

# World Journal of *Clinical Cases*

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## Retrospective Cohort Study

## Cost-effective screening using a two-antibody panel for detecting mismatch repair deficiency in sporadic colorectal cancer

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## Abstract

## BACKGROUND

The microsatellite instability (MSI) test and immunohistochemistry (IHC) are widely used to screen DNA mismatch repair (MMR) deficiency in sporadic colorectal cancer (CRC). For IHC, a two-antibody panel of MLH1 and MSH2 or four-antibody panel of MLH1, MSH2, PMS2, and MSH6 are used. In general, MSI is known as a more accurate screening test than IHC.

## AIM

To compare two- and four-antibody panels of IHC in terms of accuracy and cost benefit on the basis of MSI testing for detecting MMR deficiency.

## METHODS

We retrospectively analyzed patients with CRC who underwent curative surgery between 2015 and 2017 at a tertiary referral center. Both IHC with four antibodies and MSI tests were routinely performed. The sensitivity and specificity of a four- and two types of two-antibody panels (PMS2/MSH6 and MLH1/MSH2) were compared on the basis of MSI testing for detecting MMR deficiency.

## RESULTS

High-frequency MSI was found in 5.5% ( $n = 193$ ) of the patients ( $n = 3486$ ). The sensitivities of the four- and two types of two-antibody panels were 97.4%, 92.2%, and 87.6%, respectively. The specificities of the three types of panels did not differ



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significantly (99.6% for the four-antibody and PMS2/MSH6 panels, 99.7% for the MLH1/MSH2 panel). Based on Cohen's kappa statistic ( $\kappa$ ), four- and two-antibody panels were in almost perfect agreement with the MSI test ( $\kappa > 0.9$ ). The costs of the MSI test and the four- and two-antibody panels of IHC were approximately \$200, \$160, and \$80, respectively.

**CONCLUSION**

Considering the cost of the four-antibody panel IHC compared to that of the two-antibody panel IHC, a two-antibody panel of PMS2/MSH6 might be the best choice in terms of balancing cost-effectiveness and accuracy.

**Key Words:** Adenocarcinoma; DNA mismatch repair; Immunohistochemistry; Monoclonal antibody; Microsatellite instability; Cost-effectiveness

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**Core Tip:** Screening for mismatch repair deficiency in sporadic colorectal cancer has not been established. This study compared microsatellite instability test to four- and two types of two-antibody panels of immunohistochemistry. A two-antibody panel of PMS2/MSH6 may be the best choice in terms of balancing cost-effectiveness and accuracy for screening.

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**INTRODUCTION**

Chromosomal instability and DNA mismatch repair (MMR) deficiency are the most common genetic features associated with most sporadic colorectal cancers (CRCs)[1]. Among them, MMR deficiency is caused by one or more mutations in MMR genes, such as MLH1, MSH2, PMS2, and MSH6, resulting in microsatellite instability (MSI). In general, high-frequency MSI (MSI-H) appears in 10%-15% of the patients with sporadic CRC[2,3]. MSI-H has recently been classified as consensus molecular subtype 1, and patients with MSI-H generally have a good prognosis[4,5]. However, these patients typically have a poor prognosis after relapse and exhibit different responses to chemotherapy compared to patients who are microsatellite stable (MSS)[4,5]. Evaluation of MMR mutations in patients with CRC is very important to determine treatment and prognosis.

The MSI test and immunohistochemistry (IHC) are commonly used for screening MMR deficiency. Moreover, in IHC, the four-antibody panel of MLH1, MSH2, PMS2, and MSH6 and the two-antibody panel of MLH1 and MSH2 are widely used in clinical practice. Several studies have compared four- and two-antibody panels in terms of accuracy and cost-effectiveness[6-9]. However, large-scale studies examining all four types of IHC and comparing two- vs four-antibody panel of IHC are rare[6,7]. Our institution has performed both MSI tests and IHC routinely for CRC since 2003. Before August 2015, a two-antibody panel of MLH1 and MSH2 was routinely used for investigating CRC pathology using IHC. To improve the accuracy of IHC, four-antibody panel IHC was introduced during the study period (Aug 2015 to Dec 2017). In 2018, the Korean government stopped insurance coverage for duplicated tests of MSI and IHC. Subsequently, only the MSI test is being used for routine testing for MMR deficiency after surgery for CRC at our institution. The purpose of this study was to compare two- and four-antibody panels of IHC in terms of accuracy and cost benefit, on the basis of MSI test for detecting MMR deficiency in patients with sporadic CRC. With this comparison, we tried to provide better options for screening for MMR deficiency.



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## MATERIALS AND METHODS

### Patient selection and data collection

A total of 3486 patients with sporadic CRC were retrospectively included in this study. All patients underwent curative-intended surgical resection and had both MSI test and four-antibody panel IHC at Asan Medical Center, Seoul, South Korea between August 2015 and December 2017. All patients were histologically confirmed for colorectal adenocarcinoma. Patients missing any results of the MSI test or IHC were excluded from this study.

The tumor location was defined as "right colon" from the cecum to the transverse colon, "left colon" from the splenic flexure to the sigmoid colon, and "rectum" from the rectosigmoid junction to the rectum in which the confluence of the *taeniae coli* and presence of *epiploica appendices* are absent. Serum carcinoembryonic antigen levels were checked prior to surgery. Pathological tumor stage, pathological nodal stage, pathological metastatic stage, differentiation grade, lymphovascular invasion (LVI), and perineural invasion (PNI) were also investigated. We conducted this study in compliance with the principles of the Declaration of Helsinki.

### MSI test

The MSI status of the tumor samples was evaluated for MSI testing using the five microsatellite markers recommended for the NCI-5 Bethesda panel (BAT26, D5S346, BAT25, D17S250, and D2S123) described previously[10]. Tumors were classified as follows: (1) High-frequency MSI (MSI-H), two or more unstable markers; (2) Microsatellite stability (MSS), no unstable markers; and (3) Low-frequency MSI (MSI-L), one unstable marker. MSS and MSI-L were included as MSS groups for analysis.

### Immunohistochemistry

Tumor tissues obtained during surgery for routine diagnostic pathological examinations were used for IHC. Primary monoclonal antibodies against MLH1 (1:50, mouse monoclonal, clone ES05, catalog No. NCL-L-MLH1, Novo, Newcastle, United Kingdom), MSH2 (1:200, mouse monoclonal, clone G219-1129, catalog No. 286M-16, Cell Marque, Rocklin, CA, United States), PMS2 (1:100, mouse monoclonal, clone MRQ-28, catalog No. 288M-16, Cell Marque, Rocklin, CA, United States), and MSH6 (1:400, mouse monoclonal, clone 44, catalog No. 287M-16, Cell Marque, Rocklin, CA, United States) were used. Formalin-fixed paraffin-embedded tissue sections subjected to immunohistochemistry using a BenchMark XT automatic immunostaining device (Ventana Medical Systems, Tucson, AZ, United States) with an OptiView DAB IHC Detection Kit (Ventana Medical Systems, Tucson, AZ, United States) according to the manufacturer's instructions. Then, 4  $\mu$ m-thick sections obtained with a microtome were transferred onto silanized slides and allowed to dry for 10 min at room temperature, followed by 20 min in an incubator at 65°C. Heat-induced epitope retrieval was performed using Cell Conditioning 1 buffer for 32 min (MSH2 and MSH6) or 64 min (MLH1 and PMS2) and sections were incubated for 16 min (MSH2, MSH6, and PMS2) or 32 min (MLH1) with antibodies in an autoimmunostainer. Antigen-antibody reactions were visualized using a Ventana OptiView DAB IHC Detection Kit (Optiview HQ Linker 8 min, Optiview HRP Multimer 8 min, Optiview H2O2/DAB 8 min, and Optiview Copper 4 min). Counterstaining was performed using Ventana Hematoxylin II for 12 min and Ventana Bluing reagent for 4 min. Finally, all slides are removed from the stainer, dehydrated, and cover-slipped for microscopic examination. Distinct nuclear staining of more than 10% of all nuclei was interpreted as positive staining. All IHC results were confirmed by two pathologists, and discrepancies with the results of MSI tests were reviewed again.

### Statistical analysis

Categorical variables were represented by the number of patients (%), and normally distributed continuous variables were represented by mean and standard deviation. Skewed continuous variables were described using the median and interquartile range. For the comparison of groups between MSI-H and MSS, clinicopathological variables were analyzed using Pearson's Chi-squared test. Using the results of the MSI test as the true status, the sensitivities and specificities of four- and the two types of two-antibody panels (MLH1/MSH2 *vs* PMS2/MSH6) were calculated. The similarities of the four- and two-antibody panels of IHC were also investigated. The sensitivity and specificity of the two- and four-antibody panels of IHC are presented as percentages (%) and 95% confidence intervals. Cohen's kappa statistics ( $\kappa$ ) were used to measure the similarity between the MSI test and IHC[11]. The *P* value < 0.05 was

considered significant for all analyses, and all statistical analyses were performed using SPSS® version 21.0 (IBM Corp., Armonk, New York, United States).

## RESULTS

### *Clinicopathological characteristics and IHC patterns*

Among the 3486 patients with sporadic CRC, MSI-H was checked in 5.5% of them ( $n = 193$ ). The MSI-H group was younger ( $\leq 50$  years) and had characteristics of frequent right colon, lesser lymph node and distant metastasis, poorer differentiated differentiation grade, and fewer LVIs and PNIs (all  $P < 0.001$ , [Table 1](#)). In the four-antibody panel of IHC, 5.8% ( $n = 201$ ) of the patients showed loss of one or more MMR protein. Loss of PMS2 expression was most frequent (3.9%), followed by MLH1 (3.8%), MSH6 (1.7%), and MSH2 (1.4%, [Table 2](#)).

### *Sensitivity, specificity, and cost of each IHC method*

Considering the results of the MSI test as the true status, the sensitivity of the four-antibody panel IHC was 97.4%, which was higher than that of the PMS2/MSH6 (92.2%) and MLH1/MSH2 (87.6%) panel IHCs. The specificity of the four-antibody panel IHC was 99.6%, which was not significantly different from that of the other two-antibody panel IHCs. Based on  $\kappa$ , the results of the MSI test and IHC seemed to be in good agreement, regardless of whether the panel comprised two- or four-antibodies, showing an almost perfect agreement ( $\kappa > 0.9$ ) ([Table 3](#)). The costs of the MSI test and four- and two-antibody panels of IHC were approximately \$200, \$160, and \$80, respectively.

### *Discrepancy analysis between the MSI test and IHC*

IHC was re-reviewed in 32 cases where discrepancy was identified between the results of the MSI test and IHC. The cause of the discrepancy was not identified in five patients with MSI-H who retained MMR protein expression, even after re-examination of IHC. There were 27 patients with MSS and a loss of at least one MMR protein, and the cause of the discrepancy identified in 14 patients after re-review was false loss of expression due to poor fixation (PF) or low expression (LE).

In other patients, no cause of discrepancy was identified. PF ( $n = 11$ ) was a more common cause of the discrepancy than LE ( $n = 3$ ). Three patients showed discrepancy due to LE, two of whom had a history of preoperative radiotherapy. In the case of a loss of expression in MLH1 or PMS2, discrepancy was most often caused by PF. In the case of a loss of expression in MSH2 or MSH6, the cause of discrepancy was not well-identified ([Table 4](#)).

## DISCUSSION

IHC is faster and cheaper than the MSI test and does not require both tumor and normal tissue samples[6]. Therefore, IHC using monoclonal antibodies against the MMR proteins is widely used as a primary screening test in clinical practice[12]. However, the accuracy of IHC is lower than that of the MSI test[6]. Previous studies have demonstrated that IHC cannot replace MSI analysis because certain CRCs harboring loss-of-function MMR gene mutations show detectable MMR protein expressions[13,14]. The accuracy of IHC likely depends on the quality of the antibody panel and ability of the interpreter. Further, IHC data can be misleading if there is a defect in another gene that has not been tested. For this reason, at present, the MSI test is widely used for screening MMR deficiency, and costs are gradually decreasing due to the advancement of diagnostic technology[15]. However, unlike IHC, the MSI test requires both tumor and matched normal tissues, and has a limitation in that the causative gene cannot be identified[16]. *MSH6* is a component of the DNA MMR machinery, but tumors with germline mutations in *MSH6* tend to show lower levels of MSI, thus they may not exhibit MSI-H status[15]. Although this situation may lead to discrepancies between the results of the MSI test and IHC, the sensitivity and specificity of IHC are essentially consistent with those of PCR-based molecular MSI tests[6].

In our IHC results, the loss of PMS2 expression was slightly more frequent than that of MLH1 (3.9% *vs* 3.8%). A similar phenomenon was observed for MSH6 and MSH2 (1.7% *vs* 1.4%). MLH1-PMS2 is a dimer that forms the MutLa complex, and MSH2-

**Table 1 Clinicopathological characteristics according to microsatellite instability (n = 3486)**

Characteristics		MSS	MSI-H	P value
n (%)		3293 (94.5)	193 (5.5)	
Sex	Male	1958 (59.5)	106 (54.9)	0.213
	Female	1335 (40.5)	87 (45.1)	
Age (mean $\pm$ SD, yr)		62.37 $\pm$ 11.68	59.84 $\pm$ 15.36	< 0.001
	$\leq$ 50	513 (15.6)	56 (29.0)	
	> 50	2780 (84.4)	137 (71.0)	
CEA (median $\pm$ IQR)		2.4 $\pm$ 1.4-5.3	2.1 $\pm$ 1.1-5.4	0.630
	< 6 ng/mL	2515 (77.1)	142 (75.5)	
	$\geq$ 6 ng/mL	749 (22.9)	46 (24.5)	
Location	Right colon	767 (23.3)	145 (75.1)	< 0.001
	Left colon	989 (30.0)	31 (16.1)	
	Rectum	1537 (46.7)	17 (8.8)	
pT	T0 / T1/ T2	828 (25.1)	47 (24.4)	0.805
	T3/ T4	2465 (74.9)	146 (75.6)	
pN	N0	1765 (53.6)	142 (73.6)	< 0.001
	N1/ N2	1526 (46.4)	51 (26.4)	
pM	M0	2742 (83.3)	185 (95.9)	< 0.001
	M1	551 (16.7)	8 (4.1)	
Differentiation grade	WD/MD	3022 (95.2)	138 (81.2)	< 0.001
	PD/MA	154 (4.8)	32 (18.8)	
LVI	No	1782 (54.2)	133 (69.3)	< 0.001
	Yes	1504 (45.8)	59 (30.7)	
PNI	No	2299 (70.2)	169 (88.5)	< 0.001
	Yes	977 (29.8)	22 (11.5)	

MSS: Microsatellite stable; MSI-H: High-frequency microsatellite instability; SD: Standard deviation; CEA: Carcinoembryonic antigen; IQR: Interquartile range; pT: Pathological tumor stage; pN: Pathological nodal stage; pM: Pathological metastatic stage; WD: Well-differentiated adenocarcinomas; MD: Moderately-differentiated adenocarcinomas; PD: Poorly-differentiated adenocarcinomas; MA: Mucinous adenocarcinomas; LVI: Lymphovascular invasion; PNI: Perineural invasion.

MSH6 is a dimer that forms the MutS $\alpha$  complex. When the function of MLH1 is lost, the function of PMS2 is also lost, and PMS2 is destabilized and degraded. Similarly, when the function of MSH2 is lost, the MSH6 expression is also lost. However, PMS2 or MSH6 mutations do not affect the function of MLH1 or MSH2[12,17,18]. Therefore, choosing a two-antibody panel of PMS2 and MSH6 over that of MLH1 and MSH2 can increase the sensitivity and specificity. Under the medical insurance of the Republic of Korea, an MSI test requires approximately \$200, four-antibody panel IHC requires approximately \$160, and two-antibody panel IHC requires approximately \$80. This information regarding costs of tests were not compared at the same period but we could indirectly estimate that the two-antibody panels of IHC was approximately half the price of MSI tests in represented countries[8,19,20]. Based on this, and considering the fact that there is almost perfect agreement between the results of the MSI test and IHC regardless of the two- and four-antibody panel (based on  $\kappa$ ), a two-antibody panel of PMS2/MSH6 may be the most cost-effective choice for screening in the Republic of Korea.

MMR deficiency is present in 10%-15% of patients with sporadic CRC[2,3]. Previously, we had reported the prevalence of MSI-H as approximately 10%, which is higher than that identified in the present study (6%)[1,21]. A possible cause is that the inclusion criteria differ between our studies. Our previous studies excluded patients

**Table 2 Immunohistochemistry patterns (*n* = 3486)**

Expression patterns	<i>n</i> (%)
Retained expression of 4 proteins	3285 (94.2)
Loss of at least 1 protein	201 (5.8)
Loss of PMS2	136 (3.9)
Loss of MLH1	133 (3.8)
Loss of MSH6	58 (1.7)
Loss of MSH2	49 (1.4)
Concurrent loss of MLH1 and PMS2	126 (3.6)
Loss of PMS2 alone	10 (0.3)
Loss of MLH1 alone	7 (0.2)
Concurrent loss of MSH2 and MSH6	43 (1.2)
Loss of MSH6 alone	15 (0.4)
Loss of MSH2 alone	6 (0.2)

**Table 3 Validity of 4- and 2-antibody panels in immunohistochemistry based on a microsatellite instability test**

	4-antibody IHC	2-antibody IHC	
		PMS2/ MSH6	MLH1/MSH2
Sensitivity (95%CI)	97.4% (93.7-99.0)	92.2% (87.3-95.4)	87.6% (81.9-91.7)
Specificity (95%CI)	99.6% (99.3-99.8)	99.6% (99.3-99.8)	99.7% (99.5-99.9)
$\kappa$	0.952	0.923	0.906

CI: Confidence interval;  $\kappa$ : Cohen's kappa statistic (value of kappa  $\geq$  0.90, almost perfect agreement)[10]. IHC: Immunohistochemistry.

**Table 4 Discrepancy between the results of microsatellite instability test and immunohistochemistry**

MSI status	IHC				(n = 32)			
	MLH1	MSH2	PMS2	MSH6	Causes of discrepancy			Overall
					PF	LE	Unknown	
MSI-H	+	+	+	+	0	0	5	5
MSS	Loss	+	Loss	+	6	1 <sup>1</sup>	4	11
	+	Loss	+	Loss	0	1 <sup>1</sup>	5	6
	+	+	Loss	+	2	1	1	4
	+	+	+	Loss	0	0	3	3
	Loss	+	+	+	2	0		2
	Loss	Loss	+	Loss	1	0		1

MSI-H: High-frequency microsatellite instability; MSS: Microsatellite stable; "+": Retained expression of protein; Loss: Loss of MMR protein expression; PF: Poor fixation; LE: Low expression (*i.e.*, <sup>1</sup>radiotherapy).

who had undergone preoperative radiotherapy for rectal cancer. Therefore, the increased proportion of patients with rectal cancer in the present study may have decreased the relative prevalence of MSI-H, because MSI-H is infrequent in rectal cancer compared to that in colon cancer[22]. Another cause may be racial differences, as the incidence of MSI-H in East Asian patients is slightly lower than that in Europeans[23,24].

We collected cases of mismatch between the results of the MSI test and IHC with respect to MMR deficiency and reviewed the IHC again. However, in certain circumstances, the IHC review did not explain the cause of discrepancy. In cases where IHC revealed a loss of MMR protein expression but MSI test revealed MSS, the presumed cause was insufficient tumor purity of the specimen, resulting in inaccurate MSI test results. In addition, when the cause of MSI was loss-of-function point mutations in the MMR proteins, the expression of all four MMR proteins was retained in MSI-H tumors [12]. Therefore, this will require further research using MSI re-testing or next-generation sequencing (NGS), a highly accurate screening method for MMR deficiency through fast DNA/RNA sequencing [25,26].

Weak staining, PF, and LE, which may be observed in rare poorly-processed tissue samples, can contribute to the loss of MMR protein expression in MSS tumors. PF may cause significant protein degradation that may compromise IHC, and it was identified as the most common cause of discrepancy in this study. The most frequent scenario was the central part of the resected specimen showing PF due to insufficient time [27]. In this study, discrepancy caused by PF was mainly found in MLH1 or PMS2, suggesting that MLH1 and PMS2 IHC are more vulnerable to PF than MSH2 and MSH6 IHC. LE was caused by lymphocytes or endothelial cells around tumor cells being well-expressed and tumor cells not being well-expressed, phenomenon that are often caused by tumor intrinsic factors or radiotherapy [28]. In this study, although the expression of all proteins was identified in IHC in 1202 patients with rectal cancer in the MSS group who did not receive preoperative radiotherapy, of the 335 patients who had received preoperative radiotherapy, 3 exhibited loss of at least one protein in the IHC. MSI-H occurred in only 1.1% of the patients with rectal cancer. Therefore, if IHC revealed the loss of at least one protein in rectal cancer, a false positive should be excluded before suspecting MSI-H. Additionally, 10 patients with MSS tumors exhibited loss of MSH6 expression, nine of whom still showed discrepancy after careful review. This might be attributed to the instability of the microsatellite sequence that is present within the exonic region of *MSH6* [15].

There are several limitations to this study. First, the design of retrospective studies has inherent limitations. All data were as complete as possible but patients with missing information with respect to the results of MSI tests or IHC were excluded. Second, this study was conducted at a single center. There may be a problem of external validation. However, both IHC and MSI tests are commonly used worldwide and nationwide, thus, the results should be reliable. Third, we were unable to resolve all discrepancies due to time and budget constraints. For cases in which a discrepancy was present, MSI test repetition using PCR and NGS may be helpful in future studies. Additionally, this present study was limited to assessing cost-effectiveness and accuracy of different tests. To analyze clinical benefits, survival data (disease-free survival or overall survival) needs to be collected. A follow-up study should be performed for comparing survival outcome and if the clinical outcome is also comparable between two- and four-antibody panels, it would provide a stronger evidence for applying the two-antibody panels in clinical practice as it is more cost-effective.

## CONCLUSION

When the cost aspect is not considered, screening through MSI tests may be preferred. However, considering the economic status of individual patients and different health care systems in different countries, a two-antibody panel of PMS2/MSH6 might be the best choice in terms of cost-effectiveness and accuracy. For cases in which a discrepancy is present, MSI re-testing and NGS may be helpful for identifying the cause.

## ARTICLE HIGHLIGHTS

### Research background

The microsatellite instability (MSI) test and immunohistochemistry (IHC) are widely used to screen DNA mismatch repair (MMR) deficiency in sporadic colorectal cancer (CRC). For IHC, a two-antibody panel of MLH1 and MSH2 or four-antibody panel of MLH1, MSH2, PMS2, and MSH6 are used. In general, MSI is known as a more accurate screening test than IHC.



### Research motivation

Several studies have compared four- and two-antibody panels in terms of accuracy and cost-effectiveness. However, large-scale studies examining all four types of IHC and comparing two- *vs* four-antibody panel of IHC are rare.

### Research objectives

This study aimed to compare two- and four-antibody panels of IHC in terms of accuracy and cost benefit on the basis of MSI testing for detecting MMR deficiency.

### Research methods

We retrospectively analyzed patients with CRC who underwent curative surgery between 2015 and 2017 at a tertiary referral center. Both IHC with four antibodies and MSI tests were routinely performed. The sensitivity and specificity of a four- and two types of two-antibody panels (PMS2/MSH6 and MLH1/MSH2) were compared on the basis of MSI testing for detecting MMR deficiency.

### Research results

High-frequency MSI was found in 5.5% ( $n = 193$ ) of the patients ( $n = 3486$ ). The sensitivities of the four- and two types of two-antibody panels were 97.4%, 92.2%, and 87.6%, respectively. The specificities of the three types of panels did not differ significantly (99.6% for the four-antibody and PMS2/MSH6 panels, 99.7% for the MLH1/MSH2 panel). Based on Cohen's kappa statistic ( $\kappa$ ), four- and two-antibody panels were in almost perfect agreement with the MSI test ( $\kappa > 0.9$ ). The costs of the MSI test and the four- and two-antibody panels of IHC were approximately \$200, \$160, and \$80, respectively.

### Research conclusions

Considering the cost of the four-antibody panel IHC compared to that of the two-antibody panel IHC, a two-antibody panel of PMS2/MSH6 might be the best choice in terms of balancing cost-effectiveness and accuracy.

### Research perspectives

Based on this study, medical policy could be altered to minimize expense for detecting MMR deficiency. Further studies including multicenter from different nations is needed for a more accurate comparison and additional assessment of oncologic outcomes.

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