**National Quality Forum—Evidence (subcriterion 1a)**

**Measure Number** (*if previously endorsed*)**:** 1857

**Measure Title**: HER2 negative or undocumented breast cancer patients spared treatment with HER2-targeted therapies

**IF the measure is a component in a composite performance measure, provide the title of the Composite Measure here:** Click here to enter composite measure #/ title

**Date of Submission**: 3/11/2016

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| **Instructions**  *For composite performance measures:*  *A separate evidence form is required for each component measure unless several components were studied together.*  *If a component measure is submitted as an individual performance measure, attach the evidence form to the individual measure submission.*   * Respond to all questions as instructed with answers immediately following the question. All information needed to demonstrate meeting the evidence subcriterion (1a) must be in this form. An appendix of *supplemental* materials may be submitted, but there is no guarantee it will be reviewed. * If you are unable to check a box, please highlight or shade the box for your response. * Maximum of 10 pages (*incudes questions/instructions*; minimum font size 11 pt; do not change margins). ***Contact NQF staff if more pages are needed.*** * Contact NQF staff regarding questions. Check for resources at [Submitting Standards webpage](http://www.qualityforum.org/Measuring_Performance/Submitting_Standards.aspx). |

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| **Note: The information provided in this form is intended to aid the Steering Committee and other stakeholders in understanding to what degree the evidence for this measure meets NQF’s evaluation criteria.**   1a. Evidence to Support the Measure Focus The measure focus is evidence-based, demonstrated as follows:   * Health outcome: [**3**](#Note3) a rationale supports the relationship of the health outcome to processes or structures of care. Applies to patient-reported outcomes (PRO), including health-related quality of life/functional status, symptom/symptom burden, experience with care, health-related behavior. * Intermediate clinical outcome: a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence [**4**](#Note4)that the measured intermediate clinical outcome leads to a desired health outcome. * Process: [**5**](#Note5) a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence [**4**](#Note4) that the measured process leads to a desired health outcome. * Structure: a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence [**4**](#Note4) that the measured structure leads to a desired health outcome. * Efficiency: [**6**](#Note6) evidence not required for the resource use component.   **Notes**  **3.** Generally, rare event outcomes do not provide adequate information for improvement or discrimination; however, serious reportable events that are compared to zero are appropriate outcomes for public reporting and quality improvement.  **4.** The preferred systems for grading the evidence are the U.S. Preventive Services Task Force (USPSTF) [grading definitions](http://www.uspreventiveservicestaskforce.org/uspstf/grades.htm) and [methods](http://www.uspreventiveservicestaskforce.org/methods.htm), or Grading of Recommendations, Assessment, Development and Evaluation [(GRADE) guidelines](http://www.gradeworkinggroup.org/publications/index.htm).  **5.** Clinical care processes typically include multiple steps: assess → identify problem/potential problem → choose/plan intervention (with patient input) → provide intervention → evaluate impact on health status. If the measure focus is one step in such a multistep process, the step with the strongest evidence for the link to the desired outcome should be selected as the focus of measurement. Note: A measure focused only on collecting PROM data is not a PRO-PM.  **6.** Measures of efficiency combine the concepts of resource use and quality (see NQF’s [Measurement Framework: Evaluating Efficiency Across Episodes of Care](http://www.qualityforum.org/Publications/2010/01/Measurement_Framework__Evaluating_Efficiency_Across_Patient-Focused_Episodes_of_Care.aspx); [AQA Principles of Efficiency Measures](http://www.aqaalliance.org/files/PrinciplesofEfficiencyMeasurementApril2006.doc)). |

**1a.1.This is a measure of**: (*should be consistent with type of measure entered in De.1*)

Outcome

Health outcome: Click here to name the health outcome

Patient-reported outcome (PRO): Click here to name the PRO

*PROs include HRQoL/functional status, symptom/symptom burden, experience with care, health-related behaviors*

Intermediate clinical outcome (*e.g., lab value*): Click here to name the intermediate outcome

Process: HER2 targeted therapy spared for patients who are HER2 negative or undocumented

Structure: Click here to name the structure

Other: Click here to name what is being measured

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**HEALTH OUTCOME/PRO PERFORMANCE MEASURE**  *If not a health outcome or PRO, skip to* [*1a.3*](#Section1a3)

**1a.2.** **Briefly state or diagram the path between the health outcome (or PRO) and the healthcare structures, processes, interventions, or services that influence it.**

**1a.2.1.** **State the rationale supporting the relationship between the health outcome (or PRO) to at least one healthcare structure, process, intervention, or service (*i.e., influence on outcome/PRO*).**

*Note: For health outcome/PRO performance measures, no further information is required; however, you may provide evidence for any of the structures, processes, interventions, or service identified above.*

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**intermediate outcome, PROCESS, or STRUCTURE PERFORMANCE measure**

**1a.3.****Briefly state or diagram the path between structure, process, intermediate outcome, and health outcomes**. Include all the steps between the measure focus and the health outcome.

Human epidermal growth factor receptor (HER2) gene is amplified and/or overexpressed in

approximately 15% to 20% of primary breast cancers (Giordano, 2014). The ASCO/CAP joint guideline on HER2 testing recommends all patients with invasive breast cancer should be tested for HER2 status and only those who test positive for HER2 status should receive HER2 targeted therapies. Additionally data have shown that the administration of HER2 targeted therapies such as Pertuzumab offer no clinical benefit in patients with HER2 negative metastatic disease (Wolff, 2013).

The contraindicated administration of HER2 targeted therapy to patients with HER2 negative breast cancer can propagate potentially toxic, costly and adverse effects as well as decrease the patient’s overall quality of life (Partridge, 2014).

Citations:

Giordano, S.H., Temin, S., et. al., “Systemic Therapy for Patients with Advanced Human Epidermal Growth Factor Receptor 2- Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline.” J Clin Onc 32.19 (2014): 2078-099. Available at:

<http://jco.ascopubs.org/content/32/19/2078.full.pdf+html>

Partridge, A.H., Smith, I.E., et. al., “Chemo- and Targeted Therapy for Women with Human Epidermal Growth Factor Receptor 2- Negative (or Unknown) Advanced Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline.” J Onc Pr 11.1 (2014): 3307-3329. Available at: <http://jco.ascopubs.org/content/32/29/3307.full>

Wolff, A.C, Hammond, M.E.H, 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.” J Clin Onc 31.31 (2013): 3997-4013. Available at: <http://jco.ascopubs.org/content/31/31/3997.full>

**1a.3.1.** **What is the source of the systematic review of the body of evidence that supports the performance measure?**

Clinical Practice Guideline recommendation – ***complete sections*** [***1a.4***](#Section1a4)***, and*** [***1a.7***](#Section1a7)

US Preventive Services Task Force Recommendation – ***complete sections*** [***1a.5***](#Section1a5) ***and*** [***1a.7***](#Section1a7)

Other systematic review and grading of the body of evidence (*e.g., Cochrane Collaboration, AHRQ Evidence Practice Center*) – ***complete sections*** [***1a.6***](#Section1a6) ***and*** [***1a.7***](#Section1a7)

Other – ***complete section*** [***1a.8***](#Section1a8)

*Please complete the sections indicated above for the source of evidence. You may skip the sections that do not apply.*

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**1a.4. CLINICAL PRACTICE GUIDELINE RECOMMENDATION**

**1a.4.1.** **Guideline citation** (*including date*) and **URL for guideline** (*if available online*):

Giordano, S.H., Temin, S., et. al., “Systemic Therapy for Patients with Advanced Human Epidermal Growth Factor Receptor 2- Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline.” J Clin Onc 32.19 (2014): 2078-099. Available at:

<http://jco.ascopubs.org/content/32/19/2078.full.pdf+html>

Eisen, A., K.G, Fletcher, et.al, “Optimal Systemic Therapy for Early Breast Cancer in Women: A Clinical Practice Guideline.” Curr Onc 22.0 (2014): Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4381792/>

Wolff, A.C, Hammond, M.E.H, 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.” J Clin Onc 31.31 (2013): 3997-4013. Available at: <http://jco.ascopubs.org/content/31/31/3997.full>

**1a.4.2.** **Identify guideline recommendation number and/or page number** and **quote verbatim, the specific guideline recommendation**.

ASCO guideline on systemic therapy for patients with advanced cancer:

Pg. 2081

Recommendation 1:

“Clinicians should recommend HER2-targeted therapy–based combinations for first-line treatment, except for highly selected patients with ER-positive or PgR-positive and HER2-positive disease, for whom clinicians may use endocrine therapy alone.” Strength of recommendation: Strong. Evidence Quality: High

CCO guideline on optimal systemic therapy for women with early breast cancer:

Page S75

Recommendation 26:

“Only patients with her2-positive breast cancer [ihc 3+, *in situ* hybridization (ish) ratio ≥ 2, or 6+

her2 gene copies per cell nucleus] should be offered adjuvant trastuzumab.”

ASCO/CAP Joint Guideline on HER2 Testing:

Page 3998:

“Must request HER2 testing on every primary invasive breast cancer (and on metastatic site, if stage IV and if specimen available) from a patient with breast cancer to guide decision to pursue HER2-targeted therapy. This should be especially considered for a patient who previously tested HER2 negative in a primary tumor and presents with disease recurrence with clinical behavior suggestive of HER2-positive or triple-negative disease”

“Must not recommend HER2-targeted therapy if HER2 test result is negativeand if there is no apparent

histopathologic discordance with HER2 testing (Tables 1 and 2). If the pathologist or oncologist observes

an apparent histopathologic discordance after HER2 testing, the need for additional HER2 testing

should be discussed.”

**1a.4.3.** **Grade assigned to the quoted recommendation with definition of the grade:**

ASCO guideline: Strength of recommendation: Strong.

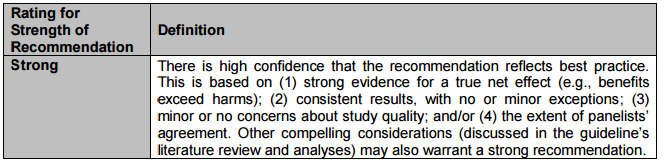
Definition: There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent of panelists’ agreement. Other compelling considerations (discussed in the guideline’s literature review and analyses) may also warrant a strong recommendation

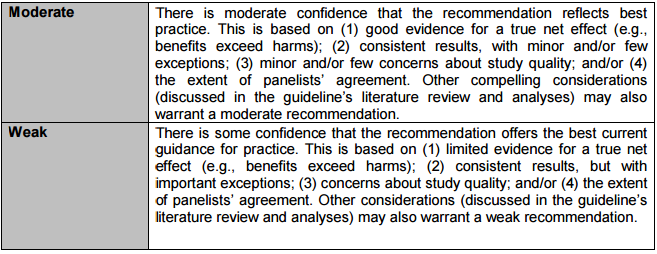
CCO guideline: CCO Guidelines use a narrative approach to grade the strength of recommendations. Additional details are not provided in the guideline.

ASCO/CAP Joint Guideline: recommendation not graded.

**1a.4.4. Provide all other grades and associated definitions for recommendations in the grading system.** (*Note: If separate grades for the strength of the evidence, report them in section 1a.7.*)

ASCO Guideline:





**1a.4.5. Citation and URL for methodology for grading recommendations** (*if different from 1a.4.1*)**:**

[**http://www.instituteforquality.org/sites/instituteforquality.org/files/her2\_treatment\_ms\_5.21.pdf**](http://www.instituteforquality.org/sites/instituteforquality.org/files/her2_treatment_ms_5.21.pdf)

**1a.4.6. If guideline is evidence-based (rather than expert opinion), are the details of the quantity, quality, and consistency of the body of evidence available (e.g., evidence tables)?**

Yes **→ *complete section*** [***1a.7***](#Section1a7)

No **→ *report on another systematic review of the evidence in sections*** [***1a.6***](#Section1a6) ***and*** [***1a.7***](#Section1a7)***; if another review does not exist, provide what is known from the guideline review of evidence in*** [***1a.7***](#Section1a7)

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**1a.5.** **UNITED STATES PREVENTIVE SERVICES TASK FORCE RECOMMENDATION**

**1a.5.1.** **Recommendation citation** (*including date*) and **URL for recommendation** (*if available online*):

**1a.5.2.** **Identify recommendation number and/or page number** and **quote verbatim, the specific recommendation**.

**1a.5.3.** **Grade assigned to the quoted recommendation with definition of the grade**:

**1a.5.4. Provide all other grades and associated definitions for recommendations in the grading system.** (*Note: the* *grading system for the evidence should be reported in section 1a.7.*)

**1a.5.5. Citation and URL for methodology for grading recommendations** (*if different from 1a.5.1*)**:**

***Complete section*** [***1a.7***](#Section1a7)

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**1a.6. OTHER SYSTEMATIC REVIEW OF THE BODY OF EVIDENCE**

**1a.6.1.** **Citation** (*including date*) and **URL** (*if available online*):

**1a.6.2.** **Citation and** **URL for methodology for evidence review and grading** (*if different from 1a.6.1*)**:**

***Complete section*** [***1a.7***](#Section1a7)

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**1a.7. FINDINGS FROM SYSTEMATIC REVIEW OF BODY OF THE EVIDENCE supporting the measure**

*If more than one systematic review of the evidence is identified above, you may choose to summarize the one (or more) for which the best information is available to provide a summary of the quantity, quality, and consistency of the body of evidence. Be sure to identify which review is the basis of the responses in this section and if more than one, provide a separate response for each review.*

**1a.7.1.** **What was the specific structure, treatment, intervention, service, or intermediate outcome addressed in the evidence review?**

ASCO Guideline:

p. 2078

To provide evidence-based recommendations to practicing oncologists and others on systemic

therapy for patients with human epidermal growth factor receptor 2 (HER2) –positive advanced

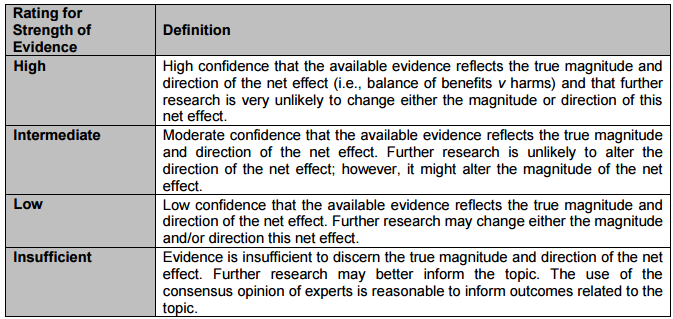
breast cancer.

**1a.7.2.** **Grade assigned for the quality of the quoted evidence with definition of the grade**:

Evidence Quality: High

Definition: High confidence that the available evidence reflects the true magnitude and direction of the net effect (i.e. balance of benefits v harms) and that further research is very unlikely to change either the magnitude or direction of this net effect.

**1a.7.3. Provide all other grades and associated definitions for strength of the evidence in the grading system.**



**1a.7.4.** **What is the time period covered by the body of evidence? (*provide the date range, e.g., 1990-2010*). Date range**: 1966-2012

**QUANTITY AND QUALITY OF BODY OF EVIDENCE**

**1a.7.5.****How many and what type of study designs are included in the body of evidence**? (*e.g., 3 randomized controlled trials and 1 observational study*)

11 randomized controlled clinical trials

**1a.7.6.** **What is the overall quality of evidence across studies in the body of evidence**? (*discuss the certainty or confidence in the estimates of effect particularly in relation to study factors such as design flaws, imprecision due to small numbers, indirectness of studies to the measure focus or target population*)

ASCO guideline:

P. 2081

This recommendation is based on a body of evidence regarding first-line therapy, found both in the ASCO and CCO systematic reviews. CCO included the pivotal trial by Slamon et al and nine other RCTs of trastuzumab. These trials found a benefit for HER2-targeted therapy combinations, specifically with trastuzumab. The study by Slamon et al was the only first-line phase III trial that compared an HER2-targeted therapy plus chemotherapy with chemotherapy alone. That trial found survival, time to progression (TTP), and overall response rate benefits in the trastuzumab arm. The CCO review found two phase III trials that compared HER2-targeted therapy plus endocrine therapy with endocrine therapy alone. Both of those trials found progression-free survival (PFS) and TTP benefits, but no overall survival (OS) benefit, in the combination arm and will be discussed in the section on endocrine therapy (Clinical Question 2), along with another more recent trial.

**ESTIMATES OF BENEFIT AND CONSISTENCY ACROSS STUDIES IN BODY OF EVIDENCE**

**1a.7.7.** **What are the estimates of benefit—magnitude and direction of effect on outcome(s) across studies in the body of evidence**? (*e.g., ranges of percentages or odds ratios for improvement/ decline across studies, results of meta-analysis, and statistical significance*)

ASCO guideline:

P. 2092

Overall, HER2-targeted therapy in combination with chemotherapy in the first-line setting is associated with improvements in response rate, PFS (progression-free survival), TTP (time to progression), and OS (overall survival) when compared with chemotherapy alone. In trials of endocrine therapy, the addition of HER2-targeted therapy is associated with improvements in response rate and PFS but not in survival. These data support the use of HER2-targeted therapy in the first-line treatment of metastatic breast cancer.

**1a.7.8.** **What harms were studied and how do they affect the net benefit (benefits over harms)?**

ASCO guideline:

P.2092

There are some contraindications to HER2-targeted therapy, as a result of its cardiovascular toxicity effects (Table 4). The single most important contraindication is a decreased left ventricular ejection fraction (LVEF) and/or clinical evidence of congestive heart failure arising from low LVEF. Among patients with congestive heart failure or low ejection fraction, the decision to use HER2-targeted therapy must be made on an individual basis, assessing the relative risks of cardiac dysfunction from a specific regimen versus disease progression.

**UPDATE TO THE SYSTEMATIC REVIEW(S) OF THE BODY OF EVIDENCE**

**1a.7.9.** **If new studies have been conducted since the systematic review of the body of evidence, provide for each new study: 1) citation, 2) description, 3) results, 4) impact on conclusions of systematic review**.

No relevant studies have been conducted and published since the systematic reviews.

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**1a.8 OTHER SOURCE OF EVIDENCE**

*If source of evidence is NOT from a clinical practice guideline, USPSTF, or systematic review, please describe the evidence on which you are basing the performance measure.*

**1a.8.1** **What process was used to identify the evidence?**

**1a.8.2.** **Provide the citation and summary for each piece of evidence.**