Genomic Health

June 17, 2016
To: submissions@nccn.org
Re: Submission Request – Breast Cancer

Submitted by:
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NCCN Guidelines Panel: Breast Cancer- July 11, 2016

On behalf of Genomic Health Inc., I respectfully request the **NCCN Breast Panel** to review the cited data for the elevation from a footnote to inclusion into the algorithm for Systemic Adjuvant Treatment Hormone Receptor Positive Her2 negative Disease algorithm of the **Onco*type* DX® Breast Cancer Assay** in the recurrence risk assessment and chemotherapy (CT) treatment decision of patients with 1-3 positive nodes.

Specific change: Recommend the Onco*type* DX Breast Cancer Assay as a component of the treatment guideline for HER-2 neg, ER+ tumors (BINV-6) as an additional bullet (*Proposed bullet: The panel recommends the Oncotype DX Breast Cancer Assay for patients with 1-3 Node Positive, ER Positive, HER-2 negative early stage breast cancer to inform the individualized adjuvant treatment decision*).

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: Inclusion of the Recurrence Score assay (studied in over 8000 N+ patients including prospective outcomes) in the treatment decision algorithm for patients with 1-3 positive nodes, ER+, HER-2-neg early stage breast cancer will reduce variability of recurrence risk assessment and provide prediction of CT benefit, which will lead to a more informed treatment decision based on the individual patient's tumor biology and thus, increasing the confidence of physicians and patients in personalizing care by ensuring the right patient receives the right treatment based on their unique tumor biology.

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

Analytical validation studies:
1. Cronin M et al. *Am J Pathol*. 2004; 164(1):35–42.
2. Cronin M et al. *Clin Chem*. 2007; 53(6):1084-91.

Clinical validation studies in node-positive patients:
3. Albain KS et al. *Lancet Oncol*. 2010; 11(1): 55-65.
4. Dowsett M et al. *J Clin Oncol*. 2010; 28 (11): 1829-34.
5. Sparano JA, Gray RJ, Makower DF, et al. *N Engl J Med.* 2015;373(21):2005-14

Additional clinical studies in node-positive patients (supportive):
6. Gianni L et al. *J Clin Oncol*. 2005; 23(29): 7265-77.
7. Badve SS et al. *J Clin Oncol*. 2008; 26(15):2473-81.
8. Chang J et al. *Breast Cancer Res Treat*. 2008; 108(2): 233-40.
9. Akashi-Tanaka S et al. *Breast*. 2009; 18(3): 171-4.
10. Mamounas EP et al. ASCO Breast Cancer Symposium; September 2012; San Francisco, CA. Abstract #1.
11. Vacirca J et al. American Society for Clinical Oncology; June 2013; Chicago, IL. Abstract #565.
12. Penault-Llorca FM et al. American Society for Clinical Oncology; June 2014; Chicago, IL. Abstract #11052.
13. Swain SM, et al. Adv Ther. 2015;32(12):1222-36.
14. Gluz O, Nitz UA, Christgen M, et al. *J Clin Oncol*. 2016 Feb 29. pii: JCO635383. [Epub ahead of print].
15. Petkov VI, Miller DP, Howlader N, et al. *npj Breast Cancer*. 2016;2:16017
16. Gluz O et al. American Society for Clinical Oncology; June 2016; Chicago, IL Abstract #556
17. Roberts M et al. American Society for Clinical Oncology; June 2016; Chicago, IL Abstract #6675

Clinical and economic utility studies in node-positive patients:
18. de Boer RH et al. *Med J Aus*. 2013;199: 205-8.
19. Eiermann W et al. *Ann Oncol*. 2013; 24(3): 618-24.
20. Yamauchi H et al. *Clin Breast Cancer*. 2014; 14(3):191-7.
21. Oratz R et al. *J Oncol Pract*. 2011; 7(2): 94-9.
22. Bargallo JER et al. European Society for Medical Oncology Congress; September 2012; Vienna, Austria. Abstract 289P.
23. Hornberger J et al. *J Oncol Pract*. 2011; 7(3 Suppl): e38s-45s.
24. Hornberger J et al. *J Natl Cancer Inst*. 2012;104(14):1068-79.
25. Reed SD et al. *Genet Med*. 2013;15(3):203-11.

Sincerely,

Amy P. Sing, MD Senior Director, Medical Affairs

Additional Information:

Since the June 27, 2014 submission, multiple analyses including prospective outcomes studies, have shown the clinical value of the Recurrence Score (RS) assay in ER+, Her2(-) patients with 1-3 positive nodes (N+). While there have been numerous studies worldwide showing that use of the RS result in clinical practice changes treatment decisions and is cost-effective/cost-saving, the clinical utility of the RS for N+ patients based on prospective use has only recently been published.

The original clinical validation studies showed that the RS result was significantly associated with the risk of distant recurrence (DR) and that patients with 1 positive node had similar outcomes to N0 patients. Patients with 2 or 3 positive nodes and low RS results had slightly higher DR rates and patients with 4+ nodes had substantially higher DR rates for all RS risk groups, although the RS still stratified patients significantly[4]. The SWOG S8814 study further elucidated the ability of the RS to predict the likelihood of CT benefit in N+ patients. This study showed that patients with a low RS had no benefit from the addition of CT whereas the patients with a high RS derived ~ 25% reduction in BCSS when treated with CT, which is similar to the relative reduction shown in the N0 patients with a high RS[3]. Despite the strength of the results of these 2 studies, questions remained regarding the applicability to contemporary patients and practice because they were relatively small cohorts, and from studies conducted 20-25 yrs ago.

Recently, data from contemporary cohorts have been published and/or presented. An analysis of 394,000+ patients and ***30,000+*** N+ patients in the Genomic Health database published by Swain et al showed that the distribution of the RS result in N+ (1-3) was similar when compared to N0 patients with 61% having a low RS vs 58%, 31% vs 33% with an intermediate RS and 7% vs 8.5% with a high RS, respectively[13]. Furthermore, the RS distribution in N+ patients 40-50y or >70y was 62%; 62%, 32%; 31% and 7%; 8% for low, intermediate and high RS, respectively indicating that age and 1-3 nodes was not as informative of the underlying biology as the RS.

There are now published reports of prospective outcomes confirming that patients with N1-3 and a low RS can be safely and effectively treated with hormone therapy (HT) alone [14-17]. The West German Study Group PlanB study in ~2,000 N+ patients showed a 3-yr DFS of 98% in patients with N1-3 or clinical high risk N0 and RS 0-11 treated with HT only, which was the same in patients with RS 12-25 treated with CT[14] (5-yr update presented at ASCO 2016 showed DFS of 95% and 94%, respectively[16]). This result is similar to the TAILORx reporting 5-yr DFS of 93.8% in the N0 RS <11 group treated with HT only.[5] Prospective outcomes in 4897 patients with Nmic,1-3, within the SEER (Surveillance, Epidemiology and End Results) program have just been published[15] with a more detailed presentation at ASCO 2016[17]. Clinical and pathologic features were similar to the SEER N0 cohort; most tumors were 1-2cm and grade 2. Of the N+ patients, 42% were Nmic, 39%, 11% and 4% were 1, 2, and 3 nodes, respectively. RS distribution with standard cutpoints (18 and 31) ranged from 58%-53% low, 35% -36% intermediate and 7%-11% high for Nmic to 3, respectively[17]. Similar to N0 patients, the RS was highly significantly associated with 5-yr BCSM ($p < 0.001$). The unadjusted 5-yr BCSM for the RS low, intermediate and high groups were: 1.0%, 2.3% and 14.3%, respectively[15]. Of note, the 5-yr BCSM for the 21,000+ N0 patients with a low RS was 0.4%[15]. The 5-yr BCSS for the Nmic low RS group was 99.4% and 99.2% for the N1 group; 19% and 23% of whom were treated with CT, respectively[17]. These results are comparable to the N0 low RS group that had a 5-yr BCSS of 99.6%[15].

RS guided treatment decisions have improved outcomes for N0 patients for 10+ years and now prospective data has shown that the RS is similarly valuable in personalizing treatment decisions for patients with N+ EBC. The consistency with which the RS risk stratifies patients with N+ EBC and now clear evidence that N+ patients with low RS results can be effectively and safely spared CT will result in an overall reduction in needless exposure to CT and ultimately save healthcare dollars while advancing the field towards personalizing care. This warrants a more standardized approach to the diagnostic workup of all patients with ER+, Her2-neg EBC prior to making a CT decision. Incorporation into the guideline algorithm will be an effective way to ensure all patients have access to the Onco*type* DX test and benefit from the information on their individual tumor biology.