Liquid biopsy: is tissue still the issue?

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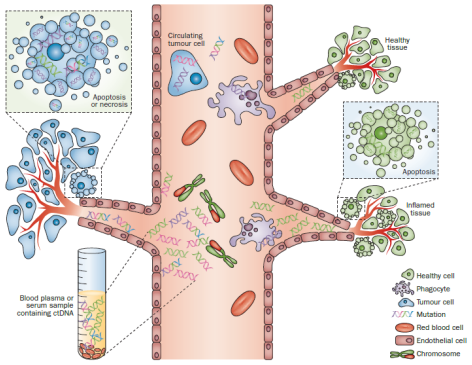
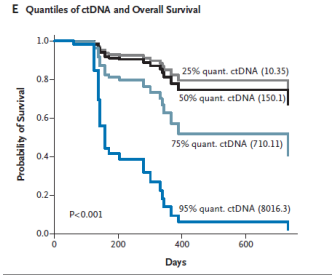
Kennis / Ervaring / Zorg



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Analysis of Circulating Tumor DNA to Monitor Metastatic Breast Cancer



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Clinical Cancer Research

Human Cancer Biology
See related article by Stravegna and Bardelli, p. 2505

Detection of Cancer DNA in Plasma of Patients with Early-Stage Breast Cancer

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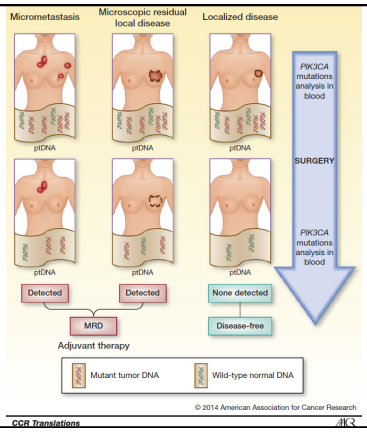

SCIENTIFIC REPORTS

OPEN

SUBJECT AREAS:
DIAGNOSTIC MARKERS
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Diagnostic value of circulating free DNA for the detection of EGFR mutation status in NSCLC: a systematic review and meta-analysis

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In conclusion, in our meta-analysis of 20 studies including >2000 participants, detection EGFR mutations in cfDNA appears to be of adequate diagnostic value in NSCLC. Due to its high specificity and non-invasive nature, cfDNA might be a promising screening test for NSCLC.

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Original Article

Monitoring of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor-Sensitizing and Resistance Mutations in the Plasma DNA of Patients With Advanced Non-Small Cell Lung Cancer During Treatment With Erlotinib

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DOI: 10.1002/cncr.28964

Patients with T790M-mutated tumors have been characterized as a subgroup whose prognosis is relatively favorable with an indolent type of disease progression.[19] This is in agreement with the results from the current study among a limited number of patients, in whom we demonstrated that the median time to disease progression more than doubled compared with the patients without T790M mutations. Most interestingly, when examining the appearance of the T790M mutation in the serial blood samples, we demonstrated that the mutation can be detected in the plasma DNA up to 344 days before disease progression is clinically evident by RECIST criteria (range, 15-344 days before). The ability to detect T790M might be important for the identification of those patients who are eligible for treatment with emerging new third-generation inhibitors that target T790M-mutated EGFR.

DOI: 10.1002/cncr.28964

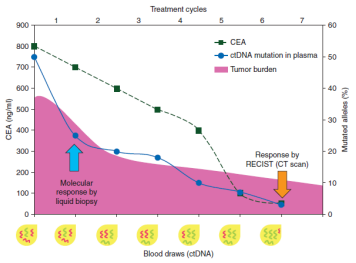


Figure 1. Liquid biopsies to monitor early therapeutic response in a representative CRC patient. Dark grey line (blue online) and black dotted line (green online) indicate mutations in ctDNA and CEA likely levels, respectively, at different time points. Light grey area (pink online) represents tumor load (cm). The dark grey (red online) and the light grey (green online) helices represent mutated and wild-type plasma DNA fragments, respectively. Molecular assessment of response by liquid biopsy anticipates clinical response by RECIST (cycle 6), as emphasized by the drop of the mutant alleles before cycle 2.

Annals of Oncology Advance Access published June 12, 2015

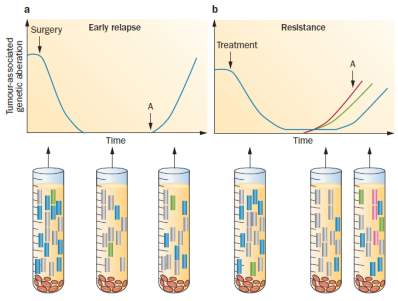


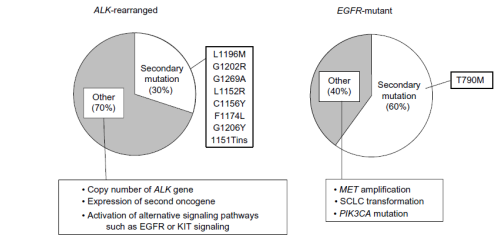
Table 2 | Mutations responsible for acquired resistance to targeted therapies

Gene	Genetic aberration	Tumour type	Acquired drug resistance	Reference*
EGFR	T790M	Advanced NSCLC	Gefitinib Erlotinib	Yun *et al.* (2008)[112] Murtaza *et al.* (2013)[105]
KRAS	Codon 12, 13 and 61	Colorectal cancer	Cetuximab	Diaz *et al.* (2012)‡ Misale *et al.* (2012)‡
KIT	T670I	GIST	Imatinib	Tamborini *et al.* (2006)[135]
PIK3CA	NS	NSCLC	Erlotinib Gefitinib	Sequist *et al.* (2011)[134] Murtaza *et al.* (2013)[105]
ALK	C1156Y L1196M	NSCLC	Crizotinib	Choi *et al.* (2010)[156]
MEK1	C121S	Melanoma	Vemurafenib	Wagle *et al.* (2011)[128]
BRAF	Amplification	Melanoma	Vemurafenib	Shi *et al.* (2012)[123] Gevensleben *et al.* (2013)[66]
NRAS	Q61K	Melanoma	Vemurafenib	Nazarian *et al.* (2010)[124]

*References include a selection of studies in which detection of the genetic alteration has been technically achieved in circulating DNA of patients with cancer or proof-of-principle demonstrated. Abbreviations: GIST, gastrointestinal stromal tumour; NS, not specified; NSCLC, non-small-cell lung cancer.

Crowley, E. *et al. Nat. Rev. Clin. Oncol.* **10**, 472–484 (2013); published online 9 July 2013; doi:10.1038/nrclinonc.2013.110

Iwama et al



TECHNICAL REPORTS

nature medicine

An ultrasensitive method for quantitating circulating tumor DNA with broad patient coverage

Aaron M Newman[1,2,7], Scott V Bratman[1,3,7], Jacqueline To[3], Jacob F Wynne[3], Neville C W Eclov[3], Leslie A Modlin[3], Chih Long Liu[1,2], Joel W Neal[2], Heather A Wakelee[2], Robert E Merritt[4], Joseph B Shrager[4], Billy W Loo Jr[3], Ash A Alizadeh[1,2,5] & Maximilian Diehn[1,3,6]

Early Prediction of Response to Tyrosine Kinase Inhibitors by Quantification of *EGFR* Mutations in Plasma of NSCLC Patients

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(*J Thorac Oncol.* 2015;10: 1437–1443)

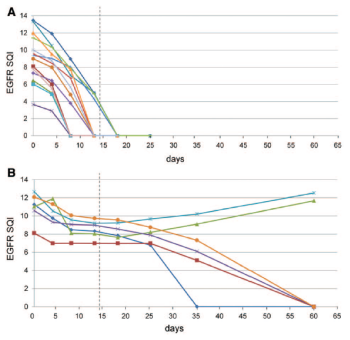

TABLE 2. Correlation between Mutated Plasma *EGFR* Response and Percentage Tumor Shrinkage

Patient No.	Mutated *EGFR* Response at 14 Days	Tumor Shrinkage (%)
1	Rapid	69
2	Rapid	58
3	Rapid	67
4	Rapid	61
5	Rapid	49
6	Rapid	63
7	Rapid	66
8	Rapid	59
9	Rapid	52
10	Rapid	65
11	Rapid	55
12	Rapid	60
13	Rapid	56
14	Rapid	48
15	Slow	10
16	Slow	35
17	Slow	20
18	Slow	12
19	Slow	18
20	Slow	15

(*J Thorac Oncol.* 2015;10: 1437–1443)

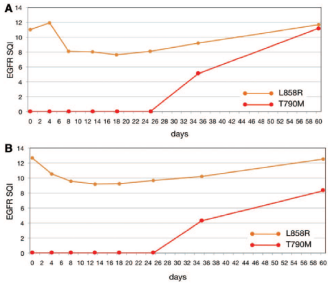

FIGURE 3. Quantification of mutated *EGFR* DNA from plasma of two slow responders with T790M mutation by the PCR test. The figures show the failure to clear the initial *EGFR* mutated DNA (L858R) and the emergence of T790M DNA during week 3 after initiating *EGFR* TKI treatment. PCR, polymerase chain reaction; SQI, semi-quantitative index; TKI, tyrosine kinase inhibitor.

an early increase in the circulating levels of the T790M mutation was observed. No T790M mutations were seen in serial plasma samples of the rapid responders. We therefore speculate that slow responders are more prone to develop early resistance. However, further clinical validation is required to assess the long-term impact of TKI treatment on rapid versus slow responders relative to progression-free and overall survival.