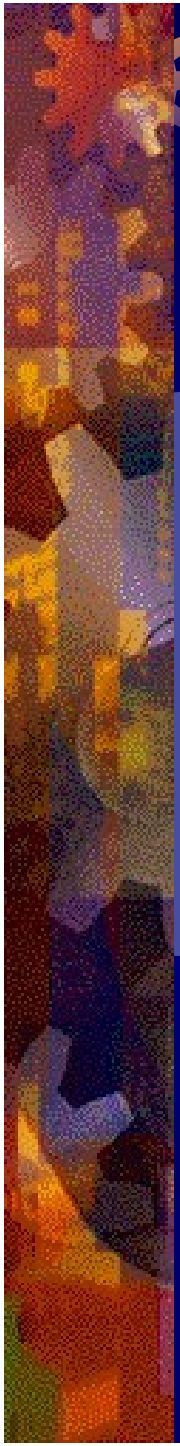

Genetic Testing and Counseling in *Hereditary Colorectal Cancer*

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Hereditary Colorectal Cancer

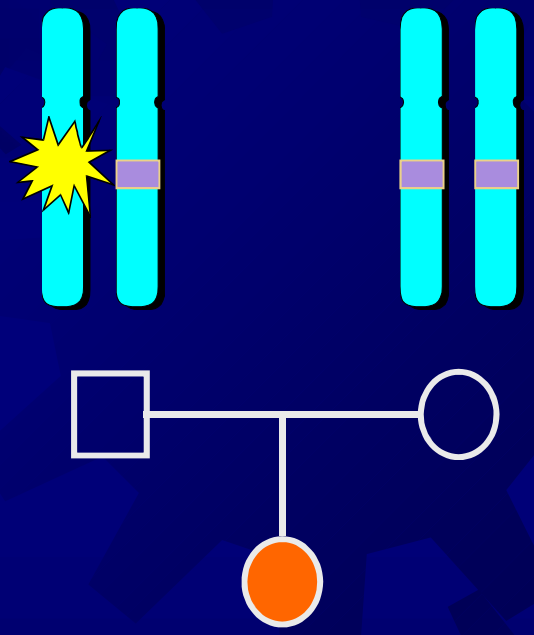
- Familial adenomatous polyposis (FAP) and Gardner syndrome
- Hereditary non-polyposis colorectal cancer (HNPCC)
- Peutz-Jeghers syndrome (PJS)
- Juvenile polyposis syndrome (JPS)
- Turcot syndrome
- Muir-Torre syndrome

Common features

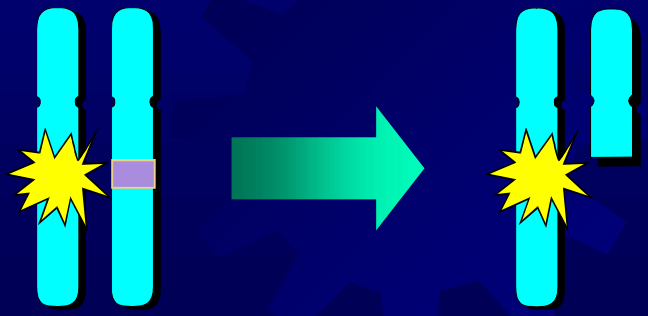
- All is inherited in autosomal dominant manner
- All is caused by tumor suppressor gene (and mismatch repair gene)
- All cancers follow adenoma-carcinoma sequence

The Two-Hit Hypothesis

First hit

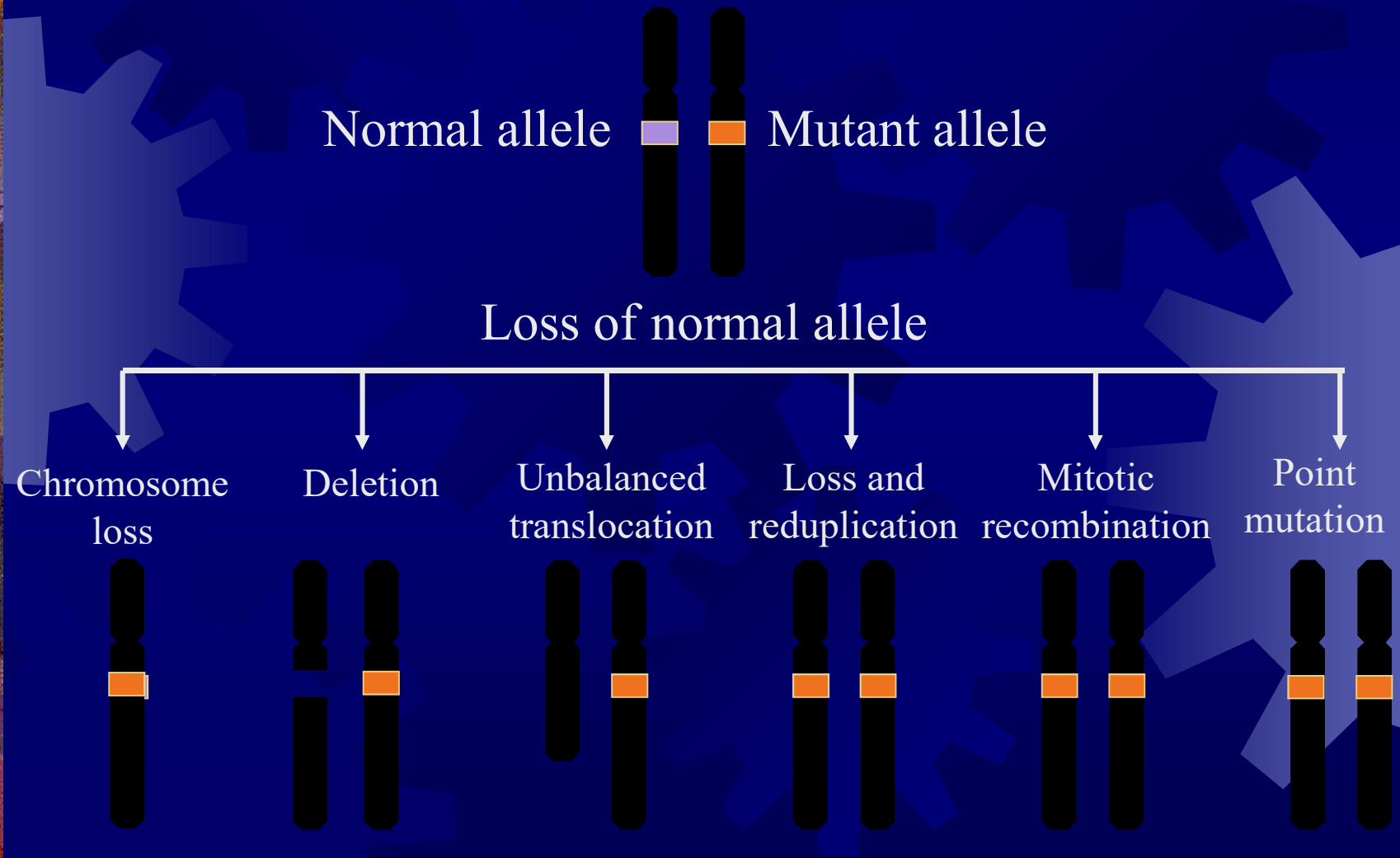


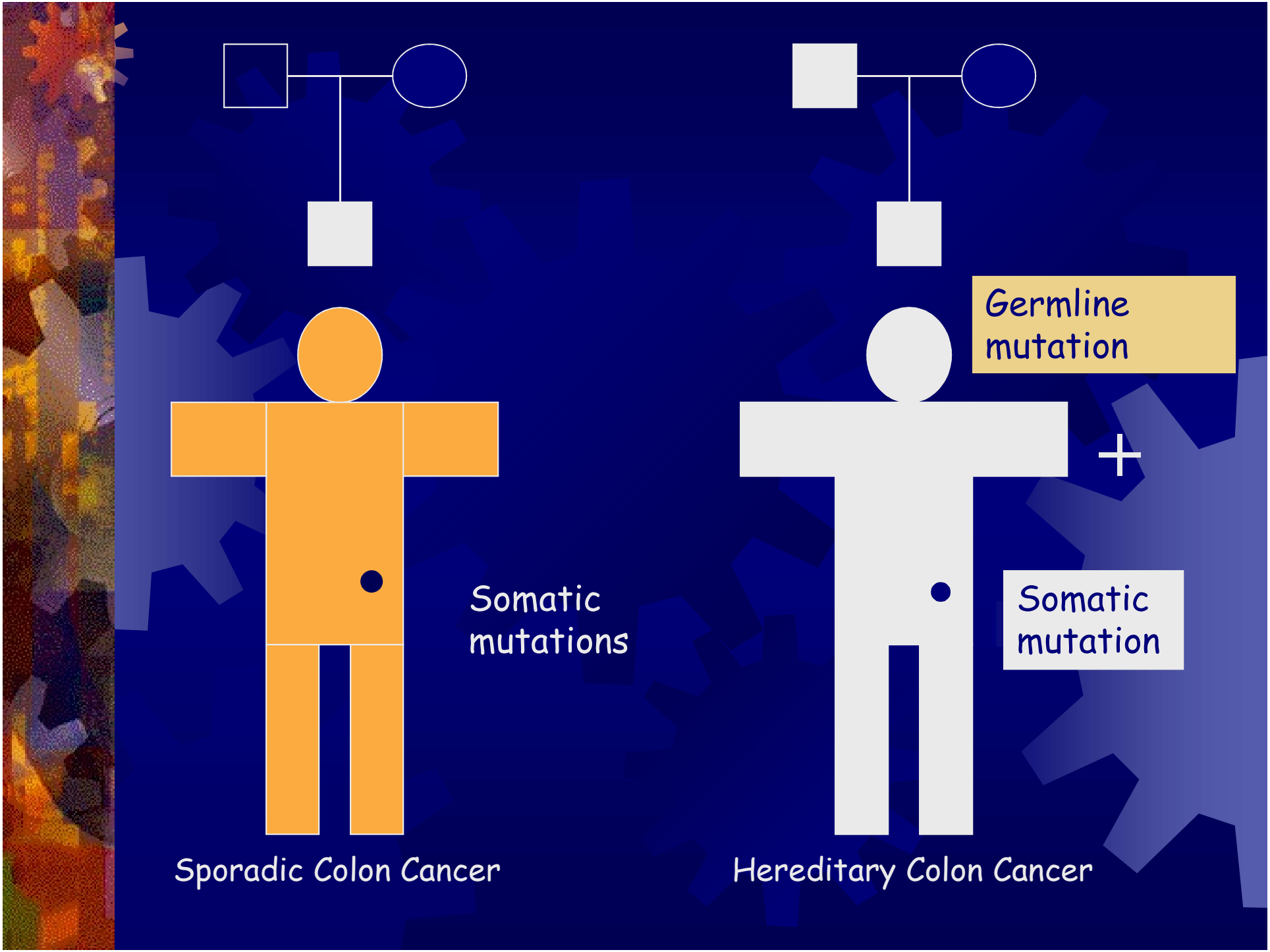
First hit in germline of child

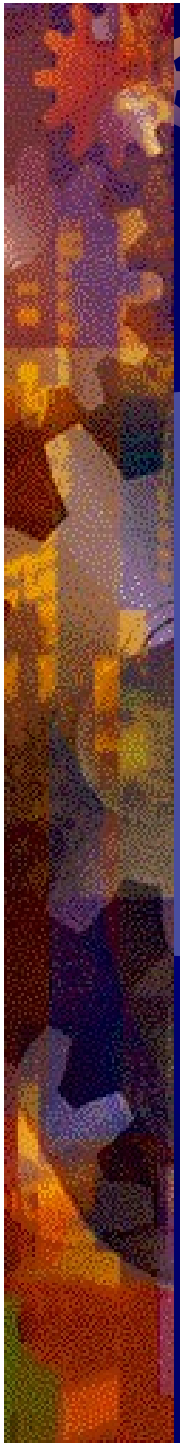


Second hit (tumor)

Mechanisms Leading to Loss of Heterozygosity




Somatic mutations
Sporadic Colon Cancer
Germline mutation
+
Somatic mutation
Hereditary Colon Cancer



Familial adenomatous polyposis

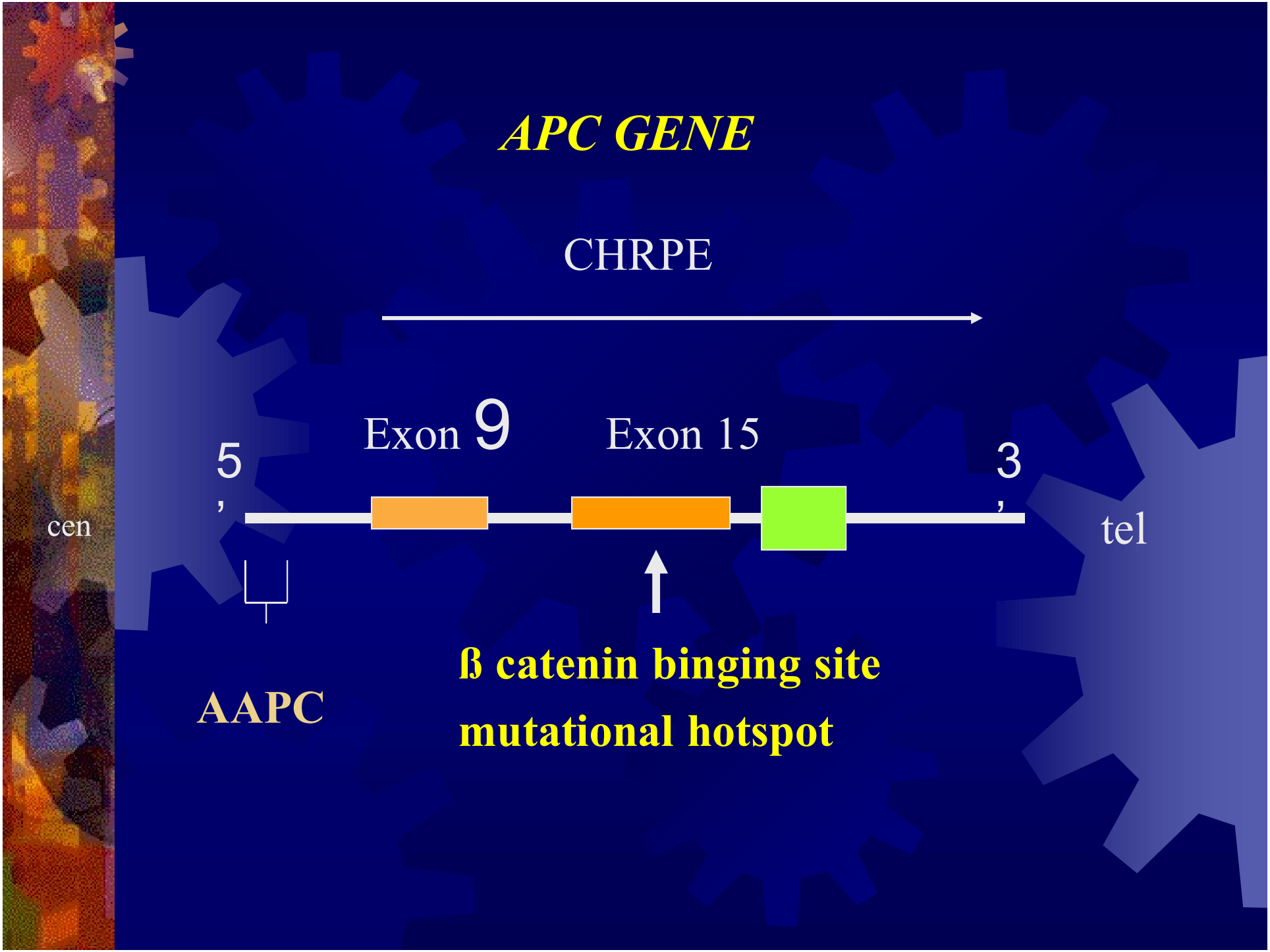
APC Gene

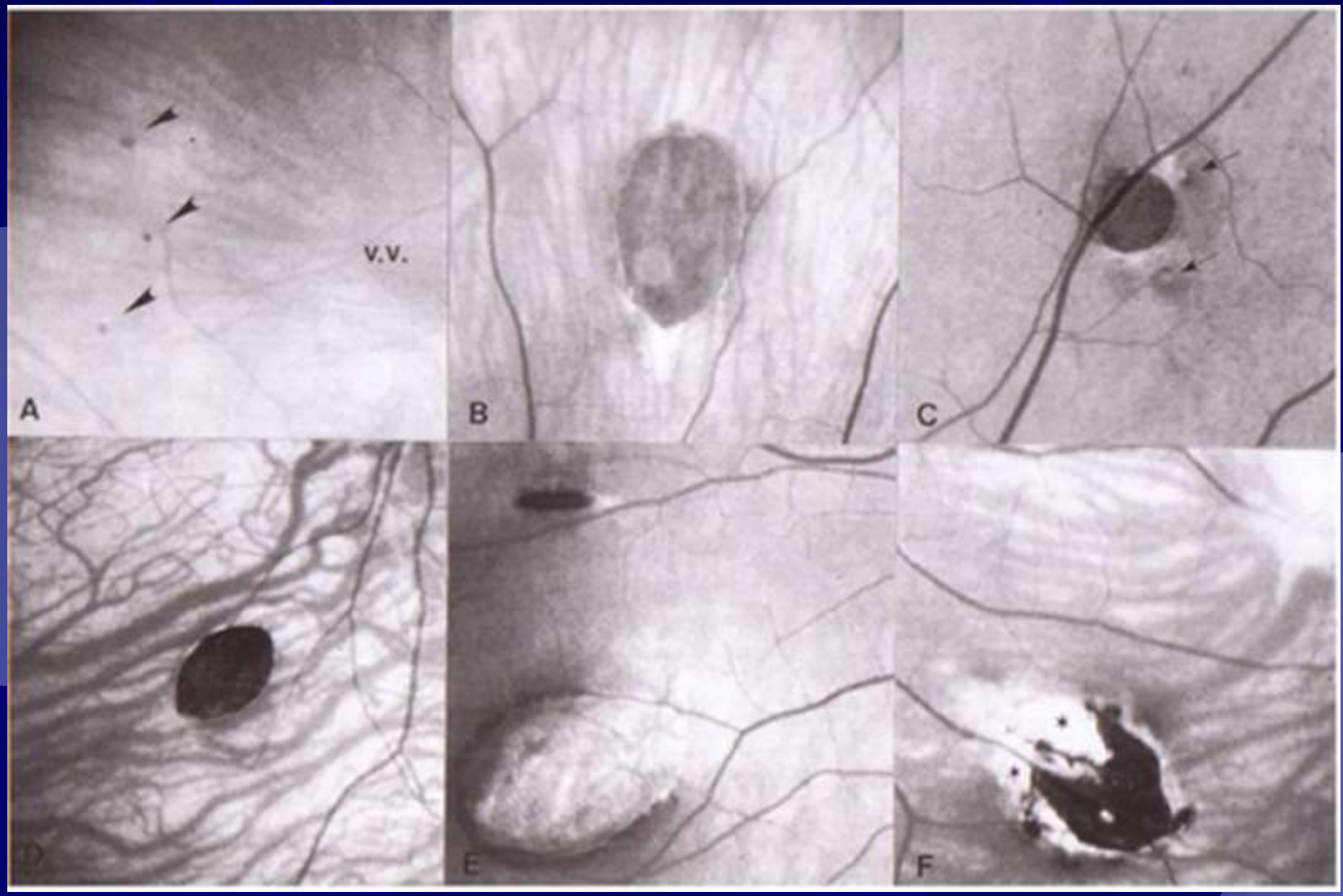
- Phenotype-genotype correlation

first 3 exon	attenuated APC
exon 4-14	sparse type APC
exon 15	profused type APC
exon 16-3'	sparse type APC

- Currently available testing uses protein truncation test to detect truncating and splicing mutation accounting for 70%

APC GENE


CHRPE
Exon 9
Exon 15
5'
3'
cen
tel
AAPC
ß catenin binging site
mutational hotspot



CONGENITAL HYPERTROPHIC RETINAL PIGMENTED EPITHELIUM

Treatment

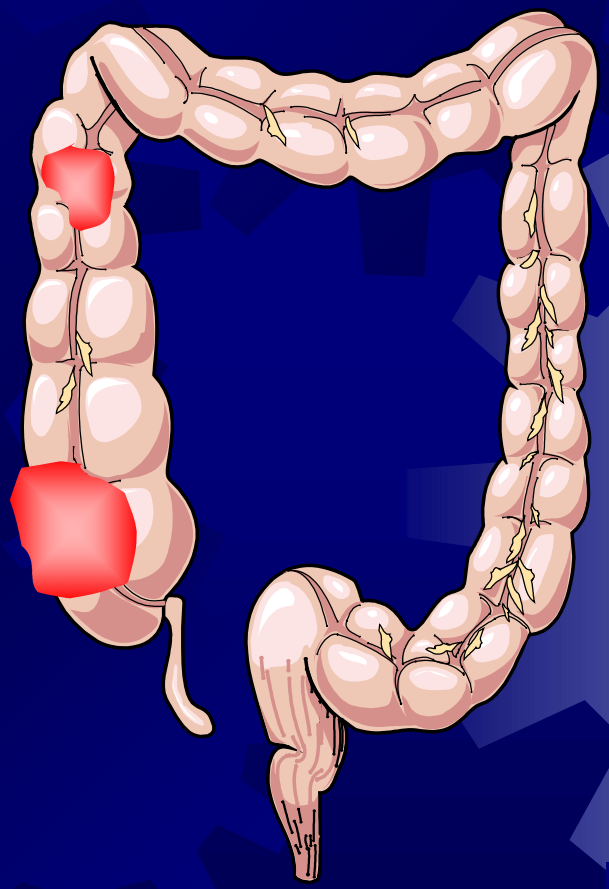
- Proctocolectomy w or w/o IPAA
- Colectomy w IRA not recommended
- Attenuated FAP can be treated with rectal sparing surgery if no rectal polyposis
- Medical intervention with COX-2 inhibitor is recommended for patients with polyposis
- Doxorubicin-Dacarbazine followed by carboplatin-dacarbazine may be effective for Desmoid tumor (Dis Colon Rectum 2001 Sep;44(9):1268-73)

NSAIDs and polyposis

- Celecoxib decreased duodenal polyposis 14% (Gut 2002 Jun;50(6):857-60)
- Celecoxib reduced polyposis in dose dependent manner 14-30%(N Engl J Med 2000 Jun 29;342 (26):1946-52)
- Sulindac decreased rectal polyp formation but doesn't seem to have primary preventive effects (N Engl J Med 2002 Apr4;346(14):1054-9)

Clinical Features of HNPCC

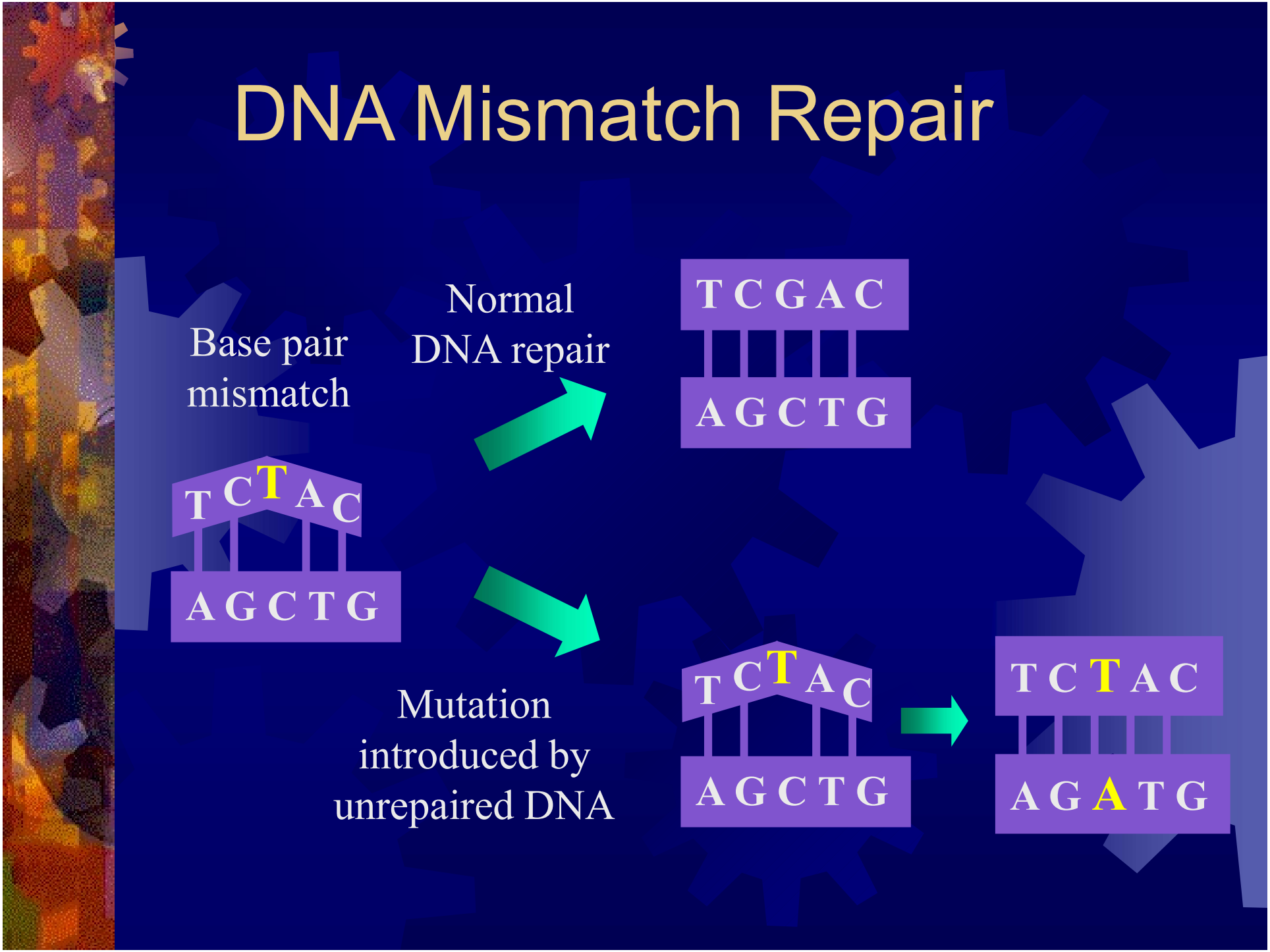
- Early but variable age at CRC diagnosis (~45 years)
- Tumor site in proximal colon predominates
- Extracolonic cancers: endometrium, ovary, stomach, urinary tract, small bowel, bile ducts, sebaceous skin tumors



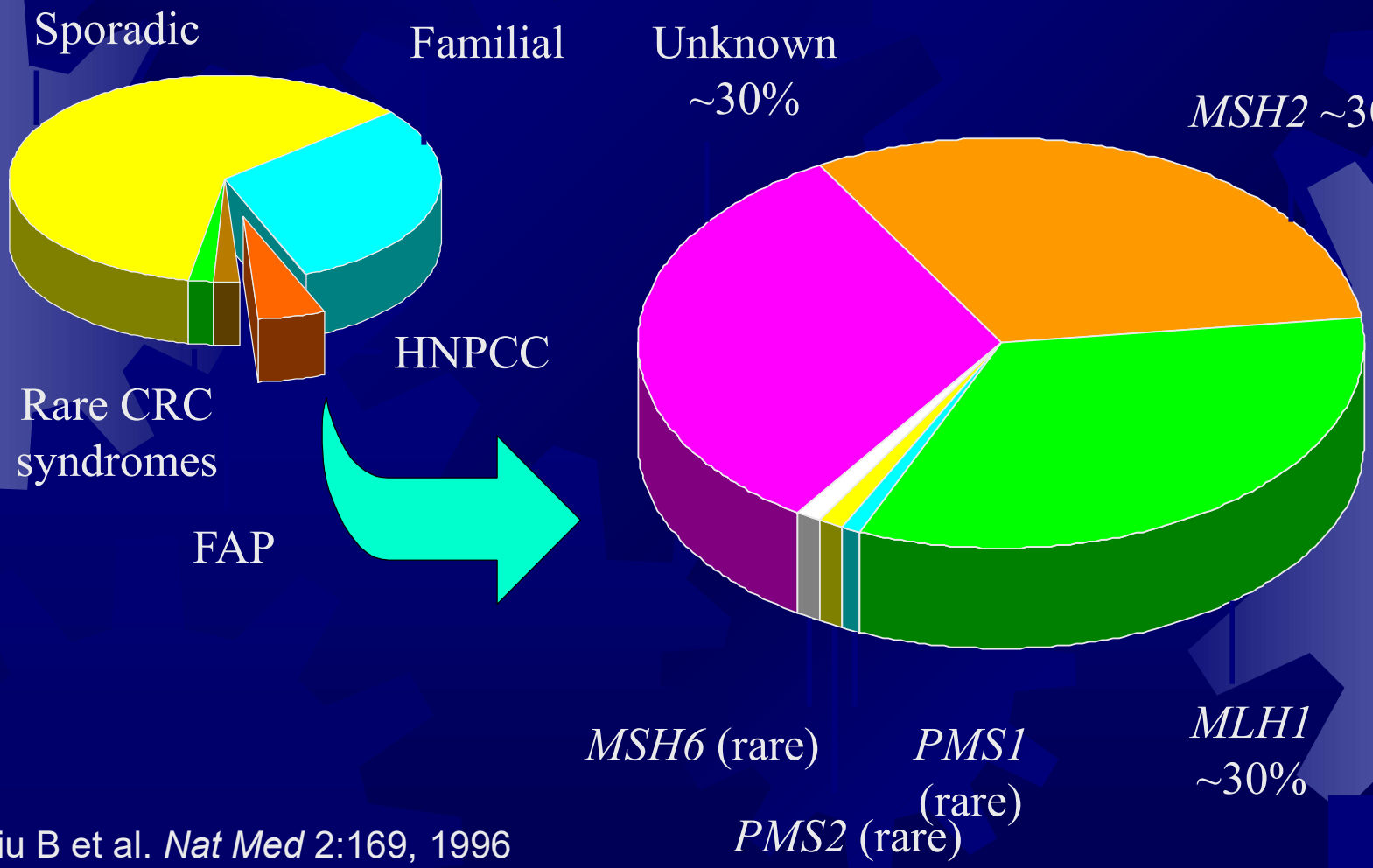
Genetic Features of HNPCC

- Autosomal dominant inheritance
- Penetrance ~80%
- Genes belong to DNA mismatch repair (MMR) family
- Genetic heterogeneity (*MLH1, MSH2, MLH3, MSH6, PMS1, PMS2*)

DNA Mismatch Repair



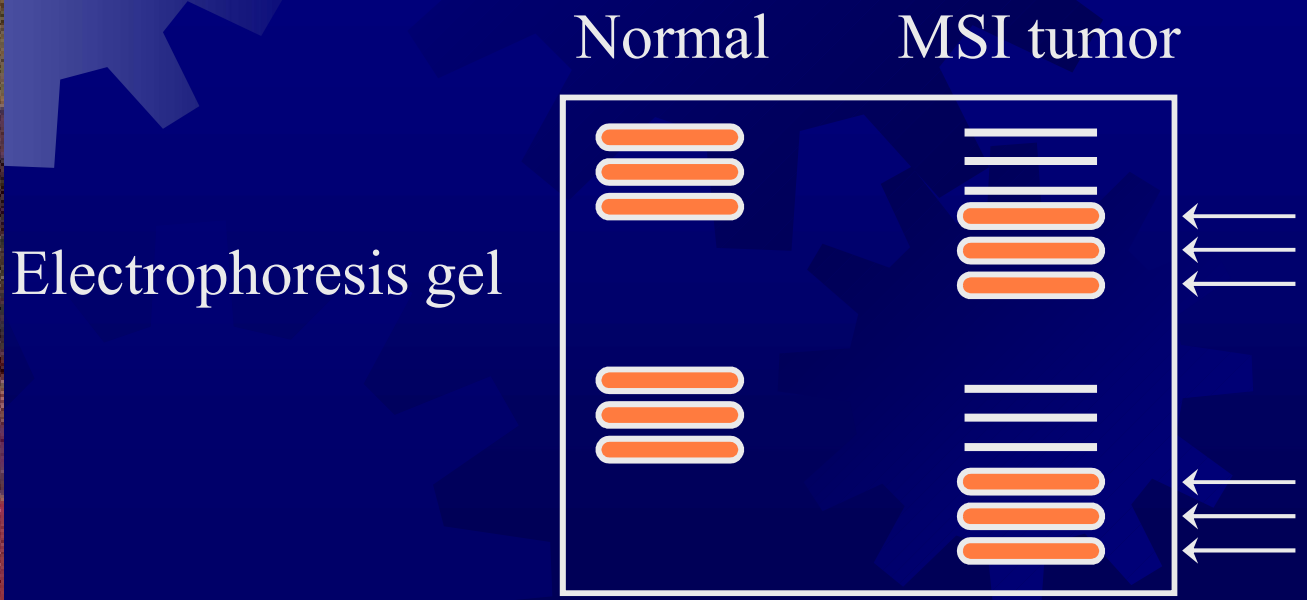
Contribution of Gene Mutations to HNPCC Families



Liu B et al. *Nat Med* 2:169, 1996

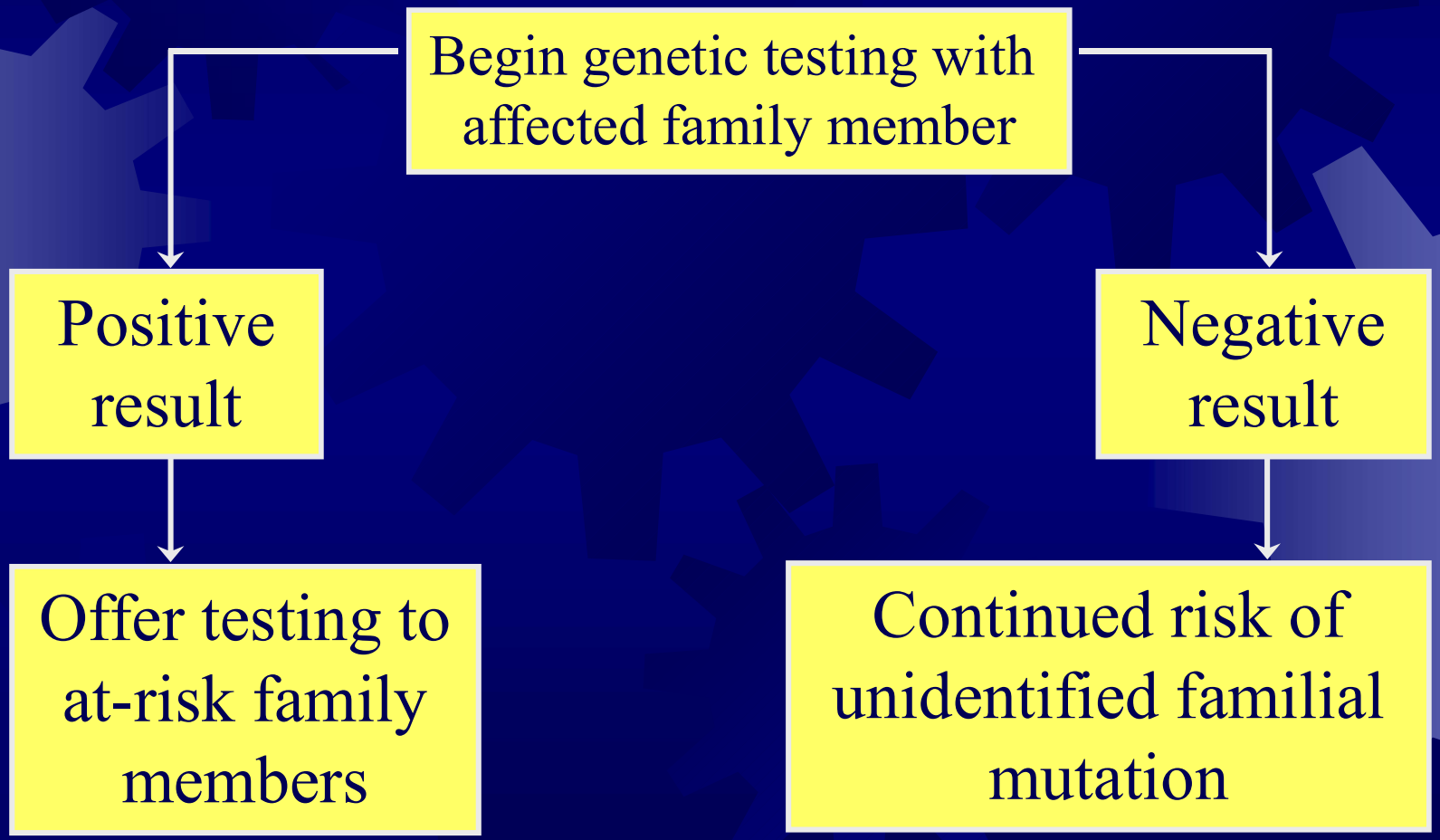
Microsatellite Instability (MSI)

- 10%–15% of sporadic tumors have MSI
- 95% of HNPCC tumors have MSI at multiple loci
- Assc with loss of *MSH2* or *MLH1* expression

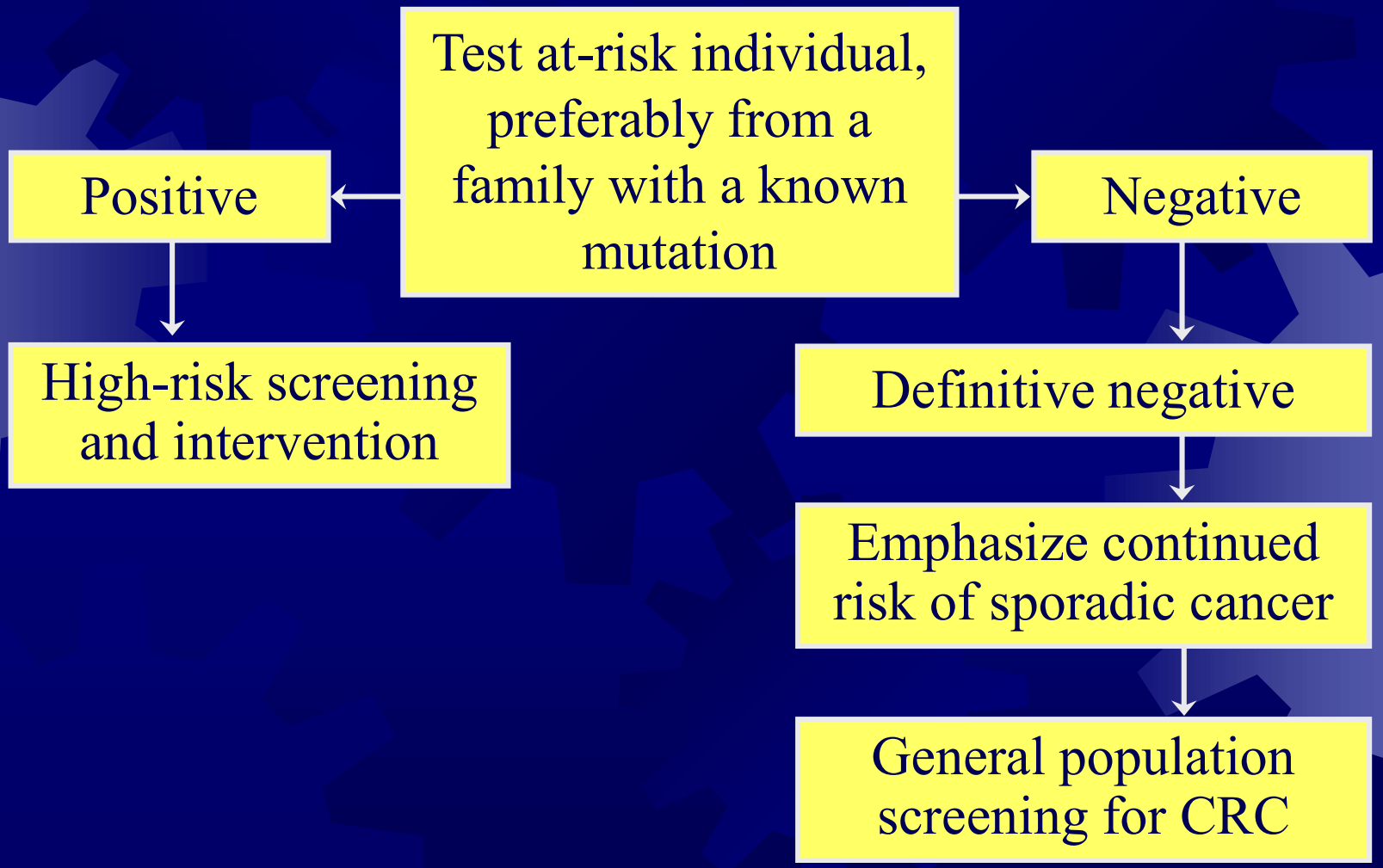


SSCP analysis in a Thai family

Genetic Testing for HNPCC Susceptibility



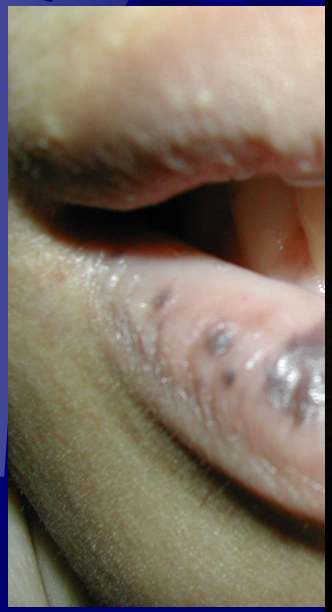
Genetic Testing for HNPCC Susceptibility in Unaffected Patients

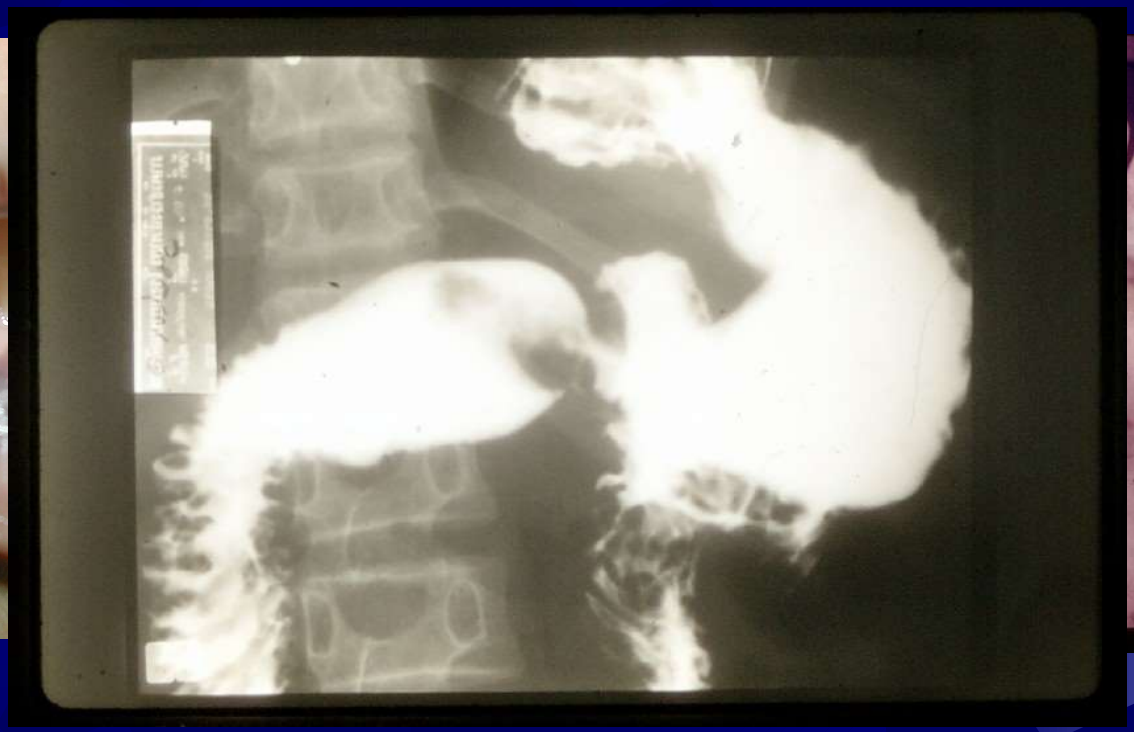


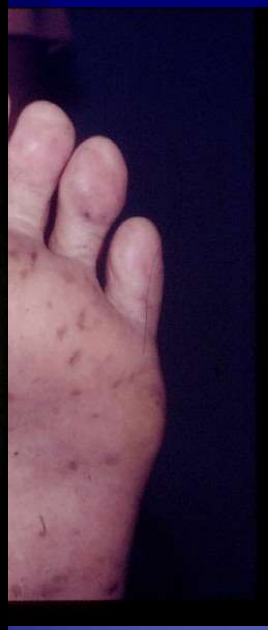
Benefits and Limitations of Genetic Testing for HNPCC

Benefits	Limitations
Identifies mutation carriers	Current tests do not identify all mutation carriers (limited clinical sensitivity)
Identifies noncarriers in families w/known mutations	Noncarriers have continued risk of sporadic CRC
Colon surveillance in at-risk persons is proven to reduce mortality	Efficacy for surveillance of other cancers (eg, ovarian) is unknown

Peutz-Jeghers syndrome



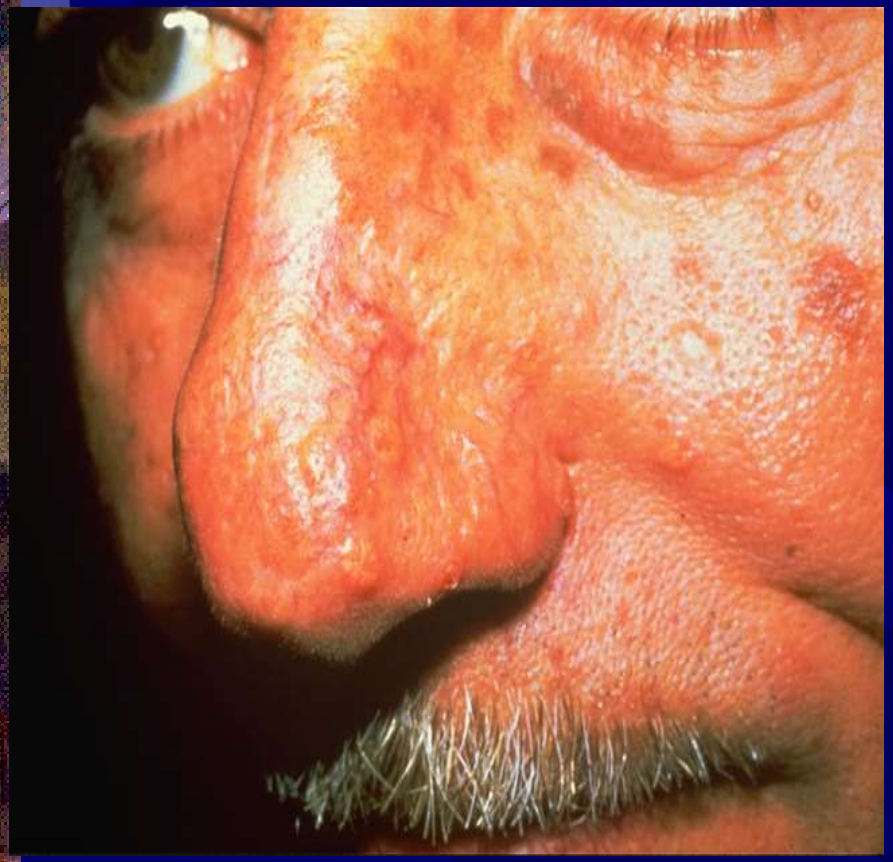




Peutz-Jeghers syndrome

- LKB1 mutation
- Risk for multiple tumor : colon, GI, sex cord ovarian tumor, breast, Sertoli cell tumor
- Cancer is risk is unknown
- Surgery not indicated in those without obstructive / malignant complications

Muir-Torre Syndrome: A Variant of HNPCC



Associated with *MSH2* or *MLH1* mutations

Typical features of HNPCC *and*:

- Sebaceous gland tumors
- Keratoacanthomas

Turcot Syndrome

- Rare hereditary syndrome of multiple colorectal adenomas and primary brain tumors
- Two distinct subtypes
  - *APC* mutations associated w / medulloblastomas
  - MMR mutations associated w/glioblastomas
- Genetic testing may clarify diagnosis

Hamilton SR et al. *N Engl J Med* 332:839, 1995