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The de-centralization perspective for liquid biopsy use in thoracic pathology the way to go ☆

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ABSTRACT

The liquid biopsy (LBx) concept in thoracic oncology has optimized treatment decision-making for patients with advanced/metastatic non-small cell lung cancer (NSCLC). The clinical practice of LBx in thoracic oncology is based on international guidelines. However, aside from the recommendations for adoption of LBx in daily clinical practice for late-stage NSCLC, other indications evaluate the role of LBx in clinical trials, particularly for early stage NSCLC. Transferring LBx into routine practice requires robust data from clinical research programs that are able to sustain the novel indications of LBx. Equity of access to treatment is linked to access to molecular testing for thoracic malignancies. In this context, widespread dissemination of molecular testing, avoiding centralization to commercially available platforms or to unique national academic institutions, becomes a major component of the current strategy for lung cancer care. Therefore, de-centralized LBx in thoracic oncology is the best approach to democratize molecular testing, optimizing access to personalized therapeutic options for lung cancer patients. LBx de-centralization needs to be perfectly mastered using a high quality approach that gives specific and sensitive results. However, several challenges significantly affect this approach, such as the lack of harmonized technical procedures, pre-analytical challenges and issues in interpreting the molecular records, which can imped significantly the widespread practice of LBx. Our aim was to investigate the interest in and advantages of LBx de-centralization in thoracic oncology. The bottlenecks of this strategy that aim to fill the gaps toward widespread integration of LBx into the daily life of health care systems for lung cancer patients will be discussed.

1. Introduction

The therapeutic innovations into the field of thoracic oncology correlate with the chance of detecting predictive biomarkers and selecting lung cancer patients who should benefit from personalized schemes, such as targeted therapies, immunotherapies, and more recently, antibody drug conjugates and bi-specific antibodies (Liu et al., 2024). Lung cancer biomarkers may be successfully detected in both tissues and/or biofluids grouped as "liquid biopsies". The term liquid biopsy (LBx) includes a plethora of biological fluids (peripheral blood, urine, peritoneal washing, cerebrospinal fluid, tears, saliva, etc), which contain clinically informative biomarkers (Alix-Panabières and Pantel, 2025). Obtaining a tissue biopsy is a traumatic procedure and patients may be reluctant to comply with removal of multiple biopsies, LBx have become used more and more in clinical routine practice, particularly in thoracic oncology (Aggarwal et al. 2021). Therefore, LBx are highly advantageous because they are not traumatic, easy to obtain, repeatable, reflect the overall state of the tumor and allow for real-time monitoring, notably in patients receiving targeted therapies (Hofman, 2023a). Moreover, LBx can be the only way to identify druggable genomic alterations if a tissue biopsy is not available at diagnosis and at tumor progression (Rolfo et al., 2021). To date, circulating free DNA (cfDNA) is the only approved material in clinical practice to assess the genomic profile of druggable alterations that point to targeted treatments for lung cancer patients (Aggarwal et al. 2021; Rolfo et al., 2021). It has emerged that since LBx are less invasive and easily collected they are a dynamic tool to track tumor evolution thanks to rapid access to the molecular results. However, the analysis of a LBx may give non-informative results depending on the heterogeneous shedding of circulating tumor DNA (ctDNA) into the blood flow. Consequently, the analysis of aberrant rearrangements and copy number variations (CNVs) with LBx is challenging compared to a tissue based molecular analysis. However,

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identification of somatic single-nucleotide variants (SNVs) usually shows good concordance with tissue biopsies (Bontoux et al., 2025; Lin et al., 2021; Sugimoto et al., 2023). These limitations and discrepancies may dramatically affect the demand for LBx by oncologists of many clinical centers. It is recognized that technically consistent results are crucial to accelerate implementation of LBx into clinical care. Nowadays, a plethora of commercially available technical solutions have been developed to perform genomic tests on-site, even in the absence of a benchmarking activity. Aside from limitations to early access to drugs, depending on the countries, molecular testing may benefit from harmonized protocols supporting equity of clinical schemes for lung cancer patients (Barrios et al., 2023; Bayle et al., 2023a; Hofman et al., 2023b; Horgan et al., 2022a; Horgan et al. 2022b). In particular, limited access to LBx reinforces these discrepancies, with less access to personalized treatments, either in a routine clinical practice and in clinical trials (Fairley et al., 2023).

By optimizing de-centralized LBx based approaches, more widespread administration of targeted therapies may be achieved in routine clinical practice. Therefore, LBx democratization certainly correlates with the diffusion of a de-centralized model that is able to tailor dedicated strategies to each healthcare system. For this purpose, it is mandatory that the setup of programs be performed in accordance with good manufacturing procedures. To be competitive with LBx the outsourcing strategies of these programs must exploit multidisciplinary expertise. The question as to where lies the frontier between an excessive and a not well-controlled LBx de-centralized activity and a monopoly of a few central platforms can be raised. The meaning of the term "decentralization" varies depending on national institutions. The French National Cancer Institute ("Inca") has identified n = 28 molecular hubs with proven expertise in next-generation sequencing (NGS) technologies, in particular for lung cancer patients (Hofman et al., 2020). In contrast, the Institute Gustave Roussy (Villejuif, France) has implemented an on-site comprehensive genomic profiling (CGP) program, thanks to a partnership with Roche Dx (Tucson, AZ, US), analyzing cfDNA from LBx collected by many spoke institutions (Bayle et al., 2023a; Rouleau et al., 2024). Moreover, simple, compact molecular platforms with performance similar to that of expert laboratories have created new opportunities to move testing faster and nearer to the patient, along with challenges to use wisely some technologies. So, in addition, a second level of de-centralizing can be reenforced in France by integrating private laboratories and laboratories from community hospitals that achieve a high standard of quality.

As the clinical value of LBx continues to expand, there is growing interest in moving beyond centralized testing models towards more accessible, locally integrated approaches. Since there is an urgent need in this setting, we explored the practical implementation of de-centralized LBx testing for routine care in the field of thoracic oncology. We examined the advantages and issues associated with this strategy, as well as some of the solutions that could bridge the gap to some of the constraints that are described.

2. Advantages and potential of LBx de-centralization in thoracic oncology

The advantages and opportunities of LBx de-centralization are summarized in Fig. 1.

2.1. LBx de-centralization may shorten the turnaround time for treatment decision-making

LBx de-centralization can shorten the time to perform molecular tests and identify the best therapeutically options for advanced/metastatic NSCLC patients (Makarem and Leighl, 2020; Raez et al., 2023). Stage IIIB/IV non-squamous-NSCLC is usually diagnosed with a tissue biopsy or cytological samples. Assessment of genomic alterations can identify potential druggable molecular targets. Among the different therapeutic options associated with these targets, it is important to distinguish those indicated by international guidelines of the ESMO and NCCN (Hendricks et al., 2023; Rieley et al., 2025). In particular, according to the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT), a therapeutic molecule has to be rapidly administrated, particularly when ESCAT I target are identified (Mosele et al., 2024). However, the molecular profile cannot be obtained from a tissue biopsy, but a targeted therapy can be rapidly administered thanks to genomic alterations identified with a LBx at baseline, notably in the case of an urgent clinical need (Bayle et al., 2023a, Bouhlel et al., 2017). Moreover, even if a tissue biopsy is available, the turnaround time (TAT) to obtain molecular results is much longer than when using a LBx at the same time, due to differences in the pre-analytical workflow, depending on the sample type. In addition, the TAT depends on the organization on-site, since histological diagnosis and genomic analyzes from a tissue biopsy can sometimes be outsourced in different laboratories. At tumor progression, a tissue sample may take a long time to obtain or may not be collected due to the poor status of a patient or inaccessible to the tumor site. It should also be kept in mind that a biopsy procedure can be associated with side effects (Chouaid et al., 2014; Scheffler et al., 2022). However, it is pivotal to obtain rapid genomic data from these patients to adapt the therapeutic options according to the presence or not of druggable molecular targets, since molecular assessment may detect acquired resistance mechanisms (such as *EGFR* p.T790M, p.S797C, *ALK* mutations, and *MET* amplifications). LBx may allow rapid detection of these acquired resistance mechanisms (Hofman et al., 2019a; Hofman 2021a; Koulouris et al., 2022; Minari et al., 2020; Zhao et al., 2026). Globally, a LBx has a high sensitivity and specificity for the detection of SNVs, which correlate well with identification in paired tissue biopsies (Bontoux 2025). In this context, taking a blood sample and sequencing

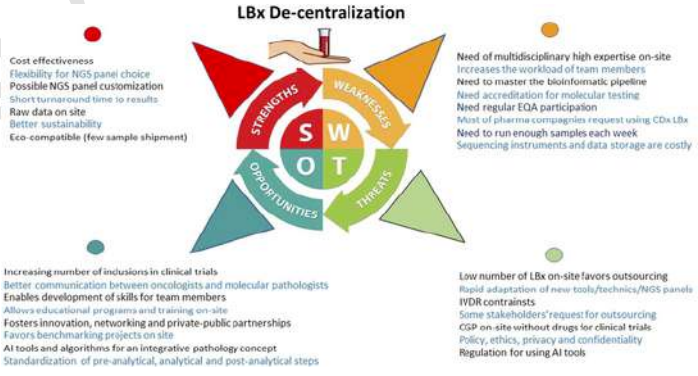

Fig. 1. "SWOT" analysis for a de-centralization strategy when using liquid biopsy testing in thoracic oncology.

the cfDNA on-site should allow rapid treatment decision-making. Gene fusions and copy number variations (CNV) are most often more difficult to detect in LBx, which show a lower sensitivity than a tissue biopsy for the detection of these genomic alterations (Bontoux et al., 2025). Moreover, even if specific genomic alterations, such as *MET* CNV, can be better identified in a tissue biopsy than with a LBx, some studies showed that a tissue re-biopsy does not correlate with an increase in the overall survival of patients (Bronstein et al., 2025).

Taken together, the TAT to identify a druggable mutation using LBx on-site is shorter than using a tissue biopsy. This is particularly true when using single gene testing (SGT) or medium NGS panels. In this context, many NGS panels contain the set of all genes and their variants that have to be systematically evaluated nowadays to point to potential administration of a targeted therapy that is available on the market in daily practice (Mosele et al., 2024). When using external platforms for LBx the TAT is generally longer mainly due to shipment, the different processing steps and the time to validate and transmit the report to the care center.

The inclusion into a clinical trial needs comprehensive genomic profiling (CGP) to identify potential genomic alterations to select patients for ongoing trials (Bayle et al., 2023b, Trédan et al., 2025). For this, a shorter TAT with a LBx on-site *versus* outsourced to a commercially or external national expert centers may be more challenging. Therefore, a de-centralized LBx strategy may be more difficult to administrate when using CGP LBx due to some analytical and post-analytical requirements, which can necessitate a very high level of expertise. Moreover, it is noteworthy that overtime it is mandatory to evaluate more and more genes, at least at tumor progression, and in this regard, all the CGP used on-site may not contain certain genes of recent interest to adapt treatment as of now and in the near future (Table 1). In this regard, external expert centers may be able to rapidly adapt their panels to implement and screen new genes of interest for treatment decision-making.

2.2. Setting up both tissue and LBx next-generation sequencing in-house and tissue and LBx single gene testing in-house

As for in-house NGS with a tissue biopsy, analysis on-site with a LBx allows accurate selection of the NGS panels as part of daily practice (Hofman, 2023a). This enables an economic business plan for each molecular pathology laboratory and institution to be defined. The number of LBx that are routinely tested and the size of commercially available NGS panels to run according to the sequencing platforms available in-house must be taken into account. Finally, certain molecular pathology laboratories favor internal customized NGS panels, integrating molecular targets not referenced in commercial NGS panels. SGT approaches, mainly for *EGFR* and/or *ALK* status assessment, play a pivotal role in the diagnostic routine setting of institutions engaged in rapid molecular testing (Boulhel et al., 2017; Heeke et al., 2021). SGT from both tissue and LBx demonstrated a shorter TAT than NGS approaches, which allowed rapid therapeutic decision-making for NSCLC patients. For example, this is notably true when using PCR technologies such as those using the Idylla instrument (Biocartis, Menchen, Belgium) and the Cobas instrument (Roche Diagnostics, USA) for *EGFR* status evaluation. When PCR is used the results can be obtained in one day, from blood sampling to reporting. Despite several limitations that include the scant reference range and lower technical sensitivity than NGS, it is noteworthy that the current global cost of SGT for a unique gene status such as *EGFR* is still lower than the technical cost of NGS strategies. Moreover, SGT does not need competent analytical and post-analytical on-site expertise (Heeke et al., 2020a; Heeke et al., 2021). Centralized LBx platforms are perfectly able to perform SGT with a LBx, even though most of them today perform NGS with a LBx. In this setting, it is an advantage to obtain the results on-site in one day, which is not possible when SGT is outsourced due to the shipment time and time for external pre-analytical treatment of the blood. In our opinion, SGT with a LBx should nowadays be considering as point of care testing. Moreover, we think that using SGT with a LBx on-site can only be useful in the case a physician requests an urgent result, notably when a tissue biopsy is not

Table 1
Examples of the availability of molecular targets of recent interest in thoracic oncology according to the next-generation sequencing panels used on-site at a particular cancer center (IHU RespirERA, Nice, France).

Company	Assay	List of Genes	Size (probe)	LBx or TBx	NRG1 fusion	MTAP CNV deletion	STK11 SNV	KEAP1 SNV	SMARCA4 SNV	RB1 SNV	MSI	TMB
ThermoFisher Scientific	**O**ncomine **C**omprehensive **A**ssay PLUS	517	1.4 Mb	TBx	✓	✓	✓	✓	✓	✓	✓	✓
Illumina	**TruSight Oncogoly 500**	524 (DNA) + 55 (RNA)	1.94 Mb	TBx	✓ (RNA panel)	NA	✓	✓	✓	✓	✓	✓
Agilent	SureSelect Cancer CGP	679 (DNA) + 80 (RNA)	2.7 Mb	TBx	✓ (RNA panel)	NA	✓	✓	✓	✓	✓	✓
Roche	Avenio CGP	324 (DNA)	1.8 Mb	TBx	NA	✓	✓	✓	✓	✓	✓	✓
SOPHiA Genetics	MSK IMPACT	505 (DNA) + 140 (RNA)	2.4 Mb	TBx	✓ (RNA panel)	✓	✓	✓	✓	✓	✓	✓
Company	**Assay**	**Genes List**	**Size (probe)**	**LBx or TBx**	**NRG1 fusion**	**MTAP CNV deletion**	**STK11 SNV**	**KEAP1 SNV**	**SMARCA4 SNV**	**RB1 SNV**	**MSI**	**TMB**
ThermoFisher Scientific	**O**ncomine **P**recision **A**ssay Gx	50	14,5 kb	LBx and TBx	✓	NA	NA	NA	NA	NA	NA	NA
HederaDx	**H**edera **P**rofiling 1	106 (DNA) + 28 (RNA)	289 kb + 74,6 kb	LBx and TBx	✓	✓	✓	✓	✓	✓	✓	NA
Company	**Assay**	**Genes List**	**Size (probe footprint)**	**LBx or TBx**	**NRG1 fusion**	**MTAP CNV deletion**	**STK11 SNV**	**KEAP1 SNV**	**SMARCA4 SNV**	**RB1 SNV**	**MSI**	**TMB**
HederaDx	**H**edera **P**rofiling 2 ctDNA	32 (DNA)	90 kb	LBx	NA	NA	✓	✓	NA	NA	✓	NA
Agilent	Avida DNA Onco LB	179 (DNA)	1,17 Mb	LBx	✓	NA	✓	✓	✓	✓	✓	NA
Roche	Avenio Expanded	77 (DNA)	200 kb	LBx	NA	NA	✓	✓	NA	✓	NA	NA
SOPHiA Genetics	MSK Access	146 (DNA)	422, 558 kb	LBx	NA	NA	✓	✓	✓	✓	NA	NA
Pillar Bioscience	Pillar Core and Fusion	104 (DNA) + 18 (RNA)	12,9 kb	LBx	✓ (RNA panel)	NA	✓	NA	NA	✓	✓	NA

available and if the patient is a never smoker with a high probability of having an *EGFR* mutation at diagnosis or an *EGFR* mutation mechanism of resistance at tumor progression. However, SGT with a LBx may miss important variants, notably in case of a *EGFR* exon 20 insertion and do not allow investigation at the same time of other genomic alterations of interest in different genes as does NGS (Molina et al., 2026).

2.3. LBx de-centralization fosters multidisciplinary team member expertise

In-house testing with LBx permits easy access to the raw data (allowing rapid repetition of the analysis in the case of an uncertain result, for example, or to perform additional research), and to interpretation of the molecular data of a diagnostic workflow for which the pre-analytical and analytical parameters can be inspected. As a consequence, it is crucial to improve the expertise of the healthcare members of the multidisciplinary team and to maintain a permanent dialogue and interaction with the different actors participating in the LBx journey (physicians, nurses, technicians, pathologists, geneticists, bioinformaticians, secretaries). In this scenario, it is of interest to manage on-site all the pre-analytical, analytical and post-analytical procedures of each critical step and to motivate each member of multidisciplinary working team. The biobanking of leftover samples (plasma, extracted nucleic acids, buffy coat and/or PBMCs) is also important to collect molecular data (Bontoux et al., 2025; Corradi et al., 2025). In our opinion, biobanking of LBx on centralized platform, even if theorically possible, is rarely done, since it is not the initial goal when sending a LBx externally. If samples join a biobank, they need to be associated to a contract, a material transfer agreement and must follow the rules established by the ISO 20 387 norm (Annaratone et al., 2021). Moreover, most of the centralized platforms request a whole blood volume (at least 20 mL) for NGS testing, which most of the time is not compatible with obtaining additional blood for biobanking in daily practice. In our opinion, most of the centralized platforms, notably commercial platforms, do not routinely do biobanking with extra samples for research purposes. Interestingly, biobanked collections on-site can be easily used for benchmarking activities, like technical comparison of the analytical performance of NGS panels and the different LBx circuits, including possible automation, analytical and post-analytical procedures (Bontoux et al., 2025; Heeke et al., 2020). Benchmarking using LBx is certainly possible on external platforms depending on the amount of extracted cfDNA left over after NGS testing, which is the initial goal. However, this requires agreement from different local sites, which can be difficult to obtain depending on the country and the regulations for use of human specimens for research purposes.

LBx de-centralization should better foster interaction among the different actors of the health care institution in-house than outsourcing of LBx (Fig. 1). Communication between the different health care actors is essential. Communication between the clinical oncologists and the molecular pathologists is a cornerstone of the entire process, when clinically validating the results of the different molecular tests from tissue, cytological and biofluid samples, which can be taken from the same patient. In our opinion multidisciplinary discussions are much easier to make on-site between all actors, notably oncologists, pathologists, biologists, technicians and bioinformaticians, since they are all locally present.

Information and interpretation of the molecular data are easier when all the analytical and post-analytical phases are managed in the same institution. In particular, this approach allows easy administrating of genomic data for inclusion of patients into clinical trials that are evaluated by molecular tumor boards (MTB) (Segui et al., 2025). MTB can also be centralized, but MTB are more and more often set up in-house and the oncologists are aware of this, since they have their own expertise and the treatment decision-making is under their direct responsibility. In daily practice the oncologists working on-site can be part of MTB that are organized on-site and have their own treatment strategy (Aldea et al., 2025).

In parallel, setting up training and educational programs dedicated to the best practices of LBx should be more easily approached in-house where all pre-analytical, analytical and post-analytical steps are mastered on the same site, which improves the skills of healthcare workers. Partnerships and establishment of projects with different academic teams can also be developed, particularly to set up inter-laboratory validation. Similarly, participation with different certified organisms (such as IQNPATH, GENETISS, UK NEQAS) in external quality assessment (EQA) schemes can be easier to perform in-house, even if these EQA can be set up when LBx are sent externally (Ramsden et al., 2006; Dufraing et al., 2021; Kalimulaeva et al., 2026). Public-private partnerships, with biotechnology and pharmacology companies can benefit from the use of LBx on-site, and so, open up room for participation in innovative programs. In our opinion, when samples are sent to an external platform (notably commercially available platforms) it is certainly more difficult to then establish public-private partnerships using biological specimens that have been analyzed first on these external platforms.

Finally, LBx de-centralization should probably open the way to more equity in access to personalized treatment (Kurzock et al., 2024).

2.4. Potential optimization of best practices to foster green laboratory practices

The development and improvement in techniques, the deployment of different actions aimed at reducing energy, have raised the awareness of a collective effort to cap energy consumption (; Furuta et al., 2025). The concept of “green” laboratories and biobanks is rapidly emerging. To be more eco-compatible, different options of shipment of LBx should be examined. To reduce the global energy requirements of laboratories on-site education programs into an eco-compatible attitude could be set up (Mattman and Simons, 2026; Scott, 2022). The optimization of the in-house workflow of LBx by eliminating unnecessary steps can lead to both environmentally sound and cost-effective operation. Even if green laboratory practices can be developed when LBx are centralized, the transportation of many LBx would not reduce the impact on the carbon footprint. Finally, in-house testing is pivotal to maintaining care of patients with lung cancer, even if external events, such as pandemia, can block diagnostic routine testing thus limiting access to outsourced LBx management (Jabbal et al., 2023).

3. Issues and constraints for LBx de-centralization in thoracic oncology

3.1. Increase in the workload for team members participating in LBx procedures

Setting up, optimizing and maintaining processes to carry out LBx testing, must take into consideration the continual development of techniques and rapid improvements in the different therapeutic strategies for lung cancer patients. This requires complying with several technical parameters and factors. Firstly, developing and maintaining the expertise of the different actors participating in LBx programs, including nurses, physicians, technicians, pathologists, biologists, geneticists and bioinformaticians, is a key factor. These actors need to keep up to date their knowledge into developments in the field of LBx. From the physician’s request, blood sampling and processing, molecular testing for clinically relevant biomarkers, to a easily interpretable clinical report. One major consequence of internalizing LBx testing is the challenge of the workload of the laboratory receiving the LBx. This includes the pre-analytical steps (centrifugation, nucleic acid extraction and qualification, storage), the analytical and post-analytical phases and the need to continuously follow international guidelines and requirements (Heitzer et al., 2022). The number of NGS of LBx may be higher than

that of NGS of tissue biopsies, since blood sampling is easily repeatable, avoids a tissue re-biopsy, and is non-invasive. LBx testing can also monitor progression of the disease. Moreover, some strategies can combine testing of both a LBx and a tissue biopsy while adopting a dedicated NGS panel (medium or comprehensive). However, this considerably increases the workload not only of the technicians, but also the molecular pathologists and the bioinformaticians (Bontoux et al., 2025; Hofman et al., 2023b; Sugimoto et al., 2023). When CGP assays are adapted to the analysis of LBx, mastering variant analyzes to confirm the actionability class may be a challenge (Bayle et al., 2022; Bayle et al., 2023b). Finally, the business model to integrate on-site LBx testing should be compared with an outsourced LBx strategy. This business plan needs to integrate different parameters such as the cost of personnel, reagents and instruments, of the bioinformatic pipeline, and of data storage and security for a long time.

3.2. The need to maintain the quality of the results and a stable economic model in-house

The quality of the results is a priority for good practice of the laboratory. It requires following international standards. In this context, accreditation of LBx diagnostic laboratories according to the ISO 15189 standard in Europe or to CLIA/CAP (College of American Pathologists) accreditation in the USA, is the best way to adapt LBx testing into the clinical setting by assuring reliable results for the clinicians (Ntzifa and Lianidou, 2023). The major goal is to have, as many as possible, a low number of false negative results and to be able to detect false positive results. The process of obtaining and maintaining accreditation is costly for on-site laboratories, since ideally it should be managed at least by a full-time quality control staff member and is associated with some extra-costs notably for the development of intra- and inter-laboratory validation, and internal and external audits (Schneider et al., 2017). Moreover, maintaining accreditation over time requires a great deal of continual personal motivation from all the team members of the laboratory. One of the challenges for LBx de-centralization in the USA depends on a tight connection between target drugs and companion diagnostic tests (CDx). However, in Europe members need to apply for In vitro Diagnostic Regulation (IVDR) assays. The different rules have led to adopt CE ("Conformité Européenne") to perform In Vitro Diagnostic (IVD) (CE-IVD) LBx and not Laboratory (Verbaanderd et al., 2023) Developed Tests (LDTs), to respect the upcoming European regulations (Verbannderd et al., 2023). This will certainly have a strong impact on the budget of laboratories, but it will be the only way to practice de-centralized LBx. The cost of de-centralized LBx procedures is certainly lower compared to LBx analyzed on commercial platforms. At least when performed in some national institutional and large expert centers. However, this should be considered with caution and needs further comparative and benchmarking studies in real life, also including comparative cost analyses for SGT and NGS (Malapelle et al., 2025). Finally, analysis of the budget includes the gene panel size, the cost of personnel, sequencer acquisition and maintenance, the accreditation process, bioinformatic activities and data storage. Moreover, the number of LBx received per week by each institution should be considered in order to optimize the use of reagents without wastage. When only a few cases are routinely collected, a hub-spoke model of sharing samples with experienced institutions may serve to preserve resources while maintaining a reasonable TAT to generate the clinical report.

3.3. Adapting to the clinical and therapeutic needs in thoracic oncology

For LBx de-centralization, a number of challenges need to be met, which demands considerable effort. The composition of the gene panel is constantly modified according to its size. Mandatory validation associated with accreditation and the robustness of the results, as well as technical advances and optimization must be maintained. For example, emerging therapeutic schemes for NSCLC will certainly be driven by novel promising biomarkers such as the *STK11, KEAP1, RB1, SMARCA4, MTAP* status (Hofman et al., 2024). The rapidity with which in-house sequencing adapts may be slower than in large expert centers or commercial platforms. Similarly, only large gene panels provide the blood tumor mutational burden and microsatellite instability data or genomic instability status while collecting clinically relevant data of the genomic assessment of the patient's tumor (Meri-Abad et al., 2023; Tian et al., 2023). Taken together, obtaining access to all this data is challenging when using de-centralized LBx, which could make possible inclusion of patients into a clinical trial on-site. Other issues concerning the use of LBx in-house include the lack or the difficulty of using standardized procedures to measure the circulating DNA tumor fraction (Tf). These procedures distinguish between the germline or clonal hematopoiesis mutations and tumor related alterations (Rolfo et al., 2024). These analyzes need expert bioinformaticians and the use of different filters for the analysis.

4. Opportunities and potential solutions for implanting LBx in a de-centralized way

Despite the hurdles in establishing LBx de-centralization it can hold advantages and provide different opportunities, as listed in Table 2.

4.1. Optimization of the LBx diagnostic workflow

Rapid access to the results of the molecular biology of an NGS analysis depends on automation of sample processing, both for pre-analytical and analytical handling. According to the NGS panels and the technologies, automation is now more and more accessible. This avoids performing manually technical steps that are time consuming and can have a drastic impact on the success of molecular analysis. The new indication of LBx for lung cancer will allow periodic collection of blood sample to monitor the disease over time while looking for genomic alterations associated with resistance mechanisms. In addition, in the peri-operative setting, the upcoming immunotherapy predictive biomarker blood tests and the integration of the ctDNA level in prognostic evaluation, will rapidly lead to a massive increase in the number of LBx requested by physicians (Hofman et al., 2019b; Hofman 2023c). Thus, these different approaches may revolutionize the LBx diagnostic workflow, accelerat-

Table 2
Potential solutions and opportunities for bridging the existing gaps to the use of de-centralized liquid biopsies for lung cancer patients.

Current and Future Opportunities for LBx Dissemination in Thoracic Oncology
Automation of the pre analytical and analytical phases for LBx, including nucleic acids extraction, library preparation and sequencing steps
Optimization of the bioinformatic pipelines for CGP large panels, artificial intelligence tools integration, and algorithms for variants data analyses
Increase in the number of LBx requests by clinicians due to upcoming applications, such as real time monitoring of disease and treatment efficacy, new predictive biomarkers for immunotherapy, assessment of the minimal residual disease, lung cancer screening, and interception therapeutic strategy in thoracic oncology
Decrease in the CGP LBx cost over time and strategy for LBx reimbursement at the national level
Increase in the number of inclusions into clinical trials based on the CGP LBx results, notably for certain indications, such as in young lung cancer patients, in never-smokers, on tumor progression
Setting up educational and training programs for LBx processing on-site for different stakeholders
Harmonization of different procedures at the international level for complex genomic report recommandations
Developing a reflex LBx strategy at tumor diagnosis and at tumor progression
Increase the number of programs for external quality assessment and for accreditation associated with LBx
Assessment of germline and clonal hematopoeisis of indeterminate potential associated mutations thanks to DNA sequencing from PBMCs or buffy coat
Increase the integrative pathology workflow concept including multi-omic perspectives for biospecimen analyses

ing molecular analysis of LBx samples in routine practice, paving the way for in-house approaches. However, it is possible that depending on the clinical situation, it would be necessary to use different types of gene panels, which could also limit on-site LBx development. Optimization of the LBx on-site should benefit from the increase in the number of requested tests allowing integration each week of a sufficient number of samples for each batch. This should reduce the global cost and allow the TAT to be respected for optimal treatment decision-making.

4.2. Decrease the cost of next-generation sequencing LBx and examine the future policy of reimbursement

The cost of NGS based analysis is decreasing and should become cheaper than multiple SGT for predictive biomarker assessment in thoracic oncology (Malapelle et al., 2025). There is no doubt that NGS panels and the entire molecular testing workflow will be less expensive over time, depending on the countries and/or institutions. National entities will bear the cost of LBx with possible reimbursement, but the latter may depend on the panel size (Hofman et al., 2020). Alternatively, the costs could depend on the technology and the insurance coverage. CGP with LBx may also be reserved for some specific clinical cases and indications, such as in young lung cancer patients, a never smoker population, or on tumor progression when on a tyrosine kinase inhibitor (TKI), which could lead inclusion of some patients into clinical trials or treatment with an alternative targeted therapy. It is noteworthy that germline and clonal hematopoiesis of indeterminate potential mutation assessment can be better done using CGP with LBx when sequencing circulating DNA from the buffy coat or from peripheral blood mononuclear cells (PBMCs) in parallel to ctDNA sequencing. This may be a very robust approach, even if it increases the sequencing cost (Magee et al., 2025; Tell et al., 2026). The overall cost of LBx analyzed on external platforms is also decreasing progressively, even if this cost is still elevated for most of the commercially available platforms that are comparative with the academic platforms. However, using this latter strategy routinely may have some disadvantages, notably in European countries that have different reimbursement models. However, in our experience the global cost of LBx is usually higher in the centralization setup since it includes higher fees for the work of the personal, including pre-analytical blood management, analysis of the sequencing results and reporting.

The economic landscape of diagnostics in the field of molecular pathology, including the routine use of LBx is a complicated interplay between different stakeholders (Horgan et al., 2024; Horgan et al., 2025; Sireci et al., 2020). Adding to the complexity is the limited time available to adopt novel technologies and indications into molecular pathology, which require constant changes to coding, coverage and reimbursement. It is the right and responsibility of molecular professionals to take part in discussions surrounding these changes to the system. The decisions that are made will ultimately impact the ability to offer LBx and novel and potentially life-saving diagnostics to patients. Economic models for the use of assays in molecular pathology, notably LBx, varies according to the country and the challenges of their health care policy. In some countries, such as in the USA, the policies include variable private payer coverage. For example, the plans offered by commercial carriers vary considerably compared to the USA Medicare coverage. Individual laboratories may strategically develop a preferred vendor status with a commercial carrier on a competitive basis to capture a share of the market. In this context, it is pivotal that all stakeholders involved in precision oncology be able to establish a common business model for LBx use at the national level and integrate the different constraints of the health care policy (Horgan et al., 2022). It will be of interest to foster policy makers to better support different laboratories of each country dealing with de-centralization of LBx. However, ideally a policy of full reimbursement of LBx should be adopted. It should follow the current international guidelines both at diagnosis, if no tissue biopsy is available, and at tumor progression for patients with non-squamous NSCLC specifically resistant to TKI.

4.3. Setting up educational and training programs related to LBx use in thoracic oncology

The implementation and strategy for de-centralized LBx use in thoracic oncology requires education and training programs, including workplace seminars for technicians, nurses, oncologists, molecular pathologists and bioinformaticians, including both practical and theoretical sessions. Pathologists would benefit from training on-site since they usually are not aware of the advantages and the limitations when using LBx and/or tissue biopsies for lung cancer patients (Hofman et al.; ESP Advanced Training Centre for Molecular Pathology with an emphasis on liquid biopsy. https://www.esppathology.org; Ilie et al., 2016 et al.; Ilie et al., 2025). Incorporating training into the university curricula would enhance the efficient adoption of LBx into clinical practice (Ilie et al., 2024; Ilie et al., 2025). A specific part of the program needs to focus on different recommendations concerning reporting genomic alterations identified with biomolecular tests (de Jager et al., 2025; van de Haar et al., 2024). These programs, including different formats such as on-site training, webinars, and masterclasses should highlight the current guidelines and international recommendations and good practices for LBx use in routine clinical practice. They should evaluate innovative developments and the use of LBx in clinical trials versus in daily practice (Fusco et al., 2025; Heitzer et al., 2022; Pantel et al., 2025; Pascual et al., 2022; Rolfo et al., 2021). These programs provide an opportunity to challenge the use of LBx as "reflex testing" and not only on request by a clinician. However, reflex LBx testing has limits. Some physicians and the institutions question the use of reflex testing and the cost, either at tumor progression or at baseline (Gosney et al., 2023; Heeke et al., 2020b; Hofman, 2021b; Hofman, 2023a). This strategy will need to obtain results in a short TAT, since the results of both LBx and tissue biopsies should be accessible at the same time. In addition, participating in EQA programs should help set up in-house LBx. These latter programs should reach an ultimate goal: to obtain specific accreditation for LBx use according to the ISO15189:2022 norm (mainly in Europe), or to the CAP (in USA) (Werner et al., 2025). Finally, the use of new tools of artificial intelligence (AI) and algorithms for complex genomic alterations and variants will become more and more helpful for rapid interpretation within each center for lung cancer patient care (Hamamoto et al., 2026) These tools will adapt to both tissue biopsies and development of LBx (AbdelHamid et al., 2026). Therefore, educational programs should also include how to deal not only with new technologies but also with new applications such as AI algorithms, which can be rapidly used in-house.

5. Conclusions

Despite extensive interest in thoracic oncology, LBx is yet to be widely adopted by the oncologist community, at least in Europe. To improve the clinical administration of target drugs LBx de-centralization is a challenge in thoracic oncology that needs urgent attention. Many studies highlight the potential of LBx to transform lung cancer care, since LBx sampling is a less non-invasive tool, faster and clinically relevant approach to detect earlier the disease and monitor treatment responses (Black et al., 2025; Alix-Panabieres et al., 2025; Ma et al., 2024). Widespread availability of LBx should lead to the best treatment decision-making for lung cancer. Advanced forms can already benefit, and early stages will do so in the future. This strategy requires strict mastery of in-house LBx approaches, which need to be associated with an "accreditation label" and a solid economic business model to help sustainability over time. LBx de-centralization must be under the supervision of a multidisciplinary team of experts trained to the best practices to implement LBx in clinical practice and to follow updated guide-

lines (Fusco et al., 2025; Heitzer et al., 2022; Pascual et al., 2022; Rolfo et al., 2021). Pre-analytical management of peripheral blood, analytical strategies for molecular tests, post-analytical interpretation of molecular records need to be optimized in successfully capturing clinically informative data from peripheral blood. Nowadays, it is possible to perform a LBx for advanced/metastatic NSCLC according to the international recommendations (Pascual et al., 2022; Rolfo et al., 2021). However, the perspective of disseminating the concept of LBx decentralization requires mastering the upcoming LBx indications. LBx de-centralization can be applied to any type of solid tumor, notably breast, colon and prostatic carcinomas and others. However, a LBx decentralization strategy in thoracic oncology should be rapidly considered due to the increasing number of requests and indications in this domain. In particular LBx should be indicated more and more in the peri-operative setting of lung cancer, including disease monitoring for de-escalation therapy and in screening programs to distinguish pulmonary lesions from aggressive tumors, especially for early lung cancer interception and detection in association with low-dose computed tomography thoracic scanner analyses (Al-Obeidi et al., 2023; Dong et al., 2024; Ma et al., 2024; Malapelle et al., 2022; Mazzone et al., 2024; Pepe et al., 2025; Rolfo et al., 2023).

6. Critical view section

An increasing number of blood tests will certainly be more and more difficult to perform in a centralized manner and will require programs into distributed analyzes in peripheral care centers, aiming to provide rapid equity to access to the best treatment. Different barriers need to be rapidly broken down for better control of the variability in assay sensitivity and specificity and the lack of standardization across different LBx platforms. In addition, it is pivotal to harmonize as much as possible the variability in the costs of LBx, which is a major bottleneck, limits patient access and contributes to non-acceptable disparity in care of lung cancer patients.

Ethical statement

Not applicable

Uncited references

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Declaration of Competing Interest

There are no competing financial interests concerning this work. **Author 1** reports consulting fees and honoraria for advisory board participation from ThermoFisher Scientist, Illumina, Qiagen, Amgen, Bristol-Myers Squibb, Biocartis, Novartis, Roche, GSK, MSD, Pierre Fabre, Bayer, Biodena, Sophia Genetics, Daichi Sankyo, Pfizer, Eli Lilly, and AstraZeneca. **Author 2** reports their spouse's employment by Roche; board of directors for International Society of Liquid Biopsy; consulting fees from Amgen, AstraZeneca, Boehringer Ingelheim, Diaceutics, Diatech, Eli Lilly, GlaxoSmithKline plc, Hedera, Janssen, Merck, Merck Sharp & Dohme, Novartis, Roche, and Thermo Fisher Scientific; grants/funding from AstraZeneca, Menarini Steamline, and Thermo Fisher Scientific; non-financial conflicts include: Scientific President of the International Society of Liquid Biopsy and membership of AIOM, ESMO, IASLC, and SIAPEC.

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