The Precision Oncology Annual Trend Report
Perspectives From Payers, Oncologists, and Pathologists
Third Edition
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Foreword

We know that the movement from one-size-fits-all, trial-and-error medicine to an approach that is targeted to each patient’s individual molecular profile is far from easy. The trend toward precision or personalized medicine requires the concerted efforts of all stakeholders across the health care spectrum. Providers and payers must partner with pharmaceutical and diagnostic developers, which, in turn, must also work together to help create an environment that incentivizes the development of personalized medicine products and services. Those products and services have been shown to improve patient outcomes and may also lower systemic health care costs.

The Precision Oncology Annual Trend Report: Perspectives From Payers, Oncologists, and Pathologists, Third Edition, helps decision makers in industry and government recognize the salient issues through quantitative insights based on survey data into how the oncology community both understands and incorporates personalized medicine into policy and practice. Focusing on these issues will accelerate the progress upon which patients depend.

This report encourages patients, providers, and especially payers to promote broader biomarker test utilization, including the latest technologies, so that more medicines are targeted at those who will benefit, sparing side effects for those who will not. It calls on insurance companies and governments to put in place coverage and reimbursement policies that will stimulate the development and adoption of companion diagnostic tests when evidence suggests that they will improve health and lower overall costs. And finally, it calls on the entire medical community to examine all current policies and procedures to ensure that the rapid advances in technology and the broader appreciation of molecular biology make their way to patients sooner than later.

In this report, 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 and increased value.

The data in this report also help us recognize that the quality and cost-effectiveness of patient care can be improved through the use of predictive biomarker tests and companion diagnostics and that next-generation sequencing has the potential to facilitate widespread utilization of precision oncology to determine treatment.

Reports such as this one provide physicians with the data they need to consider when treating patients with cancer. With regulators demanding demonstration of increased efficacy in selected populations based on molecular profiling and payers showing a growing interest in covering personalized medicines, we are beginning to enter a new era in medicine.

Edward Abrahams, PhD
President
Personalized Medicine Coalition
Introduction

Welcome to The Precision Oncology Annual Trend Report: Perspectives From Payers, Oncologists, and Pathologists, Third Edition, which provides insights into the trends affecting utilization and coverage of predictive biomarkers in oncology. Nowhere in medicine has the impact of personalized medicine been greater than in oncology which today is moving away from a treatment model based on histology to one that is based on the molecular profile of an individual patient’s cancer. Precision medicine in oncology embodies the use of an individual patient’s molecular information (including genomics and proteomics) to inform the diagnosis, prognosis, treatment, and prevention of cancer for that patient.

At the time of this research (Q3-Q4 2016), 53 drugs were associated with biomarkers that predict efficacy in patients with cancer, some of which target more than 1 biomarker. Seventeen oncology therapeutics have been approved by the U.S. Food and Drug Administration (FDA) with a companion diagnostic—a test that is designed to provide essential information for the safe and effective use of a corresponding therapeutic product. However, precision care in oncology will only be as good as the tests that guide diagnosis and treatment. Despite the availability of FDA-approved companion diagnostics, there is widespread use of clinically unvalidated laboratory-developed tests (LDTs). In recognition of the increasing complexity and availability of LDTs and the potential for great harm to the patient associated with a faulty LDT result, the FDA announced regulatory oversight of LDTs in July 2014. Among the many insights revealed by this report, providers and payers strongly agree that regulatory oversight of LDTs is a requirement in the continued evolution of precision medicine in oncology.

Next-generation sequencing (NGS) has the potential to make single-gene biomarker testing obsolete. While in limited use today, gene sequencing panels (GSPs) can target as many as 400 genes that are known to be important for cancer biology or disease management. In some institutions, GSPs serve as the foundation of personalized medicine programs, which provide holistic care to patients with cancer. However, the integrity of information revealed by single-gene tests or GSPs is dependent on how well the patient’s cancer is represented in a biopsy specimen. Tumor heterogeneity undermines targeted therapy of cancer when more than 1 “driver” mutation is present. Cancer-derived material circulating in the bloodstream has become an appealing alternative when there is limited availability of tumor biopsy tissue for molecular testing. Currently underway is an evaluation of “liquid biopsies” of circulating tumor DNA as a less invasive and complementary way to assess a patient’s cancer genome and even monitor response to surgery or pharmacotherapy.

Precision medicine in oncology has the potential to increase survival and enhance the quality of life of patients with cancer. It also holds promise for cost savings because only those patients who are likely to benefit from a treatment receive it, thereby minimizing patients’ exposure to potentially toxic therapy for which there is little or no clinical benefit. The appropriate reimbursement, promotion, and use of diagnostic testing may serve to enhance the patient experience, improve patient outcomes, and minimize resource utilization.

New to this report is a historical perspective on precision oncology that includes recent initiatives that have fueled the growth and excitement about this new approach to the treatment of cancer. In addition, and where relevant, background information is provided as context for many of the questions posed to survey participants. Lastly, a new section has been added to the report that includes a glimpse into what the future holds for precision medicine in oncology.

Novartis continues to produce this report as an annual service to the oncology community and to shed light on the developing impact and utilization of biomarkers with the aim of accelerating the adoption of biomarker testing in precision oncology. This report and the overview of the potential benefits, coverage, and utilization of precision medicine in oncology provide a timely snapshot of this rapidly evolving new clinical paradigm.
Executive Summary

The cost of cancer care in the United States is estimated to increase to $158 billion in 2020—more than 20% higher than it was a decade earlier. What constitutes value in health care has been an enduring and controversial topic in medicine for many years. The American Society of Clinical Oncology (ASCO) defines value in cancer care in terms of 3 critical elements articulated by the Institute of Medicine: clinical benefit (efficacy), toxicity (safety), and cost (efficiency). According to ASCO, the net health benefit of a drug is often appreciably greater when introduced with a biomarker test that can identify patients most likely to benefit from the treatment.

Cancer biomarkers, which include both germline and somatic mutations, can influence disease outcome and/or response to therapy and can be classified as prognostic (associated with disease outcome) or predictive (associated with drug response). Precision oncology relies on an assessment of predictive biomarkers to inform clinical treatment decisions. Predictive biomarker tests are beginning to help physicians make better treatment decisions for individual patients based on the likelihood of response to certain therapies. While precision oncology is still in its infancy, it is advancing rapidly, aided by the discovery of new predictive biomarkers, advances in gene sequencing, and the creation of GSPs that help to match targeted therapies with patients who are most likely to respond.

Also advancing at record pace is the discovery and development of cutting-edge therapies for newly discovered molecular targets. Among them are immunotherapies, such as checkpoint inhibitors, which have delivered extraordinary outcomes for some hard-to-treat solid tumors, such as lung cancer and metastatic melanoma. Motivated by successes achieved in certain cancers, researchers are optimistic that it may be possible to manage all cancers as a serious chronic disease, similar to how HIV/AIDS and diabetes are treated today.

Precision medicine has the capacity to revolutionize oncology care, but if payers are unwilling to provide coverage for genomic testing, this important progress will be stalled. The widespread implementation and accepted coverage of biomarker tests in precision oncology faces several challenges, including the need for:

- Cost-effectiveness data supporting the use of genomic testing to inform the diagnosis, prognosis, treatment, and prevention of cancer for an individual patient and demonstrating that cost savings can be realized by sparing patients from ineffective and toxic therapies
- More evidence to support the notion that personalized cancer medicine can increase health care quality and improve patient outcomes while lowering overall costs
- Regulatory oversight of laboratory-developed tests to ensure that biomarker testing is performed comparably to validated, FDA-approved companion diagnostics
- Stronger cooperation between payers, oncologists, and pathologists to implement aligned precision medicine programs at the local level
- Education for all stakeholders, including health care professionals, patients and their advocacy groups, biomedical researchers, the pharmaceutical and biotechnology industries, diagnostic and device industries, regulators, health economists, and payers to further drive adoption of personalized medicine in oncology

The findings in this report are based on market research conducted with commercial health plans. Government payers were not included, as they were beyond the scope of this report. While the nation is poised to move forward with advances in biomarker discovery and genomic sequencing that will undoubtedly form the foundation for much of patient cancer care in the future, the Centers for Medicare & Medicaid Services (CMS) and other government offices need to lead by example and establish appropriate reimbursement for genomic testing at a national level that ensures that all Americans have access to the benefits of this new technology.
Key Findings

• For the majority of payers (70%), cost has risen to become the most important factor influencing biomarker coverage, followed closely by clinical validity (64%) and utility (62%)

• Providers and payers strongly agree that LDTs require regulation and oversight of their effectiveness to ensure comparability to validated, FDA-approved companion diagnostics

• An encouraging sign of wider utilization and coverage of precision oncology is the 28% of payers who report being involved in a coordinated personalized medicine program

• While almost one-third of oncologists expressed concerns with PD-L1 biomarker testing and using it to select patients for a PD-1 inhibitor who fail first-line therapy, ordering and coverage for PD-L1 testing increased in both melanoma and non-small cell lung cancer (NSCLC). In addition, dramatic increases in genomic testing for patients with NSCLC were reported by both oncologists and pathologists

• While 16% of payers reported having a step-therapy approach for PD-1 coverage in second-line NSCLC today, an additional 62% are evaluating (40%) or plan to implement (22%) a step-therapy approach to coverage over the next 12 months

• Provider participation on alternate payment models is significant and likely to rise in 2017

• Oncologists and pathologists agree that predictive power to identify treatment options, FDA approval, and guideline or pathway approval are the top 3 factors influencing biomarker test selection. Reimbursement coverage is of a greater concern for oncologists vs pathologists

• Compared to 2015, quality of response and improved duration of remission of targeted therapies, which increased by 10% and 8%, respectively, in 2016, were more important to payers in determining coverage than improved survival vs current standard of care, which decreased almost 20%

• While oncologists are less specific than pathologists when ordering a biomarker test, neither group (16% of oncologists and 24% of pathologists) favors any specific brand of test to a great extent; therefore, the FDA-approved companion diagnostic is rarely ordered. Only 26% of payers reported publishing guidance on biomarker coverage and only 8% of payer biomarker coverage guidance specifies a biomarker test by brand

• The majority of payers (60%) are very engaged in evaluating or planning to evaluate the impact and cost-effectiveness of oncology biomarker tests, including genomic sequencing panels (GSPs)

• Payer coverage of GSPs as part of a clinical pathway is well below that of predictive biomarkers (19%) and companion diagnostics (48%), with no increase in coverage expected in the next 12 months. The majority of payers (54%) are waiting for FDA approval before extending coverage to GSPs but suggested that coverage of a GSP by Medicare and/or the availability of prospective clinical trial data can strongly influence a coverage decision

• Widespread adoption of NGS GSPs is still nascent, with only 8% of pathologists and 10% of oncologists currently utilizing an NGS GSP to profile solid and liquid tumor biopsies. Providers and payers agree that cost is currently a barrier to uptake, with only 19% of payers reporting to have coverage for GSPs. An FDA-approved GSP companion diagnostic may have a significant impact on coverage and utilization
Methodology

Primary research for this report consisted of data obtained between August 2016 and October 2016 through a Web-based survey. In addition, qualitative, in-depth interviews were conducted with providers (ie, oncologists and pathologists) and individuals from commercial health plans (ie, medical directors and pharmacy directors) who are familiar with their company’s current coverage of predictive oncology biomarkers. All surveys and in-depth interviews were conducted anonymously.

The report provides data on the following:

- Market trends and the evolution of precision oncology
- Influencers of utilization and coverage
- Current and anticipated predictive biomarker utilization and coverage
- Predictive biomarkers as drivers of precision oncology therapy cost-effectiveness
- New technology, including NGS and GSPs

For the purpose of the market research study, an oncology predictive biomarker and/or companion diagnostic was defined as a biomarker test that determines the likely benefit from a specific targeted therapeutic treatment. A prognostic biomarker 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 biomarkers. 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.

Table 1 | Sample Demographics

<table>
<thead>
<tr>
<th></th>
<th>ONLINE SURVEY SAMPLE SIZE</th>
<th>IN-DEPTH TELEPHONE INTERVIEW SAMPLE SIZE</th>
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<td>5</td>
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<td>Pathologists</td>
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<td>5</td>
</tr>
<tr>
<td>Payers</td>
<td>50</td>
<td>5</td>
</tr>
</tbody>
</table>
## Provider Demographics

Oncologists and pathologists participating in the survey spend most of their clinical practice time in hospital-affiliated practices. However, a large percentage of respondents maintain clinical practices at independent, community-based practices and academic cancer centers. There was national representation in the sample, and the mean time spent in active clinical practice for both groups was 93% (Figure 1).

**Figure 1 | Clinical Practice Location**

- **Independent community-based practice**: 50% (Oncologists), 24% (Pathologists)
- **Hospital-affiliated practice**: 40% (Oncologists), 60% (Pathologists)
- **Academic cancer center**: 10% (Oncologists), 16% (Pathologists)

N=50 oncologists, 25 pathologists.

## Payer Demographics

Of the commercial payers who participated in this study, 56% were pharmacy and medical directors employed by larger-sized health plans, (i.e., 1 million or more covered lives) with the remaining 44% of lives managed through medium-sized plans (400,001 to 999,999 managed lives) (30%) and small plans (400,000 or less managed lives) (14%) (Figure 2). Pharmacy directors made up the majority of payer participants (62%) with medical directors making up the remaining 38%. Payer participants represented plans throughout the United States (Figure 3). Payer plan member lives are covered by managed Medicare (59%) and managed Medicaid (41%) (Figure 4), with an equal distribution providing medical and pharmacy benefits (Figure 5).
Figure 2 | **Percent of Participating Payers by Number of Lives Managed Annually**

- **Small** (400,000 or less): 14%
- **Medium** (400,001 to 999,999): 30%
- **Large** (1 million or more): 56%

N=50 payers.

Figure 3 | **Coverage by Region**

- **West**: 28%
- **National**: 18%
- **South**: 20%
- **Northeast**: 14%
- **Midwest**: 20%

N=50 payers.

Figure 4 | **Payer Member Lives Coverage**

- **Managed Medicare**: 59%
- **Managed Medicaid**: 41%

N=50 payers.

Figure 5 | **Medical and Pharmacy Benefit Distribution**

- **Medical and pharmacy benefit**: 33%
- **Pharmacy benefit only**: 33%
- **Medical benefit only**: 33%

N=50 payers.
Market Trends and the Evolution of Precision Oncology

Historical Perspective

In 2003, the Human Genome Project announced the first sequencing of human DNA. Supporting this effort were the emerging fields of bioinformatics and computational biology, which helped to make the project a success. A variety of specialized fields, including genomics, transcriptomics, proteomics, metabolomics, and epigenomics, also emerged that were, in part, fueled by a technology explosion that included Sanger sequencing in 1977, polymerase chain reaction (PCR) in 1983, microarray analysis in the 1990s, and NGS in 2008.11-13

Decoding the human genome facilitated efforts to better understand the molecular pathways involved in the transformation of normal cells into cancer.14 In the last few decades, an increased understanding of the genetic basis for disease has resulted in the discovery of drugs that are targeted to genetic mutations believed to cause disease, and a new field of science called “pharmacogenomics” has emerged.15,16 Using “information about a person’s genes, proteins, and environment to prevent, diagnose, and treat disease” is a form of medicine that the National Cancer Institute (NCI) has termed “personalized medicine,” also called “precision medicine.”17 Applied to the diagnosis and treatment of cancer, this form of medicine has been termed “precision oncology.” However, the discovery of genetic alterations that cause cancer predates the Human Genome Project. In 1960, researchers discovered that some patients with chronic myelogenous leukemia possessed a genetic abnormality caused by a translocation between chromosomes 9 and 22. This abnormality, which came to be known as the Philadelphia chromosome, produces a protein with elevated tyrosine kinase activity that causes this form of leukemia. With a biomarker for disease in hand, the race to identify drug candidates to inhibit that activity led to one of the early precision treatments for cancer.18

Bioinformatics and computational biology continue to play a vital role in cancer research. In the evolving treatment landscape, providers and payers are now faced with the problem of “big data:” how to collect it, maintain it, integrate it into electronic health records, and utilize it. Efforts are under way to make data more broadly accessible in hopes of accelerating our understanding of the biological mechanisms of cancer and the development of personalized treatments for individual patients.19,20

Four types of biomarker tests are used for making clinical decisions: diagnostic, prognostic, predictive, and pharmacodynamic. Diagnostic biomarker tests help pathologists identify a cancer type or subtype. Prognostic biomarker tests help clinicians better understand and communicate the likely course of a disease without treatment and suggest the risk of relapse or progression with treatment. Predictive biomarker tests suggest the population of patients likely to respond to a specific treatment. Pharmacodynamic biomarker tests help to increase our understanding of what happens when a drug interacts with its target.4,10

Many targeted-therapy predictive biomarker/companion diagnostics consist of single-gene assays that reveal the mutation status of frequently mutated genes or “hot-spot” mutations. Examples include BRAF gene mutation testing in patients with melanoma who are likely to respond to BRAF inhibitors and anaplastic lymphoma kinase (ALK) gene fusion testing in patients with metastatic lung cancer who are likely to respond to ALK inhibitors.4 A historical timeline that documents the introduction of cancer-related biomarker tests and companion diagnostics into the market appears on page 11 (Figure 6).

The acceptance and use of precision medicine in oncology continues to expand, with numerous biopharma companies in the process of developing new oncology products that require biomarker tests. At the time of publication, there were 17 oncology therapeutics approved by the FDA with a companion diagnostic. In 2016, however, only 1 of 7 newly approved oncology drugs was indicated for a specific genetic mutation, which can be detected by an FDA-approved test.2,22,23
Initiatives Advancing Precision Medicine

In the last 4 years, numerous government and industry initiatives have fueled the growth and excitement about precision medicine (Figure 7)²¹,²⁴-³²:

- **March 29, 2012**: President Obama launches the Big Data Research and Development Initiative
- **July 15, 2012**: ASCO begins first phase of CancerLinQ™ development
- **January 30, 2015**: President Obama launches the Precision Medicine Initiative (PMI)
- **July 10, 2015**: US House of Representatives passes the 21st Century Cures Act, a bill to accelerate the discovery, development, and delivery of 21st century cures
- **August 2015**: NCI Molecular Analysis for Therapy Choice (NCI-MATCH) trial opens for enrollment
- **December 15, 2015**: FDA launches the precision FDA Web platform to foster innovation and develop the science behind NGS
- **February 1, 2016**: Vice President Biden launches the Cancer Moonshot initiative
- **March 14, 2016**: ASCO Targeted Agent and Profiling Utilization Registry (TAPUR) trial opens for enrollment
- **May 27, 2016**: National Institutes of Health funds biobank to support PMI Cohort Program
- **June 6, 2016**: Cancer Moonshot task force launches the Genomic Data Commons database, which allows cancer researchers from anywhere in the world to upload data
- **December 7, 2016**: Senate passes the 21st Century Cures Act
- **December 13, 2016**: 21st Century Cures Act signed into law
Recent Advances in the Use of Biomarkers in Cancer Therapy

The recent approval of several immune checkpoint inhibitors represents a major paradigm shift in the treatment of patients with advanced NSCLC who progress on or after platinum-based chemotherapy. For some of these drugs, use of a companion diagnostic for PD-L1 expression is required by the FDA to stratify patients to therapy. Developed independently in conjunction with the approved drug, each assay uses different levels of PD-L1 expression to predict response to therapy. PD-L1 can be expressed by both tumor and inflammatory cells within the tumor microenvironment, but the relative importance of either is unclear. How PD-L1 positivity is defined differs among these assays, and this has led to confusion among providers and payers.\(^{33}\) In addition, each assay uses a different antibody and different techniques. In an attempt to clarify the analytical performance characteristics of these assays, a consortium of pharmaceutical companies, diagnostic companies, and others initiated a study called the Blueprint PD-L1 IHC Assay Comparison Project. Results of this study, which will delineate differences and similarities among the assays, will be published shortly.\(^{34,35}\)

Whereas most cancer biomarker tests evaluate gene mutations that do not vary considerably over time (eg, EGFR, KRAS), PD-L1 expression is dynamic and has the potential to change in concert with an evolving immune response. PD-L1 expression is also affected by concurrent or prior treatments, including radiation or chemotherapy, which may have been administered after a biopsy was obtained.\(^{33,34}\)
PD-L1 Biomarker Testing for Patients With NSCLC

Almost one-third of oncologists expressed concerns with PD-L1 biomarker testing and using it to select patients for a PD-1 inhibitor who fail first-line therapy (Figure 8).

Figure 8 | Providers Who Strongly Agree With the Following Statements Regarding PD-1 and PD-L1 Biomarkers

- All patients should have their tumor biopsied and undergo biomarker testing for PD-L1: 50% agree, 16% agree.
- PD-L1 biomarker tests are not sufficiently predictive to select patients for a PD-1 inhibitor: 30% agree, 8% agree.
- A PD-1 inhibitor should only be used in patients positive for PD-L1 expression: 32% agree, 20% agree.

N=50 oncologists, 25 pathologists.

PD-1 Inhibitor Coverage Based on PD-L1 Biomarker Status

While only 16% of payers reported having a step-therapy approach for PD-1 coverage, however an additional 62% are evaluating (40%) or plan to implement (22%) a step-therapy approach to coverage over the next 12 months (Figure 9).

Figure 9 | Payers Using a Step-Therapy Approach to PD-1 Inhibitor Coverage Based on PD-L1 Biomarker Status

N=50 payers.
Influencers of Utilization and Coverage

The cost of cancer care is estimated to increase from $125 billion in 2010 to $158 billion in 2020. ASCO defines value in cancer care in terms of 3 critical elements articulated by the Institute of Medicine: clinical benefit (efficacy), toxicity (safety), and cost (efficiency). According to ASCO, the net health benefit of a drug is often appreciably greater when introduced with a biomarker test that can identify patients most likely to benefit from the treatment. Predictive biomarker tests are beginning to help physicians assign value to therapies in terms of likelihood of benefit and benefit-to-risk profiles for individual patients.

Payers have emerged as gatekeepers to personalized medicine. Payer reimbursement of diagnostics is highly variable. Drugs are being reimbursed independent of companion diagnostic coverage, even in cases of co-developed combinations. When making coverage decisions for new targeted therapies, 80% of payers considered improving patient survival as the most important factor influencing coverage in 2015. Other key factors include:

- Direct cost of therapy
- Overall response rate
- Improved duration of remission

Precision oncology may have the ability to transform clinical practice, but if genomic testing is not covered by insurance companies and Medicare, this progress may be stalled. For a diagnostic test to achieve acceptability by patients, clinicians, payers, and regulators, it has to successfully answer 2 questions: Does it work? And is it worth the cost? In 2004, the Centers for Disease Control and Prevention launched the Evaluation of Genomic Applications in Practice and Prevention initiative. The group defined 4 evaluation criteria for clinical genomics tests:

- Analytic validity (How well does the test measure what it is supposed to measure?)
- Clinical validity (How well does the test predict its specified outcome?)
- Clinical utility (How well does the test improve or harm outcomes to patients?)
- Ethical, legal, and social issues

If precision oncology is to reach its full potential, payers must be convinced of the necessity of targeted therapies and their companion diagnostics. However, payers are under pressure to contain the growing cost of cancer care while maintaining or improving quality and are focused on achieving the Triple Aim: improving the experience of care, improving the health of populations, and reducing per-capita costs of health care.

Reimbursement cost-related factors were reported to be a more important concern when ordering biomarker tests in 2016 than in 2015 among oncologists and pathologists.

Oncologists and pathologists agree that lack of evidence-based guidelines and lack of clinical utility data are their top 2 concerns when ordering biomarkers. Concerns among oncologists about obtaining insurance authorization and provider reimbursement for biomarker testing has risen since 2015 (52% vs 38% and 44% vs 32%, respectively). Oncologists appear to be less concerned about the delay in care while waiting for test results (32% in 2016 vs 46% in 2015).

Concerns among pathologists about provider reimbursement, and cost also increased since 2015 (36% vs 32%, 48% vs 40%, and 52% vs 40%, respectively). Compared with 2015, pathologists reported decreased concern over lack of clinical utility data (48% vs 68%), lack of familiarity (20% vs 28%), and complexity of the testing process (20% vs 32%).
“When choosing to use a new oncology predictive biomarker, the most important thing I consider is the data that’s available. I want to see that its use is based on a Phase III solid clinical trial. Or if it is FDA approved, NCCN guideline approved, or something that is well reported on in the scientific journals, then we will consider use.”

– Oncologist
“Factors that I consider when deciding to use a new biomarker are, if we start broad, I look at medical literature, the vetting analysis, [and] trial data. The number 1 consideration in 2016: I think it’s important to consider FDA approval and non-approval. Endorsements from national societies, and specifically, we consider the bigger societies, ie, College of American Pathologists, ASCO, and, to a certain extent, the Association of Molecular Pathology.”

– Pathologist

While current use of clinical pathways is lower among oncologists than pathologists, use in both groups is expected to increase next year.

Current use of clinical pathways is lower among oncologists than pathologists, but both groups reported plans to use them in the next 12 months (32% for oncologists and 28% for pathologists) (Figure 13). A subset of respondents (oncologists, N=12; pathologists, N=11) reported nearly equal tracking of compliance (50% for oncologists and 55% for pathologists) and receipt of financial incentives for staying on pathway (25% of oncologists and 9% of pathologists). Some already have biomarkers as part of their pathway (25% of oncologists and 36% of pathologists), while others are planning to include them in the next 12 months (50% of oncologists and 27% of pathologists).

Provider use of pathways and inclusion of GSPs to manage patient care is growing.
Figure 13 | Providers Reporting the Use of Oncology Clinical Pathways

- No plans to use oncology clinical pathways in the next 12 months:
  - Oncologists: 38%
  - Pathologists: 8%
- Plan to use in the next 12 months:
  - Oncologists: 32%
  - Pathologists: 28%
- Currently use:
  - Oncologists: 44%
- Don’t know:
  - Oncologists: 20%
  - Pathologists: 6%

N=50 oncologists, 25 pathologists.

Figure 14 | Percent of Providers Using Pathways and/or Guidelines from Payers

- No:
  - Oncologists: 50%
  - Pathologists: 60%
- Yes, for oncology predictive biomarkers and/or companion diagnostics:
  - Oncologists: 36%
  - Pathologists: 42%
- Yes, for genomic sequencing panels:
  - Oncologists: 18%
  - Pathologists: 12%
- Yes, for prognostic biomarkers:
  - Oncologists: 16%
  - Pathologists: 26%

N=50 oncologists, 25 pathologists.
Participation in alternative payment models (APMs) will likely rise to significant levels in 2017.

A repeal of Medicare’s sustainable growth rate formula created new opportunities for physicians to develop and participate in APMs. The Medicare Access and CHIP Reauthorization Act (MACRA) of 2015 provides a 5% annual lump-sum payment to physicians who participate in qualified APMs at certain threshold levels, and it exempts them from the new merit-based incentive payment systems. APMs can provide participating physicians with a way to overcome current payment systems’ obstacles, allowing delivery of high-quality care at lower costs.43,44
Oncologists and pathologists agree on top 3 factors that influence selection.

Oncologists and pathologists agree that predictive power to identify treatment options, FDA approval and guideline or pathway approval are the top 3 factors influencing biomarker test selection. Reimbursement coverage is of a greater concern for oncologist vs the pathologist.

“Analytic sensitivity is not typically on my radar screen anymore. I say that perhaps from the advantage of knowing and being involved in a lot of molecular diagnostic testing over the years. I’m much more interested in analytic specificity, firstly, and then I need to understand sort of the underlying diagnostic question. I want to know what value this molecular or genetic marker adds to confirming or refuting the diagnosis.”

– Pathologist

Figure 17 | Providers’ Use of Third Parties for Pathway Guidance

- Utilize the NCCN Biomarkers Compendium® category evidence level 2A and 1:
  - Oncologists: 46%
  - Pathologists: 64%
- Monitor and incorporate guidance issued by professional and regulatory organizations (ie, AACR, ASCO, AUA, CAP, FDA):
  - Oncologists: 40%
  - Pathologists: 76%
- Managed by contracted consultant or pathway company:
  - Oncologists: 10%
  - Pathologists: 4%

N=50 oncologists, 25 pathologists.
Figure 18 | Factors Important in the Selection of an Oncology Predictive Biomarker, Companion Diagnostic, or GSP

- Predictive power to identify treatment responders and nonresponders: 66% (Oncologists), 80% (Pathologists)
- Companion diagnostic is mandated in the therapeutic’s FDA labeling: 56% (Oncologists), 64% (Pathologists)
- Recommended in patient-relevant, clinical pathway/guidelines (ie, payer, health system, NCCN): 50% (Oncologists), 76% (Pathologists)
- Reimbursement coverage by the patient’s payer: 40% (Oncologists)
- Direct cost of diagnostic test (if not covered by payer): 36% (Oncologists), 32% (Pathologists)
- Cost-effectiveness of the diagnostic test, ie, diagnostic test cost for a patient population relative to the direct treatment cost for nonresponding patients: 34% (Oncologists), 28% (Pathologists)
- Oncologist or pathologist recommendation: 28% (Oncologists), 60% (Pathologists)
- Impact on patient satisfaction with treatment: 18% (Oncologists), 20% (Pathologists)
- Patient or caregiver request for test: 10% (Oncologists), 52% (Pathologists)
- Quality metric requirement (ie, QOPI measure): 8% (Oncologists), 40% (Pathologists)

N=50 oncologists, 25 pathologists.
Oncologists are less aware of coverage issues of biomarker testing than pathologists.

Oncologists reported being less aware than pathologists that payer coverage is insufficient and a burden to patients.

Figure 19  | Providers’ Level of Agreement With the Following Statements Regarding Reimbursement

<table>
<thead>
<tr>
<th>Statement</th>
<th>Oncologists</th>
<th>Pathologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>For the most part, payer reimbursement covers the cost of the test</td>
<td>22%</td>
<td>12%</td>
</tr>
<tr>
<td>In the hospital, the cost of the biomarker test is sufficiently reimbursed as part of the overall procedure amount covered by the payer</td>
<td>16%</td>
<td>52%</td>
</tr>
<tr>
<td>Pharmaceutical biomarker test co-pay coupons effectively cover any out-of-pocket expense for patients (non-Medicare/Medicaid)</td>
<td>16%</td>
<td>8%</td>
</tr>
<tr>
<td>The lab works directly with the payer or invoices the patient so I am unaware of any reimbursement issues</td>
<td>26%</td>
<td>44%</td>
</tr>
</tbody>
</table>

N=50 oncologists.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Oncologists</th>
<th>Pathologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>For the most part, payer reimbursement covers the cost of the test</td>
<td>12%</td>
<td>44%</td>
</tr>
<tr>
<td>In the hospital, the cost of the biomarker test is sufficiently reimbursed as part of the overall procedure amount covered by the payer</td>
<td>52%</td>
<td>44%</td>
</tr>
<tr>
<td>Pharmaceutical biomarker test co-pay coupons effectively cover any out-of-pocket expense for patients (non-Medicare/Medicaid)</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td>The lack of biomarker coverage and poor reimbursement for biomarker tests is a significant burden for patients that can impact our utilization of a test</td>
<td>44%</td>
<td>44%</td>
</tr>
</tbody>
</table>

N=25 pathologists.
Improved survival and duration of remission are the 2 most important factors impacting coverage decisions in 2016.

This finding aligns with findings from the first and second edition trend reports, in which improving patient survival was reported to be the most important factor impacting coverage decisions. Cost remains in the top 3 areas of consideration at 58%.

Figure 20 | **Most Important Factors for Payers When Making Coverage Decisions for Targeted Therapies**

- **Improved duration of remission** (ie, progression-free survival): 64% (2016), 56% (2015)
- **Improved survival vs current standard of care**: 62% (2016), 80% (2015)
- **Direct cost of therapy**: 58% (2016), 64% (2015)
- **Overall response rate**: 48% (2016), 60% (2015)
- **Quality of the response**: 46% (2016), 36% (2015)
- **Improved side effect profile vs standard of care**: 32% (2016), 36% (2015)
- **Direct cost of a predictive biomarker and/or companion diagnostic test**: 32% (2016), 32% (2015)
- **Indirect cost of therapy**: 30% (2016), 26% (2015)
- **Improved quality of life**: 26% (2016), 28% (2015)

N=50 payers.
Use of oncology clinical pathways by commercial payers continues to grow.

Institutions, clinicians, commercial organizations, payers, and other health systems are using clinical pathways in oncology as a way to improve patient care by limiting undesirable variability while reducing cost. Some payers are providing incentives to providers to use oncology pathways, such as increased reimbursement and case management fees. While a number of studies have demonstrated cost savings with maintaining or improving the quality of patient care, oncologists have become increasingly concerned about how clinical pathway programs are being developed and implemented in oncology practice. In response to these concerns, ASCO has proposed recommendations on developing and implementing clinical pathways aimed at improving overall patient care.45,46

“We must be thoughtful and deliberate in the development and implementation of pathways to ensure that our patients receive the best and most appropriate evidence-based cancer care possible, as well as have access to well-designed clinical trials.”

– ASCO Task Force46

Figure 21 | Percent of Payers Using Oncology Clinical Pathways

<table>
<thead>
<tr>
<th>Category</th>
<th>2016</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Currently use</td>
<td>42%</td>
<td>38%</td>
</tr>
<tr>
<td>Plan to use in the next 12 months</td>
<td>30%</td>
<td>18%</td>
</tr>
<tr>
<td>No plans to use</td>
<td>22%</td>
<td>40%</td>
</tr>
<tr>
<td>Don’t know</td>
<td>6%</td>
<td>4%</td>
</tr>
</tbody>
</table>

N=50 payers.
The majority of payers who utilize oncology pathways use them to monitor physician compliance.

Figure 22 | Percent of Payers Tracking Physician Compliance to Clinical Pathways

<table>
<thead>
<tr>
<th></th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>68%</td>
<td>71%</td>
</tr>
<tr>
<td>No</td>
<td>21%</td>
<td>14%</td>
</tr>
<tr>
<td>Don’t know</td>
<td>11%</td>
<td>14%</td>
</tr>
</tbody>
</table>

N=21 payers.

Almost half of payers with oncology pathways who measure compliance provide financial incentives.

Figure 23 | Percent of Payers Providing Financial Incentives for Pathway Compliance

<table>
<thead>
<tr>
<th></th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>47%</td>
<td>57%</td>
</tr>
<tr>
<td>Yes</td>
<td>47%</td>
<td>38%</td>
</tr>
<tr>
<td>Don’t know</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

N=21 payers.
Increasingly, payers are developing their own proprietary pathways in collaboration with oncologists and relying less on third-party pathway vendors.

Figure 24 | Strategies Used by Payers for Oncology Clinical Pathway Development

<table>
<thead>
<tr>
<th>Method</th>
<th>2016</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collaborate with oncologists</td>
<td>46%</td>
<td>57%</td>
</tr>
<tr>
<td>Create proprietary pathways</td>
<td>26%</td>
<td>43%</td>
</tr>
<tr>
<td>Utilize third-party vendor</td>
<td>28%</td>
<td>38%</td>
</tr>
<tr>
<td>Rely on oncologists'</td>
<td>12%</td>
<td>29%</td>
</tr>
</tbody>
</table>

GSPs lag behind oncology predictive biomarkers, companion diagnostics, and prognostic biomarkers in current coverage.

Payer coverage of GSPs is well below that of predictive biomarkers and companion diagnostics (19% vs 48%) with no increase in coverage expected in the next 12 months.

Figure 25 | Payers’ Coverage of Biomarker Tests as Part of an Oncology Clinical Pathway Measurement

<table>
<thead>
<tr>
<th>Biomarker Type</th>
<th>2016</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncology predictive biomarkers,</td>
<td>48%</td>
<td>29%</td>
</tr>
<tr>
<td>companion diagnostics</td>
<td>19%</td>
<td>4%</td>
</tr>
<tr>
<td>Prognostic biomarkers</td>
<td>52%</td>
<td>24%</td>
</tr>
<tr>
<td>GSPs</td>
<td>19%</td>
<td>14%</td>
</tr>
</tbody>
</table>

N=50 payers.
Some payers are participating in the Oncology Care Model.

The Oncology Care Model (OCM) was developed by the Centers for Medicare and Medicaid Services to provide higher quality, more highly coordinated oncology care at the same or lower cost as Medicare. At the time of publication, there were 190 oncology practices and 16 payers participating in the OCM, all of which have committed to providing enhanced services to Medicare beneficiaries such as care coordination, navigation, and national treatment guidelines for care. The OCM encourages participating practices to improve care and lower costs through an Episode of Care Model that financially incentivizes high-quality, coordinated care. Two forms of payment are provided to oncology practices. A $160 per-beneficiary monthly enhanced oncology services payment assists participating practices in effectively managing and coordinating care for oncology patients during episodes of care. A performance-based payment incentivizes practices to lower the total cost of care and improve care for beneficiaries during treatment episodes. There are 17 commercial payers also participating in the OCM in alignment with Medicare to create broader incentives for care transformation at the physician practice level. Participating payers have the flexibility to design their own payment incentives to support their beneficiaries while aligning with OCM goals for care improvement and efficiency.

Payers’ use of oncology episodic reimbursement is expected to increase next year.

The majority of payers (52%) report currently using or planning to use oncology episodic care reimbursement (Figure 27). While current use is limited to national and regional plans, all plan types are considering use in the next 12 months (Figure 28).

“We are involved in exploring episode-of-care models, clinical pathways, and we can increase the alignment of incentives through shared savings. So the Oncology Care Model... [is] just the right direction. It is about a comprehensive approach, and that includes preventing unnecessary ER visits, hospitalizations, educating patients, especially around nausea, vomiting, dehydration, [and] pain, and to contact their prescriber, and hopefully it becomes part of that performance piece, including the discussion around palliative care and shared decision making. So the Oncology Care Model is quite interesting.”

– Medical director
Figure 26 | Percent of Payers Participating in Medicare’s Oncology Care Model

- Yes: 60%
- No: 24%
- Don’t know: 16%

N=50 payers.

Figure 27 | Percent of Payers Using Oncology Episodic Care Reimbursement

- Currently use: 40%
- Plan to use in the next 12 months: 40%
- No plan to use: 12%
- Don’t know: 8%

N=50 payers.

Figure 28 | Percent of Payers’ Use of Oncology Episodic Care Reimbursement by Geographic Plan Type

- Currently use
  - National: 17%
  - Regional: 13%
  - Statewide: 4%

- Plan to use in the next 12 months
  - National: 39%
  - Regional: 39%
  - Statewide: 44%

- No plans to use
  - National: 33%
  - Regional: 44%
  - Statewide: 44%

- Don’t know
  - National: 11%
  - Regional: 11%
  - Statewide: 11%

N=50 payers.
Payers cite cost as the most important factor influencing biomarker coverage.

For the majority of payers (70%), cost is now the most important factor influencing biomarker coverage, followed closely by clinical validity (64%) and utility (62%).

Figure 29 | Most Important Factors Influencing Payers’ Coverage Decisions (Top 2 Box Score)

- **Cost**: 70%
- **Clinical validity**: 64%
- **Clinical utility**: 62%
- **Mandated in a therapeutics**: 56%
- **FDA labeling**: 44%
- **External clinical pathway (eg, NCCN)**: 50%
- **Comparative effectiveness**: 48%
- **Cost-effectiveness**: 50%
- **Test performance (sensitivity, specificity)**: 50%
- **Test results must change patient management**: 54%
- **The need to test many to identify the few who will benefit**: 32%
- **Quality metric performance**: 30%
- **Per member per year impact**: 34%
- **Unnecessary, nonpredictive tests conducted by research hospitals**: 24%
- **Impact on patient and provider satisfaction**: 28%
- **Overall increased use of diagnostic tests**: 24%
- **Increased test complexity**: 14%

N=50 payers.
Most organizations reported using third-party guidelines to help guide coverage decisions for oncology predictive biomarkers.

Half of payers reported using third-party guidelines to help guide coverage decisions for oncology predictive biomarkers. Interestingly, some overlap in the use of third-parties was observed, with the National Comprehensive Cancer Network® (NCCN®) Biomarkers Compendium®, as well as professional and regulatory organizations to guide coverage decisions (Figure 30). A consultant or benefit management company is used by only a minority of payers to guide coverage decisions.

**Figure 30 | Payers’ Use of Third Parties to Guide Coverage Decisions for Oncology Predictive Biomarkers**

- Utilize the NCCN Biomarkers Compendium® category evidence level 2A and 1 79%
- Monitor and incorporate guidance issued by professional and regulatory organizations (ie, AACR, ASCO, AUA, CAP, FDA) 64%
- Managed by contracted consultant or benefit management company 28%

N=50 payers.

**Predictive Biomarker Test Utilization and Coverage**

*Only a minority of oncologists and pathologists will order a specific brand of biomarker test.*

Compared with pathologists, oncologists are much less specific when ordering a biomarker test. Only a minority of orders (16% for oncologists and 24% for pathologists) actually specify a specific brand of test; hence, rarely is the FDA-approved companion diagnostic ordered.
PD-L1 testing increased dramatically in 2016.

In 2016, dramatic increases in testing for PD-L1 expression among patients with melanoma and NSCLC were reported by both oncologists and pathologists. MET mutation testing in NSCLC also increased substantially (Table 2).
### Table 2 | Percent of Respondents Indicating the Biomarker Is Ordered or Covered

<table>
<thead>
<tr>
<th>BIOMARKER TEST</th>
<th>ONCOLOGISTS</th>
<th>PATHOLOGISTS</th>
<th>PAYERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2 in breast cancer</td>
<td>92%</td>
<td>88%</td>
<td>96%</td>
</tr>
<tr>
<td>HER2 in esophagogastric adenocarcinoma</td>
<td>88%</td>
<td>74%</td>
<td>84%</td>
</tr>
<tr>
<td>HER2 in NSCLC adenocarcinoma</td>
<td>22%</td>
<td>22%</td>
<td>20%</td>
</tr>
<tr>
<td>BRACA 1/2 in breast cancer</td>
<td>22%</td>
<td>26%</td>
<td>24%</td>
</tr>
<tr>
<td>Oncotype DX in breast cancer</td>
<td>Not asked</td>
<td>76%</td>
<td>Not asked</td>
</tr>
<tr>
<td>KRAS in colorectal cancer</td>
<td>88%</td>
<td>70%</td>
<td>88%</td>
</tr>
<tr>
<td>KRAS in NSCLC</td>
<td>38%</td>
<td>36%</td>
<td>84%</td>
</tr>
<tr>
<td>KIT in GIST</td>
<td>78%</td>
<td>62%</td>
<td>84%</td>
</tr>
<tr>
<td>KIT in melanoma</td>
<td>Not asked</td>
<td>36%</td>
<td>Not asked</td>
</tr>
<tr>
<td>BCR-ABL in CML</td>
<td>94%</td>
<td>62%</td>
<td>80%</td>
</tr>
<tr>
<td>PML-RARa in APL</td>
<td>68%</td>
<td>58%</td>
<td>40%</td>
</tr>
<tr>
<td>FLT3 in AML</td>
<td>Not asked</td>
<td>58%</td>
<td>Not asked</td>
</tr>
<tr>
<td>17P deletion in CLL</td>
<td>Not asked</td>
<td>74%</td>
<td>Not asked</td>
</tr>
<tr>
<td>PDGFRB in MDS</td>
<td>24%</td>
<td>32%</td>
<td>36%</td>
</tr>
<tr>
<td>EGFR in NSCLC</td>
<td>82%</td>
<td>74%</td>
<td>100%</td>
</tr>
<tr>
<td>EGFR in colorectal cancer</td>
<td>Not asked</td>
<td>40%</td>
<td>Not asked</td>
</tr>
<tr>
<td>EGFR cfDNA “liquid biopsy”</td>
<td>Not asked</td>
<td>Not asked</td>
<td>Not asked</td>
</tr>
<tr>
<td>BRAF V600 in NSCLC</td>
<td>30%</td>
<td>36%</td>
<td>32%</td>
</tr>
<tr>
<td>BRAF V600 E/K in NSCLC</td>
<td>Not asked</td>
<td>26%</td>
<td>Not asked</td>
</tr>
<tr>
<td>BRAFV600 in melanoma</td>
<td>84%</td>
<td>78%</td>
<td>72%</td>
</tr>
<tr>
<td>BRAF V600 E/K in melanoma</td>
<td>Not asked</td>
<td>70%</td>
<td>Not asked</td>
</tr>
<tr>
<td>PD-L1 in melanoma</td>
<td>28%</td>
<td>40%</td>
<td>8%</td>
</tr>
<tr>
<td>PD-L1 in NSCLC</td>
<td>26%</td>
<td>52%</td>
<td>4%</td>
</tr>
<tr>
<td>ALK in NSCLC</td>
<td>92%</td>
<td>72%</td>
<td>92%</td>
</tr>
<tr>
<td>MET in NSCLC</td>
<td>12%</td>
<td>30%</td>
<td>8%</td>
</tr>
<tr>
<td>MEK1 in NSCLC</td>
<td>16%</td>
<td>16%</td>
<td>0%</td>
</tr>
<tr>
<td>PIK3CA in NSCLC</td>
<td>10%</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>ROS1 in NSCLC</td>
<td>52%</td>
<td>60%</td>
<td>40%</td>
</tr>
<tr>
<td>5-50 gene solid tumor GSP (CPT 81445)</td>
<td>28%</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td>5+ gene solid and hematologic tumor GSP (CPT 81455)</td>
<td>28%</td>
<td>16%</td>
<td>20%</td>
</tr>
<tr>
<td>Academic GSPs</td>
<td>Not asked</td>
<td>8%</td>
<td>Not asked</td>
</tr>
<tr>
<td>Commercial Lab GSPs</td>
<td>Not asked</td>
<td>26%</td>
<td>Not asked</td>
</tr>
</tbody>
</table>
Most pathologists do not specify a specific brand of biomarker tests.

Only 16% of orders specify the specific brand of test. There is rarely reference to the specific companion diagnostic. Payers are also unable to discern if they are covering a companion diagnostic or LDT.

Figure 32 | Pathologists’ Level of Specificity When Ordering a Biomarker Test

![Pie chart showing percentages of specificity levels for ordering biomarker tests.](image)

- 76% specify biomarker + indication (e.g., HER2 in breast cancer)
- 16% specify biomarker + indication + technology (e.g., HER in breast cancer by FISH)
- 8% specify brand name + indication (e.g., HercepTest™ in breast cancer)
- 8% specify biomarker + indication (e.g., HER2 in breast cancer)

N=25 pathologists.

Few payers publish biomarker coverage guidance or specify a biomarker test by brand.

Only 26% of payers reported publishing guidance on biomarker coverage and only 8% of payer biomarker coverage guidance specifies a biomarker test by brand. Hence, rarely are payers requiring use of the FDA-approved companion diagnostic (brand specific).

“Practically speaking, if there’s a lab-developed test that we’ve evaluated and we’re comfortable with the laboratory – the technology, the personnel performing it – in essence, we would use it. Typically, if there is an FDA-sanctioned test, we will stick with the FDA-sanctioned test.”

– Payer, pharmacy director
“The reality is that the codes are the same and we really don’t know whether the test is being done as an LDT or by an FDA-approved test.”

– Payer, medical director

**Coverage of GSPs is mostly dependent on FDA approval.**

The majority of payers (54%) are waiting for a GSP to be approved by the FDA as a companion diagnostic before covering it. However, coverage of a GSP by Medicare and the availability of prospective clinical trial data can strongly influence a coverage decision.

**Figure 33 | Payers Who Strongly Agree With the Following Statements (Top 2 Box Score)**

- **Prospective clinical trials will be required to validate that this technology can accurately identify patients for specific therapy(ies) in order to make a coverage decision.**
  - 2016: 60%
  - 2015: 70%

- **The GSP will not be covered unless approved by the FDA as a companion diagnostic for specific therapeutics.**
  - 2016: 52%
  - 2015: 54%

- **Coverage by Medicare of the oncology GSPs will strongly influence a positive coverage decision by my company.**
  - 2016: 44%
  - 2015: 46%

- **Previous clinical trial data done with other single mutation biomarker tests are sufficient to support the effectiveness and reimbursement of oncology GSPs.**
  - 2016: 28%
  - 2015: 26%

N=50 payers.
In most cases, fees for biomarker testing are negotiated with laboratories.

Most payers surveyed (42%) negotiate contracted rates with a lab or restricted network of labs that must be used for the test to be covered.

Figure 34 | Payers’ Reimbursement Strategies for Predictive Biomarkers

- Negotiate contracted rates with a lab or restricted network of labs that must be used for the test to be covered (42%)
- Use the CMS laboratory fee schedule (22%)
- Set a maximum allowable based on a methodology that reflects the typical amount charged by labs (28%)
- Other (8%)

N=50 payers.

Few payers cover a specific BRAF test for melanoma.

FDA approvals of 3 agents that target V600E or V600K mutations in the BRAF gene of patients with advanced melanoma include a companion diagnostic assay as a requirement for use. One of these agents is only approved for patients with the BRAF V600E mutation, while the other 2 agents are approved for BRAF V600E and V600K.48

At the time of printing, 4 agents were approved by the FDA for the treatment of patients with advanced melanoma and a BRAF V600E or V600K mutation (2 BRAF inhibitors and 2 MEK inhibitors). Just 32% of payers reported only covering a specific BRAF test, such as the cobas® 4800 BRAF V600 Mutation Test (Roche Molecular Systems Inc). Two of the 3 agents that include a companion diagnostic assay as a requirement for use are approved with both BRAF V600 E and K mutations yet only 50% of payers specify coverage for BRAF tests that capture both mutations. Payer policy decisions to not provide coverage for the BRAF V600K mutation appears to be adversely impacting testing for the other agents.48

Figure 35 | Payers’ Coverage Policies for BRAF Biomarker Test in Melanoma

- Cover all BRAF biomarker tests (23%)
- Cover only BRAF V600 E/K biomarker tests (17%)
- Cover only BRAF V600 E (32%)
- Cover only a specific BRAF test(s) (ie, cobas 4800 BRAF V600 Mutation Test) (13%)
- Any of the above and specify by tumor type (15%)

N=50 payers.

cobas 4800 BRAF V600 Mutation Test is a registered trademark of Roche Molecular Systems Inc.
Cost-Effectiveness

Despite dramatic drops in DNA sequencing costs, there are concerns that the integration of genomic testing into clinical settings will drastically increase health care expenditures. In addition, the identification of secondary findings during genomic sequencing has the potential to initiate a cascade of confirmatory testing and follow-up screening that may only be warranted in a subset of patients. However, there are hopes that the widespread integration of genomic sequencing into medicine, while associated with upfront investments, will reduce downstream health expenditures. The cost-effectiveness of genomic sequencing has been evaluated for only a few conditions and contexts. In some studies, cost-effectiveness has been shown to improve when treatment is stratified to patients with genetic biomarkers. Cost-utility analyses are commonly used to determine the value of an intervention based on clinical benefits and costs, with results usually presented in terms of an incremental cost-effectiveness ratio (ICER) and cost per quality-adjusted life-year (QALY).

- Comparing cost-effectiveness across 3 patient populations with metastatic colorectal cancer (intention to treat [ITT], wild-type Kirsten rat sarcoma [KRAS wt], and RAS wt) in the randomized phase 3 study, the RAS wt cohort had the lowest ICER. The combination of monoclonal antibody (targeting EGFR) plus chemotherapy compared with chemotherapy alone was associated with an incremental life-year gain of 0.16 in the ITT population, 0.29 in the KRAS wt population, 0.45 in the RAS wt population, and an incremental QALY gain of 0.12 in the ITT population, 0.22 in the KRAS wt population, and 0.24 in the RAS wt population.

- In a budget impact analysis of EGFR mutation testing for EGFR-TKI therapy vs platinum-doublet-based chemotherapy in the first-line treatment of patients with EGFR mutation-positive advanced NSCLC, increasing EGFR testing rates from 50% to 100% increased overall health plan expenditures by $0.013 per member per month (PMPM). The cost of EGFR mutation testing was estimated at $0.002 PMPM, but was offset by the cost savings associated with treatment of chemotherapy-related adverse events (-$0.002 PMPM). Treatment costs were $0.012 PMPM, mostly reflecting the extended duration of treatment.

- In an analysis of clinical and outcomes data from 3 cancer therapies and societal cost data from cancer centers in Singapore, EGFR mutation-guided therapy produced an incremental cost savings of $1872 US compared with no EGFR testing, with an ICER of 0.04. Cost savings, which were primarily driven by not providing a specific treatment to patients without EGFR mutations and thus much less likely to derive a clinical benefit, dwarf the costs of EGFR mutation testing.

*2010 SGD converted to USD. http://www.x-rates.com/historical/?from=USD&amount=1&date=2010-12-31.
Payers report being very engaged in evaluating or planning to evaluate the impact and cost-effectiveness of oncology biomarker tests.

The majority of payers (60%) are very engaged in evaluating or planning to evaluate the impact and cost-effectiveness of oncology biomarker tests, including GSPs.

Figure 36 | Payers' Intent to Conduct an Internal Analysis to Evaluate the Impact of Oncology Predictive Biomarkers

- Yes, currently conduct analysis: 38%
- Intend to conduct analysis in the next 12 months: 34%
- Do not intend to conduct analysis in the next 12 months: 22%
- Don’t know: 6%

N=50 payers.

Overall cost-effectiveness assessments of genomic testing are underway and likely to increase.

Of those surveyed, 32% of pathologists and 48% of oncologists are either currently conducting cost evaluations or are planning to do so in the next 12 months. This activity may be occurring because of a greater interest in utilizing biomarkers and GSPs under APMs.

Figure 37 | Percent of Providers Conducting Cost-Effectiveness Evaluations

- Oncologists: 16% currently participating, 16% intend to participate in the next 12 months, 56% do not intend to participate, 12% don’t know
- Pathologists: 16% currently participating, 32% intend to participate in the next 12 months, 40% do not intend to participate, 12% don’t know

N=50 oncologists, 25 pathologists.
The Future

The future of precision oncology hinges on the development of valid biomarker tests, which can identify key aberrant pathways that are susceptible to molecular targeted or immunologic therapies. The identification and targeting of aberrant pathways at the molecular level has been fueled by:

• The recent revolution in molecular biology
• The rise of high-throughput sequencing
• Increased molecular characterization of tumor tissue

Treating patients who have cancer today and in the future not only requires a clinical examination but an in-depth knowledge of molecular testing, novel therapeutics, and ongoing clinical trials, as well as an ability to tap into the information disseminated by big data as it becomes available. Only through the integration of these capabilities will providers be able to deliver better, more comprehensive personalized care to patients.

The Expanding Role of the FDA

The FDA is a partner in the Precision Medicine Initiative (PMI), which aims to take advantage of the progress made in genomic testing to accelerate the development of new treatments designed to meet patients’ individual characteristics. The PMI is committed to helping clinicians target the right treatments to the right patients at the right time. However, precision care can only be as good as the tests that guide diagnosis and treatment.

In 2014, the FDA issued a draft guidance in which a companion diagnostic was defined as an in vitro diagnostic device that provides essential information for the safe and effective use of a corresponding therapeutic product. A companion diagnostic ensures labeled safety and effectiveness claims are met by helping to:

• Identify patients who are most likely to benefit from the therapeutic product
• Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with the therapeutic product
• Monitor response to treatment with the therapeutic product for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness
• Identify patients in the population for whom the therapeutic product has been adequately studied and found safe and effective

An LDT is a type of in vitro diagnostic test that is designed, manufactured, and used within a single laboratory in the following ways:

• Screening for cancer or precancerous conditions prior to the onset of any symptoms of disease
• Helping to diagnose cancer
• Providing information about the stage of a tumor
• Planning treatment
• Monitoring the health of a patient during treatment and checking for potential treatment-related side effects
• Assessing response to treatment, including recurrence or progression

Types of LDTs used to diagnose cancer include:

• Cytogenetic analyses: measures changes in the number and/or structure of chromosomes in a patient’s white blood cells or bone marrow cells
• Immunophenotyping: identifies cells based on the types of antigens present on the cell surface
• Tumor marker tests: measures the presence, levels, or activity of specific proteins or genes in tissue, blood, or other bodily fluids that may be signs of cancer

In recognition of the increased complexity of LDTs and the potential for great harm to the patient associated with a faulty LDT result, regulatory oversight of LDTs was announced in July 2014, accompanied by a statement from FDA Commissioner Margaret A. Hamburg, MD:

“Ensuring that doctors and patients have access to safe, accurate, and reliable diagnostic tests to help guide treatment decisions is a priority for the FDA. Inaccurate test results could cause patients to seek unnecessary treatment or delay and sometimes forgo treatment altogether. Today’s action demonstrates the agency’s commitment to personalized medicine, which depends on accurate and reliable tests to get the right treatment to the right patient.”

Both companion diagnostics and LDTs, can advise the treatment plan. The FDA maintains a list of cleared or approved companion diagnostic devices on its website.
Providers and payers strongly agree that LDTs require regulation and oversight of their effectiveness.

Figure 38 | Providers Who Strongly Agree With the Following Statements

- **The FDA should regulate predictive biomarker LDTs by requiring LDTs to meet in vitro performance criteria (ie, false +ve, false -ve) vs a standard, FDA-approved biomarker test**
  - Oncologists: 56%
  - Pathologists: 52%
  - Payers: 66%

- **Precision medicine and biomarker developers need to collaborate on the development of outcomes data for oncology predictive biomarkers related to their products**
  - Oncologists: 54%
  - Pathologists: 54%
  - Payers: 75%

- **The FDA should regulate predictive biomarker LDTs by requiring clinical outcomes data to prove the effectiveness of each LDT**
  - Oncologists: 52%
  - Pathologists: 60%
  - Payers: 64%

- **The short-term costs for increased biomarker-based diagnostic testing is worth the potential long-term savings**
  - Oncologists: 28%
  - Pathologists: 44%
  - Payers: 38%

- **A nongovernmental professional organization should set standards for predictive biomarker LDTs by requiring LDTs to meet in vitro performance criteria (ie, false +ve, false -ve) vs a standard, FDA-approved biomarker test**
  - Oncologists: 26%
  - Pathologists: 40%
  - Payers: 34%

- **LDTs are currently very effective and can be utilized for clinical decision making without further regulation**
  - Oncologists: 12%
  - Pathologists: 0%
  - Payers: 16%

N=50 oncologists, 25 pathologists, 50 payers.
Next-Generation Sequencing

NGS is a new method of sequencing millions of small DNA fragments at the same time to create a massive pool of personalized patient data. Mutant genes that cause cancer (and perhaps others that have potential clinical relevance) could be sequenced all at once in a single test. NGS has the potential to make companion diagnostic testing obsolete. Instead of ordering tests specifically developed to evaluate a patient prior to the use of a drug, genetic screens performed using NGS could be done up front, at the time of diagnosis, to identify a vast number of biomarkers. Upon identification of a tumor, an oncologist could order a screening of the tumor’s genetic makeup and thus, reveal a large number of biomarkers, including those that would have been tested by a companion diagnostic. NGS can also be used to monitor the efficacy of treatment over time or facilitate clinical decision making and identify therapeutic approaches for which no established treatment protocols exist.

The FDA is presently dealing with a variety of regulatory issues borne out of the vast amount of information generated through NGS by issuing discussion papers, holding workshops, and collaborating with stakeholders. In addition, the FDA has created precisionFDA, a new community portal that allows for testing, piloting, and validating existing and new bioinformatics approaches to processing NGS data.

The FDA recently published 2 draft guidances for NGS-based tests to help ensure such tests are safe and effective while providing test developers adaptability and flexibility needed to innovate in this dynamic field. The first draft guidance, entitled “Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Used for Diagnosing Germline Diseases,” provides recommendations for designing, developing, and validating NGS-based tests for hereditary diseases and addresses the potential for using FDA-recognized standards to demonstrate analytical validity. The second draft guidance, entitled “Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics,” proposes the use of data and assertions from FDA-recognized public genome databases as valid scientific evidence to support clinical claims for their tests, which can be an easier path for marketing clearance or approval.

Several studies have evaluated the analytical validity of NGS to accurately detect mutations and copy number alterations (CNAs). In a study designed to test the analytical validity of a panel of 287 cancer-related genes, in which a total of 118 samples were tested for mutations and 185 for CNAs, high concordance between the genomic profiling using NGS and standard assays was observed, both for mutation detection and identifying CNAs.

Gene Sequencing Panels

Rather than perform individual gene assays, many commercial and academic laboratories have developed targeted GSPs focused on 25 to 400 genes that are known to be important for cancer biology or disease management. Since 2012, thousands of cancer patients have undergone genomic testing with cancer GSPs in the United States.

The 2 best-known GSPs currently available in the United States are produced by Foundation Medicine and Caris Life Sciences. Thermo Fisher has an NSCLC GSP that it is currently under FDA review as a companion diagnostic.

- The FoundationOne panel looks at the entire coding sequence of 315 cancer-related genes, as well as select introns from 28 genes that are often rearranged or altered in patients with cancer. Validation testing demonstrated a sensitivity and specificity of over 95%. The report listing testing results matches targeted therapies to the specific mutations identified. When the panel was applied to 2221 cases, clinically actionable alterations were found in 76% of tumors.

- Caris Life Sciences uses immunohistochemistry, fluorescence in situ hybridization, and polymerase chain reaction, in addition to NGS, in order to detect and interrogate each biomarker in its panel.
Widespread adoption of NGS GSPs is likely to increase in the future.

While only 8% of pathologists and 10% of oncologists are currently utilizing an NGS GSP to profile all solid and liquid tumor biopsies, 16% of pathologists would recommend their use. Most oncologists (48%) and pathologists (52%) are waiting for guidance from professional organizations or for FDA approval before utilizing biomarker status as the primary measure for determining treatment (Figure 39).

**Figure 39 | Providers Who Strongly Agree With the Following Statements Regarding TAPUR and NCI-MATCH**

```
<table>
<thead>
<tr>
<th>Statement</th>
<th>Oncologists</th>
<th>Pathologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>I would wait for inclusion into NCCN, payer, or my organization’s guidelines/pathways before utilizing an NGS GSP to profile all solid and liquid tumor biopsies</td>
<td>48%</td>
<td>52%</td>
</tr>
<tr>
<td>I would wait for FDA approval before utilizing an NGS GSP to profile all solid and liquid tumor biopsies</td>
<td>34%</td>
<td>40%</td>
</tr>
<tr>
<td>I would recommend utilizing an NGS GSP to profile all solid and liquid tumor biopsies</td>
<td>10%</td>
<td>16%</td>
</tr>
<tr>
<td>I am not waiting for results of these studies; I am currently utilizing an NGS GSP to profile all solid and liquid tumor biopsies</td>
<td>10%</td>
<td>8%</td>
</tr>
</tbody>
</table>
```

N=50 oncologists, 25 pathologists.

Oncologists and pathologists express different views about NGS and GSPs.

The time required to acquire a biopsy and receive test results appears to be more of an issue with oncologists than pathologists (42% vs 28%). However, pathologists more strongly disagreed than oncologists that payer coverage and reimbursement is sufficient (36% vs 24%). Pathologists again more strongly disagreed than oncologists that their provider organization (hospital, clinic) has collaborated with local payers and testing laboratories to develop a covered, standard protocol for utilizing NGS (72% vs 40%). Finally, and as expected, pathologists appear to be more sensitive to the issue of obtaining enough tumor tissue from a biopsy for testing; more strongly disagreeing than oncologists that it is not an issue (48% vs 16%) (Figure 40).
Figure 40 | Providers’ Level of Agreement With the Following Statements Regarding NGS and GSPs

**ONCOLOGISTS**

- **Obtaining enough tumor from the biopsy for the test is not a problem**
  - Strongly agree: 8%
  - Neutral: 76%
  - Strongly disagree: 16%

- **Payer coverage and reimbursement is sufficient**
  - Strongly agree: 10%
  - Neutral: 66%
  - Strongly disagree: 24%

- **The time required to acquire a biopsy and receive the test results can be an issue**
  - Strongly agree: 42%
  - Neutral: 50%
  - Strongly disagree: 8%

- **My provider organization (hospital, clinic) has collaborated with local payers and testing laboratory(ies) to develop a covered, standard protocol for utilizing NGS**
  - Strongly agree: 8%
  - Neutral: 52%
  - Strongly disagree: 40%

**PATHOLOGISTS**

- **Obtaining enough tumor from the biopsy for the test is not a problem**
  - Strongly agree: 4%
  - Neutral: 48%
  - Strongly disagree: 48%

- **Payer coverage and reimbursement is sufficient**
  - Strongly agree: 8%
  - Neutral: 56%
  - Strongly disagree: 36%

- **The time required to acquire a biopsy and receive the test results can be an issue**
  - Strongly agree: 28%
  - Neutral: 52%
  - Strongly disagree: 20%

- **My provider organization (hospital, clinic) has collaborated with local payers and testing laboratory(ies) to develop a covered, standard protocol for utilizing NGS**
  - Strongly agree: 8%
  - Neutral: 24%
  - Strongly disagree: 72%

N=50 oncologists.

N=25 pathologists.
The cost threshold of NGS has fallen since 2015.

The cost threshold of NGS has fallen vs 2015 ($1533 mean cost in 2016 vs $2406 mean cost in 2015). When NGS or GSP costs less than 4 individual biomarkers (approximately $900), it will become disruptive and could potentially replace single biomarker testing. A majority of payers (72%) would likely cover NGS at that price.

Figure 41 | Threshold Price Where NGS Becomes Disruptive and Replaces a Single Mutation Biomarker Test

Don’t know

<table>
<thead>
<tr>
<th>Oncologists</th>
<th>Pathologists</th>
<th>Payers</th>
</tr>
</thead>
<tbody>
<tr>
<td>32%</td>
<td>28%</td>
<td></td>
</tr>
</tbody>
</table>

Comparable to 2 to 4 single biomarker predictive tests and/or companion diagnostic tests

<table>
<thead>
<tr>
<th>Oncologists</th>
<th>Pathologists</th>
<th>Payers</th>
</tr>
</thead>
<tbody>
<tr>
<td>24%</td>
<td>28%</td>
<td></td>
</tr>
</tbody>
</table>

Comparable to a single biomarker predictive test and/or companion diagnostic test

<table>
<thead>
<tr>
<th>Oncologists</th>
<th>Pathologists</th>
<th>Payers</th>
</tr>
</thead>
<tbody>
<tr>
<td>18%</td>
<td>28%</td>
<td></td>
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</table>

Entered a dollar amount

<table>
<thead>
<tr>
<th>Oncologists</th>
<th>Pathologists</th>
<th>Payers</th>
</tr>
</thead>
<tbody>
<tr>
<td>12%</td>
<td>18%</td>
<td></td>
</tr>
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</table>

Oncologists and pathologists express different views on deciding which genomic tests to order.

While oncologists and pathologists almost equally reported being open to collaboration in determining which test should be ordered for a patient, a greater percentage of oncologists reported making the decision independently (38% oncologists vs 20% pathologists).

Figure 42 | Process for Determining Biomarker Choice for Solid and Liquid Tumors

I make the decision independently and order the test according to my clinical judgement of what is appropriate

<table>
<thead>
<tr>
<th>Oncologists</th>
<th>Pathologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>38%</td>
<td>20%</td>
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</tbody>
</table>

We confer (oncologist and pathologist) and make a joint decision for each patient through direct contact or at a tumor board

<table>
<thead>
<tr>
<th>Oncologists</th>
<th>Pathologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>34%</td>
<td>36%</td>
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</tbody>
</table>

We have standard pathways/guidelines that were mutually agreed upon between oncology and pathology that I follow for the majority of patients

<table>
<thead>
<tr>
<th>Oncologists</th>
<th>Pathologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>30%</td>
<td>32%</td>
</tr>
</tbody>
</table>

I have a standing order for a biomarker panel for all solid tumor biopsies at diagnosis

<table>
<thead>
<tr>
<th>Oncologists</th>
<th>Pathologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>8%</td>
<td>12%</td>
</tr>
</tbody>
</table>

N=50 oncologists, 25 pathologists.
Personalized Medicine Programs

NGS has revolutionized cancer genomics research and diagnostics, causing a shift away from single-gene mutation analysis to cancer genome profiling in a single multiplexed assay. Because routine sequencing of an entire cancer genome by diagnostic laboratories is currently unfeasible, several cancer gene panels have been recently developed and validated for clinical diagnostic use by both research laboratories and commercial companies. The JAX Cancer Treatment Profile™ (The Jackson Laboratory) is one example of a GSP designed to identify mutations in 190 potentially actionable genes across multiple cancer relevant pathways.

As a key element in its personalized medicine program (PMP), the Swedish Cancer Institute in Seattle, Washington, developed their own GSP of genes that are most relevant to known cancer treatments. Results of testing are captured in a report that provides a detailed portrait of a patient’s tumor, enabling the patient care team to select the most promising targeted therapies for an individual patient. In addition, the report includes hyperlinks to literature that provides context for the findings, as well as links to clinical trials that represent viable options for the patient.

Key Issues to Consider:

- Educate physicians about the detailed molecular pathways that drive oncogenesis and the agents designed to target molecular changes
- Determine how success is measured
- Pinpoint mutations that drive the patient’s tumor and create an individualized treatment plan that avoids therapies with little benefit to the patient

The Swedish Cancer Institute Recommends the Following Key Steps to Setting up a PMP Using a GSP:

- Decide whether to use a commercial GSP or develop a proprietary panel of genes for NGS that are most relevant to known cancer treatments
- Work with payers to ensure reimbursement for molecular testing
- Create an environment in which physicians and pathologists can collaborate in optimizing specimen collection, evaluating test results, confirming diagnoses, and identifying the most promising treatments or clinical trials for each patient
- Construct a database that allows your treatment team to mine patient data and research results to identify which treatments work best for tumors with particular gene alterations

The JAX Cancer Treatment Profile™ is a trademark of The Jackson Laboratory.
Some payers report being involved in a coordinated PMP.

Of those surveyed, 28% of payers reported being involved in a coordinated PMP. Interestingly, almost half of payers reported not being aware nor interested in predictive biomarker utilization or coverage.

Figure 43 | Payers Who Strongly Agree With the Following Statements

- **My organization is aware and interested in the utilization and coverage of predictive biomarkers**
  - 52%

- **When making coverage or formulary decisions for an oncology therapeutic, my organization includes the value of predictive biomarkers in the overall cost/benefit analysis**
  - 50%

- **Our clinical recommendations and/or pathways include predictive biomarkers**
  - 32%

- **My organization collects predictive biomarker real-world cost/benefit data**
  - 30%

- **My organization actively communicates to providers regarding coverage and appropriate utilization of predictive biomarkers**
  - 28%

- **My organization collaborates with local IDNs/providers and diagnostic labs/pathologists to provide a coordinated oncology precision medicine program**
  - 28%

N=50 payers.
Non-Traditional Trial Designs

Classic trial designs are unable to test targeted therapeutics against low-frequency genomic mutations with sufficient power. New biomarker-driven clinical trials have emerged, this issue and the importance of interpatient heterogeneity in cancer therapeutic responses and outcomes.

- Umbrella trials are designed to test the impact of different drugs on various mutations in a single cancer type. Examples of this type of trial include I-SPY 2 and SAFIR-01 in breast cancer, Master Protocol and ALCHEMIST in lung cancer, and FOCUS4 in colorectal cancer.

- Basket trials are designed to test the effectiveness of a single targeted drug on a single mutation in a variety of cancer types. Examples of this type of trial are the NCI-MATCH study and the TAPUR study.

- N-of-1 trials compare a target-drug matching approach with the most recent unmatched regimen on which the patient experienced disease progression. An example of this type of trial is the WIN Ther trial led by the Worldwide Innovative Networking Consortium.

NCI-MATCH

In the NCI-MATCH trial, patients’ tumors are tested to determine whether they contain genetic mutations for which a targeted drug exists. Patients are then assigned treatment, based on the gene mutation or deletion identified, to determine whether treatment according to these mutations will show evidence of effectiveness. Enrollment in this trial began in August 2015 with 10 treatment arms, paused for an interim analysis in November 2015, and reopened in May 2016 with a total of 24 treatment arms. Eligible patients were adults with advanced solid tumors and lymphomas who were no longer responding (or never responded) to standard therapy. The drugs included in the trial have either been approved by the FDA for another indication or are still being tested in other clinical trials. but have shown some effectiveness against tumors with a particular genetic alteration(s). Treatments that produce tumor shrinkage in at least 16% of the patients may be studied further in future studies.

Results of an interim analysis were presented in April 2016 at the 2016 Annual Meeting of the American Association for Cancer Research. Some of these findings included:

- Patient mutations that matching a targeted treatment in the first 10 arms was 9%; close to what was anticipated in the initial trial design (10%)
- Fifty-eight percent of trial participants were found to have rare cancers, which exceeded what was anticipated at enrollment (25%)
- DNA sequencing was performed on 87% of tumor samples, which is slightly higher than the industry standard (80%)
- For a variety of reasons (eg, longer-than-anticipated wait times for biopsy results, health status may have changed before assignment, etc), not all patients whose tumors were sequenced and matched 1 of the first 10 study arms ended up being treated
- Data from The Cancer Genome Atlas and other genomic studies were used to estimate prevalence rates of mutations upon which NCI-MATCH arms were determined, but these estimates ultimately did not give a true idea of what the match rate would be in heavily treated populations, such as those enrolled in NCI-MATCH. The interim analysis found that the initial match rate was 9%, but an increase is expected as the trial resumes.
**Pediatric MATCH**

An NCI trial for pediatric patients that will use a similar approach as the adult NCI-MATCH trial is being led by the Children’s Oncology Group. This trial is still in development and is expected to launch in 2017.²⁹

**TAPUR**

The TAPUR study is a nonrandomized clinical trial led by ASCO that is designed to evaluate the effectiveness of commercially available targeted drug therapies for patients with advanced cancer with a potentially actionable (driver) mutation. The study provides approved targeted therapies that are contributed by collaborating pharmaceutical companies and catalogs the genomic profiling test chosen by clinical oncologists. The goal of the study is to learn about additional uses of these drugs outside of indications already approved by the FDA and the utility of registry data for additional clinical trials.³⁰ TAPUR is currently under way at 37 clinical sites with additional sites to be added in the coming months. Nearly 100 clinical sites around the country have expressed interest in participating in the study.³¹

A TAPUR substudy, which consists of 2 brief surveys administered to TAPUR physicians at time points before and after TAPUR participation, will provide insights to help the oncology community understand how tumor genomic testing is being used by clinical oncologists and how to provide assistance with provider and patient education.³¹

Pharmaceutical companies currently participating in TAPUR include Astellas Pharma, AstraZeneca, Bayer, Bristol-Myers Squibb, Eli Lilly and Company, Genentech, Merck, and Pfizer, which will provide 17 drugs that yield 15 different targeted therapy options (some of the drugs are used in combination with one another) for participants with advanced solid tumors, multiple myeloma, or B-cell non-Hodgkin lymphoma.³¹

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**Positive results from NCI-MATCH and TAPUR may not guarantee coverage.**

If results from the NCI-MATCH and TAPUR studies are encouraging, the majority of payers (52%) will wait for the FDA to approve the indication or for listing in a recognized compendia.

**Figure 44 | Payers Who Strongly Agree With the Following Statements**

If these trials are successful, my organization will provide coverage for the biomarker and corresponding therapeutic, regardless of tumor type only upon FDA approval or recognized compendia listing

If these trials are successful, my organization will provide coverage for the biomarker, regardless of tumor type

If these trials are successful, my organization will provide coverage for the biomarker and corresponding therapeutic, regardless of tumor type

N=50 payers.
Liquid Biopsies
Looking for cancer-derived material circulating in the bloodstream has become an appealing alternative when there is limited availability of tumor biopsy tissue for molecular testing. “Liquid biopsy” is the term used to describe a diagnostic test performed on cancer-derived material present in a blood sample. Cell-free or complexed nucleic acids, including circulating cell-free DNA, of which circulating tumor DNA (ctDNA) is a subset, cell-free RNA, and circulating tumor cells are sources of genetic information that can be assessed by liquid biopsy.  

A liquid biopsy offers the following advantages over a tissue biopsy:  

- Provides a fresh source of tumor-derived material, free of preservatives  
- The procedure is minimally invasive, avoiding the complications of tumor biopsies while allowing for repeatable assessments of clonal dynamics during therapy and the early identification of resistance drivers  
- Offers the clinician a reasonable alternative sample type in routine clinical practice when a biopsy sample is unavailable, or difficult to obtain, or of insufficient quantity to meet increasing diagnostic demands  
- May better reflect the global (primary and metastatic sites) molecular status of the patient with regard to the tumor heterogeneity  
- Offers the potential for significantly shorter turnaround times than tissue-based testing  

Not only can ctDNA be detected in the blood of most metastatic cancer patients, it has convincing analytical validity to detect hotspot mutations using digital PCR, which can detect mutations in ctDNA with frequencies as low as 0.01%. However, this requires a prior knowledge of the exact mutations to be investigated. Utilizing NGS, tumor mutations have been identified in ctDNA from 69% of unselected patients with advanced cancers.  

Despite the advantages of ctDNA, not all tumors shed DNA into the plasma. In addition, ctDNA testing has reduced sensitivity compared with tissue testing, and negative results via ctDNA testing may be followed up via biopsy.
**Liquid Biopsies: A New Tool for Personalized Medicine**

By Daryl Pritchard, PhD, Vice President, Science Policy, Personalized Medicine Coalition

An innovation in the field called personalized medicine is, in some cases, providing experts with important information about a patient’s cancer faster—and more safely—than ever before.

Liquid biopsy tests are gaining traction as a viable alternative to traditional diagnostic tests for cancer. These tests allow cancer care providers to screen patients for the presence of cancer indicators from a simple blood sample, instead of using a costly, painful and sometimes-risky surgery called a tumor tissue biopsy.

Liquid biopsies have the potential to help detect cancer at earlier stages, provide a less-expensive and less-invasive way to monitor patients throughout treatment, provide more rapid results, and can help doctors make better decisions about which drugs are the best fit for patients. Liquid biopsies represent an important new set of tools in a field called personalized medicine, which aims to provide safer and more effective treatments based on a patient’s individual biological characteristics.

**Guiding Precision Treatments**

Personalized medicine is an evolving field in which physicians use diagnostic tests to determine which medical treatments will work best for each patient. By combining the data from those tests with an individual’s medical history, circumstances and values, health care providers can develop targeted treatment and prevention plans.

The use of diagnostic tests to help guide treatment decisions is becoming increasingly common. A recent report from a company called NextGxDx, for example, estimates that nearly 4000 new diagnostic tests were introduced to the market in 2015. In addition, more than 25% of all the medicines the US Food and Drug Administration (FDA) approved in 2015 are associated with a diagnostic test identified on the product label.

The FDA approved the first liquid biopsy test to detect a gene mutation associated with lung cancer earlier this year, and more are being considered for approval.

**Testing the Blood**

Liquid biopsies work by detecting DNA from circulating tumor cells or fragments of DNA shed by tumor cells into the bloodstream. A recent study of metastatic colorectal cancer patients showed that liquid biopsies could detect important gene mutations using this information 87.2% of the time.

As the US and other health care systems shift away from one-size-fits-all, trial-and-error treatment approaches and toward personalized medicine, liquid biopsies could be used instead of extensive imaging and invasive tissue biopsies for earlier detection of cancer and as a tool to guide cancer treatment decisions.

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Whole Genome Sequencing

While whole genome sequencing (WGS) has been proposed as the future of cancer genome diagnostics, it has some significant challenges to overcome:

- Most mutations detected by WGS occur in noncoding regions of the genome and are more likely to be passenger mutations than driver mutations, which are not informative for clinical practice.
- Coverage of regions to be sequenced is not controlled, resulting in the coverage of clinically relevant regions by only a few sequencing reads, which is insufficient to reliably detect mutations.
- High costs are associated with sequencing an entire genome at diagnostic sensitivity (several-hundred-coverage), accompanied by complex bioinformatic analyses without consensus on the optimal bioinformatic strategies for such analyses.

Despite these challenges, in January 2016, Independence Blue Cross and NantHealth announced the nation’s first insurance coverage for a comprehensive whole genome and proteome molecular diagnostic platform (GPS Cancer™, NantHealth) to diagnose molecular alterations in an individual’s cancer and to identify personalized therapeutic regimens. NantHealth announced the commercial availability of GPS Cancer in June 2016.

The Cancer Genome Atlas

Supported by the NCI and the National Human Genome Research Institute at the National Institutes of Health, The Cancer Genome Atlas (TCGA) is a landmark research program that was launched to catalog all potential cancer driver mutations, identify robust prognostic and predictive biomarkers and novel therapeutic targets, and uncover molecular subtypes of tumors that are different in prognosis and response to treatments. By using various analytical platforms, TCGA currently gathers somatic mutation data, messenger RNA and microRNA expression data, DNA methylation data, CNA data, and proteomic data. The project plans to collect genomic and proteomic data from more than 500 tissues for each of at least 33 different human tumor types and release the data to the public without any restriction in use. The overarching goal is to improve understanding of the molecular basis of cancer development by elucidating the landscape of DNA and RNA aberrations within and across tumor lineages and integrating the information with clinical characteristics, including patient outcomes.

New Technology

Ion Torrent™ NGS directly translates chemically encoded information (adenine, cytosine, guanine, and thymine) into digital information (0, 1) on a semiconductor chip; supports many popular NGS applications, including targeted DNA, transcriptome, targeted RNA, and exome sequencing; and claims to be simpler, faster, and more cost-effective and scalable than any other NGS technology available. Target selection is via Ion AmpliSeq™ panels that require as little as 10 ng of input material. Ion AmpliSeq technology delivers simple and fast library construction for affordable targeted sequencing of specific genes or genomic regions. Based on ultrahigh-multiplex PCR, Ion AmpliSeq technology requires as little as 1 ng of input DNA to target sets of genes, making sequencing of formalin-fixed, paraffin-embedded samples routine on Ion PGM™ or Ion S5™ systems.

GPS Cancer is a trademark of NantHealth, Inc. Ion Torrent, Ion AmpliSeq, Ion PGM, and Ion S5 are trademarks of Thermo Fisher Scientific Inc.
CancerLinQ™

Less than 3% of adult cancer patients participate in trials in the United States. The real world contains large numbers of patients who do not meet eligibility criteria of clinical trials, including those with poor performance status, organ dysfunction, obesity, advanced age, or comorbidity.

ASCO’s CancerLinQ™ (Learning Intelligence Network for Quality, American Society of Clinical Oncology) is a health information technology platform that collects and analyzes real-world cancer care data from electronic record sources and makes that data searchable. Individual patient-level data is loaded into CancerLinQ via a daily feed that originates from source systems at oncology practices.

This subscription service provides data analytics tools with the goal of increasing quality measurement scores, and helping to ensure high quality of care.

- Helps a practice to comply with federal, state, and quality program reporting requirements by automating data collection and clinical quality measure reporting, thereby driving reimbursements and saving time and money typically spent on manual chart abstractions

CancerLinQ is a trademark of the American Society of Clinical Oncology.

Abbreviations

- AACR, American Association for Cancer Research
- ALK, anaplastic lymphoma kinase
- AML, acute myelogenous leukemia
- APL, acute promyelocytic leukemia
- ASCO, American Society of Clinical Oncology
- AUA, American Urological Association
- BCR-ABL, breakpoint cluster region-Abelson
- BRACA, BRAC analysis
- BRAF, serine/threonine-protein kinase B-Raf
- CAP, College of American Pathologists
- CDx, companion diagnostics
- cfDNA, cell-free DNA
- C-Kit, tyrosine-protein kinase Kit
- CLL, chronic lymphocytic leukemia
- CML, chronic myeloid leukemia
- CMS, Centers for Medicare & Medicaid Services
- CPT, current procedural terminology
- EGFR, epidermal growth factor receptor
- FDA, U.S. Food and Drug Administration
- FISH, fluorescence in situ hybridization
- FLT3, Fms-related tyrosine kinase 3
- GIST, gastrointestinal stromal tumor
- GSP, gene sequencing panel
- HER2/neu, human epidermal growth factor receptor-2
- IDN, integrated delivery network
- KIT, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog
- KRAS, Kirsten rat sarcoma
- LDT, laboratory-developed test
- MDS, myelodysplastic syndromes
- MEK1, mitogen-activated protein kinase/extracellular signal-regulated kinase 1 [arabidopsis thaliana (thale cress)]
- MET, Mesenchymal-epithelial transition factor
- NCCN, National Comprehensive Cancer Network
- NCI-MATCH, National Cancer Institute Molecular Analysis for Therapy Choice
- NGS, next-generation sequencing
- NIH, National Institutes of Health
- NSCLC, non-small cell lung cancer
- PCR, pathologic complete response
- PD-1, programmed death-1
- PDGFRB, platelet derived growth factor receptor beta
- PD-L1, programmed death-ligand 1
- PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
- PMI, Precision Medicine Initiative
- PML-RARa, promyelocytic leukemia/retinoic acid receptor alpha
- QOPI, Quality Oncology Practice Initiative
- ROS1, ROS Proto-Oncogene 1, Receptor Tyrosine Kinase
- RSQ, response to stress questionnaire
- TAPUR, Targeted Agent and Profiling Utilization Registry
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