recurrence surveillance is likely as part of an integrated, verifiable decision-support framework that combines staging, treatment history, imaging, and other biomarkers (Kasi et al., 2022; Kobayashi et al., 2025).

4 Clinical Misunderstandings and Challenges in the Practical Application of ctDNA-MRD

4.1 Biological differences and false-negative results caused by low ctDNA release

In clinical practice, many people mistakenly believe that a negative postoperative ctDNA result indicates the absence of residual lesions in the body. However, this is not the case. ctDNA-MRD testing relies on capturing the DNA released by residual tumor clones to predict the risk of recurrence. However, this core biological assumption is not applicable in all situations. Especially in early-stage tumors or after radical treatment, the ctDNA levels in the body are already very low. Tumors that are small in size, grow slowly, have a mild degree of necrosis, or are located in areas with limited release capabilities (such as the central nervous system or abdominal cavity) are difficult to release sufficient DNA into the bloodstream. Even if there are residual lesions, the signals may not be detectable (Pellini and Chaudhuri, 2022; Zhong et al., 2023).

Although the specificity of ctDNA-MRD is usually quite high, its sensitivity is only 40% to 70%, and this problem becomes more obvious when conducting a single test (Pellini and Chaudhuri, 2022; Sato, 2025). In my research, I found that continuous multiple samplings can improve the accuracy of the detection. Additionally, the heterogeneity of tumors and clonal evolution make the interpretation of results more complex-those residual subclonal lesions that were not tracked or new dominant clones that emerged may not be captured by the preset detection panel (Semencovich et al., 2023). Moreover, postoperative inflammation, tissue repair, and adjuvant therapy can temporarily change the background environment of cfDNA, so the negative results in the early postoperative period are not reliable and cannot be regarded as evidence of complete cfDNA clearance (Faulkner et al., 2022; Zhong et al., 2023). Therefore, for low-release tumors, a negative ctDNA result can only be understood as "not detected", not equivalent to "absent", and must be combined with pathological risk factors and imaging follow-up for comprehensive judgment (Zhu et al., 2023; Wang et al., 2025).

4.2 Technical noise, chip interference and platform differences

Apart from the biological factors mentioned earlier, technical issues also introduce considerable uncertainty to the ctDNA-MRD detection. The core of MRD detection is to capture extremely subtle frequency changes, which makes the detection results highly susceptible to various factors, such as errors in polymerase chain reaction products, sequencing errors, oxidative damage, and various interferences during the in vitro processing. Even with the use of UMI tagging, dual-end sequencing, and computational noise reduction techniques, background errors cannot be completely eliminated. Once the true variant signal approaches the detection threshold, the risks of false negatives and false positives will significantly increase (Semenkovich et al., 2023).

Among them, the ambiguous potential clonal hematopoiesis (CHIP) is a crucial interfering factor. Genes such as *DNMT3A, TET2, ASXL1*, and *TP53*, which are age-related mutations, often appear in plasma cfDNA and can overlap with the tumor mutation profile. Without paired leukocyte sequencing or without a strict screening process, these mutations may be misidentified as ctDNA from tumor sources, thereby leading to false positive results (Kasi et al., 2022; Sato, 2025). In addition, the differences between different detection platforms are also significant, such as target design, library preparation, cfDNA input volume, sequencing depth, error models, and positive thresholds. These differences limit the comparability of the detection results. Low VAF variations may also lead to different results from different platforms, causing difficulties in individual result interpretation and cross-study integration (Figure 2). Therefore, standardized operating procedures and cross-platform validation are still necessary to improve the reliability of the detection (Pellini and Chaudhuri, 2022; Zhong et al., 2023; Hoang et al., 2025).

4.3 Risks of over-reliance on ctDNA-MRD in clinical decision-making

As the prognostic value of ctDNA-MRD has been increasingly recognized by more and more people, in clinical decision-making, sometimes its role is overemphasized. However, from the perspective of practical application, due to its limited sensitivity, a negative ctDNA result does not mean that the patient has completely recovered. I have found that some patients who later relapsed had negative ctDNA test results at key follow-up time points. If