The Genetics Consultation in OB-GYN :

Hereditary cancers

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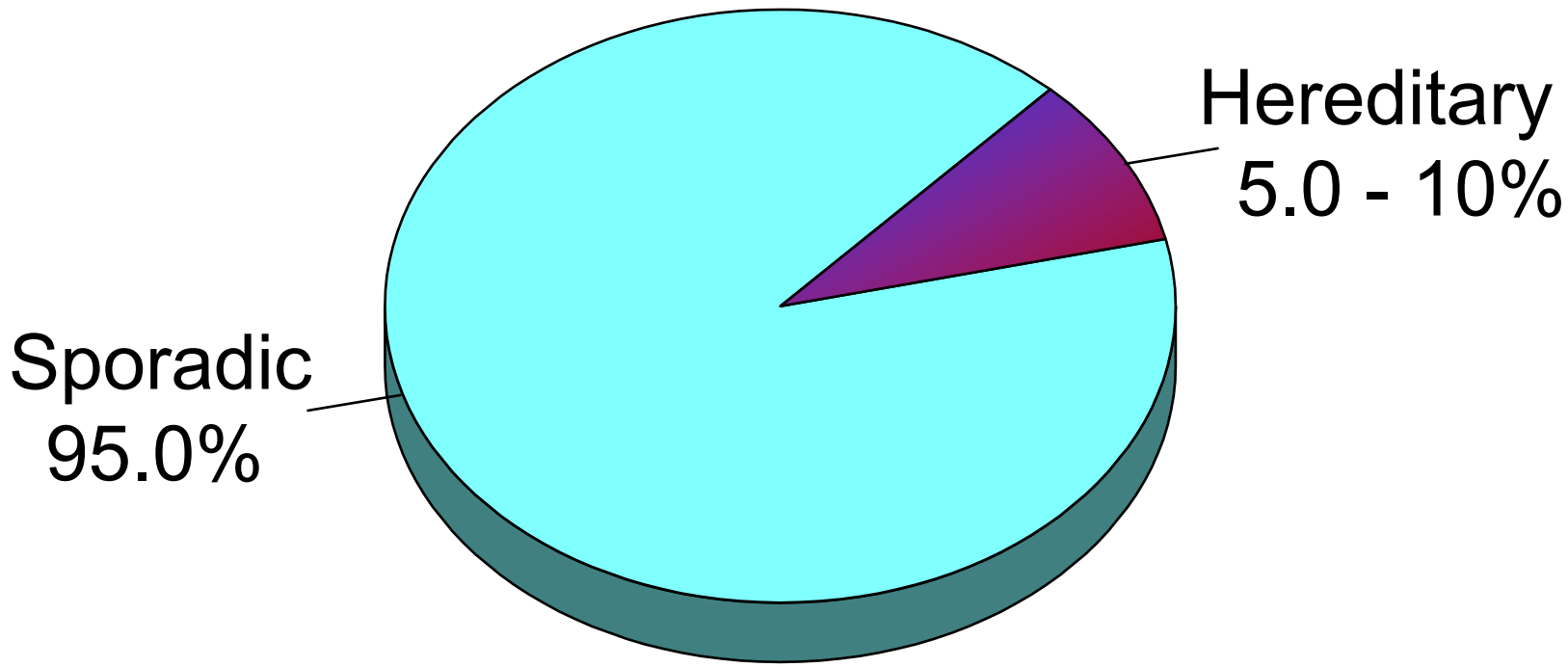
It is probable that all cancers are genetic!

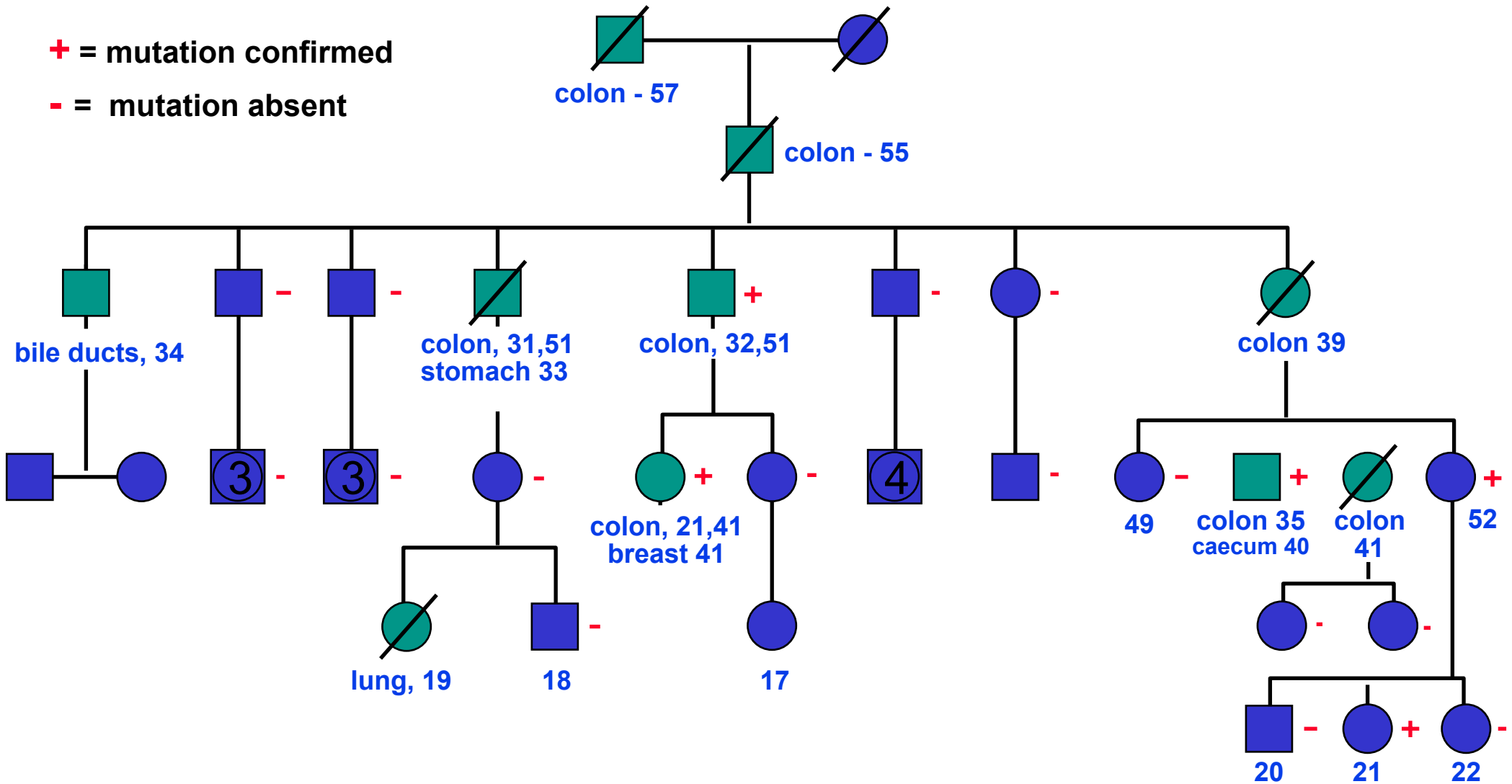
- genetic vs. hereditary
- constitutional vs. somatic

Hereditary vs. sporadic cancers



“Cancer Families”

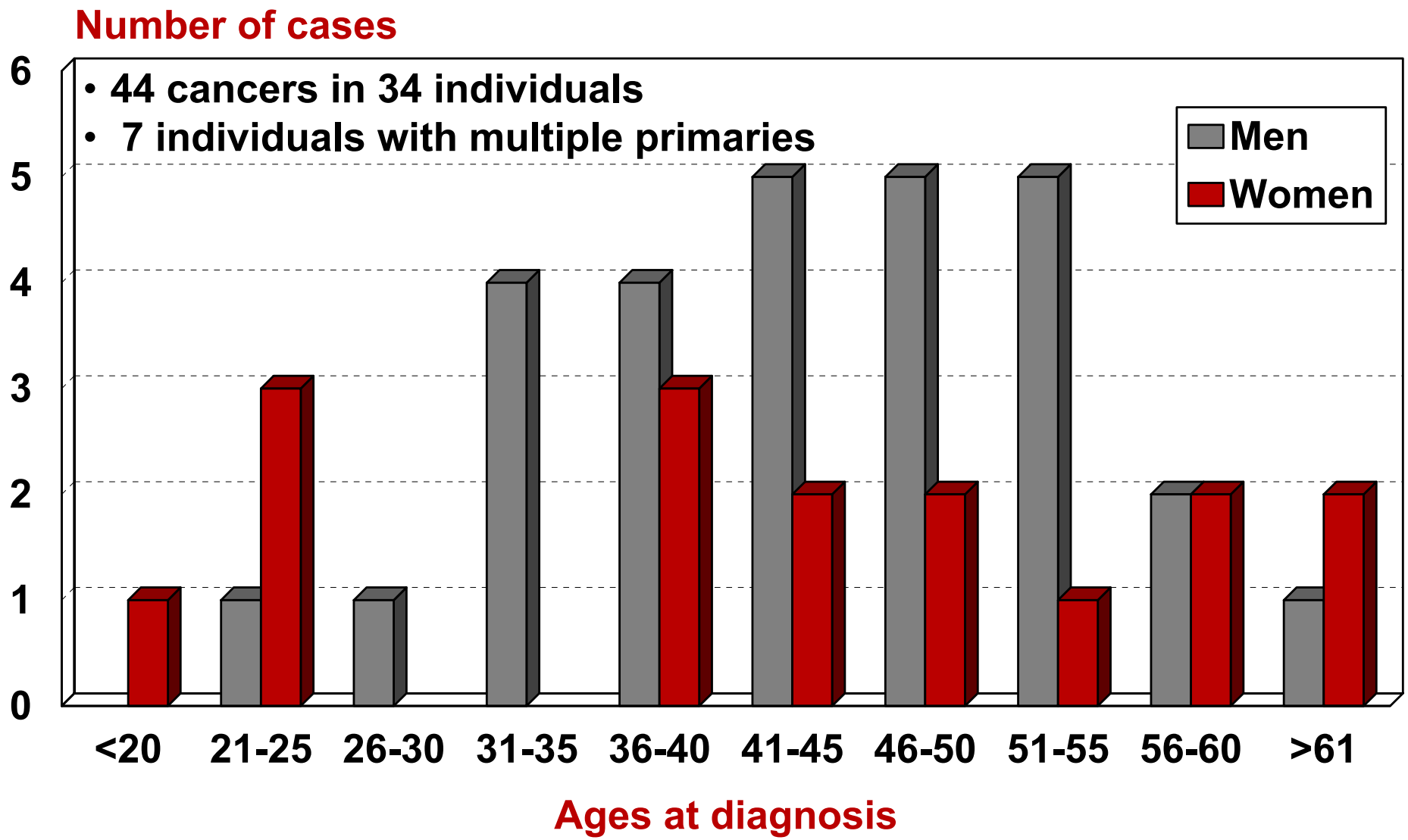
Family R (Geneva - HNPCC)
Branch D



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!

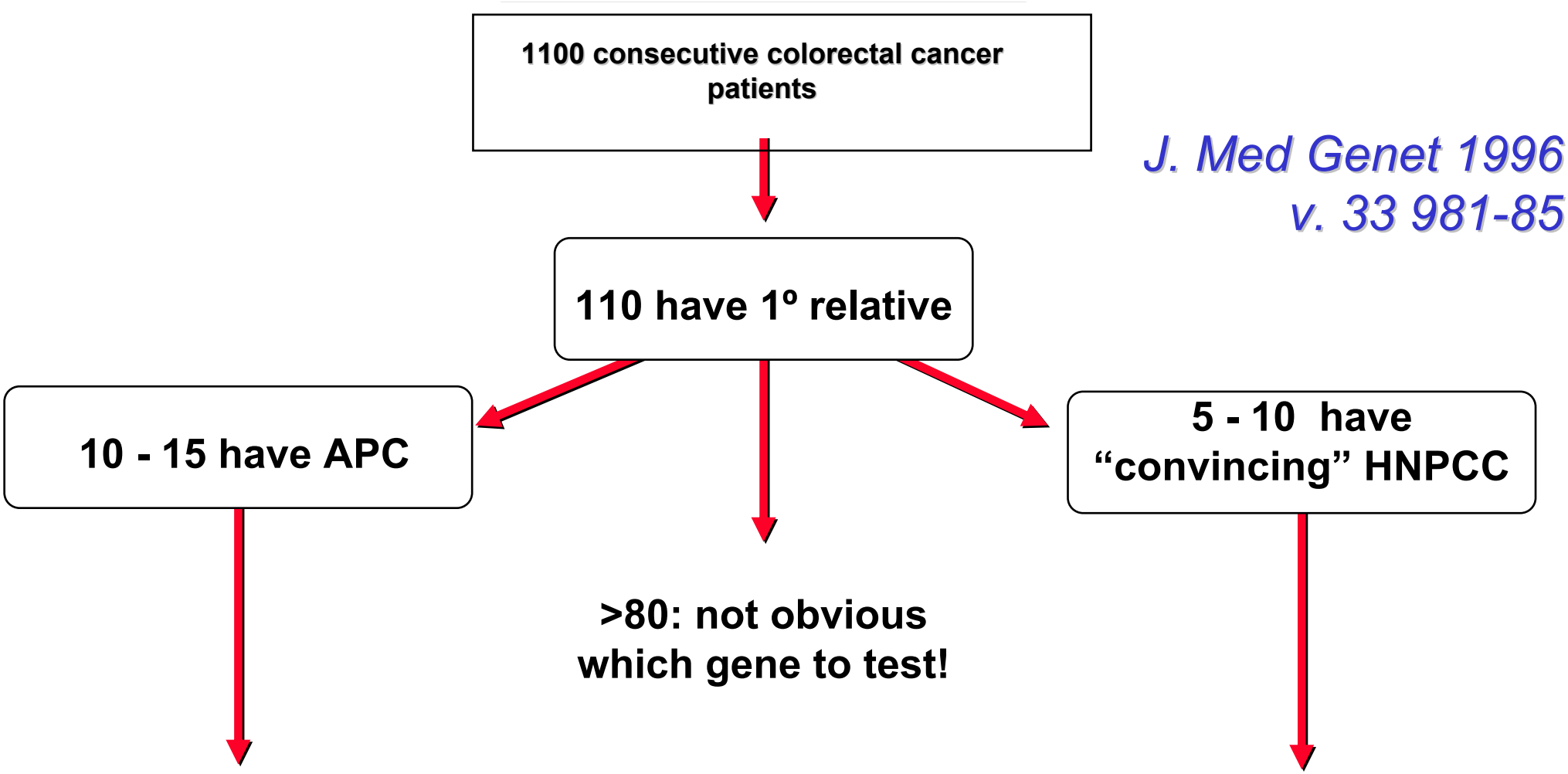
Hereditary cancers : when to offer genetic testing

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

If positive family history, most have mutation in gene on chromosome 5q: ***CALL THE GENETICIST!***

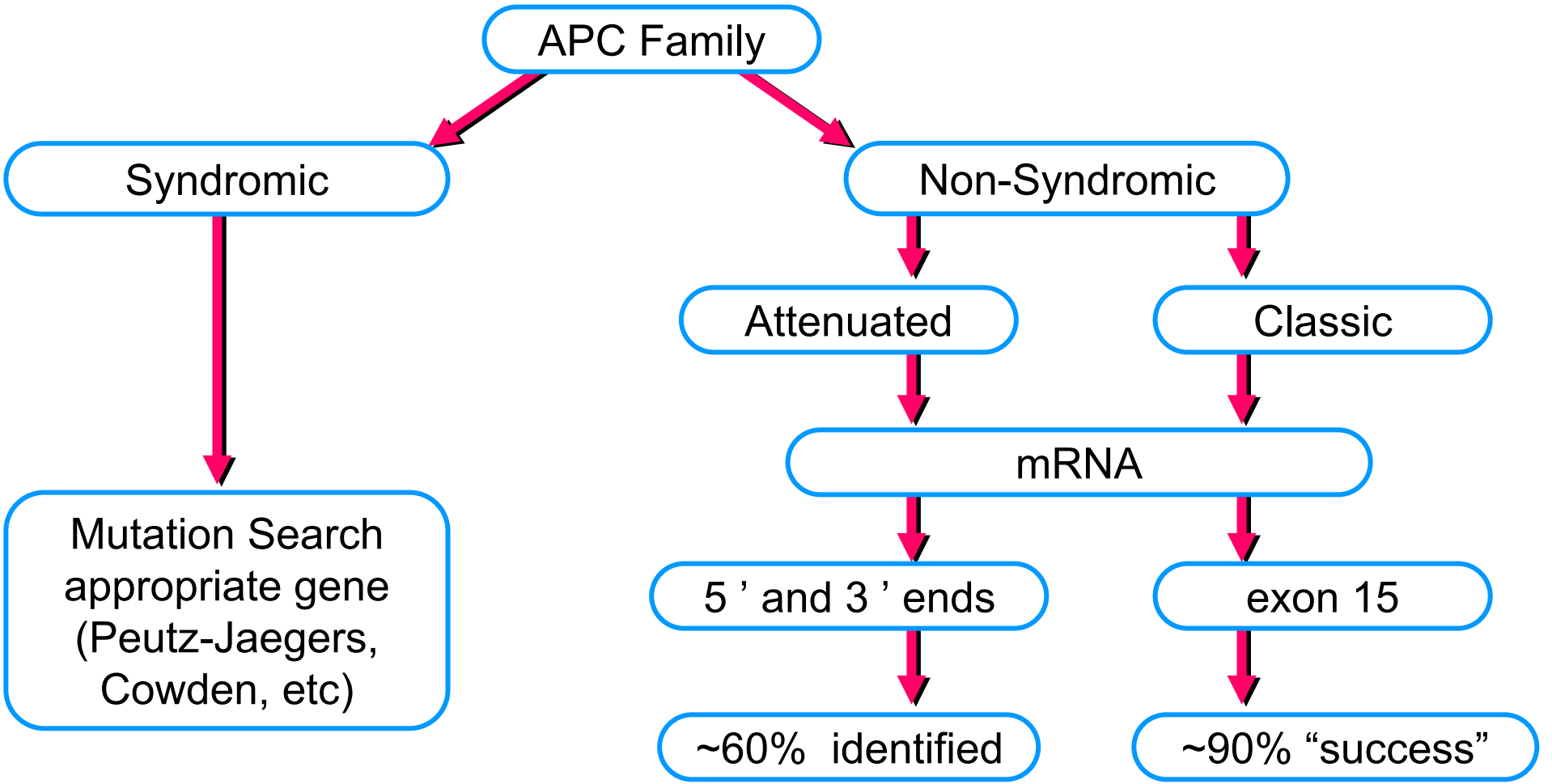
If "Amsterdam Criteria" met, most will have mutations that can be defined, genes on 2p, 3p, 7p: ***CALL THE GENETICIST!***

What (gene) to test?

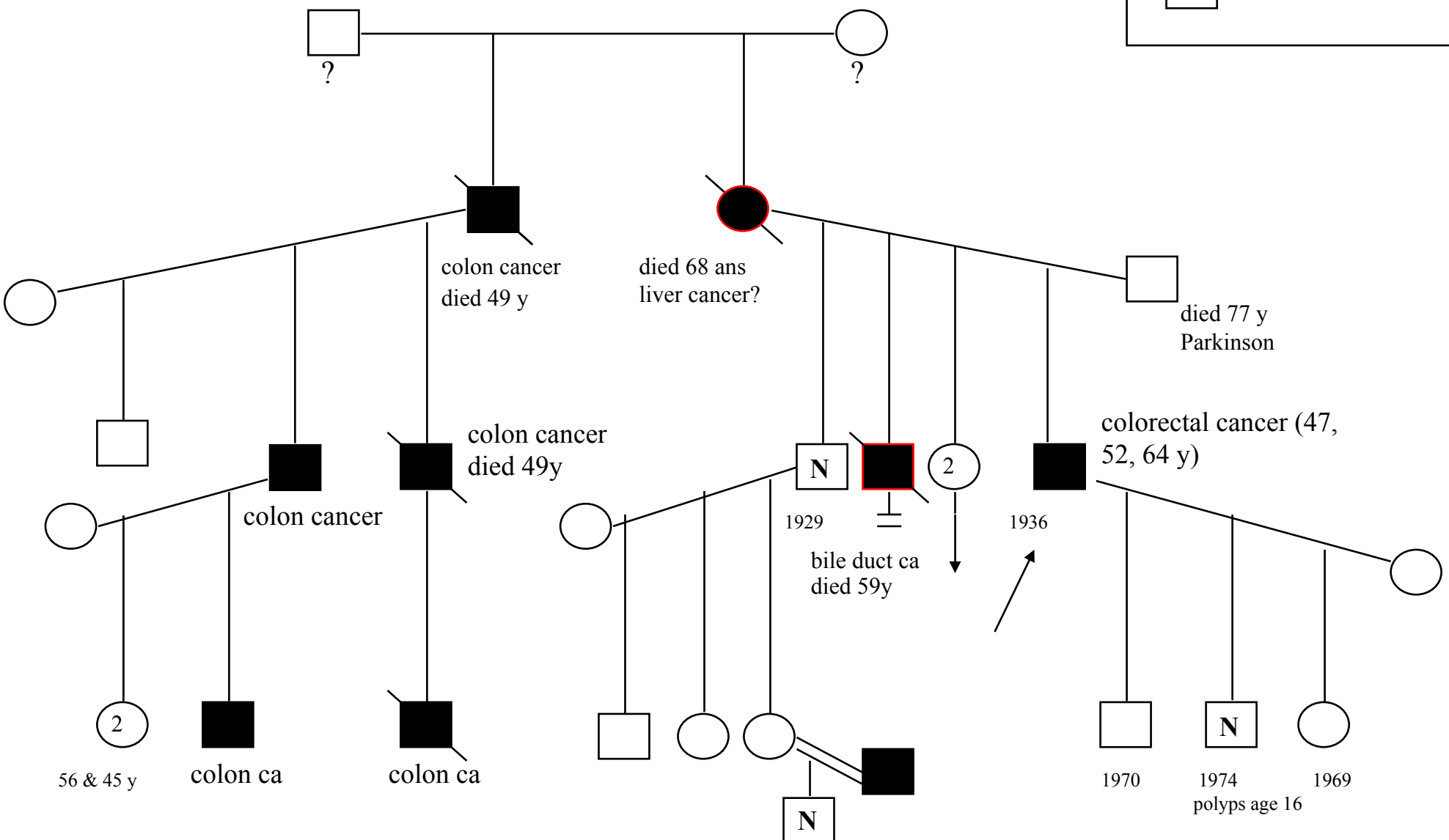
Known colon cancer genes

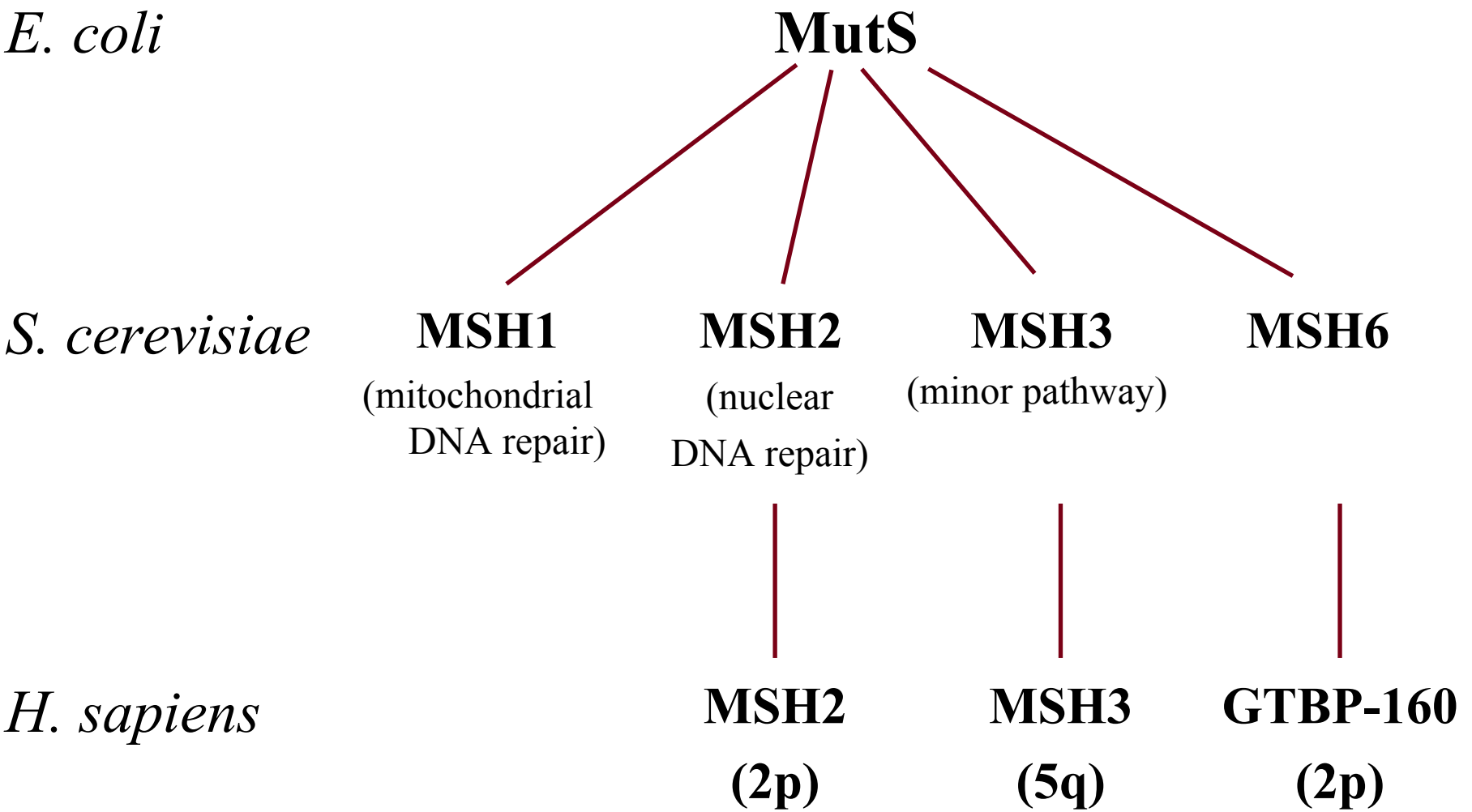
- Familial adenomatosis polyposis 5q
- Hereditary non-polyposis colorectal cancer (HNPCC)
  - Lynch I (colorectal) 2p; 3p
  - Lynch II (colorectal and others) 2q;18q
- Others!

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)





Peltomaki and de la Chapelle (1996).

Colorectal Cancer Genes and their Mutations

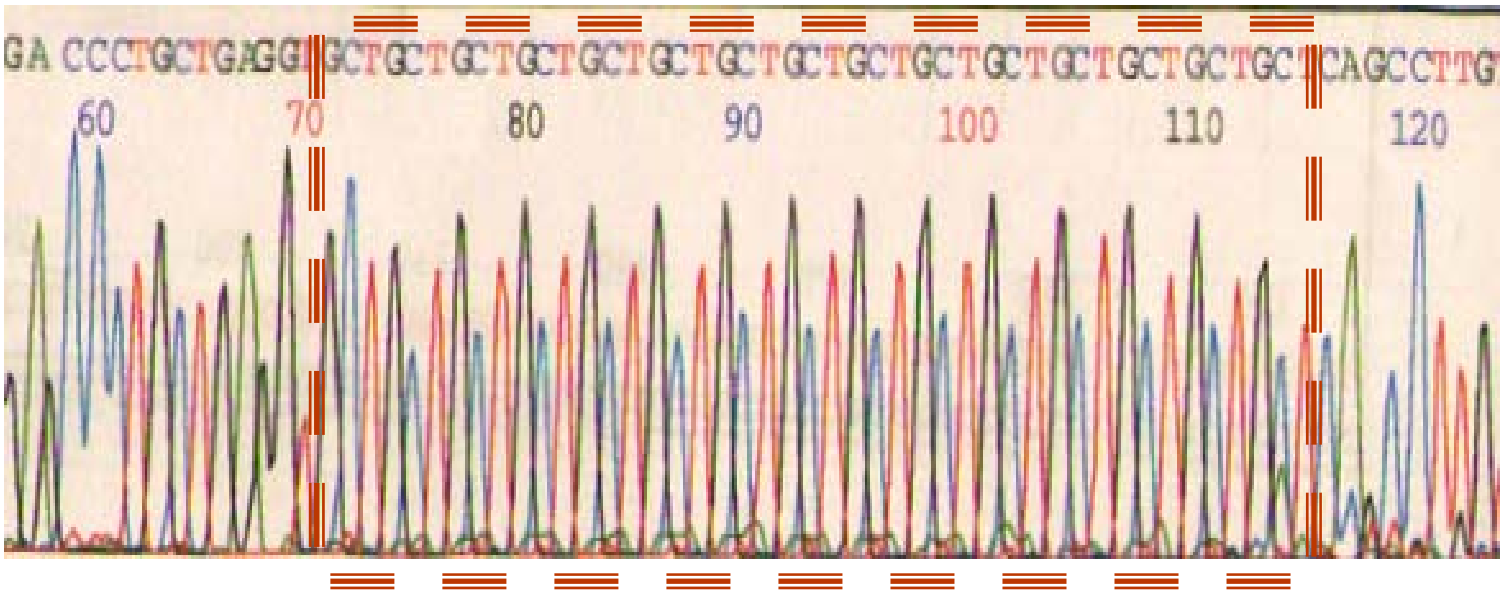
hMLH1 (3p; 19 exons, 100 kB) : up to 60% of HNPCC

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?)

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...)**



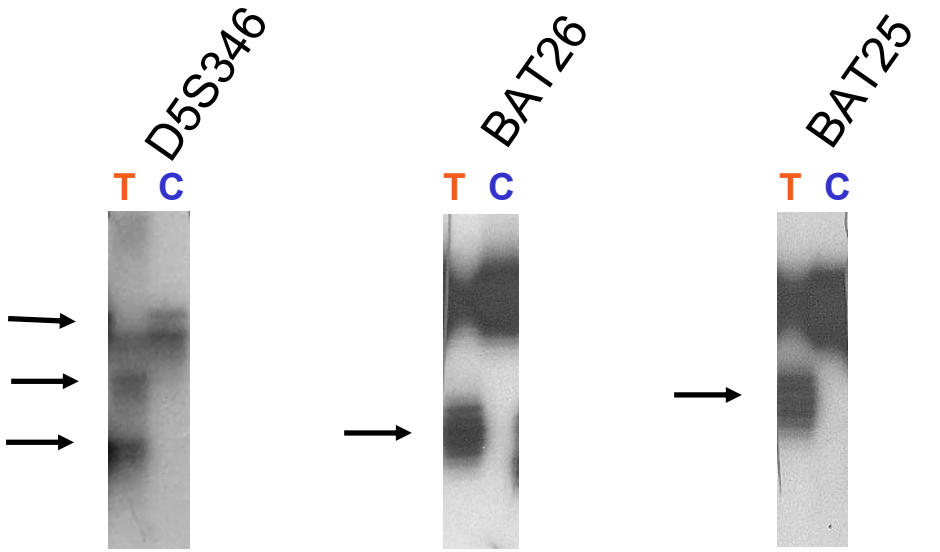
- **The number of repetitions is highly variable**
- **Such microsatellites are present every 10,000-50,000 nucleotides throughout the human genome**
- **Most microsatellites are situated between genes, or outside of exons**

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)

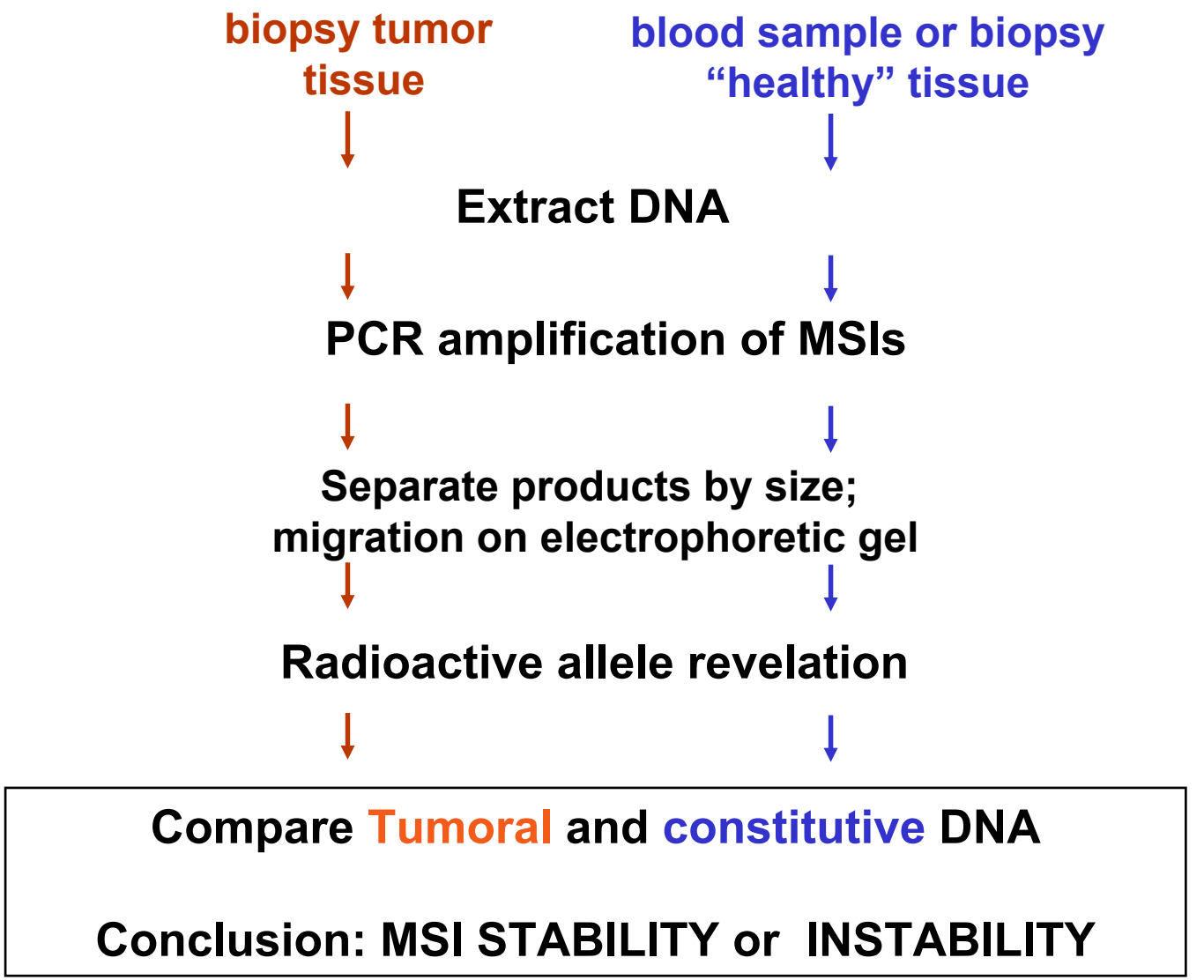
- 1 / 5 MSIs instable : MSI-L (weak instability)

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

69 cases tested in 2000

- 12 MSI-H
- 0 MSI-L

Analysis of MSI in patient's 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

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

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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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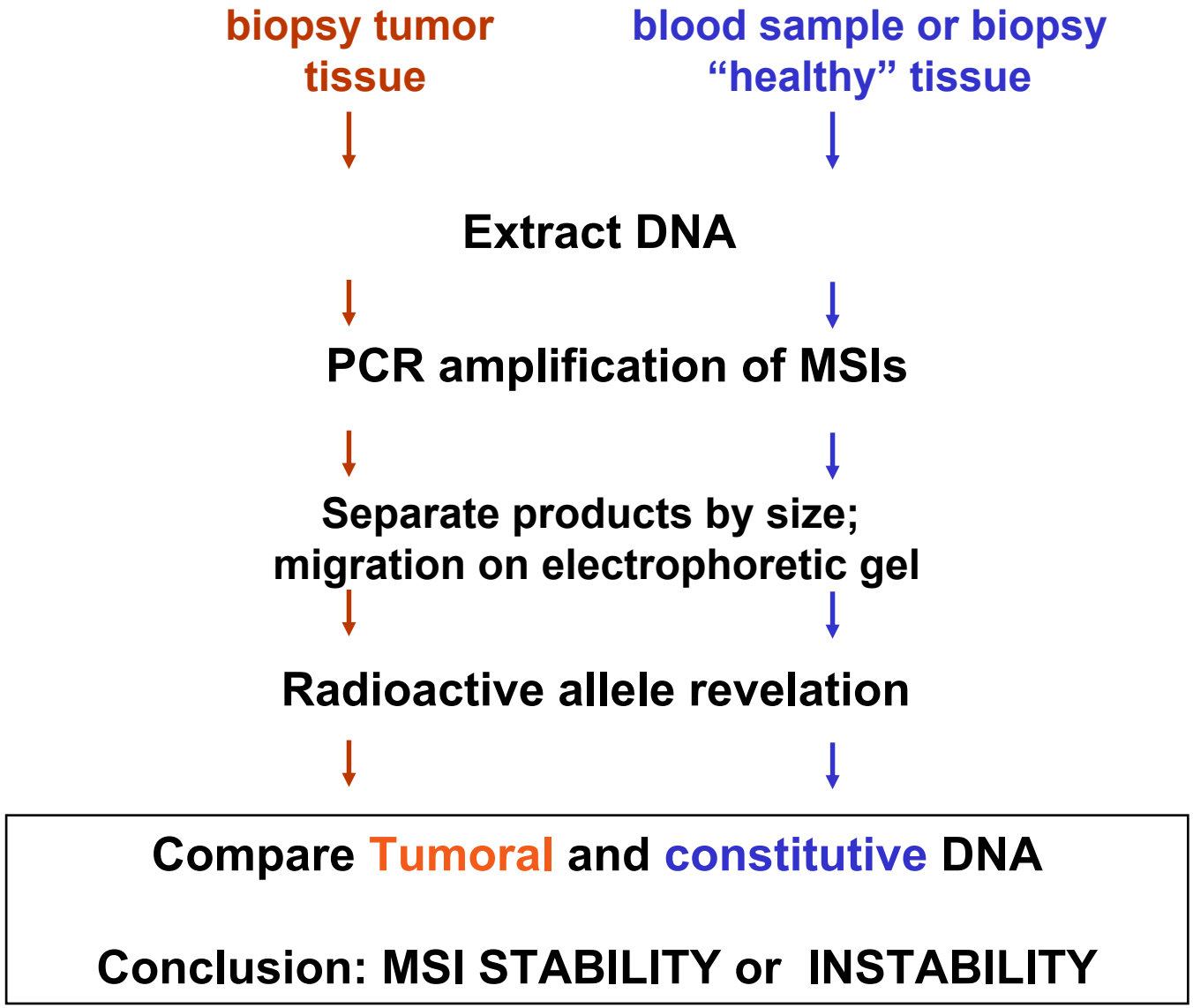

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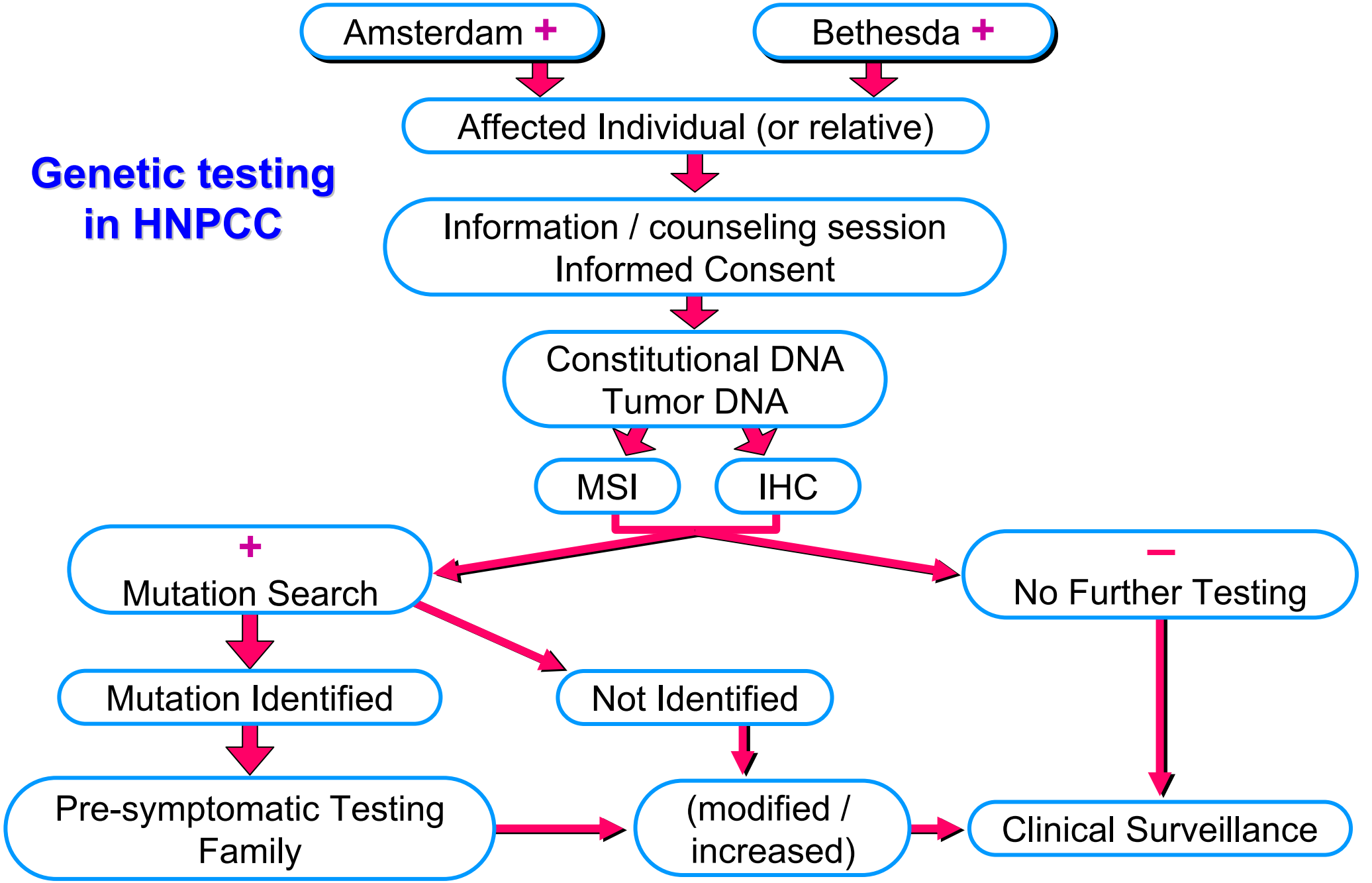
Genetic testing in HNPCC



Why test?

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...

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

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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?