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Cancer Drug Resistance

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Circulating tumor DNA in gynecologic cancers: linking minimal residual disease to therapy resistance

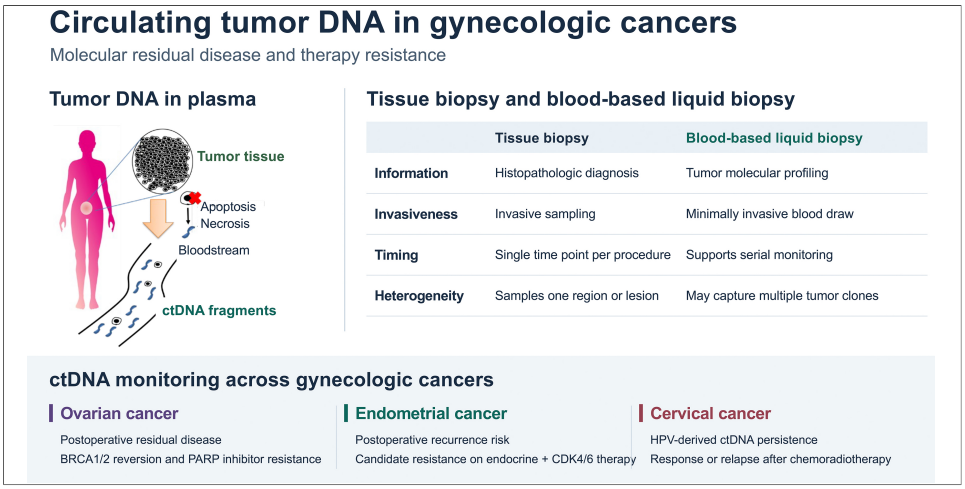
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Abstract

Circulating tumor DNA (ctDNA) provides a minimally invasive window into molecular residual disease (MRD) and tumor evolution under therapeutic pressure, two clinically related but biologically distinct states. In ovarian cancer, postoperative tumor fraction and fragmentomic analyses support molecular risk stratification, while serial plasma profiling can reveal *BRCA1/2* reversion mutations and other mechanisms of resistance to platinum and poly(ADP-ribose) polymerase inhibition. In endometrial cancer, postoperative tumor-informed assays and high-sensitivity mutation profiling identify patients at increased risk of recurrence, whereas longitudinal ctDNA during endocrine and cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor therapy can capture molecular response and emergent phosphoinositide 3-kinase (PI3K), receptor tyrosine kinase, cell-cycle, *ESR1*, and mitogen-activated protein kinase (MAPK) alterations. In cervical cancer, circulating human papillomavirus (HPV) DNA and personalized ctDNA assays provide tumor-specific measures of persistence after chemoradiotherapy and have demonstrated prognostic value in prospective cohorts and trial-embedded analyses. This review focuses specifically on ctDNA-defined MRD, treatment-selected molecular evolution, and therapy resistance; screening and early diagnosis are outside scope except where an assay principle directly informs low-burden MRD detection. Across all three malignancies, low tumor shedding,

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assay heterogeneity, clonal hematopoiesis, variable sampling landmarks, and uncertain intervention thresholds limit clinical implementation. We distinguish analytical sensitivity, prognostic validity, resistance genotyping, and true clinical utility, and propose a staged framework in which assay validation and prespecified longitudinal sampling precede randomized MRD- or resistance-guided intervention trials. ctDNA is increasingly informative as a prognostic and evolutionary biomarker, but treatment escalation, de-escalation, or switching solely on the basis of ctDNA remains unproven and should be tested prospectively.

INTRODUCTION

Gynecologic cancers comprise biologically diverse diseases in which recurrence can arise from tumor populations that survive apparently successful local and systemic treatment. Ovarian cancer commonly presents with disseminated disease and can relapse after cytoreduction, platinum chemotherapy, and maintenance therapy; endometrial cancer spans molecularly and clinically distinct groups in which postoperative risk remains heterogeneous; and cervical cancer offers the unusual advantage of a tumor-specific viral signal in most cases. Across these settings, conventional imaging and serum biomarkers identify only part of the residual-disease landscape. Circulating tumor DNA (ctDNA) provides an orthogonal measurement because it can quantify tumor-derived material, capture genomic heterogeneity, and be sampled repeatedly with relatively low burden[1-4].

The clinical vocabulary requires precision. In this review, molecular residual disease (MRD) denotes tumor-derived molecular material detected after curative-intent or treatment intended to eliminate detectable disease when overt disease may be absent by standard assessment. The term is often used interchangeably with minimal residual disease, but a plasma-positive result is not direct proof that viable resistant cells remain at a particular anatomical site. Conversely, a plasma-negative result does not establish eradication because shedding, input volume, assay design, and sampling time constrain sensitivity. Resistance monitoring is a related but distinct task: it aims to identify the genotype or molecular state of a clone that has survived or evolved under treatment pressure. The distinction matters because a prognostic MRD signal, a predictive resistance biomarker, and a biomarker that improves outcomes when acted upon represent different levels of evidence[5-7].

This distinction is especially important in 2026. Broad reviews have already summarized the diagnostic, screening, monitoring, and prognostic applications of ctDNA in gynecologic malignancies[8,9]. This review deliberately does not reproduce that broad landscape. Screening and early diagnosis are outside its scope except where an assay principle is necessary to interpret low-burden MRD or resistance monitoring. The clinically sharper question is whether serial ctDNA can connect residual disease with therapy-resistant clonal evolution and, ultimately, support treatment adaptation. That question aligns closely with the Cancer Drug Resistance Special Topic on circulating biomarkers and MRD in therapy resistance, and it creates a coherent comparison across three disease-specific models: BRCA reversion and other resistance mechanisms after poly(ADP-ribose) polymerase (PARP) inhibitor exposure in ovarian cancer; molecular evolution during endocrine/cyclin-dependent kinase 4 and 6 (CDK4/6) inhibition in endometrial cancer; and persistent human papillomavirus (HPV)-derived ctDNA after chemoradiotherapy in cervical cancer.

This narrative review critically synthesizes contemporary evidence on ctDNA-based molecular residual disease monitoring and therapeutic resistance in ovarian, endometrial, and cervical cancers. Relevant literature was identified through a targeted PubMed search emphasizing studies published between January 2020 and September 2026, supplemented by earlier landmark studies. Particular attention was given to prospective clinical investigations, trial-associated biomarker analyses, and emerging molecular approaches relevant to resistance detection and treatment guidance.

Table 1. Operational definitions of longitudinal ctDNA states relevant to MRD and therapy resistance

Readout	Operational definition	Clinical interpretation	Therapy-resistance relevance	Key caveat	Representative Refs.
Molecular persistence (MRD)	Tumor-derived signal remains detectable after definitive or curative-intent treatment at a prespecified landmark	Residual-risk stratification and recurrence prognosis	Indicates survival of tumor-derived material after treatment, but not the mechanism of survival	Does not localize viable disease or prove that a specific resistant clone is present	[5-7]
Molecular response/clearance	Quantitative fall or clearance of ctDNA during treatment relative to baseline	Early pharmacodynamic response and outcome association	Incomplete clearance may identify treatment-tolerant residual disease	Non-clearance does not establish benefit from switching therapy	[5,7,89]
Molecular progression/relapse	Reproducible new or rising ctDNA before conventional radiographic or clinical progression	Earlier warning of recurrence or progression	Can reflect expansion of a treatment-selected population	Lead time alone is not evidence of clinical utility	[5,7,92]
Resistance genotype	Acquired or selected alteration with a plausible mechanistic link to treatment failure	Mechanism-oriented stratification and potential matched-trial selection	Interrogates what survived therapy and why	A low-frequency variant may be non-dominant, non-causal, or non-tumor-derived	[5-7,10,11]
ctDNA-guided clinical utility	Improved patient outcome when management is changed according to a prespecified ctDNA rule	Supports implementation of MRD- or resistance-guided care	Links a molecular state to a beneficial treatment adaptation	Requires prospective intervention evidence rather than prognostic association alone	[89,92,93]

MRD is used here as molecular residual disease detected in circulating tumor-derived material; a positive result is not direct proof of viable resistant cells at a specific anatomical site. MRD: Molecular residual disease; ctDNA: circulating tumor DNA.

MRD AND THERAPY RESISTANCE: RELATED BUT DISTINCT BIOLOGICAL STATES

MRD is a measurement, not a mechanism

A postoperative or post-radiotherapy ctDNA-positive sample supports the presence of residual tumor-derived material, but it does not by itself explain why disease survived. Residual populations may include drug-tolerant persister cells, quiescent clones, subclones with pre-existing resistance, newly selected genomic variants, or disease that remained untreated because of anatomical or pharmacologic sanctuary. ctDNA observes a consequence of residual disease; mechanistic inference requires the identity, dynamics, and treatment context of the detected alterations. This is why the same positive assay may be strongly prognostic yet weakly predictive of benefit from a particular intervention[10,11].

Four longitudinal ctDNA readouts should be separated

Four readouts recur across gynecologic studies. Molecular persistence is detectable ctDNA after treatment. Molecular response is a quantitative fall or clearance during therapy. Molecular progression is a reproducible new or rising signal before conventional progression is established. A resistance genotype is narrower: an acquired or selected alteration with plausible mechanistic linkage to treatment failure. A rise in tumor fraction can predict progression without identifying the mechanism, while a low-frequency BRCA reversion or other resistance allele can be clinically important before total ctDNA rises substantially. These endpoints should not be pooled as if they were interchangeable[7]. The operational definitions of longitudinal ctDNA readouts are summarized in Table 1.

Table 2. ctDNA assay strategies for MRD and therapy-resistance monitoring in gynecologic cancers

Strategy	Molecular signal	Strength for MRD	Strength for resistance monitoring	Principal limitation	Representative Refs.
Tumor-informed mutation tracking	Patient-specific SNVs/indels selected from tumor tissue	High attribution to the index tumor; sensitive low-level tracking	Tracks known clones but may miss newly acquired alterations outside the selected targets	Requires tumor tissue and assay design time	[31,62,63]
Tumor-agnostic broad NGS	Broad mutations plus CNA/SV profiling without a patient-specific panel	Useful when tissue is unavailable, but sensitivity falls at very low tumor fraction	Can discover emerging resistance alterations and clonal remodeling	CHIP and low tumor fraction can confound low-VAF calls	[20,71]
Methylation/fragmentomics	Epigenetic patterns and genome-wide fragment-size or nucleosome features	Provides orthogonal signal for low-burden disease and multimodal MRD models	May capture tumor-state changes independent of a single mutation	Thresholds, pipelines, and prospective intervention cutoffs remain immature	[14-16,47,48]
Viral ctDNA (HPV DNA)	Tumor-associated high-risk HPV sequences in plasma	Highly tumor-specific persistence marker in HPV-associated cervical cancer	Excellent for persistence/relapse monitoring, but usually does not specify the genomic resistance mechanism	Not applicable to HPV-negative disease; assay and genotype coverage vary	[83,85,86]

Assay selection should follow the intended clinical claim (low-level MRD detection *vs.* resistance discovery). CHIP: Clonal hematopoiesis of indeterminate potential; CNA: copy-number alteration; CRT: chemoradiotherapy; ctDNA: circulating tumor DNA; HPV: human papillomavirus; MRD: molecular residual disease; NGS: next-generation sequencing; SNV: single-nucleotide variant; indel: insertion/deletion; SV: structural variant; VAF: variant allele fraction.

Prognostic, predictive, and interventional evidence

The minimum translational sequence is analytical validity, clinical validity, predictive validity where relevant, and clinical utility. Analytical validity asks whether the assay reproducibly detects the intended signal at the required allele fraction. Clinical validity asks whether the result stratifies recurrence or survival risk beyond established variables. Predictive validity asks whether a marker identifies differential benefit from a therapy. Clinical utility asks whether using the assay to change management improves an outcome that matters to patients. Current gynecologic evidence is strongest at the first two steps. European Society for Medical Oncology (ESMO) has emphasized that MRD detection can have clinical validity while MRD-directed treatment remains investigational outside settings supported by prospective evidence[5].

ANALYTICAL FRAMEWORK FOR ctDNA-DEFINED MRD AND RESISTANCE MONITORING

Tumor-informed and tumor-agnostic strategies answer different questions

Tumor-informed assays first identify patient-specific tumor variants and then track a selected set in plasma. This can suppress background noise and increase confidence that a low-frequency event originates from the known cancer, making the approach attractive for postoperative MRD. The trade-off is that fixed tracking of primary-tumor variants can miss a newly acquired resistance clone if that clone is not represented among the selected targets. Tumor-agnostic approaches avoid a tissue-sequencing prerequisite and can interrogate broader mutations, copy-number alterations, methylation, and fragmentomic features; they may therefore be better suited to discovery of new resistance mechanisms, although low tumor fraction and biological background remain challenging. Plasma-only multimodal assays illustrate how genomic and epigenomic information can increase sensitivity beyond mutation-only analysis[12,13]. The strengths and limitations of different ctDNA assay strategies for MRD detection and resistance monitoring are summarized in Table 2.

Orthogonal signals for low-burden MRD and resistance monitoring

Mutation tracking is only one layer of an MRD or resistance-monitoring signal. Copy-number profiles can estimate tumor fraction and expose amplifications or deletions associated with clonal evolution. Methylation may provide orthogonal information when individual driver mutations are sparse, while fragmentomic features exploit differences in fragment length, end motifs, and nucleosomal organization between tumor-derived and non-tumor cell-free DNA (cfDNA). Genome-wide fragmentation studies established the analytical basis for these features, and recent ovarian work has moved multimodal fragmentomics directly into the MRD setting[14-16]. In this review, these modalities are considered for their ability to improve low-burden residual-disease detection or characterize treatment-selected evolution, not for population screening.

Pre-analytical variables, timing, and the meaning of a negative result

A negative ctDNA result is conditional on plasma volume, cfDNA input, assay limit of detection, variant number, sequencing depth, error suppression, sampling time, disease distribution, and biological shedding. Early postoperative sampling adds a further problem: surgery can transiently increase non-tumor cfDNA and dilute the tumor fraction. Studies across solid tumors suggest that ctDNA can be informative in the immediate postoperative setting, but the optimal landmark depends on the intended clinical decision[17]. For gynecologic trials, the blood draw should therefore be linked prospectively to a decision window rather than selected retrospectively because it produced the strongest hazard ratio.

Clonal hematopoiesis is a particular problem for resistance profiling

Age-related clonal hematopoiesis can create pathogenic-appearing variants in plasma that are derived from blood cells rather than cancer. This is especially consequential when broad panels are used to search for acquired resistance mutations at low allele fractions. Paired leukocyte sequencing, fragment-level features, consistency with tumor tissue, and longitudinal behavior can reduce misattribution[18,19]. The EVOLVE ctDNA analysis provides a disease-specific example: several novel *TP53* variants detected in cfDNA were attributed to clonal hematopoiesis after fragmentation analysis, demonstrating how an apparently plausible ovarian cancer signal can be biologically misleading without source adjudication[20].

OVARIAN CANCER: FROM MOLECULAR PERSISTENCE TO RESISTANT CLONAL EVOLUTION

Postoperative MRD and longitudinal disease burden

Ovarian cancer is the gynecologic setting in which the distinction between macroscopic residual disease and molecular persistence is most intuitive. Surgical residual disease, CA125, imaging, histology, and homologous-recombination status each capture different aspects of risk; ctDNA can add a dynamic dimension. Earlier studies demonstrated feasibility of serial plasma mutation profiling, including *TP53*-based tracking, broad mutation panels, and postoperative detection associated with adverse outcomes[21-27]. Systematic reviews have consistently identified heterogeneity in assay design and sampling but also a recurring association between persistent ctDNA and relapse[28-30].

The evidence has matured. Tumor-informed or personalized approaches have shown high sensitivity for residual disease in selected epithelial ovarian cancer cohorts, and longitudinal studies indicate that ctDNA may precede conventional clinical progression in some patients[31-33]. In a prospective study of primary advanced high-grade serous ovarian cancer, personalized postoperative ctDNA was detectable in most patients shortly after surgery, underscoring that molecular persistence can remain substantial despite cytoreduction[34]. These studies are limited by small sample sizes, disease-stage enrichment, and treatment heterogeneity, but they establish a biologically credible signal.

The 2026 MITO16a/MaNGO-OV2 translational analysis is particularly relevant because it combined tumor fraction with fragmentomic features in serial plasma rather than relying on a single mutation readout. The multimodal design supports tumor-agnostic risk stratification and longitudinal observation of copy-number

evolution, including acquired genomic changes during treatment[16]. A 2026 retrospective cohort also reported strong recurrence discrimination with longitudinal ctDNA monitoring, while a 2026 meta-analysis of 11 studies and 627 patients found postoperative ctDNA positivity associated with worse progression-free and overall survival; post-adjuvant positivity showed still larger risk estimates[35,36]. The meta-analysis strengthens clinical validity, but it does not establish that escalating therapy when ctDNA is positive improves survival.

BRCA reversion provides the clearest mechanistic bridge to resistance

BRCA1/2 reversion provides one of the clearest mechanistic examples linking ctDNA-detected clonal evolution to drug resistance in gynecologic oncology. BRCA-deficient tumors are vulnerable to platinum and PARP inhibition because homologous recombination repair is impaired. Under treatment pressure, secondary sequence alterations can restore an open reading frame and partially or fully restore BRCA function, allowing homologous recombination to recover. Whole-genome studies of chemoresistant ovarian cancer first established the broader evolutionary landscape in which reversion can occur[37]. Subsequent analyses demonstrated that multiple distinct reversion clones can coexist, consistent with convergent evolution under a shared selective pressure[38-40].

Lin *et al.* showed that BRCA reversion mutations detectable in ctDNA were associated with primary and acquired resistance to rucaparib in high-grade ovarian carcinoma, converting ctDNA from a generic burden marker into a mechanistically interpretable resistance assay[41]. Larger cross-tumor analyses identified recurrent reversion hotspots and repair signatures, reinforcing the biological reproducibility of the phenomenon[42,43]. Serial ovarian ctDNA studies then showed that reversion and other candidate resistance alterations can emerge over time during PARP inhibitor exposure[44].

Resistance beyond BRCA reversion

BRCA reversion is important precisely because it illustrates both the promise and the limitation of a resistance-focused ctDNA strategy. A negative reversion assay does not imply PARP sensitivity. Resistance can arise through restoration of homologous recombination involving other genes, replication-fork protection, drug efflux, cell-cycle rewiring, epigenetic change, or altered DNA-damage signaling. The EVOLVE study identified post-PARP inhibitor alterations that included *BRCA1*, *BRCA2*, or *RAD51B* reversions, *CCNE1* amplification, *ABCB1* upregulation, and *SLFN11* downregulation in tissue-based analyses[45]. Longitudinal cfDNA in the same clinical program captured known tumor mutations and selected resistance events, but not every event was detectable in plasma[20]. This argues for a dual readout: one component optimized for sensitive burden detection and another sufficiently broad to identify plausible acquired mechanisms.

Epigenetic measurements may add another dimension to MRD and resistance monitoring. *BRCA1* promoter methylation can be detected in circulating DNA and may track a homologous-recombination-deficient state, although methylation can itself be lost or become heterogeneous under therapy[46]. Ovarian cfDNA methylation and methylome studies have largely been developed in detection settings[47-50]. Their relevance here is analytical rather than diagnostic: they demonstrate that orthogonal epigenetic information can be recovered from low-abundance cfDNA, but they do not establish MRD or resistance-guided clinical utility. The clinically relevant next test is whether methylation improves sensitivity at post-treatment low tumor fractions or identifies therapy-selected epigenetic states when mutation-only tracking underestimates the surviving clone.

Therapeutic implications of homologous-recombination restoration

Mechanistic identification is clinically useful only if it changes an effective treatment choice. Polymerase theta has emerged as a synthetic-lethal target in homologous-recombination-deficient tumors and as a

potential strategy against selected PARP inhibitor-resistant states in preclinical work[51,52]. However, detecting a reversion does not automatically identify the optimal next therapy, and heterogeneous subclones can make single-lesion or single-plasma-timepoint interpretation incomplete. Resistance-informed trials should therefore define an alteration-action pair prospectively and test it against a conventional progression-triggered strategy.

ENDOMETRIAL CANCER: MRD WITHIN A MOLECULARLY CLASSIFIED DISEASE

The tissue molecular class and the post-treatment state answer different questions

Endometrial cancer now has a molecular framework that separates *POLE*-ultramutated, mismatch repair-deficient, p53-abnormal, and no-specific-molecular-profile tumors, with major prognostic and therapeutic implications[53,54]. Tissue classification describes baseline tumor biology; postoperative ctDNA asks whether tumor-derived material remains after treatment. The two dimensions should be integrated rather than treated as competing biomarkers. A p53-abnormal tumor with repeatedly negative ctDNA and a *POLE*-mutated tumor with persistent ctDNA represent biologically different scenarios that cannot be resolved by either tissue class or plasma alone.

Postoperative ctDNA and recurrence risk

Early endometrial studies showed that plasma mutations could be detected before treatment and tracked after surgery. Personalized mutation assays in high-risk disease and serial monitoring cohorts linked postoperative detection with relapse, while broader high-sensitivity approaches demonstrated that cfDNA could track recurrence and progression[55-57]. Additional assay-development studies established technical feasibility using tumor-related plasma variants, MSI-compatible liquid biopsy methods, and personalized tumor-specific DNA junctions[58-61]. For the present review, their relevance is limited to whether such platforms can support postoperative residual-disease assessment or longitudinal treatment monitoring; preoperative diagnostic performance is not a focus. These studies were also small and used markedly different assays and sampling schedules.

Larger and more contemporary data strengthen the prognostic signal. In 101 patients with stage I uterine malignancies, a tumor-informed assay applied to 267 plasma samples showed strong association between postoperative ctDNA positivity and recurrence, including in multivariable analyses[62]. A 2025 real-world study of 61 early-stage uterine cancer patients and 233 time points similarly reported markedly shorter recurrence-free survival among ctDNA-positive patients after surgery and after definitive therapy[63]. Additional disease-monitoring series show that ctDNA can precede clinical or biomarker progression in selected endometrial and ovarian cases[33].

The 2026 evidence synthesis is clinically important. A systematic review and meta-analysis incorporating 11 studies and 1,298 patients found that both preoperative and postoperative ctDNA positivity were associated with worse progression-free survival, with a substantially larger pooled hazard ratio after surgery[64]. A prospective high-risk cohort published in 2026 provides additional perioperative support, while personalized DNA-junction assays continue to show that serial ctDNA can precede clinical recurrence in some aggressive endometrial cancers[65,66]. These data argue that postoperative detection is a high-risk marker, but differences in assay class, stage, histology, and adjuvant treatment prevent a single universal threshold from being assumed.

Tumor-informed *vs*. endometrial-specific panels

The endometrial literature provides a useful comparison between highly personalized and disease-focused designs. Tumor-informed assays maximize attribution to the index tumor but require adequate tissue and added workflow. A custom endometrial ctDNA panel reported in 2026 was designed from The Cancer

Genome Atlas (TCGA)/Clinical Proteomic Tumor Analysis Consortium (CPTAC) and tumor sequencing data and achieved high specificity for recurrence, but sensitivity remained incomplete at the tested input and limit of detection[67]. This is a clinically realistic reminder that a negative result is assay-conditional. Endometrial reviews increasingly emphasize that implementation must be matched to disease risk and the decision being made rather than treating ctDNA as a single generic test[68,69].

Longitudinal ctDNA can reveal acquired resistance during systemic therapy

The most direct endometrial link to drug resistance comes from serial profiling during endocrine and CDK4/6 inhibition. In a phase II letrozole/abemaciclib study, 99 of 102 plasma specimens from 28 patients were successfully analyzed. Higher baseline tumor fraction and lack of early molecular response were associated with substantially worse outcomes. At progression, candidate acquired alterations involved phosphoinositide 3-kinase (PI3K) signaling, *FGFR1/2* or *ERBB2*, *RB1*/*CCNE1*, *ESR1*, and mitogen-activated protein kinase (MAPK) signaling[70]. Although the cohort was small, it illustrates the conceptual transition from MRD as a binary recurrence marker to ctDNA as a dynamic evolutionary readout of therapeutic escape.

Advanced endometrial cohorts also demonstrate that ctDNA can reflect the broader genomic landscape and real-world outcomes[71]. Microsatellite instability (MSI) assessment from liquid biopsy is technically feasible in selected settings, providing a potential bridge to immunotherapy biology[72]. However, predicting response to immune checkpoint inhibition from ctDNA requires distinction between baseline genotype, tumor fraction, clearance kinetics, and emergent resistance. Current data do not support replacing tissue molecular classification or standard clinical evaluation with a single plasma metric.

CERVICAL CANCER: VIRAL ctDNA AS A MODEL OF POST-TREATMENT MOLECULAR PERSISTENCE

A tumor-specific viral target changes the analytical problem

Most cervical cancers are driven by high-risk HPV, creating a circulating target that is biologically linked to the malignant clone and can be measured without first sequencing each tumor. This differentiates cervical cancer from mutation-only MRD paradigms and reduces some, but not all, attribution problems. Meta-analytic and review data have shown high specificity for circulating HPV DNA, while sensitivity varies with disease burden, assay, genotype coverage, and sampling time[73-76]. Baseline diagnostic performance is not considered further here; the clinically relevant question for this review is whether HPV-derived ctDNA clears after definitive therapy, persists as molecular residual disease, or re-emerges before clinically apparent relapse.

Kinetics during chemoradiotherapy

Prospective and serial studies have demonstrated rapid changes in circulating HPV DNA during chemoradiotherapy. Cabel *et al.* showed that high-risk HPV ctDNA could be tracked during treatment, and Jeannot *et al.* demonstrated that circulating HPV DNA can identify relapse before conventional detection in some patients[77,78]. Other studies extended genotype coverage and supported use of circulating HPV DNA or plasma cfDNA as response and recurrence biomarkers[79-81]. In metastatic or recurrent disease, serial mutation-based ctDNA can also reflect treatment response, indicating that the viral marker and tumor genomic profiling are complementary rather than mutually exclusive[82].

A prospective multicenter clinical validation study in locally advanced cervical cancer strengthened the post-treatment landmark concept. Detectable HPV ctDNA at the end of chemoradiation, 4-6 weeks after treatment, or 3 months after treatment was associated with inferior progression-free survival, and the study compared digital PCR with HPV sequencing[83]. A 2025 kinetics study of 66 patients further showed dynamic

HPV cfDNA changes during definitive chemoradiation and found that follow-up clearance was strongly associated with recurrence-free survival; combining the molecular result with magnetic resonance imaging (MRI) response improved discrimination[84]. These studies suggest that timing after treatment is part of the biomarker definition, not a technical afterthought.

The CALLA analysis moves the field toward trial-embedded evidence

The exploratory biomarker analysis embedded in the phase III CALLA trial is the largest cervical data set linking ultrasensitive ctDNA and circulating HPV DNA with relapse and survival in a randomized-treatment population, although the biomarker itself did not randomize management. ctDNA was detectable in nearly all evaluable baseline samples, and an on-treatment molecular signal preceded clinical progression by a median of 164 days in the reported analysis[85]. The key interpretation is prognostic rather than interventional: the analysis shows that a molecular warning can occur earlier, not that acting on that warning improves survival.

Meta-analytic evidence and the danger of de-escalating on a negative test

A 2026 systematic review and meta-analysis included 20 studies; pooled diagnostic specificity for HPV cfDNA was high, and HPV cfDNA positivity at 3 months after treatment was strongly associated with reduced progression-free survival[86]. The same evidence also explains why a single negative test should not justify de-escalation. Sensitivity is not perfect, HPV-negative cervical cancers require a different approach, and even HPV-positive tumors can be below the assay's detection threshold. A negative result should be interpreted as a probability-modifying observation rather than proof of cure.

Genomic ctDNA can complement viral monitoring

Mutation-based approaches remain relevant in cervical cancer because they can identify tumor-specific alterations not captured by viral load. Plasma *PBRM1* has been explored as a marker of response to neoadjuvant chemotherapy, while broader plasma profiling can reveal pathway-level alterations and potentially inform salvage therapy[3,87,88]. A future cervical strategy may therefore use HPV-derived ctDNA for high-sensitivity persistence monitoring and broader sequencing selectively when persistence or progression is documented and a resistance mechanism is clinically actionable.

COMPARING THE THREE DISEASE MODELS

The three gynecologic cancers illustrate different positions on the MRD-resistance continuum. Ovarian cancer provides the strongest mechanistic resistance example because a ctDNA-detected BRCA reversion can be linked directly to restoration of homologous recombination and failure of platinum/PARP-directed pressure. Endometrial cancer provides an emerging model in which tissue molecular class establishes baseline biology and serial ctDNA can measure postoperative risk and reveal pathway-specific escape during endocrine/CDK4/6 inhibition. Cervical cancer provides the most tumor-specific post-treatment marker because viral DNA can be followed independently of a patient-specific mutation panel. The differences are an advantage: they allow the field to separate what is assay-specific from what is generalizable about MRD biology. Representative clinical studies supporting ctDNA-based MRD and resistance monitoring are summarized in Table 3, while Figure 1 illustrates the distinct longitudinal trajectories observed across ovarian, endometrial, and cervical cancers.

FROM PROGNOSTIC BIOMARKER TO TREATMENT ADAPTATION

Lessons from randomized MRD-guided studies outside gynecologic oncology

The central translational risk is to assume that earlier detection automatically produces better outcomes. Randomized and interventional studies in other solid tumors show why that assumption is unsafe. In stage II colon cancer, the DYNAMIC trial demonstrated that a ctDNA-guided strategy could reduce use of adjuvant

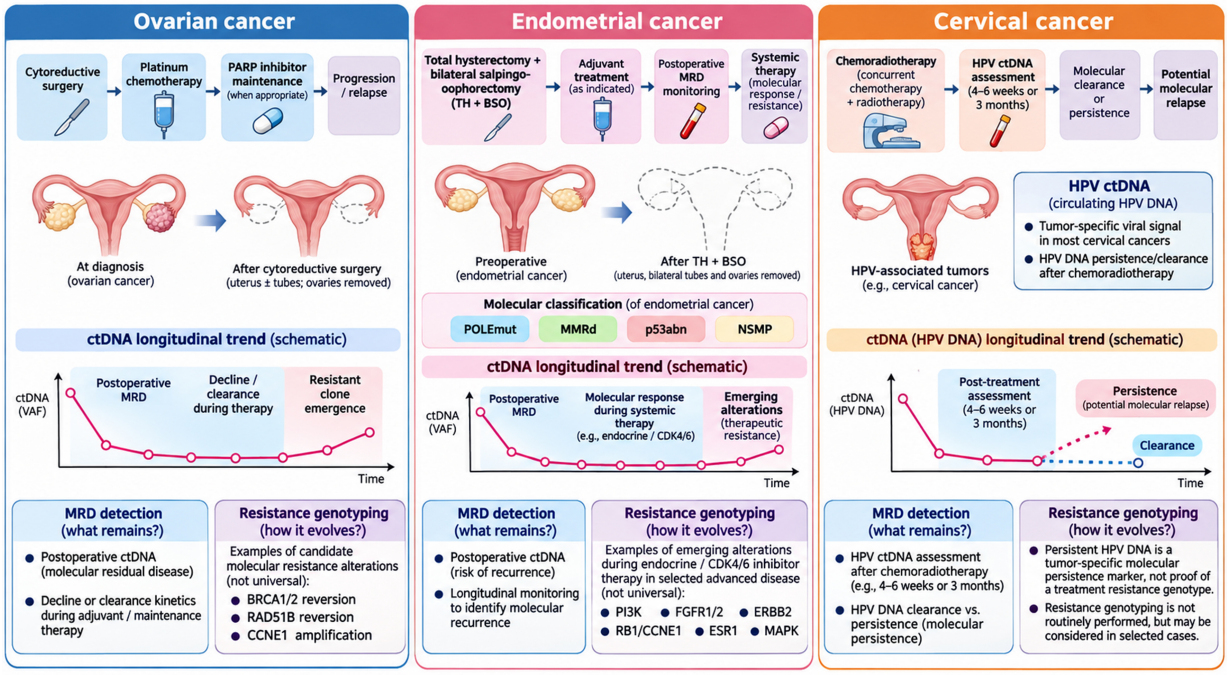


Figure 1. Disease-specific longitudinal ctDNA monitoring of molecular residual disease and therapy resistance in gynecologic cancers. In ovarian cancer, postoperative ctDNA dynamics are distinguished from candidate resistance alterations, including *BRCA1/2* and *RAD51B* reversions and *CCNE1* amplification. In endometrial cancer, the standard surgical pathway is shown as total hysterectomy with bilateral salpingo-oophorectomy, followed by postoperative MRD assessment; examples of molecular alterations emerging during endocrine/CDK4/6-targeted treatment include PI3K, *FGFR1/2*, *ERBB2*, *RB1/CCNE1*, *ESR1*, and MAPK pathway changes. In cervical cancer, circulating HPV DNA clearance or persistence after chemoradiotherapy reflects a tumor-specific molecular signal; HPV DNA persistence alone does not identify a genomic resistance mechanism. Trajectories and molecular examples are schematic, not individual patient data. This revised schematic was prepared with assistance from ChatGPT (OpenAI; GPT-6 used for the present revision) for content organization and an OpenAI image-generation tool (exact image-model version not retained) for illustration. The authors reviewed and corrected the scientific content; all depictions are conceptual and are not derived from individual patient data. HPV: Human papillomavirus; ctDNA: circulating tumor DNA; MRD: molecular residual disease; PARP: poly(ADP-ribose) polymerase; BSO: bilateral salpingo-oophorectomy; VAF: variant allele fraction; TH: total hysterectomy; *POLE*mut: *POLE*-mutated; MMRd: mismatch repair deficient; p53abn: p53-abnormal; NSMP: no specific molecular profile; CDK4/6: cyclin-dependent kinases 4 and 6; PI3K: phosphoinositide 3-kinase; *FGFR1/2*: fibroblast growth factor receptor 1/2; *ERBB2*: Erb-B2 receptor tyrosine kinase 2; *RB1*: RB transcriptional corepressor 1; *ESR1*: estrogen receptor 1; MAPK: mitogen-activated protein kinase.

chemotherapy without compromising recurrence-free survival, and 5-year follow-up supported durable outcome equivalence while showing that persistent ctDNA after chemotherapy identified an extremely high-risk subgroup[89,90]. In stage III colon cancer, the DYNAMIC-III trial has extended randomized testing of ctDNA-guided adjuvant intensity, emphasizing that stage, baseline risk, and treatment context determine whether escalation or de-escalation is appropriate[91].

Other trials expose limitations. In c-TRAK TN, many patients who became ctDNA positive already had radiographically detectable metastatic disease by the time of intervention assessment, narrowing the window in which a molecularly triggered treatment could plausibly prevent overt relapse[92]. In the 2026 ALTAIR randomized phase III trial, additional post-adjuvant therapy in ctDNA-positive colorectal cancer did not simply validate the idea that any treatment given earlier is beneficial[93]. The lesson for gynecologic oncology is specific: the biomarker, the sampling schedule, the confirmatory rule, and the drug selected for the detected biological state all have to be appropriate.

Trial designs should match the clinical claim

For postoperative MRD, an escalation trial should enroll patients at a fixed landmark, confirm positivity when analytically appropriate, exclude radiographically evident disease, and randomize a defined intervention against standard management. A de-escalation trial requires even stronger negative predictive

Table 3. Representative clinical studies directly informing MRD and therapy resistance in gynecologic cancers

Study	Cancer/design	Assay and sampling	Clinical setting	Key quantitative result	MRD/resistance implication	Ref.
Paracchini *et al.*, 2026	Ovarian; phase IV translational cohort; *n* = 173; 393 plasma samples	Tumor-agnostic shallow WGS; tumor fraction + fragmentomics at post-surgery, post-chemotherapy, and end-maintenance/progression	Postoperative MRD and longitudinal evolution	Post-surgery tumor fraction detectable in 97%; combined TF/PF stratified PFS (HR 1.76) and OS (HR 2.06); recurrent 19q13.42 amplification emerged under therapy	Multimodal MRD can refine postoperative risk while serial CNA profiling captures treatment-driven evolution	[16]
Kallio *et al.*, 2024	Ovarian; retrospective EOC cohort: *n* = 63, 264 plasma samples; time-to-progression and OS estimates from the HGSC subgroup	Tumor-guided personalized mutation tracking	Residual disease and surveillance	Last on-treatment ctDNA positivity predicted shorter progression time (1.02 *vs.* 3.38 years; HR 5.63) and OS (2.31 years *vs.* NR; HR 8.22) (HGSC subgroup); median lead time 5.9 months (12 patients)	Strong prognostic MRD signal; intervention benefit remains untested	[31]
Lin *et al.*, 2019	Ovarian; BRCA-mutant high-grade ovarian carcinoma treated with rucaparib	Targeted cfDNA sequencing before and after PARP inhibition	PARP inhibitor resistance	Pretreatment BRCA reversions were detected in 18% of platinum-refractory, 13% of platinum-resistant, and 2% of platinum-sensitive cancers. Median PFS: 9.0 *vs.* 1.8 months without *vs.* with reversion (HR 0.12 for no reversion *vs.* reversion; $P < 0.0001$)	Canonical example of a plasma genotype directly linked to treatment resistance	[41]
Lheureux *et al.*, 2023 (EVOLVE)	Ovarian; phase II translational analysis; *n* = 30; 78 longitudinal cfDNA samples	Targeted cfDNA sequencing at PARPi progression, on treatment, and end of treatment	PARPi progression/resistance evolution	cfDNA recovered 74.4% of tumor-WES mutations and 3/5 expected *BRCA1/2* reversions; fragmentation analysis attributed 5 novel *TP53* variants to CHIP	Shows both the utility and biological confounding of longitudinal resistance genotyping	[20]
Recio *et al.*, 2024	Endometrial/uterine; stage I real-world cohort; *n* = 101; 267 plasma samples	Tumor-informed personalized mPCR-NGS	Post-surgical MRD	ctDNA positivity at first postoperative testing and longitudinally predicted inferior RFS (HR 6.2 and 15.5, respectively); recurrence 58%/52% *vs.* 6%/0% in negative groups	Supports postoperative MRD as an independent prognostic marker beyond clinicopathologic risk	[62]
Ketch *et al.*, 2025	Endometrial/uterine; early-stage cohort; *n* = 61; 233 plasma time points	Tumor-informed personalized assay with serial postoperative testing	Postoperative and post-definitive-therapy MRD	ctDNA positivity predicted shorter RFS postoperatively (HR 7.6; $P = 0.003$) and after definitive therapy (HR 25.4; $P = 0.0009$)	Reinforces longitudinal MRD as a high-risk state but does not establish escalation benefit	[63]
Konstantinopoulos *et al.*, 2025	Endometrial; recurrent ER-positive disease; phase II translational cohort; *n* = 28	Methylation-based tumor fraction + > 700-gene plasma genotyping across serial time points	Response and acquired resistance to letrozole/abemaciclib	High baseline TF: median PFS 2.0 months *vs.* 16.5 months (HR 24.1) and OS 10.7 months *vs.* NR (HR 14.8); acquired PI3K/RTK, *RB1/CCNE1*, *ESR1*, and MAPK alterations emerged in > 50% of evaluable progressions	Links molecular response kinetics to outcome and serial ctDNA to pathway-specific escape	[70]
Wadsley *et al.*, 2026	Endometrial; recurrence-detection cohort; 14 recurrent and 25 non-recurrent patients	Custom EC-specific mutation panel	Recurrence/residual-disease detection	Sensitivity 71.4%, specificity 96%, accuracy 87.2%; validated detection to 0.74% VAF in 5 ng DNA	Illustrates feasibility and the need to define sensitivity limits before clinical MRD use	[67]

Cabel *et al*., 2021	Cervical; HPV-positive LACC; total *n* = 55 (retrospective *n* = 41, prospective *n* = 14); survival HRs from the prospective cohort	Genotype-specific HPV ddPCR before, during, and after CRT	Post-CRT persistence	Baseline HPV ctDNA detected in 69% (38/55). In the prospective cohort (*n* = 14), end-of-CRT/follow-up HPV ctDNA positivity was associated with worse DFS (HR 5.1; *P* = 0.048) and OS (HR 25.4; *P* = 0.0013); unadjusted exploratory estimates	Residual HPV ctDNA after CRT identifies a high-risk persistence state	[77]
Jeannot *et al*., 2021	Cervical; BioRAIDs prospective cohort; *n* = 94 HPV16/18 tumors	HPV E7 ddPCR with serial post-treatment sampling	Molecular relapse surveillance	Baseline detection 63%; complete clearance by end of treatment associated with longer PFS (*P* < 0.0001); persistent-positive patients relapsed a median 10 months after detection	Supports HPV ctDNA as a tumor-specific residual and relapse marker	[78]
Han *et al*., 2024	Cervical; prospective multicenter validation; 70 HPV-positive evaluable patients	HPV genotype-specific dPCR and HPV-seq at end of CRT, 4-6 weeks, and 3 months	Residual disease after CRT	Detectable HPV ctDNA predicted inferior 2-year PFS at end CRT (51% *vs.* 77%), 4-6 weeks (15% *vs.* 82%), and 3 months (24% *vs.* 82%); median lead time 5.9 months	Prospective validation of post-CRT molecular persistence for future intensification trials	[83]
Mayadev *et al*., 2025 (CALLA)	Cervical; phase III trial-embedded biomarker analysis; baseline evaluable *n* = 185	Ultrasensitive tumor-informed assay (up to 1,800 variants) + cHPV DNA at baseline, post-CRT, and 3 months post-CRT	Trial-embedded response and relapse monitoring	Baseline ctDNA detected in 98.9%; post-CRT ctDNA detection preceded clinical progression by median 164 days (95%CI: 85-250 days)	Large trial-embedded evidence for prognostic molecular persistence; treatment was not randomized by ctDNA status	[85]

Studies are representative rather than exhaustive. Quantitative results are reported as presented in the original publications and are not inferred from figures. CHIP: Clonal hematopoiesis of indeterminate potential; cfDNA: cell-free DNA; CI: confidence interval; CNA: copy-number alteration; cHPV: circulating human papillomavirus; CRT: chemoradiotherapy; ctDNA: circulating tumor DNA; ddPCR: droplet digital polymerase chain reaction; dPCR: digital polymerase chain reaction; DFS: disease-free survival; EC: endometrial cancer; EOC: epithelial ovarian cancer; ER: estrogen receptor; HGSC: high-grade serous carcinoma; HPV: human papillomavirus; HPV-seq: human papillomavirus sequencing; HR: hazard ratio; LACC: locally advanced cervical cancer; MAPK: mitogen-activated protein kinase; mPCR-NGS: multiplex polymerase chain reaction-next-generation sequencing; MRD: molecular residual disease; NR: not reached; OS: overall survival; PARP: poly(ADP-ribose) polymerase; PARPi: poly(ADP-ribose) polymerase inhibitor; PFS: progression-free survival; PF: plasma fragmentation profile; PI3K: phosphoinositide 3-kinase; RFS: recurrence-free survival; RTK: receptor tyrosine kinase; TF: tumor fraction; VAF: variant allele fraction; WES: whole-exome sequencing; WGS: whole-genome sequencing.

performance because a false-negative result can deny effective therapy. For resistance monitoring during maintenance or metastatic treatment, an adaptive design can test whether switching therapy in response to a prespecified acquired alteration improves outcome compared with changing treatment at conventional progression. Protocols such as TRACC illustrate how ctDNA status can be built prospectively into treatment assignment, while observational stage III colorectal studies demonstrate the value of serial clearance and persistence endpoints[94,95]. Potential trial designs for ctDNA-guided treatment adaptation are summarized in Table 4, and the proposed translational framework from biomarker validation to demonstrated clinical utility is illustrated in Figure 2.

Design features that reduce misleading conclusions

Several design rules should be considered mandatory. First, sampling landmarks and schedules should be independent of symptoms to reduce ascertainment and immortal-time biases. Second, analytical failure and unevaluable samples should remain visible in the denominator. Third, the assay's limit of detection, input amount, tissue availability, leukocyte sequencing, and confirmation strategy should be reported. Fourth,

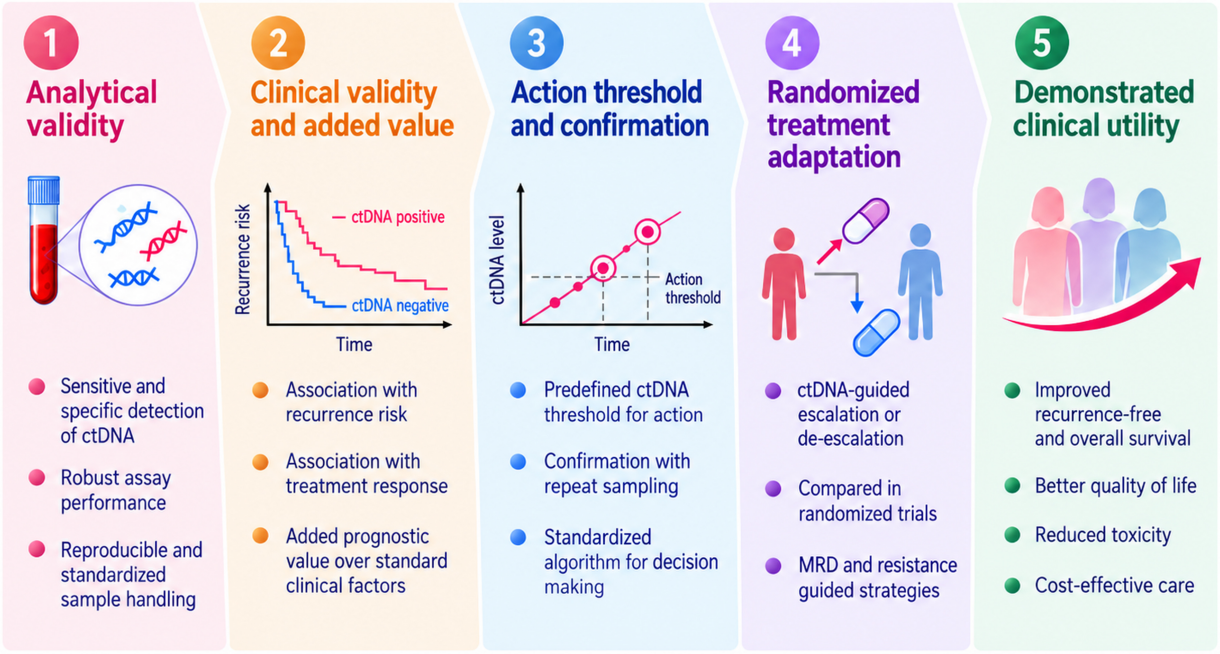


Figure 2. Roadmap from ctDNA biomarker detection to MRD-guided and resistance-guided treatment adaptation. Translation requires analytical validity, clinical validity and added value, a prespecified action threshold with confirmation, randomized treatment adaptation, and demonstrated clinical utility. Earlier molecular detection alone is not sufficient evidence of benefit. ChatGPT (OpenAI; historical model/version not retained) assisted with the original conceptual layout; GPT-6 was used to review the accompanying legend during the present revision. The authors independently reviewed and verified its scientific content. MRD: Molecular residual disease; ctDNA: circulating tumor DNA.

Table 4. Prospective trial architectures needed to establish clinical utility of ctDNA-guided management

Setting	Landmark/eligibility	Molecular trigger	Experimental strategy	Comparator	Primary endpoint/question
Ovarian after frontline therapy	No radiographic progression; fixed post-chemotherapy or maintenance landmark	Confirmed ctDNA-positive MRD	Randomize a biologically defined escalation or maintenance-switch strategy	Standard maintenance/surveillance	Does treating molecular persistence improve PFS/OS rather than only advance relapse detection?
Ovarian during PARP maintenance	On maintenance; no conventional progression	Emergent prespecified resistance genotype (e.g., validated reversion event)	Switch to a matched or resistance-directed strategy before RECIST progression	Continue standard therapy until conventional progression	Does genotype-guided switching improve outcome compared with progression-triggered change?
Endometrial after surgery/adjuvant therapy	Molecular-class and clinicopathologic risk stratification plus fixed post-treatment blood draw	Confirmed postoperative or post-adjuvant ctDNA positivity	Randomized escalation; de-escalation should be studied separately after robust negative validation	Guideline-based adjuvant management	Does ctDNA add actionable benefit beyond *POLE*/MMRd/p53abn/NSMP and standard risk factors?
Cervical after definitive CRT	HPV-positive disease; fixed 6-12 weeks and/or 3-month landmark; no overt progression	Persistent HPV ctDNA confirmed serially	Protocolized localization followed by randomized salvage or systemic intervention	Standard surveillance and salvage at conventional detection	Does acting on molecular persistence improve cure-related outcomes without excess overtreatment?

Proposed designs are conceptual. Any escalation, de-escalation, or early switch should be tested prospectively with patient-important outcomes and safeguards against false-positive and false-negative treatment decisions. CRT: Chemoradiotherapy; ctDNA: circulating tumor DNA; HPV: human papillomavirus; MMRd: mismatch repair deficient; MRD: molecular residual disease; NSMP: no specific molecular profile; OS: overall survival; PARP: poly(ADP-ribose) polymerase; PFS: progression-free survival; *POLE*: DNA polymerase epsilon; RECIST: Response Evaluation Criteria in Solid Tumors; p53abn: p53-abnormal.

prognostic association, prediction of differential treatment benefit, and benefit from an assay-guided intervention should be presented as separate claims. Fifth, molecular lead time is the interval between the first detection of molecular recurrence by ctDNA and subsequent detection of recurrence by conventional clinical assessment or imaging. A longer lead time should not be interpreted as evidence of clinical benefit, because earlier detection alone does not establish that a ctDNA-guided intervention improves patient outcomes. Finally, trials should measure toxicity, quality of life, unnecessary treatment, and financial burden as well as progression-free and overall survival[5,6].

The intervention should target the biology revealed by ctDNA

The strongest future trials will not merely randomize ctDNA-positive patients to 'more treatment.' They will use molecular information to select an intervention that is plausible for the residual clone. A BRCA-reverted ovarian cancer should not be grouped uncritically with a tumor showing *CCNE1* amplification or *ABCB1* upregulation; an endometrial tumor acquiring *RB1* loss during CDK4/6 inhibition represents a different problem from emergent *ESR1* or MAPK signaling; persistent cervical HPV ctDNA after chemoradiotherapy creates a need to localize residual disease and define whether salvage should be local, systemic, immune-based, or investigational. In this sense, the decisive transition is from risk-informed MRD to resistance-informed MRD.

FUTURE DIRECTIONS

Quantitative rather than binary MRD

Binary positive/negative reporting is convenient but discards biological information. Tumor fraction, mutant molecules per milliliter, variant allele fraction, clearance kinetics, growth rate, and the number of tracked variants can all contribute. In breast cancer, neoadjuvant and postoperative studies show that ctDNA kinetics and persistence provide information beyond a single baseline sample[96-100]. Similar quantitative modeling in gynecologic cancer could distinguish transient low-level detection from sustained molecular growth and define rational confirmation thresholds.

Multimodal MRD and resistance profiling

The next generation of MRD and resistance assays is likely to combine orthogonal signals. Mutation tracking offers specificity, copy-number profiles capture broad genomic change, methylation may add information at low tumor fraction, fragmentomics can strengthen residual-disease detection, and viral sequences provide an exceptionally specific marker in HPV-driven disease. A multimodal design may also separate total molecular burden from the genotype or state of a treatment-selected clone. The 2026 ovarian tumor-agnostic MRD study is an early example of this direction[16]. The cost of multimodality is increased analytical complexity and a greater need for transparent reporting, external validation, and locked decision rules tied to a specific post-treatment or on-treatment clinical decision.

Integrating tissue biology and plasma evolution

ctDNA should be viewed as a longitudinal layer added to, not substituted for, tissue biology. In endometrial cancer, molecular class, histology, stage, lymphovascular invasion, and adjuvant therapy remain essential. In ovarian cancer, histotype, BRCA/homologous recombination deficiency (HRD) status, surgical residual disease, prior platinum sensitivity, and maintenance exposure contextualize every plasma result. In cervical cancer, HPV genotype, stage, nodal status, treatment delivery, and imaging response remain necessary. The clinically useful model will therefore be multimodal in a broader sense: tissue establishes the starting state, ctDNA tracks evolution, and imaging/local assessment identifies where intervention is required.

Machine learning for longitudinal MRD kinetics and resistance-state inference

Machine-learning approaches may help integrate high-dimensional cfDNA features with serial MRD measurements. Proof-of-principle ovarian methylation models were developed primarily for detection[48]. Their relevance to this review is methodological, not diagnostic: future models should be trained specifically on prespecified post-treatment or on-treatment landmarks and should infer sustained molecular persistence, molecular growth, or resistance-state transition. Algorithmic complexity cannot compensate for weak clinical labels, leakage from future clinical information, or lack of external validation. The relevant target is not generic cancer classification but a decision-calibrated probability that can be linked to a tested intervention.

Standardization and external validation

Clinical implementation will require harmonization of sample handling, reporting, and interpretation. Consensus recommendations for cfDNA reporting emphasize assay characteristics, variant attribution, analytical limitations, and transparent presentation of uncertainty[6]. External validation should include low-shedding subgroups and clinically difficult settings rather than reproducing only highly selected proof-of-concept populations. Platform performance must also be reported separately by tumor type, stage, therapy, and sampling landmark.

CONCLUSION

ctDNA can connect two states that have often been studied separately: residual disease after treatment and clonal evolution under therapeutic pressure. The connection is most mechanistically explicit in ovarian cancer, where *BRCA1/2* reversion and other post-PARP inhibitor alterations can be observed in plasma; it is emerging in endometrial cancer, where postoperative MRD and longitudinal resistance profiling can complement molecular classification; and it is clinically distinctive in cervical cancer, where HPV-derived ctDNA provides a tumor-specific measure of persistence after chemoradiotherapy. Recent 2026 meta-analyses now strengthen the prognostic evidence in all three disease areas, but prognostic validity is not equivalent to treatment-decision utility[36,64,86].

The next advance should therefore not be defined by expanding ctDNA into additional diagnostic applications or by detecting relapse a few months earlier. It should be defined by demonstrating that a prespecified MRD or resistance result identifies a residual biological state for which a specific management change improves outcomes. Until such trials are completed, ctDNA should be interpreted alongside tissue biology, imaging, clinical findings, and the limitations of a negative assay. The critical transition is from molecular persistence to biologically informed, evidence-based treatment adaptation.

DECLARATIONS

Authors' contributions

Conceptualization and design of the study: Iwahashi N, Noguchi T, Ino K
Original drafting: Iwahashi N
Review and editing: Noguchi T, Ino K
Revision: Iwahashi N, Noguchi T, Ino K

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

During the preparation and revision of this review, the authors used ChatGPT (OpenAI; GPT-6 for the current revision) for English-language editing, improving readability and organization, and drafting assistance. ChatGPT was also used during earlier manuscript-development sessions, for which complete model and version information is no longer available. An OpenAI image-generation tool (exact model version not retained) was used to assist in creating the schematic artwork for the revised Figure 1. ChatGPT

also assisted with the conceptual layout and presentation of the retained roadmap illustration in the revised Figure 2. The authors independently verified the scientific content, figure annotations, clinical interpretation, and supporting citations. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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