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Validation: A Critical Step in Bringing Biomarkers to Clinical Fruition

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Abstract

Screening is vital to reducing morbidity and mortality due to cancer. A primary cause of poor survival is that many cancers are detected late and often after they have metastasized to distant sites. Therapies, therefore, become challenging for late-stage disease and are not successful for nearly all cancer types. The mortality rates from cancers where screening tools are available are lower than from cancers for which no viable screening tools exist. Even for cancers where screening tools currently exist, there is room for improvement, either in the accuracy of the tests or in increasing widespread use of screening by making the tests less invasive. For instance, despite widely available screening methods that can detect early-stage colon cancer or its precursors, only approximately 40% of newly diagnosed colon cancers are localized. It is a challenge to develop screening tests that are not only highly sensitive, but also highly specific, to avoid putting patients through unnecessary biopsies and treatment. Biomarkers have great potential to improve the existing diagnostic accuracies of screening modalities and substitute invasive screening methods with non-invasive methodologies utilizing bodily fluids such as plasma, serum, saliva, urine, etc. Biomarkers are defined by the NIH as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention." In this commentary, we discuss important measures that could be taken to increase the chances of bringing biomarkers to clinical fruition.

Biomarkers for Cancer Diagnostics

Thousands of research articles are published every year raising expectations that effective biomarker-based diagnostics will rapidly be realized. However, much of the literature includes studies that were conducted without appropriate rigor in study design and population statistics. In reality, only a handful of biomarkers have been approved by the Food and Drug Administration (FDA) to date. It is therefore important to have an organized effort to systematically assess the reported biomarkers and select the truly promising ones to undergo rigorous validation and translate into biomarkers with clearly defined clinical utilities.

In 2000, the National Cancer Institute's (NCI) Division of Cancer Prevention developed the Early Detection Research Network (EDRN), an investigator-driven network designed to conduct translational research for the identification of biomarkers, both for the early detection of cancer and for cancer risk. The EDRN focuses on the goal of developing validated biomarkers ready for large-scale clinical testing and ultimately clinical application. A consortium of more than 300 investigators from across the United States and abroad are working together to bring biomarkers to clinical fruition. These scientists from private sectors and academic institutions represent diverse disciplines, including genomics, proteomics, metabolomics, bioinformatics and public health.

Biomarkers with both high sensitivity and specificity are desired for accurate diagnosis of disease. The sensitivity of a clinical test refers to the fraction of individuals with a disease who test positive for the disease. The specificity of a clinical test is the fraction of individuals without the disease who test negative for the disease. No medical tests are 100% sensitive or specific, and some people with or without the disease will not be identified correctly. Clinicians are also concerned with a test's positive predictive value (PPV) and negative predictive value (NPV). PPV is how likely it is for test-positive individuals to have the disease, and NPV is how likely it is for test-negative individuals to not have the disease. PPV and NPV depend on the prevalence of the disease in the population of interest. If a test has a high NPV, a large fraction of patients incorrectly diagnosed as having cancer and unnecessarily undergo invasive testing or treatment.

The EDRN has adopted a series of validation benchmarks to effectively compare one biomarker candidate/technology with another. This helps the field to avoid numerous competing claims of being