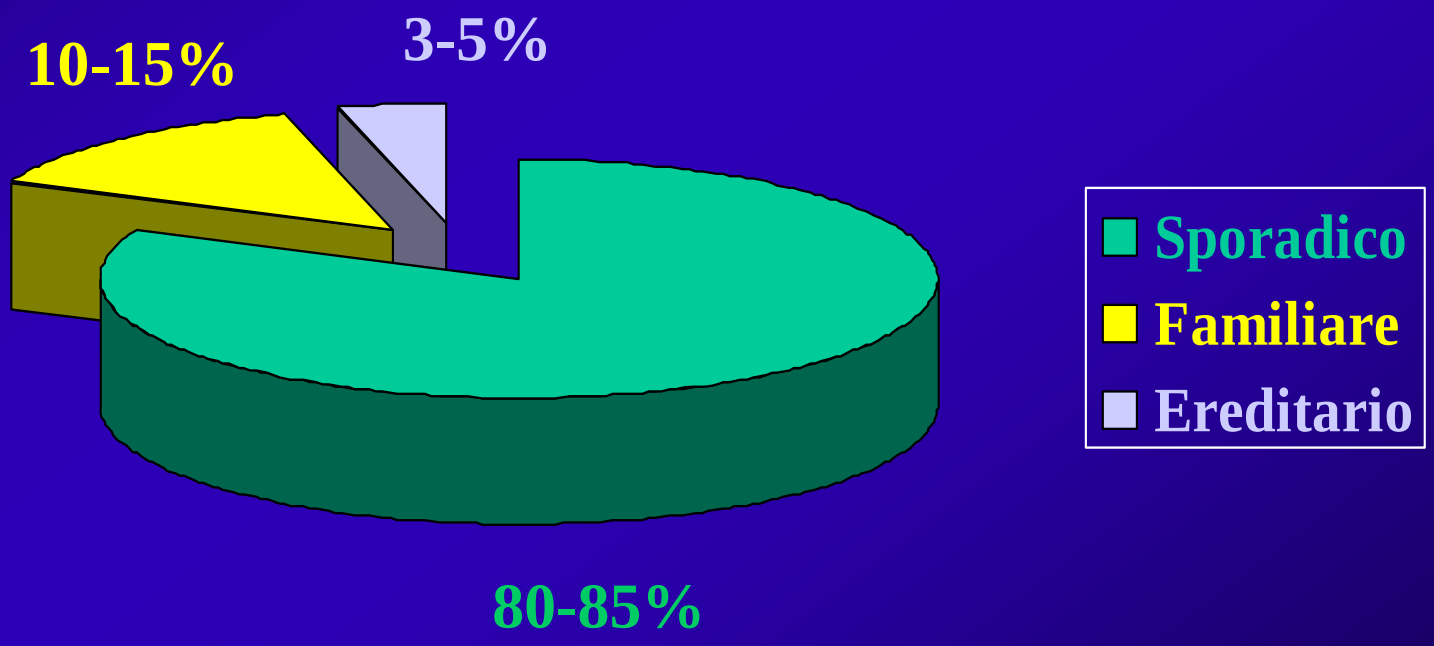
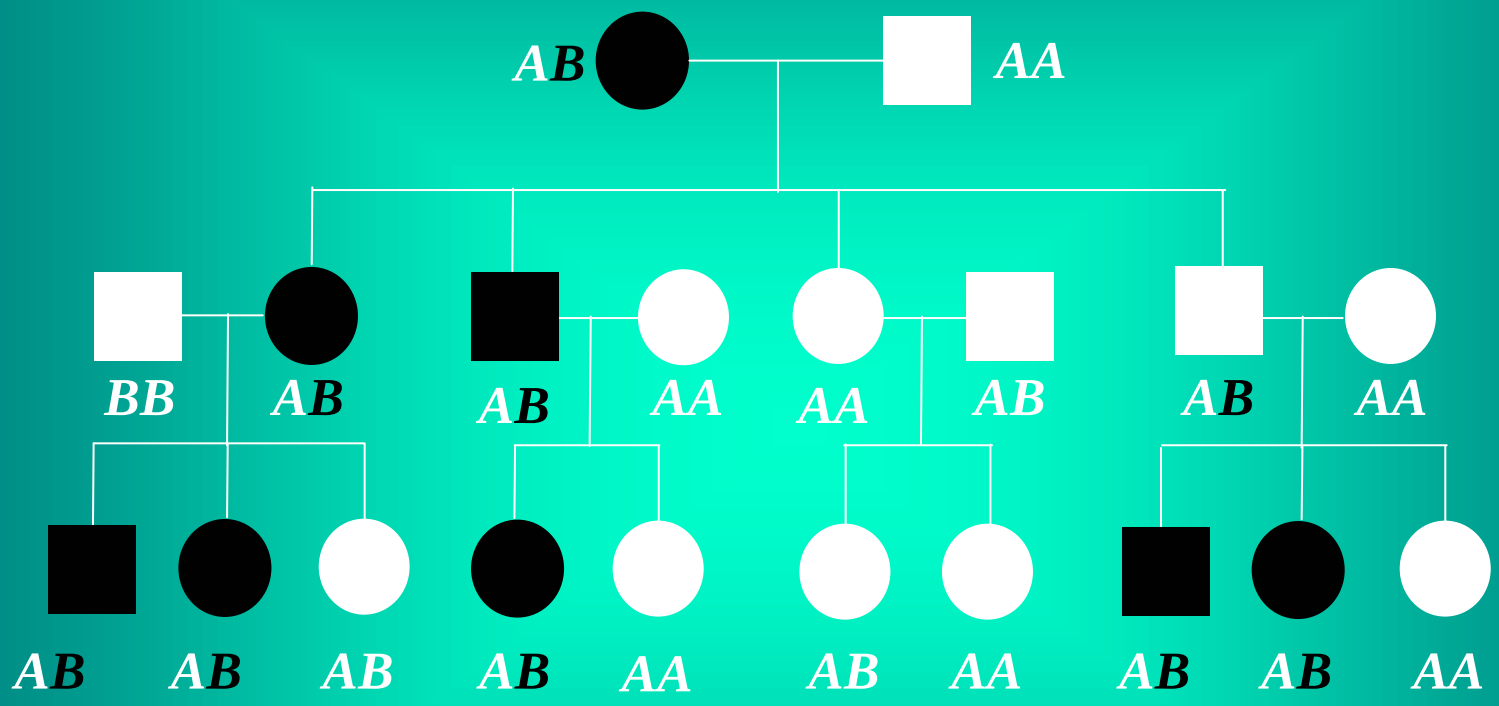
# EPIDEMIOLOGIA GENETICA DEL CANCRO COLORETTALE



# Predisposizione Ereditaria ai Tumori del Colon-Retto

| SINDROME | FREQUENZA | TRASMISSIONE | GENI |
|---|---|---|---|
| **Forme Poliposiche** | | | |
| FAP/Gardner/Turcot | 1/5.000 -1/7.500 | AD | *APC* |
| MAP (*MUTYH*-relata) | 1/10.000? | AR | *MUTYH* |
| Poliposi giovanile | Rara | AD | *SMAD4, BMPR1A* |
| Peutz-Jeghers | Rara | AD | *LKB1* |
| **Forme Non Poliposiche** | | | |
| HNPCC | 1/2.000? | AD | *MLH1, MSH2 PMS2, MSH6* |


AB
AA
BB
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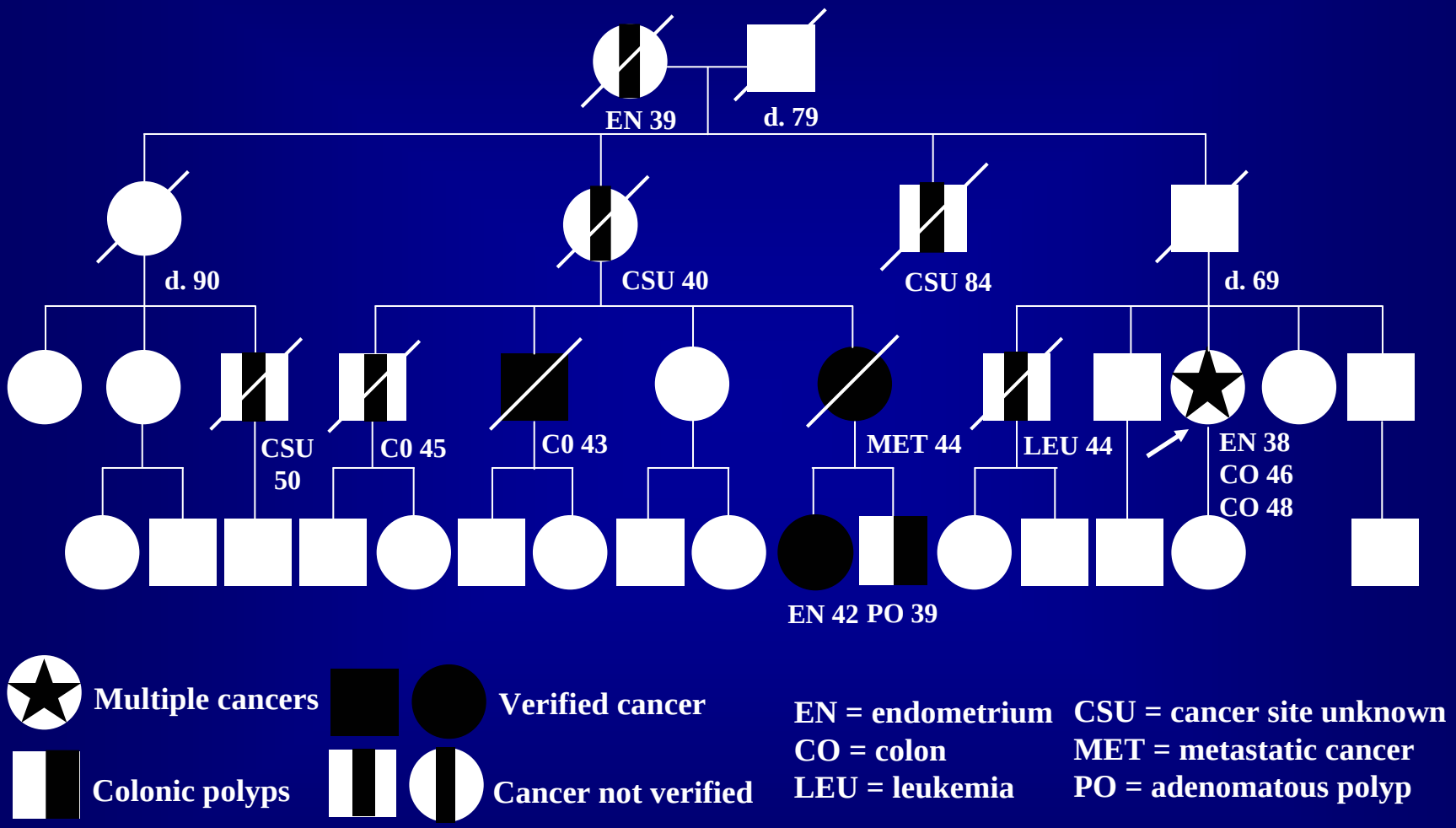
AB
AA

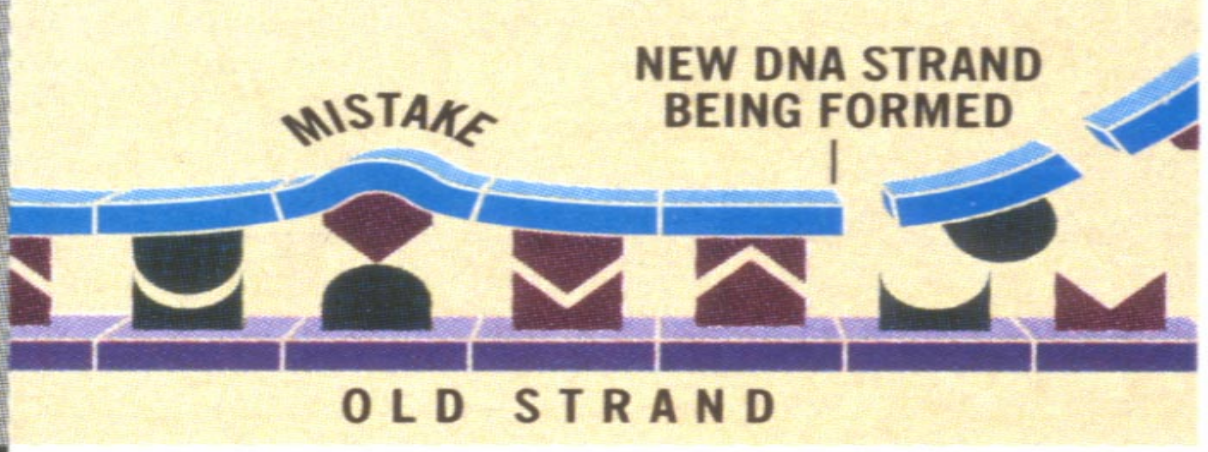
# Hereditary NonPolyposis Colorectal Cancer (HNPCC; sindrome di Lynch) Criteri Diagnostici Clinico-Genetici

- ≥3 individui affetti da carcinoma colorettale (*o* endometriale *o* delle vie urinarie *o* dell'intestino tenue) in 2 generazioni, uno dei quali dev'essere imparentato in 1° grado con gli altri due
- Almeno 2 generazioni successive coinvolte
- Almeno 1 tumore diagnosticato ≤50 aa.
- FAP esclusa

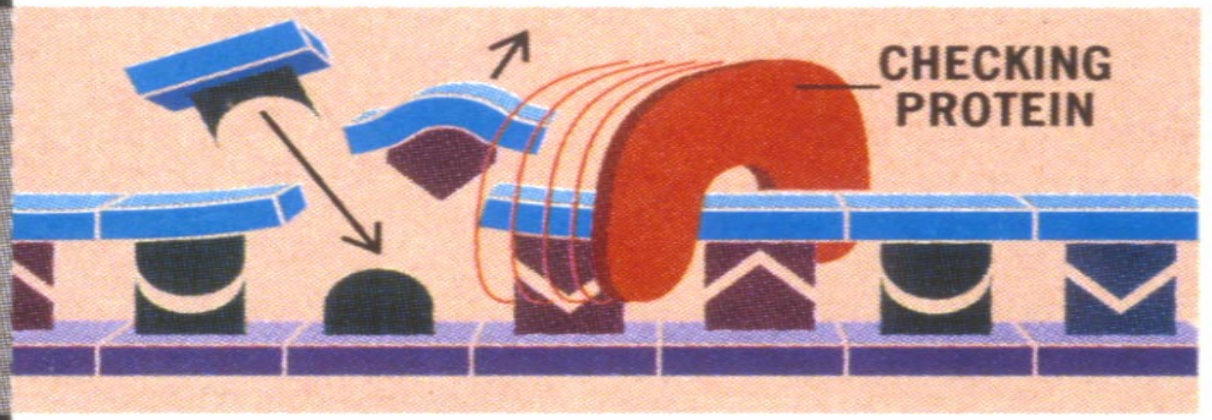

EN 39
d. 79
d. 90
CSU 40
CSU 84
d. 69
CSU 50
C0 45
C0 43
MET 44
LEU 44
EN 38
CO 46
CO 48
EN 42 PO 39
Multiple cancers
Verified cancer
Colonic polyps
Cancer not verified
EN = endometrium
CO = colon
LEU = leukemia
CSU = cancer site unknown
MET = metastatic cancer
PO = adenomatous polyp

# A Tragedy Of Errors

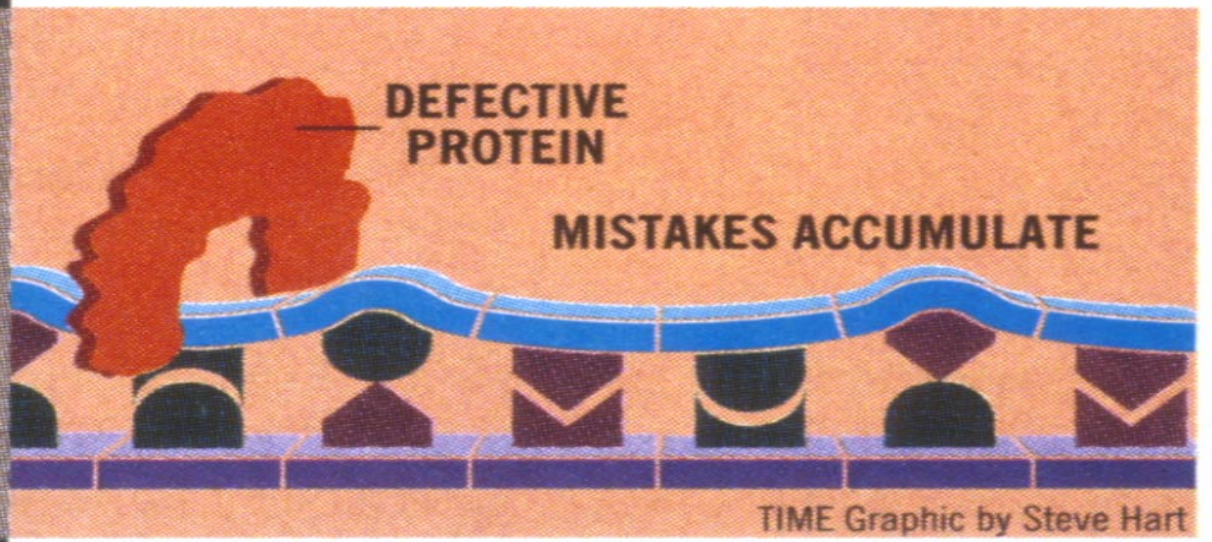
**1** As DNA is duplicated, mistakes occasionally occur.




**2** A checking protein scans the DNA and directs repairs.




**3** If the checking protein is defective, mistakes accumulate in genes. When this occurs in genes that regulate cell growth, they lose their effectiveness, allowing cancer to develop.




TIME Graphic by Steve Hart

# GENI DEL MMR UMANO IMPLICATI NELL'HNPCC

| GENE | PARTNERS | FUNZIONI | PHENOTYPE |
|---|---|---|---|
| ***mutS* homol.** | | | |
| *MSH2* | MSH3<br>MSH6 | Riconoscimento single base mismatches e IDLs (1-4 bp) | -HNPCC (20%-40%), MSI-H<br>-Tumori nei topi KO |
| *MSH6* | MSH2 | Riconoscimento single base mismatches e 1 bp IDLs | - HNPCC atipica (5-10%), MSI-L<br>-Pochi tumori nei topi KO, MSI-L |
| ***mutL* homol.** | | | |
| *MLH1* | PMS2<br>MLH3 | Reclutamento endonucleasi (mismatches e IDLs) | -HNPCC (20%-40%), MSI-H<br>-Tumori nei topi KO, MSI-H |
| *PMS2* | MLH1 | Reclutamento endonucleasi (mismatches and IDLs) | -HNPCC (rara, autos. rec.), MSI-H<br>-No tumori nei topi KO |

# Caratteristiche della HNPCC

- ✓ Storia familiare
- ✓ Prevalenza tumori colon destro
- ✓ Età dalla diagnosi relatiavemente precoce
- ✓ Tumori extraintestinali associati
- ✓ Tumori multipli sincroni o metacroni
- ✓ Tumori mucinosi, infiltrazione linfocitaria, reazione Crohn-like
- ✓ Progressione adenoma→carcinoma accelerata

# Criteri di Bethesda Revisionati

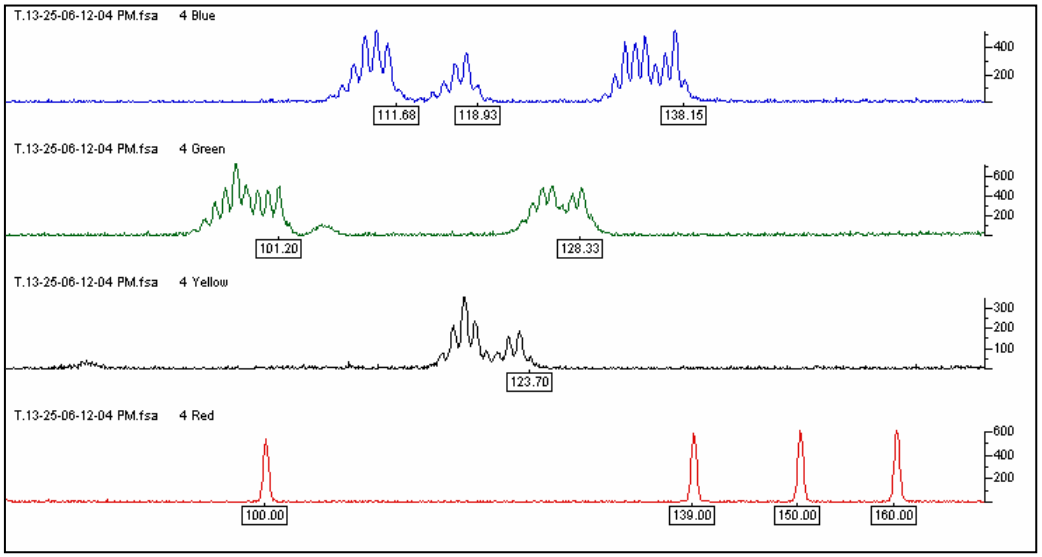
*Umar et al. Revised Bethesda Guidelines for Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome) and Microsatellite Instability. J. Natl. Cancer Inst. 96:261-268, 2004.*

1. **≥1 casi di carcinoma colorettale < 50 anni**
2. **≥1 casi di tumori dello spettro HNPCC sincroni o metacroni, a qualunque età**
3. **≥1 casi di carcinoma colorettale con aspetti istologici associati a MSI-H <60 anni**
4. **≥1 casi di carcinoma colorettale in parenti di 1° grado di un paziente affetto da tumore dello spettro HNPCC; uno dei tumori deve essere diagnosticato <50 anni**
5. **Carcinoma colorettale in ≥2 parenti di 1° o 2° grado di un paziente affetto da tumore dello spettro HNPCC, indipendentemente dall'età**

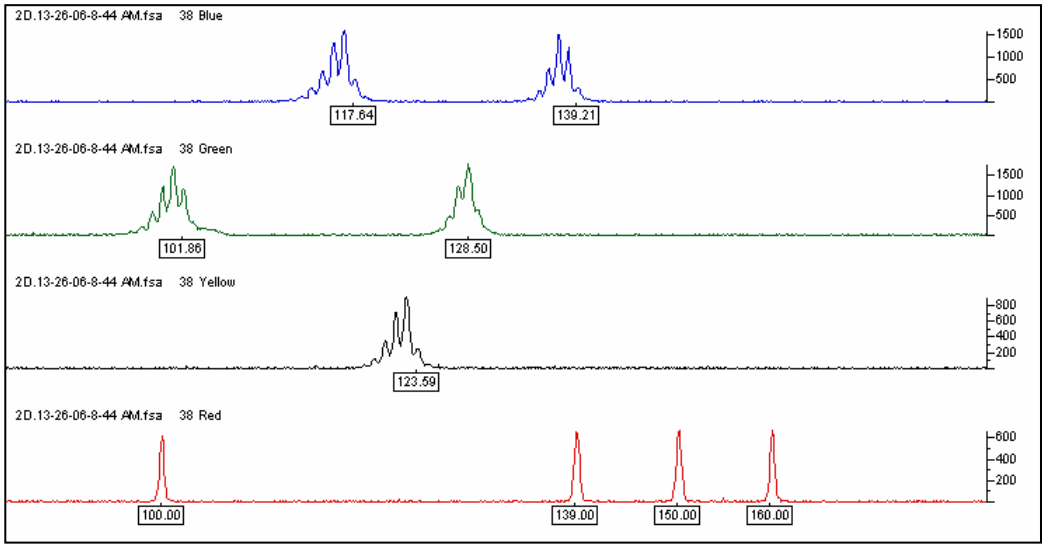
Tumori HNPCC-associati: ca. colon-retto, endometrio, stomaco, ovaio, pancreas, uretere e pelvi renale, vie biliari, intestino tenue; tumori SNC (usualmente glioblastoma); adenomi sebacei e cheratoacantomi

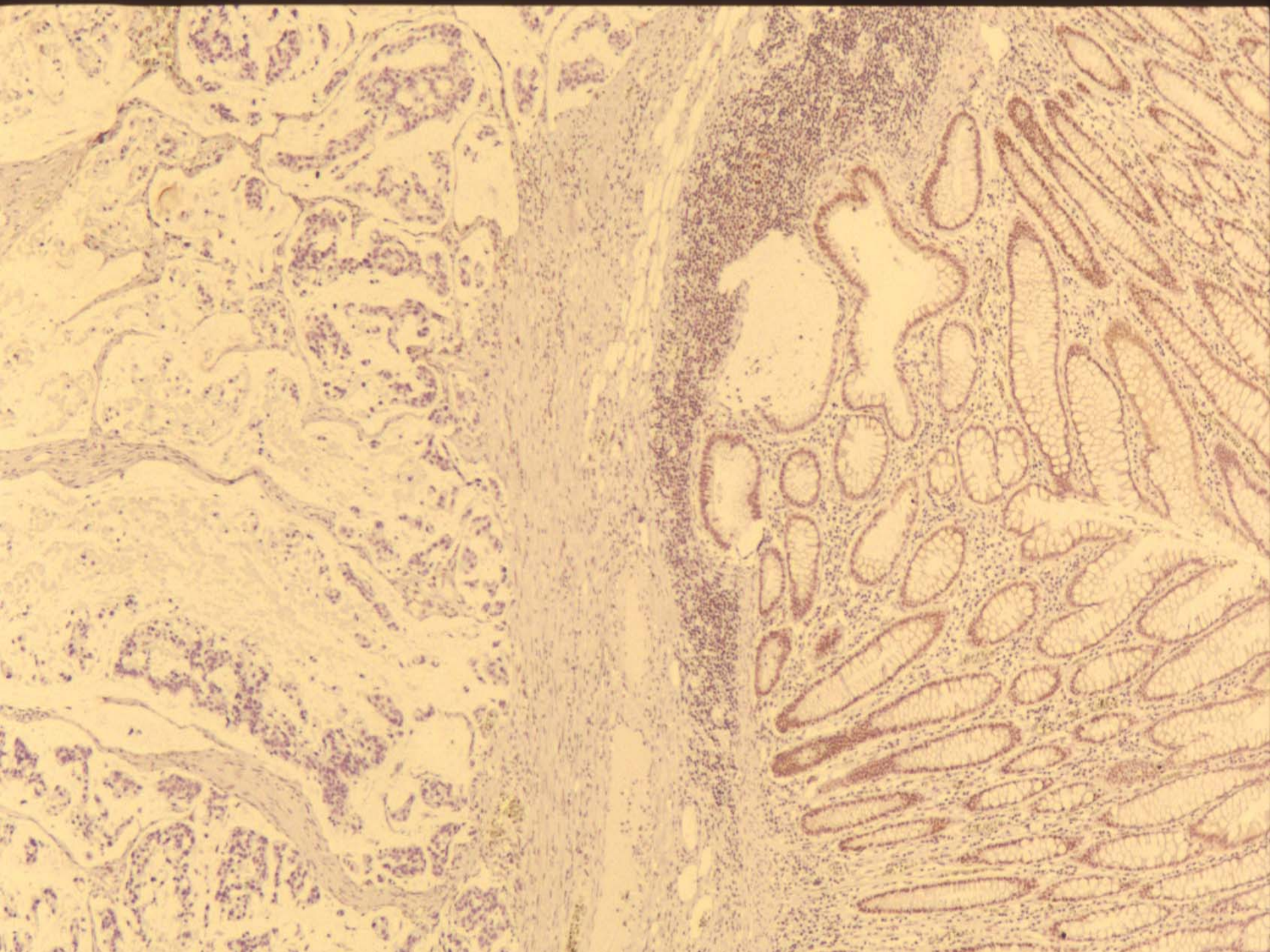
Istologia associata a tumori MSI-H: presenza di TIL, reazione linfocitaria Crohn-like, differenziamento mucinoso con cellule ad anello con castone, pattern di crescita midollare

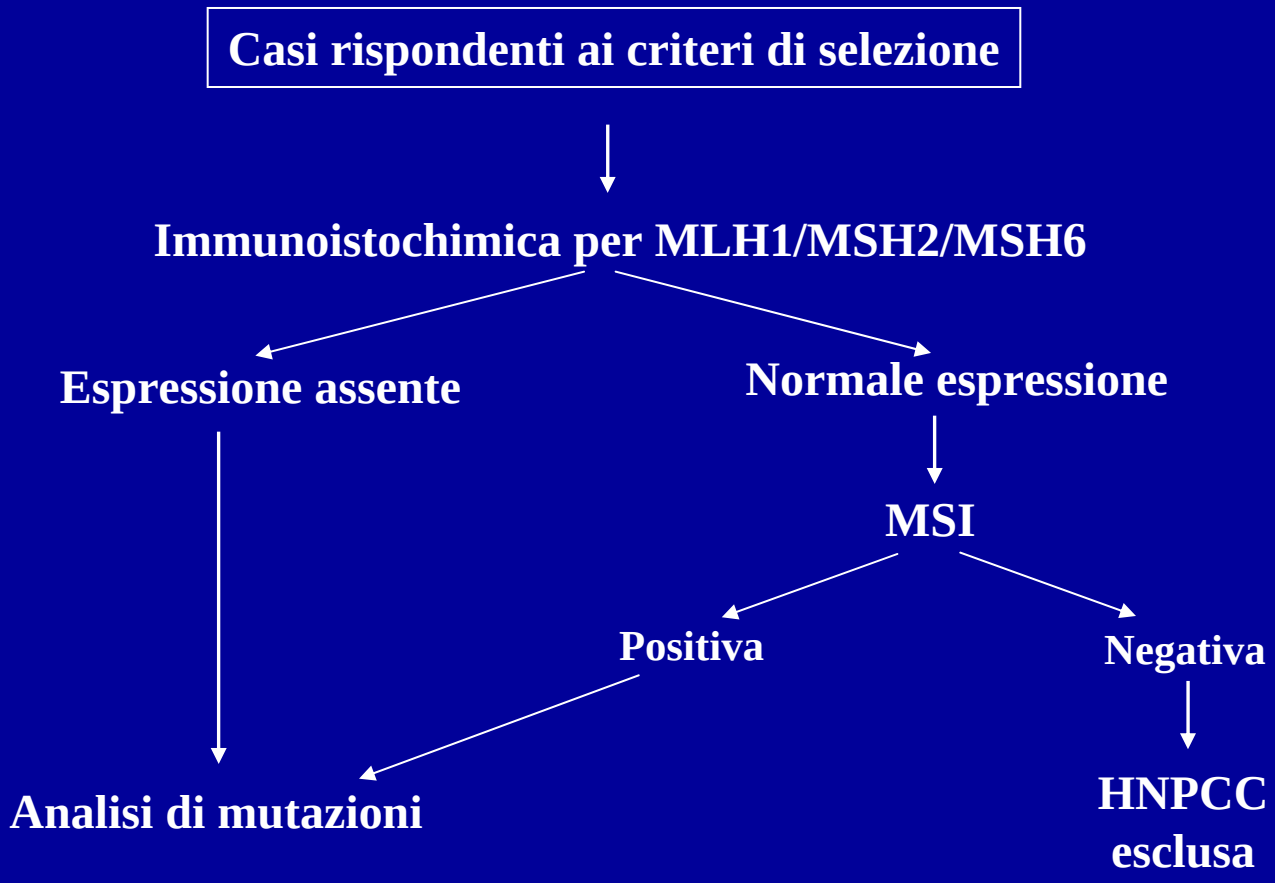
MSI-H


T.13-25-06-12-04 PM.fsa 4 Blue
111.68
118.93
138.15
400
200
T.13-25-06-12-04 PM.fsa 4 Green
101.20
128.33
600
400
200
T.13-25-06-12-04 PM.fsa 4 Yellow
123.70
300
200
100
T.13-25-06-12-04 PM.fsa 4 Red
100.00
139.00
150.00
160.00
600
400
200

MSS

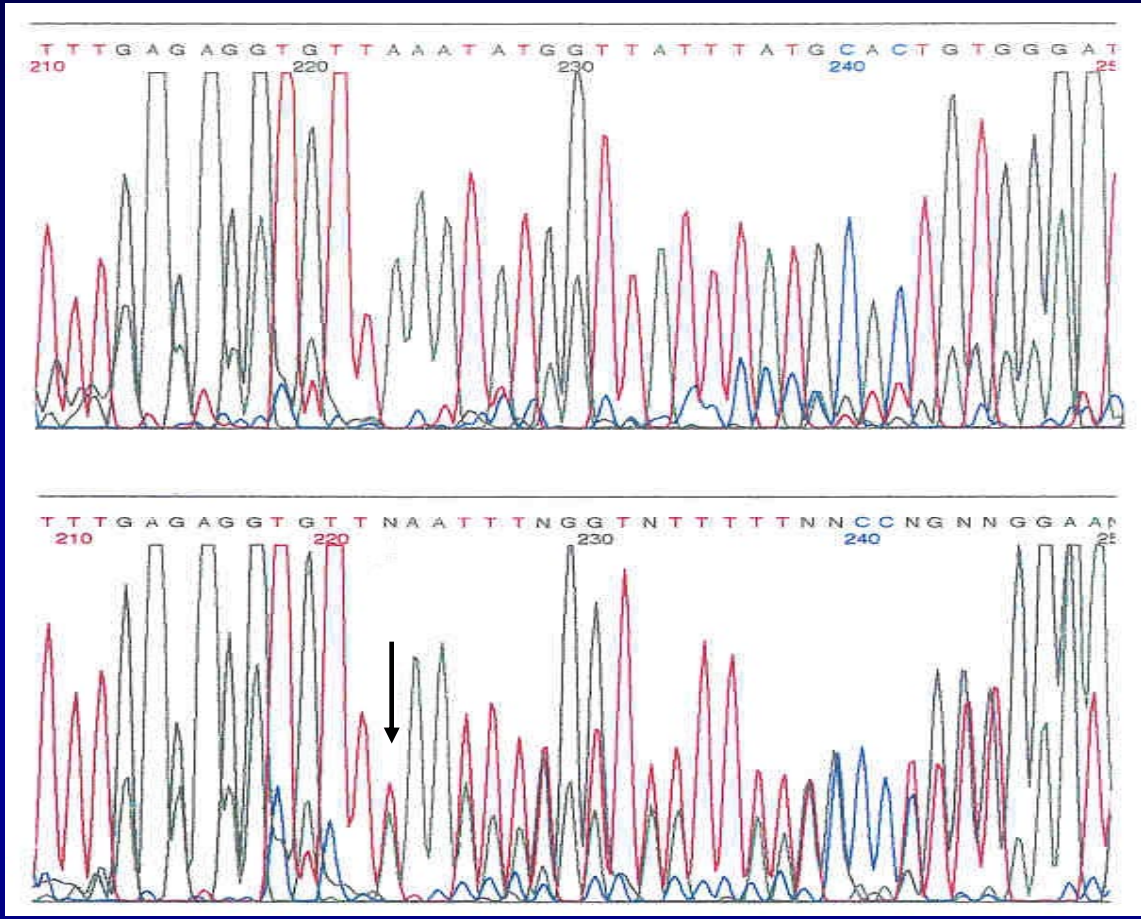

2D.13-26-06-8-44 AM.fsa 38 Blue
117.64
139.21
1500
1000
500
2D.13-26-06-8-44 AM.fsa 38 Green
101.86
128.50
1500
1000
500
2D.13-26-06-8-44 AM.fsa 38 Yellow
123.59
800
600
400
200
2D.13-26-06-8-44 AM.fsa 38 Red
100.00
139.00
150.00
160.00
600
400
200




Casi rispondenti ai criteri di selezione
Immunoistochimica per MLH1/MSH2/MSH6
Espressione assente
Normale espressione
MSI
Positiva
Negativa
Analisi di mutazioni
HNPCC esclusa

Wt

Mut

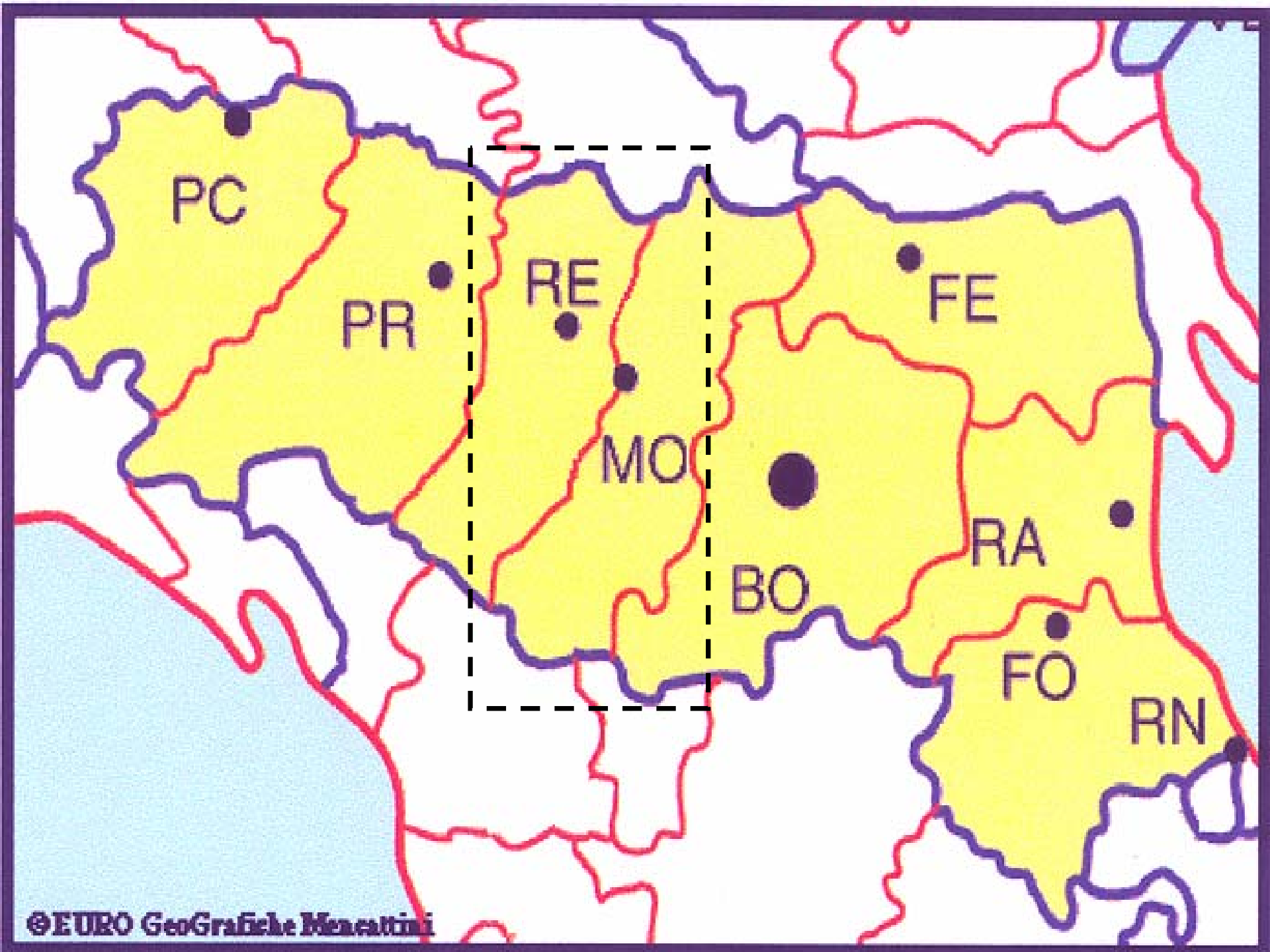



**DNA Wt: AGG TGT TAA ATATTGG…**

**Prot. R C ***

**DNA Mut: AGG TGT TIA AAA TAT TGG ...**

**Prot. R C I K Y W ...**



# A founder MLH1 mutation in families from the districts of Modena and Reggio-Emilia in northern Italy with hereditary non-polyposis colorectal cancer associated with protein elongation and instability

O Caluseriu, C Di Gregorio, E Lucci-Cordisco, M Santarosa, J Trojan, A Brieger, P Benatti, M Pedroni, T Colibazzi, A Bellacosa, G Neri, M Ponz de Leon, A Viel and M Genuardi

***J Med. Genet. 2004; 41:34***

*Scandinavian Journal of Gastroenterology*, 2007; 42: 746–753

informa
healthcare

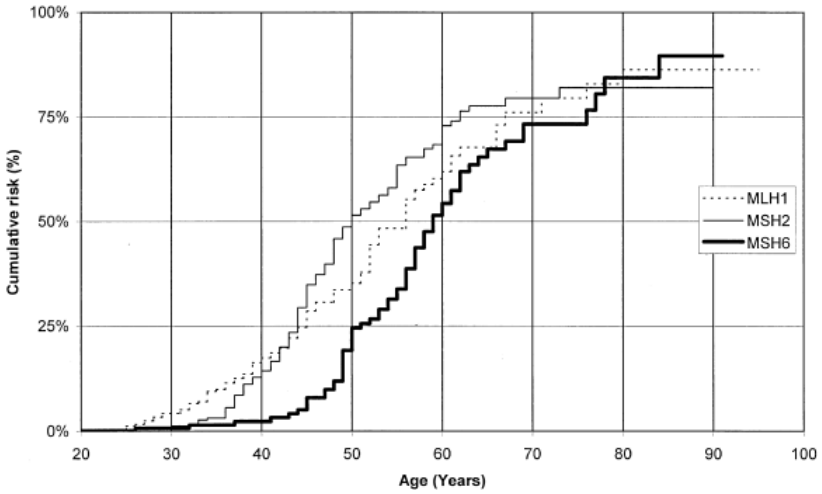
ORIGINAL ARTICLE

# Genotype-phenotype correlations in individuals with a founder mutation in the MLH1 gene and hereditary non-polyposis colorectal cancer

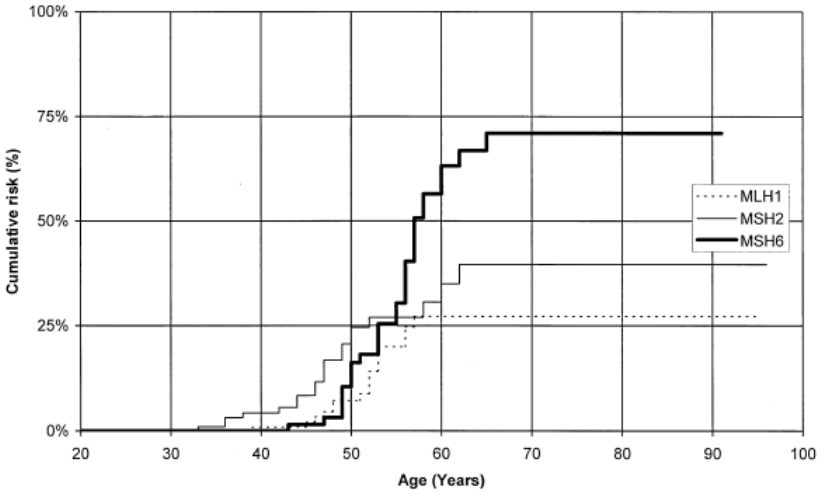
MAURIZIO PONZ DE LEON[1], PIERO BENATTI[1], CARMELA DI GREGORIO[2], LORENA LOSI[3], MONICA PEDRONI[1], GIOVANNI PONTI[1], MAURIZIO GENUARDI[4], ALESSANDRA VIEL[5], EMANUELA LUCCI-CORDISCO[4], GIUSEPPINA ROSSI[1] & LUCA RONCUCCI[1]

Hendriks YM, Wagner A, Morreau H, Menko F, Stormoken A, Quehenberger F, Sandkuijl L, Moller P, Genuardi M, Van Houwelingen H, Tops C, Van Puijenbroek M, Verkuijlen P, Kenter G, Van Mil A, Meijers-Heijboer H, Tan GB, Breuning MH, Fodde R, Wijnen JT, Brocker-Vriends AH, Vasen H.

"Cancer risk in hereditary nonpolyposis colorectal cancer due to *MSH6* mutations: Impact on counseling and surveillance". *Gastroenterology 127:17-25 (2004).*




All cancers




Endometrial cancer

# Mutazioni *MSH6*

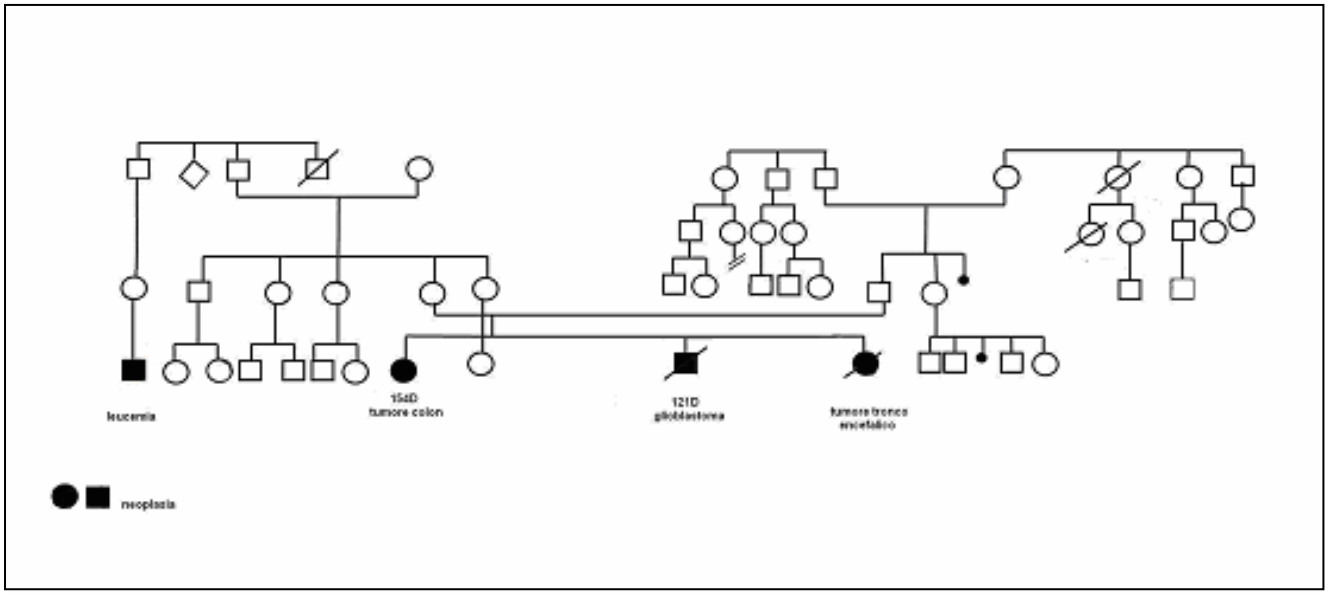
- HNPCC “atipica”
- Età d’insorgenza del CCR più avanzata rispetto alle forme associate a *MSH2* e *MLH1*
- Rischio particolarmente elevato di carcinoma dell’endometrio
- Status MSI variabile nei tumori: MSI-H, MSI-L o MSS

# *Mutazioni monoalleliche di PMS2*

- HNPCC (attenuata?)
- Nessun fenotipo nei genitori di pazienti con mutazioni bialleliche (mutazione founder R508X nei Pakistani)

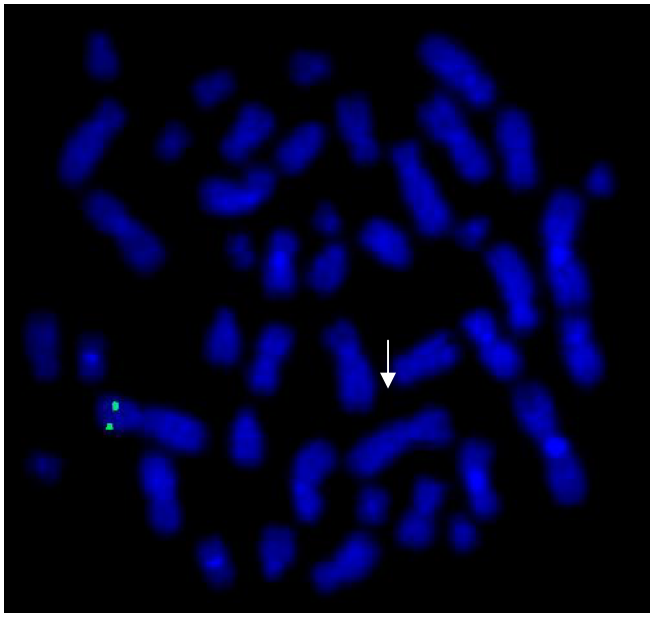
# Mutazioni bialleliche dei geni MMR

- Insorgenza in età pediatrica
- Tumori SNC (prevalentemente di derivazione gliale)
- Leucemie e linfomi (prevalentemente di derivazione linfocitaria)
- Adenomi e carcinomi colorettali molto precoci (anche a 7 anni!)
- Fenotipo NF1-like (macchie caffelatte, neurofibromi sottocutanei)
- In alcuni pedigree assenza di manifestazioni nei genitori eterozigoti

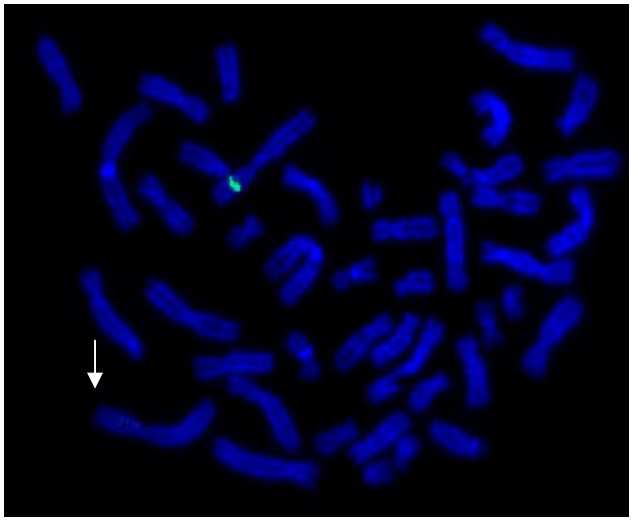

leucemia
154D
tumore colon
121D
glioblastoma
tumore bronco
epiteliale
neoplasia

- Età 38 anni
- Ritardo mentale
- Altezza 146 cm; peso 90 kg
- Brachicefalia
- Padiglioni auricolari semplificati
- Sopracciglia folte
- Columella nasale sporgente
  Diastema incisivi centr. sup.
- Philtrum molto breve
- Brachidattilia
- *Eccesso di archi sui polpastrelli*
- Cariotipo (500 bande): normale
- *A 37 aa. ca. flessura splenica*

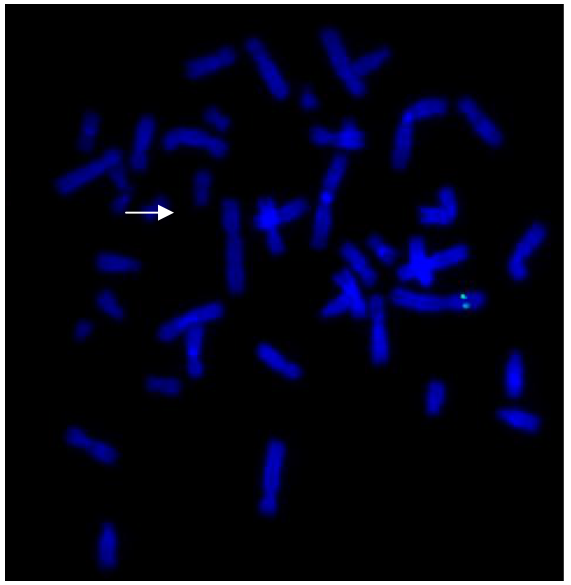
RP11-417P11



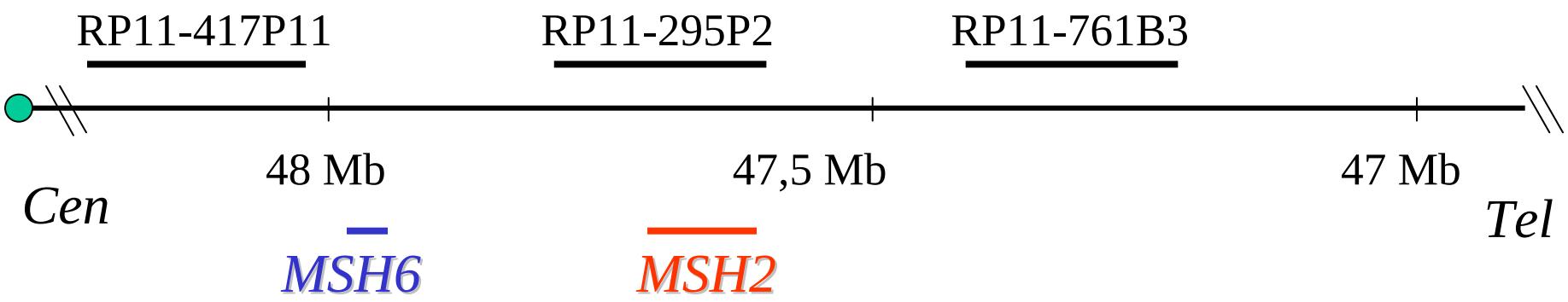
RP11-295P2



RP11-761B3



Regione 2p16.3p21



# A novel microdeletion syndrome with loss of the *MSH2* locus and hereditary non-polyposis colorectal cancer

Lucci-Cordisco E, Zollino M, Baglioni S, Mancuso I, Lecce R, Gurrieri F, Crucitti A, Papi L, Neri G, Genuardi M. A novel microdeletion syndrome with loss of the *MSH2* locus and hereditary non-polyposis colorectal cancer.
Clin Genet 2004: 67: 178–182. 

# AIMS

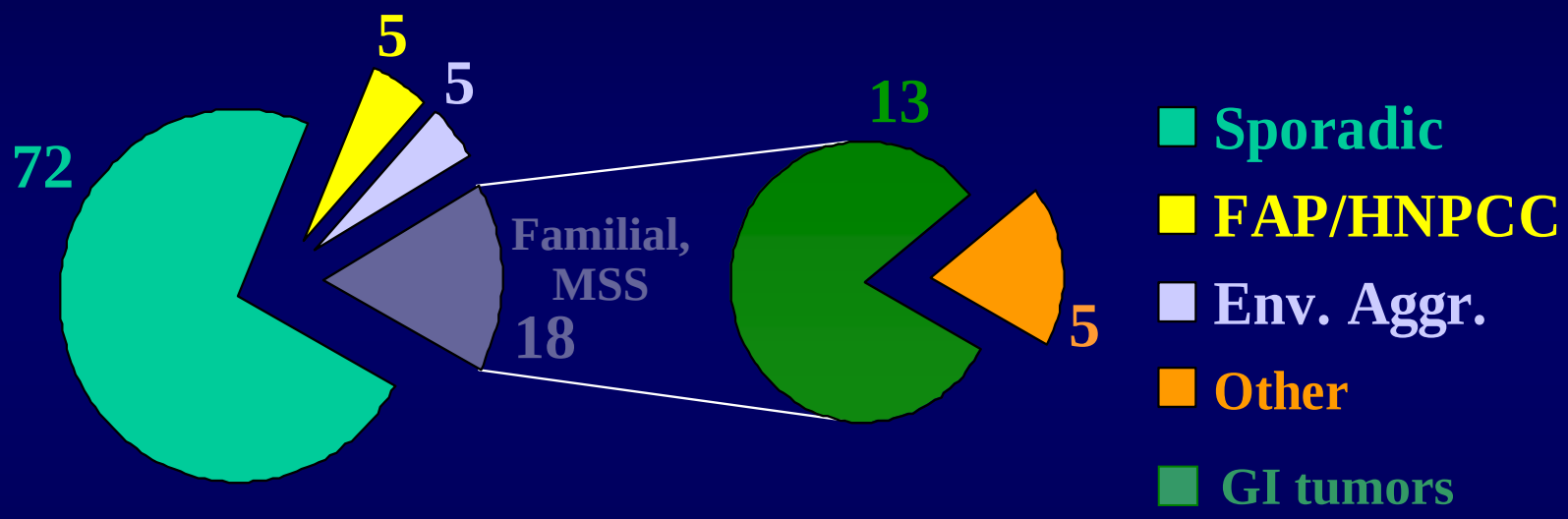
**To identify familial CRCs not related to:**

- **MMR DEFICIENCY (*MLH1/MSH2*)**
- ***APC* GENE MUTATIONS**

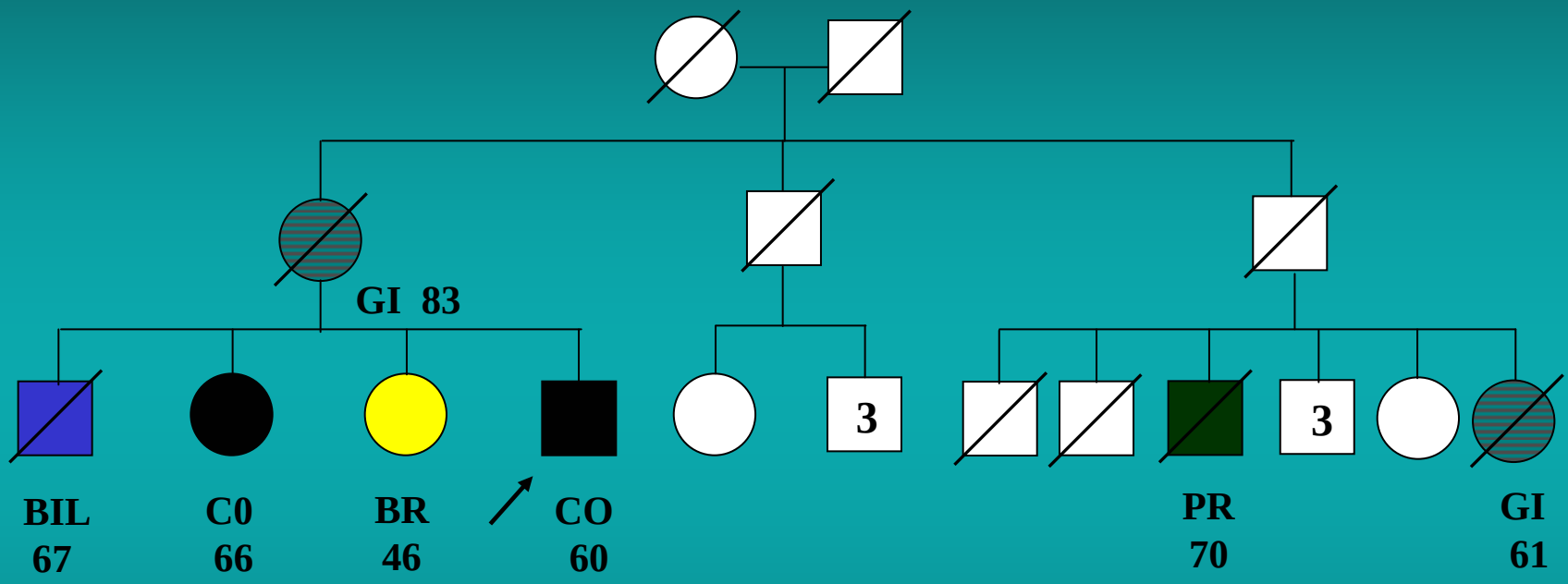
**100 consecutive CRCs investigated for:**

- **MSI**
- **CLINICAL CHARACTERISTICS**
- **FAMILY HISTORY OF CANCER**

Rovella V et al. "Familial microsatellite-stable non-polyposis colorectal cancer: incidence and characteristics in a clinic-based population". *Ann. Oncol., 12:813-818 (2001)*


72
5
5
Familial, MSS
18
13
5
Sporadic
FAP/HNPCC
Env. Aggr.
Other
GI tumors

# MSI-NEGATIVE CRC FAMILY



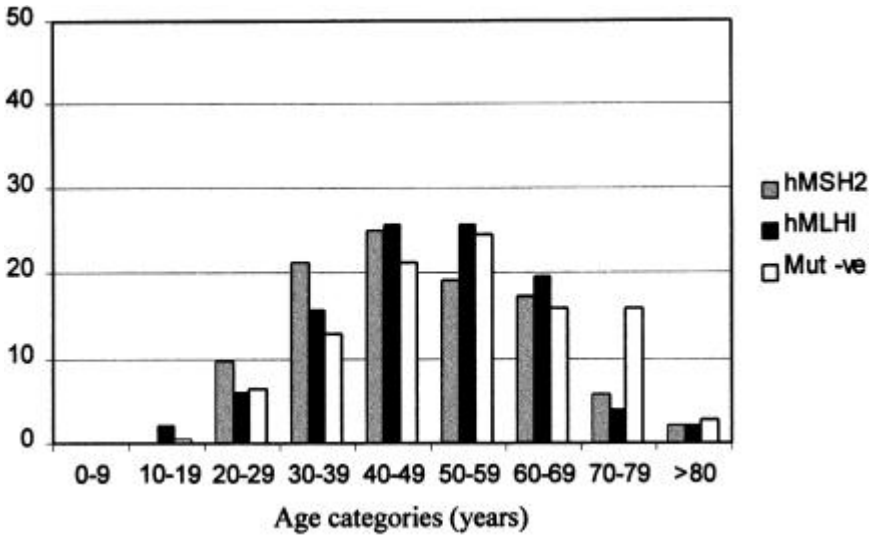

Right colon ca.

GI tract ca., not specified

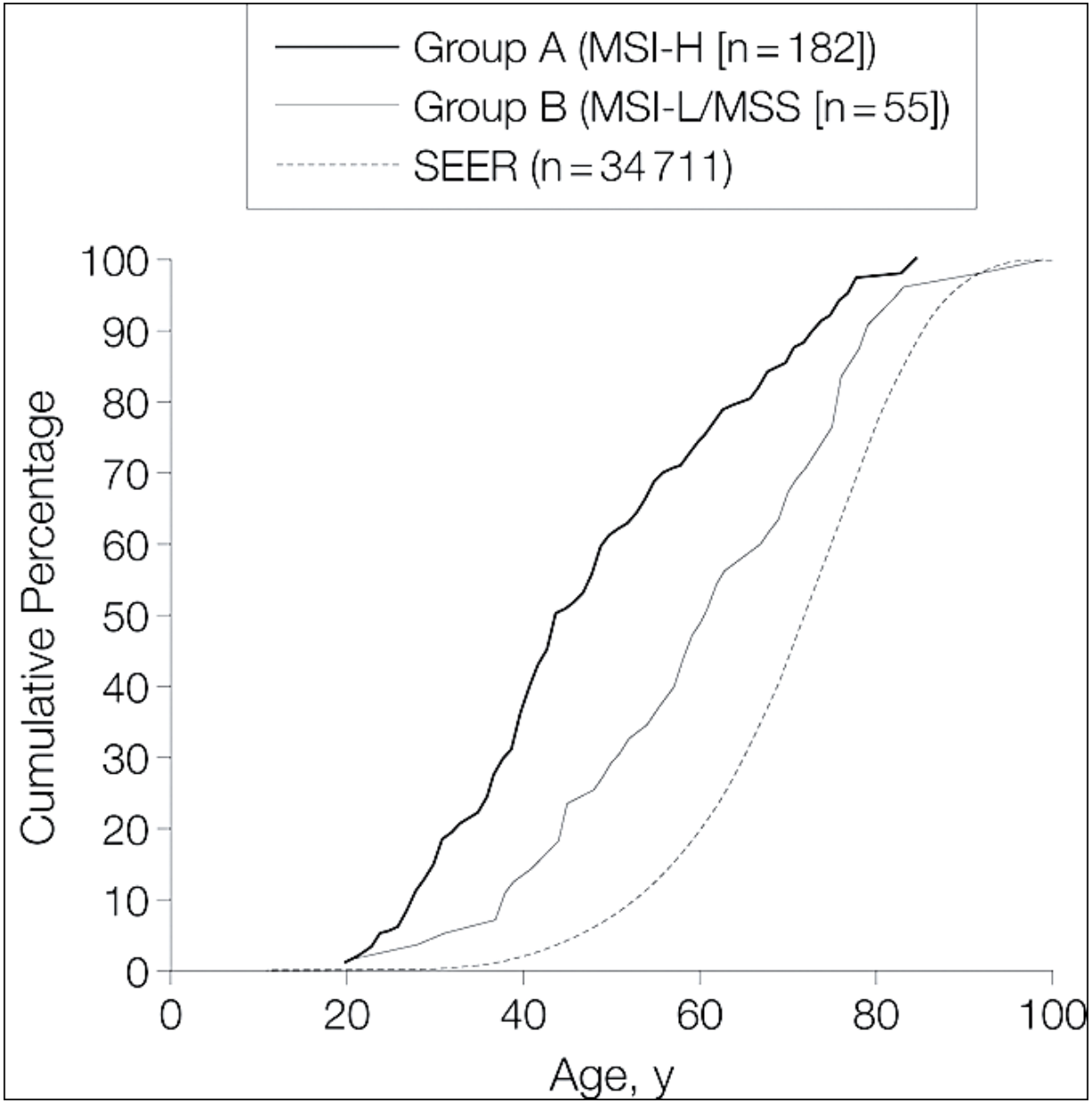
Biliary tract ca

Breast ca.

Prostate ca.



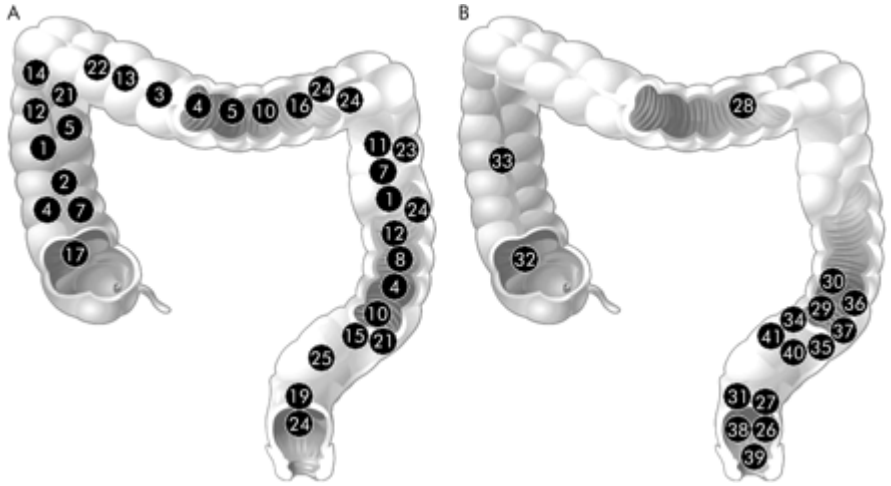

**Scott RJ et al. Hereditary Nonpolyposis Colorectal Cancer in 95 Families: Differences and Similarities between Mutation-Positive and Mutation-Negative Kindreds. *Am. J. Hum. Genet. 68:118-127 (2001)***




**Lindor NM et al. Lower Cancer Incidence in Amsterdam-I Criteria Families Without Mismatch Repair Deficiency. *JAMA 293:1979-1985 (2005)***

MMR-mutation +

**MMR-mutation –**
**MSI -**



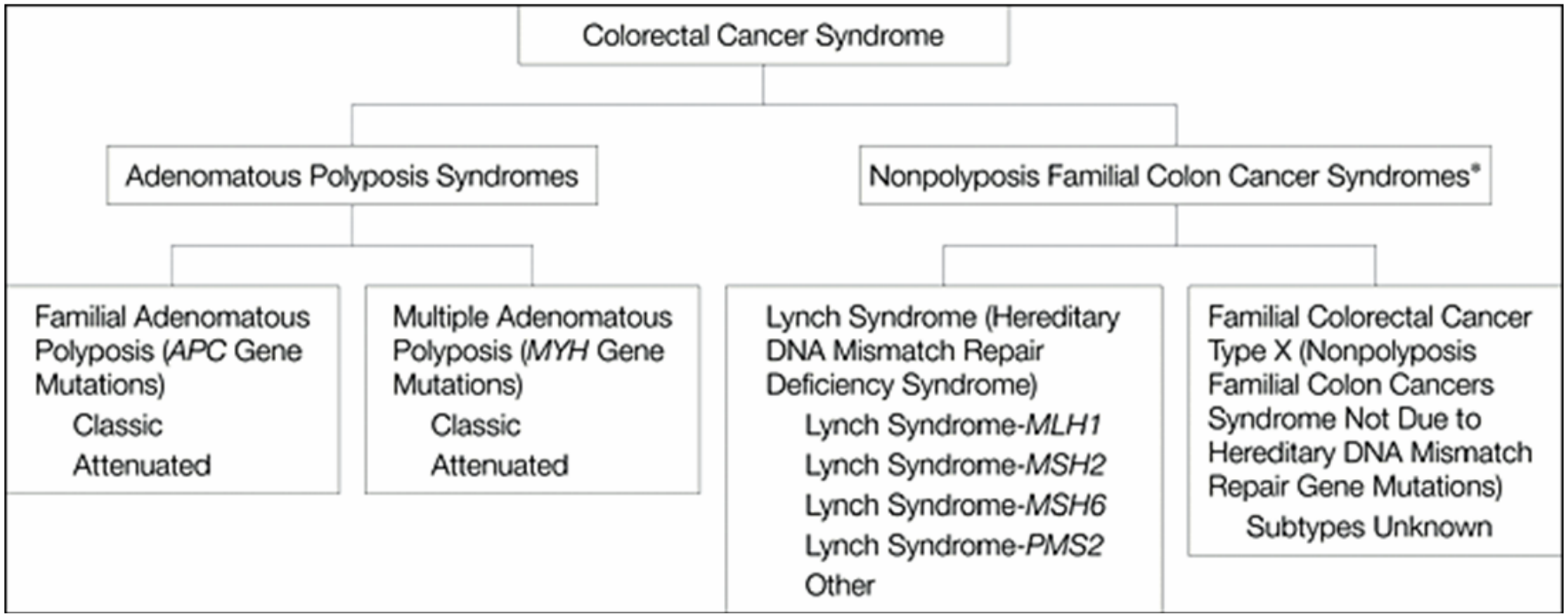

**Mueller-Koch Y et al. Hereditary non-polyposis colorectal cancer: clinical and molecular evidence for a new entity of hereditary colorectal cancer.**
***Gut 54:1733-1740 (2005)***

# CRC FAMILIARI
# MSS *vs* MSI-H

- β-catenina nucleare
- Colon sinistro
- Età media 58,6 anni
- CIN
- Stabilizzazione P53

- β-catenina membranosa
- Colon destro
- Età media 53,7 anni
- Stabilità cromosomica
- Alterazioni P53 rare

**Abdel-Rahmani WM et al. Oncogene 24:1542-1551 (2005)**




**Lindor NM et al. Lower Cancer Incidence in Amsterdam-I Criteria Families Without Mismatch Repair Deficiency. *JAMA 293:1979-1985 (2005)***

Diseases of the Colon & Rectum

# Identification and Classification of Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome): Adapting Old Concepts to Recent Advancements. Report from the Italian Association for the Study of Hereditary Colorectal Tumors Consensus Group.

**Maurizio Ponz de Leon, Lucio Bertario, Maurizio Genuardi, Giovanni Lanza, Cristina Oliani, Guglielmina Nadia Ranzani, Giovanni Battista Rossi, Liliana Varesco, Tiziana Venesio, Alessandra Viel**

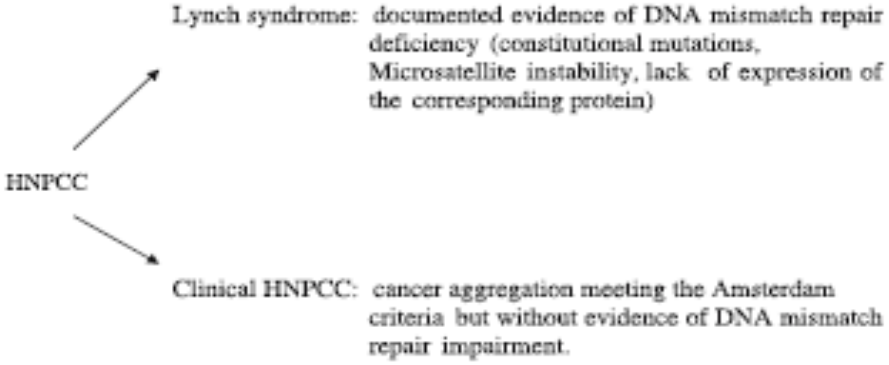
***Dis Colon Rectum 2007; 50: 2126–2134***

Table 4.
Recent Advancements of Knowledge of Hereditary Nonpolyposis Colorectal Cancer [22,23,40,43,45]

| | Hereditary Nonpolyposis Colorectal Cancer During 1990s | Hereditary Nonpolyposis Colorectal Cancer at 2007 |
|---|---|---|
| Amsterdam criteria II | Necessary for clinical diagnosis | Documented inheritance (germline mutations) even without the Amsterdam criteria |
| Survival advantage | Documented in families meeting Amsterdam criteria | Limited to families with evidence of DNA mismatch repair deficiency |
| Penetrance (lifetime risk of cancer, excluding probands) | 80–90% | 25–60% |
| Average age of cancer diagnosis among affected family members (yr) | 45–50 | 60–65 |
| Age of cancer diagnosis in the proband (yr) | Younger than aged 50 in the majority of cases | Older than aged 50 in the majority of cases |

**Table 5.**

Proposed Classification of Hereditary Nonpolyposis Colorectal Cancer



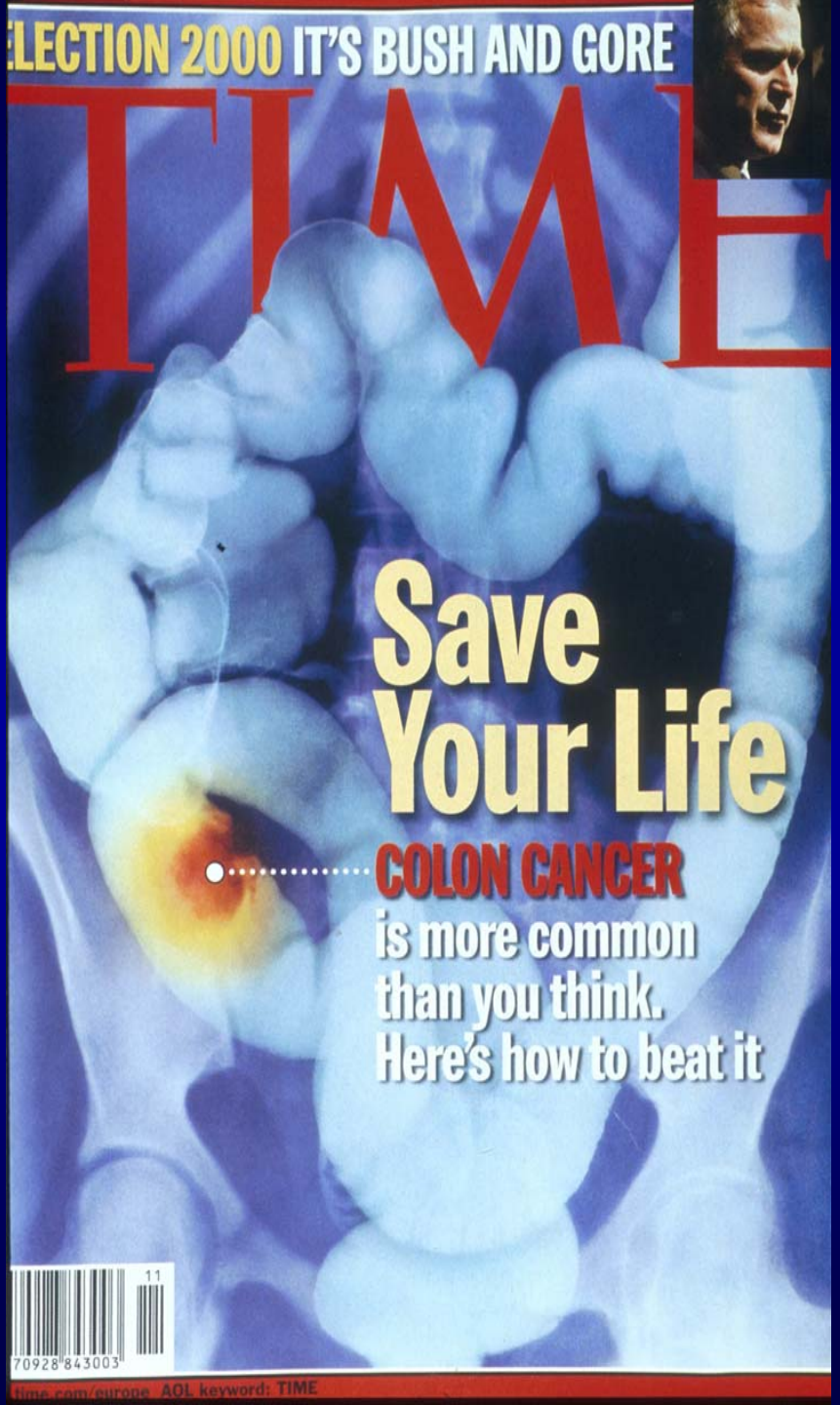

Suspected HNPCC: any family meeting at least one of the Bethesda criteria

# DIAGNOSI DI CRC EREDITARIO

- Storia familiare: CCR, altri tumori, polipi, nanifestazioni extraintestinali
- Età alla diagnosi
- Tumori singoli/multipli
- Istologia
- Polipi: quanti e di quale tipo?
- Manifestazioni extraintestinali (segni cutanei, CHRPE, desmoidi, ecc.)
- Test di screening (molecolari – MSI - e/o immunoistochimici)

# CATEGORIE DI TEST PER LA PREDISPOSIZIONE GENETICA A TUMORI E POSSIBILI ESITI

- **Test di screening mutazionale**
  - **positivo**
  - ***non informativo***
- **Test predittivo**
  - **positivo**
  - **(vero) negativo**


ELECTION 2000 IT'S BUSH AND GORE
TIME
Save Your Life
COLON CANCER
is more common than you think. Here's how to beat it
70928 843003 11
time.com/europe AOL keyword: TIME