a. Predictive Markers Versus Prognostic Markers

The most common uses for biomarkers are to determine the likely outcome of a disease in the absence of therapy, and to determine whether a given drug is likely to be effective against that disease. According to Mandrekar and Sargent (13), these two uses are referred to by the terms, *prognostic* marker and *predictive* marker, respectively. These concepts are illustrated below with data on breast cancer and colorectal cancer.

Overexpression of *HER2* by breast cancer cells increases invasiveness and tumorigenicity of breast cancer, where the oncogenic effects of *HER2* result from gene amplification rather than from mutations (14). Trastuzumab (Herceptin®), an antibody that binds to *HER2*, generally mediates the killing only of tumors that overexpress *HER2* (15). Tumors showing negative staining for *HER2* are not killed by *HER2*-targeted therapies. In fact, the package insert for Herceptin expressly states that this drug has been FDA-approved only for patients having tumors that overexpress *HER2*. The package insert reads, "Herceptin as a single agent is indicated for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease" (16).

Breast cancer patients with *HER2* overexpression face bad news and good news. The bad news is that this overexpression is associated with a more aggressive cancer. But the good news is that this overexpression is associated with enhanced efficacy of Herceptin.

This concerns a different marker, *KRAS*. RAS is a protein that is part of a cell signaling pathway (17). RAS actually represents a family of three different genes, namely, *KRAS*, *HRAS*, and *NRAS*. *KRAS*, also called Ki-RAS or Kirsten-RAS, was named after Werner Kirsten (18,19). Oncogenic mutations in *KRAS* occur in about 40% of colorectal cancers. These mutations are associated with a somewhat poorer prognosis.

This concerns predicting responses of a patient to a drug. In summarizing the results from a clinical trial on colorectal cancer, Mandrekar and Sargent (20) state that *KRAS* status was assessed on 427 subjects, where 43% were found to have *KRAS* mutations. Subjects were then randomized to receive either anti-epidermal growth factor receptor (anti-EGFR) antibody (panitumumab) or placebo. The results demonstrated that the anti-EGFR antibody was more effective in subjects where tumors expressed wild-type *KRAS*, and less effective where tumors expressed mutated *KRAS*.

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