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A non-invasive system for monitoring resistance to EGFR tyrosine kinase inhibitors with plasma DNA

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EGFR tyrosine kinase inhibitors (EGFR-TKIs) have great response to lung adenocarinoma with EGFR activating mutations. However, acquired resistance eventually developed, and the half of these patients has the gatekeeper T790M mutation of EGFR in lung cancer tissue. A non-invasive mutation detection system is desired considering the difficulty in obtaining tissue specimens during disease progression—the majority of lung cancer recurrences occur in distant sites. We report a novel non-invasive monitoring system, MBP-QP (mutation-biased PCR and quenching probe) method, to detect the mutation using plasma DNA. The MBP-QP method combines mutated-biased PCR and genotyping based on analysis of the melting curve of the probe DNA binding the target mutated site using a fluorescence quenching probe system. The detection limit was two copies of control plasmid, and 0.2 ng of genomic DNA isolated from a lung caner cell line harboring T790M. 0.3 % mutant plasmid could be detected in the mixture of plasmids inserted with EGFR exon 20 with or without T790M. With this method, T790M mutations were detected in plasma DNA of 50% of patients who acquired resistance, but not in primary EGFR-TKI non-responders, patients responding to treatment, or patients not treated with EGFR-TKI, which is consistent with the clinical course. The non-invasive MBP-QP method enabled us to monitor T790M repeatedly and will be useful for determining appropriate lung cancer treatment strategies in practice.