CMS Measure ID/CMS QCDR ID:

Measure Title: Endometrial Carcinoma Testing for MMR, MSI, or Both

Measure Description	Percentage of surgical pathology reports with a pathological diagnosis of endometrial carcinoma that include a statement on microsatellite instability (MSI) and/or mismatch repair immunohistochemistry.
Denominator Statement	All surgical pathology reports with a pathological diagnosis of primary or metastatic endometrial carcinoma in either biopsy or resection specimen.
Denominator Exclusions	Patients known to have Lynch Syndrome, tumors that have previously been tested for MSI or MMR deficiency, insufficient tumor for testing, patient declines testing Documentation of reason(s) MMR, MSI, or both tests were not performed. For example: • No residual carcinoma is present in the sample (e.g. tissue exhausted or status post neoadjuvant treatment) • Payor-related limitations Patients receiving hospice
Denominator Exceptions	None
Numerator Statement	Surgical pathology reports that contain impression or conclusion of, or recommendation for testing of MMR, MSI, or both. Numerator guidance: 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 endometrial carcinoma present. A short note can be made in the final report, such as or combination of: • No loss of nuclear expression of MMR proteins (intact expression) • Loss of nuclear expression of MMR protein(s) • Microsatellite instability (MSI) • Microsatellite instability high (MSI-H) • Microsatellite instability low (MSI-L) • Microsatellite stable (MSS) • MMR, MSI, or both were previously performed • MMR, MSI, or both is recommended • MMR, MSI, or both cannot be determined MMR/MSI status may be derived from either the primary or a reference laboratory.
Numerator Exclusions	None
Measure Information	
NQS Domain	Communication and Care Coordination
Meaningful	Transfer of Health Information and Interoperability

Measures Area(s)	Detection of hereditary cancer syndromes, and in this case Lynch Syndrome due to defective mismatch repair, has clinical implications for treatment of the affected patient and family members. Screening for Lynch Syndrome may be accomplished by either microsatellite instability testing or immunohistochemistry (IHC) testing for expression of four proteins involved in mismatch repair. Patients with a microsatellite instability-high (MSI-H) phenotype in their cancer tissues may have a germline mutation in one of several DNA mismatch repair (MMR) genes (eg, *MLH1*, *MSH2*, *MSH6*, or *PMS2*) or an altered EPCAM (*TACSTD1*) gene. 3-5 Similarly, patients with deficient mismatch repair protein expression may have a germline mutation in one of those genes. An advantage of using immunohistochemistry for testing is that the results will help identify the specific protein/gene that may be affected. A MSI-H phenotype or loss of MLH1 and PMS2 expression by IHC may be observed in sporadic endometrial cancers (about 15% of cases) due to somatic abnormalities, usually hypermethylation of the *MLH1* gene promoter. Therefore, additional testing is necessary to distinguish Lynch Syndrome related tumors from sporadic cancers. After appropriate genetic counseling, patients with a positive screening test result may want to consider testing to identify the causative heritable abnormality. MSI testing protocols are similar to those developed for colon cancer. These are briefly summarized here, but more complete details are available in the separately issued "Template for Reporting Results of Biomarker Testing of Specimens From Patients With Carcinoma of the Colon and Rectum." 7 Testing is generally performed with at least 5 microsatellite markers, generally mononucleotide or dinucleotide repeat markers. In 1998, a National Institutes of Health consensus panel proposed that laboratories use a 5-marker panel consisting of 3 dinucleotide and 2 mononucleotide repeats for MSI testing. Recent data suggest that dinucleotide repeats may have lower sensitivity and specificity for identifying tumors with an MSI-H phenotype. As a consequence, there has been a move towards including more mononucleotides and fewer dinucleotides in MSI testing panels. Many laboratories now use a commercially available kit for MSI testing that utilizes 5 mononucleotide markers. 3. Haraldsdottir S, Hampel H, Tomsic J, et al. Colon and endometrial cancers with mismatch repair deficiency can arise from somatic, rather than germline, mutations. Gastroenterology. 2014;147(6):1308-1316. 4. Ligtenberg MJ, Kuiper RP, Chan TL, et al. Heritable somatic methylation and inactivation of MSH2 in families with Lynch syndrome due to deletion of the 3' exons of TACSTD1. Nat Genet. 2009;41(1):112-117. 5. Geurts-Giele WR, Leenen CH, Dubbink HJ, et al. Somatic aberrations of mismatch repair genes as a cause of microsatellite-unstable cancers. J Pathol. 2014;234(4):548-559. 6. McConechy MK, Talhouk A, Li-Chang HH, et al. Detection of DNA mismatch repair (MMR) deficiencies by immunohistochemistry can effectively diagnose the microsatellite instability (MSI) phenotype in endometrial carcinomas. Gynecol Oncol. 2015;137(2):306-310. 7. Bartley AN, Hamilton SR, Alsabeh EP, et at. Template for Reporting Results of Biomarker Testing of Specimens From Patients With Carcinoma of the Colon and Rectum. http://www.cap.org/ShowProperty?nodePath=/UCMCon/Contribution%20Folders/WebContent/pdf/cpcolorectalbiomarker-14.pdf. Published December 2014. Accessed May 25, 2016

Meaningful Measure Rationale	Lynch Syndrome is a hereditary cancer syndrome that accounts for approximately 5% of endometrial carcinomas. Universal screening for Lynch Syndrome has become standard of care in patients with colorectal carcinoma or endometrial carcinoma. Screening can be achieved through microsatellite instability (MSI) testing and/or immunohistochemistry testing for four proteins involved in mismatch repair (MMR). Deficiency of mismatch repair protein expression (dMMR) or microsatellite instability high (MSI-High) are positive screening results indicating further workup is needed to diagnose Lynch Syndrome. Identifying cases of Lynch Syndrome is so important not only because it has health implications for family members of the affected patients but because it can also change cancer screening algorithms and influence choices for prophylactic procedures in affected patients. Microsatellite Instability Testing Detection of hereditary defective mismatch repair has clinical implications for the treatment of the affected patient and family members. NCCN recommends that all patients with a personal history of endometrial cancer should have MMR or MSI testing. Patients with a microsatellite instability-high (MSI-H) phenotype in their cancer tissues may have a germline mutation in one of several DNA mismatch repair (MMR) genes (eg, MLH1, MSH2, MSH6, or PMS2) or an altered EPCAM (TACSTD1) gene (1-4). After appropriate genetic counseling, patients may want to consider testing to identify the causative heritable abnormality. An MSI-H phenotype is more frequently observed in sporadic endometrial cancers (about 15% of cases) due to somatic abnormalities, usually hypermethylation of the MLH1 gene promoter. The results of this testing will impact patient management, as an abnormal result could lead to additional screening or operative interventions or alteration in chemotherapeutic plan, as MSI-H tumors are now eligible for immunomodulatory agents. MSI testing protocols are similar to those developed for colon cancer. These are briefly summarized here, but more complete details are available in the separately issued “Template for Reporting Results of Biomarker Testing of Specimens From Patients With Carcinoma of the Colon and Rectum.” 5 Testing is generally performed with at least 5 microsatellite markers, generally mononucleotide or dinucleotide repeat markers. In 1998, a National Institutes of Health consensus panel proposed that laboratories use a 5-marker panel consisting of 3 dinucleotide and 2 mononucleotide repeats for MSI testing. Recent data suggest that dinucleotide repeats may have lower sensitivity and specificity for identifying tumors with an MSI-H phenotype. As a consequence, there has been a move towards including more mononucleotides and fewer dinucleotides in MSI testing panels. Many laboratories now use a commercially available kit for MSI testing that utilizes 5 mononucleotide markers. If DNA MMR IHC has not been performed, this testing should be recommended for any case that shows an MSI-H phenotype, because this information will help identify the gene that is most likely to harbor a germline (or somatic) mutation. 1. NCCN Guidelines V 1.2018 Uterine Neoplasms. https://www2.tri-kobe.org/nccn/guideline/gynecological/english/uterine.pdf 2. Haraldsdottir S, Hampel H, Tomsic J, et al. Colon and endometrial cancers with mismatch repair deficiency can arise from somatic, rather than germline, mutations. Gastroenterology. 2014;147(6):1308-1316. 2. Ligtenberg MJ, Kuiper RP, Chan TL, et al. Heritable somatic methylation and inactivation of MSH2 in families with Lynch syndrome due to deletion of the 3’ exons of TACSTD1. Nat Genet. 2009;41(1):112-117. 3. Geurts-Giele WR, Leenen CH, Dubbink HJ, et al. Somatic aberrations of mismatch

	repair genes as a cause of microsatellite-unstable cancers. J Pathol. 2014;234(4):548-559. 4. McConechy MK, Talhouk A, Li-Chang HH, et al. Detection of DNA mismatch repair (MMR) deficiencies by immunohistochemistry can effectively diagnose the microsatellite instability (MSI) phenotype in endometrial carcinomas. Gynecol Oncol. 2015;137(2):306-310. 5. Bartley AN, Hamilton SR, Alsabeh EP, et at. Template for Reporting Results of Biomarker Testing of Specimens From Patients With Carcinoma of the Colon and Rectum. http://www.cap.org/ShowProperty?nodePath=/UCMCon/Contribution%20Folders/WebContent/pdf/cpcolorectalbiomarker-14.pdf. Published December 2014. Accessed May 25, 2016
Measure Type	Process
Data Source	Laboratory Information Systems; pathology reports
Summary of Performance Gap Evidence	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 (1). Laboratories and regulatory agencies are faced with challenges to rapidly and efficiently provide new test results for the management of patients with cancer. There is a need for current evidence-based recommendations for the appropriate utilization of molecular testing to guide targeted therapies within this patient population. Recent recommendations indicate a need to test all patients with endometrial carcinoma for mutations in MMR genes, as previous screening parameters missed a significant number (2). 1.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. 2. One size may not fit all: The debate of universal tumor testing for Lynch syndrome Lu, Karen H. et al. Gynecologic Oncology, Volume 137, Issue 1, 2 - 3
Measure Owner	College of American Pathologists
NQF ID	N/A
Number of Performance Rates	1
Overall Performance Rate	1st Performance Rate

High-priority	
Improvement Notation	
Specialty	
Current Clinical Guideline the Measure is Derived From	https://documents.cap.org/protocols/endometrium-16biomarker-1100.pdf