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Clinical use of liquid biopsy in metastatic breast cancer – an ESSO-EYSAC international survey

submitted by
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Graz, 15th July 2025

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ZUSAMMENFASSUNG

Einleitung

Obwohl Empfehlungen zur Verwendung der Liquid Biopsy (LB) zur therapeutischen Entscheidungsfindung bei metastasiertem Brustkrebs (mBC) in verschiedenen Leitlinien verankert sind, erfolgt die Umsetzung in der klinischen Praxis nur schleppend. Ziel dieser Studie war es, die Nutzung sowie zentrale Herausforderungen bei der Implementierung von LB in Europa zu erfassen.

Material und Methoden

Über die Redcap-Plattform wurde ein Online-Fragebogen mit insgesamt neunzehn Fragen erstellt, der drei Hauptbereiche abdeckte: demografische Angaben der Teilnehmenden; Bewusstsein, Wissen und Zugang zu LB-Verfahren; sowie zukünftige Perspektiven der LB. Die Umfrage wurde von März bis Mai 2023 über E-Mail, soziale Medien und die ESSO-EYSAC-Website innerhalb von Netzwerken chirurgischer Onkologen verbreitet.

Ergebnisse

Insgesamt nahmen 292 Brustkrebsexpert:innen aus 39 verschiedenen Ländern an der Umfrage teil. Nur 58 Teilnehmende (20 %) berichteten, dass Leitlinien zur LB-Testung in ihrer Praxis umgesetzt werden. Insgesamt gaben 119 Personen (40,7 %) an, LB derzeit zu verwenden. Die drei häufigsten Anwendungsgebiete waren „klinische Studien“ (n = 107, 36,8 %), „Bewertung therapeutischer Möglichkeiten“ (n = 109, 37,5 %) und „Prognoseabschätzung“ (n = 59, 20,3 %). Die Hauptgründe gegen die Anwendung von LB bei mBC-Patient:innen waren hohe Kosten und fehlende Erstattung (n = 133, 38,7 %), gefolgt von mangelndem Zugang (n = 126, 36,6 %) und fehlender Evidenz zur klinischen Relevanz (n = 62, 18,0 %).

Schlussfolgerung

Die Anwendung von LB in der klinischen Praxis nimmt langsam zu, steht jedoch weiterhin vor großen Herausforderungen wie hohen Kosten und fehlender Erstattung. Es bedarf weiterer Evidenz, dass eine individualisierte Therapie mittels LB tatsächlich zu besseren Behandlungsergebnissen bei Patient:innen mit metastasiertem Brustkrebs führt.

ABSTRACT

Introduction

Although recommendations for using Liquid Biopsy (LB) approaches to guide therapeutic decisions in metastatic breast cancer (mBC) have been embedded in various guidelines, uptake in clinical practice is slow. Here, we aimed to assess the utilization and key issues for implementation of LB across Europe.

Materials and Methods

Using the Redcap platform, we developed an online questionnaire including nineteen questions investigating three principal areas: respondent demographics; awareness, knowledge, and access to LB approaches; as well as future perspectives of LB. The survey was distributed to networks of surgical oncologists, via email, social media, and the ESSO-EYSAC website from March 2023 to May 2023.

Results

A total of 292 breast cancer experts from 39 different countries completed the survey. Only 58 participants (20%) reported implementation of guidelines regarding LB testing. Overall, 119 participants (40.7%) indicated current use of liquid biopsy. The top three indications for LB utilization were “clinical studies” (n = 107, 36.8%), the “evaluation of therapeutic possibilities” (n = 109, 37.5%) and “prognostication” (n = 59, 20.3%). The major reasons for not using LB testing in the treatment of mBC patients were high costs and lack of reimbursement (n = 133, 38.7%) followed by lack of access (n = 126, 36.6%) and lack of evidence of the clinical utility (n = 62, 18.0%).

Conclusion

LB testing is slowly becoming more popular in clinical practice, but still faces major difficulties such as high costs, and lack of reimbursement. More evidence is needed to show that individualization of treatment by utilization of LB leads to better outcome in mBC patients.

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Introduction

Personalized oncology has undergone a significant transformation in recent years. With the emergence of innovative molecular diagnostic techniques, particularly liquid biopsy (LB), new opportunities have arisen to non-invasively characterize and monitor tumor diseases such as metastatic breast cancer (mBC). LB enables the analysis of circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and other biomarkers that are highly relevant for therapeutic decisions, prognosis, and disease monitoring. Despite these promising prospects, the implementation of LB in clinical routine remains limited.

Knowledge and Research Gap

Although international professional societies such as ESMO, ASCO, and NCCN emphasize the importance of LB in their guidelines, and its clinical utility has been demonstrated in studies like SOLAR-1 and EMERALD, there is still a noticeable gap between scientific evidence and practical application. Reasons include insufficient cost-effectiveness data, lack of reimbursement by healthcare systems, and infrastructural deficiencies, particularly in low- and middle-income countries. A comprehensive picture of the current usage and perceived barriers on an international scale is largely missing.

Rationale for the Research Question

Against this backdrop, the international survey presented in the publication was initiated. The aim was to assess the current use of LB in mBC management, identify barriers to its implementation, and develop strategies for better integration into clinical practice. This research question is of high relevance as it addresses the existing gap between research findings and practical adoption while also providing insights into international differences in access and utilization of LB.

Objectives and Scope

The objective of this master's thesis is to analyze the results of the survey and to critically discuss their significance for the future clinical implementation of LB. The focus is placed on reimbursement, acceptance, and technical infrastructure. The work concentrates on metastatic breast cancer as a model for LB application and deliberately

excludes other cancer types and detailed technological development of testing methods.

Own Contribution

The personal contribution includes the conceptual development of the research question, the critical evaluation of survey results within the context of current research, and the derivation of practical recommendations for broader LB implementation. Additionally, the methodology of data collection and analysis is presented transparently and compared with existing studies.

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RESEARCH ARTICLE

Clinical Use of Liquid Biopsy in Metastatic Breast Cancer—An ESSO-EYSAC International Survey

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ABSTRACT

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Results: A total of 292 breast cancer experts from 39 different countries completed the survey. Only 58 participants (20%) reported implementation of guidelines regarding LB testing. Overall, 119 participants (40.7%) indicated current use of liquid biopsy. The top three indications for LB utilization were "clinical studies" ($n = 107$, 36.8%), the "evaluation of therapeutic possibilities" ($n = 109$, 37.5%) and "prognostication" ($n = 59$, 20.3%). The major reasons for not using LB testing in the treatment of mBC patients were high costs and lack of reimbursement ($n = 133$, 38.7%) followed by lack of access ($n = 126$, 36.6%) and lack of evidence of the clinical utility ($n = 62$, 18.0%).

Conclusion: LB testing is slowly becoming more popular in clinical practice, but still faces major difficulties such as high costs, and lack of reimbursement. More evidence is needed to show that individualization of treatment by utilization of LB leads to better outcome in mBC patients.

1 | Introduction

Liquid biopsy (LB) refers to analytical procedures to detect cancer-derived biomarkers from blood and other body fluids such as urine, saliva, ascites, pleural fluid or even vaginal secretions. LB analytes include cell-free circulating DNA (cfDNA), which in cancer patients also contains tumor-derived DNA (ctDNA), circulating tumor cells (CTCs) as well as extracellular vesicles, thrombocytes, (so-called "tumor-educated platelets" [TEPs]), RNAs, proteins and metabolites [1].

While conventional tumor tissue biopsy still represents the gold standard diagnostic procedure to identify actionable targets, tumor heterogeneity and tumor cell evolution can pose a

Ellen Heitzer and Andreas Brandl have contributed equally to the study.

problem, especially in the metastatic setting due to anatomical accessibility and potential complications associated with biopsies. In the last decades, liquid biopsy (LB) approaches were developed as promising alternatives to tissue testing [2] and applicability has been demonstrated for various clinical scenarios including screening, diagnostics and monitoring, therapy decision-making, as well as prognosis assessment and detection of residual or recurrent disease. Furthermore, LB is also used for determining resistance to specific anticancer therapies [2]. In metastatic breast cancer (mBC), the benefit of LB testing has been demonstrated in numerous studies [3, 4]

Recently, ctDNA detection of actionable mutations in mBC has gained endorsement from leading oncology societies including ESMO [5], ASCO [6], AGO [7], and NCCN [8]. Notably, markers such as PIK3CA and ESR1 have demonstrated clinical utility for targeted therapies in trials like SOLAR-1 [9], EMERALD [4], and plasma MATCH [10]. With the approval of PI3K-inhibitor Alpelisib and ESR1-inhibitor Elacestrant, routine monitoring for *PIK3CA* and *ESR1* mutations is advised upon disease recurrence or progression in ER-positive, HER2-negative mBC patients undergoing endocrine therapy [4]. As the approval of Elacestrant is tied to the presence of an *ESR1* mutation detectable in the plasma, liquid biopsy must be integrated into routine diagnostics and is recommended for guiding therapeutic decisions in HR(+)/HER2(-) mBC.

Although LB can provide valuable prognostic and therapeutic information for mBC, uptake in clinical practice is still slow. Many countries lack LB implementation mostly likely due to lack of clinical evidence, reimbursement, and accessibility. Research indicates significant disparities in the adoption of LB between high-resource European countries and low- and middle-income countries (LMICs). Limited resources and infrastructure in LMICs present challenges for the widespread implementation of LB in clinical practice [11].

This study aims to address the slow adoption of LB testing in clinical practice by conducting a worldwide snapshot survey among breast cancer specialists. Specifically, the survey seeks to evaluate current LB utilization rates, identify barriers to implementation, and provide insights into strategies for integrating LB into routine clinical practice.

2 | Materials and Methods

2.1 | Questionnaire Development

A comprehensive literature review identified key factors affecting the implementation of Liquid Biopsy (LB) in breast cancer patients. Based on this, a draft questionnaire was created with input from an LB specialist (E.H.). An international group of healthcare professionals from the ESSO Young Surgeons and Alumni Club (EYSAC) Research Academy reviewed the questionnaire for validity and reliability. After feedback from a global group of surgical oncologists, a senior expert (W.C.) provided final validation. The finalized 19-question survey, focused on participant demographics, LB awareness, access, and future perspectives, was built and managed using REDCap, [12] a secure web-based application.

2.1.1 | Question Selection and Relevance

The survey questions were designed to gather information across three main areas. First, demographic data (age, region, and institution type) was collected to allow for the stratification of responses by geographical location and institution, which are important for understanding access to healthcare technologies like LB. Second, questions about LB awareness and barriers to implementation (e.g., lack of reimbursement, high costs) were designed to uncover the practical challenges in adopting LB in the clinical practice. Lastly, questions were included to assess the clinical utility of LB, such as its role in therapeutic decision-making and treatment monitoring in mBC.

2.1.2 | Sample Size Calculation

The sample size was calculated based on the healthcare professional population across the EU, Great Britain, Switzerland, and EU candidate countries, with an estimated 2.67 million doctors. Using an 85% confidence level and a 5% margin of error, the target sample size was 208 participants. A 15% buffer for incomplete responses brought this to 239. With 292 respondents, the survey exceeded this threshold, ensuring sufficient data for robust conclusions.

The formula used for sample size calculation was as follows:

The 85% confidence level ($z = 1.44$) was chosen to balance precision and feasibility given the very large total population ($N = 2.67$ million healthcare professionals). The estimated population proportion ($p = 0.5$) represents the most conservative estimate to maximize the required sample size, ensuring robustness. A 5% margin of error ($e = 0.05$) reflects the acceptable variability in this large-scale survey. This methodology ensures statistical validity while considering the real-world limitations of response collection.

$$n = \frac{\frac{z^2 \cdot p \cdot (1-p)}{e^2} \cdot N}{N + \left(\frac{z^2 \cdot p \cdot (1-p)}{e^2}\right)}$$

Where:

- $z = 1.44$ (for an 85% confidence level)
- $p = 0.5$ (estimated population proportion)
- $e = 0.05$ (margin of error)
- $N = 2\,670\,000$ (total number of doctors)

2.1.3 | Survey Saturation

The total number of respondents (292) exceeds the calculated sample size, indicating that the survey has achieved sufficient saturation. While the sample is heterogeneous, this diversity was intentional. The survey aimed to capture a broad range of perspectives from healthcare professionals across different regions and institutions, which we believe enhances the

robustness of the findings. Additionally, we conducted subgroup analyses to account for variations in region, institution type, and income level, allowing us to identify specific trends and disparities in LB use.

2.1.4 | Survey Distribution and Data Collection

The questionnaire was piloted with a small EYSAC Research Academy sample for clarity, then distributed via the ESSO homepage, committees (EYSAC, ESSO National Representatives), partner societies (BIG, ESMO) email, and social media. It was also featured in ESSO's first-quarter newsletter (14 855 recipients) on 6th April, and promoted through a video on Twitter, Instagram, and LinkedIn, garnering 5249 impressions.

Data collection occurred over 8 weeks (March–May 2023) via REDCap. Descriptive statistics and Chi-squared tests ($p < 0.05$) were used for analysis. Respondents who missed key Likert scale questions were excluded. Subgroup analyses by region, institution type, and income level were performed. Ethical guidelines were followed, ensuring informed consent and confidentiality.

2.2 | Rehearsal Process and Feedback

A pilot poll was conducted among a small sample of surgical oncologists from the EYSAC Research Academy to test the clarity, relevance, and feasibility of the survey. Feedback from this pilot group led to several key adjustments. For instance, some of the technical terms related to LB and reimbursement were revised for clarity to ensure that the questions were comprehensible to participants from diverse linguistic and professional backgrounds. Additionally, we added questions specifically addressing reimbursement issues and infrastructure challenges, as these concerns were frequently raised during the pilot stage.

3 | Results

3.1 | Demographics

The questionnaire was disseminated to the ESSO-EYSAC mailing list of 14 855 recipients, to national partner societies, 100 individual ESSO members, as well as via instant messaging platforms. The primary social media accounts of ESSO promoting the survey counted a total of 4801 impressions during the survey period. A promotion video was shared on LinkedIn and YouTube, which generated 1260 views. Overall, 369 individuals participated in the survey including 292 breast cancer experts from 39 different countries (117 respondents from EU member countries, 175 respondents from non-EU countries including EU candidates) (Figure 1). A total of 77 participants needed to be excluded due to incomplete data set.

Most participants [77.7% (227/292)] reported their age between 30 and 50 years, with 46.9% (137/292) of respondents reporting their age between 30 and 40 years and 30.8% (90/292) of

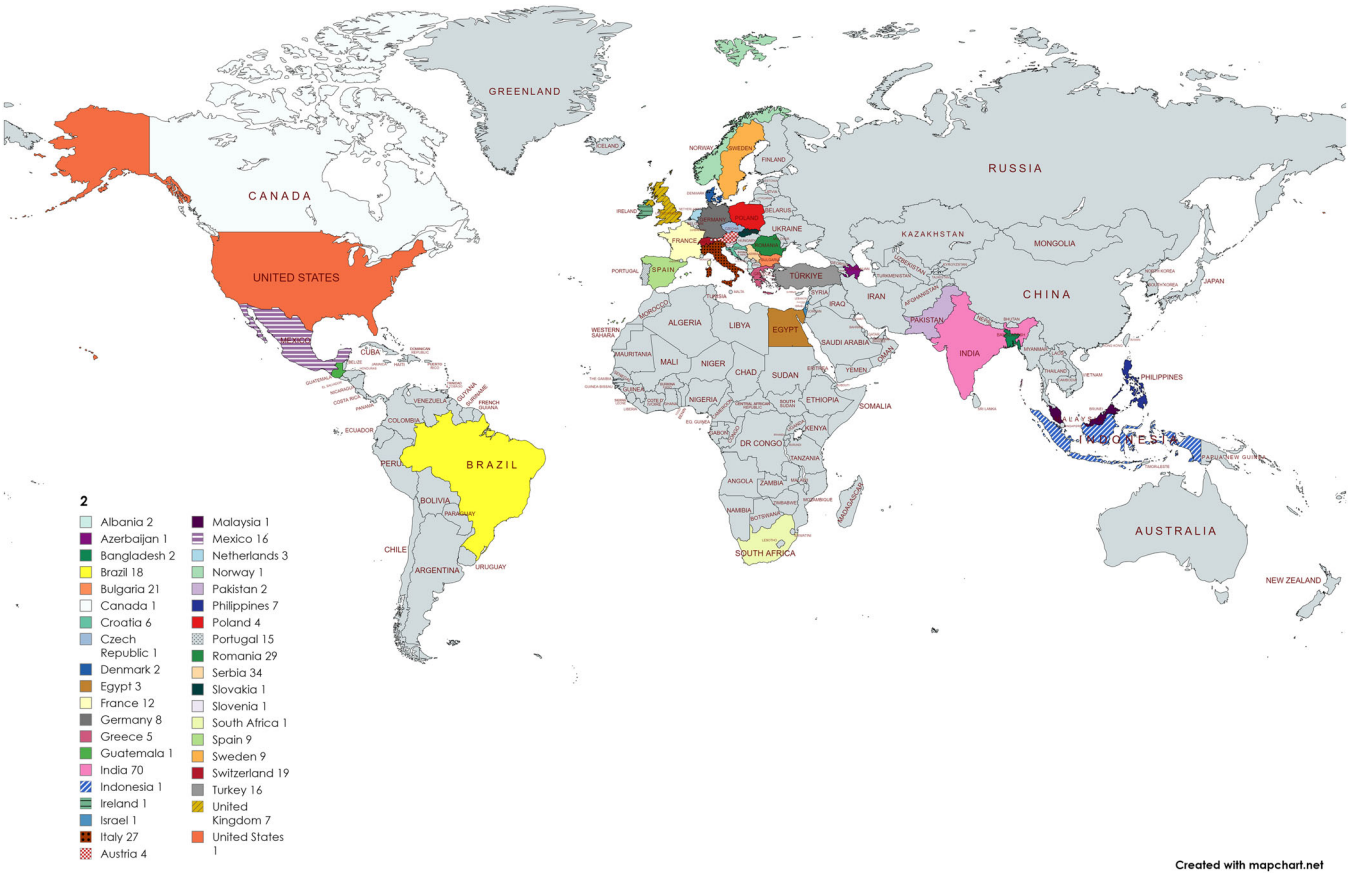

FIGURE 1 | Demographics.

respondents reporting their age between 40 and 50 years. "Surgeon" 42.1% (123/292) and "Oncologist," 38% (111/292) were the most reported profession while the remainder included "Pathology," "Gynecology," "Radiology," "Radio-oncology," "Cancer Nurse" and "other." "Consultant" was the most reported position with 51.2% (149/292). The most common setting of employment for respondents was a University Hospital (62.2%, 181/292). Most respondents (66.3%, 193/292) reported that they work in a hospital with a dedicated breast cancer unit. The average number of patients treated per institution per year ranged from 100 to 500.

3.2 | Utilization of LB

The results of our survey are visually represented in the Sankey diagram (Figure 2). This diagram shows that only 28.1% of respondents reported using LB, while 66.8% indicated they do not use it. Notably, the majority of respondents were from university hospitals, which generally have better access to infrastructure. In fact, 62% of participants worked in such institutions, and 43.6% of EU respondents cited high costs as the main barrier to implementing LB. For EU candidate countries, this figure rises to 55.8%. The diagram further highlights that most respondents, particularly those between the ages of 30 and 50, are the primary users of this technology.

Overall, 119 (40.7%) participants reported having circulating tumor cell (CTC)-based and/or circulating tumor DNA (ctDNA)-based methodologies available in their centers. Among these, 106 reported to be "familiar with LB testing." The most common indications for the use of liquid biopsy (LB) in metastatic breast cancer (mBC) patients were "clinical studies" (41/106, 38.5%) and the "evaluation of therapeutic possibilities" (41/106, 38.5%), as shown in Figure 3. Prognostication was also a significant reason for LB use, reported by 20% (21/106) of participants. Other indications, though less common, included uses such as "lung cancer," "colorectal cancer," "micro metastasis," and the "follow-up of patients after treatment completion."

The primary reasons for not utilizing LB testing in mBC patients were high costs and lack of reimbursement, reported by 42.5% (45/106) of respondents, followed by a lack of access, cited by 28% (30/106), and lack of evidence for clinical utility, mentioned by 21.7% (23/106) (Figure 4). Other reasons included concerns about accreditation of labs and reliability of the tests. Importantly, 93.4% (99/106) of respondents stated that they would use LB if it were more accessible, underscoring the demand for better access and affordability in LB testing.

Of note, although the clinical relevance of measuring CTC counts before and 3 weeks after starting chemotherapy in mBC patients was rated with 3.5 (1-not relevant, 5-most relevant) (Figure 5), CTC enumeration was reported by only 21/292 of participants (7.2%) (11/117 EU member countries vs. 10/132 non-EU countries Fisher's exact test, not significant).

4 | Discussion

The body of evidence supporting circulating tumor DNA (ctDNA) testing for identifying actionable targets and guiding treatment in cancer, particularly metastatic breast cancer (mBC), is increasingly compelling [11, 13]. However, despite promising results, its clinical adoption remains uneven across

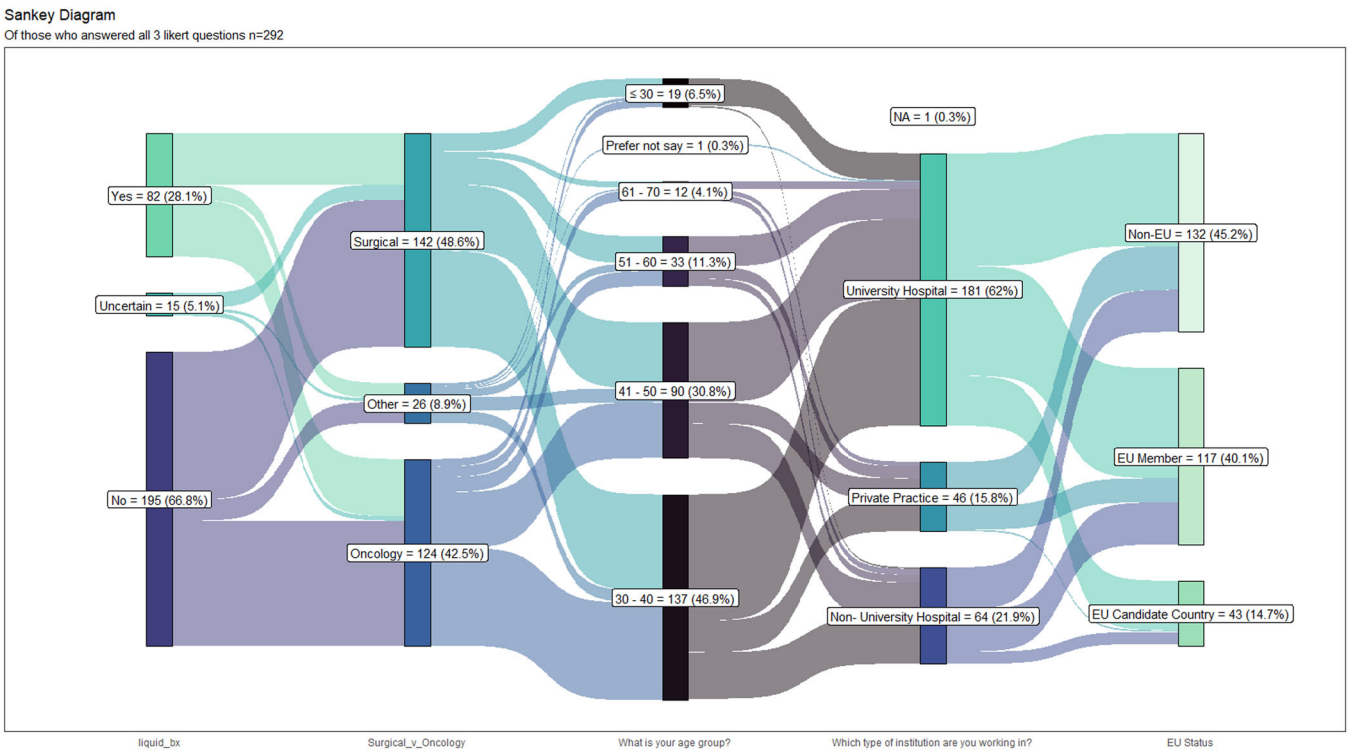

FIGURE 2 | Sankey diagram.

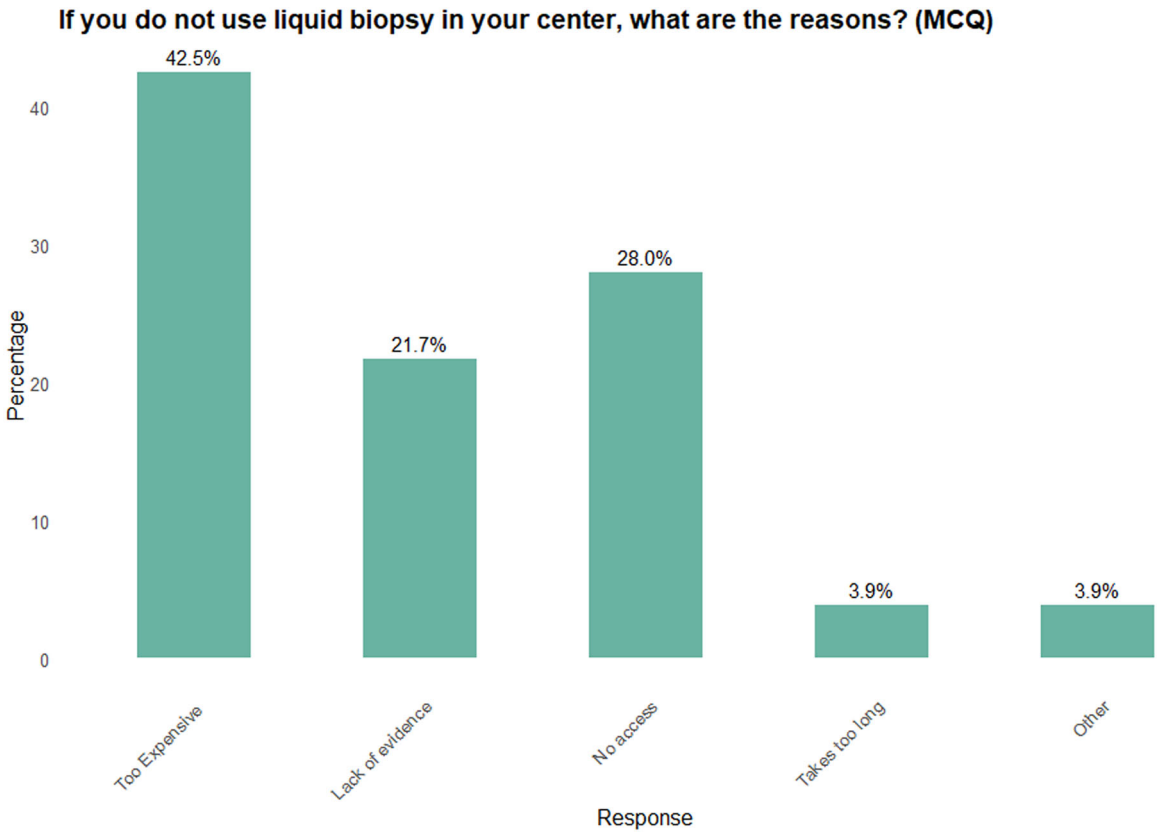

FIGURE 3 | Reasons not to use [MCQ].

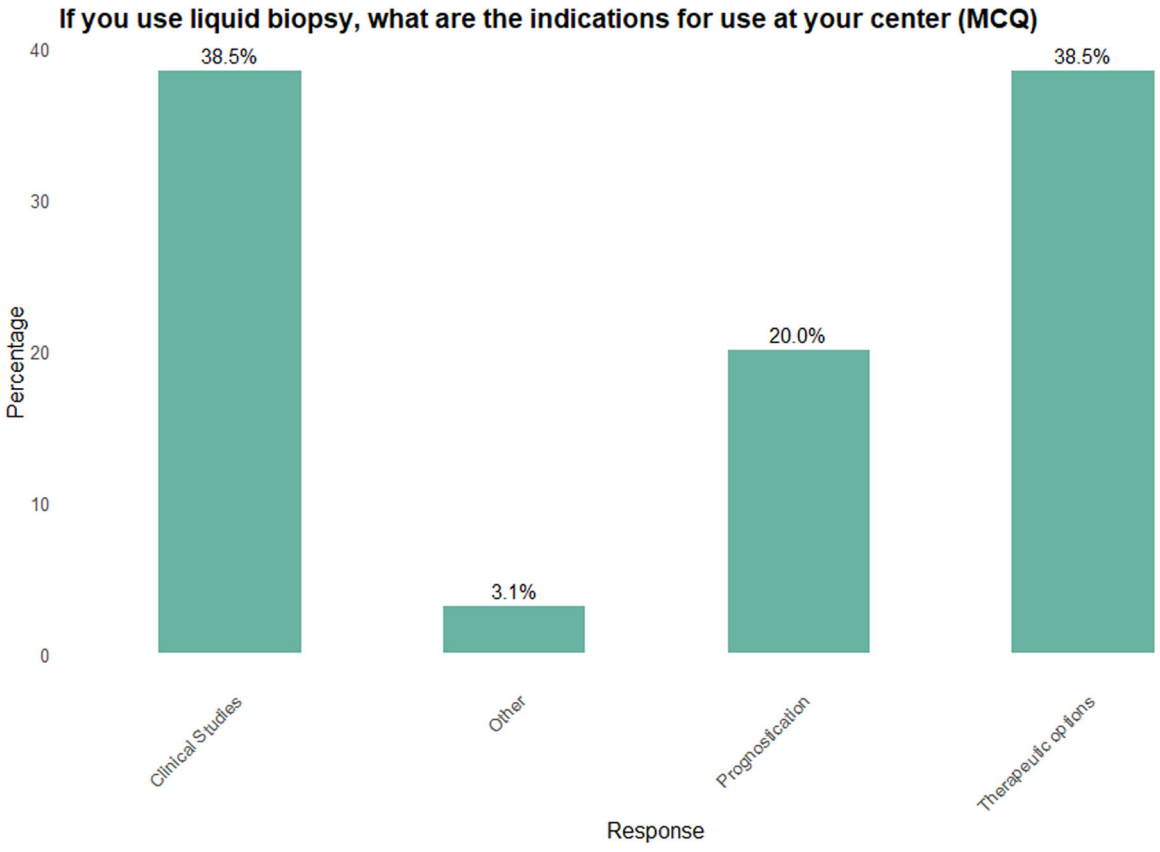

FIGURE 4 | Indications for use [MCQ].

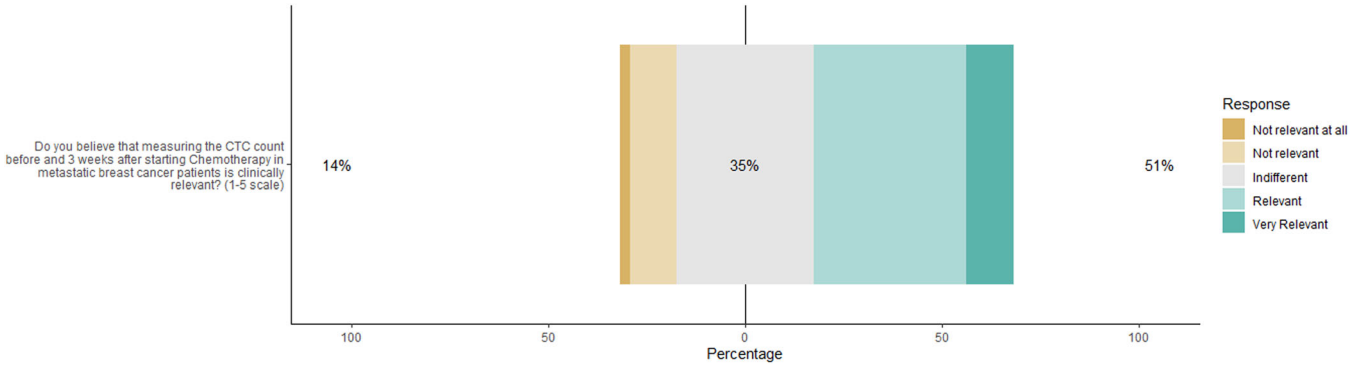

FIGURE 5 | Relevance.

different cancer types and healthcare settings [14]. Liquid biopsy (LB), which allows for noninvasive monitoring of tumor response [15] and evolution [16], offers a powerful tool for precision oncology [17–19]. Yet, challenges such as accessibility, reimbursement, and high costs continue to impede its broader clinical application.

4.1 | Role of LB in mBC Care

One of the striking findings in our study is the apparent lack of a clear correlation between the economic status of a country and the use of LB technologies. While it might be expected that countries with greater economic resources would have higher LB usage rates, our findings suggest otherwise. This discrepancy may be explained by differences in national healthcare policies, variations in the availability of local reimbursement systems, and potential mismatches between existing medical infrastructure and funding priorities. These nuances suggest that policy-level barriers, rather than sheer economic capacity, may be driving disparities in LB access.

Despite these barriers, ctDNA testing is rapidly gaining importance, especially in the context of metastatic breast cancer (mBC), where the identification of specific genetic mutations is pivotal for the development of personalized therapies. Recent therapeutic advances, driven by ctDNA testing, highlight its role in delivering targeted treatments for patients with mBC. For instance, elacestrant, which was approved following the EMERALD trial [20], specifically targets ESR1 mutations that can be identified through ctDNA testing. This illustrates how ctDNA-guided treatment can significantly improve outcomes by tailoring therapies to individual patient profiles.

Other selective estrogen receptor degraders (SERDs), such as camizestrant (from the SERENA-2 trial [21]) and giredestrant (evERA trial [22]), are tested in phase III studies. These therapies also target ESR1 mutations, which can be detected using ctDNA, further reinforcing the importance of LB in developing more effective, individualized treatment plans. Similarly, drugs like PI3K inhibitors (e.g., alpelisib, as demonstrated in the SOLAR-1 trial [23]) and AKT inhibitors (e.g., capivasertib, as seen in the CAPItello-291 trial [24]) underscore the potential of ctDNA testing to direct therapeutic strategies. These advancements highlight the increasing role of ctDNA in shaping the future of mBC care, offering patients targeted therapies that were previously unavailable without molecular profiling.

Despite the advances in sequencing technologies and decreasing costs, ctDNA testing remains financially burdensome, and reimbursement is inconsistent across different healthcare systems [25]. While some insurance companies cover the costs of testing, pharmaceutical companies often subsidize ctDNA tests within the framework of clinical trials or therapies targeting specific mutations. As ctDNA testing becomes more integrated into national and international healthcare guidelines, broader payer coverage is anticipated. This could be a critical step in addressing some of the financial barriers and facilitating wider adoption of ctDNA testing in clinical practice.

4.2 | LB Access: Hypothesis and Study Findings

Our study sought to explore whether resource-rich European countries would have better access to liquid biopsy (LB) technology due to their greater financial and infrastructural resources. The hypothesis was based on the assumption that countries with more advanced healthcare systems and stronger economies would be better positioned to adopt cutting-edge technologies like ctDNA testing. However, the survey results only partially supported this hypothesis. While infrastructure is available in these wealthier nations, financial barriers, particularly the high costs associated with ctDNA testing and inconsistent reimbursement policies, remain substantial obstacles.

The survey revealed that 62% of respondents were employed in university hospitals, which tend to have access to advanced diagnostic tools and more robust infrastructures. Despite this, only 28.1% of respondents reported using LB regularly in their clinical practice. This disparity points to the high costs and lack of reimbursement as critical factors limiting LB utilization, even in resource-rich settings. Notably, 43.6% of respondents explicitly cited the high cost of ctDNA testing as a significant barrier, reinforcing the conclusion that financial challenges, rather than infrastructural limitations, are the key hindrances to broader implementation of ctDNA testing.

The European Society of Medical Oncology (ESMO) study [26] echoes these findings, emphasizing that even in well-funded healthcare systems, financial and logistical challenges impede

the widespread adoption of ctDNA testing. While countries with greater resources might be expected to have better access, the reality is more nuanced. High sequencing costs and uneven reimbursement policies across European nations create significant disparities in the availability of LB technologies. Publications from the International Quality Network for Pathology (IQN Path) and the European Cancer Patient Coalition (ECPC) [27] similarly highlight these financial barriers, pointing to the inconsistent availability of biomarker testing, even within wealthier regions of Europe. This demonstrates that while infrastructure may be present, financial barriers remain the most pressing issue limiting LB access.

4.3 | Supporting Studies and Broader Context

Several studies have demonstrated that while ctDNA testing shows great potential in precision medicine, it remains underutilized due to financial and logistical barriers. Foundation Medicine has noted that liquid biopsies, despite their increasing use for genomic testing, face challenges due to high costs and inconsistent reimbursement [28]. Similarly, research published in ESMO's Magazine [29] highlights the complexity of integrating liquid biopsy into routine care, particularly due to the difficulty of interpreting ctDNA results in clinical settings and the financial burden associated with comprehensive genomic profiling.

These findings underline the importance of addressing both cost-related issues and the need for clearer guidelines in interpreting ctDNA results to facilitate broader adoption in clinical practice. The findings from these studies align with our hypothesis and survey data, reinforcing the idea that financial barriers, rather than infrastructural limitations, are the primary factors impeding the broader use of ctDNA testing. These barriers are particularly evident in the context of metastatic breast cancer, where the identification of actionable mutations through ctDNA testing is critical for guiding treatment. Without wider access to ctDNA testing, many patients may miss out on potentially life-saving targeted therapies.

Moreover, an increasing number of studies underline the growing clinical relevance of liquid biopsy in oncology. For instance, Huang et al. highlighted the substantial complexity involved in integrating LB into clinical practice, citing technical and logistical challenges as key barriers [30]. Similarly, Hewitt et al. identified four central themes impeding LB adoption in cancer care: limited resources, disease-specific factors, biomarker reliability, and regulatory hurdles [31]. Zhou et al. demonstrated that ctDNA analysis can predict treatment response in metastatic breast cancer (mBC) even before changes become visible through imaging techniques [32]. At the policy level, Febbo et al. offered comprehensive recommendations aimed at overcoming structural barriers and promoting equitable access to LB technologies [33].

4.4 | Addressing Cost and Access Issues

Addressing the financial and access challenges of ctDNA testing will require coordinated efforts across the healthcare ecosystem. Demonstrating its cost-effectiveness is essential to convincing payers to broaden reimbursement. Studies can highlight that, despite upfront costs, ctDNA testing can reduce long-term treatment expenses by enabling timely, targeted therapies. This approach not only improves patient outcomes but also reduces the economic burden on healthcare systems.

Policymakers, along with industry stakeholders, including pharmaceutical companies and diagnostic labs, should collaborate to create standardized reimbursement processes. Streamlining these pathways will help reduce access disparities and ensure more patients benefit from advanced ctDNA testing.

5 | Limitations

While our survey provides important insights into the barriers to LB access, it has limitations. Most respondents were surgeons and oncologists from university hospitals, potentially skewing results towards an overestimation of LB use in broader practice. Additionally, healthcare professionals without internet access or those unaffiliated with professional societies were likely underrepresented. Future studies should aim for a more diverse sample to reflect a wider range of healthcare settings.

6 | Future Perspectives

Collaboration between healthcare providers, payers, policymakers, and industry stakeholders is crucial to overcoming access and reimbursement barriers for LB. Standardizing coding, reimbursement processes, and conducting cost-effectiveness studies will promote wider adoption of ctDNA testing. Groups like the European Cancer Organisation (ECO) and Young Cancer Professionals Group (YCP40) are working to reduce these disparities, particularly through initiatives like Europe's Beating Cancer Plan [34].

The European Society of Surgical Oncology (ESSO) also plays a key role in promoting new technologies by educating healthcare professionals about the importance of ctDNA testing. Continued collaboration across these sectors will help build the clinical evidence, regulatory pathways, and financial frameworks needed to support the broader implementation of liquid biopsy in oncology.

EYSAC Research Academy

The members of the EYSAC Research Academy include the following: H. G. Smith (Abdominalcenter K, Copenhagen University Hospital - Bispebjerg and Frederiksberg, Copenhagen, Denmark), M. Vasileva-Slaveva (Dr Shterev Hospital, Sofia, Bulgaria), A. Ben-Yaacov (Chaim Sheba Medical Center, Ramat Gan, Isreal), W. Ceelen (Department of GI Surgery, Ghent University Hospital and Cancer Research InstituteGhent (CRIG)), J. H. Herrera-Kok (General and Digestive Surgery Departement, University Hospital of Léon, Spain), C. J. Holmberg (Department of Surgery, Clinical Sciences, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden), L. Lorenzon (Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy), H. Mohan (Peter MacCallum Cancer Centre, Melbourne, Australia), G.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Appendix: Liquid Biopsy Survey

Introduction

Thank you for participating in this survey. It takes 6 minutes to complete. Please share with other members of your MDT. This is a project led by the European Society of Surgical Oncology (ESSO) Young Surgeon's Alumni Club (EYSAC)

Background:

Over the last decade liquid biopsy has become a fast and feasible prognostic tool for patients with metastatic breast cancer. Recommendations of using this technique for certain indications in metastatic breast cancer have been embedded in guidelines from AGO, ASCO and NCCN. However, there seems to be a lack of awareness regarding the possibilities of liquid biopsy today and in the future, which prevents this technique from being implemented in everyday clinical practice.

This study aims to investigate variations in the utilization of liquid biopsy for patients with metastatic breast cancer and the feasibility to implement this technique in clinical decision making across Europe.

Questions

a. Respondent's specialty and grade

1.) Which is your specialty?

- Surgery
- Pathology
- Oncology
- Gynaecology
- Radiology
- Radiooncology
- Cancer Nurse
- Other (please specify)

2.) What is your age group?

- ≤ 30
- 30 - 40
- 41 - 50
- 51 - 60
- 61 - 70
- Prefer not to say

3.) Which is your position?

- Head of Department
- Consultant
- Fellow Trainee
- Other (please specify)
-

4.) In which country is your institution based?

5.) Which type of institution are you working in?

- University Hospital
- Non- University Hospital
- Private Practice

6.) How many breast cancer cases do you treat per year in your institution?

- 0-100
- 101-500
- 501-1000
- >1000

7.) Does your institution have a dedicated breast cancer unit?

- Yes
- No

8.) Does your institution hold regular MDT discussions for patients with breast cancer/ metastatic breast cancer?

- Yes
- No

b. Knowledge and awareness of LB in general

9.) Is your institution implementing any national or cancer society guideline with regards to the use of liquid biopsies? (If yes, please specify)

- Yes
- No

Which guideline?

- NCCN
- ASCO
- AGO
- Other

10.) How familiar are you with liquid biopsy testing? (1(not familiar) -5(very familiar) scale)

- not familiar at_____very familiar

(place a mark on the scale above)

11.) Are you aware of the possible indications for liquid biopsy testing in metastatic breast cancer patients? (1-5 scale)

- not familiar at very familiar

  (place a mark on the scale above)

12.) Do you believe that measuring the CTC count before and 3 weeks after starting Chemotherapy in metastatic breast cancer patients is clinically relevant? (1(very relevant)-5 (irrelevant) scale)

c. Role of liquid biopsy for determining systemic therapy

13.) Do you perform CTC testing in your center? (CTC=circulating tumor cell)

- Yes
- No
- Uncertain

14.) Do you perform ctDNA testing in your center? (ctDNA= circulating tumor DNA)

- Yes
- No
- Uncertain

15.) If both methods are available in your center, which one is used preferentially?

- CTC
- ctDNA
- Neither

16.) If you do not have access to liquid biopsy testing, would you use it if it was accessible to you?

- Yes
- No

17.) If you do not use liquid biopsy in your center, which are the reasons? (If you have multiple reasons, please rank from most important to least important)

- Too expensive/ not reimbursed.
- Lack of evidence of the clinical utility of liquid biopsy testing in metastatic breast cancer
- No access
- Takes too long
- Other reasons (please specify)
- Indicate other reasons for not using liquid biopsy

18.) If liquid biopsy is used in your Institution, which are the Indications? (multiple answers possible)

- Clinical Studies
- To evaluate prognosis in patients with metastatic breast cancer
- To evaluate therapeutic possibilities in patients with metastatic breast cancer
- Other (please specify)

19.) In patients with metastatic breast cancer, which biomarkers are used by your MDT (Multidisciplinary Tumor Board) to determine the type and duration of systemic treatment? (choice=Histological subtype):

- Her2 (tissue)
- Histologic Subtype
- PIK3Ca (tissue)
- PIK3Ca (plasma)
- ESR1 (tissue)
- ESR1 (plasma)
- BRCA1/2 status
- PDL1- status
- CTC monitoring