c. Endpoint That Is a Combination of a Biomarker and a Clinical Parameter

An endpoint can take the form of a composite that is the combination of a biomarker and a clinical parameter. Nolen and Lokshin (141) described the combination of a protein (carbohydrate antigen-125; CA125) and a clinical parameter (ultrasound). Where CA125 alone is used, this biomarker is sensitive to only half of early-stage ovarian cancers. A problem with using *ultrasound alone*, is a high rate of false positives (142). The composite endpoint provides the most reliable endpoint.

A panel of biomarkers, typically used with an algorithm to generate a score, is sometimes used in clinical trials. To this end, Pinsky and Zhu (143) stated that, "[a] widely held viewpoint in the field of predictive markers for disease holds that no single marker can provide high enough discrimination and that a panel of markers ... will be needed." Although it might be intuitively obvious that a panel of markers is more accurate than using only one biomarker, attempts at discovering useful panels often fail. For example, one study which concerned CA125, an established biomarker for ovarian cancer, determined that a panel of eight biomarkers that included CA125 is no more predictive than CA125 alone (144). *False positives* occur with the CA125 biomarker, because CA125 can be elevated in benign conditions, such as endometriosis, pelvic inflammatory disease, pregnancy, and diverticulosis. Another problem with the CA125 biomarker, is *false negatives* in about half of early-stage ovarian cancers (145).

Another example of a combination of a biomarker with clinical parameters, is use of the CA125 biomarker and ultrasound and menopausal status clinical parameters. The algorithm takes the form (146):

$$\text{Risk Malignancy Index} = [\text{serum concentration of } CA125] \times [\text{ultrasound score}] \times \left[\text{menopausal status}\right]$$

The algorithm provides a score called the Risk Malignancy Index (RMI). The CA125 component of this score is the concentration of CA125 in serum (units/mL). The ultrasound component of this algorithm is itself the result of an algorithm. In other words, the ultrasound component is the result of the following sum. To arrive at this sum, one point is given for each of septations, solid areas, metastatic disease, ascites, and bilateral lesions, as determined by ultrasound. Regarding the menopausal component of this algorithm, one point is given if premenopausal, and three points is given if postmenopausal.

Jordan and Bristow (147) were careful to disclose that the risk malignancy index (RMI) has been periodically refined and updated

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