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Prostate Cancer Biomarkers in Context

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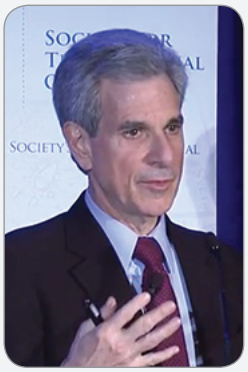
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Introduction

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic intervention. Biomarkers can be clinical, laboratory, molecular, or something else.

Rules Of Biomarker Development

The development of biomarkers follows a structured regulatory pathway: context of use, method validation, clinical validation, and clinical utility. Within the United States regulatory framework drugs are approved for indications, but biomarkers are developed for a context of use. The contexts of use for which biomarkers can inform a medical decision include pre- and post-intervention. In the pre-intervention setting, biomarkers can be used to assess the degree of risk for disease occurrence or progression, to provide information about the natural history of disease in the absence of therapy, and to identify subgroups of patients who differ in the benefit they receive from a particular form of therapy or the likelihood of response to a specific therapy. Post-intervention, biomarkers can confirm that a biologic response has occurred after a therapeutic intervention (the response may or may not reflect a "clinical benefit") or as a surrogate for clinical efficacy.

Analytical validation is the process of assessing the assay and its measurement performance characteristics and determining the range of conditions under which the assay will give reproducible and accurate data. As an example, it was discovered that Decadron could change the uptake in the glucose tracer used in fluorinated dihydrotestosterone (FDG) positron emission tomography (PET) scans. Additionally, clinicians need to understand how to collect specimens, how to store and ship specimens, and how to interpret and use the test results

Clinical validation is the evidentiary process of linking a biomarker with biological processes and clinical endpoints. This is analogous to the phase I, phase II, and phase III trials that are done with drugs. The goal is to provide proof that the biomarker result will mean something in terms of patient treatment and care.

The final goal is establishing clinical utility by showing that using the result of the test to change management or to guide therapy improves the outcome—the risk-benefit ratio to the patient in relation to not having performed the test. This aspect of development is grossly under-studied in clinical trials; showing that there is significance between the result with or without the biomarker does not mean that it has utility. The patient wants to know what the biomarker tells them about their disease; the physician wants to know why the test should be ordered in preference to a different test and how the results will help with patient management; the investigators want to know if the test will streamline research, while sponsors want to know if the test will accelerate drug development. Regulators will ask if the biomarker and assay should be cleared or given an approval, and insurers or third-party payers want justification for paying for the test.

Once a biomarker is qualified, it can be used by anyone in a regulatory submission without filing the biomarker result itself.

Biomarker Applications

Biomarkers are currently being used in the setting of androgen-targeted therapies to confirm a drug's mechanism of action, to establish the optimal drug dose, to generate evidence toward qualification of a surrogate for survival, and for predictive purposes.

FDG-PET scan was used to establish proof of mechanism (block androgen uptake) [1–3], and the optimal dose of the androgen-targeted therapies enzalutamide and ARN-509 [4]. With respect to androgen-targeted therapies, an EpCAM-based immunomagnetic selection process [5] is being used to determine if circulating tumor cells are a marker of treatment effect; they are being studied within a number of different drug development programs, including abiraterone, enzalutamide, arterenol, ipilimumab, and cabozantinib.

The abiraterone results have shown that circulating tumor cells (CTCs) combined with lactate dehydrogenase (LDH) can be used to stratify patients into high, intermediate, and low-risk groups [6].

While the EpCAM platform captures individual CTCs, the EPIC platform can isolate multiple cell types within the blood. Using this method, researchers are able to identify different cell types and variant protein levels. A large proportion of cytokeratin-negative cells appear particularly in later stage disease. It is believed that these cells have undergone an epithelial mesenchymal transition, which may be part of the process of metastasis. The ability to identify cells that undergo apoptosis affords an opportunity to look at changes in cell death over time as a pharmacodynamic measure. The EPIC platform is being used to assess patients who have primary resistance to abiraterone, as well as the so-called "drifter patients" who have been on treatment for a period of time and whose disease is later progressing. The platform is also being used to evaluate both pre-treatment and on-treatment patients to identify biomarkers that could be prognostic for treatment response.

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