Harmonized liquid biopsy precision medicine platform for molecular tumor boards (hilib-mtb)

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Abstract

Background: Next-generation sequencing (NGS) of circulating tumor DNA (ctDNA) is a promising, minimally invasive method for genomic tumor profiling. It offers a comprehensive view of tumor heterogeneity and enables longitudinal monitoring. However, its integration into routine clinical decision-making, particularly within Molecular Tumor Boards (MTBs), is still pending.

Objective: The HiLiB-MTB project seeks to establish and validate a standardized liquid biopsy (LB) platform for MTBs across Germany that will be non-inferior to tissue biopsy (TB) sequencing in terms of recall rate of variants and recommendation rate, while improving turnaround time (TAT).

Methods: We have developed customized targeted NGS panels and bioinformatic workflows that will be harmonized within HiLiB. We here report the validation of a pilot LB NGS panel to detect cancer-related mutations across the 100 most relevant cancer genes. Raw sequencing output was analyzed employing an in-house workflow including demultiplexing and assembly-based realignment followed by variant calling. In a retrospective study currently being launched, we aim to investigate whether NGS of ctDNA improves TAT compared to TB sequencing while not compromising recall rates of variants. Currently, we are expanding the panel to 300 cancer genes as well as tumor mutational burden (TMB), microsatellite instability (MSI) and homologous recombination deficiency (HRD).

Results: Validation of the 100 gene panel using 78 retrospective cross-entity samples showed strong concordance between ctDNA and tissue genotyping ($R^2 = 0.975$), reliably detecting low-frequency mutations. Longitudinal LB analysis successfully tracked tumor evolution. First results indicate that integrating LB into MTBs is feasible with the potential to significantly reduce TAT, facilitating faster clinical decision-making. We aim to harmonize panel design and bioinformatic workflows across HiLiB sites, perform a retrospective validation study and launch a prospective multicenter trial comparing LB to TB sequencing across 11 MTBs within Germany. Key endpoints include TAT, recommendation rate and concordance of treatment recommendations.

Conclusion: HiLiB-MTB aims to establish a standardized LB MTB platform, enabling baseline genotyping, real-time monitoring of cancer response and detection of treatment resistance. By complementing the limitations of TB genotyping – such as sample availability, long processing times, and incomplete representation of tumor heterogeneity – our initiative will advance precision oncology.

Do you have any conflicts of interest?

No, I do not have a conflict of interest.