Shifting to a Biomarker Paradigm Across Cancer Care

Precision medicine has revolutionized multiple facets of care across the cancer trajectory, from prevention through treatment. Sometimes referred to as personalized medicine, precision medicine uses information contained in an individual’s genes, as well as biomarkers and genetic alterations detected in tumor cells, to prevent, diagnose, and treat malignancy. It can provide valuable information about an individual’s risk for developing malignancy, facilitate an accurate diagnosis, inform or revise a plan of treatment, or offer information about prognosis.

**Pathogenesis**

The foundation for personalized medicine starts with an understanding of pathogenesis. Cancer is caused by changes in DNA. Harmful alterations in DNA, referred to as pathogenic variants (formerly known as mutations) can affect how cells grow, divide, and function. Somatic, or acquired, pathogenic variants are the most common cause of cancer and may be induced by a variety of carcinogens, including tobacco use, ultraviolet radiation, chemical exposures, and aging. Somatic pathogenic variants are not found in every cell in the body, and they are not passed from parent to child.

Germline pathogenic variants are far less common and are associated with a hereditary predisposition toward developing cancer. The error occurs in either the egg cell or sperm cell, and it is passed directly at conception from a parent to a child. As the embryo develops into a fetus, the error from the initial egg cell or sperm cell is copied into every cell in the body. Because the pathogenic variant affects reproductive cells, it can be passed from generation to generation.

Each individual tumor has a unique combination of genetic alterations. Some of these changes may be the result of additional errors that occur as cancer cells divide, rather than the initiating event that led to the malignancy. Even within the same tumor and over time, cancer cells may have different and evolving genetic changes (Forman & Sotelo, 2019).

DNA sequencing techniques can identify germline and somatic pathogenic variants by comparing the sequence of DNA to sequencing in normal cells. To test for germline pathogenic variants, typically saliva or blood samples are evaluated. Acquired pathogenic variants, which drive tumor growth, are identified with biomarker testing of the tumor. Because new pathogenic variants can develop, repeat tumor sample testing may be warranted to confirm pathogenic variants. As an alternative to tumor specimen biopsies, liquid (blood product) biopsies may be used, particularly when tissue biopsies are not feasible. Liquid biopsies detect alterations in circulating tumor DNA, or small fragments of DNA released by malignant lesions.

**Personalized Medicine and Oncology Care**

Personalized medicine is not new in cancer care. In 1977, the U.S. Food and Drug Administration (FDA) approved tamoxifen as an adjuvant therapy for postmenopausal women with estrogen-driven breast cancer (Lukong, 2017). More than 40 years later, tamoxifen is still a personalized treatment used in all stages of estrogen receptor-positive breast cancers. It is an example of an early biomarker-driven treatment.

In 1998, trastuzumab and an immunohistochemistry assay for HER2 expression received approval by the FDA as a combined diagnostic drug tool (a biomarker assay that determines if a specific therapy will be effective, which must be used to prescribe the drug) to select treatment in breast cancer (Lukong, 2017). Tumors with HER2 expression can now be treated with trastuzumab, pertuzumab, lapatinib, and neratinib (National Comprehensive Cancer Network, 2020).

In 2004, Genomic Health released the Oncotype DX® Breast Cancer Assay to help guide decisions on whether the addition of chemotherapy is beneficial in women with early-stage breast cancer (Lukong, 2017). This assay analyzes 21 genes in a breast tumor with reverse transcription polymerase chain reaction to predict chemotherapy benefit, as well as the probability of recurrence and survival within 10 years of diagnosis. This is an example of a predictive biomarker; it helps identify individuals who may benefit—or not benefit—from specific treatments. The Oncotype DX Breast Cancer Assay also serves as a prognostic biomarker, identifying the likelihood of a clinical event, such as disease recurrence or progression.

As of November 2020, there are more than 70 FDA-approved targeted agents for the treatment of solid and hematologic malignancies based on biomarkers detected in the tumor (Abramson, 2018). The number of agents will continue to grow.

There is an emerging convergence of germline testing and tumor testing. For example, the relevance of germline BRCA1/2 pathogenic variants drives decisions about cancer prevention and early detection, including the possibility of risk-reducing surgery in individuals at an elevated risk for developing cancer. Germline and acquired pathogenic variants also provide insight into the efficacy of poly(ADP-ribose) polymerase inhibitor therapy in patients with breast, ovarian,