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REVIEW ARTICLE

The evolution of the clinical utility of cell-free DNA in ovarian cancer

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Abstract

Ovarian cancer remains a leading cause of cancer-related morbidity and mortality. It is one of the few malignancies for which a protein-based biomarker, CA-125, is routinely used for clinical monitoring. However, the limited sensitivity and specificity of CA-125, particularly in early-stage or low-volume disease, restrict its broader clinical utility and highlight the need for more accurate biomarkers. The emergence of circulating tumour DNA (ctDNA) offers potential applications across multiple points in the disease course through its sensitivity, specificity, and ability to genotype tumours non-invasively. ctDNA enables near-real-time molecular profiling, allowing dynamic assessment of tumour burden, treatment response, and resistance evolution. The critical evaluation of its clinical performance and potential integration with existing protein-based assays is essential to determine its added value. Increasingly, combined protein and ctDNA data highlight a growing trend towards multi-omic analyses, requiring advanced analytical and bioinformatic approaches. This review examines the current landscape, technical challenges, and translational potential of ctDNA and multi-omic assays in ovarian cancer, outlining key steps towards clinical implementation, drawing on lessons from established circulating biomarkers to guide future applications in precision oncology.

Keywords: Ovarian cancer; Liquid biopsy; Circulating tumour DNA; Diagnostics

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1. Introduction

Gynaecological cancers are among the most prevalent cancers in the UK and worldwide, affecting thousands of women each year. In the UK, ovarian cancer ranks as the sixth most common cause of female cancer mortality.[1]

The use of cancer antigen 125 (CA-125) for disease monitoring in ovarian cancer is one of the most established blood-based cancer markers, having been identified as a circulating marker of ovarian cancer in 1983.[2] Given its correlation with disease burden, CA-125 is now highly integrated into clinical practice: Routine monitoring of CA-125 is common practice during both first-line therapies, for surveillance thereafter, and during treatment of recurrences.[3] In addition, CA-125 can provide useful clinical cues; for example, the decline in CA-125 in response to neoadjuvant treatment is associated with a higher chemotherapy response score (CRS), and therefore an increased likelihood of complete interval cytoreductive surgery and a lower risk of subsequent relapse.[4,5] However, CA-125 is limited in specificity—it is frequently raised in benign conditions

and cancer types other than ovarian cancer.[6] Estimates of specificity range from 80% to 98.7%, depending on clinical context.[7,8]

Cell-free DNA (cfDNA) was first identified in 1948[9] and was subsequently found to be raised in concentration in the serum of individuals with cancer in 1977.[10] Analogous to CA-125, circulating tumour DNA (ctDNA) analysis has emerging applications at almost every stage of the journey of the individual with cancer, ranging from early detection[11] through to cancer monitoring and disease profiling, including identification of treatment resistant clones.[12]

In this review, we will discuss the current progress towards ctDNA-based detection and monitoring of ovarian cancer. The well-established nature of CA-125 allows comparison between these modalities and also provides a gold-standard marker for performance comparisons. We suggest that clinicians and scientists seeking to implement novel diagnostics in this field can learn lessons from the decades of use of the preceding protein-based assays that are routinely used in clinical practice.

2. Early detection of ovarian cancer using cfDNA

Given that *TP53* mutations are almost universal in high-grade serous epithelial ovarian carcinoma (HGSOC),[13] PCR-based assays targeting *TP53* could provide a broadly applicable approach. PCR-based methods for ctDNA represent some of the most specific cancer markers and were the earliest ctDNA tests in the early 2000s for multiple cancer types.[14,15] Now, the state-of-the-art circulating DNA-based liquid biopsy sequencing approaches are being employed, spanning up to the whole genome, with the associated use of increasingly complex analytical methods.

The ubiquity of PCR reflects its high specificity and relative ease of methodological and analytical application. For example, Swisher *et al.*[15] demonstrated detection of tumour-specific *TP53* sequences using PCR in 30% of individuals with International Federation of Gynecology and Obstetrics (FIGO) stage I–IV epithelial ovarian cancer (n = 69), the majority of whom had FIGO Stage III disease. Subsequent PCR approaches have shown that detection rates can reach 73–86%[16,17] in HGSOC. Table 1 summarises the performance of ctDNA assays for the detection of ovarian cancer.

Recent ctDNA assays have explored the potential of multi-cancer early detection (MCED), targeting recurrently mutated regions across multiple tumour types. One targeted mutation-based approach, TEC-Seq[18] was applied in a proof-of-concept study to plasma from 42 individuals with Stage I–IV ovarian cancer (the majority of whom were stage I–II) and 44 individuals without cancer. This approach identified point mutations in cfDNA in 68% with cancer, as opposed to 0% in the 44 non-cancer controls.

Methylation-based cfDNA detection approaches have emerged over recent decades, showing promising performance across multiple cancer types.[25,26] These approaches leverage known differences in methylation profiles between cancer and non-cancer tissues.[27] By design, these methylation approaches are thus applicable to individuals without requiring knowledge of their specific *TP53* mutation. They are not patient-specific; rather, they are tumour-type specific. Early approaches targeted a limited number of methylation loci; by targeting three loci, a targeted approach achieved 90% sensitivity and 86% specificity.[28]

Methylation-based approaches have rapidly expanded to target hundreds of loci per tumour type.[11] In ovarian cancer, sensitivity using the GRAIL methylation approach in a large case–control study ranged from 50.0% in Stage I ovarian cancer to 94.7% in Stage IV disease,[20] with a specificity of >99%. Now, large clinical trials are underway to assess the utility of such approaches for cancer screening.[29]

Other properties of cfDNA are being leveraged by MCED assays, such as alterations in fragmentation pattern (termed fragmentomics), which have been shown to differ between tumour-derived and non-tumour-derived cfDNA.[30] Fragmentomic assays tend to use whole-genome sequencing, enabling fragment size differences between tumour versus non-tumour cfDNA to be used to classify samples using machine learning. In a case–control study of 208 individuals with cancer, the DELFI fragmentomic cfDNA assay included 28 individuals with ovarian cancer.[22] The sensitivity for ovarian cancer detection using this approach was 89%, with a specificity of 98%. While such methodology might be suitable for ovarian cancer detection in individuals with symptoms, an assay with a 2% false-positive rate may be unacceptably high for population-based screening, given the large number of individuals that would subsequently require confirmatory imaging—unless imaging capacity is substantially increased.

2.1. Emerging detection approaches

Now, liquid biopsy methods are combining multiple omics to detect cancers, including ovarian cancers. Emerging evidence suggests that the combination of cfDNA analysis alongside proteins seems to provide a promising avenue. For example, combining ctDNA and CA-125 testing has been explored as part of the CancerSEEK assay, which achieved sensitivity and specificity of 98% and 99%,[19] respectively.

Table 1. Summary of key studies evaluating ctDNA for the detection of ovarian cancer

Study and patient cohort	Assay	Sensitivity and specificity	Notes
Phallen *et al.*[18] — 42 individuals with stage I–IV ovarian cancer	TEC-Seq — targeted mutation sequencing panel (81 kb panel, 58 genes)	Sensitivity: 68% (stage I–II) Specificity: 100% (*n*=44 healthy individuals)	Analysis of mutations in ctDNA revealed concordance with tumour mutations.
Cohen *et al.*[19] — 54 individuals with stage I–III epithelial ovarian cancer	CancerSEEK — targeted mutation sequencing panel and protein markers (61 amplicon panel of 16 genes)	Sensitivity: 98% (stage I–III) Specificity: 99% (*n*=812 healthy individuals)	Across all cancer types, CancerSEEK was able to localise the site of cancer to a limited number of anatomical sites in a median of 83% of individuals.
Klein *et al.*[20] — 65 individuals with stage I–IV ovarian cancer	GRAIL, Inc. assay — cfDNA methylation sequencing (targeted panel)	Sensitivity: 83.1% (stage I: ~50%; stage II: 80%; stage III: ~87%; stage IV: ~95%) Specificity: 99.5% specificity	The overall accuracy of tissue-of-origin identification in true positive cases was 88.7%.
Li *et al.*[21] — 251 individuals with stage I–IV epithelial ovarian cancer in the validation set	Methylation Bidirectional Encoder Representations from Transformers for Epithelial Ovarian Cancer (MethylBERT-EOC) — cfDNA methylation sequencing panel (3.3 million CpG sites)	Sensitivity: 80% (stage I–II, in the validation set) Specificity: 95% (*n*=374 healthy individuals in the validation set)	
Cristiano *et al.*[22] — 28 individuals with stage I–IV ovarian cancer	DELFI — cfDNA fragmentomic assay (1–2×Whole-Genome Sequencing (WGS) depth)	Sensitivity: 89% (stage I–IV) Specificity: 98% (*n*=214)	
Nguyen *et al.*[23] — 38 individuals with stage I–IV ovarian cancer	Screening for the Presence Of Tumor by Methylation And Size (SPOT-MAS) — cfDNA fragmentomic and methylation assay	Sensitivity: 73.7% (stage I–IV; 71.4% sensitivity for stage I–II only) Specificity: 96.2% (*n*=739 healthy individuals)	
Medina *et al.*[24] — 94 individuals with stage I–IV ovarian cancer	DELFI-Pro — cfDNA fragmentomic and protein assay (2×WGS depth)	Sensitivity: 77% (stage I: 72%; stage II: 69%; stage III: 87%; stage IV: 100% in the discovery cohort) Specificity: >99% (*n*=182 healthy individuals in the discovery cohort)	The validation cohort showed an all-stage sensitivity of 73%, with sensitivity ranging from 81% in stage I disease to 83% in stage IV disease, with a specificity of 100% (*n*=22 healthy individuals)

Abbreviation: ctDNA: Circulating tumour DNA.

The performance gain achieved may reflect the advantage conferred by combining both a high-sensitivity and high-specificity marker together. Recently, the addition of protein markers to fragmentome analyses in a cohort of 591 women with either ovarian cancer, benign adnexal masses, or without ovarian lesions, has demonstrated a sensitivity of 72% for stage I ovarian cancer with a specificity of >99%, with increasing sensitivity by stage.[24] This latter approach was also able to differentiate ovarian cancers from benign pathologies, with an area under the curve of 0.88, which was validated in an independent cohort.

Alternative approaches have sought to combine fragmentation with methylation, which may boost sensitivity, but with lower specificity than their counterparts that incorporate proteins. By combining fragmentation with methylation, Nguyen *et al.*[23] achieved a sensitivity for stage I–IV ovarian cancer of 73.7%, with a specificity of 96.2%. It has previously been suggested that epigenetic profiles and cfDNA fragmentation are associated,[31] hence, the degree of added performance benefit of this particular combination of analytes might be more limited.

Alternative approaches to boost assay performance are to leverage proximal sampling to boost yield. De la Fuente *et al.*[32] demonstrated the potential for copy-number-based screening for HGSOC using cervical sampling of pre-symptomatic individuals, collected up to almost a decade before diagnosis. The limit of detection of prior copy number alteration (CNA)-based approaches has been benchmarked to a ctDNA-fraction of approximately 3%.[33] While novel computational methods can be used to detect early-stage cancer signatures, proximal sampling can be used to enrich for tumour DNA, which has been used in an analogous way through urine sampling for bladder tumours.[34] Future approaches may explore protein and/or fragmentome analyses from these proximal fluids.

Increasingly large AI models are being used to interrogate cfDNA data for early detection; for example, utilising a transformer model (MethylBERT) on methylation cfDNA data,[21] reaching 80% sensitivity and 95% specificity in early-stage ovarian cancer diagnosis in a validation cohort. In theory, larger numbers of markers should boost performance; though in this example, the

specificity achieved by MethylBERT was lower than alternative (non-transformer-based approaches). Aside from greater pre-training and more diverse training data representing varied noise types, it is important that model interpretability efforts keep pace with the development of increasingly complex models.

3. Treatment monitoring and prognostication

The high correlation between ctDNA and disease burden has been shown in multiple tumour types, including in ovarian cancer,[17,35,36] such as between *TP53* mutant allele fraction (MAF) and disease volume.[17] Others have used CNAs, finding that increased cfDNA fractions are an independent prognosticator for relapse.[37] However, the correlation between imaging and ctDNA can be affected by ascites, which has been shown to reduce the correlation between *TP53* MAF and disease volume. This may suggest either a direct impact of ascites on ctDNA concentration, or on the measurement of disease burden. Interestingly, the burden of ctDNA in ascites also predicts paracentesis-free interval,[38] suggesting an additional prognostic role of circulating DNA from ascitic fluid.

Similar to the role of CA-125, ctDNA may have utility in treatment monitoring. In the Parkinson *et al.*[17] study, in patients with relapsed HGSOC whose ctDNA was monitored during chemotherapy, a decrease of >60% was an independent predictor of time to progression in a multivariate analysis. Similarly, the CHIVA trial (NCT01583322) collected blood samples and analysed ctDNA pre-treatment and with every cycle of neoadjuvant chemotherapy.[39] In this study of 188 patients, a decrease in ctDNA MAF of >80% was associated with significant benefit in either progression-free survival (PFS; p=0.0017) or overall survival (OS; p=0.0036) in favour of early decrease of ctDNA ratio. Table 2 summarises the performance of ctDNA assays for monitoring and prognostication.

In contrast to protein-based markers, the rapid half-life of cfDNA (on the order of hours)[12] may provide insight into rapid changes in disease burden in response to treatment. For example, during first-line platinum therapy in HGSOC,

Table 2. Summary of key studies evaluating circulating tumour DNA (ctDNA) for monitoring and prognostication in ovarian cancer

Study and patient cohort	Assay	Prognostic finding (s)	Notes
Swisher *et al.*[15] — 69 individuals with stage I–IV ovarian cancer undergoing first-line chemotherapy	Targeted sequencing of TP53 using an ABI 3100 DNA sequencer	ctDNA detection was a significant predictor of survival (28 vs. 54 months, p=0.01)	ctDNA was also detected in the peritoneal fluid of 93% of individuals.
Pereira *et al.*[40] — 22 individuals with stage I–IV ovarian cancer monitored following surgery and adjuvant therapy	Personalised ddPCR assays	Patients with undetectable ctDNA at 6 months after initial therapy (surgery and adjuvant therapy) had significantly longer PFS (p=0.001) and OS (p=0.019). In six individuals, the average lead-time for recurrence compared to imaging was 7 months.	
Parkinson *et al.*[17] — 40 individuals with HGSOC were monitored during standard of care treatments	Personalised ddPCR assays	A >60% drop in ctDNA after one chemotherapy cycle was associated with prolonged time to progression (HR=0.22). ctDNA levels fell faster with chemotherapy than CA-125 (median 37 days to nadir vs. 84 days for CA-125).	
Hou *et al.*[16] — 69 individuals with stage I–IV ovarian cancer monitored following surgery	Signatera – personalised (tumour-informed) targeted sequencing panel	The presence of ctDNA at a single timepoint after completion of surgery +/– adjuvant chemotherapy was a strong predictor of relapse (HR=17.6, P=0.001) ctDNA detection preceded radiologic recurrence by ~10 months on average.	In contrast, CA-125 positivity postoperatively was not associated with prognosis (p>0.05).
Minato *et al.*[41] — 11 individuals with stage II–IV ovarian cancer monitored following surgery	Personalised ddPCR assays	ctDNA detection during follow-up was a significant predictor of survival (11.4 months vs. median not reached, p=0.0038). ctDNA provided a median lead time of ~49 days before radiologic recurrence, whereas CA-125 increased ~ 7 days before imaging confirmation (p<0.05).	
Azaïs *et al.*[39] — 188 individuals with advanced epithelial ovarian cancer enrolled on the CHIVA trial	Ampliseq targeted panel sequencing of >500 hot-spot mutations	ctDNA decrease of >80% by cycle 1 of neoadjuvant chemotherapy was significantly associated with PFS (p=0.0017) and OS (p=0.0036). A favourable decrease in ctDNA was significantly associated with an increased likelihood of being able to perform cytoreductive surgery (OR=3.94, p=0.0074).	

Abbreviations: ctDNA: Circulating tumour DNA; ddPCR: Droplet digital polymerase chain reaction; HR: Hazard ratio; OR: Odds ratio; OS: Overall survival; PFS: Progression-free survival.

the median time to ctDNA nadir was 37 days, in contrast to 84 days with CA-125.[17] While ctDNA decline predicts progression, a decline in CA-125 of >50% did not predict progression in either univariate or multivariate analysis.

3.1. ctDNA for residual disease and relapse monitoring

Personalised ctDNA monitoring, which uses tumour-guided mutations,[35] has been utilised to identify recurrent disease and relapse in a number of tumour types.[42,43] Interventional clinical trials are now randomising patients with ctDNA evidence of residual disease to escalated treatment.

First, Kim *et al.*[44] found that the *TP53* MAF at 3 months after completing chemotherapy was significantly associated with the time to progression (p=0.038), thereby serving as a marker of residual disease. In addition, the OvBIOMark (NCT03010124) study showed that even despite macroscopically complete surgery (n = 26),[45] 30% of patients had detection of ctDNA postoperatively, which was associated with worse survival than individuals with undetected ctDNA. Next, in a cohort study of 44 individuals with gynaecological cancers, it was shown that undetected ctDNA at 6 months following initial treatment was a prognostic marker (PFS, p=0.001; OS, p=0.0194).[40] This recapitulates findings in other tumour types.[46,47]

In the relapse monitoring setting, again, currently only small studies have been performed: Minato *et al.*[41] demonstrated that ctDNA may become positive before rising CA-125, albeit in a sample size of six patients. Pereira *et al.*[40] quantify this lead time between ctDNA detection and imaging detection computed tomography (CT) by 7 months.

4. Disease profiling and monitoring of clonal evolution

Intratumour heterogeneity is a challenge across tumour types,[48] limiting the ability of individual biopsies to sample disease. ctDNA may better capture mutations missed by individual biopsies of heterogeneous disease, demonstrated in other tumour types.[49,50] As such, targeted mutation sequencing of cfDNA has been used to identify *BRCA* reversion mutations, which were not present in archival tumour specimens. Presence of reversion mutation was associated with a significantly shorter PFS on rucaparib (1.8 months vs. 9.0 months).[51]

Ascites and peritoneal fluid may also provide an additional opportunity for liquid biopsy, again mitigating sampling error of tissue biopsy and failure of tumour testing. For example, ascites fluid was collected from 53 individuals with epithelial ovarian cancer and next-generation sequencing (NGS) was applied for *TP53* analysis and genomic instability testing.[52] In the cfDNA sequenced, *TP53* was detected in 86% (all with HGSOC), *BRCA1/2* mutations were identified in 10%–14%. Genomic instability testing provided a result in 18 out of 18 samples, including in patients whose tumour testing had failed.

4.1. Studying the evolution of ovarian cancer

The repeatability of liquid biopsies enables longitudinal monitoring for the identification of emergent mutations, which is highly pertinent in the context of ovarian cancer and PARP inhibitors. Hence, there may be opportunities for serial liquid biopsies in both research and clinical settings, as is being explored in other fields, such as non-small cell lung cancer (NSCLC).[53]

For example, Lin *et al.*[51] monitored patients on rucaparib, identifying reversion mutations using cfDNA (Figure 1). In a cohort of eight individuals, reversion mutations were identified in individuals that were either platinum-refractory, platinum-resistant and platinum-sensitive. Larger studies of the clonal dynamics of such mutations in cfDNA, and in a broader set of genes associated with acquired chemotherapy resistance,[54] would be informative for the study of the clonal evolution of ovarian cancer.

Other longitudinal approaches may identify other emergent mutations. In a small proof-of-concept study of 12 individuals with HGSOC, ctDNA was monitored using a 500-gene panel during treatment. In one case, identification of an *ERBB2* amplification in ctDNA led to ctDNA-guided treatment in one patient who had progressed on carboplatin/caelyx,[55] who then received carboplatin, paclitaxel, and trastuzumab. In the future, larger studies, combined with personalised medicine/genomic multidisciplinary teams, might identify and propose further ctDNA-guided treatments.

5. Discussion

While we have outlined the multitude of possibilities for ctDNA-based monitoring in ovarian cancer, the utility of ctDNA over and above existing markers likely would vary by clinical context (Figure 1). Across each of the potential clinical applications, any additional clinical utility provided by ctDNA versus CA-125 must be weighed against the relative cost. A ctDNA-based approach may cost up to 10 times the cost of CA-125, at current pricing[56]—though this differential may reduce over time as sequencing costs decline. There are domains where ctDNA may provide an additive benefit over CA-125, such as a marker of disease burden, and other domains where protein-based markers are uninformative, such as the identification of resistance or reversion mutations.

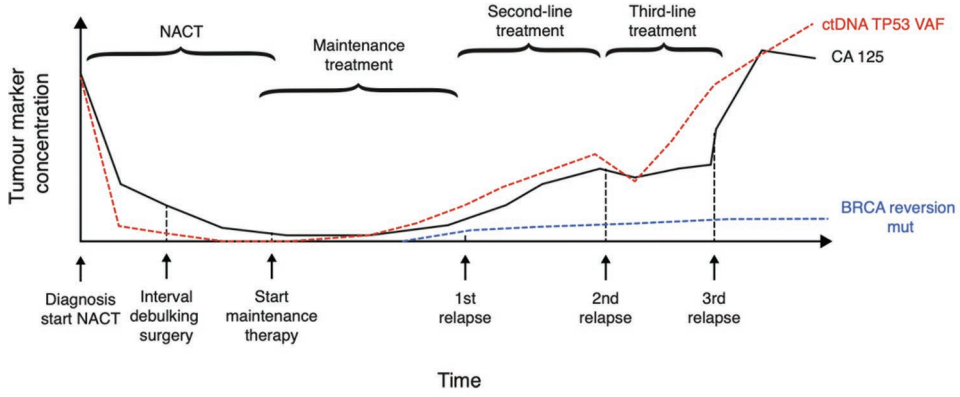

Figure 1. ctDNA as a biomarker for ovarian cancer. In this patient-time course example, the ctDNA fraction for *TP53* is shown alongside that of CA-125 (red). Subtle differences in the time course may arise from performance differences in terms of sensitivity and specificity. These discrepancies are potential areas where cfDNA-based liquid biopsies may provide utility, in the context of an already established marker. In addition, the blue dashed line shows the emergence of a *BRCA* reversion mutation, which may be identified through targeted sequencing of cfDNA. Image created by the authors.
Abbreviations: cfDNA: Cell-free DNA; ctDNA: Circulating tumour DNA; NACT: Neoadjuvant chemotherapy; VAF: Variant allele fraction.

Early cancer detection and screening represent a domain where both high specificity and sensitivity are required. Notably, in early-stage ovarian cancer, as many as 50% may not have elevated CA-125,[57] for whom alternative monitoring approaches may be of benefit. Proof-of-concept studies suggest that using ctDNA alongside protein-based markers in assays such as CancerSEEK may achieve sensitivities and specificities of 98% and 99%, respectively.[19] However, validation studies in asymptomatic average-risk individuals suggest that when analysed by stage, the sensitivity falls to 50% for Stage I ovarian cancer using a leading methylation assay.[20]

Early-stage sensitivity thus remains a challenge, and it remains to be seen whether future iterations of ctDNA assays can boost this metric. In NSCLC, personalised sequencing approaches—which are currently the most sensitive for ctDNA quantification to parts per million—have demonstrated that stage I sensitivity might reach over 50%,[58] as opposed to the current sensitivity of 22% using (non-personalised) MCED tests.[20] Hence, while it is biologically possible to achieve higher detection rates of early-stage disease, this will require technological innovation in liquid biopsy assays. Future technical approaches may explore not only multiple features from cfDNA but may venture into cell-free RNA,[59] potentially alongside proteins and other circulating markers.

Next, whether ctDNA-based prediction of response in the context of a higher disease burden provides a clinical advantage over CA-125 remains to be demonstrated. Although ctDNA kinetics might predict response sooner than CA-125,[17] *i.e.*, after the first cycle, interventional clinical trials randomising to ctDNA-guided versus standard-of-care management would be required to demonstrate the clinical utility of being able to measure more rapid changes in disease. Theoretically, such an early response predictor might aid decision-making in cases where individuals experience toxicities in early cycles, before interval response scans or CA-125 are informative.

The above considerations may have transferability to other tumour types with protein-based markers, such as prostate cancer, where prostate-specific antigen monitoring is ubiquitous—albeit with notable caveats. In contrast to the 83.1% all-stage sensitivity for ovarian cancer using the GRAIL cfDNA assay,[20] the all-stage sensitivity for prostate cancer was 11.2%. This highlights the current differential in applicability across cancer types of such assays, which is influenced by ctDNA shedding rates by cancer type.[60] For prostate cancer monitoring, mutation-based ctDNA approaches alone face the challenge of a lower rate of recurrent mutations[61] compared to HGSOC.

5.1. Considerations for implementation

While proof-of-concept data have been shown in this field, sample sizes remain small and are often retrospective—underscoring the importance of high-quality evidence towards the goal of bringing cost-effective, novel diagnostics to patients. In the future, large prospective studies, as exemplified by the studies in the pan-cancer MCED detection field,[11] plus interventional clinical trials guided by ctDNA[43] would begin to quantify the clinical utility of this approach across each of the applications discussed.

Considering future assay designs, the eventual form of ovarian cancer liquid biopsies is yet to be determined.

Targeted sequencing of *TP53* might provide a practical working point, balancing sensitivity with ease of use, given the ubiquity of this mutation in HGSOC. Alternatively, methylation assays have demonstrated promising performance so far. Combination approaches of both methylation and mutations might be considered, as emerging methods are exploring this possibility in other cancer types.[62] As in other tumour types, we may find that different assay types are utilised for each clinical purpose.

6. Conclusion

The field of ovarian cancer, combined with the ubiquity of CA-125, presents an opportunity to reflect on the standards required for emergent technologies and disease markers, such as ctDNA. While the evidence for the clinical validity of ctDNA in this context is emerging, clinical application of such methods remains at a very early stage. To achieve implementation in this field, ctDNA faces the dual challenge of not only reaching analytical performance benchmarks, but doing so in the context of existing protein markers. So far, combination approaches of nucleic acids and proteins together have demonstrated exciting synergy, which is an advantage unique to this cancer type that might be leveraged.

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Conflict of interest

Jonathan C. M. Wan is an inventor on patents related to methods for circulating tumour DNA detection. He is a co-founder, shareholder, and consultant of Prima Mente, and has served as a consultant for Cleary Gottlieb and Delfi Diagnostics, and Rostrum. Michael Flynn declares no conflicts of interest.

Author contributions

Conceptualization: All authors
Visualization: All authors
Writing–original draft: All authors
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