



To: submissions@nccn.org

Re: Submission Request – Cervical/Uterine Cancers Panel

Submitted by:

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NCCN Guidelines Panel: Cervical/Uterine Cancers Panel

On behalf of Promega Corporation, we respectfully request the NCCN Cervical/Uterine Cancers Panel to review the enclosed information in support of making changes to the current guidelines for Uterine Neoplasms cancer diagnosis using PCR-based Microsatellite Instability (MSI) assays.

Specific Changes:

We ask the panel to emphasize that MSI testing needs to be given equal weight and be recommended as a parallel technology with mismatch repair deficiency (MMR) protein expression analysis by immunohistochemistry (IHC) for endometrial cancer patients.

FDA Clearance:

The recommendation to assess MSI status is not associated with any specific FDA-cleared product/s. Laboratory developed tests (LDT) and Site Specific IVDs to assess MSI status are currently widely available for clinical use to inform patient treatment options.

Rationale:

Assays for MSI and MMR protein expression measure separate but related cellular events. Inactivation or loss of MMR proteins causes instability at microsatellite regions in DNA. Immunohistochemistry testing for MMR protein expression can miss up to 12% of dMMR cases, which is thought to be due to retained expression and immunoreactivity in non-functional proteins or defects in MMR genes other than the four major genes available for IHC testing (Funkhouser *et al.* Abstract, Tables 1 & 2, p96; Dudley *et al.* p816).^{1,2} Moreover, in practice there is substantial interobserver variation, which varies by the expertise of the pathologist (Funkhouser *et al.* p94; Klarskov *et al.*)^{1,11}. Current NCCN guidelines for Genetic/Familial Assessment state that IHC testing for MMR has a 5-10% false negative rate. MSI by PCR has a false negative rate of just 0.3-5% (Funkhouser *et al.*, Table 1)¹. Several studies have noted discordant results between IHC and MSI by PCR (Bartley *et al.*, Table 3; Goodfellow *et al.*, Table 1; Bruegl *et al.*, Table 3 & Figure 1)^{3,4,8}. Due to the complementary nature of these technologies and the potential impact of misdiagnosis, there is growing recognition in the field that these



tests should be performed together for maximal sensitivity when identifying patients for hereditary cancer risk and immunotherapy eligibility (Goodfellow et al., p4307; Leenen et al., p419)^{4,12}.

MSI analysis by PCR using mononucleotide loci can be performed with less than a section of tissue and is extremely cost effective, making it amenable to being performed alongside IHC as an initial screening tool (Muller et al., p313)⁹. In addition, Promega's MSI Analysis System has been used as the reagent basis for LDTs in clinical laboratories and research organizations worldwide for over 15 years. This assay has been used as a gold standard to determine MSI status in numerous clinical trials as well as drug and companion diagnostic submissions for FDA approval^{5,13,14}.

To this end, the Society of Gynecologic Oncology clinical practice states "All women diagnosed with endometrial carcinoma should undergo systematic clinical screening (review of personal and family history) and/or molecular screening for Lynch syndrome, a hereditary cancer syndrome.... molecular screening of endometrial cancers for Lynch syndrome is the preferred strategy when resources are available⁸." In addition, the European Society for Medical Oncology (ESMO) recently provided recommendations on MSI testing for immunotherapy in endometrial cancer stating that "MSI-PCR molecular testing is indicated in case of indeterminate IHC results, including disagreement or difficulties in interpreting IHC..." (Luchini et. al, tables 1 & 2)¹⁰.

We believe the evidence provided below supports our request for changes in the following areas of the Uterine Neoplasms Guidelines and Evidence Blocks (proposed changes are highlighted in **bold**):

NCCN Guidelines version 3.2019 – February 11, 2019 Updates (Uterine Neoplasms)

Section	Page#	current update	Promega proposal	Evidence/Publication
MS-3 and MS-4	48, 49	Universal testing of endometrial tumors for defects in DNA MMR is recommended (eg. <i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i>).	Universal testing of endometrial tumors for DNA MMR by both MSI and IHC (eg, <i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i>) is recommended.	Funkhouser et al. J Mol Diagnostics 2012 ; 14(2) :91-103

NCCN Evidence Blocks version 3.2019 – Endometrial Carcinoma: NCCN Evidence Blocks:

Section	Page#	current update	Promega proposal	Evidence/Publication
ENDO-D, 1 of 2	27	For recurrent endometrial cancer NCCN recommends MSI-H or dMMR testing if not previously done.	For recurrent endometrial cancer, NCCN recommends MSI and dMMR testing if not previously done.	Bartley et al Cancer Prev Res 5:320-327 (2012); Bruegl et al. Cancer Prev Res 10:108-115 (2017)
MS-3	49,50	Screening of the tumor for defective DNA mismatch repair (MMR) using immunohistochemistry and/or microsatellite instability (MSI) is used to identify which patients should undergo mutation testing for Lynch Syndrome	Screening of the tumor for defective DNA mismatch repair (MMR) using microsatellite instability (MSI) and immunohistochemistry is used to identify which patients should undergo mutation testing for Lynch Syndrome	Bartley et al Cancer Prev Res 5:320-327 (2012); Bruegl et al. Cancer Prev Res 10:108-115 (2017); Goodfellow et al. J Clin Oncol 33:4301-4308 (2015)
MS-3 and MS-4	49,50	Universal testing of endometrial tumors for defects in DNA MMR is recommended (eg, MLH1, MSH2, MSH6).	Universal testing of endometrial tumors for MSI and defects in DNA MMR by IHC is recommended (eg, MLH1, MSH2, MSH6).	Funkhouser et al. J Mol Diagnostics 2012 ; 14(2) :91-103
MS-21	67	Among patients with dMMR endometrial carcinoma who received pembrolizumab (n=15), the objective response rate was 52% and the disease control rate was 73% (3 complete response, 5 partial response, and 3 stable disease).	Among patients with dMMR endometrial carcinoma identified by MSI or IHC who received pembrolizumab (n=15), the objective response rate was 52% and the disease control rate was 73% (3 complete response, 5 partial response, and 3 stable disease).	Le DT Science 2017; 357: 409-413

MS-21	67	The panel voted to include pembrolizumab as a treatment option for MSI-H/dMMR endometrial tumors and recommends that recurrent endometrial tumors be tested for MSI-H or dMMR if not done previously	The panel voted to include pembrolizumab as a treatment option for MSI-H/dMMR endometrial tumors and recommends that recurrent endometrial tumors be tested for MSI-H and dMMR if not done previously	
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The following scholarly research publications are submitted in support of the proposed changes above.

1. Funkhouser WK, Lubin IM, Monzon FA, Zehnbaue BA, Evans JP, et al. Relevance, Pathogenesis, and Testing Algorithm for Mismatch Repair-Defective Colorectal Carcinomas. *Journal of Molecular Diagnostics* 2012; 14(2): 91-103. DOI: 10.1016/j.jmoldx.2011.11.001.
2. Dudley JC, Lin M-T, Le D-T and Eshleman JR. Microsatellite Instability as a Biomarker for PD-1 Blockade. *Clin. Cancer Res*, 2016, 22:813-829.
3. Bartley AN, Luthra R, Saraiya DS, Urbauer DL, and Broaddus RR. Identification of Cancer Patients with Lynch Syndrome: Clinically Significant Discordances and Problems in Tissue-Based Mismatch Repair Testing. *Cancer Prevention Research*, 2012; 5(2): 320-327. Epub 2011 Nov 14. DOI: 10.1158/1940-6207. PubMed PMID: 22086678.
4. Goodfellow PJ, Billingsley CC, Lankes HA, Ali S, Cohn DE, Broaddus RJ, Ramirez NR, et al. Combined Microsatellite Instability, *MLH1* Methylation Analysis, and Immunohistochemistry for Lynch Syndrome Screening in Endometrial Cancers from GOG210: An NRG Oncology and Gynecologic Oncology Group Study. *Journal of Clinical Oncology* 2015; 33(36): 4301-4308. DOI: 10.1200/JCO.2015.63.9518. PubMed PMID: 266552419.
5. Le DT, Jennifer N. Durham JN, Kellie N. Smith KN, Hao Wang H, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science*, 2017; 357 (6349): 409-413. Epub 2017 Jun 8. DOI: 10.1126/science.aan6733. PubMed PMID: 28596308.
6. <https://www.sgo.org/clinical-practice/guidelines/screening-for-lynch-syndrome-in-endometrial-cancer/>
7. Zhang, L. Immunohistochemistry versus Microsatellite Instability Testing for Screening Colorectal Cancer Patients at Risk for Hereditary Nonpolyposis Colorectal Cancer Syndrome. *Journal of Molecular Diagnostics*, 2008; 10(4): 301-307. doi: 10.2353/jmoldx.2008.080062. PubMed PMID: 18556776.



8. Bruegl AS, Ring KL, Daniels M, Fellman BM, Urbauer DL and Broaddus RR. Clinical Challenges Associated with Universal Screening for Lynch Syndrome–Associated Endometrial Cancer. *Cancer Prevention Research*, 2017; 10(2): 108-115. Epub 2016 Dec 13. DOI: 10.1158/1940-6207. PubMed PMID: 27965287.
9. Muller A, Giuffre G, Edmonston TB, Mathiak M, Roggendorf B et al. Challenges and Pitfalls in HNPCC Screening by Microsatellite Analysis and Immunohistochemistry. *Journal of Molecular Diagnostics*, 2004; 6(4): 308-315. DOI: 10.1016/S1525-1578(10)60526-0. PubMed PMID: 15507669.
10. Luchini C, Bibeau F, Ligtenberg MJL, Singh N et al. ESMO recommendations on microsatellite instability testing for immunotherapy in cancer, and its relationship with PD-1/PD-L1 expression and tumour mutational burden: a systematic review-based approach. *Annals of Oncology*, 2019; 0:1-12. DOI:10.1093/annoc/mdz116
11. Klarskov L, Ladelund S, Holck S, Roenlund K, Lindebjerg J et al. Interobserver variability in the evaluation of mismatch repair protein immunostaining. *Human Pathology*, 2010; 41(10): 1387-1396.
12. Leenen CH, van Lier MG, van Doorn HC, van Leerdam ME et al. *Gynecologic Oncology*, 2012; 125(2): 414-20. PMID: 22306203. DOI:10.1016/j.ygyno.2012.01.049
13. Ott PA, Bang YJ, Berton-Rigaud D, Elez E et al. Safety and Antitumor Activity of Pembrolizumab in Advanced Programmed Death Ligand 1–Positive Endometrial Cancer: Results From the KEYNOTE-028. *Journal of Clinical Oncology*, 2017; 35(22): 2535-41. DOI: <https://doi.org/10.1200/JCO.2017.72.5952>
14. Le DT, Uram JM, Wang H, Bartlett BR et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *New England Journal of Medicine*, 2015; 372: 2509-20. DOI: 10.1056/NEJMoa1500596

Thank you for your consideration.

Sincerely,

A handwritten signature in black ink, appearing to read 'Ashley Anderson MD'.

Ashley Anderson, MD
Chief Medical Officer
Promega Corporation

A handwritten signature in black ink, appearing to read 'Randall Dimond'.

Randall Dimond, Ph.D.
Vice President & Chief Scientific Officer
Promega Corporation