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EDITORIAL

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Multigene assays: Implications for breast cancer staging

In the excellent analysis of six commercially available multigene assays for breast cancer management appearing in this issue of the Journal,[1] Hyams and his colleagues provide critical reviews and analyses of the current literature assessing the role of each assay in the clinical management of appropriate sub-sets of breast cancer. They highlight the critical role that these assays play as both prognostic and predictive factors in modern therapy. Their analysis concludes that only Oncotype DX and MammaPrint assays have reached significance levels that warrant unqualified use in patient management. What are not mentioned in this critical analysis are the implications of these gene signatures for staging of breast cancer.

It is noteworthy to remember that the Tumor (T), Node (N), Metastasis (M) system was first proposed for stratification of breast cancer by Pierre Denoix, a surgeon working in Paris in the 1940's and 50's.[2] The TNM system, initially based on anatomical and morphological criteria, has metamorphosed over six decades into a prognostic tool using biological and molecular criteria to build on a traditional anatomical framework.[3] Particularly in the staging of breast cancer, a concern by experts working in the field has been when and how to incorporate new criteria into traditional TNM staging. Biomarkers such as histologic grade, estrogen (ER) and progesterone (PR) receptors, human epidermal growth factor receptor-2 (HER2), although critical in determining clinical management, have previously not been incorporated into breast cancer staging. With the publication of the Eighth Edition of the *AJCC Cancer Staging Manual* in 2017,[4] that has changed.

Over the past decade, there have been fundamental changes to our understanding of the biology of breast cancer. In addition to the above noted markers, genomic prognostic panels such as Oncotype DX, MammaPrint, Endopredict, PAM 50(Prosigna), Breast Cancer Index and potential future multigene panels should be considered as adjuncts along with traditional clinical and pathological criteria. These models of gene expression profiling should be combined with immunohistochemistry, proteomics and other molecular techniques in order to give a more universal basis that assures that traditional staging will not become irrelevant. Organizations such as the US Food and Drug Administration (FDA), the American Society of Clinical Oncology (ASCO)[5] and the National Comprehensive Cancer Network (NCCN)[6] have supported and endorsed the use of Oncotype DX and MammaPrint in breast cancer management and have given further credence that these gene expression assays may provide additional prognostic and predictive information beyond anatomical staging and determination of ER, PR and HER2 status.

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The challenge for breast cancer staging experts was to decide if the inclusion of any of these multigene panels was ready for TNM prime time. Should these be used as prognostic factors that are secondary modifiers to traditional TNM? Should these be components of multifactorial prognostic models that calculate individual risk of recurrence and individual sensitivity to therapy? Should these be components of simple prognostic scoring systems that add to, but do not alter the traditional anatomical TNM staging structure? In short, should these multigene panels be included in staging especially in an era when many treatment decisions for patients with newly diagnosed breast cancer are not based on anatomical TNM stage and certainly not on stage alone. Such treatment decisions are currently based on biologic characteristics of the primary tumor rather than merely the extent of disease.

The conclusion reached for the current iteration of TNM staging that will be used for breast cancer patients beginning January 1, 2018 is that certain currently recognized multigene panels should be used in TNM staging strategies—but with caveats. Along with the incorporation of multigene panels, traditional ER, PR and HER2 must be assessed since the use of predictive gene models should only be used in patients with specific breast cancer sub-types (hormone receptor–positive, HER2 negative). In addition the multigene panel should only be included in the staging of certain breast cancer sub-sets (hormone receptor −positive, HER2 negative, node negative, TNM Stage I/II) and should not be included in the staging of triple negative tumors. In addition, to effectively measure outcomes of individual patients and population groups, appropriate registry coding must be created and utilized to capture both the application and data acquired from assessment of gene signatures in breast cancer.

The well-done and critical assessment of six multigene panels by Hyams et al. reviews the current biology and trial information supportive of these gene expression models. Based on this background, it has been concluded that the Oncotype DX score supported by Level I evidence (large −scale prospective clinical trial data) should be included into traditional TNM staging for the appropriate sub-group of patients and should be staged according to the AJCC Prognostic Stage Groups grid outlined in the newly released *AJCC Cancer Staging Manual*, Eighth Edition. It is likely that other panels reviewed by Hyams, et al. may provide similar information, but available data at the time of publication of the latest *AJCC Cancer Staging Manual* does not support assignment of the prognostic stage at this time.

There is no doubt that future editions of TNM will include more robust examples of gene signatures in the staging and treatment of

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breast cancer. Although advances in molecular diagnosis and outcome prediction have provided compelling new insights into cancer therapy, economic considerations limit the relevance of these observations to the societies in which resources permit widespread screening, molecular evaluation of tumor tissue and application of cutting-edge biologically- directed therapies. For this reason, the purely anatomical basis of TNM for the staging of breast cancer must also be preserved to enable effective staging to be conducted for patients where analysis of multigene assays is currently not feasible.

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