

EDITORIAL

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How will the reporting recommendations for tumor marker prognostic studies affect clinical trials?

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“The direction of modern medicine is changing, focusing more on treatments tailored to the specific characteristics of a patient’s disease.”

The direction of modern medicine is changing, focusing more on treatments tailored to the specific characteristics of a patient’s disease. The sequencing of the human genome has enabled significant progress in understanding the underlying biology of a number of diseases; this has been seen particularly in the field of oncology. As pathways are elucidated and the effects of alterations in these pathways are defined, new drugs are being developed to take advantage of this new knowledge. The principles articulated here apply to biological marker studies in other diseases; however, our examples are drawn from the extensive oncology literature.

The need to use new and existing therapeutics most effectively has highlighted the necessity for informative biological markers (also called tumor biomarkers in oncology) to help guide clinical decisions and for the development of assays to appropriately measure these biological markers. Over the last few decades, thousands of publications have reported associations between various tumor biomarkers and clinical parameters and outcomes, including prognostication, prediction of response to therapeutics or monitoring disease progression. However, few of these tumor biomarkers have found their way into regular clinical use.

Many factors have contributed to the apparent gap between the number of reports of promising biological markers and the number of tumor biomarker tests that are in regular clinical use. Often the relationships discovered in model systems, such as cell culture or animal models, do not translate to the human disease setting. Other problems, including development of an assay that reproducibly measures the biomarker in the appropriate clinical setting, prove to be more challenging and expensive than anticipated. Research on biological markers, and the assays used to measure them, has often been poorly designed, lacking clear hypotheses and appropriate statistical designs [1].

One of the greatest obstacles to determining the clinical utility of a tumor biomarker stems from the lack of sufficient information in published reports to allow informed interpretation of the data or comparison with other reports about the same biological markers and assays. To address this concern, an international collaboration developed the reporting recommendations for tumor marker prognostic studies (REMARK), originally published simultaneously in five international journals and republished in others [2–8]. The REMARK guidelines include a checklist of items that should be fully reported in all publications, including a diagram that transparently illustrates selection and disposition of patients who ultimately comprised the study population, as well as details about the assay, statistical design and analyses of clinical correlations.

Keywords: clinical trials • clinical utility • guidelines • REMARK • tumor marker

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Recently, four of the original authors published a longer explanatory paper to provide a more complete understanding of what information is needed and why each item in the checklist should be reported [9,10]. Although initially directed toward studies of prognostic markers, the REMARK guidelines also apply to studies of predictive markers. The examples cited in the explanatory paper all come from the oncology literature; however the items in the checklist would generally apply to reports of biological marker studies in other diseases, with some tailoring to the specifics of the research area [11].

Three important terms are used in the discussions of biomarker tests: analytical validity, clinical validity and clinical utility. The definitions put forth by the Evaluation of Genomic Applications in Practice and Prevention Initiative Working Group have been widely adopted. Analytical validity addresses the reproducibility, accuracy and general reliability of the biomarker test. Clinical validity refers to the strength of the association between the biomarker test result and the clinical outcome of interest, or the ability of the test to divide a population into subset(s) that differ in outcome. Clinical utility of a test means that a patient's outcome is improved by virtue of a clinical decision based on the test results when compared with a decision that would have been made in the absence of the tumor biomarker test results [12]. Both analytical and clinical validity must be demonstrated prior to testing the utility of a biomarker test to guide a clinical decision.

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It is clear that clinical trials are crucial to the evaluation of the clinical utility of prognostic and predictive markers. Trials are very expensive to run so it is imperative that every effort is made to make them efficient and to get the maximum information from them. Problems related to the reporting of clinical trial data led to development of the Consolidated Standards of Reporting Trials statement [13], which was recently updated [14]. One of the main issues was that without adequate information in the publications, it was difficult to draw appropriate conclusions. The Consolidated Standards of Reporting Trials statement served as a model for the development of the REMARK guidelines.

Clinical trials that include studies of tumor biomarkers require the collection of high-quality specimens from trial participants. These collections, with associated carefully documented clinical and outcome data, form extremely valuable resources for future studies. The

National Cancer Institute (MD, USA) and other organizations have focused on the development of standards for collection and long-term storage of specimens [15,101]. The Biospecimen Reporting for Improved Study Quality (BRISQ) guidelines were developed to ensure that relevant information, related to the source and handling of specimens, would be included in reports of studies that depend on the use of specimens [16]. The BRISQ guidelines expand on specific reporting requirements for items relating to specimens in the REMARK guidelines.

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Studies of the utility of biological markers are increasingly being incorporated into clinical trials, but the trial designers often do not have adequate information about the tests that will be used to measure the markers. Tests are often developed in academic laboratories that focus more on the biological questions than on test performance. A test to be used to direct clinical care, including in a clinical trial, must be performed in Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories. Even if the test is performed to initially assess a correlation, if the investigator is planning to generate data that would support potential clinical utility, performance of the test within a CLIA-certified laboratory is recommended. The transfer from a development laboratory to a CLIA laboratory requires significant testing of assay performance and clinical validation. The developmental assay may not have been performed on the same type of clinical specimens that will be routinely available; for example, frozen samples versus formalin-fixed specimens, and scale-up of the assay may be complicated. These problems were encountered in the development of a test for overexpression of HER-2, which was required for the approval of trastuzumab (Herceptin™). This led to substantial confusion within subsequent clinical trials, as well as in clinical practice. Ultimately, a panel was convened jointly by the American Society of Clinical Oncology (VA, USA) and the College of American Pathology (IL, USA) to address many of the problems in a set of laboratory guidelines, and to establish a proficiency testing program that has helped standardize assays for this marker, as well as for hormone receptors [17]. The National Cancer Institute is attempting to facilitate the transition of developmental assays to well-documented and clinically ready assays with its Clinical Assay Development Program [102].

Trials that include marker tests that have not been adequately evaluated and standardized will result in questionable interpretation of the data. The REMARK

and BRISQ guidelines, if followed, should result in greater understanding of the biological markers and tests to measure them that are proposed for inclusion in clinical trials and in more reliable and interpretable data. Adherence to the guidelines will provide a high level of evidence for the determination of the clinical utility of the biomarker test.

Since it will be impossible to perform randomized clinical trials to evaluate the clinical utility of every new, promising biological marker, researchers will have to make effective use of collections of specimens from earlier trials [18]. It is imperative that these collections be adequately documented and conserved. Researchers must be encouraged to follow the relevant published guidelines, and journals should make clear, to both submitters and reviewers, that adherence to these

guidelines will be part of the review process. In turn, this should result in more effective and efficient use of clinical trials and in more reliable data emerging from these trials.

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