



Il cancro coloretale ereditario (Sindrome di Lynch)
Modena, 19 dicembre 2007

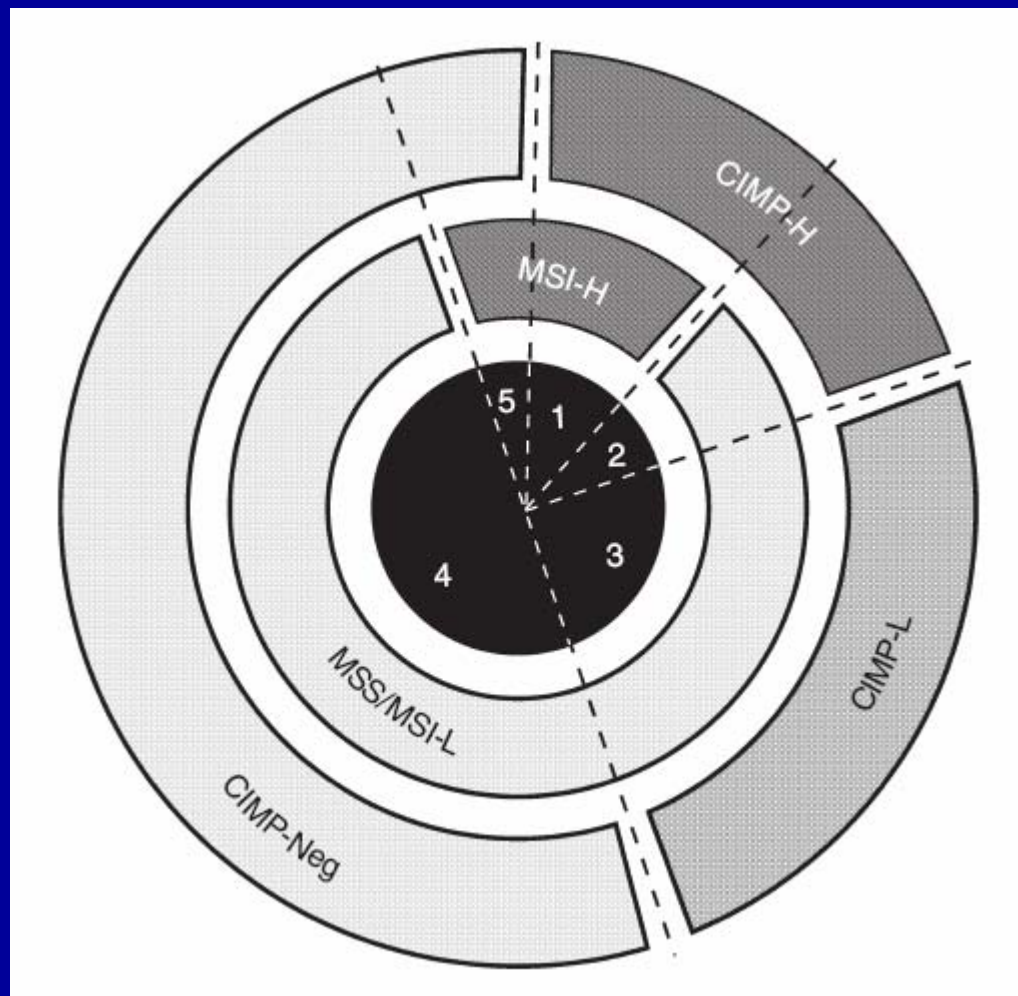


Aspetti molecolari della Sindrome di Lynch

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Classificazione molecolare del carcinoma coloretta



Feature	Group 1	Group 2	Group 3	Group 4	Group 5
MSI status	H	S/L	S/L	S	H
Methylation	+++	+++	++	+/-	+/-
Ploidy	Dip > An	Dip > An	An > Dip	An > Dip	Dip > An
<i>APC</i>	+/-	+/-	+	+++	++
<i>KRAS</i>	-	+	+++	++	++
<i>BRAF</i>	+++	++	-	-	-
<i>TP53</i>	-	+	++	+++	+
Location	R > L	R > L	L > R	L > R	R > L
Gender	F > M	F > M	M > F	M > F	M > F
Precursor	SP	SP	SP/AD	AD	AD
Serration	+++	+++	+	+/-	+/-
Mucinous	+++	+++	+	+	++
Dirty necrosis	+	+	?	+++	+
Poor differentiation	+++	+++	+	+	++
Circumscribed	+++	+	?	++	++
Tumour budding	+/-	+	?	+++	+
Lymphocytes	+++	+	?	+	+++

MSI, microsatellite instability; H, high; S, stable; L, low; Dip, diploid; An, aneuploid; Serration, serrated morphology; SP, serrated polyp; AD, adenoma; Circumscribed, circumscribed invasive margin.

MOLECULAR GENETIC PATHWAYS TO COLORECTAL CANCER

**SUPPRESSOR
PATHWAY**
85%

**MUTATOR
PATHWAY**
15%

NORMAL MUCOSA

**Chromosomal
instability**

Genomic instability

**Microsatellite
instability**

Cytogenetic
abnormalities
Allelic losses
Aneuploidy

Stable Karyotype
No allelic losses
Diploidy

Target genes:

APC

p53

genes on 18q

(DCC, Smad4, Smad2)

CARCINOMA

Target genes:

TGFR II

Bax, IGFRII

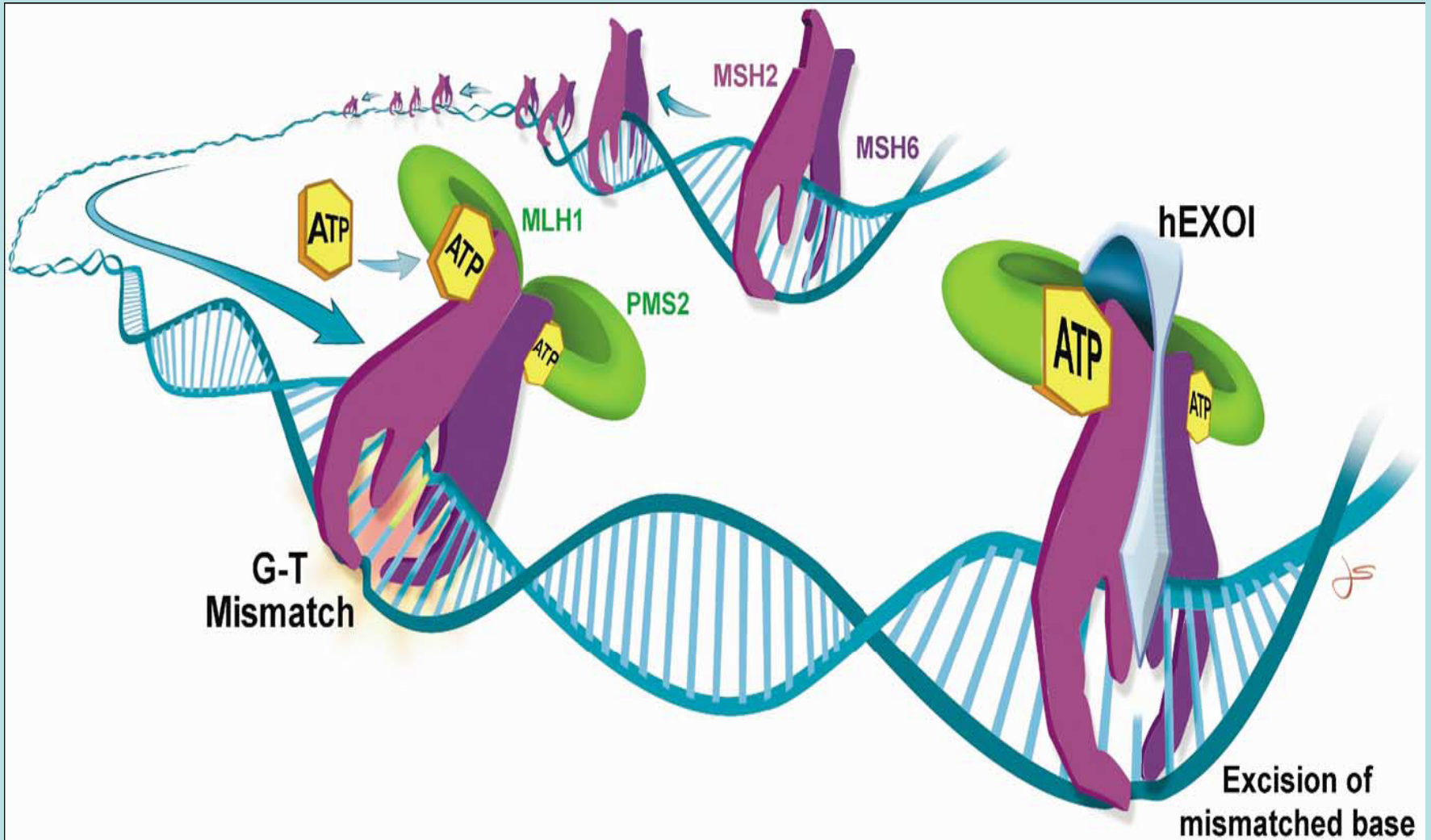
hMSH3, hMSH6

B-catenin

CLASSIFICAZIONE MOLECOLARE DEL CCR IN BASE AL TIPO DI INSTABILITA' GENETICA

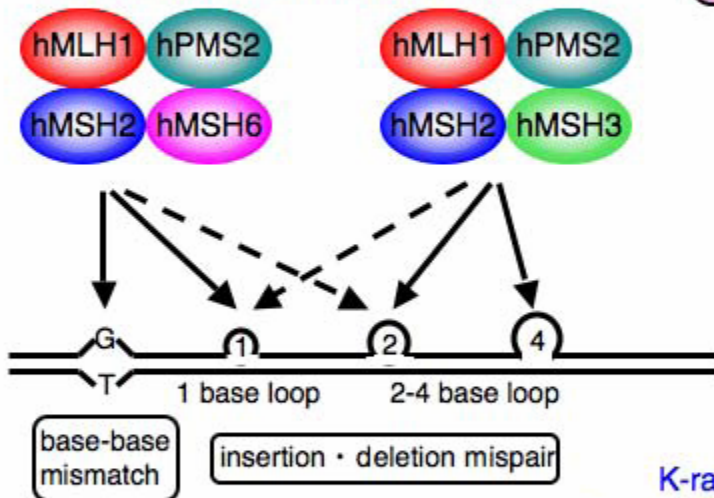
	INSTABILITA' CROMOSOMICA	INSTABILITA' DEI MICROSATELLITI
SEDE	COLON DISTALE	COLON PROSSIMALE
SESSO	MASCHILE	FEMMINILE
ETA'	MEDIO-AVANZATA	AVANZATA
POTENZIALE METASTATICO	ELEVATO	BASSO
PROGNOSI	SFAVOREVOLE	FAVOREVOLE
RISPOSTA AL 5-FU	PRESENTE/ASSENTE	ASSENTE
DIFFERENZIAZIONE	BASSO GRADO	ALTO GRADO
ISTOTIPO	ADENOCARCINOMA	MUCOIDE/MIDOLLARE
TIL	ASSENTI	PRESENTI
ALTERAZIONI CROMOSOMICHE	FREQUENTI	RARE
CONTENUTO NUCLEARE DI DNA	ANEUPLOIDE	DIPLOIDE
ALTERAZIONI DI APC, p53, 18q	FREQUENTI	RARE

DNA mismatch repair system

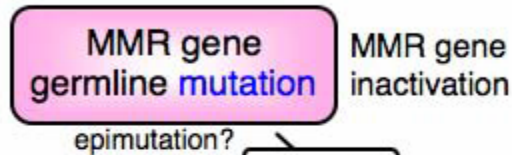


DNA mismatch repair model

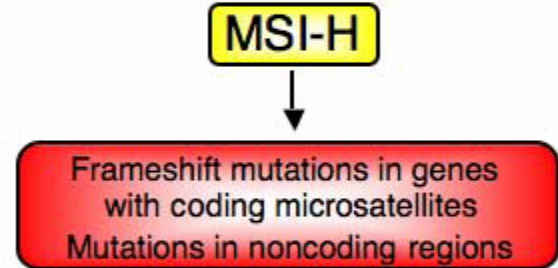
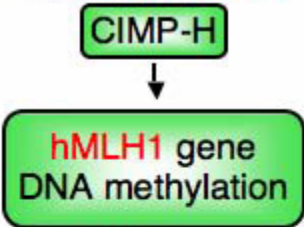
DNA mismatch repair (MMR) gene



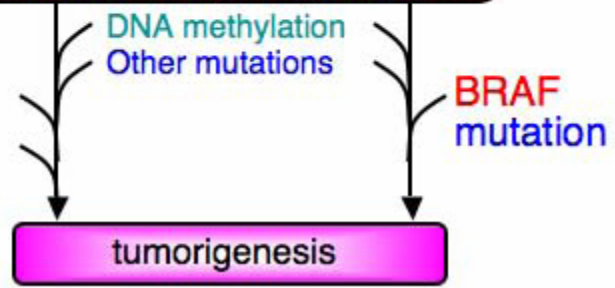
Lynch syndrome (HNPCC)



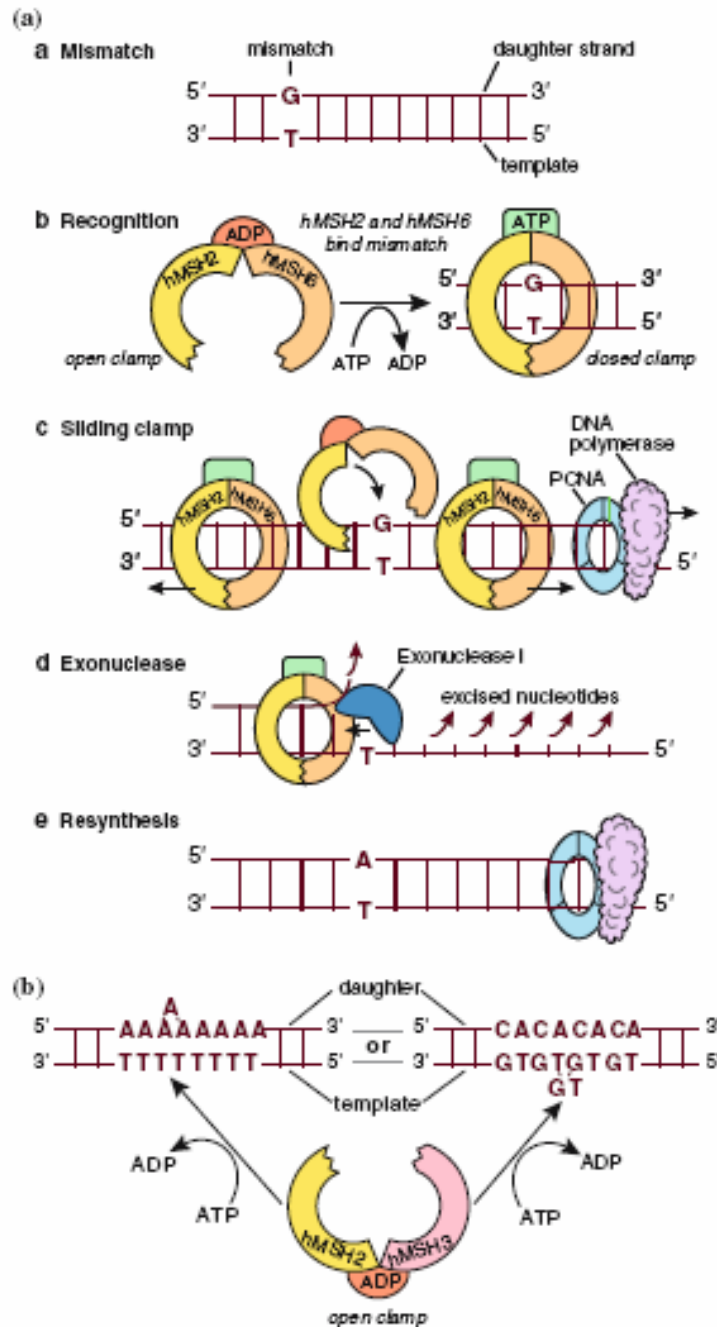
Sporadic CRC

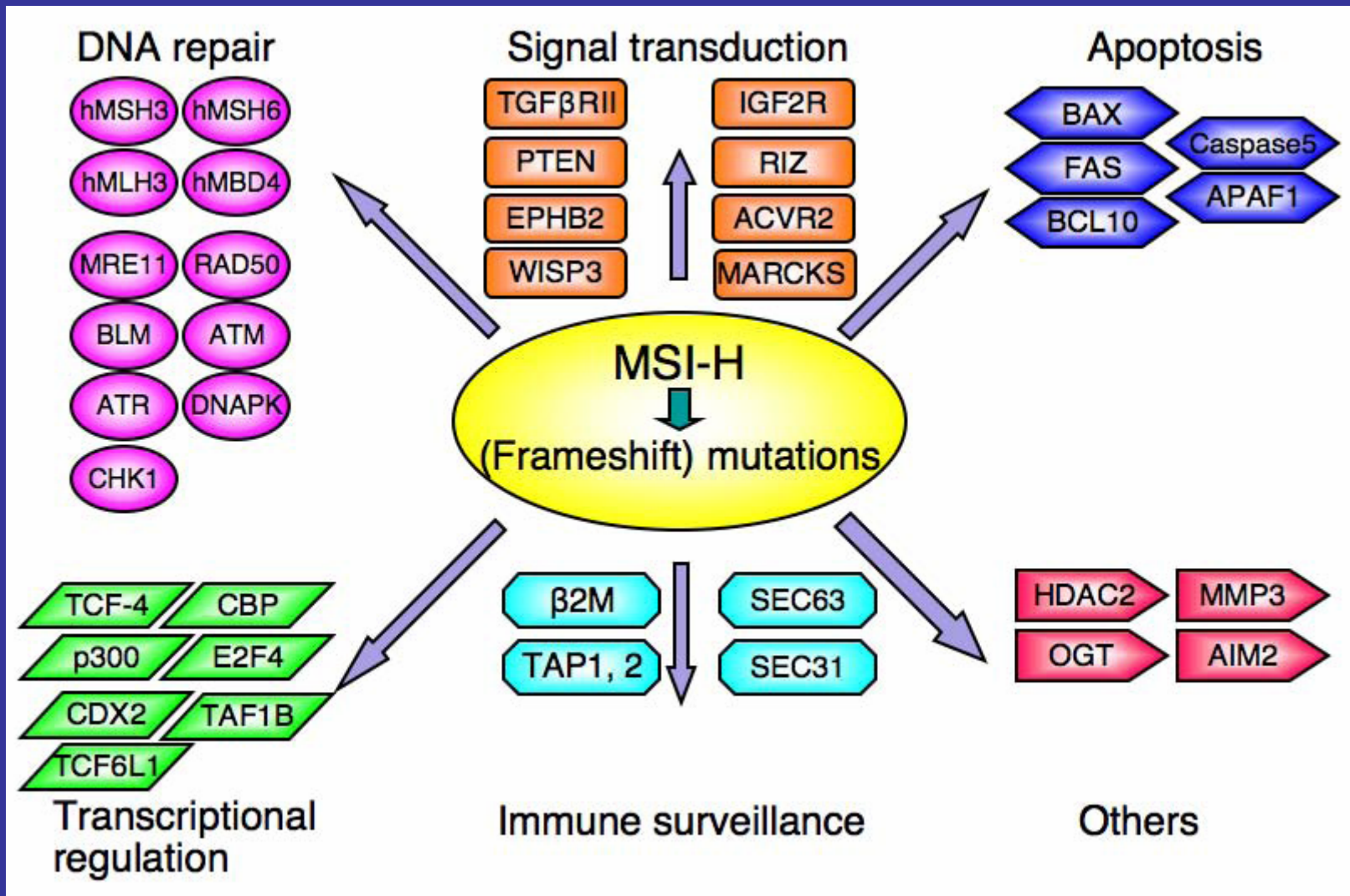


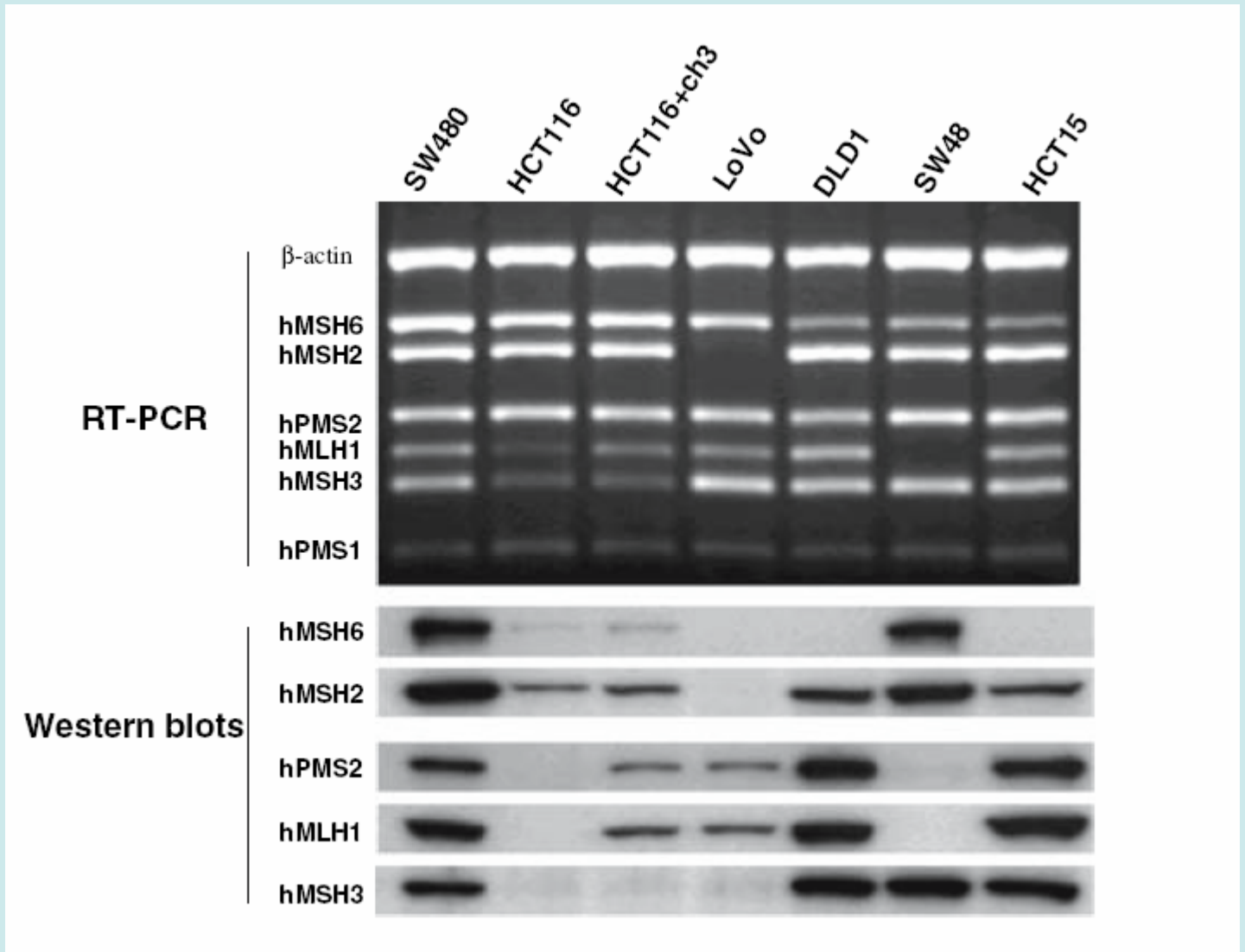
K-ras mutation
β-catenin mutation

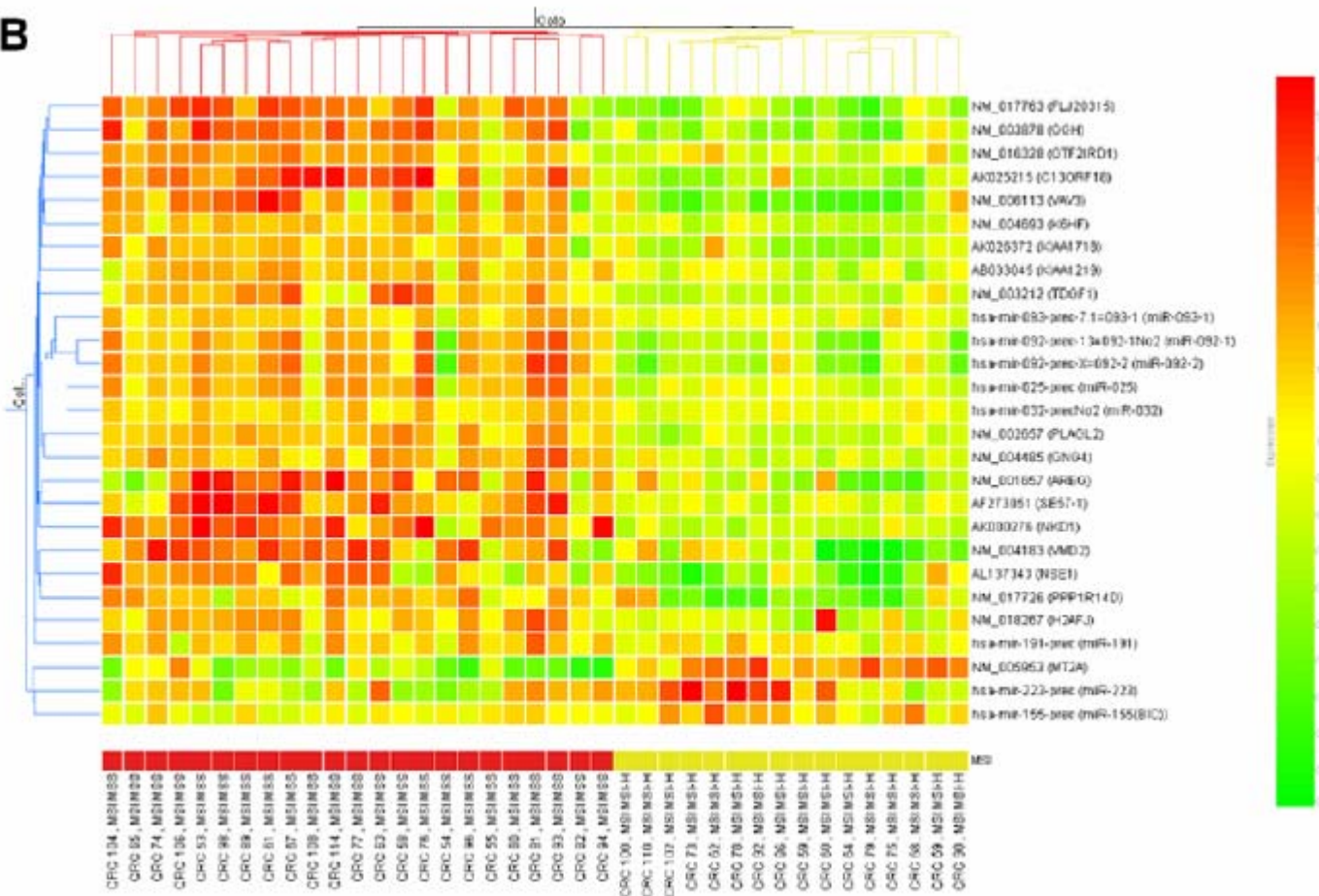


DNA MMR

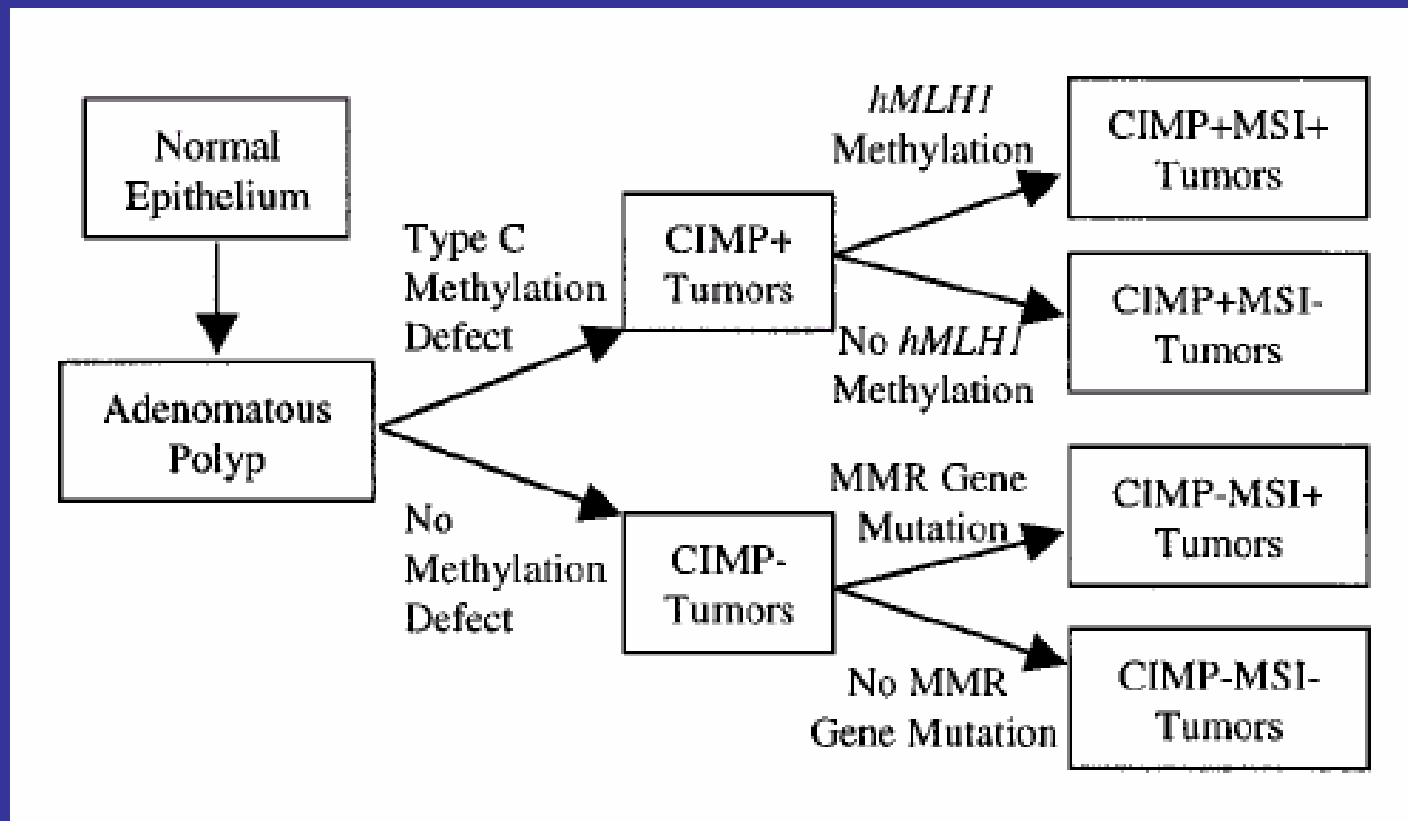




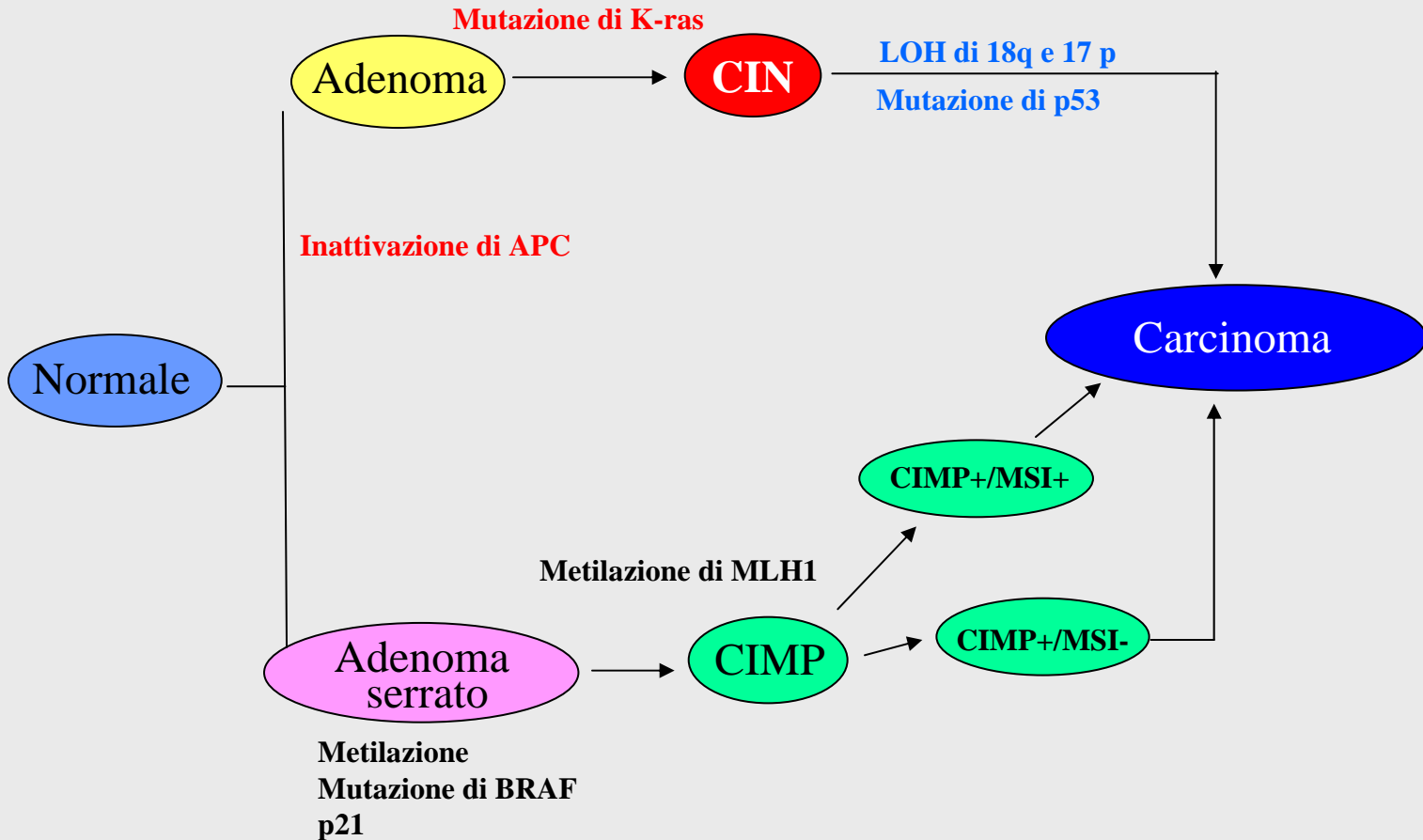


B

CpG island methylator phenotype (CIMP)

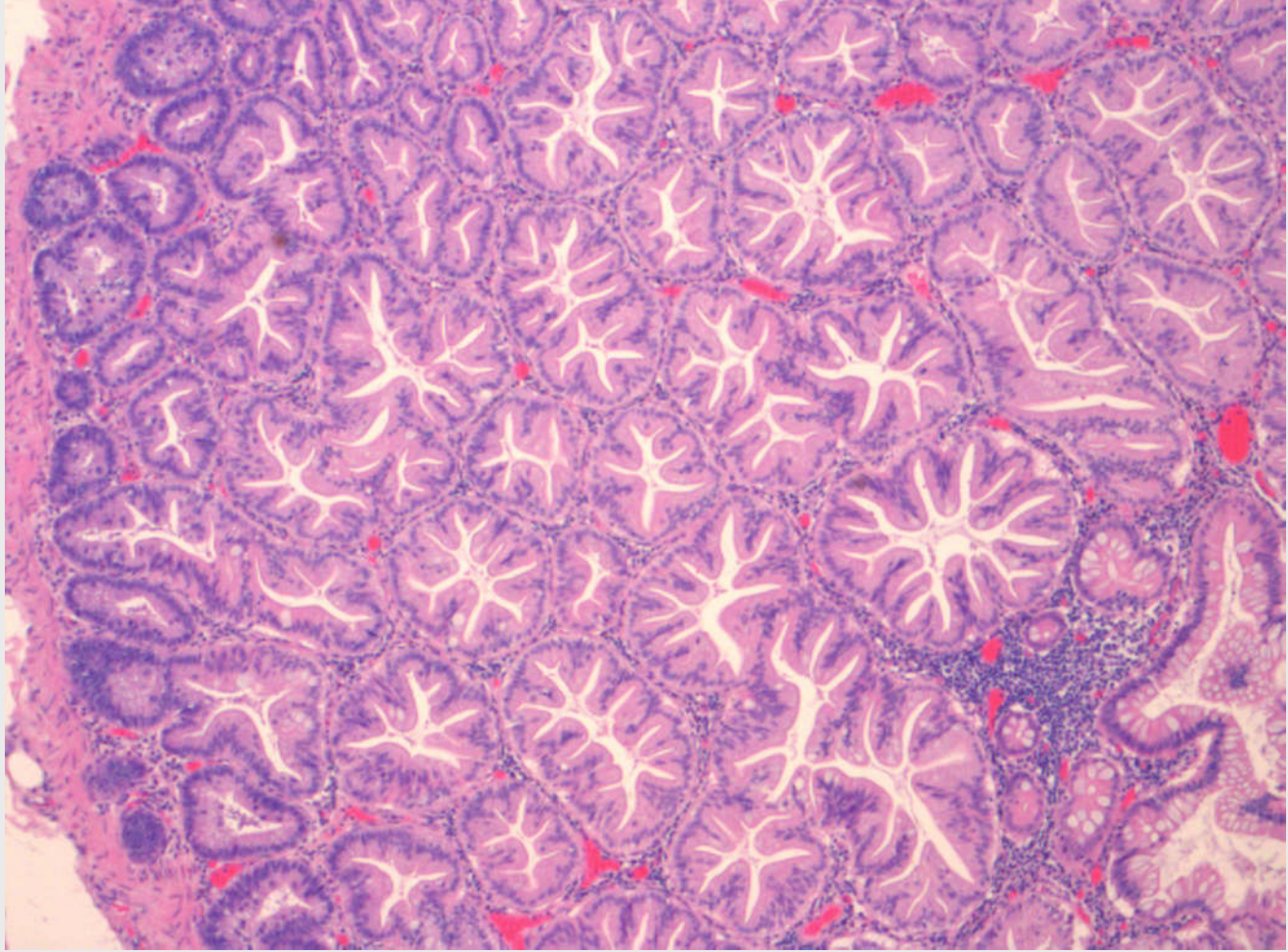


Sequenza adenoma-carcinoma

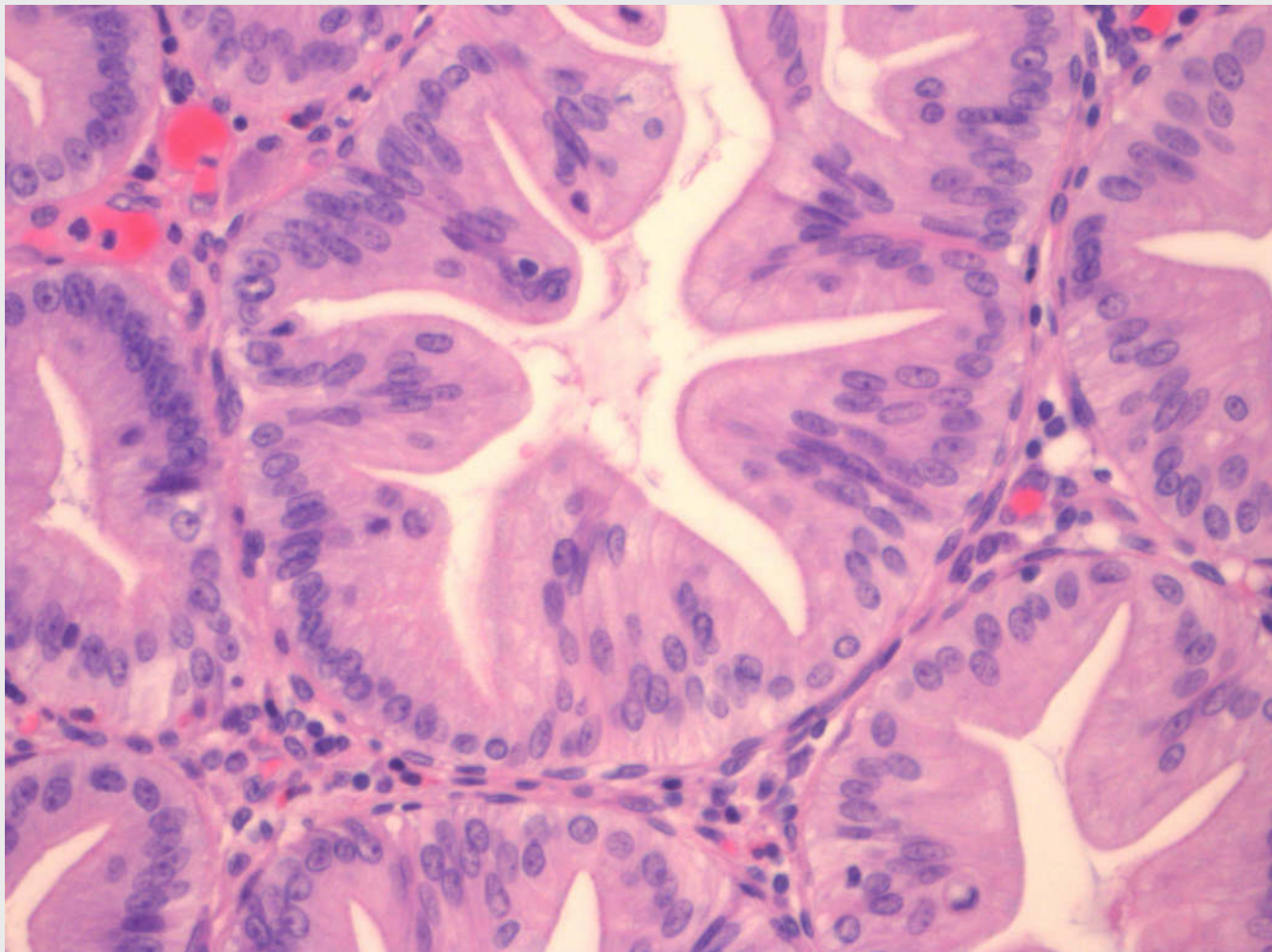


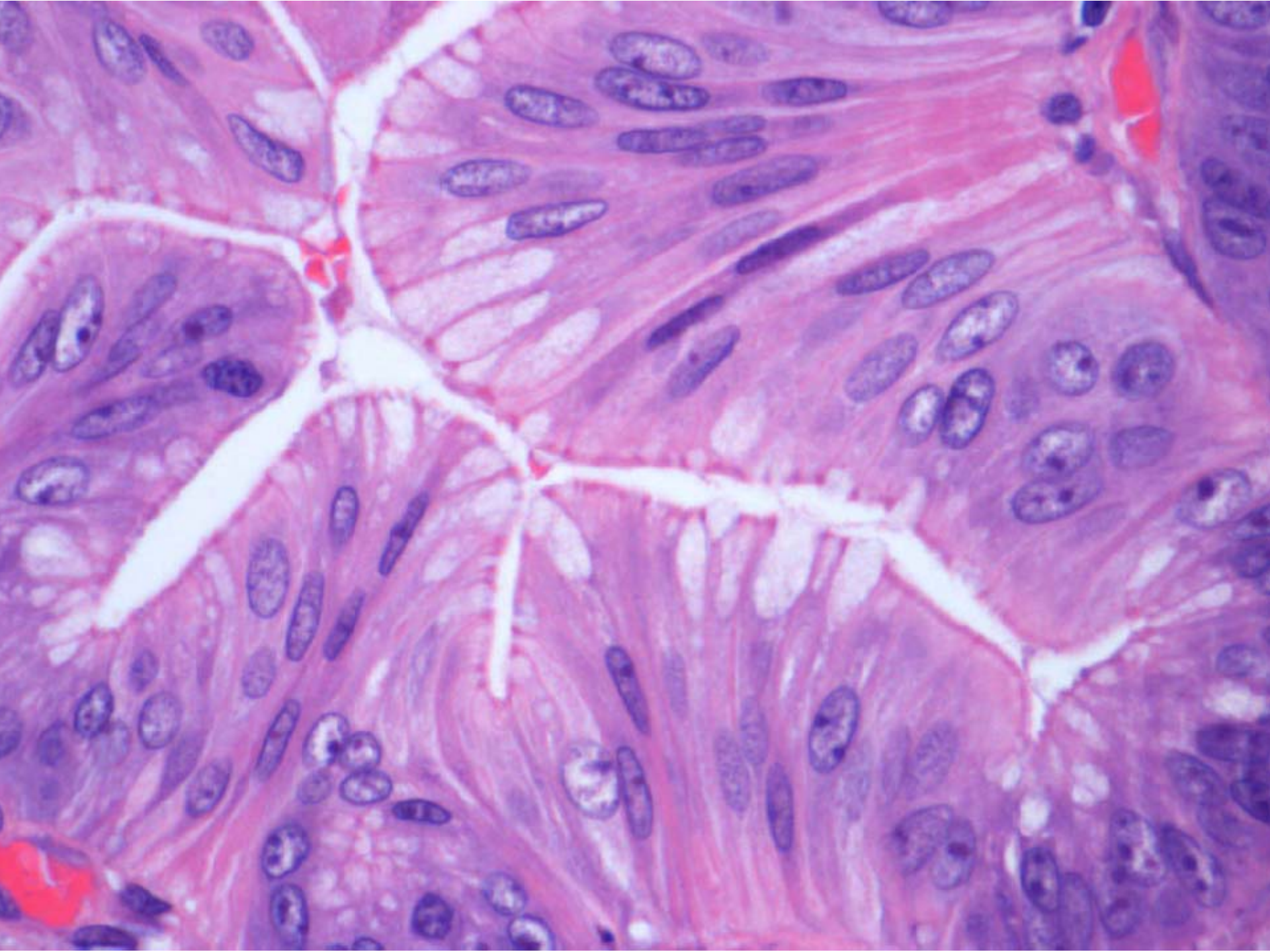
Serrated neoplasia pathway

HPP



Adenoma serrato tradizionale





Classificazione dei polipi serrati

	DISPLASIA ARCHITETTURALE	DISPLASIA CITOLOGICA
POLIPO IPERPLASTICO	ASSENTE	ASSENTE
ADENOMA SERRATO SESSILE	PRESENTE	ASSENTE
ADENOMA SERRATO TRADIZIONALE	PRESENTE	PRESENTE
POLIPO SERRATO MISTO	PRESENTE	PRESENTE

■ Table 1 ■

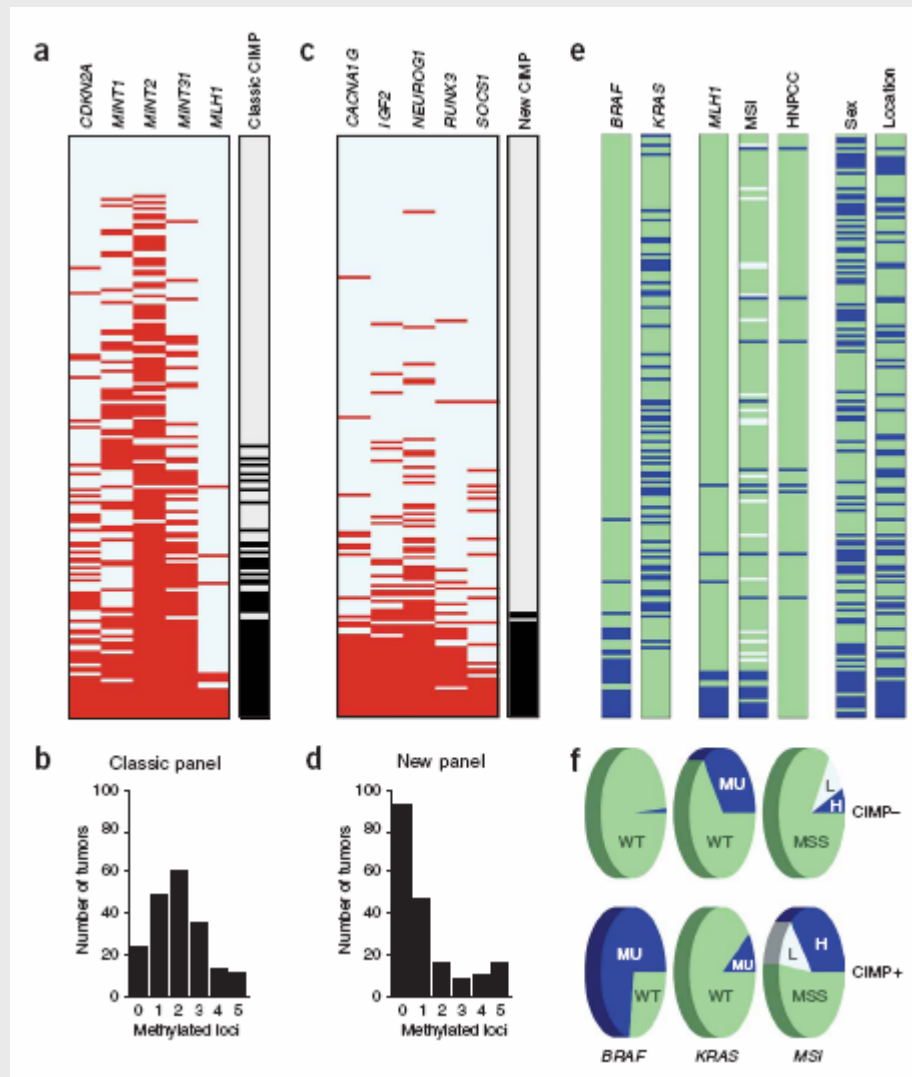
Terminology for Reporting Serrated Polyps of the Large Intestine

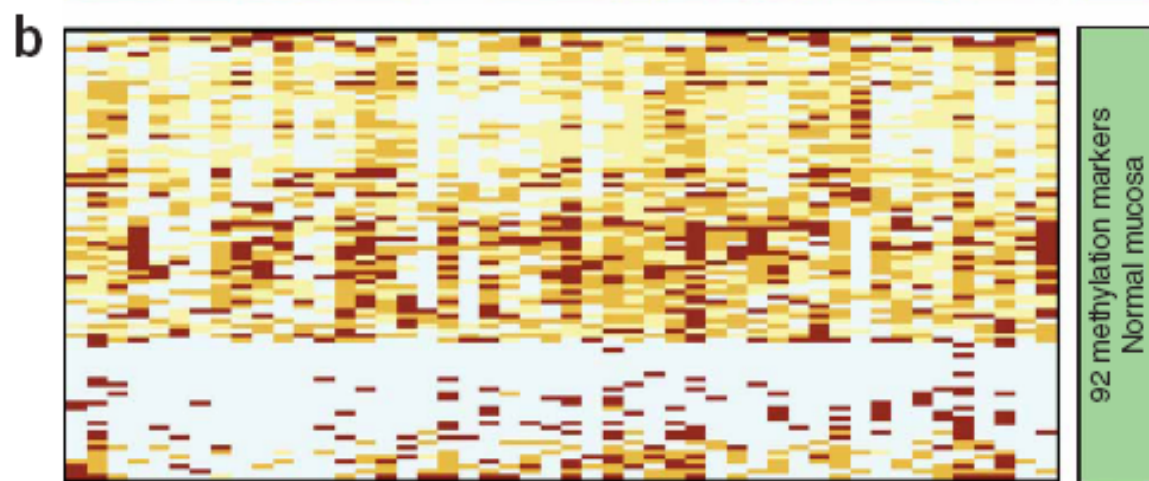
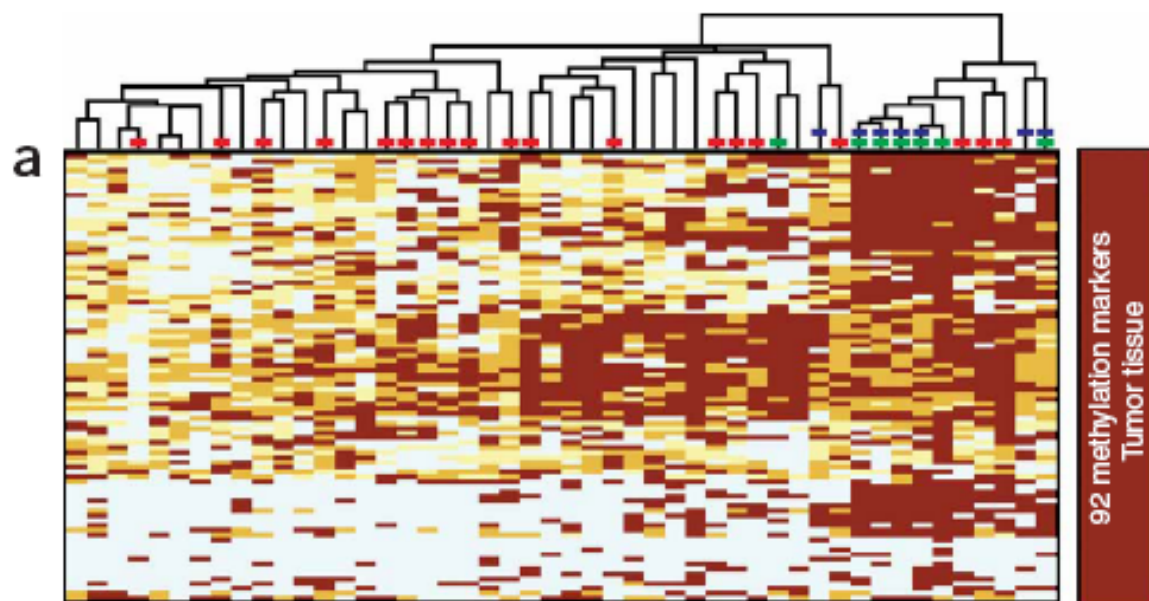
1. Hyperplastic polyp
 - Microvesicular type (optional)
 - Goblet cell-rich type (optional)
 - Mucin-poor type (optional)
 2. Sessile serrated adenoma
 3. Traditional serrated adenoma
 4. Mixed serrated polyp (list individual components in parentheses, eg, mixed sessile serrated adenoma-tubular adenoma)
 5. Sessile serrated polyp (with a comment that this is an equivocal diagnosis that includes both hyperplastic polyp and sessile serrated adenoma; one should try to favor 1 or the other in the comment, based on the location and size of the lesion, eg, large right-sided lesions “favor” SSA, small left-sided lesions favor HPP)
-

CpG island methylator phenotype underlies sporadic microsatellite instability and is tightly associated with *BRAF* mutation in colorectal cancer

Daniel J Weisenberger^{1,9}, Kimberly D Siegmund^{2,9}, Mihaela Campan¹, Joanne Young³, Tiffany I Long¹, Mark A Faasse¹, Gyeong Hoon Kang⁴, Martin Widschwendter⁵, Deborah Weener¹, Daniel Buchanan³, Hoey Koh⁶, Lisa Simms⁶, Melissa Barker³, Barbara Leggett⁶, Joan Levine², Myungjin Kim¹, Amy J French⁷, Stephen N Thibodeau⁷, Jeremy Jass⁸, Robert Haile² & Peter W Laird¹

***Nature Genetics* 2006; 38: 787-793**





48 colorectal cancer cases

Classificazione molecolare del CRC

in base a:

MSI-status

Metilazione di MLH1

Espressione MMRP

Fenotipo CIMP

ID database	MSI status	CACNA1G		IGF2	NEUROG1	RUNX3	SOCS1	hMLH1	CIMP	MMRP
		M	M							
# 3596	MSI-H	0	0	0	0	0	0	0	0	MLH1
# 3622	MSI-H	0	0	0	0	0	0	0	0	MSH2
# 3574	MSI-H	0	0	1	0	0	0	0	1	MSH2
# 3586	MSI-H	0	0	0	0	0	1	0	1	MLH1
# 3589	MSI-H	0	0	0	0	0	0	1	0	MLH1
# 3608	MSI-H	0	0	0	0	0	0	1	0	MLH1
# 3603	MSI-H	1	0	1	0	0	0	0	2	POS
# 3610	MSI-H	1	0	1	0	0	0	0	2	MSH2
# 3616	MSI-H	1	1	0	0	0	0	1	2	MLH1
# 3582	MSI-H	1	0	1	1	0	1	0	3	MLH1
# 3597	MSI-H	1	1	1	1	0	0	0	4	MLH1
# 3578	MSI-H	1	1	1	1	0	0	1	4	MLH1
# 3587	MSI-H	1	1	1	1	0	1	0	4	MLH1
# 3588	MSI-H	1	1	1	1	0	1	0	4	MLH1
# 3593	MSI-H	1	1	1	1	0	1	0	4	MLH1
# 3606	MSI-H	1	1	1	1	0	1	0	4	MLH1
# 3617	MSI-H	1	1	1	1	0	1	0	4	MLH1
# 3621	MSI-H	1	1	1	1	0	1	0	4	MLH1
# 3577	MSI-H	1	1	1	1	1	1	1	5	MLH1
# 3580	MSI-H	1	1	1	1	1	1	1	5	MLH1
# 3590	MSI-H	1	1	1	1	1	1	1	5	MLH1
# 3591	MSI-H	1	1	1	1	1	1	1	5	MLH1
# 3601	MSI-H	1	1	1	1	1	1	1	5	MLH1
# 3604	MSI-H	1	1	1	1	1	1	1	5	MLH1
# 3609	MSI-H	1	1	1	1	1	1	1	5	MLH1
# 3571	MSS	0	0	0	0	0	0	0	0	POS
# 3581	MSS	0	0	0	0	0	0	0	0	POS
# 3583	MSS	0	0	0	0	0	0	0	0	POS
# 3602	MSS	0	0	0	0	0	0	0	0	POS
# 3612	MSS	0	0	0	0	0	0	0	0	POS
# 3575	MSS	0	0	1	0	0	0	0	1	POS
# 3576	MSS	0	0	1	0	0	0	0	1	POS
# 3584	MSS	0	0	1	0	0	0	0	1	POS
# 3585	MSS	0	0	1	0	0	0	0	1	POS
# 3592	MSS	0	0	1	0	0	0	0	1	POS
# 3595	MSS	0	0	1	0	0	0	0	1	POS
# 3600	MSS	0	0	1	0	0	0	0	1	POS
# 3611	MSS	0	0	1	0	0	0	0	1	POS
# 3614	MSS	0	0	1	0	0	0	0	1	POS
# 3615	MSS	1	0	0	0	0	0	0	1	POS
# 3618	MSS	0	0	1	0	0	0	0	1	POS
# 3579	MSS	1	0	1	0	0	0	0	2	POS
# 3594	MSS	0	0	1	0	1	0	0	2	POS
# 3599	MSS	0	0	1	0	1	0	0	2	POS
# 3607	MSS	1	0	1	0	0	0	0	2	POS
# 3572	MSS	1	1	1	1	0	0	0	4	POS
# 3573	MSS	1	1	1	1	0	0	0	4	POS
# 3598	MSS	1	1	1	1	0	0	0	4	POS
# 3613	MSS	1	1	1	1	0	0	0	4	POS
# 3605	MSS	1	1	1	1	1	0	0	5	POS

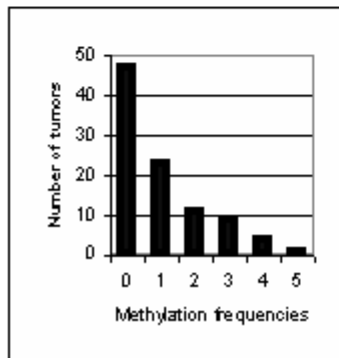
MSI-H/CIMP-

MSI-H/CIMP+

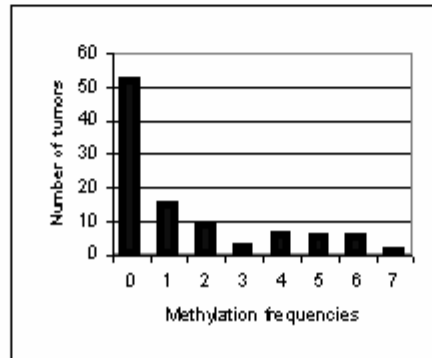
MSS/CIMP-

MSS/CIMP+

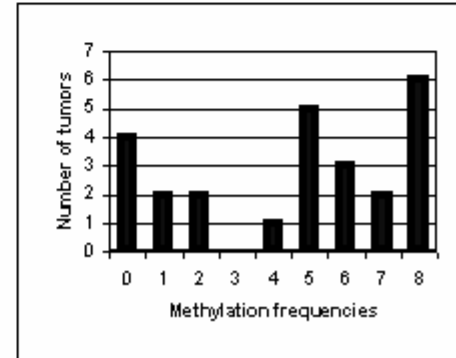
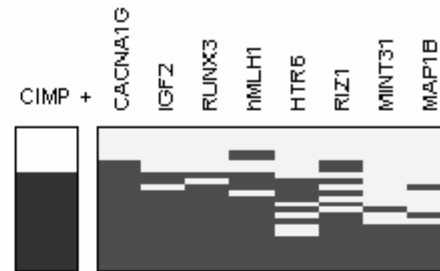
MSS CRCs



MSS CRCs

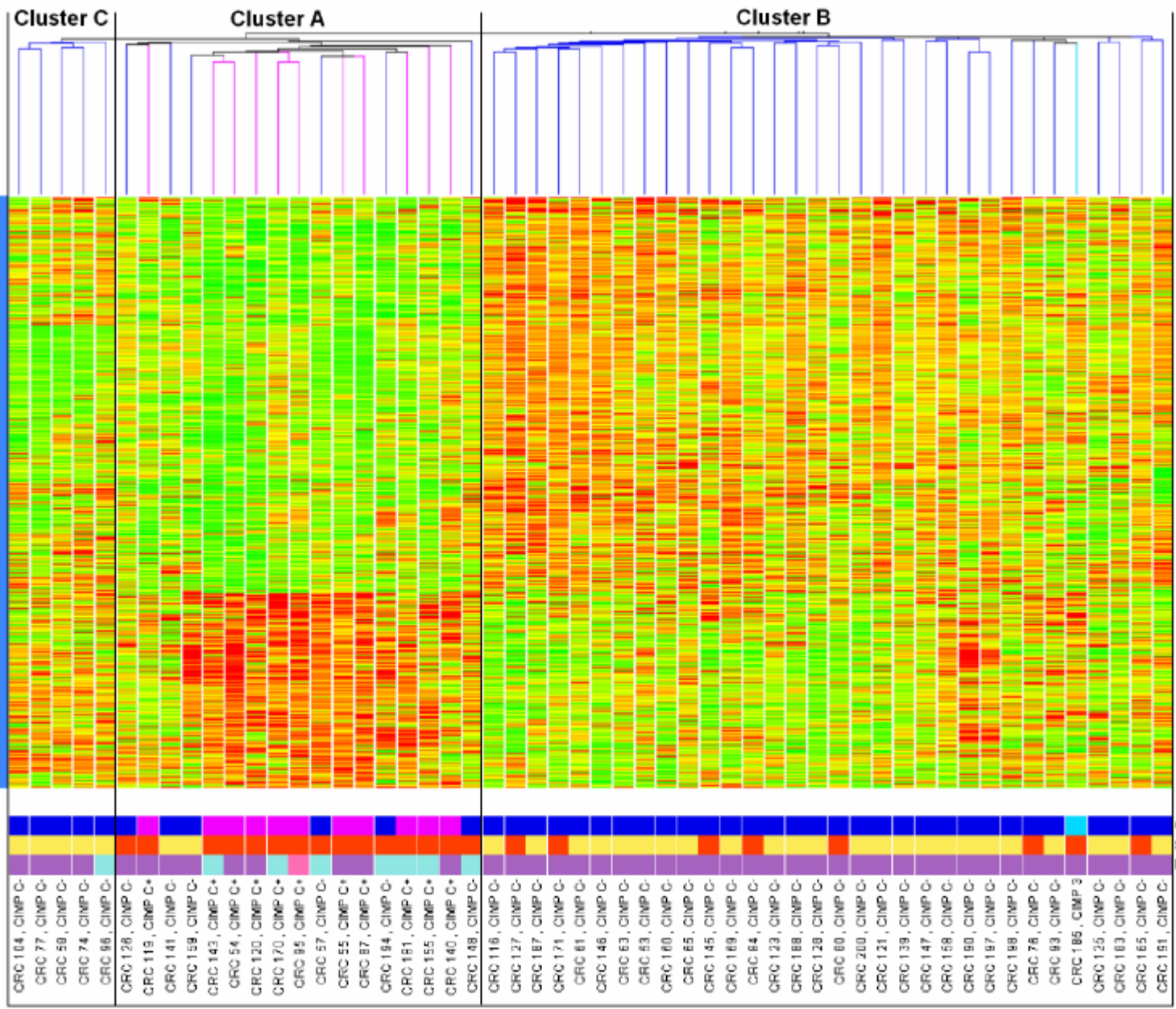


MSI CRCs



Status CIMP e caratteristiche clinico-patologiche e molecolari (CCR MSS)

Sesso	NS
Età	NS
Sede	0,003
Stadio	NS
Istotipo	0,008
Grado	0,07
LOH 18q	0,01
LOH 8p	NS
LOH 17p	0,007
Mutazione BRAF	0,0002
Mutazione KRAS	NS



LEGEND CIMP

- CIMP+
- CIMP-
- Uncertain

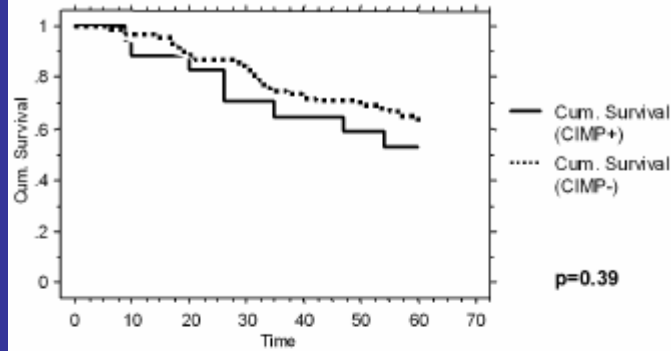
SITE

- Proximal
- Distal

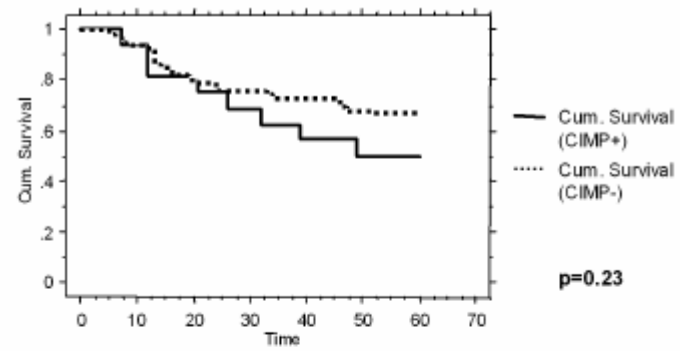
HISTOTYPE

- AD
- AD-MUC
- MUC

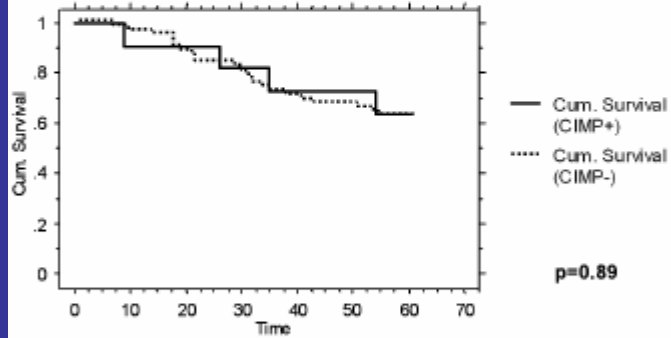
Disease-specific survival
CIMP groups (all patients)



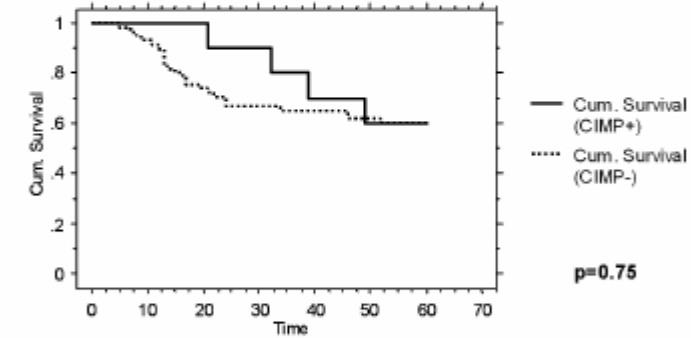
Relapse-free survival
CIMP groups (all patients)



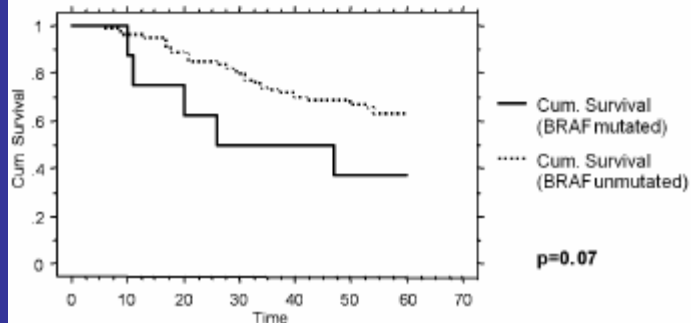
Disease-specific survival
CIMP groups (Mutant BRAF
excluded)



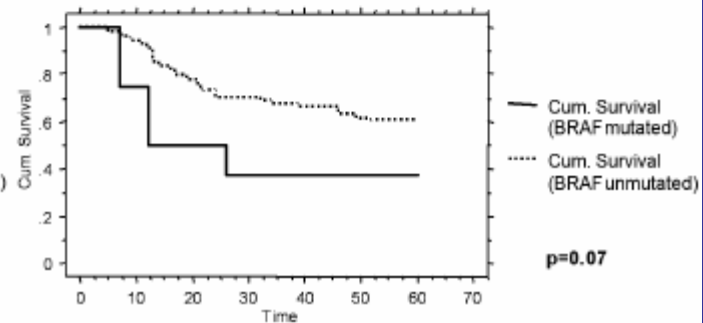
Relapse-free survival
CIMP groups (Mutant BRAF
excluded)



Disease-specific survival
BRAF mutation groups



Relapse-free survival
BRAF mutation groups



Molecular correlates with *MGMT* promoter methylation and silencing support CpG island methylator phenotype-low (CIMP-low) in colorectal cancer

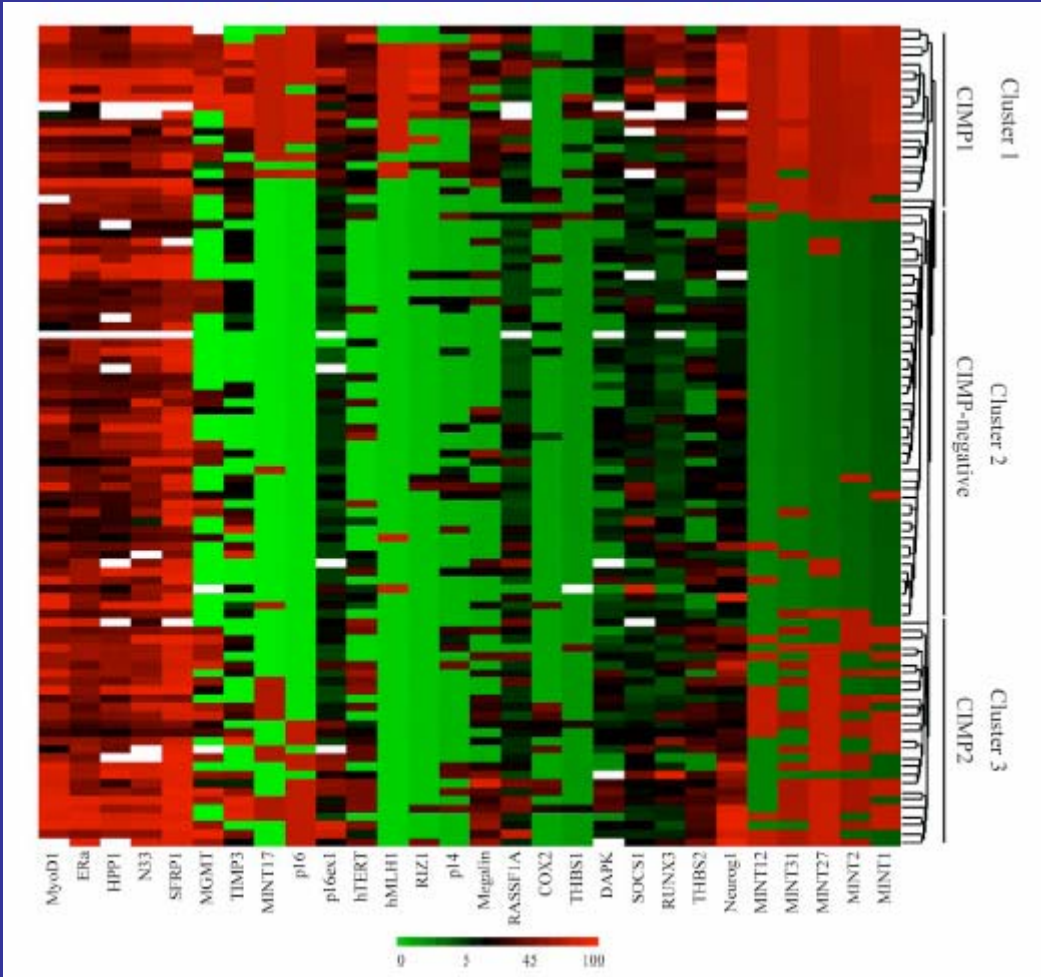
Shuji Ogino, Takako Kawasaki, Gregory J Kirkner, Yuko Suemoto, Jeffrey A Meyerhardt, Charles S Fuchs

Gut 2007;56:1564–1571. doi: 10.1136/gut.2007.119750

Integrated genetic and epigenetic analysis identifies three different subclasses of colon cancer

Lanlan Shen*, Minoru Toyota[†], Yutaka Kondo[‡], E Lin[§], Li Zhang[§], Yi Guo*, Natalie Supunpong Hernandez*, Xinli Chen*, Saira Ahmed*, Kazuo Konishi*, Stanley R. Hamilton[¶], and Jean-Pierre J. Issa*^{||}

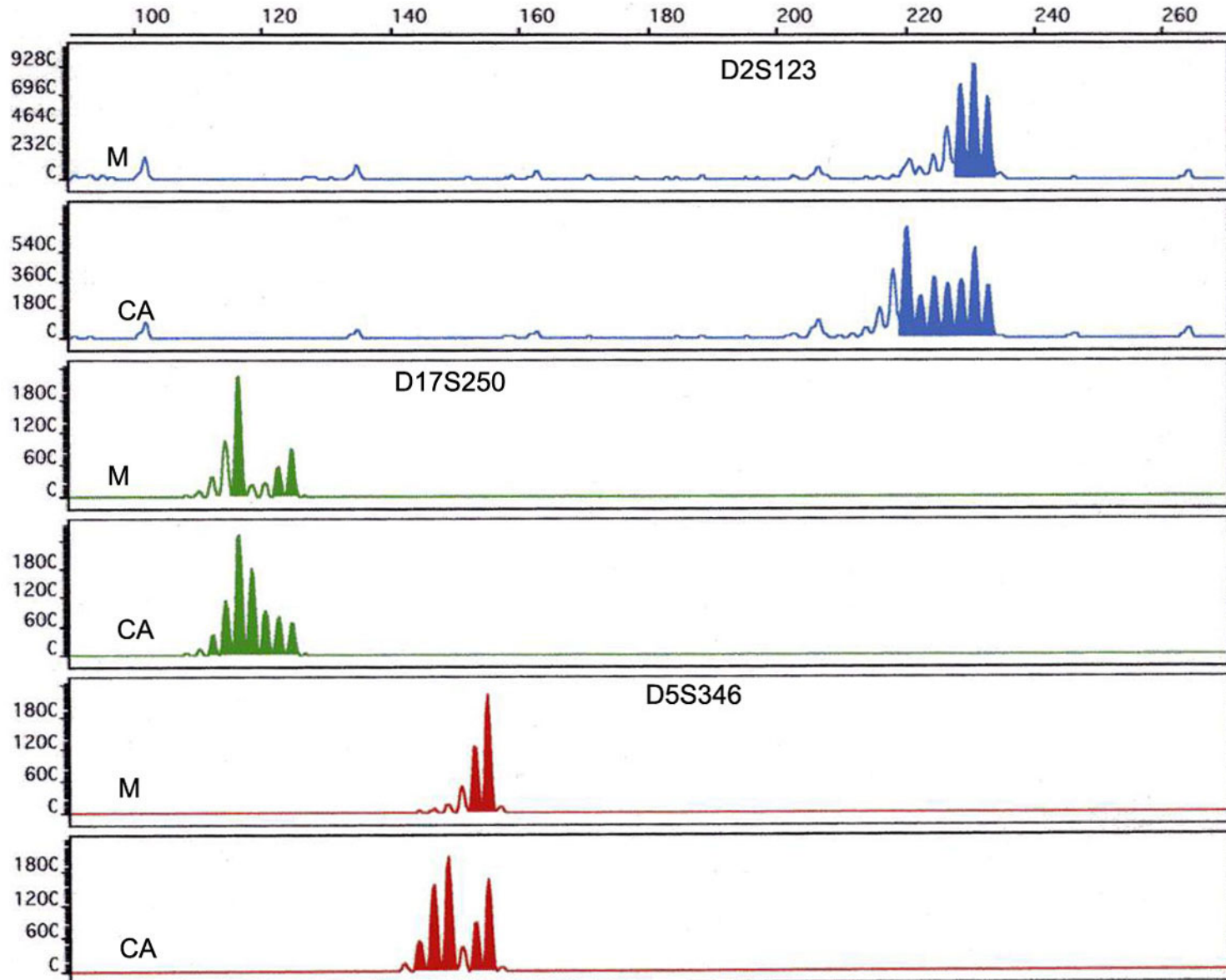
*Departments of Leukemia, [§]Biostatistics and Applied Biomathematics, and [¶]Pathology, University of Texas M. D. Anderson Cancer Center, Houston, TX 77030; [†]Sapporo Medical University, S1W17, Chuo-ku, Sapporo 060-8556, Japan; and [‡]Aichi Cancer Center, Division of Molecular Oncology, 1-1 Kanakonden, Chikusa-Ku, Nagoya, Japan



Sottotipi molecolari di CCR

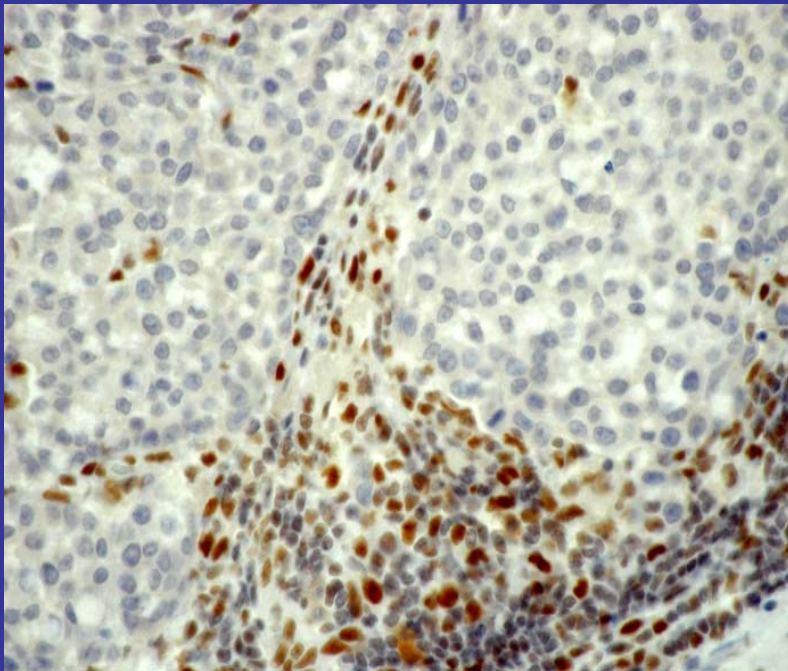
- **Gruppo 1:** CIMP-high, metilazione di MLH1, MSI-H, BRAF+, CIN-, origine da polipi serrati (MSI-H sporadici, 12%)
- **Gruppo 2:** CIMP-high, BRAF+, CIN-, MSS/MSI-L, origine da polipi serrati (8%)
- **Gruppo 3:** CIMP-low, KRAS+, metilazione di MGMT, CIN+, MSS/MSI-L, origine da adenomi o polipi serrati (20%)
- **Gruppo 4:** CIMP-, CIN+, MSS, origine da adenomi (57%)
- **Gruppo 5:** MSI-H, CIMP-, BRAF-, CIN-, origine da adenomi (sindrome di Lynch, 3%)

Instabilità dei microsatelliti (MSI)

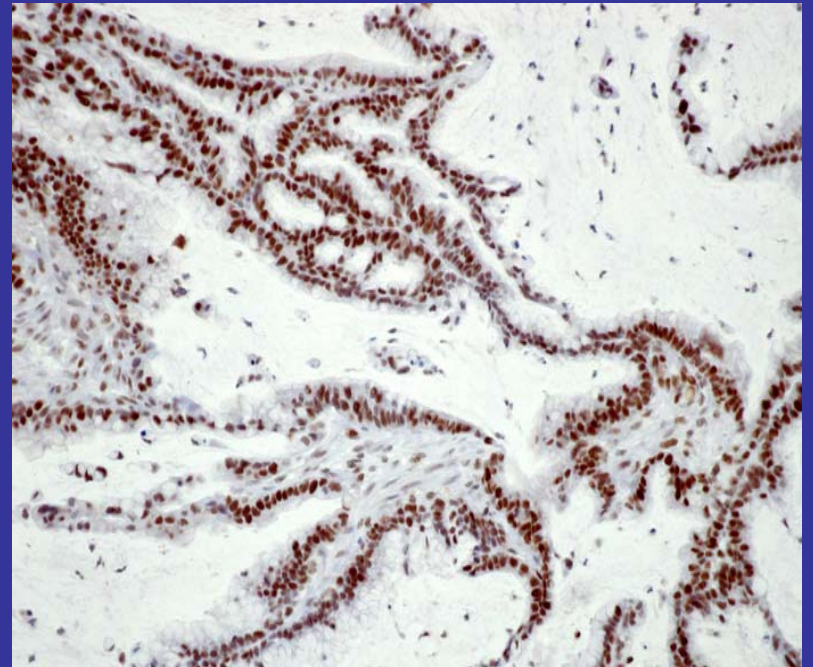


Espressione immunoistochimica della proteina MSH2

Negativa



Positiva



Microsatellite genotyping versus immunohistochemistry for the detection of MSI-H colorectal tumors

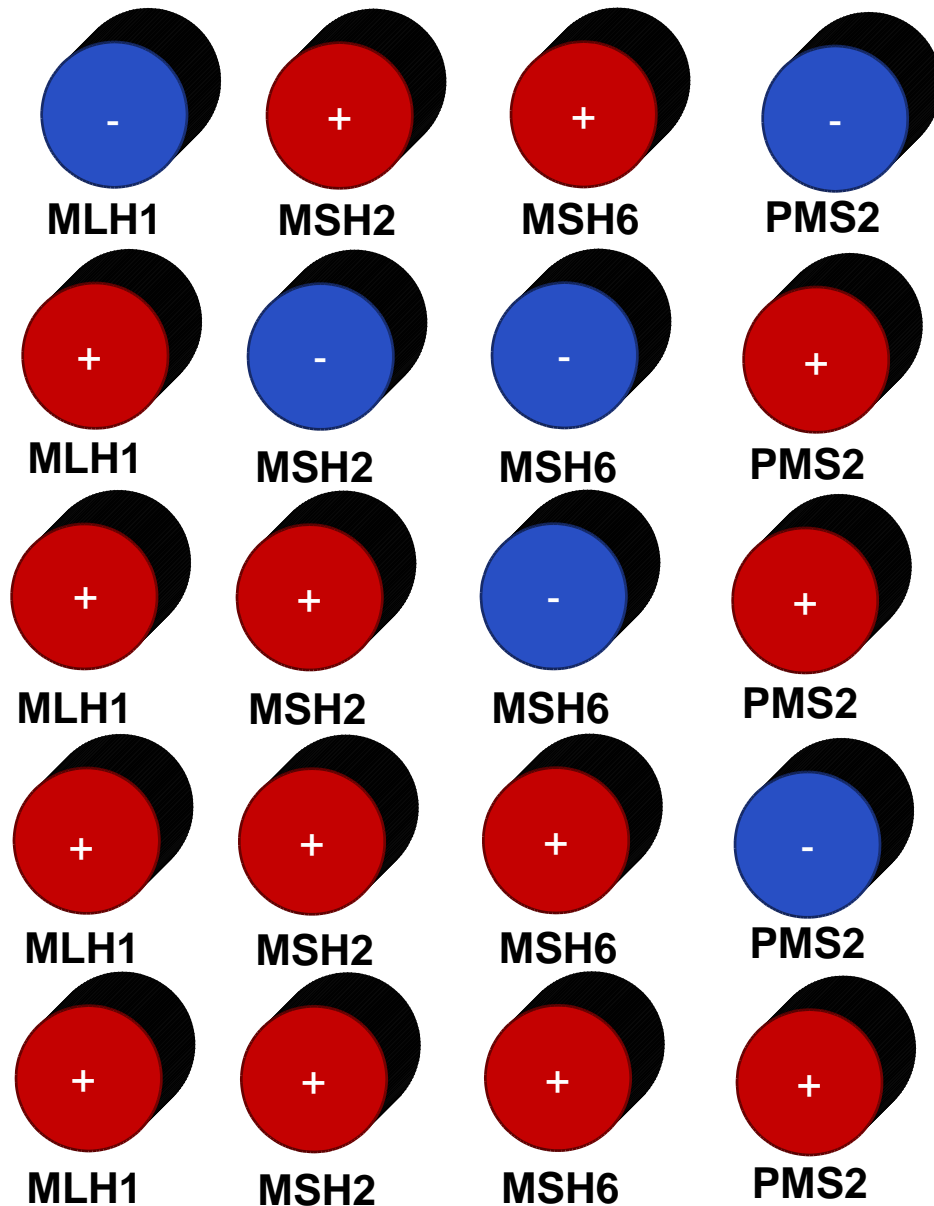
Pattern of immunoreactivity (%)

MSI status	n	MLH1-negative	MSH2-negative	MLH1/MSH2-positive
MSI-H	132	106 (80.3)	14 (10.6)	12 (9.1)
MSI-L	23			23 (100)
MSS	150			150 (100)

Lanza et al. Mod Pathol 2002;15:741-749.

Pattern immunoistochimico

Alterazione molecolare



Metilazione promotore MLH1
Mutazione MLH1

Mutazione MSH2

Mutazione MSH6

Mutazione PMS2

Mutazione MLH1
Mutazione altri geni ?

Screening patologico CCR

Incidenza tumori con deficit del MMR

MMR status	n	%
Normale	279	84,5
Deficit	51	15,5
Totale	330	100

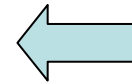
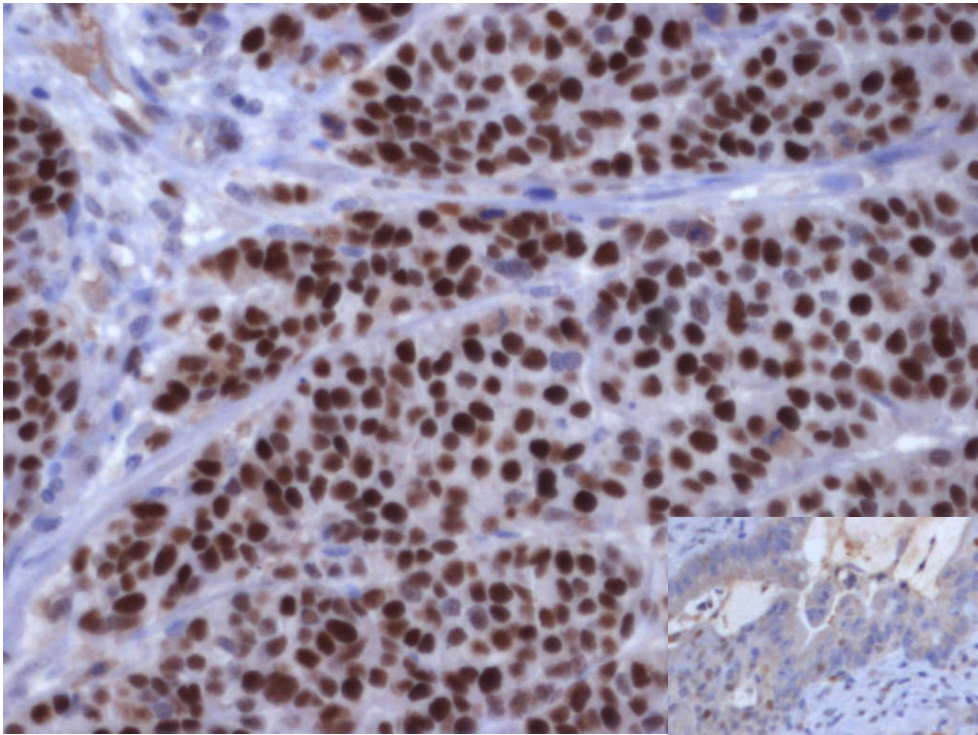
Status MSI vs. espressione proteine

	MMRP-	MMRP+
MSI-H	49	1
MSI-L	1	15
MSS	0	264

Pattern di espressione immunohistochimica nei tumori con deficit del MMR

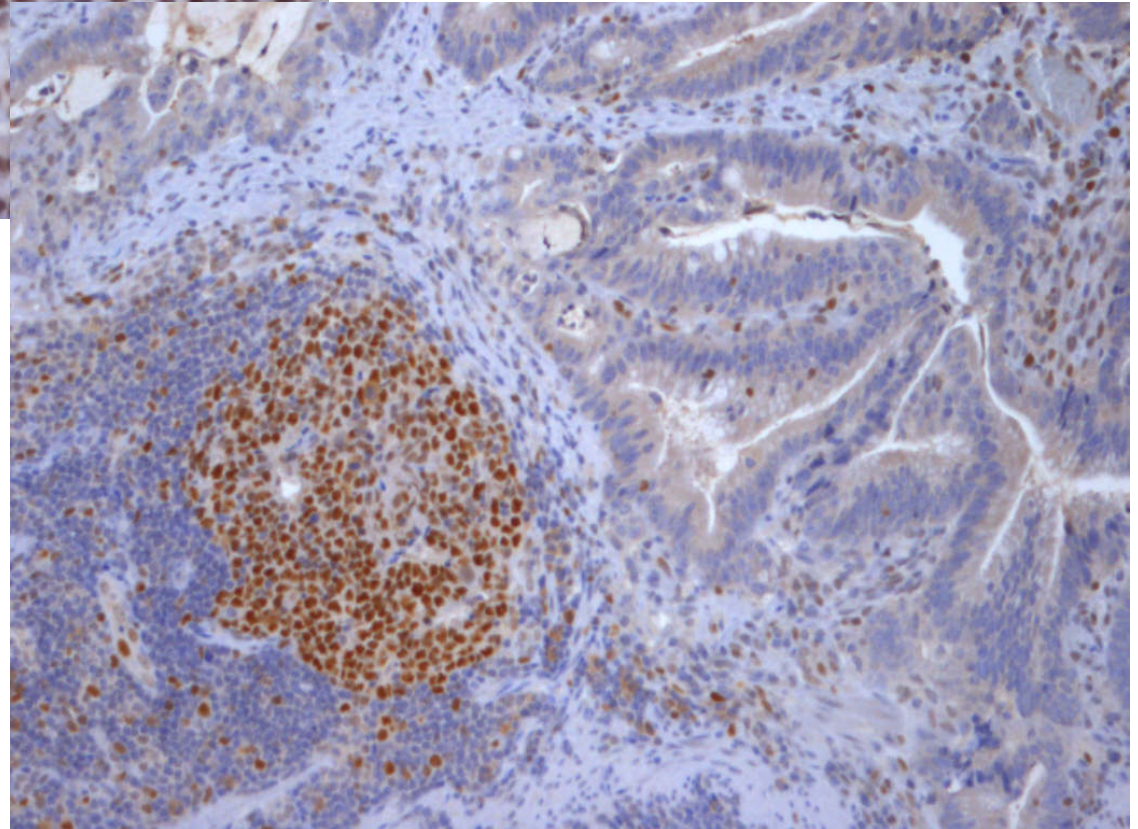
Pattern IIC	n° casi
MLH1-negativo	39
MSH2-negativo	3
MSH6-negativo	7
PMS2-negativo	1
Espressione normale	1
Totale	51





*Normale espressione
di MSH6*

*Perdita completa
di espressione
di MSH6*



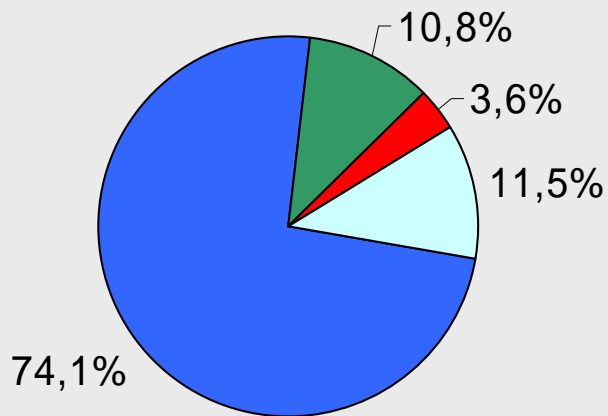
Carcinoma colo-rettale

CCR con deficit del MMR non-MLH1 negativi

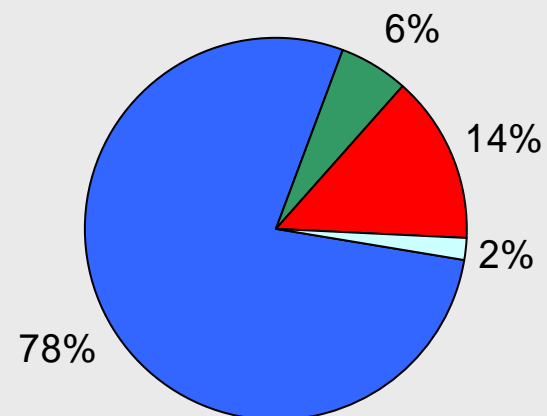
n	Età	Sesso	Sede	Stadio	Istotipo	Grado	Inst. Panel	Inst. Din.	Note
MSH2-negativo									
1	63	F	R	1	AD	BG	4 su 4	SI	
2	65	M	SIG	3	MUC	BG	2 su 5	SI	
3	40	F	SIG	3	IND	AG	2 su 5	NO	Madre ca colon a 25aa
MSH6-negativo									
1	54	M	TR	2	AD	AG	5 su 5	SI	
2	69	F	DX	2	AD/MUC	BG	4 su 5	SI	
3	59	M	R	4	AD/MUC	BG	4 su 5	SI	Ca. colon nel 1992
4	72	M	TR	2	MUC	AG	3 su 5	SI	Carcinoide ileo sincrono
5	73	M	R	2	AD	BG	4 su 5	SI	
6	71	F	DX	2	AD	BG	4 su 5	SI	
7	49	M	R	2	MUC	BG	1 su 5	SI	MSI-L
PMS2-negativo									
1	38	M	TR	2	AD/MUC	BG	4 su 5	SI	
Normale									
1	60	F	TR	3	MUC	BG	3 su 5	SI	

Truninger et al. (2005)
Alterata espressione MMR:
139/1048 (13,2%)

Casistica Ferrara 2004
Alterata espressione MMR:
50/330 (15,1%)



■ MLH1 - ■ MSH2 - ■ MSH6 - ■ PMS2 -

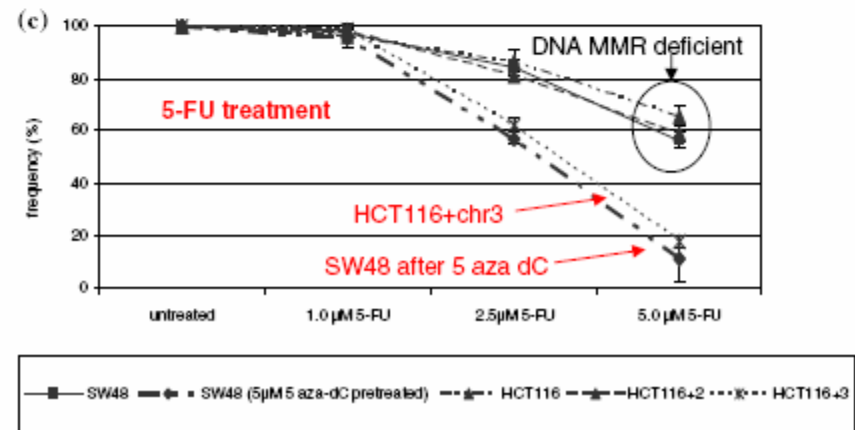
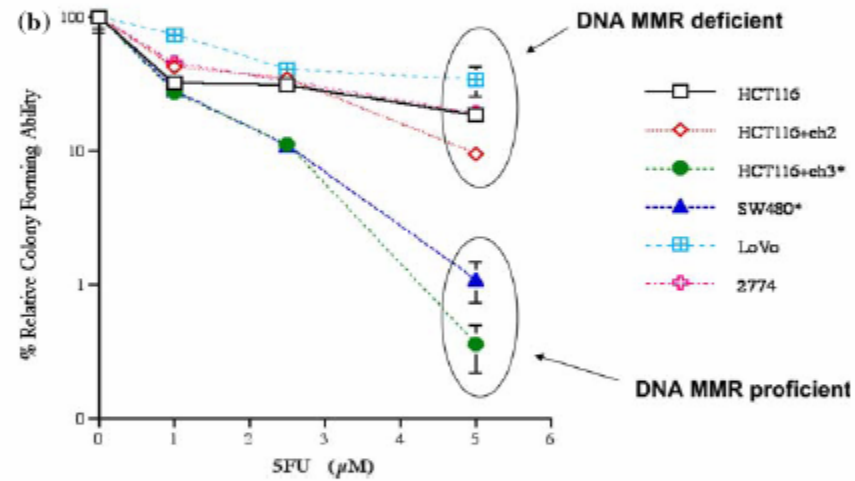
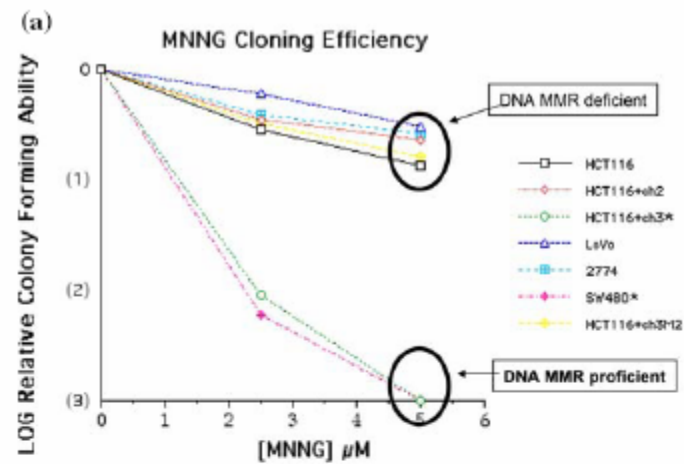


■ MLH1 - ■ MSH2 - ■ MSH6 - ■ PMS2 -

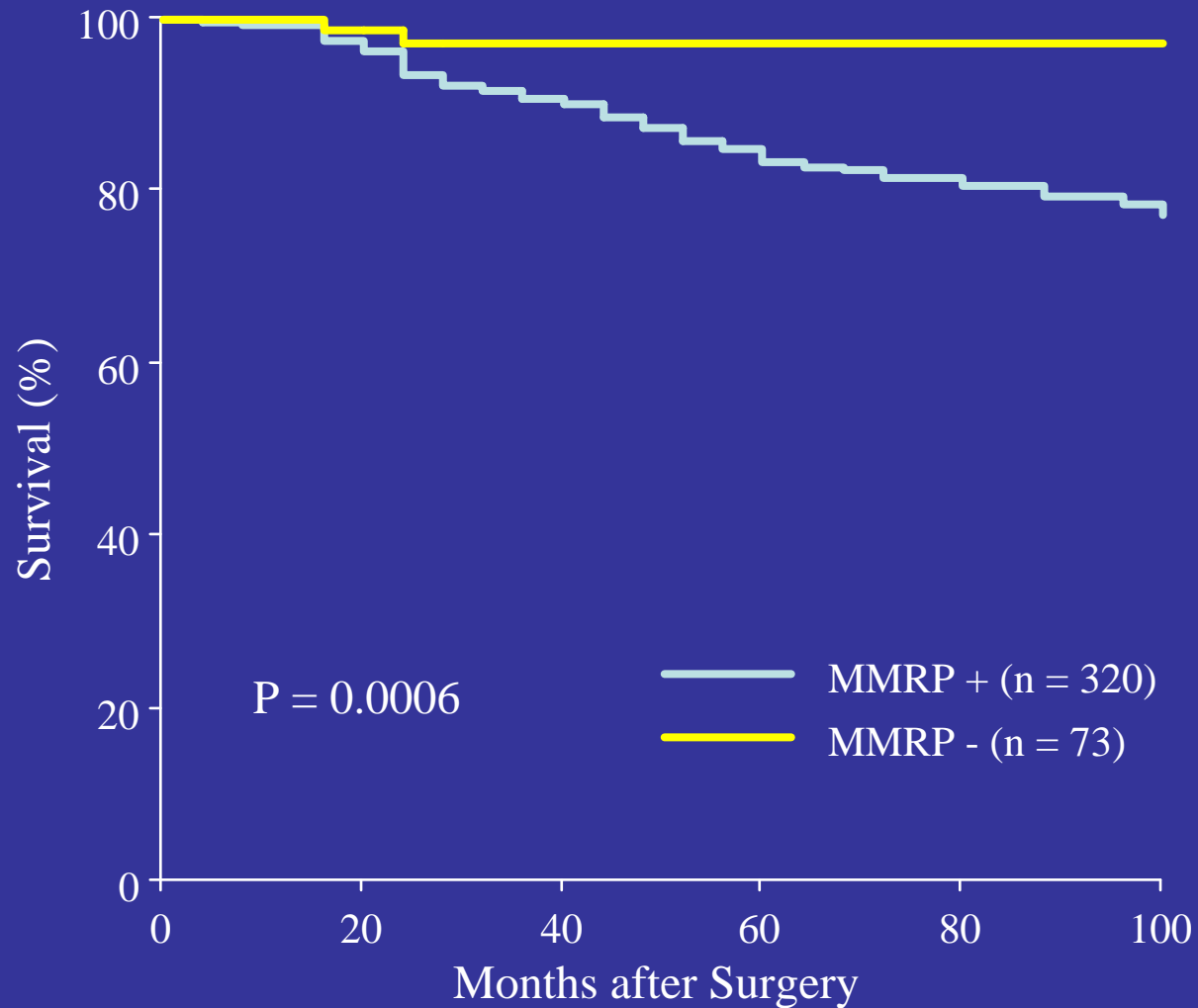
Pattern di alterata espressione delle proteine del MMR

Screening – sospette forme ereditarie (sindrome di Lynch)

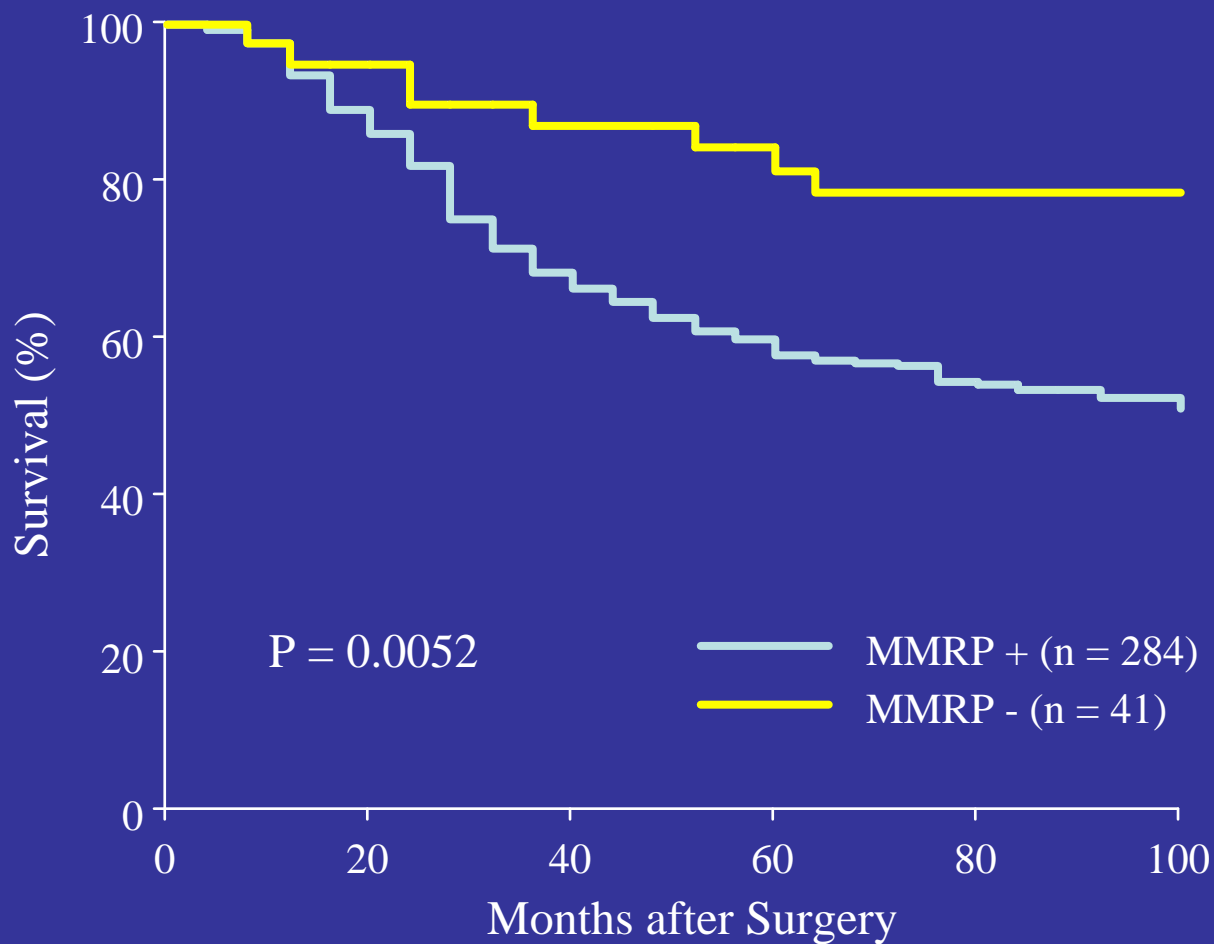
Sesso	Età	Sede	Stadio	Tipo	IIC	MSI
M	52	Dx	1	AD	MLH1-	MSI-H
F	63	Dis	2	Muc <50%	MSH2-	MSI-H
M	59	Dx	2	Muc <50%	MSH6-	MSI-H
F	67	Dx	2	Muc <50%	MSH6-	MSI-H



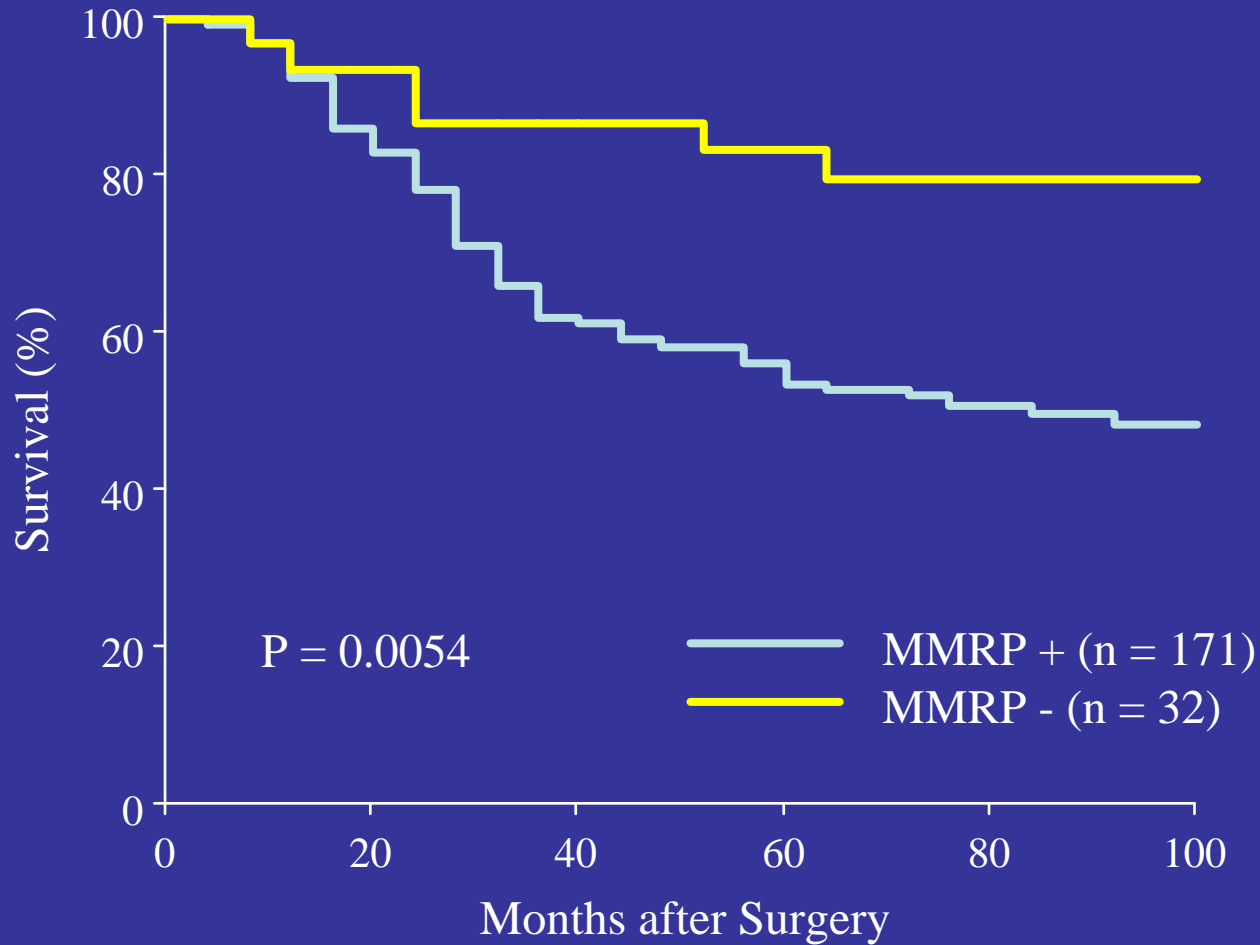
Stage II patients



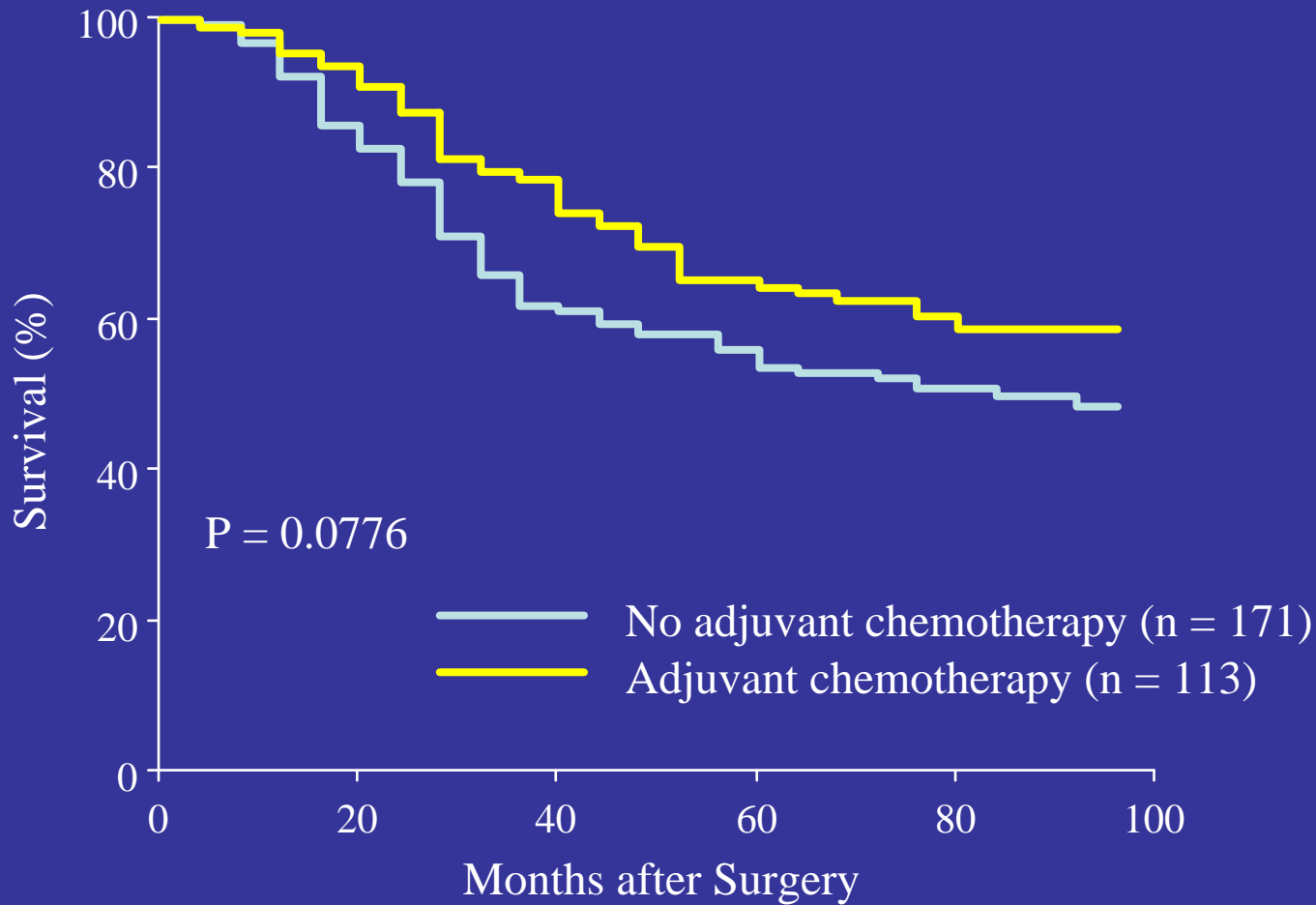
Stage III patients



Stage III patients - No adjuvant chemotherapy

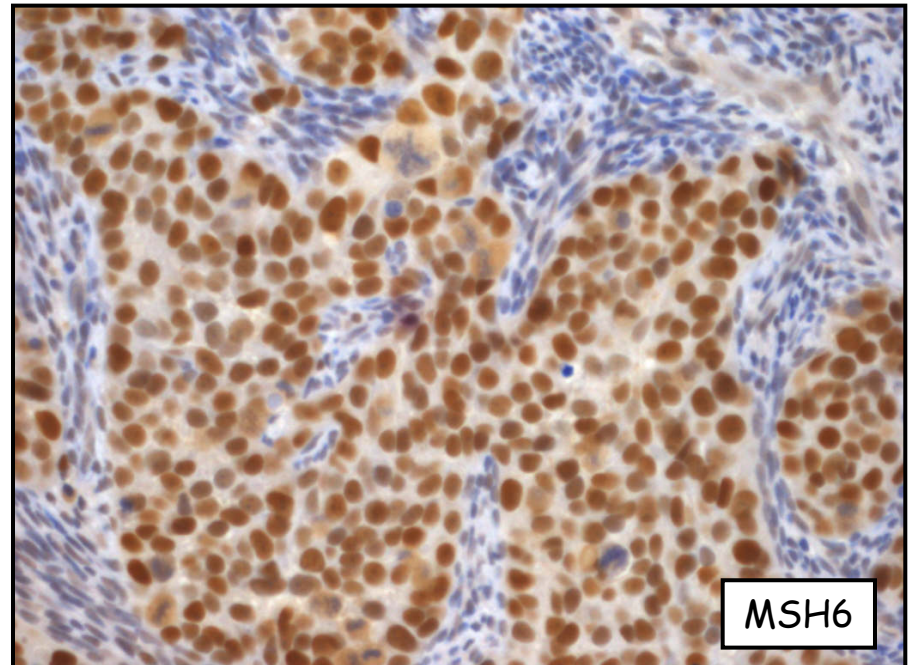
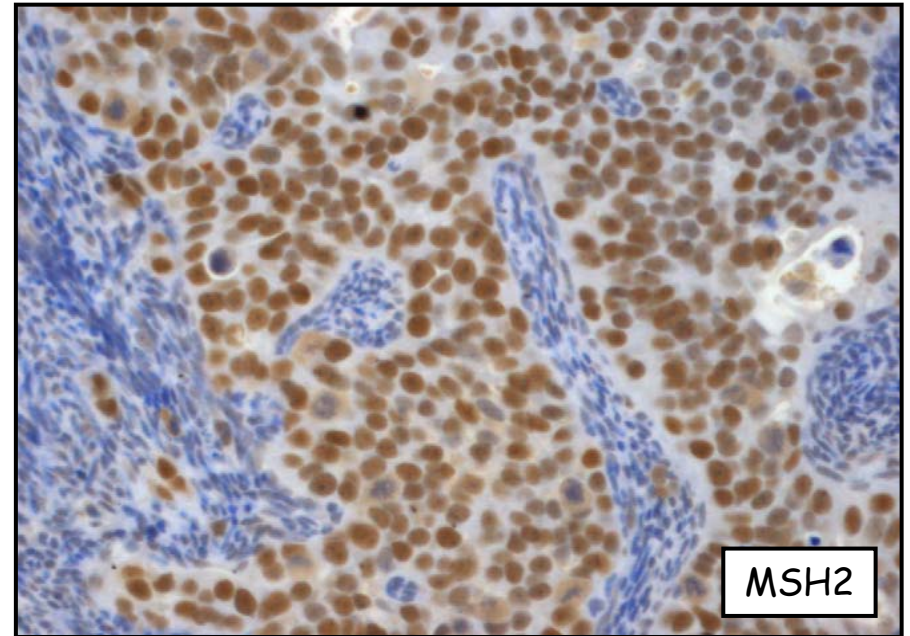
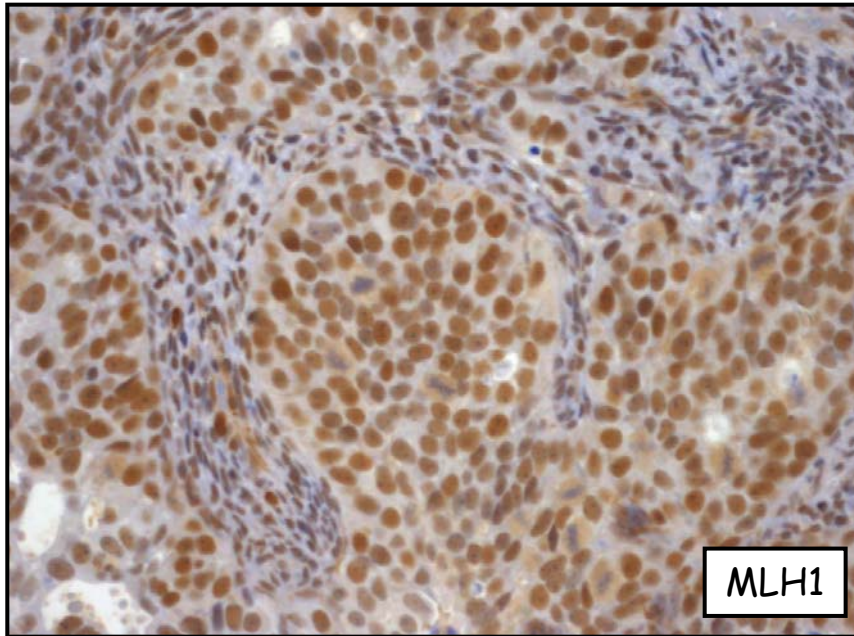


Stage III patients with MMRP+ tumors

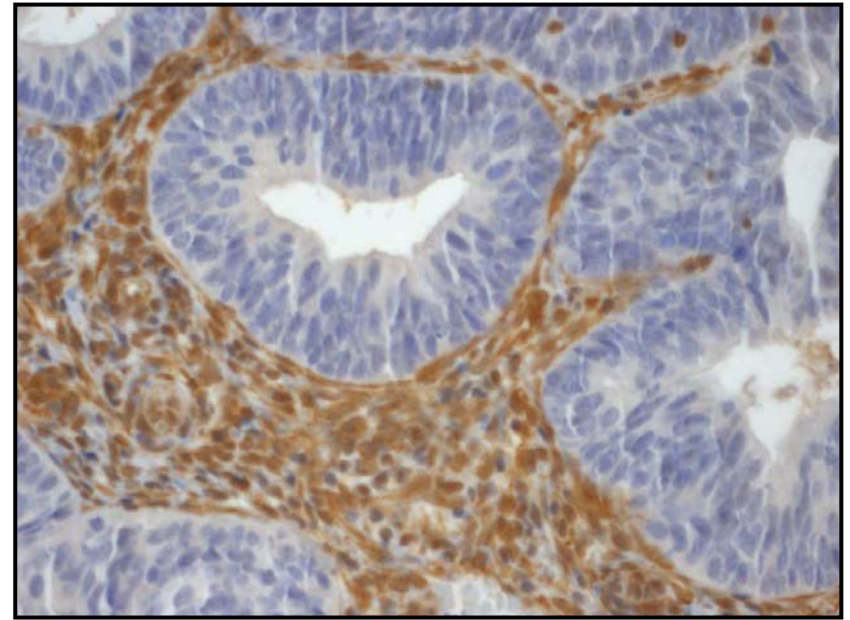
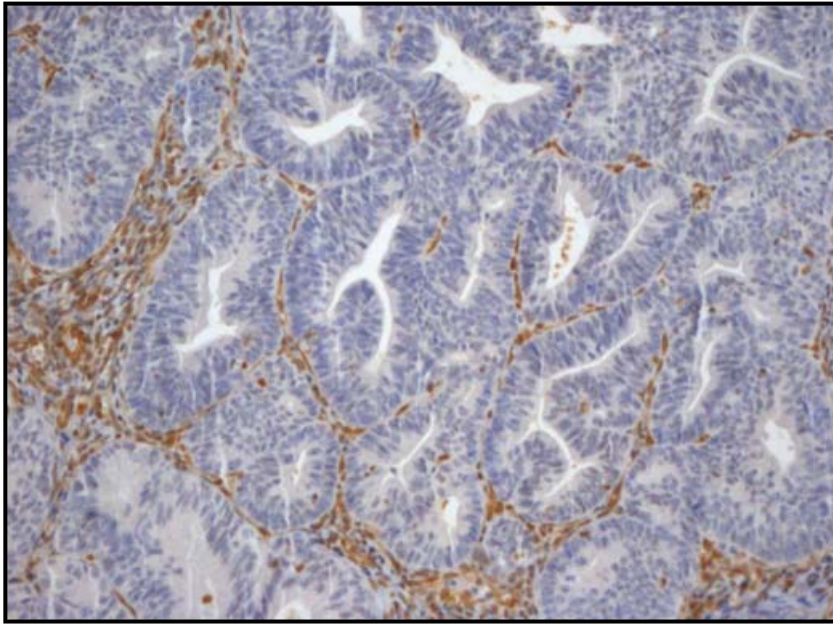


It is reasonable to exercise caution regarding chemotherapy in Lynch syndrome patients with stage III, or especially stage II, CRCs.

Boland 2007



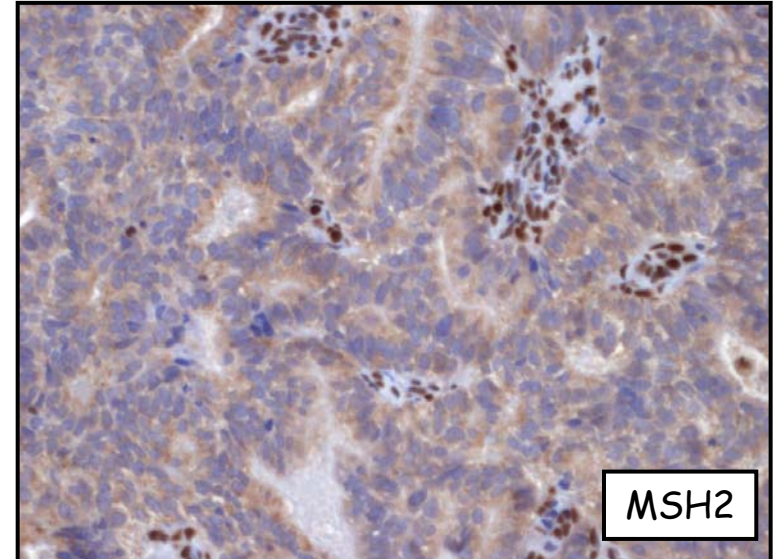
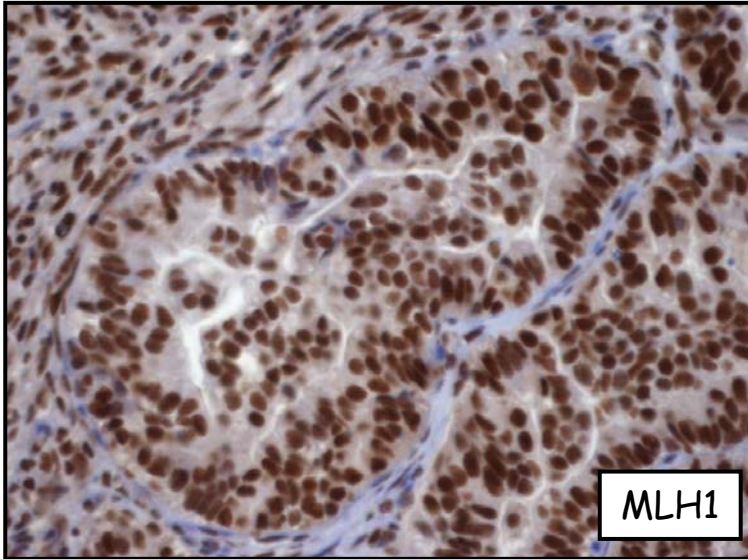
***Utero
Adenocarcinoma endometrioid
scarsamente differenziato***



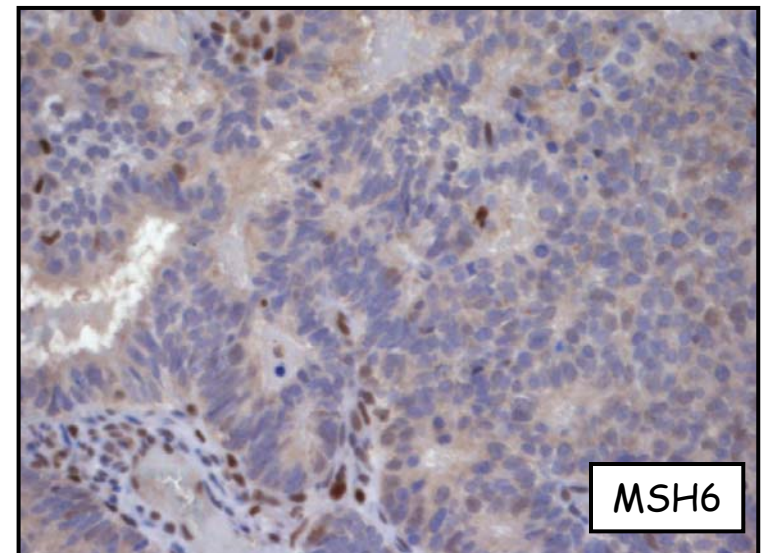
Utero

Adenocarcinoma endometriode bene differenziato

Perdita completa di espressione di MLH1



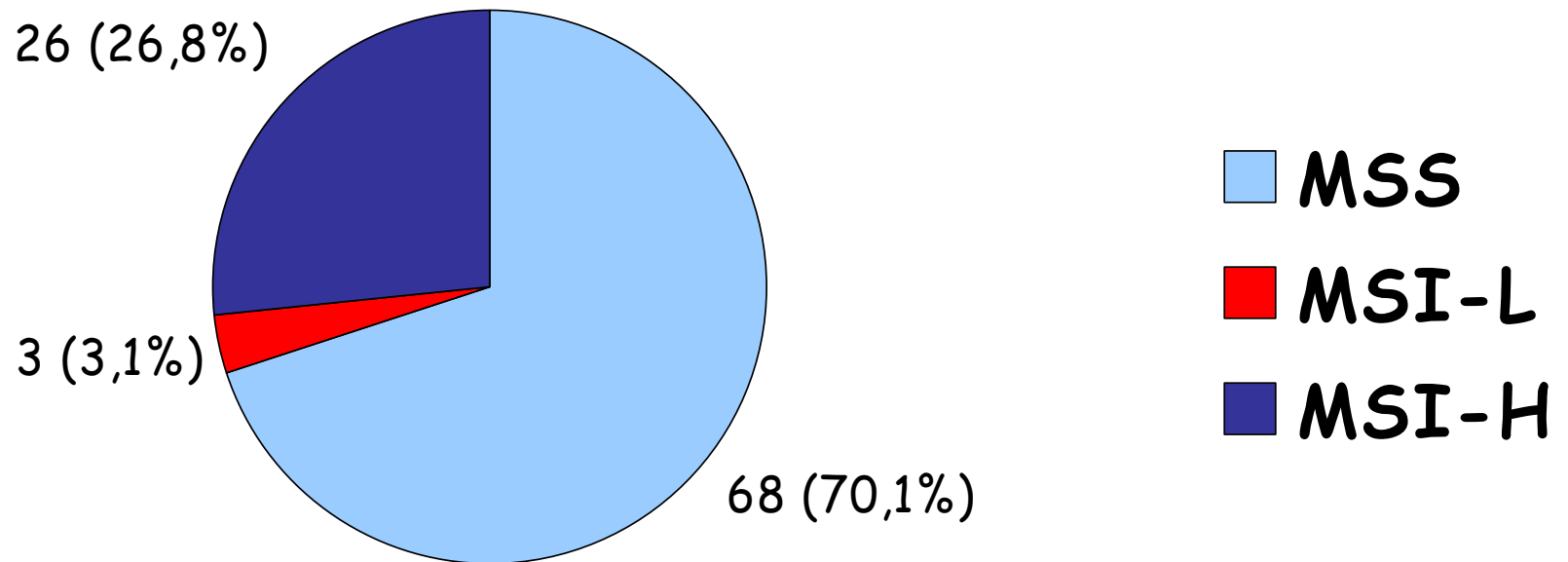
Utero
Adenocarcinoma endometrioid
Perdita completa di espressione
di MSH2 e MSH6



Carcinoma endometriale

Risultati analisi MSI

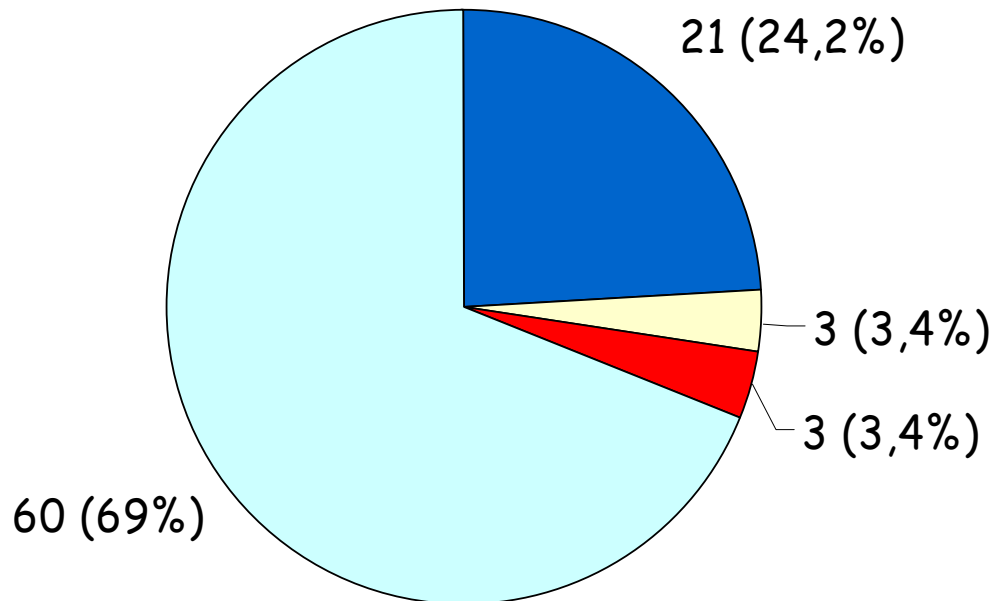
n. totale casi = 97



Carcinoma endometriale

Risultati analisi immunoistochimica espressione proteine del MMR

n. totale casi = 87



■ MLH1- MSH2+ MSH6+

■ MLH1+ MSH2- MSH6-

■ MLH1+ MSH2+ MSH6-

■ MLH1+ MSH2+ MSH6+

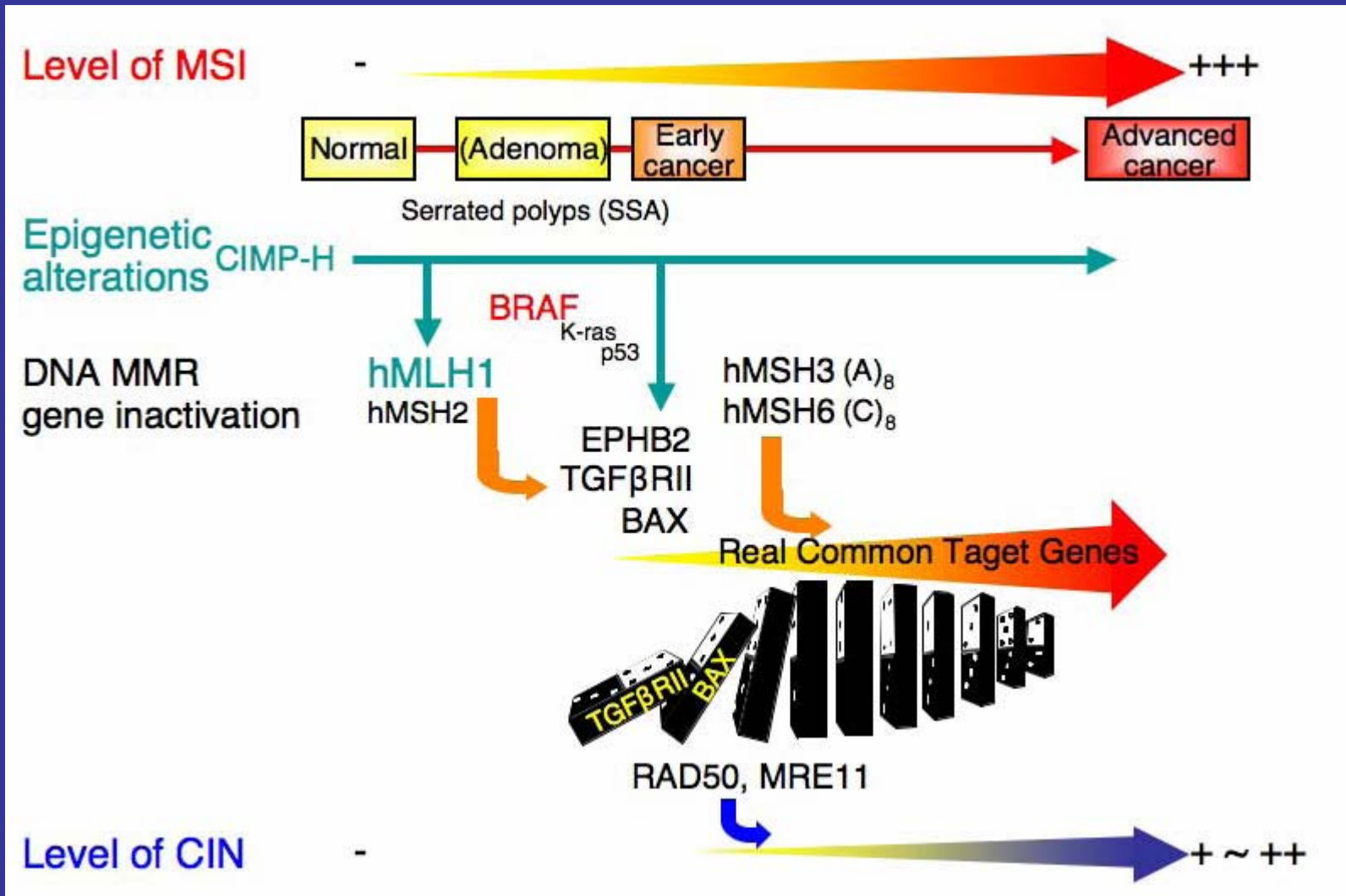
Carcinoma endometriale

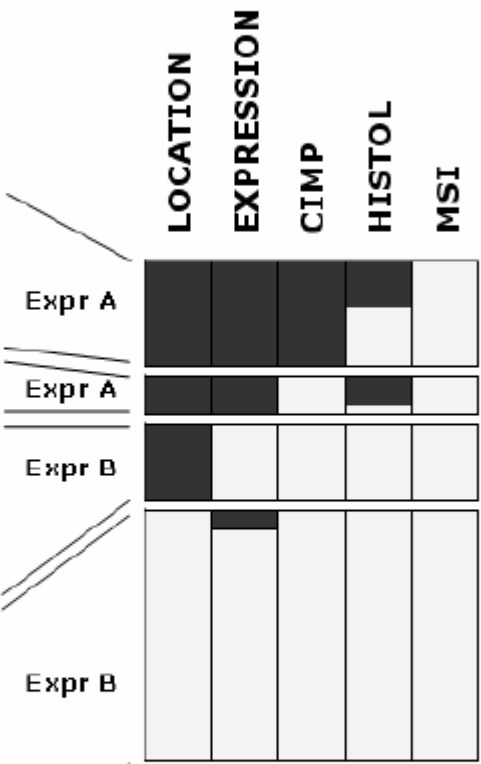
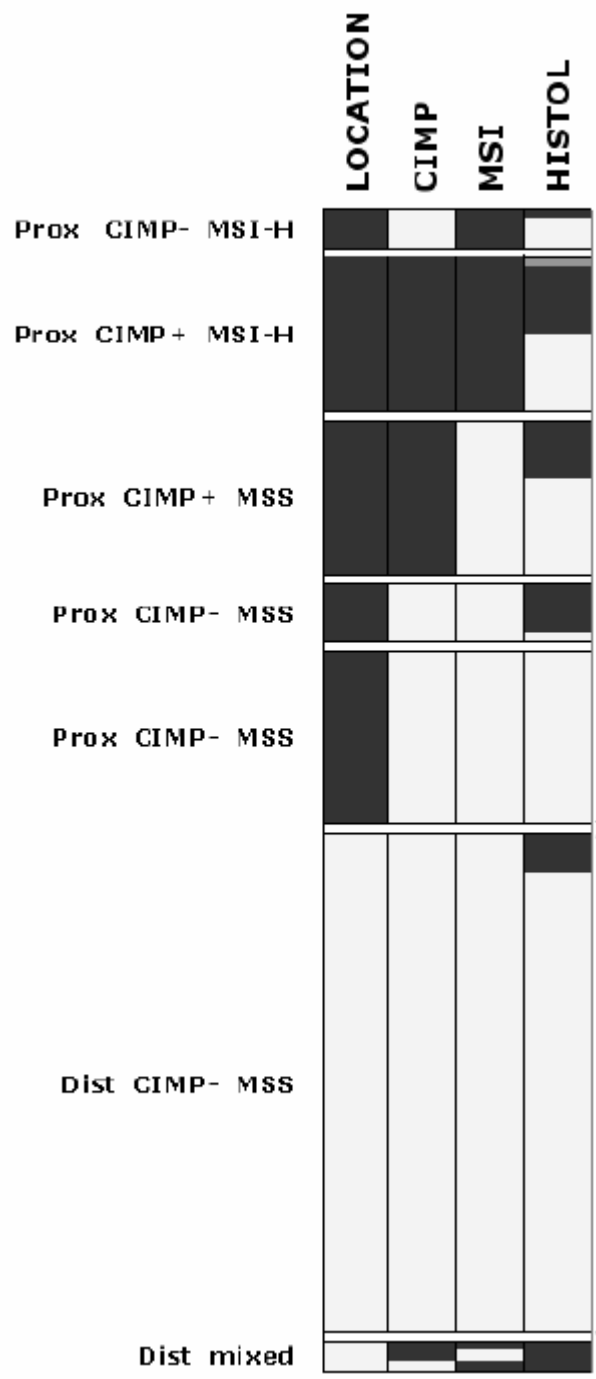
Status MSI ed espressione proteine del MMR

	MSS	MSI-L	MSI-H	P
MMRP +	59 (95,2%)		1 (4,5%)	< 0,001
MMRP -	3 (4,8%)	3 (100%)	21 (95,5%)	

n. totale casi = 87







Adenoma serrato tradizionale

