The Future of Precision Medicine in Oncology

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KEYWORDS

• Liquid biopsy • Targeted therapy • Circulating tumor cell (CTC)
• Cell-free nucleic acid (cfNA) • Exosomes • Extracellular vesicle (EV)

KEY POINTS

- Precision medicine in oncology is focused on identifying therapies that are based on genetic characterization of a patient's tumor.
- One of the newest additions to the precision medicine arsenal is the liquid biopsy, which is based on circulating tumor cells (CTCs), cell-free nucleic acid (cfNA), and exosomes.
- Liquid biopsies allow longitudinal information regarding a patient's tumoral genotype to be obtained through peripheral blood draws and are less invasive than traditional tissue biopsies.

NEED FOR PRECISION MEDICINE IN ONCOLOGY

Precision medicine in oncology is focused on identifying which therapies will be most effective for each patient based on genetic characterization of their cancer. Traditional chemotherapy is cytotoxic and destroys all cells that are rapidly dividing. The foundation of precision medicine is targeted therapies, first developed in the late 1990s. Targeted therapies inhibit specific molecules involved in tumor growth and dissemination of cancer cells. Studies have also been performed to discover targets that predict effectiveness in radiation therapy. The proportion of clinical trials requiring a genetic alteration for enrollment has increased dramatically over the past several years, and many studies have demonstrated benefit of targeted therapies over cytotoxic therapies in both progression-free survival (PFS) and overall survival (OS).[1,2]

Precision medicine requires an understanding of the vast heterogeneity and complexity of tumors as well as the processes that drive heterogeneity. Mechanisms of tumoral heterogeneity acquisition include somatic mutations, C > T transitions at CpG sites, activity of apolipoprotein B mRNA editing enzyme, therapy, chromothripsis,

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and whole-genome doublings.[3] The result of these processes is a diverse tumor that can harbor many different subclonal populations. Currently, targeted therapies are often effective against only a subclonal population of cells; therefore, other methods that can better assess heterogeneity are needed. This review discusses roles that biomarkers serve, including predictive, prognostic, pharmacodynamic, and diagnostic purposes. The discussion includes targeted therapies already in use for many cancers as well as biomarkers in development. Special attention is paid to the rise of the use of liquid biopsies in the field of precision medicine in oncology, including CTCs, circulating cfNA, and extracellular vesicles (EVs).

TYPES OF BIOMARKERS: DIAGNOSTIC, PREDICTIVE, PROGNOSTIC, AND PHARMACODYNAMIC

"A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathologic processes, or biological responses to a therapeutic intervention is the definition given by the Biomarkers Working Group."[4] This biomarker should serve as a sign of a normal or abnormal process or of a condition or disease.[5] The Food and Drug Administration (FDA) defines biomarkers into 4 general categories, mainly related to uses in therapy development. Several biomarkers can fall within multiple categories, because the surrogate endpoint can vary (**Fig. 1**).

1. Diagnostic biomarker: categorizes patients by presence or absence of a specific physiologic or pathophysiological state or disease
2. Prognostic biomarker: indicates degree of risk for disease occurrence or progression, distinguishing "good" and "poor" outcomes
3. Predictive biomarker: categorizes patients by the likelihood of response to a particular beneficial or harmful therapy

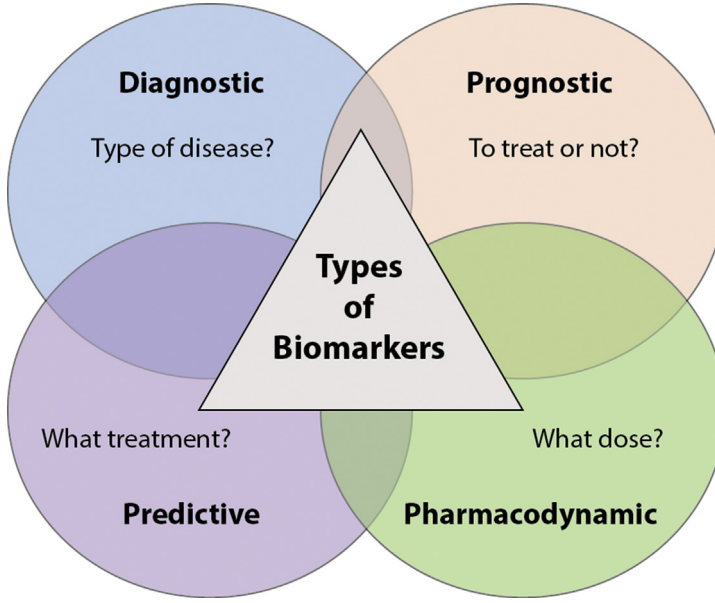

Fig. 1. Types of biomarkers.