

From the Editor

This issue of the *American Journal of Hematology/Oncology*[®] contains an important editorial and call to action for a change in how we interpret *HER2* at the genomic level. As one of the early discovered gene amplifications that soon became a “druggable” target, *HER2* analysis had a shaky start. One of the initial antibodies



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used to qualify patients for the trastuzumab trials was a rabbit polyclonal antibody that was rather sensitive, but not very specific. As monoclonal antibodies were validated to perform this task, there was still concern about tissue processing and accuracy—either false positives due to “antigen retrieval” using microwave heating or false negatives due to formalin fixation over a long weekend and loss of the epitope. The advent of fluorescence in situ hybridization (FISH) promised to solve this problem, in particular for *HER2*, where overexpression was felt to be uniformly driven by excess gene copy number and appeared to better predict clinical response to single-agent trastuzumab therapy.¹

Fast forward to the last 5 years and several iterations of American Society of Clinical Oncology/College of American Pathologists guidelines that have tried to accommodate both single- and dual-probe (normalized) FISH to define positivity and equivocal results—which have become the bane of clinical decision making and heated discussions at tumor boards. This is in distinction to next-generation sequencing assays that make amplifications calls on the basis of copy number alone since whole chromosome polysomy is less common than loss or gain at loci at or around the centromere to which dual-probe FISH results are normalized and there is evidence that cases with low *HER2* expression and borderline *HER2* copy number may not benefit from trastuzumab.² As Dr Gunn points out, we may be better off simply casting off centromeric normalization and use absolute *HER2* copy number. Of course, this may lower the number of equivocal results, but it will be very difficult to prove that this allows for more accurate decision making and treatment assignment and, ultimately, improved outcomes. Data from NSABB B-47 testing adjuvant trastuzumab in *HER2*-low cases and correlations with newer genomic assays may eventually provide more definitive data to change the standard.³

References

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