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Title: The “COLD-PCR-approach” for early and cost-effective detection of tyrosine kinase inhibitor resistance

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Body: Background: Activating Epidermal Growth Factor Receptor (EGFR) gene mutations can be successfully treated by EGFR Tyrosine Kinase Inhibitors (EGFR-TKIs) but nearly 50% of all patients’ exhibit progression of the disease until treatment. It is proposed that this is mostly caused by therapy-resistant tumor clones harboring a T790M mutation. Until now no cost-effective routine-diagnostic method for EGFR-resistance mutation status analysis is available leaving long-time response to TKI treatment to chance. Unambiguous identification of T790M EGFR mutations is mandatory to optimize initial treatment strategies. Material and Methods: Artificial EGFR T790M mutations and human wild type gDNA were prepared in several dilution series. Preferential amplification using Co-amplification at Lower Denaturation-temperature-PCR (COLD-PCR) of the mutant sequence and subsequent HybProbe melting curve detection or pyrosequencing were performed in comparison to normal processing. Results: COLD-PCR based amplification allowed the detection of 0.125% T790M mutant DNA in a background of wild type DNA in comparison to 5% while normal processing. These results were reproducible. Conclusions: COLD-PCR is a powerful and cost-effective tool for routine diagnostic to detect underrepresented tumor clones in clinical samples. A diagnostic tool for unambiguous identification of T790M-mutated minor tumor clones is now available enabling optimized therapy.