**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

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| **Measure Description** | 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 |
| **Numerator Statement** | 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 |
| **Denominator Statement** | All surgical pathology reports for primary colorectal, endometrial, gastroesophageal or small bowel carcinoma, biopsy or resection<br><br>CPT: 88305, 88307, 88309<br>AND<br>ICD-10:<br><br>• C18.0: Malignant neoplasm of cecum<br>• C18.2: Malignant neoplasm of ascending colon<br>• C18.3: Malignant neoplasm of hepatic flexure<br>• C18.4: Malignant neoplasm of transverse colon<br>• C18.5: Malignant neoplasm of splenic flexure<br>• C18.6: Malignant neoplasm of descending colon<br>• C18.7: Malignant neoplasm of sigmoid colon<br>• C18.8: Malignant neoplasm of overlapping sites of colon<br>• C18.9: Malignant neoplasm of colon, unspecified<br>• C19: Malignant neoplasm of rectosigmoid junction<br>• C20: Malignant neoplasm of rectum<br><br>• C54.1 Malignant neoplasm of endometrium<br>• C54.3 Malignant neoplasm of fundus uteri<br>• C54.8 Malignant neoplasm of overlapping sites of corpus uteri<br>• C54.9 Malignant neoplasm of corpus uteri, unspecified<br>• C55 Malignant neoplasm of uterus, unspecified<br><br>• C15.3: Malignant neoplasm of upper third of esophagus<br>• C15.4: Malignant neoplasm of middle third of esophagus<br>• C15.5: Malignant neoplasm of lower third of esophagus<br>• C15.8: Malignant neoplasm of overlapping sites of esophagus<br>• C15.9: Malignant neoplasm of esophagus, unspecified<br>• C16.0: Malignant neoplasm of cardia<br>• C16.1: Malignant neoplasm of fundus of stomach |

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| | • C16.2: Malignant neoplasm of body of stomach<br>• C16.3: Malignant neoplasm of pyloric antrum<br>• C16.4: Malignant neoplasm of pylorus<br>• C16.5: Malignant neoplasm of lesser curvature of stomach, unspecified<br>• C16.6: Malignant neoplasm of greater curvature of stomach, unspecified<br>• C16.8: Malignant neoplasm of overlapping sites of stomach<br>• C16.9: Malignant neoplasm of stomach, unspecified<br>• C17.0 Malignant neoplasm of duodenum<br>• C17.1 Malignant neoplasm of jejunum<br>• C17.2 Malignant neoplasm of ileum<br>• C17.3 Meckel's diverticulum, malignant<br>• C17.8 Malignant neoplasm of overlapping sites of small intestine<br>• C17.9 Malignant neoplasm of small intestine, unspecified<br>• C26.0 Malignant neoplasm of intestinal tract, part unspecified. |
| **Denominator Exclusions** | Patients with an existing diagnosis of Lynch Syndrome (ICD-10-CM Z15.0, Z15.04, Z15.09, Z80.0)<br><br>Squamous cell carcinoma of the esophagus |
| **Denominator Exceptions** | Documentation of medical reasons MMR, MSI, or both tests were not performed (e.g., patient receiving hospice or will not be treated with checkpoint inhibitor therapy, no residual carcinoma is present in the sample [tissue exhausted or status post neoadjuvant treatment], insufficient tumor for testing)<br><br>Documentation of patient reasons MMR, MSI, or both tests were not performed (e.g., patient declined testing, patient refused checkpoint inhibitor therapy)<br><br>Documentation of system reasons MMR, MSI, or both tests were not performed (e.g., payor-related limitations) |
| **Supporting Guidelines and Other References** | **Colorectal Cancer**<br><br>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. (Strong recommendation)[1]<br><br>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. (Strong recommendation)[2] |

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| | Universal MMR or MSI testing is recommended in all patients with a personal history of colon and rectal cancer (Strong recommendation).[3]<br><br>**Endometrial Cancer**<br><br>Universal testing of endometrial carcinomas for mismatch repair (MMR) proteins/microsatellite instability (MSI) (All Category 2A Recommendations)[4]<br><br>• Testing may be performed on the hysterectomy specimen (can also be done on presurgical biopsy)<br>• MLH1 loss should be further evaluated for promoter methylation to assess epigenetic process<br>• Genetic counseling and testing for all other MMR abnormalities<br>• for those who are dMMR negative of those who have not been screened, but who have a family history of endometrial and/or colorectal cancer, genetic counseling and testing for patient is recommended<br><br>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. (Strong recommendation)2<br><br>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]<br><br>**Gastroesophageal and Small Bowel Cancer**<br><br>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. (Strong recommendation)2 |
| **Rationale** | 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 |

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| | 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.<br><br>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. |
| **Guidance** | 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.<br><br>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:<br>• No loss of nuclear expression of MMR proteins<br>• Loss of nuclear expression of MMR proteins (intact expression)<br>• Microsatellite instability (MSI)<br>• Microsatellite instability high (MSI-H)<br>• Microsatellite instability low (MSI-L)<br>• Microsatellite stable (MSS)<br>• MMR, MSI, or both previously performed<br>• MMR, MSI, or both recommended<br>• MMR, MSI, or both cannot be determined<br><br>MMR/MSI status may be derived from either the primary or a reference laboratory, but the specific results (as noted above) need to be included within the final pathology report. |
| **Measure Designation** | |
| **NQS Domain** | Communication and Care Coordination |

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| **Meaningful Measure Area** | Transfer of Health Information and Interoperability |
| **NQF ID** | N/A |
| **High Priority** | Yes |
| **Measure Purpose** | Quality Improvement<br><br>Accountability |
| **Measure Type** | Process |
| **Summary of Performance Gap Information** | For colorectal carcinoma:<br>In 2019, sixteen practices entered data in the Pathologists Quality Registry for a stand-alone MMR/MSI testing in colorectal carcinoma measure. Performance rates ranged from 0% to 100%, with an average performance rate of 59.8%. The standard deviation was 38 percentage points, indicating a significant variation in performance.<br>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"<br><br>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<br><br>For endometrial carcinoma:<br>Prior to the release of the NCCN guideline, the utility of incorporating prognostic biomarkers in the management of patients with endometrial cancer had not been well defined in clinical practice and treatment decisions were not impacted. However, as chemotherapeutic regimens become refined and patient management decisions altered based on those results, it is becoming increasing important that panels of prognostic biomarkers are established to determine which patients should receive these new chemotherapeutic agents and/or genetic counseling. Previous practice patterns led to only 18% of women being recommended for genetic referral.<br><br>Pokharel, H. P., Hacker, N. F. and Andrews, L. (2016), Changing patterns of referrals and outcomes of genetic participation in gynaecological-oncology multidisciplinary care. Aust N Z J Obstet Gynaecol, 56: 633-638.<br><br>For gastroesophageal and small bowel carcinoma: |

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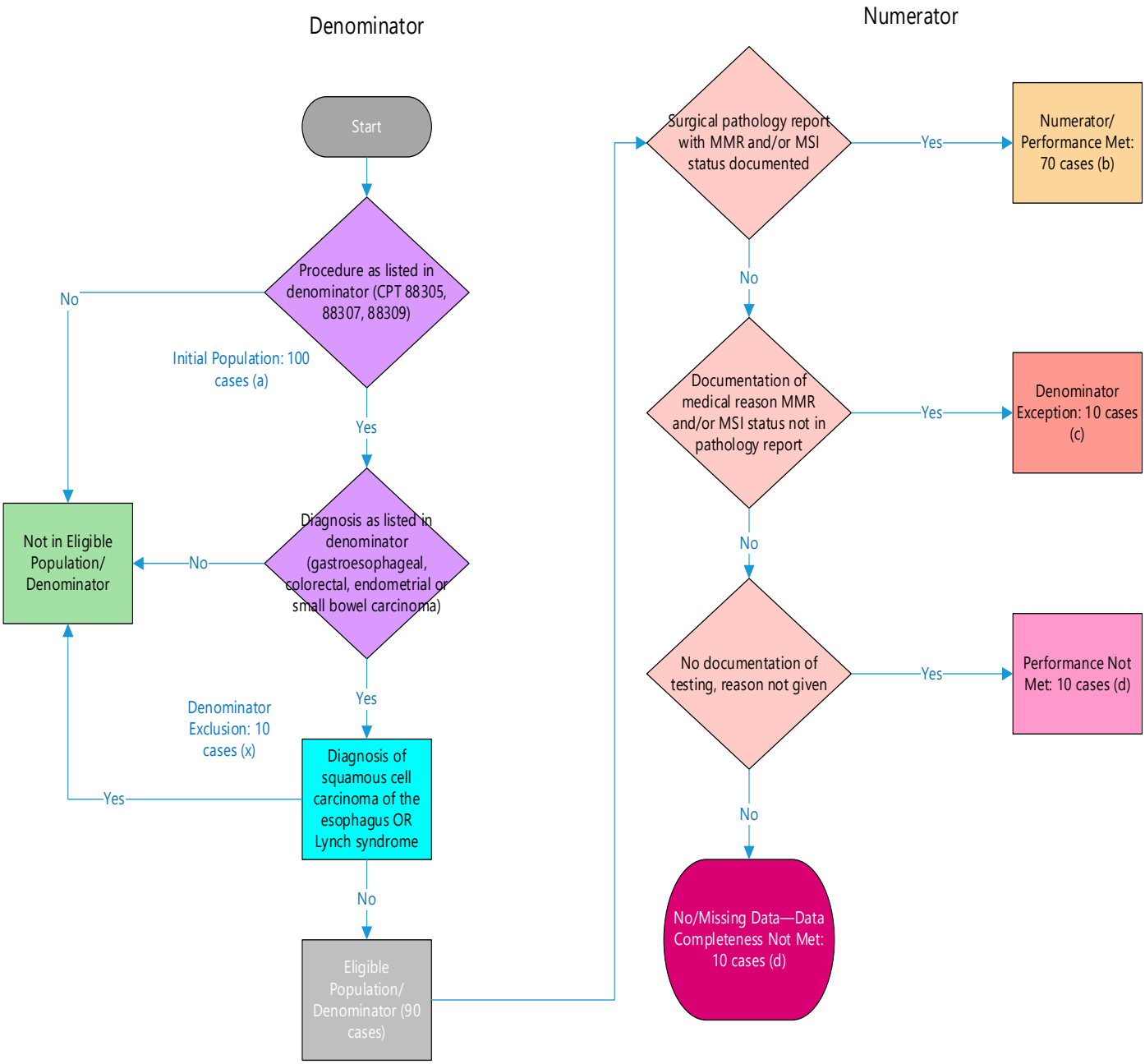
| | Prior to the release of the CAP guideline regarding MMR/MSI testing for patients being considered for checkpoint inhibitor therapy, a 2017 study found that MMR/MSI testing was performed in only 51% of studies of gastric carcinoma (1). The number of studies that included results from all four MMR 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 (2).<br>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.<br>2. Bae Y S, Kim H, Noh SH, and Kim H (2015). Usefulness of Immunohistochemistry for Microsatellite Instability Screening in Gastric Cancer. Gut and Liver; 9(5): 629-635. |
| **Overall Performance Rate** | 1st Performance Rate |
| **Level of Measurement** | Individual Practitioner<br><br>Group Practice |
| **Care Setting and Specialty** | Care Setting: Other—Laboratories; Telehealth not applicable<br>Specialty: Pathology |
| **Improvement Notation** | Inverse Measure: No<br>**Proportional Measure: Yes (Higher score indicates better quality)**<br>Continuous Variable Measure: No<br>Ratio Measure: No<br>Risk-adjusted: No |

## Measure Flow




**SAMPLE CALCULATION:**

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

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# References

[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.
[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.
[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.
[4] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Uterine Neoplasms. Version 5.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf
[5] Society of Gynecologic Oncology Clinical Practice Statement. 1 March 2014. Available at: https://www.sgo.org/resources/screening-for-lynch-syndrome-in-endometrial-cancer/