Key Words: Biomarkers; technologies; development.

1. INTRODUCTION

The field of tumor markers is enigmatic. On the one hand, the explosion of technology in medicine has provided an enormous number of complex tools that might be used to screen for, diagnose, or prevent a newly diagnosed cancer and/or its metastases. Indeed, the preceding chapters have highlighted remarkable progress in these technologies, and potential areas in which they might be useful. On the other hand, very few markers have actually been accepted for routine clinical use in breast cancer. The American Society of Clinical Oncology Tumor Marker Expert Guidelines Panel has issued three sets of guidelines since its inception in 1996. In the initial set of guidelines, the use of estrogen and progesterone receptors (ERs, PgRs) to select patients for hormone therapy and the use of circulating CA15-3 and/or carcinoembryonic antigen (CEA) to monitor selected patients with...
metastatic disease were the only recommended markers (1). In subsequent updates, the Panel recommended routine measurement of HER2 in cancer tissue to select trastuzumab for patients with metastatic disease (2,3). None of the other markers that have been reported and proposed for breast cancer was felt to be sufficiently validated for routine use by the Panel. Similar recommendations have been made by the College of American Pathologists (4).

Why are these guidelines so conservative? There are several answers to this question, and each of these questions should serve as the basis for future studies (5).

1. A marker is helpful only if it separates an entire population into two different groups whose outcome is likely to be so different that one group might be treated differently than another. Both ER and HER2 are classic examples of this category. Patients with ER-negative tumors appear very unlikely to benefit from hormone therapy (6), and, likewise, it appears that patients with HER2-low or -negative cancers are very unlikely to benefit from trastuzumab (5,7).

Therefore, future studies should be focused on identifying markers with sufficient strength that outcomes of patients who are “positive” (by whatever criteria used) have sufficiently different outcomes that a clinician would treat them differently than those who are “negative.” It is certainly possible that selected, single-gene or single-protein markers might fall into this category. For example, data from Europe support the notion that patients whose tumors do not express urokinase plasminogen activator (uPA) and the plasminogen activator inhibitor 1 (PAI-1) proteins have a sufficiently favorable prognosis that the benefits from chemotherapy would be so low that they might forego this toxic form of therapy (8,9).

The new technologies that permit high-throughput analysis may well identify such a marker. These technologies have two promises: new gene or protein identification and pattern recognition. Currently, the latter has achieved the most notoriety. High-profile publications and presentations have suggested that selected combinations of multiplex gene expressions are associated with very good or poor prognosis (10–12). However, although promising, these observations require validation in prospective, properly designed clinical trials.

Proteomics also offers great promise in identifying specific patterns that might be helpful in the clinic (13,14). However, this field is in its infancy, with many methods and techniques, and at this writing there have been few if any studies that suggest any clinical utility for proteomic pattern recognition in breast cancer.

The use of high-throughput technologies also provides the opportunity to identify new, previously unrecognized genes and their products that might be of value. However, so far, none has been recognized that appear to be of clinical value.