Liquid biopsy analysis of advanced cancer patients – a real-life perspective of actionable variants

Abstract Submitter: Thomas Kessler, Germany*

Co-Authors: Simon von Ameln, Julia Berghaus, Andreas Risch, Moritz Fujera, Verena Steinke-Lange, Wilfried Stücker, Elke Holinski-Feder, Barbara Klink, Ariane Hallermayr

*MGZ – Medizinisch Genetisches Zentrum

Abstract

Background: Detection of minimal residual disease (MRD) or potentially actionable variants by circulating tumor DNA (ctDNA) analysis of cancer patients requires highly sensitive methods to detect minimal amounts of ctDNA. Routine duplex sequencing enables the detection of low variant allele frequency (VAF) variants in ctDNA, facilitating the identification of therapeutic options for patients (Hallermayr et al., 2023). Yet, few studies addressed the diagnostic yield that can be achieved through liquid biopsy analyses in routine clinical practice.

Objective: We identify the diagnostic yield of routine liquid biopsy ctDNA analysis approaches at two independent laboratories in Germany. We highlight the importance of low detection limits for variant detection in a pooled cohort of cancer patients.

Method: ctDNA variant calls were pooled for 184 breast cancer patients (145 site 1, 39 Site 2) and subjected to retrospective bioinformatic analysis of actionable variants in ESR1, PTEN, PIK3CA and AKT1 known from literature and ClinVar.

Results: We find that ~35% of actionable variants are detected in a low-frequency window of 0.1-0.5% VAF. By simulating theoretical assay cutoffs of 0.1%, 0.25% and 0.5% VAF, we show that ~60.9% of patients would benefit from an assay that detects variants from 0.1% VAF compared to 44% of patients at a cutoff of 0.5%. At 0.1% VAF, ~21.1% of actionable variants in PIK3CA locate outside of PIK3CA-hotspot exons and ~18.6% of actionable variants in ESR1 locate outside of hotspot codons defined for single ESR1-ctDNA assays, reimbursed by the health system in Germany. Thereby, we highlight the benefits of broad- and high sensitivity ctDNA analyses for the identification of therapeutic options in the routine diagnostic setting.

Conclusion: Actionable variants found in ctDNA of breast cancer patients are overrepresented in the low VAF range (down to 0.1%), underscoring the benefit of high-sensitivity duplex sequencing methods for comprehensive variant detection in routine diagnostics. A low ctDNA fraction in patients with low tumor burden make high sensitivity methods, such as targeted duplex sequencing, a prerequisite for reliable variant identification to enable further therapy options. Improving sensitivities and precision of duplex sequencing will enable the detection of relevant variants at even lower VAFs.

Do you have any conflicts of interest?

No, I do not have a conflict of interest.