Decision-Making For Patients With Resectable Breast Cancer: Individualized Decisions For and By Patients and Their Physicians

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Abstract

Decisions regarding the use of adjuvant cytotoxic and hormonal therapies for women with breast cancer ideally should be made jointly by the patient and oncologist. For patients to be adequately involved in this decision-making process, they must be provided with appropriate education regarding the potential benefits and risks of adjuvant therapies. The recommended steps for doing this are: 1) understand baseline prognosis with locoregional therapy (surgery, radiation, or both) alone for the individual patient at hand; 2) determine the estimated benefit afforded by adjuvant therapy options for the individual patient; 3) estimate the risk of side effects of adjuvant therapy options; 4) convey the above information to the individual patient; 5) facilitate the individual patient's decision regarding adjuvant systemic therapy; and 6) support the patient's decision. Two computer-based tools *(Numeracy and Adjuvant!)* are available to facilitate this process. *(JNCCN* 2003;1:189–196)

As evidence-based guidelines have come into widespread use and as medical information has become more easily accessible, doctor-patient interaction has changed, with patients becoming more active in the review of information and in decision making about options for their care. Approaches to better patient understanding of issues to address adjuvant systemic therapy decision making, such as "Decision Boards"[1–3] and estimates of quality adjusted years gained (Q-TWiST),[4] have been described. However, these approaches are not widely available to facilitate individualized decisions for patients.

This article discusses two tools that have been applied to this process (*Adjuvant!*, developed in San Antonio, Texas,[5] and *Numeracy*, developed at the Mayo Clinic[6]), which were specifically designed for facilitating adjuvant therapy decision making. These tools are described, compared and contrasted, and some of the strengths, weaknesses, and uncertainties regarding their use are examined. The developers of these tools produced them in an effort to better understand prognostic information for themselves and their patients. The tools were developed in response to recommendations from many sources that patients need better prognostic information to be adequately involved in the decision-making process for their future care. It is important to keep in mind that neither of these tools is perfect, and that they will need revision as new information becomes available. Nonetheless, these tools provide insight that many clinicians find helpful as they help patients make appropriate decisions regarding adjuvant systemic therapy choices.

Adjuvant Therapy of Breast Cancer Guidelines

All patients with early breast cancer face the decision about whether to receive adjuvant therapy and what type of therapy would be most appropriate. The two main ways to address these issues are through the use of guidelines and through the use of specific tools

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developed for this process. Figure 1 illustrates recent guideline recommendations for the use of systemic adjuvant chemotherapy for patients with stage 1 breast cancer as formulated by the National Cancer Institute (NCI),[8] the NCCN,[9] and the St. Gallens conference.[10]

The use of such guidelines helps standardize practice, but their use is, in a number of ways, not completely satisfying. First, different guidelines use different parameters to decide on treatment options for patients with stage 1 breast cancer. The NCI guidelines primarily use tumor size; the NCCN uses primarily tumor size and estrogen-receptor status; and the St. Gallens guidelines use primarily tumor size, estrogen-receptor status, and tumor grade. This leads to differences in recommendations. For example, the St. Gallens guidelines identify a "low risk" subset of stage 1, estrogen-receptor (ER)–positive, grade 1 patients (older than 35), and suggest that they should not receive adjuvant therapy. There are also paradoxical situations, such as for patients with N0/T1a ER-negative tumors, in which guidelines make divergent recommendations. Such patients might be told by practitioners using these guidelines that they *should* undergo adjuvant chemotherapy (St. Gallens), *should not* undergo adjuvant chemotherapy (NCCN), or that they *should consider* undergoing adjuvant chemotherapy (NCI).

Second, if applied without a detailed discussion with the patient, these guidelines could be viewed as being paternalistic, perhaps lifting decision–making from a paternalistic individual doctor to a paternalistic committee. Thus, using guidelines alone does not truly engage the patient in the decision-making process. Therefore, to better engage patients in this process, the *Adjuvant!* and *Numeracy* tools were developed to provide more specific prognostic information for individual scenarios, both with and without various adjuvant systemic therapy options.

Requirements for Making Adjuvant Therapy Decisions

Appropriate determination of whether or not an individual patient should receive adjuvant therapy for breast cancer depends on integrating a number of factors, conveying this information to the patient, and helping the patient reach an appropriate decision. The following individual steps in this process can be identified:

1) Estimating baseline prognosis for an individual patient;
2) Estimating the generalized efficacy of various adjuvant therapy options;
3) Determining estimated benefit afforded by adjuvant therapy options for individual patients;
4) Estimating risks of side effects of adjuvant therapy options;
5) Conveying the above information to a patient;
6) Providing information regarding available clinical trials for which the patient might be eligible and describing the benefits for clinical trial participation;
7) Facilitating patient decisions regarding adjuvant systemic therapy; and
8) Supporting patient decisions.

Estimating Baseline Prognosis for an Individual Patient

Over the past two decades, extensive literature has shown multiple factors that impact on prognosis for patients diagnosed with primary breast cancer. Many of these factors provide statistically significant prognostic information in univariate models, and several of them also show significant prognostic discriminant value for groups of patients, as judged by multivariate statistical analyses, taking into account other known prognostic factors.[11] Despite this wealth of prognostic data, until recently, little information was available to help provide accurate prognoses for individual patients presenting in a clinical practice. The available information clearly shows that, without the use of specific tools to indi-
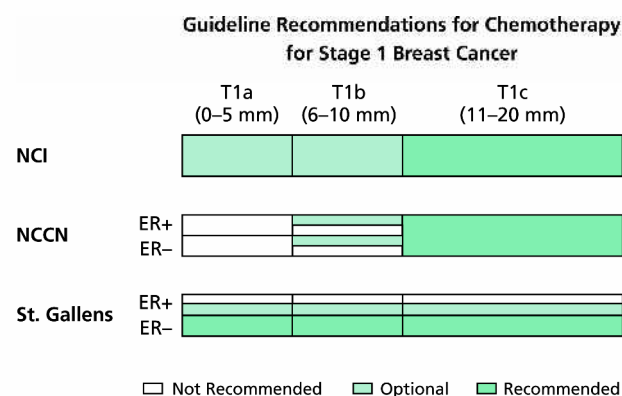

Figure 1 Comparison of Guideline recommendations for patients with stage 1 breast cancer: This figure is an updated modification of a previously published figure.[7] The top white box in the St. Gallens section represents a subset of stage 1, ER positive, grade 1 patients who are older than 35 years. Abbreviations are: NCI, National Cancer Institute; NCCN, National Comprehensive Cancer Network; ER, estrogen receptor.

vidualize patient prognoses, opinions vary widely regarding prognoses of individual patients by practicing oncologists, including "breast cancer experts."[6,12]

Some special problems exist when estimating outcome. The first is that the low rate of events for patients with stage 1 tumors leads to relatively broad confidence intervals. The second problem is the definition of "prognosis" itself. Should the endpoint be overall mortality, breast cancer-specific mortality, risk of relapse, quality of life, or a mixture of these factors? Ideally, accurate information for all of these factors would be available to individual patients. At a minimum, however, it would seem that prognosis should include information about all–cause mortality and breast cancer-specific mortality, because in many instances (particularly in older patients with stage 1 tumors), all–cause mortality is much larger than breast cancer-specific mortality, and some estimate of both may help to view these risks in full context.

Estimates of breast cancer-specific mortality present some special issues. Relapse, which can be defined in a number of ways, can be a combination of in-breast local recurrences, second contralateral breast primaries, and distant metastatic disease. These various forms of relapse, however, may have quite different consequences, and are affected in different ways by local and systemic adjuvant therapy.

In addition, the time of follow-up is an important issue for which the prognosis is being estimated. For breast cancer, with its period of relapse and mortality extending beyond five years, estimates of five-year outcomes present an incomplete picture. Even estimates of 10-year outcomes are imperfect. However, estimates beyond 10 years are problematic because most databases do not include patients with such extended follow-up and because our estimates of how systemic adjuvant therapy impacts these late events is incomplete. For these reasons, explaining prognoses in terms of 10-year survival probabilities is recommended. Therefore, both *Adjuvant!* and *Numeracy* display prognostic information in terms of how a patient will fare at 10 years after diagnosis. *Adjuvant!* estimates either the risk of breast cancer-related mortality or risk of recurrence at 10 years, *Numeracy* presents individual patients' probabilities of not experiencing relapse at 10 years.

Adjuvant! and *Numeracy* use somewhat different approaches to obtain the baseline prognostic information in each tool. *Adjuvant!* uses information from the Surveillance, Epidemiology and End Results (SEER) database, making estimates of outcomes at 10 years by drawing on information about tumor size, the number of involved nodes, and histologic grade.[13] The *Adjuvant!* data input page for prognostic information is illustrated in Figure 2A. Notably, other laboratory-derived information, such as Her-2 and S-phase, may have some value but are currently controversial and are not endorsed by current American Society of Clinical Oncology (ASCO) Guidelines.[14] In addition to providing information about 10-year breast cancer-specific survival, *Adjuvant!* also gives age- and comorbidity-derived estimates of nonbreast cancer mortality. *Adjuvant!* also can be used to produce relapse risk estimates. This tool, however, cautions the user that these estimates are not as firmly based (compared with estimates for mortality), because details of local therapy (surgery and radiation therapy) affect the risk of relapse more than mortality. The tool also cautions the user that the definition of relapse is complex.

Numeracy's approach to determining baseline prognoses for individual patients was to assemble estimates from a panel of experts (whose individual estimates were, in fact, widely divergent, as was expected). These

Figure 2 (Top) Patient data input screen for Numeracy. (Bottom) Patient data input screen for *Adjuvant!*.

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individual opinions were based solely on the number of involved axillary lymph nodes and the primary tumor size. The average value of all the individual estimates (which was actually close to the median value for each estimate) was then used for the final prognosis of each patient group. The reason that other prognostic factors such as tumor grade and patient age were not used was based on previous work suggesting that oncologists could not use such data accurately to improve on estimates generated by tumor size and lymph node status.[12] The *Numeracy* data input page for prognostic information is shown in Figure 2B.

It is reasonable to ask how these two methods compare to each other in terms of predicting baseline prognoses. The answer is provided in Figure 3, which shows a good degree of concurrence and helps to validate each methodology.

Estimating Generalized Efficacy of Adjuvant Therapy Options

For any evidence-based tool, the estimates of efficacy of adjuvant therapy options should be based on clinical trial data. The best "overview" of this information is found in the publications of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), which appear about every five years. This information consists of analyzed evidence from all available randomized adjuvant therapy clinical trials.[15,16] Quantitative estimates of the efficacy of therapy are given in terms of "proportional risk reductions," with the suggestion that these reductions be multiplied by the absolute risk to give the estimates of absolute benefit.
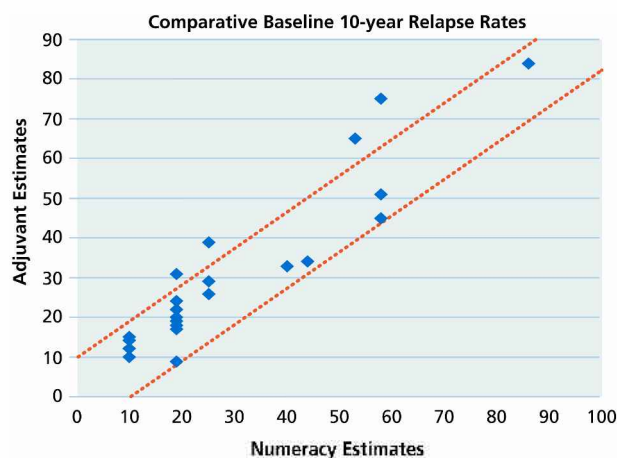

Figure 3 Comparative 10-year relapse rates. Ten-year breast cancer relapse rates were derived from *Adjuvant!* and *Numeracy* for 29 recent cases seen in clinical practice. Points between the parallel lines represent baseline prognostic values that were within 10% of each other.

This process includes some important subtleties, however. One is that the proportional risk reductions given by the EBCTCG are provided as reductions of the annual risk. This annual risk (and the risk reduction) compounds every year, and the resulting total risk (and risk reduction) is somewhat less than that of a simple multiplication of the total risk times the proportional risk reduction.[5] Proportional reductions in annual risks are somewhat confusing to health care professionals and the lay public alike because they appear to over-inflate benefits provided for individual patients. For example, for a patient in whom baseline prognostic information suggests a 10-year survival of 70%, a therapy with an annual proportional risk reduction of 25% can easily be misunderstood as predicting that the patient getting such therapy would now have a 95% 10-year survival probability; whereas the true prediction from these numbers is 77%.

Another subtlety in using proportional risk reductions is that when a patient undergoes two different treatment modalities thought to act independently, the benefit of the these modalities is not simply additive. For example, if chemotherapy affords a 30% proportional risk reduction and tamoxifen provides an additional 30% risk reduction, the benefit of combined chemo-endocrine therapy is not 60%, but rather 100% –(100–30) × (100–30), which equals about 50%.

Determining Estimated Benefit Afforded by Adjuvant Therapy Options for Individual Patients

Both *Adjuvant!* and *Numeracy* use variants of actuarial analysis to predict the improved prognoses for individual patients with different treatment options. In both tools, the proportional risk reductions afforded by different adjuvant options vary based on the ages of the patients (< 50 vs > 50 years), estrogen receptor status, and type of adjuvant therapy planned. The EBCTCG's analysis suggests that the proportional risk reductions afforded by different adjuvant options are roughly equal in both node-negative and node-positive patients. Understanding that this has not been fully validated for low risk (stage 1) populations, both programs calculate proportional risk reductions for patients with varying degrees of baseline prognoses. Both *Adjuvant!* and *Numeracy* use EBCCTG-derived estimates[15,16] as the backbone of their estimates. Both, however, provide varying degrees of additional information from large clinical trials (such as those more recent trials evaluating regimens that include an-

thracyclines or taxanes), noting that the provided information from these sources often does not include 10-year follow-up data. Therefore, efficacy estimates must be extrapolated from results with shorter follow-up periods.

Although the actuarial analyses calculations of individual patient prognoses for *Adjuvant!* and *Numeracy* are done in slightly different manners, the outcomes for pairs of individual patients with identical baseline prognoses are very similar, providing validation for each method.[2] Of note, *Adjuvant!* includes a function that can account for projected nonbreast cancer–related age-specific mortality adjusted for comorbid states. This allows the user to view breast cancer–specific events in the greater context of other events, and, for patients older than 70, decreases the projected benefit somewhat because of competing mortality from other diseases.

Estimating the Risks of Side Effects From Adjuvant Therapy

Informing a patient of the potential benefits of therapy is only part of the equation. It is also important to inform patients of the side effects and toxicities related to different treatment options. *Adjuvant!* facilitates this aspect of decision making with information sheets that present schemata for the planned regimen, toxicity data from trials using the regimen, and a general overview of the toxicities that might be expected. *Adjuvant!* also discusses the concept of four major classes of toxicity. For example, an anthracycline-based adjuvant regimen would have 1) side effects that, if they occur, usually last only a few days (eg, nausea or vomiting); 2) side effects that, if they occur, usually occur on many or all days of a treatment cycle but resolve after treatment (eg, hair loss, fatigue); 3) side effects that may be permanent (eg, early menopause, a small reduction in the force of the heart); and 4) side effects that are rare but very serious (eg, heart failure, acute leukemia, life-threatening infections).

Conveying Information to a Patient

After baseline prognosis and benefit from adjuvant systemic therapy are projected for an individual patient, these data can be shared with the patient and family. It is suggested that patients first be asked whether they wish to receive specific numbers regarding baseline prognosis and adjuvant therapy benefits. Most patients will agree but a minority will ask to not receive this information.

It is reasonable to begin a presentation by noting that the patient has had newly diagnosed breast cancer, and that all known disease was resected. Physicians can then state that there are two possibilities with regard to this newly diagnosed breast cancer and the rest of the patient's life. One possibility is that all breast cancer has been effectively treated with locoregional therapy and the patient may go on to live a long, healthy life without ever experiencing a recurrence of breast cancer. The other possibility, however, is that there are "seeds of the tumor" left behind that are too small to be found on testing, but may grow and lead to cancer recurrence and an eventual death due to breast cancer.

It is next worth noting that, for any individual patient, it is impossible to tell which of the above situations apply. Nonetheless, prognostic information can give a better idea of a patient's chances of a being effectively cured of her breast cancer. As noted previously, it is reasonable to talk in terms of 10-year survival probabilities for individual patients, informing the patient that there may be a small chance of disease recurrence that may become apparent beyond 10 years.

Next, individualized data, as generated from either of the tools noted earlier, can be explained to the patient. As an example, using individualized data for a 60-year-old woman with a 1.7-cm, grade 3 ER-positive adenocarcinoma with no involved axillary lymph nodes, such a patient can be told that approximately 80 of 100 women should be fine 10 years later without adjuvant systemic therapy. Such a patient can then be told that this number would be approximately 85 of 100 if adjuvant tamoxifen was used, and it would increase to 87% if standard cytotoxic adjuvant chemotherapy was given as well. In concert with discussing the information, both tools allow a visual data presentation that can be given to patients and families for reference (Figure 4). In addition, the toxicity information related to different adjuvant therapies needs to be shared with the patient.

Patient acceptance of such visually supplied information has been evaluated in a randomized trial in which groups of patients were randomized to receive, or not, specific prognostic information from *Adjuvant!*. The results from this evaluation revealed that the patients who received specific individual prognostic information reported greater overall satisfaction with their decision making ($P = .01$) and a greater understanding of adjuvant therapy issues ($P = .03$).[17]

Shared Decision Making

Name: _____ (Breast Cancer)

Age: 60   General Health: Good

Estrogen Receptor Status: Positive   Histologic Grade: 2
Tumor Size: 1.6 - 2.0 cm   Nodes Involved: 1 - 3
Chemotherapy Regimen: CMF-Like (Overview 98)

Decision: No Additional Therapy

73 out of 100 women are alive in 10 years.
19 out of 100 women die because of cancer.
8 out of 100 women die of other causes.

Decision: Hormonal Therapy

5 out of 100 women are alive because of therapy.

Decision: Chemotherapy

1 out of 100 women are alive because of therapy.

Decision: Combined Therapy

6 out of 100 women are alive because of therapy.

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Numeracy

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New Calculator

Adjuvant Systemic Therapy for Breast Cancer

User input the following information

Age:	> 50 yrs
Positive Nodes:	1 to 3
Tumor Size:	1.1cm up to 2.0cm
Hormone Receptor:	Positive

Estimates for baseline prognosis and 10-year outcomes

Ten-year baseline prognosis (chance of being alive without recurrent cancer if no adjuvant therapy is given) - based on tumor size and lymph node status.

Baseline prognosis for survival without adjuvant treatment:	56%

Ten-year estimates for survival associated with adjuvant systemic therapy.

Tamoxifen	64.9 %
Standard adjuvant chemotherapy	59.4 %
Standard adjuvant chemotherapy and tamoxifen	68.9 %

Estimated 10-year survival

| 56.0% base | 64.9% tam | 59.4% std chemo | 68.9% both |

Estimates for proportional reductions in annual mortality associated with adjuvant systemic therapy used for the calculations above.

Tamoxifen	25%
Standard adjuvant chemotherapy	10%
Standard adjuvant chemotherapy and tamoxifen	35%

Figure 4 (A) Representative output printout sheet for *Adjuvant!*. (B) Representative results screen for *Numeracy*.

Facilitating Patient Decisions Regarding Adjuvant Systemic Therapy

After receiving this information, some patients will give clear answers to whether they want to receive systemic adjuvant therapy and which types (ie, hormonal therapy, chemotherapy, or both) they want to receive. Some patients will clearly not wish to receive adjuvant chemotherapy and others will; by this time in the evaluation, note that they wish to get started on therapy as quickly as possible.

Nonetheless, there are other patients who will not have made a decision by this time in the consultation. We have three suggestions regarding patient communication in this setting. First, it is reasonable to note that it is acceptable for the patient to take some time in making this decision. A future consul-

tation can be arranged for patients needing more time to decide.

Second, providing patients and families with a "continuum story" can be helpful in some instances. In this situation, it can be noted that virtually all patients view the available information to different degrees. For example, using the previously described scenario in which adjuvant cytotoxic chemotherapy was predicted to provide 2% absolute benefit in 10-year disease-free survival (eg, from 85% to 87%), patients at one extreme end of the continuum dislike doctors, shots and hospitals, and do not want therapy unless it is proven to be extremely beneficial. Physicians can explain to the patient that this is clearly not her situation, because she would have already said so. At the

other end of the spectrum, some patients feel that they want to do anything possible that might improve survival probabilities even slightly, despite the risk of substantial toxicity. Again, it is worth noting that this situation probably does not describe this patient, because she would have already stated the desire to receive therapy. After being given these extremes of the continuum, the patient can be told that the decision comes down to where they sit on this continuum. If they agree more with the first extreme, the answer is to forgo the therapy being considered. If they agree more with the second situation, it is reasonable to proceed with the adjuvant systemic therapy.

The third strategy to use with patients contemplating a decision is to relate what other patients have said about undergoing adjuvant systemic chemotherapy. In one study, selected women who had previously undergone adjuvant chemotherapy were asked how much benefit, in terms of 10-year survival improvements, would have been necessary for them to view the toxicities that they incurred as worthwhile.[18] Understanding the potential biases present in such a study, almost all of the women reported that the side effects of chemotherapy they incurred were worth a 10% absolute improvement in 10–year survival probabilities, and 50% of women felt that they were worth a 1% improvement in survival. In addition, it may be reasonable to inform the patient of the national guideline recommendations for their treatment, with the caveat that these are recommendations for the average patient in that situation and that they may disagree with them. Finally, many patients express surprise and some degree of disappointment that the proportional benefits are not larger. For these patients (and for most patients), a discussion of what clinical trials might be relevant to their situation is appropriate. In fact, it is appropriate to consider the available clinical trails for all eligible patients. The clinical trial discussion can easily come after a discussion of standard therapy options noted earlier in this article, explaining that the clinical trial is designed to try to lead to even better results.

Supporting Patient Decisions

After receiving the information previously described, most patients will eventually make a decision with which they are comfortable. In the clinic, virtually identical clinical situations will result in different decisions by individual patients given their views of the provided data. Once a patient makes a decision, it is appropriate to support that decision for the patient, noting the particular positive aspects for that individual decision. Having the physician follow the path of this decision lets the patient know that this is a reasonable decision.

Strengths, Weaknesses and Availability of the Two Tools

Each tool has strengths and weaknesses. Two of the major strengths of *Adjuvant!* are that it comes with multiple functions that allow for a multitude of calculations and the data can be displayed in a wide array of formats. Multiple data factors can be input into the program to try to provide a precise individual prognosis for a patient. It allows a wide variety of different chemotherapy options to be displayed for each patient and allows an individual physician the opportunity to modify expected benefits for different chemotherapy regimens. *Adjuvant!* also provides toxicity information. However, these strengths can be viewed by some as a weakness. *Adjuvant!* has a level of complexity (and flexibility) that requires a knowledgeable health professional for appropriate use and interpretation.

The major strength of *Numeracy*, on the other hand, is its simplicity. Only four data input items are required and only one answer set is provided. Again, these factors can be viewed by some to be a major weakness.

Both *Adjuvant!* and *Numeracy* are readily available. *Adjuvant!* can be obtained by request at www.adjuvantsite.com or AdjuvantProgram@aol.com. It can be sent to the user on a CD-ROM, with an installer, and runs on Windows-based computers. A web–based version of *Adjuvant!* for health professionals is available also at www.adjuvantonline.com. Because of concerns about lay persons misunderstanding or misentering tumor-related data, it is suggested that this program be used only by health professionals who then generate patient information sheets to share with patients.

Numeracy is a web-based program that can be run from www.mhs.mayo.edu/adjuvant. It also has been developed into a patient education tool that is available for lay public use at www.mayoclinic.com/takecharge/healthdecisionguides/avt/index.cfm. As such, it is recommended that patients not use the tool as a process of making a final decision about adjuvant systemic therapy, but rather as a means of having more information that will allow them to make a decision in conjunction with their oncologist.

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Conclusions

In summary, practicing oncologists may find it helpful to use both *Adjuvant!* and *Numeracy* as teaching tools and to help provide patients with individualized data to facilitate decision making. Readers who would like more specific information on these tools are referred to the published articles describing them,[5,6] or to their authors.

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