

these markers are used to identify an adverse reaction at an early stage in a subject receiving drug.

2.3 Is the Therapy More Effective in One Population?

Stratification biomarkers predict efficacy and categorize patients by likelihood of response to a particular treatment, enabling enrichment of patients most likely to respond to therapy. The best described example is again HER2 status for treatment with trastuzumab (Herceptin[®]). Stratification biomarkers also predict whether a patient develops an adverse reaction to a prescribed drug, enabling enrichment of patients that can be safely treated with a specific drug. For example, P450 variants predict drug metabolism in multiple indications. Many genetic variants have been identified that are known to alter cytochrome P450 (CYP) enzymes and drug receptors, transporters, and targets (Crews et al. 2012). Known mutations in cytochrome P450 are, for example, used to select the starting dose of the anticoagulant warfarin.

2.4 Does the Biomarker Predict Survival?

Prognostic biomarkers are biomarkers that provide information on the risk or likely course of the disease in an individual and the potential overall outcome. Sometimes the terms susceptibility or risk biomarker are used for biomarkers linked to the risk of developing a disease. The BRCA1 and BRCA2 mutations are typical examples in oncology. Germline mutations in the BRCA1 or BRCA2 tumor-suppressor genes are strong predictors of breast and/or ovarian cancer development (Fackenthal and Olopade 2007). In addition, four gene signature panels, the Oncotype DX[®] (Genomic Health), the MammaPrint[®] (Agendia), the ProSigna[™] (Nanostring), and the Mammostrat[®] (Clariant Diagnostic) panels, are commonly used to test breast cancer patients. While all four tests are somewhat similar, there are differences: The Oncotype DX[®] test is used to estimate a woman's risk of recurrence of early-stage, hormone-receptor-positive breast cancer, as well as how likely she is to benefit from chemotherapy after breast cancer surgery. The Oncotype DX[®] test also is used to estimate a woman's recurrence risk of DCIS (ductal carcinoma in situ) and/or the risk of a new invasive cancer developing in the same breast, as well as how likely she is to benefit from radiation therapy after DCIS surgery. The Oncotype DX[®] test analyzes the activity of 21 genes. The MammaPrint[®] test is used to estimate a women's recurrence risk for early-stage breast cancer. The breast cancer can be hormone-receptor positive or hormone-receptor negative. The MammaPrint[®] test analyzes 70 genes to see how active they are and then calculates either a high-risk or a low-risk recurrence score. MammaPrint[®] results can help a woman and her doctor make a more informed decision about whether to use chemotherapy to reduce recurrence risk. The Mammostrat[®] test is used to estimate a woman's risk of recurrence of early-stage, hormone-receptor-positive breast