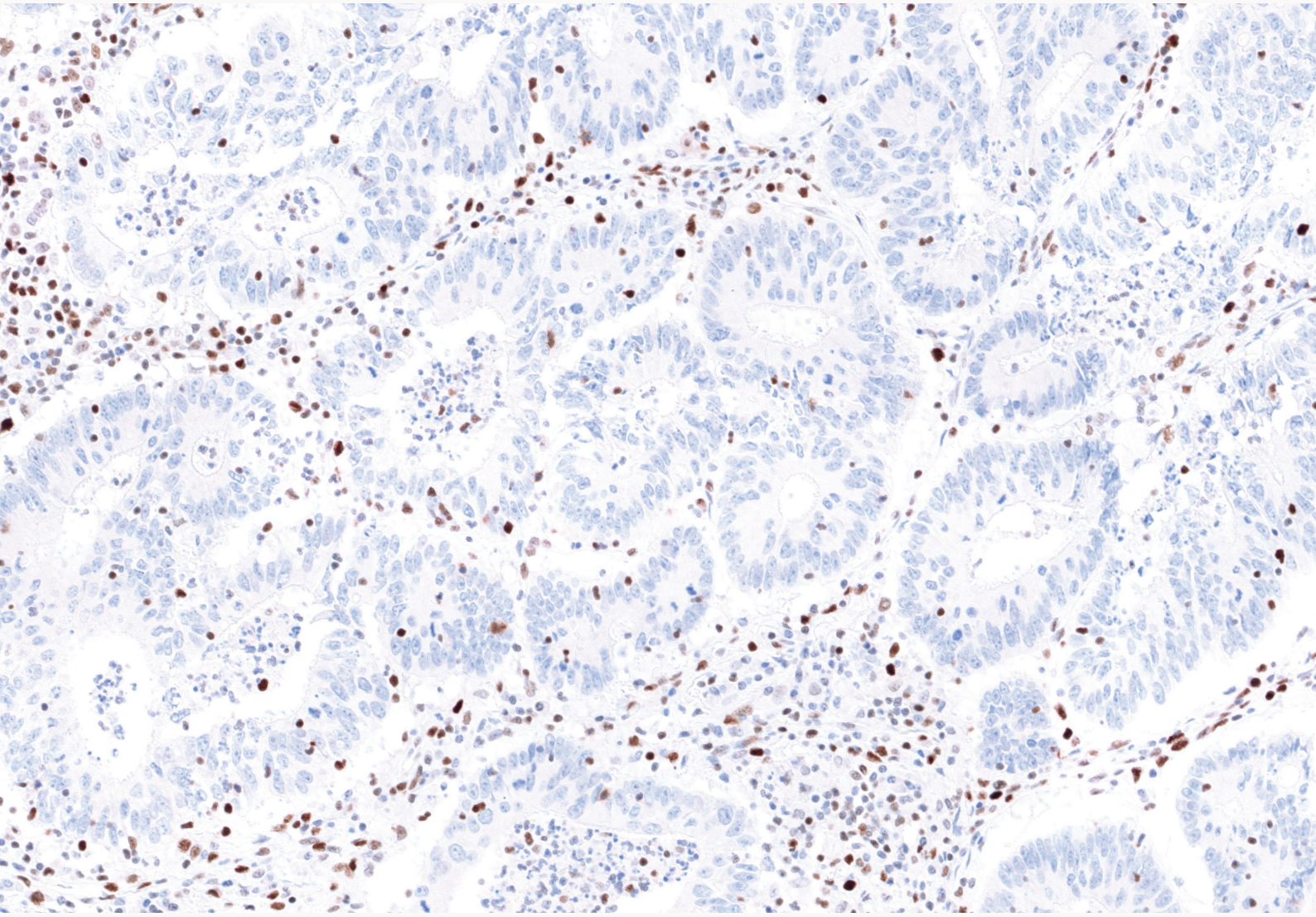
VENTANA®

Roche

VENTANA® MMR Panel

Your assay choice matters



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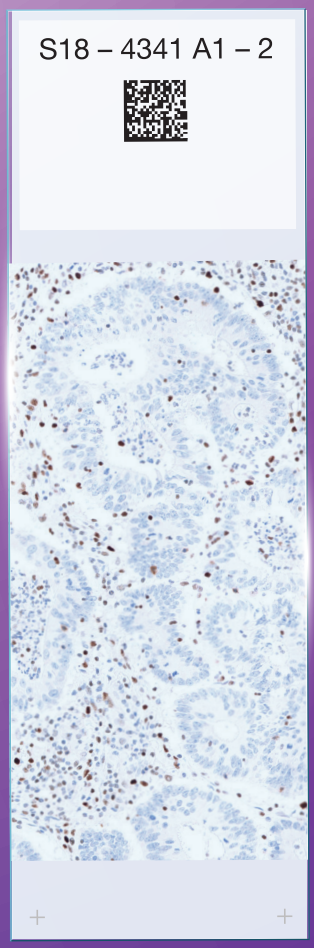


First MMR IHC-based assay approved to identify endometrial carcinoma patients

VENTANA MMR RxDx Panel includes the following antibodies:

- VENTANA anti-MLH1 (M1) Mouse Monoclonal Primary Antibody
- VENTANA anti-PMS2 (A16-4) Mouse Monoclonal Primary Antibody
- VENTANA anti-MSH2 (G219-1129) Mouse Monoclonal Primary Antibody
- VENTANA anti-MSH6 (SP93) Rabbit Monoclonal Primary Antibody

VENTANA MMR RxDx Panel is a qualitative immunohistochemistry test intended for use in the assessment of mismatch repair (MMR) proteins (MLH1, PMS2, MSH2 and MSH6) in formalin-fixed, paraffin-embedded (FFPE) endometrial carcinoma tissue by light microscopy. The OptiView DAB IHC Detection Kit is used for MLH1, MSH2 and MSH6, and the OptiView DAB IHC Detection Kit with the OptiView Amplification Kit is used for PMS2 on a VENTANA BenchMark ULTRA instrument.

VENTANA MMR RxDx Panel is indicated as an aid in identifying patients eligible for treatment with therapy for MMR deficient endometrial carcinoma in accordance with the approved therapeutic product labeling.

MMR proteins and their interactions with DNA

DNA mismatch repair (MMR) is a conserved molecular mechanism that corrects the improper base substitutions that spontaneously occur during DNA replication.[1] Defects in the MMR machinery have been attributed to mutations in the MMR proteins, most commonly MLH1, PMS2, MSH2, and MSH6.

The MLH1 and PMS2 proteins normally function together in a heterodimeric complex, as do the MSH2 and MSH6 proteins. When MMR is functioning normally, the MSH6/MSH2 heterodimer binds to mismatched DNA. This binding induces a conformational change that allows the MLH1/PMS2 heterodimer to bind the DNA-bound MSH6/MSH2 complex, resulting in excision repair of the affected DNA.[2,3] Mutations or deficiencies in these proteins result in frequent MSI and somatic mutations due to replication error. MMR immunohistochemistry (IHC) testing can be useful in identifying MMR genes likely to contain germline or somatic alterations.[4]

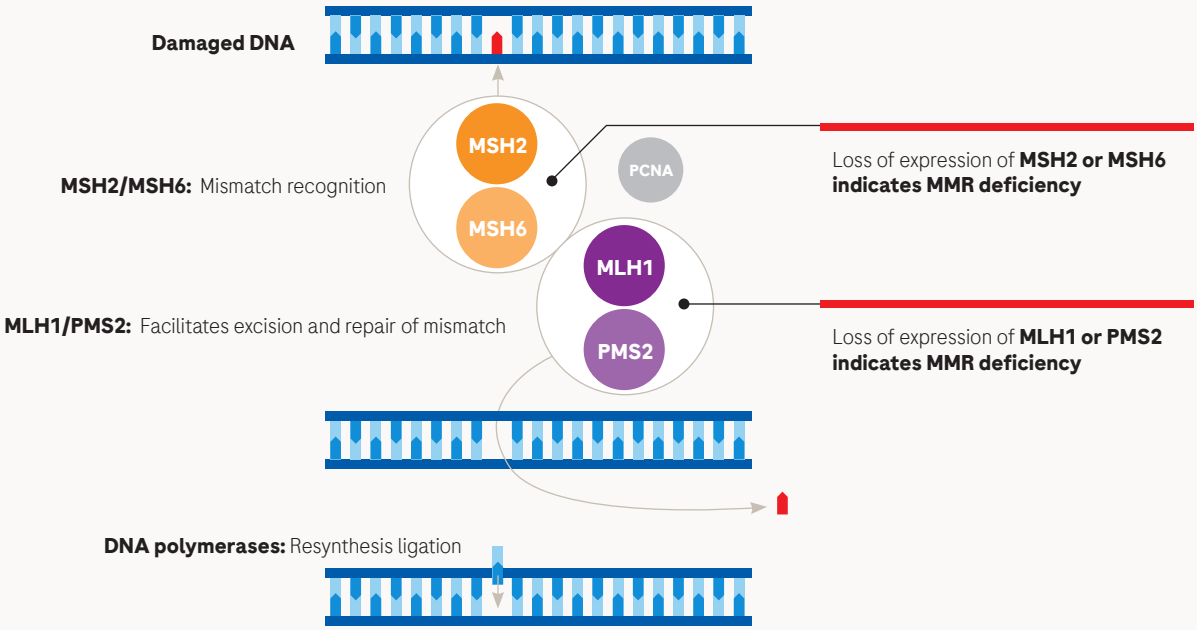


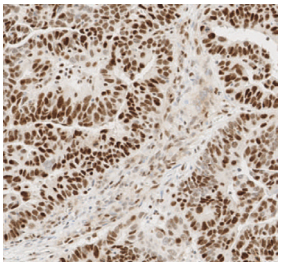
Figure 1: MMR proteins and their interactions with DNA. The MSH2–MSH6 complex recognises mismatches and insertion/deletion loops. The MLH1–PMS2 complex facilitates excision and repair of the mutant base(s).

MMR proteins as predictive biomarkers

Multiple studies have demonstrated that MMR deficiency correlates with a higher expression of PD-1 or PD-L1, possibly due to increased neoantigen expression associated with tumour mutation burden that results from replication errors.[5,6] Thus, MMR proteins will be useful as predictive biomarkers for PD-1 targeted therapy; specifically, a loss of expression of one or more MMR proteins might predict an increased likelihood of response to such therapy.[7,8,9] PD-1 inhibitors can be beneficial in cancers with a high frequency of MMR deficiency and/or MSI-H such as endometrial carcinoma.[7,9]

Panel interpretation

A loss of expression of any of the essential MMR proteins, including MLH1, PMS2, MSH2, or MSH6, in the presence of evaluable internal controls causes MMR deficiency. Staining for all four MMR protein markers in the presence of evaluable internal controls indicates that the case is proficient for mismatch repair status.



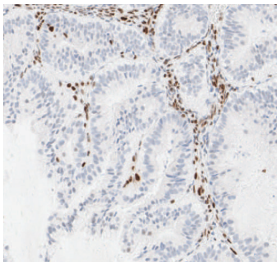
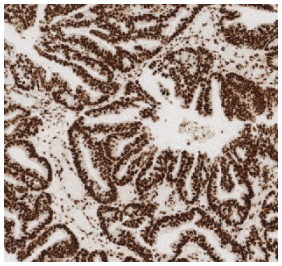


Figure 1: VENTANA anti-MLH1 (M1) Mouse Monoclonal Primary Antibody staining with Intact (left) or Loss (right) of expression in the presence of evaluable internal controls in endometrial carcinoma tissue.



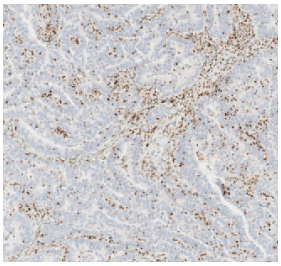
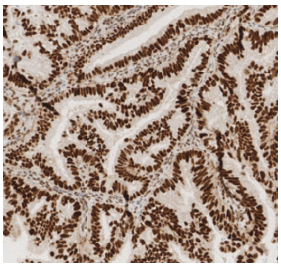


Figure 2: VENTANA anti-MSH6 (SP93) Rabbit Monoclonal Primary Antibody staining with Intact (left) or Loss (right) of expression in the presence of evaluable internal controls in endometrial carcinoma tissue.



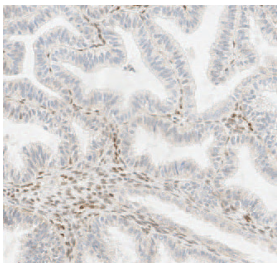
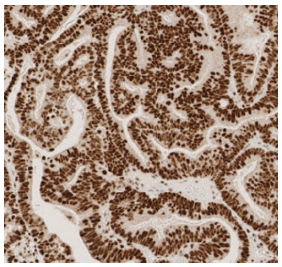


Figure 3: VENTANA anti-MSH2 (G219-1129) Mouse Monoclonal Primary Antibody staining with Intact (left) or Loss (right) of expression in the presence of evaluable internal controls in endometrial carcinoma tissue.



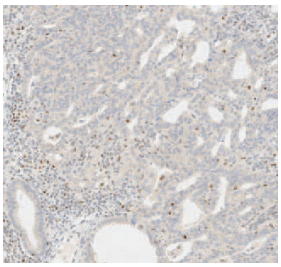


Figure 4: VENTANA anti-PMS2 (A16-4) Rabbit Monoclonal Primary Antibody staining with Intact (left) or Loss (right) of expression in the presence of evaluable internal controls in endometrial carcinoma tissue.

Interpretation of protein expression with the VENTANA MMR RxDx Panel

Intact protein expression	Loss protein expression
Unequivocal nuclear staining in viable tumour cells in the presence of acceptable internal positive controls (e.g., nuclear staining in lymphocytes, fibroblasts or normal epithelium in the vicinity of the tumour).	Unequivocal loss of nuclear staining or focal weak equivocal nuclear staining in the viable tumour cells in the presence of acceptable internal positive controls. Punctate nuclear staining is considered negative.

Interpretation of MMR status using the VENTANA MMR RxDx Panel

Proficient	Deficient
All four proteins (MLH1, PMS2, MSH2 and MSH6) in the panel exhibit intact expression.	At least one protein (MLH1, PMS2, MSH2 and MSH6) in the panel exhibit loss of expression.

Clinical data

MMR status concordance between GARNET study Clinical Trial Assay* and VENTANA MMR RxDx Panel (IU Population**)

VENTANA MMR RxDx Panel Status	CDx MMR Status	Clinical Trial Assay MMR Status			Agreement		
		dMMR	pMMR	Total	Measure[(b)]	n/N	(95% CI)[(a)]
IU Concordance	dMMR	51	0	51	PPA	51/55	92.7 (82.7, 97.1)
	pMMR	4	68	72	NPA	68/68	100.0 (94.7, 100.0)
	Total	55	68	123	OPA	119/123	96.7 (91.9, 98.7)
ITD Concordance	dMMR	70	1	71	PPA	70/76	92.1 (83.8, 96.3)
	pMMR	6	90	96	NPA	90/91	98.9 (94.0, 99.8)
	Total	76	91	167	OPA	160/167	95.8 (91.6, 98.0)

(a) Two-sided 95% CIs were calculated using the Wilson score method. (b) For the purpose of the analyses, a pMMR status was considered negative, and dMMR status was considered positive. PPA = positive percent agreement; NPA = negative percent agreement; OPA = overall percent agreement

*MMR by IHC, not necessarily Roche **Intended Use (IU) population includes only the subset of patients for whom VENTANA MMR RxDx Panel testing attempt was performed according to the requirements of the Dx protocol

Analyses were performed in the Concordance population (all patients in the Safety Population with an evaluable VENTANA MMR RxDx Panel (CDx) staining result). The Intent-to-Diagnose (ITD) and Concordance populations were equivalent in this study. The Intended Use (IU) Concordance population includes only the subset of patients who are also in the IU population (i.e., for whom VENTANA MMR RxDx Panel testing attempt was performed according to the requirements of the diagnostic protocol).

Ordering information

Product name	Catalog number	Ordering code	Quantity
VENTANA anti-MLH1 (M1) Mouse Monoclonal Primary Antibody	730-7159	09605584001	50 tests
VENTANA anti-PMS2 (A16-4) Mouse Monoclonal Primary Antibody	730-7158	09607161001	50 tests
VENTANA anti-MSH2 (G219-1129) Mouse Monoclonal Primary Antibody	730-7160	09607137001	50 tests
VENTANA anti-MSH6 (SP93) Rabbit Monoclonal Primary Antibody	730-7161	09606769001	50 tests
OptiView DAB IHC Detection Kit	760-500	05269806001	250 tests
OptiView Amplification Kit*	860-099	06718663001	250 tests

*Required with VENTANA anti-PMS2 (A16-4) Mouse Monoclonal Primary Antibody For a complete list of materials required, please refer to the product package inserts

References

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[4] Cunningham JM, Tester DJ, Thibodeau SN. Mutation detection in colorectal cancers: direct sequencing of DNA mismatch repair genes. *Methods Mol Med.* 2001;50:87-98.

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[9] Dudley JC, Lin MT, Le DT, et al. Microsatellite instability as a biomarker for PD-1 blockade. *Clin Cancer Res.* 2016;22(4):813-820.

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