Hereditary colon cancer syndromes: genetic and translational insights

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I HAVE NO CONFLICTS OF INTEREST TO DISCLOSE

Learning Objectives

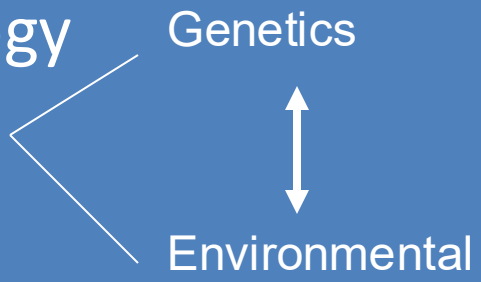
- Understand the causes of colorectal cancer
- Understand the hereditary colorectal cancer syndromes
- Understand the roles of tumor suppressor genes and oncogenes in the pathogenesis of hereditary and sporadic colorectal cancer
- Understand how knowledge of the pathogenesis can translate into diagnostics and therapeutics

Reading Materials

- Li et al. Genetic and Biological Hallmarks of Colorectal Cancer. *Genes & Development* 2021, 35:787-820 (Review Article)
- Shin AE, Giancotti FG, Rustgi AK. Metastatic colorectal cancer: mechanisms and emerging therapeutics; *Trends Pharmacological Sciences* 2023,44:222-236.

Colorectal Cancer

- Epidemiology
- Etiology



- Key Aspects:
  - Prevention/Chemoprevention (specific pathway targets: COX-2)
  - Diagnosis
    - Clinical
    - Endoscopic/radiographic (molecular imaging)
    - Biomarkers (molecular diagnostics)
      - Blood (DNA/RNA/Protein—genomics, proteomics)
      - Stool (DNA, Protein)
  - Prognosis
  - Therapy (rationale drug design of molecular targets)

Epidemiology

- Nearly 2 million cases worldwide; nearly 900,00 deaths
- 2024: Nearly 152,810 cases in US; about 53,000 deaths
- Equal gender distribution; increases in 50-80 y.o. range. Ethnic differences. Increased incidence <50 yo
- 2nd leading cause of cancer related mortality in men and women

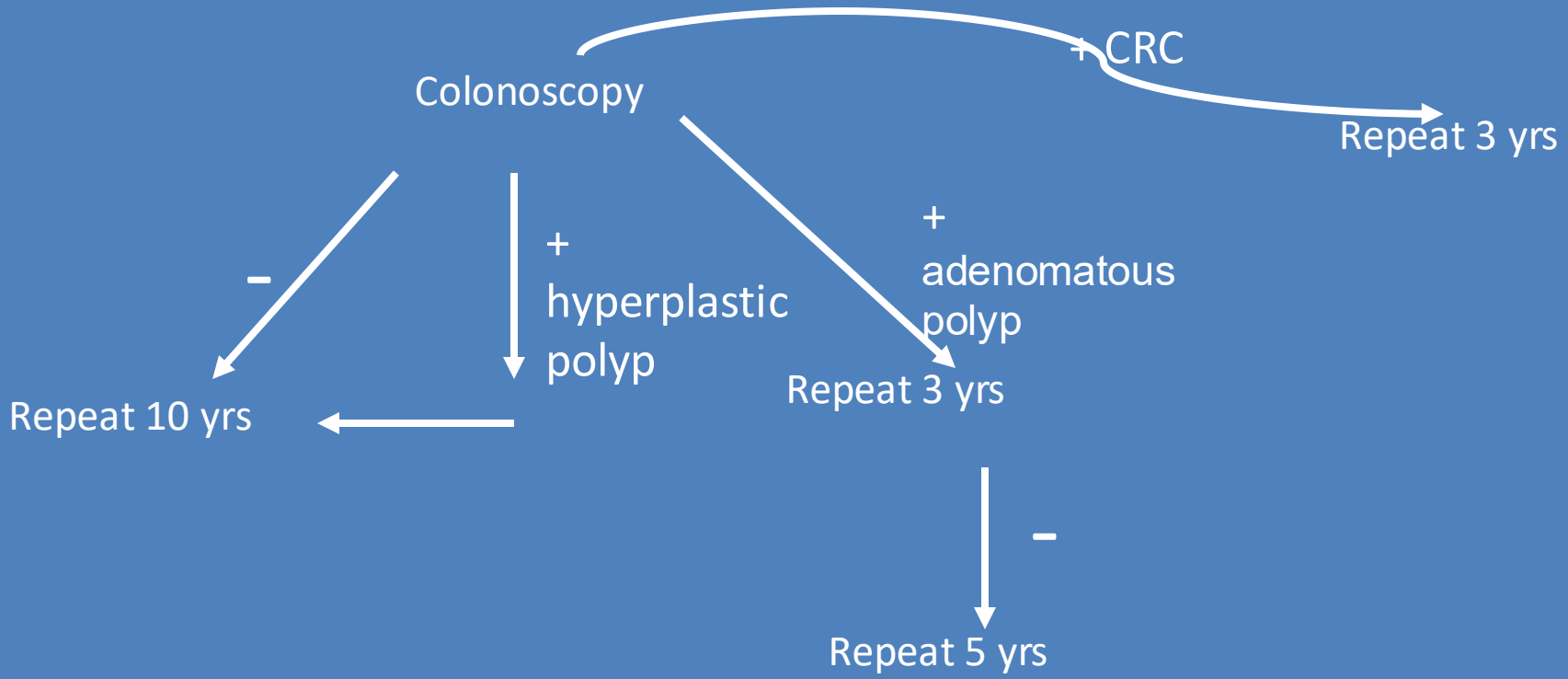
Colorectal Cancer (CRC) risk factors: gene-environment interactions and genetic predisposition

- Aging, High-fat diet, +/- cig-smoking, +/- obesity
- Inflammatory bowel disease (chronic inflammation with dysplasia)
- Personal history of adenoma
- Family history of CRC
- Hereditary colon cancer syndromes

Screening

- FOBT and sigmoidoscopy do decrease polyp and CRC incidence
- No trials for BaE
- Colonoscopy is effective
- Avg risk: colonoscopy every 10 yrs
- ?Roles of virtual colonoscopy and fecal DNA markers

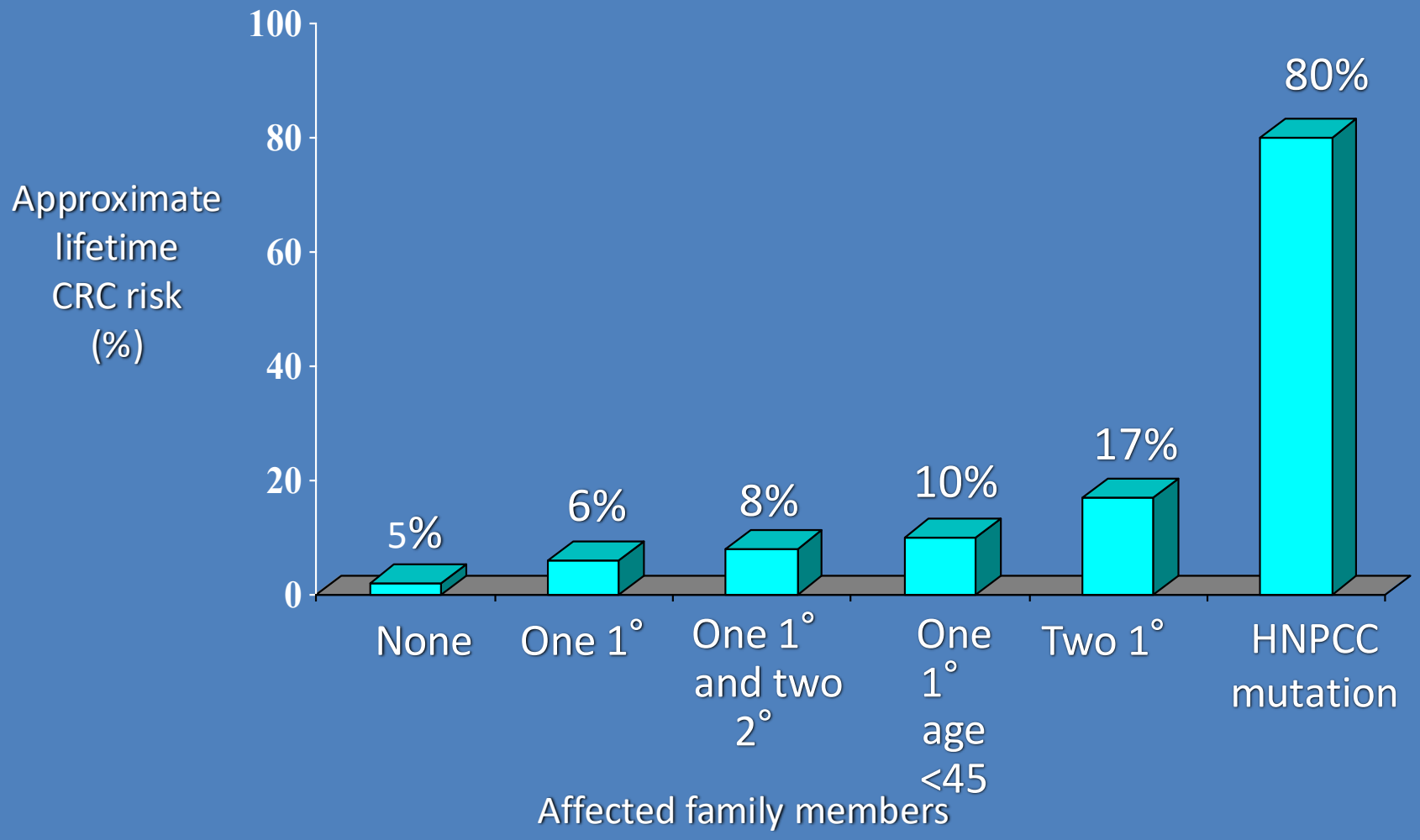
Average-risk patient

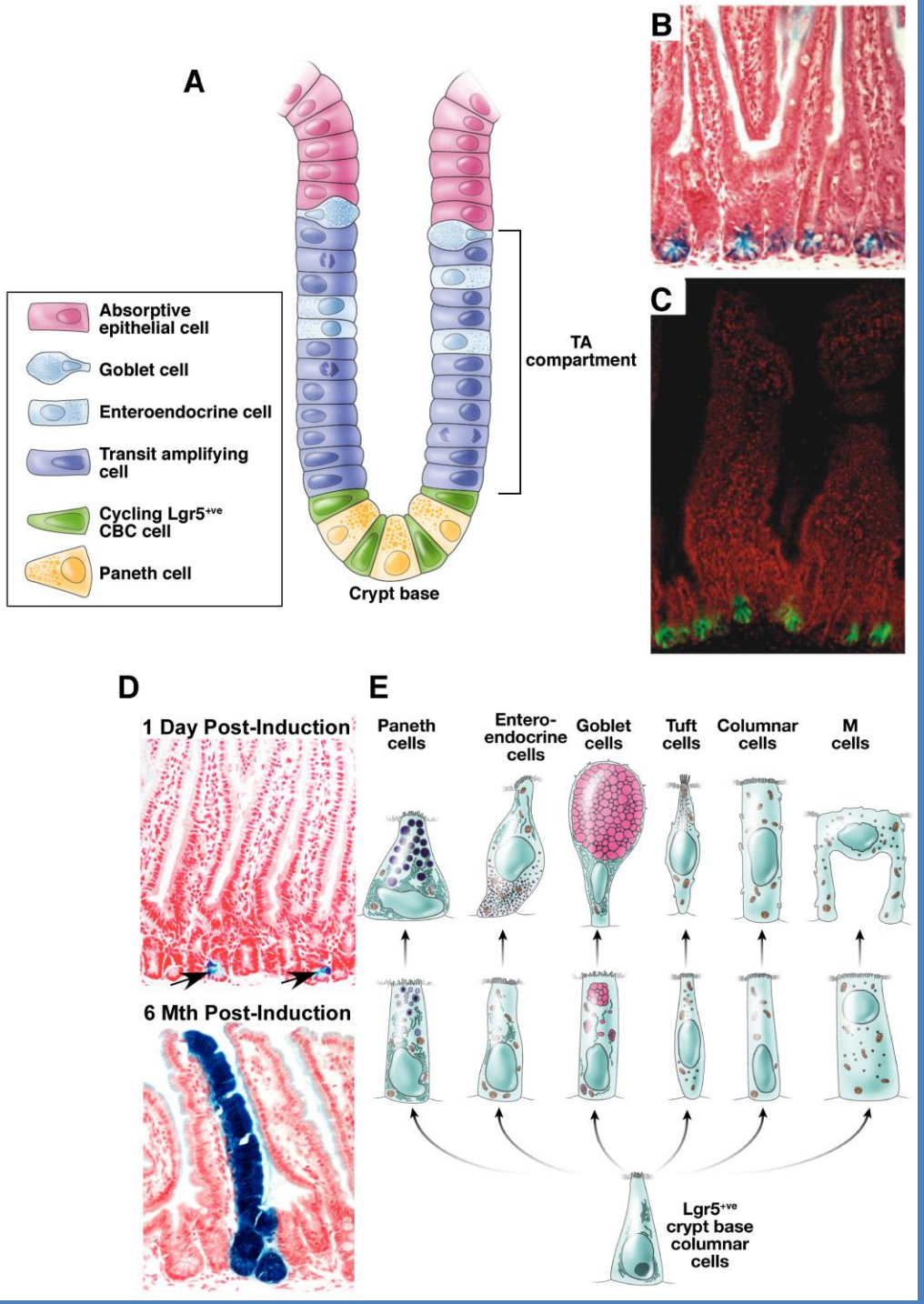


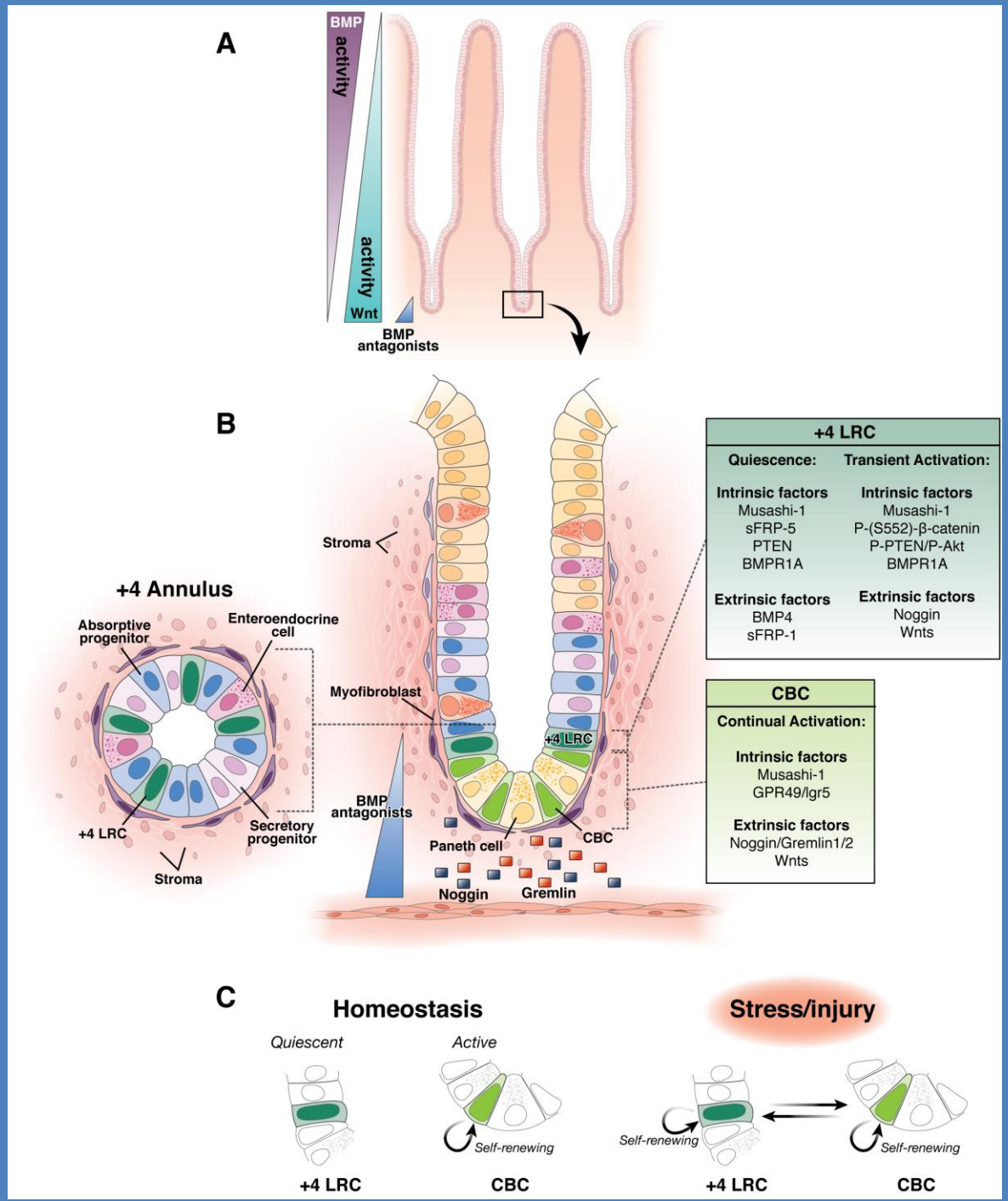
Moderate and high-risk patients

- Personal or family history of polyp(s): colonoscopy every 3-5 years. Start between ages 40-50 if family history positive (not FAP, HNPCC)
- Family history of CRC (not FAP, HNPCC). Individualize, but colonoscopy 10 yrs. younger than index case

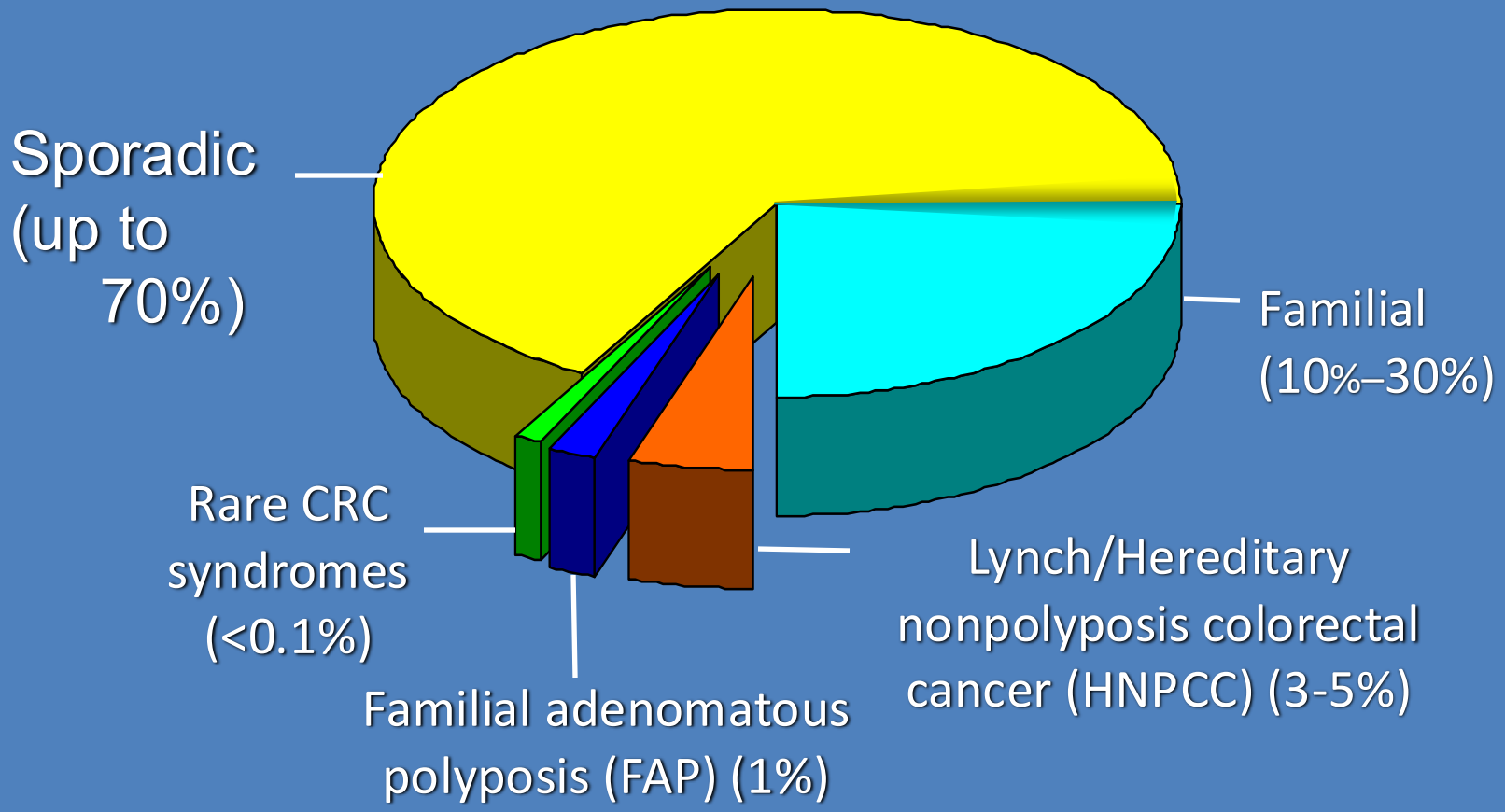
Familial Risk for Colorectal Cancer




A
Absorptive epithelial cell
Goblet cell
Enteroendocrine cell
Transit amplifying cell
Cycling Lgr5+ve CBC cell
Paneth cell
Crypt base
TA compartment
B
C
D
1 Day Post-Induction
6 Mth Post-Induction
E
Paneth cells
Entero-endocrine cells
Goblet cells
Tuft cells
Columnar cells
M cells
Lgr5+ve crypt base columnar cells

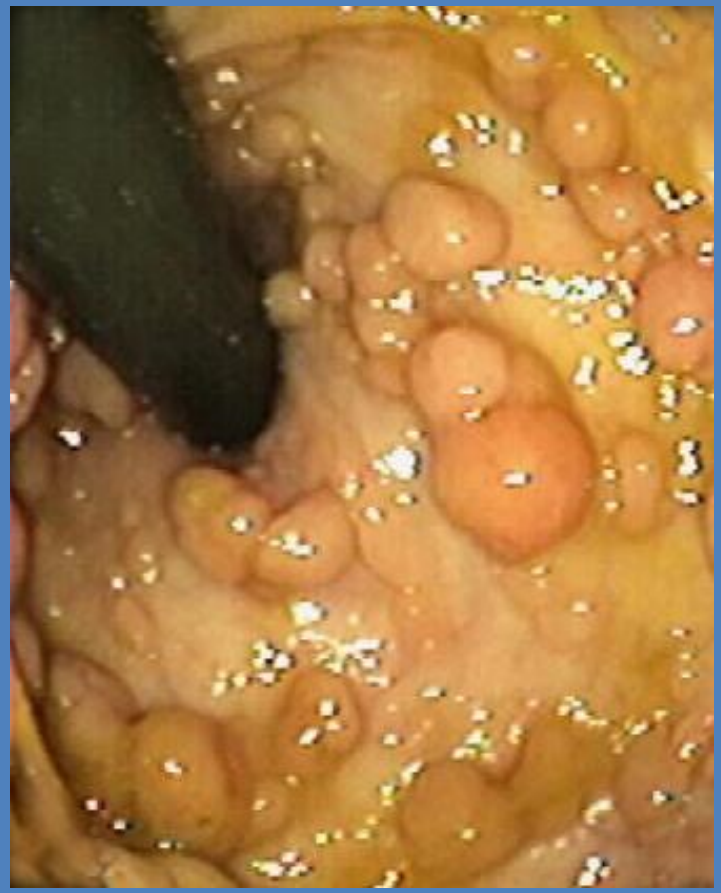

A
BMP activity
Wnt activity
BMP antagonists
B
Stroma
+4 Annulus
Absorptive progenitor
Enteroendocrine cell
Myofibroblast
+4 LRC
Secretory progenitor
Stroma
BMP antagonists
Paneth cell
CBC
Noggin
Gremlin
+4 LRC
Quiescence:
Intrinsic factors
Musashi-1
sFRP-5
PTEN
BMPR1A
Extrinsic factors
BMP4
sFRP-1
Transient Activation:
Intrinsic factors
Musashi-1
P-(S552)-β-catenin
P-PTEN/P-Akt
BMPR1A
Extrinsic factors
Noggin
Wnts
CBC
Continual Activation:
Intrinsic factors
Musashi-1
GPR49/lgr5
Extrinsic factors
Noggin/Gremlin1/2
Wnts
C
Homeostasis
Stress/injury
Quiescent
Active
Self-renewing
Self-renewing
Self-renewing
+4 LRC
CBC
+4 LRC
CBC

Causes of Hereditary Susceptibility to CRC



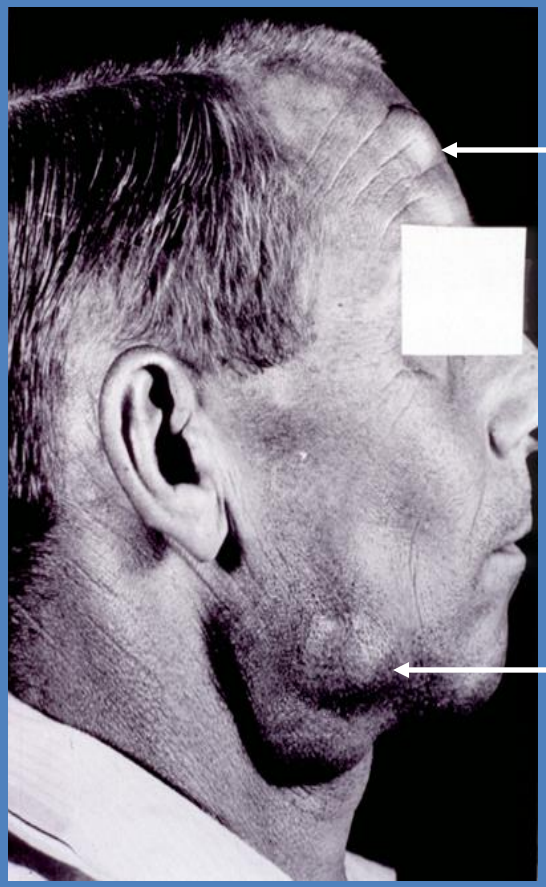
Features of FAP

- Penetrance for adenomas 100%
- Risk of extracolonic tumors (gastric, duodenal/ampullary, desmoid, thyroid, brain, adrenal, neonatal hepatoblastoma) and benign lesions (CHRPE, epidermoid cysts, bone)
- Untreated polyposis leads to 100% risk of colorectal cancer

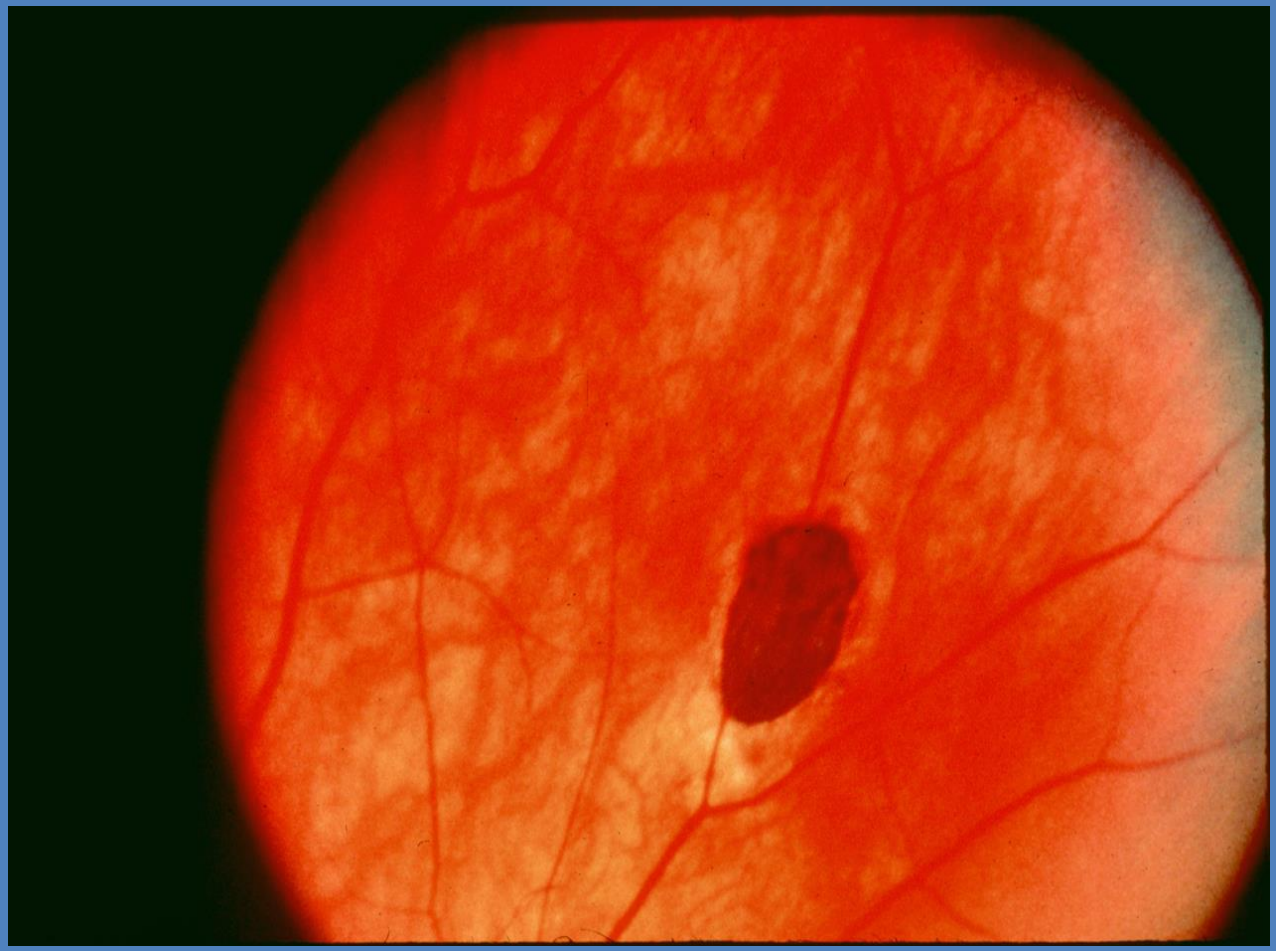


FAP: benign extracolonic manifestations

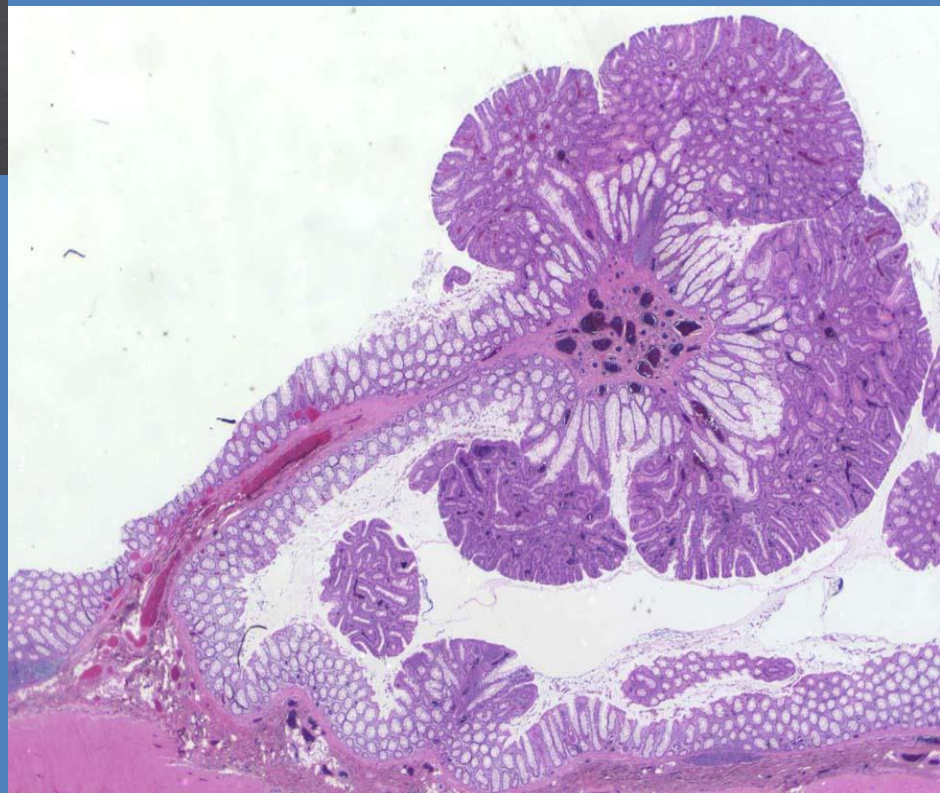
- Osteomas
- Supernumerary teeth
- Epidermoid cysts
- CHRPE

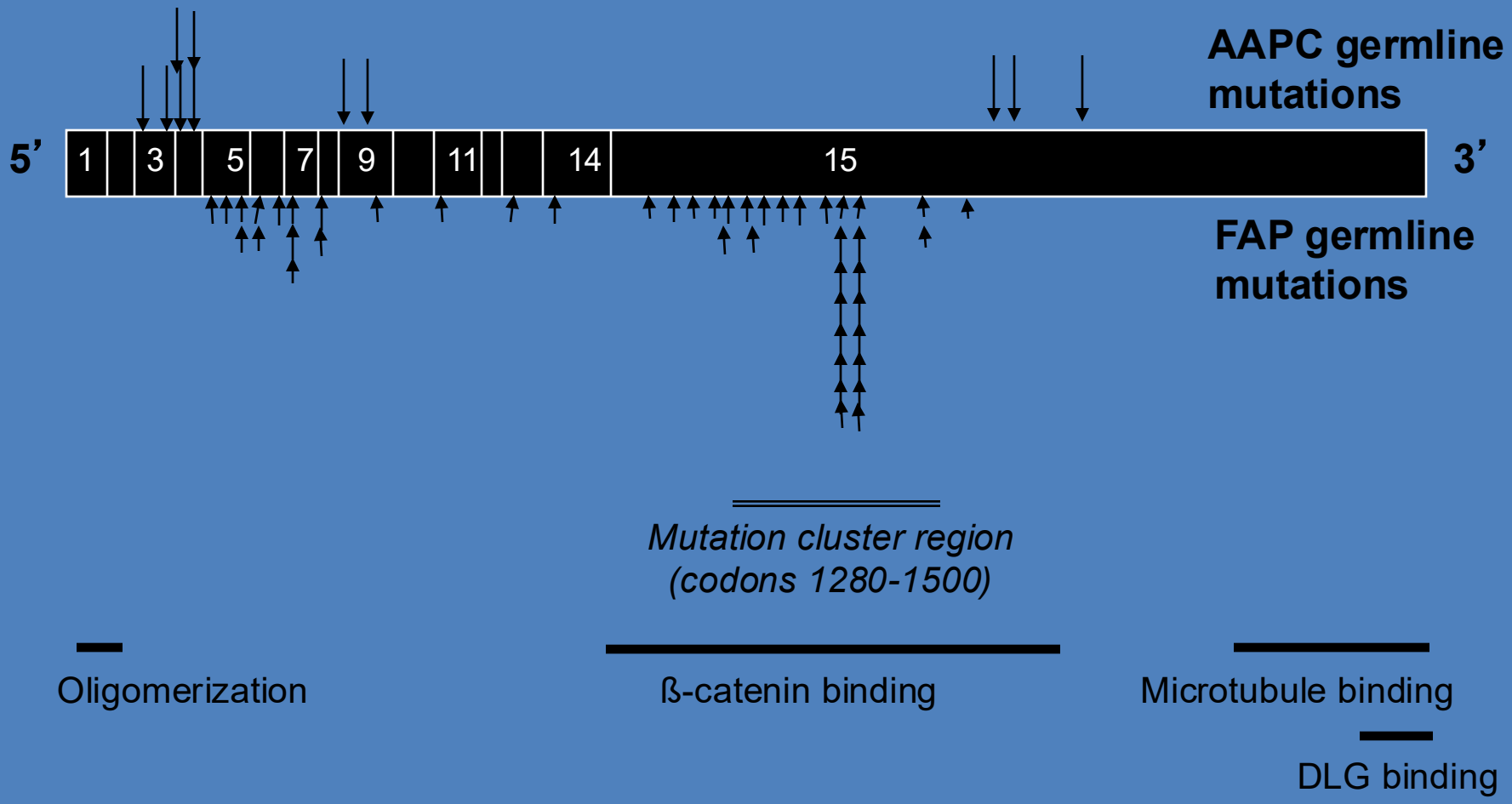


Congenital Hypertrophy of the Retinal Pigment Epithelium (CHRPE)

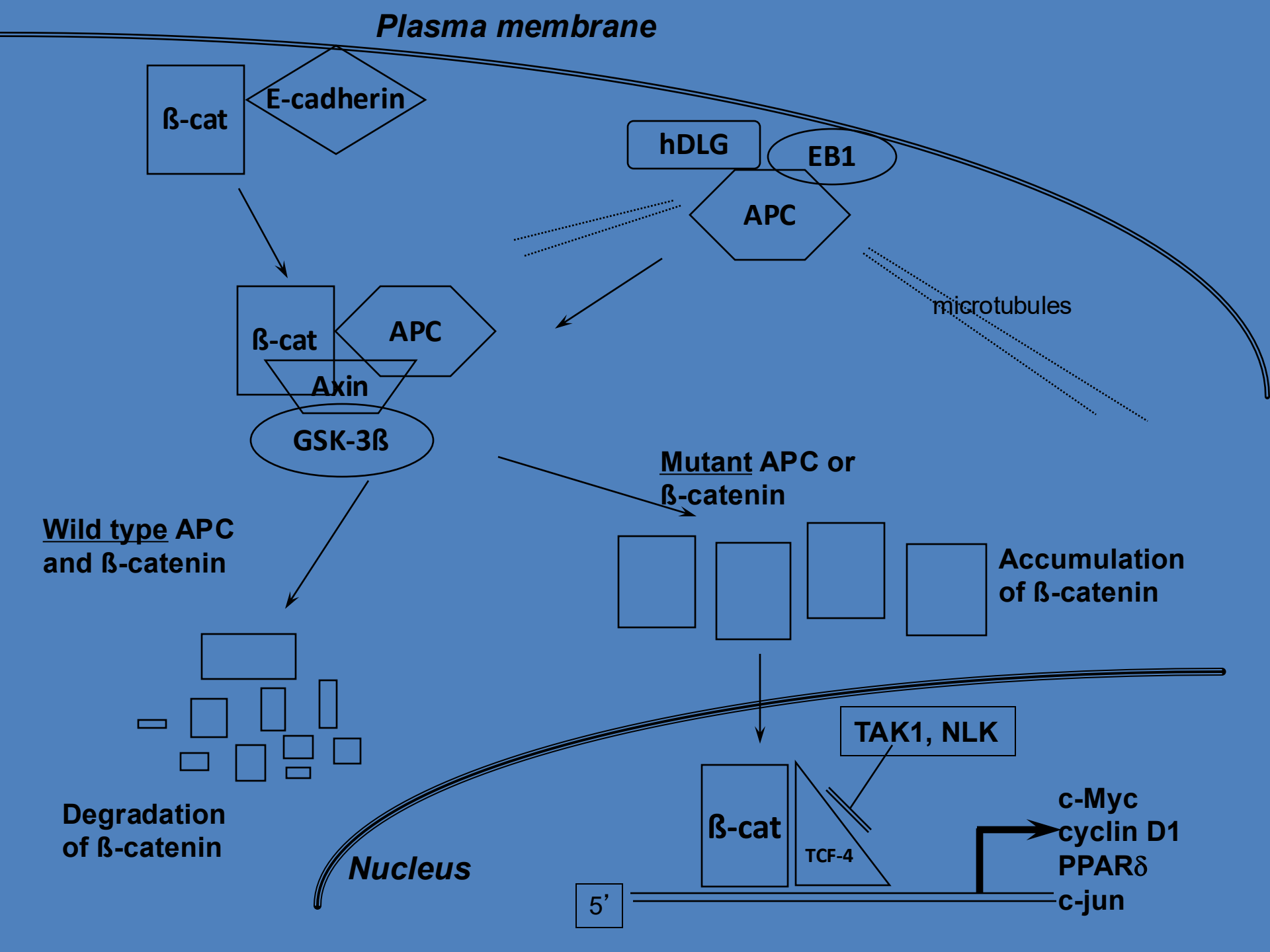


Total colectomy specimen and histology from FAP patient

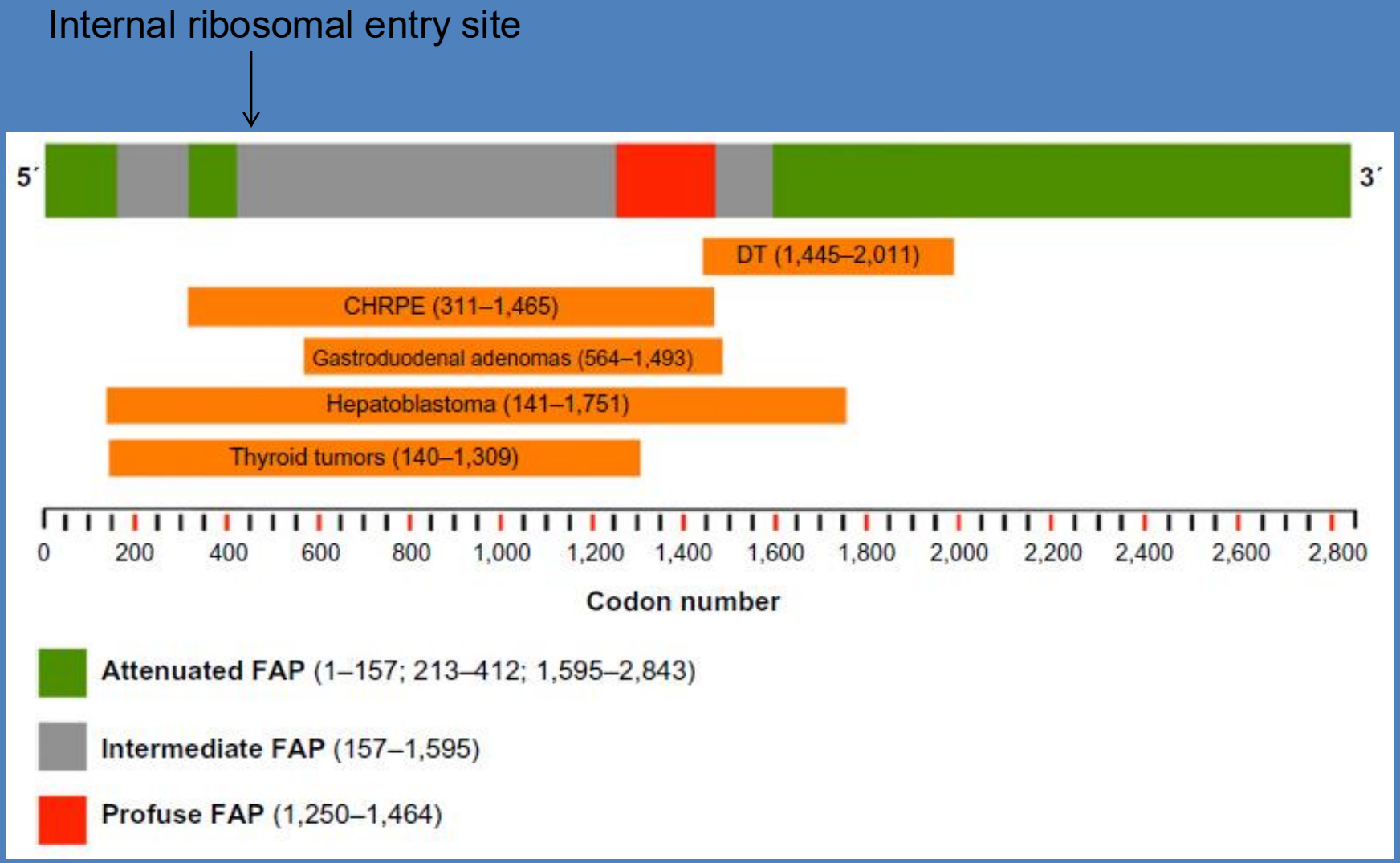




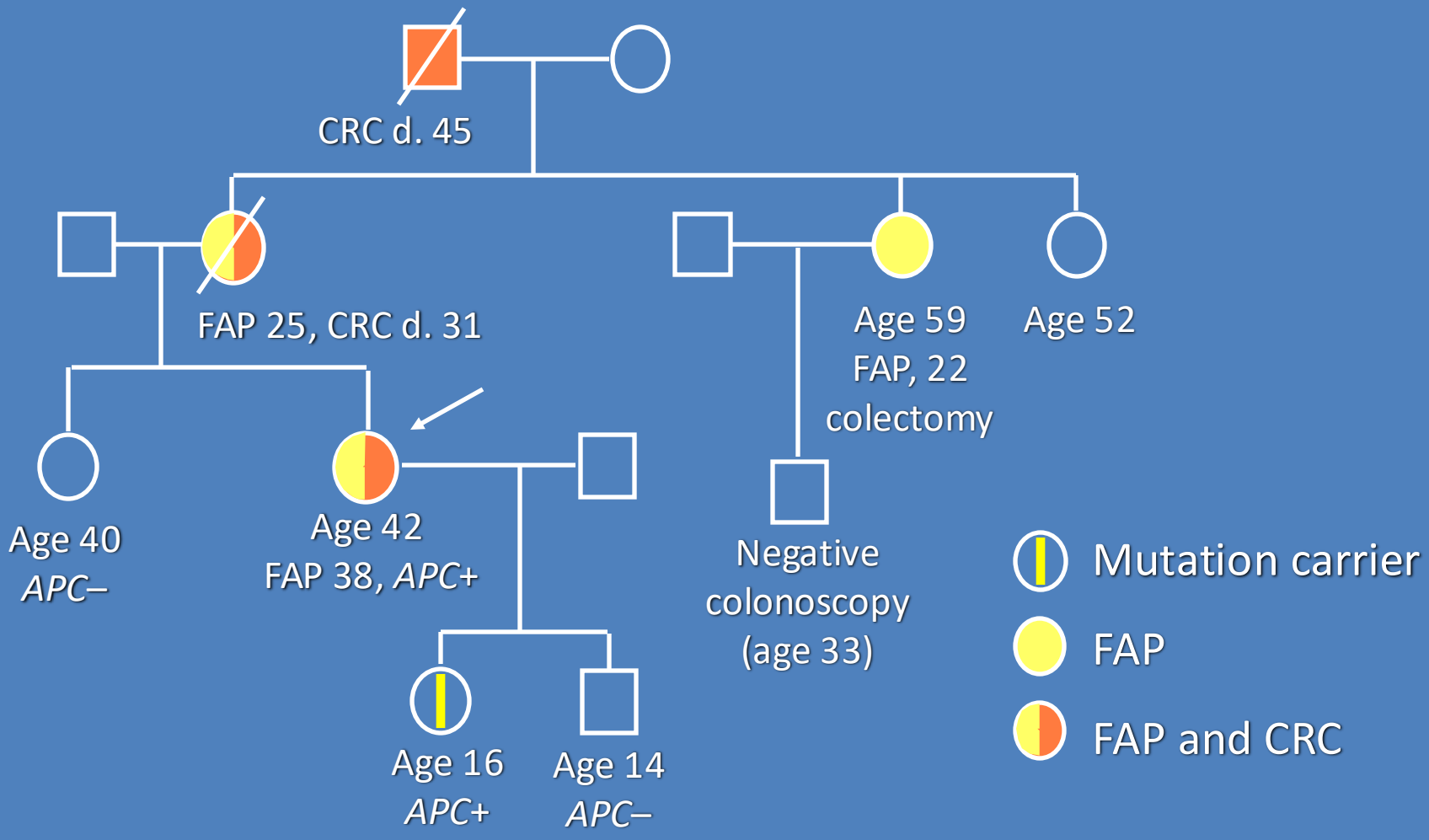
80-90% of all germline APC mutations lead to a prematurely truncated protein.


Plasma membrane
ß-cat
E-cadherin
hDLG
EB1
APC
microtubules
ß-cat
APC
Axin
GSK-3ß
Mutant APC or
ß-catenin
Wild type APC
and ß-catenin
Accumulation
of ß-catenin
Degradation
of ß-catenin
TAK1, NLK
ß-cat
TCF-4
c-Myc
cyclin D1
PPARδ
c-jun
Nucleus
5'

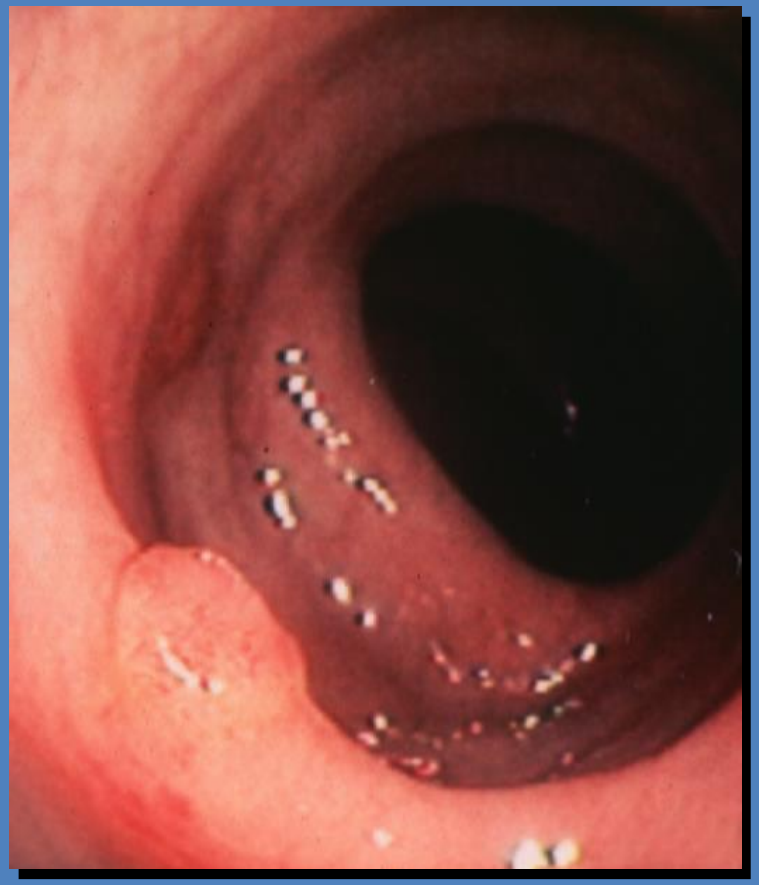
APC mutation correlates with FAP severity



FAP Family With *APC* Mutation



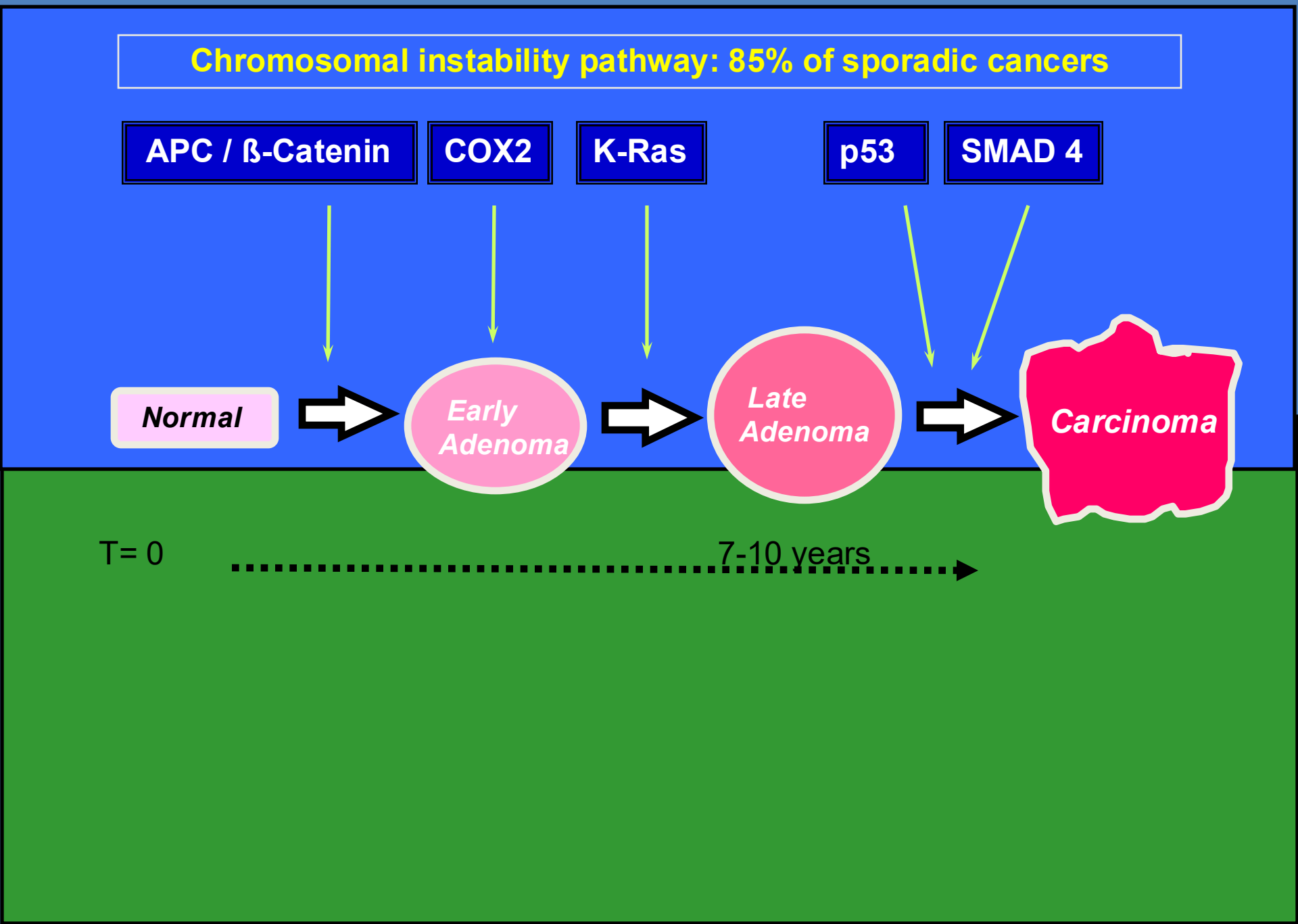
Attenuated FAP

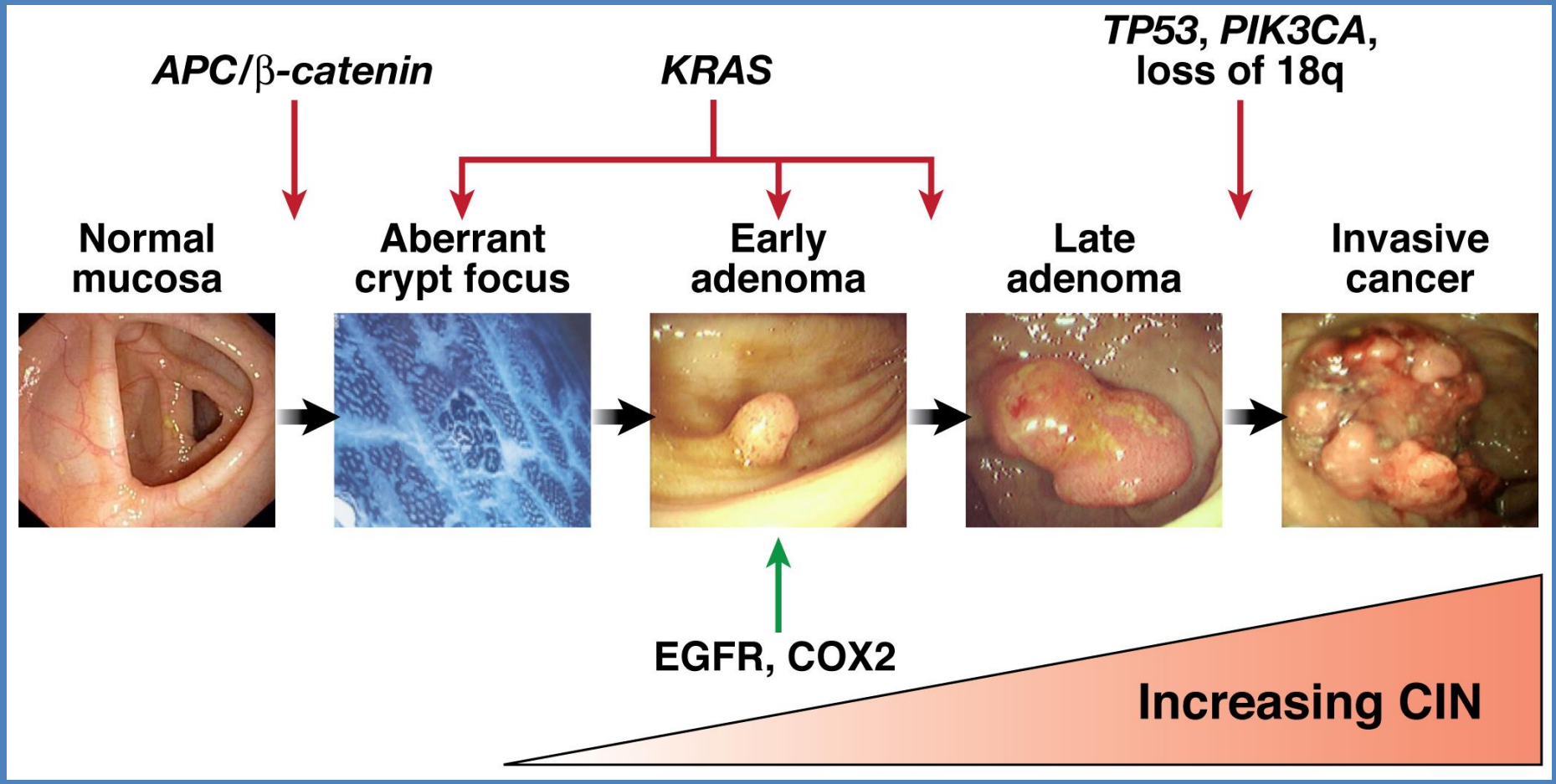


- Later onset (CRC ~age 50)
- Fewer than 100 adenomas
- UGI polyps
- Associated with mutations at 5' and 3' ends of *APC* gene

Genetic and clinical screening in FAP

- Genetic testing (*APC* gene sequencing; APC genomic deletions-rare)
  - polyposis (>100 adenomas)
  - attenuated FAP
- Screen at-risk individuals (age 12)
- Clinical
  - Examination (dental, skin)
  - Colonoscopy
  - EGD (side-viewing scope); baseline capsule endoscopy
  - Thyroid Ultrasound


Chromosomal instability pathway: 85% of sporadic cancers
APC / ß-Catenin
COX2
K-Ras
p53
SMAD 4
Normal
Early Adenoma
Late Adenoma
Carcinoma
T= 0
7-10 years


APC/β-catenin
KRAS
TP53, PIK3CA, loss of 18q
Normal mucosa
Aberrant crypt focus
Early adenoma
Late adenoma
Invasive cancer
EGFR, COX2
Increasing CIN

MUTYH-associated polyposis (MAP)

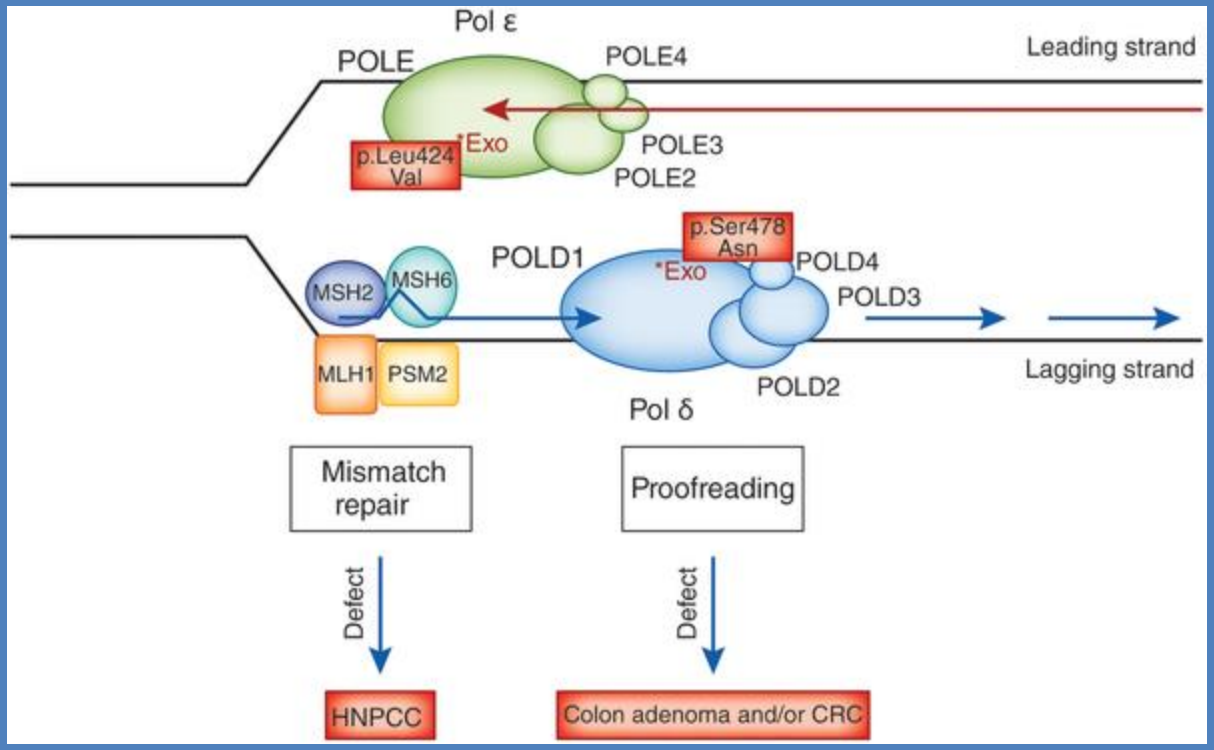
- MUTYH = base excision repair gene that repairs damaged DNA
- **Autosomal recessive**
- Monoallelic MUTYH found in ~1-2% of the population
- Lifetime risk of CRC of ~75% with biallelic mutation
- MAP accounts for < 1% of all CRC
- Monoallelic mutation carriers have only minimally increased risk

- Typically have 10-100 polyps, that present in the 5^{th} – 6^{th} decades
- Typically the polyps are tubular adenomas
- At risk of developing other cancers: duodenum, ovaries, bladder, thyroid, skin

Polymerase Proofreading-associated Polyposis (PPAP)

- Polymerase proof-reading associated polyposis
- Two most frequently mutated genes are POLE/POLD1
- Similar presentation to FAP
- Increased risk of endometrial cancer, and possibly breast and brain cancer as well

- Surveillance with colonoscopy every 1-2 years, and EGD every 3 years, both starting at age 20-25

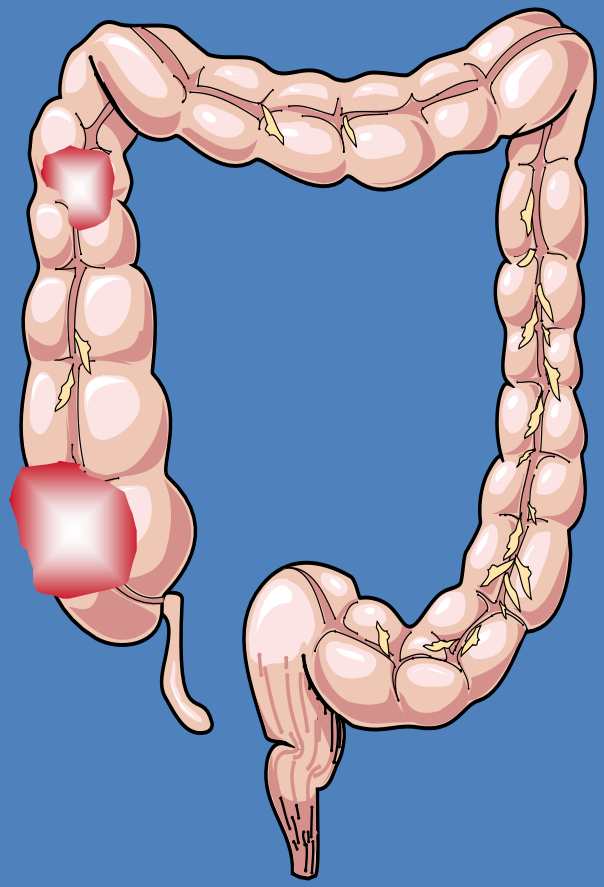


Seshagari S. *Nat Genet*.

Features of Lynch syndrome

- Up to 100 adenomas (small, flat)
- Early but variable age at CRC diagnosis (~45 years)
- Tumor site in proximal colon predominates (about 70%)
- Extracolonic cancers: endometrium, ovary, stomach, small bowel, bile ducts, kidney, sebaceous skin tumors, ?pancreas

(NO breast cancers)



Amsterdam Criteria

-3 or more relatives with verified CRC in family

-One case a first-degree relative of the other two

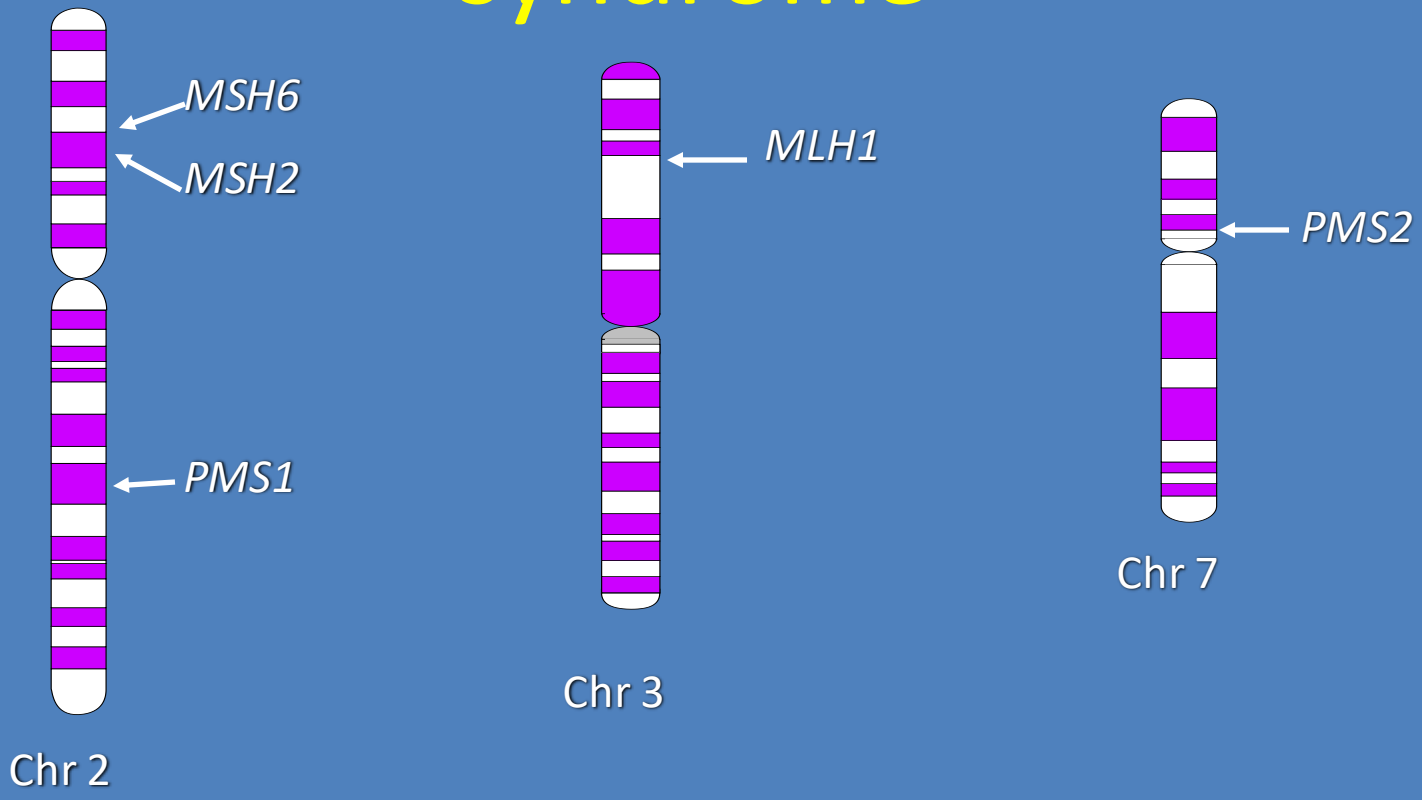
-Two or more generations

-One CRC by age 50

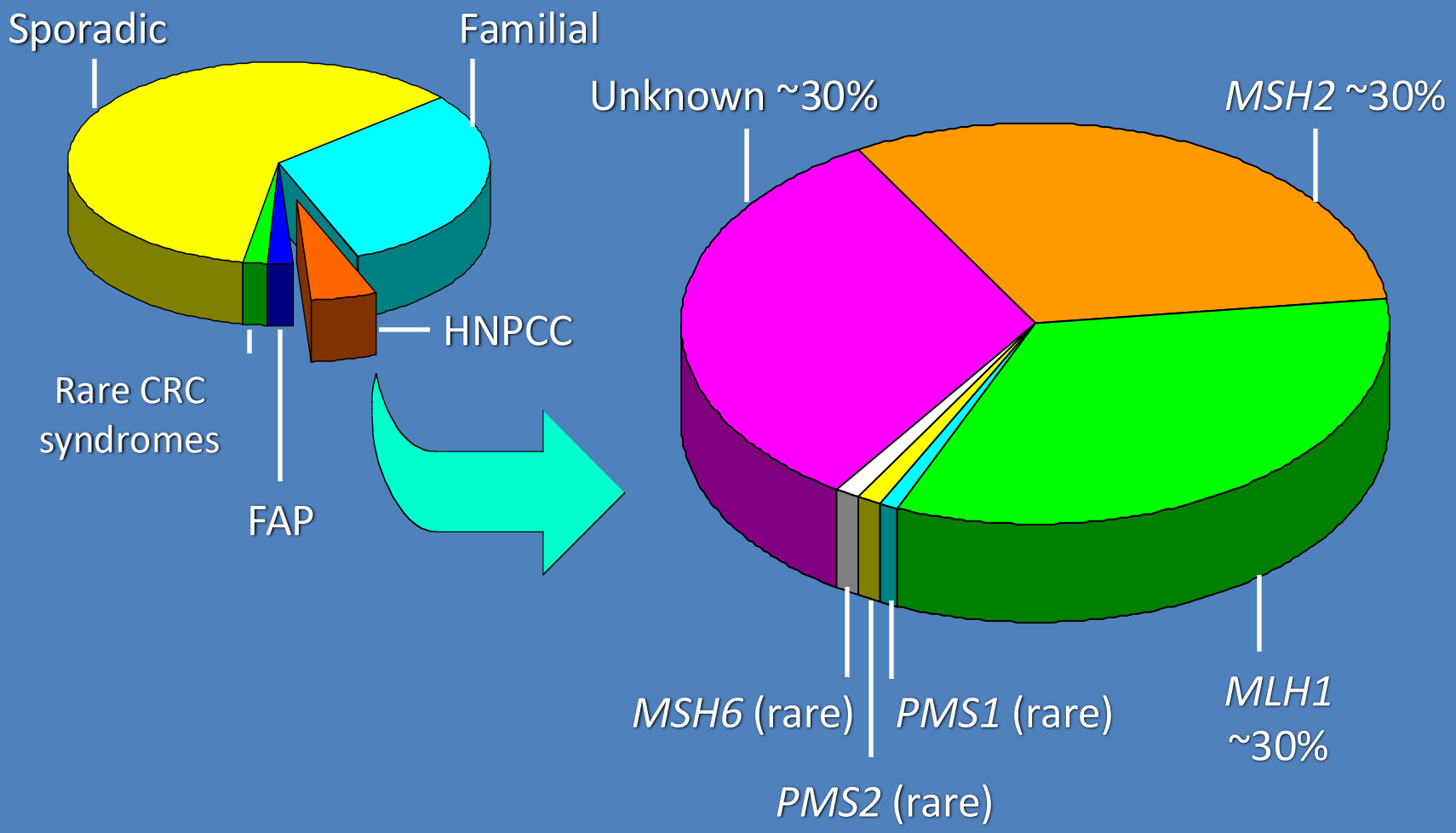
-FAP excluded

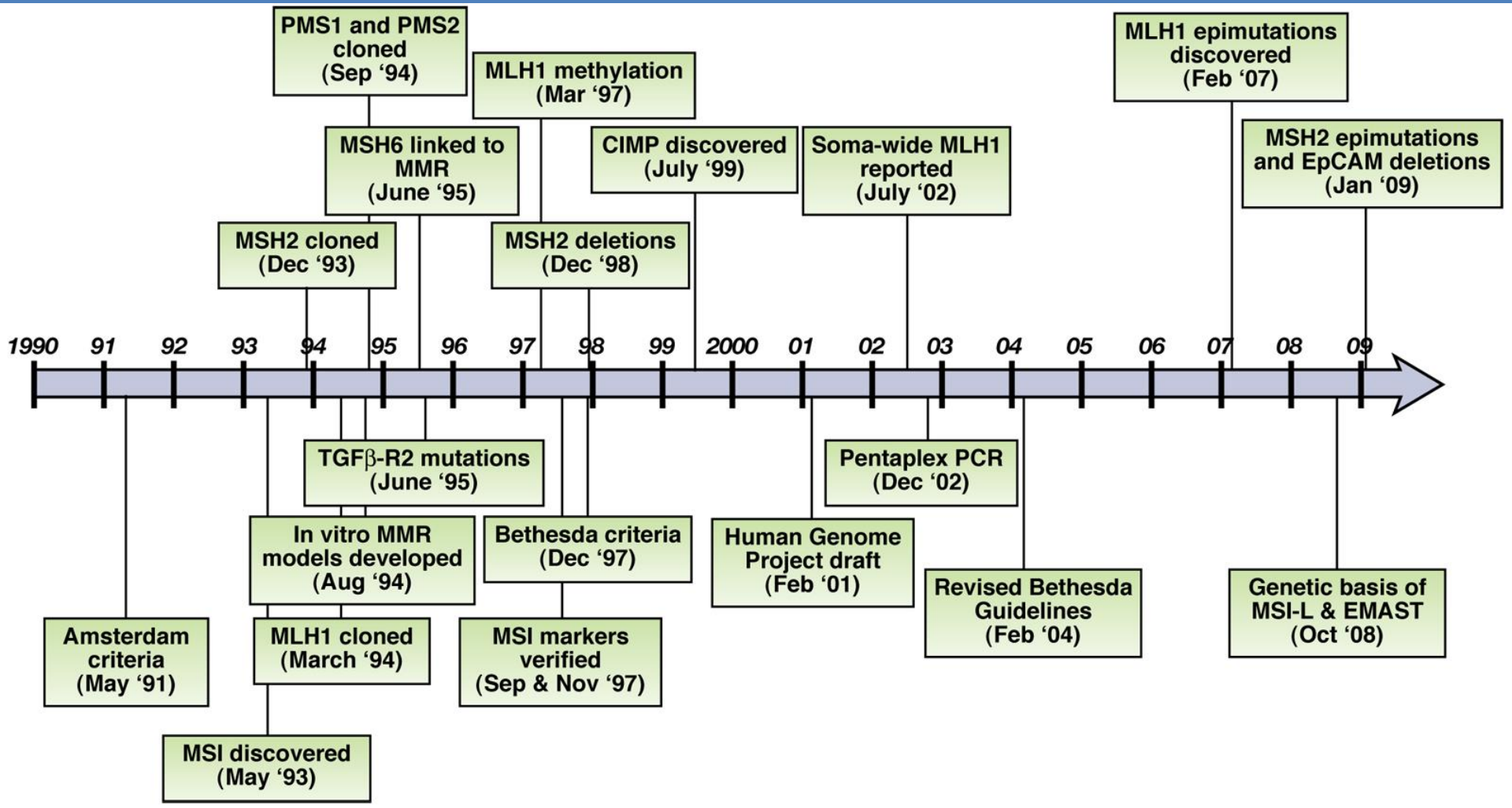
Failure to meet these criteria
does *not* exclude Lynch

Genetic Heterogeneity in Lynch syndrome

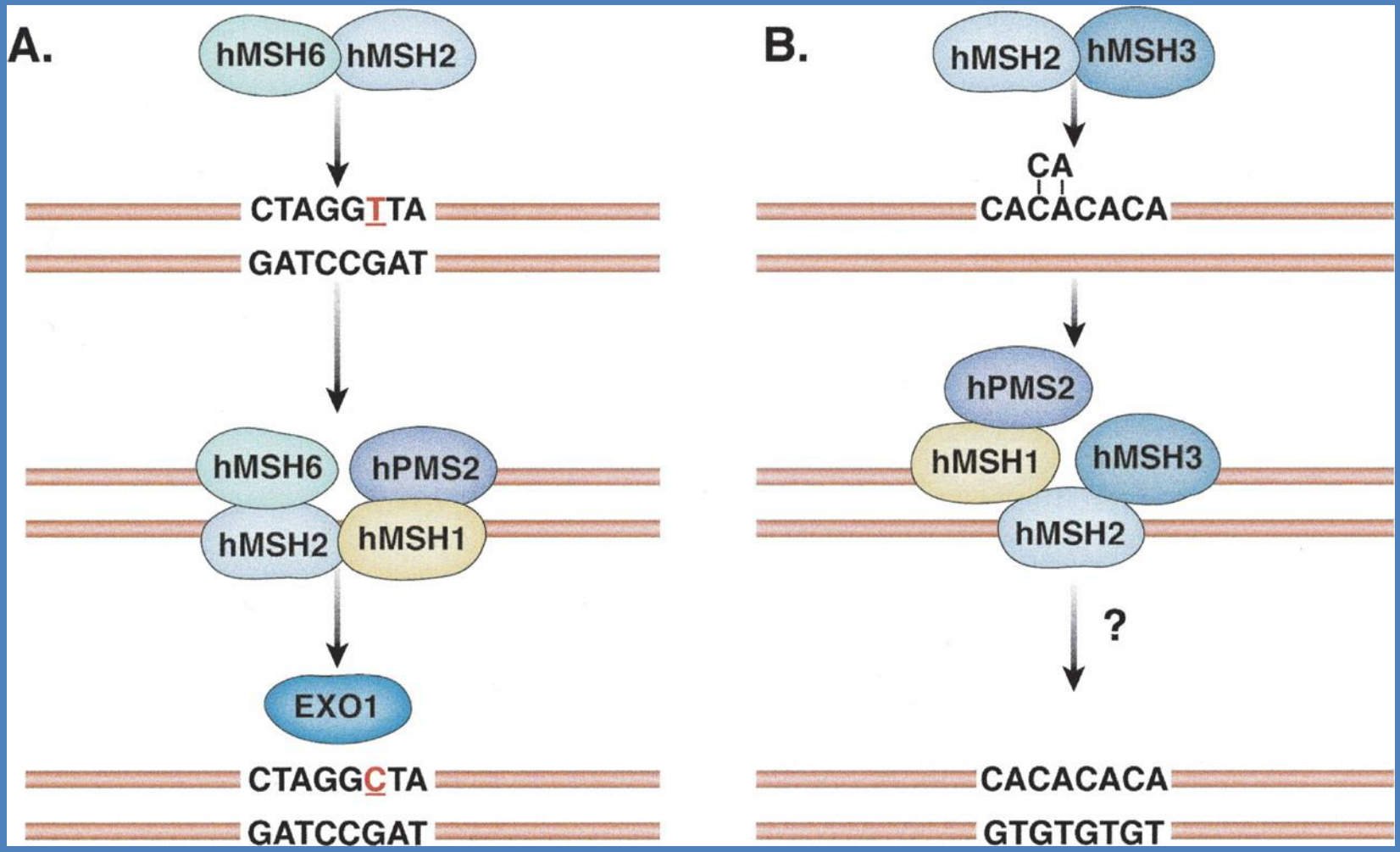


Contribution of Gene Mutations to Lynch syndrome Families

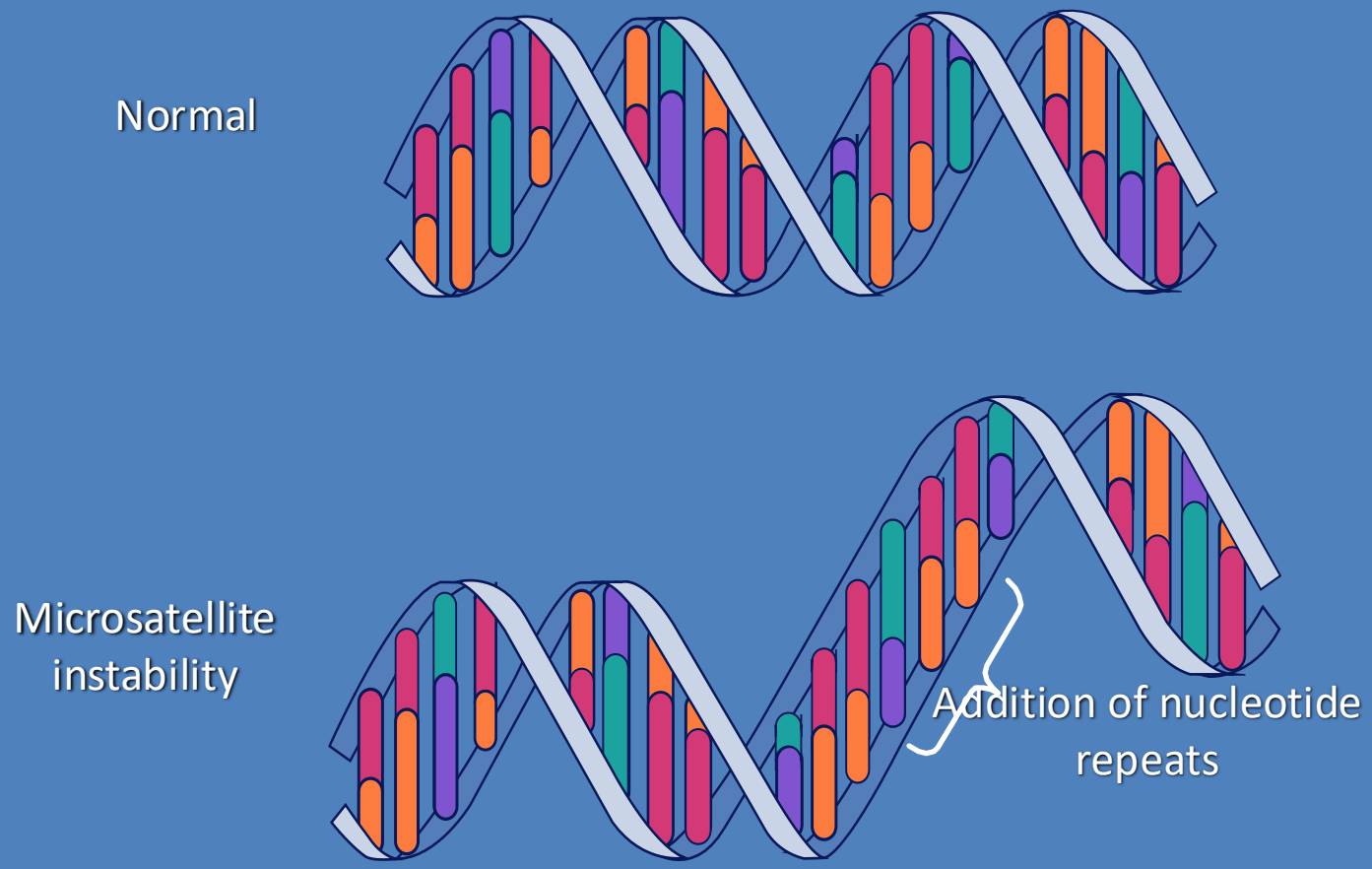



PMS1 and PMS2 cloned (Sep '94)
MLH1 methylation (Mar '97)
MLH1 epimutations discovered (Feb '07)
MSH6 linked to MMR (June '95)
CIMP discovered (July '99)
Soma-wide MLH1 reported (July '02)
MSH2 epimutations and EpCAM deletions (Jan '09)
MSH2 cloned (Dec '93)
MSH2 deletions (Dec '98)
1990 91 92 93 94 95 96 97 98 99 2000 01 02 03 04 05 06 07 08 09
TGFβ-R2 mutations (June '95)
Pentaplex PCR (Dec '02)
In vitro MMR models developed (Aug '94)
Bethesda criteria (Dec '97)
Human Genome Project draft (Feb '01)
Revised Bethesda Guidelines (Feb '04)
Genetic basis of MSI-L & EMAST (Oct '08)
Amsterdam criteria (May '91)
MLH1 cloned (March '94)
MSI markers verified (Sep & Nov '97)
MSI discovered (May '93)

DNA MMR system in mammalian cells that perform recognition and editing functions, which have escaped DNA polymerase. Mutations in MMR lead to Microsatellite instability, high mutational burden, generation of neoantigens, success in immune checkpoint blockade

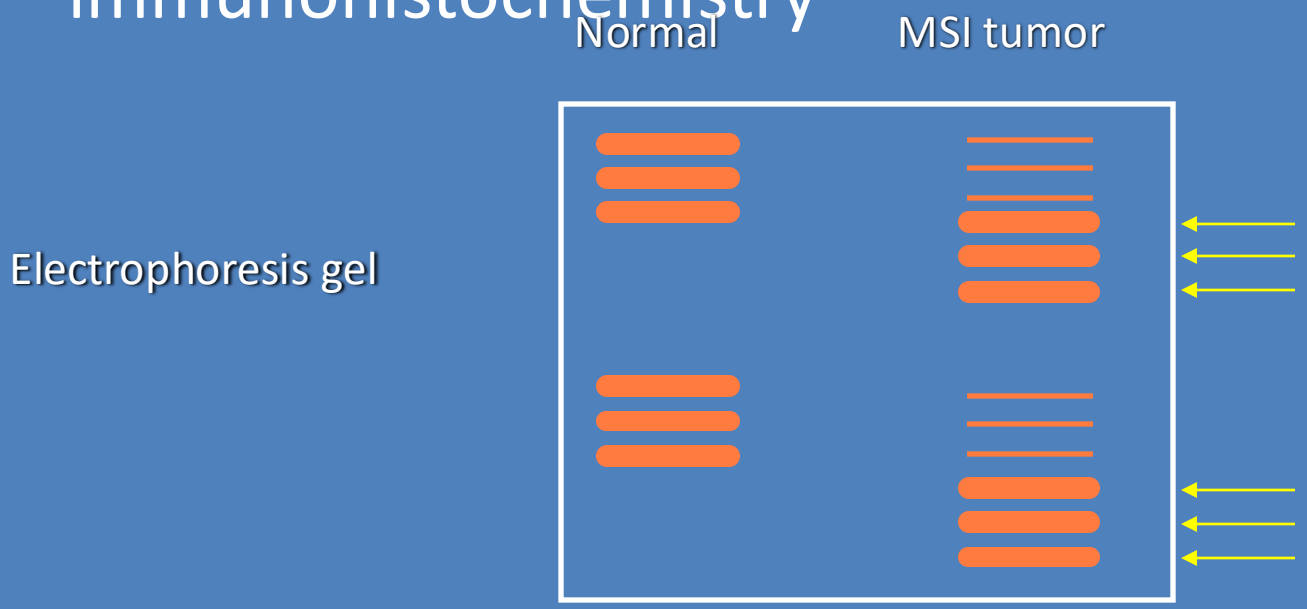


Mismatch Repair Failure Leads to Microsatellite Instability (MSI)

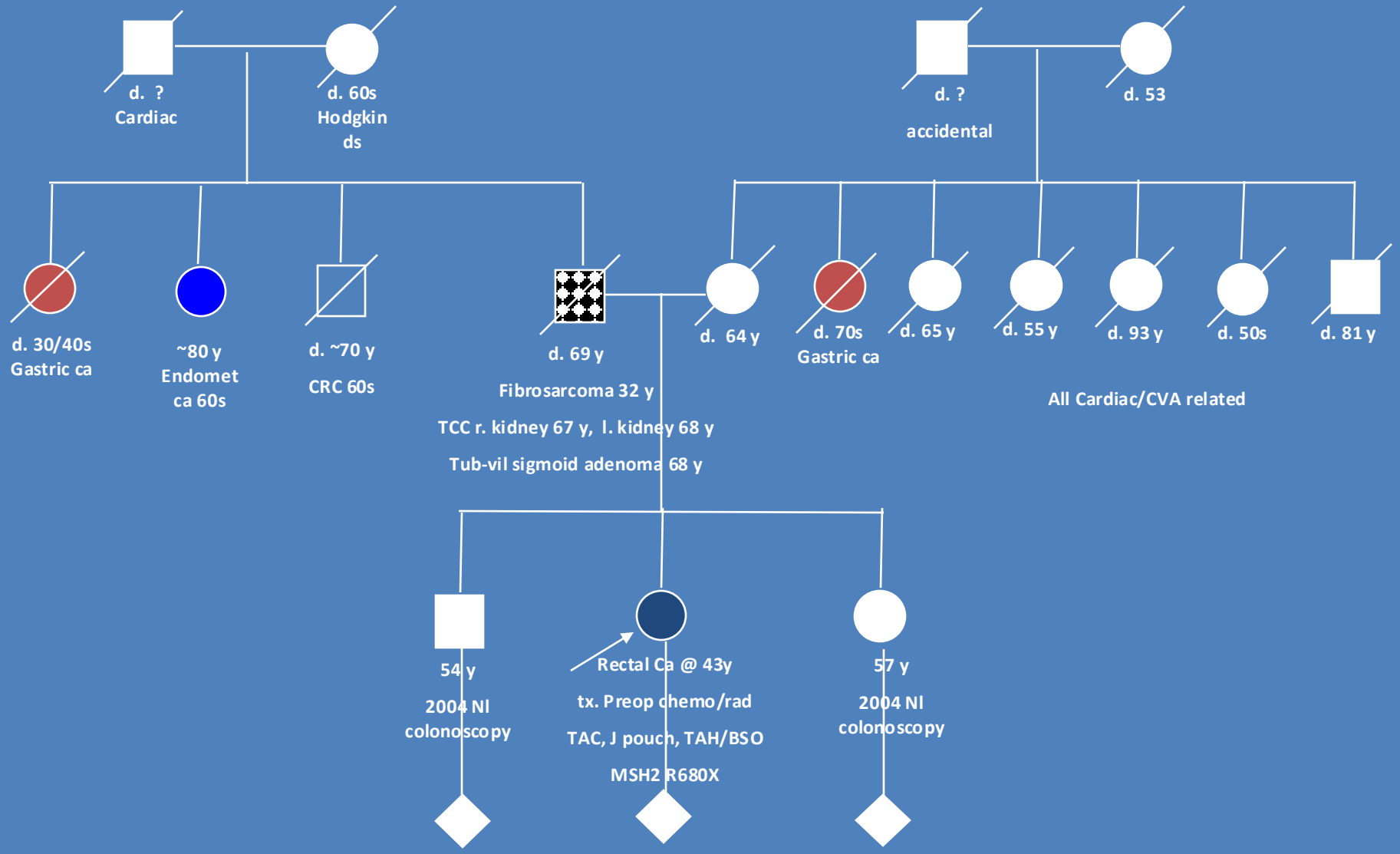


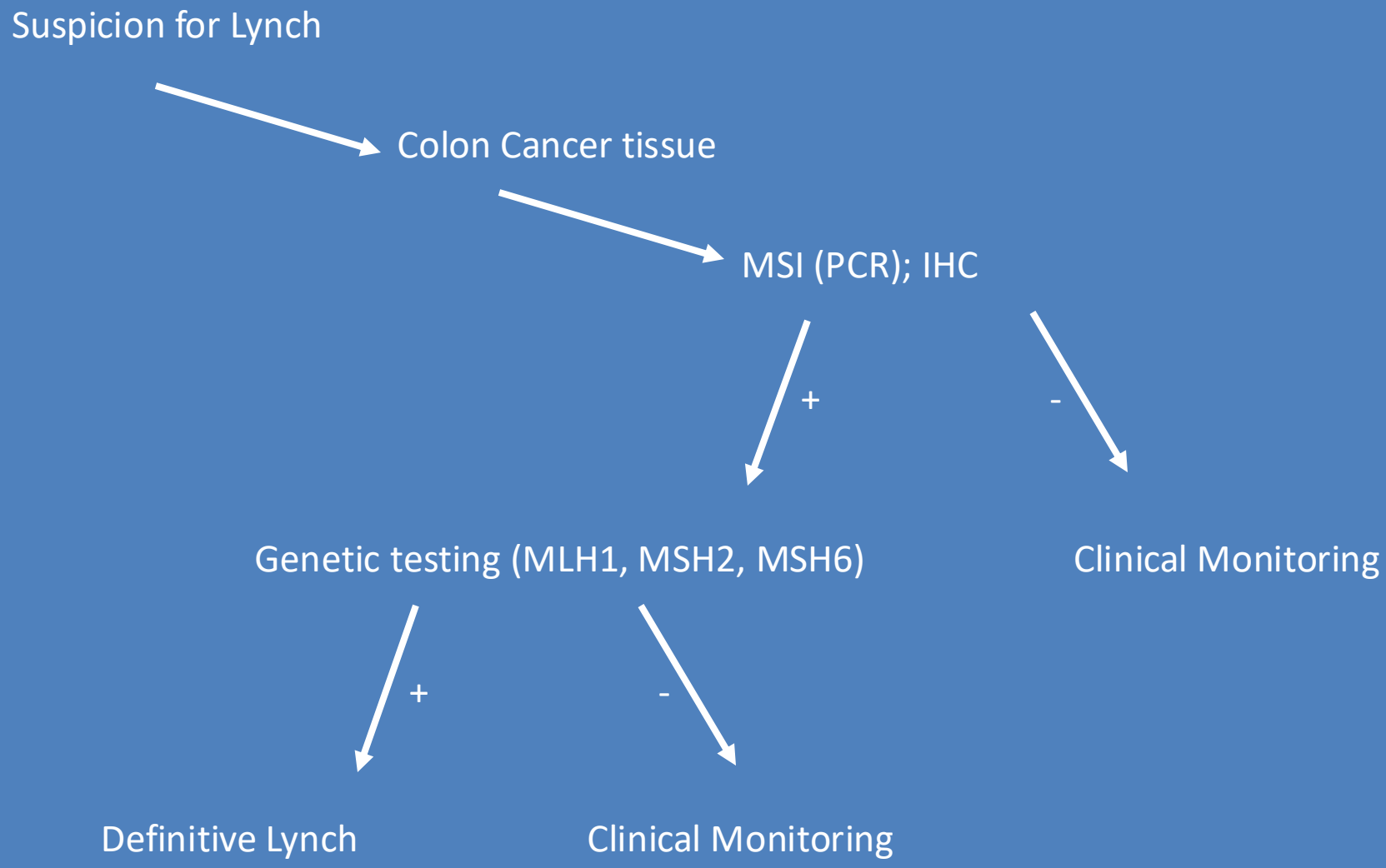
Microsatellite Instability (MSI)

- 10%–15% of sporadic tumors have MSI
- 95% of Lynch tumors have MSI at multiple loci
- Routine MSI assays available but replaced by immunohistochemistry



Patient with a MSH2 mutation




Suspicion for Lynch
Colon Cancer tissue
MSI (PCR); IHC
+
-
Genetic testing (MLH1, MSH2, MSH6)
Clinical Monitoring
+
-
Definitive Lynch
Clinical Monitoring

Surveillance options for carriers of Lynch-Associated Mutations

Malignancy	Intervention	Surveillance
Colorectal cancer	Colonoscopy	Begin at age 20–25, repeat every 1–2 yrs
Gastric cancer	EGD	Baseline (repeat prn)
Endometrial cancer	Transvaginal ultrasound Endometrial aspirate	Annually, starting at age 25–35
Bladder cancer	Urine cytology	Annually

Prophylactic surgery options for Lynch-associated mutation carriers

- Options include subtotal colectomy/total colectomy, hysterectomy, and ophorectomies. Will often try to do concurrently.
- Surgery does not eliminate cancer risk in other sites.

Lynch Syndrome – Lifetime risks are related to specific germline mutations

- Up to an 80% lifetime CRC risk.
- CRC can develop at young age, and often in the right colon.
- Accelerated neoplastic progression (ex. polyp → cancer in a couple years or less).
- Risk is different based on which mutation is present:
  - Highest risk → *MLH1* and *MSH2*
  - Lowest risk → *MSH6* and *PMS2*

Table 3. Gene-specific cumulative risks of colorectal cancer by age 70 years in Lynch syndrome

Gene mutation carriers	Risk, %	Mean age at diagnosis, y	References
Sporadic cancer	5.5	69	(29)
MLH1/MSH2	Male: 27–74 Female: 22–53	27–46	(17–21,23)
MSH6	Male: 22		
	Female: 10 Male and female: 18	54–63	(17,22)
PMS2	Male: 20 Female: 15	47–66	(25)

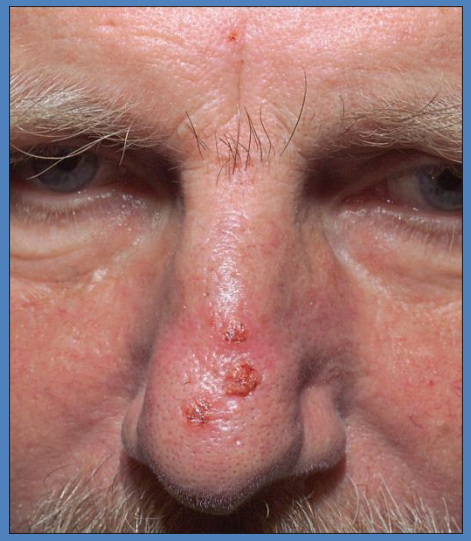
Giardiello FM, et al, *Am J Gastroenterol*, 2014.

Lynch Syndrome – Extra-colonic Cancers

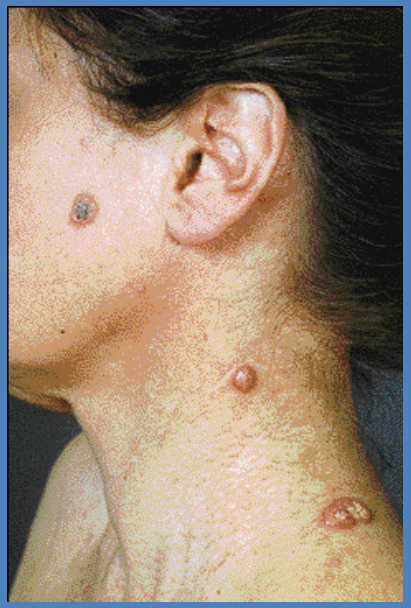
- Some cancer risks can be gene dependent:
  - Endometrial cancer
    - Lower risk: *PMS2*
    - Higher risk: all other Lynch genes
  - Urinary tract cancer
    - Higher risk: *MSH2*

Muir-Torre Syndrome

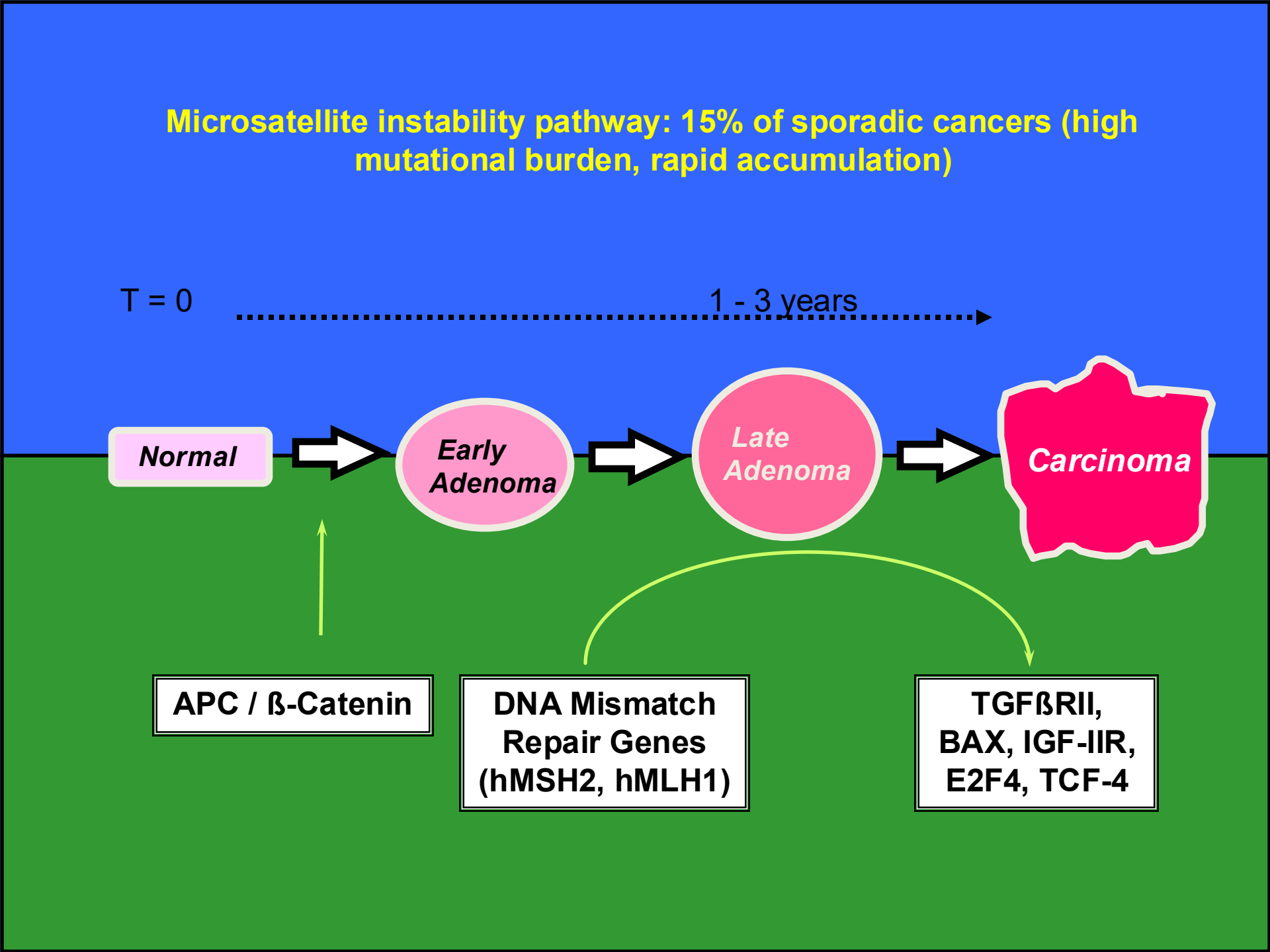
- Phenotypic variant of Lynch Syndrome
- Characterized by at least 1 sebaceous gland tumor & 1 internal malignancy
- Sebaceous gland tumors:
  - Sebaceous adenomas
  - Sebaceous carcinomas
- Also associated with keratoacanthomas of the skin
- Predominantly caused by *MLH1* and *MSH2* mutations



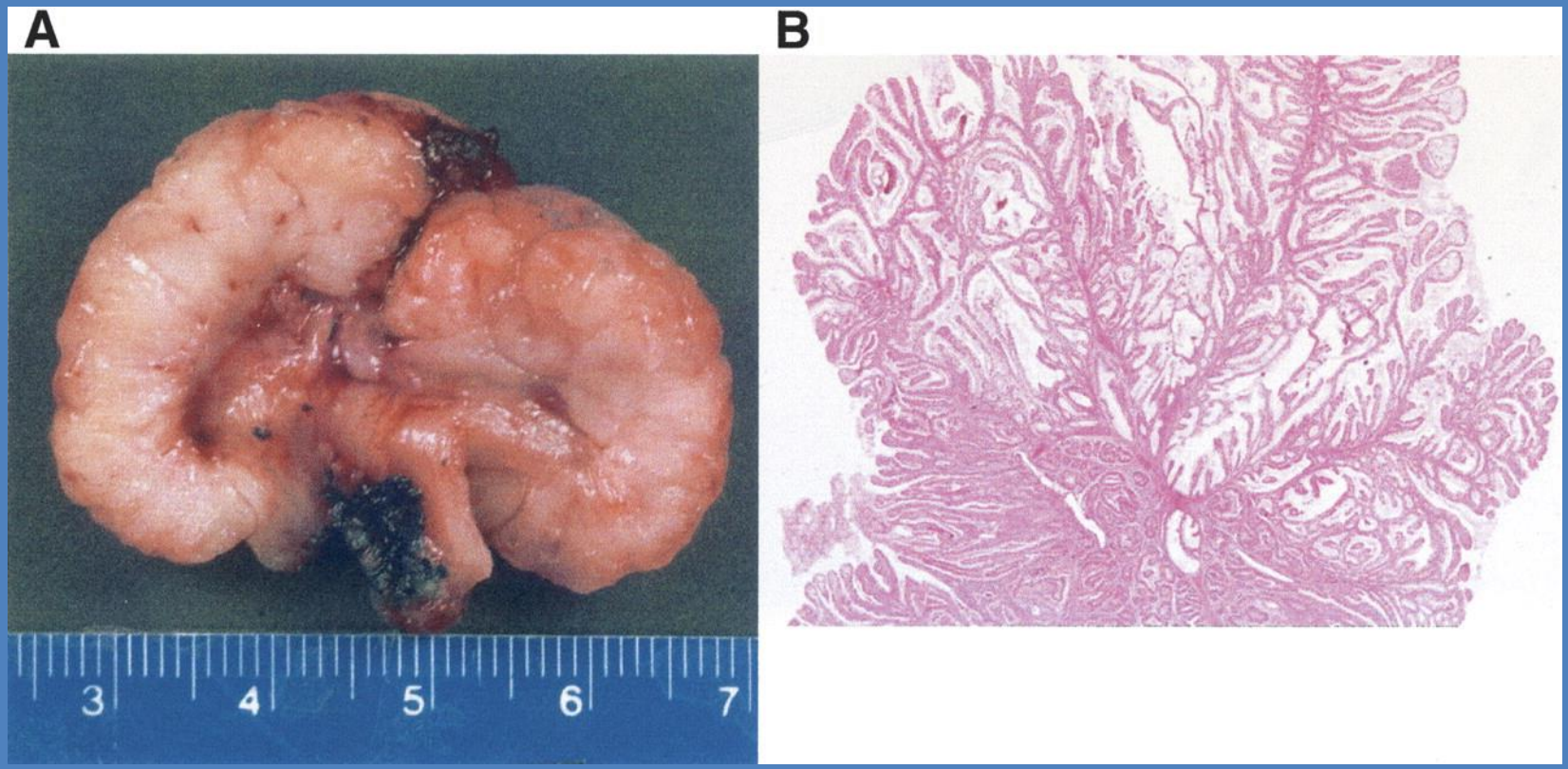
Mazzara, G. et al. *Arch Dermatol*. 2006



Gjersvik P, Egass E, & Clausen OP. *Eur J Dermatol*. 2000


Microsatellite instability pathway: 15% of sporadic cancers (high mutational burden, rapid accumulation)
T = 0
1 - 3 years
Normal
Early Adenoma
Late Adenoma
Carcinoma
APC / ß-Catenin
DNA Mismatch Repair Genes (hMSH2, hMLH1)
TGFßRII, BAX, IGF-IIR, E2F4, TCF-4

Peutz-Jegher syndrome
Pigmentation; PJ polyps/SB, colon cancer; sex cord tumors;breast,pancreatic,lung, cervical cancers



Peutz-Jeghers syndrome

- Disease characterized by mucocutaneous pigmentation and hamar polyps in the GI tract

- First recognized in 1921 by Dr. Johannes Peutz and classified as an inherited disease by Dr. Harold Jeghers in 1949

- Autosomal dominant

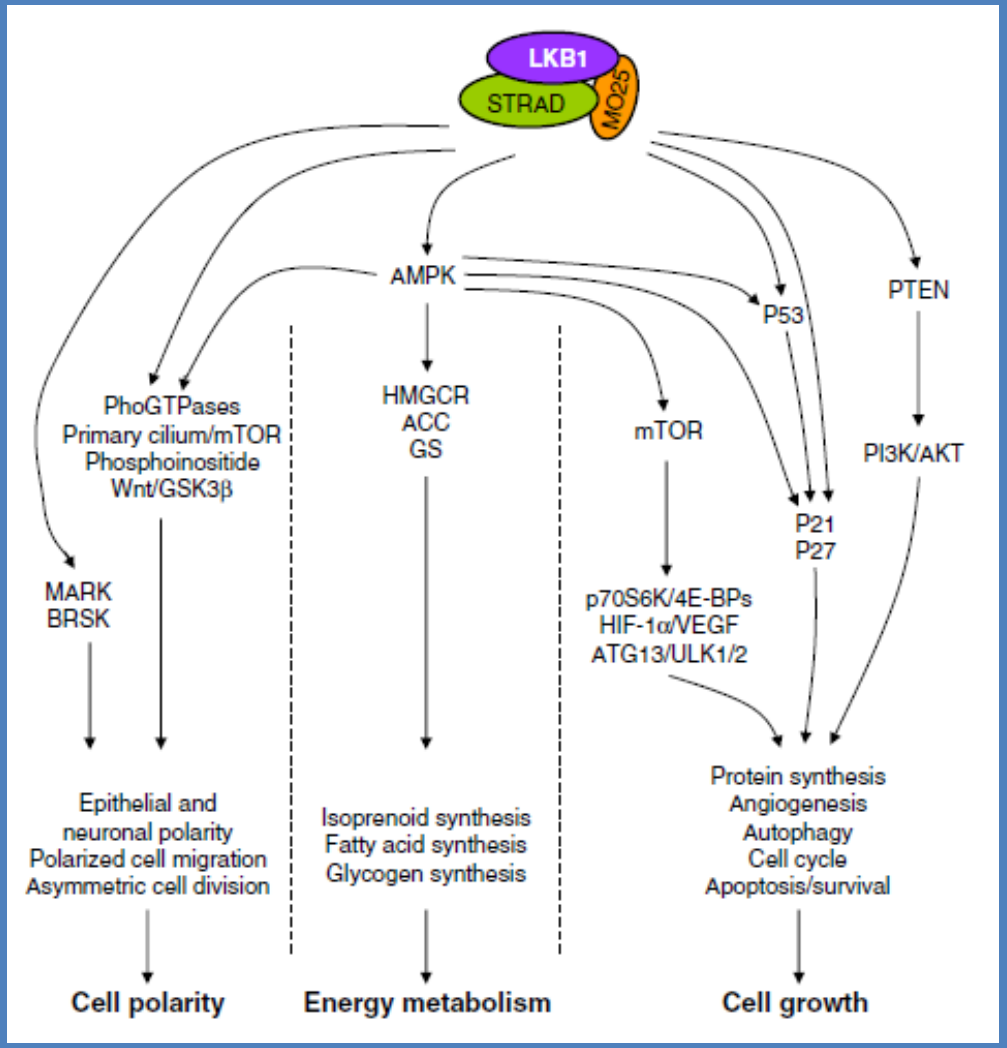
- STK11 (LKB1) is the most commonly mutated gene (50-80% of families)

- 20% of patients will not have an affected parent → *de novo* mutation

- At least 2 of the following:
  - ≥ 2 PJ hamartomatous polyps
  - Mucocutaneous hyperpigmentation
  - Family history of PJS

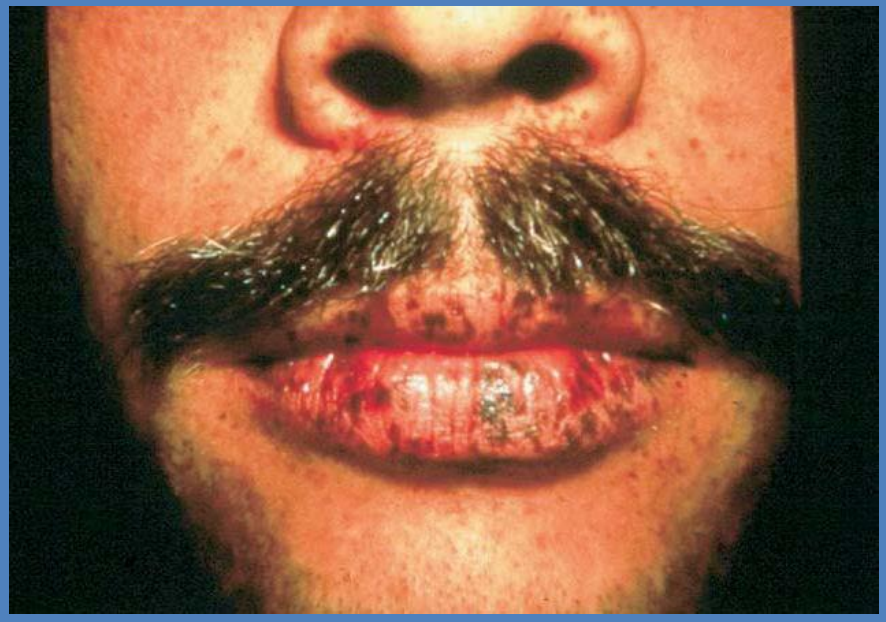
STK11/LKB1
Serine-Threonine Kinase 11/Liver Kinase B1

- Mutation found in only 30-70% of sporadic cases and ~80-94% of families
- 150 mutations detected (truncation = earlier age of onset)
- LKB1 is a tumor suppressor



Mucocutaneous pigmentation

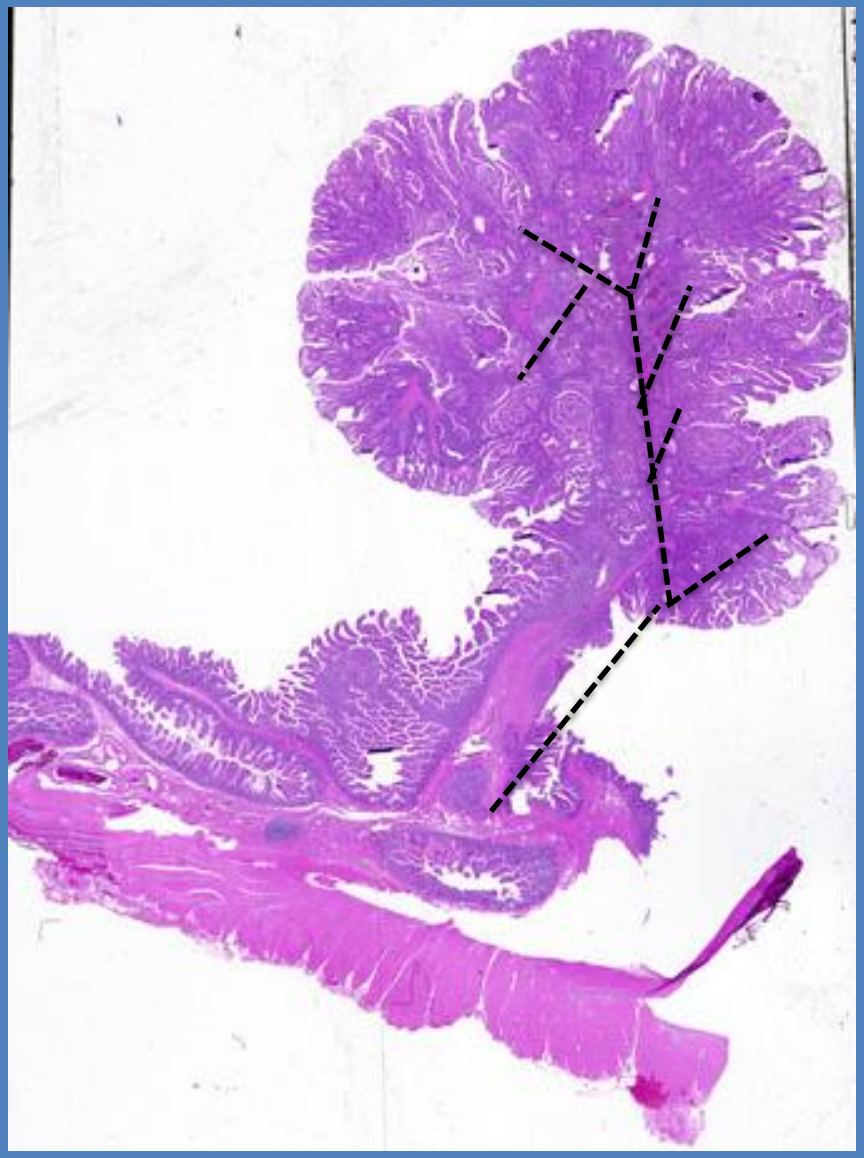
- 95% of patients
- Flat macules, blue/grey-brown, 1-5mm → like “freckles”
- Lips/perioral region, hand, feet, buccal mucosa. Less commonly periorbital, perianal, and genital
- Occurs at 1-2 years, fades after puberty
- Similar features seen in the “melanotic mucocutaneous pigmentation syndrome”
- Increased melanogenesis with no increase in melanocytes



PJS Hamartomatous Polyps

- Glandular epithelium supported by smooth muscle that is contiguous with the muscularis mucosa
- Become symptomatic between 10-30 yo
- Location:
  - Small bowel (60%-90%) - (Jej > Ileum > Duo)
  - Colon (60%)
  - Stomach (30%)
  - Renal pelvis, bladder, lungs, nares (uncommon, reports only)

- Presenting symptoms:
  - Abdominal pain
  - Blood in the stool
  - Anal extrusion
  - Obstruction
    - Often due to intussusception

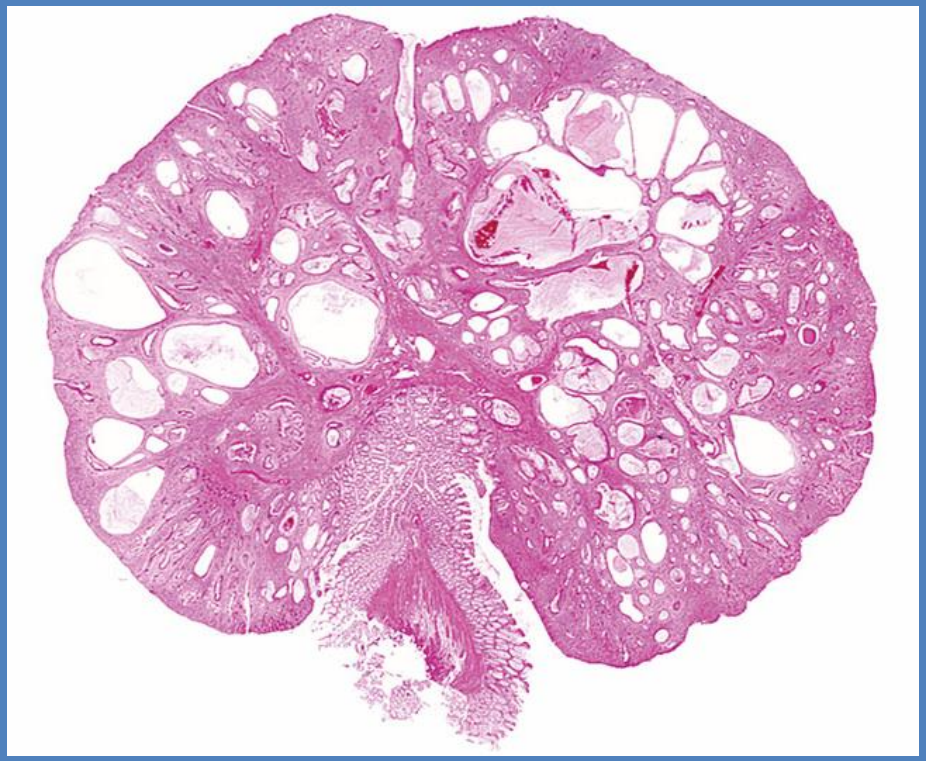


Juvenile Polyposis Syndrome (JPS)

- Autosomal dominant (Familial Juvenile Polyposis = FJP)
- 50% of cases are due to a mutation in BMPR1A or SMAD4
- ENG has also been implicated
- SMAD4 can lead to JPS and hereditary hemorrhagic telangiectasia (HHT)
- Most become symptomatic by age 20 → rectal bleeding, anemia, polyp prolapse out of rectum, obstruction

Juvenile Polyposis Syndrome (JPS)

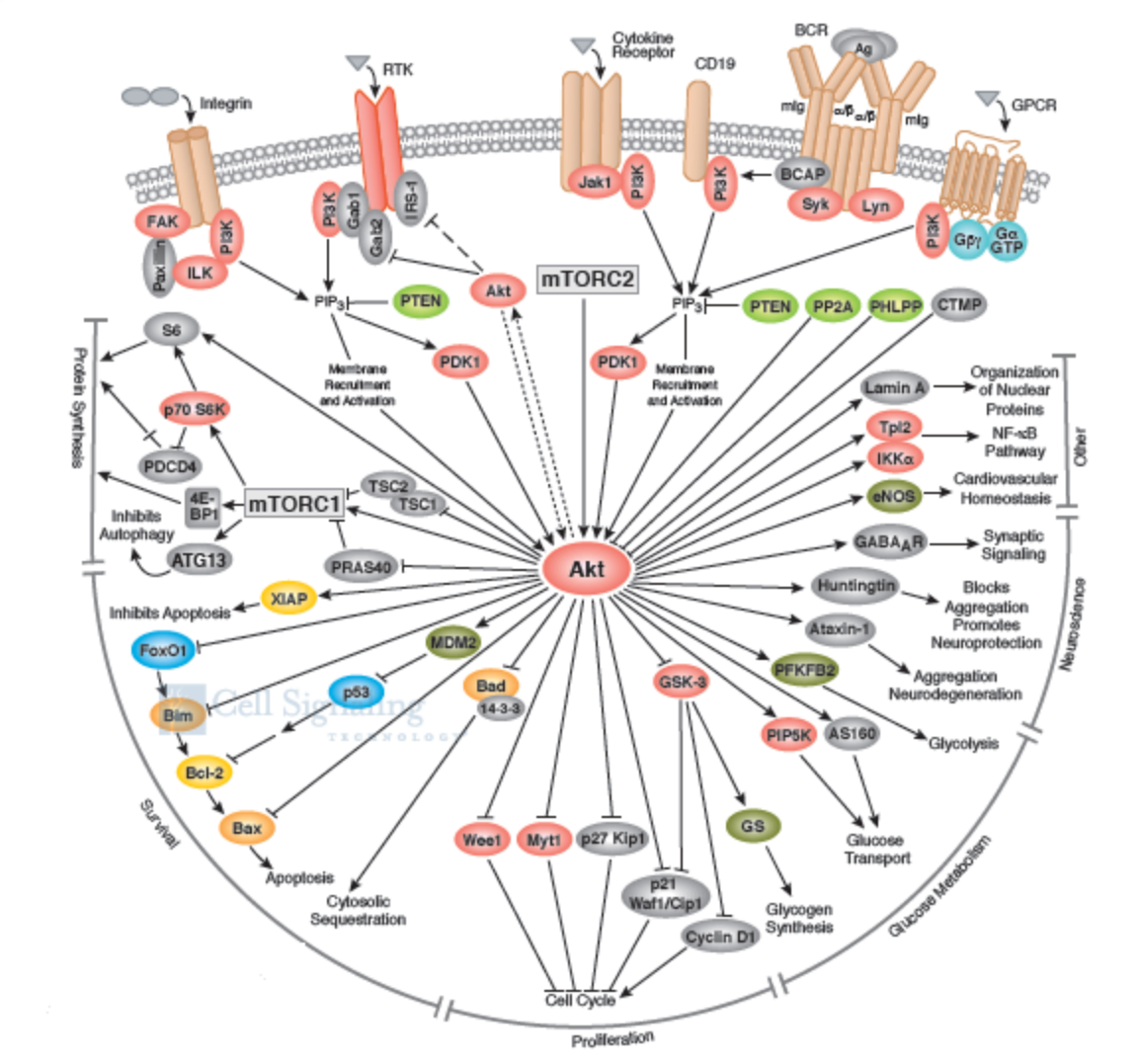
- Juvenile polyps are hamartomatous polyps with dilated cystic glands
- Isolated juvenile polyps of the colon are common in children (1-2%)
- Diagnosis: Patient meets at least 1 of the following:
  - ≥ 3 juvenile polyps of the colon
  - Multiple juvenile polyps found throughout the GI tract
  - Any juvenile polyps with a family history of JPS



PTEN hamartoma tumor syndromes

- PTEN = tumor suppressor
- PTEN negatively regulates AKT signaling

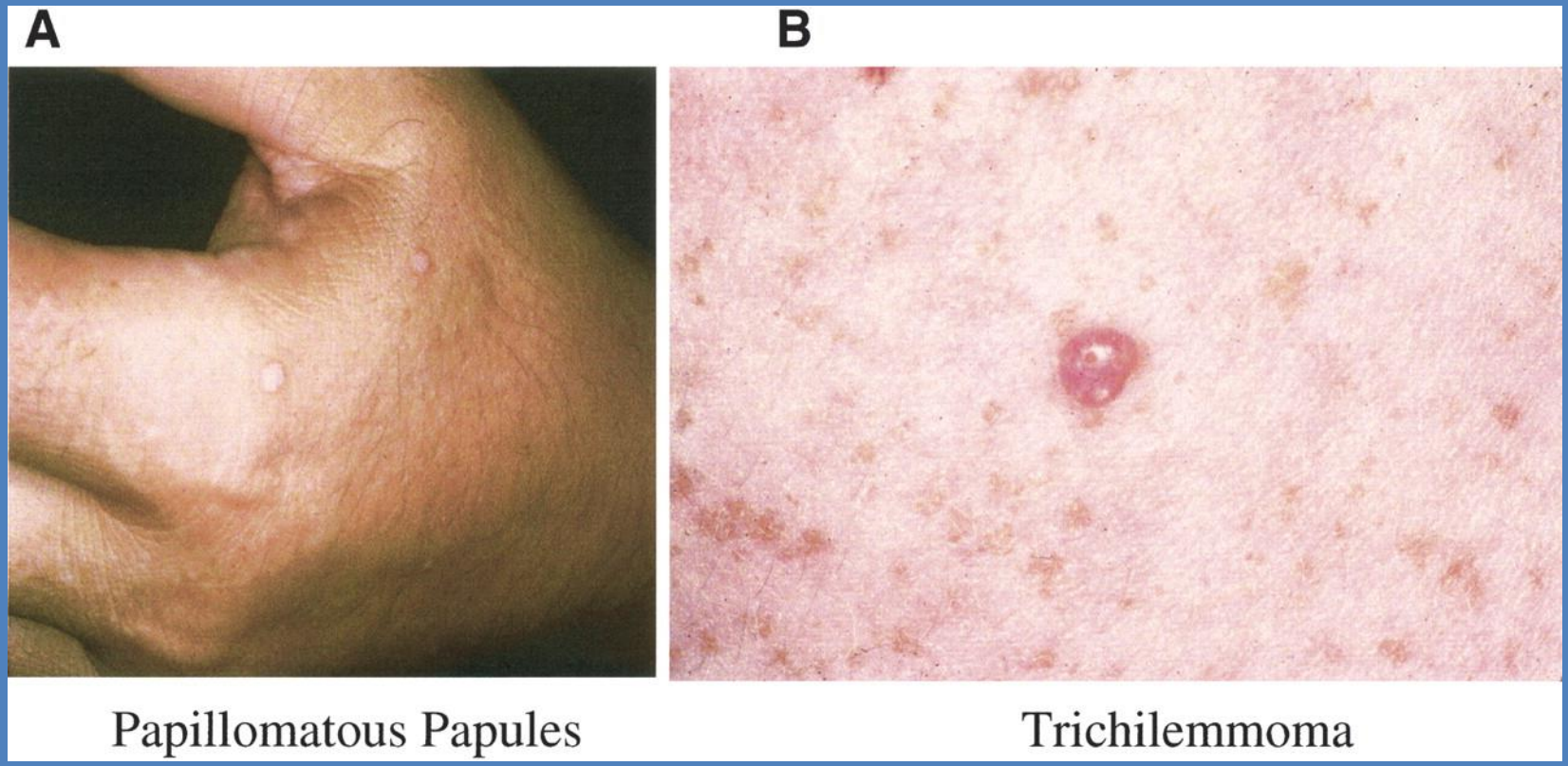
- PTEN mutation syndromes associated with GI polyposis:
  - Cowden syndrome
  - Bannayan-Riley-Ruvalcaba syndrome (BRRS)



Cowden Syndrome (CS)

- Best characterized PTEN disorder, but only 1/3 of CS patients have a documented PTEN mutation
- Prevalence of 1 in 250,000
- Autosomal dominant
- Multiple hamartomas in addition to trichilemmomas, oral fibromas, palmoplantar keratoses
- Increased risk of breast, endometrial, thyroid, kidney, and colorectal cancers

Cutaneous manifestations of Cowden's syndrome: papules and tricholemmomas



Serrated Polyposis Syndrome (SPS)

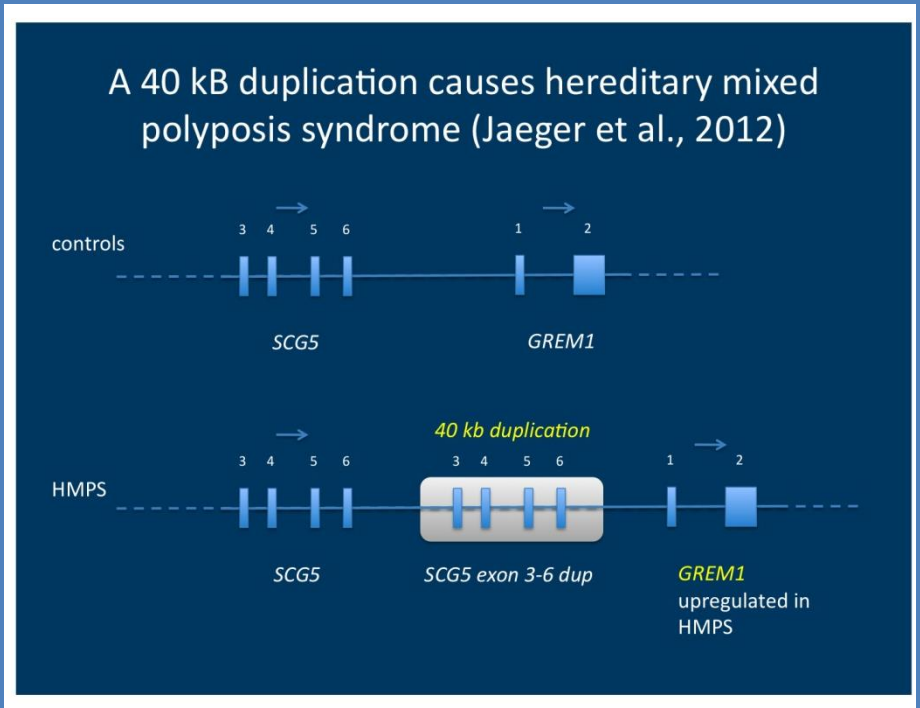
- Previously known as hyperplastic polyposis syndrome (HPS)
- Serrated polyp = Hyperplastic polyp (proximal to sigmoid or ≥1cm in the rectosigmoid), SSAs, and traditional serrated adenomas
- Diagnosis (1 of the following):
  - 5 serrated polyps proximal to sigmoid with at least 2 being ≥1cm
  - Any serrated polyps proximal to sigmoid with a 1st degree relative with SPS
  - More than 20 serrated polyps

Serrated Polyposis Syndrome (SPS)

- No causative gene identified yet, but thought to have a “familial component”
- Increased risk of colon cancer → usually with somatic BRAFV600E mutation
- Surveillance
  - Colonoscopy every 1-3 years
  - In 1st degree relatives, start at 40yo, then q5years, or start at the youngest age of SPS diagnosis

Hereditary Mixed Polyposis Syndrome (HMPS)

- Patients can develop a combination of hamartomatous, adenomatous, and hyperplastic/serrated polyps
- Rare
- Autosomal dominant
- Primarily in the Ashkenazi Jewish population
- Thought to be due to duplication upstream of GREM1 → increased GREM1 expression → disruption of BMP/TGFbeta signaling pathway



- Given its rarity, there are no consensus surveillance recommendations for HMPS

Hyperplastic or serrated polyps

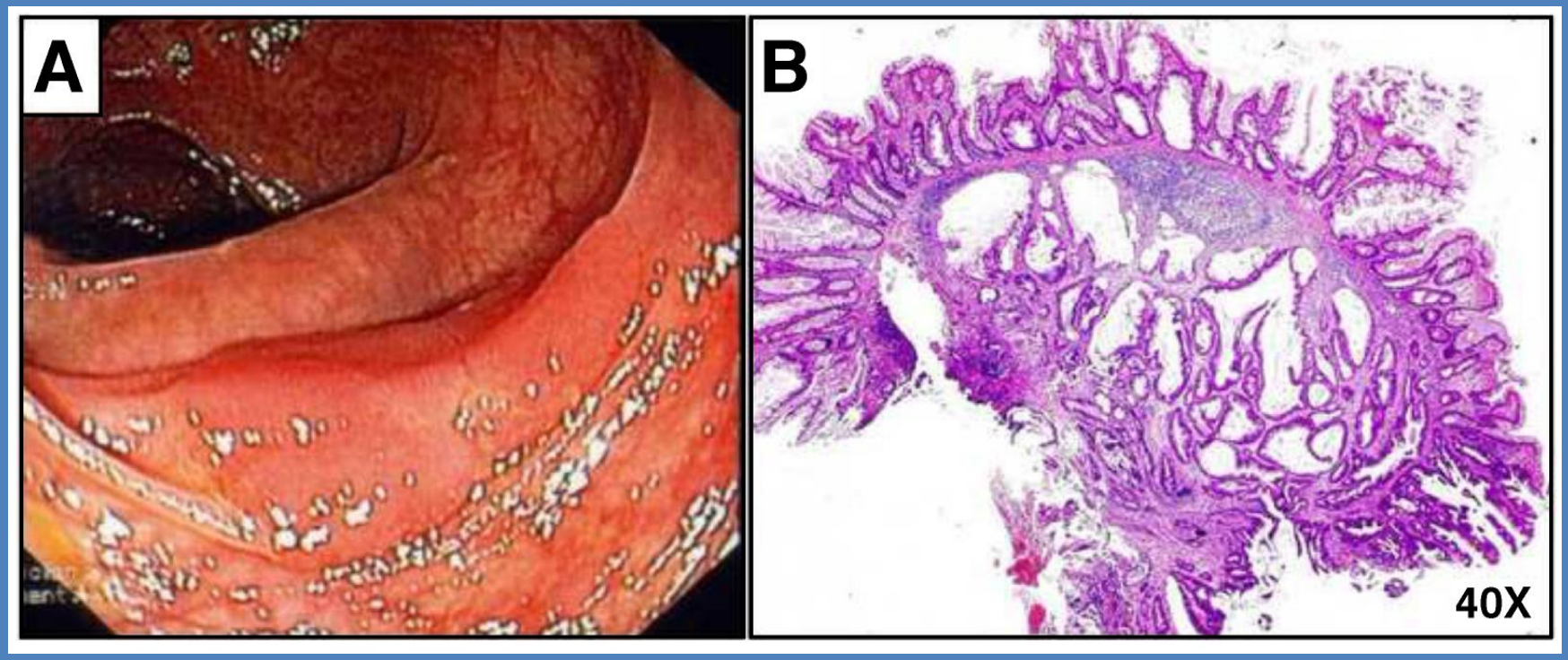
Common subtypes of hyperplastic polyps
- Microvesicular
- Goblet-rich
- Mucin-poor

Sessile serrated adenoma (SSA)

Traditional serrated adenoma (TSA)

Mixed polyps (TSA and tubular adenomas)

(Rare): Hyperplastic polyposis (mixed polyps; *MYH* mutations and also, serrated pathway; increased CRC risk)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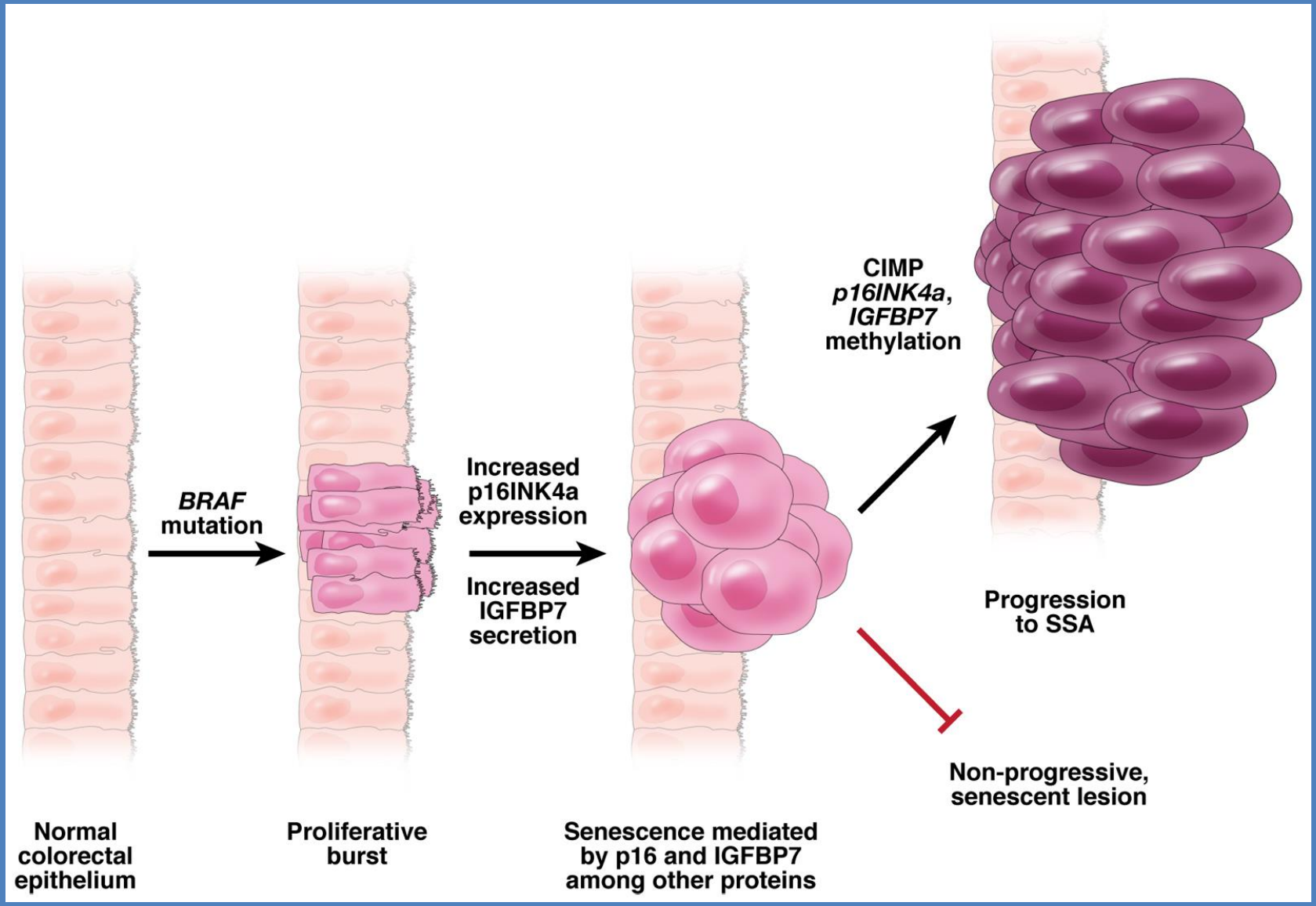
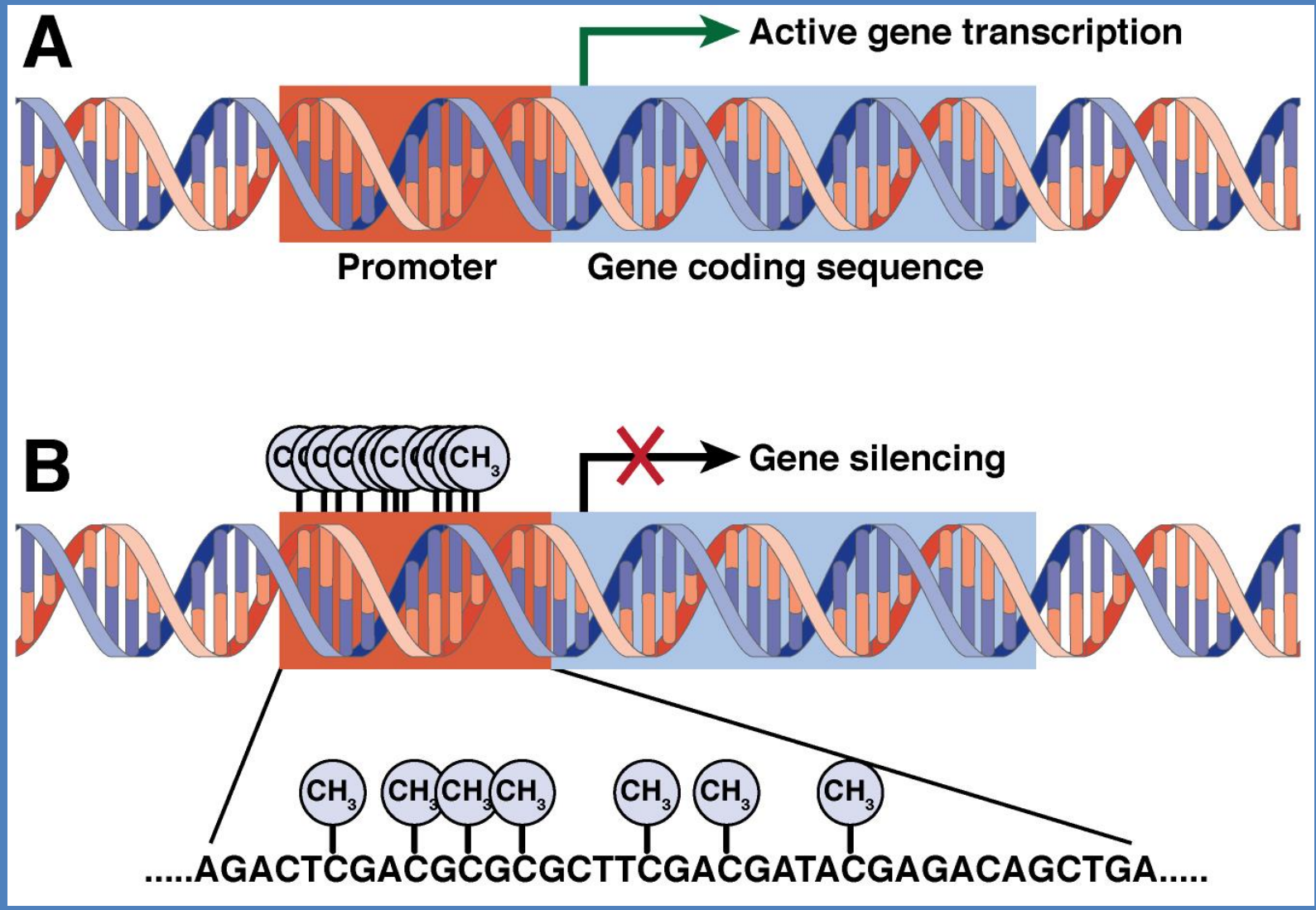
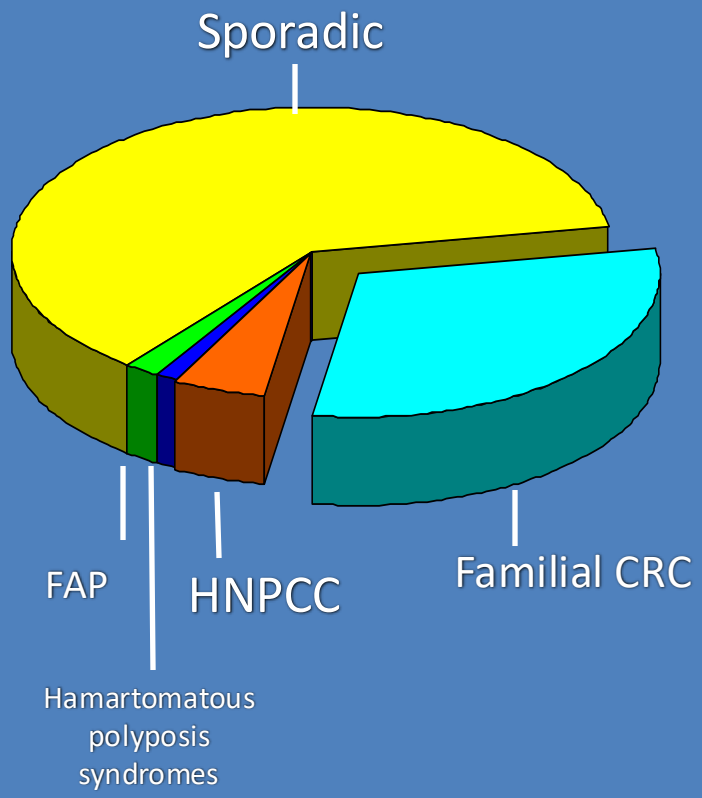

BRAF mutation
Increased p16INK4a expression
Increased IGFBP7 secretion
CIMP p16INK4a, IGFBP7 methylation
Progression to SSA
Non-progressive, senescent lesion
Normal colorectal epithelium
Proliferative burst
Senescence mediated by p16 and IGFBP7 among other proteins

Çhromosomal instability methylator phenotype (CIMP)

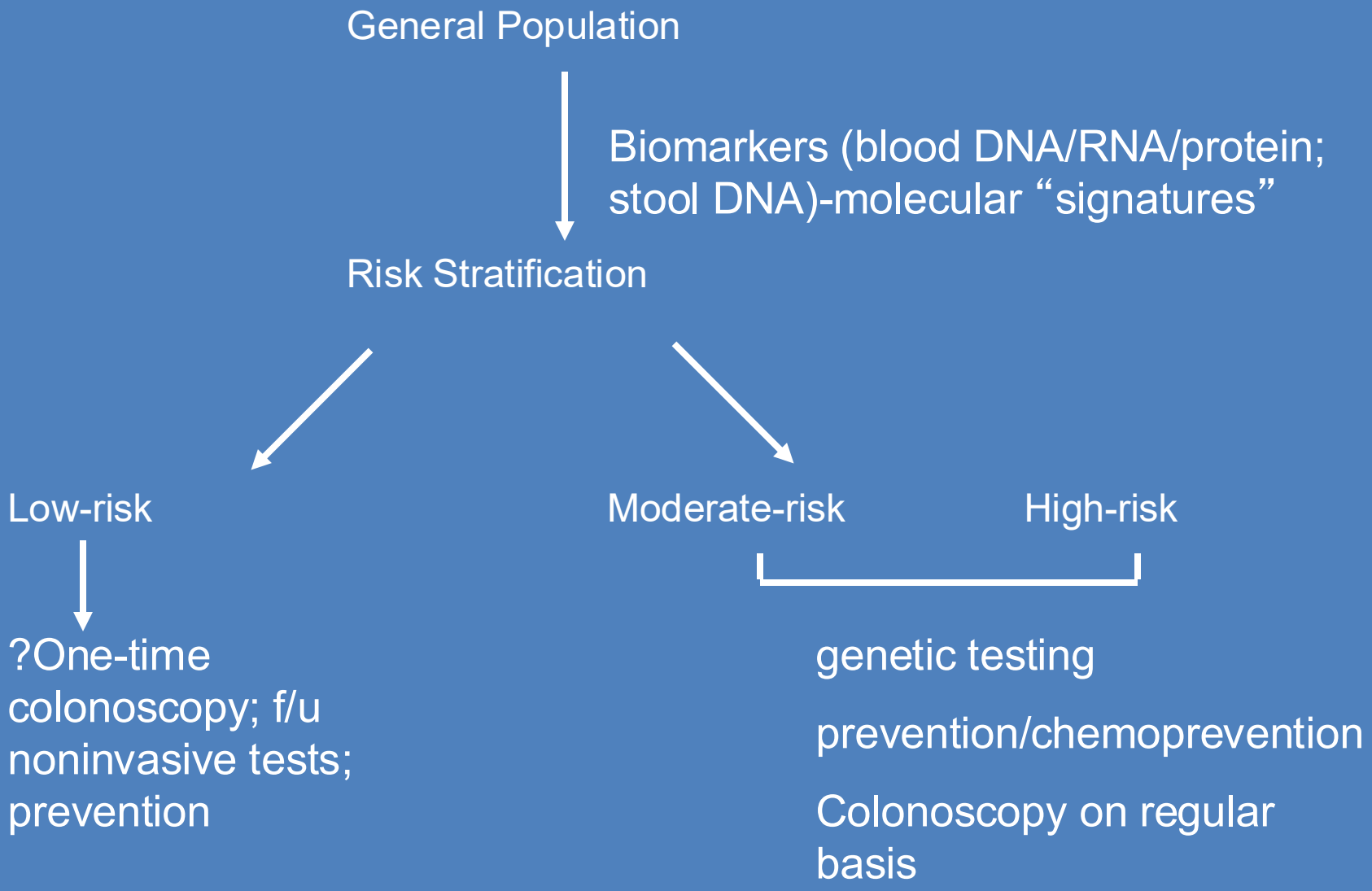


Features of Familial CRC

- Family history of CRC with no clear inheritance pattern
- Age at onset typical of sporadic CRC
- Multiple causes
- Few adenomas
- Several clues based on linkage analyses and GWAS



"Ideal" scenario: genetic-clinical interface



Question 1

What syndrome is characterized by 20-100 colonic polyps, extraintestinal Manifestations and autosomal recessive transmission?

Attenuated FAP
MYH associated polyposis (MAP)
Lynch syndrome
Juvenile polyposis
Peutz-Jeghers

Question 2

Match the syndrome below with the gene mutation:
MSH2, MYH, APC, SMAD4, STK11

Familial Adenomatous Polyposis
Lynch Syndrome

MAP

Peutz-Jeghers

Juvenile Polyposis