CHAPTER 5
MOLECULAR MARKERS IN BREAST CANCER
Current Practice and Future Possibilities

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1. INTRODUCTION

What are we actually speaking of when we use the term “marker”? Practicing pathologists and oncologists have applied the concept for many years without necessarily giving deep thought to what they were doing. Markers are features (of tumors, in the context we are using) that predict future behavior. In fact, the whole exercise of histopathology could arguably be thought of as interpretation of “markers.” Traditionally, the features that proved most useful were tumor stage and grade. As useful as these have been there was always an element of stock market disclaimer to them: “Past performance does not necessarily predict future results.” The effort to identify important features of tumors has moved inexorably to attempts to identify molecular features of tumors or biomarkers. Ideally, biomarkers would impact oncology in five main areas: cancer screening, diagnosis, tumor classification, prognosis, and predicting therapeutic response.

In breast cancer, stage and grade are statistically successful at predicting the outcome of a population of cancer sufferers, but they lack the ability to aid the therapeutic decision-making process for individuals. For example, a critical question that defies the application of stage and grade is whether a stage I breast cancer will recur and the patient should therefore receive additional therapy at the time of diagnosis. The 1980 National Cancer Institute consensus report recommended therapy for late-stage breast cancer but could find no convincing evidence that women with early-stage tumors benefited from adjuvant therapy. The only useful marker identified beside stage and grade was hormone receptor status. The 2000 consensus report recommended that most women with early-stage tumors should receive adjuvant therapy, but as before the only markers added to stage and grade were hormone receptors. cerbB2, p53, tumor angiogenesis and vascular

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invasion were mentioned as possible important markers but were not yet considered sufficiently validated to direct patient management.²

Despite this relatively disappointing history of biomarkers, there has been renewed interest in them for two major reasons. First, high-throughput methods in biology allow the simultaneous evaluation of thousands of parameters. This raises the possibility that large panels of markers will be sufficiently sensitive and specific to allow prediction of prognosis in individual patients. Second, pharmacology and pharmaceutical chemistry are identifying molecular targets for therapy. These therapies will only succeed if the target is present, thus driving the industry to develop methods to evaluate tumors for the presence or absence of specific molecular features, that is, amplified c-Kit in gastrointestinal stromal tumors.

2. POTENTIAL USES OF BIOMARKERS

2.1 Screening

The ultimate goal of cancer screening is to inexpensively identify tumors early enough in their histogenesis that they can be extirpated without affecting the host. To date only the PAP smear has served as a proven screening test. Serum PSA and mammography have their advocates but controversy surrounds them. Of these few tests only PSA fits into the biomarker universe. More recently, the use of mass spectrometry of serum has successfully identified ovarian cancer sufferers; however, this there are problems of reproducibility and cost that are likely to restrict this as a screening modality. Ultimately, the species identified by mass spectrometry may be assayed in a more cost-effective manner, allowing cost-effective screening.

2.2 Diagnosis

Essentially, diagnostic markers are nonexistent. B-cell clonality comes close as a diagnostic marker of lymphoma, but clonal populations are identified in benign processes. Again, mass spectrometry of serum proteins is touted as a potential diagnostic technique, but it is far from a routine clinical application.

2.3 Classification

This is the one area where molecular signatures commonly impact pathologic diagnosis and ultimately treatment. Virtually all of the currently available immunohistochemical stains play a role in the classification of tumors. Crude classifications are derived from stains such as broad-spectrum keratin, S-100, and leukocyte common antigen, whereas finer subdivisions are made with antibodies to antigens such as prostate-specific antigen and keratin subtypes.

2.4 Prognosis/Therapy

Prognostic markers are of relatively little use unless they can be utilized as determinants of therapeutic action. In breast cancer the two markers currently utilized are the estrogen receptor and the cerbB2 receptor. The expression of these two molecules has specific therapeutic consequences in early- and late-stage breast cancers. Other markers