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RE: Advanced Breast Cancer Definitions by Staging System Examined in the Breast Cancer Surveillance Consortium

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As investigators for ECOG-ACRIN's Tomosynthesis Mammographic Imaging Screening Trial (TMIST) trial, we are writing to draw attention to conceptual issues in the outcome definitions and study population in Kerlikowske et al. (1), which limit inferences with respect to the TMIST trial.

Kerlikowske et al. (1) converted the TMIST primary outcome definition into a staging system for breast cancer and compared it with other staging systems in association with 5-year breast cancer mortality. However, the primary outcome of TMIST is not a cancer staging system but simply a binary classification of cancers as "advanced" or not. TMIST's endpoint of advanced cancers was defined to identify cancers that generally require chemotherapy, because although chemotherapy prevents many cancer-related deaths, it is also associated with clinically significant morbidity. Reducing chemotherapy-related morbidity is a valuable goal of breast cancer screening.

The authors constructed an ordinal categorical response using elements of the TMIST binary endpoint and performed Receiver Operating Characteristic (ROC) analysis on this ordinal categorical response (1). Although ROC analysis cannot be performed as a binary outcome, the relevance of the ordinal comparison for TMIST is not clear. A more relevant comparison would be conducted with the binary assessment that would result from using an American Joint Committee on Cancer stage as threshold for advanced cancer. For example, if stage IIA or IIB is used as the threshold, as was done by Kerlikowske et al. (1), one can estimate measures of performance that are appropriate for binary tests. The relevant measures for predicting cancer death in 5 years, given at the bottom of Table 2 in the *JNCI* article for the American Joint Committee on Cancer staging systems and at the bottom of Table 3 for the TMIST definition (1), are combined in Table 1 here.

Another important difference in the outcomes relates to follow-up. The article considers 5-year risk of death, which overrepresents deaths from Estrogen Receptor (ER)-negative cancer and neglects longer term risk of ER+ deaths. The majority of screen-detected breast cancers are ER+, and it is important to address mortality from these cancers. The 2-county trial in Sweden showed that more than 15 years of follow-up was needed to demonstrate the full mortality reduction of breast

Table 1. Measures for predicting cancer death in 5 years by AJCC staging systems and by TMIST definition[a]

	AJCC Anat		AJCC Progn		
Measures	IIA or higher	IIB or higher	IIA or higher	IIB or higher	TMIST
Sensitivity, %	88.9	72.6	76.7	62.9	96.1
Specificity, %	56.0	78.9	81.6	89.9	41.1
Positive Predictive Value, %	11.5	18.1	21.0	28.4	9.9
Sample size, No.	50 114		48 049		45 366
Proportion of "advanced cancers," %	46.8	24.2	21.9	13.3	61.2

[a] AJCC = American Joint Committee on Cancer; AJCC Anat = American Joint Committee on Cancer Anatomic stage; AJCC Progn = American Joint Committee on Cancer Prognostic Pathologic stage; TMIST = Tomosynthesis Mammographic Imaging Screening Trial.

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cancer screening and showed that even at 10 years, fewer than one-half of the averted deaths had been observed (2-4).

Finally, Kerlikowske et al. (1) report a large (approximately 60%) proportion of advanced cancer in the Breast Cancer Surveillance Consortium (BCSC) population (Table 3), underscoring that the study population was probably not a pure screening population and likely includes symptomatic women, as commonly seen in practice-based (nontrial) data (5). These important conceptual differences limit the implications of Kerlikowske et al. (1) for TMIST.

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Data Availability

The data underlying this correspondence are available in the correspondence itself.

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