The Holy Grail of biomarkers

The literature is swamped with studies on biomarkers and it seems that almost every other publication promises identification of a new biomarker associated with disease prognosis or treatment prediction. A crude search of PubMed reveals over 450,000 publications on the subject, with tens of thousands of these articles related to cancer biomarkers. This is one of the most confusing, unclear and complicated aspects of oncology, not least because as soon as one publication confirms the role of a new biomarker, another concludes that it is no more convincing regarding disease prognostication or treatment prediction than a more-established one.

A biomarker is a biochemical feature used as an indicator of a biologic state that, if objectively measured and evaluated, signifies normal biologic or pathogenic processes, or response to a therapeutic intervention. Prognostic biomarkers provide very general information regarding outcome before therapy; most of the molecular profiles in breast cancer fall into this category. Predictive markers dictate response to a particular therapy. Currently, the most effective predictive biomarkers are *KRAS* mutations in colorectal cancer that predict unresponsiveness to EGFR inhibitors, and *EGFR* mutations in patients with lung cancer who respond to EGFR inhibitors. These markers are of real practical value.

In this issue, two Research Highlights summarize important studies relating to prognostic biomarkers. O'Brien and coauthors assessed whether pretreatment prostate-specific antigen (PSA) velocity or PSA doubling time according to a number of different definitions could predict outcome in men undergoing radical prostatectomy. They demonstrated that although some definitions of PSA velocity or PSA doubling time do correlate with outcome, the accuracy of these markers for predicting outcome is less than that of PSA measurement alone. Sorensen *et al.* used an advanced MRI technique to evaluate three biomarkers and showed that they can predict progression-free survival and overall survival in patients with recurrent glioblastoma just 1 day after treatment with the anti-VEGF agent cediranib.

The third type of biomarker is one that can indicate when the tumor has totally gone—this is the 'Holy Grail' of biomarkers. This is the biomarker that is of the most value to oncologists. The best example of the effectiveness of this type of biomarker is human chorionic gonadatropin (hCG), which is used to monitor treatment in choriocarcinoma. It is both sensitive and, more importantly, specific. No hCG, no tumor. A poor example is CA-125, which is measured in most patients with ovarian cancer yet is not very sensitive or specific—levels can drop to zero even when tumor is diagnostically detectable.

Cancer is a heterogeneous set of diseases with many subtypes that differ genetically and epigenetically. It is important to determine the stability of a biomarker, and how its behavior in controls varies over time, before it can then be assessed as a reflection of natural history of the disease. Definitions of a biomarker can vary greatly in different studies and establishing a consistent common terminology is paramount to ensure cohesiveness for future studies.

Perhaps the most controversial area is the issue of randomized trial design. Although randomization to different treatments, regardless of the presence or absence of the biomarker, may be an ideal strategy, it could mask the positive effects of a drug if it is only efficacious in those patients who express the biomarker. Conversely, if different techniques with diverse specificity and sensitivity are used to determine marker presence then the true benefit or detriment of a treatment might be missed.

Top research priority should be given to finding the Holy Grail of biomarkers—something that is specific for the tumor being assessed, and only for that tumor. Yet studies of this type of marker are vastly underrepresented. Just think about what such a marker would mean to patients with newly diagnosed breast cancer. It would tell you if surgery was enough. Only people who needed chemotherapy would get it. Furthermore, if patients needed adjuvant chemotherapy, you would know the precise time to stop.

Despite their limitations, marginal biomarkers are often ordered for cancer patients. In general they do little to advance the effectiveness of treatment. We will continue to flounder in this field until we are able to find markers that are specific for malignant versions of normal cells. That's the Holy Grail and it seems a long way away.

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Lisa Hutchinson is the Editor and **Vincent T. DeVita Jr** is the Editor-in-Chief of *Nature Reviews Clinical Oncology*.

Competing interests
The authors declare no competing interests.