The Genetics of Colorectal Cancer

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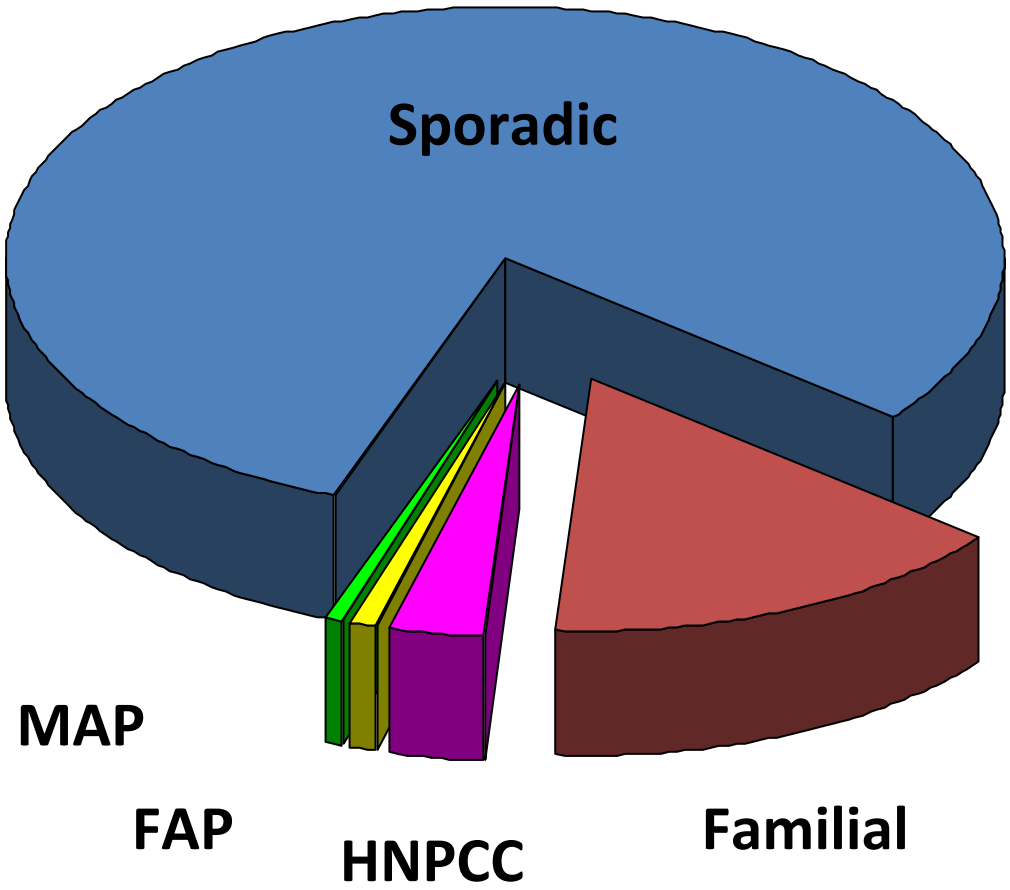
Colorectal Cancer

- Second leading cause of cancer death
- 150,000 cases per year
- 57,000 deaths per year
- Medical treatment not curative

COLORECTAL CANCER



Hereditary Syndromes

- Hereditary nonpolyposis CRC (HNPCC)
- Familial adenomatous polyposis (FAP)
- Attenuated FAP
- MYH associated polyposis (MAP)

Hereditary Nonpolyposis Colorectal Cancer

Hereditary Nonpolyposis Colorectal Cancer

- Autosomal dominant disease
- Mismatch repair gene mutation
- Proximal location of colorectal cancer
- Early age of onset
- Multiple primary malignancies
- Other family cancer

Hereditary Nonpolyposis Colorectal Cancer

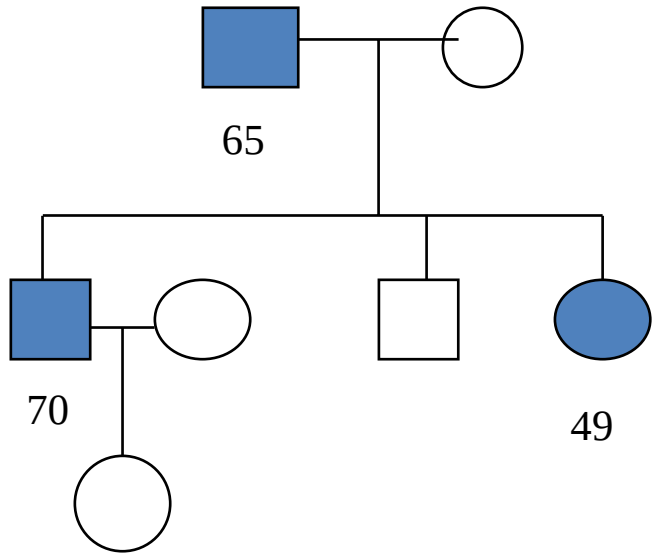
- Warthin-Lynch Syndrome
- Lynch Syndrome

Amsterdam Criteria

3 or more with CRC

2 generations

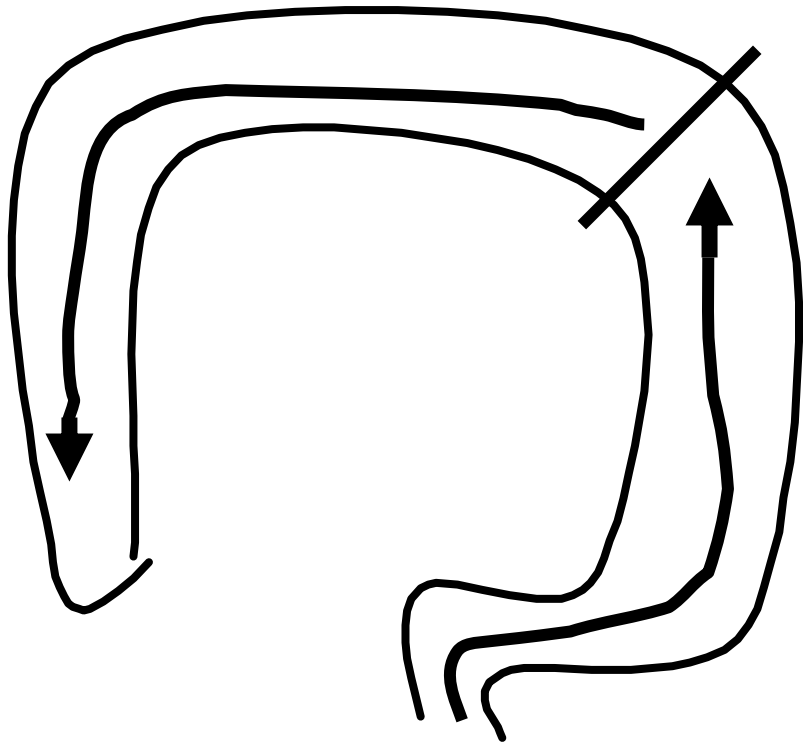
1 diagnosed age < 50 yrs



COLORECTAL CANCER

HNPCC
right sided

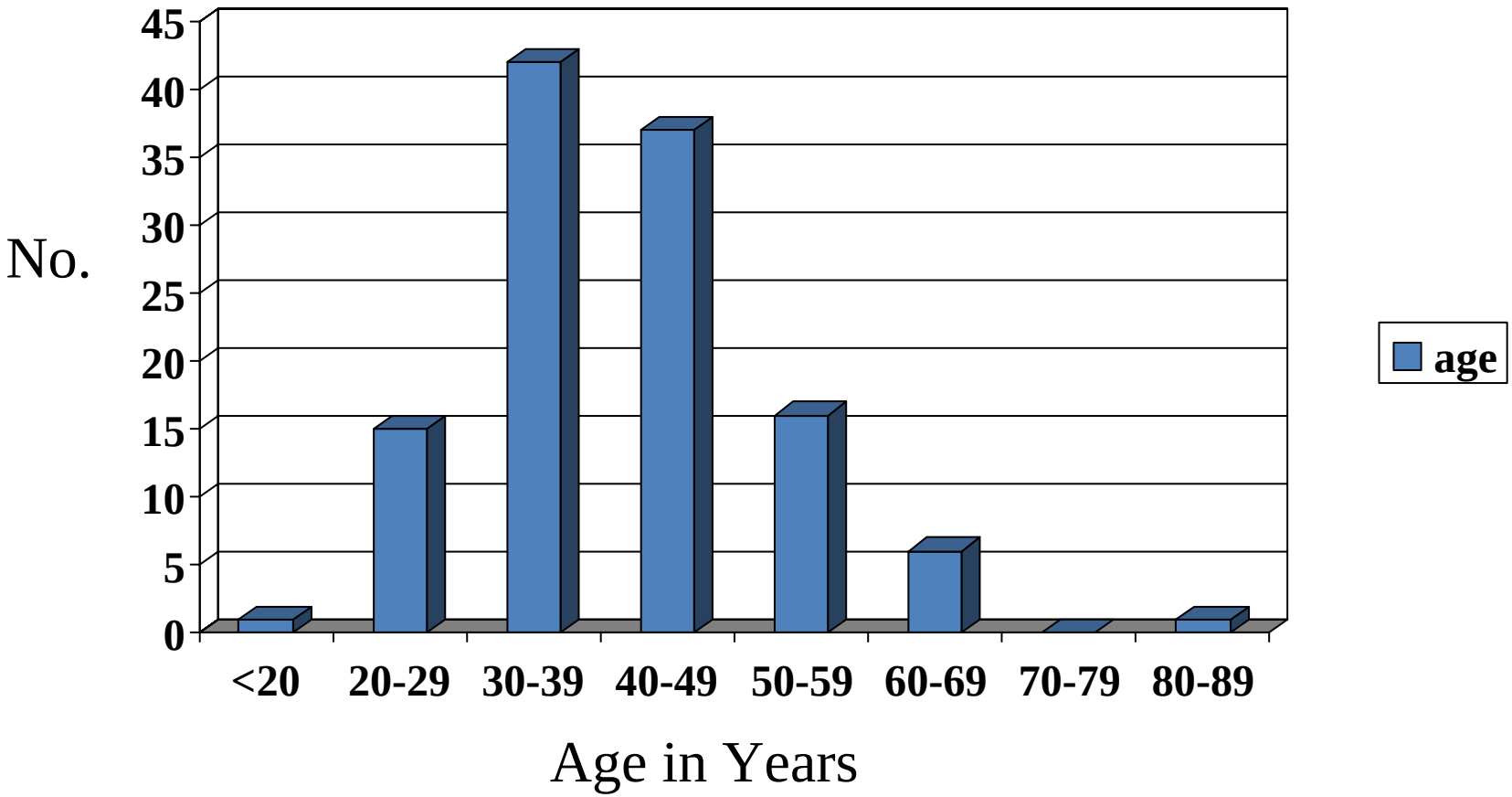
Sporadic
left sided



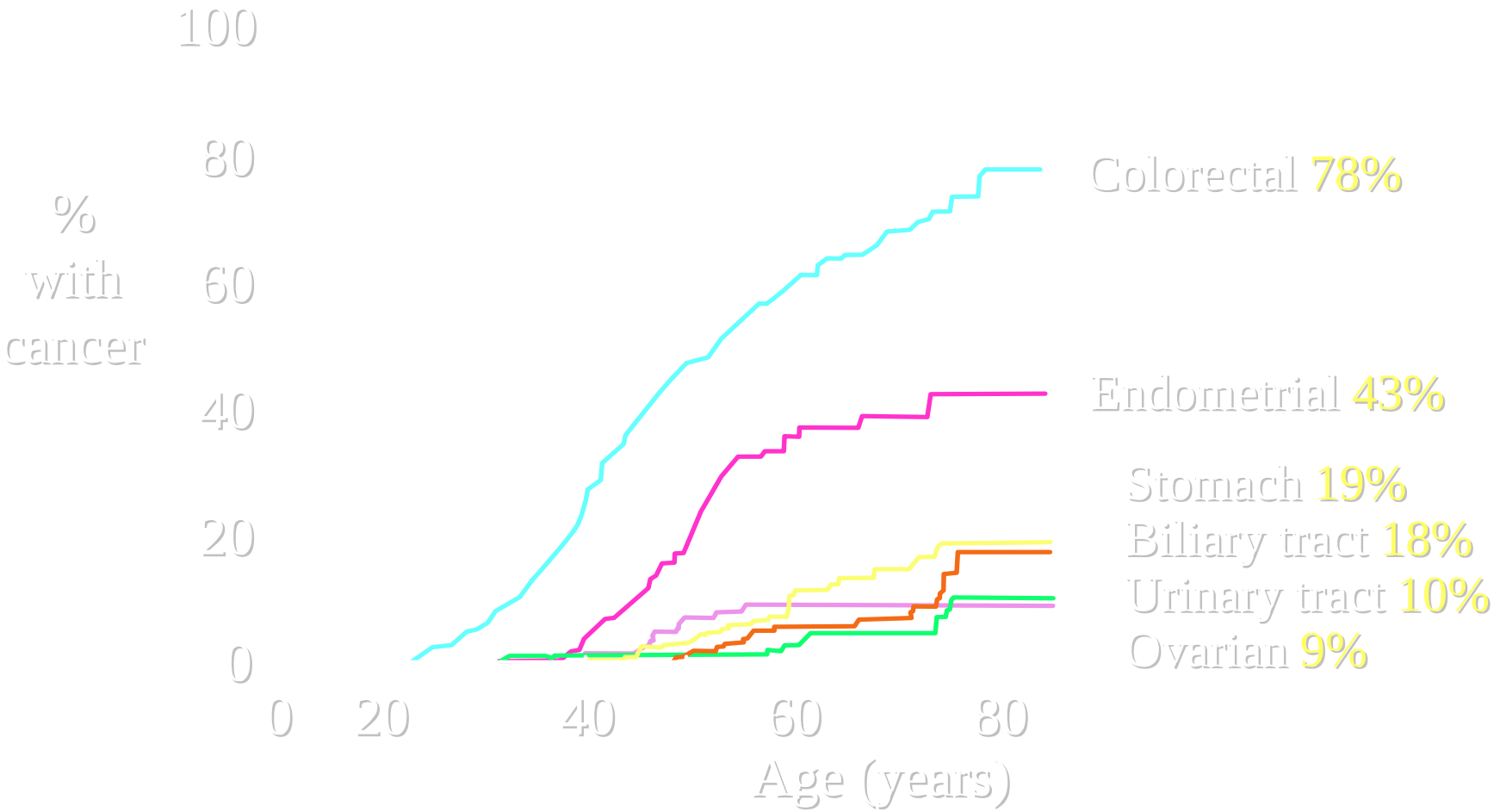
44 yo

64 yo

Age of Diagnosis of Colorectal Cancer in HNPCC



Cancer Risks in HNPCC



Aarnio M et al. *Int J Cancer* 64:430, 1995

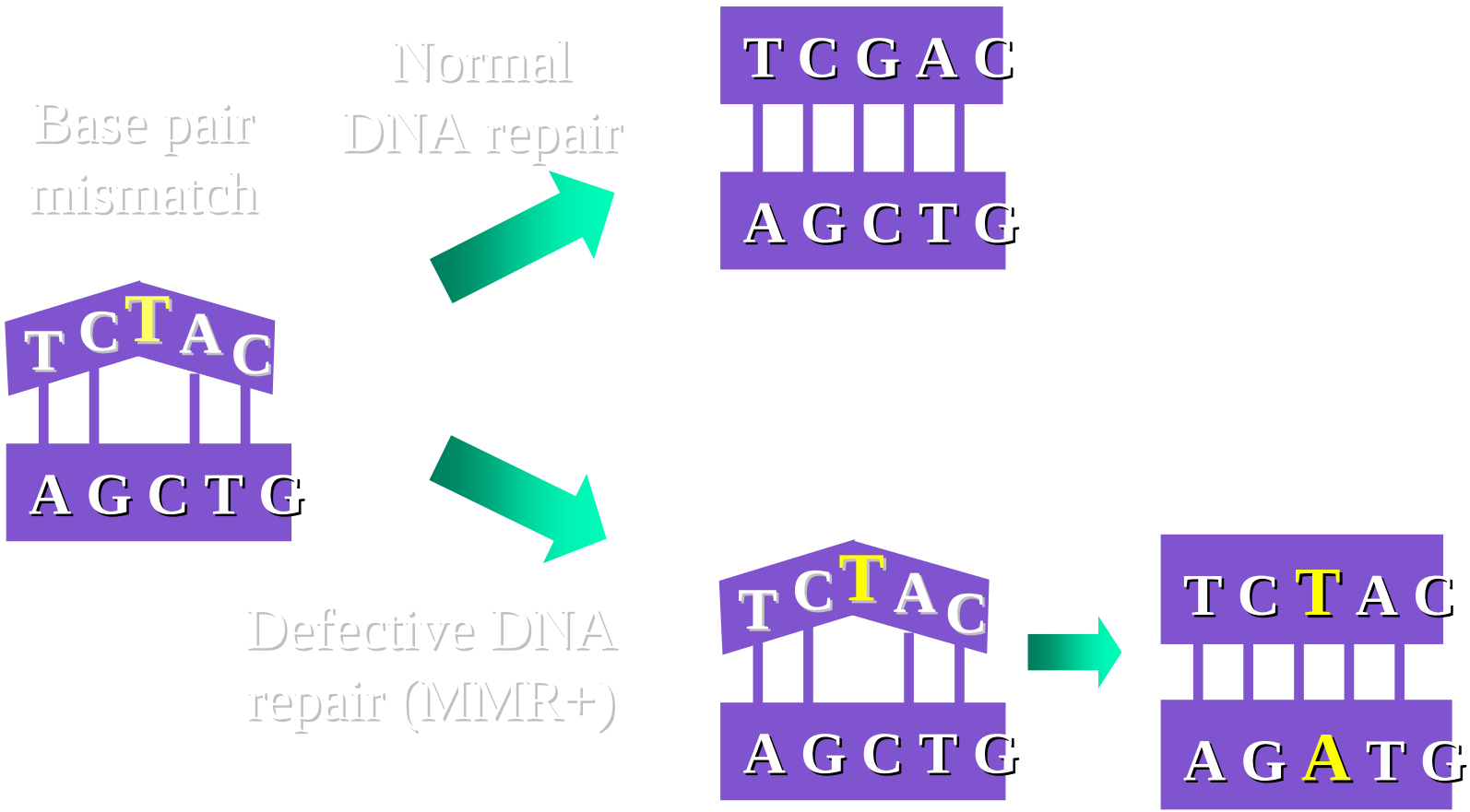
Screening At- Risk Members

- Colonoscopy q 1-2 years starting age 20-25, then annually after 40 yo
- GYN exams in women annually, biopsy of endometrium and transvaginal ultrasound
- Screening for gastric and urologic cancer

Screening: Genetic Testing

- Mutation of the mismatch repair genes
- hMSH2, hMLH1, hPMS2, hMSH6

HNPCC Results From Failure of Mismatch Repair Genes



HNPCC GENETIC TESTING

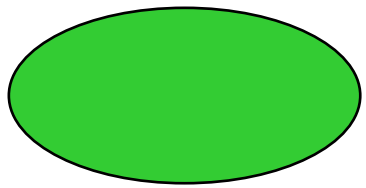
Germline

MSH2
MLH1
MSH6

Blood

Somatic

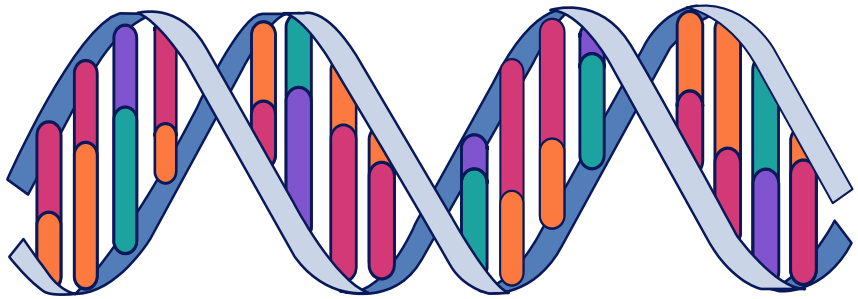
Microsatellite Instability
& Immunohistochemistry



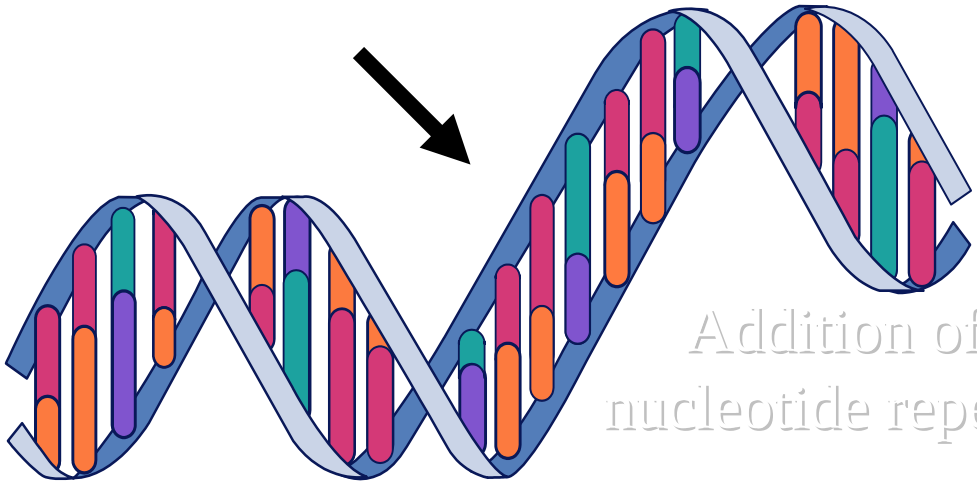
Cancer

Microsatellite Instability (MSI)

Normal



Microsatellite instability



Addition of nucleotide repeats

Immunohistochemistry

- Stain tumor for gene proteins
- Pursue absent of proteins

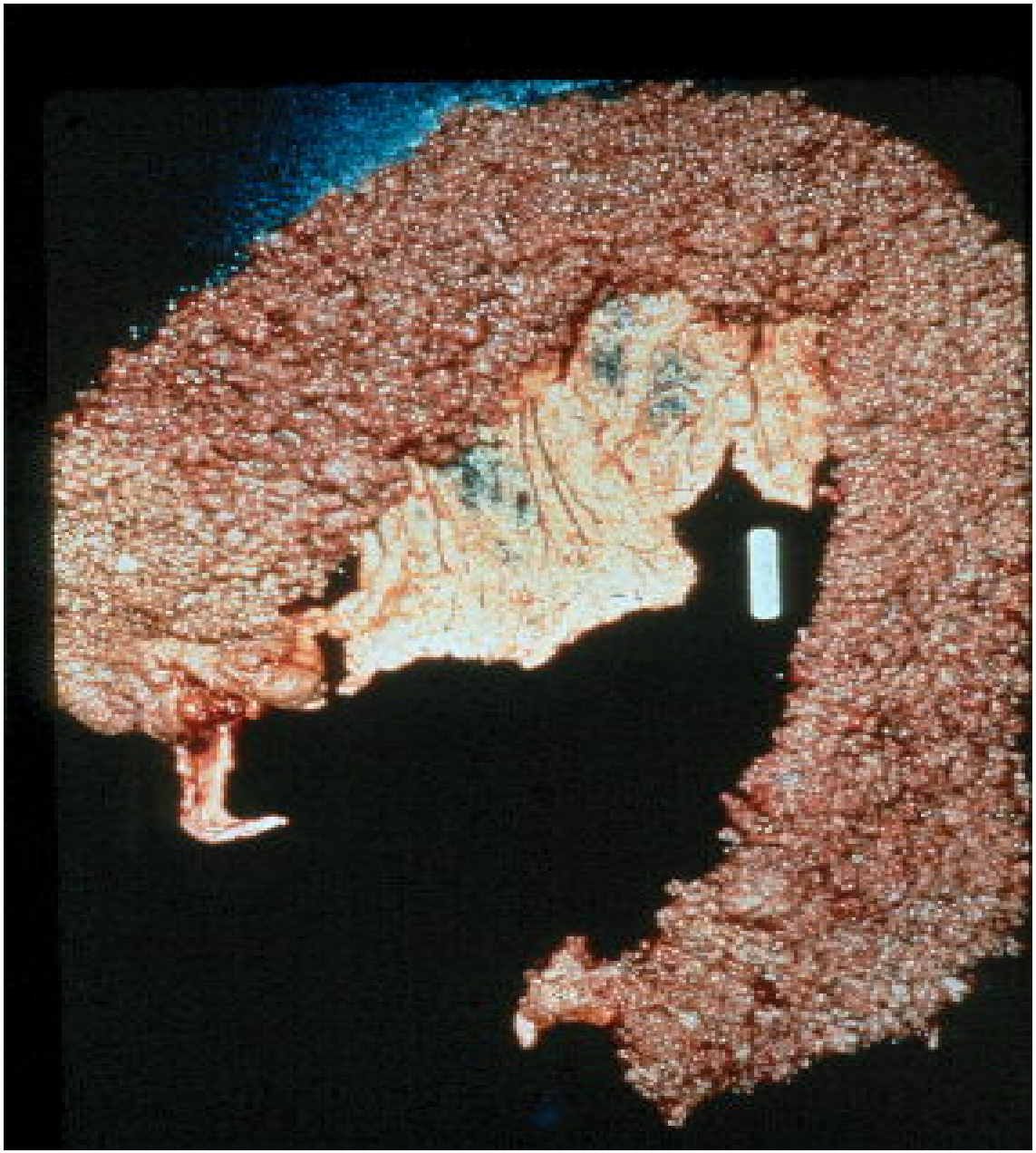
Revised Bethesda Criteria

- CRC less than 50 yo
- CRC and HNPCC related cancer
- CRC Crohns like less than 60 yo
- CRC and 1^{o} relative CRC less than 50 yo
- CRC and two 1^{o} or 2^{o} degree relatives with any HNPCC related tumor

Familial Adenomatous Polyposis

Familial Adenomatous Polyposis

- Autosomal dominant disease
- Mutation of APC gene
- Hundreds of adenomas in colorectum
- Presence/absence extracolonic lesions
- Colorectal cancer inevitable



Cause of FAP

- Mutation of APC gene (Adenomatous Polyposis Coli)
- Located chromosome 5q 21
- Discovered 1991

Clinical Course

Puberty - polyps appear

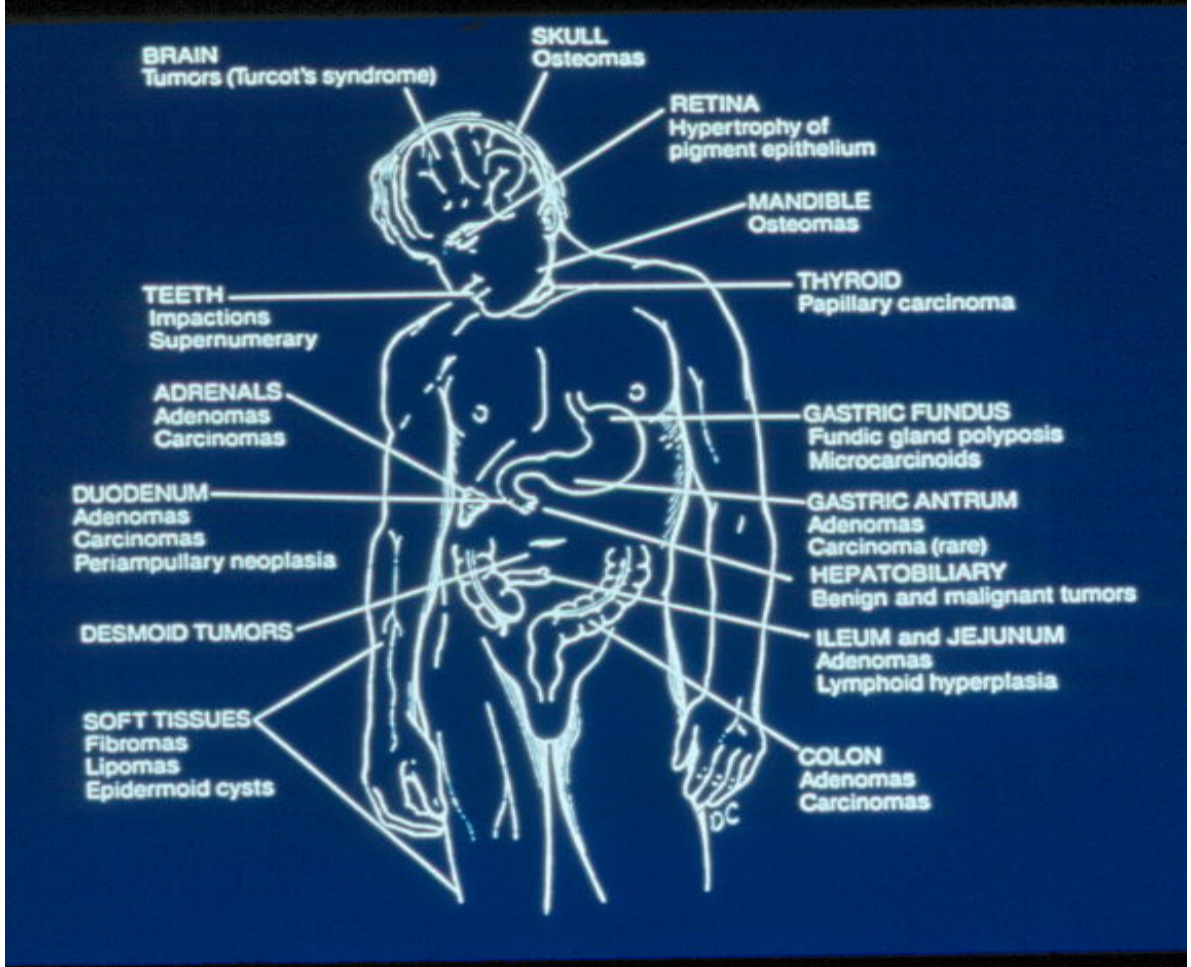
15 y.o. – onset of polyps

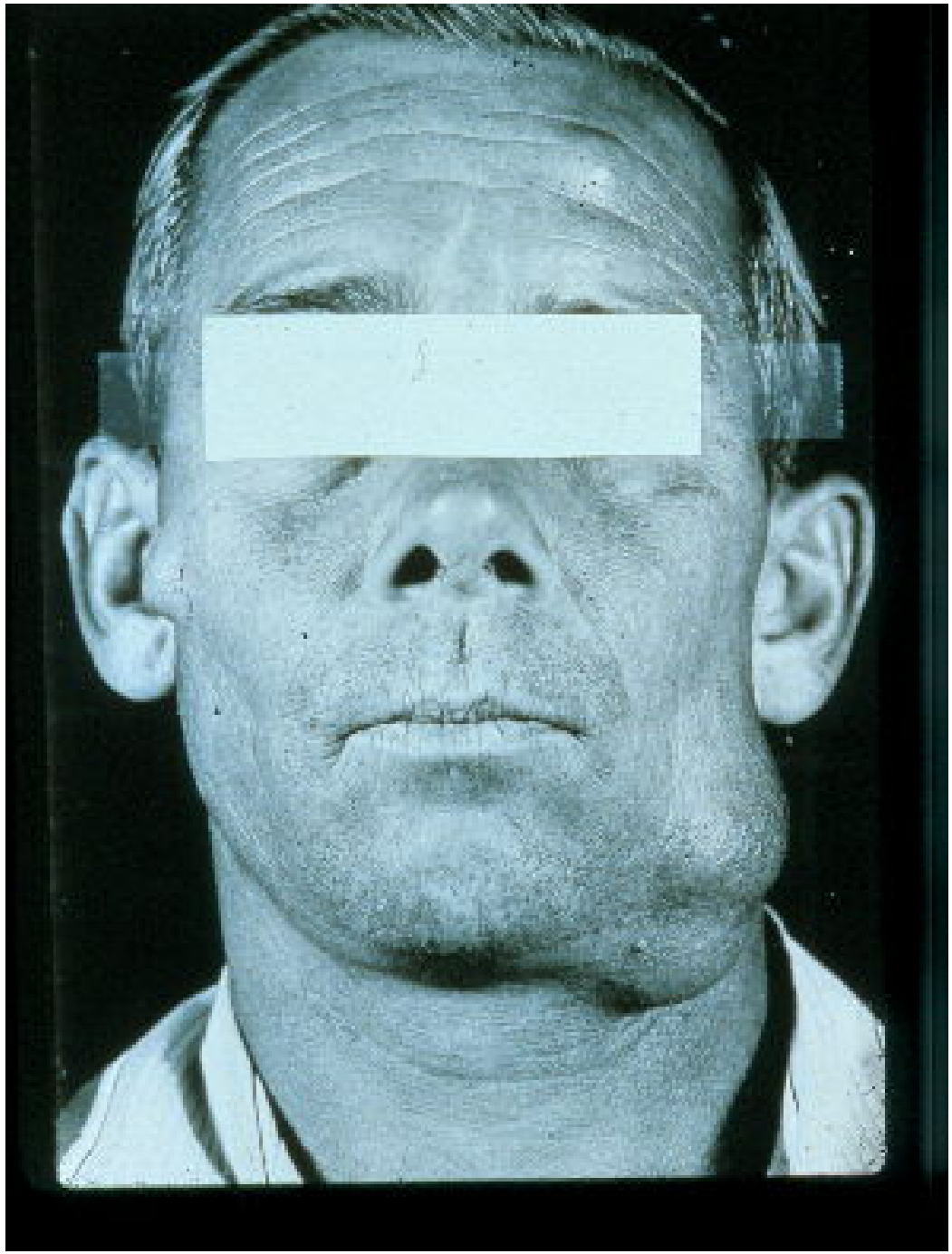
33 y.o. - symptoms appear

36 y.o. – age of diagnosis

39 y.o. – age of colorectal cancer dx

42 y.o. - death from colorectal cancer

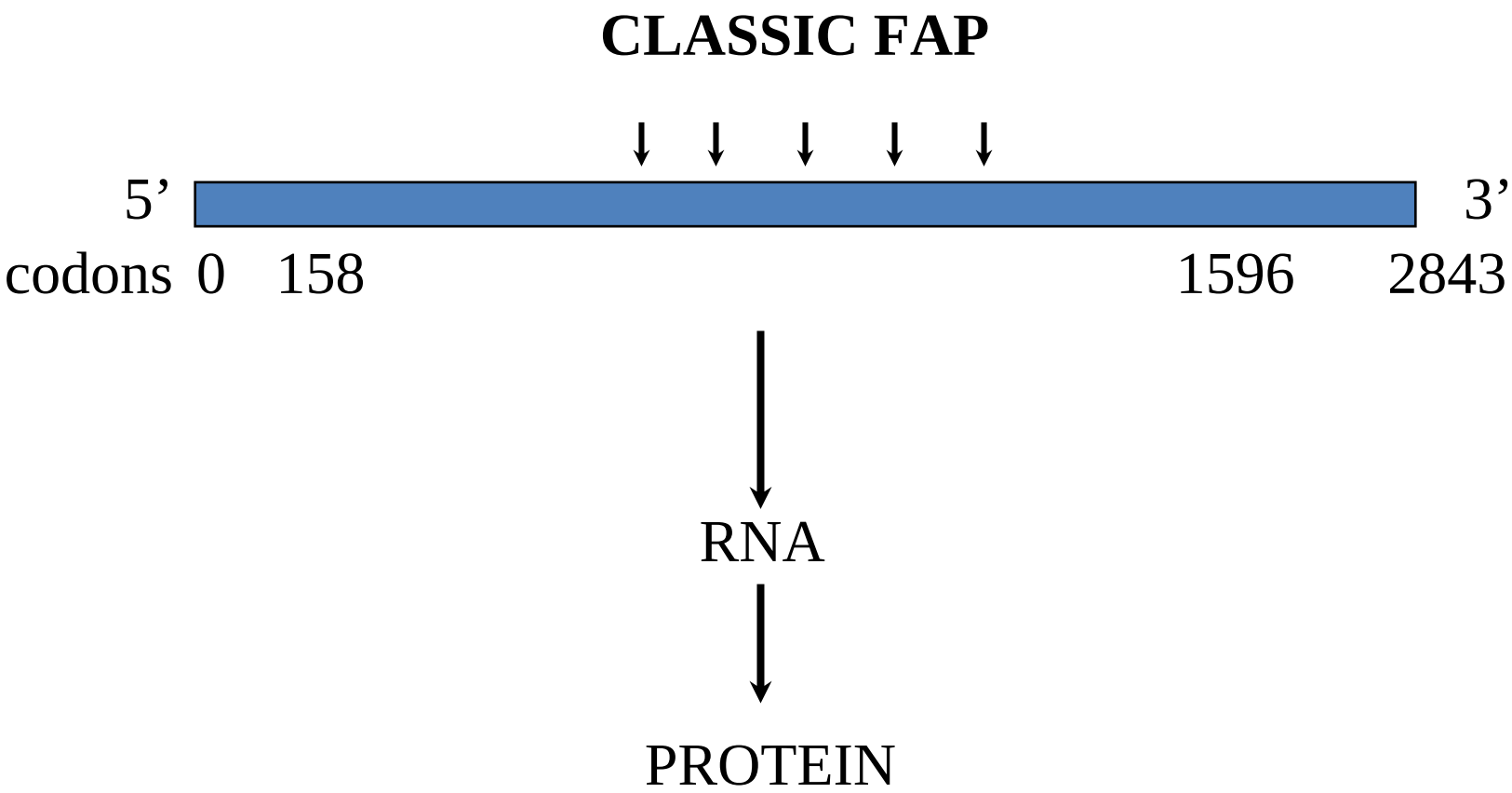

BRAIN
Tumors (Turcot's syndrome)
SKULL
Osteomas
RETINA
Hypertrophy of
pigment epithelium
MANDIBLE
Osteomas
THYROID
Papillary carcinoma
TEETH
Impactions
Supernumerary
ADRENALS
Adenomas
Carcinomas
GASTRIC FUNDUS
Fundic gland polyposis
Microcarcinoids
DUODENUM
Adenomas
Carcinomas
Periampullary neoplasia
GASTRIC ANTRUM
Adenomas
Carcinoma (rare)
HEPATOBILIARY
Benign and malignant tumors
DESMOID TUMORS
ILEUM and JEJUNUM
Adenomas
Lymphoid hyperplasia
SOFT TISSUES
Fibromas
Lipomas
Epidermoid cysts
COLON
Adenomas
Carcinomas
DC



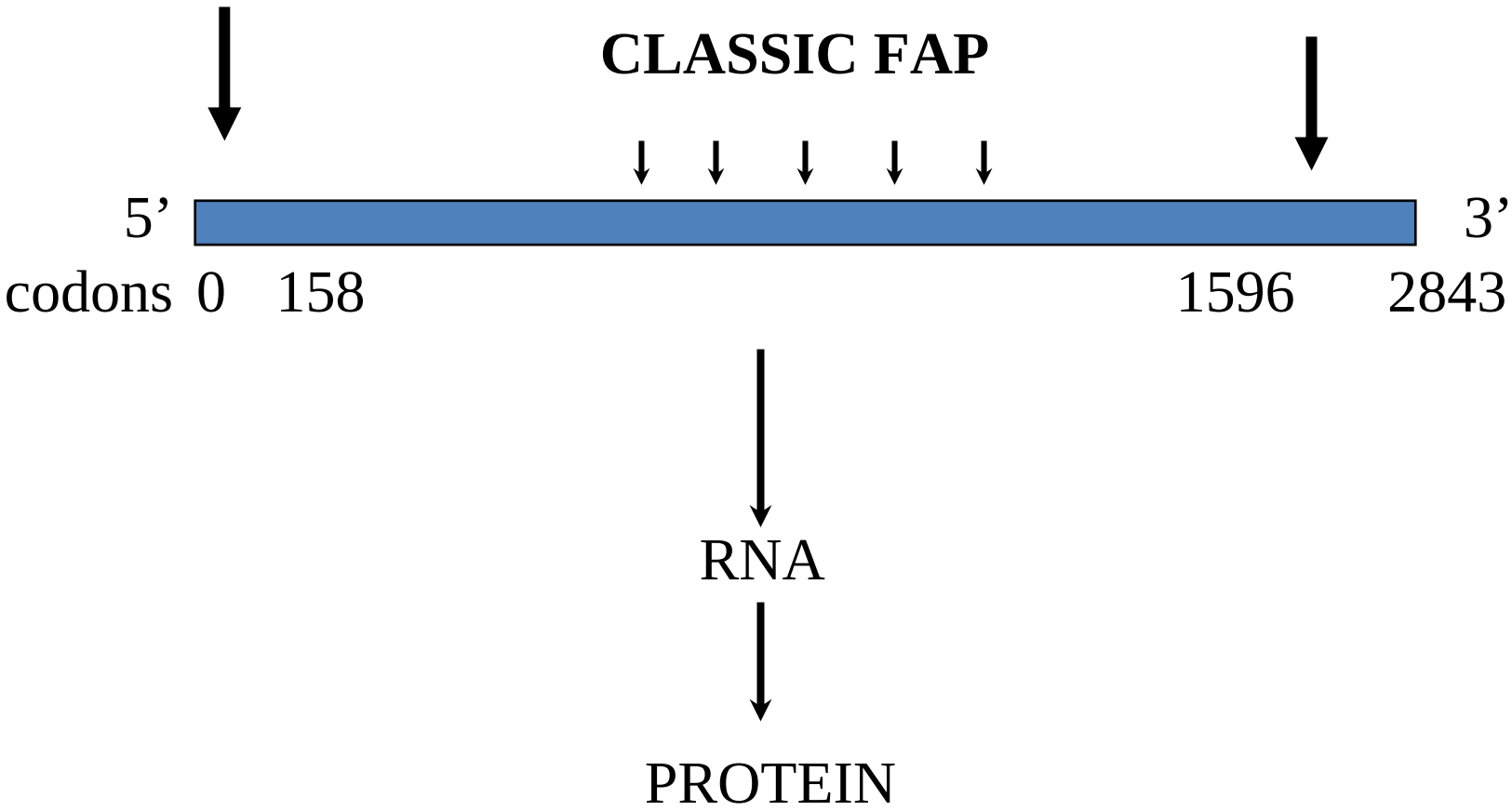
Treatment

- Proctocolectomy/ ileostomy
- Proctocolectomy/ ileoanal pull through
- Colectomy/ ileorectal anastomosis

APC GENE



APC GENE



Attenuated FAP

- 5’ and 3’ APC gene mutations
- 6% of FAP pedigrees
- Oligopolyposis (<100 adenomas),
- Polyps right-sided
- Heterogeneous phenotype
- Later CRC (51 vs 39 y.o.)

Screening

- At-risk persons (1st degree relatives)
- Sigmoidoscopy

  q yr starting age 12,

  q 2 yrs after age 25,

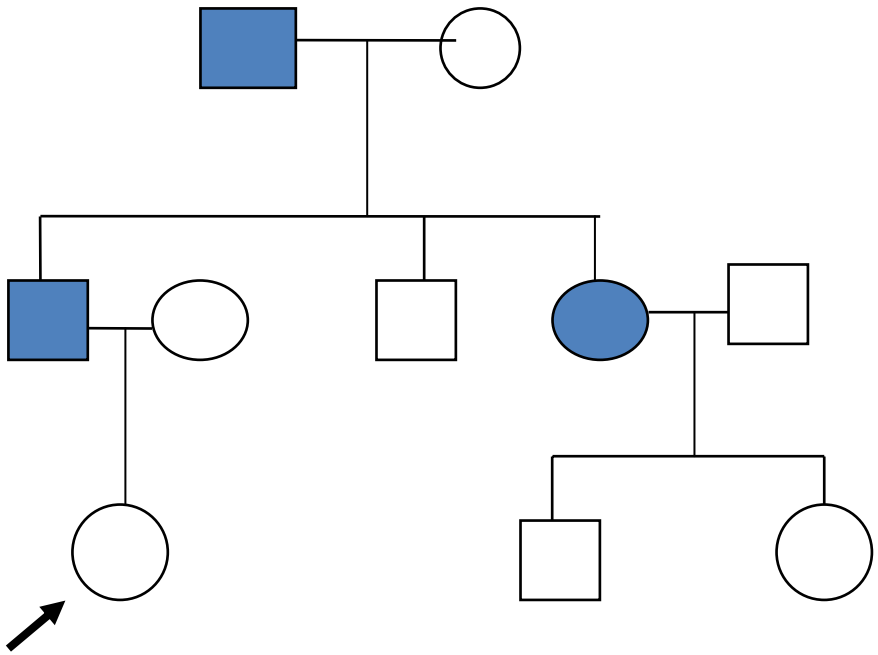
  q 3 yrs after age 35,

  average risk guidelines after age 50

Screening: APC Gene Testing

- Gene test for mutation of APC gene
- Start at-risk persons age 10-12
- Pretest genetic counseling/ consent
- Test affected pedigree member first

APC Gene Testing - At Risk



APC Gene Test Result

- Positive - FAP- sigmoid. yearly
- Negative - No FAP- sigmoid. age 25

MYH Associated Polyposis (MAP)

MYH Associated Polyposis

- Discovered in 2003
- Caused by mutation in MYH gene
- Polyposis (> 100 polyps)
- Oligopolyposis (< 100 polyps)
- Autosomal recessive condition

MAP

- Polyposis (> 100 polyps) - <1%
- Oligopolyposis (5-100 polyps)- 4% to 33%

MYH Gene

- Base excision gene
- Two deleterious mutations
  - Y165C and G382D
- Prevents mutations in DNA
- Fixes damaged base pairs
- Damaged by oxidative stress

Oxidative Damage

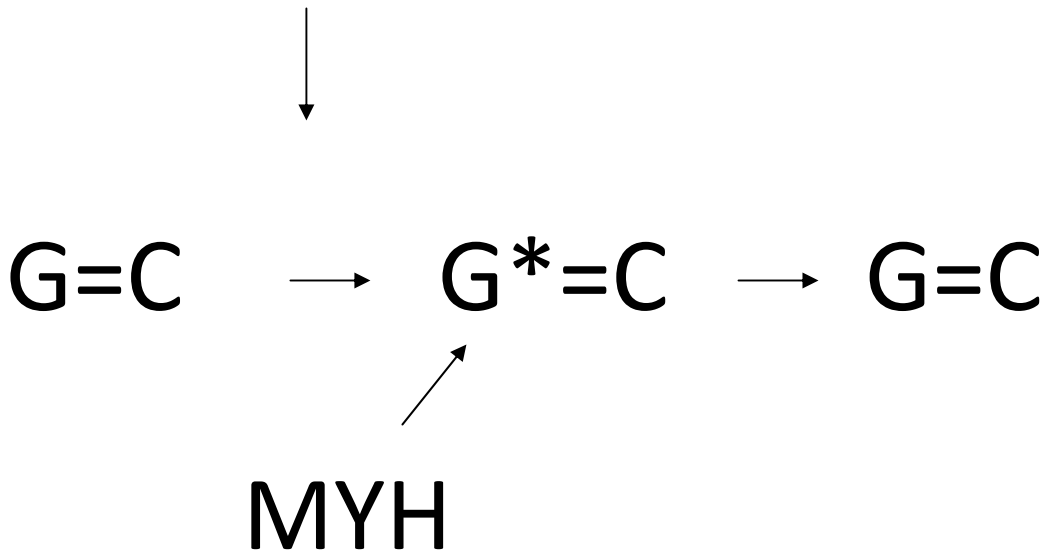
G=C → G*=C → G*=A → T=A

Oxidative Damage

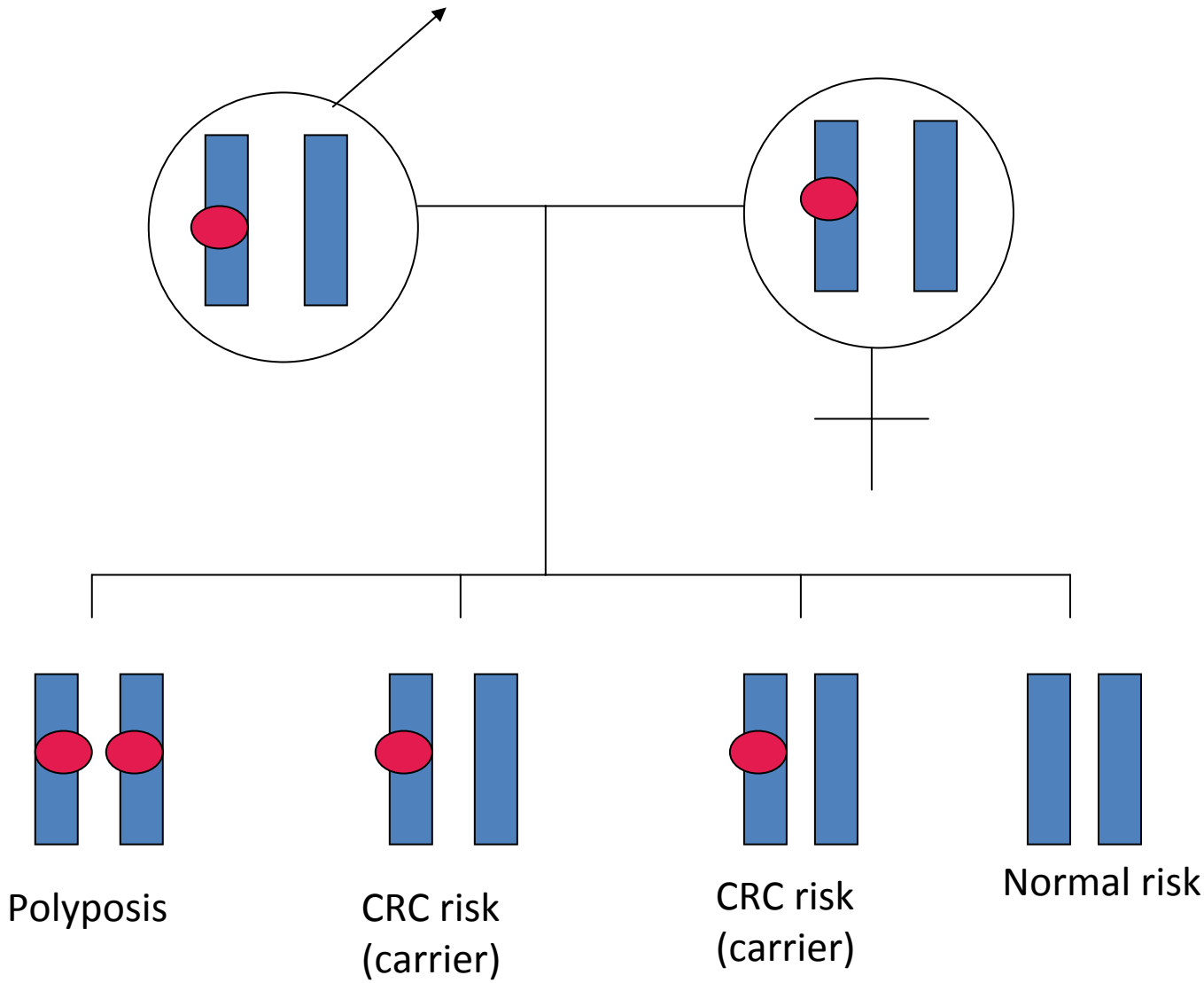
G=C → G*=C

MYH

Oxidative Damage



MYH Gene



MYH Management

- Biallelic mutations- like FAP or AFAP

- Monoallelic mutation- colonoscopy at 40 yr q 10 yrs (q 5 yrs).

Summary

- HNPCC
  - colonoscopic screening
  - MSI/IHC testing, MMR gene testing
- FAP/AFAP
  - APC gene testing
  - sigmoid/colonoscopy screening
- MAP
  - MYH gene testing