

Improving Access to Biomarker Testing

Advancing Precision Medicine in Cancer Care

September 2020



Introduction

Precision Medicine in Cancer Care

Precision medicine* uses information about a person's own genes or proteins to prevent, diagnose, or treat disease.¹ Often synonymous with *personalized* or *genomic medicine*, precision medicine is most developed in the field of cancer. When used in the treatment of cancer, precision medicine incorporates specific information (e.g. **genetic alterations, molecular signatures**) about a person's cancer to inform diagnosis, prognosis, therapy selection, and to monitor how well therapy is working. The ability to identify the specific genetic alteration or molecular signature of an individual's cancer has led to the increasing sub-categorization of cancer types. While it has long been known that genetic alterations cause cancer, and that a variety of different alterations can lead to the same result – cancer – we have only recently realized that those different alterations can be treated differently.

The knowledge and practice of precision medicine in cancer have been progressing rapidly. Advances in precision medicine in cancer have led to **targeted cancer therapies**, which work by interfering with specific cellular processes involved in the growth, spread, and progression of cancer. Currently, targeted therapy is the exception rather than the rule and is more developed in some cancers than in others, but in cases where patients are able to be treated with targeted therapies, studies have shown improved patient outcomes across cancer types.^{2,3}

Treatment with targeted cancer therapy often requires diagnostic testing to analyze biological samples (e.g. blood, tumor tissue) taken from patients to identify and evaluate specific **biomarkers**. Biomarkers, also called *molecular markers*, are biological molecules, found in blood, tissues, or other bodily fluids that provide insight into normal or abnormal physiological processes, medical conditions, or diseases.⁴ Cancer biomarkers can include molecules like proteins or genetic alterations like mutations, rearrangements, or fusions. Testing patients for specific biomarkers is integral to precision medicine in cancer care, but unfortunately many patients who should be tested are not.

Patient access to appropriate biomarker testing relies on a combination of factors. First, there must be reliable, valid, and relevant tests available. The close connection between the performance of a test and the clinical decisions made as a result of testing, such as the initiation of a targeted cancer therapy, underscores the need for tests available on the market to be appropriately validated. Second, as new and validated tests become

* Bolded terms listed in glossary on page 20

available, insurer coverage is an important factor in provider uptake and patient access. Without coverage, patients will not have access. Third, testing relies on knowledgeable health care providers, aware of what tests to utilize and when, as well as how to utilize the results in caring for their patients. **Clinical treatment guidelines** play a critical role in driving practice, and therefore must be updated regularly as evidence establishes new linkages between biomarkers and targeted therapies. Finally, health care facilities need to be equipped with the appropriate testing infrastructure for the efficient and sufficient collection and handling of tissue for testing, and health information technology to manage testing results and assist health care providers in clinical decision making. Failure to achieve any one of these factors can create challenges that limit access to biomarker testing and prevent cancer patients from realizing the full potential of precision medicine.

This paper explores the current landscape of cancer biomarker testing, sheds light on the nature of challenges limiting adoption of appropriate testing, and proposes recommendations to increase the uptake of testing and advance the use of precision medicine in cancer care.

Defining Appropriate Testing

Categories of Biomarkers

Diagnostic

Diagnostic biomarkers are used to confirm presence of a disease or condition of interest, or to identify individuals with a subtype of the disease.⁵ This is one of the earliest uses of biomarker testing in cancer.⁶ A diagnostic biomarker can allow for the early detection and treatment of a disease. An example of a diagnostic biomarker is the BCR-ABL fusion gene (Philadelphia Chromosome) used to help diagnose leukemias.⁷

Therapeutic Selection

Therapeutic selection biomarkers, also known as *predictive biomarkers*, are used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a medical product or an environmental agent.⁵ Cancer cells are characterized by their uninhibited, rapid growth. Traditional cytotoxic chemotherapy generally works by inhibiting any rapidly growing and dividing cells in the body without discerning between cancer cells and some types of normal cells that also happen to grow quickly. This mechanism of action is responsible for many of the side



effects frequently associated with chemotherapy including hair loss, nausea, and low blood counts. Some targeted therapies are developed in a way that specifically target a cancer's unique genetic alteration, typically manifested through cellular proteins, that are responsible for cellular processes like growth, repair, and communication. These proteins are specifically altered only in cancerous cells. For example, some cancers like non-small cell lung cancer (NSCLC) are associated with an overexpression of a biomarker called epidermal growth factor receptor (EGFR) protein, due to a mutation. The EGFR mutation causes a mis-regulation of normal cellular processes and drives the growth of the cancerous cells. Today, multiple EGFR therapies are available that target this mis-regulation in cancerous cells with EGFR mutations, disrupting their ability to divide.

Since targeted therapies only work for a subset of cancers, many rely on therapeutic selection tests, also known as **companion diagnostics**, which identify the appropriate patients who will benefit from therapy. Companion diagnostics are often reviewed by the U. S. Food and Drug Administration (FDA) simultaneously with the drug they are paired with and provide essential information for the safe and effective use of a drug. For example, *HercepTest* is an FDA-approved companion diagnostic for Herceptin (trastuzumab), a drug used to treat HER2 receptor positive breast, gastric, and gastroesophageal cancers.⁸

Similar to companion diagnostics, **complementary diagnostics** support the decision making around the use of a particular drug. However, they are distinct in that they are not required for the safe and effective use of a drug but aid in the assessment of risks and benefits of a particular drug. For example, the *PD-L1 IHC 28-8 pharmDx* test is an FDA-approved complementary diagnostic for Opdivo (nivolumab), a drug used to treat PD-L1 positive NSCLC.⁸ While Opdivo (nivolumab) works progressively better in patients with higher PD-L1 expression, those with lower PD-L1 expression may also benefit.⁹ As a complementary diagnostic, the test is not required but may provide added information related to the use of the drug.

Prognostic

A **prognostic biomarker** is used to identify the likelihood of a clinical event, disease recurrence, or progression in patients who have a disease or medical condition of interest.⁵ For instance, the *Oncotype DX Breast Recurrence Score*[®] Test¹⁰ is a prognostic test that measures the expression of specific genes in a breast biopsy sample that can help determine the risk of recurrence of early-stage ER positive, HER2 negative breast cancer, and guide treatment decision making.

Susceptibility or Risk

A **susceptibility or risk biomarker** is used to identify the potential for developing a disease or medical condition in an individual who *does not* currently have clinically apparent

disease or the medical condition.⁵ Certain biomarkers in a person’s normal DNA can be an indicator of elevated risk for developing a given cancer. For example, BRCA1 and BRCA2 **germline genetic mutations** are recognized for their link to breast, ovarian, and prostate cancer. Individuals at higher risk can engage in preventive measures or enhanced surveillance. Germline genetic mutations are inherited from parents and are present in every cell at birth. *Genetic testing for germline mutations for inherited cancer risk is distinct from biomarker testing for **somatic alterations**, which occur in a specific cell after conception and is limited to only cells originating from that specific cell. This document is concerned with somatic alterations.*

Monitoring

Monitoring biomarkers are used in assessing the status of a disease or medical condition or for evidence of exposure to or effect of a medical product or environmental agent.⁵ A monitoring biomarker can be assessed serially over time such as, prior to the initiation of treatment, during treatment, and following treatment. Monitoring a biomarker over time can allow for comparisons to detect signs of disease worsening, concentration and toxicity of drugs, and to determine therapeutic response. As tumors rapidly grow and die, they release DNA fragments that circulate in the bloodstream. This DNA is identifiable as coming from tumor tissue, rather than healthy tissue, by the presence of specific mutations and is known as **circulating tumor DNA (ctDNA)**. Tumors have traditionally been imaged to monitor their size as an indication of treatment progress, but monitoring ctDNA in patients offers an additional approach that can potentially detect earlier indications that tumors are returning or to detect residual cancer not detected by imaging.

Patient Outcomes

Research continues to show that cancer patients who receive biomarker testing and are eligible for and receive targeted cancer therapy have improved **progression free survival** and **overall survival**. For example, a 2017 study that compared outcomes of patients with NSCLC treated with targeted therapies with patients treated with cytotoxic chemotherapy, found that patients who received targeted therapy lived on average 1.4 years longer.²

Additional studies have reported similar findings when comparing diverse metastatic cancers. A 2015 study which compared the impact of targeted therapy in diverse metastatic cancers found that patients that received targeted therapy compared to non-targeted therapy had an over two-fold increase in median progression free survival and a one- and one-half fold increase in overall survival.³ Ensuring access to biomarker testing will allow clinicians to identify more patients who are eligible for targeted therapy.



A Changing Paradigm

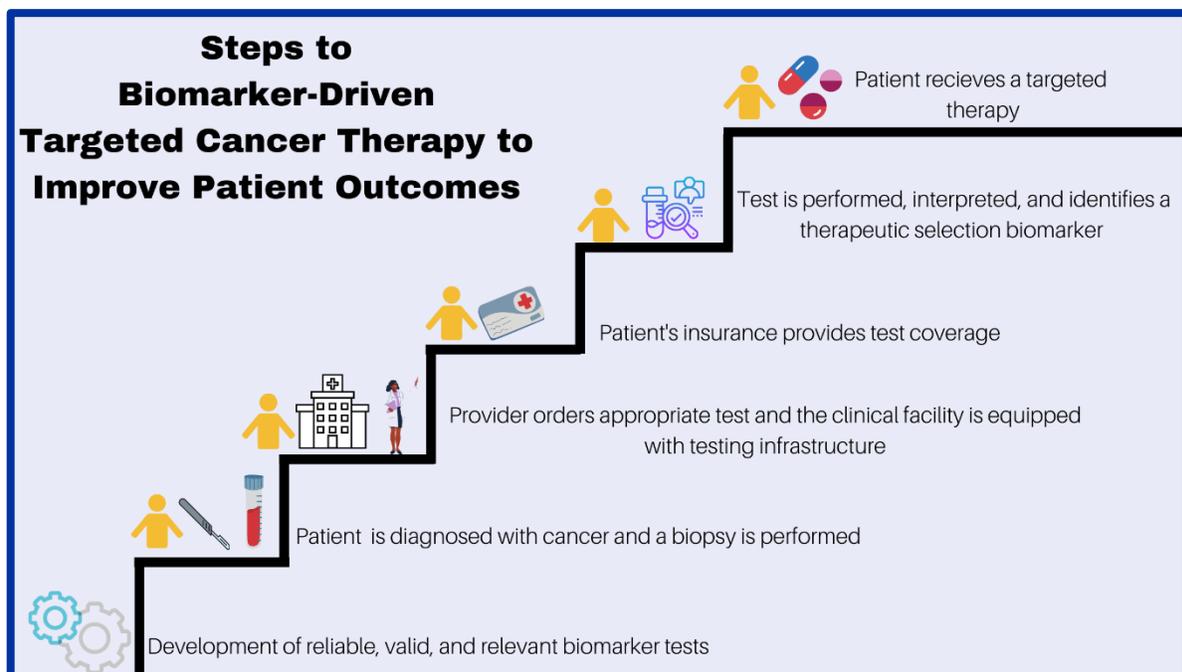
Tissue-Agnostic Targeted Therapies

Traditionally, health care providers have treated cancer based on where it developed in the body. However, the approval of **tissue-agnostic targeted therapies** characterizes a shift in how health care providers, payers, and patients will need to consider cancer therapy. Tissue-agnostic targeted therapies are used to treat cancer types that have the same biomarker regardless of where it occurs in the body (e.g. breast, lung, melanoma). Since most somatic alterations in cancer can be found across cancer types,¹¹ the development and use of tissue-agnostic targeted therapies will have considerable implications as to which patients should have biomarker testing. However, there are currently only three FDA-approved tissue-agnostic targeted therapies.

FDA-Approved Tissue-Agnostic Targeted Therapies

Therapy	Biomarker
Rozlytrek (entrectinib)	NTRK gene fusions
Keytruda (pembrolizumab)	MSI-H or dMMR
Vitrakvi (larotrectinib)	NTRK gene fusions

As illustrated below, several steps are involved before a cancer patient can receive a targeted cancer therapy. Many therapies require that a patient is first tested to identify and evaluate specific biomarkers to determine if they are eligible for therapy. However, barriers to patient access for biomarker testing can arise beginning at test development and can persist through the interpretation of test results in the clinic and can prevent cancer patients from receiving therapies that improve survival and quality of life.



Role of Clinical Practice Guidelines in Determining Appropriate Testing

As clinical research confirms new links between biomarkers and therapy decision making, several professional associations, including the National Comprehensive Cancer Network (NCCN), the American Association of Clinical Oncology (ASCO), and the College of American Pathologists (CAP) have developed biomarker testing and treatment guidelines. In a recent survey, the most commonly cited source for recommended biomarker testing used by payers and oncologists was NCCN’s Clinical Practice Guidelines in Oncology®.¹² NCCN’s guidelines contain recommendations on biomarker testing and are based on categories of evidence and consensus among its alliance of 30 cancer centers around the United States. NCCN has reached uniform consensus (category 1 and 2A recommendations) and has made recommendations for testing an array of biomarkers across cancer types.¹³ The use of evidence-based clinical treatment guidelines is one way to assure that testing and treatment decisions take advantage of the latest knowledge of a disease. The rapid development of new tests and clinical understanding of biomarkers requires frequent updates to clinical practice guidelines to stay current.

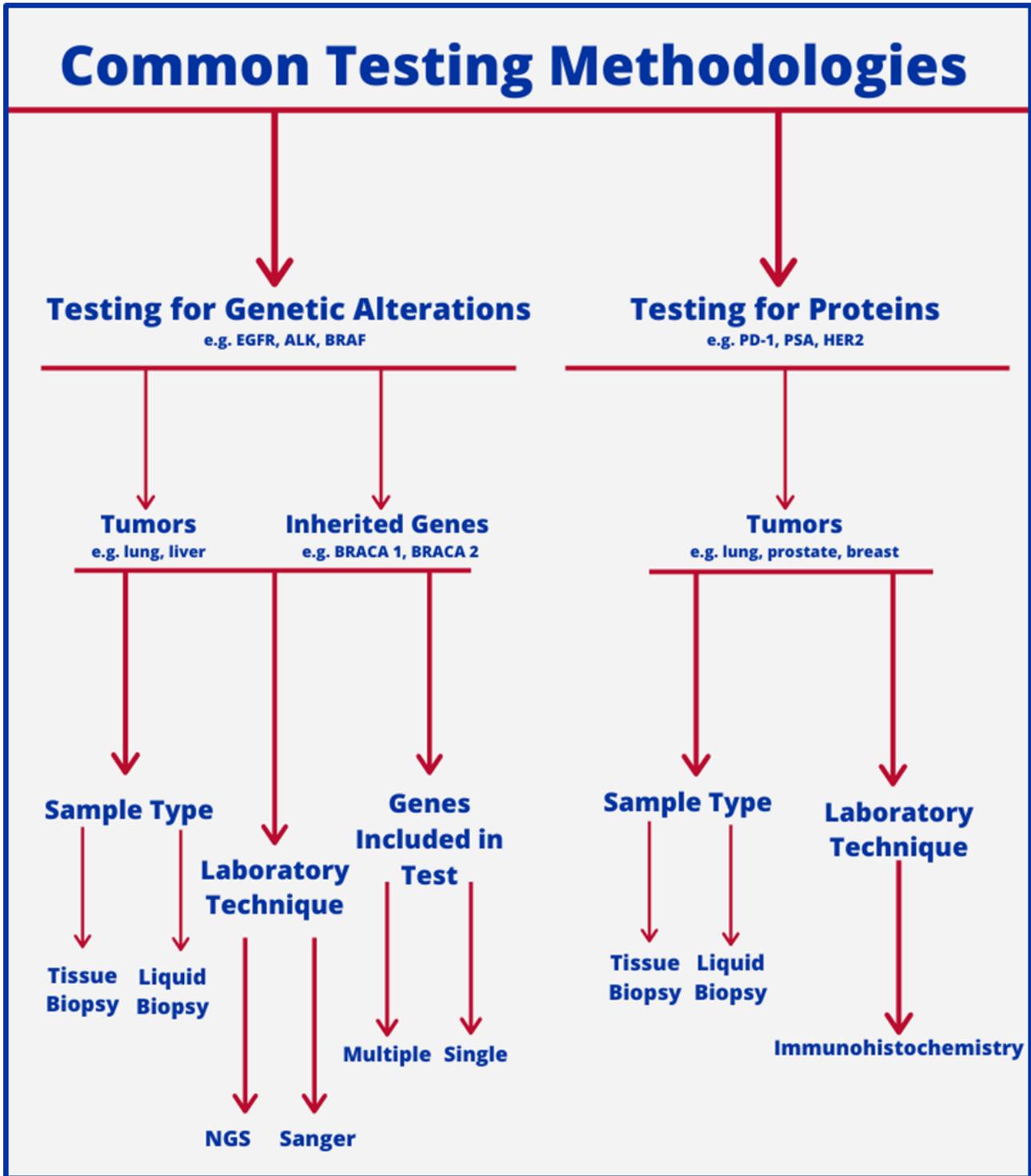
Select NCCN Biomarkers by Cancer Type

Cancer Type	NCCN Category 1 or 2A Recommended Biomarkers
Non-Small Cell Lung Cancer ¹⁴	PD-L1, ALK, EGFR, ROS1, KRAS, BRAF, NTRK, MET, RET, TMB
Colorectal Cancer ^{15†}	KRAS/NRAS, BRAF V600E, MSI, HER2, NTRK
Prostate Cancer ^{16†}	CHEK2, PALB2, RAD51D, ATM, BRCA1, BRCA2, FANCA, CDK12, AR-V7, MLH1, MSH2, MSH6, PMS2, MSI
Breast Cancer ^{17†}	ER, PR, HER2, BRCA1, BRCA2, NTRK, MLH1, MSH2, MSH6, PMS2, MSI, PIK3CA, PD-L1

The number of guideline-recommended biomarkers for testing varies by cancer type.

[†] Includes multiple sub-types and stages.

Tissue for biomarker assessment is typically obtained through tissue biopsies, however novel “liquid biopsies” can detect biomarkers through blood samples. For genetic biomarkers, **next-generation sequencing (NGS)** or **Sanger sequencing** are commonly utilized, and one or more genes can be included in a given test. **Immunohistochemistry** is a laboratory technique commonly used to detect protein biomarkers.



Single Analyte Test – Identifies or measures one analyte (e.g. gene or molecule). For example, a single-gene biomarker test.

Panel Test – Identifies or measures multiple analytes (ranging from a few to several hundred) in the same test. For instance, a multi-gene panel test. In oncology, panel tests are often referred to as *tumor profiling* or *comprehensive biomarker testing*.

Diagnostic Test – A test to confirm the presence of a disease or medical condition.

Prognostic Test – A test that provides information on the likely clinical outcome of a disease or medical condition.

Companion Diagnostic (therapeutic selection test) – A test that helps to determine the benefit from a specific therapy. Companion diagnostics are paired with a particular therapy and are required before the therapy's use.

Complementary Diagnostic— A test that can support the decision making around the use of a particular therapy but is not required for a therapy's use.

Multi-Analyte with Algorithmic Analysis (MAAA) – A test that combines multiple results from two or more tests with other patient information (e.g. age, sex) into an algorithmic analysis which generates a numeric or probabilistic risk score.

Test Development and Marketing

To effectively inform clinical decision making, tests that accurately identify biomarkers relevant to a patient's health must be readily available. Simple biomarker tests such as a basic metabolic panel are used in many health care settings and can identify a variety of common analytes found in individuals (e.g. calcium level, glucose level, etc.). However, tests for cancer biomarkers, often required for precision medicine, are more complex. Tests can take one of two regulatory pathways to market and are generally categorized as an **FDA-cleared or -approved** (FDA-authorized) **diagnostic** or **Laboratory-Developed Test (LDT)**. Each path involves different oversight systems, evidence standards, and evaluation processes.

FDA-Authorized Diagnostics

The Medical Device Amendments of 1976 gave FDA statutory authority to regulate diagnostic tests, including biomarker tests, as medical devices.¹⁸ Before market approval, FDA-authorized diagnostics undergo FDA premarket review in which the diagnostic is reviewed based on risk, with higher risk tests undergoing full review. FDA reviews biomarker tests for safety and effectiveness by assessing their **analytical** and **clinical validity**. Once authorized, the test can be used clinically. Many of these tests are shipped as “kits” that are run in clinical laboratories.

Laboratory-Developed Tests

The Clinical Laboratory Improvement Amendments of 1988 (CLIA) gave the Centers for Medicare and Medicaid Services (CMS) statutory authority over clinical laboratories. CLIA-certified laboratories can produce another category of diagnostic tests known as laboratory-developed tests (LDTs).¹⁹ In addition to creating LDTs,

Evidence Standards for Diagnostic Tests

CLIA certification allows laboratories to perform and modify FDA-authorized tests.²⁰ LDTs do not undergo premarket review so they can be developed and offered commercially in a short time frame. While not reviewed prior to marketing, CLIA labs are inspected by CMS laboratory surveyors biennially to review analytical validity of LDTs.

Historically, LDTs represented simple tests conducted by laboratories within the same health care institution for unique circumstances and were generally not commercially available outside of that institution. Increasingly, laboratories are developing more complex LDTs, including nearly identical versions of FDA-authorized companion diagnostics, without having to seek FDA approval.²¹ Currently, FDA has authorized over 40 companion diagnostics.⁸ With the simpler path to market of LDTs, there are potentially thousands of tests available, sometimes with very subtle differences even though they assess the same analytes. Without formal premarket FDA review, LDTs also often lack the same volume of available evidence, compared to FDA-authorized companion diagnostics, which payers review when making coverage determinations. Finally, FDA-authorized companion diagnostics are not afforded market exclusivity. The creation of LDT versions of companion diagnostics may have the effect of reducing the willingness of device manufacturers to invest the time and resources to develop tests through the FDA pathway.

Three fundamental concepts that manufacturers or laboratories consider when developing diagnostic tests are analytical validity, clinical validity, and clinical utility.

Analytical Validity refers to the ability of a test to detect or measure the analyte it is intended to detect or measure.⁵⁶

For example: If a patient's cholesterol level is 200 mg/dl, an analytically valid test for cholesterol will measure a cholesterol level of 200 mg/dl.

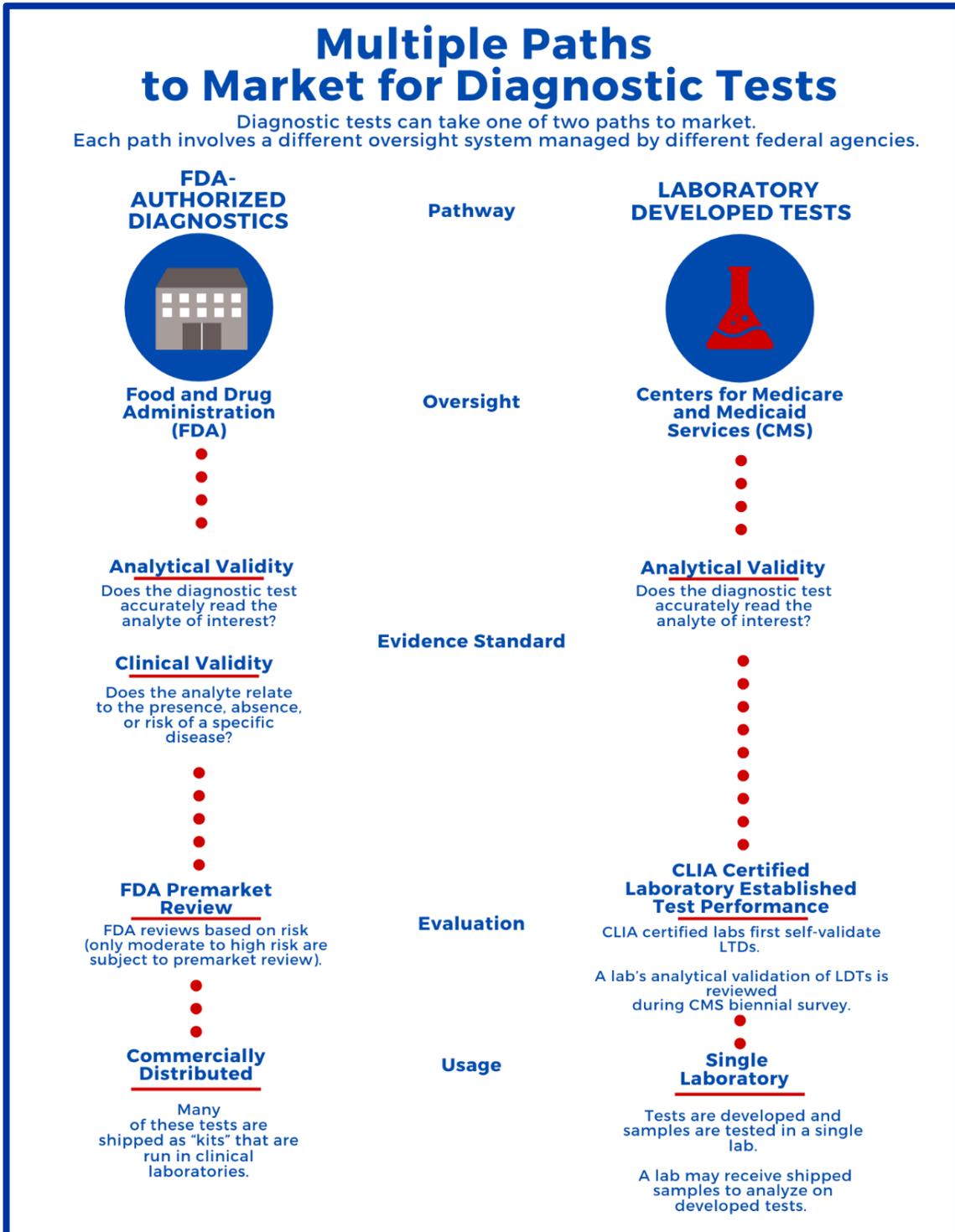
Clinical Validity refers to the ability of a test to accurately diagnose or predict the risk of a particular clinical outcome⁵⁶ or how well the analyte being analyzed by the test relates to the presence, absence, or risk of a specific disease.

For example: Specific mutations within the BRCA1 or BRCA2 genes are clinically valid biomarkers because there is scientific evidence that they increase an individual's risk for breast, ovarian, or prostate cancer.

Clinical Utility refers to whether a test can provide information about diagnosis, treatment, management, or prevention of a disease that will be helpful to patients and their providers.⁵⁷

For example: The presence of immature or abnormal white blood cells can be an indicator of leukemia. A biomarker test that measures the types of white blood cells in a blood sample has clinical utility when used for a patient with suspected leukemia as it can guide therapeutic interventions.

As illustrated below, diagnostic tests can take one of two pathways to market and are categorized as an FDA-cleared or -approved (FDA-authorized) diagnostic or laboratory-developed test (LDT). Each path involves different oversight systems, evidence standards, and evaluation processes. FDA-authorized diagnostics are able to be commercially distributed to multiple laboratories, while LDTs are developed and samples are tested in a single laboratory.



Coverage of Biomarker Tests

Insurer coverage is important for provider uptake and patient access to biomarker testing. However, coverage of tests differs greatly across the multiple public and private payers in the U.S. health care system. Payers take different approaches in making coverage decisions and base decisions on a number of factors. Evidence of clinical utility is typically a precondition for coverage^{22,23} as tests that demonstrate clinical utility can improve clinical outcomes by informing diagnosis, prevention, or treatment. Several studies,²⁴ including a 2020 payer coverage analysis sponsored by the American Cancer Society Cancer Action Network and LUNGevity Foundation,²³ found that when establishing clinical utility, payers consider evidence from different sources, such as NCCN guidelines, technology assessment organizations, and peer-reviewed published evidence (e.g. randomized controlled trials, cohort studies). FDA drug labeling information also plays a key role in payer coverage decisions.²⁴

Clear, positive coverage policies and reimbursement for single-gene tests are more common among public and private payers, as compared to multi-gene panel tests. This is often traced to greater consensus in clinical guidelines for single-gene tests across professional associations (NCCN, ASCO, etc.).^{24,25} However, the development of NGS technology has spurred the transition from single-gene tests to panel tests which presents new coverage challenges.²⁵ The results of panel tests, which often examine hundreds of genes at a time, can yield information on multiple biomarkers with well-established clinical utility. But such tests typically also provide information on dozens or even hundreds of additional biomarkers that are considered “experimental” or “investigational.” While analyzing experimental or investigational biomarkers is useful for research, off-label drug use, and in matching

Advancements in Gene Sequencing Lead to New Diagnostics

Diagnostic testing is an essential component of health care delivery and since the late twentieth century, diagnostic technologies have been developing at a rapid pace, particularly those that test for genetic alterations and molecular signatures.⁵⁸ Contributing to this advancement was the completion of the Human Genome project in 2003. This 13-year project used a technique developed in the 1990s known as Sanger sequencing to identify the 20,000 – 25,000 genes in the human genome.⁵⁹ Often considered the “gold standard,” Sanger sequencing sequences single DNA fragments at a time.

While Sanger sequencing is still used for some applications, it has given way to new techniques collectively known as next-generation sequencing (NGS), which can sequence millions of DNA fragments at a time. Advantages of NGS include shorter turnaround time, lower costs when sequencing multiple genes at a time, and smaller tissue samples required for testing, while providing a high **sensitivity** for detecting alterations.⁶⁰ Over the last two decades as more genes have been linked to causes of disease, NGS has become the underlying technique behind many advanced diagnostics in cancer care.

patients to clinical trials, payers typically only cover tests considered medically necessary and not experimental or investigational.²⁴

The number of biomarkers with clinical utility can vary by cancer type. Often the same panel test is used to analyze biomarkers among cancer types, therefore such a test used in one cancer may identify more biomarkers with clinical utility than in another. In some instances, the only FDA-authorized companion diagnostic for a targeted therapy will be a panel test rather than a single-gene test. For example, the *FoundationOne*[®]*CDx*²⁶ panel test is the only FDA-approved companion diagnostic for Tabrecta (capmatinib), a drug used to treat NSCLC sub-types that have mutations that lead to MET exon 14 skipping.⁸

Medicare

The Centers for Medicare and Medicaid Services (CMS) is the largest public payer of medical services and administers the Medicare program and the Medicaid program in partnership with state governments. Medicare coverage is limited to items and services that are considered “reasonable and necessary” for the diagnosis or treatment of an illness or injury.²⁷ Most Medicare coverage determinations are decided on a regional basis through local coverage determinations (LCDs) made by Medicare Administrative Contractors (MACs) who manage policy and reimbursement for their jurisdictions. This structure means coverage of certain items and services may vary across jurisdictions that MACs oversee. There have been several LCDs issued related to cancer biomarker testing and coverage is relatively consistent across MACs.²⁴ Notably, in 2011, Palmetto GBA, a Medicare MAC, developed the MolDx[®] program which assists MACs in claims processing, utilization tracking, health technology assessments, and coverage and reimbursement for biomarker tests.²⁸

Occasionally, Medicare will make national coverage determinations (NCDs), which create uniform coverage policies across regions. In March 2018, CMS issued a national coverage determination related to NGS panel testing for Medicare beneficiaries with advanced cancer. Specifically, the NCD applies to patients with recurrent, relapsed, refractory, metastatic, or advanced stages of cancer who have not been previously tested using the same NGS test for the same diagnosis.²⁹ Also, the NGS test must have FDA authorization as a companion diagnostic and an FDA-authorized indication for use in that patient’s cancer.²⁹ More recently in January 2020, Medicare expanded coverage of NGS for germline NGS testing in patients with ovarian or breast cancer with suspected germline origins.³⁰

Many stakeholders have acknowledged Medicare’s 2018 NCD as a positive step forward for precision medicine, but they have also noted several concerns. For NGS tests that are not FDA-authorized (i.e. laboratory developed tests), Medicare has traditionally allowed MACs to make coverage decisions through LCDs. However, the NCD includes language

that restricts MAC's use of LCDs for NGS technology to narrowly defined use cases. Additionally, the NCD limits the timing and the frequency of NGS testing.

Medicaid

Medicaid is an insurance program for low-income Americans, funded jointly by the states and the federal government. Each state's program is required to meet minimal federal requirements but can vary in the items and services that are covered and beneficiary eligibility. Much has been documented on the differences in coverage and eligibility among state Medicaid programs. These differences extend to coverage policies for biomarker testing. For example, many Medicaid state plans lack explicit coverage policies regarding comprehensive biomarker testing,³¹ and some studies have indicated that Medicaid patients are less likely to be tested for some biomarkers compared to patients with private coverage.³²

A recent analysis of state Medicaid coverage policies found that Medicaid expansion, as provided under the Patient Protection and Affordable Care Act, was correlated with Medicaid coverage policies for comprehensive biomarker testing.³¹ Medicaid expansion may also be associated with a reduction in racial inequity of NGS testing in cancer patients.³³

Private Payers

The adoption of positive coverage policies for biomarker testing has been increasing among private payers, but there are still limitations and wide variation.^{23,24,25} With the exception of NSCLC, positive coverage policies are generally more common for single-gene tests versus panel tests.²⁴ Coverage decisions are associated with factors such as the number of genes included in a test, the scope of the test, and the population being tested.²⁵ Furthermore, payers often cite limited evidence of clinical utility as a justification for a non-coverage decision for a given test.²⁴ These tests are often labeled as experimental or investigational. Payers may also require that all genes in a panel have

Value in Clinical Trial Screening

The number and percentage of cancer clinical trials that involve biomarkers has grown significantly, from 15 percent in 2000 to 55 percent in 2018⁶¹ and the inventory of FDA-approved targeted cancer therapies continues to expand. However, there are many biomarkers expressed in cancer that are still not well understood or lack a corresponding targeted therapy. As a result, not all patients with identified genetic alterations or molecular signatures will have an approved targeted therapy available to them. Many, however, may find that their test results qualify them for a clinical trial of an investigational targeted therapy. While targeted therapies were traditionally developed to treat a specific cancer type, increasingly new genomic-based clinical trials do not restrict eligibility based on cancer type or histology.⁶² For example, the Targeted Agent and Profiling Utilization Registry (TAPURTM) Study is a clinical trial with broad eligibility criteria designed for patients with advanced staged cancers and genetic alterations that can be targeted with a study drug.⁶³

evidence of clinical utility or may require utilization review, such as prior authorization.²⁵

Another reason cited for lagging coverage for panel tests is the lack of consensus among clinical guidelines recommending when to use panel tests, with the exception being NSCLC, which has a relatively large number of biomarkers linked to a targeted therapy.²⁴

Coding of Diagnostic Tests

For reimbursement of single-gene and multi-gene panel tests, laboratories must bill payers using the appropriate procedural code. The Current Procedural Terminology (CPT®) is the most frequently used coding standard by diagnostics laboratories in the United States.^{34,35} Historically, providers have billed payers using a series of codes for the multiple technical steps typically involved in a cancer biomarker test, a process known as “**code stacking**.” Stacked codes are independent of gene or disease and make it challenging for payers to tell which test is being performed and for what purpose.³⁵ To accommodate the growth of biomarker testing there have been several updates to coding standards of biomarker tests which have shifted away from stacked codes to more procedural or analyte specific codes (e.g. Genomic Sequencing Procedures).^{34,35} While new codes have enabled more precise coding of molecular tests, this increased level of complexity has created additional considerations for payers and laboratories. Claims can often contain multiple codes and variations of codes for similar tests.³⁴ In the U.S. health care system, which still widely operates on a fee-for-service payment system, code variations and the time required to process them could lead to increased use of prior authorization and administrative costs.³⁴

Provider and Institutional Barriers

Despite evidence pointing to the clinical benefits associated with biomarker testing, routine clinical use does not always follow. Testing rates lag behind guideline recommendations and are, in part, influenced by care setting. For example, community oncology practices, where most cancer patients are treated, were recently documented as testing less than 50 percent of eligible NSCLC patients for EGFR mutations, several years after testing became the standard of care.³⁶ And although there are several FDA-approved targeted therapies for NSCLC, there is underutilization of testing across NSCLC sub-types and use of targeted therapy in community oncology settings.³⁷ Lower rates of multi-gene panel testing have also been observed among patients treated in community settings.^{38,39} A survey of oncologists conducted by the Friends of Cancer Research and Deerfield Institute demonstrated a significant difference in the reported use of panel tests among academic, private, and community practice settings at 59, 33, and 29 percent, respectively.⁴⁰ Lagging testing rates have also been noted in other cancers and in academic settings. Recent data indicate that only 40 percent of patients with metastatic

colorectal cancer treated at academic and community settings received guideline recommended testing between 2013 and 2017.⁴¹ These missed opportunities potentially prevented cancer patients from receiving therapies that could have improved outcomes.

While additional research is needed to fully understand incomplete clinician uptake of guideline-recommended testing, several barriers to uptake have been identified. First, the field of precision medicine continues to quickly evolve, creating a challenge for health care providers to stay up-to-date with the latest clinical developments in testing and treatment. Health care providers must be aware of not only what tests are appropriate and when to test, but also knowledgeable in the interpretation of testing results. Evidence-based clinical treatment guidelines are one tool that aid in this process. Second, diagnosing, staging, and testing of solid tumors requires tissue obtained from biopsies which involve the surgical removal of tissue from the body. Diagnosing and staging of tissue generally precedes biomarker testing and only a limited amount of tissue may be available for testing. Repeat biopsies may be required in order to obtain the necessary tissue for testing. Although the use of NGS panel tests is increasing and requires less tissue, single-gene tests are still widely used.⁴² The evidence base demonstrating the utility of minimally invasive liquid biopsies, which involve analyzing bodily fluids for ctDNA, has been growing and could potentially address problems with tissue insufficiency.⁴³ However, they have yet to be widely adopted by clinical guidelines or payers,^{23,43} and there are currently only two FDA-approved multi-gene liquid biopsy tests.⁸

Finally, while there has been much effort over the last two decades to incentivize the adoption and use of electronic health records (EHR), most modern EHR systems and workflows were not designed with the sophistication required to efficiently process and interpret data associated with the delivery of precision medicine.⁴⁴ Some physicians may not be familiar with and lack confidence in interpreting biomarker test results.^{45,46,47} Clinical decision support tools that are integrated into EHRs and are available at the point of care could promote testing of biomarkers and subsequent selection of targeted therapy. However, systems will need to be regularly updated to keep pace with scientific discoveries.

Patient Education and Awareness

Patients should be empowered with accurate information to actively participate in their health care decisions. The benefits of incorporating precision medicine testing (e.g. biomarker testing) into a cancer patient's care plan highlights the need for increased patient awareness and understanding so that patients can seek appropriate testing. However, confusion related to the various terms used in precision medicine testing has been reported by patients, in part, due to conflicting terminology which can lead to

missed testing opportunities.^{48,49} For example, a working group of patient advocacy organizations and other stakeholders identified 33 terms related to precision medicine testing used in patient education and clinical care across stakeholders, often with different terms used to describe the same test.⁴⁹ Consistent terminology among stakeholders would reduce patient confusion and be a step toward increasing access to appropriate testing.⁴⁹ Finally, genetic counseling can play an important role in empowering patients with information and guidance prior to and after the interpretation of testing results.



Summary

The rapid development of targeted cancer therapies across cancer types, has improved patient survival and quality of life. But many of these advances depend on access to biomarker testing. Barriers to biomarker testing can arise beginning at test development and persist through the interpretation of test results in the clinic. As precision medicine shifts the way health care providers and patients think about cancer treatments, it will be important to identify and address obstacles to appropriate biomarker testing. Addressing these barriers will require buy-in from diverse stakeholders across the health care system.

ACS CAN Recommendations

Patient Considerations

Insurer coverage is important for provider uptake and patient access to cancer biomarker testing. However, coverage of tests differs across the multiple public and private payers in the U.S. health care system.



1. Payers should provide coverage for National Comprehensive Cancer Network (NCCN) guideline-indicated biomarker tests and FDA-cleared or -approved companion and complementary diagnostics as necessary to evaluate patient eligibility for a given targeted cancer therapy.*
 - a. Coverage of biomarker testing should not be arbitrarily constrained to specific cancer stages (e.g. III, IV, metastatic), but rather coverage should follow guideline recommendations and FDA-cleared or -approved uses.
 - b. Payers should ensure that any utilization review practices (e.g. prior authorization) are timely and efficient and do not delay the initiation of biomarker testing after a diagnosis.
 - c. Coverage of biomarker testing should not be restricted to one single occurrence and should allow for retesting after a medically appropriate interval, indication of a change in the genetic makeup of the patient's cancer (e.g. such as acquired resistance), or if the test is designed to monitor disease progression and therefore must be serially administered.
 - d. Payers should provide coverage for multi-gene panel testing as indicated by NCCN guidelines, when it is more efficient, when a single analyte test does not exist, or when tissue availability is too limited for use of multiple single analyte testing.
 - e. Coverage should be provided for tumor-agnostic biomarker tests as medically appropriate.
2. Payers should provide coverage and access to appropriate services for the interpretation of biomarker tests.*
3. Comprehensive biomarker testing provides value beyond therapy selection, and results from testing should be utilized to inform patients of relevant clinical trial opportunities.

Provider and Institutional Considerations

Providers and institutions have a significant impact on which patients receive cancer biomarker testing and consequently whether they receive targeted cancer therapy. Despite evidence pointing to the clinical benefits, testing rates lag behind clinical guidelines and advancements in the field.

1. Biomarker tests should be reliable, valid, and relevant to a patient's cancer diagnosis. This should be realized with a harmonized system of regulatory oversight for all biomarker tests that features tiered requirements based on the risk posed by a given biomarker test.
2. Providers and institutions should be equipped with tools (e.g. clinical decision support), resources (e.g. access to a tumor board), and training for the efficient and sufficient collection and handling of tissue for testing, and for proper test selection, administration, and interpretation.
 - a. Quality measures and accreditation standards should promote adoption and utilization of clinical decision support tools for biomarker testing that incorporate evidence-based clinical guidelines at the point of care to guide testing and treatment decisions.
 - b. High-quality clinical biomarker testing guidelines should adhere to guideline development best practices including appropriate transparency, conflict of interest rules, systematic evidence review, and timely updating.
 - c. Licensing and clinical specialty boards should encourage use of current biomarker testing guidelines through continuing education requirements.

Glossary

Analytical Validity – The ability of a diagnostic test to detect or measure the analyte it is intended to detect or measure.⁵⁶

Biomarker – A biological molecule found in blood, tissues, or other bodily fluids that provides insight into physiological processes, medical conditions, or diseases.⁴ Also known as a *molecular marker*.

Biomarker Testing – The process of evaluating biomarkers for diagnosis, therapeutic selection, prognosis, or disease monitoring. In cancer, biomarker testing is used to detect the presence of specific genetic alterations or molecular signatures within cancerous cells.

Circulating Tumor DNA (ctDNA) – Tumor DNA fragments that circulate in the bloodstream. This DNA is identifiable as coming from tumor tissue, rather than healthy tissue by the presence of specific genetic alterations.

Clinical Treatment Guidelines – A way to formalize the best practices for treating specific diseases and medical conditions. In cancer, they can be thought of as a decision tree that evaluates inputs like tumor stage, biomarkers, previous treatments, etc., to guide treatment toward the most effective therapeutic options.

Clinical Validity – The ability of a diagnostic test to accurately diagnose or predict the risk of a particular clinical outcome⁵⁶ or how well the analyte being analyzed by the test relates to the presence, absence, or risk of a specific disease.

Clinical Utility – The ability of a diagnostic test to provide information about diagnosis, treatment, management, or prevention of a disease that will be helpful to patients and their providers.⁵⁷

Code Stacking – A process in which health claims payer is billed using a series of codes for the multiple technical steps typically involved in a biomarker test.

Companion Diagnostic – A diagnostic test that helps determine benefit or risk from a specific therapy. Also known as a *therapeutic selection test*.

Complementary Diagnostic – A diagnostic test that can support the decision making around the use of a particular therapy, but is not required for a therapy's use.

Diagnostic Biomarker – A type of biomarker used to confirm the presence of a disease or condition of interest, or to identify individuals with a subtype of the disease.⁵

Diagnostic Test – A test used to confirm the presence of a disease or health condition.

FDA-Cleared or -Approved (FDA-Authorized) Diagnostic – A diagnostic test that has been cleared or approved by the U.S. Food and Drug Administration (FDA) after premarket review in which the diagnostic test is reviewed based on risk.

Gene Sequencing – The process of determining the order of DNA bases (e.g. adenine, guanine, cytosine, thymine) in a gene.

Genetic Alteration – A change in the normally occurring DNA sequence in a gene. Genetic alterations can include mutations, rearrangements, or fusions.

Germline Mutations – A genetic mutation that is inherited from one's parents and is present in all cells at birth.

Immunohistochemistry – A laboratory technique that can be used to detect protein biomarkers.

Laboratory-Developed Test (LDT) – A type of in vitro diagnostic test that is designed, manufactured and used within a single laboratory.⁵⁰

Medicare Administrative Contractor (MAC) – A private health care insurer that has been awarded a geographic jurisdiction to process Medicare Part A and Part B medical claims or Durable Medical Equipment claims for Medicare Fee-For-Service beneficiaries.⁵¹

Molecular Signature – A set of characteristics, such as the expression of genes or proteins that indicate whether abnormal cells or tissues are present in a biological sample.⁵²

Monitoring Biomarker – A type of biomarker used in assessing the status of a disease or medical condition or for evidence of exposure to or effect of treatment.⁴

Multi-Analyte with Algorithmic Analysis (MAAA) – A diagnostic test that combines multiple results from two or more tests with other patient information (e.g. age, sex) into an algorithmic analysis which generates a numeric or probabilistic risk score.

Next Generation Sequencing (NGS) – A laboratory processes that allows for sequencing of millions of DNA fragments at a time.

Overall Survival –The length of time from either the date of diagnosis or the start of treatment for a disease, that patients diagnosed with the disease are still alive.⁵³

Panel Test – A type of diagnostic test that measures multiple analytes (ranging from a few to several hundred) in the same test. In oncology, panel tests are often referred to as *tumor profiling* or *comprehensive biomarker testing*.

Precision Medicine – An approach that uses information about a person’s own genes or proteins to prevent, diagnose, or treat disease.¹ It is often synonymous with *personalized* or *genomic medicine*.

Prognostic Biomarker – A biomarker used to identify the likelihood of a clinical event, disease recurrence or progression in patients who have a disease or medical condition of interest.⁴

Prognostic Test – A type of diagnostic test that provides information on the likely clinical outcome of a disease or health condition.

Progression Free Survival – The length of time during and after the treatment of a disease that a patient lives with the disease but it does not get worse.⁵⁴

Sanger Sequencing – A laboratory process involves sequencing single DNA fragments at a time. The earliest method to sequence human DNA, often referred to as “first-generation sequencing.”

Sensitivity – The ability of a medical test to detect a specific disease or condition in people who actually have the disease or condition.⁵⁵

Single Analyte Test – A type of diagnostic test that measures one analyte (e.g. gene or molecular) for analysis.

Somatic Alteration – A genetic alteration that occurs in a specific cell after conception and is limited to only cells originating from that specific cell. Cancer is the result of somatic alterations.

Susceptibility or Risk Biomarker – A biomarker used to identify the potential for developing a disease or medical condition in an individual who does not currently have clinically apparent disease or the medical condition.⁵

Targeted Cancer Therapy – A type of cancer therapy that works by interfering with specific cellular processes involved in the growth, spread, and progression of cancer.

Tissue-Agnostic Targeted Therapy – A type of targeted therapy used to treat cancer types that have the same cancer biomarker regardless of where it occurs in the body (e.g. breast, lung, melanoma).

Therapeutic Selection Biomarker – A type of biomarker used to identify individuals who are more likely to respond to a given medical treatment.⁴ Also known as a *predictive biomarker*.

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