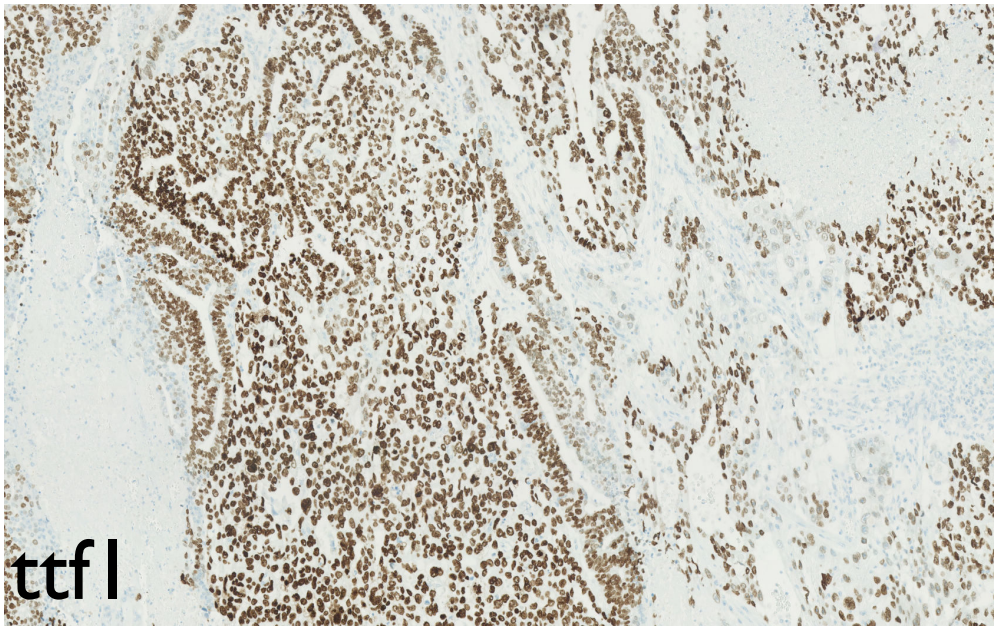


PDL1 (22C3)

The Diagnostic algorithm



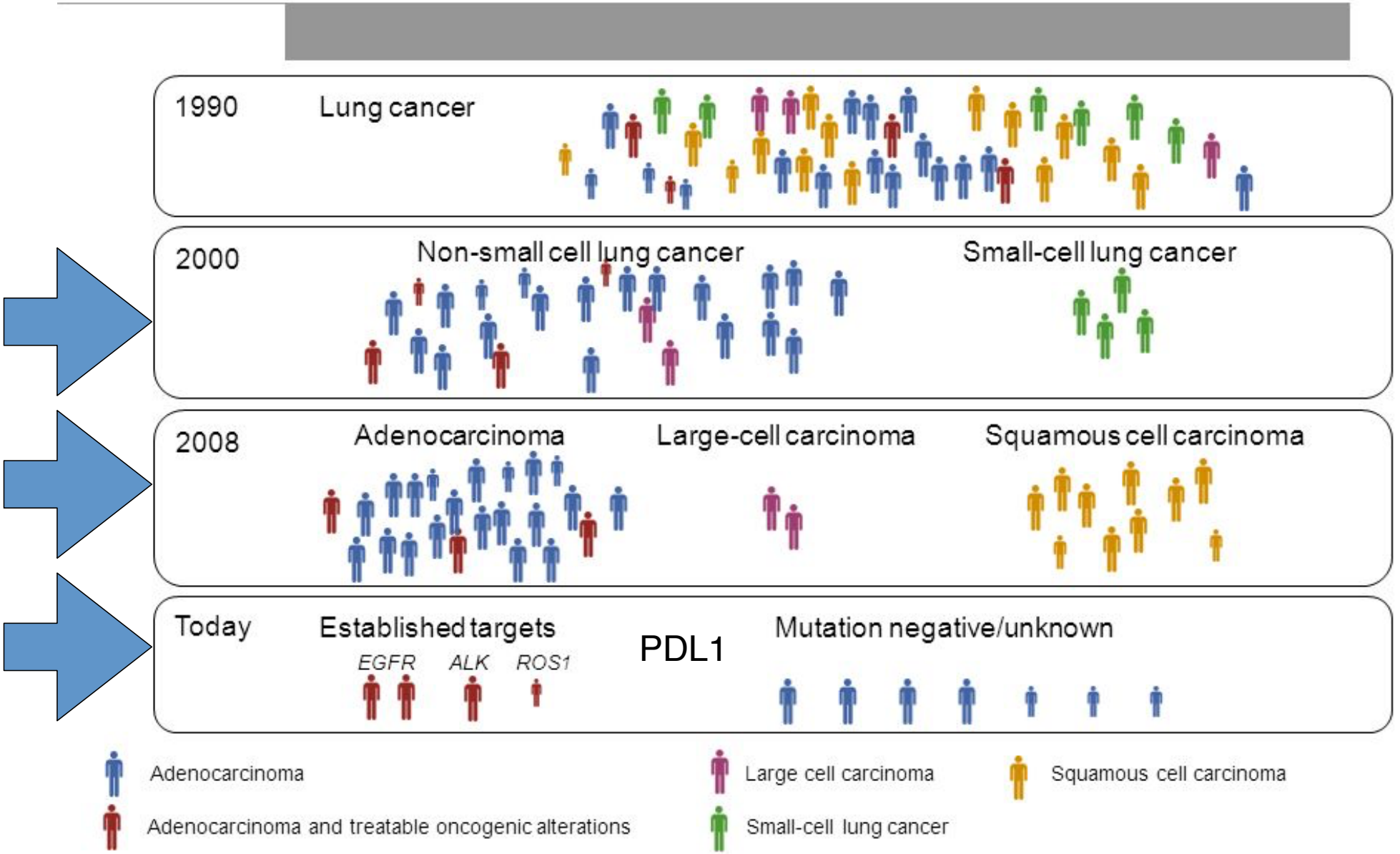




Large tumor intra uterine

Endometrial cancer (yolk sac tumor)

Patient selection in lung cancer: Evolution over time



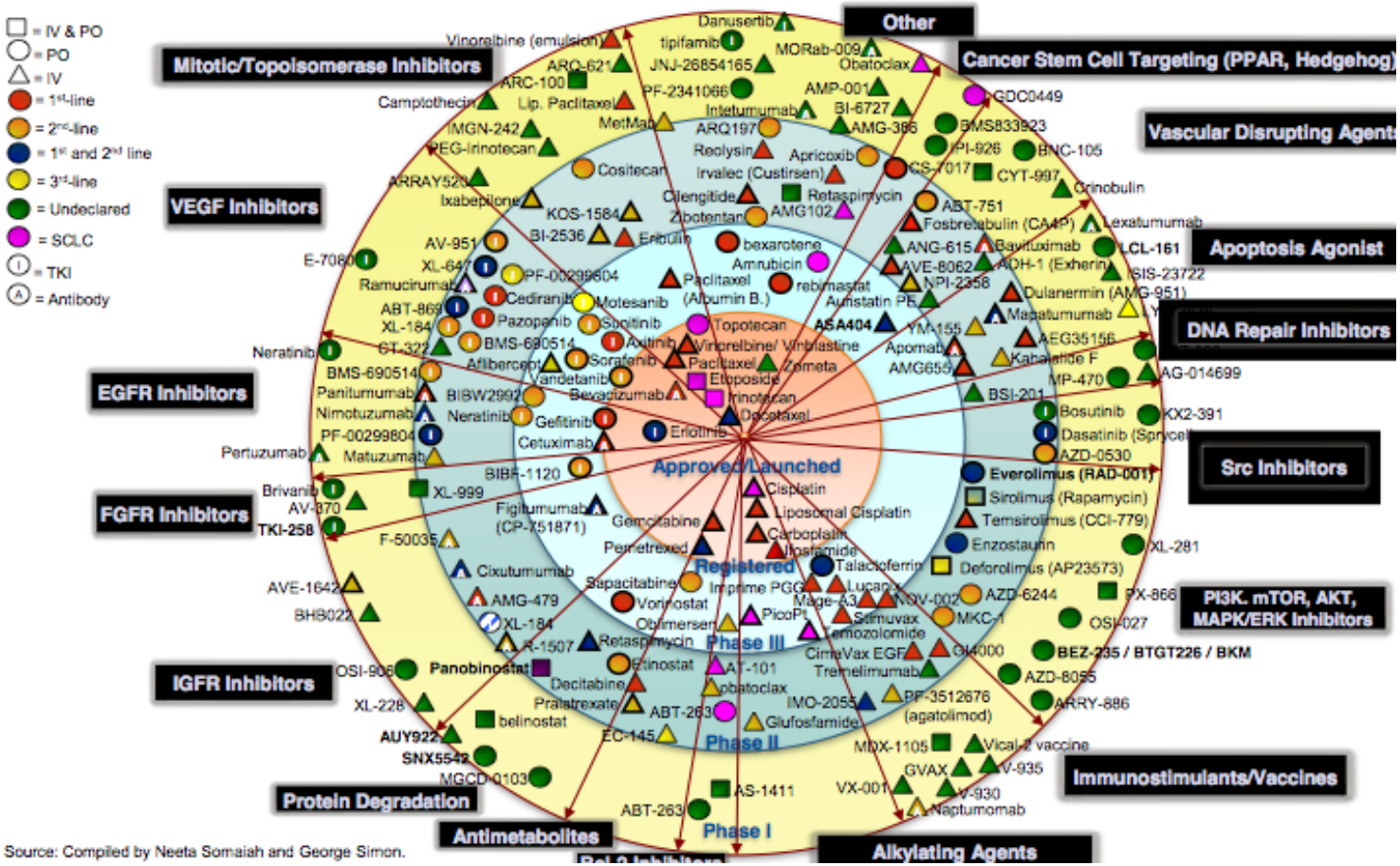
Adapted from Reck M, et al. Lancet 2013;382:709–19

Immunohistochemcal classification of

Lung cancer,

diagnosis and prediction.

Lung cancer research landscape – MoA group and phase



Source: Compiled by Neeta Somaiah and George Simon.

Future