# Risk Assessment for HNPCC

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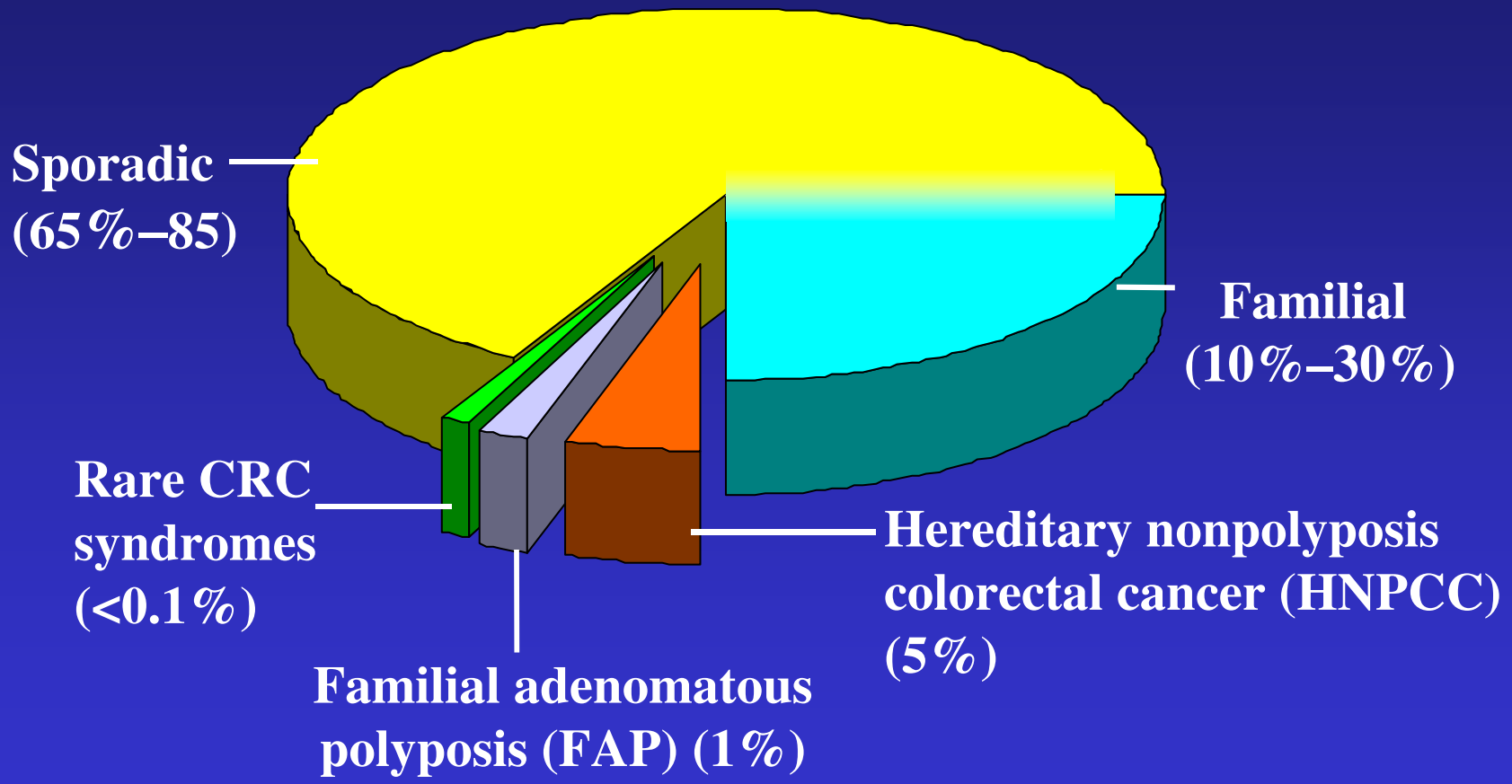
# Outline

- Background (not covered in detail)
- Observations from Clinical Studies
  - Time to onset for colorectal cancer and Cyclin D1
  - Risk for endometrial cancer
  - Pathological observations of breast cancer in HNPCC
- Issues from clinical groups

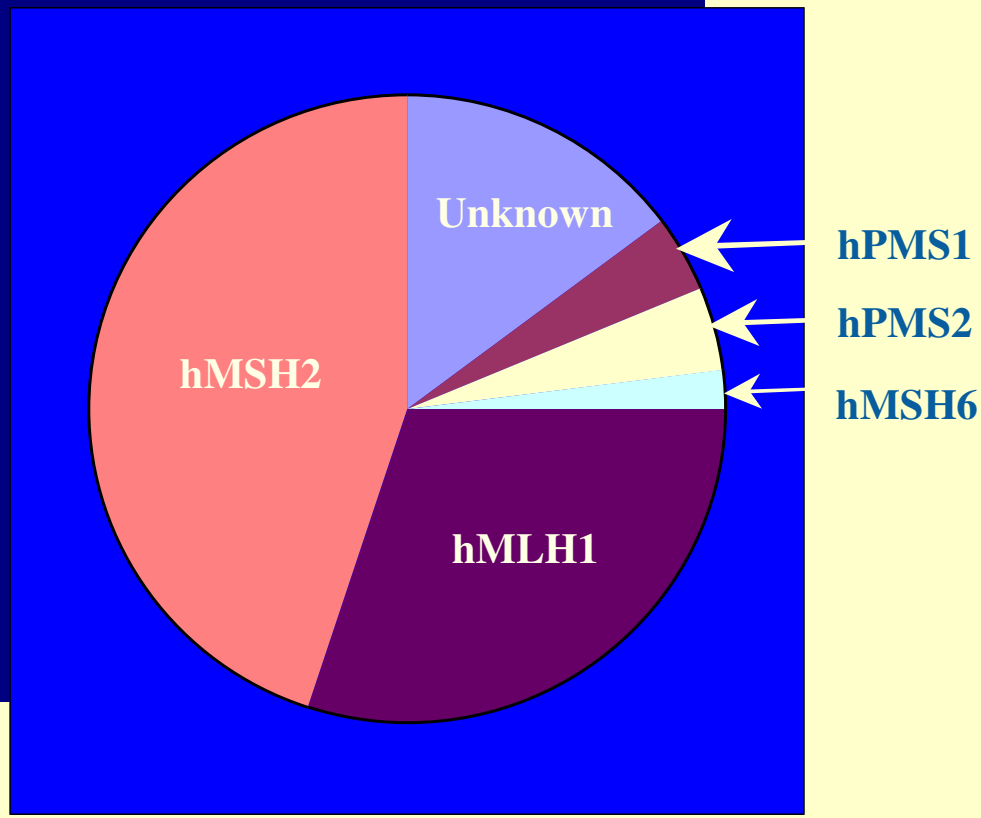
# Causes of Hereditary Susceptibility to CRC




Adapted from Burt RW et al. *Prevention and Early Detection of CRC*, 1996

## Most HNPCC alterations are from germline mutations in mismatch repair (MMR) genes:

- hMLH1
- hMSH2
- hPMS1
- hPMS2
- hMSH6



# Tumorigenesis in HNPCC

Unaffected MMR mutation carrier


MMR Proficient

Tumor development

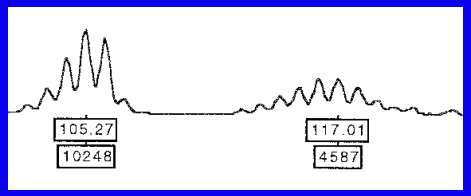

MMR Deficient

Accumulation of Mutations
(especially in mononucleotide repeats)

# Microsatellite Instability

## BAT 26

T

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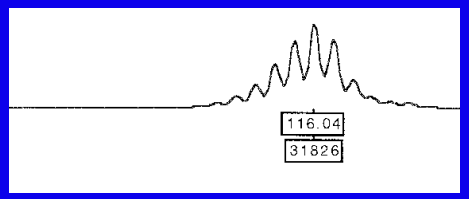


## BAT 25

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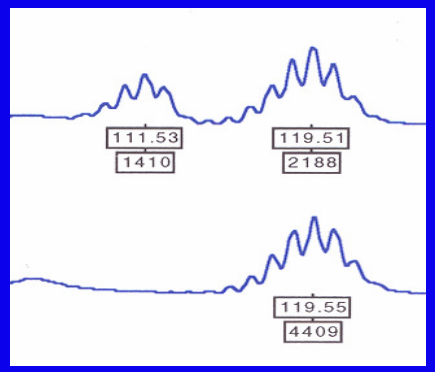


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## D2S123

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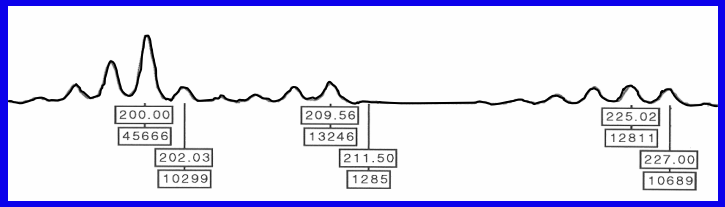


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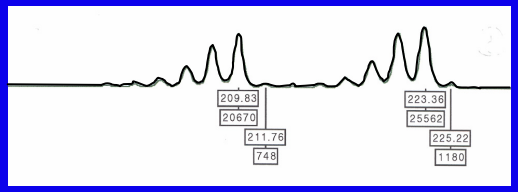


## D17S250

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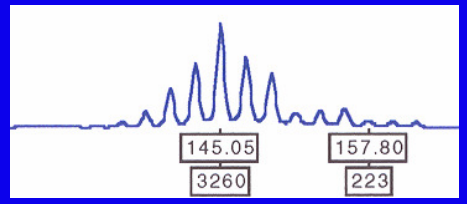


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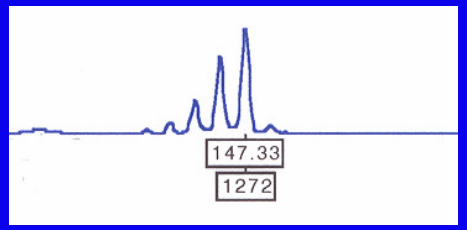


# NCI REFERENCE PANEL

BAT25
BAT26
D5S346
D2S123
D17S250

# Genes Mutated in HNPCC

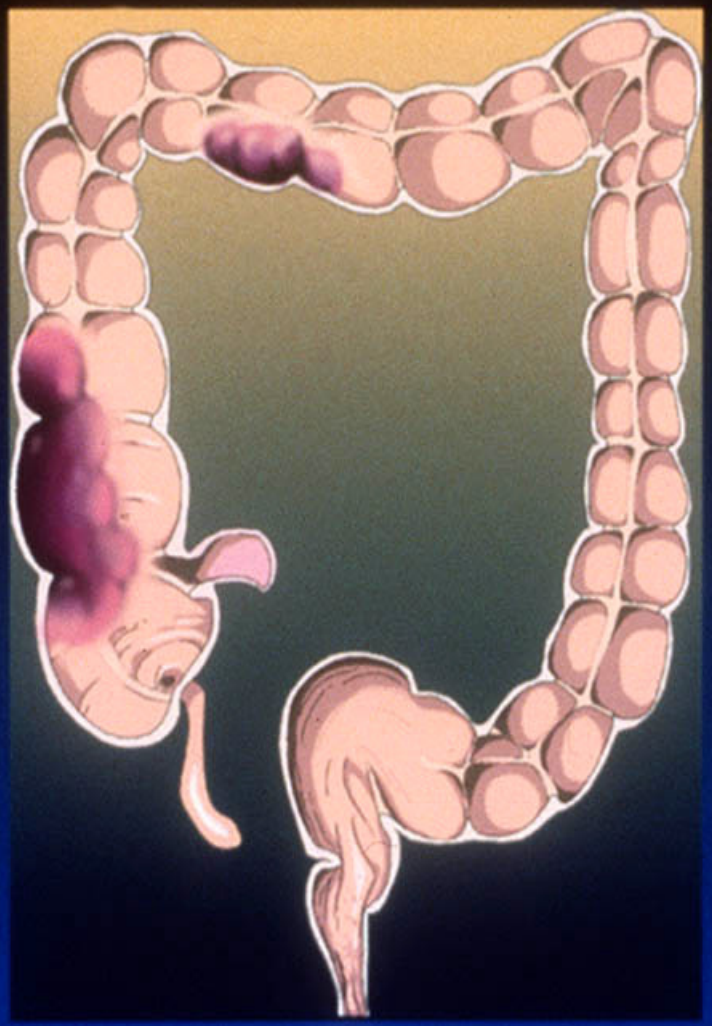
- TGF-βRII
- IGFIIR
- BAX
- $\beta_2$MICROGLOBULIN
- E2F-4

# Hereditary Nonpolyposis Colorectal Cancer

Early age at onset

Multiple primary cancers

Right colon predominance



Few or no adenomas

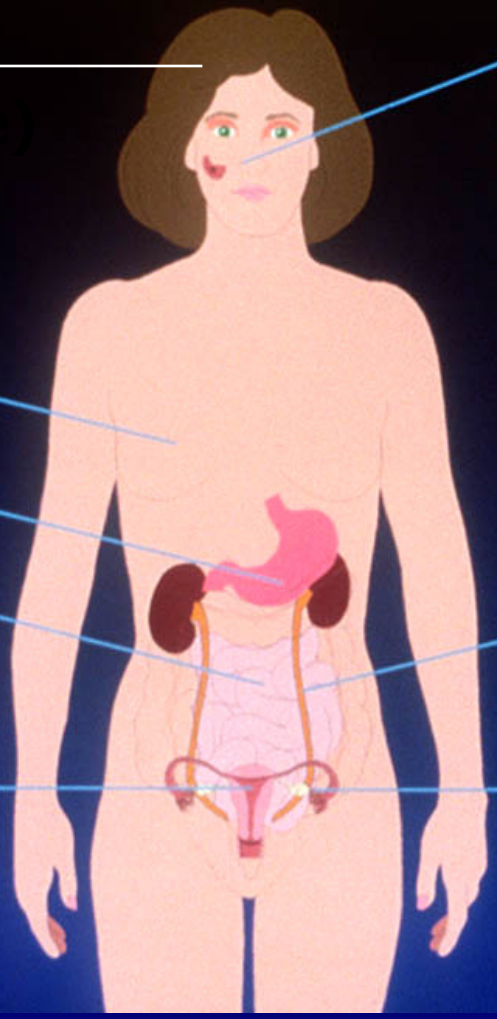
Autosomal dominance

Tumors are MSI +

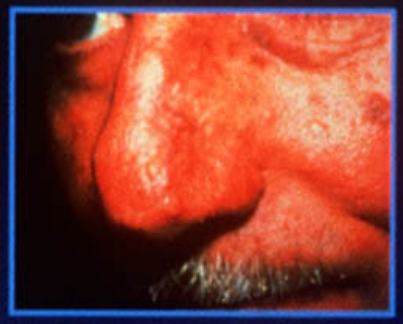
Endometrial cancer

Hereditary Nonpolyposis Colorectal Cancer

# Extracolonic Malignancy



Keratoacanthomas /
Sebaceous gland neoplasia
(Muir-Torre syndrome)



Breast

Stomach

Small bowel

Endometrium

Uroepithelium

Ovary

# Existing Risk Models for HNPCC

- Aarnio et al. (1995) – 40 families, 414 individuals, 78% lifetime risk for CRC, 43% for EC
- Aaltonen et al. (1998) – systematic study of 509 patients, screened for MSI, 2% have MMR
- Peltomaki and Vasen (1997) – mutaions from 126 subjects in ICGHNPCC, high proportion of missense mutations in hMLH1
- Wijnen et al., (1998) – 184 families with colon cancer, 26% with MMR, predictors of MMR include Amsterdam criteria, EC, early onset CRC

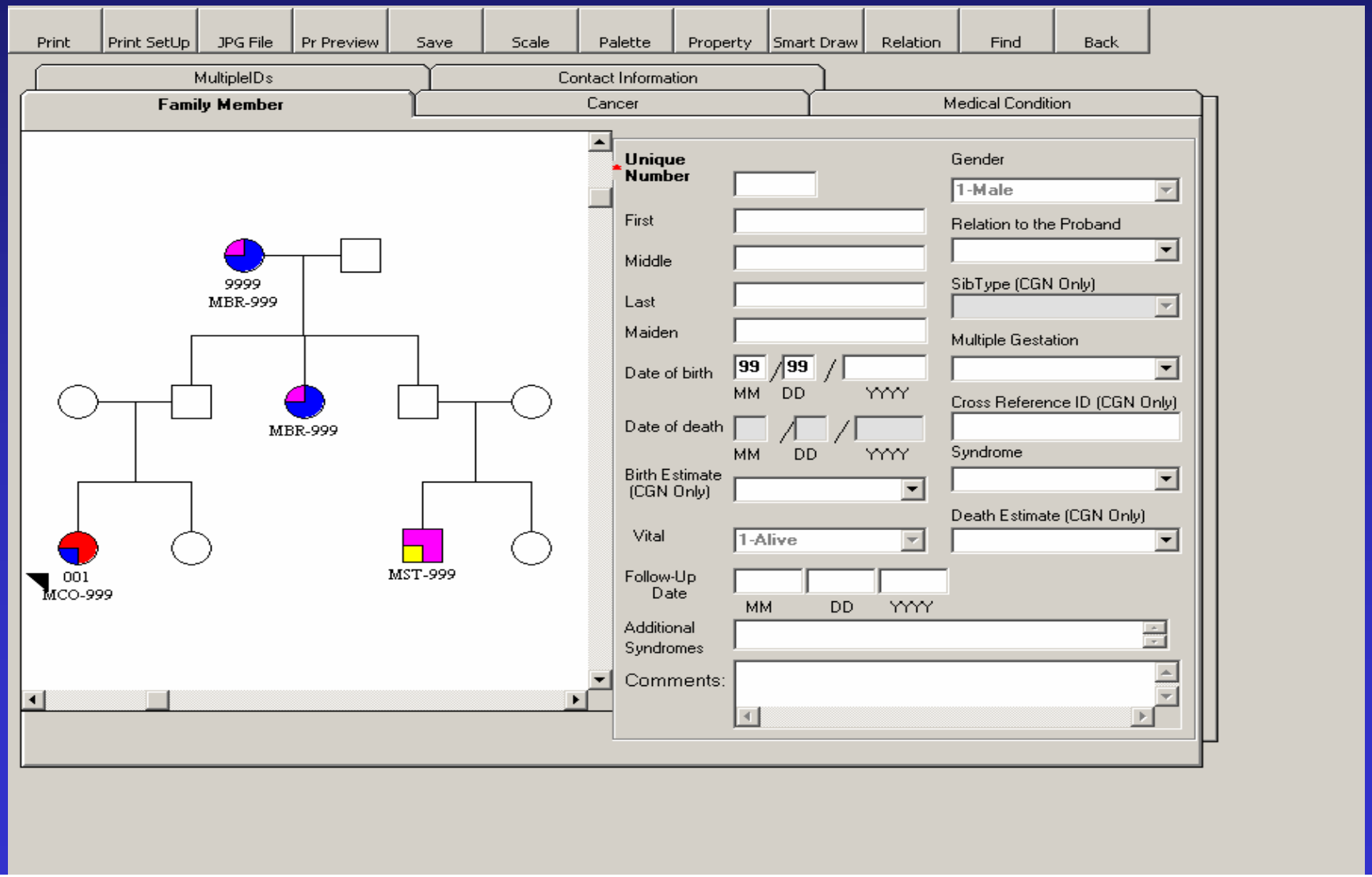
# Descriptive Epidemiology of HNPCC

- The lifetime risk for CRC is 80% in MMR mutation carriers.
- Although individuals with HNPCC have similar pathophysiology, their age of cancer onset varies significantly from early to late in life.
- This variation cannot be explained by the MMR genotype alone, suggesting that other genetic or environmental factors are involved in determining age of onset.

# Human Pedigree Analysis Resource - UTMDACC

- 3 mechanisms for data capture:
  - New patients can complete questionnaire prior to the visit (more common in breast center)
  - New patients may provide information only at the time of the clinical visit (more common for colon cancer families)
  - Updates require different scheme

# Updating Pedigree Data



# Data Collection

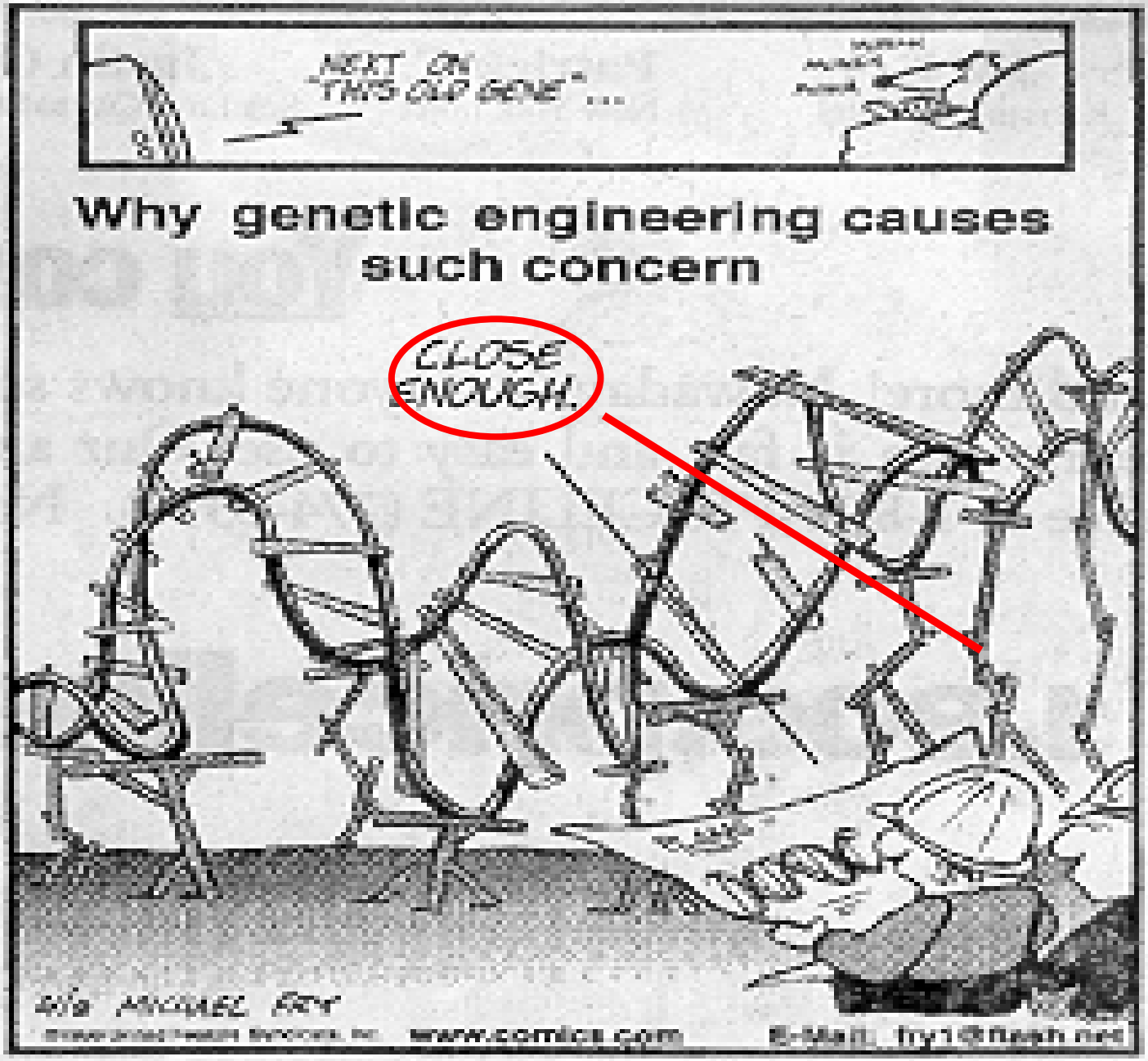
- Epidemiologic data:

  Age, gender, ethnicity, cancer status, colorectal cancer age of diagnosis and MMR mutation type
- Genotyping of DNA:

  Polymerase Chain Reaction (PCR) and

  Single Strand Conformation Polymorphism (SSCP) gel electrophoresis technique to assess polymorphism in SULT1A1
- DNA sequencing analysis to determine the genotype of each of the banding patterns detected by SSCP analysis

# Committed


NEXT ON "THIS OLD GENE"...
Why genetic engineering causes such concern
CLOSE ENOUGH
MICHAEL FRY
www.comics.com

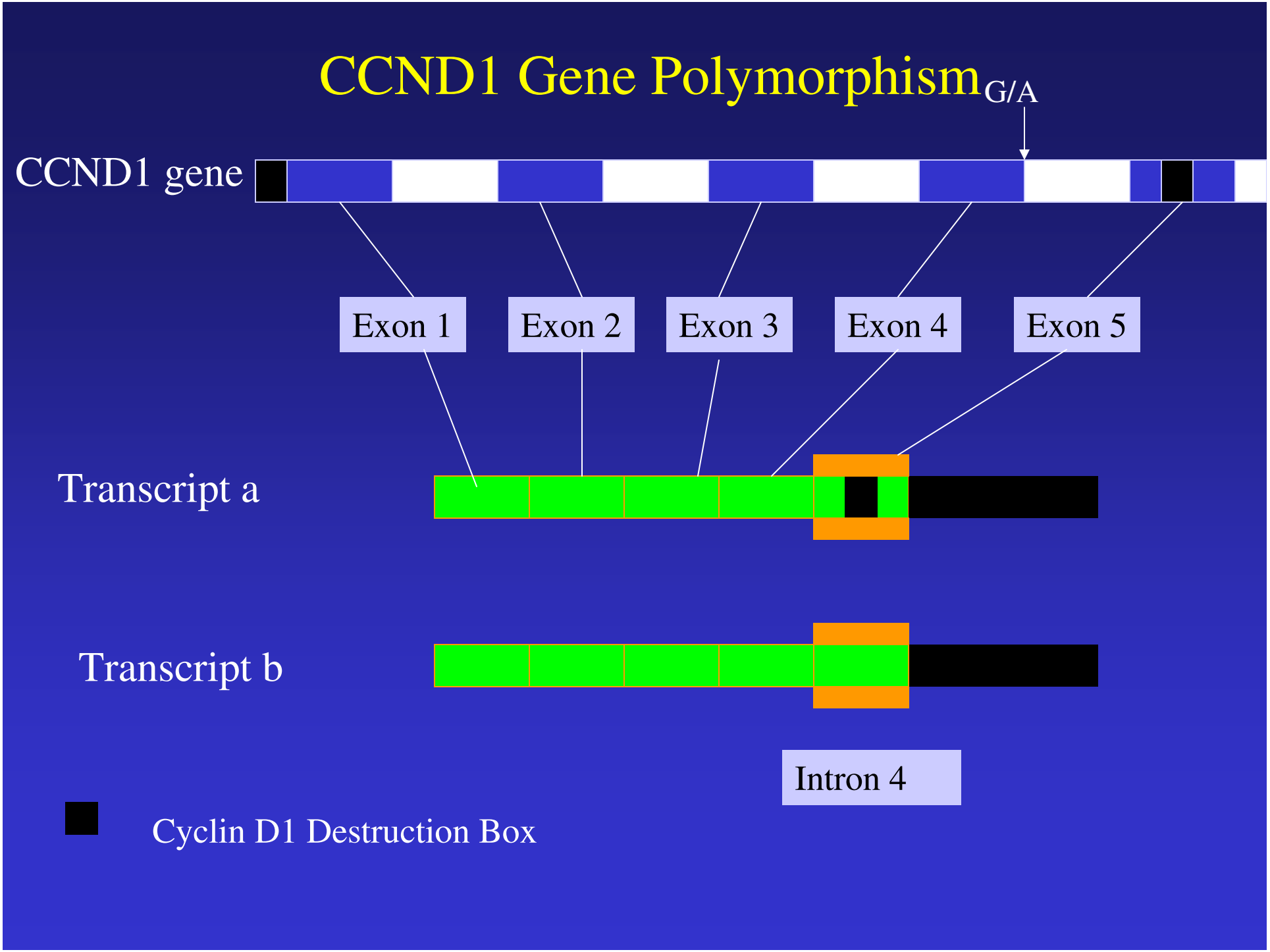
# Modifying Factors

- The lifetime risk for CRC is 80% in MMR mutation carriers.
- There is significant heterogeneity in the age of onset of CRC in HNPCC families.
- Preliminary laboratory studies on this patient population suggest that among MMR mutation carriers, the type of MMR mutation *hMSH2* or *hMLH1* does not have a significant influence on the age-associated risk for CRC.
- Environmental and other genetic factors may play a role.
- Evidence that Cyclin D1 polymorphic variant affects risk and type to onset for canccer

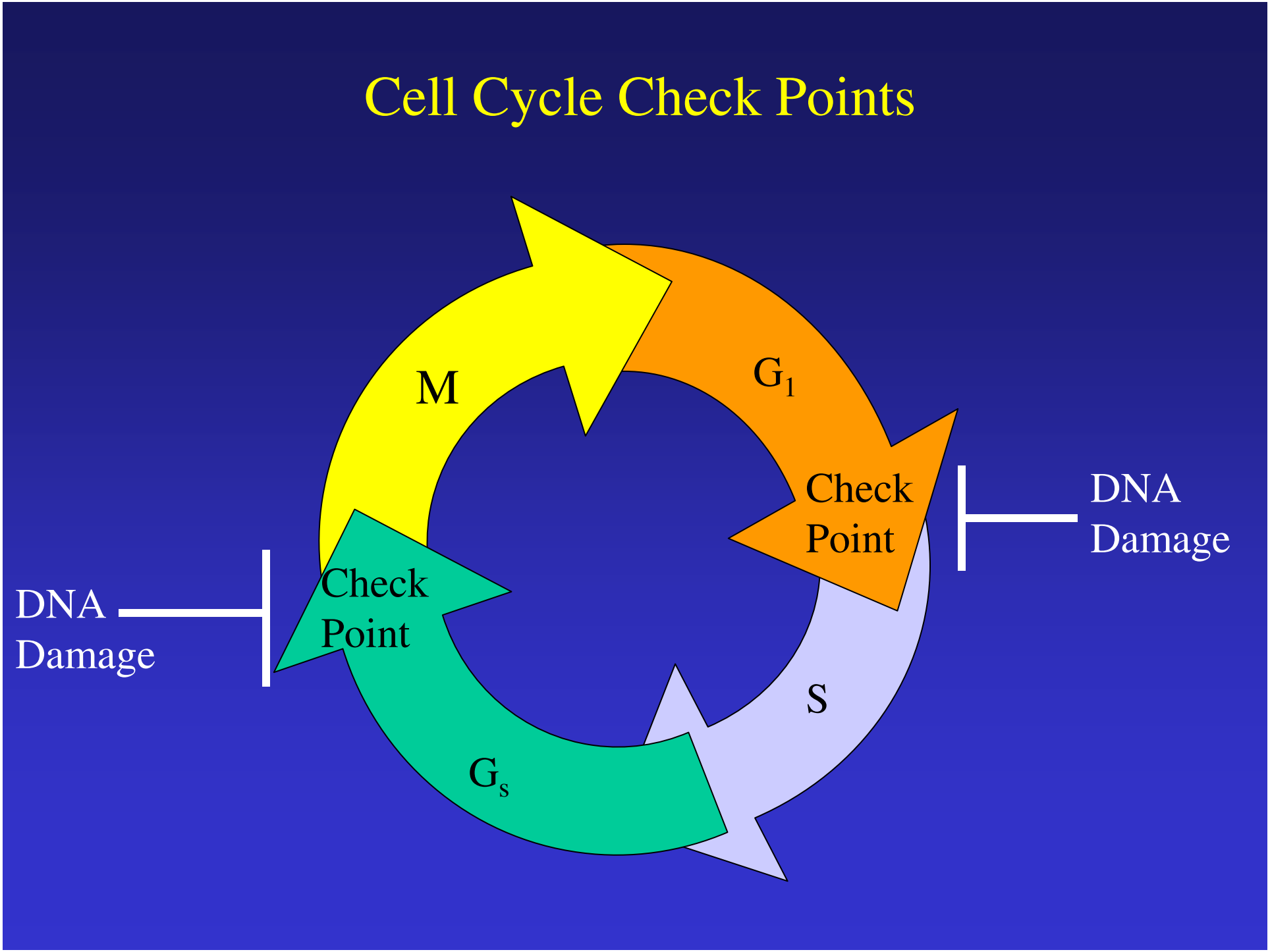
# Participant Characteristics

- Study sample: 137 participants from 65 families
  - Signed an informed consent for Protocol DM94-060
  - Donated a blood sample (20 cc)
  - MMR mutation positive
- Sample size analyzed: 132 participants
  - With colorectal cancer: 66
  - No history of colorectal cancer : 66

# CCND1 Gene Polymorphism$_{G/A}$



# Cell Cycle Check Points

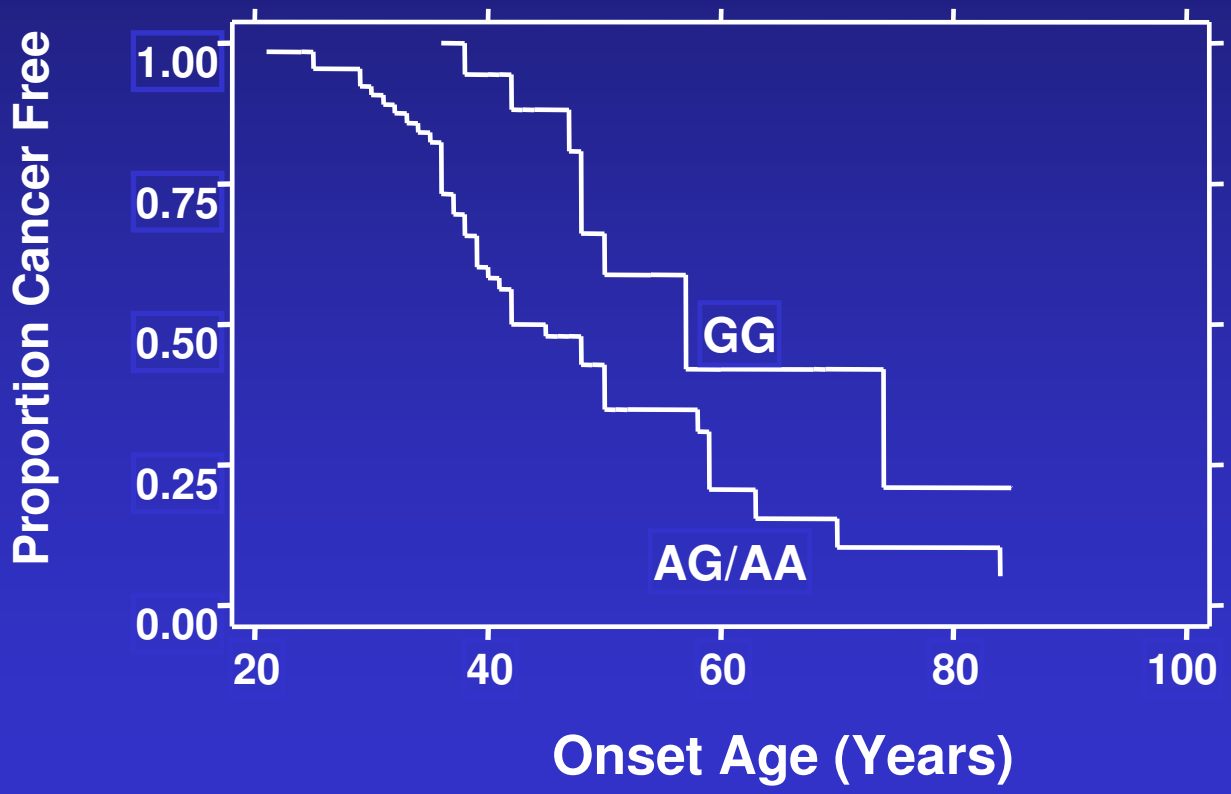


# Differential Functions of Transcript/Protein a and b

- Protein a and b both co-immunoprecipitate with CDK4
- Protein b is a less efficient catalyst of RB protein phosphorylation
- Protein b had potent transforming activity when expressed in NIH3T3 cells which was not observed with protein a

Solomon et al. J. Biol Chem. 278:30339, 2003

# Kaplan-Meier survival analysis by various CCND1 genotypes

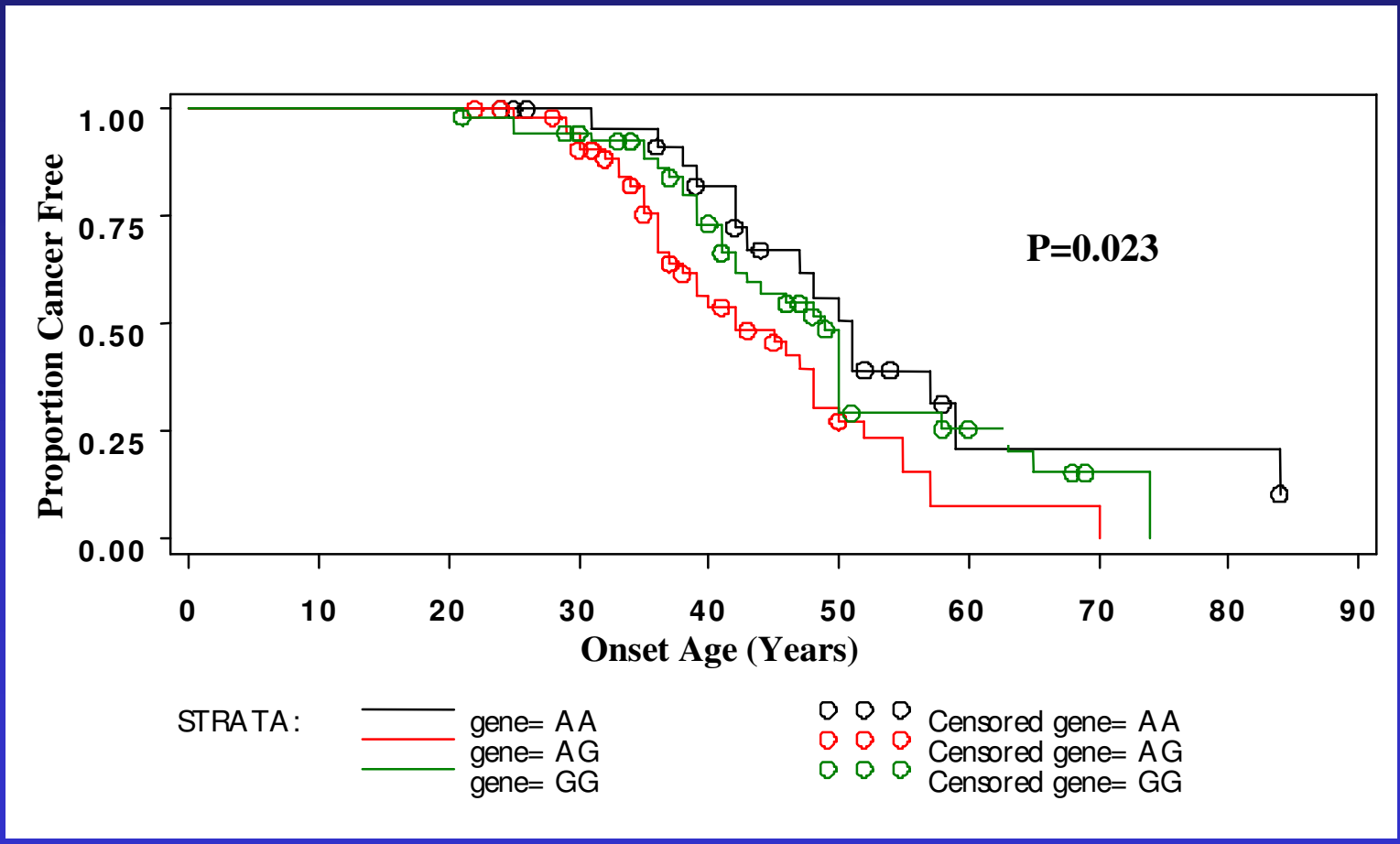



P=0.007

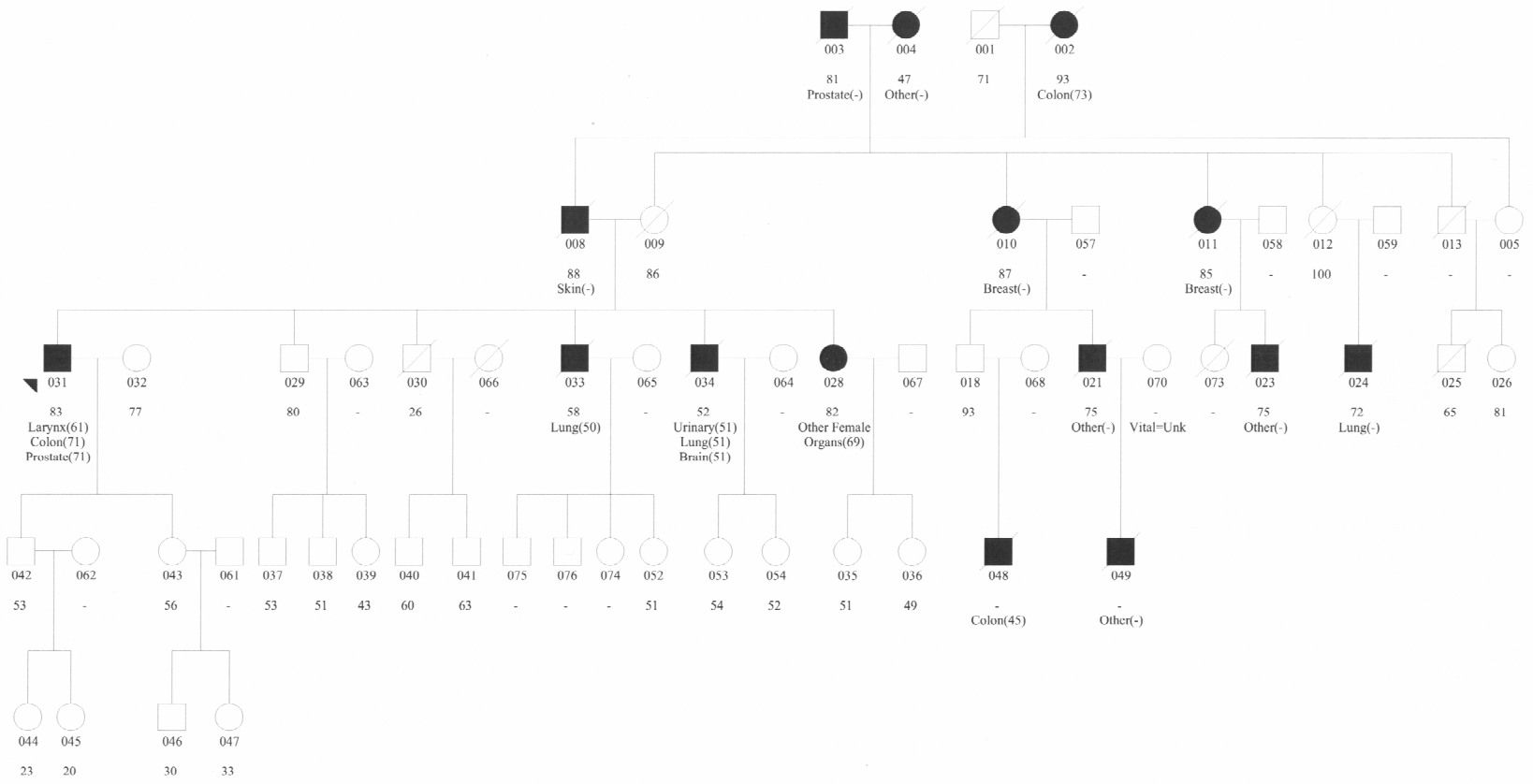
# X-ray Repair Cross-complementing Group I (XRCC1)

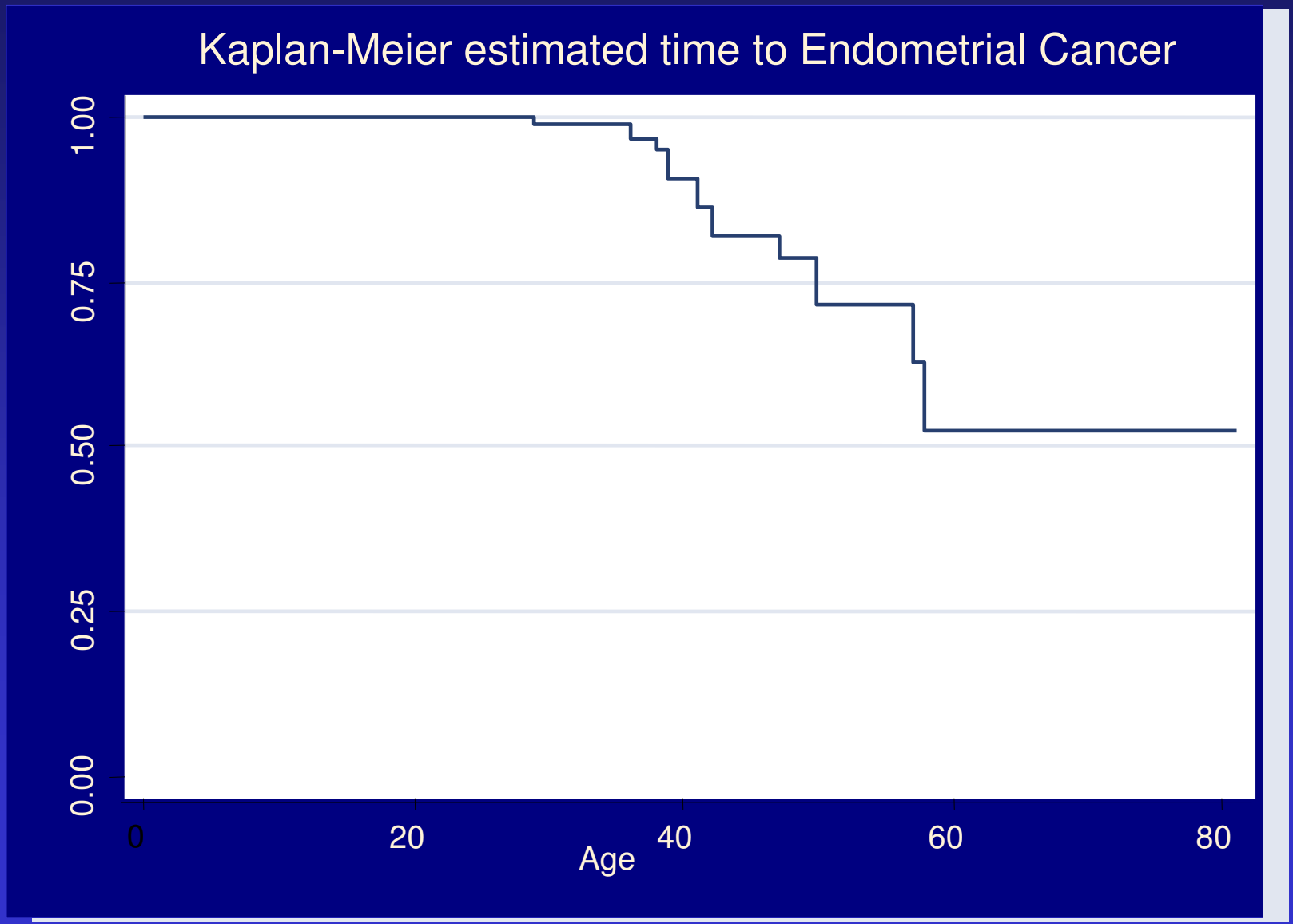
- Important role in the base-excision repair pathway
- G-to-A substitution at codon 399 in exon 10
- Arg to Gln

# Kaplan-Meier survival analysis plot of age-of-onset of colorectal cancer for each of the three genotypes of the *XRCC1* polymorphism



# Pedigree of a CRC Patient With Methylation at All Four Loci Tested




Kaplan-Meier estimated time to Endometrial Cancer
1.00
0.75
0.50
0.25
0.00
0
20
40
60
80
Age

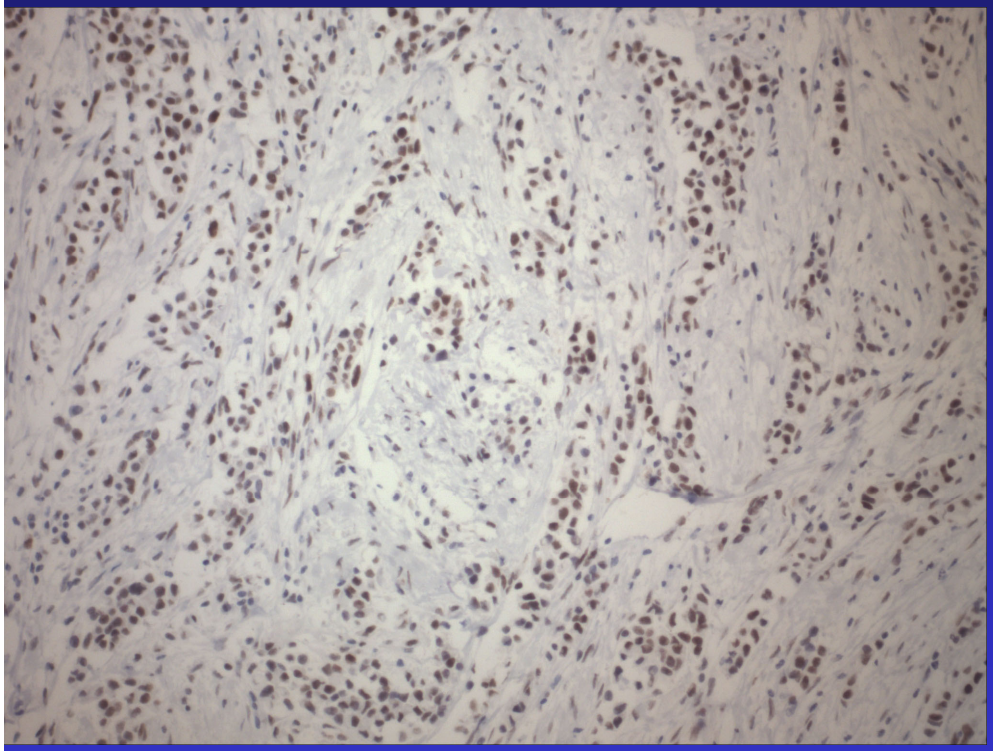
# Case Study

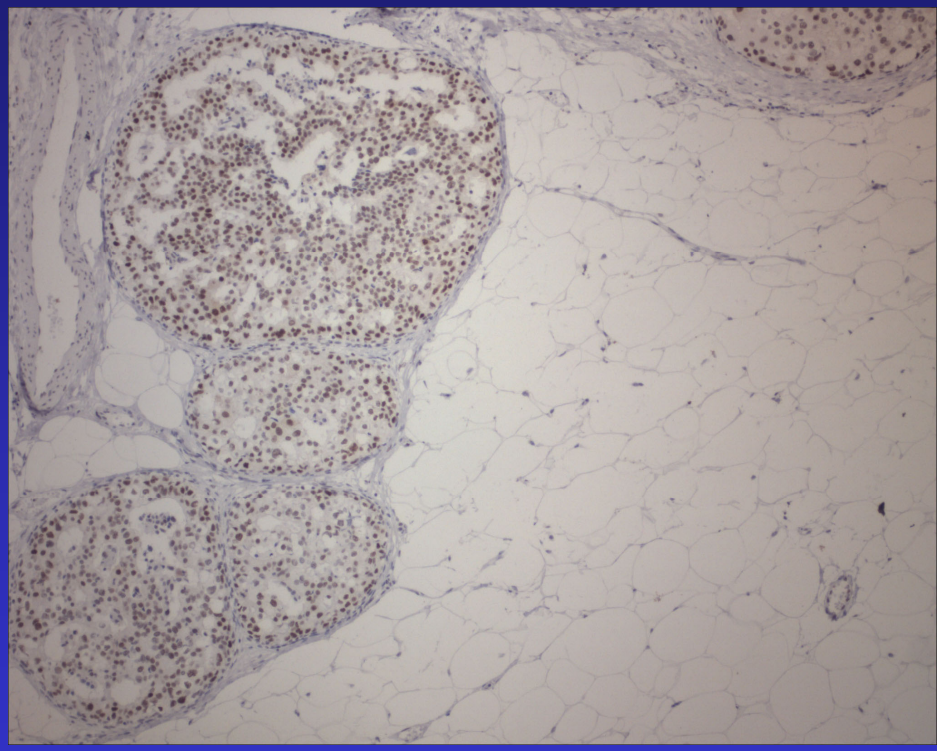
36 year old woman with breast cancer (infiltrating ductal carcinoma) and axillary lymph node metastasis.

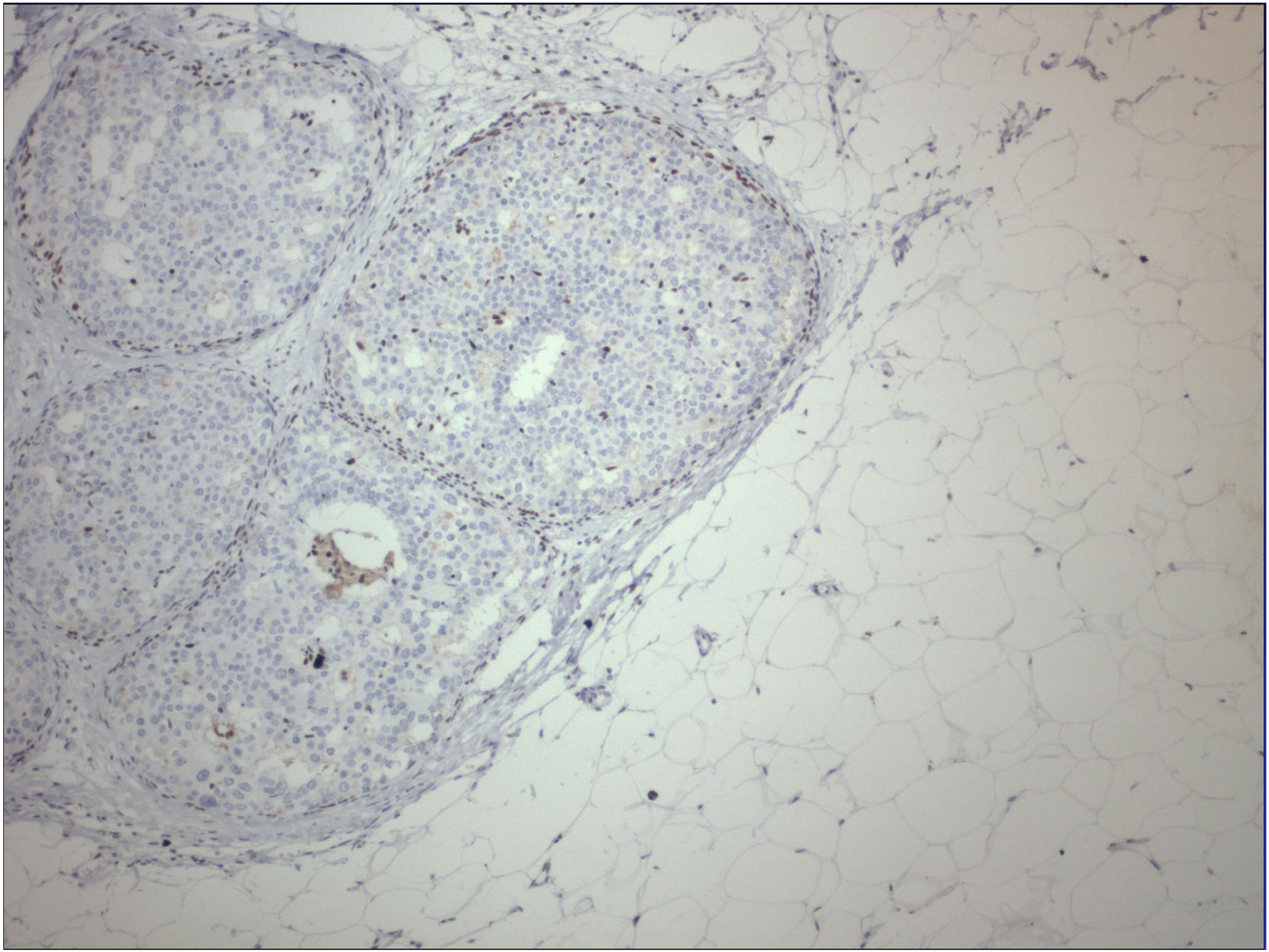
Age 39 – developed spine metastasis

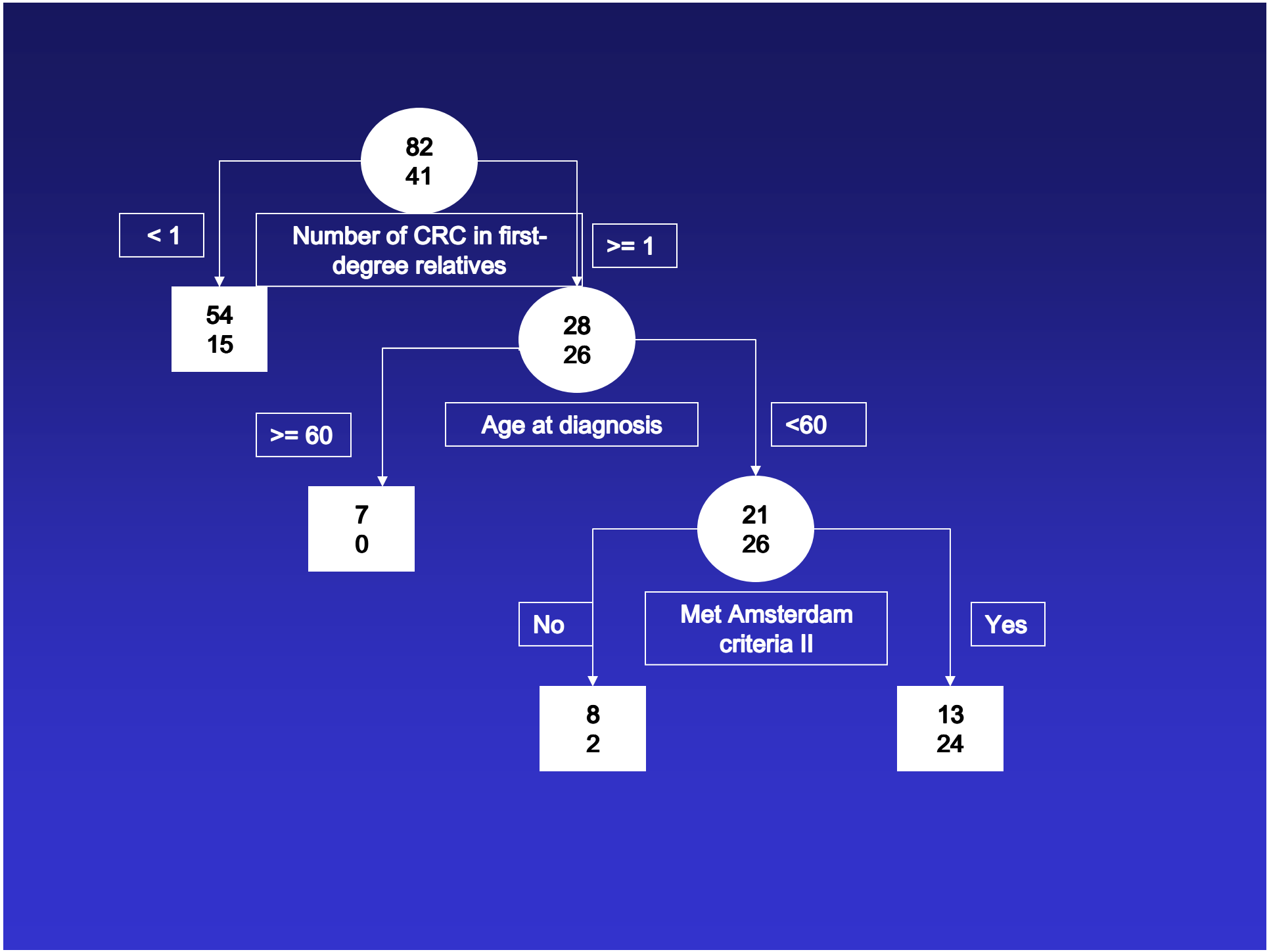
Currently, age 40 with numerous bone metastases.

Family history of endometrial (2 aunts) and colorectal cancer (father).








82
41
Number of CRC in first-degree relatives
< 1
>= 1
54
15
28
26
Age at diagnosis
>= 60
<60
7
0
21
26
Met Amsterdam criteria II
No
Yes
8
2
13
24

# Issues in Analysis from Clinical Groups

- Important source for well characterized data
  - Access to tissue and blood for further studies
  - Willingness to participate in behavioral studies and interventions
- Generalizing to other populations is difficult without population-based data and novel statistical tools
- Studies of time-dependent endpoints provide valid estimates or relative risks but not absolute risks
- High proportion of missense mutations in hMLH1 impedes counseling, protein structure would help