



To: [submissions@nccn.org](mailto:submissions@nccn.org)

Re: Submission Request – Pancreatic Cancer Panel

**Submitted by:**

**Name:** Dr. Randall Dimond, Ph.D., Vice President & Chief Scientific Officer

**Company:** Promega Corporation

**Address:** 2800 Woods Hollow Rd., Madison, WI 53711

**Phone:** 608-277-2517

**Email:** [randy.dimond@promega.com](mailto:randy.dimond@promega.com)

**Date of request:** June 25, 2019

**NCCN Guidelines Panel:** Pancreatic Cancer Panel

On behalf of Promega Corporation, we respectfully request the NCCN Pancreatic Cancer Panel to review the enclosed information in support of making changes to the current guidelines for Pancreatic Adenocarcinoma (PDAC) cancer diagnosis using PCR or NGS-based Microsatellite Instability (MSI) assays.

**Specific Changes:**

We ask the panel to equally emphasize any assay for the detection of microsatellite instability (MSI) that has been validated in pancreatic cancer be given equal weight and be recommended as a parallel technology with mismatch repair deficiency (MMR) protein expression analysis by immunohistochemistry (IHC) for pancreatic 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 (Hu, 2018, p1332)<sup>11</sup>. Mutations or epigenetic silencing events at MMR genes result in inactivation or loss of MMR proteins. The resulting loss of mismatch repair function then allows detectable errors to accumulate 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, 2012; Dudley, 2016; Hu, 2018).<sup>1,2,11</sup>. Moreover, in practice there is substantial interobserver variation, which varies by the expertise of the pathologist (Funkhouser, 2012; Klarskov, 2010)<sup>1,3</sup>. Current NCCN guidelines for Genetic/Familial Assessment state that IHC testing for MMR has a 5-10% false negative rate (page LS-A, 1 of 5 and 3 of 5)<sup>4</sup>. Contemporary MSI by PCR panels have a false negative rate of just 0.3-5% (Funkhouser, 2012; Bacher 2004; Xicola 2007)<sup>1,13,14</sup>. Several studies have noted discordant results between IHC and MSI by PCR (Bartley, 2012; Goodfellow, 2015; Bruegl,



2017)<sup>5,6,7</sup>. The benefit from PD-1 and PD-L1 inhibitors has been shown to prolong survival in mismatch repair deficient PDAC patients. (Latham, 2019; Le, 2017; Hu, 2018; Middha, 2017; Singhi, 2019)<sup>16,17,11,9, 18</sup>. Recent publications on occurrence of MSI in large numbers of pancreatic cancers, such as Latham *et al.*, Middha *et al.* or Hu *et al.*, have utilized the MSISensor algorithm to interpret NGS MSI results. MSISensor is calibrated against the Promega MSI v1.2 loci, which allows laboratories to utilize either NGS or PCR based MSI assays.<sup>16, 17</sup> While mismatch repair deficiency accounts for a small fraction of the PDAC population, there are significant implications for individual patients with mismatch repair deficient PDAC (Hu, 2018, p.1334)<sup>11</sup>. 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, 2015)<sup>6</sup>.

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 (Goodfellow, 2015; Muller, 2004)<sup>8,6</sup>. 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<sup>9,10</sup>.

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

**NCCN Guidelines version 2.2019- April 29, 2019 Updates (Pancreatic Cancer)**

Section	Page#	current update	Promega proposal	Evidence/Publication
PANC-6	13	Consider microsatellite instability (MSI) testing and/or mismatch repair (MMR) testing on available tumor tissue (category 2B)	Consider microsatellite instability (MSI) testing <b>and</b> mismatch repair <b>protein expression by IHC (MMR)</b> on available tumor tissue (category 2B)	Hu, 2018; Bruegl, 2017; Bartley, 2012; Goodfellow, 2015
PANC-8	15	Consider MSI testing and/or MMR testing on available tumor tissue (category 2B)	Consider MSI testing <b>and</b> MMR testing on available tumor tissue (category 2B)	Hu, 2018; Bruegl, 2017; Bartley, 2012; Goodfellow, 2015
MS-6	54	Microsatellite instability (MSI) is also a prognostic factor for survival in many	The NCCN Panel recommends considering MSI testing <b>and</b> MMR testing on	Hu, 2018; Bruegl, 2017; Bartley, 2012; Goodfellow, 2015

		<p>cancers, notably for colon cancer although rare in pancreatic adenocarcinoma. Microsatellites are regions of coding and noncoding DNA where short sequences or single nucleotides of DNA are repeated. MSI is caused by a loss of DNA MMR activity. Mutations in germline MMR genes result in a lack of repair of any errors, such as destabilizing errors introduced during DNA replication that shorten or lengthen microsatellites, which then persist in somatic cells. Tumor samples can be assessed for the sizes of microsatellite markers and classified as MSI high (MSI-H), low (MSI-L), and stable (MSS).<sup>91,94</sup> The NCCN Panel recommends considering MSI testing and/or MMR testing on available tumor tissue for patients with locally advanced or metastatic pancreatic adenocarcinoma (category 2B).</p>	<p>available tumor tissue for patients with locally advanced or metastatic pancreatic adenocarcinoma (category 2B).</p> <p>Recommend deleting: “Mutations in germline MMR genes result in a lack of repair of any errors, such as destabilizing errors introduced during DNA replication that shorten or lengthen microsatellites, which then persist in somatic cells.”</p>	
--	--	--	--	--





**NCCN Evidence Blocks version 2.2019-April 29, 2019 – Pancreatic Cancer:**

<b>Section</b>	<b>Page#</b>	<b>current update</b>	<b>Promega proposal</b>	<b>Evidence/Publication</b>
PANC-6	11	Consider microsatellite instability (MSI) testing and/or mismatch repair (MMR) testing on available tumor tissue (category 2B)	Consider microsatellite instability (MSI) testing <b>and</b> mismatch repair (MMR) testing on available tumor tissue (category 2B).	Hu, 2018; Bruegl, 2017; Bartley, 2012; Goodfellow, 2015
PANC-8	13	Consider MSI testing and/or MMR testing on available tumor tissue (category 2B)	Consider MSI testing <b>and</b> MMR testing on available tumor tissue (category 2B)	Hu, 2018; Bruegl, 2017; Bartley, 2012; Goodfellow, 2015
MS-6	56	The NCCN Panel recommends considering MSI testing and/or MMR testing on available tumor tissue for patients with locally advanced or metastatic pancreatic adenocarcinoma (category 2B)	The NCCN Panel recommends considering MSI testing <b>and</b> MMR testing on available tumor tissue for patients with locally advanced or metastatic pancreatic adenocarcinoma (category 2B).	Hu, 2018; Bruegl, 2017; Bartley, 2012; Goodfellow, 2015

The following scholarly research publications are submitted in support of the proposed changes above.

1. Funkhouser WK, Lubin IM, Monzon FA, Zehnbaauer 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. 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. DOI: 10.1016/j.humpath.2010.03.003
4. National Comprehensive Cancer Network. "Genetic/Familial High-Risk Assessment: Colorectal". Version 1.2018 – July 12, 2018.  
[https://www.nccn.org/professionals/physician\\_gls/pdf/genetics\\_colon.pdf](https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf)
5. 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.
6. 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.
7. 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.
8. 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.
9. 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.
10. 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
11. Hu, ZI, Shia, J, Stadler, ZK, Varghese, AM, Capanu, M et al. Evaluating Mismatch Repair Deficiency in Pancreatic Adenocarcinoma: Challenges and Recommendations. *Clinical Cancer Research*, 2018; 24 (6): 1326-1336. DOI: 10.1158/1078-0432.
12. Graff JN, Alumkal JJ, Drake, CG, Thomas GV et al. Early evidence of anti-PD-1 activity in enzalutamide-resistant prostate cancer. *Oncotarget*, 2016; 7(33): 52810-52817. DOI: 10.18632/oncotarget.10547
13. Bacher JW, Flanagan LA, Smalley RL, Nassif NA et al. Development of a fluorescent multiplex assay for detection of MSI-H tumors. *Disease Markers*, 2004; 20:237-250.



14. Xicola, RM, Llor X, Pons E, Castells A et al. Performance of Different Microsatellite Marker Panels for Detection of Mismatch Repair-Deficient Colorectal tumors. *Journal of National Cancer Institute*, 2007; 99(3): 244-252. DOI: 10.1093/jnci/djk033
15. Baudrin, LG, Deleuze, JF and How-Kit, A. Molecular and Computational Methods for the Detection of Microsatellite Instability in Cancer. *Frontiers in Oncology*, 2018. DOI: doi.org/10.3389/fonc.2018.00621
16. Latham *et al.* Microsatellite Instability is Associated with the Presence of Lynch Syndrome Pan-Cancer. *J Clin Oncology* (2019) 37:286-95
17. Middha *et al.* Reliable Pan-Cancer Microsatellite Instability Assessment by Using Targeted Next-Generation Sequencing Data. *JCO Precis Oncol* (2017) 1-17.
18. Singhi *et al.* Real-Time Targeted Genome Profile Analysis of Pancreatic Ductal Adenocarcinomas Identifies Genetic Alterations That Might Be Targeted with Existing Drugs or Used as Biomarkers. *Gastroenterol.* (2019) 156:2242-53.

Thank you for your consideration.

Sincerely,

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

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