3. The surrogate is not in the pathway of the drug's effect.
4. The study drug has mechanisms of action that are independent of the disease process.

d. Clinical Trials Focusing on Utility of a Biomarker

It is common practice, in clinical trials, to stratify subjects according to the grade or stage of the disease or pathological lesion, gender, and study site (city or nation). During the event of allocation and randomization, study personnel ensure that the number of subjects in each of these subgroups, for study drug subjects, is equal to the number of subjects in each corresponding subgroup, for control subjects.

But where the goal of a clinical trial is to assess the value of a biomarker, study subjects are also stratified into a first subgroup where biomarker is highly expressed, and into a subgroup where biomarker expression is low.

1. Biomarkers in Breast Cancer —The Stratton Study

Biomarkers relevant to breast cancer include *BRCA1* gene, *BRCA2* gene, human EGFR-2 (*HER2*), *estrogen receptor*, and *progesterone receptor*. Women with mutations in *BRCA1* or *BRCA2* are at increased risk for breast cancer (30). These women have a 50% chance of developing breast cancer. *BRCA1* mutations also result in an increased risk for ovarian cancer and, in men, prostate cancer. Women screening positive for these mutations have the choice of frequent cancer surveillance by magnetic resonance imaging, chemoprevention, or preemptive mastectomy (31). Table 19.1 lists the contribution of *BRCA1* mutations to ovarian cancer.

TABLE 19.1 Contribution of BRCA1 Mutations to Ovarian Cancer[a]

Patient	Mutation in *BRCA1* Gene
Breast cancer, age 50	Deletion of AA (adenine-adenine) at nucleotide 230
Ovarian cancer, age 38	Four base pair deletion at nucleotide 1942
Ovarian cancer, age 34	Four base pair deletion at nucleotide 3452
Breast cancer, age 38	Deletion of GT (guanine-thymine) at nucleotide 4287
Breast cancer, age 60	Conversion of C (cytosine) to T (thymidine) at nucleotide 4446, resulting in a stop codon
Breast cancer, age 44	Four base pair deletion at nucleotide 5149
Ovarian cancer, age 44	Insertion of C (cytosine) at nucleotide 5382
Ovarian cancer, age 40	Deletion of G (guanine) at nucleotide 5629

[a]*Stratton JF, Gayther SA, Russell P, et al. Contribution of BRCA1 mutations to ovarian cancer. New Engl. J. Med. 1997;336:1125–30.*

[30]Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. New Engl. J. Med. 2009;361:123–34.

[31]Olopade OI, Grushko TA, Nanda R, Huo D. Advances in breast cancer: pathways to personalized medicine. Clin. Cancer Res. 2008;14:7988–99.