Adding precision to 2018 ASCO/CAP HER2 testing guidelines in breast cancer with genomic profiling

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BACKGROUND

• Biological heterogeneity of HER2 positive breast cancers is supported by a modest benefit of HER2-targeted therapies reported in the APHINITY and ExeNET trials. This highlights the need for improved biomarkers that more precisely identify patients who benefit from HER2-directed agents.

• The R0gene molecular subtyping signature, BluePrint (BP), classifies breast tumors into Luminal, HER2 or Basal subtype based on the gene expression of downstream signaling pathways (1). Previous work showed a substantial proportion of tumors identified as HER2 equivocal or HER2 positive by 2013 ASCO/CAP guidelines may be reclassified as non-HER2 subtype by BP (2).

• In 2018, ASCO/CAP HER2 IHC/ISH classification guidelines were revised to reduce the frequency of HER2 equivocal, for which treatment recommendations have been ambiguous (3). Here we evaluated concordance between HER2 status by 2018 ASCO/CAP guideline classification and BP molecular subtyping.

METHODS

• Pathology reports are provided by physicians for samples that are tested with the 70-gene risk of distant recurrence signature, MammaPrint (MP), and BluePrint as part of routine diagnostic care.

• BP indices for each subtype (HER2, HER2, and Basal) were calculated based on expression of 80 genes and range from −1.6 to +1.6. The subtype with the highest index of the three is the dominant molecular subtype reported for the tumor. MP was used to further stratify BP Luminal into Luminal A and Luminal B.

• This analysis includes breast tumor specimens sent to Agenda (Irvine, CA) from January 2019 to January 2020. HER2 IHC/ISH results, which were determined locally based on ASCO/CAP 2018 guidelines, were available for 4,535 samples. Specimens were obtained by either core biopsy (n=4,535), surgical excision (n=796), or information was unavailable (n=1). There was no significant difference in MP stratification between samples obtained by these methods.

RESULTS

• Comparison between HER2 IHC/ISH and BP subtyping. Of 1,453 samples, 1336 (92%) were HER2 negative, 99 (7%) were HER2 positive, and 18 (1.2%) were HER2 equivocal under 2018 guidelines (Table 1). BP reclassified 17 of 99 (17%) HER2 positive tumors as Luminal A, 40 of 99 (40%) as Luminal B, and 11 of 99 (11%) as Basal; the remaining 31% were confirmed HER2 (Table 1 and Figure 1). Furthermore, 55 of 99 (55%) HER2 positive tumors were also ER+ and/or PR+, with 48 (87%) of these reclassified as BP Luminal. Of HER2 equivocal tumors, 18 of 18 (100%) reclassified as Luminal and 2 of 18 (11%) as Basal. Of HER2 negative tumors, BP classified 96 of 1336 (7%) as Basal and 2 of 1336 (0.15%) as HER2.

• Evaluation of BP indices in tumors classified as HER2 by IHC/ISH. BP indices for each subtype were calculated for HER2 positive tumors that were reclassified to Luminal by BP (Figure 2A), as HER2 by BP (Figure 2B), and reclassified as Basal by BP (Figure 2C). The dominant molecular subtype is reported based on the highest BP index. Of HER2 positive tumors that reclassified as BP Luminal, 18 of 56 (1 patient excluded due to unknown HR status) had positive indices for both BP HER2 and BP Luminal (Figure 3).