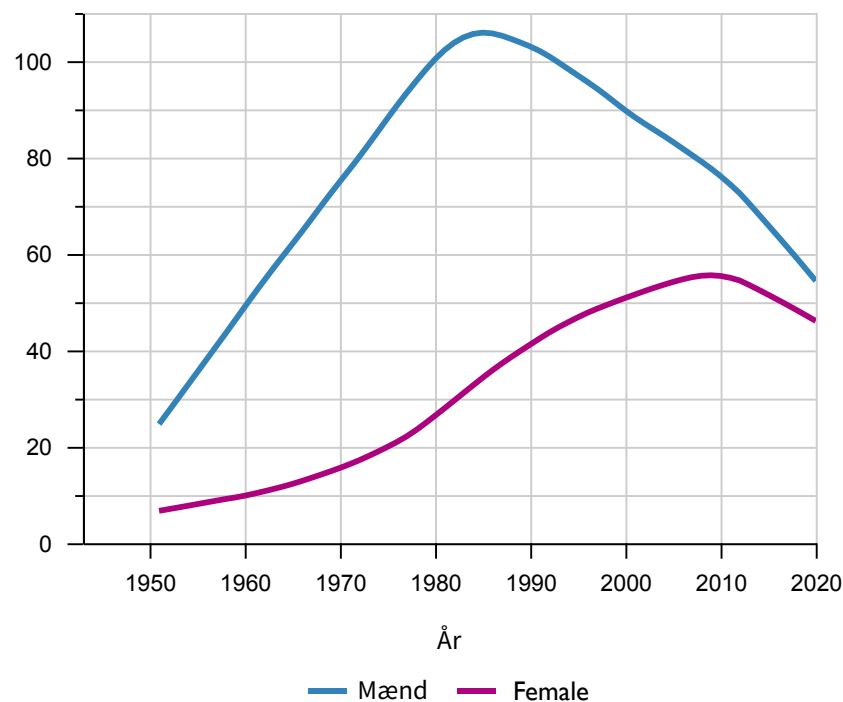
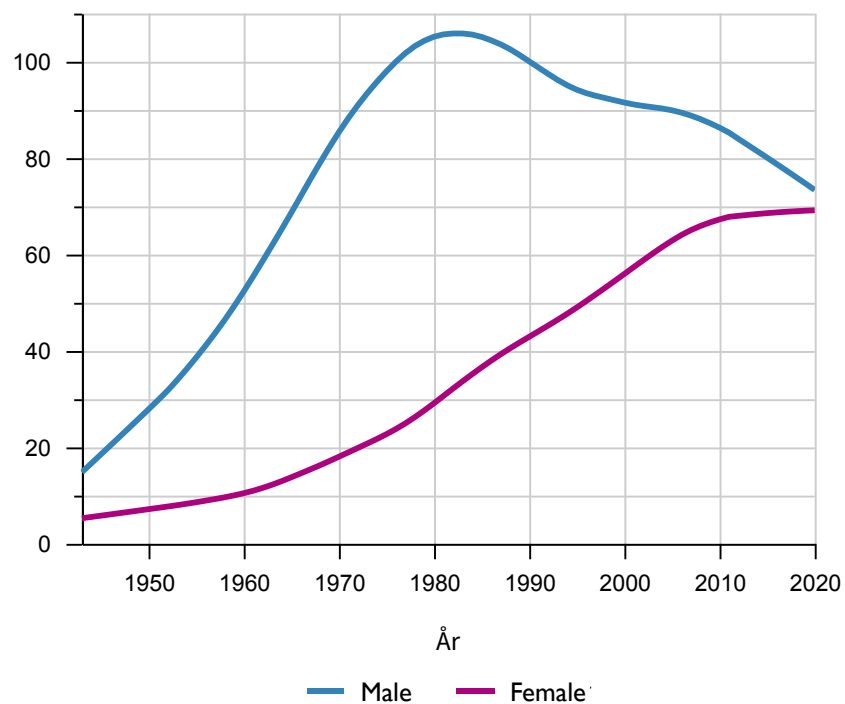


Lung cancer Age's standardized

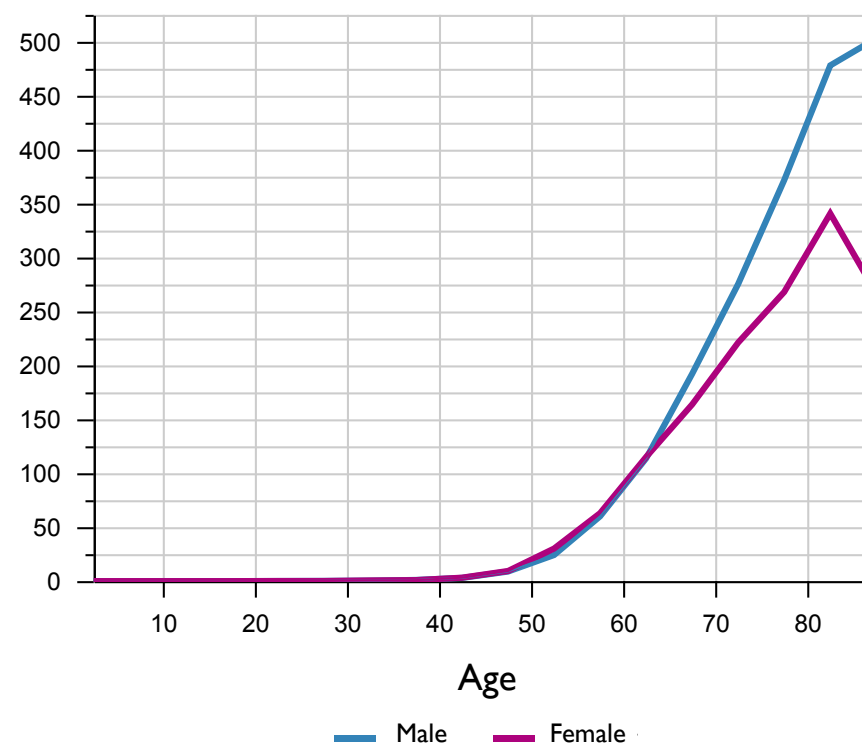
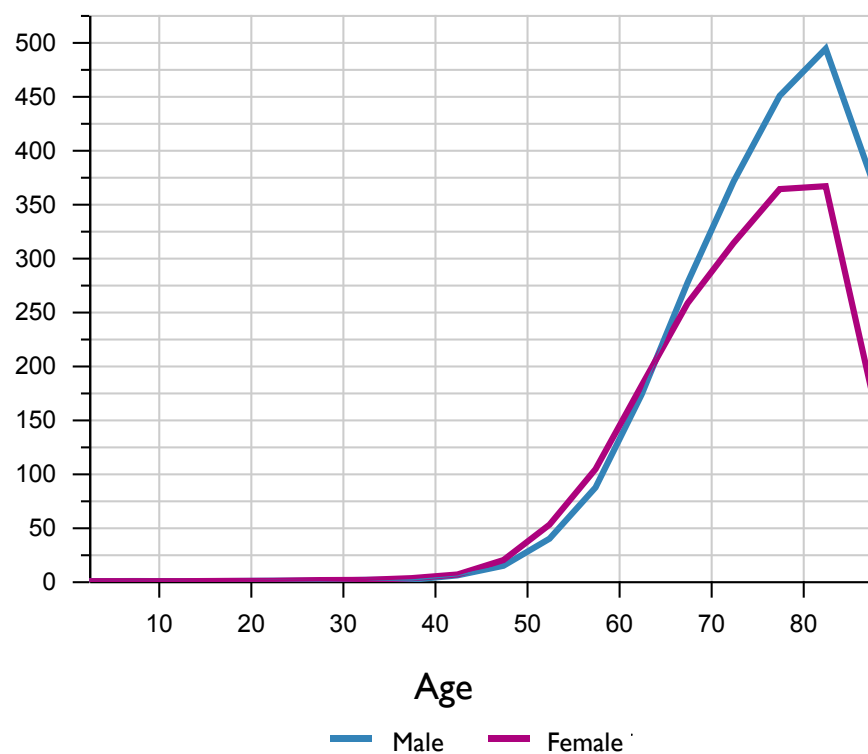
Incidence new cases/100.000

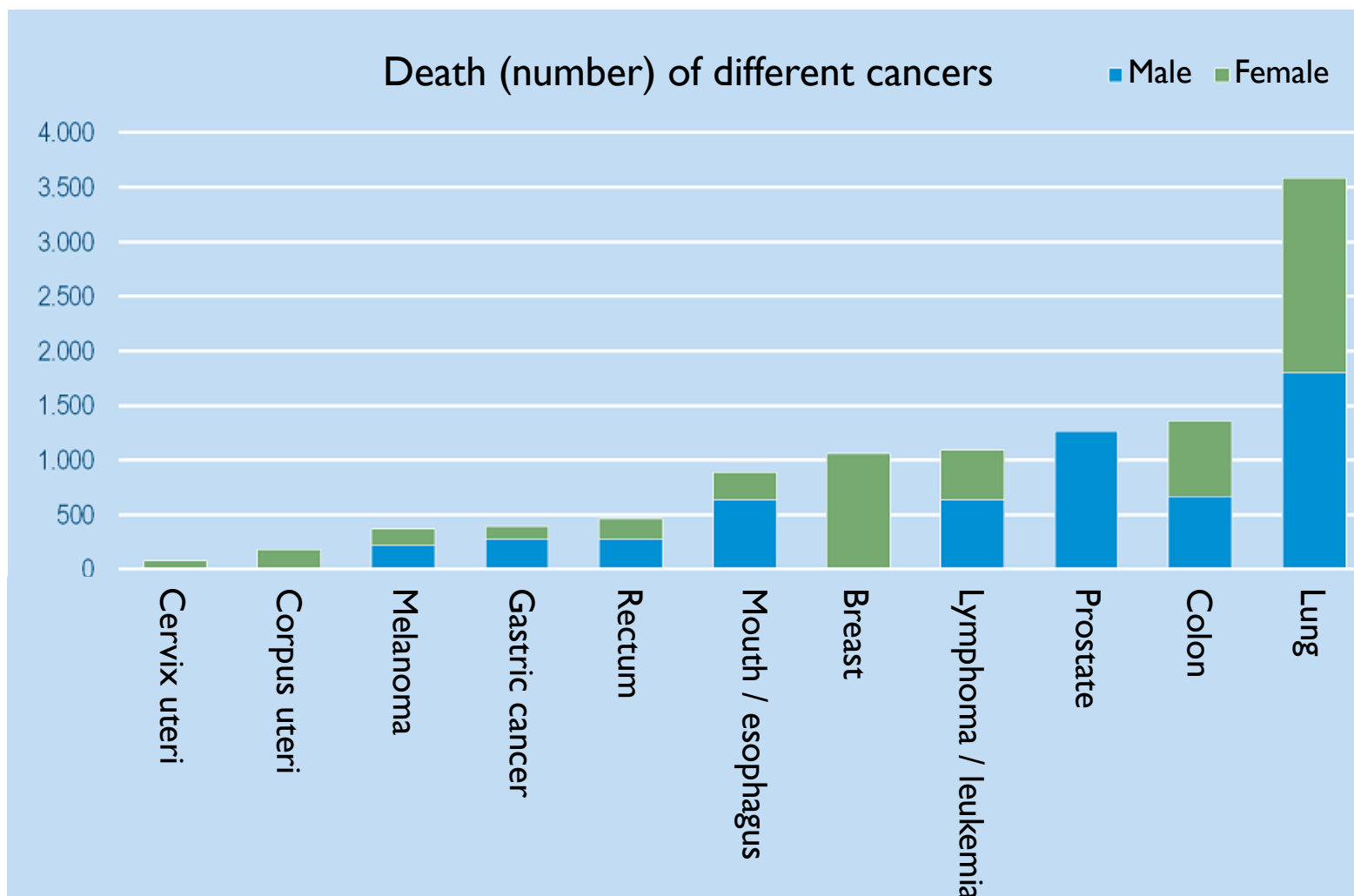
Mortality Death/100.000



Lung cancer

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





Risk Factors

SMOKING

Smoking is the leading cause of lung cancer. It causes about **9 out of 10 cases** of lung cancer in men and about 8 out of 10 cases of lung cancer in women.

SECONDHAND SMOKE

People who inhale secondhand smoke may be exposed to cancer-causing agents, making this a potential contributing risk factor.



FAMILY HISTORY

People with a first-degree relative (i.e., parent, child or sibling) who has or had lung cancer may be **twice as likely** to develop the disease.



DIETARY SUPPLEMENTS

Taking **beta carotene** supplements increases lung cancer risk in smokers who smoke one or more packs a day.

EXPOSURE TO:



RADON GAS

Radon is a colorless, scentless radioactive gas found in some houses. **Radon exposure is a leading cause of lung cancer.**



ASBESTOS OR OTHER POLLUTANTS

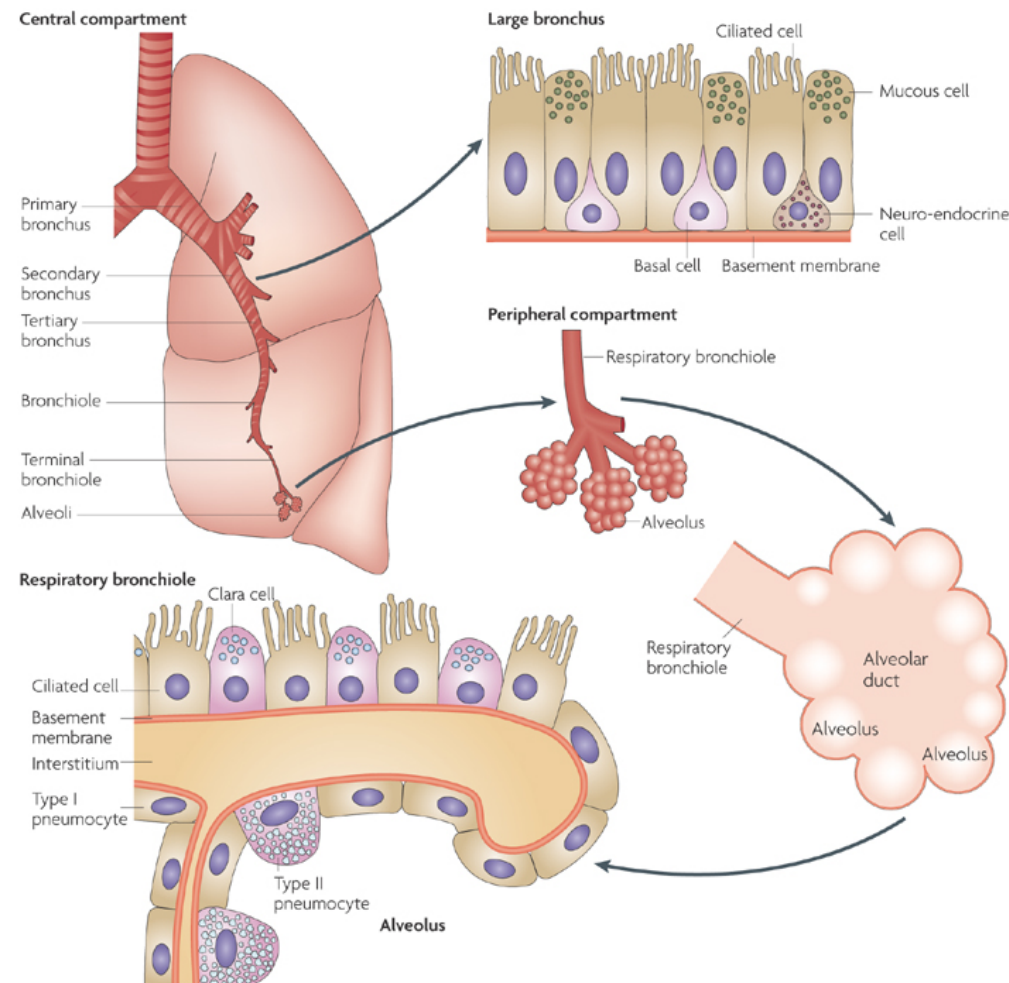
Carcinogenic chemicals in the workplace increase lung cancer risk, especially if you smoke.



RADIATION

People who have had extensive radiation to the chest may be at increased risk of lung cancer.

Lung Carcinoma



Lung carcinoma derives from stem cells
in the lung epithelium

malignant epithelial tumors
(carcinomas)

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

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

(Continued)

TABLE 1. (Continued)

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

Metastatic tumors

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

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

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

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

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



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

(Continued)

TABLE 1. (Continued)

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

Metastatic tumors

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

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

Carcinoids I - 2%

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

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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
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Spindle cell carcinoma	8032/3
Giant cell carcinoma	8031/3
Carcinosarcoma	8980/3
Pulmonary blastoma	8972/3
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NUT carcinoma ^e	8023/3 ^d
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Mucoepidermoid carcinoma	8430/3
Adenoid cystic carcinoma	8200/3
Epithelial-myoepithelial carcinoma	8562/3
Pleomorphic adenoma	8940/0

(Continued)

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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	
Lymphangi leiomyomatosis	9174/1
PEComa, benign ^e	8714/0
Clear cell tumor	8005/0
PEComa, malignant ^e	8714/3
Congenital peribronchial myofibroblastic tumor	8827/1
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Inflammatory myofibroblastic tumor	8825/1
Epithelioid hemangioendothelioma	9133/3
Pleuropulmonary blastoma	8973/3
Synovial sarcoma	9040/3
Pulmonary artery intimal sarcoma	9137/3
Pulmonary myxoid sarcoma with <i>EWSR1-CREB1</i> translocation ^e	8842/3 ^d
Myoepithelial tumors ^e	
Myoepithelioma	8982/0
Myoepithelial carcinoma	8982/3
Lymphohistiocytic tumors	
Extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT lymphoma)	9699/3
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Lymphomatoid granulomatosis	9766/1
Intravascular large B cell lymphoma ^e	9712/3
Pulmonary Langerhans cell histiocytosis	9751/1
Erdheim-Chester disease	9750/1
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Germ cell tumors	
Teratoma, mature	9080/0
Teratoma, immature	9080/1
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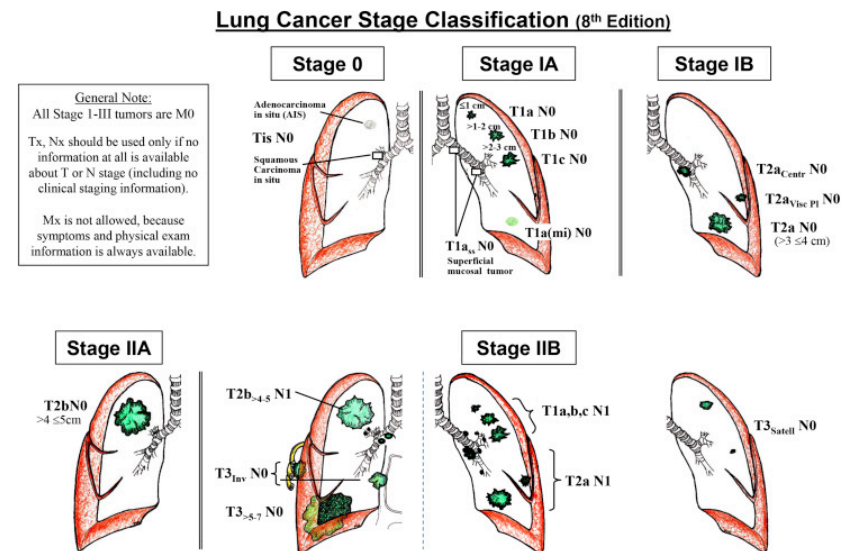
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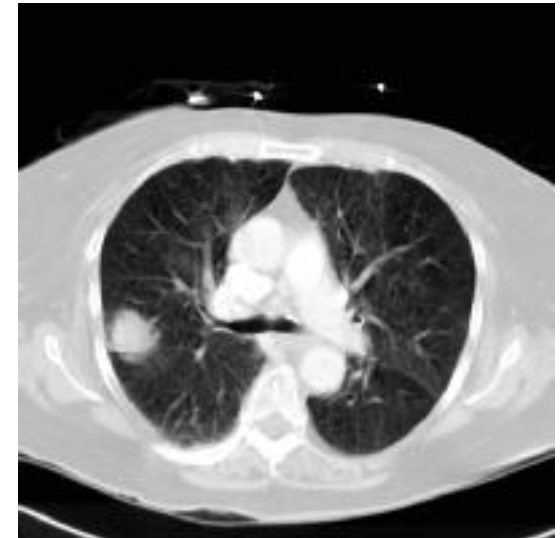
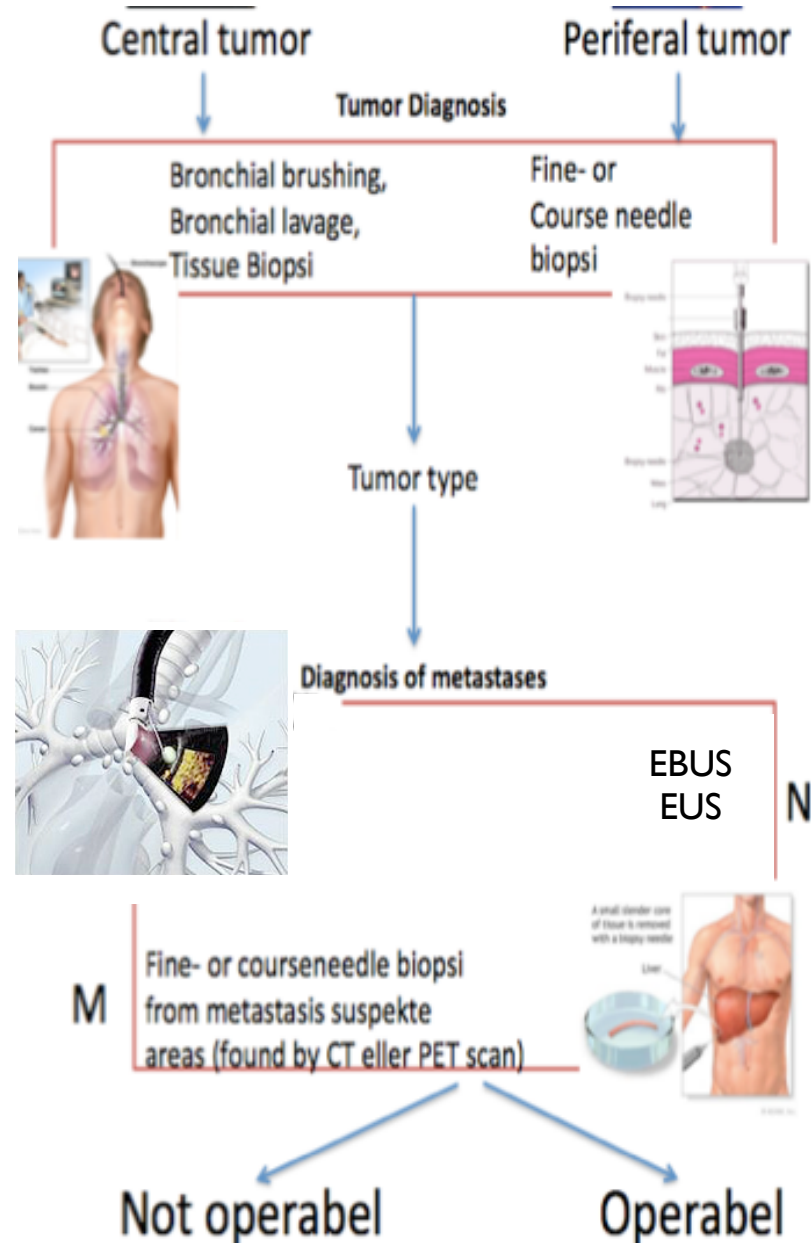
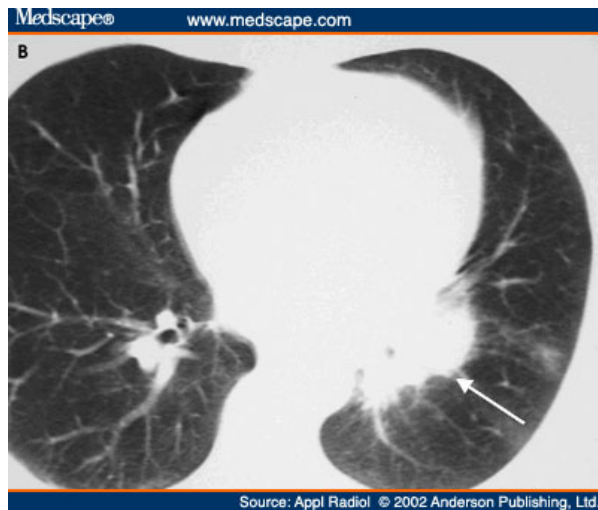


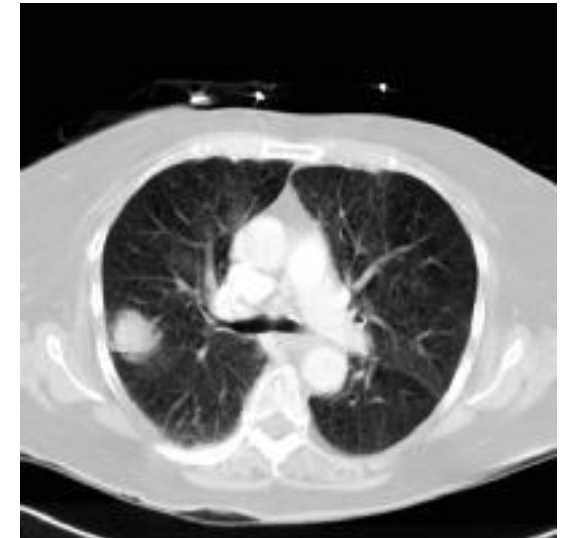
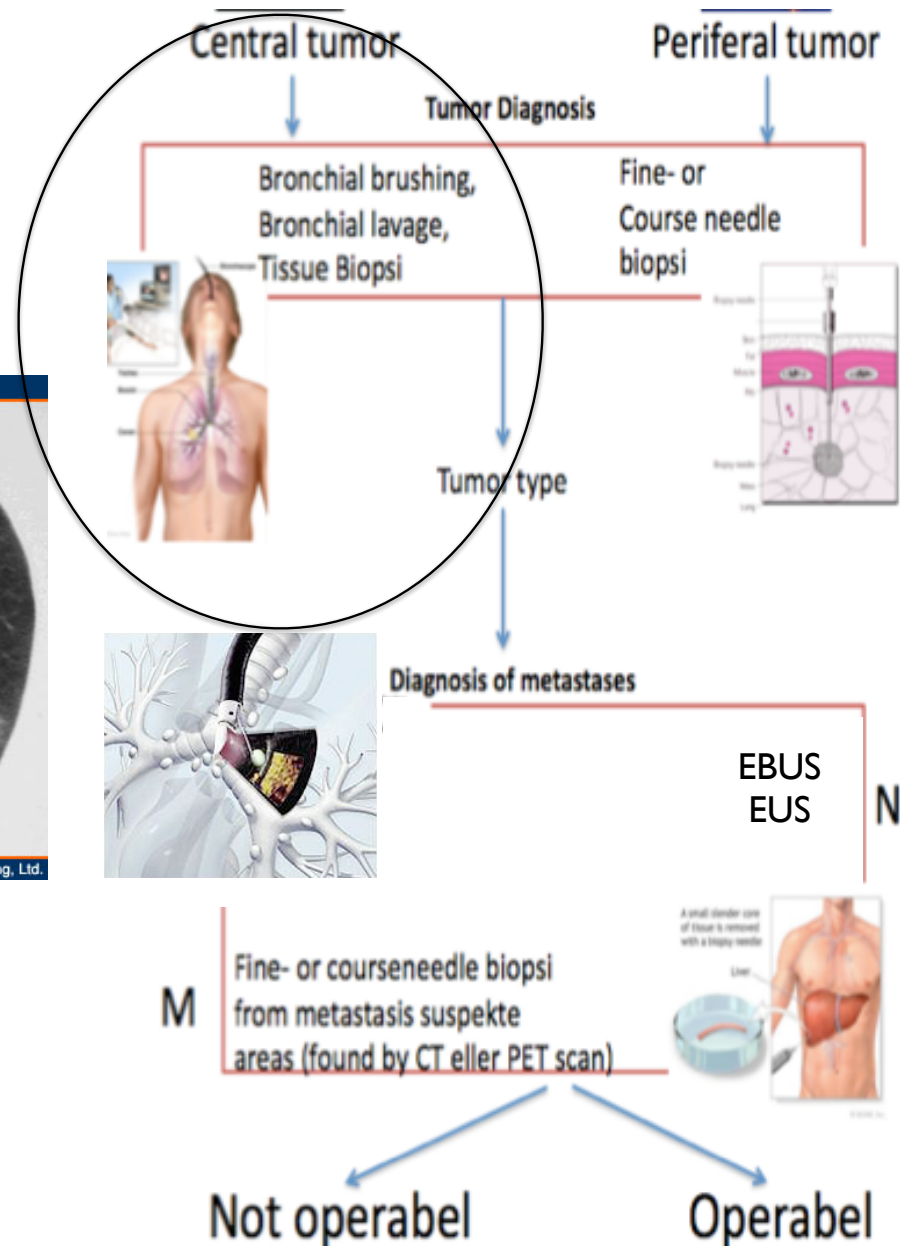
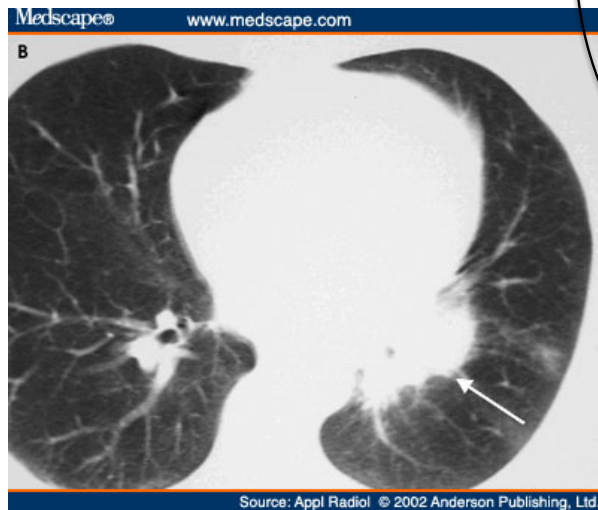
Diagnostic sampling

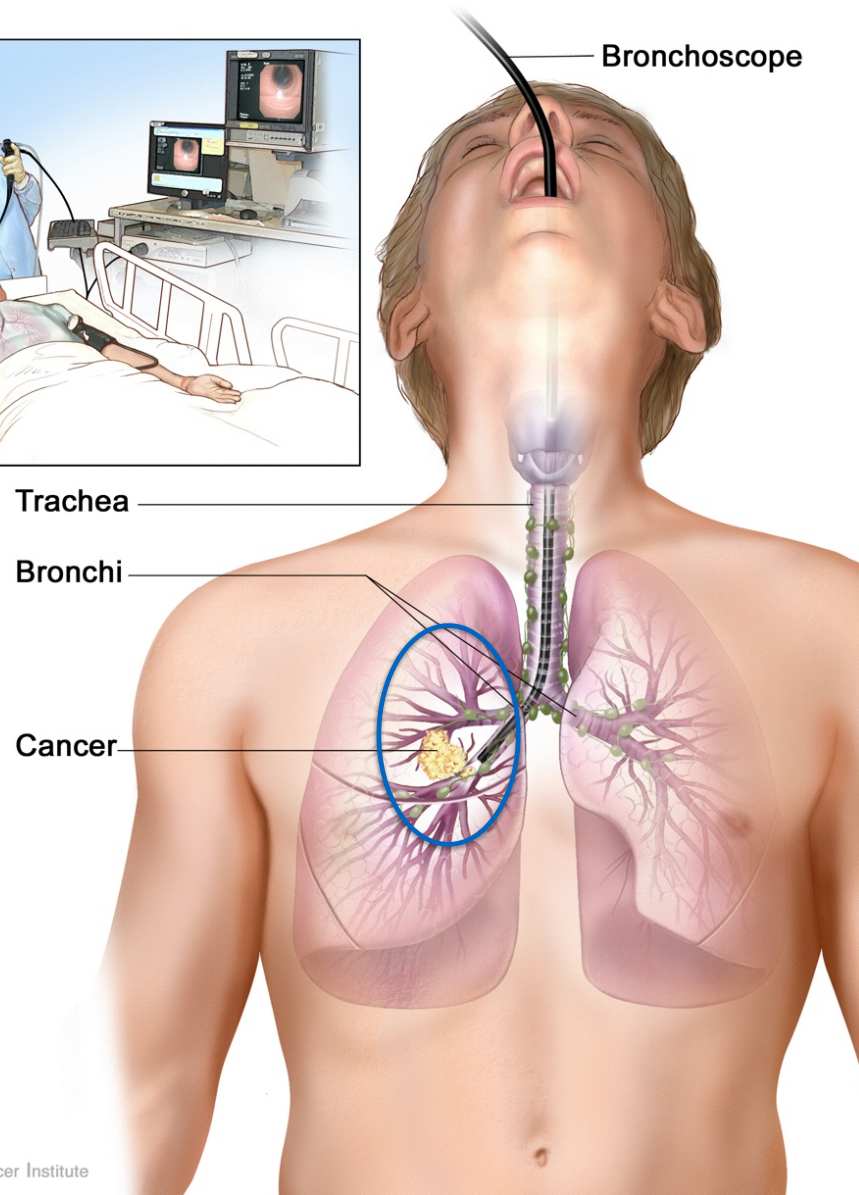
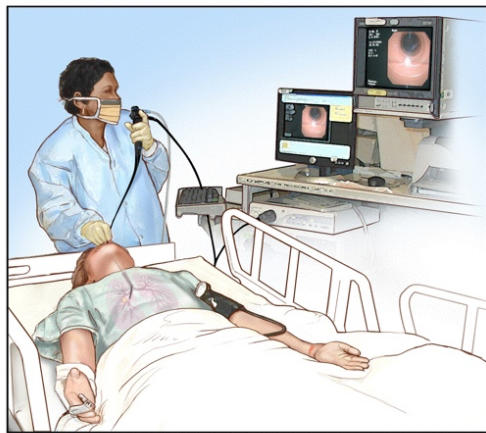
Adenocarcinoma (45%)
Squamous carcinoma (18%)
Large cell neuroendocrine carcinoma (1%)
Small cell carcinoma (12%)

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









National Cancer Institute

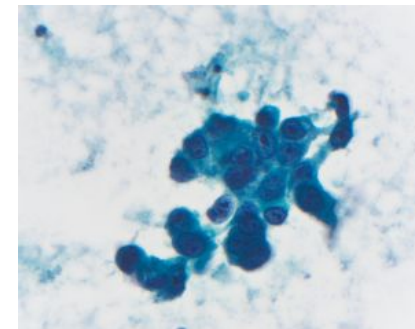
Bronkialwash
Brushbiopsy

EBUS Endobronchial Ultrasound Scanning

EUS Esophageal Ultrasound Scanning

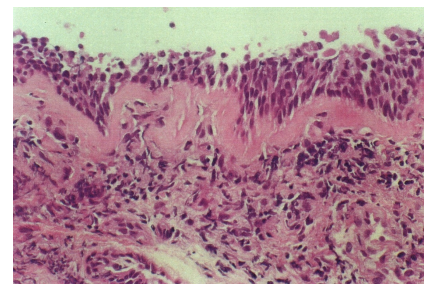
Nordi*IQ*C

} TBNA

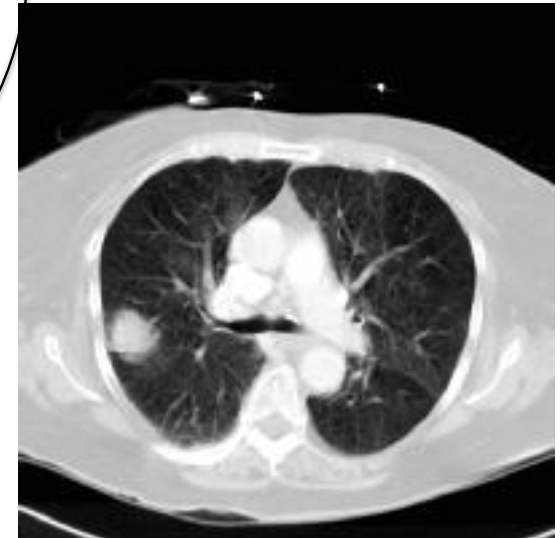
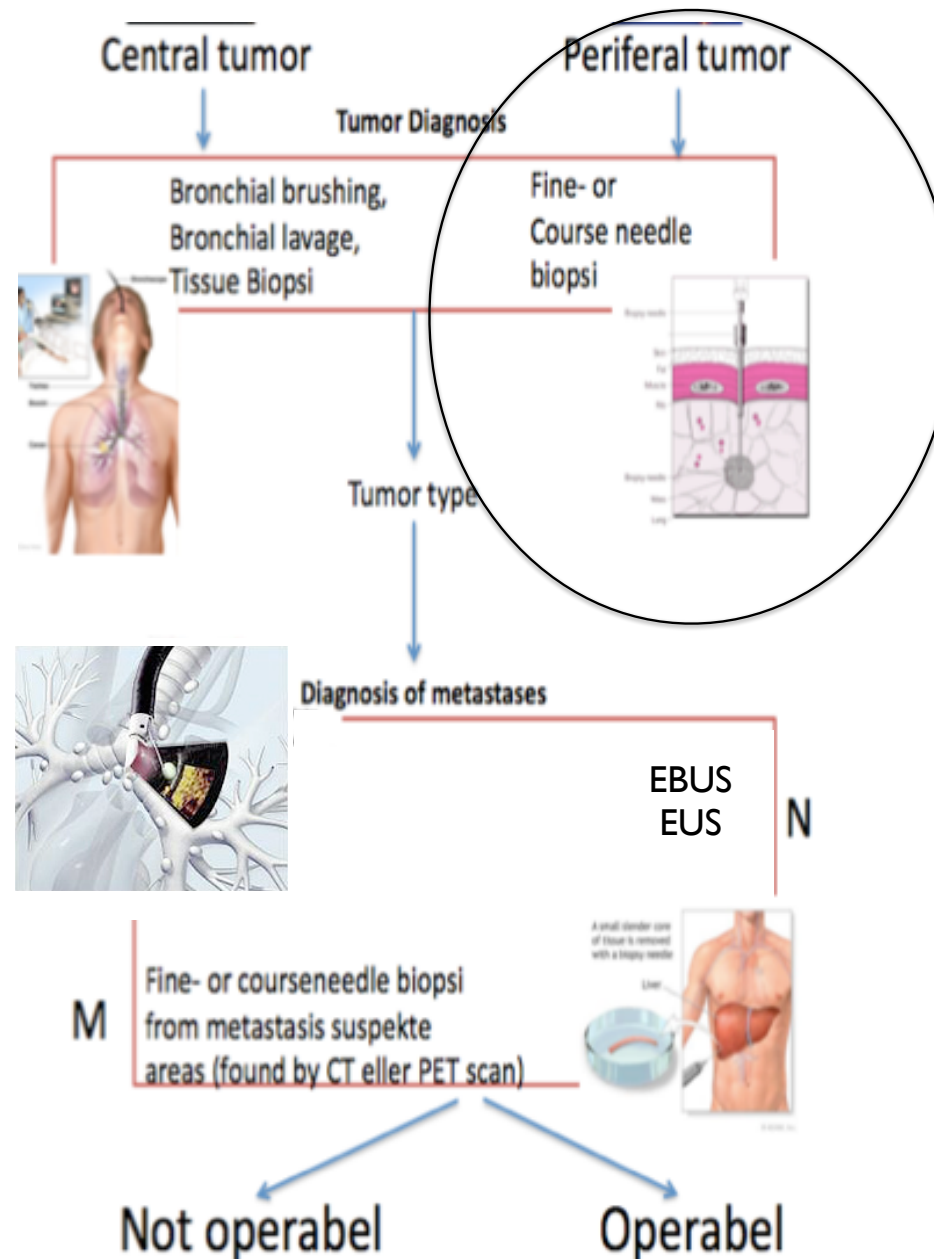
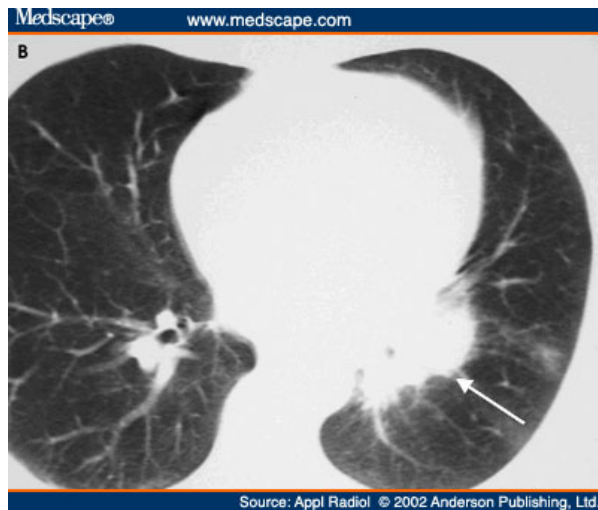


Cytology

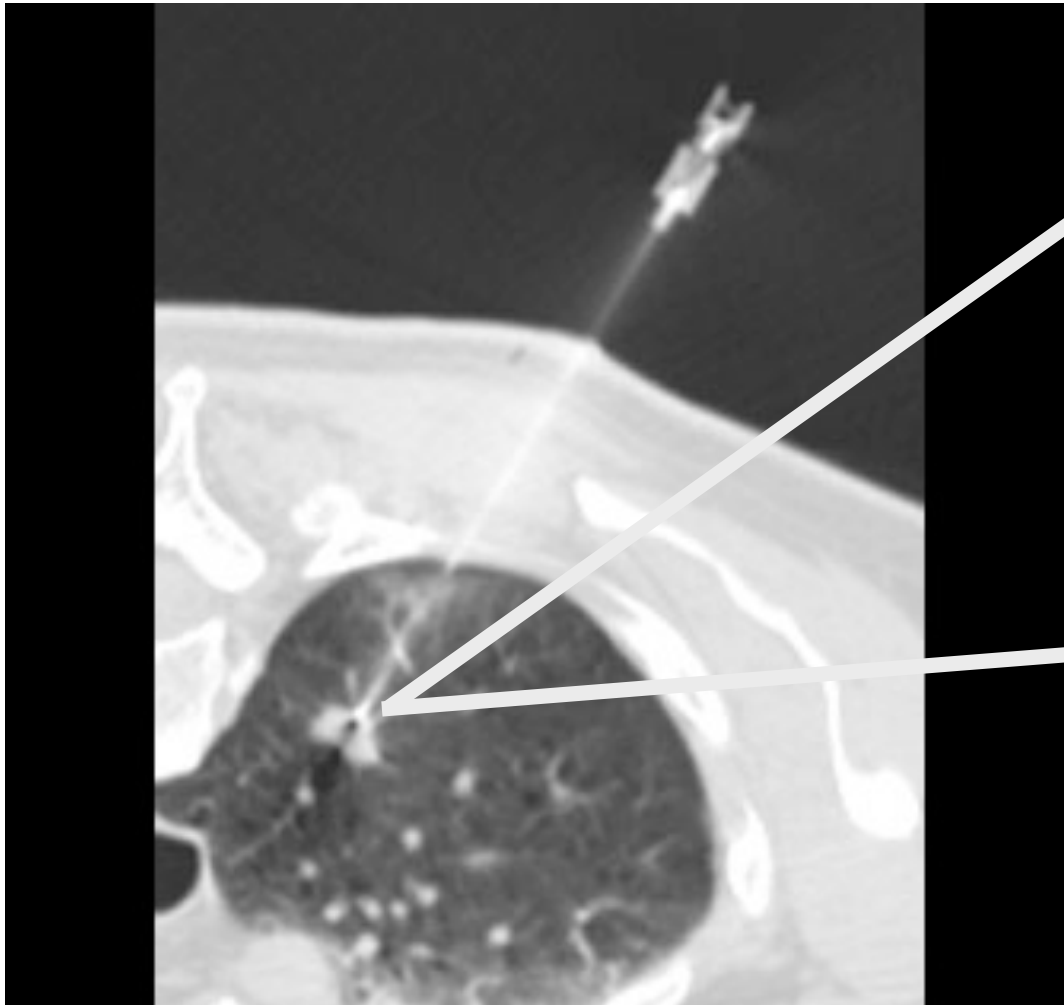
forceps biopsy



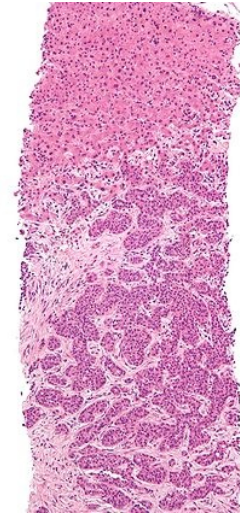
Histology



CT guided needle biopsy

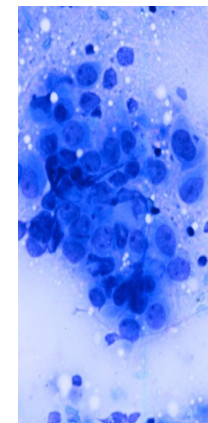


Coarse needle

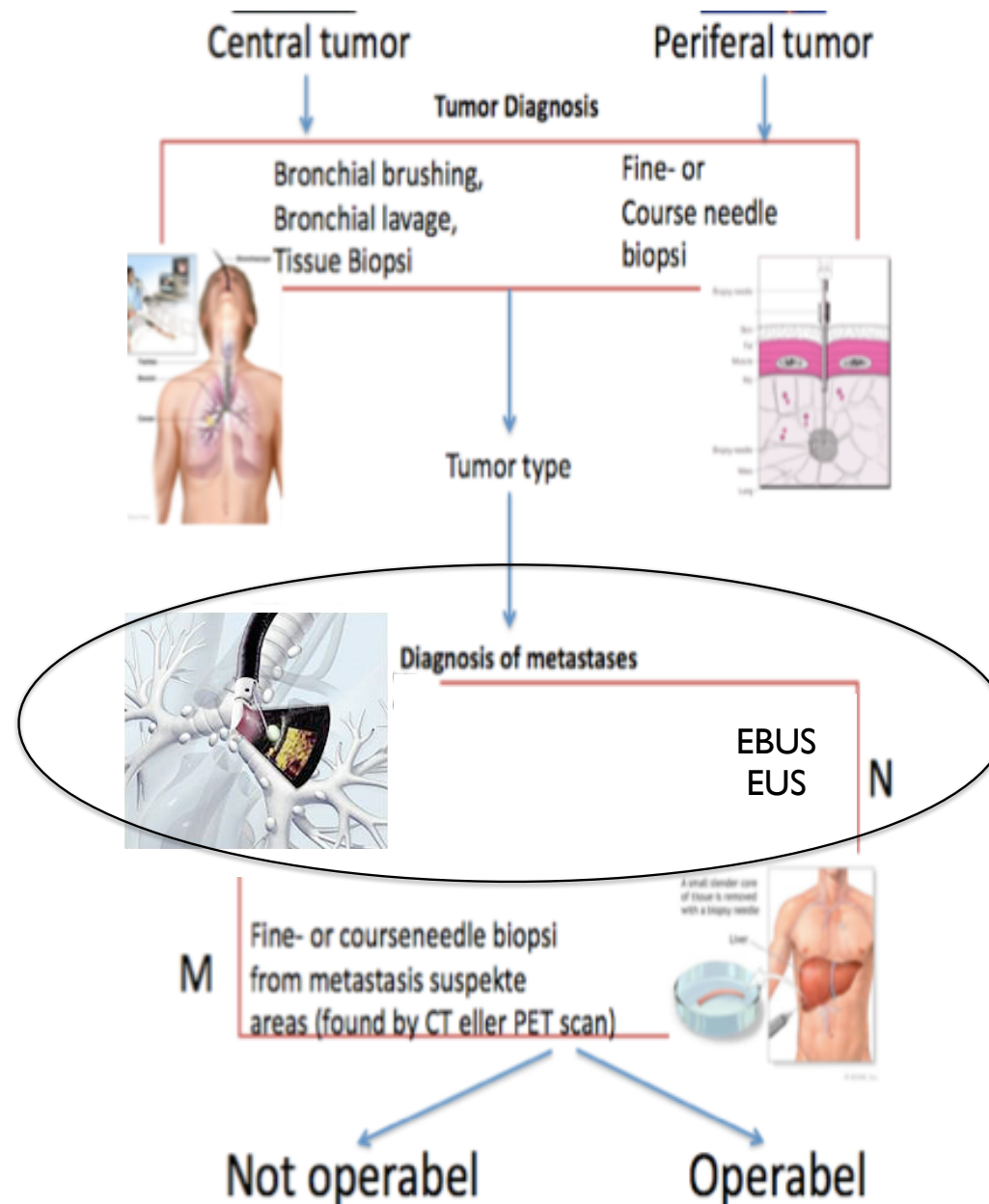


Histology

Fine needle



Cytology



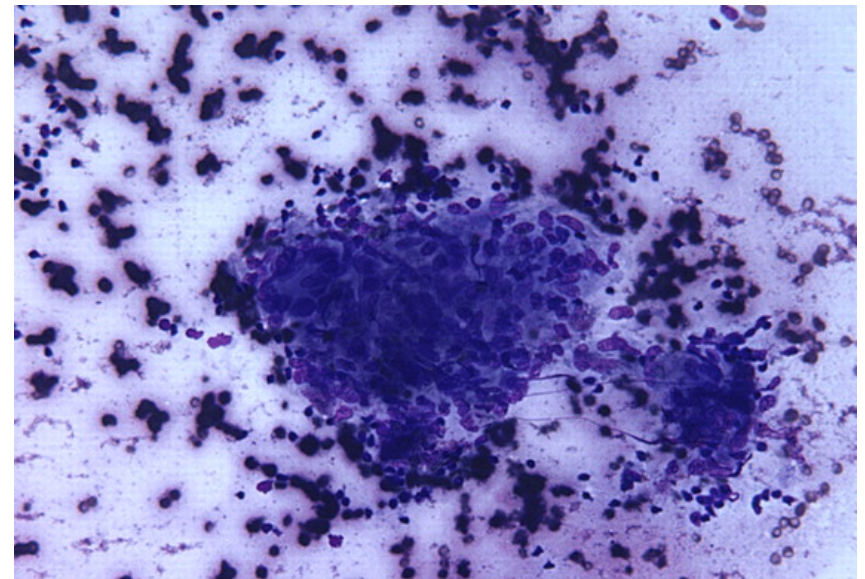


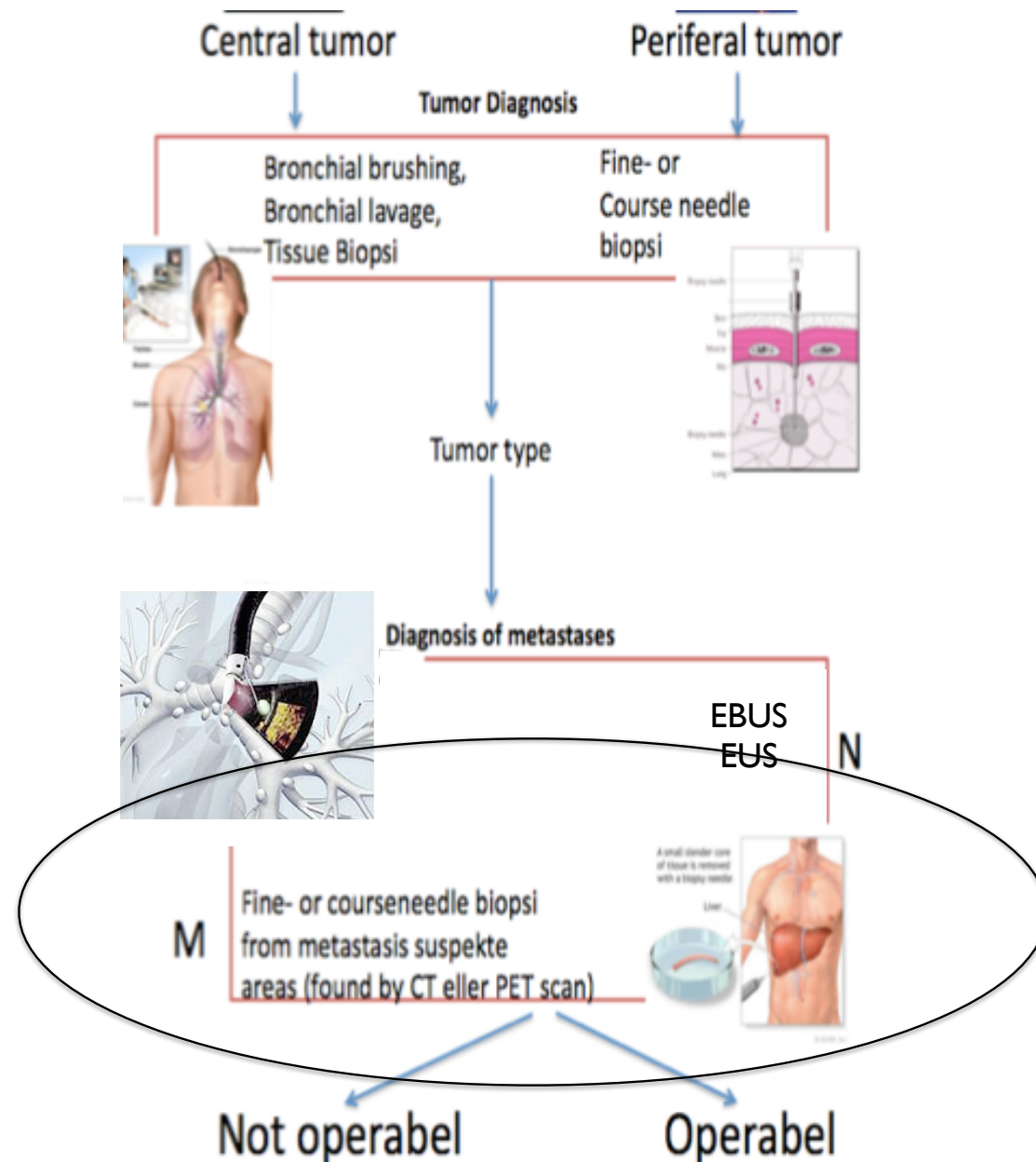
EBUS Endobronchial Ultrasound Scanning

EUS Esophageal Ultrasound Scanning

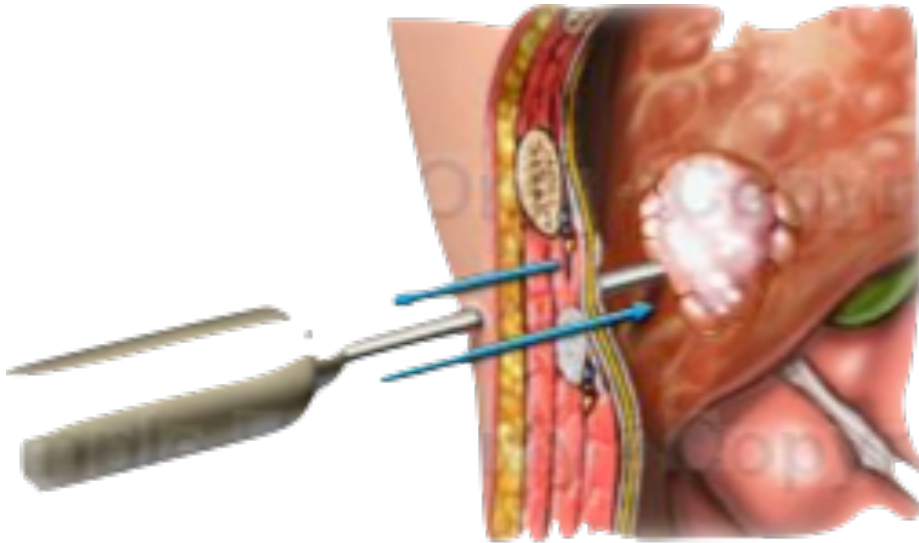
} TBNA

Cytology

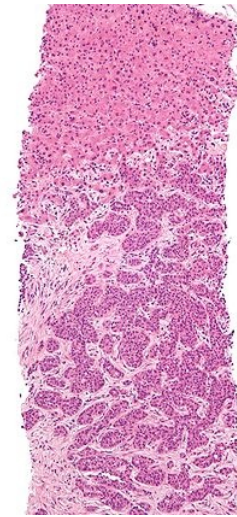




Coarse needle



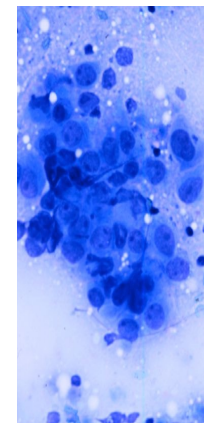
Histology



Fine needle



Cytology



Patoanatomical specimen

Histology

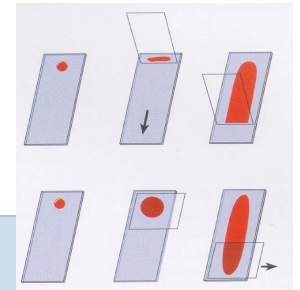
Cytologi



Fixation
Dehydration
Parafinembedding
Microtomy

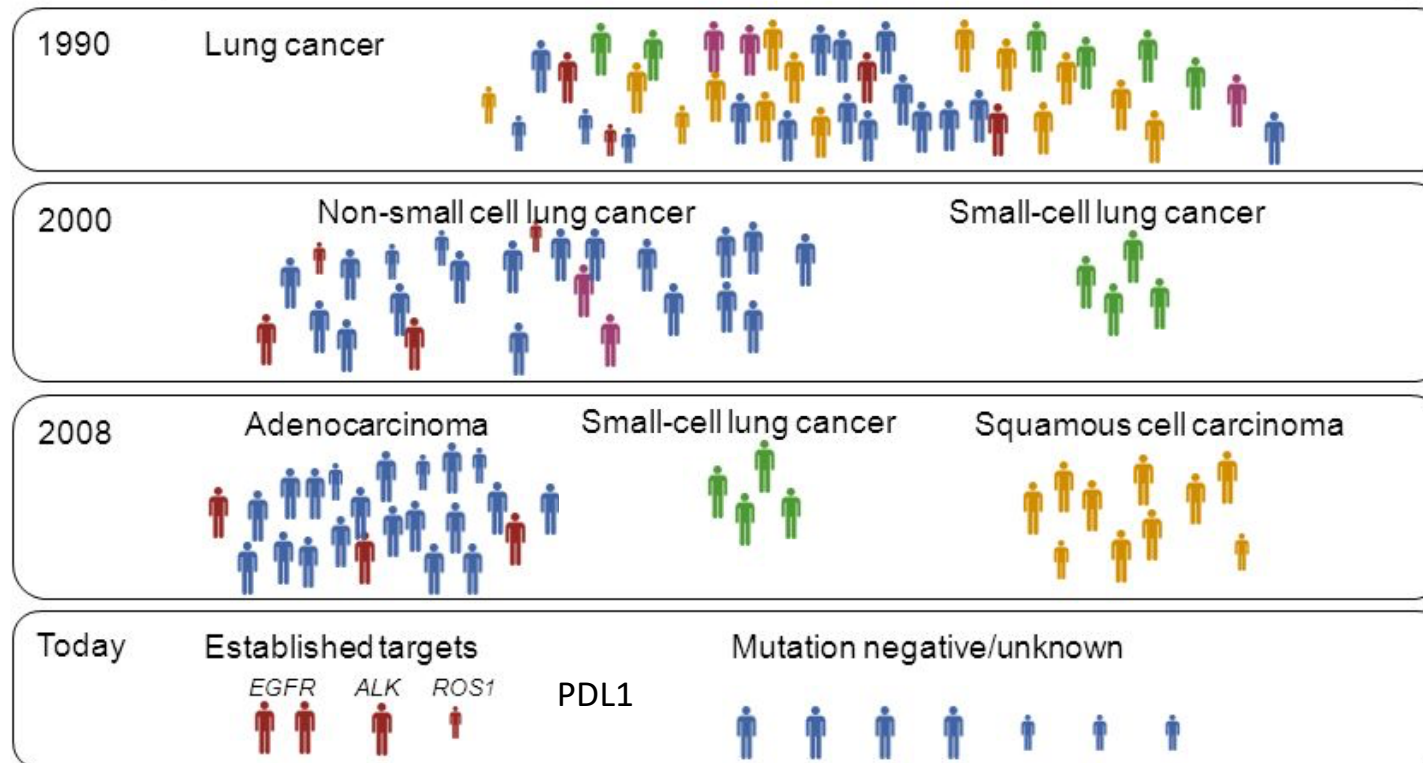
Præparation

Smear preparation



Visualization (Staining)

Patient selection in lung cancer: Evolution over time



Diagnosis

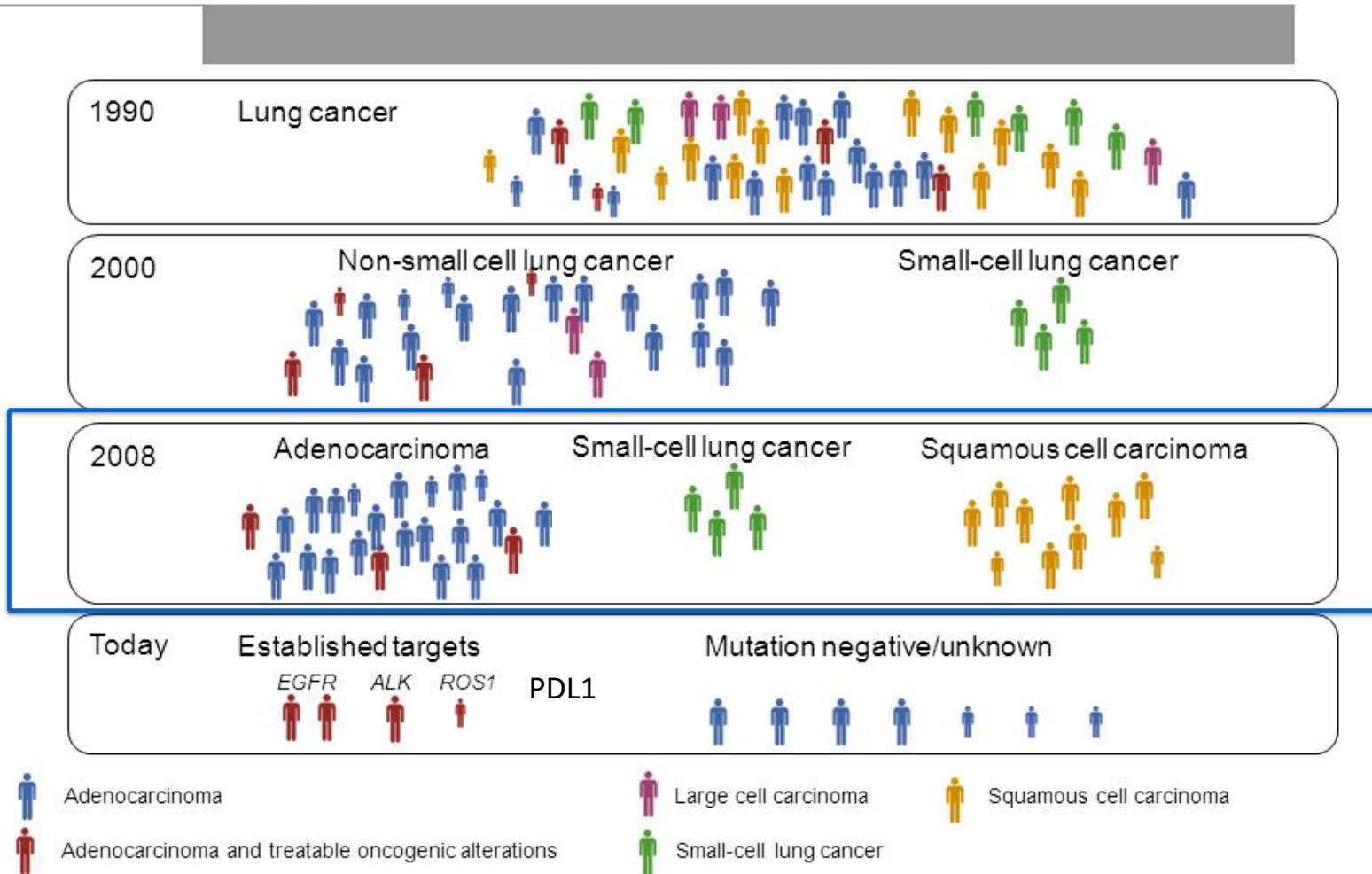
Diagnosis

Diagnosis

Prediction



Patient selection in lung cancer: Evolution over time



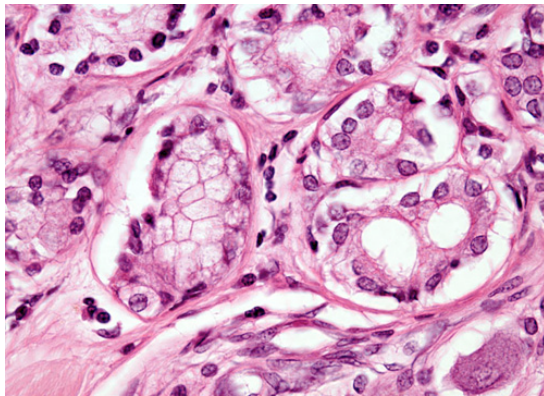
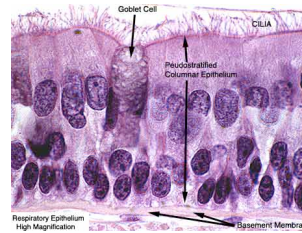
Diagnosis

Diagnosis

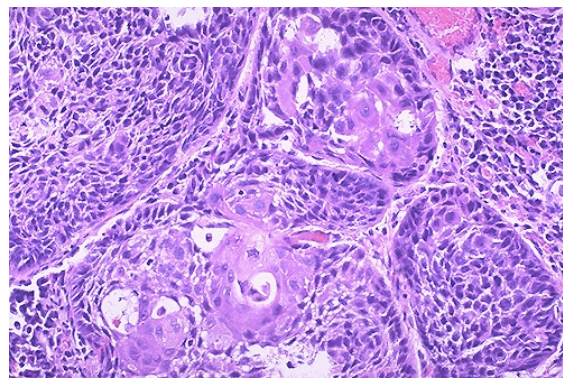
Diagnosis

Prediction

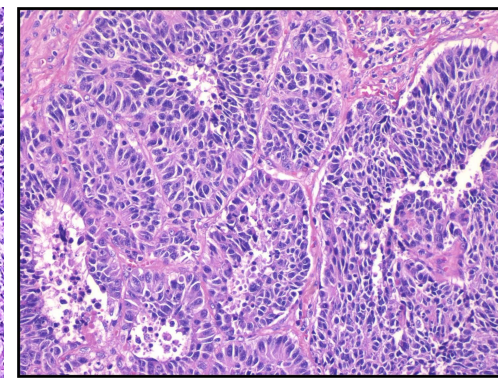
Morphology



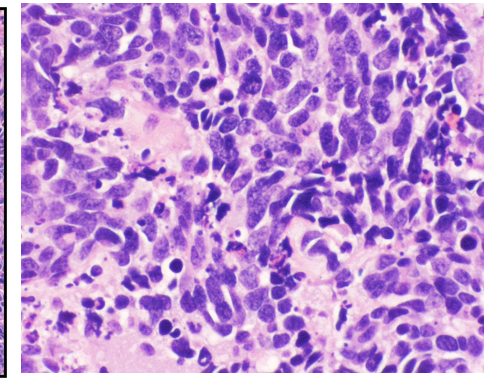
Adenocarcinoma



Squamous carcinoma



Large cell
neuroendocrine carc.

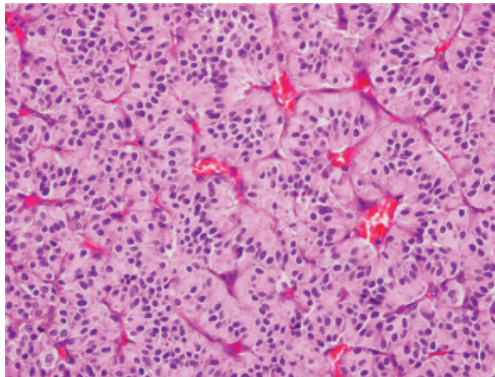
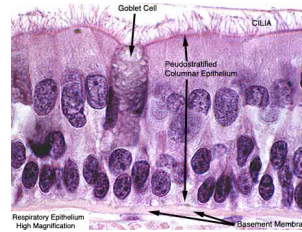


Small cell carcinoma

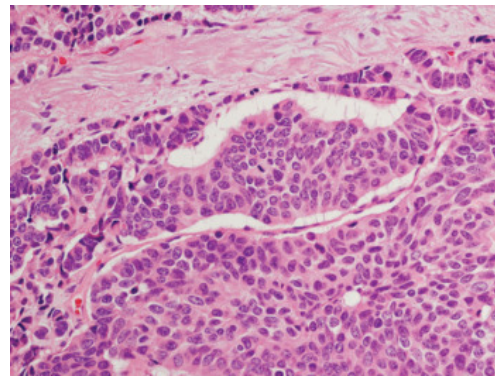
Non Small Cell Lung Carcinoma (NSCLC)

Neuroendocrine carcinoma

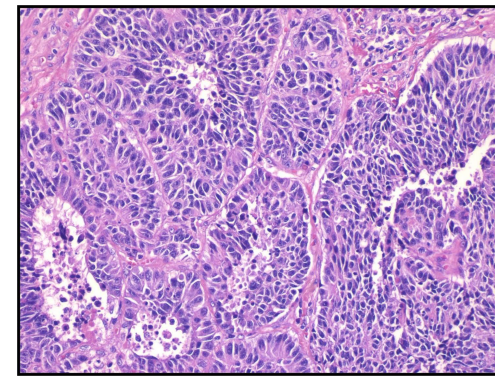
Morphology



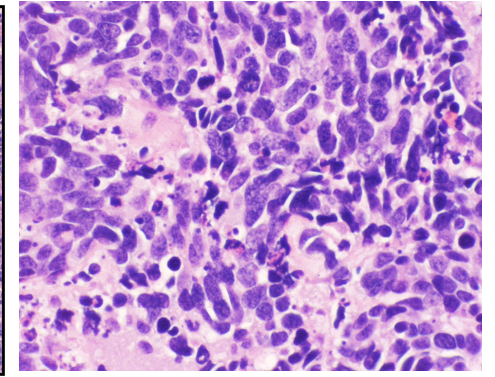
Typical carcinoid



Atypical carcinoid



Large cell
neuroendocrine carc.



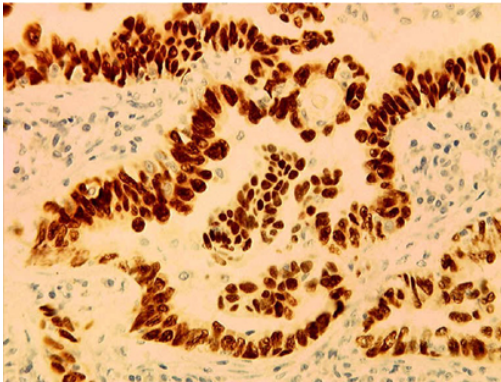
Small cell carcinoma

Neuroendocrine tumor

Neuroendocrine carcinoma

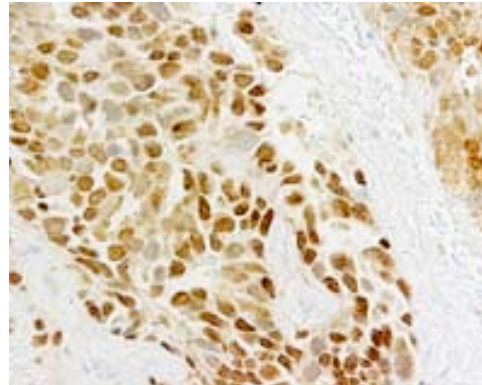
Immunohistochemistry

ttf1



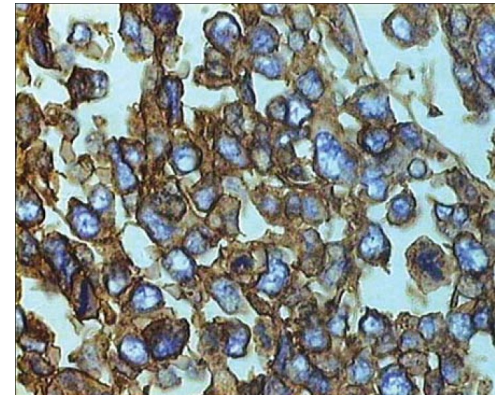
Adenocarcinoma

p63



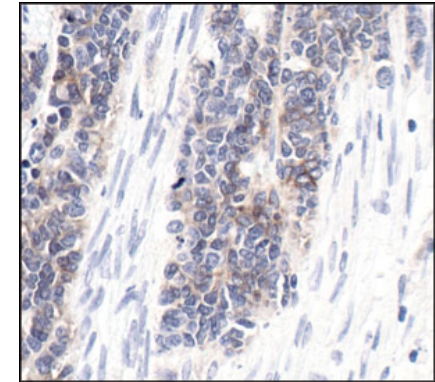
Squamous carcinoma

cd56



Large cell
neuroendocrine carc

cd56

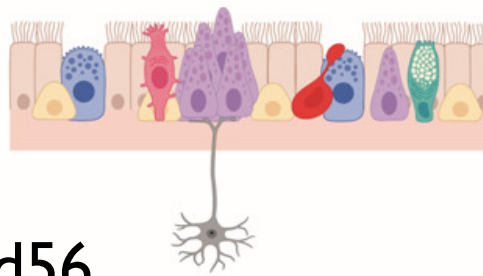


Small cell carcinoma

Non Small Cell Lung Carcinoma (NSCLC)

Neuroendocrine carcinoma

Immunohistochemistry

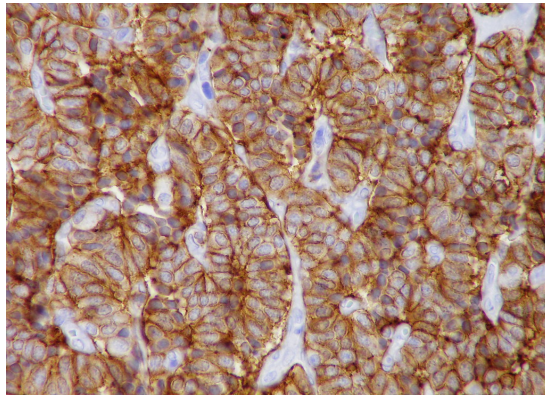


cd56

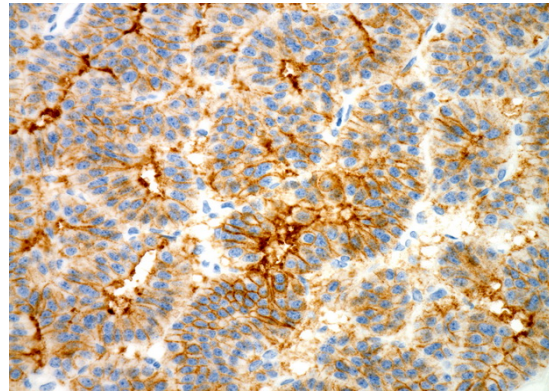
cd56

cd56

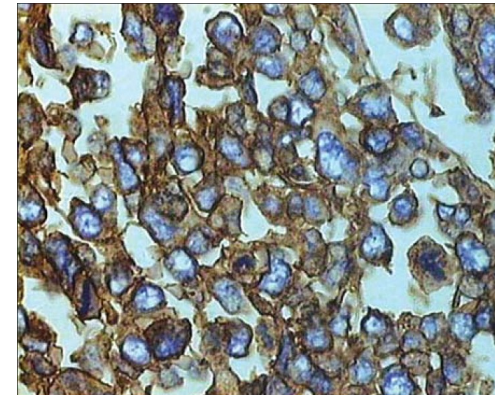
cd56



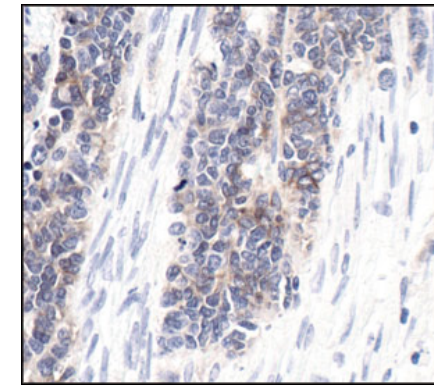
Typical carcinoid



Atypical carcinoid



Large cell
neuroendocrine carc



Small cell carcinoma

Neuroendocrine tumor

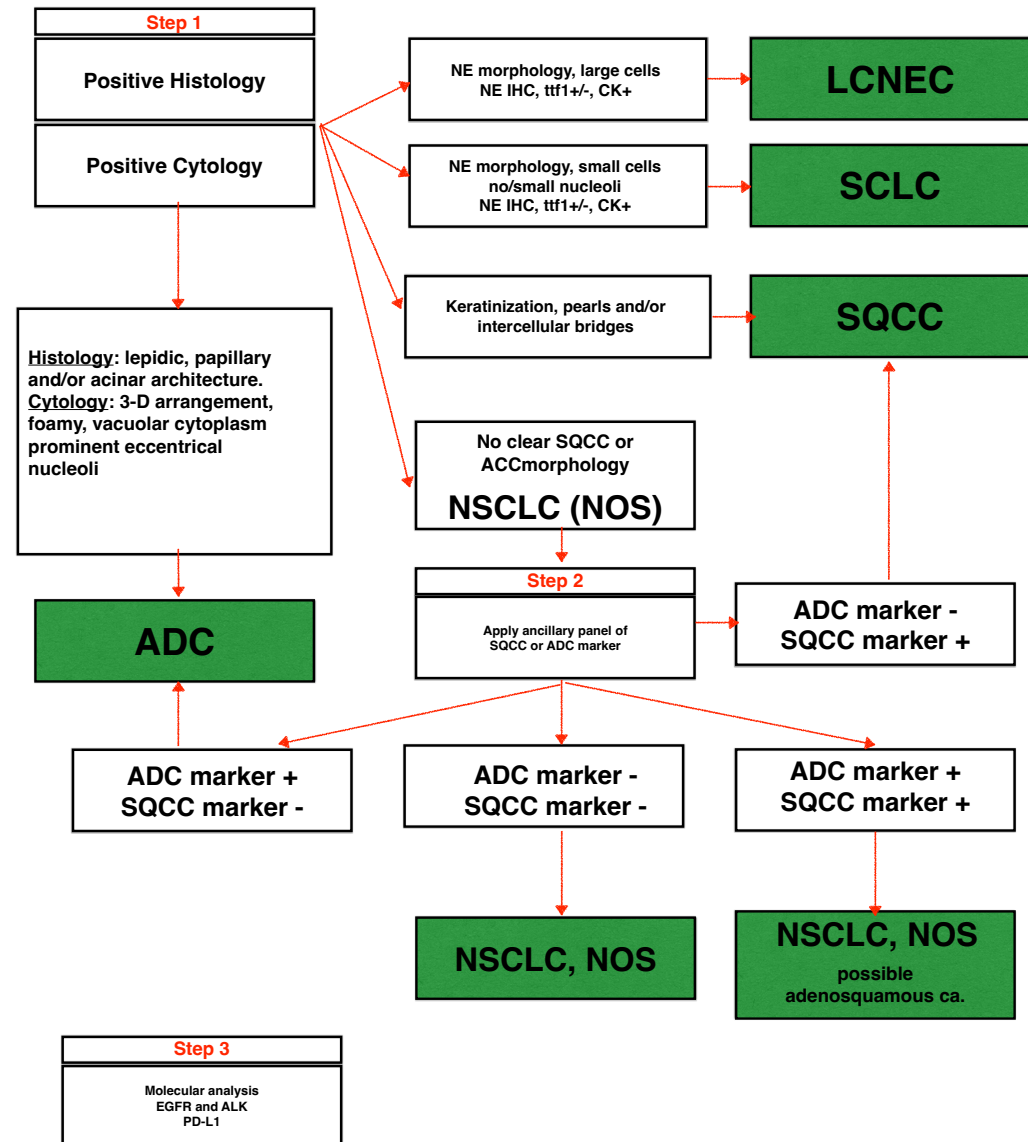
Neuroendocrine carcinoma

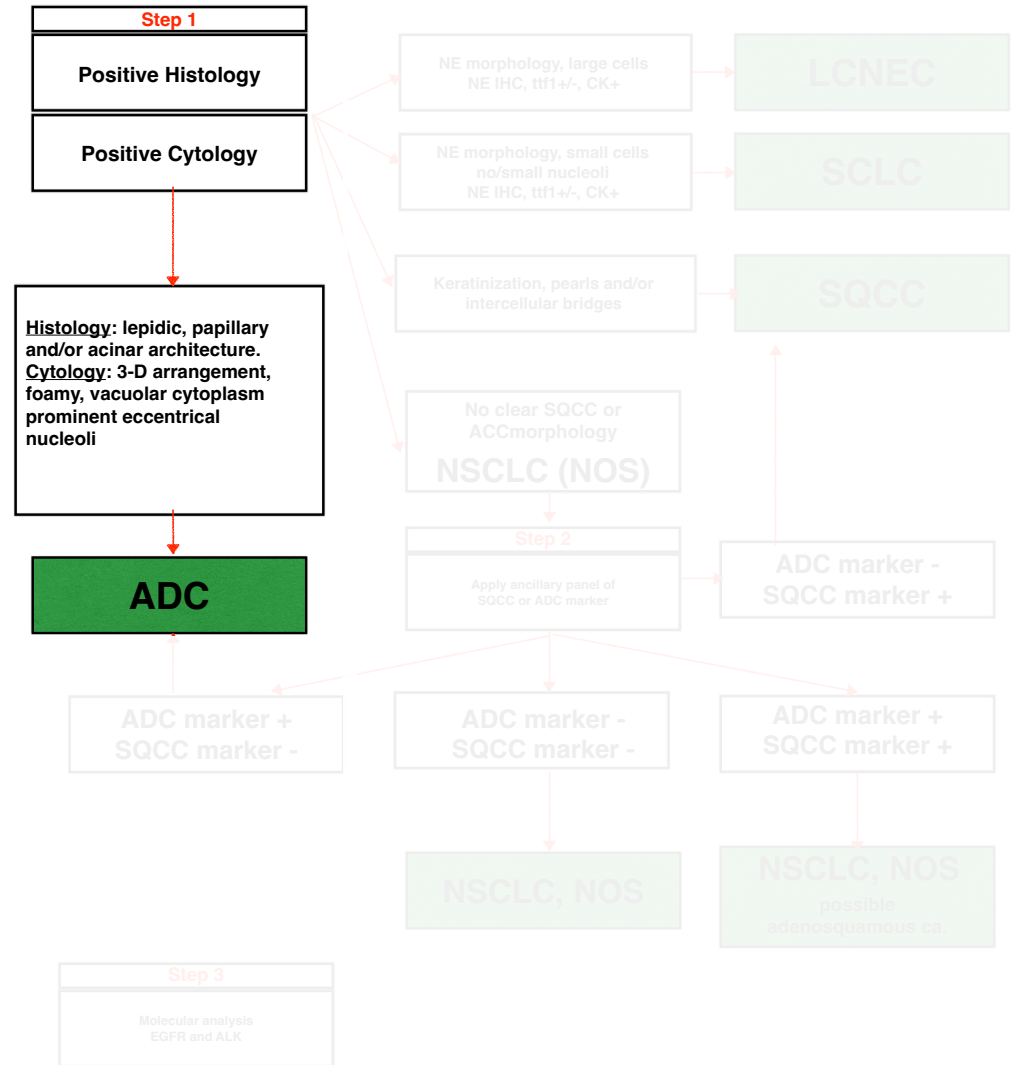
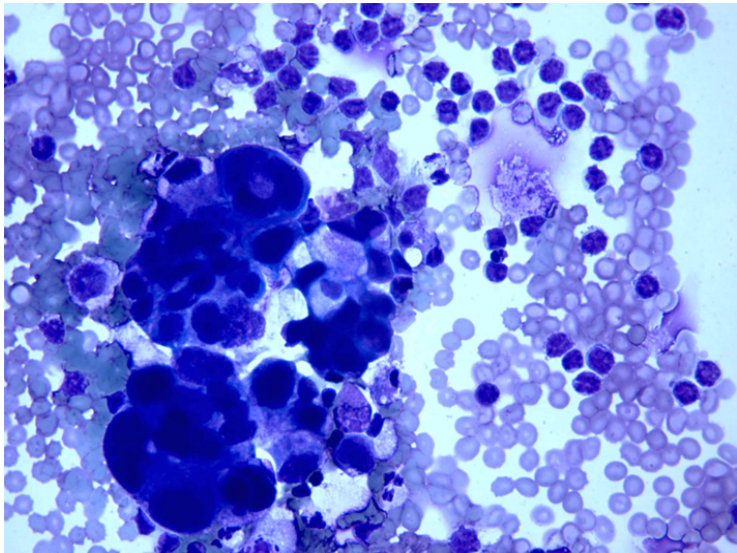
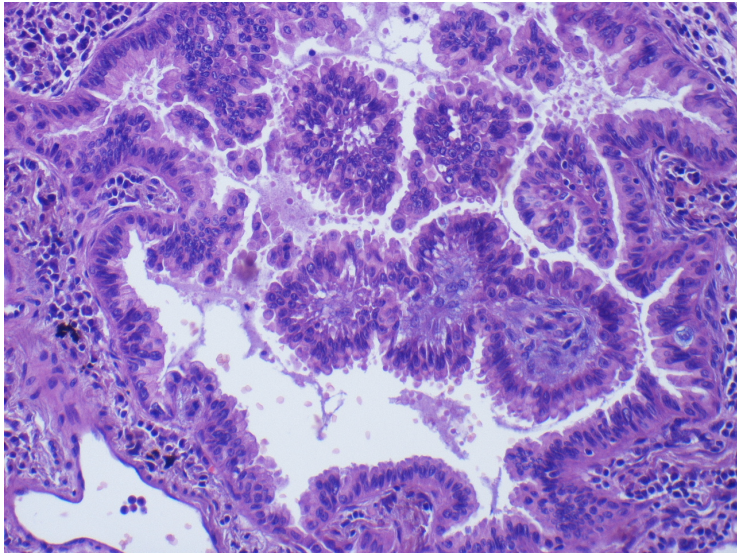
Algorithm modified from

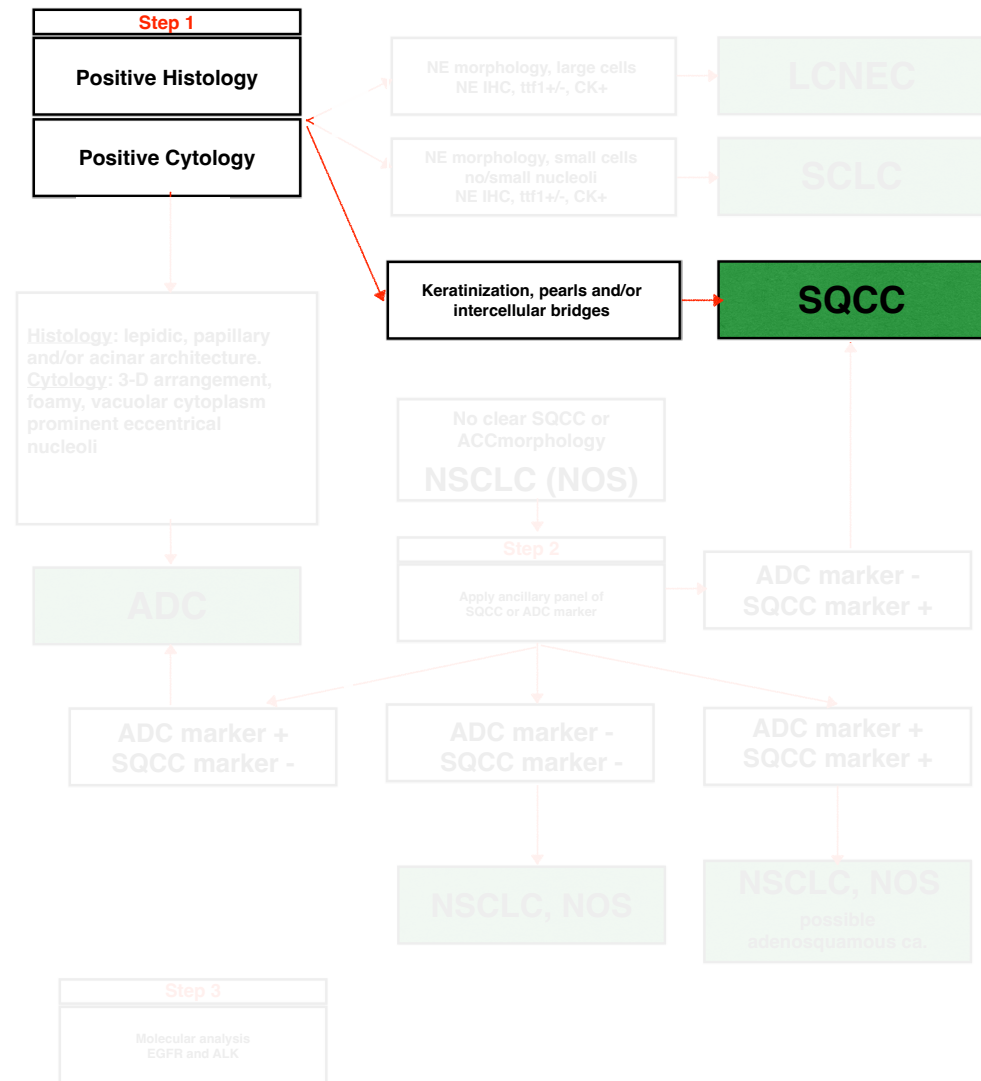
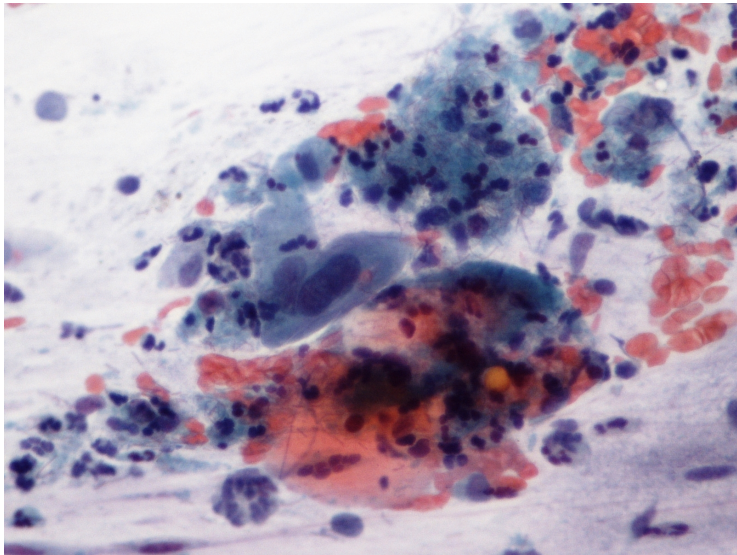
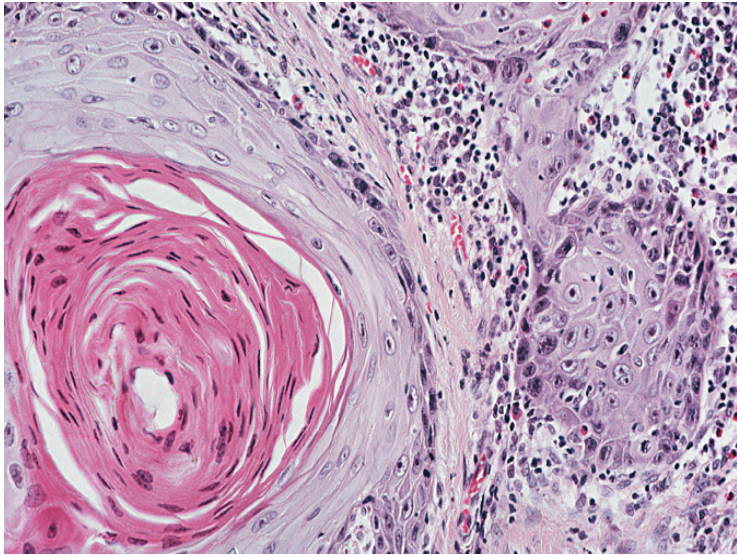
Diagnosis of Lung Cancer in Small Biopsies and Cytology

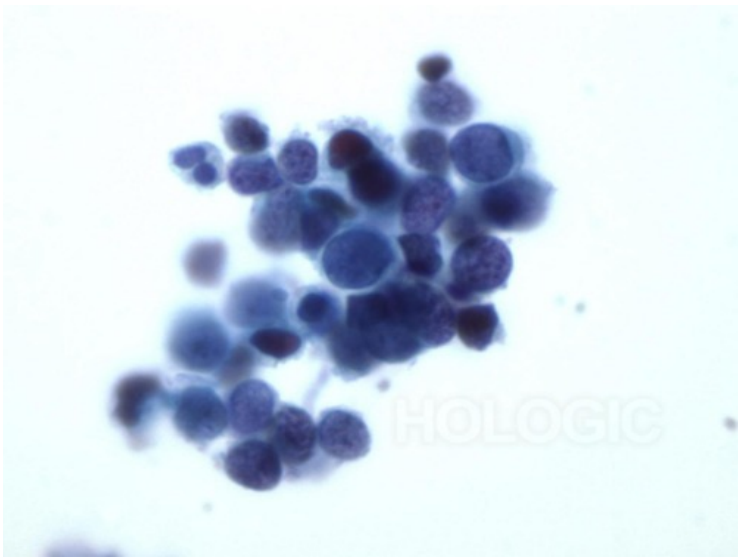
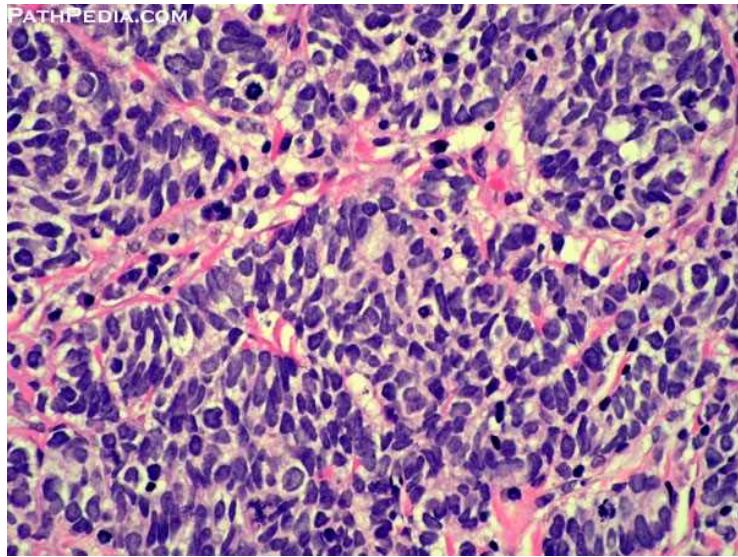
Implications of the 2011 International Association for the Study of Lung Cancer/
American Thoracic Society/European Respiratory Society Classification

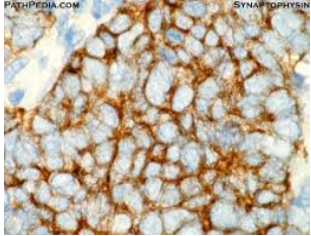
*William D. Travis, MD; Elisabeth Brambilla, MD; Masayuki Noguchi, MD; Andrew C. Nicholson, DM; Kim Geisinger, MD;
Yasushi Yatabe, MD; Yuichi Ishikawa, MD; Ignacio Wistuba, MD; Douglas B. Flieder, MD; Wilbur Franklin, MD; Adi Cazdar, MD;
Philip S. Hasleton, MD; Douglas W. Henderson, MD; Keith M. Kerr, MD; Iver Petersen, MD; Victor Roggli, MD;
Erik Thunnissen, MD; Ming Tsao, MD*



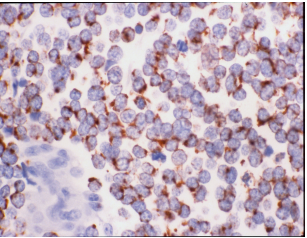




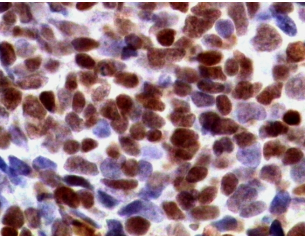




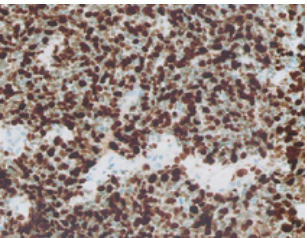
Neuroendocrine marker



Cytokeratin

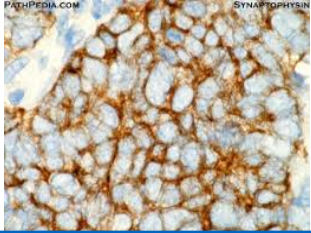


ttf1

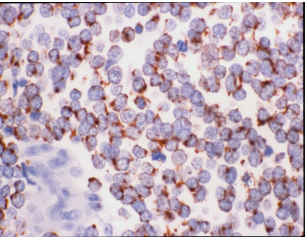


Ki67

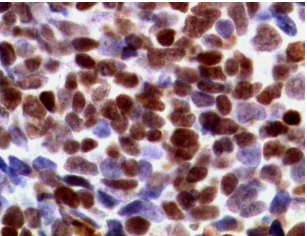




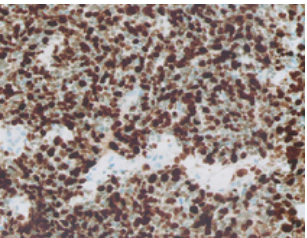
Neuroendocrine marker



Cytokeratin



ttf1



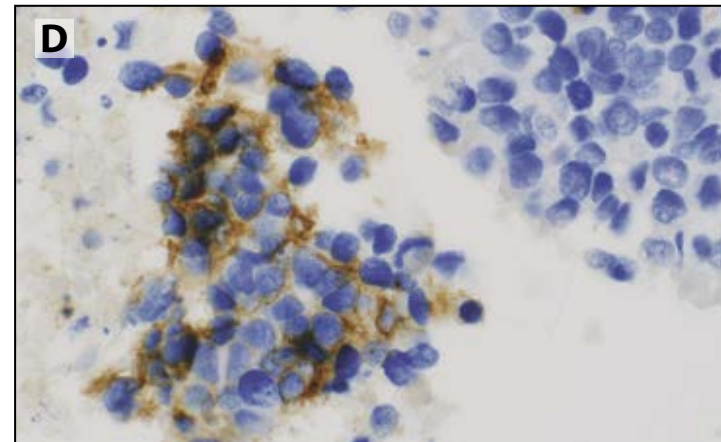
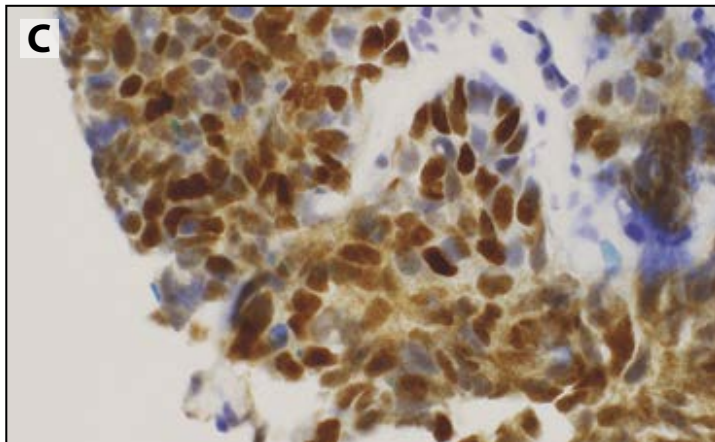
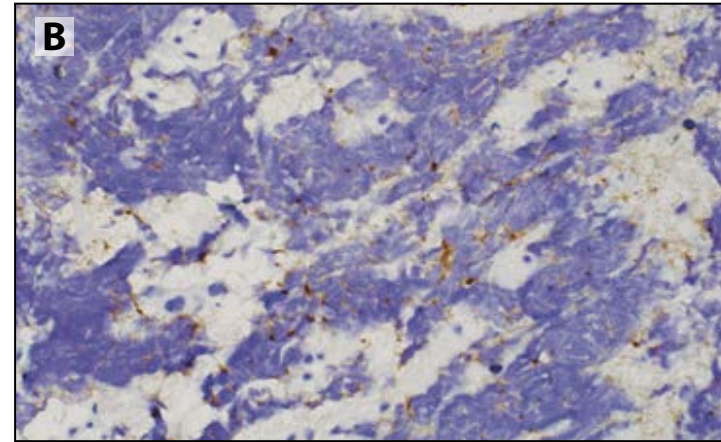
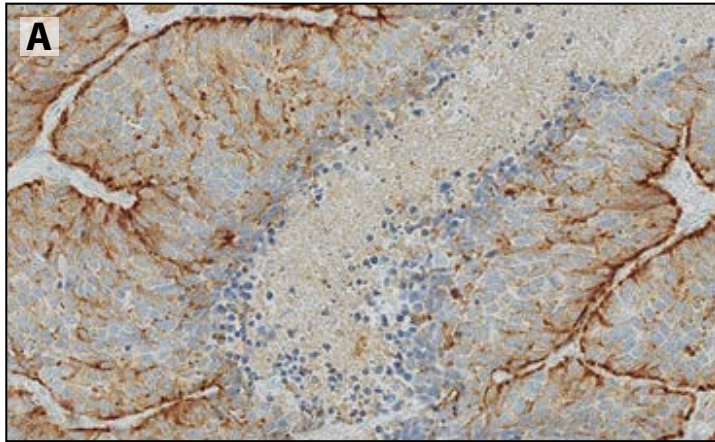
Ki67



Neuroendocrine markers

Chromogranin A

Synaptophysin



INSM1 Insulinoma-Associated Protein 1

CD56

Neuroendocrine markers



Sensitivity

Entity	Overall Cases Analyzed (N)	Positive Cases [n (%)]*				
		INSM1	SYN	CHRA	CD56	Any Conventional (SYN/CHRA/CD56)
LCNEC	77	32 (42)	47 (61)	32 (42)	66 (86)	70 (91)
SCLC	144	124 (86)	122 (85)	107 (74)	132 (92)	137 (95)

Insulinoma-associated Protein 1 (INSM1) in Thoracic Tumors is Less Sensitive but More Specific Compared With Synaptophysin, Chromogranin A, and CD56

Katharina Kriegsmann, MD, MBA,* Christiane Zgorzelski,† Daniel Kazdal, PhD,†‡
 Martin Cremer, MD,* Thomas Muley, PhD,§|| Hauke Winter, MD, PhD,‡||
 Rémi Longuespée, PhD,† Jörg Kriegsmann, MD, PhD,¶ Arne Warth, MD, PhD,#
 and Mark Kriegsmann, MD†

Neuroendocrine markers

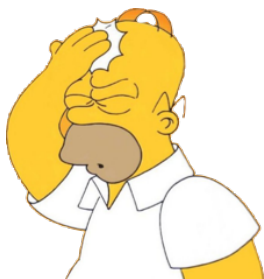


Specificity

Entity	Overall Cases Analyzed (N)	Positive Cases [n (%)]*				
		INSM1	SYN	CHRA	CD56	Any Conventional (SYN/CHRA/CD56)
ADC	47	1 (2)	6 (13)	4 (9)	7 (15)	10 (21)
SqCC	44	0 (0)	2 (5)	0 (0)	9 (20)	10 (23)

Insulinoma-associated Protein 1 (INSM1) in Thoracic Tumors is Less Sensitive but More Specific Compared With Synaptophysin, Chromogranin A, and CD56

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 Rémi Longuespée, PhD,† Jörg Kriegsmann, MD, PhD,¶ Arne Warth, MD, PhD,#
 and Mark Kriegsmann, MD†

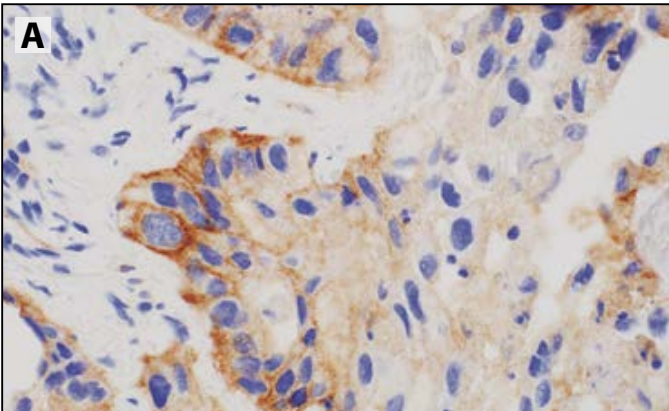


Neuroendocrine markers

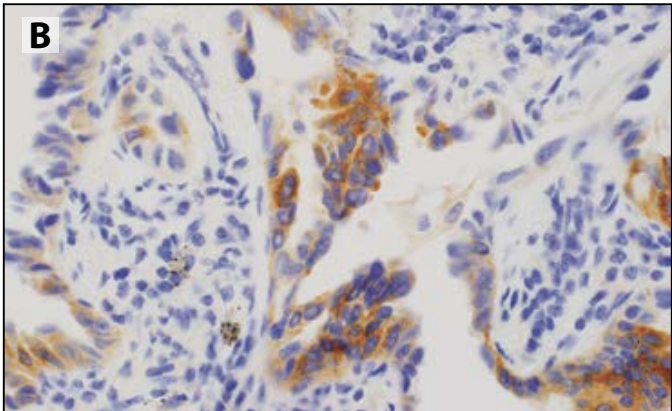


Specificity

Entity	Overall Cases Analyzed (N)	Positive Cases [n (%)]*				
		INSM1	SYN	CHRA	CD56	Any Conventional (SYN/CHRA/CD56)
ADC	47	1 (2)	6 (13)	4 (9)	7 (15)	10 (21)
SqCC	44	0 (0)	2 (5)	0 (0)	9 (20)	10 (23)



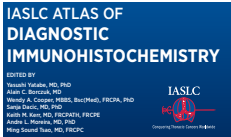
SqCC, CD56



ADC, syn

Insulinoma-associated Protein 1 (INSM1) in Thoracic Tumors is Less Sensitive but More Specific Compared With Synaptophysin, Chromogranin A, and CD56

Katharina Kriegsmann, MD, MBA,* Christiane Zgorzelski,† Daniel Kazdal, PhD,‡
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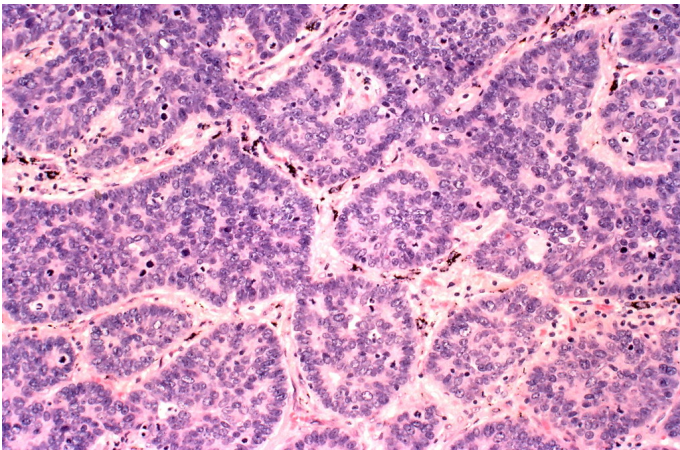
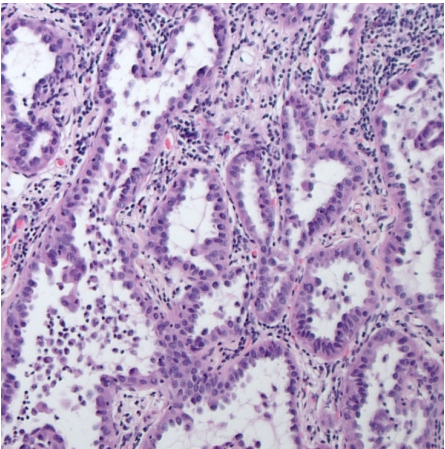
Neuroendocrine markers



Specificity

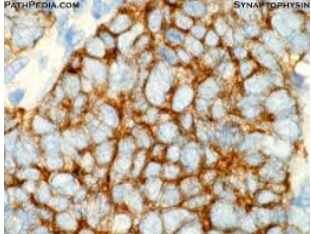
Entity	Overall Cases Analyzed (N)	Positive Cases [n (%)]*				
		INSM1	SYN	CHRA	CD56	Any Conventional (SYN/CHRA/CD56)
ADC	47	1 (2)	6 (13)	4 (9)	7 (15)	10 (21)
SqCC	44	0 (0)	2 (5)	0 (0)	9 (20)	10 (23)

Morphology

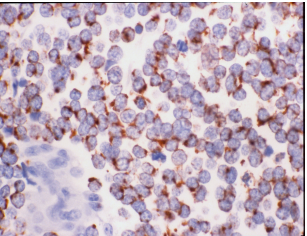


Insulinoma-associated Protein 1 (INSM1) in Thoracic Tumors is Less Sensitive but More Specific Compared With Synaptophysin, Chromogranin A, and CD56

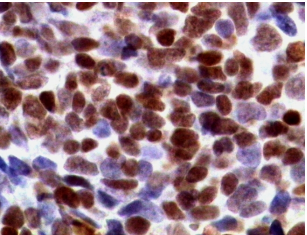
Katharina Kriegsmann, MD, MBA,* Christiane Zgorzelski,† Daniel Kazdal, PhD,‡
Martin Cremer, MD,* Thomas Muley, PhD,§|| Hauke Winter, MD, PhD,‡||
Rémi Longuespée, PhD,† Jörg Kriegsmann, MD, PhD,¶ Arne Warth, MD, PhD,#
and Mark Kriegsmann, MD†



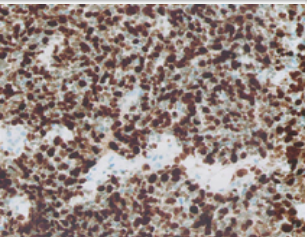
Neuroendocrine marker



Cytokeratin



ttf1



Ki67





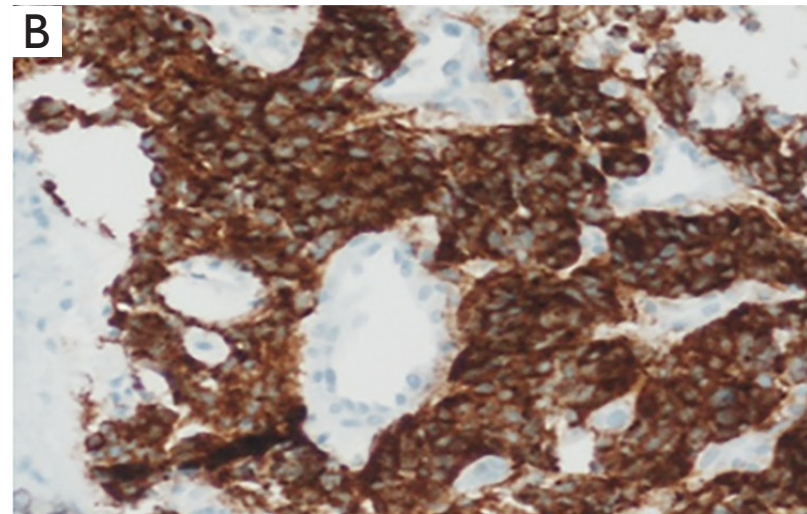
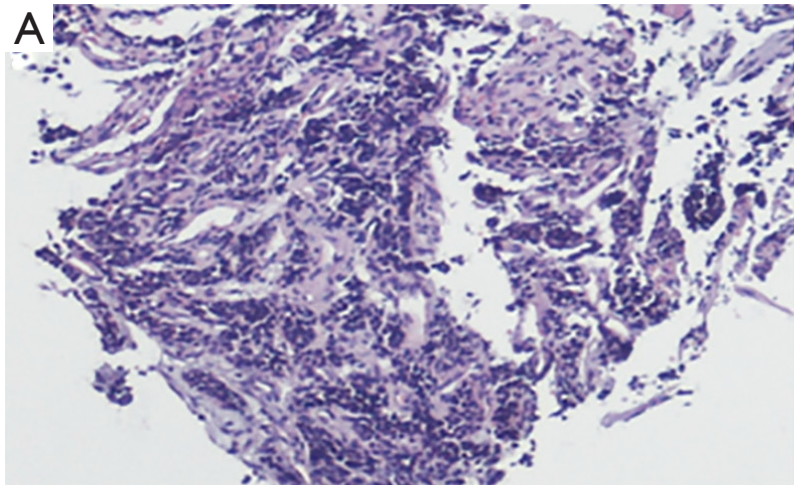
Neuroendocrine markers

Case Report

Erroneous diagnosis of small cell lung cancer based on small biopsies with far-reaching consequences: case report of a typical carcinoid tumor

Ioannis Kyritsis¹, Bettina Krebs¹, Sandra Kampe², Dirk Theegarten³, Clemens Aigner¹, Stefan Welter¹

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CD56

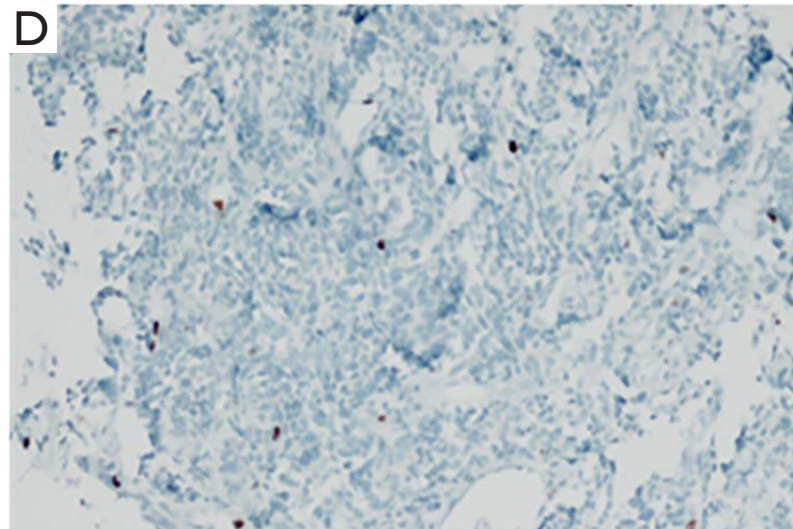
Neuroendocrine markers

Case Report

Erroneous diagnosis of small cell lung cancer based on small biopsies with far-reaching consequences: case report of a typical carcinoid tumor

Ioannis Kyritsis¹, Bettina Krebs¹, Sandra Kampe², Dirk Theegarten³, Clemens Aigner¹, Stefan Welter¹

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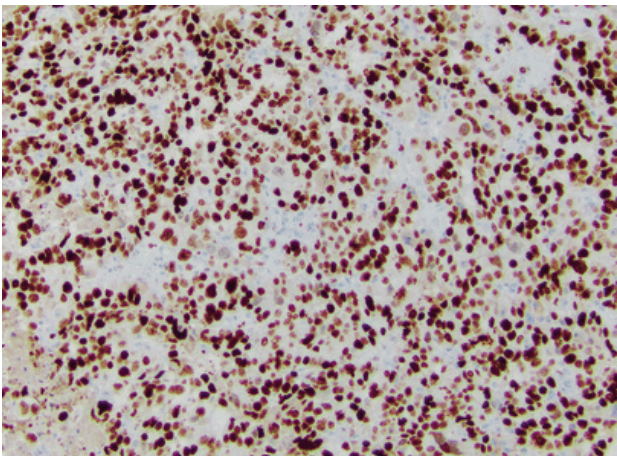
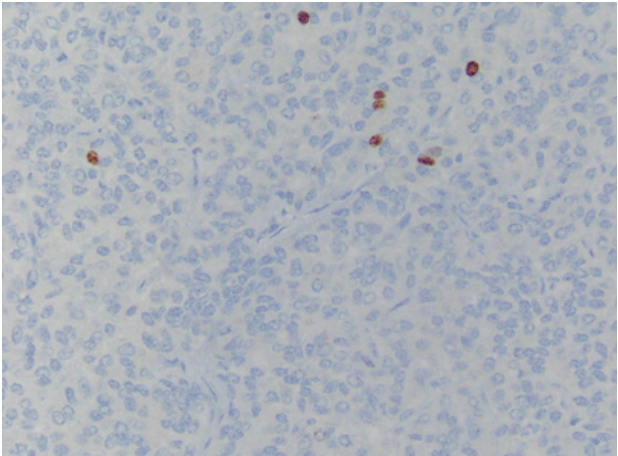
Ki67, re-evaluation



Neuroendocrine markers

Specificity

Entity	Overall Cases Analyzed (N)	Positive Cases [n (%)]*				
		INSM1	SYN	CHRA	CD56	Any Conventional (SYN/CHRA/CD56)
Typical carcinoid	112	91 (81)	111 (99)	111 (99)	112 (100)	112 (100)
Atypical carcinoid	39	29 (74)	39 (100)	39 (100)	39 (100)	39 (100)



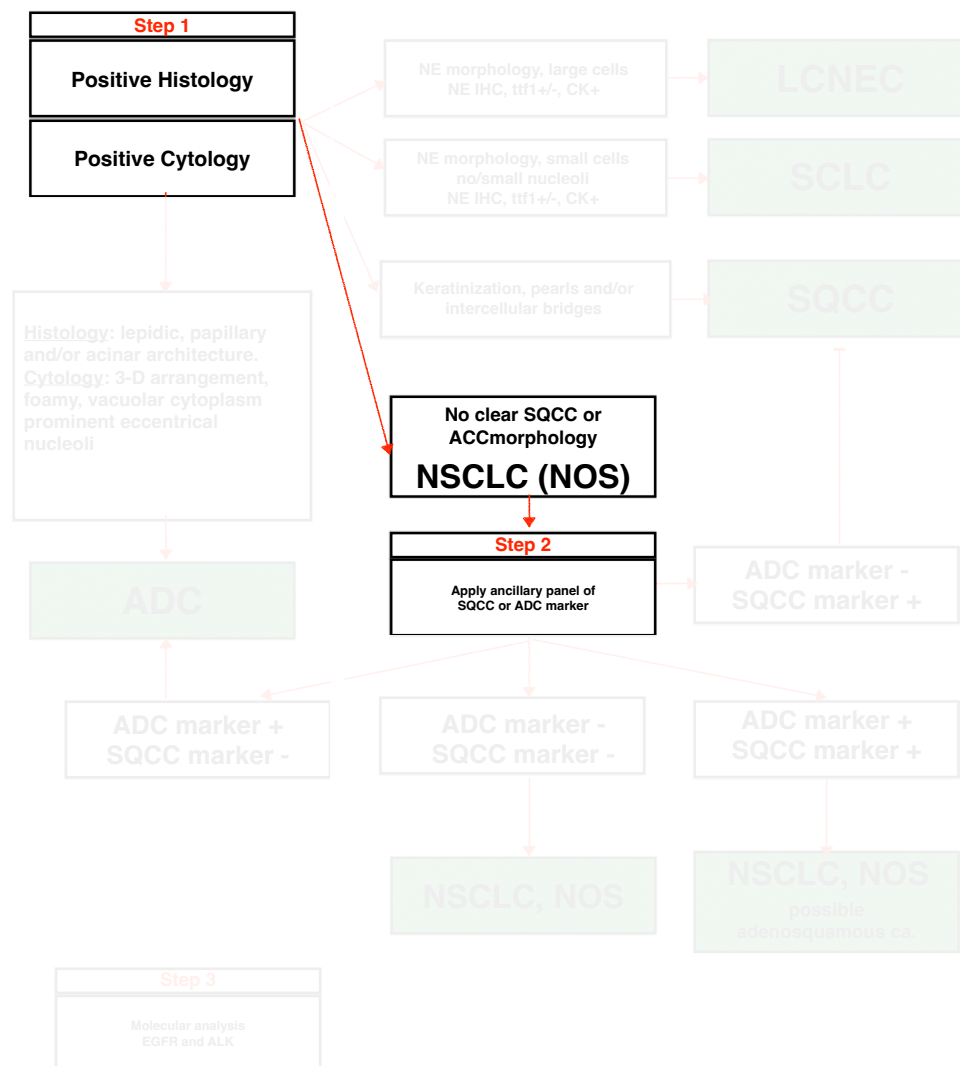
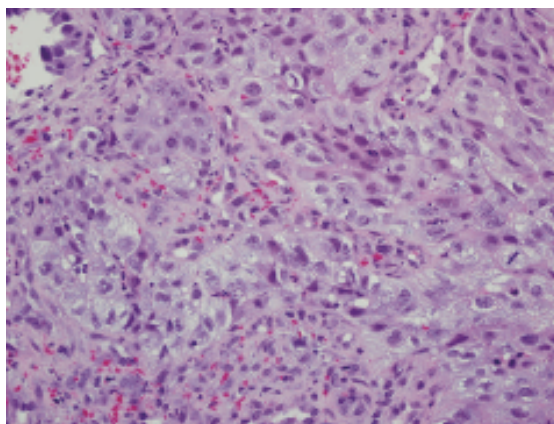
Carcinoid

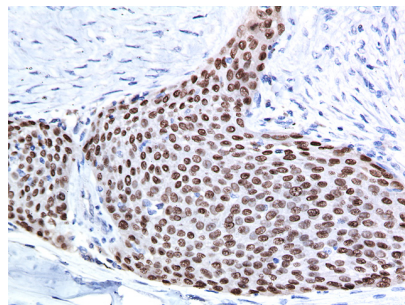
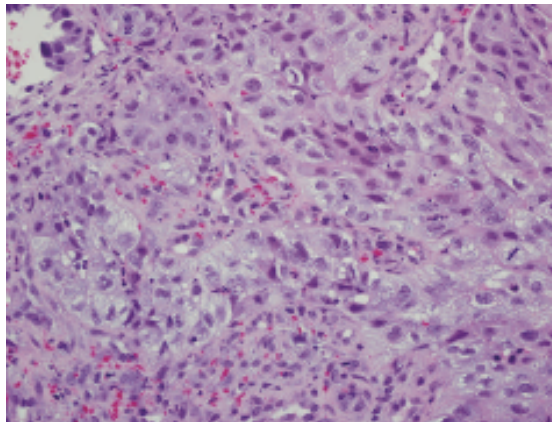
Ki67

SCLC

Insulinoma-associated Protein 1 (INSM1) in Thoracic Tumors is Less Sensitive but More Specific Compared With Synaptophysin, Chromogranin A, and CD56

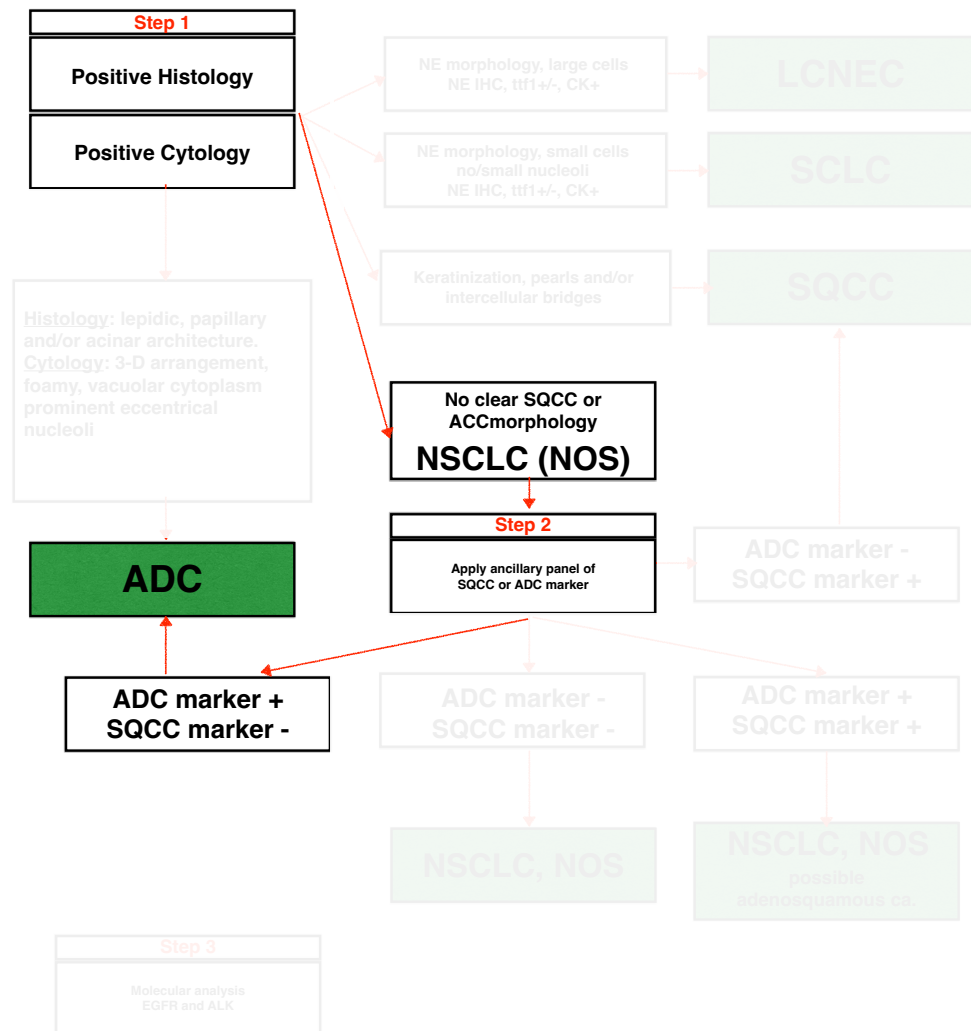
Katharina Kriegsmann, MD, MBA,* Christiane Zgorzelski,† Daniel Kazdal, PhD,‡
Martin Cremer, MD,* Thomas Muley, PhD,§|| Hauke Winter, MD, PhD,‡||
Rémi Longuespée, PhD,† Jörg Kriegsmann, MD, PhD,¶ Arne Warth, MD, PhD,#
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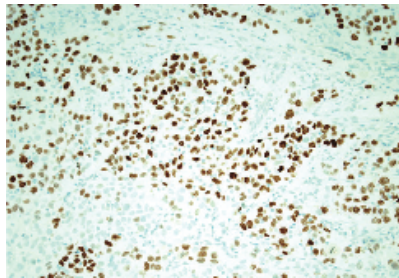
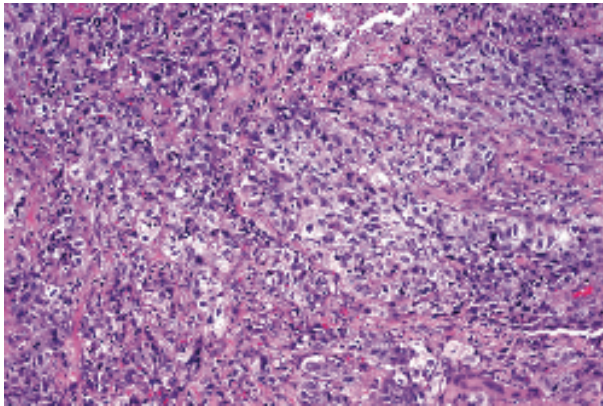




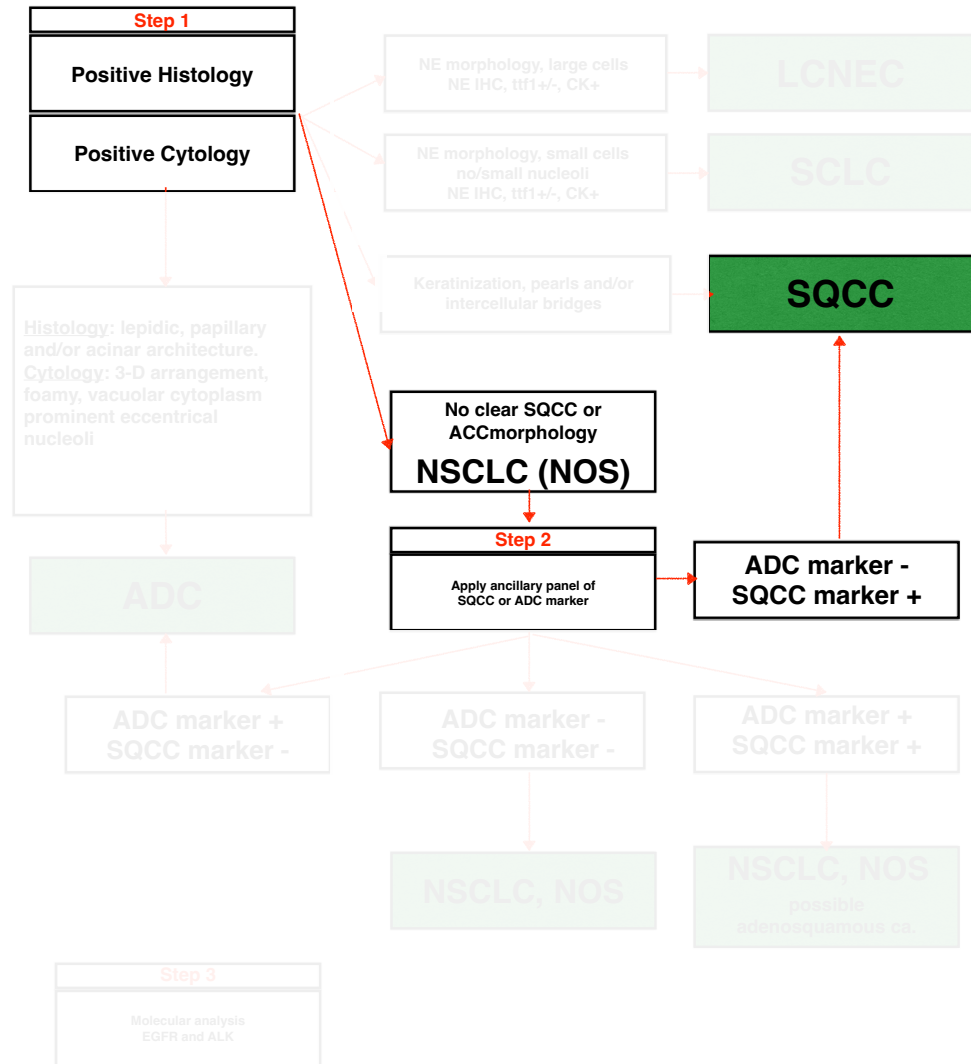
ttf1 +

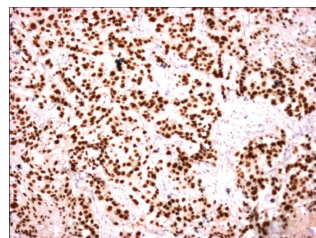
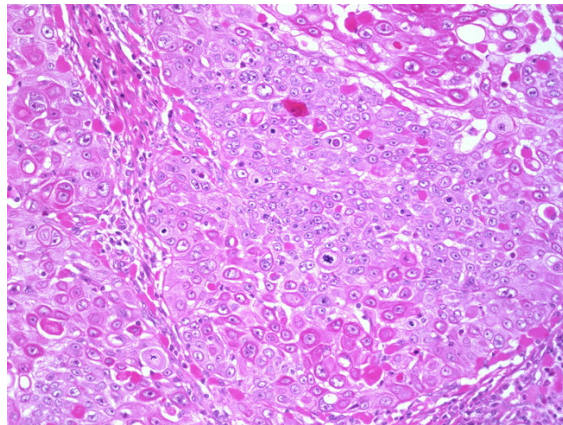
(+Cytokeratin 7)



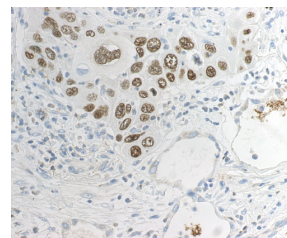


P63+ (+Cytokeratin 5/6)

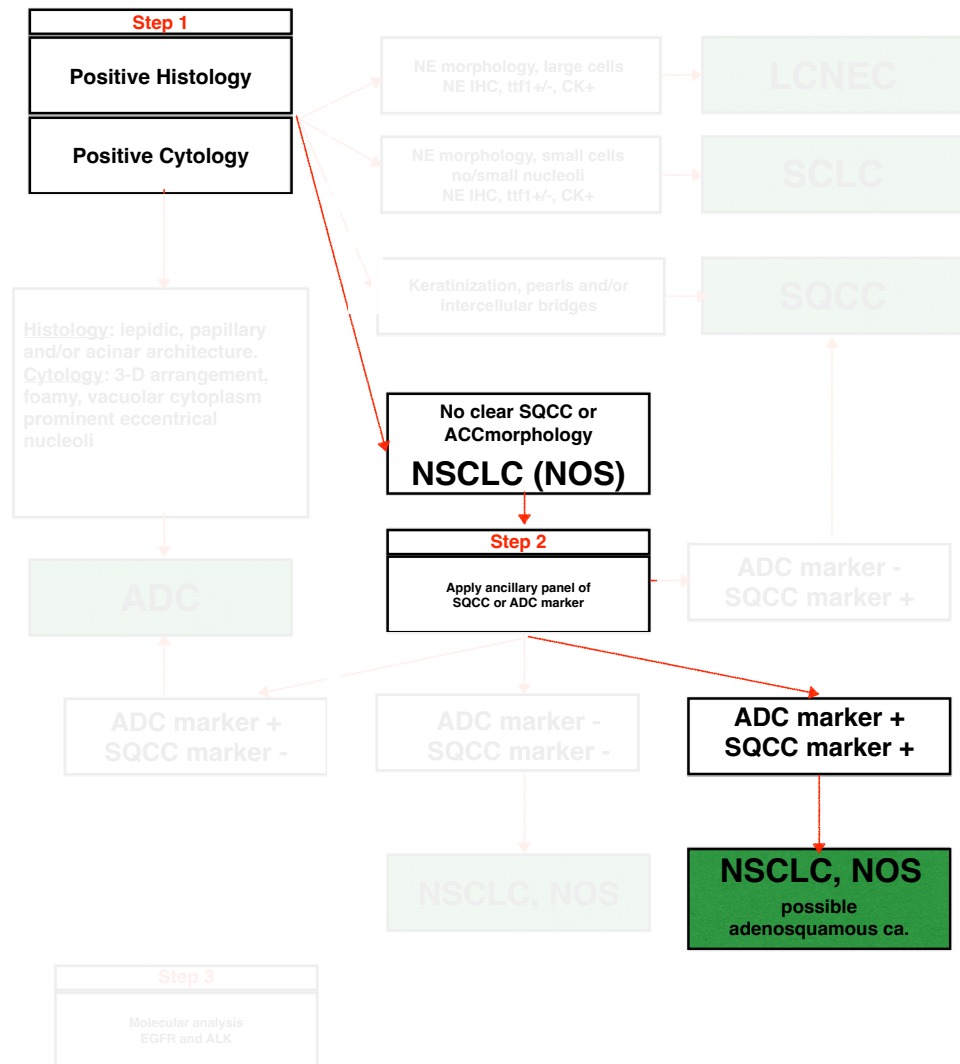


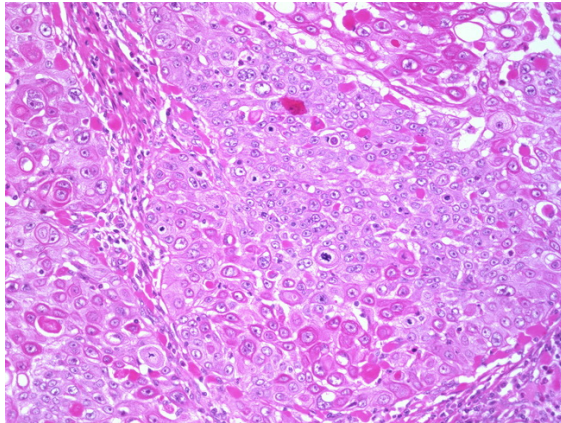


ttf1 +



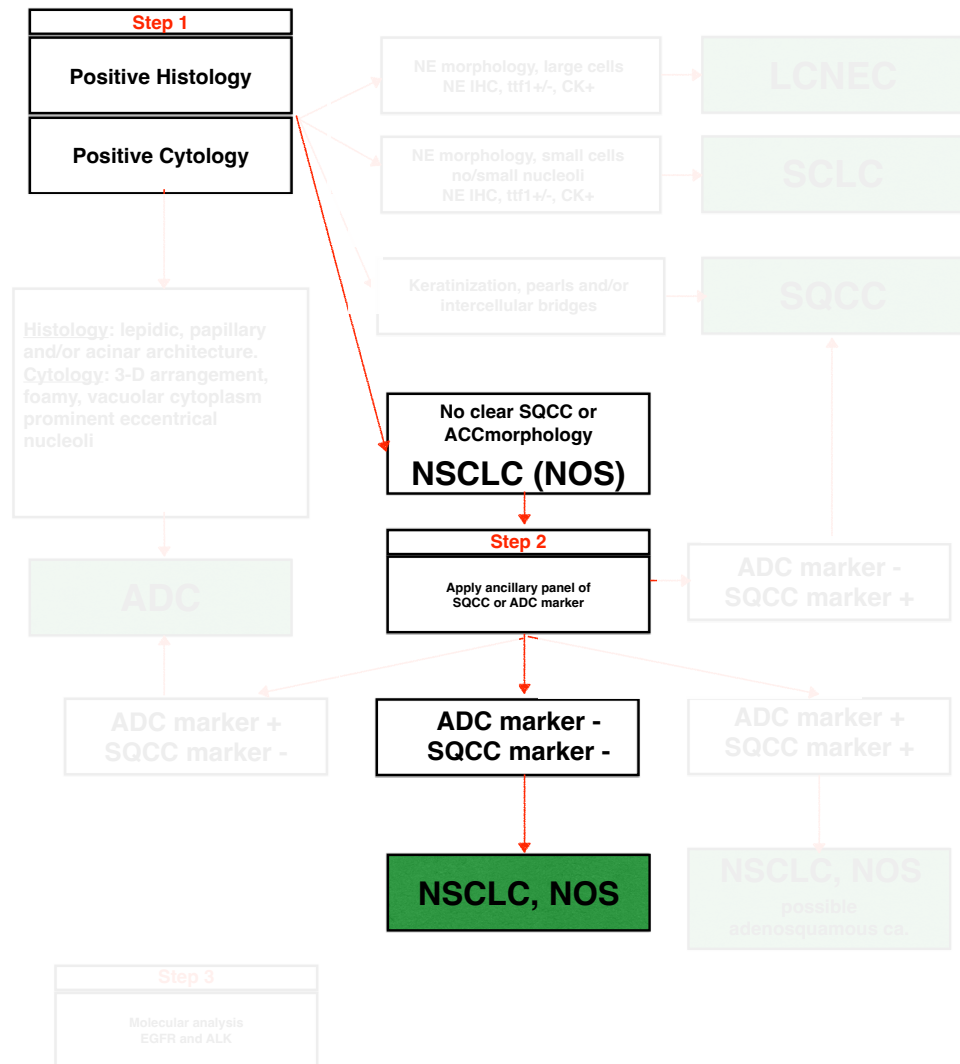
P63+

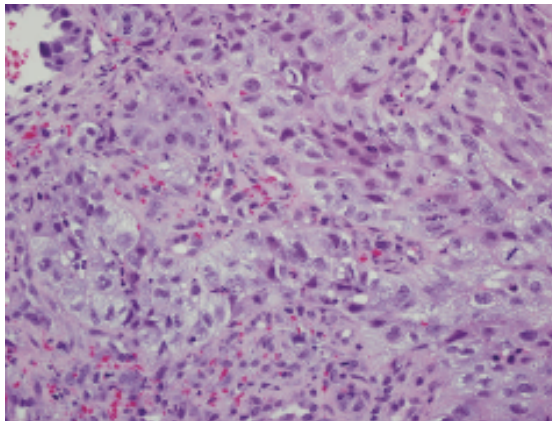




ttf1 -

P63 -





CK7

ttf1

Adenocarcinoma (+neuroendocrine)
Approx. 80%

Napsin

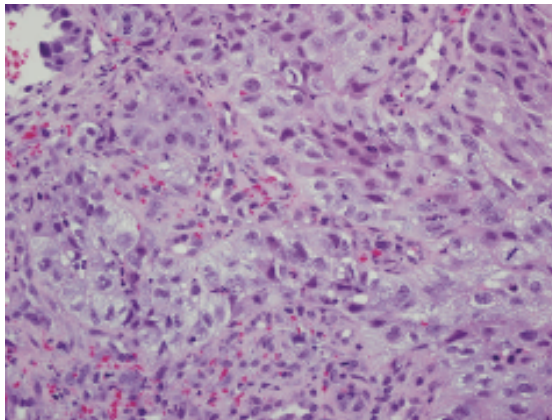
Approx. 60%

CK5/6



P63





CK7

50%

ttf1

Napsin

CK5/6

P63

Squamous
carcinoma



Diagnosis of primary lung tumor



Lung1

CK7

Ttf1

PAX8

CK5(/6)

P63 (P40)

Suggestion

Lung2

PAN CK (AE1/AE3)

CK7

Ttf1

PAX8

CK5(/6)

P63 (P40)

Synaptofycin

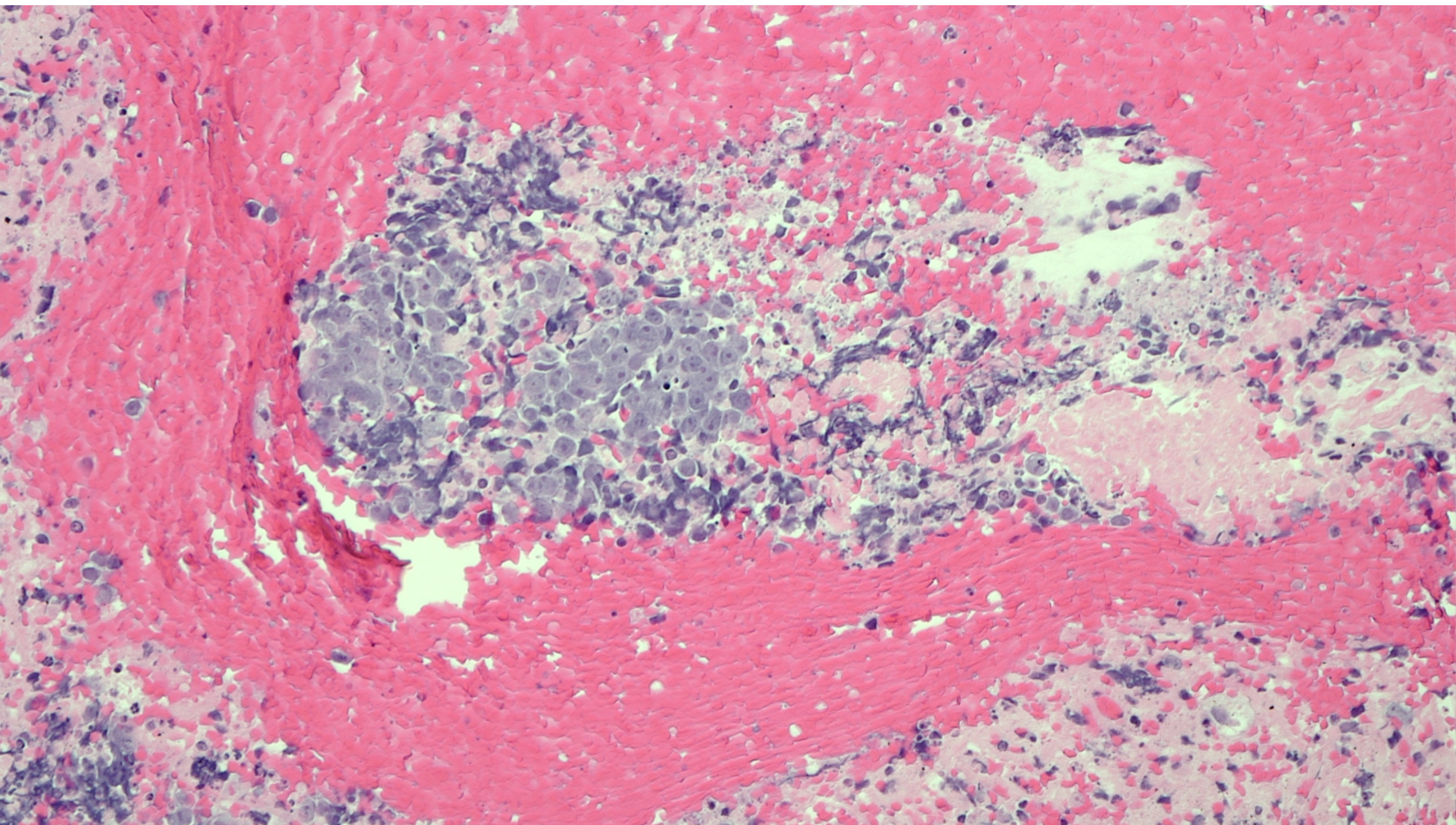
ChromograninA

CD56

Ki67







Lung2

PAN CK (AE1/AE3)

CK7

Ttf1

PAX8

CK5(/6)

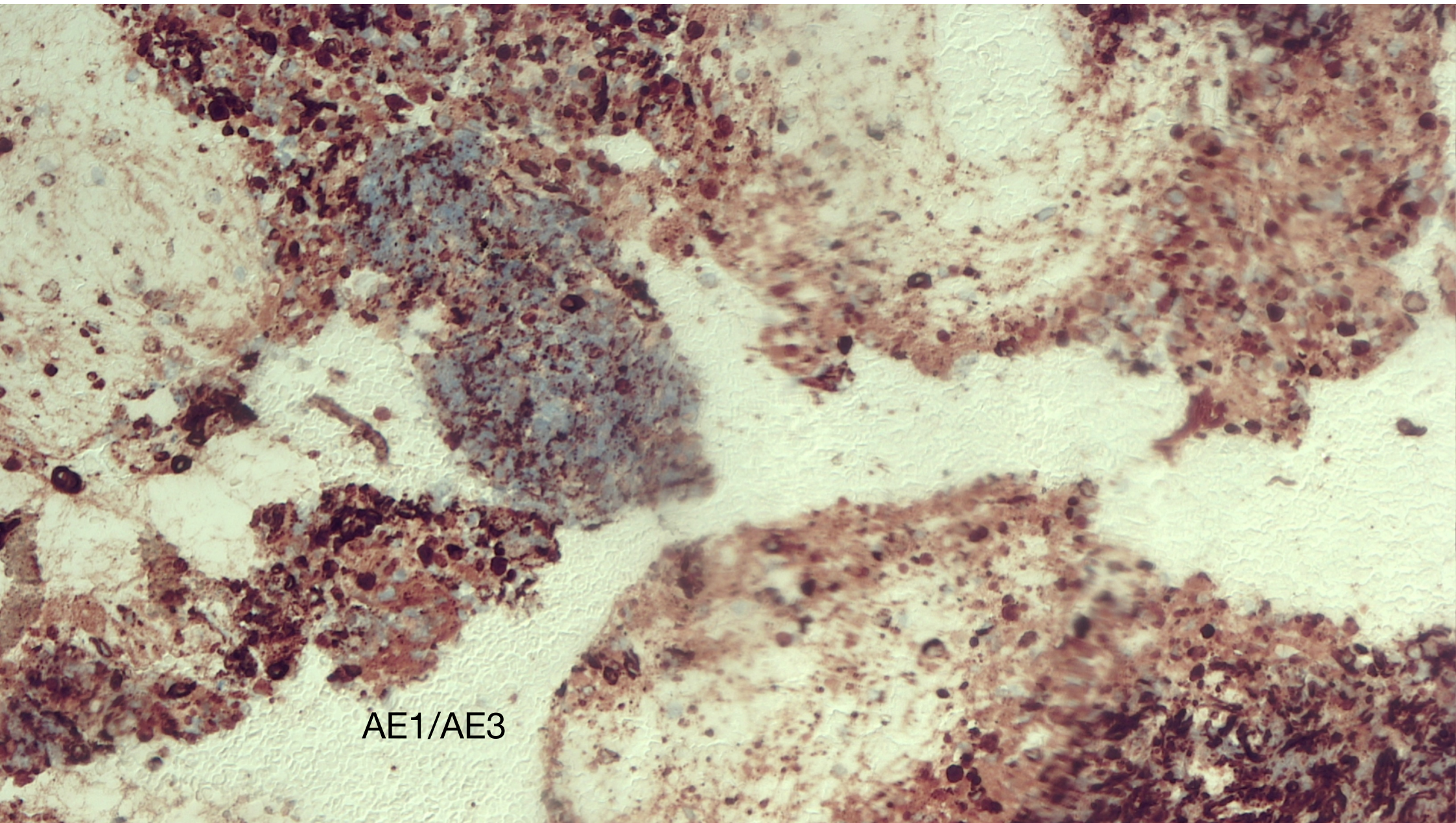
P63 (P40)

Synaptofycin

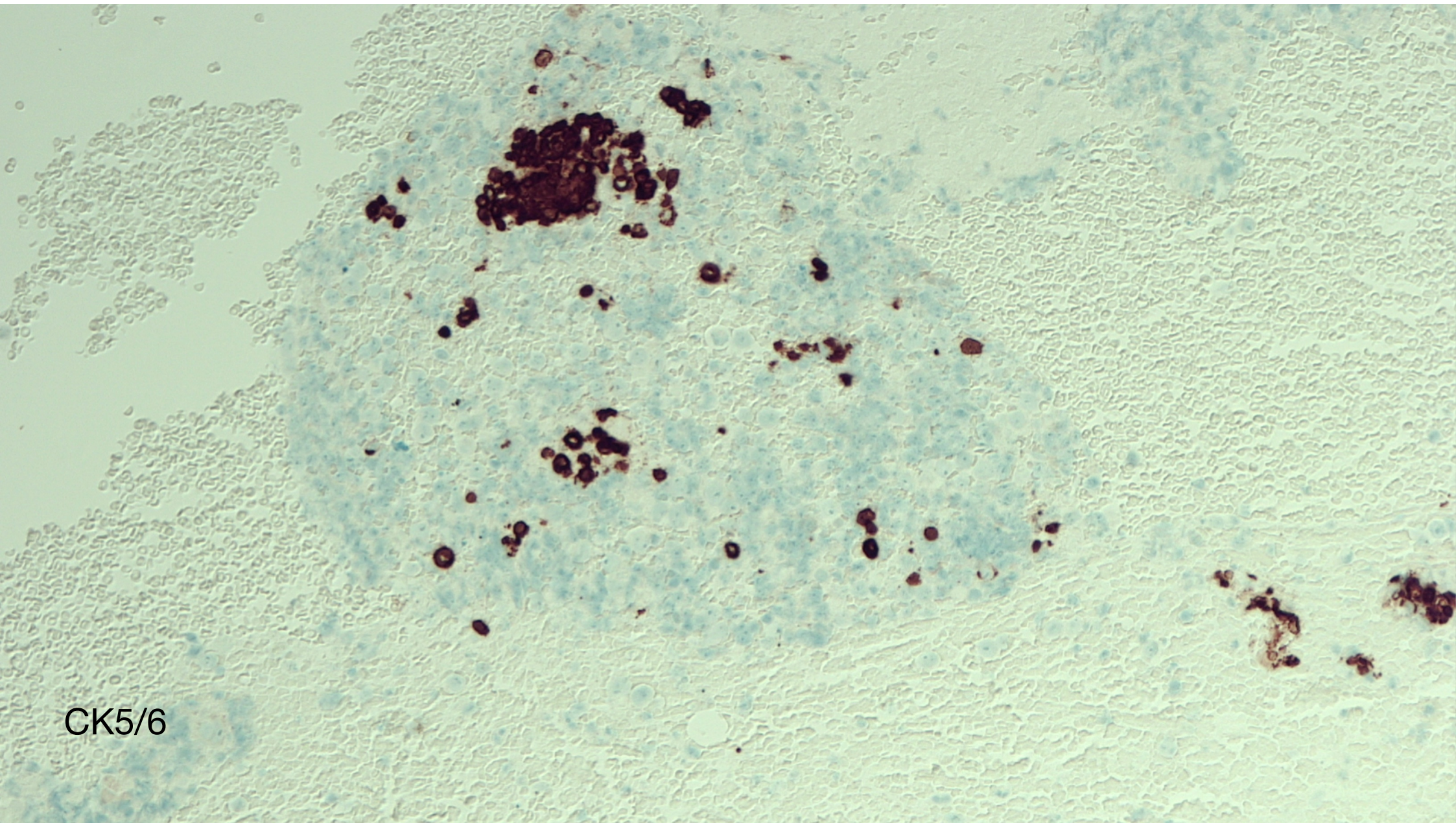
ChromograninA

CD56

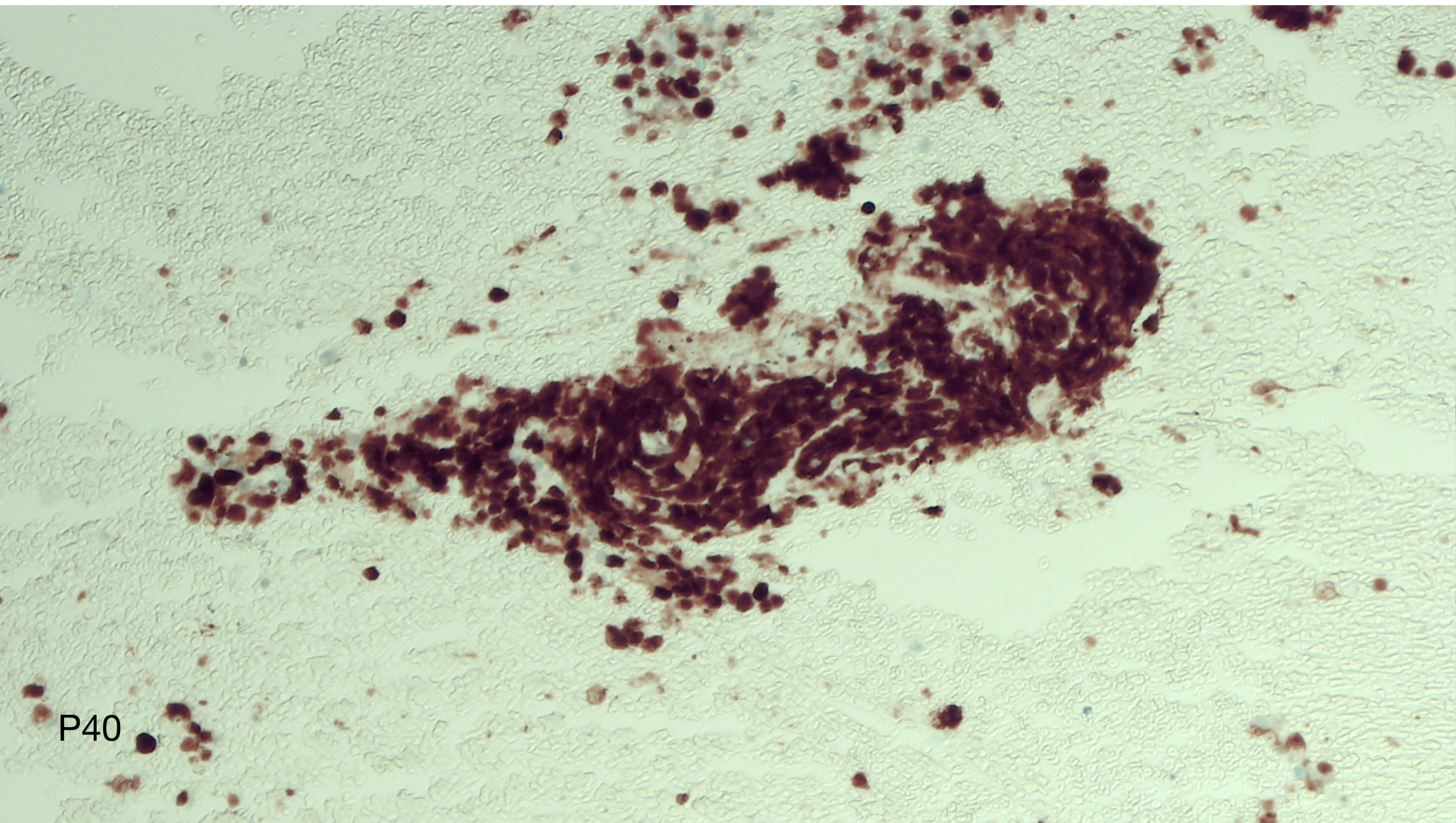
Ki67



AE1/AE3

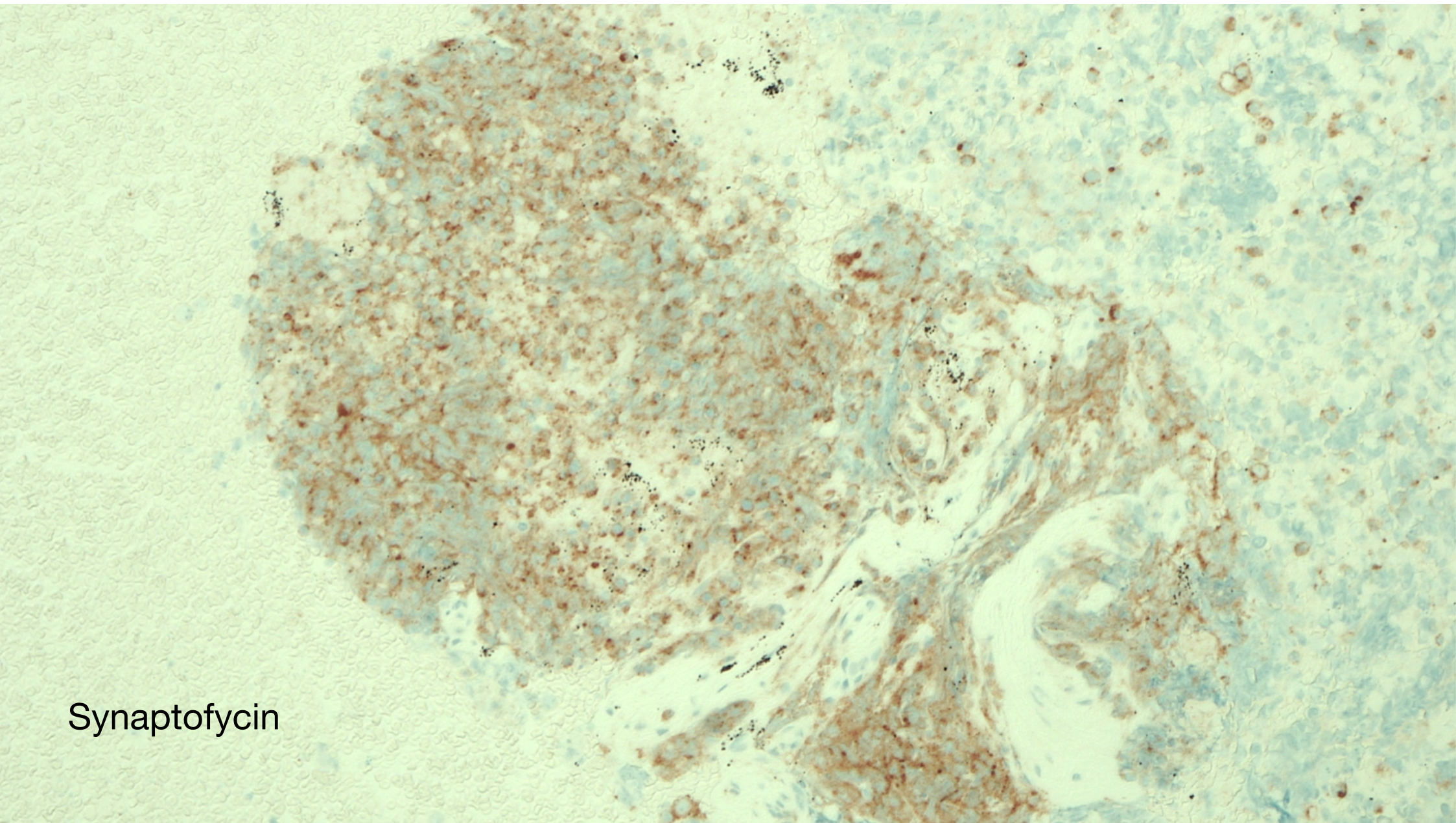


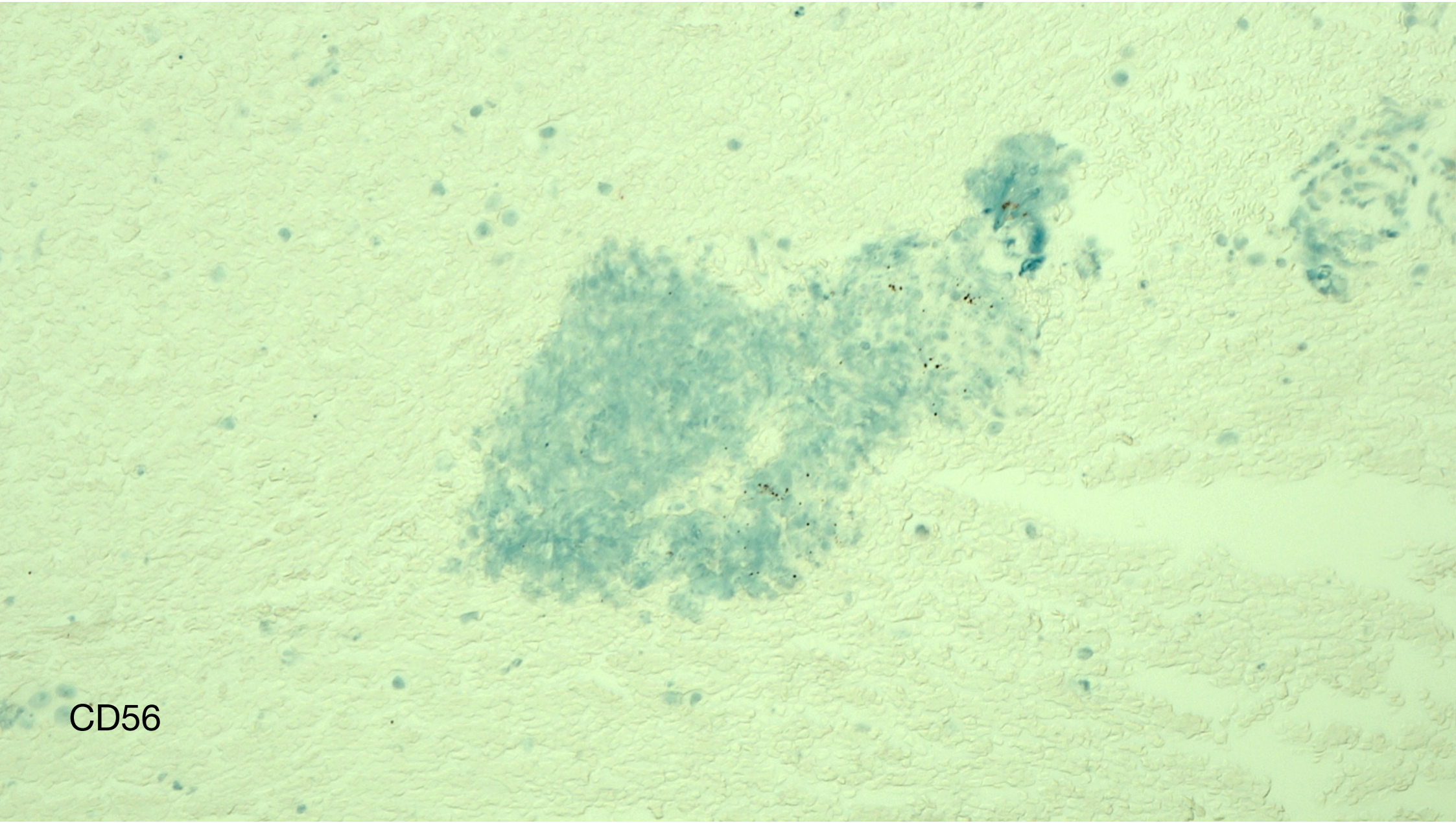
CK5/6



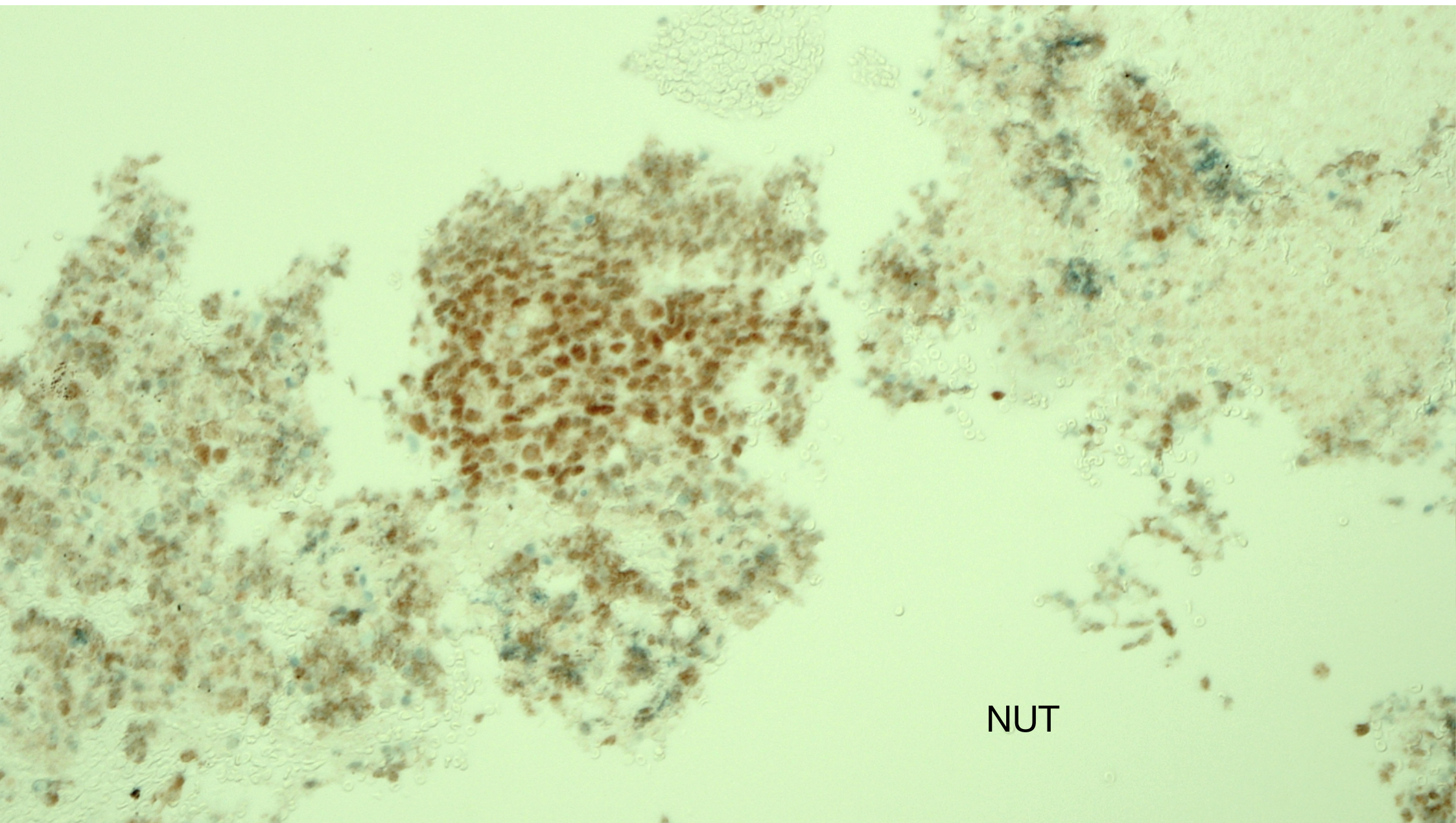
P40

Synaptofycin





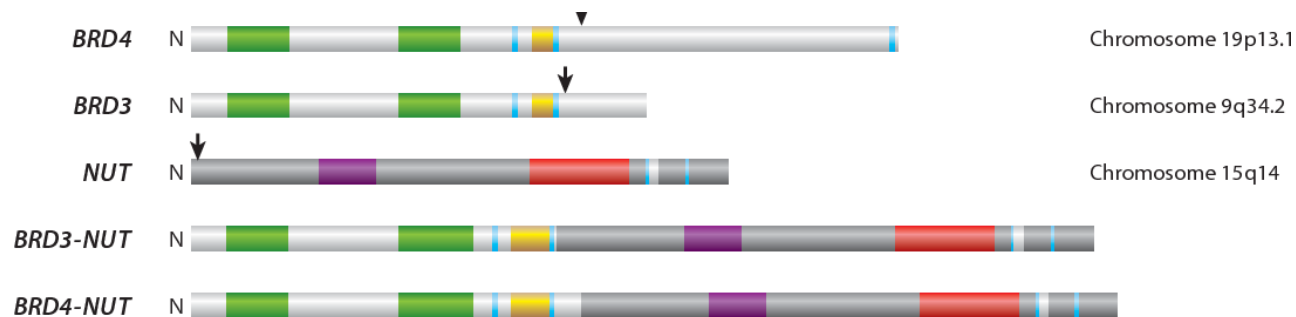
CD56



NUT

INTRODUCTION

NUT carcinoma (NC) is a rare and aggressive subtype of squamous carcinoma characterized by genetic rearrangements involving the *NUTM1* (NUT midline carcinoma family member 1) gene. Patient cases with tumors harboring a t(15;19) translocation were reported from 1991 onwards (1–3). In 2003, the fusion gene resulting from this translocation was identified as *BRD4-NUT*. Many other fusion partners have been identified since, including *BRD3*, *NSD3*, *ZNF532*, *ZNF592*, and *CIC* (4–7), leading to the notion that classification, clinical behavior, and therapeutic options may be best defined by the *NUTM1* fusion partner rather than by tumor morphology or the immunohistochemical profile (8, 9).



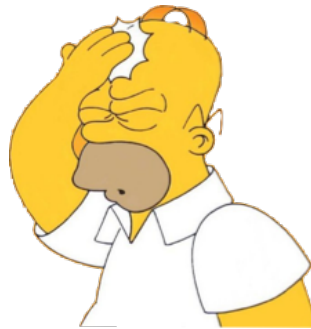
NUT Carcinoma—An Underdiagnosed Malignancy

Ulrich M. Laue^{1,2,3*}, Martina Hinterleitner^{1,2,3}, Marius Horger^{2,4},
Paul V. Ohnesorge^{1,2,3} and Lars Zender^{1,2,3}

¹Department of Hematology and Oncology, University of Würzburg, Würzburg, Germany; ²Department of Hematology and Oncology, University of Würzburg, Würzburg, Germany; ³Department of Hematology and Oncology, University of Würzburg, Würzburg, Germany; ⁴Department of Hematology and Oncology, University of Würzburg, Würzburg, Germany



Problems:



Adenocarcinoma can be P63+

The P63 family

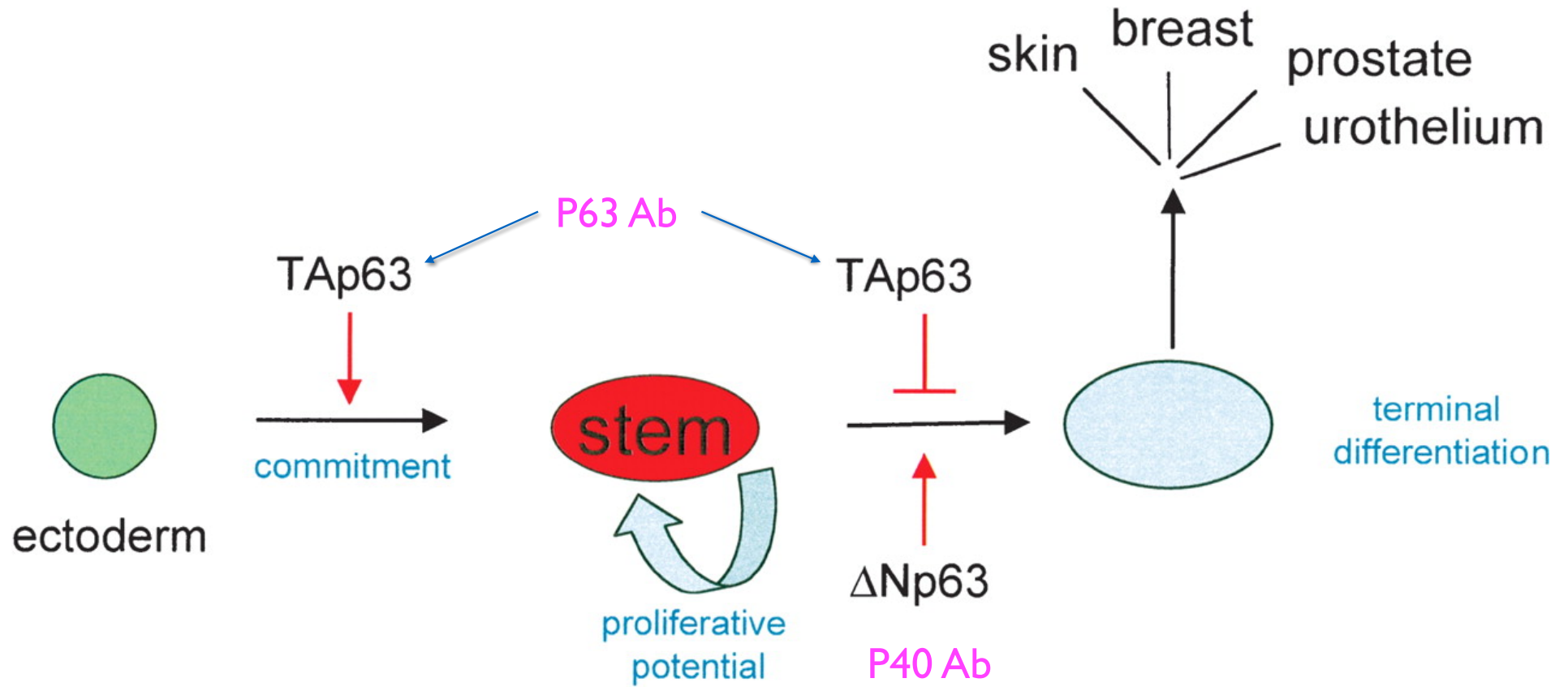
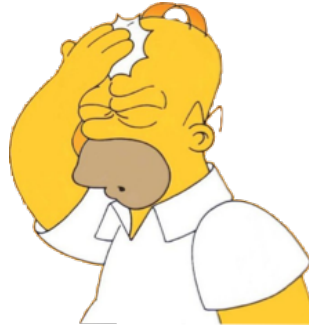




Table 8-1. Studies Comparing p40 Against p63 for Squamous Cell Carcinoma (SQCC)

Study	Total, n	SQCC, n	p40			p63		
			Clone	Sensitivity, %	Specificity, %	Clone	Sensitivity, %	Specificity, %
Bishop et al 2012	470	81	5-17	100	98	4A4	100	60
Nonaka 2012	200	50	p40	100	100	4A4	100	82
Pelosi et al 2013	141	27	Poly	100	97	4A4	100	78
Ao et al 2014	154	77	Poly	81	90	4A4	94	80
Koh et al 2014	184	59	Poly	93	98	7JUL	80	98
Tatsumori et al 2014	580	158	5-17	97	97	4A4	97	73
Kadota et al 2015	469	449	5-17	100	85	4A4	100	60
Tran et al 2016	557	167	BC28	94	96	4A4	95	87
Micke et al 2016	656	192	BC28	97	98	4A4	97	74
Affandi et al 2018	70	35	BC28	77	100	DAK-p63	86	63
Kriegsmann et al 2019	1244	569	BC28	94	97	4A4	94	84

Problems:



Differential diagnosis between primary and metastatic carcinoma

Other (adeno) carcinomas are positive for ttf1

Table 7-1. Results of TTF1 Expression in Tumors from Non-Lung Primary Sites Including Female Genital Tract, Breast, Colon, and Stomach in Some Published Studies^a

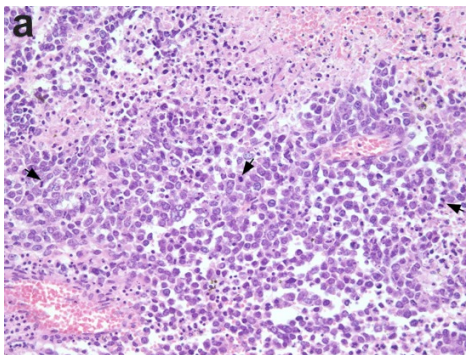
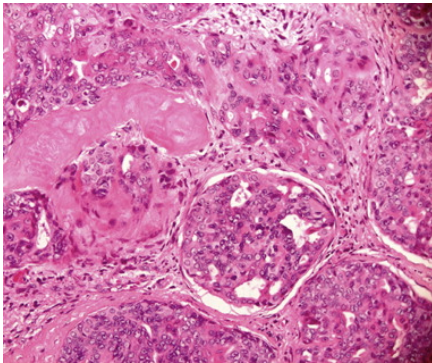
Primary carcinoma	8G7G3/1		SPT24	
	n	Positive, n (%)	n	Positive, n (%)
Ovarian carcinoma	615	22 (3.6%)	161	16 (9.9%)
Endometrial adenocarcinoma	215	17 (7.9%)	68	19 (27.9%)
Uterine cervical adenocarcinoma	92	3 (3.3%)	39	6 (15.4%)
Uterine cervical squamous carcinoma	7	0 (0%)		
Breast carcinoma	297	4 (1.5%)	580	13 (2.4%)
Colon adenocarcinoma	594	11 (1.8%)	258	15 (5.8%)
Gastric adenocarcinoma	170	3 (1.8%)	110	1 (0.9%)

^a Data for clones 8G7G3/1 and SPT24 are modified based on data from Ordonez 2012b.



Use Ab panels

Diagnosis of metastasis to the lung



AE1/AE3 

CK7

ttf1

CK20 

cdx2 

SATB2 

NKX3.1

CK5/6

P63

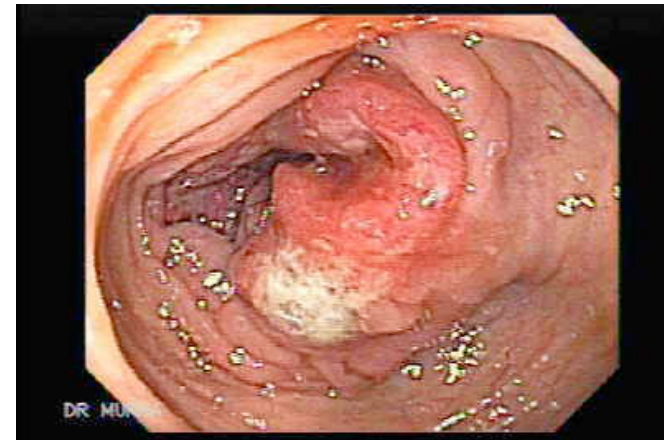
CD10

PAX8

WT1

GATA3

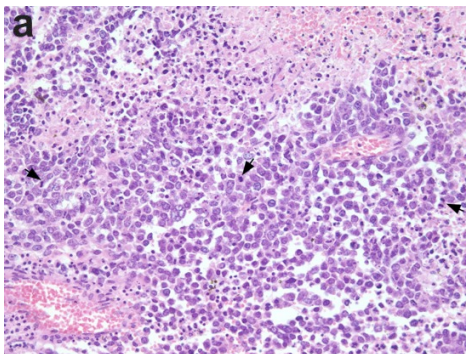
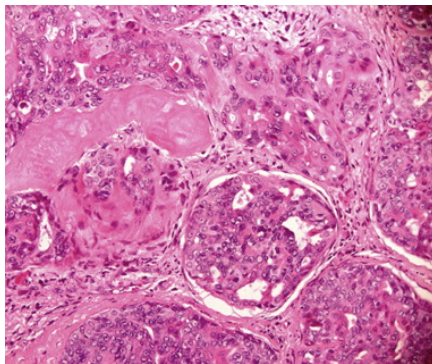
Colon





Use Ab panels

Diagnosis of metastasis to the lung



AE1/AE3 →

CK7

ttf1

CK20 →

cdx2 →

SATB2 →

NKX3.1

CK5/6

P63

CD10

PAX8

WT1

GATA3

Epithelial tumors

Adenocarcinoma

Lepidic adenocarcinoma^e

Acinar adenocarcinoma

Papillary adenocarcinoma

Micropapillary adenocarcinoma^e

Solid adenocarcinoma

Invasive mucinous adenocarcinoma^e

Mixed invasive mucinous and
nonmucinous adenocarcinoma

Colloid adenocarcinoma

Fetal adenocarcinoma

Enteric adenocarcinoma^e →

8140/3

8250/3^d

8551/3^d

8260/3

8265/3

8230/3

8253/3^d

8254/3^d

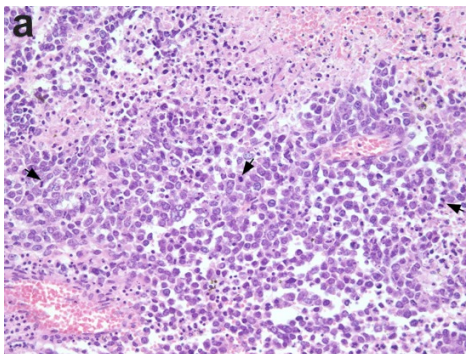
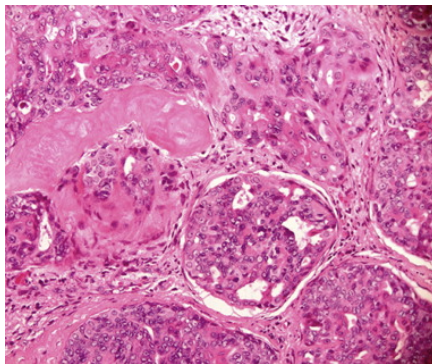
8480/3

8333/3

8144/3



Diagnosis of metastasis to the lung



AE1/AE3 ←

CK7 ←

ttf1

CK20

cdx2

SATB2

NKX3.1

CK5/6

P63

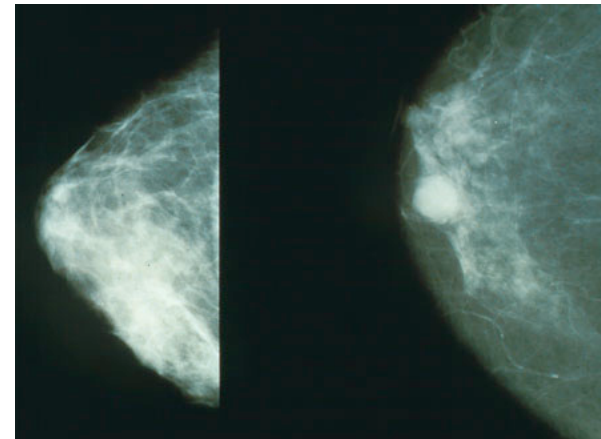
CD10

PAX8

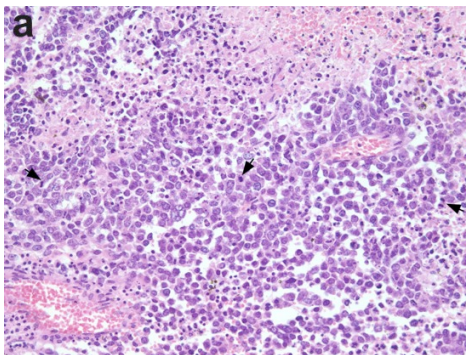
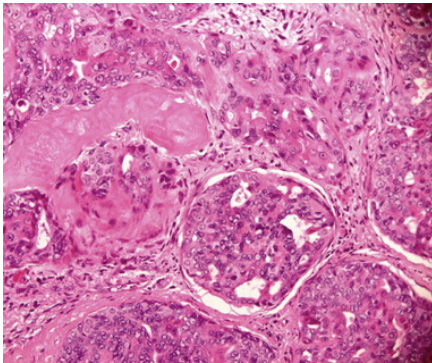
WT1

GATA3 ←

Mamma



Diagnosis of metastasis to the lung



AE1/AE3 →

CK7 →

ttf1

CK20 →

cdx2 →

SATB2 →

NKX3.1

CK5/6

P63

CD10

PAX8

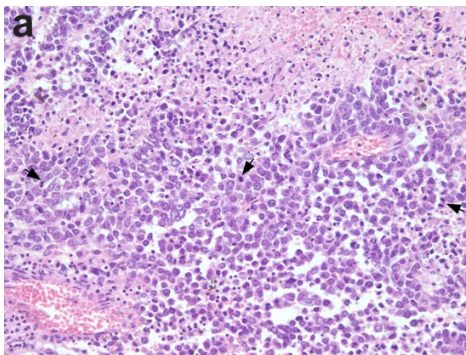
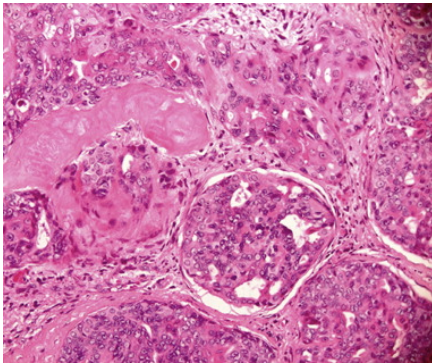
WT1

GATA3

Upper GI



Diagnosis of metastasis to the lung



AE1/AE3 ←

CK7 ←

ttf1

CK20 ←

cdx2

SATB2

NKX3.1

CK5/6 ←

P63 ←

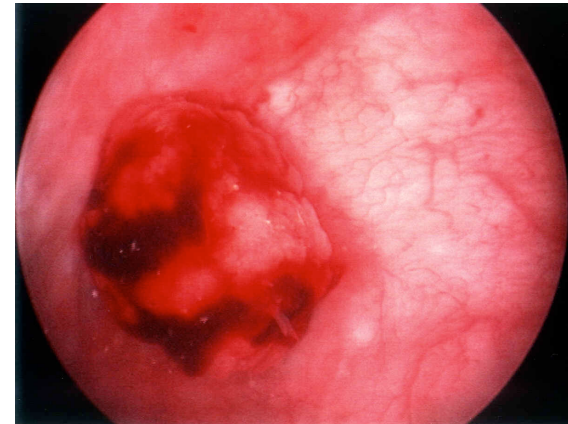
CD10

PAX8

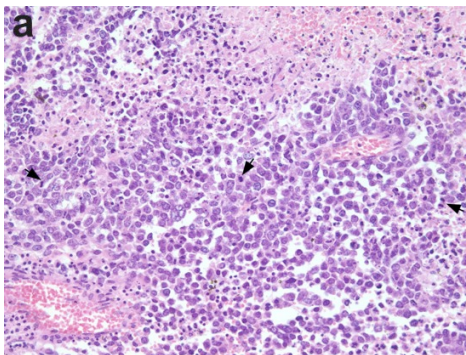
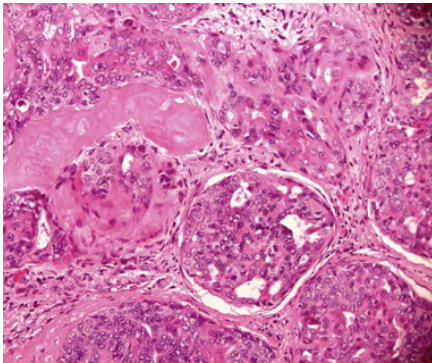
WT1

GATA3 ←

Urothelial carcinoma



Diagnosis of metastasis to the lung



AE1/AE3 ←

CK7

ttf1

CK20

cdx2

SATB2

NKX3.1

CK5/6

P63

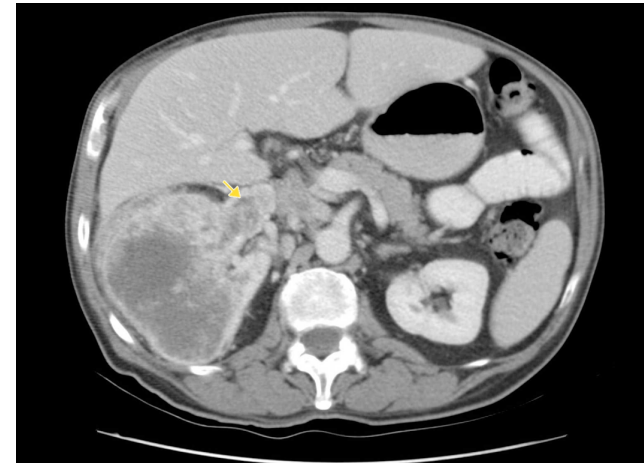
CD10 ←

PAX8 ←

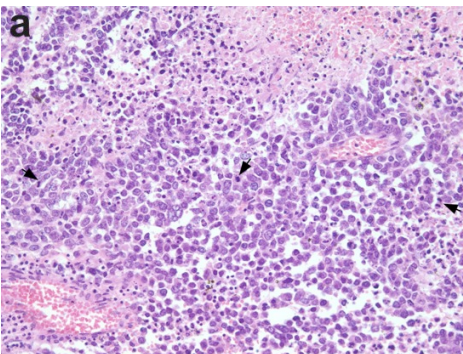
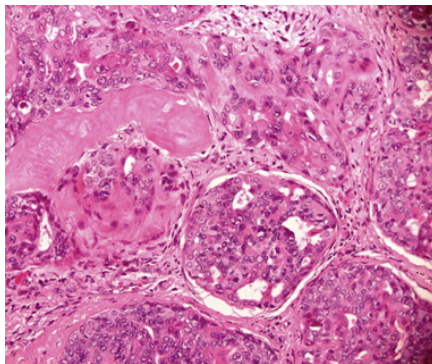
WT1

GATA3

Renal cell carcinoma



Diagnosis of metastasis to the lung



AE1/AE3 →

CK7

ttf1

CK20

cdx2

SATB2

NKX3.1 →

CK5/6

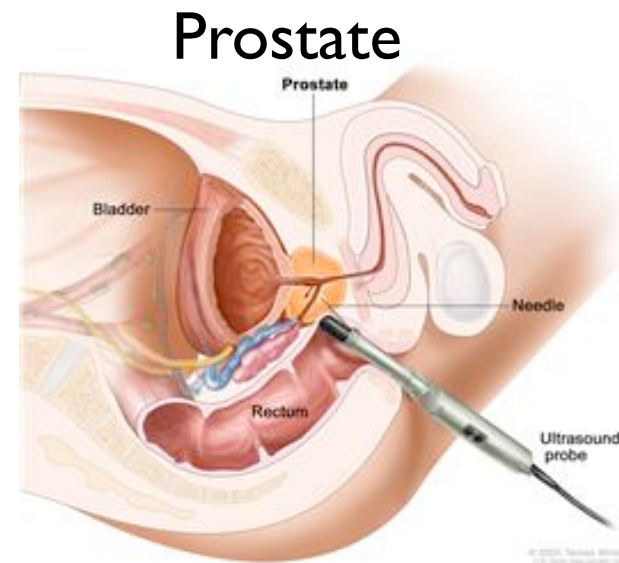
P63

CD10

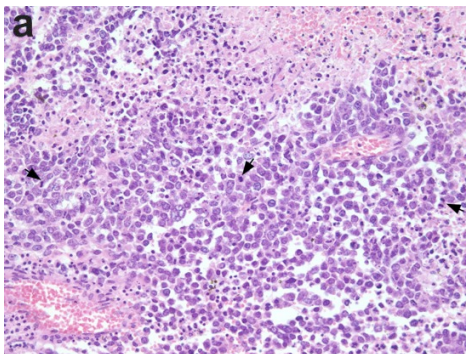
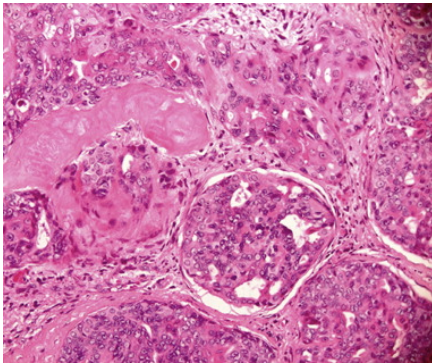
PAX8

WT1

GATA3



Diagnosis of metastasis to the lung



AE1/AE3 →

CK7 →

ttf1

CK20

cdx2

SATB2

NKX3.1

CK5/6

P63

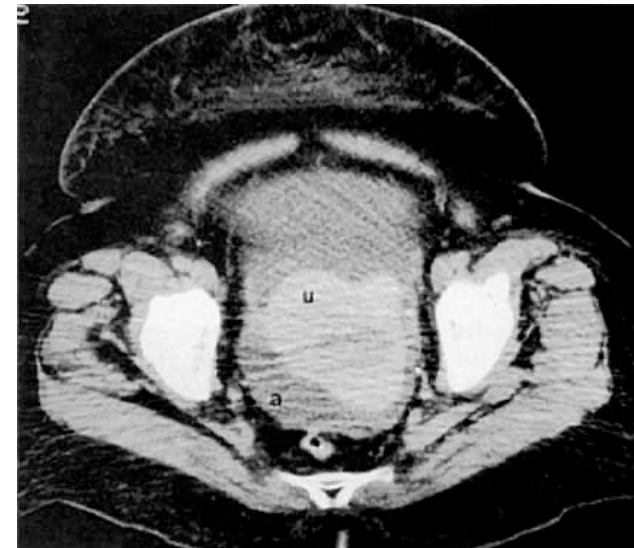
CD10

PAX8 →

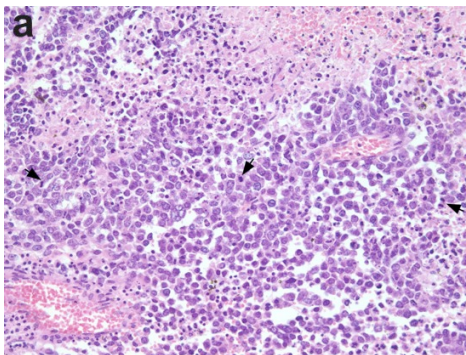
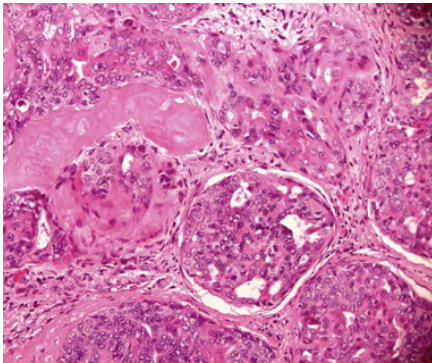
WT1 →

GATA3

Endometrial cancer



Diagnosis of metastasis to the lung



AE1/AE3 ←

CK7 ←

ttf1

CK20

cdx2

SATB2

NKX3.1

CK5/6

P63

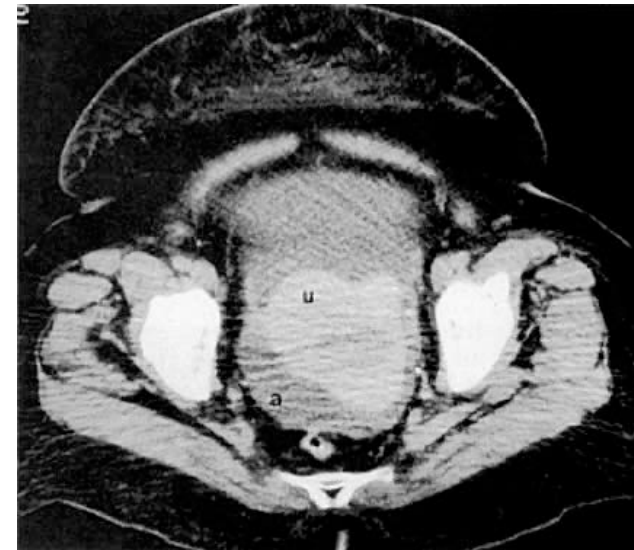
CD10

PAX8 ←

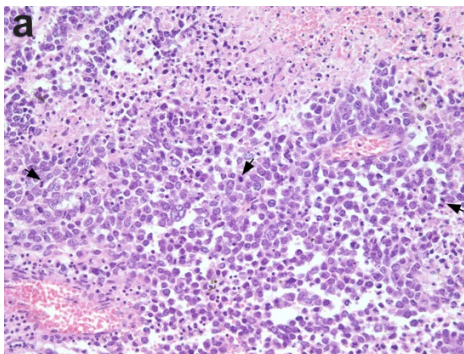
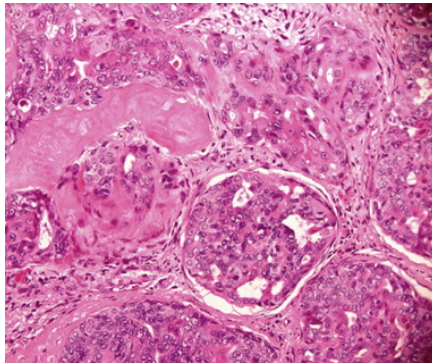
WT1 ←

GATA3

Ovarian cancer



Diagnosis of metastasis to the lung



AE1/AE3 →

CK7 →

ttf1 →

CK20

cdx2

SATB2

NKX3.1

CK5/6

P63

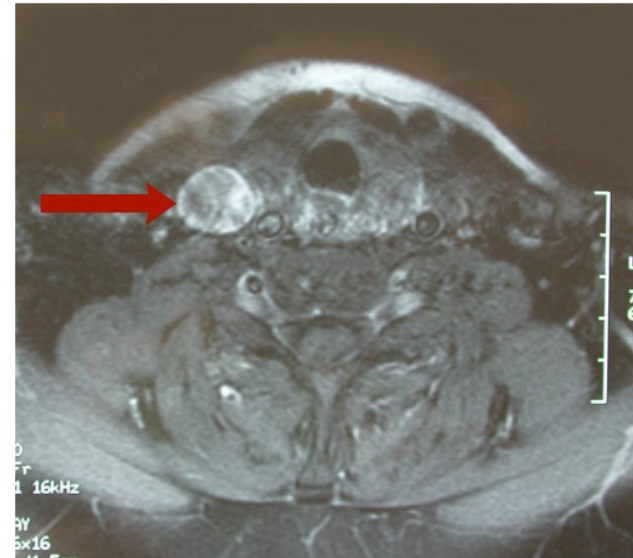
CD10

PAX8 →

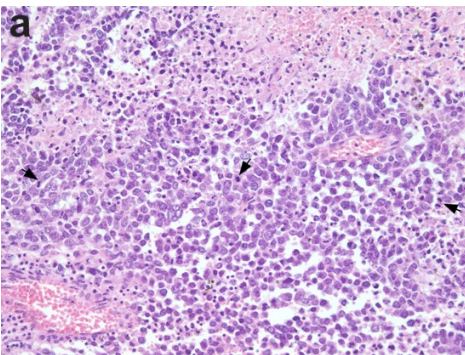
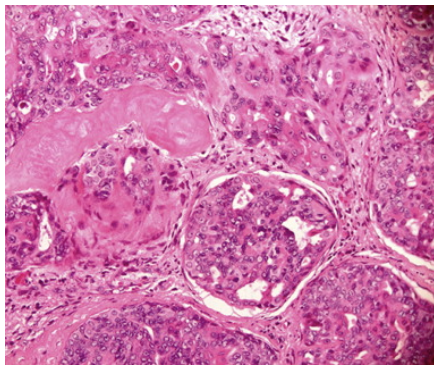
WT1

GATA3

Thyroid cancer



Diagnosis of metastasis to the lung



Calretinin
WT1
D2-40
CK7
Vim
CK5/6
(EpCam)



Mesothelioma





Diagnosis of metastasis to the lung



Adeno - male

CK7
CK20
CDX2
Ttf1
PAX8
NKX3.1

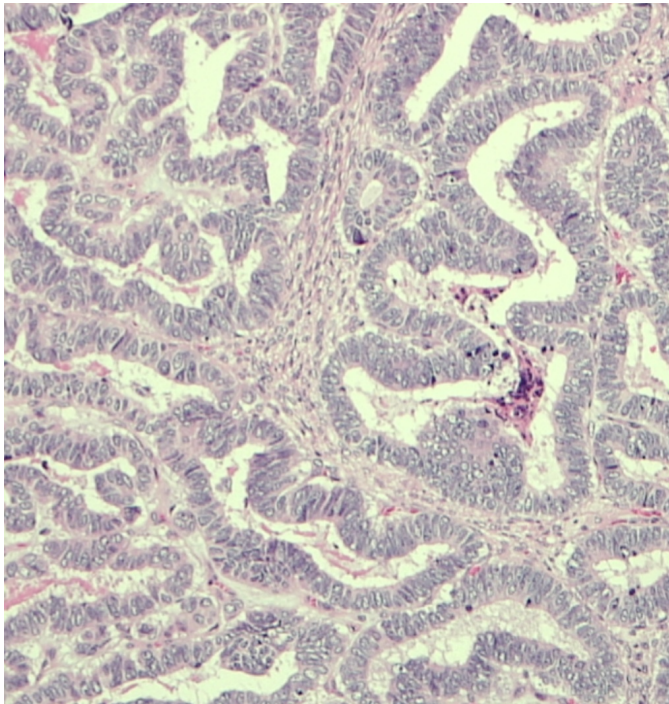
Suggestion

Adeno - female

CK7
CK20
CDX2
Ttf1
PAX8
GATA3
WT1
ER



Clinical info: C. Pulm obs. Pro.
50 years old female



Coarse needle from lung



Adenocarcinoma



Lung I

CK7

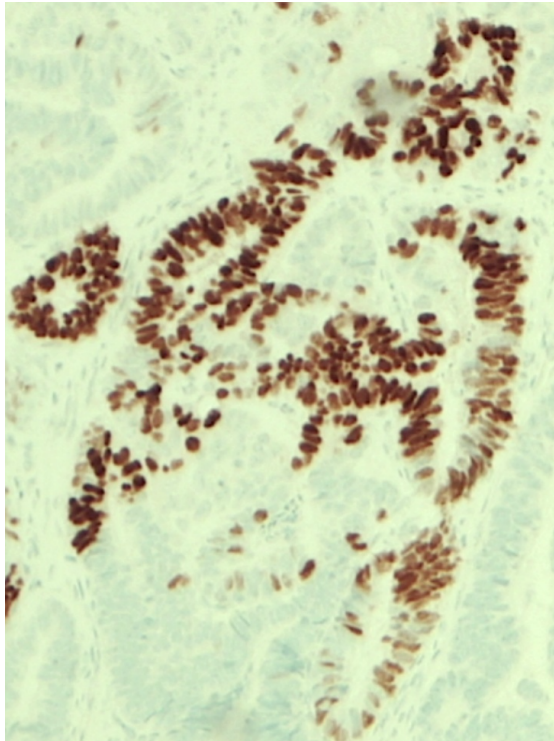
Ttf1

PAX8

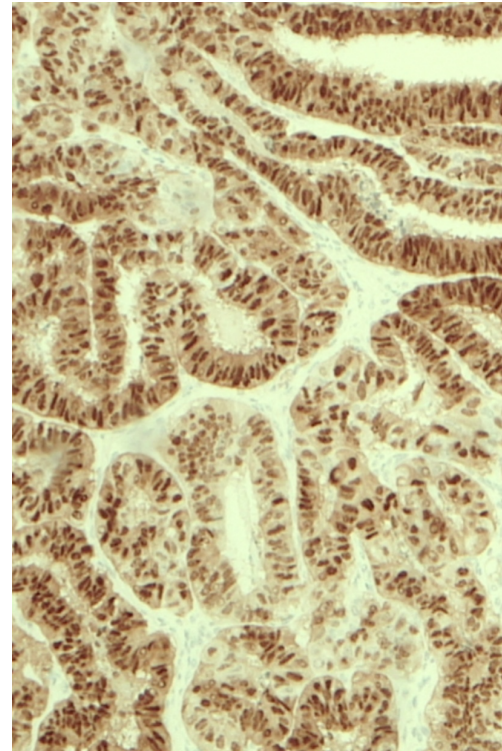
CK5(/6)

P63 (P40)

Clinical info: C. Pulm obs. Pro.
50 years old female



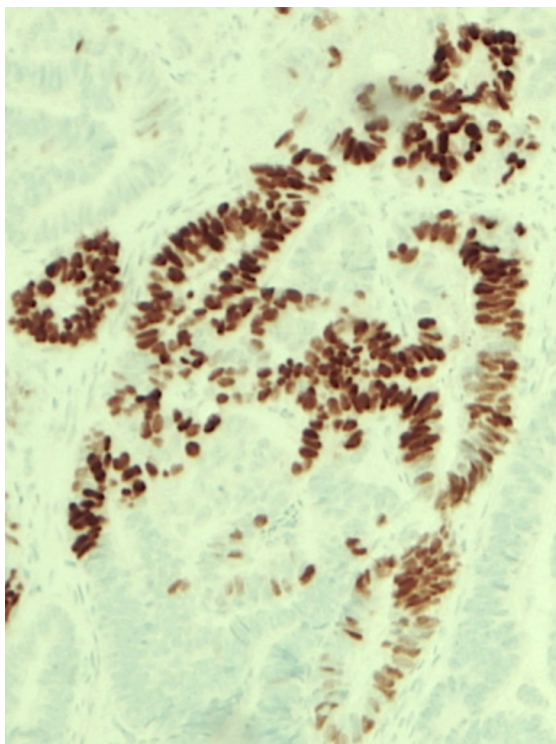
ttf1



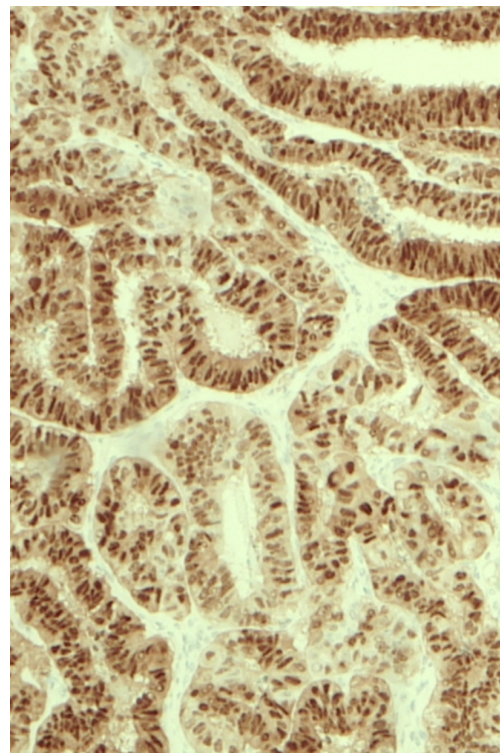
Pax 8

CK7+

Clinical info: C. Pulm obs. Pro.
50 years old female



ttf1



Pax 8

Thyroid Carcinoma

CK7+

Coarse needle from lung



Adenocarcinoma



Lung I

CK7

TtfI

PAX8

CK5(/6)

P63 (P40)



Adeno - female

CK7

CK20

CDX2

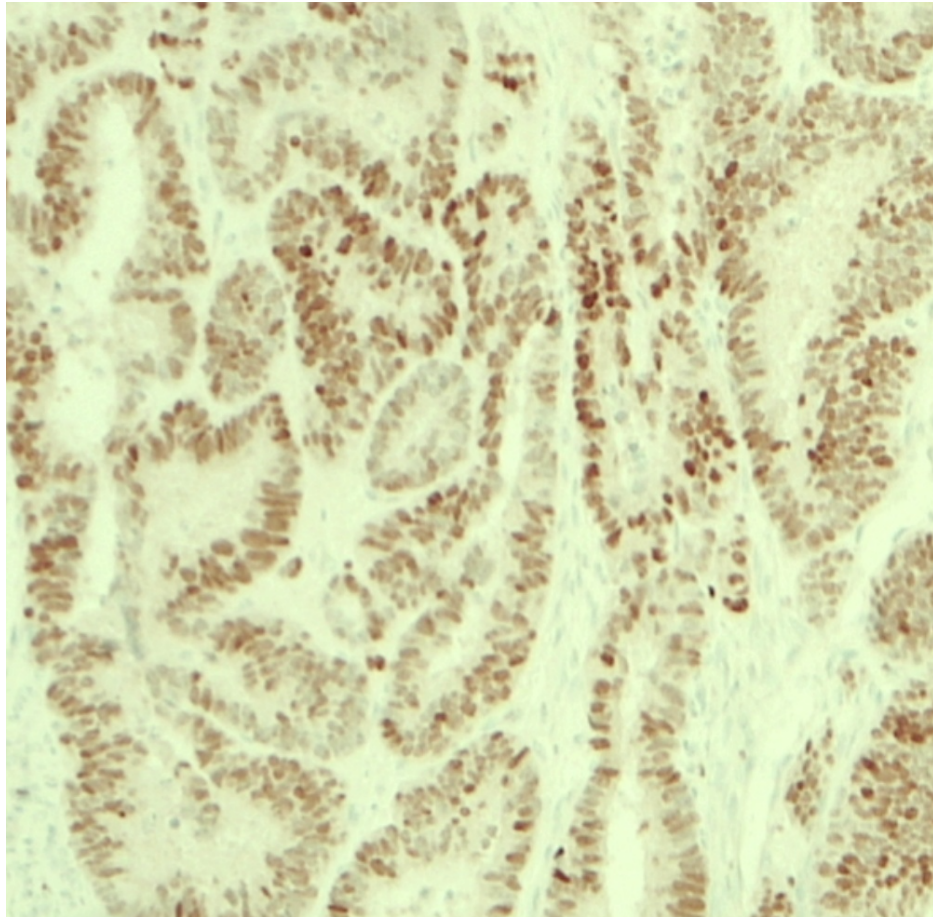
TtfI

PAX8

GATA3

WTI

ER



GATA3

Adeno - female

CK7+

CK20-

CDX2-

Ttf1+

PAX8+

GATA3+

WT1-

ER-



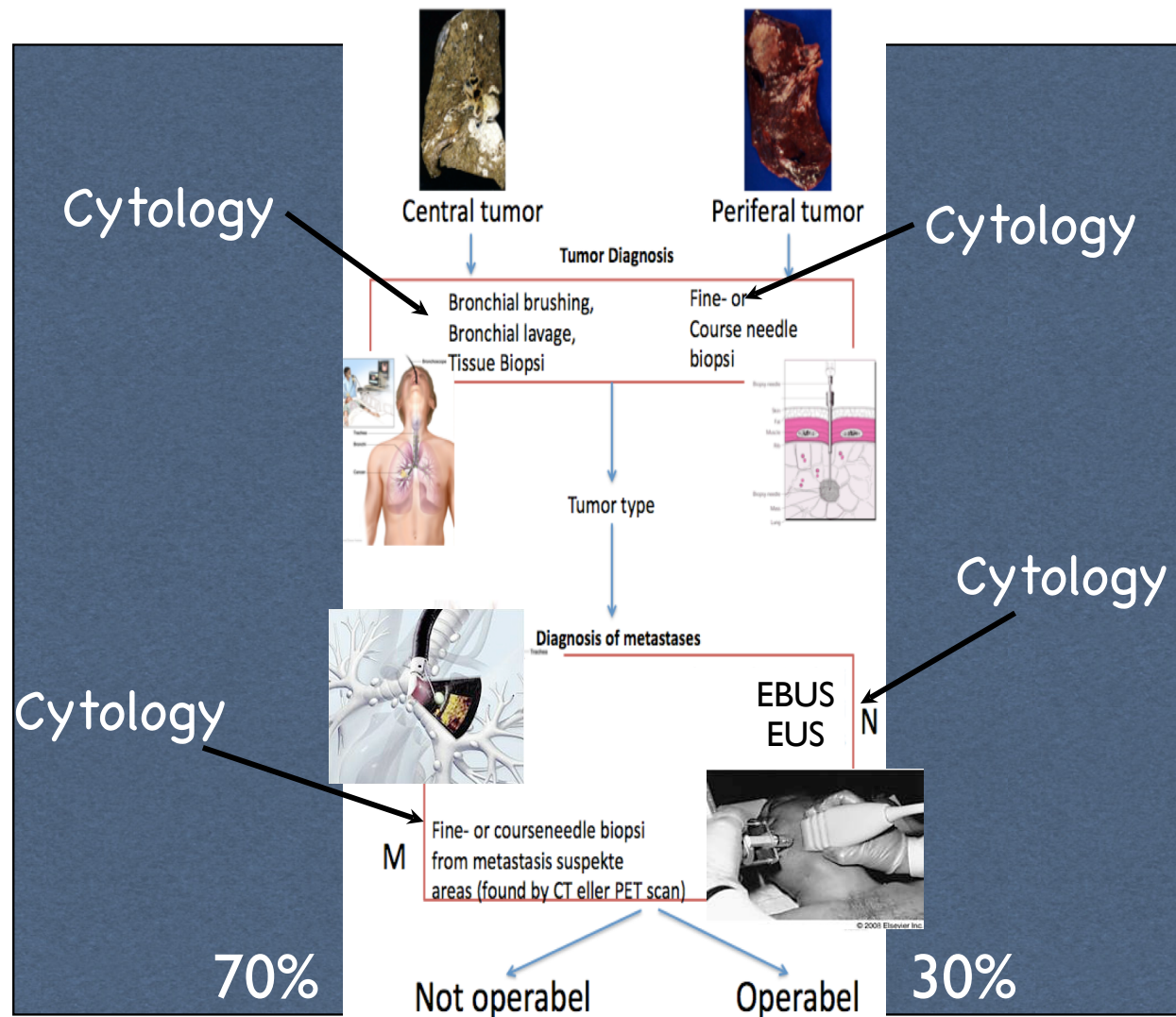
Review

Mesonephric-Like Adenocarcinoma of the Endometrium: Diagnostic Advances to Spot This Wolf in Sheep's Clothing. A Review of the Literature

Ellen Deolet ¹, Jo Van Dorpe ^{1,2} and Koen Van de Vijver ^{1,2,*} 

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





Patoanatomical specimen

Cytology



Histology



Fixation

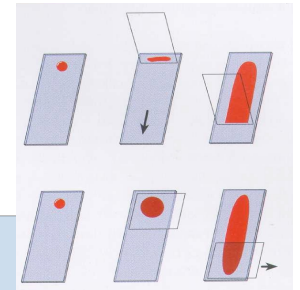
Dehydration

Parafinembedding

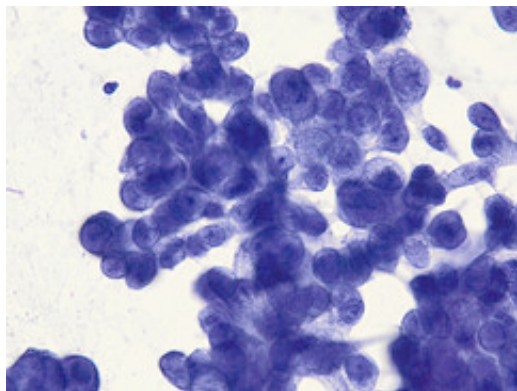
Microtomy

Præparation

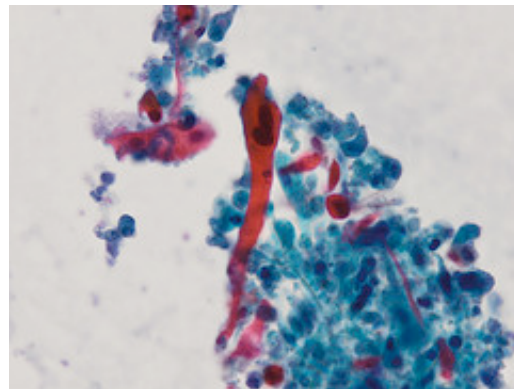
Smear preparation



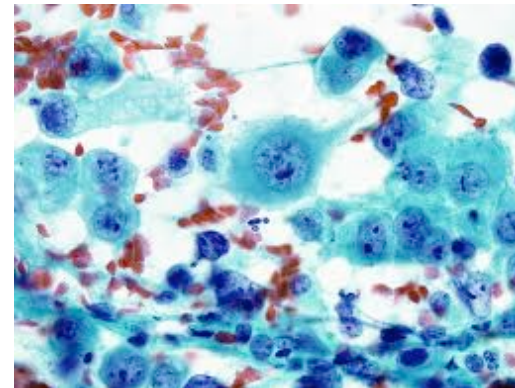
Visualization (Staining)



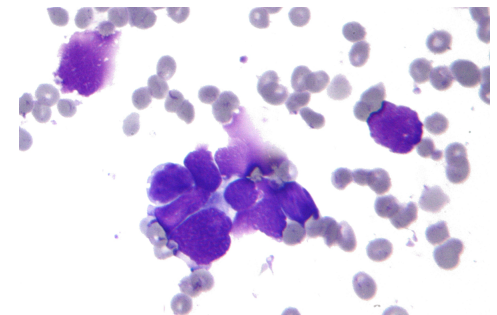
Adenocarcinoma



Squamous carcinoma



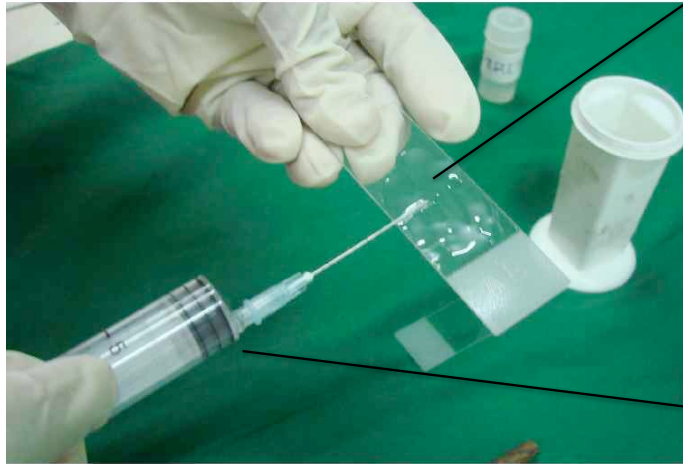
Large cell
neuroendocrine carc.



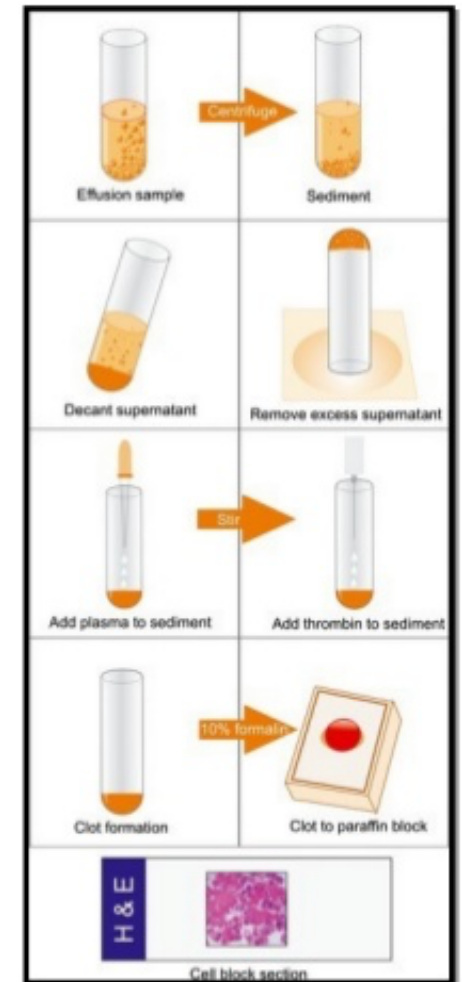
Small cell carcinoma

Non Small Cell Lung Carcinoma (NSCLC)

Immuncytology

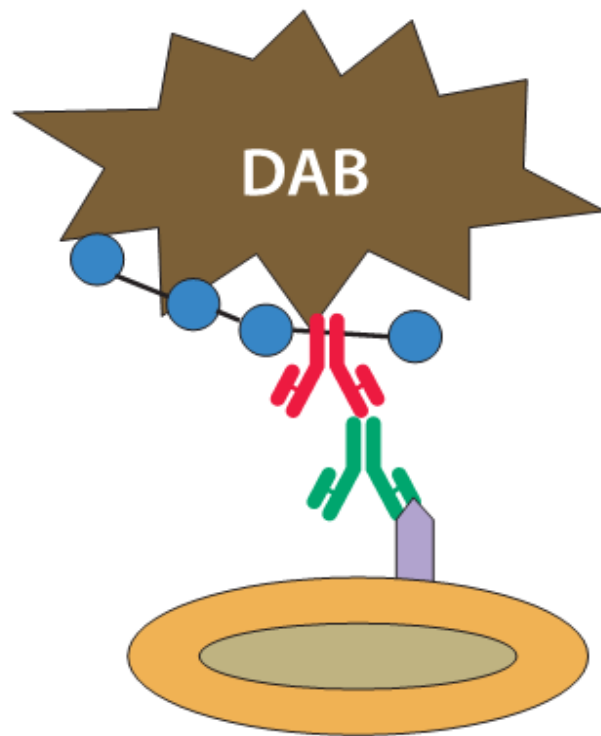


Smear



Cellblock

Immuncytology



Kromogen (farvestof)

Visualiseringssystem
(enzymer)

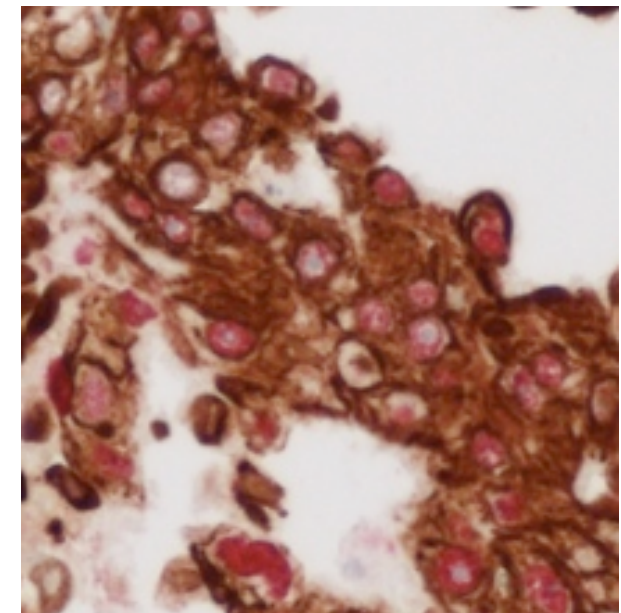
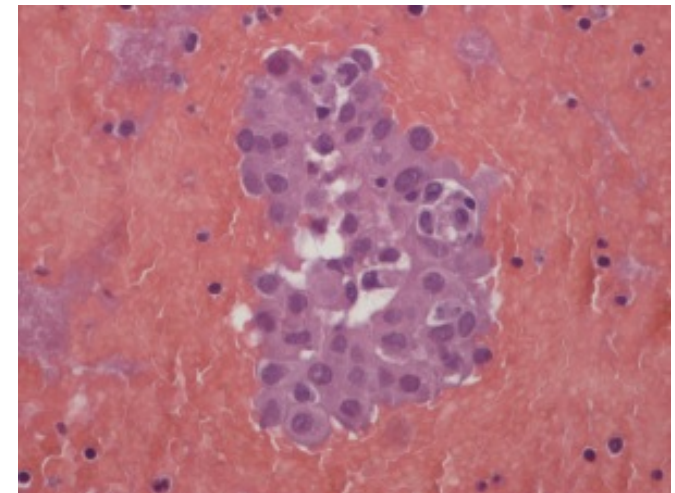
Sekundært antistof

Primært antistof

Antigen

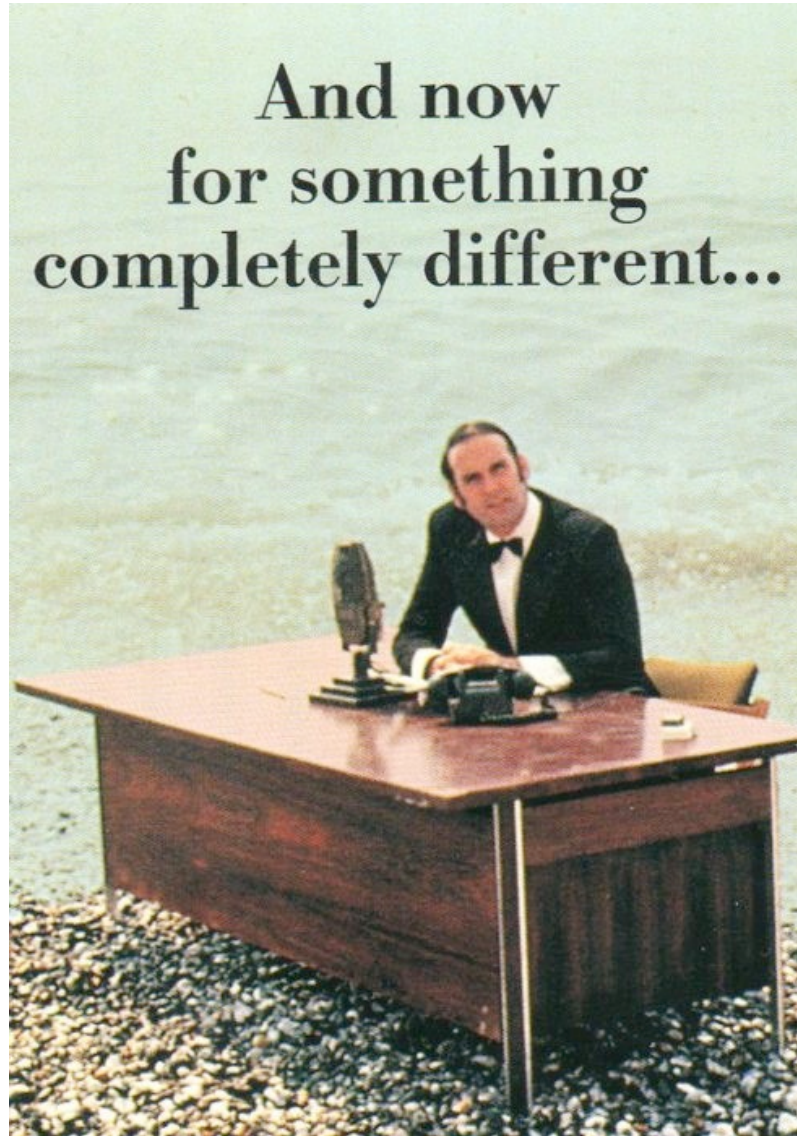
Cellens cytoplasma

Cellekerne

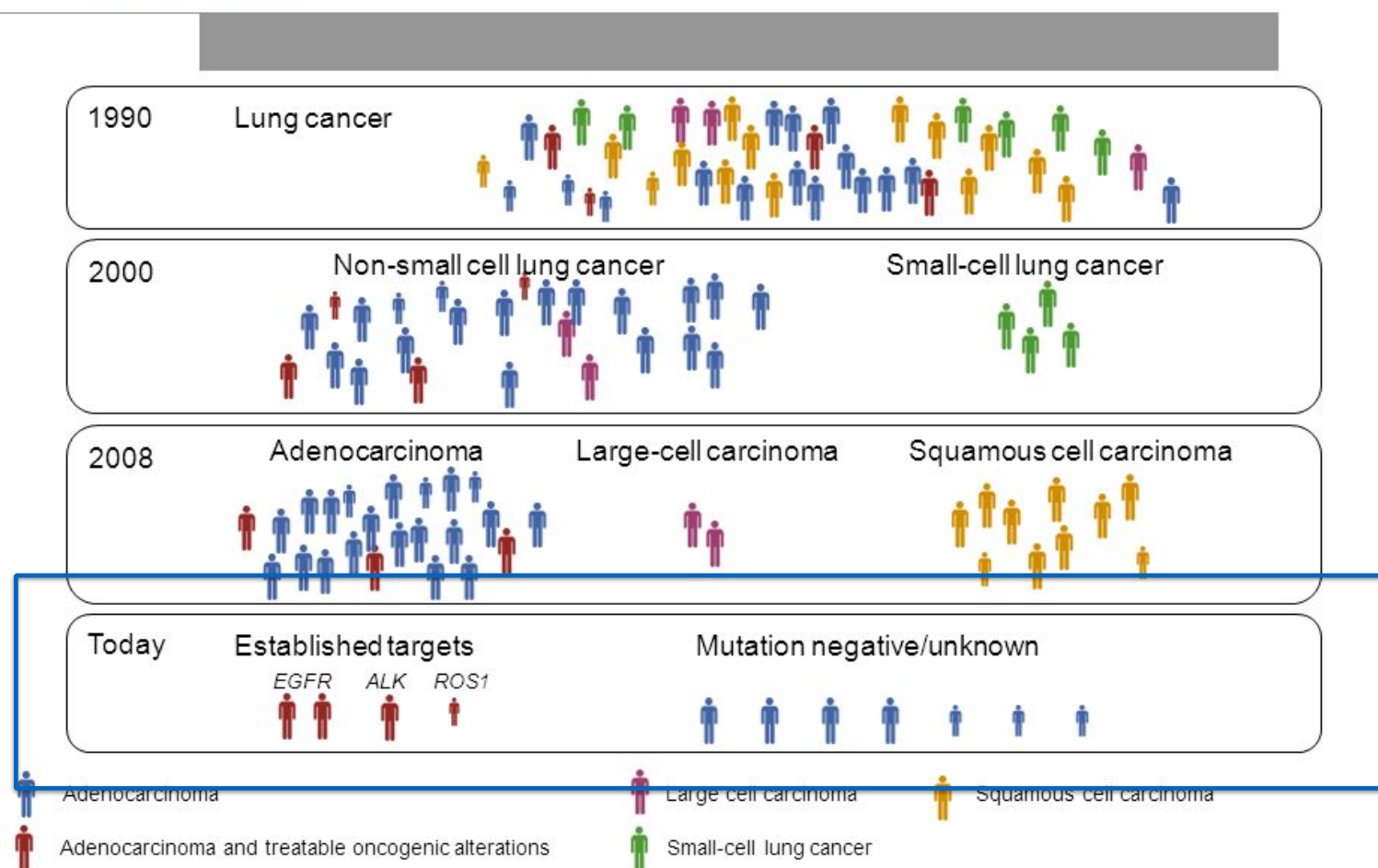


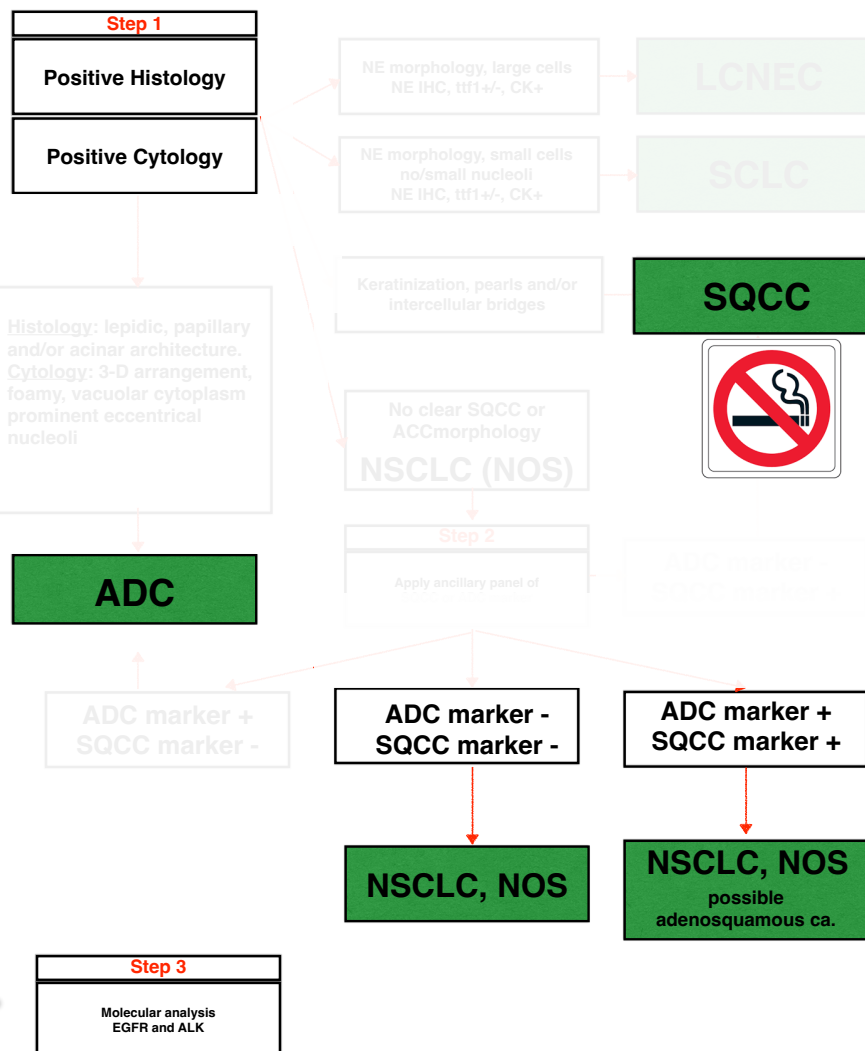
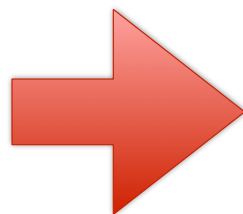
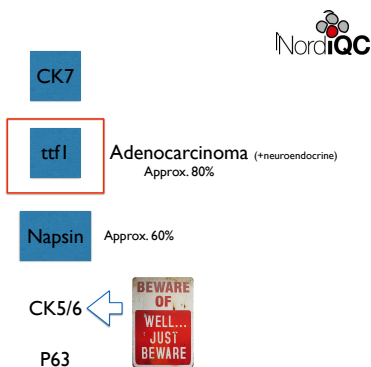
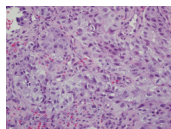
ttf1-CK7

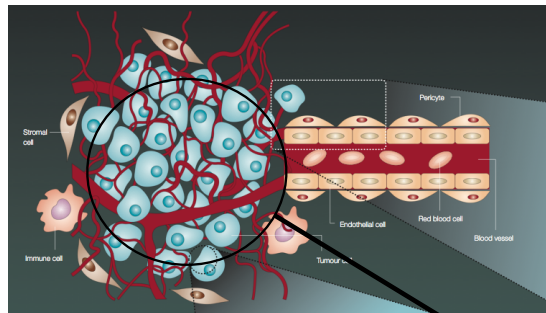
And now
for something
completely different...



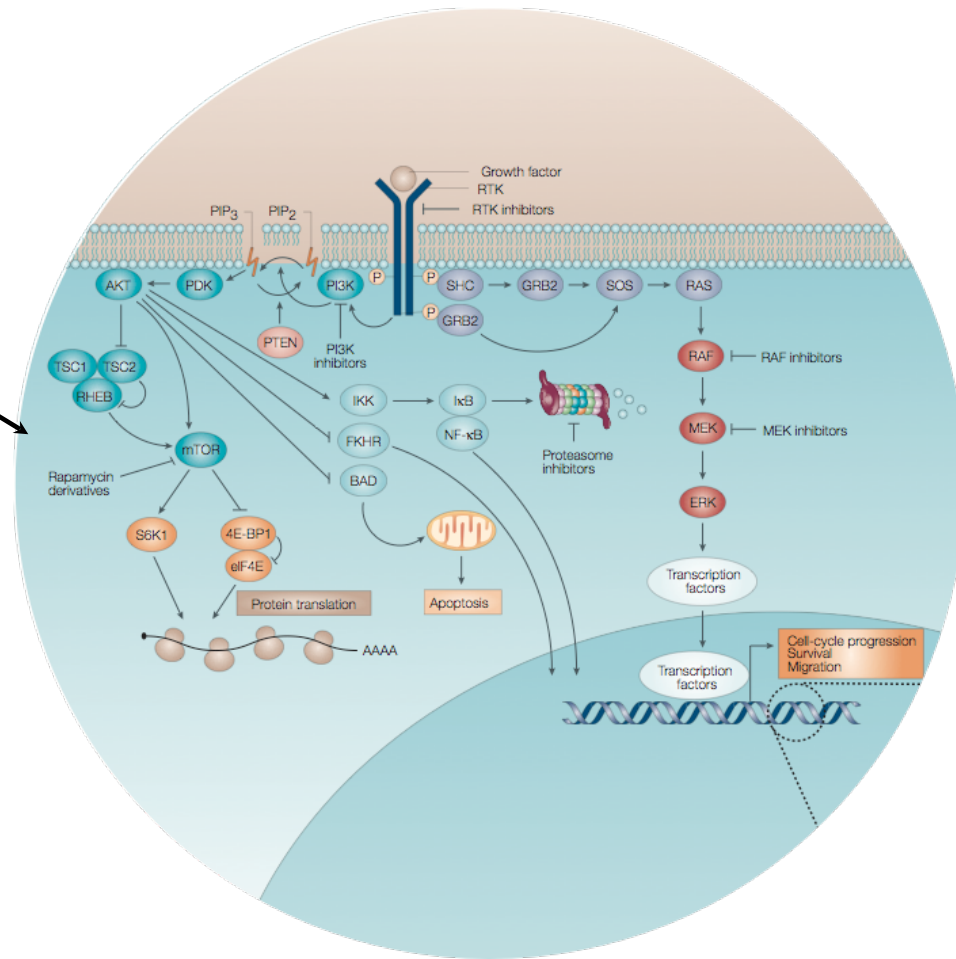
Patient selection in lung cancer: Evolution over time

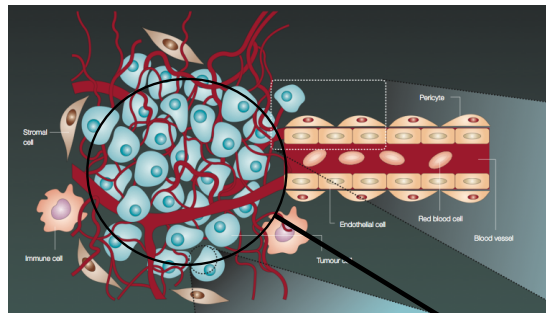




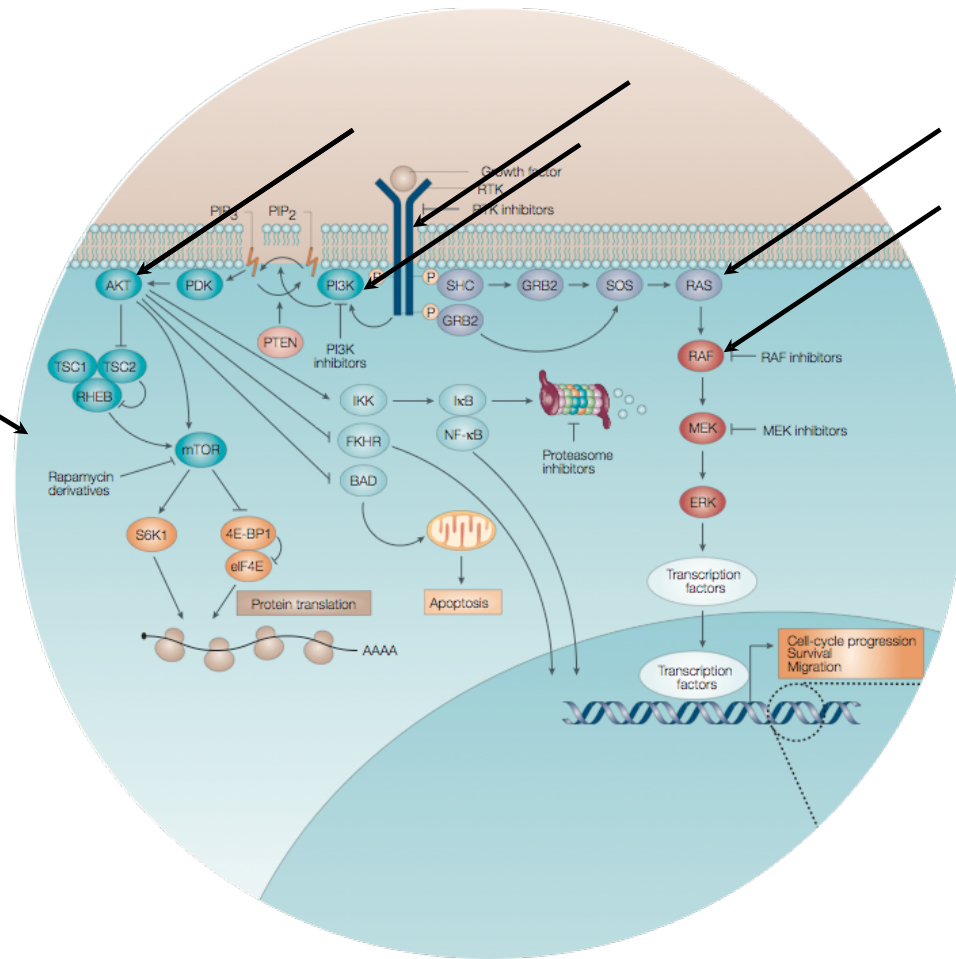


Pathways of cancer

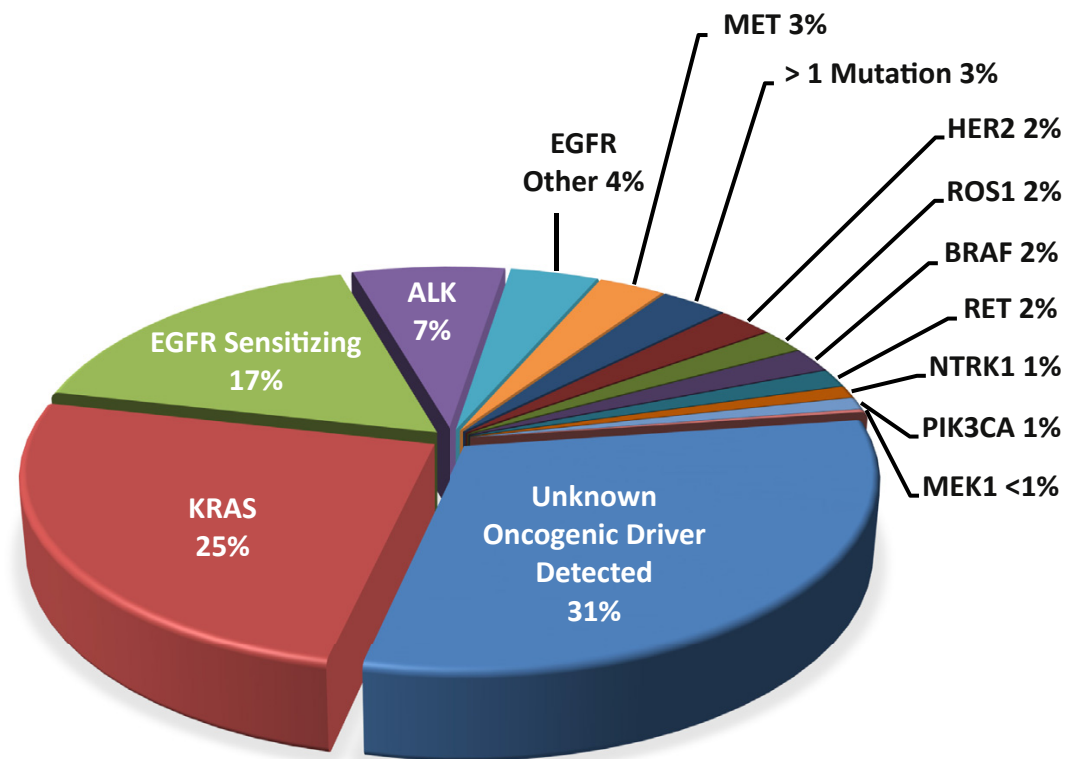




oncogenes



Driver mutations Lung Adenocarcinoma

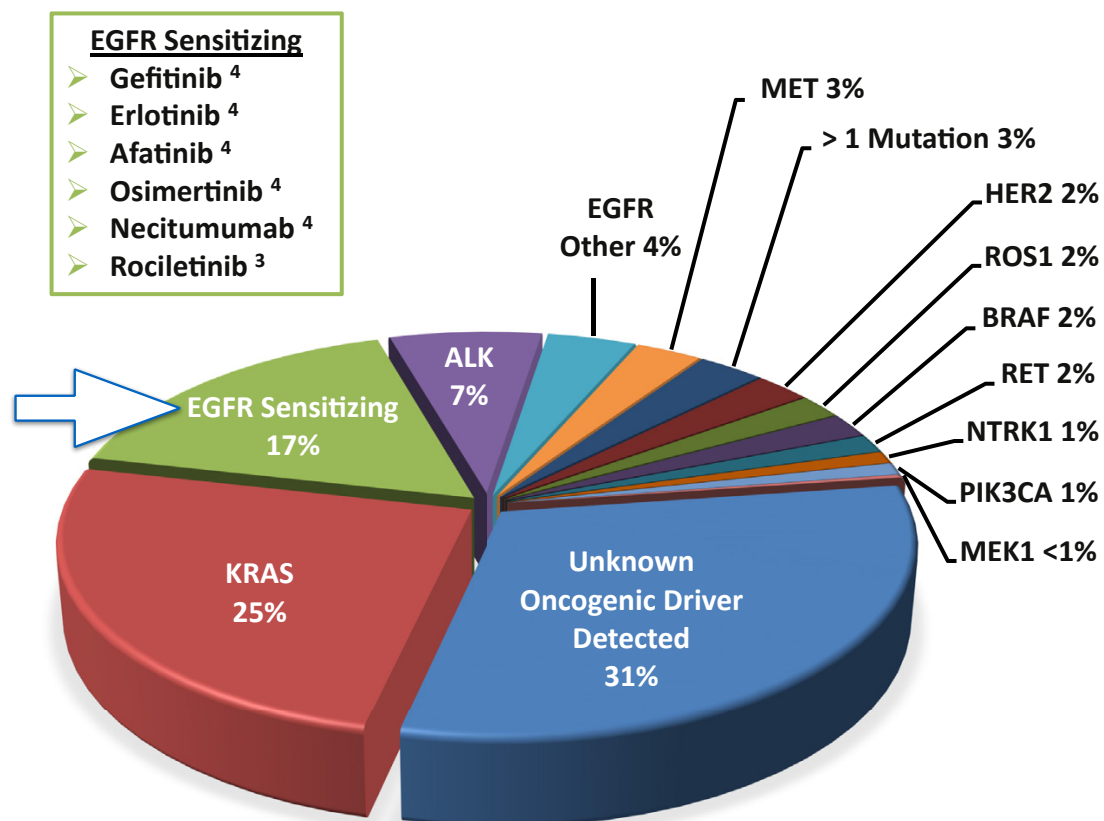


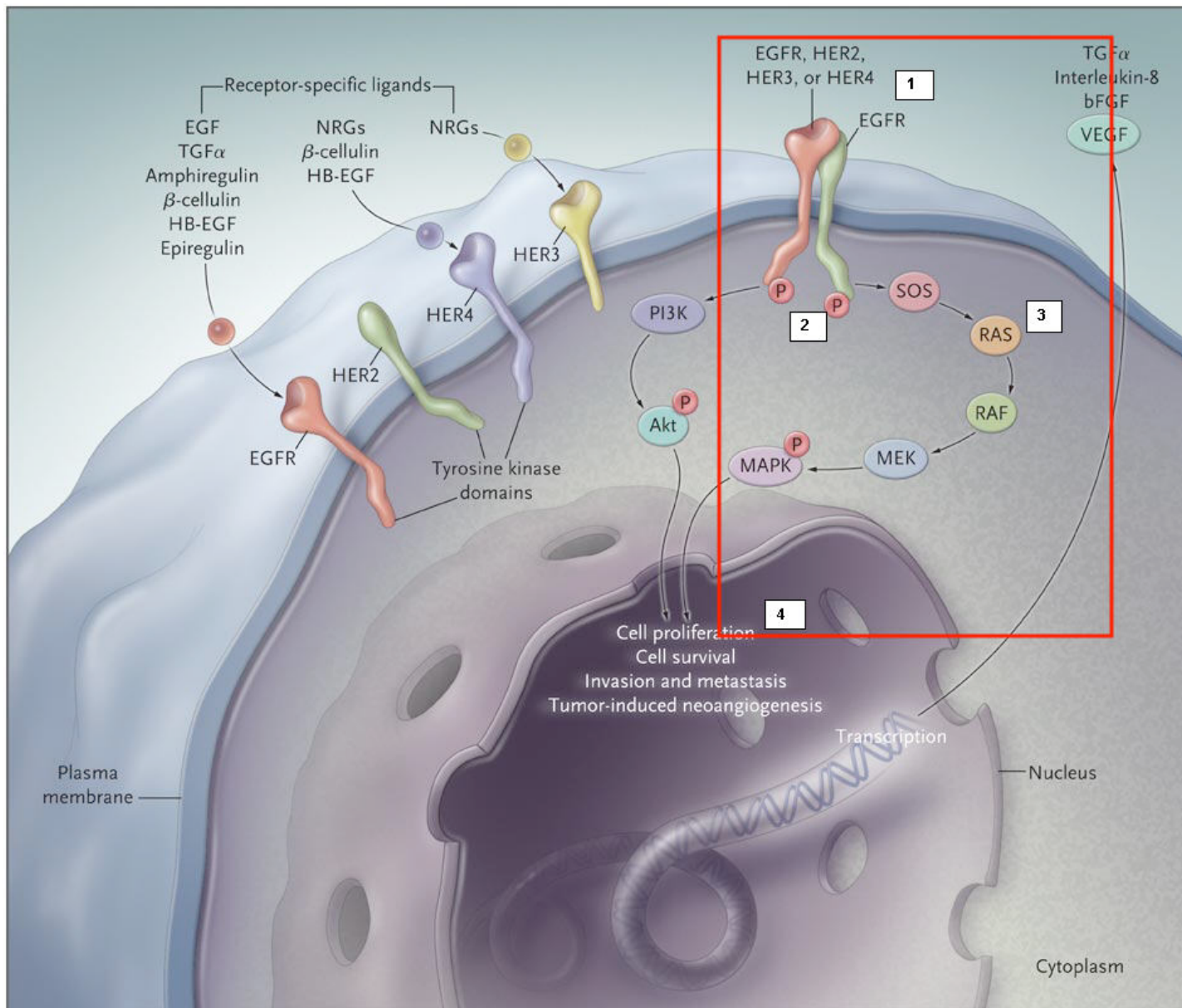
Danish Lung Cancer Group (DLCG)

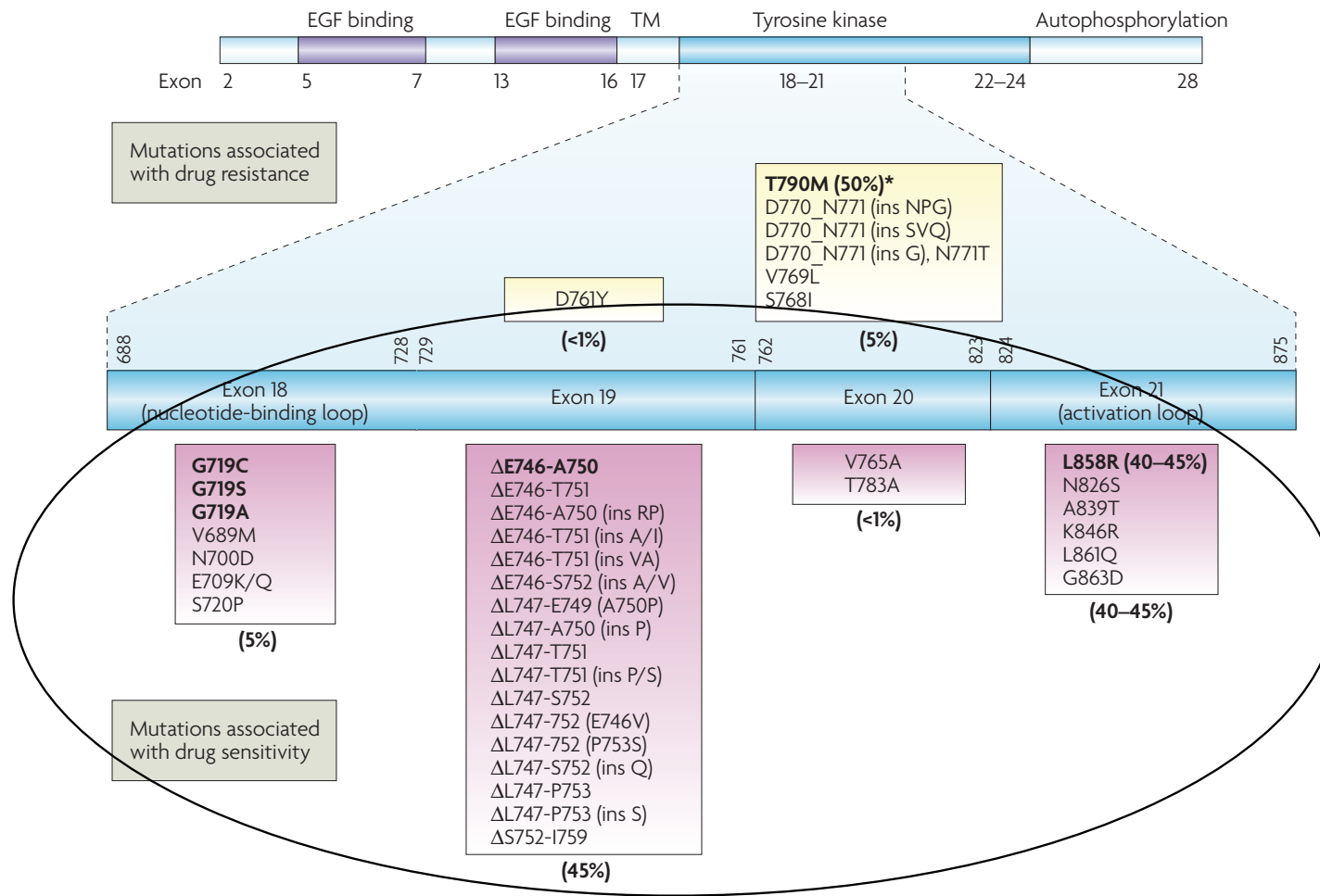


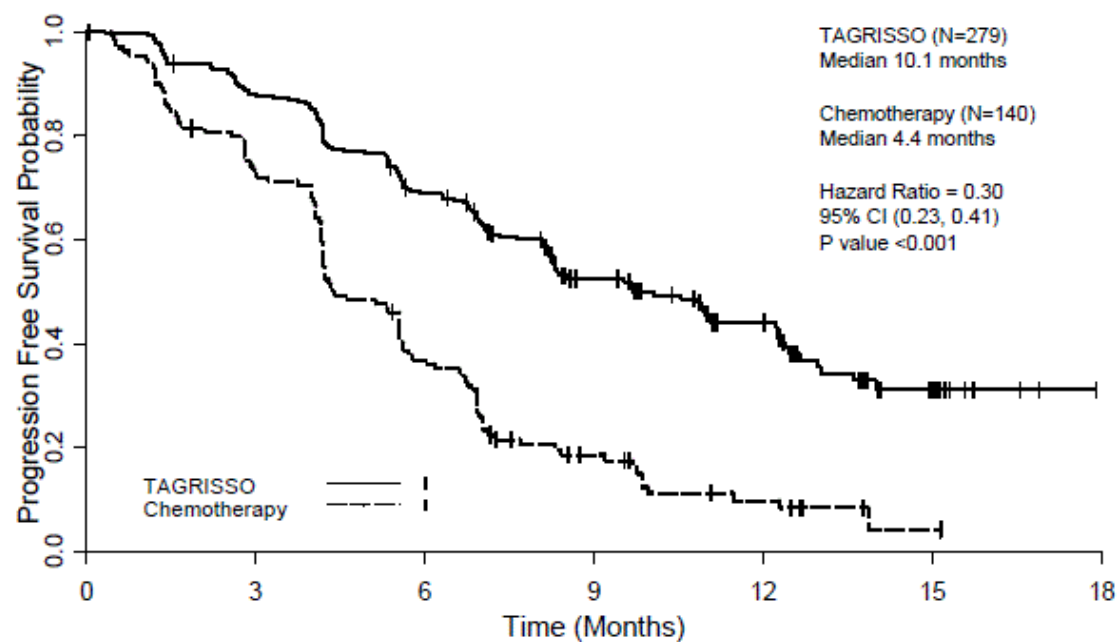
Lungecancer – Patologi

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









Number at risk

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

Tick marks represent censored observations



Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Lung Cancer

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



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



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

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

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

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

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

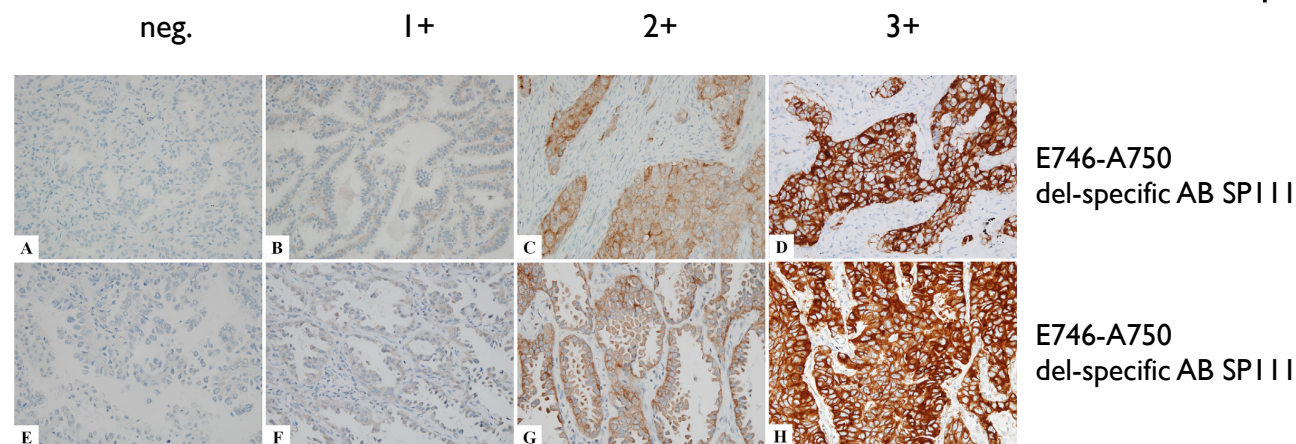
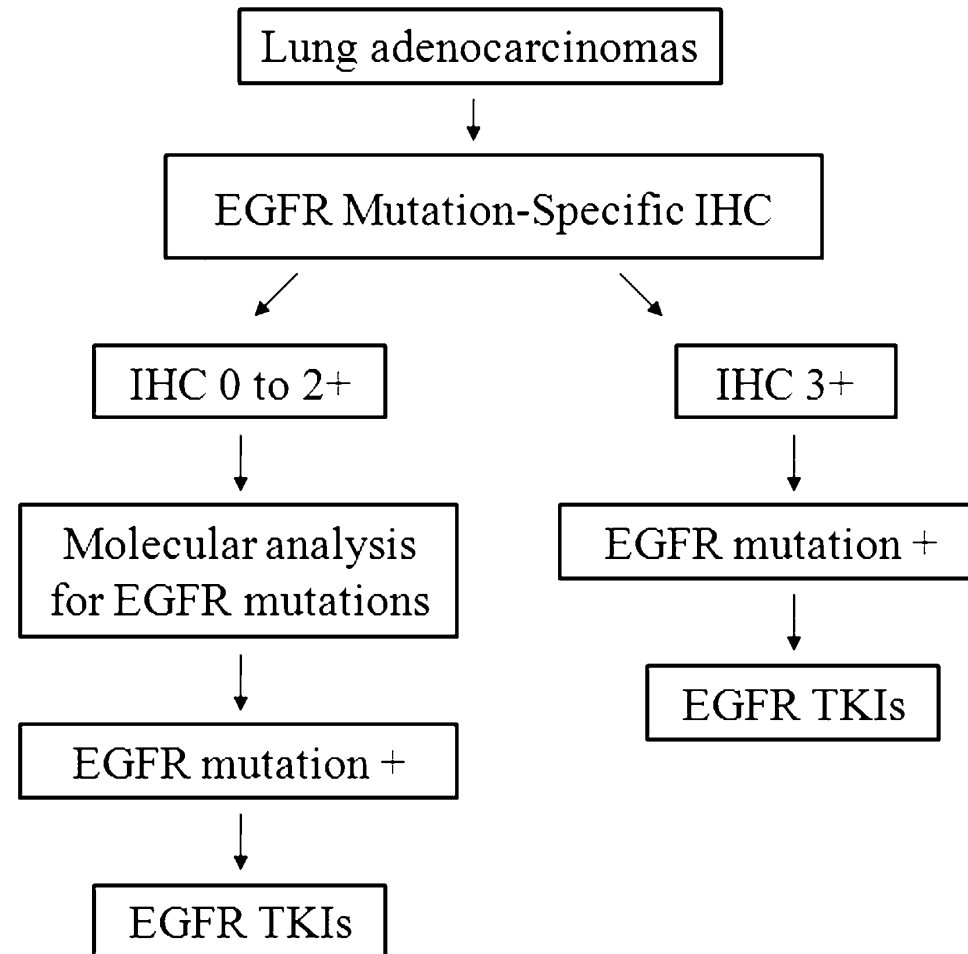


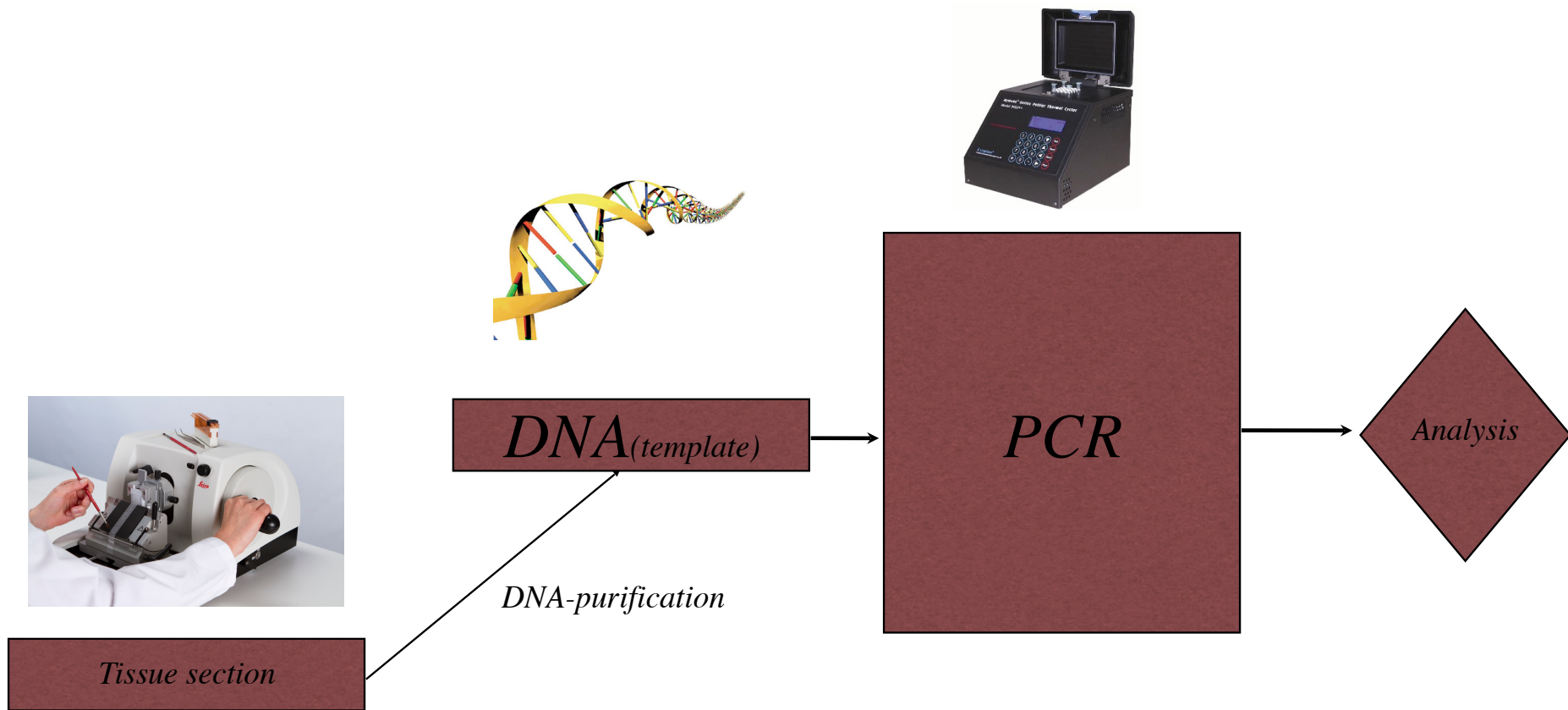
Table 2
Diagnostic power of mutation-specific antibodies comparing with *EGFR* mutational status.

Mutation-specific antibodies	<i>EGFR</i> mutations	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Anti-EGFR E746.A750 del	E746.A750 deletion	94.1%	96.1%	80.0%	99.0%
	≥Score 1 as positive	70.6%	99.0%	92.3%	95.3%
	≥Score 2 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%

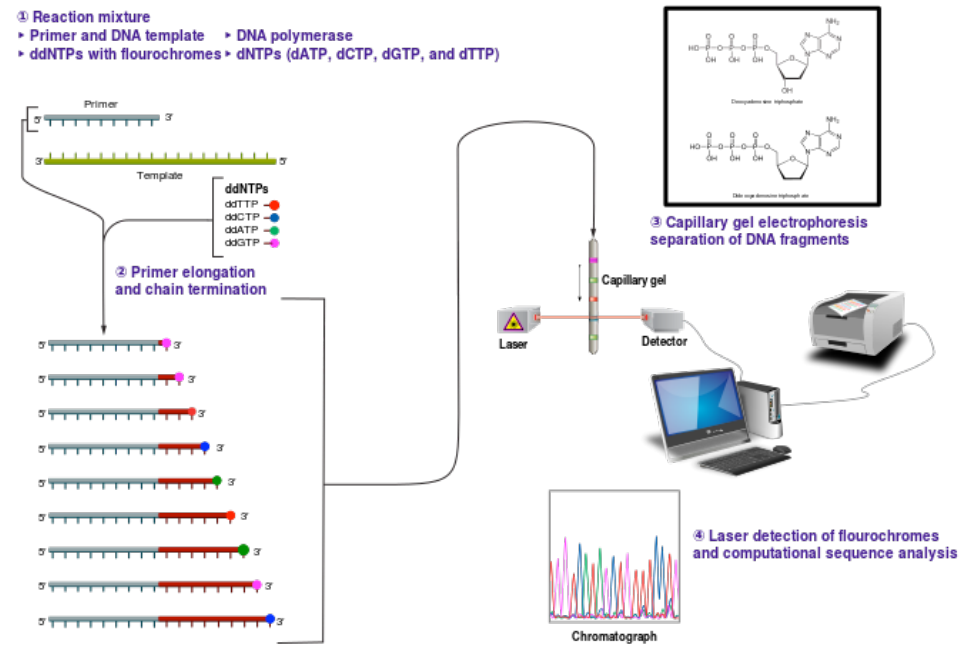
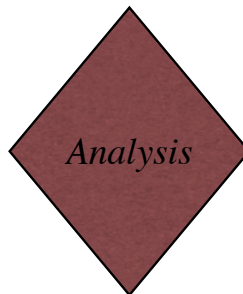
Abbreviations: PPV, positive predictive value; NPV, negative predictive value.

Algorithm

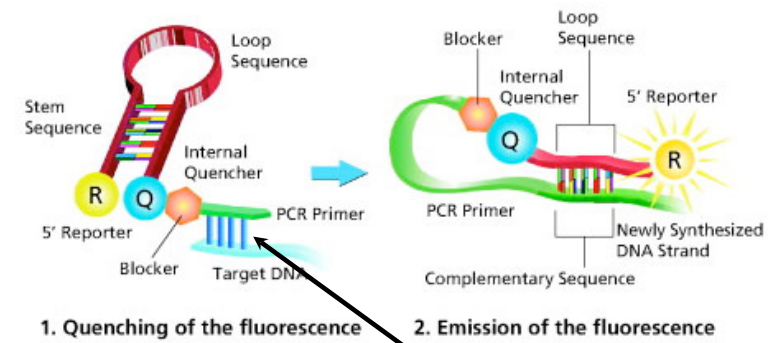




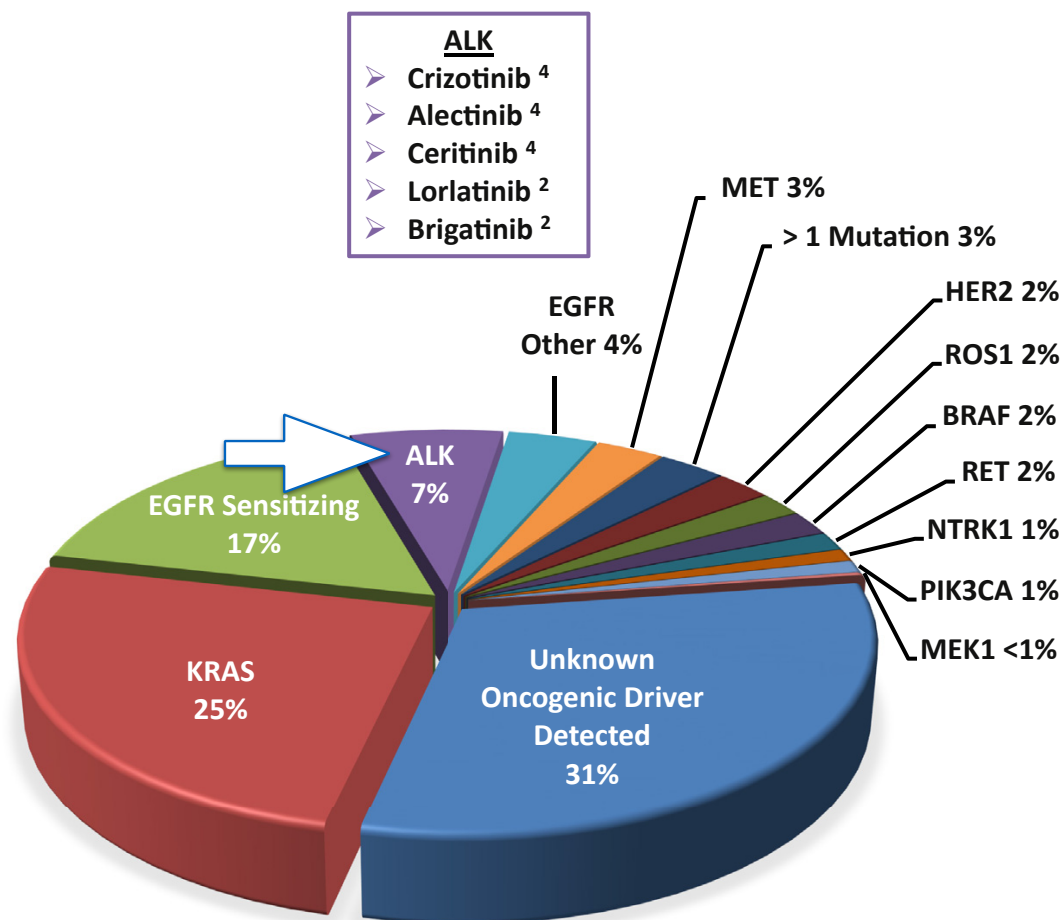
Sequencing

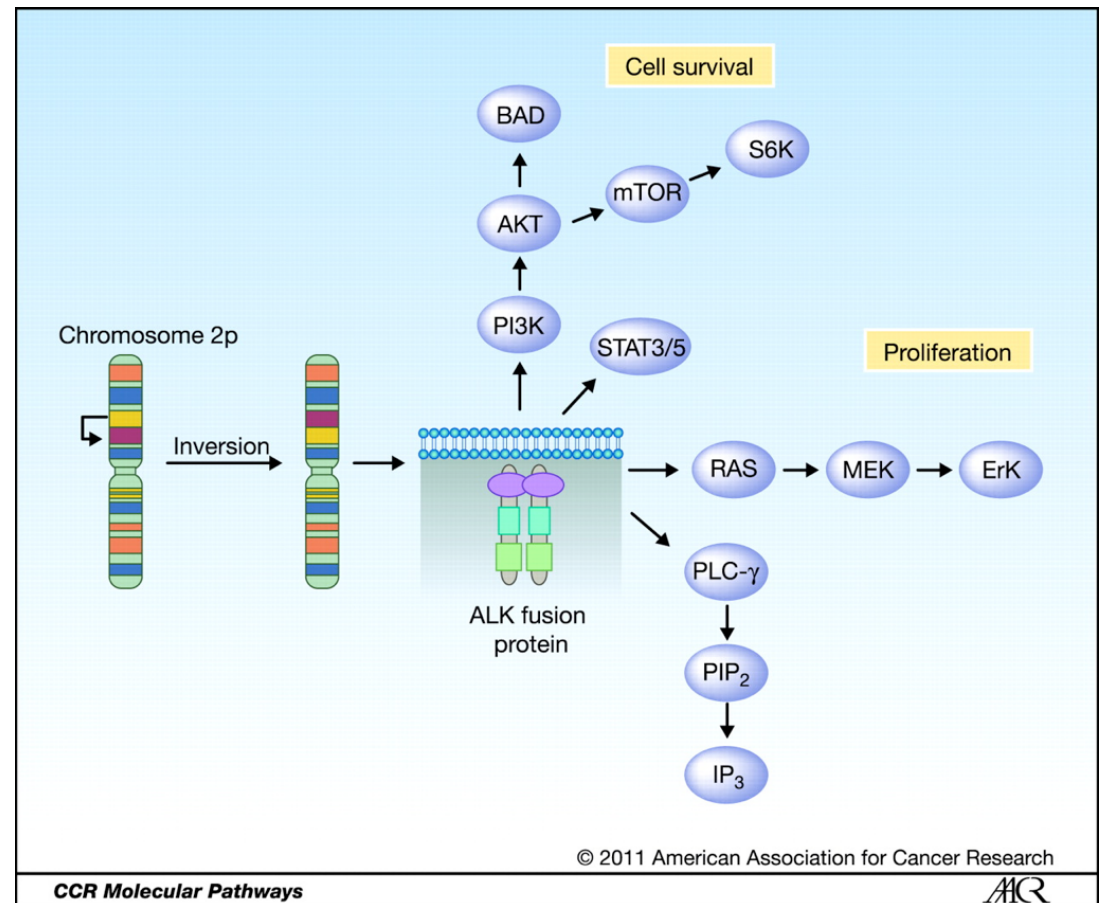
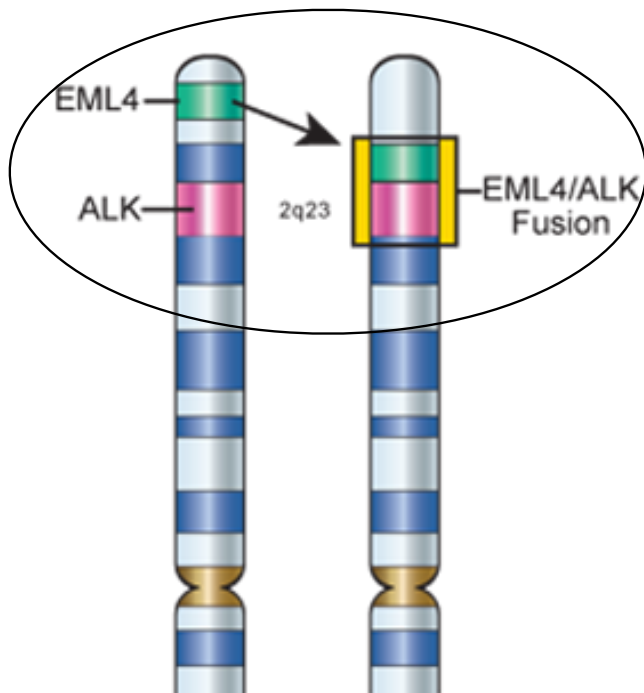


PCR based test



mutationspecific primer





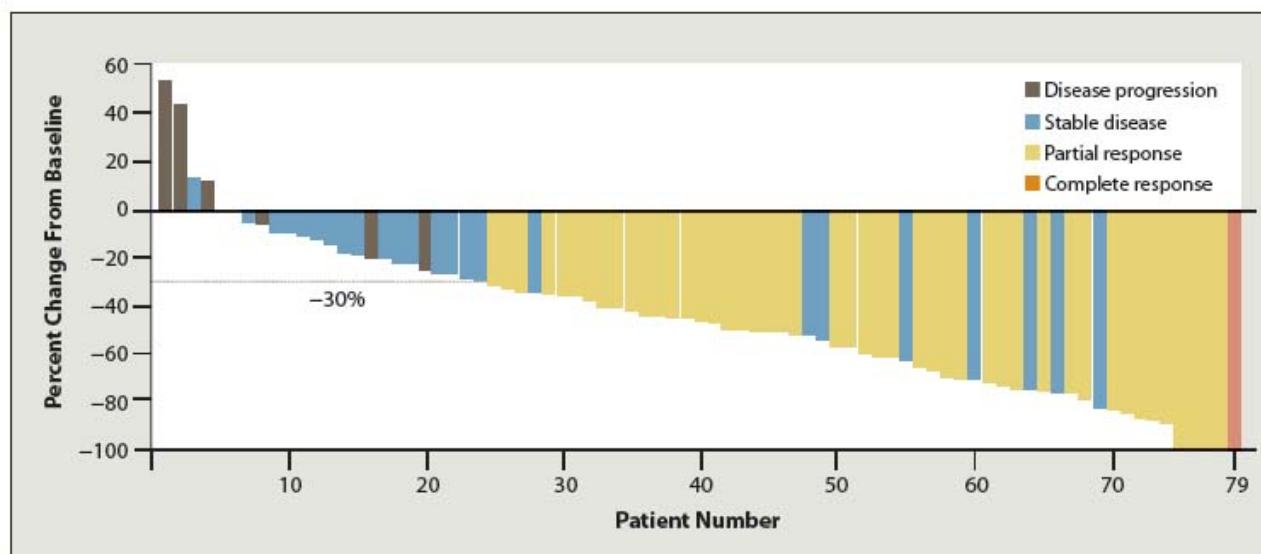
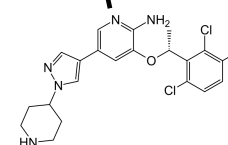
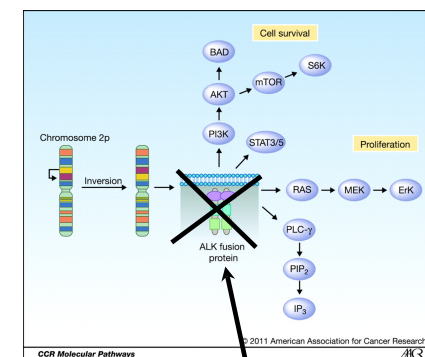
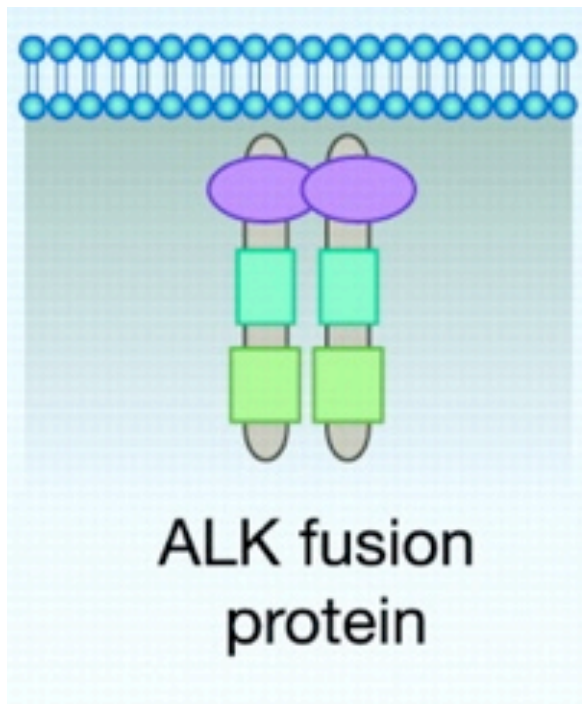


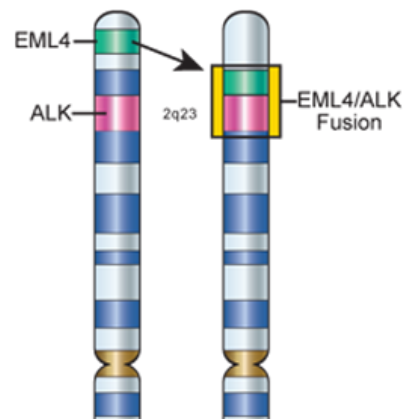
Figure 2: Waterfall plot showing response to crizotinib in patients with *EML4-ALK* NSCLC. Percent change in tumor burden relative to pretreatment baseline is represented. (Reproduced with permission from Kwak et al. *N Engl J Med*. 2010;363:1693-1703. Copyright © 2010, Massachusetts Medical Society.)



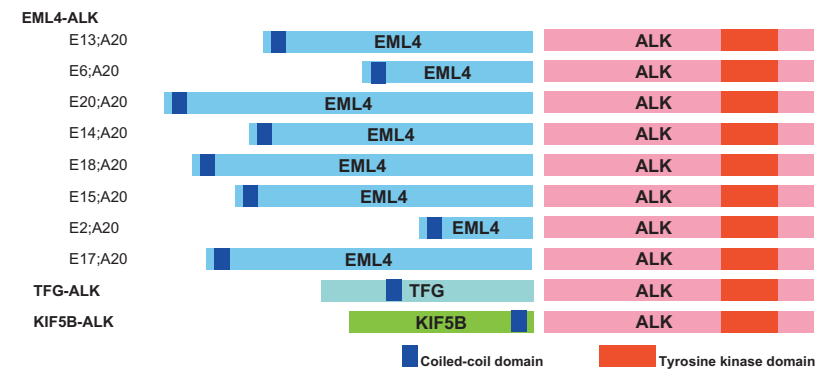
Detection of fusion protein



Detection of chromosomal changes

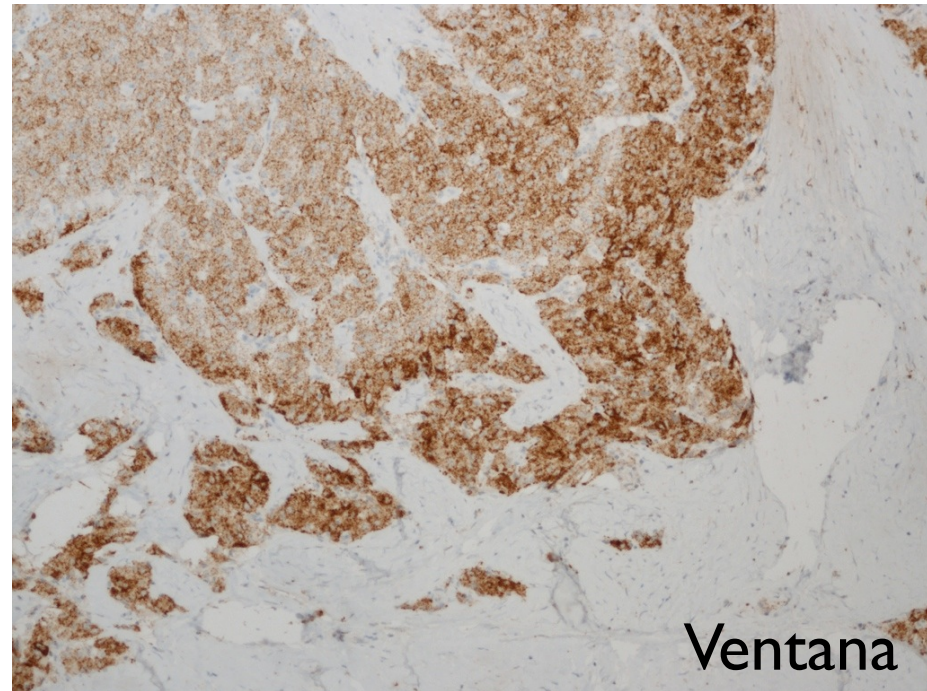
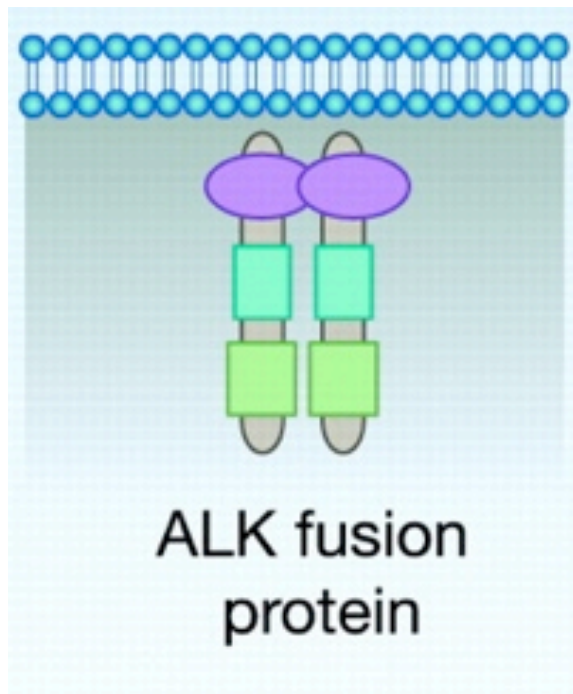


Detection of fusion RNA



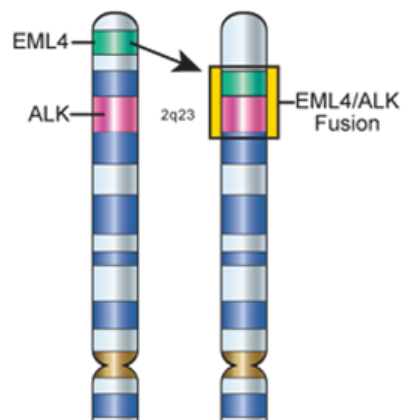
Immunohistochemistry

Detection of fusion protein



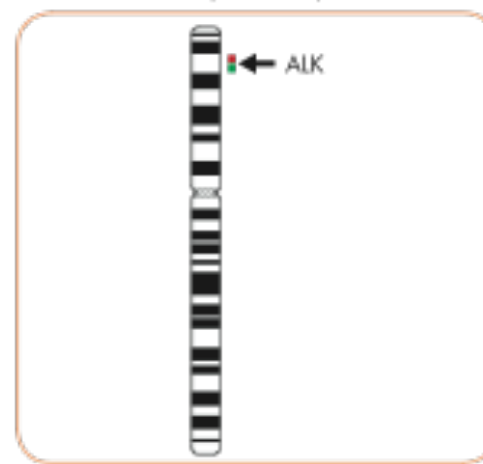
Detects ALK independent of fusion partner

Detection of chromosomal changes

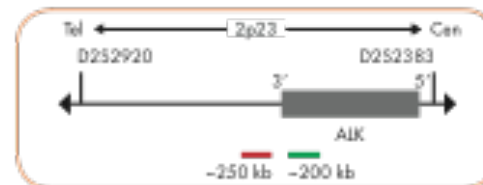


ZYTOVISION
Molecular diagnostics simplified

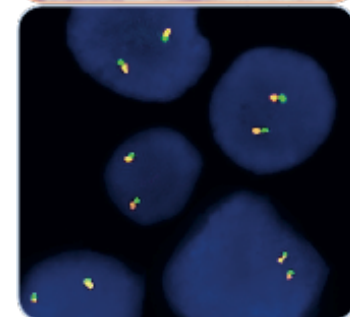
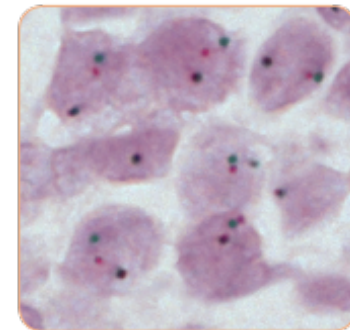
F(C)ISH



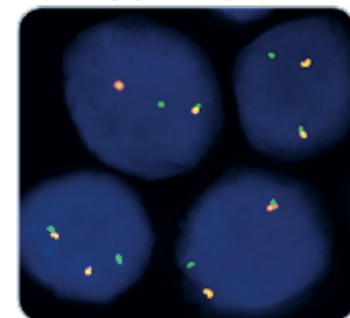
Ideogram of chromosome 2
indicating the hybridization locations.



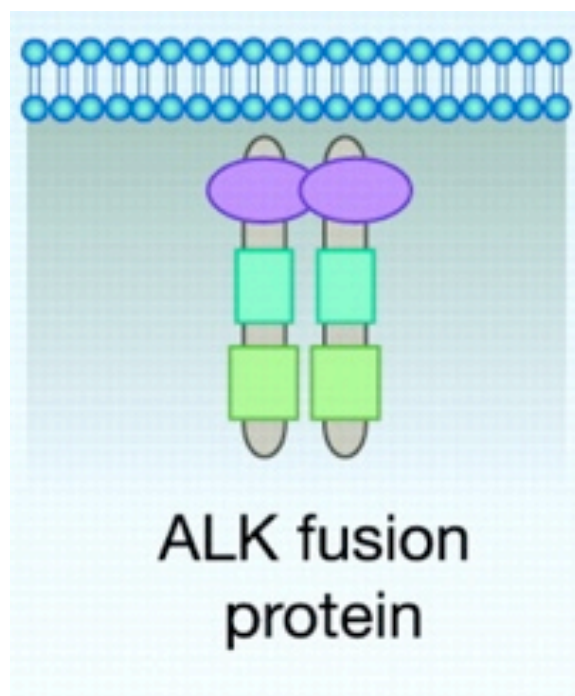
SPEC ALK Probe map (not to scale).



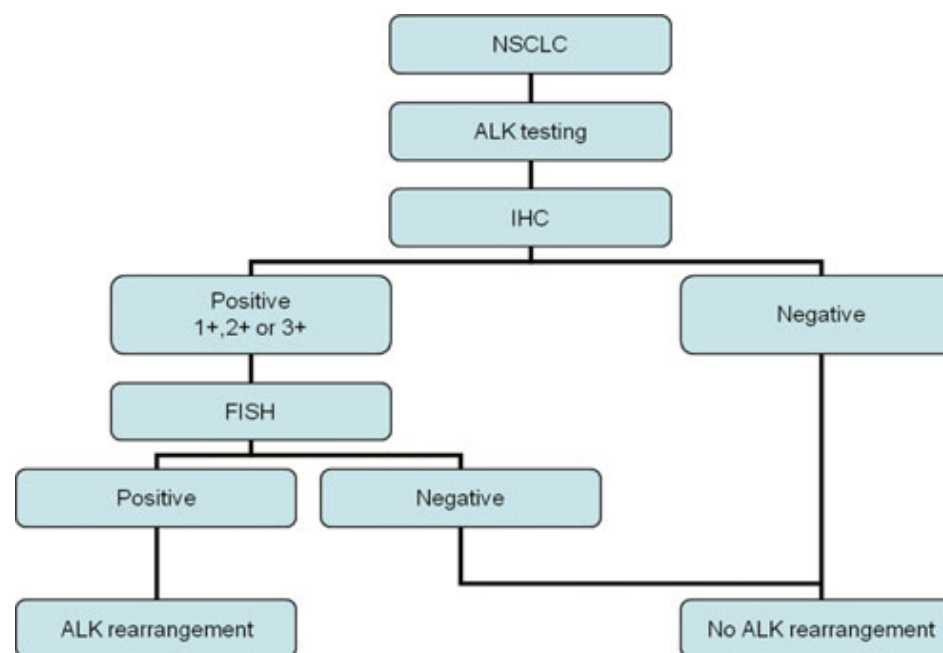
SPEC ALK Dual Color Break Apart Probe
hybridized to normal interphase cells as indicated
by two orange/green fusion signals per nucleus.



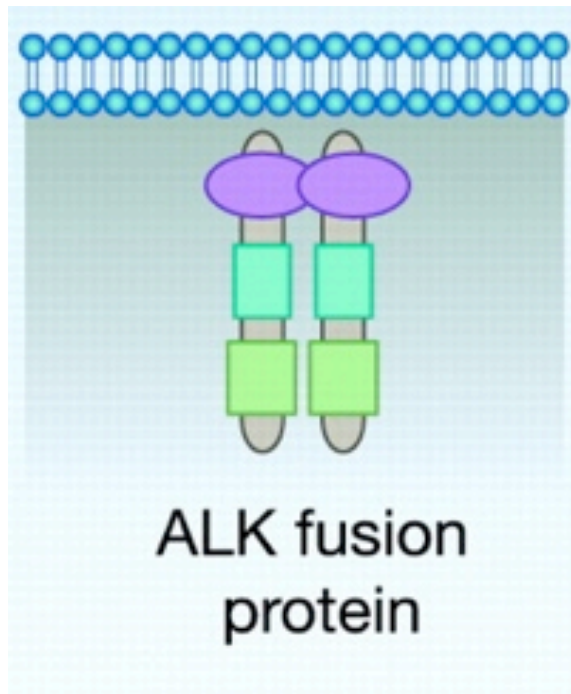
Detection of fusion protein



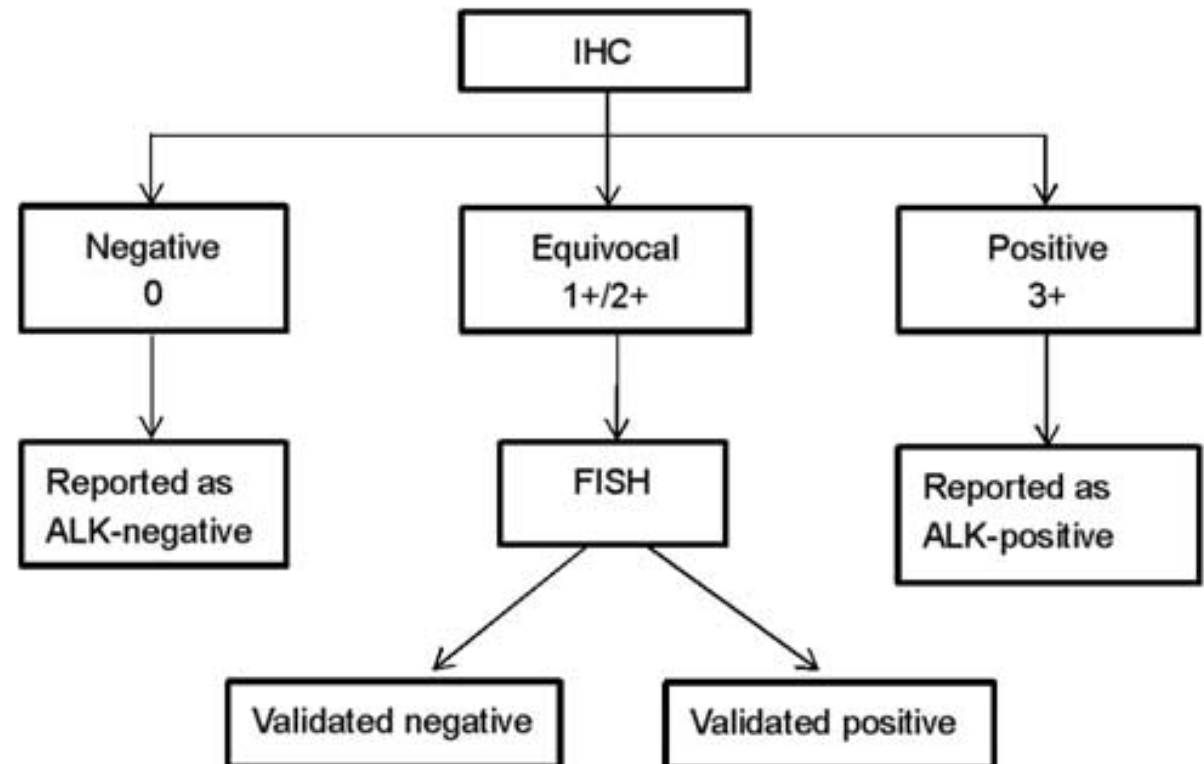
Algorithm



Detection of fusion protein

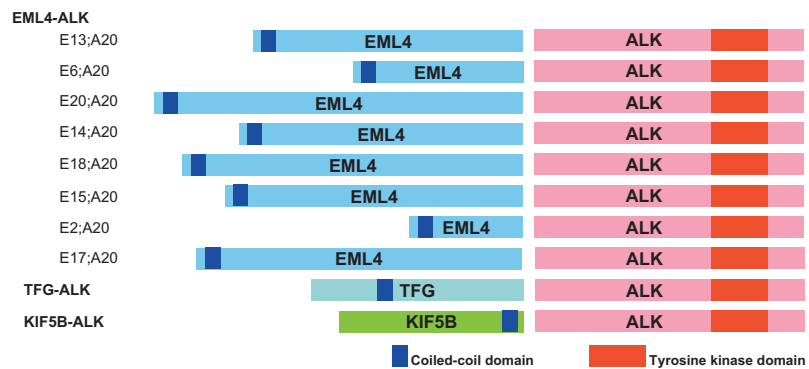


Algorithm



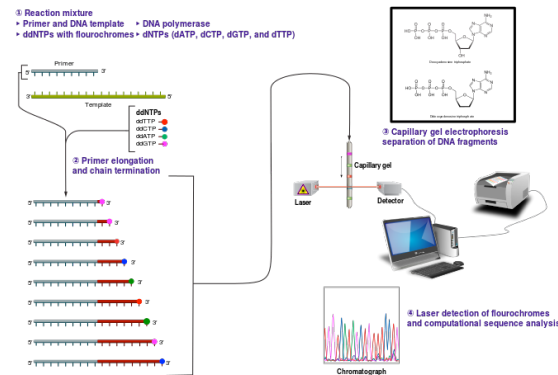
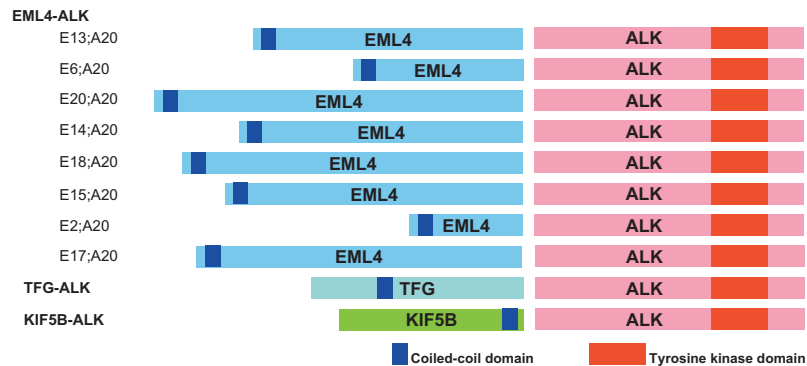
RT PCR based test

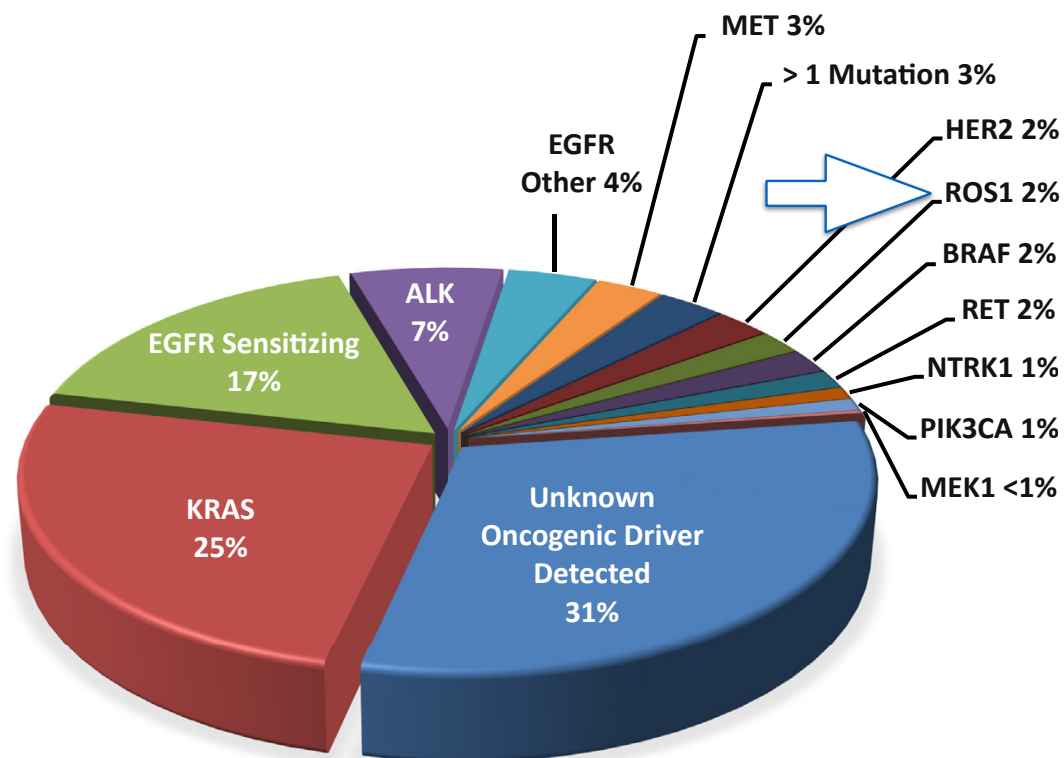
Detection of fusion RNA



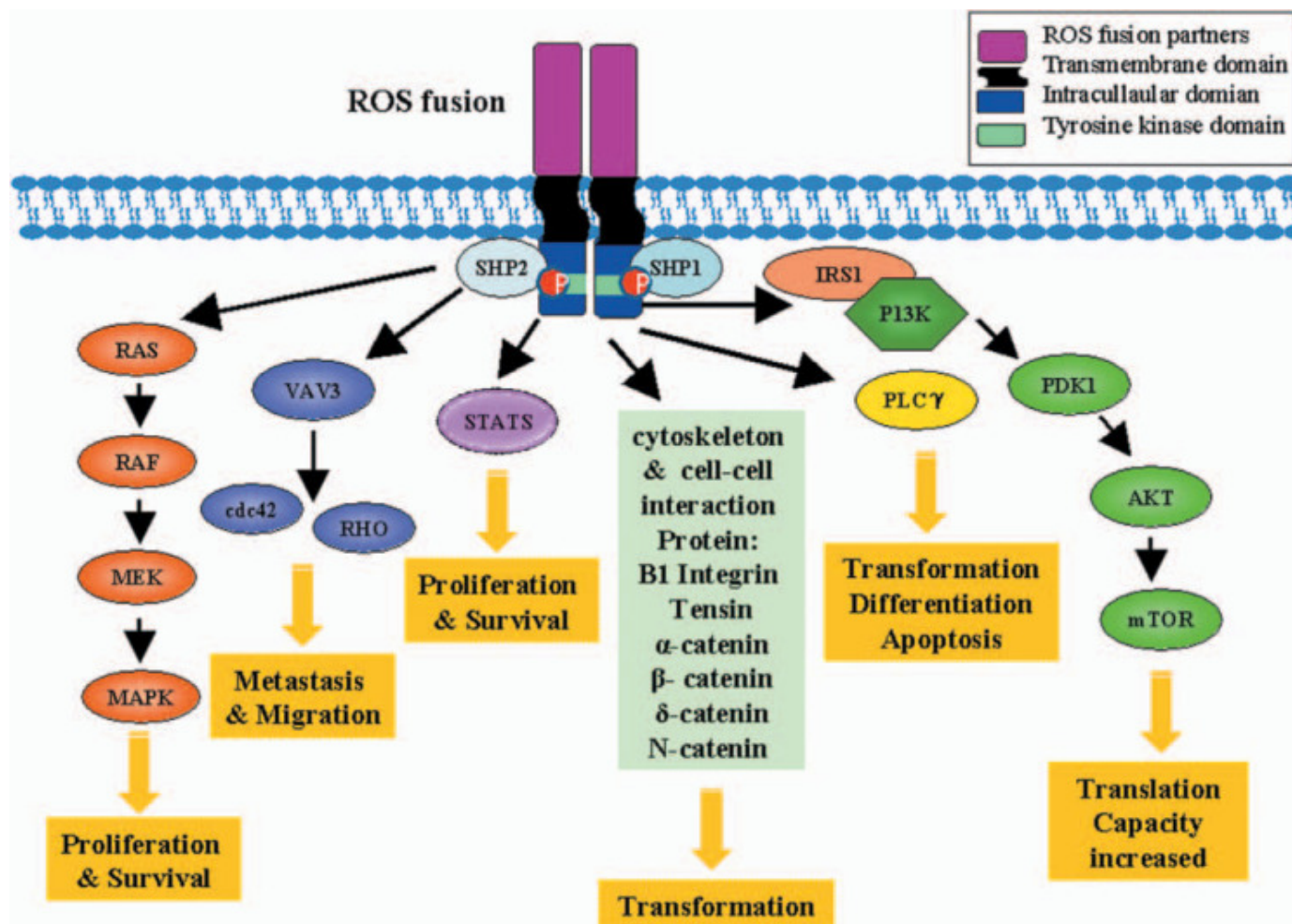
RNA Sequencing based test

Detection of fusion RNA

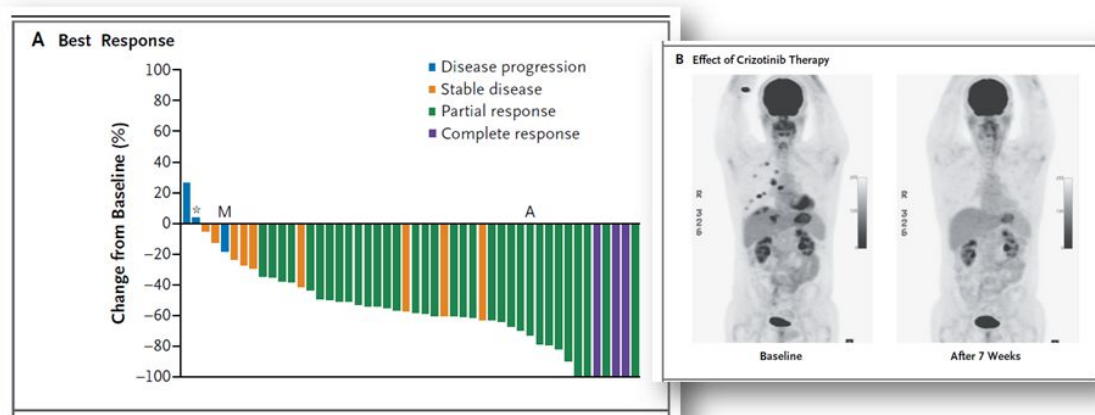




ROS1	
➤	Crizotinib ⁴
➤	Cabozantinib ²
➤	Ceritinib ²
➤	Lorlatinib ²
➤	DS-6051b ¹

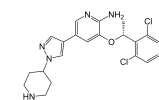


Tumor responses to crizotinib in ROS1-rearranged NSCLC

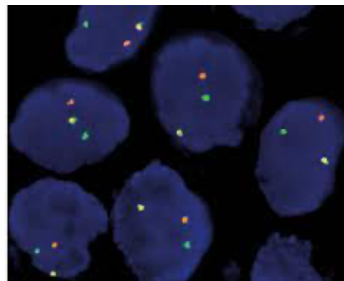


Overall response rate 72% (6% CR, 66% PR).
Median time to response 7.9 weeks (range, 4.3 - 32.0)

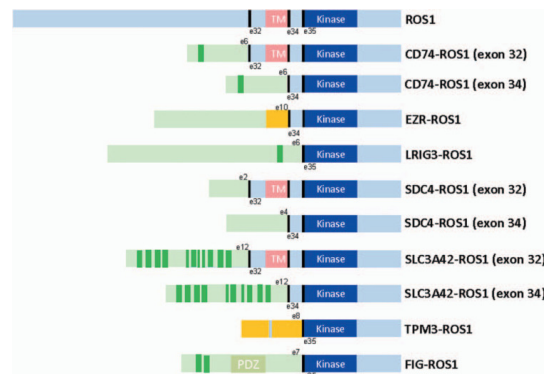
Shaw AT et al, N Engl J Med 2014;371:1963-71.



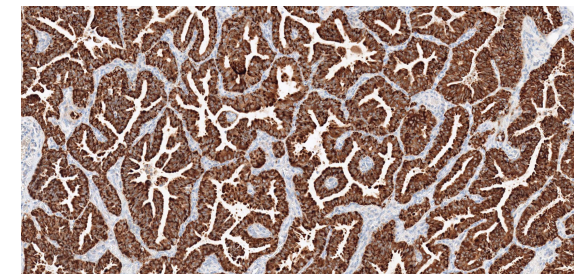
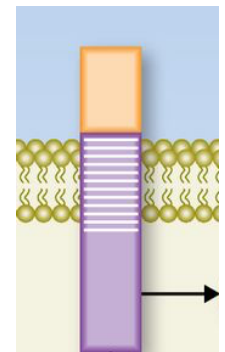
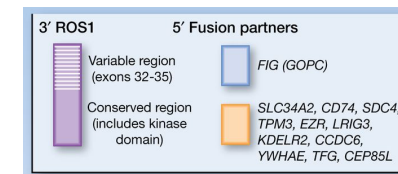
Detection of chromosomal changes



Detection of fusion RNA



Detection of fusion protein

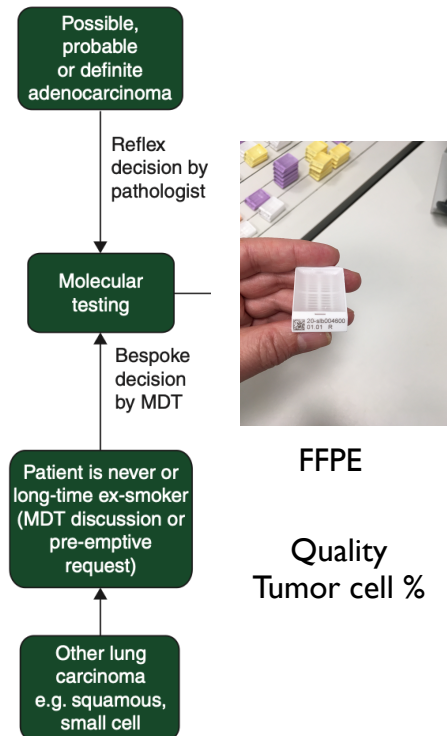




Suggestion



Next generation seq.



FFPE

Quality
Tumor cell %

DNA workflow

DNA purification	Sequencing
Library prep.	Variant calling (Bioinformatics)

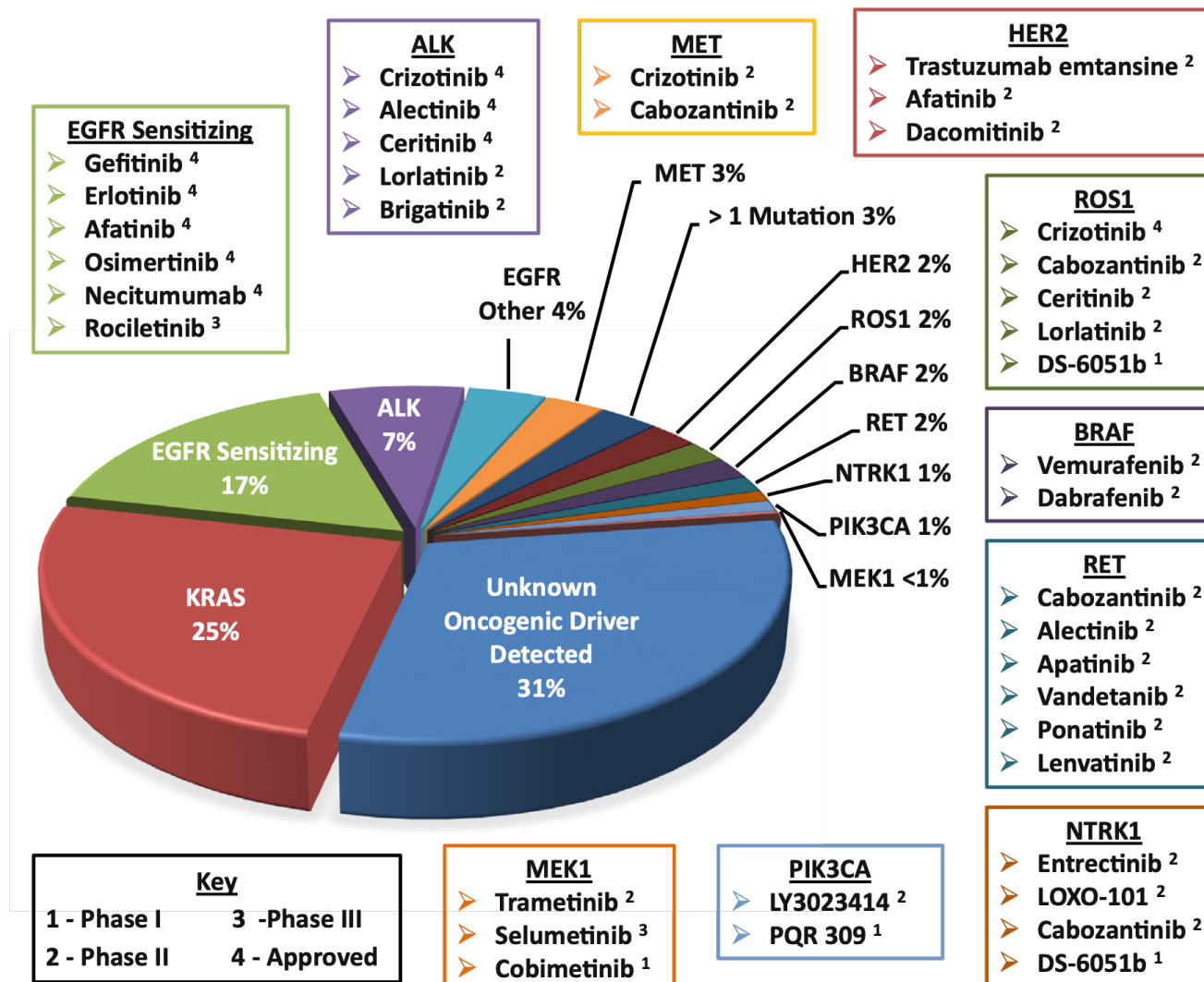
RNA workflow

RNA purification	Sequencing
Library prep.	Variant calling (Bioinformatics)

EGFR

ALK, ROS1

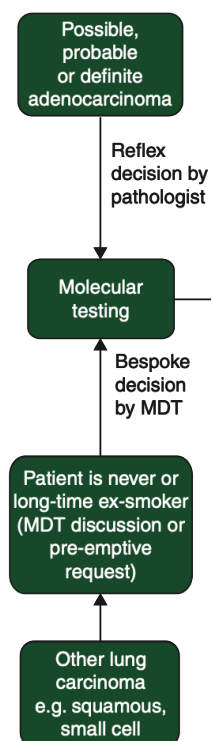






Suggestion

Next generation seq.



FFPE

Quality
Tumor cell %

DNA workflow

DNA purification Sequencing
Library prep. Variant calling (Bioinformatics)

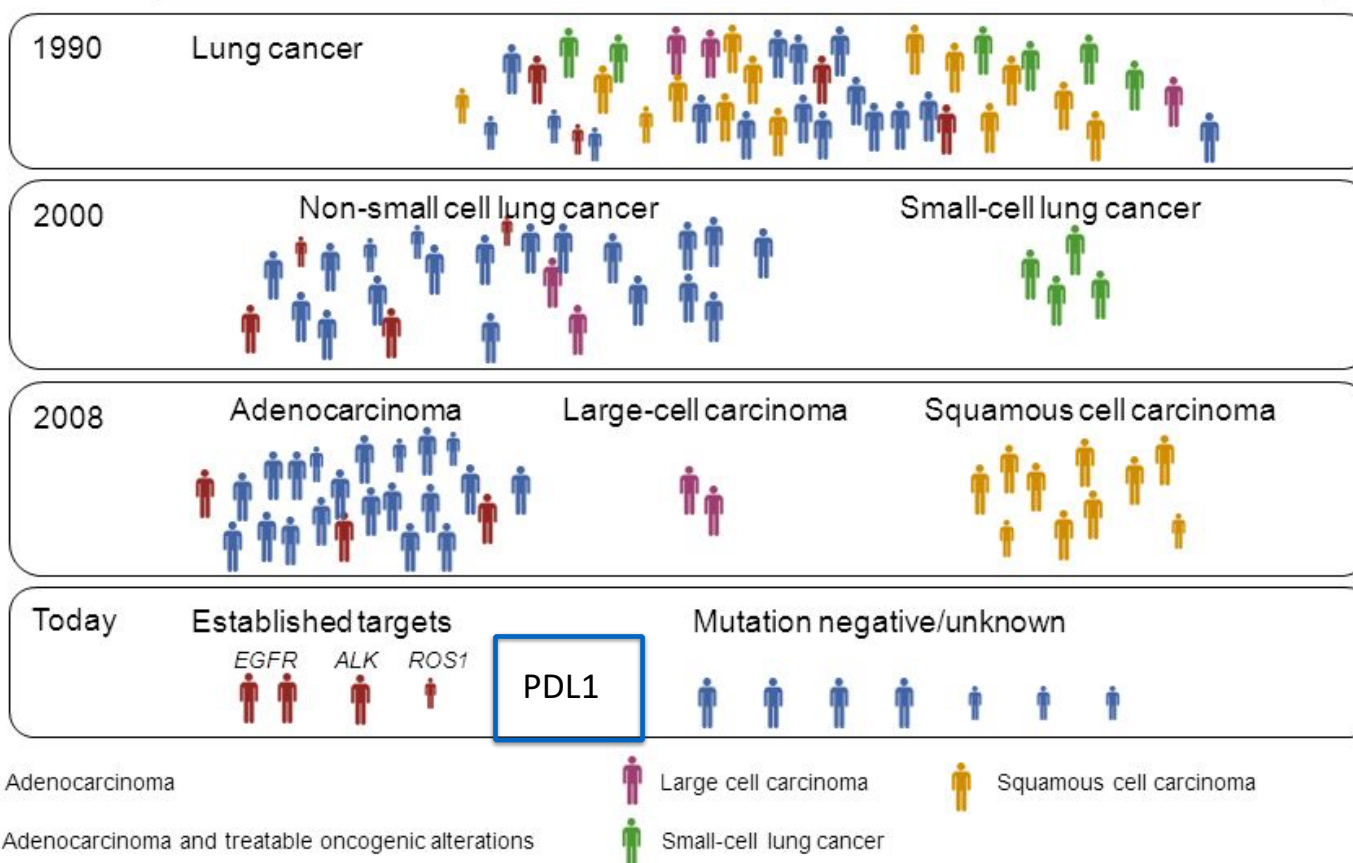
RNA workflow

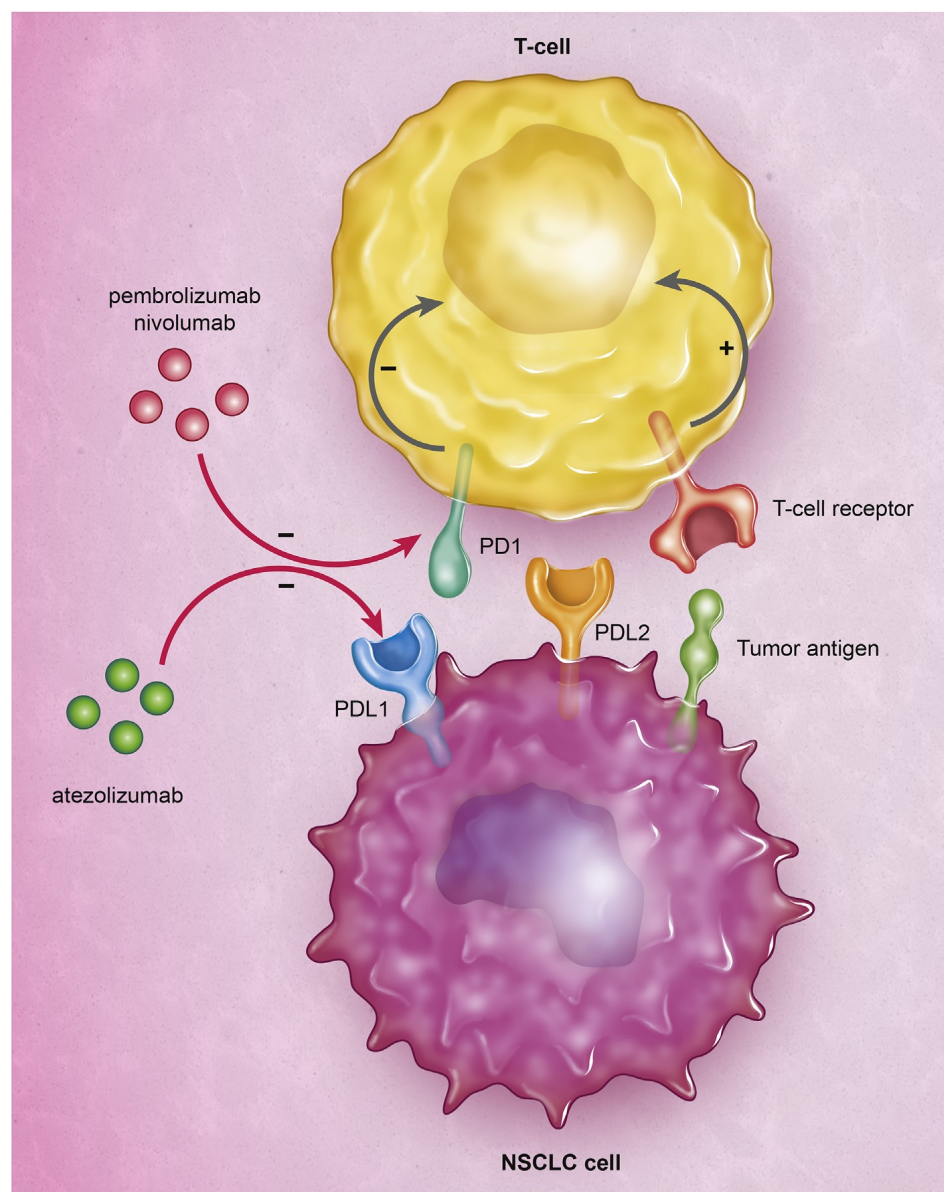
RNA purification Sequencing
Library prep. Variant calling (Bioinformatics)

Comprehensive
Result

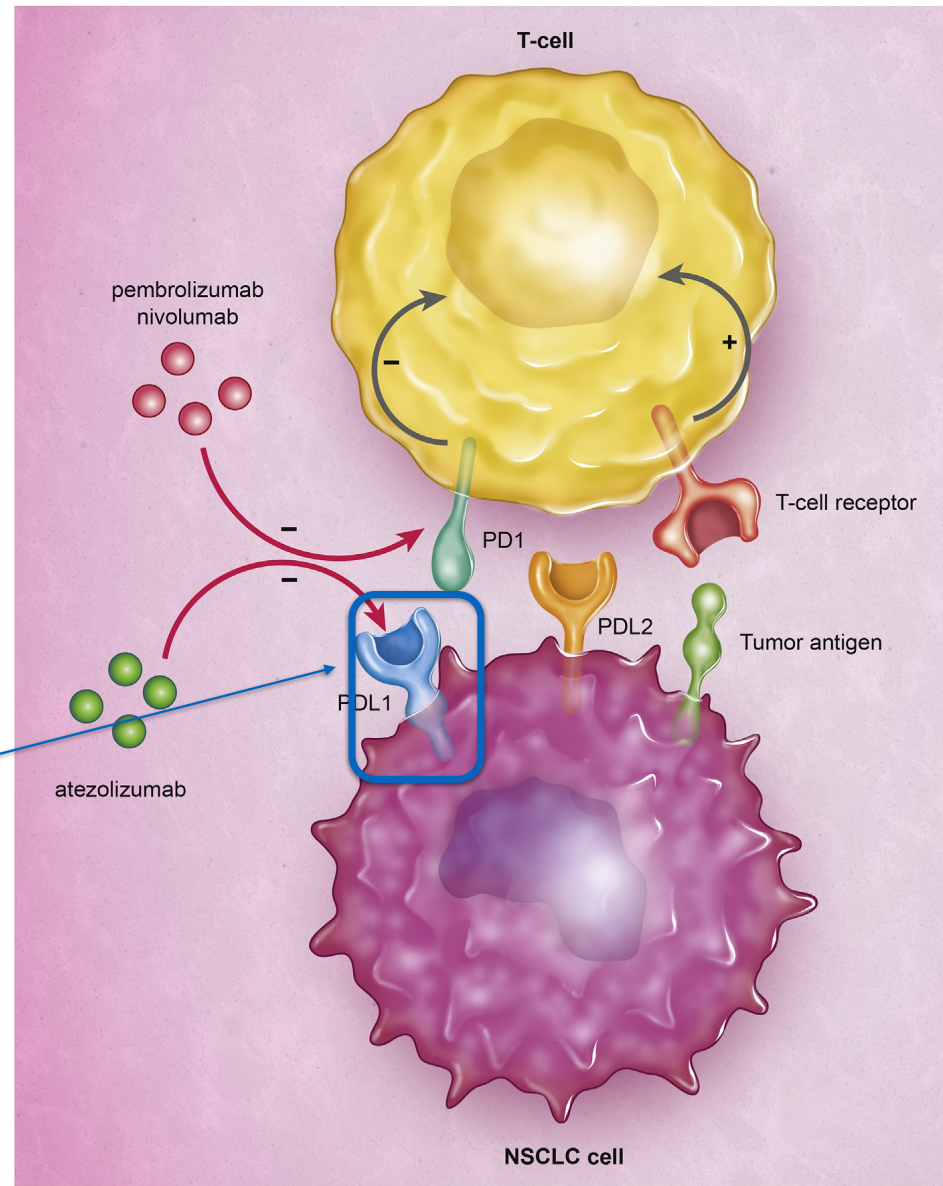


Patient selection in lung cancer: Evolution over time





Predictive marker



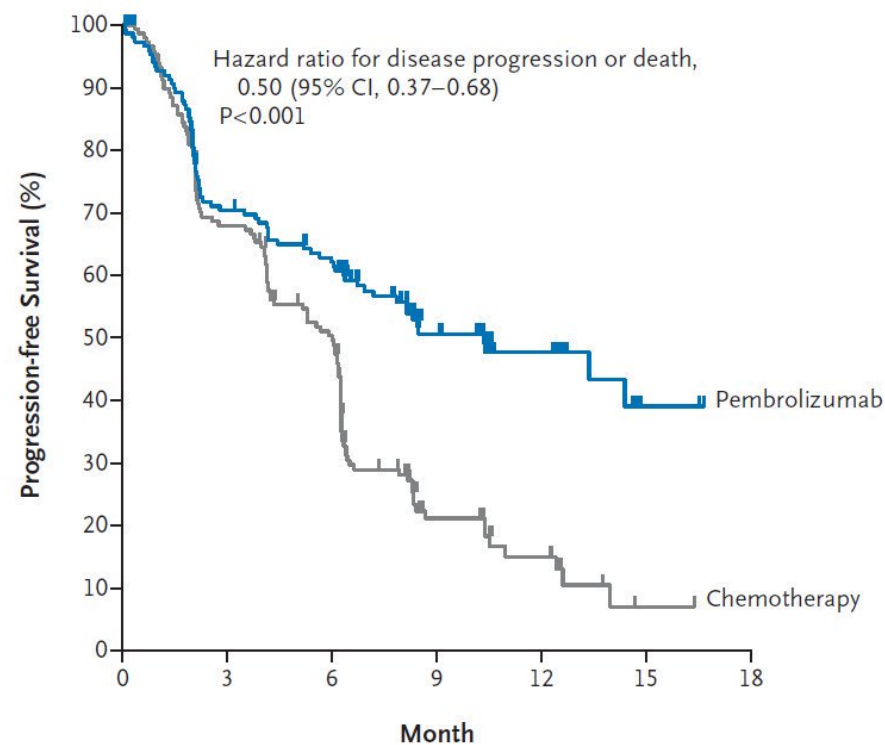


**The NEW ENGLAND
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ESTABLISHED IN 1812 NOVEMBER 10, 2016 VOL. 375 NO. 19

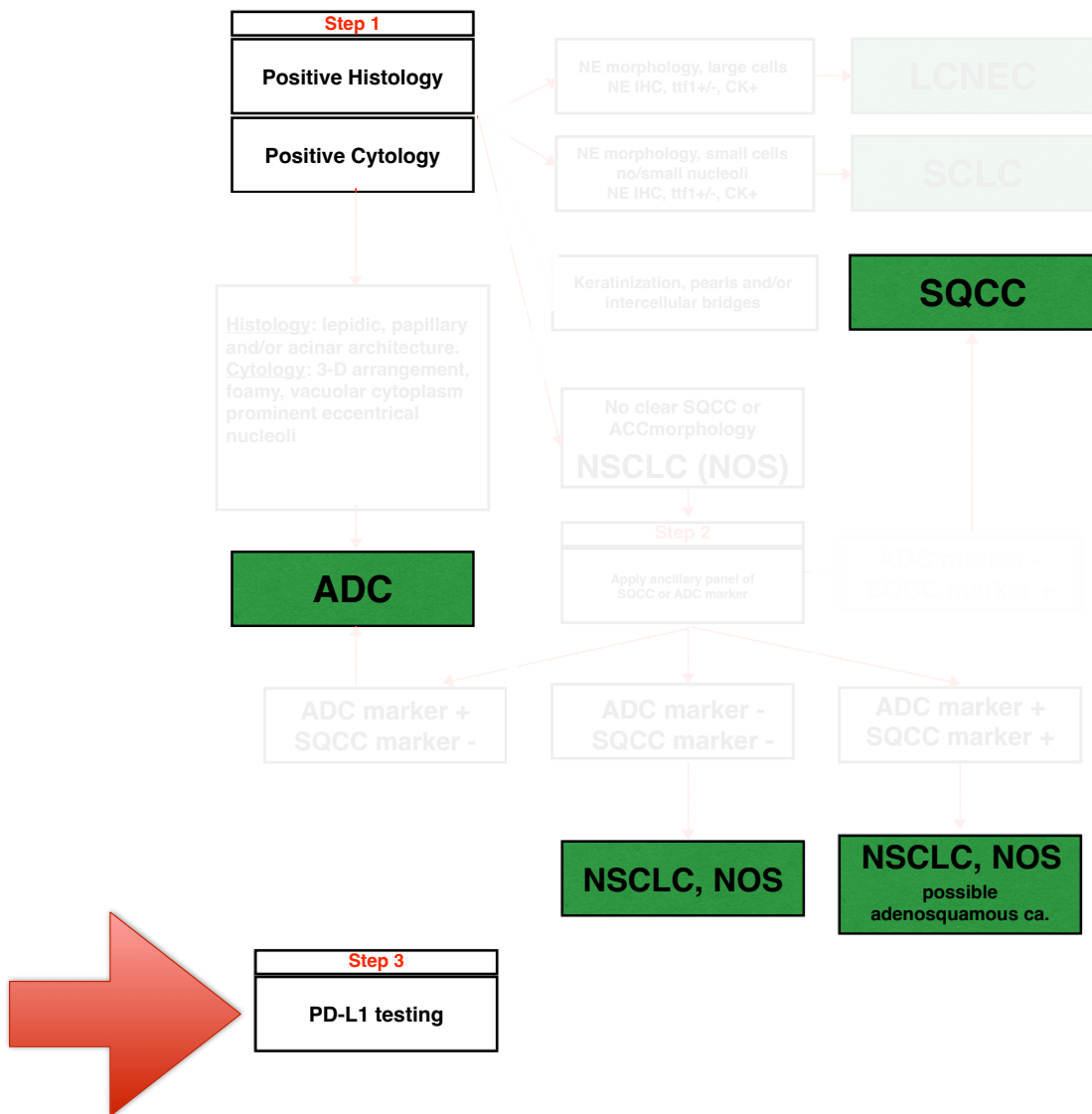
**Pembrolizumab versus Chemotherapy for PD-L1–Positive
Non–Small-Cell Lung Cancer**

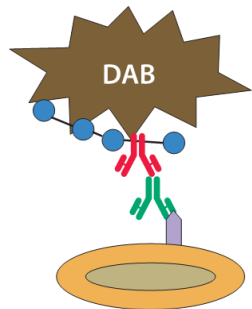
Martin Reck, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D., Andrew G. Robinson, M.D., Rina Hui, M.B., B.S., Ph.D., Tibor Csösz, M.D., Andrea Fülöp, M.D., Maya Gottfried, M.D., Nir Peled, M.D., Ph.D., Ali Tafreshi, M.D., Sinead Cuffe, M.D., Mary O'Brien, M.D., Suman Rao, M.D., Katsuyuki Hotta, M.D., Ph.D.,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



No. at Risk

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





Kromogen (farvestof)

Visualiseringssystem
(enzym)

Sekundært antistof

Primært antistof

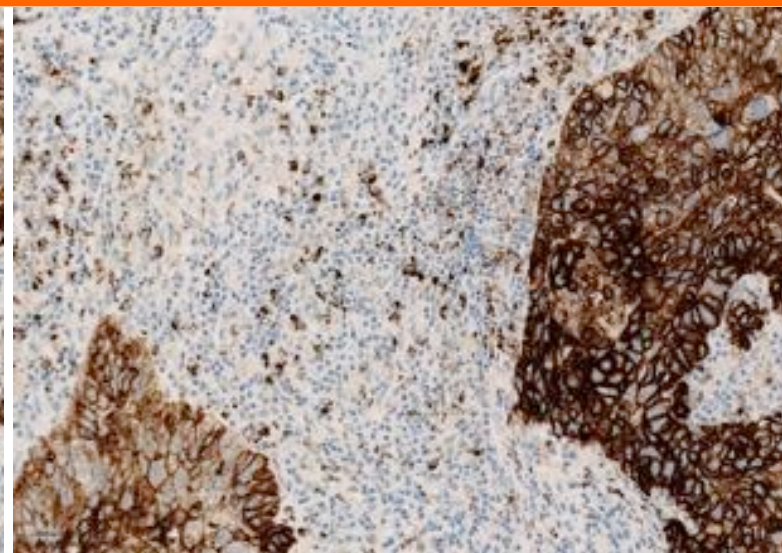
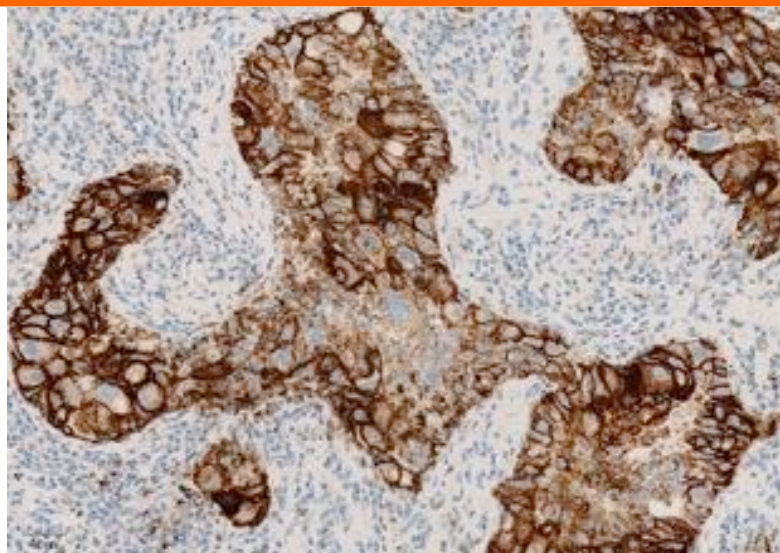
Antigen

Cellens

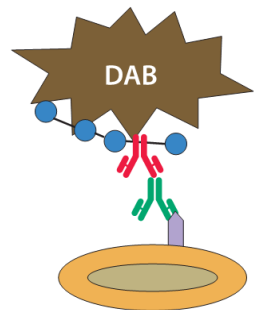
Celleke

Tumor cells (TCs)

Tumor and immune cells (TCs and ICs)



Immunohistological staining for PDL1



Kromogen (farvestof)

Visualiseringssystem
(enzym)

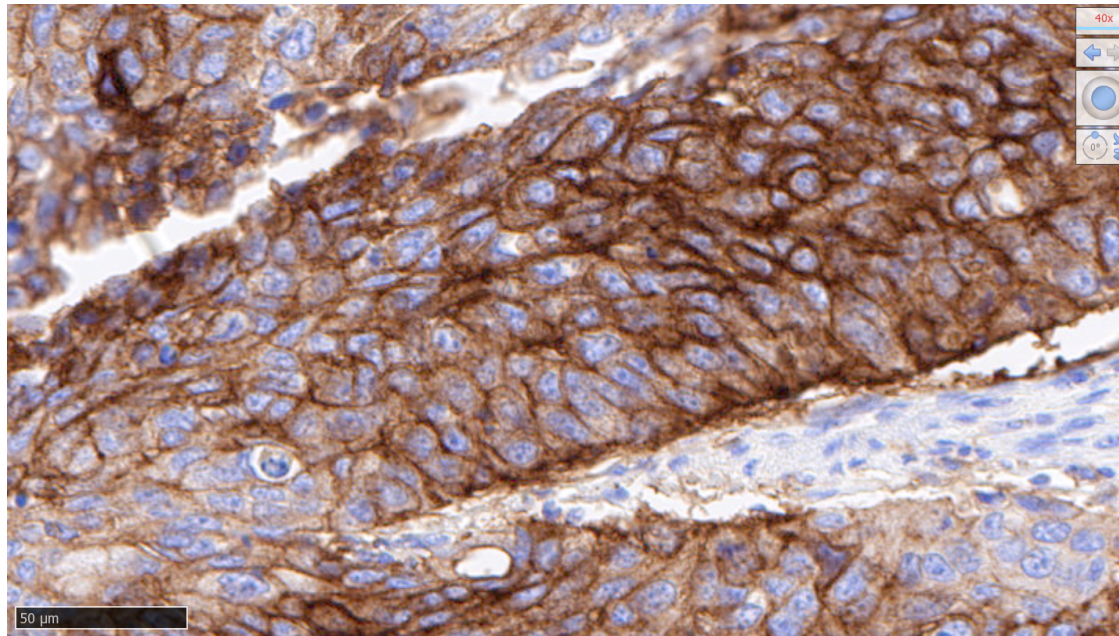
Sekundært antistof

Primært antistof

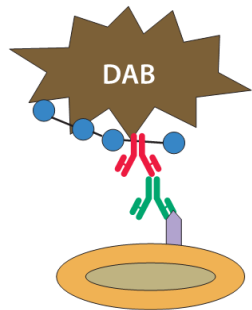
Antigen

Cellens cytoplasma

Cellekerne



Biopsy NSCLC 100% TPS



Kromogen (farvestof)

Visualiseringssystem
(enzym)

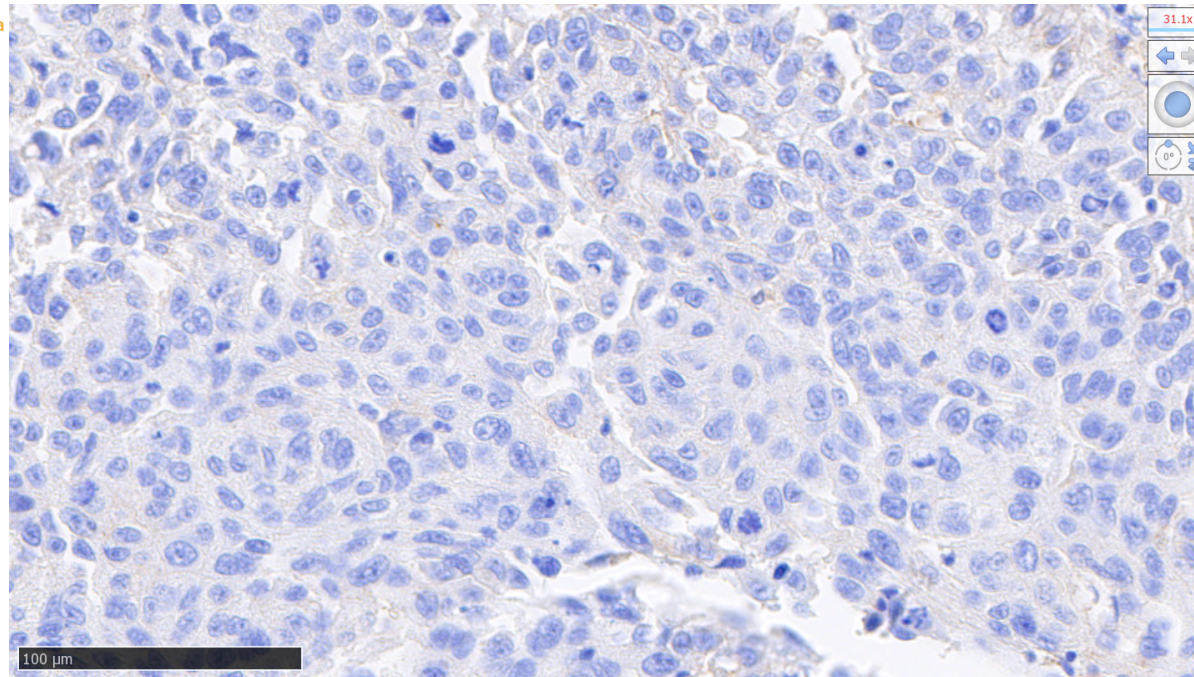
Sekundært antistof

Primært antistof

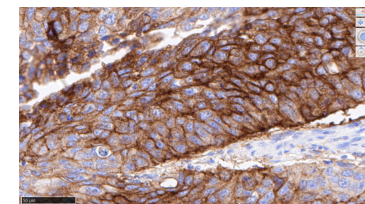
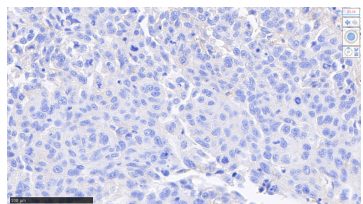
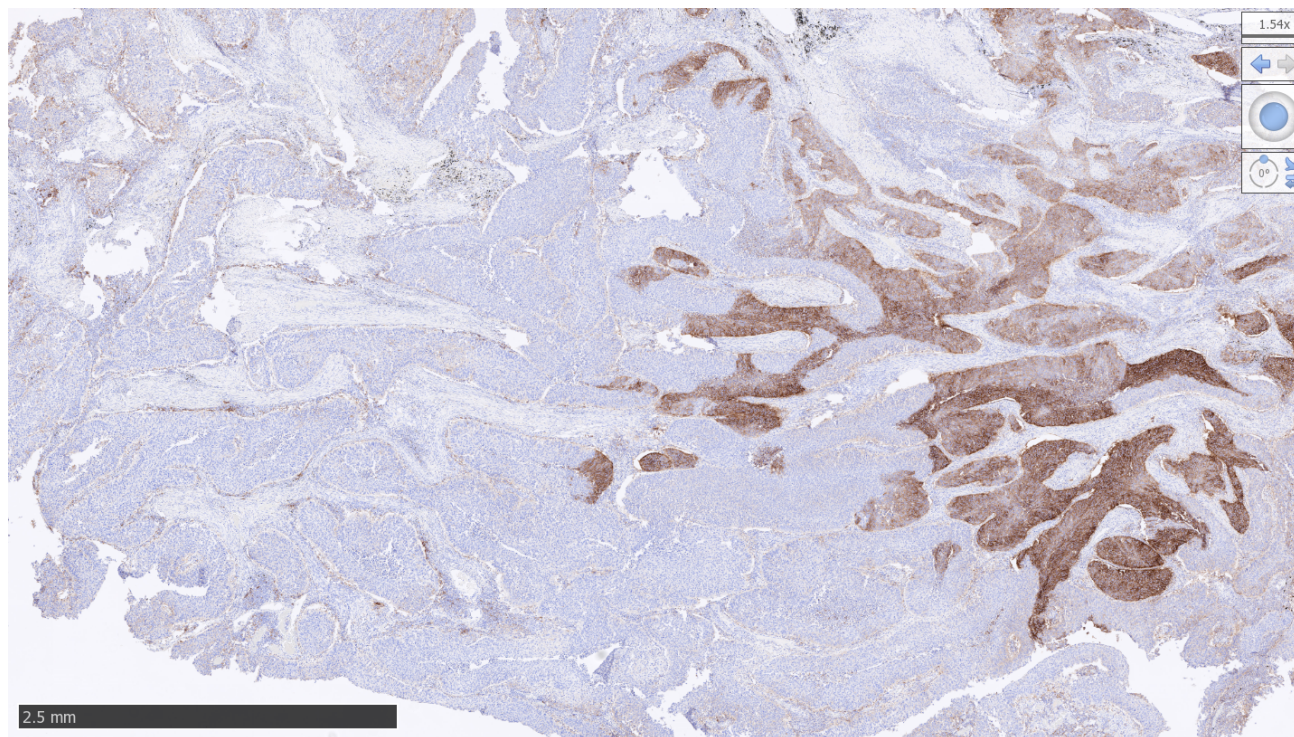
Antigen

Cellens cytoplasma

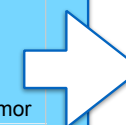
Cellekerne



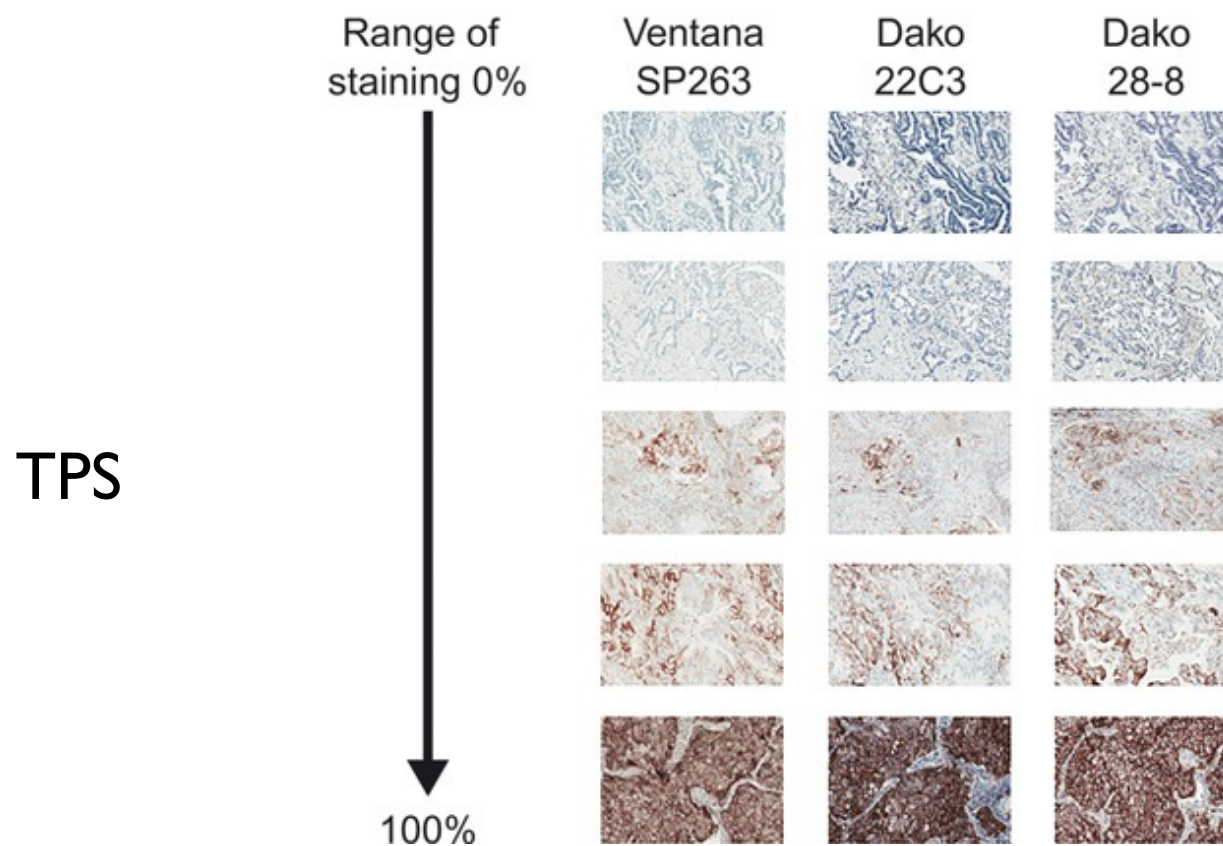
Biopsy NSCLC 0% TPS



Test	Ventana SP263 (1)	Dako 22C3 (2)	Dako 28-8 (3)	Ventana SP142 (4)
Developed as companion diagnostic assay for:	Durvalumab (AstraZeneca/MedImmune)	Pembrolizumab (Merck Sharp & Dohme)	Nivolumab (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 expression	≥25% of tumor cells (5)	≥1%; ≥50% of tumor cells (6)	≥1%; ≥5%; ≥10% of tumor cells (7)	≥50% of tumor cells or ≥10% of tumor area with immune cells (if <50% of tumor



SP142



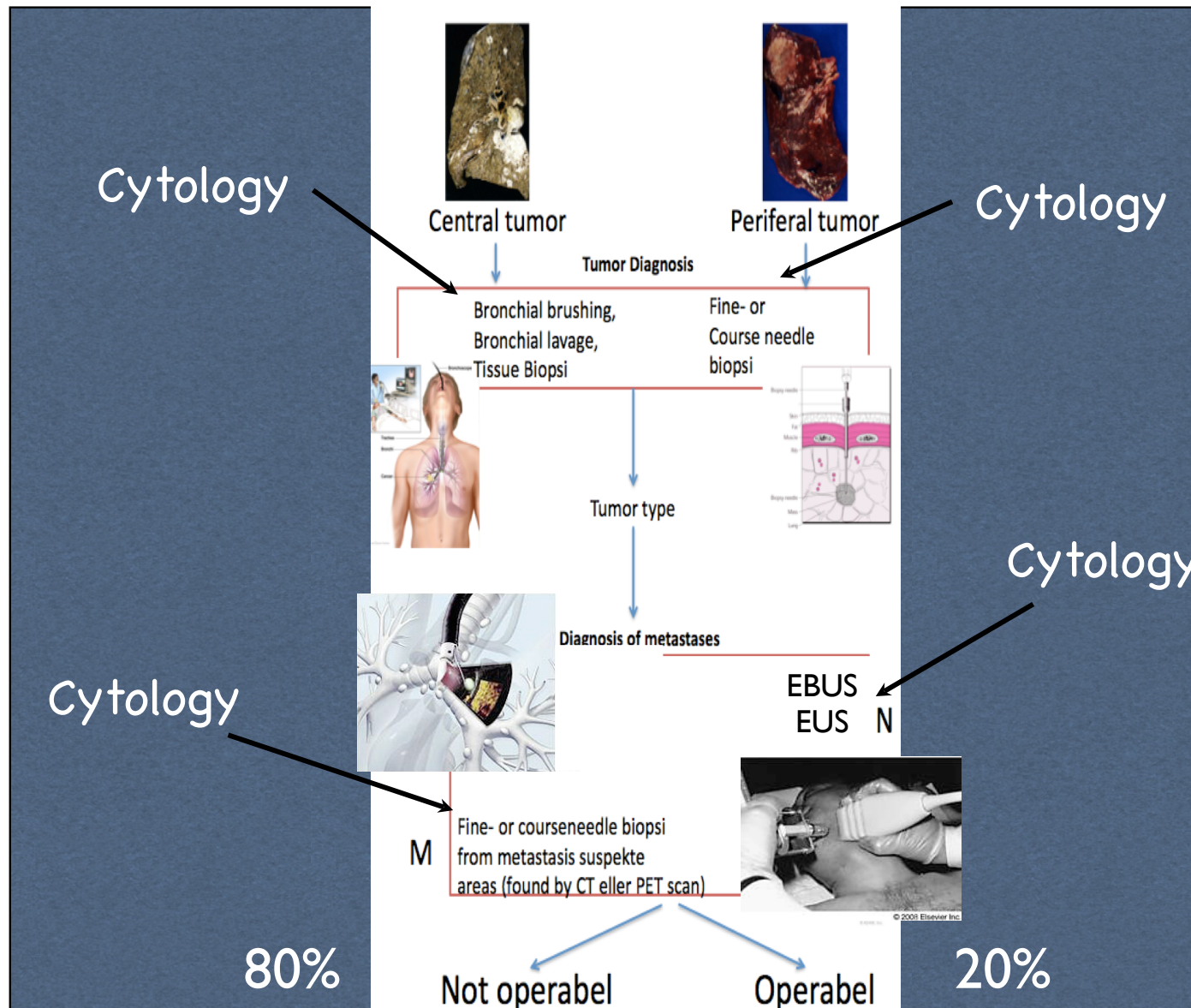
Published OnlineFirst January 10, 2017; DOI: 10.1158/1078-0432.CCR-16-2375

Cancer Therapy: Clinical

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

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

Clinical
Cancer
Research



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

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

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

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

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

Values are represented as percent, 95% CI.

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

Table 2. **Assessment marks for IHC assays and antibodies run C13, PD-L1 TPS/CPS (KEYTRUDA®)**

CE-IVD / FDA approved PD-L1 assays		n	Vendor	Optimal	Good	Borderline	Poor	Suff. ¹	OR ²
rmAb clone SP263, 741-4905 (VRPS) ³		41	Ventana/Roche	5	33	3	-	93%	12%
rmAb clone SP263, 741-4905 (LPMS) ⁴		2	Ventana/Roche	-	1	1	-	-	-
rmAb clone SP263, 740-4907 (VRPS) ³		12	Ventana/Roche	3	9	-	-	100%	25%
mAb clone 22C3 pharmDX, SK006 (VRPS) ³		19	Dako/Agilent	14	4	-	1	95%	74%
mAb clone 22C3 pharmDX, SK006 (LPMS) ⁴		20	Dako/Agilent	13	5	2	-	90%	65%
mAb clone 22C3 pharmDX, GE006 (VRPS) ³		29	Dako/Agilent	23	6	-	-	100%	79%
mAb clone 22C3 pharmDX, GE006 (LPMS) ⁴		18	Dako/Agilent	12	4	2	-	89%	67%
rmAb clone 28-8 pharmDX, SK005 (VRPS) ³		3	Dako/Agilent	2	1	-	-	-	-
Antibodies⁵ for laboratory developed PD-L1 assays, concentrated antibodies		n	Vendor	Optimal	Good	Borderline	Poor	Suff. ¹	OR ²
mAb clone 22C3		44	Dako/Agilent	18	19	7	-	84%	41%
rmAb CAL10		4	Zytomed Systems 1 Biocare Medical	2	2	-	1	80%	40%
rmAb clone E1L3N		4	Cell Signaling	1	3	-	-	-	-
rmAb clone QR1		2	Quartett	2	-	-	-	-	-
rmAb clone 28-8		1	Dako/Agilent	-	1	-	-	-	-
rmAb clone ZR3		1	Zeta Corporation	-	1	-	-	-	-
rmAb clone SP142		1	Abcam	1	-	-	-	-	-
Ready-To-Use antibodies⁶		n	Vendor	Optimal	Good	Borderline	Poor	Suff. ¹	OR ²
rmAb clone SP263, 790-4905⁶ (VRPS) ³		13	Ventana/Roche	-	11	2	-	85%	-
rmAb clone SP263, 790-4905⁶ (LPMS) ⁴		16	Ventana/Roche	1	15	-	-	100%	6%
rmAb clone 73-10 PA0832		6	Leica Biosystems	5	1	-	-	100%	83%
rmAb MX070C MAB-0854		2	Fuzhou Maixin	1	1	-	-	-	-
mAb clone C9C9 CPM-0278		1	Celnovte	-	1	-	-	-	-
rmAb clone AC37 AD80167		1	Abcarta	1	-	-	-	-	-
rmAb clone RM320 8263-C010		1	Sakura Finetek	1	-	-	-	-	-
rmAb clone BP6099 I12052E		1	Biolynx	1	-	-	-	-	-
Total		243		106	118	17	2		
Proportion				44%	48%	7%	1%	92%	

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

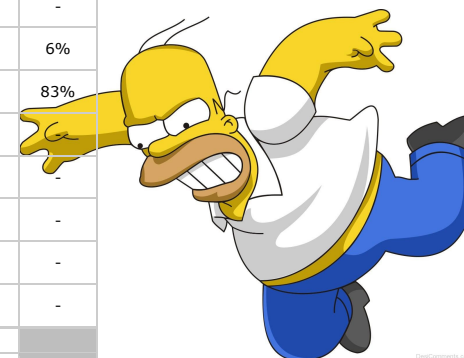
2) Proportion of optimal results.

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

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

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

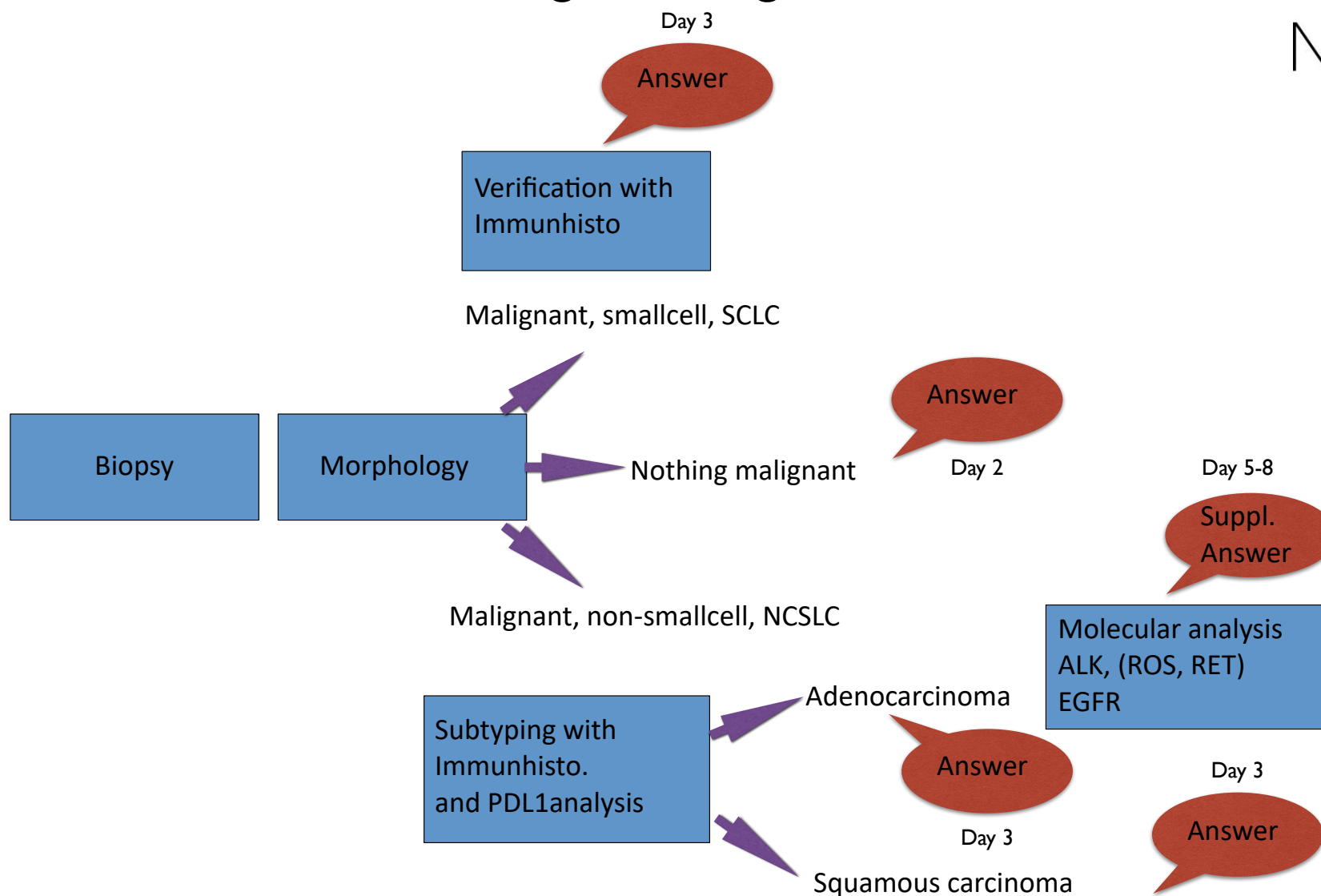
6) Ready-To-Use antibodies without predictive claim.



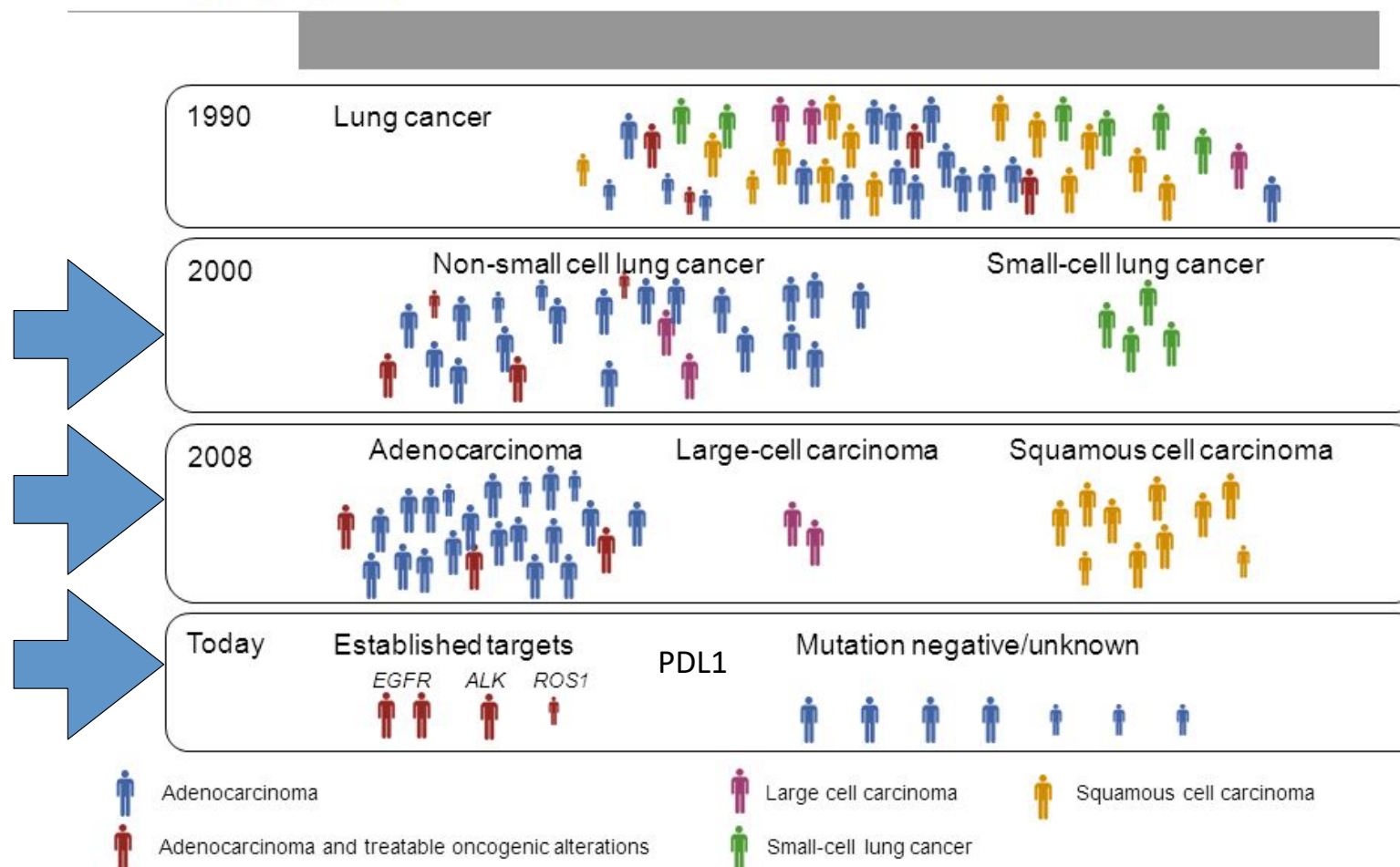
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The Diagnostic algorithm

The Diagnostic algorithm



Patient selection in lung cancer: Evolution over time



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

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Source: Compiled by Neeta Somaiah and George Simon