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Review Article

Advancing Biomarker Testing for Precision Cancer Care

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Abstract

Currently, several steps are involved before a cancer patient can receive a precision targeted 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 can improve survival and quality of life. We need to make sure biomarker testing based precision cancer care can be delivered as fast as possible and as early as possible.

Key words: targeted therapy; biomarker testing; precision cancer care

1.Introduction

Precision medicine uses information about a person's own genes or proteins to prevent, diagnose, treat disease or monitor patient response [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 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 review 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.

2. Fit-For-Purpose Biomarkers in Modern Cancer Management

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. A hallmark of a diagnostic biomarker is the BCR-ABL1 fusion gene (Philadelphia Chromosome) used to help diagnose leukemias [7].

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 de-regulation of normal cellular processes and drives the growth of the cancerous cells. Today, multiple EGFR therapies are available that target this de-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 (CDx) 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 CDx for Herceptin (trastuzumab), a drug used to treat HER2 receptor-positive breast, gastric, and gastroesophageal cancers [8].

Similar to CDx, 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.

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® Test [10] 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.

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 variants 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.

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.

Traditionally, health care providers have treated cancer based on where it developed in the body. However, the approval of tissue-agnostic biomarkers characterizes a shift in how health care providers, payers, and patients will need to consider before 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 tissue-agnostic biomarker testing (Figure 1).

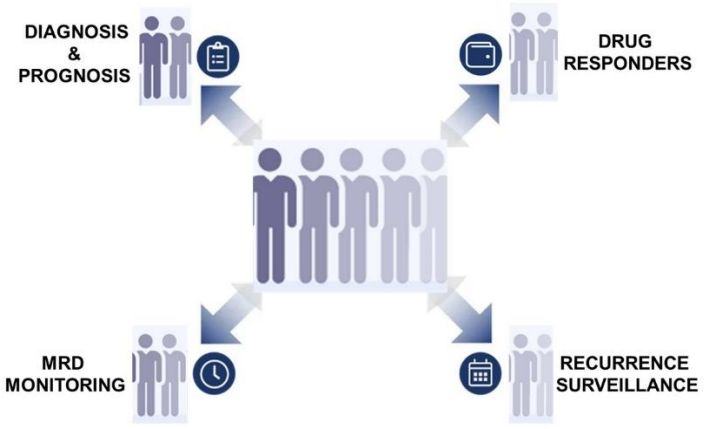

Figure 1: Clinical utility of current cancer biomarkers. A wide array of potential cancer biomarkers is used to diagnose and track disease development and progression or response to therapy. Biomarkers ideally suited to this purpose should be specific for a particular type of cancer and not present in normal tissues or healthy individuals.

1. Biomarker Test Development and Validation

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).

The Medical Device Amendments of 1976 gave FDA statutory authority to regulate diagnostic tests, including biomarker tests, as medical devices. 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.

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) [12]. In addition to creating LDTs, CLIA certification allows laboratories to perform and modify FDA-authorized tests [12]. 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 CDx, without having to seek FDA approval [12]. 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 CDx, which payers review when making coverage determinations. Finally, FDA-authorized CDx are not afforded market exclusivity. The creation of LDT versions of CDx may have the effect of reducing the willingness of device manufacturers to invest the time and resources to develop tests through the FDA pathway.

2. Current Challenges in Biomarker Testing

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. While additional research is needed to fully understand incomplete clinician uptake of guideline-recommended biomarker testing, several challenges 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 biomarker testing and precision 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 [13]. 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 [14]. However, they have yet to be widely adopted by clinical guidelines or payers [14, 15].

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 [16]. Some physicians may not be familiar with and lack confidence in interpreting biomarker test results [17-19]. 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.

3. Conclusions and Future Perspectives

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].

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.

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Conflict of interest

The author declared that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author contributions

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