NAMCP Medical Directors Spotlight Guide: Precision Medicine in Oncology 2022

Promise and Challenges: How Precision Medicine Trends and Issues in Oncology Can Affect Strategy for Medical Directors of Purchasers, Plans, and Providers

JOURNAL of MANAGED CARE MEDICINE

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WHERE MEDICAL DIRECTORS TRANSFORM KNOWLEDGE INTO IMPROVED OUTCOMES

Mission Statement

The mission of the National Association of Managed Care Physicians (NAMCP) Medical Directors Oncology Institute is to open the lines of communication between medical directors in managed care and practicing oncologists to help them jointly better navigate and understand what is happening in managed care and the daily management and practice of oncology. The NAMCP Medical Oncology Directors Institute brings resources and updates, strategic reviews, and key information to medical directors for insurers, employers, providers, and integrated delivery networks. Unique Executive Councils focus on emerging technologies, oncology and value-based contracting for manufacturers and managed market leaders.

This guide presents an overview of the growing trends of precision medicine in oncology, for physicians and purchasers of healthcare. It discusses precision medicine in the context of the current landscape, utilization and evidence, impact on the costs of care, quality and payment reform and issues and strategies for plans and purchasers seeking policy and strategy solutions for oncology management. This guide is part of a series of activities and initiatives within the NAMCP Oncology Institute to support medical directors from purchasers, plans, and provider systems, and to eventually achieve greater collaboration leading to improved patient outcomes in oncology.

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Precision Medicine in Oncology 2022

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Promise and Challenges: How Precision Medicine Trends and Issues in Oncology Can Affect Strategy for Medical Directors of Purchasers, Plans, and Providers

Dawn Holcombe, MBA, FACMPE, ACHE

Abstract

Rapid evolution in precision medicine and targeted therapy has led to wide variations across providers, payers, and patients as to the utility, evidence, justification, and value of precision oncology in practice, policy, and strategy. This guide will illuminate key issues and pivot points in the practice, policy, and strategy of precision medicine in cancer care, and suggest opportunities and challenges for enhanced evidence, utility, and value.

Precision oncology is the operative term for precision medicine for cancer. Traditional clinical trials, and thus medical treatments, are usually designed for average patients and apply a one-size-fits-all approach to care, which can lead to both successes and failures. Precision oncology offers a disease prevention and management approach that considers differences in people's genes, environments, and lifestyles. The promise of precision oncology is targeting the right treatments to the right patient at the right time.

All decision makers in the use of next generation sequencing must understand the concepts of analytic validity. Not all tests are the same in their ability to obtain the correct information generated reliably, time after time.

The combination of clinical electronic medical records data and administrative claims data can be very powerful, but to date has had limited application in answering clinical questions that have traditionally only been answered through interventional clinical trials.

The complexity of molecular medicine and its application in oncology creates hurdles for payers and employers who frequently look for outside guidance to help determine policy. But unlike the Food and Drug Administration (FDA) that approves drugs, there is no equivalent body developed for determining when molecular testing is clinically beneficial in the context of care options.

The more we can efficiently use precious tissue samples to begin a good understanding of the disease, the better we can ensure the right treatment reaches the patient at the right time or that we can avoid treatments that will not be effective.

Payers, employers, and providers can also come together in a unified effort to build a perpetually advancing evidence base of precision medicine via a master observational trial construct such as the Registry of Oncology Outcomes Associated to Testing and Treatment (ROOT) to gather prospective data at the point of care in a manner compliant with emerging Food and Drug Administration guidance on real-world data that can drive actionable coverage policy. Collaborative efforts can link data collection through ROOT to early coverage policy and lead to informed evidence-based clinical understanding for both medical decision-making and real-world data-based support for coverage for the right treatment at the right time for the right patient.

The potential of truly regulatory grade real-world data has not yet been realized, but could quickly power innovation in policy, coverage, and medical decision-making for new testing and treatments based upon quality and cost-effectiveness outcomes from the data.

The most effective and cost-efficient cancer care is the cancer that never materializes or is detected early. Payer and employer policy that supports and invests in providers and tools that create better healthcare management opportunities will lead the field in more successful and cost-effective healthcare for their customers and society.

Introduction

The costs of treating cancer are of rising concern to patients, payers, and physicians. A variety of tools and approaches have been developed to reduce costs of care, but most of these have involved authorizations, pricing limitations, stepped therapy, and drug formularies largely built on price. There is much variation in cancer presentation impacted by social-demographic factors, diagnosis at the macroscopic and molecular tumor market level, and progression based on initial treatment selection(s). Although data can be tracked on populations, the quest continues to identify the right medicine at the right time for the right patient at the right cost.

Precision medicine is often defined as an approach to healthcare that considers differences in an individual's genetic makeup, gender, race, age, comorbidities, environment, lifestyle, and other factors to promote optimal clinical outcomes. The precision medicine rubric can encompass a wide variety of testing, information, and treatments, any one of which may be considered in clinical decision-making as "evidence-based" or personalized cancer treatment with justification for coverage and care decisions. Despite the advances in these options, questions still abound as to which, or what, will make a clear difference in clinical outcomes and cost-effective care. Understanding the evolution of personalized medicine will be necessary to improve strategy and policy for practical application in coverage and treatment now and in the future.

Rapid evolution in targeted therapy and precision medicine has led to wide variations across providers, payers, and patients as to the utility, evidence, justification, and value of precision medicine in practice, policy, and strategy. This guide will illuminate key issues and pivot points in the practice, policy, and strategy of precision medicine in oncology, and suggest opportunities and challenges for enhanced evidence, utility, and value.

Why is it Important to Look at Precision Medicine in Oncology?

The general costs of healthcare continue to rise past the level of sustainability. Cancer is one of the leading causes of death and a key cost component of healthcare. Cancer touches one in three people in the United States (U.S.), and though often seen in those aged 65 years and over, it does affect those younger than 65 years of age, thus becoming a concern for employers and other purchasers of care.

Precision medicine that focuses on molecular profiling of tumors to identify targetable alterations has become known as "precision oncology." Precision oncology offers the promise of using advances in not only genomic but all other "omics" (transcriptomics, proteomics, metabolomics, epigenomics, etc.) testing, and new customized treatments that could shift many cancers from the role of palliation (needing multiple lines of therapy over months and years to try to prolong life) to early detection leading to definitive treatment, and cures.

The best cancer is the one which is prevented, or detected early, and kept from advancing to metastatic stages or death. Using the knowledge and promise of precision oncology could achieve those goals. However, there are many hurdles along the way, and managed care and employer medical directors can use the insights of this paper to inform and support strategic decisions on coverage and policy. Precision medicine can help us start to look at cancer as a journey that starts long before a person reaches a cancer diagnosis, and thus offer opportunities to engage at the community or employer level before medical intervention and before clinical progression.

Background and Overview of "Precision Medicine"

PRECISION MEDICINE VERSUS PERSONALIZED MEDICINE

The term "precision medicine" was defined in 2011 by the National Research Council as the "tailoring of medical treatment to the individual characteristics of each patient to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology and/or prognosis of those diseases they may develop, or in their response to a specific treatment. Through precision medicine, preventive or therapeutic interventions can be concentrated on those who will benefit, sparing expense and adverse events for those who will not."[1]

The Council expressed concern about confusion of precision medicine with an older term, "personalized medicine," fearing that use of the word "personalized" could be misinterpreted to imply that treatments and preventions are currently being developed uniquely for everyone. The Council noted that precision medicine was the preferable term, although many use them interchangeably. Personalized medicine refers to a patient-centric approach that considers not only genetics, but also preferences, beliefs, attitudes, knowledge, and social context. Precision medicine is a model for healthcare delivery that utilizes data, analytics, and information. Precision medicine must encompass not only patient focus and engagement, but also digital health, the vast array of genomics and other molecular technologies, broad data sharing, and strong data science to be successful.[2]

Precision oncology is the operative term for

precision medicine for cancer. Traditional clinical trials, and thus medical treatments are usually designed for average patients and apply a one-size-fits-all approach to care, which can lead to both successes and failures. Failures for complex diseases such as cancer are life-threatening, costly, and they significantly impact quality and quantity of life. Precision oncology offers a disease prevention and management approach that considers differences in people's genes, environments, and lifestyles. The promise of precision oncology is targeting the right treatments to the right patient at the right time.

HOPE THAT PRECISION ONCOLOGY CAN CONQUER THE BURDEN OF CANCER

Cancer is one of the leading causes of death in the U.S. The American Association of Cancer Care estimates that the costs of cancer-related care will rise to $246 billion by 2030.[3] The financial consequences of cancer treatment on patients and their families can be substantial, as well as on purchasers of care, including health plans and employers. Access to quality, cost-effective care is being widely discussed across a wide range of venues, from the sometimes-diverse perspectives of patients, physicians, health systems, employers, health plans, and local and national legislators. There is great interest in whether the future of precision oncology can deliver appropriate, effective care in a more efficient and cost-effective manner, without itself causing increased costs in the system in its development, execution, and implementation.

Evolution of Precision Medicine over Three Decades

THE PROMISE OF PERSONALIZED MEDICINE THROUGH THE HUMAN GENOME

On October 1, 1990, the Human Genome Project (HGP) commenced. The goal, completed in 2003, was to develop a map of the complete genetic makeup of human beings. With this knowledge we could begin to understand how individuals differed from each other on a fundamental (or molecular) level and armed with this knowledge better understand why individuals with similar diseases may behave completely differently.[4]

The overarching goal of the HGP was to fill in a key missing piece that would eventually be needed to provide a customized personalized treatment for any given patient leading to improved outcomes at lower cost by better targeting disease and avoiding unnecessary and/or ineffectual treatments. Being able to read and interpret genetic codes and to identify an individual's genetic predisposition to certain diseases became a milestone event – changing the perspective of healthcare from reactive to prospective.[5]

Although extremely valuable for all areas of medicine, the HGP has special significance to the oncology community who had known for decades that the alteration of cells at a fundamental layer was key to tumorigenesis. The hope was that being armed with genome information would allow more precise treatments to be made available to patients with life-ending diagnoses.

PRECISION ONCOLOGY

Precision oncology in its broadest sense can be defined as the ability to measure a biological process or biomarker that is related to cellular growth, and then, provide a treatment that targets the process identified by the testing, leading to improved cancer care.

THE EMERGENCE OF PRECISION ONCOLOGY

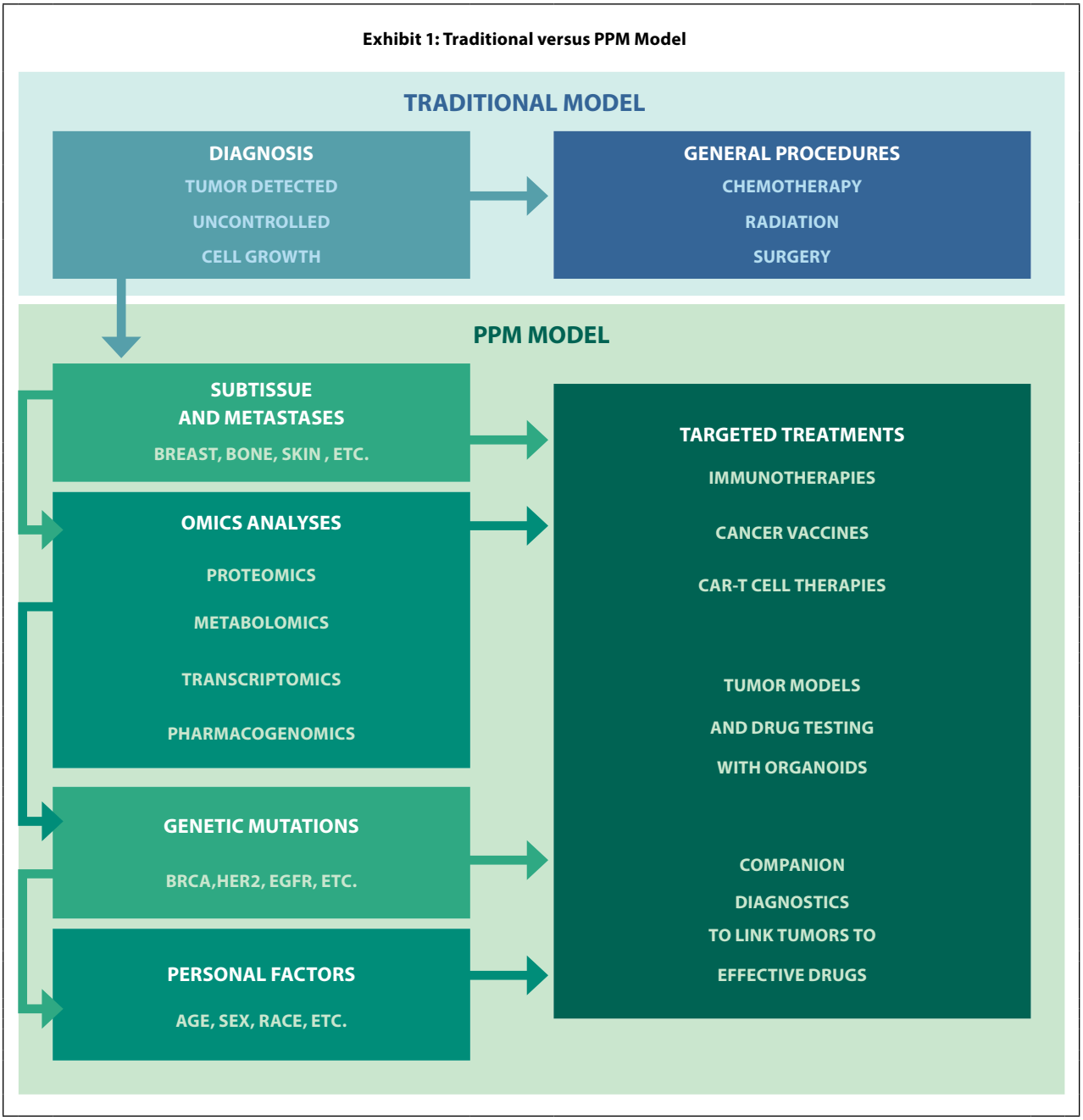
Cancer is, by definition, the alteration (or mutation) of a cell leading to abnormal growth. Early traditional treatment relied on chemotherapy, surgery and radiation given uniformly to all patients with the same disease, with varying success. Understanding the human genome, or "germ-line" cellular biology, is an essential first step. However, truly understanding cancer "somatic tumor" cellular biology, and the tumor micro-environment, is not the key to success in and of itself.

To truly understand cancer, and personalized treatment options, requires understanding the multiple mutations that result in every cancer being unique and exploiting those mutations unique to cancer cells in a targeted precision oncology cancer regimen. Early genome sequencing techniques were expensive and inefficient in determining deoxyribonucleic acid (DNA) fragments. Next Generation Sequencing (NGS) technologies have now emerged as cost-effective tools capable of high-dimensional and parallel sequencing at an industrial scale. However, the genome itself still is not the sole variable for determining a patient's state of health. Other "omics" techniques can provide insight by measures of protein structure and function, epigenetic manifestations, mechanisms of metabolism, and the concentration of metabolic intermediates,[6] (see Exhibit 1).

EARLY SUCCESS WITH TARGETED CANCER TREATMENTS

Very early in the twentieth century, scientists understood that breast and prostate cancer were usually influenced by estrogen and testosterone, respectively. It wasn't until 1977, however, that this knowledge led to a drug that could target estrogen-related growth, when the drug tamoxifen

Exhibit 1: Traditional versus PPM Model



Note: Traditional versus PPM model – A comparison of the key differences in the traditional model of cancer treatment and the emerging precision and personalized medicine (PPM) model. Traditionally, cancer has been treated using general, "one size fits all" approaches such as chemotherapy, radiation, and surgical excision of tumors. These treatments vary widely in efficacy across individuals and often cause harm to healthy, noncancerous organs and tissues. The PPM approach is characterized by individualized treatments tailored to specific tissues, gene mutations, and personal factors relevant to each unique case of cancer. Companion diagnostics (CDx) help identify which treatments will be most effective for a specific patient's tumor, and novel cell therapies are used to target the cancer with minimal damage to healthy tissues, making the PPM model more effective and safer.

Source: Krzyszozyk, P, et al., "The growing role of precision and personalized medicine for cancer treatment – Figure 1", Technology (Sinap World Sci), 2018; 6(3-4) 79-100, doi: 10.1142/S2339547818300020, last accessed 03/01/2022 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6352312/pdf/nihms-1007676.pdf

(Nolvadex®) was finally brought to market for the palliative treatment of women with advanced breast cancer. It was almost another decade before anti-testosterone drugs were approved with leuprolide acetate (Lupron®), the first gonadotropin-releasing hormone agonist (GnRH) being approved in 1985, and flutamide (Eulexin®), a direct testosterone receptor antagonist in 1989 were approved by the FDA for the palliative treatment of men with advanced prostate cancer.

Armed with these early successes, scientists looked for additional targets that directly led to the growth of additional types of cancer. This led to the discovery of trastuzumab (Herceptin®) and its eventual approval for the palliative treatment of women with advanced HER2+ breast cancer in 1998.

ADDING TECHNOLOGY TO THE EVOLUTION OF CANCER TARGETED TREATMENT

In the late twentieth century, several new and powerful techniques were improved or introduced which allowed a more precise understanding of the molecular biology of cancer. Older technologies such as immunohistochemistry (IHC) and Sanger DNA sequencing, were augmented with newer technologies such as polymerase chain reaction (PCR), and florescence in-situ hybridization (FISH). Using a combination of technologies could help us better understand the fundamental nature of this disease. In the last two decades, massively parallel next generation sequencing (NGS) emerged. NGS allows sequencing of many genes at once, allowing up to whole exome (WES), or even the entire genome (WGS) of host or tumor. NGS has transformed the ability to understand the molecular basis of cancer.

MOLECULAR MEDICINE AS A TURNING POINT IN PRECISION ONCOLOGY FOR TARGETED THERAPY

The introduction of the drug imatinib (Gleevec®) in chronic myelogenous leukemia (CML) heralded a new generation of molecular medicine. The identification of a molecule that could impede the protein that led to the uncontrolled proliferation of white blood cells in CML was based on identifying the molecular basis of disease and then finding a molecule that could disable the functionality that led to the cancer. The result was the drug imatinib. The drug was approved by the FDA in 2001 and turned CML – once a death sentence for 70 percent of people diagnosed with it – into a long-term, manageable disease for 90 percent of patients. When it was approved, Dr. Brian Druker, who was instrumental in leading the clinical research of the medication, noted that this could act as a new paradigm shift in the way that disease and drugs were treated.[7]

A 2011 article in Smithsonian magazine hailed the approval of this drug as a defining moment in the war against cancer. "The previous century of cancer treatments – intermittently successful, based on trial-and-error testing, almost always agonizing – would be known to experts as 'before Gleevec.' From then on was 'after Gleevec,' the era of targeted therapy. At a Washington, D.C. press conference on May 10, 2001 the Secretary of Health and Human Services, Tommy Thompson, called the drug a 'breakthrough' and 'the wave of the future.' The then director of the National Cancer Institute, Dr. Richard Klausner, described it as a picture of the future of cancer treatment."[8]

Understanding Molecular Medicine Introduces Complexity

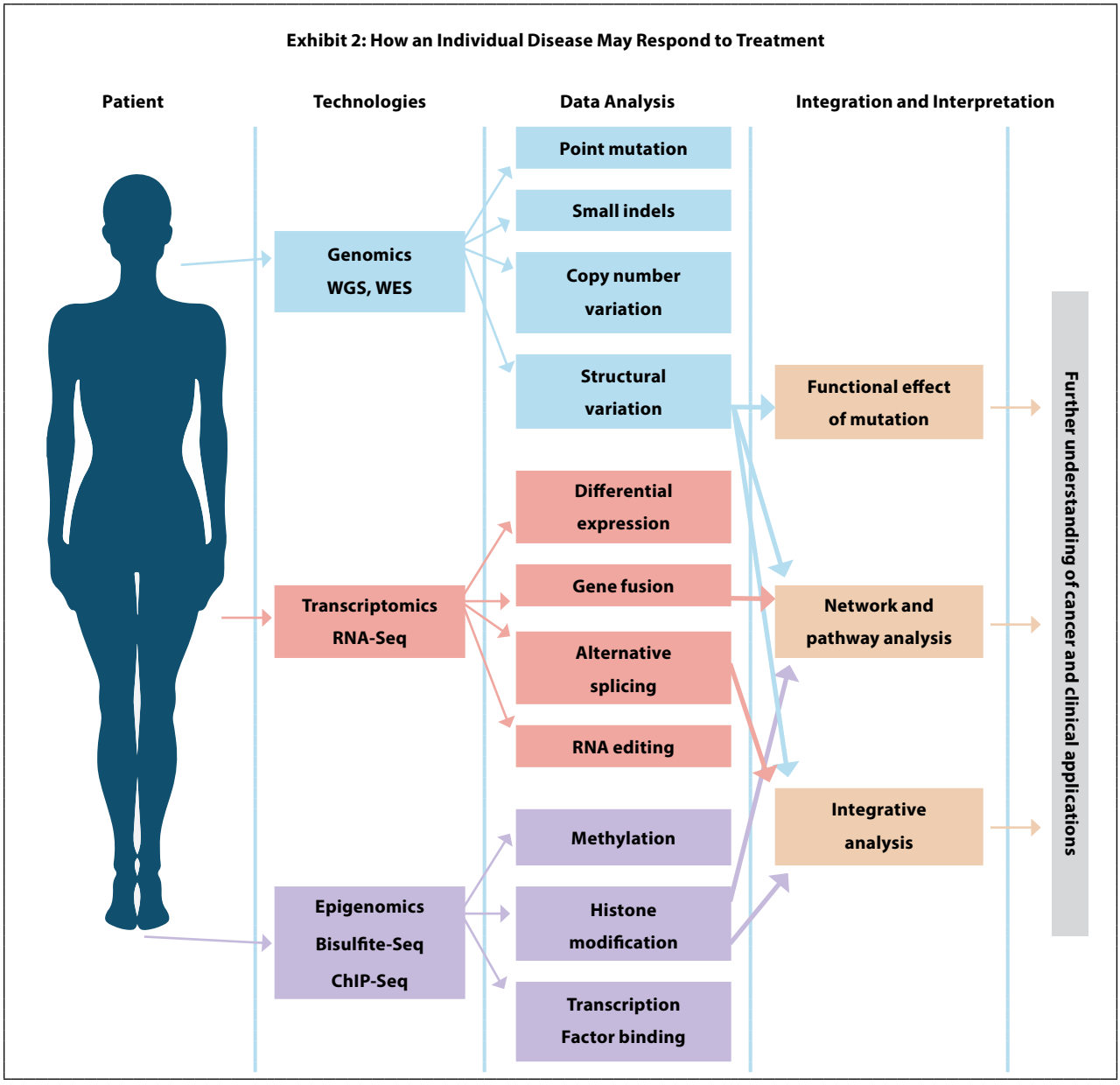
MOLECULAR LEVELS: GENOMICS, TRANSCRIPTOMICS, PROTEOMICS, METABOLOMICS, AND EPIGENOMICS

The promise of precision medicine is vast, but the difficulty with molecular medicine lies in the fact that not all diseases are as molecularly clean as CML. Frequently, multiple levels of molecular alterations are at play leading to the individual activity or functionality of a tumor at the somatic tumor genomics or tumor micro-environment level. This includes changes in genes at the DNA level, errors of transcription of DNA into ribonucleic acid (RNA), and the way those genes are transcribed into proteins, the way those proteins are being manufactured, to what degree and how those proteins interact with the cell, what are the factors that control the ways certain cellular signatures are turned on or turned off, as well as how the immune system applies surveillance in identifying self (normal cells), versus non-self (tumor cells). These genomics, transcriptomics, proteomics, metabolomics, and epigenomics all come into play with how an individual disease may respond to treatment, (see Exhibit 2).

Furthermore, we have identified that the molecular signatures of a tumor or host are not the sole factors to consider. Even the makeup of the gut flora inside our intestinal tract (microbiome) can influence the way other processes of the body function, including cancer.

TUMOR HETEROGENEITY ADDS COMPLEXITY TO DECISION-MAKING AND TREATMENT

As a malignancy continues to grow, additional mutations are introduced into some of the cells of the cancer, leading to a tumor that is heterogeneous in its molecular signature(s). Although many of the new clones may have a similar molecular subtype of the original tumor, minor changes can lead to resistance to treatments or change the growth or the spread pattern of disease in such a way as to be different



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from the original disease. It is common in metastatic solid tumor cancers to see one tumor in one part of the body respond to treatment, while a tumor in another location may not respond at all, suggesting at least two different clones of the tumor. Recent clinical studies of changing cancer biology over time, with recurrence or progression of disease, are now suggesting that clinicians become familiar with selective genomics surveillance strategies to prescribe appropriate treatments that attack the new clone. This adds further complexity to the already complex nature of understanding the multi-level molecular makeup of a tumor, and how it changes over time.

AN INDIVIDUAL'S IMMUNE SIGNATURES ADD TO THE CHALLENGES FOR CANCER TREATMENTS

External to the tumor is the body's immune system and its ability to identify cells that are "self" or part of the host, or "non-self" or foreign, and in need of destruction. Cancer tumors often mask their identity to the host, with the best-known mechanism being the tumor expression of a protein called "PD-L1", programmed death ligand one (the ligand of PD-1, or programmed death-1). These work by attaching to receptors on host-surveilling T cells called PD-1 and B7; their net effect is to mask the "non-self" identity of the cancer cells in their micro-environment, and

spare them from T cell-mediated autophagy, or death. Cancer biologists now understand how to exploit this use of PD-L1 by cancer tumor cells through new immuno-oncology drugs that cap these receptors on cancer cells. Once capped and bound, the T cell can see the cancer cells as non-self, upregulate their killing capabilities and start destroying the cancer. Examples of these immuno-oncology drugs include Keytruda®, Opdivo®, Yervoy®, among others.

The way that certain drugs are metabolized are based on a host's individual genetic makeup. This can also influence the way a tumor will respond to treatment. These pharmacogenomic factors may increase the rate of elimination of a certain drug, change absorption of medication, or lead to increased toxicity of treatment and add complexity to molecular medicine. The tumor microenvironment can also aid in understanding how an immuno-oncology drug may effectively target a cancer. Tumor mutational burden (TMB) can be reported as the total number of DNA mutations (non-inherited) per one million bases (megabases). TMB may serve as a biomarker for potential favorable response to immunotherapy. Microsatellite instability in tumor DNA (MSI-H) is the presence of alternate sized repetitive DNA sequences that are not present in the corresponding germline DNA. Tumors with high MSI-H are more immunogenic and may respond to drugs that activate the immune system.

Precision Oncology in 2022

THE DIFFERENCE BETWEEN PRECISION MEDICINE AND PERSONALIZED CARE

The difference between precision medicine and personalized care began with the technology explosion in the latter half of the twentieth century and continues today. This has allowed us to measure differences more precisely between cells; however, without knowing how to put these differences together in such a way that we can determine what treatments can be used to affect a specific individual, we are still a long way away from personalized care in most patients. Just because we can measure something precisely does not mean that we can use it to benefit an individual patient.

THE NEED FOR LARGER QUANTITIES OF DATA

The way to unravel this Gordian knot of the molecular nature of malignancies is to have large quantities of high-quality information tied to broad molecular signatures of malignancy and host. These standardized precision measurements must be related back to outcomes and allow the development of an iterative learning system to improve testing and treatment. This becomes particularly important as the library of actionable somatic tumor markers grows.

Today, in non-small cell lung cancer (NSCLC), the National Comprehensive Cancer Network® (NCCN®) guidelines point to eight families of gene and driver mutations as necessary information for therapeutic decision making: EGFR, ALK, ROS1, RET, BRAF, MET, NTRK 1/2/3, and ERBB2. Is this the totality of somatic tumor aberrations that exist today in NSCLC? No, these simply represent the tumor markers that presently have FDA-approved therapies in this tumor histology. There are other tumor markers yet to be understood at the treatment level, for which therapy today is ineffective and wasted. Only with a big data approach can we stop treating cancers with drugs that may not work, and more completely match therapeutic efficacy to tumor biology.

THE ONCOLOGY TESTING LANDSCAPE

Cancer centers are using precision oncology to support treatment decisions, but the technology, coverage, and utility are still misaligned.

The 3rd Annual Precision Oncology News Survey queried provider oncology leaders from July to November 2021 to understand the institutional investments being made in precision oncology, and the barriers that remain.[9] Half of the respondents indicated they could perform single-gene testing in-house, 45 percent noted that they could test internally for immunotherapy biomarkers, and 35 percent said that they had in-house targeted NGS capabilities. However, much of the biomarker testing is still sent to commercial labs such as Foundation Medicine, Tempus, and Caris Life Sciences. Three-quarters of those surveyed send out liquid biopsy testing, about half use commercial labs for whole genome, RNA, and exome sequencing, and almost half (45%) send targeted NGS panels to outside labs. A sizable portion (80%) of the respondents assess patients for TMB to guide immunotherapy decisions.

The FDA has increased approvals for biomarker informed treatments in earlier disease settings. Almost one-third (30) of those surveyed now offer biomarker testing to certain cancer patients with Stage 1 tumors, and more than half test for biomarkers in patients with Stage II or III tumors.

Family histories are collected in 90 percent of the responding institutions, but further information is needed to identify cancer-risk mutations. Eighty percent of the respondents urge oncologists to order germline testing when the variant allele frequency of an alteration detected via somatic analysis suggests a patient may be at risk for an inherited cancer predisposition marker. Seventy percent urge germline testing for patients with breast, ovarian, prostate, or pancreatic cancer (these tumor types are prone to high-risk mutations). Half of those surveyed add germline testing if it may help.

Challenges in the Current Landscape for Applying Precision Oncology

TECHNOLOGY IS OUTPACING THE DATA NEEDED TO UNDERSTAND HOW TO USE IT

As mentioned above, medical technologies have been advancing rapidly. Although we've developed a means to examine genetic makeup, protein functionality, immune signature, and even gut microbiota, we have not been able to create a workable and reliably evidence-based schema for how this information can be used to personalize patient care. In addition, there can be a great deal of difference in the results from one testing functionality to another.

There is only limited validation between laboratories using the same methods. This can introduce variability in testing results and resulting treatments depending on how the testing was being performed. There is a substantial unmet need for the clinical validation of testing that can help us to not only understand the exciting biomarkers identified by new technologies, but also make use of existing knowledge gathered from older technologies.

All decision makers in use of NGS must understand the concepts of analytic validity, which is the replicable precision of the testing; analytic utility, which is the relationship of the test to the defect or disease; and clinical utility, the impact on patients of using the test. Not all tests are the same in their ability to get the correct information generated reliably, time after time. Analytic validation certification is important, as well as CAP/CLIA certification and being FDA approved or cleared as a test.

The older and newer technologies may identify certain cellular functionalities or processes differently, or at various levels of sensitivity of detection. This disparity can create differences in the predictive power in use of these tests, which while technical in nature, should be understood in the approval or endorsement of specific technical methodologies as preferred or restricted. This is also a problem in research, with barriers in information comparison between users of different technologies. There is a need for better information that can help us to not only understand the biomarkers identified by new technologies but also make use of existing data gathered from older technologies.

PHARMACEUTICAL DRIVEN RESEARCH MAKES UP THE MAJORITY OF WHAT WE KNOW IN PRECISION ONCOLOGY

One Type of Testing, One Target, One Drug, One Line of Therapy has been the Rule of Thumb

To date, the most valuable information we have on precision medicine has come from the efforts of the pharmaceutical industry. Most of the data has been focused on identifying one target that can lead to the change of tumor growth and then identifying a drug that can be utilized to affect this singular target. This is usually applied at one line of therapy for a one target, one drug, one line of therapy approach to the introduction of molecular medicine. Often, the target of interest is identified by only one specific type of testing, tying a specific test to the specific target.

Molecular Testing has Generally Supported Finding Patients Eligible for Treatment, Rather Than All Patients

The pharmaceutical industry has been looking for new molecular targets to improve patient outcomes in cancer care, as targeted therapies have been found to yield strong results with a lower adverse-event profile. Little research has been done on individuals without markers of interest beyond expansion of immuno-oncology research into combination therapies. Most of the research today is done in academic medical centers and looks at a very small population of cancer patients – those with specific recorded mutations who have the access and willingness to participate in clinical research. A substantial number of cancer patients served by community oncologists go unstudied, leaving a gap in cancer research that prevents us from unlocking the full potential of precision medicine. A key to improving the clinical trials landscape is opening them up to community oncology groups, to allow participation by most oncologists who operate independent of academia.

WE HAVE ONLY SCRATCHED THE SURFACE OF MOLECULAR ONCOLOGY

Most of the treatments that have become known have focused on either genetic alterations that lead to changes in cellular growth or treating an active protein product that exists inside of a tumor. New technologies able to identify and treat more complex mutations are still in their infancy. We have not yet scratched the surface of understanding how to target broader protein signatures or transcription factors or even how those proteins are functioning on the cells and the treatments that target both genes and potential downstream protein functions. These are only the tip of the iceberg when it comes to determining what will be needed to adopt personalized medicine. There is still a long way to go.

ONLY A SMALL NUMBER OF PATIENTS HAVE A GENETIC SIGNATURE THAT LEADS TO TREATMENT

Even in the first layer of molecular analysis, namely analyzing for changes in DNA, most patients do not show a genetic signature that leads to a treatment. In the most comprehensive study to date of matching

genetic alterations to specific treatment, the NCI-Molecular Analysis for Therapy Choice (MATCH) trial, started in August 2015, could have only provided a treatment option to less than 26 percent of patients (assuming that all arms were open simultaneously and available), let alone knowing if each arm had an effective treatment associated with it.[10]

MUCH OF MOLECULAR MEDICINE PROLONGS LIFE AND IMPROVES QUALITY, BUT DOES NOT INCREASE CURES

Many of the molecular findings that have paved the way for new treatments have been able to prolong both quality and quantity of life. Some patients benefitting from advancements in precision medicine are living years beyond what would normally be considered possible. However, in most cases these drugs do not lead to more cures. Most molecularly targeted drugs in precision medicine have led to better treatments in certain patients but without increasing the chance of being cured.

THERE IS A GREAT DEAL OF "MESSINESS" THAT EXISTS IN PRECISION MEDICINE TESTING

There is no head-to-head determination of how well a laboratory test provided by one laboratory compares either clinically or analytically to another laboratory running the same test using the same technique, let alone using a different method to analyze for the same alteration. In most cases, laboratory testing is geared to identify an alteration if it is present even if at a low fraction of cancer cells. A laboratory may be able to identify alterations reliably, but when the alteration is only found in 5 percent of all cells analyzed, will this tumor respond the same way as a tumor that has 95 percent of the cells containing the same alteration? It is possible that although this minor clone of the cells may respond to targeted treatment, the dominant clone will determine outcome.

From a testing standpoint, better analytic sensitivity, and specificity (finding alterations at lower and lower limits of detection) does not necessarily correlate with clinical sensitivity and specificity. In other words, just because a mutation can be identified reliably by a laboratory, or a method, does not mean that the patient will respond in a reliable fashion to the therapy. The only way to determine the clinical sensitivity and specificity associated with a given alteration is through collecting outcome data associated with the testing and treatments and then correlating with clinical response, similar to how the testing for the HER2 gene has been developed.

THE PUSH FOR "BIG DATA" AND "AI"

Access to large quantities of clinical and genomic data (big data) and the ability to effectively clean up the data and analyze it in a way that limits bias (artificial intelligence or AI) could clarify many of the research questions that stand between current limited scientific knowledge and personalized care for everyone. Significant efforts have been seen in both community and academic settings. However, there are barriers to this research, originating from the quality, quantity, and relevance of data available for analysis. **The combination of clinical electronic medical records data and administrative claims data can be very powerful, but to date it has had limited application in answering clinical questions, that have traditionally only been answered through interventional, clinical trials. A large hurdle, beyond the usual Health Insurance Portability and Accountability Act (HIPAA) technical data security issues and data hoarding seen in healthcare, is the fact that few genomics lab vendors will share any structured data.** Many are unable to create the broad searchable data bases needed for big data insights, beyond dedicated resources devoted to commercial promotion.

Payer and Employer Perspectives

GENERALIZED PERSPECTIVE OF MOST PAYERS HAS NOT KEPT PACE WITH TECHNOLOGY ADVANCES

The rapidly evolving and complex landscape of molecular oncology challenges payers to determine the right balance between allowing covered members access to the latest testing and treatments without introducing technology and potential treatments that are not fully vetted. Payers have generally covered items that have been proven to be effective, and in some cases technology with promise to improve care. New technology continues to be introduced at a blistering pace. Although based on sound molecular biology science, without knowing how they change clinical outcomes, many new approaches need further research before they can be considered standard of care options. The potential of truly regulatory grade real-world data has not yet been realized, but could quickly power innovation in policy, coverage, and medical decision-making for new testing and treatments based upon quality and cost-effectiveness outcomes from the data.

A 2018 analysis of payer coverage policies described a challenging environment for commercial coverage of biomarker testing. The executive summary findings were that:[11]

- "***For oncology biomarkers, commercial payers uniformly cover companion diagnostics because clinical utility is established as a component of FDA review (there is typically a therapeutic agent that is approved in parallel).*** *For other biomarkers that are not FDA reviewed, commercial payers rely upon NCCN Guidelines®,*

Technology Assessment organizations, and peer-reviewed published evidence. Often, evidence of clinical utility is the determinant of coverage.

- ***Payers are skeptical that panels meet the clinical utility threshold.*** *Depending on the tumor type, the number of recognized biomarkers with clinical utility may number fewer than five. It is difficult, therefore, to justify coverage of a panel with 50 or more genes. Consequently, payers may consider the entire test to be experimental and investigational (E&I) if all genes on the panel do not have established utility. Others will cover the test but negotiate payment only for those medically necessary biomarkers.*
- ***NSCLC has an adequate number of actionable biomarkers for payers to consider coverage of NGS panels.*** *Neither breast cancer nor colon cancer has an adequate number of biomarkers with established utility to warrant coverage of panels. Payers will likely modify their policies as the number of actionable biomarkers increases, but they will do this in a tumor-specific fashion. If tumor site agnostic biomarkers are identified, this equation could change, leading to broader coverage.*
- ***Most payers aside from Medicare do not recognize biomarker testing to identify clinical trial candidates as providing clinical utility.*** *Although commercial payers are required by the Affordable Care Act (ACA) to provide coverage for clinical trials, they do not feel this extends to "screening" for somatic mutations. Many biomarker-driven trials are industry sponsored and these do not meet the statutory definition of a clinical trial that must be covered by the ACA. Further, patients are not technically enrolled until they are biomarker positive. To date, unmistakable evidence that panel testing succeeds in trial enrollment is lacking.*
- ***The current coding infrastructure does not differentiate between targeted and comprehensive NGS panels.*** *The Current Procedural Terminology (CPT) codes for NGS describe either a 5-50 gene panel or a 51+ gene panel. Some diagnostics manufacturers have obtained Proprietary Laboratory Analyses (PLA) codes to uniquely identify their proprietary NGS panels. There is a paucity of targeted NGS panels that are FDA approved, including FoundationOne® CDx, Oncomine™ Dx Target Test, and the Praxis Extended RAS Panel.*
- ***At the current time, commercial payer policies are unchanged as a result of the National Coverage Decision (NCD) on NGS.*** *This was in line with our expectation that commercial payers would continue to cover (or not) NGS panels based on evidence of clinical utility in tumor site specific analytes of interest. Companion diagnostics will continue to enjoy broad coverage, as the results are profoundly impactful on coverage policy of the associated therapeutic agent."*

Similar barriers were expressed in July 2020 by Dr. Lee Newcomer in which he noted that scientific innovations continue to expand rapidly, but the promise for patients who once had few treatment options to find actionable targeted therapies is being hampered by outdated decision-making and reimbursement practices that threaten patient accessibility and progress.[12]

Private payer policies vary widely, and even annual updates may not keep pace with changing technology, or even emerging best practices. Exhibit 3 is a very limited list of sample payer policies in existence as of May 2022.[13-25] The detailed nature of such policies are much too complex to repeat, so direct reference to the policies themselves would be the most productive for review (see Exhibit 3).

EMERGING EVIDENCE FOR CONTINUALLY UPDATED PRECISION ONCOLOGY PAYER COVERAGE

Every month new data emerges that allows more precision in the testing and treatment of cancer patients. Just as important as learning when and how to treat, is learning when treatment will not yield benefit. The knowledge of larger panel testing may soon help us to learn, through the mirror of hindsight, the value of tracking mutations and gene activity when we can, now even without known actionable identifications. Cost of panels must always be tempered with the impact and volume of such tests, but the trends are moving in the correct direction.

GENERALLY ACCEPTED STANDARDS OF CARE (HIGH EVIDENCE)

Testing Leads to Targeted Treatment

What we accept as being scientifically proven (and standard of care) in precision oncology largely has come from pharmaceutical clinical studies where a very specific test has been used to identify patients with a specific biomarker and diagnosis. These patients have been administered a treatment that targets the mutation, and they are compared to a control group (either in as part of the study, or through an external contemporaneous group) that did not receive this treatment. The improvement of outcomes that come from the combined testing and treatment have led to many of the new drug discoveries approved by the FDA in the last decade. We know that these treatments make a significant difference in patients, such as breast cancer patients who have the HER-2 mutation, lung cancer patients who have the EGFR

Exhibit 3: Select National Commercial Payers – Medical Policy Covered Biomarkers/Tests

Payer	Medical Policy	Covered Biomarkers/Tests	Date of Last Published Review
Aetna	Aetna Biomarkers #0352	https://www.aetna.com/cpb/medical/data/300_399/0352.html	3/16/2022
Aetna	Aetna Genetic Testing #0140	https://www.aetna.com/cpb/medical/data/100_199/0140.html	3/22/2022
Aetna	Aetna Genetic Counseling #0189	https://www.aetna.com/cpb/medical/data/100_199/0189.html	4/5/2022
Anthem	Anthem Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling #GENE,00052	https://www.anthem.com/dam/medpolicies/abcbs/active/policies/mp_pw_e000224.html	4/13/2022
Anthem	Anthem BCR-ABL Mutation Analysis #CG-GENE-07	https://www.anthem.com/dam/medpolicies/abcbs/active/guidelines/gl_pw_d091822.html	4/13/2022
Anthem	Anthem Genetic Testing for Inherited Diseases, #CG-GENE-13	https://www.anthem.com/dam/medpolicies/abcbs/active/guidelines/gl_pw_e000232.html	4/13/2022
Anthem	Anthem Gene Mutations Testing for Cancer Susceptibility and Management, #CG-GENE-14	https://www.anthem.com/dam/medpolicies/abcbs/active/guidelines/gl_pw_e000233.html	4/13/2022
Anthem	Anthem BRCA Genetic Testing, #CG-GENE-16	https://www.anthem.com/dam/medpolicies/abcbs/active/guidelines/gl_pw_e000233.html	4/13/2022
Anthem	Anthem Measurable Residual Disease Assessment in Lymphoid Cancers Using Next Generation Sequencing, #CG-GENE-19	https://www.anthem.com/dam/medpolicies/abcbs/active/guidelines/gl_pw_e000227.html	4/13/2022
Anthem	Anthem Circulating Tumor DNA Panel Testing (Liquid Biopsy), #GENE.00049	https://www.anthem.com/dam/medpolicies/abcbs/active/policies/mp_pw_d082650.html	4/1/2022
Anthem	Anthem Detection of Circulating Tumor Cells, #LAB.00015	https://www.anthem.com/dam/medpolicies/abcbs/active/policies/mp_pw_a049885.html	4/1/2022
Cigna	Cigna Molecular diagnostic Testing for Hematology and Oncology Indications #0520	https://static.cigna.com/assets/chcp/pdf/coveragePolicies/medical/mm_0520_coveragepositioncriteria_tumor_profiling.pdf	4/1/2022
United	United Commercial Molecular Oncology Testing for Cancer diagnosis, Prognosis and Treatment Decisions, #2022T0588V **NOTE:** Replaced by State Specific Policies in Indiana, Kentucky, Louisiana, Mississippi, Nebraska, New Jersey, North Carolina, Pennsylvania, and Tennessee.	https://www.uhcprovider.com/content/dam/provider/docs/public/policies/comm-medical-drug/molecular-oncology-testing-for-cancer.pdf	4/1/2022

Source: Each of the above referenced web pages come from Aetna, Anthem, Cigna, and United web sites, last accessed 05/23/2022

mutation, gastrointestinal stromal tumor patients who have the C-Kit alteration, and CML who have the BCR-ABL translocation, etc.

Testing Can Also Identify Non-Responders

We also know certain tests can reveal treatment inefficacy. For example, using the multiplex Oncotype DX® Recurrence Score (and others like it), breast cancer patients can be stratified into groups that determine benefit (or lack of benefit) from chemotherapy. Some payers are looking at making such recurrence scores a condition of treatment coverage, as a verification that the physician has obtained the assurance that treatment will provide benefit. For example, colorectal cancer patients who have a mutated KRAS gene will not respond to treatments that target the EGFR pathway.

MOLECULAR TESTING CAN IMPROVE CLINICAL OUTCOMES

The hope is that extensive molecular testing can lead to precise stratification of patients and better assignment of treatment. Theoretically every cancer patient would receive extensive testing to identify their precise molecular signature. This would then allow the patient to know if they would benefit from one treatment or another at this point in time, and in the future as more is learned. Those who are unlikely to benefit from any treatment options could benefit from inclusion in relevant clinical trials.

Oncology practices that participated in the CMS Oncology Care Model (OCM) were tasked with improving clinical care while reducing costs of care for Medicare. Part of the paradigm applied by many practices was enhanced use of appropriate molecular testing to guide the appropriate treatment journey for their patients, creating enhanced value and outcomes for both the patients and for Medicare.[26]

There are promising technologies on the horizon, many of which are based on ability to look for real time tumor status. These include tests such as cancer screening through identifying cancer specific biomarkers present in routine blood testing, looking at minimal residual disease (MRD) in patients diagnosed with cancer, or using circulating tumor cells (CRC) to follow disease response or prognosis. These tests are powerful and may help diagnosis or guide treatment for patients.

Concerns Can Lead to Payer Hesitancy

GAPS IN DATA HOLD BACK NEEDED UNDERSTANDING FOR DECISION SUPPORT

Nevertheless, published data on how many of these tests will lead to improved outcomes is missing. As an example, MRD testing could be beneficial to identify patients with early recurrence of cancer, but the MRD testing could cost tens of thousands of dollars a year, lead to serial imaging or earlier treatment but may not change the overall outcome of the patient because the outcome may be determined by the biology of the tumor more than our ability to detect it. An analogous situation would be to identify the earliest evidence of dandelions in grass using a magnifying glass. The overall state of the lawn is not determined by how early dandelions are identified, but whether or not the lawn is treated with an effective broad-leaf herbicide. There are ongoing studies examining how to precisely use many of these testing methods, but until they are reliably shown through broad real-world data that they can be used prospectively to improve outcomes in a cost-effective method, they may just add to the overall cost of care in patients without truly improving outcomes.

JUST BECAUSE WE CAN TEST, DOESN'T MEAN WE CAN TREAT

Molecular oncology requires the understanding of many layers and their complex interplay over time. Without being able to tie multi-dimensional testing to treatment and critical outcomes through real-world data in a way that limits bias, it is possible that we may continue down a path where we advance precision medicine through isolated advancement but not improve treatment. Without integrating this information into a much larger comprehensive whole, we may never realize personal treatment.

PRACTICAL UTILITY CAN BE FOUND IN CLINICAL PRACTICE, PROVES THE VALUE OF REAL-WORLD DATA

One OCM practice, the Utah Cancer Specialists, was able to identify, collect, and report on key indicators that shed light on prescribing patterns and that supported ensuring the best clinical outcome for their cancer patients. Connecting disparate technology systems and integrating the community oncology care team workflow made it possible to track key questions such as "How many patients with lung cancer were tested and of those tested, how many had a positive result?" and "Were all testing options made available to obtain the best clinical outcome?".[27] Unfortunately, this practical data collection is still the exception, not the rule.

Payer Sources for Policy Direction for Precision Oncology

COMPLEX SUBJECT LEADS TO HURDLES

The complexity of molecular medicine and its application in oncology creates hurdles for payers and employers who frequently look for outside

guidance to help determine policy. But unlike the FDA that approves drugs, there is no equivalent body developed for determining when molecular testing is clinically beneficial in the context of care options. The FDA drug-approval process reviews the conditions and current treatment landscape, which provide the context for weighing a drug's risks and benefits "taking into account any uncertainties that may result from imperfect or incomplete data."[28]

CMS/MEDICARE

The Center for Medicare and Medicaid Services (CMS) can be divided into two categories:
(1) Central CMS located in Baltimore, Maryland and (2) the regional Medicare Administrative Contractor (MAC), that can determine coverage decisions based on its own review of information for the geographic area they cover.

Central CMS

Central CMS generally provides guidance on innovative technology through national coverage decisions (NCDs). The Central CMS does not have the bandwidth to handle the hundreds of requests for coverage that they receive, and so they have usually crafted NCDs around broad testing methodologies rather than individual tests (e.g., next-generation sequencing). Often these NCDs arise out of a combined CMS/FDA-review process where the analytical validity and reliability of the testing is verified by the FDA, and the CMS reviews the clinical utility of the testing when applied to a defined set of patients. Frequently, the CMS relies on the MACs to determine benefit for individual testing through the crafting of Local Carrier Determinations (LCDs).

A notable change in the Central CMS coverage was contemplated in 2019, when the CMS proposed to cover any device that was deemed as receiving Breakthrough Device Designation by the FDA. With hundreds of tests and technology receiving this designation by the FDA, the CMS initially backpedaled on this change to explore how they would approach these tests through the Medicare Coverage of Innovative Technology (MCIT) project. As of fall of 2021, the CMS has decided to end the entire program, citing the lack of demonstrated clinical benefit of many of the devices that received the FDA designation.

Medicare Administrative Contractors (MACs) and Palmetto's MolDx Program

In 2011, Medicare authorized a demonstration project allowing Palmetto GBA, one of the MACs, to develop the Molecular Diagnostics Services Program (MolDX)[29] to help do the assessment of clinical utility and coverage[30] of the rapidly expanding molecular testing market. MolDx, under the direction of Dr. Elaine Jeter, initially focused on determining the clinical utility of molecular testing as the criteria for when Medicare would pay for new testing, but over the last several years, it has loosened its criteria for coverage not according to whether there is evidence of clinical benefit when the test is used in a prospective fashion (clinical utility), but whether there is potential for clinical utility based on clinical validity (or prognostic ability) alone.

This change has led to coverage of many types of molecular testing, frequently including, in the associated LCD that provides coverage, the hope that additional data will be forthcoming to either confirm or refute the hoped-for clinic benefit of the test. Palmetto has no authority to require data be collected, so once a test is covered, even if it is without having the evidence of showing clinical utility, there is no further requirement on the laboratory to collect data. This may allow potentially promising molecular testing to come to market before its application is fully understood.

The CMS does identify services that are not relevant to a Medicare beneficiary or not considered a Medicare benefit and are thus denied.[31] Commercial payers responsible for a younger population may have different perspectives themselves or face greater demand from their members for coverage of some of these uncovered Medicare services.

- Tests considered screening in the absence of clinical signs and symptoms of disease that are not specifically identified by the law.
- Tests performed to determine carrier screening.
- Tests performed for screening hereditary cancer syndromes.
- Prenatal diagnostic testing.
- Tests performed on patients without signs or symptoms to determine risk for developing a disease or condition.
- Tests performed to measure the quality of a process.
- Tests without diagnosis specific indications.
- Tests identified as investigational by available literature and/or the literature supplied by the developer and are not a part of a clinical trial.
- Screening services such as pre-symptomatic genetic tests and services used to detect an undiagnosed disease or disease predisposition are not a Medicare benefit and are not covered.

THE FOOD AND DRUG ADMINISTRATION (FDA)

The FDA Division of Translational and Precision Medicine (DTPM)[32] focuses on the integration of genomics, advancement of targeted therapies, and

support of biomarker qualification across therapeutic areas. In other words, the DTPM's role is reliably tying biomarkers to drug development. Outside of the certification of a certain molecular test in its role as a precursor to the use of a therapy (companion diagnostic), the FDA is tasked with only looking at the analytic reliability and reproducibility of a molecular test. They do not consider the clinical utility of tests they approve and have left this up to the individual payers, such as the CMS.[33]

AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO)

The American Society of Clinical Oncology published a 2015 Updated Policy Statement on Genetic and Genomic Testing for Cancer Susceptibility. This statement focused on the rising complexity of massively parallel sequencing (NGS) into the practice of cancer risk assessment and management.

ASCO makes recommendations in the following areas:

- germline implications of somatic mutation profiling
- multigene panel testing for cancer susceptibility
- quality assurance in genetic testing
- education of oncology professionals
- access to cancer genetic services.[34]

ASCO published a 2019 update to its Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women with Early-Stage Invasive Breast Cancer: ***ASCO Clinical Practice Guideline Update – Integration of Results from the Trial Assigning Individualized Options for Treatment (TAILORx).*** The results of the TAILORx clinical trial led to new ASCO guidelines related to when clinicians should consider patients for chemoendocrine therapy, endocrine therapy alone, and when clinicians should not offer chemotherapy to patients whose Oncotype DX recurrence scores indicate that there is little to no benefit of such treatment.[35]

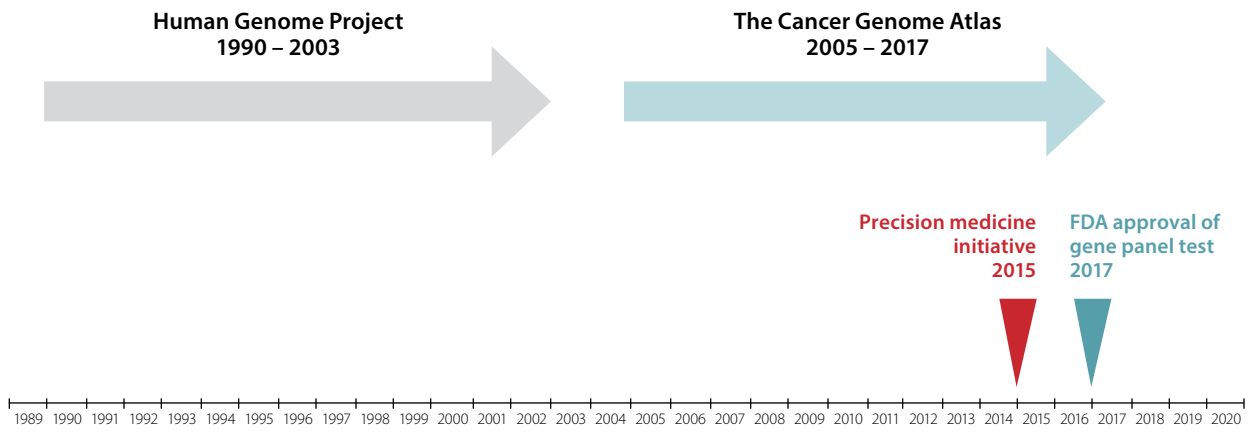
ASCO has published 10 specific guidelines on molecular testing and biomarkers since 2015 with more in development, which may be found on their website under the Practice and Patients section on Guidelines.

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)

The NCCN continues to provide universally accepted guidelines on how to approach patients diagnosed with different types and stages of cancer. These guidelines include recommendations for both testing and treatment recommended for certain clinical scenarios. The NCCN Clinical Practice Guidelines in Oncology® (NCCN Guidelines®)[36] and NCCN Biomarkers Compendium®[37] are crucial to providers, patients, and purchasers throughout the entire general oncology community. The NCCN Biomarkers Compendium® provides details for tests that measure changes in genes or gene products, and which are used for diagnosis, screening, monitoring, surveillance, prediction, or prognostication.

The NCCN has not limited their recommendations only to molecular testing that has shown evidence of clinical utility, and so may include some recommendations for prognostic testing. Their recommendations are not comprehensive, and may give broad recommendations for some testing,

Exhibit 4: Timeline for Emergence of Genetic Testing



Source: Figure 1, Page 7 Nagahashi, Masayuki, et al., "Next generation sequencing-based gene panel tests for the management of solid tumors", Wiley Cancer Science, 2019: 110.6-15, DOI: 10.1111/cas.13837, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6317963/pdf/CAS-110-6.pdf

potentially expanding or contracting the benefit of testing from laboratories that are approaching similar clinical scenarios using slightly different technology.

Data Knowledge is Crucial to Advancing Precision Oncology

The crux of precision oncology is knowledge: information about the patient, the tumor, methods of testing, the interpretation of molecular profile, the potential targets or other treatment or prognostic implications of the test.

The rapid evolution of the field of precision medicine can overwhelm clinical decision-making and utilization. The Human Genome Project started this race toward precision medicine just over 30 years ago. The Cancer Genome Atlas then identified more than 20,000 genes in the human genome. Approximately 500 of those genes were found to be potentially related to cancer. This limited number of genes to analyze led the way to deep sequencing, which is a method to increase accuracy by repeatedly sequencing the same site – the origin for oncogenic panel testing.[38] The FDA launched a new era with its first approval of next generation sequencing-based gene panel tests as companion diagnostic tools in 2017 (see Exhibit 4).

By 2018 there were more than 70,000 unique genetic testing products on the market with an average of 10 new products added each day. The clinical-sequencing market (including sequencing tests for diagnosis, risk prediction, therapy selection and monitoring and screening was growing at a compound annual rate of 28 percent in 2018.[39]

The precision oncology ecosystem requires successful and timely education, coordination, collaboration across patients, physicians, pathologists, surgeons, clinical laboratories, researchers, and payers.

Emergence of Master Observational Trials to Universally Achieve Needed Real-World Data for Precision Oncology

There are several options for data collection, but most are often siloed, not current, retrospective, and rely mistakenly on claims and medical record data. The information we need to truly understand (the variations, outcomes, and real-world performance of patients, treatment, symptoms, and decision-making) is not now being collected. An emerging new clinical trial construct, the Master Observational Trial (MOT) hybridizes the power of molecularly-based master interventional protocols with the breadth of real-world data. Traditional clinical trials, which mitigate bias by fixing as many variables as possible, provide a scientifically stringent glimpse of a specific type of patient at a specific point in time: tested, treated, followed, and reported using precise rules,[40] (see sidebar following).

Draft Guidance was issued by the FDA on its current thinking on the development of real-world data, and what should be present for registries to support regulatory decision-making for drugs and biological products. This guidance calls for many of the elements that are missing from current claims and medical records-based real-world data efforts, but which are found in the proposed MOT construct.[41]

The Master Observational Trial: A New Class of Master Protocol to Advance Precision Medicine

A new clinical trial construct, the Master Observational Trial (MOT) hybridizes the power of molecularly based master interventional protocols with the breadth of real-world data (RWD). Traditional clinical trials, which mitigate bias by fixing as many variables as possible, provide a scientifically stringent glimpse of a specific type of patient at a specific point in time: tested, treated, followed, and reported using precise rules.

However, precision medicine demands an evolution from traditional interventional trials. A MOT that uses a common testing method, unified protocol, and shared infrastructure, can allow multiple single-arm trials tied to specific biomarkers to run in parallel. Arms can be opened and closed as information is gained. The MOT will likely have the following characteristics:

- Transparent governance
- Centralized trial administrative functions
- Traditional interventional trial organization
- Institutional Review Board (IRB)-approved patient consent and HIPAA (or equivalent) privacy authorization
- Precise molecular testing classification
- Standardized clinical data elements
- Longitudinal data collection
- Modular trial design (internal to protocol)
- Seamless integration with interventional trials or RWD
- Artificial intelligence and machine learning from multiple perspectives

MOTs can fill the gap that currently exists in precision medicine, but only if the medical community supports them. Frequent barriers to other types of RWD collection and retrospective claims or medical records data mining include rights, roles, and responsibilities around data sharing, publication rights, intellectual property, financing, and governance. Current RWD efforts are not of high enough quality to provide regulatory grade data, and are fraught with issues of proprietary control, concerns about data value and gaps in needed information. The MOT provides a new vehicle to harness the power of RWD to unlock the promise of personalized medicine. The MOT could create previously unavailable opportunities to yield information that has widespread benefits to patients, families, clinicians, regulators, payers, industry, researchers, and society.

Source: Dickson, D., MD, et al, "The Master Observational Trial: A New Class of Master Protocol to Advance Precision Medicine", Cell, January 9, 2020, Volume 180, Issue 1, P 9 – 14. https://doi.org/10.1016/j.cell.2019.12.009

Implementing Precision Oncology Testing and Interpretation in Policy and Practice for Payers and Providers

There are many variables that can lead to the ultimate success or failure of appropriate utilization of precision oncology. As payers consider their own policies, and the expectations they may set forth for providers, these considerations may be useful. Payer preferred networks may help or hinder the relationships that are needed to utilize precision oncology most efficiently across specialties, institutions, and disease progression.

PLANNING BEFORE SAMPLING

Communication and planning between the medical oncologist, surgeon and pathologists are crucial. The type of test needed, the size and scale of samples, the method(s) of collection, the timing and where the sample goes for testing and interpretation, all are variables that can affect the timeliness, success, utility and accuracy of the molecular test and its reporting. The treating physician, surgeon, or pathologist may each have preferred relationships with specific internal or external tests or diagnostic facilities. These preferences could become conflicting and counter-productive if not aligned in time or ahead of time.

A molecular test should predict a positive or negative treatment response from a targeted agent for DNA, RNA, or proteins. The proliferation of choices of technologies, testing entities, and variability of reporting results can adversely affect the ability of a treating physician to access the information needed for clinical utility for their patients.

However, the rapid evolution of the field of precision medicine can overwhelm clinical decision-making and utilization. By 2018 there were more than 70,000 unique genetic testing products in the market with an average of 10 new products added each day. The clinical sequencing market (including sequencing tests for diagnosis, risk prediction, therapy selection and monitoring and screening was growing at a compound annual rate of 28 percent in 2018.[42]

LABORATORY TESTING CONSIDERATIONS

The actual tissue sampling requires clarification, and is dependent upon what, when, how and where, as well as why. The rationale for testing and the technical needs of the diagnostic laboratory must be clearly stated. Diagnostic considerations in molecular testing could include[43]

- Choice of assay and design
- Cost
- Tissue quality
- Turnaround time
- Clinical Laboratory Improvement Amendments and/or College of American Pathologists certification
- Bioinformatics analysis
- Clinical interpretation

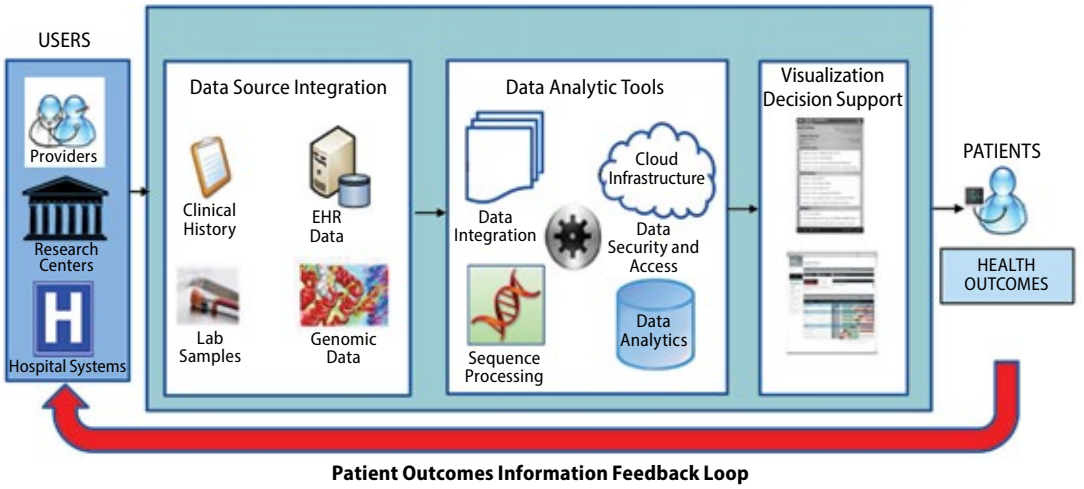
The type of sampling (i.e., tissue blocks or liquid biopsy or some combination thereof) will be driven by the planned diagnostic (individual tests, panel sequencing from a few to hundreds of genes) and the expected outcomes against future needs for further testing on the same or new samples. The amount of DNA and cellularity of samples will be subject to different expectations for different tests. Tissue blocks must have sufficient tumor tissue so that infrequent mutations can be characterized, and results be interpretable. NGS diagnostics will require formalin-fixed paraffin-embedded (FFPE) samples, including fine-needle aspirates and cytology samples with sufficient cellularity. Failure to anticipate any of these variables could result in a quantity-not-sufficient profiling with unusable information.[44]

The biopsy process can be physically, mentally, or even financially challenging for patients and returning for additional sampling for future needs (better information, running different diagnostics, clinical trials, etc.) may not be feasible. Treating physicians may find that patients or samples were directed by an unknown institutional directive to unexpected facilities or processing and then when the results are not conclusive for the desired clinical direction or decision, patient access to appropriate care could be adversely affected.

Emerging Liquid Biopsy Options

Liquid biopsy – using blood samples to look at circulating tumor DNA and circulating tumor cells – has become a feasible alternative to tissue samples. The sensitivity and specificity of results can depend upon the technology and the individual sequencing platform, and specificity at higher mutant allele frequencies can be quite high. If continuing research can identify optimum intervals and time frames for detection in relation to treatment, blood samples may provide a more cost and quality of care option for patients. Treatment changes may more easily be based on detection of known resistance mutations with potential for improvement in patient outcomes.[45] Liquid biopsy can be used as an alternative when tissue sampling through surgery or biopsy is not possible to monitor detection of postoperative recurrence, and is expected to permit monitoring using microRNA or to facilitate early detection of tumor gene mutations. Liquid biopsy is still an emerging technology, working on consistent reproducibility and accuracy of examination.[46]

Exhibit 5: Health Information Technology to Enable Precision Medicine



Source: Ginsburg, Geoffrey and Phillips, Kathryn, "Precision Medicine: From Science to Value," Health Affairs; 2018 May ; 37(5): 694-701, last accessed 02/27/2022 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5989714/pdf/nihms971591.pdf , Page 14, Exhibit 1.

Some payers are already recognizing the differences between tissue and liquid biopsies through support, policy, and coverage.

INDIVIDUAL AND PANEL TESTING CONSIDERATIONS

Biomarkers to be Tested

Clinically relevant biomarkers can be essential to match the right treatment to the right patient at the right time. For advanced disease, learning about resistance to treatment can be as informative as positive response, particularly after front-line therapy. New tools being explored for emerging clinical potential include biomarkers, including genomic alterations in tissue or blood, circulating tumor cells, gene expression assays, protein assays, and tools to predict response to immune checkpoint blockade, chemotherapy, and targeted or radiation therapy.[47]

Panel Testing

Comprehensive Genomic testing (such as NGS) can be valuable for patients with metastatic disease at different times over their clinical journey. Patients with diseases that have few or no standard treatment options are good candidates for early molecular profiling which may lead to a clinical trial identified for a particular alteration. These trials (also called basket trials/studies) are usually agnostic to the tissue of origin and more relevant to specific identified variants. Molecular aberrations often present across multiple histologies. Results from basket trials have shown different histologies with vastly different response rates, which can complicate treatment choices for individual patients.

Panel testing offers the ability to group any number of cancer gene tests. "Hot spot" NGS tests analyze alterations in exons or intron/exon junction areas of a preselected panel of cancer genes, including known activating oncogenes and tumor suppressor genes. Hot spot studies tend to concentrate on the best-annotated cancer genes (ranging from 35 to 350 individual genes) and thus provide a high depth of coverage. That depth allows for assessing lower allele frequency and can account for intratumoral heterogeneity and low allele frequency of the alteration.[48]

TREATMENT DECISIONS AND EXPECTED OUTCOMES

Understanding what the clinical test means and how to adapt it to treatment decisions that will make a clinical difference to a patient is both a science and an art. The experience and skill of the physicians, molecular pathologists, data scientists, analytics, and decision support can vary widely among testing facilities, clinical centers, and treating physicians. The interpretation of precision medicine diagnostics and treatment choices can frustrate both clinicians and payers looking for consistency in a varied world. As shown in Exhibit 5, the patient outcomes are influenced at any of several steps in the precision medicine journey: at the data source, within the data analytic tools, the visualization decision support, and by the patients and the health systems themselves.[49]

Are Current Data Collection Efforts Able to Get Us There?

There are many efforts in play to advance the promise of precision oncology. Data mining, machine learning, artificial intelligence, data analytics and linking are all in play wherever information is collected (electronic medical records, claims files, lab reports, diagnostics, etc.). Purchasers (both health plans and employers) want to feel that they are paying for appropriate care. Patients and physicians want to make appropriate choices, but the cost, complexity, and operational/coverage challenges raise frustrating hurdles. Pilot projects utilizing the master observational trial construct (see sidebar on page 18) may be valuable partnerships for the adoption of precision oncology between providers and payers.

Dr. Lee Newcomer, medical oncologist and former UnitedHealthcare executive, recently noted the frustrations for payers related to precision oncology innovation.

> *"Scientific innovation in precision oncology is evolving more rapidly than ever. Targeted therapies requiring specific marker-testing comprise 87 percent of late-stage oncology drugs in the development pipeline, and in May 2020 alone, seven new drugs were approved for non-small cell lung cancer.*
>
> *These breakthroughs mean cancer patients who once had few options are now finding gene mutations that have therapeutic options beyond chemotherapy that can extend and improve their lives, often with fewer harmful side effects. But they are tempered by outdated decision-making and reimbursement practices that threaten patient accessibility and the speed of progress in this area."*[50]

Payer Challenges for Consideration of Precision Oncology Diagnostics

Variations in precision diagnostics, even in local healthcare markets, can cause challenges for payers seeking best practice in precision oncology delivery as well as policy. Engaging with providers and, more importantly, real-world data such as master observational trials, can raise awareness of the good variants, while calling out the bad variants. Claims data and electronic records often do not track the individual source of the test, or catch variants in analysis, interpretation, and utility. Only moving to good regulatory grade real-world data will elevate the process to the next needed level.

INCONSISTENCY AFFECTS TREATMENT DECISIONS

Inconsistency in entering data into charts, sensitivities in diagnostics interpretations, new studies, new treatment options, and even sampling and testing processes create a vortex of information overload (that may or may not be precise). No one can compensate or keep on top of every bit of that information, and as many try, conflicts arise in interpretation, integration, and implementation. All this can lead to treatment courses that can cost needless additional time, resources and money that adversely affect the patient, the health system, and the medical community.

TESTING OVERLOAD

Dozens of new oncology-related diagnostic tests may be added every month. Hospitals, academic centers, and private laboratories are developing their own versions of individual and panel tests with great variation in process, interpretation, predictive results, and sensitivity success. The source of the test can result in testing and results variation. It can be difficult for payers to navigate through coverage not only for tests, but for the source of tests. Providers may have legitimate reasons to seek coverage of internal testing facilities, including patient access, medical continuity, and quality. Every testing facility will provide its own claims of quality, utility, patient access, and outcomes. Cost is often a significant variable across testing alternatives, which can be a barrier for both payers and patients.

ACCURATE CODING IS THE KEY TO UNDERSTANDING TESTING

Biomarkers may be tested, coded, and billed individually. These are easy to follow because each of the many biomarkers have their own billing code and are linked as companion diagnostics to certain diseases. Genomic sequence analysis panels are billed under just three codes and can include biomarkers and other genes not yet linked specifically as companion diagnostics.

Current Procedural Terminology (CPT) /Healthcare Common Procedure Coding System (HCPCS) codes for NGS panels are divided by the size of the panel:

> 81445 – TARGETED GENOMIC SEQUENCE ANALYSIS PANEL, SOLID ORGAN NEOPLASM, DNA ANALYSIS, AND RNA ANALYSIS WHEN PERFORMED, 5-50 GENES (EG, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), INTERROGATION FOR SEQUENCE VARIANTS AND COPY NUMBER VARIANTS OR REARRANGEMENTS, IF PERFORMED
>
> 81455 – TARGETED GENOMIC SEQUENCE ANALYSIS PANEL, SOLID ORGAN OR HEMATOLYMPHOID

NEOPLASM, DNA ANALYSIS, AND RNA ANALYSIS WHEN PERFORMED, 51 OR GREATER GENES (EG, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), INTERROGATION FOR SEQUENCE VARIANTS AND COPY NUMBER VARIANTS OR REARRANGEMENTS, IF PERFORMED

0048U – ONCOLOGY (SOLID ORGAN NEOPLASIA), DNA, TARGETED SEQUENCING OF PROTEIN-CODING EXONS OF 468 CANCER-ASSOCIATED GENES, INCLUDING INTERROGATION FOR SOMATIC MUTATIONS AND MICROSATELLITE INSTABILITY, MATCHED WITH NORMAL SPECIMENS, UTILIZING FORMALIN-FIXED PARAFFIN-EMBEDDED TUMOR TISSUE, REPORT OF CLINICALLY SIGNIFICANT MUTATION(S)[51]

CODE STACKING MASKS UTILIZATION AND EFFECTIVENESS

When diagnostics laboratories are unable to secure reimbursement for a panel of genes, they may default to billing for the genes in panels that have their own billing code on an individual basis. This is not recommended practice and may cost the payer and the patient more than if the panel were covered and reimbursed.

When labs stack codes for easier payment to work around challenges caused by payer coverage policies, this creates data and real-world data review barriers. Any review of claims data will no longer be based upon accurate data and will taint future analytics.

The solution to stacking of codes is to conduct, bill and pay for tests that appropriately meet the clinical needs of the patient and their treating provider.

PAYERS AND PROVIDERS DIFFER IN PERSPECTIVE ON GENETIC PANEL TESTING

Provider and payer perspectives differ about the utility of genetic panel testing, which leads to conflicts in policy and coverage, which in turn can adversely affect patients.

Payers often use the differentiation of billing codes 81445 (5-50 genes) and 81455 (over 50 genes) as a natural placeholder for coverage policy. The difference in reimbursement for the two codes creates a logical financial stopping point for coverage. It is easier to set coverage policy for individual companion diagnostics that are billed under their own separate codes as preferred to panels of increasing size that include many, if not all, of the individual diagnostics as well as more genes that may or may not lead to actionable outcomes.

Payers are concerned about the potential for large-panel genetic testing to have little utility where conditions may be known to have only a few gene variants, or where clinical diagnostic guidelines are readily available. Large gene panels can cause confusion due to variants of unknown significance (VUS) in off-target genes.[52]

Providers and patients, though appear to more rapidly embrace the greater breadth of additional information generated by large genetics panels. There may be many reasons for wanting to order a larger panel:[53]

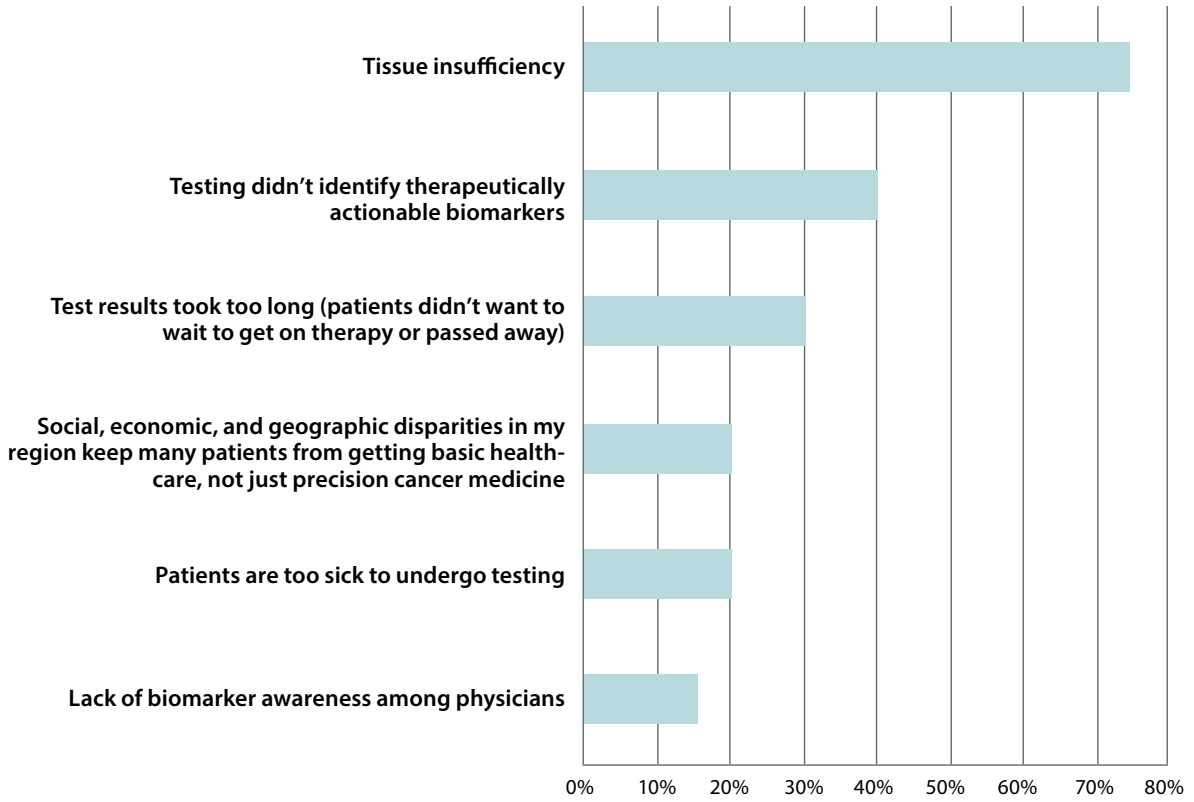
- Larger panels are now widely available, heavily advertised, and present as a one-size-fits-all solution to complex genetic testing.
- Patients with complex disease or overlapping clinical symptoms may lead providers to consider larger panels as an opportunity to reveal disease risks that a provider may not have detected otherwise.
- Known family mutations may lead to providers using larger multigene panel testing instead of cancer-specific or single-gene tests out of precaution.
- Larger gene panels cast a wider net for diagnosis. Some genes may cause a broader set of symptoms than originally thought, leading some physicians to lean away from a more specific approach to testing.
- Some conditions are showing a rapidly growing number of associated genes. Multigene testing may make more sense than single-gene testing when variants on numerous genes could present clinically with the same symptoms and clinical diagnosis.

Review and Strategies for Managed Care Moving Forward with Precision Oncology Program Policy and Support

WHAT IS THE PAYER'S ROLE IN HELPING ADVANCE THESE FIELDS?

Without testing that allows broad molecular profiling and data collection tied to treatment, it is going to be impossible to really unlock precision medicine. Payers or employers can participate in encouraging broader testing in connection with quality data collection and such participation could lead to an outcome where treatments are improved and costs are diminished, because we have a better understanding of what is going on with individual patients. In many cases, this requires that more advanced testing be ordered and utilized prior to the data having been collected. The

Exhibit 6: Biomarker Testing in Time Questionnaire



Source: Ray, Turner, "Survey of Precision Oncology Programs; Rapid pace of Advance Still a Major Challenge for Oncologists," Journal of Precision Medicine, March 2022, Volume 8, Issue 1 page 26 – 29 https://www.thejournalofprecisionmedicine.com/wp-content/uploads/precision-oncology.pdf

payer community needs to decide how to work with providers and the scientific community to ensure that patients receive not only testing that is valuable today but also testing that could be invaluable in creating a better tomorrow.

FACILITATING TIMELY TEST RESULTS TO INFLUENCE THERAPY DECISIONS

If a test doesn't deliver results in time to help physicians make informed treatment decisions, it is a lost opportunity, with significant adverse impact on patient quality of life, health status, access to appropriate care, and costs of care. There are many hurdles affecting timely test delivery, and payer policy can play a significant role in both causing and breaking down those hurdles (see Exhibit 6)

Many of the reasons noted in Exhibit 6 as to why a cancer patient may not receive testing or results in time to affect therapy decisions may be influenced by payer policy and the resulting policy impact on physician choice of test or source for test.

- If payers require preferred networks for biopsy, sampling or testing and these facilities are not familiar to the providers, disconnects can occur that can lead to any of the above challenges.
- Prior authorization processes can contribute to delays in patients being sent for needed testing or biopsies.
- Step edits for allowed tests or treatment options could not only result in delays for results and needed care, but also require multiple tests over time that could deplete tissue samples.

Other factors can include testing facility delays, miscommunication around tissue requisition and handling, and even patient challenges from health status or access to testing or treatment facilities (transportation, caregiver support, costs, loss of work, etc.).

Costs of Testing versus Value Are Still a Concern

The costs of testing to achieve precision oncology can multiply quickly. Factors may include[54]

- Multiple biomarkers for a disease state
- Increased testing as the disease progresses
- Testing that did not lead to a specific targeted treatment
- Stacked-codes billing for individual biomarker tests because coverage/payment was not available for a gene panel test that may have actually cost less than the sum of the billed codes
- More testing to reveal altered genes is now available than there are effective treatments (but that can change quickly with new discoveries)
- Lack of appropriate tissue samples. Metastatic disease that cannot be accessed through biopsy or surgery cannot generate the tissue samples needed for most NGS gene-based panel tests.

FEARS, FOUNDED OR UNFOUNDED, CONTINUE TO ABOUND, BUT CAN BE MITIGATED TO MOVE FORWARD

Payers, employers, providers, and patients all may have different perspectives and fears about the technology and speed of precision oncology. Some dichotomies include the following:

- Genetic testing may drive up costs / It may be more efficient.
- Oncology disease is complicated, and difficult to pigeonhole for treatment / The growing body of knowledge and ability to test for tumors and mutations provides hitherto unavailable knowledge to better target what may work as well as what may not work.
- Payer could spend thousands of dollars on panels with limited actionable targets to show for it / Well-designed panels may catch essential information using just one tissue sample that could fuel management of the cancer both now and in the future as targets and treatments rapidly evolve.
- Broad genetics testing may cause patient confusion and fear / Appropriate, credentialed counseling could engage and empower patients.
- Specific targeted tests may be covered while gene panel tests are not covered under current payer policy, adversely affecting patients, providers, and ultimately the employer and payer / Gene panel testing would have been the more efficient approach.
- Rapid proliferation of precision oncology biomarkers and targeted testing may tax the limits of scarce and costly tissue sampling / Further tissue sampling may not be possible as samples may be used up too quickly and before individual targeted testing is completed.
- Cancer is terrifying and can advance rapidly. Traditional medical coverage policy requiring cascading treatment and step edits, or denial of some kinds of testing but not others might delay needed knowledge for timely treatment / Precision oncology offers streamlined cancer management and decision-making.

Older payer policy that is not aligned with the opportunities afforded by precision oncology may cause adverse financial, medical, and quality of life issues for the payer, employer, providers and most of all, the patient.

Payers Can Help Advance Accountability and Effectiveness in Precision Medicine through Master Observational Trials Tied to Treatment Coverage

A longitudinal Master Observational Trial (MOT) that tracks details about the testings, patient response, physician decision-making, and outcomes to provide real-world evidence related to utility of the rapid proliferation of testing and treatment could be one of the most powerful tools to unlock the promise and value of precision medicine. Current traditional clinical trials or real-world data analytics from existing data sources are crucial for certain purposes but are unrealistic to provide the scientific rigor or transparency of a well-designed MOT built specifically to answer the questions of benefit of treatment tied to molecular testing.

One of the few working examples of a MOT is being led by a Public Benefit Corporation, Taproot Health. They are spearheading a pre-competitive national (and eventually international) observational trial called the Registry of Oncology Outcomes Associated to Testing and Treatment (ROOT). ROOT collects standardized prospective, real-world data from consenting patients across the country. ROOT will provide quality data for advancing drug discovery, personalizing treatments, and helping all stakeholders work together to advance care.[55] The ROOT trial, although in its infancy, has been adopted by several National Cancer Institute-designated cancer centers and community oncology clinics to prospectively collect regulatory grade, real-world data from consented patients. The ability to merge community clinics with academic medical centers both nationally and internationally demonstrates that the MOT can be adopted in a variety of clinical settings.

"Precision oncology is stunted when critical patient data is not broadly shared. The ROOT (Master Observational Trial) will serve as the foundational effort to collect and share the standardized and

quality data that is needed to rapidly advance precision oncology," Jennifer Johnson, director of precision medicine at Thomas Jefferson University Hospital and a principal investigator for the trial.[56]

ROOT allows payers, employers, and providers to come together in a unified effort to build a perpetually advancing evidence base of precision medicine. ROOT gathers prospective data at the point of care in a manner compliant with emerging FDA guidance on real-world data that can drive actionable coverage policy. Collaborative efforts can link data collection through ROOT to early coverage policy and lead to informed evidence-based clinical understanding for both medical decision-making and real-world data-based support for coverage for the right treatment at the right time for the right patient.

Does Current Payer Policy Set the Right Goals to Achieve Precision Oncology?

Performed correctly and to the height of its promise, precision oncology will allow providers to understand the specific and unique characteristics of a patient's tumor, and to target therapy and treatment (or decide not to treat) before numerous other traditional lines of treatment are used. This earlier intervention could save money and the burden of toxic and/or futile medical drugs for the patient and the payer.

Unfortunately, since the technology for precision oncology is outpacing policy and coverage, there is enormous potential for outdated policy to inadvertently do more harm than good, both financially and medically. Much of the payer concern can be ascribed to cost, variation, limited information on the impact of biomarkers and testing on medical decision-making, as well as the emerging large gene panel assays that collect more gene data than the count of actionable targets now in existence.

Data is the missing link, and payers now have at least one vehicle to use with providers to jointly embark upon an innovative approach for both evidence-based care and real-world data – the MOT, and specifically, the ROOT trial.

The new era of precision oncology has outpaced the traditional patterns for care and coverage that rely on traditional clinical trials, prior authorizations, step edits, and claims management.

Precision Medicine and Precision Oncology of the Future – Summary and New Payer Strategies

The most effective and cost-efficient cancer care is the cancer that never materializes or is detected early. Payer and employer policy that supports and invests in providers and tools that create better healthcare management opportunities will lead the field in more successful and cost-effective healthcare for their customers and society.

GENETIC SCREENING AND LIQUID BIOPSIES BECOMING PART OF BASIC WELLNESS AND PREVENTATIVE HEALTHCARE

Precision oncology will lead to a new era where employers and patients will demand genetic screening for proactive and directed awareness of disease risk. Patient education and awareness of cancer and other disease issues will begin at home, supported by primary care. Payers and employers should plan to cover the digital behavioral engagement, screening, and appropriate genetic counseling to manage patient understanding and awareness for their members and employees.

DISEASE MANAGEMENT WILL INCLUDE STRATEGIC USE OF LARGER GENE PANELS, AND PROACTIVE LIQUID BIOPSY AND TISSUE SAMPLING

Given the rapid growth of targeted biomarkers and targeted therapy in the cancer pipeline, it only makes sense that if a gene or mutation can be identified in a panel, that a standard workup of a patient with cancer should include a broad panel. Of course, the testing facility and the analytics and results reporting of that broad panel should be verified and trusted by both the provider and the payer, as well as compliant with current FDA and other key organizations' guidance and standards.

If standard of care treatment for a given diagnosed cancer does not yet include biomarker testing or mutation clarity, it will not be long before it does. The more we can efficiently use precious tissue samples to start with a good understanding of the disease, the better we can make sure the right treatment reaches the patient at the right time or that we can avoid treatments that will not be effective. Precision oncology should allow payer policy and provider treatment patterns to avoid long drawn out and costly lines of therapy that "might" work. More efficient care the first time will reduce the financial and medical burden of the disease on the patient and their family.

PRECOMPETITIVE NATIONAL CANCER REGISTRY MOT TRIALS WILL LEAD THE WAY TO PAYER AND PROVIDER MANAGEMENT OF ONCOLOGY UNDER PRECISION ONCOLOGY

Payer policy could remove barriers to efficient panel testing while encouraging patients and providers to participate in a precompetitive national oncology Master Observational Trial such as ROOT. This will move oncology care to the next level, where real-world data becomes routine and the relationships between diagnostics, treatments and outcomes are

routinely tracked in a longitudinal regulatory grade, patient-consented MOT.

Utilizing a national MOT will also create a flexible platform for understanding the impact of not only DNA based treatments and testing for oncology, but also the emerging messenger (mRNA) landscape. Retrospective claims data and medical record analytics, although important, will be unable to handle the complexity of knowledge that will be needed to power precision oncology by themselves.

AUTHOR'S BIOGRAPHY

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