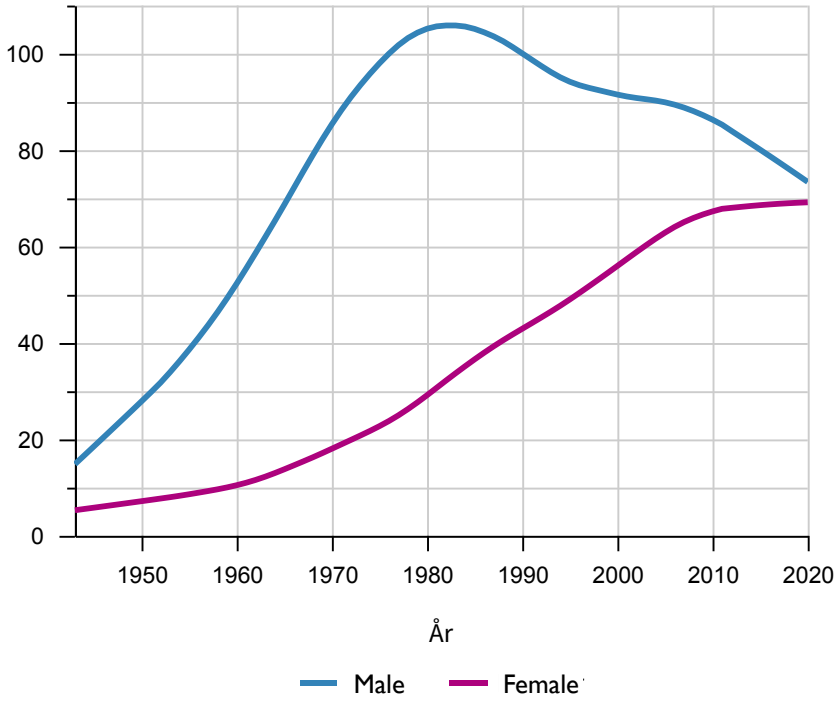
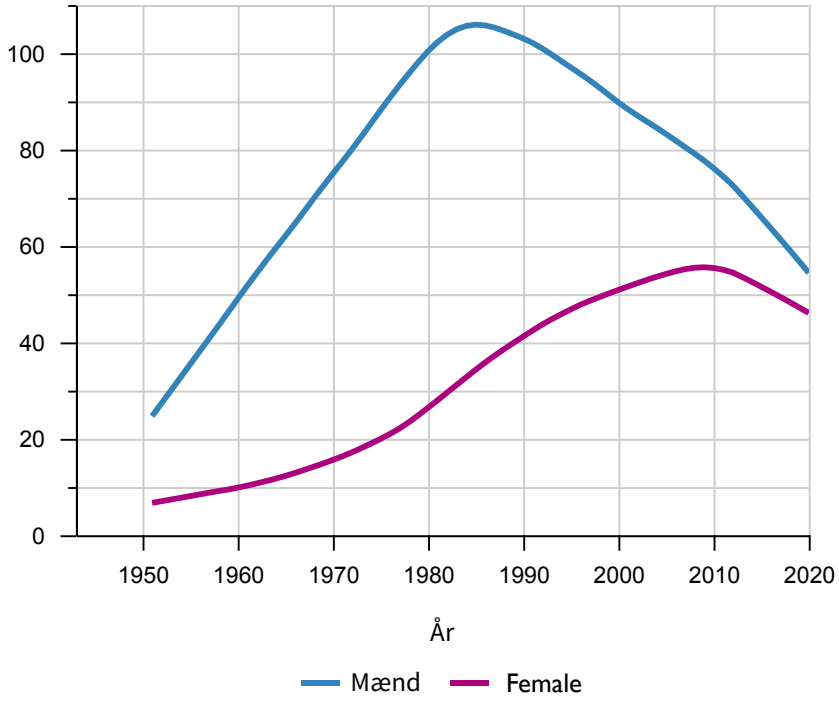
# Lung cancer Age's standardized

## Incidence new cases/100.000



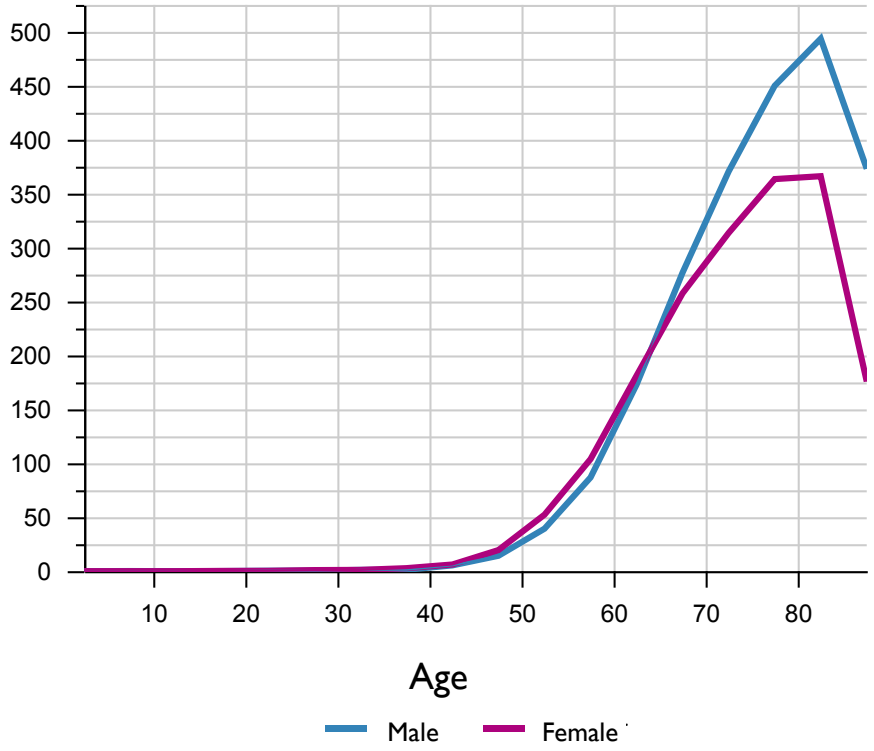

## Mortality Death/100.000



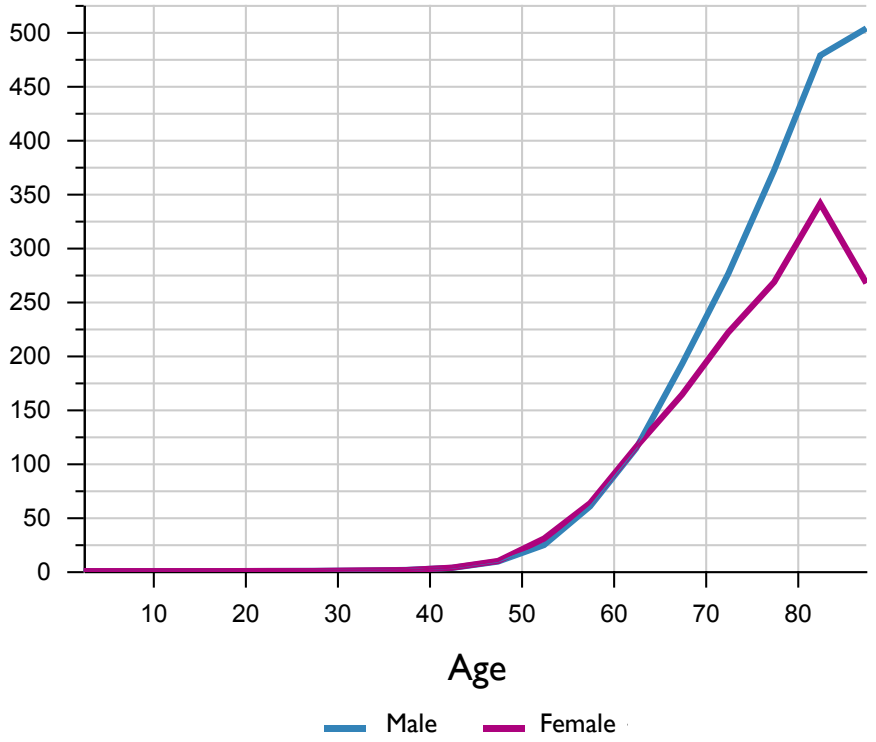

NORDCAN
Association of the Nordic Cancer Registries

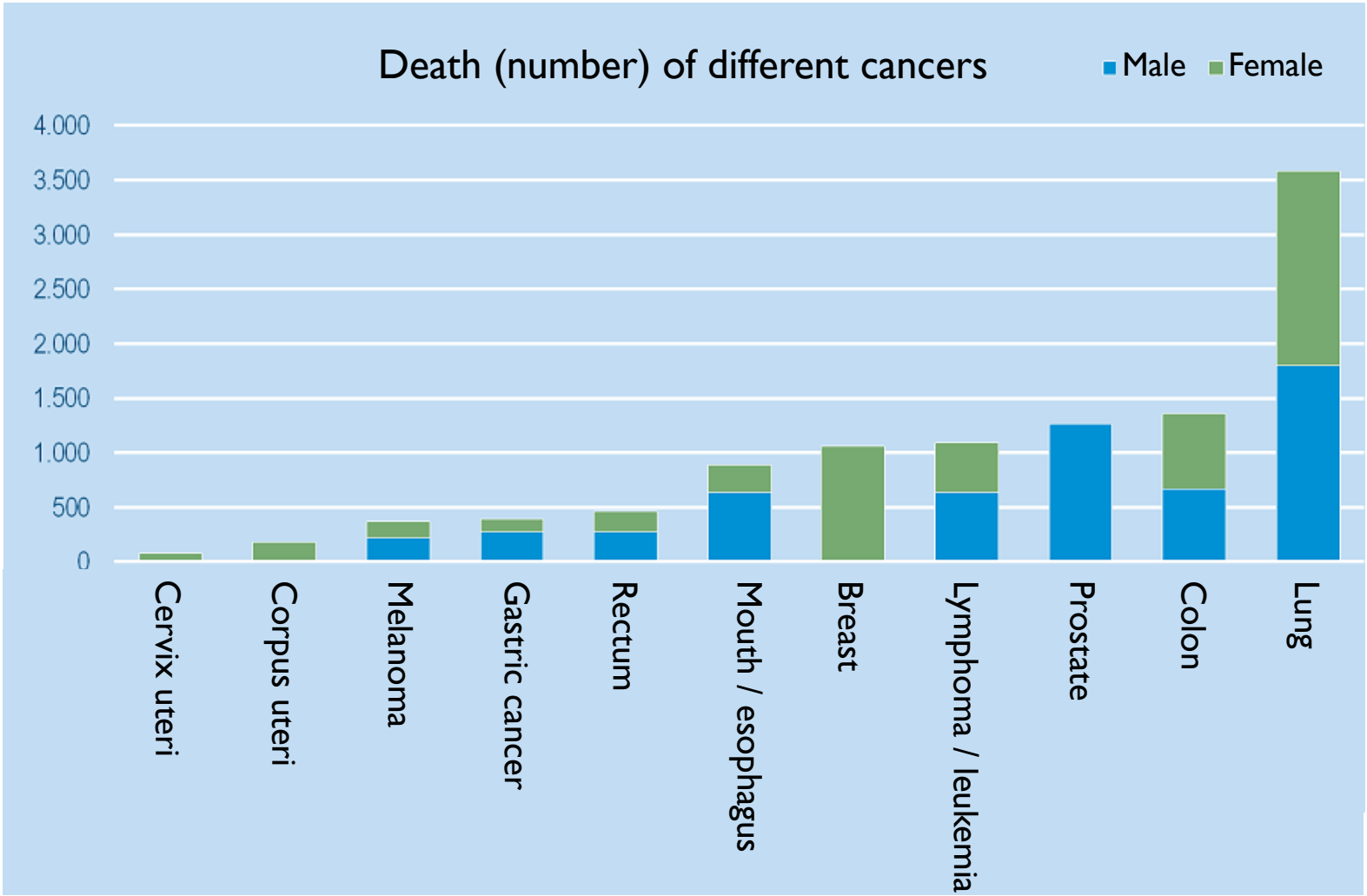
# Lung cancer

New cases/100.000 / age interval

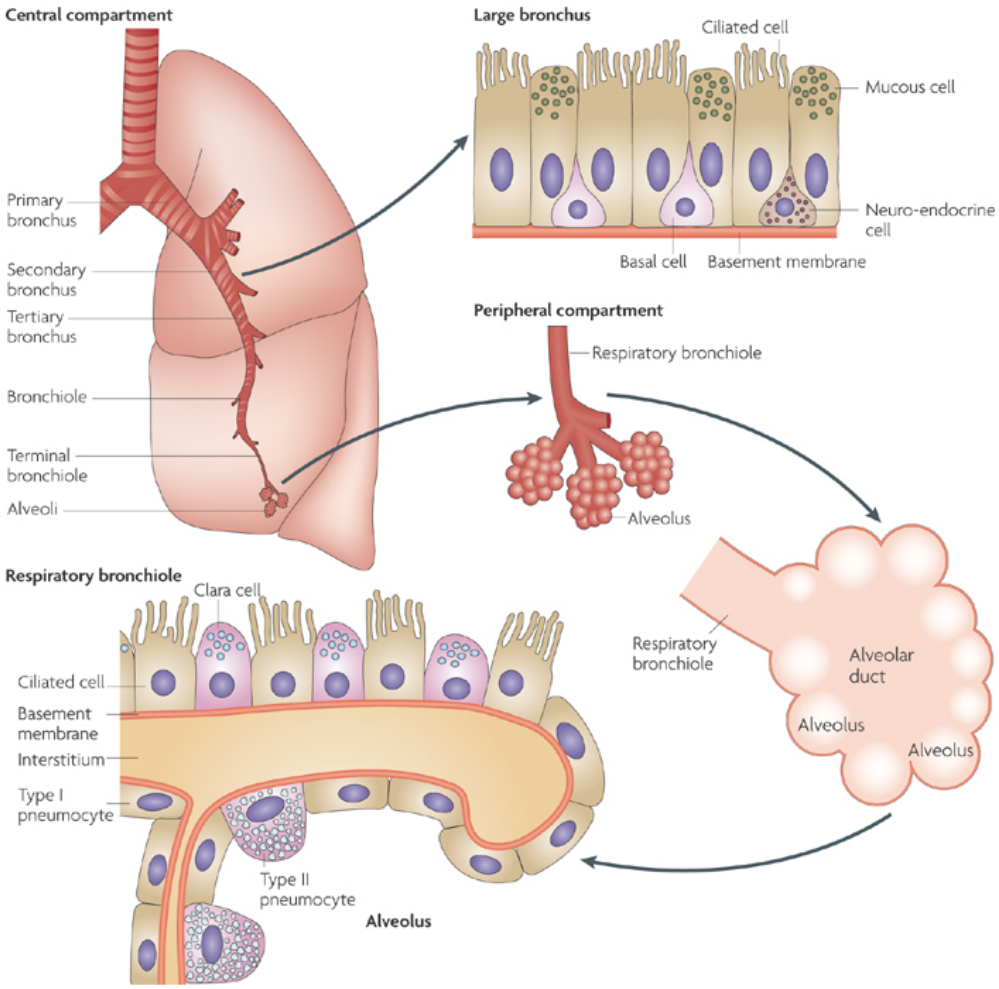



Deaths/100.00 / age interval




Death (number) of different cancers
Male
Female
4.000
3.500
3.000
2.500
2.000
1.500
1.000
500
0
Cervix uteri
Corpus uteri
Melanoma
Gastric cancer
Rectum
Mouth / esophagus
Breast
Lymphoma / leukemia
Prostate
Colon
Lung

# Lung Carcinoma




Lung carcinoma derives from stem cells in the lung epithelium

malignant epithelial tumors (carcinomas)

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

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

(*Continued*)

**TABLE 1.** (*Continued*)

| Histologic Type and Subtypes | ICDO Code |
|---|---|
| Papillomas | |
| Squamous cell papilloma | 8052/0 |
| Exophytic | 8052/0 |
| Inverted | 8053/0 |
| Glandular papilloma | 8260/0 |
| Mixed squamous and glandular papilloma | 8560/0 |
| Adenomas | |
| Sclerosing pneumocytoma[e] | 8832/0 |
| Alveolar adenoma | 8251/0 |
| Papillary adenoma | 8260/0 |
| Mucinous cystadenoma | 8470/0 |
| Mucous gland adenoma | 8480/0 |
| **Mesenchymal tumors** | |
| Pulmonary hamartoma | 8992/0[d] |
| Chondroma | 9220/0 |
| 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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[e]New terms changed or entities added since 2004 WHO Classification.[3]

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

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

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| Pleomorphic adenoma | 8940/0 |
| Papillomas | |
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| Inverted | 8053/0 |
| Glandular papilloma | 8260/0 |
| Mixed squamous and glandular papilloma | 8560/0 |
| Adenomas | |
| Sclerosing pneumocytoma[e] | 8832/0 |
| Alveolar adenoma | 8251/0 |
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Carcinoids 1 - 2%

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(*Continued*)

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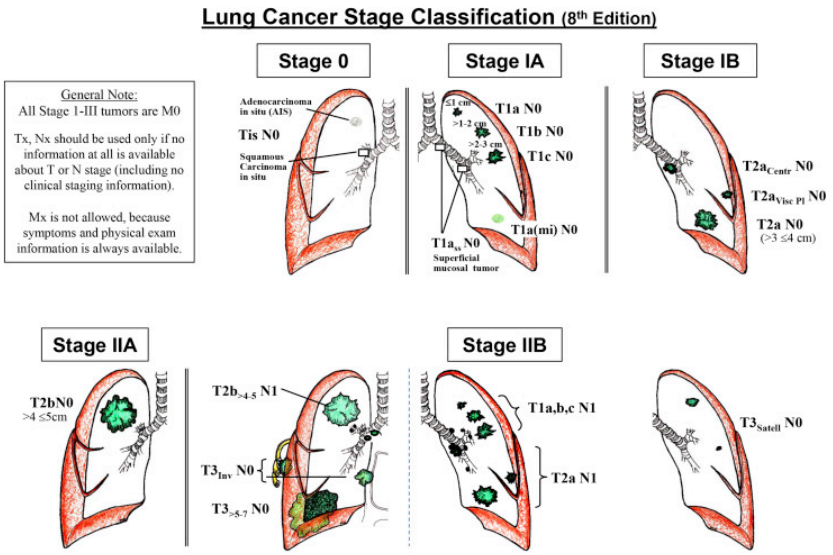
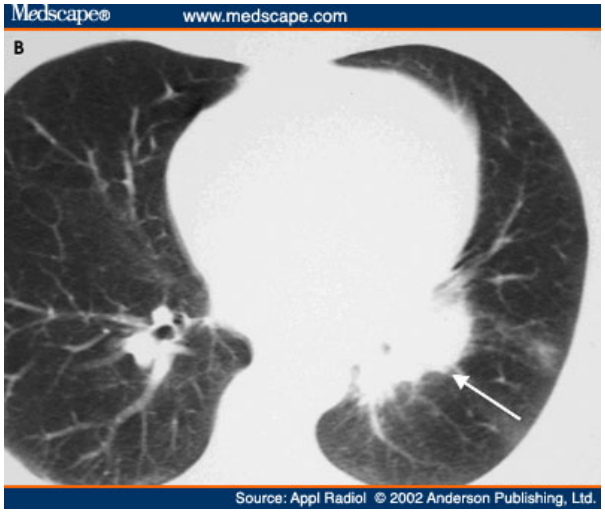
# Diagnostic sampling

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

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

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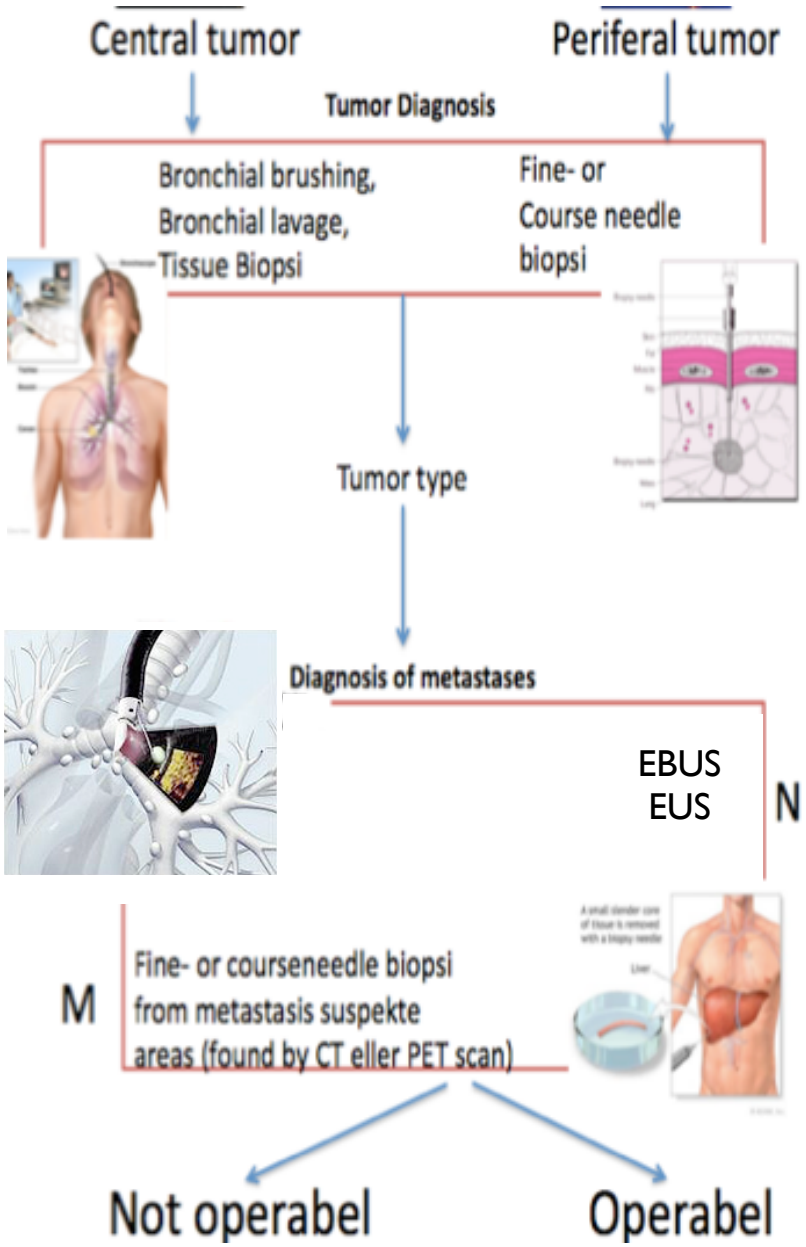
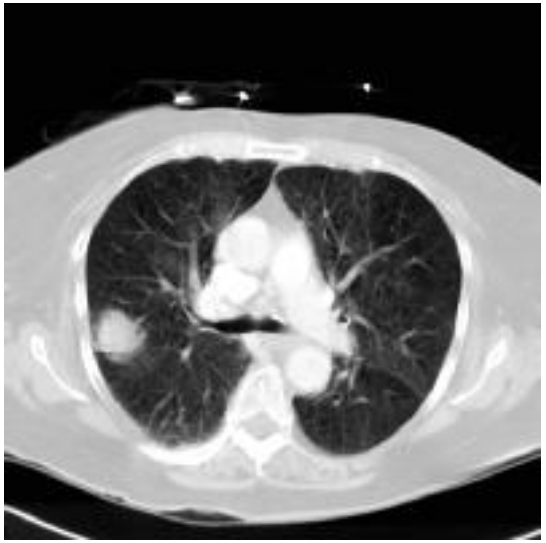
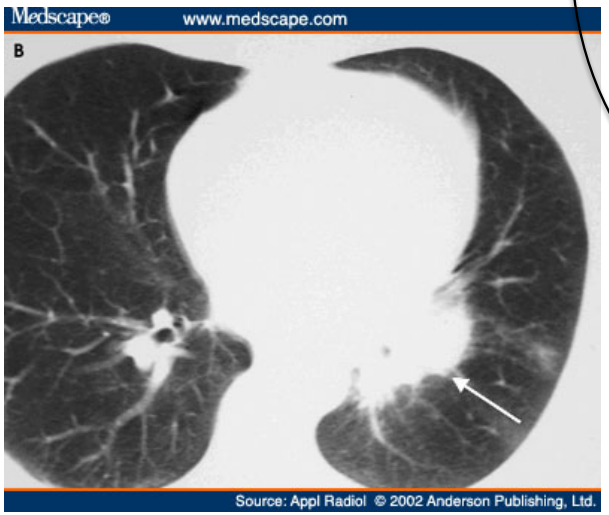

Central tumor
Periferal tumor
Tumor Diagnosis
Bronchial brushing,
Bronchial lavage,
Tissue Biopsi
Fine- or
Course needle
biopsi
Tumor type
Diagnosis of metastases
EBUS
EUS
N
M
Fine- or courseneedle biopsi
from metastasis suspekte
areas (found by CT eller PET scan)
Not operabel
Operabel

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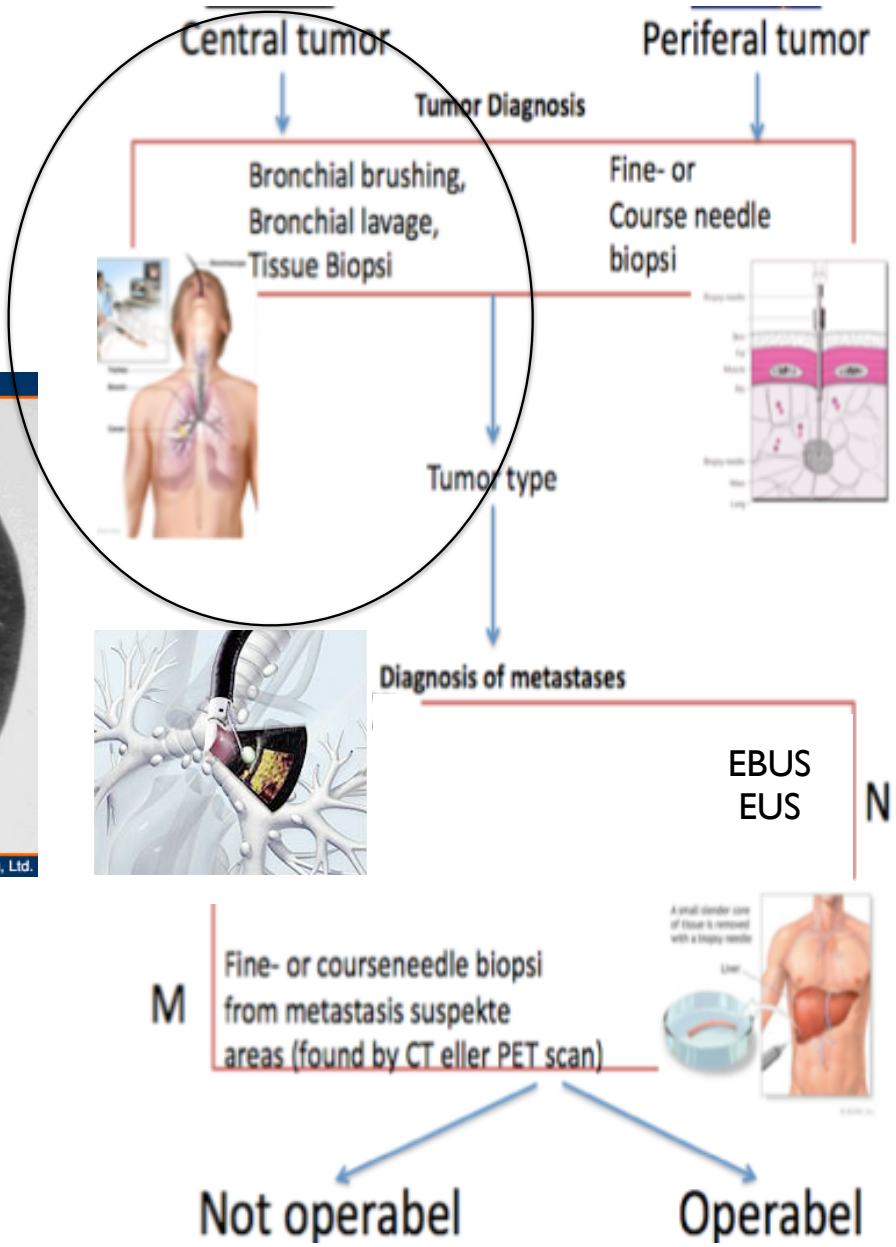
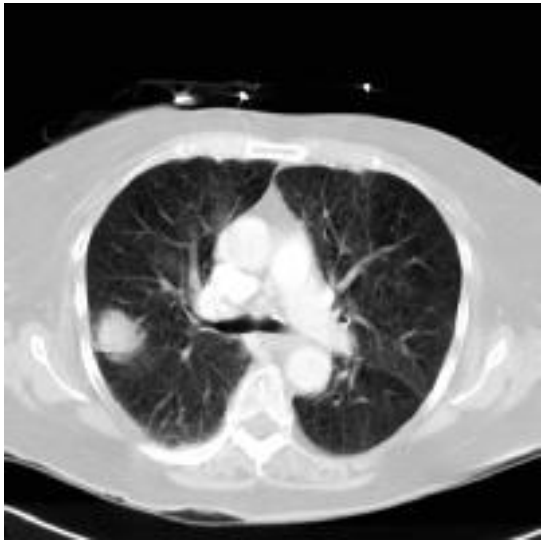
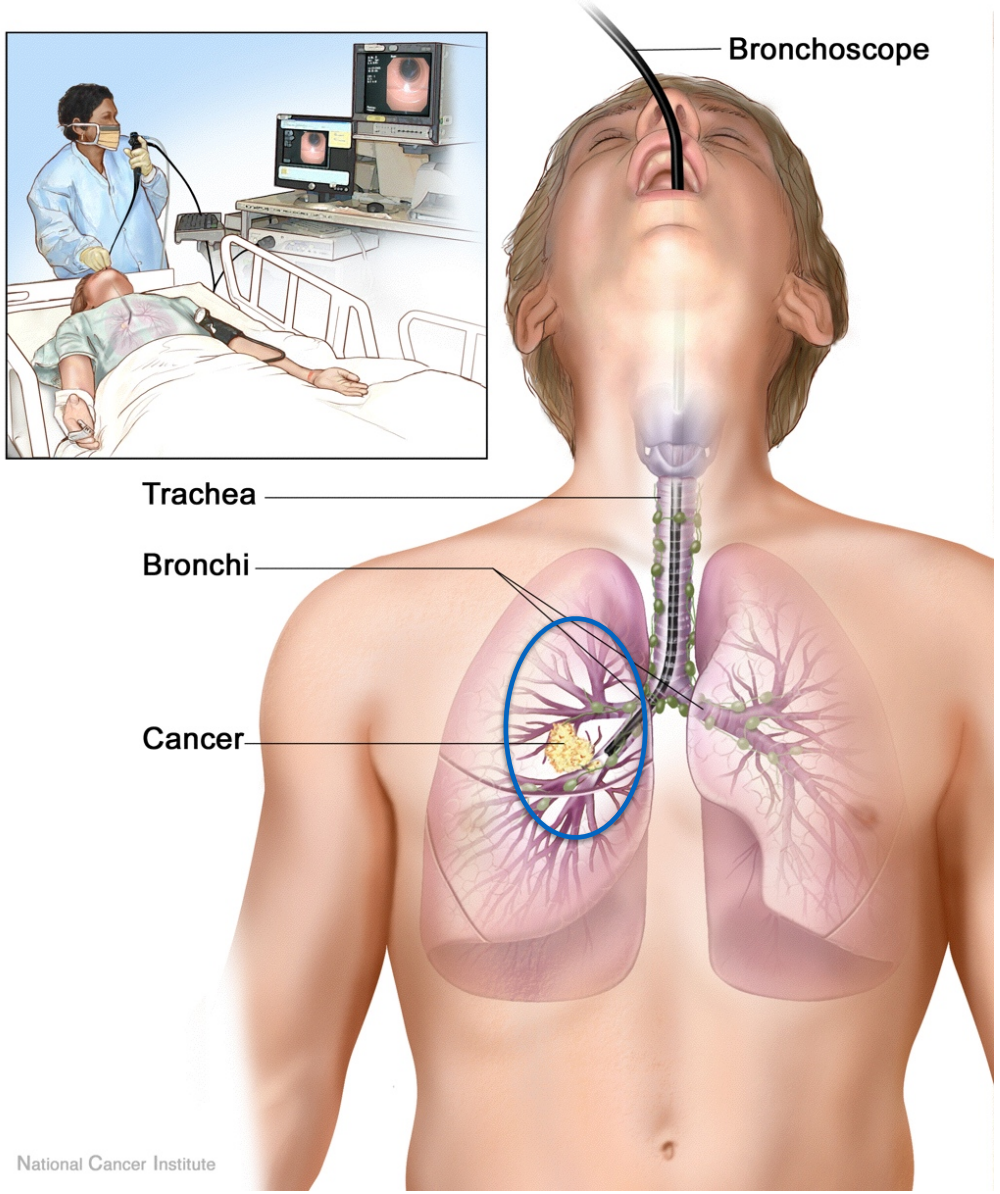

Central tumor
Periferal tumor
Tumor Diagnosis
Bronchial brushing,
Bronchial lavage,
Tissue Biopsi
Fine- or
Course needle
biopsi
Tumor type
Diagnosis of metastases
EBUS
EUS
N
M
Fine- or courseneedle biopsi
from metastasis suspekte
areas (found by CT eller PET scan)
Not operabel
Operabel





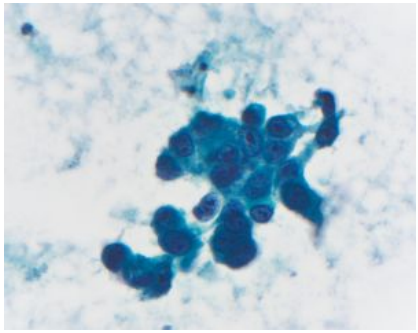

*Bronkialwash*

*Brushbiopsy*

*EBUS* *Endobronchial Ultrasound Scanning*

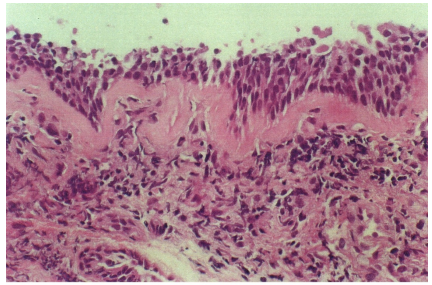
*EUS* *Esophagal Ultraspund Scanning*

} TBNA

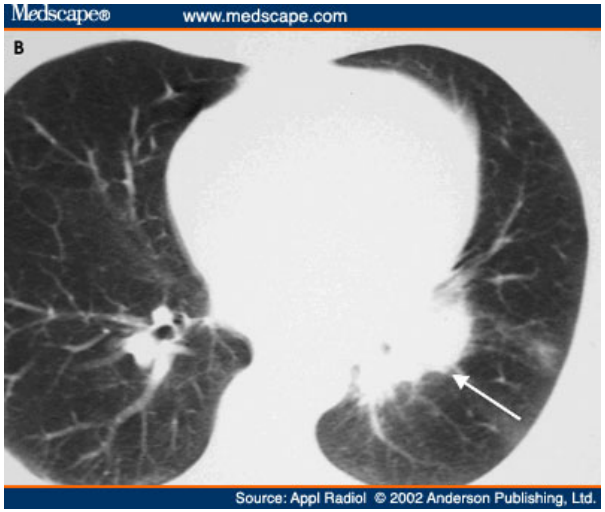


Cytology

forceps biopsy



Histology



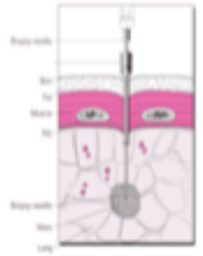

Central tumor

Periferal tumor

Tumor Diagnosis

Bronchial brushing,
Bronchial lavage,
Tissue Biopsi

Fine- or
Course needle
biopsi



Tumor type

Diagnosis of metastases

EBUS
EUS

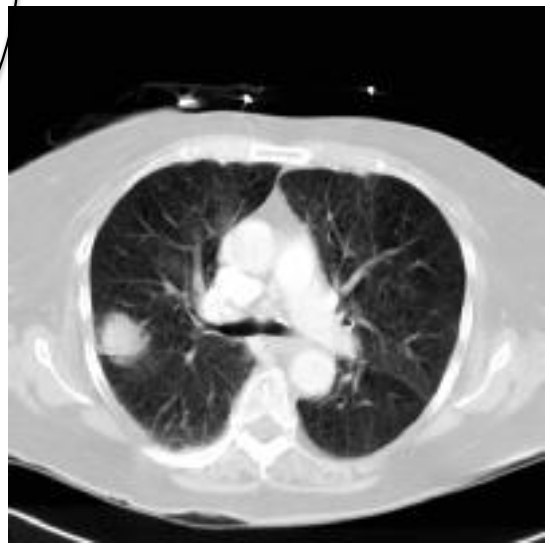
N

M

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

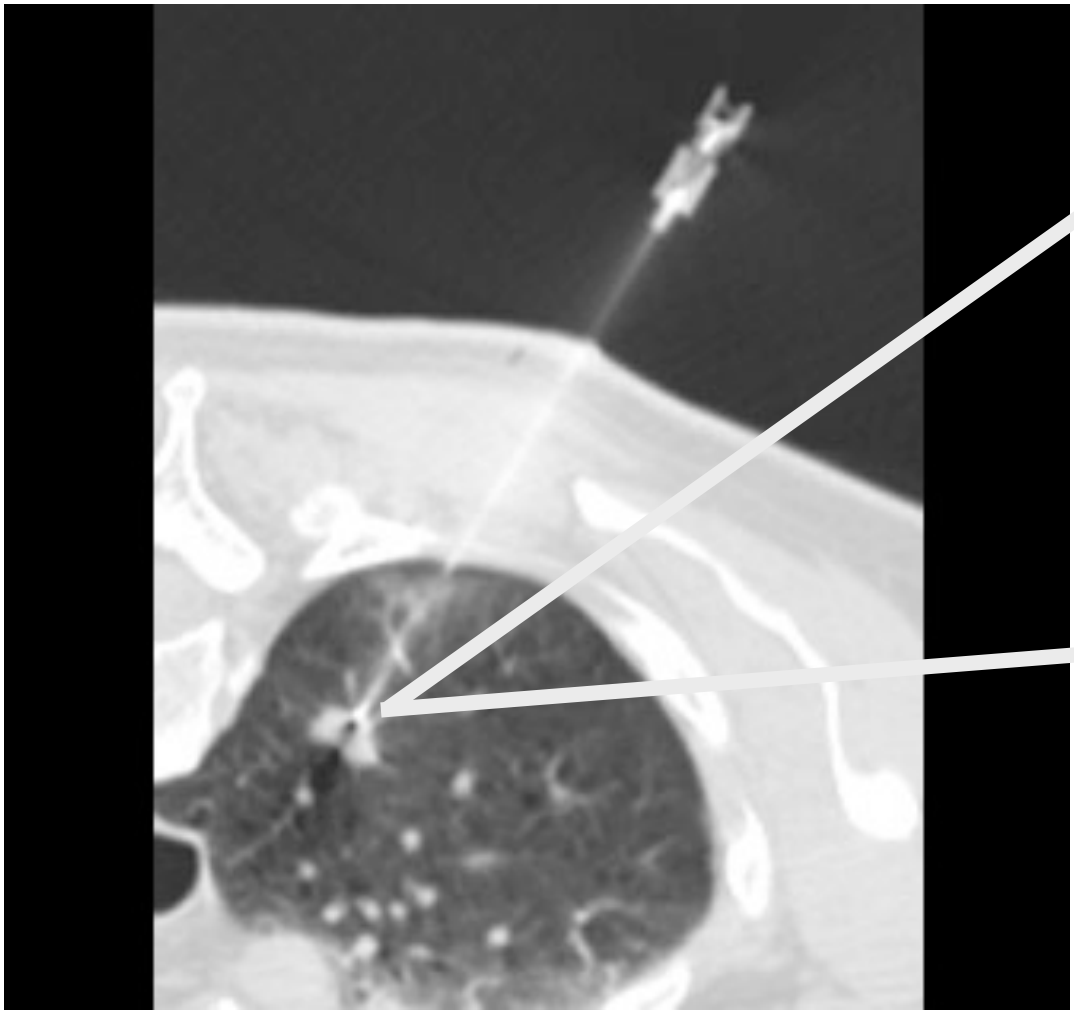
Not operabel

Operabel

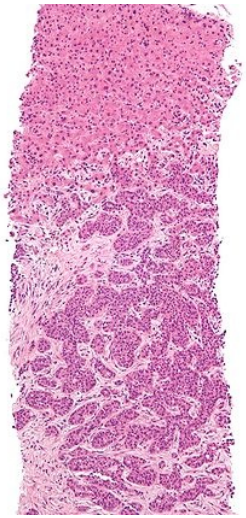


NordiQC

CT guided needle biopsy

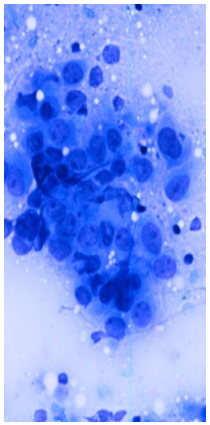


Coarse needle

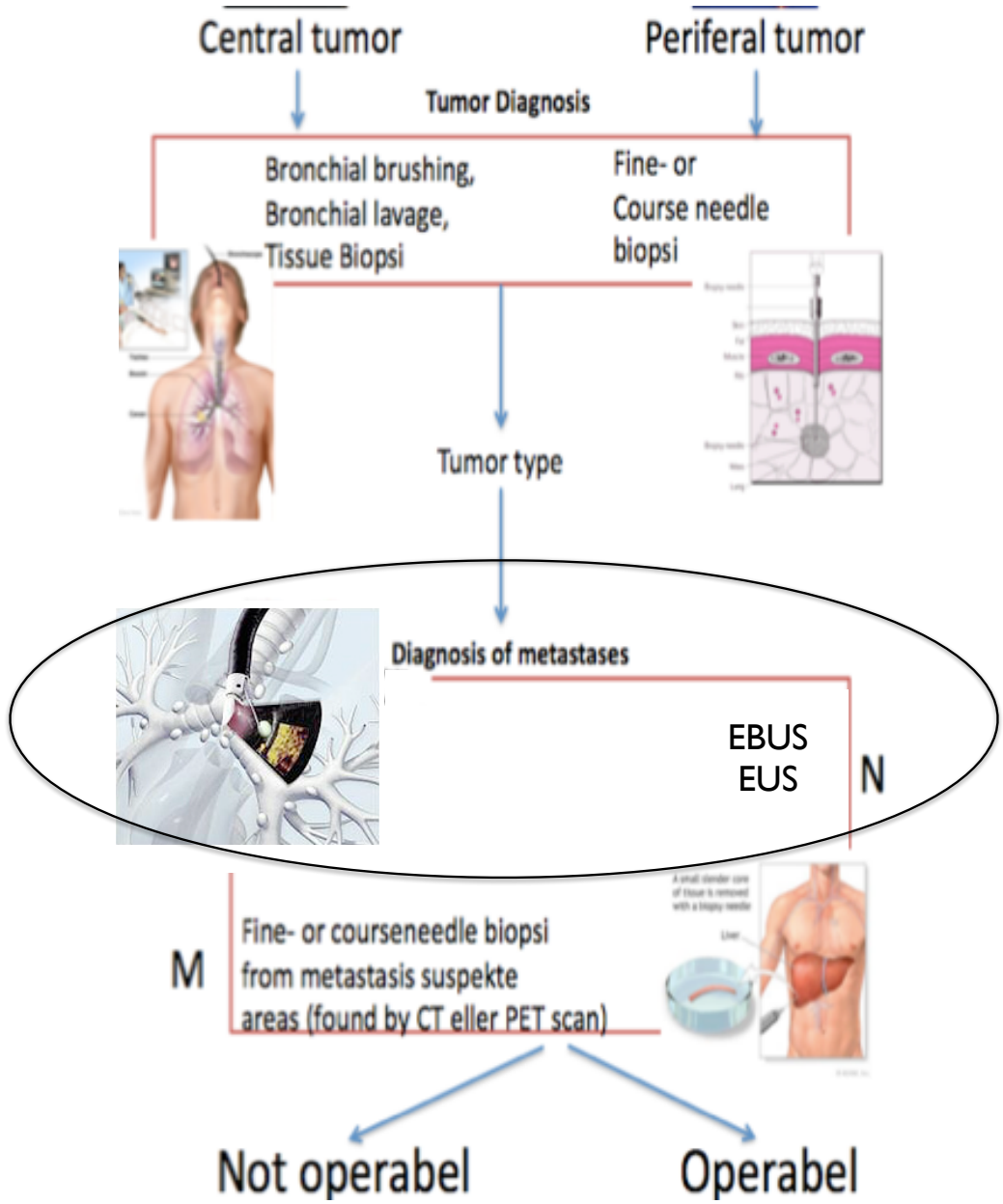


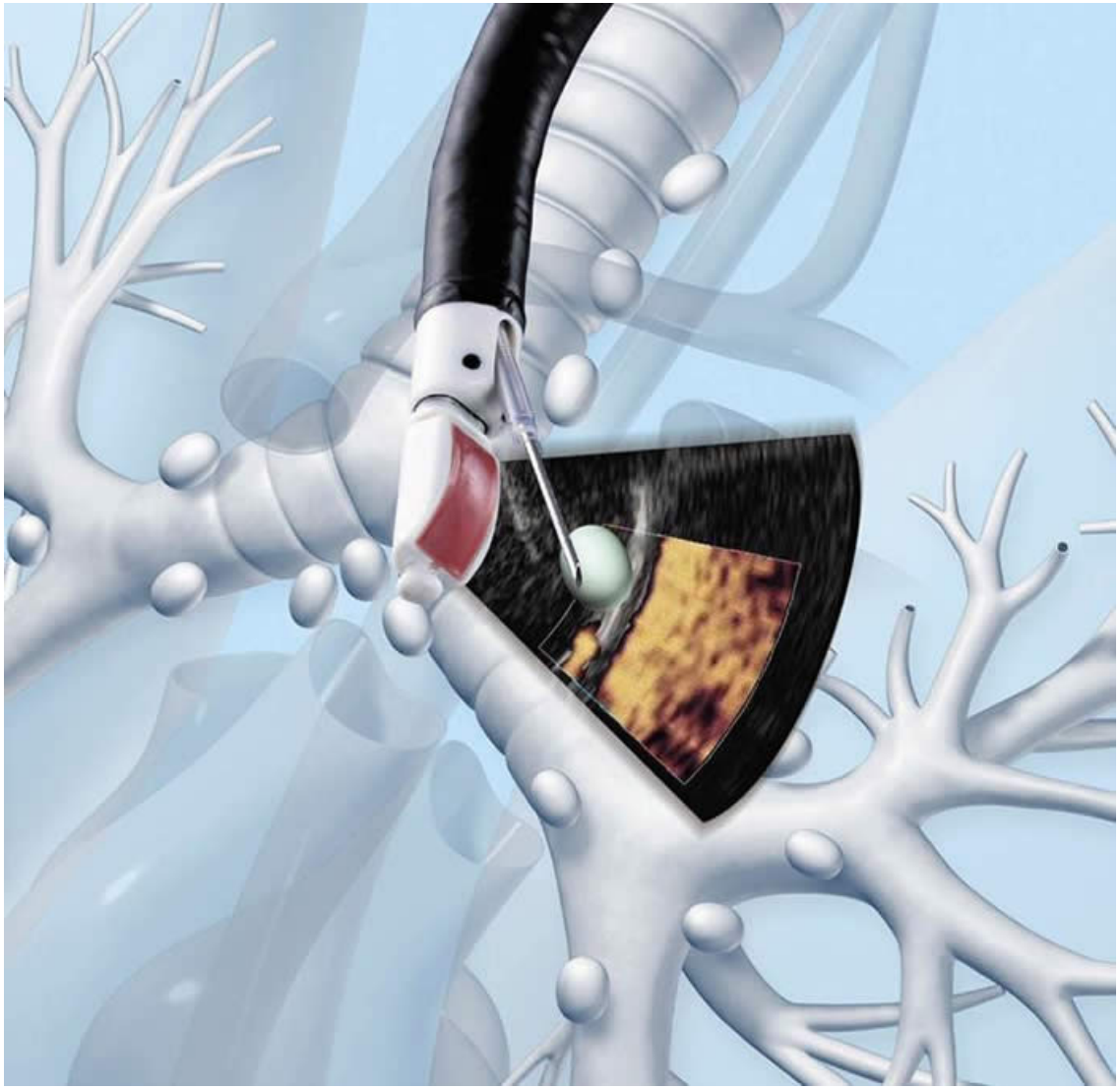
Histology

Fine needle



Cytology


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



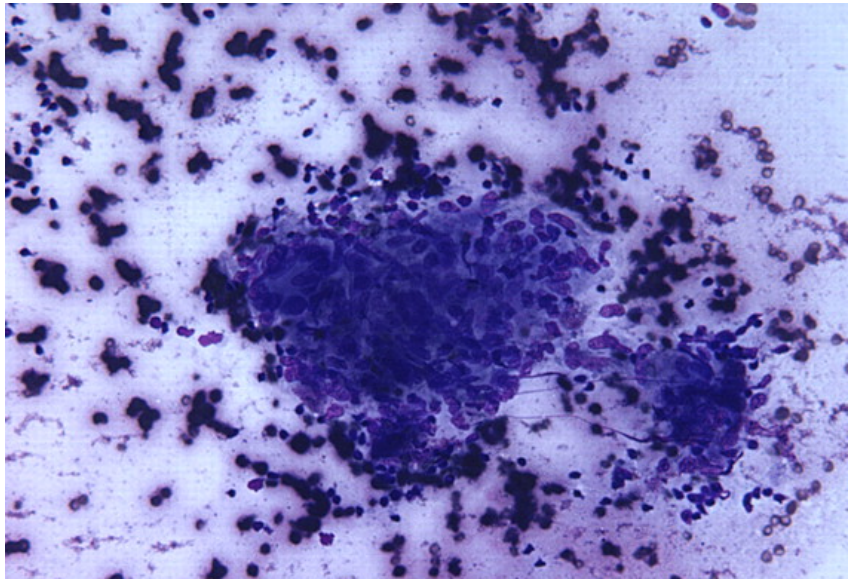
NordiQC

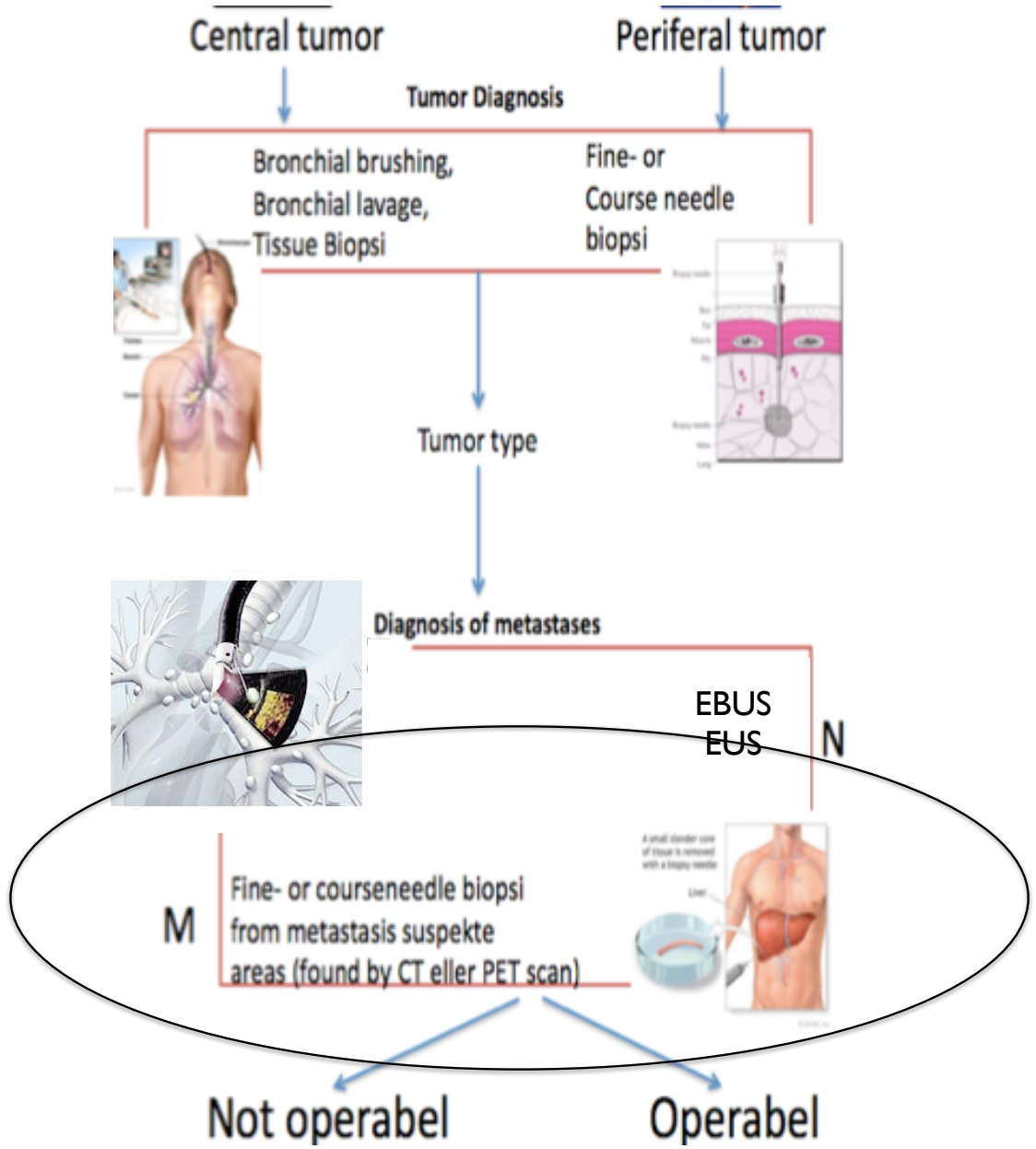
*EBUS* *Endobronchial Ultrasound Scanning*

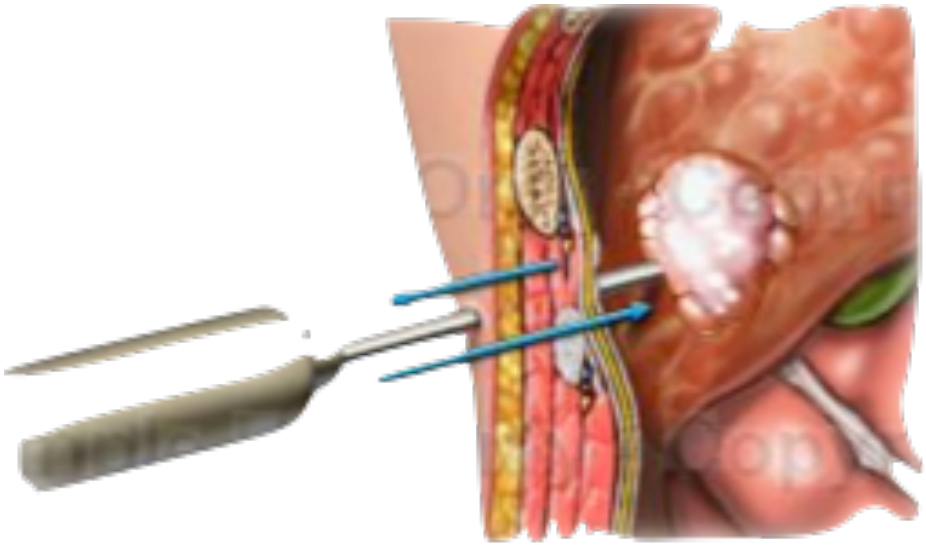
*EUS* *Esophagal Ultraspund Scanning*

} TBNA

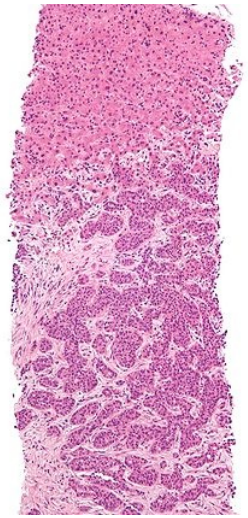
## Cytology




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

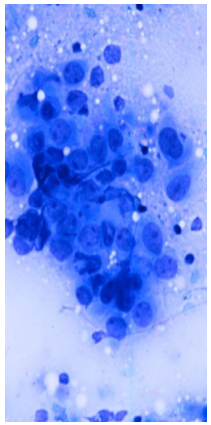



Coarse needle



Histology

Fine needle



Cytology

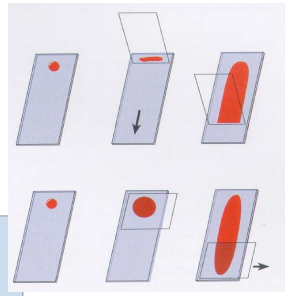
# Patoanatomical specimen

## Histology

Fixation
Dehydration
Parafinembedding
Microtomy

Præparation

Cytologi

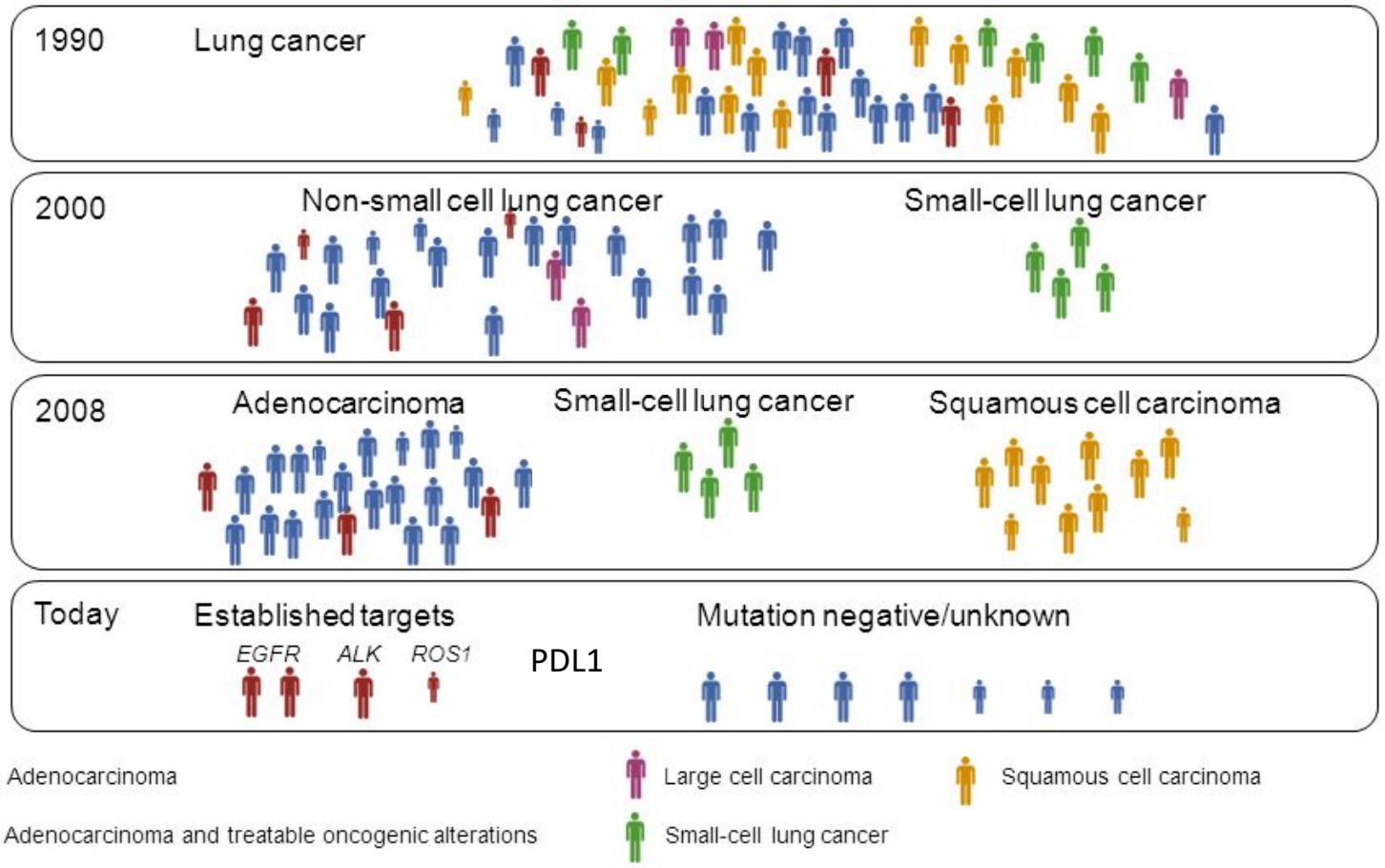


Smear preparation

## Visualization

(Staining)

# Patient selection in lung cancer: Evolution over time




Diagnosis

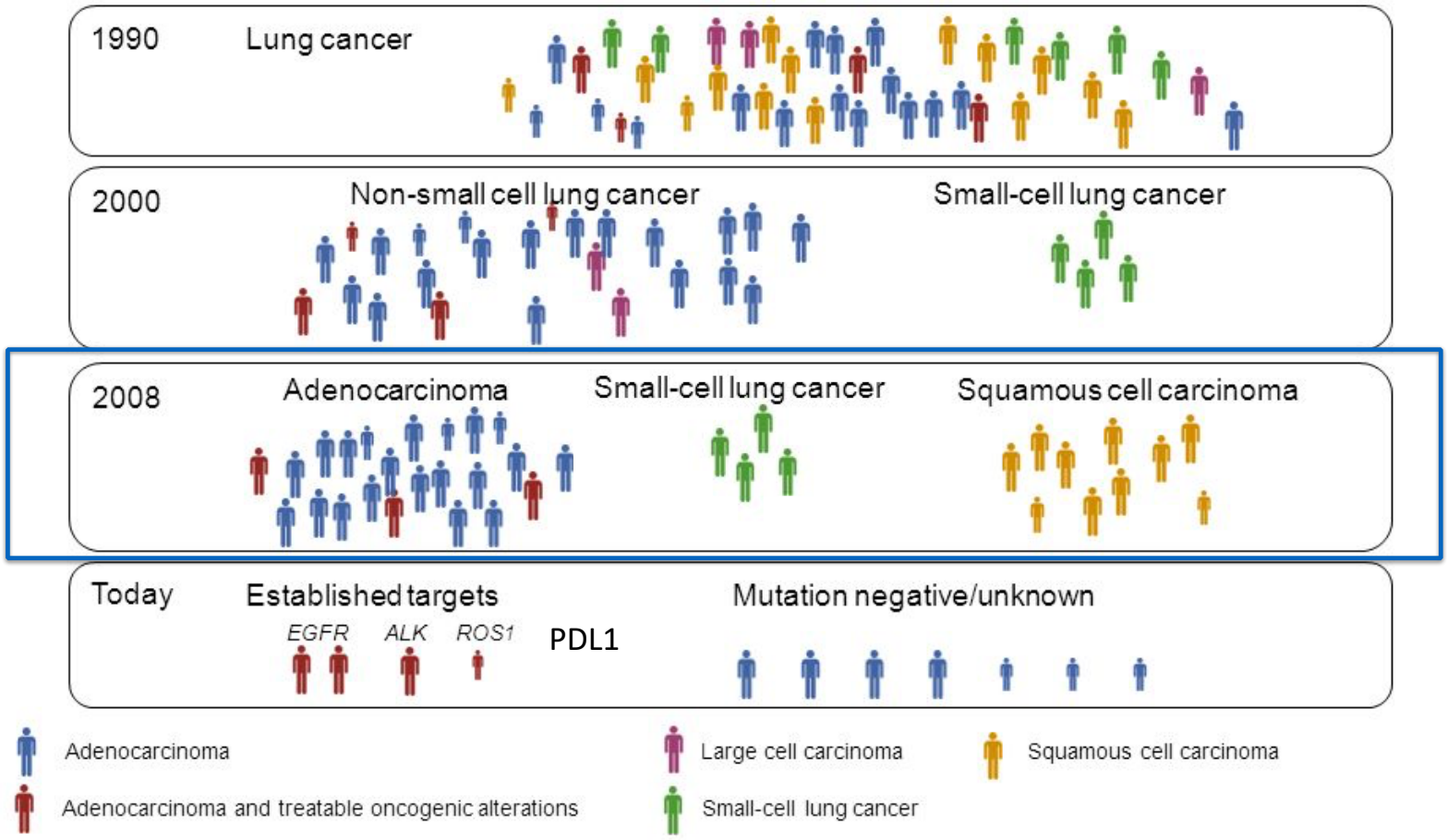
Diagnosis

Diagnosis

Prediction

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

# Patient selection in lung cancer: Evolution over time




Diagnosis

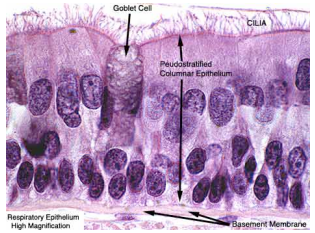
Diagnosis

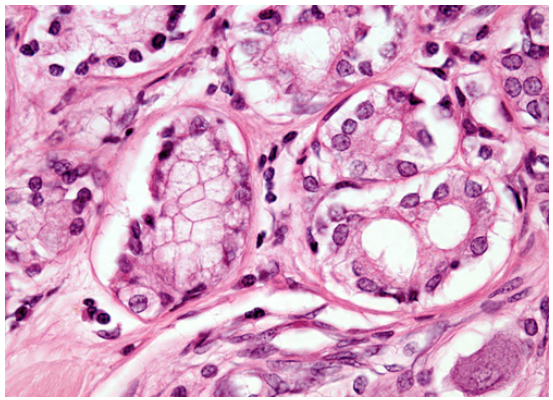
Diagnosis

Prediction

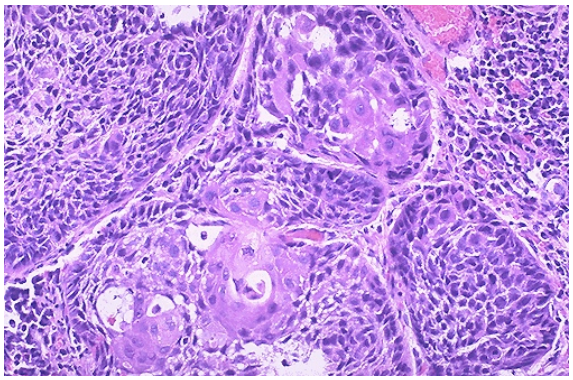
Adapted from Reck M, et al. Lancet 2013;382:709–19

# Morphology

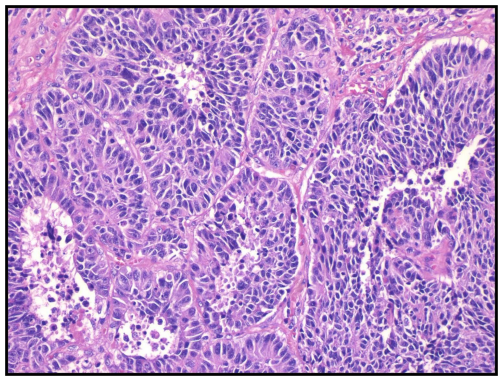


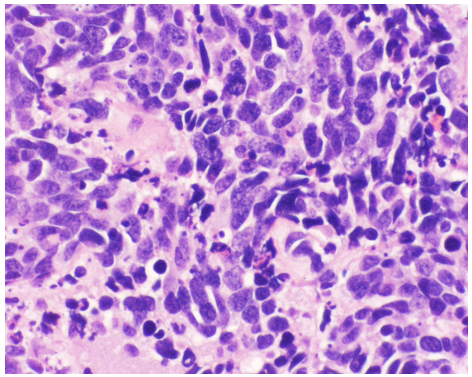
Adenocarcinoma



Squamous carcinoma



Large cell
neuroendocrine carc.

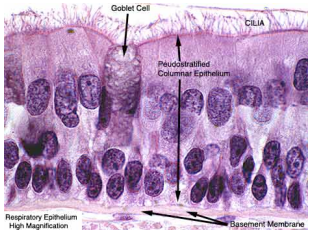


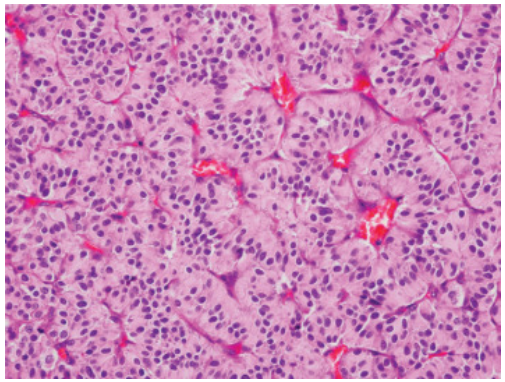
Small cell carcinoma

Non Small Cell Lung Carcinoma (NSCLC)

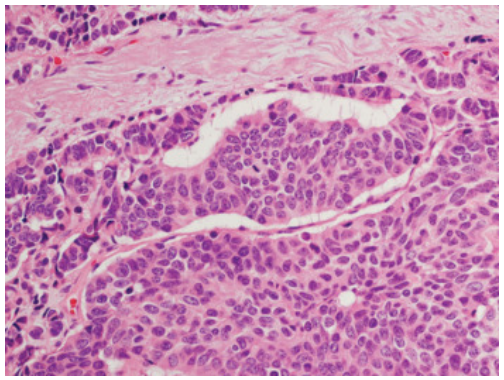
Neuroendocrine carcinoma

# Morphology

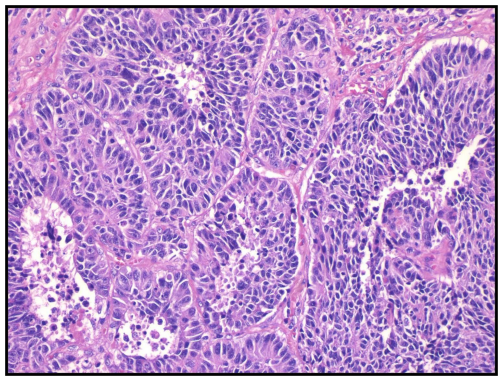


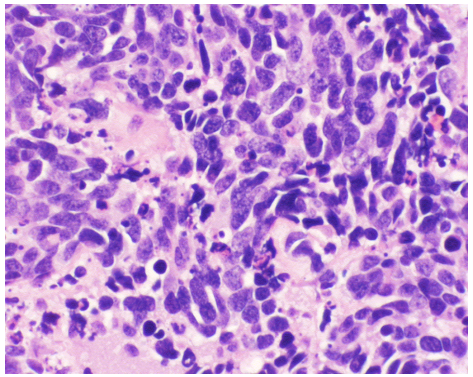
Typical carcinoid



Atypical carcinoid



Large cell
neuroendocrine carc.



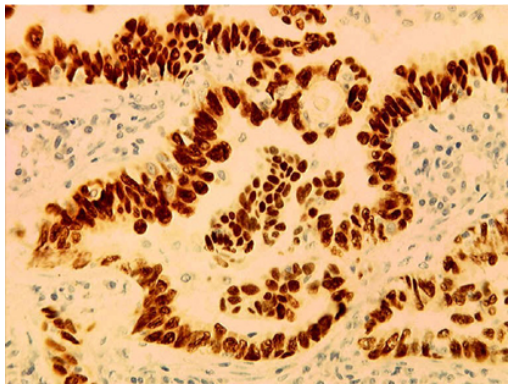
Small cell carcinoma

Neuroendocrine tumor

Neuroendocrine carcinoma

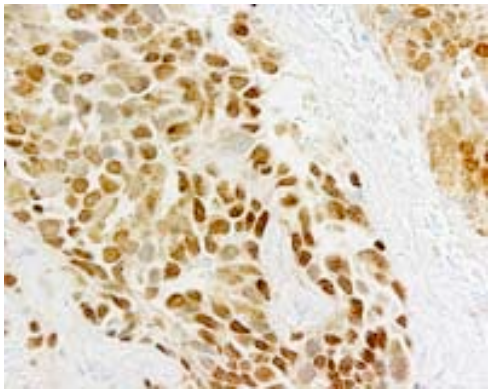
# Immunohistochemistry

ttf1



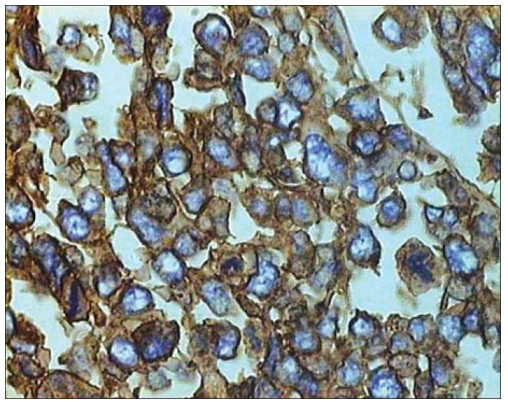
Adenocarcinoma

p63



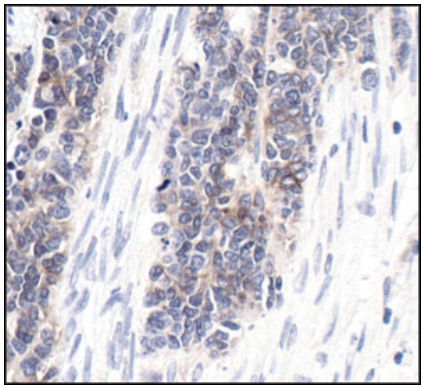
Squamous carcinoma

cd56



Large cell
neuroendocrine carc

cd56

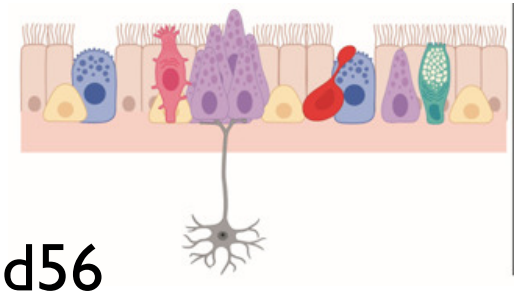


Small cell carcinoma

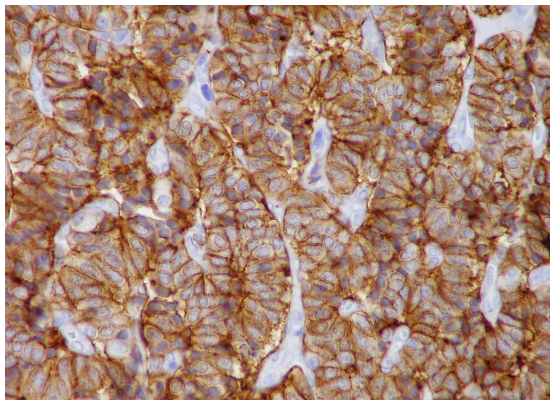
Non Small Cell Lung Carcinoma (NSCLC)

Neuroendocrine carcinoma

# Immunohistochemistry

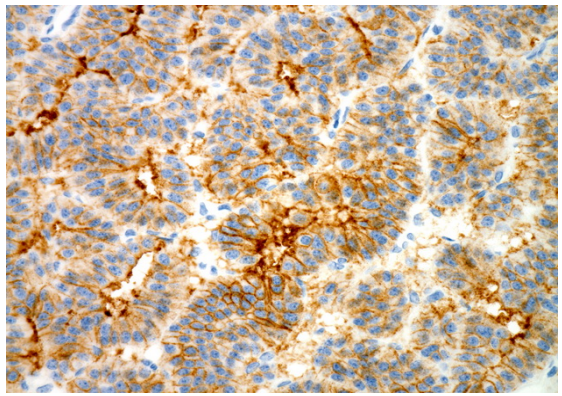


cd56



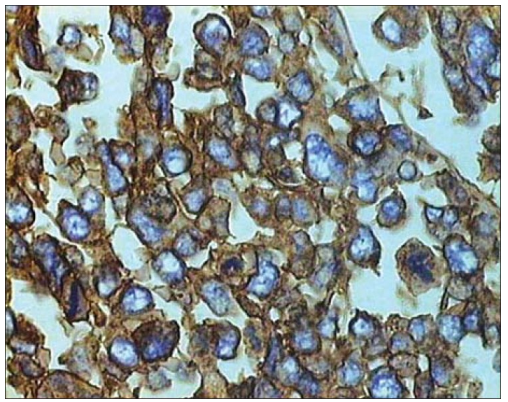
Typical carcinoid

cd56



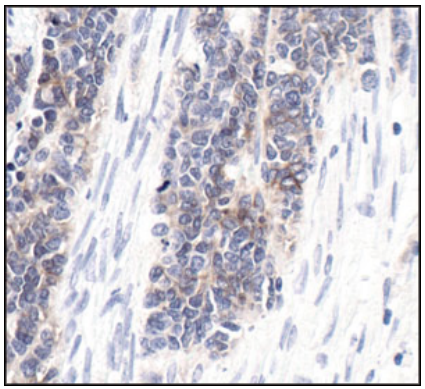
Atypical carcinoid

cd56



Large cell
neuroendocrine carc

cd56



Small cell carcinoma

Neuroendocrine tumor

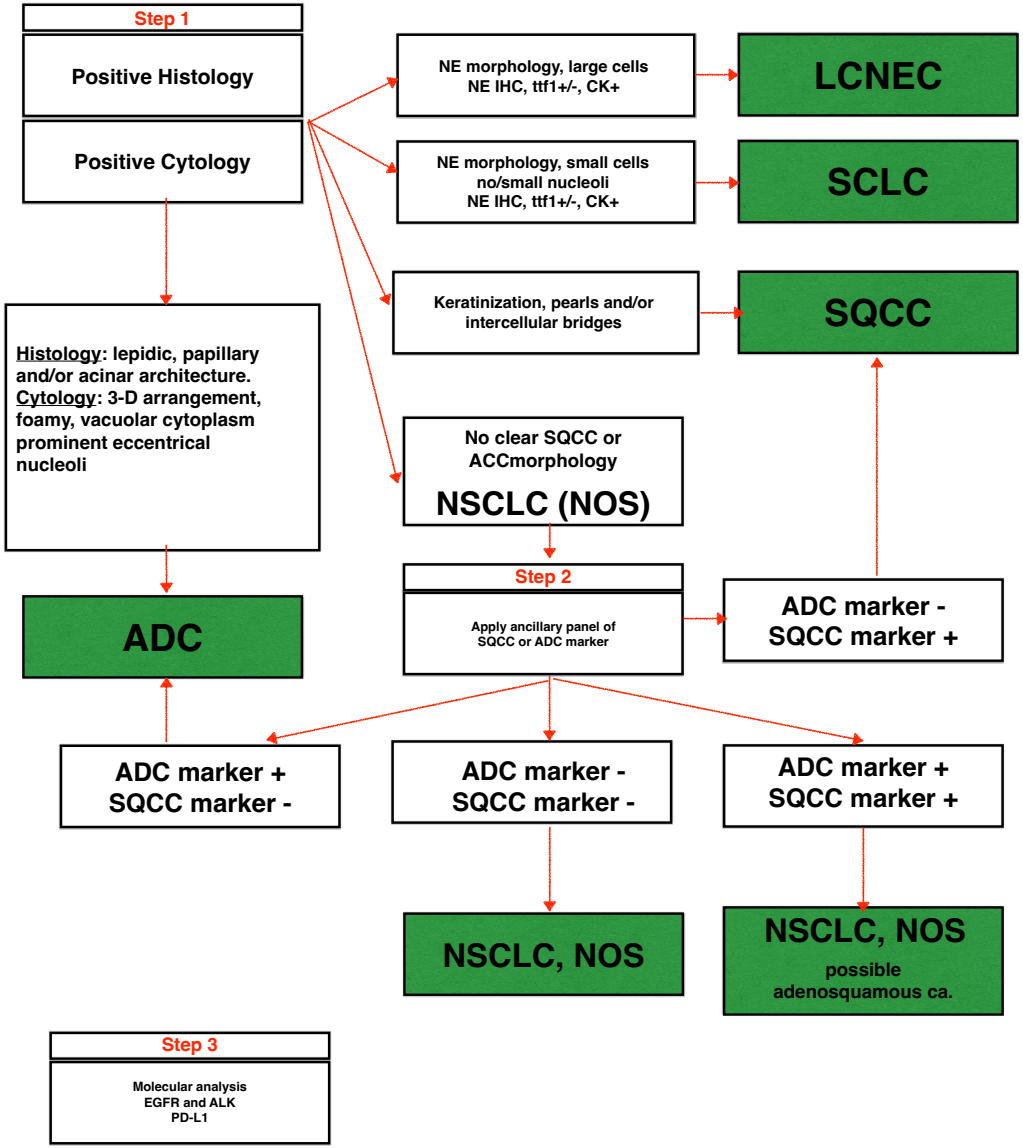
Neuroendocrine carcinoma

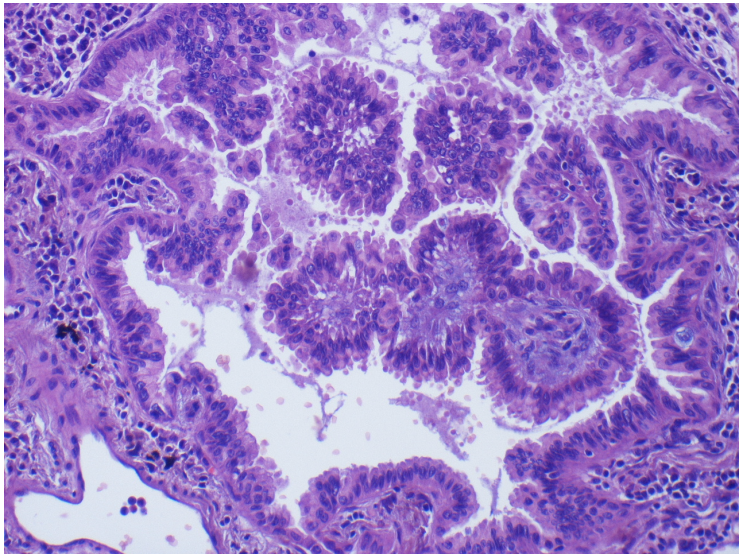
# Algorithm modified from

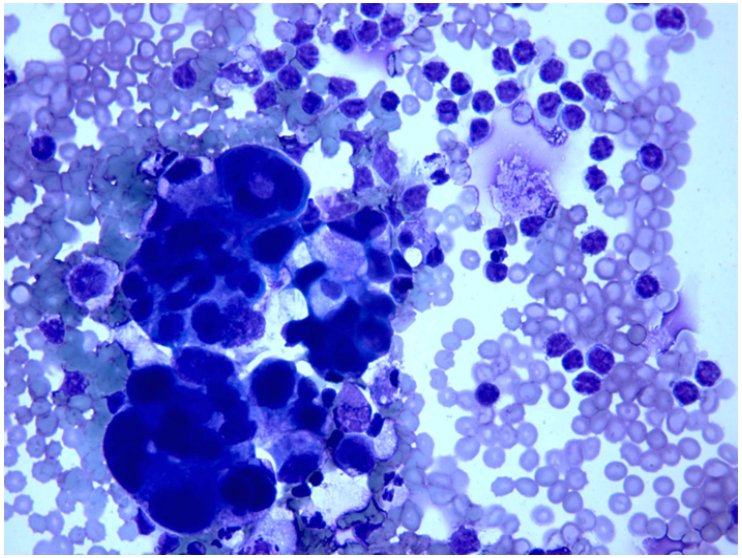
## Diagnosis of Lung Cancer in Small Biopsies and Cytology

### 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 G. Nicholson, DM; Kim Geisinger, MD; Yasushi Yatabe, MD; Yuichi Ishikawa, MD; Ignacio Wistuba, MD; Douglas B. Flieder, MD; Wilbur Franklin, MD; Adi Cagatay, 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*







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 -

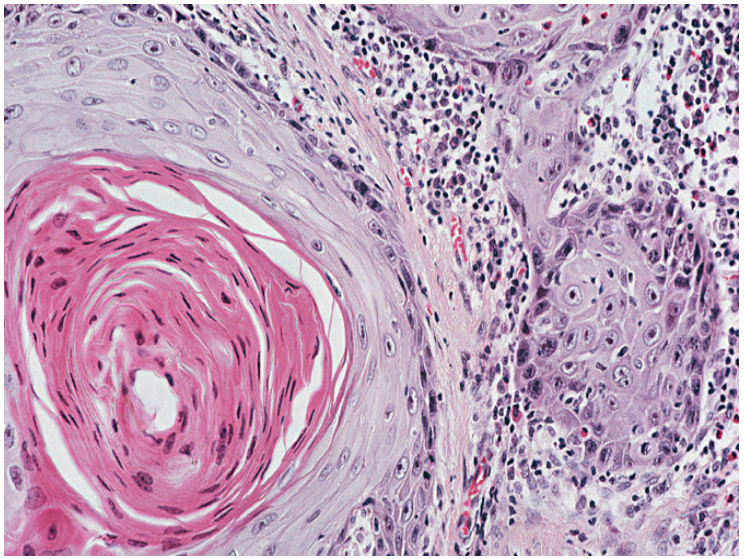
ADC marker + SQCC marker +

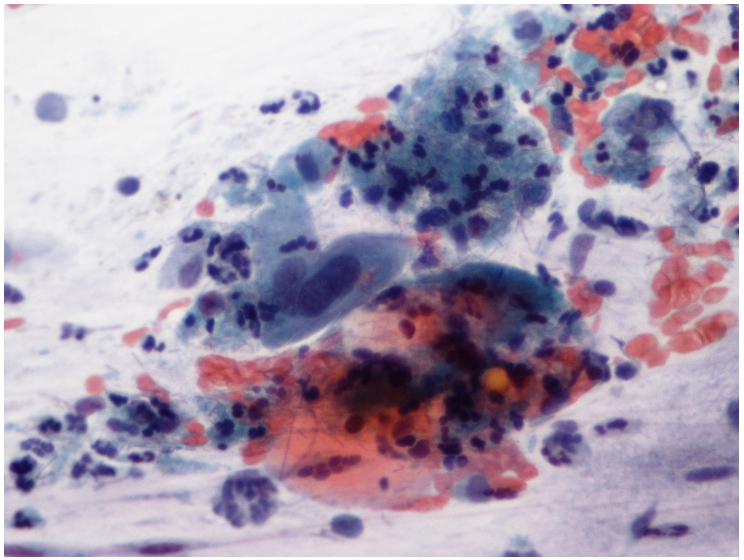
NSCLC, NOS

NSCLC, NOS
possible adenosquamous ca.

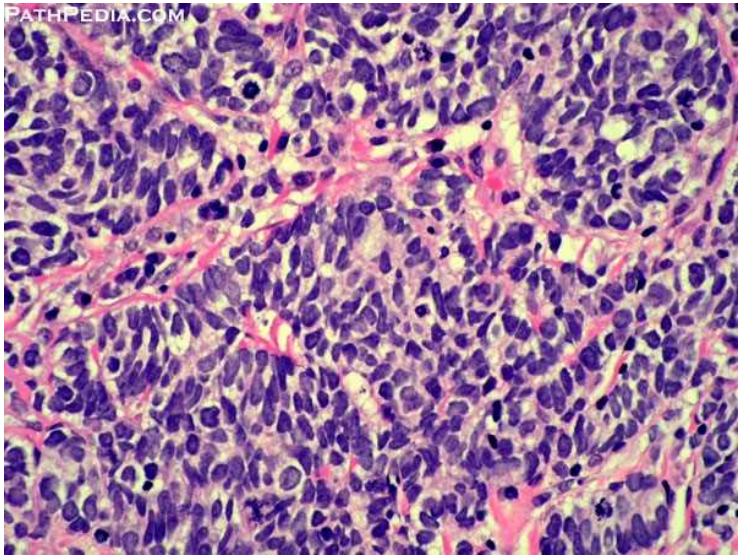
Step 3

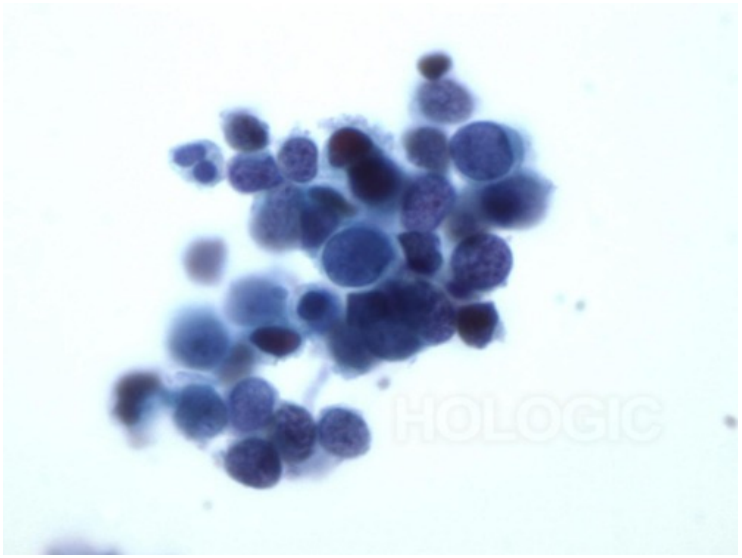
Molecular analysis
EGFR and ALK



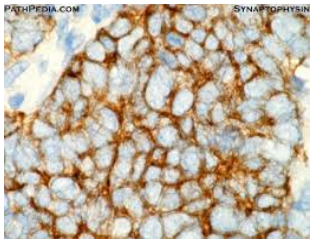



Step 1
Positive Histology
Positive Cytology
NE morphology, large cells
NE IHC, ttf1+/-, CK+
LCNEC
NE morphology, small cells
no/small nucleoli
NE IHC, ttf1+/-, CK+
SCLC
Keratinization, pearls and/or intercellular bridges
SQCC
Histology: lepidic, papillary and/or acinar architecture.
Cytology: 3-D arrangement, foamy, vacuolar cytoplasm prominent eccentrical nucleoli
No clear SQCC or ACCmorphology
NSCLC (NOS)
Step 2
Apply ancillary panel of SQCC or ADC marker
ADC marker - SQCC marker +
ADC
ADC marker + SQCC marker -
ADC marker - SQCC marker -
ADC marker + SQCC marker +
NSCLC, NOS
NSCLC, NOS
possible adenosquamous ca.
Step 3
Molecular analysis
EGFR and ALK

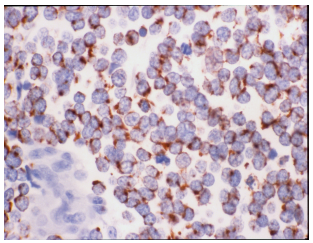

PATHPEDIA.COM


HOLOGIC

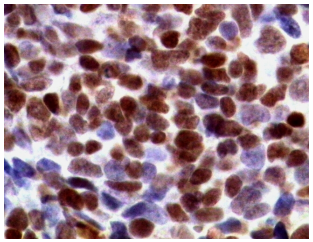

Step 1
Positive Histology
Positive Cytology
NE morphology, large cells
NE IHC, ttf1+/-, CK+
LCNEC
NE morphology, small cells
no/small nucleoli
NE IHC, ttf1+/-, CK+
SCLC
Histology: lepidic, papillary and/or acinar architecture.
Cytology: 3-D arrangement, foamy, vacuolar cytoplasm prominent eccentrical 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 marker - SQCC marker +
ADC
ADC marker + SQCC marker -
ADC marker - SQCC marker -
ADC marker + SQCC marker +
NSCLC, NOS
NSCLC, NOS
possible adenosquamous ca.
Step 3
Molecular analysis EGFR and ALK



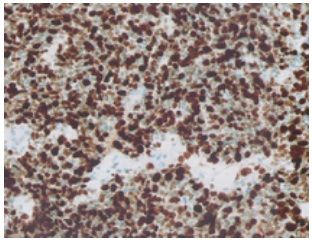

Neuroendocrine marker



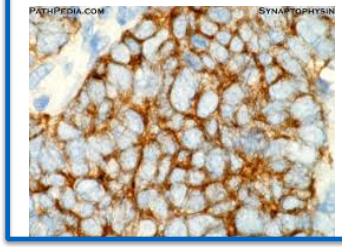
Cytokeratin



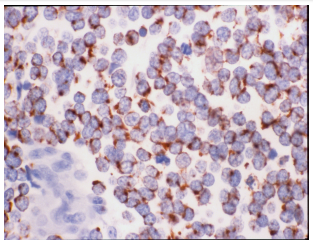
ttf1



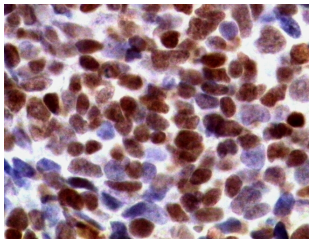
Ki67



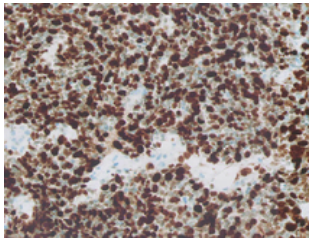

Neuroendocrine marker



Cytokeratin



ttf1

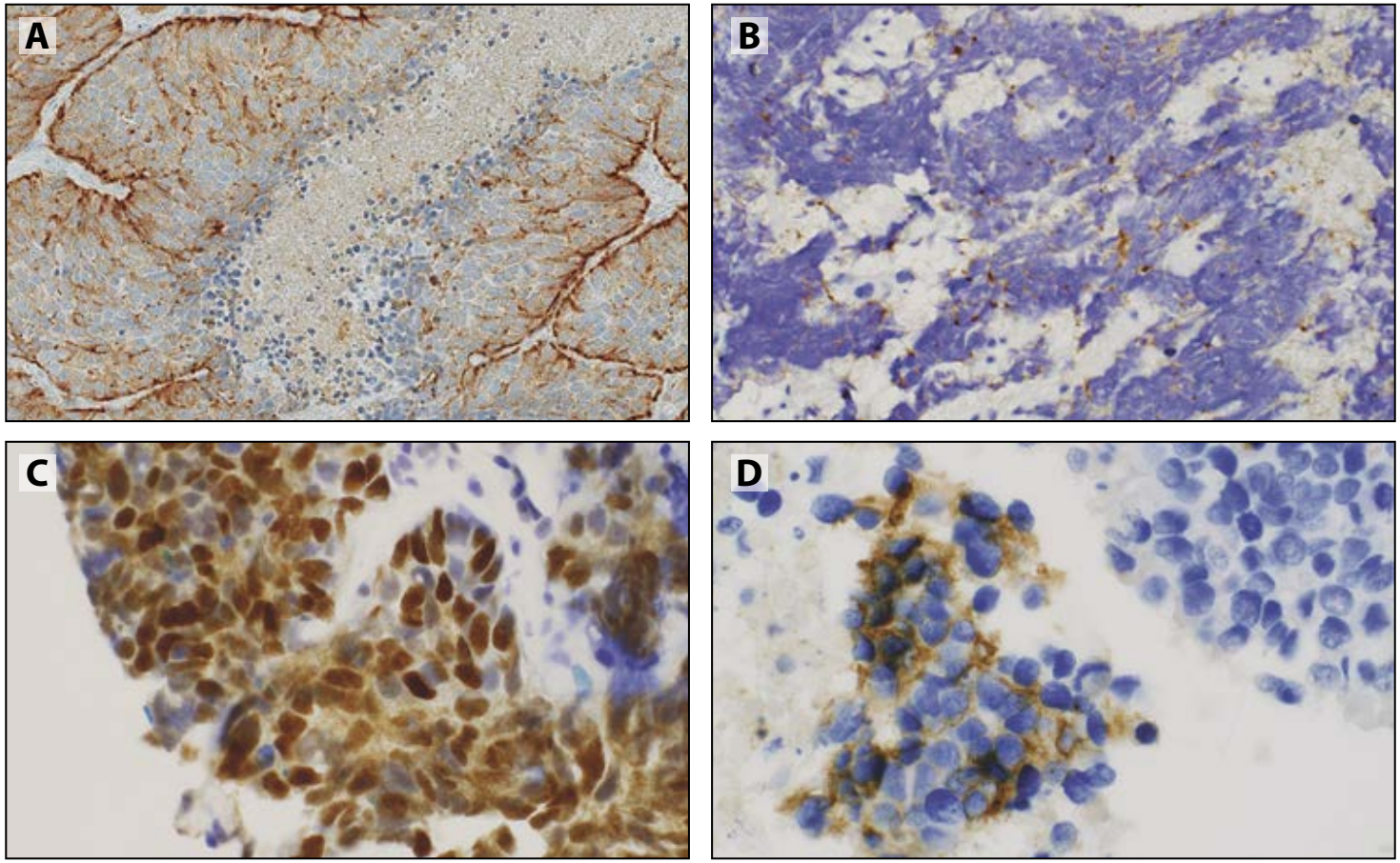


Ki67

# Neuroendocrine markers

Chromogranin A

Synaptofycin




INSM1 Insulinoma-Associated Protein 1

CD56

IASLC ATLAS OF DIAGNOSTIC IMMUNOHISTOCHEMISTRY

# 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) |

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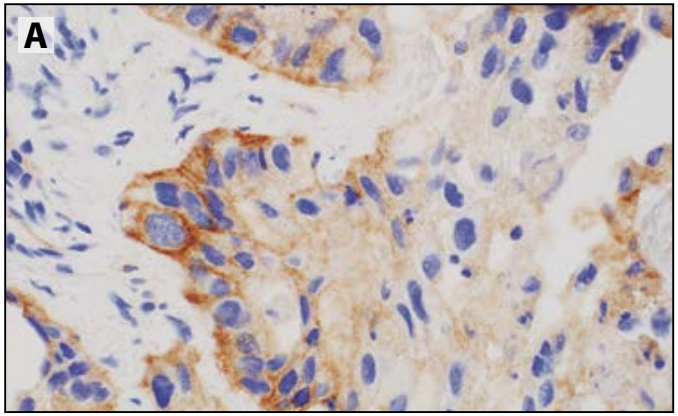
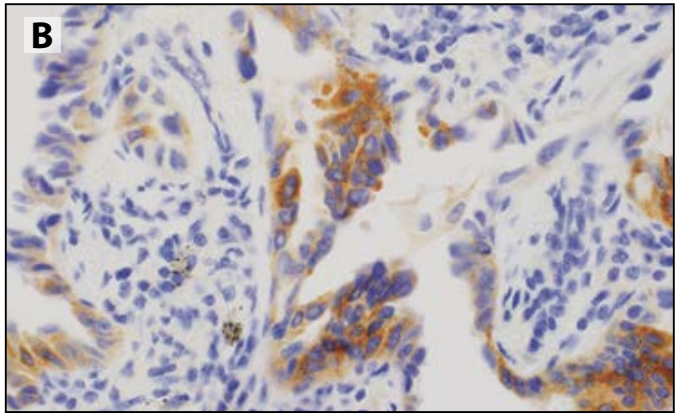



SqCC, CD56




ADC, syn

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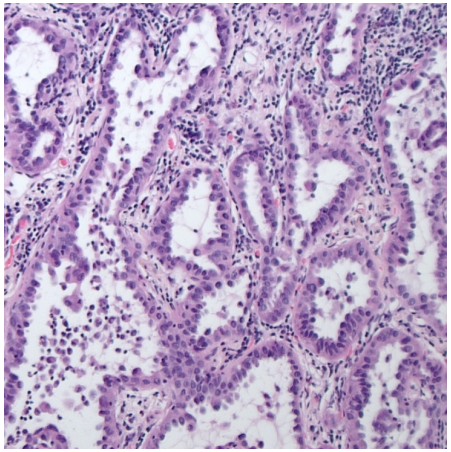
IASLC ATLAS OF DIAGNOSTIC IMMUNOHISTOCHEMISTRY

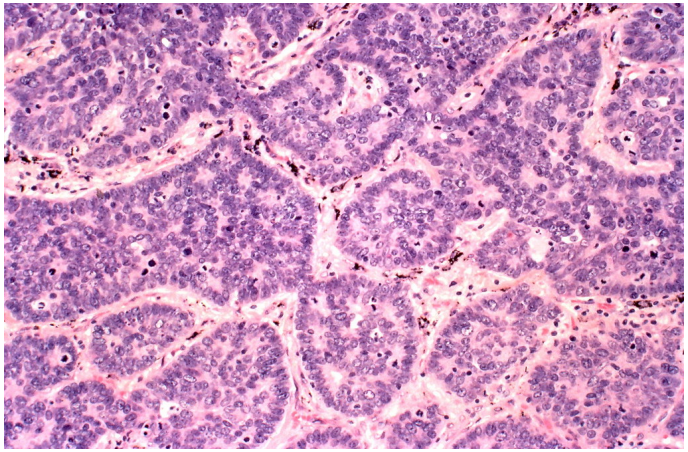
# Neuroendocrine markers

## 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





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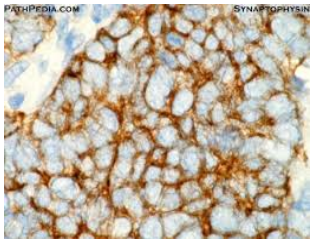
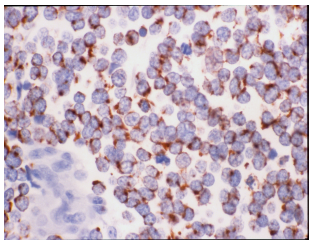
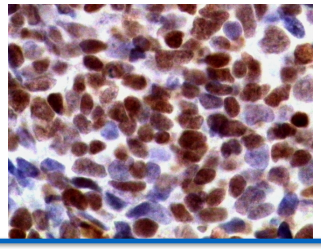


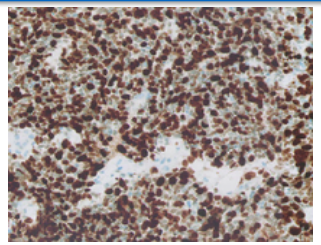

Neuroendocrine marker



Cytokeratin



ttf1



Ki67

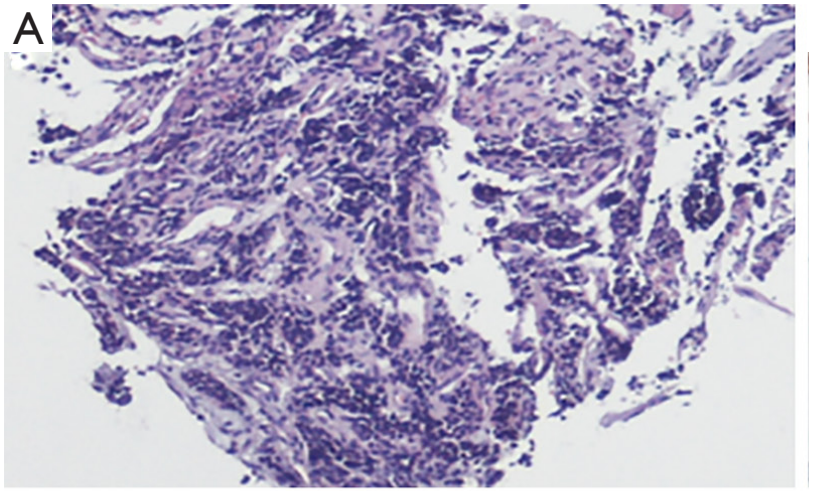
# Neuroendocrine markers

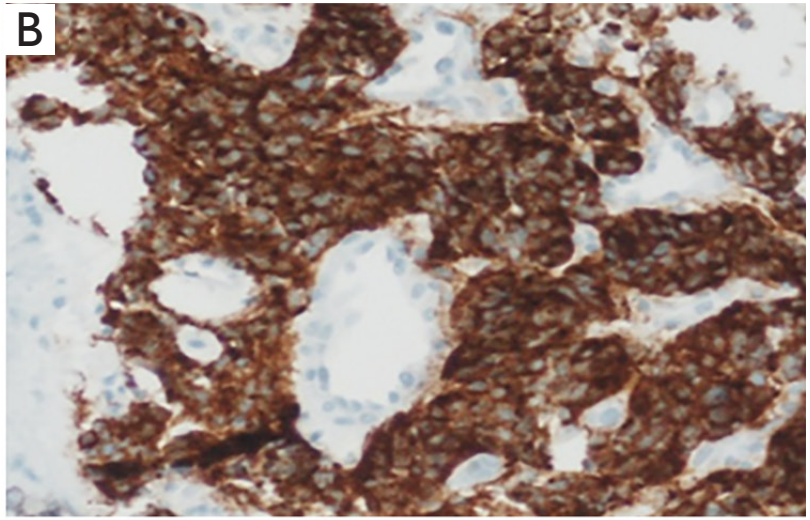
Case Report

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

Ioannis Kyritsis[1], Bettina Krebs[1], Sandra Kampe[2], Dirk Theegarten[3], Clemens Aigner[1], Stefan Welter[1]






CD56

# Neuroendocrine markers

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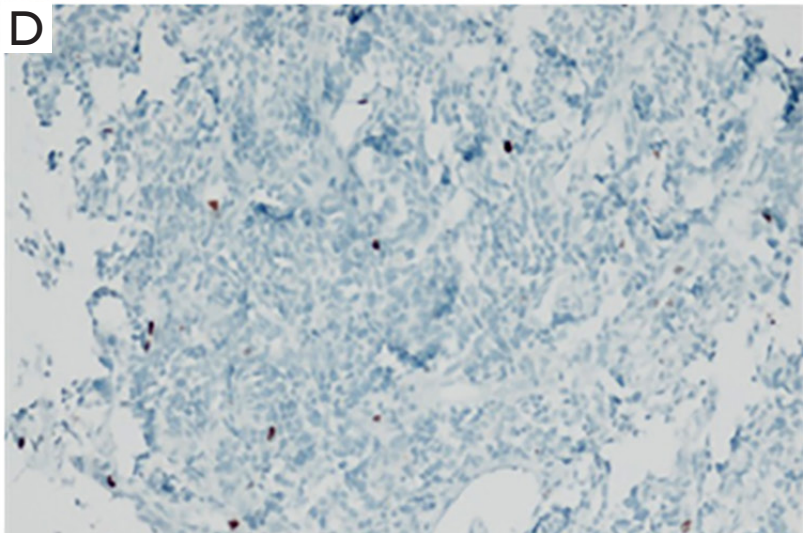


Ki67, re-evaluation

# 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) |

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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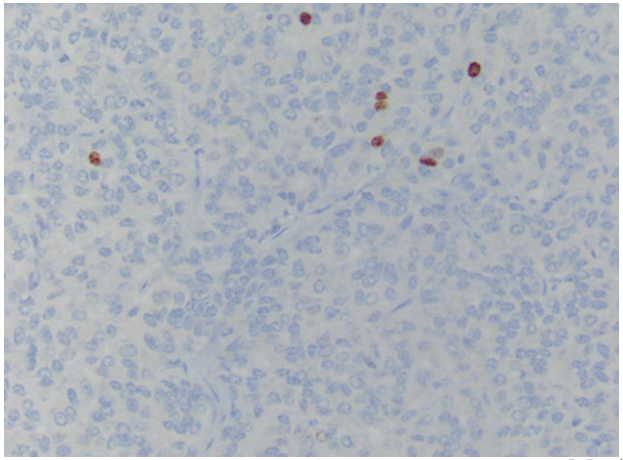
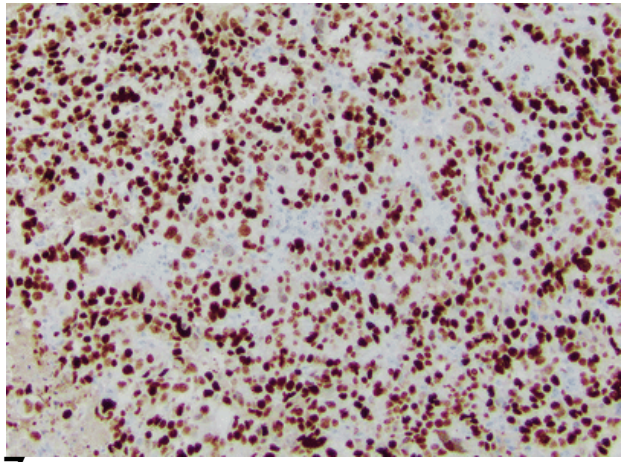
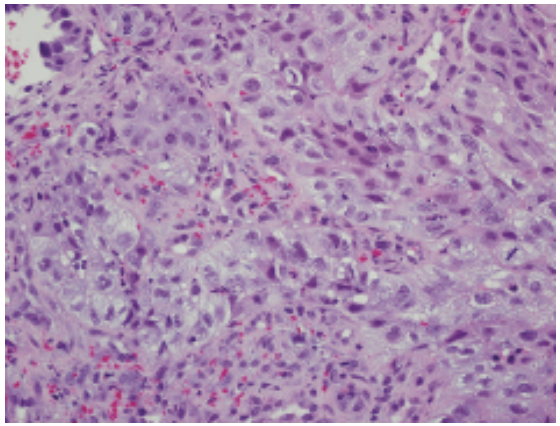


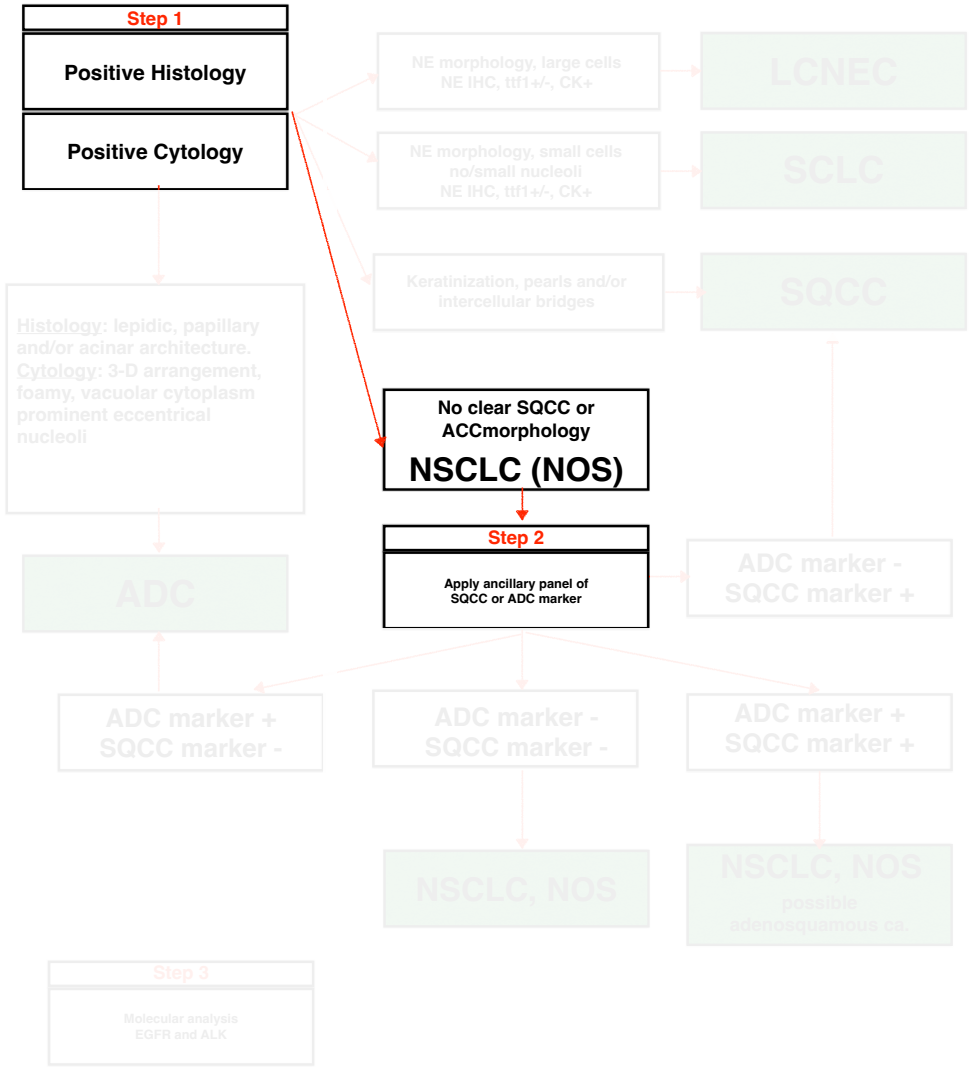
Carcinoid

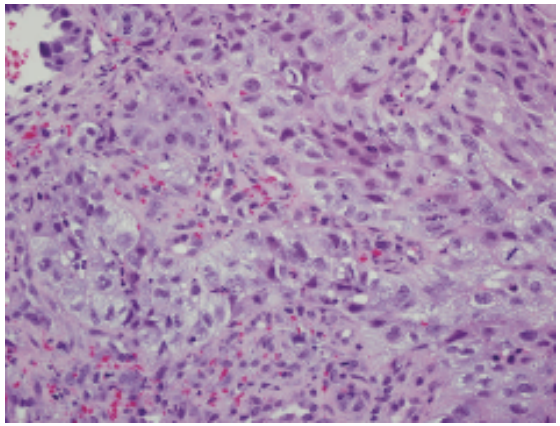
Ki67

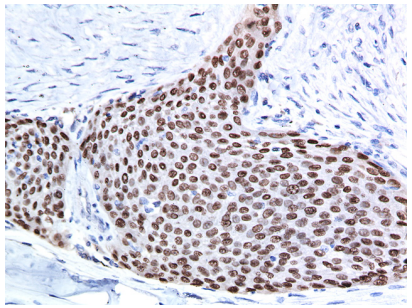


SCLC



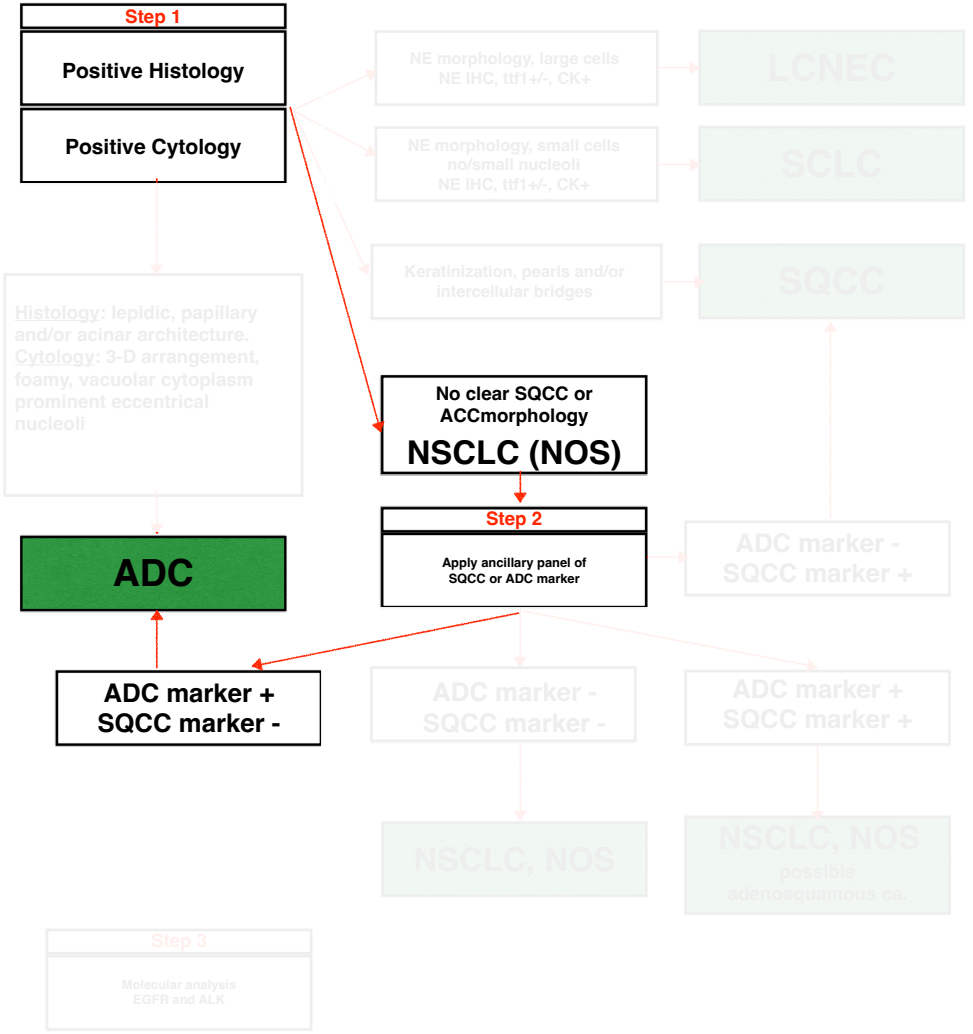

Step 1
Positive Histology
Positive Cytology
NE morphology, large cells
NE IHC, ttf1+/-, CK+
LCNEC
NE morphology, small cells
no/small nucleoli
NE IHC, ttf1+/-, CK+
SCLC
Keratinization, pearls and/or
intercellular bridges
SQCC
Histology: lepidic, papillary
and/or acinar architecture.
Cytology: 3-D arrangement,
foamy, vacuolar cytoplasm
prominent eccentrical
nucleoli
No clear SQCC or
ACCmorphology
NSCLC (NOS)
Step 2
Apply ancillary panel of
SQCC or ADC marker
ADC
ADC marker -
SQCC marker +
ADC marker +
SQCC marker -
ADC marker -
SQCC marker -
ADC marker +
SQCC marker +
NSCLC, NOS
NSCLC, NOS
possible
adenosquamous ca.
Step 3
Molecular analysis
EGFR and ALK

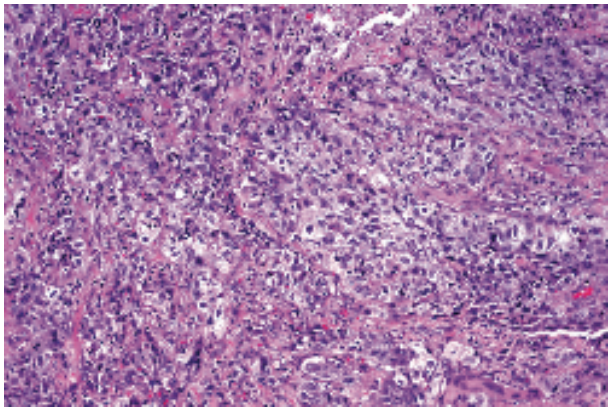


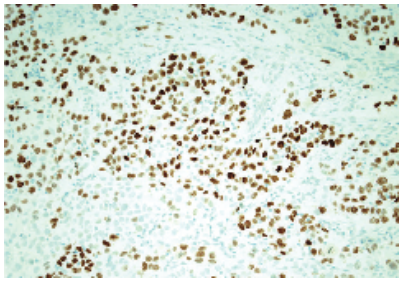


ttf l +

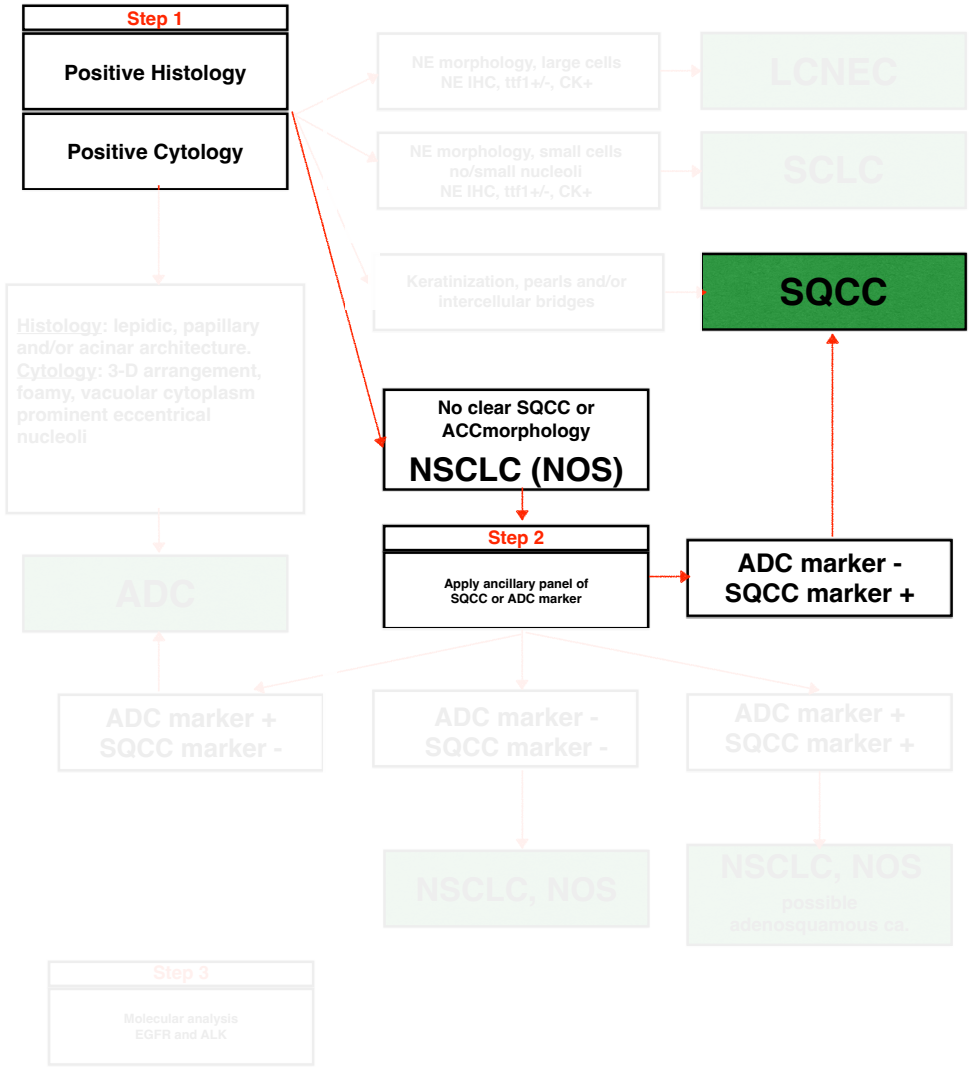
(+Cytokeratin 7)

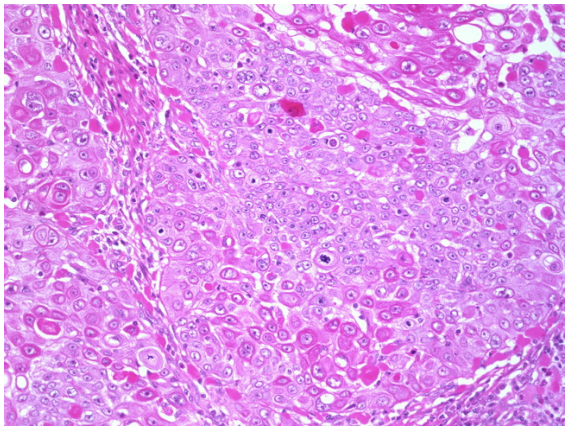


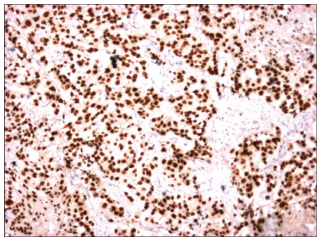




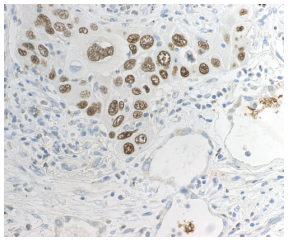
P63+ (+Cytokeratin 5/6)



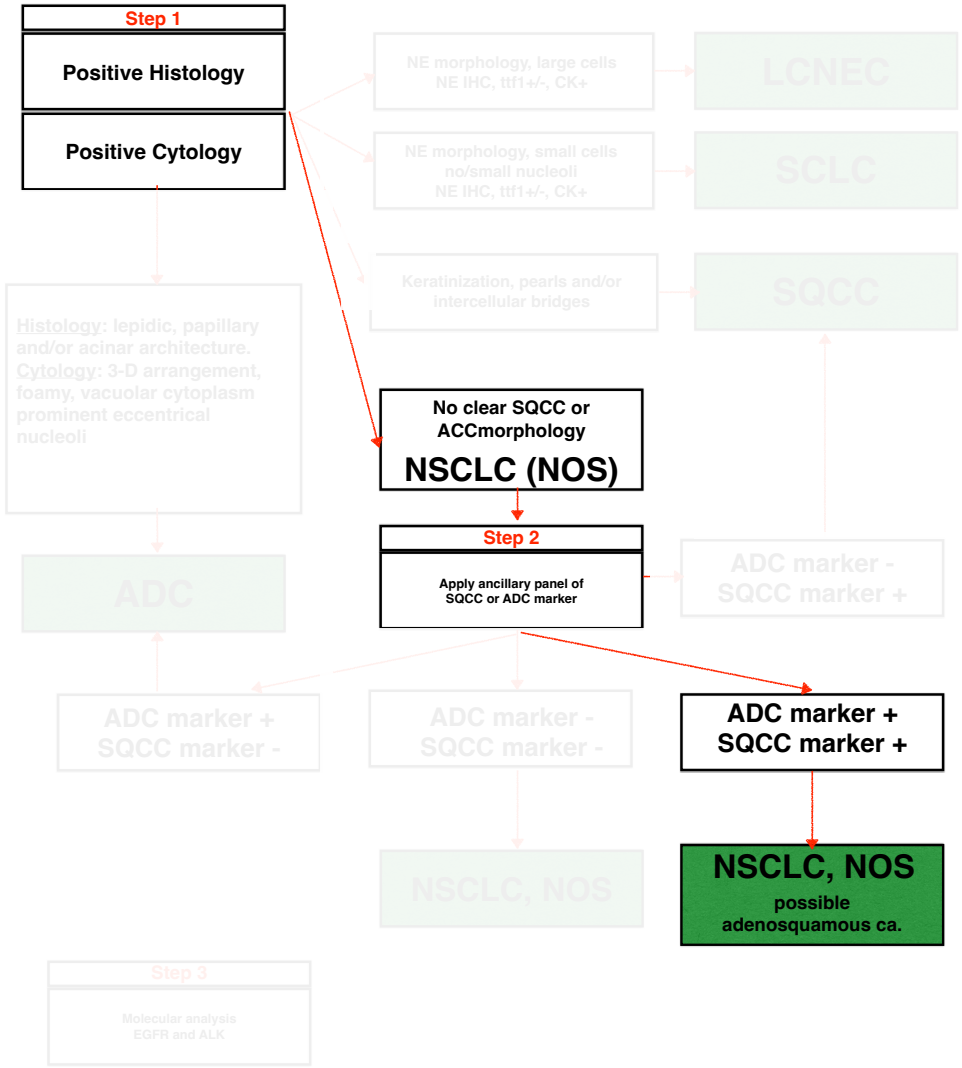




ttf1+



P63+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Keratinization, pearls and/or
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Histology: lepidic, papillary
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SQCC or ADC marker
ADC marker -
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ADC
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SQCC marker -
ADC marker -
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ADC marker +
SQCC marker +
NSCLC, NOS
possible
adenosquamous ca.
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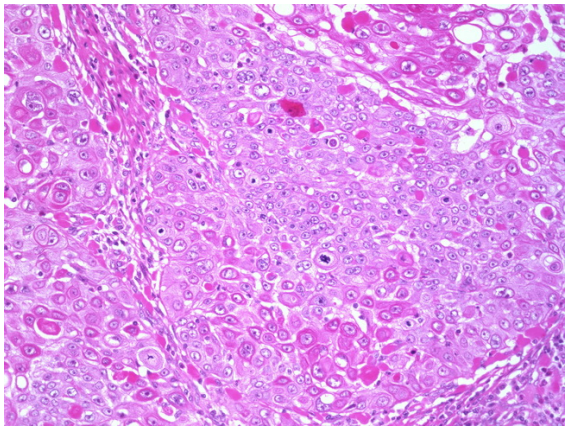

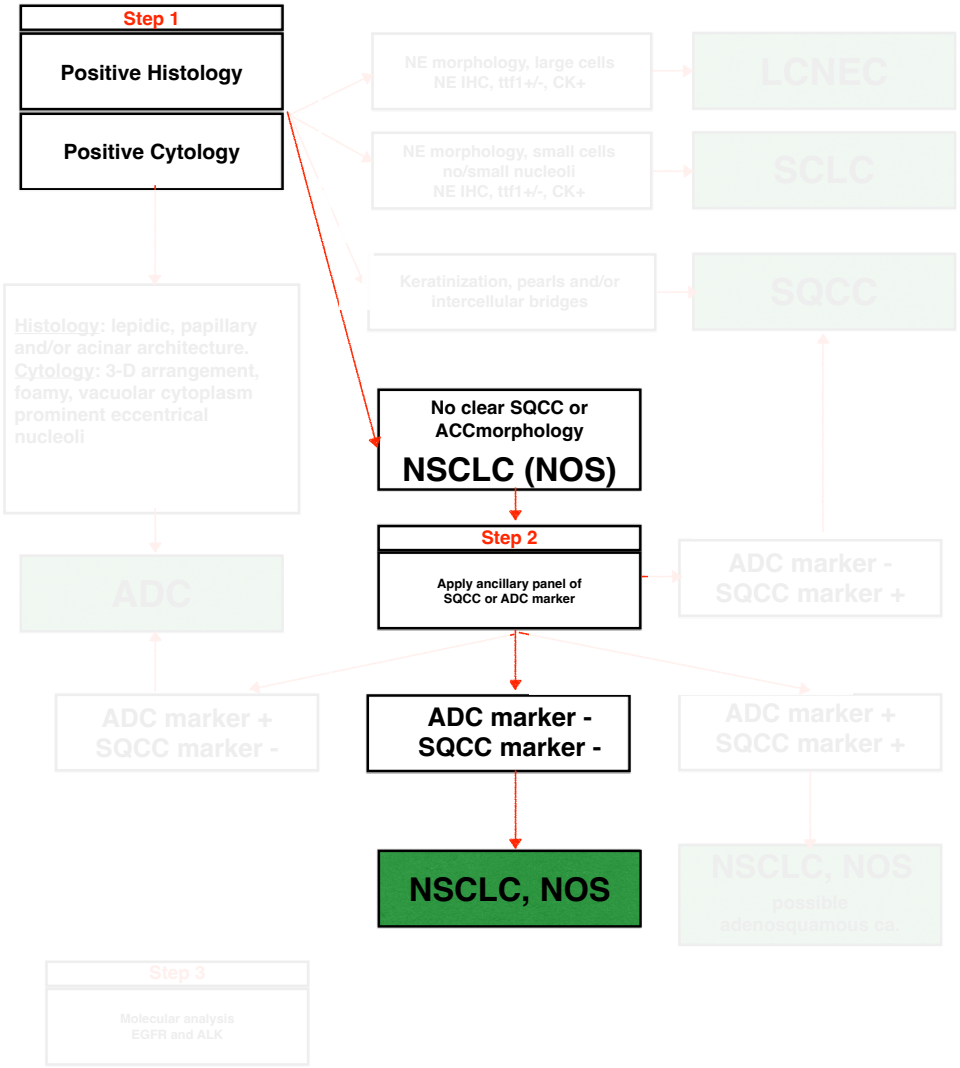
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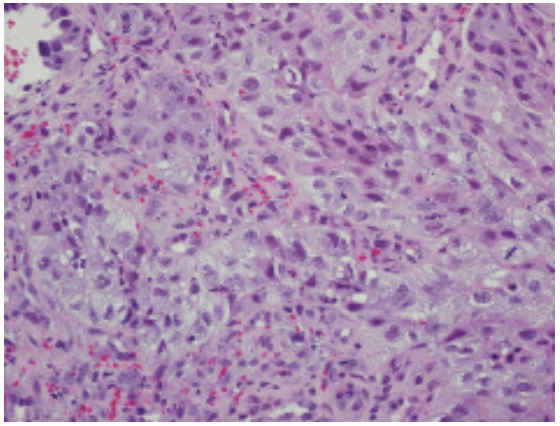
ADC
ADC marker +
SQCC marker -
ADC marker -
SQCC marker -
ADC marker +
SQCC marker +
NSCLC, NOS
NSCLC, NOS
possible
adenosquamous ca.
Step 3
Molecular analysis
EGFR and ALK

ttf1-  P63-



CK7

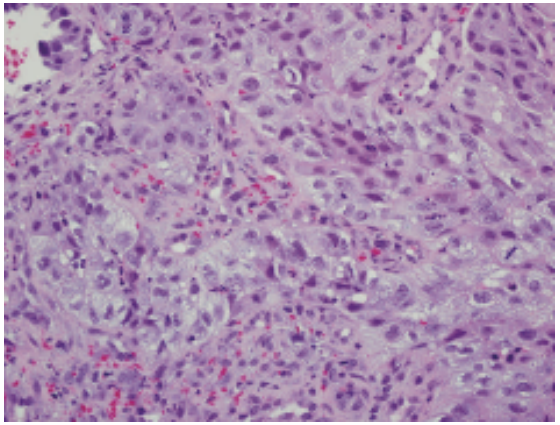
ttf1

Napsin

Adenocarcinoma (+neuroendocrine)
Approx. 80%

CK5/6

P63



CK7 50%

ttf1

Napsin

CK5/6

P63

Squamous carcinoma

# Diagnosis of primary lung tumor

NordiQC

**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

Problems:

Adenocarcinoma can be P63+

# The P63 family

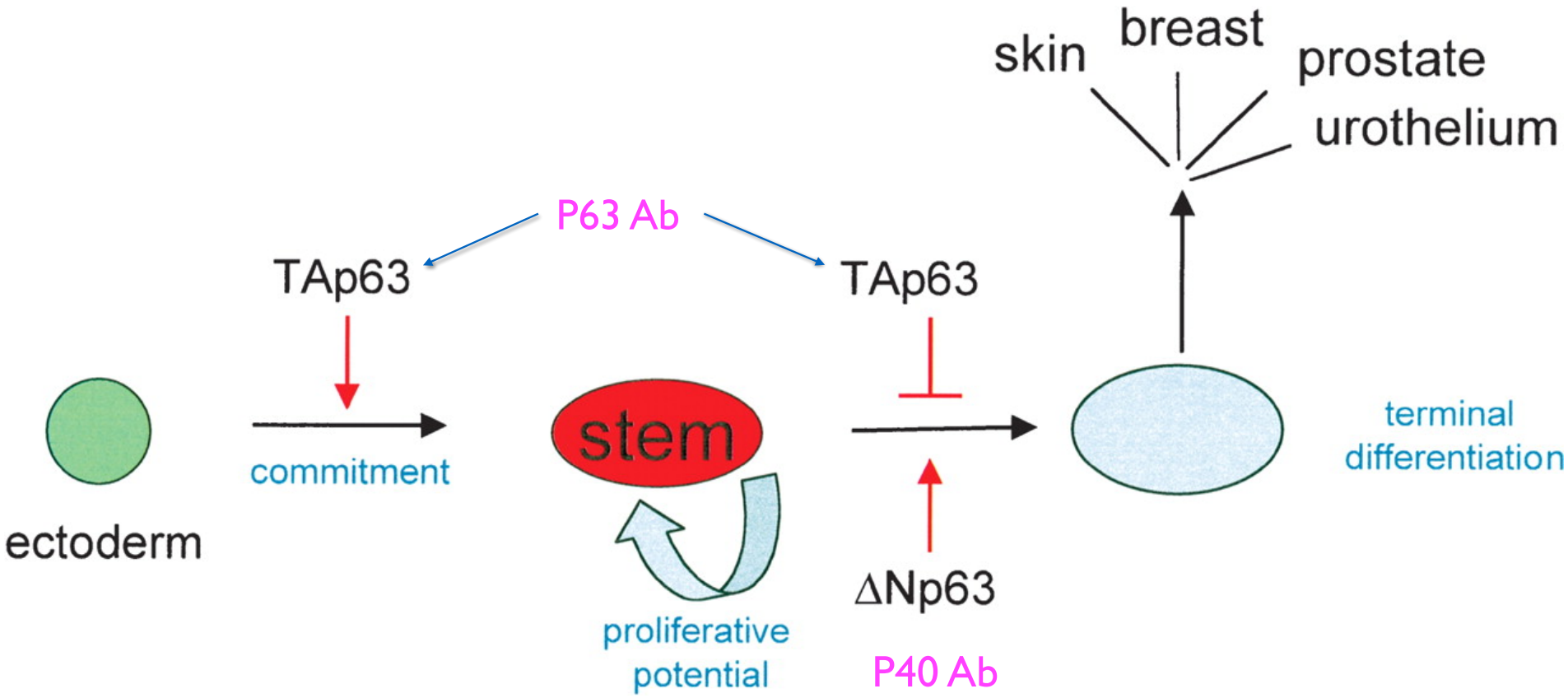


**Table 8-1.** Studies Comparing p40 Against p63 for Squamous Cell Carcinoma (SQCC)

| 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:

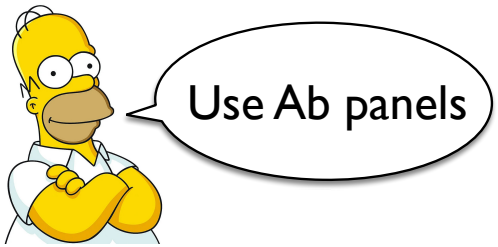
Differential diagnosis between primary and metastatic carcinoma

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]

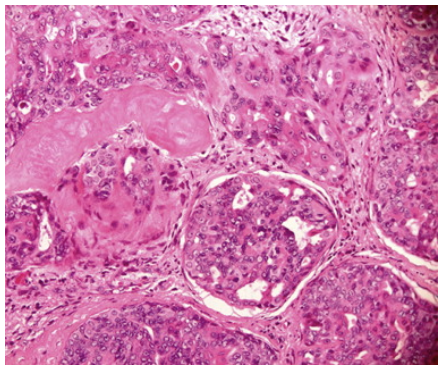
| Primary carcinoma | 8G7G3/1 | | SPT24 | |
|---|---|---|---|---|
| | n | Positive, n (%) | n | Positive, n (%) |
| Ovarian carcinoma | 615 | 22 (3.6%) | 161 | 16 (9.9%) |
| Endometrial adenocarcinoma | 215 | 17 (7.9%) | 68 | 19 (27.9%) |
| Uterine cervical adenocarcinoma | 92 | 3 (3.3%) | 39 | 6 (15.4%) |
| 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%) |

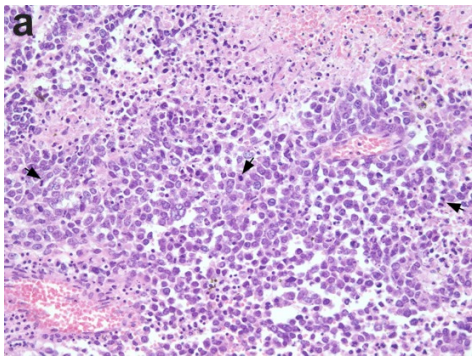
[a] Data for clones 8G7G3/1 and SPT24 are modified based on data from Ordonez 2012b.




# Diagnosis of metastasis to the lung

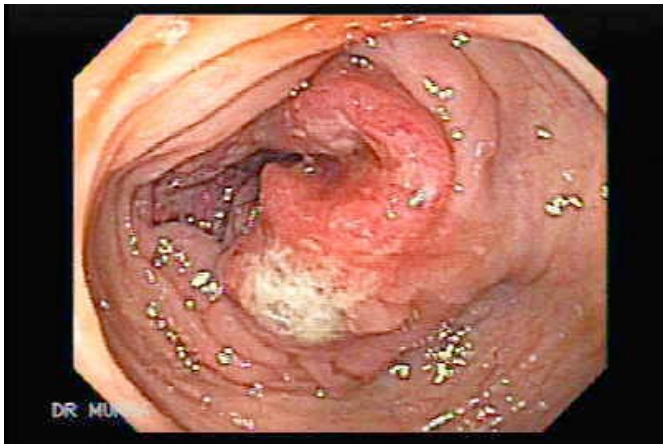
NordiQC



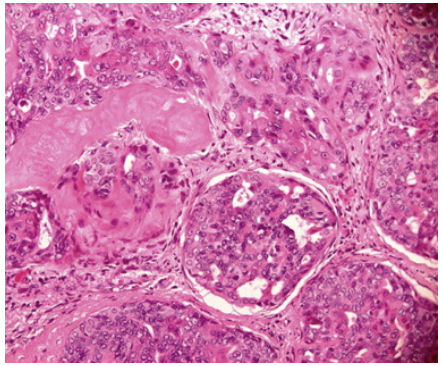


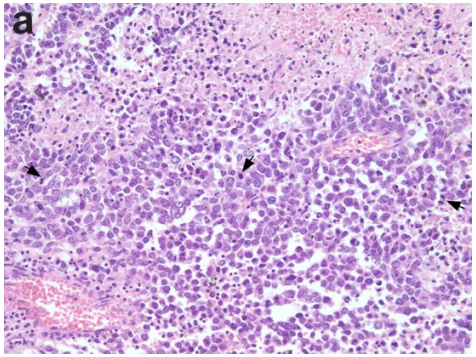

AE1/AE3 ←
CK7
ttf1
CK20 ←
cdx2 ←
SATB2 ←
NKX3.1
CK5/6
P63
CD10
PAX8
WT1
GATA3

## Colon



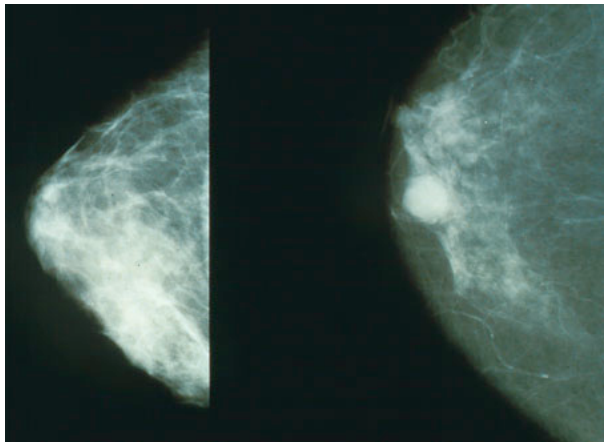
# Diagnosis of metastasis to the lung



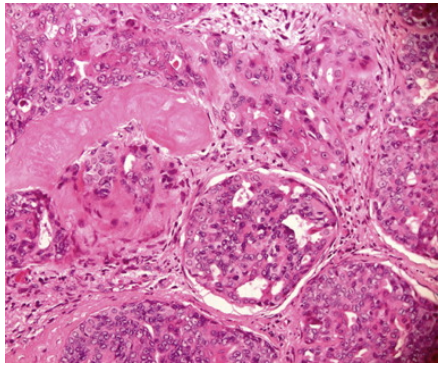


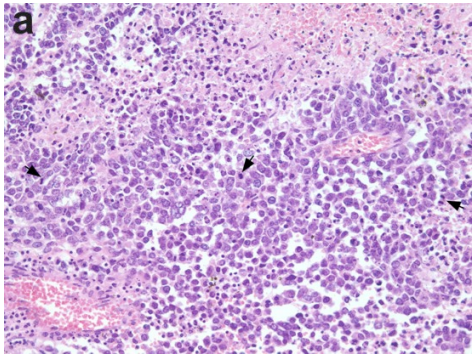

AE1/AE3 ←
CK7 ←
ttf1
CK20
cdx2
SATB2
NKX3.1
CK5/6
P63
CD10
PAX8
WT1
GATA3 ←

## Mamma



# Diagnosis of metastasis to the lung

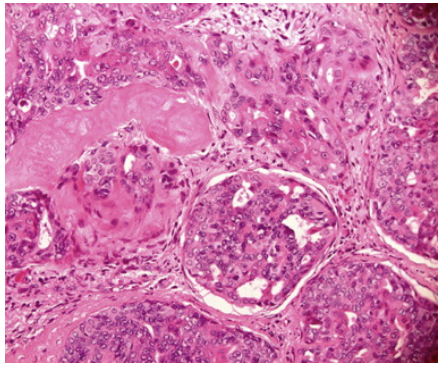


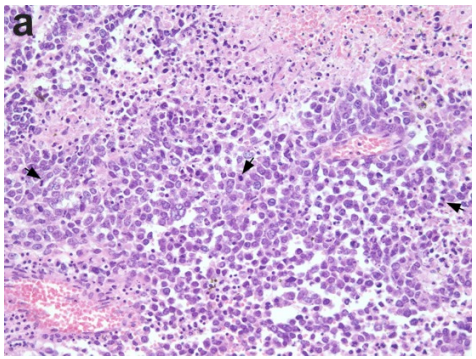



AE1/AE3 ←
CK7 ←
ttf1
CK20 ←
cdx2 ←
SATB2 ←
NKX3.1
CK5/6
P63
CD10
PAX8
WT1
GATA3

## Upper GI

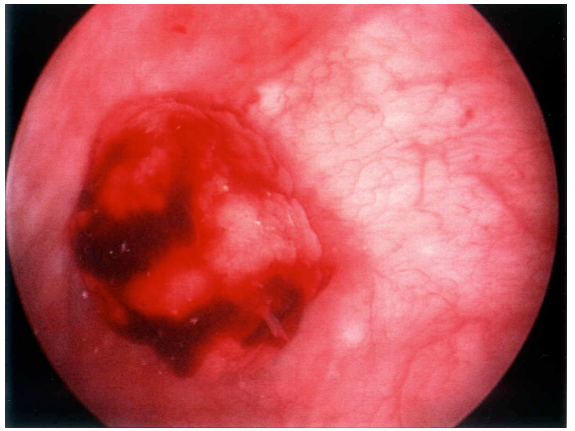
# Diagnosis of metastasis to the lung



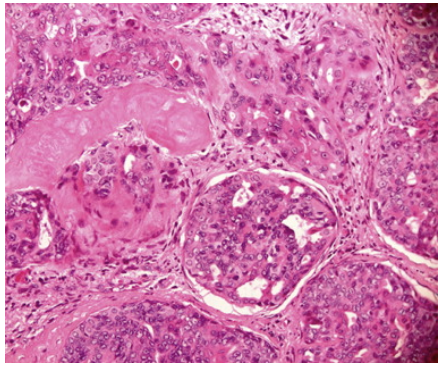


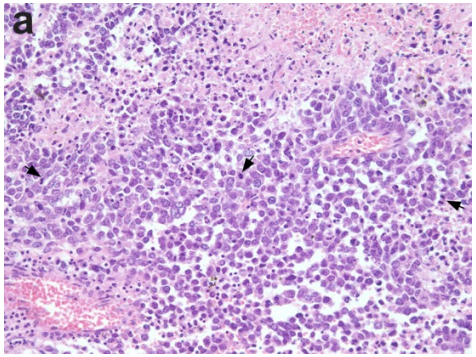

AE1/AE3 ←
CK7 ←
ttf1
CK20 ←
cdx2
SATB2
NKX3.1
CK5/6 ←
P63 ←
CD10
PAX8
WT1
GATA3 ←

## Urothelial carcinoma



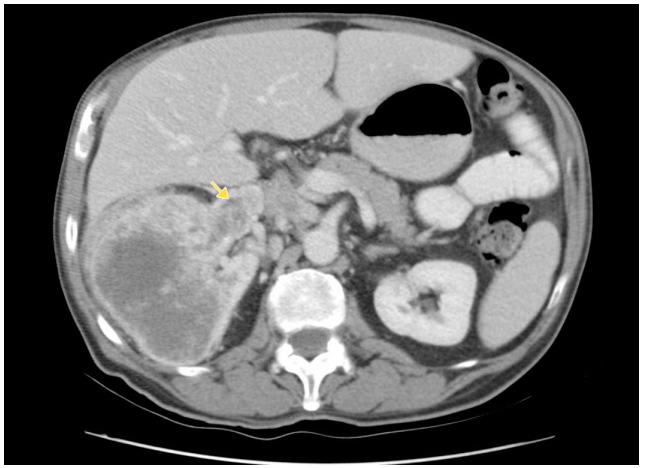
# Diagnosis of metastasis to the lung



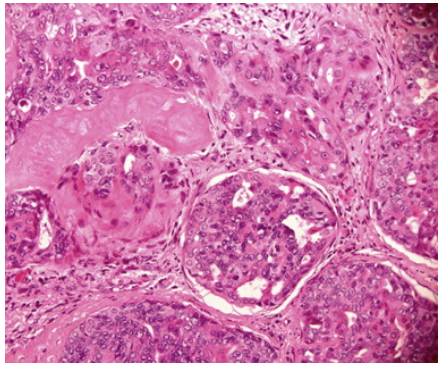


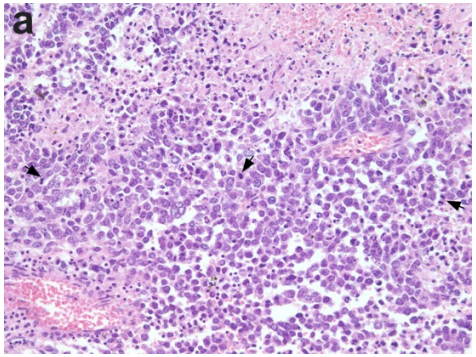

AE1/AE3 ←
CK7
ttf1
CK20
cdx2
SATB2
NKX3.1
CK5/6
P63
CD10 ←
PAX8 ←
WT1
GATA3

## Renal cell carcinoma



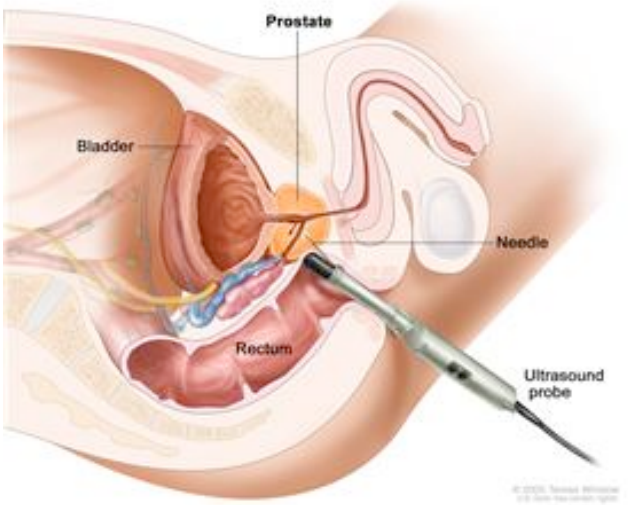
# Diagnosis of metastasis to the lung



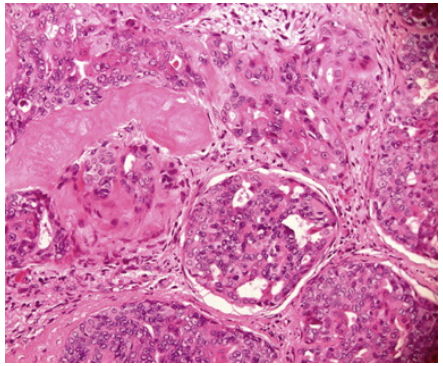


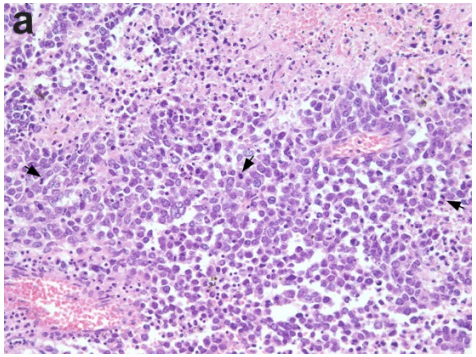

AE1/AE3 ←
CK7
ttf1
CK20
cdx2
SATB2
NKX3.1 ←
CK5/6
P63
CD10
PAX8
WT1
GATA3

## Prostate



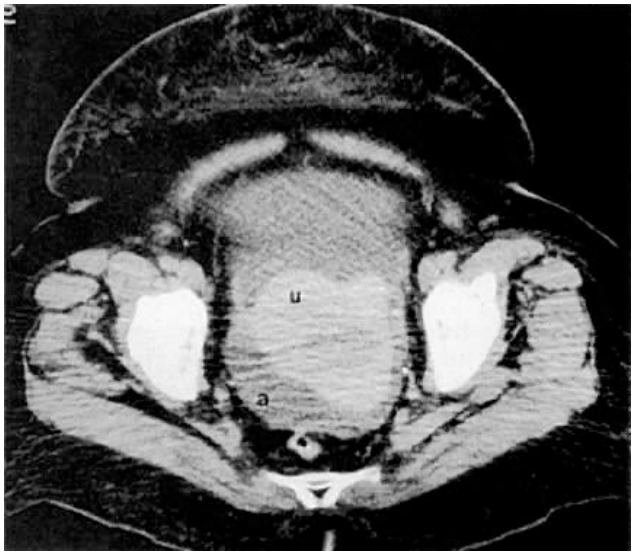
# Diagnosis of metastasis to the lung



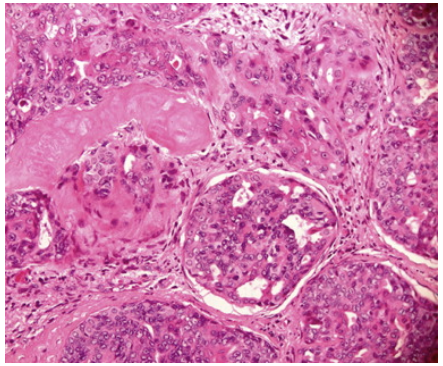


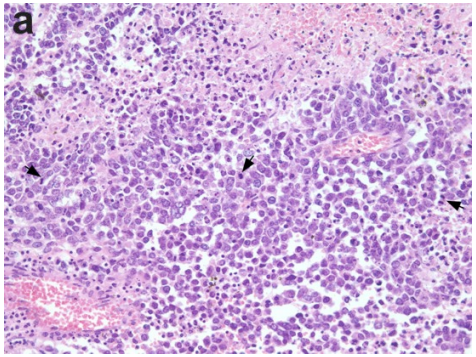

AE1/AE3 ←
CK7 ←
ttf1
CK20
cdx2
SATB2
NKX3.1
CK5/6
P63
CD10
PAX8 ←
WT1 ←
GATA3

## Endometrial cancer



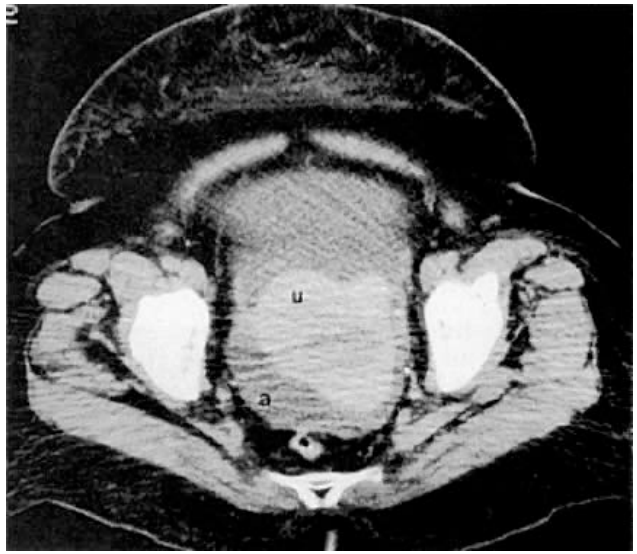
# Diagnosis of metastasis to the lung



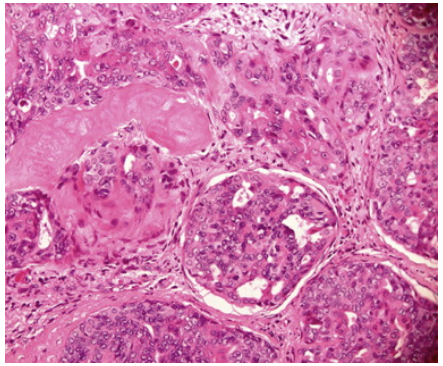


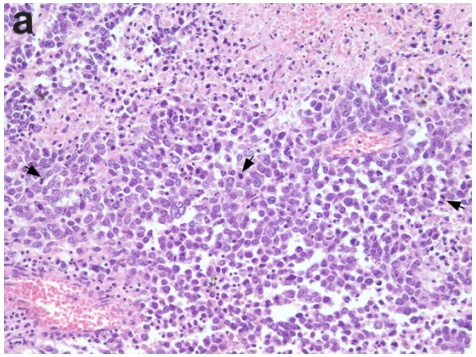

AE1/AE3 ←
CK7 ←
ttf1
CK20
cdx2
SATB2
NKX3.1
CK5/6
P63
CD10
PAX8 ←
WT1 ←
GATA3

## Ovarian cancer



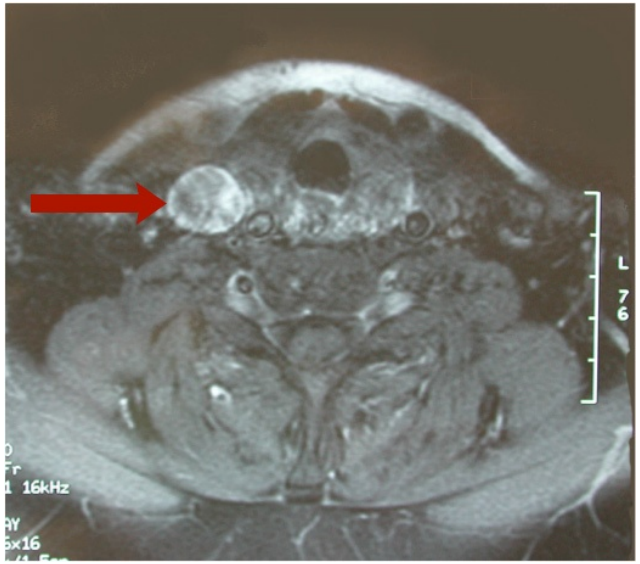
# Diagnosis of metastasis to the lung



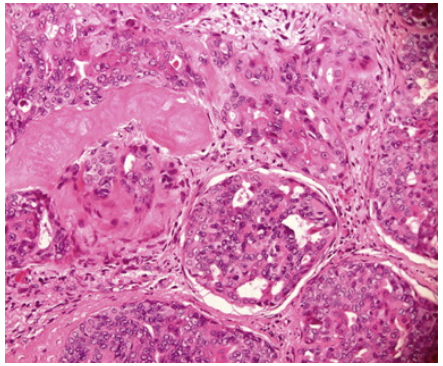


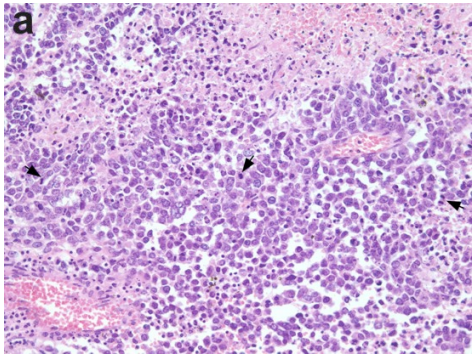

AE1/AE3 ←
CK7 ←
ttf1 ←
CK20
cdx2
SATB2
NKX3.1
CK5/6
P63
CD10
PAX8 ←
WT1
GATA3

## Thyroid cancer



# Diagnosis of metastasis to the lung






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

## Mesothelioma

# Diagnosis of metastasis to the lung

NordiQC

## Adeno - male

CK7
CK20
CDX2
Ttf1
PAX8
NKX3.1

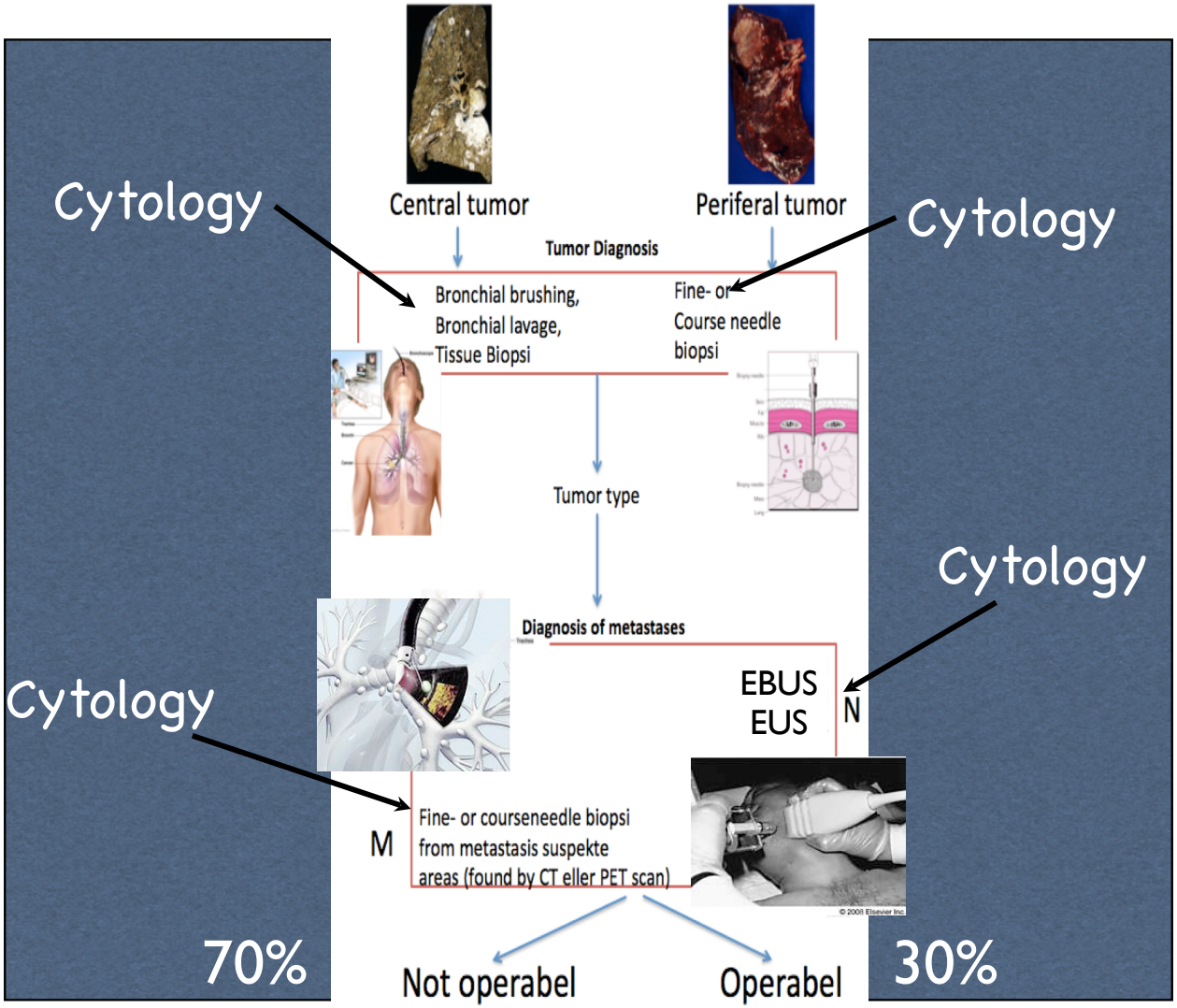
Suggestion

## Adeno - female

CK7
CK20
CDX2
Ttf1
PAX8
GATA3
WT1
ER

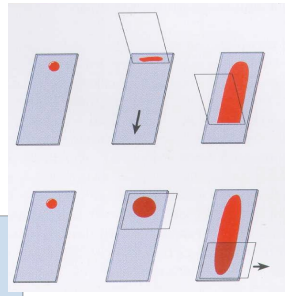
NordiQC

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


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

# Patoanatomical specimen

## Cytology



Histology

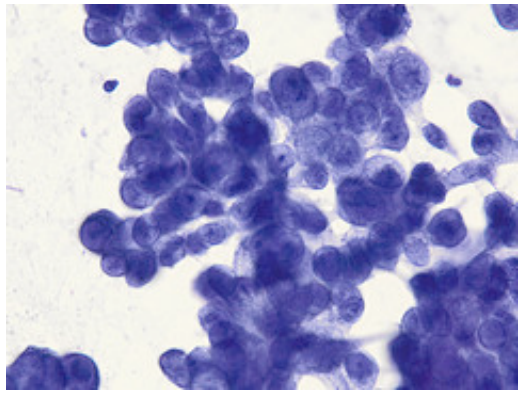
Fixation
Dehydration
Parafinembedding
Microtomy

Præparation

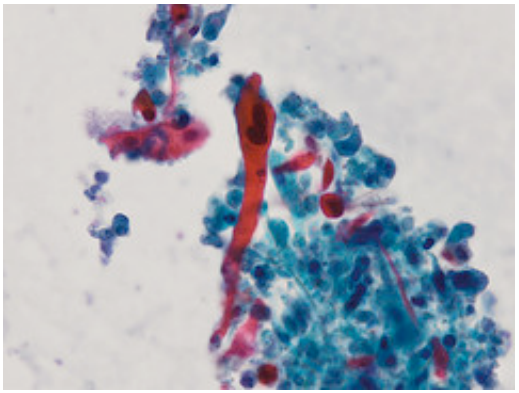
Smear preparation

## Visualization

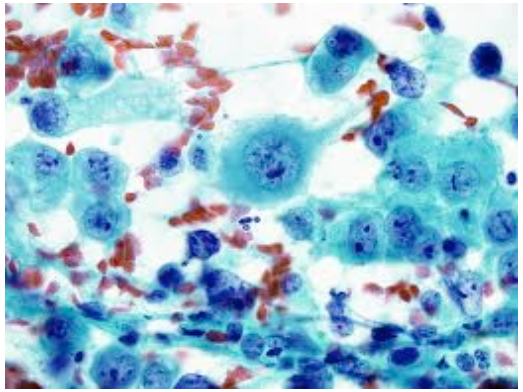
(Staining)



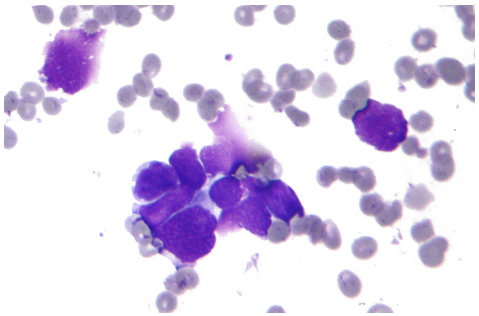
Adenocarcinoma



Squamous carcinoma



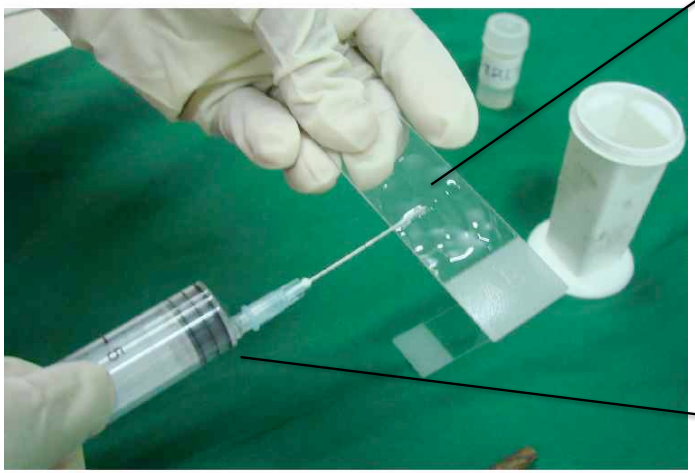
Large cell
neuroendocrine carc.

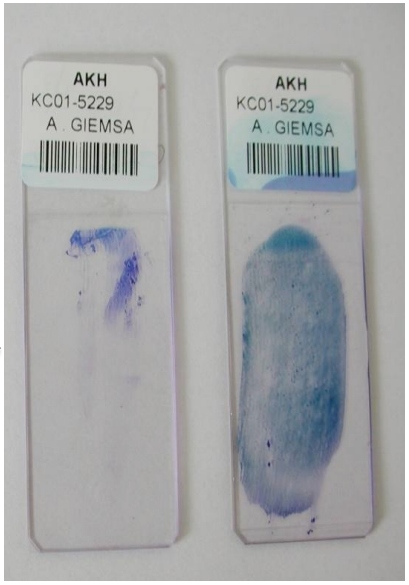


Small cell carcinoma

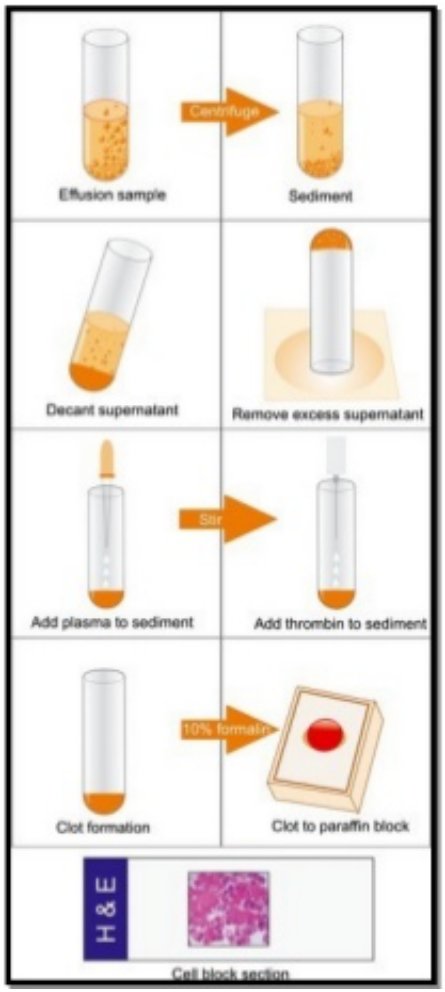
# Non Small Cell Lung Carcinoma (NSCLC)

# Immuncytology



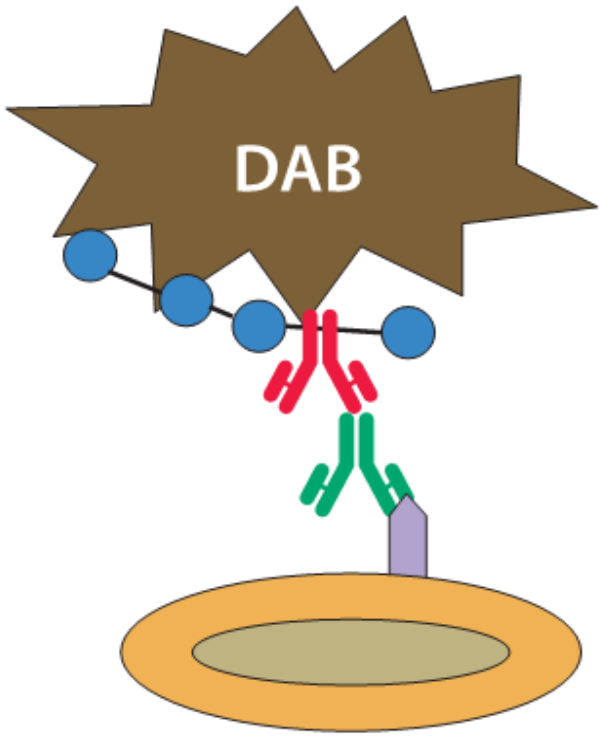



Smear




Cellblock

# Immuncytology




Kromogen (farvestof)

Visualiseringssystem (enzymer)

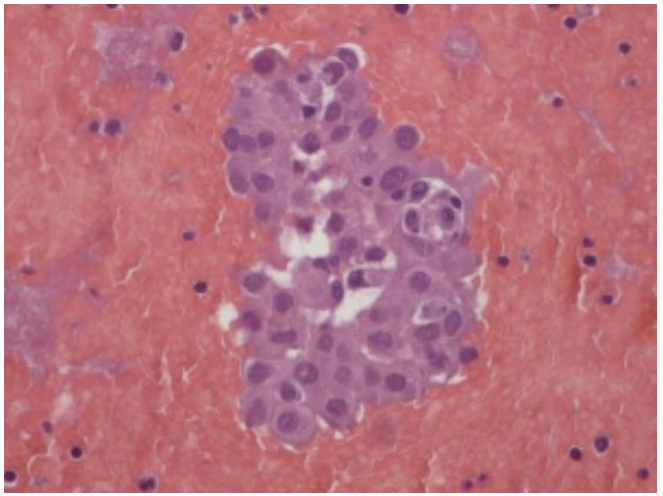
Sekundært antistof

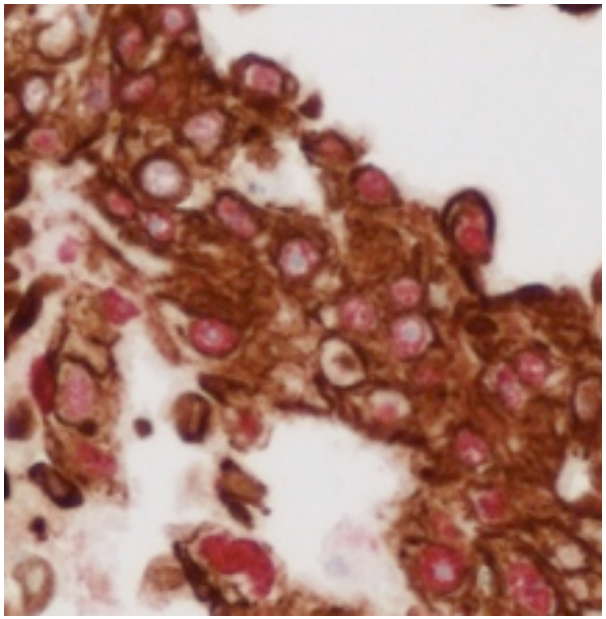
Primært antistof

Antigen

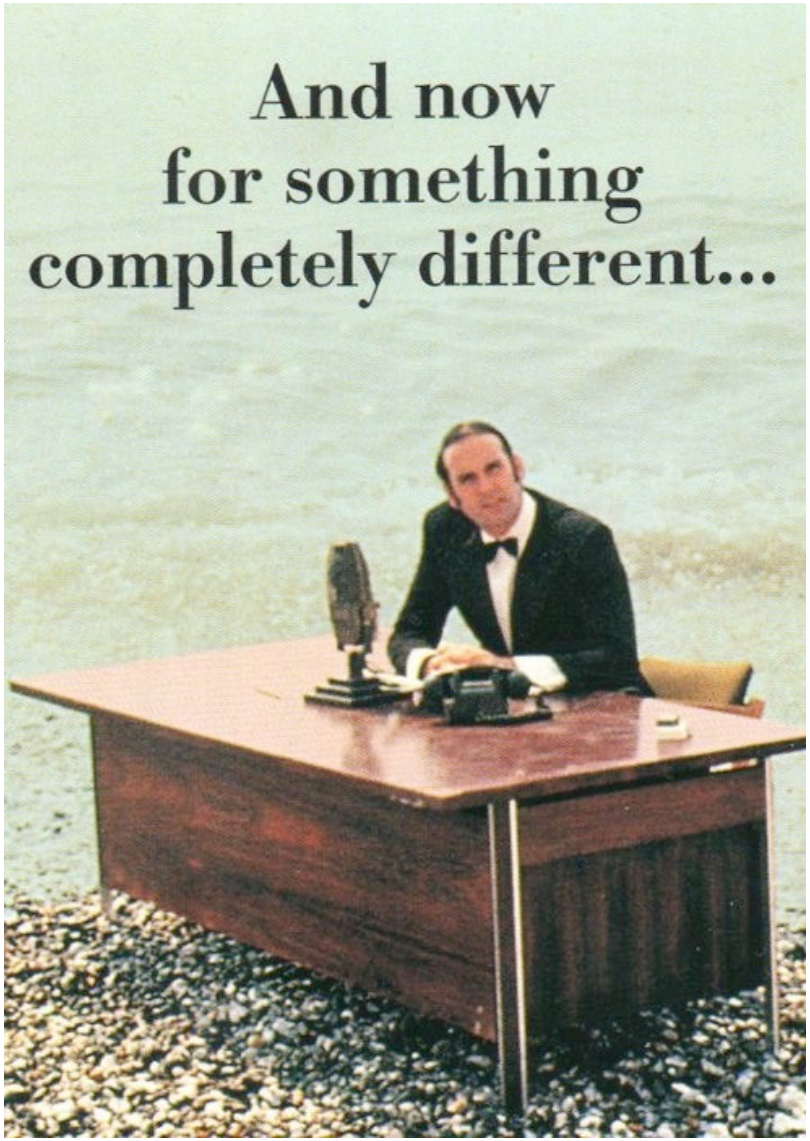
Cellens cytoplasma

Cellekerne



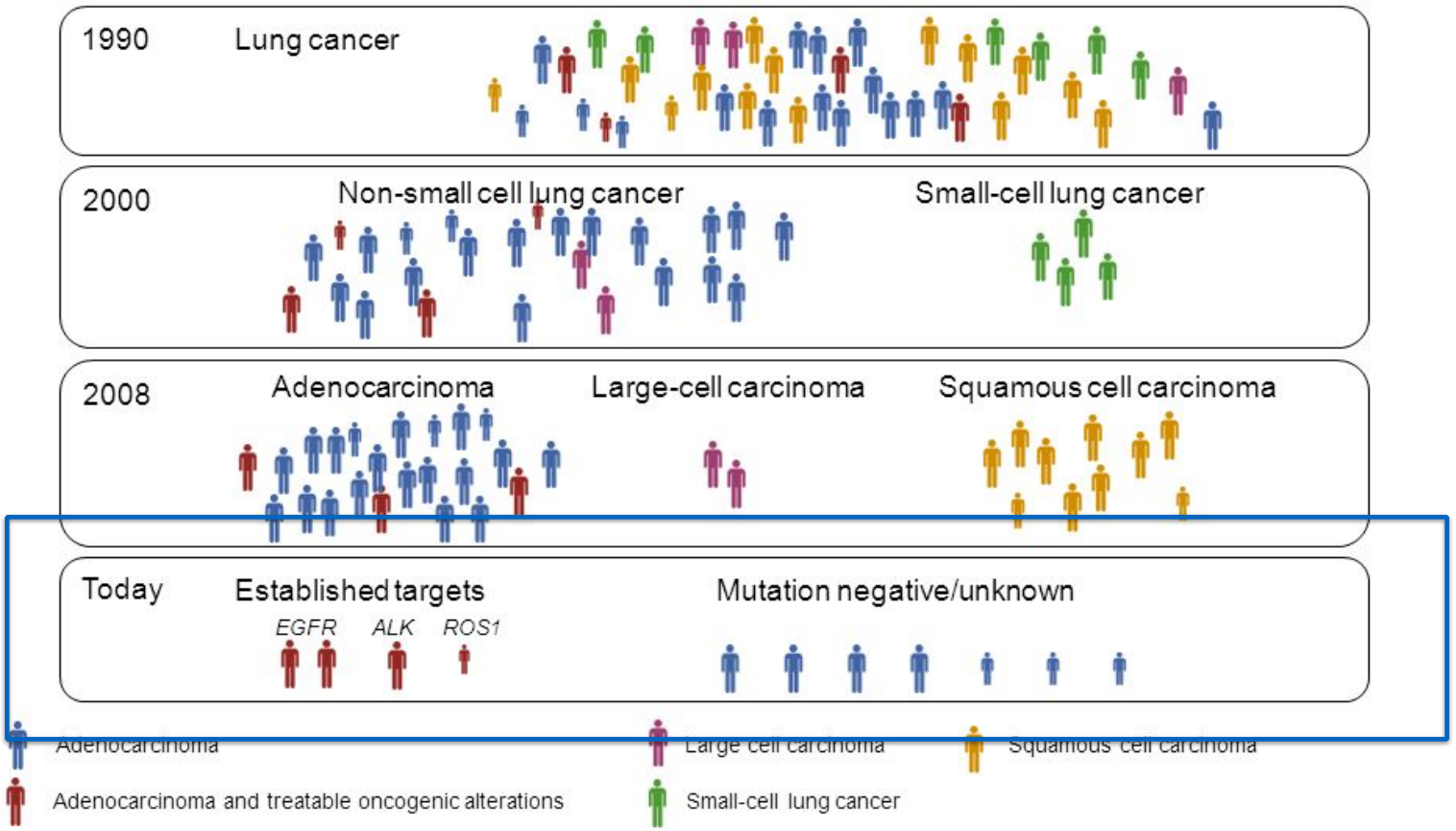


ttf1-CK7

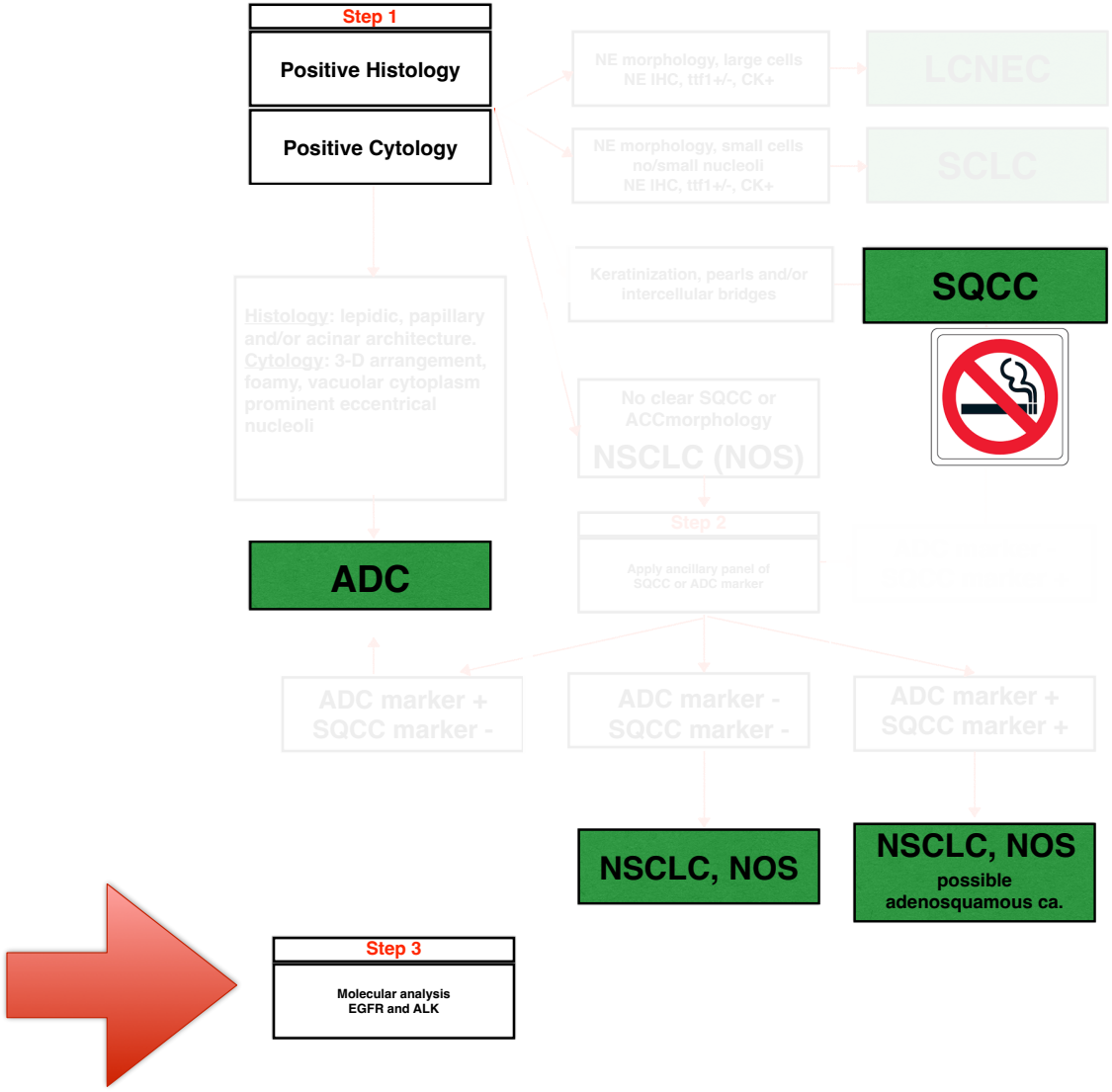


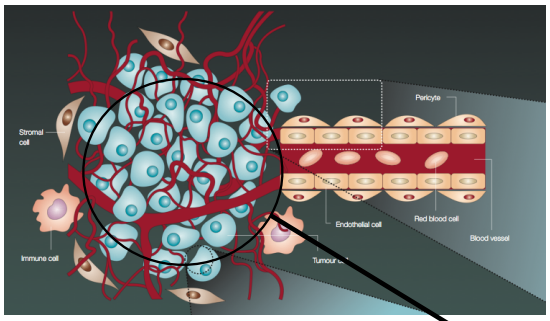

NordIQC

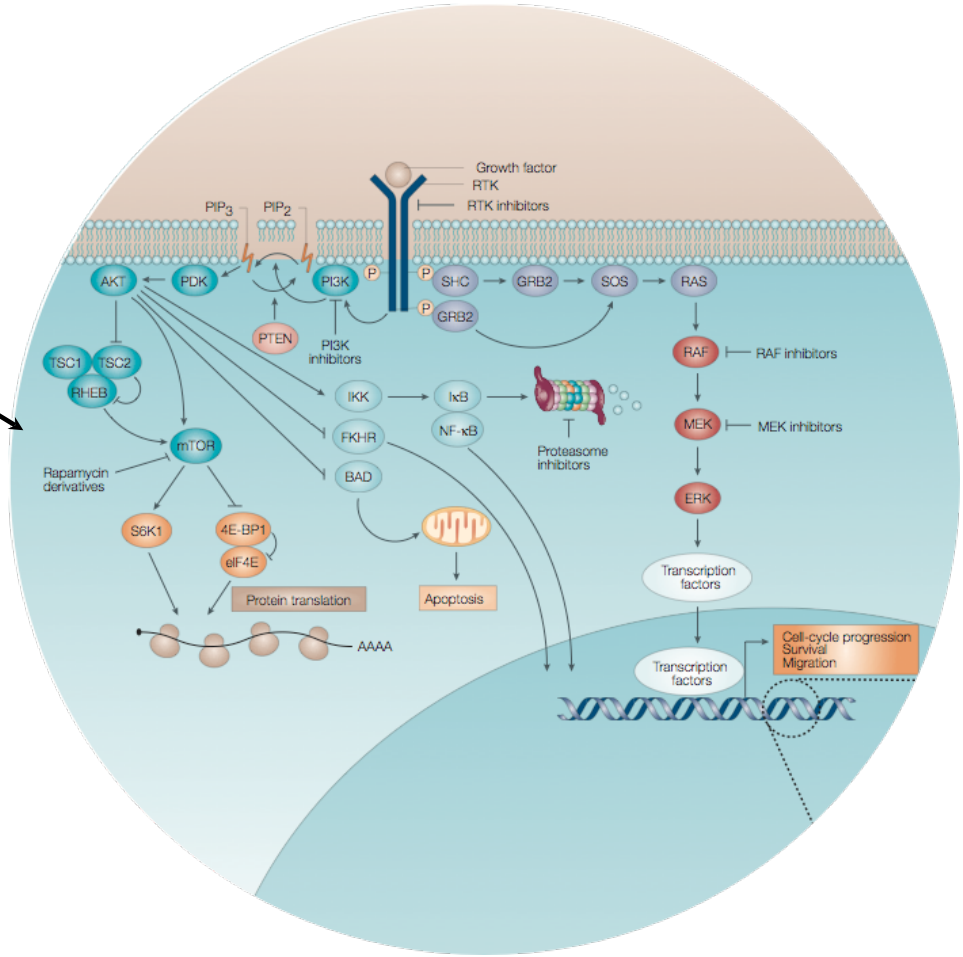
# Patient selection in lung cancer: Evolution over time



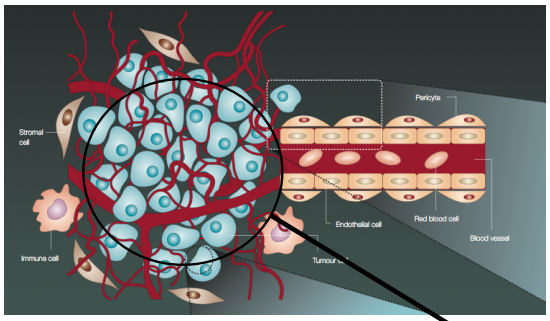

Adapted from Reck M, et al. Lancet 2013;382:709–19

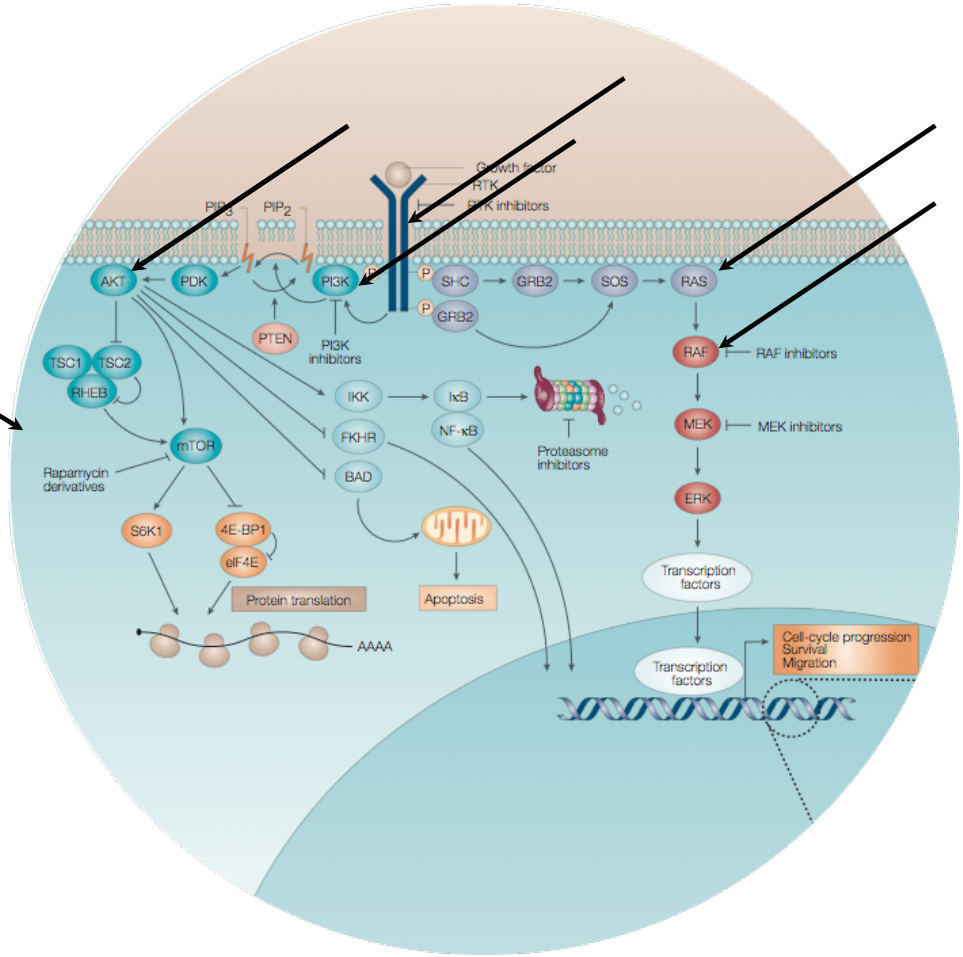

Step 1
Positive Histology
Positive Cytology
NE morphology, large cells
NE IHC, ttf1+/-, CK+
LCNEC
NE morphology, small cells
no/small nucleoli
NE IHC, ttf1+/-, CK+
SCLC
Keratinization, pearls and/or
intercellular bridges
SQCC
Histology: lepidic, papillary
and/or acinar architecture.
Cytology: 3-D arrangement,
foamy, vacuolar cytoplasm
prominent eccentrical
nucleoli
No clear SQCC or
ACCmorphology
NSCLC (NOS)
Step 2
Apply ancillary panel of
SQCC or ADC marker
ADC
ADC marker +
SQCC marker -
ADC marker -
SQCC marker -
ADC marker +
SQCC marker +
NSCLC, NOS
NSCLC, NOS
possible
adenosquamous ca.
Step 3
Molecular analysis
EGFR and ALK



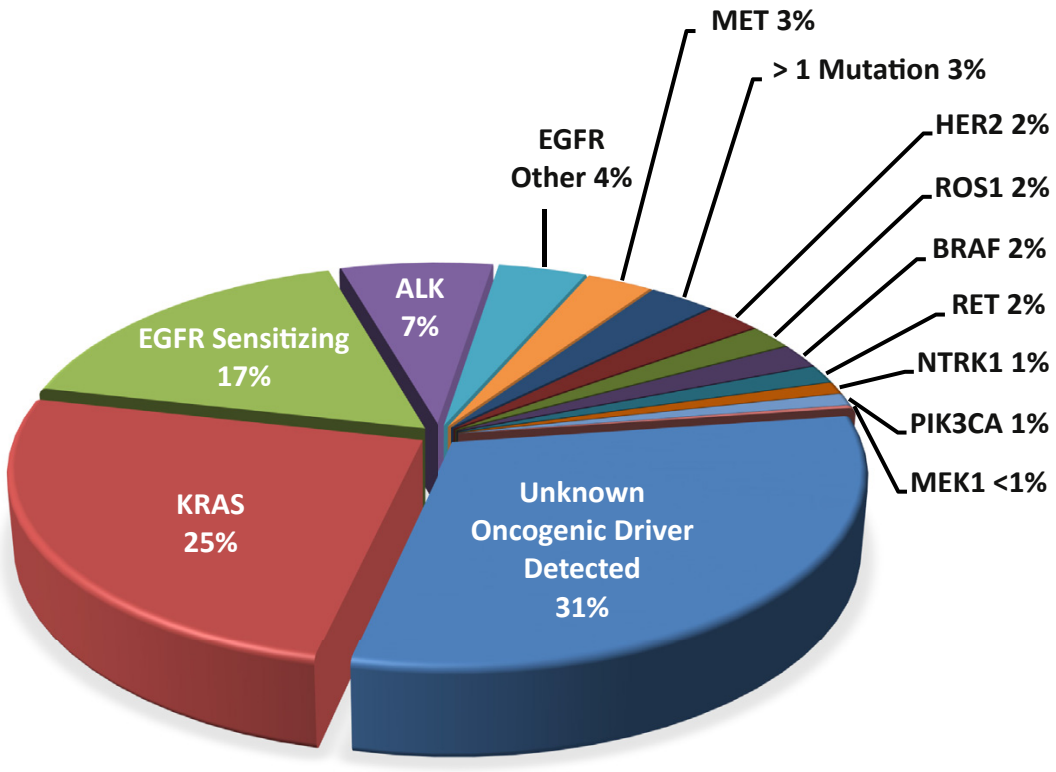

# Pathways of cancer


Pericyte
Stromal cell
Endothelial cell
Red blood cell
Blood vessel
Immune cell


Growth factor
RTK
RTK inhibitors
PIP3
PIP2
AKT
PDK
PI3K
P
SHC
GRB2
SOS
RAS
GRB2
PTEN
PI3K inhibitors
RAF
RAF inhibitors
TSC1
TSC2
RHEB
IKK
IκB
NF-κB
Proteasome inhibitors
MEK
MEK inhibitors
mTOR
FKHR
BAD
Rapamycin derivatives
ERK
S6K1
4E-BP1
eIF4E
Protein translation
Apoptosis
Transcription factors
AAAA
Transcription factors
Cell-cycle progression
Survival
Migration

oncogenes

# Driver mutations
# Lung Adenocarcinoma

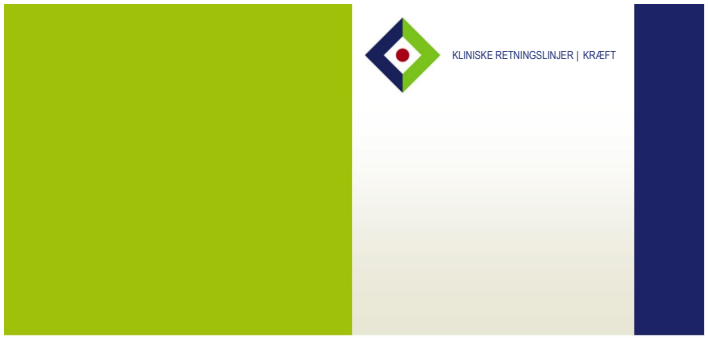



STATE OF THE ART: CONCISE REVIEW

Scientific Advances in Lung Cancer 2015

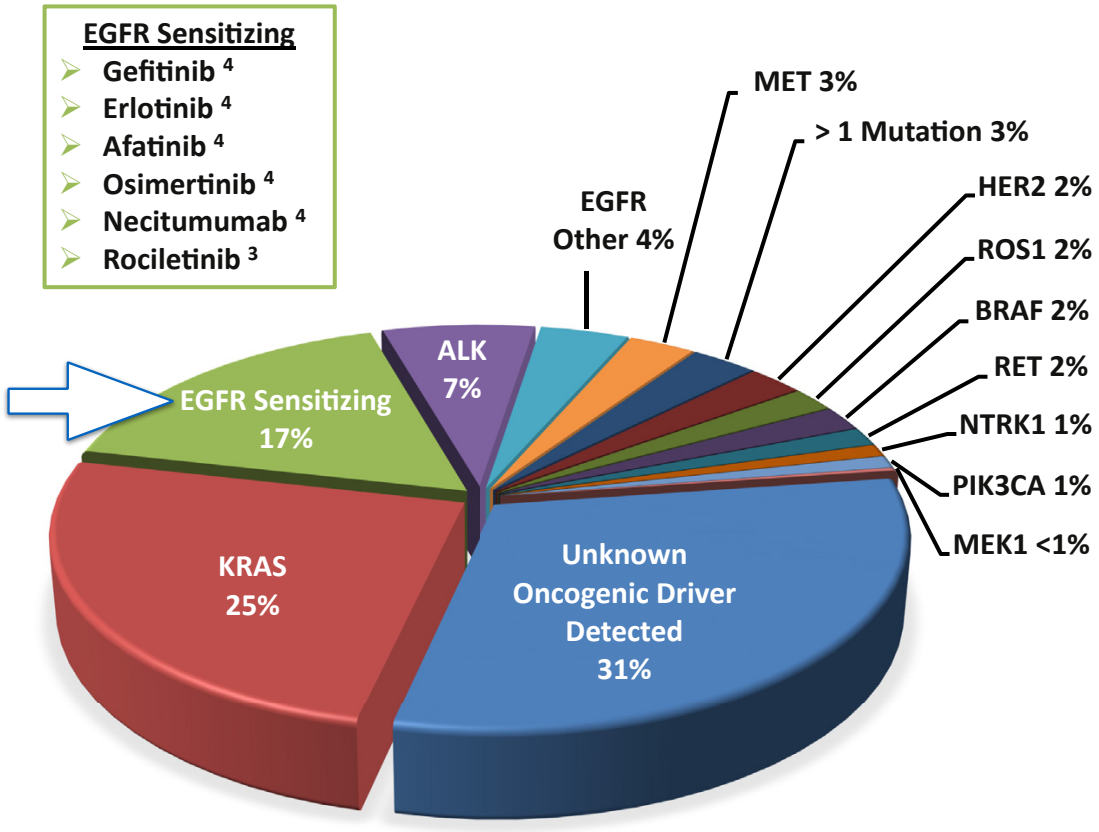
*Journal of Thoracic Oncology* *Vol. 11 No. 5: 613-638*

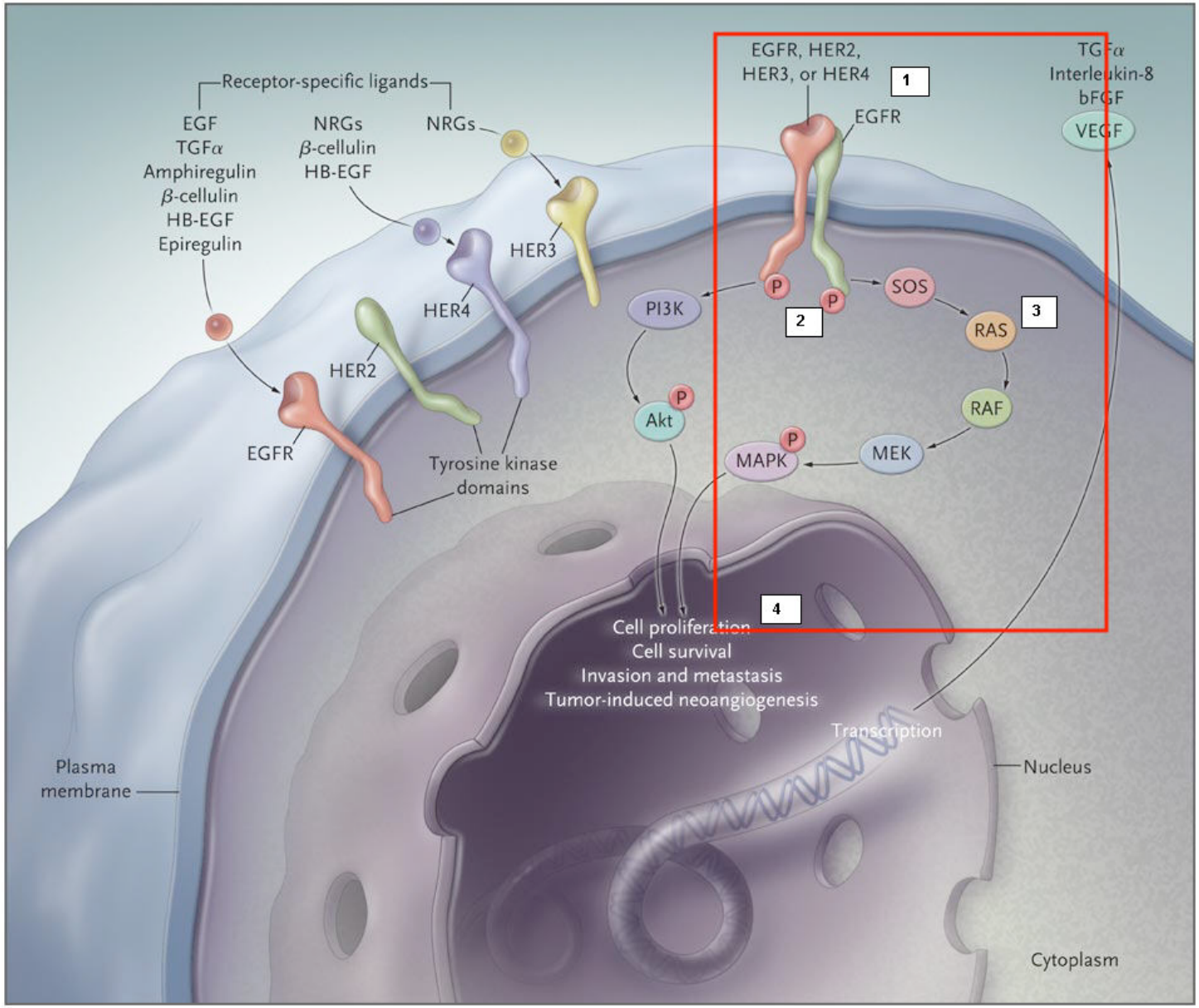
# Danish Lung Cancer Group (DLCG)

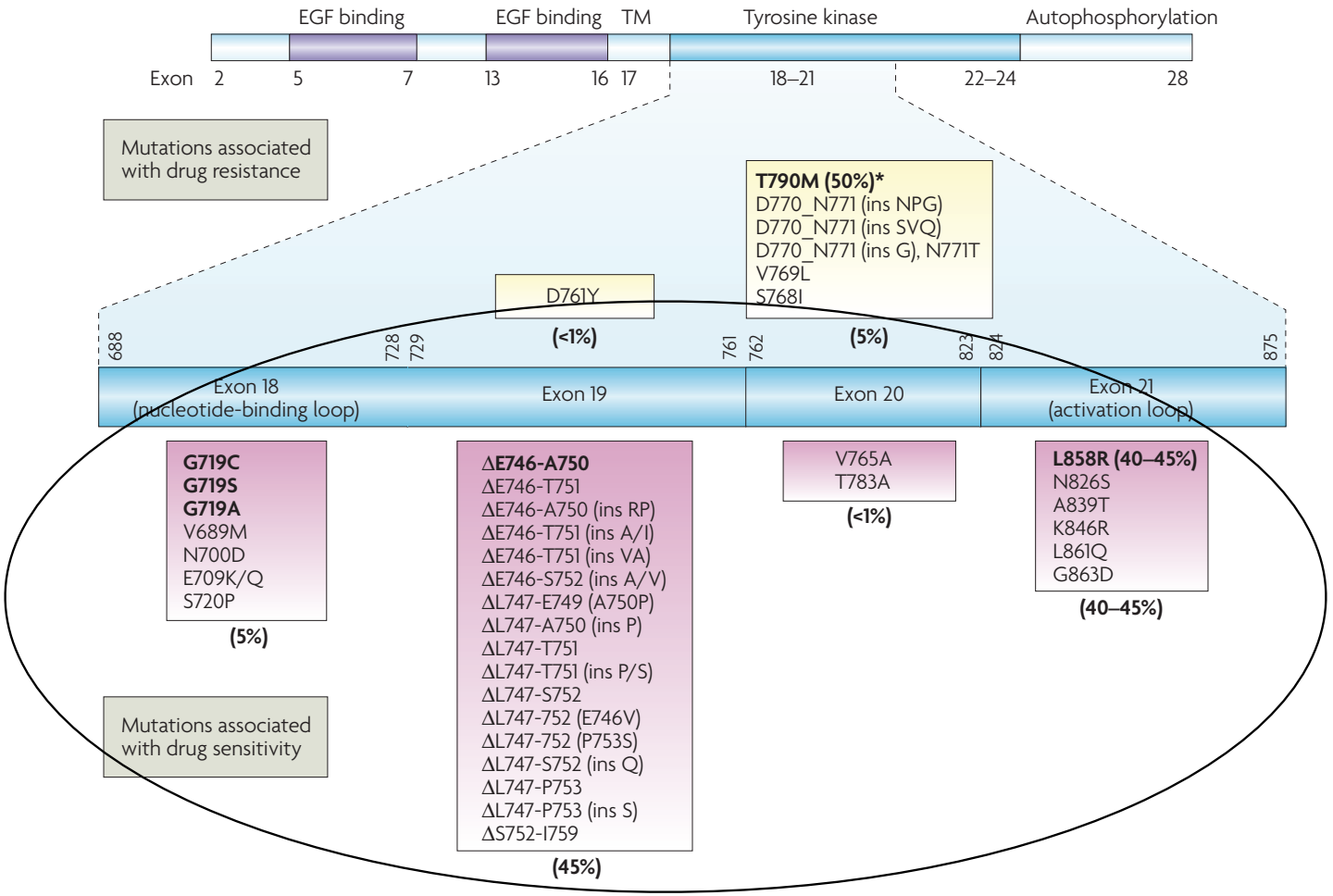



## Lungecancer – Patologi

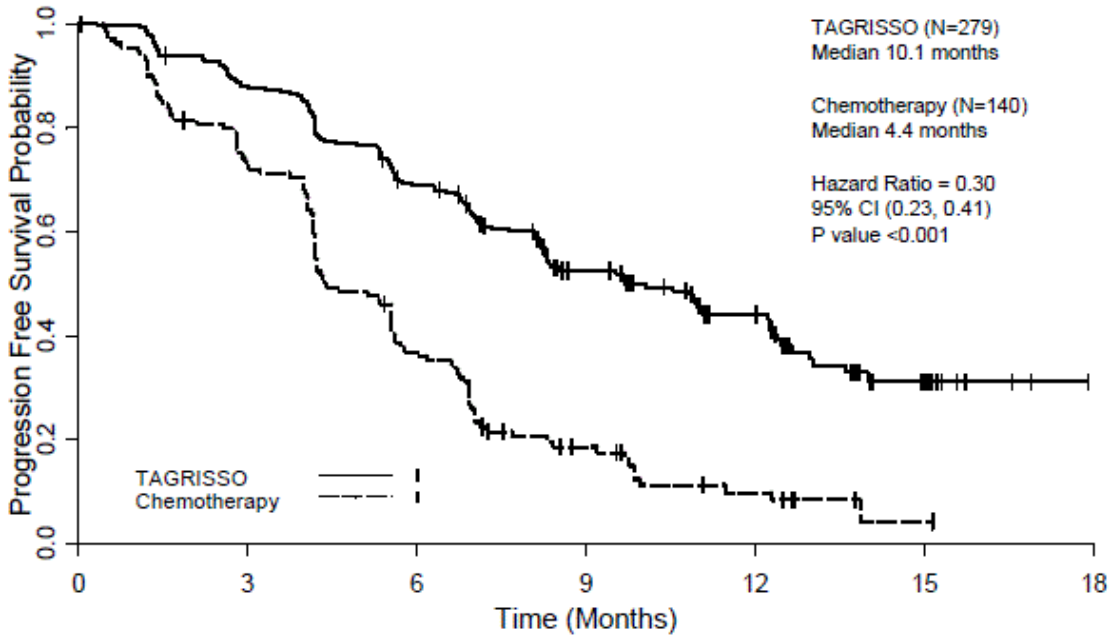
46. **Reflextest af de obligatoriske markører bør foretages ved den primære diagnostik af nedenstående grupper. (A)**
    - **EGFR, ALK, ROS1: adenokarcinomer + ikke-småcellede karcinomer, hvor typen ikke sikkert kan afgøres**
    - **PD-L1: alle ikke-småcellede karcinomer**


EGFR Sensitizing
Gefitinib 4
Erlotinib 4
Afatinib 4
Osimertinib 4
Necitumumab 4
Rociletinib 3
EGFR Sensitizing 17%
ALK 7%
EGFR Other 4%
MET 3%
> 1 Mutation 3%
HER2 2%
ROS1 2%
BRAF 2%
RET 2%
NTRK1 1%
PIK3CA 1%
MEK1 <1%
KRAS 25%
Unknown Oncogenic Driver Detected 31%


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




# autoactivates EGFR


Number at risk

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

Tick marks represent censored observations

Contents lists available at ScienceDirect

Lung Cancer

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

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

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

[a] Department of Pathology, Seoul National University Bundang Hospital, 300 Gumi-dong, Bundang-gu, Seongnam-si, Gyeonggi 463-707, Republic of Korea
[b] Department of Pathology, Kyungpook National University College of Medicine, 680 Gukchaebosang-ro, Jung-gu, Daegu 700-842, Republic of Korea
[c] Department of Pathology, Seoul National University College of Medicine, 103 Daehak-ro, Jongno-gu, Seoul 110-799, Republic of Korea
[d] Department of Internal Medicine, Seoul National University Bundang Hospital, 300 Gumi-dong, Bundang-gu, Seongnam-si, Gyeonggi 463-707, Republic of Korea

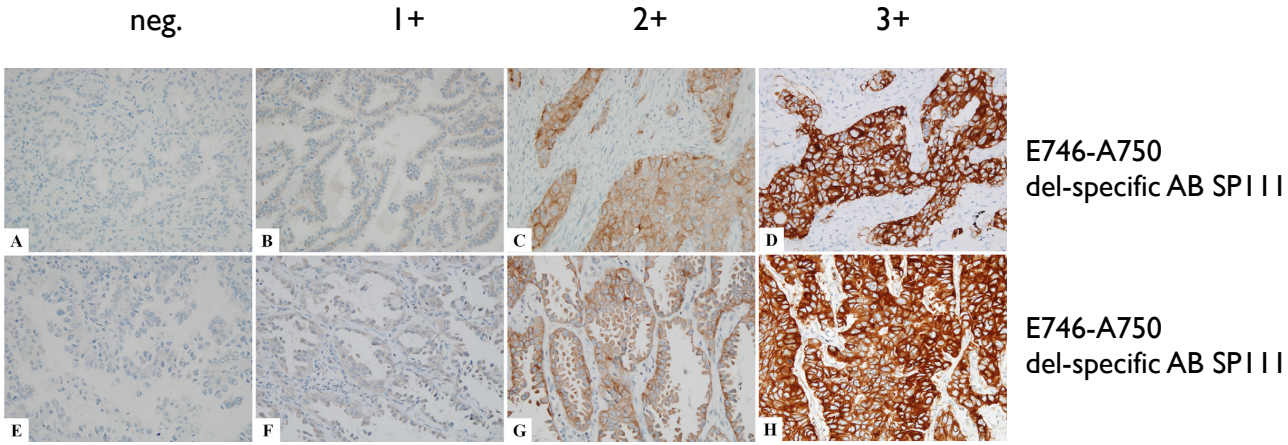
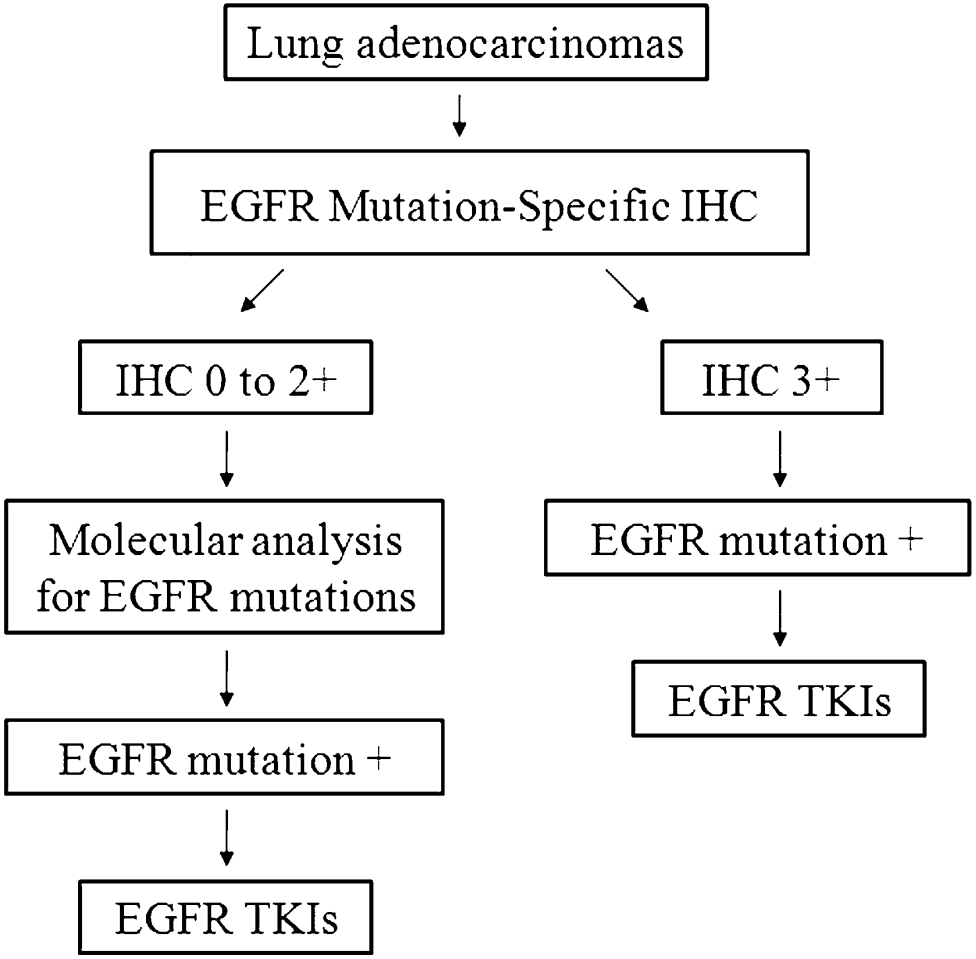



**Table 2**
Diagnostic power of mutation-specific antibodies comparing with *EGFR* mutational status.

| Mutation-specific antibodies | *EGFR* mutations | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|
| Anti-EGFR E746_A750 del | E746_A750 deletion | | | | |
| | ≥Score 1 as positive | 94.1% | 96.1% | 80.0% | 99.0% |
| | ≥Score 2 as positive | 70.6% | 99.0% | 92.3% | 95.3% |
| | ≥Score 3 as positive | 29.4% | 100.0% | 100.0% | 89.6% |
| | All deletions in exon 19 | | | | |
| | ≥Score 1 as positive | 54.8% | 96.6% | 85.0% | 86.0% |
| | ≥Score 2 as positive | 40.3% | 99.4% | 96.2% | 82.7% |
| | ≥Score 3 as positive | 16.1% | 100.0% | 100.0% | 77.4% |
| Anti-EGFR L858R | L858R | | | | |
| | ≥Score 1 as positive | 93.5% | 50.0% | 30.7% | 97.0% |
| | ≥Score 2 as positive | 80.4% | 89.7% | 64.9% | 95.1% |
| | ≥Score 3 as positive | 41.3% | 100.0% | 100.0% | 87.8% |

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

# Algorithm




Lung Cancer

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

NordiQC

*DNA(template)*

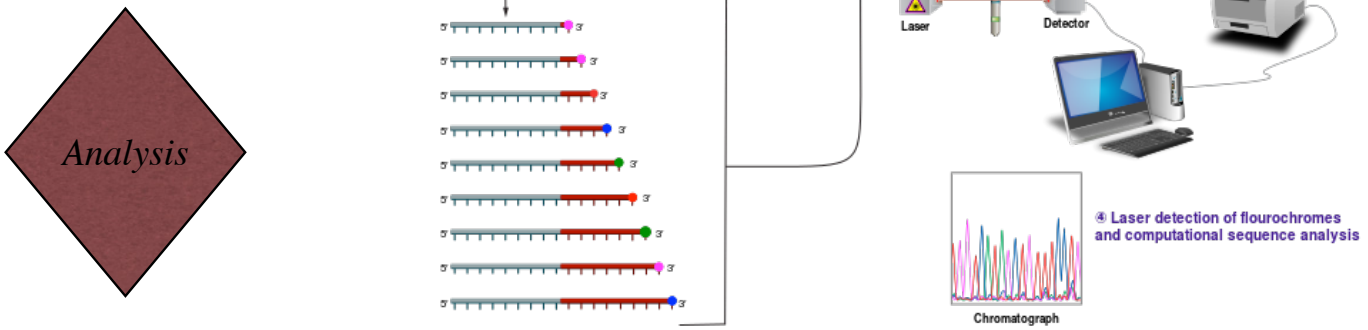
*PCR*

*Analysis*

*DNA-purification*

*Tissue section*

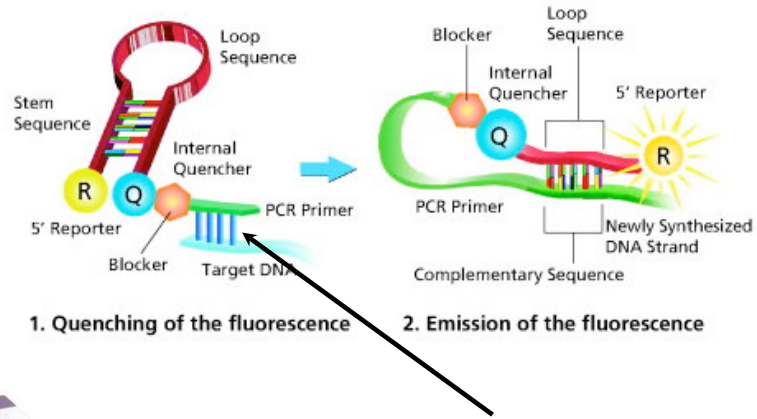
# Sequencing



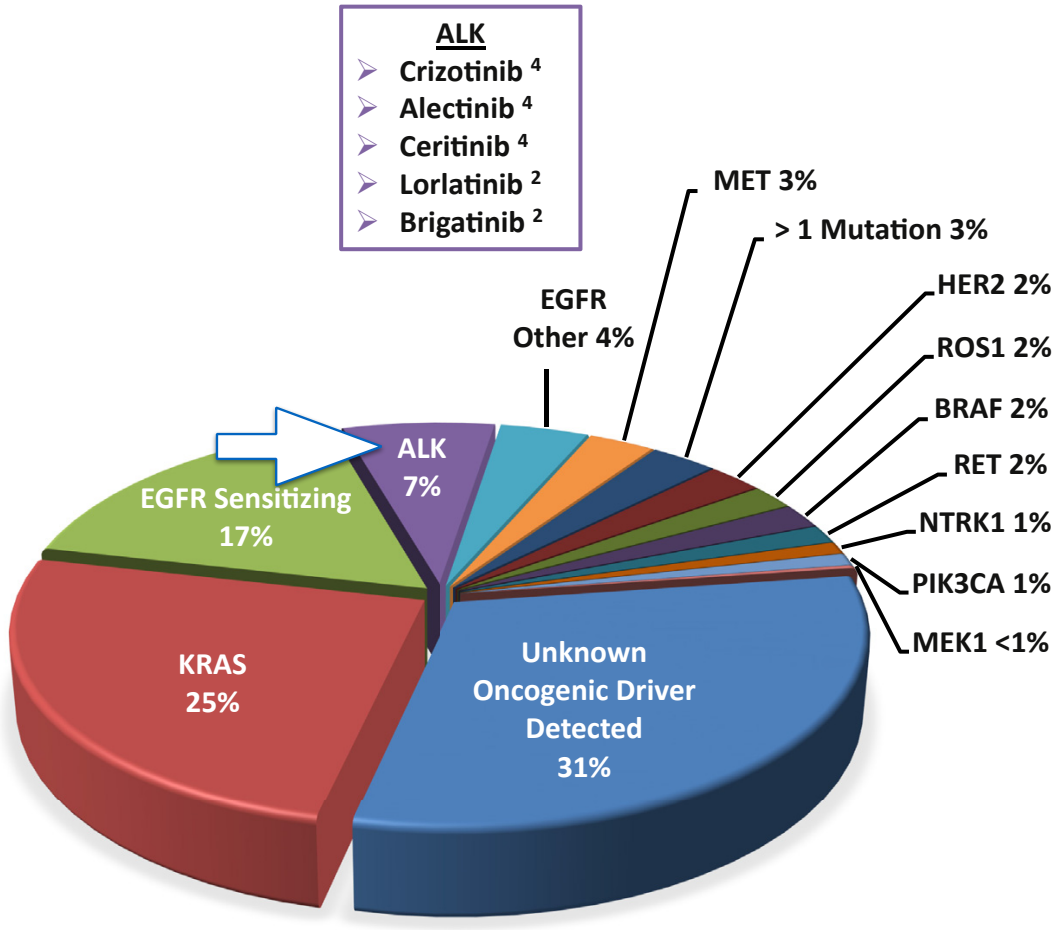

*Analysis*

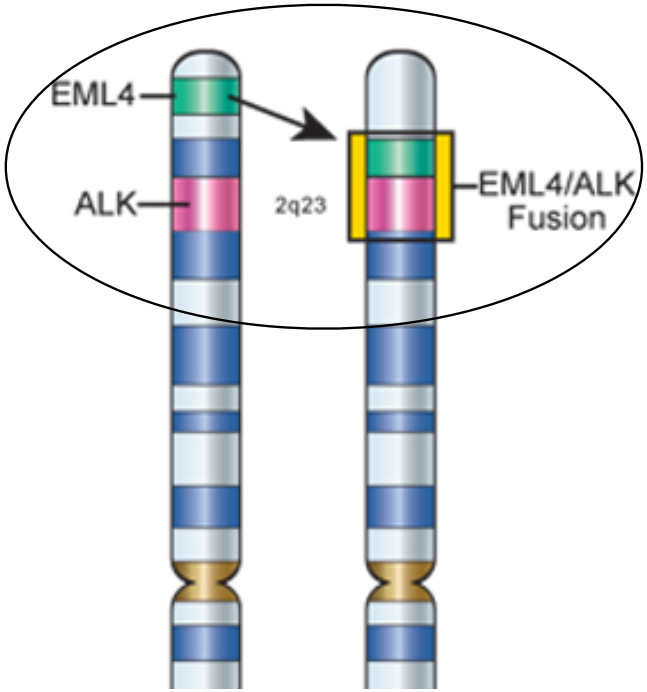
# PCR bassed test

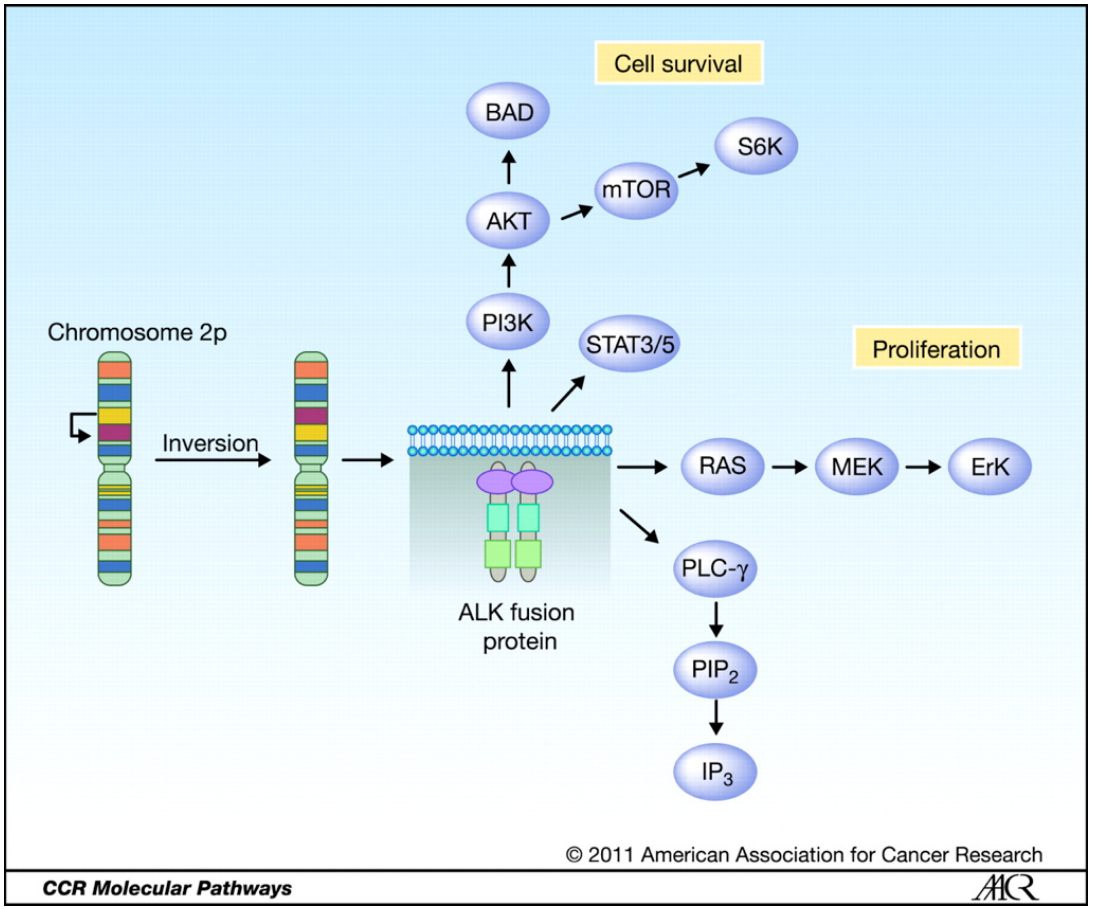



mutationspecific primer


ALK
Crizotinib 4
Alectinib 4
Ceritinib 4
Lorlatinib 2
Brigatinib 2
MET 3%
> 1 Mutation 3%
HER2 2%
ROS1 2%
BRAF 2%
RET 2%
NTRK1 1%
PIK3CA 1%
MEK1 <1%
EGFR
Other 4%
ALK
7%
EGFR Sensitizing
17%
KRAS
25%
Unknown
Oncogenic Driver
Detected
31%


EML4
ALK
2q23
EML4/ALK
Fusion


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

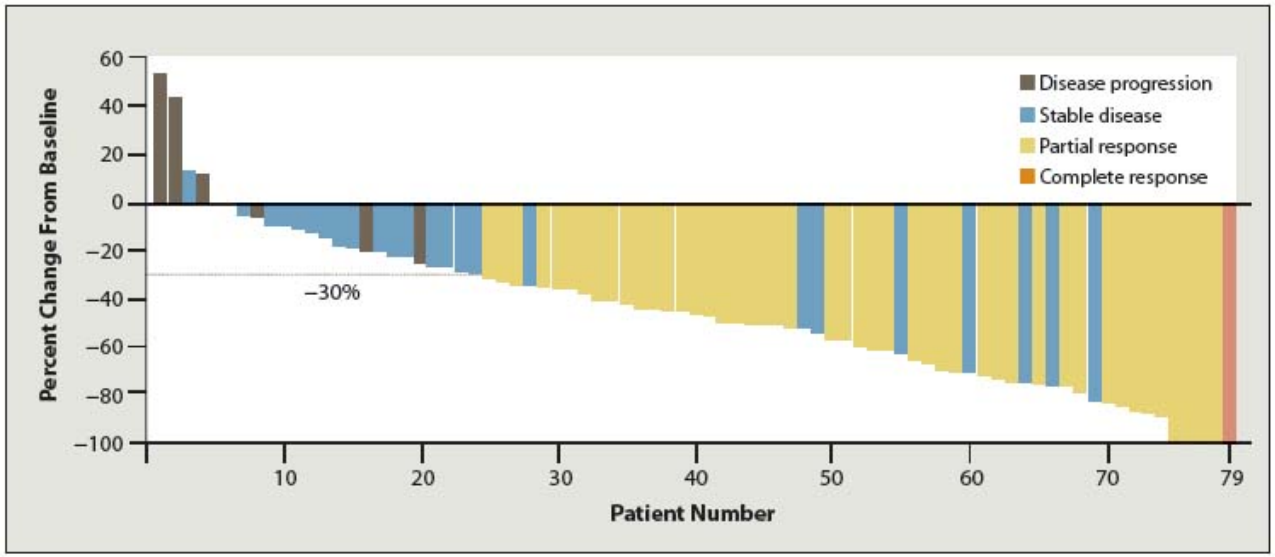
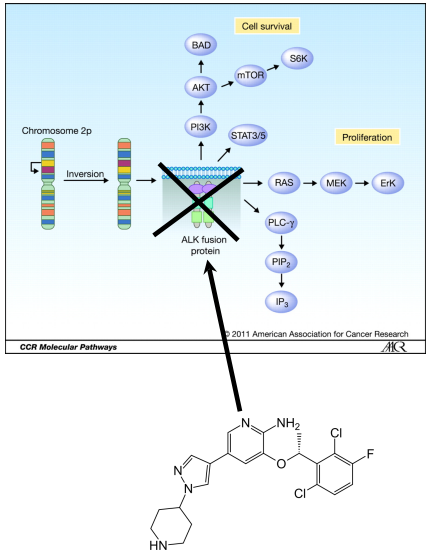
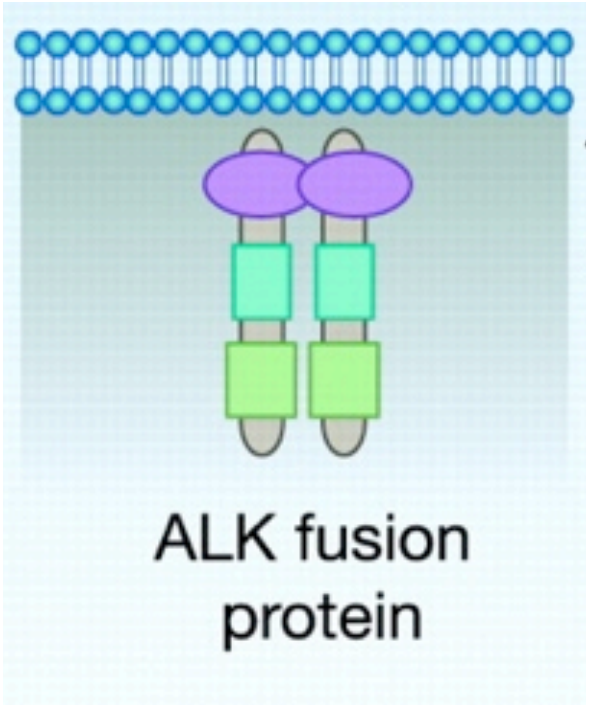


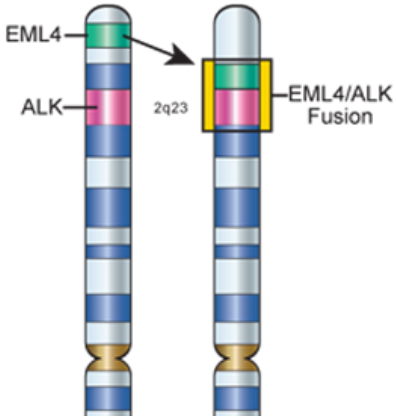

**Figure 2: Waterfall plot showing response to crizotinib in patients with *EML4-ALK* NSCLC.** Percent change in tumor burden relative to pretreatment baseline is represented. (Reproduced with permission from Kwak et al. N Engl J Med. 2010;363:1693-1703. Copyright © 2010, Massachusetts Medical Society.)



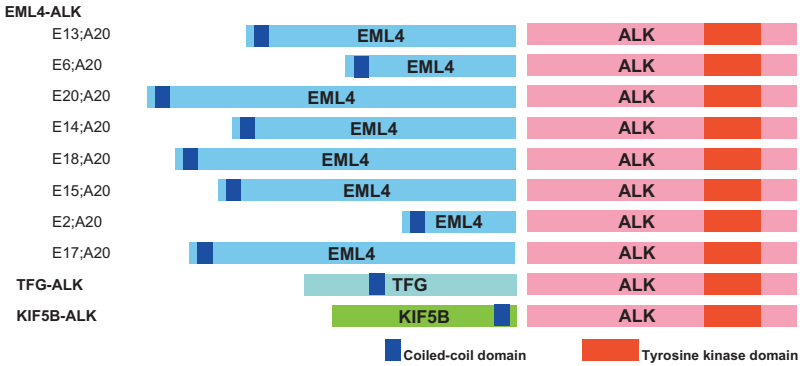

## Detection of fusion protein



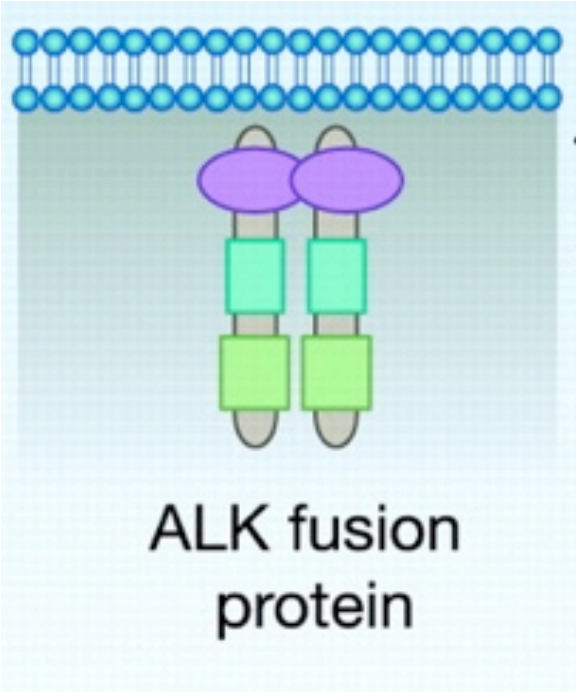

## Detection of chromosomal changes



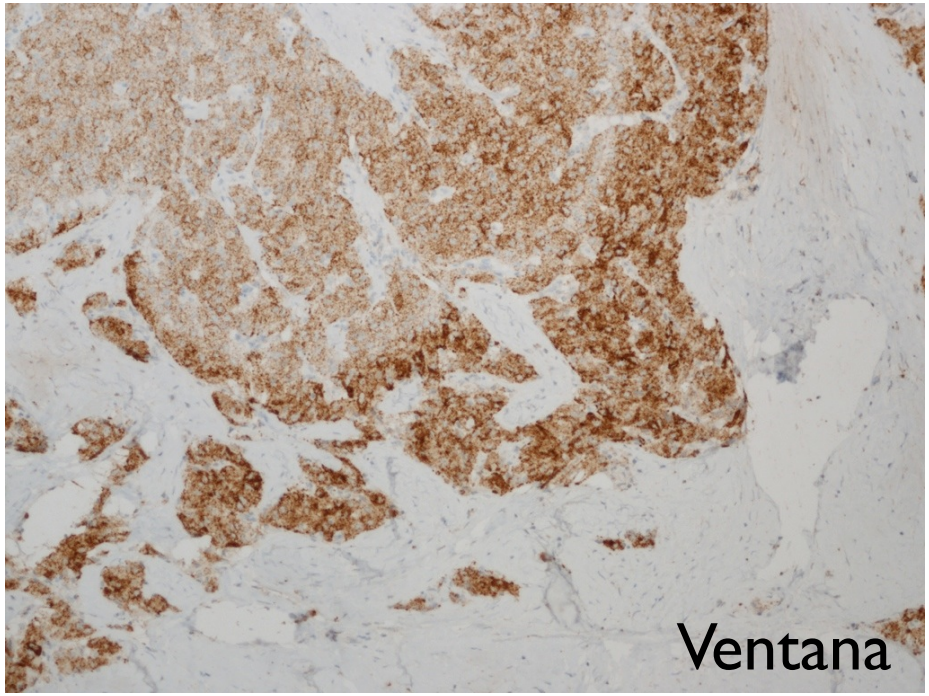

## Detection of fusion RNA



Detection of fusion protein



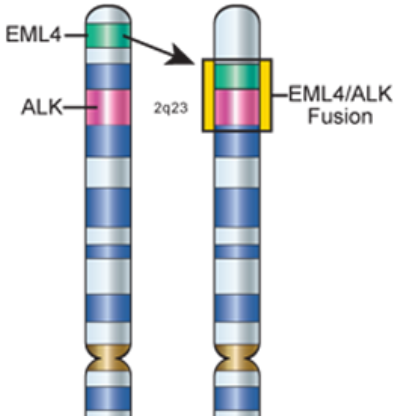

## Immunohistochemistry



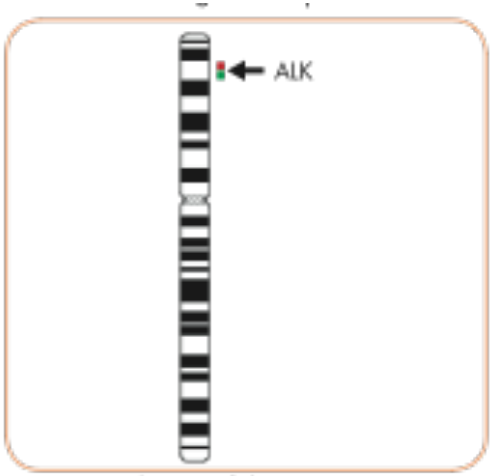

Detects ALK independent of fusion partner

# F(C)ISH

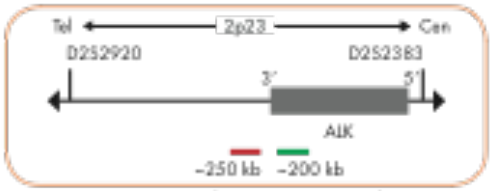
Detection of chromosomal changes



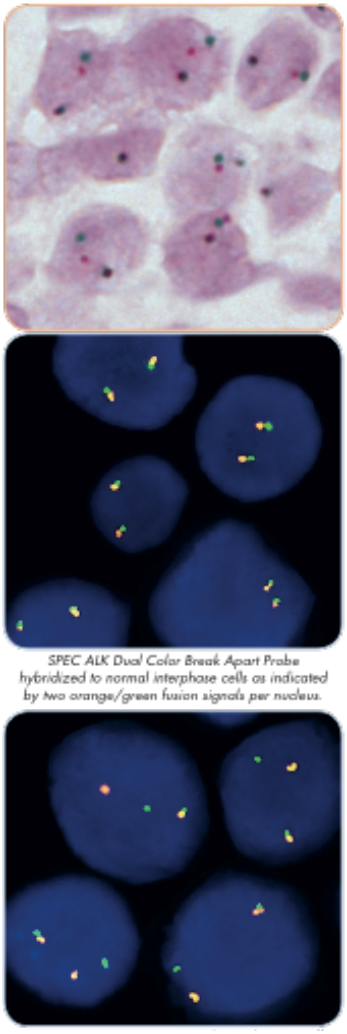

ZYTOVISION
Molecular diagnostics simplified




Ideogram of chromosome 2 indicating the hybridization locations.

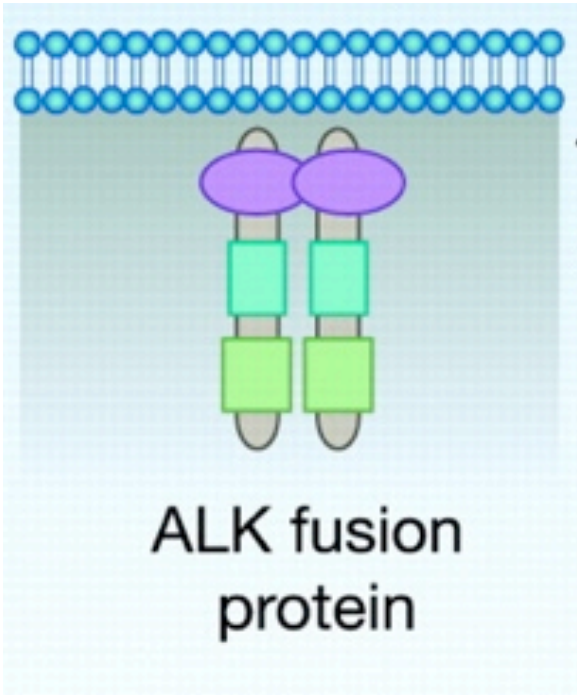



SPEC ALK Probe map (not to scale).

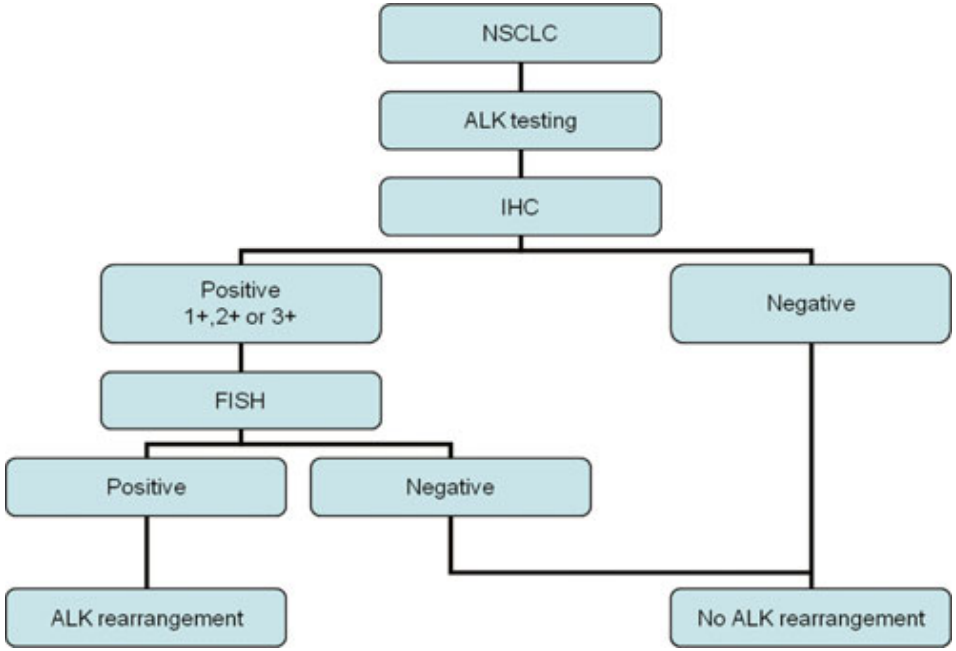


SPEC ALK Dual Color Break Apart Probe hybridized to normal interphase cells as indicated by two orange/green fusion signals per nucleus.

Detection of fusion protein




# Algorithm



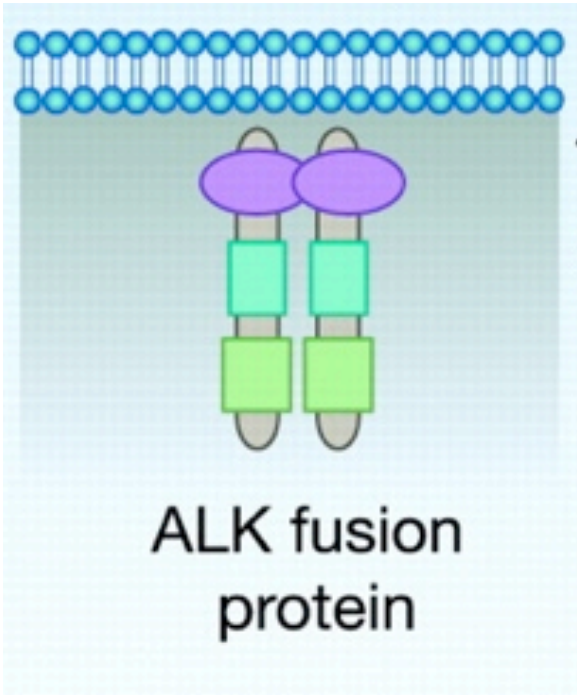

Virchows Arch (2012) 461:245–257
DOI 10.1007/s00428-012-1281-4

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 · Włodzimierz Olszewski · Patrick Pauwels · Frédérique Penault-Llorca · Giulio Rossi**

Detection of fusion protein

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REVIEW AND PERSPECTIVES

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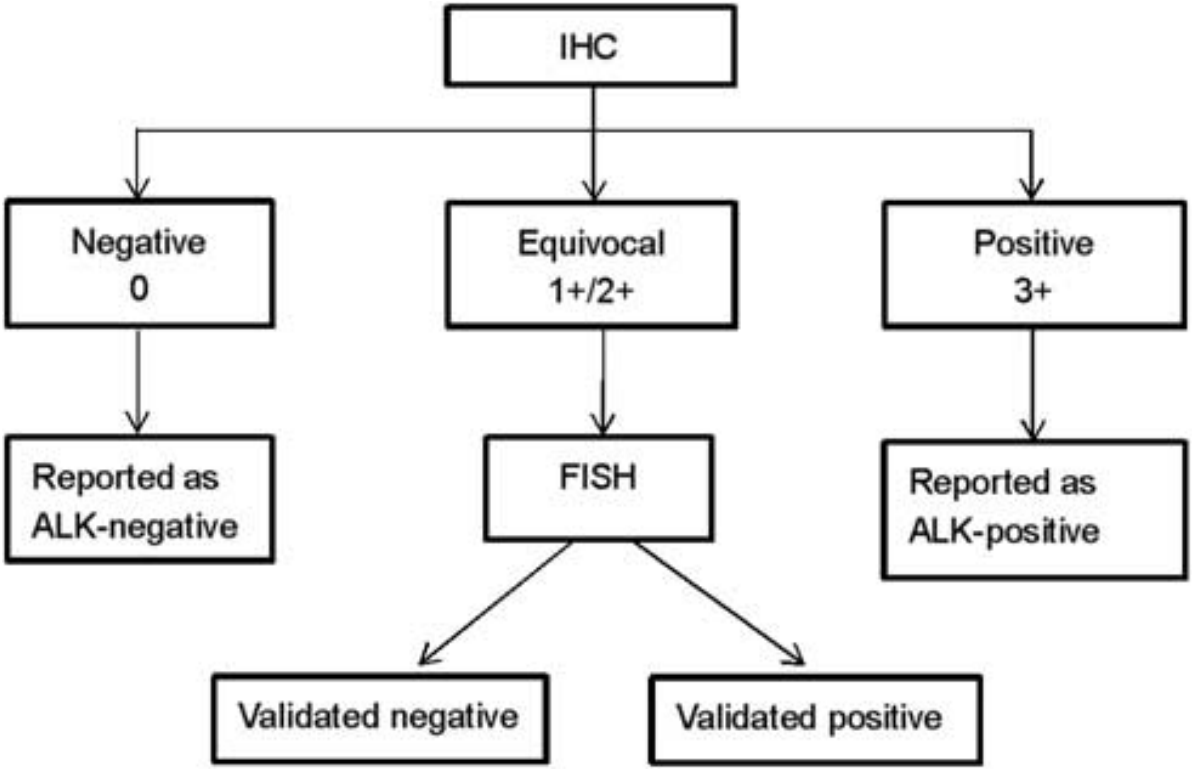
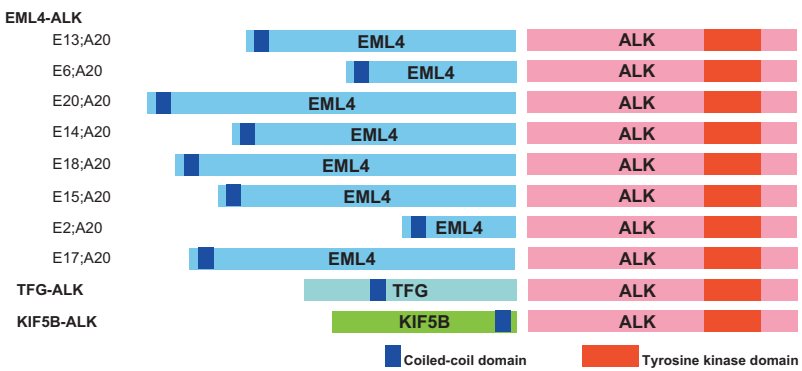
# Algorithm



# RT PCR based test

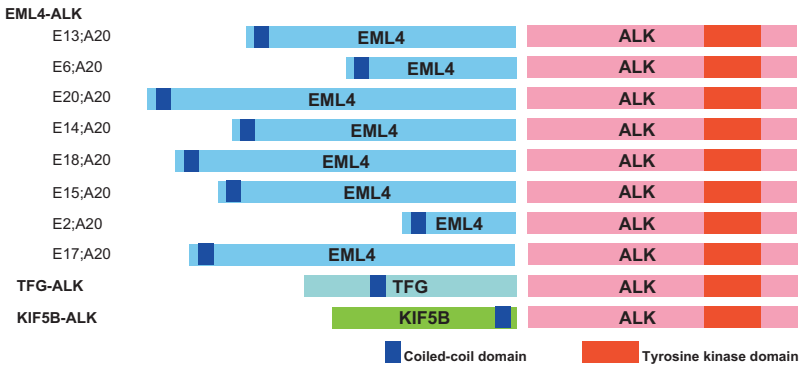
## Detection of fusion RNA

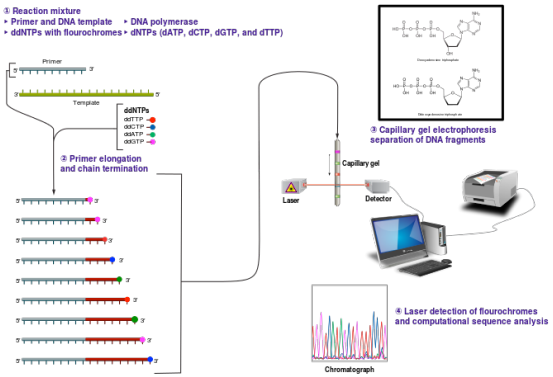


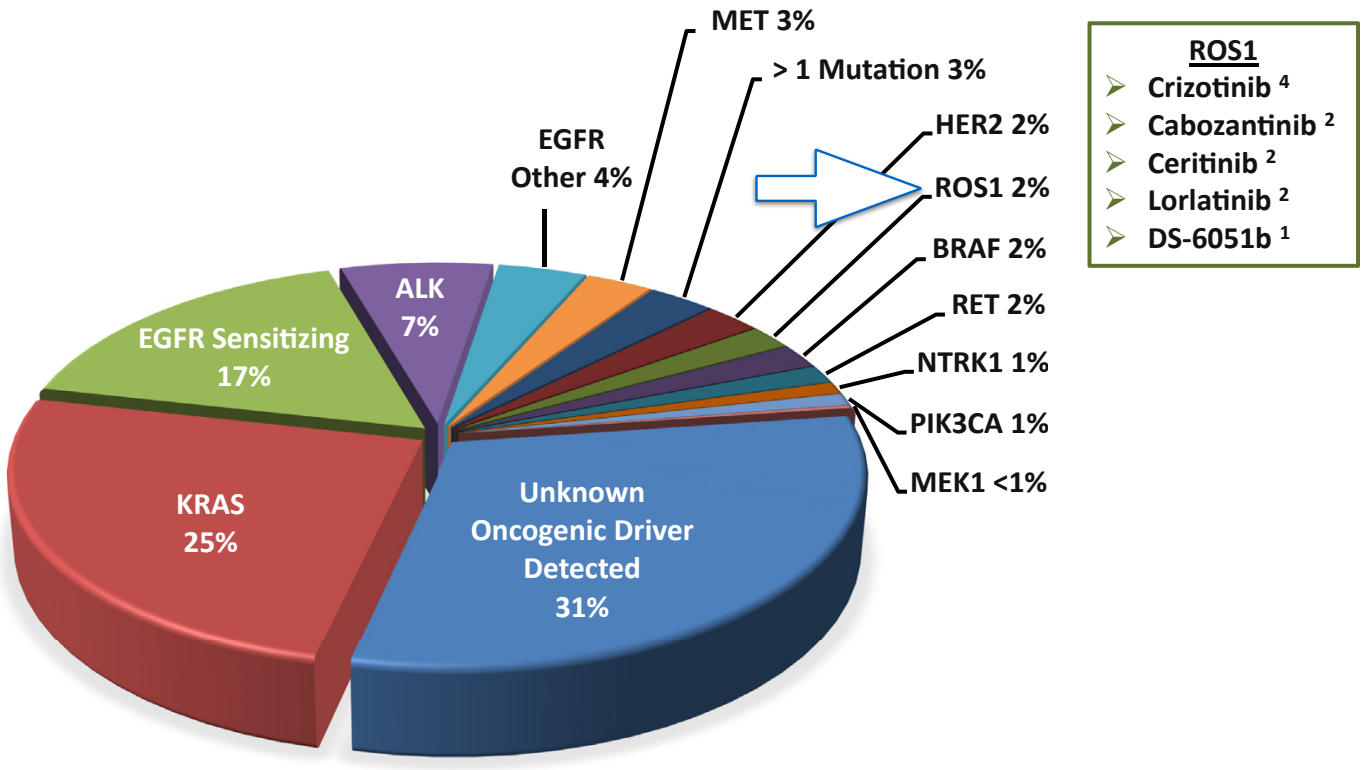


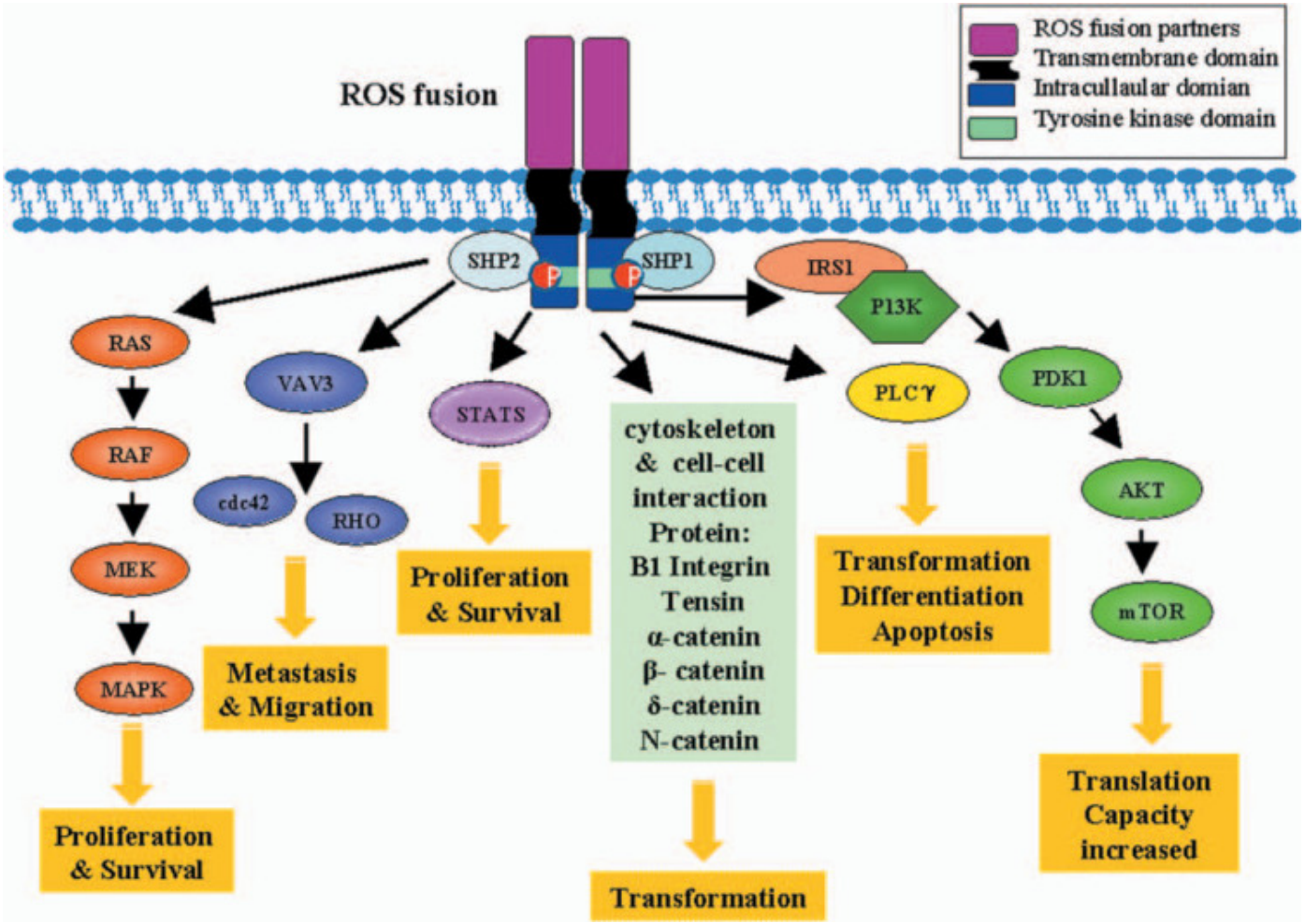

# RNA Sequencing based test

## Detection of fusion RNA



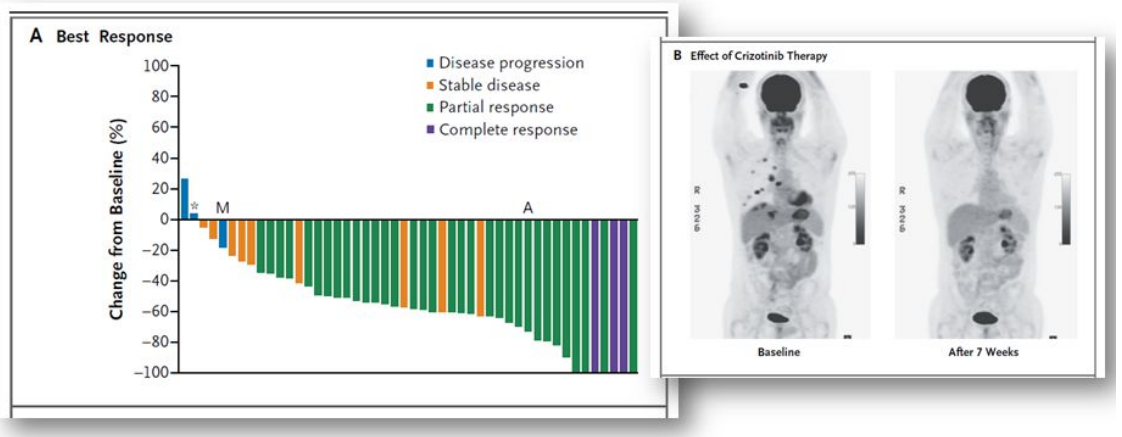





MET 3%
> 1 Mutation 3%
EGFR
Other 4%
HER2 2%
ROS1 2%
BRAF 2%
RET 2%
NTRK1 1%
PIK3CA 1%
MEK1 <1%
ALK
7%
EGFR Sensitizing
17%
KRAS
25%
Unknown
Oncogenic Driver
Detected
31%
ROS1
Crizotinib [4]
Cabozantinib [2]
Ceritinib [2]
Lorlatinib [2]
DS-6051b [1]


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

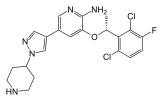
UNIVERSITY OF TORINO – DEPARTMENT OF ONCOLOGY

# Tumor responses to crizotinib in ROS1-rearranged NSCLC



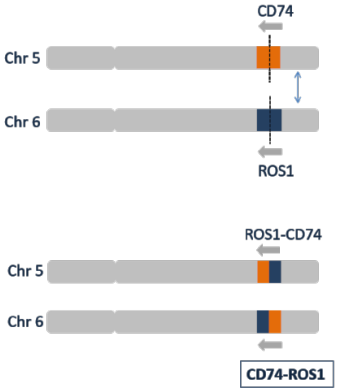

Overall response rate 72% (6% CR, 66% PR).
Median time to response 7.9 weeks (range, 4.3 - 32.0)

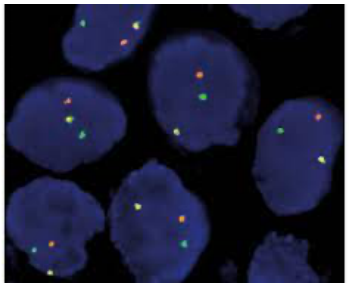
Shaw AT et al, N Engl J Med 2014;371:1963-71.



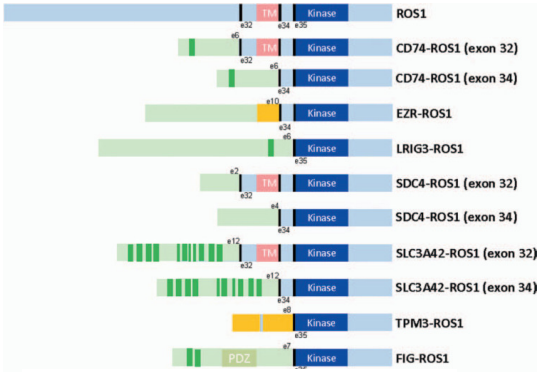
NordiQC

## Detection of chromosomal changes

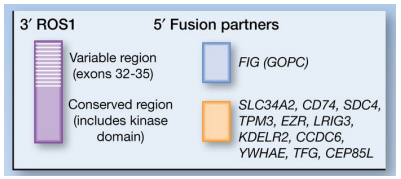


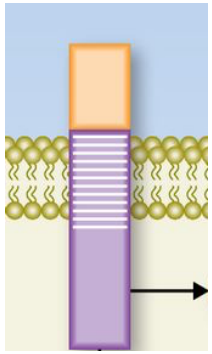



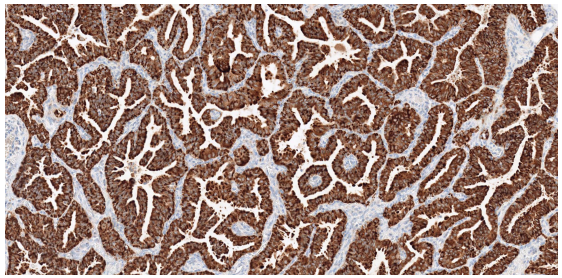
## Detection of fusion RNA




## Detection of fusion protein



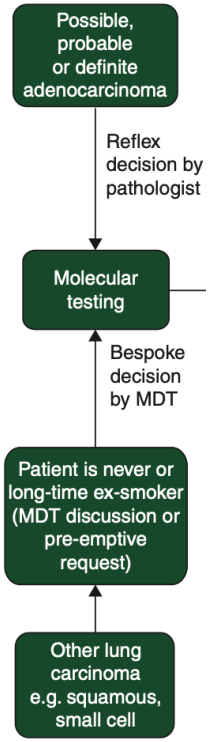





# Suggestion

NordIQC

## Next generation seq.




FFPE

Quality
Tumor cell %

DNA workflow

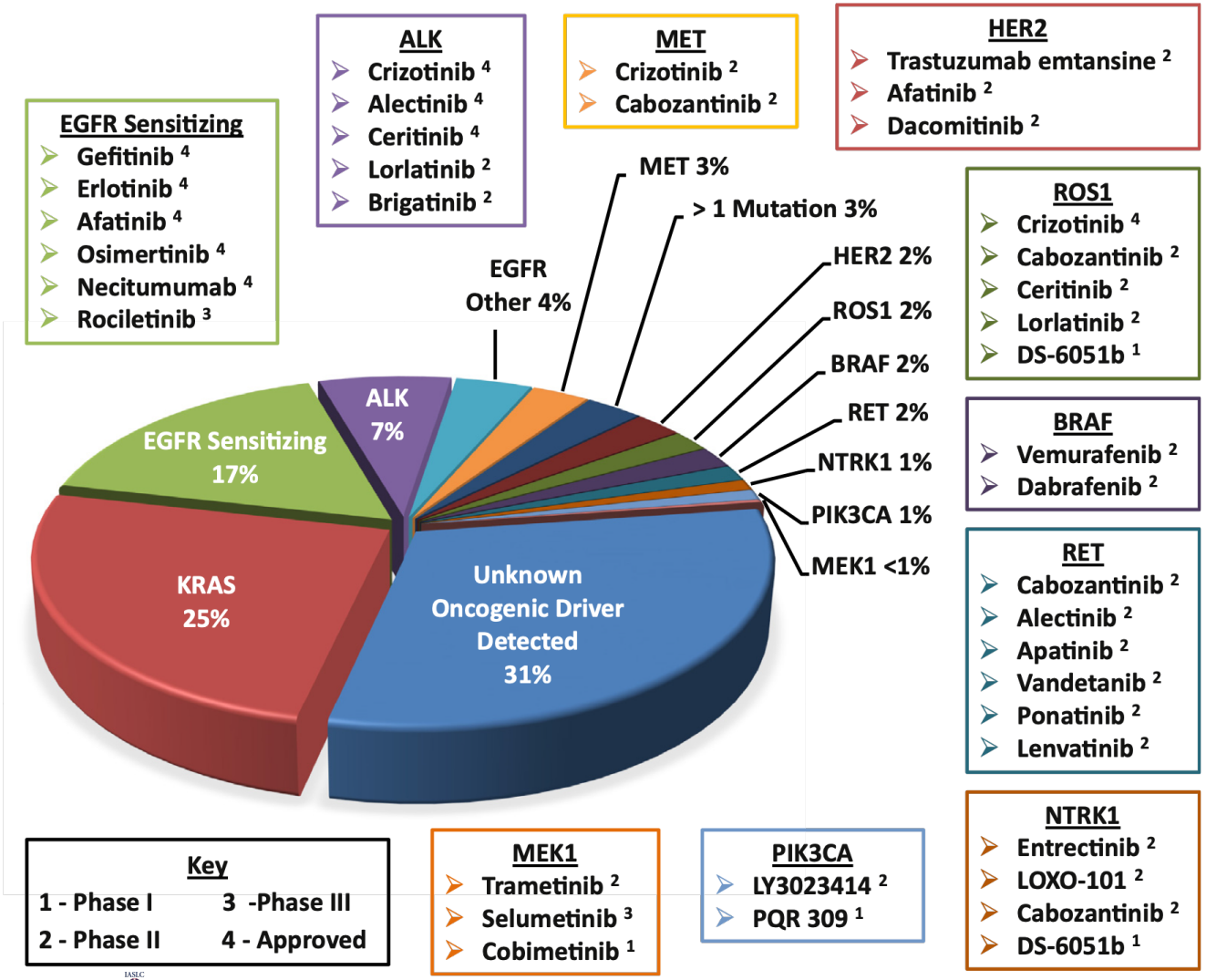
DNA purification | Sequencing | Library prep. | Variant calling (Bioinformatics)

EGFR

RNA workflow

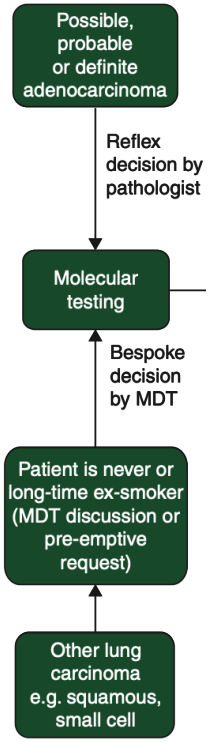
RNA purification | Sequencing | Library prep. | Variant calling (Bioinformatics)

ALK, ROS1


EGFR Sensitizing
Gefitinib 4
Erlotinib 4
Afatinib 4
Osimertinib 4
Necitumumab 4
Rociletinib 3
ALK
Crizotinib 4
Alectinib 4
Ceritinib 4
Lorlatinib 2
Brigatinib 2
MET
Crizotinib 2
Cabozantinib 2
HER2
Trastuzumab emtansine 2
Afatinib 2
Dacomitinib 2
ROS1
Crizotinib 4
Cabozantinib 2
Ceritinib 2
Lorlatinib 2
DS-6051b 1
BRAF
Vemurafenib 2
Dabrafenib 2
RET
Cabozantinib 2
Alectinib 2
Apatinib 2
Vandetanib 2
Ponatinib 2
Lenvatinib 2
NTRK1
Entrectinib 2
LOXO-101 2
Cabozantinib 2
DS-6051b 1
EGFR Other 4%
MET 3%
> 1 Mutation 3%
HER2 2%
ROS1 2%
BRAF 2%
RET 2%
NTRK1 1%
PIK3CA 1%
MEK1 <1%
ALK 7%
EGFR Sensitizing 17%
KRAS 25%
Unknown Oncogenic Driver Detected 31%
Key
1 - Phase I
2 - Phase II
3 -Phase III
4 - Approved
MEK1
Trametinib 2
Selumetinib 3
Cobimetinib 1
PIK3CA
LY3023414 2
PQR 309 1

# Suggestion

## Next generation seq.




FFPE

Quality
Tumor cell %

DNA workflow

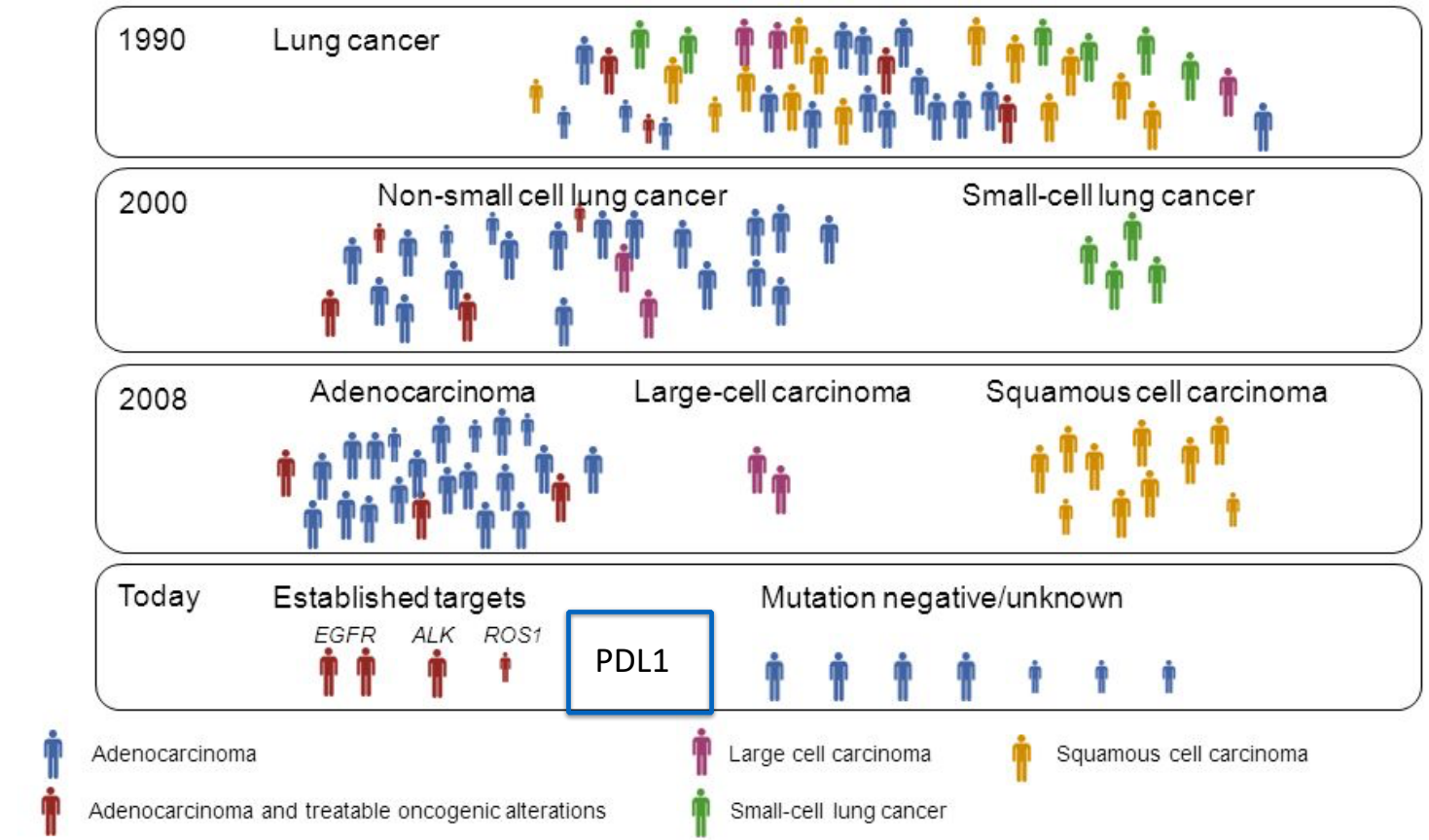
DNA purification | Sequencing | Library prep. | Variant calling (Bioinformatics)

RNA workflow

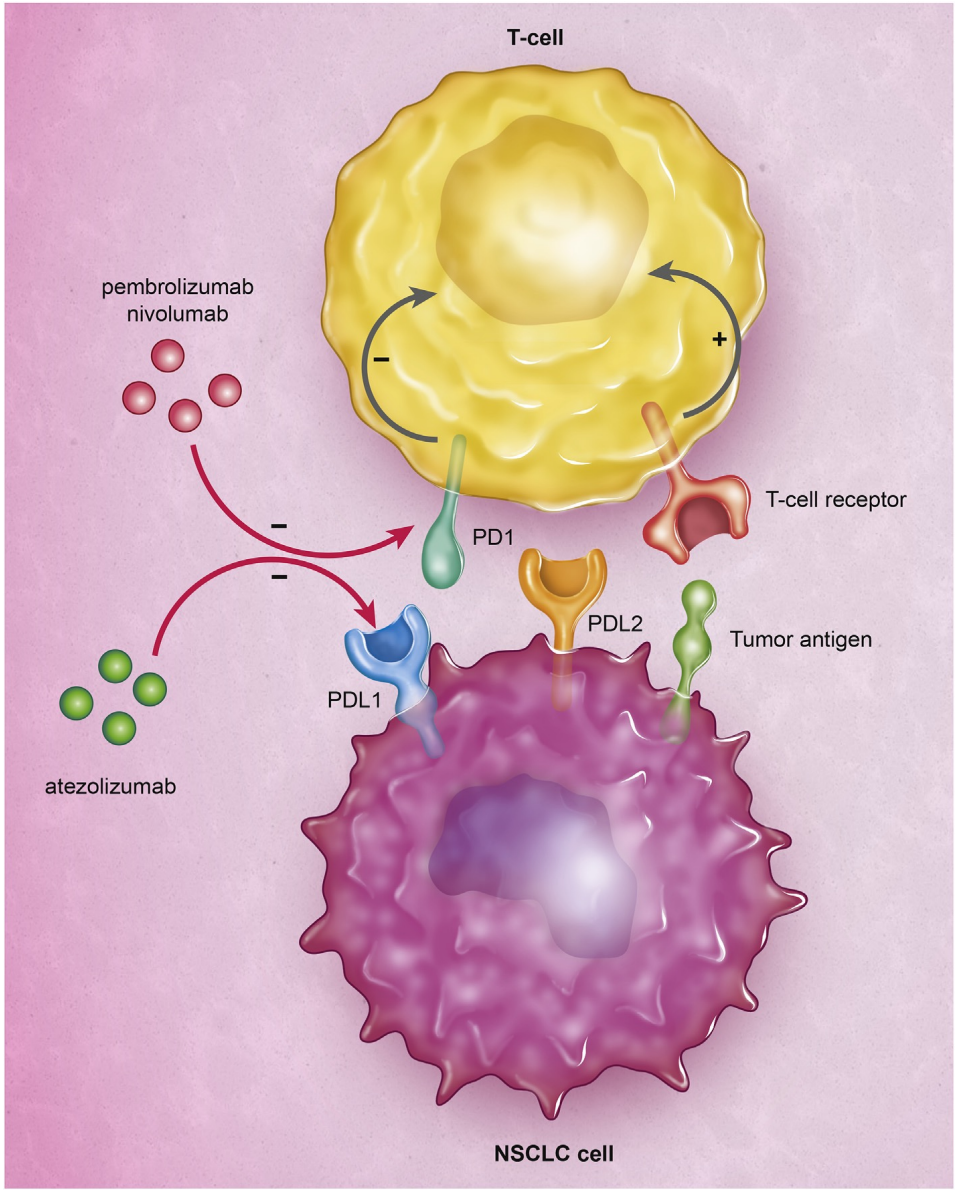
RNA purification | Sequencing | Library prep. | Variant calling (Bioinformatics)

Comprehensive Result

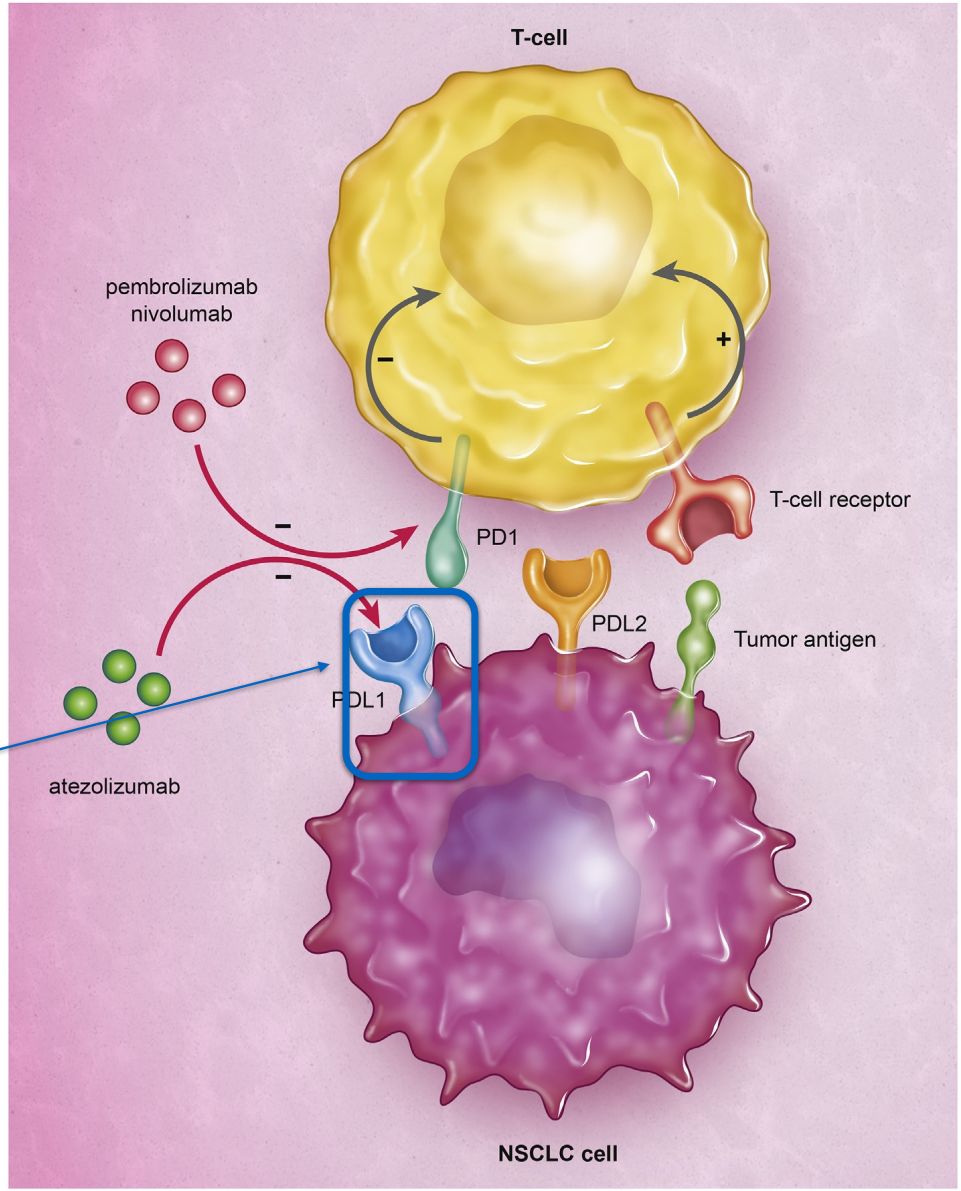
# Patient selection in lung cancer: Evolution over time

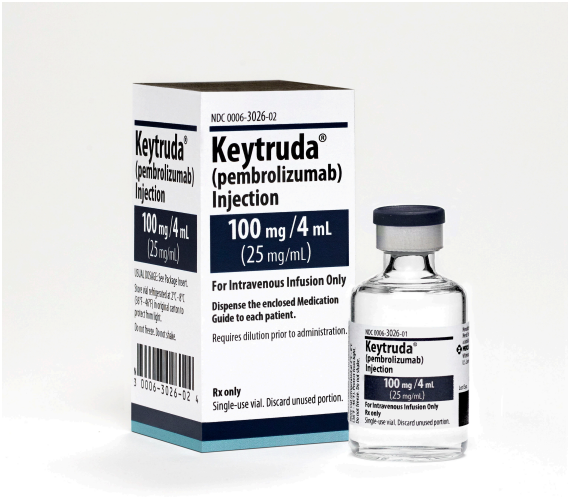



Adapted from Reck M, et al. Lancet 2013;382:709–19


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

Predictive marker



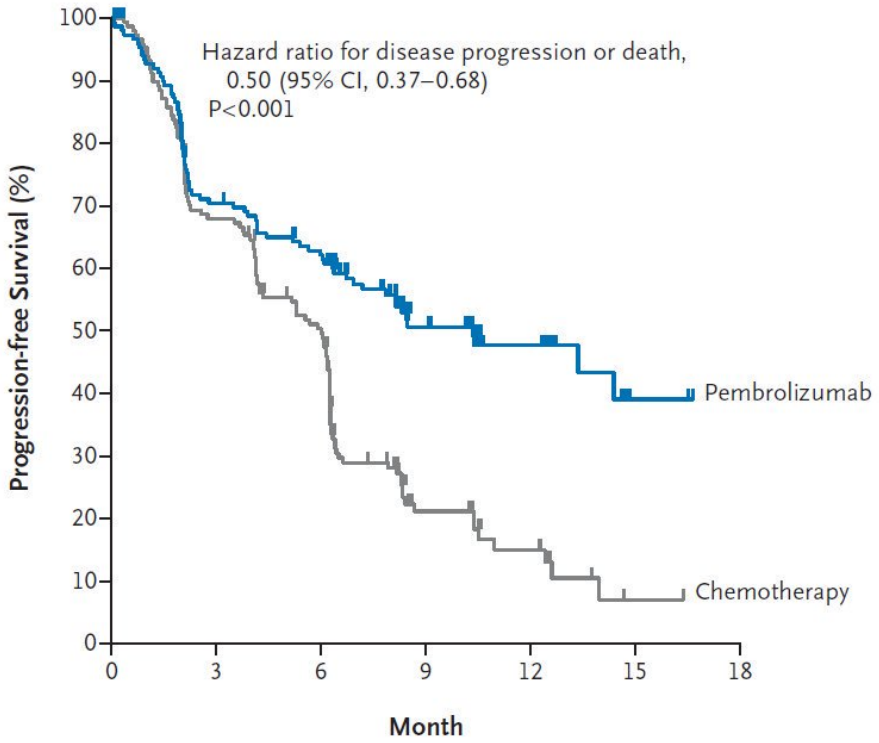



The NEW ENGLAND JOURNAL of MEDICINE

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

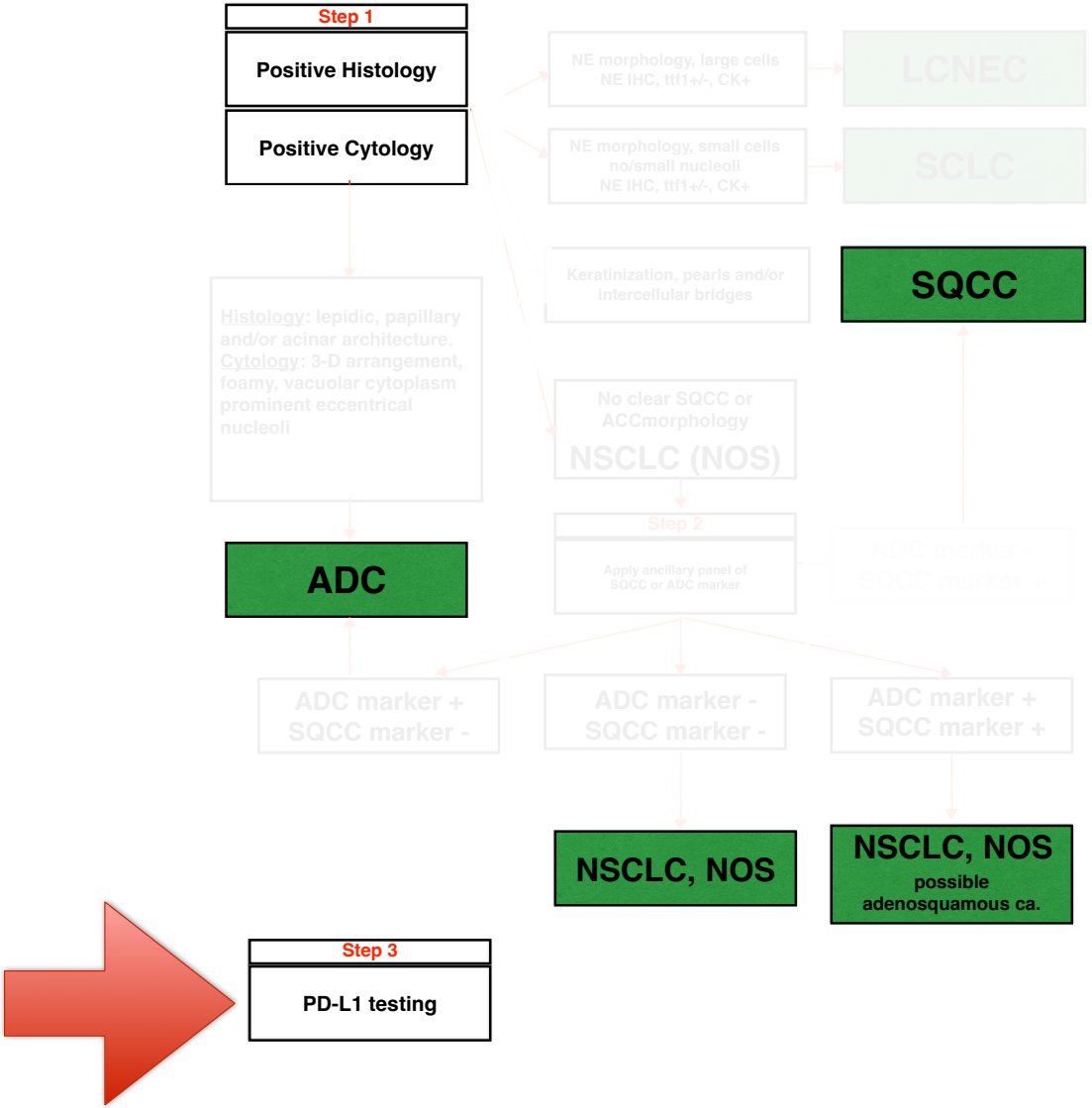
# Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

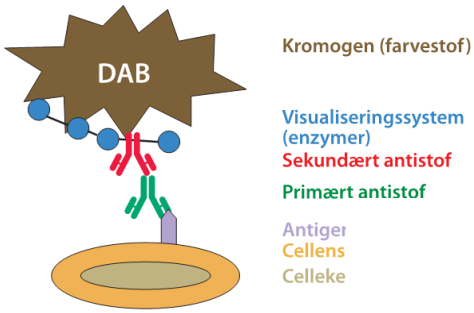
Martin Reck, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D., Andrew G. Robinson, M.D., Rina Hui, M.B., B.S., Ph.D., Tibor Csőszi, M.D., Andrea Fülöp, M.D., Maya Gottfried, M.D., Nir Peled, M.D., Ph.D., Ali Tafreshi, M.D., Sinead Cuffe, M.D., Mary O'Brien, M.D., Suman Rao, M.D., Katsuyuki Hotta, M.D., Ph.D.,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




**No. at Risk**

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

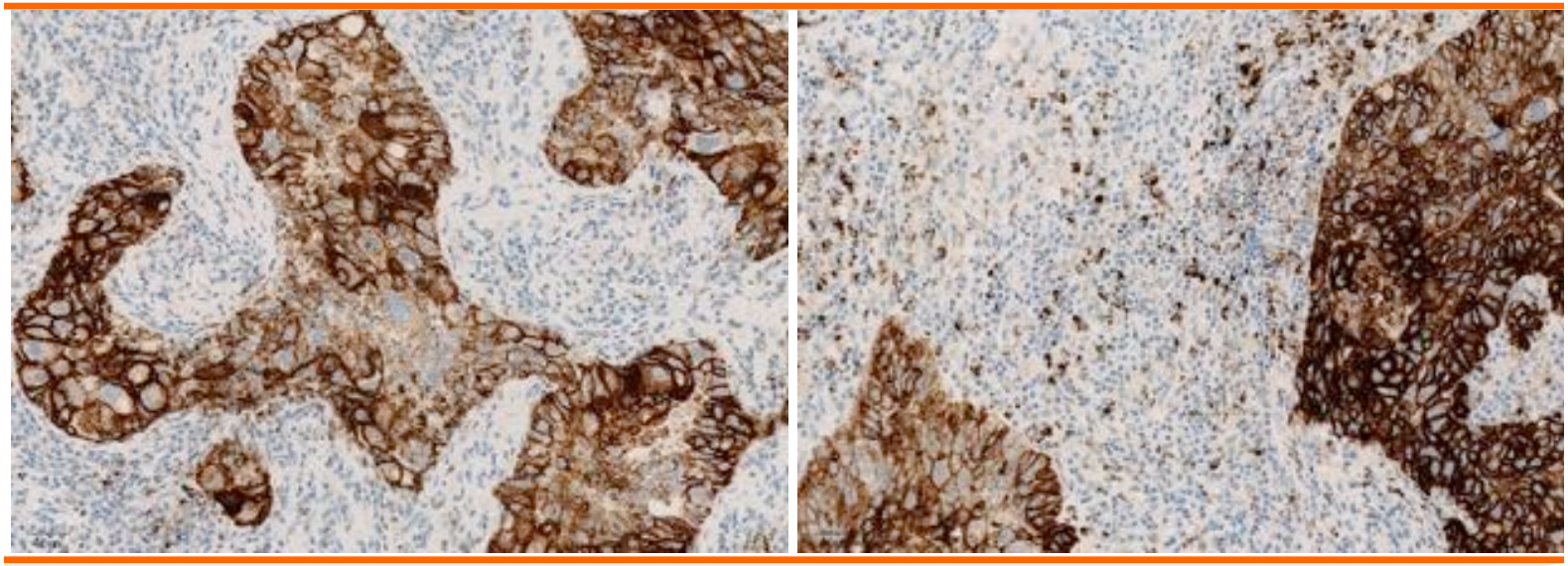

Step 1
Positive Histology
Positive Cytology
NE morphology, large cells
NE IHC, ttf1+/-, CK+
LCNEC
NE morphology, small cells
no/small nucleoli
NE IHC, ttf1+/-, CK+
SCLC
Keratinization, pearls and/or
intercellular bridges
SQCC
Histology: lepidic, papillary
and/or acinar architecture.
Cytology: 3-D arrangement,
foamy, vacuolar cytoplasm
prominent eccentrical
nucleoli
No clear SQCC or
ACCmorphology
NSCLC (NOS)
Step 2
Apply ancillary panel of
SQCC or ADC marker
ADC
ADC marker +
SQCC marker -
ADC marker -
SQCC marker -
ADC marker +
SQCC marker +
NSCLC, NOS
NSCLC, NOS
possible
adenosquamous ca.
Step 3
PD-L1 testing



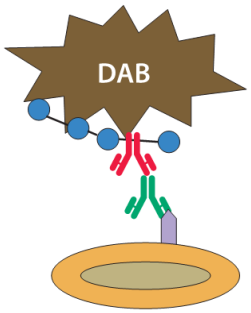

NordiQC

## *Tumor cells (TCs)*

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



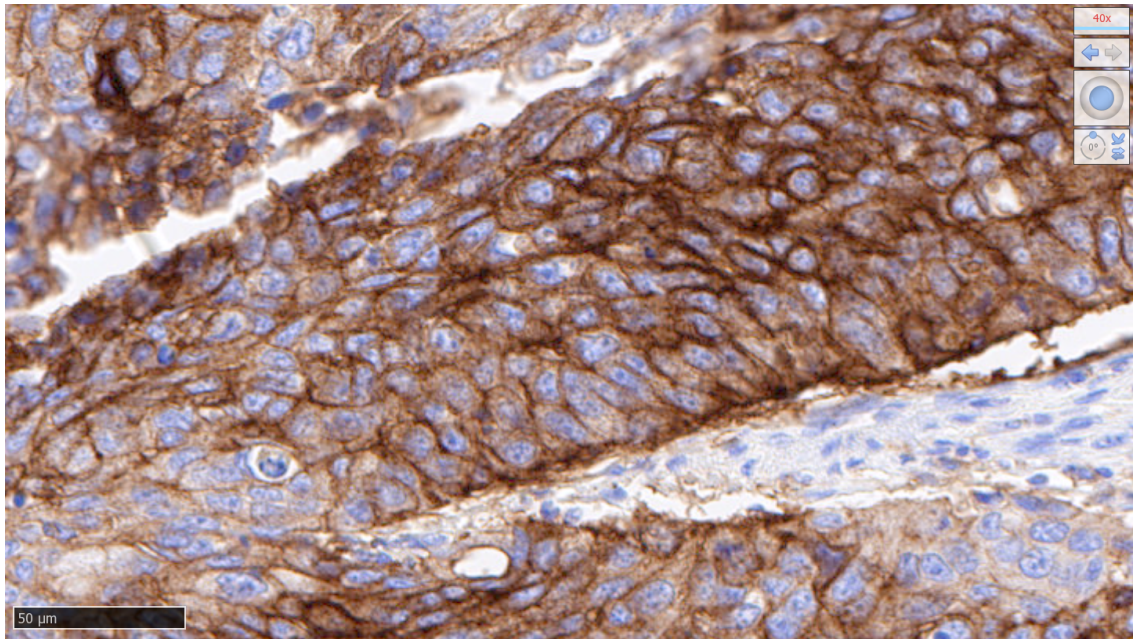
**Immunhistological staining for PDL1**



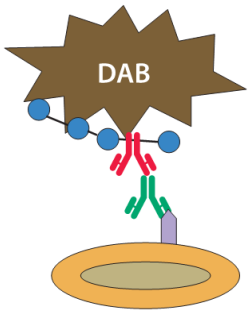

Kromogen (farvestof)

Visualiseringssystem (enzymer)
Sekundært antistof
Primært antistof

Antigen
Cellens cytoplasma
Cellekerne




# Biopsy NSCLC 100% TPS




Kromogen (farvestof)

Visualiseringssystem (enzymer)
Sekundært antistof
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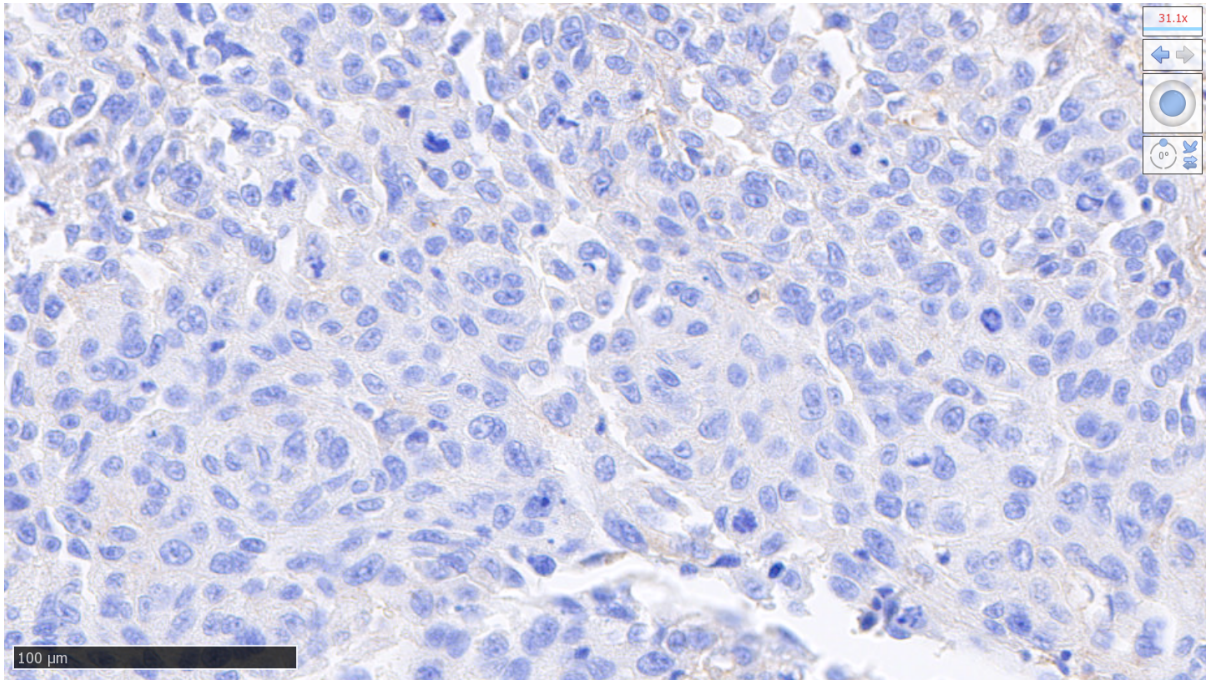
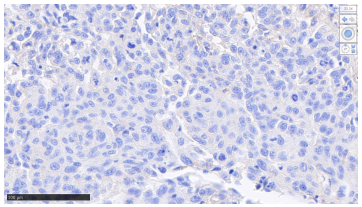
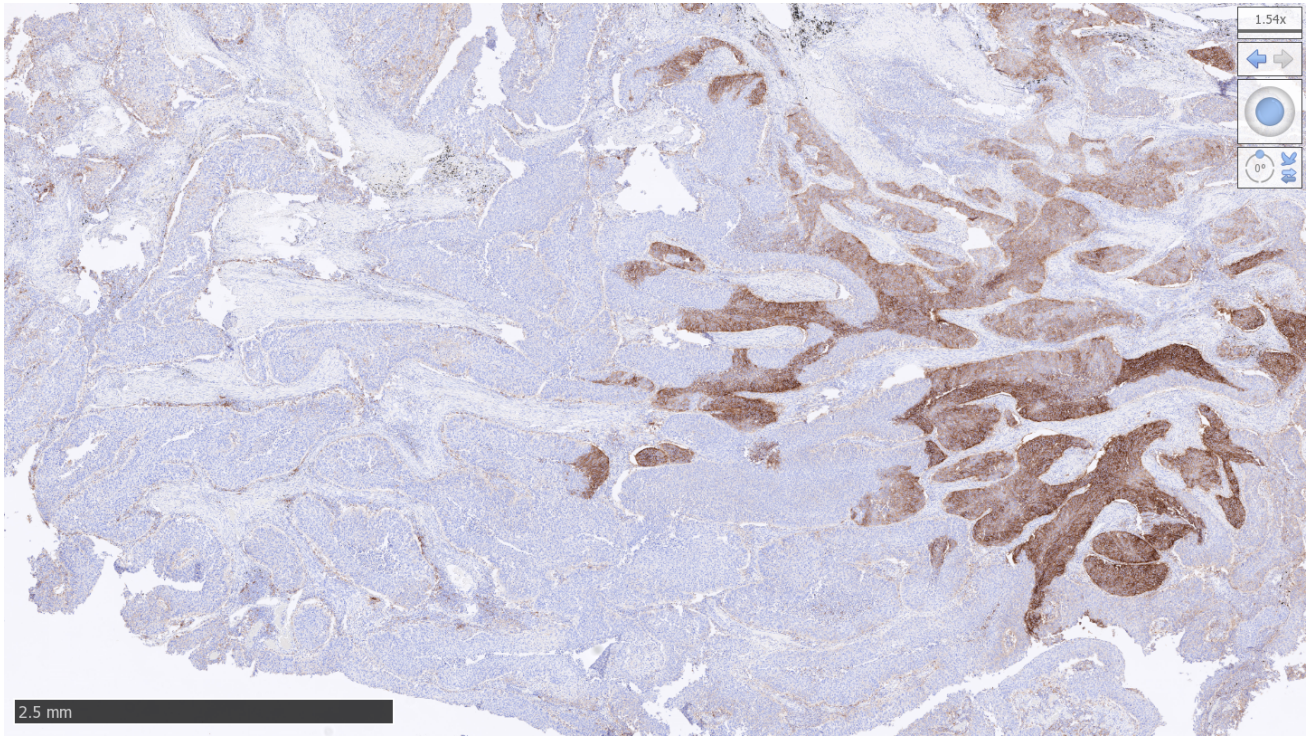
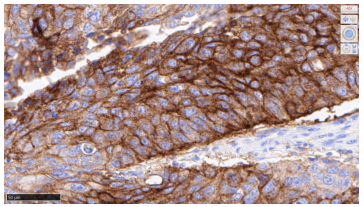



# Biopsy NSCLC 0% TPS



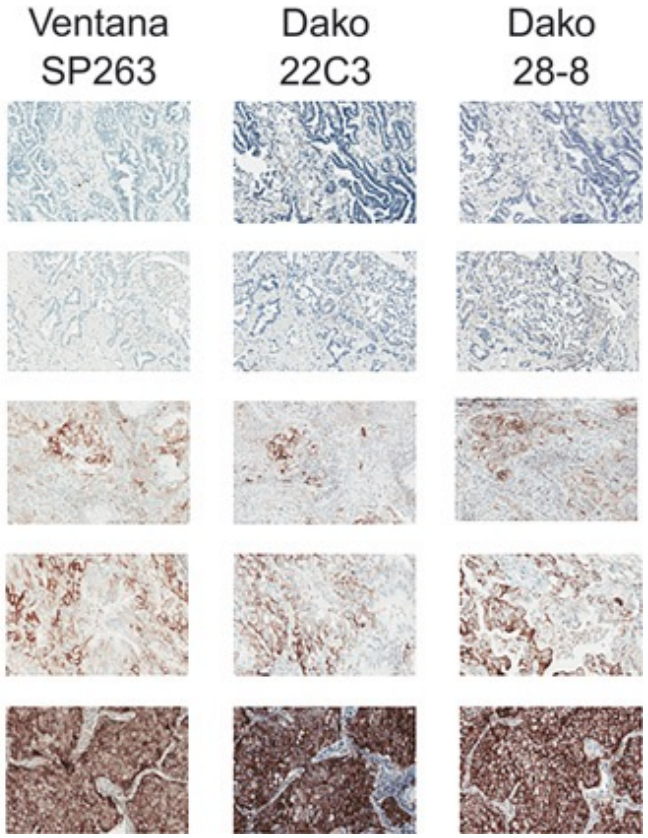

1.54x
2.5 mm



| 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

TPS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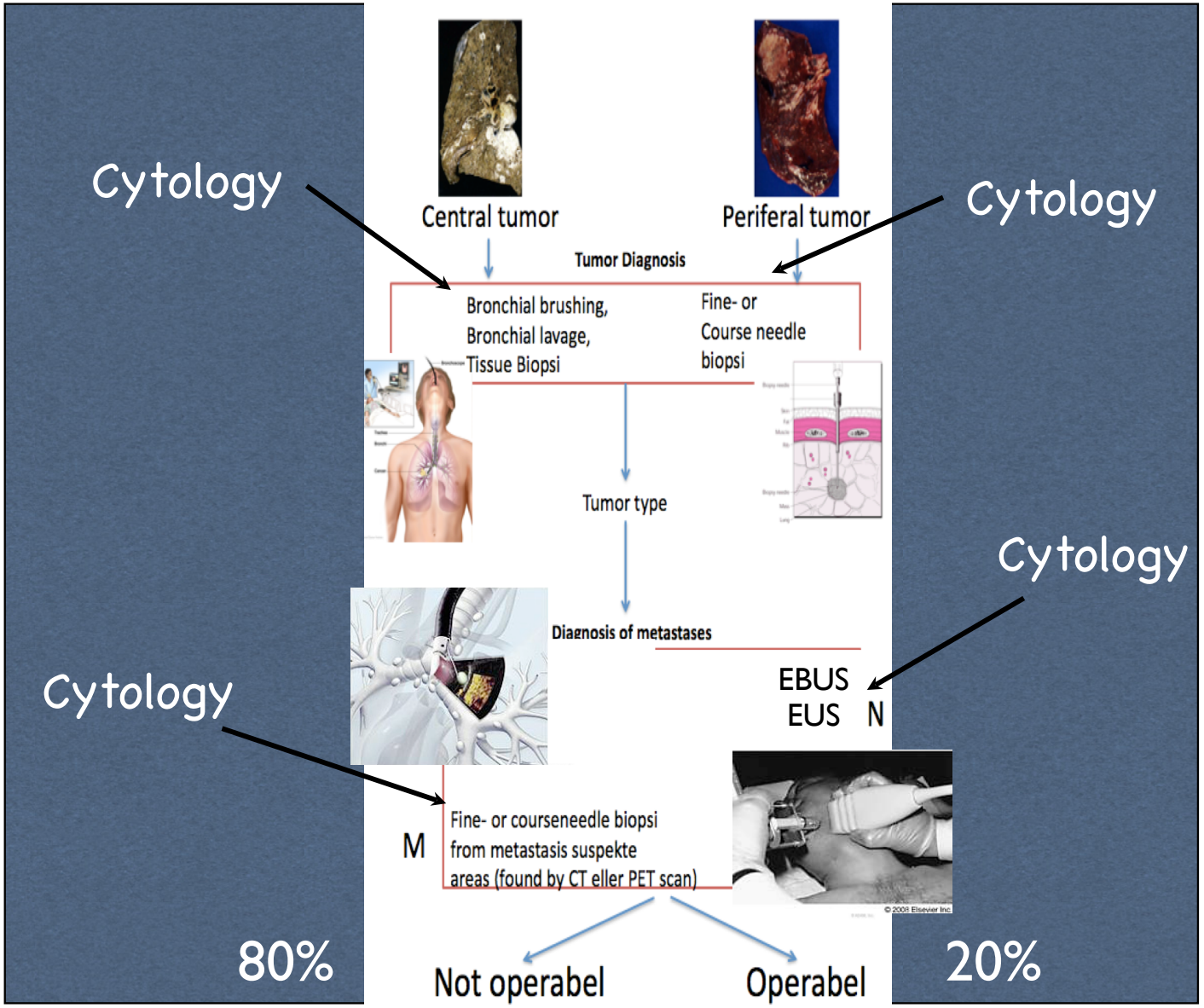
Cancer Therapy: Clinical

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]


Cytology
Central tumor
Periferal tumor
Cytology
Tumor Diagnosis
Bronchial brushing,
Bronchial lavage,
Tissue Biopsi
Fine- or
Course needle
biopsi
Tumor type
Cytology
Diagnosis of metastases
EBUS
EUS N
Cytology
M
Fine- or courseneedle biopsi
from metastasis suspekte
areas (found by CT eller PET scan)
© 2008 Elsevier Inc.
80%
Not operabel
Operabel
20%

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) |

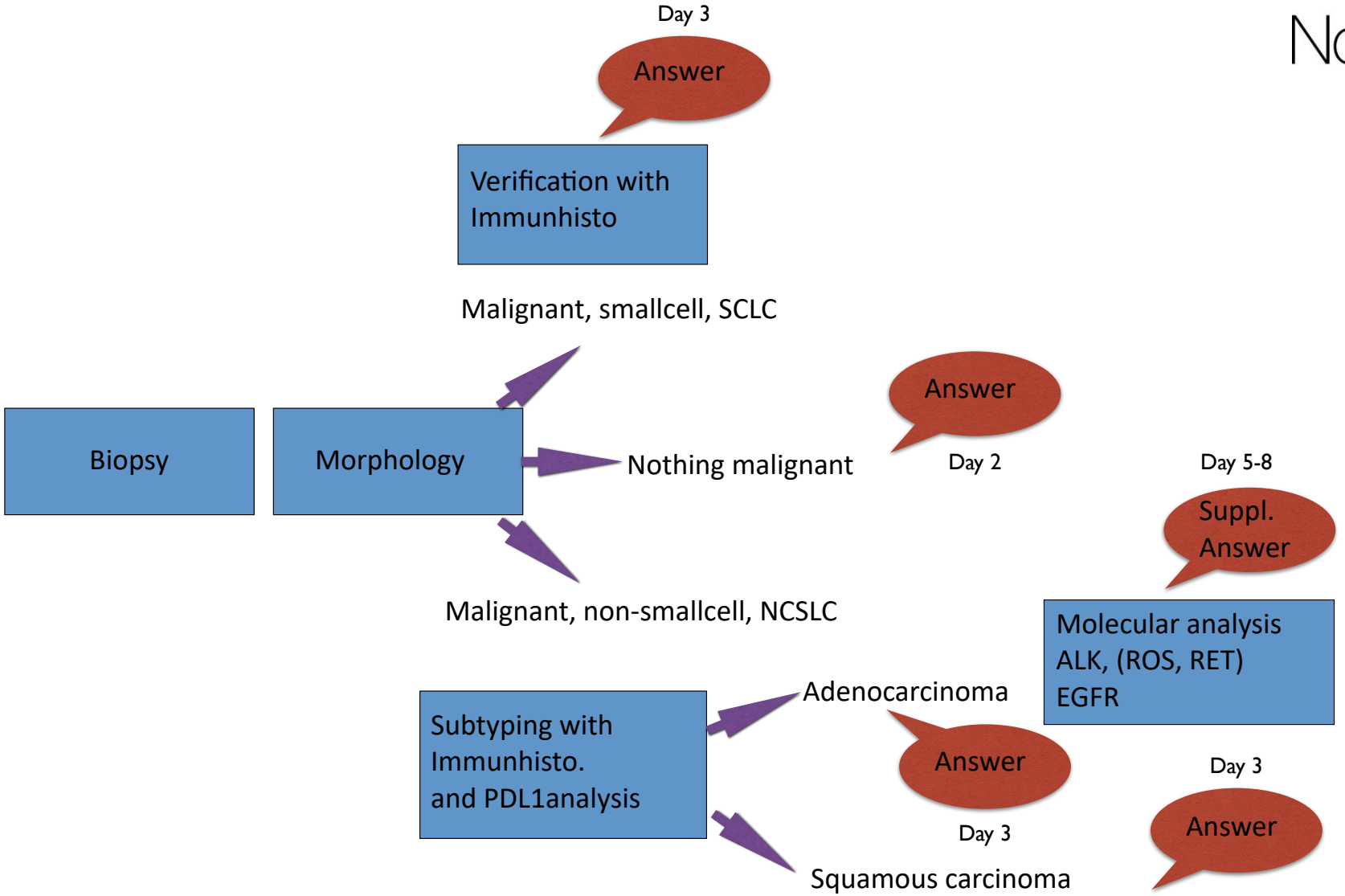
Values are represented as percent, 95% CI.
CI indicates confidence interval; IHC, immunohistochemistry; PD-L1, programmed cell death ligand-1.

Table 2a. **Overall results for PD-L1 TPS/CPS, run C15**

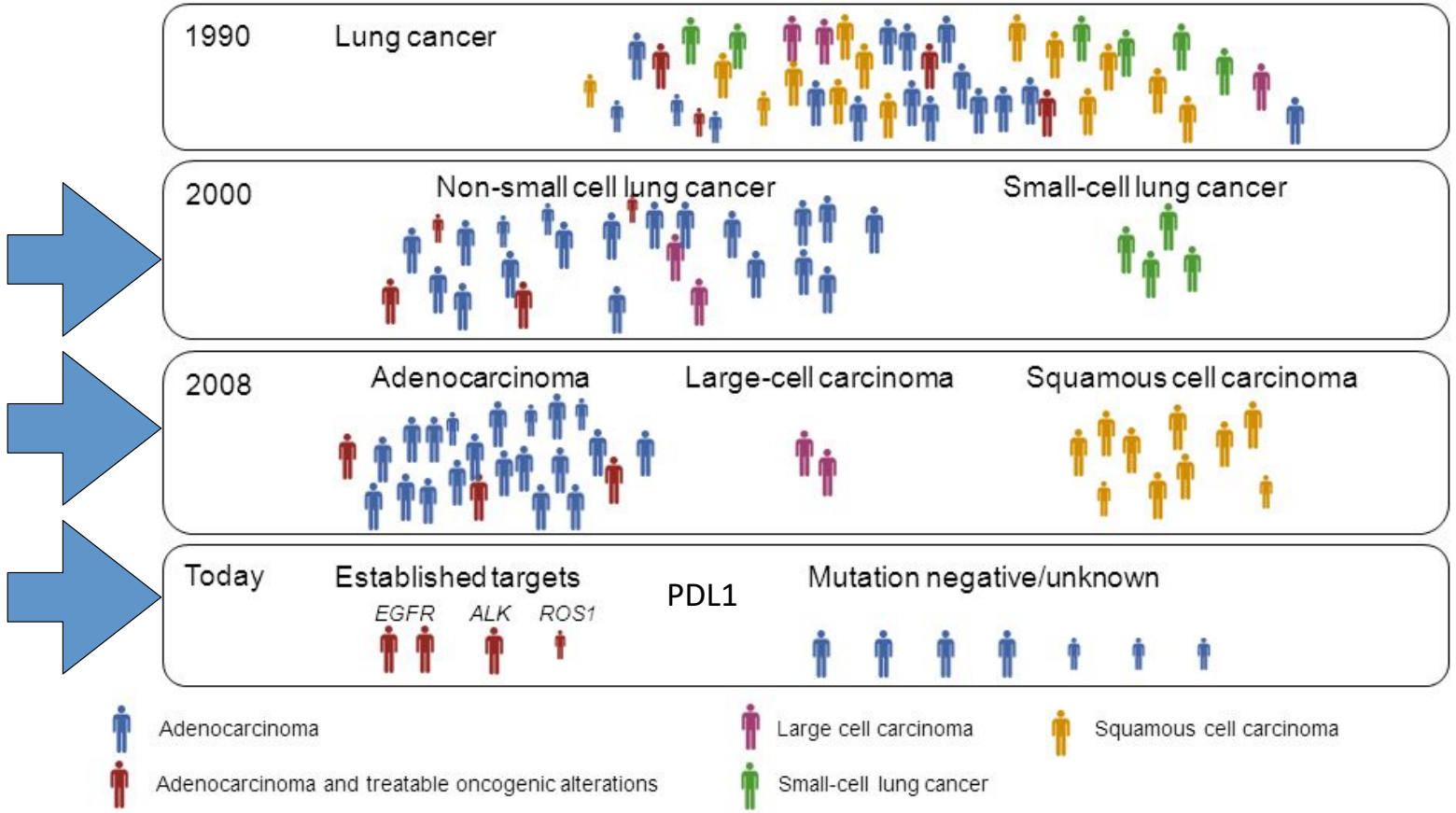
| | n | Optimal | Good | Borderline | Poor | Suff.[1] | OR[2] |
|---|---|---|---|---|---|---|---|
| CE-IVD / FDA approved PD-L1 assays* | 143 | 97 | 33 | 9 | 4 | 91% | 68% |
| Laboratory developed PD-L1 assays based on concentrated antibodies | 66 | 37 | 14 | 12 | 3 | 77% | 56% |
| PD-L1 assays based on Ready-To-Use antibodies without predictive claims | 46 | 32 | 11 | 3 | 0 | 93% | 69% |
| Total | 255 | 166 | 58 | 24 | 7 | | |
| Proportion | | 65% | 23% | 9% | 3% | 88% | |

# The Diagnostic algorithm

# The Diagnostic algorithm

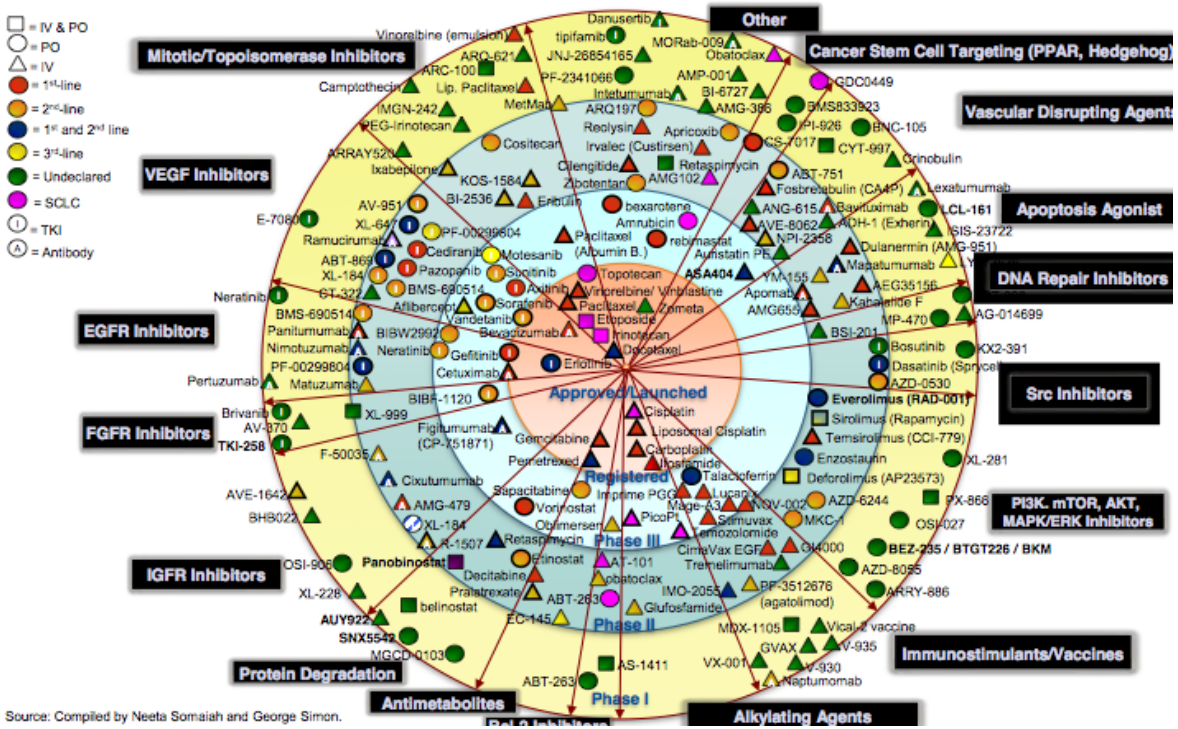


# Patient selection in lung cancer: Evolution over time




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

# Lung cancer research landscape – MoA group and phase




Future