Guidelines for the Design of Clinical Studies for the Development and Validation of Therapeutically Relevant Biomarkers and Biomarker-Based Classification Systems

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SUMMARY

Standards for the development of therapeutically relevant biomarkers and biomarker-based classification systems are lacking. The literature of prognostic marker studies for breast cancer is inconsistent, and few such markers have been adopted for widespread use in clinical practice. This is problematic, as many patients are overtreated and many others are treated ineffectively. The deficiencies in clinical development of biomarkers may become more severe as DNA
microarrays and proteomic technologies provide many new candidate markers and therapeutics become more molecularly targeted. In this chapter we address some common problems with developmental marker studies and provide recommendations for the design of clinical studies for the development and validation of robust, reproducible, and therapeutically relevant biomarkers and biomarker-based classification systems. The design of validation studies is addressed for (1) identifying node-negative breast cancer patients who do not require systemic chemotherapy; (2) identifying node-positive breast cancer patients who do not benefit from standard chemotherapy; and (3) identifying node-positive breast cancer patients who benefit from a new molecularly targeted therapeutic.

**Key Words:** Biomarkers; microarrays; classification systems; clinical trial design.

1. **INTRODUCTION**

Breast cancer is a heterogeneous set of diseases. Although substantial progress has been made in the treatment of breast cancer, many patients are overtreated and many undergo intensive chemotherapy with little apparent benefit. The literature on prognostic factors in breast cancer, although voluminous, is inconsistent (1). The process of how to develop biomarkers that are robust, reproducibly measured, and therapeutically effective has not been well established. Although many prognostic factors have been studied, treatment selection has remained based primarily on the traditional components of Tumor–Node–Metastasis (TNM) stage and hormone receptor levels. This discrepancy between an inconsistent research literature and clinical practice will become even more problematic as DNA microarray and proteomic technologies provide new markers and therapeutics become more molecularly targeted. The objectives of this chapter are to provide information that facilitates the development of biomarkers for selection of the best treatment for each patient. We use the term biomarker to include predictive classification systems based on protein or RNA transcript profiles measured using technology such as DNA microarrays.

2. **PITFALLS IN DEVELOPMENTAL STUDIES**

Most biomarkers are developed using archived tumor specimens, and many of the problems that exist in the marker literature derive from the retrospective nature of these studies. Clinical drug trials are generally prospective, with patient selection criteria, primary end point, hypotheses, and analysis plan specified in advance in a written protocol. The consumers of clinical trial reports have been educated to be skeptical of data dredging to