## BIOMARKERS VERSUS SURROGATE END POINTS

It is important to keep in mind in any discussion of biomarkers and translational medicine that not all biomarkers are useful as a substitute for a demonstration of efficacy. In fact, only a small subset of biomarkers are recognized by regulatory bodies as sufficiently validated that they are accepted as indicators of efficacy in clinical trials. Biomarkers that meet these criteria are referred to as surrogate end points. The NIH Biomarkers Definition Working Group also provided a definition of this class of biomarkers, stating that a surrogate end point is "a biomarker that is intended to substitute for a clinical endpoint and is expected to predict clinical benefit or harm, or lack of benefit or harm, based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence."[15] In other words, in order for a biomarker to be useful as a surrogate end point, there must be clear and convincing scientific evidence (e.g., epidemiological, therapeutic, and/or pathophysiological) that the biomarker in question consistently and accurately predicts the clinical outcome. If this correlation does not exist, then the biomarker cannot be used as a surrogate end point in a clinical trial, irrespective of how objective or quantifiable it may be. There are very few biomarkers that meet these stringent criteria. Some examples include blood pressure changes, serum cholesterol concentrations, and lipid fraction as measure of cardiovascular disease risk[24]; $CD4^+$ T-lymphocytes level and RNA viral load measurements for HIV progression[25]; and tumor size measurements in oncology studies, although there is an ongoing debate on the validity of this particular surrogate end point.[26]

Using surrogate end points and biomarkers in general during the prosecution of clinical programs provides a number of advantages that can translate into decreased patient risk, reduced costs, and shorter clinical trials. Consider, for example, a clinical trial designed to determine whether or not a candidate compound is capable of reducing the risk of heart attacks. In the absence of a surrogate end point, it would be necessary to recruit, treat prophylactically, and monitor a large set of patents for an extended period of time (months to years) while waiting for an infrequent event (e.g., heart attack) to occur. If, however, a surrogate end point were available, such as blood pressure changes or cholesterol concentrations, the picture becomes very different. Changes in these parameters would occur much more rapidly, substantially decreasing the length, and therefore both cost and patient risk, of a clinical trial. In addition, clinical trials of candidate compounds that failed to affect the surrogate end point (e.g., lower blood pressure or lower cholesterol) could be terminated at an earlier time point than a study designed to monitor clinical end points such as the occurrence of a heart attack or survival. The early termination of a clinical trial decreases patient risk by decreasing their exposure to failed candidate compounds. It also decreases the overall cost of drug discovery and development by allowing clinical efforts to be redirected away from a failed candidate compound at an earlier time point.