Title: Improving Publication Rates of Biomarker Results from Cancer Trials

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Running Title: Commentary on Biomarker Publication Rates.

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Summary: Mandatory non-diagnostic biopsies for biomarker research pose risk and inconvenience to cancer patients that should be justified by the knowledge gained. This commentary reflects on the publication by Freeman et. al., which points to a potentially low publication rate of biomarker results from cancer clinical trials requiring non-diagnostic biopsies.

In this issue of CLINICAL CANCER RESEARCH, Freeman et. al.¹ assess the frequency of publication of biomarker data derived from mandatory non-diagnostic tumor biopsies, and explore the reasons for non-publication. Their assessment is based on tracking the full publication of AACR and ASCO abstracts identified as including biomarker objectives based on non-diagnostic tumor biopsies. The reasons for non-publication were examined by using a questionnaire provided to authors who were determined to have published biomarker-based studies in the past. Results showed that 70 out of 90 abstracts identified from AACR and ASCO annual meetings resulted in full publication. Forty-three of these 70 included a complete description of the planned biomarker analysis, and an additional 21 included only partial biomarker data. 16 publications did not include any biomarker results; however, it was determined that some of these data were published elsewhere. 92 authors were sent questionnaires, and 33 of these were sent to corresponding authors from the ASCO and AACR abstracts included in the original survey. Among the 53 completed questionnaires, the most commonly cited reasons for non-publication included: poor patient accrual, poor quality and/or
incomplete assay results, and strategic reasons such as the interpretation of the results was unclear.

Interpretation and generalization of this study’s results are limited for several reasons. First, the sample size was small. Also, focusing on abstracts published at A merica Cancer Research Society (AACR) and American Society of Clinical Oncology (ASCO) neglects biomarker studies that did not make it to publication even in abstract form, perhaps underestimating the non-publication rate. We also do not know anything about the biomarker objectives or the study designs, which could give some insight into the whether scientific rigor influenced ultimate publication. Despite these limitations, the results will likely ring true for those familiar with oncology clinical trials, and few would disagree that we should strive for universal publication of biomarker data from studies with mandatory tumor biopsies. Even so, it’s possible to view the results with a more positive perspective. After all, fewer than 16 of the 70 published articles did not include any biomarker information (The exact number is unknown, as the authors state that “some” of the data were published separately from the primary results.). Results of the questionnaire regarding likely reasons for non-publication also ring true: poor patient accrual to biopsy mandated trials, poor quality assay and unclear interpretation. The main point of the article is not to make a case against the value of biomarker driven oncology drug development, but rather to highlight the less than optimal dissemination of biomarker data from studies that imposed an additional burden on patients to obtain new tumor biopsies. The results of the questionnaire suggest that lack of clear interpretation of the results often prevented full publication of biomarker data from such studies. This may have been on the basis of poor quality samples, not having a well-powered hypothesis or the lack of a qualified assay. This highlights the importance of assuring the scientific rigor of the biomarker objectives and their implementation. But one could also question whether this reflects the current state of oncology clinical research. It was necessary for the authors to focus on studies that were completed prior to 2005 in order to allow adequate follow-up time to assess whether a full publication resulted from the initial meeting abstract. In the decade that has passed from the time that many of these trials would have initiated, there has been an impressive increase in our understanding of the molecular drivers of cancer, as well as the prognostic and predictive value of tumor biomarkers. It is now more the norm than the exception for drug development to include predictive biomarker hypotheses. In such cases, it is often required that patients undergo non-diagnostic tumor biopsies to obtain new tumor samples. Because the molecular drivers for any given tumor may evolve in the face of initial therapy, new tumor biopsies are likely to be more relevant to subsequent treatment decisions as compared to archival specimens. While this imposes an additional burden on patients, recent examples of well executed biopsy mandated trials illustrate the potential value to both patients and the drug development process. In the Biomarker—integrated Targeted Therapies for Lung cancer Elimination (BATTLE) trial, NSCLC patients were adaptively randomized to therapies based on pre-defined biomarker hypotheses and the results of new tumor biopsies. The trial was adaptive in that the initial randomization was balanced across treatment arms; however, emerging results from the trial were used to rationally influence randomization to different therapeutic arms during the conduct of the trial, based on
the patients’ biomarker information. The results validated pre-specified biomarker hypotheses and identified new ones. As expected, erlotinib was beneficial in patients within mutated EGFR tumors. Additionally, sorafenib was noted to be active in patients with mutant and wild type KRAS tumors, but not in patients with EGFR mutations. Likewise, erlotinib plus bexarotene improved disease control in patients with high Cyclin D1 expression and KRAS mutations. The BATTLE trial has been impactful not only for the scientific contribution to our understanding of these biomarkers as they relate to treatment of NSCLC, but it also demonstrated the feasibility of executing a trial that required non-diagnostic lung tumor biopsies. As a second example, I-SPY2 (investigation of serial studies to predict your therapeutic response with imaging and molecular analysis 2), an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy, is poised to be impactful as well. In this study, initial treatment is based on standard biomarkers. The patients’ tumors will also be classified based on biomarker signatures defined by: hormone receptor status, HER2 status and two levels of MammaPrint scores. Investigational drugs were rationally selected on the basis of scientifically supported biomarker hypotheses. MRI and assessment of pathologic complete response will be used to improve the randomization to experimental arms based on biomarker signatures and associated tumor responses in the neoadjuvant breast cancer setting. During the conduct of the study, drugs will be dropped for futility, and others will be graduated to phase II trials based on probability of greater efficacy compared to standard therapy.

The BATTLE and I-SPY2 trials are two good examples of the trend to incorporate biomarker information and test biomarker hypotheses in clinical oncology development. Increasingly, biomarker data will be integral to the primary results of the clinical trials and will be uniformly included in the published results. The value of such studies and the need for non-diagnostic tumor biopsies is clear, but to the authors’ point, the risk and inconvenience to patients of nondiagnostic biopsies should be justified by the quality of the research and the potential impact of its results. Figure 1 attempts to define a checklist of requirements for inclusion of mandatory biopsies in oncology clinical trials.

References:


**Figure Legend:**

Figure 1. Checklist outlining requirements for inclusion of mandatory biopsies in oncology clinical trials
Biomarker objectives and hypotheses are clearly stated
There is adequate statistical power based on an understanding of assay variability, the expected magnitude of effect, and the expected study sample size
Procedures are in place to assure adequate tissue acquisition, handling, and storage
An analytically validated assay is available
The importance of information to be gained justifies the risk to patient
Funding to execute is assured

Figure 1:

Checklist of requirements for inclusion of mandatory biopsies for oncology patients in clinical trials

✓ Biomarker objectives and hypotheses are clearly stated
✓ There is adequate statistical power based on an understanding of assay variability, the expected magnitude of effect, and the expected study sample size
✓ Procedures are in place to assure adequate tissue acquisition, handling, and storage
✓ An analytically validated assay is available
✓ The importance of information to be gained justifies the risk to patient
✓ Funding to execute is assured

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