Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

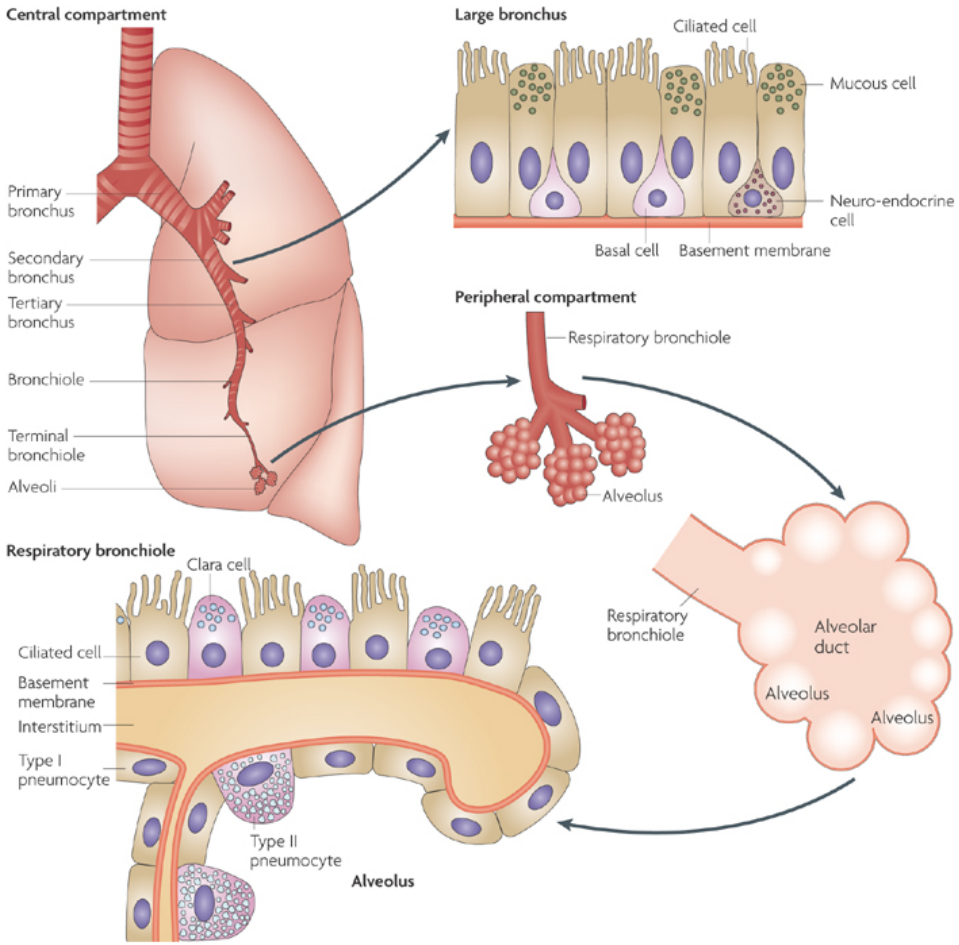
Henrik Hager

Dept. of Clinical Pathology
Vejle Hospital

Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

Lung Carcinoma

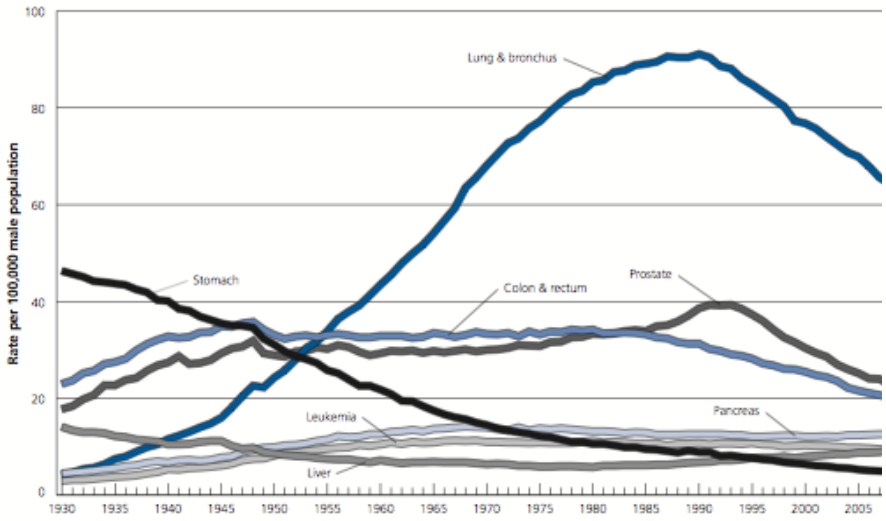


Lung carcinoma derives from stem cells
in the lung epithelium

Lung Cancer
Diagnosis and prediction

Lung Carcinoma

Age-adjusted Cancer Death Rates,* Males by Site, US, 1930-2008

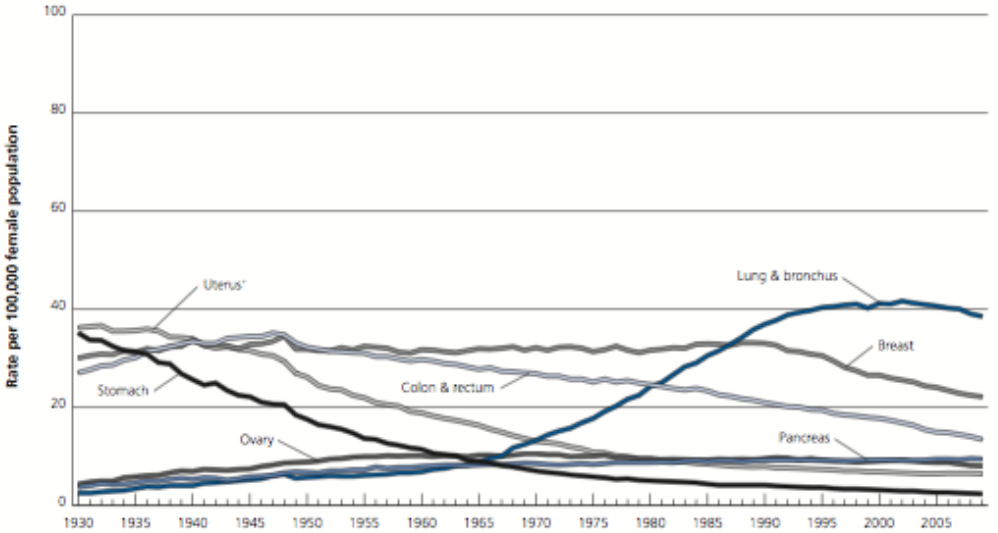


*Per 100,000, age adjusted to the 2000 US standard population.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancer of the liver, lung and bronchus, and colon and rectum are affe by these coding changes.

Source: US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2008, National Center for Health Statistics, Centers for Disease Control and Prevention.

Age-adjusted Cancer Death Rates*, Females by Site, US, 1930-2009



*Per 100,000, age adjusted to the 2000 US standard population. †Uterus refers to uterine cervix and uterine corpus combined.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancer of the lung and bronchus, colon and rectum, and ovary are affected by these coding changes.

Source: US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2009, National Center for Health Statistics, Centers for Disease Control and Prevention.

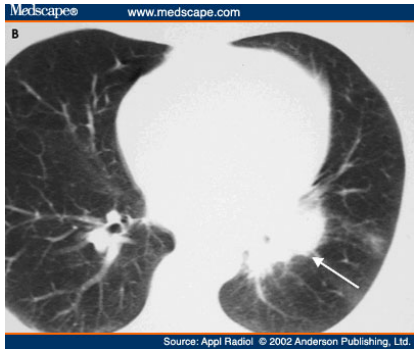
Lung Cancer

Diagnosis and prediction

Lung Carcinoma

Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt



Central tumor

Periferal tumor

Tumor Diagnosis

Bronchial brushing,
Bronchial lavage,
Tissue Biopsi

Fine- or
Course needle
biopsi

Tumor type

Diagnosis of metastases

Broncho- mediastinoskopi
including tissue biopsi
from mediastinal lymfnodes

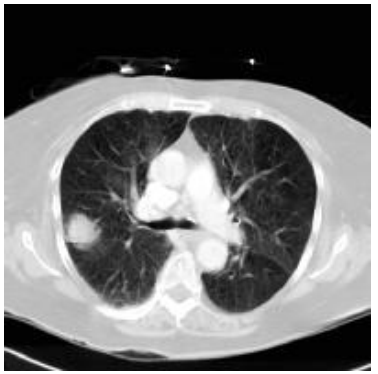
N

M

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

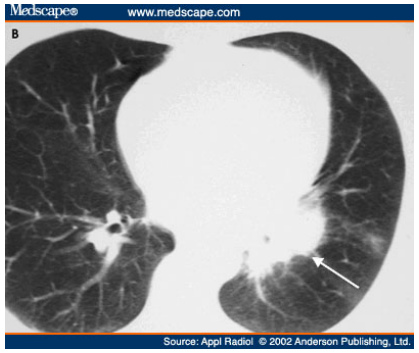
Not operabel

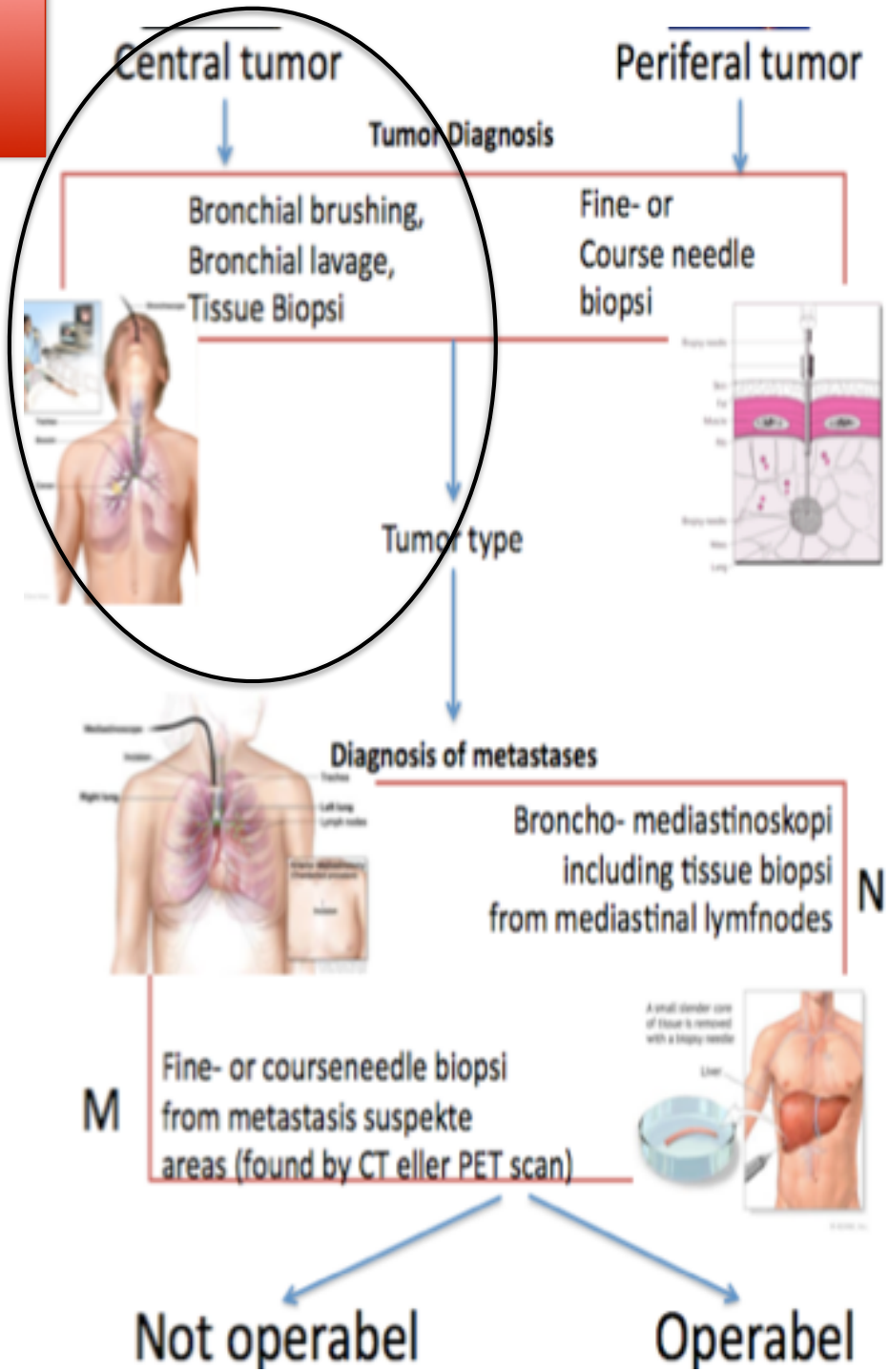
Operabel

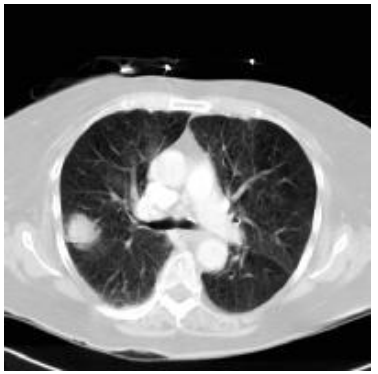


Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

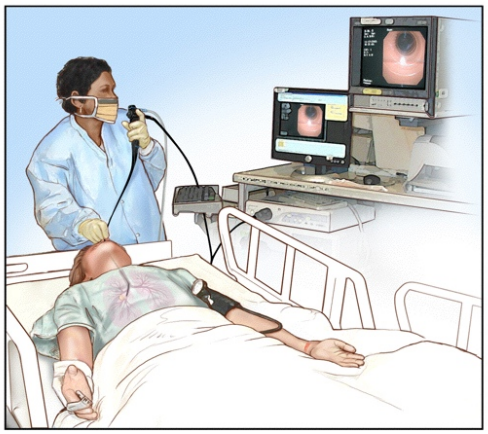






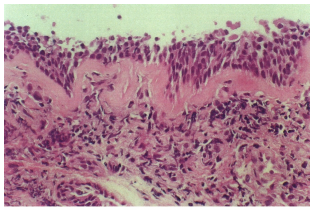
Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

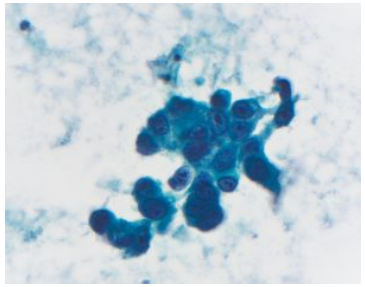


Bronkialwash *
Brushbiopsy *
EBUS *
EUS *

Biopsy §



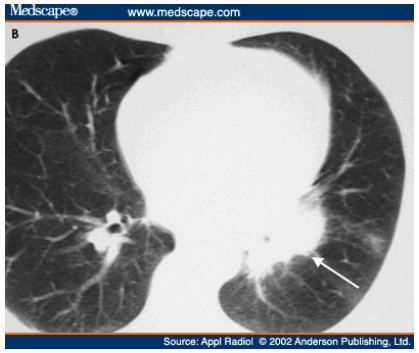
§



*

Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt



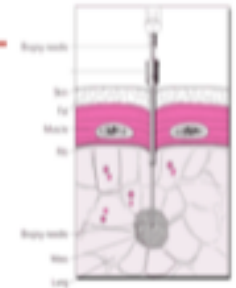
Central tumor

Periferal tumor

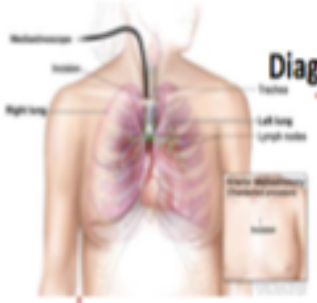
Tumor Diagnosis

Bronchial brushing,
Bronchial lavage,
Tissue Biopsi

Fine- or
Course needle
biopsi



Tumor type



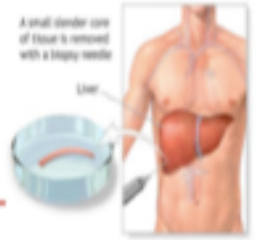
Diagnosis of metastases

Broncho- mediastinoskopi
including tissue biopsi
from mediastinal lymfnodes

N

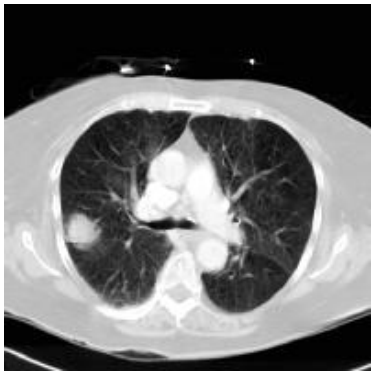
M

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



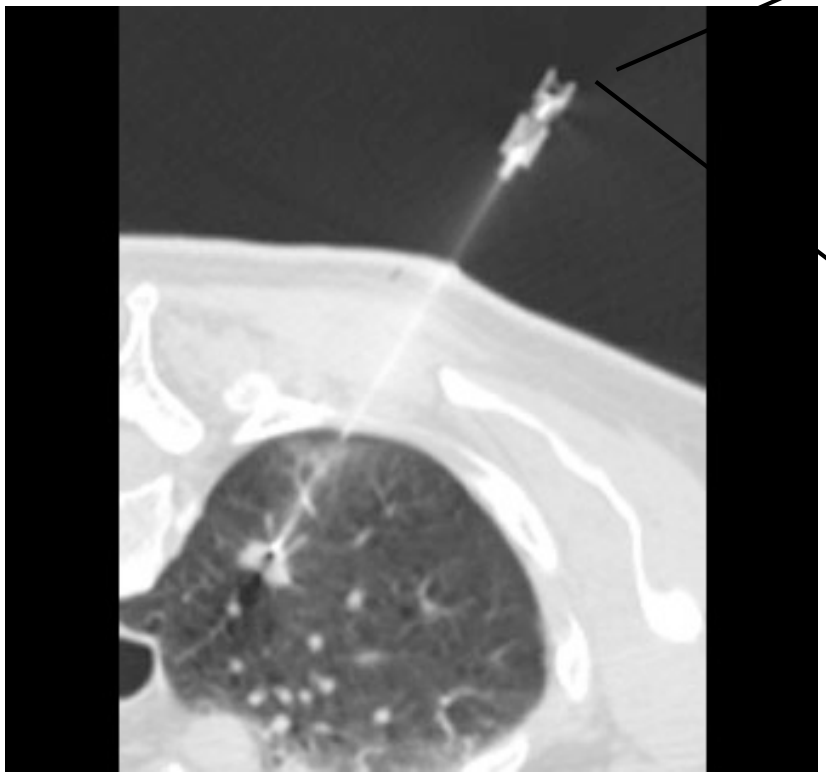
Not operabel

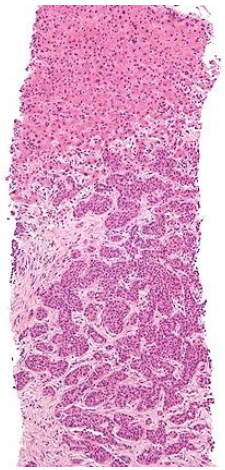
Operabel

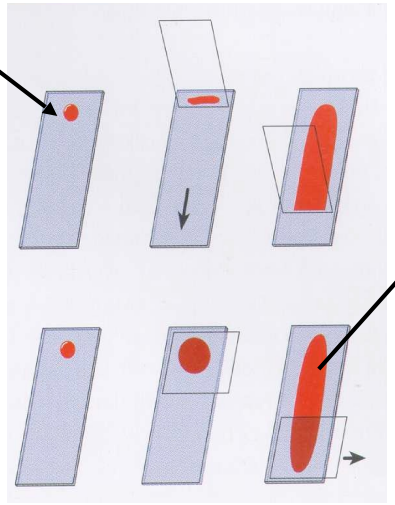


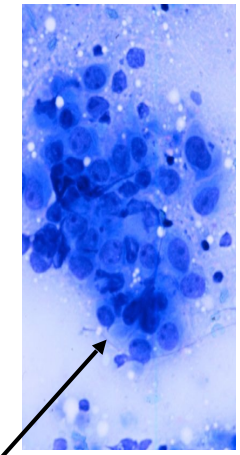
Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt



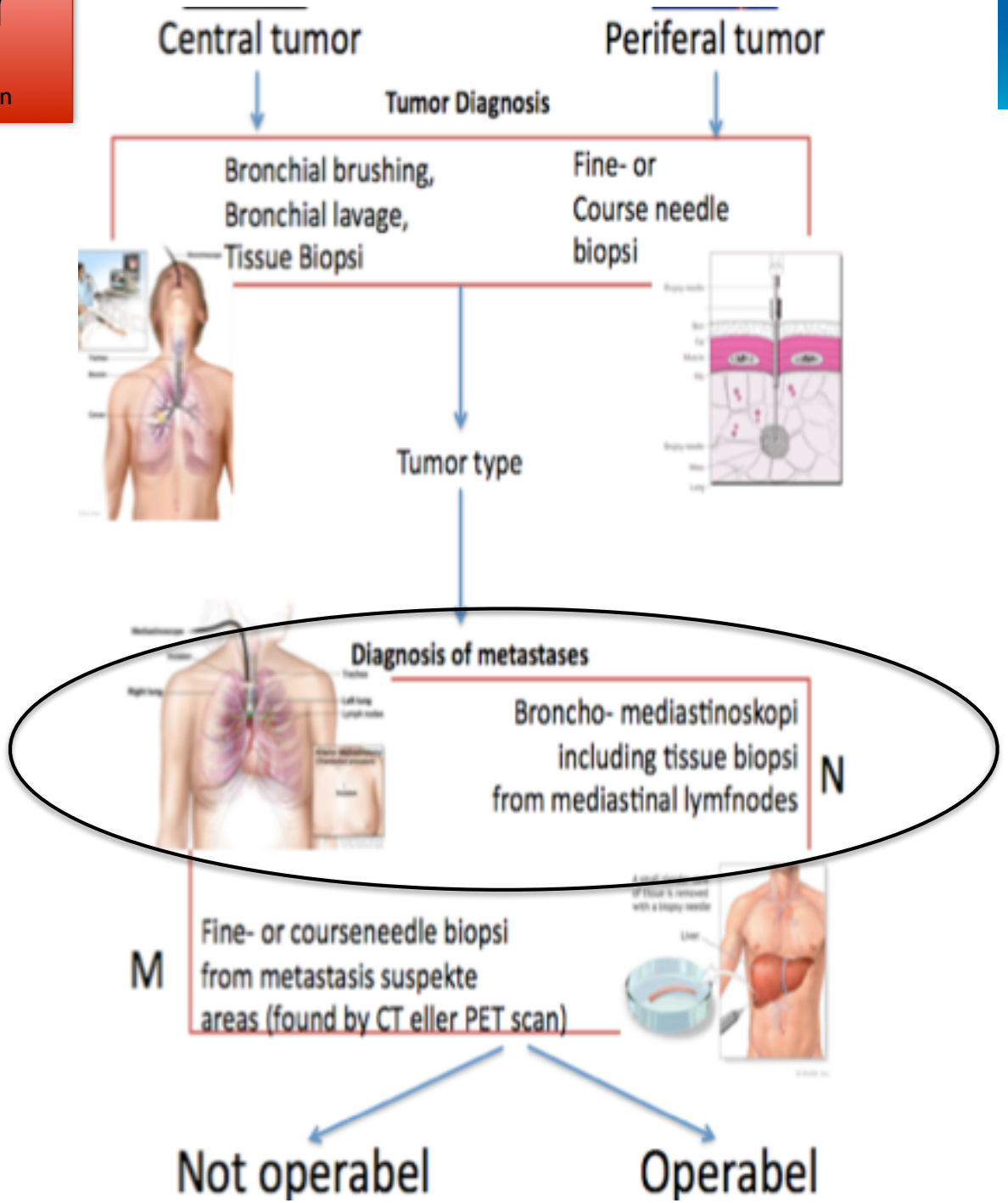






Lung Cancer
Diagnosis and prediction

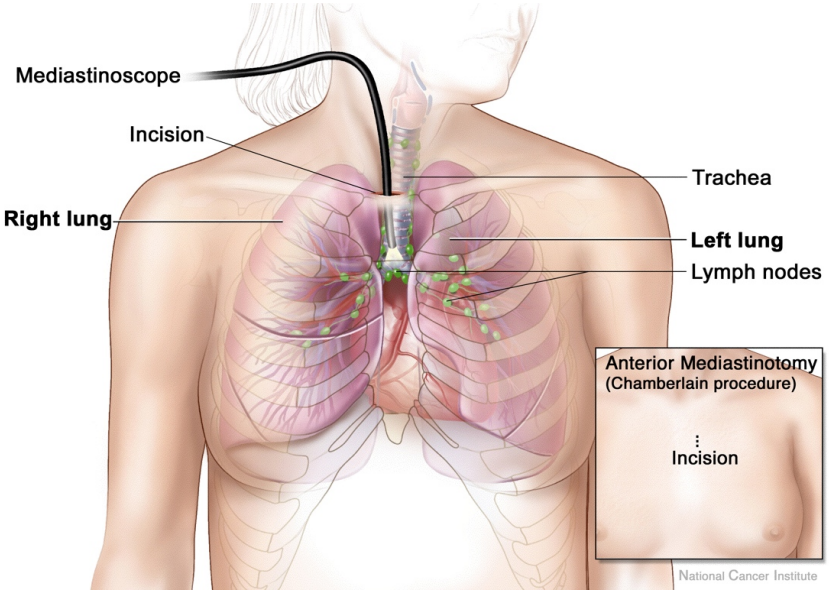
Region Syddanmark
Sygehus Lillebælt

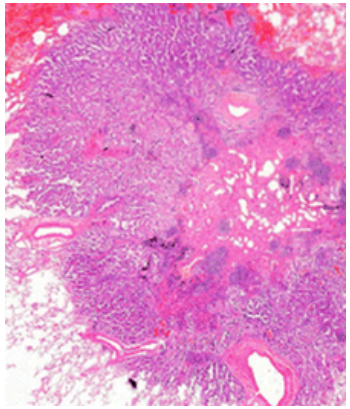


Lung Cancer
Diagnosis and prediction

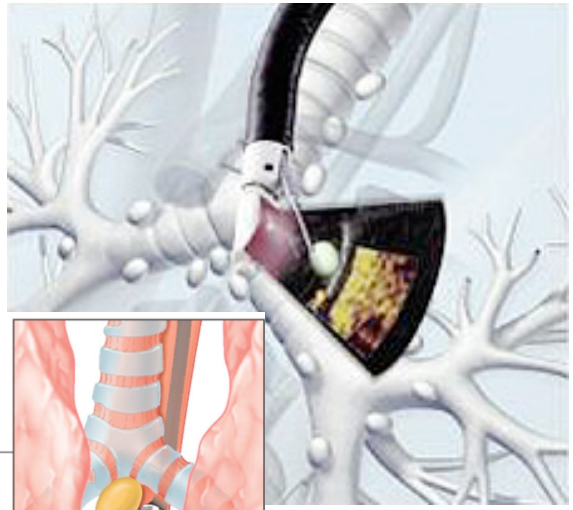
Region Syddanmark
Sygehus Lillebælt

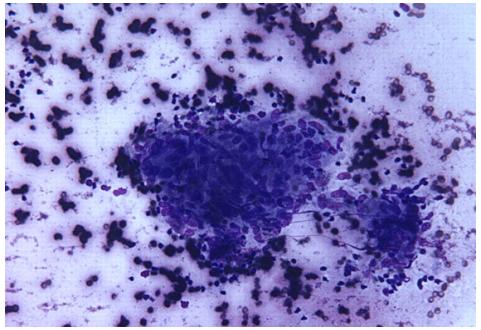
Mediastinoscopy





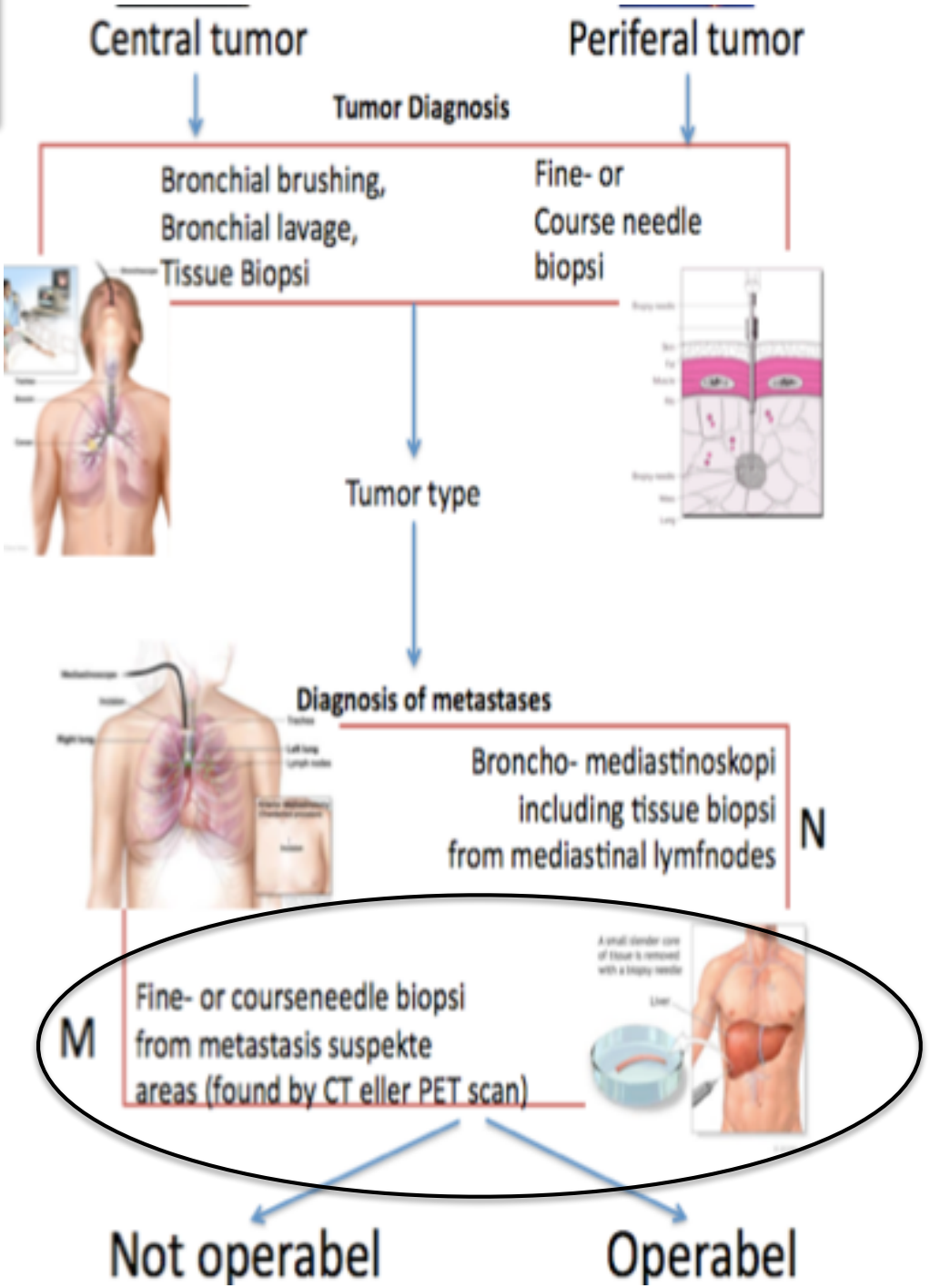
EBUS, EUS





Lung Cancer
Diagnosis and prediction

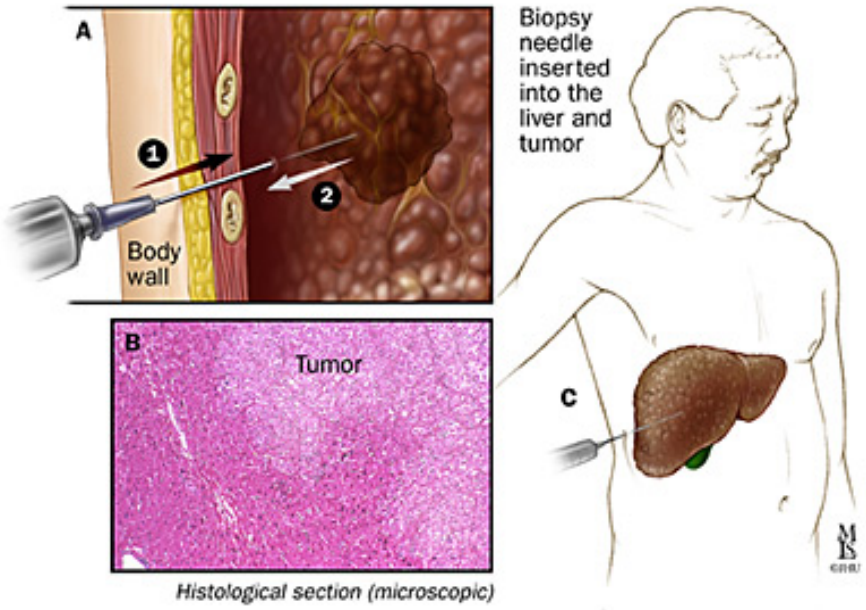
Region Syddanmark
Sygehus Lillebælt



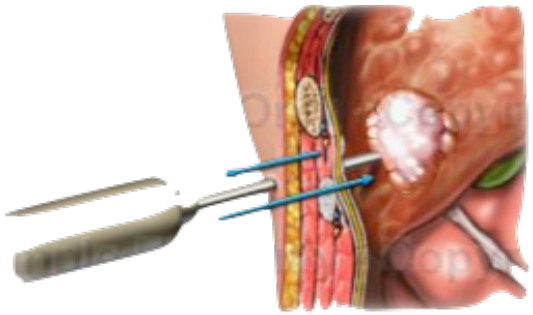
Lung Cancer
Diagnosis and prediction

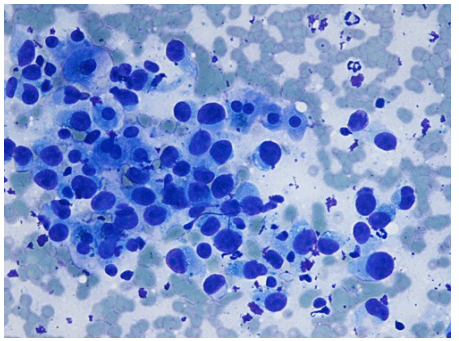
Region Syddanmark
Sygehus Lillebælt

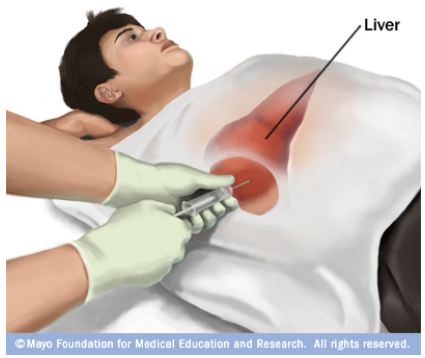
Coarse needle biopsy



Fine needle biopsy







Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

Patoanatomical specimen

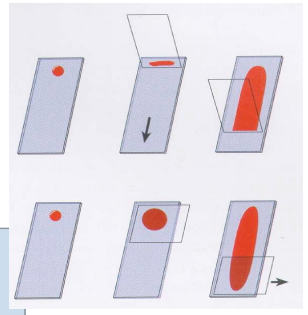
Histology

Cytologi

Fixation
Dehydration
Parafinembedding
Microtomy

Præparation

Smear preparation

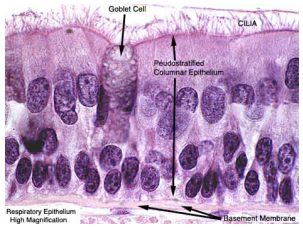


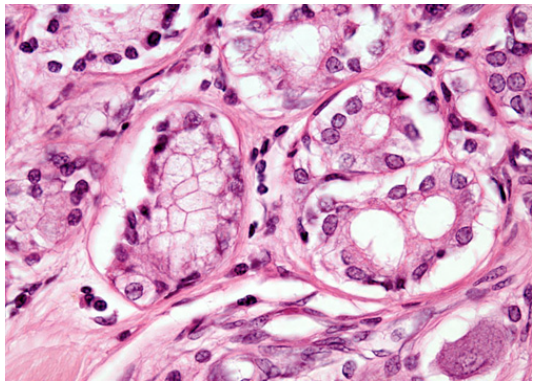
Visualization

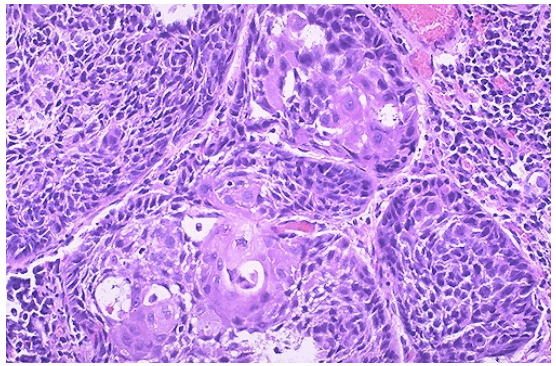
(Staining)

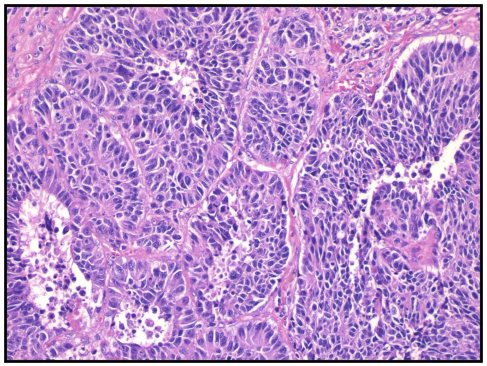
Lung Cancer
Diagnosis and prediction

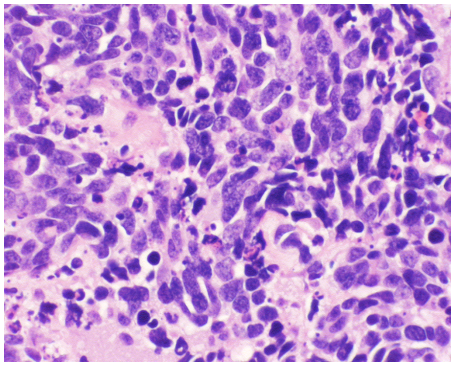
Region Syddanmark
Sygehus Lillebælt









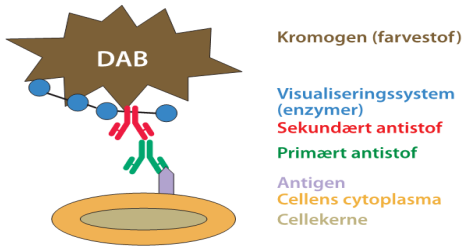


Adenocarcinoma — Squamous carcinoma — Large cell neuroendocrine carc. — Small cell carcinoma

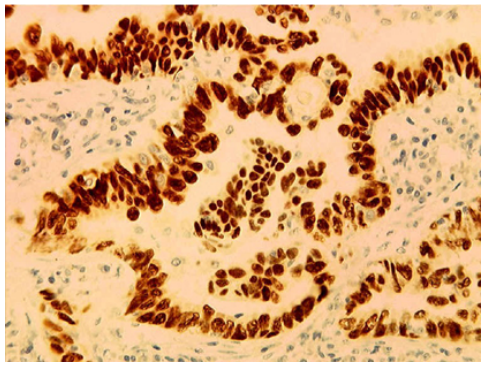
Non Small Cell Lung Carcinoma (NSCLC)

Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

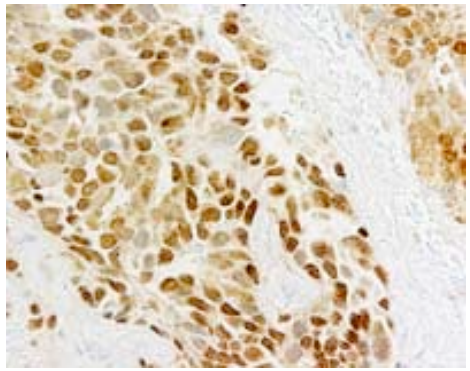


ttf1



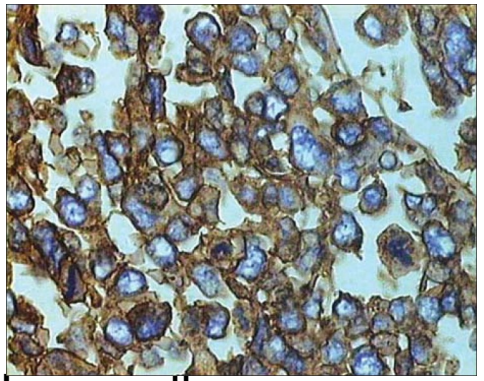
Adenocarcinoma

p63



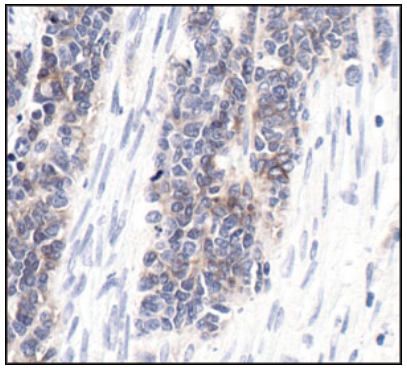
Squamous carcinoma

cd56



Large cell neuroendocrine carc

cd56



Small cell carcinoma

Non Small Cell Lung Carcinoma (NSCLC)

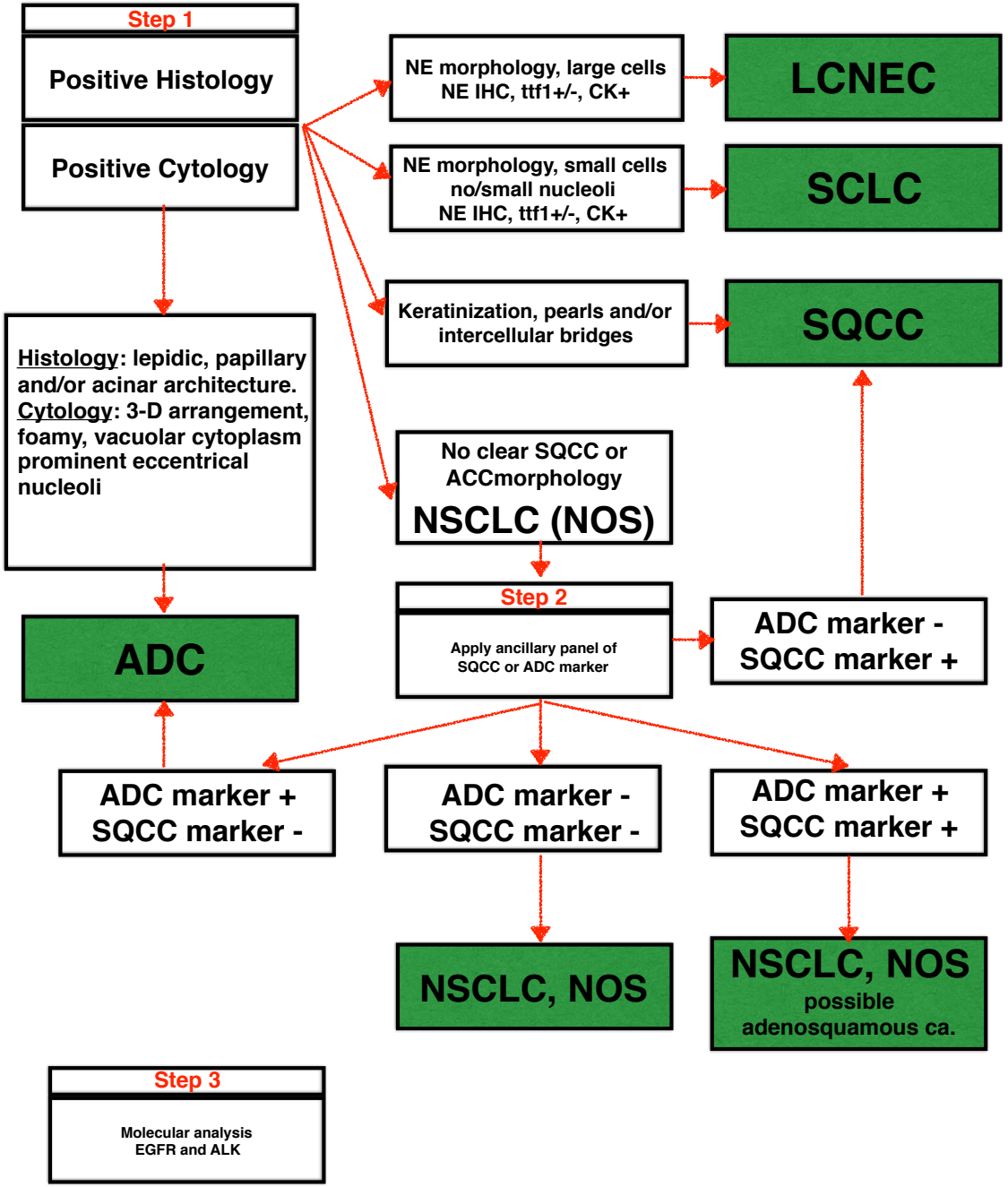
Lung Cancer
Diagnosis and prediction

Algorithm modified from

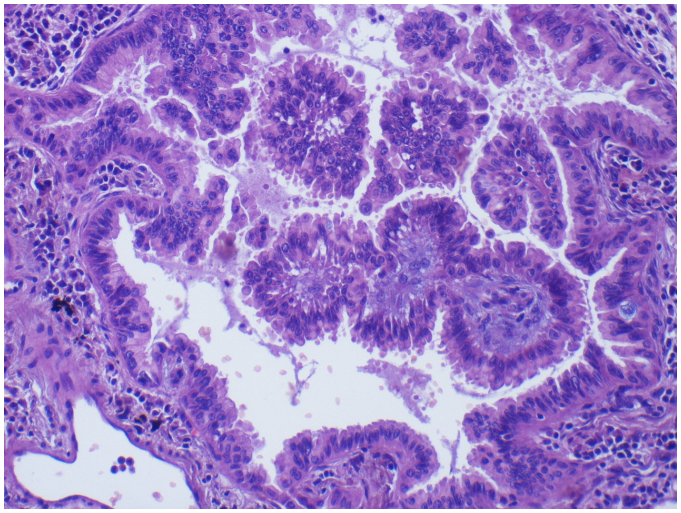
Diagnosis of Lung Cancer in Small Biopsies and Cytology

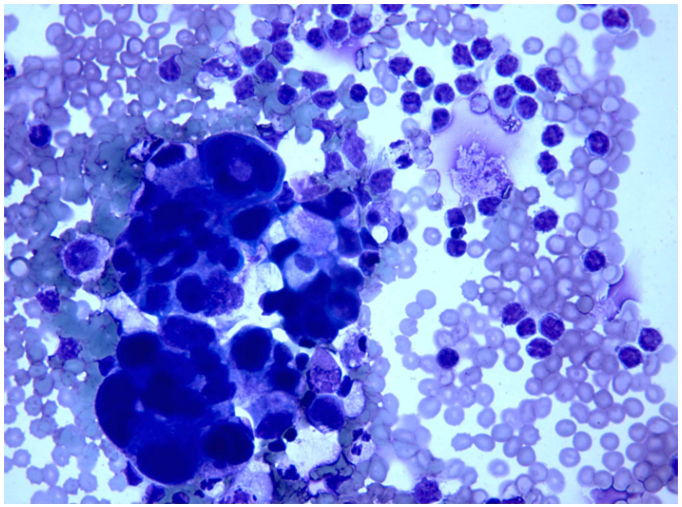
Implications of the 2011 International Association for the Study of Lung Cancer/ American Thoracic Society/European Respiratory Society Classification

William D. Travis, MD; Élisabeth 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 Gazdar, 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



Lung Cancer
Diagnosis and prediction

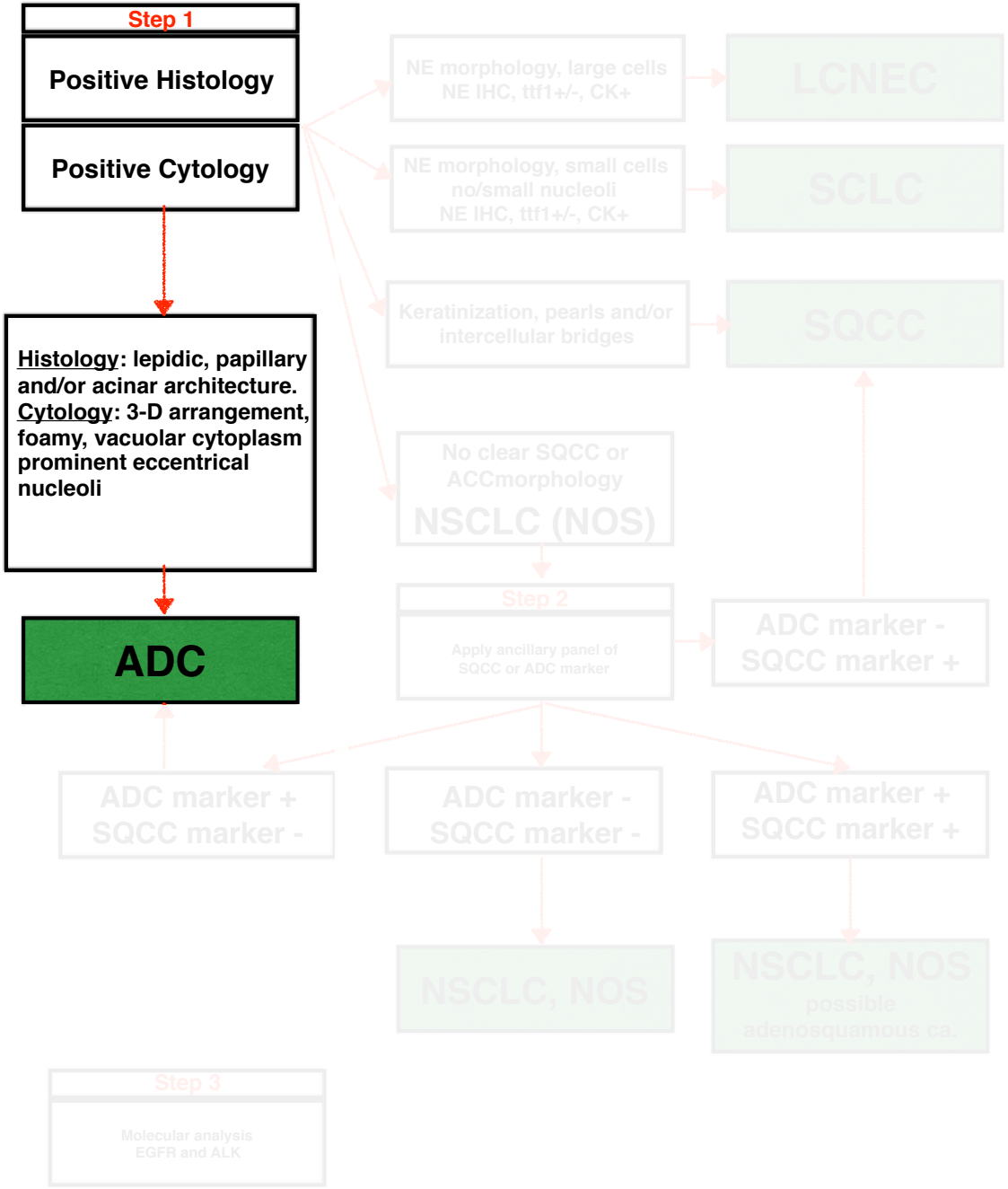




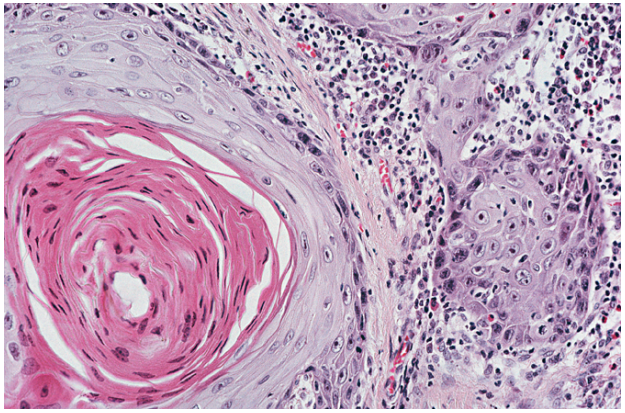
Diagnosis of Lung Cancer in Small Biopsies and Cytology

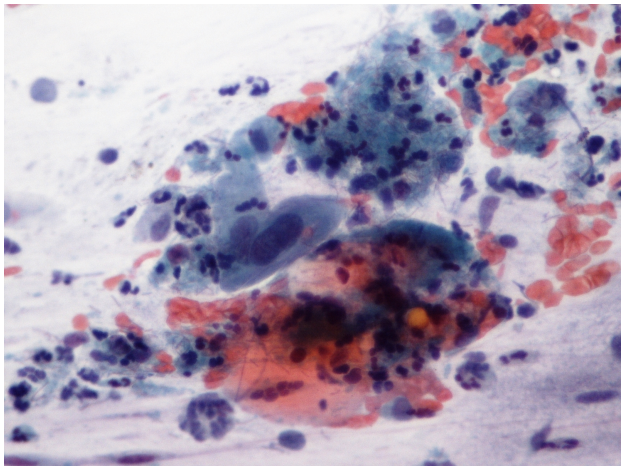
Implications of the 2011 International Association for the Study of Lung Cancer/ American Thoracic Society/European Respiratory Society Classification

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 Gazdar, 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



Lung Cancer
Diagnosis and prediction





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.

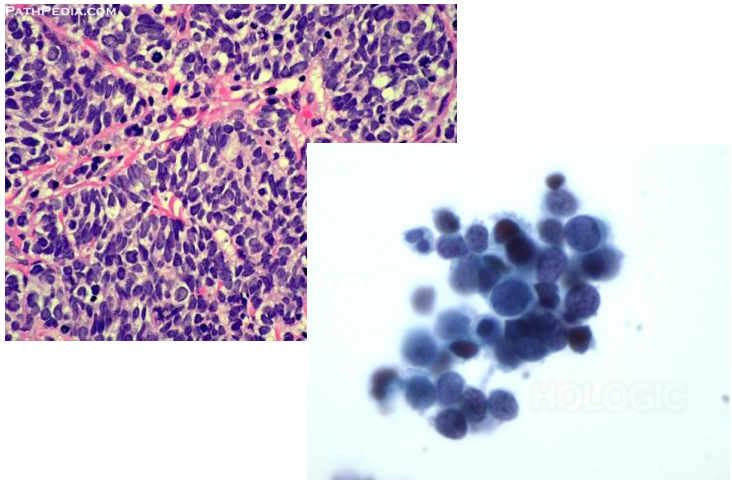
Step 3
Molecular analysis
EGFR and ALK

Diagnosis of Lung Cancer in Small Biopsies and Cytology

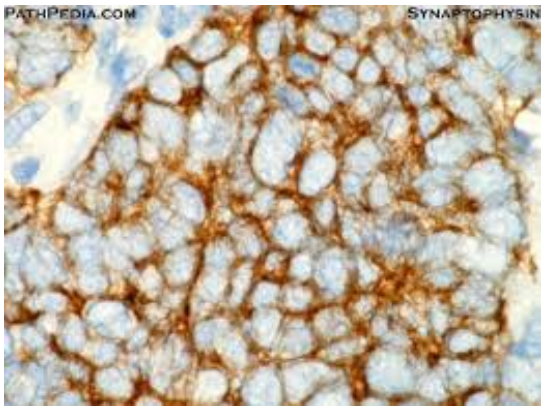
Implications of the 2011 International Association for the Study of Lung Cancer/ American Thoracic Society/European Respiratory Society Classification

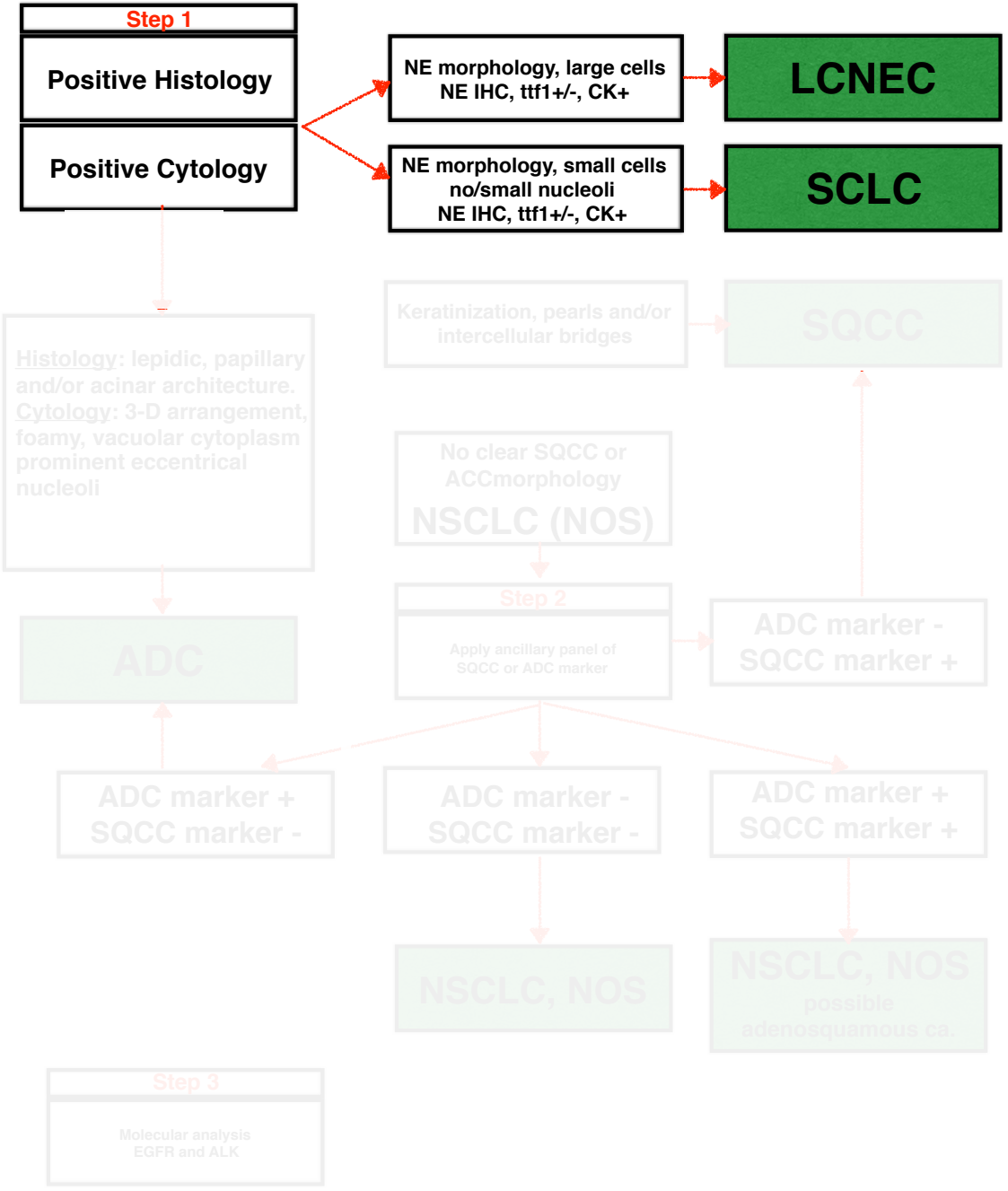
William D. Travis, MD; Elisabeth Brambilla, MD; Masayuki Noguchi, MD; Andrew G. Nicholson, DM; Kim Geisinger, MD; Yasushi Yatabe, MD; Yuichi Ishikawa, MD; Ignacio Wistuba, MD; Douglas B. Flieder, MD; Wilbur Franklin, MD; Adi Gazdar, MD; Philip S. Hasleton, MD; Douglas W. Henderson, MD; Keith M. Kerr,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

Lung Cancer
Diagnosis and prediction



CD56



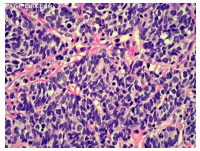


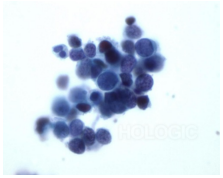
Diagnosis of Lung Cancer in Small Biopsies and Cytology

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

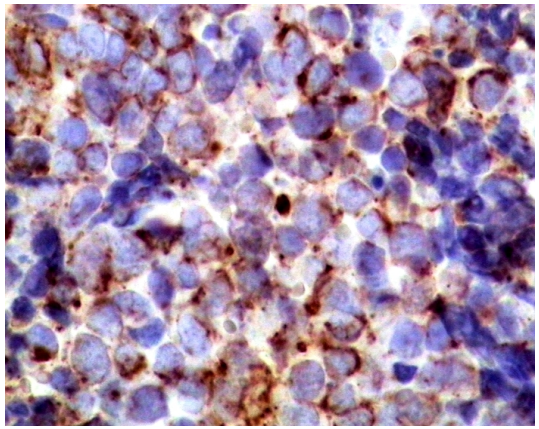
William D. Travis, MD; Elisabeth Brambilla, MD; Masayuki Noguchi, MD; Andrew G. Nicholson, DM; Kim Geisinger, MD; Yasushi Yatabe, MD; Yuichi Ishikawa, MD; Ignacio Wistuba, MD; Douglas B. Flieder, MD; Wilbur Franklin, MD; Adi Gazdar, MD; Philip S. Hasleton, MD; Douglas W. Henderson, MD; Keith M. Kerr,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

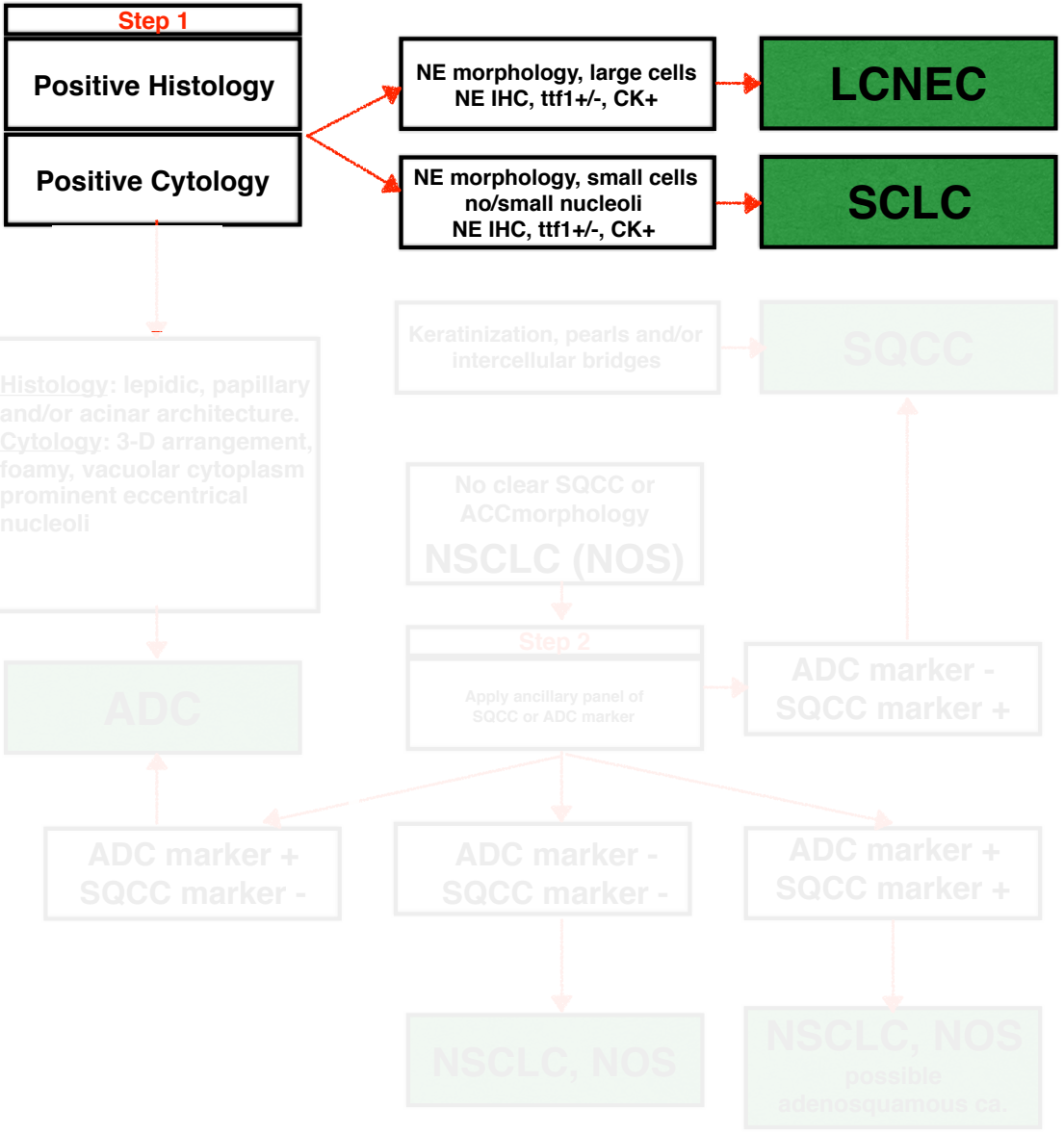
Lung Cancer
Diagnosis and prediction





Chromogranin A



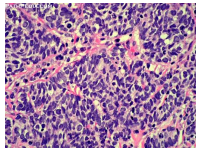


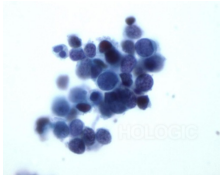
Diagnosis of Lung Cancer in Small Biopsies and Cytology

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

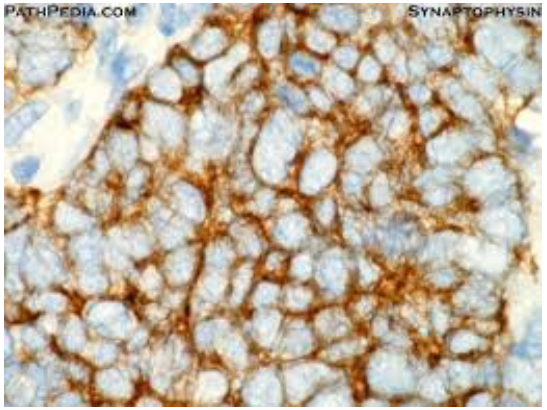
William D. Travis, MD; Elisabeth Brambilla, MD; Masayuki Noguchi, MD; Andrew G. Nicholson, DM; Kim Geisinger, MD; Yasushi Yatabe, MD; Yuichi Ishikawa, MD; Ignacio Wistuba, MD; Douglas B. Flieder, MD; Wilbur Franklin, MD; Adi Gazdar, MD; Philip S. Hasleton, MD; Douglas W. Henderson, MD; Keith M. Kerr,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

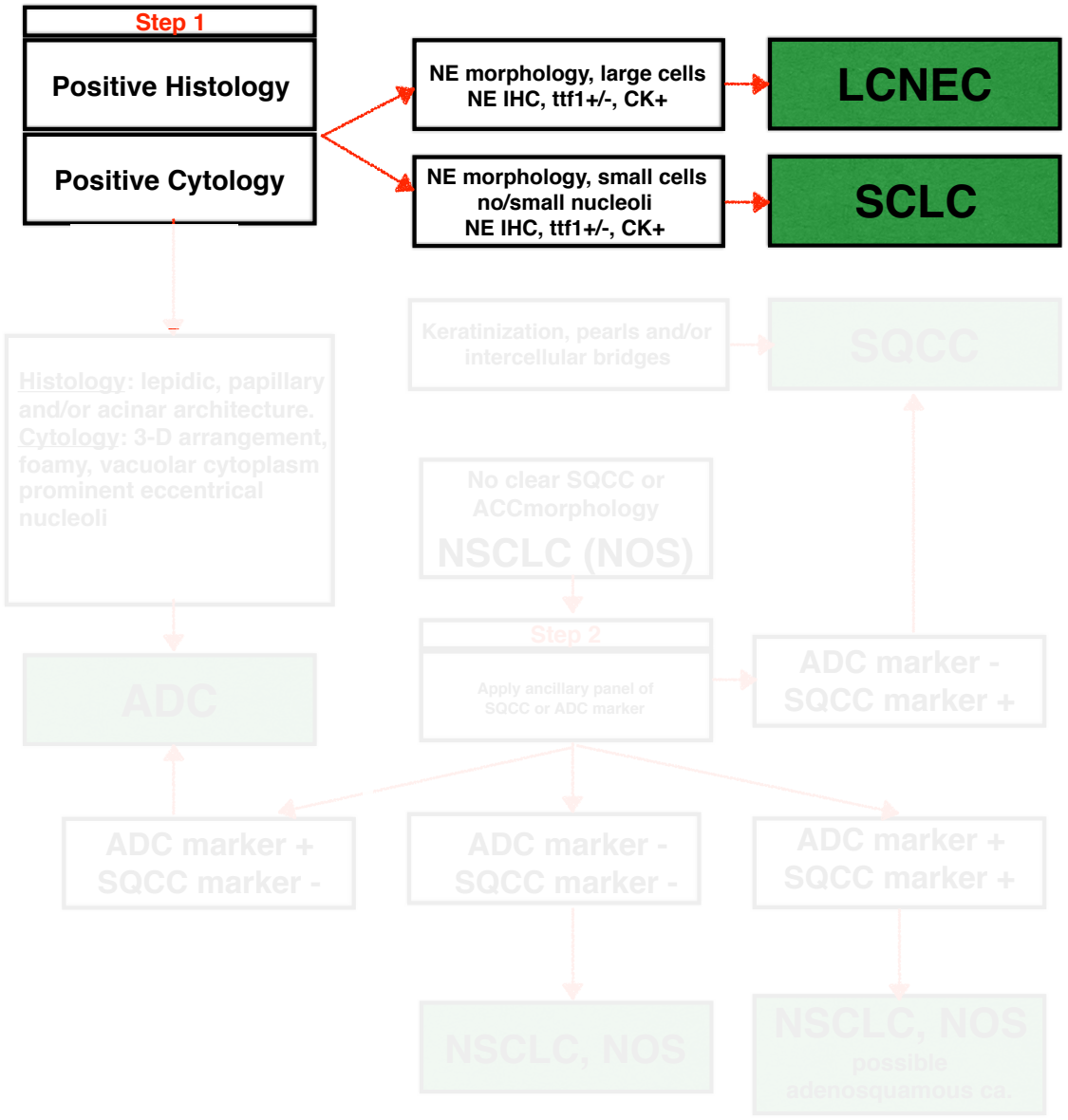
Lung Cancer
Diagnosis and prediction





Synaptophysin



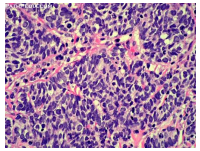


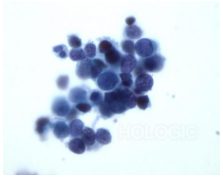
Diagnosis of Lung Cancer in Small Biopsies and Cytology

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

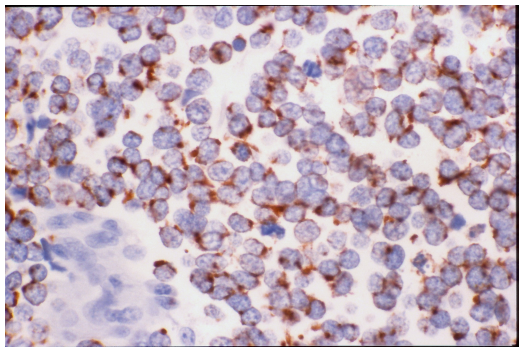
William D. Travis, MD; Elisabeth Brambilla, MD; Masayuki Noguchi, MD; Andrew G. Nicholson, DM; Kim Geisinger, MD; Yasushi Yatabe, MD; Yuichi Ishikawa, MD; Ignacio Wistuba, MD; Douglas B. Flieder, MD; Wilbur Franklin, MD; Adi Gazdar, MD; Philip S. Hasleton, MD; Douglas W. Henderson, MD; Keith M. Kerr,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

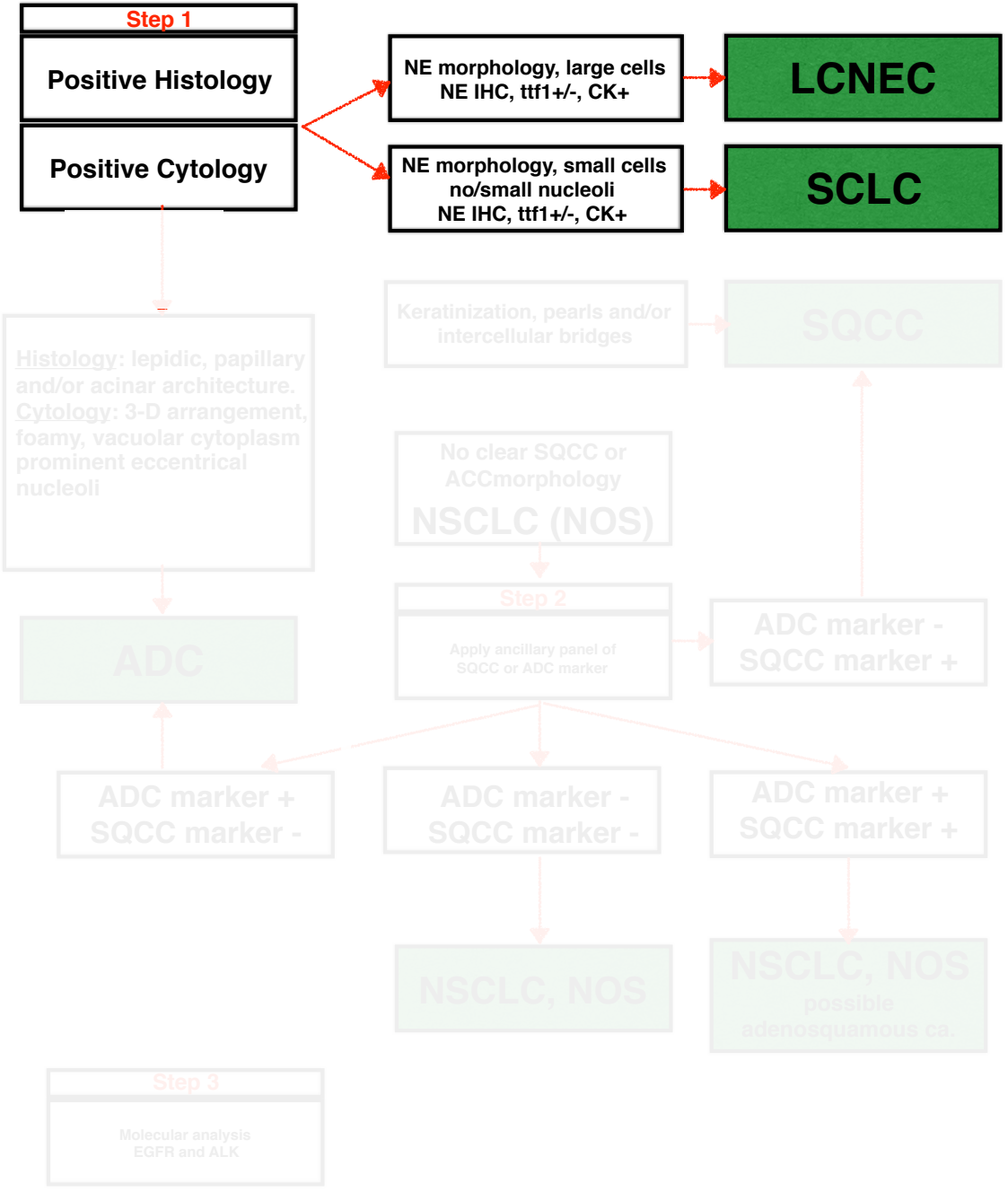
Lung Cancer
Diagnosis and prediction





Cytokeratin



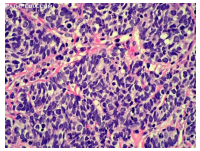


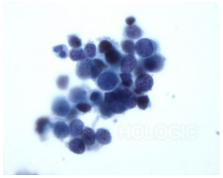
Diagnosis of Lung Cancer in Small Biopsies and Cytology

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

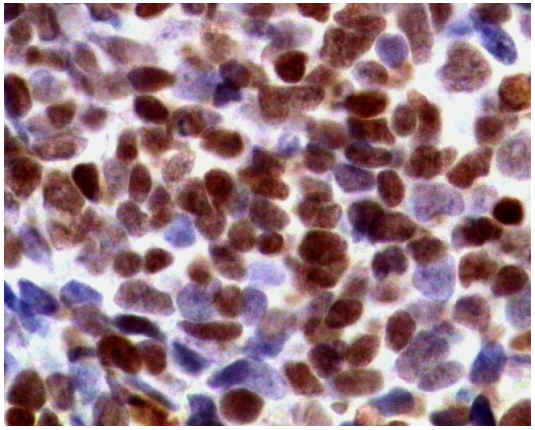
William D. Travis, MD; Elisabeth Brambilla, MD; Masayuki Noguchi, MD; Andrew G. Nicholson, DM; Kim Geisinger, MD; Yasushi Yatabe, MD; Yuichi Ishikawa, MD; Ignacio Wistuba, MD; Douglas B. Flieder, MD; Wilbur Franklin, MD; Adi Gazdar, MD; Philip S. Hasleton, MD; Douglas W. Henderson, MD; Keith M. Kerr,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

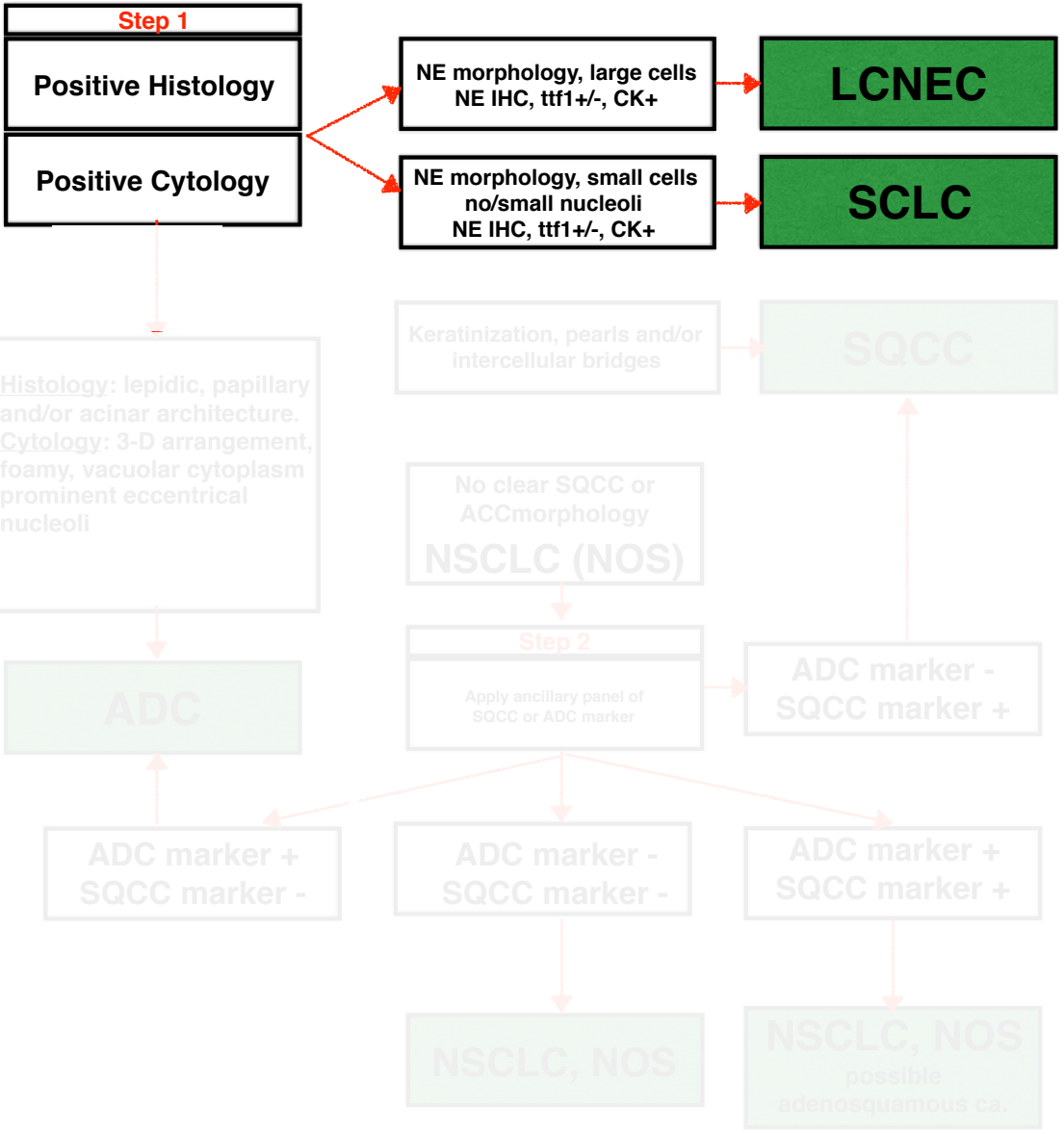
Lung Cancer
Diagnosis and prediction





ttf1



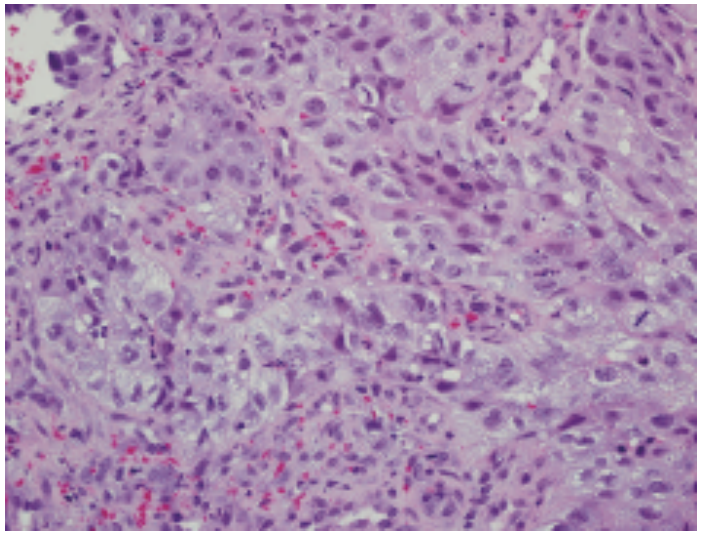


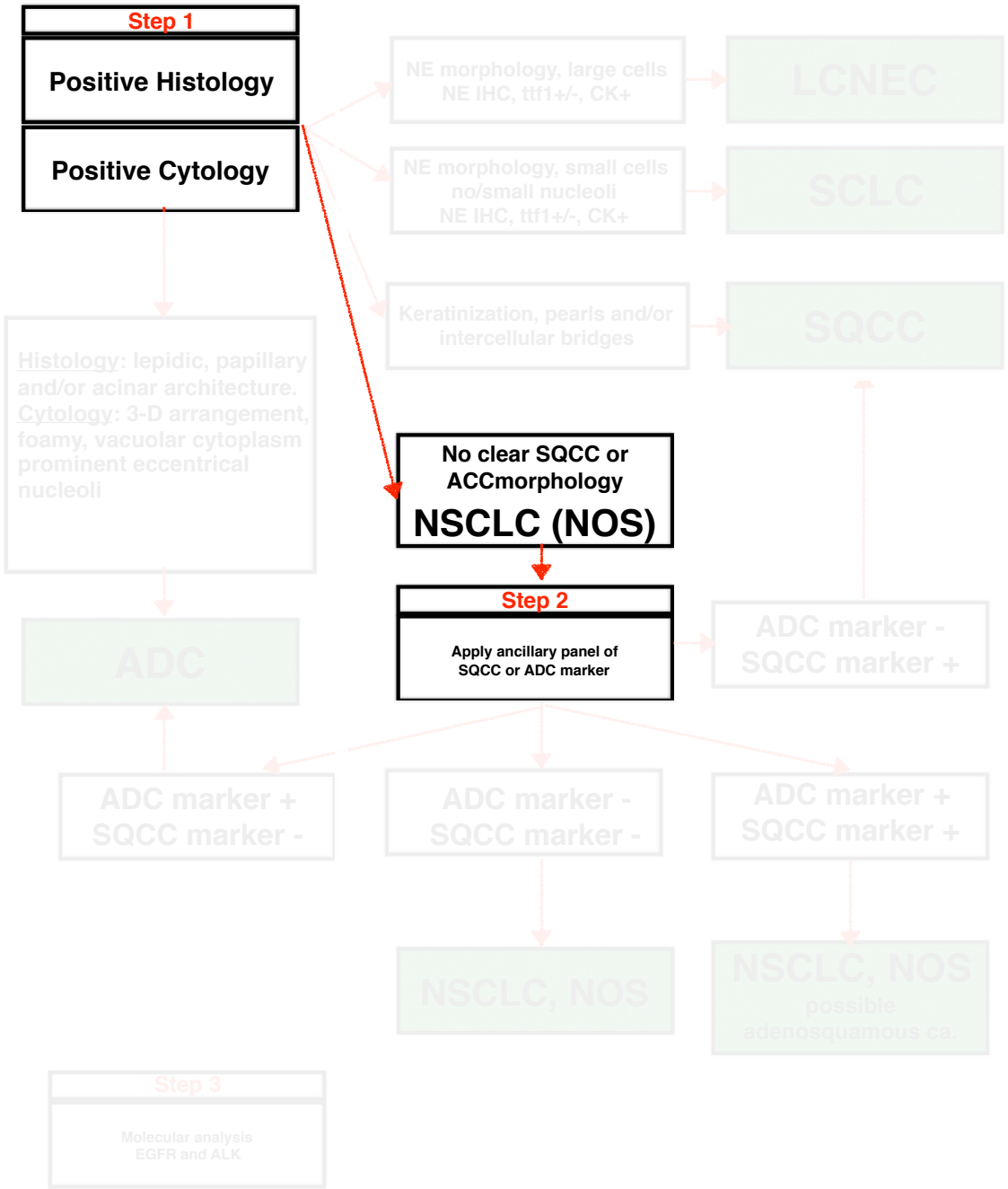
Diagnosis of Lung Cancer in Small Biopsies and Cytology

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

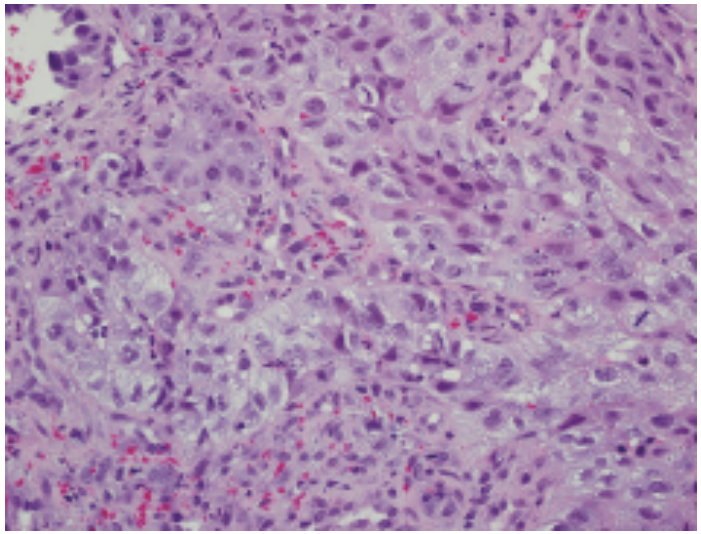
William D. Travis, MD; Elisabeth Brambilla, MD; Masayuki Noguchi, MD; Andrew G. Nicholson, DM; Kim Geisinger, MD; Yasushi Yatabe, MD; Yuichi Ishikawa, MD; Ignacio Wistuba, MD; Douglas B. Flieder, MD; Wilbur Franklin, MD; Adi Gazdar, MD; Philip S. Hasleton, MD; Douglas W. Henderson, MD; Keith M. Kerr,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

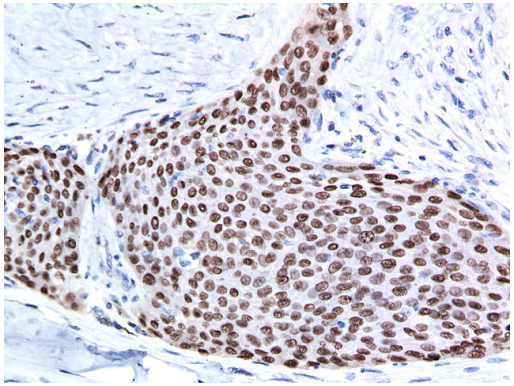
Lung Cancer
Diagnosis and prediction





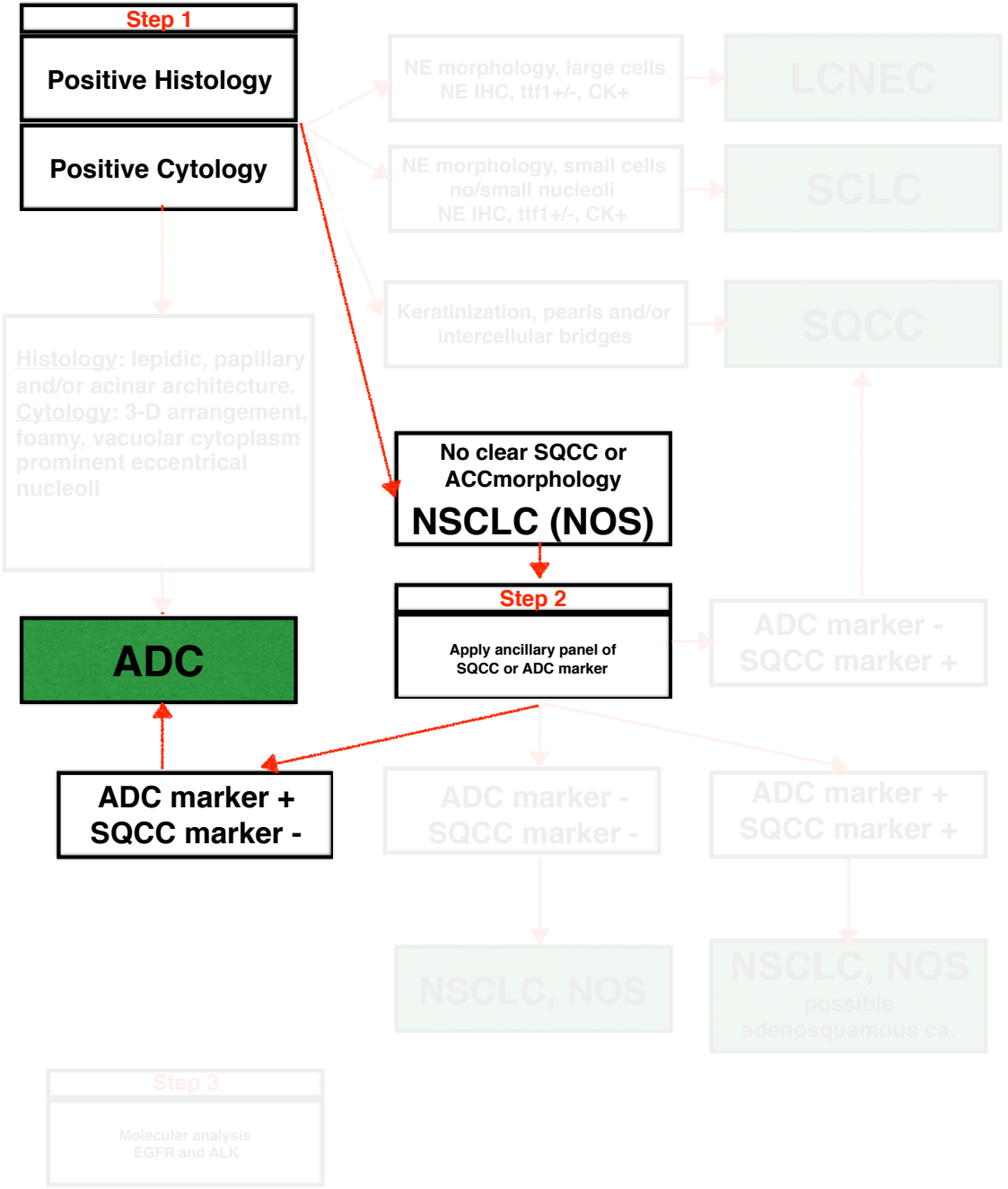
Lung Cancer
Diagnosis and prediction



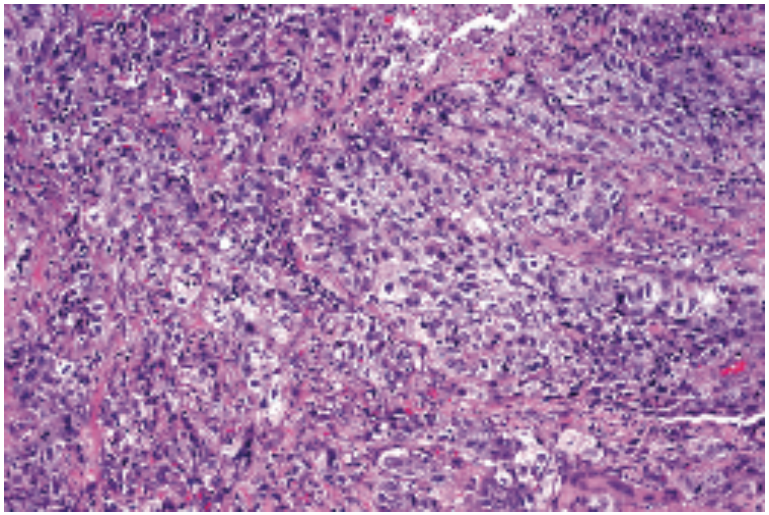


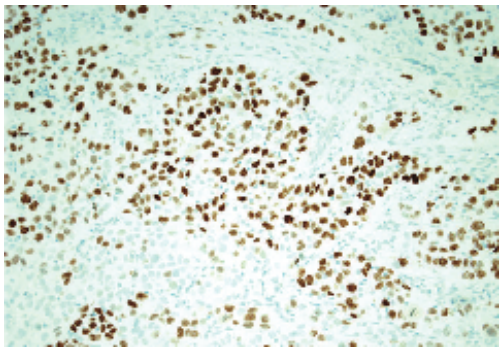
ttf1 +

(+Cytokeratin 7)

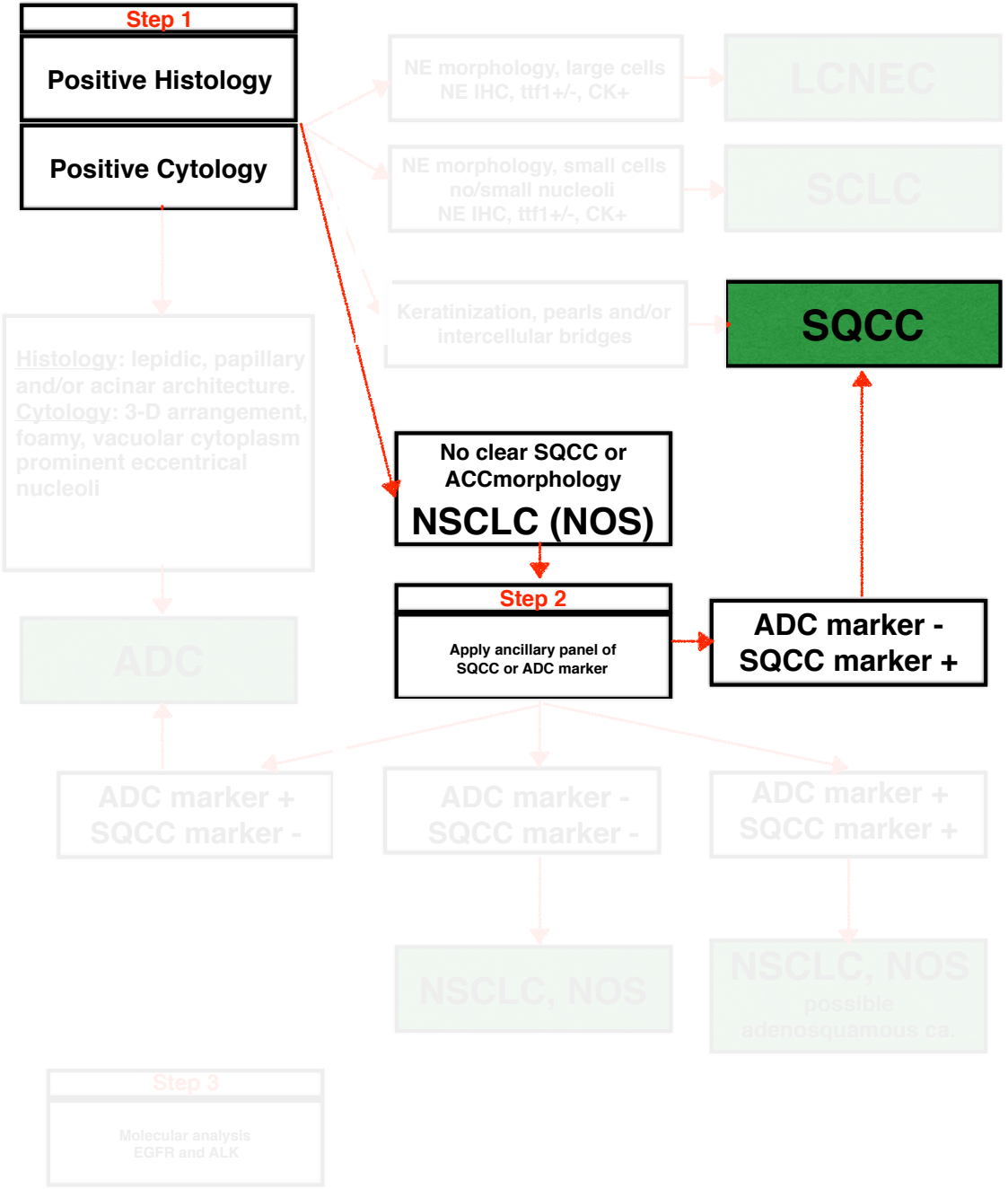


Lung Cancer
Diagnosis and prediction

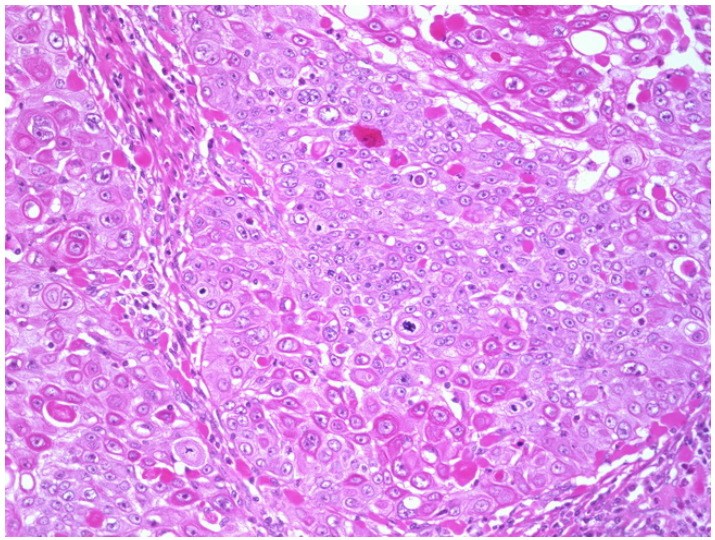


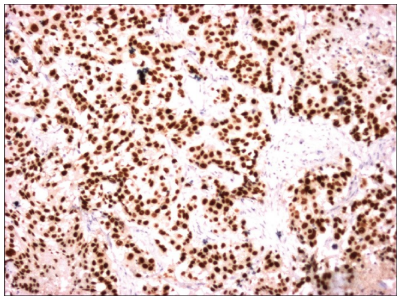


P63+ (+Cytokeratin 5/6)

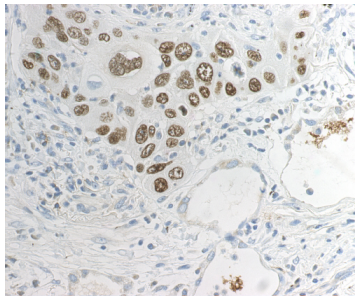


Lung Cancer
Diagnosis and prediction

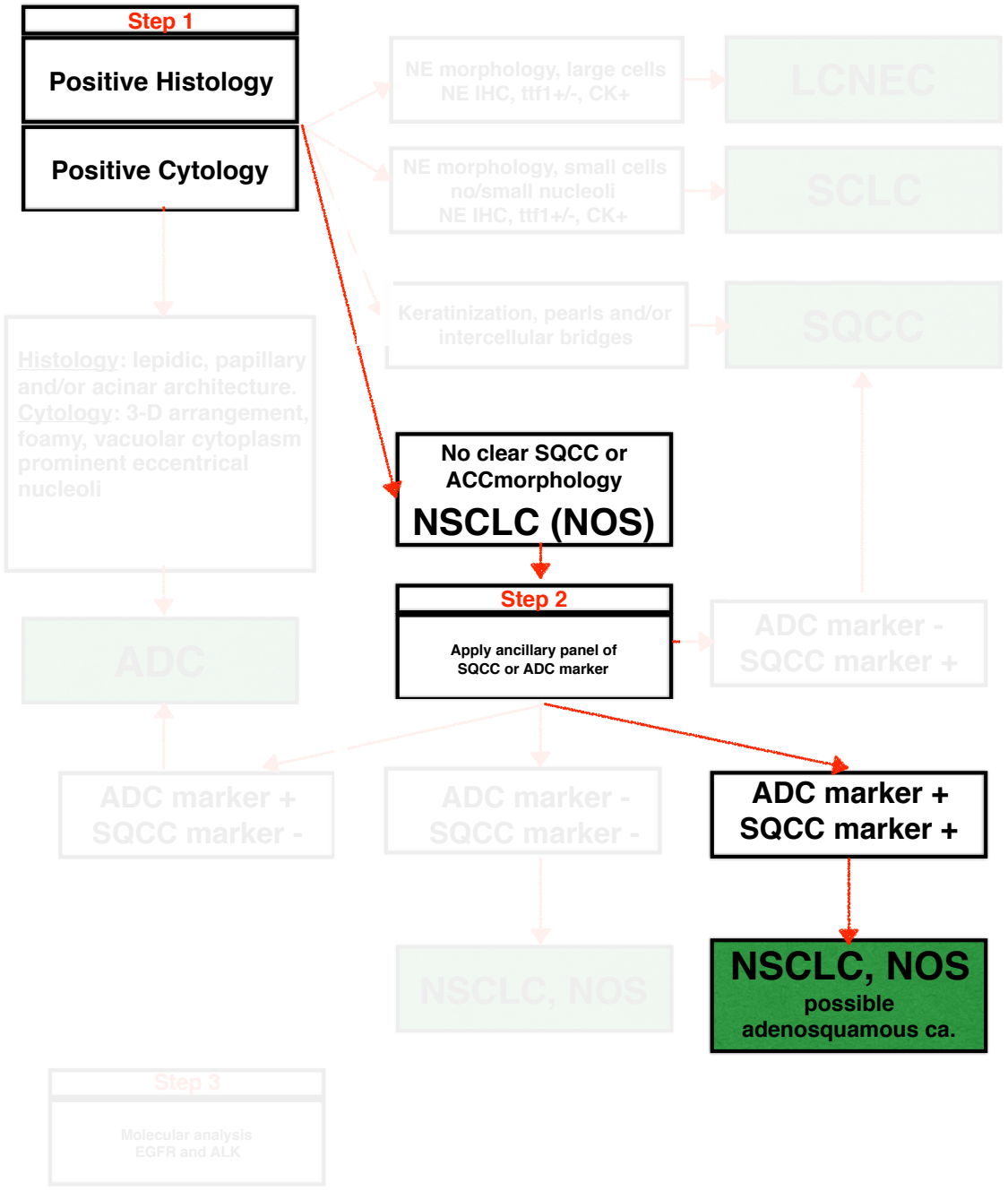




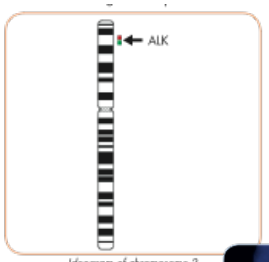
ttf1+



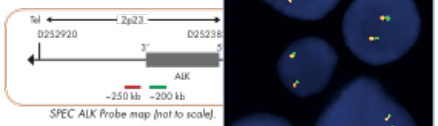
P63+



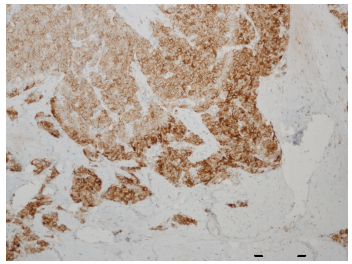
Lung Cancer
Diagnosis and prediction



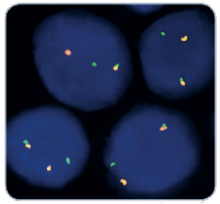
Ideogram of chromosome 2 indicating the hybridization locations.



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.



Step 1

Positive Histology

Positive Cytology

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

ADC

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

LCNEC

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

SCLC

Keratinization, pearls and/or intercellular bridges

SQCC

No clear SQCC or ACCmorphology

NSCLC (NOS)

Step 2

Apply ancillary panel of SQCC or ADC marker

ADC marker +
SQCC marker -

ADC marker -
SQCC marker -

ADC marker +
SQCC marker +

NSCLC, NOS

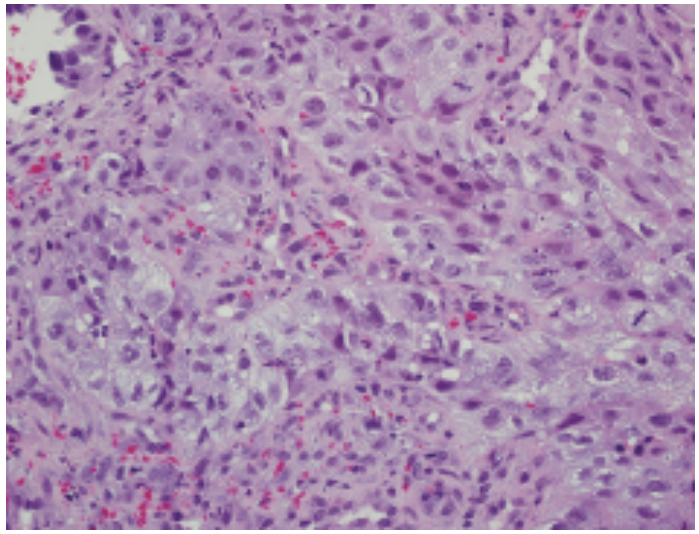
NSCLC, NOS
possible adenosquamous ca.

Step 3

Molecular analysis
EGFR and ALK

Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt



CK7

ttf1

Napsin

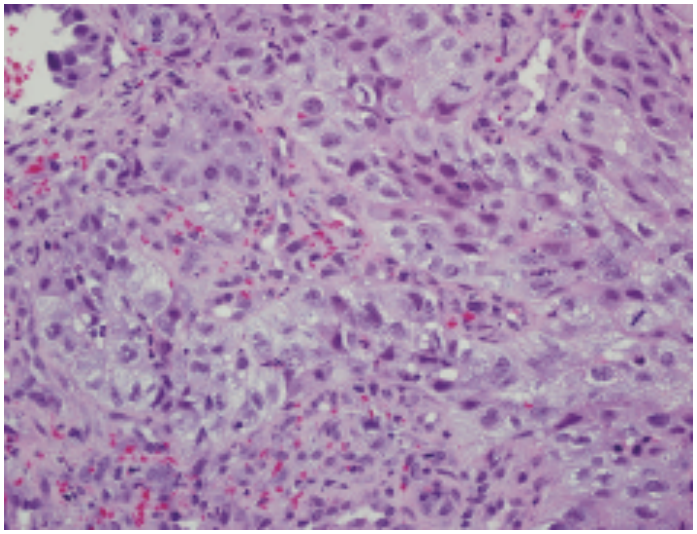
CK5/6

P63

Adenocarcinoma

Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt



CK7

ttf1

Napsin

CK5/6

P63

Squamous carcinoma

Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

Problems:

Adenocarcinoma can be P63+

p40 is the Best Marker for Diagnosing Pulmonary Squamous Cell Carcinoma: Comparison With p63, Cytokeratin 5/6, Desmocollin-3, and Sox2

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

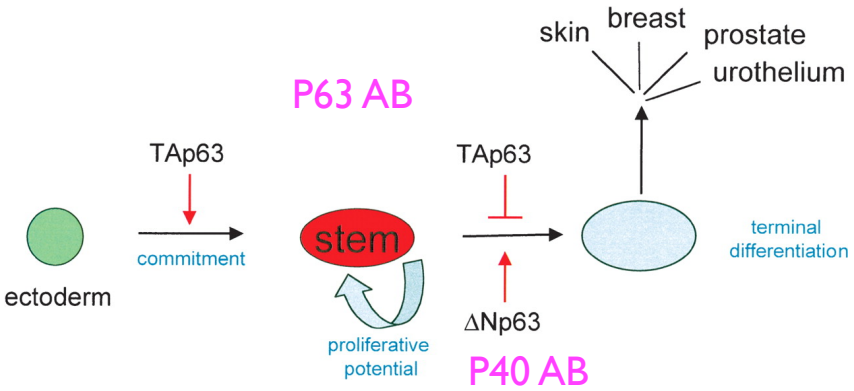
Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

Problems:

Adenocarcinoma can be P63+

	Marker	Total	No. Cases (%) Immunoreactivity		Mean Staining Score (0-300)
			Negative	Positive	
SQC	p40	158	5 (3.2)	153 (96.8)	169
	p63	154	4 (2.6)	150 (97.4)	237
Non-SQC	p40	418	405 (96.9)	13 (3.1)	1.3
	p63	419	305 (72.8)	114 (27.2)	16.9



p40 is the Best Marker for Diagnosing Pulmonary Squamous Cell Carcinoma: Comparison With p63, Cytokeratin 5/6, Desmocollin-3, and Sox2

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

Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

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

Marker	Subtype	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ΔNp63	SCC	100 (16/16)	100 (32/32)	100 (16/16)	100 (32/32)
p63	SCC	100 (16/16)	88 (28/32)	80 (16/20)	100 (28/28)
CK5/6	SCC	81 (13/16)	100 (32/32)	100 (13/13)	91 (32/35)
34βE12	SCC	94 (15/16)	47 (15/32)	47 (15/32)	94 (15/16)
TTF1	AC	80 (20/25)	87 (20/23)	87 (20/23)	80 (20/25)
Napsin A	AC	64 (16/25)	100 (23/23)	100 (16/16)	72 (23/32)
CK7	AC	100 (25/25)	35 (8/23)	63 (25/40)	100 (8/8)
CK8/18	AC	100 (25/25)	35 (8/23)	63 (25/40)	100 (8/8)

Sensitivity = TP/TP+FN; Specificity = TN/TN+FP; Positive predictive value (PPV) = TP/TP+FP; Negative predictive value (NPV) = TN/TN+FN. FN indicates false negatives; FP, false positives; TN, true negatives; TP, true positives.

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

Original Article

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

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

Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

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

Marker	Subtype	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ΔNp63	SCC	100 (16/16)	100 (32/32)	100 (16/16)	100 (32/32)
p63	SCC	100 (16/16)	88 (28/32)	80 (16/20)	100 (28/28)
CK5/6	SCC	81 (13/16)	100 (32/32)	100 (13/13)	91 (32/35)
34βE12	SCC	94 (15/16)	47 (15/32)	47 (15/32)	94 (15/16)
TTF1	AC	80 (20/25)	87 (20/23)	87 (20/23)	80 (20/25)
Napsin A	AC	64 (16/25)	100 (23/23)	100 (16/16)	72 (23/32)
CK7	AC	100 (25/25)	35 (8/23)	63 (25/40)	100 (8/8)
CK8/18	AC	100 (25/25)	35 (8/23)	63 (25/40)	100 (8/8)

Sensitivity = TP/TP+FN; Specificity = TN/TN+FP; Positive predictive value (PPV) = TP/TP+FP; Negative predictive value (NPV) = TN/TN+FN. FN indicates false negatives; FP, false positives; TN, true negatives; TP, true positives.

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

Original Article

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

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

Lung Cancer

Diagnosis and prediction

Table 3. Algorithm for subtyping of poorly-differentiated non-small cell lung carcinomas according to immunohistochemical staining in lung biopsies

ΔNp63	CK5/6	TTF1	Napsin A	Diagnosis
+	+	-	-	Squamous cell carcinoma
+	-	-	-	Squamous cell carcinoma
-	-	+	+	Adenocarcinoma
-	-	+	-	Adenocarcinoma
-	-	-	-	Poorly-differentiated non-small cell carcinoma

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

Original Article

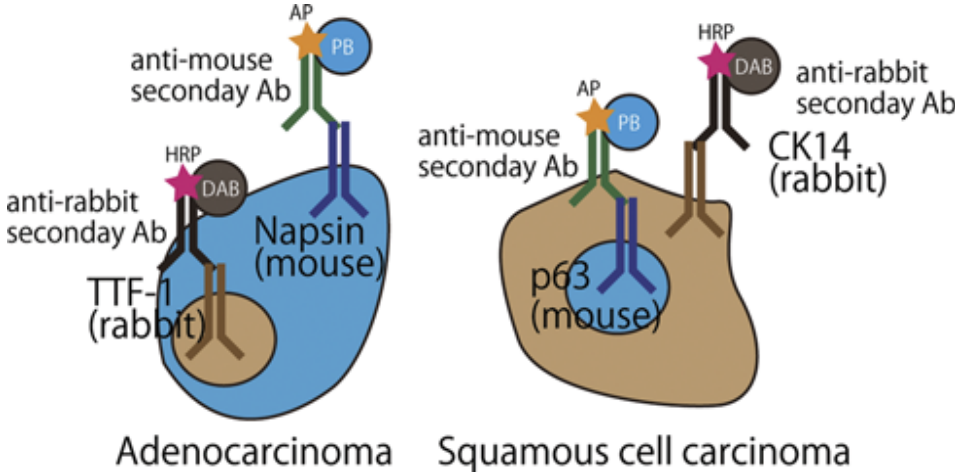
ΔNp63, CK5/6, TTF-1 and napsin A, a reliable panel to subtype non-small cell lung cancer in biopsy specimens

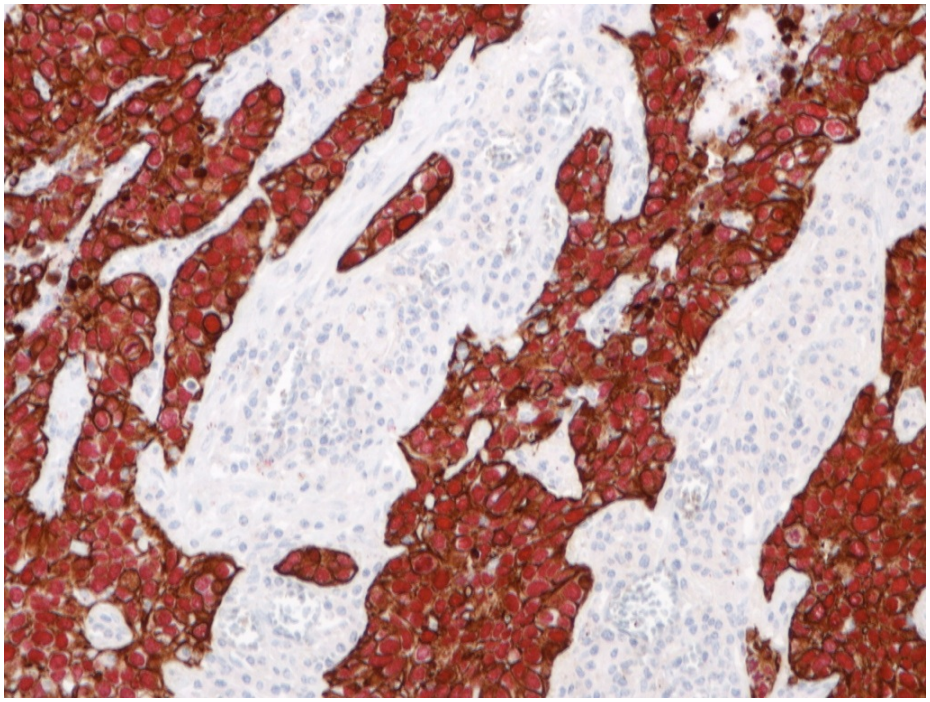
Wei Zhao, Hui Wang, Yan Peng, Bo Tian, Lei Peng, Da-Chuan Zhang

Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

Multiplex

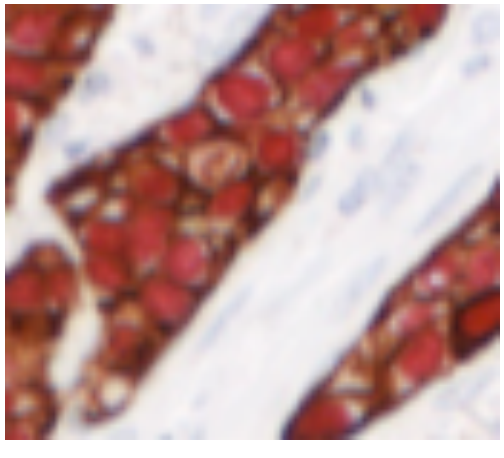




Rapid Multiplex Immunohistochemistry Using the 4-antibody Cocktail YANA-4 in Differentiating Primary Adenocarcinoma From Squamous Cell Carcinoma of the Lung

Emmy Yanagita, MT, Naoko Imagawa, MT,* Chiho Ohbayashi, MD,† and Tomoo Itoh, MD**

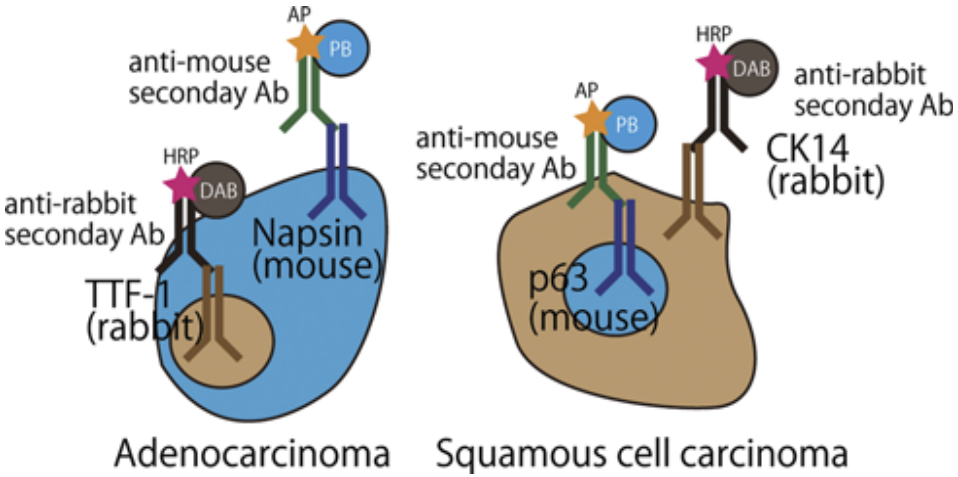
Appl Immunohistochem Mol Morphol • Volume 19, Number 6, December 2011

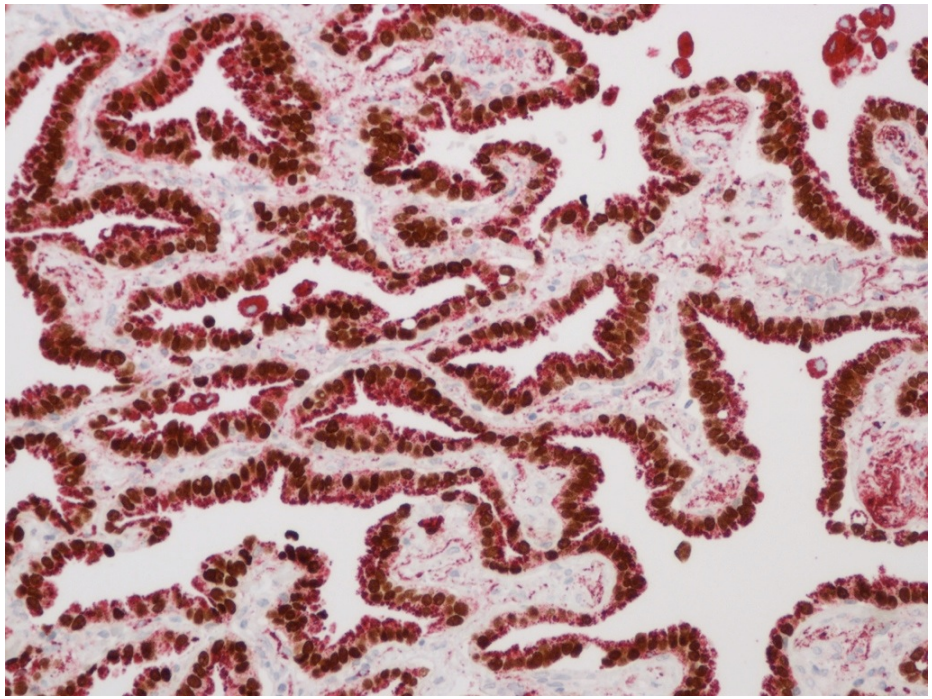


Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

Multiplex

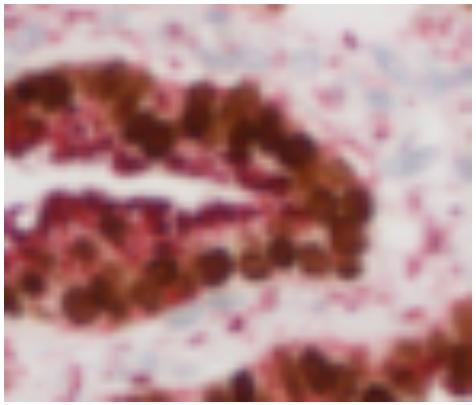




Rapid Multiplex Immunohistochemistry Using the 4-antibody Cocktail YANA-4 in Differentiating Primary Adenocarcinoma From Squamous Cell Carcinoma of the Lung

Emmy Yanagita, MT, Naoko Imagawa, MT,* Chiho Ohbayashi, MD,† and Tomoo Itoh, MD**

Appl Immunohistochem Mol Morphol • Volume 19, Number 6, December 2011



Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

Problems:

Differential diagnosis between primary and metastatic carcinoma

Other (adeno) carcinomas are positive for ttf1

Table 1

Summary of immunohistochemistry results.

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

NS: not significant

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

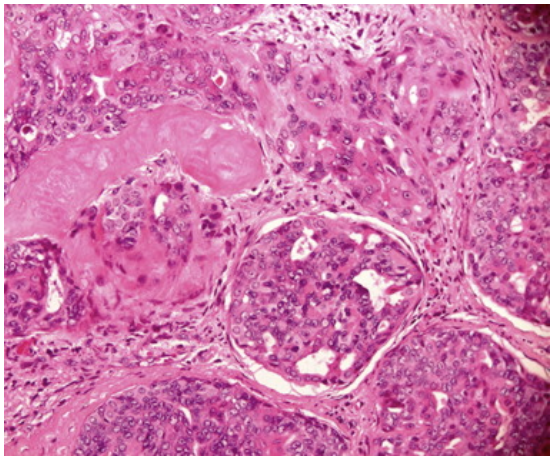
Comparison of thyroid transcription factor-1 expression by two monoclonal antibodies in pulmonary and non-pulmonary primary tumors

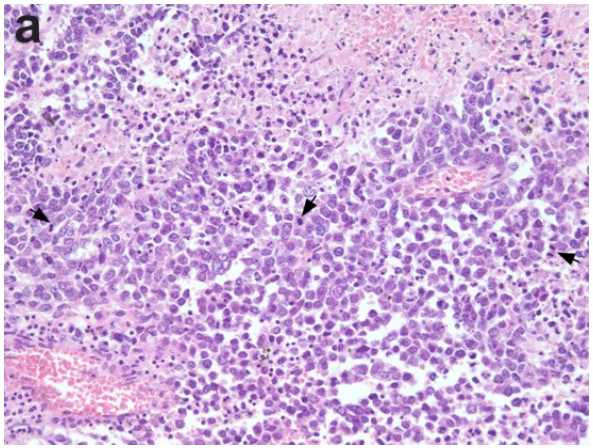
Andres Matoso, Kamaljeet Singh, Rafik Jacob, Wesley O. Greaves, Rosemarie Tavares, Lelia Noble, Murray B. Resnick, Ronald A. DeLellis, and Li J. Wang
Department of Pathology and Laboratory Medicine, Rhode Island Hospital and Brown Medical School, Providence, RI.

Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

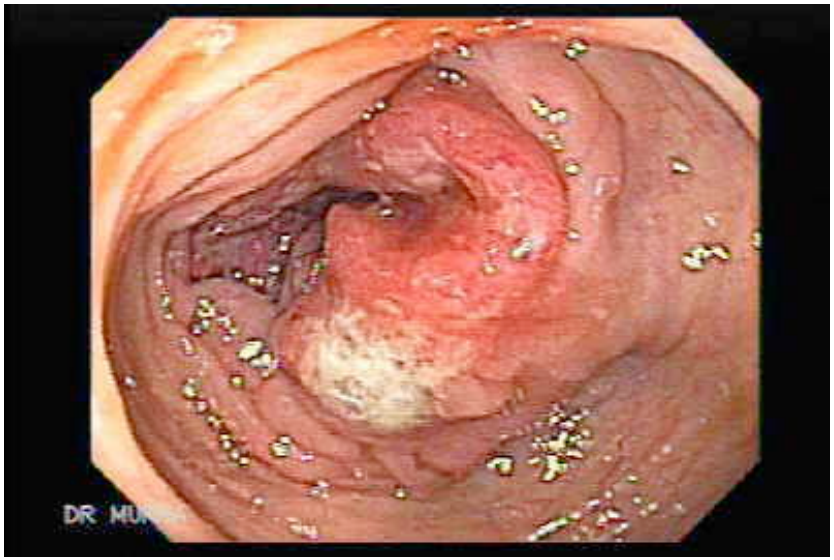
Diagnosis of metastasis to the lung





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

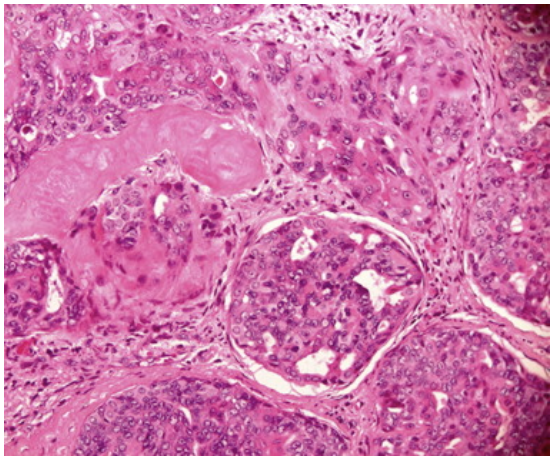
Colon

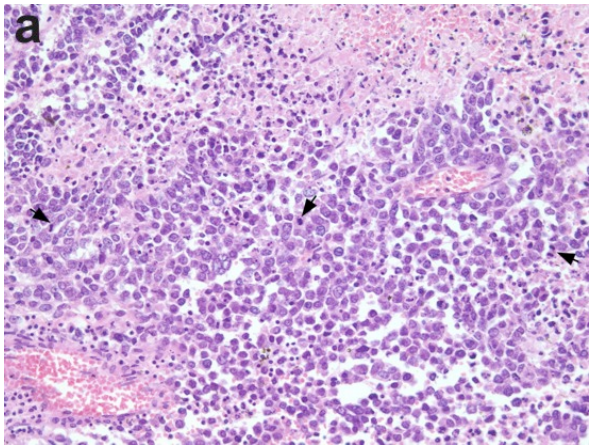


Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

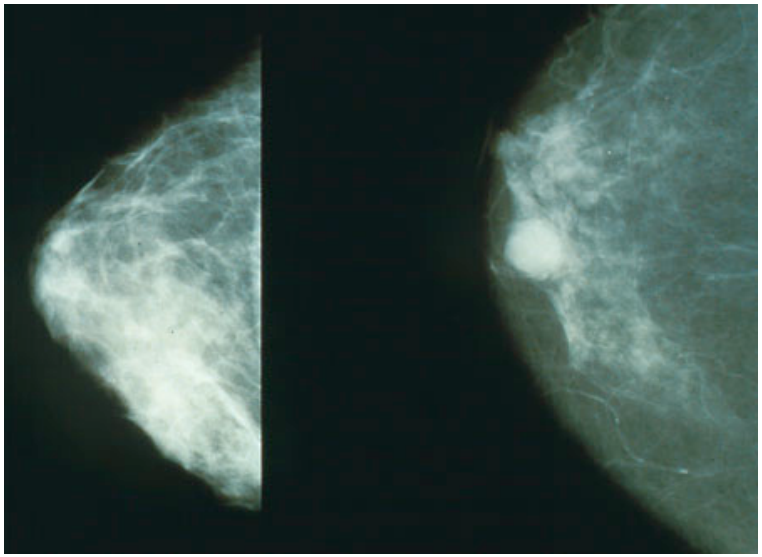
Diagnosis of metastasis to the lung





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

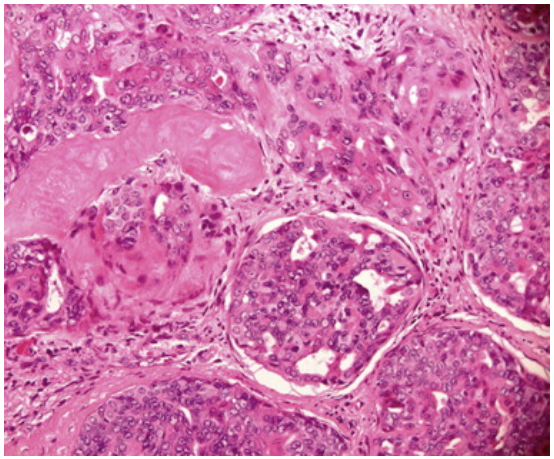
Mamma

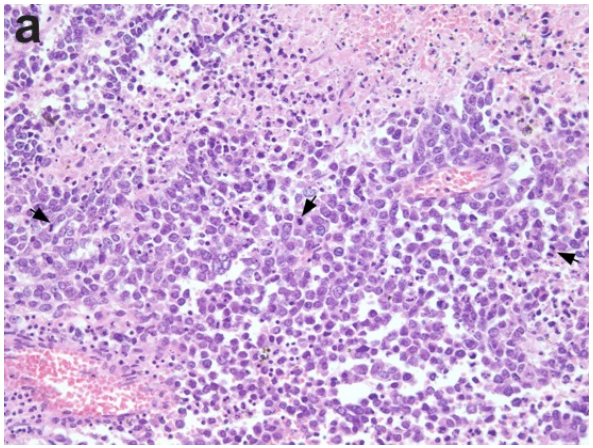


Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

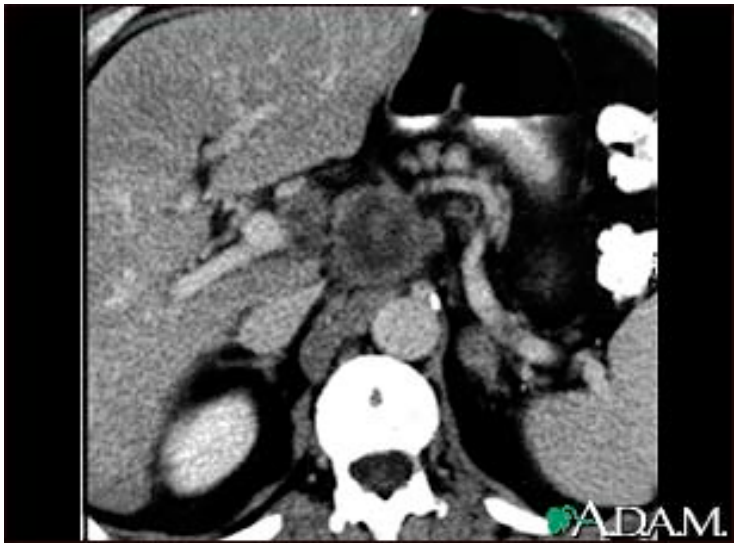
Diagnosis of metastasis to the lung





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

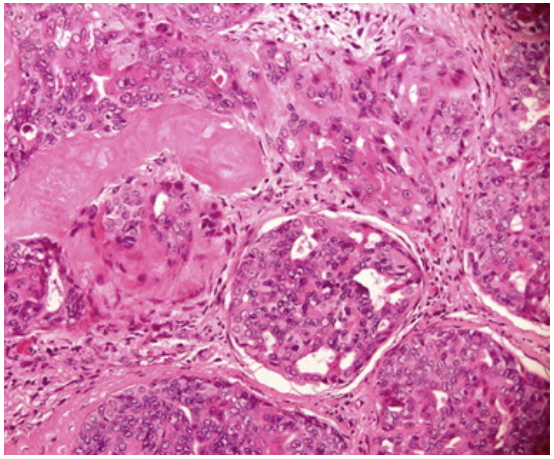
Upper GI

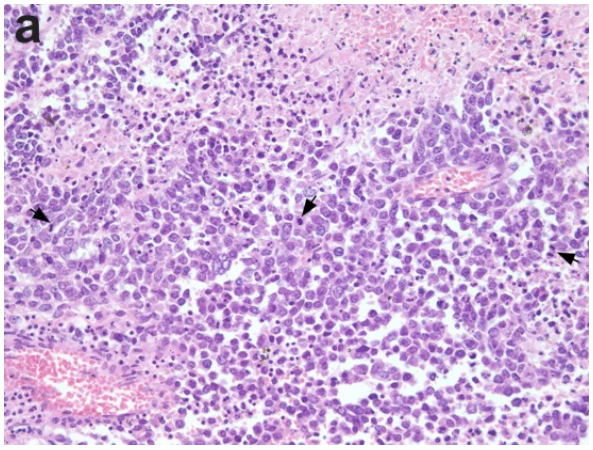


Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

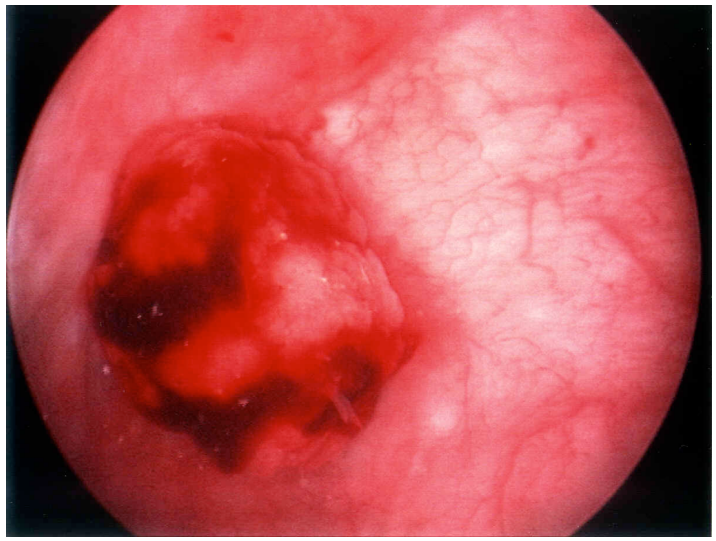
Diagnosis of metastasis to the lung





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

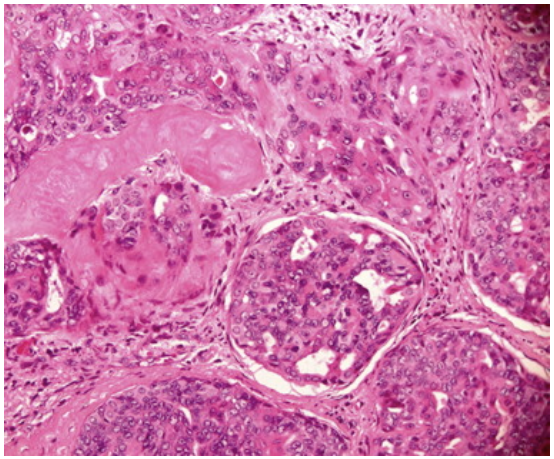
Urothelial carcinoma

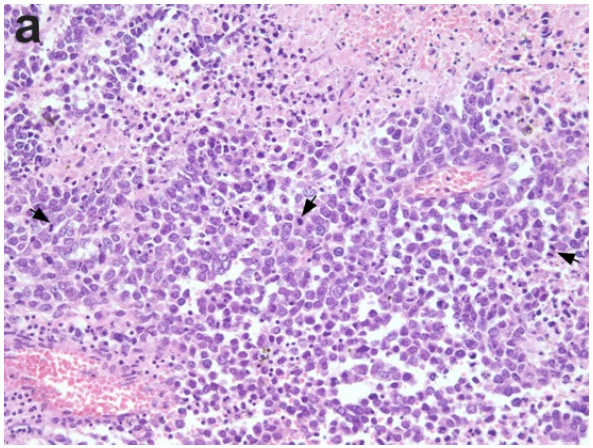


Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

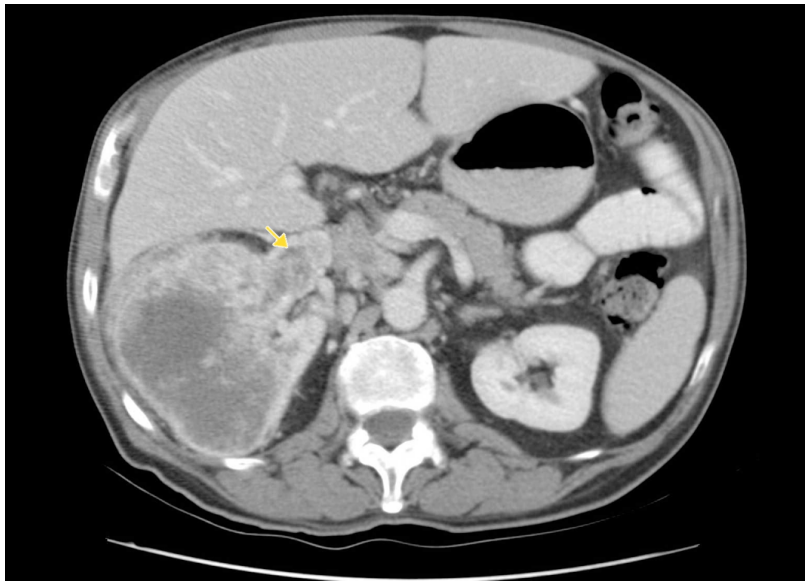
Diagnosis of metastasis to the lung





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

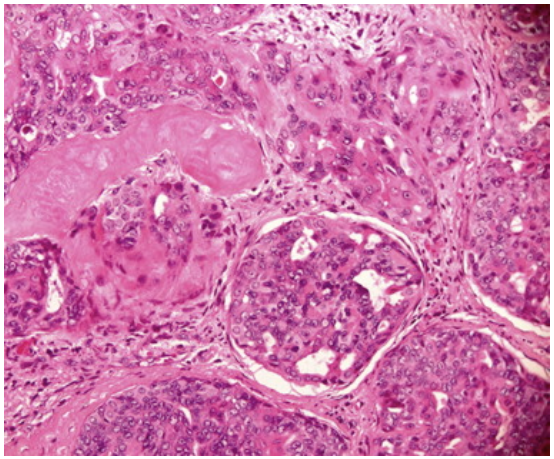
Renal cell carcinoma

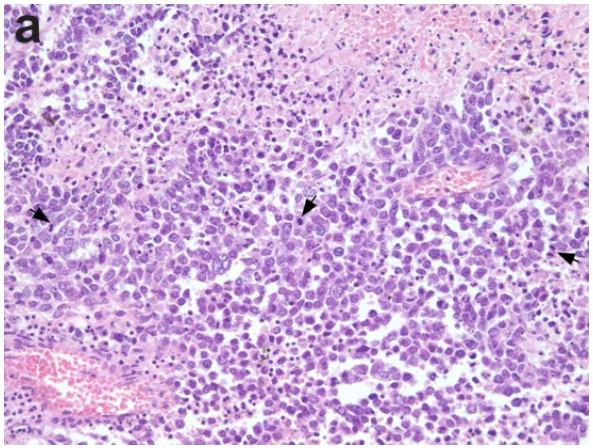


Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

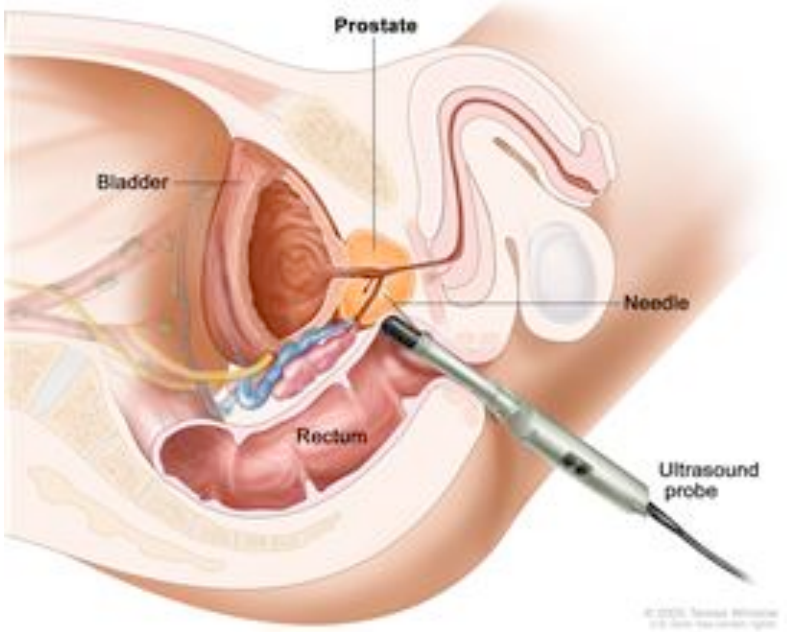
Diagnosis of metastasis to the lung





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

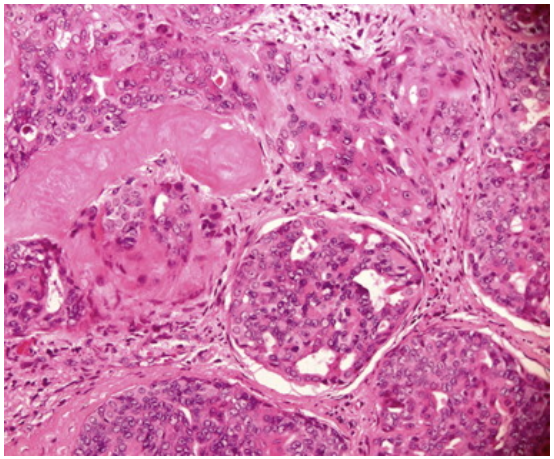
Prostate

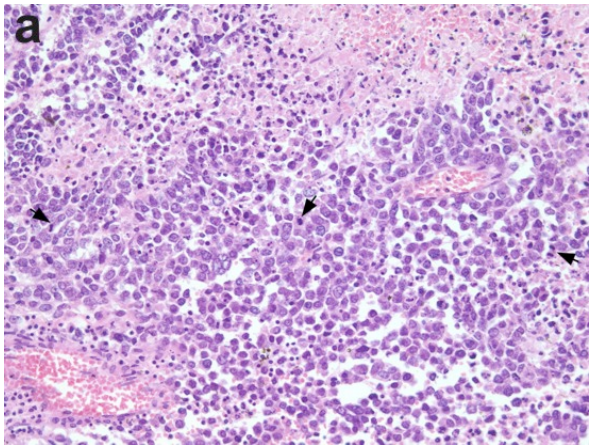


Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

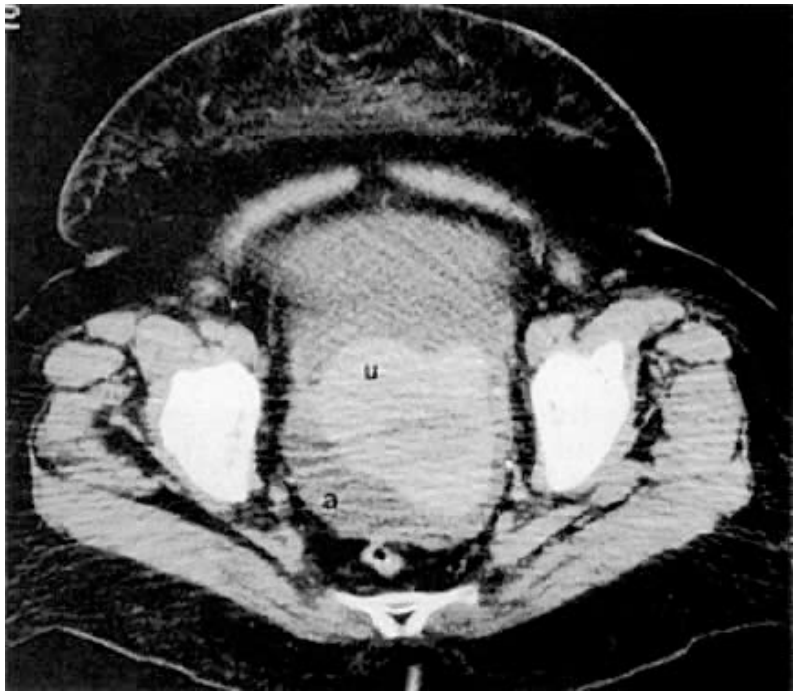
Diagnosis of metastasis to the lung





- Kl1 ←
- CK7
- ttf1
- Napsin
- CK20
- cdx2
- ER ←
- GCDFP15
- PSA
- Vim ←
- CK5/6
- P63
- CD10
- RCC
- Ca125
- PAX8 ←
- WT1
- GATA3

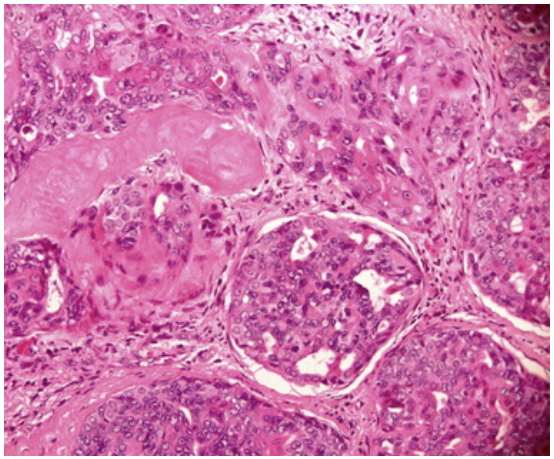
Endometrial cancer

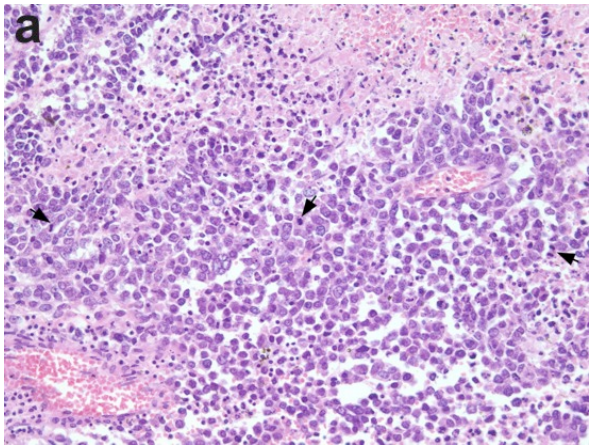


Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

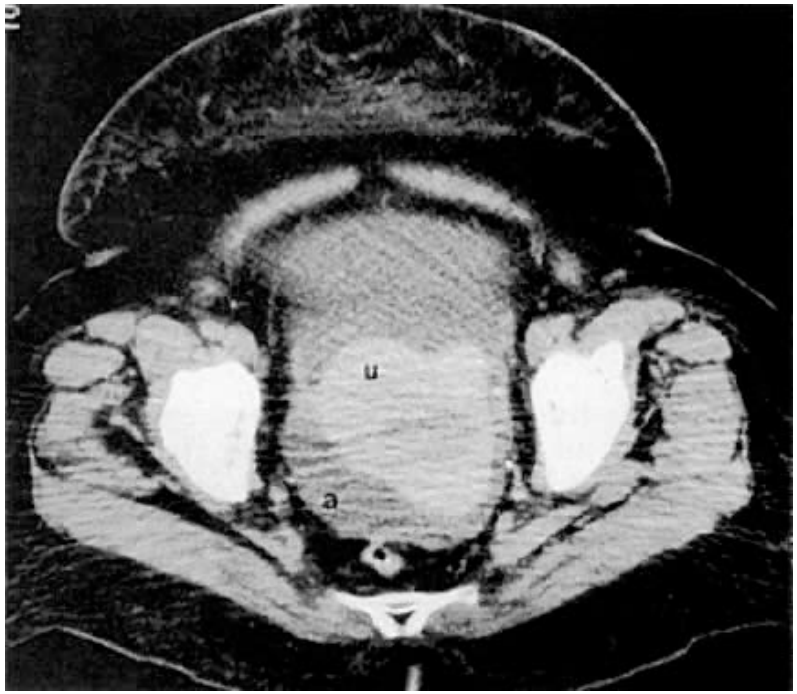
Diagnosis of metastasis to the lung





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

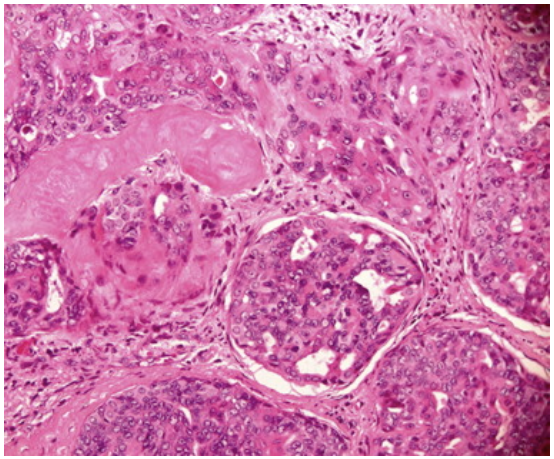
Ovarian cancer

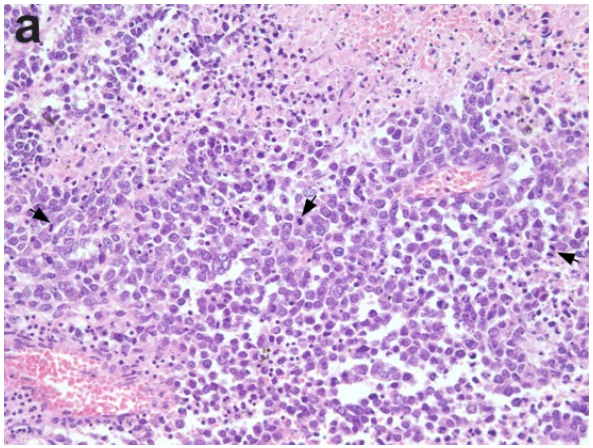


Lung Cancer
Diagnosis and prediction

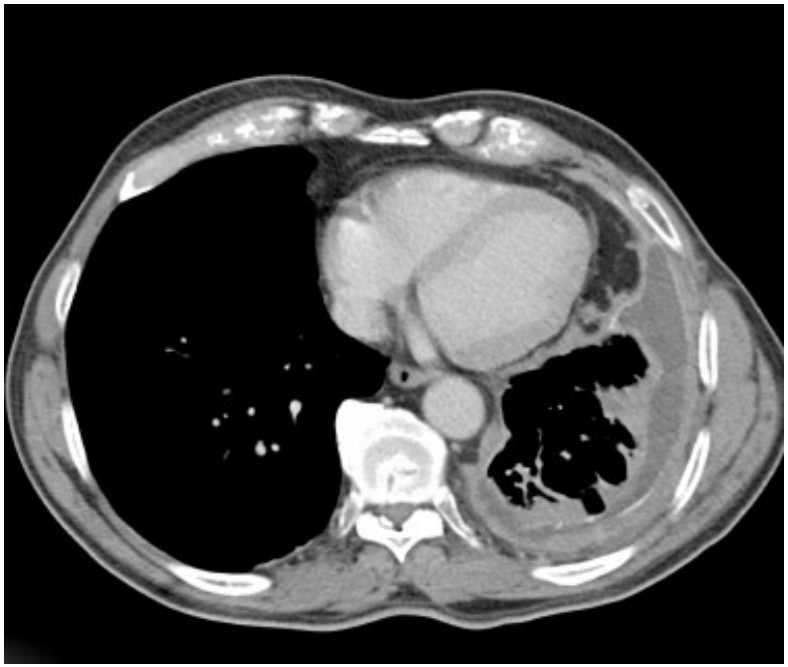
Region Syddanmark
Sygehus Lillebælt

Diagnosis of direct invasion of mesothelioma



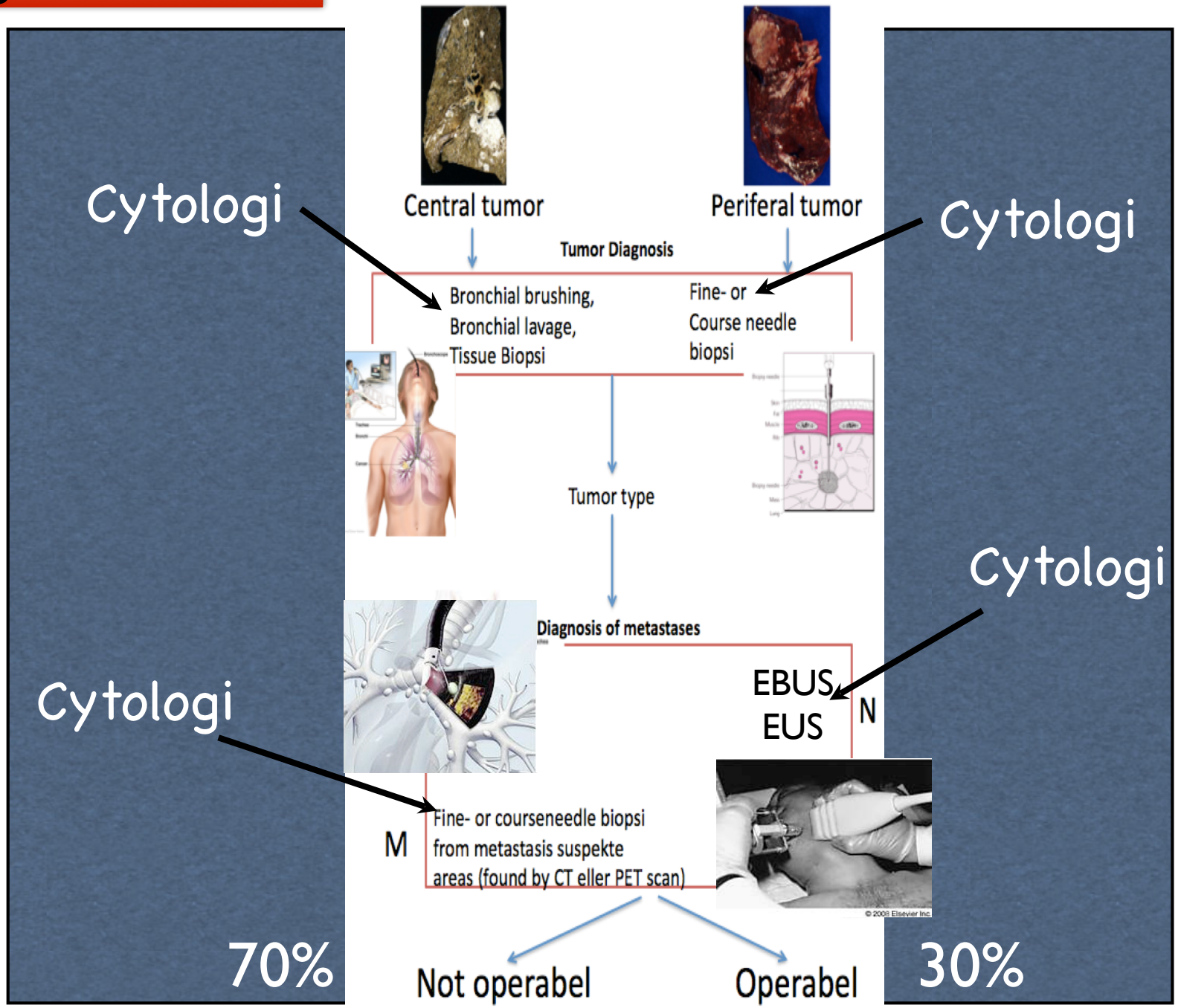


Calretinin
WT1
D2-40
CK7
Vim
CK5/6



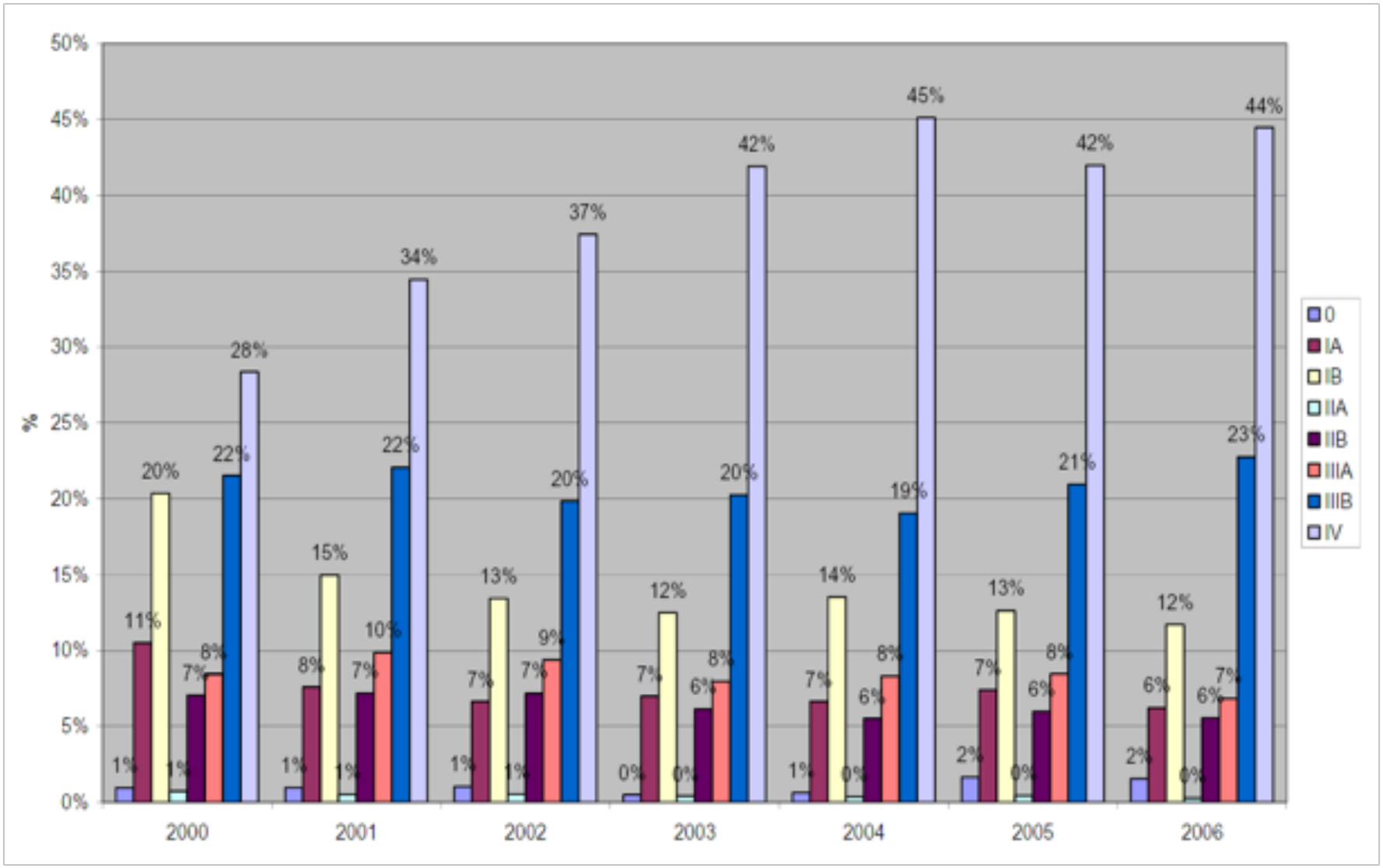
Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt



Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt



Stage at diagnosis

Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

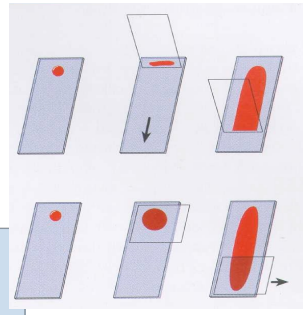
Patoanatomical specimen

Histology

Fixation
Dehydration
Parafinembedding
Microtomy

Præparation

Cytology

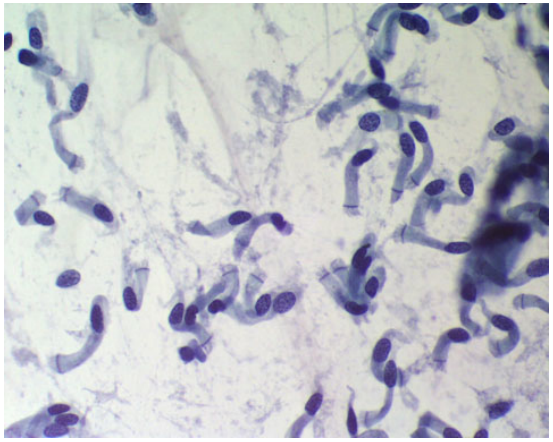


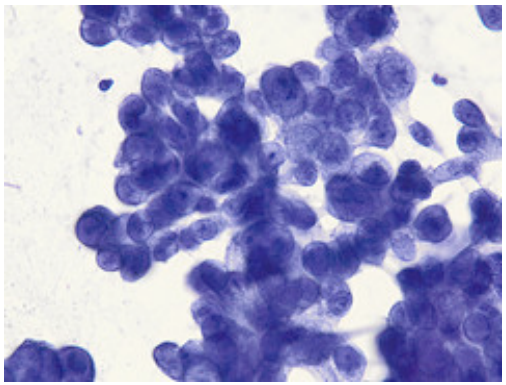
Smear preparation

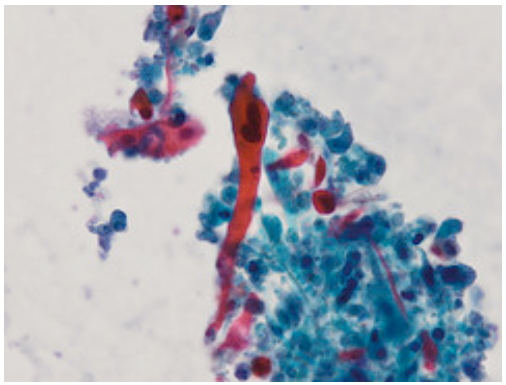
Visualization
(Staining)

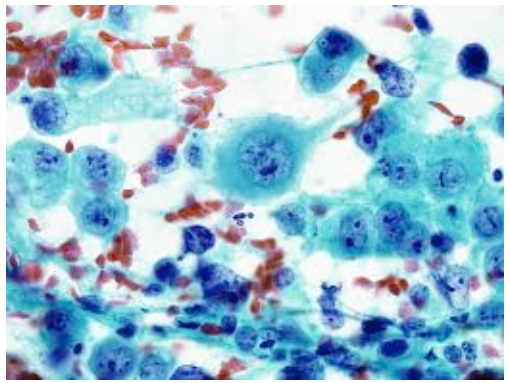
Lung Cancer
Diagnosis and prediction

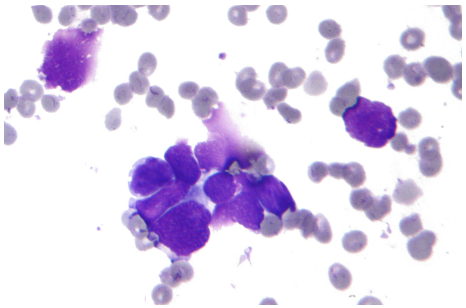
Region Syddanmark
Sygehus Lillebælt











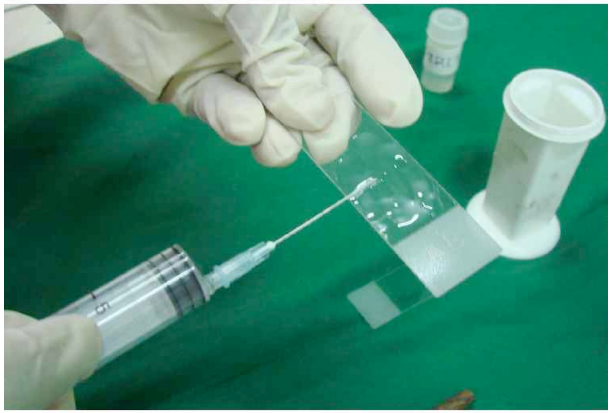
Adenocarcinoma — Squamous carcinoma — Large cell carcinoma — Small cell carcinoma

Non Small Cell Lung Carcinoma (NSCLC)

Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

Cytology



Morfologi

Thinprep
morfologi

Cellblock
Immunocytologi ←

Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

Cytology

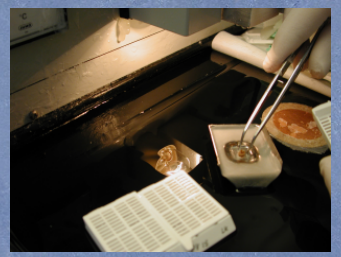
Cellblock
Immuncytologi

Dannelse af koagel

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

Til Parafin

Indstøbning



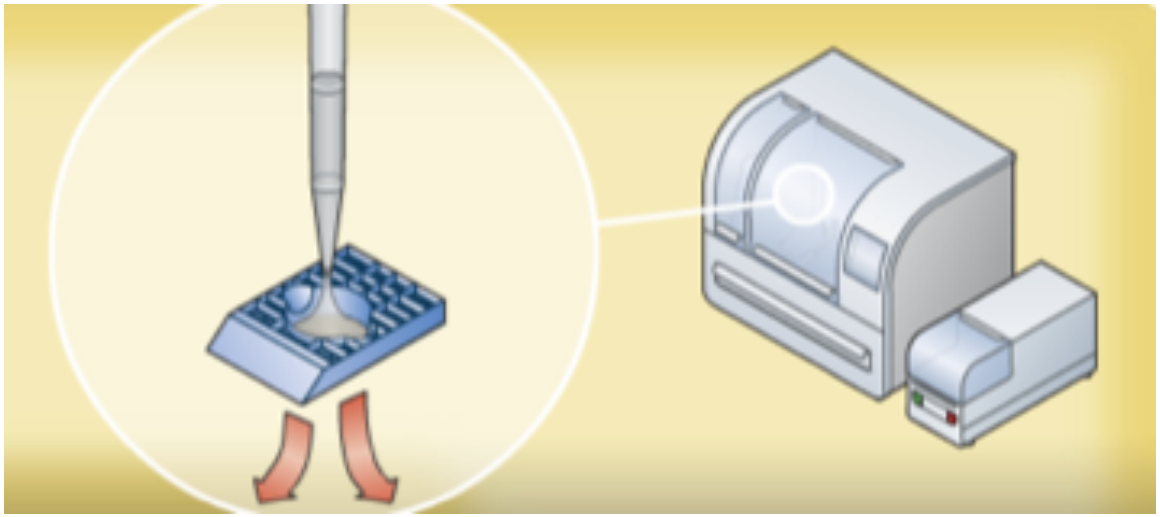
Lung Cancer
Diagnosis and prediction

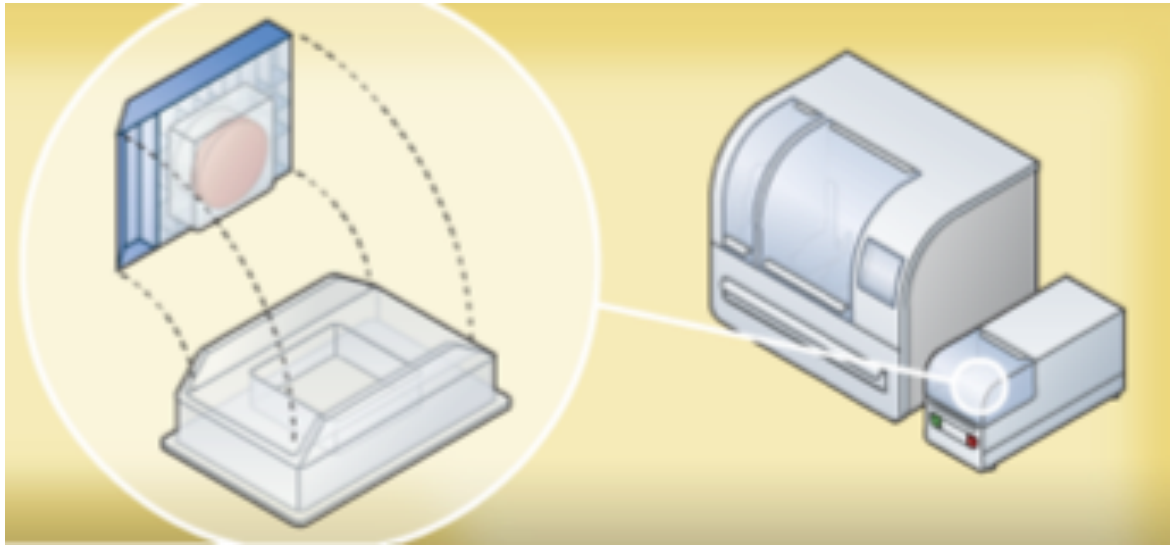
Region Syddanmark
Sygehus Lillebælt

Cytology

Cellblock

Immuncytologi





cellient™ AUTOMATED CELL BLOCK SYSTEM

HOLOGIC

Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

Cytology

Improved capture

- Vacuum-assisted filtration
- Captures available cells, maximizing cellularity even from small/scanty samples
- Built on ThinPrep® technology

Improved presentation

- Helps maintain crisp, clear cellular architecture
- Creates concentrations of cells within the block
- Reviews of cytology and cell block simultaneously
- Supports easier and more productive pathology review

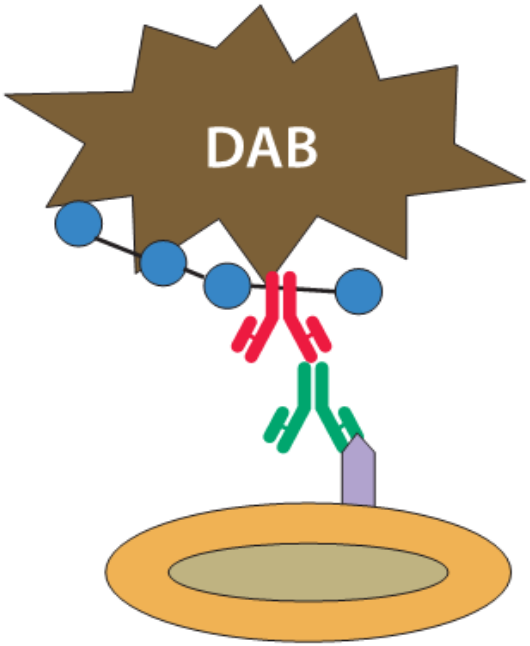
Improved consistency

- High-quality blocks
- Fully automated with minimal operator dependency
- Less cross-contamination risk
- Consistently rapid processing time (45 minutes or less)

Lung Cancer
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

Cytology

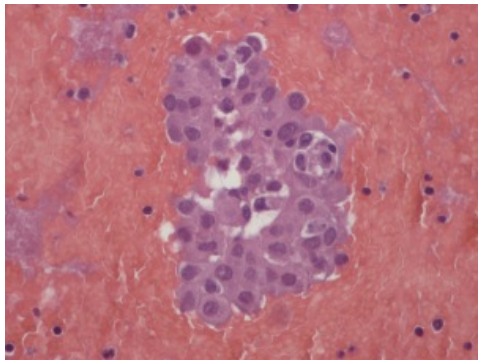


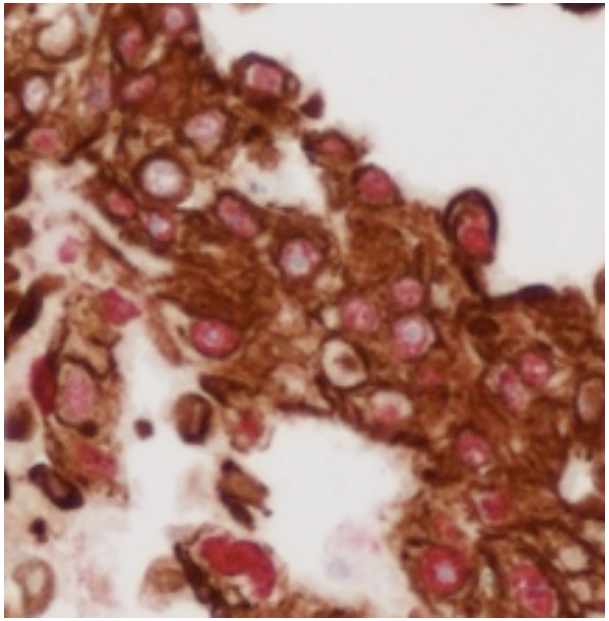
Kromogen (farvestof)

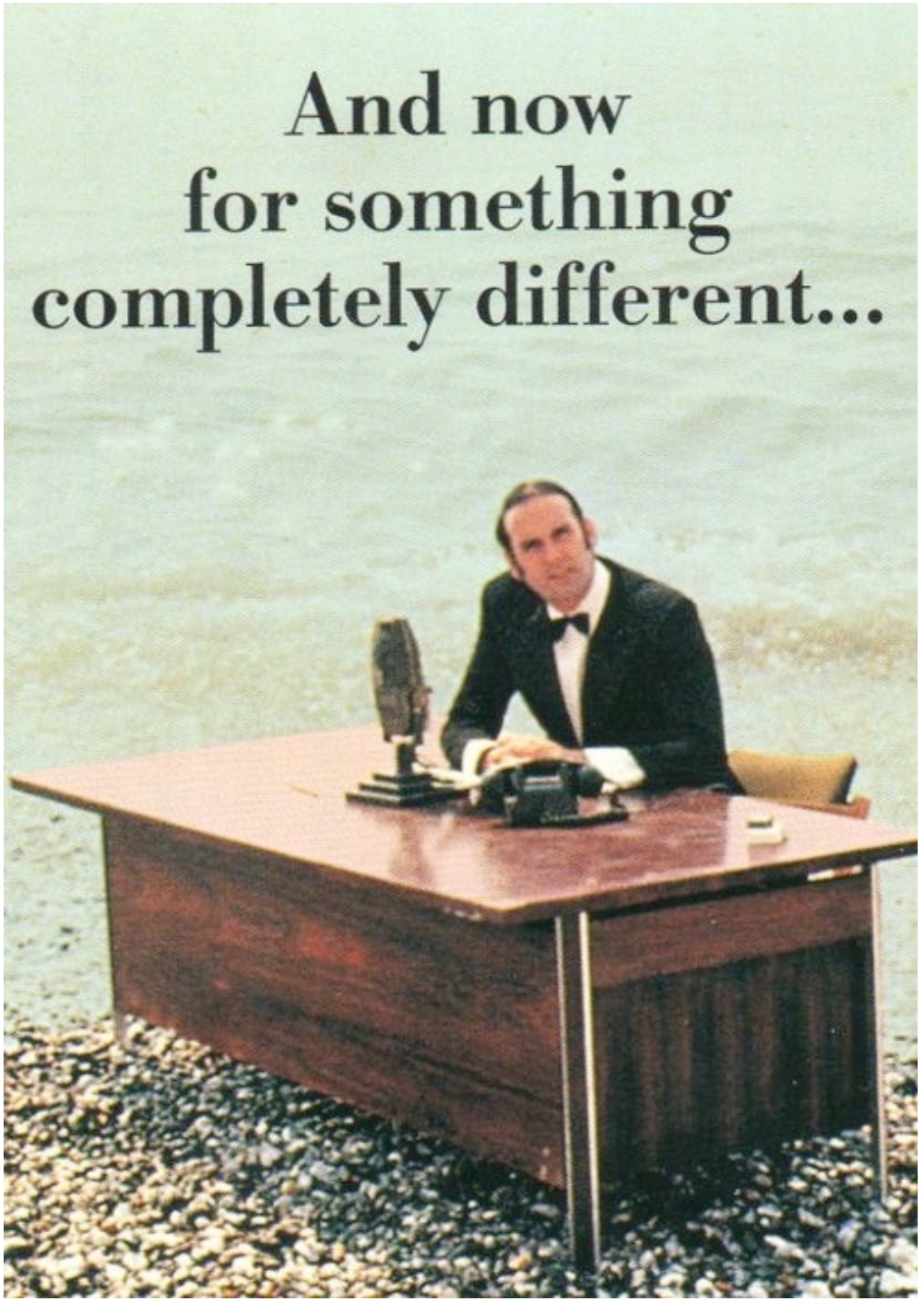
Visualiseringssystem (enzymer)
Sekundært antistof

Primært antistof

Antigen
Cellens cytoplasma
Cellekerne



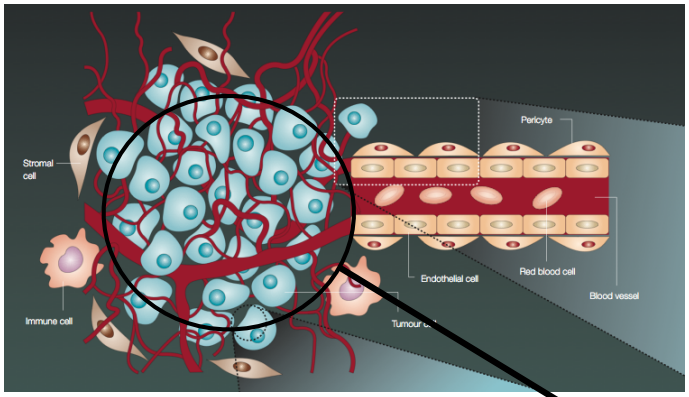


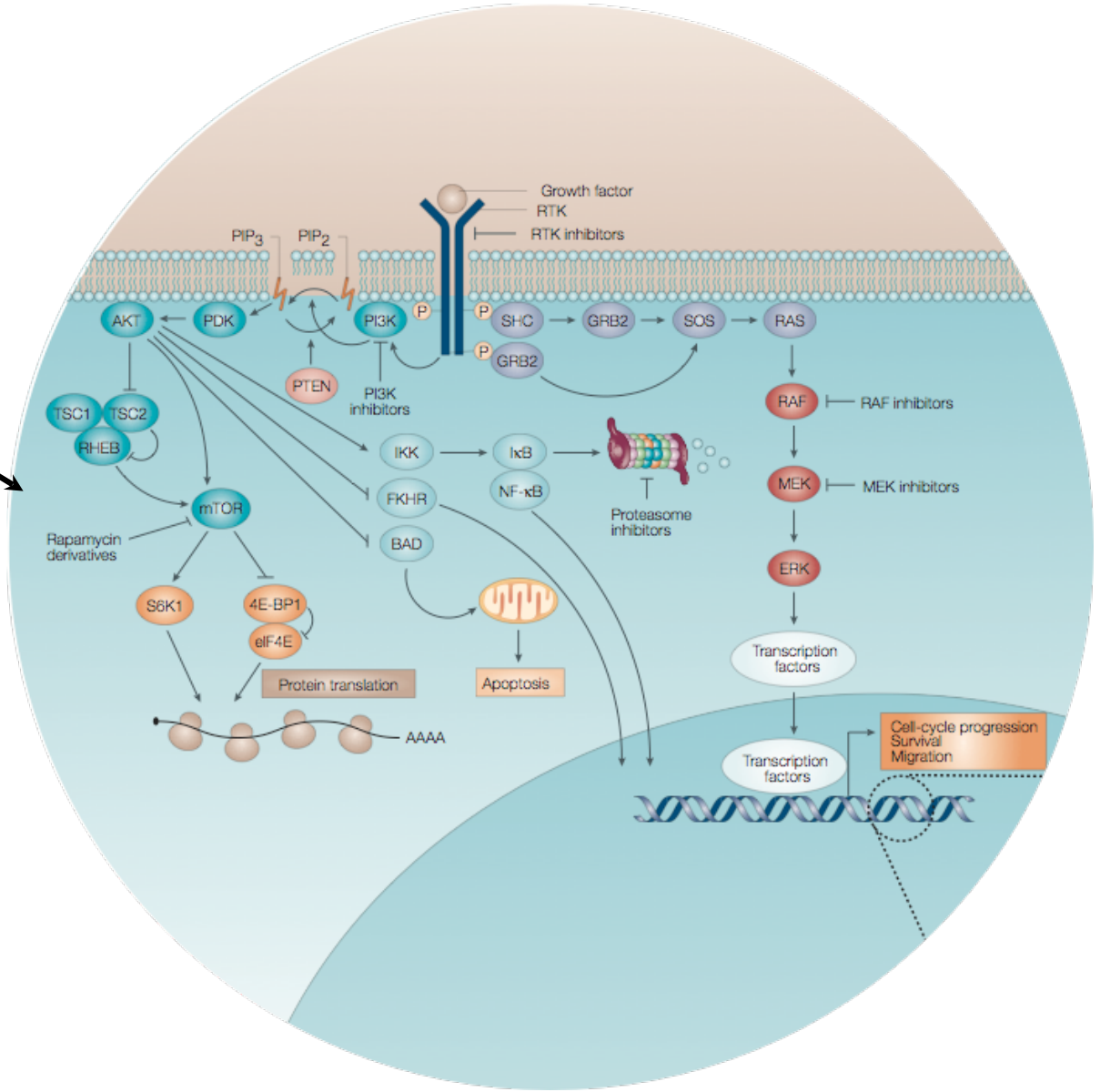

And now
for something
completely different...

Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt



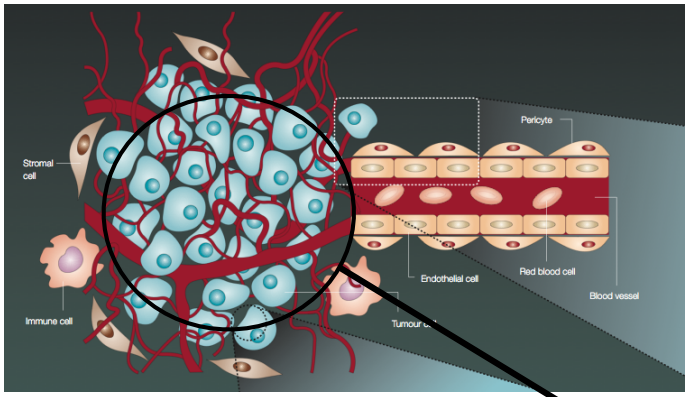


Pathways of cancer

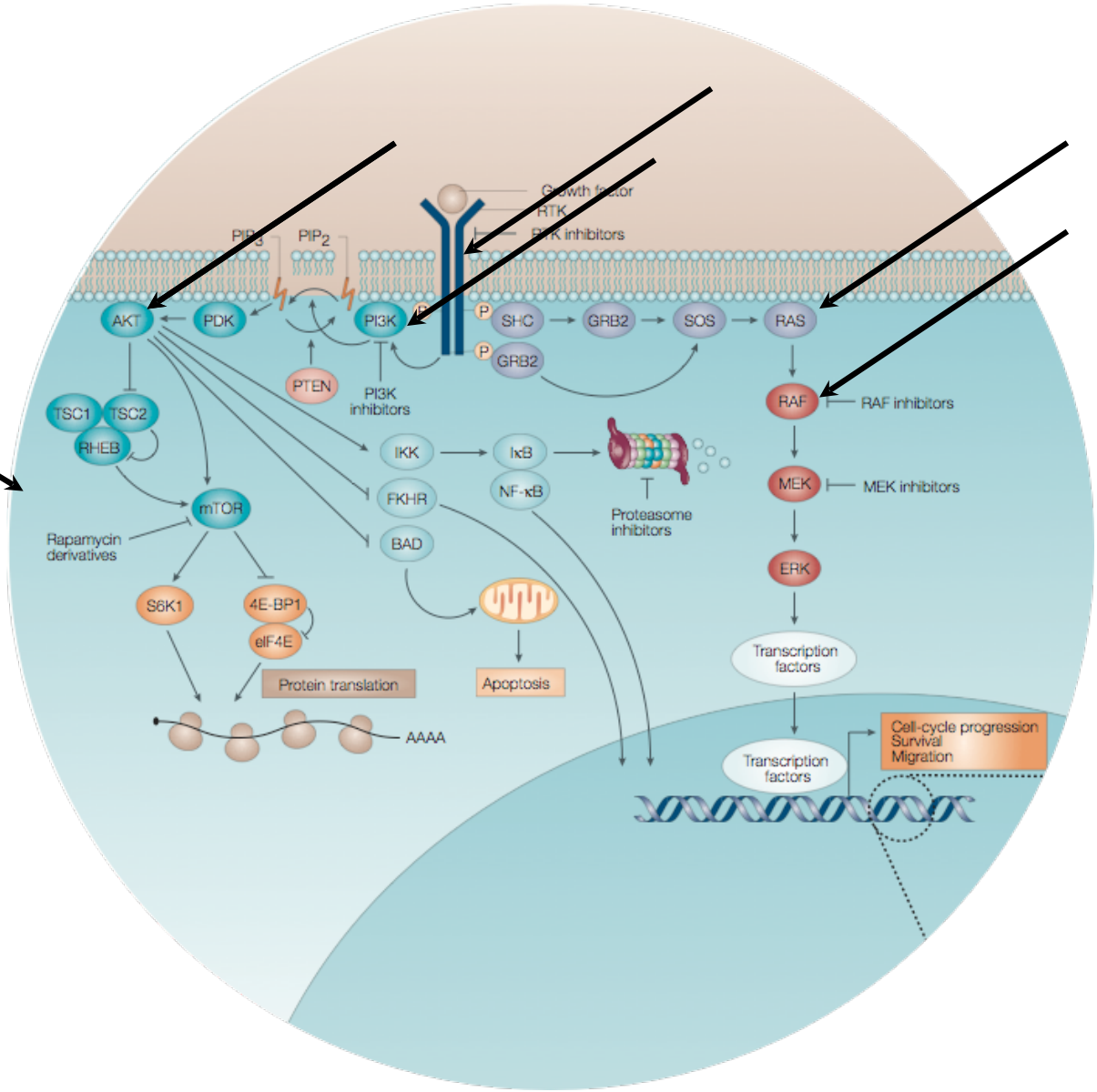
Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt



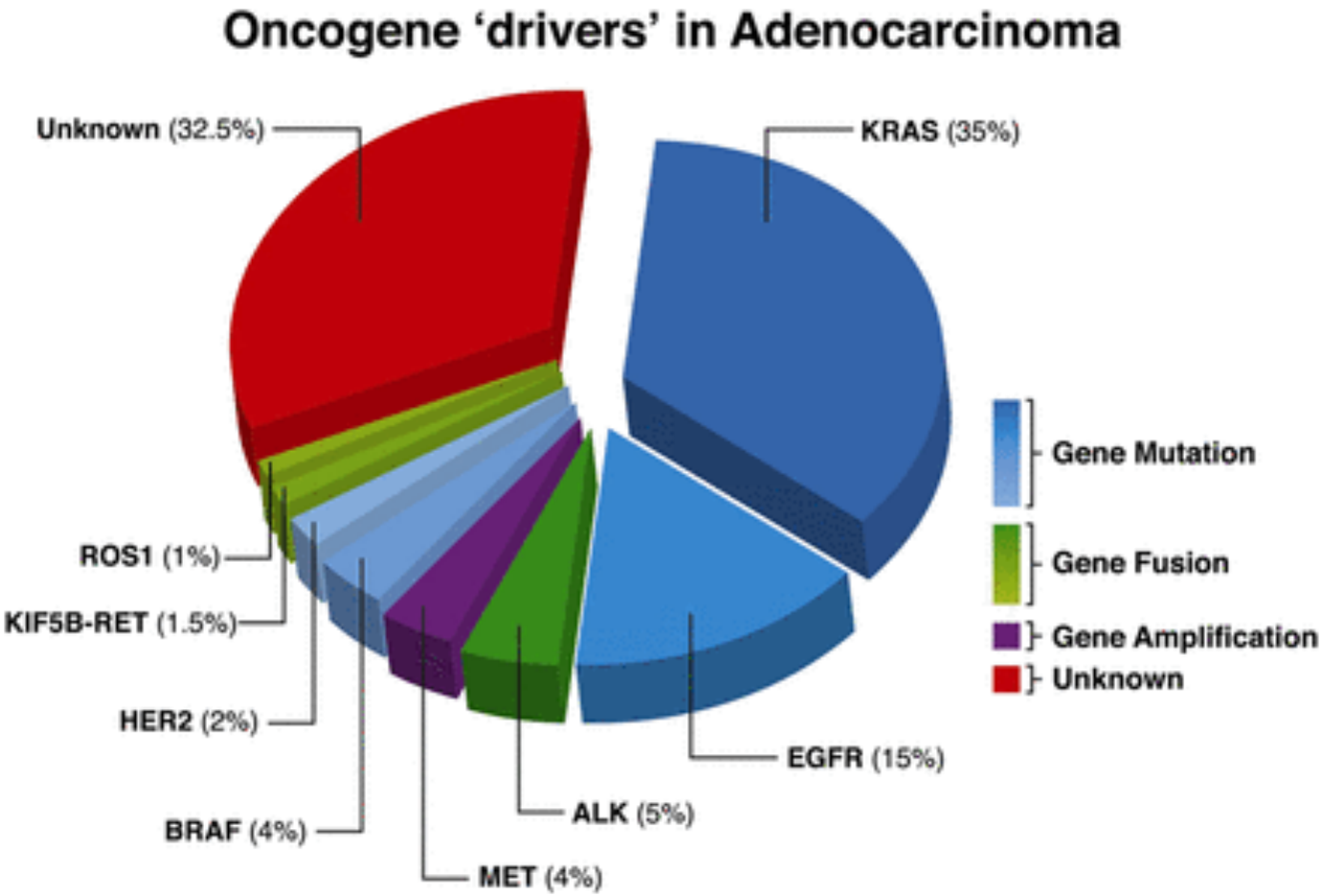
oncogenes



Lung Cancer

Diagnosis and prediction

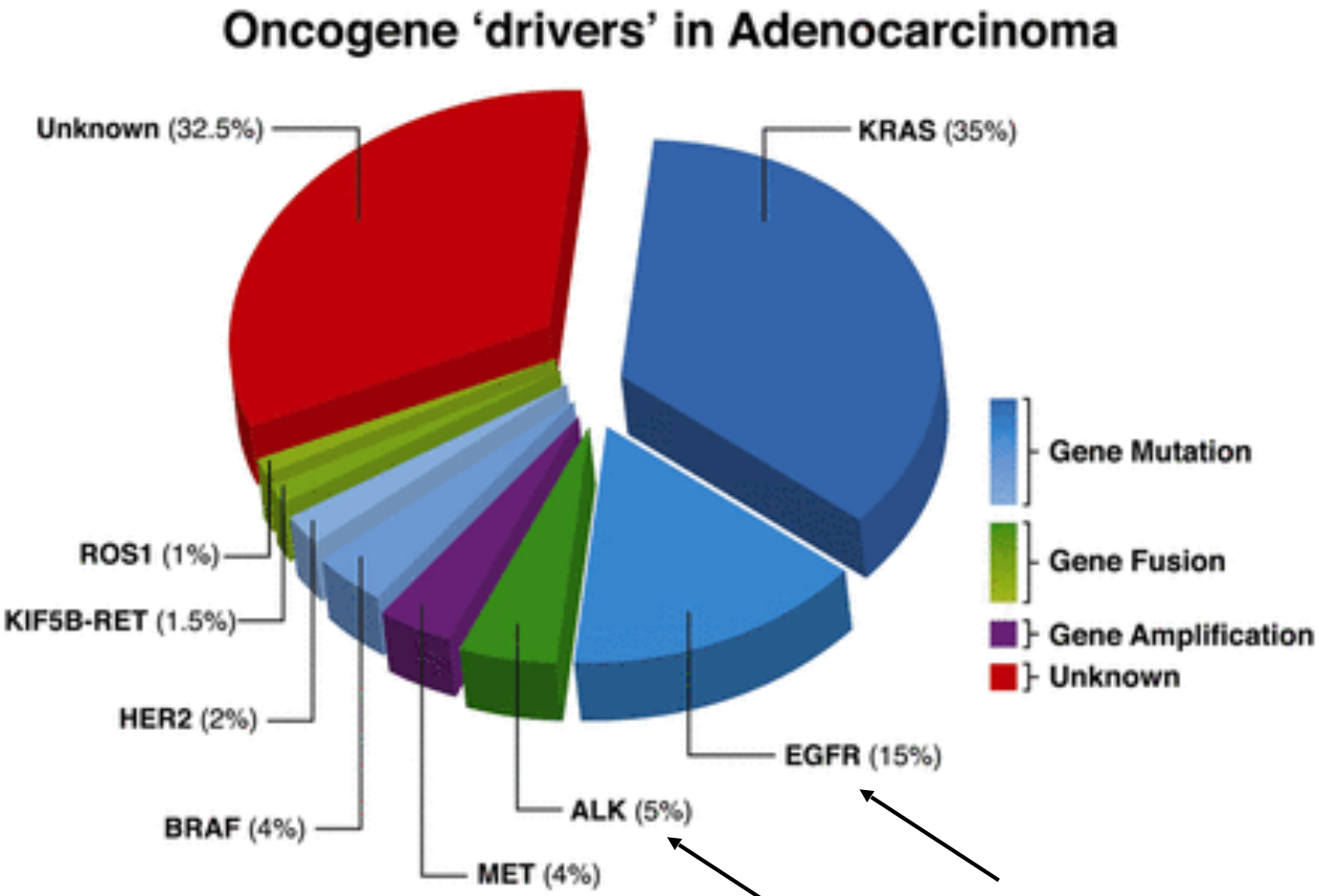
Region Syddanmark
Sygehus Lillebælt



Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

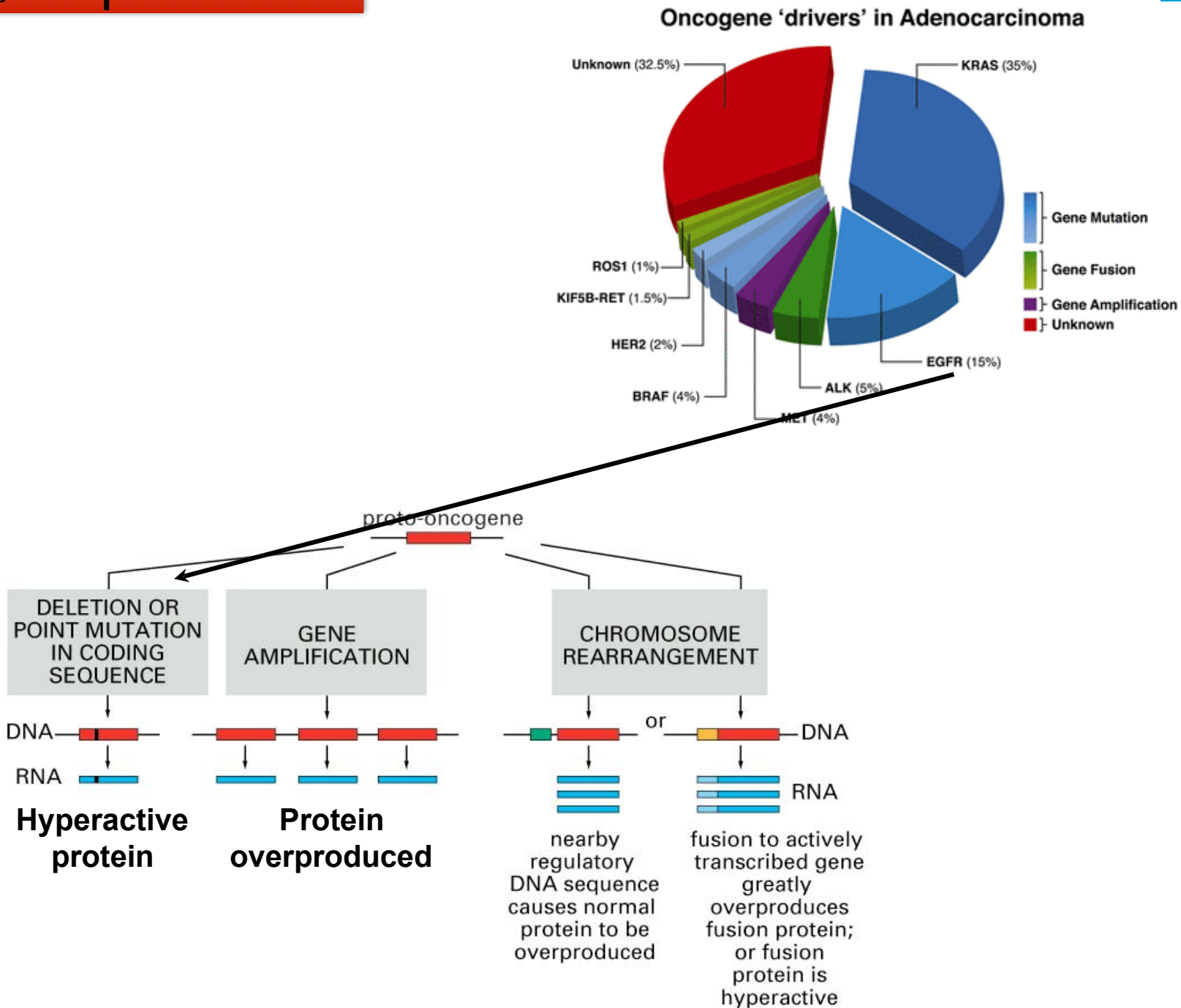


Predictive marker

Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

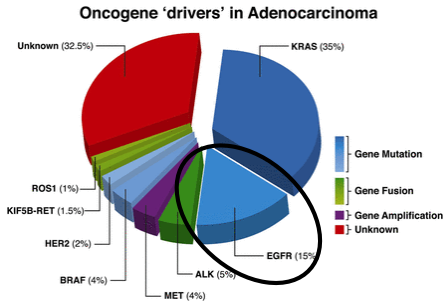


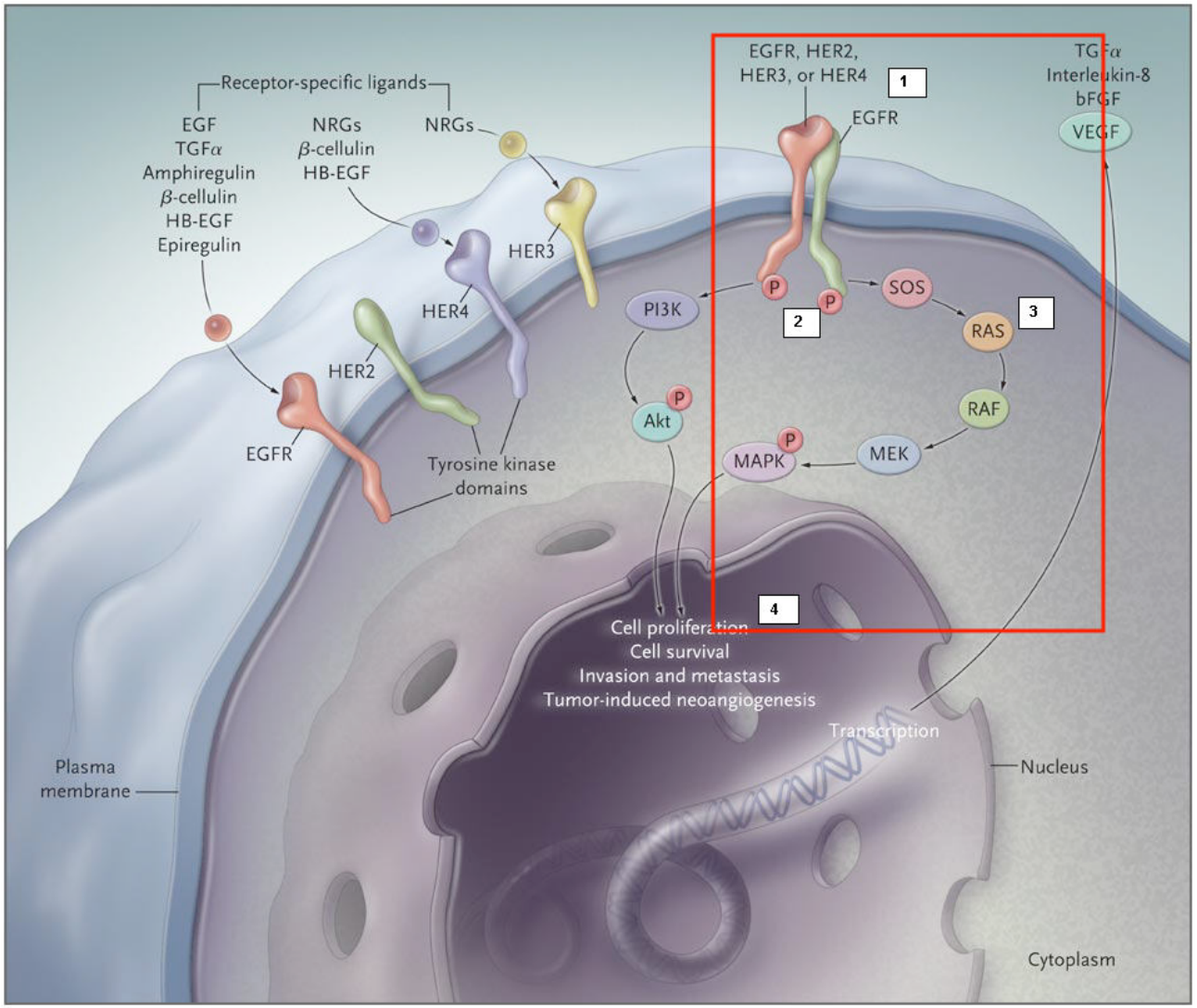
Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

EGFR



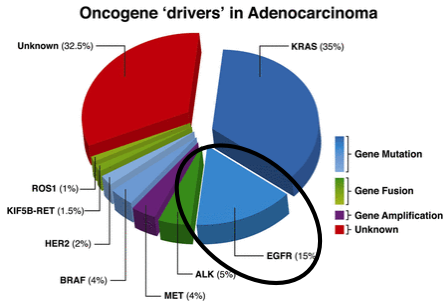


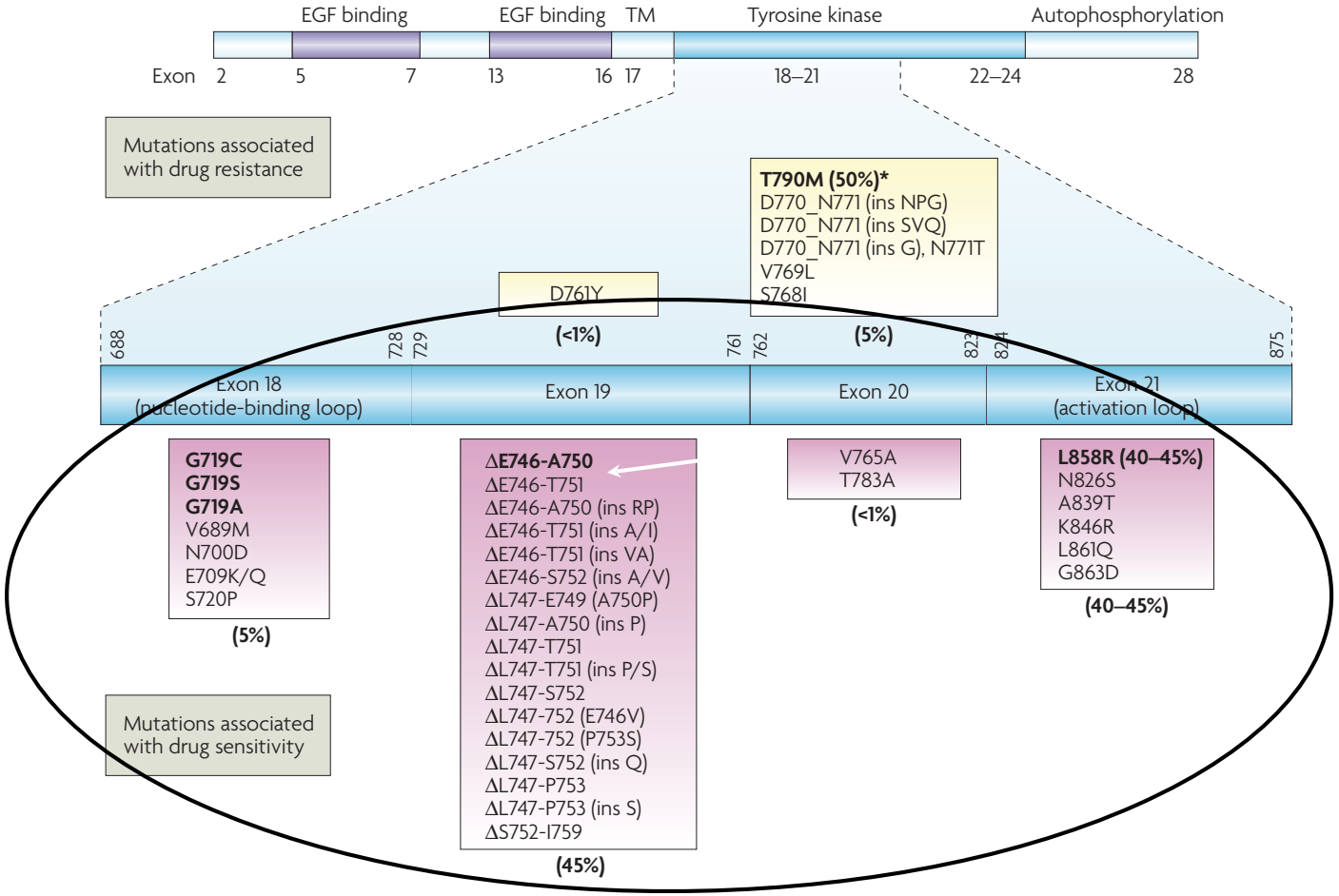
Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

EGFR





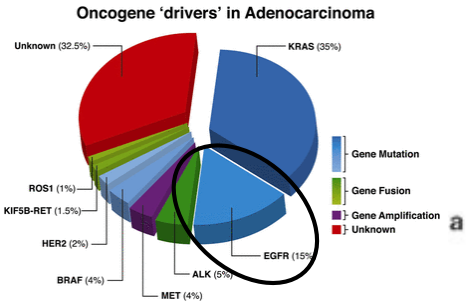
autoactivates EGFR

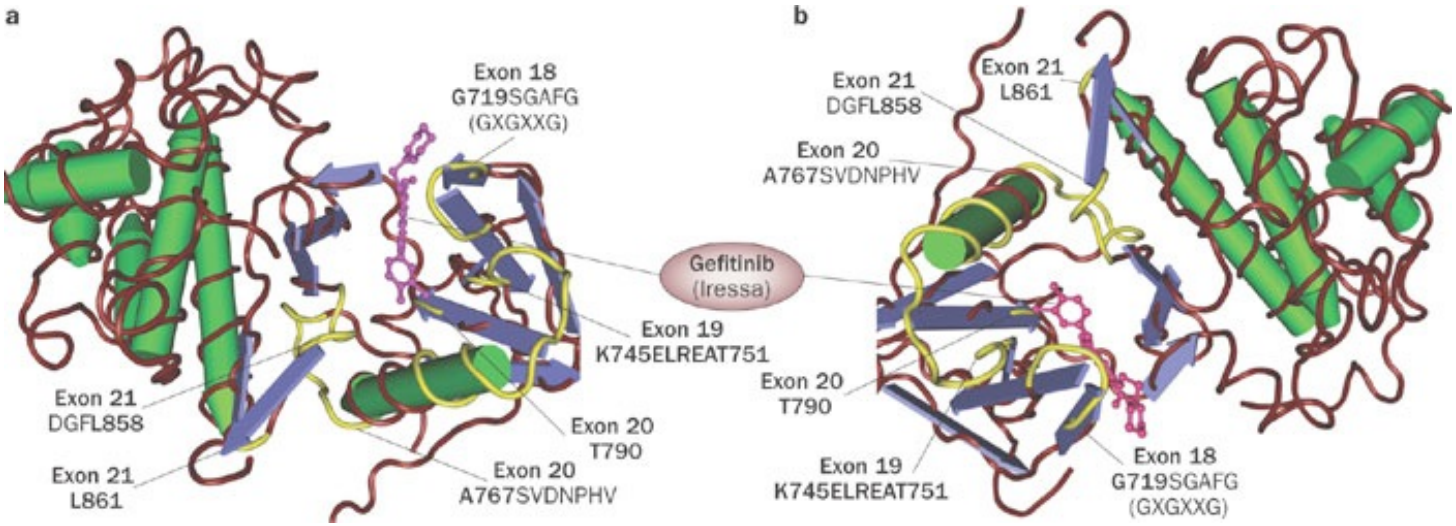
Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

EGFR



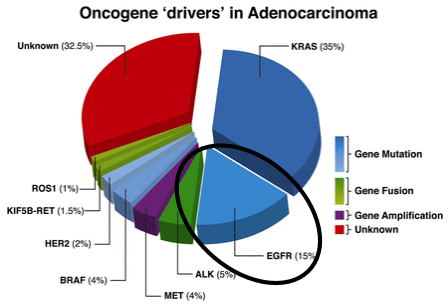


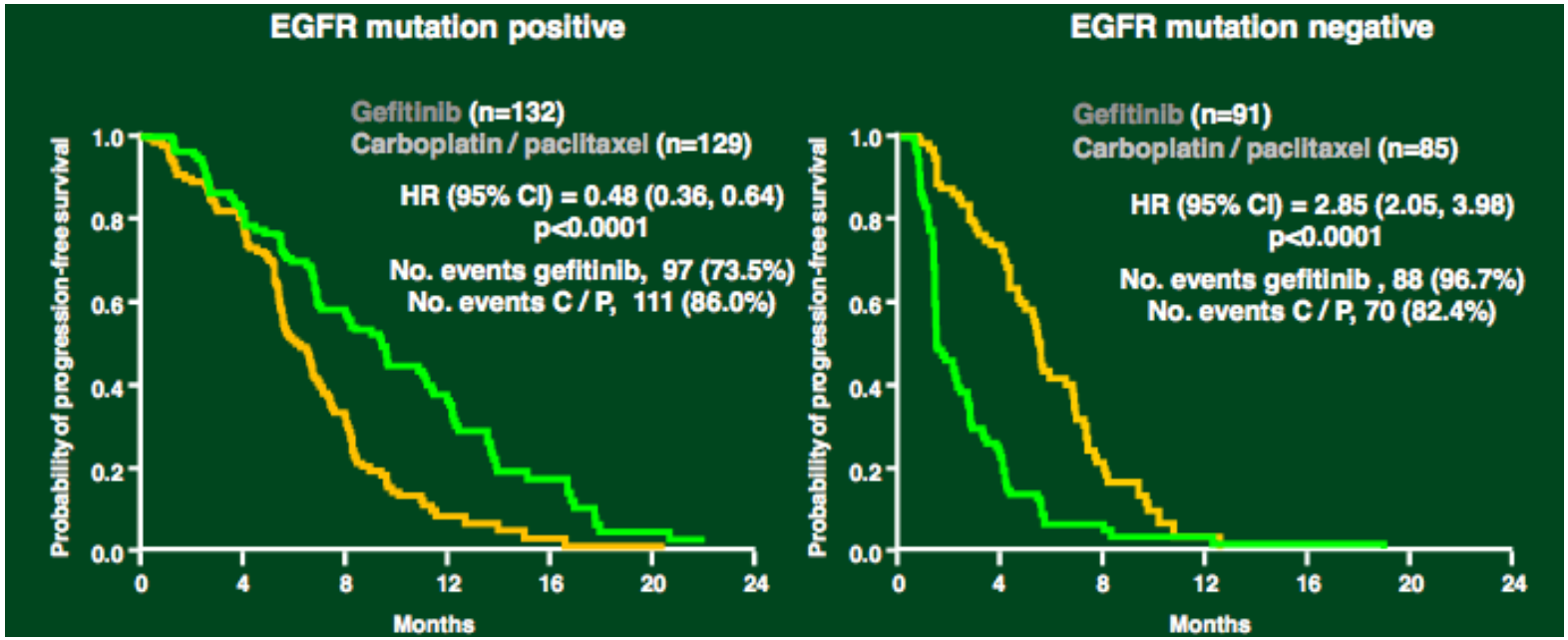
Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

EGFR



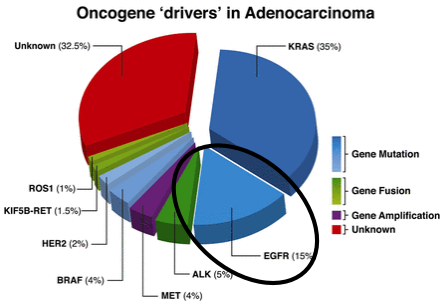


Lung Cancer

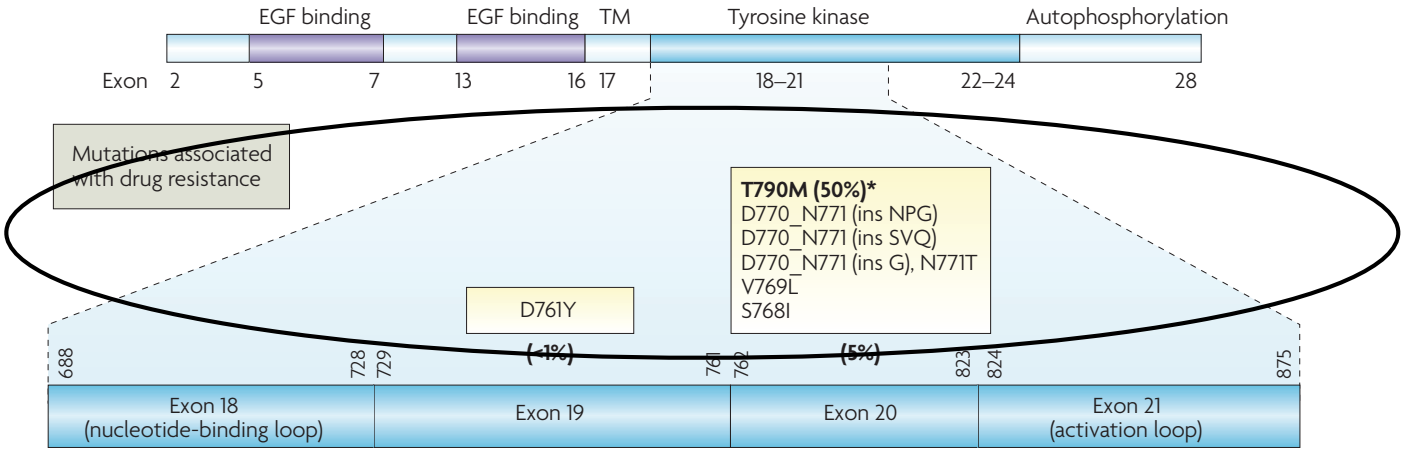
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

EGFR



Resistens

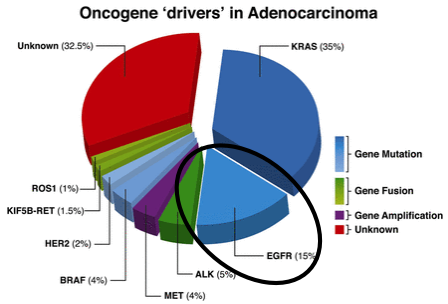


Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

EGFR



Contents lists available at ScienceDirect

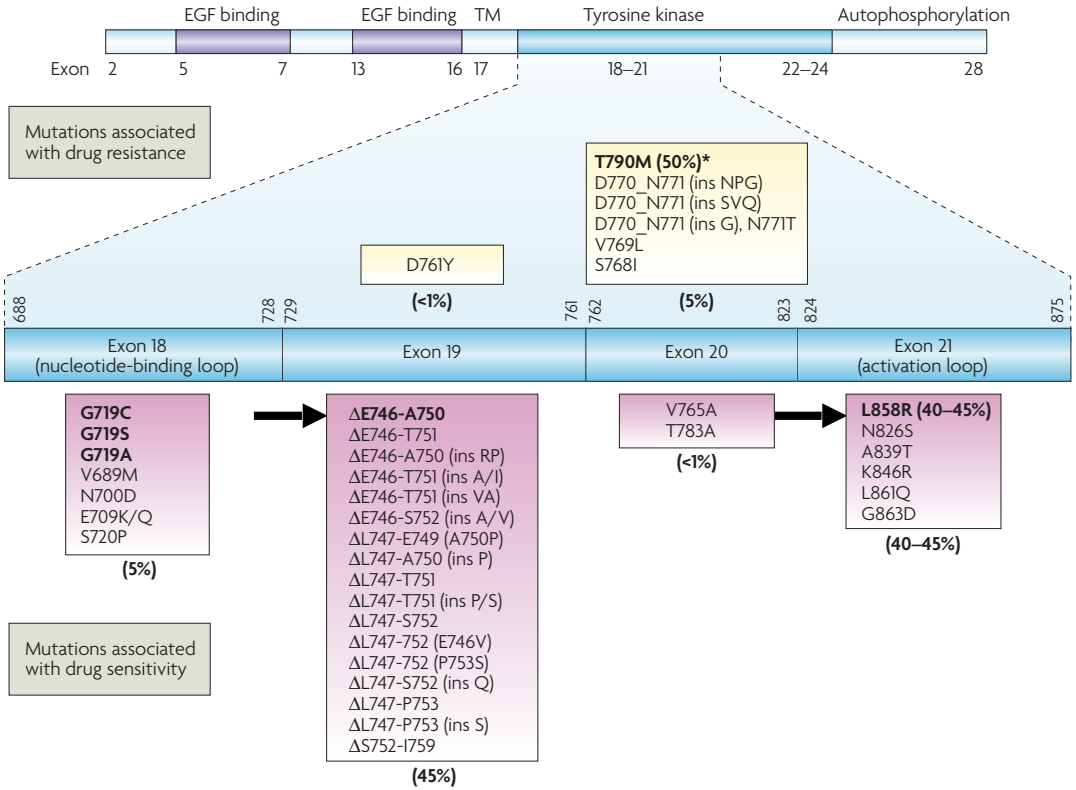
Lung Cancer

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

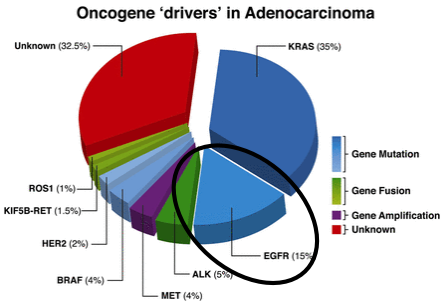


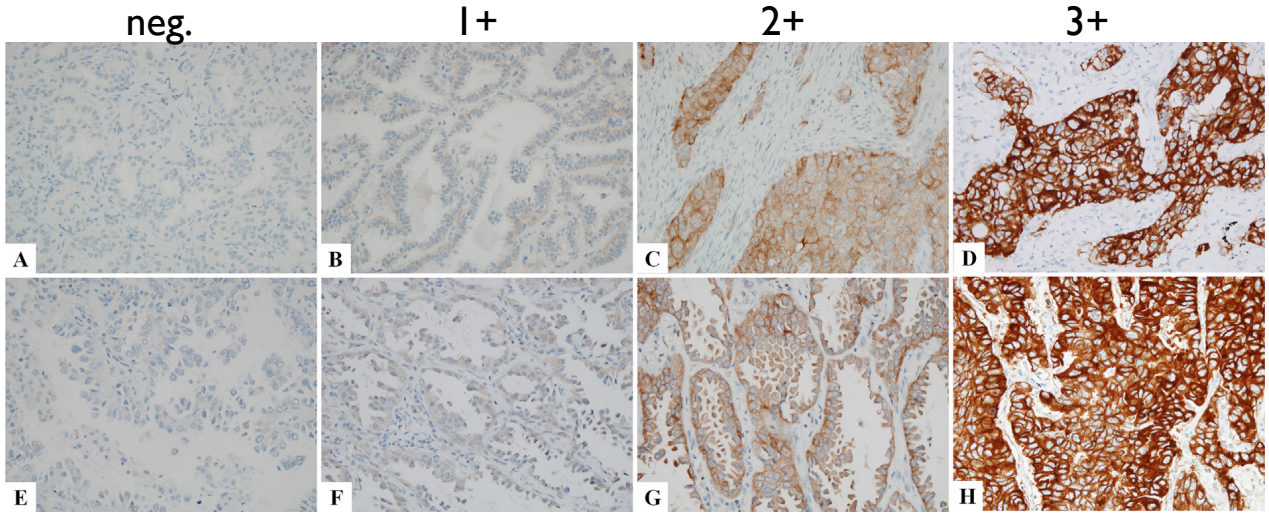
Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

EGFR





E746-A750
del-specific AB SP111

E746-A750
del-specific AB SP111

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

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

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

Contents lists available at ScienceDirect
Lung Cancer
journal homepage: www.elsevier.com/locate/lungcan
ELSEVIER

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,*]

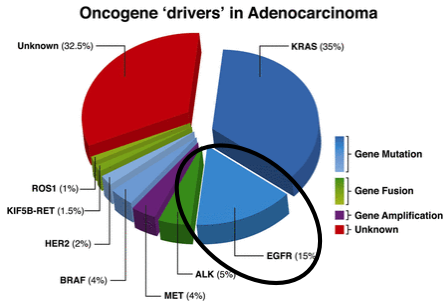
[a] Department of Pathology, Seoul National University Bundang Hospital, 300 Gumi-dong, Bundang-gu, Seongnam-si, Gyeonggi-463-707, Republic of Korea
[b] Department of Pathology, Kyungpook National University College of Medicine, 680 Gukchaebosang-ro, Jung-gu, Daegu 700-842, Republic of Korea
[c] Department of Pathology, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 110-700, 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

Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

EGFR



Algorithm

Lung adenocarcinomas

↓

EGFR Mutation-Specific IHC

↙ ↘

IHC 0 to 2+ → Molecular analysis for EGFR mutations → EGFR mutation + → EGFR TKIs

IHC 3+ → EGFR mutation + → EGFR TKIs

Contents lists available at ScienceDirect
Lung Cancer
journal homepage: www.elsevier.com/locate/lungcan

R mutation-specific antibodies for lung adenocarcinoma: cific but not sensitive detection of an E746.A750 deletion in nd 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,*]

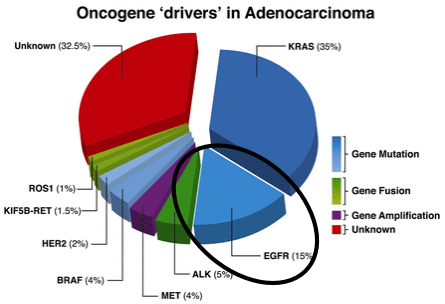
[a] Department of Pathology, Seoul National University Bundang Hospital, 300 Gumi-dong, Bundang-gu, Seongnam-si, Gyeonggi-463–707, Republic of Korea
[b] Department of Pathology, Kyungpook National University College of Medicine, 680 Gukchaebosang-ro, Jung-gu, Daegu 700-842, Republic of Korea
[c] Department of Pathology, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 110-700, 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

Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

EGFR



DNA(template) → *PCR* → *Analysis*

DNA-purification

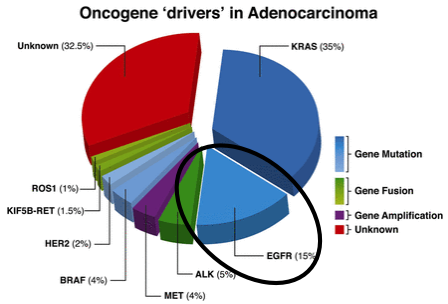
Tissue section

Lung Cancer

Diagnosis and prediction

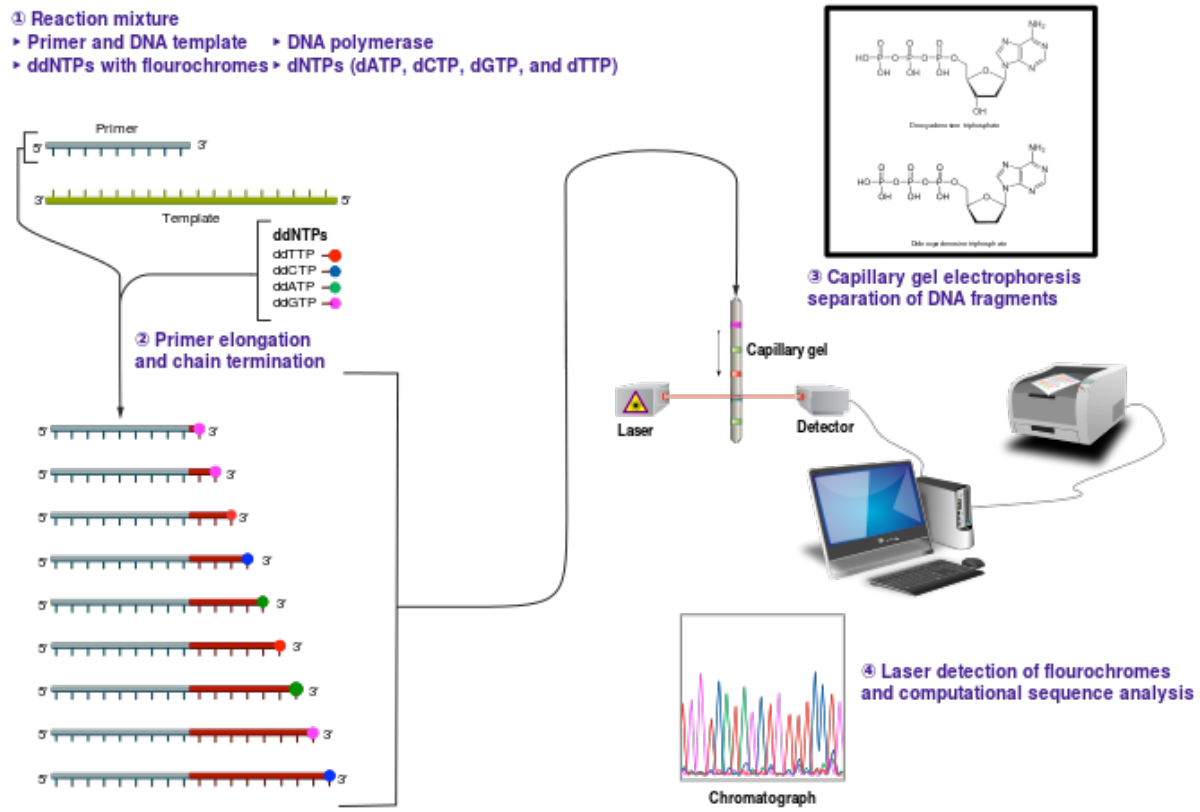
Region Syddanmark
Sygehus Lillebælt

EGFR



Analysis

Sequencing

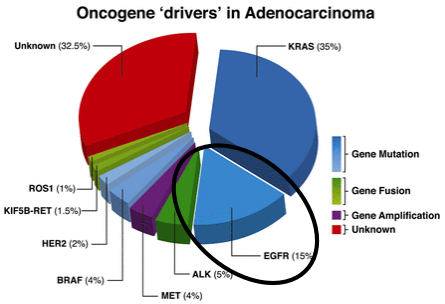


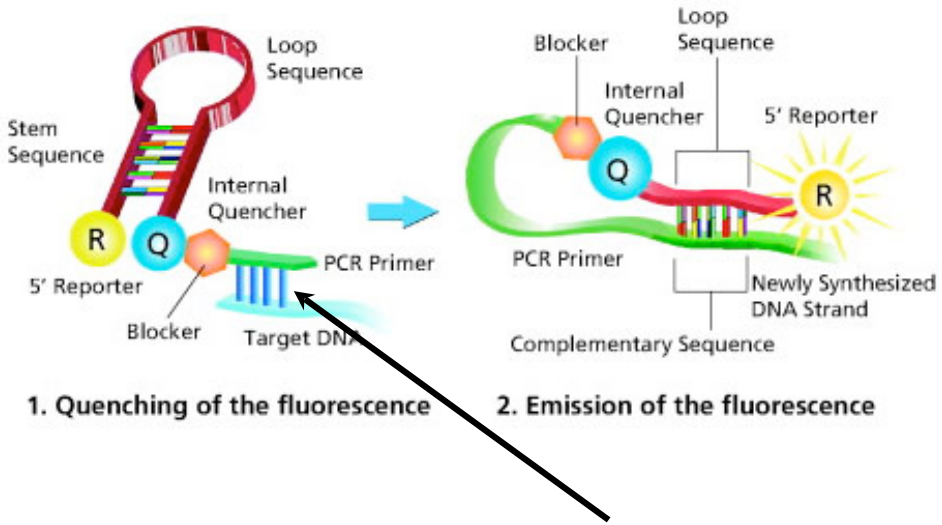
Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

EGFR



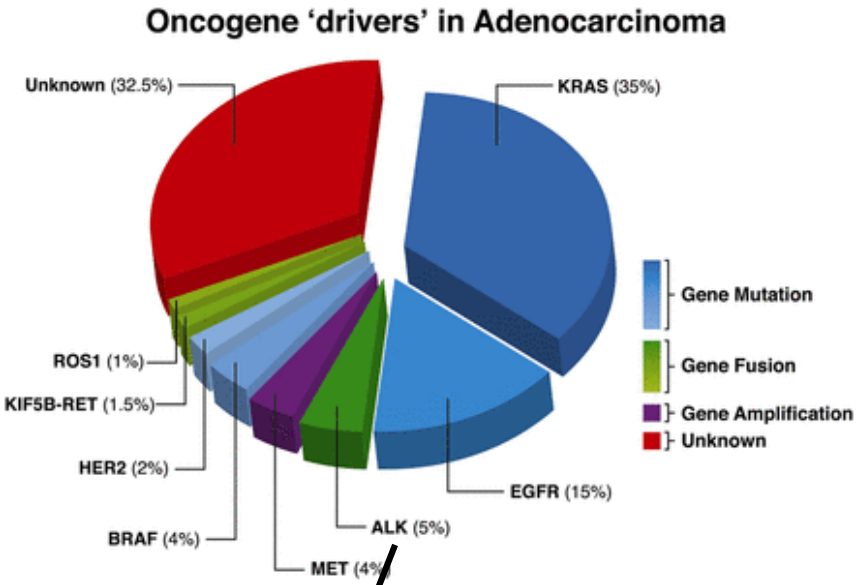


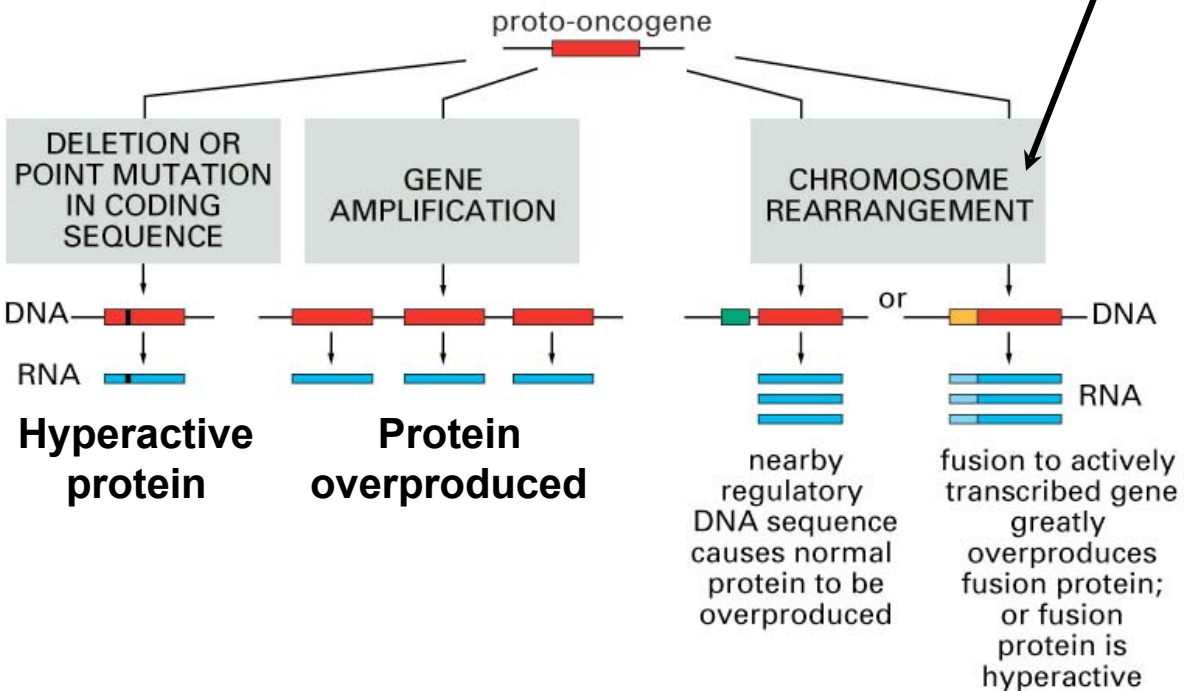
mutationspecific primer

Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt



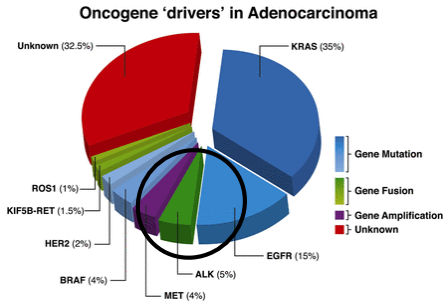


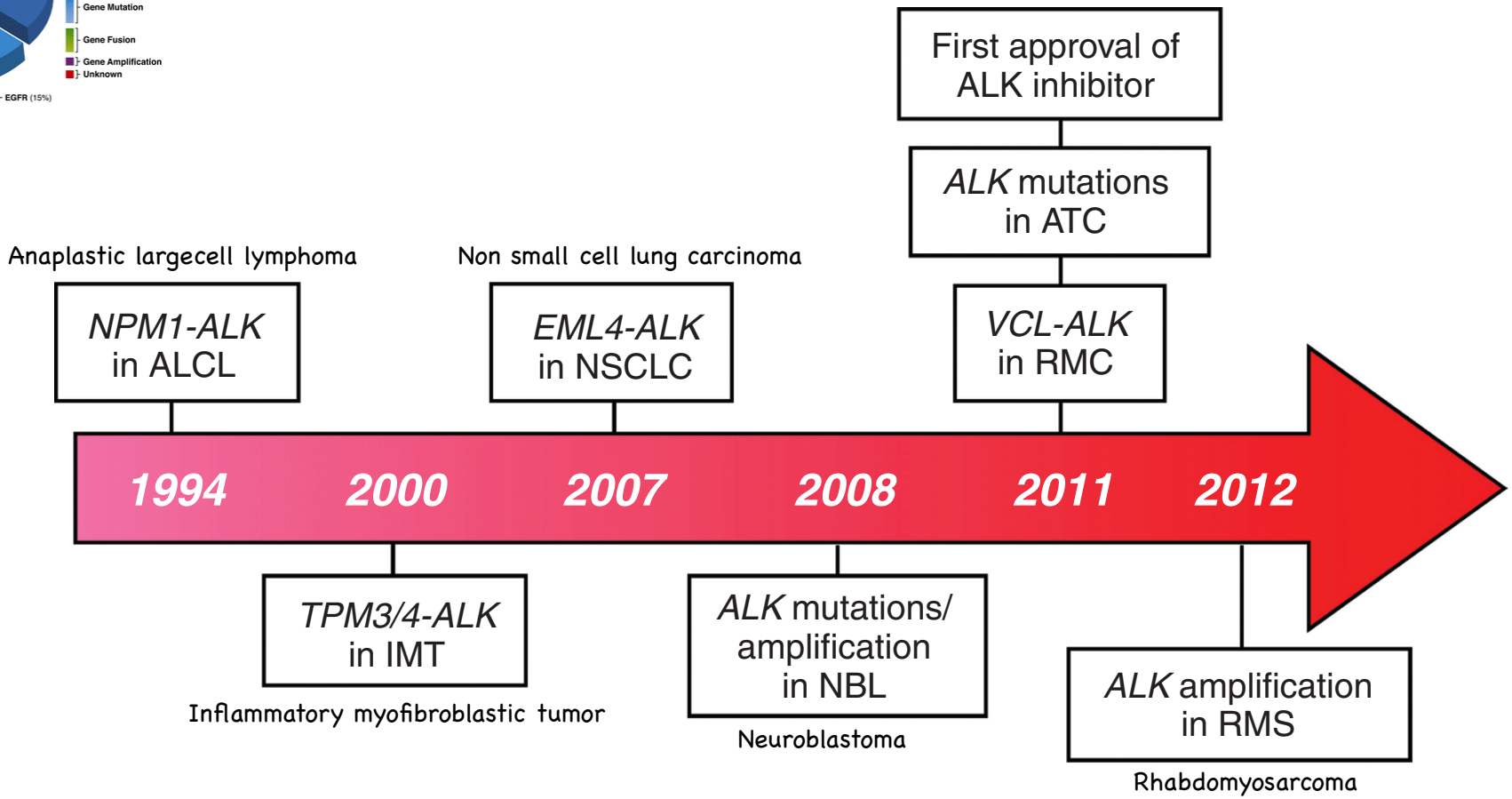
Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

ALK



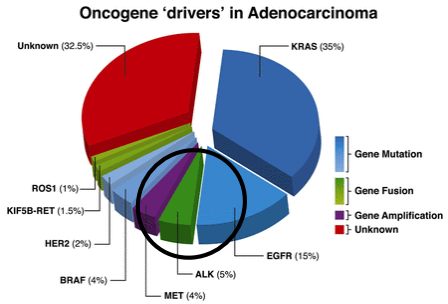


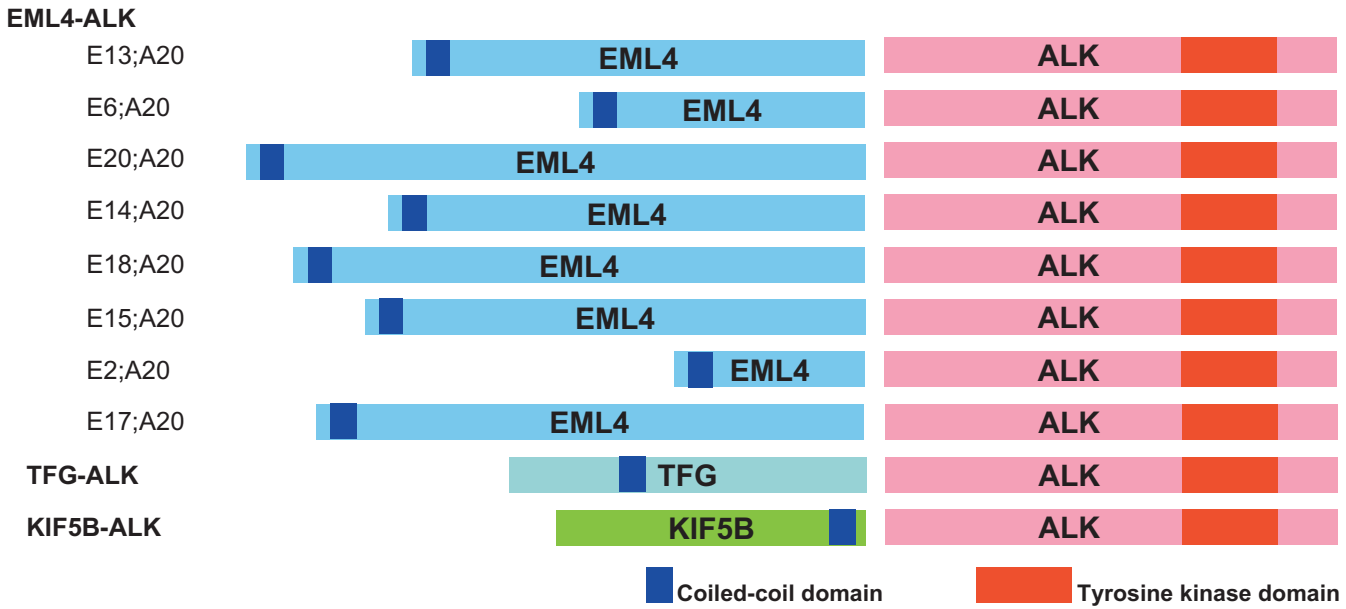
Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

ALK



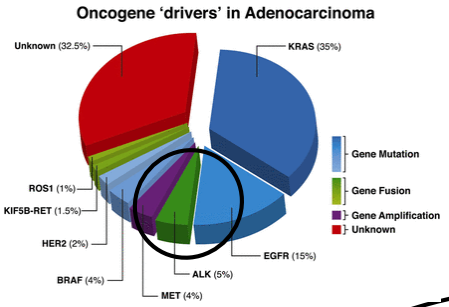


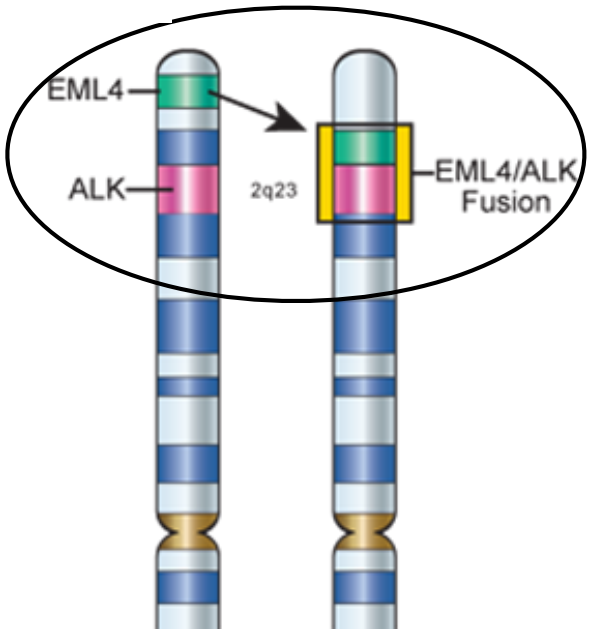
Lung Cancer

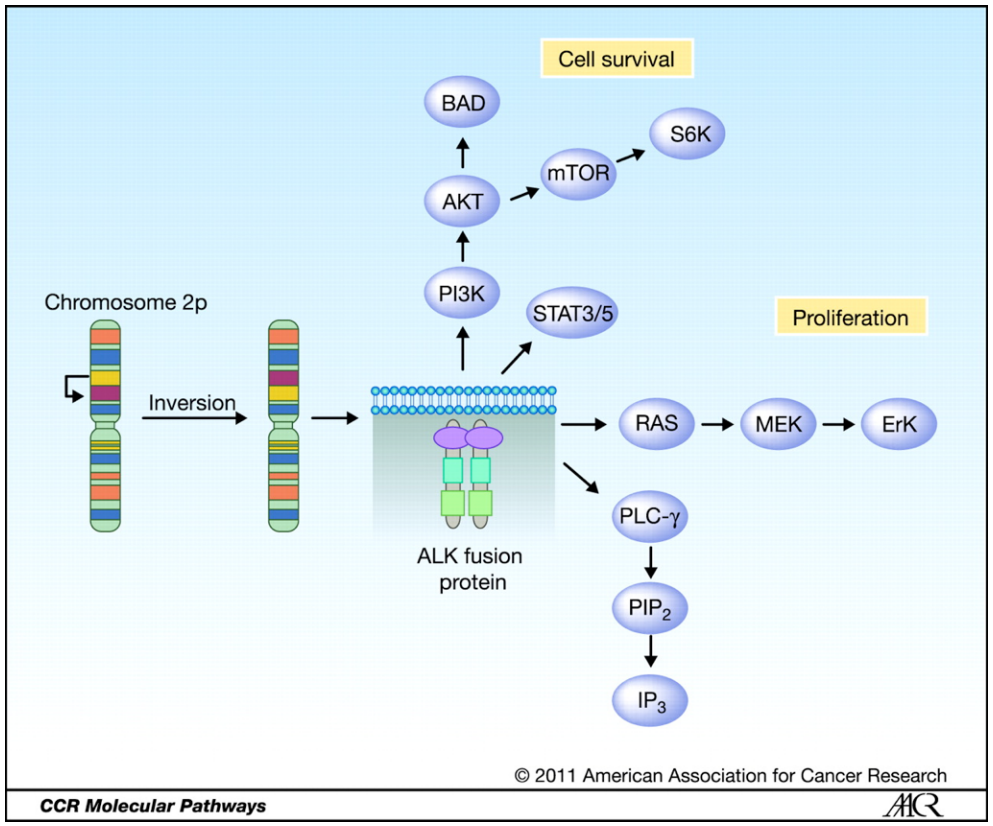
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

ALK





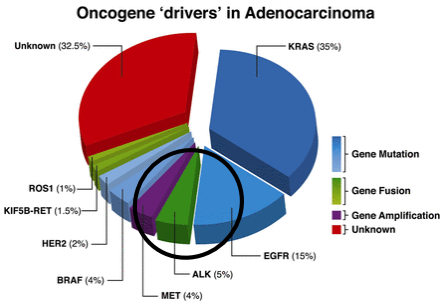


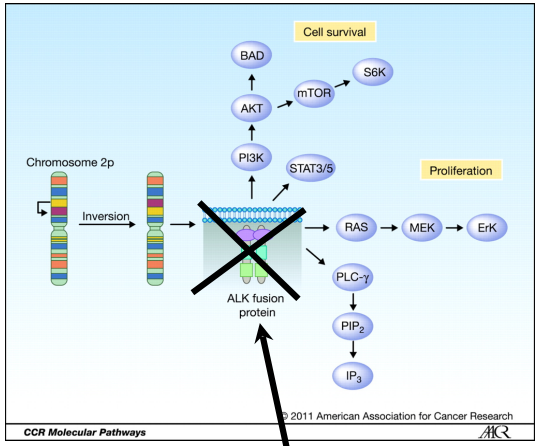
Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

ALK





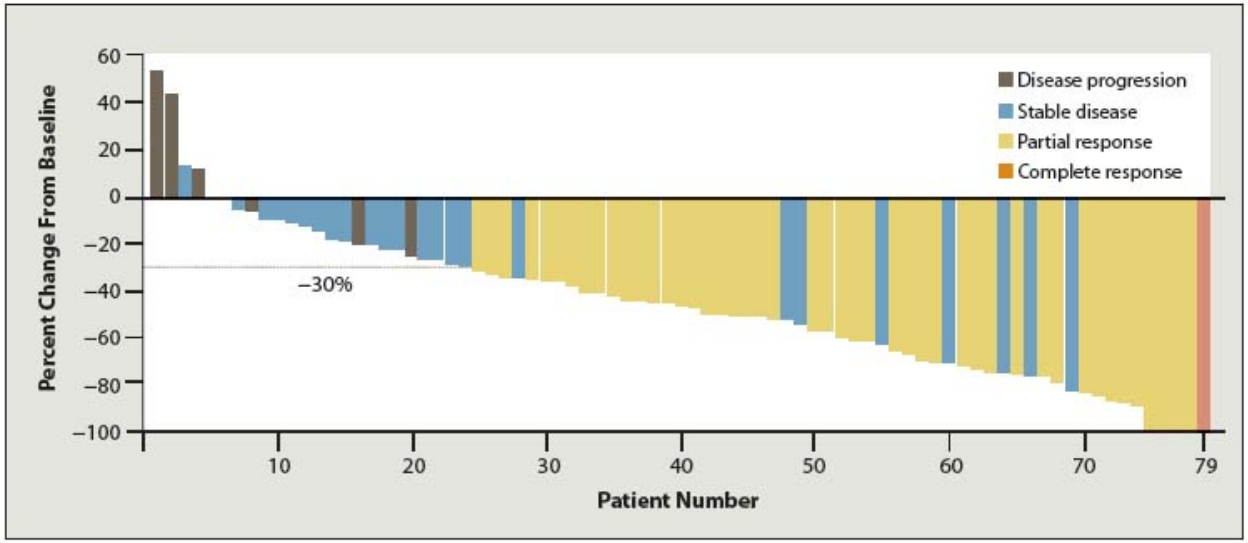


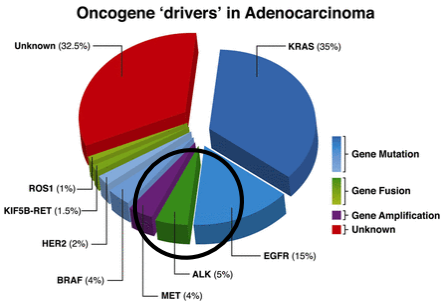
Figure 2: Waterfall plot showing response to crizotinib in patients with *EML4-ALK* NSCLC. Percent change in tumor burden relative to pretreatment baseline is represented. (Reproduced with permission from Kwak et al. N Engl J Med. 2010;363:1693-1703. Copyright © 2010, Massachusetts Medical Society.)

Lung Cancer

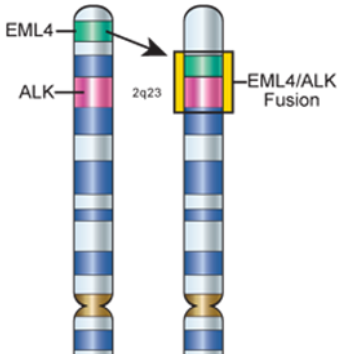
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

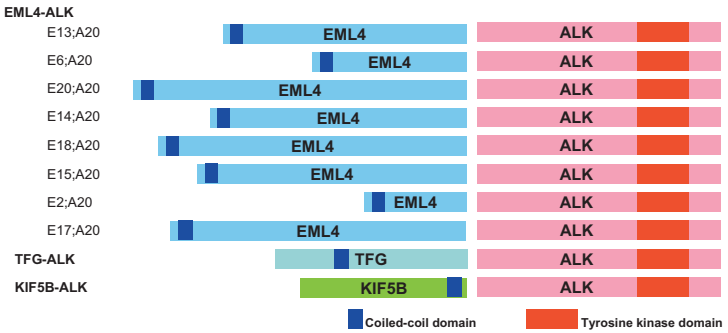
ALK



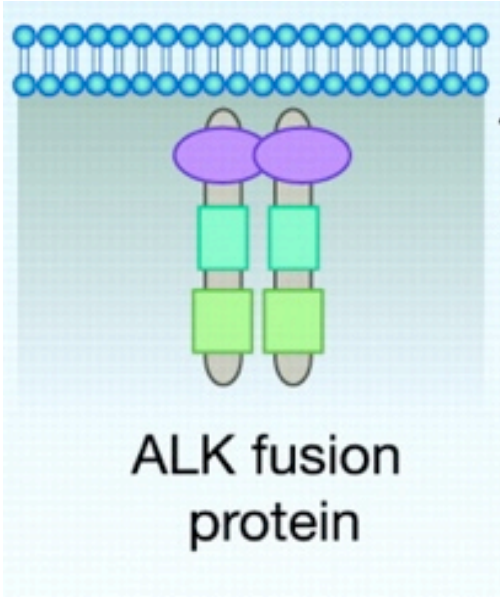
Detection of chromosomal changes



Detection of fusion RNA



Detection of fusion protein

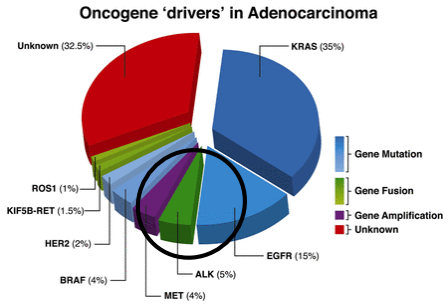


Lung Cancer

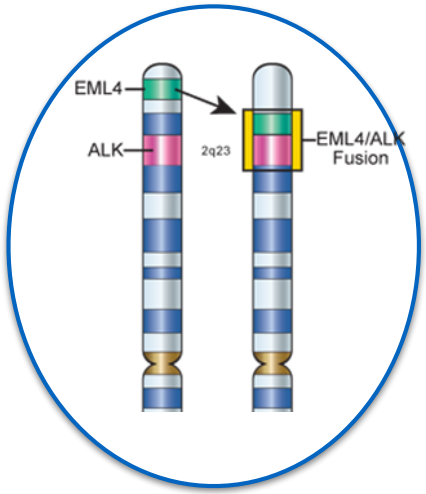
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

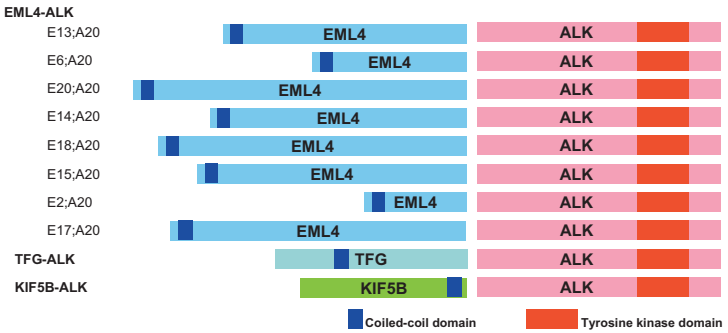
ALK



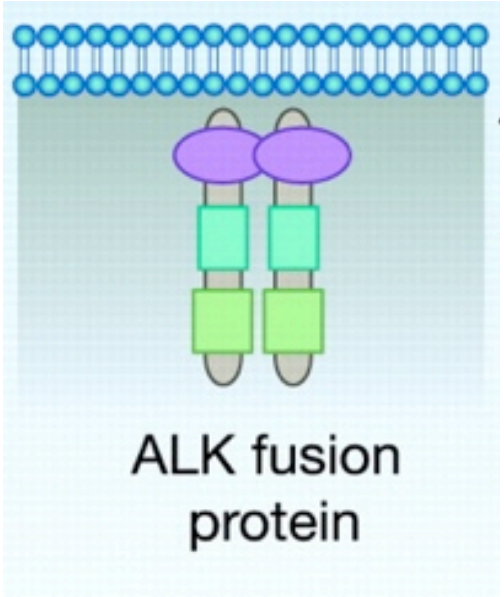
Detection of chromosomal changes



Detection of fusion RNA



Detection of fusion protein

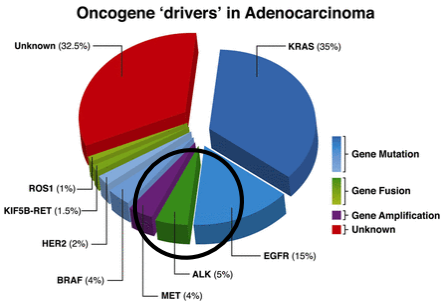


Lung Cancer

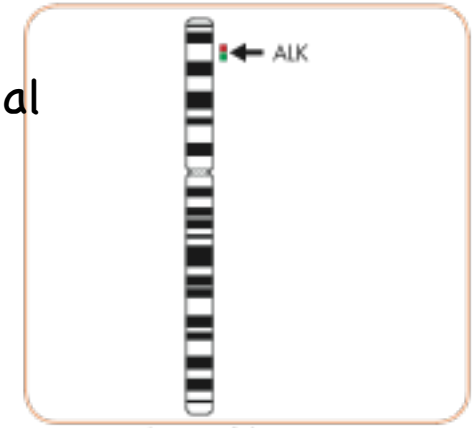
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

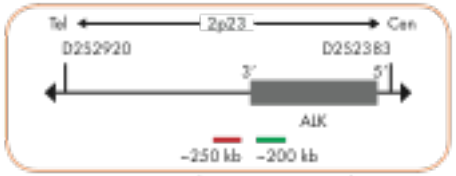
ALK



Detection of chromosomal changes



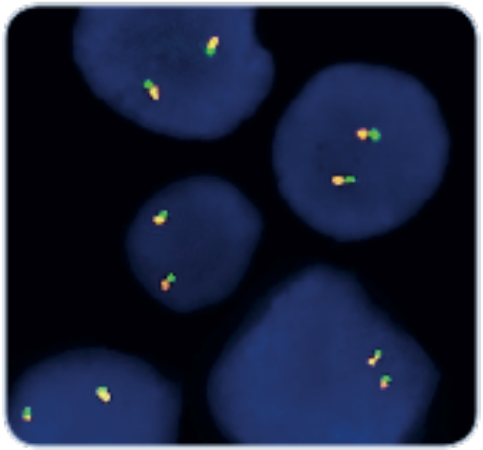
Ideogram of chromosome 2 indicating the hybridization locations.



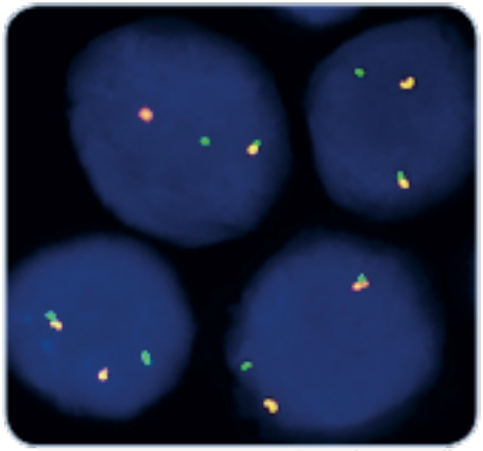
SPEC ALK Probe map (not to scale).

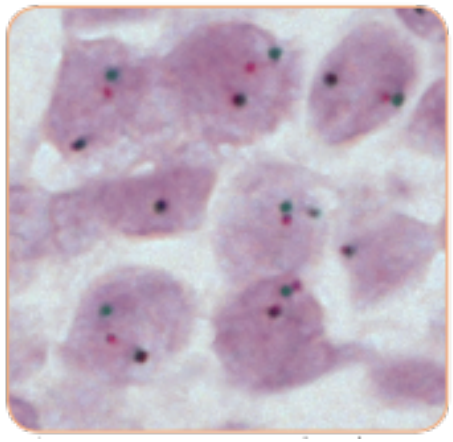
ZYTOVISION
Molecular diagnostics simplified

Inversion probe



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



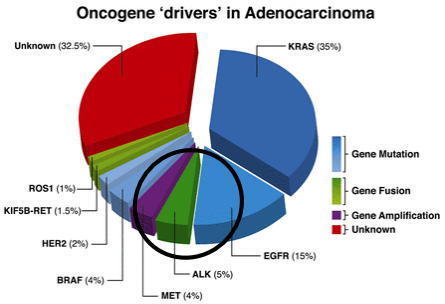


Lung Cancer

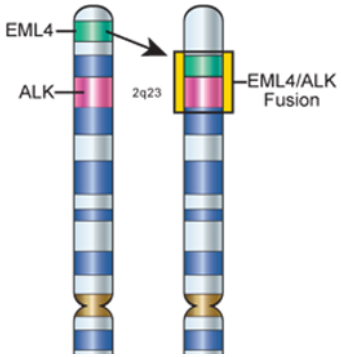
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

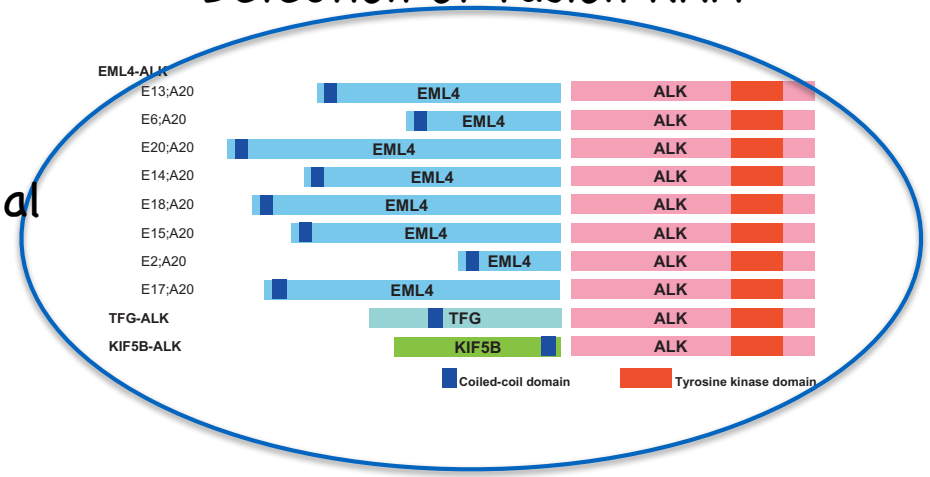
ALK



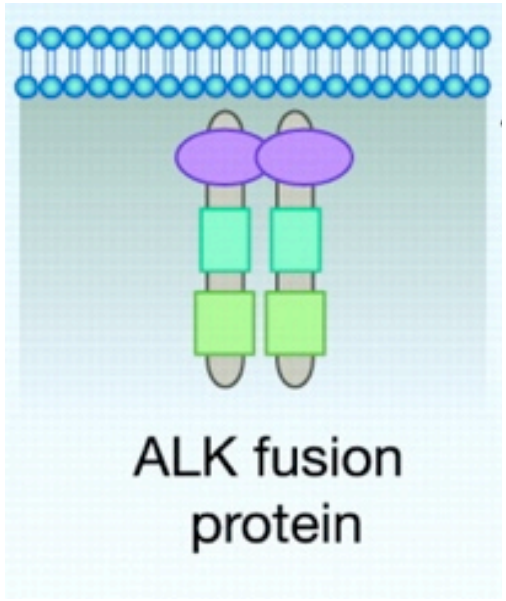
Detection of chromosomal changes



Detection of fusion RNA



Detection of fusion protein



Lung Cancer

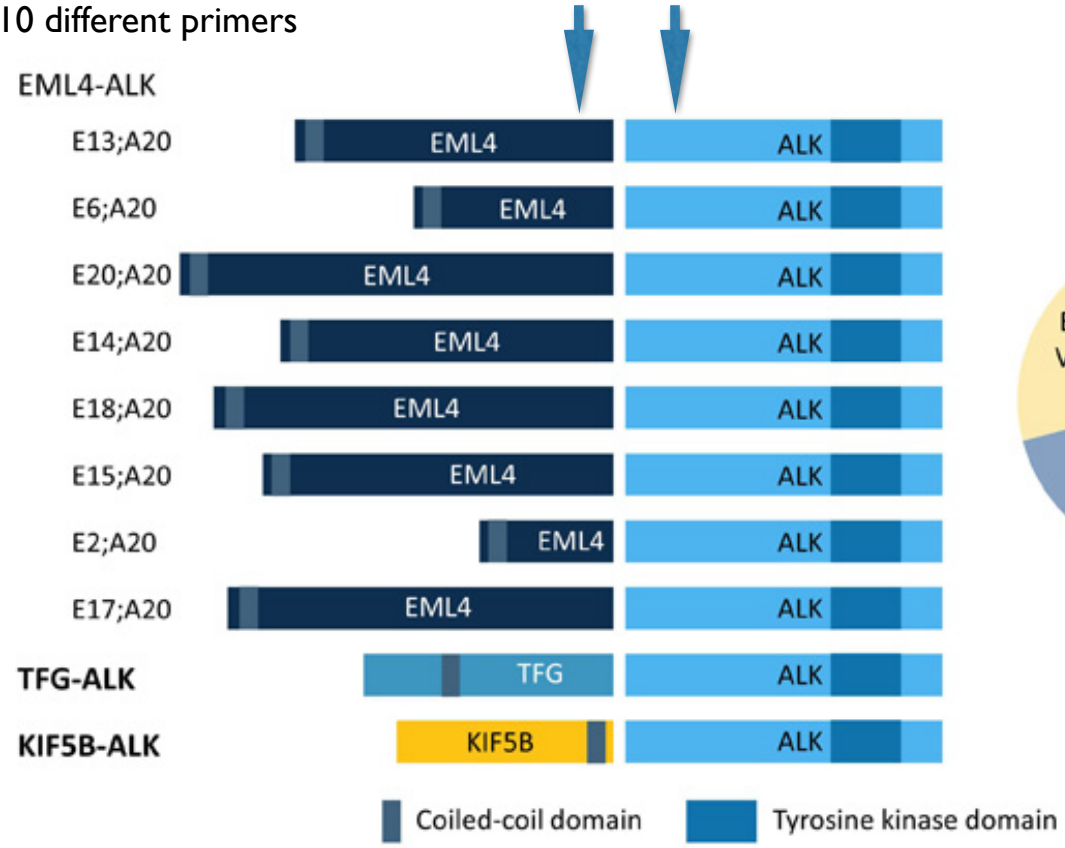
Diagnosis and prediction

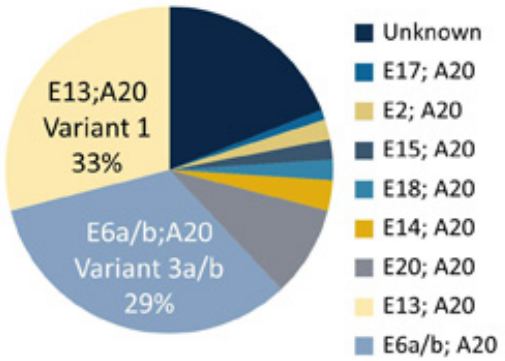
Region Syddanmark
Sygehus Lillebælt

Detection of fusion RNA

Different variants of EML4-ALK and non-EML4 fusion partners

10 different primers



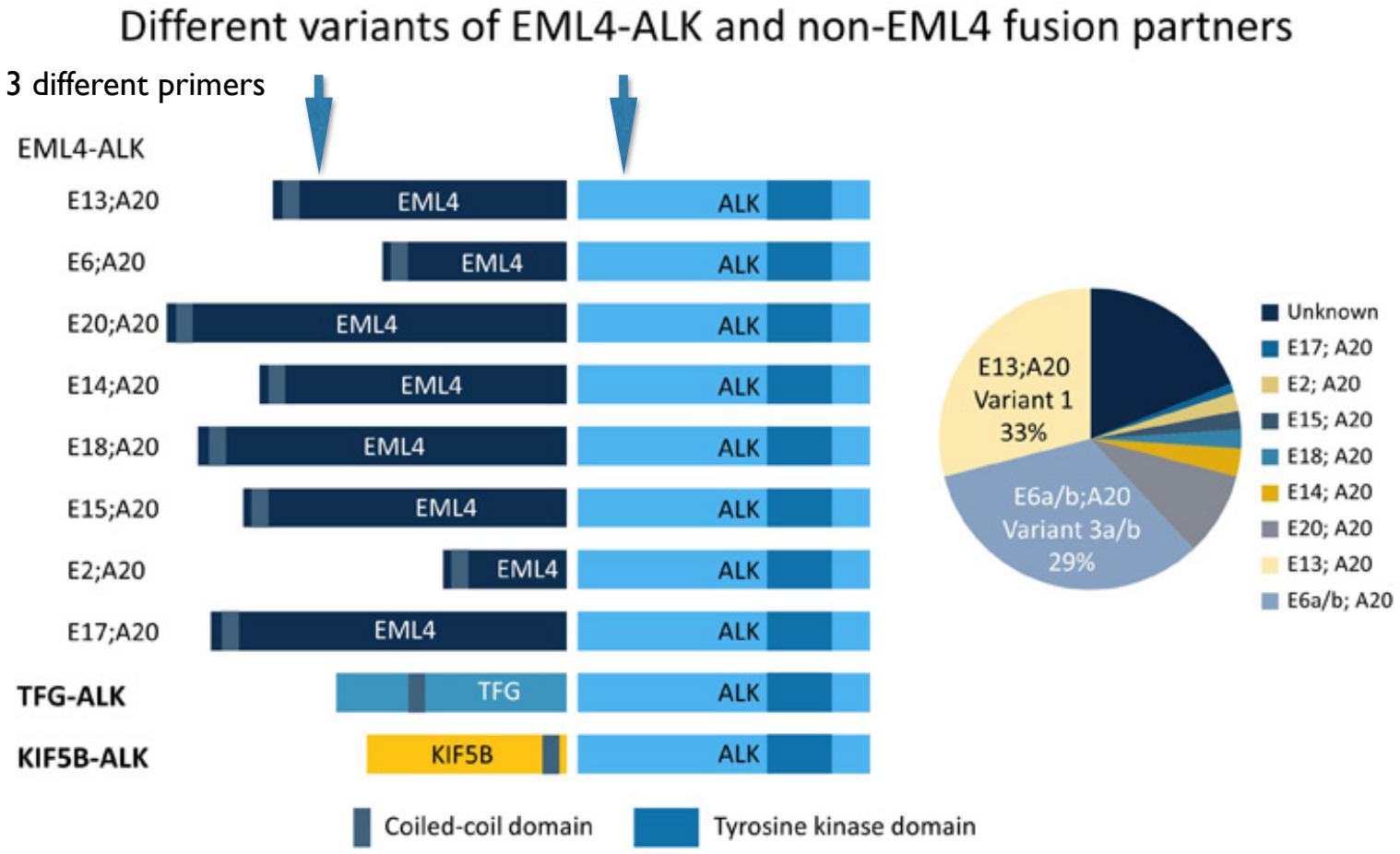


Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

Detection of fusion RNA

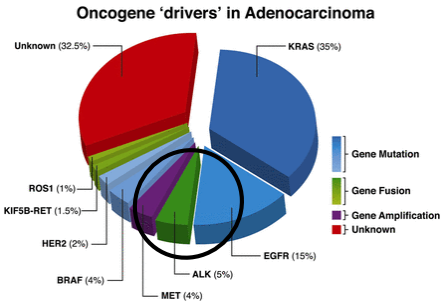


Lung Cancer

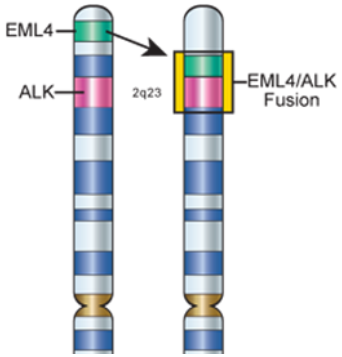
Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

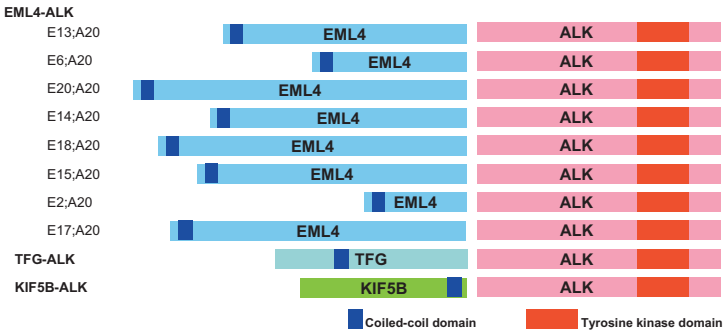
ALK



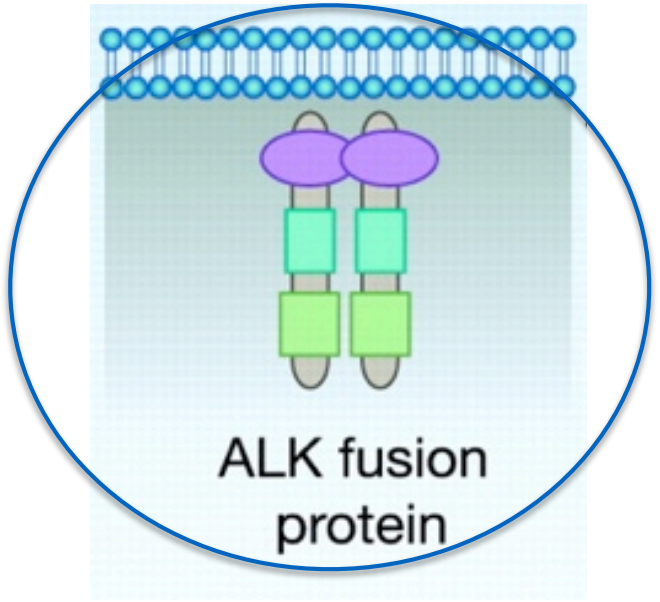
Detection of chromosomal changes



Detection of fusion RNA



Detection of fusion protein

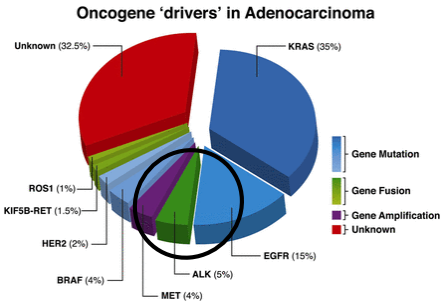


Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

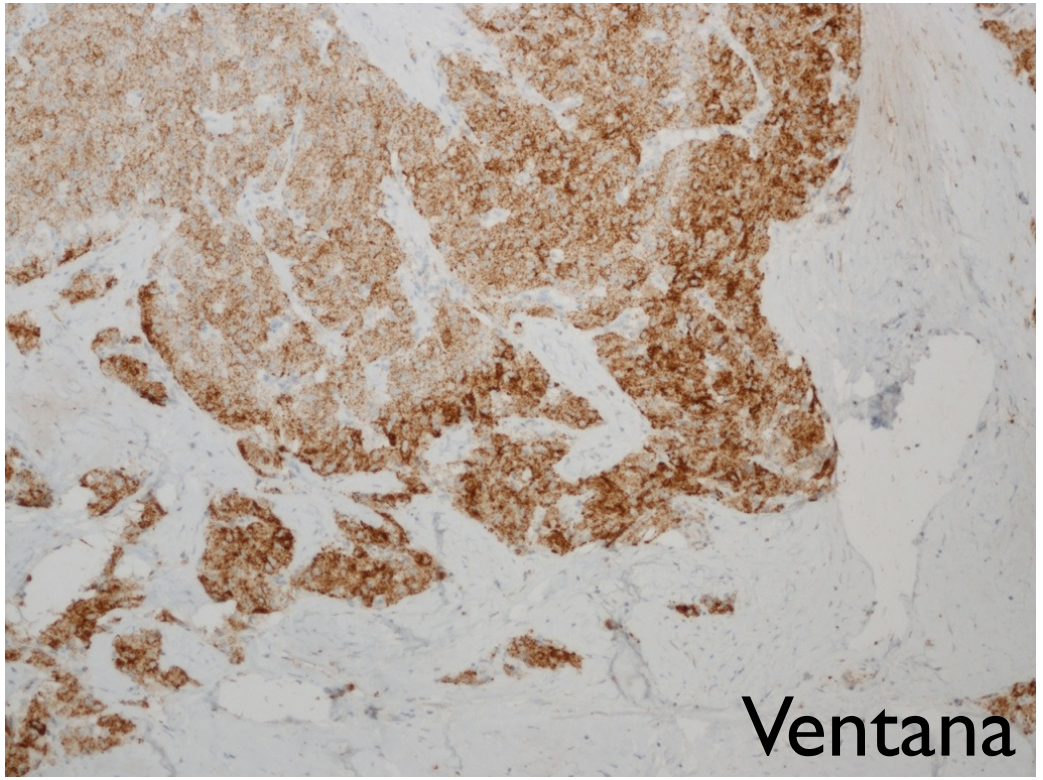
ALK



Detection of fusion protein

Immunohistolochemistry

Detects ALK independent of fusion partner

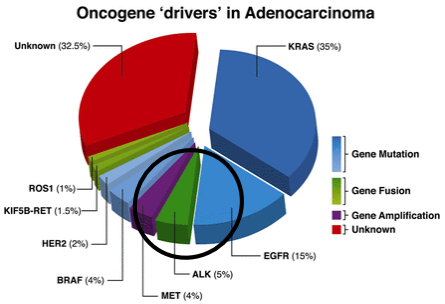


Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

ALK



Detection of fusion protein

Immunhistologi

Supplier	Type/Clone	Product code	Data Sheet
Abcam	Monoclonal (rabbit, clone SP8)	ab16670	View
Abcam	Polyclonal rabbit antibody	ab4061	View
Abcam	Monoclonal (mouse, clone 5A4)	ab17127	View
Abgent	Polyclonal rabbit antibody	AP7600a	View
Abgent	Polyclonal rabbit antibody	AP7600b	View
BD Biosciences	Monoclonal (mouse, clone ALK1)	559254	
Beckman Coulter	Monoclonal (mouse, clone 62.463.2D5.2)	IM3312	View
Biomeda	Monoclonal (rabbit, clone B651)	V10408	View
Dako	Monoclonal (mouse, clone ALK1)	M7195	View
Diagnostic Biosystems	Polyclonal rabbit antibody	RP110	View
GeneTex	Monoclonal (mouse, clone 5A4)	GTX17127	View
GeneTex	Polyclonal rabbit antibody	GTX24061	View
Imgenex	Polyclonal rabbit antibody	IMG-80443	View
Lab Vision	Polyclonal rabbit antibody	RB-9001	View
Lab Vision	Monoclonal (mouse, clone 5A4)	MS-1104	View
Lab Vision	Monoclonal (rabbit, clone SP8)	RM-9108	View
Novocastra	Monoclonal (mouse, clone 5A4)	NCL-ALK	View
Santa Cruz Biotechnology	Monoclonal (mouse, clone ALK1)	sc-53157	View
Ventana Medical Systems	Monoclonal (mouse, clone ALK-01)	790-2918	View

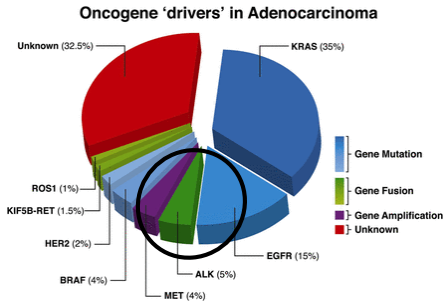
http://www.tissuemarkers.org/source.php?mol_id=2

Lung Cancer

Diagnosis and prediction

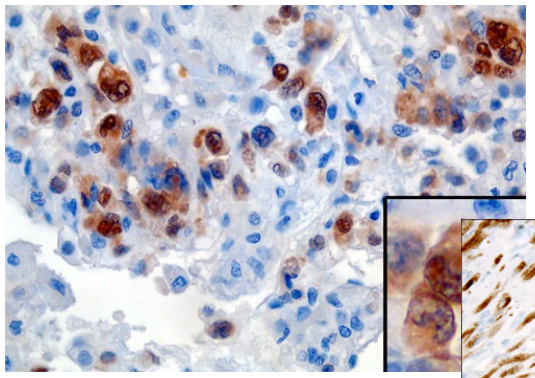
Region Syddanmark
Sygehus Lillebælt

ALK

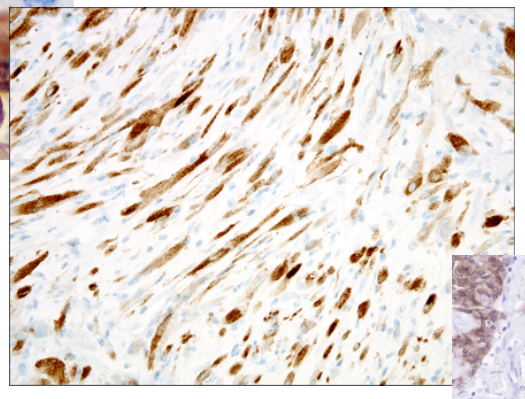


Detection of fusion protein

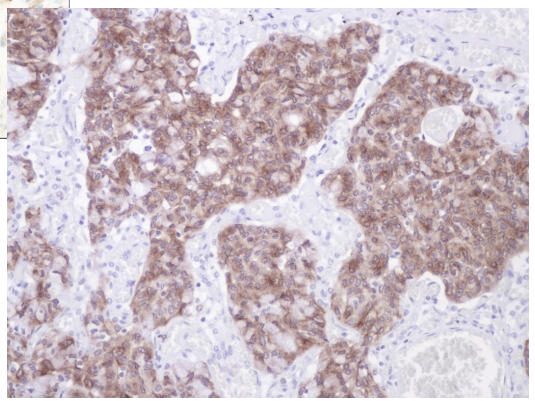
Immunhistologi



Lymfom, DAKO



IMT, DAKO



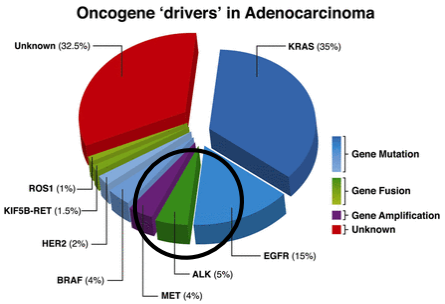
Lung Novacastra

Lung Cancer

Diagnosis and **prediction**

Region Syddanmark
Sygehus Lillebælt

ALK

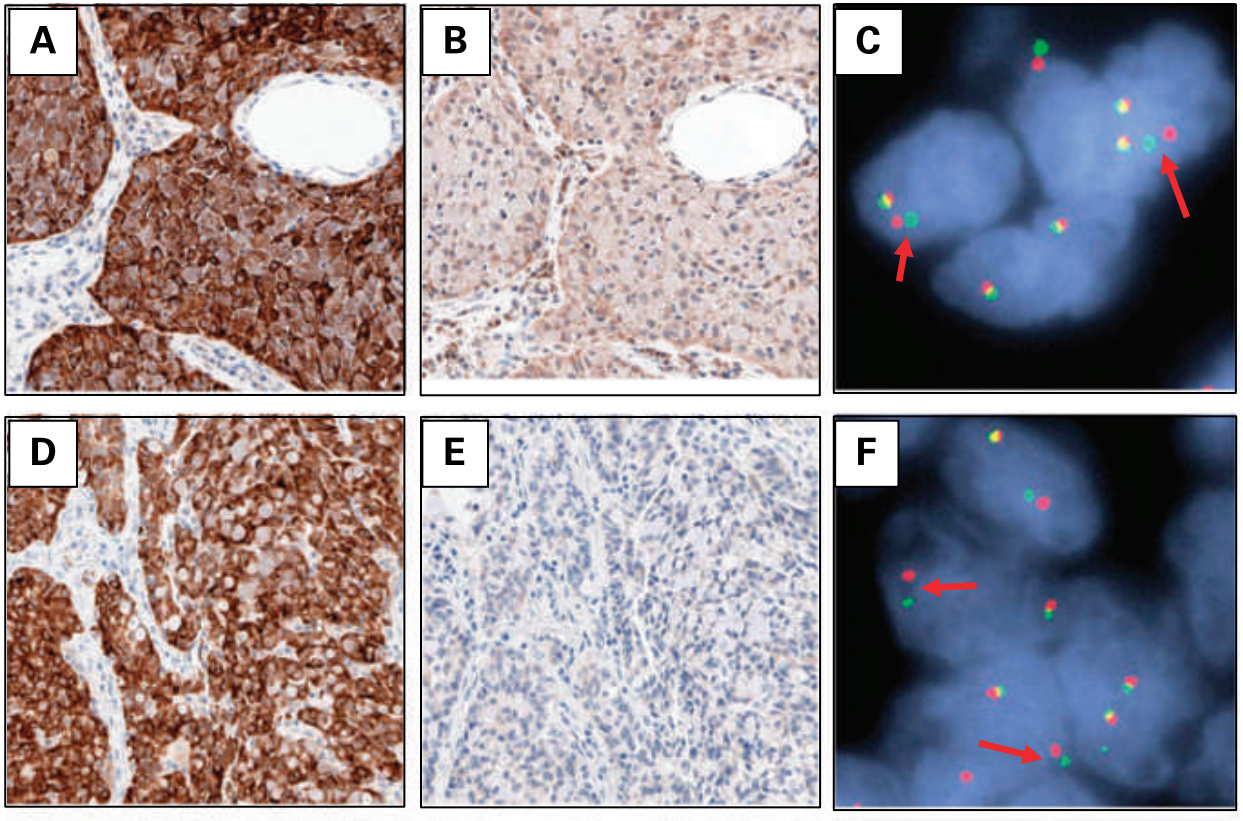


Detection of fusion protein

Immunhistologi

D5F3 Cell Signalling

ALK I DAKO



A Novel, Highly Sensitive Antibody Allows for the Routine Detection of *ALK*-Rearranged Lung Adenocarcinomas by Standard Immunohistochemistry

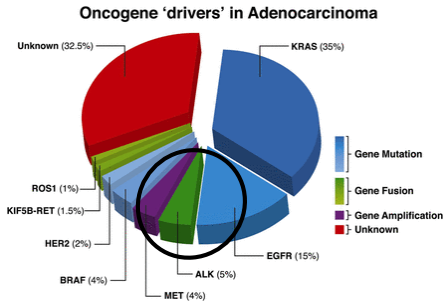
Mari Mino-Kenudson[1], Lucian R. Chirieac[2], Kenny Law[2], Jason L. Hornick[2], Neal Lindeman[2], Eugene J. Mark[1], David W. Cohen[3], Bruce E. Johnson[4], Pasi A. Jänne[4], A. John Iafrate[1], and Scott J. Rodig[2]

Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

ALK



Detection of fusion protein

Immunhistologi

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

REVIEW AND PERSPECTIVES

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

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

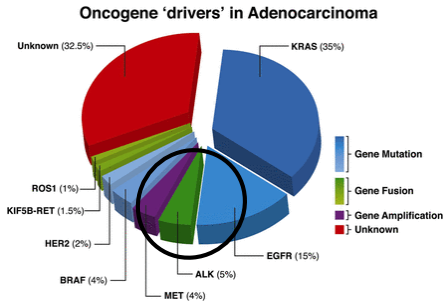
Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

Immunhistologi

ALK



Detection of fusion protein

Table 1 IHC protocols described in the literature

	Antibody	Source	HIER	Dilution	Incubation	Detection system
Yi et al. [46]	ALK1	Dako	EDTA, pH 8, 30 min	1/100	30 min at RT	Advance (Dako)
Yang et al. [43]	ALK1	Dako	EDTA, pH 8, 30 min	1/100	30 min at RT	Advance (Dako)
Paik et al. [47]	5A4	Abcam	CC1 (Ventana), 1 h	1/30	2 h at 42 °C	i-view (Ventana)
McLeer-Florin et al. [48]	5A4	Abcam	CC1 (Ventana), 1 h	1/50	2 h at 37 °C	i-view (Ventana)
Hofman et al. [45]	5A4	Abcam	pH 9, 40 min, 97 °C	1/50	30 min RT	EnVision Flex (Dako)
Kim et al. [27]	5A4	Novocastra	CC1 100 °C, 20 min	1/30	2 h at 42 °C	i-view (Ventana)
Mino-Kenudson et al. [49]	D5F3 D9E4	CST CST	EDTA pH 8 pressure cooker	1/500[a] 1/100[b]	Overnight	EnVision+ (Dako)
	ALK1	Dako		1/50[a] 1/2[b]		

HIER heat-induced epitope retrieval, *EDTA* ethylenediaminetetraacetic acid, *RT* room temperature, *CST* cell signaling technology

[a] For anaplastic large cell lymphomas

[b] For lung adenocarcinomas and inflammatory myofibroblastic tumours


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

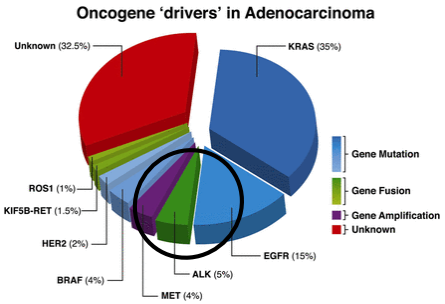
Erik Thunnissen · Lukas Bubendorf · Manfred Dietel · Göran Elmberger · Keith Kerr · Fernando Lopez-Rios · Holger Moch · Włodzimierz Olszewski · Patrick Pauwels · Frédérique Penault-Llorca · Giulio Rossi

Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

ALK



Detection of fusion protein

Immunhistologi

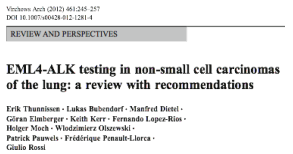
Table 2 IHC scoring systems

	Score			
	0	1+	2	3
Yi et al. [46]	No staining	Faint cytoplasmic staining	Moderate smooth cytoplasmic staining	Intense granular cytoplasmic staining in ≥10 % of tumour cells
Kim et al. [27]	No staining	Faint or weak staining intensity with >5 % tumour cells or any staining intensity with ≤5 % tumour cells [a]	Moderate staining >intensity with >5 % tumour cells [b]	Strong and granular staining intensity with >5 % tumour cells [c]

[a] Average of 14.7 % positively stained cells

[b] Average of 58.2 % positively stained cells

[c] Average of 97.3 % positively stained cells


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

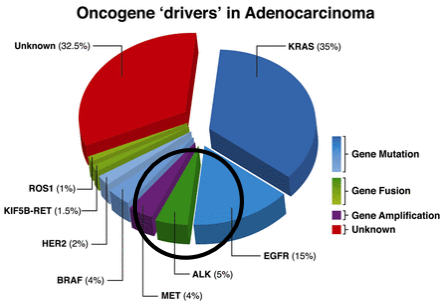
Erik Thunnissen · Lukas Bubendorf · Manfred Dietel · Göran Elmberger · Keith Kerr · Fernando Lopez-Rios · Holger Moch · Włodzimierz Olszewski · Patrick Pauwels · Frédérique Penault-Llorca · Giulio Rossi

Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

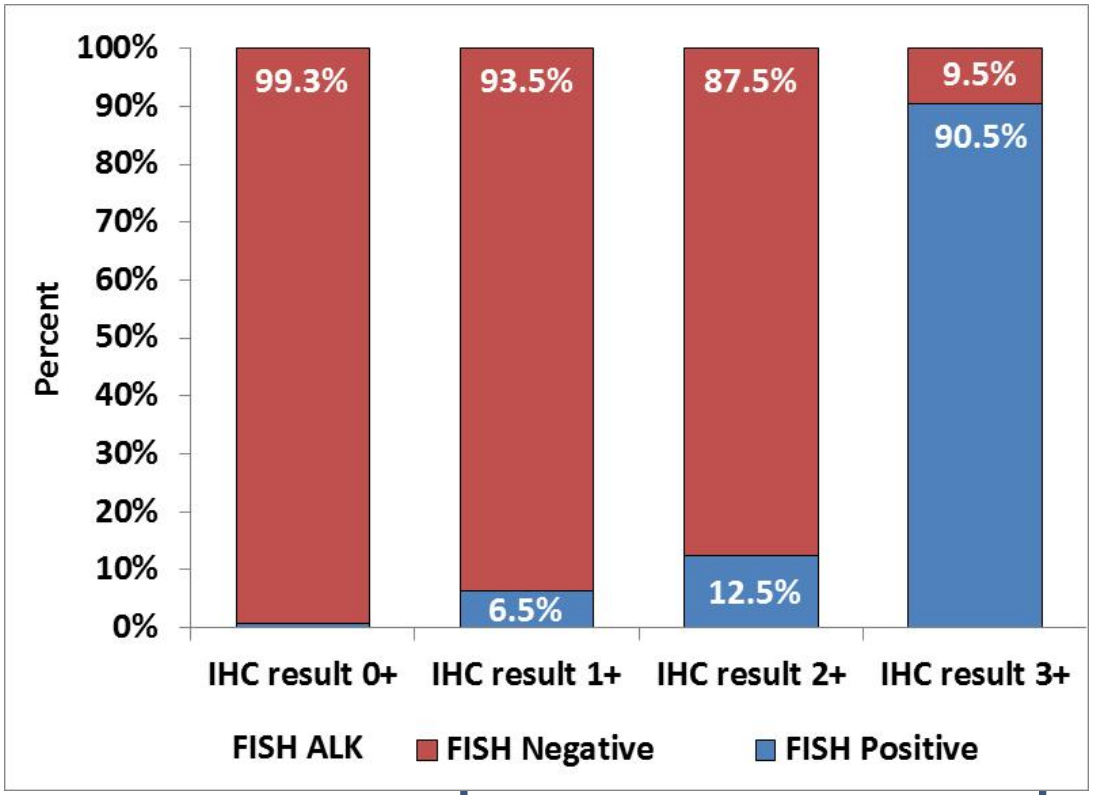
ALK



Detection of fusion protein

Immunhistologi

ESMO Association of ALK IHC and FISH, N=198



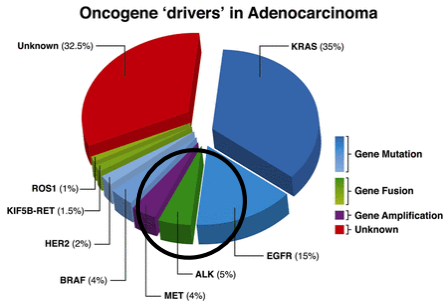
36.7% of IHC+ are FISH+

Lung Cancer

Diagnosis and prediction

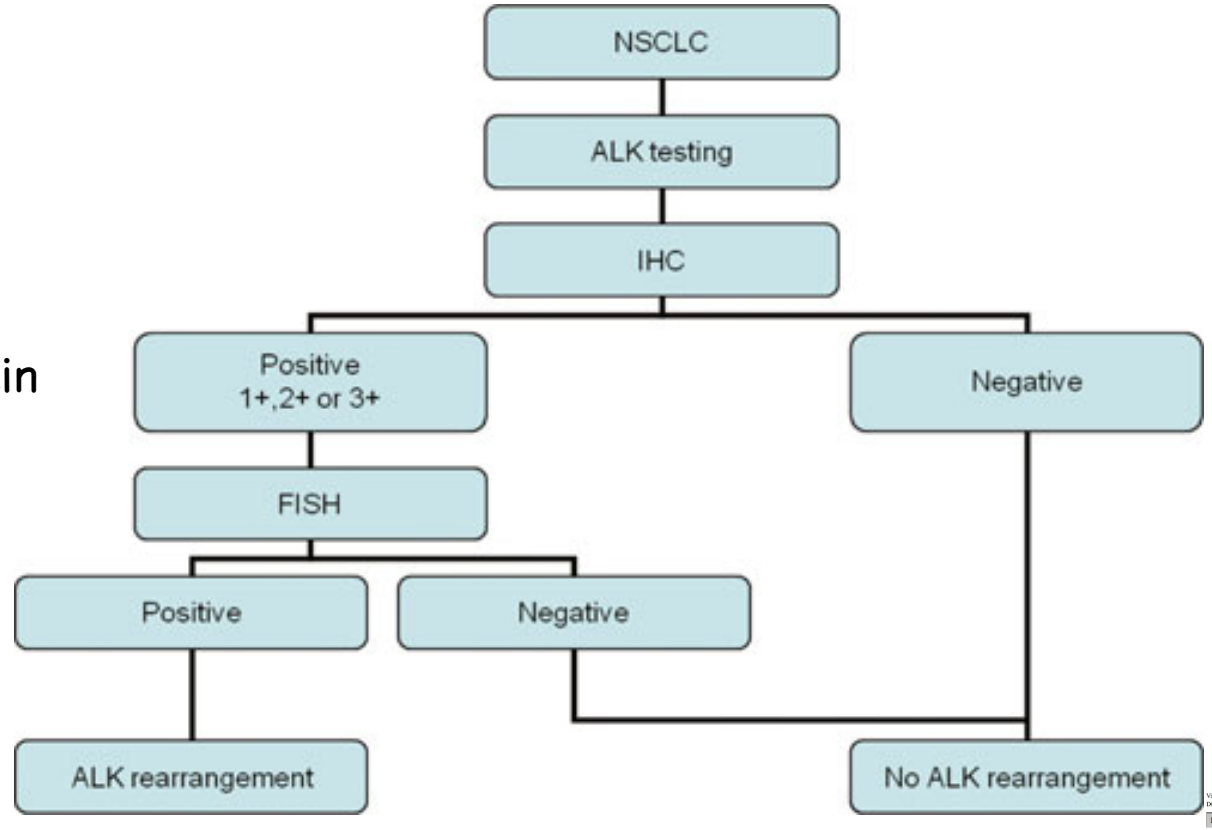
Region Syddanmark
Sygehus Lillebælt

ALK



Detection of fusion protein

Algorithm



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

REVIEW AND PERSPECTIVES

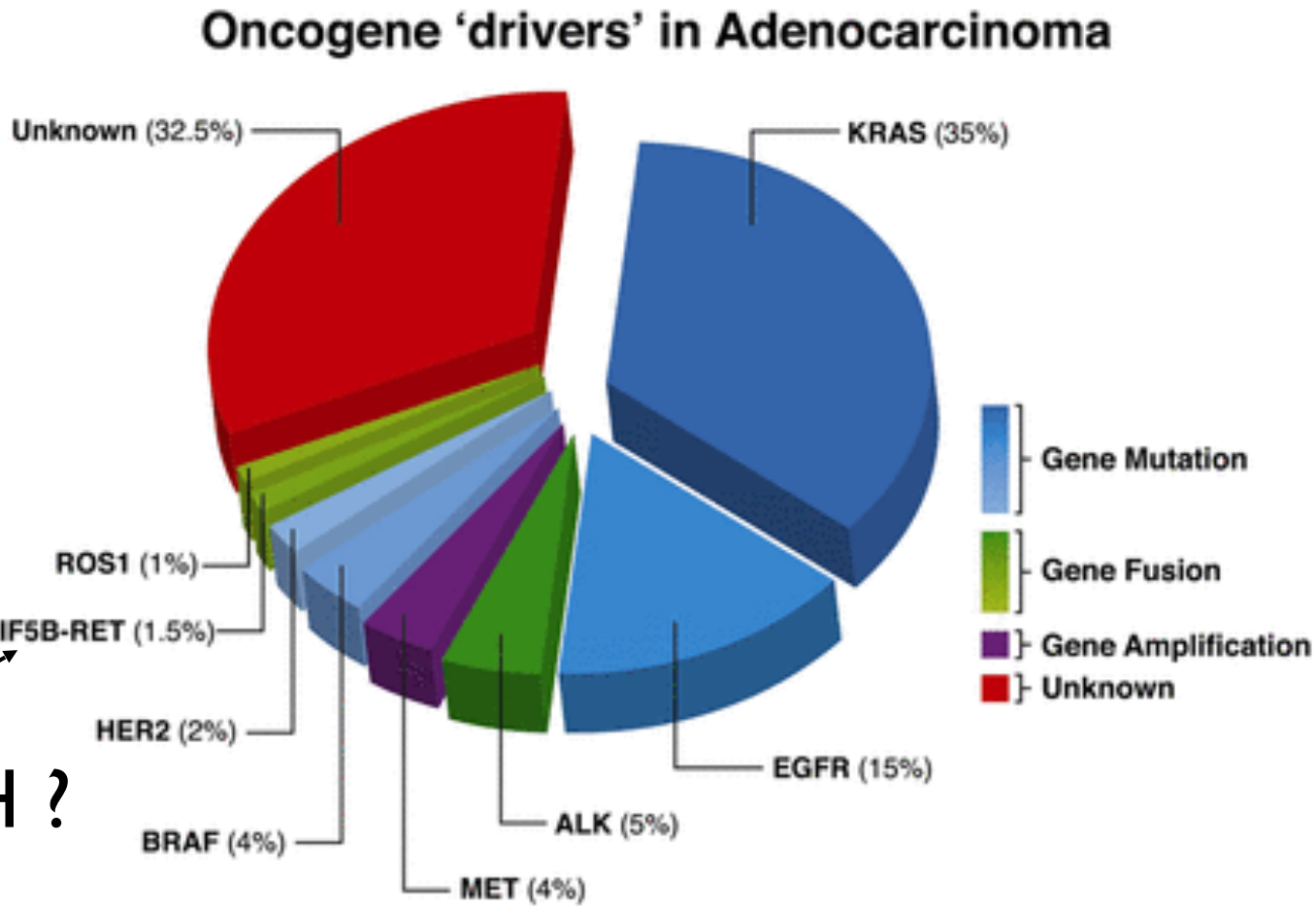
EML4-ALK testing in non-small cell carcinomas of the lung: a review with recommendations

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

Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt



XALKORI

IHC, FISH ?

Near future

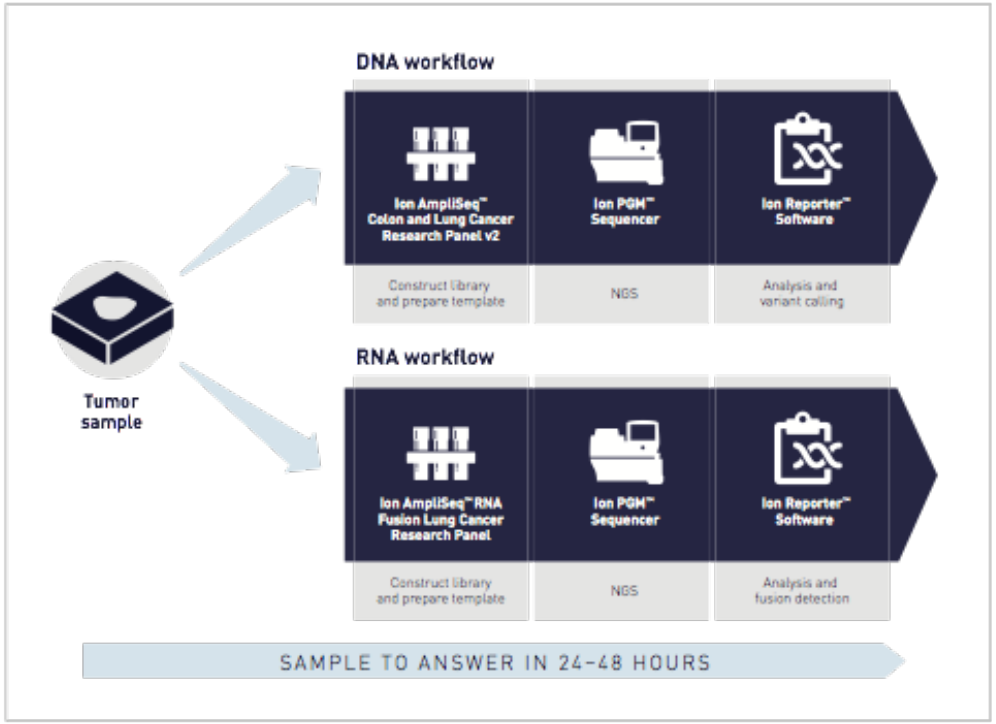
MET-Mab

IHC, FISH ?

Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt



KRAS, EGFR, BRAF, PIK3CA, AKT1, ERBB2, PTEN, NRAS, STK11, MAP2K1, ALK, DDR2, CTNNB1, MET, TP53, SMAD4, FBX7, FGFR3, NOTCH1, ERBB4, FGFR1, FGFR2

ALK, RET, ROS1, and *NTRK1* fusion transcripts, in addition to targets designed to detect 5' and 3' *ALK* gene expression

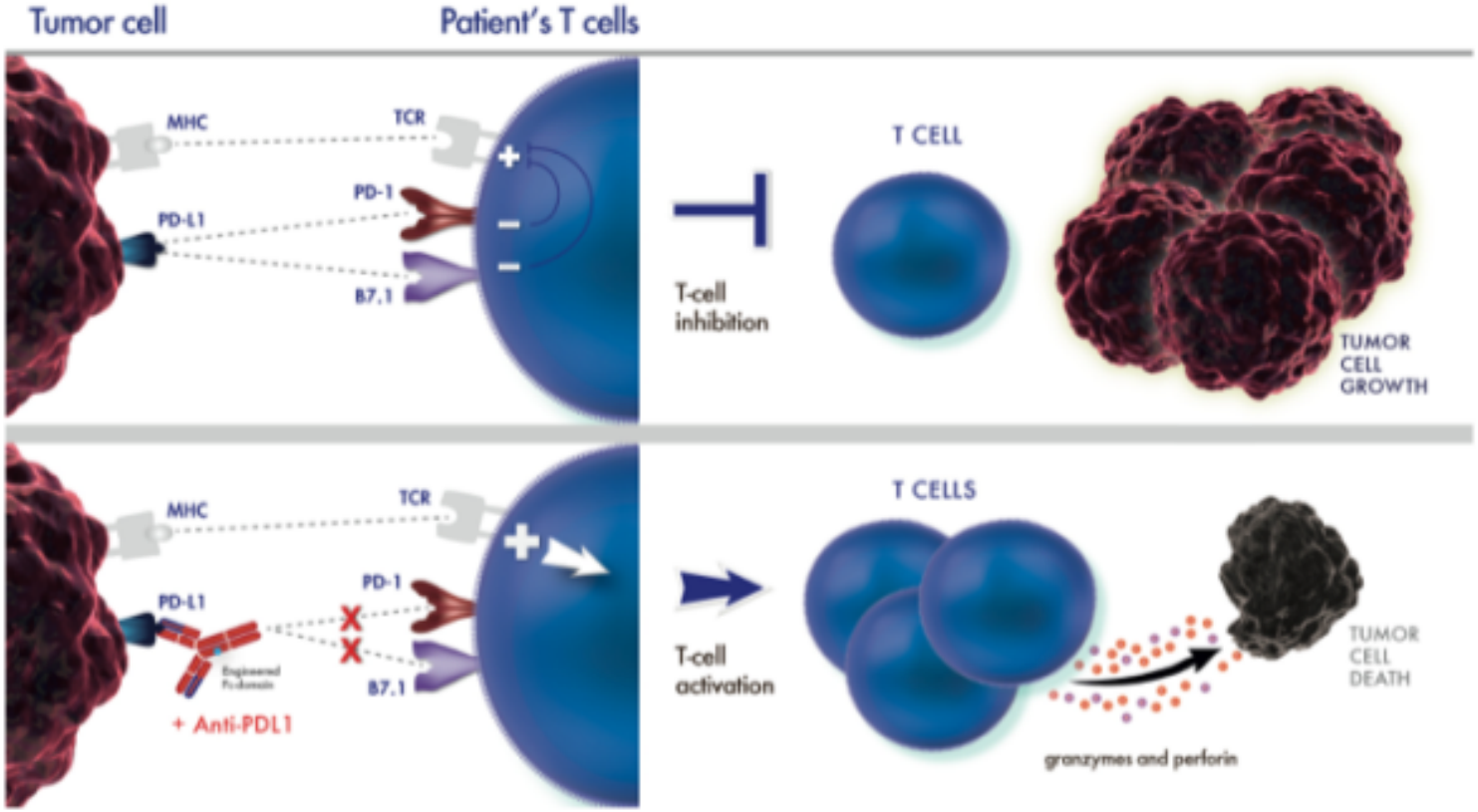
Next generation seq.

Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

Cancer Immunotherapy

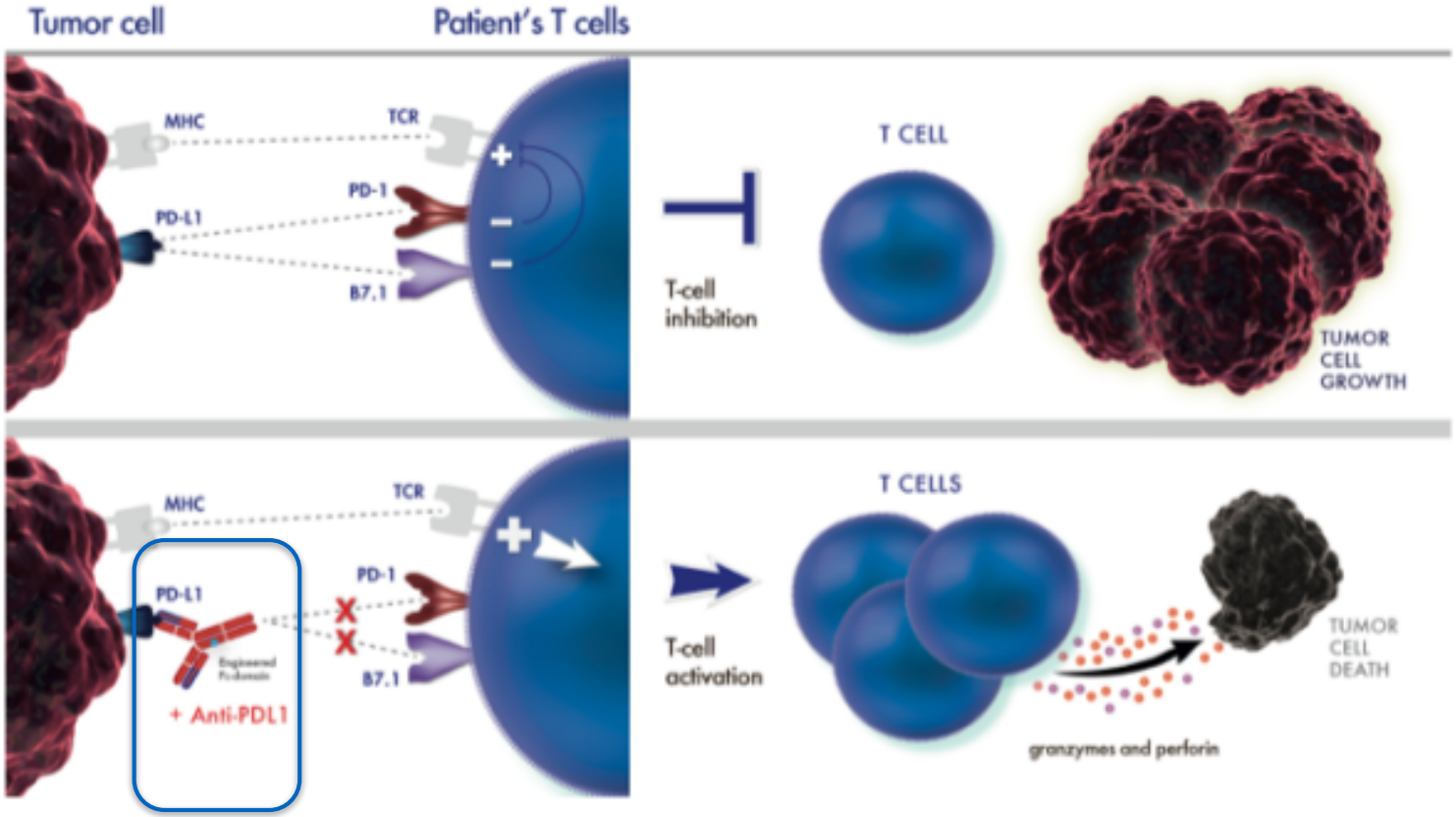


Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

Cancer Immunotherapy

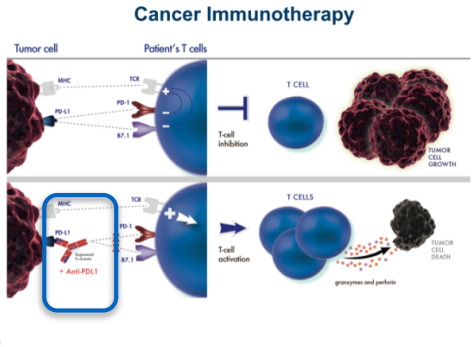


Predictive marker ?

Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt



Programmed Death-Ligand 1 Immunohistochemistry in Lung Cancer

In what state is this art?

Keith M. Kerr, MBChB, FRCPath, Ming-Sound Tsao, MD, PhD,† Andrew G. Nicholson, DM, FRCPath,‡ Yasushi Yatabe, MD, PhD,§ Ignacio I. Wistuba, MD, PhD, ‖ and Fred R. Hirsch, MD, PhD,¶ On behalf of the IASLC Pathology Committee*

(*J Thorac Oncol.* 2015;10: 985–989)

TABLE 1. Summary of Published Findings for PD-L1 Immunohistochemistry in Therapeutic Trials

Drug	Biomarker Antibody	Rx Line	Definition of "Positive"[a] (%)	N Positive (%)	Positive Predictive Outcome	ORR % IHC pos. Cases	ORR % IHC neg. Cases	Ref.
Nivolumab	Dako 28-8	1st	≥5 in >100 cells	59	Yes	31[b]	10	7,8[f]
Nivolumab	Dako 28-8	≥2nd	≥5, ≥1	49, 56	No	15, 13	14, 17	9,10
Nivolumab + Ipilimumab	Dako 28-8	1st	≥5 in >100 cells	42	No	19	14	11
Nivolumab	Dako 28-8	≥2nd	≥5	33[c]	Yes	24	14	12[f]
Nivolumab	5H1[d]	≥2nd	≥5, also studied TIICs	67	Yes	No data for lung	No data for lung	13
Pembrolizumab	Dako 22C3	Any	"Strong" ≥50, "Weak" 1–49	25, 70	Yes, Yes	37, 17	9	14
Pembrolizumab	Dako 22C3	1st	≥50, ≥1	?	Yes	47, 26	?	15
MPDL3280A	Roche Ventana, SP142	≥2nd	≥10,[e] ≥5, ≥1 TIICs	13, 28, 56	Yes	83, 46, 31	18, 18, 20	16–18
MEDI-4736	Roche Ventana, SP263	≥2nd	Data not available	41	Yes	25	3	19,20

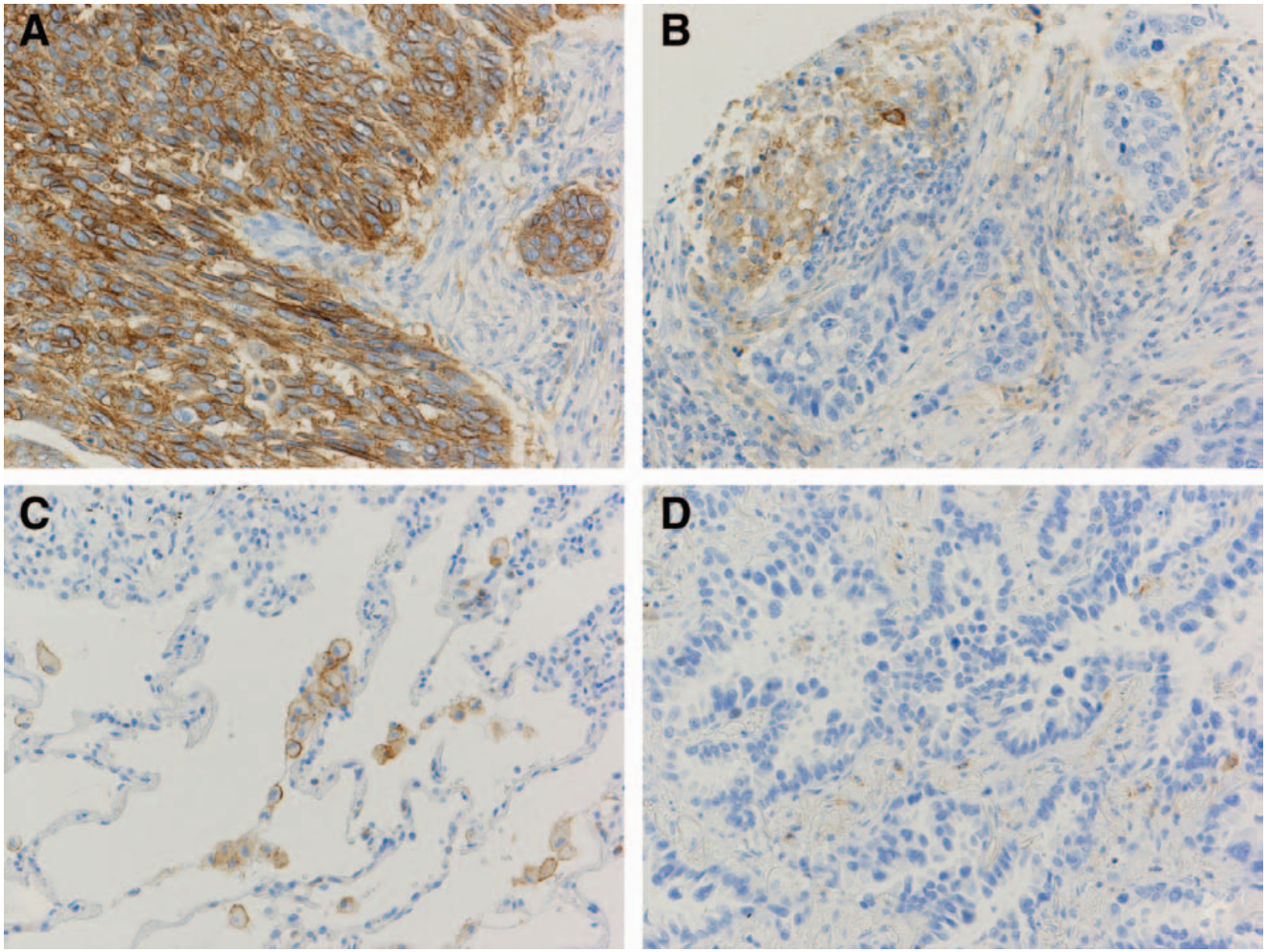
Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

SQC+

SQC-



Alveolar macr.

ADC-

E1LN3N anti-PD-L1 (cell signalling)

Programmed Death-Ligand 1
Immunohistochemistry in Lung Cancer
In what state is this art?

Keith M. Kerr, MBChB, FRCPath, Ming-Sound Tsao, MD, PhD,† Andrew G. Nicholson, DM, FRCPath,‡ Yasushi Yatabe, MD, PhD,§ Ignacio I. Wistuba, MD, PhD,‖ and Fred R. Hirsch, MD, PhD,¶ On behalf of the IASLC Pathology Committee*

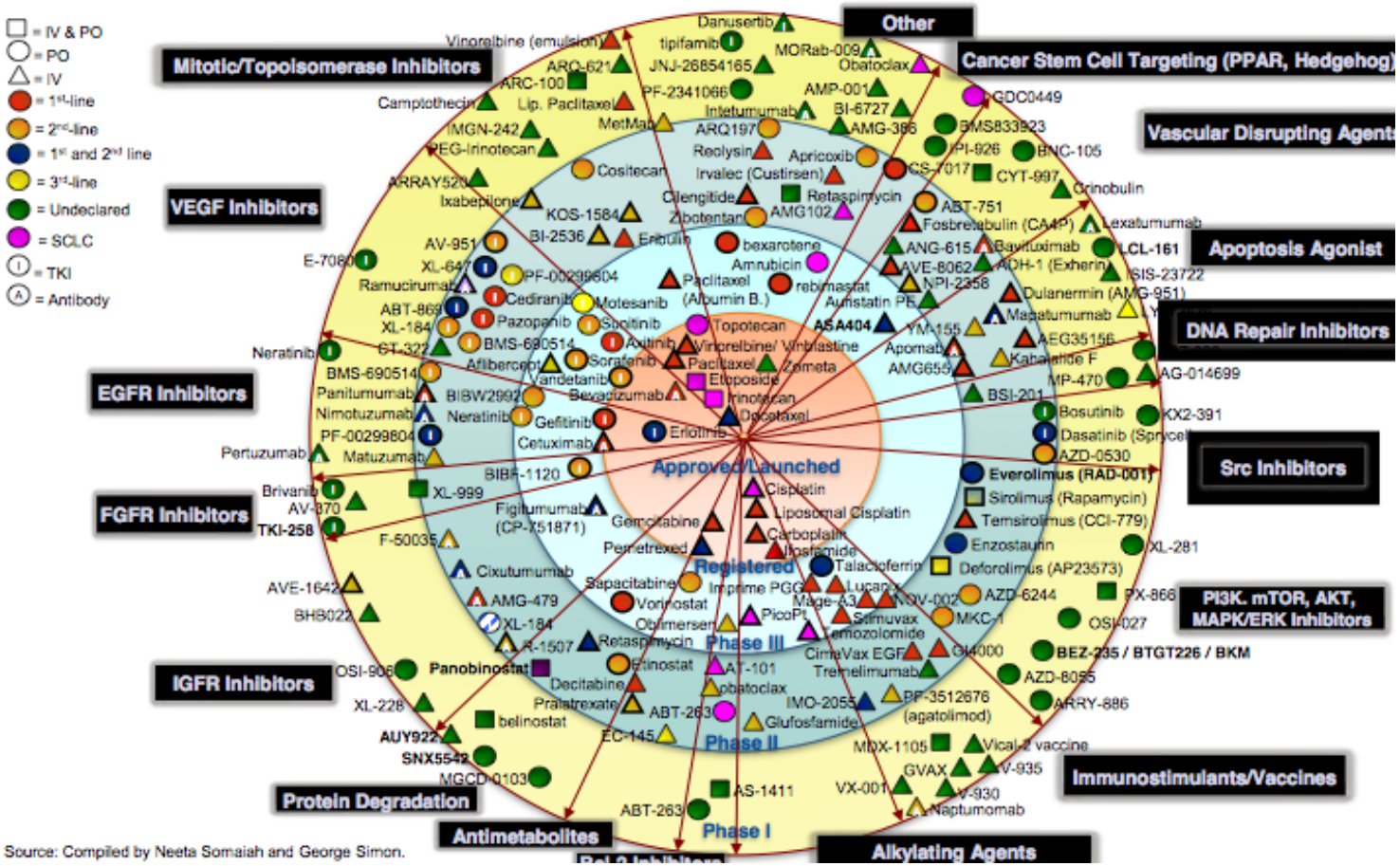
(*J Thorac Oncol.* 2015;10: 985–989)

Lung Cancer

Diagnosis and prediction

Region Syddanmark
Sygehus Lillebælt

Lung cancer research landscape – MoA group and phase



Source: Compiled by Neeta Somaiah and George Simon.

Future