Case Presentation:
Defective Mismatch Repair Gene

2021.04.21

교실집담회

서울성모병원 병리과

김수연

49/F

Chief complaint: Vaginal bleeding

- Sono: Endometrial thickening

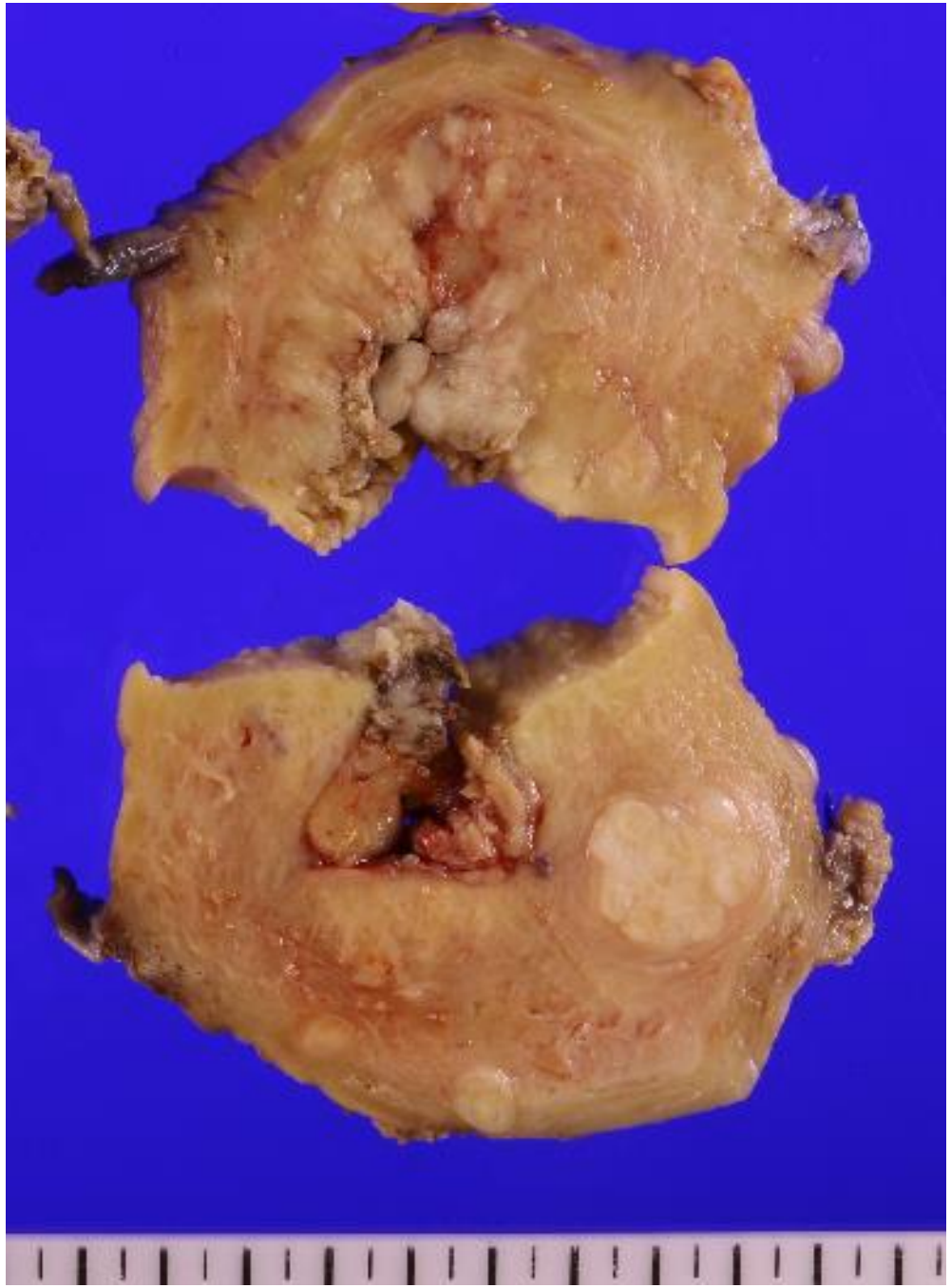
  5.7*3.8cm sized mixed echoic lesion within EM cavity (+)

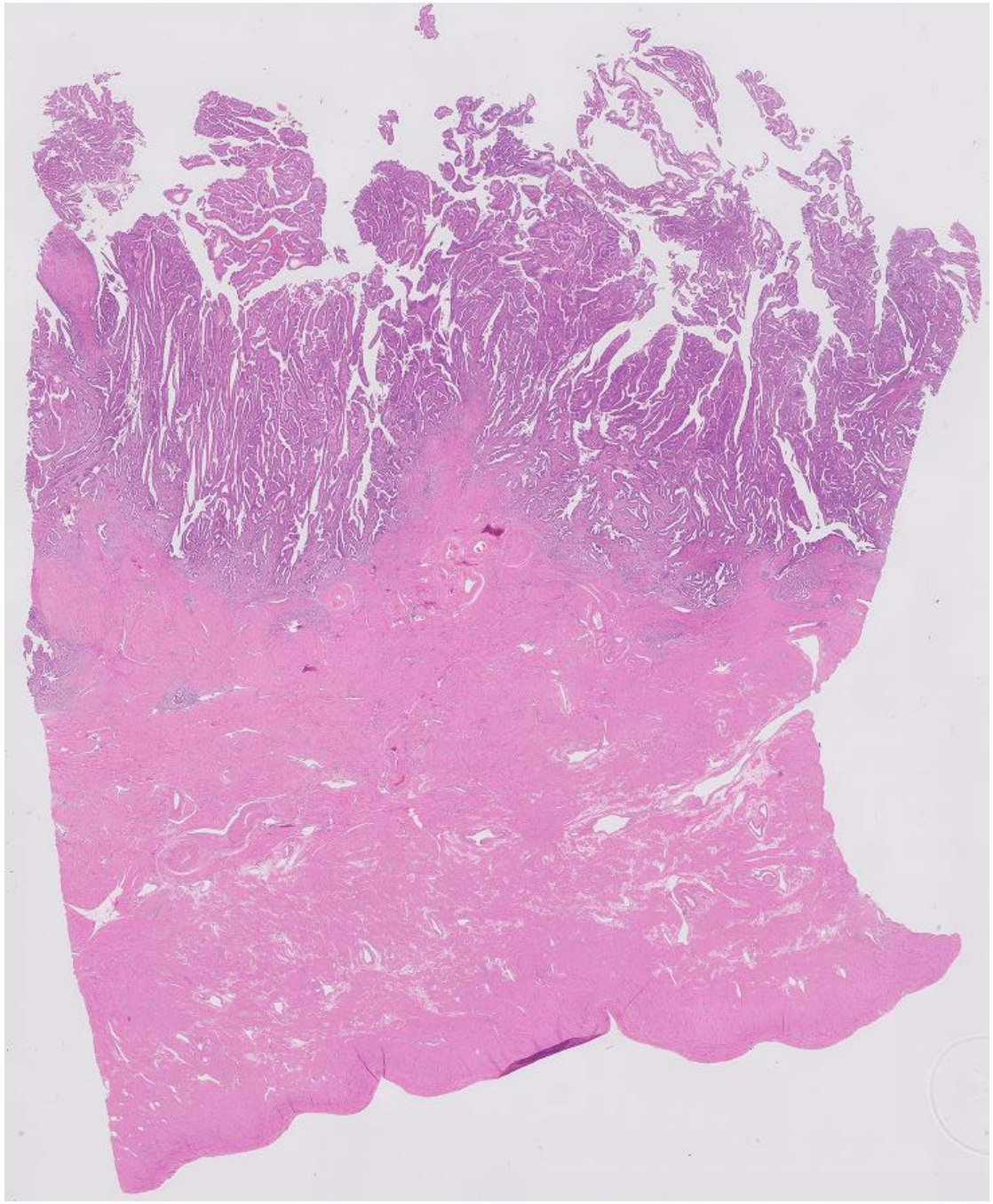
- MRI

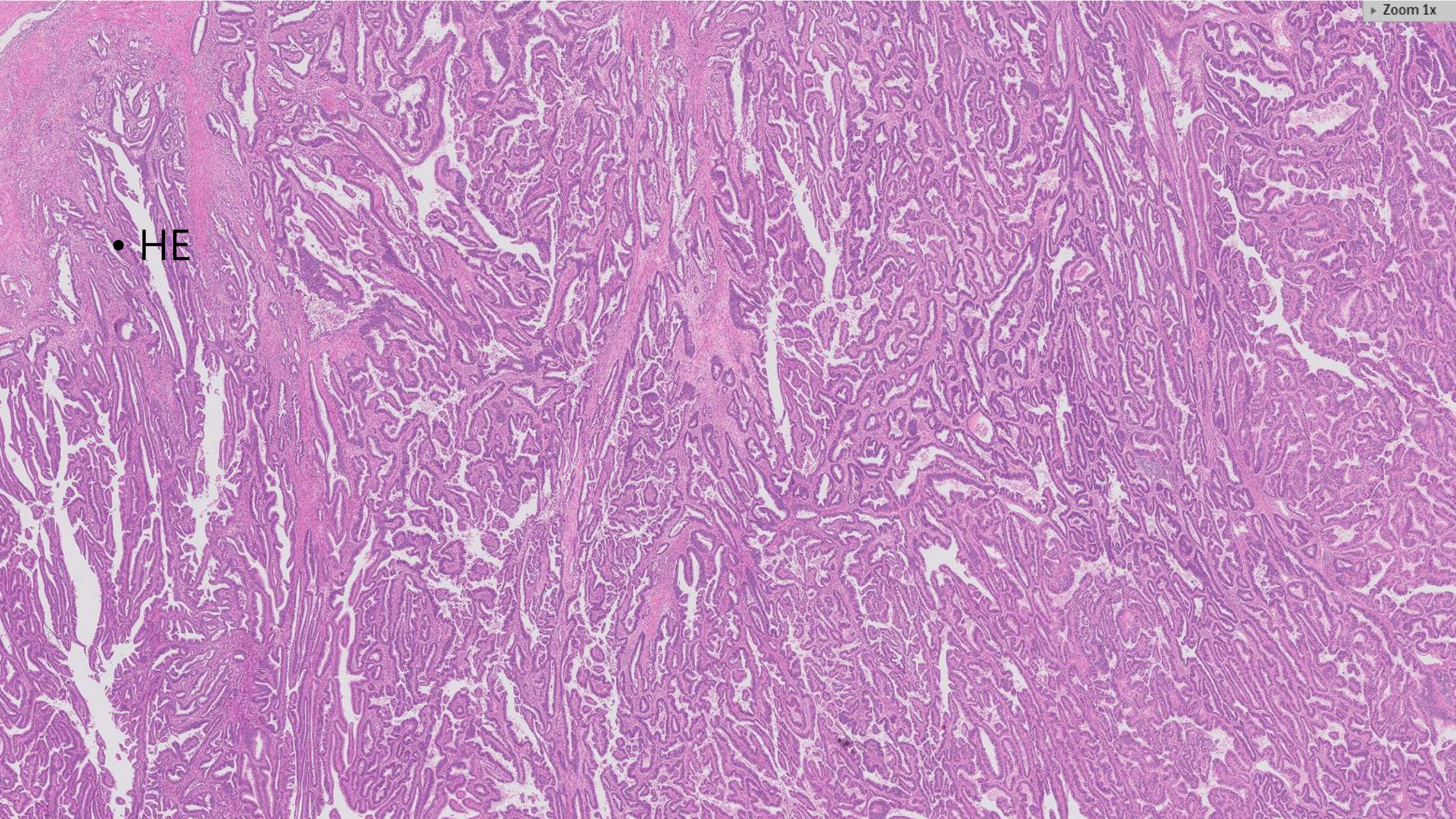
  1. Endometrial carcinoma with superficial or one half myometrial invasion.
  2. About **8.2x5.6x6.3cm sized** mixed solid and cystic mass in **the left adnexa**

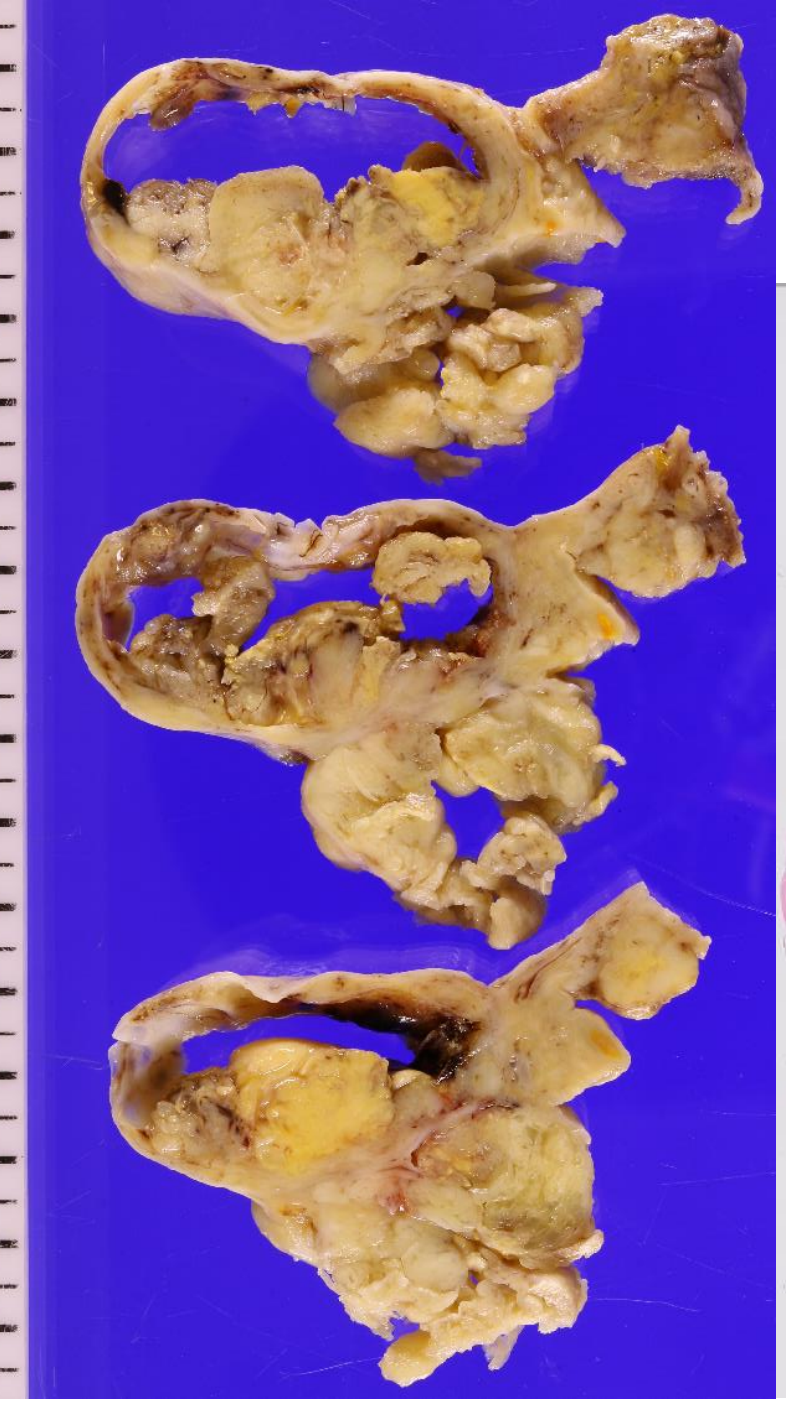
Past history

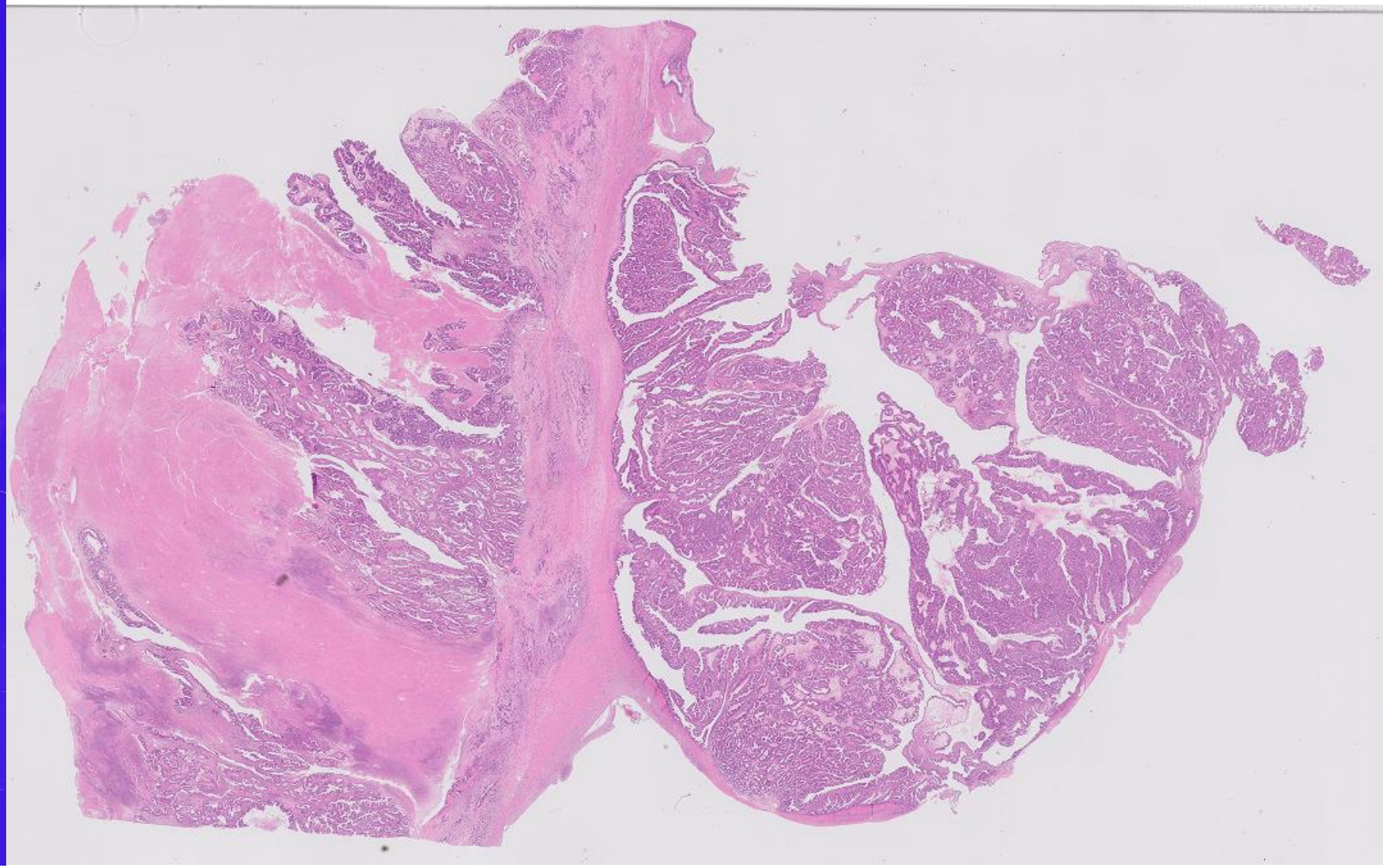
- Colon cancer – endoscopic removal (2009, CR)






Zoom 1x
• HE





S20-016401
F/49 (34838056) Endometrium&Ovary
Endometrioid carcinoma

[**DIAGNOSIS**]

Uterus, both adnexae and lymph node, total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node dissection;

Endometrioid carcinoma, involving uterine body and left ovary.

[**COMMENT**]

난소의 종양은 자궁내막과 같은 Endometrioid carcinoma 인 점과 nodular infiltrative pattern, hilum 침범은 전이를 시사합니다.

Endometrium 과 난소 둘 다 early stage 인 점과 unilateral ovarian mass 는 **double primary 를 시사**합니다.

Clinicopathologic correlation 해 주십시오.

MSI test

[검사방법]

Melting Array-mediated multiplex real-time PCR (U-TOP™ MSI Detection Kit)

[검사결과]

MSI (microsatellite instability) 분석결과: **MSS (microsatellite stable)**

BAT-26: **Negative**

NR-24: **Negative**

NR-21: **Negative**

NR-27: **Negative**

BAT-25: **Negative**

NGS

DNA and RNA extraction	관련병리번호	Key block	Tumor cell percentage	Organ	Tumor type	Pathological diagnosis
FFPE tissue	S20-016401	# 2-2	60 %	Uterus (Excision)	Endometrial Cancer	Endometrioid carcinoma

II. 검사결과

1. Clinically significant biomarkers

(1) Mutation

Gene	Amino acid change	Nucleotide change	Variant allele frequency	ID	Tier
MSH6	p.Glu1272Ter	c.3814G>T	42.31 %		II

2. Prevalent cancer biomarkers of unknown significance

(1) Mutation

Gene	Amino acid change	Nucleotide change	Variant allele frequency	ID	Tier
ERBB2	p.Val842Ile	c.2524G>A	38.95 %	COSM14065	II
POLE	p.Pro436Thr	c.1306C>A	39.49 %		II
PTEN	p.Ala126Thr	c.376G>A	38.94 %	COSM5051	II
PTEN	p.Arg130Gln	c.389G>A	42.60 %	COSM5033	II
PIK3CA	p.Glu81Lys	c.241G>A	38.57 %	COSM27502	II
PIK3CA	p.Arg93Gln	c.278G>A	42.07 %	COSM86041	II
MSH6	p.Glu1272Ter	c.3814G>T	42.31 %		II
ARID1A	p.Arg1446Ter	c.4336C>T	39.56 %		II
FBXW7	p.Arg465Cys	c.1393C>T	40.25 %	COSM22932	II
FLT3	p.Ala627Thr	c.1879G>A	37.67 %		II
TP53	p.Met237Ile	c.711G>A	40.99 %	COSM10834	II
NOTCH3	p.Gln2310fs	c.6924delG	58.42 %		
NOTCH3	p.Gln2310fs	c.6924_6930delGCCCCAG insCCCCAT	41.48 %		
CTNNB1	p.Asp32Asn	c.94G>A	7.10 %	COSM5672	

NGS

DNA and RNA extraction	관련병리번호	Key block	Tumor cell percentage	Organ	Tumor type	Pathological diagnosis
FFPE tissue	S20-016401	# 2-2	60 %	Uterus (Excision)	Endometrial Cancer	Endometrioid carcinoma

II. 검사결과

1. Clinically significant biomarkers

(1) Mutation

Gene	Amino acid change	Nucleotide change	Variant allele frequency	ID	Tier
MSH6	p.Glu1272Ter	c.3814G>T	42.31 %		II

[검사방법]

Melting Array-mediated multiplex real-time PCR (U-TOP™ MSI Detection Kit)

[검사결과]

MSI (microsatellite instability) 분석결과

: **MSS (microsatellite stable)**

BAT-26: **Negative**

NR-24: **Negative**

NR-21: **Negative**

NR-27: **Negative**

BAT-25: **Negative**

Detection of defective MMR (dMMR)

- IHC
- MSI
- Sequencing (gold standard)
  - NGS

Microsatellite Instability (MSI) Test

MeltingArray™ 기술 기반의 multiplex real-time PCR

NR21, NR24, NR27, BAT25, BAT26

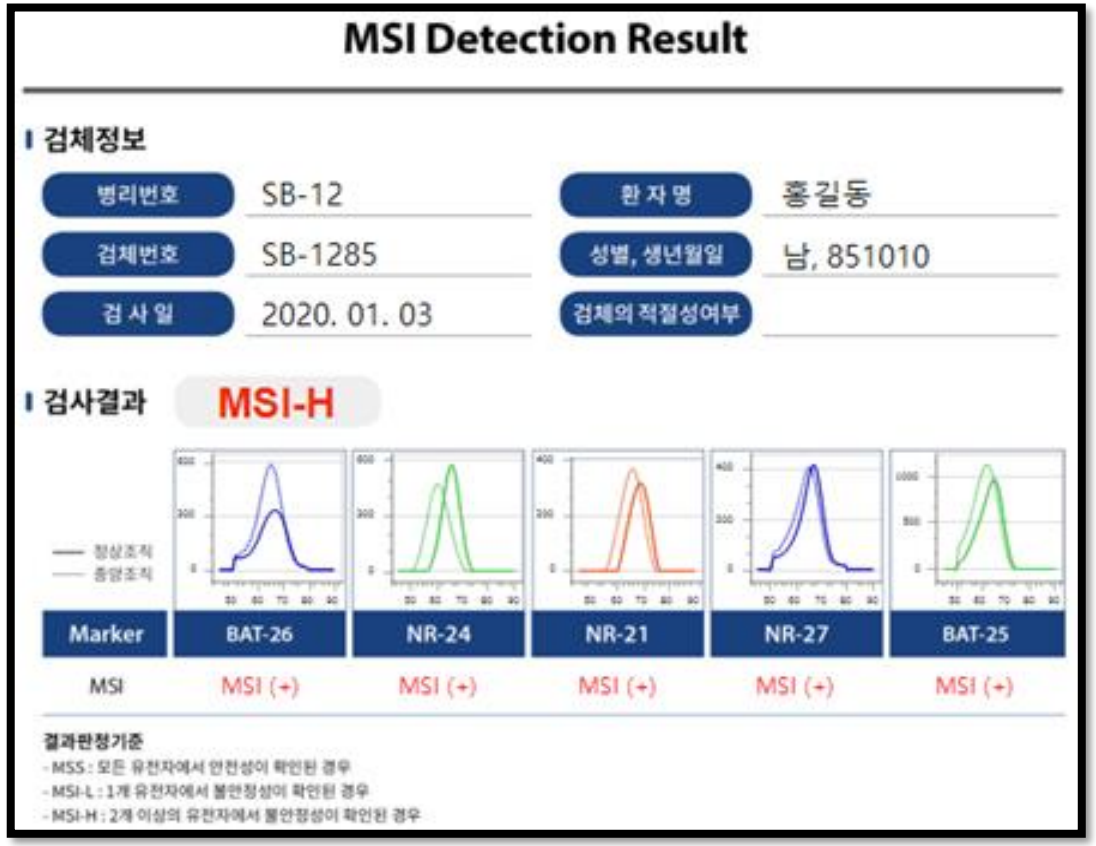
; dsDNA –(melt)→ ssDNA in ≥50%: **Tm**

Threshold

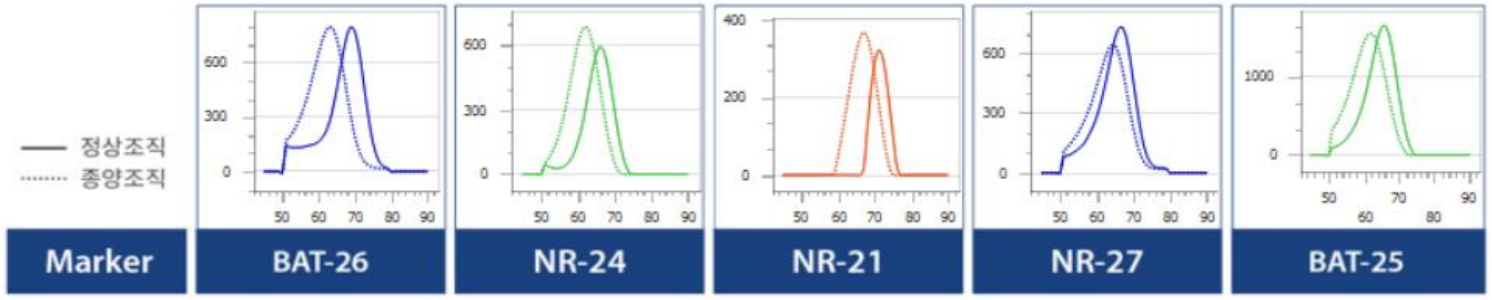
- 3°C

Interpretation

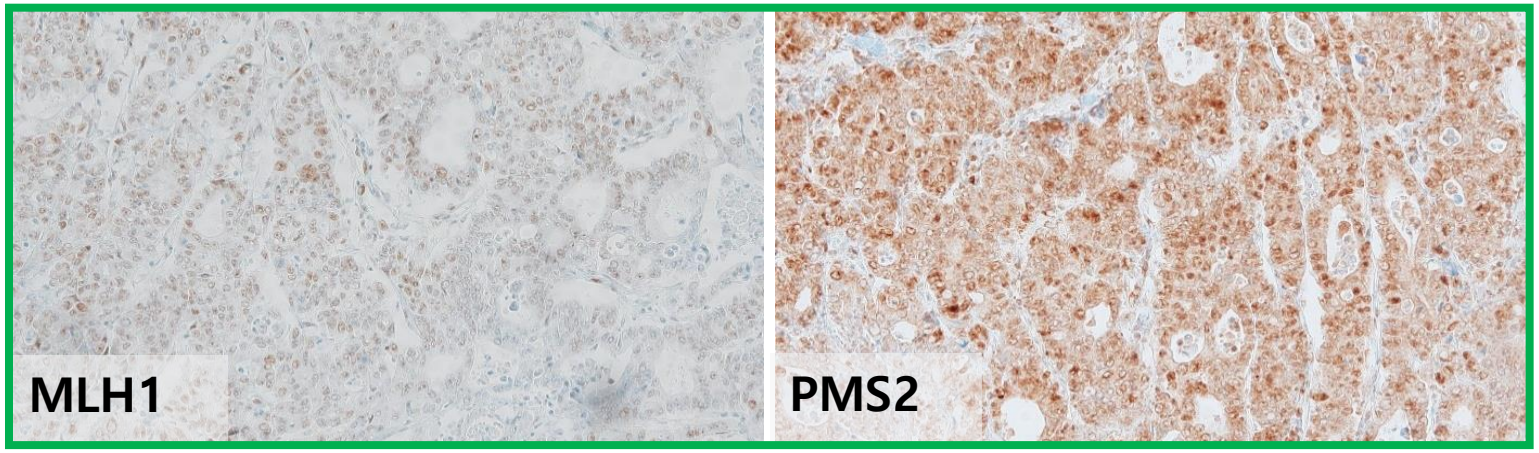
- ≥2 markers instability → MSI-H
- 1 marker instability → MSI-L
- 0 marker instability → MSS

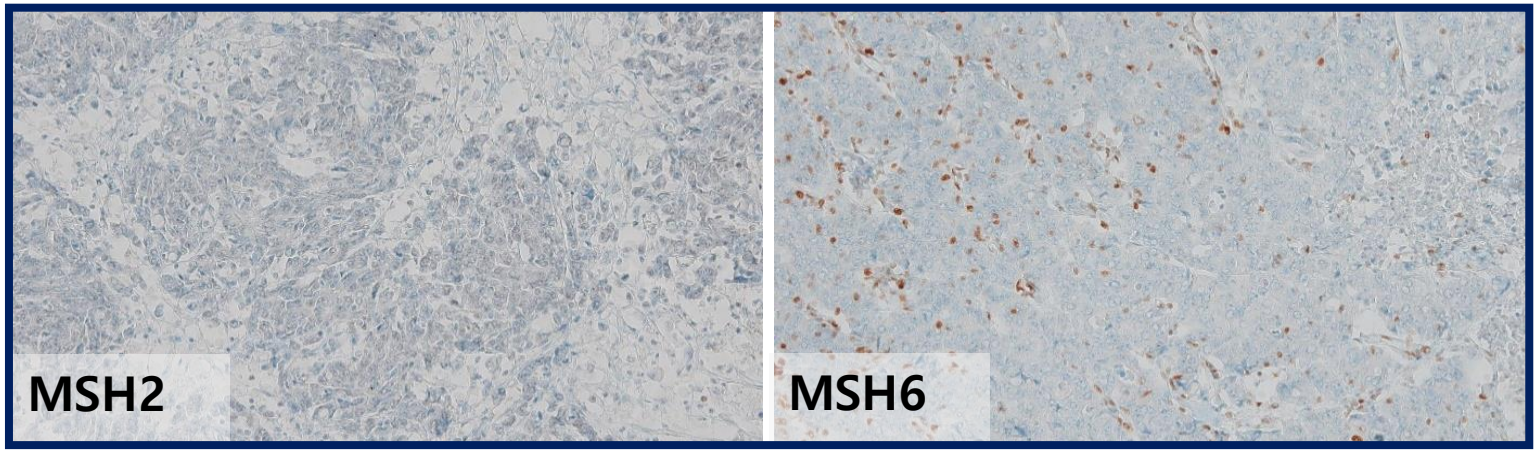


검사결과 MSI-H

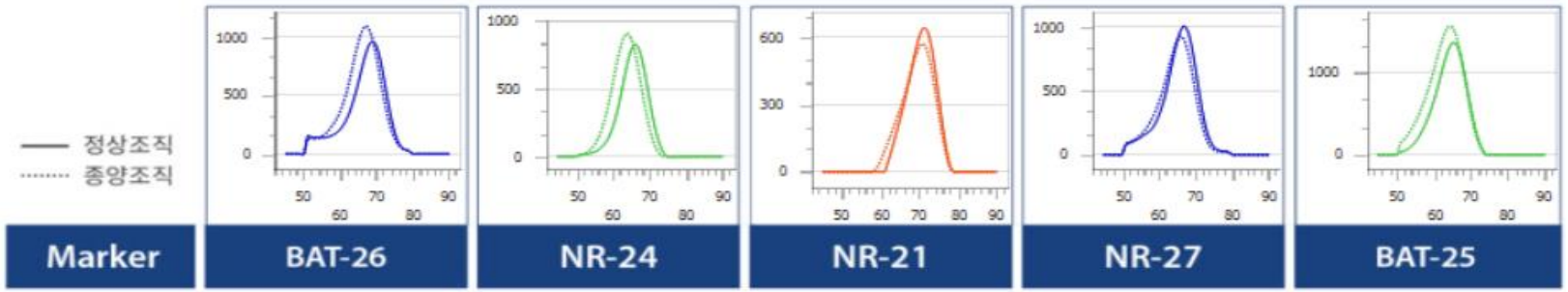


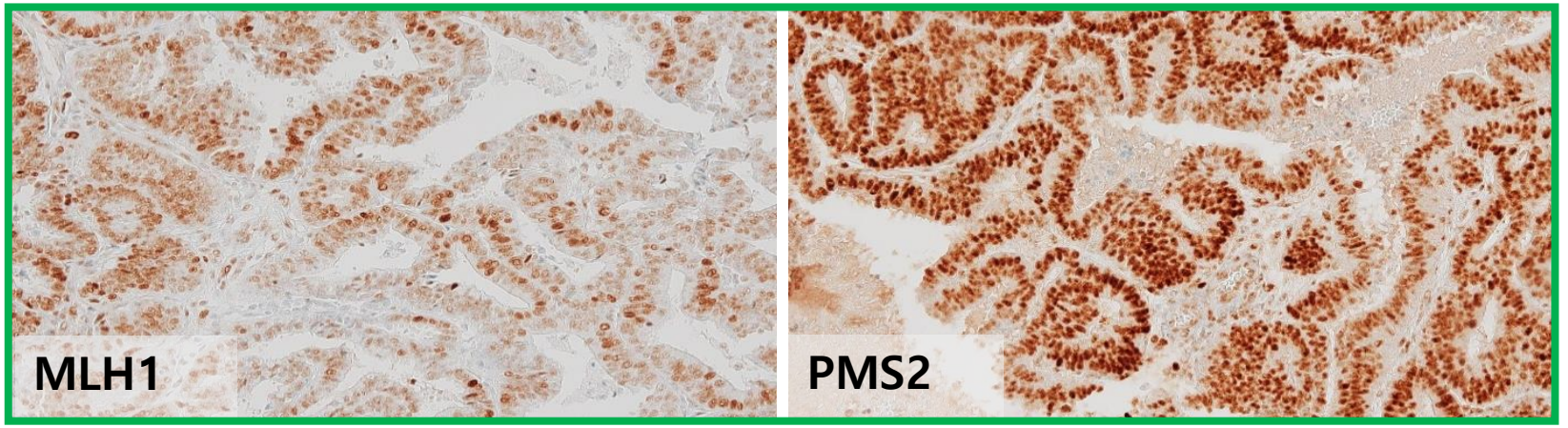
Marker	BAT-26	NR-24	NR-21	NR-27	BAT-25
MSI	MSI (+)	MSI (+)	MSI (+)	MSI (+)	MSI (+)

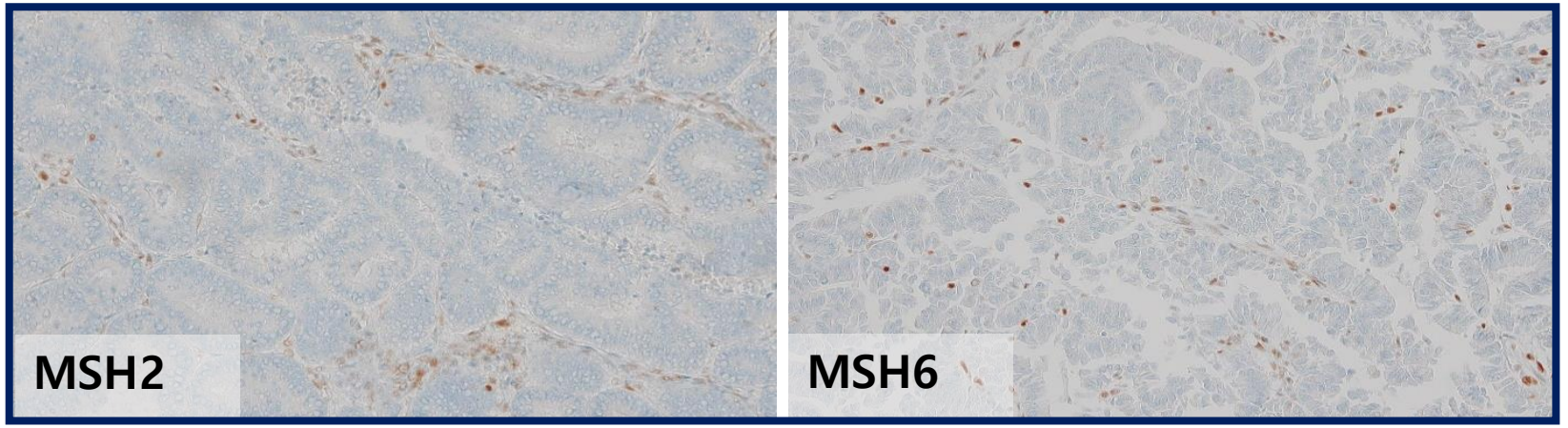




검사결과 MSS


정상조직
종양조직
Marker
BAT-26
NR-24
NR-21
NR-27
BAT-25
MSI
MSI (-)
MSI (-)
MSI (-)
MSI (-)
MSI (-)


MLH1
PMS2


MSH2
MSH6

MSI test

[검사방법]

Melting Array-mediated multiplex real-time PCR (U-TOP™ MSI Detection Kit)

[검사결과]

MSI (microsatellite instability) 분석결과: **MSS (microsatellite stable)**

BAT-26: **Negative**

NR-24: **Negative**

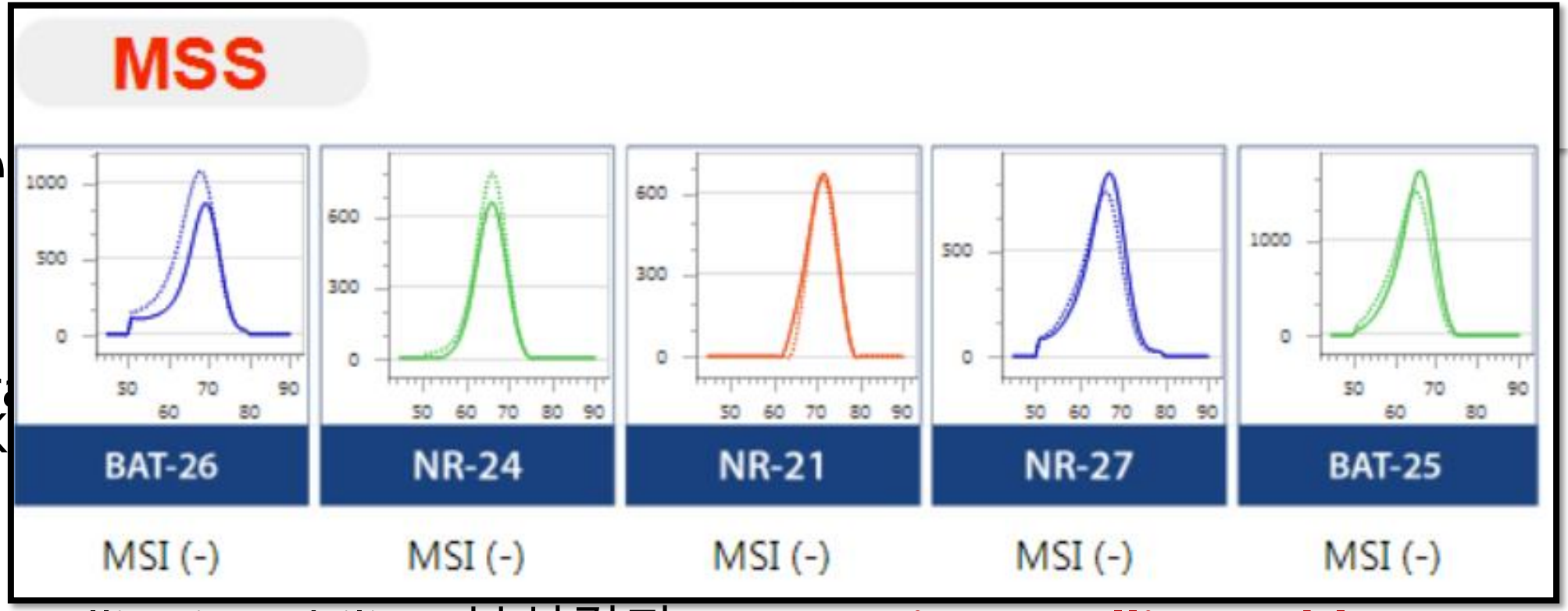
NR-21: **Negative**

NR-27: **Negative**

BAT-25: **Negative**

MSI te

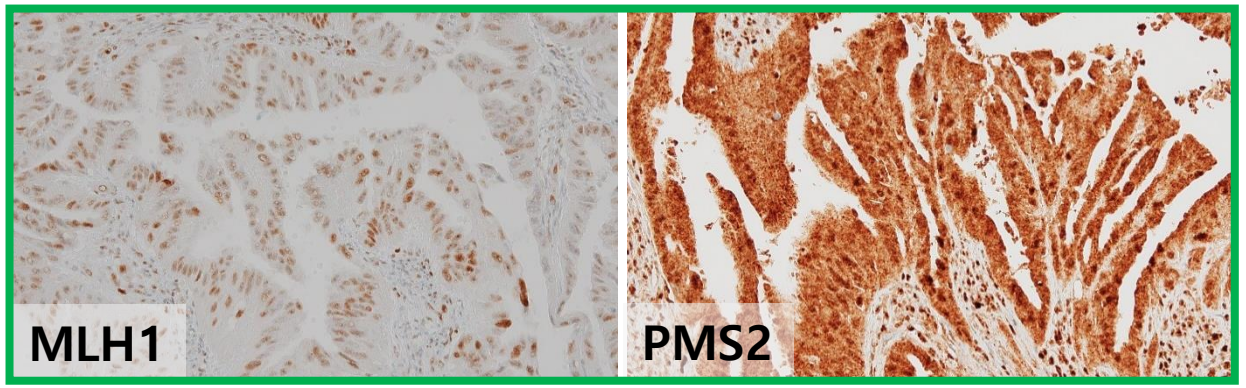
[검사방법]
Melting Arr
Detection K

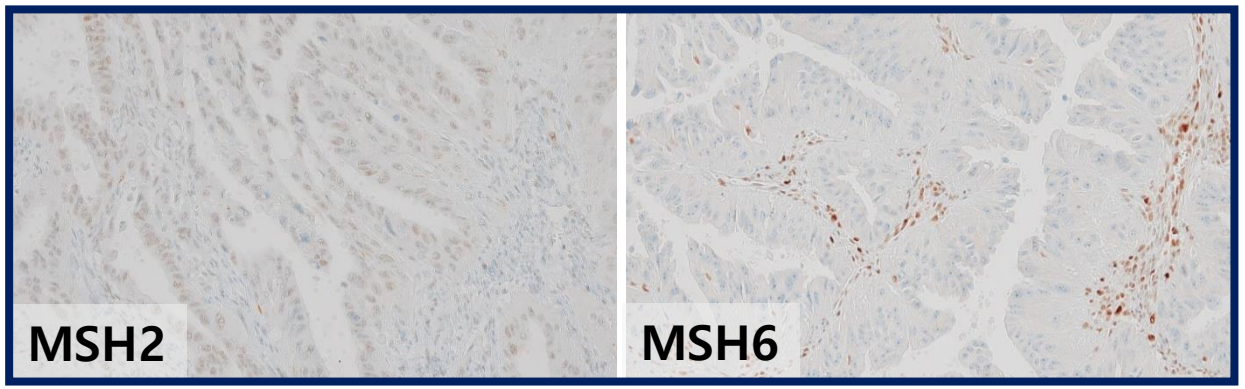


[검사결과]
MSI (microsatellite instability) 분석결과: **MSS (microsatellite stable)**

BAT-26: **Negative**
NR-24: **Negative**
NR-21: **Negative**
NR-27: **Negative**
BAT-25: **Negative**

Mutation	IHC Staining Pattern ofProtein Product
MLH1	Loss of MLH1 and PMS2 (same pattern if there is methylation of *MLH1*)
PMS2	Loss of PMS2
MSH2	Loss of MSH2 and MSH6 (same pattern if there is *EPCAM* mutation)
MSH6	Loss of MSH6





COLLEGE of AMERICAN PATHOLOGISTS

Template for Reporting Results of Biomarker Testing of Specimens From Patients With Carcinoma of the Endometrium

Version: Endometrium Biomarkers 1.2.0.0 **Template Posting Date:** August 2019

IHC Interpretation for Mismatch Repair (MMR) Proteins

___ No loss of nuclear expression of MMR proteins: low probability of microsatellite instability-high (MSI-H)#

___ Loss of nuclear expression of MLH1 and PMS2: testing for methylation of the *MLH1* promoter is indicated (the presence of *MLH1* methylation suggests that the tumor is sporadic and germline evaluation is probably not indicated; absence of *MLH1* methylation suggests the possibility of Lynch syndrome, and sequencing and/or large deletion/duplication testing of germline *MLH1* is indicated)#

___ Loss of nuclear expression of MSH2 and MSH6: high probability of Lynch syndrome (sequencing and/or large deletion/duplication testing of germline *MSH2* is indicated, and, if negative, sequencing and/or large deletion/duplication testing of germline *MSH6* is indicated. If both are negative, sequencing and/or large deletion/duplication testing of germline *EPCAM* is indicated.)#

V ___ Loss of nuclear expression of MSH6 only: high probability of Lynch syndrome (sequencing and/or large deletion/duplication testing of germline *MSH6* is indicated)#

___ Loss of nuclear expression of PMS2 only: high probability of Lynch syndrome (sequencing and/or large deletion/duplication testing of germline *PMS2* is indicated)#

There are exceptions to the above IHC interpretations. These results should not be considered in isolation, and clinical correlation with genetic counseling is recommended to assess the need for germline testing.

Note that loss of MSH6 protein expression may occur in absence of MSI-H phenotype.

Detection of defective MMR (dMMR)

- IHC
- MSI

Screening **test of choice** in **endometrial carcinoma** as significant proportion of Lynch syndrome-associated endometrial carcinomas are **microsatellite low or microsatellite stable by MSI testing, particularly when *MSH6* is mutated**

- Sequencing (gold standard)
  - NGS

AMP case report: Discordant IHC/PCR test results for mismatch repair status in colorectal adenocarcinoma

in 2018 Issues, ARTICLES, December 2018

- MSI testing by PCR and MMR protein assessment by IHC are **highly concordant**, but **neither** test alone is **sufficient** to capture 100 percent of tumors with defective MMR, and therefore **dual** PCR and IHC testing is an acceptable practice.

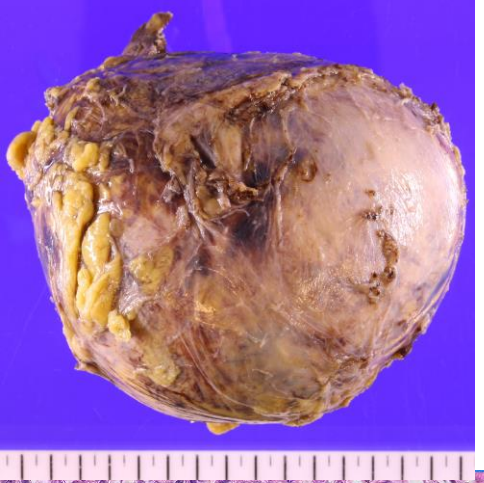
- **Discordant** IHC and PCR results, recently estimated to **occur in 2.2 percent** of colorectal tumors, most commonly reflect mutated nonfunctional MMR proteins with retained antigenicity.

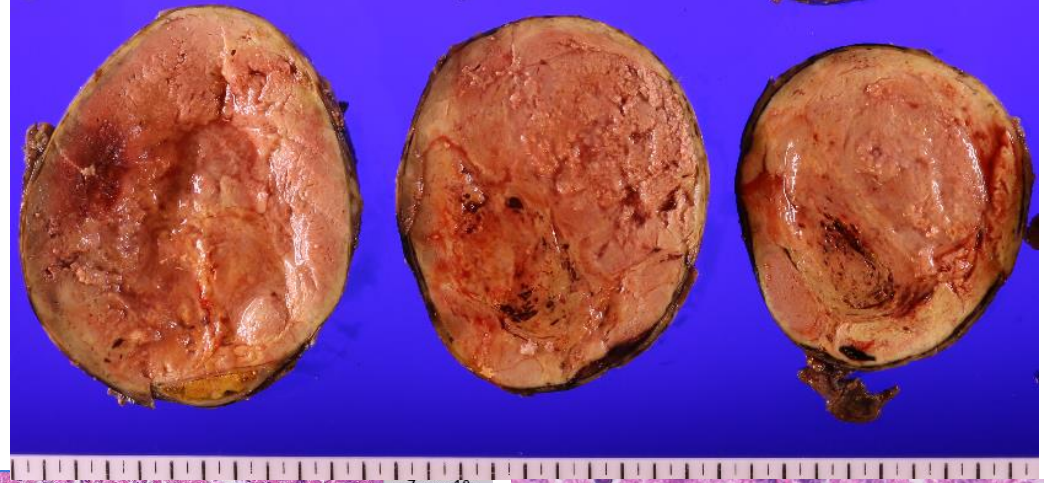
- Discordant results **should** be interpreted as **defective MMR**, and additional testing should be performed to rule out a germline mutation.

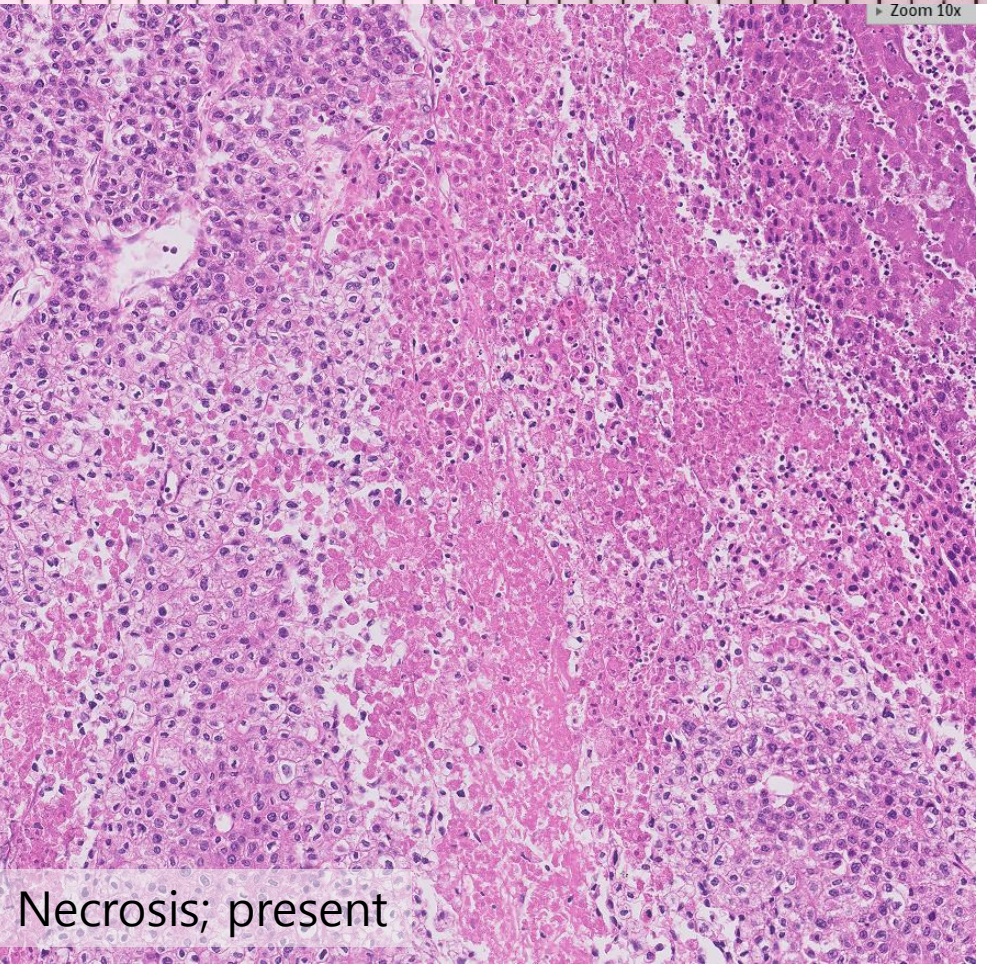
Case summary

- 49/F
- Endometrioid carcinoma (uterus, left ovary)
  - h/o colon cancer
- ***MSS*** *on MSI PCR testing*

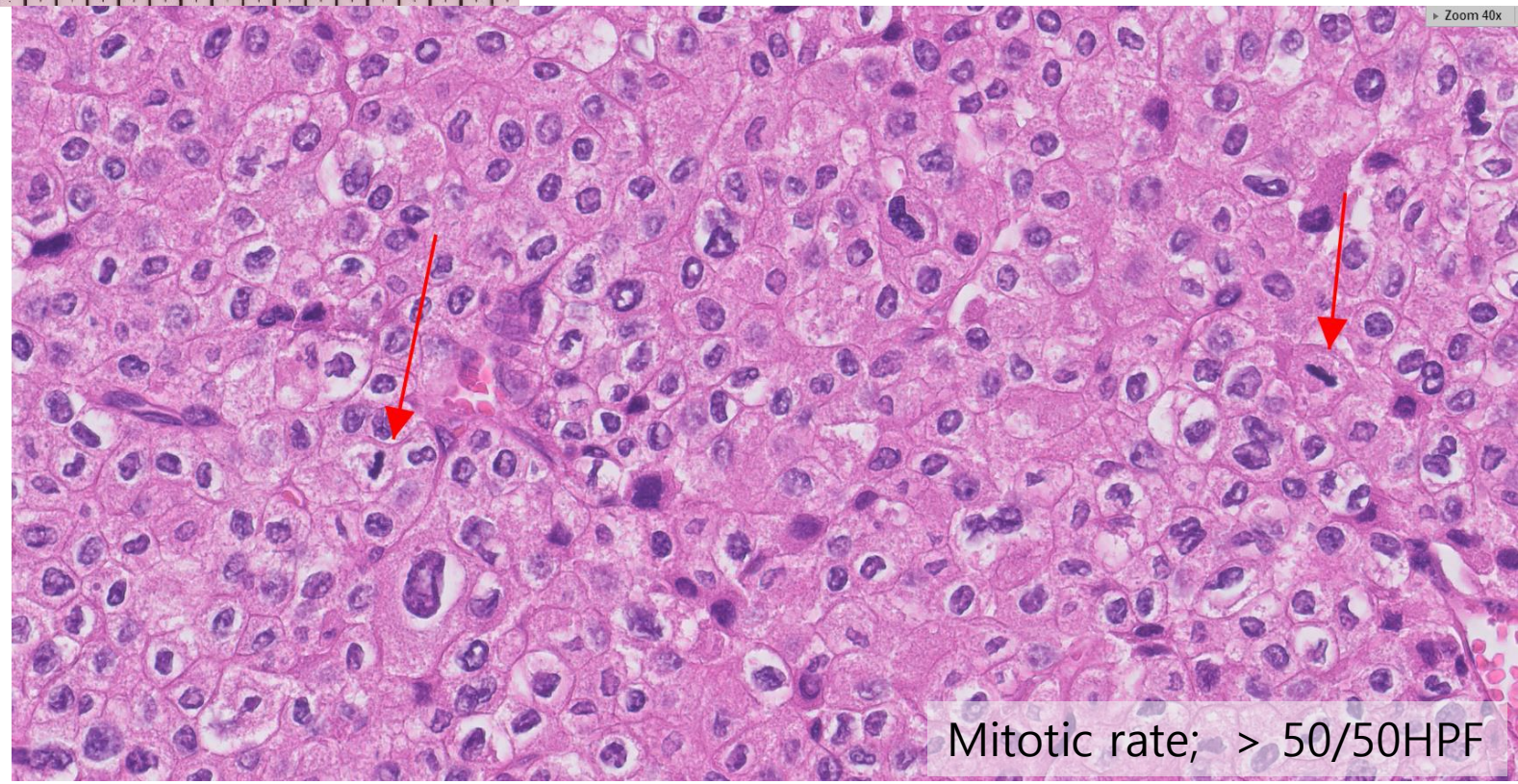
- NGS detection of **MSH6 mutation**
- IHC: **loss of MSH6**







Necrosis; present



Mitotic rate; > 50/50HPF

Adrenal gland, right, adrenalectomy;
Adrenal cortical carcinoma, high grade.

[검사결과]

MSI (microsatellite instability) 분석결과

: MSS (microsatellite stable)

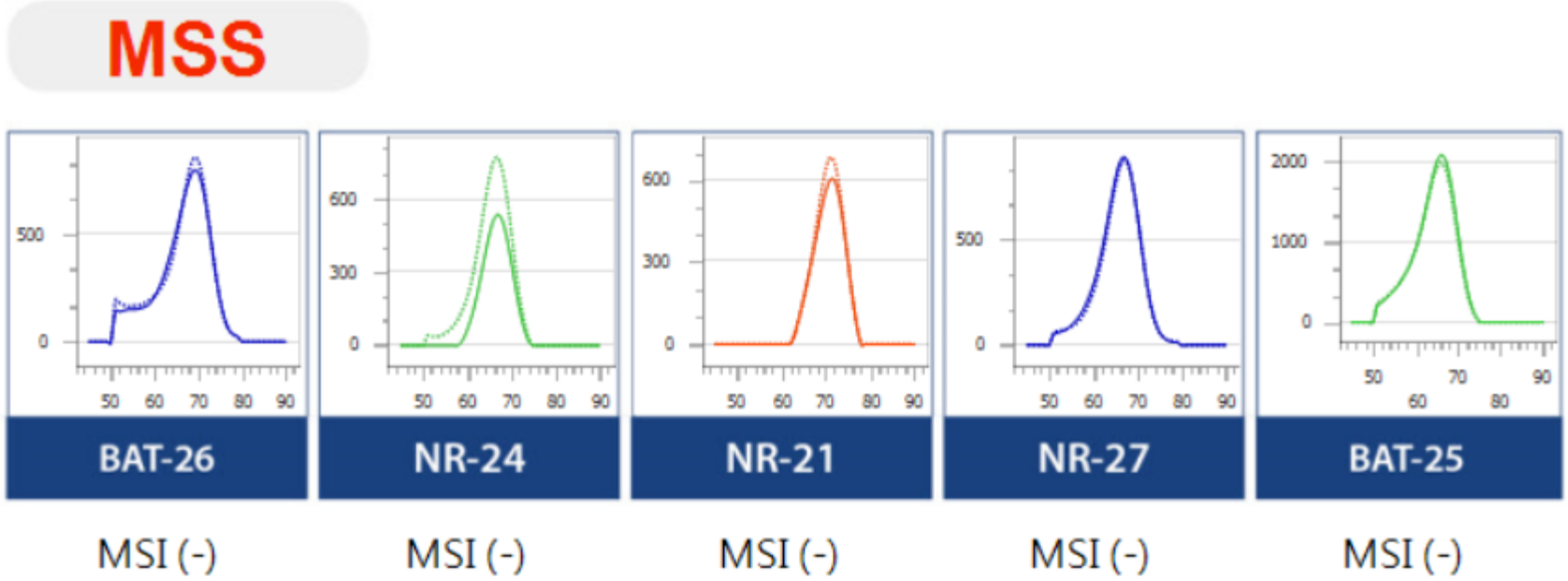
BAT-26: Negative

NR-24: Negative

NR-21: Negative

NR-27: Negative

BAT-25: Negative

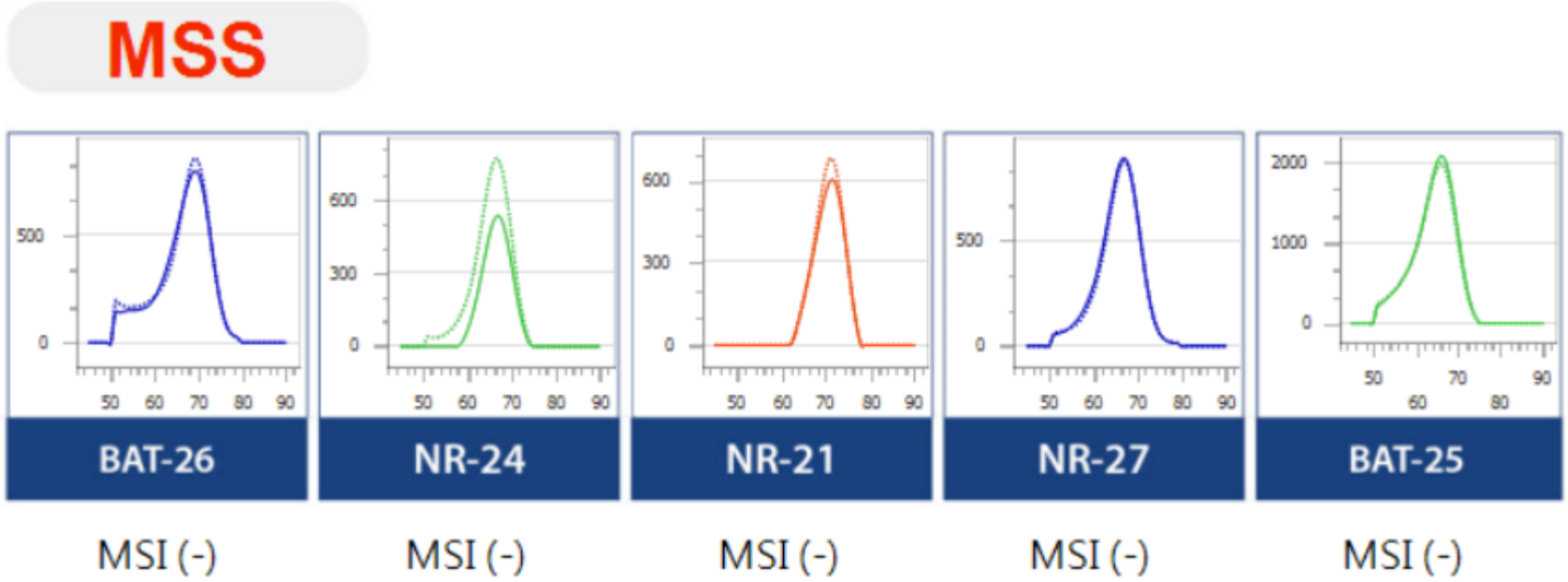


[검사결과]

MSI (microsatellite instability) 분석결과

: MSS (microsatellite stable)

BAT-26: Negative
NR-24: Negative
NR-21: Negative
NR-27: Negative
BAT-25: Negative



[Immunohistochemistry]

MLH1; intact nuclear expression
PMS2; intact nuclear expression
MSH2; loss of nuclear expression
MSH6; loss of nuclear expression

[IHC Interpretation]

Loss of nuclear expression of MSH2 and MSH6: high probability of Lynch syndrome (sequencing and/or large deletion/duplication testing of germline MSH2 is indicated, and, if negative, sequencing and/or large deletion/duplication testing of germline MSH6 is indicated. If both are negative, sequencing and/or large deletion/duplication testing of germline EPCAM is indicated.)