Lynch syndrome screening in colorectal cancers

10 October 2015

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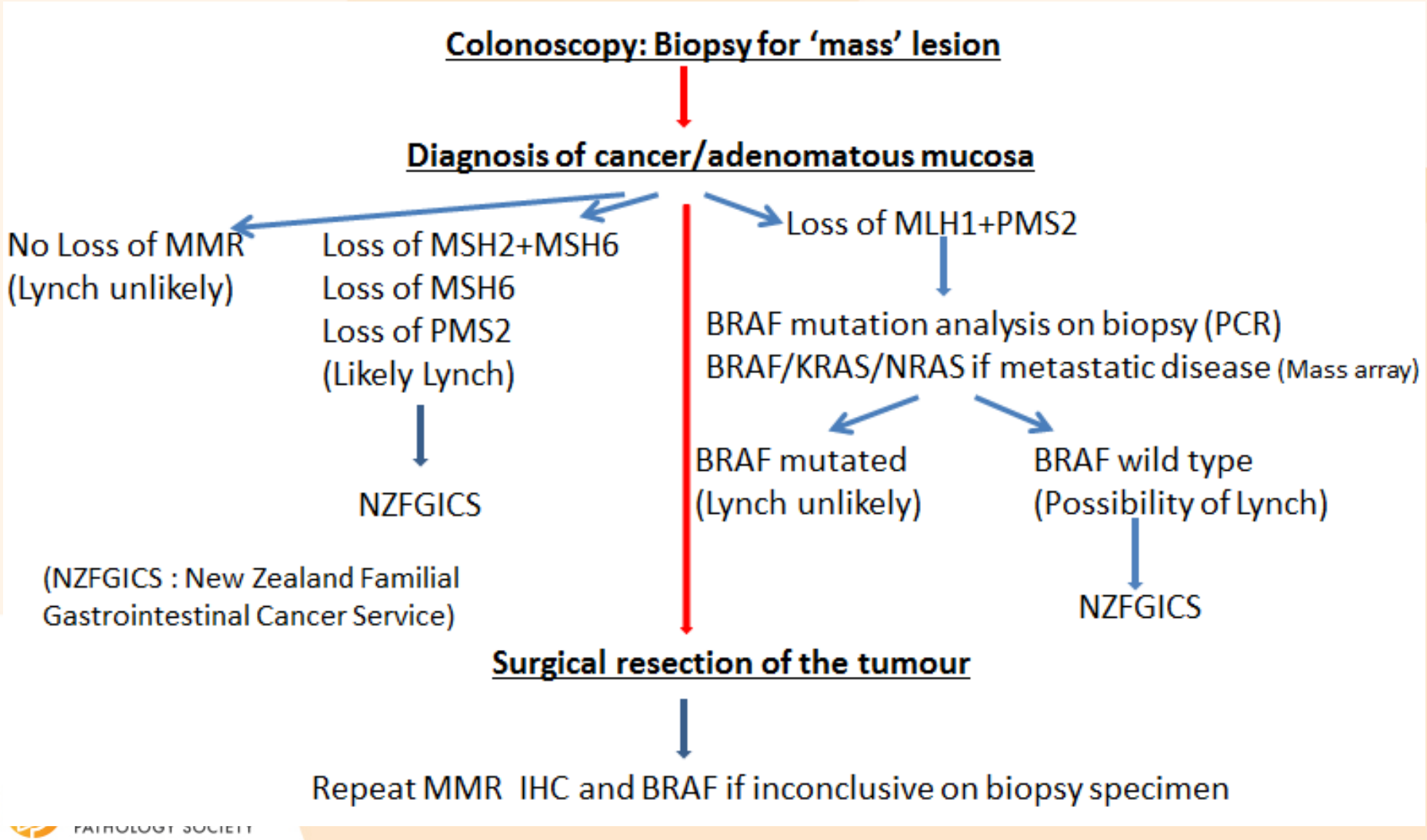
AUSTRALASIAN GASTROINTESTINAL PATHOLOGY SOCIETY

Lynch syndrome screening

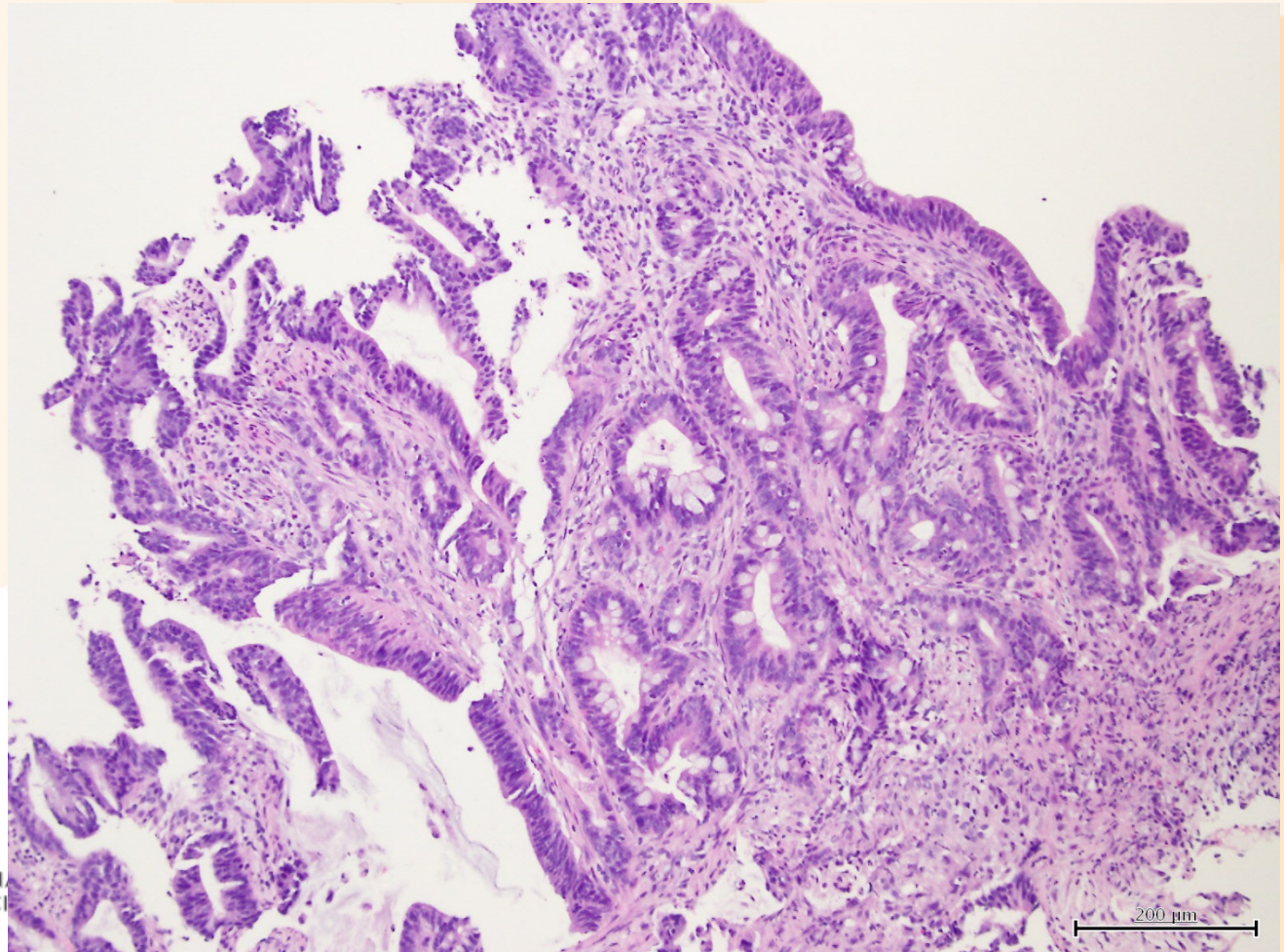


B.B. 71y F

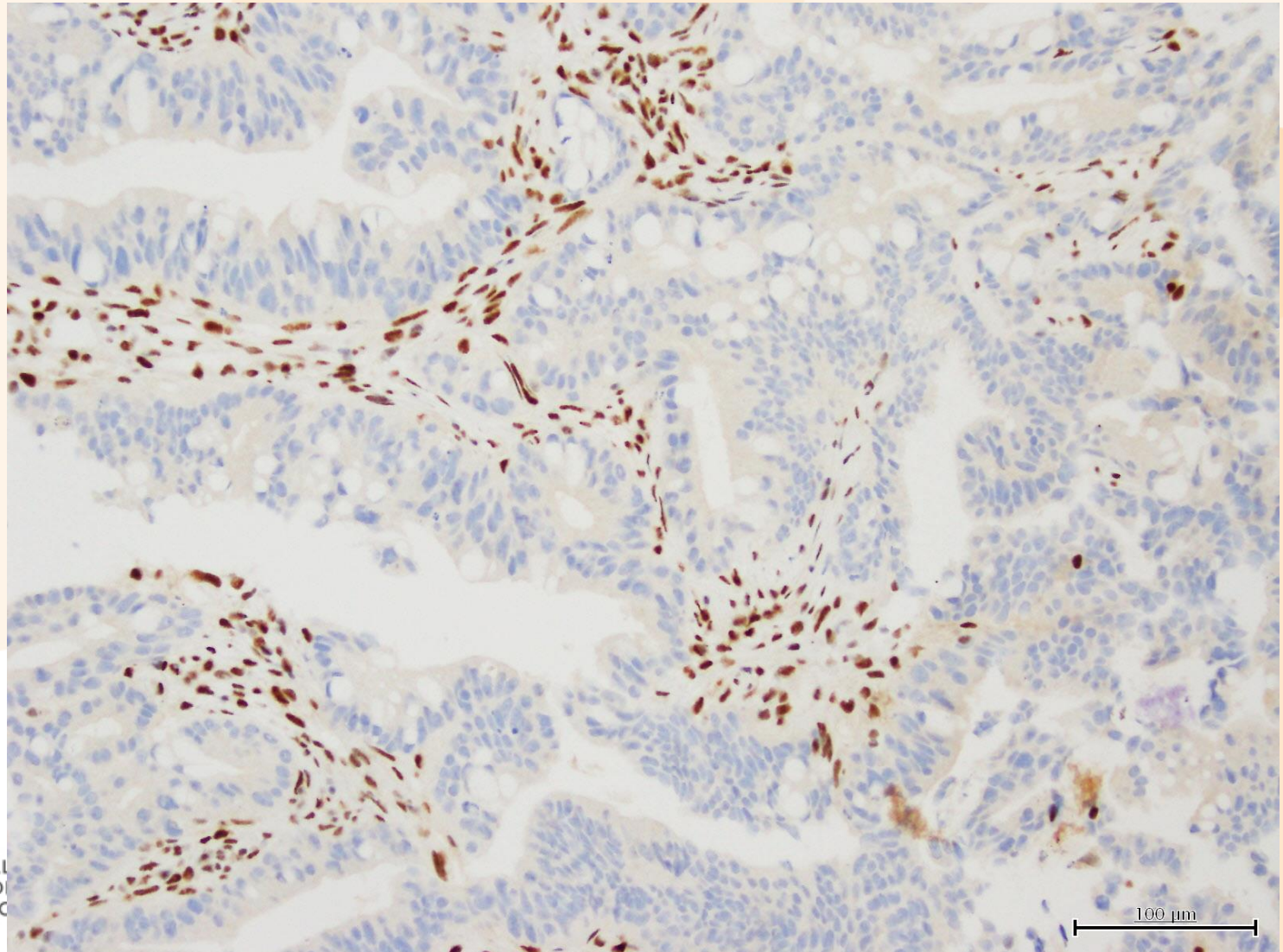
- Presented with epigastric pain and elevated tumour markers (tested by GP) : CA125 119, CEA 22
- CT :
  - Liver ill-defined mass 9cm ?primary ?metastasis
  - Left adrenal lesion 1.6cm, suspicious for metastasis
  - Omental nodules, suspicious for metastasis
- Colonoscopy: Mid ascending colon mass
- PMHx :
  - Ovarian cancer at age 55y (UK)
- FHx :
  - Not documented

Biopsy ascending colon mass

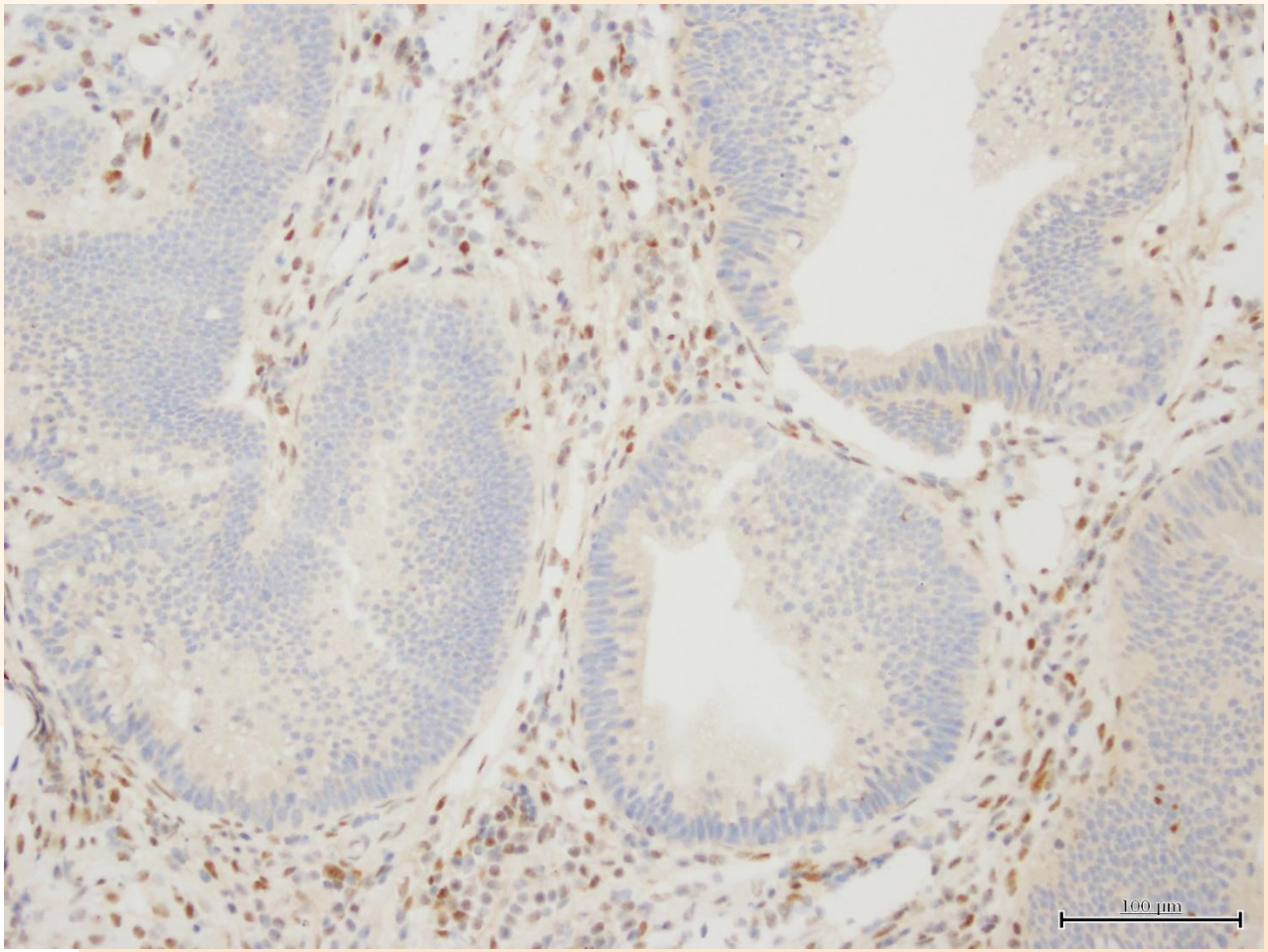
- Adenocarcinoma, low grade



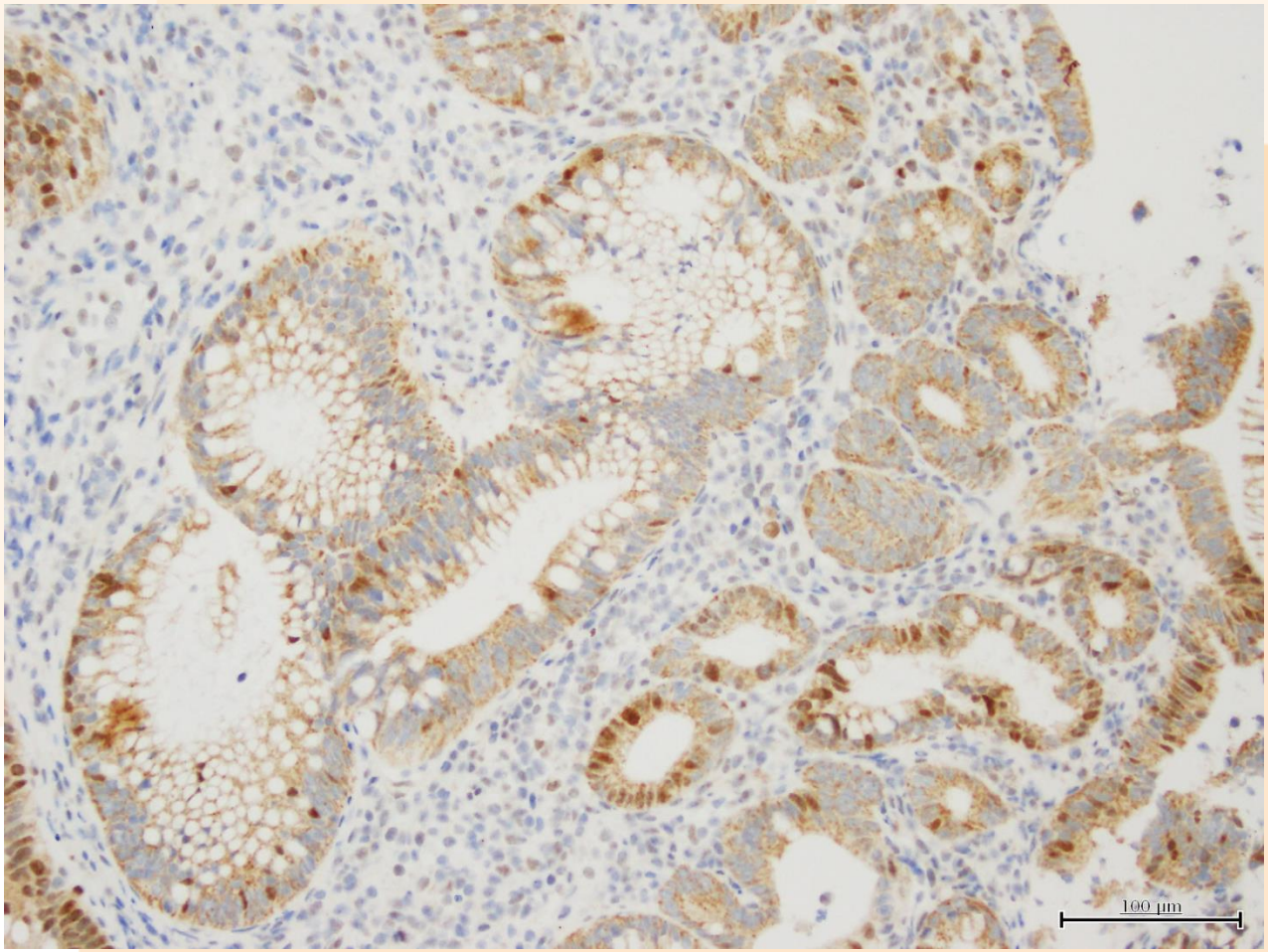
Biopsy ascending colon mass
MLH1



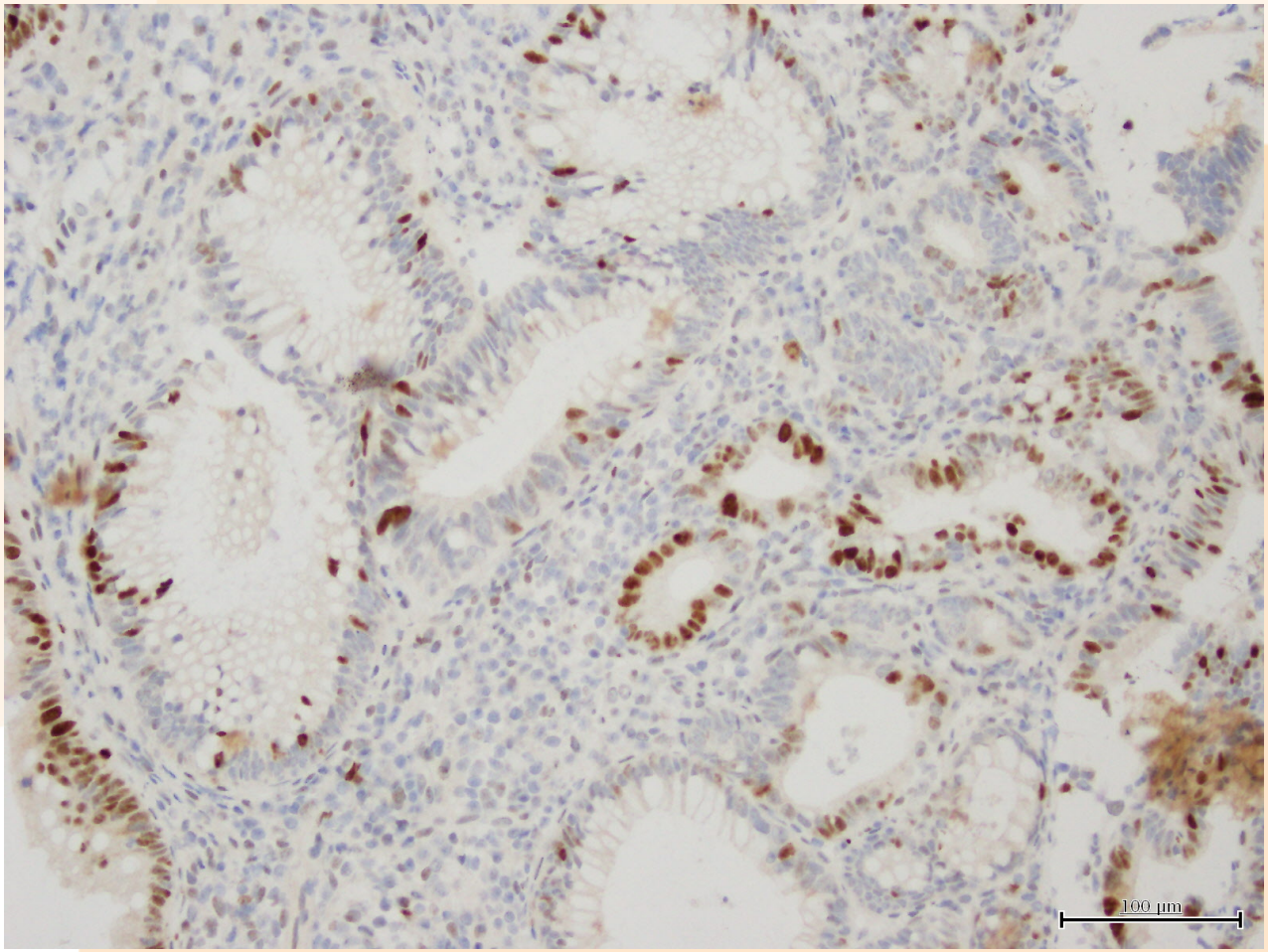
Biopsy ascending colon mass PMS2



Biopsy ascending colon mass MSH2



Biopsy ascending colon mass MSH6



Biopsy ascending colon mass

- Adenocarcinoma, low grade
  - MLH1 : Loss
  - PMS2 : Loss
  - MSH2 : Focal loss (abnormal)
  - MSH6 : Focal loss (abnormal)
- Molecular analysis (mass array)
  - BRAF : Negative
  - KRAS : Positive (G12D)
  - NRAS : Negative

Discussion
B.B. 71y F

- Assess BRAF, KRAS and NRAS mutation in clinical stage 4
- Biopsy is the only tissue available for ancillary studies.

MMR deficiency in CRCs

- 10-15% of all CRCs are MMR deficient
- 70% of MMR deficient CRCs are sporadic
- The rest are Lynch-like (60%) or Lynch syndrome (40%)

Sporadic vs Lynch syndrome

- Sporadic MLH1 loss (MLH1 promoter methylation)
  - Older age (generally)
  - No significant past medical history (generally)
  - No significant family history (generally)
  - BRAFV600E mutation mostly present (75-80%)
  - MLH1 promoter methylation mostly present (75-80%)

Note : None of above is 100% specific

Determining the 'likelihood' of Lynch syndrome

- Any MMR IHC loss involving MLH1
  - Age
  - Past medical history
  - Family history
  - MMR IHC/MSI
  - BRAF mutation analysis
  - MLH1 promoter methylation analysis

- Diagnosis of Lynch syndrome is only made by detection of pathogenic MMR gene mutation

Q.1 : MSI vs IHC

Identifying Lynch syndrome

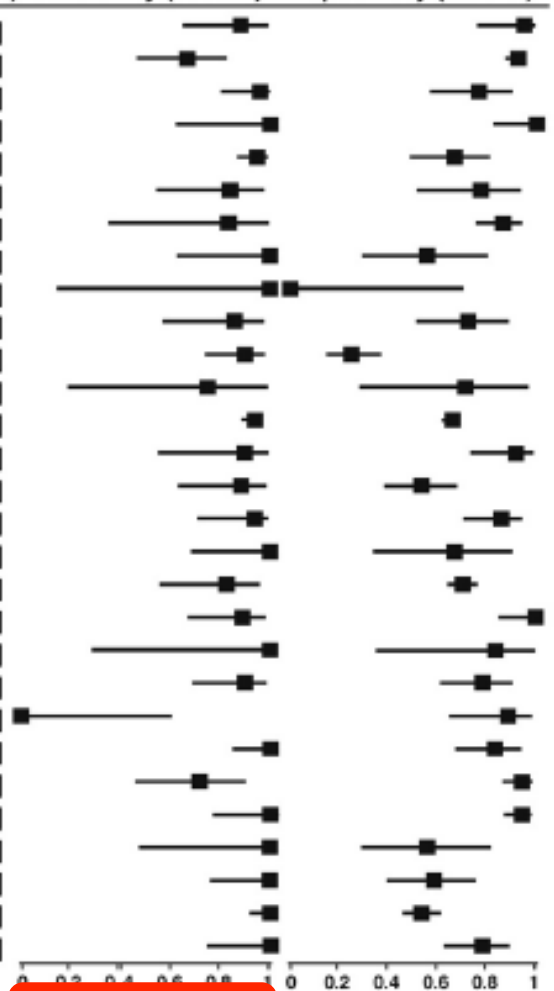
MSI

MSI or IHC?

(Gastroenterology 2015;149:783-813)

A

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bapat et al. 1999	16	1	2	21	0.89 [0.65, 0.99]	0.95 [0.77, 1.00]
Barnetson 2006	20	24	10	298	0.67 [0.47, 0.83]	0.93 [0.89, 0.95]
Caldes et al. 2004	27	7	1	23	0.96 [0.82, 1.00]	0.77 [0.58, 0.90]
Calistri et al. 2000	8	0	0	21	1.00 [0.63, 1.00]	1.00 [0.84, 1.00]
Chen et al. 2006	77	13	4	26	0.95 [0.88, 0.99]	0.67 [0.50, 0.81]
Christensen et al. 2002	11	4	2	14	0.85 [0.55, 0.98]	0.78 [0.52, 0.94]
Debniak et al. 1999	5	8	1	54	0.83 [0.36, 1.00]	0.87 [0.76, 0.94]
Dieumegard et al. 2000	8	7	0	9	1.00 [0.63, 1.00]	0.56 [0.30, 0.80]
Durno et al. 2005	2	3	0	0	1.00 [0.16, 1.00]	0.00 [0.00, 0.71]
Farrington et al. 1998	12	7	2	19	0.86 [0.57, 0.98]	0.73 [0.52, 0.88]
Hendriks et al. 2003	28	53	3	18	0.90 [0.74, 0.98]	0.25 [0.16, 0.37]
Hoedema et al. 2003	3	2	1	5	0.75 [0.19, 0.99]	0.71 [0.29, 0.96]
Kastrinos et al. 2013	146	422	9	810	0.94 [0.89, 0.97]	0.66 [0.63, 0.68]
Kataballe et al. 2002	9	2	1	23	0.90 [0.55, 1.00]	0.92 [0.74, 0.99]
Lamberti et al. 1999	15	24	2	28	0.88 [0.64, 0.99]	0.54 [0.39, 0.68]
Liu et al. 2000	16	6	1	36	0.94 [0.71, 1.00]	0.86 [0.71, 0.95]
Moslein et al. 1996	10	4	0	8	1.00 [0.69, 1.00]	0.67 [0.35, 0.90]
Niessen et al. 2006	14	75	3	178	0.82 [0.57, 0.96]	0.70 [0.64, 0.76]
Overbeek et al. 2007	17	0	2	24	0.89 [0.67, 0.99]	1.00 [0.86, 1.00]
Peel et al. 2000	3	1	0	5	1.00 [0.29, 1.00]	0.83 [0.36, 1.00]
Plevova et al. 2004	19	8	2	29	0.90 [0.70, 0.99]	0.78 [0.62, 0.90]
Scartozzi et al. 2002	0	2	4	16	0.00 [0.00, 0.60]	0.89 [0.65, 0.99]
Shia et al. 2005	24	6	0	31	1.00 [0.86, 1.00]	0.84 [0.68, 0.94]
Southey et al. 2005	13	5	5	82	0.72 [0.47, 0.90]	0.94 [0.87, 0.98]
Spaepen et al. 2006	15	6	0	101	1.00 [0.78, 1.00]	0.94 [0.88, 0.98]
Thibodeau et al. 1996	5	7	0	9	1.00 [0.48, 1.00]	0.56 [0.30, 0.80]
Wahlberg et al. 2002	14	14	0	20	1.00 [0.77, 1.00]	0.59 [0.41, 0.75]
Wang et al. 2007	48	89	0	103	1.00 [0.93, 1.00]	0.54 [0.46, 0.61]
Wolf et al. 2005	13	9	0	33	1.00 [0.75, 1.00]	0.79 [0.63, 0.90]



Pooled sensitivity/specificity 0.93 (0.87–0.96) 0.79 (0.70–0.86)

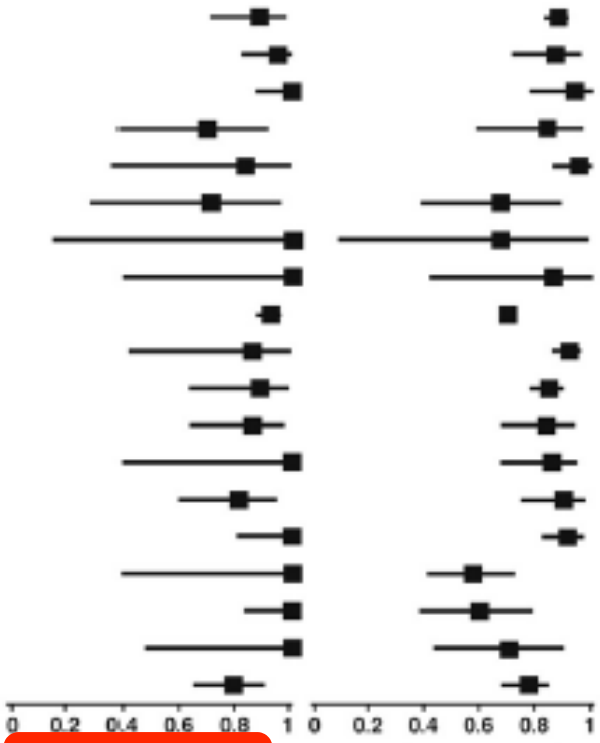
Identifying Lynch syndrome
MSI or IHC?

IHC

(Gastroenterology 2015;149:783-813)

B

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Barnetson 2006	24	39	3	274	0.89 [0.71, 0.98]	0.88 [0.83, 0.91]
Barrow et al. 2010	38	5	2	33	0.95 [0.83, 0.99]	0.87 [0.72, 0.96]
Caldes et al. 2004	28	2	0	28	1.00 [0.88, 1.00]	0.93 [0.78, 0.99]
Christensen et al. 2002	9	3	4	15	0.69 [0.39, 0.91]	0.83 [0.59, 0.96]
Debniak et al. 1999	5	3	1	59	0.83 [0.36, 1.00]	0.95 [0.87, 0.99]
Dieumegard et al. 2000	5	5	2	10	0.71 [0.29, 0.96]	0.67 [0.38, 0.88]
Durno et al. 2005	2	1	0	2	1.00 [0.16, 1.00]	0.67 [0.09, 0.99]
Hoedema et al. 2003	4	1	0	6	1.00 [0.40, 1.00]	0.86 [0.42, 1.00]
Kastrinos et al. 2013	211	411	18	944	0.92 [0.88, 0.95]	0.70 [0.67, 0.72]
Limburg et al. 2011	6	12	1	136	0.86 [0.42, 1.00]	0.92 [0.86, 0.96]
Niessen et al. 2006	15	26	2	140	0.88 [0.64, 0.99]	0.84 [0.78, 0.90]
Plevova et al. 2004	18	6	3	31	0.86 [0.64, 0.97]	0.84 [0.68, 0.94]
Scartozzi et al. 2002	4	5	0	28	1.00 [0.40, 1.00]	0.85 [0.68, 0.95]
Shia et al. 2005	21	4	5	34	0.81 [0.61, 0.93]	0.89 [0.75, 0.97]
Southey et al. 2005	18	8	0	79	1.00 [0.81, 1.00]	0.91 [0.83, 0.96]
Stone et al. 2001	4	18	0	24	1.00 [0.40, 1.00]	0.57 [0.41, 0.72]
Stormorken et al. 2005	21	11	0	16	1.00 [0.84, 1.00]	0.59 [0.39, 0.78]
Thibodeau et al. 1996	5	5	0	12	1.00 [0.48, 1.00]	0.71 [0.44, 0.90]
Wang et al. 2007	38	30	10	98	0.79 [0.65, 0.90]	0.77 [0.68, 0.84]



Pooled sensitivity/specificity **0.91 (0.85; 0.95)** **0.83 (0.77; 0.88)**

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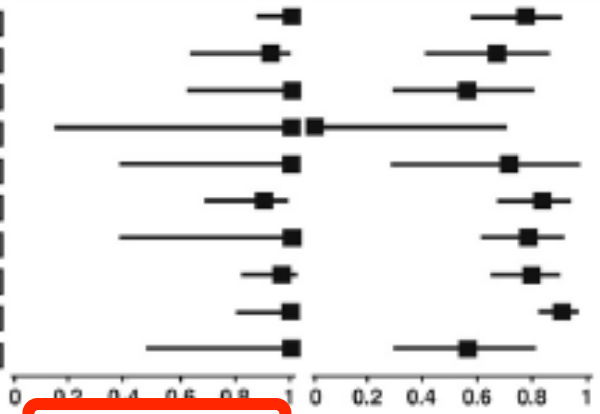
Identifying Lynch syndrome
MSI or IHC?

MSI+IHC

(Gastroenterology 2015;149:783-813)

C

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Caldes et al. 2004	28	7	0	23	1.00 [0.88, 1.00]	0.77 [0.58, 0.90]
Christensen et al. 2002	12	6	1	12	0.92 [0.64, 1.00]	0.67 [0.41, 0.87]
Dieumegard et al. 2000	8	7	0	9	1.00 [0.63, 1.00]	0.56 [0.30, 0.80]
Durno et al. 2005	2	3	0	0	1.00 [0.16, 1.00]	0.00 [0.00, 0.71]
Hoedema et al. 2003	4	2	0	5	1.00 [0.40, 1.00]	0.71 [0.29, 0.96]
Plevova et al. 2004	19	6	2	31	0.90 [0.70, 0.99]	0.84 [0.68, 0.94]
Scartozzi et al. 2002	4	7	0	26	1.00 [0.40, 1.00]	0.79 [0.61, 0.91]
Shia et al. 2005	30	11	1	43	0.97 [0.83, 1.00]	0.80 [0.66, 0.89]
Southey et al. 2005	18	8	0	79	1.00 [0.81, 1.00]	0.91 [0.83, 0.96]
Thibodeau et al. 1996	5	7	0	9	1.00 [0.48, 1.00]	0.56 [0.30, 0.80]
Pooled sensitivity/specificity					**0.97 (0.90; 0.99)**	**0.75 (0.62; 0.84)**



AUSTRALASIAN GASTROINTESTINAL PATHOLOGY SOCIETY

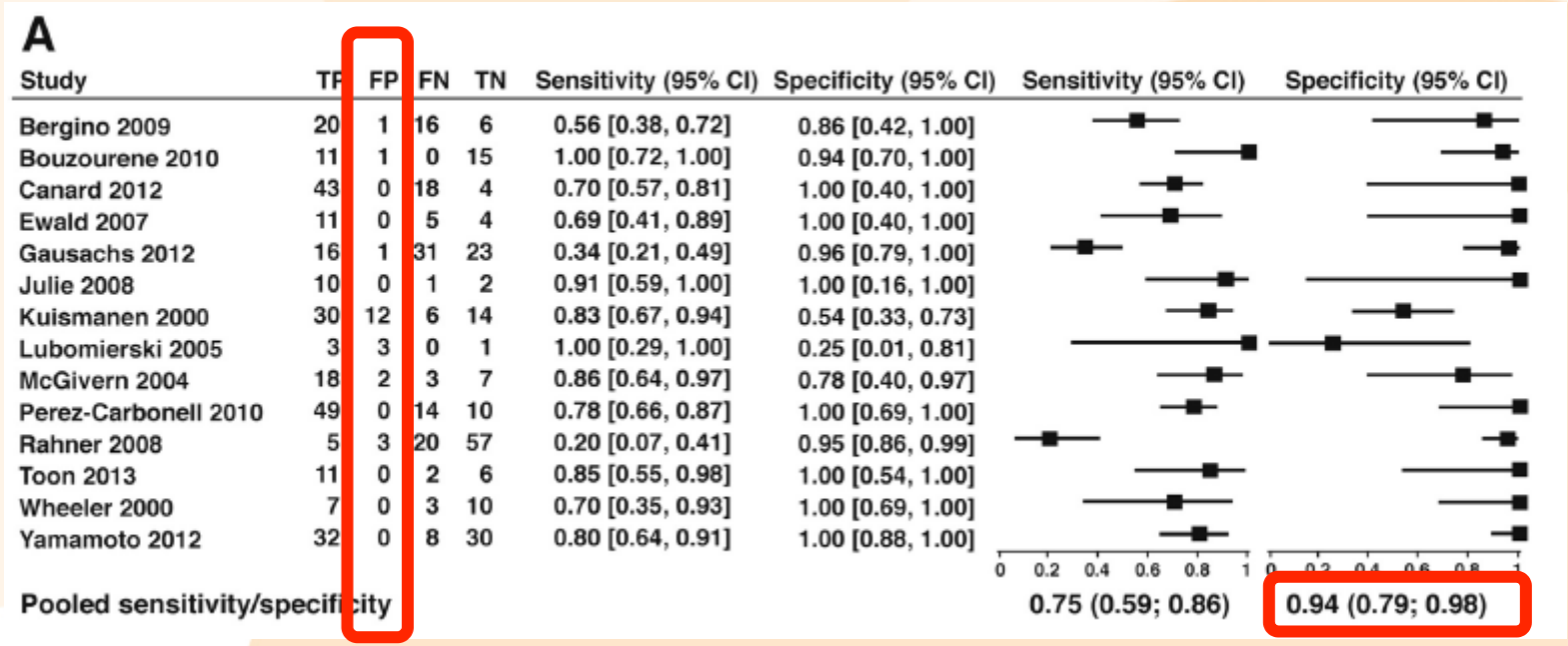
Q.2 :BRAF vs Methylation study

Identifying sporadic cases

MLH1 promoter methylation vs BRAF mutation

MLH1 promoter methylation

(Gastroenterology 2015;149:783-813)



A

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bergino 2009	20	1	16	6	0.56 [0.38, 0.72]	0.86 [0.42, 1.00]
Bouzourene 2010	11	1	0	15	1.00 [0.72, 1.00]	0.94 [0.70, 1.00]
Canard 2012	43	0	18	4	0.70 [0.57, 0.81]	1.00 [0.40, 1.00]
Ewald 2007	11	0	5	4	0.69 [0.41, 0.89]	1.00 [0.40, 1.00]
Gausachs 2012	16	1	31	23	0.34 [0.21, 0.49]	0.96 [0.79, 1.00]
Julie 2008	10	0	1	2	0.91 [0.59, 1.00]	1.00 [0.16, 1.00]
Kuismanen 2000	30	12	6	14	0.83 [0.67, 0.94]	0.54 [0.33, 0.73]
Lubomierski 2005	3	3	0	1	1.00 [0.29, 1.00]	0.25 [0.01, 0.81]
McGivern 2004	18	2	3	7	0.86 [0.64, 0.97]	0.78 [0.40, 0.97]
Perez-Carbonell 2010	49	0	14	10	0.78 [0.66, 0.87]	1.00 [0.69, 1.00]
Rahner 2008	5	3	20	57	0.20 [0.07, 0.41]	0.95 [0.86, 0.99]
Toon 2013	11	0	2	6	0.85 [0.55, 0.98]	1.00 [0.54, 1.00]
Wheeler 2000	7	0	3	10	0.70 [0.35, 0.93]	1.00 [0.69, 1.00]
Yamamoto 2012	32	0	8	30	0.80 [0.64, 0.91]	1.00 [0.88, 1.00]
Pooled sensitivity/specificity					0.75 (0.59; 0.86)	0.94 (0.79; 0.98)

AUSTRALASIAN GASTROINTESTINAL PATHOLOGY SOCIETY

Identifying sporadic cases

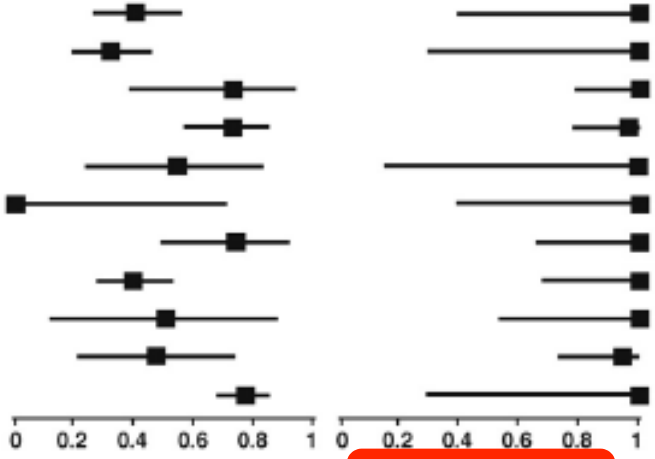
MLH1 promoter methylation vs BRAF mutation

BRAF

(Gastroenterology 2015;149:783-813)

B

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Benlloch 2006	19	0	28	4	0.40 [0.26, 0.56]	1.00 [0.40, 1.00]
Bessa 2008	18	0	39	3	0.32 [0.20, 0.45]	1.00 [0.29, 1.00]
Bouzourene 2010	8	0	3	16	0.73 [0.39, 0.94]	1.00 [0.79, 1.00]
Gausachs 2012	34	1	13	23	0.72 [0.57, 0.84]	0.96 [0.79, 1.00]
Julie 2008	6	0	5	2	0.55 [0.23, 0.83]	1.00 [0.16, 1.00]
Lubomierski 2005	0	0	3	4	0.00 [0.00, 0.71]	1.00 [0.40, 1.00]
McGivern 2004	14	0	5	9	0.74 [0.49, 0.91]	1.00 [0.66, 1.00]
Perez-Carbonell 2010	25	0	38	10	0.40 [0.28, 0.53]	1.00 [0.69, 1.00]
Thiel 2013	3	0	3	6	0.50 [0.12, 0.88]	1.00 [0.54, 1.00]
Toon 2013	7	1	8	18	0.47 [0.21, 0.73]	0.95 [0.74, 1.00]
Ward 2013	87	0	26	3	0.77 [0.68, 0.84]	1.00 [0.29, 1.00]
Pooled sensitivity/specificity					0.76 (0.60; 0.87)	0.96 (0.60; 0.99)



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Important points of MLH1 promoter methylation and BRAF testing

- Neither methods are perfectly specific
  - Very rarely CRCs in Lynch syndrome can show MLH1 promoter methylation or BRAF mutation
- Neither methods are perfectly sensitive
  - Negative result does not mean the patient has Lynch syndrome
- MLH1 promother methylation study : 'methylated' or 'unmethylated' are based on quantitative number of the degree of methylation
  - cut off dependent (cf. BRAF is qualitative)
  - MLH1 was 'methylated' in 16% of Lynch syndrome and 92% of sporadic case (Cancer 2015;121:1395-1404)

Q.3 :Biopsy vs Resection

Advantages of MMR/BRAF testing on biopsy specimen

1. Changes in surgical procedures for likely Lynch syndrome patients
   - Total colectomy
   - Prophylactic gynaecological surgery
2. Issues of MMR IHC in surgical specimen
   - False negative staining in poorly fixed specimen
3. No surgical resection in stage lV patients
4. Issues of MMR IHC/MSI in post neoadjuvant therapy specimens
   - False negative staining
   - Aberrant MSH6 nucleolar positivity
   - No tumour/minimal tumour

- “To facilitate surgical planning, tumour testing on suspected CRC should be performed on preoperative biopsy specimens, if possible.”

Consensus Statement by the US Multi-Society Task Force on Colorectal Cancer
Gastroenterology 2014;147:502-526

Q.4 :Universal vs Selected screening

Table 1. Bethesda Guidelines (Revised)

1.	Colorectal cancer diagnosed before age 50 years
2.	Multiple colorectal cancer or HNPCC-related cancers[a]
3.	Colorectal cancer with MSI-related histology[b] diagnosed before age 60 years
4.	Colorectal cancer or HNPCC-related cancer diagnosed in at least one first-degree relative before age 50 years
5.	Colorectal cancer or HNPCC-related cancer diagnosed in at least 2 first- or second-degree relatives at any age

NOTE. Any criterion (1–5) can be met.
HNPCC, hereditary nonpolyposis colorectal cancer.
[a]Includes cancer of endometrium, small bowel, pelviureter, biliary tract, stomach, ovary, pancreas, or brain (mainly glioblastoma multiforme).
[b]Tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucin/signet ring cell differentiation, medullary growth pattern.

Note : No recommendations for MSI/MMR testing in patients >60 years of age

Low sensitivity

Human Pathology (2013) 44, 2518–2528

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Original contribution

Lynch syndrome–associated colorectal carcinoma: frequent involvement of the left colon and rectum and late-onset presentation supports a universal screening approach☆

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Received 6 May 2013; revised 19 June 2013; accepted 21 June 2013

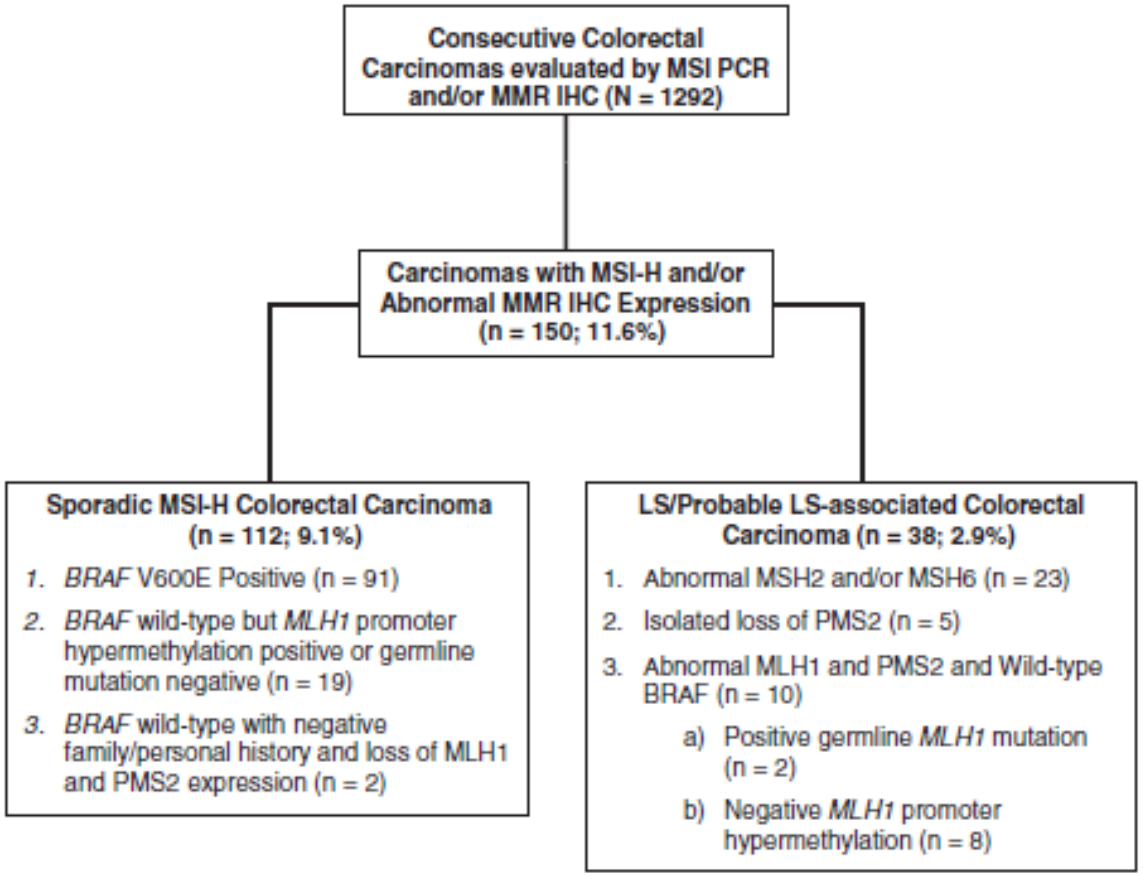

Fig. 1 Flowchart detailing the MSI-H colorectal carcinoma study group stratified into LS/probable LS-associated and sporadic subgroups.

Table 1 Clinicopathologic features of colorectal carcinoma with high levels of microsatellite instability (MSI-H) stratified into sporadic and Lynch syndrome/probable Lynch syndrome subgroups

Clinicopathologic feature	Sporadic MSI-H CRC (n = 112) (%)	LS/Probable LS MSI-H CRC (n = 38) (%)	*P*
Gender			
Male	28 (25)	18 (47)	.014
Female	84 (75)	20 (53)	
Age <50	5 (4)	12 (32)	.0001
Age <60	7 (6)	26 (68)	.0001
Location			
Right	103 (92)	26 (68)	.0008
Left	9 (8)	12 (32)	
Stage			
I-II	78 (70)	28 (74)	.69
III-IV	34 (30)	10 (26)	

- 12 out of 38 Lynch syndrome patients (32%) presented >60 years
  - Not identified with revised Bethesda guidelines

Prediction models

- MMRpredict model : hnpccpredict.hgu.mrc.ac.uk/
  - sensitivity 69% and specificity 90%
- MMRpro model : www4utsouthwestern.edu/breasthealth/cagene/
  - sensitivity 89% and specificity 85%
- PREMM model : premm.dfci.harvard.edu.
  - sensitivity 90% and specificity 67%

Note : All require accurate family history

Universal screening vs selected population screening

EGAPP RECOMMENDATION STATEMENT

Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives

*Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group**

(Genet Med 2009:11(1):35-41)

Summary : Found sufficient evidence that testing for Lynch syndrome in newly diagnosed colorectal cancer patients reduce morbidity and mortality in relatives.

Gastroenterology 2014;147:502–526

AGA SECTION

Guidelines on Genetic Evaluation and Management of Lynch Syndrome: A Consensus Statement by the US Multi-Society Task Force on Colorectal Cancer

Francis M. Giardiello,[1] John I. Allen,[2] Jennifer E. Axilbund,[1] C. Richard Boland,[3] Carol A. Burke,[4] Randall W. Burt,[5] James M. Church,[4] Jason A. Dominitz,[6,7] David A. Johnson,[8] Tonya Kaltenbach,[9] Theodore R. Levin,[10] David A. Lieberman,[11] Douglas J. Robertson,[12,13] Sapna Syngal,[14,15,16] and Douglas K. Rex[17]

- *Guideline: Testing for MMR deficiency of newly diagnosed CRC should be performed. This can be done for all CRCs, or CRC diagnosed at age 70 years or younger, and in individuals older than 70 years who have a family history concerning for LS.*
- *Analysis can be done by IHC testing for the MLH1/MSH2/MSH6/PMS2 proteins and/or testing for MSI. Tumors that demonstrate loss of MLH1 should undergo BRAF testing or analysis of MLH1 promoter hypermethylation.*

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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Hereditary Colorectal Cancer Syndromes: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the Familial Risk–Colorectal Cancer: European Society for Medical Oncology Clinical Practice Guidelines

Elena M. Stoffel, University of Michigan, Ann Arbor, MI; Pamela B. Mangu, American Society of Clinical Oncology;

Elena M. Stoffel, Pamela B. Mangu, Stephen B. Gruber, Stanley R. Hamilton, Matthew F. Kalady, Michelle Wan Yee Lau, Karen H. Lu, Nancy Roach, and Paul J. Limburg

J Clin Oncol 33:209-217

- Tumor testing ***for DNA mismatch repair (MMR) deficiency*** with immunohistochemistry for MMR proteins and/or MSI should be ***assessed*** in all CRC patients. As an alternate strategy, tumor testing should be carried out in individuals with CRC younger than 70 years, or those older than 70 years who fulfill any of the revised Bethesda guidelines (Table 1).
- If loss of MLH1/PMS2 ***protein expression*** is observed in the tumor, analysis of *BRAF* V600E mutation or analysis of methylation of the *MLH1* promoter should be carried out first to rule out a sporadic case. ***If tumor is MMR deficient and somatic BRAF mutation is not detected or MLH1 promoter methylation is not identified, testing for germline mutations is indicated.***
- If loss of any of the other proteins (MSH2, MSH6, PMS2) is observed, germline genetic testing should be carried out ***for the genes corresponding to the absent proteins (eg, MSH2, MSH6, EPCAM, PMS2, or MLH1).***

CME

ACG Clinical Guideline: Genetic Testing and Management of Hereditary Gastrointestinal Cancer Syndromes

Sapna Syngal, MD, MPH, FACG[1,2,3], Randall E. Brand, MD, FACG[4], James M. Church, MD, FACG[5,6,7], Francis M. Giardiello, MD[8], Heather L. Hampel, MS, CGC[9] and Randall W. Burt, MD, FACG[10]

Am J Gastroenterol 2015; 110:223–262; doi: 10.1038/ajg.2014.435; published online 3 February 2015

LYNCH SYNDROME (LS)

Tumor testing and indications for genetic testing

Summary statements

1. All newly diagnosed colorectal cancers (CRCs) should be evaluated for mismatch repair deficiency.
2. Analysis may be done by immunohistochemical testing for the *MLH1/MSH2/MSH6/PMS2* proteins and/or testing for microsatellite instability (MSI). Tumors that demonstrate loss of *MLH1* should undergo BRAF testing or analysis for *MLH1* promoter hypermethylation.
3. Individuals who have a personal history of a tumor showing evidence of mismatch repair deficiency (and no demonstrated BRAF mutation or hypermethylation of *MLH1)*, a known family mutation associated with LS, or a risk of ≥5% chance of LS based on risk prediction models should undergo genetic evaluation for LS.

Importance of evaluating mismatch repair deficiency outside the context of Lynch syndrome screening

Cancer Res 2005; 65: (14). July 15, 2005

Research Article

Poor Survival Associated with the *BRAF* V600E Mutation in Microsatellite-Stable Colon Cancers

Wade S. Samowitz,[1] Carol Sweeney,[2] Jennifer Herrick,[2] Hans Albertsen,[2] Theodore R. Levin,[3] Maureen A. Murtaugh,[2] Roger K. Wolff,[2] and Martha L. Slattery[2]

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MODERN PATHOLOGY (2014) 27, 644–650

OPEN

BRAFV600E immunohistochemistry in conjunction with mismatch repair status predicts survival in patients with colorectal cancer

Christopher W Toon[1,2,3], Angela Chou[4], Keshani DeSilva[5], Joseph Chan[3,6], Jillian Patterson[7], Adele Clarkson[1,5], Loretta Sioson[1,5], Lucy Jankova[3,6] and Anthony J Gill[1,3,5]

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AUSTRALASIAN GASTROINTESTINAL PATHOLOGY SOCIETY

Prevalence

N=1426	BRAF wild-type	BRAFV600E mutant
Proficient MMR	1057(74.1%)	91 (6.4%)
Deficient MMR	94 (6.6%)	184(12.9%)

Prognosis

	BRAF wild-type	BRAFV600E mutant
Proficient MMR	Intermediate	**Poor**
Deficient MMR	Good	Good

AUSTRALASIAN GASTROINTESTINAL PATHOLOGY SOCIETY

CW Toon et al. Modern Pathology (2014) 27,644-650

Clinical significance of molecular subgroup

	BRAF WT	BRAFV600E mutant
MMR proficient	○ 5FU monotherapy ○anti-EGFR X PD1 inhibitor	○ 5FU monotherapy X anti-EGFR X PD1 inhibitor 5FU+Oxaliplatin+Irinotecan (Stage 4)
MMR deficient	X 5FU monotherapy ○ anti-EGFR ○PD1 inhibitor	X 5FU monotherapy X anti-EGFR ○PD1 inhibitor

Conclusion

- Universal screening for colorectal cancer is likely to become the future national standard of care
- *But this standard requires development of sufficient local and community infrastructure to appropriately handle genetic results before implementation*

Consensus Statement by the US Multi-Society Task Force on Colorectal Cancer
Gastroenterology 2014;147:502-526

Proposed AGPS Consensus Guidelines for Lynch syndrome screening

Consensus statements

- Mismatch repair immunohistochemistry is a phenotype rather than a genotype test. Therefore genetic counselling is not required before mismatch repair immunohistochemistry, microsatellite instability, BRAF mutation testing or hypermethylation testing is performed.

Proposed AGPS Consensus Guidelines for Lynch syndrome screening

Consensus statements

- All newly diagnosed colorectal cancers should be tested for mismatch repair deficiency by immunohistochemistry for mismatch repair proteins and/or microsatellite instability analysis. This can be performed on either the biopsy or resection specimen.

  The value of evaluating mismatch repair deficiency is acknowledged not only for Lynch syndrome screening, but also as a prognostic factor and a predictive factor for chemotherapy.

Proposed AGPS Consensus Guidelines for Lynch syndrome screening

Consensus statements

- Ideally all colorectal cancers with abnormal MLH1 protein expression should undergo BRAFV600E mutation analysis as a surrogate marker of hypermethylation and MLH1 promoter methylation analysis if BRAF is wild type. Depending on the environment and available resources, a triage decision may need to be made.

  If the tumour is BRAF wild type and negative for MLH1 promoter methylation, germline mutation analysis is indicated.

Proposed AGPS Consensus Guidelines for Lynch syndrome screening

Consensus statements

- Colorectal cancers with abnormal mismatch repair protein expression that does not involve MLH1 should undergo germline mutation analysis

Thank you