Strategies to Address the Clinical Practice Gaps Affecting the Implementation of Personalized Medicine in Cancer Care

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INTRODUCTION

Biomarker testing–based personalized medicine strategies can improve outcomes for patients with cancer at the individual and population levels.[1,2] The identification of actionable molecular biomarkers and treatment with matched targeted therapies have been associated with favorable outcomes for individual patients. However, many patients with cancer do not undergo biomarker testing and do not receive targeted therapies.[3-5] Ensuring that all patients with cancer have access to and receive biomarker-driven care remains a challenge.

The factors contributing to this challenge and the gaps in clinical practice have been quantified in >38,000 newly diagnosed patients (United States) with advanced non–small cell lung cancer (aNSCLC), as part of an analysis of data from Diaceutics' multisource database, which includes commercial and Medicare claims and laboratory data.[6] For every 1,000 patients in the study cohort, 49.7% were lost to precision oncology because of factors associated with obtaining biomarker test results. Of the remaining patients who did receive results from a biomarker test, 29.2% did not receive appropriate targeted treatments. Overall, 64.4% of potentially eligible patients did not benefit from precision oncology therapies appropriate for aNSCLC. Gaps were noted at seven steps along the precision oncology pathway: tumor biopsy referral, biospecimen collection, evaluation of biospecimens, biomarker test ordering, biomarker test performance, test result reporting, and treatment selection.[6] These findings may reflect similar gaps in other tumor types, although the proportion of patients for each step in the process may vary by patient population and institution. We used the aforementioned published data to describe the gaps in clinical practice and illustrate the relative importance of each potential gap. Herein, we discuss and evaluate every step in the process to illustrate where gaps may be and to identify solutions that would help promote more consistent clinical practices (Table 1).

CLINICAL PRACTICE GAPS

Biopsy Referral

Overall, 6.6% of patients were not referred for a tumor biopsy, owing in part to going through the emergency room rather than an oncologist (which is common in low-income communities). Measures should be implemented to deliver equitable biopsy referral for all patients, regardless of their socioeconomic status. Many patients may decline treatment or die before a tumor biopsy can be performed. However, for high-risk biopsies or in the absence of tissue biopsies, liquid biopsy assays should be performed.[7]

Biospecimen Collection

In 14.5% of patients, the amount of tumor cells in the biopsy specimen was insufficient. Biospecimen samples with tumor content insufficiency may not be sent for testing or test results may not be reported. Additionally, variability in preanalytical factors may affect tissue quality. Surgical resections usually result in sufficient tumor tissue, whereas fine-needle biopsy, and to a lesser extent core needle biopsy, can lead to a quantity not sufficient (QNS) result. It is imperative to adhere to best practices and involve an experienced proceduralist and a pathologist for rapid on-site tissue evaluation. If the biospecimen collection is unsuccessful on the first attempt, a second tissue biopsy and/or a liquid biopsy should be offered where possible.

TABLE 1. Key Strategies to Address Clinical Practice Gaps for Advanced Non–Small Cell Lung Cancer, and the Percentage of Patients Who Could Potentially Benefit From Improved Delivery at Each Step of the Precision Oncology Pathway

Clinical Practice Gap	Patient Attrition	Potential Solution Strategies
Step 1: Biopsy referral—initial tissue or blood biopsy was never performed	66/1,000 (6.6%)	Assure equitable access to standards of care regarding biopsy referral Perform liquid biopsy where applicable
Step 2: Biospecimen collection—insufficient tissue or tumor cell content inhibited biomarker testing and its accuracy	136/934 (14.6%)	Adhere to biopsy collection best practices Involve pathologists at the biopsy collection stage Comply with recognized tissue handling preanalytic processing guidelines such as the CAP checklist
Step 3: Biospecimen evaluation/pathology—biospecimen tumor cell content was overestimated, inhibiting biomarker testing and/or its accuracy	14/798 (1.7%)	Develop a standard definition of tumor cell content Implement standard operating procedures and tumor cell content quality assurance processes during the diagnostic workup Use modern error-corrected platforms for NGS-based testing Use microdissection techniques for cases with expected borderline tumor cell content Ensure reimbursement for tumor cell content assessment services Upfront cotesting of both liquid (ctDNA) and tissue biopsies at the time of diagnosis when possible
Step 4: Biomarker test ordering—appropriate testing was not ordered, or treatment began before testing was ordered	142/784 (18.1%)	Implement multiplex NGS-based testing where possible Harmonize clinical guidelines Provide continued education of health care providers and raise awareness of the value of testing and of new validated biomarker tests as they become available Standardize and incentivize molecular testing as part of the initial tumor diagnostic procedures and when considering treatment change decisions Implement reflexive or routine biomarker test ordering practices Accelerate and track the transfer and availability of ordering and molecular profiling data from the time of tumor biopsy/blood collection Ensure appropriate and consistent coverage and reimbursement of biomarker testing; ensure staff is aware of coverage policies and can seamlessly handle any previous authorization requests Ensure physician confidence in quality sample processing Engage and inform the patient
Step 5: Biomarker testing performance—biomarker testing provided inconclusive or false-negative results	118/642(18.4%)	Follow good laboratory practices Ensure routine training/proficiency of staff Engage in maintenance of instruments at regular intervals as required by manufacturers and/or regulatory bodies Mandate institutional quality control measures Optimize protocols for minimal hands-on time and, where possible, automation and error-proof engineering Ensure tissue handling preanalytic processes meet key standards such as those laid out in CAP guidelines Use consistent, routine processes for rebiopsy where applicable Use error-corrected DNA and RNA platforms for NGS-based testing
Step 6: Test result reporting—as a result of turnaround time delays, treatment was initiated without consideration of test results	21/524 (4.0%)	Review electronic pathology reports as early in care as possible and order tumor molecular analysis at the time of diagnosis Simultaneous genetic and PD-L1 test ordering and processing Optimize interdepartmental handoffs and track sample processing timelines Optimize sample shipping timelines Review and reconsider treatment decisions when biomarker testing results become available Schedule blood collection for ctDNA analysis along with tissue biopsy at the time of diagnosis and at the time of disease progression
Step 7: Treatment decision—targeted treatment was not selected despite positive test results	147/503 (29.2%)	Improve testing result report formats Incentivize genetic counseling services Integrate biomarker test results into EHRs Improve clinical decision support systems Facilitate equitable access to targeted treatments Embrace value-based payer coverage and reimbursement policies

NOTE. The study had some limitations. The results were based on population-level data (may differ across cohorts) and practice gap attrition levels for some variables were estimated from published data (with variable downstream effects, depending on institutional practices/tumor types). Notably, the number of patients each of these strategies could help can be estimated on the basis of the relative impact each clinical practice gap has been shown to have on the delivery of precision oncology in aNSCLC. The suggested solutions represent optimal scenarios for addressing practice gaps. The implementation of solution strategies would likely need to take into consideration the financial and associated costs *v* benefits.
Abbreviations: aNSCLC, advanced non–small cell lung cancer; CAP, College of American Pathologists; EHRs, electronic health records; NGS, next-generation sequencing.

Additionally, laboratories should perform comprehensive biomarker testing. The College of American Pathologists (CAP) has developed guidelines for collecting and handling biopsy specimens.[8] Suboptimal processing can alter morphologic, immunohistochemical, and molecular characteristics. Preanalytic factors may affect the quality of biospecimens and include cold ischemia time, fixation conditions, tissue processing and storage, and data documentation.[9] CAP published recommendations for controlling and documenting essential preanalytical factors regarding the fitness of specimens for biomarker testing, the quality and reliability of analyses, and the quality of data output affecting treatment selection decisions.[10] The personalized medicine community must promote awareness of and compliance with these guidelines.

Biospecimen Evaluation/Pathology

In 1.7% of patients, the tumor cell content in biopsy samples had been overestimated, leading to false-negative results. No gold standard for assessing tumor cell content exists. In most laboratories, board-certified pathologists provide an estimate based on a hematoxylin and eosin–stained slide from formalin-fixed, paraffin-embedded tissue. However, most laboratories spend <3 minutes per sample estimating tumor cell content, and significant discrepancies in estimates between pathologists exist.[11] To address this issue, the CAP Molecular Pathology Committee developed recommendations outlining a definition of tumor cell content, standard operating procedures, and a quality assurance process to ensure compliance with best practices. Ensuring that the pathologist's assessment of tumor cell content happens during the diagnostic workup and that the evaluation process is appropriately reimbursed can improve the workflow.

Microdissection techniques for cases with borderline tumor cell content may obviate the impact of variability in pathologists' assessments. The minimum tumor cell content (20%)—based on the sensitivity of next-generation sequencing (NGS) assays to detect variants and subclonal and/or heterozygous alterations[12]—may be decreased using modern error-corrected NGS-based platforms and by avoiding Sanger sequencing assays. To limit the impact of overestimation of tumor cell content, simultaneous liquid and tissue biopsy analyses at the time of diagnosis should be considered.[13]

Biomarker Test Ordering

Biomarker tests were never ordered, or treatment was started before ordering testing, in 18.1% of patients. Although ordering individual tests for all relevant biomarkers is a possibility, the use of multiplex NGS-based testing is recommended by several associations, including the National Comprehensive Cancer Network,[14] ASCO, and CAP,[15] and allows tumor mutational burden (TMB) status assessment (an immunotherapy marker). To ensure that biomarker tests are ordered, clinical guidelines should be harmonized, and best practices should be clear and applied consistently. Institutional barriers and physician perceptions of access challenges may also contribute to suboptimal testing rates. Policies/routine practices should incentivize and accelerate test ordering and result acquisition. These can include grading physicians on ordering/using biomarker testing, tying reflexive biomarker test ordering to initial diagnosis, sharing best practices across sites to standardize the integration of biomarker test results into patient records, and increasing staff and information transfer capacity.

Limited funding, tissue unavailability, and poor sample quality are barriers to the routine testing of patients with lung cancer. NGS testing coverage policies vary among payers by test (targeted *v* comprehensive) or specimen type (tissue *v* plasma).[16] Unclear coverage and reimbursement policies may adversely affect physician likelihood to order multiplex testing. Medicare and Medicaid claims data suggest that testing is suboptimal (single-gene testing for most patients), limiting comprehensive testing and consuming limited biopsy tissue. Institutional practices should be implemented for routine test ordering and for navigating patient health plan coverage, reimbursement, and approval of previous authorization requests.

Biomarker Testing Performance

Overall, 14.5% had inconclusive (technical failures, 7.5%; QNS results, 5.8%; and inconclusive data, 1.1%) or false-negative (3.9%) laboratory results (total, 18.4%). To minimize expected failures, laboratories should follow good laboratory practices, ensure routine training of staff, and perform instrument maintenance at regular intervals as required by manufacturers and regulations such as the Clinical Laboratory Improvement Amendments at the Centers for Medicare and Medicaid Services (CMS). Quality assurance programs such as mandated institutional quality control measures or proficiency testing offered by CAP help ensure the quality of test results and can identify problems before catastrophic batch failures occur. Manufacturers also play a role in minimizing technical failures by decreasing complexity, optimizing protocols for minimal hands-on time, and using automation and error-proof engineering when designing platforms for clinical use.

QNS samples are often identified in preanalytical testing. To ensure DNA/RNA quality and quantity (essential elements for accurate test result), tissue sample processing should meet key standards, including fixation within a reasonable time frame after resection/biopsy to avoid ischemia and degradation of nucleic acids, avoidance of harsh decalcification steps before nucleic acid testing, and use of samples collected closest to the time of clinical decisions. False-negative results are associated with the sensitivity of an assay. At lower tumor input, a more sensitive assay detects lower allele frequency

variants. Therefore, multiplexed and sensitive assays, such as error-corrected DNA and RNA NGS-based platforms, would minimize false-negative results, optimizing tissue utilization.

Test Result Reporting

In 4% of patients, treatment was initiated before testing results were interpreted by the treating physician. The required steps for molecular testing include scheduling a tumor biopsy, processing and sending the tissue to a laboratory, performing the molecular analysis, generating and sending the report to the treating oncologist, and receiving, interpreting, and acting on the results. Reported turnaround times for molecular tests ordered for patients with aNSCLC were ≥1-3 weeks depending on the test (NGS [solid or plasma] or other). Waiting for ≥3 weeks prompted oncologists to initiate nontargeted treatment (particularly for patients with symptomatic or rapidly progressing disease) or not to order molecular tests.[17] However, treatment should be optimized based upon availability of test results indicating targetable alterations.

As rapid sample processing is necessary to accelerate the availability of results, molecular profiling (eg, NGS, PD-L1 testing) should be ordered at the time of pathologic diagnosis and reimbursement policies (including at CMS) should be modified to allow for physician payments related to simultaneous initial diagnosis, staging, and biomarker testing. Although most laboratories have implemented processes to ensure efficient processing of samples, efforts should focus on shortening of sample shipping timelines, optimization of interdepartmental handoffs, and quality assurance. Sample tracking by each team member that includes quality checks may accelerate molecular testing.

Turnaround times may improve with simultaneous ordering of tissue and liquid biopsy DNA/RNA analysis. Cell-free analysis (turnaround time, 7-19 days)[18] should be ordered for all patients with multiple tumor actionable biomarkers, although tumor tissue analysis remains necessary for immune markers such as PD-L1 expression and microsatellite instability and TMB statuses.

Treatment Decision

Overall, 29.2% of patients did not receive the appropriate matched targeted treatment. Of these patients, 18.5% did not receive any treatment (presumably owing to mortality, hospice/palliative care, or decision to forego therapy) and 81.5% received treatment not selected using biomarker testing results. Suboptimal therapeutic management may be associated with inaccurate interpretation of test results. In a recent report, 83% of physicians were aware of at least one instance of genetic test misinterpretation, owing to difficulty in classifying actionable variants, unclear reporting, a physician's unfamiliarity with genetic concepts/counseling, and suboptimal communication among providers. These data emphasize the need for clear and concise formatting of molecular testing results that are easily interpretable. Reporting formats should be reviewed by diagnostic organizations, physicians, laboratory leaders, genetic counselors, biomarker experts, and clinical interpretation organizations (eg, CAP, Association of Molecular Pathologists). Interpretation of results should involve experts in genomic variants analysis. Genetic counselors may help discuss treatment decision making with patients. Test end points, reporting, and variants of unknown significance should be continuously updated for accurate interpretation of variants (benign or pathogenic).

Integrating biomarker data into electronic health records (EHRs) can facilitate precision oncology care. However, practical challenges include managing complex test results from multiple sources, limited EHR capacity to store big data, and privacy/security concerns specific to genetic testing information. Thus, successful integration of biomarkers will require updated EHR system management processes and policies. Global ongoing projects may facilitate the seamless uptake of biomarker testing information into the EHR. Stakeholders should help execute the relevant policies.

Improving clinical decision support (CDS) systems can facilitate biomarker reporting to physicians, ensuring accurate interpretation of results. Many oncology care systems have molecular tumor boards (MTBs), which are panels of experts who review patients with complex biomarker results and match them with targeted therapy. The implementation of MTB CDS should be expanded broadly throughout the health care system.[19] Electronic CDS tools can sort through biomarker data and provide clinicians with actionable insights. As poorly designed/implemented CDS tools may cause alarm fatigue and diagnostic errors, this information should be provided in a user-friendly manner to physicians, including careful incorporation of hard stops (requiring response before moving forward) to avoid possible harms related to continuous user involvement and frustration. Physicians should be involved in all aspects of the design, pretesting, and implementation of CDS tools and related updates to clinical practice standards.

Addressing the barriers to accessing targeted treatments, including continuous education of providers and insurers about actionable biomarkers and new targeted therapies, will help overcome inertia.[20] Policies to ensure equitable deployment of personalized medicine technologies to benefit underserved patients should be implemented. Payers must ensure that patients can access precision oncology technologies/services. By embracing evidence-based strategies in policies, CMS can encourage consistent utilization of personalized medicine, influencing clearer and more consistent coverage and reimbursement policies for all payers.

In conclusion, our analysis indicates the need to develop process reforms and strategies to improve the clinical practice of precision oncology. Innovative technologies provide opportunities to improve the safety and efficacy of oncology

treatments. However, biomedical discoveries may be outpacing our health system's ability to effectively implement them in clinical practice. Therefore, efforts should focus on, and resources should be allocated to, translating novel discoveries into improved precision oncology practices. We propose solutions to improve population-level outcomes and systemic efficiencies, calling for a multistakeholder approach to improve the clinical implementation of precision oncology. Updated policies, clinical practice reforms, and strategies designed to encourage the delivery of personalized medicine are needed. This article is a call to action, providing broad-based strategies to overcome the various precision oncology practice gaps. Stakeholders should contribute to developing these strategies to promote and implement necessary changes in practice. Addressing these gaps will optimize the delivery of precision oncology, leading to improved clinical outcomes and more efficient health systems.

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REFERENCES

1. Centers for Disease Control and Prevention: Precision health: Improving health for each of us and all of us. 2022
2. Tsimberidou AM, Fountzilas E, Nikanjam M, et al: Review of precision cancer medicine: Evolution of the treatment paradigm. Cancer Treat Rev 86:102019, 2020
3. Steuten L, Goulart B, Meropol NJ, et al: Cost effectiveness of multigene panel sequencing for patients with advanced non-small-cell lung cancer. JCO Clin Cancer Inform 10.1200/CCI.19.00002
4. Presley CJ, Tang D, Soulos PR, et al: Association of broad-based genomic sequencing with survival among patients with advanced non-small cell lung cancer in the community oncology setting. JAMA 320:469-477, 2018
5. Vashistha V, Armstrong J, Winski D, et al: Barriers to prescribing targeted therapies for patients with NSCLC with highly actionable gene variants in the veterans affairs National precision oncology program. JCO Oncol Pract 17:e1012-e1020, 2021
6. Sadik H, Pritchard D, Keeling DM, et al: Impact of clinical practice gaps on the implementation of personalized medicine in advanced non-small-cell lung cancer. JCO Precis Oncol 10.1200/PO.22.00246
7. Rolfo C, Mack P, Scagliotti GV, et al: Liquid biopsy for advanced NSCLC: A Consensus Statement from the International Association for the Study of Lung Cancer. J Thorac Oncol 16:1647-1662, 2021
8. College of American Pathologists: Accreditation Checklists. https://www.cap.org/laboratory-improvement/accreditation/accreditation-checklists
9. Mino-Kenudson M: Immunohistochemistry for predictive biomarkers in non-small cell lung cancer. Transl Lung Cancer Res 6:570-587, 2017
10. Compton CC, Robb JA, Anderson MW, et al: Preanalytics and precision pathology: Pathology practices to ensure molecular integrity of cancer patient biospecimens for precision medicine. Arch Pathol Lab Med 143:1346-1363, 2019
11. Smits AJ, Kummer JA, de Bruin PC, et al: The estimation of tumor cell percentage for molecular testing by pathologists is not accurate. Mod Pathol 27:168-174, 2014
12. Mikubo M, Seto K, Kitamura A, et al: Calculating the tumor nuclei content for comprehensive cancer panel testing. J Thorac Oncol 15:130-137, 2020
13. Aggarwal C, Marmarelis ME, Hwang W-T, et al: Association of comprehensive molecular genotyping and overall survival in patients with advanced non-squamous non-small cell lung cancer. J Clin Oncol 40, 2022 (16_suppl; abstr 9022)
14. National Comprehensive Cancer Network: NCCN Guidelines: Treatment by Cancer Type. 2022
15. College of American Pathologists: Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With TKI. 2018
16. Network LFaACSCA: Landscape Analysis: Payer Coverage Policies of Tumor Biomarker Testing. 2023
17. Mileham KF, Schenkel C, Bruinooge SS, et al: Defining comprehensive biomarker-related testing and treatment practices for advanced non-small-cell lung cancer: Results of a survey of U.S. oncologists. Cancer Med 11:530-538, 2022

18. Lockwood CM, Borsu L, Cankovic M, et al: Recommendations for cell-free DNA assay validations: A Joint Consensus recommendation of the Association for Molecular Pathology and College of American Pathologists. J Mol Diagn 25:876-897, 2023
19. Tsimberidou AM, Kahle M, Vo HH, et al: Molecular tumour boards—Current and future considerations for precision oncology. Nat Rev Clin Oncol 20:843-863, 2023
20. Tsimberidou AM, Elkin S, Dumanois R, et al: Clinical and economic value of genetic sequencing for personalized therapy in non-small-cell lung cancer. Clin Lung Cancer 21:477-481, 2020

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