processing steps in the early stage have a particularly significant impact on the accuracy of the final detection results. For instance, the type of collection tube, centrifugation conditions, the time of plasma separation, the sample storage method, and the sample volume all can change the background level of cfDNA. If the operation is improper, it may lead to white blood cell lysis, increase genomic DNA contamination, reduce the proportion of ctDNA, and thereby increase the risk of false negatives (Chen and Zhou, 2023). Therefore, using dedicated cfDNA collection tubes and strictly controlling the processing time window are the key to ensuring the consistency of the detection results (Quinn et al., 2025).

In addition, the performance of the detection is not only related to the sequencing depth, but also influenced by error suppression techniques (such as UMI, double-strand sequencing, algorithm noise reduction), the number of target sites, and the multi-signal integration method. To accurately identify ultra-low-frequency genetic changes, systematic errors must be controlled within the order of 10^{-5}. Currently, different detection platforms have differences in positive thresholds and interpretation rules, which also limits the comparability of the detection results of each platform. At the same time, biological factors such as clonal hematopoiesis may lead to false positive results, which requires a comprehensive judgment combined with paired controls, longitudinal follow-up, as well as imaging and clinical information (Semenkovich et al., 2023).

3 Clinical Application of Blood-Free DNA (ctDNA)-Minimal Residual Disease (MRD) in Early Solid Tumors

3.1 Detection of postoperative minimal residual disease and risk stratification of recurrence

Even if radical resection surgery is performed on patients with early-stage solid tumors, the risk of recurrence cannot be completely eliminated. In my research, I found that some early-stage patients did not detect any abnormalities during postoperative imaging examinations, but their conditions still progressed during the follow-up period. This situation occurs mostly because there are still molecular-level lesions remaining in the body. Relevant studies have confirmed that during the "microscopic residual disease window period" of approximately 2 to 10 weeks after surgery, if ctDNA is positive during the test, it has a strong correlation with subsequent recurrence, and it usually occurs much earlier than the changes shown on imaging (Elliott et al., 2025).

Specifically for different types of tumors, for instance localized lung cancer, using deep sequencing based on tissue information can detect recurrence signs earlier than imaging examinations; while for resectable colorectal cancer, the status of ctDNA after surgery, in predicting the risk of recurrence, is even better than the traditional pathological staging, which also makes ctDNA-MRD an important molecular stratification tool (Chidharla et al., 2023). Unlike the static TNM staging system, ctDNA can reflect the dynamic changes of residual tumor clones. Large-scale prospective studies like GALAXY have confirmed that early positive ctDNA after surgery can independently predict disease-free survival and overall survival (Nakamura et al., 2024). However, it should be noted that the interpretation of these results requires considering signal intensity, duration, and clinical reality, and a negative ctDNA result does not mean there is absolutely no recurrence risk.

3.2 Application of ctDNA-MRD in treatment guidance and efficacy monitoring

Traditional adjuvant treatments are usually stratified based on population risk, which can easily lead to over-treatment or under-treatment issues. However, ctDNA-MRD can precisely provide a basis for individualized treatment decisions: if ctDNA remains positive, it indicates that there are still active tumor lesions in the body, and it may be necessary to strengthen the treatment or extend the treatment period; if it remains negative, unnecessary treatment interventions can be reduced, avoiding patients from bearing excessive treatment burdens (Semenkovich et al., 2023; Abidoye et al., 2025).

In patients with non-small cell lung cancer and colorectal cancer, patients with positive MRD showed more significant benefits from adjuvant therapy, while patients with negative MRD benefited less from chemotherapy. Currently, there are relevant randomized studies exploring strategies to adjust treatment intensity based on ctDNA test results (Vellanki et al., 2023). A longitudinal analysis of the GALAXY cohort also further demonstrated that continuous ctDNA clearance was associated with improved disease-free survival (DFS) and overall survival (OS), and a recurrence risk increase was indicated when ctDNA turned positive again (Nakamura et al., 2024).