Template for Reporting Results of *HER2 (ERBB2)* Biomarker Testing of Specimens from Patients with Adenocarcinoma of the Stomach or Gastroesophageal Junction

Version: GastricHER2Biomarkers 1.0.0.1 **Protocol Posting Date:** June 2017

Includes elements from the 2016 HER2 Testing and Clinical Decision Making in Gastroesophageal Adenocarcinoma: Guideline From the College of American Pathologists, American Society for Clinical Pathology, and American Society of Clinical Oncology.

This biomarker template is NOT required for accreditation purposes

Authors
Angela N. Bartley, MD*; Jessi Christ, CTR; Patrick Fitzgibbons, MD; Stanley R. Hamilton, MD; Sanjay Kakar, MD; Manish A. Shah, MD; Laura H. Tang, MD, PhD; Megan L. Troxell MD, PhD.

With guidance from the CAP Cancer Biomarker Reporting Committee

** Denotes primary author. All other contributing authors are listed alphabetically.*

Summary of Changes
This is a revised template.

Gastric HER2 Biomarker Reporting Template

Template posting date: June 2017

Completion of the template is the responsibility of the laboratory performing the biomarker testing and/or providing the interpretation. When both testing and interpretation are performed elsewhere (eg, a reference laboratory), synoptic reporting of the results by the laboratory submitting the tissue for testing is also encouraged to ensure that all information is included in the patient's medical record and thus readily available to the treating clinical team. **This template is not required for accreditation purposes.**

STOMACH/GASTROESOPHAGEAL JUNCTION

Select a single response unless otherwise indicated.

+ RESULTS

+ HER2 (by immunohistochemistry)
+ ___ Negative (score 0)
+ ___ Negative (score 1+)
+ ___ Equivocal (score 2+)
+ ___ Positive (score 3+)
+ ___ Cannot be determined (explain): _____

+ *HER2* (*ERBB2*) (by in situ hybridization)
+ ___ Negative (not amplified)
+ ___ Positive (amplified)
+ ___ Cannot be determined (explain): _____

+ Number of invasive cancer cells counted: _____
+ ___ Using dual-probe assay
    + *HER2* (*ERBB2*):CEP17 ratio: _____
    + Average number of *HER2* (*ERBB2*) signals per cancer cell: _____
    + Average number of CEP17 signals per cancer cell: _____
    + Range of number of *HER2* (*ERBB2*) signals per cancer cell: _____

+ ___ Using single-probe assay
    + Average number of *HER2* (*ERBB2*) signals per cancer cell: _____
    + Range of number of *HER2* (*ERBB2*) signals per cancer cell: _____

+ *HER2* (*ERBB2*) (genomic test: specify findings, eg, gene amplification, nucleotide sequence of specific mutation[s])
+ ___ Negative
+ ___ Positive (specify):
+ ___ Cannot be determined (explain): _____

+ METHODS

+ HER2 (protein expression by immunohistochemistry)
+ ___ US Food and Drug Administration (FDA) cleared (specify test/vendor): _____
+ ___ Laboratory-developed test

+ Data elements preceded by this symbol are not required for accreditation purposes.

+ Primary Antibody
+ ___ 4B5
+ ___ HercepTest™
+ ___ A0485
+ ___ SP3
+ ___ CB11
+ ___ Other (specify): _____

+ *HER2 (ERBB2*) (gene amplification by in situ hybridization)
+ ___ FDA cleared (specify test/vendor): _____
+ ___ Laboratory-developed test (specify FISH or ISH and probes): _____

+ *HER2 (ERBB2*) (genomic test for amplification or mutation)
+ ___ Laboratory-developed test (specify method):_____

Gene names should follow recommendations of The Human Genome Organisation (HUGO) Nomenclature Committee (www.genenames.org; accessed May 24, 2017).

All reported gene sequence variations should be identified following the recommendations of the Human Genome Variation Society (http://varnomen.hgvs.org/; accessed May 24, 2017).

+ Data elements preceded by this symbol are not required for accreditation purposes.

Explanatory Notes

HER2 (ERBB2) is a proto-oncogene located on chromosome 17 that encodes a 185-kd tyrosine kinase receptor belonging to the epidermal growth factor receptor (EGFR) family whose phosphorylation initiates signaling pathways that lead to cell division, proliferation, differentiation, and apoptosis.[1-3]

The Human Genome Organisation (HUGO) Nomenclature Committee (HGNC) has designated *ERBB2* as the approved symbol and CD340, HER-2, HER2, and NEU as synonyms (http://www.genenames.org/cgi-bin/gene_symbol_report?hgnc_id=3430; accessed May 24, 2017). HER2 gene product is expressed in normal epithelial cells, and amplification and/or overexpression of this gene has been reported in up to 30% of breast cancers[4] and in 9% to 38% of patients with gastric cancer. Overexpression in stomach cancer varies with histologic type (intestinal type greater than diffuse type) and differentiation (moderately differentiated greater than poorly differentiated).[5]

For patients with inoperable locally advanced, recurrent, or metastatic adenocarcinoma of the stomach or gastroesophageal junction for whom trastuzumab (Herceptin) is under consideration for therapy, assessment for tumor HER2 overexpression using immunohistochemistry (IHC) or in situ hybridization (ISH) is recommended by the National Comprehensive Cancer Network (NCCN).[5] Results of an open-label, international, phase 3 randomized controlled trial in 2010 (Trastuzumab for Gastric Cancer [ToGA]) showed that the anti-HER2 humanized monoclonal antibody trastuzumab is effective in prolonging survival compared with chemotherapy alone in patients with HER2-positive adenocarcinoma of the stomach and the gastroesophageal junction.[6] *HER2 (ERBB2)* appears to be an important prognostic factor in gastric cancer, although the literature is conflicting, and not all studies have shown an association between HER2 overexpression and poor prognosis.[4,7] Clinical trials with antibodies to HER2 in gastric cancer patients are in progress.

HER2 (ERBB2) status can be assessed by testing either biopsy or surgical resection specimens. IHC evaluates membranous protein expression of cancer cells. Both intensity and percentage of immunoreactive cancer cells is assessed with scores ranging from 0 to 3+ (Table 1). ISH, which encompasses fluorescence in situ hybridization (FISH), chromogenic in situ hybridization (CISH), silver-enhanced in situ hybridization (SISH), and dual in situ hybridization (DISH), identifies the presence or absence of gene amplification. Some assays use a single *HER2 (ERBB2)* probe to determine the number of *HER2 (ERBB2)* gene copies present, but most assays include a chromosome enumeration probe (CEP17) to determine the ratio of *HER2 (ERBB2)* signals to copies of chromosome 17. ISH has been used to verify IHC-equivocal cases.[5] HER2-positive gastric cancer has been defined as IHC 3+ or ISH positive in the USA and Japan, and IHC 3+ or 2+ with ISH positivity in Europe.[4,8] In the US, the FDA has approved trastuzumab in association with chemotherapy for metastatic gastric cancer utilizing the eligibility criteria of the ToGA trial, limited to patients with a score of IHC 3+ or 2+ and ISH positivity. No significant survival benefit was seen for patients who were IHC 0 or 1+ and FISH positive.[9]

HER2 protein expression is more heterogeneous in gastric cancers than in breast cancers.[7,8,10] The completeness of membrane staining required for positivity in breast cancers is infrequent in gastric adenocarcinomas, which often exhibit a basolateral staining pattern. Detection of *HER2 (ERBB2)* gene amplification by FISH is similar to that in breast cancer according to the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) 2013 guidelines, in which *HER2 (ERBB2)* amplification is defined as *HER2 (ERBB2)*:CEP17 ratio of ≥2.[11] Hoffman et al developed a four-tier scoring system for IHC (Table 1), also used in the ToGA trial, for gastric cancer by using the assessment area cutoff of at least 10% stained tumor cells for resection specimens and a small cluster of cells (≥5 neoplastic cells) for biopsy specimens.[7] The NCCN guidelines recommend that assessment for HER2 status should be performed first using immunohistochemistry following the modified scoring system used in the ToGA trial. A score of 0 or 1+ is considered to be negative for HER2 expression. A score of 2+ is considered equivocal and should be confirmed with FISH or other in situ hybridization techniques. The NCCN panel recommends FISH only for cases with IHC 2+, although some institutions routinely perform both IHC and FISH on all cases. The guidelines recommend trastuzumab with chemotherapy only for patients with IHC 3+ and IHC 2+ with evidence of *HER2 (ERBB2)* amplification by ISH (*HER2 (ERBB2)*:CEP17 ratio ≥2). Trastuzumab is not recommended if the IHC score is 0 or 1+.[5]

A recently published joint guideline from the College of American Pathologists, American Society for Clinical Pathology, and American Society of Clinical Oncology outlined 11 proposed recommendations for HER2 testing and clinical decision making in gastroesophageal adenocarcinoma. This guideline gives recommendations based on peer-reviewed literature and expert panel opinion for the assessment of HER2 in patients with advanced gastroesophageal adenocarcinoma, including both technical and clinical implications.[12]

Table 1. Criteria Used in the ToGA Trial[6] for Scoring HER2 Expression by Immunohistochemistry (IHC) in Gastric and Gastroesophageal Junction Adenocarcinoma

HER2 IHC Score	HER2 IHC Pattern in Surgical Specimen	HER2 IHC Pattern in Biopsy Specimen	HER2 Expression Assessment
0	No reactivity or membranous reactivity in <10% of cancer cells	No reactivity or no membranous reactivity in any cancer cell	Negative by IHC
1+	Faint or barely perceptible membranous reactivity in ≥10% of cancer cells; cells are reactive only in part of their membrane	Cancer cell cluster* with a faint or barely perceptible membranous reactivity irrespective of percentage of cancer cells positive	Negative by IHC
2+	Weak to moderate complete, basolateral or lateral membranous reactivity in ≥10% of tumor cells	Cancer cell cluster* with a weak to moderate complete, basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive	Equivocal by IHC
3+	Strong complete, basolateral or lateral membranous reactivity in ≥10% of cancer cells	Cancer cell cluster* with a strong complete basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive	Positive

* Cancer cell cluster consisting of ≥5 neoplastic cells.

References

1. Akiyama T, Sudo C, Ogawara H, Toyoshima K, Yamamoto T. The product of the human c-erbB-2 gene: a 185-kilodalton glycoprotein with tyrosine kinase activity. *Science*. 1986;232(4758):1644-1646
2. Ménard S, Pupa SM, Campiglio M, Tagliabue E. Biologic and therapeutic role of HER2 in cancer. *Oncogene*. 2003;22(42):6570-6578.
3. Liu L, Wu N, Li J. Novel targeted agents for gastric cancer. *J Hematol Oncol*. 2012;5:31.
4. Boku N. HER2 positive gastric cancer. *Gastric Cancer*. 2014;17(1):1-12.
5. Ajani JA, Bentrem DJ, Besh S, et al. Gastric cancer, version 2.2013: featured updates to the NCCN Guidelines. *J Natl Compr Canc Netw.* 2013;11(5):531-546.
6. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomized controlled trial. *Lancet*. 2010;376(9742):687-697.
7. Hofmann M, Stoss O, Shi D, et al. Assessment of a HER2 scoring system for gastric cancer: results from a validation study. *Histopathology.* 2008;52(7):797-805.
8. Albarello L, Pecciarini L, Doglioni C. HER2 testing in gastric cancer. *Adv Anat Pathol.* 2011;18(1):53-9.
9. Bang YJ. Advances in the management of HER2-positive advanced gastric and gastroesophageal junction cancer. *J Clin Gastroenterol*. 2012;46(8):637-648.
10. Pirrelli M, Caruso ML, Di Maggio M, Armentano R, Valentini AM**.** Are biopsy specimens predictive of HER2 status in gastric cancer patients? *Digest Dis Sci.* 2013;58(2):397-404.
11. Wolff AC, Hammond MEH, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *Arch Pathol Lab Med*. 2014;138(2):241-256.

12. Bartley, AN, Washington, MK, Ventura, CB et al. *HER2* Testing and Clinical Decision Making in Gastroesophageal Adenocarcinoma: Guideline From the College of American Pathologists, American Society for Clinical Pathology, and American Society of Clinical Oncology. *Arch Pathol Lab Med.* 2016 Dec; 140(12):1345-1363.