Review

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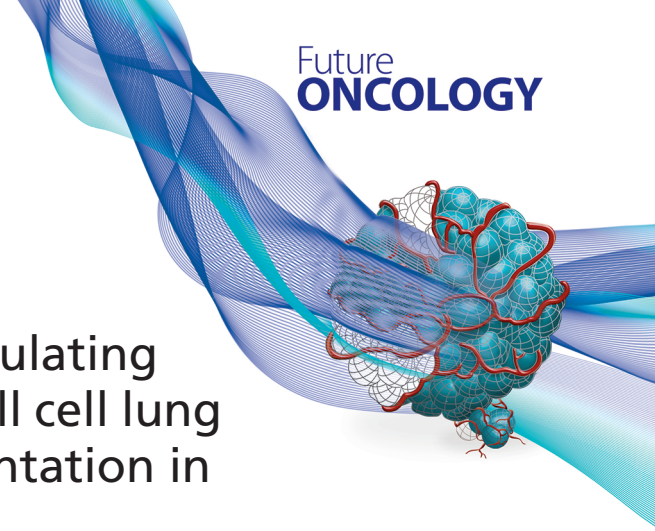

Next-generation sequencing of circulating tumor DNA for metastatic non-small cell lung cancer: a discussion on its implementation in the Brazilian clinical practice

Luiz H Araujo*[,1], Carlos Gil Ferreira[2], Clarissa S Baldotto[3], Clarissa Mathias[4], Gilberto Castro Jr.[5] & Renata Coudry[6]

[1]Brazilian National Cancer Institute & COI Institute for Research & Education, Rio de Janeiro, Brazil
[2]Oncoclínicas Institute for Research & Education, Rio de Janeiro, Brazil
[3]Instituto D'Or for Research & Education, Rio de Janeiro, Brazil
[4]NOB/Oncoclínicas, Salvador, Brazil
[5]Instituto do Câncer do Estado de São Paulo, Faculdade de Medicina da USP & Hospital Sírio Libanês, São Paulo, Brazil
[6]United Health Group Brazil, Sao Paulo, Brazil
*Author for correspondence: Tel.: +55 21 3207 6566; luizaraujo.md@gmail.com

The objective of this review is to address the barriers limiting access to next-generation sequencing (NGS) of circulating tumor DNA (ctDNA) for metastatic nonsquamous non-small cell lung cancer in Brazil and to propose its implementation in practice. A selected panel of lung cancer experts was provided with relevant prompts to address at a conference; a paper was then compiled on the topic. The authors propose specific and realistic recommendations for implementing access to ctDNA NGS. Further, the authors address all barriers and impediments mentioned within this review. There is a great need to increase ctDNA NGS for cancer care in Brazil. Adapting the current cancer testing framework is essential to expanding the use of this tool.

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According to an estimate from 2018, approximately two million new cases of lung cancer were reported worldwide (1.3 million male and 722,000 female cases). This report also indicated lung cancer had the highest rate of cancer-related mortality [1]. In Brazil, lung cancer was responsible for the highest number of cancer-related deaths in 2018. Additionally, this cancer remains the third most frequent and accounts for an annual incidence of approximately 30,000 cases [2].

In line with global trends, cigarette smoking is the most important risk factor for the development of lung cancer in Brazil [3]. National public health policies were implemented in response to an increase in tobacco consumption between the 1950s and 1970s [3,4]. These measures led to a reduction of approximately 50% in smoking prevalence as well as smoking-related deaths between 2011 and 2015 [5]. It is estimated that in 2020, 83.3% of lung cancer cases in men and 64.8% in women will be related to smoking [6]. Adenocarcinoma is the predominant histological subtype in the country (43%), followed by squamous cell carcinoma (36%) [7].

One of the main challenges in lung cancer in Brazil is delayed diagnosis. This contributes to the high rate of late-stage diagnosis, as well as the low percentage of patients receiving therapy with curative intent [8]. This situation is evident in a significant delay and inefficiency of the diagnostic process, both in the public and private health care systems. When diagnosed, non-small cell lung cancer (NSCLC) is usually found at an advanced stage with low survival rates. Approximately 70% of patients have locally advanced or metastatic disease (stage III and IV, respectively). Considering data collected between 2000 and 2010 in the state of São Paulo, only 8.8% of the 20,850 lung cancer patients had stage I disease [4].

In a retrospective study, the authors described the characteristics, treatments, and survival of patients in a Brazilian private cancer care institution. In this study, 288 patients (52.9%) were diagnosed at stage IV, 145 (26.7%) at stage III, 38 (7.0%) at stage II and 73 (13.4%) at stage I. The median overall survival (OS) decreased as the stage of the disease was more advanced (99.7 months, 32.5 months, 20.2 months and 13.3 months at stages I, II, III and IV, respectively). Those who had longer survival rates were female patients, those with better performance status, no weight loss and no previous smoking history [6].

The role of molecular profiling to guide targeted therapy

Lung adenocarcinoma is the most common subtype of NSCLC and can be considered a cluster of distinct molecular subtypes defined by oncogenic driver abnormalities [9]. Actionable oncogenic drivers are widely known and have led to the development of targeted agents effective in the treatment of nonsquamous NSCLC. *EGFR*, *ALK* and *ROS1* are the most widely studied. Among *EGFR* mutations, different primary mutations may lead to distinct tumor sensitivity to targeted therapies. For instance, *EGFR* exon 19 deletions and exon 21 p.L858R are classic driver mutations, related to high sensitivity to EGFR tyrosine kinase inhibitors (TKI). However, numerous uncommon mutations may still be related to treatment sensitivity [10]. Other targets are in different stages of clinical development, as is implementation of specific agents, such as *MET*, *RET*, *BRAF* and *NTRK* [11,12]. *KRAS* is not a classic actionable gene; however, recent research has shown that tumors presenting a specific *KRAS* mutation called p.G12C may be responsive to two new compounds that specifically target KRAS p.G12C (AMG510 and BI-2852) [13,14]. Furthermore, new upcoming targets are being discovered and evaluated in multiple clinical trials.

Once genetically altered, the signaling pathways involved may become constitutively activated and stimulate carcinogenesis, making them attractive targets for therapy [11]. The treatment of NSCLC is increasingly focused on the knowledge acquired from biomarkers because treatments are selected on the basis of agents capable of inhibiting the effects of genetic changes. Despite this, tumors treated with targeted therapy will eventually develop resistance mechanisms and cause disease progression. In other cases, primary resistance may occur due to driver mutations that are insensitive to therapy or due to intrinsic concomitant mutations that impair response to targeted therapies. Resistance mechanisms can happen in the specific target (on-target) or through activation of parallel signaling partners (off-target) that may cause a cross-talk to maintain cell survival and growth [15]. In the case of EGFR TKIs, the mechanism most commonly associated with acquired resistance is the p.T790M mutation in the exon 20 of *EGFR*. It confers a change in the spatial conformation of the protein, preventing the binding of first- and second-generation EGFR TKIs [11]. Importantly, testing for p.T790M is an established strategy for selecting patients for third-generation EGFR inhibitors in this setting.

The role of molecular profiling to predict response to immunotherapy

The emergence of immune checkpoint inhibitors (ICI) has revolutionized treatment of numerous solid cancers. Immune checkpoints function as negative feedback mechanisms to regulate inflammatory responses that may emerge after T-cell activation against cancer cells. By targeting negative regulators such as PD-1 and PD-L1, ICI have provided durable responses in a subset of patients with advanced NSCLC. Understanding the mechanisms of resistance and sensitivity to ICI is a challenging task, especially in complex cancers such as NSCLC [16]. PD-L1 expression is the most disseminated biomarker to select NSCLC patients for immunotherapy. For instance, patients with PD-L1-positive NSCLC may be offered immunotherapy alone in first-line therapy, provided that *EGFR* and *ALK* abnormalities have been excluded [17]. Currently, data are limited to support the activity of this class in patients whose tumors harbor classic driver mutations. In general, ICI demonstrates lower activity in driver-positive NSCLC, as opposed to targeted therapy. Lee and colleagues performed a meta-analysis to evaluate the role of ICI in second-line therapy in advanced *EGFR*-mutant NSCLC [18]. As a result, ICI significantly prolonged OS over docetaxel only in *EGFR*-wild type NSCLC but failed in *EGFR* mutants [18].

In a large retrospective study (IMMUNOTARGET), the effectiveness of ICI was addressed based on the presence of driver mutations [19]. ICI activity was lower in most groups of driver-positive NSCLC compared with the *KRAS*-mutant group, and there was no response in the *ALK*-positive cohort [19]. In another study, low objective response rates (ORR; 3.6%) were observed when *EGFR* mutations or ALK expression were present, whereas *EGFR* wild-type and ALK-negative/unknown patients had better responses (ORR = 23.3%). These findings highlight the importance of determining the molecular pattern of NSCLC and also help select patients for ICI. In this context, next-generation sequencing (NGS) techniques are essential for the success of immunotherapy [20].

A phase III trial evaluated the combination of atezolizumab (an anti-PD-L1 inhibitor), bevacizumab and chemotherapy in treatment-naive NSCLC patients [18]. The study showed a significant increase in progression-free survival (PFS) and OS in patients, which was independent of *EGFR* and *ALK* genetic alteration status; however, only a minority of cases presented with these drivers [18]. Of note, other first-line immunotherapy trials have consistently excluded patients with driver-mutant NSCLC.

In addition to the limited activity of ICI in driver-positive NSCLC, adverse events associated with this class cannot be overlooked. For example, the association of durvalumab (an anti-PD-L1 inhibitor) plus osimertinib (a targeted therapy against EGFR) was related to serious immune adverse events in *EGFR*-mutant NSCLC [21]. An elevated rate of pneumonitis was also observed after the sequential use of PD-L1 inhibitors followed by osimertinib [21]. Therefore, the indiscriminate use of ICI in first-line therapy should be discouraged, unless the presence of driver mutations have been excluded. Patients may require close monitoring for severe toxicity in these instances [21].

Barriers to molecular profile implementation

In recent years, personalized therapy for nonsquamous NSCLC patients has evolved greatly. Molecular testing has become key for decision-making in the personalized therapy. However, access to molecular testing and targeted therapy still faces social and economic barriers in the global context, such as lack of infrastructure, lack of technical knowledge, high costs and adoption of new drugs. In most low- and middle-income countries, personalized therapy is far from a reality, especially in public settings. Furthermore, the prevalence of molecular abnormalities in NSCLC is widely heterogeneous in these countries. Routine tests involving biomarkers are restricted to large hospitals in the most populous capital cities. In general, the few available tests are limited to detecting mutations in *EGFR* or *ALK* rearrangement.

To make matters worse, access to new therapeutic agents in these countries is usually achieved long after high-income countries and after a relationship has been studied between the implementation of these therapies and molecular testing [22]. Furthermore, the high cost of new molecular testing and therapeutic technologies pose a serious challenge for health services in low- and middle-income countries, which may increase healthcare inequities [23]. In comparison with high-income countries, the incorporation of technologies such as NGS and novel systemic therapies for lung cancer diagnosis and treatment has suffered from significant delays in Brazil.

Brazilian studies on lung cancer demonstrate that late access to specialized care, heterogeneity in the treatment regimens and lack of use of innovative technologies negatively influence OS for these patients. Moreover, the country-wide implementation of molecular testing has been a challenge [12]. For instance, *EGFR* mutation tests are performed in about half of lung cancer patients in Brazil, but the majority of these tests are done in the private health sector [24]. Some key topics in molecular genotyping should be considered in this context and need to be addressed. These include reimbursement and logistics, access to specific therapy, physician and patient education and limited laboratory infrastructure for molecular testing. Additionally, an important issue to molecular profiling in Brazil is insufficient tissue sample due to small biopsies [25]. A list of barriers and opportunities is presented in Figure 1.

Clinical utility of circulating tumor analysis for evaluation of oncogenic mutations

Tumor biopsies are the gold standard for cancer genotyping. However, tissue biopsy is not always feasible, especially in difficult-to-reach tumors or elderly and frail patients. Studies have shown that approximately 20–30% of NSCLC patients lack tissue material for the evaluation of oncogenic driver mutation [26,27]. In this setting, methods that seek tumor diagnostic information using biological fluids such as blood (liquid biopsy) emerge as an important tool [28]. Liquid biopsy methods can evaluate several soluble factors that primarily originate from cancer cells, including protein, tumor markers, circulating tumor nucleic acids (including circulating tumor [ctDNA]) and circulating tumor cells. ctDNA are likely derived from apoptotic cancer cells, and evidence suggests that ctDNA may reflect the intratumoral and intertumoral heterogeneity of mutations that emerge throughout cancer progression [29]. ctDNA testing has proven to be a reliable and affordable tool to include in the molecular diagnosis of cancer and may provide the same diagnostic information as tissue biopsy.

Several studies have shown the clinical utility of ctDNA analysis to interrogate the molecular background of NSCLC, specifically at advanced stages. Of note, all patients diagnosed with advanced or metastatic nonsquamous NSCLC are eligible for molecular characterization in ctDNA at the time of initial diagnosis [30]. This analysis could also be applicable to patients with squamous NSCLC at younger age, those who have never smoked or those who have only small biopsies that could have missed a nonsquamous component in heterogeneous tumors. For

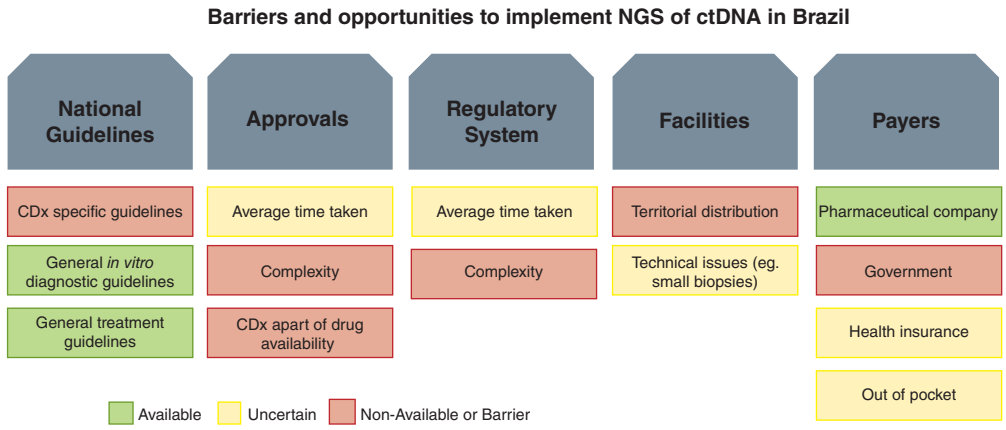

Figure 1. Barriers and opportunities to implementing next-generation sequencing of circulating tumor in Brazil.

patients progressing during a first- or second-generation EGFR TKI, liquid biopsy is considered the primary test to assess *EGFR* p.T90M. Positive results are sufficient to recommend a third-generation EGFR TKI, whereas negative results require further testing in rebiopsy tissue. Currently, ctDNA analyses to detect *EGFR* mutations are US FDA-approved in the settings of treatment-naive patients and for resistance to EGFR TKI (for detection of p.T790M). In 2020, a comprehensive ctDNA NGS panel was approved by the US FDA as a pan-tumor test covering all solid tumors.

One of the challenges of ctDNA analysis is delicacy of the sample and the process. Time of processing, specimen collection, handling variables and storage conditions play important roles in the quality of the results of ctDNA analysis [31]. In samples taken from patients in early stages and with low disease burden, the amount of ctDNA may be limited and varies from patient to patient. Therefore, the total amount of ctDNA extracted can affect sequencing accuracy and the end result [30]. The source of ctDNA is also critical, and plasma is suggested to be the optimal specimen type for ctDNA analysis. It is crucial that international laboratory standards are followed and monitored to optimize preanalytical and analytical factors. Moreover, internal validations should be carefully provided before the implementation of a diagnostic workflow. The use of ctDNA analysis for nonsquamous NSCLC is a stride toward the adoption of comprehensive molecular testing in Brazil. The benefits of using ctDNA analysis in Brazil may be seen in the socioeconomic scenario, its large aging population, the high incidence of cancer, healthcare inequities, financial constraints and regulatory limitations, all of which should be considered when contemplating its inclusion as a feasible opportunity in cancer diagnosis. However, there are still some barriers to be overcome for ctDNA to be widely used for cancer treatment decisions. The implementation of this new technology requires personnel trained in testing and interpretation, as well as specific equipment. In addition, evolving technology necessitates constant updating. Nevertheless, efforts to adopt ctDNA analysis in the therapeutic routine of lung cancer in Brazil should be pursued due to the potential benefits it may represent [28].

In Brazil, a cost-effectiveness analysis was performed based on a decision-tree model and a Markov model to evaluate the clinical and economic impact of the NGS panel of ctDNA in the clinical decision of first-line therapy for patients with metastatic nonsquamous NSCLC who lack tissue material for evaluation of oncogenic driver mutation. The use of the NGS ctDNA panel proved to be a dominant alternative compared with ctDNA EGFR testing [32], although another study suggested that ctDNA approach may not be the best diagnostic strategy to evaluate resistance mechanisms. Blood samples from patients with post-EGFR inhibitor progression were subjected to PCR-based *EGFR* mutation testing. The authors identified a lower than expected positivity rate and concluded that tissue biopsy should continue to be recommended as the gold standard, especially in detecting p.T790M [33]. However, this study did not use the most sensitive ctDNA assays, did not consider NGS-based approaches and did not include the hurdles of conducting a tissue-based gene sequencing in this patient population.

NGS methods for molecular profiling of NSCLC

Targeted molecular therapies have shown benefits for cancer patients, specifically when the tumor has relevant genetic abnormalities. Therefore, knowing the driver gene mutations has become a key step in treating advanced nonsquamous NSCLC. Since the discovery of point mutations, insertions and deletions of *EGFR*, knowledge of NSCLC tumor genetic alterations has expanded. Likewise, *ALK* rearrangements are now recognized as important markers. In addition to these two markers, the National Comprehensive Cancer Network guidelines recommend testing *BRAF* and *ERBB2* (erb-B2 receptor tyrosine kinase 2) mutations, *MET* amplification, *MET* exon 14 skipping mutations, *NTRK*, *ROS1* and *RET* rearrangements [34].

The various technologies currently in use for the clinical evaluation of genomic alterations usually search for a limited number of oncogenic markers. Techniques such as PCR, FISH, Sanger sequencing, immunohistochemistry and mass spectrometric genotyping are among those that lack the ability to analyze a large number of markers. Consequently, it becomes unfeasible to subject a biopsied tissue sample to all types of analyses, due to both the cost and the small amount of material available. In addition, the number of known genomic changes is ever increasing, which makes the therapeutic setting even more complex [35].

To overcome these limitations, comprehensive genomic profiling (CGP) assays have been developed. CGP utilizes hybridization-capture NGS to find base substitutions, short insertions and deletions, copy number changes and selected fusions in hundreds of cancer-related genes. This approach may also identify rare or unusual genomic alterations. In addition, the test requires small amounts of biopsy tissue for analysis and provides high specificity (>99%) and sensitivity (95 to 99%) [35]. NGS-based approaches (including CGP) are excellent choices for optimal ctDNA profiling in patients with advanced NSCLC. With these methods, all seven genomic changes cited in the National Comprehensive Cancer Network guidelines (*EGFR*, *ALK*, *BRAF*, *ERBB2*, *MET*, *ROS1* and *RET*) can be identified [34]. Still, single-gene ctDNA testing may have great clinical utility. PCR-based ctDNA platforms such as digital PCR provide high sensitivity and specificity to assess single genes or hotspot mutations such as *EGFR* p.T790M [36].

Physicians may benefit from concomitant regulatory approval of targeted therapy and a companion diagnostic tool, which is a medical device that helps a healthcare professional determine whether the benefits of a therapeutic product outweigh the potential side effects and provides essential information for choosing a medicine or corresponding biological product. In thoracic oncology, high-quality diagnosis is essential to provide adequate personalized therapy [20]. Hence, regulatory agencies should consider incorporating companion tests linked to novel targeted therapies that require molecular profiling. In Brazil, coverage of NGS and ctDNA testing is imperative to increase access to personalized care for NSCLC patients.

NGS panel of ctDNA: recommendations to guide clinical management of advanced NSCLC

Many analytical methods using ctDNA can identify molecular alterations, and choosing the right methodology for each case should take into account the sensitivity. NGS-based methods were designed to provide simultaneous information on dozens of genetic abnormalities, which is useful in cancer treatment selection. Different NGS-based methods have been developed and validated for NSCLC ctDNA abnormalities with the advantage that these methods can detect rare mutations that have not been characterized before. Other important advantages of NGS-based platforms include the ability to evaluate tumor suppressor genes, quantify gene copy number variations and identify oncogenic fusions. Different outputs can be expected using distinct NGS platforms available in the market. For instance, NGS hotspot panels may be applied to cover the most relevant oncogenes, whereas CGP may provide more comprehensive information, as defined in a latter section.

The International Association for the Study of Lung Cancer has convened a multidisciplinary panel of specialists in the field of thoracic oncology to evaluate available evidence regarding liquid biopsy [30]. At the end of the conference, recommendations were published to guide the clinical management of advanced NSCLC patients. These determined that an NGS multiplex panel is recommended over PCR-based methods. They also attested that liquid biopsy techniques have the potential to improve patient care and treatment. Different therapeutic conformations for NSCLC may benefit from the clinical implementation of this diagnostic method [30].

Panel recommendations

A panel of selected lung cancer experts was provided with relevant prompts to address in a conference. Through the presentations on the prompts, a cohesive paper was compiled on the topic. On the basis of the discussion by the expert panel, the following recommendations are proposed to improve the diagnosis and treatment of NSCLC

Table 1. Summary of recommendations for improving access to ctDNA testing for metastatic NSCLC in Brazil.

Recommendations
1. ctDNA testing should be performed in patients with treatment-naive metastatic nonsquamous NSCLC who lack tissue material
2. ctDNA testing should cover at least *EGFR*, *ALK*, *ROS1*, *BRAF* and *NTRK*
3. Immunotherapy should be initiated only after results of gene profiling
4. *EGFR* p.T790M should be initially tested in ctDNA after progression to a first- or second-generation EGFR TKI
5. Comprehensive ctDNA NGS panels are not routinely recommended to assess mechanisms of resistance
6. International laboratory standards should be followed
7. ctDNA analysis should be incorporated by national regulatory agencies

ctDNA: Circulating tumor DNA; NGS: next-generation sequencing; NSCLC: Non-small cell lung cancer; TKI: tyrosine kinase inhibitor.

in Brazil (Table 1). These recommendations were based not only on literature evidence (as discussed in this paper) but also on the current reality of the Brazilian context to ensure access to proper diagnosis and treatment in that country. For instance, the current proposal clearly states a minimum list of five genes that should be covered by NGS-based liquid biopsy. This list is based on currently available treatments in the country. Of note, NGS-based liquid biopsy is not routinely recommended in the current proposal after progression to a first- or second-generation EGFR TKI except in the context of a clinical trial.

1. The panel strongly recommends that ctDNA testing be performed in patients with treatment-naive metastatic nonsquamous NSCLC that lack tissue material. Whenever possible, an NGS test should be performed.
2. The panel recommends that ctDNA NGS cover at least five gene alterations that are linked to locally approved targeted therapies: *EGFR*, *ALK*, *ROS1*, *BRAF* and *NTRK*. The gene panel should be updated as new drugs are approved.
3. If possible, clinicians should not initiate immunotherapy before results of gene profiling. Moreover, PD-L1 expression should not be analyzed alone before results of gene profiling.
4. After progression on a first- or second-generation EGFR kinase inhibitor, the panel strongly recommends ctDNA testing for the presence of p.T790M. In the case of a negative result, a tissue rebiopsy must be considered if feasible.
5. The panel does not routinely recommend comprehensive ctDNA NGS panel after progression to targeted therapies except for cases that are considered for clinical trials.
6. The panel emphasizes the importance of following international laboratory standards to optimize preanalytical and analytical factors.
7. The panel recommends regulatory agencies to consider incorporating companion testing when evaluating drug incorporation. In particular, coverage of NGS and ctDNA testing should be considered when evaluating drugs for lung cancer.

Conclusion

In the new era of precision oncology, detecting genomic alterations is the first priority and guiding principle for personalized care. Comprehensive molecular testing will provide better information for patients to receive the appropriate therapy, decrease toxicity and remove unnecessary costs. As NGS sensitivity increases and data on other actionable mutations are discovered, comprehensive molecular profiling will become the standard for all patients with a diagnosis of advanced cancer.

As more data supporting the validity for ctDNA testing becomes available, its clinical indications will broaden. In turn, the use of this noninvasive, quick, and comprehensive analysis must increase. As the demand for ctDNA testing grows, cost should decrease and cost-effectiveness studies will more readily demonstrate that complete ctDNA NGS at time of diagnosis is beneficial for the patient and the healthcare system.

Future perspective

Much progress is awaited in the field of liquid biopsy and ctDNA analysis for lung cancer in the coming years. Molecular methods to assess biomarkers in fluid will become more comprehensive, accurate and affordable and should be common place in the clinic. Likely, liquid biopsy will be used in parallel with tumor analysis but may become an obligatory test to follow patients in many scenarios, which includes evaluation of disease response to treatment but also to prospectively assess minimal residual disease and screening in high-risk populations. In the near future, one could envision that liquid biopsy will be collected and likely run at home, using portable and

friendly apps that will deliver molecular data in real time. As a growing amount of data are generated, real-world data storage and analysis will be highly relevant both for patients and payers. All these processes will be facilitated by concerted efforts to improve data sharing through large genomic networks.

Executive summary

Lung cancer epidemiology & burden in Brazil

- Lung cancer is the leading cause of cancer-related mortality in Brazil. In line with global trends, cigarette smoking is the most important risk factor, and adenocarcinoma is the predominant histological subtype. One of the main challenges is delayed diagnosis, which contributes to the high rate of late-stage diagnosis.

The role of molecular profiling to guide targeted therapy

- Knowledge on actionable oncogenic drivers have led to the development of targeted agents effective in the treatment of nonsquamous non-small cell lung cancer (NSCLC). Once genetically altered, the signaling pathways involved may become constitutively activated and stimulate carcinogenesis, making them attractive targets for therapy.
- Biomarkers are clinically assessed to determine the best targeted options for NSCLC patients.

The role of molecular profiling to predict response to immunotherapy

- Data are limited to support the activity of immune checkpoint inhibitors (ICI) in patients whose tumors harbor classic driver mutations. In general, ICI demonstrates lower activity in driver-positive NSCLC, as opposed to targeted therapy.
- Moreover, adverse events associated with this class may be increased in this subset. Therefore, clinicians should defer ICI until results of molecular profiling are clinically available.

Barriers to molecular profile implementation

- Access to molecular testing and targeted therapy still faces social and economic barriers in the global context, such as lack of infrastructure, lack of technical knowledge, high costs, and adoption of new drugs.
- In most low- and middle-income countries, personalized therapy is far from a reality, especially in public settings.

Clinical utility of circulating tumor DNA (ctDNA) analysis for evaluation of oncogenic mutations

- ctDNA testing has proven to be a reliable and affordable tool to include in the molecular diagnosis of NSCLC.
- The benefits of using ctDNA analysis in Brazil may be seen in the socioeconomic scenario, large aging population, high incidence of cancer, healthcare inequities, financial constraints and regulatory limitations, all of which should be considered when contemplating its inclusion as a feasible opportunity in cancer diagnosis.

Next-generation sequencing methods for molecular profiling of NSCLC

- The various technologies currently in use for the clinical evaluation of genomic alterations usually search for a limited number of oncogenic markers.
- Consequently, it becomes unfeasible to subject a biopsied tissue sample to all types of analyses, due to both the cost and the small amount of material available. In addition, the number of known genomic changes is ever increasing, which makes the therapeutic setting even more complex.
- Next-generation sequencing (NGS) methods are capable of detecting base substitutions, short insertions and deletions, copy number changes and selected fusions in hundreds of cancer-related genes. This approach may also identify rare or unusual genomic alterations.
- In Brazil, coverage of NGS and ctDNA testing is imperative to increase access to personalized care for NSCLC patients.

NGS panel of ctDNA: recommendations to guide clinical management of advanced NSCLC

- NGS-based methods were designed to provide simultaneous information on dozens of genetic abnormalities, which is useful in NSCLC treatment selection.
- Different NGS-based methods have been developed and validated for NSCLC ctDNA abnormalities with the advantage that these methods can detect rare mutations that have not been characterized before. Other important advantages of NGS-based platforms include the ability to evaluate tumor suppressor genes, quantify gene copy number variations and identify oncogenic fusions.
- NGS multiplex panels have been recommended for NSCLC ctDNA assessment, which has the potential to improve patient care and treatment.

Panel recommendations

- A panel of selected lung cancer experts was gathered to discuss and propose recommendations on the use of NGS for ctDNA analysis in advanced NSCLC. These recommendations were based not only on literature evidence (as discussed in this paper) but also on the current reality of the Brazilian context to ensure access to proper diagnosis and treatment in that country.

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