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CIRCULATING TUMOUR DNA IN AFRICA: A STRATEGIC ANALYSIS OF A MINIMALLY INVASIVE BIOMARKER FOR CANCER DETECTION AND MONITORING

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ABSTRACT

Cancer diagnostic pathways in Africa face delays, uneven pathology access and limited molecular testing. Circulating tumour DNA (ctDNA) offers minimally invasive access to tumour-derived molecular information, but its value depends on the clinical question, assay performance and availability of subsequent care. This narrative review examines ctDNA biology, analytical platforms and clinical applications, then evaluates priorities for African implementation. Targeted literature checks for this revision covered clinical trials, professional recommendations, cancer surveillance sources, and African studies. Plasma genotyping has defined uses in advanced cancer, while negative results may require tissue testing. Molecular residual disease predicts recurrence, but evidence for treatment changes is tumour- and stage-specific. A methylation-based multi-cancer validation study reported 99.5% specificity but only 16.8% stage I sensitivity. Ghanaian breast-cancer research demonstrates genomic feasibility; a multicentre East African Burkitt lymphoma study provides stronger evidence of diagnostic accuracy and shorter turnaround time. Neither establishes effectiveness across all cancers or African health systems. Specimen handling, clonal haematopoiesis, assay costs, pathology access and access to appropriate treatment remain decisive constraints. Implementation should begin with defined indications, locally evaluated workflows and quality assurance. Prospective evaluation should measure clinical benefit, total pathway costs and equitable access before wider expansion.

Keywords: Circulating tumour DNA; Liquid biopsy; Africa; Molecular residual disease; Molecular profiling; Cancer diagnostics

1 INTRODUCTION

GLOBOCAN estimated approximately 20 million new cancer cases and 9.7 million cancer deaths worldwide in 2022 (1). Africa is experiencing one of the fastest increases in cancer incidence and mortality due to population growth, ageing, urbanization, and epidemiological transition. Nigerian registry and regional studies illustrate the need for stronger cancer surveillance, but individual study populations cannot represent the continent as a whole (2,3). Improving diagnostic pathways requires molecular innovation to be considered alongside pathology, referral services, and treatment access.

Precision oncology has transformed cancer management by enabling therapies to be tailored according to the molecular characteristics of individual tumours. However, implementation of precision medicine in Africa remains constrained by limited access to high-quality tissue samples, shortages of pathology and genomic sequencing infrastructure, prolonged diagnostic turnaround times, and the high costs associated with molecular testing (4,5). Conventional tissue biopsy, while considered the diagnostic reference approach, is invasive, may not adequately capture tumour heterogeneity, and is often impractical for serial monitoring of disease progression or treatment response (6,7). These limitations have stimulated growing interest in minimally invasive biomarkers that provide dynamic molecular information throughout the cancer continuum.

Circulating tumour DNA (ctDNA) has emerged as one of the most promising liquid biopsy biomarkers for precision oncology. Tumour cells release it into the bloodstream primarily through apoptosis, necrosis, and active secretion. ctDNA contains tumour-specific genetic and epigenetic alterations, including somatic mutations, copy number alterations, methylation signatures, chromosomal rearrangements, and fragmentation profiles that closely reflect the molecular landscape of the primary tumour (7,8). Advances in highly sensitive molecular technologies, including digital droplet polymerase chain reaction (ddPCR), BEAMing, targeted next-generation sequencing (NGS), and methylation-based assays, have substantially improved the detection of low-frequency ctDNA variants, facilitating its integration into clinical oncology research and practice (4,6).

The strength of evidence differs across ctDNA applications. Validated plasma genotyping can support treatment selection in advanced cancer, particularly when tissue testing is impractical or inadequate. Post-treatment ctDNA is also a strong prognostic marker in several cancers, but prognostic validity does not automatically establish benefit from changing therapy. Population screening, broad molecular surveillance and treatment adaptation require indication-specific evaluation (9). This distinction is essential when considering adoption within health systems with competing diagnostic priorities.

African implementation should therefore address a defined service gap rather than assume that liquid biopsy can replace tissue diagnosis. Existing molecular laboratory networks may provide equipment, staff, or specimen transport capacity, but this is an implementation hypothesis that requires site-level assessment (10,11). Oncology testing introduces different requirements for low-frequency variant detection, interpretation, and clinical action. Underrepresentation in genomic research also supports local validation, although greater germline diversity alone does not establish poorer ctDNA assay performance (12).

This review examines the biological basis, analytical approaches and clinical applications of ctDNA while assessing their relevance to African oncology. Its strategic contribution is to distinguish established uses from emerging applications, summarise selected African evidence and propose a staged implementation pathway linked to clinical benefit and affordability.

1.1 Review approach

This is a narrative review with targeted evidence verification. For this revision, PubMed-indexed records, publisher sources and IARC-related cancer surveillance reports were checked using combinations of “circulating tumour DNA”, “cell-free DNA”, “liquid biopsy”, “Africa”, “lymphoma” and “molecular residual disease. Searches were supplemented by citation tracking. Priority was given to primary African studies, randomized trials, independent diagnostic validation and professional recommendations available by 4 September 2026. Foundational biological studies were retained where relevant. Evidence was considered according to study design, intended population, assay characteristics, reference standard, and outcome measured. This targeted approach was not an exhaustive systematic search; no pooled estimates or formal risk-of-bias scoring were undertaken. Selection bias and heterogeneity limit the completeness and generalizability of the synthesis.

2 BIOLOGY AND ANALYTICAL BASIS OF CIRCULATING TUMOUR DNA

Circulating tumour DNA (ctDNA) is a fraction of circulating cell-free DNA (cfDNA) that originates from malignant cells and carries tumour-specific genetic and epigenetic alterations reflective of the primary tumour and metastatic lesions (6,7). While cfDNA is released into the circulation during normal cellular turnover, ctDNA arises predominantly from apoptosis, necrosis, and, to a lesser extent, active secretion by viable tumour cells (6,13). Consequently, ctDNA contains clinically informative molecular features, including somatic mutations, copy number variations, chromosomal rearrangements, DNA methylation signatures, microsatellite instability, and characteristic fragmentation patterns that can be exploited for cancer diagnosis, prognosis, and therapeutic monitoring (4,8).

The ctDNA fraction varies with tumour burden, anatomical site, vascularity, metastatic distribution, and treatment (6,14). Advanced disease often produces more detectable ctDNA than localized disease, but this pattern is not uniform. Plasma is therefore a shedding-weighted representation of the tumour, not a complete census of every lesion. Rapid clearance permits repeated assessment of molecular changes; however, concentration also reflects release and clearance dynamics, not viable tumour volume alone (13).

Methylation and fragmentation provide additional information beyond somatic variants. Methylation-based assays can identify cancer-associated signals and predict their likely origin, although diagnostic performance depends on the specific population, cancer type, and stage of cancer (15,16). Fragmentomics analyses of the cfDNA pool, including fragment size distributions, nucleosome positioning, and end-motif signatures, have further expanded the diagnostic capabilities of liquid biopsy by improving discrimination between malignant and non-malignant DNA fragments (17). Performance in selected case-control datasets, however, must be distinguished from effectiveness in asymptomatic screening populations.

The successful clinical application of ctDNA relies heavily on highly sensitive molecular technologies capable of detecting low-frequency tumour-derived variants against a background of abundant normal cfDNA. Digital polymerase chain reaction (dPCR) and digital droplet PCR (ddPCR) provide exceptional analytical sensitivity for quantifying predefined hotspot mutations and monitoring treatment response, particularly where known driver mutations have already been identified (4). However, these approaches are limited to targeted genomic regions and are less suitable for comprehensive molecular profiling.

Targeted NGS can interrogate multiple alterations in a single plasma specimen, including substitutions, insertions, deletions and selected structural or copy-number changes. Detection of fusions, copy-number alterations, microsatellite instability or blood-based tumour mutational burden depends on panel design, tumour fraction and assay validation (5,7,9). Whole-genome approaches provide broader information but have different depth and cost requirements. The optimal platform follows the intended clinical use; broader coverage alone does not establish better clinical performance.

Pre-analytical handling and analytical validation are integral to assay performance. Collection tubes, time to plasma separation, centrifugation, storage and extraction affect DNA integrity and contamination by leukocyte DNA (4,7). Analytical reports should state the validated variant classes, detection limits, and relevant limitations. Clonal haematopoiesis can produce plasma variants unrelated to the solid tumour; paired leukocyte analysis or other validated methods may be required to distinguish their origin (18). A negative result must be interpreted in relation to specimen adequacy, assay coverage and expected tumour shedding.

For African services, specimen integrity must be established across the entire referral pathway. A regional laboratory may offer specialist testing, provided that peripheral collection sites can meet validated transport and processing requirements. Decisions about local versus referral testing should consider failed specimens, turnaround time, maintenance, quality assurance, and access to specialist interpretation. The East African lymphoma programme demonstrates that molecular testing can be evaluated within a coordinated diagnostic pathway; it does not show that any existing PCR laboratory can deliver equivalent results (19,20).

These biological and analytical properties make ctDNA a useful source of molecular information. Its suitability for a particular service depends on analytical validity, clinical validity and evidence that the result can improve a management decision. These requirements should guide assessment of the applications discussed below (9).

3 CLINICAL APPLICATIONS OF CIRCULATING TUMOUR DNA

3.1 Early Cancer Detection

Early diagnosis can improve outcomes when linked to effective care, but population screening requires evidence concerning both benefits and harms. Conventional screening programmes use cancer-specific methods; tissue biopsy is generally a diagnostic investigation rather than a population screening test. Blood-based testing could simplify specimen collection, but a positive result may still require imaging, endoscopy or tissue diagnosis (15,16).

Early-stage cancers may release ctDNA at levels below an assay's detection limit. Error-corrected sequencing and digital PCR improve analytical detection, but analytical sensitivity for a mutation does not equal clinical sensitivity for cancer. Assays must be evaluated in the intended population, including people without cancer and patients with low-shedding tumours (4,14).

Methylation-based and fragmentomic approaches can complement mutation analysis. Their performance reflects both the molecular features measured and the training populations used to develop classification algorithms (15,16,17). Validation should account for stage distribution, cancer prevalence, and non-malignant conditions. Positive predictive value in routine screening cannot be inferred directly from a case-control study enriched for cancer.

In the independent validation of a targeted methylation-based multi-cancer test, specificity was 99.5%, whereas sensitivity increased from 16.8% at stage I to 90.1% at stage IV (16). This contrast is central to interpretation: high specificity did not provide high sensitivity for the earliest cancers. Diagnostic validation also does not establish a mortality benefit from screening. Population adoption requires evaluation of downstream investigations, false reassurance, overdiagnosis and clinically meaningful outcomes.

Despite these advances, important limitations remain. The extremely low abundance of ctDNA in early-stage disease increases the risk of false-negative results, particularly for small or biologically indolent tumours (14). Conversely, age-related clonal haematopoiesis may introduce somatic mutations unrelated to cancer, reducing assay specificity if appropriate bioinformatic filtering is not applied (18). Furthermore, analytical performance varies considerably across tumour types because ctDNA shedding differs according to tumour biology, anatomical location, vascularity, and tumour burden (7).

For Africa, screening research should first establish whether a blood-based pathway can improve outcomes relative to feasible alternatives within the same budget. Referral completion, time to definitive diagnosis, and access to treatment are as important as assay accuracy. The available Ghanaian study assessed genomic feasibility in patients already diagnosed with breast cancer; it did not validate screening in asymptomatic women (21).

3.2 Molecular Profiling and Precision Medicine

Precision oncology relies on the identification of tumour-specific molecular alterations that inform prognosis, predict therapeutic response, and guide individualized treatment decisions. Traditionally, molecular profiling has depended on tissue biopsy, which provides valuable genomic information but is limited by its invasive nature, sampling bias, and inability to capture the spatial and temporal heterogeneity of evolving tumours (4,7). Circulating tumour DNA (ctDNA) has emerged as an attractive alternative, offering a minimally invasive approach for comprehensive genomic profiling through repeated blood sampling.

ctDNA may integrate molecular information from several lesions, but the contribution of each lesion depends on its shedding into the sampled circulation. Low-shedding or anatomically sequestered disease may be underrepresented. Plasma testing complements tissue profiling by allowing repeated sampling; it does not reliably replace histology or capture all spatial heterogeneity (6,7,9).

Advances in next-generation sequencing (NGS) have greatly expanded the utility of ctDNA for molecular characterization. Modern targeted sequencing panels can simultaneously identify single nucleotide variants, insertions and deletions, copy number alterations, structural rearrangements, microsatellite instability (MSI), and tumour mutational burden (TMB) from a single plasma sample (5,7). These molecular alterations increasingly serve as predictive biomarkers for targeted therapies and immunotherapies across multiple cancer types.

Advanced NSCLC is an established setting for validated plasma genotyping. Actionable findings can guide treatment when interpreted within the relevant clinical pathway, while a non-informative plasma result may require tissue testing (5,9). Other cancers also have indication-specific molecular testing pathways. Statements about treatment selection should identify the validated alteration, tumour type, and available treatment. Variants in hereditary cancer genes

require appropriate assessment of germline versus somatic origin rather than assuming that a plasma finding alone establishes inherited susceptibility (9).

Serial sampling can reveal clonal evolution and emerging resistance. However, detecting a molecular change before radiological progression does not itself demonstrate that immediate treatment modification improves outcomes. Such changes should be acted upon only within an evidence-supported pathway or a clinical trial designed to test that strategy (9).

Integrating mutations with methylation or fragmentation may improve classification in selected studies. Each combined assay nevertheless requires independent validation, because additional features can introduce model overfitting or population-dependent performance. Clinical interpretation should follow validated assay outputs rather than extrapolate from exploratory signatures (15,16,17).

Despite its considerable advantages, ctDNA-based molecular profiling has several important limitations. Low ctDNA concentrations in early-stage disease may reduce analytical sensitivity, while tumour types characterized by limited DNA shedding, such as certain brain tumours and indolent malignancies, remain challenging to detect using plasma-based assays (14). Furthermore, false-positive variants resulting from clonal haematopoiesis require careful interpretation and confirmatory analytical strategies to distinguish age-related somatic mutations from tumour-derived alterations (18). Standardization of sequencing platforms, variant calling pipelines, and reporting frameworks therefore remains essential for ensuring consistent clinical implementation.

African deployment of plasma genotyping should prioritize patients for whom a result can change an accessible treatment decision. A technically successful assay has limited clinical value if the indicated medicine, tissue confirmation, or specialist review is unavailable. Regional referral models may support access, but their effectiveness must be measured rather than assumed from the presence of sequencing infrastructure (21,20).

3.3 Monitoring Treatment Response

Treatment response is assessed through clinical review, imaging and other disease-specific measures. Serial ctDNA may provide additional information about molecular response, particularly when a tumour-associated signal was detectable before treatment. Its value depends on standardized sampling, validated thresholds and an evidence-based interpretation pathway (13,22,9).

A decline in ctDNA can accompany treatment response, while persistence or an increase may signal residual disease or progression. The relationship is influenced by tumour shedding, treatment-induced cell death and sampling time (13). A change should therefore be interpreted alongside clinical and radiological findings rather than treated as a direct measurement of viable tumour burden.

Studies across solid tumours have associated ctDNA dynamics with subsequent outcomes. Bratman and colleagues evaluated personalized ctDNA measurements in patients receiving pembrolizumab, supporting investigation of molecular response as a biomarker (22). Such associations establish prognostic information; they do not prove that switching therapy in response to a molecular rise improves survival.

During immunotherapy, ctDNA may complement imaging when response assessment is difficult. Proposed applications include investigating pseudoprogression, but a molecular result should not independently override clinical deterioration or established response criteria. Prospective studies must test prespecified management algorithms before broad clinical adoption (22,9).

Treatment-associated fluctuations further emphasize the importance of sampling schedules. Research protocols should distinguish transient changes from sustained molecular response and should report baseline detectability, missing specimens, and the timing of plasma collection relative to treatment (13,9).

Despite these advantages, several factors influence the interpretation of ctDNA during treatment monitoring. The magnitude and timing of ctDNA changes vary according to tumour type, disease stage, treatment modality, and biological characteristics such as tumour vascularity and DNA shedding (14). Moreover, standardized thresholds for defining molecular response have not yet been universally established, limiting direct comparison across studies and clinical settings (4).

African treatment-monitoring studies should evaluate whether adding ctDNA changes management or outcomes at an acceptable cost. Limited imaging access does not make an unvalidated molecular substitute appropriate. Useful outcomes include time to confirmed progression, unnecessary treatment changes, patient retention and access to salvage therapy. ctDNA should initially be assessed as a complementary component of a defined care pathway.

3.4 Molecular Residual Disease Detection and Surveillance for Recurrence

In solid tumours, molecular residual disease (MRD) describes tumour-associated molecular signals detected after treatment with curative intent, when disease may not be apparent clinically or radiologically. Post-treatment ctDNA can predict recurrence, but sensitivity depends on the assay and sampling schedule. This distinction between recurrence prediction and evidence for treatment benefit is fundamental to interpretation (23,24,25,9).

Persistent or recurrent ctDNA positivity after curative-intent treatment is associated with increased recurrence risk in several cancers (24,25,26). A negative result does not establish absence of residual disease, particularly with low shedding or limited assay sensitivity. Molecular positivity must also be interpreted in relation to postoperative timing and assay specificity. Treatment decisions require evidence from the relevant tumour and stage.

The randomized “DYNAMIC trial” in stage II colon cancer demonstrated that a ctDNA-guided strategy could reduce adjuvant chemotherapy use without compromising its prespecified recurrence-free survival comparison (27). Five-year follow-up reported recurrence-free survival of 88% with ctDNA-guided management and 87% with standard management (28). These findings support the tested strategy in its study population; they should not be generalized to all postoperative cancers.

DYNAMIC-III provides an important counterpoint in stage III colon cancer. ctDNA remained strongly prognostic, but the de-escalation strategy did not meet the trial’s non-inferiority criterion, while escalation in ctDNA-positive patients did not improve recurrence-free survival (29). Molecular risk stratification therefore does not guarantee that a proposed therapeutic adjustment is beneficial.

In IMvigor011, patients with muscle-invasive bladder cancer who became ctDNA-positive after surgery were randomized to atezolizumab or placebo. Treatment improved disease-free and overall survival in this selected population (30). This is direct interventional evidence for a defined indication. Persistently ctDNA-negative patients were not randomized to treatment, so their outcomes do not establish the safety of withholding every form of adjuvant therapy.

Observational lung- and breast-cancer studies have demonstrated molecular detection of recurrence before clinical or radiological recognition (23,25). This lead time may create an opportunity for intervention, but earlier detection alone does not establish improved survival. Trials should measure whether intervention during molecular relapse is effective, rather than assume that advancing the date of detection changes the disease course.

MRD assays differ in whether they are tumour-informed or tumour-naïve. Tumour-informed assays require suitable tumour material and patient-specific assay development; plasma-only approaches use predefined molecular features and require rigorous specificity control (31,9). Cost, turnaround time, tissue access and the validated sampling schedule must be considered when selecting a platform.

For African oncology, initial MRD implementation should be restricted to clearly specified, evidence-supported indications or prospective studies. Protocols must define what follows a positive, negative, or indeterminate result and ensure access to the proposed intervention. Imaging, pathology, and clinical follow-up remain necessary. Research should measure both patient outcomes and the additional cost of serial testing.

3.5 Detection of Therapeutic Resistance and Clonal Evolution

The emergence of therapeutic resistance remains a major challenge in cancer management and is a leading cause of treatment failure and disease progression. Tumours evolve continuously under therapeutic pressure, acquiring new genetic and epigenetic alterations that enable malignant cells to evade targeted therapies, chemotherapy, immunotherapy, and hormonal treatment (8). Because tissue biopsy is invasive and often impractical to repeat, it provides only a static representation of tumour biology and may fail to capture the dynamic molecular changes associated with resistance. Circulating tumour DNA (ctDNA) overcomes these limitations by enabling serial, minimally invasive monitoring of tumour evolution throughout the course of treatment.

Serial ctDNA analysis can identify emerging resistant clones, but their representation depends on tumour shedding and assay coverage (8). Molecular emergence, radiological progression and clinical deterioration are distinct events. Their relationship should be assessed within tumour-specific treatment pathways rather than assuming that every molecular change requires immediate intervention (9).

One of the earliest and most successful applications of ctDNA-guided resistance monitoring has been in non-small cell lung cancer (NSCLC). Patients receiving first- or second-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors frequently develop the EGFR T790M resistance mutation, which can be accurately detected using plasma ctDNA (32). Identification of this mutation enables selection of third-generation EGFR inhibitors such as

osimertinib, significantly improving clinical outcomes while avoiding repeat tissue biopsy (5). Plasma genotyping is now incorporated into international clinical guidelines for managing advanced EGFR-mutant NSCLC.

In colorectal cancer, ctDNA can identify alterations associated with resistance to anti-EGFR therapy. Changes in resistant clone abundance have generated interest in molecularly selected rechallenge strategies (8). A treatment decision nevertheless requires evidence for the specific regimen, clinical setting, and assay; detection of a resistance-associated variant should not be presented as a universal instruction to stop therapy.

In breast cancer, ESR1 and PIK3CA alterations illustrate the relevance of molecular testing to endocrine and targeted treatment pathways. The clinical action depends on the alteration, prior treatment, and evidence supporting the selected therapy. Broad statements about acting on molecular resistance before clinical progression require trial-specific support (9).

The expanding use of immunotherapy has further highlighted the value of ctDNA in monitoring treatment resistance. Changes in ctDNA levels often precede radiological evidence of response or progression and may help distinguish true disease progression from immune-related pseudoprogression, a phenomenon that complicates interpretation of conventional imaging (22). Emerging evidence also suggests that ctDNA may identify genomic alterations associated with resistance to immune checkpoint inhibitors, although these applications require further validation before widespread clinical adoption.

Longitudinal profiling can describe the emergence and decline of tumour subclones. This provides biological insight and may identify therapeutic hypotheses, but reconstructing clonal evolution does not by itself establish a superior treatment strategy. Clinical benefit requires prospective testing of the decision generated by that information (8,9).

Despite its considerable promise, several challenges remain. The sensitivity of ctDNA for detecting resistance mutations depends on tumour burden, DNA shedding, sequencing depth, and assay design, while low-frequency resistant clones may remain below the detection threshold in some patients (4). In addition, distinguishing clinically relevant resistance mutations from passenger variants and clonal haematopoiesis requires robust bioinformatic analysis and careful clinical interpretation (18). Standardized analytical pipelines and prospective validation studies remain essential for broader clinical implementation.

4 CHALLENGES AND OPPORTUNITIES FOR CTDNA IMPLEMENTATION IN AFRICA

4.1 Current Landscape of Precision Oncology in Africa

African oncology services differ substantially between and within countries. Registry studies document cancer burden but do not measure continent-wide access to precision oncology (1,2,3). An implementation assessment should therefore describe the population served, diagnostic pathway and available treatment rather than infer readiness from a national or continental label. Selected African studies provide a more concrete basis for evaluating ctDNA opportunities.

The Ghana Breast Health Study analysed plasma from 15 women with breast cancer using low- and higher-depth whole-genome sequencing. It demonstrated the feasibility of detecting tumour-derived copy-number information (21). The study lacked cancer-free controls and outcome data, so it could not establish diagnostic sensitivity, specificity, or benefit from using the result in care. Its contribution is genomic feasibility in an understudied population.

In East Africa, the AI-REAL protocol proposed prospective comparison of liquid biopsy with pathology for suspected infection-related lymphoma (19). Subsequent targeted sequencing research investigated MYC-immunoglobulin translocations and EBV-derived signals in plasma (33). These publications represent different stages of evidence development: a protocol defines planned evaluation, whereas an analytical study demonstrates performance within its sampled population.

A completed multicentre study published in 2026 evaluated 377 children and young adults with suspected lymphoma in Tanzania and Uganda. Models were developed in 212 participants, with external validation in 56; head-to-head diagnostic comparison involved 58 participants. The comprehensive model achieved an AUC of 0.95, with sensitivity of 0.86 and specificity of 0.95, while external-validation AUC was 0.98. Median diagnostic turnaround time fell from 46.8 to 6.5 days in the comparative assessment (20). These findings support an indication-specific pathway; they do not establish survival benefit or performance in unrelated cancers.

African representation should be addressed through validation across relevant patient populations, stages and clinical pathways. Germline ancestry, somatic tumour biology, infection-associated cancers, comorbid conditions and pre-

analytical differences are related but distinct considerations (12,21,20). Local validation should test identifiable sources of error and model transferability rather than assume that genomic diversity necessarily reduces assay accuracy.

The East African programme also illustrates the role of coordinated pathology review, molecular laboratories and multidisciplinary interpretation (19,20). General genomic capacity-building initiatives provide useful background (11), but ctDNA implementation requires dedicated clinical pathways and assay-specific quality assurance. Partnerships should build locally retained skills and decision-making capacity.

Table 1 summarises selected African evidence rather than a complete inventory. Together, these studies support targeted evaluation of ctDNA in well-defined services. They leave important questions about affordability, wider transportability and patient outcomes unanswered.

Table 1: Selected African ctDNA evidence

Study and setting	Design and assay	Main contribution	Limits for implementation
Ahuno et al., Ghana (21)	15 breast-cancer patients; low- and higher-depth plasma whole-genome sequencing	Tumour-derived copy-number information was detectable	No cancer-free controls or outcome data; genomic feasibility, not screening validation
Legason et al., Tanzania and Uganda (19)	AI-REAL protocol; planned prospective comparison with pathology	Defined diagnostic accuracy, turnaround time and economic evaluation	Protocol reports planned methods, not completed effectiveness
Chamba et al., East Africa (33)	Exploratory targeted plasma sequencing for MYC-Ig and EBV signals	Supported molecular-marker development for Burkitt lymphoma	Small exploratory study; larger independent validation required
Chamba et al., Tanzania and Uganda (20)	377 participants overall; model development n=212; external validation n=56; paired comparison n=58	Model AUC 0.95; external AUC 0.98; median turnaround 46.8 versus 6.5 days	Indication-specific diagnostic evidence; no demonstrated survival benefit; costs and transferability need evaluation

Abbreviations: AUC, area under the receiver-operating-characteristic curve; EBV, Epstein–Barr virus; MYC-Ig, MYC-immunoglobulin. Cohort subsets are reported separately and should not be added together.

4.2 Technical, Economic, and Health System Challenges

The barriers to ctDNA implementation extend beyond acquiring an instrument. A reliable service requires validated specimen handling, assay performance, interpretation, reporting, and a management pathway that can act on the result (4,9). Failure at any stage can remove the expected clinical benefit.

A major technical challenge lies in the extremely low abundance of ctDNA, especially in patients with early-stage disease or minimal residual disease. Since ctDNA often constitutes less than 1% of total circulating cell-free DNA, highly sensitive analytical platforms are required to reliably distinguish tumour-derived variants from background DNA (6,14). Assay performance is further influenced by pre-analytical factors including blood collection methods, sample transport, plasma separation, DNA extraction procedures, storage conditions, and sequencing depth. Variability in these processes may compromise reproducibility and contribute to inconsistent clinical interpretation (4, 34, 35, 36).

Bioinformatic analysis presents an additional challenge. High-throughput sequencing generates large and complex datasets that require sophisticated computational pipelines for variant calling, annotation, and interpretation. Furthermore, age-related clonal haematopoiesis of indeterminate potential (CHIP) may introduce somatic mutations unrelated to cancer, increasing the risk of false-positive results if appropriate filtering strategies are not applied (18). Standardized analytical pipelines and external quality assurance programmes are therefore essential for ensuring reliable ctDNA testing.

Affordability should be assessed using total pathway costs rather than sequencing price alone. Relevant costs include collection tubes, transport, extraction, repeat tests, bioinformatics, equipment maintenance, quality assurance, specialist interpretation and downstream investigations. The East African lymphoma study reported substantially higher per-patient liquid-biopsy costs than histopathology costs at the throughput evaluated, despite shorter

turnaround time (20). Scale and faster diagnosis may change value, but they do not justify assuming that liquid biopsy is cheaper.

Genomic testing requires appropriate consent, data protection and transparent governance. Agreements should specify access to raw data, cross-border transfer, secondary use and responsibility for clinically relevant findings. Potential germline findings need a defined counselling and confirmation pathway (9). African institutions should participate in decisions about data access, interpretation and reuse; local governance cannot be reduced to overseas assay procurement.

Existing molecular laboratories may contribute staff, instruments or referral networks, but their suitability must be assessed against the proposed ctDNA assay. Required additions may include error-controlled sequencing, oncology interpretation, external quality assessment and validated reporting. Repurposing should therefore be budgeted and evaluated as service development rather than assumed to be immediate (11,19).

Equity should be assessed explicitly. A service concentrated in referral centres may increase geographic or financial exclusion unless transport, referral completion and patient charges are addressed. Evaluation should report who receives testing, whose samples fail, who obtains confirmatory investigation and who accesses the treatment indicated by the result.

4.3 Future Perspectives

Future development should follow an indication-led sequence. The first step is to select a clinical problem for which ctDNA can generate an actionable result, with an assay validated for that purpose. Examples include plasma genotyping when tissue is inadequate or prospective evaluation of a lymphoma diagnostic pathway (5,20). Selection should account for locally accessible treatment and competing diagnostic priorities.

The second step is to establish the specimen and laboratory pathway. Collection sites need written requirements for tubes, processing, transport, and storage. Referral laboratories need validated detection limits, variant-class coverage, controls and external quality assessment. Reports should explain negative and indeterminate results and identify when tissue testing remains necessary (4,9).

The third step is to link reporting to clinical action. Multidisciplinary review should define which results can guide treatment, which require confirmation, and which are investigational. A positive result must lead to an accessible diagnostic or treatment pathway. Where effectiveness is uncertain, testing should occur within a prospective study with a prespecified management algorithm.

The fourth step is prospective service evaluation. Core measures should include specimen failure, turnaround time, concordance with an appropriate reference, treatment changes, patient retention, clinical outcomes, and total costs. Implementation should also measure false-positive investigations and financial burden. Faster molecular reporting is valuable only when the subsequent care pathway can use the information.

The fifth step is expansion after demonstrating benefit and feasibility. Regional hubs may serve peripheral collection sites, but expansion requires evidence that specimen quality, interpretation, and follow-up remain reliable. Budget-impact and cost-effectiveness analyses should use observed local data. Coverage should be monitored across income groups and geographic areas to prevent growth that benefits only patients able to pay.

Research priorities include independent validation of diagnostic models, standardized MRD sampling, and trials of specific ctDNA-guided management decisions. Multicentre African studies should separate laboratory performance from clinical effectiveness and should include comparison groups representative of the intended pathway. Equitable collaborations should support local laboratory leadership, pathology review and access to analysed data (21,19,20).

Artificial intelligence and multimodal assays may improve classification, but their value requires independent validation and assessment of calibration, missing data and performance across populations (17,20). More complex models can increase computing and maintenance requirements. Adoption should follow demonstrable improvement in a clinical decision rather than technological novelty alone.

A sustainable programme must combine diagnostic innovation with existing cancer-control priorities. National or institutional planning should specify financing, quality oversight, procurement and accountability for patient follow-up. The proposed sequence provides a practical route to evaluate ctDNA without diverting resources from essential pathology, effective screening or treatment services.

5 CONCLUSION

ctDNA provides clinically useful molecular information in defined oncology settings. Validated plasma genotyping can guide treatment selection, while molecular residual disease has strong prognostic value. Evidence that ctDNA-guided management improves outcomes is specific to the cancer, disease stage, assay and intervention tested. Early detection and broad serial monitoring should therefore be discussed according to their actual level of evidence.

African research now includes genomic feasibility studies and multicentre evidence of improved diagnostic turnaround time for EBV-positive Burkitt lymphoma. These findings justify further indication-specific implementation, but do not establish universal effectiveness or affordability. The priorities are reliable specimen pathways, quality assurance, pathology integration and access to clinically appropriate treatment.

Implementation should proceed through defined indications, validated workflows and prospective evaluation before wider expansion. Measuring clinical outcomes, total pathway costs and equitable access will determine whether ctDNA adds value to African cancer care. Its contribution depends on the decisions and services connected to the result.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of conflict of interest

No Conflicts of interest declared.

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