**NATIONAL QUALITY FORUM—Evidence (subcriterion 1a)**

**Measure Number** (*if previously endorsed*)**:** 1859

**Measure Title**: RAS gene mutation testing performed for patients with metastatic colorectal cancer who receive anti-epidermal growth factor receptor monoclonal antibody therapy

**IF the measure is a component in a composite performance measure, provide the title of the Composite Measure here:** N/A

**Date of Submission**: 11/12/19

**Instructions**

* *Complete 1a.1 and 1a.2 for all measures. If instrument-based measure, complete 1a.3.*
* *Complete* ***EITHER 1a.2, 1a.3 or 1a.4*** *as applicable for the type of measure and evidence.*
* *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.*
* 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.
* Contact NQF staff regarding questions. Check for resources at [Submitting Standards webpage.](http://www.qualityforum.org/Measuring_Performance/Submitting_Standards.aspx)

### Note: The information provided in this form is intended to aid the Standing 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:

* Outcome: [**3**](#_bookmark0) Empirical data demonstrate a relationship between the outcome and at least one healthcare structure, process, intervention, or service. If not available, wide variation in performance can be used as evidence, assuming the data are from a robust number of providers and results are not subject to systematic bias.
* Intermediate clinical outcome: a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence [**4**](#_bookmark1) that the measured intermediate clinical outcome leads to a desired health outcome.
* Process: [**5**](#_bookmark2) a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence [**4**](#_bookmark1) 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**](#_bookmark1)that the measured structure leads to a desired health outcome.
* Efficiency: [**6**](#_bookmark3) evidence not required for the resource use component.
* For measures derived from patient reports, evidence should demonstrate that the target population values the measured outcome, process, or structure and finds it meaningful.
* Process measures incorporating Appropriate Use Criteria: See NQF’s guidance for evidence for measures, in general; guidance for measures specifically based on clinical practice guidelines apply as well.

### Notes

1. 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.
2. The preferred systems for grading the evidence are the Grading of Recommendations, Assessment, Development and Evaluation [(GRADE) guidelines](http://www.gradeworkinggroup.org/) and/or modified GRADE.
3. 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

## 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.* (*A PRO-based performance measure is not a survey instrument. Data may be collected using a survey instrument to construct a PRO measure.)*

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

☒ Process: Click here to name what is being measured

☒ Appropriate use measure: Administration of anti-EGFR monoclonal antibody targeted therapies based on RAS mutation status

* Structure: Click here to name the structure
* Composite: Click here to name what is being measured

**1a.2 LOGIC MODEL** Diagram or briefly describe the steps between the healthcare structures and processes (e.g., interventions, or services) and the patient’s health outcome(s). The relationships in the diagram should be easily understood by general, non-technical audiences. Indicate the structure, process or outcome being measured.

The process evaluated in this measure is the completion of RAS testing to identify those patients who will not benefit from anti-EGFR therapy. Multiple studies, including a randomized controlled trial (RCT) support knowing a patient’s tumor mutation status before consideration of use of an EGFR inhibitor in the treatment regimen.

The body of evidence addresses the relationship between RAS status in patients with metastatic colorectal cancer who underwent of anti-EGFR MoAB therapy, specifically cetuximab or panitumumab, and the outcomes of tumor response, progression-free survival, and overall survival. Patients with and without KRAS or NRAS mutations to exons 2, 3 or 4 who underwent anti-EGFR MoAb therapy were evaluated with respect to these outcomes in both single-arm and randomized trials. Additionally, this measure is directly supported by recommendations in American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology and NCCN clinical practice guidelines.

**1a.3 Value and Meaningfulness: IF** this measure is derived from patient report, provide evidence that the target population values the measured ***outcome, process, or structure*** and finds it meaningful. (Describe how and from whom their input was obtained.)

# \*\*RESPOND TO ONLY ONE SECTION BELOW -EITHER 1a.2, 1a.3 or 1a.4) \*\*

**1a.2 FOR OUTCOME MEASURES including PATIENT REPORTED OUTCOMES - Provide empirical data demonstrating the relationship between the outcome (or PRO) to at least one healthcare structure, process, intervention, or service.**

**1a.3. SYSTEMATIC REVIEW(SR) OF THE EVIDENCE (for INTERMEDIATE OUTCOME, PROCESS, OR STRUCTURE PERFORMANCE MEASURES, INCLUDING THOSE THAT ARE INSTRUMENT-BASED) If the**

**evidence is not based on a systematic review go to section 1a.4) If you wish to include more than one systematic review, add additional tables.**

**What is the source of the systematic review of the body of evidence that supports the performance measure? A systematic review is a scientific investigation that focuses on a specific question and uses explicit, prespecified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies. It may include a quantitative synthesis (meta-analysis), depending on the available data. (IOM)**

## ☒Clinical Practice Guideline recommendation (with evidence review)

* US Preventive Services Task Force Recommendation
* Other systematic review and grading of the body of evidence (*e.g., Cochrane Collaboration, AHRQ Evidence Practice Center*)

## Other

|  |  |
| --- | --- |
| **Source of Systematic Review:**   * **Title** * **Author** * **Date** * **Citation, including page number** * **URL** | Molecular Biomarkers for the Evaluation of Colorectal Cancer  Antonia R. Sepulveda, Stanley R. Hamilton, Carmen J. Allegra, Wayne Grody, Allison M. Cushman-Vokoun, William K. Funkhouser, Scott E. Kopetz, Christopher Lieu, Noralane M. Lindor, Bruce D. Minsky, Federico A. Monzon, Daniel J. Sargent[†](javascript:popRef('fn1')) Veena M. Singh, Joseph Willis, Jennifer Clark, Carol Colasacco, R. Bryan Rumble, Robyn Temple-Smolkin, Christina B. Ventura, and Jan A. Nowak  May 21, 2017  Sepulveda AR, Hamilton SR, Allegra CJ, et al: Molecular Biomarkers for the Evaluation of Colorectal Cancer: Guideline From the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology. Journal of Clinical Oncology 35:1453-1486, 2017  <https://ascopubs.org/doi/full/10.1200/JCO.2016.71.9807> |
| Quote the guideline or recommendation verbatim about the process, structure or intermediate outcome being measured. If not a guideline, summarize the  conclusions from the SR. | “Colorectal carcinoma patients being considered for anti-EGFR therapy must receive RAS mutational testing. Mutational analysis should include KRAS and NRAS codons 12, 13 of exon 2; 59, 61 of exon 3; and 117 and 146 of exon 4 (“expanded” or “extended” RAS)” |
| Grade assigned to the **evidence** associated with the recommendation with the  definition of the grade | Strength of Evidence: convincing/adequate, benefits  outweigh harms; Quality of Evidence: high/intermediate   * Convincing: High confidence that available evidence reflects true effect. Further research is very unlikely to change the confidence in the estimate of effect. High/intermediate quality of evidence. * Adequate: Moderate confidence that available evidence reflects true effect. Further research is likely to have an important impact on the confidence in estimate of effect and may change the estimate. Intermediate/low quality of evidence. |
| Provide all other grades and definitions  from the evidence grading system | Grades for Strength of Evidence   * Convincing: High confidence that available evidence reflects true effect. Further research is very unlikely to change the confidence in the estimate of effect. High/intermediate quality of evidence. * Adequate: Moderate confidence that available evidence reflects true effect. Further research is likely to have an important impact on the confidence in estimate of effect and may change the estimate. Intermediate/low quality of evidence. * Inadequate: Little confidence that available evidence reflects true effect. Further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate. Low/insufficient quality of evidence and Expert Panel uses formal consensus process to reach recommendation. * Insufficient: Evidence is insufficient to discern net effect. Any estimate of effect is very uncertain. Insufficient evidence and Expert Panel uses formal consensus process to reach recommendation. |
| Grade assigned to the **recommendation**  with definition of the grade | Recommendation: Some limitations in strength of evidence (adequate or inadequate) and quality of evidence (intermediate or low), balance of benefits  and harms, values, or costs, but panel concludes that there is sufficient evidence and/or benefit to inform a recommendation |
| Provide all other grades and definitions  from the recommendation grading system | Grades for Strength of Recommendation   * Strong recommendation: Supported by convincing or adequate strength of evidence, high or intermediate quality of evidence, and clear benefit that outweighs any harms. * Recommendation: Some limitations in strength of evidence (adequate or inadequate) and quality of evidence (intermediate or low), balance of benefits and harms, values, or costs, but panel concludes that there is sufficient evidence and/or benefit to inform a recommendation. * Expert consensus opinion: Serious limitations in strength of evidence (inadequate of insufficient), quality of evidence (intermediate or low), balance of benefits and harms, values, or costs, but panel consensus is that a statement is necessary. * No recommendation: Insufficient evidence or agreement of the balance of benefits and harms, values, or costs to provide a recommendation. |
| Body of evidence:   * Quantity – how many studies? * Quality – what type of studies? | This recommendation is based on 34 studies, including 29 systematic studies, two meta-analyses, one randomized controlled trial, one prospective cohort study and one retrospective cohort study.  Of the 29 systematic reviews, 13 examined important patient subtypes and one reported accounting for patient preferences. Only 3 of the systematic reviews reported using a multidisciplinary panel. All but one included robust method sections. Nine of the systematic reviews rated the quality and strength of evidence reported. The systematic reviews were assessed by the authors for risk of bias: two systematic reviews were deemed low risk, 14 low to moderate risk, 12 moderate risk of bias and one was deemed to have a high risk of bias.  Of the two meta-analyses, both included robust and reproducible methods sections, described the planned pooling a priori and discussed limitations of their analysis. Neither meta-analyses provided an assessment of the quality of the studies included. The systematic reviews were assessed by the authors for risk of bias: one was deemed to have a low to moderate risk of bias and the other a moderate risk of bias.  The single RCT did not report on the details of randomization but did report on differences in baseline patient characteristics. The RTC was deemed to have a low to moderate risk of bias.  The single prospective cohort study reported a balance between the treatment and assessment groups, reported baseline patient characteristics, and made adjustments in the analysis accordingly. The prospective cohort study was deemed to have a low risk of bias.  The single retrospective cohort study reported balance between the treatment and assessment groups and reported baseline patient characteristics but did not make adjustments in the analysis to account for differences where found. The retrospective cohort study was deemed to have a low risk of bias.  All of the evidence that supported this recommendation was assessed and no methodologic flaws were found to raise concerns regarding the findings. |
| Estimates of benefit and consistency  across studies | The evidence described in the studies are directly relevant to this measure, as these data support knowing a patient’s tumor mutation status before consideration of use of an EGFR inhibitor in the treatment regimen. Mutational status provides clinically actionable information as negative predictors of benefit to anti-EGFR monoclonal antibody therapies for targeted therapy of colorectal cancer. Early studies included only mutations of KRAS exon 2; however, a large body of evidence is now available to support current guideline recommendations for expanded RAS testing. The evidence is consistent in showing that in addition to mutations in KRAS exon 2, additional RAS mutations in KRAS exons 3 and 4 and NRAS exons 2, 3 and 4 are associated with nonresponse of metastatic colorectal cancer to anti-EGFR monoclonal antibody therapy. The studies are consistent in indicating that EGFR inhibitors (cetuximab and panitumumab) should only be prescribed for patients with metastatic colorectal cancer that are nonmutated/wild type for all known RAS-activating mutations.  A reanalysis of the Panitumumab Randomized control Trial in Combination with Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy (PRIME) trial reported that patients with any RAS mutations were associated with inferior progression free survival (PFS) and overall survival (OS) with anti-EGFR treatment. These findings are consistent with previously reported findings for patients with KRAS mutations in exon 2. A meta-analysis of nine RCT’s subsequently provided further evidence that not all KRAS exon 2 nonmutated/wild-type tumors benefit from anti-EGFR monoclonal antibody treatment in metastatic colorectal cancer; patients with colorectal cancer that are KRAS exon 2 nonmutated/wildtype but harbor RAS mutations in KRAS exons 3 and 4 or NRAS exons 2, 3 and 4 also have significantly inferior anti-EGFR treatment outcomes benefit compared to patients without any RAS mutations.  The data show that the clinical benefit of using EGFR inhibitors in treating metastatic colorectal cancer, either as monotherapy or in combination with other treatment regimens, is not seen in patients with RAS-mutated tumors. These data support knowing a patient’s tumor mutation status before consideration of use of an EGFR inhibitor in the treatment regimen. Identifying patients whose tumors express mutated RAS will avoid exposing patients to ineffective drugs, avoid exposure to unnecessary drug toxicities, and expedite the use of the best available alternative therapy. |
| What harms were identified? | The benefits of undergoing testing to determine RAS status outweigh the potential harms associated with a therapy that does not have any efficacy because of RAS status. |
| Identify any new studies conducted since  the SR. Do the new studies change the conclusions from the SR? | Updated guidelines continue to support this measure. Early studies included only mutations of KRAS exon 2; however, a large body of evidence is now available to support current guideline recommendations for expanded RAS testing and this measure has been maintained accordingly. |

|  |  |
| --- | --- |
| **Source of Systematic Review:**   * **Title** * **Author** * **Date** * **Citation, including page number** * **URL** | NCCN Guidelines Version 3.2019 Colon Cancer  National Comprehensive Cancer Network  Version 3.2019 – September 26, 2019  NCCN Clinical Practice Guidelines in Oncology™. Colon Cancer, V.3.2019 (MS-30)  <https://www.nccn.org> |
| Quote the guideline or recommendation verbatim about the process, structure or intermediate outcome being measured. If not a guideline, summarize the  conclusions from the SR. | “All patients with metastatic colorectal cancer should have tumor tissue genotyped for RAS (KRAS and NRAS) and BRAF mutations individually or as part of a next-generation sequencing (NGS) panel. Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab.”  “A sizeable body of literature has shown that tumors with a mutation in codon 12 or 13 of exon 2 of the KRAS gene are essentially insensitive to cetuximab or panitumumab therapy... More recent evidence shows mutations in KRAS outside of exon 2 and mutations in NRAS are also predictive for a lack of benefit of anti-EGFR therapies.  The panel therefore strongly recommends RAS (KRAS/NRAS) genotyping of tumor tissue (either primary tumor or metastasis) in all patients with metastatic colorectal cancer. Patients with known KRAS or NRAS mutations should not be treated with either cetuximab or panitumumab, either alone or in combination with other anticancer agents, because they have virtually no chance of benefit and the exposure to toxicity and expense cannot be justified. It is implied throughout the guidelines that NCCN recommendations involving cetuximab or panitumumab relate only to patients with disease characterized by RAS wild-type genes. ASCO released a Provisional Clinical Opinion Update on extended RAS testing in patients with metastatic colorectal cancer that is consistent with the NCCN Panel’s recommendations. A guideline on molecular biomarkers for colorectal cancer developed by the ASCP, CAP, AMP and ASCO also recommends RAS testing consistent with the NCCN recommendations”  (MS-43) |
| Grade assigned to the **evidence** associated with the recommendation with the  definition of the grade | Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. |
| Provide all other grades and definitions  from the evidence grading system | NCCN Categories of Evidence and Consensus:   * Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. * Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. * Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. * Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate. |
| Grade assigned to the **recommendation**  with definition of the grade | Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. |
| Provide all other grades and definitions  from the recommendation grading system | NCCN Categories of Evidence and Consensus:   * Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. * Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. * Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. * Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate. |
| Body of evidence:   * Quantity – how many studies? * Quality – what type of studies? | The NCCN guidelines does not include an overview of the body of evidence used for the recommendations specific to RAS mutation status. However, the guidelines does provide an in-depth discussion on the evidence, benefits and harms of EGFR inhibitors.  The NCCN guideline presents this data for KRAS Exon 2 Mutations separately from NRAS and other KRAS mutations. This analysis includes the following summary (MS-44 to MS-45):   * “KRAS Exon 2 Mutations: A sizeable body of literature has shown that these KRAS exon 2 mutations are predictive of lack of response to cetuximab or panitumumab therapy, and FDA labels for cetuximab and panitumumab specifically state that these agents are not recommended for the treatment of colorectal cancer characterized by these mutations. Results are mixed as far as the prognostic value of KRAS mutations. In the Alliance N0147 trial, patients with KRAS exon 2 mutations experienced a shorter DFS than patients without such mutations. At this time, however, the test is not recommended for prognostic reasons.   A retrospective study from De Roock et al raised the possibility that codon 13 mutations (G13D) in KRAS may not be absolutely predictive of non-response. Another retrospective study showed similar results. However, more recent retrospective analysis of 3 randomized controlled phase III trials concluded that patients with KRAS G13D mutations were unlikely to respond to panitumumab. Results from a prospective phase II single-arm trial assessed the benefit of cetuximab monotherapy in 12 patients with refractory metastatic colorectal cancer whose tumors contained KRAS G13D mutations. The primary endpoint of 4-month progression-free rate was note met (25%), AND NO RESPONSES WERE SEEN. Preliminary results of the AGITG phase II ICE CREAM trial also failed to see a benefit of cetuximab monotherapy in patients with KRAS G13D mutations. However, partial responses were reported after treatment with irinotecan plus cetuximab in 9% of this irinotecan-refractory population. A meta-analysis of 8 RCTs came to the same conclusion: that tumors with KRAS G13D mutations are no more likely to respond to EGFR inhibitors than tumors with other KRAS mutations. The panel believes that patients with any known KRAS mutation, including G13D, should not be treated with cetuximab or panitumumab. (MS-44)   * “NRAS and Other KRAS Mutations: In the AGITG MAX study, 10% of patients with wild-type KRAS exon 2 had mutations in KRAS exons 3 or 4 or in NRAS exons 2, 3 and 4. In the PRIME trial, 17% of 641 patients without KRAS exon 2 mutations were found to have mutations in exons 3 and 4 of KRAS or mutations in exons 2, 3 and 4 or NRAS. A predefined retrospective subset analysis of data from PRIME revealed that PFS (HR, 1.31; 95% CI, 1.07-1.60; P = .008) and OS (HR, 1.21; 95% CI, 1.01-1.45; P= .04) were decreased in patients with any KRAS or NRAS mutation who received panitumumab plus FOLFOX compared to those who received FOLFOX alone. These results show that panitumumab does not benefit patients with KRAS or NRAS mutations and may even have a detrimental effect in these patients.   Updated analysis of the FIRE-3 trial… was recently published. When all RAS (KRAS/NRAS) mutations were considered, PFS was significantly worse in patients with RAS-mutant tumors receiving FOLFIRI plus cetuximab than in patients with RAS-mutant tumors receiving FOLFIRI plus bevacizumab (6.1 months vs. 12.2 months; P = .004). on the other hand, patients with KRAS/NRAS wild-type tumors showed no difference in PFS between the regimens (10.4 months vs. 10.2 months, P = .54). This result indicates that cetuximab likely has a detrimental effect in patients with KRAS or NRAS mutations  The FDA indication for panitumumab was recently updated to state that panitumumab is not indicated for the treatment of patients with KRAS or NRAS mutation-positive disease in combination with oxaliplatin-based chemotherapy. The NCCN Colon/Rectal Cancer Panel believes that RAS mutation status should be determined as diagnosis of stage IV disease. Patients with any known RAS mutation should not be treated with either cetuximab or panitumumab. (MS-44/MS-45) |
| Estimates of benefit and consistency  across studies | See Body of Evidence section. |
| What harms were identified? | See Body of Evidence section. |
| Identify any new studies conducted since  the SR. Do the new studies change the conclusions from the SR? | Updated guidelines continue to support this measure. |

**1a.4 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.4.1 Briefly SYNTHESIZE the evidence that supports the measure.** A list of references without a summary is not acceptable.

# 1a.4.2 What process was used to identify the evidence? 1a.4.3. Provide the citation(s) for the evidence.