et al., 2023). Neither approach is sufficient alone. ctDNA lacks spatial resolution, and imaging may miss small or diffuse lesions. For this reason, several studies advocate placing ctDNA results alongside imaging and conventional markers within the same follow-up pathway, using molecular changes to prompt more focused radiological evaluation and guide intervention (Bent et al., 2022; Chidharla et al., 2023; Pantel and Alix-Panabières, 2024).

5.2 Managing discordant results

In real-world follow-up, discrepancies between ctDNA and imaging are not unusual. Rather than treating one test as definitive, it is more reasonable to interpret both within a structured clinical context. When both ctDNA and imaging are positive, the likelihood of residual or recurrent disease is high, and timely restaging with multidisciplinary discussion is warranted (Wang et al., 2025).

Positive imaging but negative ctDNA may be related to low release or detection sensitivity, or it could be caused by inflammation or post-operative changes. Repeated imaging, tissue biopsy, or dynamic ctDNA monitoring can help clarify (Semenkovich et al., 2023). On the contrary, a single positive ctDNA result often indicates molecular recurrence below the resolution of imaging (Zheng et al., 2024), and the recurrence risk has significantly increased before imaging diagnosis (Zhu et al., 2023; Azzi et al., 2025; Negro et al., 2025). Enhanced imaging or shortening the follow-up interval may detect hidden lesions (Dasari et al., 2023; Maddalena et al., 2024). At present, a more reliable approach is to repeat confirmation and dynamic follow-up rather than immediately upgrading treatment (Pantel and Alix-Panabières, 2024).

5.3 Integration of functional imaging and artificial intelligence

Functional imaging techniques such as PET-CT, DWI-MRI and dynamic enhancement technology can capture metabolic or perfusion abnormalities before structural changes occur, thereby shortening the time gap between molecular and imaging recurrence (Semenkovich et al., 2023; Pantel and Alix-Panabières, 2024). In cases where ctDNA is positive but conventional imaging is negative, functional imaging is helpful for localization; if ctDNA and functional indicators decrease simultaneously, it can also support the judgment of therapeutic efficacy (Emiloju et al., 2024).

Radiomics and artificial intelligence enhance the ability of individualized recurrence prediction by integrating imaging features, ctDNA dynamics, and clinical variables (Semenkovich et al., 2023; Hoang et al., 2025). Multimodal omics models that integrate ctDNA, protein markers, and imaging information show certain predictive gains (Sabit et al., 2025). However, inconsistent imaging collection standards, differences in ctDNA platforms, and the lack of prospective validation still limit its widespread application. To achieve the integrated application of multimodal MRD, a unified process, standardized time points, and clear clinical endpoints are required (Pantel and Alix-Panabières, 2024; Wang et al., 2025).

6 Concluding Remarks

Over the years, the emergence of ctDNA-MRD has led us to re-evaluate how "residual lesions" should be assessed. In the past, more reliance was placed on imaging, and only visible lesions were considered valid; now, there is an additional molecular perspective. Especially during the uncertain period following radical treatment for early solid tumors, ctDNA can capture extremely low levels of tumor molecular traces throughout the body, which are difficult to cover by imaging and traditional pathological indicators. A large number of prospective studies and systematic reviews have repeatedly proven that if ctDNA remains positive after treatment, the risk of recurrence and death will significantly increase. In cancers such as colorectal cancer and non-small cell lung cancer, the performance of ctDNA-MRD in risk classification often outperforms traditional staging and pathological high-risk factors, and thus has gradually become an important reference in postoperative stratification, adjuvant treatment decision-making, and follow-up optimization.

However, when it comes to actual clinical application, problems arise. The sensitivity of a single test remains limited in MRD or early disease scenarios. Although longitudinal monitoring can increase the detection rate, false negatives still exist. Low tumor release, limited lesions confined to specific anatomical regions, inappropriate