NCCN Oncology Research Program's Investigator Steering Committee and NCCN Best Practices Committee Molecular Profiling Surveys

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Abstract

Background: With advances such as next-generation sequencing (NGS) increasing understanding of the basis of cancer and its response to treatment, NCCN believes it is important to understand how molecular profiling/diagnostic testing is being performed and used at NCCN Member Institutions and their community affiliates. **Methods:** The NCCN Oncology Research Program's Investigator Steering Committee and the NCCN Best Practices Committee gathered baseline information on the use of cancer-related molecular testing at NCCN Member Institutions and community members of the NCCN Affiliate Research Consortium through 2 separate surveys distributed in December 2013 and September 2014, respectively. **Results:** A total of 24 NCCN Member Institutions and 8 affiliate sites provided quantitative and qualitative data. In the context of these surveys, "molecular profiling/diagnostics" was defined as a panel of at least 10 genes examined as a diagnostic DNA test in a Clinical Laboratory Improvement Amendments (CLIA)–certified laboratory. **Conclusions:** Results indicated that molecular profiling/diagnostics are used at 100% of survey respondents' institutions to make patient care decisions. However, challenges relating to reimbursement, lack of data regarding actionable targets and targeted therapies, and access to drugs on or off clinical trials were cited as barriers to integration of molecular profiling into patient care. Frameworks for using molecular diagnostic results based on levels of evidence, alongside continued research into the predictive value of biomarkers and targeted therapies, are recommended to advance understanding of the role of genomic biomarkers. Greater evidence and consensus regarding the clinical and cost-effectiveness of molecular profiling may lead to broader insurance coverage and increased integration into patient care. (J Natl Compr Canc Netw 2015;13:1337–1346)

Background

Increasingly, personalized/precision medicine has become a primary focus in oncology research and practice. Through personalized/precision medicine, molecular biomarkers can be leveraged for cancer risk assessment, disease diagnosis and classification, prognostication, response and toxicity prediction, and dose determination.[1] Indeed, the results of the personalized/precision medicine PREDICT/IMPACT and BATTLE studies at The University of Texas MD Anderson Cancer Center,[2,3] numerous studies of ALK and EGFR inhibitors in lung cancer,[4,5] and recent histology-independent stud-

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ies of vemurafenib in *BRAF*-mutant diverse malignancies,[6] as well as meta-analyses of phase II and III data,[7,8] provide support for the use of molecular diagnostics in treating patients with advanced refractory cancer. Several targeted drugs have now been FDA-approved with a companion molecular test to identify the patients with the cognate target. However, for the most part, a personalized/precision medicine strategy that uses molecular diagnostics has not yet been evaluated in prospective randomized trials.

The diagnostic technologies that permit the analysis of a patient's tumor genomic (DNA or RNA), proteomic (active enzymes), or phosphoproteomic (active and inactive enzymes) markers are referred to as *molecular diagnostics*. These tests are used in oncology clinical research to study "targeted agents matched with tumor molecular aberrations"[2] and in patient care settings to direct cancer treatment. In the United States, these diagnostics must be performed in a CLIA (Clinical Laboratory Improvement Amendment)–certified laboratory in order to be used for patient care decisions. (CLIA certification defines standards and methods for processing of tests but does not certify clinical utility).

The introduction of next-generation sequencing (NGS) revolutionized the way oncology researchers and practitioners use molecular profiling to study and treat patients with cancer. NGS provides increased sequencing speed along with greatly reduced cost, compared with the classic Sanger method.[9] These advances have led to the sequencing of thousands of human genomes.[10]

With such advances in human genome sequencing increasing understanding of the basis of disease, NCCN believes it is important to understand how such testing is being performed and used at NCCN Member Institutions and their community affiliates. In order to do so, the NCCN Oncology Research Program's (ORP) Investigator Steering Committee (ISC) and the NCCN Best Practices Committee developed surveys for molecular profiling/diagnostics at NCCN Member Institutions and community sites participating in the NCCN Affiliate Research Consortium.

The NCCN ISC plays a critical role in the operations of the NCCN ORP. The NCCN ISC is comprised of 26 senior research physicians, with one representative appointed by each NCCN Member Institution. The committee is responsible for advising the NCCN ORP on research policies. Members also serve as key contacts for channeling studies into the research framework of each NCCN Member Institution and identifying appropriate investigators for NCCN ORP research projects.

The NCCN Best Practices Committee provides a unique opportunity for 27 senior physician and administrative leaders from NCCN Member Institutions to collaborate, network, and share forward-looking strategies aimed toward improving the effectiveness and efficiency of cancer center operations. Committee members have extensive experience and knowledge regarding the management of academic cancer centers, and all share the same goal of working together to improve cancer care across the nation.

The objectives of the surveys were to obtain data on

- Where, when, and how testing is performed,
- The use of molecular profiling/diagnostics in treatment decision-making for patients,
- Barriers and challenges to incorporating molecular profiling/diagnostics in clinical practice,
- Barriers and challenges to incorporating molecular profiling/diagnostics in clinical research,
- General management of testing and testing results, and
- Funding and reimbursement for testing services.

In the context of these surveys and the following report, "molecular profiling/diagnostics" is confined to DNA testing and denotes a panel of at least 10 genes examined as a diagnostic test in a CLIA-certified laboratory.

Results from these surveys are intended to provide baseline information on the current use of cancer-related molecular testing at NCCN Member Institutions and community members of the NCCN Affiliate Research Consortium, which may lead to the development of policies and practices regarding these tests, as well as research to improve the use of and outcomes associated with their use.

Methods

ISC Survey

The survey questions were initially developed and further clarified by the ISC. The survey was accessible through SurveyMonkey, an online cloud-based software for creating and publishing questionnaires. In December 2013, the survey was sent to ISC mem-

bers, with instructions to distribute it to appropriate staff at their respective institutions for completion and submission to NCCN. Survey responses were collected through SurveyMonkey and then downloaded for analysis into a spreadsheet application. See supplemental eAppendix 1 for the ISC survey (available online with this article at JNCCN.org).

Initial analysis of survey data was conducted by NCCN ORP staff in December 2013, and preliminary results were presented at the December 2013 ISC meeting. Updated survey results were then discussed at the January 2014 ISC meeting. The Committee Chair indicated that more responses were needed, especially from Affiliate Research Consortium community sites. Additional responses were collected through September 2014. Results were analyzed and are presented herein. These results are based on data collected primarily from January 2014 through September 2014.

Best Practices Committee Survey

Molecular diagnostic testing was highly rated on the September 2014 Best Practices Committee meeting topics survey, leading to the development of a specific molecular profiling/diagnostics survey to obtain information regarding the general management of testing and testing results, as well as funding and reimbursement for testing services.

Two members of the Best Practices Committee piloted the survey before it was disseminated to the entire committee via SurveyMonkey in July 2014. Committee members were provided a list of ISC survey respondents and asked to consult with someone other than the person who responded to the ISC survey in order to obtain a business perspective for the Best Practices survey. The survey results were presented to the committee at the September 2014 meeting. See supplemental eAppendix 2 for the Best Practices Committee Survey.

Results

Overall, 24 of 25 NCCN Member Institutions (96%) and 8 of 10 affiliate sites (80%) responded and provided quantitative and qualitative data for one or both of the surveys.

ISC Survey

A total of 23 of 25 NCCN Member Institutions (92%) and 8 of 10 affiliate sites (80%) responded to the ISC survey (a list of participating institutions is provided in supplemental eAppendix 3). There were 41 respondents, 7 of whom provided incomplete responses (83% complete response rate). Respondents included individuals with various roles within their institutions, including department chairs, medical directors, laboratory directors, research administrators, physicians, executives, professors, and managers.

Use of Molecular Profiling/Diagnostics: Molecular profiling/diagnostics are used at 100% of the respondents' institutions to make patient care decisions. Figure 1 represents the purposes for which molecular profiling/diagnostics are used at the institutions surveyed. Figure 2 specifies the settings in which NCCN Member Institutions use molecular profiling/diagnostics to make patient care decisions.

Responses of "other settings" included testing for specific malignancies (eg, leukemia and lung cancer), clinical studies, and other research-based testing.

Processes: Among the respondents, 72.2% (n=26) indicated that molecular profiling/diagnostics were performed in-house and 2.8% (n=1) were unsure who provided molecular profiling/diagnostics.

Approximately 83% (n=30) indicated that some molecular profiling/diagnostics were outsourced. Testing was outsourced to the organizations listed in Table 1.

The fact that 72.2% of respondents stated that molecular profiling/diagnostics were performed in-house and 83% outsourced indicates that many institutions used both in-house and outsourced molecular profiling/diagnostics.

Respondents not currently performing molecular profiling/diagnostics in their institutions' CLIA laboratories were asked if there were plans for it to be performed in-house within the next year. Approximately 47.1% of respondents indicated "yes," 35.3% indicated "no," and 17.6% were "not sure."

Among respondents' institutions, numerous platforms were used alone or in conjunction with NGS. Therefore, although approximately 64% of respondents indicated that the most frequently used technology for in-house molecular profiling/diagnostics at their institution was NGS, 27% indicated that other technologies, such as immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), single-gene Sanger sequencing, and genomic microarray, were also used at their institutions.

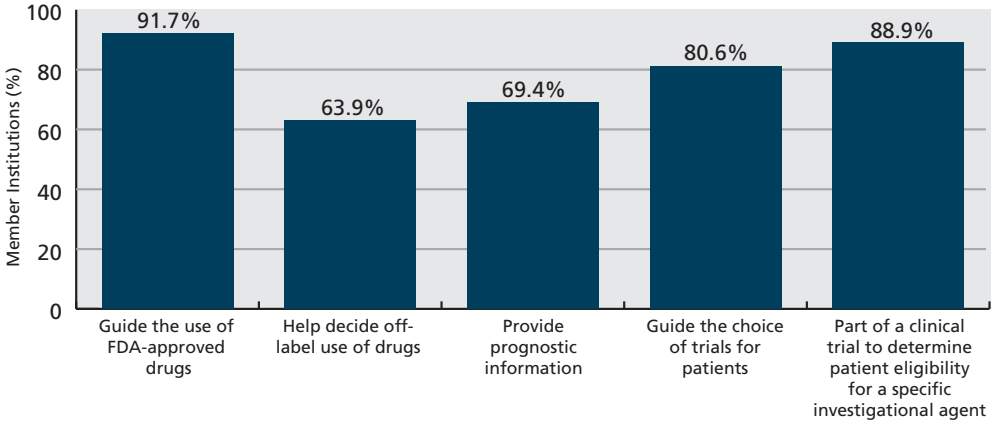

Figure 1 Use of molecular profiling/diagnostics at NCCN Member Institutions (n=36).

Based on available self-report responses, it appears that the most commonly used "in-house" NGS panel includes 50 genes or less, as depicted in Table 2.

Samples: At respondents' institutions (n=33), molecular profiling/diagnostics are most frequently performed on either new biopsies or archived tissue (78.8%), new biopsies only (12.1%), or archived tissue only (9.1%). The most frequent sources of tissue specimens are either primary tumors or metastatic sites (60.6%), primary tumors only (21.2%), or metastatic sites only (15.2%); 3% were unsure of the most frequent source.

Informing Patient Care: Therapeutic decisions informed by molecular profiling/diagnostics may include a choice of either specific clinical trials or approved drugs used on- or off-label. Most respondents (57.6%) indicated that results from molecular profiling/diagnostics influence less than 30% of patients. However, 18% felt that these tests influenced more than 50% of patient care decisions. It should be noted that the percentage of results that impact patient therapy might be influenced by factors not assessed in this survey, including training of the oncologists, the number of genes in the panel, drug availability, and the focus of the ordering physician. Table 3 demonstrates the estimated percent of molecular profiling/diagnostics results that help to inform decisions regarding choice of patient therapy (therapy decisions informed by molecular profiling/diagnostics may include a choice of either specific clinical trials or approved drugs used on- or off-label).

A number of challenges regarding the use of NGS results to influence patient care decisions were also evident, as depicted in Figure 3. In addition to coded responses, institutions also flagged delayed availability of results, mutations of uncertain clinical significance, test interpretation, lack of efficacy evidence (drug vs target), and clinical

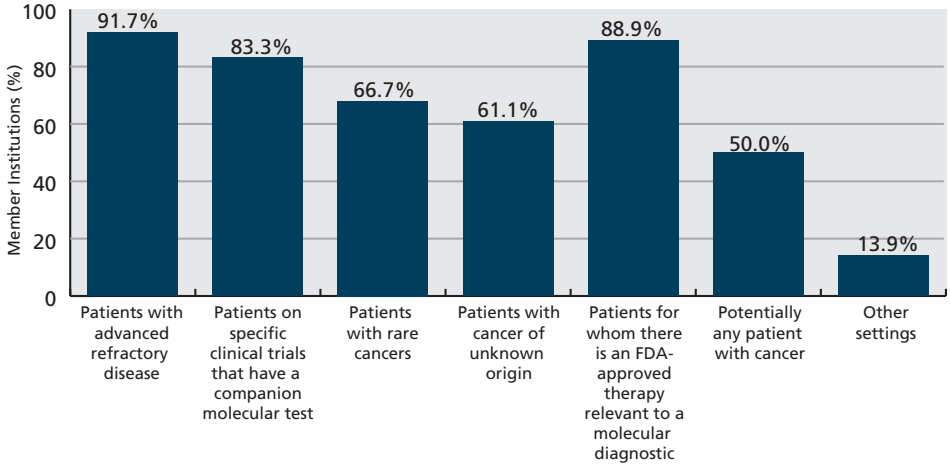

Figure 2 Use of molecular profiling/diagnostics in the patient care setting (n=36).

Table 1 Outsourced Organizations Used for Molecular Profiling/Diagnostics (n=36)

Outsourced Organization	Percentage of Member Institutions
Oncotype Dx, Genomic Health	75.0%
Foundation One	63.9%
Other	36.1%
Caris Molecular Intelligence	27.8%
Response Genetics	16.7%
MammaPrint	13.9%
Not sure	11.1%
Knight Diagnostics	8.3%
Not applicable	2.8%

Table 3 Estimated Percent of Results That Inform Patient Therapy Decisions (n=33)

Molecular Profiling/Diagnostics Results that Inform Patient Therapy Decisions	Percentage of Respondents
0%–10%	27.3%
10%–20%	21.2%
20%–30%	9.1%
30%–40%	12.1%
40%–50%	12.1%
>50%	18.2%
Total	**100.0%**

trial eligibility issues as other important barriers to effective translation of NGS results to patient care.

The most significant challenges for the use of NGS reported by the 33 respondents, in both routine and clinical research settings, related to cost/reimbursement, the lack of data regarding actionable targets and targeted therapies, and obtaining tissue. The list of specific challenges is detailed in supplemental eAppendix 4. It should, however, be kept in mind that even the definition of "actionable" may be highly controversial among the NCCN Member Institution respondents participating in this project. To some, it is any molecular abnormality in a pathway for which there exists a drug. For others, it is a mutated or amplified entity targeted by a specific drug. And to many others, it is formal evidence shown by clinical trials that the use of the drug in this setting is beneficial.

Frequently, molecular profiling/diagnostic assays are associated with a report of findings and may offer further guidance. Table 4 specifies the elements of these reports that are helpful in practice. Although a number of components were considered to be of high importance, the top 3 most helpful elements included a summary of available drugs, analysis of supportive literature, and availability of relevant clinical trials.

Table 2 Number of Genes Analyzed by the Most Frequently Used In-House Technology (n=33)

Number of Genes Analyzed	Percentage of Respondents
1–25	18.2%
26–50	24.3%
51–100	3.0%
101–200	6.1%
201–300	12.1%
301–400	3.0%
401–500	3.0%
Not applicable	18.2%
Unsure	12.1%
Total	**100.0%**

Ordering and Reimbursement: A number of practical challenges related to ordering and reimbursement regarding the use of NGS also emerged. The most commonly cited difficulty was a lack of reimbursement for the performed test. However, tissue availability and result turnaround time were also reported as issues in more than 70% of respondents. Figure 4 specifies the challenges respondents experience when ordering molecular profiling/diagnostics.

For this particular question, a number of "other" challenges were also identified, including excessive patient cost/value and a lack of scientific evidence.

The most common reasons for inadequate reimbursement by insurance for tests were reported as "refusal to cover specific test(s)" (72.7%), "denial of any coverage" (57.6%), "high copay for patients" (36.4%), and "other" reasons (21.2%), including those outlined as follows (n=33):

- Limitations on reimbursements close to hospitalization
- Inadequate reimbursement
- Low coverage amounts despite high cost of performing the testing

Clinical Trials: Approximately 88% of respondents indicated that they use molecular profiling/diagnostics for decision-making in clinical trials. Figure 5 specifies the challenges that respondents experience when using the results of molecular profiling/diagnostics in clinical trials.

"Other" challenges noted by respondents included:

- Excessive/overlapping testing
- Patient cost, anxiety, and relative value

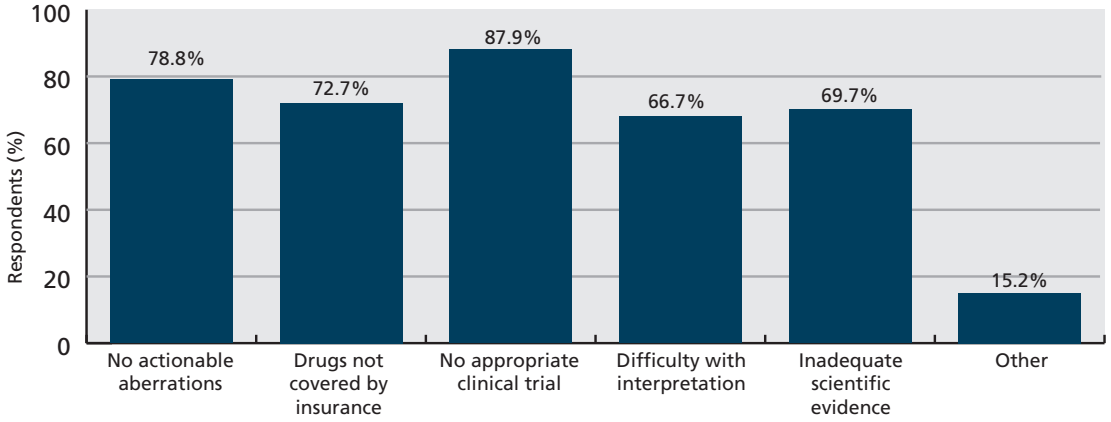

Figure 3 Challenges in using the results of molecular profiling/diagnostics testing to make patient care decisions (n=33).

- Managing media "hype" and unrealistic patient expectations
- Obtaining archival tissue

Approximately 88% of respondents indicated that more clinical trials are needed to better refine the appropriate use of molecular profiling/diagnostics.

Best Practices Committee Survey

A total of 15 NCCN Member Institutions (60%) responded to the Best Practices Committee survey. Respondents included individuals with various roles, including medical directors, executive directors, laboratory and business managers, and division heads.

Management of Testing and Testing Results: Figure 6 specifies which molecular diagnostic testing results are placed in patient medical records. Some centers indicated that all test results are reported in the medical record, whereas other centers indicated that only CLIA-certified nonresearch testing becomes part of the medical record. "Other" test results included clinical trials results.

Approximately 73% of respondents' institutions have policies (formal or informal) regarding the management of clinical lab results in repositories, databases, registries, etc. Figure 7 specifies the current governances within institutions that oversee molecular testing.

Approximately 93% of respondents' institutions have a research and development infrastructure to promote the creation and development of new molecular diagnostic tests. Details on these infrastructures are listed in supplemental eAppendix 5.

Funding and Reimbursement for Testing Services: Among 7 respondents, 4 indicated that between 50%

Table 4 Elements of Molecular Profiling/Diagnostics Reports That Help in Practice (n=33)

	Percentage of Respondents Who Found This Helpful
Listing of agents associated with potential clinical benefit[a]	72.7%
Analysis of scientific literature to provide a level of evidence supporting recommended agents associated with potential clinical benefit	72.7%
Relevant clinical trials based on the patient's tumor type and biomarker expression	69.7%
Listing of agents associated with lack of potential clinical benefit	57.6%
Breakdown of specific results for all biomarkers analyzed by IHC, FISH and CISH, PCR, DNA sequence analysis, and next-generation sequencing	57.6%
Patient-specific information such as biomarker expression levels and pathologic diagnosis	54.5%
Analysis of scientific literature to provide a level of evidence associated with agents associated with lack of clinical benefit	54.5%
Description of each of the relevant biomarkers, as well as a summary of these biomarkers' roles in cancer biology and treatment	48.5%
Other	9.1%

[a]The definition of "clinical benefit" and the evidence needed to determine it is a matter of debate, especially as related to molecular diagnostics.[14]
Abbreviations: CISH, chromogenic in situ hybridization; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; PCR, polymerase chain reaction.

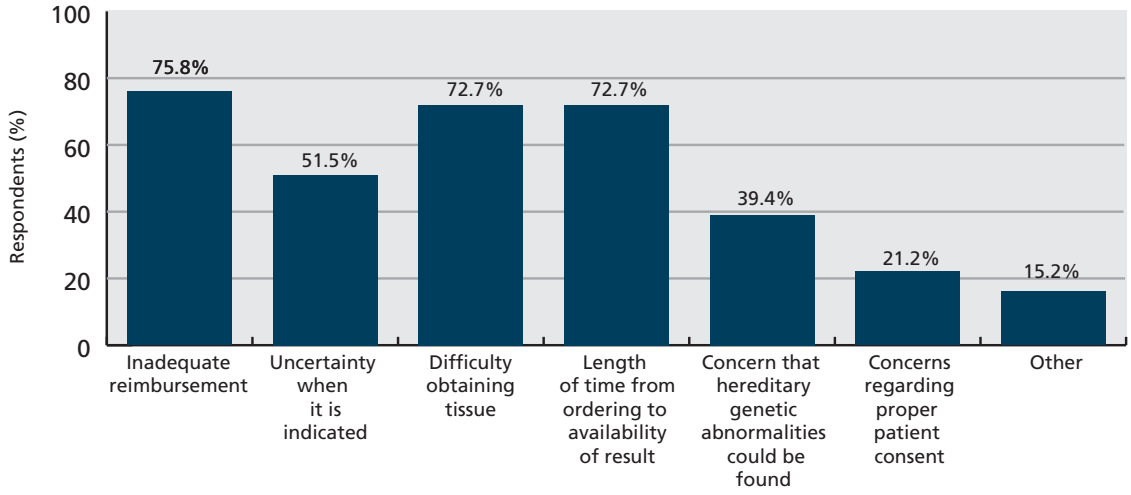

Figure 4 Challenges in ordering molecular profiling /diagnostics (n=33).

and 74% and 3 indicated that between 75% and 90% of all molecular diagnostic testing cases receive third-party reimbursement at their institutions. Reimbursement rates (actual reimbursement/actual test cost) were not queried. The small number of respondents precludes definitive conclusions regarding this important issue.

Approximately 47% of respondents' institutions bill patients if a molecular test is not covered; 20% of respondents' institutions "sometimes" bill patients if a molecular test is not covered.

Sixty percent of respondents' institutions receive reimbursement for new or developing tests and/or panels from third-party payers. Explanations of institutional reimbursement structures and funding for molecular testing conducted solely for research purposes are listed in supplemental eAppendix 5.

Discussion

The NCCN Molecular Profiling/Diagnostics Surveys yielded a high volume of quantitative and qualitative data for the ISC and Best Practices Committee. It appears that most respondents used multigene molecular diagnostics panels in some capacity. Most had in-house molecular diagnostics or planned to initiate it within a year, but most institutes also outsourced some of their testing to a variety of providers/vendors. Molecular diagnostics were most commonly used in patients with advanced or refractory tumors, rare malignancies, and tumors of unknown origin, and for FDA-approved indications and specific molecularly driven trials, but 50% of respondents claimed to use these diagnostics for potentially any patient

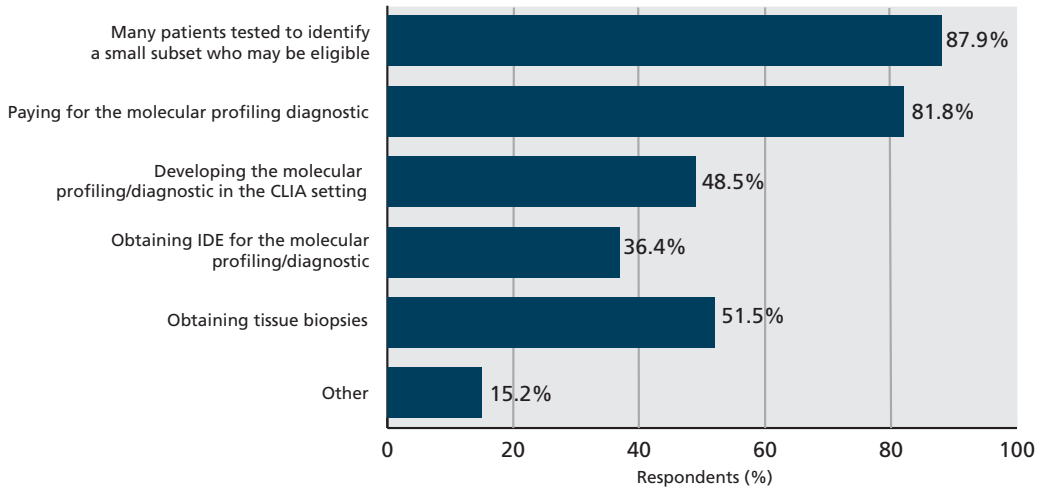

Figure 5 Challenges in using the results of molecular profiling/diagnostics in clinical trials (n=33).
Abbreviations: CLIA, Clinical Laboratory Improvement Amendment; IDE, investigational device exemption.

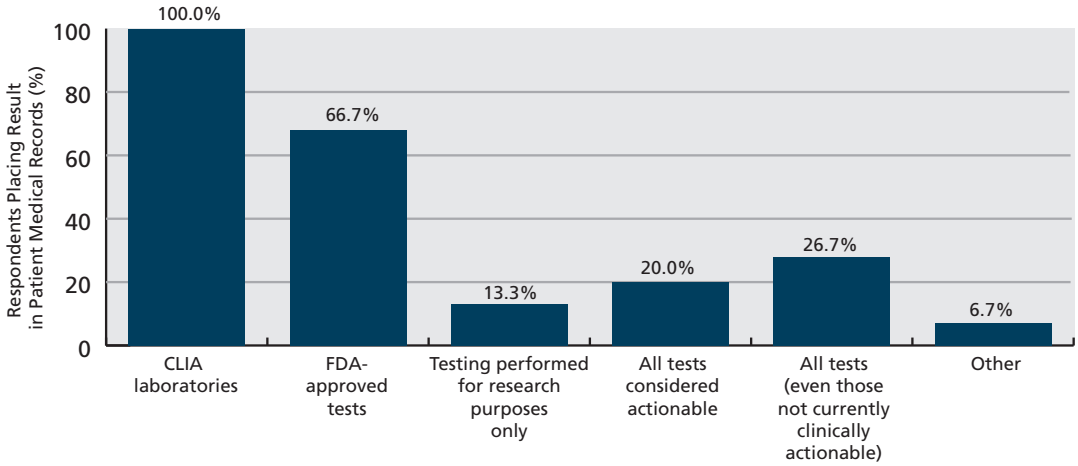

Figure 6 Molecular diagnostic results placed in patient medical records (n=15).
Abbreviation: CLIA, Clinical Laboratory Improvement Amendment.

with cancer. Results from this survey complement data from a survey of more than 100 oncology clinicians who attended the 2015 ASCO annual meeting.[11] More than half of clinicians surveyed indicated they would be likely to use molecular diagnostics for patients who lack other therapy options. However, only 24% indicated they would use molecular diagnostics for patients who had other therapy options. The surveyed clinicians expect that emerging molecular diagnostic tests will account for one-quarter of their treatment decisions over the next decade.

Challenges to the use of molecular diagnostics in clinical trials included those related to identifying small subsets of patients, paying for the tests, developing the tests in a CLIA environment, challenges associated with obtaining an FDA-required Investigational Drug Exemption, and difficulty with obtaining tissue and/or tissue biopsies. Challenges regarding ordering related mostly to difficulty obtaining tissue and length of time to availability of results. Obstacles to the use of the results of these tests included lack of access to an appropriate clinical trial, difficulty with insurance paying for the drugs, and scientific issues related to levels of evidence or actionability.

Concern about reimbursement was a recurring theme at responding NCCN Member Institutions, consistent with the challenges currently facing many investigators, practicing physicians, and health care institutions.[12] Insurance companies may be unwilling to reimburse the cost of molecular profiling in many tumor types, and the lack of consensus on what constitutes clear evidence that molecular

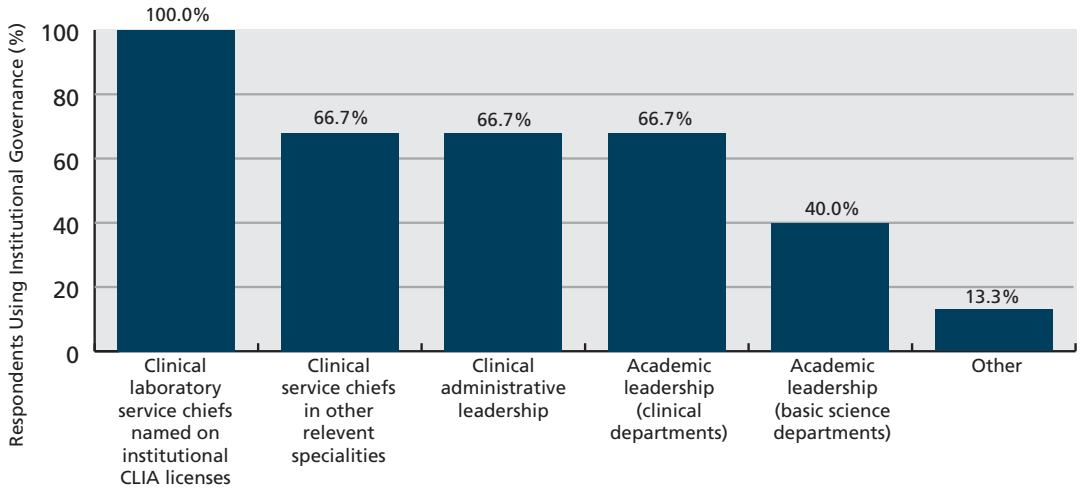

Figure 7 Current institutional governances overseeing molecular testing (n=15).
Abbreviation: CLIA, Clinical Laboratory Improvement Amendment.

profiling is clinically relevant and cost-effective is a challenge, outside of a few select molecular tests in melanoma and lung, colorectal, breast, and gastroesophageal cancers.[13] For patients enrolled in approved clinical trials, the Patient Protection and Affordable Care Act (ACA) established a national minimal coverage standard. However, enforcement issues, debate regarding the definition of "standard of care," and lack of consensus regarding coverage for services in clinical trials create many uncertainties. In a recent paper in the *Journal of Clinical Oncology*, Martin et al[12] recommended that items/services necessary for the care of the patient should be covered if the patient is participating in a clinical trial. Because molecular diagnostics are being used within clinical trials to make patient care decisions, coverage of molecular profiling within clinical trials would fall under this rubric, but the real-world situation may be less certain.

The need for additional data regarding actionable targets and targeted therapies was a recurring theme. The number of genomic biomarkers identified through NGS has outpaced researchers' and clinicians' knowledge of the way in which many biomarkers predict therapeutic response and the development of new cancer therapies.[14,15] In response to this challenge, Vidwans et al[14] proposed a framework for using the results of molecular diagnostics in patient care based on the level of evidence regarding the biomarker's actionability. Frameworks such as these, combined with continued research into the predictive value of biomarkers and targeted therapies, are needed in order to advance our understanding of the use of genomic biomarkers in patient care.

Once an actionable target is implicated, however, respondents at NCCN Member Institutions also reported subsequent challenges in medication acquisition. A targeted therapeutic agent may be sought after for use within the labeled indication, use within a clinical trial, off-label use of a marketed product, or compassionate use of a drug that is undergoing regulatory review.[15] Several barriers to medication access exist within each of these uses, including reimbursement and matching patients to clinical trials, because eligibility criteria are often numerous and strict, and clinical trials may be performed far from where the patient resides. New models for clinical trial design have been suggested to more effectively match patients with appropriate clinical trials. Examples include trials that "test a variety of drugs against the 'actionable mutations' detected in a specific tumor type or that test a single drug against a single aberration that occurs in several tumor types,"[15] or a more patient-centric approach, as described by Wheler et al.[16] Similar recommendations were outlined by an NCCN Working Group regarding a clinical trials process that allows for the concurrent evaluation of multiple targeted strategies and broad testing of novel strategies across tumor types that share predictive markers.[17] Major initiatives are underway that will begin to address some of these questions, including the NCI-MATCH trial and Lung-MAP trial (ClinicalTrials.gov identifier: NCT02154490), both of which are comprehensive precision medicine trials backed by the NCI.[18,19] It seems reasonable to prioritize testing on limited samples for patients who are most likely to benefit by virtue of the probability of their having an actionable alteration or their being included in a clinical trial, and hence their data will inform future practice.

There were several limitations to this study. First, the surveys were answered by only a small number of representatives of each institution, and the types of institutions were heterogeneous, and hence might not reflect the perspective of all stakeholders. Prior evidence also suggests diverse opinions regarding molecular diagnostics, a range of test availability, and diverse adoption patterns.[20,21] Second, when speaking about actionability or informing patient care decisions, percentages might be influenced by factors such as the comprehensiveness of the panel used at the institution, familiarity of the oncologists with molecular testing, availability of clinical trials, and threshold for defining scientific evidence used by the respondent.[14,20,21] Some of these factors, such as the training of the oncologists, precise number of genes in the panel, drug availability, and the exact cancer type under consideration could not be well assessed by this survey. Third, certain assays such as Onco*type*Dx and MammaPrint, although they are molecular assays, have a very different history and use pattern compared with other genomic panels, and have been studied far more extensively. However, their distinctions suggest that the use of these assays alone may not reflect institutional commitment to molecular profiling.

Conclusions

Most NCCN Member Institutions and their Affiliated Institutions are using molecular/diagnostic testing panels. Our survey, as well as other reports, have demonstrated challenges to adoption of molecular diagnostics, both for clinical trials and clinical practice.[20,22] The placement of these tests is becoming progressively more important to define, as recent data suggest an increasing proportion of patients who have an aberration that is at least theoretically actionable.[23] Challenges related to reimbursement, the need for more trials and clinic evidence, regulatory hurdles, access to drugs on or off clinical trials, coverage of costs for off-label drugs, factors regarding obtaining tissue, educating physicians on how to interpret and act on genomic results, and communication of results to patients are all concerns surrounding molecular profiling/diagnostics that need to be addressed.

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