On behalf of Genomic Health Inc., I respectfully request the Breast Cancer Panel review the enclosed data and a change in the language pertaining to the Oncotype DX® Invasive Breast Cancer Assay for the prediction of chemotherapy (CT) benefit of patients with node-negative N0, Hormone Receptor Positive (HR+), Her2 (-) early breast cancer (EBC).

Specific Changes: The Oncotype DX Invasive Breast Cancer Assay language to be changed from “consider” to “recommend” in the N0 and pN1mic (micrometastases) component of the invasive breast cancer algorithm.

FDA Clearance: FDA clearance is not required for this assay because the assay is performed in the central laboratory at Genomic Health that is regulated and certified under the Clinical Laboratory Improvement Amendments (CLIA) and the College of American Pathologists (CAP).

Rationale: The reporting of prospective outcomes from multiple studies including the RS<11 arm of TAILORx7, the WSG planB trial23-29, the Israeli Clalit registry30 and the SEER/NCI analysis31 that include > 50K ER+, EBC patients tested with the 21-gene assay and treated based on the Recurrence Score (RS) result, is definitive evidence that the RS identifies patients who should not be treated with CT, confirms that the NSABP B-20 validation study32 identified patients who were unlikely to benefit from the addition to CT and would do well with hormone therapy (HT) only (RS <18) and underscores the importance of having the RS information on every appropriate patient as part of the standard diagnostic work-up prior to treating with CT.

The following articles are submitted in support of this proposed change.

Analytical validation studies:

Clinical validation studies (node-negative):

Supportive Clinical Studies (node-negative):
22. NICE Diagnostics Guidance (DG10) September 2013. Available at www.nice.org.uk/guidance/dg10
29. Gluz O et al. American Society for Clinical Oncology; June 2016; Chicago, IL Abstract #556
Additional Background: The 21-gene RS has been clinically validated in multiple large cohorts of HR+, HER2(−) breast cancer patients with N0 and N(+) disease.3–6 The NCI recently published initial findings from the Trial Assigning Individual Options for Treatment (TAILORx) in The New England Journal of Medicine.7 TAILORx enrolled over 10,000 ER+, NO patients worldwide, 1626 of whom had RS <11, treated uniformly with HT only and followed for clinical outcomes. With a median follow-up of 69 months, the results show that 99.3% of these patients were free from distant recurrence (DR) at 5 yrs; 5-yr DFS was 93.8%, freedom from any recurrence was 98.7% and 5-yr OS was 98%. These results confirmed the original clinical validation studies5–6 which showed that patients with a low RS result treated with HT only, have a very low rate of breast cancer specific mortality (BCSM) or DR as shown in the B-14 study with a BCSM of 0.9% at 5-yr5,28 or a DR rate of 96.8% at 10 yrs in the HT treated arm of the B-20 study6.

Recently, 3 reports of real-world, prospective outcomes have been presented and/or published. The Israeli Clalit Health Services breast registry reported 5yr outcomes in an unselected cohort of patients (N= 2023) that were ER+, Her2(−), NO with standard RS testing, and showed that the 5-yr risk of DR was 0.5% in the RS <18 group, which is remarkably similar to the TAILORx findings in the RS <11 with a 5-yr risk of DR of 0.7%. Of note, only 2% of the patients in the RS<18 group received CT and all received standard HT.29 Recently published results from the West German Study Group planB study showed a 3-yr DFS in clinical high risk NO-1 patients with RS 0-11 treated with hormone therapy alone of 98% and was the same for patients with RS 12-25 who had been treated with chemotherapy25 (5-yr update was 94%29), which is similar to the TAILORx report of 5-yr DFS of 93.8% in the RS <11 group25. Finally, the 5-yr prospective outcomes in >38,000 patients with NO, ER+, Her2(−) EBC within the SEER (Surveillance, Epidemiology and End Results) program have just been published28. Patients meeting specific criteria (ER+, Her2(−), NO, age 40-84y) from 2004-2011 with a RS result were included in the analysis. Clinical and pathologic features were as expected: median age-57y, 84% white, 29% grade 1 and 54% grade 2, 25% size <1cm, ~50% 1-2cm. Median follow-up was 39 mos. RS distribution with standard cutpoints (18 and 31): 55% (21,023) low, 38% (14,494) intermediate and 8% (3051) high. The RS is highly significantly associated with 5-yr BCSM (p < 0.001). The unadjusted 5-yr BCSM for the RS low, inter and high risk groups was: 0.4%, 1.4% and 4.4%, respectively with known CT use in 7%, 38% and 69%, respectively. The RS stratification across all clin/path factors was consistent with ~55% being in the low RS group with a 5-yr BCSM <1% in all low RS groups including age, size and grade, indicating that the RS provides information on risk not readily apparent from the clin/path factors. Conversely, in patients with clin/path factors traditionally associated with a more favorable outcome (eg older age, smaller tumors, lower grade), ~10% had high RS results and would likely be potentially under-treated without the genomic information. This becomes particularly important as expected median life span extends beyond 80y. These results are clinically significant since the predominant effect of CT in reducing DR risk and mortality is in the first 5 yrs after diagnosis. Moreover, the ability of the RS to predict risk of DR beyond 5 yrs has recently been published by Wolmark, et al27. The analysis of patients with an ER level >9.1 in the B-14 study showed that the RS was significantly associated with DR risk in yrs 5-15 (not 5-10) with a p-value < 0.01 and that the risk for high RS patients was ~16% vs ~7% for low RS patients, providing physicians greater insight into the individual patient’s risk of DR beyond 5yrs, and the ability to balance the potential absolute benefit of extended HT with the risk and potential toxicity and inconvenience of extended HT.

The RS has been a part of the treatment decision algorithm for the prediction of CT benefit in patients with ER+, Her2(−) EBC for 10+ yrs. With unprecedented prospective clinical outcomes in >50,000 patients, it has now been confirmed that the Oncotype DX assay identifies both patients with a low RS who can be safely and effectively spared CT, and patients with a high RS who will likely derive the greatest benefit from CT where the clin/path factors would indicate otherwise (eg. older pt or small tumors) and solidifies the true clinical utility of the 21-gene RS assay. The quantitative risk estimate provided by the RS leads to an informed treatment decision based on the unique underlying biology of the tumor and enhances the confidence physicians and patients have in personalizing care by incorporating individualized estimates of DR risk and expected benefit from CT. Furthermore, health economic analyses have shown use of the test can reduce overall cost by reducing CT use which further optimizes care and healthcare spending.10,12,14,16