The Evolving Role of Multi-Gene Tests in Breast Cancer Management

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If MGTs could predict which patients were most prone to late recurrence and thus might benefit from extended adjuvant endocrine therapy, it would be a huge advancement in the care and survivorship of our patients. More studies of MGTs are required to clarify their role in evaluating prognosis and predicting response to therapy in breast cancer.

The current review by Drs. Zelnak and O'Regan aptly summarizes multi-gene tests (MGTs), their prognostic role, and how gene expression profiling has aided the definition of molecular breast cancer subtypes. However, while the current role of MGTs in the clinical care of breast cancer patients is evolving, it remains somewhat unclear. For instance, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (EWG), established by the Centers for Disease Control and Prevention (CDC), determined in 2009 that there was “insufficient evidence to make a recommendation for or against the use of tumor gene expression profiles to improve outcomes in defined populations of women with breast cancer.” The group stated they believed that until the TAILORx (Trial Assigning IndividuALized Options for Treatment [Rx]) and MINDACT (Microarray In Node-Negative Disease may Avoid ChemoTherapy) trials are reported, they were not able to offer firm guidance on the use of these tests. Additionally, all of the commercial assays for breast cancer prognostication are laboratory-developed, contain proprietary information, and with the exception of the MammaPrint test that has been approved by the US Food and Drug Administration (FDA), have not been fully independently evaluated.

Conversely, the 21-gene recurrence score ([RS] Oncotype DX) has reached a level 1B evidence score according to the proposed Simon modification to the marker utility grading system, based on its development using archived specimens from a prospective trial.[1] Moreover, it is listed as an option for clinicians to aid in chemotherapy decision-making in the National Comprehensive Cancer Network (NCCN) guidelines.

MGTs have been cited as “reproducible and reliable clinical assays that are less prone to technical errors and subjective interpretation” than immunohistochemistry (IHC) markers.[2] This is likely due in part to the fact that these assays are all performed by commercial reference laboratories, and thus are not prone to the errors introduced by local testing with diagnostic kits. The exact improvement of these MGTs over standard biomarkers is thus hard to assess. For example, when a set of four standard IHC markers that have been used for many years (IHC-4) is used in a single reference laboratory, it performs as well as several MGTs.[3] The differences between the MGTs are also hard to assess, as few studies have compared them head-to-head, given that the test is performed in various commercial reference laboratories. However, limited data suggest that current MGTs have similar prognostic abilities in ER-positive, HER2-negative patients, despite the fact that they contain different gene sets.[4]

One aspect of MGTs that has not been studied in detail is the effect of intra-tumor heterogeneity—both in terms of biomarker levels within tumor cells and cellular heterogeneity with normal and other tissue components—on the ability to prognosticate. All of the MGTs make measurements on RNA extracted from frozen tumor, or a section of fixed tumor tissue (sometimes with macro-dissection). The resulting value represents an average for the whole tissue and is affected in an unknown manner by cellular and intra-tumor heterogeneity. Development of IHC and immunofluorescence for ER allowed assessment of ER levels within specific tumor cells and showed that there was significant intra-tumor heterogeneity of signal within a tumor.[5] Similarly, fluorescence in situ hybridization (FISH) for HER2 amplification also showed different levels of amplification between different areas of a breast cancer.[6] The concept of intra-tumor heterogeneity is now well established and accepted.[7] Importantly, there have been very few studies of how intra-tumor heterogeneity and cellularity affects multi-gene tests, but concerns have recently arisen. For example, the RS shows a high false-negative rate of HER2 measurement by...
quantitative real-time reverse transcriptase polymerase chain reaction (Q-RT-PCR) compared with FISH and IHC.[8] This may be due to many factors, such as low levels of HER2 amplification being diluted by non-tumor tissue. A study directly examining the effect of intra-tumor heterogeneity on RS scoring by comparing 0.6-mm cores vs whole sections of tumors showed high correlation between RS scores based upon the average RS on tissue sections or cores; however, there was significant variation in RS between the individual cores, with some RS changing prognostic classification.[9] The need to measure intra-tumor heterogeneity of MGTs was recently shown by a study in renal cancer, in which comparison of different areas of a single cancer showed regions with a "good" prognosis gene expression profile and others with a "poor" prognosis profile.[10] Of note, one region (out of nine studied) showed a gene expression and somatic mutation profile similar to that of a metastasis from the renal tumor, indicating that there may have been clonal spread. It is important to note that this would likely have been missed by simply examining gene expression as an average across the whole tumor. Clearly more studies on the effect of intra-tumor heterogeneity and cellularity on the ability of MGTs to predict patient prognosis are needed.

In our estimation, there are areas of great unmet clinical need that could be furthered by future studies of MGTs. For instance, one of the greatest challenges for breast cancer patients and their treating physicians is the burden of ongoing risk of relapse over an indefinite length of time.[11] In particular, patients with ER-positive tumors have initially lower rates of recurrence, but their constant rate of relapse over time results in higher rates of late recurrence.[12,13] The major molecular subtypes of breast cancer also show divergent recurrence rates.[14,15] MGT predictors of recurrence have shown a strong time-dependence of patient classification, with generally weaker performance over long-term follow-up due to an inability to predict late recurrence.[16] However, in a recent comparison of the prognostic value of three signatures (Breast Cancer Index [BCI], RS, and IHC-4 scores), all three signatures were prognostic for early distant recurrence (0 to 5 years), but only BCI was significant for late distant recurrence (5 to 10 years).[3] Articulating individual risk of late recurrence in ER-positive patients is of major clinical importance, given existing evidence of benefit from prolonged endocrine therapy beyond 5 years for both premenopausal women, based on the recent analysis of the international ATLAS (Adjuvant Tamoxifen, Longer Against Shorter) study,[17] and for postmenopausal women, based on the ATLAS and the MA17 study.[18] Premenopausal women at diagnosis in MA17 experienced significantly greater benefit with extended adjuvant letrozole than those who were postmenopausal at diagnosis.[19] Thus, it seems that our youngest patients may experience the greatest benefit from additional adjuvant endocrine therapy, but such therapies significantly affect quality of life in many women, leading to notoriously low compliance and adherence rates in the adjuvant setting.[20-22] If MGTs could predict which patients were most prone to late recurrence and thus might benefit from extended adjuvant endocrine therapy, it would be a huge advancement in the care and survivorship of our patients. More studies of MGTs are required to clarify their role in evaluating prognosis and predicting response to therapy in breast cancer.

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