The Advanced Practitioner's Role in the Rapidly Evolving Landscape of Precision Medicine

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Abstract

The advent of precision medicine targeting oncogenic mutations and other alterations has led to a paradigm shift in the treatment of many solid tumors and hematologic malignancies. For many of these agents, predictive biomarker testing is necessary to determine the presence of such alterations in order to select patients who are most likely to respond, and to avoid the use of ineffective and potentially harmful alternative therapy. Recent technological advances such as next-generation sequencing have facilitated the identification of targetable biomarkers in patients with cancer and thus help inform treatment decisions. Moreover, new molecular-guided therapies and associated predictive biomarkers continue to be discovered. For some cancer therapeutics, regulatory approval requires the use of a companion diagnostic to ensure proper patient selection. Advanced practitioners therefore need to be aware of current biomarker testing guidelines regarding who should be tested, how and when to test, and how these results can guide treatment decisions using molecular-based therapies. They should also recognize and address potential barriers and disparities in biomarker testing to ensure equitable care for all patients, and assist in educating patients and colleagues alike on the importance of testing and integration into clinical practice to enhance outcomes.

Recent advances in the use of targeted therapy and immunotherapy have radically altered the treatment paradigm for many solid tumors and hematologic malignancies. This has occurred in part due to the discovery of oncogenic somatic mutations and other alterations in antitumor immune responses that have enabled the clinical development of therapeutics targeting these molecular changes. In many cases, predictive biomarkers based on these alterations are used to identify individuals most likely to benefit from such treatments. Clinically verified predictive biomarkers, such as

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programmed cell death ligand 1 (PD-L1) expression, are now routinely used to select patients who are eligible for treatment with certain immune checkpoint inhibitors (ICIs). Other potential predictive biomarkers being investigated include tumor mutational burden, neoantigens, circulating tumor cells or tumor DNA, circulating tumor proteins, genomic and epigenetic signatures, and the immune microenvironment (Mino-Kenudson et al., 2022; Wang et al., 2021). New advances in technology, including rapid genomic sequencing, artificial intelligence, and the use of "-omics," are also helping to identify novel biomarkers, leading to improved personalized medicine for patients with cancer (Lee et al., 2019).

Numerous oncologic targeted agents and immunotherapeutics have been approved to date, and this is expected to further increase as new products are brought to market. Many rely on the presence of specific molecular alterations in tumors, so testing for their corresponding target biomarkers is required as noted in the product labeling (US Food and Drug Administration [FDA], 2023). With the rapid growth in the number of precision medicines available, the number of patients eligible for such treatments has also risen. A recent review of approved targeted agents across 18 cancer types found that the proportion of US patients eligible for genome-targeted agents climbed from 8.8% in 2006 to 13.6% by 2020 (Haslam et al., 2021). An earlier review revealed an even greater rise in the use of approved ICIs, from 1.5% in 2011 to 43.6% in 2018 (Haslam & Prasad, 2019). One study using next-generation sequencing (NGS) found that over 70% of patients with cancer had at least one reported mutation, with alterations in potentially actionable genes detected in 30% of these cases (Boland et al., 2015). These and similar results have led to the routine use of NGS to screen patients for actionable alterations that could guide the selection of therapy.

Advanced practitioners, including oncology pharmacists, nurse practitioners, clinical nurse specialists, and physician assistants, are uniquely positioned to aid in biomarker testing and the clinical integration of such results. These roles are expected to take on increasing importance as more agents are approved and the rate of testing continues to grow. Advanced practitioners are challenged to stay current on the rapidly increasing number and variety of cancer biomarkers, as well as updates to treatment guidelines, in order to provide evidence-based care that relies on biomarker data. This article highlights some of the key issues related to the use of predictive biomarkers, particularly those relevant for oncology advanced practitioners, and ways in which they can help advance testing and clinical integration of results to enhance patient outcomes.

BIOMARKER TESTING GUIDELINES AND COMPANION DIAGNOSTICS

Biomarkers and biomarker testing guidelines vary considerably across tumor types. This is due in part to the fact that specific biomarkers have clinically significant predictive value in specific malignancies and in certain stages of disease. What functions as a predictive biomarker for one malignancy and molecular therapy may not hold true for others. Tumor expression of PD-L1 is in some cases required for the use of pembrolizumab (Keytruda) in patients with advanced non–small cell lung cancer (NSCLC), for example, but this is not necessary for this agent to be used in locally advanced or metastatic urothelial carcinoma (Merck & Co., Inc., 2023). Clinicians must therefore refer to tumor-specific guidelines, which may also differ by country, methodology, cut-off value, interpretation of results, and how biomarker data for each inform therapeutic options (Bartley et al., 2022; Henry et al., 2022; Kalemkerian et al., 2018; Yilmaz et al., 2022).

The National Comprehensive Cancer Network (NCCN) provides perhaps the most complete collection of tumor-specific guidelines. Current evidence-based lung cancer guidelines suggest, for instance, that all patients with advanced NSCLC undergo broad molecular testing, ideally prior to the initiation of therapy (Kalemkerian et al., 2018; NCCN, 2023a). Yet molecular profiling is not indicated for patients with small cell lung cancer, except those who are never-smokers or light smokers with extensive-stage disease (NCCN, 2023b). The lack of uniformity among tumor types and targeted agents presents challenges to advanced practitioners regarding the use of biomarker-guided precision medicine, so consultation with current treatment guidelines and professional recommendations for specific tumor types is essential.

Most targeted therapies and many ICIs require the use of an FDA-approved predictive companion diagnostic to confirm the presence of genomic alterations or expression of a target protein and thus ensure their appropriate use. While the term "companion diagnostic" may be unfamiliar, the concept is not new. Clinicians have been ensuring that breast cancer tumors are estrogen receptor (ER) positive prior to endocrine therapy for decades now. The MET inhibitor capmatinib (Tabrecta), for example, was approved for the treatment of patients with metastatic NSCLC bearing a *MET* exon 14 skipping mutation and thus requires confirmation of the presence of this alteration using a companion diagnostic (Jørgensen, 2021).

As of January 2022, 47 oncology therapeutic–companion diagnostic combinations had been FDA approved, and more have followed (Cooper & Chen, 2022; US Food and Drug Administration, 2023). In two thirds of these cases, drug–companion diagnostic combinations were approved under an FDA expedited program. The rapidly growing number and variety of companion diagnostics creates a challenge for advanced practitioners who must know which companion diagnostic to use for biomarker assessment in specific malignancies, understand differences among these tests, including inter-assay variability and cut-offs, and be able to correctly interpret and apply results clinically to select the optimal therapy (Doroshow et al., 2021; Twomey & Zhang, 2021).

MOLECULAR TUMOR BOARDS

Multidisciplinary molecular tumor boards (MTBs) or precision medicine clinics are increasingly being used to assess biomarker and genomic data, and to make treatment recommendations based on alterations detected and current treatment guidelines. Molecular tumor boards are designed to support the oncology team by identifying patients who are eligible for biomarker testing; interpreting results; recommending targeted agents based on test results and the strength of supporting data; ensuring the availability of targeted therapies; and suggesting clinical trials when appropriate (Arnall et al., 2019). Molecular tumor boards can address any barriers to molecular testing and precision medicine, thus increasing testing rates and their utility in patient care (Huang et al., 2021). They also may refer patients and family members for genetic counseling and further testing if a germline mutation is suspected or detected. Molecular tumor boards typically comprise medical oncologists, surgical oncologists, pathologists, basic scientists, pharmacists, clinical nurses, physician assistants, and genetic counselors. Some authors have recommended that patients also be included to increase their engagement and knowledge of biomarker testing (Cannon et al., 2022). Several groups have developed precision medicine practice models that include MTBs, which involve oncology pharmacists, physician assistants, and nurses, with the goal of improving patient care (Walko et al., 2016).

A systematic review of studies involving previously treated patients with various types of solid tumors indicated that the use of MTBs may improve clinical outcomes (Larson et al., 2021). Similarly, in a phase II study, MTB-recommended therapy for advanced cancers improved progression-free survival in most patients (Miller et al., 2022). For patients with NSCLC, the use of MTBs was shown to improve survival in both academic and rural treatment care settings (Huang et al., 2021). Larger, prospective clinical trials are needed to confirm these benefits.

ORDERING BIOMARKER TESTING

Providers should understand when biomarker testing should be ordered during a patient's diagnostic assessment. Guidelines recommend upfront testing for certain advanced malignancies to better inform diagnosis, prognosis, and early assessment of targeted therapeutic options (Henry et al., 2022; NCCN, 2022a, 2022b, 2023c). Clinicians must also recognize what type of assay is indicated for a specific tumor type (e.g., NGS, single-gene assay, immunohistochemistry) and preferred tissue (primary tumor or metastasis, solid or liquid biopsy). They should recognize somatic and germline mutations that may guide treatment decisions, and inherited mutations that could affect future cancer risk for patients or other family members and suggest the need for genetic counseling.

There is a need for rapid biomarker testing and acquisition of results since delays can adversely

affect patient care. A 2020 American Society of Clinical Oncology survey of US oncologists found that more than one third waited 3 or more weeks to receive biomarker testing results, which in some cases led to the initiation of potentially less effective non-targeted therapy in the interim (Mileham et al., 2022). Nonadherence to guidelines may also negatively impact patient outcomes. A retrospective study of patients with advanced NSCLC reported that those who were adherent to NCCN biomarker testing guidelines had a significantly lower risk of mortality and treatment discontinuation with first-line therapy compared with nonadherent patients (John et al., 2021). Such results demonstrate the importance of rapid biomarker testing and adherence to guideline recommendations, and the potential impact on outcomes.

Advanced practitioners should also recognize when it may not be appropriate to order molecular testing, particularly when results are unlikely to impact patient outcomes. Examples include patients with rapidly progressing tumors, poor performance status, or a life expectancy of less than 3 months—situations where molecular-based therapy is often not indicated (Colomer et al., 2020). Additionally, such testing may not be warranted for certain patients with early-stage disease who currently can be effectively managed without the use of precision medicine.

BARRIERS AND DISPARITIES IN BIOMARKER ASSESSMENT

Advanced practitioners should recognize potential barriers that may hinder cancer biomarker testing and its integration into clinical practice. Examples include issues related to testing itself (e.g., availability of approved tests, identifying candidate patients, cost of testing); education and knowledge (interpretation of test results, awareness of guidelines, application of results to decision making); patient financial or insurance limitations; and ethnic, racial, or transgender disparities (ASCO, 2022; Cohn et al., 2018). With germline testing, patient fears about appropriate safeguards, misuse of genetic information, and religious or cultural concerns may also exist (Elewa & Awaisu, 2019).

Despite greater use of biomarker testing, significant racial and ethnic disparities remain. Curtin and colleagues (2022) found that genomic testing and the use of molecularly targeted therapy for NSCLC was underrepresented among patients with Black ethnicity, lower socioeconomic class, inadequate or no health insurance, or rural residence. Similarly, those with advanced NSCLC who were on Medicare also were less likely to undergo biomarker testing and to receive first-line biomarker-directed therapy compared with patients covered by private insurance (Gross et al., 2022). In this study, Medicare patients lacking biomarker testing had a higher risk of death compared with those who received testing. A review of the Surveillance, Epidemiology, and End Results (SEER) database of precision oncology studies in patients with various solid tumor types, including breast, lung, and prostate cancers, found underrepresentation of non-White populations (Aldrighetti et al., 2021). A real-world study also noted significant differences in NGS-based testing rates for metastatic NSCLC and metastatic colorectal cancer among Black populations compared with White populations (Bruno et al., 2022). Enrollment rates in precision oncology clinical trials to identify targetable tumor alterations also differed with respect to minorities. In women with gynecologic malignancies, Asian, Hispanic, and Black women were all significantly underrepresented in trials using tumor molecular profiling (Mattei et al., 2022).

Such ethnic and socioeconomic differences could result in the use of inappropriate therapy and contribute to worse outcomes for minority patient populations. These data highlight existing inequities in biomarker testing and the need to boost the enrollment of minorities so all patients can benefit from recent advances in personalized medicine. A policy statement by the American Society of Clinical Oncology endorsed improved patient access to biomarker testing to reduce health disparities (ASCO, 2022). Identifying barriers to the enrollment of minorities and ways to increase the use of biomarker testing across diverse racial, ethnic, gender, and socioeconomic populations will help mitigate disparities in biomarker testing and ensure that the process is accurate, evidence-driven, and equitable (Wang et al., 2020).

IMPORTANCE OF BIOMARKER TESTING

Effective implementation of biomarker testing requires the continued involvement of advanced practitioners to facilitate early testing and apply these results to patient care. Increased testing will provide advanced practitioners with information needed to make more informed treatment decisions based on each patient's tumor profile. They must therefore understand the scientific basis of molecular alterations that can occur in various tumor types and how these may inform the selection of current and future therapy. Prompt testing immediately following cancer diagnosis is recommended for many tumors to ensure that the correct targeted therapy is selected and initiated as soon as possible, which will help avoid treatment delays, the use of ineffective therapy, and unnecessary treatment-related toxicity. This is particularly important for patients with advanced malignancies who often have a shorter life expectancy and may not benefit from standard-of-care therapy. Advanced practitioners can also help patients understand biomarker testing, explain the significance of biomarker findings, and address any questions patients may have.

ROLE OF ONCOLOGY PHARMACISTS, ADVANCED PRACTICE NURSES, AND PHYSICIAN ASSISTANTS

As therapeutic experts, oncology pharmacists, advanced practice nurses, and physician assistants should strive to ensure that biomarker testing is initiated for all eligible patients, performed in a consistent manner and according to published guidelines, and correctly interpreted and applied to guide clinical care. These health-care professionals can help provide individualized education to patients regarding the importance of biomarker assessment and how results will be used to select the best therapeutic options, setting realistic limitations for patients. They should be able to address questions from patients or family members regarding targeted therapy and provide patient follow-up as needed. Additionally, they can educate and train professional colleagues, students, residents, fellows, and other practitioners on the value of biomarker testing and how to interpret and integrate results into clinical practice.

Pharmacists

Pharmacists function as key stakeholders in the clinical implementation of biomarker testing and pharmacogenomics to advance personalized therapy. In their roles on the MTB, they can identify patients who may be candidates for biomarker testing; assist oncologists with interpreting results; and recommend biomarker-based therapeutic options (Figure 1). As with other therapies, pharmacists are critical in monitoring and mitigating drug-related adverse events, identifying potential drug-drug interactions or drug-disease interactions (interactions with comorbidities), and addressing other drug administration concerns (Arnall et al., 2019; Chen et al., 2020). They may also assist with drug procurement, data collection, and precision medicine clinical trials.

Pharmacists serve as a pivotal point of contact with patients who are being evaluated and treated for cancer. As such, they are uniquely suited to educate patients and their caregivers on the need for biomarker testing and how it can inform the selection of therapy (Arnall et al., 2019; Martin et al., 2022). This can be accomplished through in-person discussions and by referrals to online resources and videos (Arnall et al., 2019; Hicks et al., 2019). Pharmacists can also refer eligible patients to precision medicine clinical trials such as basket or umbrella trials. Additionally, they can help ensure patient access to medications by minimizing financial or insurance barriers related to testing or the use of targeted therapy, including obtaining prior authorization and facilitating financial assistance through pharmaceutical manufacturers where available.

The American Association of Colleges of Pharmacy Pharmacogenomics Special Interest Group recently updated and expanded the core competencies required of pharmacists to better reflect their expanding role in the clinical application of precision medicine (Gammal et al., 2022). Their goal is to ensure that pharmacists are adequately trained and "practice ready" so biomarker testing and pharmacogenomics can be fully integrated into patient care. This group and others (Walko et al., 2016) have noted the need for regular education and training as an integral component of pharmacy school curricula and postgraduate continuing education programs, a need that is sure to grow as the number of actionable

Figure 1. Roles and responsibilities of oncology advanced practitioners in precision medicine. Adapted from Nagy et al. (2020).

biomarkers and novel technological advances continues to increase. In light of the increasing importance of biomarkers and pharmacogenomics in patient care, pharmacy schools have implemented courses on precision medicine in their curricula (Nagy et al., 2020). Practice-based education programs have also proved effective, resulting in a significant increase in pharmacists' knowledge and competence in this area (Hayashi et al., 2022).

Pharmacist professional organizations likewise have issued guidelines aimed at improving precision medicine education and its clinical integration into routine cancer care. While the functions recommended depend on the level of education, training, and experience, all pharmacists are expected to have some basic level of understanding in this area, and those with more experience and education should assume greater responsibilities. These guidelines stress the need

for greater education of pharmacists through increased pharmacy curricula, postgraduate education, and continuing education programs using various approaches such as online instruction, live presentations (e.g., grand rounds), and continuing education programs. They also note pharmacists' ability to promote implementation, education, and research related to precision medicine through the evaluation and integration of emerging biomarker and genomics data into clinical practice. Such educational efforts could enhance the delivery of patient-centered, personalized medication therapy regardless of pharmacists' level of education, practice experience, or prior pharmacogenomics knowledge.

Despite the clear potential benefits, few precision oncology programs in the United States have strong involvement of oncology pharmacists in making treatment recommendations, assessing biomarker analyses, and facilitating drug procurement (Raheem et al., 2020). A pilot study was developed to integrate clinical pharmacists into a precision medicine program for patients with cancer. Patients and oncologists alike accepted and appreciated the involvement of the clinical pharmacist, who was able to provide logistical and educational support, findings that reinforce their role as an essential member of the cancer multidisciplinary team (Arnall et al., 2019). Such results illustrate the potential benefits of greater involvement of oncology pharmacists in precision medicine for both patients and clinicians.

Oncology Advanced Practice Nurses and Physician Assistants

Oncology advanced practice nurses and physician assistants are well positioned to contribute to the implementation and integration of biomarker testing, given their key role in the coordination of precision medicine care. They are uniquely involved in the care of patients who may undergo biomarker or pharmacogenomics testing and subsequently receive targeted therapy or immunotherapy.

In addition to participating in the development of treatment plans and administration of therapy, advanced practice nurses may be involved in ordering appropriate biomarker testing and biopsies, monitoring and management of adverse events, and palliation (Jacobs & Rahman, 2021). They often obtain comprehensive individual and family health histories, which may identify risks that could signal the need for tumor or germline mutation testing, or the presence of comorbidities that might preclude the use of certain targeted therapies (Fu et al., 2019). Advanced practitioners can also work with pathologists to ensure that biopsies obtained are adequate to perform all biomarker tests and are routed appropriately, and that results are promptly recorded in a database so this information can be accessed and evaluated by the oncologist or MTB (Al-Kaiyat, 2018). Additionally, advanced practice nurses and physician assistants can collaborate with oncologists, pharmacists, and other members of the multidisciplinary heathcare team to coordinate care related to biomarker and pharmacogenomic results (Figure 1).

Professional training and continuing education of advanced practitioners is essential to ensure they stay current and competent on recent advances in biomarkers and pharmacogenomics to better guide precision medicine. Yet some studies have reported shortcomings in nurses' core competencies in these areas and a lack of recent progress, indicating the need for additional education and training (Calzone et al., 2018; Wright et al., 2018). A global nursing survey, for example, cited significant deficiencies in nurses' knowledge of precision medicine in both academic and practice settings, with many respondents noting limited access to genomic expertise and training opportunities (Calzone et al., 2018). Nursing consensus framework statements have therefore recommended inclusion of precision health concepts and skills into all levels of nursing education as well as continuing education and training programs (Fu et al., 2019). Additionally, a review of the literature and existing Oncology Nursing Society (ONS) materials identified inconsistencies and inaccuracies in the terminology used regarding pharmacogenomics and biomarker testing, which could result in miscommunication or selection of incorrect treatments (Friend et al., 2021). To this end, ONS created the Genomics and Precision Oncology Learning Library to help develop a standardized lexicon, improve literacy and communication, and serve as an educational resource for nurses and other clinicians involved in making treatment decisions based on molecular profiling

(www.ons.org/learning-libraries/precision-oncology). The ONS Biomarker Database (https://biomarkers.ons.org/biomarkers) also functions as an online resource for oncology nurses and other health-care professionals by supporting clinical decision-making regarding the use of targeted agents, and by aiding with patient education on biomarkers (ONS, 2022a, 2022b).

In addition to their own education and competency related to biomarker testing, advanced practitioners have an important role in educating both patients and professional colleagues. Advanced practitioners often serve as a primary point of contact for patients and can thus help educate patients and families on the significance and potential benefits of biomarker testing. They can then guide patients to make educated treatment decisions based on biomarker test results. They may also refer patients and their families for genetic counseling if germline mutations are detected or suspected. In some cases, nurse practitioners and physician assistants may assist with ordering genetic testing and discuss results with patients. Advanced practitioners with advanced training or experience in this area can help educate and train other clinical staff on the rationale for testing, administration of biomarker tests, and interpretation of results. They may also provide valuable feedback to the multidisciplinary team that could improve testing implementation and clinical application of these data.

CONCLUSION

The increasing number of novel targeted therapies and recent advances in technology have led to the clinical application of many predictive biomarkers that are improving outcomes with precision medicine for patients with cancer. As essential members of the multidisciplinary oncology team, oncology pharmacists, advanced practice nurses, and physician assistants must work to advance biomarker testing and its clinical integration into routine patient care. Continued education of advanced practitioners as well as patients on the value of predictive biomarkers and their role in personalized medicine is needed. By "delivering the right treatment, to the right patient, at the right time" (ASCO, 2022), use of biomarker-driven individualized cancer therapy will help provide the highest level of patient care.

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