Taiwan Association for the Study of Lung Cancer

The Future of Precision Cancer Therapy: NGS Liquid Biopsy Development Trends and Prospects

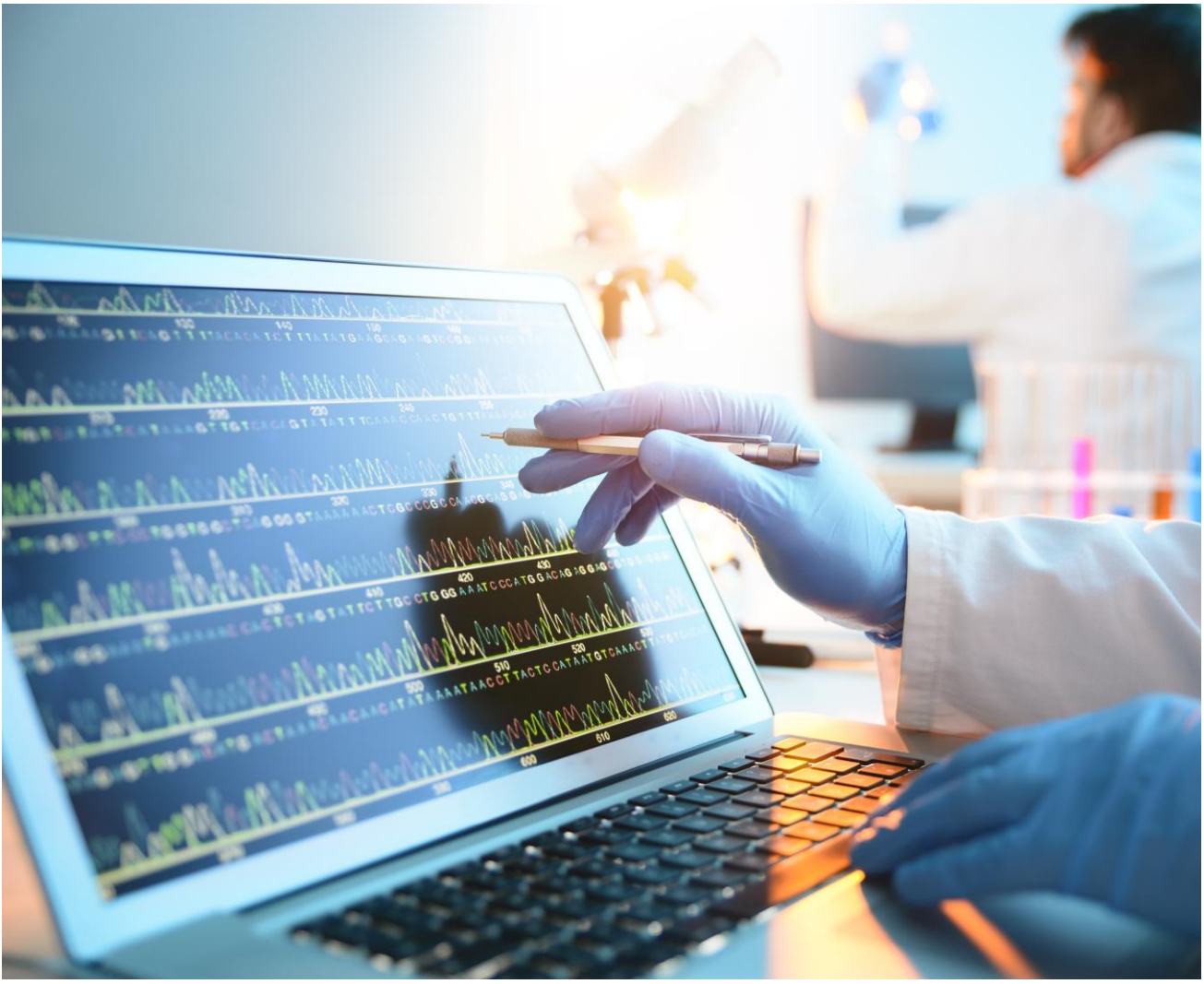

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Table of contents

Summary

In April 2025, the Taiwan Association for the Study of Lung Cancer (TASLC) hosted an expert consensus meeting titled "NGS Liquid Biopsy Development Trends and Prospects." This event aimed to gather expert opinions on the adoption of NGS liquid biopsy in Taiwan and to discuss related regulatory and reimbursement policies. Attendees at this meeting included leading professionals from the medical field and public health policy sectors. Throughout this report, the term "expert opinions" refers specifically to the conclusions reached during the expert consensus meeting. Besides contents discussed during the meeting, this report is supplemented by additional figures and reference studies compiled by PwC Taiwan. For a detailed list of the experts and organizations involved in the expert consensus meeting, please refer to the acknowledgments section of this report.

Accurate genetic testing and targeted therapies are crucial for reducing cancer mortality rates. Patients benefit from health insurance coverage that reimburses tissue-based NGS testing and targeted drugs like osimertinib, which require accompanying tissue-based genetic test reports. As technology advances, liquid biopsy technology, using blood tests to analyze circulating tumor DNA for genetic mutations and other tumor information, has become well developed and adopted in clinical practice in Taiwan. In Taiwan, the Ministry of Health and Welfare has approved a few selected NGS liquid biopsy tests as Laboratory Developed Tests (LDTs) across multiple hospitals to ensure the quality of NGS liquid biopsy.

Liquid biopsy offers an essential alternative for patients unable to undergo tissue biopsies due to difficult tumor positioning or high biopsy risks. It analyzes cell-free DNA in blood samples, detecting genomic and epigenomic alterations to guide personalized treatment and monitor tumor evolution. The accuracy of genetic mutation detection through liquid biopsy is consistent with tissue samples, and its therapeutic efficacy is comparable. However, the current National Health Insurance (NHI) reimbursement policies for drugs only accept genetic testing reports derived from tissue samples, and NGS testing does not include liquid biopsy, leaving patients with unmet medical needs.

Given both international and Taiwan research demonstrating the clinical and economic benefits of liquid biopsy and expanding coverage, many large medical institutions see the

complementary use of liquid biopsy and tissue samples as a trend. Therefore, Taiwan experts recommend that NHI reimbursement for cancer drugs and genetic testing be expanded to include coverage for liquid biopsy, particularly for late-stage cancer patients and those unsuitable for tissue biopsies.

In 2024, the Executive Yuan approved a multi-billion-dollar new cancer drug fund, with NT$5 billion injected into the National Health Insurance Fund from the public budget in 2025, gradually scaling up to NT$10 billion in the future. It is hoped that increased national budget investment in cancer treatment, along with patient cost-sharing mechanisms, will enhance the financial resources for reimbursing liquid biopsy for cancer drug companion diagnostics. These efforts aim to provide affordable genetic testing and more precise targeted cancer treatment options, contributing significantly to the realization of President Lai’s Healthy Taiwan initiative, which targets reducing cancer mortality in Taiwan by 2030.

Vision for Precision Medicine in Cancer

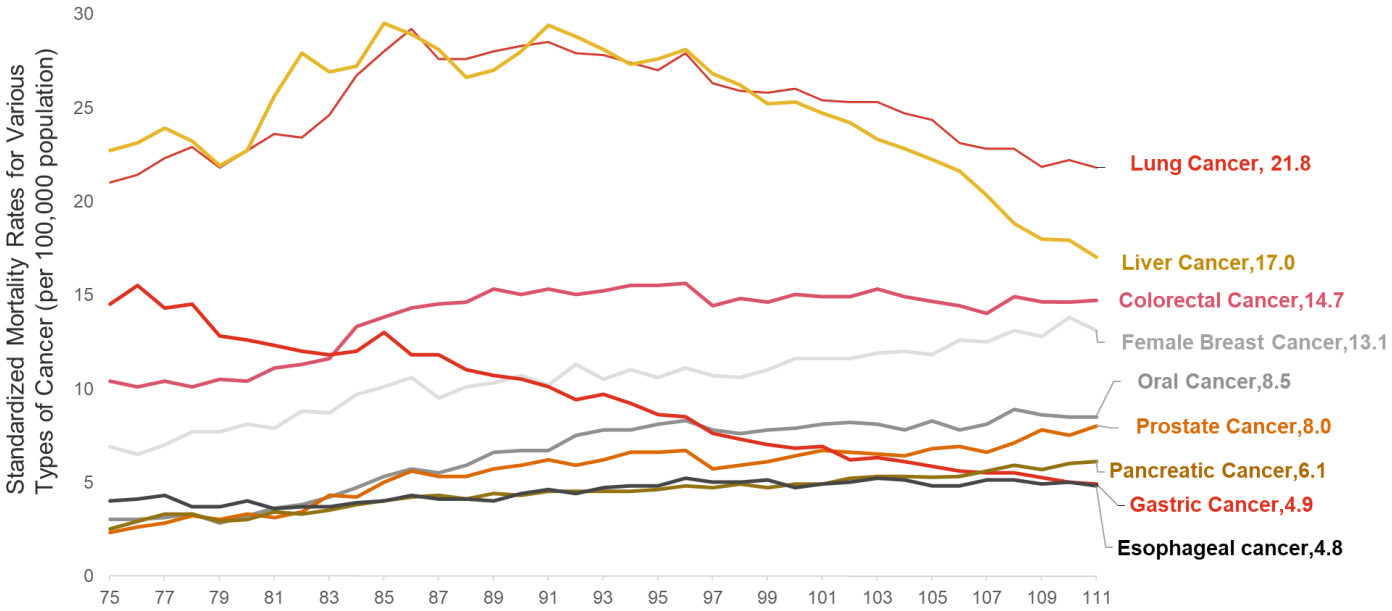
Healthy Taiwan: Reducing Cancer Mortality by One-third by 2030

President Lai has set a clear national goal of reducing cancer mortality by one-third by 2030. To fulfil the vision of a “Healthy Taiwan,” the government is placing precision medicine at the centre of its cancer-control strategy. Key initiatives include expanding early-detection programmes, emphasising genetic testing and precision therapies, and creating a multi-billion fund for innovative oncology drugs. These measures aim both to improve patient survival and to lessen the social and economic burden of cancer.

Currently, national health resources are primarily invested in new cancer drugs. Meanwhile, the National Health Insurance Administration (NHIA) has been actively inviting experts in related fields to devise treatment strategies for major cancers to align the payment scope with NCCN international guidelines and fill gaps in late-stage treatment.[1] Even though with series of measures, mortality rates for major cancer types are still high (Figure 1). The government is addressing these issues with systemic policies and resource investments to lay the groundwork for reducing cancer mortality by 2030.

Even the best drugs cannot achieve this goal without accurate diagnosis. NHI coverage should therefore prioritize interventions that improve population health and patient survival. Incorporating comprehensive diagnostic testing and precision therapeutics into innovative reimbursement pathways is essential to building a robust precision medicine ecosystem. Doing so will further raise cancer survival rates, reduce the disease’s socio-economic impact, and ensure that all citizens receive timely care.

[1] Ministry of Health and Welfare, National Health Insurance Administration (2024) Latest News - Press Release: "Aligning with International Treatment Guidelines, Health Insurance to Expand Coverage from October for Third-Generation Targeted Drug Osimertinib-Based Medications"



Source：Statistics on Causes of Death by the Department of Statistics, Ministry of Health and Welfare, and Cancer Registry Data by the Health Promotion Administration (excluding carcinoma in situ).

Figure 1: Trends in Standardized Mortality Rates for the Top Ten Cancers in Taiwan

Current Status of Targeted Drug Coverage in Taiwan

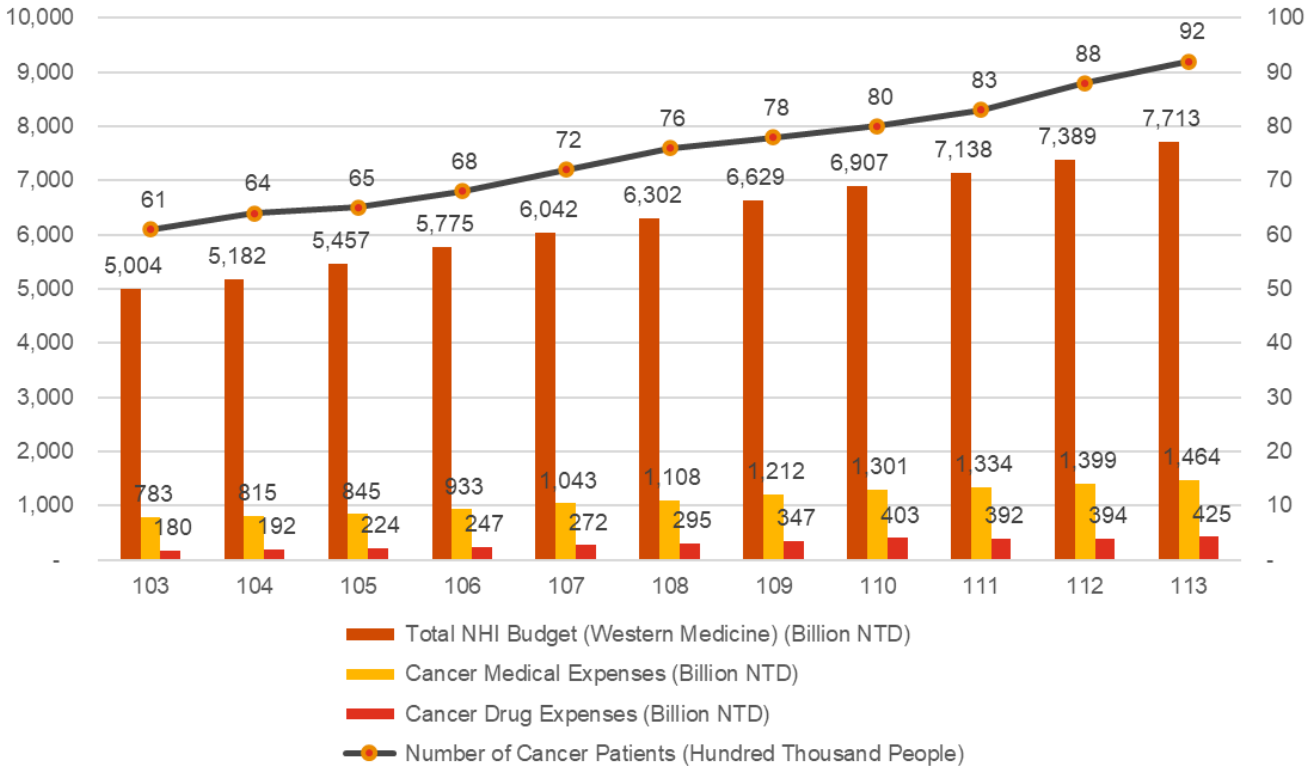
Based on Health Technology Assessment (HTA), the NHIA has been striving in recent years to include therapeutically beneficial drugs in its coverage and align with international treatment guidelines. This aims to perfect drug treatment at every stage for cancer patients, enhancing their quality of life and hope for survival. As a result, there has been rapid growth in cancer-related medical expenses and cancer drug fees in recent years. By 2024, the number of cancer patients is projected to reach 920,000, with cancer drug expenses having an average annual growth rate of 9.2% from 2014 to 2024 (Figure 2).[2]

Several cancer-related driver gene mutations have been identified, including *EGFR*, *ALK*, *ROS1*, *KRAS*, *MET*, *HER2*, *NTRK*, *FGFR2*, and *BRCA1/2* mutations. Tissue-based genetic testing results are often a prerequisite for determining treatment methods and obtaining NHI coverage. In Taiwan, currently genetic testing—such as Next-Generation Sequencing (NGS)is used to identify actionable mutations in cancer patients, enabling personalized treatment strategies. While it is especially valuable for patients who cannot undergo surgery, genetic testing also guides the use of targeted therapies and chemotherapy, either as first-line treatments or during disease progression to optimize treatment outcomes across various stages of cancer. There are various cancer targeted drugs covered by NHI that require

[2]2025 Cancer Forum - Policies and Prospects of Precision Cancer Treatment - Presentation by Director-General Shih Chung-liang (2025 Video)

companion diagnostics, encompassing lung cancer, breast cancer, colorectal cancer, ovarian cancer, prostate cancer, and other solid tumors.

(For detailed information, please refer to the appendix—listing the targeted cancer drugs that require companion genetic diagnostics.)



Source: 2025 Cancer Forum - Policies and Prospects of Precision Cancer Treatment, Presentation by Director-General Shih Chung-liang (2025 Video)

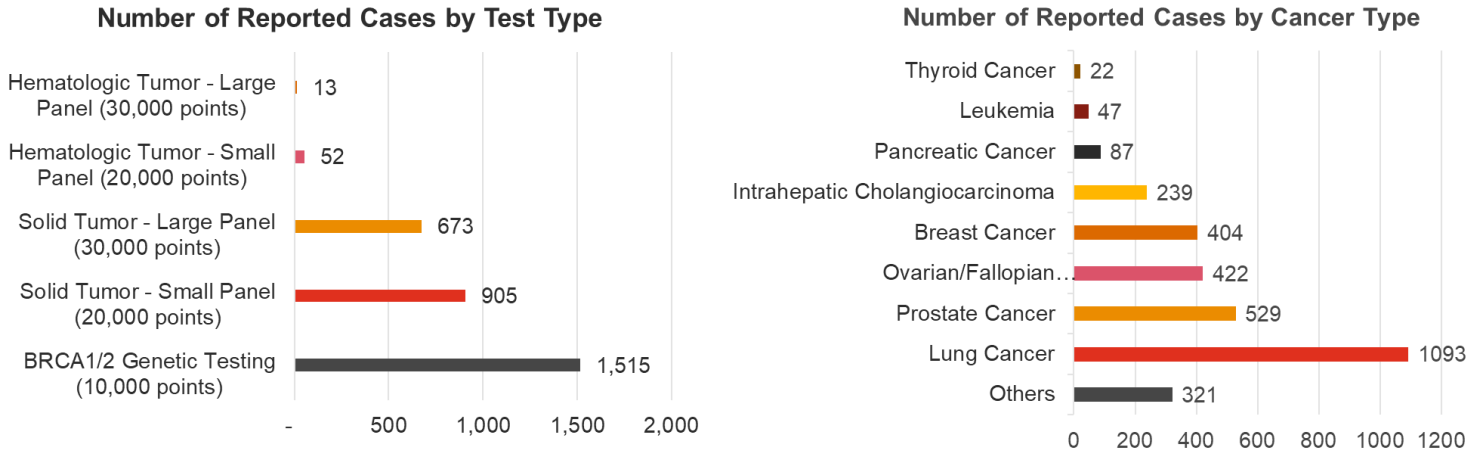
Figure 2: Trends in Cancer Healthcare Expenses and Patient Numbers

The Role of Next-Generation Sequencing in Cancer Treatment and Precision Medicine

Tissue-based Next-generation sequencing (NGS) was included in health insurance coverage starting May 1, 2024, demonstrating the authorities' commitment to advancing precision medicine. NGS technology plays a pivotal role in promoting precision medicine for cancer by facilitating targeted treatments to enhance therapeutic efficacy, offering patients more precise medical options and hope.

According to data from the NHIA, from May 2024 to June 2025, there were a total of 3,164 NGS applications. Among these, lung cancer cases were the most prevalent, accounting for 1,093 applications, followed by prostate cancer with 529, ovarian/fallopian tube/peritoneal cancer with 422, breast cancer with 404, intrahepatic cholangiocarcinoma with 239, pancreatic cancer with 87, thyroid cancer with 22, leukemia with 47, and other types of cancers with 321 cases (Figure 3)[2].

When categorized by type of test, the *BRCA1/2* gene testing for breast cancer, ovarian cancer, and prostate cancer had the highest usage of 1,515 cases. Other categories included 905 applications for small panels of solid tumors (≤100 genes), 679 for large panels of solid tumors (>100 genes), 52 for small panels of hematological malignancies, and 13 for large panels of hematological malignancies (Figure 3)[3]. According to the current NHI reimbursement regulation for NGS, except for germline BRCA1/2 gene testing which uses blood samples, all other tests are restricted to using confirmed tumor pathological tissue for NGS analysis.



Source: 2025 Cancer Forum - Policies and Prospects of Precision Cancer Treatment, Presentation by Director-General Shih Chung-liang (2025 Video); NHIA data, Compiled by PwC Taiwan.

Figure 3: Number of Applications (As of June 2025)

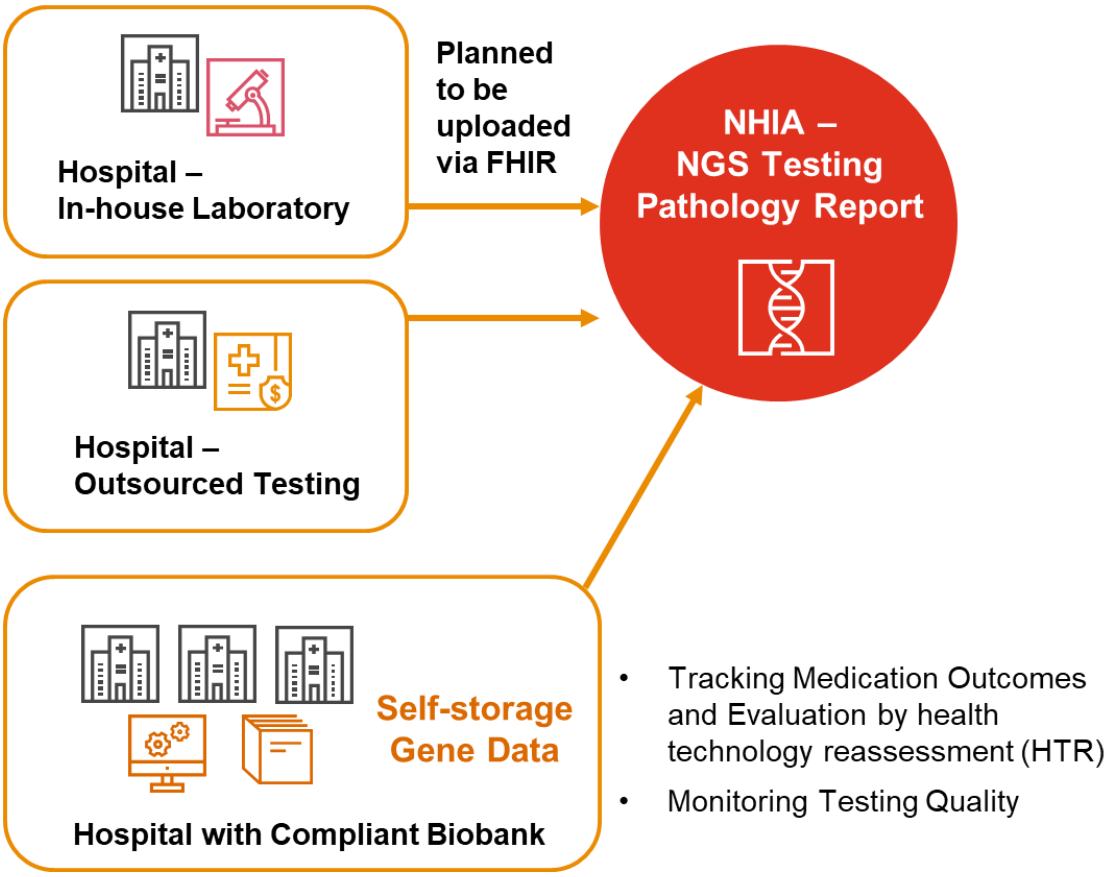
[3] 聯合新聞網（2025）《次世代基因定序給付快一年...申報前 5 癌別曝光 肺癌最多》"Nearly a Year of Coverage for Next-Generation Gene Sequencing... Top 5 Reported Cancers Revealed, Lung Cancer Leads the Way"

Considering the different timing of testing for each type of cancer, the NGS payment guidelines announced by the NHIA set indications and necessary testing genes according to the type of cancer, with lifetime coverage limited to one test per person per cancer type. Reimbursement for NGS testing is restricted to applications from "regional hospitals or above" or "cancer care quality certified hospitals" and must be conducted by medical institutions included in the Ministry of Health and Welfare's list of approved Laboratory Developed Tests (LDTs) implementation plans. Additionally, these institutions need to establish or participate in a Molecular Tumor Board (MTB). As of June 2025, 70 hospitals have provided NGS testing services.

Although NGS samples are primarily collected in hospitals, the subsequent analysis can take place either in the hospital's own laboratory or be outsourced to external testing labs certified by the TFDA. Consequently, cross-institutional data exchange and interoperability are crucial for effective data management. To address this issue, the NHIA has begun trialing the FHIR (Fast Healthcare Interoperability Resources) standardized format for NGS report uploads at seven medical centers, including Chang Gung Memorial Hospital (Linkou), Chi Mei, and National Cheng Kung University Hospital, with plans to issue additional guidelines in the future[4].

In terms of specification design, the NHIA aims to standardize the structure of the test reports, compiling key information needed from major illness applications, pre-approval of cancer drugs, to clinical tracking. This includes patient demographics, tumor pathology staging, genetic testing methods, and results, with clear definitions of field structure, data types, and codes, ensuring a common language for data transmission across institutions. In the future, once hospitals submit NGS report data in FHIR format, the system can automatically verify the completeness of fields and create a database, achieving the goal of tracking medication outcomes and evaluating clinical efficacy (Figure 4).

[4] 中國時報（2025）《提升醫療資料互通性 NGS 檢測報告下半年拚標準化》China Times (2025) "Enhancing Interoperability of Medical Data: NGS Testing Reports Aim for Standardization in the Second Half of the Year"



Source: "NGS Liquid Biopsy Development Trends and Prospects " Expert Meeting, Compiled by PwC Taiwan

Figure 4: Data Collection Plan by the NHIA

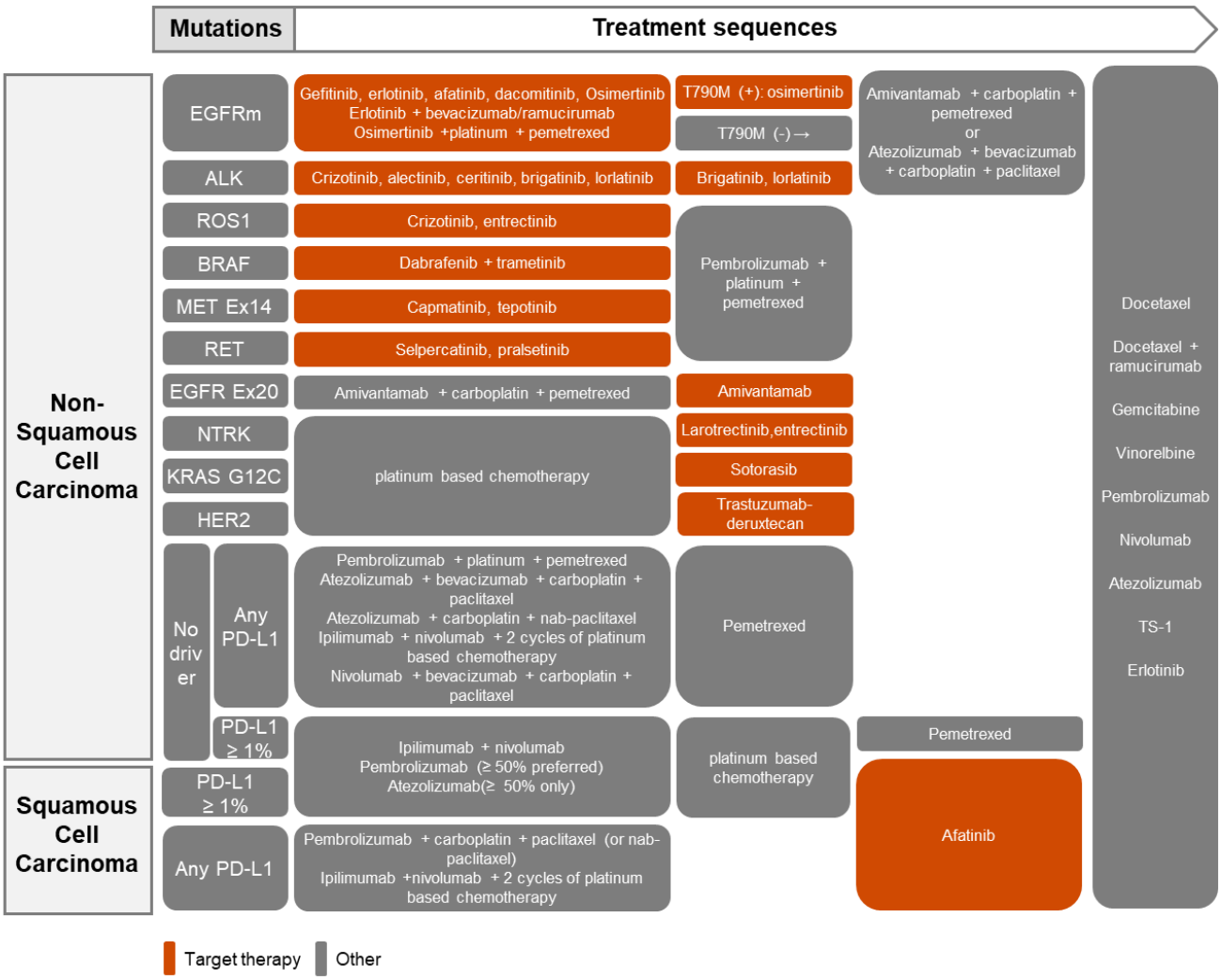
Current Clinical Applications of NGS Liquid Biopsy in Cancer Treatment

Milestone in Cancer Treatment with Precision Medicine

To fulfill President Lai's vision for "Healthy Taiwan," the authorities in Taiwan are proactively introducing novel cancer drugs, with higher efficacy while reducing side effects and unnecessary treatment and resource wastage. However, due to the polymorphic nature of cancer, even effective drugs face challenges in achieving treatment goals without proper diagnosis. Taking lung cancer, the leading cause of cancer mortality in Taiwan's top ten cancers, as an example, the primary treatments include chemotherapy, immunotherapy, and targeted therapy.

Non-small cell lung cancer (NSCLC), which constitutes the largest proportion of lung cancer, often carries significant driver gene mutations that can be targeted for precision medicine (Figure 5). Several driver genes related to NSCLC have been identified[5], and clinical trials data indicates that targeted therapies against specific driver gene mutations can increase the tumor shrinkage rate in patients, significantly enhancing drug response and survival rates compared to those receiving chemotherapy without targeted therapies. This also reduces the occurrence of adverse reactions[6,7]. The availability of multiple targeted therapies for driver gene mutations in lung cancer makes it exemplary in precision cancer medicine. Therefore, how genetic testing is conducted to find corresponding targeted therapies is key to achieving milestones in precision cancer medicine.

[5] Zhang B, et al. (2020). Genomic Characteristics in Chinese Non-Small Cell Lung Cancer Patients and Its Value in Prediction of Postoperative Prognosis. Translational Lung Cancer Research.
[6] Stockley TL, et al. (2016). Molecular Profiling of Advanced Solid Tumors and Patient Outcomes with Genotype-Matched Clinical Trials: The Princess Margaret IMPACT/COMPACT Trial. Genome Medicine.
[7] Kris MG, et al. (2014). Using Multiplexed Assays of Oncogenic Drivers in Lung Cancers to Select Targeted Drugs. JAMA.



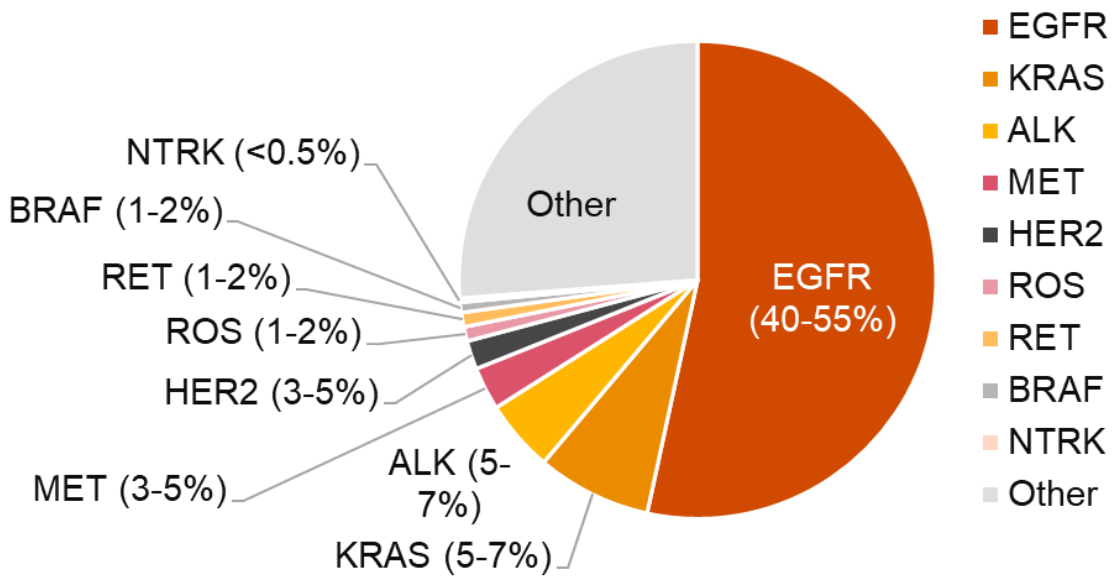
Source: "NGS Liquid Biopsy Development Trends and Prospects " Expert Meeting, Compiled by PwC Taiwan

Figure 5: Treatment Guidelines for NSCLC and Corresponding Drugs

Genetic Testing and Precision Medicine for Lung Cancer

In Taiwan, there are approximately 16,000 new lung cancer cases annually, with about 8,000 to 9,000 diagnosed at stage IV. Lung cancer consists of about 5% small cell lung cancer (SCLC) and 85% NSCLC. NSCLC can be further classified into squamous cell carcinoma (about 10%), large cell carcinoma (around 5%), and adenocarcinoma, which accounts for the majority at roughly 70%. Within NSCLC, the mutation of the driver gene *EGFR* is present in approximately 50% of patients, *KRAS* mutations account for about 8-12%, *ALK* gene fusions approximately 5-7%, while *ROS1* gene fusions, *RET* gene fusions, and *BRAF* mutations each represent 1-2% (Figure 6)[8].

For early-stage NSCLC, surgical removal is the primary treatment approach. However, for stage IV NSCLC patients, identifying driver genes becomes critical. Genetic testing that screens for driver genes can allow patients to receive targeted therapy early, effectively improving survival rates. If no driver genes are detected, patients should undergo chemotherapy or immunotherapy.



Source：Yang, C. Y., et al. (2020). Precision Management of Advanced Non-Small Cell Lung Cancer. Annual Review of Medicine.

Figure 6: Proportion of Gene Mutations in Taiwanese Lung Adenocarcinoma Patients

[8] Yang, C. Y., et al. (2020). Precision Management of Advanced Non-Small Cell Lung Cancer. Annual Review of Medicine.

For lung cancer patients with *EGFR* mutations, if the mutation is an exon 19 deletion or L858R, Tagrisso (osimertinib) is the targeted therapy, commonly considered as the first-line treatment. If patients initially receive first-generation or second-generation targeted drugs such as Gefitinib, Erlotinib, Afatinib, or Dacomitinib, over time, most will develop resistance, and approximately 50% will exhibit a T790M mutation[9]. In such cases, physicians may consider implementing second-line treatment with osimertinib for the T790M mutation.

According to the AURA3 study published in the New England Journal of Medicine (NEJM) in 2017, for T790M mutations emerging after first- or second-generation targeted treatment, Tagrisso has shown a significant extension in progression-free survival (PFS)[10]. In first-line clinical trials, patients with *EGFR* exon 19 deletion or L858R mutations were divided into two groups: one receiving osimertinib treatment and the other receiving first-generation targeted therapy. The study demonstrated that while both groups had similar response rates, the median PFS in the osimertinib group reached 18 months, displaying nearly an eight-month advantage[11]. Based on these findings, osimertinib has become one of the standard treatments for *EGFR*-mutated NSCLC.

Previously, NHIA only reimbursed osimertinib for stage IV patients with brain metastases. Starting from October 1, 2024, NHIA expanded coverage for osimertinib to reimburse first-line treatment for patients with locally invasive or metastatic (i.e., stage IIIB, IIIC, or stage IV) lung adenocarcinoma patient and align with international treatment guidelines. According to health insurance drug expenditure statistics, osimertinib has topped the list of reimbursed drugs since 2011, underscoring its significance in lung cancer treatment. Early adoption of the most suitable medication through genetic testing will be crucial for achieving precision treatment in lung cancer.

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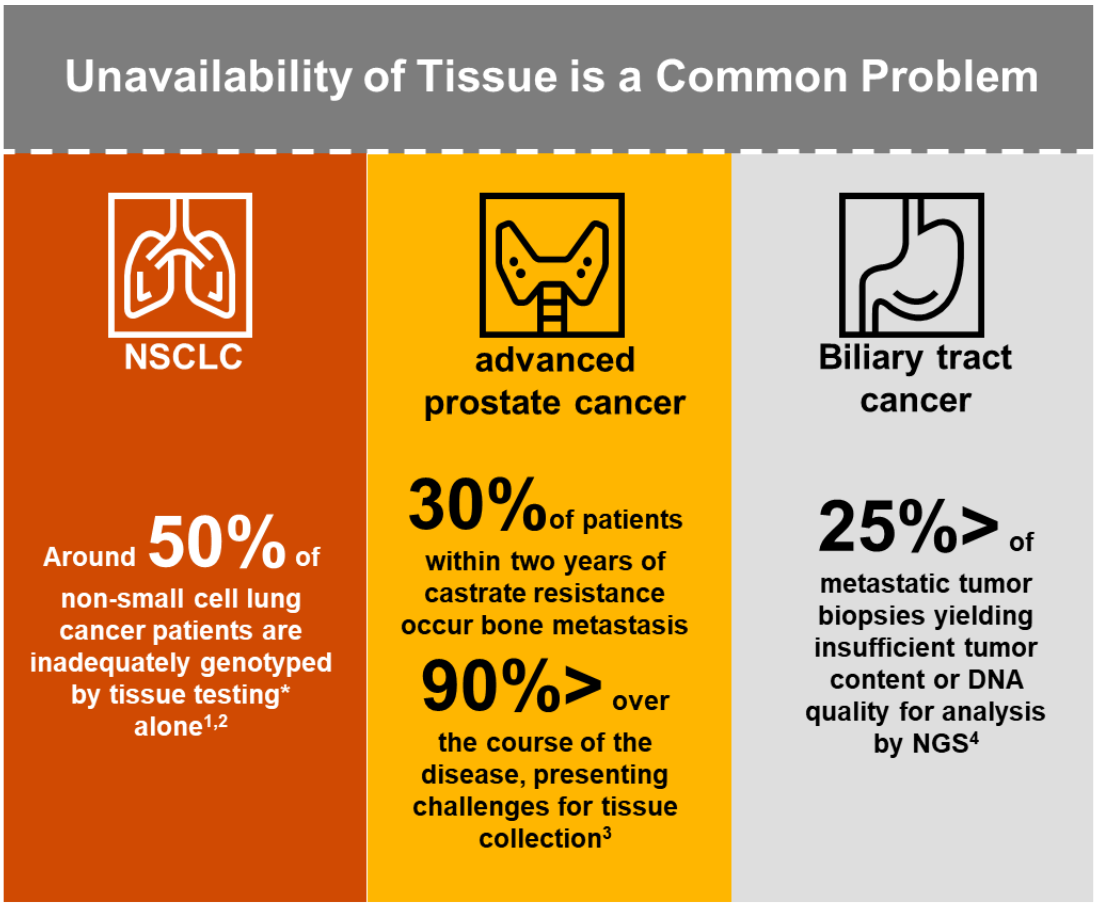
[9] Miura, S., et al. (2022). Sequential Afatinib and Osimertinib in Asian Patients with EGFR Mutation-Positive Non-Small Cell Lung Cancer and Acquired T790M: Combined Analysis of Two Global Non-Interventional Studies. OncoTargets and Therapy.

[10] Mok, T. S., et al, & AURA3 Investigators. (2017). Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. The New England Journal of Medicine.

[11] Soria, J. C., et al & FLAURA Investigators. (2018). Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. The New England Journal of Medicine.

Challenges Faced in Tissue Testing

Although NGS testing can provide companion diagnostics for patients and improves medication guidance towards precision medicine, research indicates that many types of cancer often face challenges with tissue biopsies (Figure 7). In lung cancer, half of the patients are inadequately genotyped by tissue testing.[12,13] In advanced prostate cancer, approximately 30% of patients face bone metastasis complications within two years after developing castrate resistance, and over 90% of patients experience bone metastasis throughout the course of the disease.



*Genes assessed by tissue testing are EGFR, ALK, ROS1, BRAF and PD-L1

Source: [1] Aggarwal, C. et al. (2019). Clinical Implications of Plasma-Based Genotyping with the Delivery of Personalized Therapy in Metastatic Non-Small Cell Lung Cancer. JAMA Oncology ; [2] Robert, N. J., et al. (2022). Biomarker Testing and Tissue Journey Among Patients with Metastatic Non-small Cell Lung Cancer Receiving First-Line Therapy in the US Oncology Network. Lung Cancer ; [3] Den, R. B., et al. (2019). Ra-223 Treatment for Bone Metastases in Castrate-Resistant Prostate Cancer: Practical Management Issues for Patient Selection. American Journal of Clinical Oncology ; [4] Lamarca, A., et al. (2020). Molecular Profiling in Daily Clinical Practice: Practicalities in Advanced Cholangiocarcinoma and Other Biliary Tract Cancers. Journal of Clinical Medicine.

Figure 7: Common Challenges in Cancer Tissue Testing

[12] Aggarwal, C. et al. (2019). Clinical Implications of Plasma-Based Genotyping with the Delivery of Personalized Therapy in Metastatic Non-Small Cell Lung Cancer. JAMA Oncology.
[13] Robert, N. J., et al. (2022). Biomarker Testing and Tissue Journey Among Patients with Metastatic Non-Small Cell Lung Cancer Receiving First-Line Therapy in the US Oncology Network. Lung Cancer.

Bone metastasis presents higher difficulty for tissue biopsy, making testing challenging[14]. In biliary tract cancer, due to its characteristics, genetic diagnosis can be difficult, with 25% of metastatic tumor samples lacking sufficient nucleic acid quality for subsequent NGS analysis.[15]

Studies showed several conditions that NSCLC patients may have challenges with obtaining tissue samples or with poor quality of samples[13,16,17], leading to difficulties in conducting subsequent NGS testing. In some metastatic and high-risk patients, tissue biopsy maybe too risky. Studies from Japan show that 15-24% of metastatic NSCLC patients experience sampling failures[18]. Due to the invasive nature of tissue biopsy, patients may be less willing to undergo the procedure or may encounter other related issues[19,20], and obtaining tissue samples typically requires a longer time[21]. These factors create numerous challenges for performing tissue-based NGS testing in clinical practice (Figure 8). Below is a summary of the primary challenges that lung cancer patients and physicians encounter when conducting tissue testing in clinical practice:

1. **Inability to sample tumor tissue, difficulty in accessing tumor location, or excessively high risk of sampling**

   Experts indicate that, based on clinical experience, approximately 10-20% of newly diagnosed patients are unable to undergo tissue testing, and re-sampling after each disease progression becomes even more challenging. Elderly patients or those with poor

[14] Den, R. B., et al. (2019). Ra-223 Treatment for Bone Metastases in Castrate-Resistant Prostate Cancer: Practical Management Issues for Patient Selection. American Journal of Clinical Oncology.
[15] Lamarca, A., et al. (2020). Molecular Profiling in Daily Clinical Practice: Practicalities in Advanced Cholangiocarcinoma and Other Biliary Tract Cancers. Journal of Clinical Medicine.
[16] Aggarwal, C., et al. (2019). Clinical Implications of Plasma-Based Genotyping With the Delivery of Personalized Therapy in Metastatic Non-Small Cell Lung Cancer. JAMA Oncology.
[17] Kawamura et al. (2016). Rebiopsy for Patients with Non-Small-Cell Lung Cancer after Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor Failure. Cancer Science.
[18] Hayashi et al. (2020). Clinical Impact of a Cancer Genomic Profiling Test Using an In-House Comprehensive Targeted Sequencing System. Cancer Science.
[19] Niwa et al. (2009). Bronchoscopy in Japan: A Survey by the Japan Society for Respiratory Endoscopy in 2006. Respirology.
[20] Questionnaire Survey on Patient Awareness of Invasive Rebiopsy in Advanced Non-Small Cell Lung Cancer.
[21] Cui, W. et al. (2022). Up-front Cell-Free DNA Next Generation Sequencing Improves Target Identification in UK first Line Advanced Non-Small Cell Lung Cancer (NSCLC) Patients. European Journal of Cancer.

physical condition and other comorbidities may not be able to tolerate lung puncture or surgical sampling. Furthermore, in practice, when physicians need to obtain tissue biopsies, they must consider the location of the tissue sampling. This is mainly because tumors may shrink following targeted therapy, but they may face tumor metastasis years later, leading to difficulties in sampling or excessively high sampling risks. The potential risks associated with tumor metastasis are summarized as follows:

(1) Multiple Lung Metastases: Each metastatic tumor is very small, and there is nearly a 50% chance of being unable to obtain tissue samples. Furthermore, during a CT-guided biopsy, if the tumor is near major blood vessels, deeply embedded within lung tissue, or if the exacerbated lesions are close to the heart, the patient may face risks such as significant bleeding or pneumothorax, posing higher sampling risks. For instance, among patients undergoing percutaneous lung tissue biopsy, the incidence of pneumothorax is approximately 20%.[22]

(2) Brain Metastases: The location of metastases can be difficult for tissue sampling. Patient may have to administer local radiation therapies.

(3) Bone Metastases: Like brain metastases, these locations also present sampling challenges, with biopsies feasible only at specific sites. Radiologists and surgeons may be reluctant to take on the risk of sampling, with treatment typically focused on local radiation and symptomatic relief.

(4) Liver Metastases: If the sampling site is deep and near blood vessels, biopsies involve a certain degree of difficulty and bleeding risk, necessitating hospitalization.

2. Insufficient Tumor Tissue Sample

Even if a sample can be obtained, it needs to be sufficient in quantity and of high quality for NGS analysis. After obtaining a biopsy, a pathologist must evaluate the quantity and quality of the sample. If the tumor purity is not high enough, or if the quality of the nucleic acids (DNA or RNA) is poor, subsequent NGS analysis cannot be performed. Clinical data from abroad indicate that about 10-20% of tissue biopsy samples fail to meet the molecular testing requirements of NGS due to insufficient tumor tissue or amplifiable DNA[23]. This may necessitate another biopsy, requiring patients to undergo the sampling

[22] Malapelle U, et al. (2021). Liquid Biopsy for Biomarker Testing in Non-Small Cell Lung Cancer: A European Perspective. Journal of Molecular Pathology.
[23] Liam, C. K., et al. (2020). Is Tissue Still the Issue in Detecting Molecular Alterations in Lung Cancer? Respirology.

process again. However, re-biopsies may not be feasible in cases of disease progression.

3. Financial and Time Burden of Tumor Tissue Sampling

Clinically, doctors can opt to obtain tissue samples via bronchoscopy or CT-guided biopsy. However, both methods involve arranging for hospitalization. In Taiwan, the waiting time for such procedures is about one month at medical centers and 2-3 weeks at regional hospitals. Throughout the process of obtaining a tissue sample, patients often face significant waiting times during which their tumors may continue to worsen. This presents a considerable challenge for many patients undergoing tissue testing. Additionally, the financial burden of hospitalization, surgical biopsies, and other related medical costs can be substantial, especially with tight medical resource constraints. A study from the United States found that after going through the tissue sampling process, only 36% of 1,000 advanced-stage patients ended up receiving drug treatment. The others faced issues such as insufficient samples. These processes may take 2-4 weeks and combined with hospitalization waiting times. The total duration can be around two months. The study further suggests that using blood-based liquid biopsy testing can reduce timeframe and with a success rate of up to 99%[24]. In addition, surgeries performed to access tumors can be both invasive and uncomfortable. Repeated tissue biopsies may adversely affect a patient's quality of life and lead to considerable recovery time.

4. Need for Additional Testing Methods Due to Tumor Heterogeneity

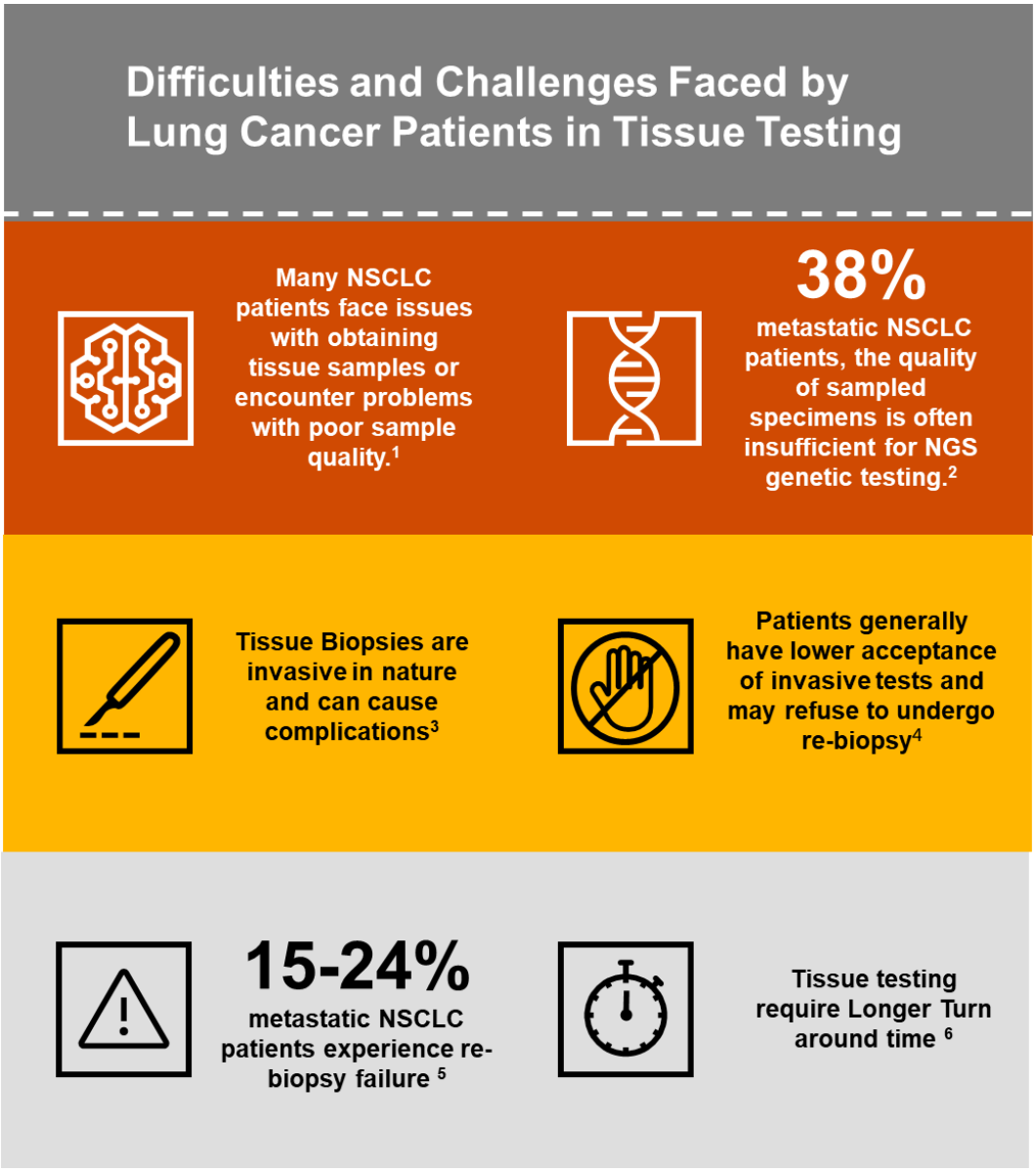
Tumor heterogeneity poses a challenge for tissue testing in representing the complete tumor genotype. Numerous large research institutions worldwide advocate for genetic testing via liquid biopsy as an important complementary method to tissue testing. Liquid biopsy reveals spatial and temporal heterogeneity[25] and can identify mechanisms of

[24] Sadik, H., et al. (2022). Impact of Clinical Practice Gaps on the Implementation of Personalized Medicine in Advanced Non-Small-Cell Lung Cancer. JCO precision oncology.

[25] Parikh, A.R., et al. (2019). Liquid Versus Tissue Biopsy for Detecting Acquired Resistance and Tumor Heterogeneity in Gastrointestinal Cancers. Nature Medicine.

treatment resistance/cancer evolution biomarkers5[26,27]. Clinical evidence shows that some patients who test negative in tissue biopsies can test positive in liquid biopsies, underscoring the necessity of additional genetic testing[28]. Additionally, for NSCLC patients known to have EGFR mutations, long-term use of first-generation tyrosine kinase inhibitors (TKIs, such as Erlotinib/Gefitinib) can lead to treatment resistance due to tumor resistance. When disease progression warrants re-testing, re-performing tissue biopsies can be cumbersome and resource intensive. Monitoring for *EGFR* T790M mutations through liquid biopsy can quickly determine whether to switch to second-line therapies (such as osimertinib)[29]. Finally, providing diverse genetic testing tools is important for patients. For example, early detection of abnormalities in *EGFR* exon 19 deletions and L858R mutations allows for early use of osimertinib as a first-line treatment, significantly improving clinical outcomes.

[26] Hahn, A.W., et al. (2019). Application of Liquid Biopsy in Cancer Treatment. Cancer Treatment and Research Communications.
[27] Cowling, T., et al. (2019). An Overview of Liquid Biopsy for Screening and Early Detection of Cancer. CADTH Issues in Emerging Health Technologies. Canadian Agency for Drugs and Technologies in Health.
[28] Chen, C. H., et al. (2022). Real-world Afatinib Outcomes in Advanced Non-small Cell Lung Cancer Harboring EGFR Mutations. Anticancer Research.
[29] Planchard, D., et al. (2018). Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology.



Source：[1]Robert, N. J., et al. (2022). Biomarker Testing And Tissue Journey Among Patients with Metastatic Non-Small Cell Lung Cancer Receiving First-Line Therapy in The US Oncology Network. Lung Cancer；[2]Kawamura, T., et al. (2016). Rebiopsy for patients with non-small-cell lung cancer after epidermal growth factor receptor-tyrosine kinase inhibitor failure. Cancer Science；[3]Niwa, H., et al. (2009). Bronchoscopy in Japan: A Survey by the Japan Society for Respiratory Endoscopy in 2006. Respirology；[4] Questionnaire Survey on Patient Awareness of Invasive Rebiopsy in Advanced NSCLC；[5]Hayashi, H., et al. (2020). Clinical Impact of a Cancer Genomic Profiling Test Using an In-house Comprehensive Targeted Sequencing System. Cancer Science；[6]Cui, W., et al. (2022). Up-Front Cell-free DNA Next Generation Sequencing Improves Target Identification in UK First Line Advanced Non-small Cell Lung Cancer (NSCLC) Patients. European Journal of Cancer.

Figure 8: Difficulties and Challenges Faced by Lung Cancer Patients in Tissue Testing

NGS Liquid Biopsy Technology is Fully Developed

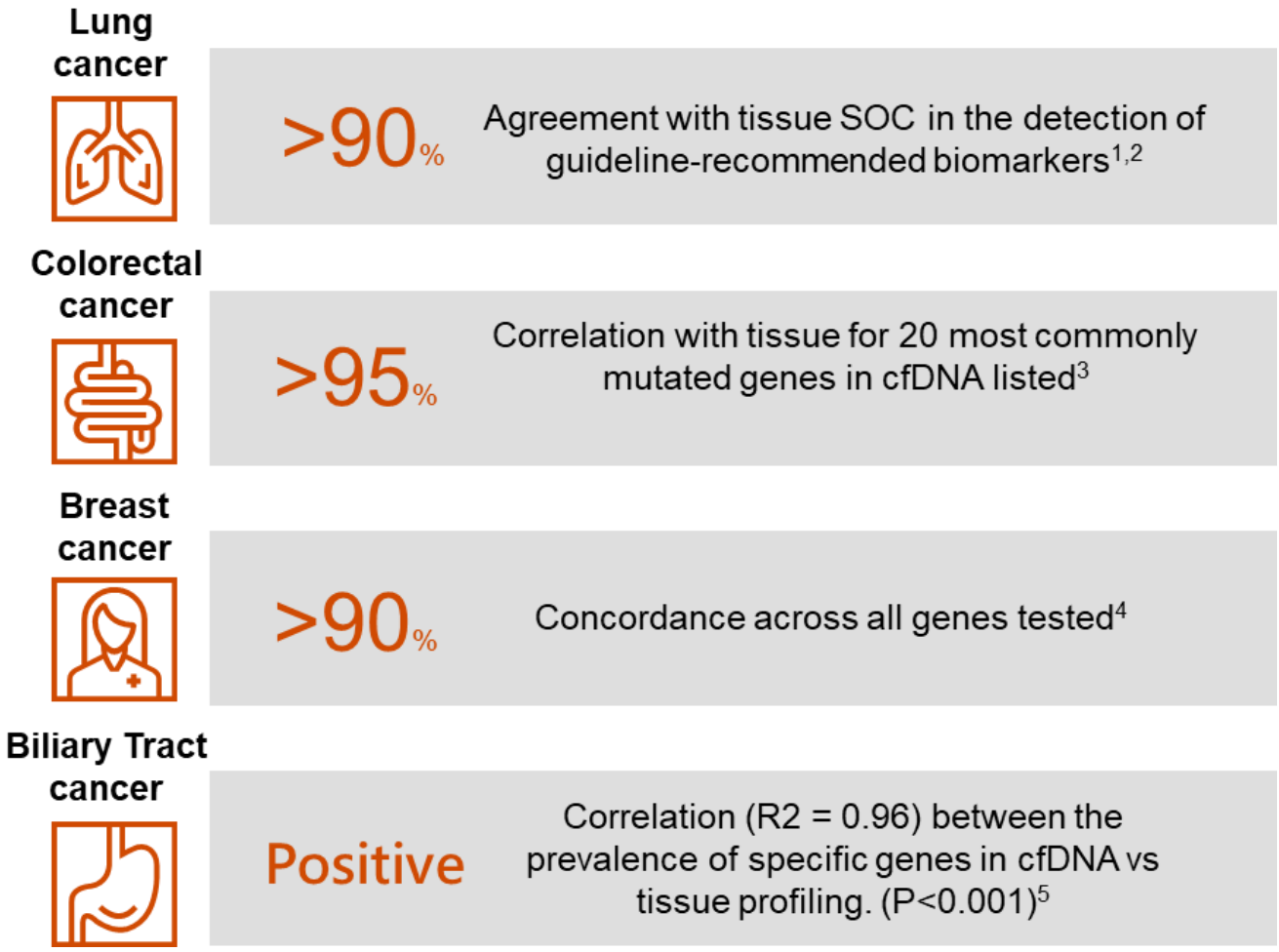
Liquid biopsy is a non-invasive diagnostic method that analyzes cell-free DNA in blood samples, detecting genomic and epigenomic alterations to guide personalized treatment and monitor tumor evolution, representing an emerging technology in the field. Liquid biopsy can be applied to early disease diagnosis, detection of post-surgery minimal residual disease (MRD), treatment monitoring, cancer recurrence surveillance, treatment-resistance mutations testing, and as companion diagnostics to guide precision medicine. For example, with Guardant360 liquid biopsy, cfDNA testing in advanced cancer cases achieves a tumor profiling success rate exceeding 90% (Table 1), significantly solving the challenges of conducting NGS with tissue testing.

Table 1: Tumor profiling success rate for liquid biopsy

NILE (Non-invasive versus Invasive Lung Evaluation) Research[1] **95%**	SLLIP (Study of Liquid biopsy for Lung cancer In Plasma) Research [4] **90.8%**
W Cui research [2] **91%**	LC-SCRUM-Liquid (Lung Cancer – Screening Project for Personalized Medicine) Research Project [3] **91%**

Source : [1] Leighl, N. B., et al. (2019). Clinical Utility of Comprehensive Cell-free DNA Analysis to Identify Genomic Biomarkers in Patients with Newly Diagnosed Metastatic Non-small Cell Lung Cancer. Clinical Cancer Research ; [2] Cui, W., et al. (2022). Up-Front Cell-Free DNA Next Generation Sequencing Improves Target Identification in UK First Line Advanced Non-Small Cell Lung Cancer (NSCLC) Patients. European Journal of Cancer ; [3] Sugimoto, A., et al. (2023). A Large-Scale Prospective Concordance Study of Plasma- and Tissue-Based Next-Generation Targeted Sequencing for Advanced Non-Small Cell Lung Cancer. Clinical Cancer Research ; [4] Palmero, R., et al (2021). Biomarker Discovery and Outcomes for Comprehensive Cell-Free Circulating Tumor DNA Versus Standard-of-Care Tissue Testing in Advanced Non-Small-Cell Lung Cancer. JCO Precision Oncology.

For example, products like Guardant360 liquid biopsy require only 5 ng of nucleic acid to detect guideline-relevant genetic mutations, including single nucleotide variants (SNVs), insertions/deletions (indels), copy number variations (CNVs), and fusions, achieving sensitivity of over 95% and specificity of 98%. Several studies have shown high concordance of liquid biopsy testing result with that of tissue biopsy in cancer gene diagnostics (Figure 9).



Source : [1] Leighl, N. B., et al. (2019). Clinical Utility of Comprehensive Cell-free DNA Analysis to Identify Genomic Biomarkers in Patients with Newly Diagnosed Metastatic Non-small Cell Lung Cancer. Clinical Cancer Research ; [2] Palmero, R., et al (2021). Biomarker Discovery and Outcomes for Comprehensive Cell-Free Circulating Tumor DNA Versus Standard-of-Care Tissue Testing in Advanced Non-Small-Cell Lung Cancer. JCO Precision Oncology ; [3] Strickler, J. H., et al. (2018). Genomic Landscape of Cell-Free DNA in Patients with Colorectal Cancer. Cancer Discovery ; [4] Chae, Y. K., et al. (2017). Concordance of Genomic Alterations by Next-Generation Sequencing in Tumor Tissue versus Circulating Tumor DNA in Breast Cancer. Molecular Cancer Therapeutics ; [5] Berchuck, J. E., et al. (2022). The Clinical Landscape of Cell-Free DNA Alterations in 1671 Patients with Advanced Biliary Tract Cancer. Annals of Oncology.

Figure 9: Liquid biopsies show high concordance with tissue testing across multiple tumor types

In Taiwan, a few selected LDTs based on liquid biopsy have been approved by the Ministry of Health and Welfare, highlighting the advanced development of liquid biopsy technology. Many doctors are adopting liquid biopsy as a supplement to tissue testing because it offers broader genetic information, enabling a more comprehensive understanding of cancer progression and informing treatment decisions.

Clinical Benefits and Evidence of NGS Liquid Biopsy

There is substantial evidence supporting the use of liquid biopsy. Liquid biopsy has been shown to have clinical benefits comparable to tissue testing, with additional advantages in time efficiency and monitoring (Figure 10). For instance, a study by Yang et al. showed that adopting a “liquid-biopsy-first” strategy allows targeted therapy to begin eight days earlier (Table 2). Studies by Chmielecki et al. and Liao et al. further underscored the value of liquid biopsy for real-time disease monitoring. Evidently, liquid biopsy has become an important tool to achieve cancer precision therapy.

Table 2: Key Research Literature Supporting the Clinical Benefits of Liquid Biopsy (based on expert meeting discussion)

Study	Outcome
Yang, C. Y., et al. 2023[30]	There were 180 NSCLC patients underwent liquid-biopsies, followed by tissue biopsies and randomly assigned into two groups: Group A (Delayed Disclosure): Physicians received the liquid-biopsy report only after tissue-genotyping results were available. Group B (Immediate Disclosure): Once pathology confirmed advanced NSCLC, physicians immediately received the liquid-biopsy report to expedite treatment decisions. Liquid biopsy identified actionable driver targets in over 60% of patients and, in tissue-negative cases, revealed additional actionable mutations in 42.6% of cases that tissue testing had missed. Moreover, treatment initiation in the immediate-disclosure group (Group B) occurred 8 days earlier than in the delayed-disclosure group (Group A) (28 days vs 20 days), a difference that is particularly crucial for patients with rapidly progressing disease.

[30] Yang, C. Y., et al. （2023）. Upfront liquid next-generation sequencing in treatment-naïve advanced non-small cell lung cancer patients: A prospective randomised study in the Taiwanese health system. European journal of cancer （Oxford, England : 1990）

Study	Outcome
PLASMA Study, 2023[31]	After progression on first- or second-generation *EGFR* TKIs, detection of a T790M mutation by droplet digital PCR (ddPCR) supports switching to the third-generation inhibitor osimertinib, achieving an objective response rate (ORR) of 50.9 % and a median PFS of 7.4 months, showing that plasma testing reliably identifies patients who remain sensitive to osimertinib.
Gray, J. E., et al. 2024[32]	A bridging analysis shows that in the FLAURA study, when *EGFR* mutations were detected by liquid biopsy and patients received osimertinib, the median PFS was 15.2 months, closely matching those obtained with tissue PCR screening. In the AURA 3 study, once liquid biopsy detected the T790M mutation, patients who switched to osimertinib achieved a median PFS of 8.3 months, substantially longer than the 4.2 months seen with chemotherapy alone. These findings confirm that liquid biopsy effectively identifies patients likely to benefit from osimertinib and is, therefore, an important approach to extending patient survival.
Chmielecki, J., et al. 2023[33]	Liquid biopsy not only identifies *EGFR* mutations but also tracks drug-resistance mechanisms. In the AURA 3 study, about 18% of patients treated with osimertinib as second-line therapy exhibited *MET* amplification and detected by liquid biopsy. In the FLAURA study, among patients who received osimertinib as first-line treatment, 16% of patients were detected with *MET* amplification by liquid biopsy. These patients were treated with a combination of osimertinib and a MET inhibitor, resulting in a 55% ORR and offering a beneficial treatment option for later-stage patients.
Paik, P. K., et al. 2020[34]	Whether *MET* exon 14 skipping mutations were confirmed by liquid or tissue biopsy, treatment with tepotinib yielded an ORR of 46 % and a median duration of response of 11.1 months.

[31] Ang, Y. L. E., et al. (2023). A Phase II Study of Osimertinib in Patients with Advanced-Stage Non-Small Cell Lung Cancer following Prior Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR TKI) Therapy with EGFR and T790M Mutations Detected in Plasma Circulating Tumour DNA (PLASMA Study). Cancers.

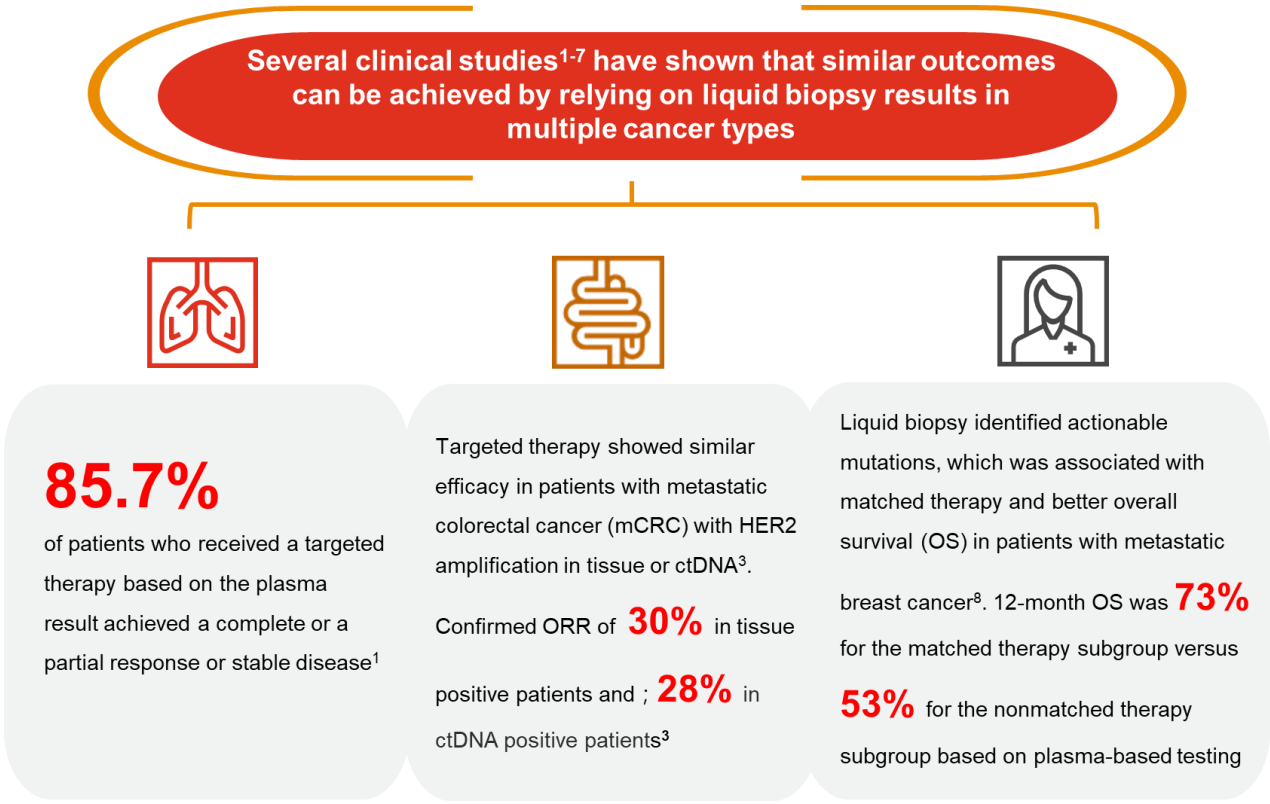
[32] Gray, J. E., et al. (2024). Pan-Tumor Analytical Validation and Osimertinib Clinical Validation in EGFR Mutant Non-Small-Cell Lung Cancer, Supporting the First Next-Generation Sequencing Liquid Biopsy in Vitro Diagnostic. The Journal of Molecular Diagnostics.

[33] Chmielecki, J., et al. (2023). Candidate Mechanisms of Acquired Resistance to First-line Osimertinib in EGFR-mutated Advanced Non-small Cell Lung Cancer. Nature Communications.

[34] Paik, P. K., et al. (2020). Tepotinib in Non-Small-Cell Lung Cancer with MET Exon 14 Skipping Mutations. The New England Journal of Medicine.

Study	Outcome
Nakamura, Y., et al 2021[35]	In a phase 2 trial (UMIN000027887), ctDNA genotyping demonstrated clinical utility in identifying patients with HER2-amplified metastatic colorectal cancer (mCRC) eligible for targeted therapy. Subsequent target therapy yielded an objective response rate (ORR) of 28% in ctDNA-positive cohorts. These outcomes contrast sharply with a 0% ORR observed in a matched real-world population receiving standard salvage therapy. Furthermore, a decline in ctDNA levels within three weeks of treatment initiation was associated with clinical response, underscoring its potential as a dynamic biomarker.
Vidula, N., et al 2021[36]	A comparative analysis shows that in patients with metastatic breast cancer (MBC), plasma-based genotyping using cfDNA identified actionable mutations in 78% of cases, significantly higher than the 50% detection rate seen with tissue-based genotyping. Among cfDNA-positive patients, 34% received matched therapy, compared to only 11% in the tissue cohort. Importantly, matched therapy based on cfDNA results was associated with improved overall survival (HR 0.41, 95% CI: 0.23–0.73, P = 0.002), and this benefit remained significant after multivariable adjustment (HR 0.46, 95% CI: 0.26–0.83, P = 0.010).
Erica L. Mayer., et al 2025[37]	The SERENA-6 trial evaluated the use of ctDNA in advanced breast cancer to detect *ESR1* mutations, a resistance mechanism to aromatase inhibitors and CDK4/6 inhibitors, in HR+/HER2– advanced breast cancer patients. Detecting mutations early allowed a treatment switch to camizestrant, a selective ER degrader, before disease progression. Camizestrant significantly improved progression-free survival, with median PFS of 16.0 months versus 9.2 months in controls, and quality of life was prolonged from 6.4 months to 23 months.

[35] Nakamura, Y., et al. (2021). Circulating Tumor DNA-guided Treatment with Pertuzumab Plus Trastuzumab for HER2-Amplified Metastatic Colorectal Cancer: A Phase 2 Trial. Nature Medicine.
[36] Vidula, N., et al. (2021). Tumor Tissue- versus Plasma-based Genotyping for Selection of Matched Therapy and Impact on Clinical Outcomes in Patients with Metastatic Breast Cancer. Clinical Cancer Research.
[37] Erica L. Mayer, et al. (2025). Camizestrant + CDK4/6 inhibitor (CDK4/6i) for the Treatment of Emergent ESR1 Mutations During First-line (1L) Endocrine-based Therapy (ET) and Ahead of Disease Progression in Patients (pts) With HR+/HER2– Advanced Breast Cancer (ABC): Phase 3, Double-blind ctDNA-guided SERENA-6 Trial. Journal of Clinical Oncology.



Source : [1] Aggarwal, et al. (2019). Clinical Implications of Plasma-Based Genotyping with the Delivery of Personalized Therapy in Metastatic Non-Small Cell Lung Cancer. JAMA Oncology ; [2] Paik, P. K., et al (2020). Tepotinib in Non-Small-Cell Lung Cancer with MET Exon 14 Skipping Mutations. The New England Journal of Medicine ; [3] Nakamura, Y., et al. (2021). Circulating Tumor DNA-guided Treatment with Pertuzumab Plus Trastuzumab for HER2-amplified Metastatic Colorectal Cancer: A Phase 2 Trial. Nature Medicine ; [4] Jacobs et al. (2018). Use of Low-Frequency Driver Mutations Detected by Cell-Free Circulating Tumor DNA to Guide Targeted Therapy in Non–Small-Cell Lung Cancer: A Multicenter Case Series. JCO Precision Oncology ; [5] Olsen, S., et al. (2022). Real-World Clinical Outcomes after Genomic Profiling of Circulating Tumor DNA in Patients with Previously Treated Advanced Non-Small Cell Lung Cancer. Current Oncology ; [6] Nakamura, Y., et al. (2022). Comprehensive Genomic Profiling of Circulating Tumor DNA in Patients with Previously Treated Metastatic Colorectal Cancer: Analysis of a Real-World Healthcare Claims Database. Current Oncology ; [7] Vidula, N., et al. (2021). Tumor Tissue- versus Plasma-based Genotyping for Selection of Matched Therapy and Impact on Clinical Outcomes in Patients with Metastatic Breast Cancer. Clinical Cancer Research.

Figure 10: Clinical Outcomes of Patients Treated Based on Liquid Biopsy[38]

[38] Clinical outcome data based on Guardant360 test results.

The International Adoption of NGS Liquid Biopsy into National Health Insurance Coverage

International Guideline Recommendations on Liquid Biopsy

Multiple international guidelines, which are pivotal in directing global clinical practices, now endorse the use of liquid biopsy as a clinically valuable tool in oncology. The ESMO[39], NCCN[40], IASLC[41], ASCO PCO[42], and Asia Consensus[43] all support the use of liquid biopsy for genotyping advanced NSCLC and other advanced cancers. These guidelines recommend ctDNA liquid-based testing when tissue is unavailable or when rapid molecular results are needed. Additionally, ctDNA is recognized as a useful modality for detecting resistance mutations, such as those emerging during tyrosine kinase inhibitor (TKI) therapy in NSCLC.

Notably, The ASCO Expert Panel advises use NGS liquid biopsy to routine test for *ESR1* mutations in patients with ER-positive, HER2-negative metastatic breast cancer at recurrence or progression on endocrine therapy, with or without CDK4/6 inhibitors. They suggest these tests should be conducted on blood or tissue at the time of progression, as these mutations arise due to treatment pressure and are usually absent in the primary tumor[44].

Collectively, these recommendations highlight the growing consensus on the clinical utility of liquid biopsy in precision oncology.

[39] Pascual, J., et al. (2022). ESMO recommendations on the Use of Circulating Tumour DNA Assays for Patients with Cancer: A Report from the ESMO Precision Medicine Working Group. Annals of oncology.
[40] NCCN Clinical Practice Guidelines in Oncology for Non-Small Cell Lung Cancer. (2024).
[41] Rolfo, C., et al. (2021). Liquid Biopsy for Advanced NSCLC: A Consensus Statement from the International Association for the Study of Lung Cancer. Journal of Thoracic Oncology.
[42] Chakravarty, D. et al. (2022). Somatic Genomic Testing in Patients with Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion. Journal of Clinical Oncology.
[43] Mitsudomi, T., et al. (2023). Expert Consensus Recommendations on Biomarker Testing in Metastatic and Nonmetastatic NSCLC in Asia. Journal of Thoracic Oncology.
[44] Burstein, H. J., et al & Biomarker Testing and Endocrine and Targeted Therapy in Metastatic Breast Cancer Expert Panels (2023). Testing for ESR1 Mutations to Guide Therapy for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer: ASCO Guideline Rapid Recommendation Update. Journal of Clinical Oncology.

US FDA and Japan MHLW Have Approved NGS Liquid Biopsy Companion Diagnostics

The U.S. FDA has approved several NGS liquid biopsy companion diagnostic products[45] (see Table 3), enhancing precision medicine for cancer patients. Additionally, Medicare cover multiple NGS liquid biopsy products, applicable to a wide range of solid tumors.

Table 3: US FDA-Approved NGS Liquid Biopsy Companion Diagnostic Products

Product	Indication	Biomarker	Drug
Guardant 360 CDx	NSCLC	*EGFR* exon 19 deletions, EGFR exon 21 L858R, and T790M	Osimertinib
		EGFR exon 20 insertions	Amivantamb
		ERBB2 Activating Mutations (SNVs And Exon 20 Insertions)	Fam-trastuzumab deruxtecan-nxki
		ESR1 missense mutations between codons 310 and 547	Sotorasib
	Breast Cancer	*KRAS* G12C	Elacestrant
FoundationOne Liquid CDx	NSCLC	*ALK* rearrangements	Alectinib
		BRAF V600E	Encorafenib in combination with

[45] U.S. Food and Drug Administration. (2025). List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools).

Product	Indication	Biomarker	Drug
			Binimetinib
		Exon 19 deletion or exon 21 L858R substitution mutation	Osimertinib, Gefitinib, Erlotinib
		MET single nucleotide variants and indels that lead to MET exon 14 skipping	Capmatinib, Tepotinib
		ROS1 fusions	Entrectinib
	Breast Cancer	*PIK3CA* mutations	Alpelisib, Inavolisib in combination with Palbociclib and Fulvestrant
	Metastatic Castration-Resistant Prostate Cancer	*BRCA1* and *BRCA2*	Rucaparib, Olaparib, Niraparib +Abiraterone acetate
	Metastatic Colorectal Cancer	BRAF V600E	Encorafenib in combination with Cetuximab
	Solid Tumor	NTRK1/2/3 fusions	Entrectinib

Source: U.S. FDA data, compiled by PwC Taiwan

Table 4: Japan MHLW-Approved NGS Liquid Biopsy Companion Diagnostic

Product	Indication	Biomarker	Drug
Guardant 360 CDx	NSCLC	*KRAS* G12C mutations	Sotrasiv
		ERBB2 (HER2) gene mutations	Trastuzumab deruxtecan (genetical recombination)
	Colon and rectal Cancer	*BRAF* V600E mutations	Encorafenib, binimetinib, and cetuximab (genetical recombination) Encorafenib, cetuximab (genetical recombination)
		KRAS/NRAS wild type	Cetuximab (genetical recombination) or Panitumumab (genetical recombination)
		ERBB2 copy number abnormalities (HER2 gene amplification positive)	Trastuzumab (genetical recombination) and Pertuzumab (genetical recombination)
		MSI-H	Nivolumab (genetical recombination)
	Solid tumors	MSI-H	Pembrolizumab (genetical recombination)

Source: Japan, compiled by PwC Taiwan

Current International Reimbursement Status for NGS Liquid Biopsy

1. Canada

New Brunswick Plans to offer liquid biopsy for lung cancer patients who difficult-to-obtain tissue samples during the 2024-2025 period, while Quebec is recommending incorporating it into healthcare reimbursement to enhance treatment options for NSCLC patients.

- Healthcare funding in Canada is autonomously managed by the governments of each province and territory. In 2024, the New Brunswick health department announced plans to provide liquid biopsy for lung cancer patients who have difficulty obtaining tissue samples or are physically frail during the 2024-2025 period, with fundings for the implementation of these tests.[46]
- The Institut national d'excellence en santé et en services sociaux (INESSS) in Quebec has recommended including liquid biopsy in the Québec Directory and Measurement System for Medical Biology Procedures reimbursement. This is particularly aimed at stage 3B to 4 NSCLC patients, especially those with insufficient samples, who cannot safely obtain tissue samples, have rapidly worsening conditions, or need to identify drug resistance for second-line therapies. Establishment of reporting standards and tracking mechanisms is also proposed.[47]

2. United Kingdom

NHS England has begun offering reimbursement for liquid biopsy tests in lung and breast cancer, launching research initiatives to provide more patients access to these tests, analyzing their cost-effectiveness and clinical practicality.

- The UK's "National Genomic Test Directory" lists genetic testing services covered by NHS, which now includes NGS liquid biopsy for lung and breast cancer.[48]
- NHS launched a pilot study in 2022 to assess the integration of ctDNA testing into its standard lung cancer management protocols, refining ctDNA testing procedures and evaluating cost-effectiveness and clinical utility, aiming to provide ctDNA testing for

[46] Government of New Brunswick. (2024). New Collaboration to Introduce Liquid Biopsy Testing for Lung Cancer.
[47] INESSS (2024). Panel multigène diagnostique, pronostique ou prédictif pour le carcinome pulmonaire non à petites cellules (CPNPC) par biopsie liquid.
[48] NHS England. (2025). National Genomic Test Directory.

10,000 patients.[49]

3. France

Gustave Roussy Cancer Research Institute initiated a liquid biopsy program to provide nationwide access, ensuring patients with detected variants receive personalized treatment.

- Liquid biopsy is an alternative diagnostic option for patients with challenging tumor sample acquisition or who are unfit for invasive surgery, with results available in an average of 15 days. In July 2024, Gustave Roussy Cancer Research Institute launched a project to provide 8,000 liquid biopsies annually. Patients with detected mutations are referred to nearby cancer centers for personalized treatment, promoting equitable access to precision medicine in France.[50]

4. Japan

The Ministry of Health, Labour and Welfare (MHLW) has approved and reimbursed multiple liquid biopsy products, designing processes to collect data to advance precision medicine.

- Japan has integrated liquid biopsy products into national health insurance coverage, granting 44,000 points for specimen submission and 12,000 points for result explanation, totaling 56,000 points (JPY$560,000).[51] Applicable to patients either: (1) with solid tumors who have not yet undergone standard treatments; or (2) who have completed standard treatments or are projected to complete them.
- Sample collection is required to be conducted in hospitals designated as Cancer Gene Medical Institutions, Centers, and Consortia, with data submitted to the National Cancer Center's Gene Data Center (C-CAT) after testing.

5. Germany

Germany's statutory insurance system (GKV) and private insurance system (PKV) have included NGS liquid biopsy in national health insurance coverage and accept specimen acquisition via liquid biopsy.

- OPS (Operationen- und Prozedurenschlüssel) is the German official classification

[49] NHS England. (2024). Thousands more Lung Cancer Patients to Get Innovative Blood Test as Part of NHS Pilot.
[50] Gustave Roussy. (2024). Biopsie Liquide Programme FRESH.
[51] 厚生労働省 (2023) <個別事項（その 19）>

system for surgeries, treatment procedures, and medical interventions, managed by the Federal Institute for Drugs and Medical Devices (BfArM). It serves as the core basis for inpatient reimbursement. Since 2021, NGS liquid biopsy has been incorporated into OPS, allowing the use of liquid biopsy to analyze genetic mutations in several solid tumors.[52]

6. **United States**

Medicare covers plasma-based genomic profiling as it facilitates targeted cancer treatment decisions for patients with advanced solid tumors[53].

- Medicare covers plasma-based genomic profiling in solid tumors with several criteria:
  - The patient must have advanced or metastatic solid tumors not originating from the CNS that are untreated or not responding to current therapies.
  - The patient should not have undergone previous plasma-based profiling for the same genetic content, unless cancer progression indicates significant genetic changes.
  - Patients must be candidates for FDA-approved or NCCN-recommended treatments based on genetic markers identified through the profiling.
  - Tissue-based genomic profiling is not feasible due to insufficient tissue or contraindications to invasive biopsy procedures or Tissue-based testing has shown no actionable mutations.

International Cost-Effectiveness Evaluation of NGS Liquid Biopsy

1. Canada

Liquid biopsies detect more actionable genes compared to tissue biopsy, increase QALY, lower overall healthcare costs, and reduce unnecessary biopsy procedures.

- INESSS conducted a cost-effectiveness evaluation of liquid biopsy, suggesting that it increases the proportion of patients eligible for appropriate targeted treatments, thus improving quality-adjusted life years (QALY). Different studies indicate potential cost savings or additional costs, with cost-effectiveness ratios per QALY gained ranging

[52] BfArM. (2021). Kode-Suche in OPS Version 2021.
[53] CMS, MCD data base, MolDX: Plasma-Based Genomic Profiling in Solid Tumors, L38043.

between CAD$50,000 to CAD$100,000.[54]

- Combining liquid biopsy and tissue biopsy identifies more actionable genes (68.5% versus 52.7%) than using tissue biopsy alone. With this strategy, incremental cost savings per patient were CAD$3,065, along with an increase of 0.02 QALY.[55]
- Health Quality Ontario's health technology assessment on lung cancer EGFR T790M liquid biopsy indicated short-term cost savings of CAD$505 compared to tissue biopsy, avoiding approximately 400 tissue biopsies while enabling the most accurate treatment decisions.[56] A systematic literature review indicates that liquid biopsy is associated with gains in QALYs compared to tissue testing alone and proves to be cost-effective when considering the budget impact of public funding for NSCLC patients in Ontario. Family members and care partners perceive liquid biopsy favorably due to its quicker turnaround time and less invasive nature[57].

2. United Kingdom

Liquid biopsies reduce costs and minimize the need for invasive biopsy procedures.

- Liquid biopsy offers significant help in detecting resistance to EGFR-TKI drugs. Cost-effectiveness assessments indicate costs of EGFR liquid biopsy between £138.05 and £230.22 (excluding VAT), with resource impacts similar to standard care. Reducing the number of tissue biopsies could result in cost savings.[58]
- The NHS in England is the first to offer a groundbreaking liquid biopsy blood test for lung and breast cancer patients, allowing quicker access to targeted therapies. NHS suggest that liquid biopsy enable treatment up to two weeks earlier and reducing the need for additional tests and chemotherapy. Initially benefiting up to 15,000 lung and 5,000 breast cancer patients annually, the implementation is expected to save the NHS up to £11 million a year, with plans to extend testing to other cancers[59].

3. Australia

Liquid biopsies reduce overtreatment, increase QALY, and lower overall healthcare costs, with an ICER dominating standard care.

- A study using a state-transition model from prospective cohort data analyzed the cost-effectiveness of ctDNA-guided adjuvant chemotherapy versus standard care. For stage II colorectal cancer, excess adjuvant chemotherapy posed health and financial burdens. The ctDNA-guided chemotherapy reduced overtreatment, increased QALY by 0.2, and

[54] INESSS. (2024). Panel multigène diagnostique, pronostique ou prédictif pour le carcinome pulmonaire non à petites cellules (CPNPC) par biopsie liquid.
[55] Ezeife, D. A., et al. (2022). The Economic Value of liquid Biopsy for Genomic Profiling in Advanced Non-Small Cell Lung Cancer. Therapeutic Advances in Medical Oncology.
[56] Health Quality Ontario. (2020). Cell-Free Circulating Tumour DNA Blood Testing to Detect EGFR T790M Mutation in People With Advanced Non-Small Cell Lung Cancer: A Health Technology Assessment. Ontario Health Technology Assessment Series.
[57] Health Quality Ontario. (2024). Plasma-Based Comprehensive Genomic Profiling DNA Assays for Non–Small Cell Lung Cancer.
[58] NICE. (2018). Plasma EGFR Mutation Tests for Adults with Locally Advanced or Metastatic Non-Small-Cell Lung Cancer.
[59] NHS. (2025) NHS First in World to Roll Out ‘Revolutionary’ Blood Test for Cancer Patients. Press Release.

decreased costs from AUD$42,980 to AUD$38,925. The ICER showed that liquid biopsy is a dominant cost-effectiveness strategy[60].

4. United States

Population-wide NGS, particularly CGP, improves survival outcomes and reduces costs in advanced NSCLC[61].

- Replacing single gene testing with CGP results in over 2,000 life years gained and reduction in cost per life-year gained by an average of around USD 600 per life year.
- Every 10% increase in NGS testing adoption results in 2,627.4 additional life-years and $75 savings per life-years gained, highlighting the value of broader implementation.
- If 100% of eligible patients received NGS and matched targeted therapies, the average cost per LYG would be $16,641.57, demonstrating favorable cost-effectiveness.

5. Germany

For patients without obtainable tissue samples or insufficient samples for testing, liquid biopsies significantly improved PFS and OS compared to tissue biopsies[62].

- A model built from the perspective of Statutory Health Insurance (SHI) analyzed the cost-effectiveness of adding liquid biopsy to routine tissue biopsy procedures. For patients lacking tissue samples for molecular testing, liquid biopsy improved PFS (10.2 months vs. 8.8 months) and OS (24.2 months vs. 23.1 months). For EGFR mutation patients, the ICER for liquid biopsy was €-13,247/QALY, showing a increased QALY and reduced costs, making it highly cost-effective.

[60] To, Y. H., et al. (2021). Circulating Tumour DNA as a Potential Cost-Effective Biomarker to Reduce Adjuvant Chemotherapy Overtreatment in Stage II Colorectal Cancer. Pharmacoeconomics.
[61] Lemmon, C. A., et al. (2023). Modeling Costs and Life-Years Gained by Population-Wide Next-Generation Sequencing or Single-Gene Testing in Nonsquamous Non-Small-Cell Lung Cancer in the United States. JCO Precision Oncology.
[62] Englmeier, F., et al. (2023). Clinical Benefit and Cost-Effectiveness Analysis of Liquid Biopsy Application in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC): A Modelling Approach. Journal of Cancer Research and Clinical Oncology.

Expert Recommendations for Reimbursement and Application of NGS Liquid Biopsy

The Importance of Reimbursement for Drugs Corresponding to NGS Liquid Biopsy

Research conducted at Taipei Veterans General Hospital and Chang Gung Memorial Hospital revealed that patients with the *EGFR* T790M mutation who received Osimertinib had survival rates of up to five years. Additionally, a study at Chang Gung Memorial Hospital found that out of 22 patients who underwent both tissue biopsy and liquid biopsy, seven were tissue-negative but liquid-positive for T790M.[63] These findings underscore the importance of integrating diagnostic testing with targeted treatment to improve patient outcomes. Since some patients cannot obtain mutation gene testing results through tissue biopsy, providing reimbursement for osimertinib based on liquid biopsy testing results is essential for facilitating timely therapy access.

Adopting NGS liquid biopsy testing could help address current challenges in NGS companion diagnostics. Tissue-based NGS often involves lengthy waiting periods of 3-4 weeks, not including preparatory work, and incurs significant out-of-pocket expenses ranging from NT$50,000 to NT$100,000. By adopting liquid biopsy for NGS, the reporting wait time could be significantly reduced to approximately one week, thereby enhancing the quality of life for patients and their families. A real-world clinical case shows how NGS liquid biopsy and the corresponding drug reimbursement provide clinical benefit for patients.

[63] Chen, C. H., et al. (2022). Real-world Afatinib Outcomes in Advanced Non-small Cell Lung Cancer Harboring EGFR Mutations. Anticancer Research.

Real World Clinical Case

A 61-year-old female patient with no history of smoking and family history of lung cancer presented with a persistent cough for two months accompanied by difficulty breathing. After examination, she was diagnosed with lung adenocarcinoma with multiple pulmonary metastases and malignant pleural effusion. Pathology results indicated positive TTF-1 status, while *EGFR*, *ALK*, *ROS1*, and *BRAF* V600E tests were negative. Subsequent in-house NGS liquid biopsy testing revealed an *EGFR* C797S mutation. The patient showed poor response to chemotherapy. The patient underwent a liquid biopsy that detected a *KRAS* G12C mutation. Based on these results, she received the novel *KRAS* G12C inhibitor Sotorasib through a clinical trial, which extended her survival by 7-8 months.

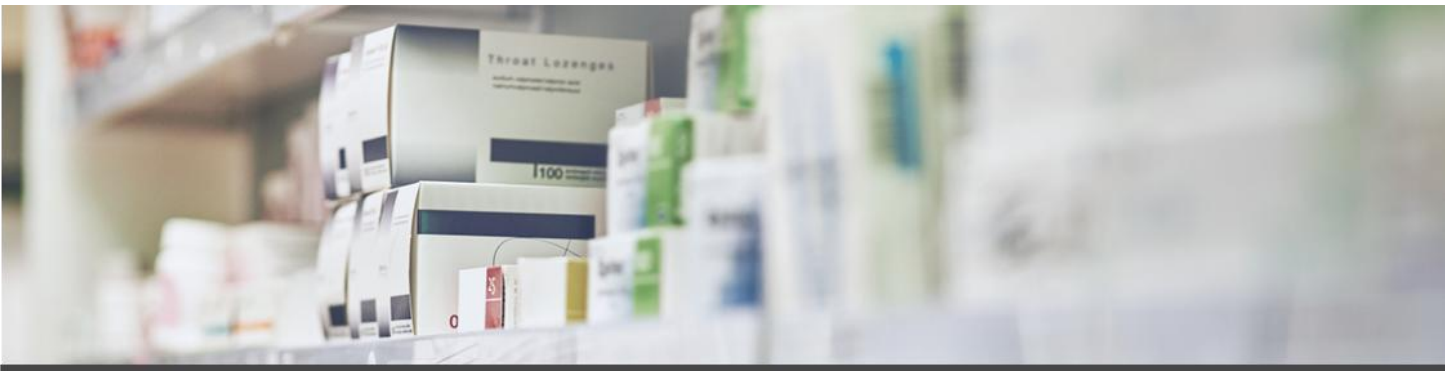
Current Gaps in NHIA Reimbursement for NGS Liquid Biopsy Concerning Targeted Drugs and Testing

Liquid biopsy has demonstrated considerable clinical benefits, yet current NHIA reimbursement policies do not cover liquid biopsy testing or the associated medications. NHIA has planned a phased relaxation to allow gene testing using liquid biopsy. However, such testing is not yet included in the current reimbursement scope for genetic testing. Additionally, the applicability of cancer drugs must be considered—specifically whether their indications include companion diagnostics performed via liquid biopsy. For example, in the case of NSCLC, drug reimbursement applications must be accompanied by pathology or cytology reports confirming lung adenocarcinoma or NSCLC, along with EGFR gene testing results obtained exclusively from tissue biopsy samples. These results must be obtained either via an in vitro diagnostic (IVD) test approved by the Ministry of Health and Welfare for companion diagnostics or through certified laboratories under the Ministry's approved LDTs implementation plan, adhering to specified technical criteria that meet analytical targets. It is crucial to accurately interpret the results and select the appropriate treatment based on liquid biopsy.

Additionally, NHIA reimbursement for NGS in solid tumors restricts testing to tumor pathology tissue, except for Germline BRCA1/2 testing, which uses blood samples. NHI NGS reimbursement applies to 14 major solid tumor types and 5 hematologic tumor categories, reimbursement for NGS tests relies exclusively on tumor tissue biopsy reports from patients.

Experts' Recommendations for Liquid Biopsy Reimbursement Criteria

Liquid biopsy is particularly valuable when tumor sampling is challenging, tissue biopsy risk is high, tissue samples are insufficient, or drug-resistance mutations need to be assessed post-treatment. Moreover, liquid biopsy can detect cases missed by tissue samples, enabling patients to begin treatment earlier and highlighting its value in cancer care.



> Liquid biopsy can serve as a basis for diagnosing driver genes in lung cancer, especially when patient tissue samples are insufficient. It is recommended that all patients with stage III or IV, or recurrent non-small cell lung cancer, should have the opportunity to undergo liquid biopsy at least once. If lifetime coverage for liquid biopsy is provided, it is believed that both doctors and patients will value the opportunity for this testing more. It is hoped that Taiwan Nation Health Insurance will cover liquid biopsy for use in companion diagnostics for targeted cancer therapies.
>
> Dr. Bin-Chi Liao, Physician in the Oncology Medical Department at NTU Hospital

Experts suggest that whether reimbursing targeted drugs based on liquid biopsy evidence or covering NGS testing, liquid biopsy represents a value-driven investment with significant clinical and economic benefits. Studies in Canada, the UK, Australia, the US, and Germany have shown potential in liquid biopsy for early diagnosis, fewer biopsies, detecting more actionable genes, and minimizing overtreatment. This is especially true for patients with difficult tissue sampling, where liquid biopsy enhances efficacy while reducing costs overall.

Reimbursement of Corresponding Targeted Drugs

Experts propose that both tissue and liquid biopsy testing reports are applicable to TFDA label indications, the drug reimbursement should align with these labels to prevent undue financial burdens on patients. Given the alignment of liquid biopsy with public health improvement and mortality reduction goals, supported by research and global policies, strengthening drug reimbursement rationality is crucial. If potential financial impact on national healthcare budgets is excessive, the government should consider cover it by cancer drug fund.

Reimbursement for NGS Liquid Biopsy Testing

Experts suggest expanding reimbursement for NGS liquid biopsy for major cancers, including stage three and four NSCLC patients, incorporating T790M mutation. Other mutations with corresponding drugs, such as *KRAS*, *MET*, and *RET*, could be further discussed. Reimbursement should also cover patients with metastasis and recurrence, as well as major cancers like colorectal and breast cancer, especially under worsening tumor conditions or high biopsy risks. Evidence for sampling difficulties could rely on advice from Multidisciplinary Molecular Tumor Boards (MTB).

Overall Considerations

To fundamentally address unmet needs in cancer precision therapeutics, patients should be granted a once-in-a-lifetime reimbursement for either tissue or liquid biopsy. Patients should have equal access to diagnostic testing and medications.

> Liquid Biopsy has been in use for over fifteen years in many advanced countries, and numerous nations have already incorporated Liquid Biopsy into their national or private insurance systems. In the United States, many private insurers routinely reimburse it. This trend indicates that Liquid Biopsy is likely to see even wider adoption globally. Utilizing Liquid Biopsy will enhance the completeness of overall cancer care and contribute to progress in medical technology. As members of the medical community, we must consider how to apply high technology to benefit patients; otherwise, Taiwan's medical technology development may fall significantly behind that of other advanced nations.
>
> Dr. James Chih-Hsin Yang, Chairman of Taiwan Association for the Study of Lung Cancer

Appendix

List of Cancer Targeted Drugs Requiring Companion Genetic Diagnostics

Drug	Indication	TFDA Label Guidelines	National Health Insurance (NHIA) Reimbursement rule
Osimertinib	NSCLC	Patients are selected based on the presence of *EGFR* mutations in tumor or plasma samples	Pathology or cytology report confirming the diagnosis of lung adenocarcinoma or non-small cell lung cancer, along with an EGFR gene test result report based on tissue biopsy only.
Tepotinib	NSCLC	Patients are selected based on the presence of *MET* exon 14 skipping mutation in plasma or tumor tissue	Pathology or cytology report confirming NSCLC, while test report confirming a MET exon 14 skipping mutation based on tissue biopsy only.
Afatinib	NSCLC	Confirmed as *EGFR* mutation-positive NSCLC, no restriction for sample type	Must include a pathology or cytology report confirming the lung adenocarcinoma diagnosis, as well as an EGFR-TK gene mutation test report based on tissue biopsy only.
Olaparib	Newly diagnosed advanced ovarian, fallopian tube, or primary peritoneal cancer	Both germline or somatic BRCA1/2 mutation test	A germline or somatic BRCA1/2 mutation test report or HRD-positive report is required
	Triple-negative breast cancer	Germline BRCA1/2 mutation test	Documentation that ER, PR, and HER2 are all negative is required, as well as a germline BRCA1/2 mutation test report
	Metastatic castration-resistant prostate cancer (mCRPC)	Both germline or somatic BRCA1/2 mutation test	A germline or somatic BRCA1/2 mutation test report is required
Niraparib	Ovarian, fallopian tube, or primary peritoneal cancer	No specific test method mandated in label	A germline or somatic BRCA1/2 mutation test report is required.
Talazoparib	Triple-negative breast cancer	Should be selected based on the presence of a germline BRCA mutation	Documentation that ER, PR, and HER2 are all negative is required, as well as a germline BRCA1/2 mutation test report
Cetuximab and Panitumumab	Metastatic colorectal cancer (mCRC)	Determined by an experienced laboratory using validated methods to detect mutations in KRAS exon 2, 3, 4 and NRAS exon 2, 3, 4	A comprehensive all-RAS mutation analysis test report is required, based exclusively on tissue biopsy specimens.
Pemigatinib	Cholangiocarcinoma	Select patients that has FGFR2 fusions or rearrangements	A genetic test report confirming that the tumor tissue harbors an FGFR2 fusion or rearrangement must be submitted
Larotrectinib	Solid tumors that have an *NTRK* gene fusion	An appropriate test method must confirm that the tumor tissue itself harbors an NTRK gene fusion (for example, by NGS).	For first-time applications, an NTRK gene fusion test report must be provided, performed by a certified laboratory.

Source: NHIA and TFDA ; Data compiled by PwC Taiwan (April 2025)

Glossary of Terms

ctDNA：circulating tumor DNA

cfDNA：cell-free DNA，cfDNA)

EGFR：Epidermal growth factor receptor

FDA：Food and Drug Administration

HTA：Health Technology Assessment

ICER：Incremental Cost-Effectiveness Ratio

INESSS：l'Institut national d'excellence en santé et en services sociaux

IVD：In Vitro Diagnostic Device

LDTs：Laboratory Developed Tests and Services

MCED：Multi-cancer early detection

MRD：Minimal residual disease

NGS：Next-generation sequencing

NHS：National Health Service

NSCLC：Non-small cell lung cancer

OECD：Organisation for Economic Cooperation and Development

ORR：Objective response rate, ORR

OS：Overall Survival

PFS：Progression Free Survival

QALY：Quality-Adjusted Life Year

TFDA：Taiwan Food and Drug Administration

TKI：Tyrosine kinase inhibitor

WHO：World Health Organizatio

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