HistoCyte Laboratories

Quality in Control

MMR Analyte Control

Product Introduction

Product Codes:

HCL041 to HCL052

Issue 1. 061021

Contents

The Mismatch Repair (MMR) product range

This family of products has a four core format that covers all the MMR biomarkers: MLH1/PMS2, MSH2 and MSH6. There are three more formats consisting of 2 core products. These provide a more cost effective means of quality control for each test.

Product Name	Format	Code
MMR Analyte Control	Slide (2)	HCL041
	Slide (5)	HCL042
	Block	HCL043
MLH1/PMS2 Analyte Control	Slide (2)	HCL044
	Slide (5)	HCL045
	Block	HCL046
MSH2 Analyte Control	Slide (2)	HCL047
	Slide (5)	HCL048
	Block	HCL049
MSH6 Analyte Control	Slide (2)	HCL050
	Slide (5)	HCL051
	Block	HCL052

(For research use only)

Quality Control

One of the requirements of quality standardization is the appropriate use of controls. These need to be robust enough for IHC and in situ hybridization (ISH), be reproducible and cost-effective. Additionally, the control material should be consistent from batch to batch and throughout the block it is cut from.

Same slide control versus batch controls

In laboratories with automated platforms these controls need to be on the same slide. Batch controls are typically not representative of how slides have been treated as the instruments treat the slides completely independently.

External Quality Assurance

External quality assurance (EQA) schemes or proficiency testing (PT) have shown standardized assays typically perform better than laboratory developed tests (LDTs). In 2017 over 60% of UKNEQAS participants in RUN118/47 were using standardized ER vendor assays. Again in the NordiQC assessment B25 in 2018 >80% were using standardized ER assays.

Cell Lines as Controls

The issue with tissue

Laboratories often struggle for low and intermediate expressing material that is consistent, one example being HER2 2+ tissue. Not only is it hard to find tissue in sufficient amounts, but biomarker expression can also vary throughout tissue, often due to a number of factors including but not limited to:

- Fixation
- Processing artefact
- Heterogeneity of the protein, see Figure 1 (taken from Nitta H *et al*[1])

This means that tissue selected for use as control can vary to the point that it makes its use as a control redundant.

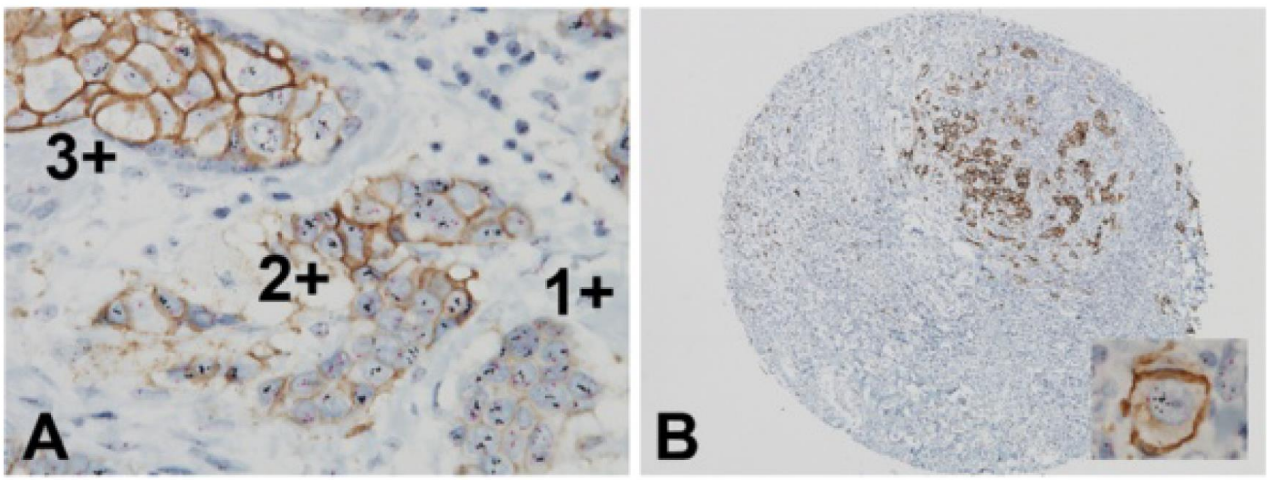


Figure 1. Results of HER2 gene-protein staining of FFPE breast cancer tissues exhibiting heterogeneity of HER2 positive tumor cell populations or isolated tumour cell populations. (A) The HER2 gene-protein assay demonstrated the heterogeneity of HER2 positive tumour cell populations in FFPE breast cancer tissues. In the sample shown, cell populations with HER2 IHC scores of 3+, 2+ and 1+ neighbor each other and all tumor populations present amplified *HER2* gene. However, the HER2 IHC 3+ tumor cell population contains dispersed *HER2* gene copies while the HER2 IHC 2+ and 1+ population contains clustered *HER2* gene copies [40x]. **(B)** The HER2 gene-protein assay clearly visualized small groups of HER2 3+IHC breast cancer cells [4x]. The insert shows an isolated individual HER2 IHC positive tumor cell with *HER2* gene amplification [100x].[6]

1. Nitta et al. Diagnostic Pathology 2012, 7:60

Cell lines

Cell lines are typically included in or with assays as pre-cut slides. These are not designed for use as same slide controls and pre-cut slides are not always practical for day to day use in a high volume laboratory. They are used by EQA schemes as standardized materials for their assessments. So while adequately performing by IHC or FISH, the preparations are often sparse and the cellular integrity or morphology is generally poor. So while they can be reproducibly manufactured to provide standardized material there is room for improvement.

Our solution

HistoCyte Laboratories provide cell lines that are compact and typically "tissue-like". In particular the breast ductal carcinoma cells often create "pseudo-acini" producing a more tissue like appearance. The morphology of our cells means that they can tell you more about how the slide has been treated. It is quite obvious when the morphology is disrupted. The HistoCyte Laboratories cell lines are intended to be used for quality control only. They are standardized, developed and manufactured to provide consistent results throughout the block. This is what differentiates them from tissue controls. It should be remembered that these still need validating in each laboratory that adopts them.

Tissue is still important

It is important to remember that HistoCyte controls are a quality control material designed only to demonstrate that the assay has worked consistently. They reduce the burden on a laboratory to identify and obtain suitable materials for use as a same slide control. This means tissue can be preserved for other uses such as trouble shooting and validations.

Introduction to MMR

What is it?

Mismatch repair (MMR) proteins are involved in repairing errors in DNA (e.g. point mutations) that are formed as part of DNA replication. Although there are several known MMR proteins, four of these play a particularly important clinical role in human cancer biology – MLH1, MSH2, MSH6 and PMS2[1]. These four proteins are arranged as heterodimers (MLH1 complexing with PMS2 and MSH2 complexing with MSH6) to recognise mismatched nucleotide base pairs caused by errors in deletion or insertion[2]. A mutation in one or more of these MMR proteins leads to impaired DNA repair which can result in microsatellite instability (MSI) and increased likelihood of cancers such as colorectal and endometrial carcinomas. MMR deficiency (dMMR) caused by mutations to MMR proteins can be termed as Lynch syndrome[3] and accounts for 3-5% and 2-3% of colorectal and endometrial carcinomas, respectively.

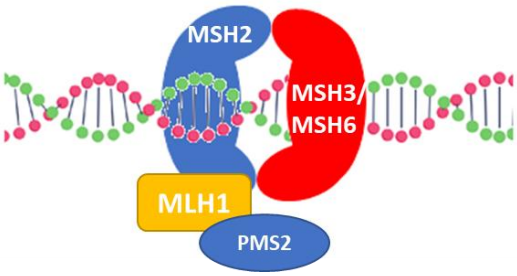
Utility

In colorectal cancer, dMMR is associated with improved stage-adjusted prognosis but reduced response to conventional chemotherapy drugs such as 5-fluorouracil[4]. However, in dMMR endometrial cancer cases, these patients may show an increased response to adjuvant radiotherapy[5]. dMMR can be diagnosed either molecularly (through detection of MSI) or by showing loss of nuclear protein expression in tumour cells using immunohistochemistry (IHC).

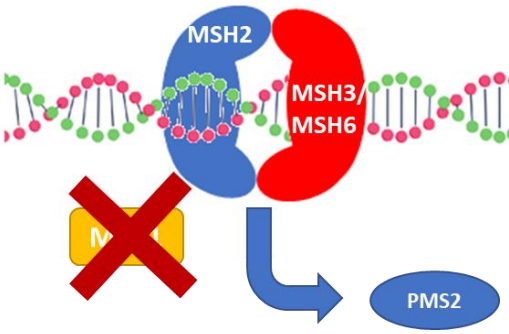
1. Pal T, Permuth-Wey J, Sellers TA. A review of the clinical relevance of mismatch-repair deficiency in ovarian cancer. *Cancer.* 2008;113:733–42.
2. Tamura K, Kaneda M, Futagawa M. Genetic and genomic basis of the mismatch repair system involved in Lynch syndrome. *International Journal of Clinical Oncology*. 2019;24:999-1011.
3. Lynch HT, Shaw MW, Magnuson CW. Hereditary factors in cancer. Study of two large midwestern kindreds. *Arch Intern Med.* 1966;117:206–12.
4. Kawakami H, Zaanan A, Sinicrope FA. MSI testing and its role in the management of colorectal cancer. *Curr Treat Options Oncol.* 2015;16:30.
5. Reijnen C, Küsters-Vandevelde HVN, Prinsen CF. Mismatch repair deficiency as a predictive marker for response to adjuvant radiotherapy in endometrial cancer. *Gynecol Oncol*. 2019;154:124–30

The illustration below demonstrates the relationship between the MMR protein heterodimers when each protein is lost.

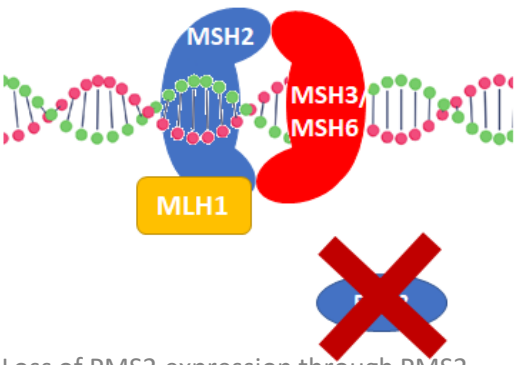
Mismatch repair complexing and relationship



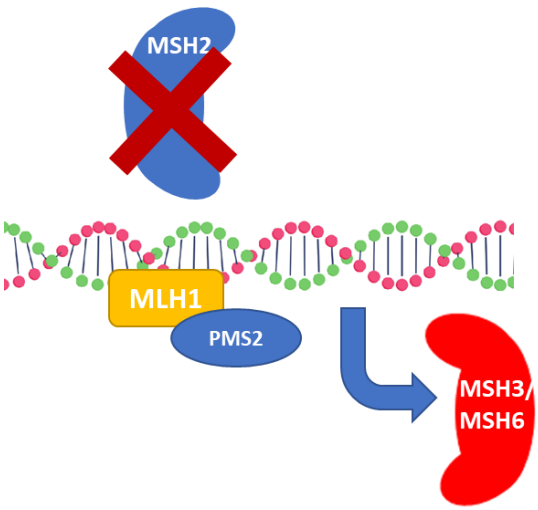
Normal expression of the mismatch repair proteins. These complex in the nuclei in order to repair the DNA.



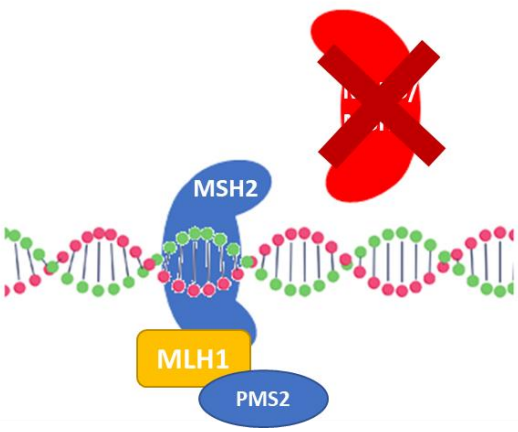
Loss of MLH1 due to MLH1 mutation or promoter hypermethylation. This results in PMS2 failing to complex in the nuclei.



Loss of PMS2 expression through PMS2 mutation



Loss of MSH2 also results in the loss of MSH6 complexing in the nuclei



Loss of MSH6 expression through MSH6 mutation

MMR immunohistochemistry

The tests

The most commonly used assays for detection of nuclear MMR protein expression are:

MLH1

- Roche (Ventana), M1, mouse monoclonal
- Agilent (Dako), ES05, mouse monoclonal
- Leica Biosystems (Novocastra), ES05, mouse monoclonal

MSH2

- Roche (Ventana), G219-1129, mouse monoclonal[R]
- Agilent (Dako), FE11, mouse monoclonal[C/R]
- Leica Biosystems (Novocastra), 79H11, mouse monoclonal[R]

MSH6

- Roche (Ventana), SP93, rabbit monoclonal[R]
- Agilent (Dako), EP49, rabbit monoclonal[C/R]
- Leica Biosystems (Novocastra), rabbit monoclonal[R]

PMS2

- Roche (Ventana), A16-4, mouse monoclonal[R]
- Agilent (Dako), EP51, mouse monoclonal[C/R]
- Leica Biosystems (Novocastra), EP51, mouse monoclonal[R]

[C] Available as a concentrate

[R] Available in a ready to use format

MMR IHC scoring algorithm

Intact protein expression

- Unequivocal nuclear staining, of at least 50% of cells[1]

Loss of protein expression

- Unequivocal loss of nuclear staining or focal weak equivocal nuclear staining
- Punctate nuclear staining of cells should be considered as loss of expression

MMR Analyte Control

The **MMR Analyte Control** is sold in two formats: as pre-prepared slides (Figure 1) or as a cell microarray (CMA) paraffin wax block (Figure 2).

Product Name	Format	Code
MMR Analyte Control	Slide (2)	HCL041
	Slide (5)	HCL042
	Block	HCL043

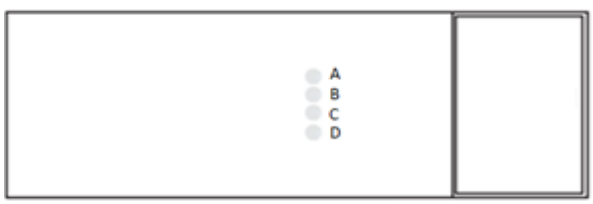


Figure 1: Cell Line Control Slide

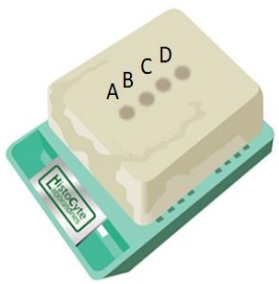


Figure 2: CMA block

1. Markow M. et al. Surg Pathol Clin. 2017 Dec;10(4):977-1007

Our CMA block provides the most cost effective solution for clinical histology laboratories and other high volume centers. They have been purposely designed to fit seamlessly into the work flow of the laboratory.

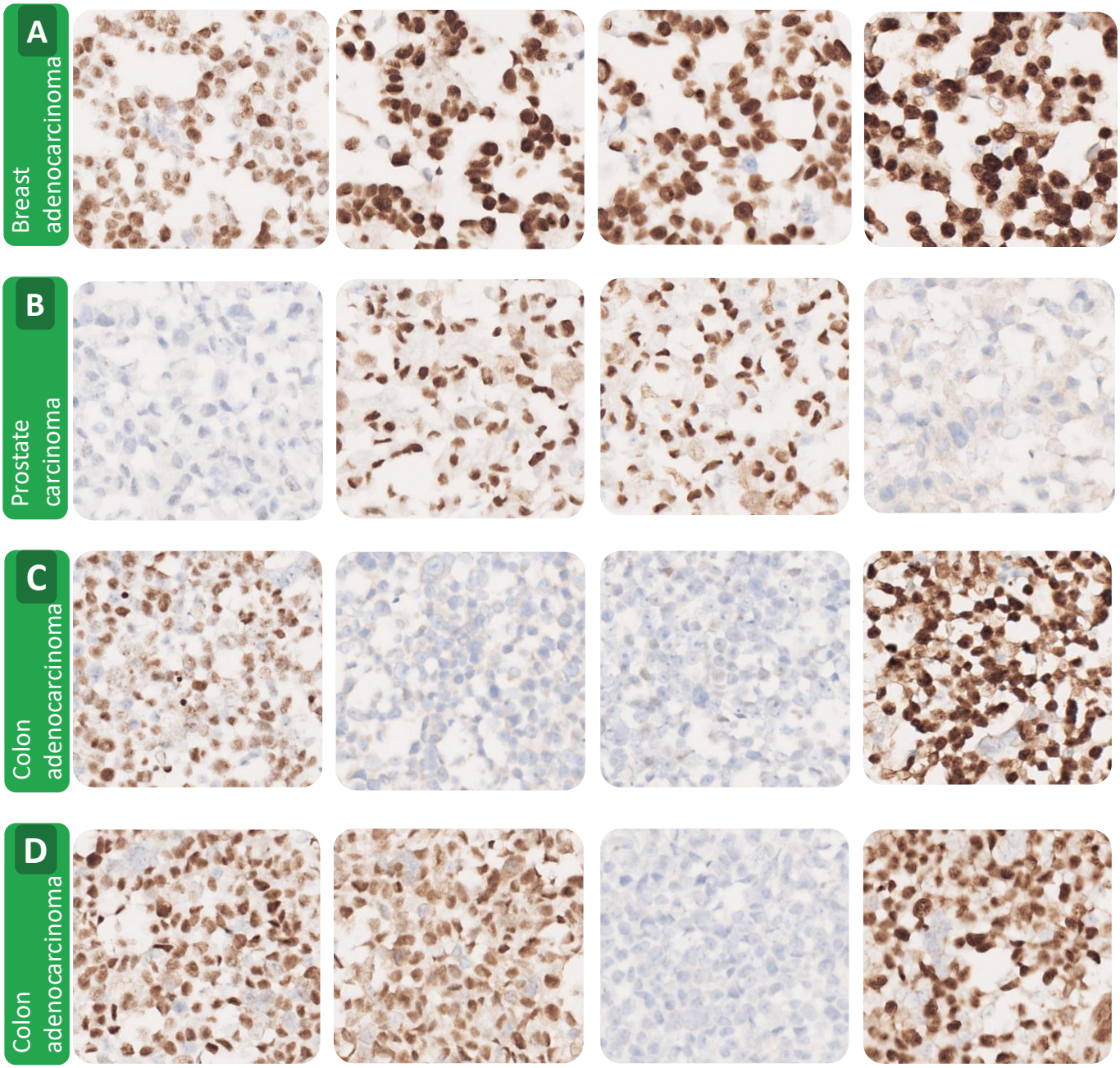
Our pre-prepared slides offer a ready-to-go alternative that saves time in preparation. These are ideal for one-off assessments, research laboratories and preliminary product trials.

The expression patterns of the 4 cell lines for MMR are shown below:

Core	MLH1	MSH2	MSH6	PMS2
A	Intact	Intact	Intact	Intact
B	**Loss of expression**	Intact	Intact	**Loss of expression**
C	Intact	**Loss of expression**	Loss of expression	Intact
D	Intact	Intact	**Loss of expression**	Intact

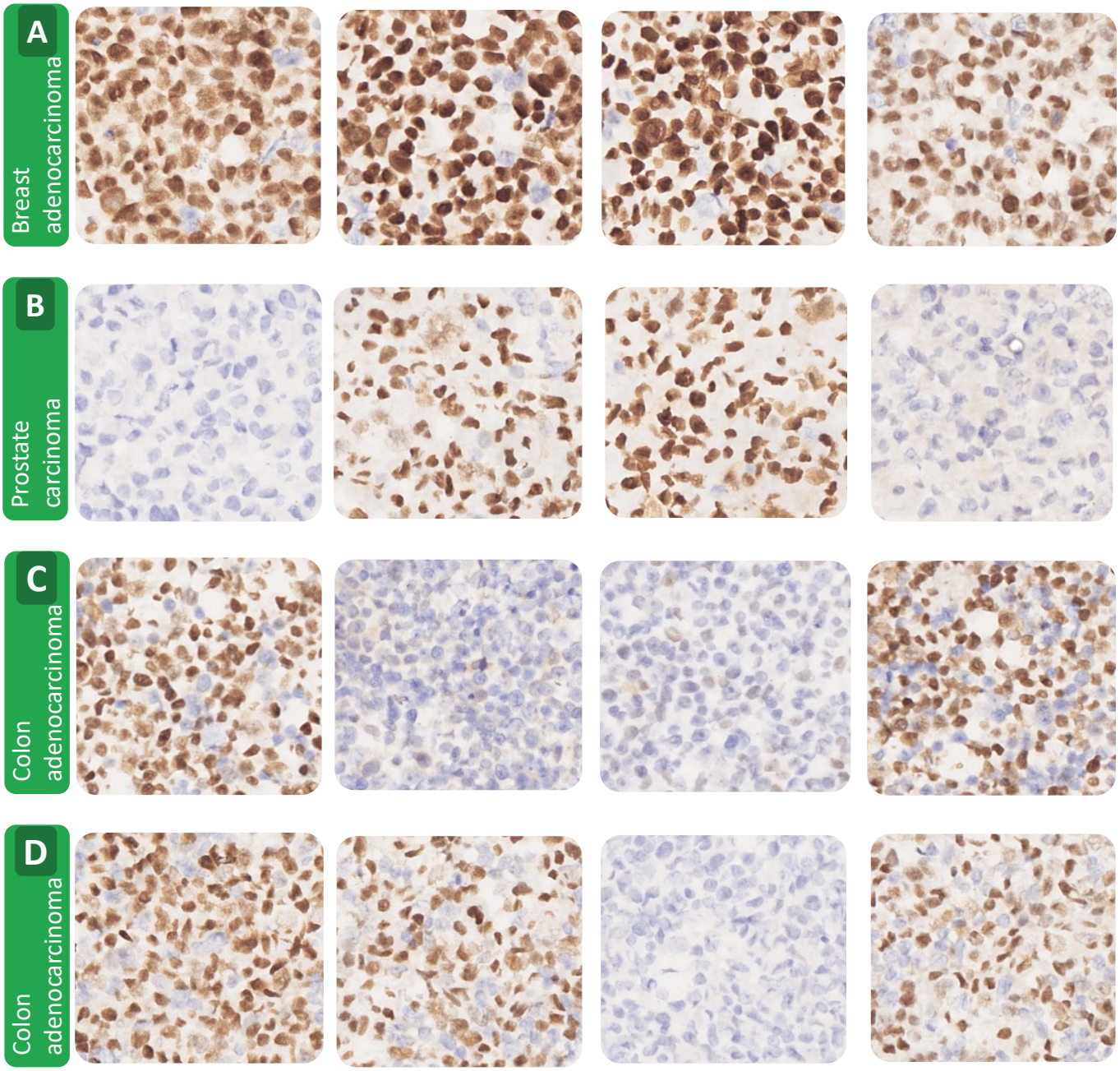
The following pages demonstrate the expected staining pattern with the cells on the most common platforms and assays found in immunohistochemistry laboratories.

MMR Analyte Control IHC: Roche Ventana



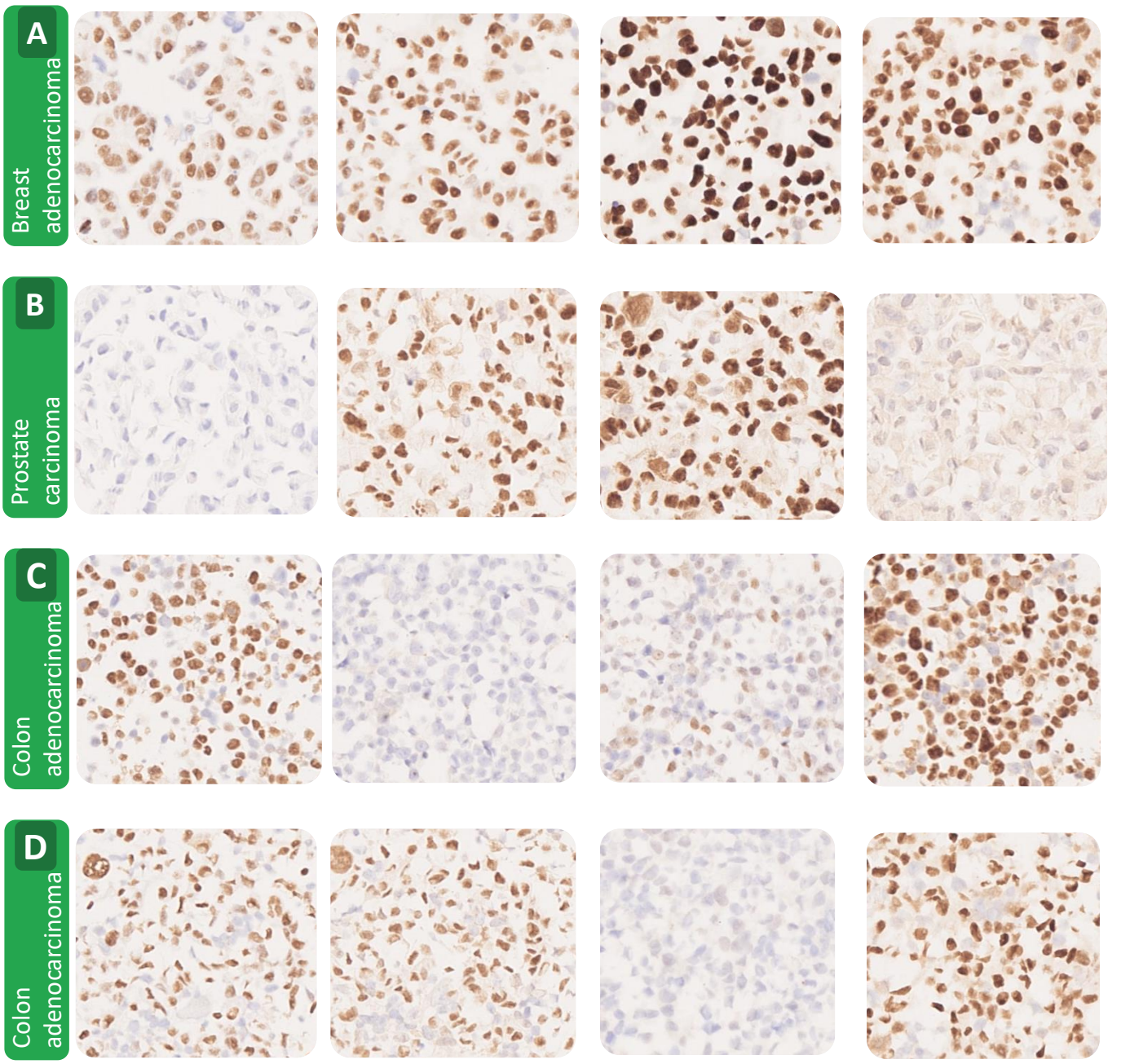
MLH1	MSH2	MSH6	PMS2
VENTANA anti-MLH1 (M1) Mouse Monoclonal Primary Antibody	**VENTANA anti-MSH2 (G219-1129)** Mouse Monoclonal Primary Antibody	**VENTANA anti-MSH6 (SP93)** Rabbit Monoclonal Primary Antibody	**VENTANA anti-PMS2 (A16-4)** Mouse Monoclonal Primary Antibody

MMR Analyte Control IHC: Agilent



MLH1	MSH2	MSH6	PMS2
Agilent Dako anti-MLH1 (ES05) Mouse Monoclonal Primary Antibody	**Agilent Dako anti-MSH2 (FE11)** Mouse Monoclonal Primary Antibody	**Agilent Dako anti-MSH6 (EP49)** Rabbit Monoclonal Primary Antibody	**Agilent Dako anti-PMS2 (EP51)** Mouse Monoclonal Primary Antibody

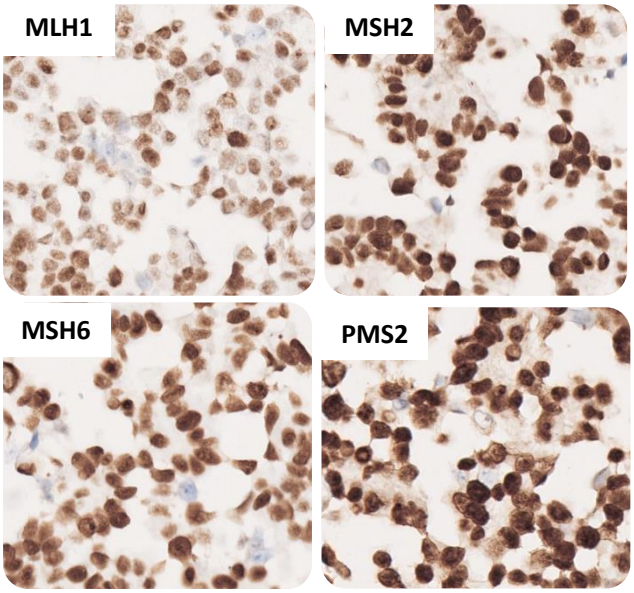
MMR Analyte Control IHC: Leica Biosytems



MLH1	MSH2	MSH6	PMS2
Leica Biosystems anti-MLH1 (ES05) Mouse Monoclonal Primary Antibody	**Leica Biosystems anti-MSH2 (79H11)** Mouse Monoclonal Primary Antibody	**Leica Biosystems anti-MSH6 (EP49)** Rabbit Monoclonal Primary Antibody	**Leica Biosystems anti-PMS2 (EP51)** Mouse Monoclonal Primary Antibody

MMR Analyte Control Core A staining

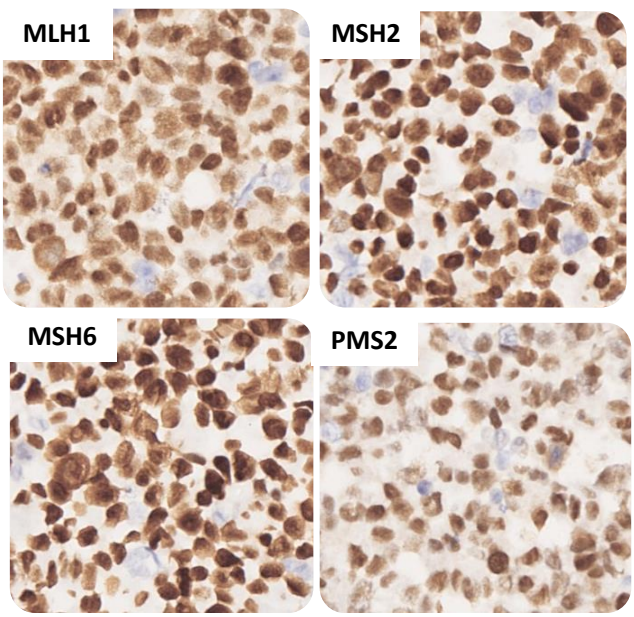
Roche/Ventana



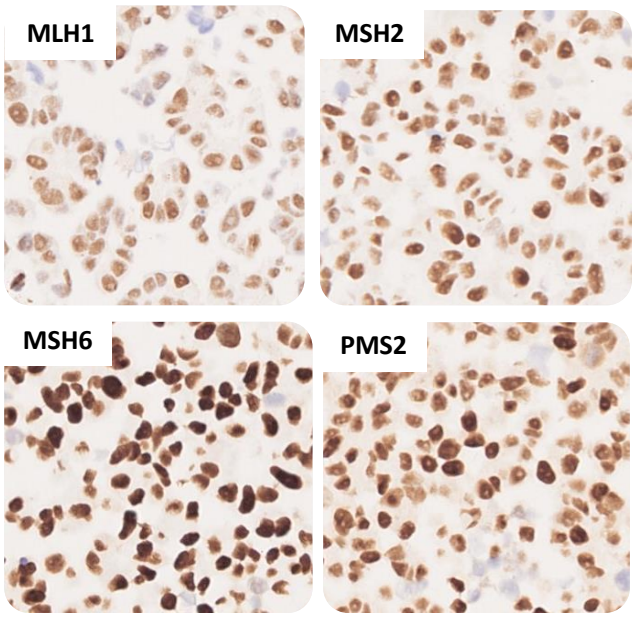
Cell line A is a breast adenocarcinoma cell line that carries no specific MMR mutations and is therefore MMR proficient and multi satellite stable (MSS).

This cell line is used as a control of intact expression (unequivocal nuclear staining, of at least 50% of cells) across all of the MMR products for all four proteins.

Agilent

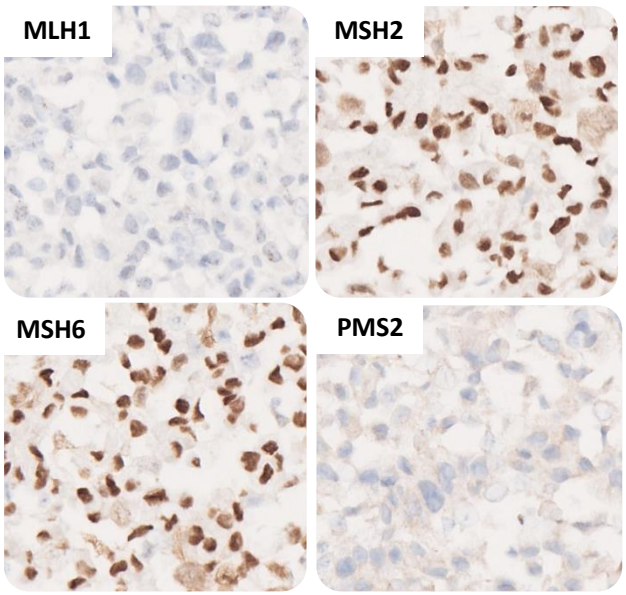


Leica Biosystems



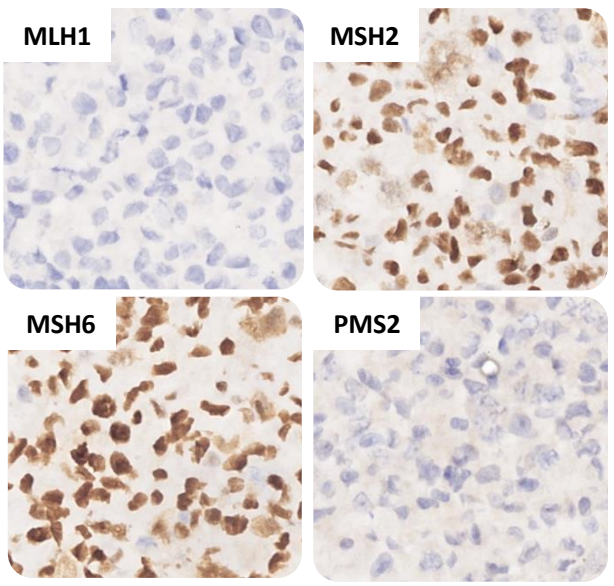
MMR Analyte Control Core B staining

Roche/Ventana

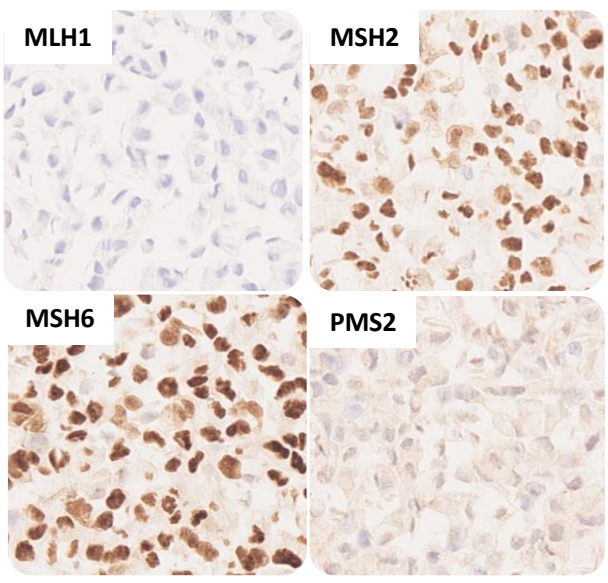


Cell Line B is a prostate carcinoma cell line. This cell line has a splice site mutation between exon 1 and exon 2 of the *MLH1* gene which causes the deletion of 5 coding nucleotides[1]. This nonsense mutation results in a premature stop codon in the transcribed mRNA and in a shortened, truncated, non-functional MLH1 protein product. PMS2 expression is also lost as PMS2 can no longer complex with MLH1 to form a heterodimer.

Agilent



Leica Biosystems

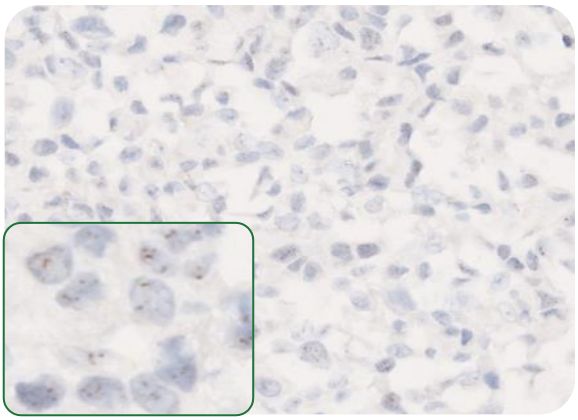


1. Chen Y, et al . Defects of DNA mismatch repair in human prostate cancer. *Molecular biology and genetics.* 2001;61:4112-4121.

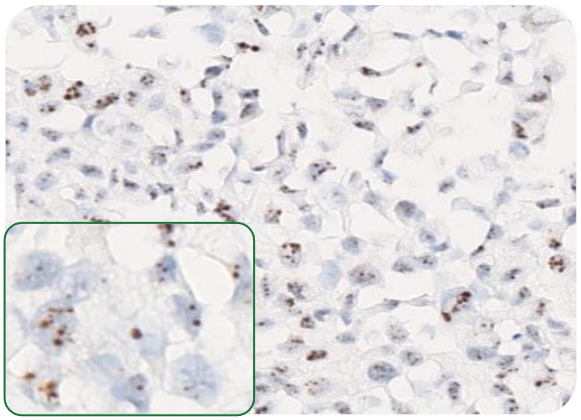
MMR Analyte Control Core B staining

MLH1 nuclear punctate staining

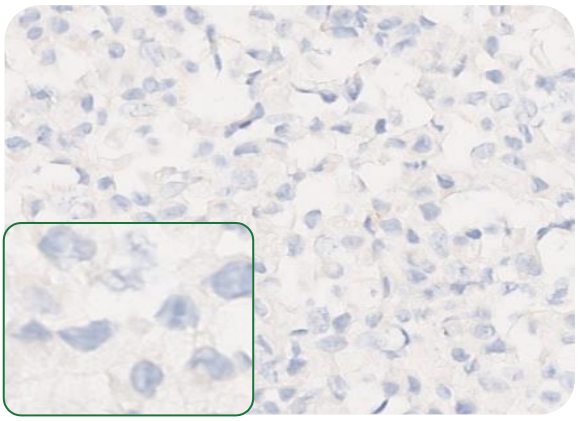
Laboratories have observed distinct MLH1 punctate nuclear staining, which is mostly associated with the MLH1 M1 (Roche) and G168-1129 (Cell Marque) clones[1]. The intensity of this punctate nuclear staining is increased when amplification is used as part of the IHC staining protocol, see below. This staining pattern is not replicated when using the MLH1 ES05 clone. This could be due to both the M1 and G168-1129 clones being full length recombinant proteins which are able to partially recognise truncated forms of non-functional MLH1 resulting in punctate nuclear staining.



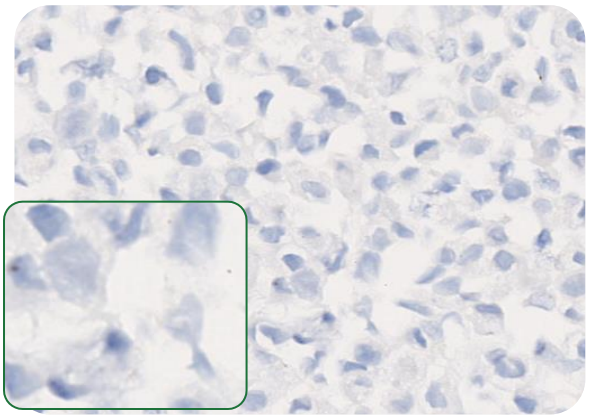
VENTANA anti-MLH1 (M1)



VENTANA anti-MLH1 (M1) + amplification



Leica Biosystems anti-MLH1 (ES05)



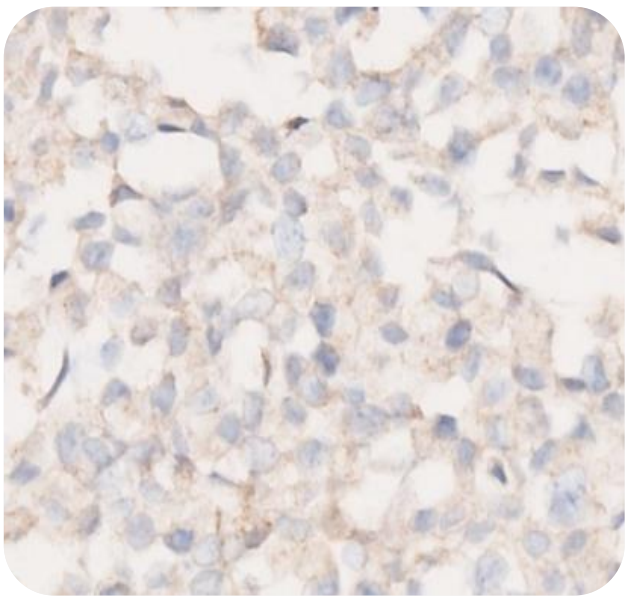
Leica Biosystems anti-MLH1 + amplification (ES05)

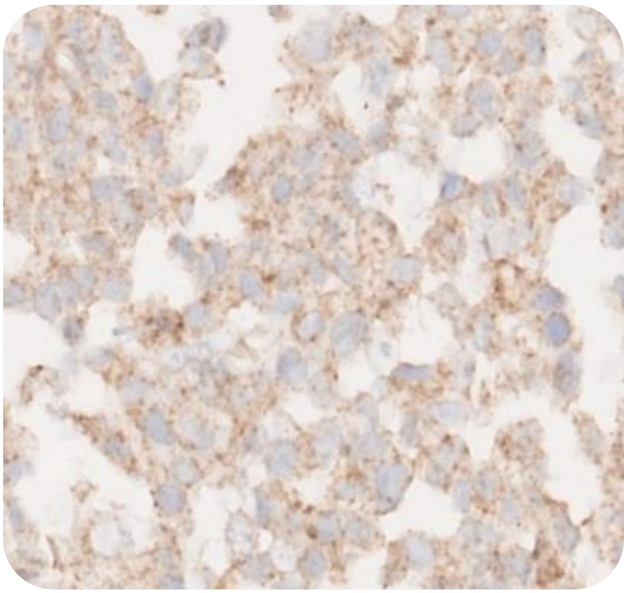
1. Dasgupta S, et al. Granular dot-like staining with MLH1 immunohistochemistry is a clone-dependent artefact. *Pathology, research and practice*. 2020;216:152581.

MMR Analyte Control Core B staining

PMS2 cytoplasmic background staining

Cytoplasmic staining is abnormal (loss of expression) and should not be misinterpreted as normal staining. There are varying degrees of cytoplasmic background staining observed in Cell Line B, see below. However, the nuclei of these cells have unequivocal loss of expression.

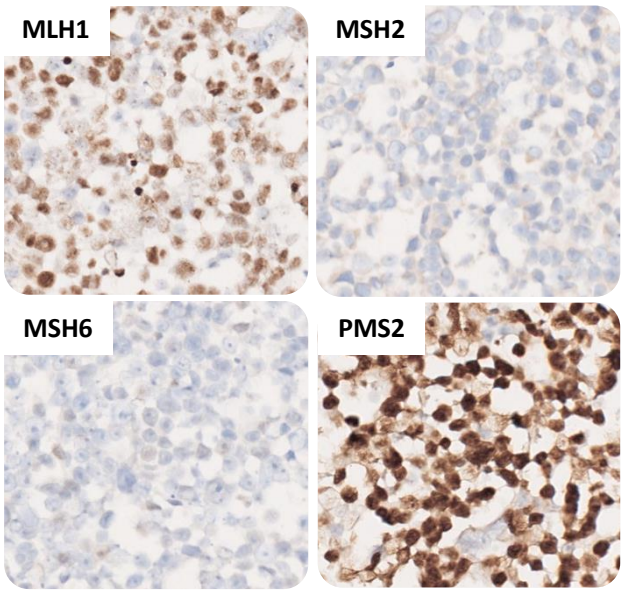




VENTANA anti-PMS2 (A16-4)

MMR Analyte Control Core C staining

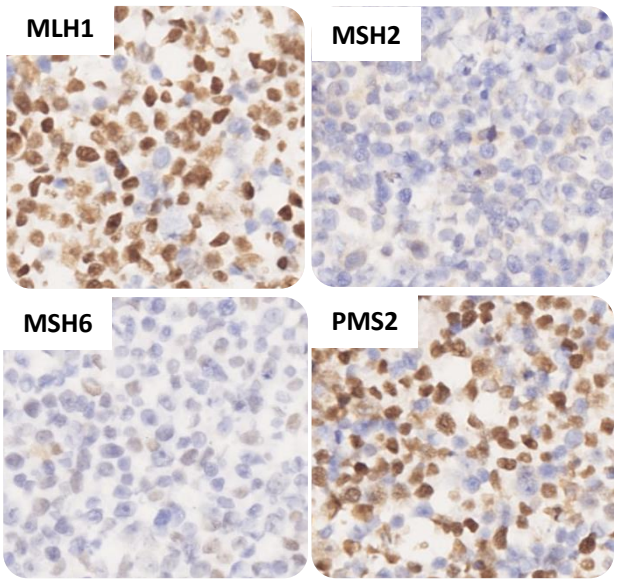
Roche/Ventana



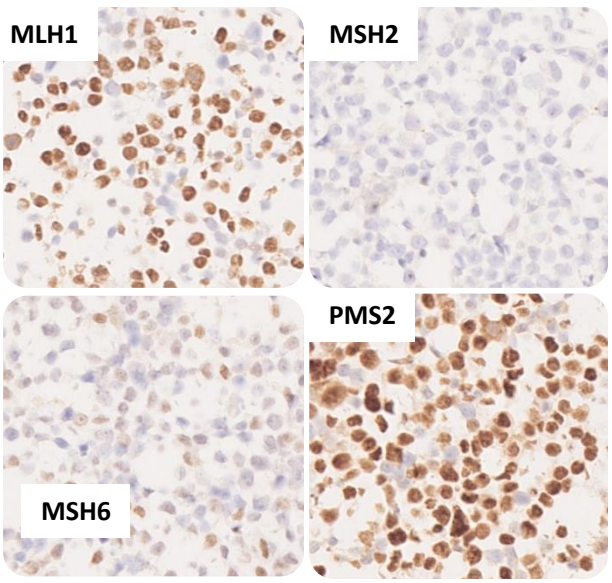
Cell line C is a colon adenocarcinoma cell line that carries a homozygous deletion of exons 3 to 8 in the *MSH2* gene[9]. This deletion leads to a truncated form of MSH2 protein and loss of nuclear expression.

Cell line C features as part of the MMR Analyte Control and the MSH2 Analyte Control, serving as a loss of expression control for MSH2.

Agilent



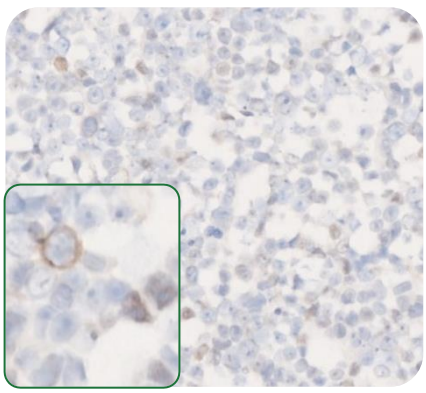
Leica Biosystems



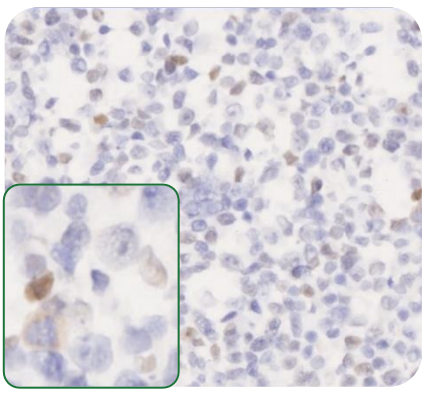
MMR Analyte Control Core C staining

MSH6 aberrant staining

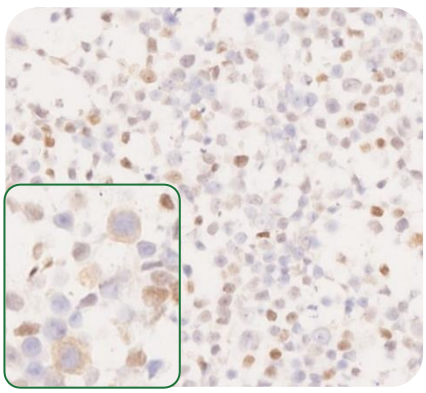
Cell line C should be used exclusively as an MSH2 loss of expression control. MSH6 staining of Cell line C reveals aberrant staining as seen below. These images show that at high magnification the nuclei of cells remain negative and staining is mostly localised in the cytoplasm. Therefore, the staining observed is likely due to MSH6 complexing with non-functional MSH2 protein located in the cytoplasm.



VENTANA anti-MSH6 (SP93) Rabbit Monoclonal Primary Antibody



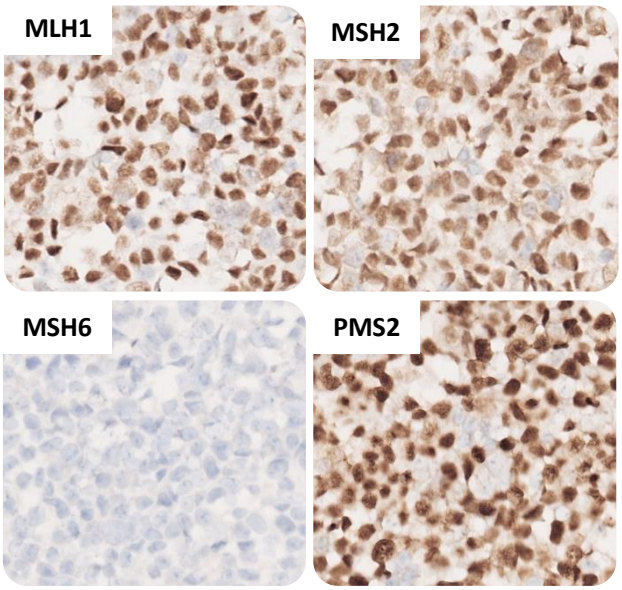
Agilent Dako anti-MSH6 (EP49) Rabbit Monoclonal Primary Antibody



Leica Biosystems anti-MSH6 (EP49) Rabbit Monoclonal Primary Antibody

MMR Analyte Control Core D staining

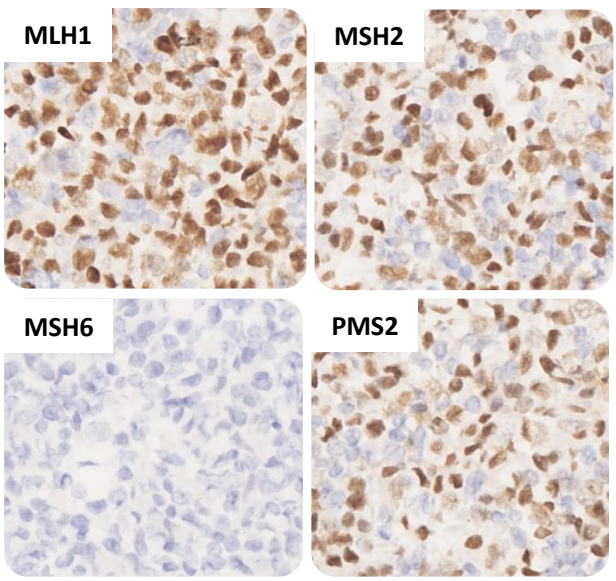
Roche/Ventana



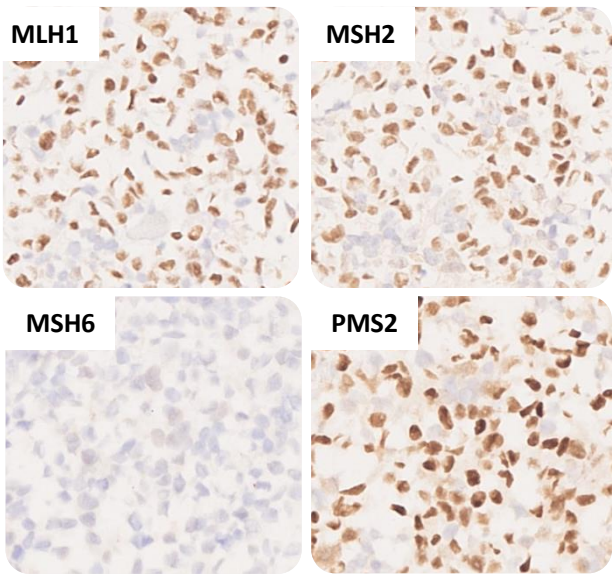
Cell Line D is a colon adenocarcinoma cell line. This cell line is known to harbour a 1 base pair deletion mutation in one allele of the *MSH6* gene and a sequence deletion/insertion involving 5 base pairs in the other allele[1]. This leads to the isolated loss of MSH6 protein expression.

Cell line D features as part of the MMR Analyte Control and the MSH6 Analyte Control, serving as a loss of expression control for both MSH6.

Agilent



Leica Biosystems



1. Boyer JC, Umar A, Risinger, JI, Lipford JR, Kane M, Yin S, Barrett JC, Kolodner RD, Kunkel TA. Microsatellite Instability, Mismatch Repair Deficiency, and Genetic Defects in Human Cancer Cell Lines.

MLH1/PMS2 Analyte Control

The **MLH1/PMS2 Analyte Control** is sold in two formats: as pre-prepared slides (Figure 3) or as a cell microarray (CMA) paraffin wax block (Figure 4).

Figure 3: Cell Line Control Slide

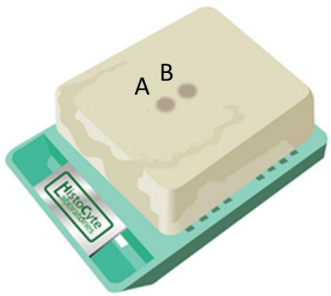


Figure 4: CMA block

Our CMA block provides the most cost effective solution for clinical histology laboratories and other high volume centers. They have been purposely designed to fit seamlessly into the work flow of the laboratory.

Our pre-prepared slides offer a ready-to-go alternative that saves time in preparation. These are ideal for one-off assessments, research laboratories and preliminary product trials.

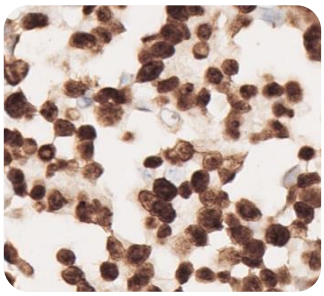
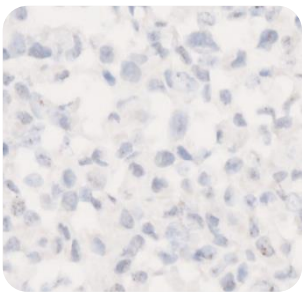
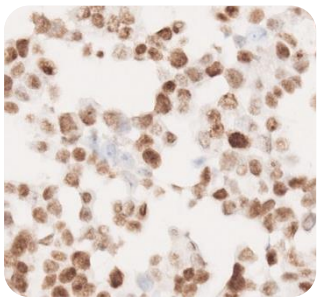
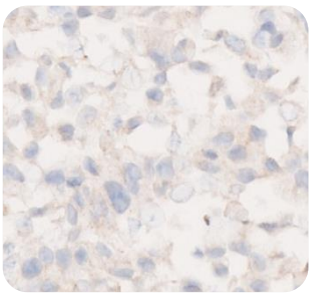
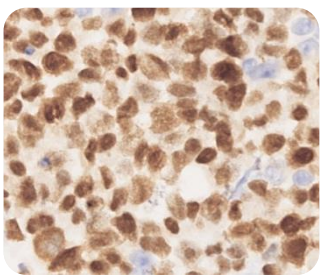
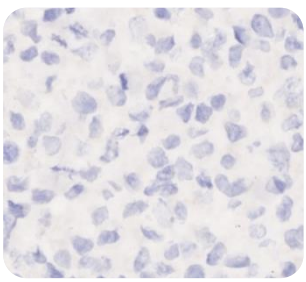
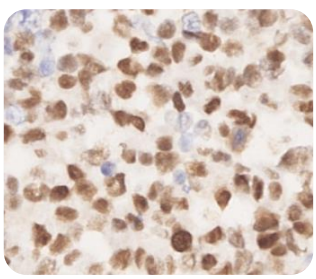
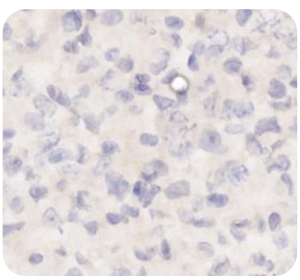
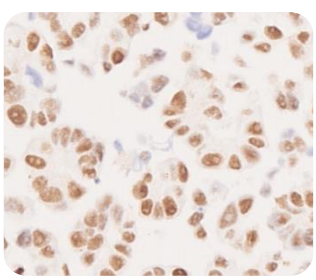
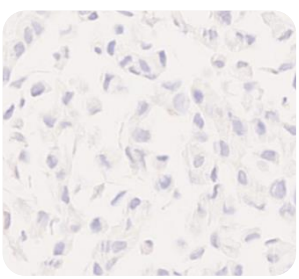
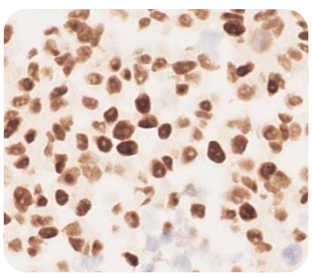
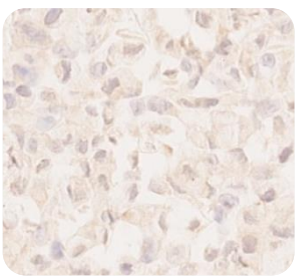
Product Name	Format	Code
MLH1/PMS2 Analyte Control	**Slide (2)**	**HCL044**
	Slide (5)	**HCL045**
	Block	**HCL046**

The expression patterns of the 2 cell lines for MLH1/PMS2:

Core	MLH1	PMS2
A	Intact	Intact
B	**Loss of expression**	**Loss of expression**

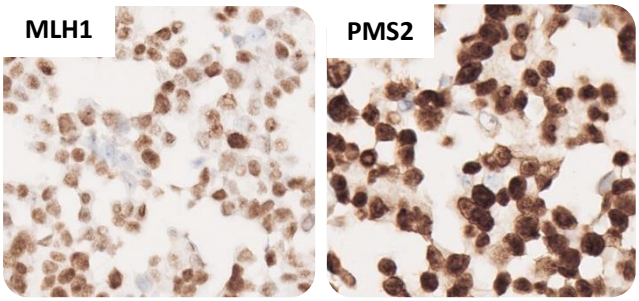
MLH1/PMS2 Analyte Control

Expected staining with commonly used assay for MLH1 and PMS2

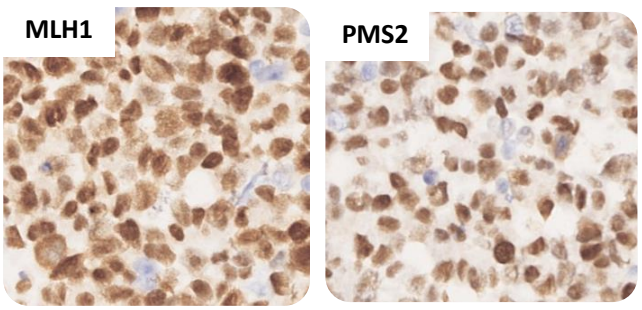
	Breast adenocarcinoma A	Prostate carcinoma B	
MLH1 — **VENTANA anti-MLH1 (M1)** Mouse Monoclonal Primary Antibody			**Roche Ventana**
PMS2 — **VENTANA anti-PMS2 (A16-4)** Mouse Monoclonal Primary Antibody			
MLH1 — **Agilent Dako anti-MLH1 (ES05)** Mouse Monoclonal Primary Antibody			**Agilent**
PMS2 — **Agilent Dako anti-PMS2 (EP51)** Mouse Monoclonal Primary Antibody			
MLH1 — **Leica Biosystems anti-MLH1 (ES05)** Mouse Monoclonal Primary Antibody			**Leica Biosystems**
PMS2 — **Leica Biosystems anti-PMS2 (EP51)** Mouse Monoclonal Primary Antibody			

MLH1/PMS2 Analyte Control
Core A staining

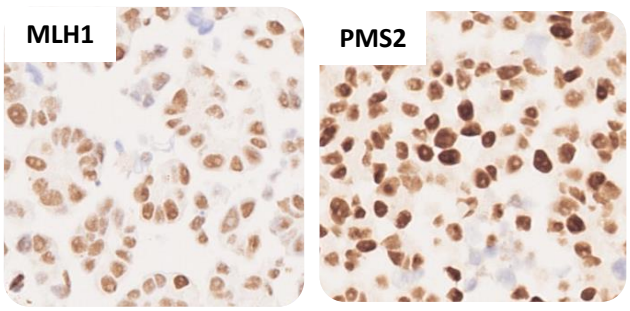
Roche/Ventana



Agilent



Leica Biosystems

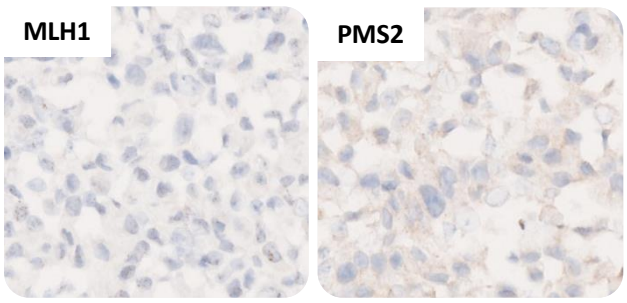


Cell line A is a breast adenocarcinoma cell line that carries no specific MMR mutations and is therefore MMR proficient and multi satellite stable (MSS).

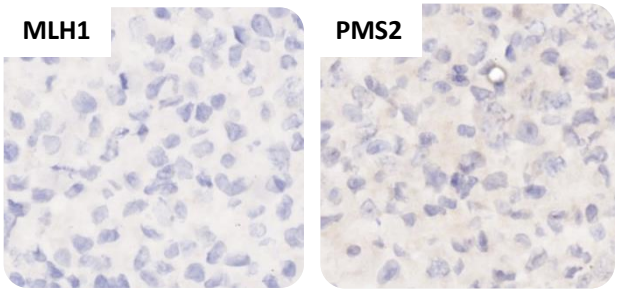
This cell line is used as a control of intact expression (unequivocal nuclear staining, of at least 50% of cells) across all of the MMR products for all four proteins.

MLH1/PMS2 Analyte Control
Core B staining

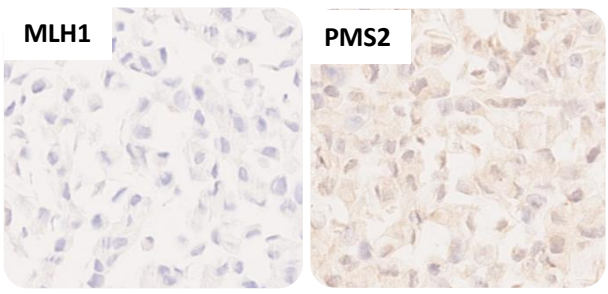
Roche/Ventana



Agilent



Leica Biosystems



Cell Line B is a prostate carcinoma cell line. This cell line has a splice site mutation between exon 1 and exon 2 of the *MLH1* gene which causes the deletion of 5 coding nucleotides[1]. This nonsense mutation results in a premature stop codon in the transcribed mRNA and in a shortened, truncated, non-functional MLH1 protein product. PMS2 expression is also lost as PMS2 can no longer complex with MLH1 to form a heterodimer.

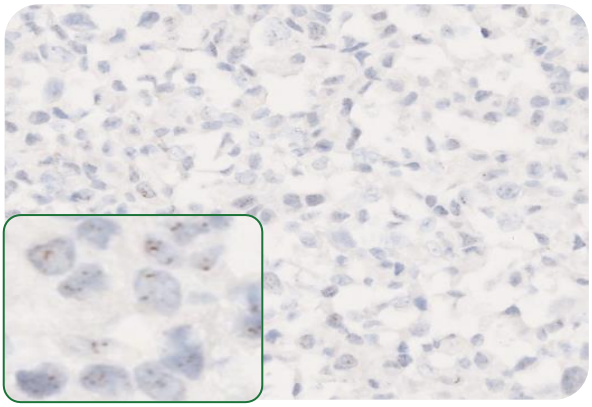
Cell line B features as part of the MMR Analyte Control and the MLH1/PMS2 Analyte Control, serving as a loss of expression control for both MLH1 and PMS2.

1. Chen Y, et al . Defects of DNA mismatch repair in human prostate cancer. *Molecular biology and genetics*. 2001;61:4112-4121.

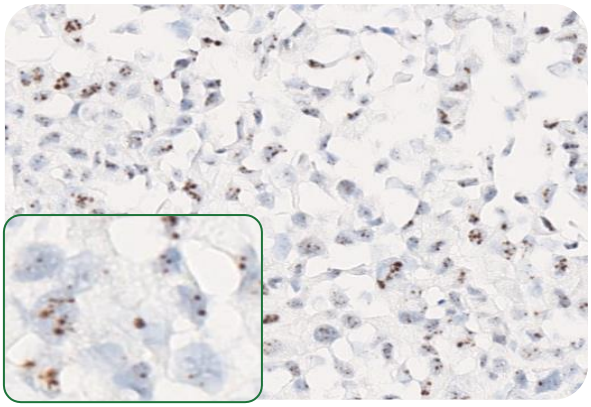
MLH1/PMS2 Analyte Control
Core B staining

MLH1 nuclear punctate staining

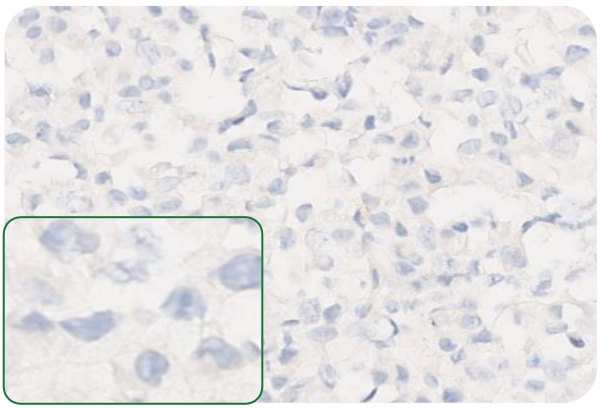
Laboratories have observed distinct MLH1 punctate nuclear staining, which is mostly associated with the MLH1 M1 (Roche) and G168-1129 (Cell Marque) clones[1]. The intensity of this punctate nuclear staining is increased when amplification is used as part of the IHC staining protocol (Figure X). This staining pattern is not replicated when using the MLH1 ES05 clone. This could be due to both the M1 and G168-1129 clones being full length recombinant proteins which are able to partially recognise truncated forms of non-functional MLH1 resulting in punctate nuclear staining.



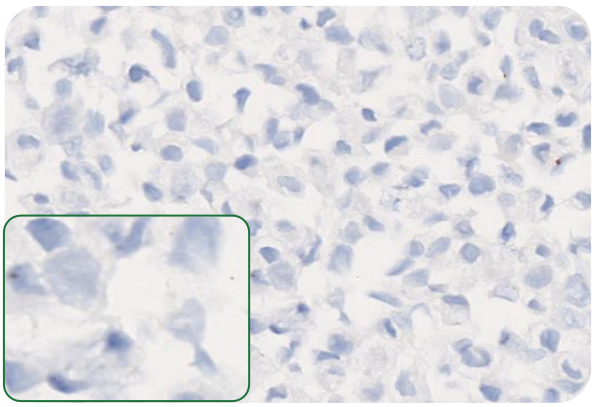
VENTANA anti-MLH1 (M1)



VENTANA anti-MLH1 (M1) + amplification



Leica Biosystems anti-MLH1 (ES05)



Leica Biosystems anti-MLH1 + amplification (ES05)

1. Dasgupta S, et al. Granular dot-like staining with MLH1 immunohistochemistry is a clone-dependent artefact. *Pathology, research and practice*. 2020;216:152581.

MSH2 Analyte Control

The **MSH2 Analyte Control** is sold in two formats: as pre-prepared slides (Figure 5) or as a cell microarray (CMA) paraffin wax block (Figure 6).

Figure 5: Cell Line Control Slide

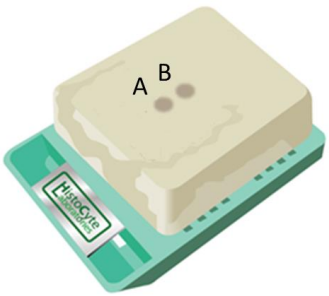


Figure 6: CMA block

Our CMA block provides the most cost effective solution for clinical histology laboratories and other high volume centers. They have been purposely designed to fit seamlessly into the work flow of the laboratory.

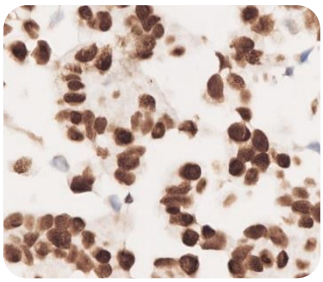
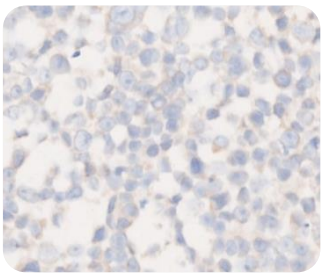
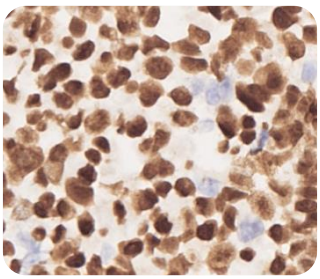
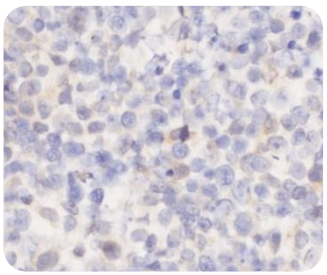
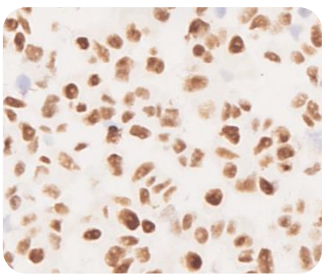
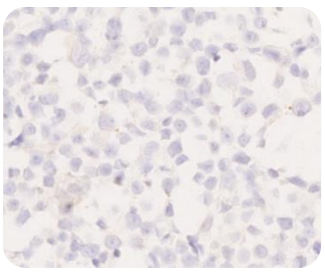
Our pre-prepared slides offer a ready-to-go alternative that saves time in preparation. These are ideal for one-off assessments, research laboratories and preliminary product trials.

Product Name	Format	Code
MSH2 Analyte Control	Slide (2)	HCL047
	Slide (5)	HCL048
	Block	HCL049

The expression patterns of the 2 cell lines for MSH2 are :

Core	MSH2
A	Intact
B	**Loss of expression**

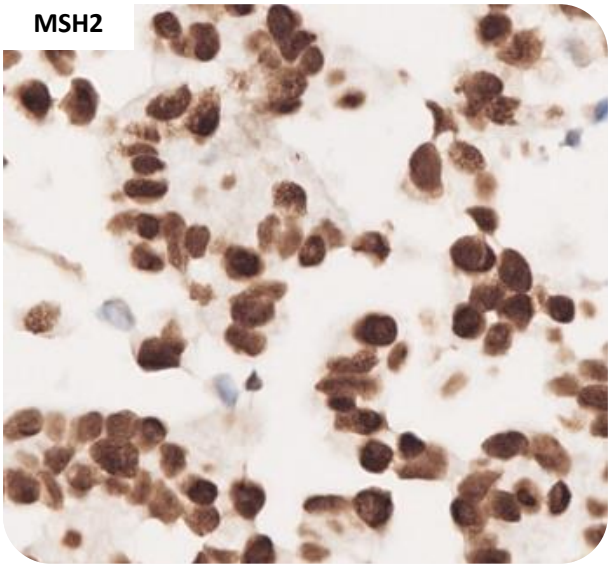
MSH2 Analyte Control

	Breast adenocarcinoma A	Colon adenocarcinoma B
MSH2 **VENTANA anti-MSH2 (G219-1129)** Mouse Monoclonal Primary Antibody		
MSH2 **Agilent Dako anti-MSH2 (FE11)** Mouse Monoclonal Primary Antibody		
MSH2 **Leica Biosystems anti-MSH2 (79H11)** Mouse Monoclonal Primary Antibody		

Expected staining with commonly used assay for MSH2

MSH2 Analyte Control
Core A staining

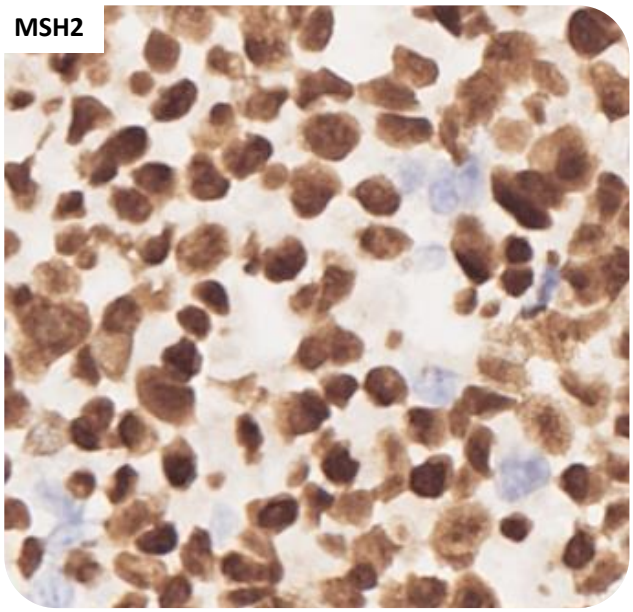
Roche/Ventana



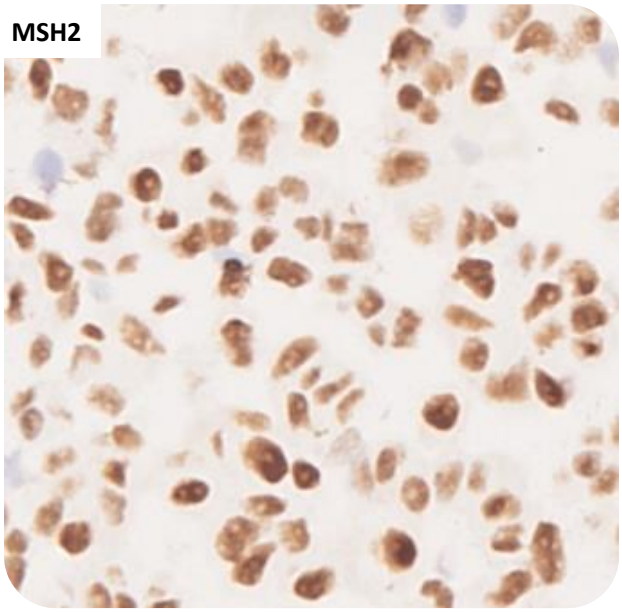
Cell line A is a breast adenocarcinoma cell line that carries no specific MMR mutations and is therefore MMR proficient and multi satellite stable (MSS).

This cell line is used as a control of intact expression (unequivocal nuclear staining, of at least 50% of cells) across all of the MMR products for all four proteins.

Agilent

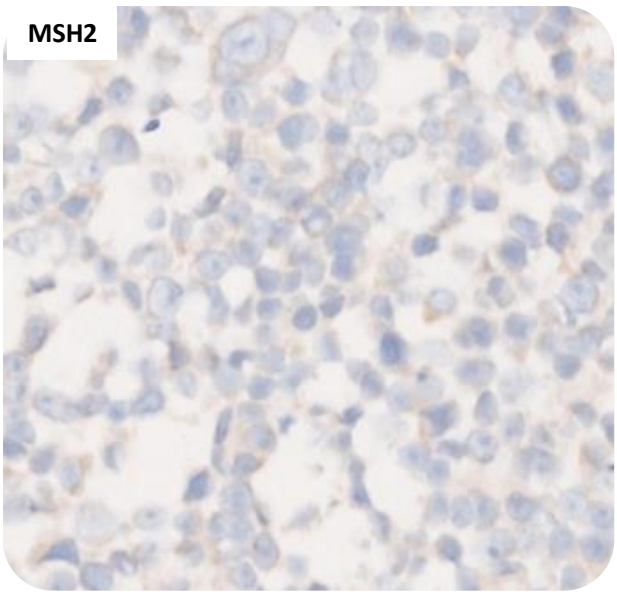


Leica Biosystems



MSH2 Analyte Control
Core B staining

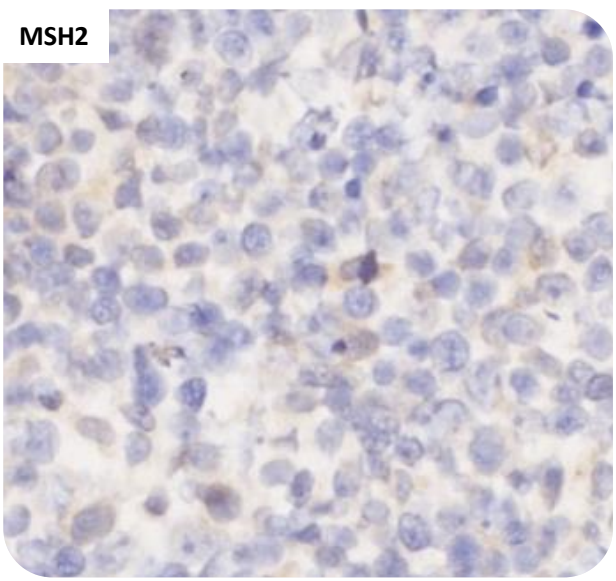
Roche/Ventana



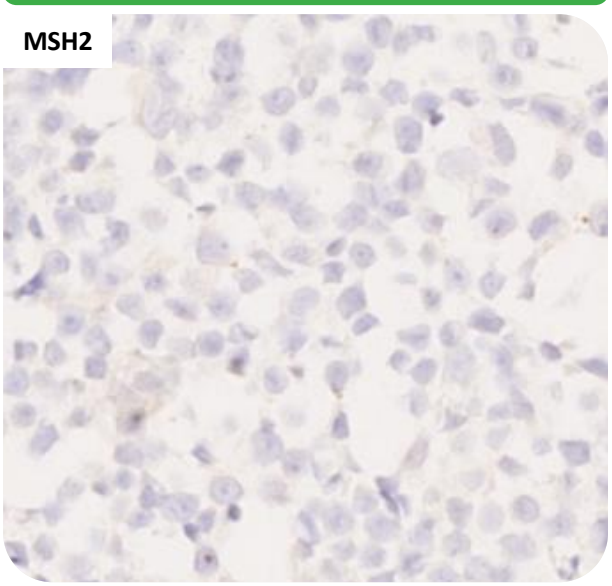
Cell line B is a colon adenocarcinoma cell line that carries a homozygous deletion of exons 3 to 8 in the *MSH2* gene[9]. This deletion leads to a truncated form of MSH2 protein and loss of nuclear expression.

Cell line C features as part of the MMR Analyte Control and the MSH2 Analyte Control, serving as a loss of expression control for MSH2.

Agilent



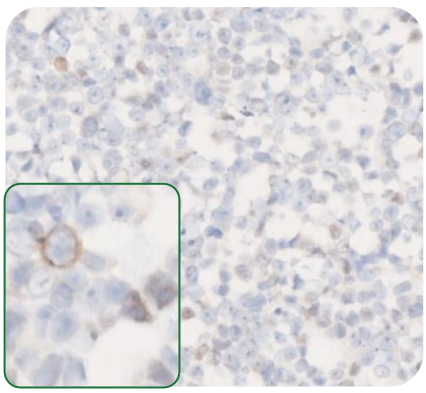
Leica Biosystems



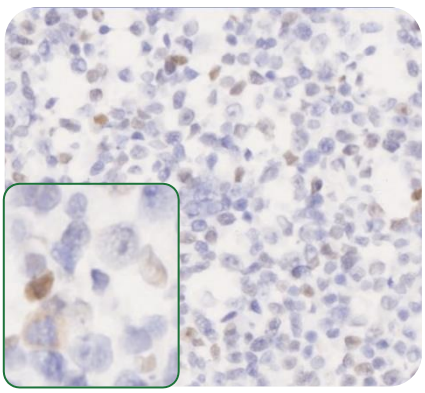
MSH2 Analyte Control
Core B staining

MSH6 aberrant staining

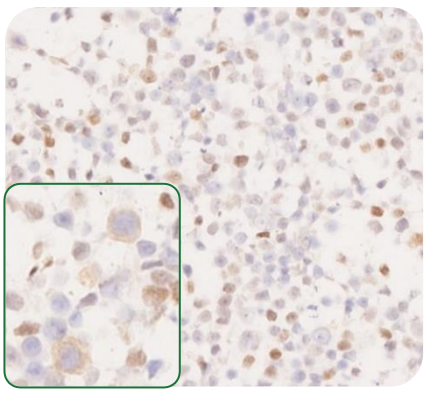
Cell line B should be used exclusively as an MSH2 loss of expression control. MSH6 staining of Cell line B reveals aberrant staining as seen below. These images show that at high magnification the nuclei of cells remain negative and staining is mostly localised in the cytoplasm. Therefore, the staining observed is likely due to MSH6 complexing with non-functional MSH2 protein located in the cytoplasm.



VENTANA anti-MSH6 (SP93) Rabbit Monoclonal Primary Antibody



Agilent Dako anti-MSH6 (EP49) Rabbit Monoclonal Primary Antibody



Leica Biosystems anti-MSH6 (EP49) Rabbit Monoclonal Primary Antibody

MSH6 Analyte Control

The **MSH6 Analyte Control** is sold in two formats: as pre-prepared slides (Figure 7) or as a cell microarray (CMA) paraffin wax block (Figure 8).

Figure 7: Cell Line Control Slide

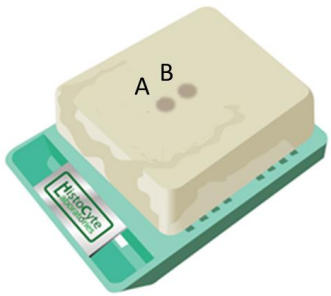


Figure 8: CMA block

Our CMA block provides the most cost effective solution for clinical histology laboratories and other high volume centers. They have been purposely designed to fit seamlessly into the work flow of the laboratory.

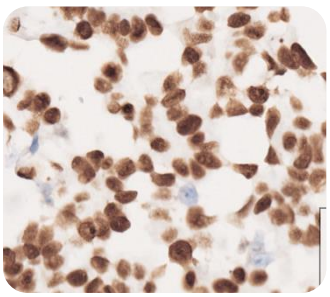
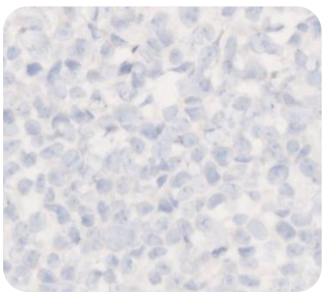
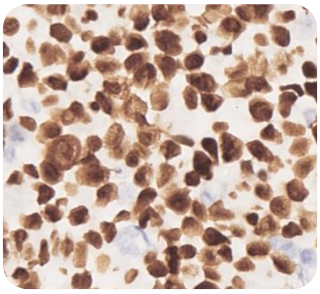
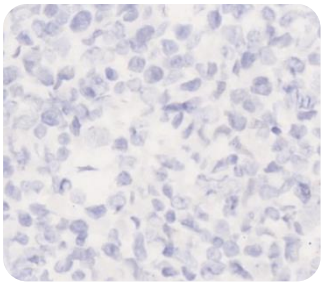
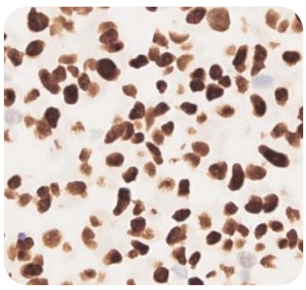
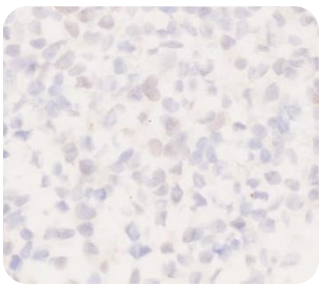
Our pre-prepared slides offer a ready-to-go alternative that saves time in preparation. These are ideal for one-off assessments, research laboratories and preliminary product trials.

Product Name	Format	Code
MSH6 Analyte Control	Slide (2)	HCL050
	Slide (5)	HCL051
	Block	HCL052

The expression patterns of the 2 cell lines for MSH6 are:

Core	MSH6
A	Intact
B	Loss of expression

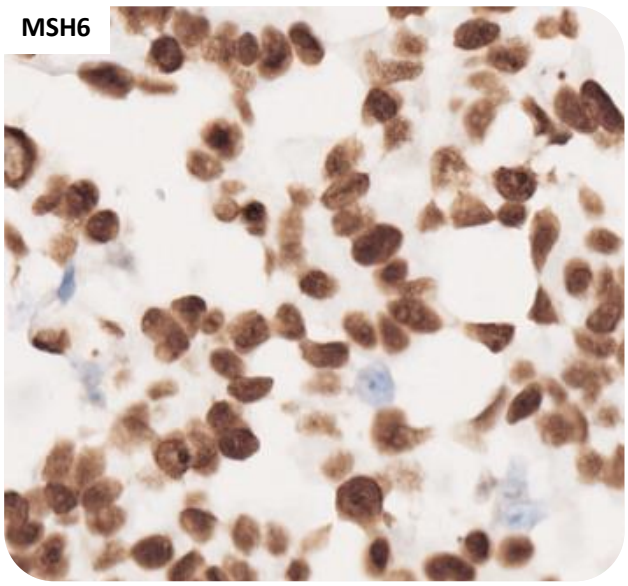
MSH6 Analyte Control

	Breast adenocarcinoma A	Colon adenocarcinoma B
MSH6 **VENTANA anti-MSH6 (SP93)** Rabbit Monoclonal Primary Antibody		
MSH6 **Agilent Dako anti-MSH6 (EP49)** Rabbit Monoclonal Primary Antibody		
MSH6 **Leica Biosystems anti-MSH6 (EP49)** Rabbit Monoclonal Primary Antibody		

Expected staining with commonly used assay for MSH6

MSH6 Analyte Control
Core A staining

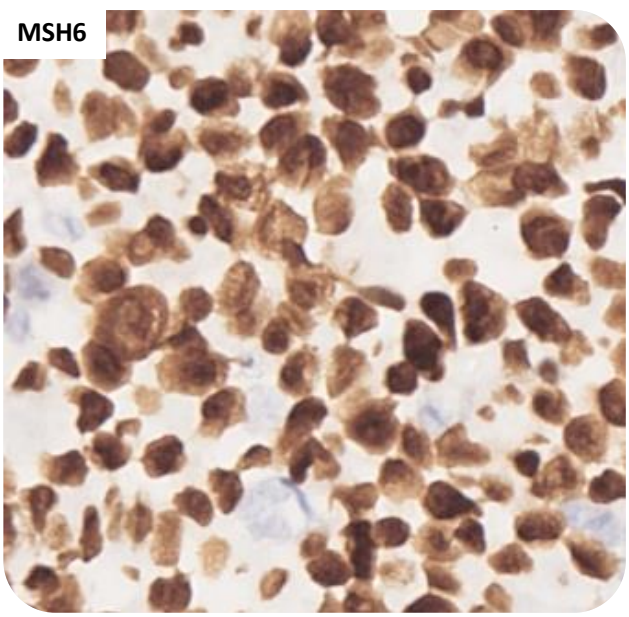
Roche/Ventana



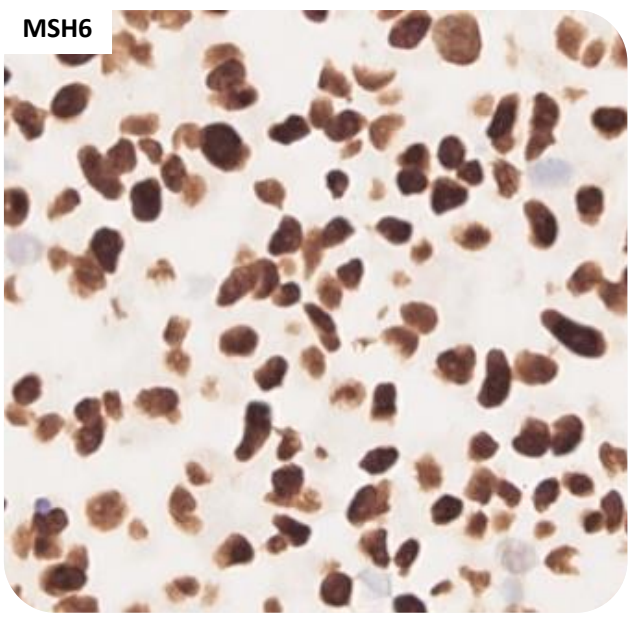
Cell line A is a breast adenocarcinoma cell line that carries no specific MMR mutations and is therefore MMR proficient and multi satellite stable (MSS).

This cell line is used as a control of intact expression (unequivocal nuclear staining, of at least 50% of cells) across all of the MMR products for all four proteins.

Agilent

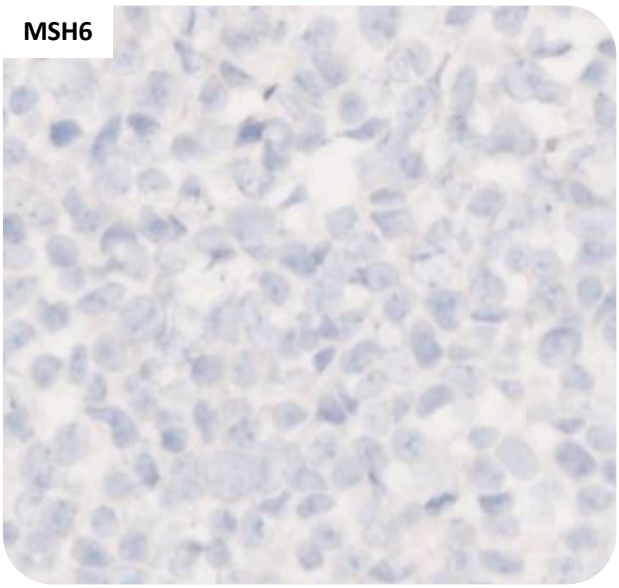


Leica Biosystems



MSH6 Analyte Control
Core B staining

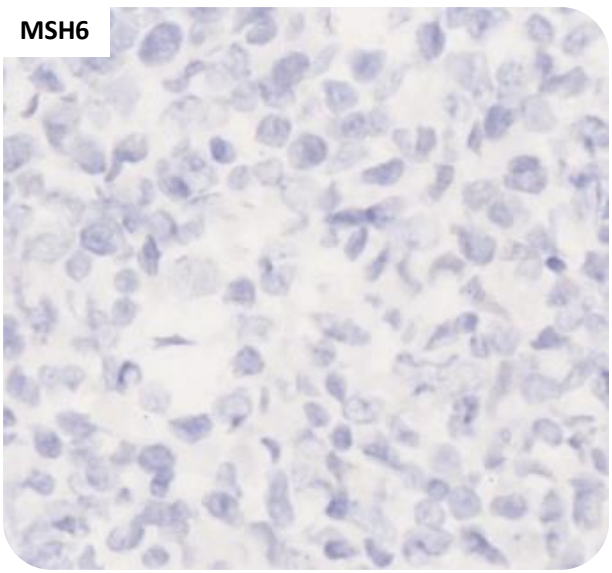
Roche/Ventana



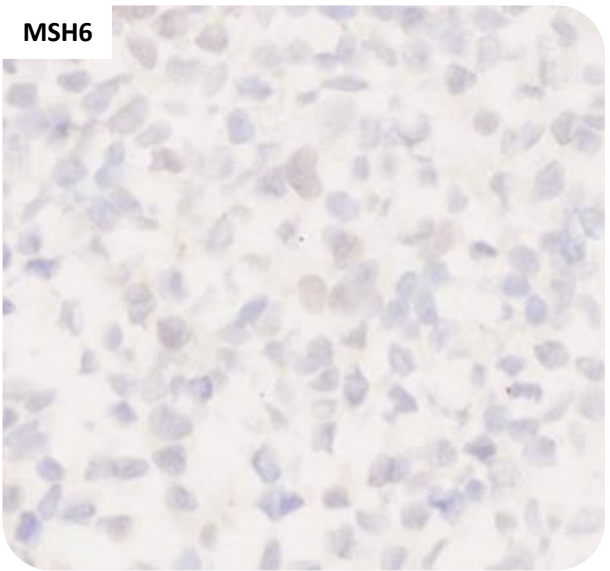
Cell Line B is a colon adenocarcinoma cell line. This cell line is known to harbour a 1 base pair deletion mutation in one allele of the *MSH6* gene and a sequence deletion/insertion involving 5 base pairs in the other allele[1]. This leads to the isolated loss of MSH6 protein expression.

Cell line D features as part of the MMR Analyte Control and the MSH6 Analyte Control, serving as a loss of expression control for both MSH6.

Agilent



Leica Biosystems



1. Boyer JC et al. Microsatellite Instability, Mismatch Repair Deficiency, and Genetic Defects in Human Cancer Cell Lines.

HistoCyte Laboratories

Quality in Control

Also Available From HistoCyte Laboratories Ltd

Product Name	Format	Code
HPV/p16 Analyte Control[DR] (Four cores: negative and three positive with dynamic range of HPV gene copies and p16 expression)	Slide(2)	HCL001
	Slide(5)	HCL002
	Block	HCL003
HPV/p16 Analyte Control (Three cores: negative and two positive for p16 and HPV gene copies)	Slide(2)	HCL004
	Slide(5)	HCL005
	Block	HCL006
ALK-Lung Analyte Control (Two cores: negative and a positive for the EML4-ALK translocation)	Slide(2)	HCL007
	Slide(5)	HCL008
	Block	HCL009
ALK-Lymphoma Analyte Control (Two cores: negative and a positive for the NPM-ALK translocation)	Slide(2)	HCL010
	Slide(5)	HCL011
	Block	HCL012
Breast Analyte Control (Two cores: negative and positive for HER2, ER and PR)	Slide(2)	HCL013
	Slide(5)	HCL014
	Block	HCL015
Breast Analyte Control[DR] (Five cores: variable levels of expression of HER2, ER and PR. Including negative control)	Slide(2)	HCL016
	Slide(5)	HCL017
	Block	HCL018
PD-L1 Analyte Control[DR] (Four cores: negative, low, intermediate and high levels of expression of PD-L1)	Slide(2)	HCL019
	Slide(5)	HCL020
	Block	HCL021
ROS1 Analyte Control (Two cores: negative and positive for ROS1 translocation SLC34A2-ROS1 and high expression of fusion protein)	Slide(2)	HCL022
	Slide(5)	HCL023
	Block	HCL024
ROS1 Analyte Control[DR] (Three cores: negative, FIG-ROS1 (very low fusion protein), SLC34A2-ROS1 (high fusion protein)	Slide(2)	HCL035
	Slide(5)	HCL036
	Block	HCL037
HER2 Analyte Control[DR] (Four cores: 0, 1+ (both non-amplified), 2+ (equivocal) and 3+ (amplified))	Slide(2)	HCL026
	Slide(5)	HCL027
	Block	HCL028
Estrogen Receptor Analyte Control[DR] (Four cores: negative, low, intermediate and high)	Slide(2)	HCL029
	Slide(5)	HCL030
	Block	HCL031
Progesterone Receptor Analyte Control[DR] (Four cores: negative, low, intermediate and high)	Slide(2)	HCL032
	Slide(5)	HCL033
	Block	HCL034
NTRK Analyte Control (Two cores: negative and positive for WT TrkA protein)	Slide(2)	HCL038
	Slide(5)	HCL039
	Block	HCL040
Mismatch Repair Analyte Control[DR] (Four cores, intact expression for MLH1/PMS/MSH2/MSH6, loss of exprssion for MLH1/PMS2, loss of expression for MSH2, loss of expression for MSH2/MSH6)	Slide(2)	HCL041
	Slide(5)	HCL042
	Block	HCL043
MLH1/PMS2 Analyte Control (Two cores, one with MLH1 deletion and loss of expression of MLH1 and PMS2, one with intact expression for MLH1 and PMS2)	Slide(2)	HCL044
	Slide(5)	HCL045
	Block	HCL046
MSH2 Anlayte Control (Two cores, one with loss of MSH2 expression, one with intact expression of MSH2)	Slide(2)	HCL047
	Slide(5)	HCL048
	Block	HCL049
MSH6 Anlayte Control (Two cores, one with loss of MSH6 expression, one with intact expression of MSH6)	Slide(2)	HCL050
	Slide(5)	HCL051
	Block	HCL052

HistoCyte Laboratories
Quality in Control

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