The Precision Oncology Annual Trend Report

Perspectives From Payers, Oncologists, and Pathologists

Second Edition

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Foreword

In his 2015 State of the Union message, President Obama launched a Precision Medicine Initiative to, in his words, "bring us closer to curing diseases like cancer and diabetes." In doing so, he underlined the promise of a new medical paradigm. Equally dramatic, and with major implications for the future of medicine, 20% of the new molecular entities approved by the U.S. Food and Drug Administration (FDA) in 2014 are personalized medicines; that is to say they include biomarker test data in their labels to guide their applications. And this trend is continuing.

Yet, we know that the movement from one-size-fits-all, trial-and-error medicine to medicine that is targeted and based on each patient's individual molecular profile is far from easy, presidential proclamations and FDA encouragement notwithstanding. It is going to take deliberate efforts by stakeholders from across the health care spectrum to change the status quo. In particular, providers and payers must join pharmaceutical and diagnostic developers to move medicine toward a commercial environment that incentivizes the development of evidence-based, personalized medicine products.

This is why *The Precision Oncology Annual Trend Report: Perspectives From Payers, Oncologists, and Pathologists,* Second Edition, is so important. By providing quantitative insights based on survey data into how communities both understand and incorporate personalized or precision medicine into policy and practice, the report helps decision makers in industry and government recognize the salient issues that must be addressed in order to accelerate the progress upon which patients depend.

Through these findings, we learn, for example, that while most oncologists and payers indicate they welcome the development of more targeted therapeutics, they also say they want to see more evidence of improved survival vs standard of care. They are also very concerned about the cost of the new drugs and, therefore, want to see more evidence of clinical utility.

But the good news is that when these thresholds are met, physicians are willing to change the way they treat cancer. In addition, payers are willing to pay for the new therapies, thus offering hope that we are on the precipice of a new era.

Edward Abrahams, PhD
President
Personalized Medicine Coalition

Introduction

Welcome to *The Precision Oncology Annual Trend Report: Perspectives From Payers, Oncologists, and Pathologists*, Second Edition. Developed to provide updated information on the usage of precision medicine in oncology, this report provides insights into the trends affecting utilization and coverage of predictive biomarker tests. Biomarker tests offer an objectively measured characteristic that describes a normal or abnormal biological state in an organism through analysis of biomolecules including DNA, RNA, protein, peptide, and biomolecule chemical modification.[1,2] Predictive biomarker tests predict response to specific therapeutic interventions, such as positivity/activation of HER2 that predict response in breast cancer.[2-5] A subset of these predictive biomarker tests includes companion diagnostic devices, which are FDA approved for the safe and effective use of a corresponding therapeutic product.[2,6]

As you will see in this report, precision medicine in oncology holds many potential treatment benefits including increased efficacy, and reduced costs.[7-11] The results of this report reveal the growing impact and importance that predictive biomarker tests have on treatment decision making. Appropriate reimbursement, promotion, and use of diagnostic testing can serve to enhance the patient experience, patient outcomes, and appropriate resource utilization.

Please note that although prognostic biomarker tests have an influence on treatment by determining the aggressiveness of the disease, this report does not review them in detail, as they do not directly determine therapeutic usage.

Another change that has been incorporated into the data of this report compared with its previous iteration is the inclusion of pathologists in the research. Because pathologists typically use predictive, prognostic, and diagnostic biomarker tests when evaluating a tumor biopsy, the inclusion of this key member of the patient care team offers new insights.

Novartis continues to produce this report for the oncology community to shed light on the developing impact and utilization of biomarker tests, with the aim of accelerating the adoption of precision medicine in oncology. This report and the overview of the potential benefits, coverage, and utilization of precision medicine in oncology provides a timely snapshot of this rapidly evolving new clinical paradigm.

Executive Summary

The promise of precision medicine in oncology is not a new one; however, after many years of research, we are at a point where precision medicine is no longer an idea but a reality that continues to gain acceptance. The growing availability of detailed genetic and other molecular information enables the selection of oncology treatments that are more effective and patient specific.[8]

Research discoveries continue, as evidenced by the approval of 9 new anticancer therapeutics by the FDA between August 1, 2014, and July 31, 2015. Of these, 4 are molecularly targeted agents.[12] A strong pipeline speaks to the breakneck speed at which these innovations in targeted therapeutics continue to advance.

Even as President Obama recognizes the potential of precision medicine to revolutionize oncology care, improve quality of care, and reduce costs, there remains an urgency to strengthen adoption.[7] To achieve these goals, manufacturers, oncologists, pathologists, and payers must work together to ensure appropriate adoption of precision medicine in oncology.

Specifically, the widespread implementation and accepted coverage of biomarker tests in oncology precision medicine faces several challenges, including:

- The further development of payer-relevant health economics data
- Overcoming regulatory challenges
- Stronger cooperation between diagnostic and therapeutic manufacturers, oncologists, and reference labs to develop outcomes data

The findings in this report are based on market research conducted with commercial plans; government payers were not included, as they were beyond the scope of this report. Medicare reimbursement for oncology predictive biomarker tests is also shifting the landscape as the Centers for Medicare and Medicaid Services (CMS) attempts to manage the cost of testing. Unfortunately, Medicare's and other payers' underpayment or unclear payment policies have dampened molecular biomarker test innovation and development.[13]

"The issue of cost is going to play a much bigger role in impacting biomarker testing in the future."

– Pathologist

Key Findings

- Payers act as de facto arbitrators of predictive biomarker test utilization through the influence of their coverage decisions. Coverage tends to lag the desire to utilize predictive biomarker tests by oncologists and pathologists
- As the primary cancer care providers, oncologists are key drivers of oncology predictive biomarker utilization. Their vital influence also affects the creation of clinical guidelines for respected organizations including the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network® (NCCN®), payers, and local practices (ie, hospitals and community-based practices)
- Payers and providers consider the following to be key drivers for guideline inclusion:
  - Clinical utility of test
  - Endorsement by influential organizations (eg, ASCO, NCCN, College of American Pathologists [CAP], FDA)
  - Reasonable cost. As biomarker test cost increases (eg, more than $1000), scrutiny increases and payers look for alternatives in the absence of a strong cost-benefit analysis
- The most important data sources driving biomarker test coverage and/or guidelines (eg, genomic sequencing panels) are clinical utility and cost
- Payers who are currently generating cost-benefit data are very committed to utilizing predictive biomarker tests and have realized improvements in outcomes and cost savings
- As the cost of therapeutics rises, predictive biomarker tests and the quality of associated outcomes could become important cost-effectiveness differentiators. This research indicates that a PD-1/PD-L1 biomarker test may impact payer and provider preference between PD-1/PD-L1 inhibitors
- As the cost of next generation sequencing (NGS) falls and evidence of its clinical utility accumulates, expanded payer coverage is anticipated
- Results of the ongoing large basket trials (Targeted agent and profiling utilization registry [TAPUR] and molecular analysis for therapy choice [MATCH]) that utilize NGS could redefine patient treatment based on biomarker test status regardless of tumor type

Methodology

Primary research for this report consisted of data obtained between August 2015 and September 2015 through a web-based survey. In addition, qualitative, in-depth interviews were conducted with providers (ie, oncologists and pathologists) and individuals from commercial health care (ie, medical directors and pharmacy directors) who are familiar with their companies' current coverage of predictive oncology biomarker tests during this same time period. While not surveyed in last year's report, pathologists were included in this year's research, as they are an important part of the treatment team and are expert users of oncology predictive biomarker tests. The survey and in-depth interviews were conducted anonymously.

The report provides data on the following:

- Influencers of utilization and coverage
- Current and anticipated predictive biomarker test utilization and coverage
- Predictive biomarker tests as drivers of precision oncology therapy cost effectiveness
- Next generation sequencing
- Market trends and the evolution of precision oncology

For the purpose of the market research study, an oncology predictive biomarker test and/or companion diagnostic was defined as a biomarker test that determines the likely benefit from a specific targeted therapeutic treatment. A prognostic biomarker test was defined as a test that provides information on the likely outcome of the cancer (ie, risk for progression). The research did not look at the use of prognostic biomarker tests. While considered important tools in determining the aggressiveness of the disease that may indirectly influence treatment, they do not directly influence choice of a specific therapeutic agent.

Sample Demographics

	Online Survey Sample Size	In-Depth Telephone Interviews Sample Size
Oncologists	50	5
Pathologists	25	5
Payers	50	5

Oncologist Demographics

Oncologist respondents in the study practiced at a variety of settings, including privately owned community practices, hospitals, and academic cancer centers. There was national representation in the sample, and the mean time spent in active clinical practice was 93% (Figure 1).

Figure 1 **Oncologists' Site of Care**

n=50 oncologists

Payer Demographics

The majority of payer respondents in this study were medical and pharmacy directors employed by larger-sized health plans, (ie, 1 million or more covered lives) with the remaining 5% of lives managed through medium-sized plans (400,001 to 999,999 managed lives) (4%) and small plans (400,000 or less managed lives) (1%) (Figure 2). Medical directors made up the majority of payer respondents (62%). Pharmacy directors were also surveyed (38%). These payer respondents represented plans covering 175 million lives.

Figure 2 **Percent of Participating Payers by Number of Lives Managed Annually**

Plan Size	Mean No. of Lives Managed
Small (400,000 or less managed lives)	80,000
Medium (400,001 to 999,999)	780,000
Large (1 million or more managed lives)	3.3 million

n=50 payers

Market Trends and the Evolution of Precision Oncology

The acceptance and usage of precision medicine in oncology continues to expand, with numerous biopharma companies in the process of developing new oncology products that require biomarker tests.[14-17] At the time of print, there were 9 oncology therapeutics approved by the FDA with a companion diagnostic.[6]

Most stakeholders surveyed support that the appropriate reimbursement of companion diagnostics by payers coupled with the utilization of diagnostic testing by providers will lead to appropriate resource utilization while improving patient outcomes and quality of care.

Positive Basket Trials Will Change Payer Coverage and How Physicians Treat Cancer Patients

Basket trials, designed to define treatment according to biomarkers regardless of tumor type, are poised to change payer coverage and how physicians treat all cancer patients if the results are positive.[18-20] The majority of providers and payers surveyed for this report will make biomarker test status more important than a patient's tumor type when deciding treatment and its coverage, based on positive data from these trials.

Though most oncologists (88%) expected the trials to be successful in redefining the appropriate use of targeted oncology therapeutics by relevant predictive biomarker test/companion diagnostic as opposed to by tumor type (eg, breast, non-small cell lung cancer [NSCLC], prostate, etc), only half of the payers agreed. This mixed reaction is most likely driven by the need to see published clinical results.

Providers and payers believe successful TAPUR and MATCH data will make biomarker test results more important than a patient's tumor type when making coverage or treatment decisions.

Oncologists	Payers
92%	**72%**

Immuno-oncology Products Show Efficacy and Gain Approvals

Recently approved treatments such as pembrolizumab and nivolumab have demonstrated remarkable response rates in melanoma and NSCLC but at a significant price (approximately $150,000 [pembrolizumab] and $103,000 [nivolumab] per year of treatment).[21-24]

In October 2015, pembrolizumab was approved by the FDA for second-line treatment of NSCLC tumors that express high levels of the PD-L1 protein and included the first companion diagnostic to test PD-L1 levels.[25]

Could a PD-L1 Biomarker Test Improve Cost Effectiveness and Define PD-1/PD-L1 Therapeutic Utilization?

Providers and payers indicate a preference to prescribe and cover a PD-1/PD-L1 inhibitor with an effective biomarker test. A PD-1/PD-L1 inhibitor with a highly predictive biomarker test demonstrating significantly higher efficacy in the select patient population will be considered more cost effective than other PD-1/PD-L1 inhibitors that have not demonstrated this, and would gain preferred coverage and usage.

Providers' and Payers' Responses to PD-1/PD-L1 Inhibitor Coverage

Broader Adoption of Next Generation Sequencing and Genomic-Sequence Panel Utilization and Coverage

The development of NGS technology will increase the opportunity to identify multiple cancer-related gene mutations in a single, rapid, and eventually low-cost test. While current coverage is low, this report suggests an increase in the coverage of genomic-sequence panel tests over the next 12 months (Figure 3). Many providers and payers believe that NGS technology could change the face of cancer treatment and lead to greatly improved outcomes.

Payers' Current and Intended Coverage Over the Next 12 Months

Figure 3 **Percent of Respondents**

n=50 oncologists, 25 pathologists, and 50 payers

Payers surveyed indicated that a price threshold of just under $1000 would disrupt the market and potentially replace single mutation tests.

Influencers of Utilization and Coverage

Due to the cost of biomarker tests, their reimbursement can be critical to utilization by oncologists and pathologists (Figure 4). As a result, payers effectively act as the arbitrators of biomarker test utilization.

"We are trying to achieve the best outcomes possible for our members. That may mean the most efficient medication or it may mean the most efficient treatment pathway. Providing coverage for oncology predictive biomarker tests is critical to reach that goal."

– Medical director at a large-sized plan (>1 million lives managed)

The Impact of Predictive Biomarker Tests and Targeted Therapies to Enhance the Patient Experience

For the providers surveyed, the arrival of oncology predictive biomarker tests and the subsequent use of targeted therapies have resulted in marked improvements in outcomes as well as patient quality of life for some specific tumor types. Oncologists and pathologists expressed enthusiasm that new oncology biomarker tests will provide similar benefits across multiple tumor types.

Oncologists and pathologists cited the top factors that influence the decision to order an oncology predictive biomarker test (Figure 5), which include:

- The predictive power to identify treatment responders and non-responders
- Whether the test is recommended in patient-relevant clinical pathways and/or guidelines
- Whether the biomarker test is mandated in the therapeutic agent's FDA labeling

These findings are consistent with oncologists' reported factors in the first edition of *The Precision Oncology Annual Trend Report* (Figure 4).

Additional factors that were important to providers were revealed during the in-depth interviews. Pathologists expressed concern regarding the need to ensure test sensitivity/reliability, reference lab reliability, treatment team consensus, and whether there was enough tissue to perform the test. Several of the community-based providers mentioned that payers are starting to dictate preferred networks for reference lab testing.

In addition to lack of clinical utility data and guidelines, oncologists cited delays in care while awaiting test results as a key factor when making the decision to order an oncology predictive biomarker test.

During the in-depth interviews, pathologists reported that they have concerns regarding the future costs associated with biomarker tests and the need to keep the clinical utility at the forefront of decision making. Pathologists also mentioned concern over the amount of tissue that is needed to conduct large panels. Oncologists echoed this sentiment, citing that the clinical utility of biomarker tests will remain a major focus in the future.

Oncologists' Top 3 Concerns in 2014
1. Lack of clinical utility data
2. Lack of evidence-based guidlines
3. Obtaining insurance authorization

Oncologists' and Pathologists' Key Concerns When Making the Decision to Order an Oncology Predictive Biomarker Test Are Focused on Lack of Clinical Utility Data and Guidelines

Figure 4 **Percent of Respondents (Top 2 box score)**

n=50 oncologists and 25 pathologists

"Clinical utility is the most important factor. The best-case scenario is when you get prognostic and predictive results from a biomarker test."

– Oncologist

Oncologists' and Pathologists' Key Factors When Making the Decision to Order an Oncology Predictive Biomarker Test Are Focused on Predictive Power and Clinical Pathways/Guidelines

Figure 5 **Percent of Respondents (Top 2 box score)**

n=50 oncologists and 25 pathologists

Collaboration Opportunities

Interactions between oncologists, pathologists, and payers typically take place during payer advisory committee meetings. Pathologists and oncologists have more opportunities for interaction, as they routinely discuss biomarker testing at regular tumor board meetings to decide on specific tests for an individual patient.

Oncologists also reported an increased level of confidence in their genetic knowledge to inform clinical decision making for the use of oncology predictive biomarker tests in 2015 vs 2014. Of the oncologists surveyed, 45% consider themselves very confident with respect to their knowledge vs only 11% of oncologists in 2014.

Oncologists and pathologists rated the key factors influencing their decision to order a predictive oncology biomarker test for a solid tumor biopsy (Figure 6). Pathologists report that more standard pathways or guidelines are in place for testing of solid tumors vs hematological malignancies (75% vs 60%, respectively).

"We think about costs, but they are so small compared with the cost of the treatment that is being considered."

– Pathologist

Oncologists and Pathologists Rate Key Factors Influencing the Decision to Order a Predictive Oncology Biomarker Test for a Solid Tumor Biopsy

Figure 6 **Percent of Respondents (Top 2 box score)**

n=50 oncologists and 25 pathologists

Influence of Utilization and Coverage – Payers

Therapeutics

When making coverage decisions for new targeted therapies, 80% of payers consider improving patient survival as the most important factor. This data remains consistent with findings from the 2014 edition of *The Precision Oncology Annual Trend Report*. Other factors of meaningful importance in 2015 include direct cost of therapy, overall response rate, and improved duration of remission. Surprisingly, in 2014, payers ranked indirect cost of therapy as the third most important criteria when making coverage decisions, whereas it was rated the least important in 2015. This may reflect increased concern with the direct costs of new oncology therapeutics.

Companion Diagnostics and Predictive Biomarker Tests

Payers rated data that supports a biomarker's clinical utility as most important (78%) when making coverage decisions (Figure 7). Payers rated the test results gleaned from using a biomarker test and its ability to change or direct the course of treatment as second in importance (70%) followed closely by test performance (ie, specificity and sensitivity) and clinical validity, both rated as 68%.

Payers focused on lack of clinical utility data, ordering of test by physicians who do not use the test results, and lack of cost-effectiveness data as key factors (Figure 8). These results are similar to the findings from the 2014 edition of *The Precision Oncology Annual Trend Report* with the exception that cost of the test ranked second in importance in 2014.

"When we identify the genetic abnormality, we know that certain markers have been identified and there is specific therapy. So targeted treatment produces better outcomes and increases quality of life."

– Pathologist

Payers Rate the Importance of Data Sources When Making Coverage Decision for Companion Diagnostics

Figure 7 **Percent of Payers (Top 2 box score)**

n=50 payers

Payers' Top 3 Priorities in 2014
1. Clinical validity
2. Clinical utility
3. Test performance

When asked to comment on what factors may become more influential in the decision-making process for oncology predictive biomarker test coverage over the next 3 years, payers identified cost, new technology (eg, more specific biomarker tests driving better outcomes), and directives from provider organizations (ie, ASCO, NCCN, CAP).

Summary of Key Influencers for Provider Use and Payer Coverage of Oncology Predictive Biomarker Tests

- Data demonstrating clinical utility
- FDA approved in drug labeling
- Recommended/endorsed by ASCO, NCCN, CAP
- Reasonable cost

"Developers of companion diagnostics will need to provide tests that have very good clinical evidence that supports value. [They] must have very high clinical utility. If you keep costs at the lower end of the spectrum, it facilitates adoption because cost becomes less of a barrier."

– Pharmacy director at a large-sized plan (>1 million lives managed)

Payers' Key Concerns When Making Coverage Decision for Companion Diagnostics

Figure 8 **Percent of Respondents (Top 2 box score)**

n=50 payers

Payers' Top 3 Concerns in 2014
1. Lack of clinical utility data
2. Cost
3. Ordering of tests by physicians who do not use the results to support clinical decision making

Most Common Reasons Payers Do Not Cover Oncology Predictive Biomarker Tests

Payers were asked in the in-depth interviews which factors most commonly affect the exclusion of oncology predictive biomarker tests from being covered. Payers disclosed the following factors as being the most common reasons biomarker tests are not covered:

- The test does not result in a clinical decision
- The test has not made its way into guidelines
- The test is not FDA approved
- The test does not have specificity

Another common reason was whether the patient would seek treatment based on the test result (eg, for end-stage disease, returning to their permanent country of residence).

Although responses were mixed from payers regarding coverage of a new predictive biomarker test, they do suggest that the cost would be a strong influencer in final decision making to cover a new predictive biomarker test.

Current and Anticipated Predictive Biomarker Test Utilization and Coverage

Rising costs associated with cancer care alongside the arrival of increasingly expensive oncology predictive biomarker tests and/or genome sequencing panels drive payers to look for key areas or criteria that will help them make coverage decisions for oncology predictive biomarker tests.

Critical Areas When Making Coverage Decisions

Figure 9 explores the critical areas for payer consideration when making coverage decisions for companion diagnostics. Of those surveyed, 72% of payers consider the most important factor to be whether the biomarker test has clearly demonstrated predictive power to identify treatment responders, and non-responders, and 66% look to see if the oncology predictive biomarker test is mandated in the therapeutic's FDA labeling.

Other key areas payers considered very important were diagnostic test cost effectiveness (48%), recognition of the biomarker test on a recognized external clinical pathway (46%), and direct cost and per-member, per-year impact of the diagnostic test (46%).

Payers reported that they use a variety of management strategies to control the use and cost of oncology predictive biomarker tests. Leading strategies currently employed by payers included prior authorization requirements (56%), attestation of test results from the provider (46%), and requiring the use of the biomarker test before approval of the therapeutic (44%).

Looking at payers' intentions to use a management strategy in the next 12 months, the 2 strategies that will most likely increase in use are the requirement to use the biomarker test prior to receiving drug approval (40%) and payers' intention to conduct internal retrospective reviews to determine appropriate test use (38%) (Figure 10).

Payers' Key Areas for Consideration when Making Coverage Decisions for Companion Diagnostics

Figure 9 **Percent of Payers (Top 2 box score)**

n=50 payers

Payers' Use of Oncology Clinical Pathways

Figure 10 **Percent of Payers Using Oncology Clinical Pathways**

n=50 payers

Payers are currently including biomarker tests as part of their clinical pathway measurements. Of the payers surveyed, 56% reported including oncology predictive biomarker tests and 35% are including prognostic biomarker tests. Additionally, payers intend to include both prognostic (28%) and predictive biomarker tests (20%) in the next 12 months (Figure 11).

Pathways are typically reviewed annually or more frequently if market events dictate (ie, new drugs or tests become available).

"It will come down to cost. If the manufacturer of a drug with a companion diagnostic prices their test too high, we may look for alternatives."

– Medical director at a large-sized plan (>1 million lives managed)

"The value we glean from the diagnostic test is very high in assessing the overall value proposition of a treatment. We are very interested in data that could lead to better assessments of a patient's diagnosis. That would be one of the highest factors when making coverage decisions for biomarker tests."

– Pharmacy director at a large-sized plan (>1 million lives managed)

Payers' Current and Intended Inclusion of Oncology Predictive Biomarker Tests as a Part of an Oncology Clinical Pathway Measurement

Figure 11 **Percent of Payers**

n=50 payers

Payers Current Inclusion and Intent to Include Oncology Predictive Biomarker Tests as Part of an Oncology Clinical Pathway Measurement

During the in-depth interviews, payers reported that adherence to clinical pathways for the use of oncology predictive biomarker tests are not necessarily mandated. Of those using pathways, 68% of payers reported that they track physician compliance and 47% of those provided financial incentives to providers for adherence to them (Figure 12).

When developing clinical pathways for the use of oncology predictive biomarker tests, payers most frequently rely on collaborations with oncologists (46%) to develop their pathways (Figure 13), followed by 28% utilizing third-party pathway vendors and 26% creating proprietary pathways internally.

Among surveyed providers, 56% of oncologists and 48% of pathologists reported no involvement with the development of biomarker test guidelines at this time.

Figure 12 **Percent of Payers Tracking Physician Compliance**

n=19

"Making sure the right patient gets the right medicine: this is critical in an era where cancer medicines have never been more expensive."

– Payer at a medium-sized plan (400,001 to 999,999 lives managed)

Providers' Current/Intended Use vs Payers' Current/Intended Coverage of Oncology Predictive Biomarker Tests

Respondents were asked about their current use and coverage and intended use and coverage in the next 12 months of a series of oncology predictive biomarker tests in present-day clinical use. Oncologists and pathologists were asked to indicate their utilization independent of the reimbursement status of a biomarker test in order to reveal differences between payer coverage and provider utilization.

Payers Most Commonly Collaborate With Oncologists to Develop Oncology Clinical Pathways

Figure 13 **Percent of Payers Most Frequently Using (Top 2 box score)**

n=50 payers

"I think where we could be in 3 years may be dramatically different from where we are at now. It really needs to be led by great technology and science with an evidence-based approach that demonstrates improved patient outcomes."

– Pharmacy director at a large-sized plan (>1 million lives managed)

Consistent with oncologists' and pathologists' reports during the in-depth interviews, current use of the HER2 biomarker test in breast cancer and esophagogastric adenocarcinoma, the KRAS biomarker test for colorectal cancer, and the KIT biomarker test in GIST all have high usage and corresponding payer coverage (Figure 14).

Interesting findings show oncologists' use of the KRAS biomarker test for NSCLC lagging behind pathologists' current use (38% vs 84%, respectively). Another interesting finding is that payers' coverage for the HER2 biomarker test in NSCLC adenocarcinoma remains fairly high, with 50% of payers covering this test; however, current use among oncologists and pathologists is low (22% vs 20%, respectively) (Figure 14).

Pathologists' current use lags behind oncologists' use for PD-L1 test in melanoma (8% vs 28%), the PD-L1 biomarker test in NSCLC (4% vs 26%), MEK1 biomarker test in NSCLC (0% vs 16%). These variances are likely attributed to a lack of confidence in the predictive power of the biomarker test (PD-L1) and the lack of an FDA-approved MEK1 inhibitor and PD-L1 biomarker test at the time of this survey. Pathologists' current use is similar to oncologists' use for the ROS biomarker test (52% vs 40%) and the PIK3CA biomarker test in NSCLC (12% vs 10%). Oncologists' intent to use the MET biomarker test in NSCLC and the BRAF V600 biomarker test in NSCLC (36% for both tests) is high (Figure 14).

Overall, there is a trend toward greater intent to utilize these biomarker tests by oncologists and pathologists vs coverage by payers.

"The value we glean from the diagnostic test is very high in assessing the overall value proposition of a treatment. We are very interested in data that could lead to better assessments of a patient's diagnosis."

– Pharmacy director at a large-sized plan (>1 million lives managed)

Figure 14 **Percent of Respondents**

n=50 oncologists, 25 pathologists, and 50 payers

CML, chronic myelogenous leukemia; GIST, gastrointestinal stromal tumor; NSCLC, non-small cell lung cancer.

Predictive Biomarker Tests as Drivers of Precision Oncology Therapy Cost Effectiveness

Payers report that the use of oncology clinical biomarker tests is integral to ensuring that patients get the best possible care and can be integral to managing the rising costs associated with cancer care.

Figure 15 shows 24% of payers reported that they currently conduct an annual cost-effectiveness analysis on the impact of oncology predictive biomarker tests. In addition, 36% of payers reported that they plan to conduct analyses over the next 12 months.

Over 50% of Payers Are Conducting or Implementing Cost-Effectiveness Analysis on the Impact of Oncology Predictive Biomarker Tests

Figure 15 **Percent of Payers**

n=50 payers

While the in-depth interview numbers were few (N=5), the ability of a plan to conduct internal cost-benefit analysis appears to be related to the size of the organization, staffing, available data, and internal staff's expertise in conducting cost-benefit analysis. In one interview, the payer suggested calling upon the manufacturers of biomarkers to provide cost-benefit information for usage.

"We are looking for information that will tell us what the cost-benefit analysis is for the use of oncology predictive biomarker tests. If the test costs $200 but we save $5000 on an oncology infusion because it is not going to work, that is probably the biggest thing we are taking a close look at."

– Medical director at a large-sized plan (>1 million lives managed)

Providers and payers were asked to comment on statements related to oncology predictive biomarker tests. The statement, "The higher short-term costs for increased biomarker-based diagnostic testing is worth the potential long-term savings," was generally readily accepted by oncologists, pathologists, and payers (56%, 40%, and 38%), respectively, strongly agree/agree with the statement). This acceptance is most likely driven by payers' desire to improve outcomes while managing costs (Figure 16).

This data, and that certain biomarker tests are linked with cost savings, potentially supports the opportunity for biopharmaceutical companies to partner with diagnostic developers and payers.[8-11] Guidelines from influential organizations such as the NCCN, combined with outcomes data and cost modeling, may also support payer decision making.

Respondents' Opinions on Oncology Predictive Biomarker Tests

During the in-depth interviews, payers reported that the amount of pathologist analysis can have a significant impact on the direct cost of the biomarker test.

Figure 16 **Percent of Respondents Who Strongly Agree (Top 2 box score)**

n=50 oncologists, 25 pathologists, and 50 payers

Next Generation Sequencing: The Game Changer?

While NGS technologies are not yet the standard of care, their use is integral to the premise of personalized oncology medicine as they enable the sequencing of large genomic regions, a large number of genes, from a single biopsy in an assay that is more efficient, potentially more cost effective, and more sensitive than traditional techniques.[9,11,26] A comprehensive tumor exome analysis promises to inform prognoses and target precise cancer care with a single, rapid, and low-cost test.[26]

Oncology procedural codes for these genomic-sequence panels (GSPs) utilizing NGS have been established (81445, 81450, and 81455).[27] Providers and payers have great hopes that NGS technology could change the face of cancer treatment and lead to greatly improved outcomes.

"I think with next generation sequencing, there is going to be an explosion of tests available and the price is just going to drop like a rock. It is going to continue to get cheaper and cheaper over time."

– Medical director at a large-sized plan (>1 million lives managed)

Payers believe prospective trials will be required to validate the use of GSPs to accurately identify patients for specific therapy in order to make a coverage decision. They agreed that coverage by Medicare of the oncology GSPs will strongly influence a positive coverage decision for their respective organizations, as well as FDA approval as a companion diagnostic. Generally, payers considered clinical trial data done with other single mutation biomarker tests to be insufficient to support the effectiveness and reimbursement of a biomarker test that is part of an oncology GSP.

Figure 17 **Median Price Threshold**

n=50 oncologists, 25 pathologists, and 50 payers

Are Oncology Biomarker Tests Cost Effective?

Although certain NGS tests may remain above the disruption threshold for the time being, the utilization of some biomarker tests has been shown to be cost effective.[8,11] One recent study found $604 million annual potential savings among patients with metastatic colorectal cancer who received a genetic test for the KRAS gene prior to treatment.[11] Additionally, an economic analysis of the Oncotype DX® test looked at the real costs of treating women with breast cancer in a health plan with 2 million members. It was determined that if half of the 773 eligible patients received the test, then the savings in terms of adjuvant chemotherapy, supportive care, and management of adverse events would be about $1930 per patient tested (based on a 34% reduction in chemotherapy use).[8]

Median Price Thresholds for Next Generation Sequencing to Become Disruptive

Payers indicated that a price threshold of just under $1000 would disrupt the market and potentially replace single-mutation biomarker tests. Pathologists favored a lower threshold ($825), while oncologists skewed higher ($1417) (Figure 17). The cost associated with the Foundation Medicine Panel was reported to be around $5000.

In the in-depth interviews, payers stated that the key areas driving coverage for GSPs are clinical utility, data supporting improved outcomes, and cost. Cost and reimbursement of this new technology remain key factors for wider adoption of NGS and GSPs.

"The biomarker has the potential to add value for us. This is an area that we are aware of and are tracking. The test could be very influential on our choice of a particular product, especially if the science behind the biomarker test is very strong."

– Pharmacy director at a large-sized plan (>1 million lives managed)

Oncotype DX is a registered trademark of Genomic Health, Inc.

Conclusions

While the adoption of predictive biomarker tests in oncology continues, the key learnings of this report provide valuable insights into the evolution of predictive oncology.

Through their reimbursement power in the commercial oncology market, payers have become the de facto arbitrators of biomarker test utilization. They have expressed a strong need for outcomes data to validate the clinical utility of a biomarker test when making coverage decisions.

Key drivers of payer coverage include:

- Availability of clinical outcomes data to verify the validity and utility of the biomarker test
- Having the biomarker test included in all relevant guidelines
- Providing a value proposition for the combined use of the therapeutic and companion diagnostic

Payers are influencing biomarker test utilization through the prior-authorization process for an oncology therapeutic and evidence from a predictive marker and increasingly, pathways.

The utilization of a predictive biomarker test by oncologists and pathologists is driven primarily by:

- Clinical utility
- Cost
- Guideline recommendations

As the cost of therapeutics rises, predictive biomarker tests and their quality could become important cost-effectiveness differentiators, particularly between the PD-1/PDL1 inhibitors.

As the basket trials advance and the coverage of NGS expands, the adoption of precision medicine in oncology is on the brink of rapidly accelerated adoption that could change how cancer treatments are chosen and improve the quality of patient care while reducing costs.

The results of this report illustrate the growth, utilization, and coverage of oncology predictive biomarker tests and the evolution of precision oncology. Despite the barriers to adoption, all stakeholder groups interviewed for this report are united in their desire to enhance the oncology patient experience, improve quality and outcomes, and support appropriate resource utilization.

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Notes

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MMO-1129376