Standards for Reporting Prognostic Tumor Marker Studies

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Technologic and scientific advances have led to an explosion in the number of new tumor markers being studied for the early detection and prognosis of cancer. It is imperative that the design and results of tumor marker studies are reported in a comprehensive manner so that they can be evaluated critically. However, this is often not the case. This problem motivated the Statistics Subcommittee of the National Cancer Institute-European Organization for Research and Treatment of Cancer working group on cancer diagnostics to develop guidelines, referred to as REMARK, for the reporting of tumor marker studies. In this issue of Journal of Clinical Oncology, McShane et al. present these REMARK guidelines for the reporting of prognostic tumor marker studies. These guidelines are similar in spirit to the Consolidated Standards of Reporting Trials initiative for randomized clinical trials and Standards for Reporting of Diagnostic Accuracy statement for diagnostic accuracy studies.

The REMARK contains 20 recommendations about the reporting of the study design, statistical analysis methods, preplanned hypotheses, patient and specimen characteristics, and assay methods for tumor marker studies. The guidelines are intended for studies of prognostic markers, which McShane et al. define to be markers that “have an association with some clinical outcome” and which “may be considered in the clinical management of a patient.” As an excellent example of how a prognostic marker study should be reported, Dome et al. in this issue of Journal of Clinical Oncology report the results of a study investigating the prognostic significance of telomerase expression level in patients with favorable histology Wilms’ tumor. It clearly adheres to the reporting guidelines outlined in REMARK.

The REMARK guidelines were developed primarily for studies evaluating a single tumor marker while possibly adjusting for other known prognostic factors. However, the guidelines should also be applicable to studies of a small number of tumor markers such as in the study by Dome et al. of expression levels of TERT mRNA and TERC/hTR in patients with favorable histology in a Wilms’ tumor. However, the guidelines are not suggested for studies of a large number of candidate markers that could be obtained, for example, from protein mass spectrometry profiles or gene expression arrays, because the guidelines do not discuss the additional statistical considerations required for high-dimensional data.

Biomarkers are increasingly being developed to detect tumors early enough that treatment is likely to be successful. Five phases of biomarker development for early detection of cancer have been proposed. Specifically, preclinical exploratory studies (phase 1), clinical assay development for clinical disease (phase 2), retrospective longitudinal repository studies (phase 3), prospective screening studies (phase 4), and cancer control studies (phase 5). The REMARK guidelines appear to be most relevant to phase 2 and 3 biomarker studies. In these phases the receiver operating characteristic (ROC) curve can be used to estimate the ability of a continuous biomarker to predict or classify the patients who are likely and those who are not likely to have the outcome. A ROC curve is a graphical display of the tradeoffs of the true-positive rate (ie, sensitivity) and false-positive rate (ie, 1 – specificity) corresponding to all possible binary tests that can be formed from a continuous biomarker. Baker provides a useful description of the use of ROC curves in the evaluation of early detection biomarkers.

The disappointing performance of markers that were initially shown to have a strong association with outcome in part may be because a marker that is strongly associated with outcome may not be effective for predicting those who are likely and those who are not likely to have the outcome. Pepe et al. note that a marker with an odds ratio as high as 3 will be a poor predictor of risk. The classification ability of a continuous marker should be assessed using ROC curves, whereas sensitivity and specificity can be used for dichotomous markers.

The use of the REMARK guidelines will allow tumor marker studies to be evaluated critically as well as interpreted.
appropriately. Therefore, the editors of *Journal of Clinical Oncology* encourage authors who plan to report results of prognostic marker studies to use the REMARK guidelines.

**Author’s Disclosures of Potential Conflicts of Interest**

The author indicated no potential conflicts of interest.

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REFERENCES


