

**Statistical Considerations for
Soluble Mesothelin Related
Peptide (SMRP) and
Osteopontin (OPN) as Early
Detection Markers for
Malignant Mesothelioma (MM)**

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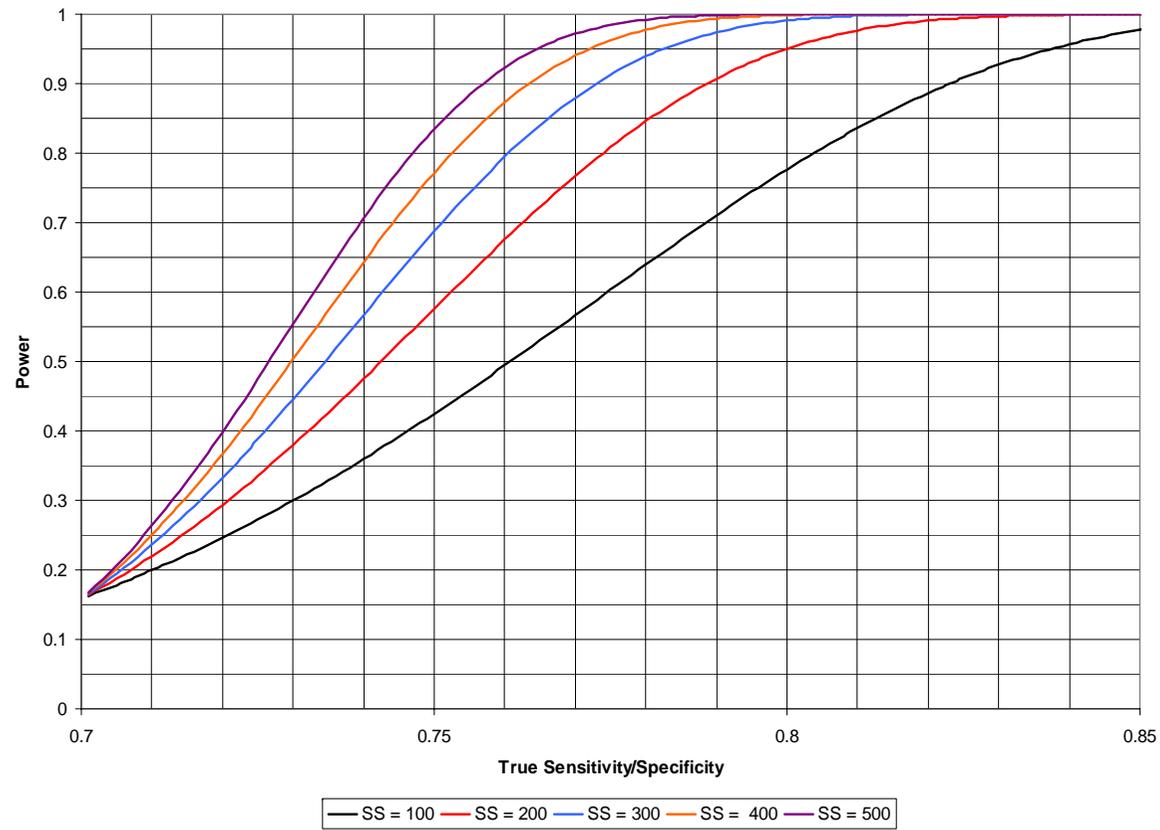
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Phases

- Phase I: Identification and consolidation of specimen sets of cases of malignant mesothelioma, asbestos-exposed non-diseased controls, other controls with potentially confounding conditions (e.g., lung cancer, cigarette smoking, common non-lung malignancies)
- Phase II: Sensitivity and specificity of concurrent SMRP and osteopontin, alone and in combination, in mesothelioma cases and asbestos-exposed controls (representing the anticipated primary screening context)
- Phase III: Specificity of concurrent SMRP and osteopontin, alone and in combination, for potentially confounding conditions (lung cancer, other cancers, cigarette smoking)
- Phase IV: Anticipatory sensitivity and specificity of SMRP and osteopontin, alone and in combination, using specimens from CARET, PLCO, and Wittenoom
- (Phase V): Sensitivity and specificity of SMRP and osteopontin in erionite-exposed individuals

Power

Power to Detect Joint Sensitivity/Specificity –
Null Hypothesis Sensitivity/Specificity = 0.70



Analysis Plans—Phase II

- Concurrent sensitivity and specificity for the screening context of surveillance of asbestos-exposed individuals
 - Primary analysis will examine currently established cutpoints for SMRP and osteopontin for the individual marker evaluations
 - Secondary analyses:
 - ROC curves for individual marker performance
 - Identification of an optimal combination panel of SMRP and osteopontin and estimation of the ROC curve for the combination, using training and test sets
 - Examination of other potential markers that, used in conjunction with SMRP and osteopontin, may improve the performance of the marker panel, using training and test sets
- Comparison of the performance characteristics of serum vs. plasma osteopontin

Analysis Plans—Phase III

- Similar to the analysis plan for Phase II, but using the optimal individual cutpoints and marker panel identified in the secondary analyses of Phase II
- These analyses will focus on the specificity of the markers and panel to mesothelioma vs. the other potentially confounding conditions examined in this phase
- It is not planned that this phase would modify cutpoints or the marker combination rule, but rather could modify the screening context in which the marker will be applied. Since the primary at-risk population (at least in this country) is known, it is important to optimize the panel to that risk population; non-specificity to confounding conditions is likely to affect the choice of further screening activities that would follow a positive test

Analysis Plans—Phase IV

- Concurrent sensitivity and specificity of the markers and marker panel developed in Phases II-III, in prospectively-collected specimens from prevention trials where bias between cases and controls is implausible
- Anticipatory sensitivity and specificity of the markers and the marker panel developed in Phases II-III, i.e., sensitivity and specificity of a marker at time $t-s$ to predict mesothelioma disease status at time t . These analyses will be performed using GEE to account for intra-individual correlation of marker values.