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Liquid biopsies, are we ready for prime time?

Nicola Normanno,[1] Kathi Apostolidis,[2] Mark Stewart[3]

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[1]Cell Biology and Biotherapy Unit, Istituto Nazionale Tumori IRCCS Fondazione Pascale, Napoli, Italy
[2]European Cancer Patient Coalition, Bruxelles, Belgium
[3]Friends of Cancer Research, Washington, District of Columbia, USA

Correspondence to
Dr Nicola Normanno; nicnorm@yahoo.com

The possibility to use a simple peripheral blood sample to make an early diagnosis of cancer, to gain information on the genomic profile of the tumor, and to predict prognosis and the probability to respond to therapy has fascinated researchers and clinicians for many years. The improvement of technologies for isolating and analyzing circulating tumor DNA (ctDNA), from the peripheral blood or other body fluids of patients with cancer, is transforming this fascinating hypothesis in a clinically relevant diagnostic approach.

The applications of liquid biopsy in oncology drug development and clinical care are continuously expanding. The first clinical application of liquid biopsy in oncology was the detection of resistance mutations in EGFR mutant non-small-cell lung cancer (NSCLC) patients.[1] ctDNA testing is currently recognized as an alternative approach for tumor genomic profiling of any tumor type when tissue is not available.[2] In patients with advanced cancer, the presence of ctDNA is a well-recognized negative prognostic factor.[3] Similarly, the dynamics of ctDNA do correlate with the response to any type of systemic treatment (ie, targeted therapy, chemotherapy, and immunotherapy).[3–5] Importantly, the application of liquid biopsy is now moving toward the earlier phases of the disease, from the early diagnosis to the identification of minimal residual disease (MRD) in patients undergoing surgical resection of the primary tumor.

The review article from Vellanki *et al*[6] at the US FDA describes in an accurate and detailed manner the possible application of liquid biopsy in the field of precision oncology. More importantly, the authors highlight what further evidence is needed to transition from research only applications of ctDNA tests to clinical practice and perhaps even use it as an early endpoint in clinical trials. The validation of this latter approach could be of considerable importance to accelerate the approval of new drugs.

In evaluating new approaches to cancer diagnosis and therapy, we should always ask ourselves what are the implications and possible benefits for patients with cancer. In this respect, the introduction of liquid biopsy in the management of patients with cancer can significantly improve our ability to provide a precision/personalized approach starting at the earliest stages of the disease.[7]

A significant fraction of patients with cancer, especially in the locally advanced/metastatic setting, do not have tissue available for genomic profiling. The possibility to genotype patients using ctDNA increases the likelihood of identifying actionable mutations allowing therapeutic intervention with targeted therapy. Importantly, this approach also improves the selection of patients who may qualify for immunotherapy. For example, patients with EGFR, ALK or RET mutant NSCLC do not benefit from immunotherapy. Therefore, identification of actionable mutations will spare the patients from the toxicity of therapeutics that will provide limited clinical benefit. Our current approach to cancer treatment is based on the testing of a limited amount of tumor tissue from a single cancer lesion. This methodology does not recapitulate the high level of heterogeneity of cancer and does not take into consideration possible genomic alterations that may have occurred from the time the tumor tissue was taken till the time treatment decisions are made. Combining tumor tissue and liquid biopsy testing will provide a better picture of the complexity of cancer, allowing the selection of more appropriate treatments. In this respect, preliminary data suggest that using combinations of agents that target the complex genomic landscape of the tumor rather than a single alteration might improve the outcome of patients with cancer.[8] Integration of different omics and elaboration of treatment algorithms with artificial intelligence will further improve the ability to administer increasingly effective treatments.

Clinical and pathological risk factors are currently used to select whether patients with surgically resected cancer should receive adjuvant therapy. However, these factors do not allow an accurate stratification of patients by risk for recurrence. The consequence is that patients at low risk of recurrence are overtreated, while those at high risk might not receive the most appropriate treatment. Consistent evidence from clinical trials suggest that assessment of 'molecular' MRD by ctDNA testing is a powerful risk factor in many if not all cancer types.[9] However, additional data and improvement of the technologies are needed to transfer this approach into clinical practice. Although the absence of ctDNA after surgery is a powerful favorable prognostic factor, a fraction of ctDNA negative patients still experience recurrence of the disease.[10] A MRD ctDNA negative result suggests that the tumor has been completely eradicated by surgery and adjuvant therapy. However, the relatively low sensitivity of the ctDNA assay or the lack of shedding of ctDNA by residual tumor cells may cause a false negative result in patients who are still at risk of recurrence. Indeed, the majority of recurrence events occurring in ctDNA negative patients are locoregional, suggesting that lack of systemic dissemination might result in lower levels of circulating ctDNA. Different strategies have been proposed to overcome these limits. For example, longitudinal monitoring (ie, repeated tests on samples collected over time) has been shown to reduce the risk of false negatives.[11] Combinations of different biomarkers such as variants and methylation may also increase the sensitivity and specificity of ctDNA testing.[12] However, the current limitations of the technologies used for the detection of MRD ctDNA raise questions about the appropriateness of deintensifying adjuvant therapy in patients with negative ctDNA, especially in the presence of clinical risk factors. In contrast, ctDNA positive patients have a poor prognosis as demonstrated in several studies. However, clinical trials are required in order to demonstrate the clinical utility of therapy intensification in this subgroup of high-risk patients. In this respect, as highlighted by Vellanki *et al*, ctDNA testing offers a unique opportunity to stratify patients based on a powerful prognostic biomarker and, therefore, plan appropriate clinical trials in patient populations with different levels of risk, thus allowing a precision oncology approach.

The above summarized evidence suggests that the introduction of liquid biopsy in the management of the patient with cancer, from early diagnosis to limited or metastatic disease, can help improve precision medicine approaches and possibly patient prognosis. Once the technological and clinical problems, we have highlighted have been solved, the problem remains of how to guarantee access to this fundamental innovation for all patients.

Access to high-quality biomarker testing is essential to allow patients with cancer receiving the most active treatments for their disease. A recent survey of the International Quality Network for Pathology (IQN Path), the European Cancer Patient Coalition (ECPC) and the European federation of Pharmaceutical Industries and Associations (EFPIA) revealed significant barriers in the access to biomarker testing in the majority of European countries.[13] In particular, less than 10% of tumor biopsies that required a biomarker test were analyzed with next-generation sequencing (NGS) in Europe. Lack of capability, low awareness among stakeholders, and/or limited resources were among the most frequent barriers found in several European countries. These issues are not limited to Europe as similar barriers exist in the USA that can limit access to biomarker testing. Cancer health disparities in racial/ethnic minorities in the USA may also contribute to limited access to biomarker tests and more generally to precision medicine. In this respect, efforts are needed to increase the participation of different populations in the research of cancer etiology, biology, and treatment. In addition, the access to health services should not be limited by structural inequities that affect racial/ethnic minorities in the USA.[14] However, the less invasive nature and ease of collecting a liquid biopsy sample has the potential to increase access to biomarker testing. Efforts to facilitate access and availability are necessary to avoid the risk of increasing inequities to precision medicine for patients with cancer.

What actions are needed to ensure adequate access to technological innovations for all patients with cancer? Investments in testing infrastructure and training of dedicated personnel will be required. Education of all stakeholders is necessary to increase the awareness of the importance of biomarker testing for patients with cancer. Processes should be developed to ensure laboratories are able to rapidly incorporate newly validated biomarker tests into clinical offerings as soon as they are required in the clinics. In several European countries and the USA, the regulatory and reimbursement approval of the precision medicine and the associated biomarker test have different pathways and timing, while it should be parallel and combined. Similarly, the budget for biomarker testing must be adapted continuously to support new technologies, such as liquid biopsy based biomarker tests, when they are validated and available. Finally, a relevant issue is the quality of biomarker tests, which is crucial for novel and complex assays such NGS testing of liquid biopsy.[15] In this respect, a worldwide external quality assessment of ctDNA biomarker testing in lung cancer revealed high false negative rates for samples with lower variant allele frequencies, suggesting that improvement in this field is needed.[16] Therefore, a system for verifying the quality through performance standards of biomarker tests should be implemented to guarantee patient safety.

In conclusion, the new technologies and applications of liquid biopsy are opening a novel scenario of personalized/precision treatment of patients with cancer. Ensuring equal access to high-quality liquid biopsy testing is essential to guarantee all patients with cancer can benefit from this novel diagnostic approach.

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