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CLINICAL TRIALS

From blood to breakthroughs: how multi-analyte liquid biopsies can transform precision oncology, drug development and clinical trials

Addressing key oncology drug development challenges through multi-analyte liquid biopsy approaches

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Multi-analyte and multi-omic liquid biopsy is a minimally invasive procedure that analyses multiple tumour-derived components (analytes) in body fluids (generally blood) to provide a real-time, comprehensive view of a patient's cancer. Such multi-omic analysis is transforming oncology drug development by addressing key challenges that pharmaceutical companies face in early drug development and clinical trials. Multi-analyte liquid biopsy analysis provides a cost-effective means to stratify patient cohorts, track clonal evolution and tumour heterogeneity, detect resistance mutations early, and identify minimal residual disease (MRD). As such, liquid biopsy provides real-time insights that can enhance clinical trial outcomes.

The complexity of cancer biology presents significant challenges for the pharmaceutical industry, particularly in developing effective, targeted treatments. While valuable for initial diagnostics, traditional tissue biopsies are invasive and impractical for repeat monitoring of patients. Liquid biopsy offers a transformative, minimally invasive solution for analysing multiple biomarkers circulating in the bloodstream.[1] By incorporating multi-analyte and multi-omic data, liquid biopsy can address some of the key challenges in oncology drug development and clinical trials, from patient stratification and monitoring tumour dynamics to enhancing patient safety and trial efficiency (**Figure 1**).

The multi-analyte approach

Liquid biopsy analytes, primarily circulating tumour DNA (ctDNA) and circulating tumour cells (CTCs) provide complementary insights into the tumour landscape. ctDNA – the most established analyte in liquid biopsy due to straightforward sample collection, molecular analysis and significant investment – consists of fragmented DNA released predominantly from dying cancer cells through necrosis or apoptosis.[1,2] Through analysis of ctDNA, researchers can identify mutation status and track genetic changes associated with resistance or disease progression.[1] This information can also be obtained by analysing genomic DNA (gDNA) derived from CTCs – intact, viable tumour cells that spread the cancer, often referred to as the 'seeds of metastasis'.[3] CTCs are the closest proxy to solid tissue biopsy.[4] They not only carry gDNA but also a wealth of information in their proteome, transcriptome and metabolome (multi-omic data).[4,5] By analysing proteins, RNA and metabolites within CTCs and CTC clusters, researchers can gain additional insights into tumour aggressiveness, metastatic potential and altered metabolic pathways.[1,5] Other liquid biopsy analytes include exosomes (extracellular vesicles [EVs]), circulating free RNA (cfRNA), specific proteins and metabolites that potentially offer additional clues about immune evasion and intercellular signalling.[5]

The dual analysis of ctDNA and CTCs is gaining traction and provides valuable complementary insights into tumour dynamics, enabling real-time, adaptive responses to cancer's complex behaviours.[2,6]

Some key challenges faced in oncology drug development and clinical trials

Challenge: need for real-time monitoring

Traditional biopsies are invasive, costly and unsuitable for repeat sampling, and may only be repeated once more from a metastatic site.[1,7] The unsuitability of tissue for real-time monitoring to detect changes in tumour

Figure 1: Use of liquid biopsy in the patient care pathway

dynamics prevents timely and effective treatment decisions. Multi-analyte liquid biopsy provides an ideal solution by enabling repeat sampling to provide a real-time view of tumour evolution. Through regular analysis of ctDNA, CTCs and other analytes, researchers gain continuous insights into tumour progression, mutation patterns and cell behaviour, capturing changes that could otherwise go unnoticed.[6,8] Lustberg *et al* discuss the value of this approach, highlighting the potential of monitoring liquid biopsy analytes to provide insights into tumour evolution and resistance mechanisms.[7] One study found that HER2 status changed in 37% of breast cancer recurrences, underscoring the importance of re-evaluating tumour biomarkers to optimise drug treatment.[9] Furthermore, multiple papers describe how liquid biopsy is effective in detecting minimal residual disease, often providing early indication of relapse before traditional imaging methods reveal progression.[10,11,12] In one case, CTC enumeration indicated the presence of MRD four years before clinically detectable metastatic disease, offering early insights for therapeutic management.[13] In clinical trials, real-time molecular data from liquid biopsies could prove invaluable by providing up-to-date insights into tumour dynamics. This has the potential to improve clinical trials by enabling pharmaceutical teams to monitor treatment efficacy more rapidly, evaluate biomarker changes over time and make data-driven adjustments to trial strategies, thereby minimising uncertainties, optimising patient care and ensuring that emerging disease changes are not overlooked.

Challenge: tumour heterogeneity and drug resistance monitoring

Cancer's inherent variability presents a major obstacle in oncology, as both interpatient heterogeneity (differences

across patients) and intrapatient heterogeneity (differences within a single patient) make treatment selection and efficacy difficult to predict.[14,15] Tumours evolve dynamically, with cancer cell populations mutating in response to therapies, often leading to treatment resistance.[1,14] Therefore, to develop effective treatment strategies, pharmaceutical companies need a clear understanding of the tumour and the ability to monitor its evolution.

Multi-analyte liquid biopsy tackles tumour heterogeneity and drug resistance by providing a comprehensive, real-time molecular profile that captures a tumour's evolution.[2,6] By integrating data from ctDNA, CTCs and other analytes, liquid biopsy enables researchers to track the emergence of specific mutations or adaptive characteristics as they arise.[5,6,15] A study in melanoma by Sementsov *et al* used a multi-analyte approach, and demonstrated that CTC analysis provided additional genomic information to ctDNA in 68.8% of the samples, identifying mutations in key melanoma pathways related to metastasis and therapeutic resistance, such as BRAF, NRAS, CTNNB1 and MAP2K1.[8] These findings exemplify how CTCs deliver unique and complementary insights into tumour evolution and resistance mechanisms.

This dynamic tracking is crucial in clinical trials, where treatment resistance is a frequent cause of trial failure. By detecting resistance mutations early and observing changes in tumour cell characteristics, liquid biopsy allows R&D teams to make timely, data-driven decisions. Early prediction of treatment failure may enable trials to 'fail fast', by providing an early endpoint when signs of resistance arise, and help to reduce costly later-stage failure. It may also help identify patient cohorts with a specific

biomarker profile who are either likely or unlikely to benefit from the study drug, and can therefore be included or excluded from subsequent studies.

The LIQUID IMPACT trial highlights the potential of multi-analyte liquid biopsy for addressing tumour heterogeneity and resistance in advanced cancers.[16] By measuring protein expression changes, such as EGFR and mTOR overexpression, the study demonstrated an ability to monitor key tumour characteristics.[16] This capability is valuable for pharmaceutical companies seeking to stay informed about dynamic changes in a patient's cancer.

Challenge: patient stratification for precision medicine

Accurate patient stratification is critical for targeted treatment and ensuring positive clinical trial outcomes. Selecting patients whose tumour profiles align with investigational drugs may enhance trial success rates, reduce trial costs, increase pricing and reimbursement coverage, and accelerate drug development. Multi-analyte liquid biopsy offers a comprehensive and non-invasive approach for revealing relevant genetic, transcriptomic and proteomic changes essential for targeted patient selection.

The ELIMA project exemplifies this approach by analysing CTCs, EVs and ctDNA from a single blood sample.[17] This method enabled the identification of patients who may benefit from specific therapies, such as the PIK3CA inhibitor Alpelisib, which has been approved for metastatic breast cancer patients with PIK3CA mutations detected in ctDNA.[17] Another clinical trial demonstrates that proteomics from CTCs can significantly enhance patient stratification by identifying patients most likely to benefit from advanced targeted therapies, such as antibody drug conjugates (ADCs).[18] By enabling the selection of patients with the highest likelihood of response, stratification ensures trials are both cost-effective and positioned for regulatory and commercial success, avoiding the risks associated with low response rates.

Examples for this being integrated in best practice include AstraZeneca's application of a multi-omic strategy. By integrating genomics, transcriptomics, proteomics and metabolomics data across its oncology pipeline, AstraZeneca enhances trial participant selection by focusing on specific tumour pathways, improving the accuracy of treatment response predictions.[19]

Challenge: rising costs, regulatory pressures and drug pricing

The financial and regulatory demands in oncology drug development are considerable, and developing a new drug requires substantial resources to meet strict regulatory standards for safety, efficacy and cost-effectiveness. High failure rates, especially in later phase trials, further burden budgets and delay patient access to new treatments. Multi-analyte liquid biopsy offers a strategic advantage by providing real-time molecular insights that support early trial adaptations, reduce costly late-stage failures and alleviate the financial pressures of precision oncology trials. For instance, a lung cancer trial at the University of Arkansas for Medical Sciences (UAMS), US, utilises liquid biopsy for longitudinal monitoring. This approach aims to improve efficiency by enabling earlier detection of recurrence and tailoring interventions, potentially reducing trial costs through streamlined processes and minimising the need for invasive procedures.[20]

Pantel and Alix-Panabières, in *Nature Reviews Clinical Oncology*, highlight the cost-saving potential of liquid biopsy in oncology trials, noting that monitoring CTCs and ctDNA may serve as early surrogate endpoints for clinical outcomes.[11] This approach could shorten follow-up and reduce costs, allowing pharmaceutical companies to make faster, cost-effective decisions in evaluating adjuvant therapies.

Conclusion

Multi-analyte and multi-omic liquid biopsy continues to demonstrate its potential in overcoming key challenges in the oncology space. The integration of liquid biopsy into clinical trials may pave the way for faster, more cost-effective drug development and improved regulatory compliance. By delivering precise, real-time molecular insights, liquid biopsy can enhance patient stratification, treatment monitoring and clinical trial efficiency, ultimately accelerating the development of effective precision cancer therapies. Current clinical trials are evaluating dual CTC and ctDNA analysis across multiple cancer types to stratify patients, monitor treatment response and enhance sensitivity in disease monitoring as compared to standard practice.[2]

> *The integration of liquid biopsy into clinical trials may pave the way for faster, more cost-effective drug development and improved regulatory compliance*

Once approved, targeted drugs such as ADCs, DNA damage response (DDR) inhibitors and immuno-oncology drugs require targeted treatment selection through a companion diagnostic. Utilising liquid biopsy solutions will be critical to enable real-time, repeatable biomarker assessment to support regulatory clearance and reimbursement.

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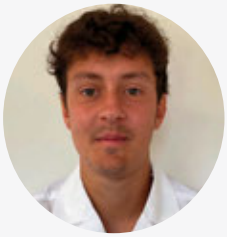
Karen Miller PhD, chief scientific officer at **ANGLE plc**, has over 30 years' experience in the biotechnology and pharmaceutical industry, with a focus on drug discovery and clinical development in a wide range of indications including oncology. Most recently, Karen was chief scientific officer at Ixaka having previously held senior roles at Adaptimmune, GlaxoSmithKline, UCB Pharma and Vertex.



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