decisions for adjuvant endocrine and chemotherapy is insufficient to recommend its use (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong).

Literature review and clinical interpretation. Prosigna (PAM50) assesses the breast cancer molecular subtypes using the nanostring technology. When integrated with tumor size, it leads to the risk-of-recurrence score (ROR). The strongest evidence for Prosigna and ROR are coming from retrospective analyses of prospective randomized trials and from population-based studies. Nevertheless, as opposed to some other genomic tests, there are no data from prospective randomized trials testing its clinical utility.

In the TransATAC study,[33] 774 postmenopausal women with ER-positive, HER2-negative breast cancer were included. In this study, a high-ROR score was associated with inferior outcome (distant metastases; HR = 2.56; 95% CI, 1.96 to 3.35). The 10-year risk of DR in node-negative patients was 3% (95% CI, 1.6 to 5.8), 14% (95% CI, 9.4 to 20.8), and 32% (95% CI, 23.4 to 43.8) in patients presenting a low-, intermediate-, or high-ROR, respectively. In patients with 1-3 positive axillary nodes, the 10-year risk of DR was 0%, 20.7% (95% CI, 12 to 34), and 30.7% (95% CI, 22 to 41) in patients with low-, intermediate-, and high-ROR scores, respectively. Importantly, only 15 (8%) of the patients with 1-3 positive nodes presented a low-ROR score, suggesting that using ROR score in patients with 1-3 positive nodes is unlikely to change treatment recommendations in more than 90% of patients. In the same study, ROR was associated with an increased risk of distant relapse occurring between 5 and 10 years of follow-up (HR = 2.77; 95% CI, 1.93 to 3.96) in patients with node-negative disease. In a population-based study from Denmark,[39] samples from 2,558 women with ER-positive, HER2-negative were analyzed for Prosigna. All patients age 50 years or older received 5 years of endocrine therapy. In node-negative disease, the 10-year risks of distant relapse were 5.0% (95% CI, 2.9 to 8.0), 7.3% (95% CI, 4.8 to 10.6), and 17.8% (95% CI, 14.0 to 22.0) in patients with low-, intermediate-, and high-risk ROR score, respectively. In 1-3 node-positive disease, the 10-year risks of DR were 3.5% (95% CI, 1.9 to 6.1), 11.5% (95% CI, 8.0 to 15.6), and 22.1% (95% CI, 18.6 to 25.8) in patients with low-, intermediate-, and high-risk ROR scores, respectively. In the retrospective analysis of the prospective observational study,[40] ROR score was associated with a poor outcome (HR = 6.82; 95% CI, 2.62 to 17.81; $P < .001$ for high-ROR *v* low-ROR). Only 33% of patients had a diagnosis of node-positive disease in this study not allowing for any clinical conclusions. Finally, Jensen et al[41] reported that ROR score was predictive for the efficacy of cyclophosphamide, epirubicin, and fluorouracil versus cyclophosphamide, methotrexate, and fluorouracil (CMF) in the Danish DBCG89D trial. The HRs for cyclophosphamide, epirubicin, and fluorouracil efficacy over CMF were 1.01 (95% CI, 0.59 to 1.73), 0.78 (95% CI, 0.53 to 1.15), and 0.54 (95% CI, 0.36 to 0.80) in patients with low-, intermediate-, and high-ROR scores, respectively.

One study assessed the clinical validity of Prosigna and ROR in premenopausal women (N = 460).[19] This analysis is a retrospective analysis of a prospective randomized trial.[42] In this analysis, ROR score was associated with prognosis in patients who did not receive systemic treatment (HR = 1.23; 95% CI, 1.09 to 1.39; $P < .001$ for a 10-point difference). Among the patients receiving CMF chemotherapy, a significant interaction was reported between ROR score and efficacy of CMF. CMF benefit appears to be greater in patients with basal-like breast cancer (HR = 0.14; 95% CI, 0.06 to 0.32). Validation of these findings is recommended through the additional testing of Prosigna and ROR in existing or ongoing chemotherapy clinical trials.

Ki67.

Recommendation 1.19. If a patient is postmenopausal and has stage I-II breast cancer, the clinician may use Ki67 expression in conjunction with other clinical and pathologic parameters to guide decisions on adjuvant endocrine and chemotherapy when multigene assays are not available. Ki67 expression levels are most informative for prognosis when the level is $< 5\%$ (low proliferation) or $> 30\%$ (high proliferation) because technical reliability of distinguishing values within this range is limited (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.20. If a patient is postmenopausal and has breast cancer, there is insufficient evidence to use baseline Ki67 expression or Ki67 level after 2 weeks of neoadjuvant AI therapy to guide decisions on adjuvant endocrine and chemotherapy (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Recommendation 1.21. Despite the limitations associated with Ki67 testing, a patient with node-positive breast cancer with a high risk of recurrence and a Ki67 score of $\geq 20\%$ as determined by an FDA-approved test may be offered two years of abemaciclib plus endocrine therapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and clinical interpretation. Tumor proliferation has been linked in multiple studies to prognosis and chemotherapy sensitivity. All clinically validated multigene prognostic assays include a proliferation module that contains proliferation-related genes such as *MKI67*. Ki67 is a quantitative measure of proliferation, and higher expression levels of Ki67 have been associated with greater response to neoadjuvant chemotherapy (NACT) and inferior long-term survival. It has not been examined as a predictor of chemotherapy benefit in large adjuvant clinical trials. However, expression of Ki67 has been challenging to standardize across laboratories, and clinical studies examining Ki67 as a