Genetics and genomics of colorectal cancer

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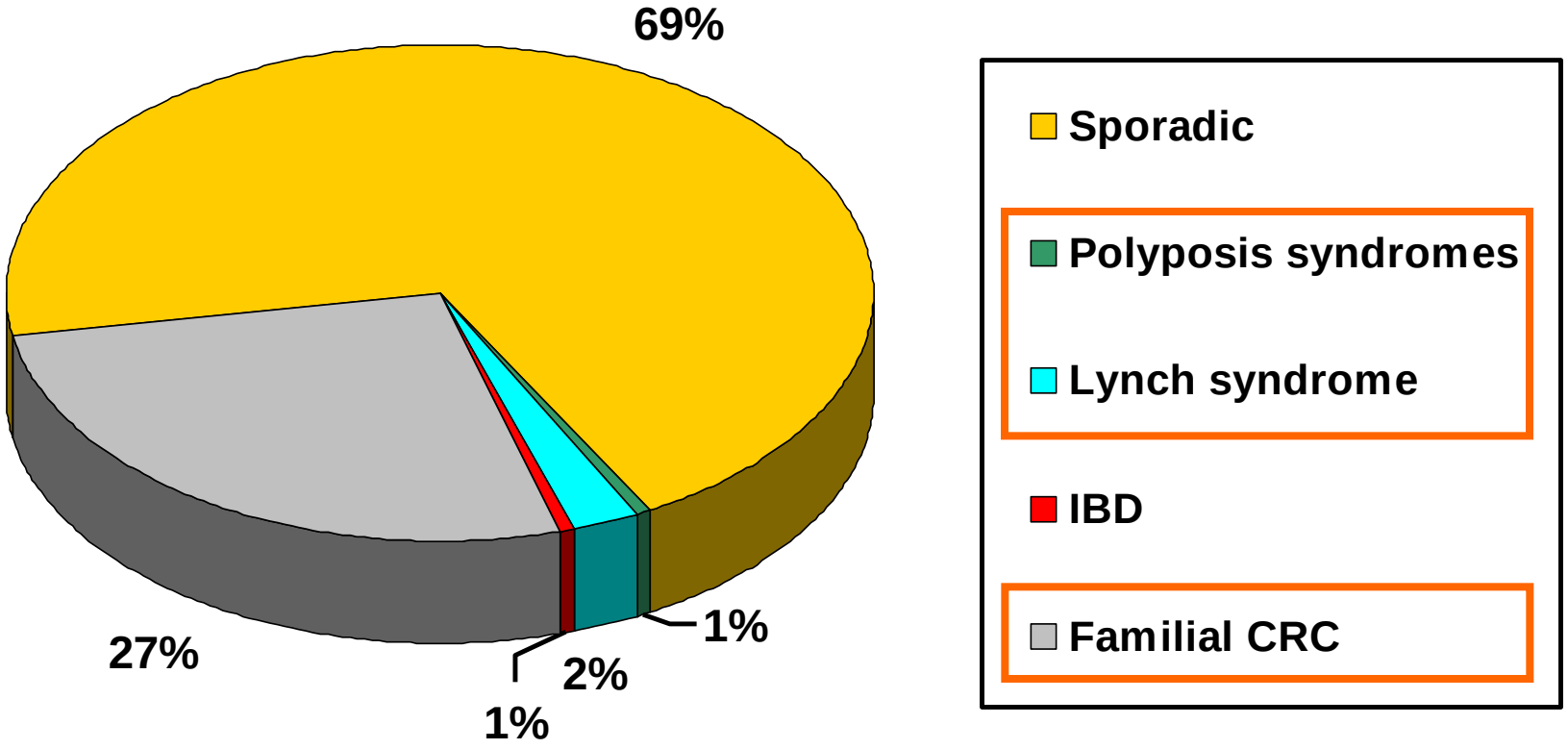
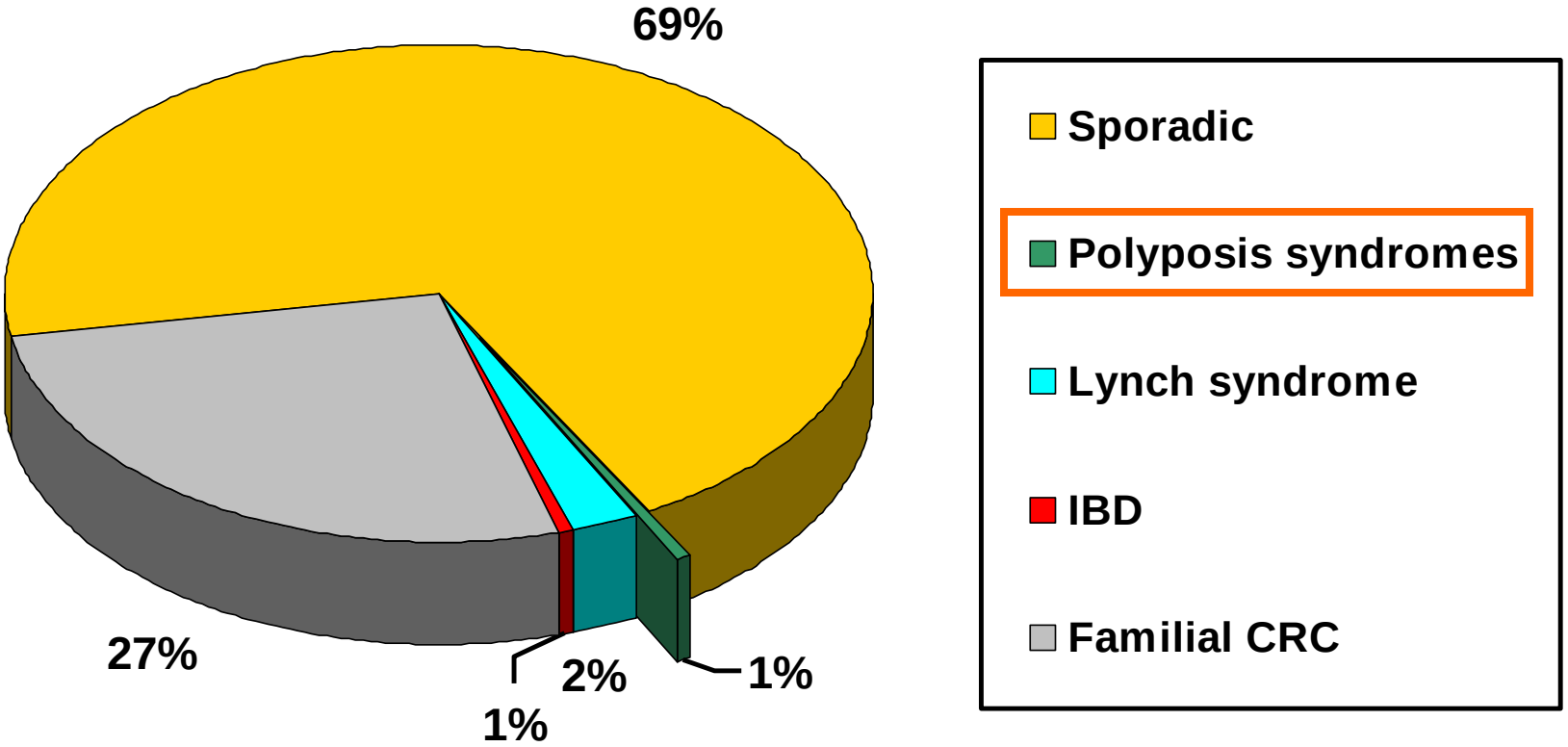
Colorectal cancer: epidemiology



Piñol *et al. Eur J Gastroent Hepatol 2004*

Colorectal cancer: epidemiology

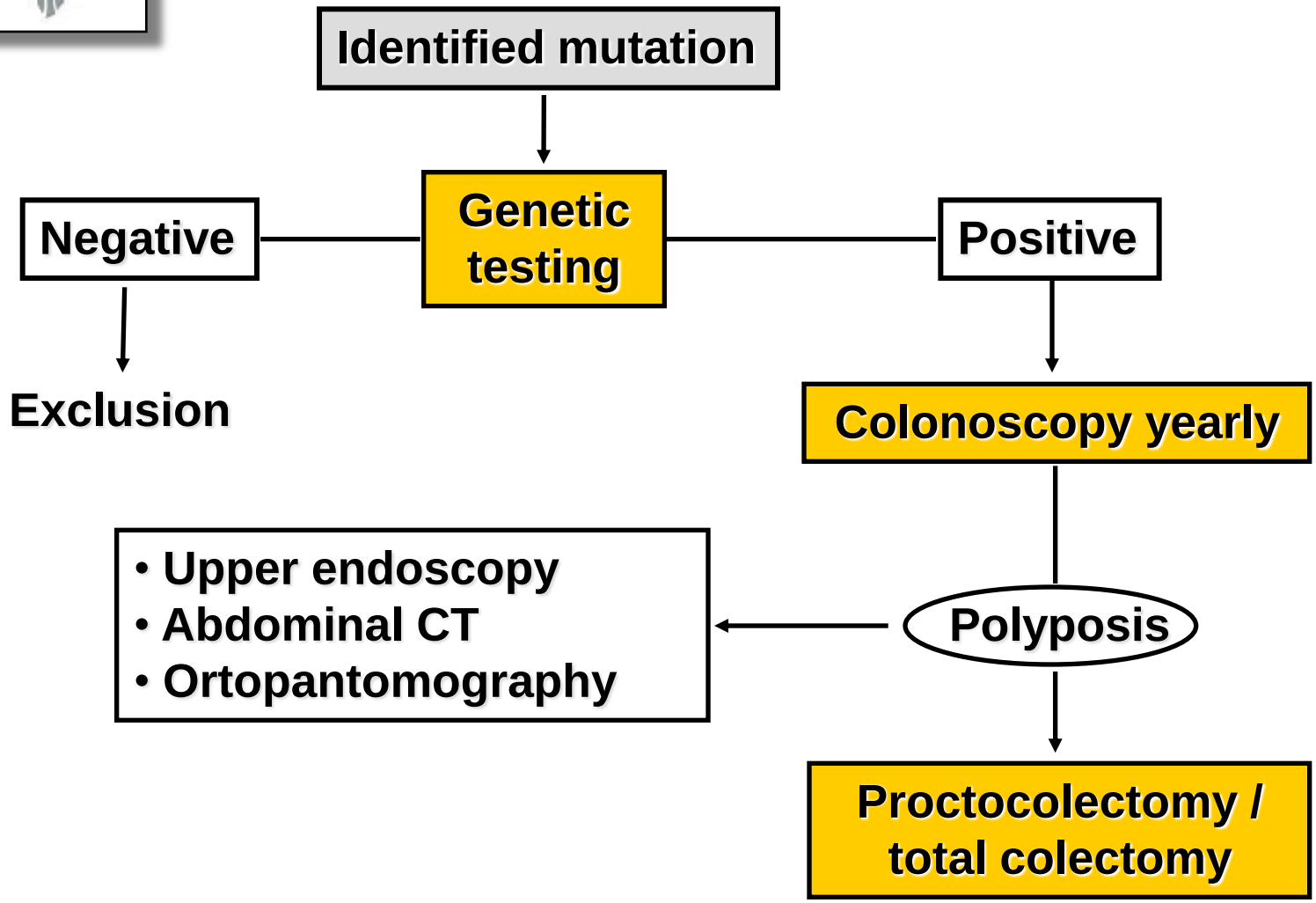


Piñol *et al. Eur J Gastroent Hepatol 2004*

Familial adenomatous polyposis

- Autosomal dominant disorder
- One in 15,000 live births
- More than 100 polyps
- Diffuse distribution
- Onset: 15-20 year-old
- Extracolonic manifestations: upper GI adenomas, congenital hypertrophy of the retinal pigment epithelium, osteomas, and dental anomalies (Gardner syndrome), brain tumor (Turcot syndrome)
- Germline *APC* gene mutations
- Overall CRC risk ~100% by age 40-50

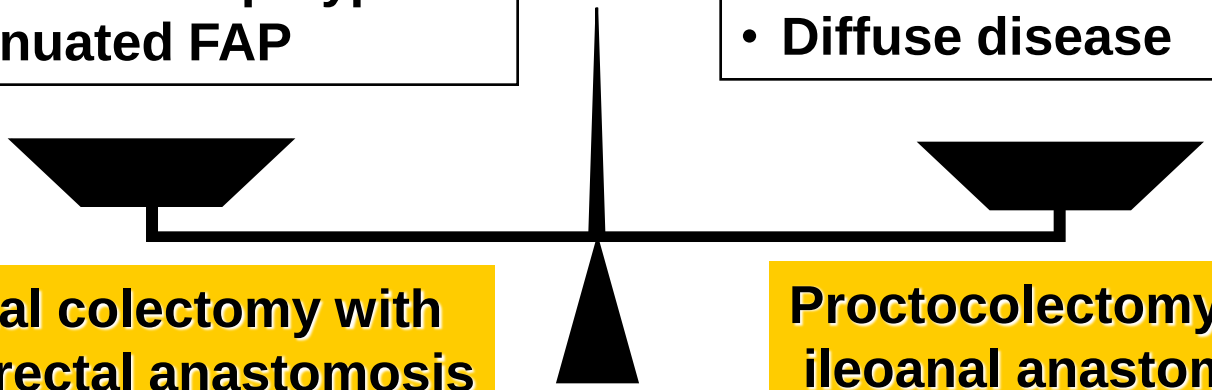
FAP: screening



Surgical treatment in FAP patients

- Mild familial phenotype and no rectal polyps
- Attenuated FAP

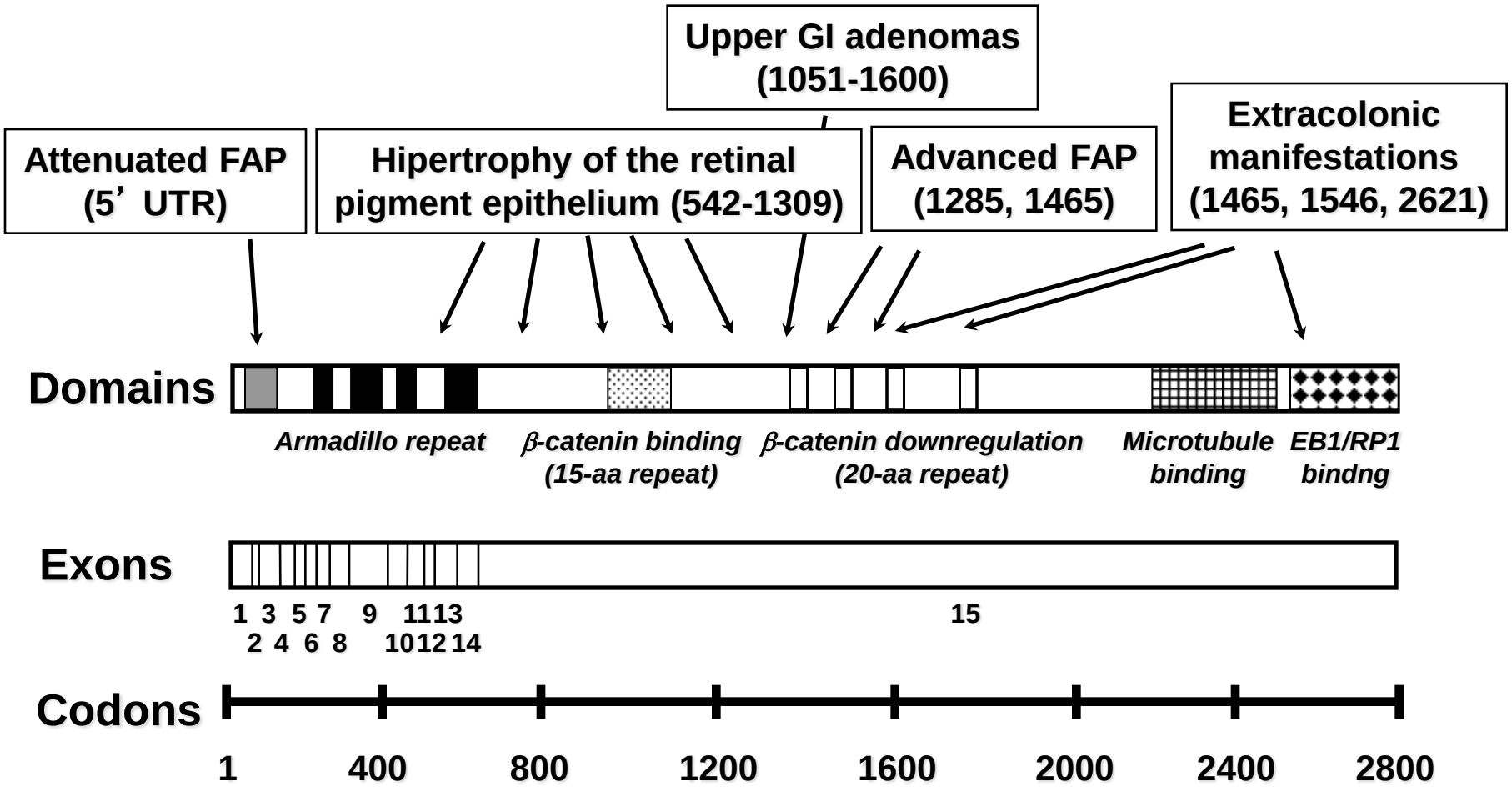
- Severe familial phenotype
- Diffuse disease



Total colectomy with ileorectal anastomosis

Proctocolectomy with ileoanal anastomosis

FAP: genotype-phenotype correlation



Surgical treatment in FAP patients

- Codon 0 - 200
- Codon >1500

- Mild familial phenotype and no rectal polyps
- Attenuated FAP

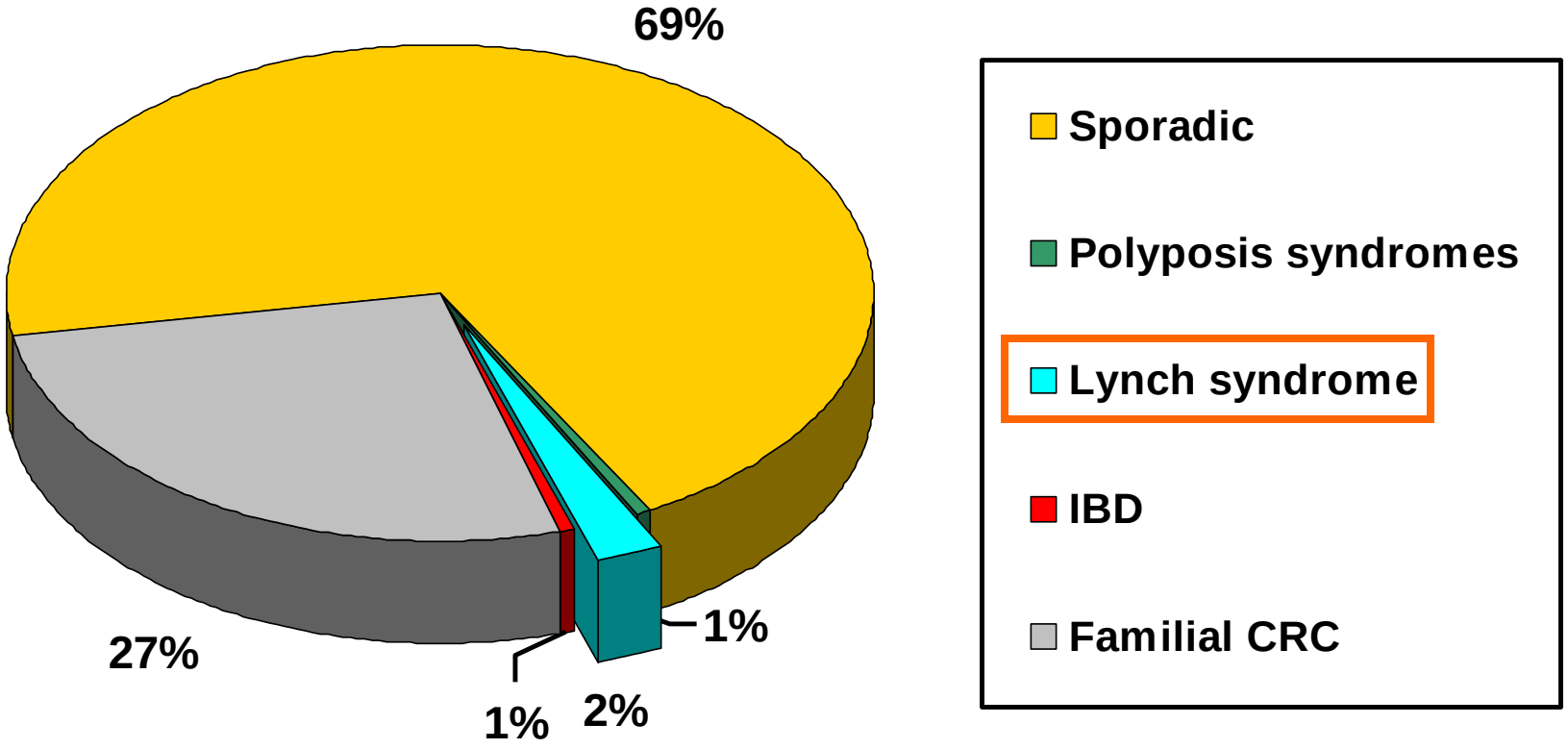
Total colectomy with ileorectal anastomosis

- Codon 200 - 1500

- Severe familial phenotype
- Diffuse disease

Proctocolectomy with ileoanal anastomosis

Colorectal cancer: epidemiology



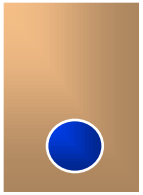
Piñol *et al. Eur J Gastroent Hepatol 2004*

Lynch syndrome
(hereditary non-polyposis colorectal cancer, HNPCC)

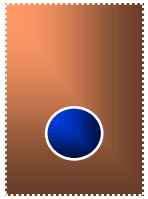
- Autosomal dominant disorder
- Early onset CRC: <45 years of age
- Location in proximal colon
- Histology: undifferentiated, signet-ring cell type
- Multiple CRC (synchronous, metachronous)
- Multiple neoplasms (endometrial, gastric, small bowel, renal, ovarian, and skin)
- Amsterdam criteria: 3 relatives with CRC and/or HNPCC-associated neoplasia, 2 successive generations, and 1 diagnosed before age 50

Lynch syndrome: pathogenesis

MSH2, MLH1, MSH6, PMS2
(germline mutation)



Normal mucosa

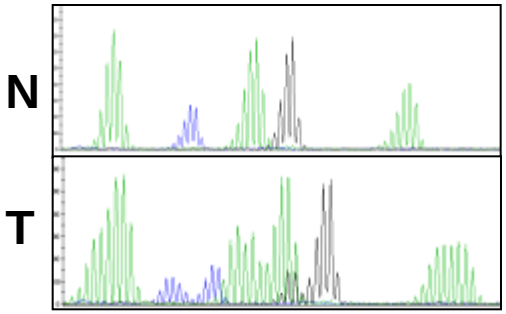


Second hit

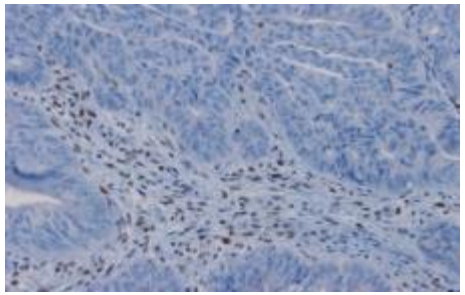
TGF-β-RII,
BAX, IGFIIR

Carcinoma

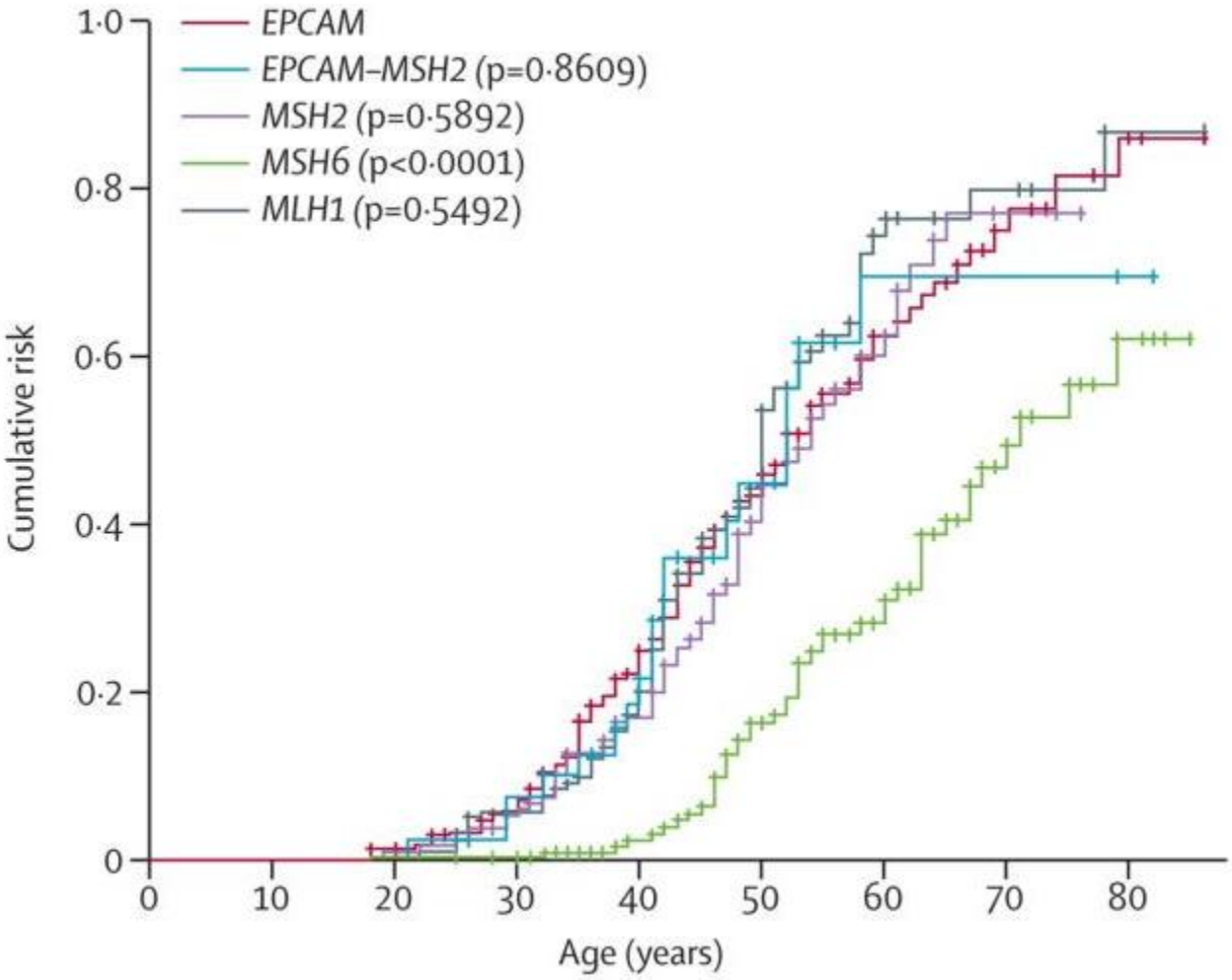
Microsatellite instability



Loss of protein expression

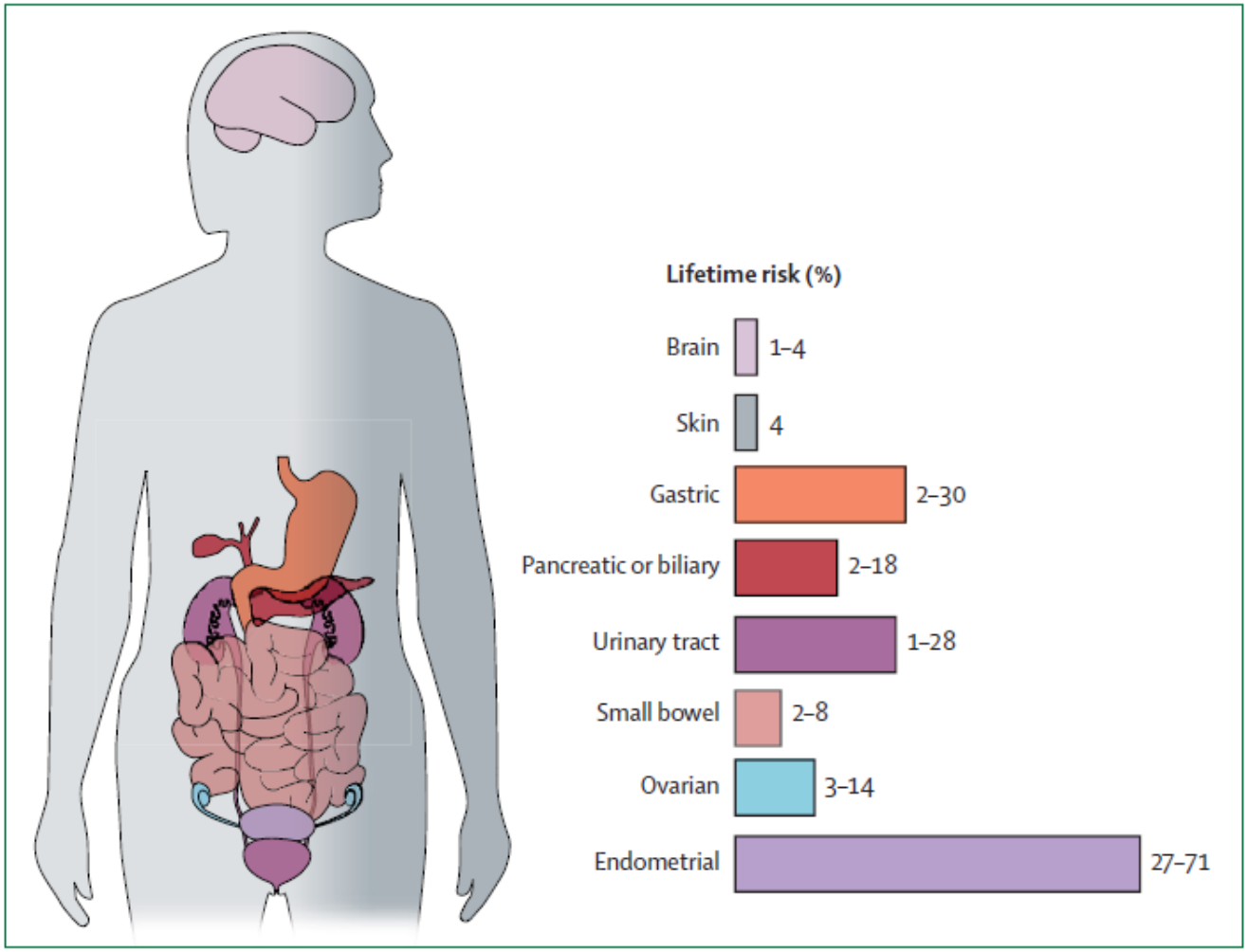


Cumulative risk of colorectal cancer in MMR gene mutation carriers



Kempers *et al*. Lancet Oncol 2011

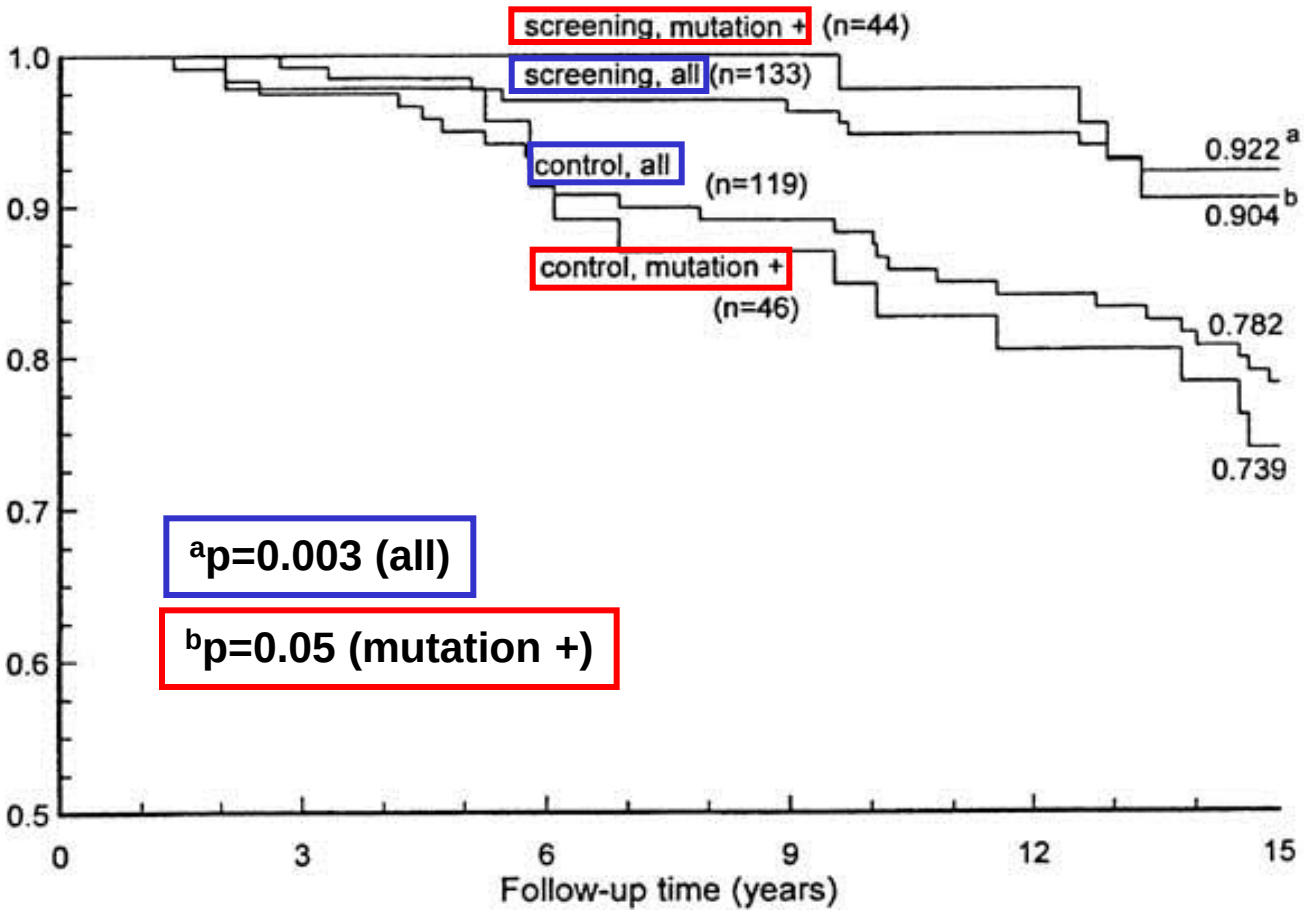
Lifetime risk of extracolonic tumors



Koornstra *et al*. Lancet Oncol 2009

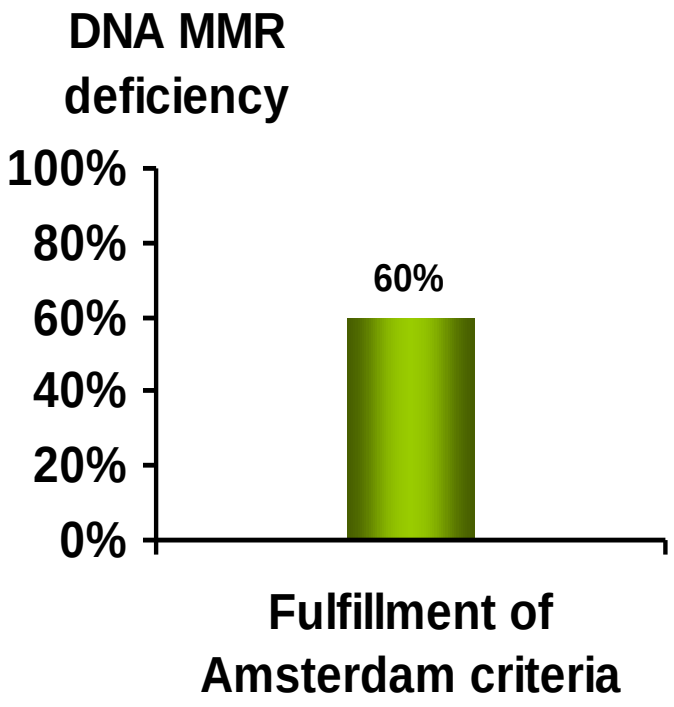
Lynch syndrome screening

Probability of overall survival



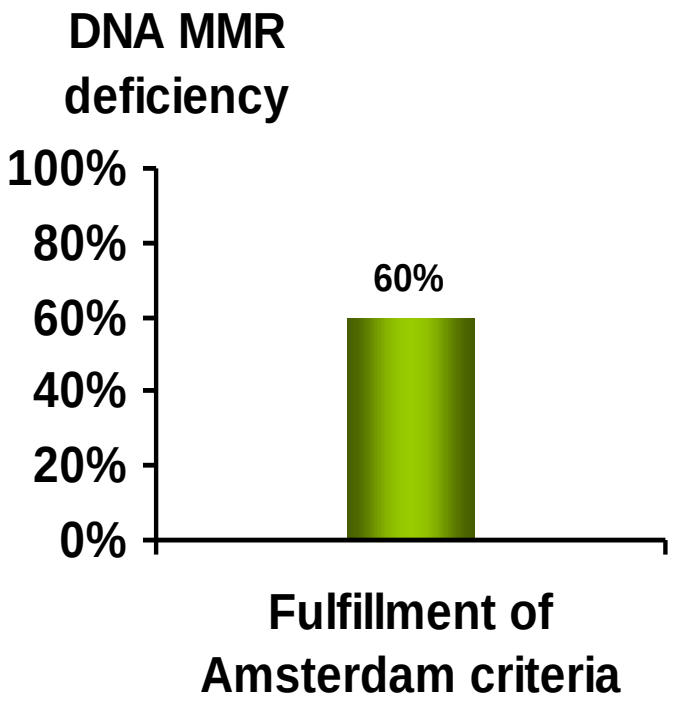
Järvinen *et al. Gastroenterology 2000*

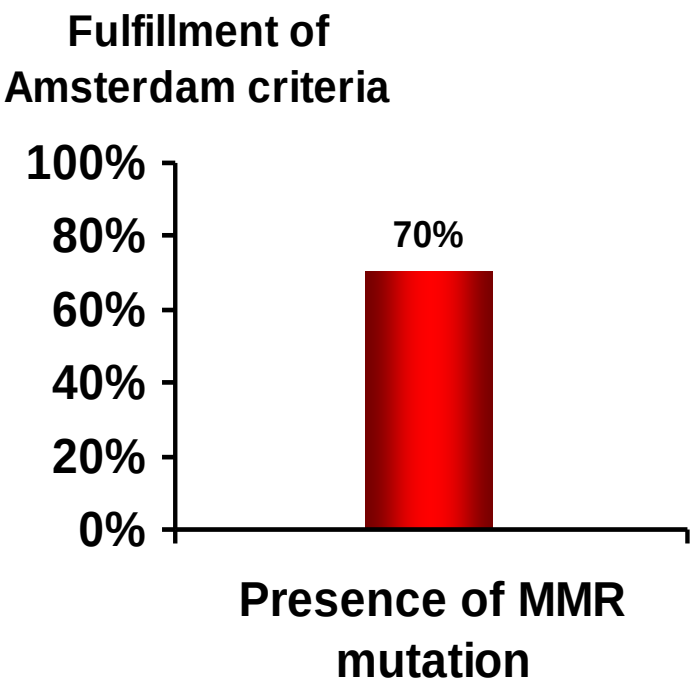
HNPCC identification: limitations



Lindor *et al.* JAMA 2005
Llor *et al.* Clin Cancer Res 2005

HNPCC identification: limitations





Lindor *et al.* JAMA 2005
Llor *et al.* Clin Cancer Res 2005

Aaltonen *et al.* N Engl J Med 1998

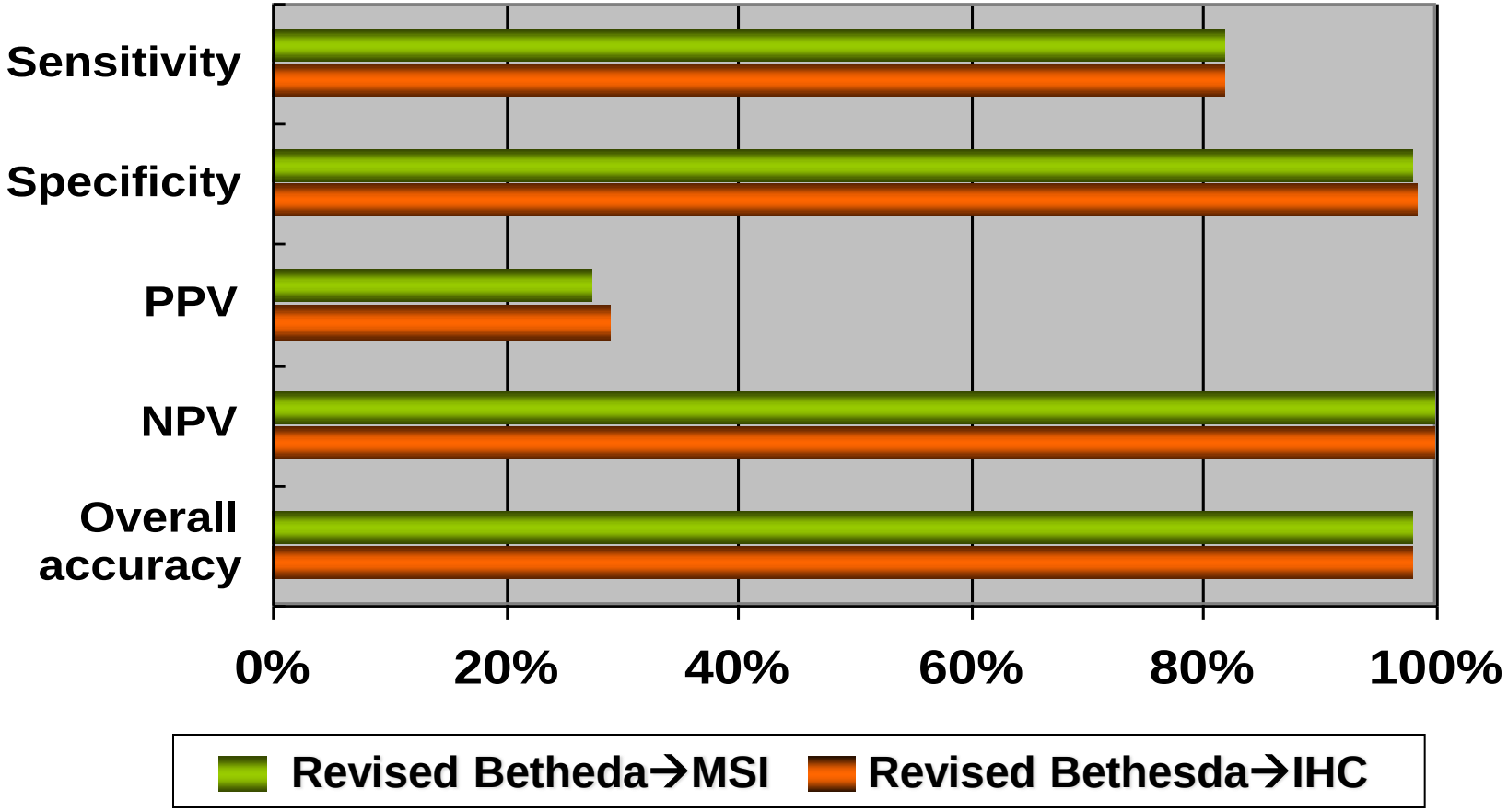
Identification of HNPCC patients: revised Bethesda guidelines

Identification of individuals who should be tested for MSI analysis:

- **CRC diagnosed <50 yrs.**
- **Synchronous CRC, metachronous CRC, or other HNPCC-related cancer (CRC, endometrial, ovarian, gastric, pancreas, biliary tract, small bowel, ureter or renal pelvis, brain), regardless of age**
- **CRC with presence of tumor infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern, diagnosed <60 yrs.**
- **One or more first-degree relatives with an HNPCC-related tumor diagnosed <50 yrs.**
- **Two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age.**

Umar *et al.* J Natl Cancer Inst 2004

Performance of MSI *vs.* IHC screening for the identification of Lynch syndrome



Piñol *et al.* JAMA 2005

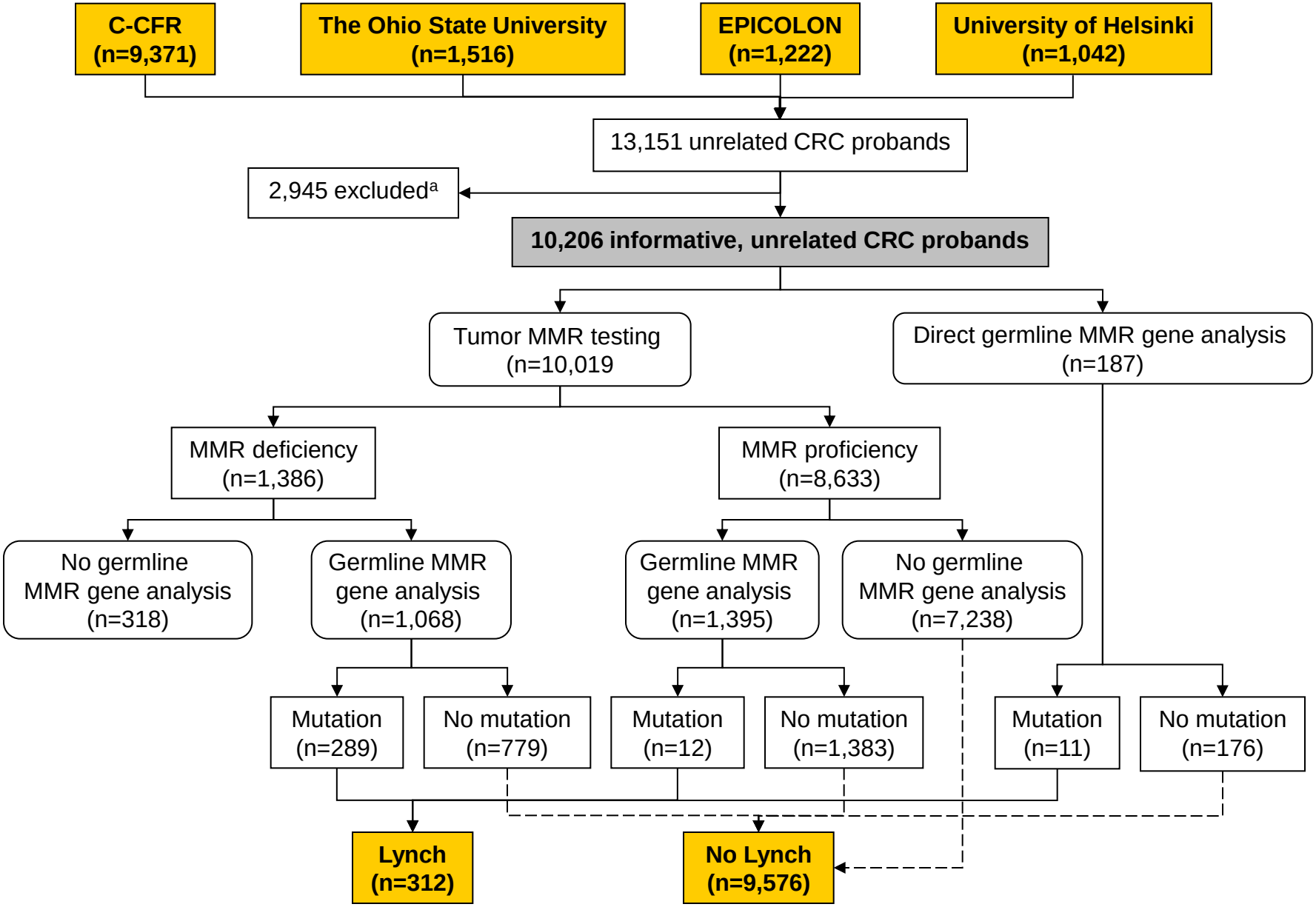
Jerusalem recommendations

Meeting Summary

Report From the Jerusalem Workshop on Lynch Syndrome-Hereditary Nonpolyposis Colorectal Cancer

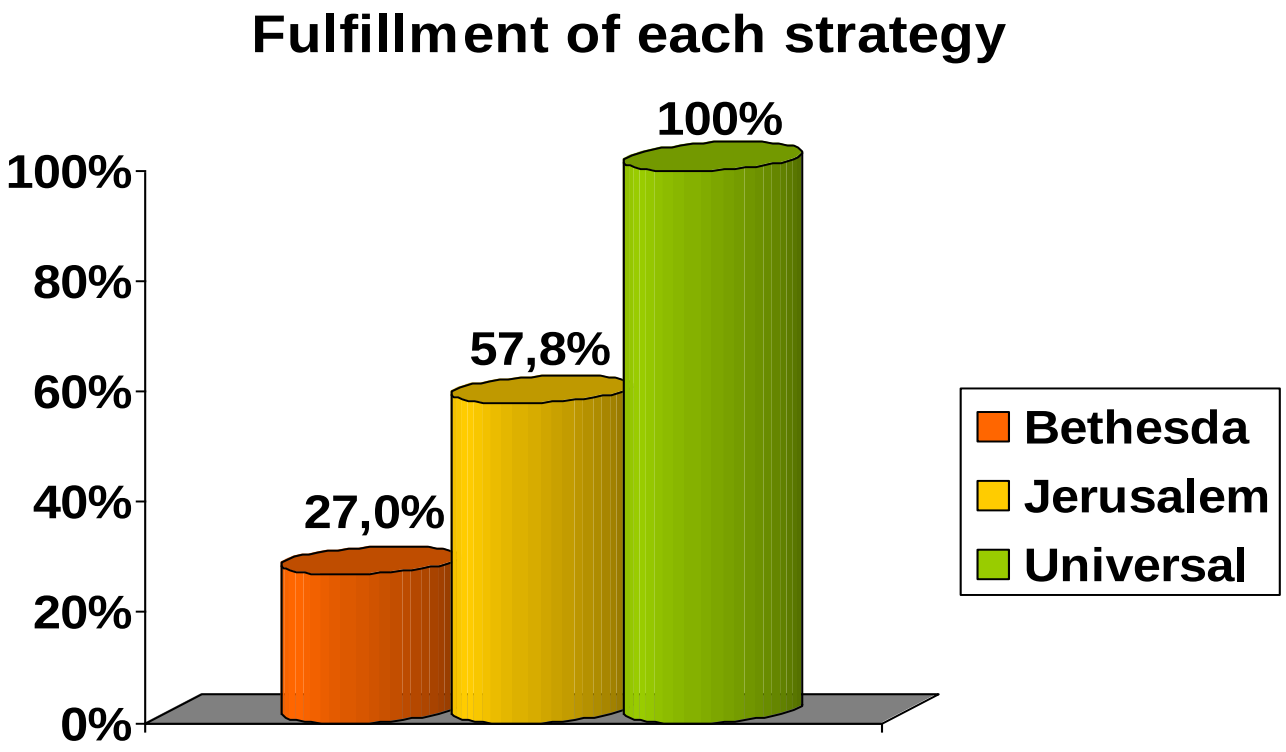
1. **All patients diagnosed with colorectal cancer before the age of 70 years should be submitted to MMR testing.**

2. **MMR testing can be done by immunostaining and/or MSI analysis.**



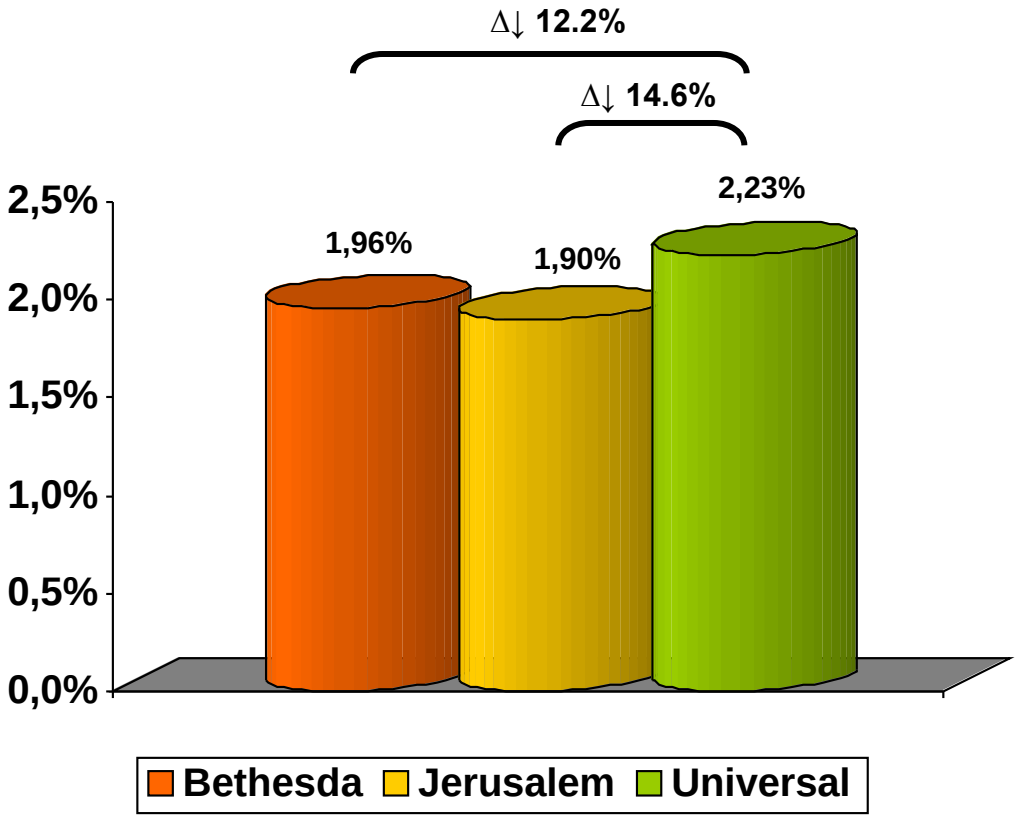
Moreira *et al.* JAMA 2012

Strategies for the identification of Lynch syndrome



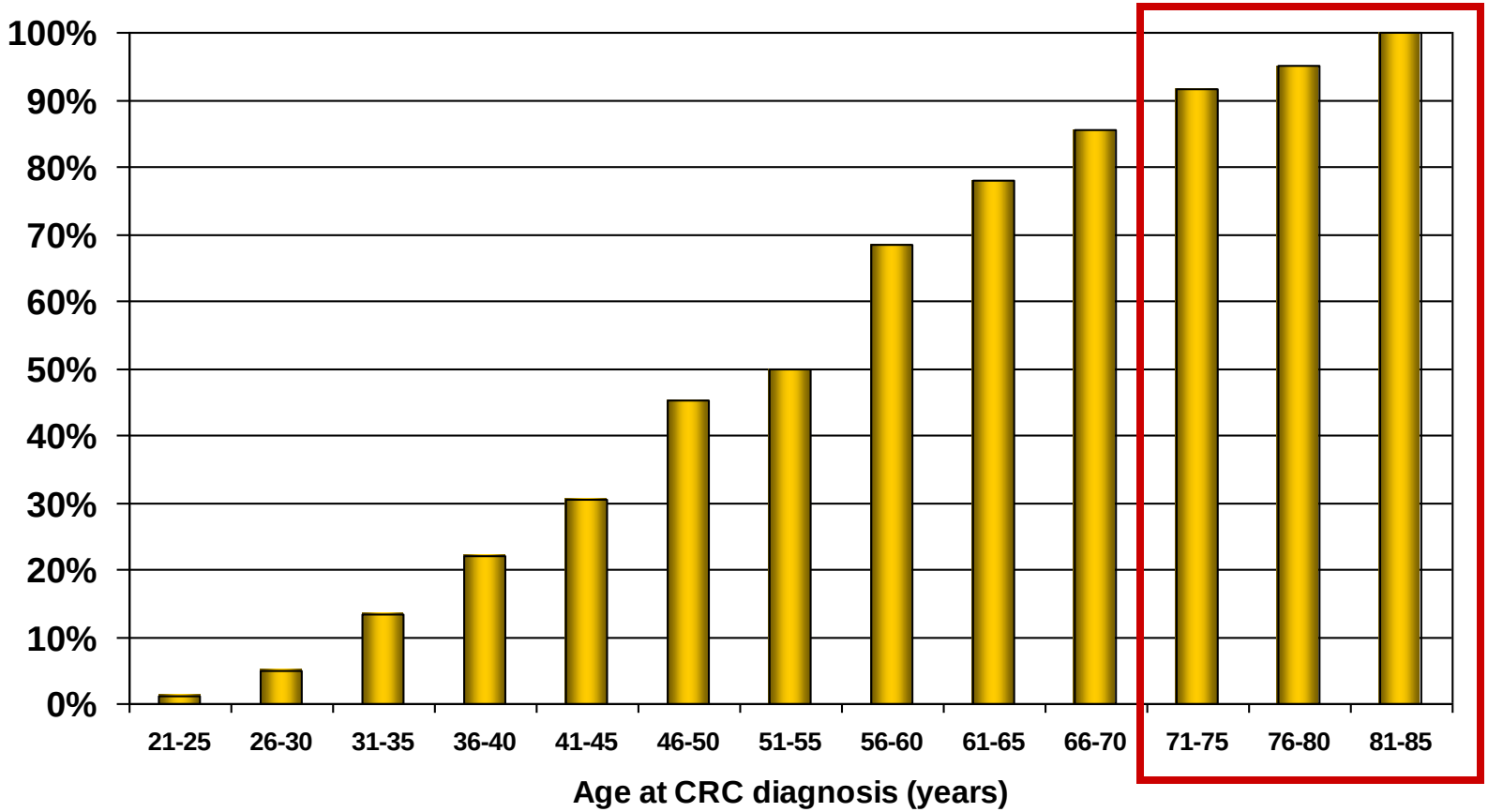
Moreira *et al.* JAMA 2012

Diagnostic yield of strategies for Lynch syndrome identification



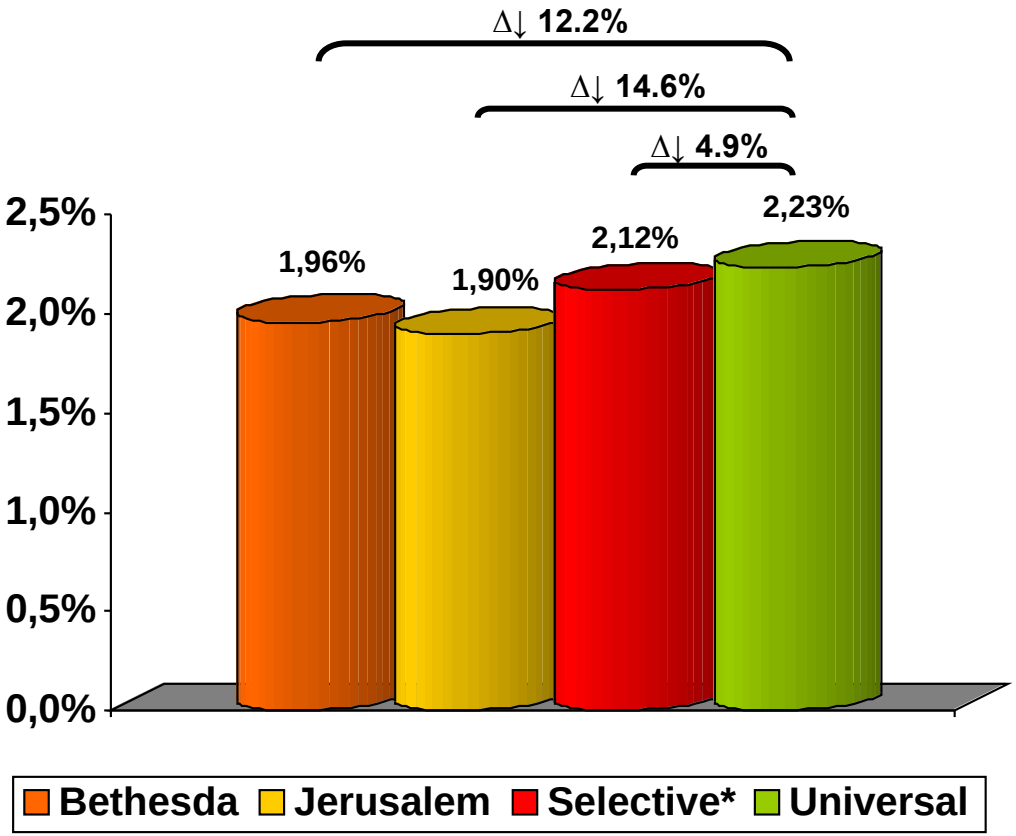
Moreira *et al.* JAMA 2012

Cumulative distribution of MMR gene mutations according to the age at CRC diagnosis



Moreira *et al.* JAMA 2012

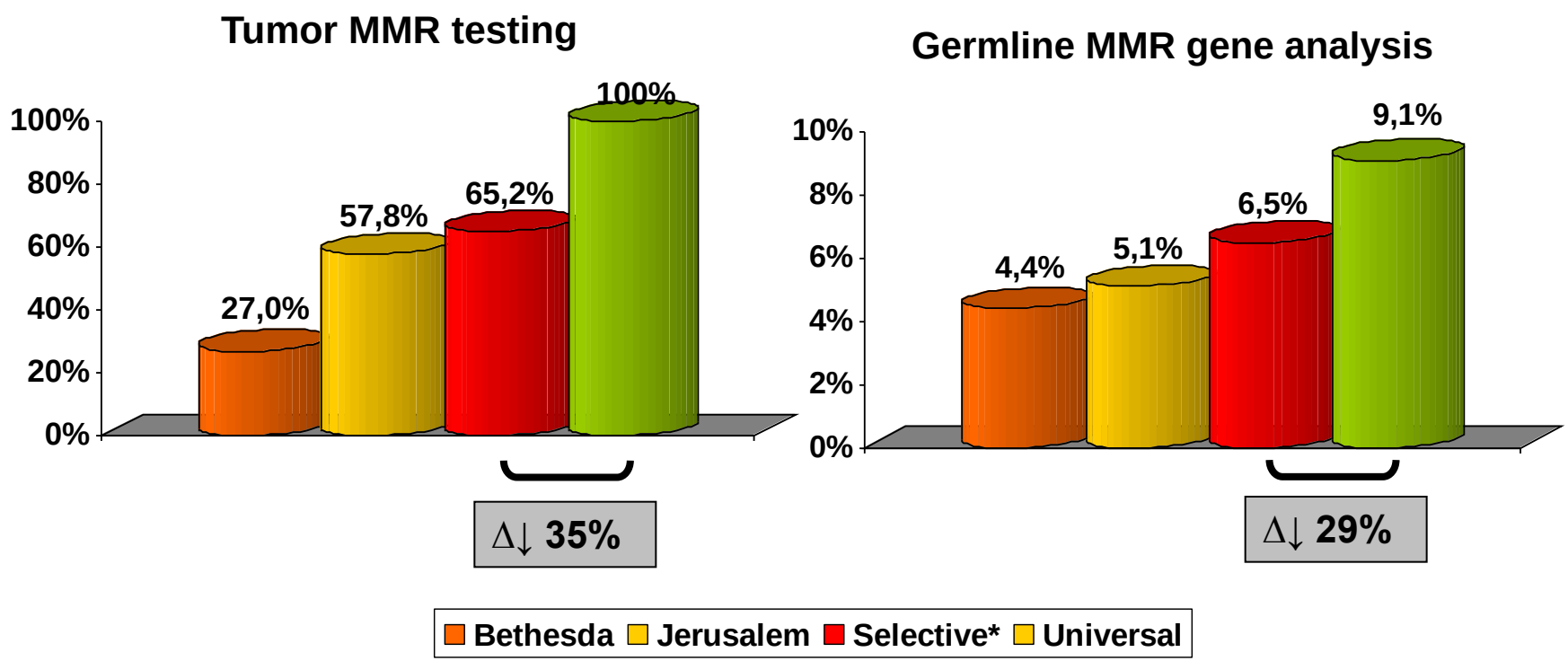
Diagnostic yield of strategies for Lynch syndrome identification



*Selective strategy: tumor MMR testing of CRC patients diagnosed ≤70 years-old, and in older patients fulfilling the Bethesda guidelines

Moreira *et al.* JAMA 2012

Strategies for the identification of Lynch syndrome



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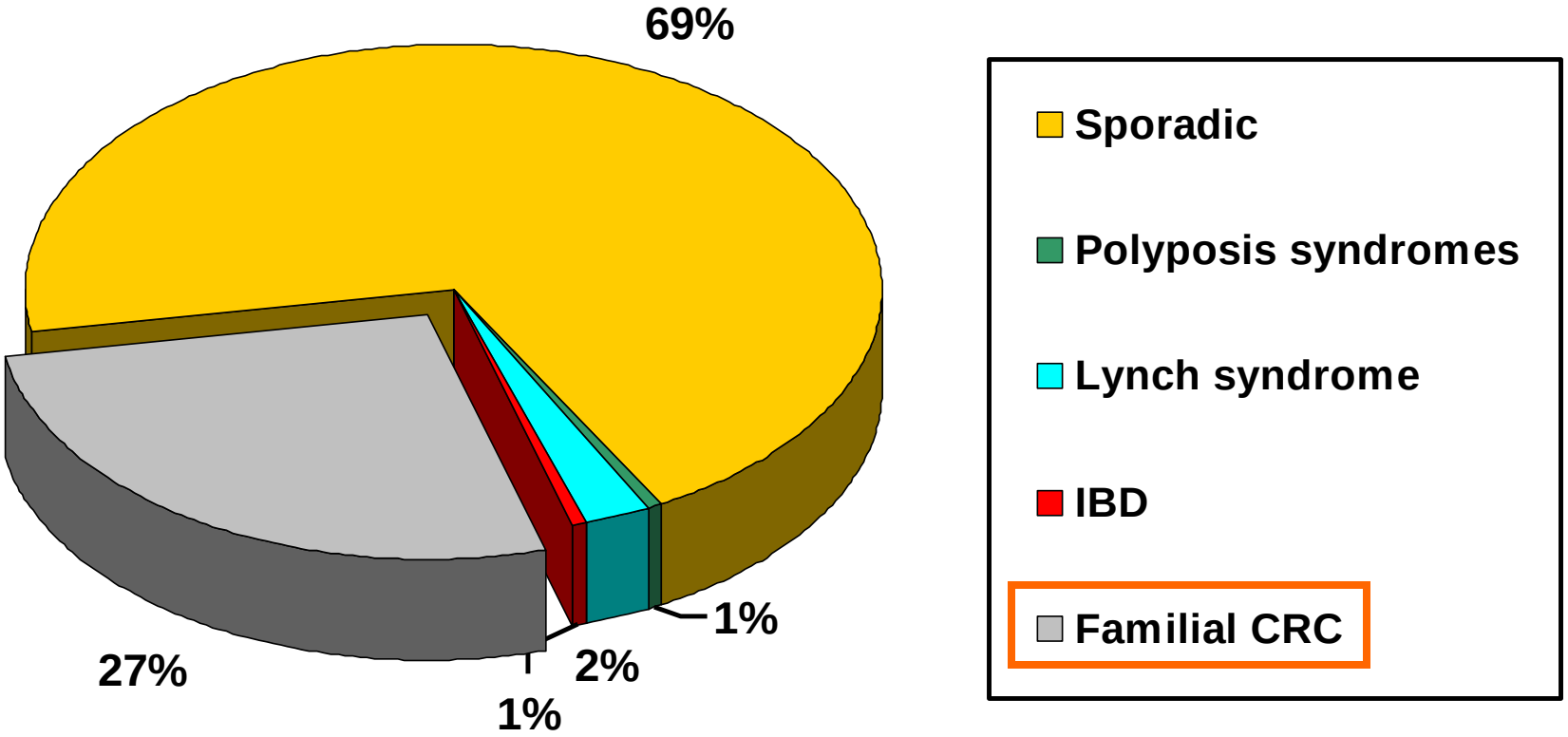
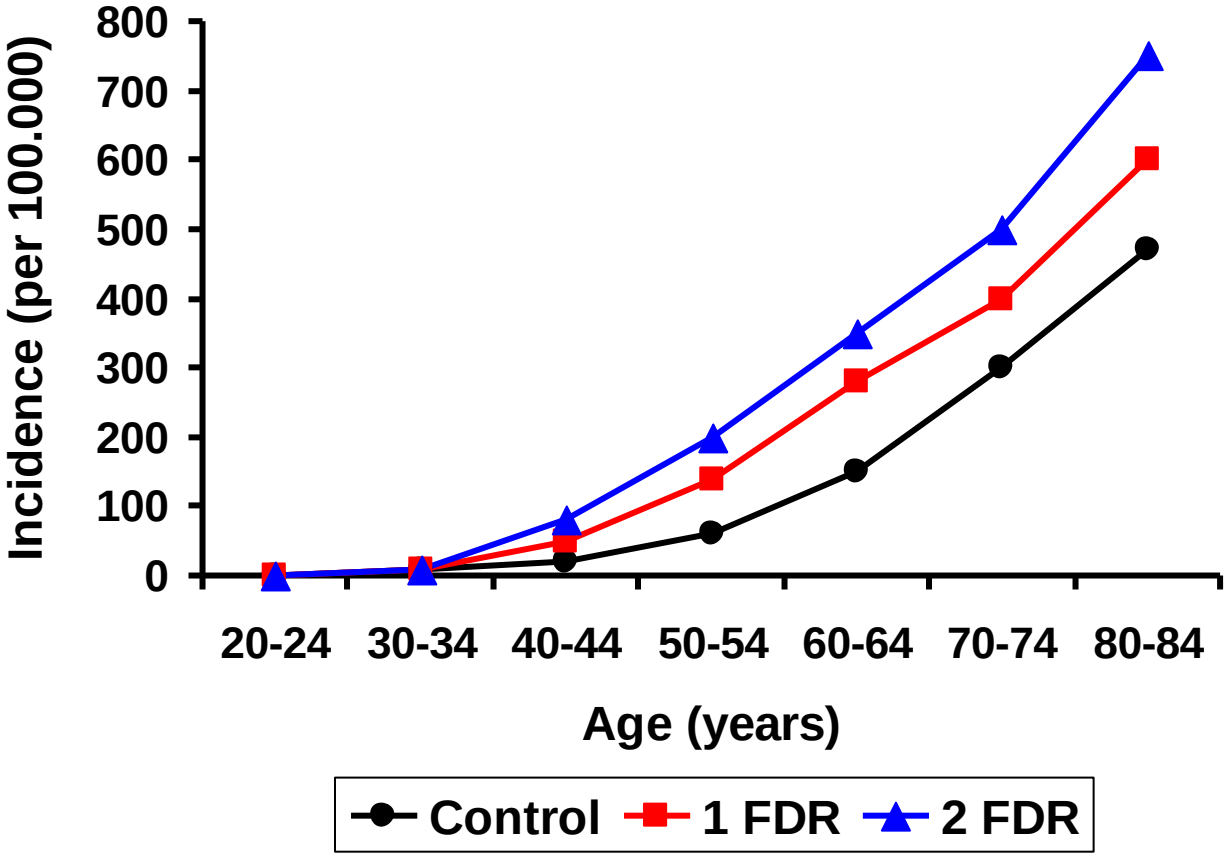


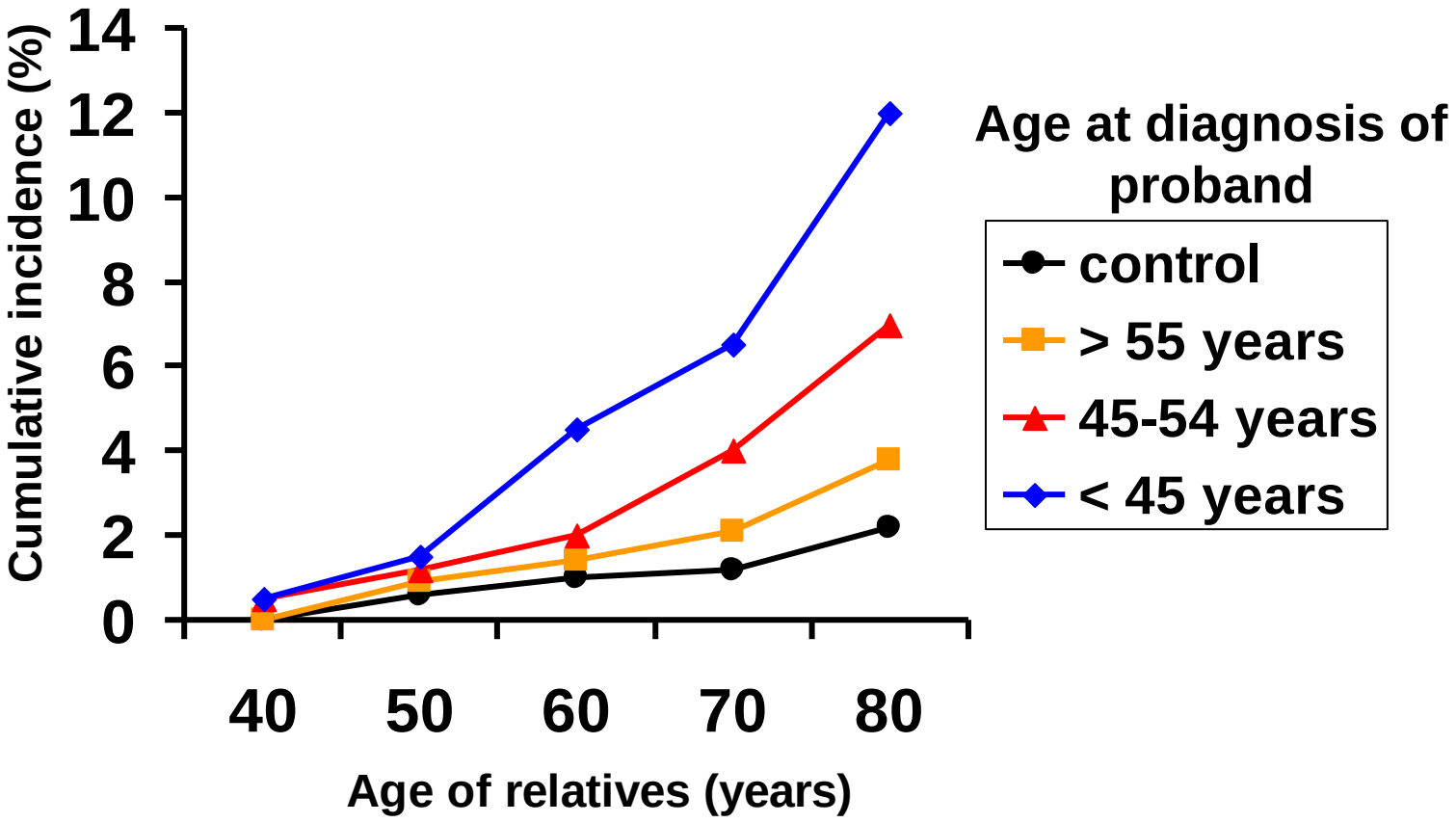
Piñol *et al. Eur J Gastroent Hepatol 2004*

Incidence of CRC according to their family history



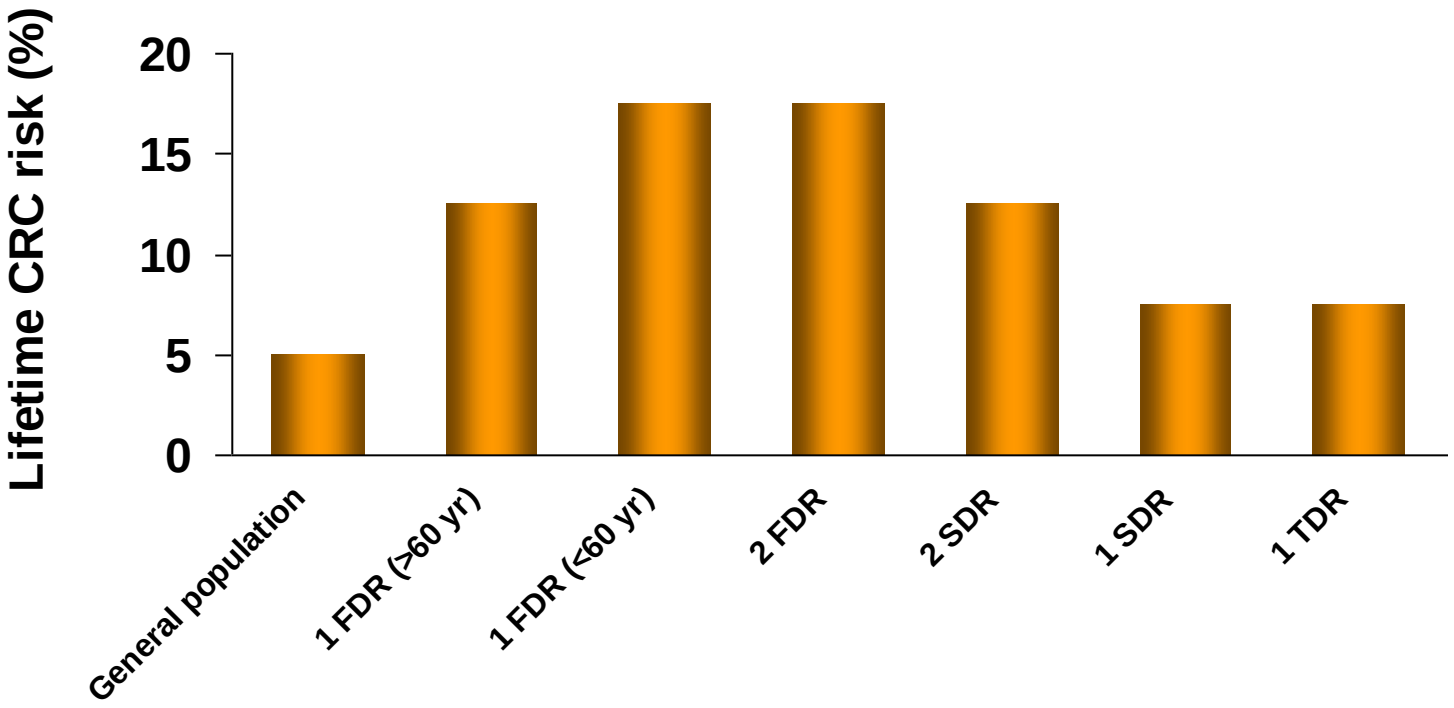
Fuchs *et al.* NEJM 1994

Incidence of CRC in relatives of patients with CRC



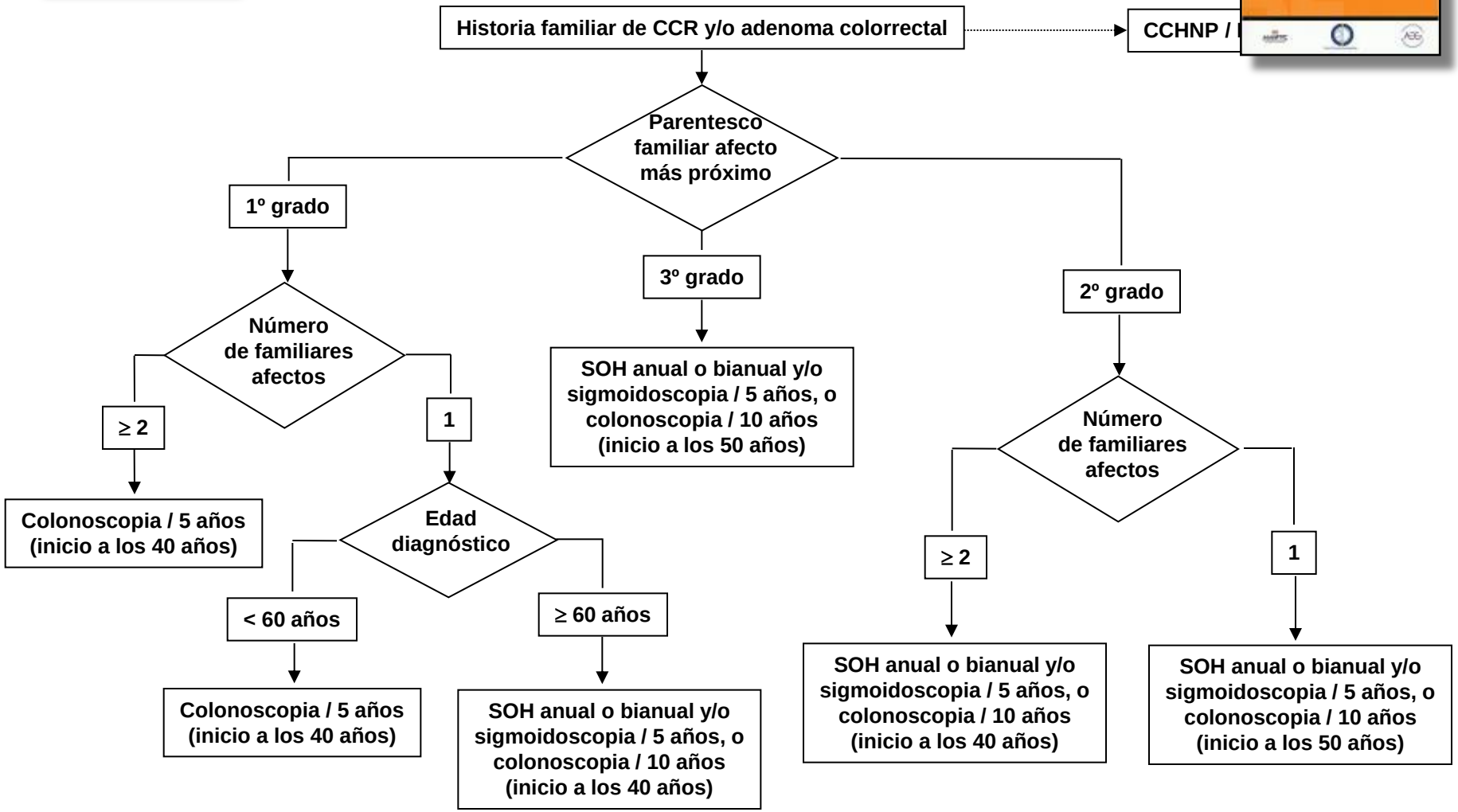
St. John *et al.* Ann Intern Med 1993

Colorectal cancer family risk



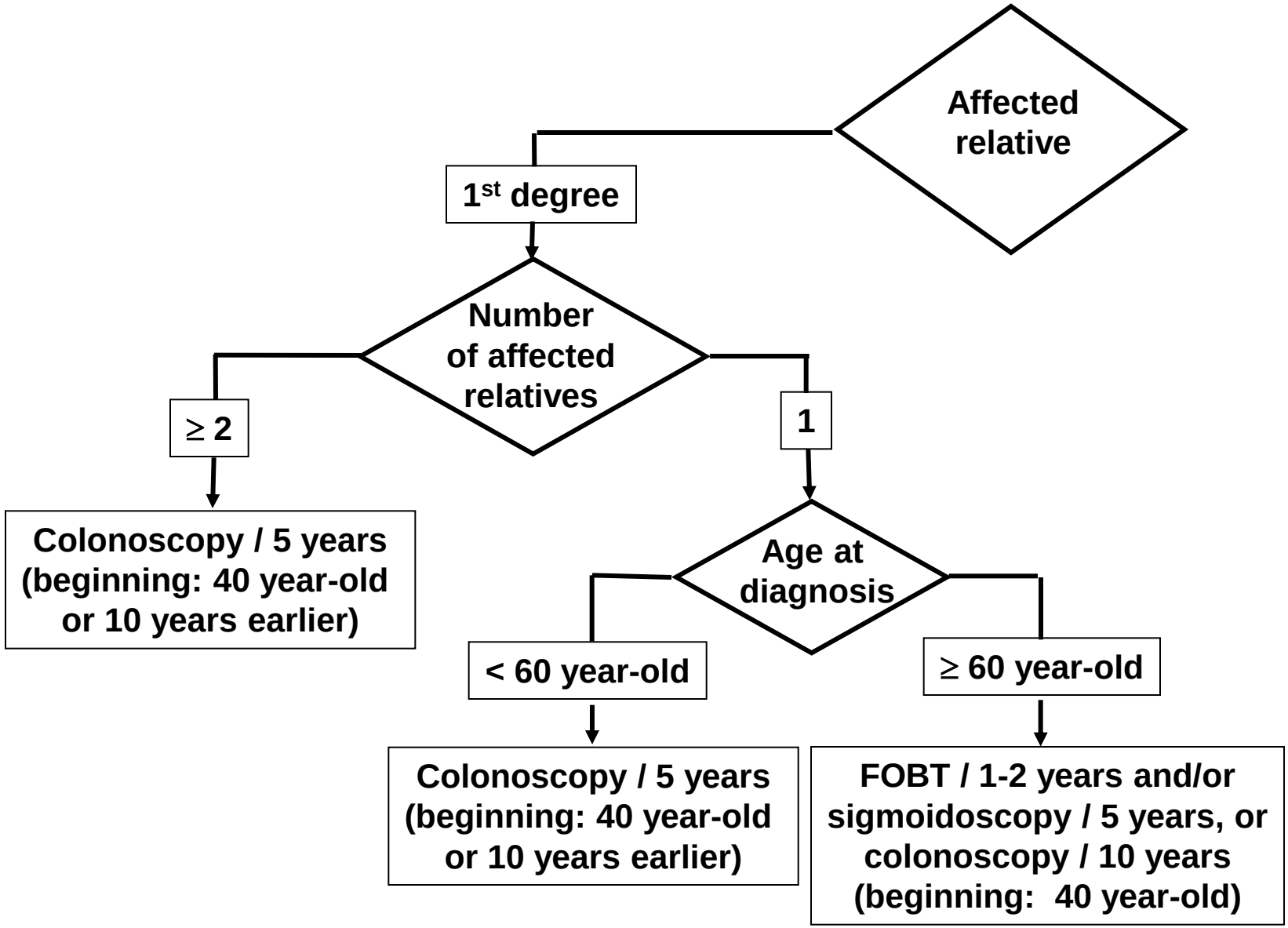
FDR: 1st degree relative
SDR: 2nd degree relative
TDR: 3rd degree relative

Familial CRC screening



Castells *et al*. Gastroent Hepatol 2009

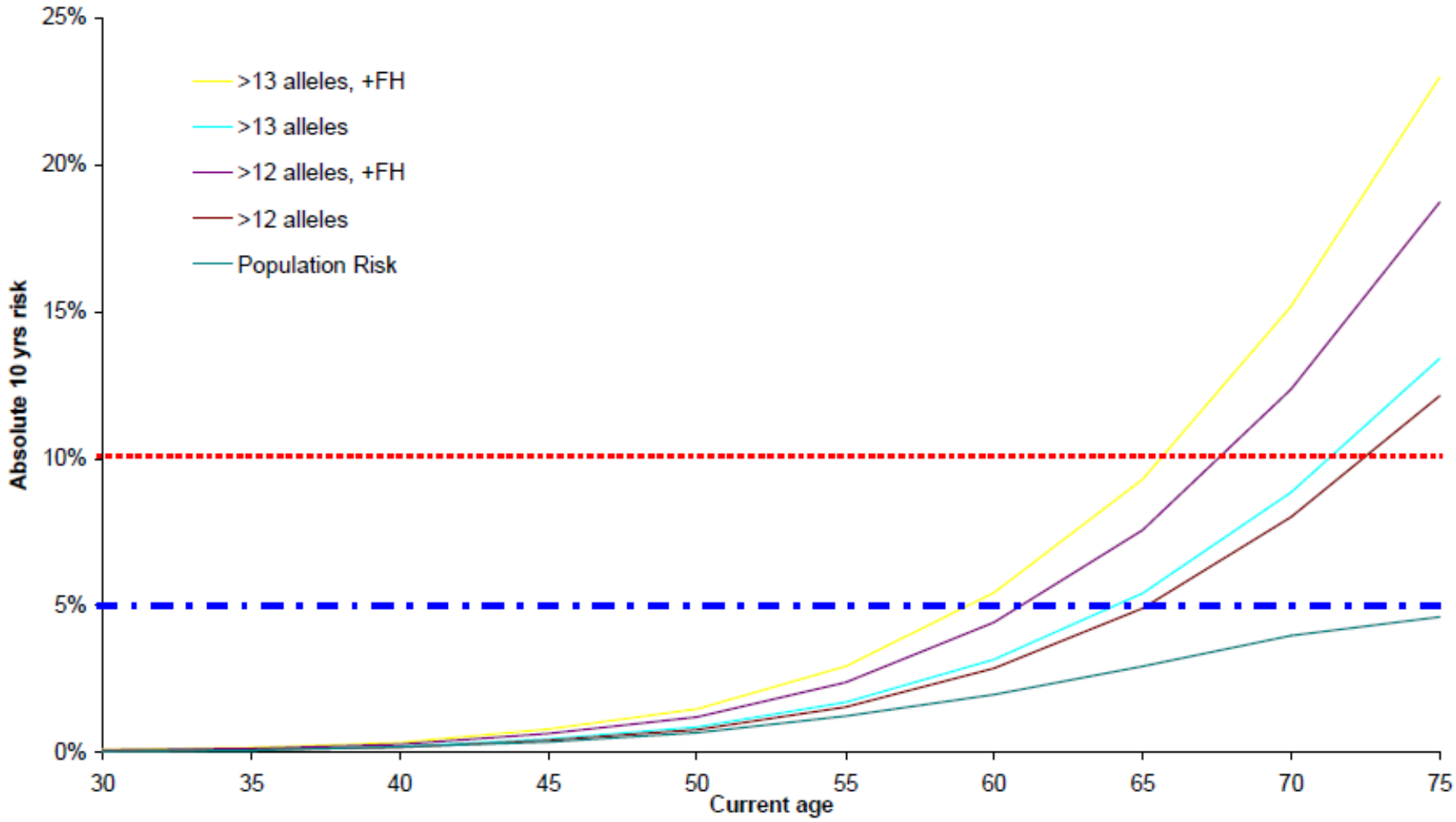
Familial CRC screening



CRC susceptibility loci in GWAS

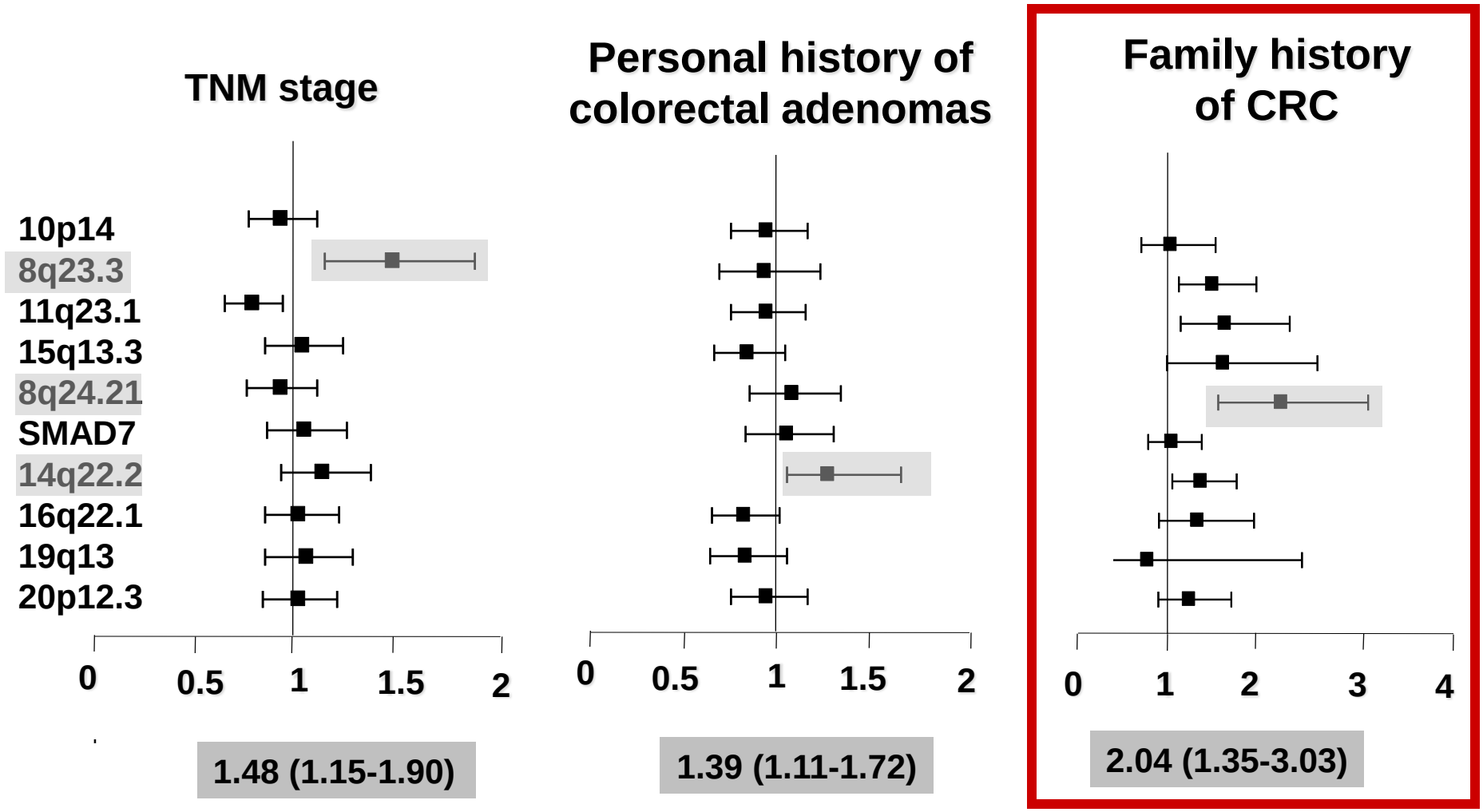
SNP	Chromosomal region	Gene	Reference
rs16892766	8q23.3	EIF3H	Tomlinson et al.
rs6983267	8q24.21		Tomlinson et al. Zanke et al. Haiman et al. Tenesa et al.
rs10795668	10p14		Tomlinson et al.
rs3802842	11q23.1		Tenesa et al. Pittman et al.
rs4779584	15q13.3	*CRAC1 (HMPS)*	Jaeger et al.
rs4939827	18q21.1	*SMAD7*	Broderick et al. Tenesa et al.
rs4444235	14q22.2	*BMP4*	Tomlinson et al.
rs9929218	16q22.1	*CDH1*	Tomlinson et al.
rs10411210	19q13	*RHPN2*	Tomlinson et al.
rs961253	20p12.3		Tomlinson et al.

Cumulative impact of 10 common genetic variants on colorectal cancer risk



Dunlop *et al.* Gut 2012

Genotype – phenotype correlation of susceptibility variants in CRC patients



Abulí *et al*. Gastroenterology 2010

Summary

- **APC gene testing allows presymptomatic diagnosis in relative at risk for FAP and it may be useful for selecting the surgical approach.**

- **Universal tumor MMR testing among CRC probands had a greater sensitivity for the identification of Lynch syndrome compared with multiple alternative strategies.**

- **Susceptibility loci identified in GWAS may help to stratify familial CRC risk in the near future.**

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