# EDITORIALS

## Tumor Marker Utility Grading System

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I am pleased to comment on the Tumor Marker Utility Grading System (TMUGS), as proposed by Hayes et al. (*1*) in this issue of the Journal. The TMUGS is intended as a tool to aid in bringing order to the process of incorporating tumor markers into clinical practice in the areas of cancer treatment, diagnosis, screening, and prevention. A secondary aim is to provide a framework for identifying tumor marker assessment research needs.

The authors propose that the utility of a particular tumor marker in relation to a particular disease be assessed by filling out a one-page worksheet. The upper portion of the worksheet lists the detailed characteristics of the marker and the marker measurement procedure(s). The authors provide several nice examples to illustrate that the details of a tumor marker assay may have a critical role in determining clinical utility. Hence, careful descriptions of the specimen source and handling, the reagent(s), the basic assay procedure, and the substance measured are required to adequately define the tumor marker measurement.

The lower portion of the worksheet deals with marker utility. It distinguishes between possible future utility, as may arise if a marker is only known to correlate with a biologic process pertinent to the disease in question, or to the disease end point itself, and present utility in the sense that marker assay results can affect practice decisions in a manner that results in a more favorable clinical outcome. This crucial distinction reminds the worksheet user that knowledge of the disease process, or of disease risk factors, becomes useful in clinical practice only if such knowledge leads to better treatment, diagnostic, screening, or preventative decisions. An orderly compilation of correlational information on tumor markers could, however, help identify research opportunities to evaluate tumor marker utility in relation to clinical practice options or help identify the need for additional such options.

The worksheet includes a list of nine possible uses of a tumor marker. Six of these uses relate to the treatment of patients with established cancer and are concerned with the prediction of disease progression or response to treatment and with monitoring disease course. Other uses include the augmentation of standard histopathology for cancer diagnosis, the early detection of cancer, and the assessment of the risk of cancer occurrence. For each such potential use, the worksheet user is to assign a semiquantitative utility grade that reflects the certainty that the marker has potential (i.e., correlates with disease or disease-related process) or actual clinical utility. Each such grade is to be accompanied by a level of evidence grade that scores the quality of the research that supports the utility grade. Only markers that receive a sufficient grade (++ or +++) for actual clinical utility are recommended for incorporation into clinical practice. If so, clinical practice guidelines will presumably be needed to describe other information that is assumed to be available, in addition to the marker measurement, for clinical decision-making, and concerning the corresponding recommended practice decisions.

The TMUGS worksheet lists four measures of clinical outcomes corresponding to each of the nine potential uses of a tumor marker; i.e., survival, disease-free survival, quality of life, and cost of care. Hence, the completed worksheet provides an assessment of the usefulness of a highly specified tumor marker measurement in one or more usage areas for each of several clinical outcomes.

Hayes et al. (*1*) are to be congratulated for trying to bring some order to the selection of marker assays, from a rapidly expanding set of possibilities, into clinical practice. The TMUGS worksheet seems to be a very useful device for organizing and communicating much of the pertinent information on a particular assay for use in relation to a specific cancer. The authors conclude that the proposed TMUGS should result in improved patient outcomes and more cost-efficient investigation and application of tumor markers. They do not, however, describe the process by which the availability of this tool may influence practice guidelines and practice decisions. Perhaps the TMUGS worksheet will be used by the American Society of Clinical Oncology (ASCO) expert panel on clinical practice guidelines for the use of tumor markers, mentioned in the authors' acknowledgment. One wonders, however, if some ongoing process is envisaged under which the utilities of a comprehensive set of promising tumor markers are conducted, compiled, and updated as necessary, with periodic review of implications for clinical practice. Such a process may be necessary for the proposed tool to have much impact on clinical outcomes.

I would like to offer a few more detailed comments on the TMUGS worksheet toward possible refinements of the utility

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*See* "Note" section following "Reference."

grading process. First, the proposed utility scales [Tables 3 and 4 in (*1*)] are concerned exclusively with the certainty of the correlation of the marker with disease outcome or process and the certainty that marker utilization in decision-making can improve clinical outcome, rather than with the magnitude or importance of such correlation or improvement. As such, the level of evidence scores [Table 5 in (*1*)] seems essentially redundant, and the two scales could usefully be combined to yield a single scoring system. On the other hand, toward the end of their article, the authors write that the utility scale scores "assess the magnitude and clinical importance of the observed benefit," suggesting that their Tables 3 and 4 scale definitions should be substantially revised to reflect magnitude and importance, in which case the level of evidence scores would include valuable complementary information and should be retained.

Another question concerns the issue of marginal versus conditional utility. The utility scale definitions [Tables 3 and 4 in (*1*)] seem to be concerned with the marginal correlations between a marker and a disease or the marginal value of a marker in decision making toward improved clinical outcomes, whereas the authors' narrative description makes clear that the marker is expected to provide additional independent correlational information (i.e., partial correlation) or additional useful information beyond that which would ordinarily be available for clinical decision making to receive a favorable utility grade. These latter conditional utilities would seem to be the more relevant to current or future clinical practice, so that the authors may wish to accordingly refine their utility scale definitions, in which case the TMUGS worksheet may require an attachment to list the other data items assumed to be available in assessing correlations or the other information assumed to be available for practice decisions. Such an attachment could also highlight key elements of the practice decisions (e.g., therapeutic recommendations) as a function of the tumor marker value and the other available data to facilitate linkage to practice guidelines.

The four clinical outcome categories chosen by the authors (i.e., survival, disease-free survival, quality of life, and cost of care) may be well chosen for applications to cancer therapy, but they are unlikely to be the outcomes to be highlighted in a cancer screening or cancer prevention application. For example, mortality from the screened disease or incidence of the disease to be prevented are, respectively, the customary primary outcomes in such contexts, while quality of life, cost of intervention, and some summary measure of overall benefit versus risk frequently would also be of interest. Usage categories, different from those given in the TMUGS worksheet, would also be natural for such applications. For example, in a primary prevention setting, a marker may be of value as an indicator of disease risk, as an indicator of response to possible preventative maneuvers, or as a means of monitoring disease risk within the follow-up of patients adhering to a preventative program. It may be that distinct worksheets would need to be developed for these nontherapeutic applications.

Finally, it would be useful to receive guidance from the authors as to how the assessments in regard to their four clinical outcomes are to be merged. For example, use of a tumor marker may lead to a therapeutic course that can marginally improve disease-free survival, but only if cost of care is noticeably increased; or marker information may signal therapeutic opportunities that can slightly improve survival for some patients, but at the expense of a prolonged reduced quality of life. Are the authors able to offer guidance that could lead to an overall summary utility score?

To reiterate, these comments and questions are not intended as criticisms of the authors' proposals but rather as encouragement to see how much order they can bring to the process of incorporating tumor marker information into routine clinical practice.

## Reference

(*1*) Hayes DF, Bast RC, Desch CE, Fritsche H Jr, Kemeny NE, Jessup JM, et al. Tumor Marker Utility Grading System: a framework to evaluate clinical utility of tumor markers. J Natl Cancer Inst 1996;88:1456-66.

## Note

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