Emerging Biomarkers and New Understanding of Traditional Markers in Personalized Therapy for Breast Cancer
Mitch Dowsett\textsuperscript{1,2} and Anita K. Dunbier\textsuperscript{1,2}

Abstract

The era of personalized medicine is likely to see an escalation in the use of biomarkers to ensure breast cancer patients receive optimal treatment. A combination of prognostic and predictive biomarkers should enable better quantification of the residual risk faced by patients and indicate the potential value of additional treatment. Established biomarkers such as estrogen receptor and progesterone receptor already play a significant role in the selection of patients for endocrine therapy. Human epidermal growth factor receptor 2 (HER2) is recognized as a strong predictor of response to trastuzumab whereas, more recently, the role of estrogen receptor and HER2 as negative and positive indicators for chemotherapy has also been explored. Ki67 has traditionally been recognized as a modest prognostic factor, but recent neoadjuvant studies suggest that on-treatment measurement may be a more effective predictor of treatment efficacy for both endocrine treatment and chemotherapy. The last decade has seen the emergence of numerous multigene expression profiles that aim to outdo traditional predictive and prognostic factors. The Oncotype DX assay and the MammaPrint profile are currently undergoing prospective clinical trials to clearly define their role. Other gene expression-based assays also show potential but are yet to be tested clinically. Rigorous comparison of these emerging markers with current treatment selection criteria will be required to determine whether they offer significant benefit to justify their use.

The last 20 years have seen a substantial decline in breast cancer mortality, and a major contributor to this is the delivery of adjuvant medical therapy (1, 2). It is important, however, that decisions are made that minimize overtreatment, undertreatment, or incorrect treatment. Improved understanding and application of traditional biomarkers and the identification of new markers is increasingly providing insight into who should receive cancer therapy and what therapy they should receive, ultimately avoiding suboptimal treatment.

The postgenome era has seen a deluge of reports claiming to identify factors or profiles that predict response to therapeutic agents or provide prognostic information. Only a small fraction has been validated to Level of Evidence I or II according to the Tumor Marker Utility Grading System endorsed by the American Society of Clinical Oncology (3, 4). Nonetheless, a subset of new markers shows substantial promise for future use. In addition, the identification and development of these markers has led to insights into their biology as well as that of existing tumor markers. Here, we review developments in the understanding of established clinical markers and examine some prominent emerging markers. We focus on characteristics of the tumor; other chapters in this issue address aspects of germ-line genetic variability that may affect clinicopathologic presentation of tumors and/or their response to therapy (5, 6). The markers discussed are summarized in Table 1.

Prognosis or Prediction?

The relative importance of prognostic and predictive factors has been debated for many years. Many factors show mixed prognostic and predictive associations that vary according to the treatment given. For example and as discussed below, markers of proliferation, such as Ki67, show strong prognostic effects and are also predictive of greater response to most chemotherapies but are not significantly predictive of benefit from endocrine therapy. More recently it has become increasingly accepted that the combination of the two parameters to define prognosis on a particular treatment may be of substantial value because this may allow the definition of residual risk and thereby indicate the potential value or not of additional treatment. This has been most notable in determining which estrogen receptor-positive, node-negative patients treated with endocrine therapy merit chemotherapy as well. Some traditional and a number of the newer markers or marker sets address this issue.

Traditional Biomarkers

A small number of single biomarkers has been used for several years in various aspects of managing breast cancer, including estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2). Their study in new...
settings and/or alongside new therapies has extended their applications. The biological importance of these established markers has been reinforced over the last decade by the results from genomic classification in which the presence or absence of these markers identifies the three main groups (7): luminal (estrogen receptor positive), HER2-like (mainly estrogen receptor negative and HER2 positive), and basal-like (mainly estrogen receptor negative, progesterone receptor negative, and HER2 negative), which approximates the so-called triple-negative group of breast cancer as described by Schneider et al. in this issue (8). The development of such different molecular groups according to estrogen receptor status may be determined at least partly by the apparent preferential emergence of estrogen receptor–positive and estrogen receptor–negative tumors in women with differing genetic susceptibility (5).

**Estrogen receptor.** Estrogen receptor α is arguably the most clinically important biological factor in all oncology. As indicated above, the major molecular features of breast cancer segregate differentially between estrogen receptor–positive and estrogen receptor–negative tumors. However, the importance of estrogen receptor as a marker stems more from estrogenic ligands, predominantly estradiol, being the most important mitogens for estrogen receptor–positive breast cancer, such that the biomarker in this instance is the direct target of the mainstream endocrine therapies. Thus, estrogen receptor expression is a powerful positive predictor for antiestrogen therapy: overview analysis confirms that patients with estrogen receptor–negative tumors overall show no significant gain from 5 years of treatment with tamoxifen (2), although there is some evidence suggesting that there may be benefit in the small group of progesterone receptor–positive, estrogen receptor–negative tumors (9).

Although the presence or absence of estrogen receptor is widely used to guide therapy, less attention has been paid to the quantitative aspects of expression. McGuire and colleagues observed 30 years ago that the response of metastatic disease to endocrine treatment was directly related to the extent of estrogen receptor expression (10). The Oxford overview analysis has extended this to primary disease showing a greater proportional reduction in recurrence rate with tamoxifen treatment in high versus low estrogen receptor–positive tumors (11). Paik et al. showed this in the NSABP B14 trial using both ligand-binding assay and mRNA analysis of estrogen receptor (12). The limited use of such quantitative information on estrogen receptor is largely ascribable to the poor dynamic

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**Table 1. Summary of traditional and emerging markers discussed in this review**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Description</th>
<th>Reference</th>
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<tbody>
<tr>
<td><strong>Traditional markers</strong></td>
<td></td>
<td></td>
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<tr>
<td>Estrogen receptor</td>
<td>Quantitative predictor of response to hormonal therapy</td>
<td>(11, 12)</td>
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<tr>
<td>Progesterone receptor</td>
<td>Prognostic in ER+ tumors</td>
<td>(9, 17)</td>
</tr>
<tr>
<td>HER2</td>
<td>Predictor of response to trastuzumab</td>
<td>(19, 20)</td>
</tr>
<tr>
<td></td>
<td>Probable predictor of response to lapatinib, HKI-272, and pertuzumab</td>
<td>(32)</td>
</tr>
<tr>
<td></td>
<td>Possible predictor of response to doxorubicin</td>
<td>(26, 27)</td>
</tr>
<tr>
<td></td>
<td>Possible predictor of response to paclitaxel</td>
<td>(28)</td>
</tr>
<tr>
<td>Ki67</td>
<td>Baseline measurements prognostic</td>
<td>(35)</td>
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<tr>
<td></td>
<td>Baseline measurements slightly predictive of response to chemotherapy</td>
<td>(36–38)</td>
</tr>
<tr>
<td></td>
<td>On-treatment values predictive of recurrence-free (residual risk) survival on aromatase inhibitors and chemotherapy</td>
<td>(45, 46)</td>
</tr>
<tr>
<td><strong>Emerging markers</strong></td>
<td></td>
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</tr>
<tr>
<td>Oncotype DX</td>
<td>Prognostic for recurrence, overall survival in node-negative ER+</td>
<td>(47, 48)</td>
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<tr>
<td></td>
<td>Predictive of chemotherapy benefit in node-negative ER+</td>
<td>(49)</td>
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<tr>
<td>MammaPrint</td>
<td>Prognostic for risk of relapse in all node-negative patients</td>
<td>(51, 52)</td>
</tr>
<tr>
<td>Breast cancer gene expression ratio</td>
<td>Prognostic for disease-free survival in node-negative, ER+, tamoxifen-treated patients</td>
<td>(54–56)</td>
</tr>
<tr>
<td>Rotterdam signature/76 gene signature</td>
<td>Index associated with time to distant metastasis</td>
<td>(57, 58)</td>
</tr>
<tr>
<td>Stroma-derived prognostic predictor</td>
<td>Prognostic for risk of distant recurrence in all node-negative patients</td>
<td>(59)</td>
</tr>
<tr>
<td>Anthracycline and taxane sensitivity signatures</td>
<td>Prognostic for risk of distant recurrence in all patients</td>
<td>(61)</td>
</tr>
<tr>
<td>uPA/PAI-1</td>
<td>Predictive of anthracycline and taxane sensitivity</td>
<td>(62)</td>
</tr>
<tr>
<td>Topoisomerase IIa</td>
<td>Prognostic for risk of distant recurrence in node-negative patients</td>
<td>(63–65)</td>
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<tr>
<td></td>
<td>Possibly predictive of response to anthracyclines</td>
<td>(67)</td>
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Abbreviation: ER, estrogen receptor.
range with immunohistochemical methods for estrogen receptor determination.

More recently there has been substantial interest in determining whether there is differential benefit from aromatase inhibitors versus tamoxifen in different subgroups of breast cancer. However, both the ATAC (Anastrozole, Tamoxifen, Alone or in Combination; ref. 13) and BIG 1-98 (letrozole versus tamoxifen; ref. 14) trials found that estrogen receptor level did not seem to influence comparative benefit of tamoxifen versus aromatase inhibitor.

The absence of estrogen receptor has recently been observed to indicate a good response to chemotherapy. This is particularly striking in the neoadjuvant setting where pathologic complete responses of 21% to 33% are seen in estrogen receptor–negative tumors and only 7% to 8% in estrogen receptor–positive tumors (15, 16). This seems to be partly but not completely explained by the higher proliferation rate in estrogen receptor–negative tumors.

**Progesterone receptor.** Expression of the progesterone receptor is strongly dependent on estrogen and, as expected, is rarely seen in estrogen receptor–negative tumors. Metastatic disease that expresses both estrogen receptor and progesterone receptor responds better to antiestrogen therapy than that which is estrogen receptor positive but progesterone receptor negative (17). In the adjuvant setting, however, tamoxifen versus control trials indicate that progesterone receptor expression is strongly prognostic with little predictive value (9). Thus, although progesterone receptor “poor” patients have worse outcomes than progesterone receptor–positive patients on tamoxifen, the relative benefit from tamoxifen is similar in both subgroups (2, 9).

The data in relation to progesterone receptor and aromatase inhibitors are somewhat less clear. A hypothesis-generating report from the ATAC trial suggested that progesterone receptor–negative patients derived substantially greater benefit than progesterone receptor–positive patients from anastrozole than from tamoxifen (18), but central analysis of a subset of trial patients failed to confirm this (13). The BIG 1-98 trial also found that the benefit of letrozole over tamoxifen seen in the overall trial population did not vary according to progesterone receptor status (14); this is the most direct test currently possible of the original hypothesis-generating study.

However, the strong relationship between progesterone receptor level and prognosis on endocrine therapy was clearly revealed from these adjuvant trials. This was particularly apparent in the ATAC study (13), where recurrence after 5 years of anastrozole-treated patients in the lowest quartile of progesterone receptor levels was 14% compared with <4% for those in the highest quartile.

**HER2.** Although HER2 was initially identified as a prognostic marker, the clinical development of trastuzumab has transformed the application of this biomarker (19, 20). Overexpression and amplification of HER2 in 15% to 20% of breast cancers is a strong predictor of benefit from treatment with trastuzumab, a monoclonal antibody against HER2 (20). To show that adjuvant treatment of patients with HER2-positive primary breast cancer improves overall survival (21, 22) requires all breast cancer patients to be tested for this marker. The importance of accurate testing for this marker to ensure appropriate application of trastuzumab has led to the creation of the American Society of Clinical Oncology/College of American Pathologists guidelines on methodology for immunohistochemistry and *in situ* hybridization techniques for establishing gene copy number for HER2 as well as on test interpretation (23).

There seems to be little or no significance to the degree of HER2 amplification above the threshold of 2.0 gene copies per copy of chromosome 17 in terms of prognosis or prediction of benefit from trastuzumab in the adjuvant setting (24). This threshold effect makes the definition of HER2 positivity particularly important. Some uncertainty in the precise level of the threshold has recently arisen because a subgroup of patients entering the NSABP-B31 trial whose tumors were HER2 negative by central analysis showed benefit from trastuzumab (25).

HER2 may also predict response to other treatments. HER2 amplification and overexpression have been associated with benefit from standard doses of doxorubicin-based adjuvant chemotherapy (26, 27). More recently, a retrospective analysis of an adjuvant chemotherapy trial adding the taxane paclitaxel after four cycles of doxorubicin plus cyclophosphamide revealed that patients with HER2-positive tumors derived appreciable benefit from paclitaxel whereas women with HER2-negative breast cancer did not benefit (28). Similarly, the benefit from anthracyclines seems to be exclusive to patients with HER2-amplified tumors (29), although this may be attributable to coamplification of the Topoisomerase IIa gene (30).

Although not definitive, a series of trials have reported poorer response to or benefit from tamoxifen in patients with estrogen receptor–positive tumors that are also HER2 positive (31). Despite expectations from experimental data, evidence to date suggests that selection of endocrine therapy should not be influenced by HER2 status: in both ATAC and BIG 1-98, no differential benefit was seen according to HER2 status between tamoxifen and either anastrozole or letrozole (13, 14).

A “second wave” of monoclonal antibodies and tyrosine kinase inhibitors (e.g., lapatinib, HKI-272, and pertuzumab) has emerged for which HER2 is likely to be a useful predictive biomarker (32). Early reports suggest that in a subgroup of HER2-positive tumors that also express p95HER2, a cytoplasmic amino terminally truncated receptor containing the kinase domain, there is a poor response to trastuzumab (33). In contrast, p95HER2-expressing tumor xenografts have been shown to be inhibited by lapatinib but not trastuzumab (34). However, more substantive data are required from randomized trials prior to this becoming a routine diagnostic.

**Ki67.** Proliferation is a key hallmark of cancer, and the nuclear nonhistone protein Ki67 is a convenient and reproducible biomarker for this process. Staining for Ki67 can be done both as a static marker of proliferative activity and, by making multiple measurements of sequential biopsies during treatment, as a marker of treatment efficacy.

When considered as a single variable, baseline Ki67 measurements have some prognostic value in node-negative breast cancer. However, in a collection of 40 studies reviewed by our group (35), the association was found to be modest, and it was
concluded that Ki67 does not merit routine inclusion in the workup of primary breast cancer.

High Ki67 has been found to predict good response to chemotherapy in early or locally advanced breast cancer (36–38). In contrast, no significant relationship between baseline Ki67 and response to treatment has been reported for neoadjuvant endocrine treatment (39, 40). The BIG 1-98 trial recently reported that although there was no interaction between Ki67 and relative benefit of letrozole over tamoxifen, the poorer prognosis of high Ki67 patients led to their deriving more absolute benefit from letrozole (14).

Detailed studies in the neoadjuvant setting support a role for change in Ki67 predicting benefit from treatment, and on-treatment Ki67 measurements being superior predictors of long-term outcome than pretreatment levels. In the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) trial, suppression of Ki67 at both 2 and 12 weeks was greater with the aromatase inhibitor anastrozole than with either tamoxifen or the combination of anastrozole and tamoxifen (41–43). This result mirrored the improved recurrence-free survival of anastrozole over the other two arms in the much larger ATAC trial, and required far less follow-up: 2 or 12 weeks for IMPACT versus 31 months for the first outcome data from ATAC (44). Such measurements are unlikely to replace the need for adjuvant trials but may be instructive in selecting or rejecting candidate approaches for phase III studies.

Higher Ki67 expression after 2 weeks of endocrine therapy was also associated with lower recurrence-free survival in the IMPACT trial (P = 0.004) in a multivariate model whereas higher Ki67 expression at baseline was not (Fig. 1; ref. 45). Confirmation and elaboration of this finding is being sought in the POETIC (PeriOperative Endocrine Treatment for Individualizing Care) trial. This trial will assess whether assessment of prognostic variables after 2 weeks of presurgical aromatase inhibitor therapy is substantially more predictive than in the absence of such treatment; if positive, the trial could radically alter the approaches to the assessment of prognostic markers.

Our group has recently found that posttreatment assessment of Ki67 in patients is also a strong indicator of recurrence-free and overall survival in patients receiving neoadjuvant chemotherapy (46). Whereas patients with high Ki67 at baseline have a good chance of achieving a pathologic complete remission, those that do not achieve this have a particularly poor outcome. Thus pathologic complete response is a very strong predictor of outcome in patients with highly proliferative lesions.

**Emerging Biomarkers**

New high-throughput genomic technologies have increased the rate of discovery of new potential markers and facilitated the development of gene expression profiles or “signatures” composed of between two and several thousand genes that purport to provide prognostic or predictive information about tumors. Below, we briefly examine five prominent gene expression-based signatures and three emerging single biomarkers.

**Oncotype DX.** Development of the Oncotype DX assay was inspired by the desire to quantify the residual risk of distant recurrence in patients with lymph node negative, estrogen receptor–positive tumors receiving tamoxifen. The levels of expression of 16 outcome-related genes and 5 reference genes are measured by multiplex reverse transcription-PCR and a mathematical algorithm used to calculate a recurrence score (47). This algorithm was established in a training set comprising mainly samples from the tamoxifen-alone arm of the NSABP-B20 trial and then validated in the tamoxifen arm of NSABP-B14. Genes associated with proliferation and endocrine response are strongly represented. Although the recurrence score is a continuous measure of risk, it is conventionally used to identify three risk groups; within the NSABP B-20 trial with a median follow-up of 10.9 years, the low-, intermediate-, and high-risk groups of tamoxifen-treated patients were associated with distant recurrence rates of ≤10%, 10% to 30%, and >30%, respectively. The recurrence score has been found to predict distant recurrence independent of age and tumor size (P < 0.001), and is predictive of overall survival (P < 0.001). It also more accurately predicted recurrence than Adjuvant! Online, an externally validated integrator of clinical and treatment information (48) and was predictive of the magnitude of chemotherapy benefit in node-negative, estrogen receptor–positive breast cancer (49). Currently, the TAILORx trial (Fig. 2) is seeking confirmation that adjuvant hormonal therapy is as effective as chemohormonal therapy in women who have midrange recurrence scores (48). The trial will randomize patients with recurrence scores between 11 and 25, lower than the 18 to 31 range conventionally regarded as intermediate to try to avoid the risk of denying patients effective treatment.

**MammaPrint.** The MammaPrint 70-gene signature is also being tested in a clinical trial called MINDACT (50). The genes used in the test were identified in a case-control study of young, node-negative women with primary breast cancer with ≥10 years of follow-up (51). Tumors from patients who suffered early metastatic relapse had gene expression profiles that were distinct from those who remained metastasis-free and, in a second validation set, the 70-gene profiler more accurately predicted outcomes than classically accepted clinical criteria (52). In the MINDACT trial, 6,000 node-negative patients will be assessed by both Adjuvant! Online and the MammaPrint. Patients for whom the analyses give discordant results will be randomly assigned to treatment based on the clinicopathologic method or the genomic results, thus identifying the more effective method for determining the need for chemotherapy in a node-negative population (50).

Unlike the Oncotype Dx, MammaPrint requires unfixed biopsy tissue (53). This is more complex to collect, but as a result MINDACT will create a large fresh tissue bank with clinical and full gene expression profiles from each tumor. Another potential disadvantage of the MammaPrint is that it is not optimized for patients with estrogen receptor–positive tumors treated with endocrine therapy. Genes that relate to the impact of such therapy—that all patients with estrogen receptor–positive tumors now receive—are included in the MammaPrint only by chance.

**The breast cancer gene expression ratio test, genomic grade index, and “Rotterdam signature.”** Three other well-known multigene assays for classifying prognosis have undergone external validation in independent data sets. The surprisingly simple two-gene signature, marketed commercially as the breast
cancer gene expression ratio test, measures the ratio of the estrogen-regulated genes HOXB6 and IL17BR (54, 55). The ratio is significantly and independently associated with poorer disease-free survival in lymph node-negative, estrogen receptor–positive, tamoxifen-treated patients with breast cancer. More recently, the addition of five cell cycle–related genes to integrate molecular grade improved the performance of the assay (56). The five added genes reflect the more complex 97-gene genomic grade index, developed to classify histologic grade 2 tumors to low- and high-risk groups alongside grade 1 and 3 tumors, respectively (57). The genes making up the genomic grade signature are mostly involved in cell cycle regulation and proliferation. When this signature was applied to a purely estrogen receptor–positive population, it identified groups with two statistically distinct clinical outcomes in both systemically untreated and tamoxifen-treated populations (58).

Interestingly, despite the fact that the genomic grade index is composed almost exclusively of proliferation genes, genomic grade index scores correlate with the well-known luminal A and B classifications (7) and to the risk groups produced using the OncotypeDX assay (47), the MammaPrint assay (52), and the 76-gene Rotterdam signature (58, 59). This overlap in groupings could perhaps be seen as even more surprising given that the Rotterdam signature does not contain any of the same genes as either Oncotype DX or MammaPrint, and was developed using patients unselected for age, tumor size, grade, or estrogen receptor/progesterone receptor status with development of metastatic disease within 5 years as a supervision criterion (59). However, given that proliferation-associated genes feature strongly in all of these signatures, this association may reflect the dominance of proliferation as a prognostic factor in breast cancer (60).

Fig. 1. Recurrence-free survival according to tertiles of tumor Ki67 expression at baseline (top) and after 2 wk of anastrozole treatment (bottom) in the IMPACT study (45). The divisions refer to the natural logarithm of the percentage of Ki67-positive cells at baseline or 2 wk. Adapted with permission from Dowsett et al.: Prognostic value of Ki67 expression after short-term presurgical endocrine therapy for primary breast cancer. Journal of the National Cancer Institute, vol. 99, issue 2, pp. 167–70, Oxford University Press, 2007.
two recent reports using quite different approaches have identified predictive and prognostic signatures that differ markedly from existing signatures. The stroma-derived prognostic predictor, generated by comparing normal and tumor stroma, stratifies the risk of breast cancer progression using molecular markers that are independent of, but add power to, standard clinical prognostic factors and existing gene expression predictors (61). The genes included in the stroma-derived prognostic predictor reveal the strong prognostic capacity of differential immune reactions as well as angiogenesis and hypoxia, and create potential new targets for therapeutic agents.

In a separate report, in vitro derived rather than tumor-derived molecular signatures indicative of anthracycline and taxane sensitivity were tested in the neoadjuvant setting (62). These regimen-predictive signatures showed a good correlation with pathologic response ($P < 0.0001$), providing one of the most compelling predictive results reported for chemotherapy to date.

Both of these studies clearly need further validation, but their potential uses are substantial.

**uPA/PAI-1.** Two emerging markers also with links to tissue stroma are the urokinase plasminogen activator (uPA) and the plasminogen activator inhibitor (PAI-1). Their overexpression has been consistently related to poor prognosis in early-stage breast cancer with combined, high levels conferring a 2- to 8-fold higher risk of recurrence and death (63–65). A prospective trial using uPA and PAI-1 levels to stratify node-negative patients found that those with low levels of uPA/PAI-1 had 3-year recurrence rates approximately half that of those with elevated levels (66). Treating patients with high uPA/PAI-1 levels with adjuvant chemotherapy reduced the hazard rate for recurrence to 0.56 compared with patients who were not treated. Further studies to address the utility of uPA/PAI-1 measurements are currently ongoing (4). Unfortunately, currently these markers can be measured only in fresh tissue.

**Topoisomerase IIα.** Topoisomerase IIα (TopoII) has been retrospectively identified as a target of inhibition for anthracyclines and a number of other cytotoxic drugs. Recent data suggest that assessment of Topo II status could be a useful method for targeting patients most likely to respond to these drugs, and the potential use of this marker is an area of intense current research (67). The Topo II gene (TOP2A) was first associated with response to anthracyclines as a result of the observation that overexpression or amplification of HER2, which is close to TOP2A on chromosome 17, is associated with increased sensitivity toward anthracycline-containing therapy (29, 68, 69). A number of retrospective analyses have found that response to anthracyclines seems to correlate positively with TopoII protein levels (70–73). However, the observation that Topo II deletion is also associated with benefit from anthracyclines has led to confusion about the use of TopoII as a biomarker (73, 74). More work is required to define these relationships before TopoII is used clinically.

Recent data from the BCIRG B-06 trial (30), which have been presented but are currently unpublished, showed that in patients with HER2-positive early breast cancer the docetaxel, cisplatinum and trastuzumab (TCH: non-anthracyclin containing chemotherapy) was as efficacious as doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC-TH) in the entire study group, and that doxorubicin and cyclophosphamide followed by docetaxel (AC-T, chemotherapy without trastuzumab) was equivalent to TCH in patients in whom the TOP2A gene was coamplified with HER2. Full publication is needed to judge these provocative results fully.
Summary and Conclusions

The use of markers such as estrogen receptor and HER2 for treatment selection is well established, yet even with these markers, deficiencies in methodologies may still affect their application. Recent interest in personalized therapy has led to the extended use of these and other well-known markers such as progesterone receptor and Ki67 and to a plethora of new individual markers and multigene profiles that are seeking establishment. The eventual validation of these and more recent and future markers developed as a result of markedly advanced technology will be required prior to their clinical application. This will require scrupulous attention to assay design and validation allied to the collection of large numbers of well-annotated, high quality tissue specimens from clinical trials that address the question of outcome for which the marker has been selected. Rigorous comparisons of established markers with those emerging are needed to avoid being misled by the seductiveness of the new.

Disclosure of Potential Conflicts of Interest

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