Additionally, the dynamic changes of ctDNA have been regarded as potential alternative endpoints and trial screening tools for research (Semenkovich et al., 2023; Vellanki et al., 2023; Kobayashi et al., 2025). However, there are differences among different tumor types and different detection platforms. Without evidence from randomized controlled studies, relying solely on ctDNA results to adjust treatment still carries certain risks (Figure 1).

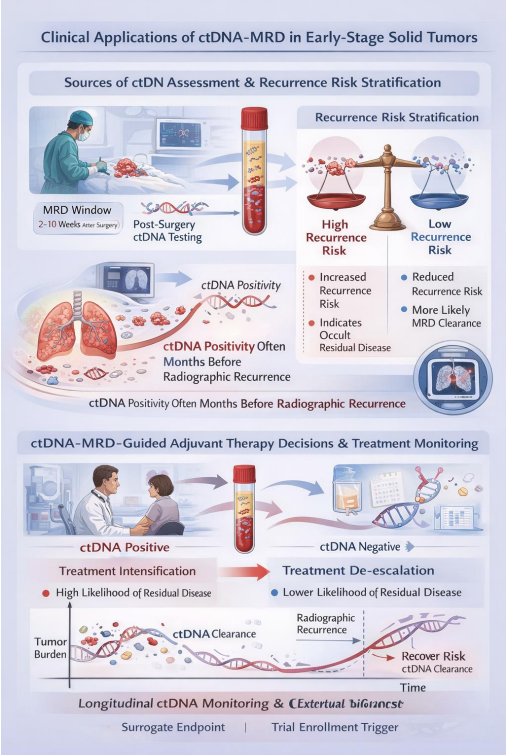

Figure 1 Role of ctDNA-MRD in Postoperative Recurrence Risk Assessment and Treatment Monitoring

3.3 Clinical significance of ctDNA dynamics for early recurrence prediction

One of the most compelling clinical advantages of ctDNA-MRD lies in its ability to predict recurrence ahead of conventional methods. Longitudinal studies across multiple cancers consistently demonstrate that conversion from ctDNA-negative to ctDNA-positive status, or persistent positivity during follow-up, predicts clinical recurrence with high sensitivity and specificity and typically precedes radiographic detection by several months, creating a "molecular recurrence window". In colorectal cancer, dynamic ctDNA monitoring detects recurrence earlier than carcinoembryonic antigen (CEA) testing and routine imaging, with lead times commonly ranging from 2 to 11.5 months; systematic reviews further show that patients who convert to or remain ctDNA-positive after surgery or adjuvant therapy have significantly worse recurrence-free or disease-free survival than those who remain ctDNA-negative (Chidharla et al., 2023; Negro et al., 2025). Similar findings have been reported in localized NSCLC, where persistent ctDNA positivity during surveillance precedes imaging-confirmed relapse by months and can be incorporated into time-to-event models for individualized risk estimation.

Beyond binary positivity, ctDNA trajectories convey additional clinically relevant information. Rates of increase, changes in mutational profiles, and the emergence of new variants can reflect clonal evolution and biological progression, and serial monitoring is better suited than single measurements to distinguish transient fluctuations from true relapse trends. These dynamic features provide a practical framework for integrating ctDNA with imaging over time—for example, using ctDNA conversion to trigger intensified imaging or biopsy, or reducing the posterior probability of "true recurrence" when imaging is equivocal but ctDNA remains persistently negative. Importantly, however, earlier detection of molecular recurrence does not automatically translate into survival benefit. Definitive evidence is still lacking to show that ctDNA-triggered early intervention universally improves outcomes, with unresolved questions regarding molecular recurrence thresholds, optimal timing of intervention, and the risk of overtreatment (Comino-Méndez et al., 2025). Consequently, the optimal role of ctDNA-MRD in