香港防癌會
THE HONG KONG ANTI-CANCER SOCIETY

癌症基因檢測新發展

專 題 講 座

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借出講座資料
香港防癌會 謹此致謝

癌症基因測試新發展：肺癌

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馬紹鈞醫生

內容

- 肺癌－本地特徵
- 肺癌生物標記
- 基因測試最新發展

Leading cancer sites in HK in 2006

HK Cancer Registry

10 Most Common Cancers

Male

Rank	Site	New cases registered	Relative frequency	Crude incidence rate*
1	Lung	2,885	22.6%	88.2
2	Colorectum	2,230	17.5%	68.2
3	Liver	1,331	10.4%	40.7
4	Prostate	1,068	8.4%	32.7
5	Nasopharynx	692	5.4%	21.2
6	Stomach	634	5.0%	19.4
7	Oesophagus	374	2.9%	11.4
8	Non-Hodgkin's lymphoma	370	2.9%	11.3
9	Bladder	344	2.7%	10.5
10	Lip, oral cavity & pharynx except nasopharynx	317	2.5%	9.7
	All sites	**12,753**	**100.0%**	**390.0**

Female

Rank	Site	New cases registered	Relative frequency	Crude incidence rate*
1	Breast	2,584	23.5%	72.0
2	Colorectum	1,688	15.3%	47.1
3	Lung	1,348	12.3%	37.6
4	Corpus uteri	570	5.2%	15.9
5	Cervix	459	4.2%	12.8
6	Ovary etc.	450	4.1%	12.5
7	Thyroid	428	3.9%	11.9
8	Liver	414	3.8%	11.5
9	Stomach	384	3.5%	10.7
10	Non-melanoma skin	315	2.9%	8.8
	All sites	**10,997**	**100.0%**	**306.6**

Both Sexes

Rank	Site	New cases registered	Relative frequency	Crude incidence rate*
1	Lung	4,233	17.8%	61.7
2	Colorectum	3,918	16.5%	57.1
3	Breast	2,595	10.9%	37.9
4	Liver	1,745	7.3%	25.4
5	Prostate	1,068	4.5%	15.6
6	Stomach	1,018	4.3%	14.8
7	Nasopharynx	959	4.0%	14.0
8	Non-Hodgkin's lymphoma	677	2.9%	9.9
9	Non-melanoma skin	624	2.6%	9.1
10	Corpus uteri	570	2.4%	8.3
	All sites	**23,750**	**100.0%**	**346.4**

10 Major Causes of Cancer Deaths

Male

Rank	Site	Deaths registered	Relative frequency	Crude mortality rate*
1	Lung	2,396	32.4%	73.3
2	Liver	1,075	14.6%	32.9
3	Colorectum	923	12.5%	28.2
4	Stomach	391	5.3%	12.0
5	Prostate	285	3.9%	8.7
6	Oesophagus	283	3.8%	8.7
7	Nasopharynx	279	3.8%	8.5
8	Pancreas	214	2.9%	6.5
9	Non-Hodgkin's lymphoma	176	2.4%	5.4
10	Leukaemia	144	1.9%	4.4
	All sites	**7,386**	**100.0%**	**225.9**

Female

Rank	Site	Deaths registered	Relative frequency	Crude mortality rate*
1	Lung	1,135	24.1%	31.6
2	Colorectum	705	15.0%	19.7
3	Breast	463	9.8%	12.9
4	Liver	387	8.2%	10.8
5	Stomach	244	5.2%	6.8
6	Pancreas	183	3.9%	5.1
7	Non-Hodgkin's lymphoma	143	3.0%	4.0
8	Ovary etc.	136	2.9%	3.8
9	Cervix	133	2.8%	3.7
10	Leukaemia	110	2.3%	3.1
	All sites	**4,707**	**100.0%**	**131.2**

Both Sexes

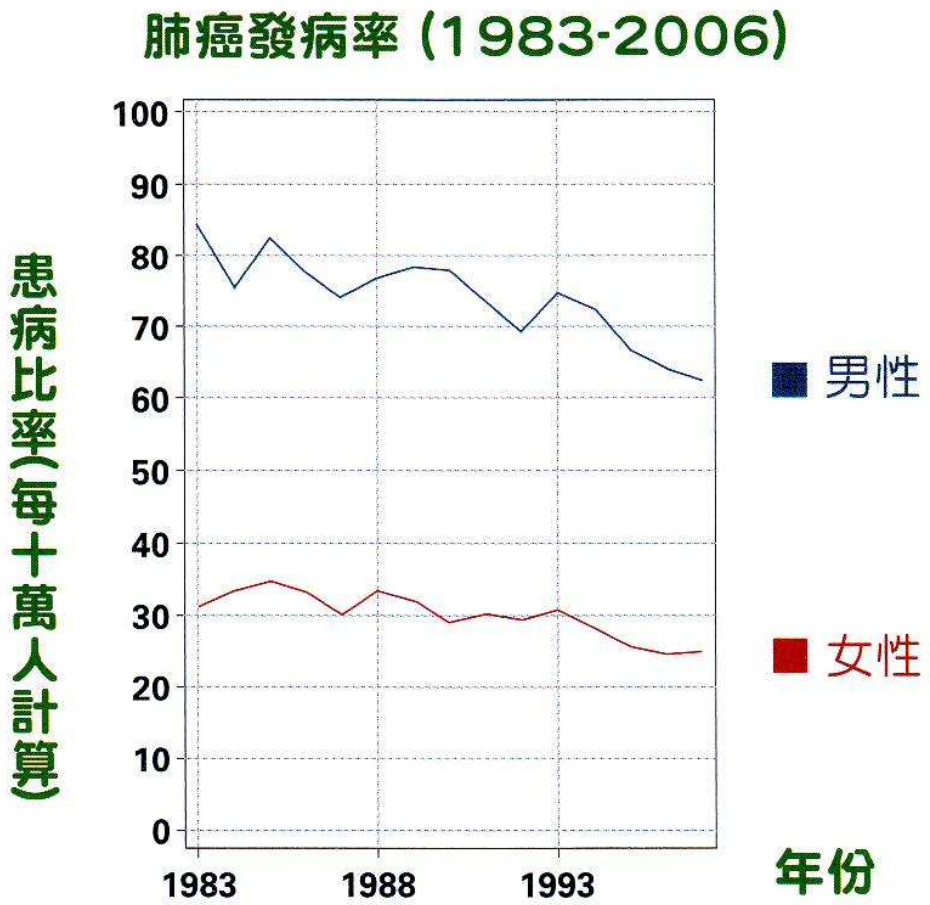
Rank	Site	Deaths registered	Relative frequency	Crude mortality rate*
1	Lung	3,531	29.2%	51.5
2	Colorectum	1,628	13.5%	23.7
3	Liver	1,462	12.1%	21.3
4	Stomach	635	5.3%	9.3
5	Breast	465	3.8%	6.8
6	Pancreas	397	3.3%	5.8
7	Oesophagus	359	3.0%	5.2
8	Nasopharynx	358	3.0%	5.2
9	Non-Hodgkin's lymphoma	319	2.6%	4.7
10	Prostate	285	2.4%	4.2
	All sites	**12,093**	**100.0%**	**176.4**

2006年全年肺癌登記數據

	男	女
登記數字	2885	1348
排名	第1位	第3位
年齡中位數(歲)	71	73
標準化年齡發病率(每十萬人計)	60.5	26.7
一生累計風險 (以0-74歲計)	每 16人有一人	每43 人有一人

取材自周倩明醫生「衝破肺癌陣」

幸好，香港的肺癌**發病率**有**下降的趨勢**，男性的發病率由1983年的84.6人(每十萬人計)下降至2006年的60人；女性發病率同時間由31.5人下降至26.7人。



取材自周倩明醫生「衝破肺癌陣」

本地肺癌特徵

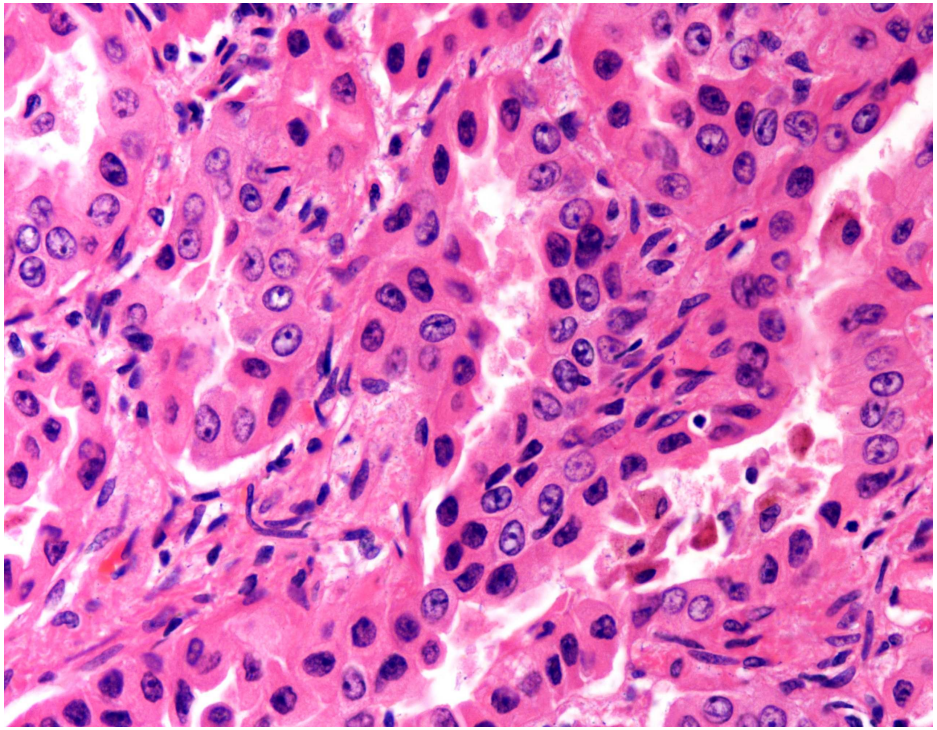
- 女性肺腺癌患者比例較高，大部分是從不吸煙的
- 肺癌患者比歐美裔人士較多呈EGFR受體陽性突變

肺癌病理分類

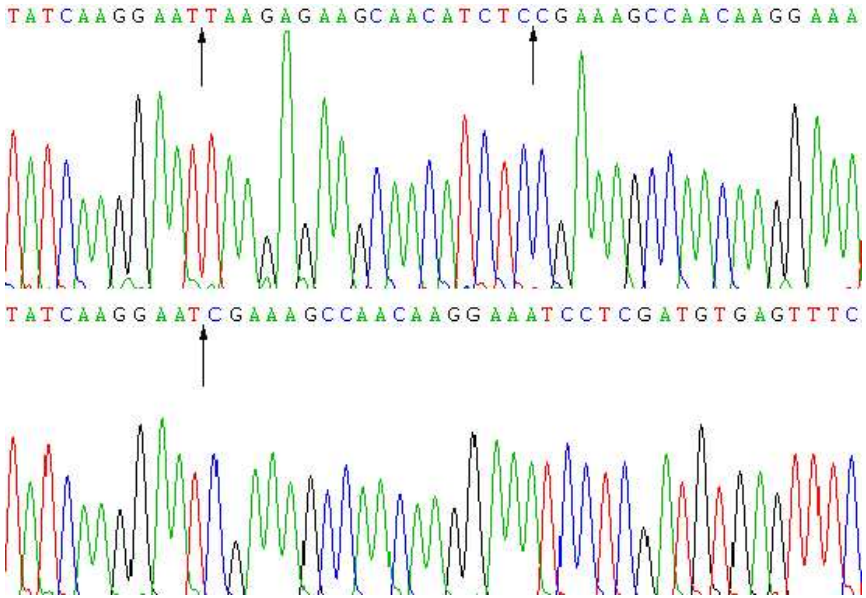
- 非小細胞癌
  - 腺癌，包括細支氣管肺泡癌　　約佔60%-80%
  - 鱗癌　　約佔10%
  - 腺鱗癌　　罕見
- 小細胞癌　　約佔10%
- 其他, 例如類癌及其他罕見原發性肺癌　　約佔10%

EGFR受體突變於亞裔，女性，從不吸煙者及腺癌患者中有較高的比例（約30-50%）

EGFR mutation in NSCLC



Adenocarcinoma of lung 腺癌



EGFR基因排序

肺癌生物標記

- EGFR gene mutation
  (上皮生長因子受體基因特變)
- KRAS gene mutation
  (KRAS基因特變)
- EGFR gene amplification
  (上皮生長因子受體基因擴大)
- EML4-ALK融合基因

Note: EGFR, KRAS and EML4-ALK usually mutually exclusive

肺癌生物標記的臨床應用

- 指導標靶藥使用
- 監察抗藥性
- 幫助肺癌分期
- 基因藥理學應用

肺癌生物標記的臨床應用

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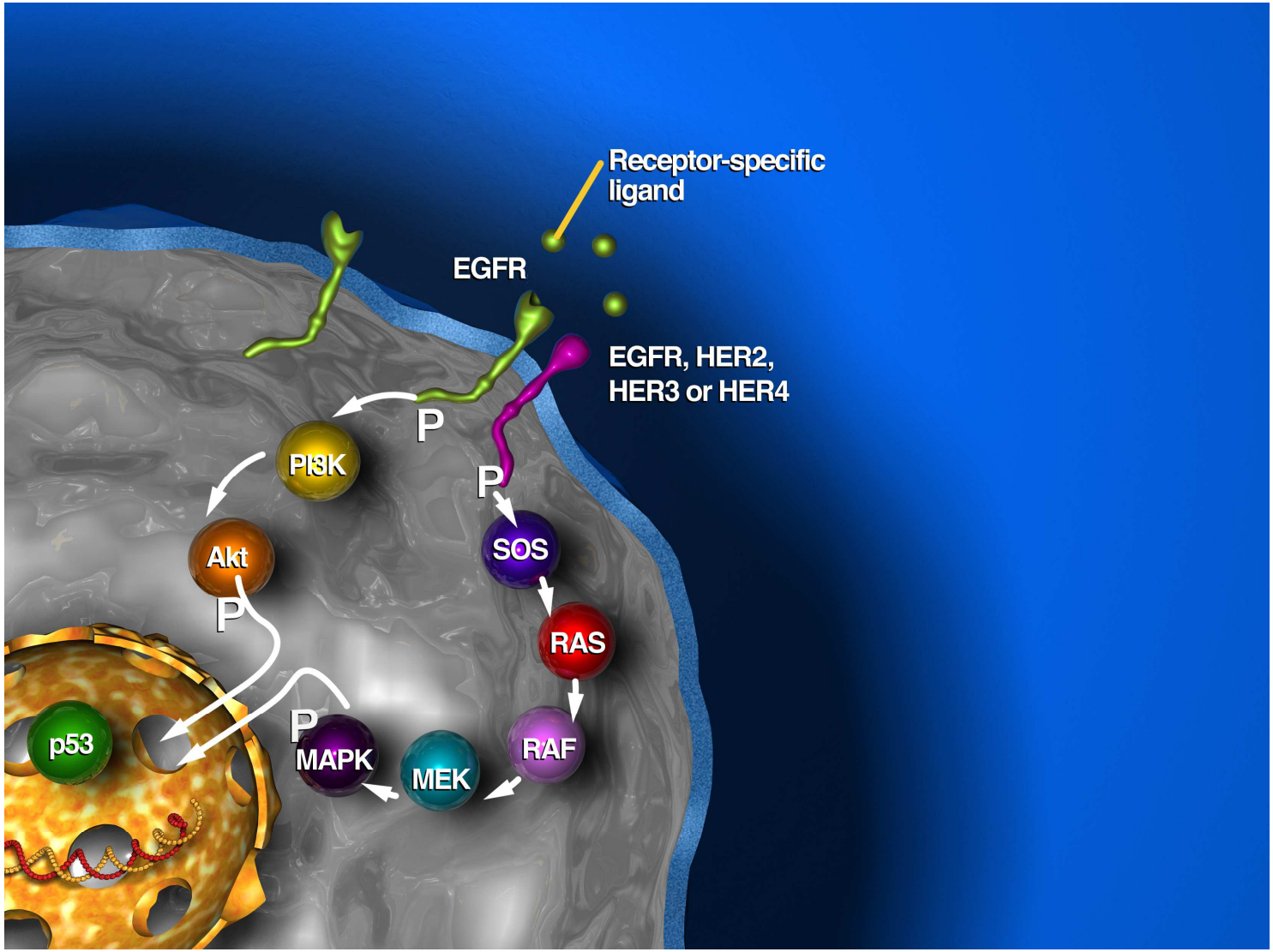
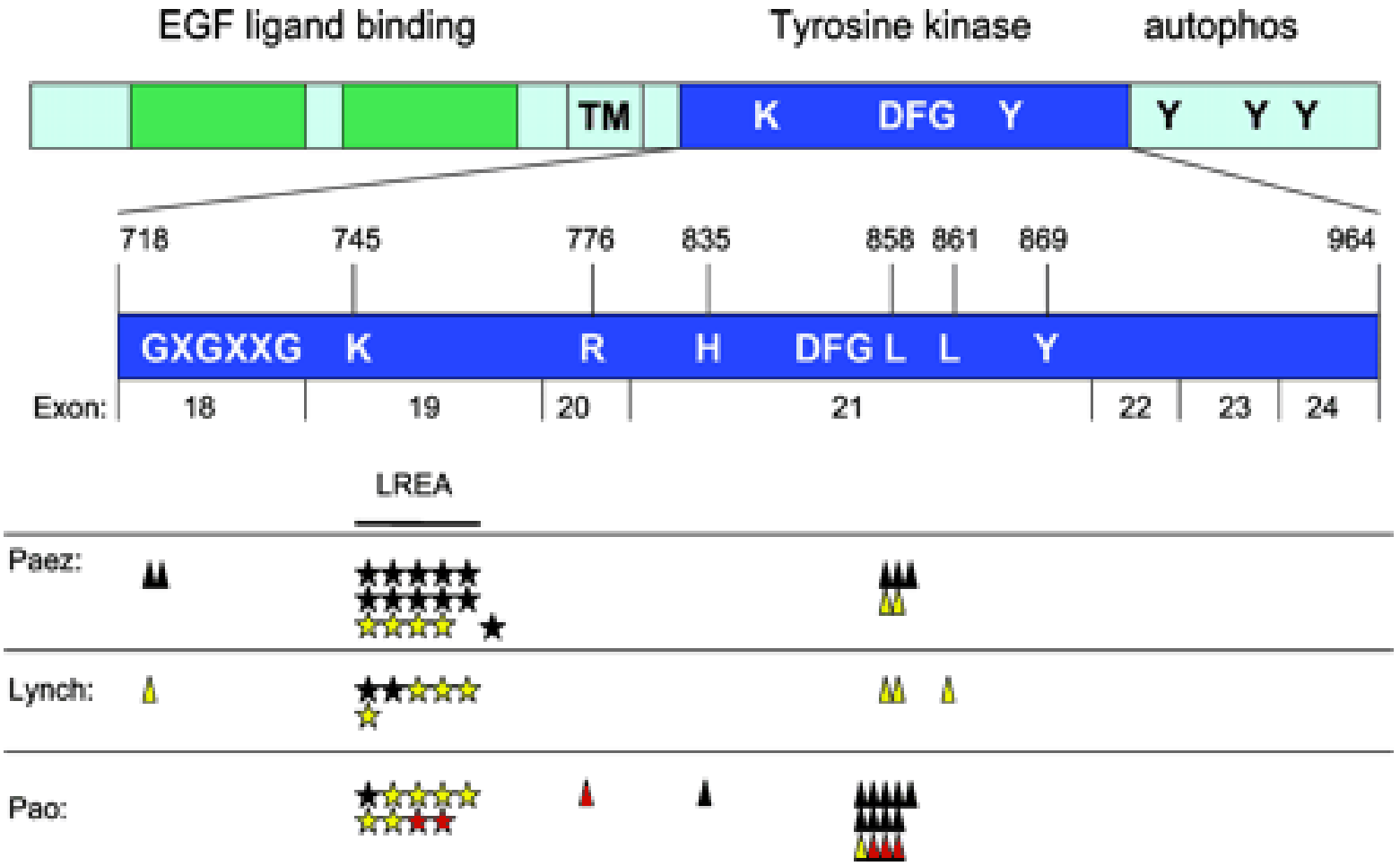
上皮生長因子受體 (EGFR)



Courtesy of Roche Diagnostics

Spectrum of mutations detected in TK domain of EGFR in NSCLC



2009 - 2010

		Cytology specimens	Surgical specimens
Number		**269**	**1141**
Male : Female (ratio)		**148 : 121 (1.2 : 1)**	**607 : 534 (1.13 : 1)**
Median age in years (range)		**66.5 (28 – 92)**	**64 (32 – 97)**
EGFR* gene mutation positive		**106 (39.4%)**	**548 (48.0%)**
	Exon 19 deletion	**42**	**242**
	Exon 21 L858R	**49**	**246**
	Exon 20 insertion/duplication/deletion	**5**	**22**
	Exon 18 G719	**5**	**21**
	Others	**5**	**17**
***EGFR* gene mutation negative**		**161 (59.9%)**	**589 (51.6%)**
	***KRAS* exon 2 gene mutation**	**22**	**88**
Failures		**2**	**4**

上皮生長因子受體基因特變

- Exon 19 deletion and exon 21 L858R
  - Predicts for favourable clinical response to gefitinib and erlotinib

EGFR exon 20 insertion/duplication/deletion mutations

- Associated with primary or *de novo* resistance
  - c.f. secondary or acquired resistance due to T790M
- Positive rate (HKS&H data from 2005 – 2010)
  - 3.6% (29 patients out of 803 tested)
- Treatment outcome
  - Available in 17 patients
  - 8 treated with TKI (gefitinib = 6, erlotinib = 2)
  - Only 1 showed stable disease and alive at 20 months
  - The rest showed progressive disease on treatment from 3 weeks to 4 months

肺癌生物標記

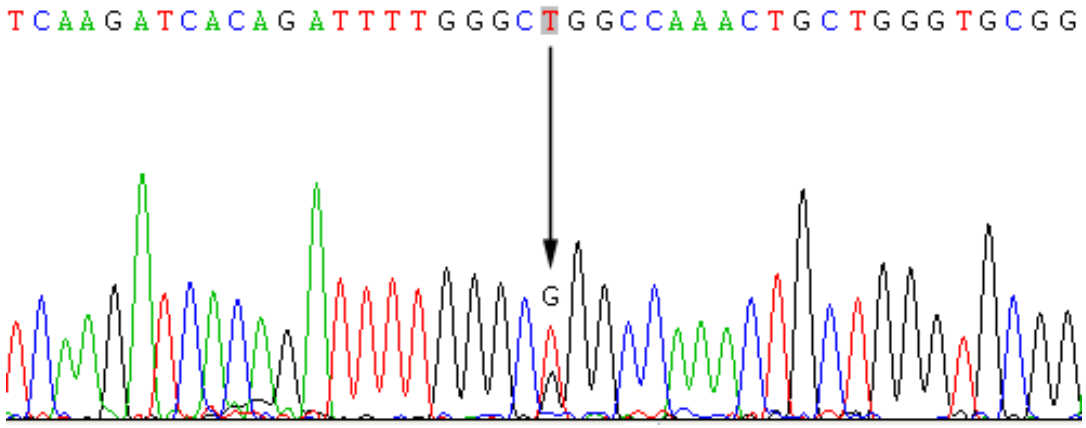
- EGFR gene mutation
  (上皮生長因子受體基因特變)
  Predicts for good response to gefitinib and erlotinib
- KRAS gene mutation
  (KRAS基因特變)
  Predicts for poor response to gefitinib and erlotinib
- EGFR gene amplification
  (上皮生長因子受體基因擴大)
  Salvage therapy by cetuximab
- EML4-ALK融合基因
  Predicts for clinical response to crizotinib

肺癌生物標記的臨床應用

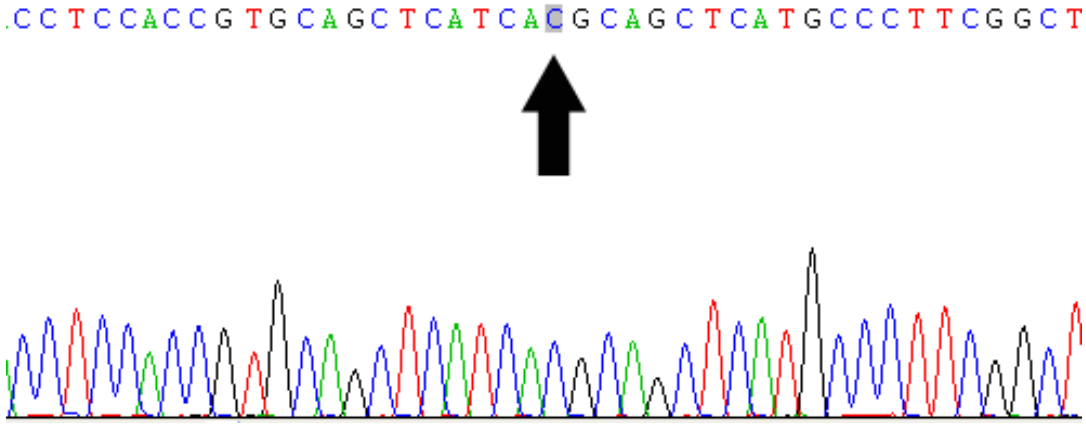
- 指導標靶藥使用
- 監察抗藥性
- 幫助肺癌分期
- 基因藥理學應用

Right lung CT-guided core biopsy

8 November 2010



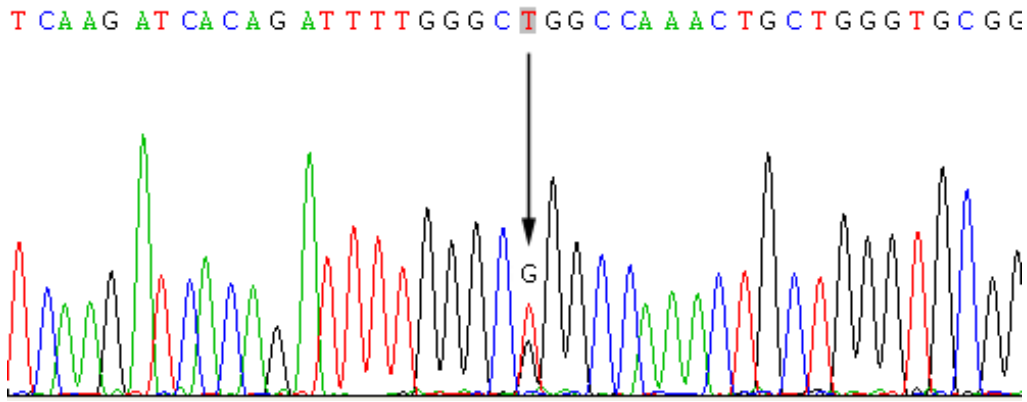
EGFR exon 21 mutation L858R: c.2573 **T**→**G**; p.Leu858Arg (45% mutant)



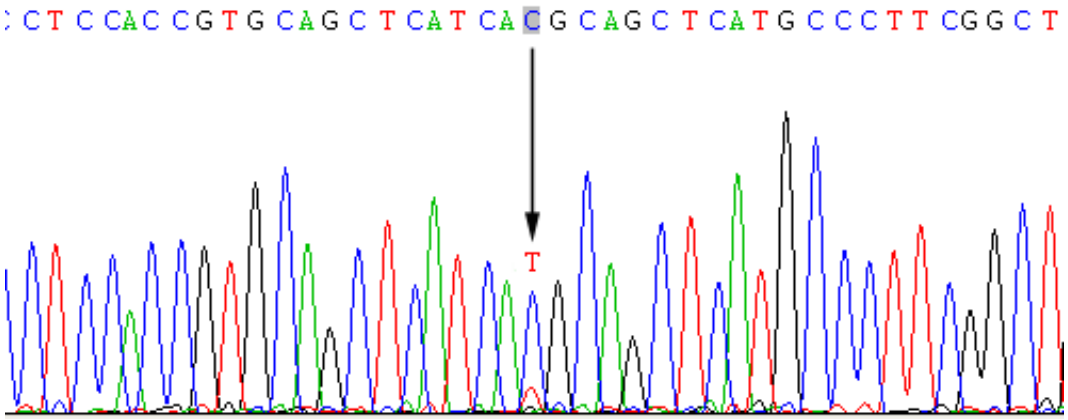
Negative for EGFR exon 20 mutation T790M: (c.2369 **C**→**T**)

Right lung VAT resection

28 July 2011



EGFR exon 21 mutation L858R: c.2573 **T**→**G**; p.Leu858Arg (50% mutant)

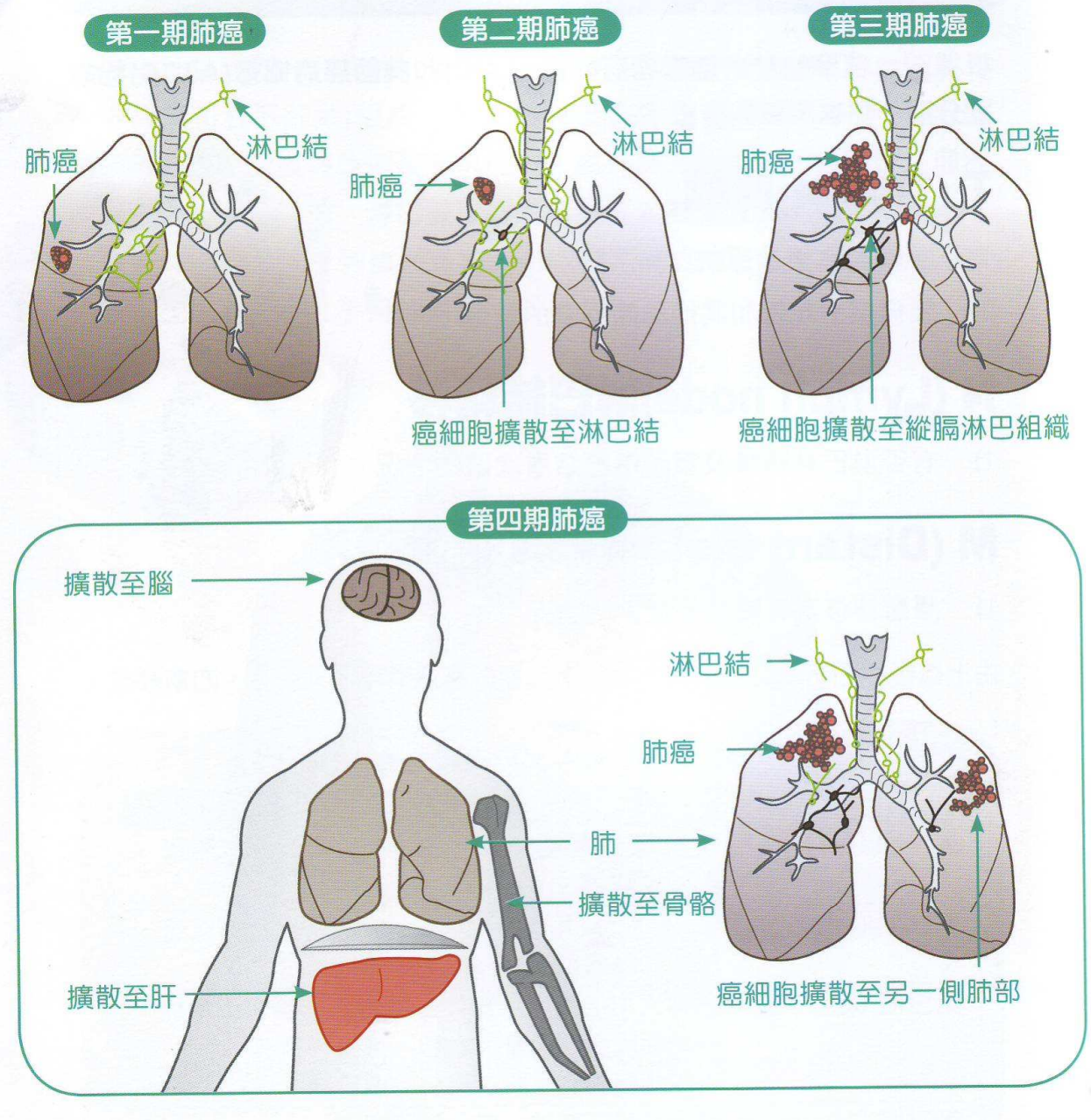


EGFR exon 20 mutation T790M: c.2369 **C**→**T**; p.Thr790Met (15% mutant)

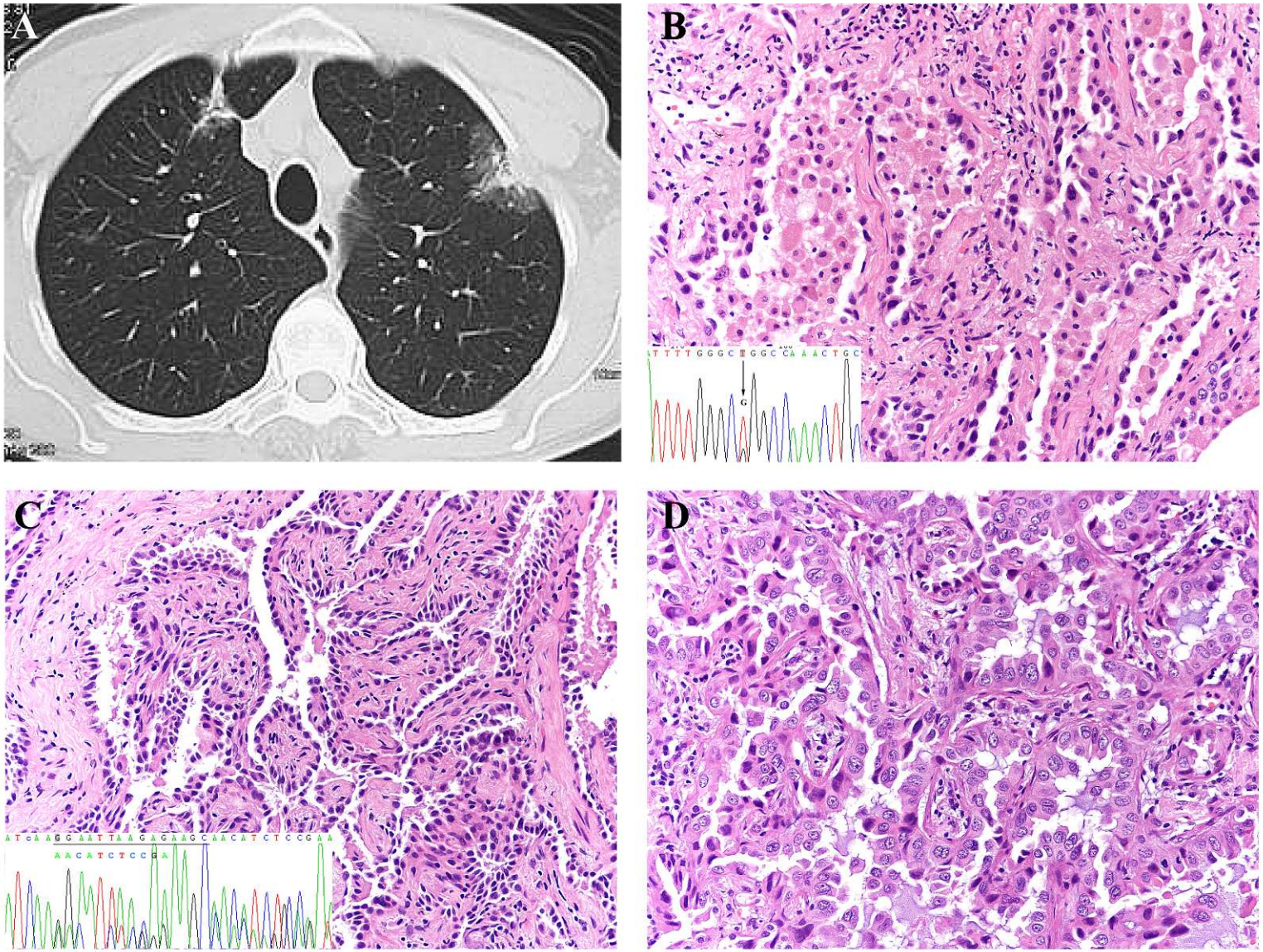
肺癌生物標記的臨床應用

- 指導標靶藥使用
- 監察抗藥性
- 幫助肺癌分期
- 基因藥理學應用

肺癌分期及發病位置


第一期肺癌
肺癌
淋巴結
第二期肺癌
肺癌
淋巴結
癌細胞擴散至淋巴結
第三期肺癌
肺癌
淋巴結
癌細胞擴散至縱膈淋巴組織
第四期肺癌
擴散至腦
擴散至肝
肺
擴散至骨骼
淋巴結
肺癌
癌細胞擴散至另一側肺部

Example 1: Non-small cell lung cancer in a Chinese male, aged 75, ex-smoker



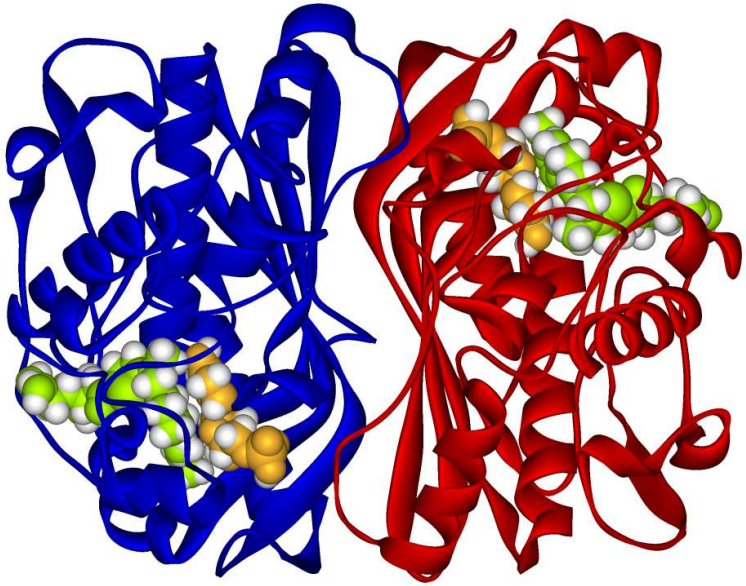
Ma ES *et al*, Ann Thorac Surg 90: e38 – 39, 2010

肺癌生物標記的臨床應用

- 指導標靶藥使用
- 監察抗藥性
- 幫助肺癌分期
- 基因藥理學應用

Thymidylate synthase

- Generates dTMP
- DNA synthesis
- Drug target of:
  - 5-FU
  - Capecitabine
  - Pemetrexed (indirect)



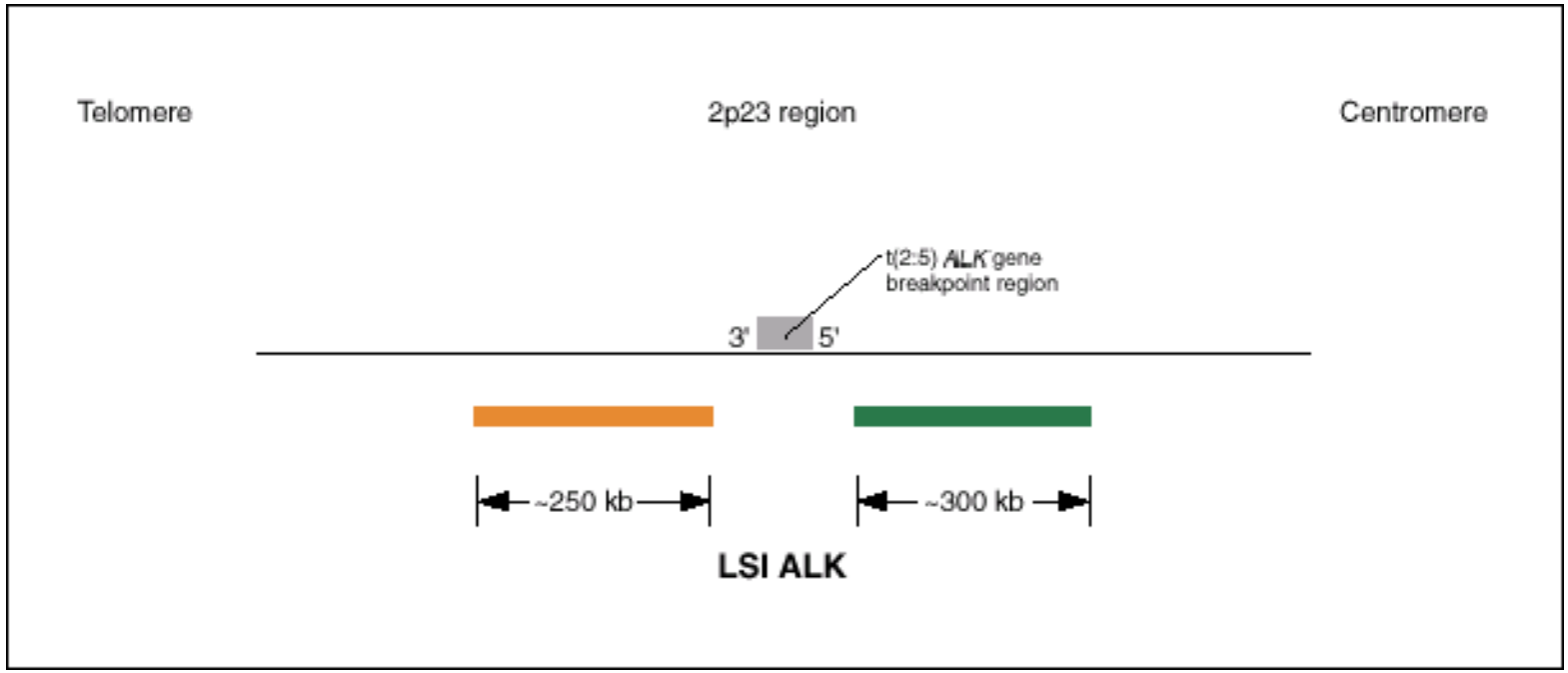
基因測試最新發展

Emerging molecular markers in NSCLC

- EML4-ALK fusion
  - First identified by Japanese group in 2007 (Nature 448: 561 – 566, 2007)
  - Associated with male patients who are young and never/light smokers
  - Mutually exclusive with EGFR and KRAS
  - Not responsive to EGFR TKI
  - Considered for trial of ALK inhibitors

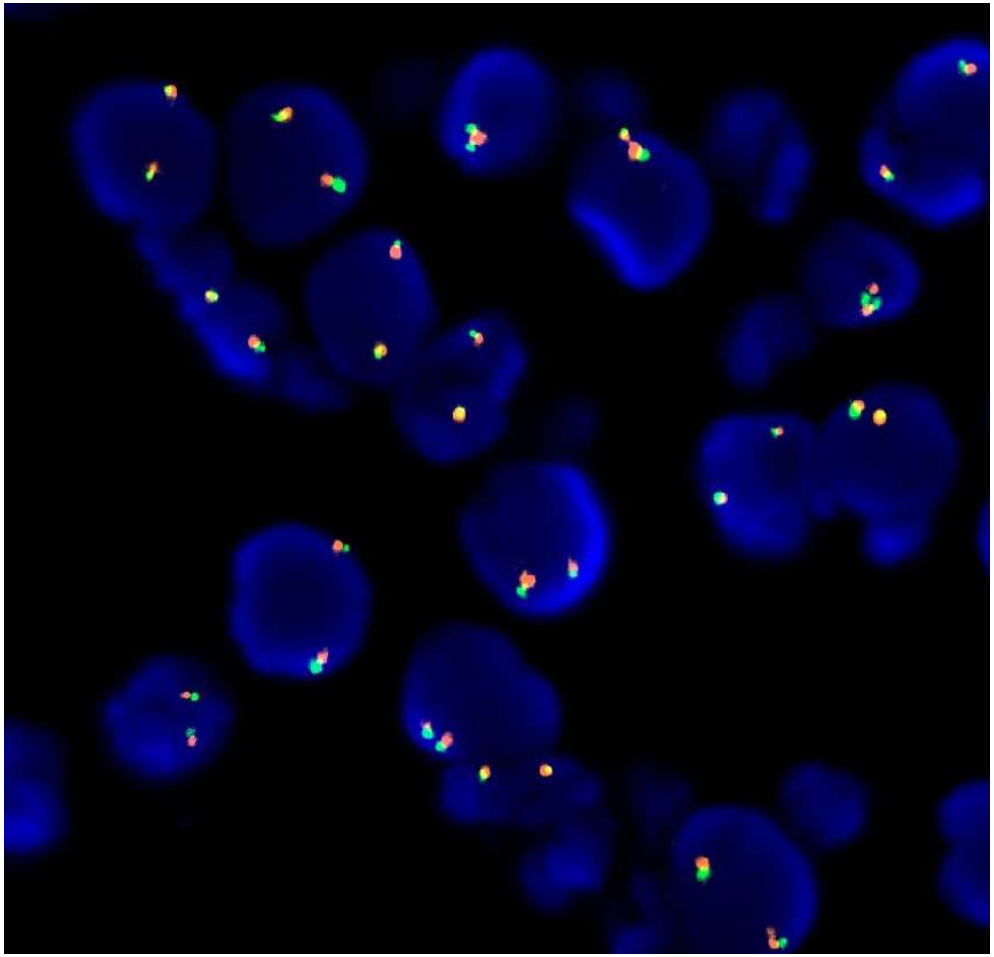
ALK dual-colour split apart FISH probe

Method employed by Shaw AT *et al*, JCO 27: 4247 – 53, 2009

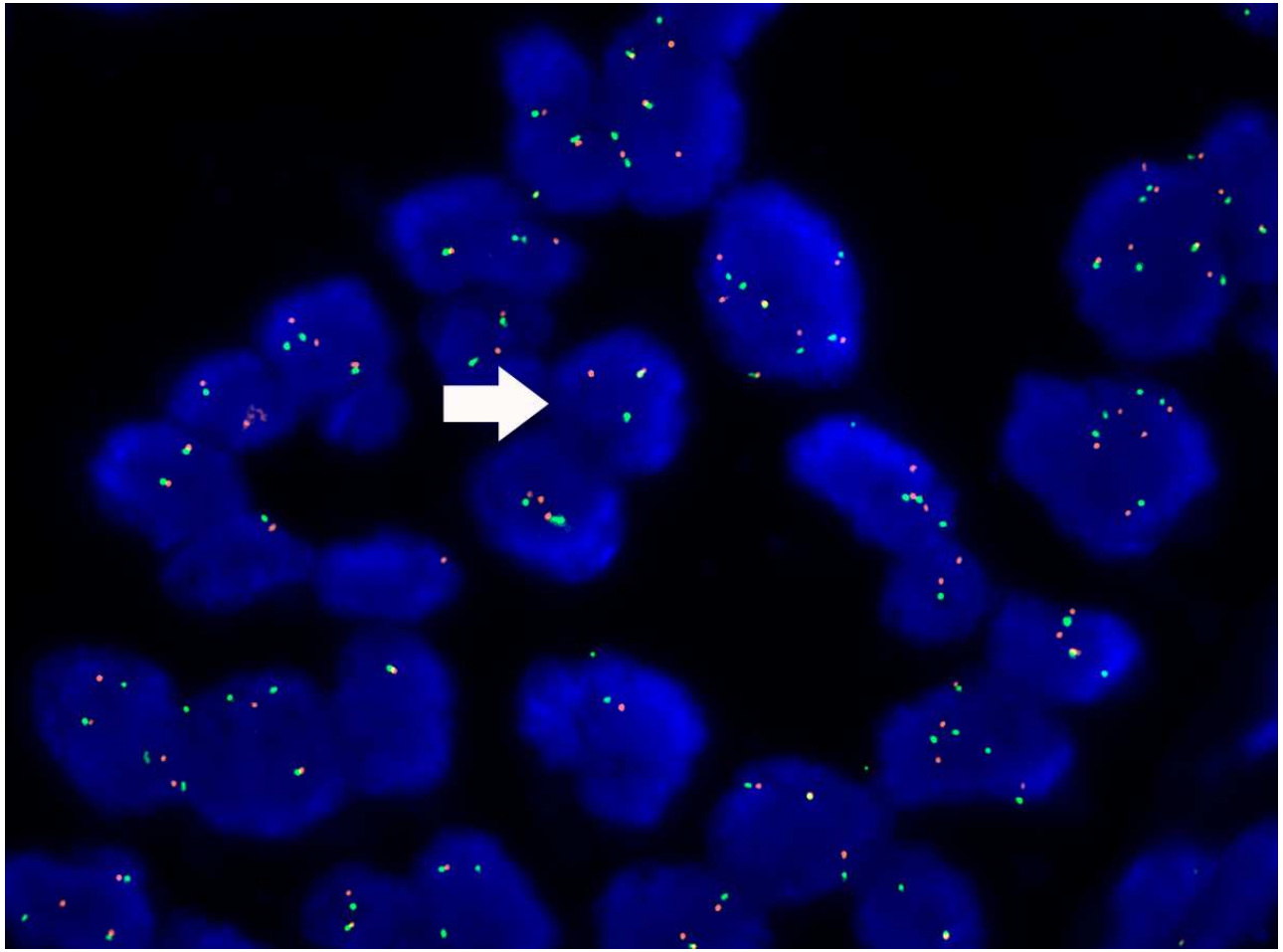


From Abbott Molecular web page

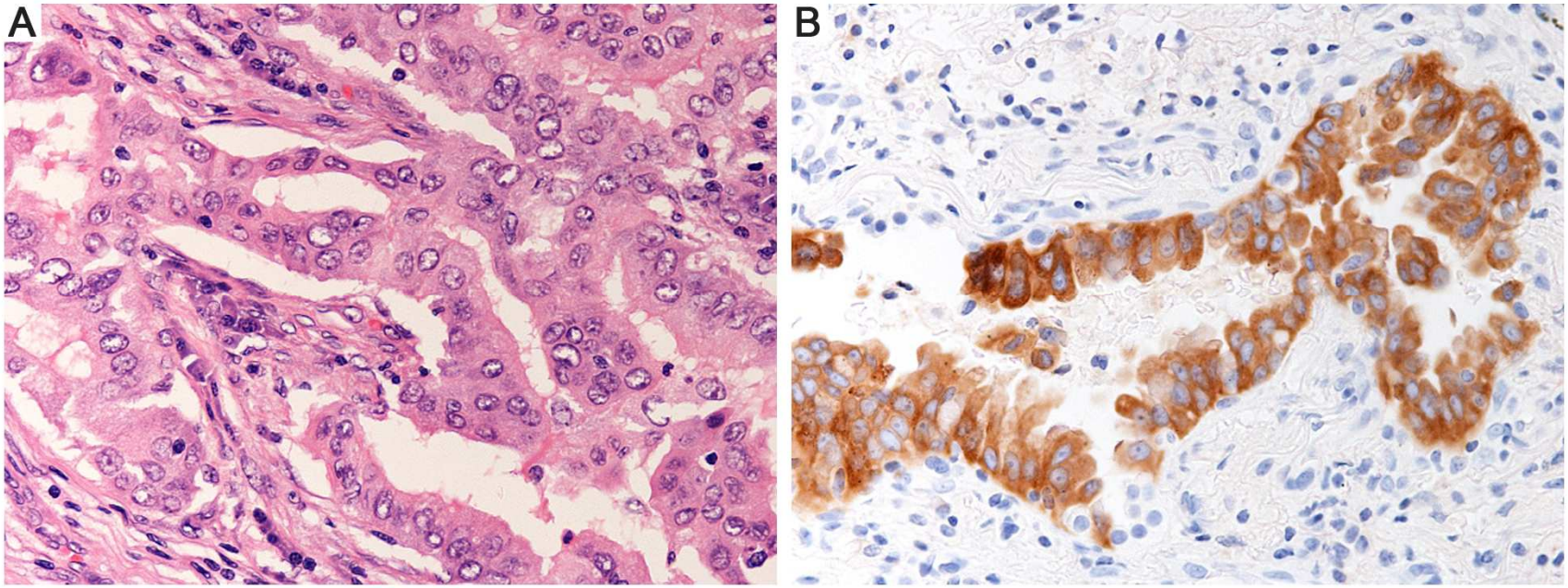
Normal signal pattern



Patient result, F/49, NSCLC



ALK immunohistochemistry



新世代基因排序可帶來什麼突破?

- 特定腫瘤基因突變資料
  Cancer specific gene mutation profiles
- 腫瘤外顯子排序
  Cancer exome sequencing
- 腫瘤的基因轉錄組研究
  Cancer transcriptome study
  - 例如：對病人特定的融合基因進行分子監測
    e.g. molecular monitoring of patient specific fusion transcripts