

Chapter 2

Clinical Importance of Prognostic Factors

Moving from Scientifically Interesting to Clinically Useful

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2.1 Introduction

The term prognostic factor, when used regarding patients with malignancies, has taken on several meanings. In general, a prognostic factor is considered to be useful because its results serve to separate a large heterogeneous population into smaller populations with more precisely predictable outcomes. In theory, if this separation is both reliable and disparate, one can apply therapy more efficiently to the population by exposing those most likely to need and benefit from the therapy while ensuring that the other group avoids needless toxicities.

In essence, the term tumor marker has come to describe a variety of molecules or processes that differ from the norm in the malignant cells, tissues, or fluids of patients with malignancies. Assessment of these alterations from normal can be used to place patients into categories that are distinguished by different outcomes, either in the absence of specific therapy, or after various treatments are applied.

Tumor markers can include changes at the genetic level (e.g., mutations, deletions, or amplifications), the transcriptional level (e.g., over- or underexpression), the translational or post-translational level (e.g., increased or decreased quantities of protein, or abnormal glycosylation of proteins), and/or the functional level (e.g., histologic description of cellular grade or presence of neovascularization). Each of these can be assessed by one or more assays, which uses one or more methods with differing reagents. This enormous heterogeneity of approaches is the root of considerable confusion regarding the true value, in clinical terms, of a given tumor marker.

The “molecular revolution” is now well into its fourth decade. Yet, in spite of impressive advances in our understanding of the biology of human malignancy, and in the technology of investigating molecular processes, the number

of clinically useful products from these advances is disappointing. For example, in 1995, the American Society of Clinical Oncology (ASCO) first convened a panel of experts to establish guidelines for the use of tumor markers in colon and breast carcinoma. Although the expert panel reviewed many putative markers (including both tissue-based and circulating markers), its ultimate recommendations were surprisingly sparse (Table 2-1) [1, 2]. In its first deliberations, the panel felt that none of the newer molecular markers (e.g., *erbB-2*, *p53*, cathepsin D) was established in a scientifically rigorous fashion to be reliable and definitive. The most recent update from the year 2000, however, reflect some progress in the field, with recognition of *erbB-2* (HER2) as a potential marker for sensitivity or resistance to certain standard therapies against breast cancer, and, more importantly, as a target of specific therapy itself [3, 4].

Why are the ASCO guidelines so conservative? In reviewing the available literature, the panel recognized that the science of clinical tumor marker investigation has been haphazard and relatively chaotic. Too often, studies of tumor markers are more inclined to “fishing expeditions” with the hope that something interesting will be detected with statistical significance, rather than being prospective, hypothesis-driven investigations. In light of this confusion, several authors of the guidelines separately developed a proposal for a framework in which previously published tumor marker studies might be critically evaluated. The authors also suggested that this framework might be used by investigators to plan future studies in a fashion that leads to more rapid acceptance, or refutation, of a given marker in the clinical arena. Details of this system, designated the Tumor Marker Utility Grading System (TMUGS), have been published elsewhere [5]. The contents of the current review will apply the principles of TMUGS to examples of evaluations of tumor markers in solid tumors, especially breast cancer, although these systems are certainly applicable to other malignancies in general. Recently developed reporting recommendations intended to guide researchers when designing and publishing tumor marker studies will also be discussed [6].

TABLE 2-1. American Society of Clinical Oncology clinical practice guidelines for use of tumor markers in breast cancer (*tissue factors only*).

Factor	Use	Guideline
Estrogen and progesterone receptors	Predictive factors for endocrine therapy	Measure on every primary breast cancer and on metastatic lesions if results influence treatment planning
DNA flow cytometrically derived parameters	Prognosis or prediction	Data are insufficient to recommend obtaining results
<i>erbB-2</i> (HER-2/neu)	Prognosis	Data are insufficient to recommend obtaining results for this use
	Prediction for: trastuzumab CMF-like regimens doxorubicin taxanes endocrine Rx	<i>erbB-2</i> should be evaluated on every primary breast cancer at time of diagnosis or at time of recurrence for use as predictive factor for trastuzumab; Committee could not make definitive recommendations regarding CMF-like regimens. <i>erbB-2</i> may identify patients who particularly benefit from anthracycline-based therapy but should not be used to exclude anthracycline treatment. <i>erbB-2</i> should not be used to prescribe taxane-based therapy or endocrine therapy
p53	Prognosis or prediction	Data are insufficient to recommend use of p53
Cathepsin-D	Prognosis	Data are insufficient to recommend use of cathepsin-D

Modified from Bast RC Jr, Ravdin P, Hayes DF, et al. 2000 Update of recommendations for the use of tumor markers in breast and colorectal cancer: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol. 2001;19:1865–1878.

2.2 Importance of Tumor Markers: Adjuvant Systemic Therapy of Breast Cancer as a Case Study

From the 1950s until about 1985, the annual odds of mortality because of breast cancer per 100,000 women increased steadily in the United States and other western countries (Fig. 2-1). In the mid-1980s, however, age-adjusted, breast cancer-mortality rates plateaued for women in the Western world, and, more recently, mortality from breast cancer has taken a rather dramatic decline [7]. Although screening and early application of local therapy (surgery, radiation) may have contributed to this decline, it is likely that these encouraging statistics are at least in part the result of widespread application of systemic therapy, including endocrine and chemotherapy [7, 8]. Indeed, several meta-analyses of worldwide data from prospective randomized clinical trials have confirmed that adjuvant systemic therapy reduces breast cancer recurrence rates by approximately 25% and, more importantly, mortality by approximately 15% in the population of women who participated in these trials, without further subgroup analyses [9–12]. These studies are not trials of treatment versus no treatment. Rather, they are trials of early treatment of the entire population versus later treatment of only those who have disease recurrence, if and when metastases occur. Because recurrent breast cancer is rarely if ever cured [13], these data illustrate the high stakes in making decisions about adjuvant systemic therapy.

Given this dramatic and life-saving progress, should all patients with newly diagnosed breast cancer be treated with all available therapy to ensure maximum benefits? Application of systemic therapy to all patients with breast cancer would be inefficient, with the majority of patients being exposed to toxicities of therapy for little or no benefit. One might argue that the toxicities of endocrine therapies, such as

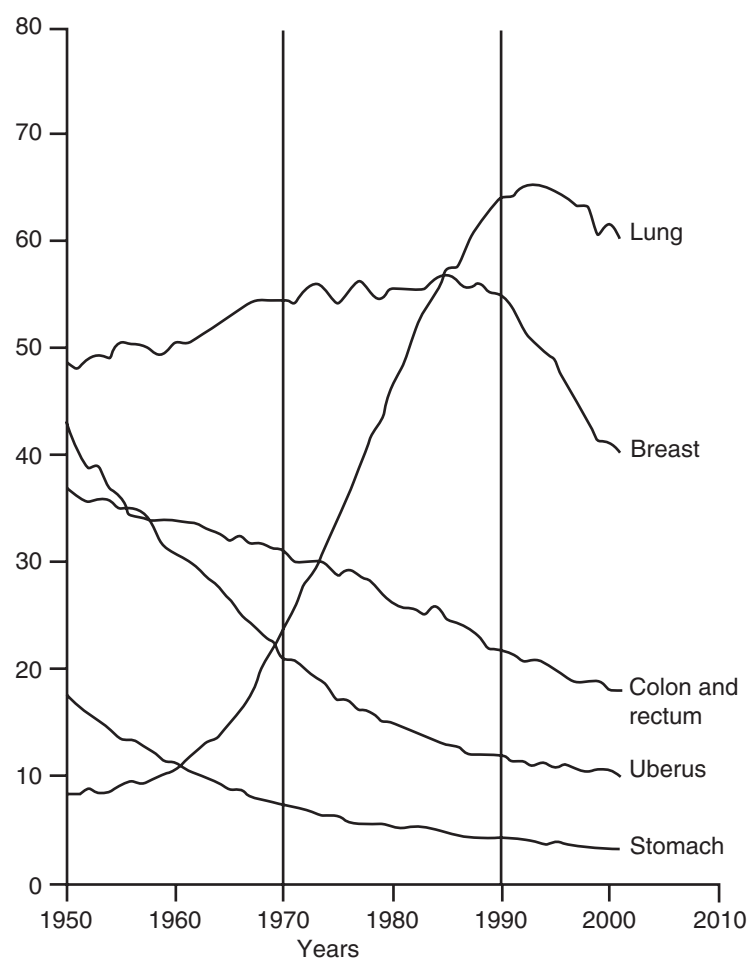
tamoxifen or aromatase inhibitors, are sufficiently tolerable that these therapies are acceptable to most if not all women. Tamoxifen is now used as a “chemopreventive” or “chemoprophylactic” to reduce risk of new breast cancers in women at high risk who have never had the disease [14]. Tamoxifen, however, causes occasional life-threatening toxicities (thromboses, second malignancies). Even the aromatase inhibitors, which may have fewer life-threatening toxicities compared with tamoxifen, at least with short follow-up, are not used indiscriminately because of side effects [15]. The side effects of chemotherapy are more dramatic, including nausea, vomiting, fatigue, and risk of infection and bleeding, and potential long-term complications such as second malignancies and congestive heart failure.

Factors that might identify those patients most likely to have disease recurrence (designated prognostic factors), and factors that might identify those patients whose disease is most likely to respond to specific therapies (designated predictive factors), would be extraordinarily helpful; however, these factors need to be accurate. If they are not, women who are likely to benefit will be excluded from therapy, blunting the decline in mortality discussed previously.

2.3 Prognosis versus Prediction

Estimating a patient’s prognosis requires a complicated set of evaluations, which includes the propensity of a malignancy to expand in volume (proliferative capacity), its ability to escape its natural site of origin and establish growth in a foreign tissue (metastatic potential), and its relative sensitivity or resistance to therapy. Therapies for most solid tumors include surgery, radiation, systemic therapies, hormone therapies, or chemotherapies. In this regard, the terms prognostic and predictive have taken on separate meanings [16, 17]. The prognostic factor designation is usually reserved for those markers

FIG. 2-1. Age-standardized breast cancer death rate of women aged 35 to 69 years in the United States from 1950 to 2001. (From Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;365:1687–1717. With permission.)



that specifically provide an estimate of the odds of a given cancer's recurrence after local therapy alone. It is usually a measure of both proliferation and metastatic potential, and it usually implies the odds of systemic recurrence or death in a patient who does not receive systemic therapy.

A schematic illustration of a pure prognostic factor is provided in Fig. 2-2A. In this case, in the absence of therapy, patients who are positive for the prognostic factor have a worse outcome than those who are negative. Therapy may be effective, but it is equally so (in relative terms) for both factor-positive and factor-negative patients, and therefore the curves from no treatment to treatment for factor-positive and factor-negative patients are parallel. The prognosis for factor-negative patients is so favorable that only a few patients, at most, will benefit, even from very effective therapy. Therefore, a prognostic factor is most helpful in determining if a patient is likely to be cured by the prior therapy, such as local therapy alone (surgery or radiation therapy or both), or whether he or she is more likely to have a subsequent recurrence. If so, and if therapy is available that has demonstrated efficacy in that setting, knowledge of an individual's prognosis permits reasonable decision-making regarding whether or not appli-

cation of further therapy is indicated, especially if the therapy is associated with modest-to-severe toxicities. The best examples of prognostic factors for most solid tumors are the tumor-node-metastasis (TNM) staging systems [18].

A predictive factor is a tumor marker that helps select therapies most likely to work against a patient's tumor. A predictive factor may be the precise target of the therapy, an associated molecule or pathway that modifies the effectiveness of the therapy, or simply an alteration that is an epiphenomenon linked to the target or pathway of the therapy (such as high levels of proliferation or coamplification of a neighboring gene). A factor that purely predicts benefit from therapy (a positive predictive factor) is illustrated in Fig. 2-2B. In this case, the prognosis in the absence of therapy is the same for factor-negative and factor-positive patients (i.e., the factor has no prognostic effects). Factor-positive patients, however, have a much better prognosis than factor-negative patients in the presence of the therapy for which the factor is predictive, and therefore the curves are not parallel. For example, it is clearly established that estrogen receptor (ER) content in breast cancer tissue is positively related to the odds of response and benefit from antiestrogen hormonal therapy, such as ovarian ablation,

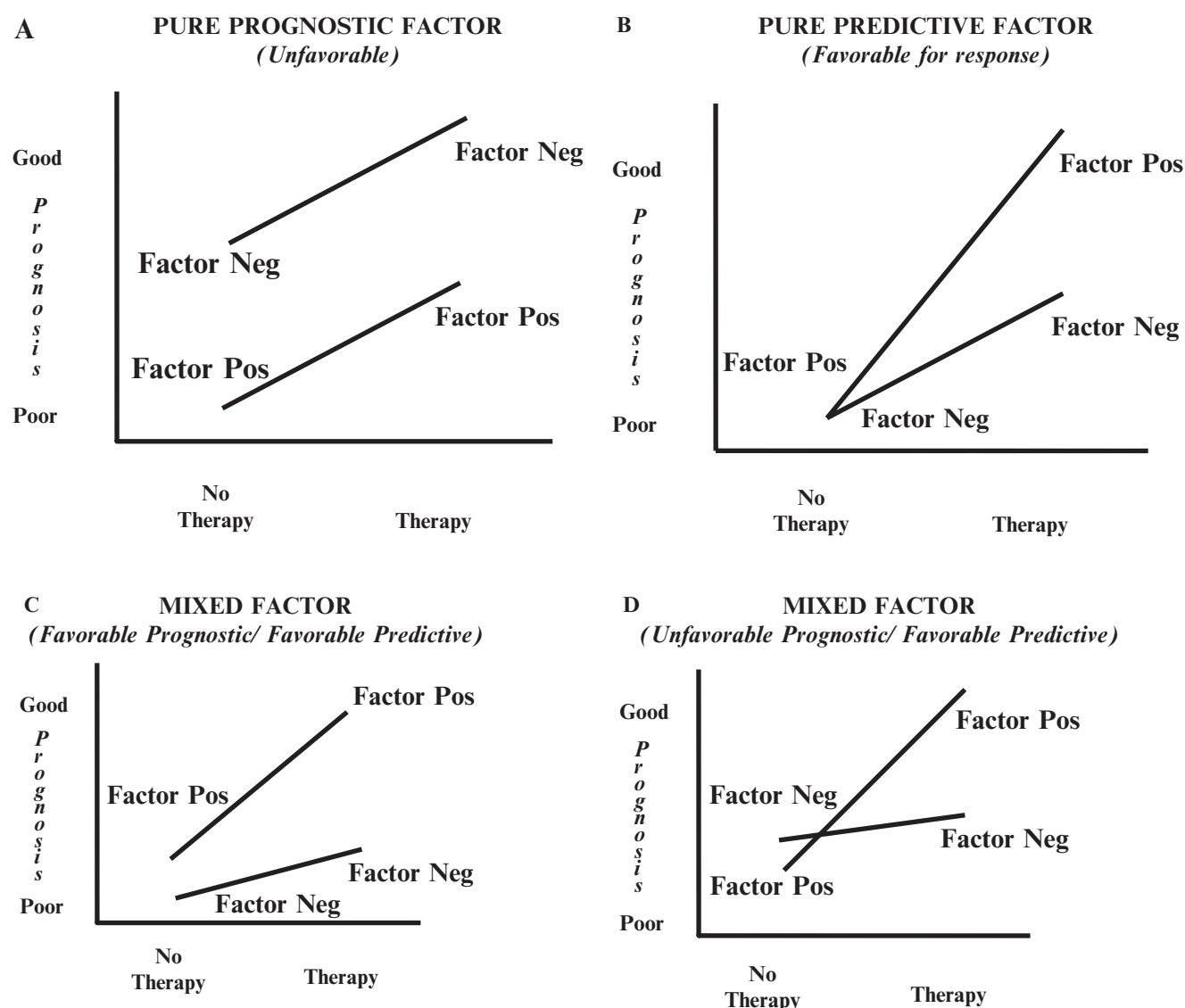


FIG. 2-2. Schematic representation of prognostic and predictive factors. **A** Illustration of pure prognostic factor that is associated with unfavorable prognosis. **B** Illustration of pure predictive factor that is associated with response to specific therapy. **C** Illustration of mixed factor that is associated with favorable prognosis and favorable response to therapy. **D** Illustration of factor that is associated with unfavorable prognosis but favorable response to therapy. (Modified from Hayes DF, Trock B, Harris A. Assessing the clinical impact of prognostic factors: When is "statistically significant" clinically useful? *Breast Cancer Res Treat.* 1998;52:305–319. With permission.)

tamoxifen, or aromatase inhibitors, because ER plays a fundamental role in estrogen-dependent tumor growth and biology [19]. By contrast, *p*-glycoprotein content is a negative predictive factor for resistance to certain drugs, because this protein modulates multidrug resistance by increasing efflux of the antineoplastic agent from the cancer cell [20].

In real life, many if not most factors may be both prognostic and predictive (Fig. 2-2C). For example, in addition to serving as a strong predictive factor, ER is also a weakly favorable prognostic factor. Breast cancers with high ER content have generally slower growth potentials, and patients

with ER-positive tumors have a better prognosis, even if they receive no treatment [21, 22].

To further complicate this discussion, some markers may be associated with a *poor* prognosis independent of therapy, but they may predict for an improved outcome related to specific treatment modalities (Fig. 2-2D). One such marker in breast cancer is the *erbB-2* (HER-2, c-neu) proto-oncogene. Since 1987, conflicting results from several studies have been reported regarding whether *erbB-2* amplification or overexpression or both is a marker of poor prognosis [23–26]. *erbB-2* is also a predictive factor. To add to the confusion, however,

it may be a predictive factor for response to some therapies and resistance to others. For example, *erbB-2* appears to predict relative resistance to hormone therapy and to alkylating agents, but sensitivity to anthracyclines [27–31]. More strikingly, *erbB-2* serves as the target for a humanized monoclonal antibody, trastuzumab. Response to and benefit from trastuzumab is closely linked to *erbB-2* amplification or overexpression or both, which was initially demonstrated in the metastatic setting [32, 33], and recently was shown to result in significantly improved outcomes in the adjuvant setting as well [34–36].

These considerations are often ignored in many prognostic factor studies. Rather, a population of patients is studied with a new, putative prognostic factor simply because the samples to be assayed are available and the outcome for the patients is known. Indeed, a prognostic factor can only be evaluated in the absence of systemic therapy, or at least in the absence of any therapy with which it interacts. A predictive factor can only be evaluated in the context of an untreated control group, preferably one that is prospectively identified and followed, as in prospective randomized trials. It is not surprising that studies of a marker that might have both prognostic and predictive capabilities, especially if these effects are in opposition (as may be the case with *erbB-2*), will provide relatively random and conflicting results if not carefully planned with both appropriate consideration of treatment effects and selection of satisfactory control groups.

2.4 How should Tumor Markers be Selected for Clinical Use?

Ideally, a specific therapy will benefit all those to whom it is administered, and no patient will be exposed to toxicity needlessly. In an imperfect world, however, only a fraction of patients who receive a given treatment will benefit, whereas all are at risk for the side effects. Although identification of favorable and poor-prognosis subgroups is important, simply having a poor prognosis is not justification for treatment. Indeed, many patients will have tumors that are already resistant to specific treatments. In this case, predictive factors will permit selection of those patients who will benefit from the specific therapy. Unfortunately, treatment for the other patients may not be available or as effective. Therefore, even though their prognosis may be relatively poor, it is unreasonable to expose them to toxicity with no benefit.

Do prognostic and predictive factors exist that permit such elegant selection of patients for treatment? Sadly, in most solid tumors, the answer is no. For patients with newly diagnosed solid malignancies, no prognostic factors predict subsequent recurrence and death with absolute certainty. Therefore, when they are applied in the clinic, both physician and patient must accept some margin of error. These decisions involve a careful assessment of several issues: the degree of separation

in outcomes between groups of patients defined by the marker results (marker strength), the reliability of the estimate of this degree of separation (assay methodology and statistical analysis), the magnitude of effectiveness of therapy for the patient's condition (proportional reduction in risk of events), the degree of toxicity of that therapy, and the patient's willingness (as well as the caregiver's and society's) to either forego potential benefit to avoid toxicity or to accept toxicity and cost to gain benefit.

Part of the art and science of medicine is to determine which markers are most reliable in separating groups of patients who will do well from those who will not, and who will benefit from therapy from those who will not. If done appropriately, tumor-marker analysis should permit delivery of therapy as efficiently as possible, providing benefit to the greatest number of patients while avoiding exposure to toxicities as much as possible.

2.5 Recommending Therapy: How Much Benefit is needed to Justify Treatment?

With an estimate of the odds of an event in the absence of therapy (the patient's prognosis), and an understanding of the proportional reduction in the odds of an event (such as recurrence or death) because of application of therapy (prediction that a specific therapy will work for a given patient), one can calculate an approximate absolute chance of that patient benefiting from the therapy.

Again, adjuvant therapy for breast cancer provides a useful example. One might estimate, using standard prognostic factors, that in the absence of systemic therapy a patient has a relatively high (e.g., 60%) chance of recurrence and death over the succeeding 10–15 years after diagnosis. Using predictive factors, one can also estimate the proportional reduction in this chance of recurrence (e.g., 30%) when adjuvant systemic therapy is applied to a population of women with similar characteristics. In this case, a 30% proportional reduction of a 60% absolute risk reduces the odds of an incurable recurrence by 20%. Put another way, 20% of women who would have had recurrent disease if untreated will not as a result of treatment. In this example, the odds of being cured increase from 40% to 60%. Consider another example: the same patient has a favorable prognosis (e.g., a 10% chance of recurrence over 10–15 years) in the absence of systemic therapy. Applying a similar predictive factor profile, the same therapy will still result in a 30% proportional reduction in events. In this case, only 3% of patients will benefit, because 90% are cured by local therapy alone. In a third example, if the same patient has a 10% chance of recurrence, but the patient's predictive marker profile suggests a 70% proportional reduction in recurrence or death, then the absolute benefit is 7%.

If you were the first patient, would you undergo 3–6 months of chemotherapy for a 20% improvement in the chances of being alive and disease free for the next 10 years? If you were

the second patient, would you agree to the same therapy for only a 3% improvement in survival? What if you had a favorable prognosis, but your chance of benefit was 7%? Several investigators have tried to address this subjective decision-making process with questionnaires that pose these dilemmas to respondents regarding adjuvant therapy for breast cancer [37–39]. Such studies are difficult to conduct, however, because an appropriately representative population is not readily identified. Unaffected subjects who are asked to serve as surrogates may not have the same perceptions as they might have if truly afflicted with the disease. Patients who must actually decide are often anxious and unsure, and their hypothetical answers may not reflect their true actions. Survivors who are separated in time from the point of making their decision may have considerable cognitive bias, because they may be more willing to accept the therapy that they perceive has led to their current state of well-being. Nonetheless, these studies have demonstrated remarkably similar and striking conclusions. For example, in one study, previously treated survivors were asked if they would reaccept adjuvant chemotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil [CMF]) for 6 months, placed in the context of various prognostic scenarios [37]. As expected, most patients stated that would take therapy again when the gains were large ($>10\%$ absolute benefit), and a decreasing fraction would be willing to do so as potential gains diminished. More than 50% said they would undergo chemotherapy for gains as small as 3–5%, and nearly 50% would be willing to accept therapy for as little as a 1% absolute improvement in outcome (Fig. 2-3) [37]. Nonetheless, given that a substantial proportion of patients would not accept therapy for an absolute benefit $<10\%$, accurate assessments of prognosis and prediction are essential.

Similar scenarios can be generated for nearly all medical decision-making situations, assuming that the odds of event

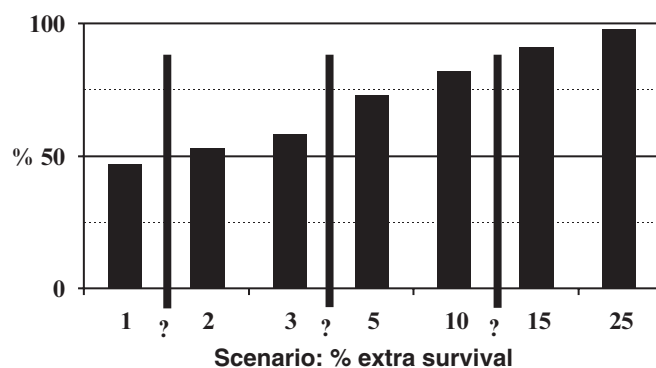


FIG. 2-3. Fraction of patients with breast cancer who would accept 6 months of adjuvant chemotherapy according to added survival benefit. Previously treated breast cancer survivors were queried regarding whether they would be willing to be retreated with 6 months of adjuvant chemotherapy (cyclophosphamide, methotrexate, 5-fluorouracil) for different scenarios regarding added survival benefits. (Modified from reference 37 with permission.) Question marks represent different “cutoffs” that might be used to select therapy or not.

occurrence, the proportional odds of reduction of the event, and the toxicities are well established. Computer models to help breast cancer patients estimate their absolute risks and benefits are now available on the World Wide Web [40–42].

2.6 How Can the Relative Strength of a Prognostic Factor be Determined?

Prognostic and predictive factors can be placed into categories based on their relative strengths to divide a single population into two or more subgroups that have distinct outcomes (Figs. 2-4A and 2-4B) [43]. Let us consider 2 prognostic factors (Fig. 2-4A). One factor separates the population very strongly, so that factor-negative patients are very likely to be cured by

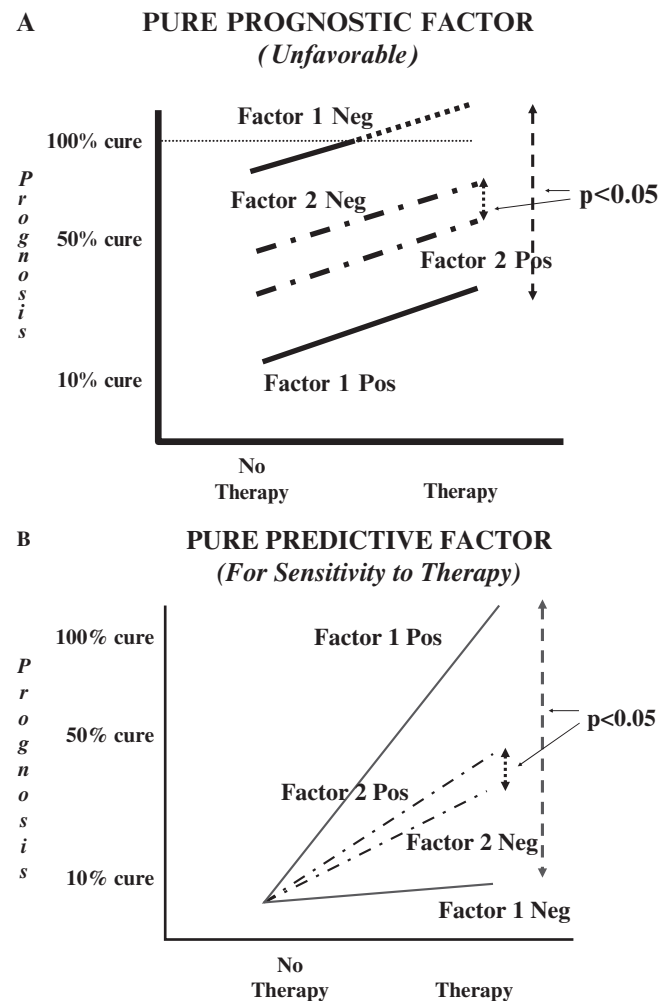


FIG. 2-4. Relative strengths of prognostic and predictive factors. **A** Relative strength of pure prognostic factor. **B** Relative strength of pure predictive factor. Factor 1 (—) is a strong factor while Factor 2 (— • —) is a relatively weak factor. Both factors reliably separate the population into 2 distinct groups not because of chance alone ($p < 0.05$).

local therapy alone and factor-positive patients have a very poor prognosis. If effective therapy is available, a sufficient number of factor-positive patients will benefit so that most patients in that population will accept the therapy and its toxicities. The second factor may also reliably separate 2 groups of patients, with 1 group having a statistically significantly more favorable outcome than the other, but not by much. If effective therapy is available, a similar number of patients will benefit in both the negative and positive groups, exceeding the cutoff required for acceptance of therapy as described earlier. Thus, the clinician would likely use the first factor to help make decisions. Although recognition of the second factor might provide insight into the biology of the disease, it would not have clinical use.

One can analyze predictive factors similarly (Fig. 2-4B). A strong predictive factor provides an indication that the therapy is so effective in factor-positive patients and unlikely to be very effective in factor-negative patients that, if the prognosis warrants therapy at all, the two groups of patients would be treated differently. By contrast, a weak predictive factor may provide an indication that factor-positive patients are a little more likely than factor-negative patients to benefit. The *p*-value suggests that the difference in efficacy between factor-positive and factor-negative patients is unlikely to be because of chance alone, but that the benefit for the factor-negative patients is still likely sufficient to justify exposure to the therapy.

For patients with newly diagnosed breast cancer, we have proposed 3 arbitrary categories for both prognostic and predictive factors, based on relative strengths: weak, moderate, and strong [43–45]. Let us assume that one can place a patient into 1 of 3 prognostic categories that fundamentally affects how he or she is treated. Patients with a very good prognosis might not accept any therapy, patients with a modest prognosis might accept some therapy, and those with a poor prognosis would be willing (assuming that effective therapy is available) to accept even more therapy or therapy with more toxicity (Fig. 2-5). A strong prognostic factor is one that moves a patient across 2 of these arbitrary prognostic categories, e.g., from very good to poor (Fig. 2-5). A modestly strong prognostic factor moves a patient less far. A weak factor may improve or worsen a patient's prognosis, but by so little that it is clinically meaningless. These arbitrary categories will differ depending on the disease, the setting, and the investigator/clinician and the patient. Again, using breast cancer as an example, we have proposed that breast cancer prognostic factors that divide the population into subgroups that differ in outcomes (risk of recurrence over 6–10 years) by twofold or more are considered *strong*. Good examples of strong prognostic factors include clinical stage, pathologic identification of involved axillary lymph nodes, and estimation of tumor size. Prognostic factors that divide the population into subgroups that differ by 1.5- to 2-fold are considered moderately strong. These include tumor grade and perhaps levels of cellular proliferation. Weak prognostic factors divide

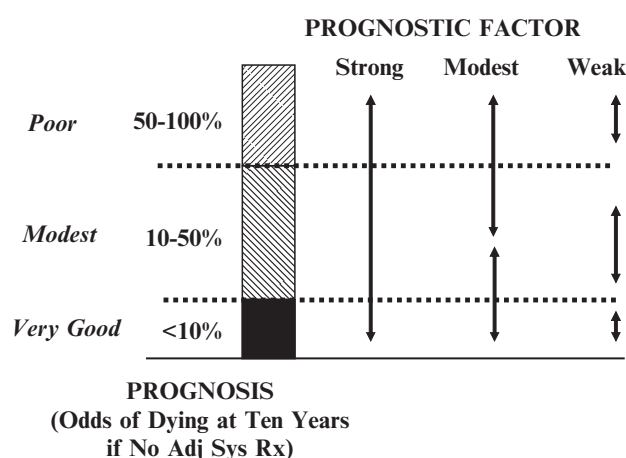


FIG. 2-5. Schematic model of relative strengths of strong, modest and weak prognostic factors. A strong prognostic factor moves patients across several prognostic categories. A modest prognostic factor might move a patient across 1 category whereas the weak prognostic factor does not move a patient outside of his/her original prognostic category. Prognostic categories are arbitrarily assigned. (Modified from Isaacs C, Stearns V, Hayes DF. New prognostic factors for breast cancer recurrence. *Semin Oncol*. 2001;28:53–67. With permission.)

the population into subgroups with outcomes that differ by 1- to 1.5-fold, and include estimates of ER expression and possibly *erbB-2* overexpression or amplification or both.

Likewise, one can also estimate the relative strengths of predictive factors. The strength of a predictive factor is best determined in the context of a prospective clinical trial in which patients are assigned randomly to the treatment of interest or not. The ratio of the likelihood that a factor-positive patient will benefit from treatment compared with a factor-negative patient has been designated the relative predictive value (RPV) [46]. Estimations of the RPV are illustrated in Fig. 2-6 in which the risk of recurrence for treated patients is compared with the risk for untreated patients for each predictive factor category. As with prognostic factors, 3 categories of predictive factors have been proposed, based on RPV. For breast cancer, it is proposed that weak, moderate, and strong predictive factors have RPV of <2-, 2- to 4-, and >4-fold, respectively. The best example of a strong predictive value is ER for tamoxifen, with an RPV >8-fold [10]. It also appears that *erbB-2* amplification is a very strong predictor for benefit from trastuzumab, as has been demonstrated in both the meta-static and adjuvant settings [32, 34, 35, 47].

An additional concept in this discussion is the issue of residual risk after a selected course of therapy (Fig. 2-7). If multiple therapies are available, some patients may only need one to achieve a prognosis sufficient to avoid further or more therapy, whereas others may benefit from additional or more aggressive or more toxic approaches. The residual risk is a function of both original prognosis and the relative benefit from specific therapies. A group of patients may have an original

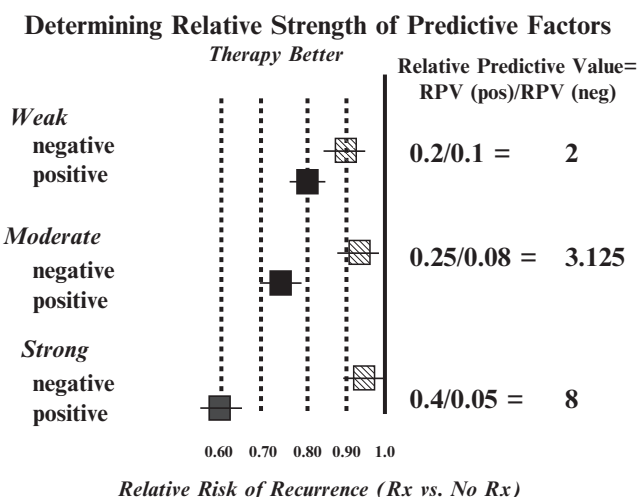


FIG. 2-6. Schematic model for relative strengths of predictive factors. The relative benefit between groups of patients who are positive (solid bar) or negative (shaded bar) for the predictive factor are indicated. The difference in outcome, charted as proportional reduction in the odds of recurrence for treated versus untreated patients, is relatively small for groups of patients that are separated by a weak predictive factor. This difference becomes larger for those separated by a moderate predictive factor and is quite large for those treated by a strong predictive factor. The solid vertical line (unity) denotes no difference in recurrence between treated patients and untreated patients. (Modified from Hayes DF, Isaacs C, Stearns V. Prognostic factors in breast cancer: current and new predictors of metastasis. *J Mammary Gland Biol Neoplasia*. 2001;6:375–392. With permission.)

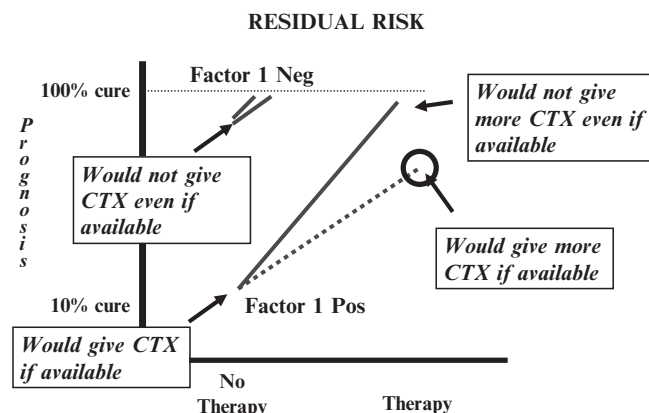


FIG. 2-7. Schematic illustration of residual risk. See text and Figs. 2-2 and 2-4 for details of graphic. (—) = patients with little residual risk. (.....) = patients with substantial residual risk. CTX: chemotherapy.

prognosis that is sufficiently poor to justify an initial therapeutic regimen. Some may respond so well and benefit so much that their post-treatment prognosis is so favorable that they would elect not to receive more treatment. Other patients might benefit less from the first approach. If further therapy is known to provide additional benefit sufficient to outweigh the risks, then these patients might accept it. Residual risk might

be estimated at baseline, before any therapy is given, using initial prognostic and/or predictive factors, as illustrated in the poor prognosis category in Fig. 2-5. For example, patients with node-positive breast cancer might be more willing to accept the increased toxicities of more therapy, such as addition of a taxane to treatment with doxorubicin and cyclophosphamide (AC), than patients with node-negative disease.

Residual risk might better be assessed at the completion of the initial therapy, however, if markers are available that suggest residual disease burden exists. For example, recent studies of neoadjuvant therapy for breast cancer may permit clinicians to estimate the residual risk for patients after several rounds of chemotherapy (e.g., 4 cycles of preoperative AC) based on the presence or absence of residual invasive cancer in the operative specimen [48]. Because it has been established that these patients have a relatively poor prognosis, ongoing studies have been designed to determine whether these patients benefit from additional chemotherapy.

2.7 How Reliable are the Estimates of Relative Strengths of Tumor Markers?

If clinicians use tumor markers to help patients avoid toxicities of therapy while still optimizing benefit, then they must be relatively confident of the estimates they have provided to patients. Clinical investigations of new cancer agents are carefully planned, using criteria and terminology that are generally agreed upon by most clinical scientists [49]. For example, new drugs are sequentially passed through phase 1, 2, and 3 studies, in which toxicity and dose, efficacy, and definitive use are determined, respectively. In these studies, scales have been developed to describe toxicities, responses, and overall outcomes. Such trials are prospectively planned, with detailed descriptions of the number and types of patients to be studied, how they will be treated, and how the statistical analysis will be performed. Indeed, these rules have been established so that the results of clinical studies approach the same veracity as those from laboratory investigations, in which variables and proper controls can be rigorously defined. Clinical studies that are not so rigorously defined, such as retrospective reviews of clinical experiences, may help generate hypotheses, but are rarely accepted as definitive.

In the past, no such consensus system has existed to study tumor markers. More commonly, marker studies are performed using retrospectively available samples from patients treated in a nonuniform manner. Hypotheses are often generated after the data are analyzed, and then presented as fact. Even when multiple studies evaluating the same hypothesis are performed, the populations studied are often heterogeneous and the methods often vary among investigators, which can be a source of bias, leading to invalid results, and the bias is frequently unrecognized [50]. Furthermore, negative

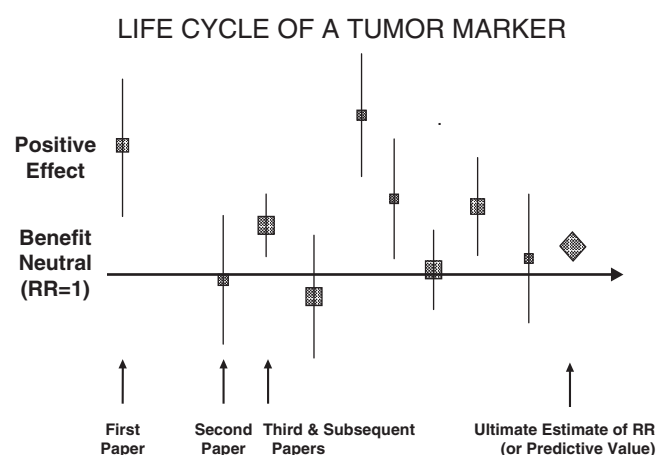


FIG. 2-8. Hypothetical life cycle of a tumor marker.

results are usually not submitted for publication (unless to refute the results of a competing laboratory). It is not surprising that most tumor markers proceed through a typical life cycle before the true use is accepted or discarded (Fig. 2-8). In fact, progression through such a life cycle is common for new therapeutic ideas as well, but because the rules are better established the time required to reach consensus may be considerably shorter.

We now return to the original TMUGS proposal [51]. Determination of relative strengths is only as good as the studies in which they are analyzed. In this regard, the relative quality of the studies is essential in reaching consensus about the strength of the marker. TMUGS was proposed to shorten the life cycle of tumor-marker analysis. One component of

TABLE 2-2. Potential uses of tumor markers.

• Determination of Risk
• Screening
• Differential Diagnosis
Benign vs Malignant
Known Malignant: Tissue of Origin
• Prognosis
• Prediction
• Monitoring Disease Course
Detect Recurrence in Patient Free of Obvious Disease
Patient with Established Recurrence

TMUGS is the importance of a precise description of the tumor marker and the assays used to detect it. Tumor markers can be used for multiple purposes, ranging from screening for disease to monitoring progression (Table 2-2). A semiquantitative scale, which ranges from 0 to 3+, was developed to grade the clinical use of a tumor marker for any specific use (Table 2-3). For example, to assess whether a marker should be used to determine prognosis, users are urged to assign a score based on their interpretation of the available published data. A grade of 0 implies that sufficient data exist to conclude that the marker has no utility, whereas a grade of 2+ or 3+ implies that the marker should be considered or that it absolutely should be used, respectively, in routine clinical practice. More importantly, users are encouraged to support their evaluation by determining the level of evidence (LOE) on which their decision is based (Table 2-4). LOE I data are generated either from a prospective, highly powered study that specifically addresses the issue of tumor-marker use or from an overview or meta-analysis of studies, each of which

TABLE 2-3. Scale to evaluate use of tumor markers for favorable clinical outcomes.

Use scale	Explanation of scale
0	Marker has been adequately evaluated for a specific use and the data definitively demonstrate it has no use. The marker should not be ordered for that clinical use.
NA	Data are not available for the marker for that use because marker has not been studied for that clinical use.
+/-	Data are suggestive that the marker may correlate with biological process and/or endpoint, and preliminary data suggest that use of the marker <i>may</i> contribute to favorable clinical outcome, but more definitive studies are required. Thus, the marker is still considered highly investigational and should not be used for standard clinical practice.
+	Sufficient data are available to demonstrate that the marker correlates with the biological process and/or endpoint related to the use, and that the marker results might affect favorable clinical outcome for that use. However, the marker is still considered investigational and should not be used for standard clinical practice, for 1 of 3 reasons: <ol style="list-style-type: none"> 1. The marker correlates with another marker or test that has been established to have clinical use, but the new marker has not been shown to clearly provide any advantage. 2. The marker may contribute independent information, but it is unclear whether that information provides clinical use because treatment options have not been shown to change outcome. 3. Preliminary data for the marker are quite encouraging, but the level of evidence (see below) is lacking to document clinical use.
++	Marker supplies information not otherwise available from other measures that is helpful to the clinician in decision making for that use, but the marker cannot be used as sole criterion for decision-making. Thus, marker has clinical utility, and it should be considered standard practice in <i>selected</i> situations.
+++	Marker can be used as the sole criterion for clinical decision making in that use. Thus, marker has clinical utility, and it should be considered standard practice.

From Hayes DF, Bast R, Desch CE, et al. A tumor marker utility grading system (TMUGS): A framework to evaluate clinical utility of tumor markers. *J Natl Cancer Inst.* 1996;88:1456-1466.

TABLE 2.4. Levels of evidence for grading clinical use of tumor markers.

Level	Type of evidence
I	Evidence from a single high-powered prospective study that is specifically designed to test marker or evidence from meta-analysis and/or overview of level of evidence II or III studies. In the former case, the study must be designed so that therapy and follow-up are dictated by protocol. Ideally, the study is a prospective randomized trial in which diagnostic and/or therapeutic clinical decisions in one group are determined based at least in part on marker results, and diagnostic and/or therapeutic clinical decisions in control group are made independently of marker results. However, may also include prospective but not randomized trials with marker data and clinical outcome as primary objective.
II	Evidence from study in which marker data are determined in relationship to prospective therapeutic trial that is performed to test therapeutic hypothesis but not specifically designed to test marker use (i.e., marker study is secondary objective of protocol). However, specimen collection for marker study and statistical analysis are prospectively determined in protocol as secondary objectives.
III	Evidence from large but retrospective studies from which variable numbers of samples are available or selected. Therapeutic aspects and follow-up of patient population may or may not have been prospectively dictated. Statistical analysis for tumor marker was not dictated prospectively at time of therapeutic trial design.
IV	Evidence from small retrospective studies which do not have prospectively dictated therapy, follow-up, specimen selection, or statistical analysis. May be matched case controls, etc.
V	Evidence from small pilot studies designed to determine or estimate distribution of marker levels in sample population. May include "correlation" with other known or investigational markers of outcome, but not designed to determine clinical use.

From Hayes DF, Bast R, Desch CE, et al. A tumor marker utility grading system (TMUGS): A framework to evaluate clinical utility of tumor markers. *J Natl Cancer Inst.* 1996;88:1456–1466.

provides lower LOE. LOE II data are derived from companion studies in which specimens are collected prospectively as part of a therapeutic clinical trial, with pre-established endpoints and statistical evaluation for the marker as well as for the therapeutic intervention. Commonly, an early LOE III study will report an extraordinary difference between 2 groups delineated by a given tumor marker analysis (Fig. 2-8). Results from subsequent studies are often more inconsistent. Therefore, we have proposed that the relative strength of a marker for clinical utilities should only be determined within the context of LOE I (or at worse LOE II) studies. In these studies, the marker is the primary objective of a well-designed, highly powered, hypothesis-driven prospective clinical trial, or it is the objective of a statistically rigorous overview of LOE II or III studies or both. Furthermore, the strength of new prognostic or predictive factors can only be estimated by multivariate analytical methods, including pre-existing, accepted factors such as TNM staging and histopathology. It is possible that a marker may be quite prognostic or predictive when considered in a univariate fashion, but that it in fact is only reflecting information already achieved through other, established methods. In this case, acceptance of the new marker would only occur if it can be performed more easily, reliably, or less expensively.

Unfortunately, most tumor-marker studies are LOE III, in which specimens happen to have been collected for a variety of reasons and are available for testing a given assay. In general, the authors of TMUGS suggested that results from LOE I studies are preferred to assign clinical use to a marker. Use of a system such as TMUGS to rigorously assess the reliability of assessment of the relative strengths of prognostic and predictive factors will substantially strengthen the clinicians' confidence as they counsel their patients.

2.8 How Can the Relative Strengths of Prognostic and Predictive Factors be Applied Clinically?

Outside a clinical trial, there is little value in determining that a patient has a poor prognosis unless therapy is available to change that prognosis. Moreover, if the patient or physician is unwilling to give up any benefit, regardless of how small and despite the risks, application of tumor markers is unnecessary unless the results are 100% accurate. Likewise, if the patient is unwilling to accept any therapy regardless of how large the benefit or how well tolerated the treatment, there is no point in applying tumor-marker data.

In most cases, the patient and physician wish to apply therapy relatively efficiently. In this case, if the patient can judge how much benefit he or she is willing to forfeit to avoid toxicities, one can construct a model in which 1 marker might be used in some situations but not others [51]. Again, the example of application of adjuvant systemic therapy for patients with newly diagnosed breast cancer is used (Fig. 2-9). In this example, the following assumptions have been made:

- Patients can be placed into 1 of the 3 prognostic categories based on the odds of systemic recurrence and death during the subsequent 10 years after diagnosis and local treatment in the absence of systemic therapy: very good (<10% chance recurrence/death); moderate (10–50%); and poor (>50%);
- Patients would accept tamoxifen or an aromatase inhibitor for a small benefit (although not for no benefit at all), but that they would accept chemotherapy for only a 4% or higher absolute benefit;
- ER is a very strong predictive factor, such that tamoxifen and aromatase inhibitors proportionally decrease odds of

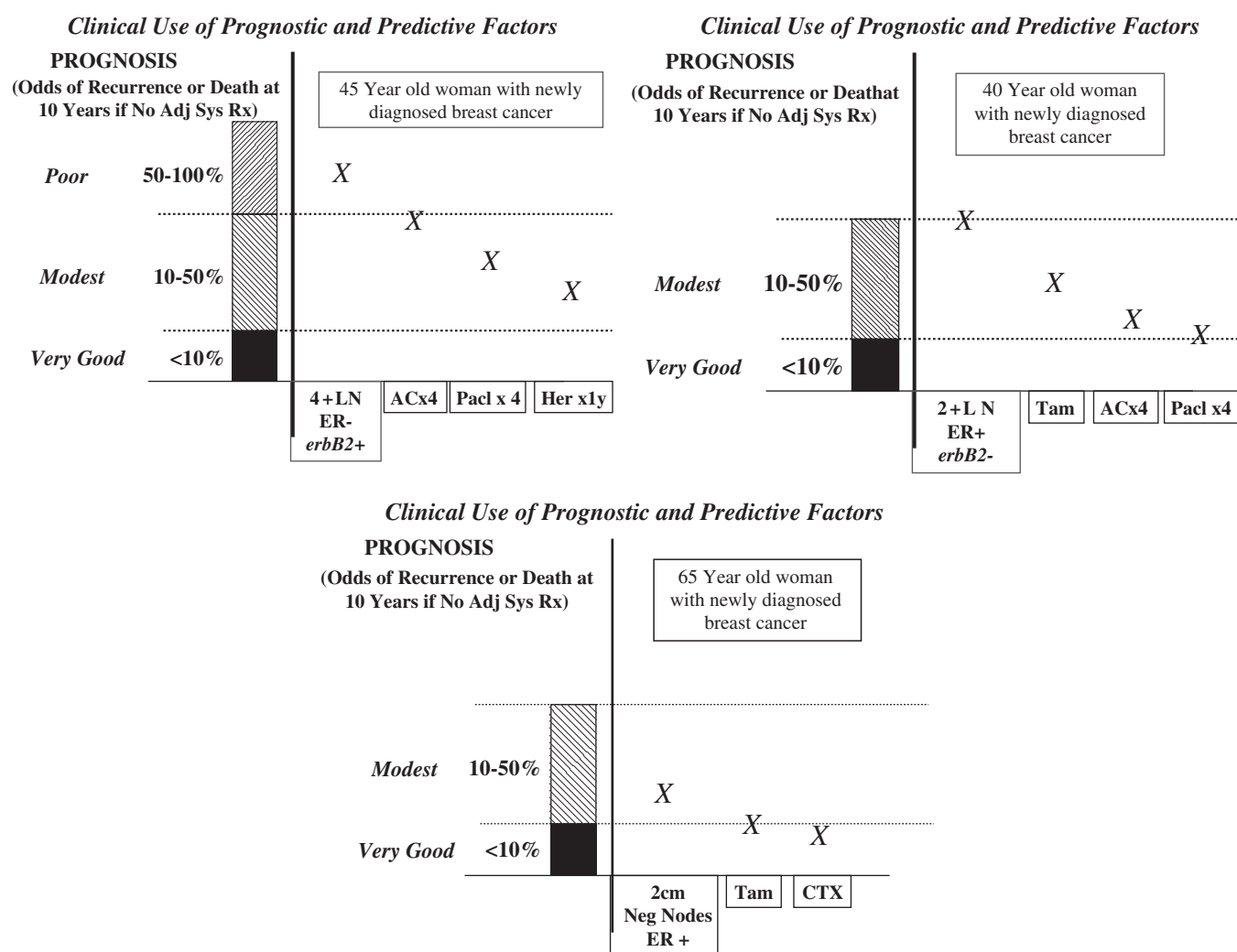


FIG. 2-9. Schematic illustration of use of prognostic and predictive factors to select appropriate treatments for individual patients with breast cancer (see text for details). CTX chemotherapy; Her trastuzumab; LN lymph node; Pacl paclitaxel; Tam tamoxifen.

recurrence by 40–45% in ER-positive patients and not at all in ER-negative patients [10, 15];

- Different chemotherapy regimens can be applied in sequence with increasing benefits and toxicities, depending on predictive factors; and
- *erbB-2* is strongly predictive for response to trastuzumab, resulting in approximately a 50% improvement in recurrence rate in women whose tumors overamplify *erbB-2* [34, 35].

For example, 4 cycles of AC might proportionally decrease odds of recurrence by 33% in younger women (aged <50 years), but by only 20% in older women (aged 50–69 years) [12]. We will also assume that 4 additional cycles of a taxane, such as paclitaxel, decrease the odds of recurrence proportionally by a further 20% in ER-negative patients, but perhaps not at all in ER-positive patients [52]. (Note: All of these assumptions are approximate estimates based on annual reduction of odds of recurrence calculations).

Figure 2-9 provides examples of how the combination of prognostic and predictive factors might be used. First, let us consider a 45-year-old patient with a 4-cm, poorly differentiated ER-negative, *erbB-2* positive breast cancer with 4 of 10 involved axillary lymph nodes (Fig. 2-9A). This patient's initial prognosis is poor. In the absence of systemic therapy, one might expect 60–70% of such patients to have a recurrence within the next 10 years. Endocrine therapy would not be expected to provide any benefit, and therefore would not be indicated. Four cycles of AC, with a proportional reduction of 33%, would prevent recurrence in 20–25% of patients, therefore reducing her absolute risk to approximately 50%. Four cycles of paclitaxel would be expected to further reduce her odds of recurrence proportionally by 20–30%, therefore reducing her absolute risk an additional 10–15%, to 35–40%. Finally, 1 year of trastuzumab, started concurrently with paclitaxel therapy, would decrease her odds of recur-

rence proportionally by 50%, decreasing her absolute risk to approximately 20%, only one third of what her overall chance of recurrence was. In this case, most clinicians and patients would agree that the combination of chemotherapy and targeted therapy with trastuzumab is indicated.

Next, consider a 40-year-old premenopausal woman with ER-positive breast cancer who has 2 positive axillary lymph nodes (Fig. 2-9B). In this case, in the absence of systemic therapy, one might estimate that her odds of recurrence over the next 10 years are approximately 50%. This patient would almost certainly find tamoxifen an acceptable adjuvant therapy, but would not be eligible for treatment with aromatase inhibitors because she is premenopausal. A proportional reduction of 40% would result in approximately 15–20 patients who would not have a recurrence, considerably exceeding the cut-off required for recommendation of the strategy. Even if the patient takes tamoxifen, however, her residual risk of recurrence over 10 years remains approximately 20–25%, still in the “moderate risk” category. Chemotherapy would result in an approximately 20–30% reduction of this 25% risk, and therefore approximately 5–7 additional patients would be alive and disease free because of the application of adjuvant AC. It would thus be reasonable to recommend 4 cycles of AC to this patient.

Should this patient also receive 4 additional cycles of adjuvant paclitaxel? The answer depends on our confidence in the available data. Multiple prospective randomized clinical trials performed in the United States have addressed the use of sequential taxanes in this setting, but different dosing regimens and patient populations were evaluated. Two trials suggested that the addition of 4 cycles of paclitaxel after AC proportionally reduced the odds of recurrence and death by approximately 20% [52, 53]. An unplanned retrospective subset analysis of one of the trials suggested that this benefit was almost entirely confined to the ER-negative subgroup [54]. A third study compared AC plus 5-fluorouracil (FAC) with AC plus docetaxel (TAC), and found a 28% relative decrease in the risk of recurrence with the addition of the taxane. Other studies of taxanes have yielded contradictory or inconclusive information, however. Should the clinician wait for more mature data, probably pooled in a meta-analysis, before making decisions regarding this extra therapy?

In this example, let us accept the data supporting the use of paclitaxel after AC. Furthermore, let us assume that all patients will have a further proportional reduction in recurrence of 20%, regardless of ER status. This patient’s residual risk of recurrence after tamoxifen and 4 cycles of AC is approximately 20% (Fig. 2-9B). A 20% proportional reduction of a 20% risk would result in a further absolute benefit of approximately 4% reduction of recurrence. Does this justify the therapy? This absolute benefit straddles the cut-off to treat or not, and the patient and her physician must discuss this issue carefully.

Finally, consider a postmenopausal 65-year-old woman with a 2-cm, moderately differentiated ER positive breast

cancer with no detectable axillary nodal involvement (Fig. 2-9C). In the absence of systemic therapy, her overall odds of recurrence over the next 10 years are approximately 20%. Therefore, she has an 80% chance of having been cured by local therapy alone. An aromatase inhibitor will proportionally reduce these chances by approximately 40%. Thus, for every 100 patients who are treated in this situation, 80 patients cannot benefit because they will not recur. Of the 20 patients who were destined to recur, 8 patients will not because of aromatase inhibitor therapy. Because aromatase inhibitors are relatively well tolerated, this percentage of absolute benefit exceeds our cut-off for recommending therapy, and most patients would accept it, resulting in an improvement of their expected cure rate from 80% to approximately 88%.

Our assumptions suggest that chemotherapy would result in a further 20% proportional reduction in the risk of recurrence over 10 years for this group of patients. With aromatase inhibitor treatment, this patient has a residual recurrence risk of 12%. A proportional reduction by 20% of this risk represents 2–3 of 100 patients who might benefit. This number is below the cut-off that most, but not all, patients and clinicians consider worthwhile, especially given the toxicities of chemotherapy. However, some patients in this group are likely to have a difficult decision regarding whether or not to undergo chemotherapy.

A promising new tool to determine prognosis has been developed for patients such as the one presented here, who have ER-positive, node-negative breast cancer. OncotypeDX is a multigene assay performed on fixed tumor tissue that is used to divide patients into 3 categories based on likelihood of disease recurrence (low, intermediate, and high) [55]. OncotypeDX is being evaluated as a predictive factor. Initial studies suggest that patients in the high-risk group are likely to benefit from chemotherapy, whereas those in the low-risk group are not [56]. It remains unclear how best to treat those in the intermediate group, however, and therefore a prospective, randomized clinical trial, designated TAILORx, has been recently opened. TAILORx will randomly assign patients in the intermediate group to chemotherapy plus endocrine therapy versus endocrine therapy alone. TAILORx and other LOE I trials may enable physicians and patients to make more informed decisions regarding the clinical use of new markers.

2.9 Are There Solid Tumor Markers that Fulfill the TMUGS Criteria for Routine Clinical Use?

The previous examples regarding breast cancer illustrate how prognostic and predictive markers might be used to tailor patient care in the adjuvant setting. In all malignancies, markers might be used in one of several different situations

(determination of risk, screening, differential diagnosis, prognosis, prediction, monitoring disease course) (Table 2-2) [5]. Different markers may perform differently in each situation for each disease (e.g., colon vs breast vs lung cancer). In general, the TNM staging system has been well accepted for prognosis for most if not all solid tumors [18]. The ASCO Guidelines Panel has made specific recommendations for breast and colon cancer based on data that they believe met criteria consistent with TMUGS (Table 2-1) [1–3]. In addition to those that have gained acceptance, newer assays such as OncotypeDX are being considered to determine if there is sufficient evidence to support routine use for prediction or prognosis or both.

Few if any prognostic or predictive factors have been accepted for the other common solid malignancies, such as prostate, lung, and ovarian cancers [57–59]. For each, the TNM and grading scales are reliably prognostic. Serial circulating prostate specific antigen levels and CA125 levels are helpful in monitoring patients with prostate and ovarian cancers, respectively [58, 60]. For most solid tumors, however, better markers that have been well characterized using results from carefully designed and well performed studies are urgently needed.

2.10 Summary

In summary, the phrase “many are called, few are chosen” seems to reflect the current state of the art regarding tumor marker analysis in solid tumors. However, the field is evolving rapidly, with a convergence of molecular biology and technology and understanding of clinical trial design and analysis. Several of the large cooperative trialists groups have established separate correlative/biologic committees that are charged with designing hypothesis-driven LOE I and II studies, based on results from pilot studies. The emergence of *erbB-2* in breast cancer as a predictive factor, in a manner similar to ER, may serve as a model of directed studies that lead to determination of the relative strength of the marker, and assignment of a TMUGS score that indicates whether or not it should be used clinically.

In an attempt to standardize reporting of tumor-marker studies, and to guide design of the trials, the National Cancer Institute – European Organization for Research and Treatment of Cancer published REporting recommendations for tumor MARKer prognostic studies (REMARK) [6]. These guidelines outline concepts that should be considered when developing clinical studies, such as prospectively defining the question being addressed, choosing an appropriate patient population, determining endpoints, and identifying potential sources of bias. We hope that careful and thoughtful consideration of study design, such as is delineated in TMUGS and the REMARK guidelines, will considerably shorten the life cycle required to bring a tumor marker from the laboratory to the clinic.

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Principles of Molecular Oncology

Bronchud, M.H.; Foote, M.; Giaccone, G.; Olopade, O.I.;
Workman, P. (Eds.)

2008, XX, 420 p. 85 illus., 21 illus. in color.,

ISBN: 978-1-59745-470-4

A product of Humana Press