Clinical Utility of Ki67 in Early Breast Cancer: We might not be there yet.

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| Challenge | **There has been significant interest in whether Ki67 IHC alone or together with other IHC markers or clinical factors could be used as a cost-effective surrogate for the Oncotype DX, a 21-gene assay used to guide treatment in early breast cancer, or to identify a subset of patients who could avoid this or other multigene tests. However, the potential role for Ki67 immunohistochemistry (IHC) in breast cancer management has remained unclear due largely to its high inter-observer variability and the lack of established cutoff points for clinical decisions.** |
| Existing Evidence | Multiple studies have found that levels of Ki67 (an established marker of proliferation and one of the genes in the 21-gene Oncotype DX assay) measured by immunohistochemistry (IHC) correlate with Oncotype DX scores. In 2011, the International Ki67 Working Group (IKWG) developed guidelines to standardize scoring and improve reproducibility of visual scoring by pathologists. In 2021, the IKWG also suggested specific cut points that could be used in treatment decisions for ER+HER2-, node negative breast cancer and that could identify patients who do not need Oncotype DX or other multi-gene tests in some settings, such as when tests are unavailable or too expensive. Data are lacking on whether these new IKWG guidelines improve reproducibility of visual scoring in a real world setting or whether the recommended cut points can be used to accurately identify patients who could avoid Oncotype DX or other multi-gene tests. |
| Target Population | Women with early, low risk breast cancer eligible for Oncotype DX testing (ie, women aged 50+ years with ER+, HER2-, lymph-node negative disease). |
| Intervention or Exposure | Testing breast biopsy tissue for Ki67 by immunohistochemistry (IHC). Scoring of IHC following IKWG recommendations by immunopathologists and by image analysis (NeoGenomics, Inc). |
| **Outcomes/Key Findings** | In our study population of low-risk breast cancer patients**, Ki67 did not appear to provide additional information beyond tumor grade.** Low grade appeared to be more strongly correlated with low RS than Ki67; however, accessing tumor grade has reproducibility problems. The IKWG’s Ki67 training resulted in moderate to strong reproducibility across readers but cut points had only moderate overlap with Oncotype DX cut points, especially for Ki67 >30% and RS>26; thus, their clinical utility for a Oncotype DX testing pathway remains unclear.  Following the guidelines for Ki67 reading was time consuming for immunopathologists and infeasible for incorporation into the IHC testing panel for all breast cancer patients. |
| **Resulting Action/Change** | Ki67 IHC is not ready to be incorporated into an Oncotype DX testing pathway among women with early, low-risk, hormone-receptor positive breast cancer. Visual IHC scoring by KPNC immunopathologists following IKWG guidelines was much more time consuming than the current scoring process for other IHC markers. Use of image analysis for Ki67 could potentially substantially reduce pathologist time, while also providing good reproducibility. |
| Additional Recommendations | Exploration of using image analysis in the regional lab.  Evaluation of the correlation between grade and other markers or clinical factors and Oncotype DX in ER+HER2- breast cancer. |
| Implementation Tools | NA |
| Implementation Measurement | NA |
| Reference | Shim VC, Baker RJ, Jin W, Puentes R, Agersborg SS, Lee TK, Goreal W, Achacoso N, Lee C, Villasenor M, Lin A, Kapali M, Habel LA. International Ki67 Working Group training and cut point recommendations for early breast cancer: Comparison with 21-gene assay results in a Large Integrated Health Care System. Submitted to Breast Cancer Research and Treatment. |