
Topic: HER2 Testing and Decision Making in Gastroesophageal Adenocarcinoma**Date:** November 10, 2016

Why is this evidence-based guideline needed?

Gastric and esophageal cancers are common malignancies worldwide, and frequently present at advanced stages when therapies are limited. In 2010, results of an open-label, international, phase 3 randomized controlled trial (Trastuzumab for Gastric Cancer, ToGA),¹ showed that the anti-HER2 humanized monoclonal antibody trastuzumab (Herceptin) statistically significantly prolonged overall survival compared with chemotherapy alone in patients with HER2-positive advanced gastroesophageal adenocarcinomas. This guideline provides evidence-based recommendations specific for HER2 testing in gastroesophageal adenocarcinoma (GEA),² to improve determination of patient eligibility for HER2-targeted therapy. The ASCO/CAP guidelines for breast cancer do not apply to several issues pertaining to HER2 in GEA; accordingly, a guideline specific for GEA was developed.

Why doesn't the guideline recommend reflex testing for HER2 for all GEA cases?

Available evidence does not support the determination of HER2 status in patients who have a surgically resectable GEA, and HER2 status is not useful to prognosticate survival or similar endpoints. However, for patients with advanced GEA with a good performance status, low cardiac risk, and who would otherwise be candidates for systemic therapy including trastuzumab, HER2 testing should be performed and patients should be offered trastuzumab if GEA is HER2 positive. Currently, there is no evidence of benefit of HER2-directed therapy in patients in early stage GEA.

How do you define "potential candidates" for HER2 Testing in GEA?

Potential candidates for HER2 testing are patients with advanced or metastatic GEA, who have a good performance status, low cardiac risk, and who would otherwise be candidates for systemic therapy. If the patient would be unable to tolerate trastuzumab due to low performance status or comorbidities, then HER2 testing is not indicated.

Should clinicians wait for the results of HER2 testing before starting therapy for patients with advanced GEA?

It is better not to wait. Most patients are symptomatic and can begin combination chemotherapy. If HER2 is reported positive, trastuzumab can be added.

Can you clarify which body site the guideline is referring to for HER2 testing – gastroesophageal or gastroesophageal junction?

The guideline refers to esophageal adenocarcinomas, gastroesophageal junction adenocarcinomas, and gastric adenocarcinomas. These tumors are collectively referred to as gastroesophageal adenocarcinomas in the guideline.

Which tumor tissue should be used for HER2 testing?

There is considerable published data to suggest that there is concordance among endoscopic biopsy, resection specimen or metastatic tissue. Therefore, it may be best to test the most abundant tissue from any of the above mentioned sources.

Our institution performs HER2 IHC and ISH on all GEA specimens. Why doesn't the guideline recommend testing both IHC and ISH on all GEA specimens?

Available data indicate that ISH-positivity alone does not correlate with response to trastuzumab therapy in GEA but that the benefit from the addition of HER2-directed therapy correlates with HER2 protein expression. Specifically, the ToGA trial demonstrated that the combination of trastuzumab plus chemotherapy significantly improved survival in patients with tumors showing high HER2 expression, defined as 3+ by IHC, or 2+ by IHC with *HER2* amplification by FISH.

Accordingly, testing with IHC first, followed by ISH for cases showing equivocal (2+) HER2 expression, is the recommended algorithm for determining eligibility for anti-HER2 therapy.

How does the guideline address the issue of tumor heterogeneity?

For biopsy specimens, current recommendations state that, when possible, a minimum of five³ and optimally, six to eight biopsies should be obtained to account for intratumoral heterogeneity and to provide sufficient tumor specimens for diagnosis and biomarker testing, and is also recommended by the NCCN Guidelines.^{4,6} When choosing a tissue block, selecting one with the lower grade or intestinal morphology appears more likely to yield HER2 positive results and is thus recommended. If the cancer comprises substantially different grades or histologic patterns, it is reasonable to test different areas which may require selection of more than one tissue block.

How will the guideline be enforced? What happens if a laboratory doesn't follow the guideline?

As with any clinical evidence-based guideline, following this guideline is not mandatory. These recommendations *may* be added to future versions of the CAP Laboratory Accreditation Program (LAP) Checklist; however, they are not currently required by LAP or any regulatory accrediting agency unless as previously defined in CLIA. It is encouraged however, that laboratories adopt these high-level evidence-based recommendations.

REFERENCES

1. 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, randomised controlled trial. *Lancet*. 2010;376(9742):687-697.
2. Bartley AN, Washington K, 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 the American Society of Clinical Oncology. *Arch Pathol Lab Med*. 2016;140(12):1345-1363. doi: [10.5858/arpa.2016-0331-CP](https://doi.org/10.5858/arpa.2016-0331-CP)
3. Gullo I, Grillo F, Molinaro L, et al. Minimum biopsy set for HER2 evaluation in gastric and gastroesophageal junction cancer. *Endosc Int Open*. 2015;3(2):E165-170.
4. Van Cutsem E, Bang YJ, Feng-Yi F, et al. HER2 screening data from ToGA: targeting HER2 in gastric and gastroesophageal junction cancer. *Gastric Cancer*. 2015;18(3):476-484.
5. Ajani JA, et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Gastric Cancer, Version 3.2015. National Comprehensive Cancer Network, Inc. Available at NCCN.org. Accessed June 28, 2016.
6. Ruschoff J, Hanna W, Bilous M, et al. HER2 testing in gastric cancer: a practical approach. *Mod Pathol*. 2012;25(5):637-650.