PERSONALIZED MEDICINE
AND BIOMARKERS

Over the past two decades, a growing number of pharmaceutical products have been approved in the United States, signaling a new era of drug development. Many of these new therapies employ the use of biomarkers (Figure 1.3.1) [1]. The FDA defines a biomarker as a characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics can function as biomarkers. A biomarker is not an assessment of how an individual feels, functions, or survives.

The use of biomarkers combined with targeted therapies appears to be a growing trend in a number of clinical areas, further developing the field of “personalized medicine.” The FDA has approved several cancer drugs for use in patients whose tumors have specific genetic characteristics identified with a companion diagnostic test for a specific biomarker (Figure 1.3.2) [2–7]. An example of this is the antibody trastuzumab, which is targeted to patients whose breast cancer tests positive for HER2, formerly a hard-to-treat form of breast cancer. Since approval for its use in the United States in 1998,
trastuzumab has transformed the treatment and improved the prognosis of women testing positive for overexpression of HER2 protein in specific tumors.

In 2015, the FDA approved a new therapy for use in certain cystic fibrosis (CF) patients with a specific genetic mutation. Ivacaftor was approved in 2012 by the FDA for treatment of the underlying cause of CF in patients with certain mutations of the CFTR gene; the gene expression in this case served as a biomarker. Also in 2015, CF patients with two copies of the F508del mutation (the biomarker) in their CFTR gene were able to take lumacaftor/Ivacaftor combination therapy to change the course of the disease. Several medications for the treatment of hepatitis C are now on the market for patients who are infected with a specific genotype of hepatitis C.

Personalized medicine as a concept has been around for many years. Clinicians have long known that patients with similar symptoms may have illnesses with different causes and respond differently to appropriate therapeutics.
What is new, however, are advanced diagnostics, such as genomic or proteomic testing for biomarkers. We are now developing therapeutic agents that are targeted to persons who have a specific genotype or whose disease has specific characteristics that allow a more focused and targeted therapy. Biomarkers are critical to the identification of patients who would benefit from these new highly targeted therapeutic agents.

1.3 • Integrating Personalized Medicine in the Health Care

**HOW DO PAYERS USE BIOMARKERS?**

This section of the chapter reviews how payers use biomarkers and why they are advantageous for payers. Payers want to ensure their members are receiving effective and appropriate care. To accomplish this goal, managed care organizations (MCOs) have set up a number of procedures and controls to avoid overuse and misuse of health care services. In general, this comes under their utilization management (UM) program. UM is a major part of how payers identify high-cost targets, whether a health care service or a pharmaceutical agent or device. Once a payer makes the determination to manage a health care service, the organization may develop a policy that describes the coverage requirements for that service. Medical policies and other UM requirements are regularly communicated to the provider network and are generally reviewed annually. These coverage requirements may be pre-service, concurrent (generally for acute care services), or post-service; when biomarkers are involved, the MCO will specify the test(s) needed to justify insurance coverage.

Prior to determining that it will manage a particular service or therapeutic agent based on the results of a biomarker test, the MCO or health plan will gather sufficient evidence to ascertain that the biomarker test is readily available, accurate, valid, and reliably predicts improved outcomes. In making this determination, the payer is relying on high-quality randomized clinical research studies published in peer-reviewed journals. The MCO will also consider evidence-based clinical guidelines developed by specialty groups or government agencies. Payers may also consider guidance from the FDA, National Institutes of Health (NIH), and Centers for Disease Control and Prevention (CDC).

MCOs and other payers publish coverage criteria detailing circumstances in which a particular service or drug will or will not be covered (generally in a medical policy statement). In many plans, the medical or pharmaceutical policy lays out these coverage criteria. Coverage policies and UM programs can vary from payer to payer. The next section will detail how and why payers use biomarkers to identify their members who are most likely to either benefit or not benefit from a specific health care service or therapeutic agent. Payers/MCOs have an interest in using biomarkers to segment or identify persons in their population who are at risk for a disease. Most payers under specific circumstances will, for example, pay for BRCA testing in certain women who meet defined criteria for BRCA testing to determine whether a patient overexpresses the HER2 protein. If the patient is HER2 positive, the therapeutic antibody trastuzumab can be used to greatly improve outcomes. Prior to trastuzumab therapy, HER2-positive cancers were a difficult-to-treat form of breast cancer. Since its FDA approval, trastuzumab has transformed the treatment and improved the prognosis of women with tumors that overexpress the HER2 protein and thus test positive for the HER2 receptor (Figure 1.3.3) [8].

**WHY ARE BIOMARKERS IMPORTANT TO A PAYER?**

**Patient Selection**

When used effectively, biomarkers can reliably determine which patients will and will not benefit from a particular therapy. The biomarker status guides the HCP to direct treatment to those individuals who can benefit from the therapy; hence, the term “personalized medicine” or “precision medicine.” Even after accounting for the cost of testing, this approach saves in unnecessary treatment costs and spares patients from adverse events, which may occur even in the absence of a therapeutic benefit. There are numerous examples of this approach to therapy resulting from advances in genetic and other advanced molecular testing. An early example was discussed in the beginning of the chapter, describing the use of HER2 protein biomarker testing of breast cancer tissue to determine whether a patient overexpresses the HER2 protein. If the patient is HER2 positive, the therapeutic antibody trastuzumab can be used to greatly improve outcomes. Prior to trastuzumab therapy, HER2-positive cancers were a difficult-to-treat form of breast cancer. Since its FDA approval, trastuzumab has transformed the treatment and improved the prognosis of women with tumors that overexpress the HER2 protein and thus test positive for the HER2 receptor (Figure 1.3.3) [8].

**Assess Disease Risk and Severity**

Biomarkers can be indicators for many clinical aspects of a condition or disease process. Payers will indicate which biomarker requirements are needed to justify insurance coverage for a specific health care service or therapeutic agent. Payers/MCOs have an interest in using biomarkers to segment or identify persons in their population who are at risk for a disease. Most payers under specific circumstances will, for example, pay for BRCA testing in certain women who meet defined criteria for BRCA testing to determine if they carry a specific gene that puts them at high risk for both familial breast and ovarian cancer. Currently, payers, including the Centers for Medicare and Medicaid Services (CMS), restrict BRCA testing to women whose clinical histories indicate that they are more likely to test positive for the BRCA gene.

There are many examples of biomarker use to assess risk for disease. Payers will generally cover such tests if they are widespread and easily accessible, such as testing for LDL-C. For high-cost tests, the payer may have medical policy or prior authorization requirements in place to ensure only people who meet clearly defined criteria will be tested. As mentioned, payers want to make sure that covered medical services are necessary, reliable, and valid and generally benefit the persons being tested.

Predictive biomarkers have been reported in a wide range of conditions such as Alzheimer’s disease, chronic obstructive pulmonary disease, rheumatoid arthritis, cardiovascular disease, and sepsis.
Track Disease Progression

An example of the use of biomarkers from 1991 is the use of tumor necrosis factor-α (TNF-α) or cachectin to determine whether an individual with multiple sclerosis had progressive disease [9].

Predict Events

Biomarkers have been used to predict a wide variety of clinical events such as cardiovascular disease and cancer. BRCA test results can reliably predict who is at very high risk for familial breast and/or ovarian cancer. These tests show only that someone has a high likelihood of developing cancer.

Inform Therapeutics

One of the most promising areas in therapeutics is the use of biomarkers to predict an individual’s response to a therapeutic agent. In 2009, the American Society of Clinical Oncology (ASCO) recommended that patients diagnosed with colon cancer be tested for a mutation of the KRAS gene before being treated with medicines such as cetuximab or panitumumab. In July 2009, the FDA approved labeling changes based on findings that cetuximab and panitumumab are not effective for patients whose KRAS gene has mutated.

Today, numerous therapeutic agents have required companion diagnostic tests to identify patients who may benefit from a specific treatment prior to initiation of therapy. Payers can legitimately deny payment for therapy when such companion diagnostic tests have not been performed prior to the initiation of therapy when required by the FDA.

Prognostic Markers

Biomarker testing can often provide prognostic information. Breast cancer is a good example. Triple-negative breast cancer describes a patient with breast cancer that is negative for all three receptors: estrogen, progesterone, and HER2/NEU. Such patients have a form of breast cancer that is difficult to treat.

Another example in breast cancer is the use of the commercially available biomarker test, Oncotype DX. This test is designed to segment women with newly diagnosed breast cancer of low risk from those who are likely to have a recurrence and thus benefit from chemotherapy.

Diagnostic Markers

Prostate-specific antigen (PSA) testing has long been used as a surrogate marker for prostate cancer risk. While not a definitive test, PSA test results have for decades been used to refer patients for diagnostic biopsy to confirm whether prostate cancer is present.

Dose Selection

Biomarkers are now being used to test for dose selection in the course of drug development to improve treatment of tuberculosis. A study examined the safety, tolerability, and pharmacokinetics of multiple ascending doses of oxazolidinone PNU-100480 in healthy volunteers using biomarkers for safety and efficacy. This randomized, controlled trial showed the agent to be safe at all doses tested, providing a role for biomarkers in accelerating drug development [10].

MEDICAL POLICY APPLICATIONS

Payers develop medical benefit policies based on best available evidence. A policy is intended to inform stakeholders of the details and the circumstances under which a member can receive coverage for a specific benefit. Medical policies are developed when there is nuanced coverage beyond a simple yes
or no, or a limitation to the benefit such as covering 30 physical therapy visits per year. Many medicines have a corresponding medical policy or a pharmaceutical policy detailing coverage. Medications distributed through retail pharmacies generally will have a pharmaceutical policy that helps the retail pharmacy and prescribing provider understand coverage requirements for a specific therapeutic agent. Internal health plan staff responsible for reviewing medications requiring prior authorization (PA) can review the policy before approving or denying coverage for a specific requested drug. Certain medications are paid for under medical benefits. These medicines are generally, but not always, administered in a physician’s office or infusion center, or they may be managed and delivered by a specialty pharmacy. They are generally not available at a retail pharmacy where most prescriptions are obtained. If the requested medication falls under the medical benefit, that policy will outline the specific coverage requirements.

Health plans aim to provide the highest value for their policyholders. They are well aware that biomarkers provide valuable information about the effectiveness and appropriateness of a specific drug. Biomarker results can inform physicians and others about choice of therapeutic agents, including risks and benefits, based on the expected response of an individual.

In general, MCOs and health plans do not cover therapies that are considered. The use of biomarkers that predict positive or negative response with a specific therapeutic agent allows health plans to formulate coverage policy. An experimental drug can also be placed into a medical policy detailing the reasoning and the evidence for noncoverage and describing what lines of business fall under the policy.

It helps to understand that commercial, Medicare, and Medicaid lines of business have different coverage requirements, and the medical policies will call these out, or there may be separate policies for each line of business.

TRENDS IN PAYER BIOMARKER ADOPTION AND MANAGEMENT

Specialized Laboratories for Biomarker Testing and Access

There is increasing pressure to provide cost-effective health care based on “best practice.” Consequently, new biomarkers are likely to be introduced into routine clinical biochemistry departments only if they are supported by strong evidence showing improved patient management and outcomes. Carefully designed audit and cost–benefit studies in relevant patient groups must demonstrate that introducing the biomarker delivers an improved clinical pathway. Good stability of the biomarker in relevant physiological matrices is essential to avoid the need for special processing. Absence of specific timing requirements for sampling and knowledge of the effect of medications that might be used to treat the patients in whom the biomarker will be measured are also highly desirable. Assays must therefore be robust, fulfilling standard requirements for linearity on dilution, precision, and reproducibility, both within- and between-run. Provision of measurements by a limited number of specialized reference laboratories may be most appropriate, especially when a new biomarker is first introduced into routine practice [11].

Successfully taking a biomarker from the research laboratory into the clinical laboratory ideally requires a four-way collaboration involving the research laboratory (which develops the fundamental concept), the diagnostics industry (which turns the concept into a practical reliable tool), the clinical laboratory (which evaluates the tool in real-life practice), and clinicians (who help identify unanswered clinical questions and needs that the measurement of a new biomarker might usefully address; clinicians also provide the carefully characterized clinical specimens necessary for its assessment).

The decision to introduce a new biomarker will clearly be influenced by different reimbursement policies and other logistical arrangements among health care systems. The introduction of a new biomarker into routine clinical practice requires rigorous assessment from three different perspectives: that of the clinician, the laboratory pathologist, and the health care funding organization. An integrated approach to funding the entire patient-care pathway, including additional tests recommended as a part of other initiatives (e.g., Quality Outcome Framework targets in the United Kingdom), is preferred to piecemeal funding of separate functions (e.g., laboratory, pharmacy, radiology), which is sometimes termed “silo budgeting.” However, such an approach is infrequently in place. In the United States, gaining approval and payment rates for new tests can be a limiting factor in determining whether a new test will be performed [12].

Additive Health Care Costs

A survey of approximately 130 oncologists/hematologists and medical oncologists conducted from 2016 to 2017 by H. Jack West, MD, Medical Director, Thoracic Oncology Program, Swedish Cancer Institute, Seattle, Washington [13], found that private health insurance is by far the most common way genomic testing is paid for among cancer patients (85%), followed by research funding (35%) and patient self-pay (29%) (Figure 1.3.4). More than 30% of the oncologists surveyed had clinical concerns with genomic testing, stating that it rarely provides clinically actionable, evidence-based information; more than 60% said that less than a quarter of their patients would benefit from the testing. Eighty-four percent of oncologists also have concerns about insurance coverage of genomic testing.

An average drug on the market today is reported to be effective in only 50% of those who take it [14]. Prescribing medications to those who are unlikely to respond not only unnecessarily inflates our annual $2.5 trillion spending on health care ($1.3 trillion of which is provided by private payers and $378 million is paid for out-of-pocket by patients) [15,16] but also exposes patients to the side effects of medications without the potential therapeutic benefit. Personalized medicine can allow for prediction of nonresponders, thereby avoiding unnecessary exposure to side effects.
from medications predicted to be ineffective. A classic example of a targeted therapy, trastuzumab, is highly effective in the 15%–25% of breast cancers that overexpress the HER2 protein (a cell growth promoter) and is generally not effective against breast tumors without HER2 overexpression. Drugs like erlotinib are effective therapies in those patients whose non-small cell lung cancer carries specific EGFR mutations but not KRAS mutations [17].

Although payers are generally familiar with the concept of selecting drugs based on genetic targets in several therapeutic areas, a hallmark example of this is the anti-thrombotic clopidogrel and the SNPs of CYP2C19, a CYP gene encoding a key enzyme in the metabolic activation of clopidogrel and associated with pharmacokinetic and pharmacodynamic responses to clopidogrel. Pharmacogenomic research of more commonly prescribed drugs such as clopidogrel, [18,19] warfarin, [20] and statins [21] has been stimulated owing to the enhanced value perceived for targeted medicines.

Health Economic Value of Biomarker Use

Health care payers represent stakeholders who can act as gatekeepers to the translation of personalized medicine into routine clinical practice. To date, the slow realization of the promise of personalized medicine has been partly attributable to the lack of clear evidence supporting the clinical utility of genetic and genomic tests—and the lag in development of clinical guidelines for the use and interpretation of tests. These factors, along with a paucity of clear guidance from health care payers and little clinical experience with genomic tests, serve as impediments to timely and consistent reimbursement decisions. The design of alternative strategies for collaborative evidence generation, clinical decision support, and educational initiatives for health care providers, patients, and the payers themselves are critical to achieve the full benefit of personalized medicine in day-to-day health care settings [22].

Payers recognize that the size of the opportunity and potential return on investment both clinically and economically in personalized medicine is tremendous, yet they are hesitant to embrace the use of molecular diagnostics when many tests’ utility is not yet fully proven. Molecular diagnostics are defined as genetic and/or esoteric tests that assay for biomarkers from gene to gene product, including RNA, miRNA, protein, metabolites, antibodies, and all varieties of genomes including human, cancers, and pathogens. Estimates suggest that genetic variation accounts for between 20% and 95% of the variability in individual response to medications [23]. The opportunity to prescribe medications only to those who are most likely to respond, or to avoid life-threatening side effects, will allow physicians to improve care with economic benefits for both patients and payers. Furthermore, although diagnostics represent a relatively modest expense, they inform a huge portion of health care decisions and subsequent expenditures. It has been estimated that diagnostic tests represent less than 5% of health care spending and influence up to 70% of health decision making [24].

Modeling the clinical and economic outcomes of pharmacogenomic interventions suggests that the medical costs potentially avoided by testing 100 patients initiating therapy for which there is an actionable pharmacogenomics test ranges from $6,000 for tests with less common variants such as HLA-B*5701 for abacavir to $50,000 for more common genotypes such as CYP2C19 metabolizer status for clopidogrel (Figure 1.3.5) [25]. At a population level, considering only the medical costs avoided, this represents up to a 200% return on investment for the cost of testing (data presented reflect 17 proprietary unpublished clinical and economic cost-effectiveness models evaluating the potential costs and benefits of pharmacogenomic interventions from a payer’s perspective).

Health care payers primarily view the clinical and health economic benefits of personalized medicine and pharmacogenomics as driven by three potential factors: better prediction of responsiveness to treatment, proactive prevention of drug adverse events, and promotion of adherence to therapy through minimization of undesirable side effects.
REFERENCES


