Lynch syndrome

9 October 2015

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Middlemore Hospital, Auckland,
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AUSTRALASIAN GASTROINTESTINAL PATHOLOGY SOCIETY

History of Lynch syndrome

Aldred Scott Warthin, MD, PhD (1866-1931)

"The father of cancer genetics"

Classics in Oncology

Heredity with Reference to Carcinoma As Shown By the Study of the Cases Examined in the Pathological Laboratory Of the University of Michigan, 1895–1913

Aldred Scott Warthin, M.D.

The statistical study of carcinoma is regarded by many writers as having been carried as far as it can be profitable; and certainly but little that is new has been gained through this method during the last decade. Nevertheless, its possibilities have not been exhausted; and it is highly desirable that the whole neoplasm problem in all of its aspects be attacked again from the statistical standpoint, though in a somewhat different way. Practically all of the old statistical studies of neoplasms, particularly those of carcinoma, were based on mortality reports; or if not on these, on morbidity reports based on clinical diagnoses. In very few instances has the statistical study been carried out only on the basis of the records of a diagnostic pathological laboratory. Statistics of neoplasm from such a source must be of infinitely greater value than those founded on mortality statistics.

In the records of the diagnostic laboratory, the diagnosis is based on the histological examination, and the percentage of error is reduced to a minimum. In the mortality statistics, on the other hand, the diagnoses are chiefly clinical, and consequently subject to the wide error inherent in the clinical diagnosis of "tumor," neoplasm, "cancer," and the like. Moreover, the material coming to the diagnostic laboratory is usually seen from two to five years earlier than the mortality age. In studies relating to the age-incidence of any form of neoplasm, it is evident that the records of the pathological laboratory for that neoplasm will be much more trustworthy than the mortality statistics. It is also possible many times in the diagnostic laboratory to follow the course of a neoplasm over a definite period, so that important practical knowledge may be gained as to rate of growth, recurrence, healing, metastases, etc.

The following study of the influence of heredity on carcinoma is taken from the records of the pathological laboratory of the University of Michigan during the years of my service from 1895 to 1913. During this period, 3,600 cases of neoplasm of all varieties have been studied, either in material taken for practical diagnosis or obtained by necropsy. Of these 3,600 cases, some 1,600 were cases of carcinoma, as was shown by the microscopic diagnosis. Practically every variety of carcinoma described in the literature, and a few others, as well, are to be found in this material; and the same is true of the other forms of neoplasm. While carcinomas of the breast, uterus, and lip form the greater part of the cases examined, all other localizations are represented. Another great advantage is that about 90 percent of the material was derived from the general population of the state of Michigan. The fact that the university hospital is a state hospital and not a charity institution gives it a much more representative population than would be found in the charity hospitals of the greater cities.

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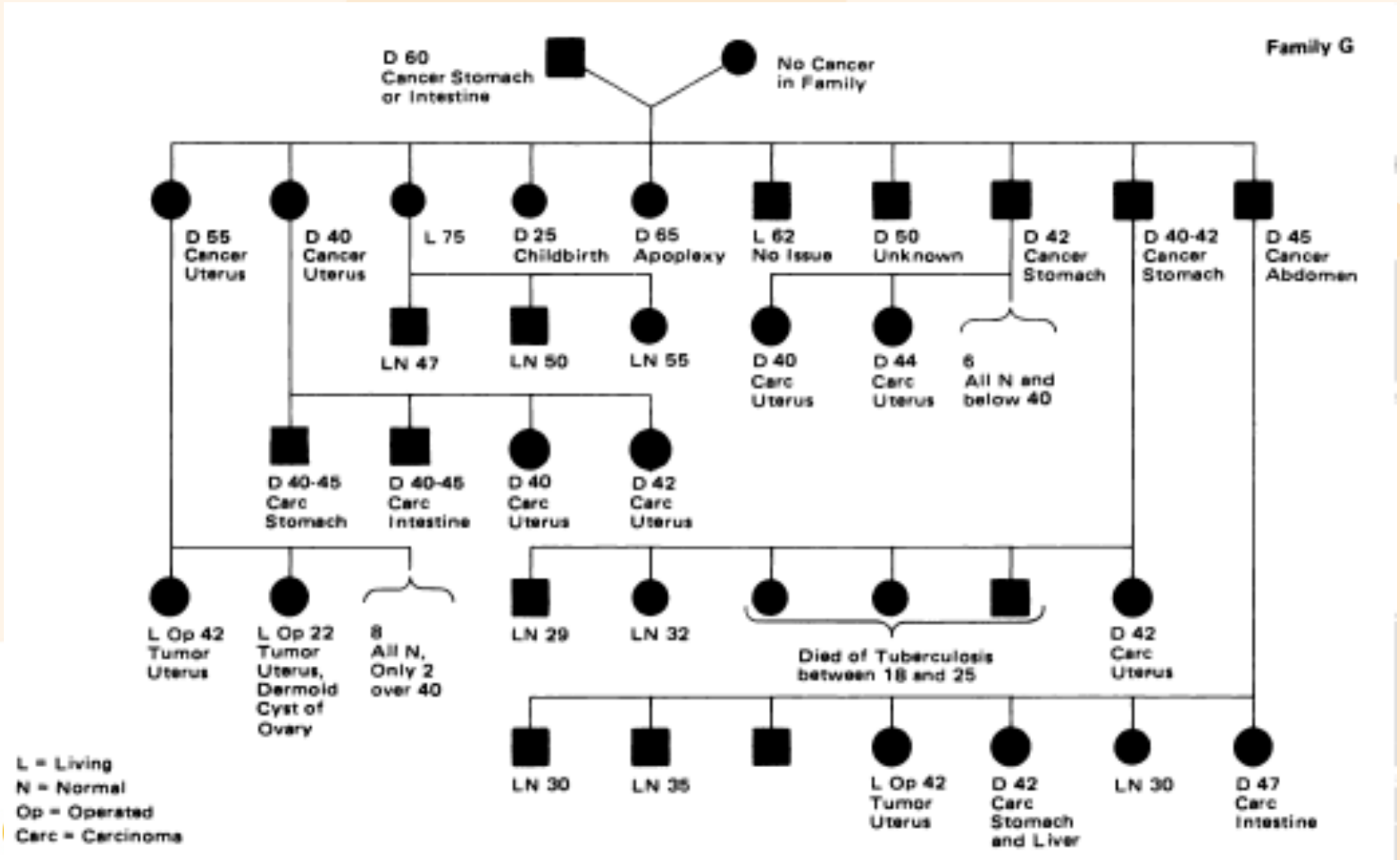
(JAMA. 2005;294(17):2195-2202)

(Arch Intern Med. 1913;12:546-555)

Family G


Family G
D 60
Cancer Stomach
or Intestine
No Cancer
in Family
D 55
Cancer
Uterus
D 40
Cancer
Uterus
L 75
D 25
Childbirth
D 65
Apoplexy
L 62
No Issue
D 50
Unknown
D 42
Cancer
Stomach
D 40-42
Cancer
Stomach
D 45
Cancer
Abdomen
LN 47
LN 50
LN 55
D 40
Carc
Uterus
D 44
Carc
Uterus
6
All N and
below 40
D 40-45
Carc
Stomach
D 40-45
Carc
Intestine
D 40
Carc
Uterus
D 42
Carc
Uterus
L Op 42
Tumor
Uterus
L Op 22
Tumor
Uterus,
Dermoid
Cyst of
Ovary
8
All N,
Only 2
over 40
LN 29
LN 32
Died of Tuberculosis
between 18 and 25
D 42
Carc
Uterus
LN 30
LN 35
L Op 42
Tumor
Uterus
D 42
Carc
Stomach
and Liver
LN 30
D 47
Carc
Intestine
L = Living
N = Normal
Op = Operated
Carc = Carcinoma

Dr. Henry T. Lynch

"The father of hereditary cancer detection and prevention"

Creighton UNIVERSITY School of Medicine

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https://medschool.creighton.edu/medicine/centers/hcc/welcome/

206

Hereditary Factors in Cancer

Study of Two Large Midwestern Kindreds

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AND A. J. KRUSH, MS, OMAHA

MENDELIAN autosomal inheritance patterns have been demonstrated in familial aggregations of polyposis coli, retinoblastoma, xeroderma pigmentosum, neurofibromatosis,[1] Gardner's syndrome[2] and the basal cell nevus syndrome.[3] In addition, an increased familial incidence of carcinoma of the breast,[4] lung,[5] stomach and colon,[6] and prostate,[7] as well as leukemia,[8] multiple myeloma,[9] Waldenström's macroglobulinemia,[10] pheochromocytoma,[11] multiple endocrine tumors,[12] cerebellar hemangioblastoma,[13] and malignant melanoma[14] has been observed. However, the mode of inheritance is not clear in these latter conditions. In appraising these data, it must be kept in mind that only those families showing a high incidence of carcinoma are "selected" for publication. When one considers the high population incidence of carcinoma, ". . . it is bound to occur in excess in some families according to the operation of the laws of probability.[15,16]

The purpose of this paper is to present the findings in two large midwestern kindreds in which a high frequency of particular histological types of malignant neoplasms involving a large variety of anatomical sites was found. In one kindred (Nebraska), there was a total of 51 malignant neoplasms of which 31 were confirmed, while in the second (Michigan) kindred, there were 27 carcinomas of which 20 were confirmed.

Received for publication Aug 6, 1965; accepted Oct 1.
Read in part before the American Society of Human Genetics, Boulder Colo, August 1964.

From the departments of internal medicine and pathology and the Eppley Institute for Research in Cancer and Allied Diseases, University of Nebraska College of Medicine, Veterans Administration Hospital, Omaha, and the Department of Human Genetics, University of Michigan Medical School, Ann Arbor.
Reprint requests to Eppley Institute, 42nd & Dewey Ave, Omaha, Neb 68105 (Dr. Lynch).

Material and Methods

These two large families have been studied in Nebraska and Michigan and shall hereafter be referred to as the "N" (Nebraska) and "M" (Michigan) kindred.

N Family.—The propositus (No. U-11770) was studied at the Omaha Veterans Administration Hospital where he expired at age 44 from adrenal cortical carcinoma. His medical history revealed that many of his immediate relatives had cancer and that they lived over a wide geographic area. A questionnaire was sent to all adult members of the family in order to elicit information regarding a history of carcinoma and to obtain permission to examine surgical and autopsy material for histologic tissue confirmation. Permission forms were included with the questionnaire enabling us to make contact with family physicians, consultants, hospitals, state divisions of vital statistics, and local departments of public welfare. Several field trips were made, and clinic facilities were kindly donated by a private physician who had managed some of the affected members of the family. Complete histories and physical examinations, including pelvic examinations, cervical cytology, and proctosigmoidoscopy, were done on 35 individuals who resided in a contiguous geographic area. When lesions were accessible to surgical biopsy, appropriate tissue was obtained. Blood was obtained for ABO typing, hemoglobin, hematocrit, and cell indices.

M Family.—The propositus (No. 945482) was studied at the University Hospital, Ann Arbor, Michigan, where she expired at age 36 from metastatic carcinoma of the breast. A strong family history of carcinoma had been elicited and similarly questionnaires were sent to members of the family. Histologic confirmation of carcinoma was made through physicians' records and pathology reports from several hospitals. In addition, cytogenetic studies were done on the proband prior to her death. These included karyotype analyses of leukocytes from two peripheral blood cultures, skin from the leg, and the pituitary gland following an ablation procedure.

Whenever possible, slides were personally reviewed from both families. In those cases showing

Nebraska : Family N
Michigan : Family M

"The pedigrees of both families are compatible with autosomal dominant inheritance."

"it seems likely that the respective members represent 'carcinoma-susceptible genotypes'"

GASTROINTESTINAL PATHOLOGY SOCIETY

Arch Intern Med. 1966;117:206-212

Update of Family G

- In 2000, MSH2 gene mutation (T to G transversion at the splice acceptor site of exon 4) was identified (Nature. 2000; 403:723-724)
- Family G now has 929 known descendants
- One of the most thoroughly documented and longest cancer family histories ever recorded

Table 2. Colorectal and Lynch Syndrome–Associated Cancers in Family G*

Site	No. of Cases	Age at Diagnosis, Mean (SD) [Range]†	Generations
Colorectum	56	55 (16) [23-93]	II, III, IV, V
Endometrium	16	53 (12) [39-78]	II, III, IV, V
Stomach	8	62 (12) [44-76]	II, III, IV, V
Brain	4	44 (16) [23-59]	III, IV, V
Ovary	1	44	V
Total	**85***		

*Includes 74 individuals; 8 were diagnosed with multiple (2-5) primary cancers.
†Actual age is given for cancer of the ovary.

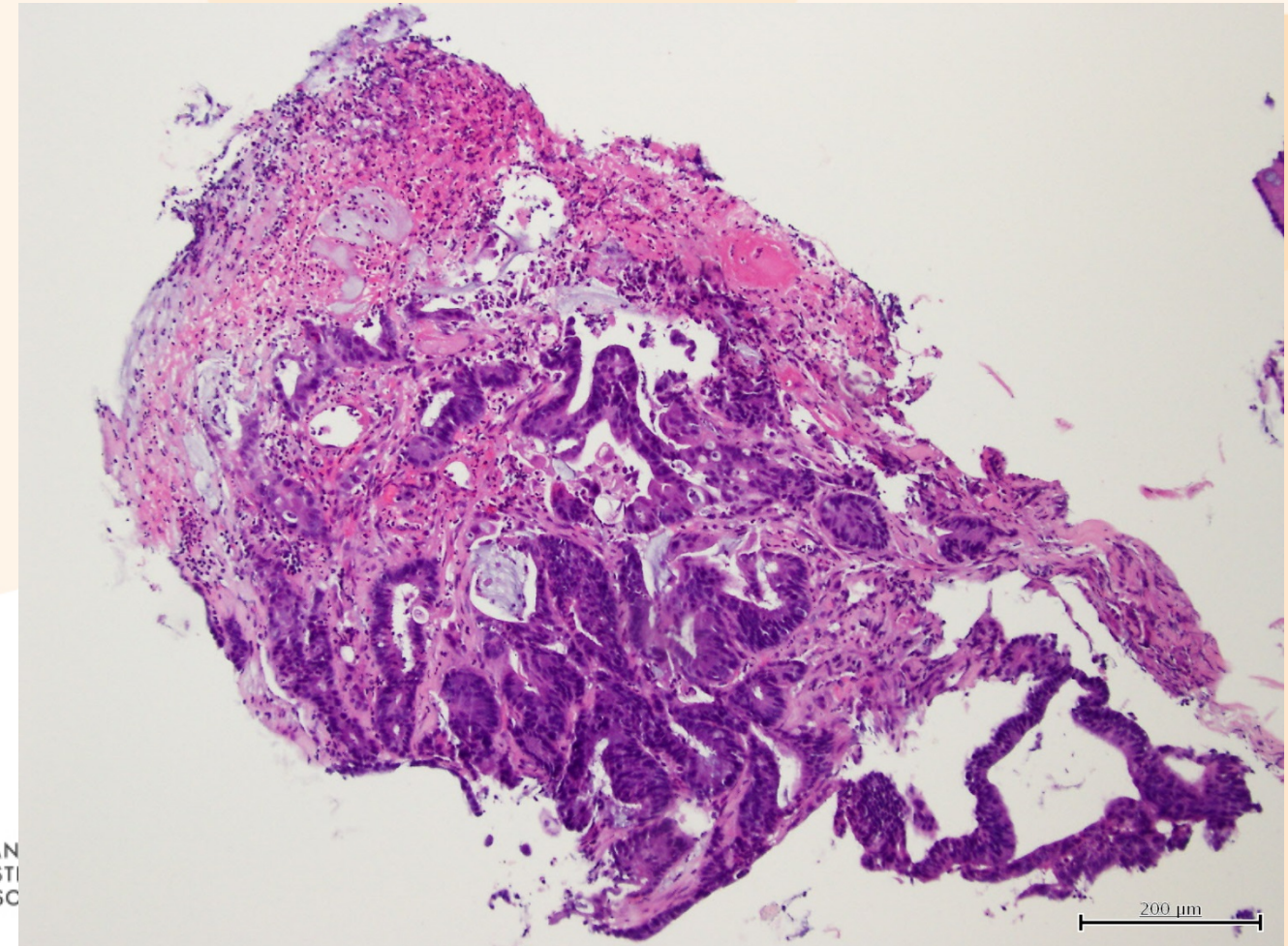
(JAMA. 2005;294(17):2195-2202)

T.U. 43y F

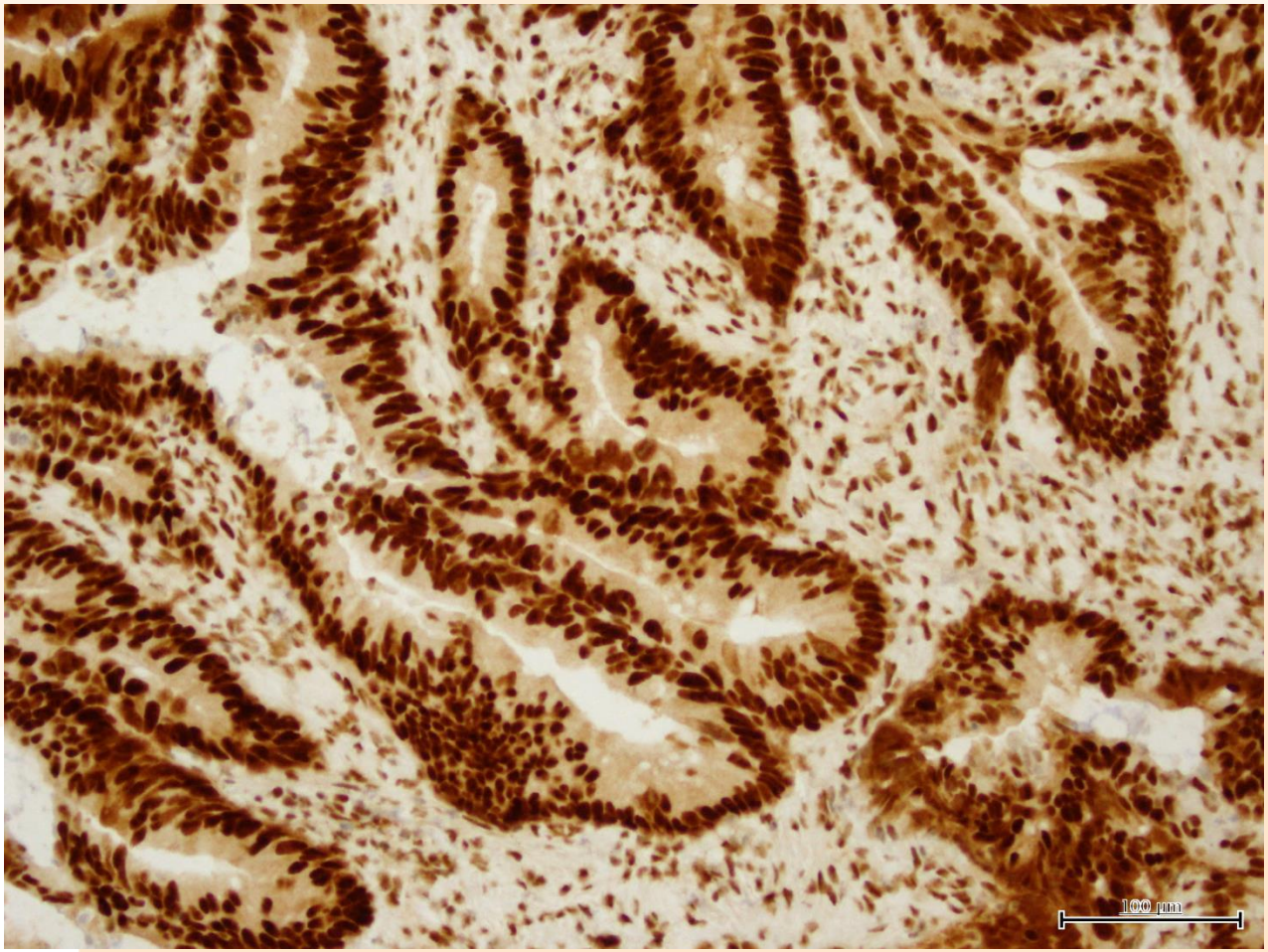
- Presented with rectal bleeding
- Colonoscopy :
  - Rectosigmoid colon mass
  - 12mm pedunculated polyp at splenic flexure
- PMHx : Menorrhagia (IUCD in situ)
- FHx :
  - Father : Rectal cancer at age 66y
  - Mother : Hepatic flexure cancer at age 54y
  - Paternal uncle : Lung cancer (smoker)

Biopsy rectosigmoid colon mass

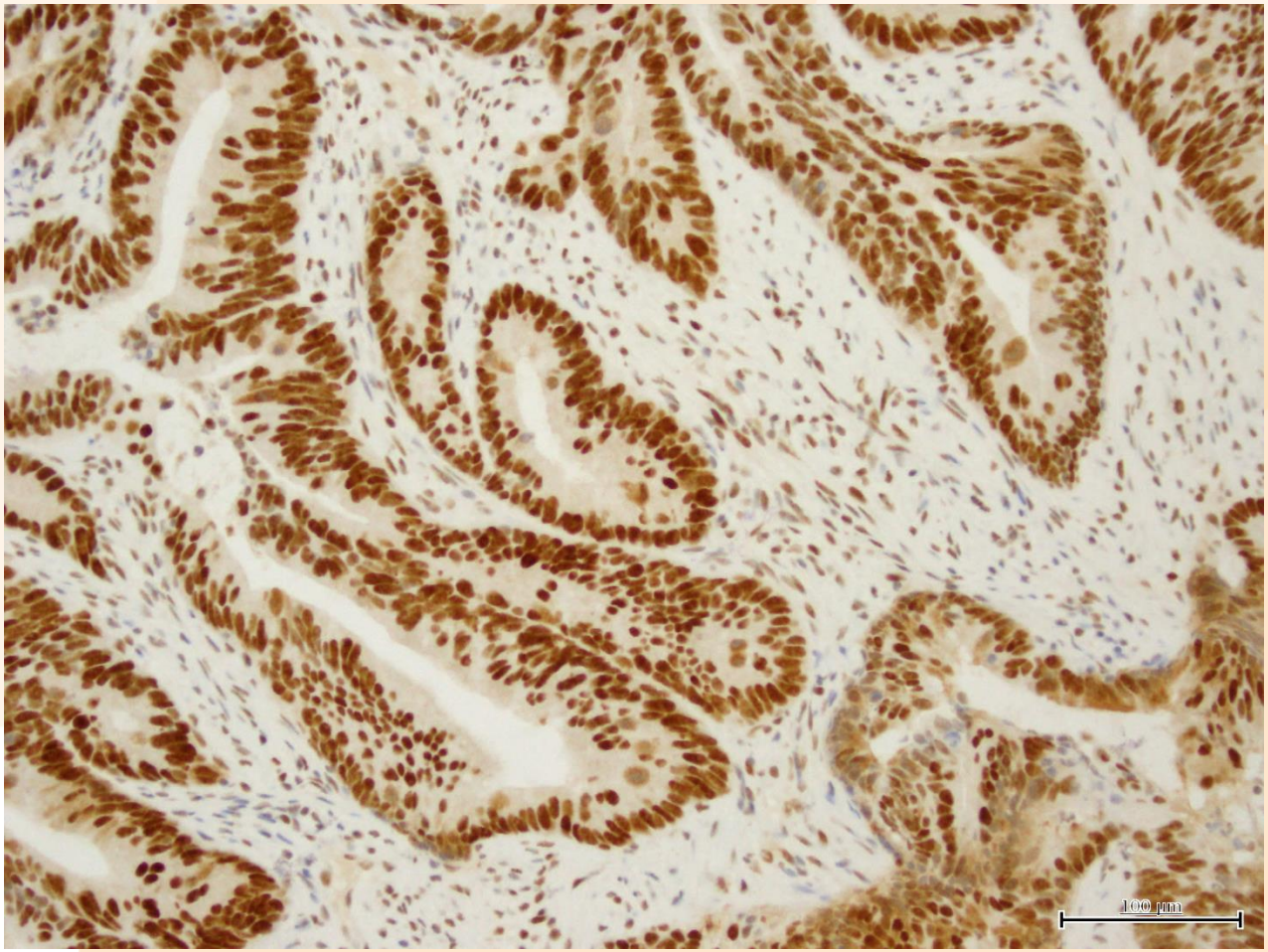
- Adenocarcinoma, low grade



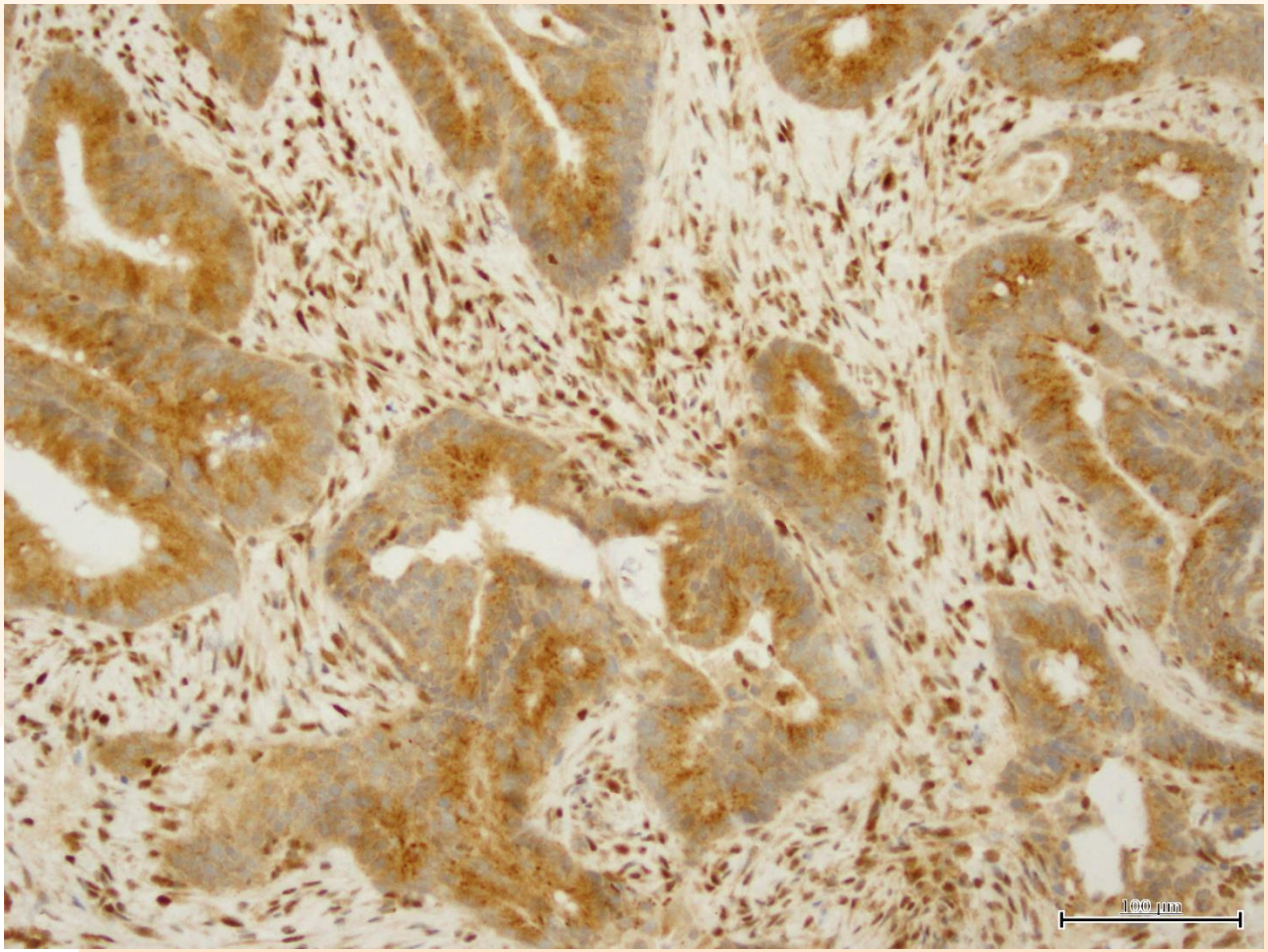
Biopsy rectosigmoid colon mass MLH1



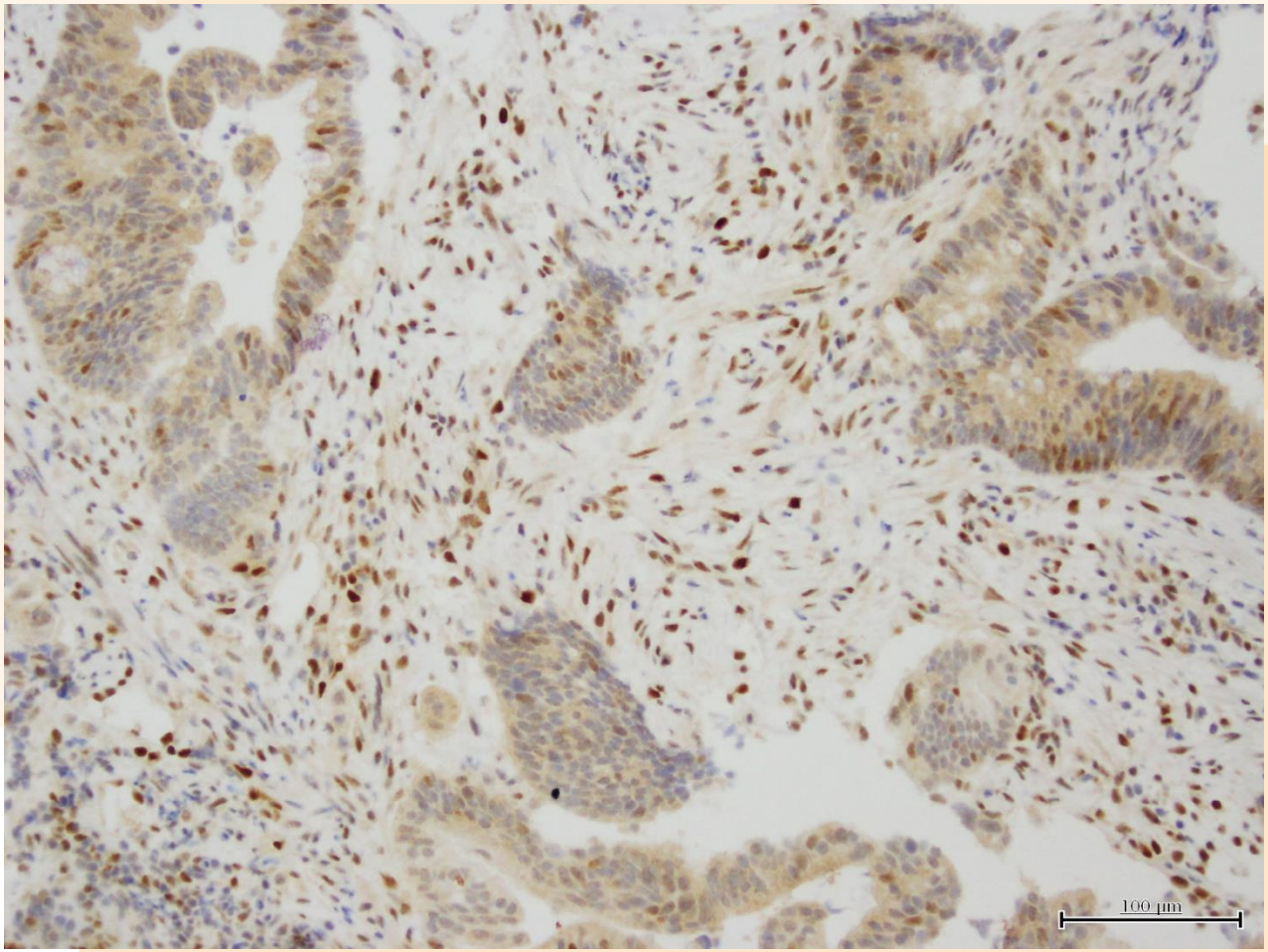
Biopsy rectosigmoid colon mass PMS2



Biopsy rectosigmoid colon mass MSH2

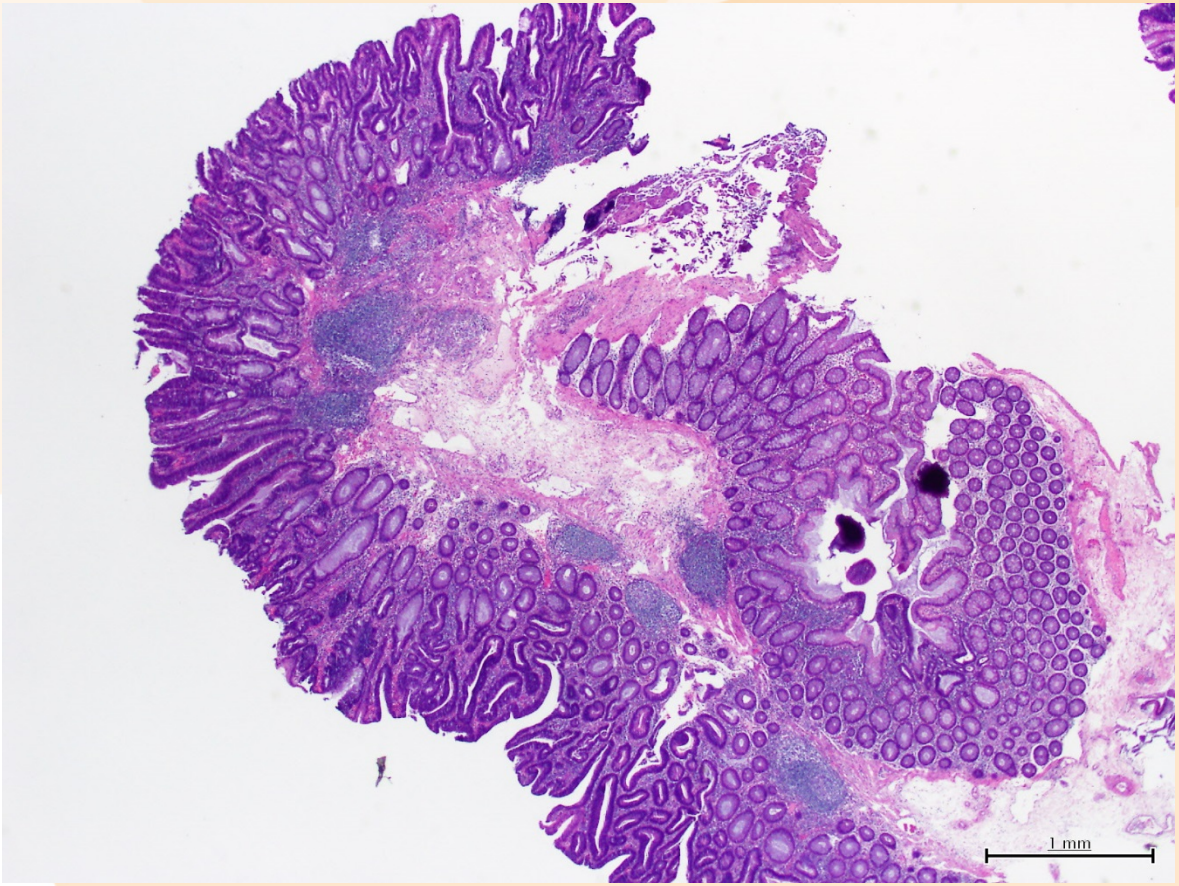


Biopsy rectosigmoid colon mass MSH6

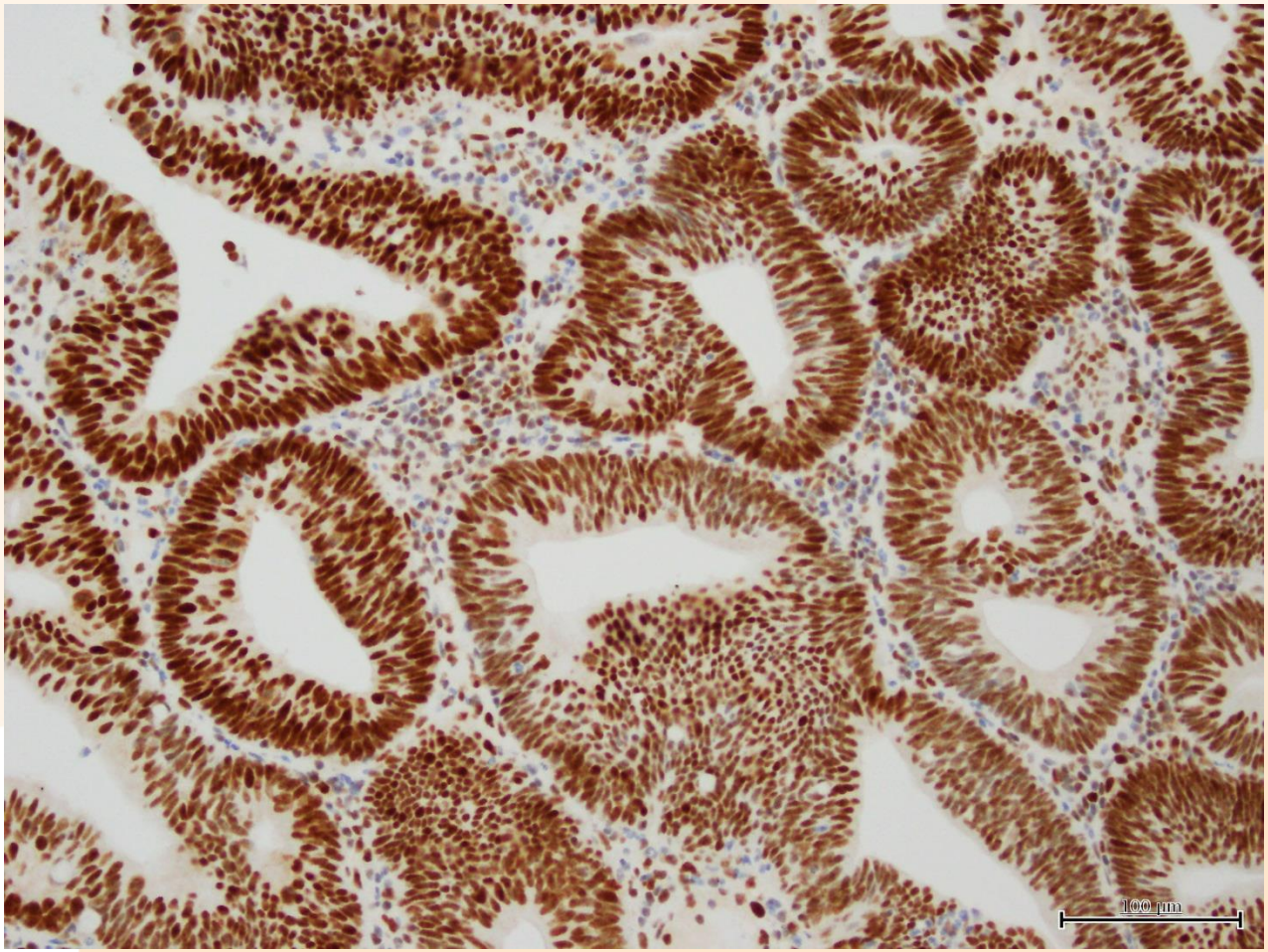


Splenic flexure polyp

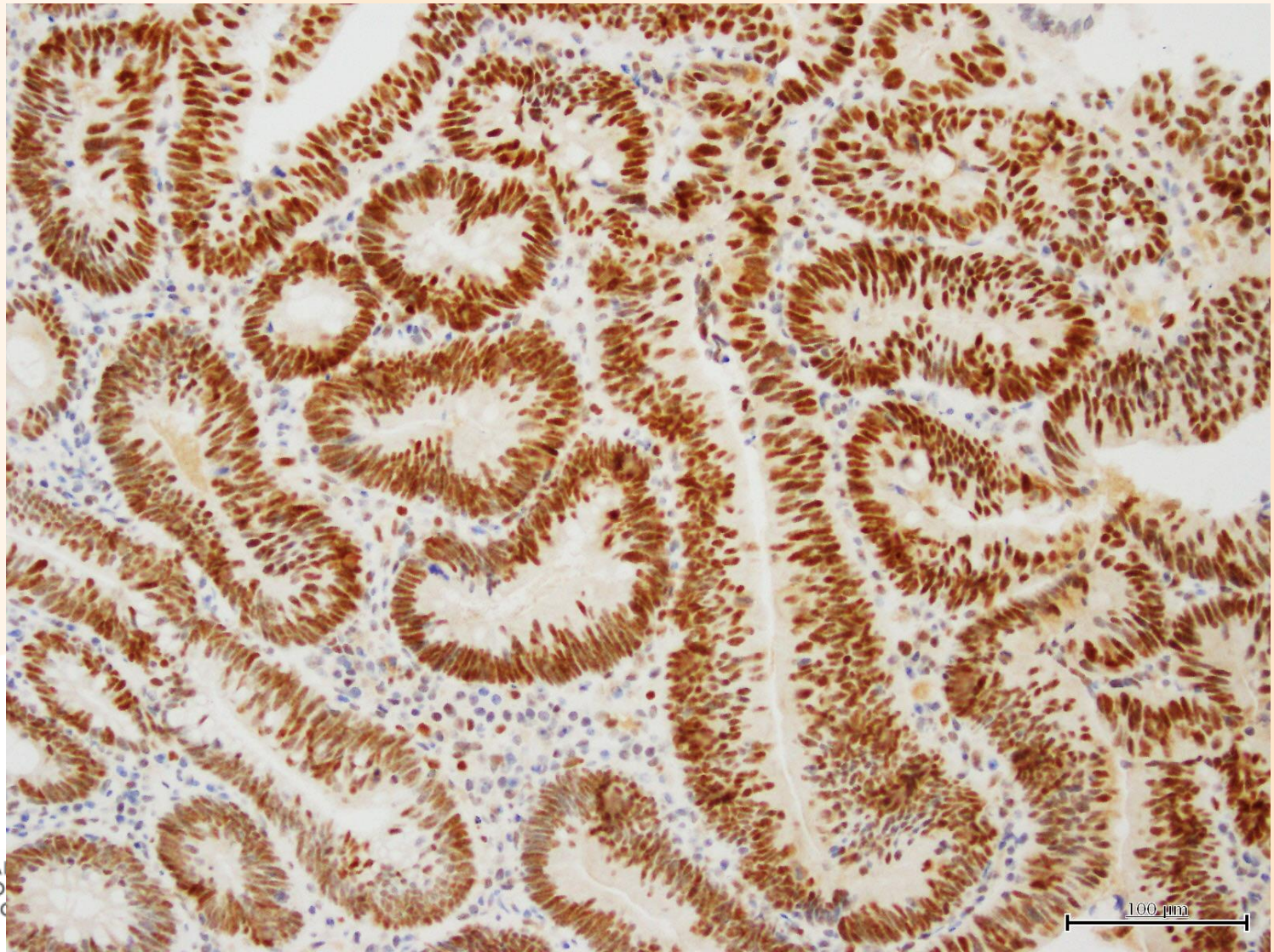
- Tubulovillous adenoma with low grade dysplasia



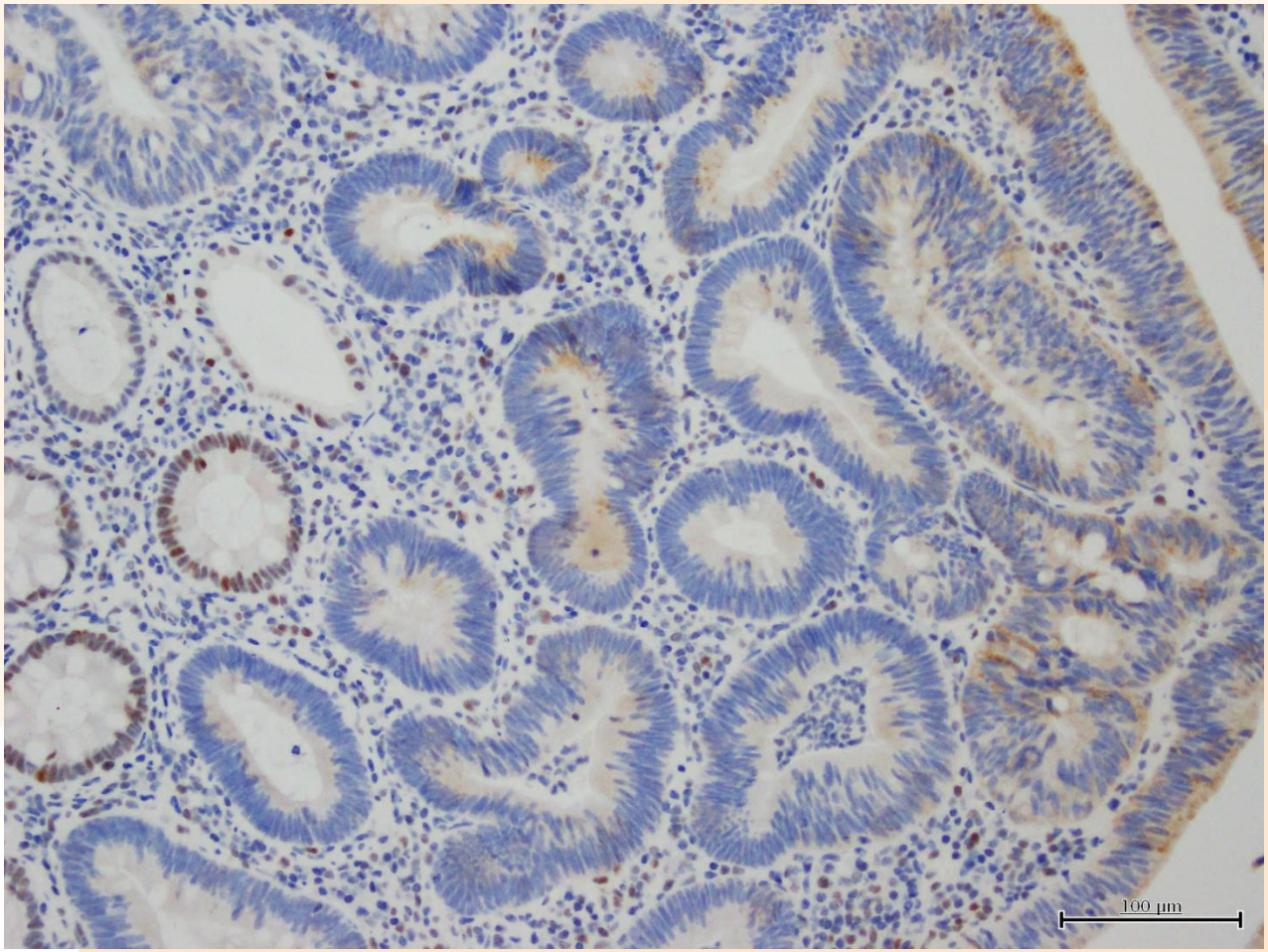
Splenic flexure polyp
MLH1



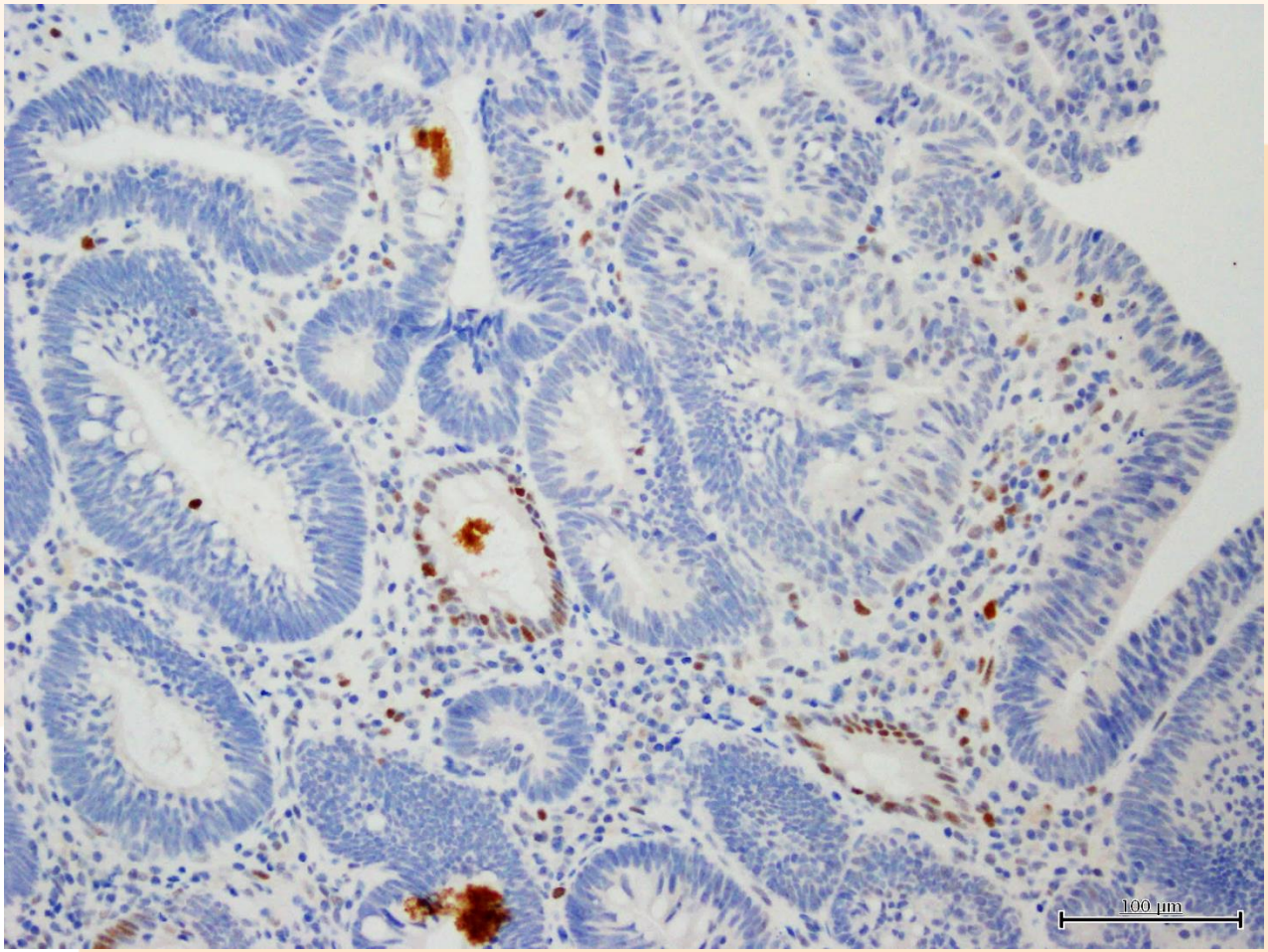
Splenic flexure polyp
PMS2



Splenic flexure polyp
MSH2



Splenic flexure polyp
MSH6

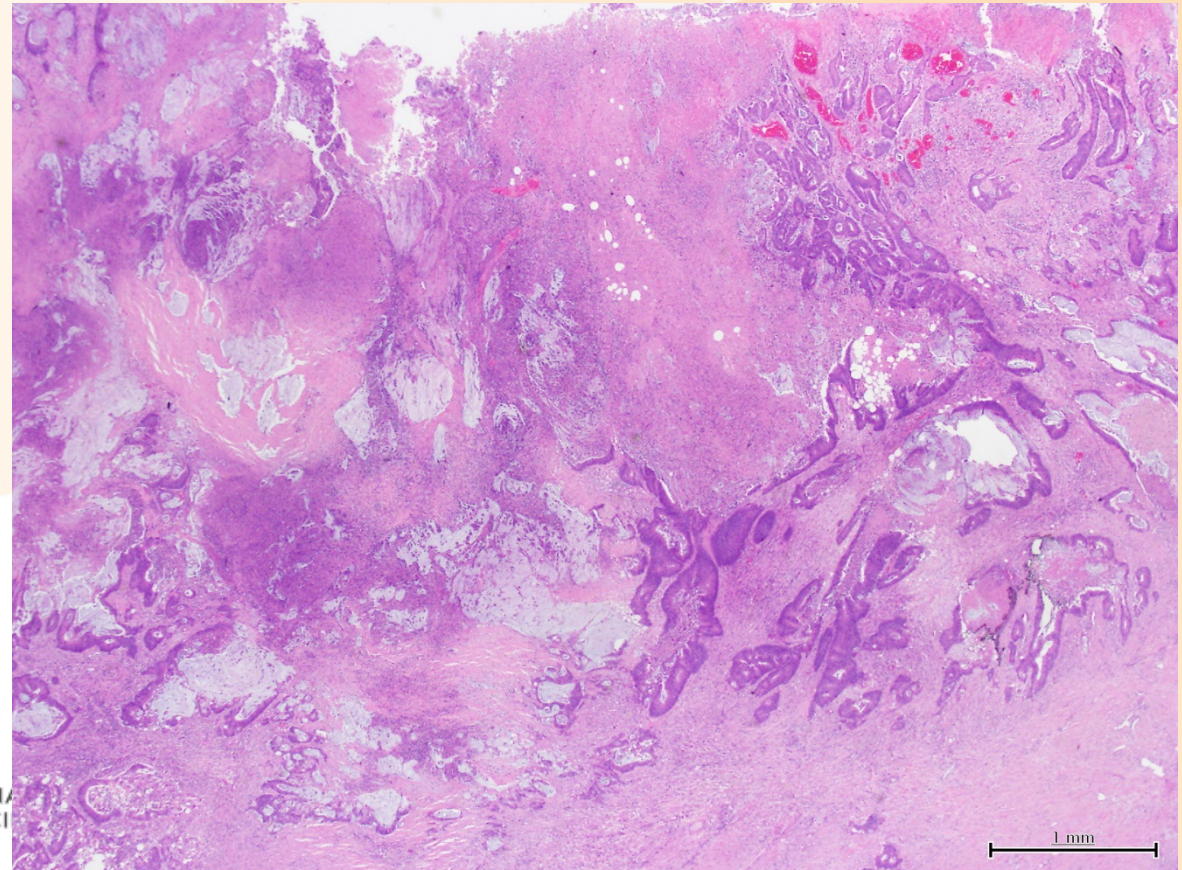


Biopsy summary

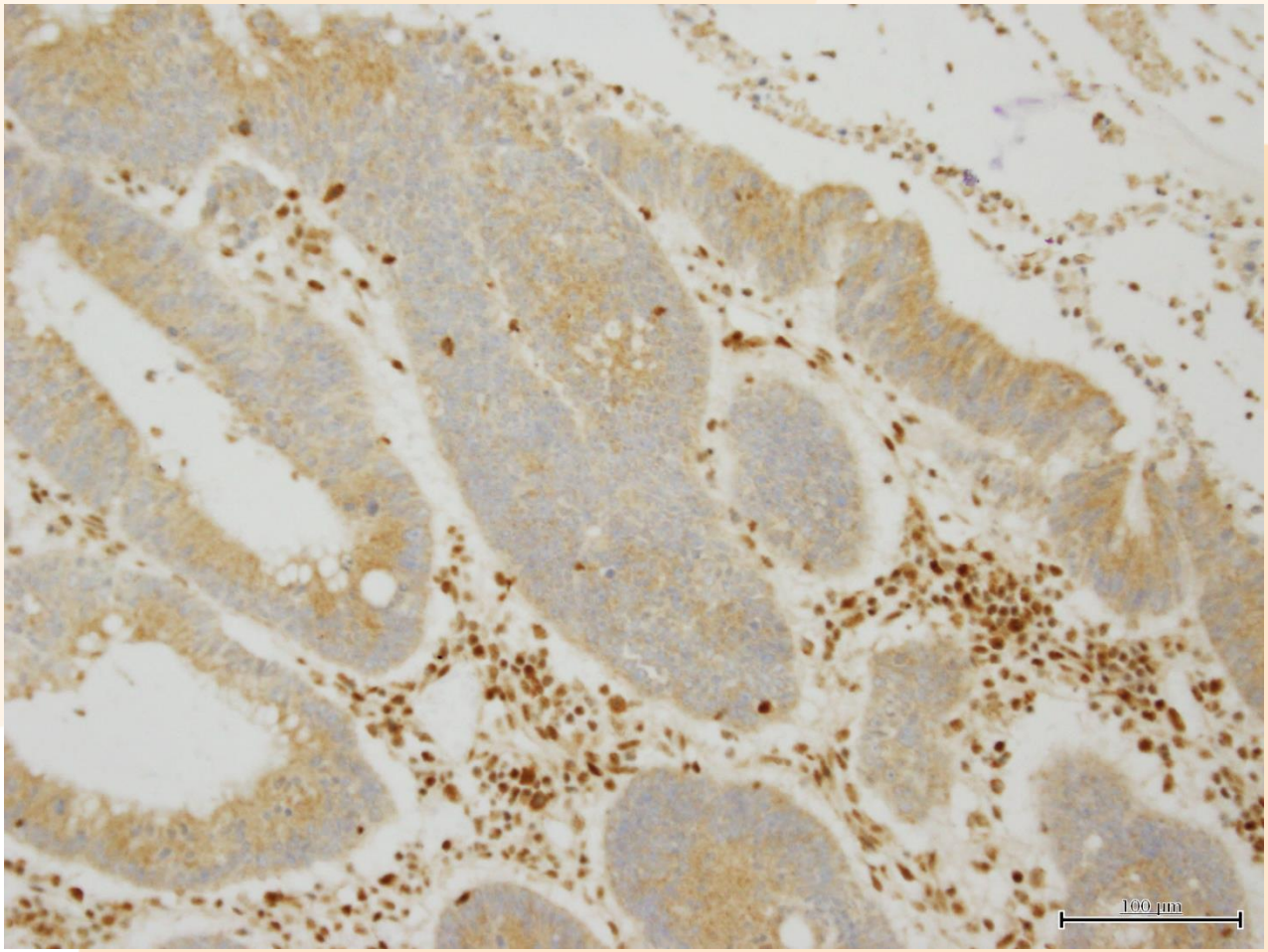
- Biopsy rectosigmoid colon mass
  - Adenocarcinoma, low grade
    - MLH1 : No loss
    - PMS2 : No loss
    - MSH2 : Loss
    - MSH6 : Focal and weak (abnormal)
- Splenic flexure polyp
  - Tubulovillous adenoma, low grade dysplasia
    - MLH1 : No loss
    - PMS2 : No Loss
    - MSH2 : Loss
    - MSH6 : Loss
- Consistent with Lynch syndrome with MSH2 germline mutation
- Operation : Total colectomy + Ileorectal anastomosis + TAH + BSO

Total colectomy + Ileorectal anastomosis + TAH + BSO

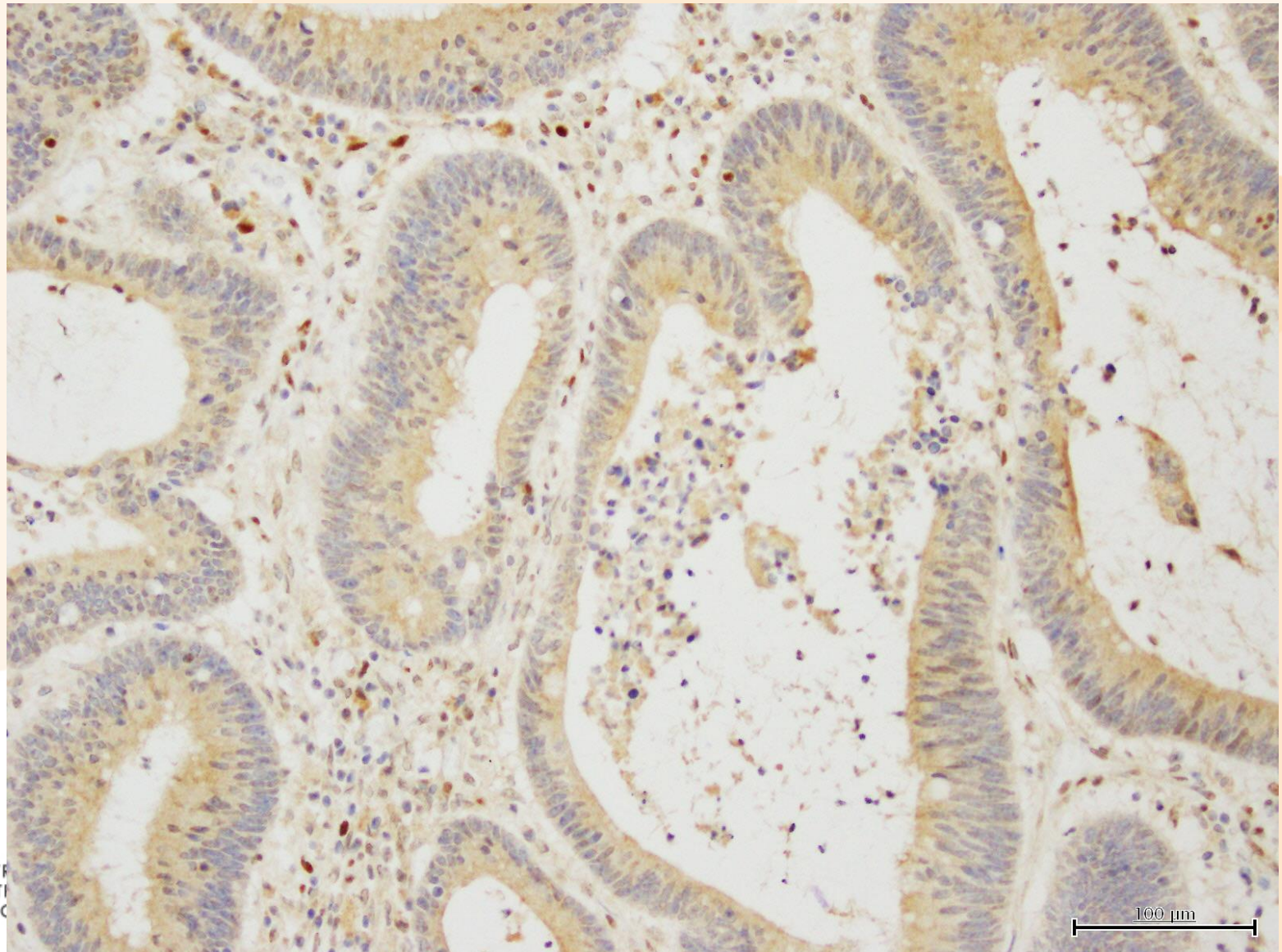
- Rectosigmoid colon tumour
  - Adenocarcinoma, low grade, with mucinous component, pT4bN1bM0, Stage IIIc



Rectosigmoid colon tumour
MSH2



Rectosigmoid colon tumour
MSH6



Total colectomy + Ileorectal anastomosis + TAH + BSO

- Rectosigmoid colon tumour
  - Adenocarcinoma, low grade, with focal mucinous component, pT4bN1bM0, Stage IIIc
    - MLH1 : No loss
    - PMS2 : No loss
    - MSH2 : Loss
    - MSH6 : Very focal and weak (abnormal)
- TAH+BSO
  - Inactive endometrium with exogenous progestin effect

Follow up

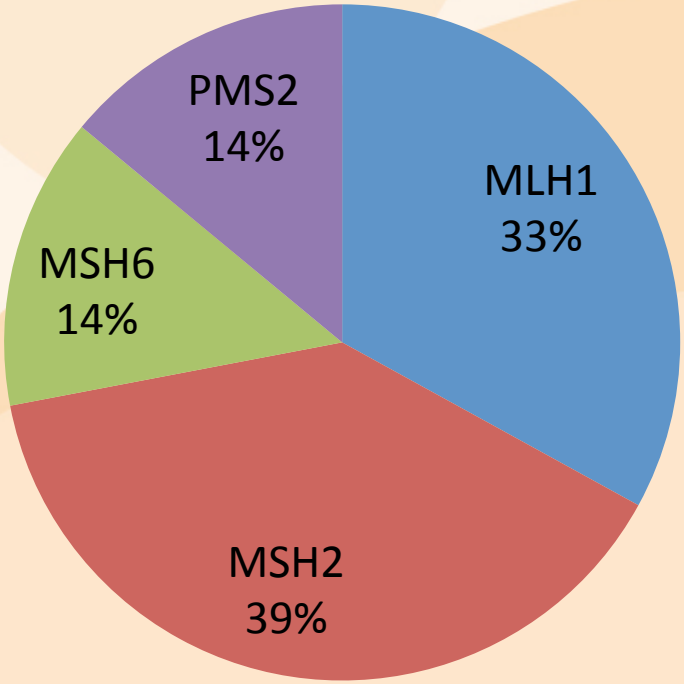
- Mutation analysis
  - Pathogenic mutation detected in MSH2 gene (c. 942+3A>T)

Lynch syndrome

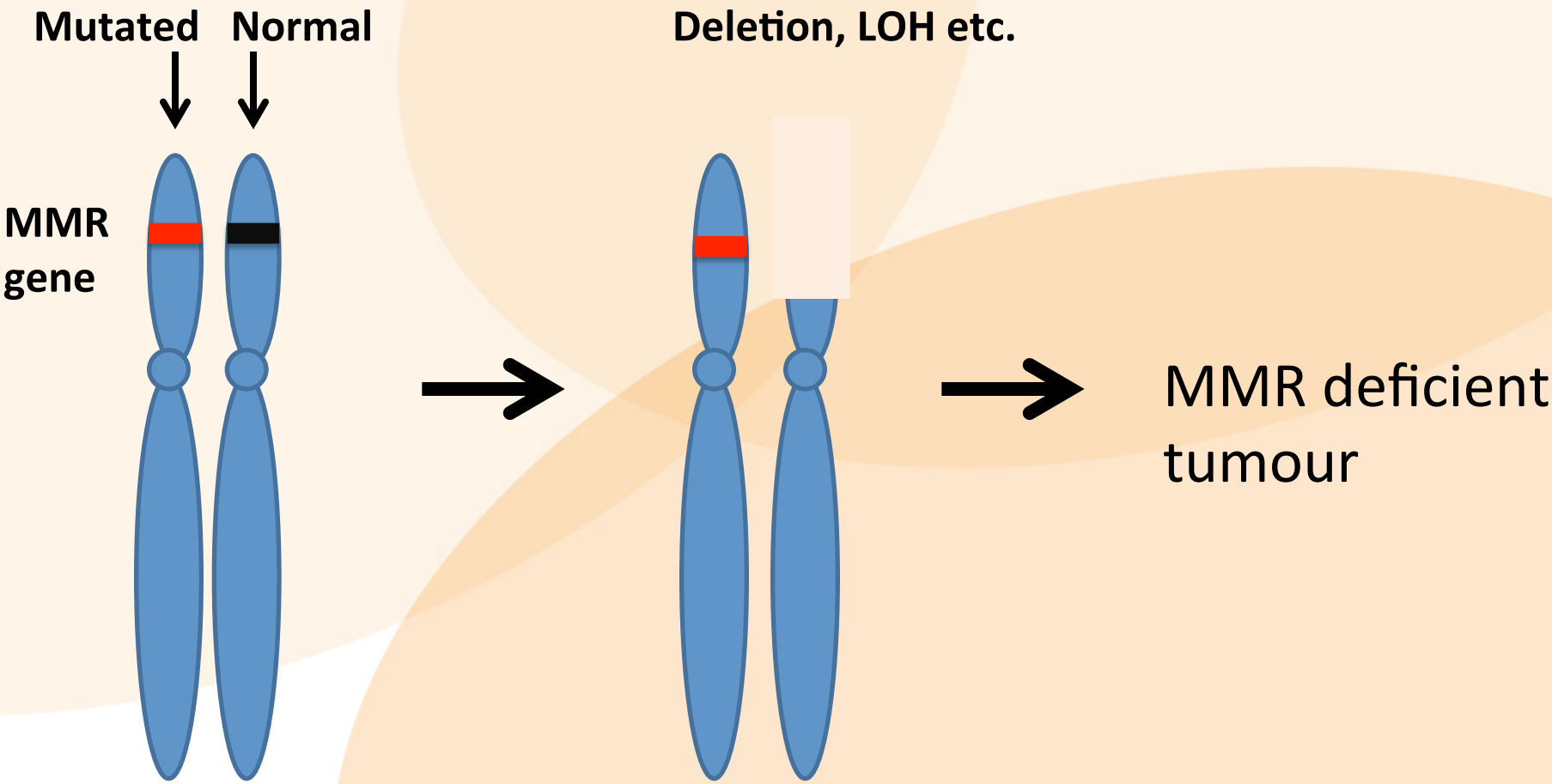
- Autosomal dominant cancer predisposition syndrome caused by mutations in :
  - DNA mismatch repair genes : MLH1, PMS2, MSH2, MSH6
  - EPCAM (TACSTD1) :
    - germline deletion of the exons at 3’ end
    - allele-specific methylation of MSH2 that is immediately downstream from EPCAM on chromosome 2
    - Silencing the transcription of MSH2

Lynch syndrome

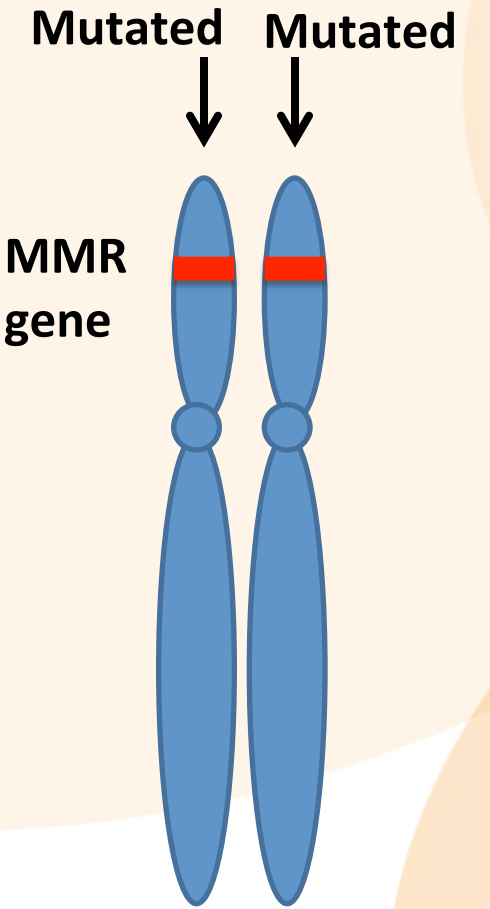
Proportion of MMR genes involved



Lynch syndrome



Constitutional mismatch repair deficiency syndrome



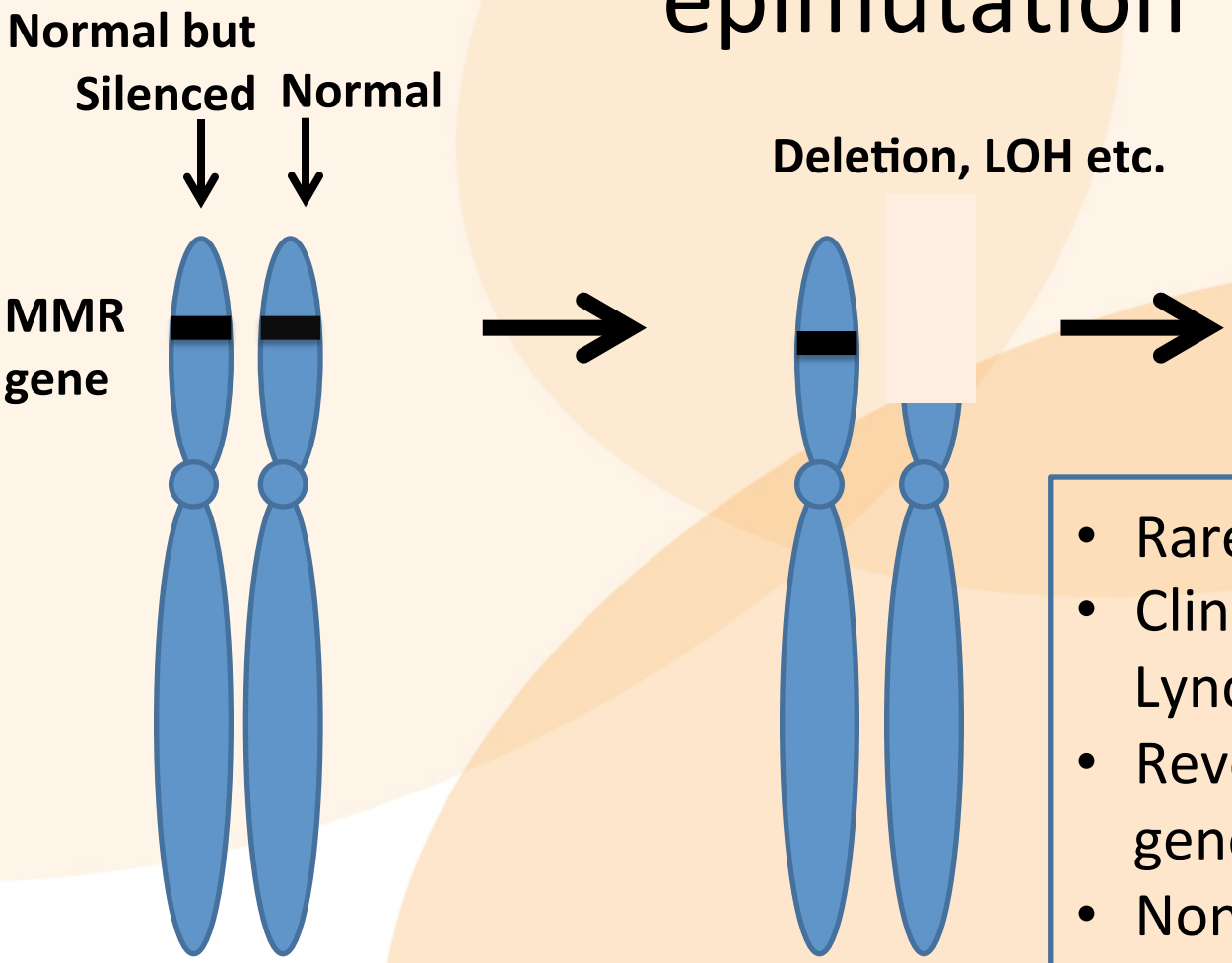
normal tissue

MMR deficient

→ MMR deficient tumour

- Café au lait spots
- Childhood and teenage onset of CRCs and Lynch-associated malignancies
- Oligopolyposis of small bowel
- Brain tumours
- Hematologic malignancies
- 55% involves PMS2 gene

Constitutioal (germline) MLH1 epimutation



- Rare
- Clinical features similar to Lynch Syndrome
- Reversible between generations
- Non-Mendelian inheritance
- BRAF wild type
- Mosaicism
- No mutation detected

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Colorectal cancers (CRCs) in Lynch syndrome

- The frequency of Lynch syndrome among CRCs is approximately 2-3% (1 in 30 CRC patients)
- Cumulative risk of developing CRCs is sex and involved gene dependent
  - Penetrance : M>F, MLH1 and MSH2 > PMS2 and MSH6

Table 3. Gene-Specific Cumulative Risks of Colorectal Cancer by Age 70 Years in Lynch Syndrome

Gene mutation carriers	Risk, %	Mean age at diagnosis, *y*	References
Sporadic cancer	5.5	69	29
MLH1/MSH2	Male: 27–74 Female: 22–53	27–46	17–21, 23
MSH6	Male: 22 Female: 10 Male and female: 18	54–63	17, 22
PMS2	Male: 20 Female: 15	47–66	25

Gastroenterology 2014;147:502-526

HNPCC, Lynch syndrome and Familial colorectal cancer type X

Hereditary nonpolyposis colorectal cancer (HNPCC)
- clinical diagnosis using Amsterdam 1 criteria

MMR deficient

MMR proficient

Lynch syndrome
- genetic diagnosis

Familial colorectal cancer type X

Lindor et al, JAMA 293 (16), pp1979-1985 (2005)

Characteristics of CRCs in Lynch syndrome

- Mismatch repair deficiency
- Proximal (70% proximal to the splenic flexure)
- Large and lymph-node-negative
- Poorly differentiated
- Excess of mucinous, signet cell and medullary subtypes
- Excess of tumour-infiltrating lymphocytes and Crohn-like reaction
- Extracolonic malignancies (endometrium, stomach, ovary, pancreas, ureter, renal pelvis, biliary-tract, brain, sebaceous neoplasms, keratoacanthoma and small bowel)
- Accelerated carcinogenesis from adenoma to carcinoma within 2-3 years in Lynch syndrome cases
  - 10-15 years in general population

Surgical Guidelines

- Guideline: Colectomy with ileorectal anastomosis is the primary treatment of patients affected with LS with colon cancer or colon neoplasia not removable by endoscopy. Consideration for less extensive surgery should be given in patients older than 60-65 years of age and those with underlying sphincter dysfunction.

- Guideline: Hysterectomy and bilateral salpingooophorectomy should be recommended to women with LS who have finished childbearing or at age 40 years.

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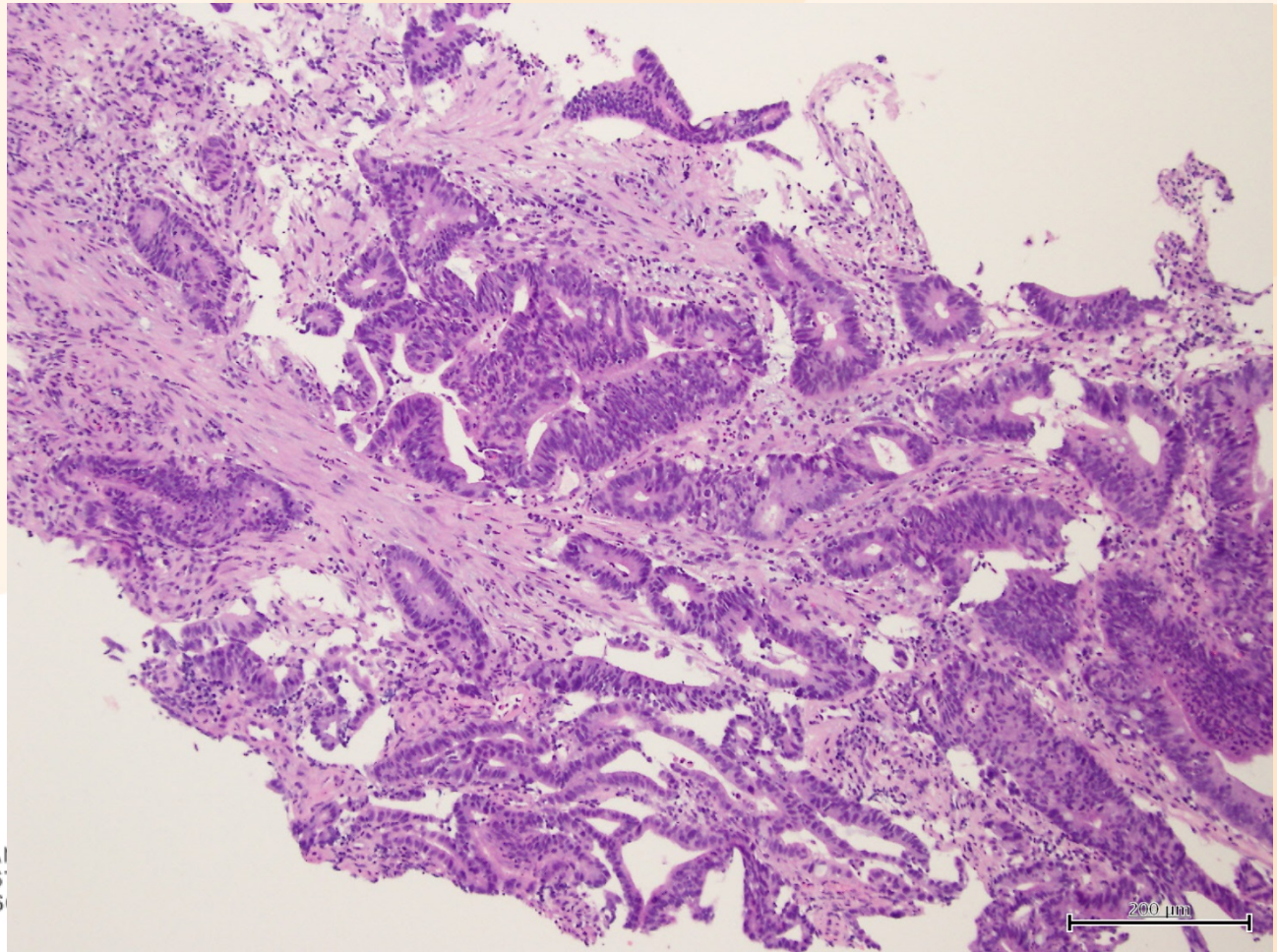
Gastroenterology 2014;147:502-526

T.M. 54y F

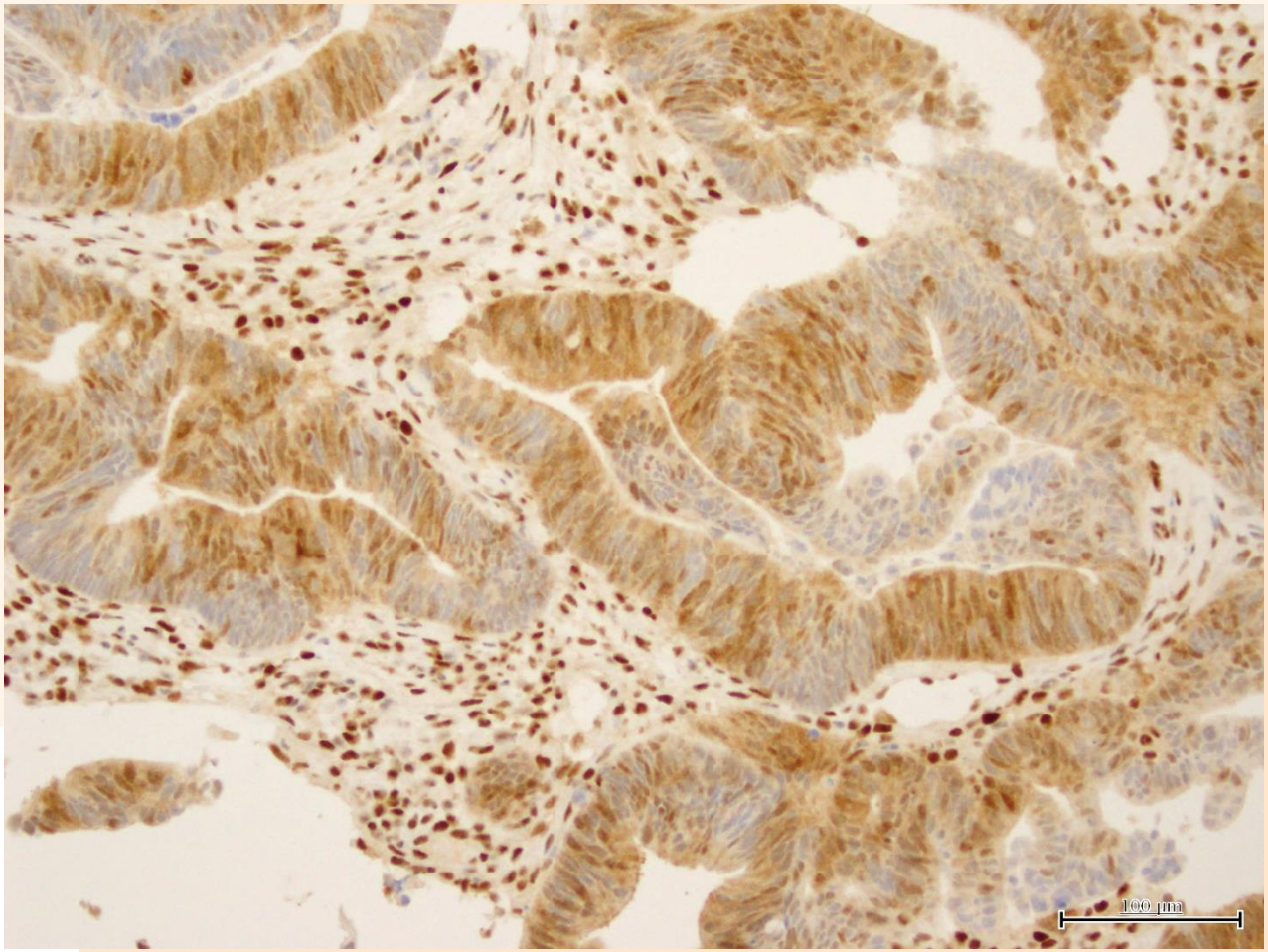
- Presented with change in bowel habit and rectal bleeding
- Colonoscopy : Mass in distal sigmoid colon
- PMHx:
  - At 41y, right hemicolectomy for ascending colon adenocarcinoma, HG, no loss of MMR IHC
  - At 42y, TAH+BSO for uterine endometrioid adenocarcinoma, FIGO G1, Stage 1B, no MMR IHC
- FHx:
  - There are 3 confirmed CRCs in 2 generations
  - Two of which showed loss of MLH1 and PMS2, with negative BRAF mutation
  - Youngest age at diagnosis was 30y
  - Also multiple extracolonic cancers in family, which include endometrial, cholangio carcinoms and gastric cancers
  - Meet the Amsterdam criteria
  - MLH1 and PMS2 germline mutation analysis : no pathogenic mutation detected

Distal sigmoid mass biopsy

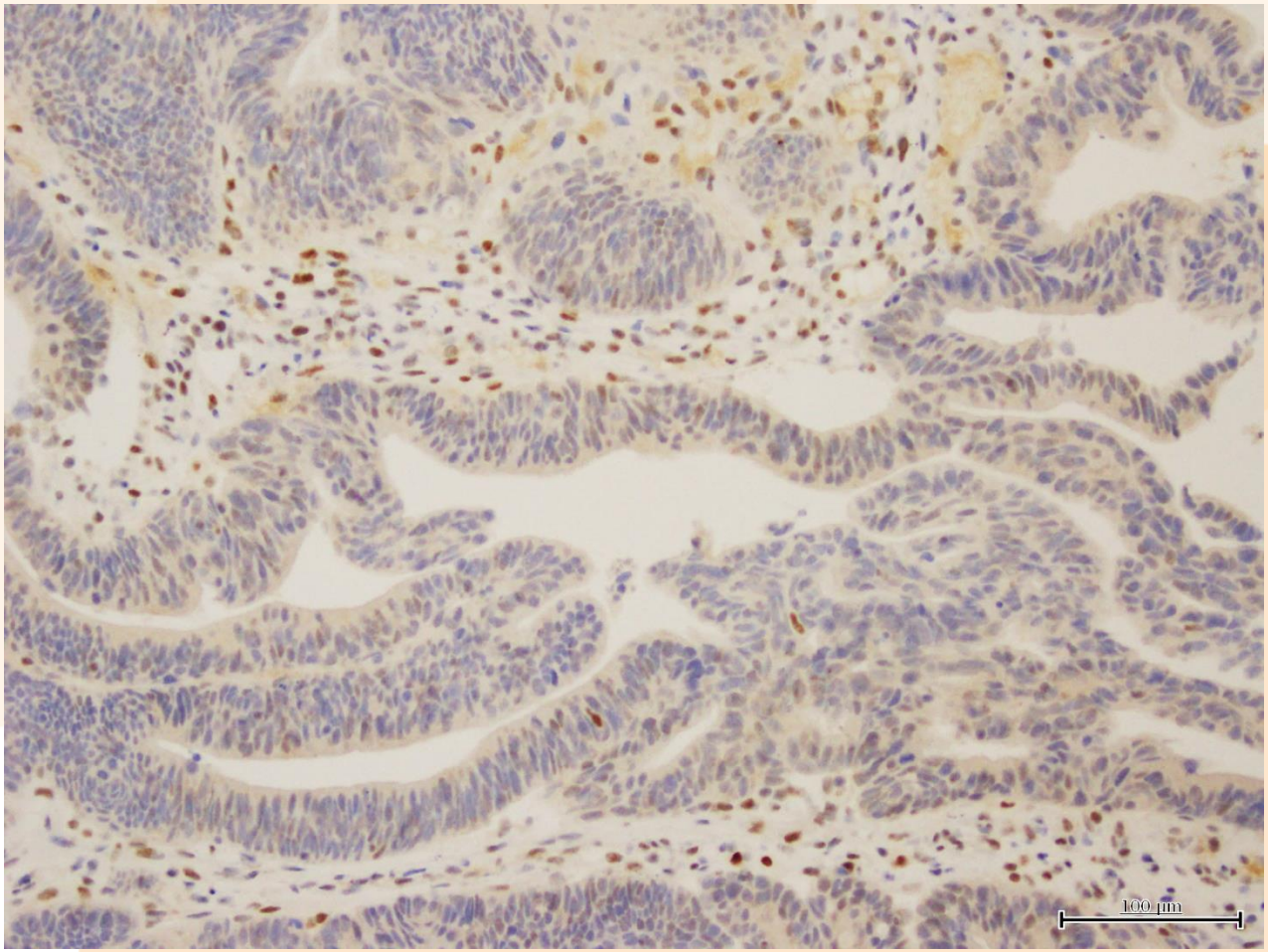
- Adenocarcinoma, low grade



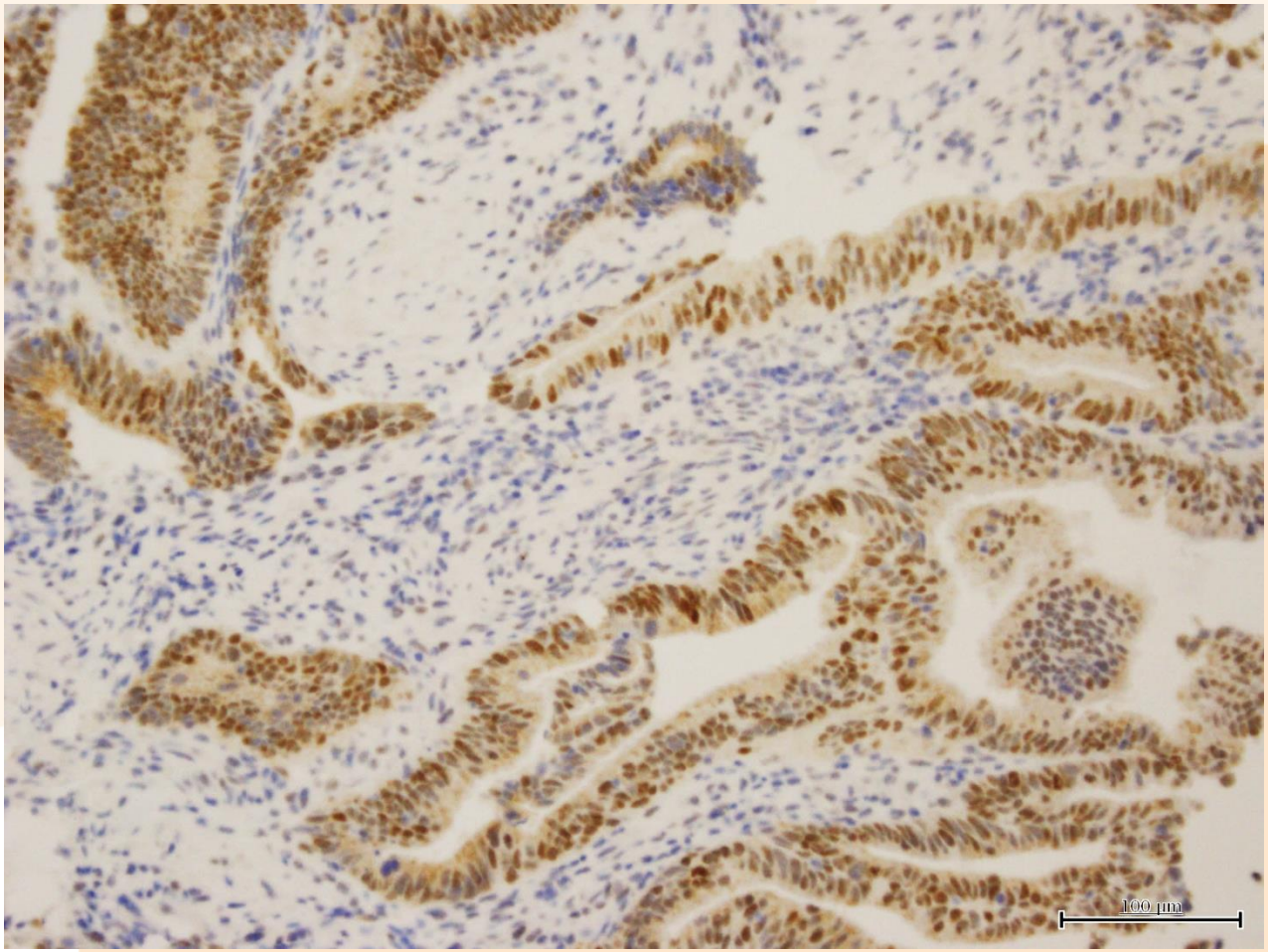
Distal sigmoid mass biopsy
MLH1



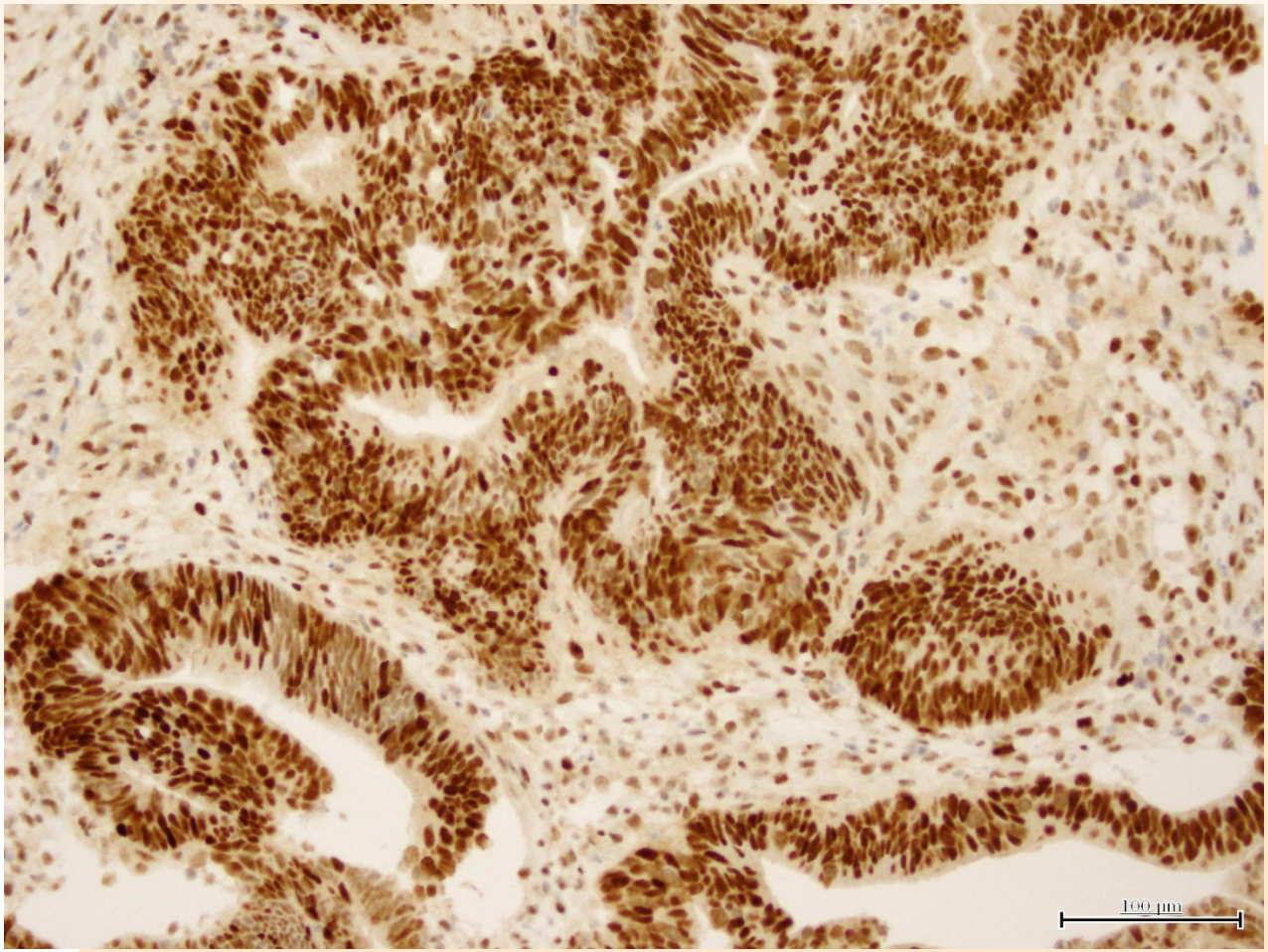
Distal sigmoid mass biopsy
PMS2



Distal sigmoid mass biopsy
MSH2



Distal sigmoid mass biopsy
MSH6

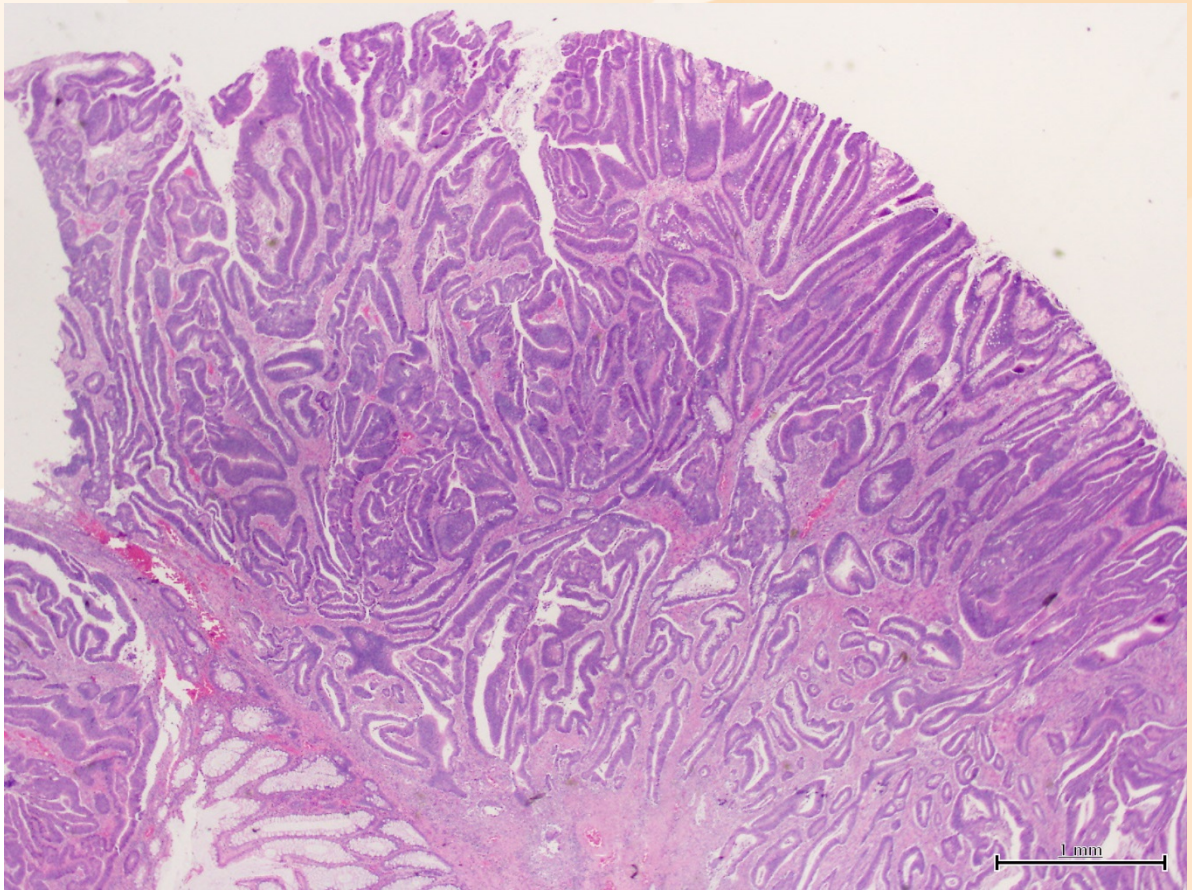


Distal sigmoid mass biopsy

- Adenocarcinoma, low grade
  - MLH1: Reduced/weak
  - PMS2: Near complete loss (very focal weak positivity only)
  - MSH2: No loss
  - MSH6: No loss

Completion colectomy and end ileostomy

– Adenocarcinoma, Low grade, distal sigmoid colon, pT2N0M0, Stage I



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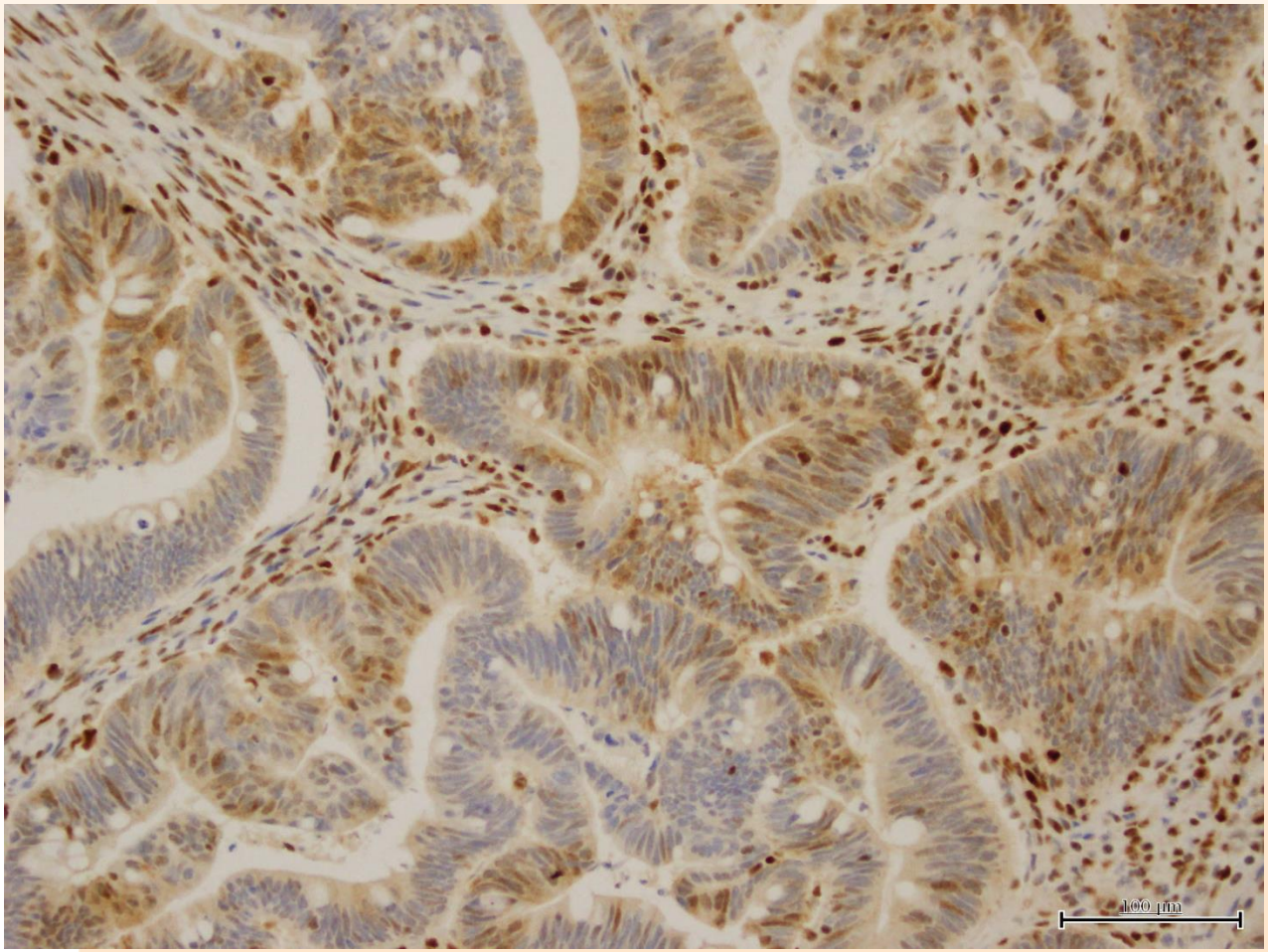
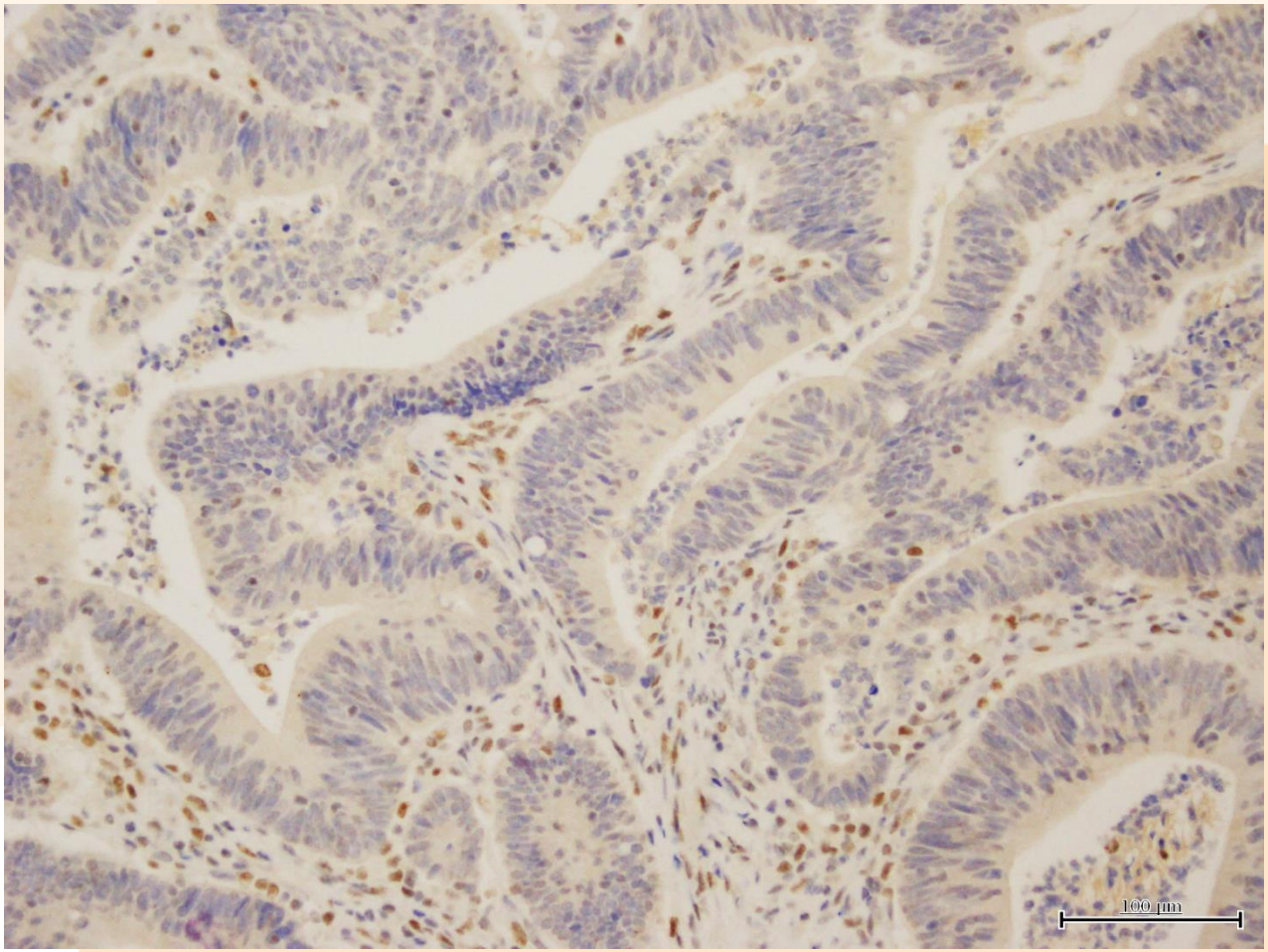
Completion colectomy and end ileostomy
MLH1



Completion colectomy and end ileostomy
PMS2



Completion colectomy and end ileostomy

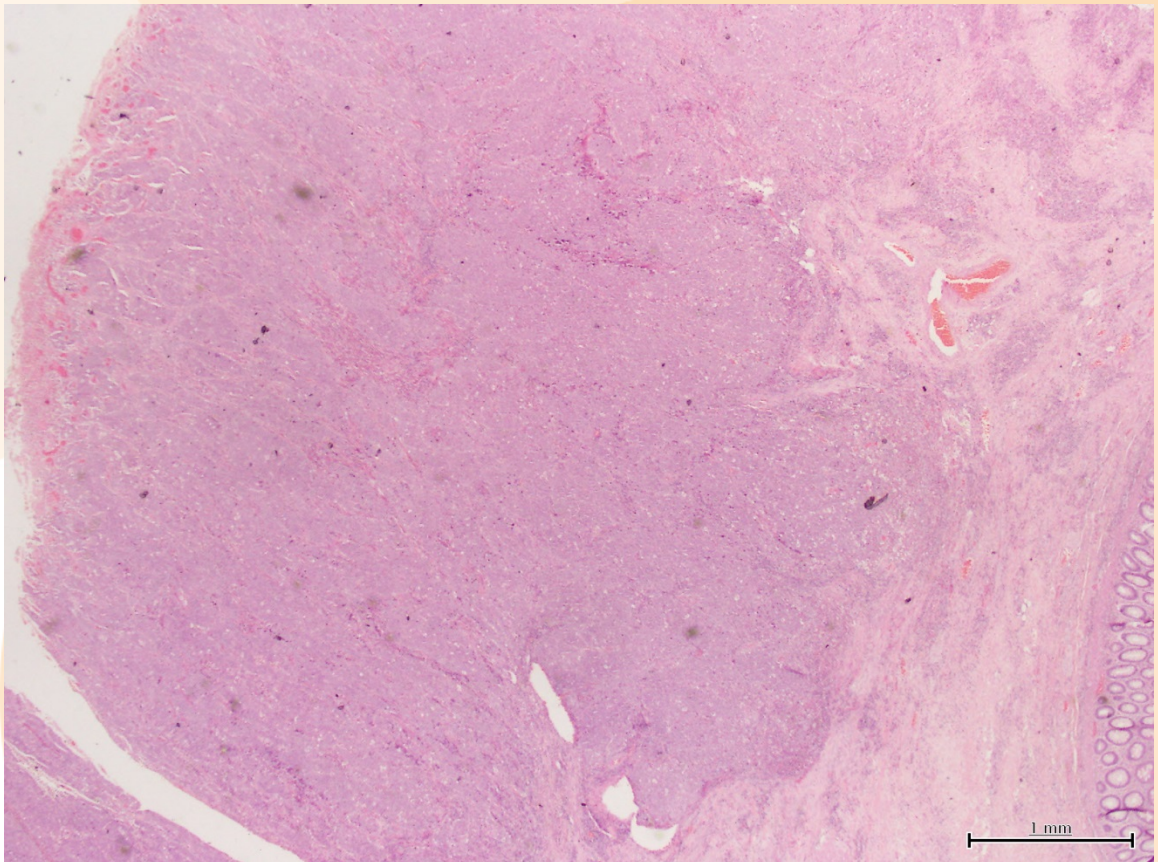
- Adenocarcinoma, Low grade, distal sigmoid colon, pT2N0M0, Stage I
  - MLH1: Weak and focal positivity (abnormal pattern)
  - PMS2: Near complete loss (abnormal pattern)
  - MSH2: No loss
  - MSH6: No loss
- BRAFV600E mutation negative (PCR)

Interpretation

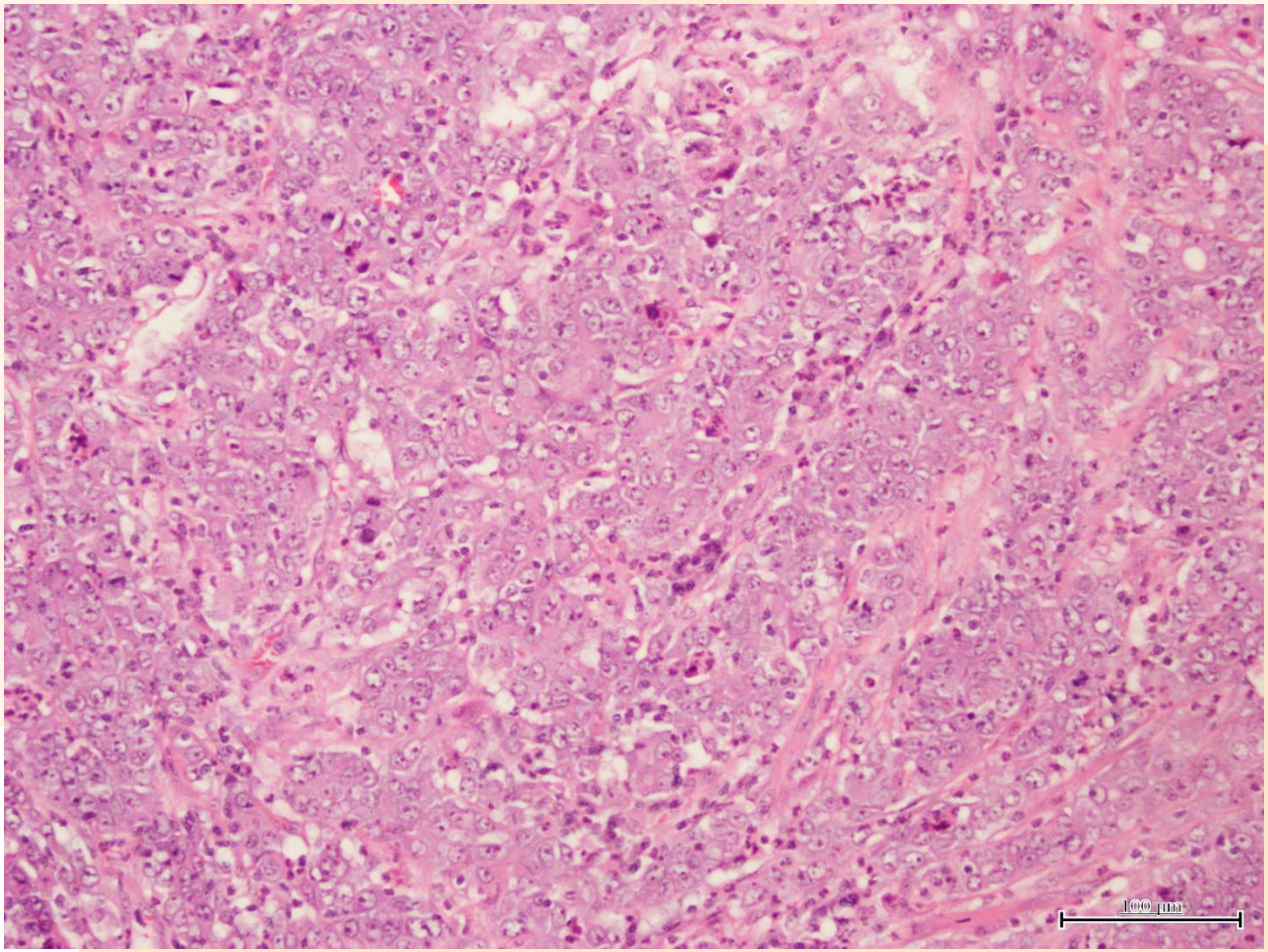
- Consistent with Lynch syndrome with germline mutation involving possibly MLH1

Right hemicolectomy (13 years ago, at age 41y)

- Adenocarcinoma, High Grade, ascending colon
  - MMR IHC ‘no loss’ (no slides for review)

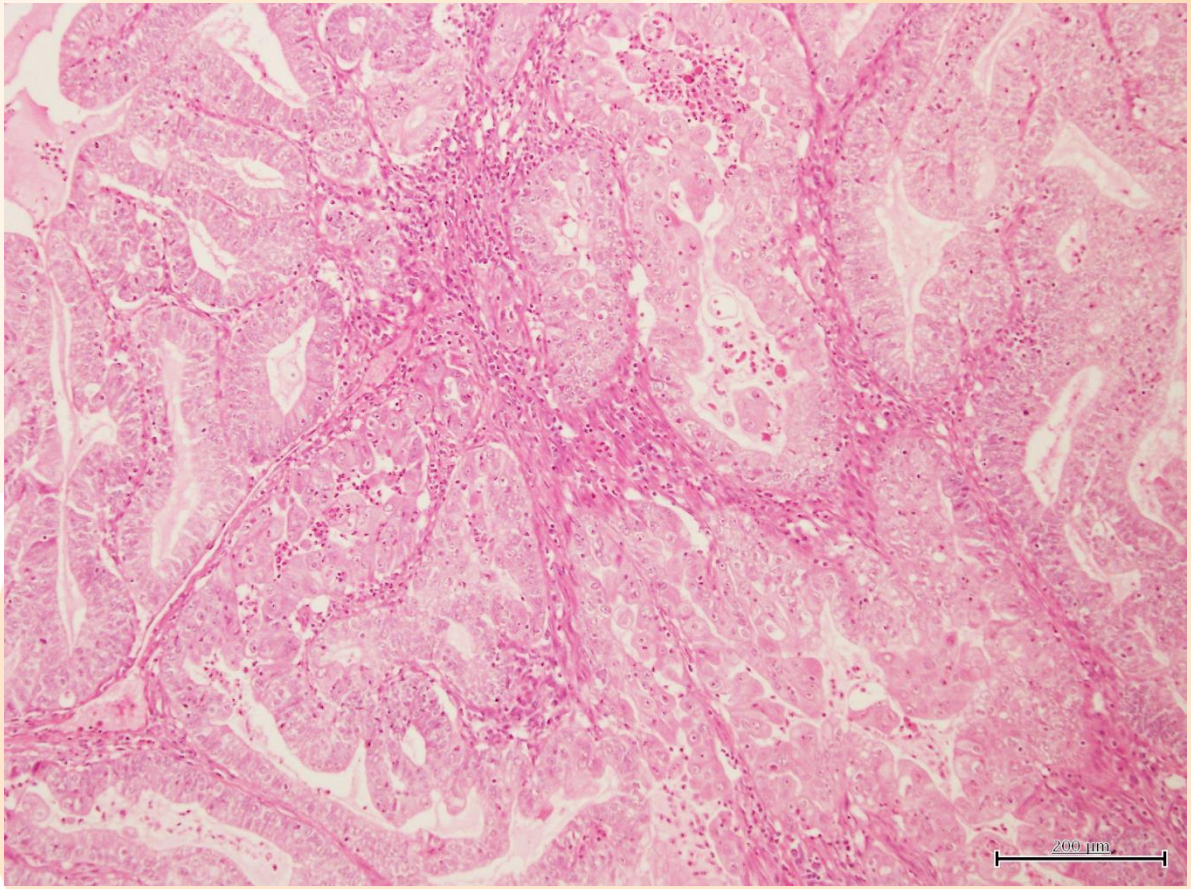


Right hemicolectomy



TAH + BSO
(12 years ago, at age 42y)

- Endometrioid adenocarcinoma, FIGO G1, Stage 1B, MMR IHC not performed



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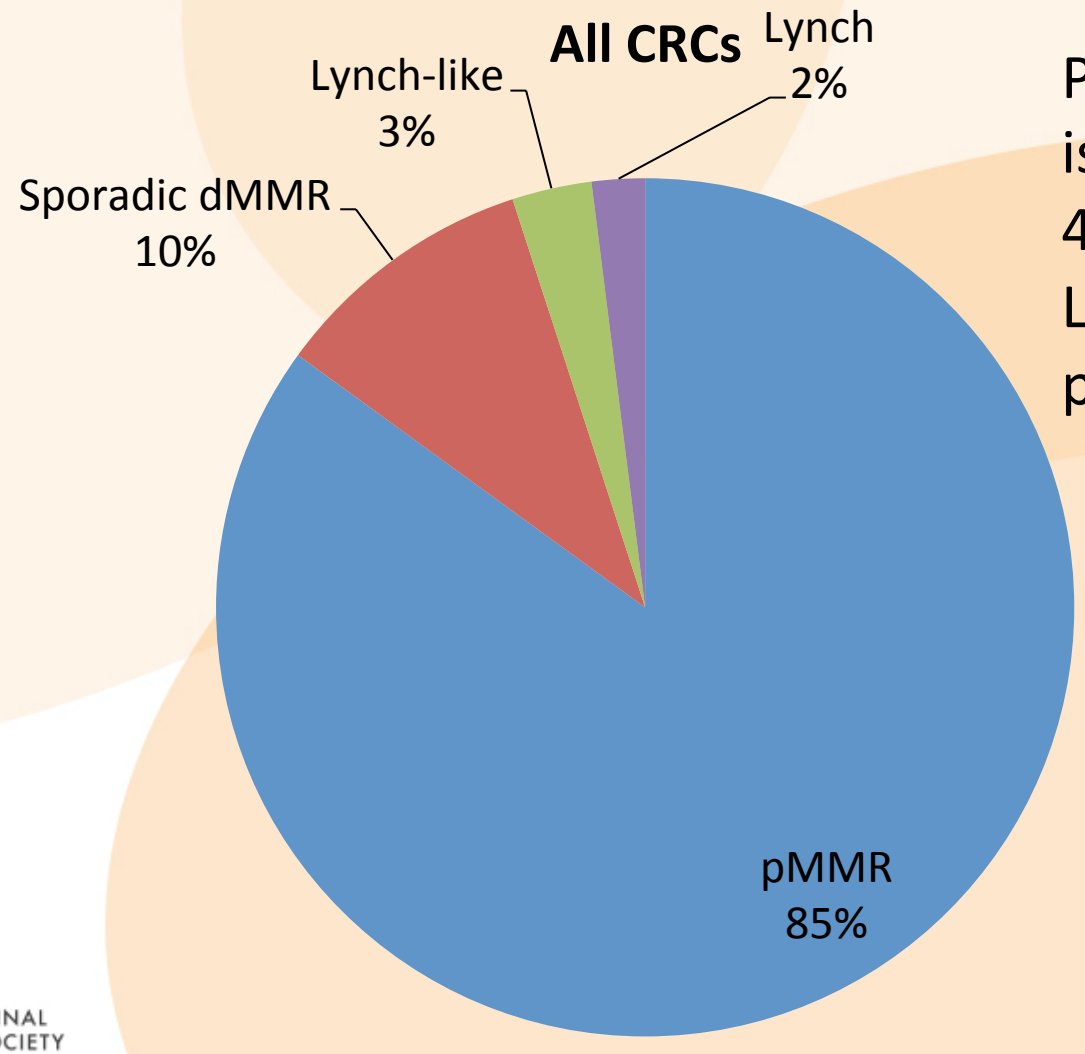
Lynch-like syndrome

- CRCs with MMR deficiency (MSI or MMR IHC)
- No MLH1 promoter methylation or BRAF mutation detected
- No pathogenic germline mutation detected or only variant of unknown significance (VUS) detected

Lynch-like syndrome



Pathogenic mutation is detected only in 40% of suspected Lynch syndrome population

AUSTRALASIAN GASTROINTESTINAL PATHOLOGY SOCIETY

Lynch-like syndrome

- Clinical features are similar to Lynch syndrome except for lower incidence of CRCs and extracolonic malignancies
- Surveillance : No uniform strategy to date, should be individualized

Lynch-like syndrome

- Causes of Lynch-like syndrome : likely heterogenous group
  - False 'positive' MMR IHC
  - Lynch syndrome but mutation may not be detectable by current methods
    - Mutations in the 5' and 3' untranslated regions of MMR genes
    - Mutations in deep intronic sequences
    - Inversion of MSH2 (exons 1-7)
    - Somatic mosaicism (newer sequencing assays are able to detect mutations in <5% of DNA)
    - EPCAM mutation (although most assays examine EPCAM now)
  - Biallelic (somatic) tumor mutations in MMR genes

TABLE 4 Mutation types associated with LS

Mutation	Description
Missense	A change in one DNA base pair that results in the substitution of one amino acid for another in the protein made by a gene
Nonsense	A change in one DNA base pair that results in a premature signal to stop building a protein. This type of mutation results in a shortened protein that may function improperly or not at all
Insertion	Changes the number of DNA bases in a gene by adding a piece of DNA. As a result, the protein made by the gene may not function properly
Deletion	Changes the number of DNA bases by removing a piece of DNA. Small deletions may remove one or a few base pairs within a gene, while larger deletions can remove an entire gene or several neighbouring genes. The deleted DNA may alter the function of the resulting protein(s)
Duplication	Consists of a piece of DNA that is abnormally copied one or more times. This type of mutation may alter the function of the resulting protein
Frameshift mutation	Occurs when the addition or loss of DNA bases changes a gene's reading frame. A reading frame consists of groups of three bases that each code for one amino acid. A frameshift mutation shifts the grouping of these bases and changes the code for amino acids. The resulting protein is usually nonfunctional. Insertions, deletions and duplications can all be frameshift mutations
Splice site	Causes abnormal mRNA processing, generally leading to in-frame deletions of whole exons or out-of-frame mRNA mutations leading to nonsense-mediated decay of mRNA. Mutations may be located deep in intronic sequences
Promoter	Mutations in the controlling region of a gene leading to its non-expression. Epigenetic mutations, i.e. abnormal methylation of CpG sites may give rise to the same effect

CpG, —C—phosphate—G—; mRNA, messenger ribonucleic acid.
Adapted from Genetics Home Reference.[27]

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TABLE 5 Genetic testing in LS

Test	Description	Comments
High-output screening techniques	SSCP CSGE DGGE DHPLC	These methods all take advantage of the observation that alteration of DNA confers chemical properties that allow it to be differentiated from normal DNA (now considered obsolescent/obsolete in the UK)
DNA sequencing	This can be used following a high-output screening technique or as a primary approach when IHC patterns allow for targeting of a MMR gene	The main method used in the UK for detecting most MMR gene mutations. However, it does not reliably allow for detection of deletions or rearrangements, which are also important in LS. DNA sequencing has become automated in recent years, greatly reducing the required time, costs and expertise[4]
Methods to detect large structural DNA abnormalities	MLPA is the preferred technique in the UK	Large structural DNA abnormalities are an important cause of LS (5–25% of cases, depending on the gene) but are not generally detected by high-output screening techniques or DNA sequencing. There are several methods for detecting these defects. MLPA, which involves measurement of the relative copy number of DNA sequences, has evolved to become a standard approach for analysing MMR genes for deletions[4]
Conversion analysis	Only a single allele is analysed at a time. This can increase the yield of genetic testing but is technically complicated, expensive and not widely available	

CSGE, conformation-sensitive gel electrophoresis; DGGE, denaturing gradient gel electrophoresis; DHPLC, denaturing high-performance liquid chromatography; MLPA, multiplex ligation-dependent probe amplification; SSCP, single-strand conformational polymorphism.

Endometrial cancer in Lynch syndrome

- The frequency of Lynch syndrome among endometrial cancer is 1.8-3.0%
- Frequently gynaecologic cancer precedes CRC as sentinel malignancy

Table 4. Cumulative Risks of Extracolorectal Cancer by Age 70 Years in Lynch Syndrome

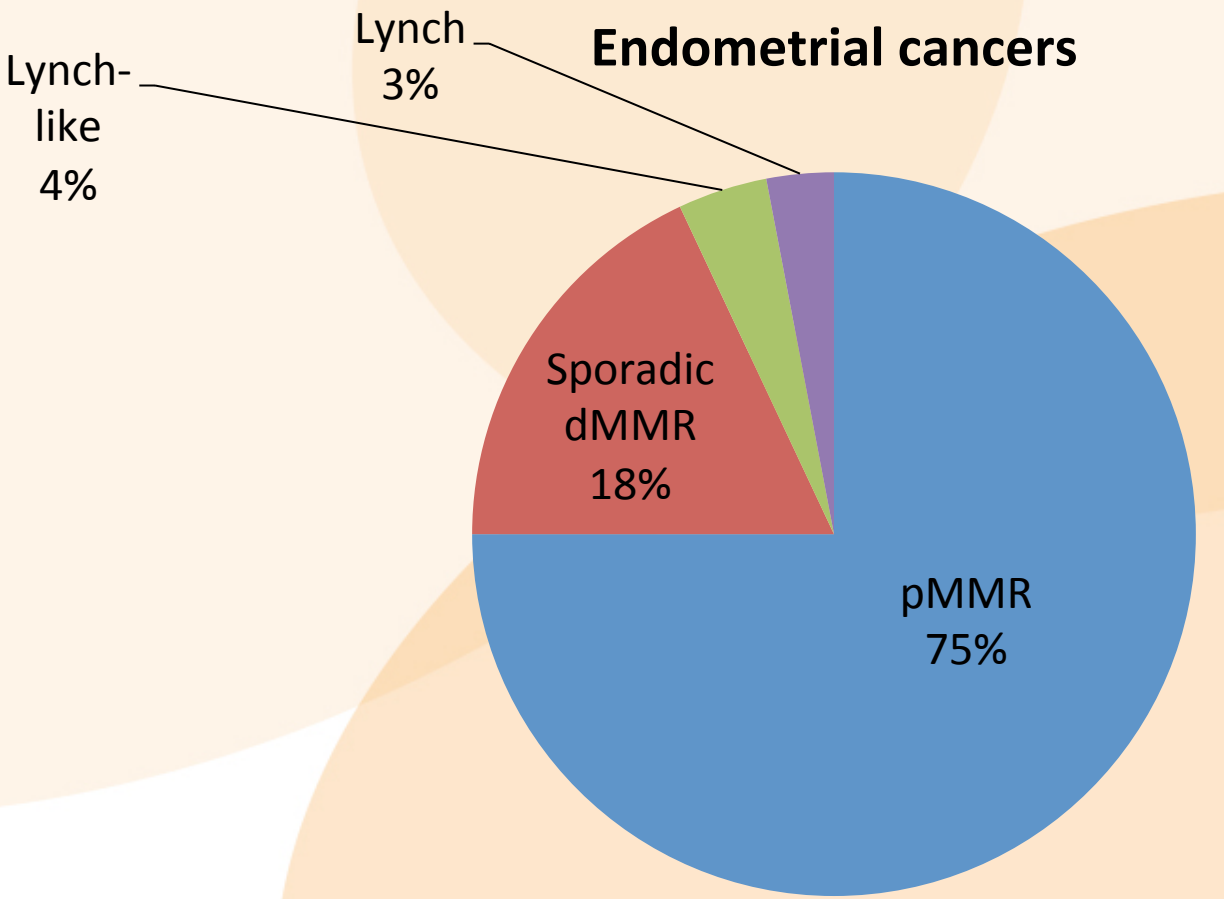
Cancer	Risk general population, %	Risk in LS, %	Mean age at diagnosis, y
Endometrium	2.7		65
MLH1/MSH2		14–54	48–62
MSH6		17–71	54–57
PMS2		15	49
Stomach	<1	0.2–13	49–55
Ovary	1.6	4–20	43–45
Hepatobiliary tract	<1	0.02–4	54–57
Urinary tract	<1	0.2–25	52–60
Small bowel	<1	0.4–12	46–49
Brain/central nervous system	<1	1–4	50
Sebaceous neoplasm	<1	1–9	NA
Pancreas	1.5	0.4–4.0	63–65
Prostate	16.2	9–30	59–60
Breast	12.4	5–18	52

Gastroenterology 2014;147:502-526

MMR deficiency in endometrial cancer

- 20-25% of endometrial cancers are MMR deficient
- 65-75% of MMR deficient endometrial cancers are sporadic (MLH1 promoter methylation)
- The rest are Lynch-like (50%) or Lynch syndrome (50%)
- BRAFV600E mutation is NOT associated with MLH1 promoter methylation (sporadic MMR deficiency)

MMR deficiency in endometrial cancer



Lynch syndrome screening in endometrial cancer patients

- Any clinical criteria using age, personal history and family history will miss Lynch syndrome patients
- Emerging trend towards universal screening

cancer Diagnosis & Pathology

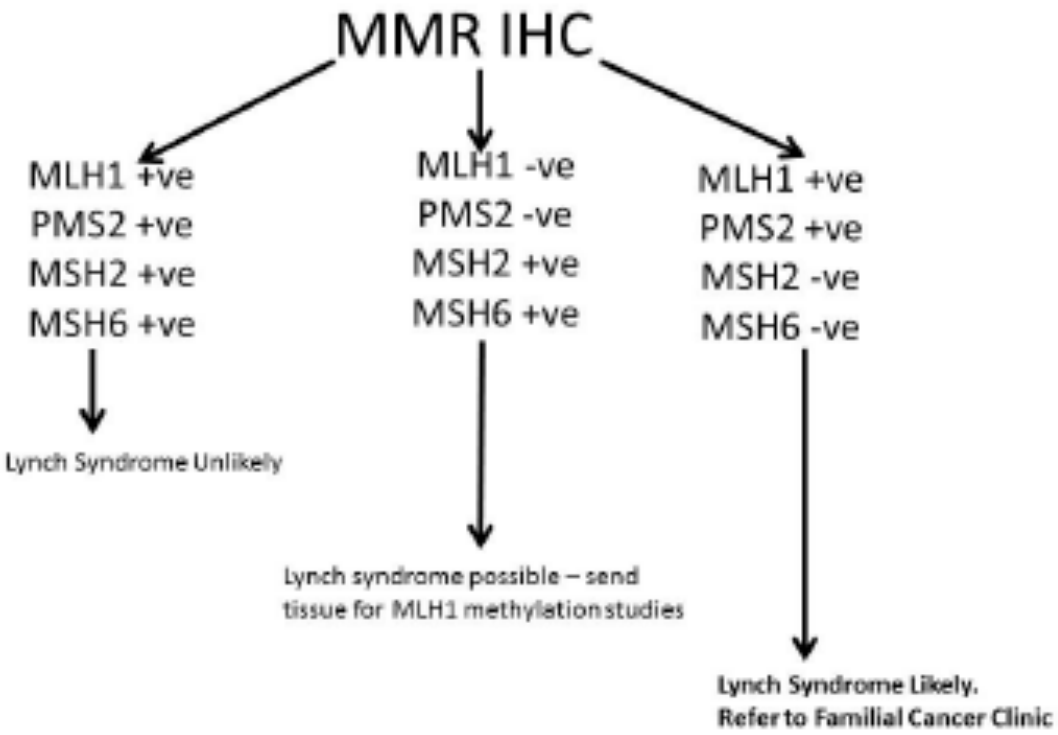
PaLMS Pacific Laboratory Medicine Services

Pathology North

Screening for Lynch Syndrome in gynaecological malignancy

Tumours recommended for Lynch Syndrome Screening with MMR IHC:

1. **All endometrial carcinomas.**
2. **Endometrioid carcinomas of any site.**
3. **Tumours from patients considered at high clinical risk for Lynch Syndrome**



Methylation studies to be performed on all cases which are MLH1-ve and PMS2-ve. If MLH1 promoter methylation is present, Lynch Syndrome is unlikely.

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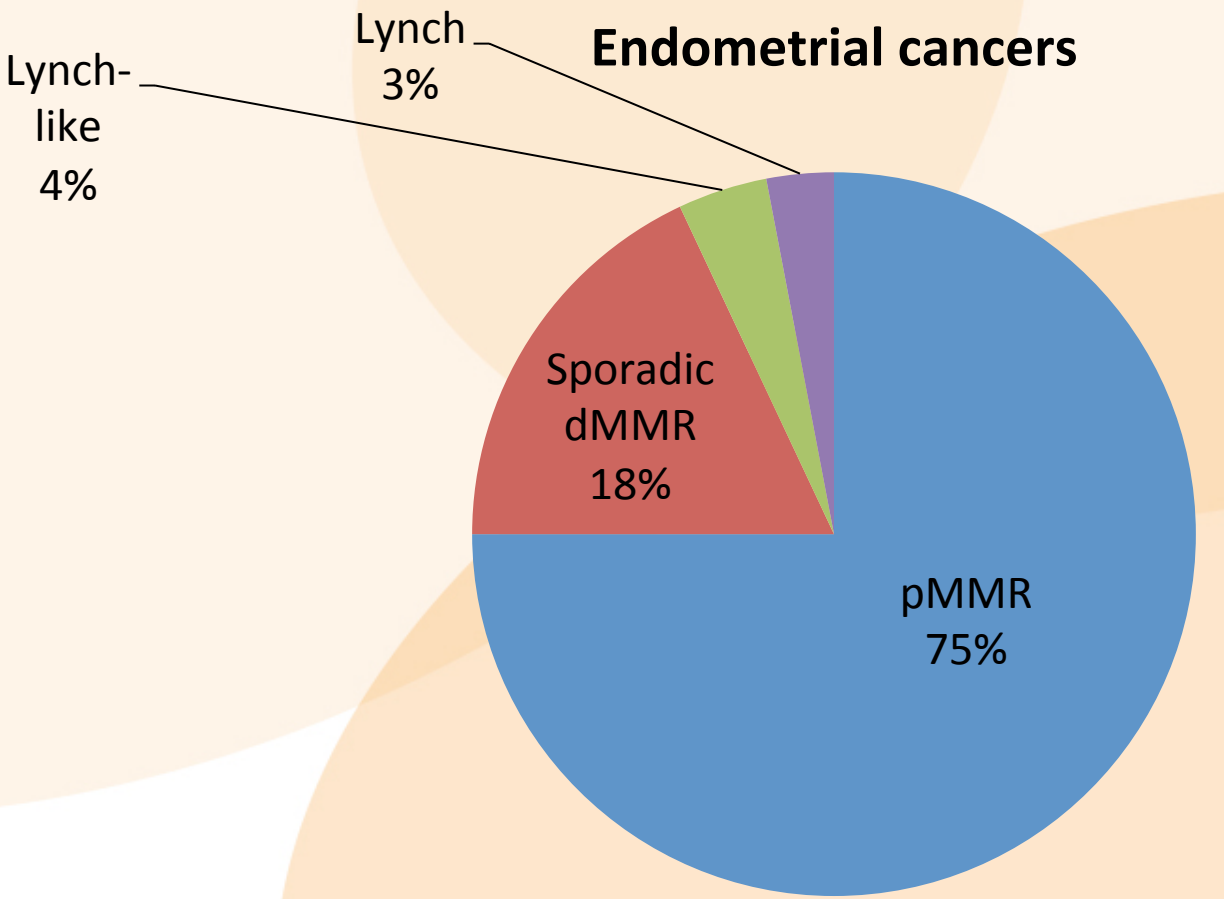
MMR deficiency in endometrial cancer

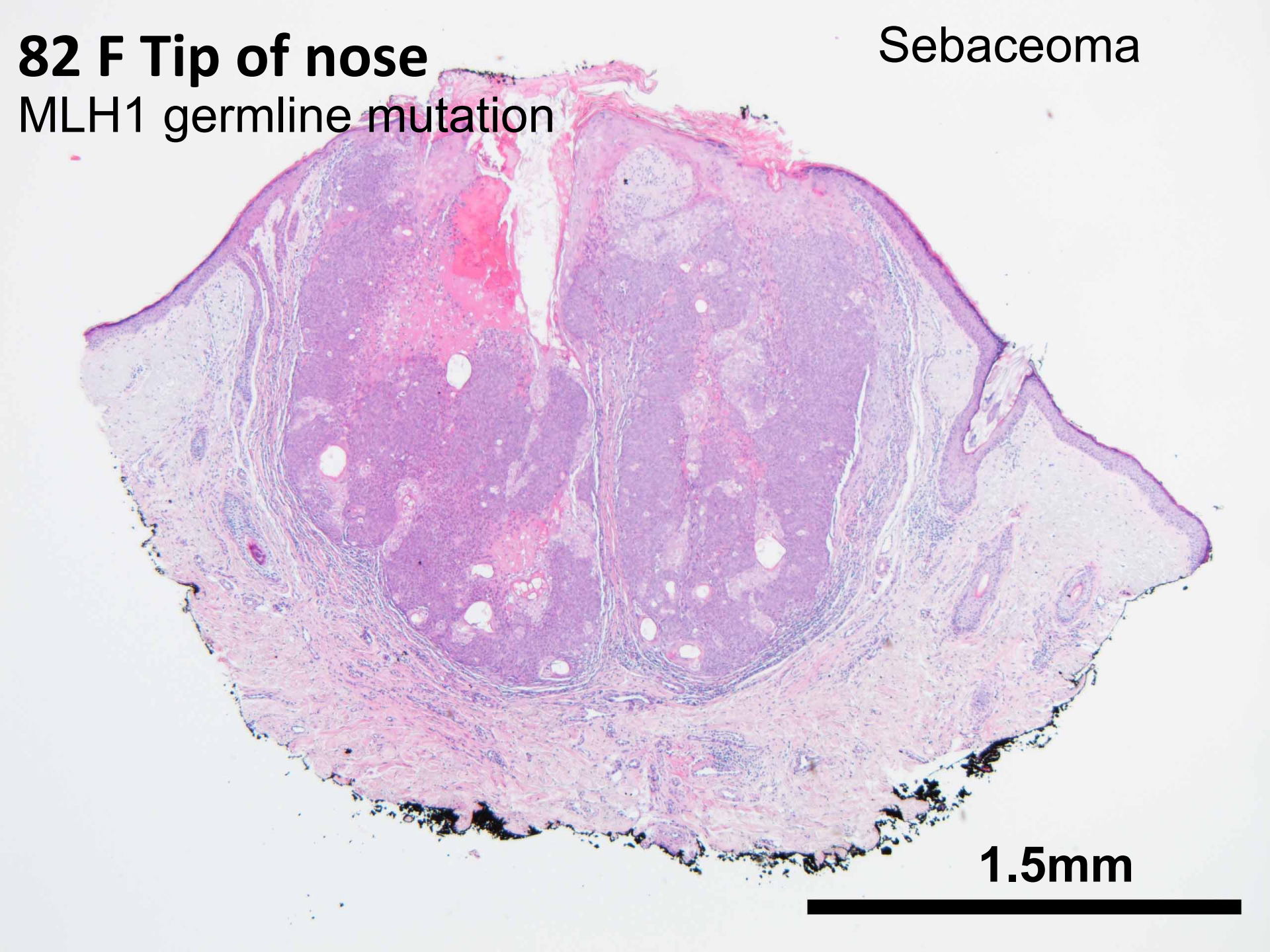


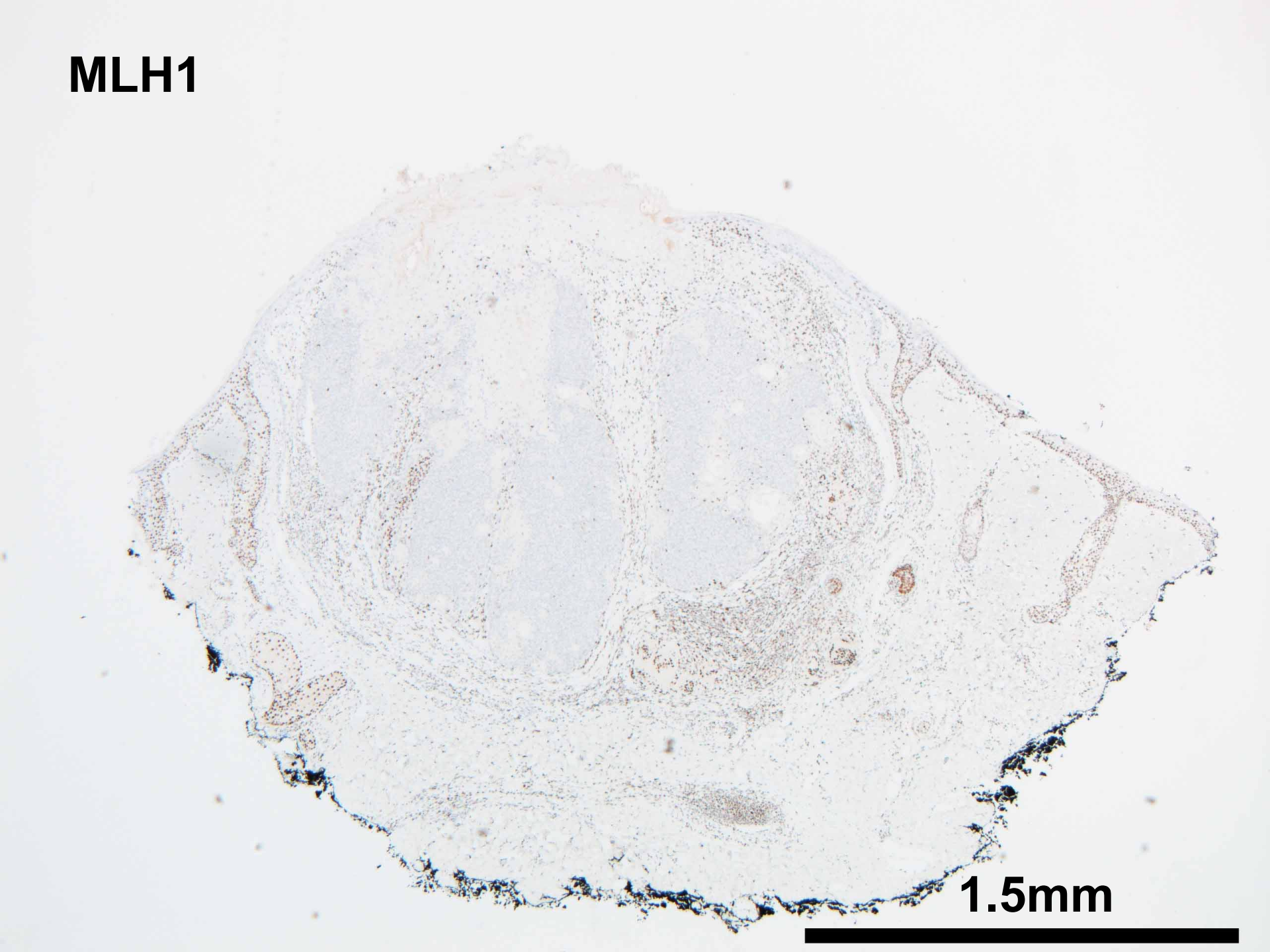
Focal and reduced MMR IHC

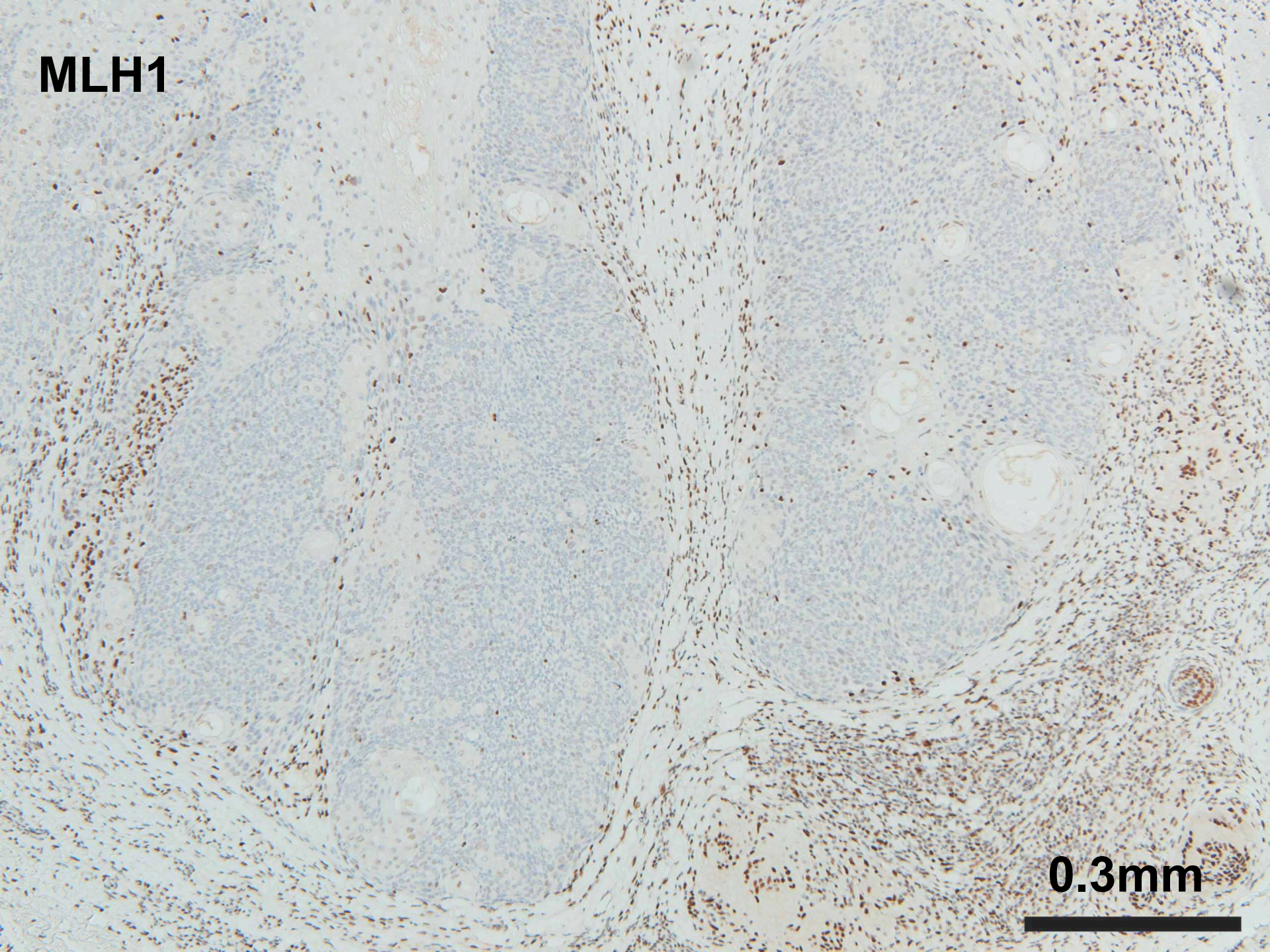
- Reduced, weak or focal MMR IHC pattern should be reported as ‘abnormal’ rather than ‘no loss’ and warrant further investigation i.e. BRAF analysis, MLH1 promoter methylation analysis

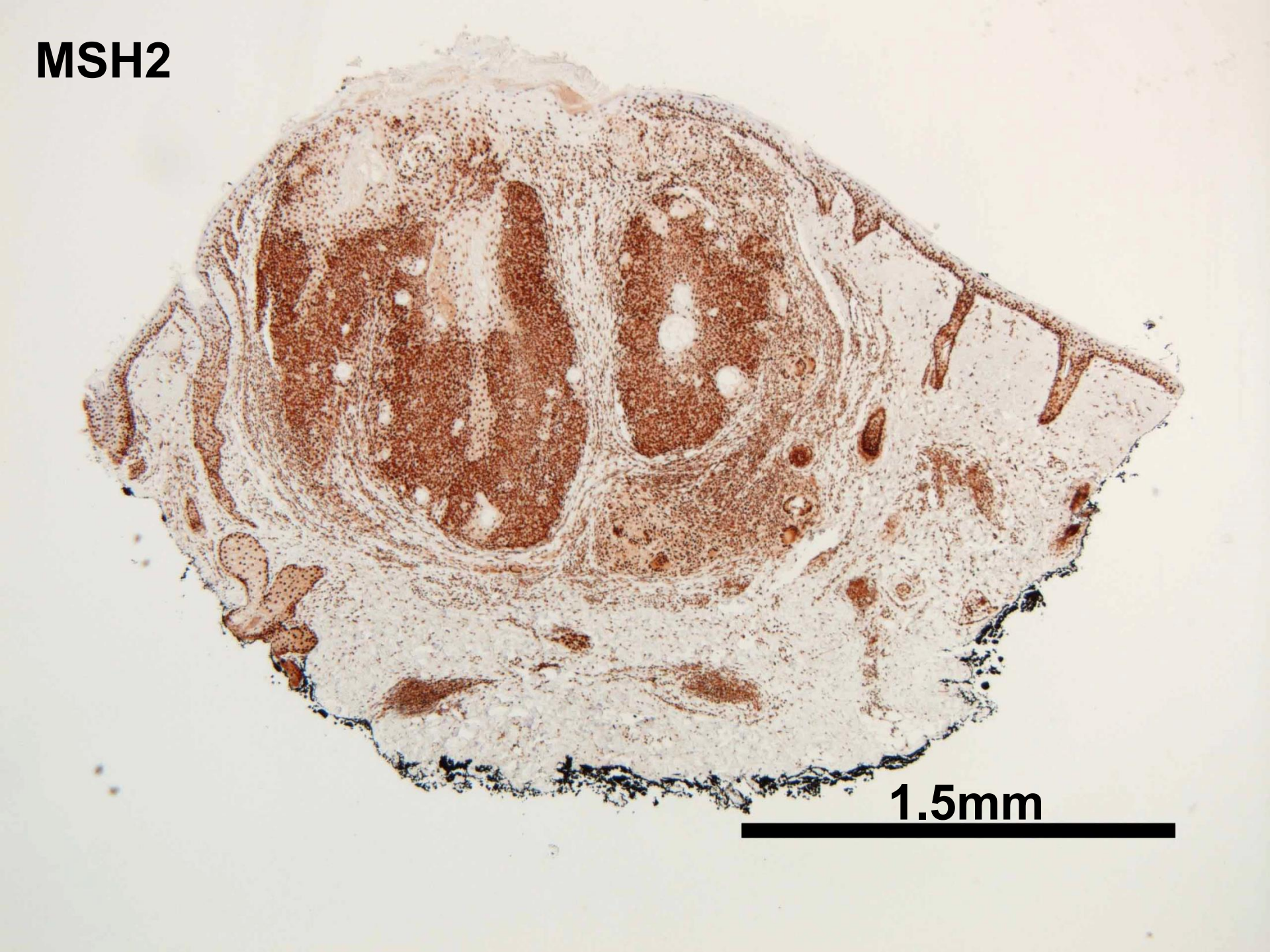
  *Artefact (focal loss) is very common in MMR IHC, therefore careful examination is required to call ‘focal loss’ or ‘reduced positivity’

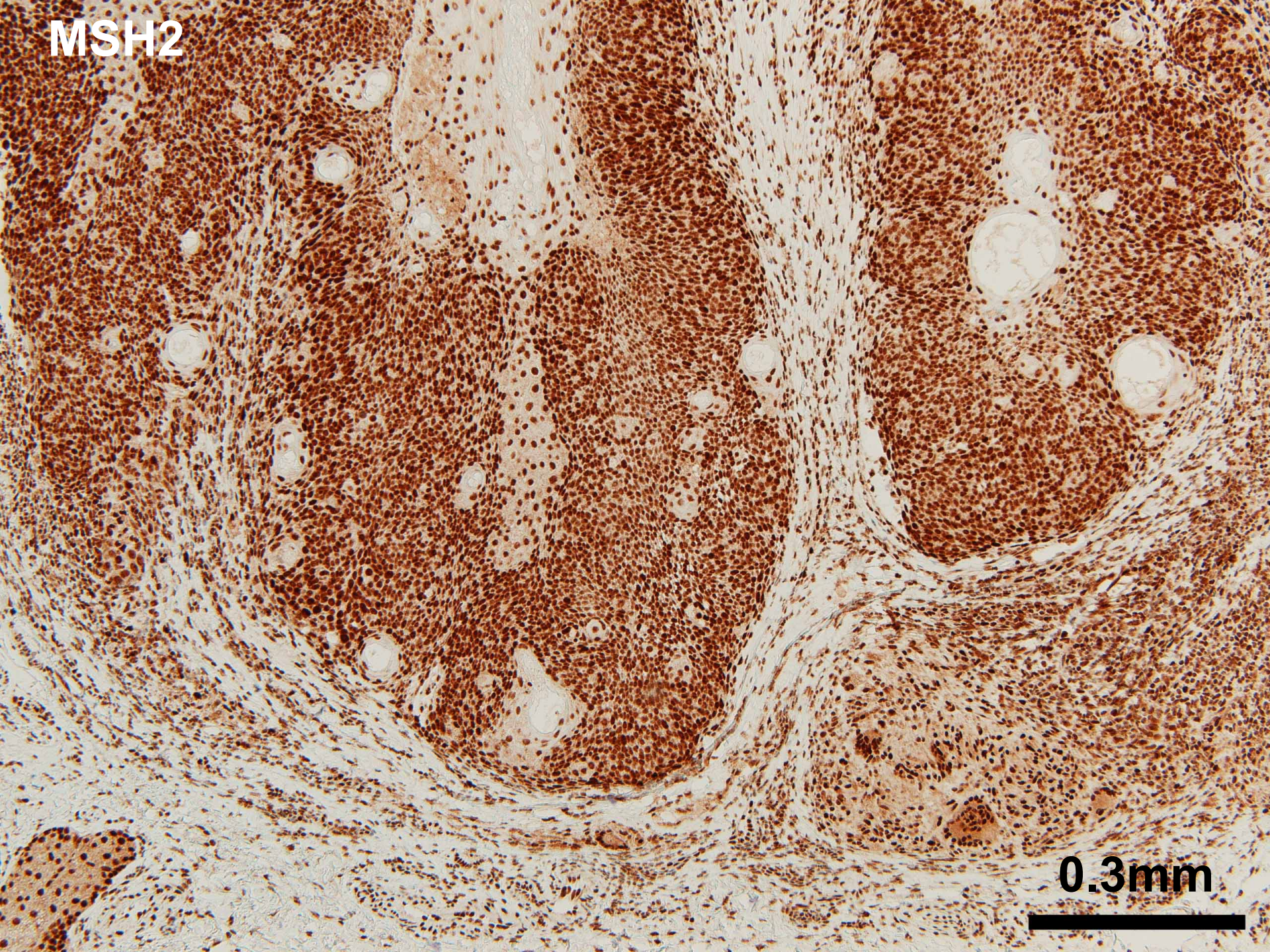
    - Repeat, select well fixed slides, compare MLH1and PMS2, MSH2 and MSH6, internal control (lymphocytes), MMR on adenomatous polyps


82 F Tip of nose
MLH1 germline mutation
Sebaceoma
1.5mm


MLH1
1.5mm


MLH1
0.3mm


MSH2
1.5mm


MSH2
0.3mm

Muir-Torre syndrome (MTS)

- A variant of Lynch syndrome
    - 1-3% of Lynch syndrome families
- Autosomal-dominant genetic condition, characterised by sebaceous neoplasms and/or keratoacanthomas associated with visceral malignancies

Sebaceous neoplasms in MTS

- Sebaceous adenoma, sebaceoma, sebaceous carcinoma
- Outside head and neck region suggests MTS
- Multiple sebaceous neoplasms suggest MTS
- Significant personal or family history of Lynch syndrome-associated cancers

Muir-Torre syndrome (MTS)

- 89–94% of the sebaceous neoplasms in MMR gene mutation carrier show MMR IHC deficiency
- MSH2 germline mutation is much more common in MTS compared to Lynch syndrome

Table 2. Comparison of the frequency of MMR gene mutations between MTS and HNPCC patients

MMR gene	MTS[20,24]	HNPCC16[22]
MLH-1	7[24] (2 of 27) to 11%[20] (1 of 9)	33%[22] (16 of 48)
MSH-2	89[20] (25 of 27) to 93%[24] (8 of 9)	31%[22] (15 of 48)
MSH-6	Few reports[24]	7.6%[25]
MLH-3	None yet	2.5%[25]
PMS-2	None yet	1.2%[25]

MMR, mismatch repair; MTS, Muir-Torre syndrome; HNPCC, hereditary nonpolyposis colorectal cancer.

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Abbas and Mahalingam, J Cutan Pathol 2009:36:613-619

Sporadic MMR deficiency in sebaceous neoplasms

- Abnormal MMR IHC shows negative predictive value (NPV) of 95% and positive predictive value (PPV) of 22% for MTS identification
- Majority of sporadic loss are MSH2/MSH6, which is frequently associated with history of solid organ transplant with immunosuppression
  - molecular mechanism is unknown

J Invest Dermatol 2001; 116:246-253
J Genet Counsel 2013;22:393-405

Sebaceous neoplasms in MUTYH-associated polyposis (MAP)

- MUTYH-associated polyposis (MAP)
  - Autosomal recessive hereditary colon cancer syndrome
  - Attenuated gastrointestinal polyposis phenotype
  - Associated with MMR proficient sebaceous neoplasms

Suggested screening for MTS

Box. Clinical Practice Algorithm for Sebaceous Neoplasm (SN)

1. Immunohistochemical screening of SN to be ordered by pathologist or clinician
2. Family history screen for Lynch syndrome (LS)-associated cancers[a] in first-degree or second-degree relatives
3. Genetics clinic referral for patients with SN and any of the following:
4. Absent mismatch repair protein expression (abnormal result) on immunohistochemical testing
5. Normal mismatch repair protein expression and personal or family history of LS-associated cancer
6. More than 1 SN **+ Non head and neck location SN**

[a] Classic LS-associated cancers include colorectal, endometrial, stomach, small bowel, ovarian, pancreatic, and urinary tract cancers and glioblastoma multiforme. Atypical LS-associated cancers include adrenocortical and hepatobiliary cancers and sarcoma.

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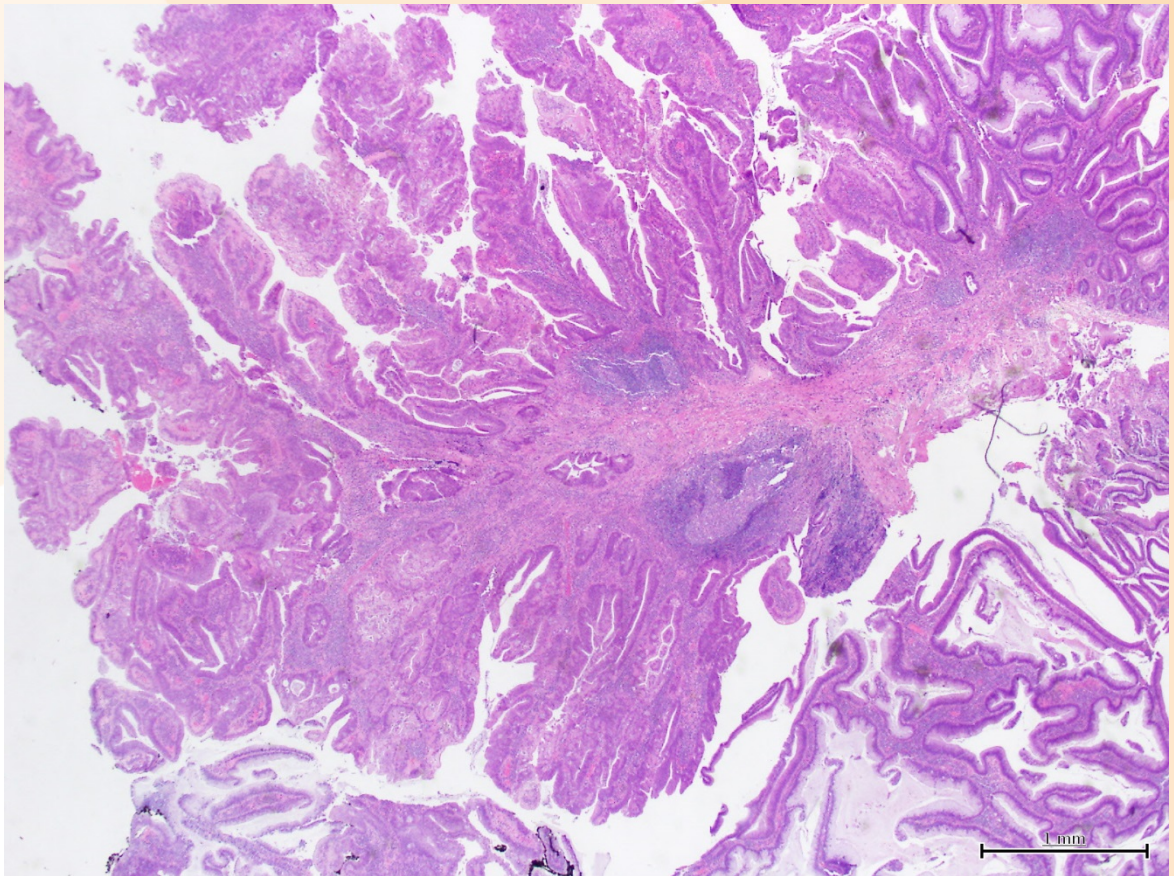
JAMA Dermatol.2014;150(12):1315-1321

P.H. 55y M

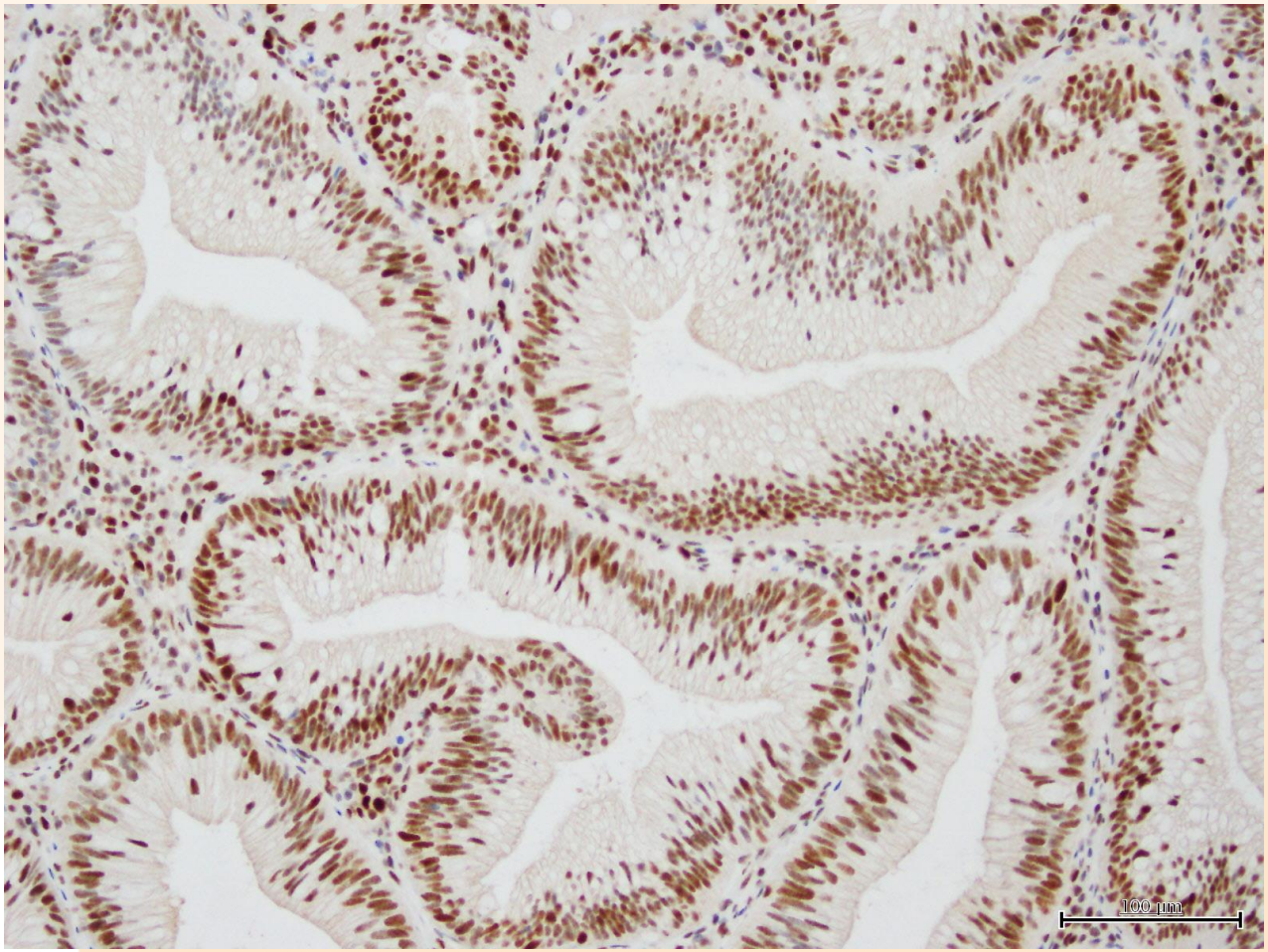
- MSH2 mutation carrier
- On regular surveillance of rectal stump
- Flexible sigmoidoscopy : 30mm sessile polyp in the rectal stump
- PMHx :
  - At age 44y, x3 synchronous CRCs, total colectomy and end-ileostomy, short rectal stump remained
- FHx :
  - Sister : Died of uterine cancer at age 43y
  - Mother : Died of bowel cancer at age 54y
  - Maternal uncles (x2) : Bowel cancer <50y
  - Maternal grandmother : Died of bowel cancer

Rectal stump polyp

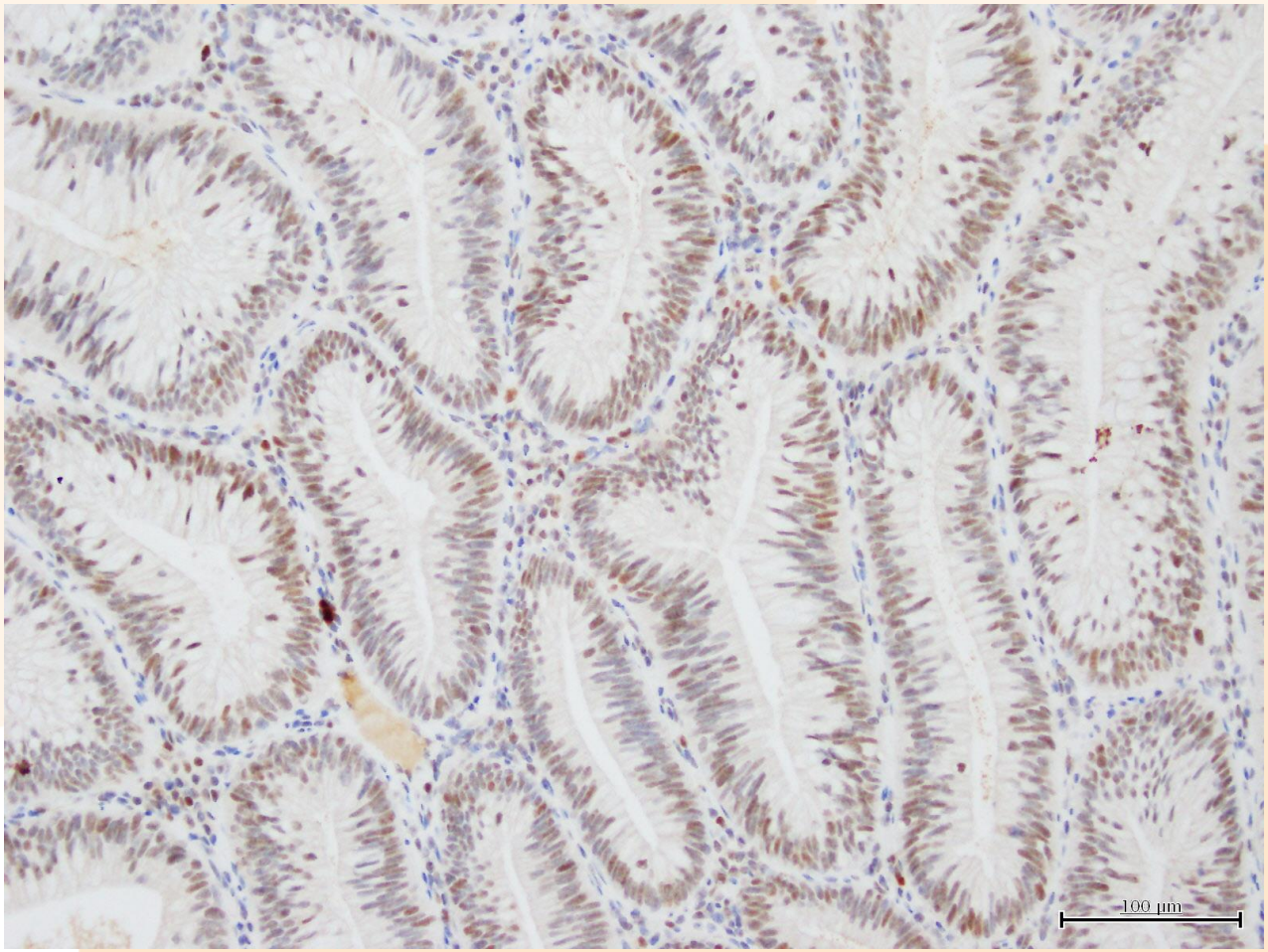
- Tubulovillous adenoma with high grade dysplasia, 30mm



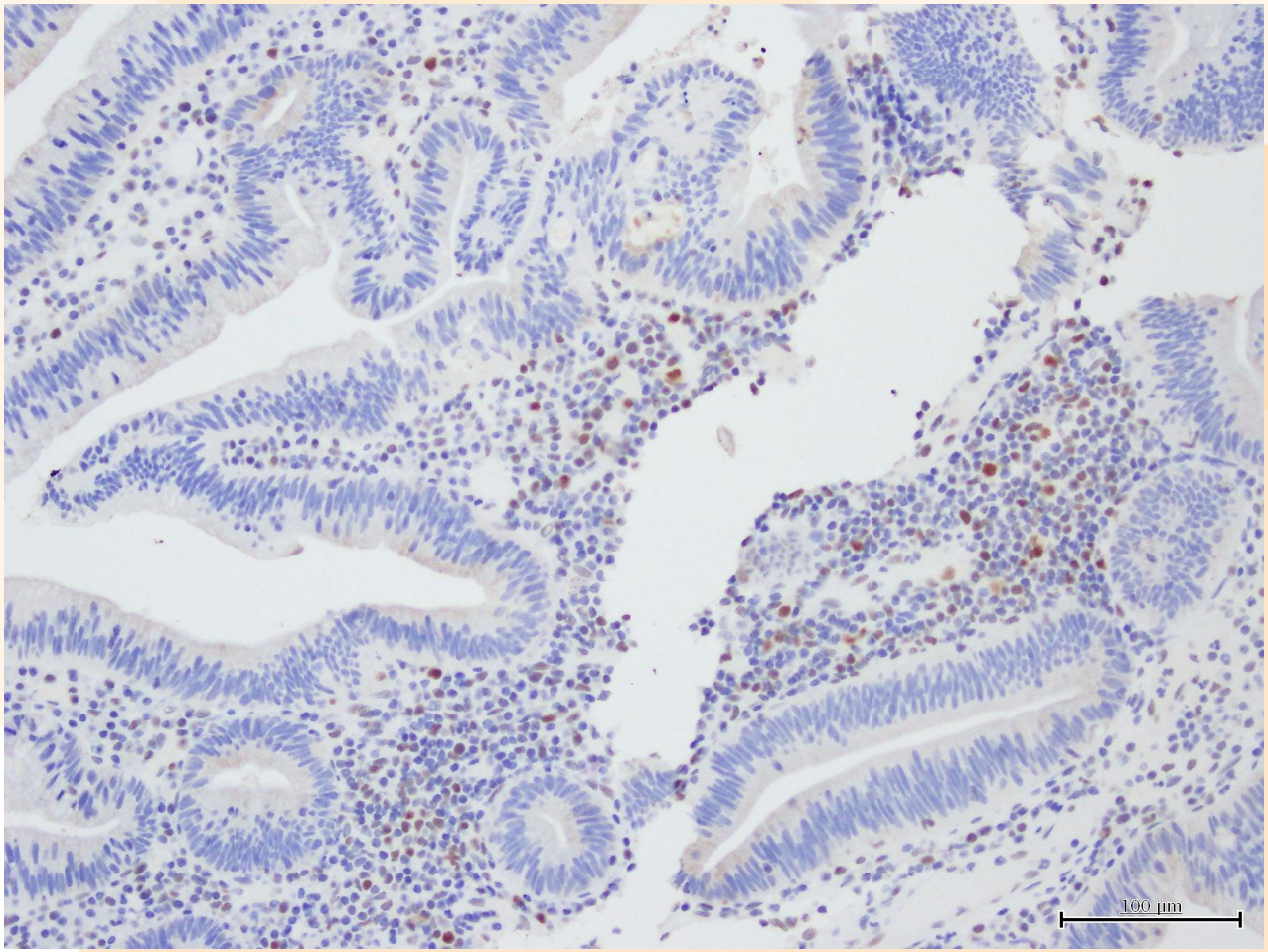
Rectal stump polyp
MLH1



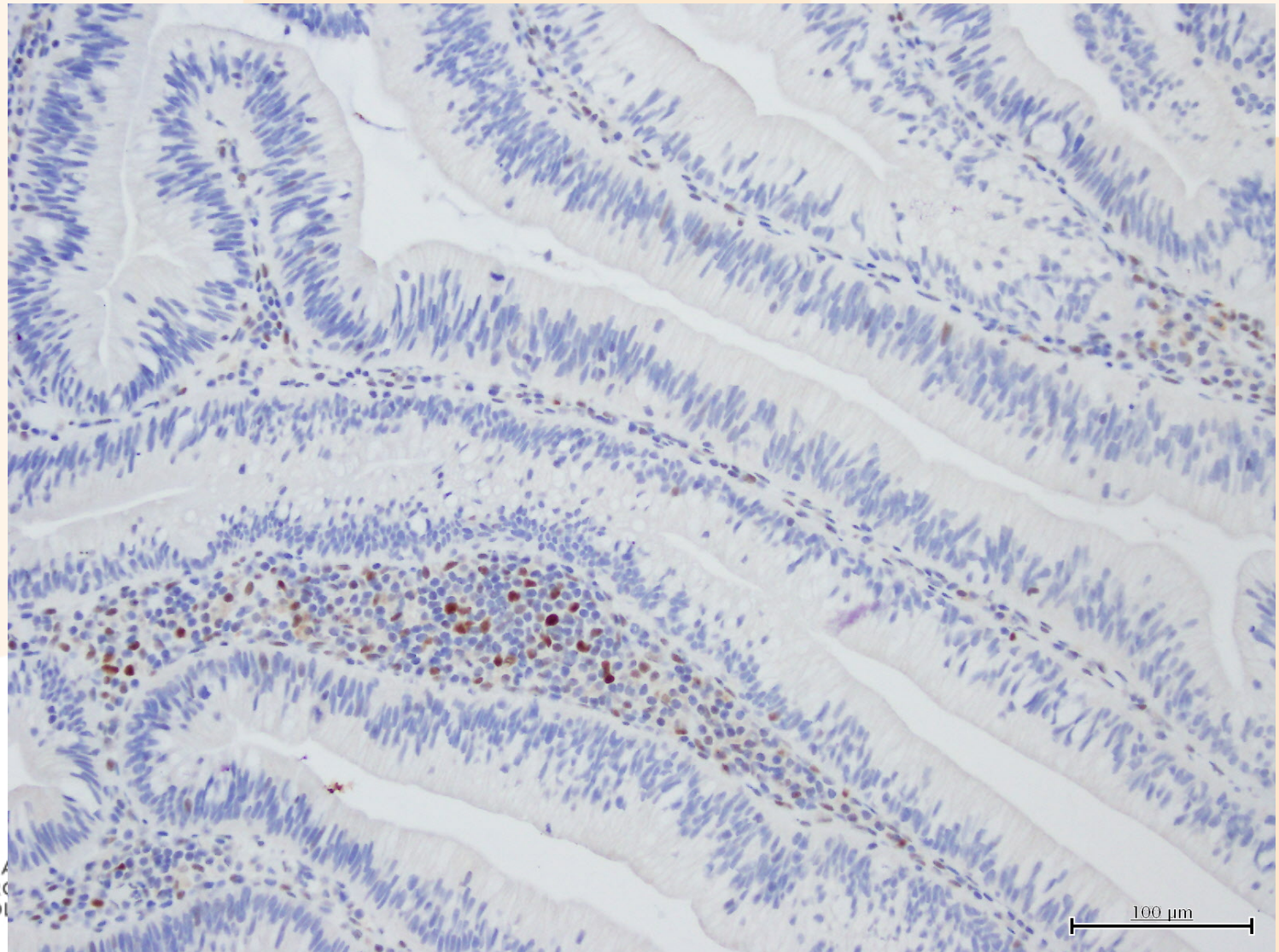
Rectal stump polyp
PMS2



Rectal stump polyp
MSH2



Rectal stump polyp
MSH6



Rectal stump polyp

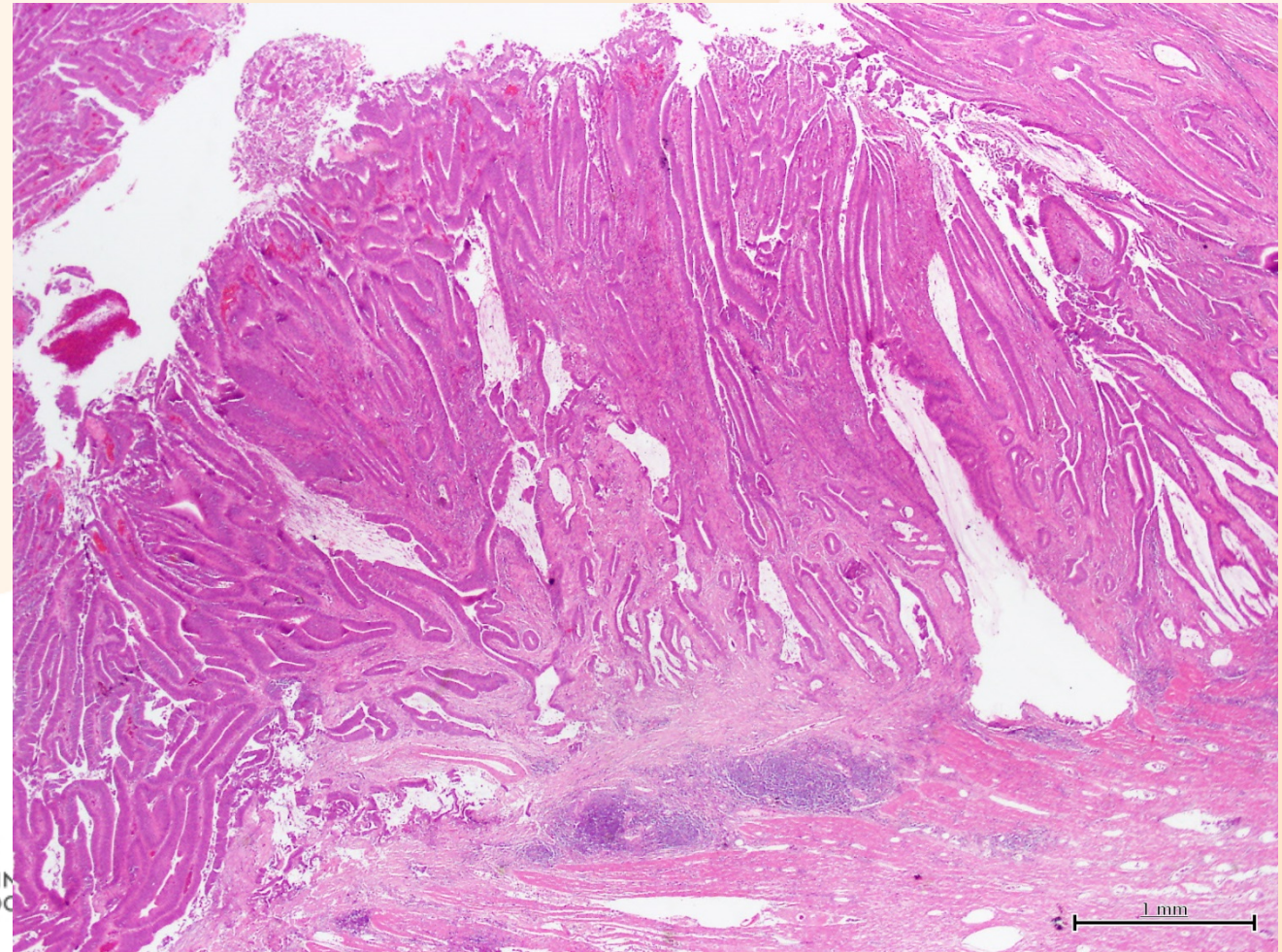
- Tubulovillous adenoma with high grade dysplasia, 30mm
  - MLH1 : No loss
  - PMS2 : No loss
  - MSH2 : Loss
  - MSH6 : Loss
- Consistent with Lynch syndrome with MSH2 germline mutation

Total colectomy + end-ileostomy at age 44y (11 years prior)

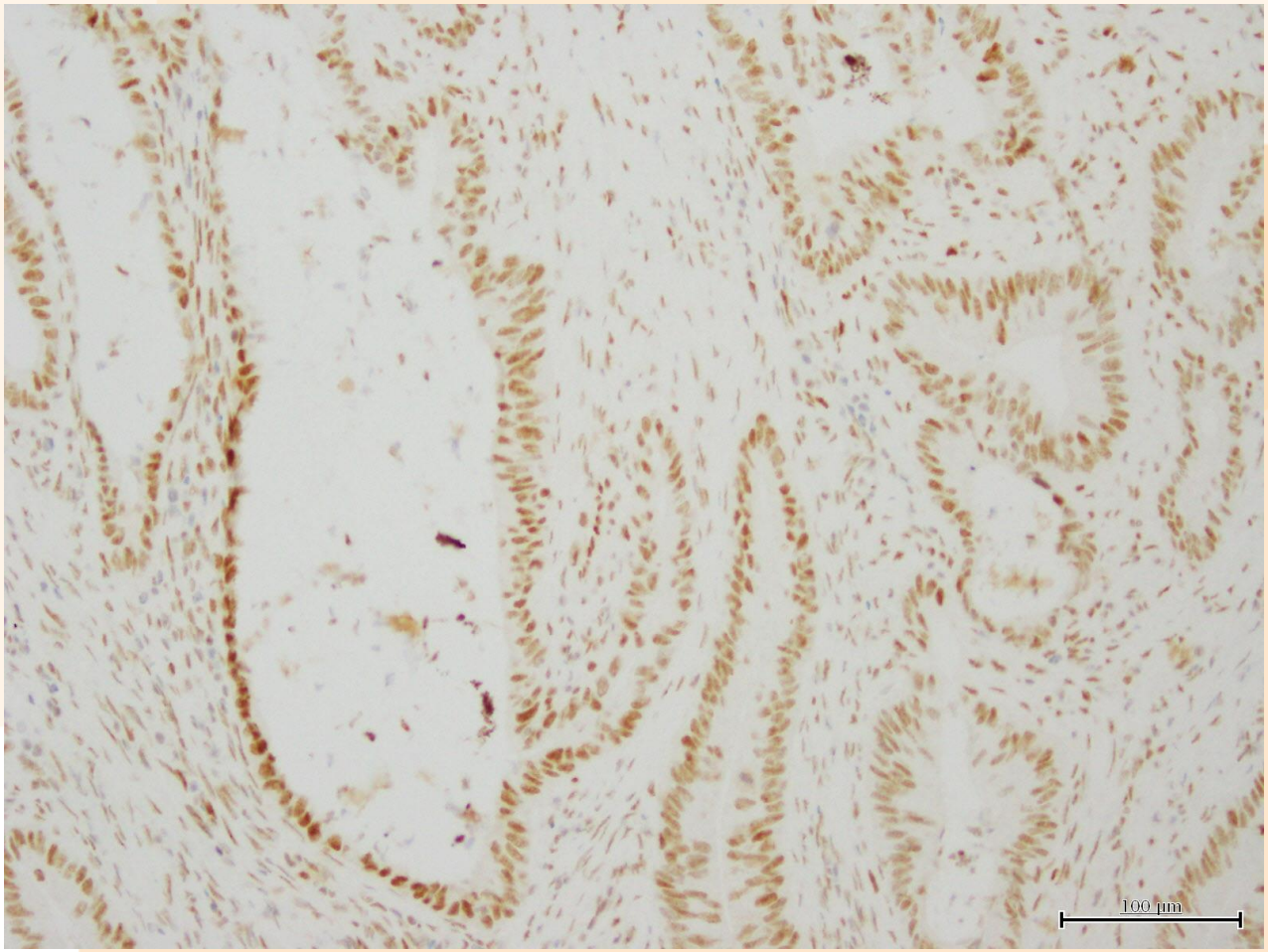
- Ascending colon tumour
- Mid transverse colon tumour
- Upper rectal tumour
- Pedunculated polyps (x2), 10mm, right colon and left colon

Ascending colon tumour

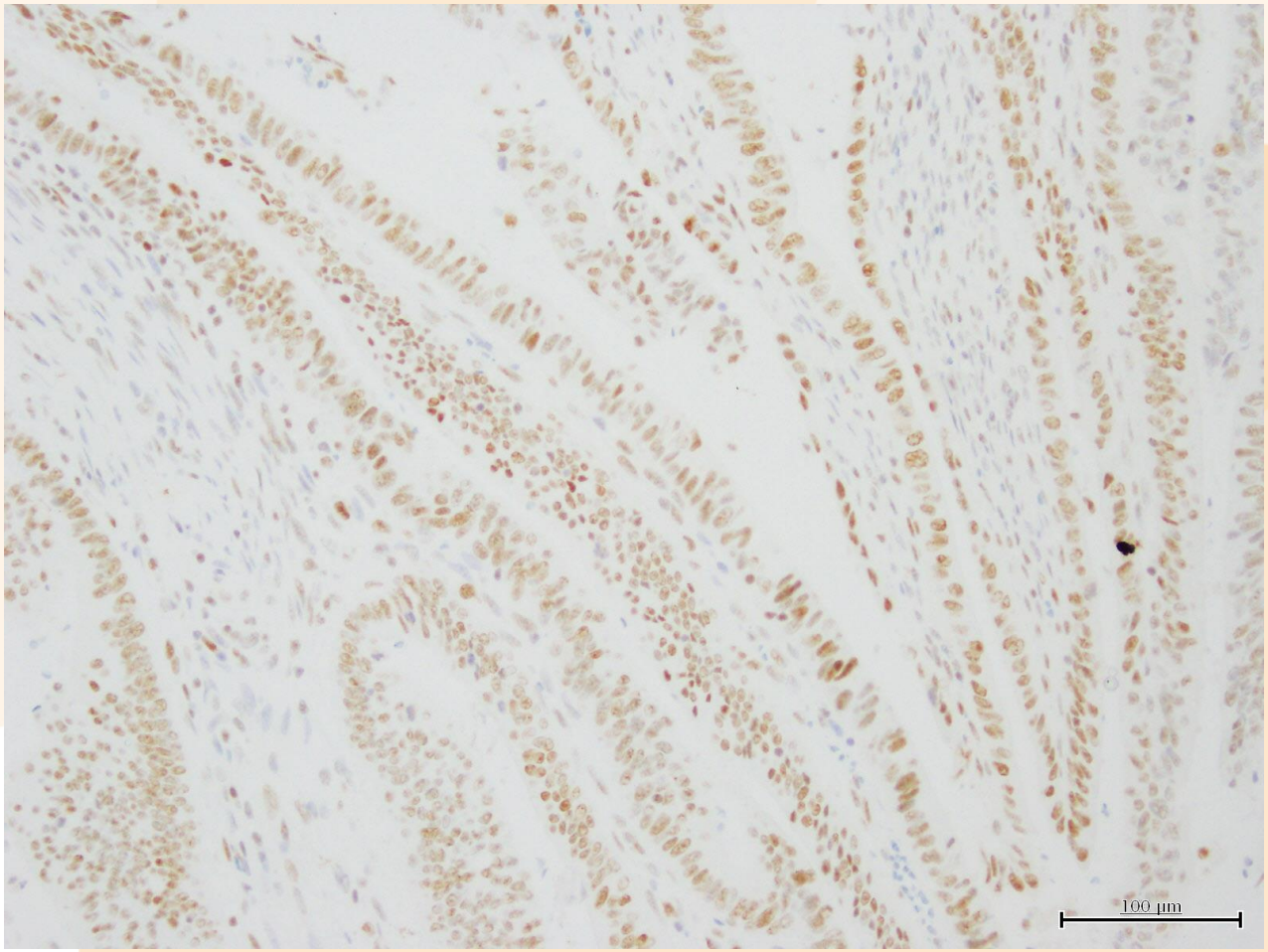
- Adenocarcinoma, low grade, pT3N1aM0



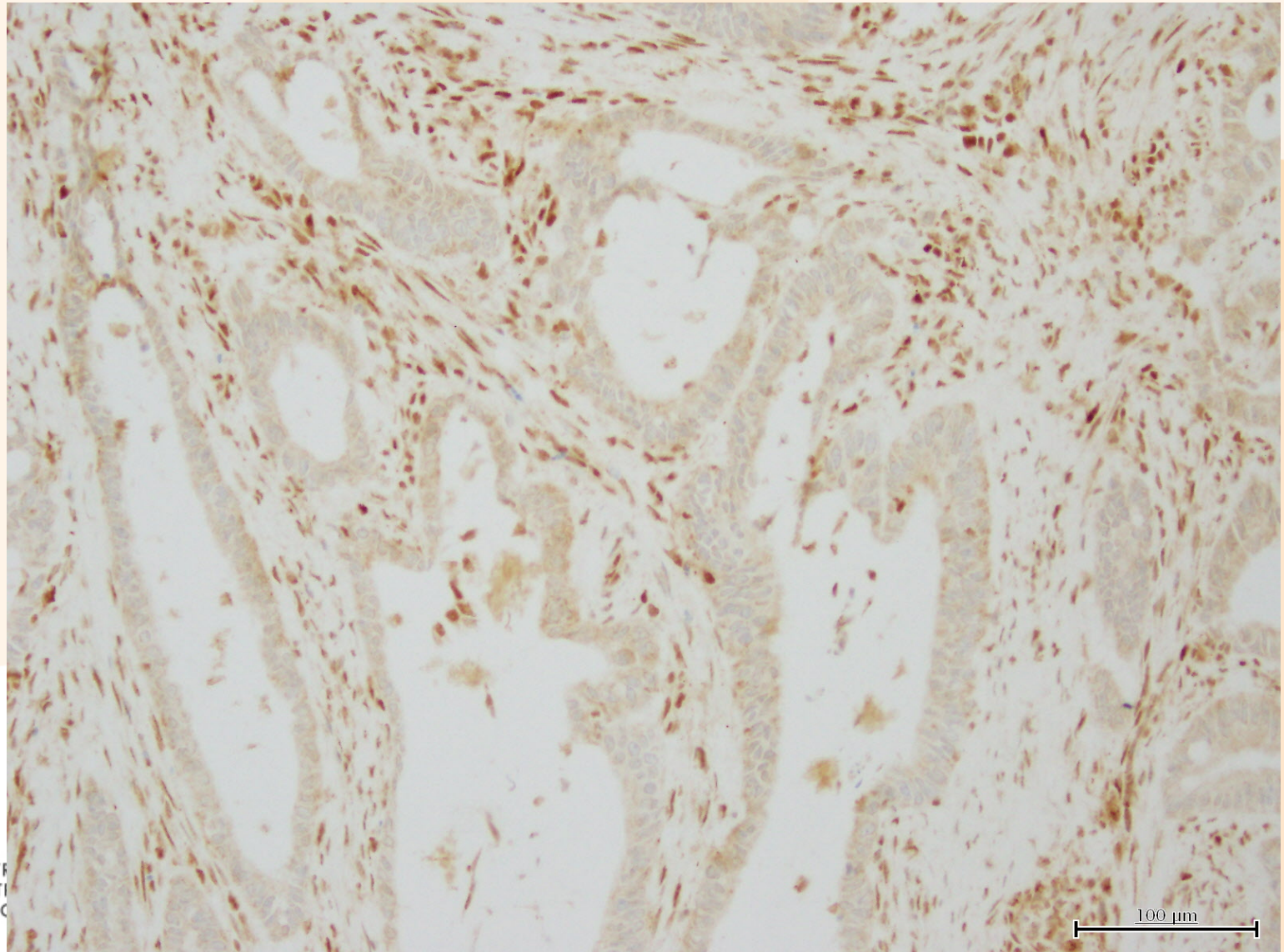
Ascending colon tumour
MLH1



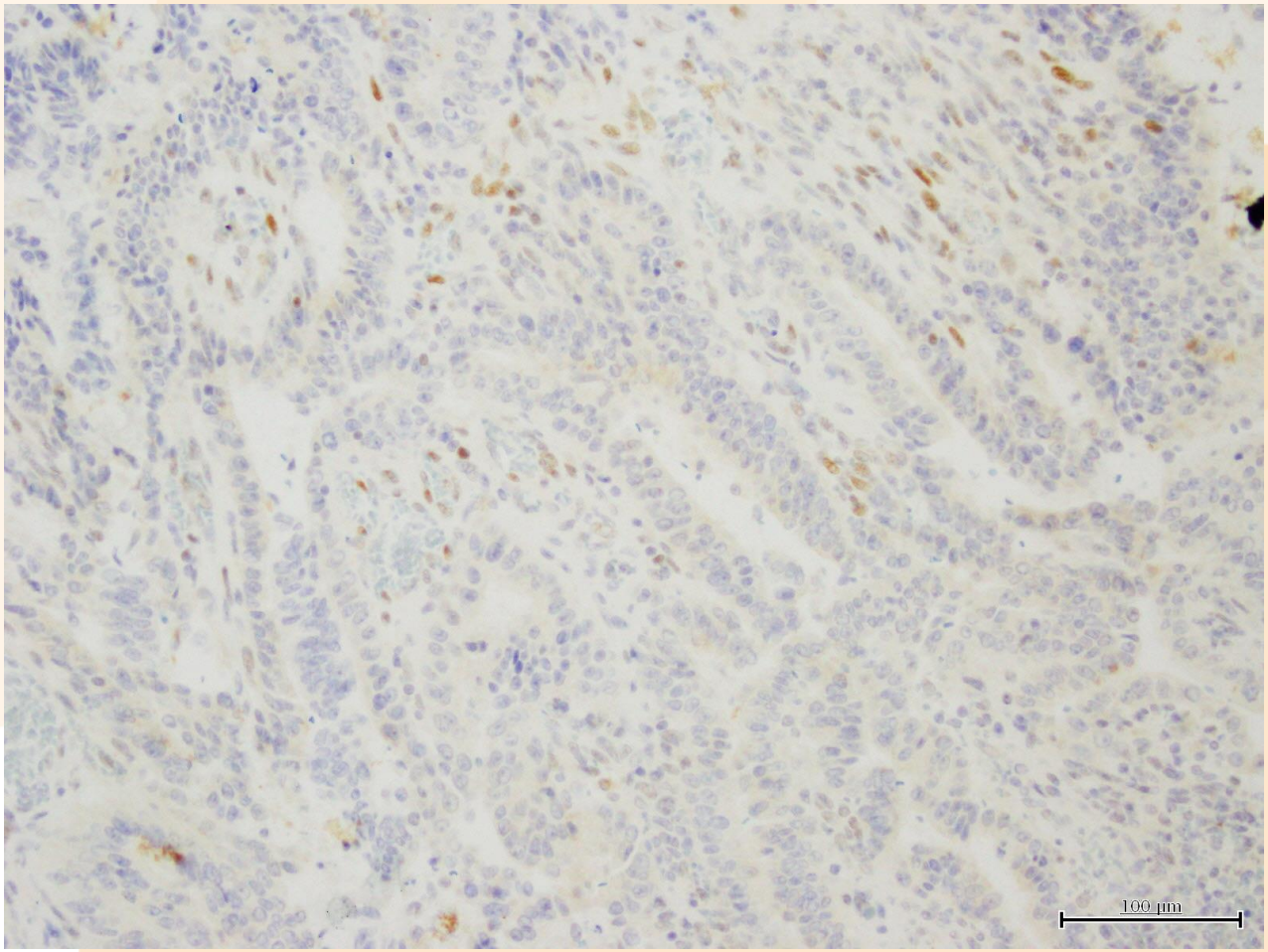
Ascending colon tumour
PMS2



Ascending colon tumour
MSH2

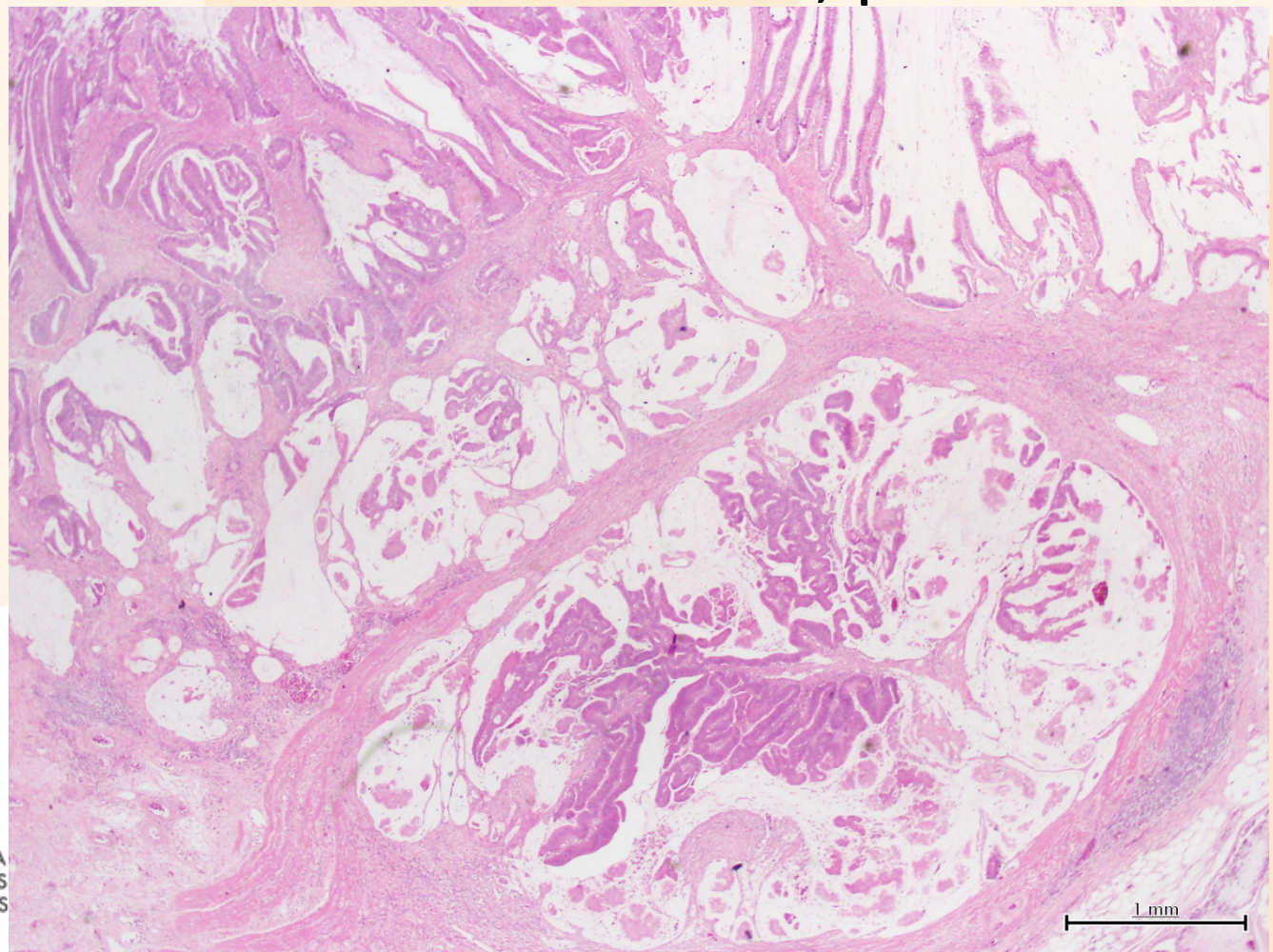


Ascending colon tumour
MSH6

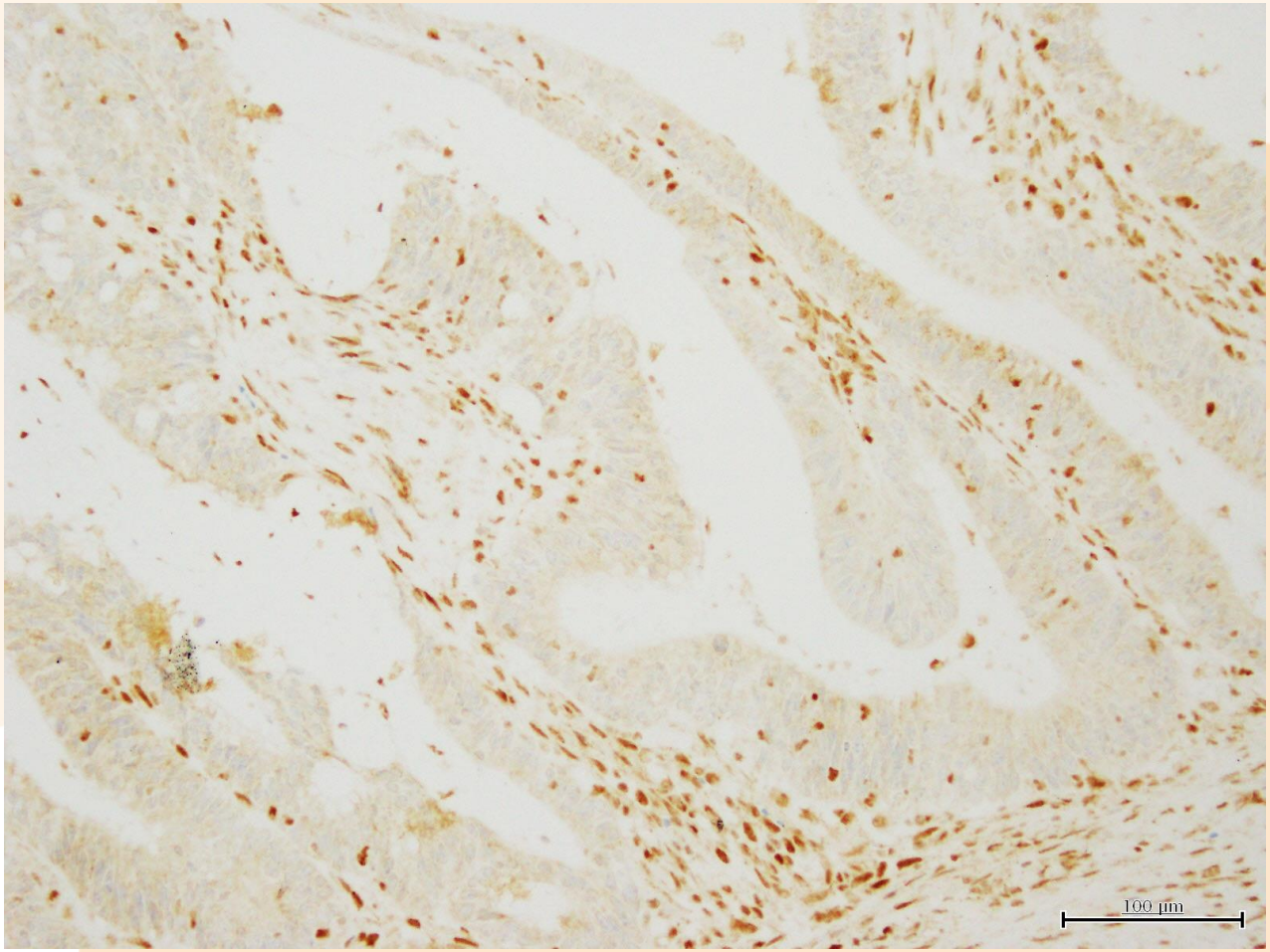


Mid transverse colon tumour

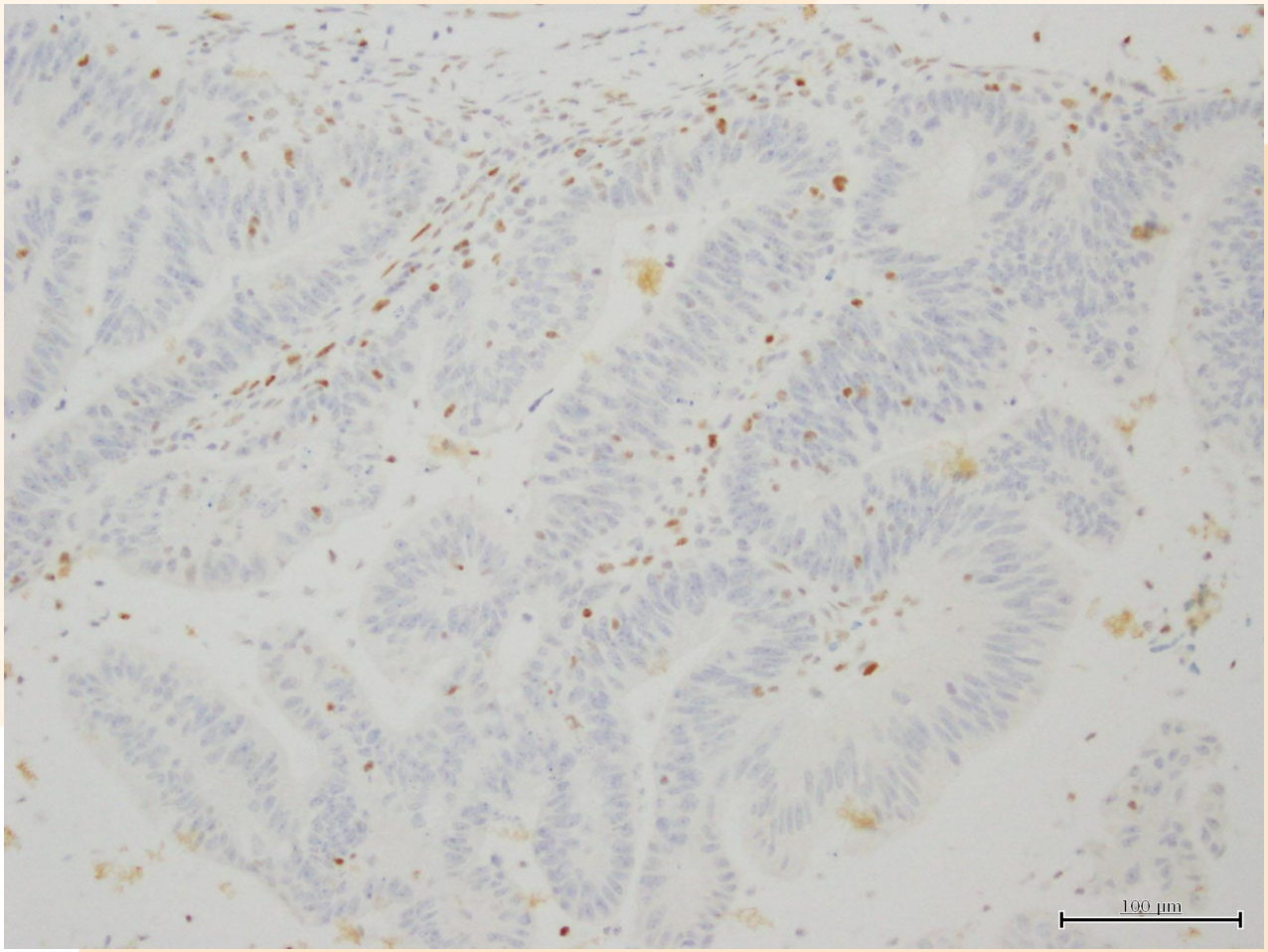
- Mucinous adenocarcinoma, pT2N1aM0



Mid transverse colon tumour MSH2

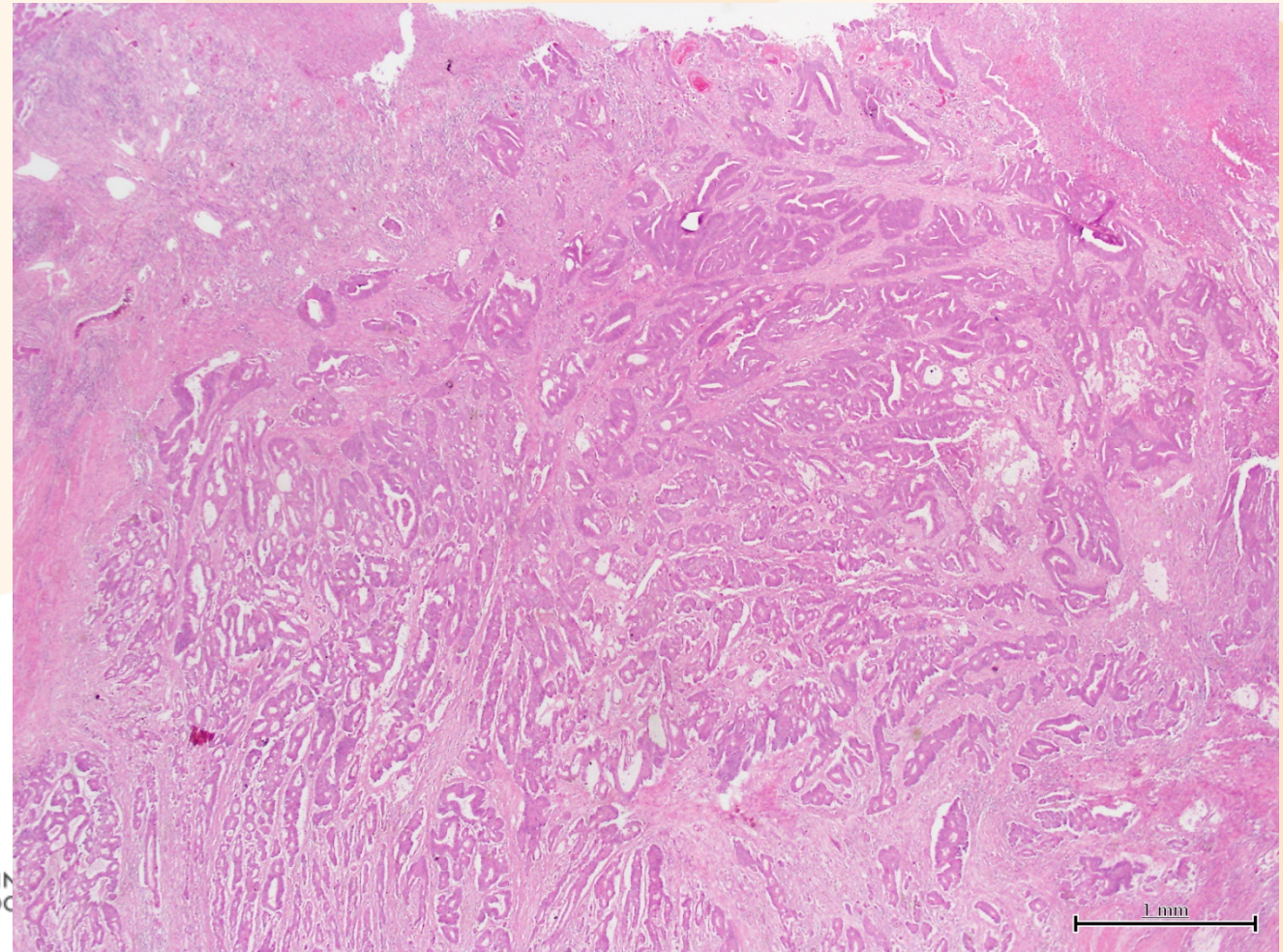


Mid transverse colon tumour MSH6

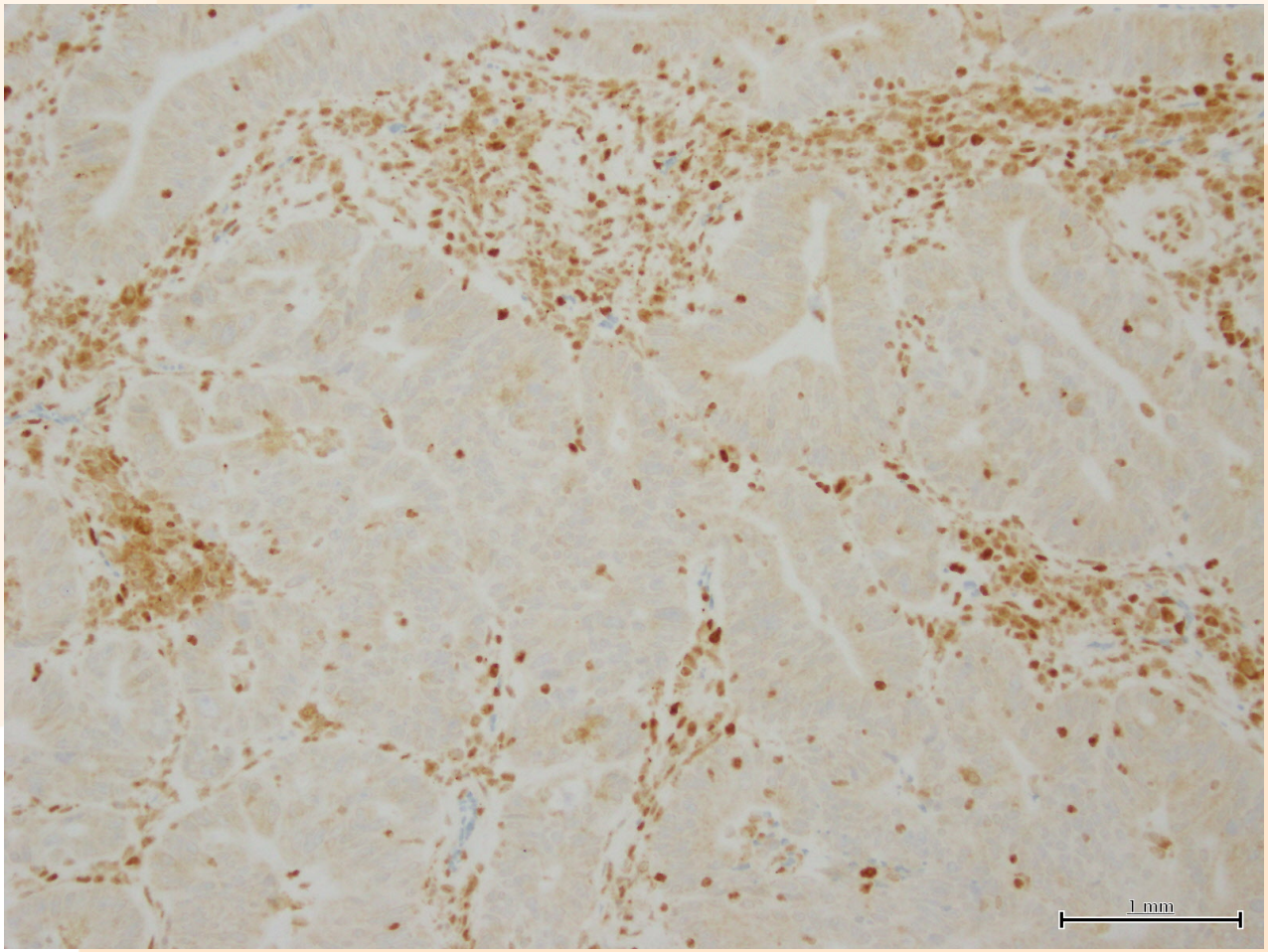


Upper rectal tumour

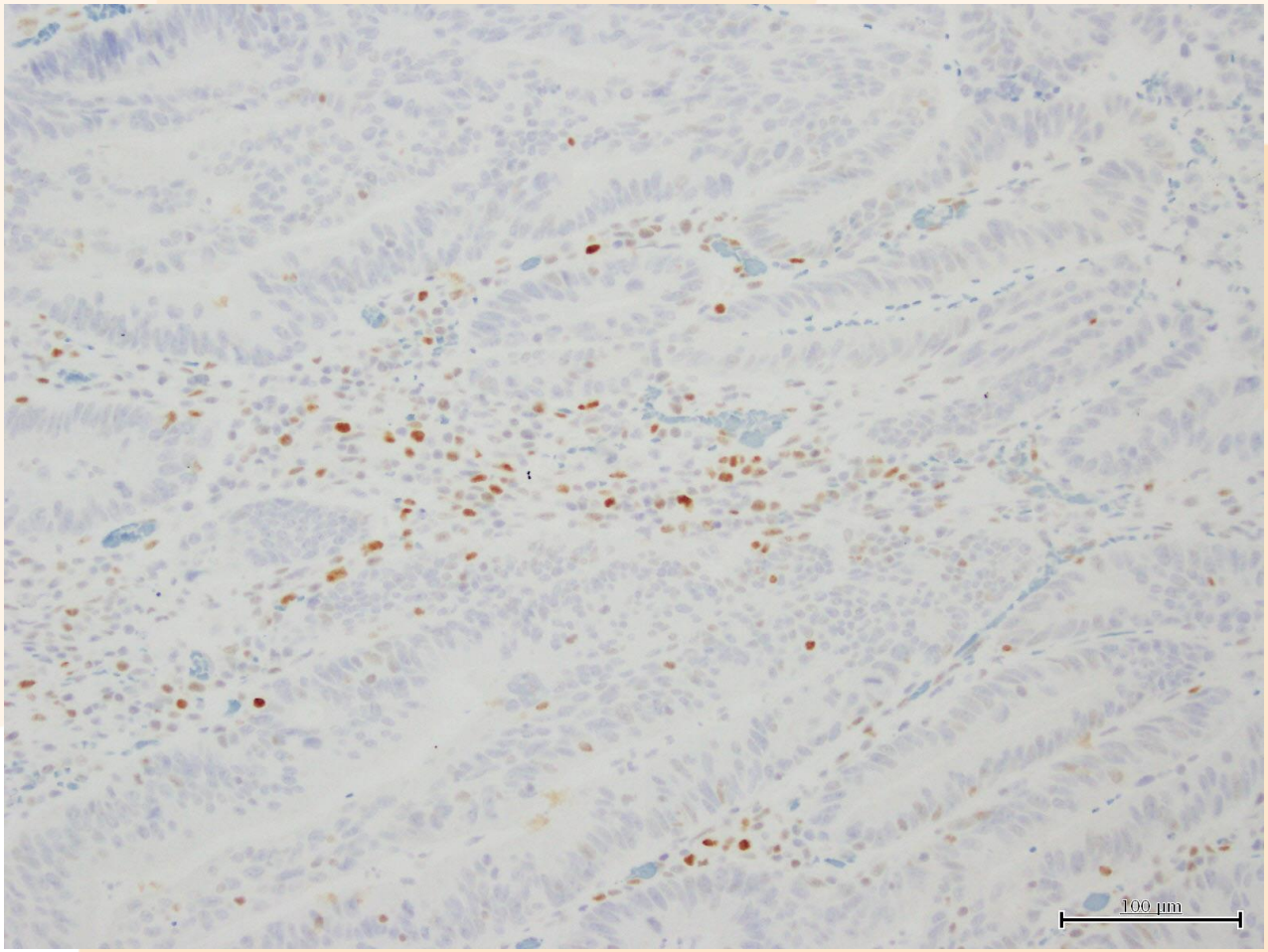
- Adenocarcinoma, low grade, pT3N1aM0



Upper rectal tumour
MSH2

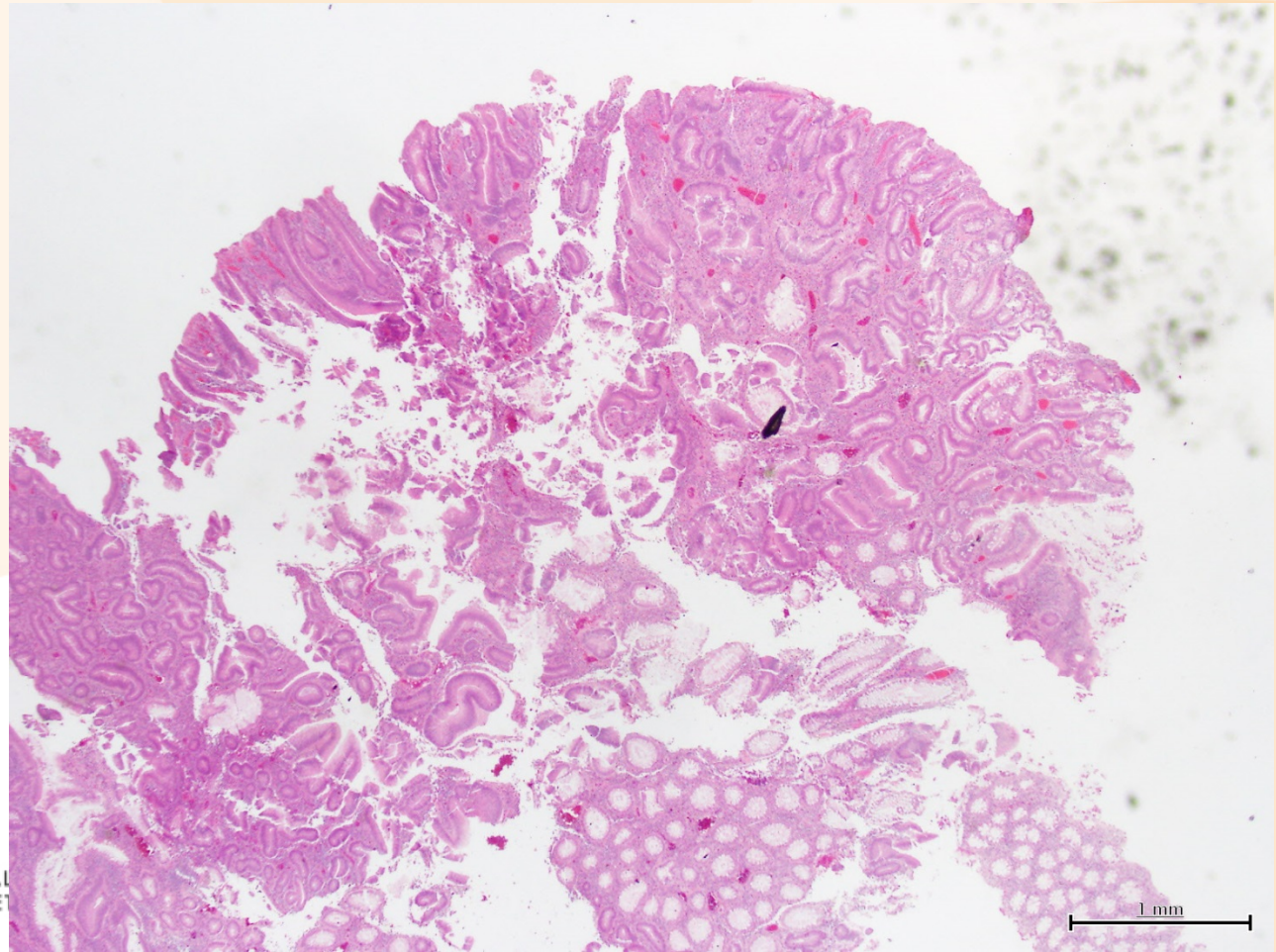


Upper rectal tumour
MSH6

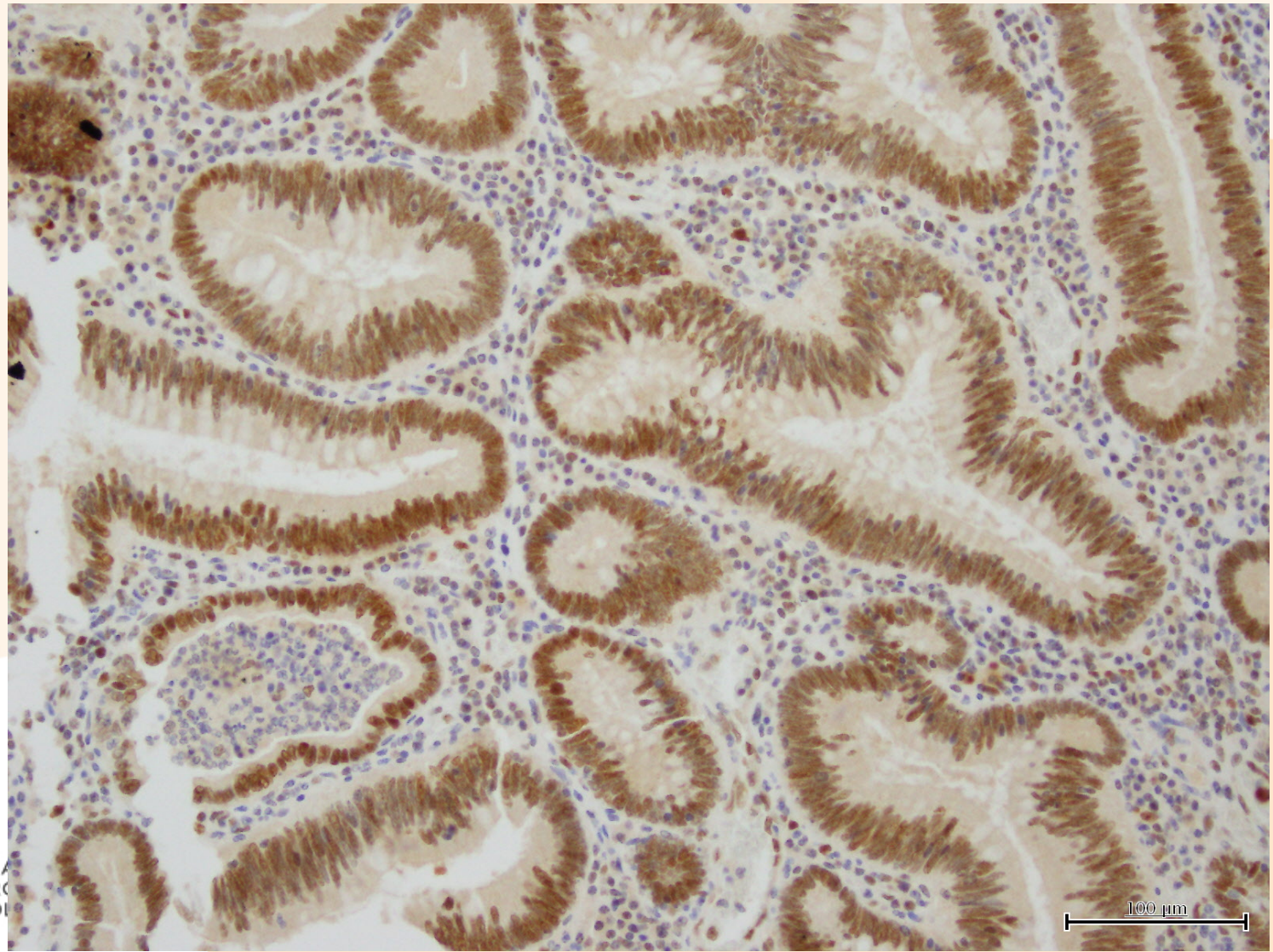


Pedunculated polyp, 10mm, right colon

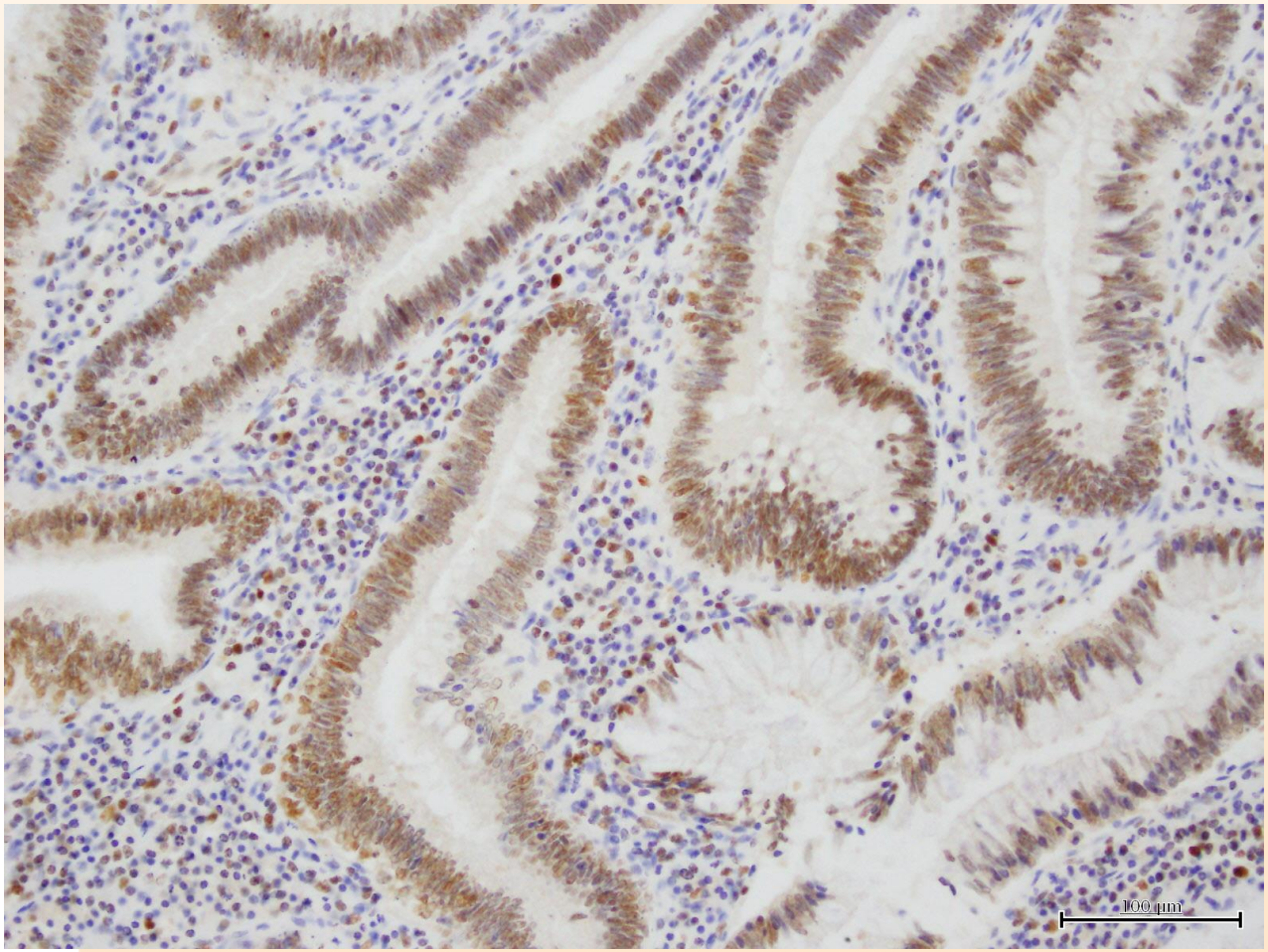
- Tubular adenoma with low grade dysplasia



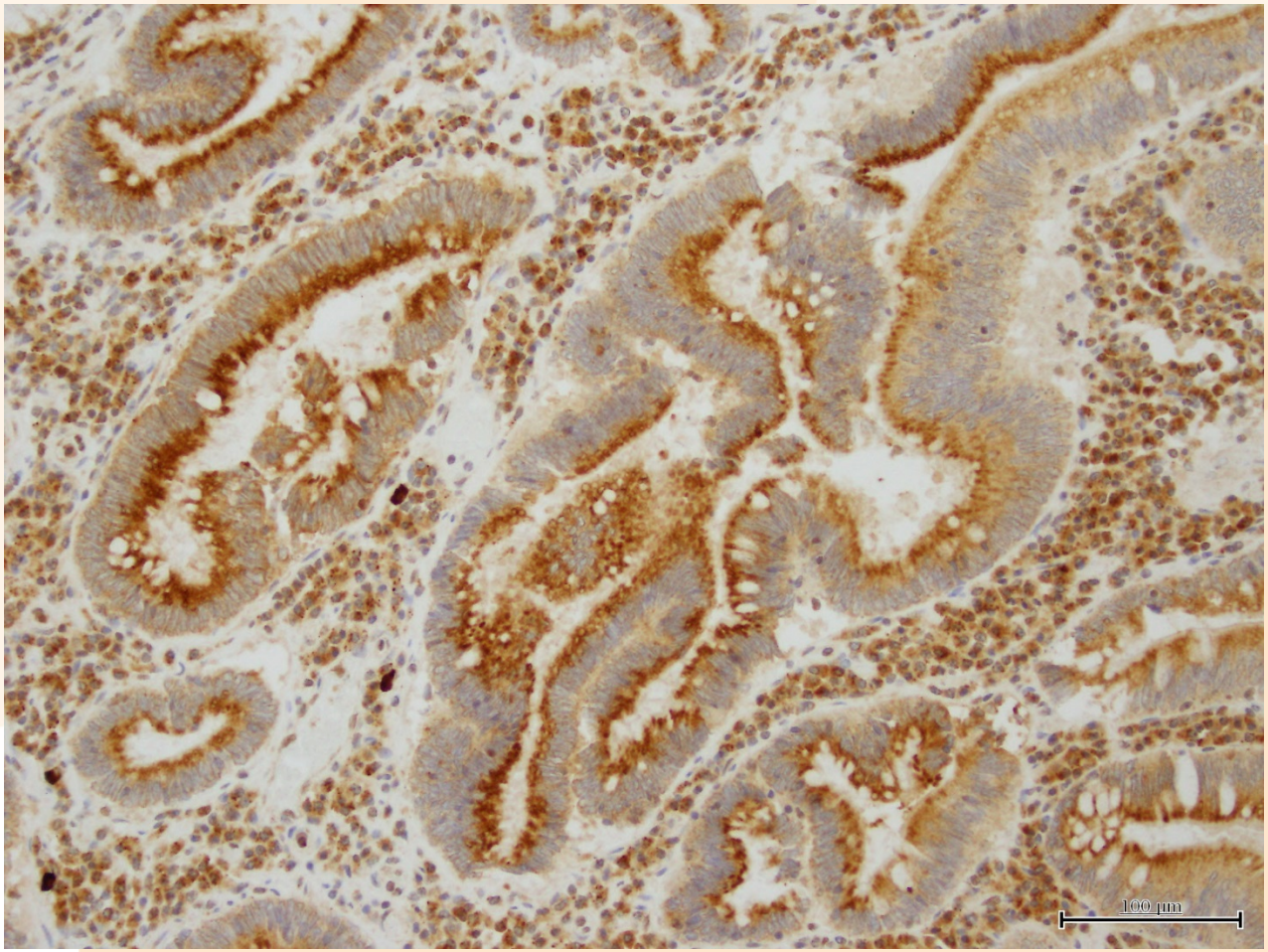
Pedunculated polyp, 10mm, right colon
MLH1



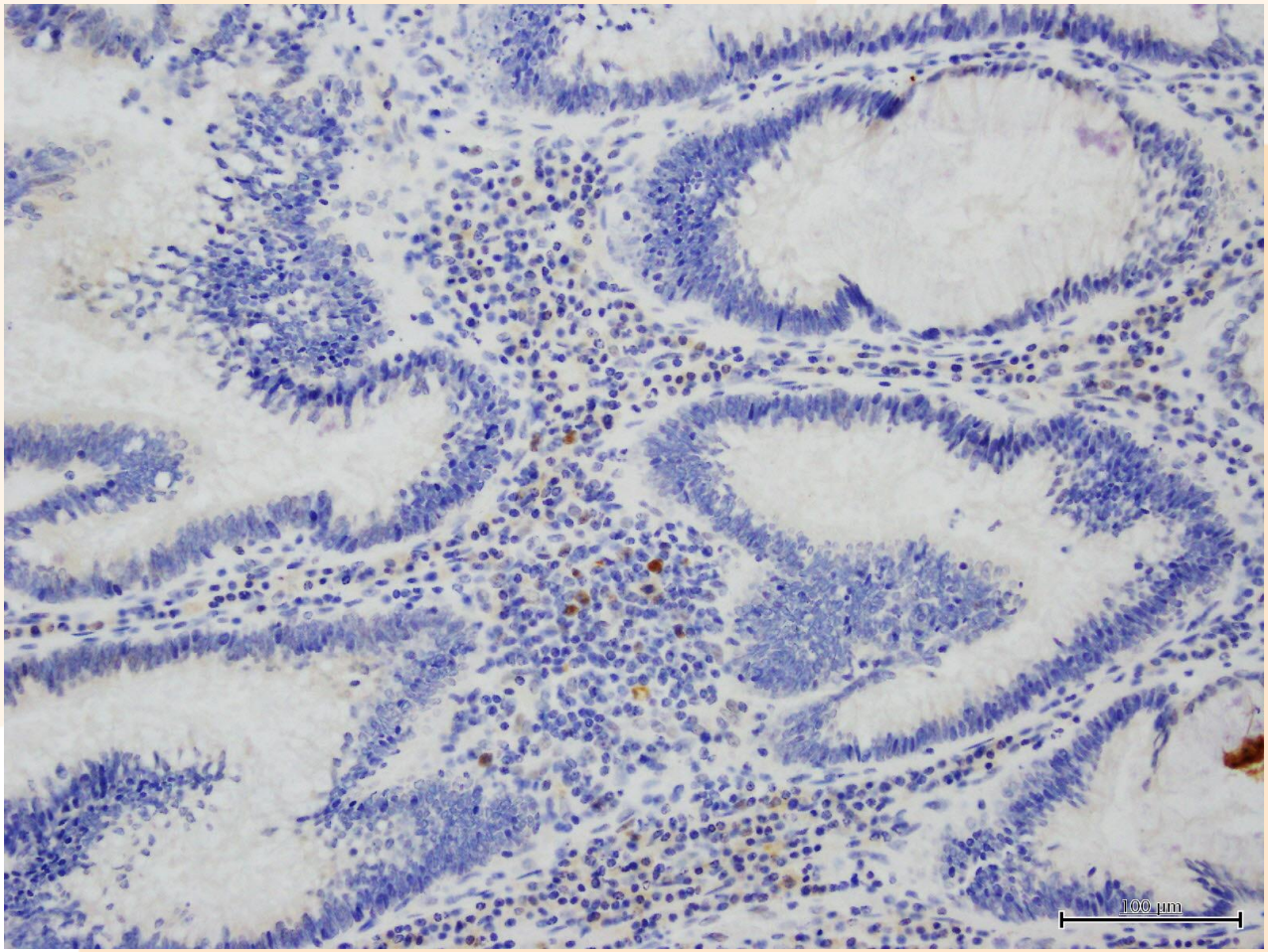
Pedunculated polyp, 10mm, right colon
PMS2



Pedunculated polyp, 10mm, right colon
MSH2

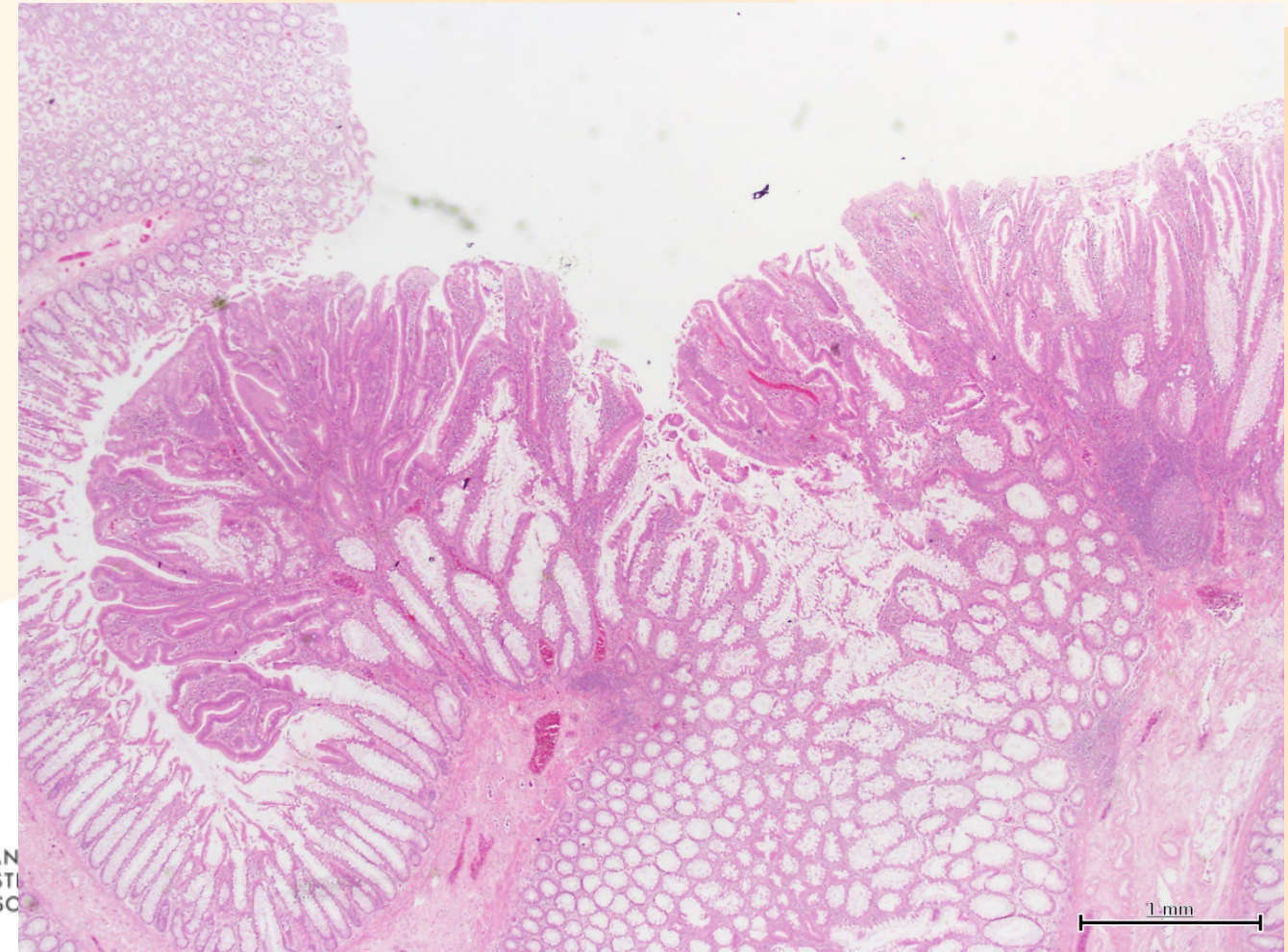


Pedunculated polyp, 10mm, right colon
MSH6

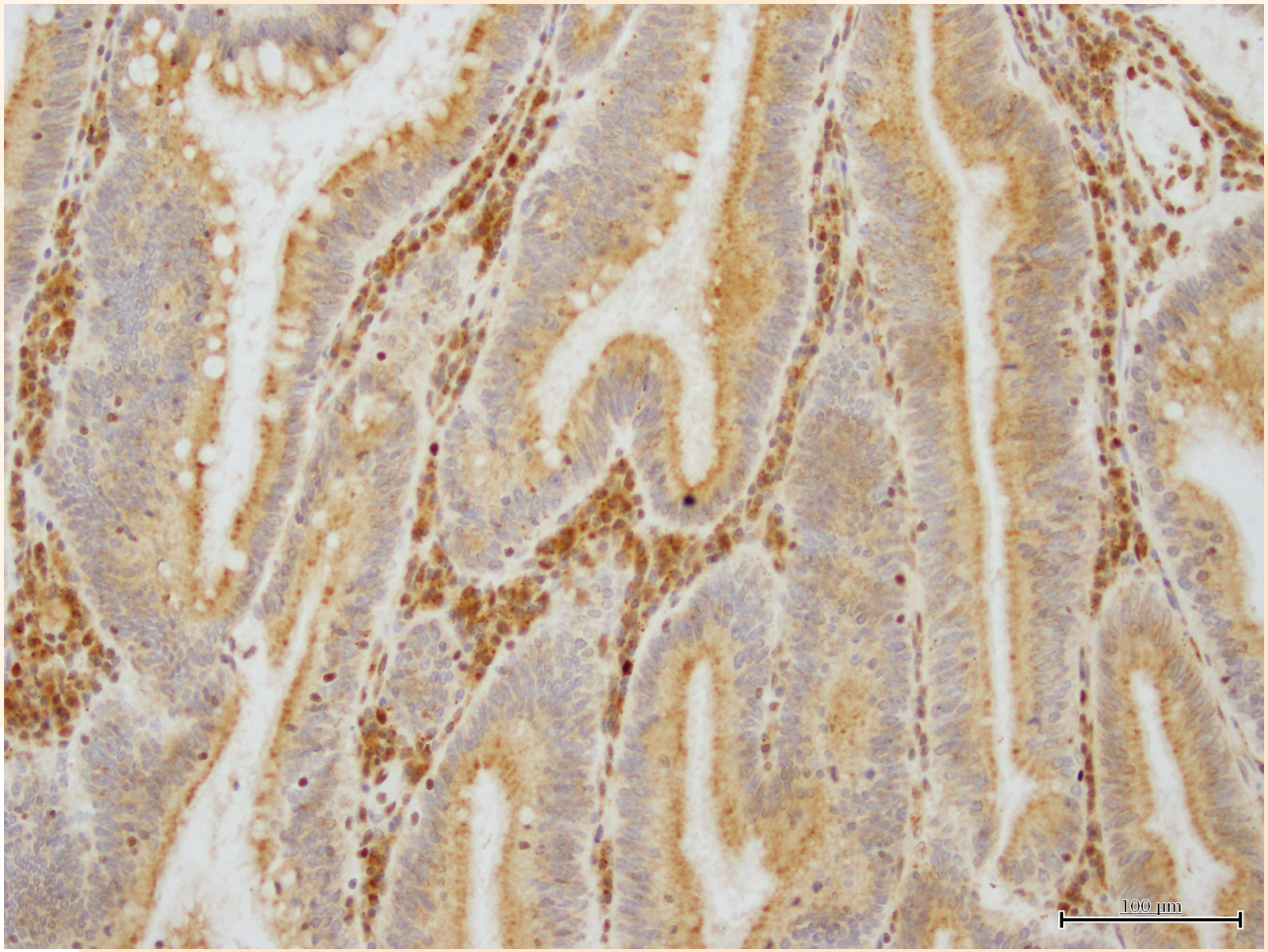


Pedunculated polyp, 10mm, left colon

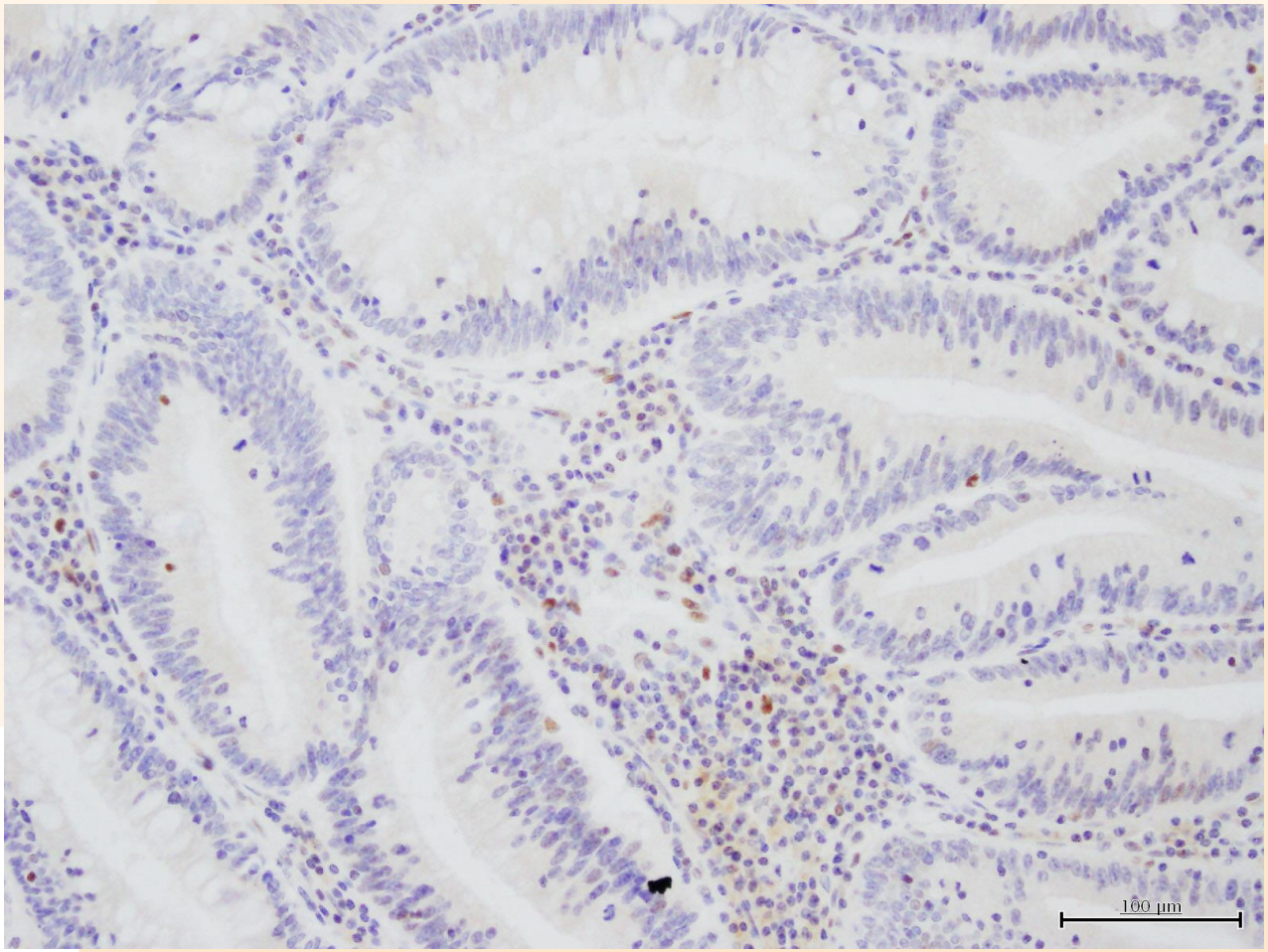
- Tubular adenoma with low grade dysplasia



Pedunculated polyp, 10mm, left colon
MSH2



Pedunculated polyp, 10mm, left colon
MSH6



Total colectomy + end-ileostomy at age 44y (11 years prior)

- Ascending colon tumour
  - Adenocarcinoma, low grade, pT3N1aM0
- Mid transverse colon tumour
  - Mucinous adenocarcinoma, pT2N1aM0
- Upper rectal tumour
  - Adenocarcinoma, low grade, pT3N1aM0
- Pedunculated polyps (x2), 10mm, right colon and left colon
  - Tubular adenoma with low grade dysplasia
- All 5 lesions
    - MLH1 : No loss
    - PMS2 : No loss
    - MSH2 : Loss
    - MSH6 : Loss
- Pathogenic MSH2 mutation detected

MMR deficient polyps in LS

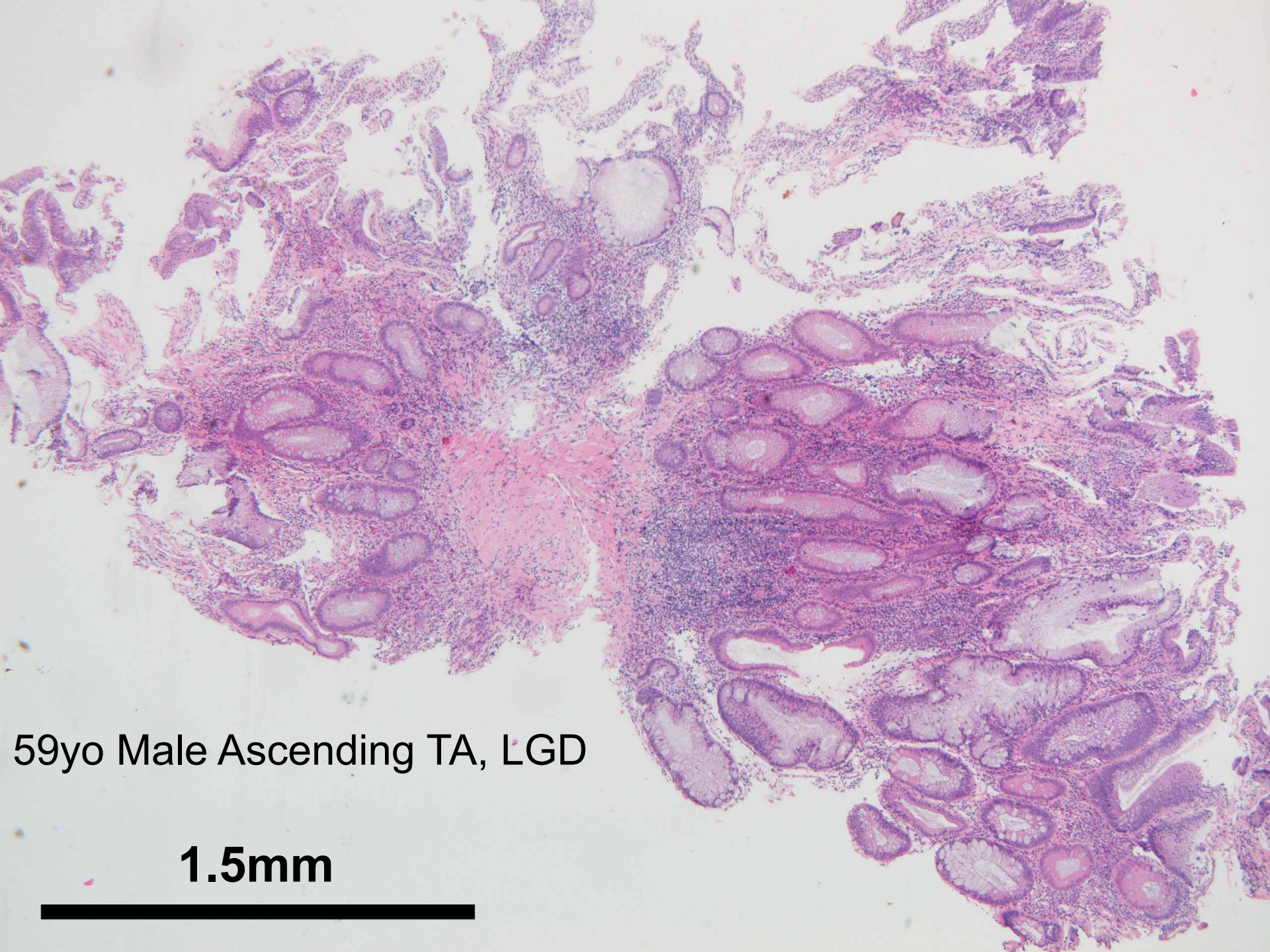
13 references (1994-2012) + current study

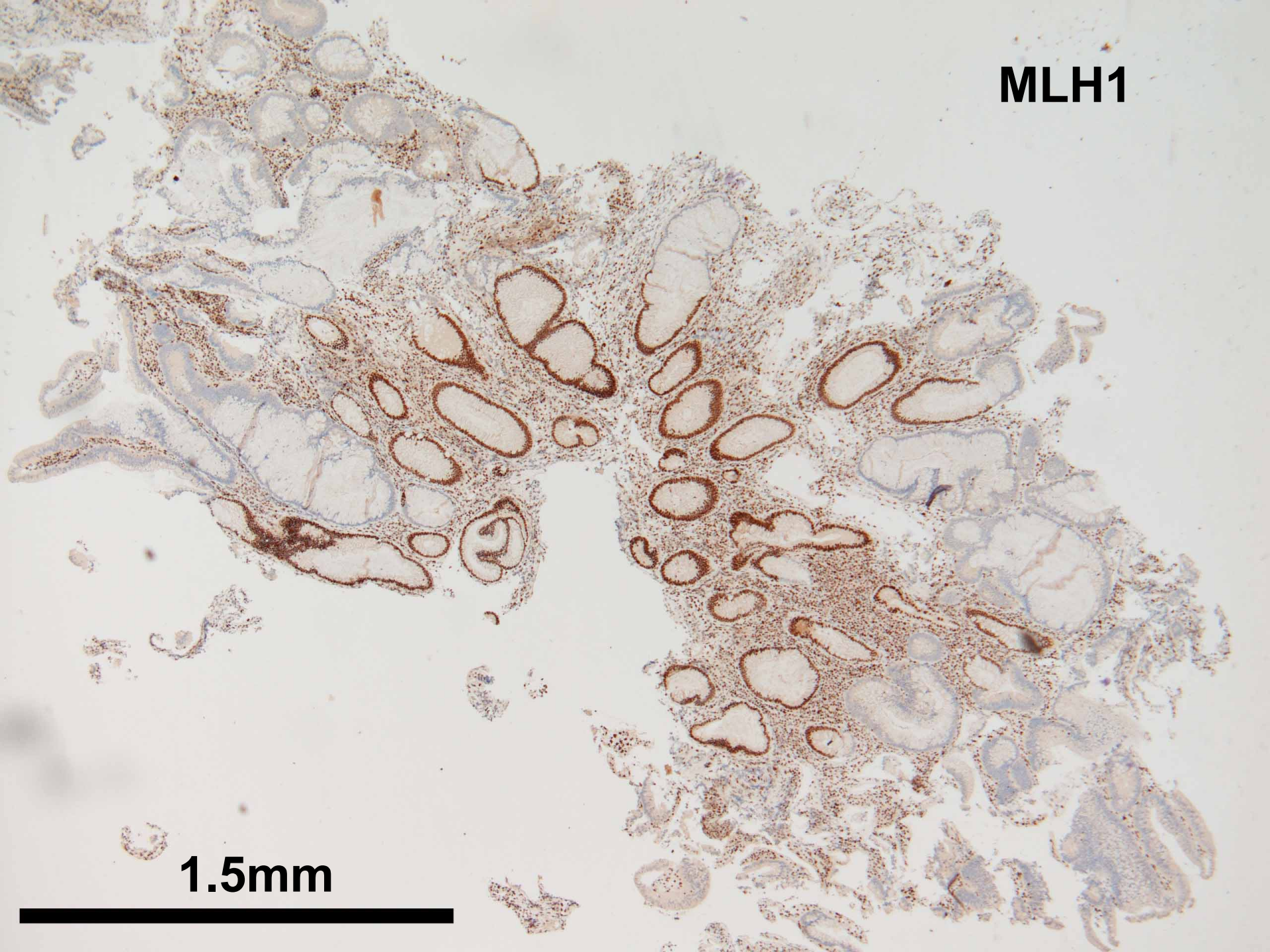
polyp	method	mutated gene				total
		MLH1	PMS2	MSH2	MSH6	
TA, TVA, VA	IHC	129/163 (79%)	2/2 (100%)	94/139 (68%)	9/25 (36%)	312/430 (73%)
TA, TVA, VA	MSI	28/55 (51%)		30/45 (67%)	2/8 (25%)	148/229 (65%)
HP	IHC	0/7 (0%)		0/19 (0%)	0/2 (0%)	0/37 (0%)
HP	MSI	1/6 (17%)		0/17 (0%)		1/40 (2.5%)

Unpublished data

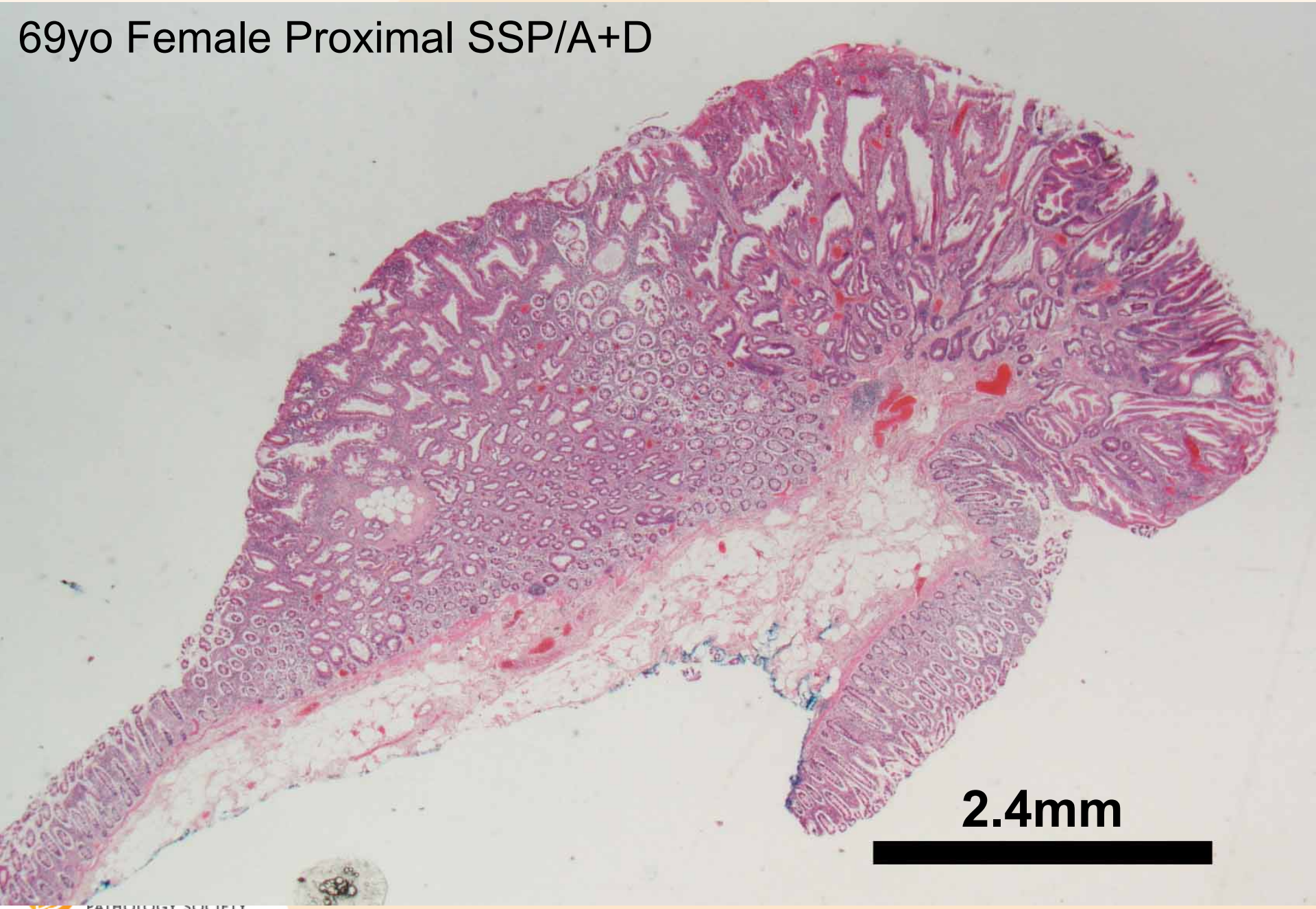
MMR deficient polyps

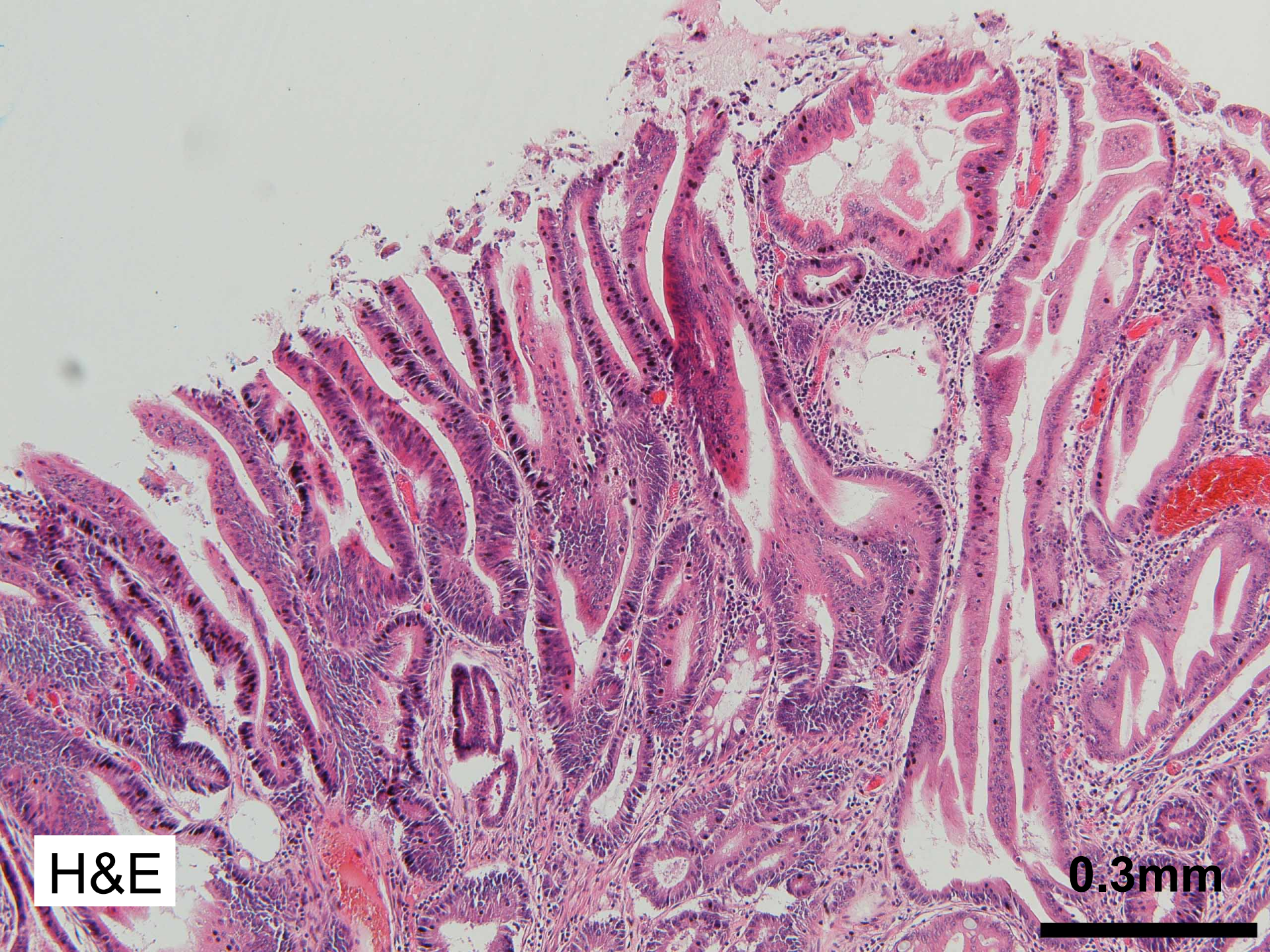
- Likely Lynch syndrome
  - Loss of MSH2 and MSH6
  - Loss of PMS2
  - Loss of MSH6
- Loss of MLH1 can be sporadic or Lynch
  - Lynch syndrome : Adenomatous polyp (TA/TVA/VA) or Traditional serrated adenoma (Modern Pathology 2012:25;722-730)
  - MLH1 promoter methylation : SSP/A with cytological dysplasia

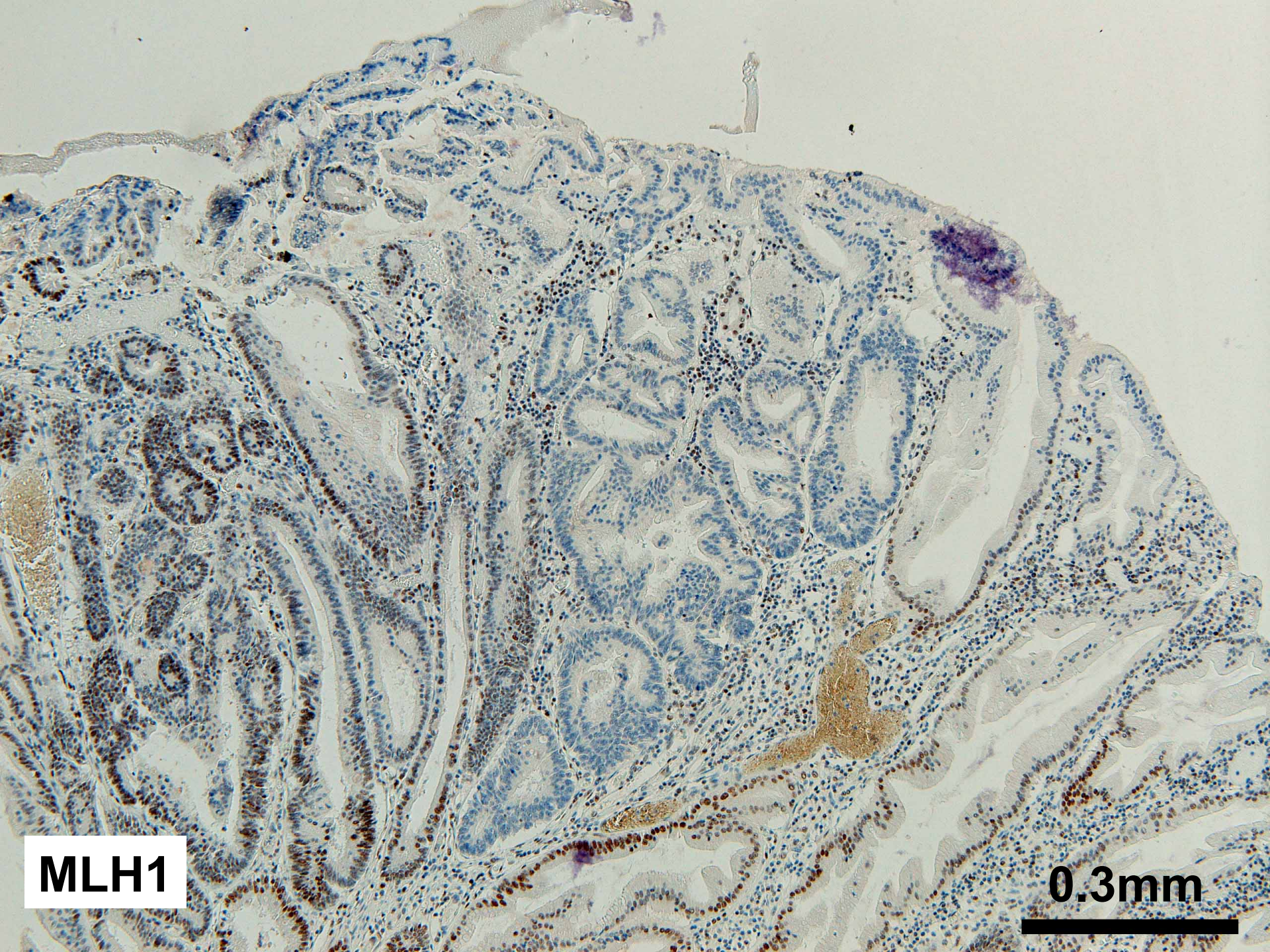

59yo Male Ascending TA, LGD
1.5mm


MLH1
1.5mm

69yo Female Proximal SSP/A+D




H&E
0.3mm


MLH1
0.3mm

MMR IHC in adenomatous polyps

- Diagnostic testing of adenomas in suspected Lynch syndrome families is a useful alternative in cases where cancers are unavailable

(Modern Pathology 2012:25;722-730)

Summary

- Laboratories should have clear screening strategies for colorectal cancers, gynaecological malignancies and sebaceous neoplasms
  - Development of sufficient local infrastructure (i.e. MLH1 promoter methylation assay)
- True focal and/or weak MMR IHC should be reported as 'abnormal' rather than 'no loss'
- Majority (70%) of adenomatous polyps in Lynch syndrome show loss of MMR IHC

Thank you