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NCCN Molecular Testing White Paper: Effectiveness, Efficiency, and Reimbursement

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Key Words

NCCN, molecular testing, biomarker, health policy

Abstract

Personalized medicine in oncology is maturing and evolving rapidly, and the use of molecular biomarkers in clinical decision-making is growing. This raises important issues regarding the safe, effective, and efficient deployment of molecular tests to guide appropriate care, specifically regarding laboratory-developed tests and companion diagnostics. In May 2011, NCCN assembled a work group composed of thought leaders from NCCN Member Institutions and other organizations to identify challenges and provide guidance regarding molecular testing in oncology and its corresponding utility from clinical, scientific, and coverage policy standpoints. The NCCN Molecular Testing Work Group identified challenges surrounding molecular testing, including health care provider knowledge, determining clinical utility, coding and billing for molecular tests, maintaining clinical and analytic validity of molecular tests, efficient use of specimens, and building clinical evidence. (*JNCCN* 2011;9[Suppl 6]:S1–S16)

Executive Summary

Personalized medicine in oncology is maturing and evolving rapidly, and the use of molecular biomarkers in clinical decision-making is growing. Molecular tests are being used for thousands of oncology patients. As information advances, so does the need to provide authoritative guidance regarding appropriate tests and their corresponding utility from the clinical, scientific, and coverage policy standpoints. The FDA recently announced plans for oversight of laboratory-developed tests (LDTs) and re-

leased draft guidance regarding the development of companion diagnostics concurrently with therapeutics, both areas over which the FDA has regulatory authority. As recognized by the FDA, these types of diagnostic tests are used increasingly to directly inform treatment decisions, and this especially impacts patients with cancer and their oncologists. However, because of the increasing complexity of some LDTs and increasing commercial interest in oncology-related LDTs in general, the FDA is considering whether its policy of exercising “enforcement discretion” for LDTs is still appropriate.

To provide guidance regarding challenges of molecular testing to health care providers and other stakeholders, NCCN assembled a work group composed of thought leaders from NCCN Member Institutions and other organizations external to NCCN. These multidisciplinary thought leaders represented providers, patients, manufacturers, payors, and government.

For the purposes of discussion, the NCCN Molecular Testing Work Group agreed to define molecular testing in oncology as procedures designed to detect somatic or germline mutations in DNA and changes in gene or protein expression that could impact the diagnosis, prognosis, prediction, and evaluation of therapy of patients with cancer. In particular, the discussion focused on molecular tests that predict outcomes for therapy, although other areas were also discussed.

The NCCN Molecular Testing Work Group was convened to advise oncology practitioners and other stakeholders regarding challenges and recommendations concerning molecular testing in oncology. The

content of this White Paper represents the work of NCCN and may not necessarily reflect the opinions of the external work group members or the organizations with which they are affiliated.

Molecular Testing in Oncology Practice: Challenges in the United States

The NCCN Molecular Testing Work Group recognized and identified challenges for molecular testing in oncology practice in the United States in the areas of regulatory policy, clinical translation, and reimbursement and coverage policy. The group emphasized that relevant stakeholders will need to work with the FDA as it considers a new framework for regulating LDTs, and, as higher-risk tests requiring more complex validation become available, to ensure access to safe, effective, and efficient tests among patients with cancer and those at increased risk for cancer. Some key issues identified by the group include how the clinical utility of molecular testing is currently being assessed, how molecular tests are currently being coded and reimbursed, and the tests' implications for private and public health insurance coverage.

Overview and Background

Molecular testing in oncology serves many roles, including risk assessment; disease diagnosis and classification; prognostication; response prediction; toxicity prediction; and dose determination. In 2010, the NCI Investigational Drug Steering Committee's Biomarkers Task Force reported that, "although nearly half of the recently approved oncology therapies have predictive markers, the qualification of putative biomarkers remains limited and the practical realization of successful biomarker use in early clinical drug development remains to be more fully developed."¹ These predictive markers allow for the development of specific molecular testing to help clinicians optimize care, thus resulting in better outcomes for patients.²

However, challenges remain for the broader integration of predictive molecular testing into oncology practice. As interest in personalized medicine continues to increase for stakeholders, including patients, providers, industry, and government organizations, a steady increase has occurred in the development of molecular tests (approximately 2000 tests are available, including oncology and non-oncology tests, with

an estimated 1000 new tests per year³), with increasing interest in the development of LDTs and companion diagnostics, and the related search for clinically meaningful molecular biomarkers.

Predictive molecular tests, which were the focus of the NCCN Molecular Testing Work Group, are regulated by the FDA. Although the FDA has regulated drugs for more than a century, in vitro diagnostics (IVDs), a broad category of products that includes molecular tests, have only been definitively regulated by the FDA since the 1976 Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act (FD&C Act).^{4,5} However, some regulation was previously in place under the drug regulations. The FDA defines IVDs as, "those reagents, instruments, and systems intended for use in diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body."⁶

IVDs are medical devices subject to premarket and postmarket approval, depending on their risk profiles. Use of IVDs in a laboratory setting to deliver clinical results is regulated by the Centers for Medicare & Medicaid Services (CMS) under the 1988 Clinical Laboratory Improvement Amendments (CLIA). Devices are classified into 3 separate risk categories: class I (low risk), II (moderate risk), or III (high risk), which determines their pathway to FDA marketing authorization.⁴ FDA regulation of IVDs focuses on safety and effectiveness of the device, primarily as demonstrated through clinical and analytic performance, whereas CMS regulation through CLIA focuses on laboratory quality. Analytic validity, clinical validity, and clinical utility are defined in Table 1.

Laboratory-Developed Tests

Some IVDs are known as LDTs. LDTs, also known as *home brew* or *in-house* tests, are developed in and by laboratories in a variety of settings (e.g., hospital-based laboratories, independent laboratories) and are then offered only by those laboratories, compared with traditional laboratory tests, which represent most of the market and are typically marketed commercially as kits and distributed to several laboratories. These kits often include all of the necessary components to perform testing in a CLIA-certified laboratory. These traditional laboratory tests, which are broadly available

Table 1 Definitions of Analytic Validity, Clinical Validity, and Clinical Utility

Analytic validity	How accurately and reliably a test measures the genotype (or analyte) of interest in the clinical laboratory, and in specimens representative of the population of interest.
Clinical validity	How accurately and reliably a test detects or predicts the clinically defined disorder or phenotype of interest.
Clinical utility	Evidence of improved measurable clinical outcomes, and the test's usefulness and added value to patient management decision-making compared with current management without testing.

Data from Teutsch SM, Bradley LA, Palomaki GE, et al. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative: methods of the EGAPP Working Group. *Genet Med* 2009;11:3–14.

commercially, are subject to FDA regulation per the FD&C Act. Depending on the risk profile of the test, a premarket review process may apply. Certain low-risk tests are exempt from premarket review; moderate-risk tests generally require test manufacturers to provide evidence that their tests are “substantially equivalent” to existing tests under the 510(k) program, and high-risk tests generally are reviewed for safety and effectiveness under the more rigorous premarket approval (PMA) process, reserved for class III IVDs.⁷

The 1997 Final Rule on Analyte Specific Reagents (ASRs) states that the “FDA believes that clinical laboratories that develop...[LDTs] are acting as manufacturers of medical devices and are subject to FDA jurisdiction under the [FD&C Act].”⁸ This rule partly affirms the FDA’s authority over LDTs. However, the FDA has historically pursued a policy of enforcement discretion toward LDTs, largely choosing in practice not to regulate LDTs because of several factors. Based on the 1997 rule, the FDA focused regulatory attention on ensuring the quality of reagents used in LDTs.

Companion Diagnostics

On July 14, 2011, the FDA released draft guidance on in vitro companion diagnostic devices, which are often predictive molecular tests. Once finalized, this guidance will represent the FDA’s position on this topic. Although this draft guidance does not address LDTs, it does provide the FDA’s current position on regulatory requirements for companion diagnostics, including a proposed review and approval process and labeling requirements. Companion diagnostics are IVD tests that are essential for the safe and effective use of a particular therapy. The draft guidance notes that a companion IVD could be used to identify patients who are “most likely to benefit from a particular therapeutic product” or are “likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product,” or

to “monitor response to treatment for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness.”⁹

Importantly, the FDA draft guidance applies to planned therapeutics that would require companion diagnostics for their safe and effective use or for sponsors planning to develop a companion diagnostic to accompany a new therapy. An exception to the requirement for co-development is noted for promising therapeutics, “when the therapeutic product is intended to treat a serious or life-threatening condition for which no satisfactory alternative treatment exists and the benefits from the use of the therapeutic product with an unapproved or uncleared IVD companion diagnostic device are so pronounced as to outweigh the risks from the lack of an approved or cleared IVD companion diagnostic device.”⁹ The FDA encourages that, “for a novel therapeutic product, an IVD companion diagnostic device should be developed and approved or cleared contemporaneously to support the therapeutic product’s safe and effective use (e.g., co-development). The results of the IVD companion diagnostic device will be *essential* for the safe and effective use of the therapeutic product, and its use will be stipulated in the labeling of the therapeutic product (i.e., the therapeutic product is considered safe and effective *only* if used with the IVD companion diagnostic device).”⁹ Furthermore, the draft guidance states that a companion diagnostic’s label must indicate its intended use, and the therapeutic agent it is used with and/or class of agent it can be used with if the evidence supports a broader use. This is an important distinction, because companion diagnostics may be used with classes of therapeutics, expanding their reach, if sufficient evidence is supplied. The draft guidance also predicts that most companion diagnostics will be considered class III devices, requiring premarket approval.¹²

Molecular Testing in the United States

Although a variety of draft FDA guidance documents have emerged that already impact the use of molecular testing in oncology and other areas, more comprehensive guidance on LDTs, especially regarding oversight of these tests, remains to be published. The FDA is expected to release draft guidance to further clarify LDT oversight in the near future, which will be critical to stakeholders concerned with the development of and access to these tests that are increasingly important for directing care, particularly laboratories that are currently performing these kinds of tests internally and offering their LDT services commercially.

This potential oversight is expected to be similar to the existing oversight that depends on the risk profiles of tests, and changes to the FDA's policy of enforcement discretion will likely be gradual and not apply to all LDTs because of differing risk profiles of these tests. As more LDTs and commercial molecular tests become available to patients, clinicians must be well informed to understand the appropriate application of molecular tests in their practice settings.

NCCN Molecular Testing Work Group Description

To provide guidance regarding the challenges molecular testing will present to health care providers and other stakeholders, NCCN convened a work group composed of thought leaders from NCCN Member Institutions and other organizations. These multidisciplinary thought leaders represented providers (physicians and pathologists), patients, manufacturers, payors, and government. The NCCN Molecular Testing Work Group meeting was held May 6, 2011, in Philadelphia. In addition, NCCN conducted an Oncology Policy Summit: Molecular Testing – Effectiveness, Efficiency, and Reimbursement, held July

14, 2011, in Washington, DC. This summit included additional thought leaders representing the aforementioned groups and other relevant stakeholders.

The overall objective of the NCCN Molecular Testing Work Group was to identify clinical, reimbursement, and regulatory issues related to molecular testing as they relate to providing high-quality care to patients with cancer. Because molecular testing in oncology encompasses a large number of potential uses, discussion focused on molecular tests that predict outcomes for therapy.

This document encapsulates the discussion during the NCCN Molecular Testing Work Group meeting and the NCCN Oncology Policy Summit, including a background on molecular testing, identified challenges of incorporating molecular testing into oncology practice from a health care provider's perspective, and the consensus statements and recommendations offered by the NCCN Work Group (Table 2).

Molecular Testing in Oncology

Molecular testing has had a major impact on oncology patient care. Predictive molecular testing is increasingly being used to direct cancer treatment, increasing the probability that patients will benefit from therapy. The recent FDA approval of vemurafenib, a treatment for late-stage melanoma, simultaneously with a companion diagnostic (the cobas 4800 BRAF V600 Mutation Test; F. Hoffman-La Roche Ltd., Basel, Switzerland) and crizotinib, a treatment for late-stage non-small cell lung cancer, simultaneously with a companion diagnostic (Vysis ALK Break Apart FISH Probe Kit; Abbott Laboratories, Abbott Park, IL) are examples of therapeutics guided by predictive molecular tests.^{10,11} The increased use of molecular testing in oncology is also evidenced by the inclusion of more than 600 molecular tests for several cancer types in the NCCN

Table 2 NCCN Molecular Testing Work Group Consensus Statements and Recommendations

- The Work Group recognizes that regulatory changes surrounding molecular testing have the potential to significantly affect oncology care, and encourages regulations that will ensure patient access to safe, effective, and efficient molecular tests without limiting the ability of CLIA-certified laboratories in NCCN Member Institutions and other major cancer centers to rapidly meet the need for new test development for new targeted cancer therapies.
- Increased education regarding molecular testing in oncology is needed for patients, clinicians, pathologists, industry, payors, and policy-makers to help ensure these tests are being used safely, effectively, and efficiently in oncology, and that their limitations and the clinical impact of their results are understood.

Abbreviation: CLIA, Clinical Laboratory Improvement Amendments.

Effectiveness, Efficiency, and Reimbursement

Clinical Practice Guidelines in Oncology (NCCN Guidelines). For example, the breast cancer guidelines (Table 3) contain recommendations for the following biomarkers: human epidermal growth factor receptor 2 (*HER2*) and estrogen and progesterone receptors (*ER/PR*), and for the *Oncotype DX* test (Genomic Health, Inc., Redwood City, CA). Other clinical guidelines include recommendations for *KRAS* mutation, *BRAF* mutation, and microsatellite instability testing. The increased use and complexity of some of the tests also increases the workload for pathologists, whom oncologists and patients depend on to provide clinically useful laboratory reports based on the molecular tests.¹² The increasing complexity of the molecular testing process in oncology is shown in Figure 1.

Although numerous molecular tests are currently used in clinical practice, much work remains to expand their reach. As noted by Haber et al.,¹³ “predominant therapeutic targets have yet to emerge for the majority of epithelial cancers, which constitute ~ 85% of all cancers.”

The analytes that could be used in molecular testing include DNA, RNA, proteins, and metabolites. These can be derived from frozen, fresh, or formalin-fixed paraffin-embedded (FFPE) samples, and can be derived directly from a tumor or through remote sampling from blood, urine, or other substances. Molecular tests in oncology are most commonly used for risk assessment (e.g., germline mutation in *BRCA1/2*), early detection (e.g., prostate-specific antigen [PSA]), diagnosis/subclassification (e.g., leukemia fusion oncogenes), prognosis (*Oncotype DX*, *MammaPrint* [Agendia, Irvine, CA]), prediction of response (e.g., *BCR-ABL* fusion oncogene used to determine patient response to Gleevec, somatic *EGFR* mutations used to determine patient response to Tarceva), or prediction of toxicity (thiopurine S-methyltransferase mu-

tation testing for response to 6-mercaptopurine, used in the treatment of acute lymphoblastic leukemia).

Molecular tests vary in complexity. Some tests are relatively simple, analyzing either a single biomarker (e.g., *HER2* amplification in breast cancer) or several biomarkers individually (e.g., *KRAS* and *BRAF* mutations in metastatic colorectal cancer), whereas others include multiple markers interpreted in a multivariate manner to derive a score, probability, or classification, as with in vitro multivariate index assays (e.g., *Oncotype DX*, *MammaPrint*).

Laboratory Requirements

All molecular testing used to modify patient management must be performed in a CLIA-certified laboratory. If the testing is not being used to inform decisions about patient care, it may be considered research and may not need to be performed in a CLIA setting. Investigational testing, used to determine the performance characteristics of a test, may indicate a CLIA setting, especially if results are used to alter patient management. Gulley et al.¹² indicate that, “to help ensure quality, laboratories in the United States are required by law to validate assays and to participate in proficiency testing at least semiannually.”

Establishing Clinical Utility

For a stakeholder, a major factor in determining the use of molecular testing is whether a test has shown clinical utility. Teutsch et al.¹⁴ define clinical utility as “...evidence of improved measurable clinical outcomes, and...usefulness and added value to patient management decision-making compared with current management without [the biomarker].” The level of evidence required to establish clinical utility is of high importance to stakeholders. Notably, the level of evidence that both private and public payors require to determine coverage of molecular testing is a critical factor for patient access.

Table 3 Molecular Testing Recommendations in the NCCN Clinical Practice Guidelines in Oncology for Breast Cancer

Biomarker Test	Recommended in Guidelines	Date Included in the Guidelines	Recommendation	Category of Evidence and Consensus
ER/PR	Yes	1997	All breast cancers	2A*
HER2- <i>neu</i>	Yes	1999	Invasive breast cancer	2A
<i>Oncotype DX</i>	Yes (consider)	2008	Node-negative, HER2-negative, ER/PR-positive breast cancer	2A

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

*Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

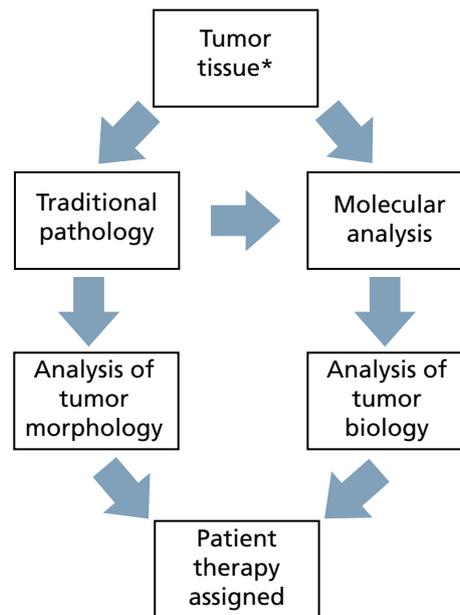


Figure 1 The increasing complexity of the molecular testing process in oncology.

*The NCCN Molecular Testing Work Group discussed the importance in the oncology setting of ensuring that all tissue specimens be evaluated for and validated to contain the appropriate levels of tumor cells before being sent for further molecular analysis.

Adapted from Pao W, Kris MG, Iafrate AJ, et al. Integration of molecular profiling into the lung cancer clinic. *Clin Cancer Res* 2009;15:5317–5322; with permission.

Because of concerns about the efficacy of molecular tests in clinical practice, an effort has been made to develop randomized clinical trials (RCTs) to provide a sufficient evidence base for their use. Two ongoing trials are the Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy (MINDACT) trial for MammaPrint and the Trial Assigning Individualized Options for Treatment (TAILORx) trial for Oncotype DX. McDermott et al.¹⁵ suggest that “... any new test be subjected to the same rigorous appraisal required for any new drug or procedure in patients.” In general practice, requiring RCTs for all molecular tests would present stakeholders with serious challenges. Much discussion remains regarding appropriate clinical end points and validation of predictive markers for future potential studies. It is important to note that any required clinical trials for molecular testing should consider appropriate time frames and end points that reasonably assure that therapeutic benefit is not withheld or removed from consideration in assessing treatment options. Evidence for these tests may also be compared with existing predictors or combinations of predictors currently in practice for the treatment or disease in question.

Efforts by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group, an independent panel established by the Office of Public Health Genomics at the Centers for Disease Control and Prevention, have helped to define an evidence-based process to evaluate rapidly evolving genetic and genomic tests. The main question the EGAPP Working Group asks when evaluating tests is whether there is “direct evidence that using the test leads to clinically meaningful improvement in outcomes or is useful in medical or personal decision-making.”¹⁵ This question is further refined through analysis of a test’s analytic validity, clinical validity, and clinical utility, which can be used to judge the quality of existing or future studies. Other efforts, such as the BlueCross BlueShield Association’s Technology Evaluation Center (TEC), have also developed criteria to determine whether a new technology, including a molecular test, improves health outcomes.¹⁶

Stakeholders must come to a consensus to determine molecular testing policies that strike the right balance between the following competing benefits: innovation, access to testing, affordability, efficiency, and safety/efficacy. This balance will be critical to ensuring patient access to high-quality

care as advances continue to bring personalized medicine closer to reality for patients with cancer.

Economics of Molecular Testing

It is estimated that the molecular testing market has doubled between 2005 and 2010, growing from approximately \$3 billion to \$6.2 billion. Tests typically cost between a few hundred dollars and a few thousand dollars.³ Substantial interest exists among stakeholders to determine the cost-effectiveness of molecular tests and demonstrate savings and benefit associated with these tests, because they have the potential to target therapies and avoid unnecessary care (the annual cost of newer oncology drugs can be more than \$50,000 a year).¹⁷ However, limited studies in this area have been performed to help establish cost-effectiveness of molecular tests, especially considering the different targets and complexity of these tests, and issues of study design. Theoretical cost-effectiveness studies are heavily dependent on their input assumptions regarding both costs and benefits.

Meckley and Neumann¹⁸ note that although some cost-effectiveness studies exist for molecular tests, and that they often display “cost-savings or cost-effectiveness, the review authors concluded the evidence of clinical effectiveness was weak for many of the interventions [or] frequently preliminary or hypothetical.” Some recent analyses have shown that tests for *KRAS* and *BRAF* status (in Switzerland)¹⁹ and *KRAS* status (in Japan)²⁰ to predict treatment response for cetuximab were cost-effective in the treatment of metastatic colorectal cancer.

As stated by Meckley and Neumann,¹⁸ “in order to achieve favorable coverage and reimbursement and to support premium prices for ... [personalized medicine] technologies, manufacturers ... will need to bring better clinical evidence to the marketplace and better support for the overall value of their products.” Additional studies are needed to definitively establish the clinical utility of molecular tests, which will help define the value of these tests. The amount of data required for FDA clearance of molecular tests will influence pricing, which will affect access to these tests.

Challenges for Molecular Testing in the United States

During the NCCN Molecular Testing Work Group meeting and the NCCN Oncology Policy Summit, many challenges were identified for molecular test-

ing in oncology clinical practice. Challenges can be divided into 3 categories: 1) regulatory issues; 2) clinical and practical issues and; 3) reimbursement issues and coverage policy. These challenges are summarized in Tables 4 through 6.

Regulatory Challenges

FDA Oversight of LDTs

- As use and interest in LDTs continues to grow, it will be important to work with the FDA to define an oversight framework that takes into account higher-risk tests that require more complex validation, equipment, and software. The FDA's policy of blanket enforcement discretion has been suggested to no longer be appropriate for the more complex, higher-risk molecular tests now available. If the FDA moves to regulate LDTs, regulatory clarity and predictability will be important to assure that high-quality tests reach the market expeditiously. This includes establishing clear conditions as to when filing an Investigational Device Exemption (IDE) with the FDA is required and what data are necessary for IDE approval.
- LDTs have been critical to recent advances in oncology, because they can be rapidly developed and targeted locally. Currently, no controls have been placed on the marketing claims of these tests and limited control of test development exists. Likewise, there are limited premarket independent review or postmarket reporting requirements. These requirements are dependent on state regulations and/or the laboratory accreditation process. Currently, some of these functions for laboratories performing molecular testing, such as postmarket performance, are conducted voluntarily.

Discussion at the NCCN Molecular Testing Work Group meeting and the NCCN Oncology Policy Summit focused on expectations for what FDA oversight of LDTs may require of stakeholders. Based on this discussion, the oversight framework will likely be risk-based and allow for some LDTs to remain under the FDA's policy of enforcement discretion. The need for this review is based on the growing complexity of the LDT process, which has substantially advanced in recent years, and the potential for higher-risk LDTs to escape review of their analytic and clinical validity. Oversight will also likely entail efforts by the FDA to classify different LDT

Table 4 Regulatory Challenges for Molecular Testing in Oncology in the United States

Regulatory Issues	Challenge, Consensus Statement, or Recommendation
FDA oversight of laboratory-developed tests	<ul style="list-style-type: none"> As use and interest in laboratory-developed tests (LDTs) continues to grow, it will be important to work with the FDA to define an oversight framework that takes into account higher-risk tests that require more complex validation, equipment, and software. The FDA's policy of blanket enforcement discretion has been suggested to no longer be adequate for the more complex molecular tests now available. If the FDA moves to regulate LDTs, regulatory clarity and predictability will be important to assure that high-quality tests reach the market expeditiously. This includes establishing clear conditions as to when filing an Investigational Device Exemption (IDE) with the FDA is required and what data are necessary for IDE approval. LDTs have been critical to recent advances in oncology, because they can be rapidly developed and targeted locally. Currently, no controls have been placed on the marketing claims of these tests and limited control of test development exists. Likewise, there are limited premarket independent review or postmarket reporting requirements. These requirements are dependent on state regulations and/or the laboratory accreditation process. Currently, some of these functions for laboratories performing molecular testing, such as postmarket performance, are conducted voluntarily.
Potential barriers to innovation	<ul style="list-style-type: none"> Some sectors are concerned that additional regulation of molecular testing may harm innovation because associated regulatory barriers may hinder the pace of progress. The product life cycles of molecular testing assays often differ from those of drugs. This could present issues related to innovation with new therapies and their companion diagnostics.
Determining clinical utility	<ul style="list-style-type: none"> Most molecular testing is performed in laboratories that meet or exceed the laboratory quality standards currently set by the Centers for Medicare & Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments (CLIA). However, CLIA regulations do not measure the clinical validity or clinical utility of individual molecular tests. The FDA does have the authority to ensure the safety and effectiveness of molecular tests, which includes an evaluation of clinical validity.
Companion diagnostics	<ul style="list-style-type: none"> New therapies that are found to be effective in patients with a specific biomarker profile may require a companion diagnostic test to be approved by the FDA if these tests are considered essential for the safe and effective use of a therapy. Label changes to already approved treatments can also be required if a companion diagnostic is shown to improve safety. It will be important to understand how clinical trials for drugs and their companion diagnostics should be designed.

panels through information gathering (requiring registration and listing) to help define the intended use of the test. It was emphasized that no specific action will be required until the pending draft guidance is finalized.

Potential Barriers to Innovation

- Some sectors are concerned that additional regulation of molecular testing may harm innovation because associated regulatory barriers may hinder the pace of progress.
- The product life cycles of molecular testing assays often differ from those of drugs. This could present issues related to innovation with new therapies and their companion diagnostics.

Some concerns were raised about the potential effects of additional regulation of molecular testing on the development of new technologies. These concerns were focused on how the FDA will determine whether the 510(k) clearance or PMA process would apply to LDTs and whether additional evidence, particularly from RCTs, might be required of manufacturers. Interest was expressed in a process that would allow molecular tests to come to market to develop evidence

regarding their clinical utility (this is already occurring outside the sphere of the FDA with some LDTs, such as *Oncotype DX*). Recent FDA draft guidance encourages co-development of companion diagnostics with therapeutics, which is intended to facilitate their joint implementation and ultimately improve patient care by targeting therapies to patients with cancers that are more likely to respond. The recent FDA approval of vemurafenib with the companion diagnostic cobas 4800 BRAF V600 Mutation Test, and crizotinib with the companion diagnostic Vysis ALK Break Apart FISH Probe Kit, shows the potential of this co-development process to directly affect care.^{11,12}

Determining Clinical Utility

- Most molecular testing is performed in laboratories that meet or exceed the laboratory quality standards currently set by CMS under CLIA. However, CLIA regulations do not measure the clinical validity or clinical utility of individual molecular tests. The FDA does have the authority to ensure the safety and effectiveness of molecular tests, which includes an evaluation of clinical validity.

Depending on how the FDA structures its potential oversight of LDTs, in some cases pre-market approvals could be required. The NCCN Molecular Testing Work Group noted that, although a test may be clinically valid in small studies, its clinical utility on a larger scale may be negligible.

Companion Diagnostics

- New therapies that are found to be effective in patients with a specific biomarker profile may require a companion diagnostic test to be approved by the FDA if these tests are considered essential for the safe and effective use of a therapy. Label changes to already approved treatments can also be required if a companion diagnostic is shown to improve safety. It will be important to understand how clinical trials for drugs and their companion diagnostics should be designed.

Notably, recent draft guidance regarding companion diagnostics includes few recommendations regarding clinical trial design for companion diagnostics. Required clinical trials would now include companion diagnostic development concurrently with drug development, though the approval of promising therapeutics without companion diagnostics would still be allowed. The recent FDA draft guidance on companion diagnostics indicated that an IDE will generally need to be filed, because “all diagnostic devices used to make treatment decisions in a clinical trial of a therapeutic product will be considered investigational devices.”¹² The draft guidance also notes that information about the intended use of a companion diagnostic and its use in clinical trials should be provided. Further guidance regarding clinical trial design would be useful to stakeholders to ensure that the potential of companion diagnostics is appropriately applied to treatment decisions that will improve patient care.

Clinical and Practical Challenges

Determining Clinical Utility

- The clinical utility of molecular tests is increasingly important to establishing coverage policy as relevant data become more available. Private and public payors need to determine how much information is required to establish clinical utility and, subsequently, the tier at which a molecular test is covered.

Considerable interest in determining clinical utility exists among stakeholders, because this is typically a prerequisite for coverage of molecular testing, leading directly to patient access to high-quality care. More information from private and public payors regarding what they consider adequate data to establish clinical utility would be very useful to manufacturers, clinicians, patients, and other relevant stakeholders. It was emphasized in discussion at the NCCN Oncology Policy Summit that if a test has no clinical utility, it has little value for patient care.

A recent NCCN Trends Survey conducted at the 2011 NCCN 16th Annual Conference to determine needs surrounding molecular testing in oncology asked a convenience sample of 240 conference attendees (including physicians, pharmacists, nurses, clinicians, and nonpracticing clinicians) what factors they believe are critical for making decisions about ordering a new molecular test. The most frequent responses were: 1) evidence supporting the recommendation and 2) the specific purpose of the test were the most frequent responses (Figure 2).

Research and Clinical Utility

- Clarification is needed regarding the difference between molecular testing used for patient care, which must be carried out in CLIA-certified laboratories, and molecular testing used for research.

Because molecular testing is becoming more complex, the NCCN Molecular Testing Work Group examined the potential overlap in molecular testing used for patient care and that used for research. The group noted that current multivariate panels examining multiple biomarkers contain both clinically useful markers and markers with undetermined clinical utility. The consequences of producing laboratory results for markers with undetermined clinical utility were also discussed.

The potential for multiplex testing to help direct patients to appropriate clinical trials was considered. As more clinically relevant findings are discovered through multiplex testing, this method may be used more in the future to match patients to trials, or in other ways to improve patient care. These potential uses of multiplex testing for both research and patient care raised additional regulatory and reimbursement questions from the NCCN Molecular Testing Work Group, specifically, how to reimburse multiplex assays that include both clinically useful markers and those with undetermined clinical utility. Clarification is needed on multiple fronts to ensure

Table 5 Clinical and Practical Challenges for Molecular Testing in Oncology in the United States

Clinical and Practical Issues	Challenge, Consensus Statement, or Recommendation
Determining clinical utility	<ul style="list-style-type: none"> The clinical utility of molecular tests is increasingly important to establishing coverage policy as relevant data become more available. Private and public payors need to determine how much information is required to establish clinical utility and, subsequently, the tier at which a molecular test is covered.
Research and clinical utility	<ul style="list-style-type: none"> Clarification is needed regarding the difference between molecular testing used for patient care, which must be carried out in CLIA-certified laboratories, and molecular testing used for research.
Efficient use of tissue specimens	<ul style="list-style-type: none"> Better communication and education are needed to ensure that tissue collected for molecular testing is used as efficiently as possible so that the most critical molecular testing can be performed on adequate tissue in a timely fashion. Multiplex assays may allow for increased efficiency through providing a path useful for research while also producing practical clinical results. In the future, this approach may help to identify additional clinically useful changes. These multiplex assays are sometimes only billed for their clinically meaningful components, but in other cases research and clinically meaningful components are billed together.
Ordering molecular tests	<ul style="list-style-type: none"> Should providers be encouraged to request assays based on the molecular event they are interested in rather than an FDA-approved or non-FDA-approved branded assay? For example, if a provider is asking for a brand name test, how would this affect the pathologist's ability to select newer, potentially more efficient tests? Could in-house LDTs substitute for the same test when companion diagnostics are included on drug labels?
Maintenance of analytic and clinical validity	<ul style="list-style-type: none"> As more LDTs are commercialized, how does this impact the maintenance of the analytic and clinical validity of molecular testing in relation to laboratory method? The laboratory process of handling tissue specimens, determining which mutations to analyze, and how test results are reported may change over time. The use of LDTs on tumor types that differ from tumor types addressed in supportive studies was discussed, in addition to how validity is assessed for LDTs that are used for different tumor stages or with different specimen sources from those researched in original supportive studies. The question was raised as to what additional research is needed to support these uses.

Abbreviations: CLIA, Clinical Laboratory Improvement Amendments; LDT, laboratory-developed test.

providers and patients realize the full potential of molecular testing and, more specifically, multiplex testing.

Efficient Use of Tissue Specimens

- Better communication and education are needed to ensure that tissue collected for molecular testing is used as efficiently as possible so that the most critical molecular testing can be performed on adequate tissue in a timely fashion.
- Multiplex assays may allow for increased efficiency through providing a path useful for research while also producing practical clinical results. In the future, this approach may help to identify additional clinically useful changes. These multiplex assays are sometimes only billed for their clinically meaningful components, but in other cases research and clinically meaningful components are billed together.

The stakeholders agreed that communication and education regarding molecular testing is critical for clinicians involved in the molecular testing process.

This can help mitigate insufficient collection of specimens or potential errors in handling of specimens, both of which could delay or negatively impact care.

Multiplex testing, in which several genes are analyzed simultaneously rather than individually, was also discussed in the context of more efficient use of tissue specimens, because more clinically relevant findings could be obtained with fewer samples. Multiplex testing is being used more frequently in practice, and its use will likely continue to increase. However, use will depend on laboratory capabilities, which will vary based on the setting (e.g., large academic centers vs. community practice).

Ordering Molecular Tests

- A question was raised regarding whether providers should be encouraged to request assays based on the molecular event they are interested in rather than an FDA-approved or non-FDA-approved branded assay. Concern was raised regarding certain situations; for example, if a provider is asking for a brand name

Effectiveness, Efficiency, and Reimbursement

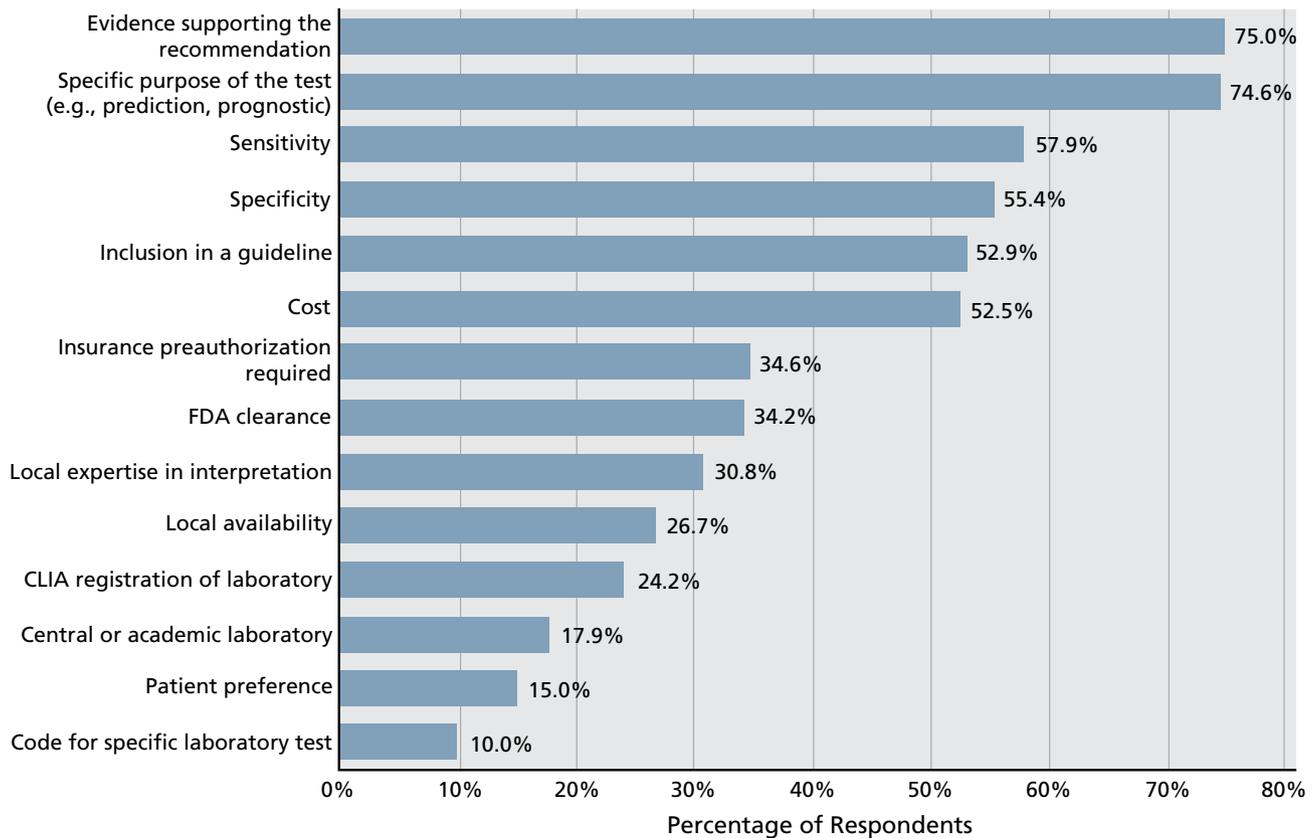


Figure 2 NCCN Trends Survey: Molecular Marker Testing: What Information is Important?

Abbreviation: CLIA, Clinical Laboratory Improvement Amendments.

From Li E. NCCN Trends Survey: Molecular Markers: What Information is Important? National Comprehensive Cancer Network Web site. Available at: http://www.nccn.org/about/news/ebulletin/2011-05-02/molecular_marker.asp. Accessed November 15, 2011.

test, how would this affect the pathologist's ability to select newer, potentially more efficient tests?

- Another concern raised was whether in-house LDTs for the same test would be considered when companion diagnostics are included on drug labels.

The NCCN Molecular Testing Work Group discussed the idea that ordering tests based on the molecular event could enable pathologists to choose the most efficient tests available, because technology is constantly advancing. Considerable interest was also shown in the FDA determining whether LDTs equivalent to the companion diagnostics indicated on drug labels would be allowed as an alternative. This situation is particularly relevant in the hospital setting, where testing of a specific molecular event could be possible using an LDT rather than the FDA-approved or non-FDA-approved branded assay.

Maintenance of Analytic and Clinical Validity

- As more LDTs are commercialized, how does this impact the maintenance of the analytic and

clinical validity of molecular testing in relation to laboratory method? The laboratory process of handling tissue specimens, determining which mutations to analyze, and how test results are reported may change over time.

- The use of LDTs on tumor types that differ from tumor types addressed in supportive studies was discussed, in addition to how validity is assessed for LDTs that are used for different tumor stages or with different specimen sources from those researched in original supportive studies. The question was raised as to what additional research is needed to support these uses.

The NCCN Molecular Testing Work Group discussed issues related to the maintenance of clinical and analytic validity for molecular tests, and additional research that may be needed to support the use of some LDTs when they are used outside the scope of supportive studies. The complexity of the molecular testing process, including the equipment

and staff expertise needed to conduct testing, makes the maintenance of clinical and analytic validity very important. The group also emphasized that the sensitivity of molecular tests in identifying mutations is very important, because testing errors could result in false-negative or false-positive readings.

Reimbursement Issues and Coverage Policy Challenges

Variation in Coverage

- Variation exists in private and public payor coverage policies regarding molecular testing. In determining coverage decisions, Medicare considers whether the available evidence is adequate to determine that a test provides more accurate diagnostic information than existing tests and, if the test is more accurate, how the changed accuracy affects health outcomes. Medicare covers diagnostic tests that are related directly to treatment if they are proven effective (i.e., they improve net health outcomes and are generalizable to the Medicare population) but covers prognostic tests more selectively.
- Differences in coverage policy regarding molecular tests for different tumor types were discussed. Parity of coverage for different tumor types was suggested.

Variation in coverage policies and cases for which no policy exists were cited as challenges for many stakeholders. Typically, the strength of evidence behind a test and its inclusion in clinical guidelines (e.g., NCCN Guidelines) are good indicators of both coverage and reimbursement by private and public health plans.¹⁹

Coding and Billing

- Currently, the coding system widely used by laboratories and payors for molecular testing does not account for individual molecular tests, but rather the procedures involved in performing the tests, referred to as *stacked coding*. A multiplex assay, including multiple molecular tests, would not indicate what tests are being performed or account effectively for the complexity of the testing. Other potential models for coding may help improve this process and differentiate between tests with proven clinical utility and those that are for basic research, and decrease variation in how codes are reported to payors.

The NCCN Molecular Testing Work Group discussed the challenges presented by the current coding system for stakeholders, mainly the lack of specific current procedural terminology (CPT) codes for molecular tests that could help to simplify the coding process, resulting in more efficient reimbursement. Stacked coding results in different laboratories often coding the same molecular testing differently, resulting in varied reimbursement rates, and increases the chances for coding errors.³ In early 2011, CMS demonstrated their interest in how Medicare should address coding for genetic and molecular tests by releasing a call for public comment and recommendations, asking for recommendations on what tests to include on their medical laboratory charge plan, how existing coding can be improved, and how genetic/molecular tests relate to existing laboratory tests.

The American Medical Association (AMA) has also recently released their recommendations for coding reform regarding molecular diagnostics, which have been under development since December 2009 by AMA's CPT Editorial Panel Molecular Pathology Codification Workgroup (MPCW). This group has "proposed codes which address greater than 90% of medically useful molecular testing currently being performed and within the realm of the workgroup's charge. The services identified by the MPCW as CPT codes will include all analytical services performed in the test (e.g., cell lysis, nucleic acid stabilization, extraction, digestion, amplification, detection, and interpretation), with robust granularity in the code descriptors to better allow providers and payers to communicate the tests that are actually performed."²² Although coding changes such as those mentioned are currently being seriously considered, broad adoption of these changes may still be years away.

Building Evidence for Reimbursement

- The CMS experience with pharmacogenetic testing for warfarin treatment may be seen as an example of how future molecular testing in oncology may be handled. Coverage may be contingent on the testing occurring in the context of a clinical trial to build evidence.

CMS established a potential framework for how reimbursement may function for molecular testing, at least in the public payor arena, that is often adopted by private payors. In 2005, CMS established the coverage with evidence development (CED)

Table 6 Reimbursement Issues and Coverage Policy Challenges for Molecular Testing in Oncology in the United States

Reimbursement and Coverage Policy Issues	Challenge, Consensus Statement, or Recommendation
Variation in coverage	<ul style="list-style-type: none"> • Variation exists in private and public payor coverage policies regarding molecular testing. In determining coverage decisions, Medicare considers whether the available evidence is adequate to determine that a test provides more accurate diagnostic information than existing tests and, if the test is more accurate, how the changed accuracy affects health outcomes. Medicare covers diagnostic tests that are related directly to treatment if they are proven effective (i.e., they improve net health outcomes and are generalizable to the Medicare population) but covers prognostic tests more selectively. • Differences in coverage policy regarding molecular tests for different tumor types were discussed. Parity of coverage for different tumor types was suggested.
Coding and billing	<ul style="list-style-type: none"> • Currently, the coding system widely used by laboratories and payors for molecular testing does not account for individual molecular tests, but rather the procedures involved in performing the tests, referred to as <i>stacked coding</i>. A multiplex assay, including multiple molecular tests, would not indicate what tests are being performed or account effectively for the complexity of the testing. Other potential models for coding may help improve this process and differentiate between tests with proven clinical utility and those that are for basic research, and decrease variation in how codes are reported to payors.
Building evidence for reimbursement	<ul style="list-style-type: none"> • The Centers for Medicare & Medicaid Services experience with pharmacogenetic testing for warfarin treatment may be seen as an example of how future molecular testing in oncology may be handled. Coverage may be contingent on the testing occurring in the context of a clinical trial to build evidence.
Off-label use of companion diagnostics and their associated therapeutics	<ul style="list-style-type: none"> • Whether a companion diagnostic could be used off-label (e.g., for a cancer or stage that has not been studied) was discussed. • How a companion diagnostic will be reimbursed if its associated drug is used for off-label purposes was considered.

pathway to reimbursement for new technologies that require further inquiry into their risks and benefits for clinical use. This path was applied to coverage of pharmacogenomic testing of warfarin in 2009 and could potentially be extrapolated more broadly to other molecular testing.²³ In the case of warfarin responsiveness testing, Medicare coverage is dependent on the testing being performed in a prospective randomized controlled trial.²⁴ This scenario could apply in other cases in which both analytic and clinical validity of a molecular test was proven in clinical trials but clinical utility was not successfully shown.

CED was discussed by the NCCN Molecular Testing Work Group and at the NCCN Oncology Policy Summit, where concern was expressed about how realistic this approach would be on a broad scale, considering the burden that data collection would place on test manufacturers, especially those that would fund the required randomized controlled trials and define meaningful end points, which could potentially discourage the development of new tests. Alternatively, the participants argued that a clear reimbursement path-

way would reassure manufacturers and would also help build a solid evidence base for clinical utility over time, which would bolster payor confidence in reimbursing molecular tests.

Off-Label Use of Companion Diagnostics and Their Associated Therapeutics

- Whether a companion diagnostic could be used off-label (e.g., for a cancer or stage that has not been studied) was discussed.
- How a companion diagnostic will be reimbursed if its associated drug is used for off-label purposes was considered.

Oncology drugs are commonly prescribed for indications that are not listed on the FDA label, and this approach is often appropriate.²⁵ Questions remain for stakeholders regarding how companion diagnostics that are associated with specific indications on the label of their associated therapeutic could be used and reimbursed if that therapeutic is used off-label. Considerable interest was also expressed in whether a companion diagnostic could be used off-label for a cancer or stage for which supportive studies do not exist.

NCCN Recommendations/Consensus Statements

Although many challenges remain for molecular testing in oncology, it represents the future of oncology care, and continuous educational efforts are needed to effectively integrate this technology's advancement into practice. The following represent the recommendations and consensus statements reached by the NCCN Molecular Testing Work Group:

- Regulatory changes surrounding molecular testing have the potential to significantly affect oncology care, and the group encourages regulations that will ensure patient access to safe, effective, and efficient molecular tests, without limiting the ability of CLIA-certified laboratories in NCCN Member Institutions and other major cancer centers to rapidly meet the need for new test development for novel targeted cancer therapies.
- Increased education regarding molecular testing in oncology is needed for patients, clinicians, pathologists, industry, payors, and policy-makers to help ensure that these tests are being used safely, effectively, and efficiently in oncology, and that their limitations and the clinical impact of their results are understood.

Health Care Provider Education

Discussion at the NCCN Oncology Policy Summit emphasized the need for stakeholder education regarding molecular testing, particularly for providers who will be analyzing the results of molecular testing and determining their application to guide treatment. Insufficient understanding of the tests can result in their ineffective use. Additionally, the large amount of data currently provided by some molecular assays is often difficult to process and use effectively. It was noted that in the future, databases or registry data could potentially be used to optimize use of molecular testing.

The Patient Perspective on Molecular Testing in Oncology

The NCCN Molecular Testing Work Group included representation from the patient advocacy community, and issues regarding molecular testing from the patient perspective were discussed. Patients look to molecular testing to help make the best treatment decisions, understand the benefits and side effects of treatment, understand their own prognosis and the

possibility of recurrence, and know if treatment is working. Additionally, patients need reassurance that the tests are accurate and reliable, and for information about testing to be clear and understandable.

The last point is critical, because a plethora of information about molecular testing and personalized medicine is available on the Internet, and therefore patients must have access to reliable information, such as NCCN Guidelines for Patients or other resources provided by expert clinical or patient advocacy groups. Patients may also face barriers to molecular tests, including their physicians not being aware of appropriate molecular tests, or lack of insurance coverage for testing.

Finally, patients encourage the inclusion of biomarker development and validation during clinical trials, increased information about the benefits and potential downsides of molecular testing, and adequate coverage for validated and clinically useful tests.

Closing Statement

The NCCN Molecular Testing Work Group supports potential FDA regulations that will ensure patient access to safe, effective, and efficient molecular tests, without limiting the ability of CLIA-certified laboratories in NCCN Member Institutions and other major cancer centers to meet the need for new test development for novel targeted cancer therapies. The ultimate goal of molecular predictive tests is to ensure that the maximum number of patients receive appropriate therapies in the most efficient manner possible. The NCCN Molecular Testing Work Group identified several challenges facing the use of molecular predictive markers in oncology practice, and it was clear from discussions during the NCCN Oncology Policy Summit that clinicians, patients, and payors will increasingly look to NCCN for guidance about their use.

The oncology community awaits the release of future FDA guidance to elucidate a regulatory framework for LDTs, which will help direct future efforts to develop tests in a variety of settings. However, many challenges exist that the guidance will not solve, including issues regarding coverage and reimbursement of these tests and procedural coding. Although molecular testing has been proven to be very beneficial to targeting therapies, much more work is needed to expand its reach in oncology and beyond.

Effectiveness, Efficiency, and Reimbursement

Additionally, the NCCN Molecular Testing Work Group recommends increased educational efforts regarding molecular testing in oncology be directed toward patients, clinicians, pathologists, industry, payors, and policy-makers to improve communication, convey appropriate expectations for the benefits and limits of personalized medicine, and ensure testing is implemented in a safe, effective, and efficient manner.

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Individual Disclosures for NCCN Molecular Testing White Paper: Effectiveness, Efficiency, and Reimbursement Panel Members					
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