The Genetics Consultation in OB-GYN :

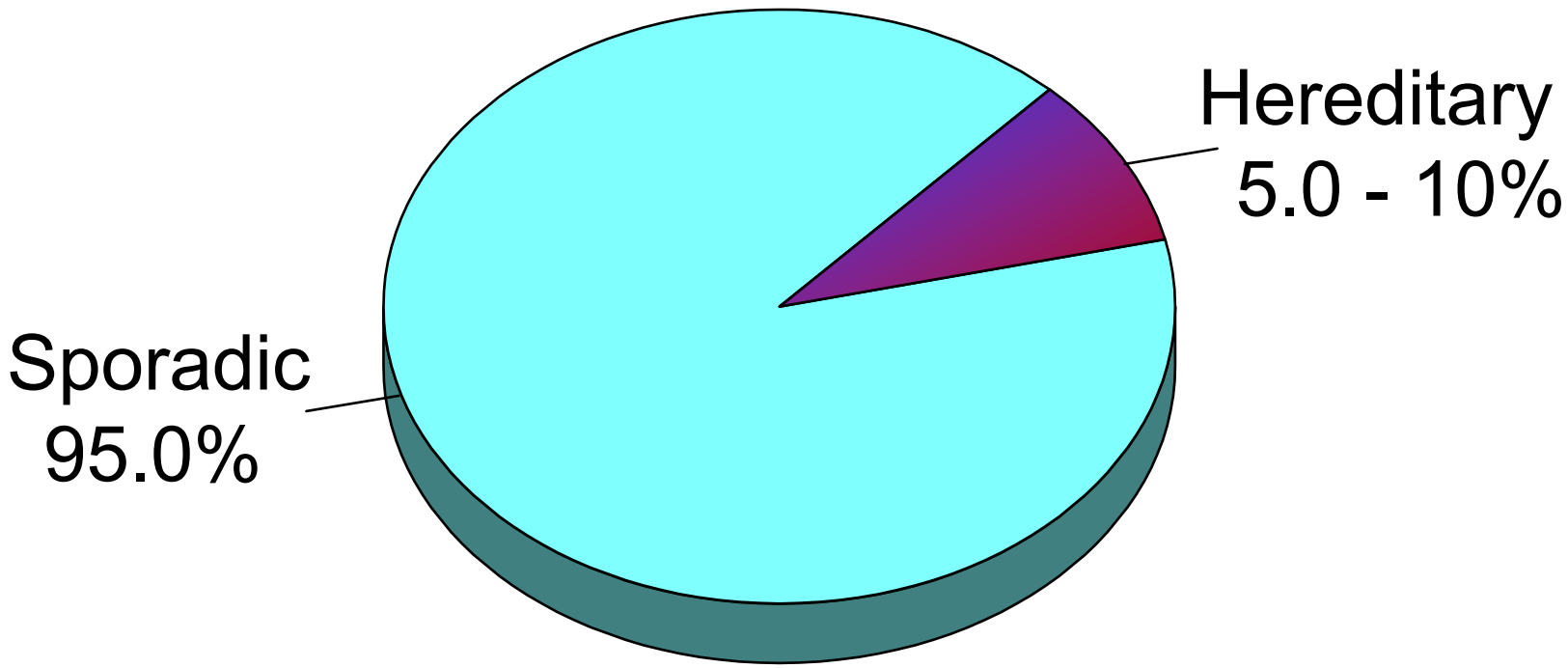
Hereditary cancers

Célia DeLozier-Blanchet
Division of Medical Genetics,
Geneva University Hospital

It is probable that all cancers are genetic!

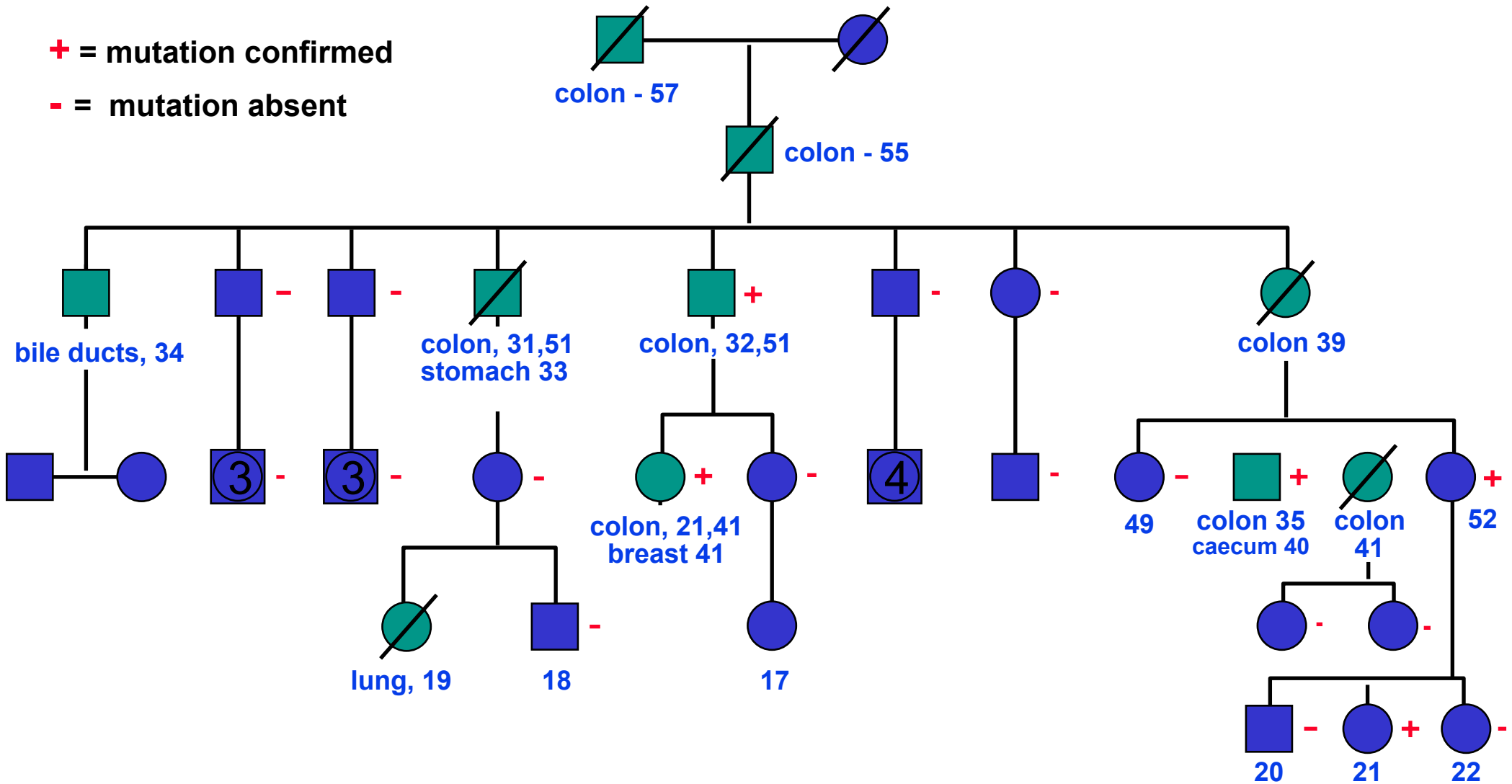
- genetic vs. hereditary
- constitutional vs. somatic

Hereditary vs. sporadic cancers



“Cancer Families”

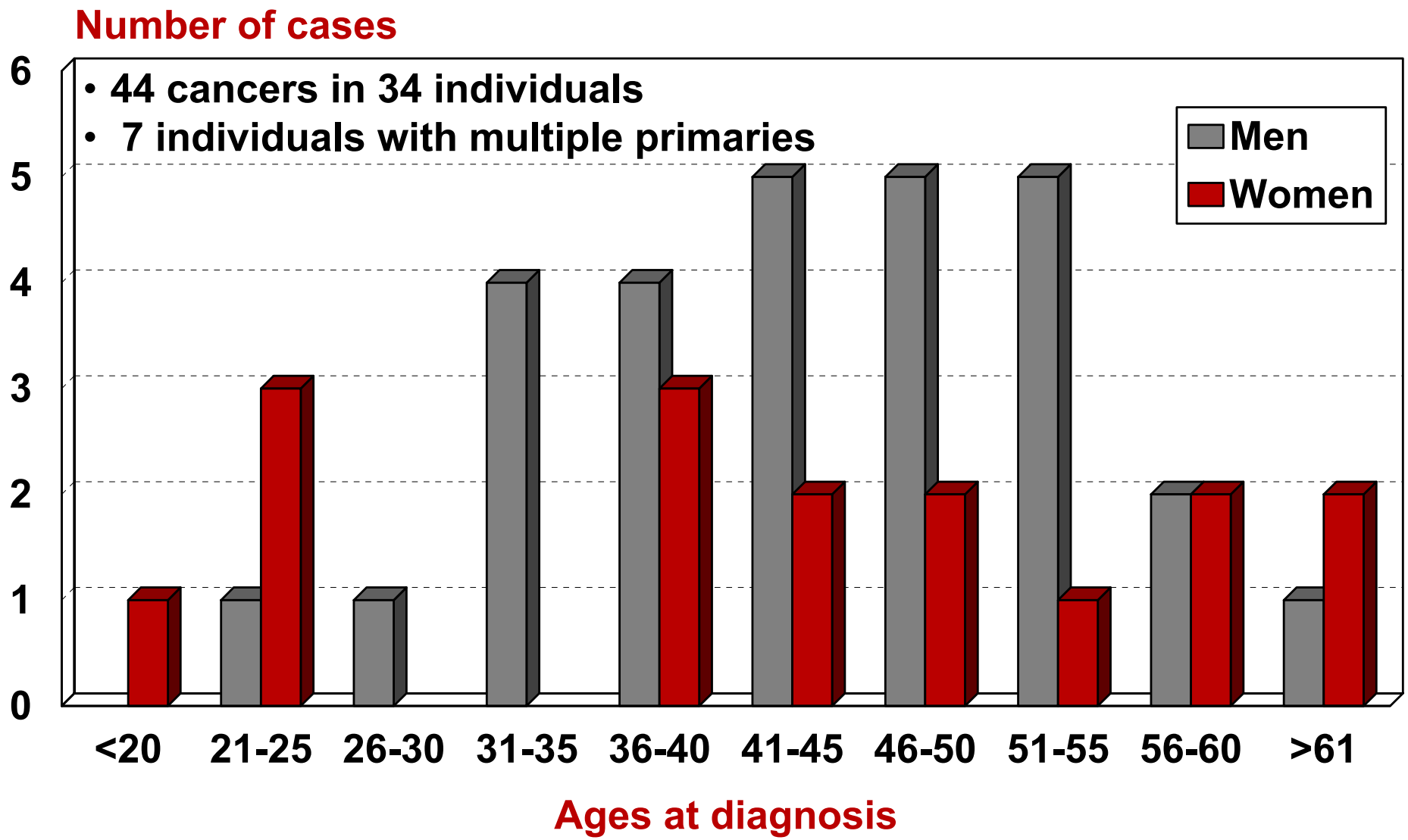
Family R (Geneva - HNPCC) Branch D



Features suggestive of an inherited cancer susceptibility

- Several close relatives with a common cancer
- Several close relatives with related cancers
- Two family members with the same rare cancer
- An unusually early age of onset
- Bilateral tumors
- Synchronous or successive tumors
- Tumors in two different systems in the same individual

Age of Onset of Cancer
Family R (HNPCC, Geneva)



Principle cancer syndromes and their genes

SYNDROME/ TRANSMISSION	MAIN CANCERS	GENE, CHROMOSOME
Breast / Ovary (AD)	breast, ovary	brca1/ 2 /3 (17q,13q)
Dysplastic Nevus (AD)	melanoma	CMM1 (1p)
Familial Polyposis Coli (AD)	colorectal, duodenal, thyroid	APC (5q)
Familial retinoblastoma (AD)	retinoblastoma	Rba (13q)
Li-Fraumini (AD)	sarcoma, breast, brain, leukemia, adrenal, etc.	p53 (17p)
Multiple endocrine neoplasia 2 (AD)	thyroid, pheochromocytoma	MEN2a (10q)
Von Hippel-Lindau (AD)	CNS, renal, pancreatic, pheochromocytoma	VHL (3p)

Classes of "cancer genes"

- Oncogenes
- Tumor suppressor genes ("anti-oncogenes")
- DNA repair genes
- Chromosome instability genes
- Others!

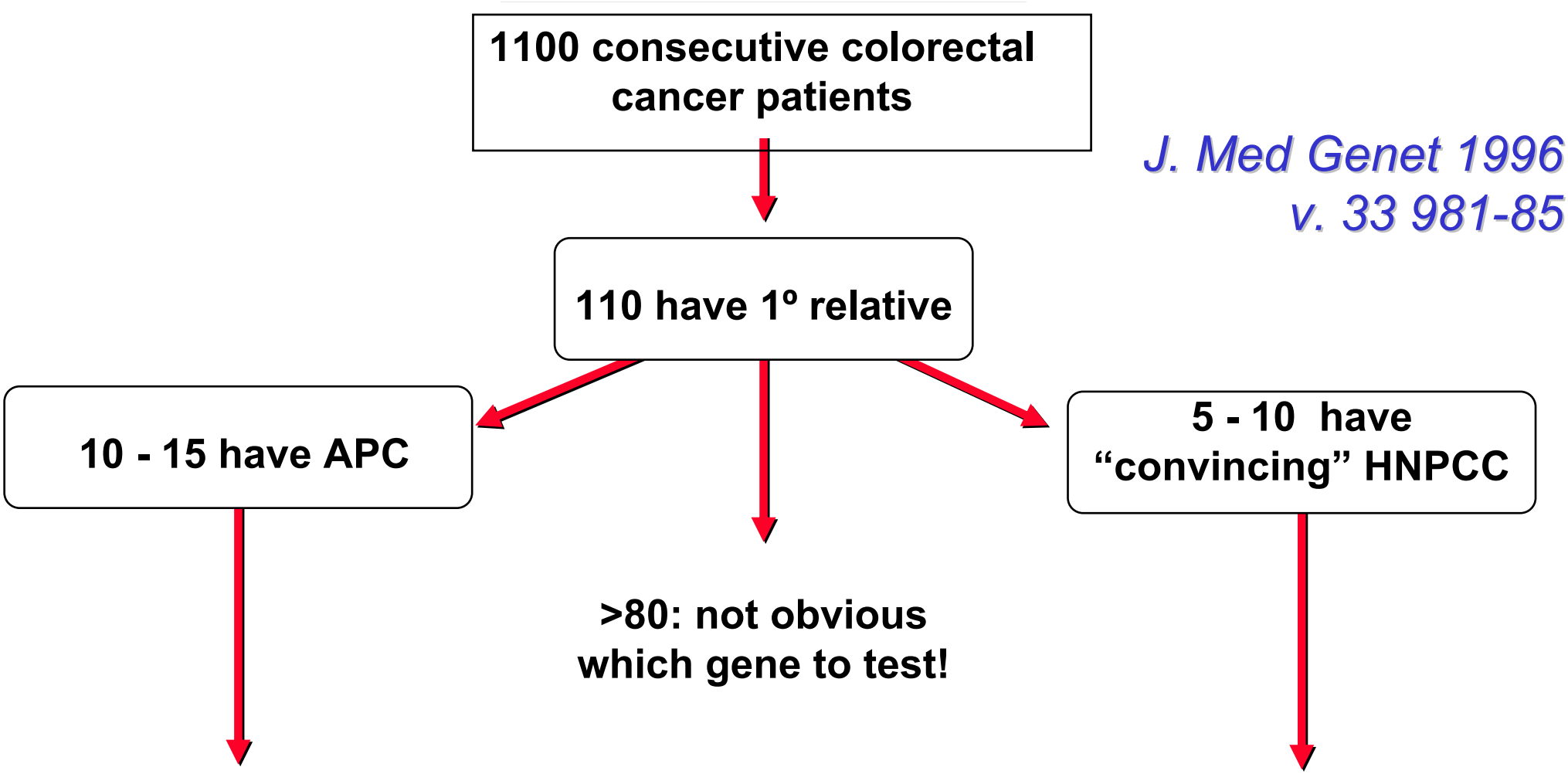
Hereditary cancers : when to offer genetic testing

Colon Cancer

Lifetime risk of colorectal cancer

(from Houlstan et al. BR MED J 301:366-368, 1990)

• population risk	1/50
• one first-degree relative affected	1/17
• one first & one second degree aff.	1/12
• one relative under 45 affected	1/10
• two first-degree relatives affected	1/6
• three or more first-degree affected	1/2



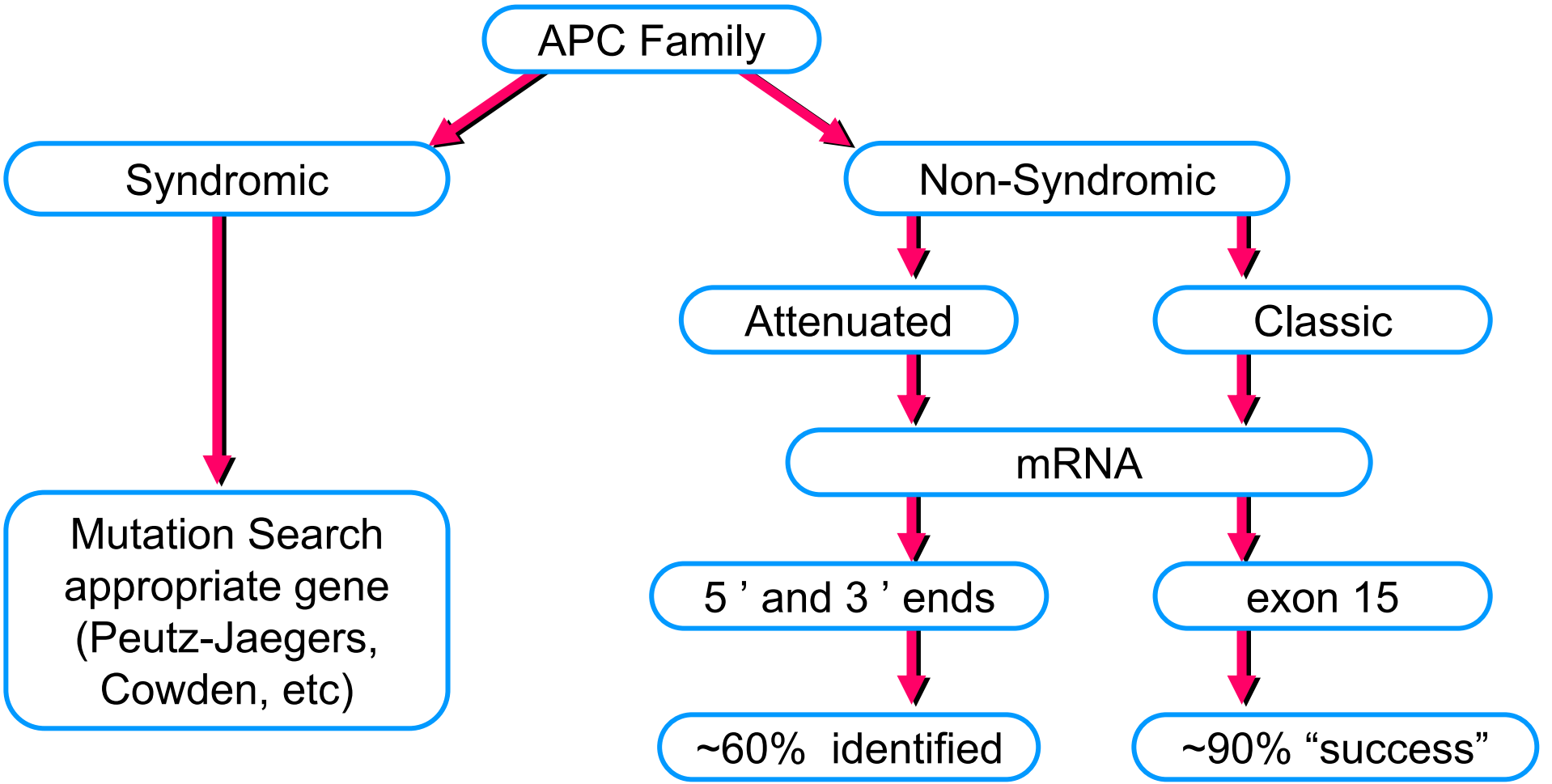
J. Med Genet 1996 v. 33 981-85

What (gene) to test?

Known colon cancer genes

- Familial adenomatosis polyposis 5q
- Hereditary non-polyposis colorectal cancer (HNPCC)
  - Lynch I (colorectal) 2p; 3p
  - Lynch II (colorectal and others) 2q;18q
- Others!

Gene Testing in Polyposis Coli



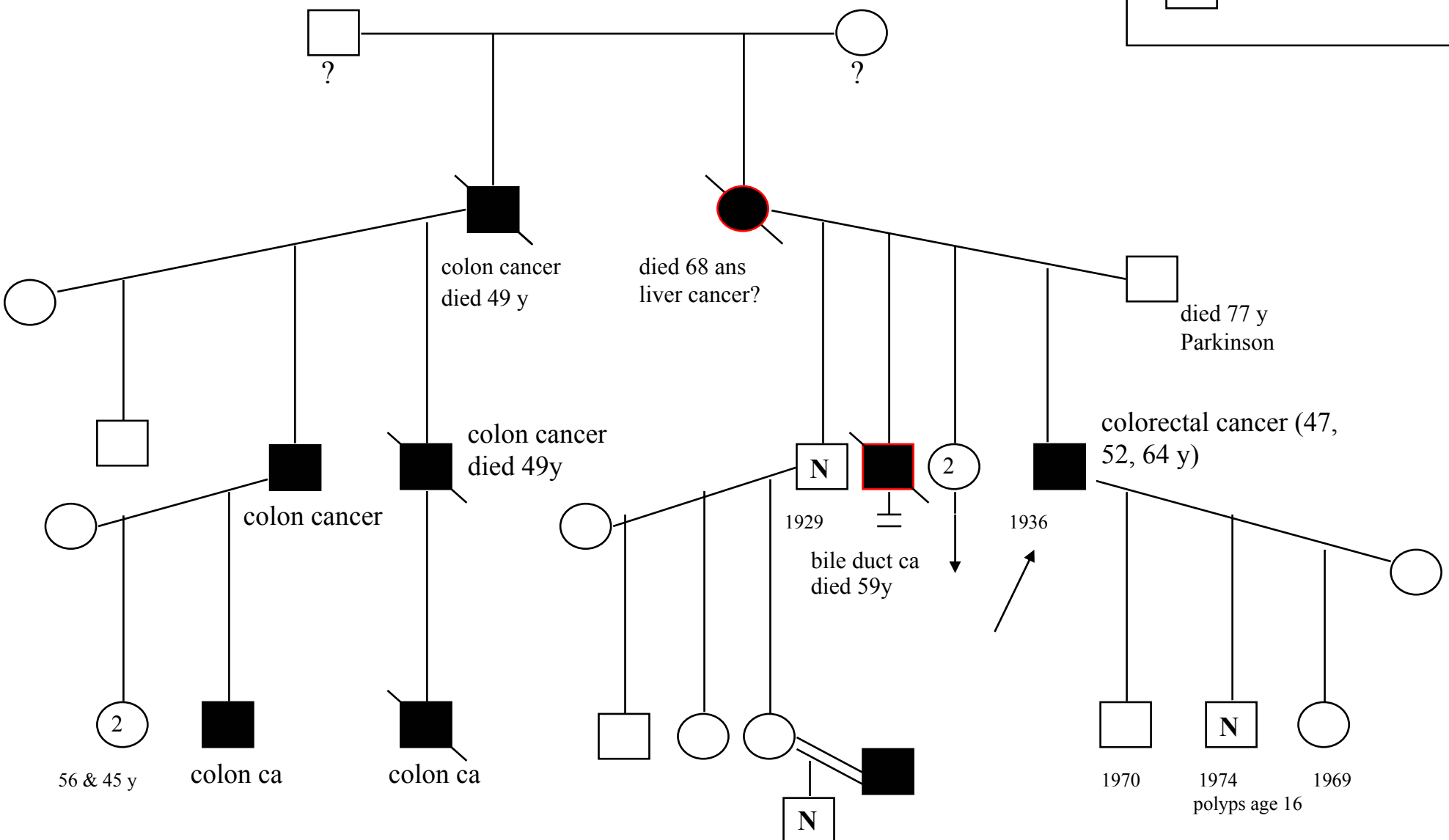
Family N (Pakistan/France/England) :

--3 colorectal malignancies in proband

--MSI-H on rectal tumor /constitutional DNA

--IHC: absence of hMLH1 protein

--mutation hMLH1 : 1528 del/ins (exon 13)

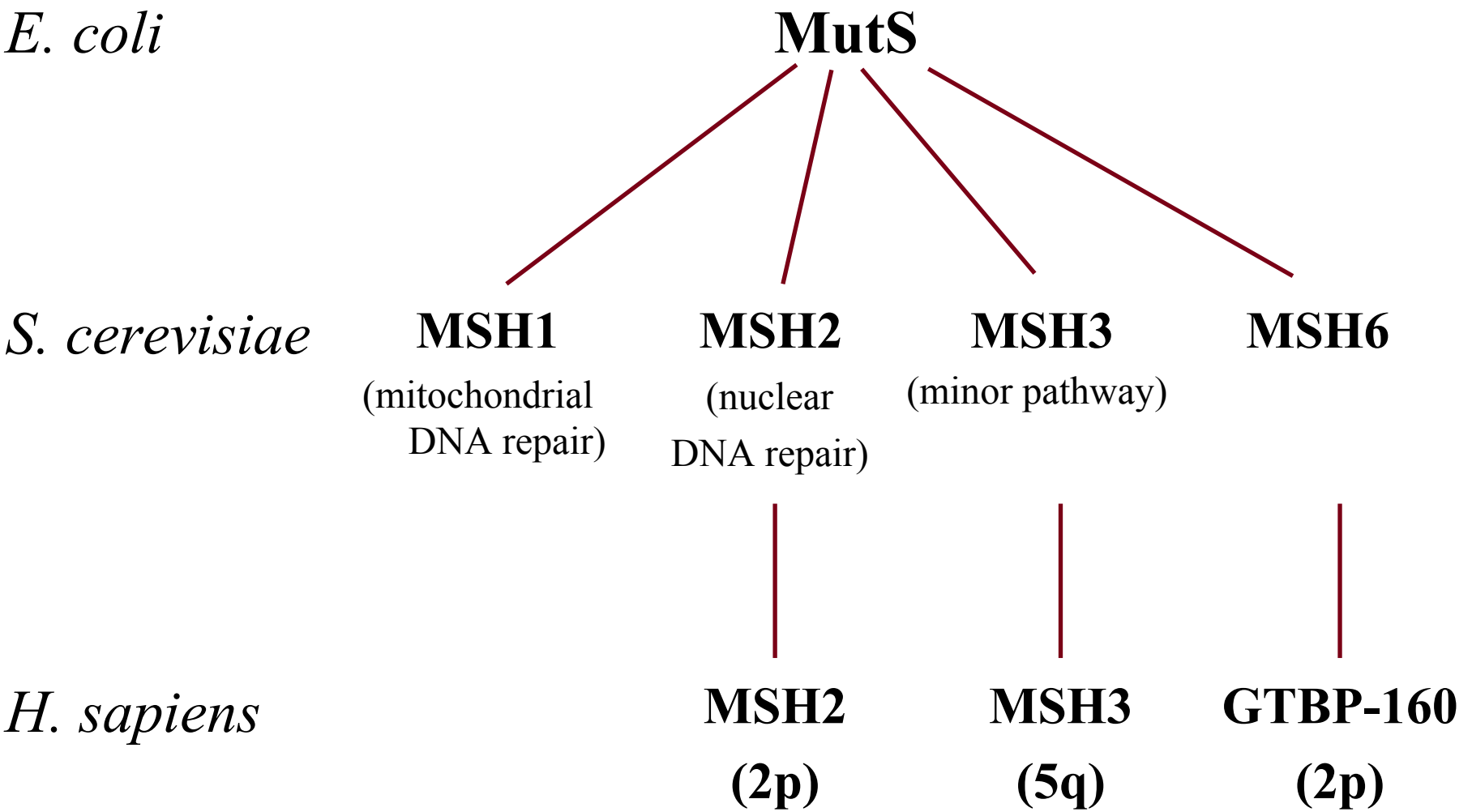


Colorectal Cancer Genes and their Mutations

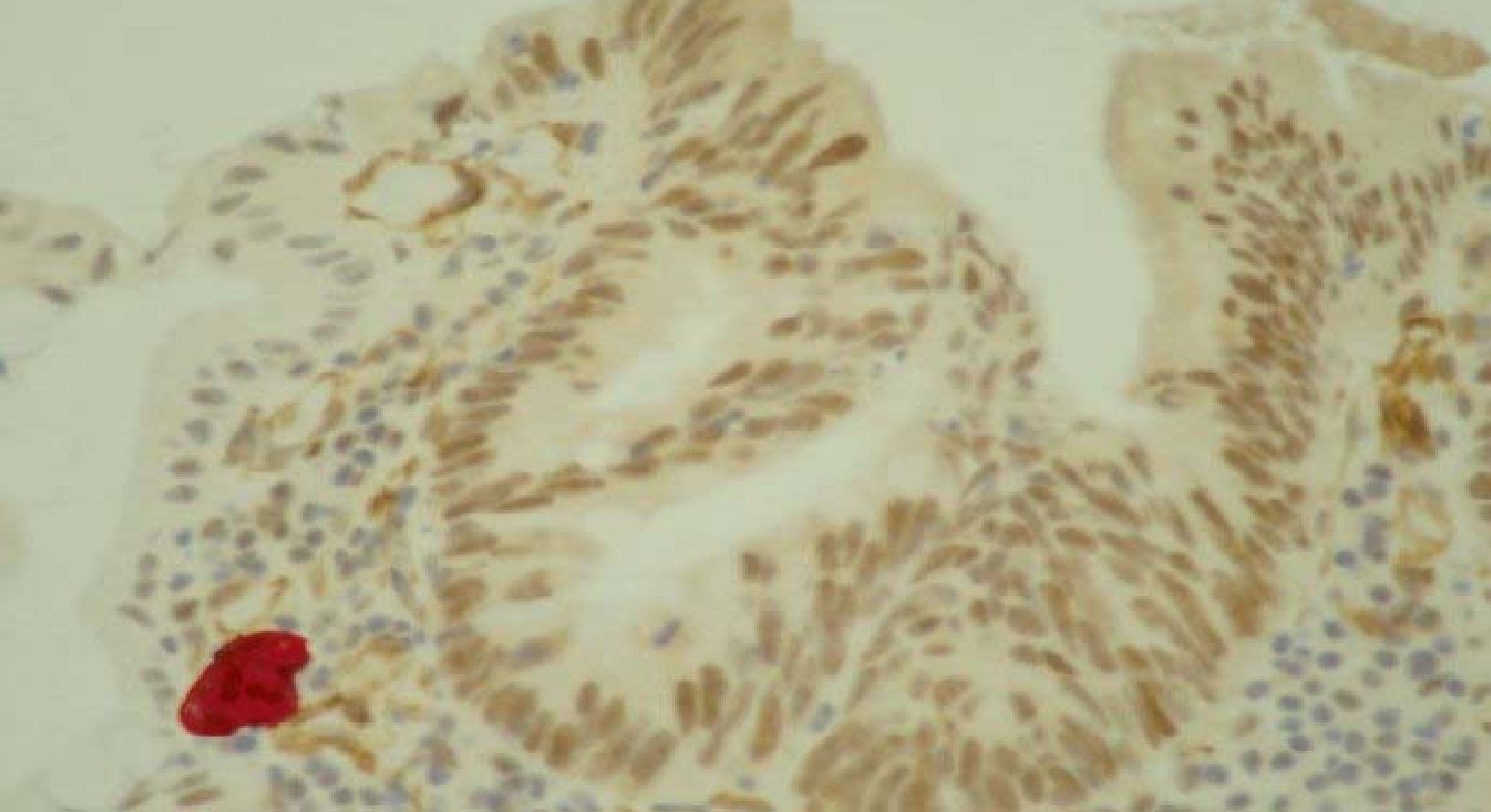
hMLH1 (3p; 19 exons, 100 kB) : up to 60% of HNPCC

hMSH2 (2p; 16 exons, 73 kB) : up to 30% of HNPCC

- Numerous distinct mutations (splice-site, missense and nonsense)
- For hMLH1, clustering in exons 15 - 16?
- Probable ethnic variations (founder effect?)

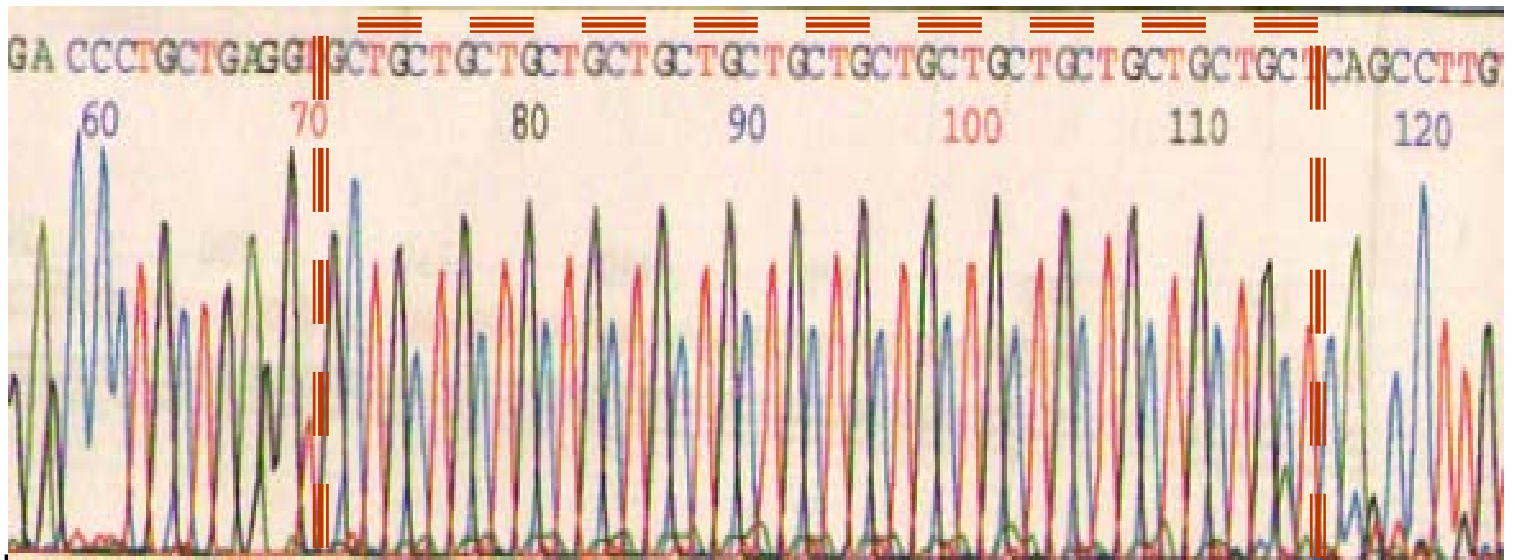


Peltomaki and de la Chapelle (1996).



What is a microsatellite?

- A short, simple DNA nucleotide sequence (CA, CGA, GCG, GCC, GAAA...)
- Which is repeated in tandem in a head-to-tail fashion (CACACACACA...)



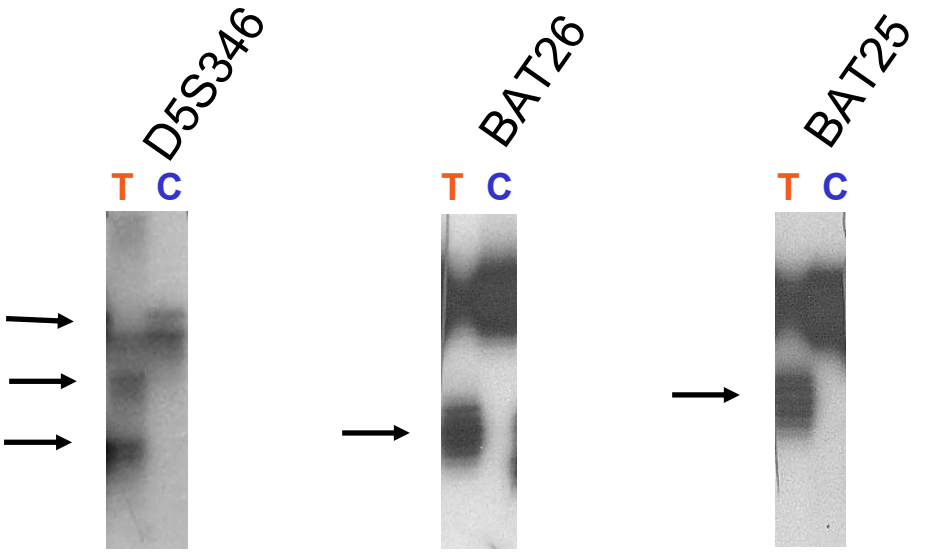
- The number of repetitions is highly variable
- Such microsatellites are present every 10,000-50,000 nucleotides throughout the human genome
- Most microsatellites are situated between genes, or outside of exons

Why use microsatellites (MSIs) to detect DNA repair defects?

- **MSIs are sensitive indicators of DNA instability**
- **They are the most hyper-mutable regions in the coding regions of human DNA (10^3-$10^{6)}$ per gamete)**
  - **unequal crossing-over**
  - **“slippage” of DNA polymerase during replication**
  - **Not recognized by DNA repair mechanisms?**

What does microsatellite instability look like?

When separated by size, tumor DNA (T) and constitutional DNA (C) show different patterns of bands in the same patient



Electrophoresis of PCR amplification products

Microsatellites: stability vs.instability ?

Extra bands in tumor vs. constitutional DNA

- 0 / 5 MSIs instable : MSS (microsatellite stability)

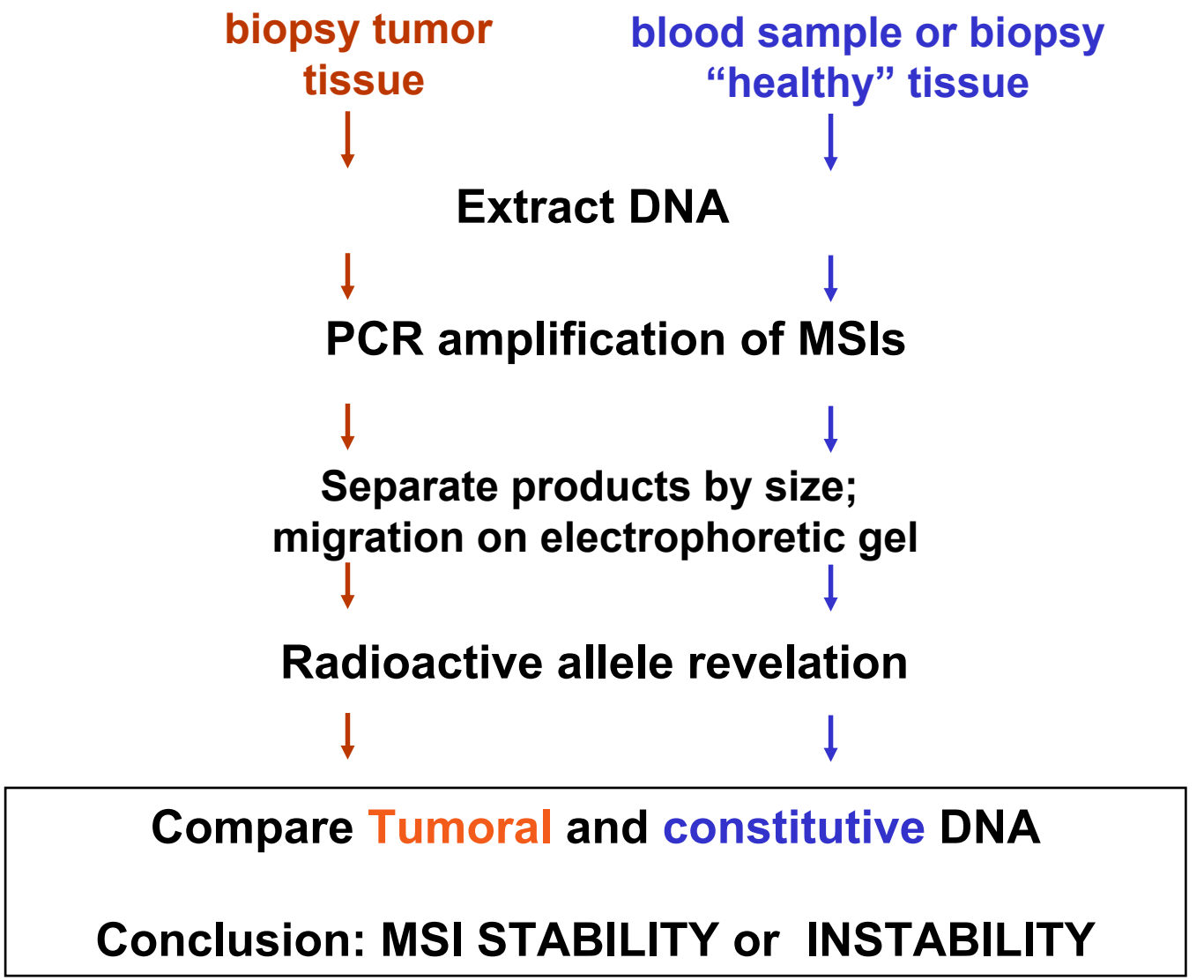
- 1 / 5 MSIs instable : MSI-L (weak instability)

- 2 or more / 5 instable : MSI-H (high instability)

69 cases tested in 2000

- 12 MSI-H
- 0 MSI-L

Analysis of MSI in patients' DNA



Conditions with potential prophylactic treatment

(from Mueller and Young, "Emery's Elements of Medical Genetics, 1995, p 179)

Disorder	Treatment
• *Accepted treatment*	
FAP (colon polyposis)	Total colectomy
Ovarian cancer families	Oophorectomy
Breast cancer families	Bilateral mastectomy
MEN2	Total thyroidectomy
• *Under evaluation*	
FAP (colon polyposis)	Non-digestible starches; Sulindac
Breast cancer families	Tamoxifen

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How is MSI instability detected?

consensus of 5 microsatellites (workshop 1997)
BAT25, BAT26, D2S123, D5S346, D17S250,

Locus/Name	chr	Primer name	Primer sequence
BAT25	4	BAT-25.1	TCGCCTCCAAGAATGTAAGT
4q12-4q12		BAT-25.2	TCTGCATTTTAACTATGGCTC
BAT26	2	BAT-26.1	TGACTACTTTTGACTTCAGCC
2p16-2p16		BAT-26.2	AACCATTCAACATTTTTAACCC
D5S346	5	LNS-CAI	ACTCACTCTAGTGATAAATCGGG
5q21-q22		LNS-CAII	AGCAGATAAGACAGTATTACTAGTT
D2S123	2	AFM093xh3a	AAACAGGATGCCTGCCTTTA
2p16		AFM093xh3m	GGACTTTCCACCTATGGGAC
D17S250	17	Mfd15CA	GGAAGAATCAAATAGACAAT
17q11.2-q12		Mfd15GT	GCTGGCCATATATATATTTAAACC

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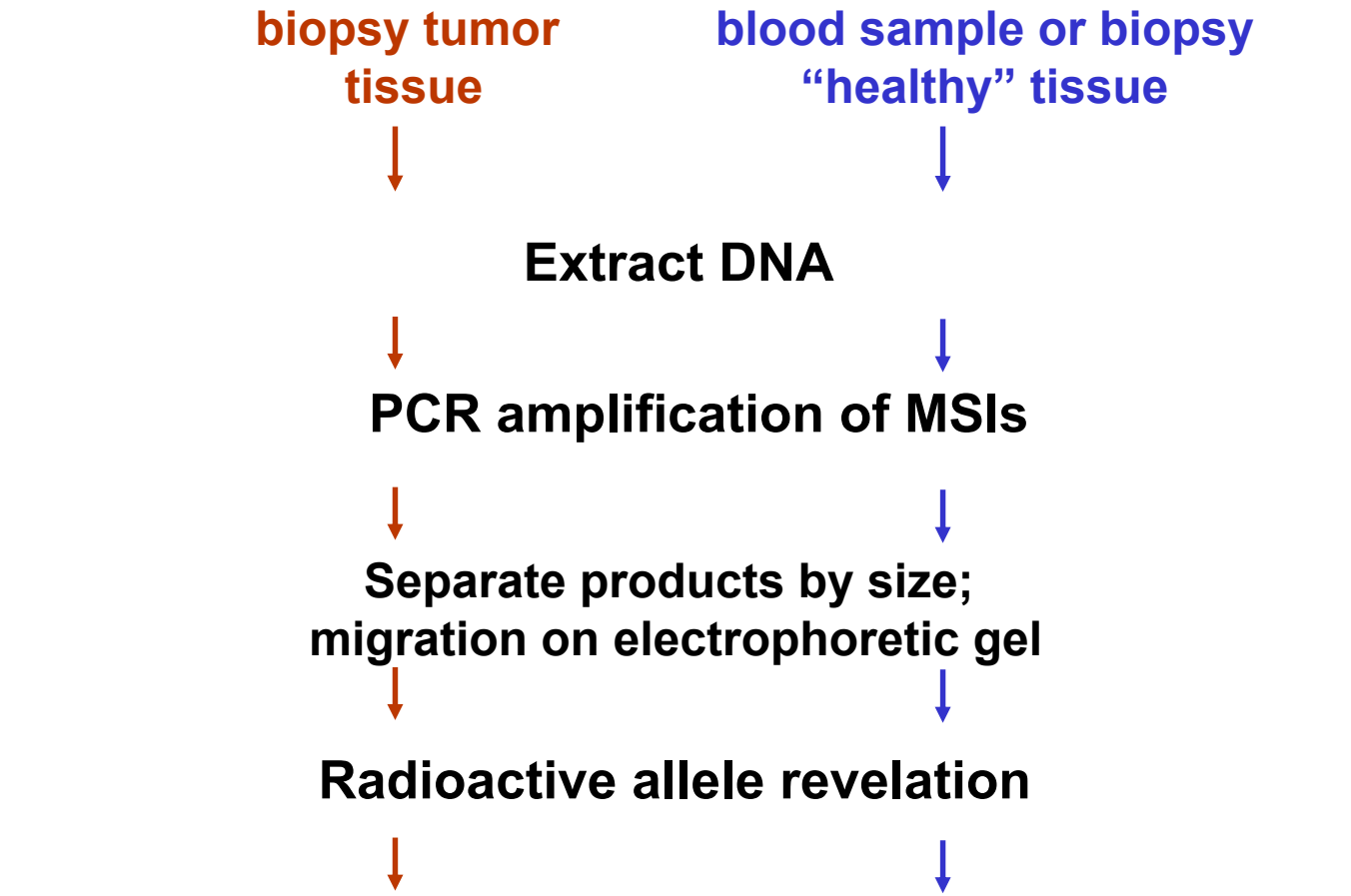

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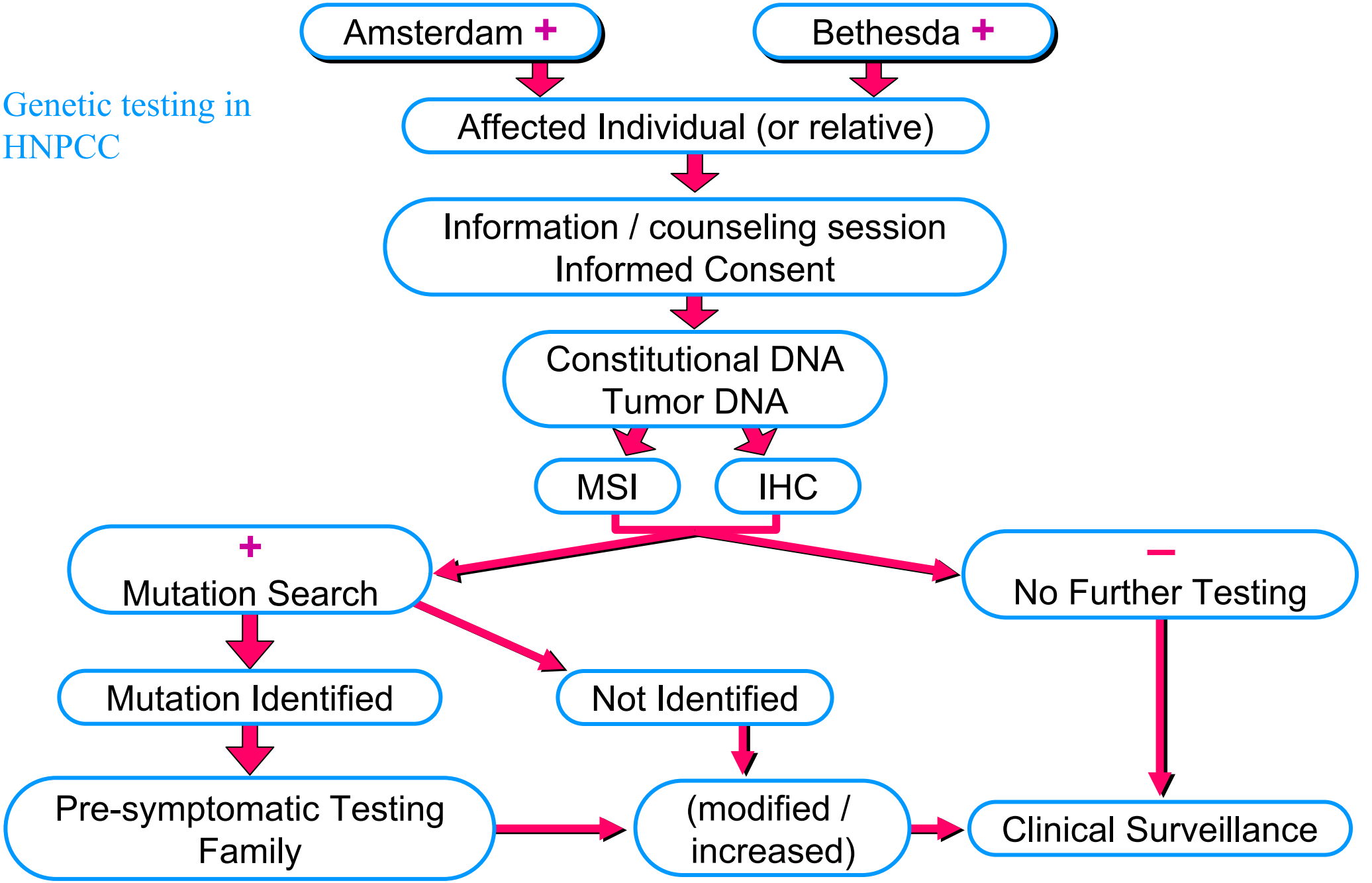
Genetic testing in HNPCC



Why test?

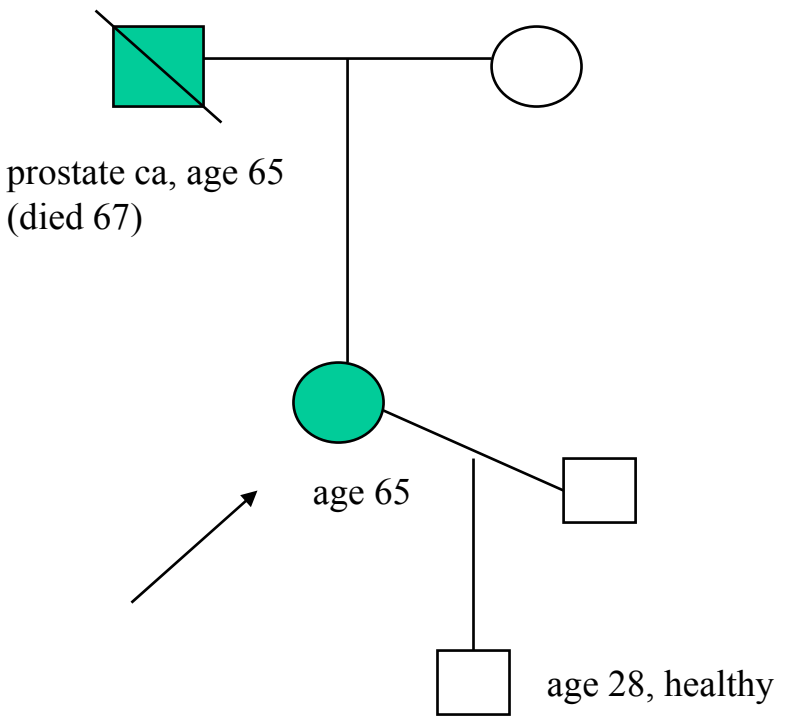
Family C- cancers of prostate, endometrium, colon

-- Mrs. C: endometrial cancer at age 56;
colon cancer at 63 and 65

-- MSI-H on second colon malignancy

-- IHC: absence of hMSH2 and 6 proteins

-- mutation identified in hMSH6 (duplication of hMSH2(



Other cancers in HNPCC carriers?

- Endometrial cancer risk: 40-60% for women (depending on the gene, is greater than the colon cancer risk!) Yearly US recommended.
- Somewhat increased risk of urinary tract, pancreas, ovary, prostate, breast??

Genotype - phenotype correlations

- The tumor spectrum (types and frequencies) is different according to the gene implicated!
  - ***hMLH1*** : paucity of extra-colonic tumors (but endometrial cancer in females; breast?)
  - ***hMLS2*** : more cancers of renal pelvis,ureter, stomach, ovaries
  - ***hMSH6*** : endometrial and ovarian outnumber CR

Amsterdam positive (but mutation-negative) families: more breast and prostate than in above groups...

Advantages of cancer gene testing

- Knowing
- Improved diagnosis and prognosis?
- Half of at-risk individuals will not have the gene!
- Advances in knowledge of genotype/phenotype correlations

HNPCC : how MSI / mutation identification affects treatment

- for the affected individual
- modifies surgical options
- may modify treatment protocols (radio- and chemotherapy)
- is NOT a negative factor for prognosis
- For the individual and the family
- allows pre-symptommatic testing
- increases/modifies clinical and paraclinical follow-up (endometrium in women)
- access to treatment trials (CAPP2)

Aspirin suppresses the mutator phenotype associated with hereditary nonpolyposis colorectal cancer by genetic selection

JOSEF RÜSCHOFF*†‡§, SABINE WALLINGER*†, WOLFGANG DIETMAIER*, TINA BOCKER¶, GERO BROCKHOFF*, FERDINAND HOFSTÄDTER*, AND RICHARD FISHEL‡¶

*Institute of Pathology, University of Regensburg, D-93042 Regensburg, Germany; and ¶Genetics and Molecular Biology Program and Department of Microbiology and Immunology, Kimmel Cancer Center, Thomas Jefferson University, 233 S. 10th Street, Philadelphia, PA 19107

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Hereditary cancer: concerns that impact genetic counseling

- concerns about insurability
- family pressure for testing and seeking results
- unresolved grief
- family solidarity
- survivor guilt
- barriers to screening (financial, psychological)
- prophylactic surgery
- patient/physician/counselor communication

from American Cancer Society second national conference on Cancer Genetics, Lynch et al., CANCER 86 (suppl):2457-2463, Dec.1999

ASHG /ACMG Report
Points to consider : Ethical, legal and psychosocial implications of genetic testing in children and adolescents (Am J Hum Genet 57:1233-1241, 1995)

Counseling and communication with child and family should include:

- assessment of the significance of the potential benefits and harms of the test
- determination of the decision-making capacity of the child
- advocacy on behalf of the interests of the child

Breast cancer genes

- 17q (BRCA1)
- 13q (BRCA2)
- 11p ?
- AT gene?