



**CMS Measure ID/CMS QCDR ID: CAP 33**

**Measure Title:** Mismatch Repair (MMR) or Microsatellite Instability (MSI) Biomarker Testing Status in Colorectal Carcinoma, Endometrial, Gastroesophageal, or Small Bowel Carcinoma

<b>Measure Description</b>	Percentage of surgical pathology reports for primary colorectal, endometrial, gastroesophageal or small bowel carcinoma, biopsy or resection, that contain impression or conclusion of or recommendation for testing of mismatch repair (MMR) by immunohistochemistry (biomarkers MLH1, MSH2, MSH6, and PMS2), or microsatellite instability (MSI) by DNA-based testing status, or both
<b>Numerator Statement</b>	Surgical pathology reports that contain impression or conclusion of or recommendation for testing of MMR by immunohistochemistry, MSI by DNA-based testing status, or both
<b>Denominator Statement</b>	<p>All surgical pathology reports for primary colorectal, endometrial, gastroesophageal or small bowel carcinoma, biopsy or resection</p> <p>CPT: 88305, 88307, 88309 AND ICD-10:</p> <ul style="list-style-type: none"><li>• C18.0: Malignant neoplasm of cecum</li><li>• C18.2: Malignant neoplasm of ascending colon</li><li>• C18.3: Malignant neoplasm of hepatic flexure</li><li>• C18.4: Malignant neoplasm of transverse colon</li><li>• C18.5: Malignant neoplasm of splenic flexure</li><li>• C18.6: Malignant neoplasm of descending colon</li><li>• C18.7: Malignant neoplasm of sigmoid colon</li><li>• C18.8: Malignant neoplasm of overlapping sites of colon</li><li>• C18.9: Malignant neoplasm of colon, unspecified</li><li>• C19: Malignant neoplasm of rectosigmoid junction</li><li>• C20: Malignant neoplasm of rectum</li><li>• C54.1 Malignant neoplasm of endometrium</li><li>• C54.3 Malignant neoplasm of fundus uteri</li><li>• C54.8 Malignant neoplasm of overlapping sites of corpus uteri</li><li>• C54.9 Malignant neoplasm of corpus uteri, unspecified</li><li>• C55 Malignant neoplasm of uterus, unspecified</li><li>• C15.3: Malignant neoplasm of upper third of esophagus</li><li>• C15.4: Malignant neoplasm of middle third of esophagus</li><li>• C15.5: Malignant neoplasm of lower third of esophagus</li><li>• C15.8: Malignant neoplasm of overlapping sites of esophagus</li><li>• C15.9: Malignant neoplasm of esophagus, unspecified</li><li>• C16.0: Malignant neoplasm of cardia</li><li>• C16.1: Malignant neoplasm of fundus of stomach</li></ul>

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	<ul style="list-style-type: none"><li>• C16.2: Malignant neoplasm of body of stomach</li><li>• C16.3: Malignant neoplasm of pyloric antrum</li><li>• C16.4: Malignant neoplasm of pylorus</li><li>• C16.5: Malignant neoplasm of lesser curvature of stomach, unspecified</li><li>• C16.6: Malignant neoplasm of greater curvature of stomach, unspecified</li><li>• C16.8: Malignant neoplasm of overlapping sites of stomach</li><li>• C16.9: Malignant neoplasm of stomach, unspecified</li><li>• C17.0 Malignant neoplasm of duodenum</li><li>• C17.1 Malignant neoplasm of jejunum</li><li>• C17.2 Malignant neoplasm of ileum</li><li>• C17.3 Meckel's diverticulum, malignant</li><li>• C17.8 Malignant neoplasm of overlapping sites of small intestine</li><li>• C17.9 Malignant neoplasm of small intestine, unspecified</li><li>• C26.0 Malignant neoplasm of intestinal tract, part unspecified.</li></ul>
<b>Denominator Exclusions</b>	<p>Squamous cell carcinoma of the esophagus</p> <p>Patients with an existing diagnosis of Lynch Syndrome (ICD-10-CM Z15.0, Z15.04, Z15.09, Z80.0)</p>
<b>Denominator Exceptions</b>	<p>MMR/MSI testing not possible or not indicated: insufficient or necrotic tissue, specimen contains metastatic carcinoma, no residual tumor or patient not a candidate for checkpoint inhibitor therapy</p>
<b>Supporting Guidelines and Other References</b>	<p>Colorectal Cancer</p> <p>Clinicians should order mismatch repair (MMR) status testing in patients with colorectal cancers for the identification of patients with a high risk for Lynch syndrome and/or prognostic stratification.(1)</p> <p>In CRC patients being considered for checkpoint blockade therapy, pathologists should use MMR IHC and/or MSI by PCR for the detection of DNA mismatch repair defects. Although MMR IHC or MSI by PCR are preferred, pathologists may use a validated MSI by NGS assay for the detection of DNA mismatch repair defects. Note: MSI by NGS assay must be validated against MMR IHC or MSI by PCR and must show equivalency. (2)</p> <p>Universal MMR or MSI testing is recommended in all patients with a personal history of colon and rectal cancer (3)</p> <p>Endometrial Cancer</p> <p>Universal testing of endometrial carcinomas for mismatch repair (MMR) proteins/microsatellite instability (MSI) (4)</p>

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	<ul style="list-style-type: none"><li>• Testing may be performed on the hysterectomy specimen (can also be done on presurgical biopsy)</li></ul> <p>In endometrial cancer patients being considered for checkpoint blockade therapy, pathologists should use MMR IHC over MSI by PCR or NGS for the detection of mismatch repair defects. (2)</p> <p>Molecular screening of endometrial cancers for Lynch syndrome is the preferred strategy when resources are available, as screening by personal and family history “will miss a significant fraction of women with Lynch syndrome who do not have a suggestive family history” (5)</p> <p>Gastroesophageal and Small Bowel Cancer</p> <p>In gastroesophageal and small bowel cancer patients being considered for checkpoint blockade therapy, pathologists should use MMR IHC and/or MSI by PCR over MSI by NGS for the detection of DNA mismatch defects. Note: This recommendation does not include esophageal squamous cell carcinoma. (2)</p> <p>References:</p> <ol style="list-style-type: none"><li>1. Sepulveda AR, 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 American Society of Clinical Oncology. Arch Pathol Lab Med. 2017 May;141(5):625-657.</li><li>2. College of American Pathologists in Collaboration with AMP, ASCO, and Fight Colorectal Cancer. MMR and MSI testing in patients being considered for checkpoint inhibitor therapy. Draft recommendation statements.</li><li>3. Benson, AB, et al. National Comprehensive Cancer Network (NCCN) Guidelines Insights. Colon Cancer, Version 2.2018. J Natl Compr Canc Netw 2018;16:359-369.</li><li>4. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Uterine Neoplasms. Version 5.2019. <a href="https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf">https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf</a></li><li>5. Society of Gynecologic Oncology Clinical Practice Statement. 1 March 2014. <a href="https://www.sgo.org/resources/screening-for-lynch-syndrome-in-endometrial-cancer/">https://www.sgo.org/resources/screening-for-lynch-syndrome-in-endometrial-cancer/</a></li></ol>
<b>Rationale</b>	<p>The results of MMR/MSI testing of a sample are frequently needed to guide treatment decisions, particularly for patients being considered for checkpoint inhibitor therapy. In the absence of MMR/MSI testing, patients may be treated with chemotherapeutic agents they will not benefit from. MMR/MSI testing is also a crucial prognostic marker to determine the presence of Lynch syndrome, an</p>



	<p>autosomal dominant genetic disorder that is associated with an increased risk for various cancers. Therefore MMR/MSI testing is critical for prognostic as well as treatment reasons.</p> <p>Pathologists are uniquely well positioned at the time of signing out the surgical pathology report to detail the disposition of MMR/MSI testing for that sample. Referring physicians depend on both the pathologists' interpretations of and any recommendations for tests in order to provide quality patient care. If the status is not indicated in each pathology report for the patient, important tests may be missed or unnecessary repeat testing may be performed delaying treatment and increasing cost. This measure monitors the success of pathologists in effectively communicating this important information for the purpose of care coordination and efficient use of resources.</p>
<b>Guidance</b>	<p>This measure is to be reported each time a primary colorectal, endometrial, gastroesophageal or small bowel carcinoma surgical pathology report is finalized during the performance period. This measure may be submitted by eligible clinicians who perform the quality actions described in the measure based on the services provided and the measure-specific denominator coding.</p> <p>This measure requires that immunohistochemistry (IHC) for the four MMR proteins (MLH1, MSH2, MSH6 and PMS2); or MSI by DNA-based testing; or both are addressed in the surgical pathology report for biopsy or resection specimens with primary or metastatic colorectal carcinoma and surgical pathology report for biopsy or resection specimens with primary or metastatic endometrial carcinoma are present. A short note can be made in the final report, such as or combination of:</p> <ul style="list-style-type: none"><li>• No loss of nuclear expression of MMR proteins (intact expression)</li><li>• Loss of nuclear expression of MMR proteins</li><li>• Microsatellite instability (MSI)</li><li>• Microsatellite instability high (MSI-H)</li><li>• Microsatellite instability low (MSI-L)</li><li>• Microsatellite stable (MSS)</li><li>• MMR or MSI previously performed</li><li>• MMR or MSI evaluation is recommended</li><li>• MMR and MSI status cannot be determined</li><li>• MMR or MSI isn't indicated for this tumor</li><li>• MMR or MSI isn't possible for this sample</li></ul> <p>MMR/MSI status may be derived from performing testing, relaying the results of testing performed elsewhere, or by provided guidance on the appropriateness of testing the sample but information about the status (as noted above) must appear within the final pathology report.</p>
<b>Measure Designation</b>	

<b>NQS Domain</b>	Communication and Care Coordination
<b>Meaningful Measure Area</b>	Transfer of Health Information and Interoperability
<b>NQF ID</b>	N/A
<b>High Priority</b>	Yes
<b>Measure Purpose</b>	Quality Improvement Accountability
<b>Measure Type</b>	Process
<b>Summary of Performance Gap Information</b>	<p>For January-December 2020, CAP 33 existed as 2 separate measures (additional diagnoses were added when the two were combined): CAP 18 (Colorectal Cancer) and 31 (Endometrial Cancer). Twelve reporting entities submitted data on CAP 18. The average score was 78.3% with a standard deviation of 20.9 points. Scores ranged from 40.35% to 100%.</p> <p>Eight reporting entities submitted data on CAP 31 although one did not meet the 20-case minimum. The average score was 77.4% with a standard deviation of 16. Scores ranged from 44.9% to 97.8%.</p> <p>For January-1 July 2021, 14 practices have entered data (6 do not meet the 20 case minimum yet). The average score so far is 86.8%.</p> <p>Data in the literature support the evidence from the Registry. In 2019, a study assessed testing practices of US physicians for MMR/MSI in colorectal cancer. Despite relatively high rates of awareness of testing guidelines (84.1%) only 68.9% of clinicians performed universal testing on all colorectal cancer patients. As noted in the study, "universal testing rates seem to be suboptimal" Eriksson J, Amonkar M, Al-Jassar G, et al. Mismatch Repair/Microsatellite Instability Testing Practices among US Physicians Treating Patients with Advanced/Metastatic Colorectal Cancer. J Clin Med. 2019;8(4):558. Published 2019 Apr 24. doi:10.3390/jcm8040558</p> <p>For endometrial carcinoma: Data in the literature support the evidence from the Registry. A 2018 survey of clinicians found that only 50% of survey respondents did reflex genetic testing for endometrial carcinoma. Pan, J. Y., Haile, R. W., Templeton, A., Macrae, F., Qin, F., Sundaram, V., &amp; Ladabaum, U. (2018). Worldwide Practice Patterns in Lynch Syndrome Diagnosis and Management, Based on Data From the International Mismatch Repair Consortium. Clin Gastroenterol Hepatol, 16(12), 1901-1910 e1911. doi:10.1016/j.cgh.2018.04.025</p>

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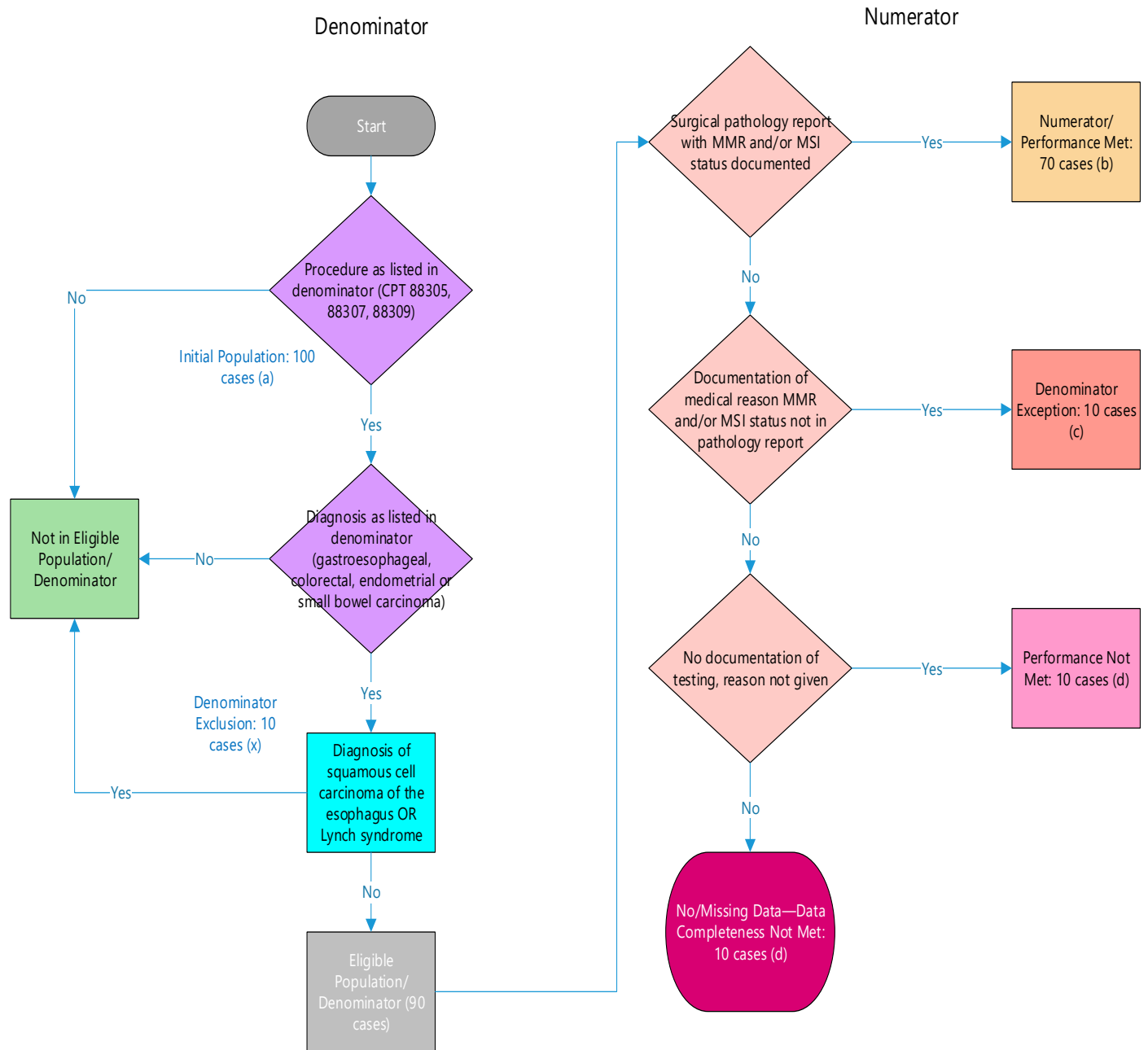
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	<p>For gastroesophageal and small bowel carcinoma: Prior to the release of the CAP guideline regarding MMR/MSI testing for patients being considered for checkpoint inhibitor therapy, a 2017 study found that MMR/MSI testing was performed in only 51% of studies of gastric carcinoma (1). The number of studies that included results from all four MMR proteins was considerably smaller, at only 14% (1). An earlier study had lower testing rates: 2959 out of a total of 7366 (40%) of patients who had surgery for gastric cancer. In 2020, a study indicated that sporadic screening of gastric cancers occurs but stated that: "However, universal screening for dMMR across all GI cancers is both uncommon and not yet well studied." (2) The same study cited above examining practice patterns of testing found that 0% of clinicians did reflex genetic testing of any kind on small bowel samples (3).</p> <p>1. Mathiak M, Warneke VS, Behrens H-M, Haag J, Boger C, Kruger S and Rocken C (2017) Clinicopathologic Characteristics of Microsatellite Instable Gastric Carcinomas Revisited: Urgent Need for Standardization. Appl Immunohistochem Mol Morphol; 25(1):12-24.</p> <p>2. Abrha, A., Shukla, N. D., Hodan, R., Longacre, T., Raghavan, S., Pritchard, C. C., . . . Haraldsdottir, S. (2020). Universal Screening of Gastrointestinal Malignancies for Mismatch Repair Deficiency at Stanford. JNCI Cancer Spectr, 4(5), pkaa054. doi:10.1093/jncics/pkaa054</p> <p>3. Pan, J. Y., Haile, R. W., Templeton, A., Macrae, F., Qin, F., Sundaram, V., &amp; Ladabaum, U. (2018). Worldwide Practice Patterns in Lynch Syndrome Diagnosis and Management, Based on Data From the International Mismatch Repair Consortium. Clin Gastroenterol Hepatol, 16(12), 1901-1910 e1911. doi:10.1016/j.cgh.2018.04.025</p>
<b>Overall Performance Rate</b>	1st Performance Rate
<b>Level of Measurement</b>	Individual Practitioner Group Practice
<b>Care Setting and Specialty</b>	Care Setting: Other—Laboratories; Telehealth not applicable Specialty: Pathology
<b>Improvement Notation</b>	<p>Inverse Measure: No <b>Proportional Measure: Yes (Higher score indicates better quality)</b> Continuous Variable Measure: No Ratio Measure: No Risk-adjusted: No</p>



Measure Flow



**SAMPLE CALCULATION:**

Numerator (b=70 reports)

$$\frac{\text{Numerator (b=70 reports)}}{\text{Denominator (a=100 cases)-Denominator Exclusions (x=10 cases)-Denominator Exceptions (c=10 cases)}} = 87.5\%$$

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