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Moving liquid biopsies to the Front-line of lung cancer treatment decisions

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ABSTRACT

Liquid biopsies have evolved as a promising non-invasive technology for cancer diagnosis and treatment, as they provide a comprehensive analysis of tumor-derived biomarkers. Prospective multicenter studies have shown the efficacy of liquid biopsies, including circulating tumoral DNA (ctDNA) and more recently cfRNA analysis, in identifying biomarkers for targeted therapies in patients with non-small cell lung cancer (NSCLC). In addition, studies have demonstrated a reduced time to treatment initiation when liquid biopsies are used in conjunction with or in lieu of tissue genotyping. Although liquid biopsies hold excellent potential, there are several obstacles to overcome, including technical limitations, standardization of methodologies, and cost-effectiveness. However, ongoing research and technological advances are conquering these obstacles, resulting in enhanced performance and dependability of liquid biopsy assays. To maximize the clinical utility of liquid biopsies, it is necessary to continue research, validation studies, and standardization initiatives. The incorporation of liquid biopsies into standard clinical practice has the potential to revolutionize the diagnosis and treatment of cancer. These noninvasive tests not only are a great tool for diagnosis but also allow real-time monitoring, guide treatment decisions, and enhance patient outcomes. As the costs of next-generation sequencing (NGS) declines, global access to liquid biopsies is anticipated to increase. Liquid biopsies arrived in the clinical practice after we were familiar with the analysis of genetic aberrations in tissue by next generation sequencing (NGS) that is considered the standard of care in new patients with the diagnosis of metastatic non-small cell lung cancer (NSCLC) and sometimes are used now as complement of tissue analysis or only when there is not enough tissue available. We already have done enough studies that show the non-inferiority and equivalence of liquid biopsies with molecular tissue testing. This article explores recent studies that demonstrate the clinical utility and potential of liquid biopsies in oncology including the possibility to use them at the same time of tissue analysis and the comparison of both with the advantage for the patient to get an earlier result due to the shorter turnaround time of liquid biopsies.

Introduction

Cancer diagnosis and treatment have significantly evolved over the years, with the introduction of liquid biopsies offering a promising new approach. Next-generation sequencing (NGS) done by liquid biopsies, which analyze genetic material and biomarkers in bodily fluids such as blood, urine and others, are increasingly being recognized as a valuable tool in cancer management. NGS done by liquid biopsies have emerged as a complement of tissue biopsies, and possible future substitute in certain circumstances like tumor resistance to NGS done by invasive tissue biopsy to guide cancer diagnosis and treatment because its not always easy to perform tissue biopsies often in lung cancer patients [1–3]. They can also be used multiple times throughout treatment to monitor a tumor and see how well a specific treatment is working [2,4]. The common biomarkers detectable in liquid biopsies are CTC, EVs, ctDNA.and lately cfRNA. There is other less frequently utilized liquid biopsies involving cfRNA, fragmentomics, methylation, and others that are under development. Each biomarker provides specific information based on its intrinsic characteristics [1,5].

Liquid biopsies have emerged as a promising avenue for the identification of cancer-related molecular alterations, offering a distinct advantage over conventional methods such as clinical or radiological

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tumor detection modalities, including imaging techniques and the assessment of minimal residual disease (MRD) stages [1,6–9]. Leveraging these unique capabilities, liquid biopsies facilitate timely intervention, potentially yielding substantial improvements in patient outcomes and overall survival rates [10–13]. Furthermore, the longitudinal assessment enabled by serial monitoring through liquid biopsies provides an unprecedented opportunity to comprehensively track the evolutionary trajectory of tumors, identify emerging mechanisms of drug resistance, and subsequently tailor treatment strategies accordingly. This manuscript aims to elucidate the distinctive merits of performing next-generation sequencing (NGS) on liquid biopsies, either in conjunction with or before traditional tissue biopsies, thereby emphasizing their transformative potential in advancing cancer diagnosis and reducing time to start therapy.

Current molecular testing guidelines of the International Association for the Study of Lung Cancer (IASLC) and International Society of Liquid Biopsies (ISLB)

In recent years, the prognosis of metastatic lung cancer has witnessed notable improvements primarily attributed to significant advancements in targeted therapies that specifically address molecular alterations, such as those involving EGFR, ALK, and ROS1 genes. Notably, in 2018, leading international associations including the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) collaboratively released comprehensive recommendations concerning molecular testing practices [1,4]. This expert panel strongly advocated for the incorporation of EGFR, ALK, and ROS1 testing as a minimum standard. Furthermore, they suggested the inclusion of an expanded gene panel encompassing BRAF, MET, RET, ERBB2 (HER2), and KRAS to facilitate the identification of additional viable treatment options. However, it is important to note that, at the time of publication, single-gene testing for KRAS was still considered an investigational approach, and therefore, the exclusion of patients from the expanded panel testing based solely on KRAS status was not deemed preferable [1,5–8].

The consensus among the expert panel favored the use of multiplexed genetic sequencing panels over multiple single-gene testing as a more comprehensive strategy to identify potential treatment options beyond EGFR, ALK, and ROS1 alterations [1,8]. Moreover, it is worth noting that the expert consensus opinion suggests utilizing molecular testing in non-adenocarcinoma histologies, particularly when clinical factors, such as younger age and absence of tobacco exposure, indicate a higher likelihood of harboring oncogenic drivers. This approach enables a more targeted and personalized therapeutic strategy for patients with NSCLC.

In a recent development in 2021, IASLC issued a new comprehensive statement, acknowledging the significant technological advancements and rapid progress observed in plasma-based next-generation sequencing (NGS). This statement presents novel recommendations regarding the utilization of liquid biopsy for advanced NSCLC [1,2,6]. The latest recommendations highlight the growing recognition of the utility of circulating tumor DNA (ctDNA) analysis, extending beyond single-gene mutation testing, towards endorsing comprehensive analysis using NGS. This broader approach enables the detection and characterization of a wider range of genomic alterations in NSCLC. Moreover, the IASLC acknowledges that plasma ctDNA analysis has the potential to overcome various limitations frequently encountered during tumor tissue genotyping, including challenges associated with tumor availability, accessibility, heterogeneity, and turnaround time (TAT). They recognize that plasma ctDNA can be considered a valid tool for genotyping in newly diagnosed advanced NSCLC, complementary to tissue analysis and even suggest a “plasma first” approach at the time of diagnosis and for monitoring the efficacy of targeted therapy mainly when tissue is not available [13–16].

Furthermore, the IASLC emphasizes the potential superiority of liquid biopsy as a preferred method for monitoring the effectiveness of targeted therapies, evaluating minimal residual disease (MRD), and identifying the emergence of resistance mechanisms. This recognition underlines the ability of liquid biopsy to provide valuable insights into the treatment response and disease progression of advanced NSCLC, facilitating informed therapeutic decisions [2,3]. The National Comprehensive Cancer Network (NCCN) guidelines [3,17,18] firmly establish molecular testing for various genetic aberrations as a level 1 recommendation for patients diagnosed with adenocarcinoma, large cell carcinoma, NSCLC-not otherwise specified, and even suggest considering testing for squamous cell carcinoma. Remarkably, the NCCN NSCLC guidelines panel regards comprehensive molecular testing as an indispensable component in elevating the quality of care provided to NSCLC patients. They strongly advocate for the integration of extensive molecular profiling through a singular assay or a combination of limited assays to identify infrequent driver mutations, which may consequently lead to the identification of potent therapeutic agents [2,7–9]. Furthermore, it is noteworthy that expert consensus opinion supports the integration of molecular testing in non-adenocarcinoma histologies, particularly when clinical factors such as younger age and lack of tobacco exposure indicate a heightened probability of harboring oncogenic drivers [9,10]. This approach facilitates a more focused and individualized therapeutic strategy for patients with NSCLC [19].

The clinical guidelines offer invaluable insights into the utilization of ctDNA testing, highlighting its potential as an alternative approach in cancer therapy. The NCCN guidelines delineate precise scenarios in which ctDNA testing is recommended, strategically addressing clinical challenges associated with tissue-based sampling. These scenarios encompass situations wherein patients are deemed medically ineligible for invasive tissue sampling procedures, cases involving limited tissue availability that impedes comprehensive molecular analysis, instances where conventional tissue-based testing fails to adequately evaluate the full spectrum of recommended biomarkers due to constraints in tissue quantity or testing methodologies, and circumstances where the feasibility of conducting timely tissue-based testing remains uncertain [2,3,10]. By addressing these limitations, ctDNA and maybe cfRNA testing emerges as a compelling option for facilitating non-invasive and efficient assessment of molecular alterations, ultimately paving the way for more effective and cost-efficient cancer treatment strategies [2,11,19].

Liquid biopsy first or liquid biopsy at the same time as tissue?

While NGS done in tissue biopsy has long been the gold standard for lung cancer diagnosis of genetic aberrations, its inherent limitations must be acknowledged. The dynamic nature of tumors, which is characterized by growth, metastasis, and exposure to anti-cancer therapies, renders tissue biopsy results potentially less accurate and fails to capture the tumor's evolving molecular landscape. Secondly, the accessibility of certain tumor locations presents difficulties for tissue biopsy procedures, thereby increasing the risk of adjacent tissue injury and complications such as pain, infection, and bleeding. Thirdly, tumor heterogeneity increases the risk of insufficient representation of the entire tumor in the sampled tissue, which can result in incorrect diagnoses and suboptimal treatment decisions. Lastly, cancer cells disseminated to distant sites may manifest genetic variations compared to the primary tumor, making it difficult to perform a biopsy from a single site to capture the comprehensive genomic profile of cancer throughout the body [2,14–16]. In response to these constraints, liquid biopsies provide a compelling alternative. Utilizing minimally invasive sampling techniques, liquid biopsies offer a non-invasive and more thorough method of cancer detection. These assays examine circulating tumor-derived components, including cell-free DNA (cfDNA), circulating tumor cells (CTCs), and extracellular vesicles (EVs), which provide a snapshot of the tumor's genetic and molecular characteristics. Liquid biopsies have the potential to surmount the limitations of tissue biopsies and enable real-time monitoring of tumor evolution, therapy response, and the development of drug resistance. In addition, the non-invasive nature of liquid biopsies reduces patient discomfort and the risk of procedural complications, while providing a more cost-effective and scalable diagnostic alternative

for extensive implementation [2,3,15].

Liquid biopsies provide a method of collecting samples that is not invasive and is simple to repeat. This method enables the detection of genetic abnormalities that may be present in tumor cells that are circulating in the bloodstream or released as circulating tumor DNA (ctDNA) or cfRNA. Before taking a tissue sample, liquid biopsies could be the next sensible step in diagnosis, prognostication, therapy monitoring, and initial treatment guiding. Liquid biopsies provide an opportunity to acquire a genetic profile of the tumor that is more comprehensive and representative. This profile can include both the main tumor and any metastatic lesions, and it can help guide decisions for individualized treatment. For instance, ctDNA is now routinely utilized to manage tyrosine kinase inhibitor treatment in EGFR-mutated non-small cell lung cancer (NSCLC). Numerous studies have shown that EGFR gene mutations discovered in ctDNA are highly concordant with those detected in the tumor tissue of NSCLC patients [3,11]. Also, other studies have demonstrated that NGS liquid biopsies have high concordance with NGS done in tissue. Patients with advanced, untreated NSCLC were studied to validate a ctDNA assay in a prospective, multicenter clinical trial. Plasma from 264 patients was examined. Tumor tissue was available in 178 patients for molecular profiling in compared to plasma profiling. The remaining 86 patients were included to compare ctDNA profiles in patients with and without tissue for profiling. The concordance of ctDNA with matching tissue profile was 97.8%, with 82.9% positive predictive value, 98.5% negative predictive value, 70.6% sensitivity, and 99.2% specificity. ctDNA testing identified 48 patients with actionable changes over the entire research, while tissue testing identified solely 38. In 53% of patients, ctDNA NGS showed either an actionable alteration or an alteration that is typically thought to be mutually exclusive for such actionable changes. In this study, plasma-based molecular profiling utilizing NGS detected 26% more actionable changes than standard-of-care tissue testing [4]. Our prior research demonstrated not only that liquid and tissue NGS are similar in terms of detecting genomic aberrations, but that liquid biopsies can also detect more genetic abnormalities [11,19].

Liquid biopsies have shown promise in reducing the time to initiate therapy. Initial studies indicate that a complementary approach or even starting with liquid biopsies may expedite the time to treatment (TT) and the turnaround time (TAT) for alteration results. In the ACCELERATE trial (NCT04863924), Garcia-Pardo et al. investigated a pilot cohort of 20 patients with advanced non-small cell lung cancer (NSCLC) based on radiographic evidence (stage IVA or B). A comparison between liquid biopsy and tissue biopsy revealed a mean TAT of 17.8 days for plasma next-generation sequencing (NGS) and 23.6 days for tissue NGS ($p = 0.10$). Notably, the mean time from referral to treatment initiation was significantly shorter in the liquid biopsy group (32.6 days, SD 13.1) compared to the tissue biopsy group (62.2 days, SD 31.2) [5].

The NILE trial (NCT03615443) prospectively evaluated the clinical utility of plasma-based NGS for first-line genotyping in metastatic NSCLC patients, comparing it with tissue genotyping. Among the 282 analyzed patients, the NGS assay detected clinically relevant NSCLC-associated biomarkers at a comparable rate to tissue testing, demonstrating non-inferiority. The combined analysis of tissue-based and plasma-based genotyping, along with circulating cell-free DNA (cfDNA) analysis, resulted in a higher frequency of detected driver mutations compared to each method alone. Additionally, the median TAT for plasma based NGS in this trial was significantly lower than for tissue genotyping (9 days vs. 15 days) [6].

Patients with previously untreated non-squamous non-small cell lung cancer (NSCLC) underwent tissue genotyping and cell-free DNA (cfDNA) analysis in a prospective multicenter study conducted by Page et al. Through tissue genotyping (21.3% of patients) and/or cfDNA analysis (27.4% of patients), actionable biomarkers were detected in 89 of 282 (31.6% of patients). Notably, 61 patients (68.5%) received targeted therapy based on somatic genotyping results, resulting in a 58% objective response rate and a 94% disease control rate among the 33 patients eligible for clinical response evaluation. When biomarker detection was informed by cfDNA, the median time to treatment initiation was significantly shorter than when tissue genotyping was used, with median times of 18 days and 31 days, respectively ($p = 0.0008$). The authors concluded that cfDNA-based analysis detects guideline-recommended biomarkers at a rate comparable to tissue genotyping, and that plasma-based comprehensive genomic profiling yields therapeutic outcomes comparable to those reported with tissue profiling, even across various healthcare settings, including academic and community hospitals [7].

In a cohort study involving 110 patients and conducted by Thompson et al., plasma-based sequencing performed at the time of diagnostic biopsy in patients with suspected advanced NSCLC revealed a shorter time to treatment (TT) compared to reflex tissue genotyping. The study examined the next-generation sequencing (NGS) results of newly diagnosed advanced NSCLC patients. Notably, the NGS results were available prior to the initial oncology visit in 85% of patients with liquid biopsy versus only 9% of those without (p 0.0001). In addition, 74% of patients in the liquid biopsy group received treatment recommendations congruent with guidelines at the first visit, compared to 46% of patients in the tissue biopsy-only group (p 0.005). Patients who underwent both liquid and tissue biopsies had a substantially shorter TT than those who received standard care with tissue biopsy alone. This was especially evident in patients with particular driver mutations, where the TT was 10 days as opposed to 19 days (p 0.001) [8].

Swalduz et al.'s multicenter, randomized, comparative, open-label LIBELULE study enrolled patients with radiologically suspicious stage IV lung cancer who had not undergone a biopsy or cytology for diagnosis. In the treatment arm, a liquid biopsy using a next-generation sequencing panel targeting 37 genes associated with NSCLC was conducted at the first visit. Patients with actionable alterations such as EGFR, BRAF V600E mutation, ALK or ROS1 rearrangement, MET exon 14 alteration, KRAS, non-V600E BRAF, LKB1 mutations, RET, or NTRK rearrangement were treated exclusively based on the liquid biopsy results. In the control arm, histological sampling was planned, genomic analysis was performed when indicated (with local liquid biopsies permitted), and treatment was initiated in accordance with established protocols. The primary endpoint was the duration between randomization and initiation of treatment based on informative genomic and pathological findings. Systemic treatment was instituted in 74.5% of patients in arm A (liquid biopsy arm) compared to 65.7% of patients in arm B (control arm). In the population intended to receive treatment, the mean time to treatment initiation was 29 days (95% CI 25.9–32.1) in arm A and 33.9 days (95% CI 28.4–39.5) in arm B ($p = 0.28$). The time to treatment initiation was substantially shorter in arm A (29.1 days) compared to arm B (38.8 days) among patients receiving systemic therapy ($p = 0.01$). The authors concluded that early implementation of liquid biopsy significantly reduces the time to conclusive molecular analysis and the time to initiating appropriate first-line therapy in patients eligible for systemic treatment, especially in those with actionable alterations indicating targeted therapy as the first-line approach [9].

Wanyuan Cui et al. conducted a pilot trial evaluating cfDNA by NGS in patients with suspected advanced-stage lung cancer based on imaging. Predicted to be less than 10%, the primary endpoint was the proportion of patients who initiated targeted treatment based on the cfDNA NGS results without tissue molecular results. 51 patients were enrolled. 86% had stage IV disease, and 80% of informative cfDNA by NGS samples were evaluable. 11 patients (22%; 95% confidence interval [CI]: 12%–27%; primary endpoint met) initiated targeted therapy based on -NGS results of cfDNA without tissue molecular results. The median time to results for this type of NGS was shorter than for standard tissue tests (9 vs. 25 days, p0.0001), indicating a shortened turnaround time leading to more precise therapy [10]. In a prospective cohort study with 323 patients, Aggarwal et al. demonstrated that adding plasma NGS to the routine management of patients with metastatic NSCLC increases detection of targetable mutations and enhances delivery of molecularly guided therapies. Among the 94 patients with plasma testing alone, 31 (33.1%) had a mutation that was therapeutically targetable, eliminating

the need for an invasive biopsy. The remaining 229 patients underwent concurrent plasma and tissue NGS; a therapeutically targetable mutation was identified in tissue alone for 47 patients (20.5%), while the addition of plasma testing increased this number to 82 (35%) patients. 36 out of 42 patients (85.7%) who received a targeted therapy based on plasma results experienced a complete or partial response, or disease stabilization. The incorporation of plasma NGS testing into the routine management of stage IV NSCLC results in an increase in the detection of therapeutically targetable mutations and an improvement in the delivery of molecularly guided therapy. Notably, there was no correlation between the plasma-based targeted mutation and the profundity of Response Evaluation Criteria for Solid Tumors (RECIST) response in this study ($p = 0.45$) [11].

In a previous retrospective analysis of 170 new NSCLC patients treated at 2 cancer centers who received both tissue and liquid biopsy at the same time, our group demonstrated that physicians based most of their treatment decisions on liquid biopsy results (73.5% vs. 25.9%) due to a much shorter turnaround time (9 days vs. 28 days) [11]. The results of this analysis were consistent with those of the previous research, indicating that NGS turnaround time for LB was 19 days faster on average than for tissue. For guideline-recommended biomarkers, liquid biopsy was at least 94.8% concordant with tissue samples. In comparing testing modalities, a liquid-first approach identified guideline-recommended biomarkers in 76.5% of patient's vs 54.9% in a tissue-first approach [12] Fig. 1. The Blood First Assay Screening Trial (BFAST) is a multi-cohort study (NCT03178552) assessing the efficacy of plasma-based NGS for detection of actionable alterations and the efficacy of targeted and immunotherapy-based therapies based solely on plasma results in patients with advanced NSCLC. Patients with plasma-detected ALK fusions who were treated with alectinib exhibited a high overall response rate (ORR) and clinical benefit, according to preliminary data in ALK-fusion-positive disease. In this study, patients over the age of 18 with stage IIIB/IVA NSCLC (detected by blood based NGS) received 600 mg of oral alectinib twice daily. Metastases of the central nervous system (CNS) that were asymptomatic or treated were allowed. Blood-based NGS yielded results in 2188 of 2219 patients screened. A total of 119 patients (5.4%) were diagnosed with ALK disease; 87 patients were enrolled and administered alectinib. The ORR was 87.4% (95% confidence interval [CI]: 78.5–93.0). The PFS median was not reached. The authors concluded that blood-based detection of ALK fusions results in a high ORR and clinical benefit in patients receiving alectinib, thereby validating the clinical utility of blood-based NGS as an additional method to guide clinical decision-making in ALK NSCLC patients [13,14].

Utilization of liquid biopsies in the context of cancer diagnosis and treatment initiation continues to be a topic of divergence among clinical guidelines. Notably, the guidelines of the International Association for the Study of Lung Cancer (IASLC) and the American Society of Clinical Oncology (ASCO) recommend concurrent analysis of circulating tumor DNA (ctDNA) in solid tumors, whereas the guidelines of the National Comprehensive Cancer Network (NCCN) do not explicitly endorse this approach. Nonetheless, it is essential to note that all four main guidelines, including that of the European Society of Medical Oncology (ESMO), concur on the significance of histologic confirmation in the diagnostic process.

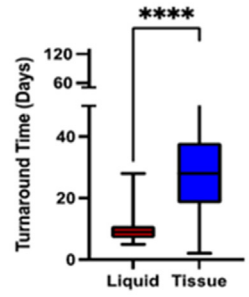
When an actionable alteration is detected through ctDNA analysis, all four guidelines agree that it provides sufficient evidence to initiate targeted treatment. This emphasizes the clinical significance of ctDNA-detected alterations as potential predictive markers for guiding therapeutic interventions [5,15,19]. Further research and ongoing discussions among experts in the field will continue to shape the incorporation of liquid biopsies into the standard management of cancer patients, ensuring that their clinical value is maximized while considering the nuances and specificities of each individual case.

Challenges and future perspectives

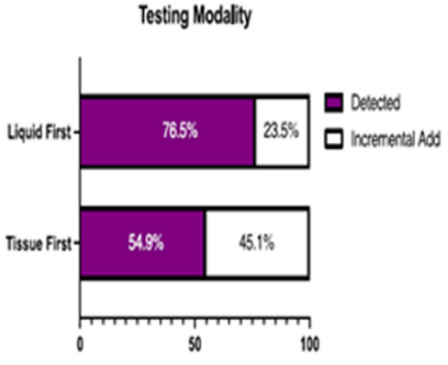
Despite the tremendous promise of liquid biopsies, their widespread adoption in clinical practice is hampered by a few barriers. Significant obstacles include sensitivity and specificity issues, as well as the impact of tumor burden or location (e.g., brain tumors). In addition, the lack of standardized methodologies across various liquid biopsy tests and concerns about their cost-effectiveness hinder their widespread implementation. However, ongoing research efforts and technological advances are rapidly overcoming these obstacles and enhancing the performance and dependability of liquid biopsies [5,19].

Liquid biopsies have the potential to revolutionize cancer diagnosis and treatment in the future. By facilitating real-time monitoring of tumor dynamics and molecular alterations, liquid biopsies have the potential to provide greater precision in treatment decisions and valuable insights into tumor evolution. This personalized approach has the potential to enhance patient outcomes and therapeutic efficacy.

However, it is essential to recognize the limitations of liquid biopsies. From the time elapsing between collection and plasma preparation we have to be careful and do standardization, this for example was very important with cfRNA that use to degrade very fast compare with ctDNA



N=165	Liquid	Tissue
TAT Mean	9.6	30.5
TAT Median	9	28
Samples QNS	0	18 (10.6%)



	Detected	Incremental Add	Total
Liquid First	39	12	51
Tissue First	28	23	51

Fig. 1. Comparing Testing Modality Liquid vs Tissue NGS.

and now thanks to the tubes for preservation its possible to work with cfRNA. It is possible to obtain false positive and false negative results, which can lead to erroneous diagnoses or inappropriate treatment interventions. In addition, liquid biopsies may not be able to detect all forms of cancer, as some tumors may only release small amounts of tumor-derived molecules into the bloodstream. Consequently, careful consideration and integration of multiple diagnostic methods are required to ensure accurate and comprehensive cancer evaluation and management. Also as more extensive panels are used in liquid biopsies similar to tissue ones the turn around time of the results can be prolonged.

Continual advances in liquid biopsy technologies, coupled with rigorous validation studies and standardization efforts, will drive their incorporation into clinical practice. These advancements will play a crucial role in the realization of liquid biopsies' maximum potential as transformative tools for precision oncology. Molecular profiling done by NGS in tissue has become standard of care for most of the solid tumors. NGS by Liquid biopsy has little by little shown the equivalence to tissue NGS and it has started to be use more and more for some tumors like lung cancer. According to our IASLC and ISLB guidelines we can use liquid biopsies as complement of tissue NGS or when the tissue NGS is not enough. However, liquid biopsies always have a reduced turnaround time (TAT) than tissue biopsies. We know that in most academic centers we have our own NGS technology and can run in two weeks, but in the real world, most patients are seen in community practices or small hospitals, and when they refer patients to larger hospitals where the NGS is ordered, the vendor will take time to get the tissue from the community, thereby increasing the TAT time, which does not occur with liquid biopsies. This is something very important for the patients, they have been waiting weeks since somebody notice a mass or nodule in their CT scans, they are not happy with the idea to wait four weeks to make a decision regarding the type of therapy they are going to have for example in lung cancer mainly deciding between targeted therapy or chemo/immunotherapy.

Frequently, in the United States, oncologists initiate chemotherapy alone for 1–2 cycles until the tissue NGS results are available, and then shift patients to targeted therapy or add immunotherapy to chemotherapy. This can be easily avoided in many patients if we perform liquid NGS on every lung cancer patient at the same time as the tissue biopsy, as we have shown in our own study, NILE, and others, and then make a therapeutic decision to initiate the ideal therapy in the majority of patients within 10 days or less. We understand that there are lot of challenges in ordering both at the same time starting with concerns about insurance coverage for both tests if they are ordered at the same time, but it has our experience that the reimbursement for both tests and the patient assistance programs available in the US have allow us to be able to practice for several years without a problem. We recognize that this reality may not apply to other nations, but it is something that must be considered seriously for the United States at least for the time being. As the price of next-generation sequencing (NGS) technology decreases and its availability increases, the concept of using liquid biopsies as the primary method for cancer diagnosis and treatment holds promise for global adoption. It is anticipated that the global availability of liquid biopsies will increase as the cost and availability of NGS increase. This paradigm shift could have a substantial global impact on cancer management strategies.

Considering the enormous potential of liquid biopsies, it is essential to emphasize the need for additional research, validation studies, and standardization efforts. These efforts are indispensable for refining and maximizing the clinical utility of liquid biopsies. We can ensure the reliability and reproducibility of diagnostic approaches based on liquid biopsy by conducting rigorous research, validating the performance of liquid biopsy technologies, and establishing standardized protocols and guidelines.

We can envision a future where liquid biopsies are used to revolutionize the diagnosis and treatment of cancer. This revolutionary technology has the potential to improve patient outcomes, enhance treatment efficacy, and facilitate a more precise and individualized approach to cancer care. This vision necessitates sustained scientific investigation, collaboration between researchers and healthcare professionals, and a dedication to advancing liquid biopsy technology. These efforts will pave the way for a future in which liquid biopsies define the landscape of cancer management.

Conclusion

In conclusion, emerging evidence supports the integration of liquid biopsies as a crucial component in the diagnostic and therapeutic management of cancer. Performing liquid biopsies prior to or in parallel with tissue biopsies offers several notable advantages. By employing a non-invasive approach, liquid biopsies provide a comprehensive and dynamic assessment of cancer, ultimately enhancing diagnostic accuracy and therapeutic decision-making. The potential to detect cancer-related alterations even before tumors become clinically or radiologically detectable, as well as during minimal residual disease stages, highlights the timely intervention and improved patient outcomes that liquid biopsies can offer.

While acknowledging the current limitations of liquid biopsies, including the possibility of false positives or false negatives, ongoing research endeavors and technological advancements hold promise for addressing these challenges. With the ability to monitor tumor evolution, track emerging drug resistance mechanisms, and tailor treatment strategies accordingly, liquid biopsies pave the way for a more personalized and effective therapeutic approach. Moreover, the non-invasive nature of liquid biopsies alleviates patient discomfort and reduces the risk of procedural complications, providing a patient-centered approach to cancer diagnosis and treatment.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Luis E. Raez reports a relationship with Community Foundation of Broward that includes: funding grants. Research grants from: BMS, Genentech, Pfizer, Novartis. Astra-Zeneca, Velos, Loxo Pharmaceuticals, Lilly Oncology, Merck, Guardant Health, Natera, Nanth Health, BioPharma, Merus, Seagen, Onc4, TGI Pharma, AnHeart.

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