Colorectal Cancer Syndromes

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Outline

- Colon cancer
  - General Genetics, Risk, Screening
- Specific Syndromes, when to suspect, what to do ?
  - Lynch Syndrome
  - Familial adenomatous polyposis (FAP)
  - MutYH-associated polyposis (MAP)
  - Hamartomatous syndromes
  - Serrated polyposis syndrome

Learning Objectives

After completion of this lecture participants should be better able to

- Obtain a thorough family history
- Understand genetic colon cancer syndromes
- Appropriately start work-up and referral of high risk individuals

Colorectal Cancer is Common and Deadly

- Approximately 150,000 Americans/year are diagnosed with colorectal cancer
- Average lifetime risk is about 6% or 1 in 16
- Increased incidence in certain populations
- Preventable at early stages, but
  - About 50% of those diagnosed die of the disease
  - Second-leading cause of cancer-related deaths in the United States
  - Strong familial component

Colorectal Cancer Genetics

- Genetic predisposition affects development of colon cancer
- Genetic defects could be inherited from the parents (cancers early in life) or
- Genetic defects can spontaneously occur in an individual or an individual tumor (cancers later in life)

Colon cancer risk is multifactorial

In 44,000 pairs of identical and non-identical twins colon cancer risk was associated with

- 0.35 Heritable factors
- 0.05 Shared environmental factor
- 0.60 Non-shared environmental factors

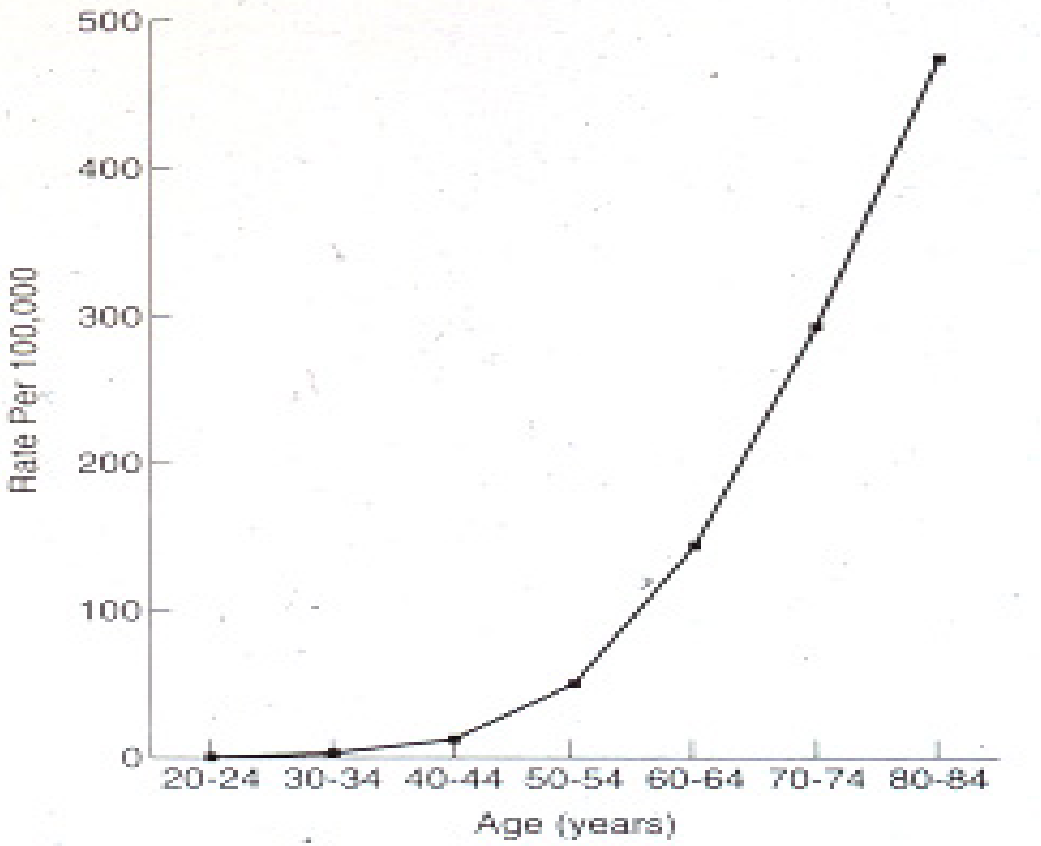
Lichtenstein P. et al. *N Eng J Med* **343**:78-85, 2000

Family History and Colon Cancer

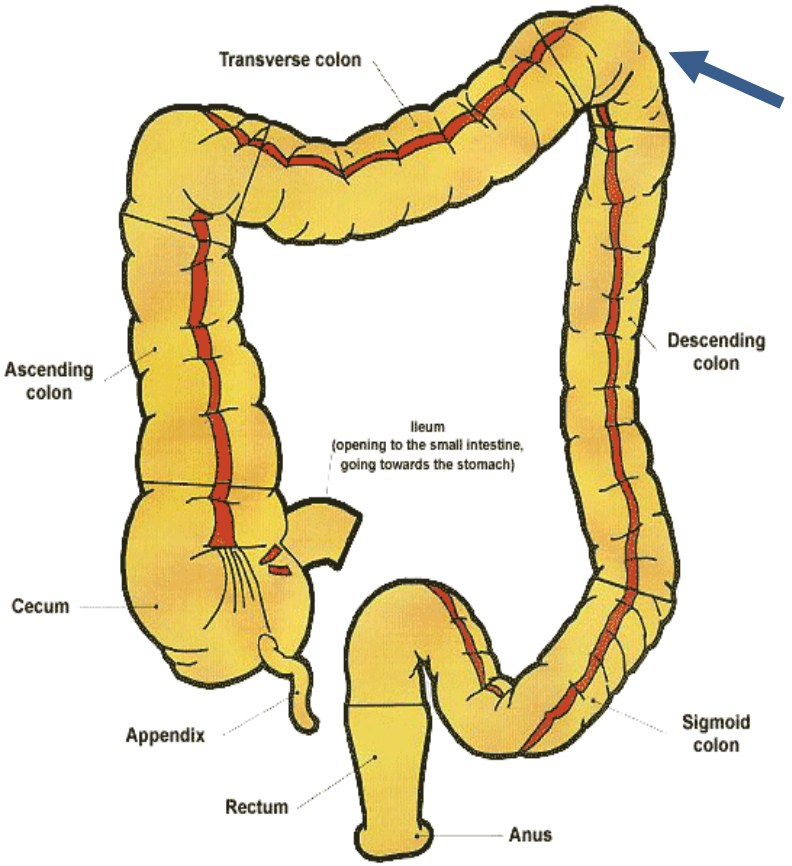
Colon Cancer in First Degree Relative	Lifetime Risk
One or more	10%
Two or more	15%
One or more younger than 45 years	33%

Reviewed in *Jung and Carethers*, GI Neoplasia, Digestive Disease Self Education Program 5.0 2007 Kendal/Hunt Publishers

Colorectal Cancer Increases with Age



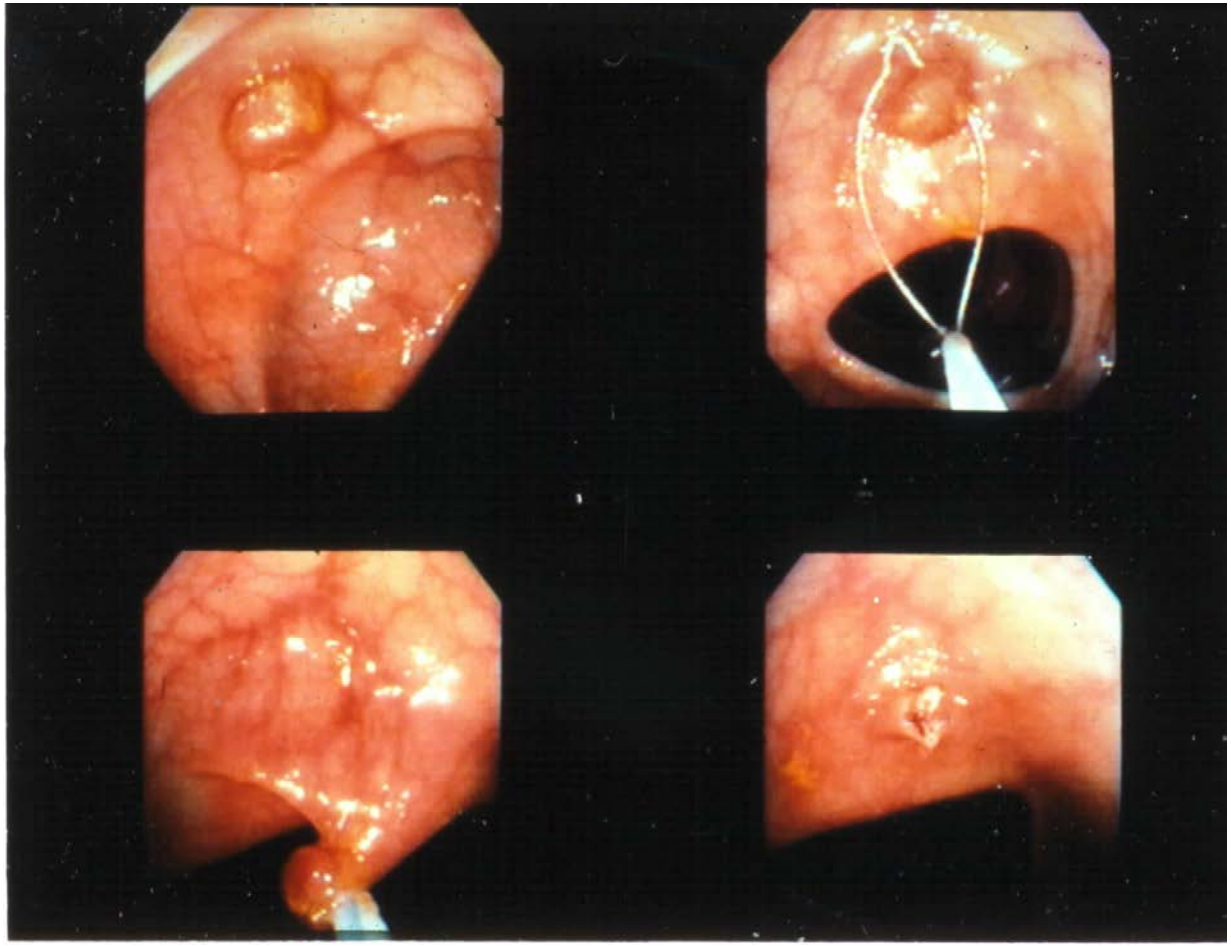
Colon Anatomy



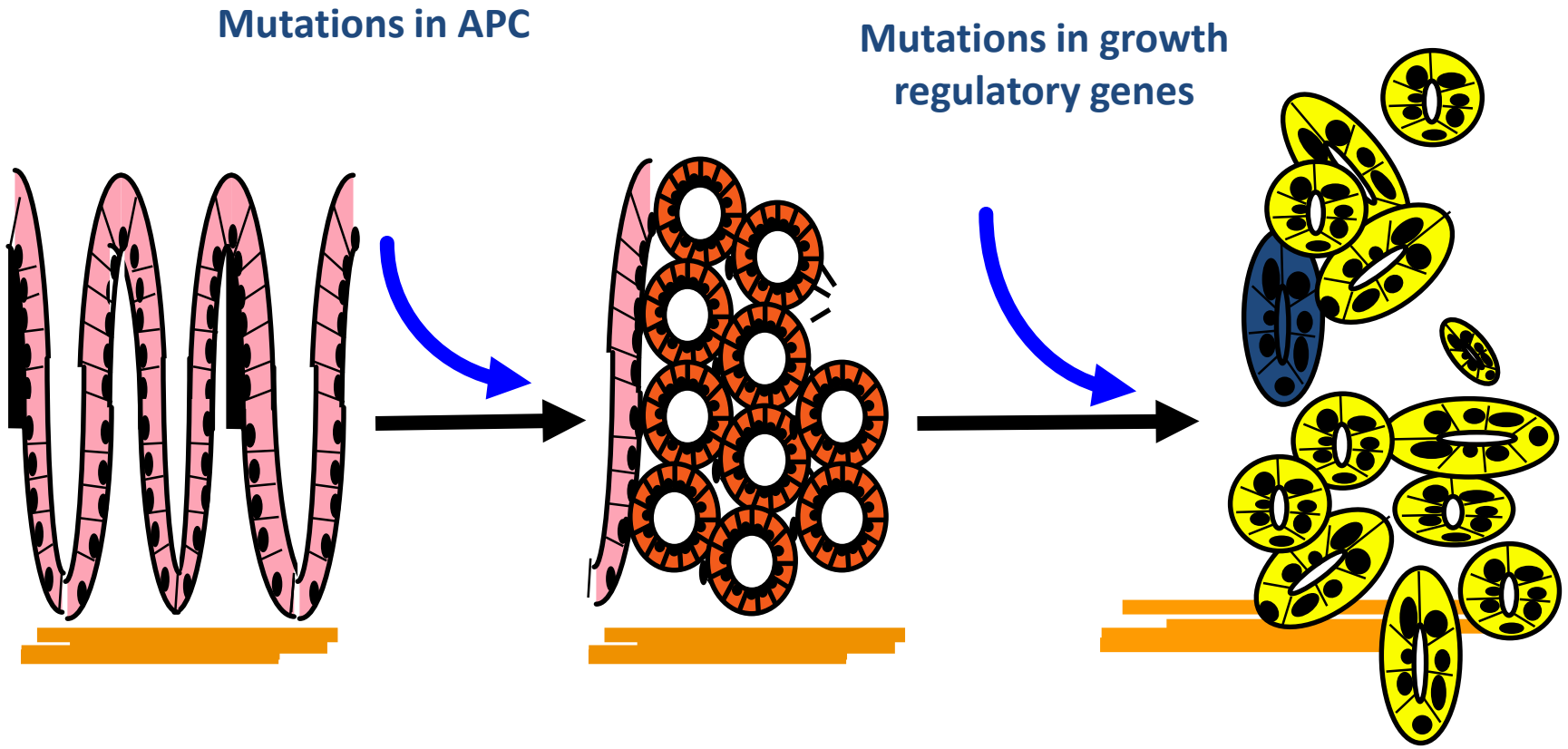
End of reach of sigmoidoscope

Colonoscope

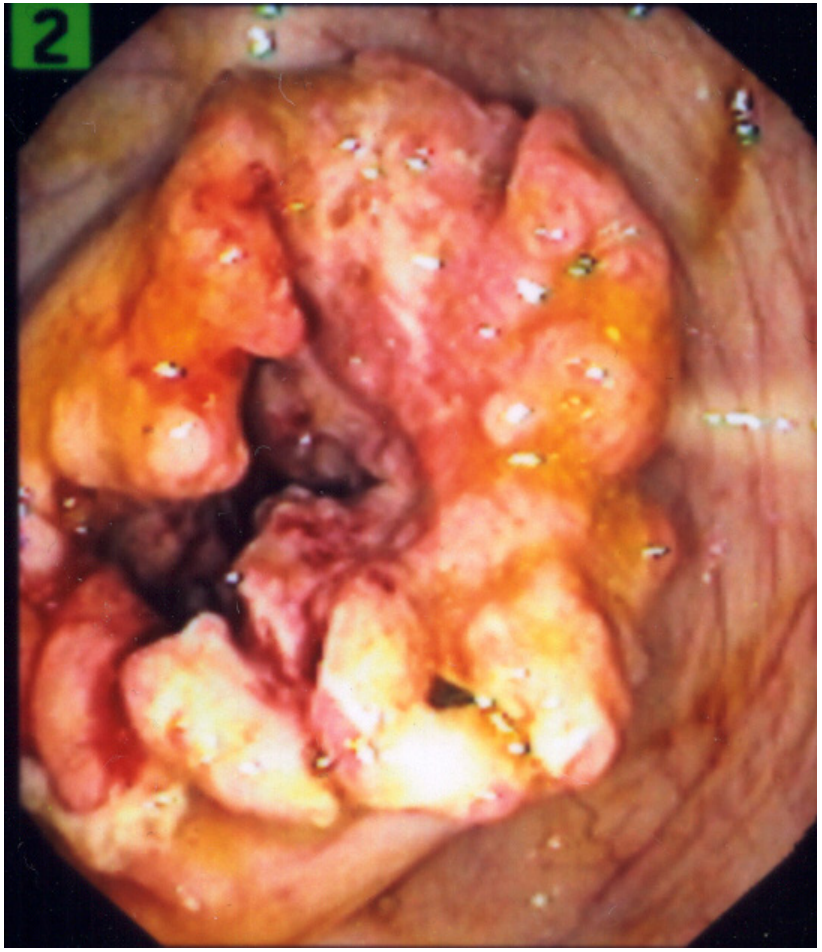
Polypectomy



Stepwise progression of colon cancer



Colon Cancer - Endoscopic View



Screening for Colorectal Cancer

- Testing asymptomatic, average risk individuals for colorectal cancer
- Screening must be:
  - sensitive
  - specific
  - acceptable to asymptomatic people
  - reduce mortality or morbidity
  - affordable

Implementation of Colorectal Cancer Screening

- Colorectal cancer screening use is 20-30 % of all eligible individuals and

under –utilized

- Prostate ~60%
- Cervical ~70%
- Breast ~78%

Screening Colonoscopy

- No published reports that directly examine effectiveness
- Indirect evidence
  - National Polyp Study shows removing polyps reduces incidence of cancer
  - Case-control study showed fewer cancers in persons after colonoscopy [Mueller, Ann Int Med 1995]
  - Interval of screening safe > 5 years [Rex Gastroenterol 1996]
- More costly, increased procedural risk

Case

You see a 40-year old male for heartburn. He has not had a colonoscopy. He reports a mother who developed endometrial cancer at age 48. What is the most appropriate next step ?

a) Full family history
b) Colonoscopy
c) Genetic testing
d) Reassurance

Case

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b) Colonoscopy
c) Genetic testing
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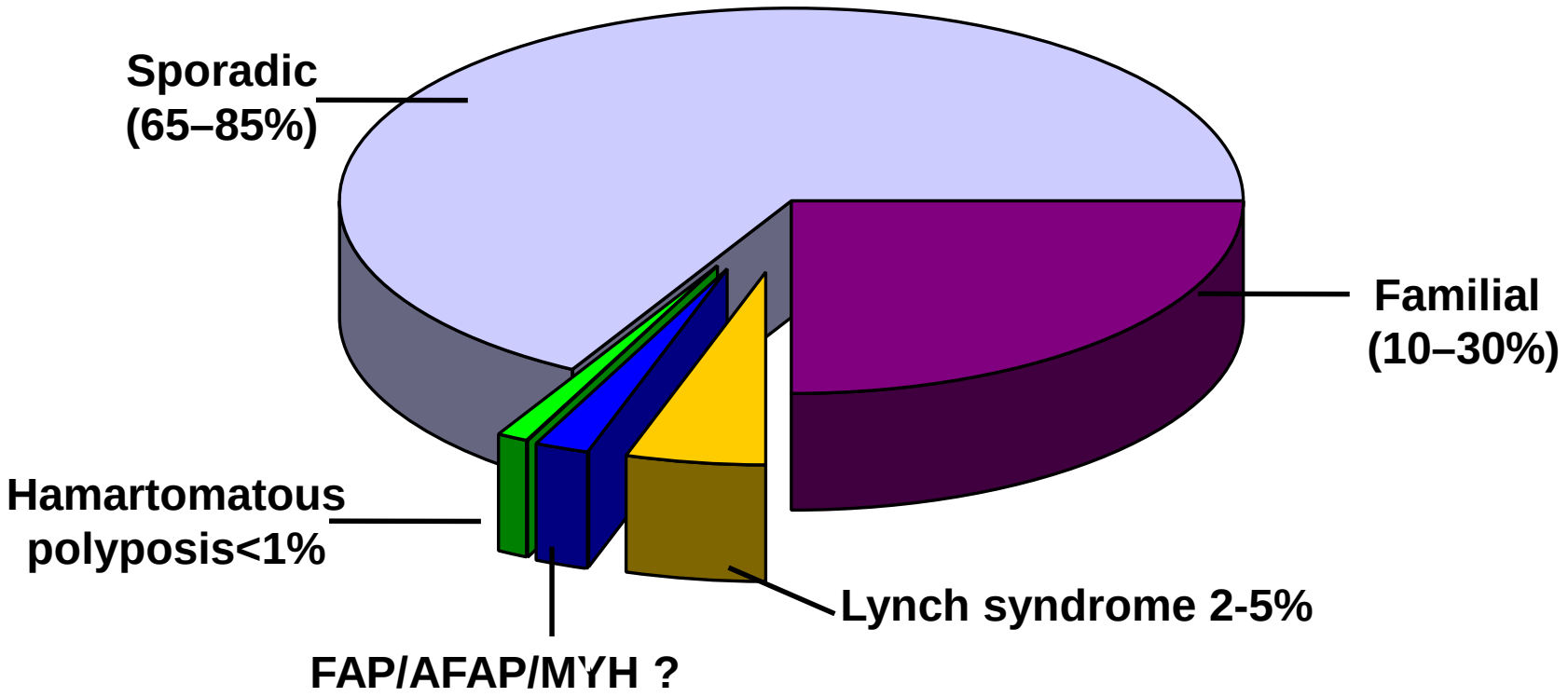
Spectrum of Genetic Susceptibility in CRC



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

FH

- Family history of cancer and premalignant GI conditions should be obtained for all patients being evaluated in outpatient and endoscopy practices
- Essential components are:
  - Presence and type of cancer in FDR and SDR
  - Presence and type (ideally) of polyps in FDR
  - Age
- Low rates of adherence to minimal family history data collection and referral especially for colorectal cancer
  - Limited by knowledge of family history in certain populations

Pre-procedure family history assessment

	YES	NO
• Do you have a **first-degree relative** (mother, father, brother, sister or child) with any of the following conditions diagnosed before age 50?		
Colon or rectal cancer	☐	☐
Cancer of the uterus, ovary, stomach, small intestine, urinary tract (kidney, ureter, bladder), bile ducts, pancreas, or brain	☐	☐
• Have **you** had any of the following conditions diagnosed before age 50?		
Colon or rectal cancer	☐	☐
Colon or rectal polyps	☐	☐
• Do you have 3 or more relatives with a history of colon or rectal cancer? (this includes parents, brothers, sisters, children, grandparents, aunts, uncles and cousins)	☐	☐

Kastrinos F et al *Am J Gastroenterol* 2009

Lynch syndrome

Lynch syndrome overview

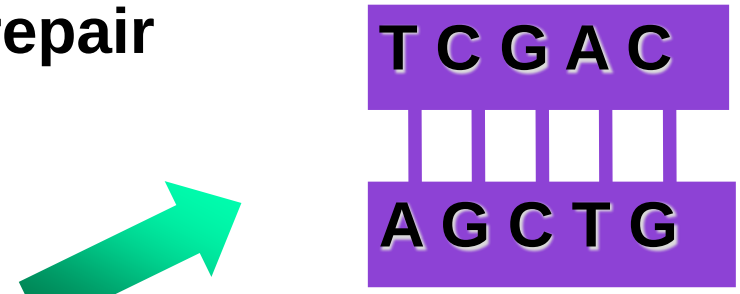
- Hereditary non-polyposis colorectal cancer (HNPCC)
  - Families who meet clinical criteria but don't necessarily have germline mutation
- Autosomal dominant
- Germline mutations in DNA mismatch repair genes (defines LS)
- Accounts for 2-3% of CRC overall
- 80% penetrance

Lindor N, JAMA 2006

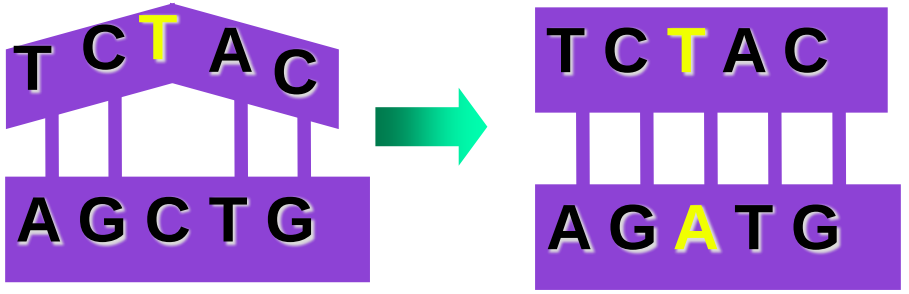
DNA mismatch repair

Normal DNA repair

Base pair mismatch

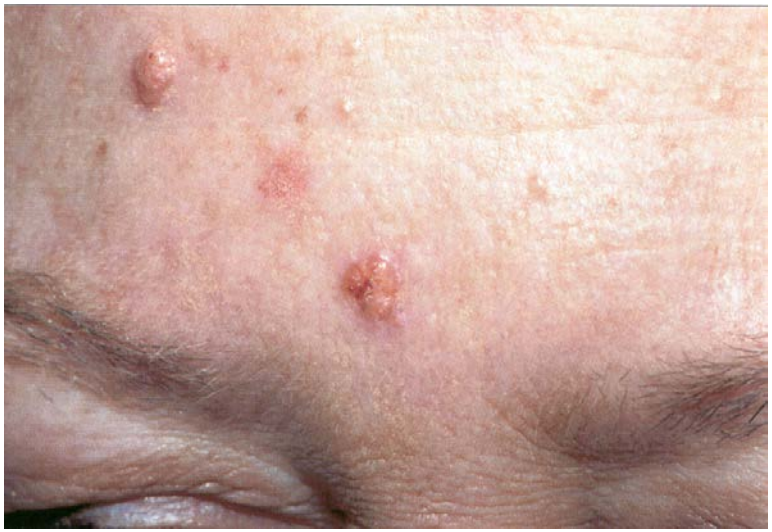


Mutation introduced by unrepaired DNA



Lynch Syndrome Variants

- Turcot syndrome
  - Hereditary syndrome of multiple CRC and primary brain tumors (glioblastomas)
- Muir-Torre Syndrome
  - Typical features of Lynch syndrome with sebaceous gland tumors and keratoacanthomas



Sebaceous adenomas

Fig : White GM et al: Diseases of the Skin – A Color Atlas. Mosby, 2000

Lynch syndrome overall cancer risks

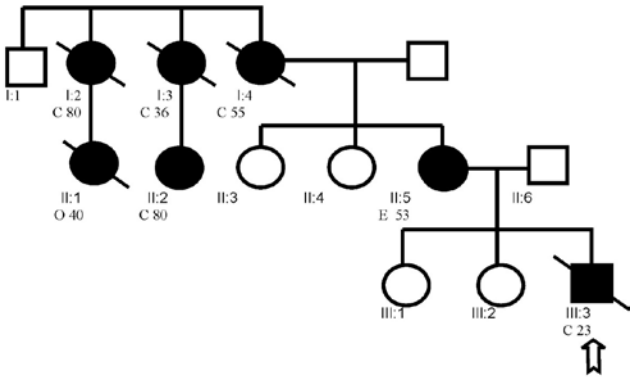
Cancer Risk Up to Age 70 Years in Individuals with Lynch Syndrome Compared to the General Population

Cancer	General Population Risk[1]	*MLH1* and *MSH2*[1,2]		*MSH6*[2]		*PMS2*[3]	
		Risk	Mean Age of Onset	Risk	Mean Age of Onset	Risk	Mean Age of Onset
Colon	5.5%	40%-80%	44-61 years	10%-22%	54 years	15%-20%	61-66 years
Endometrium	2.7%	25%-60%	48-62 years	16%-26%	55 years	15%	49 years
Stomach	<1%	1%-13%	56 years	≤3%	63 years	†	70-78 years
Ovary	1.6%	4%-24%[5]	42.5 years	1%-11%	46 years	†	42 years
Hepatobiliary tract	<1%	1.4%-4%	50-57 years	Not reported	Not reported	†	Not reported
Urinary tract	<1%	1%-4%	54-60 years	<1%	65 years	†	Not reported
Small bowel	<1%	3%-6%	47-49 years	Not reported	54 years	†	59 years
Brain/CNS	<1%	1%-3%	~50 years	Not reported	Not reported	†	45 years
Sebaceous neoplasms	<1%	1%-9%	Not reported	Not reported	Not reported	Not reported	Not reported
Pancreas[4]	<1%	1%-6%	Not reported	Not reported	Not reported	Not reported	Not reported

+ Combined risk for renal pelvic, stomach, ovary, ureter and brain is 6% by age 70

Amsterdam criteria

- Amsterdam I
  - Only includes CRC
- Amsterdam II
  - LS-associated tumors (CRC, endometrium, small bowel, ureter or renal pelvis)
- "3-2-1-1-0" rule
  - At least *3 relatives* with cancer
  - At least *2 successive generations* affected
  - One is *first-degree relative* of the other two
  - One diagnosis *<50 years*
  - *Exclude FAP*
- About 50% will be missed by these criteria and 50% will meet criteria but not have LS



Vasen HFA. *J Clin Oncol* 2000

Revised Bethesda criteria

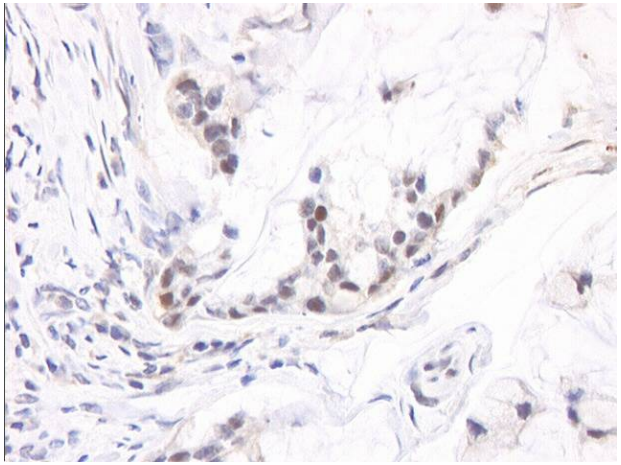
- For testing CRC for Lynch syndrome by IHC and/or MSI
  - CRC < 50 years of age
  - Presence of synchronous or metachronous CRC or other LS-associated tumors regardless of age
  - CRC with MSI-H histology in patient < 60 years
  - CRC in patient with ≥1 1st degree relative(s) with LS-associated cancers with one < 50 years
  - CRC in patient with ≥2 1st or 2nd degree relatives with LS-associated cancer regardless of age

Umar A, Boland CR, Terdiman JP et al *J Natl Cancer Inst* 2004

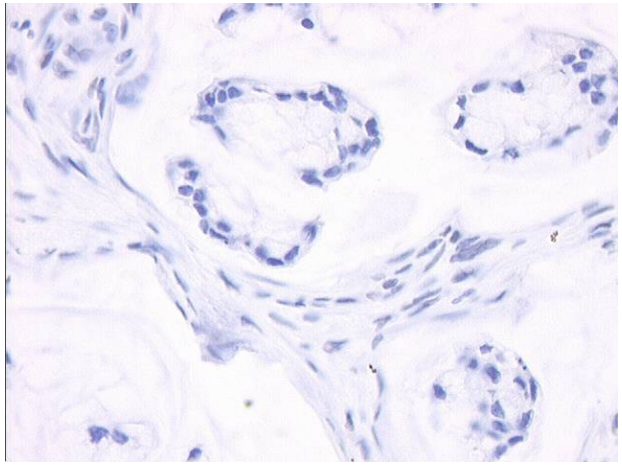
Tumor screening

- Immunohistochemistry (IHC) and microsatellite instability (MSI) analyses are screening tests
- Done on colorectal or endometrial tissue after surgery (or biopsy in some cases)
  - Do NOT test radiated rectal tumor; risk of false positives
- >90% of LS tumors are MSI-high (MSI-H) and/or lack expression by IHC
  - 10-15% of sporadic tumors are MSI-H and/or lack *MLH1* expression due to abnormal methylation

Immunohistochemistry



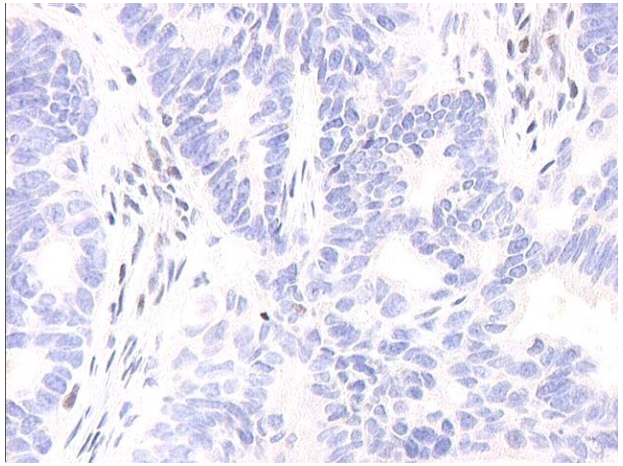
MLH1 +



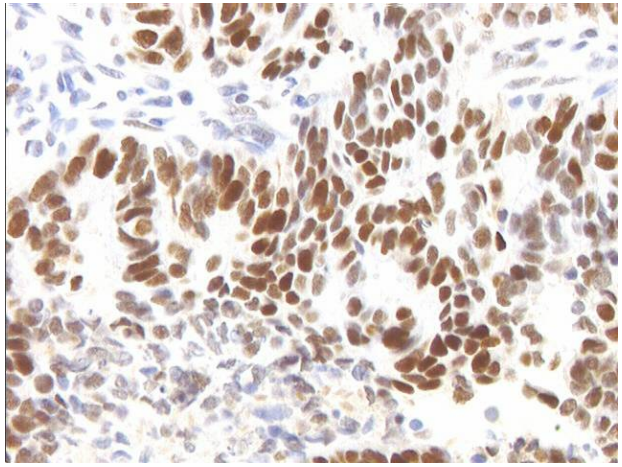
MSH2 and MSH6 -

***MSH2* mutation**

Brown staining=presence of protein

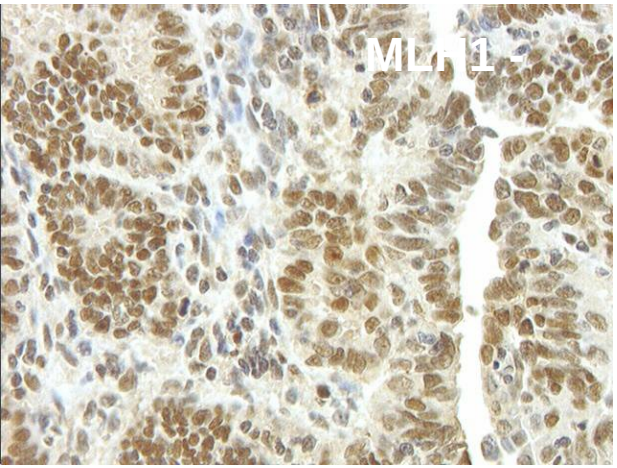


MLH1 -

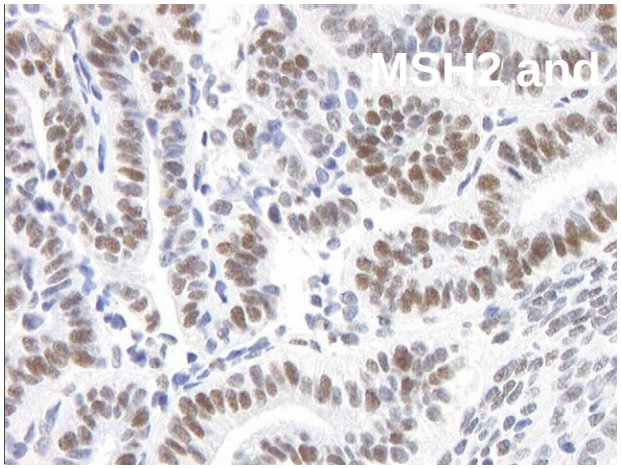


MSH2 and MSH 6+

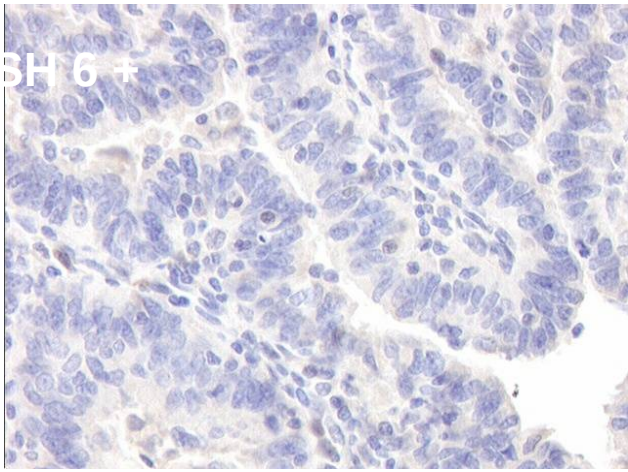
Methylation of *MLH1* promoter



MLH1 +



MSH2 +

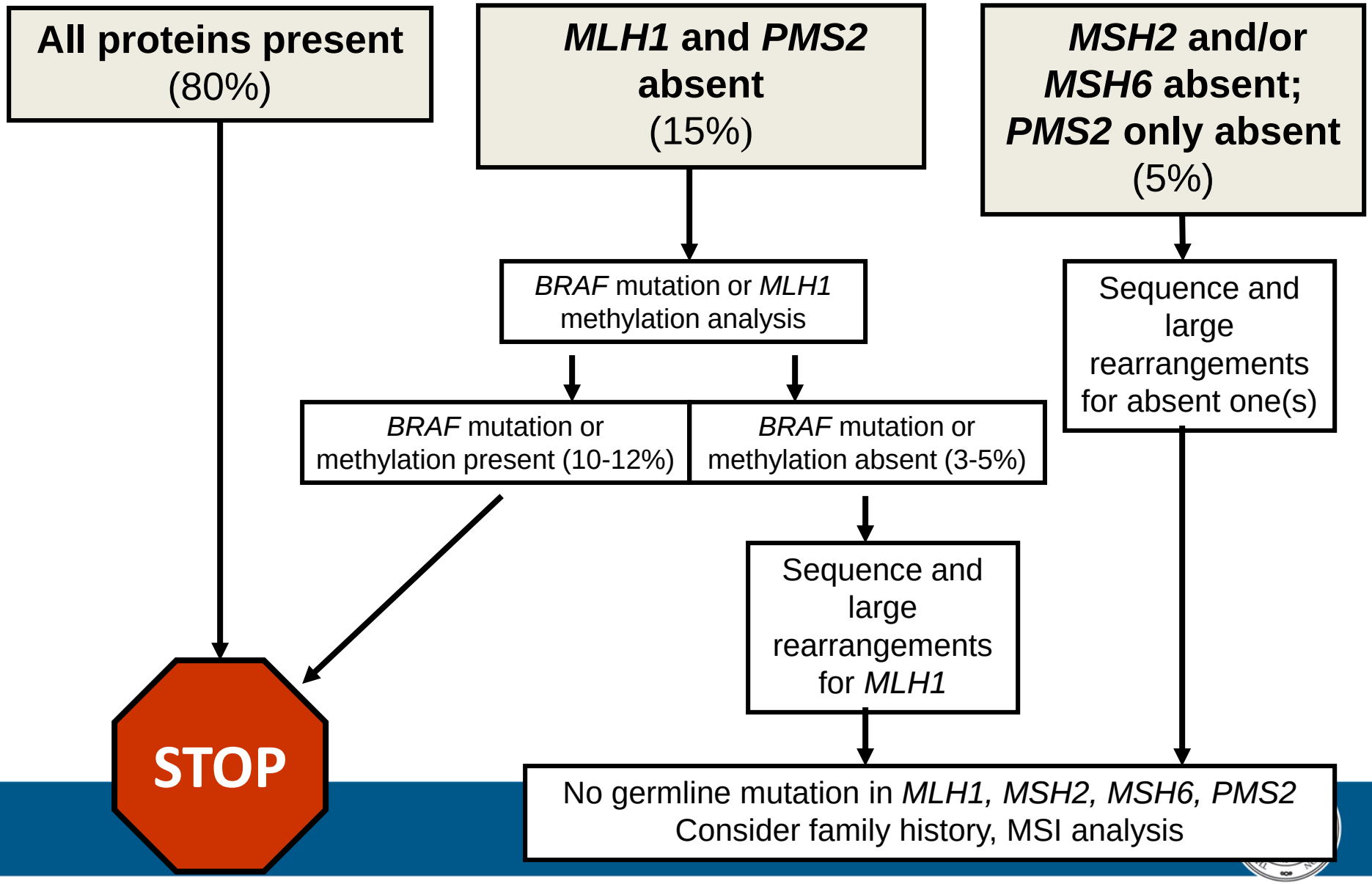


MSH6 -

***MSH6* mutation**

Brown staining=presence of protein

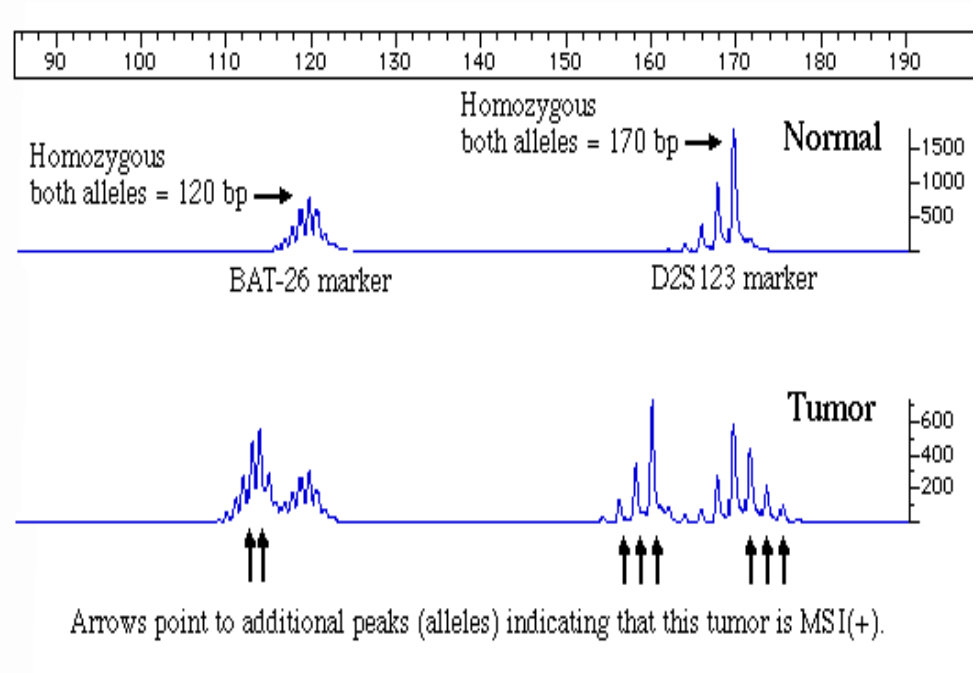
How to Follow-up on IHC Results



Adapted from Heather Hampel

MSI testing

- PCR test on tumor DNA
- Amplification of areas that are commonly mutated
- Changes in 2-5 microsatellite markers=MSI
- MSI may not be due to gene mutation
- Does not allow for narrowing down likely gene involved
- 5-10% false negative rate



Arrows point to additional peaks (alleles) indicating that this tumor is MSI(+).

MSI versus IHC – What to choose ?

- IHC can be performed by any pathology lab
- MSI requires molecular diagnostics and normal for comparison
- Cost similar, but
- IHC directs gene testing and can save $$ downstream
- Ethical issues with IHC- consent, disclosure
- Both have significant false negative rates and technical limitations

Screening and surveillance

Test	Frequency	Age to start	Evidence
Colonoscopy	Every 1-2 years	20-25 years or 2-5 years prior to earliest CRC	Cohort studies[1,2]
Upper endoscopy	Every 3-5 years	30-35 years	Expert opinion[3]
Endometrial biopsy	yearly	30-35 years?	Expert opinion[3]
Hysterectomy		After childbearing	Expert opinion[3]

Screening for other LS-associated cancers **no consensus**:

- Urothelial cancer (annual UA and/or urine cytology)
- CNS (neurological examination)
- Pancreatic cancer (MRCP/EUS)
- Small bowel (capsule endoscopy)

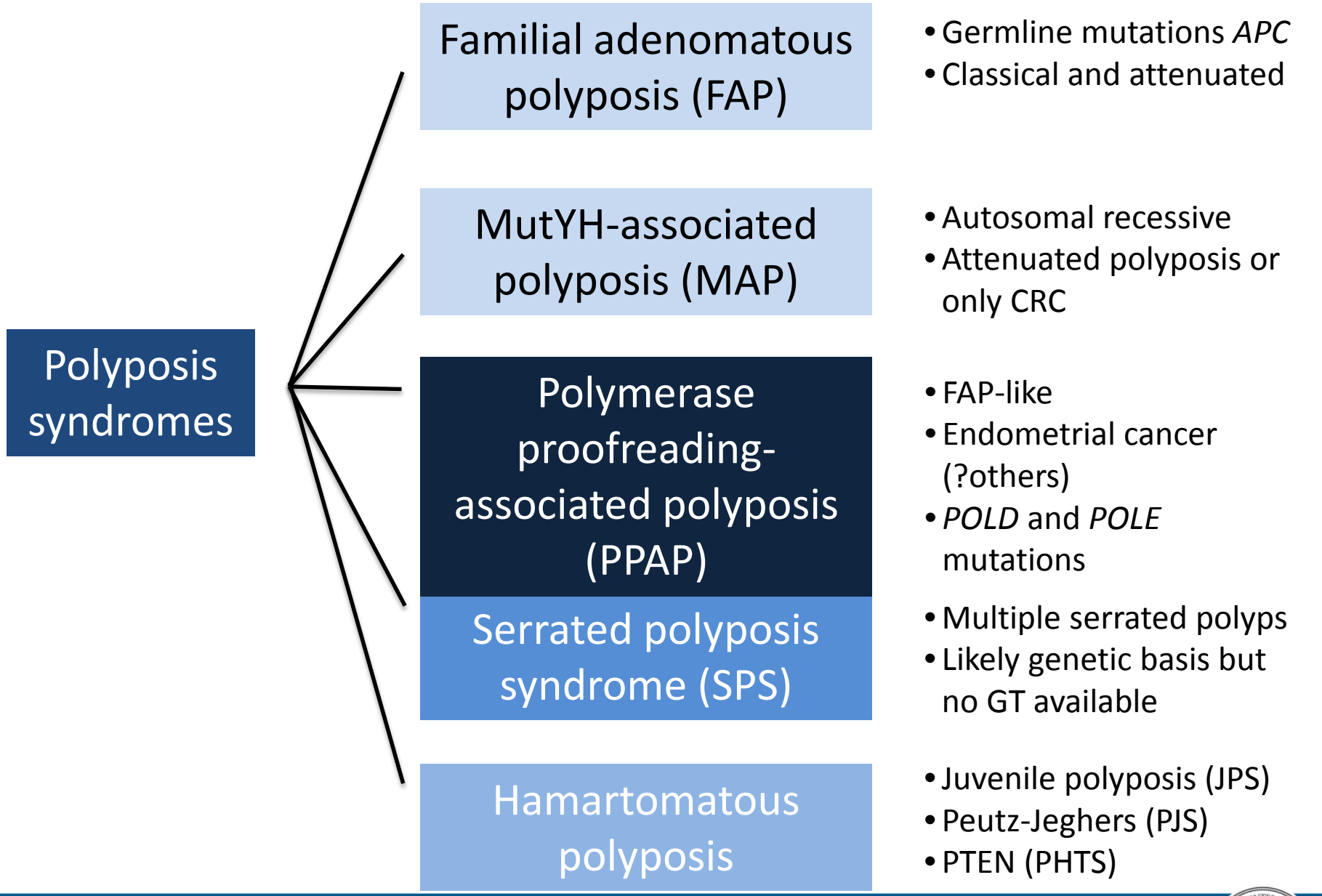
[1] Jarvinen HF et al *Gastroenterol* 2000

[2] Vasen HF. *Gastroenterol* 2010

[3] Lindor NM et al *JAMA* 2006

Mallorca Group recommendations *Gut* 2013

Familial adenomatous polyposis (FAP)



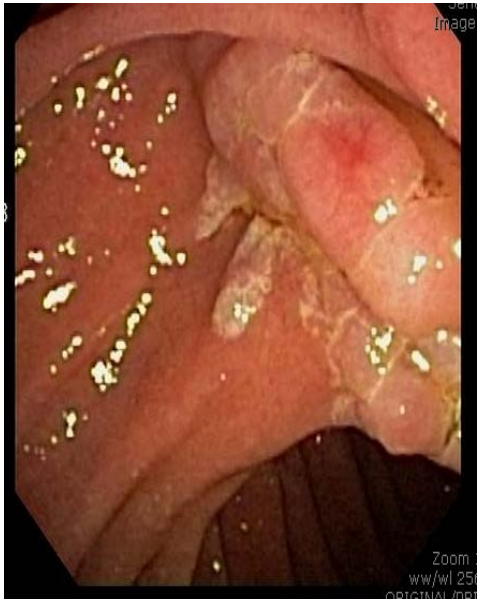
Syngal S et al *Am J Gastro* 2015

Familial adenomatous polyposis (FAP)

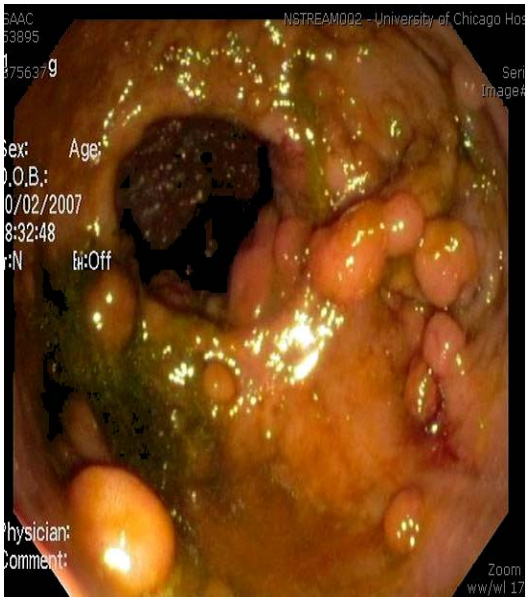
- Mutations in *APC* gene
- Autosomal dominant inheritance
- 100% penetrance
- *De novo* rate 25-30%
- Variants
  - **Attenuated FAP** (AFAP) – less polyps, different *APC* cluster
  - **Profuse polyposis**
  - **Gardners syndrome**
  - FAP + prominent extraintestinal manifestations
  - **Turcot's syndrome**
  - FAP + brain tumor (esp medulloblastoma)

1.Bodmer, Nature 1987
2.Kinzler, Science 1991
3.Groden, Cell 1991

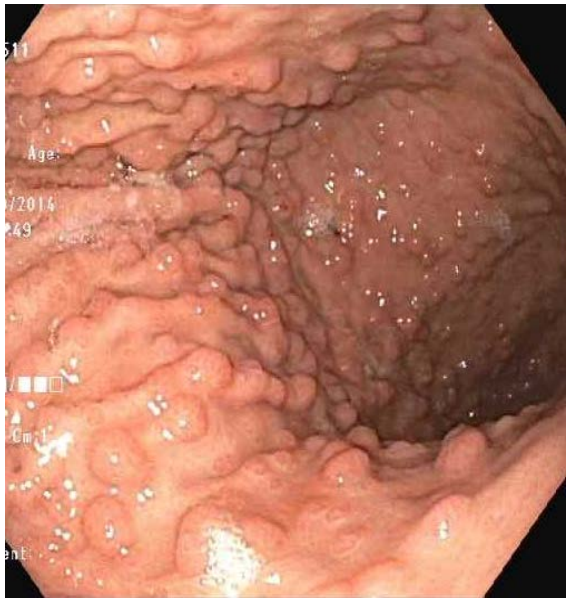
Intestinal features of FAP



Duodenal polyp*



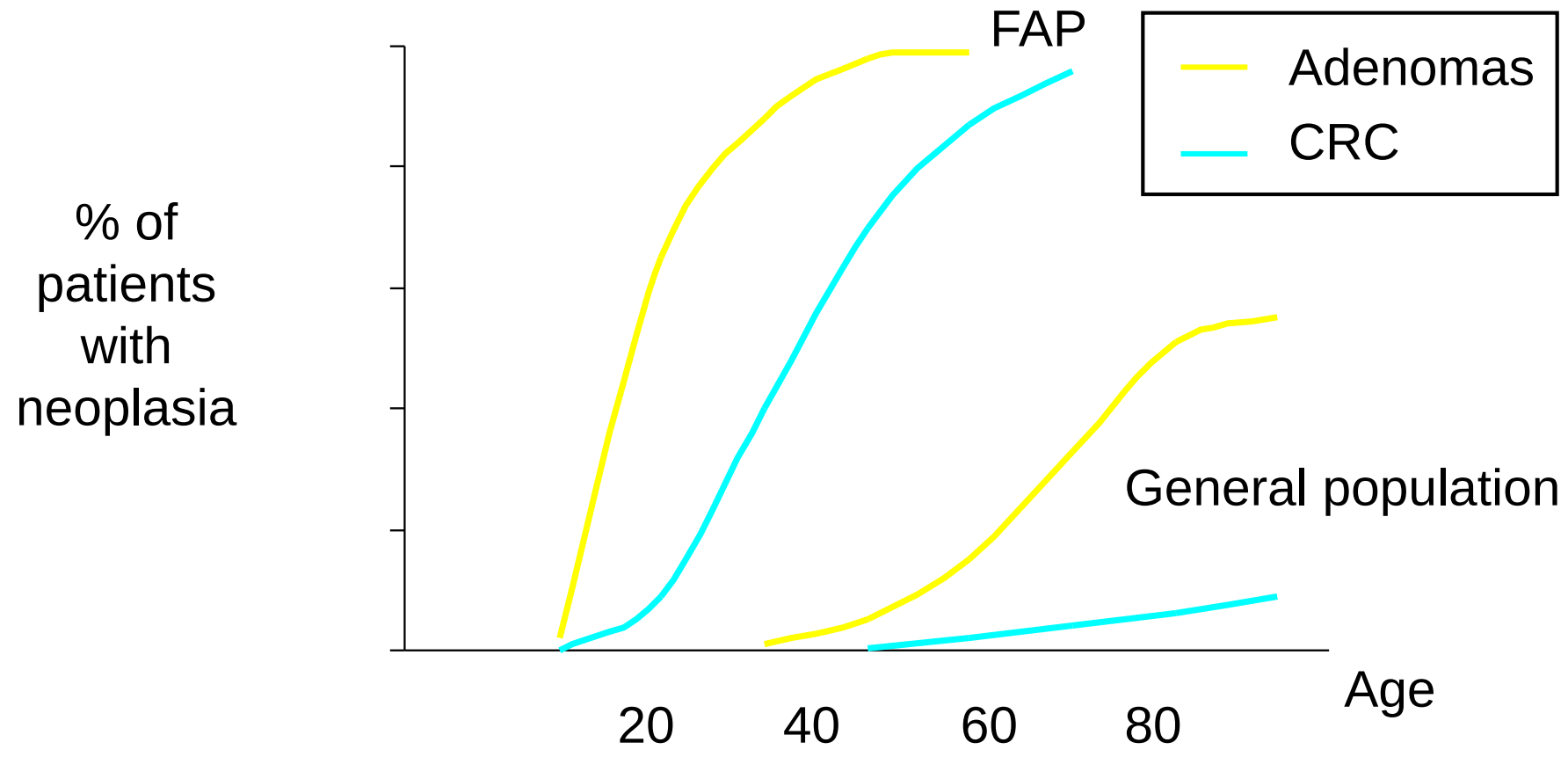
Rectal polyps*



Fundic gland polyps

* Malignant potential

Age and Development of Adenomas and CRC in FAP



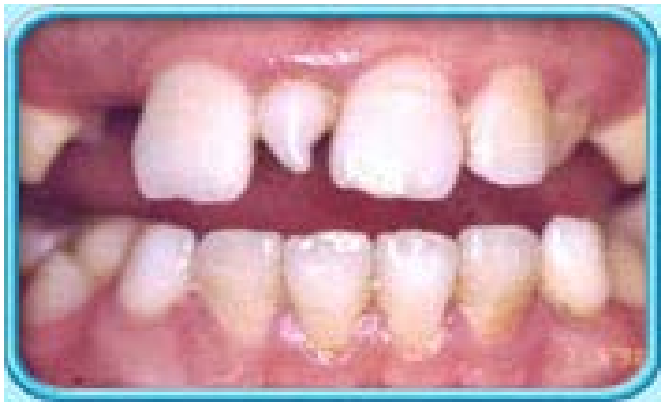
Bussey HJR. *Familial Polyposis Coli*, 1975; Petersen GM et al. *Gastro* 100:1658, 1991

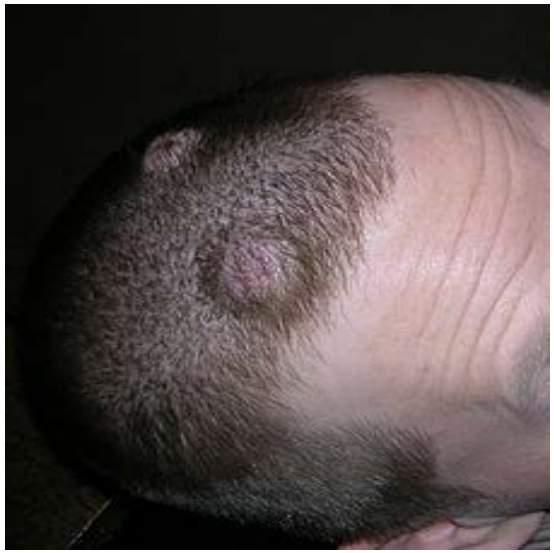
Extraintestinal features of FAP

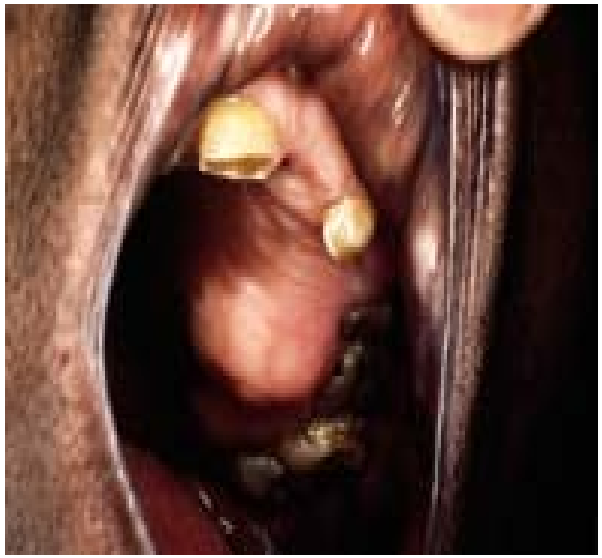
Benign lesions	Malignant lesions
Congenital hypertrophy of the retinal pigmented epithelium (CHRPE) (70-80%)	Papillary thyroid cancer (2-3%)
Epidermoid cysts (50%)	Brain tumor (<1%)
Osteoma (50-90%)	Hepatoblastoma (1%)
Desmoid tumor (10-15%)	Gastric (0.6%)
Supernumerary teeth (11-27%)	
Adrenal gland adenomas (7-13%)	

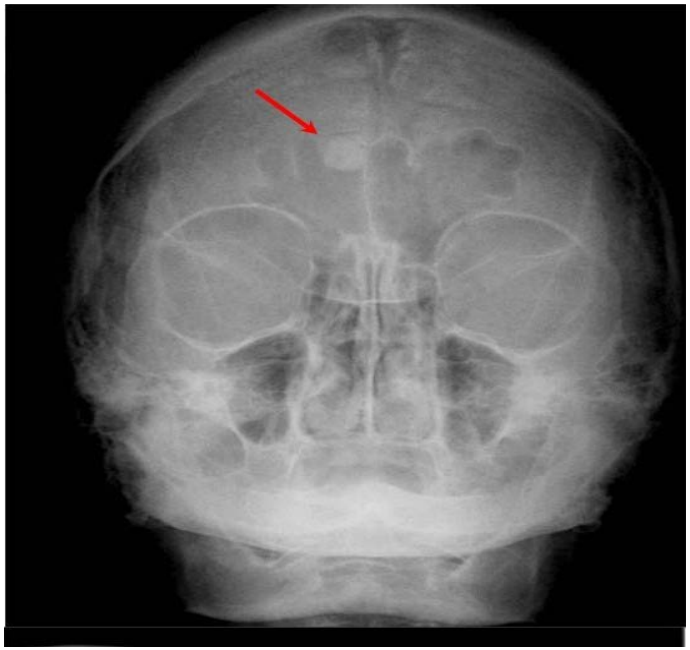
Adapted from Vasen HFA et al *Gut* 2008

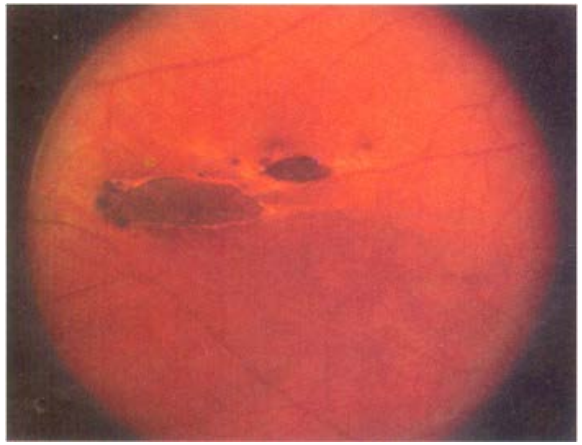
FAP: extraintestinal manifestations

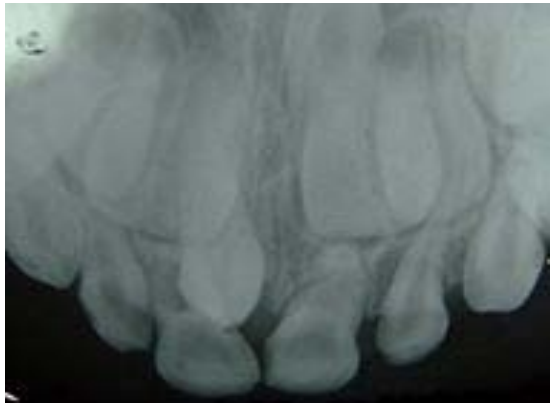






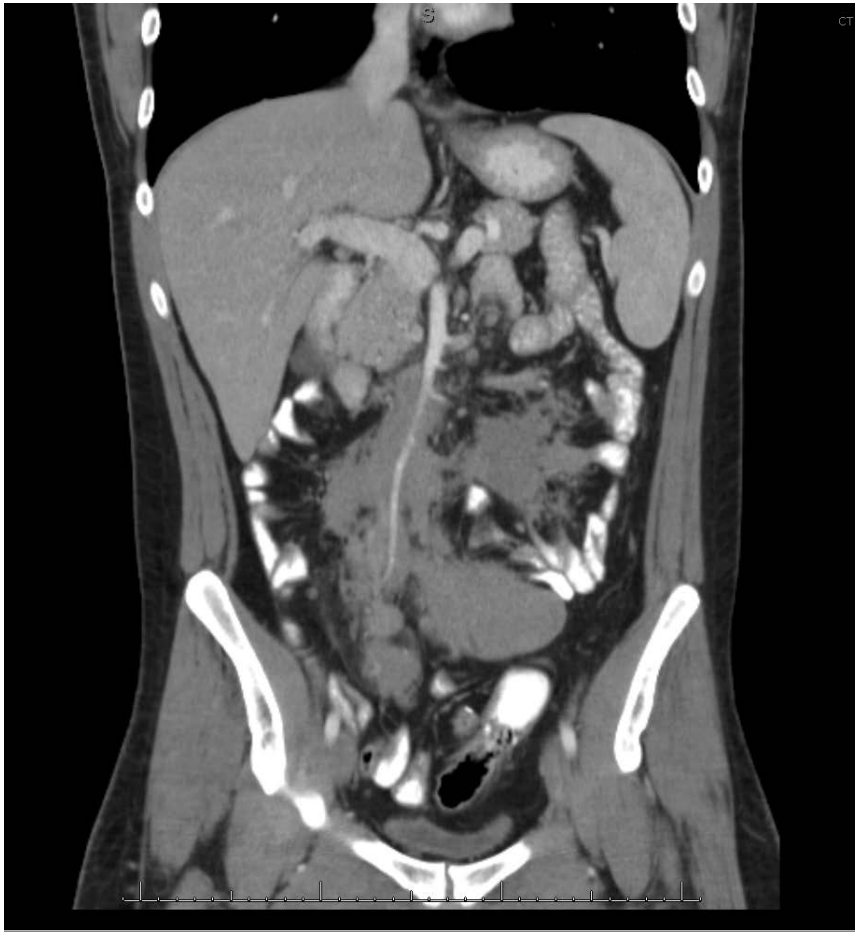






FAP: desmoid tumors

- Neoplasms of fibroblastic origin
- 10-25% prevalence in FAP
- Leading cause of death post colectomy
- Risk factors
  - trauma, *APC* mutation, family history, estrogens
- Rx: observation, NSAIDs, chemotherapy, surgery



Sturt NJH Gut 2004

FAP: diagnosis

- > 100 adenomatous colorectal polyps
  - 10-100 cumulative polyps (AFAP)
- Genetic testing
  - Clinical diagnosis:
    - full *APC* sequencing
  - Unaffected family member:
    - Test affected family member first
    - Test for specific mutation
    - If proband not available, consider full sequencing

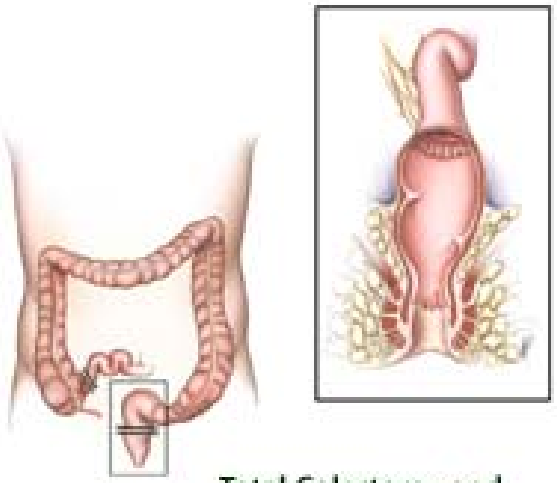
FAP management

- Genetic testing for those with clinical FAP and family members of FAP
- ? testing in children <5 years
  - hepatoblastoma screening?
- Sigmoidoscopy/colonoscopy starting age 10-12
- Appropriately timed colectomy
- Upper endoscopy with side-viewing exam every 1-5 years depending on polyp burden
  - Spigelman classification

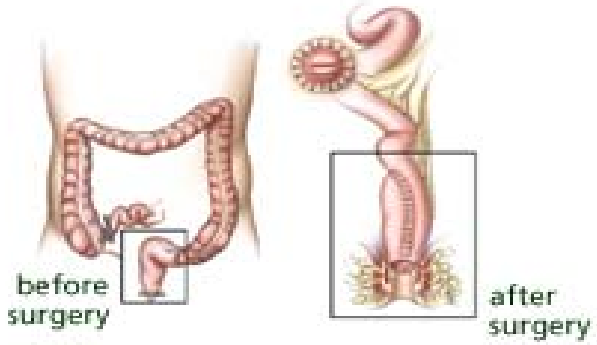
Vasen HFA et al *Gut* 2008

FAP: colectomy

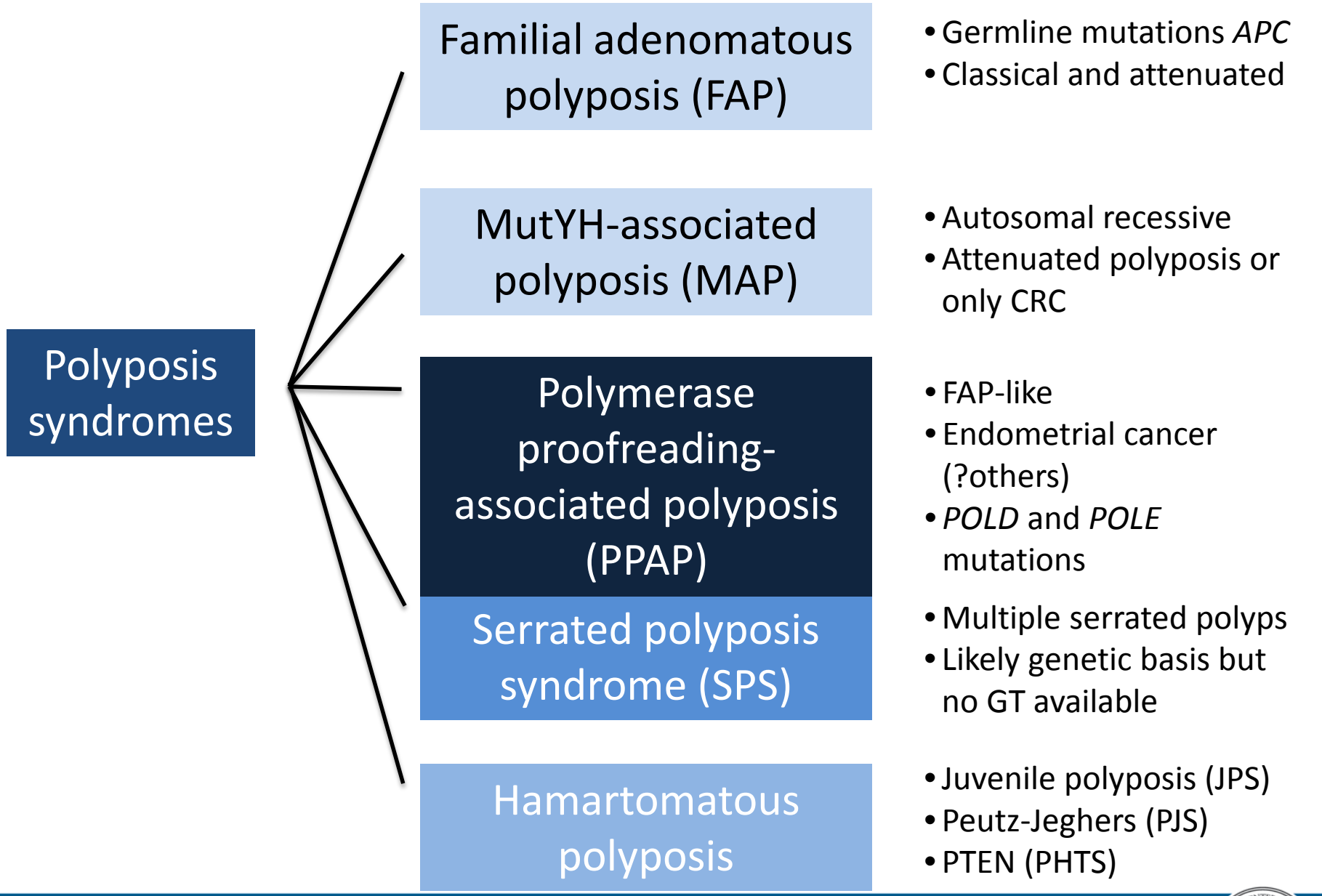
- No recommended age
- In children & adolescents, can delay with surveillance until mature enough for surgery
  - Consider delaying in patients at risk of desmoids
- Procedures
  - Subtotal with ileorectal anastamosis (IRA)
  - Proctocolectomy with ileal pouch-anal anastamosis (IPAA)



Total Colectomy and Ileorectal Anastamosis



Restorative Proctocolectomy



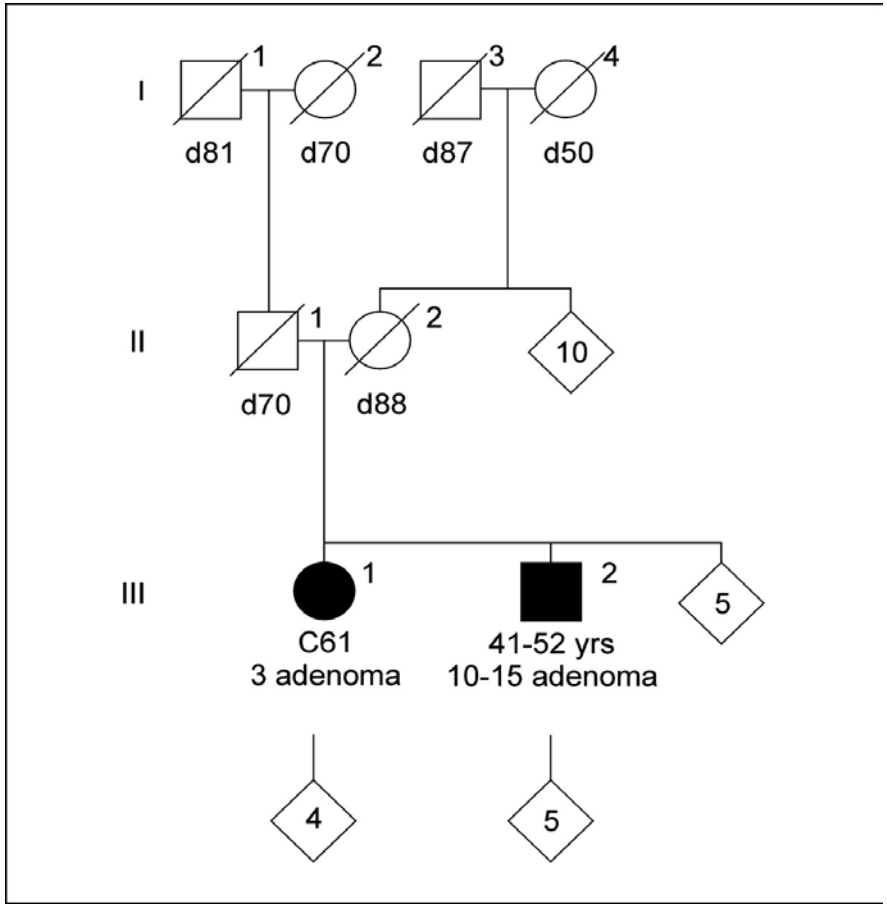
Syngal S et al *Am J Gastro* 2015

MutYH associated polyposis

MutYH-associated polyposis (MAP)

- Oligopolyposis
  - Accounts for 40% of AFAP mutation negative
- **Autosomal recessive**
- Mixed polyposis
  - adenomas, sessile serrated polyps and hyperplastic polyps
- 93-fold excess risk of CRC in biallelic carriers
- CRC not necessarily associated with polyps

MAP pedigree



MAP genetics

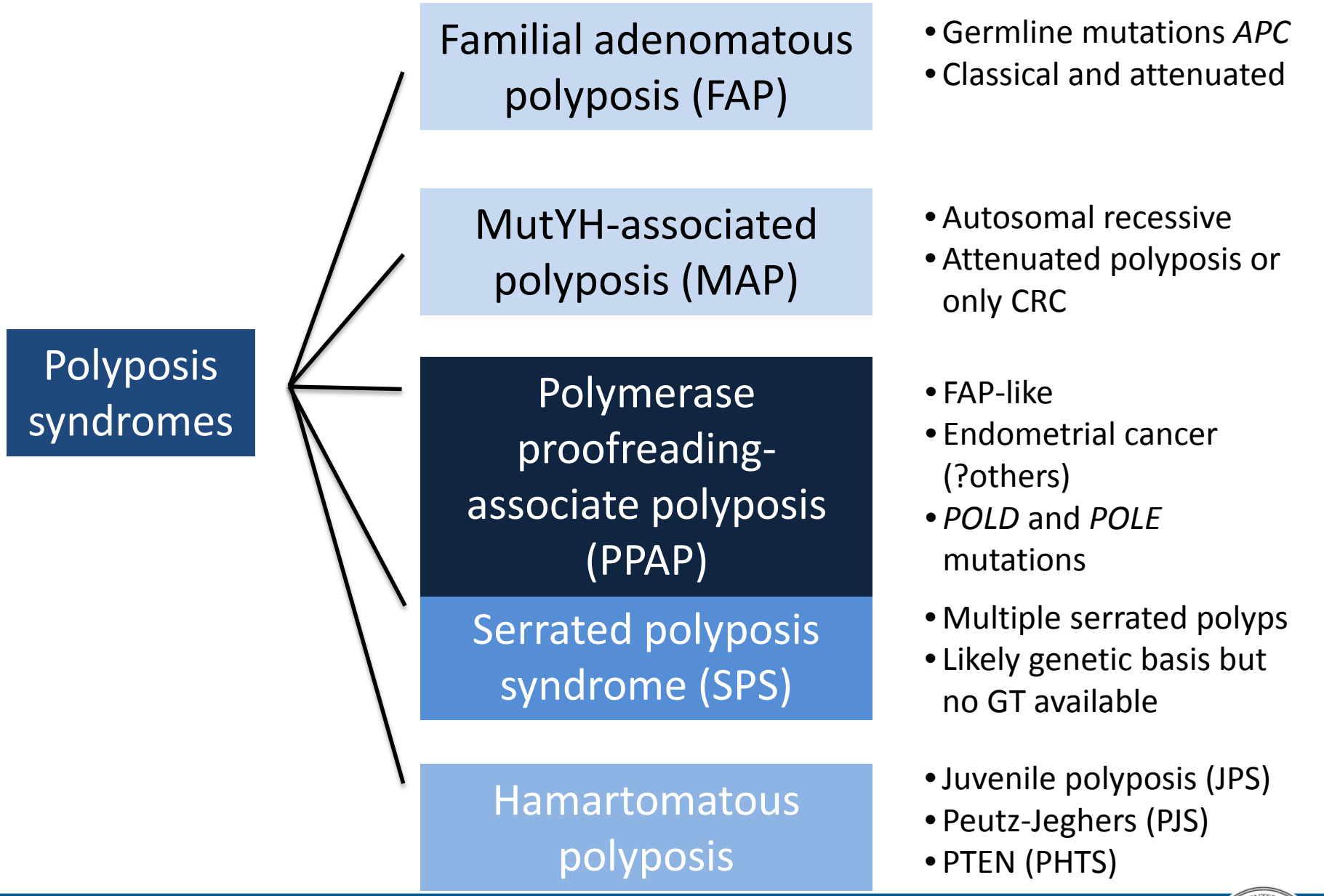
- *MutYH* gene
  - oxidative damage repair
  - Part of base excision repair pathway
- Two common mutations in Western European population (Y165C, G382D)
- Clinical testing available

MAP - Biallelic Cancer Risks

- ~80% lifetime risk for CRC
- 38% lifetime risk for extra-colonic malignancies
- Duodenal cancer risk
  - Duodenal polyps ~17%
  - Duodenal cancer ~4%
- Sebaceous gland tumors ~2%
- Ovarian, bladder, skin cancer significantly increased
- Ages of onset and spectrum of cancer suggest need for increased screening *only* for duodenum cancer risk

Nielsen M et al. *Crit Reviews in Oncology Hematology* 2010
Vogt S et al *Gastro* 2009

Hamartomatous and Serrated Polyposis Syndromes



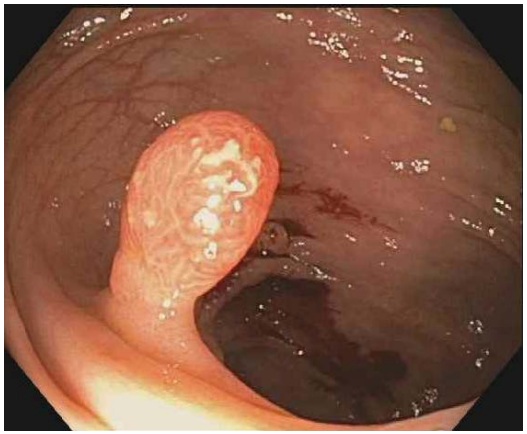
Syngal S et al *Am J Gastro* 2015

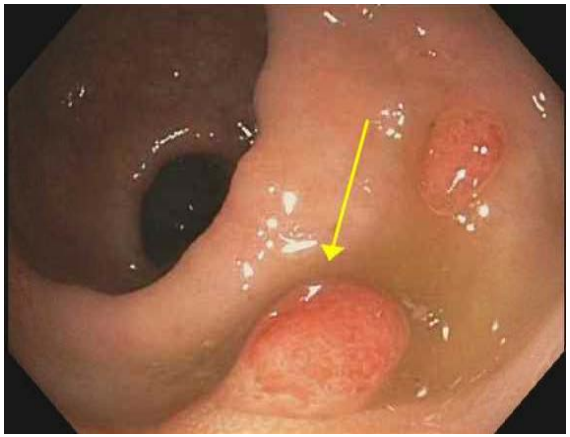
Hamartomatous Syndromes

- Juvenile Polyposis *SMAD4BMPR1A*
  - Juvenile polyps in stomach and colon
  - Isolated juvenile polyps in childhood common (2%) but not part of syndrome
- Peutz-Jeghers syndrome *STK11*
  - PJ polyps in small intestine
  - May present with bleeding or obstruction
  - Characteristic freckling
- Cowden's syndrome *PTEN*
  - Hamartomas, breast cancer, colon cancer, thyroid abnormalities

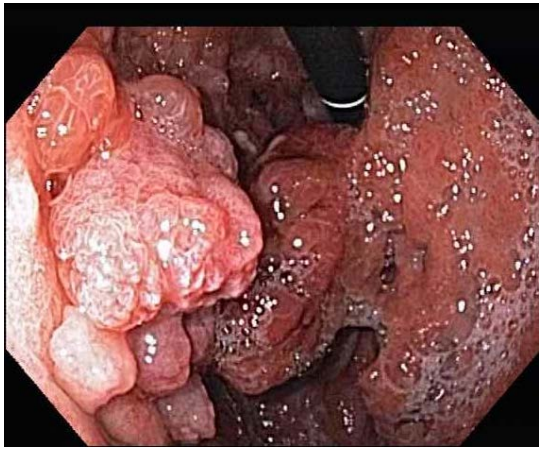
Gastric & colon juvenile polyps

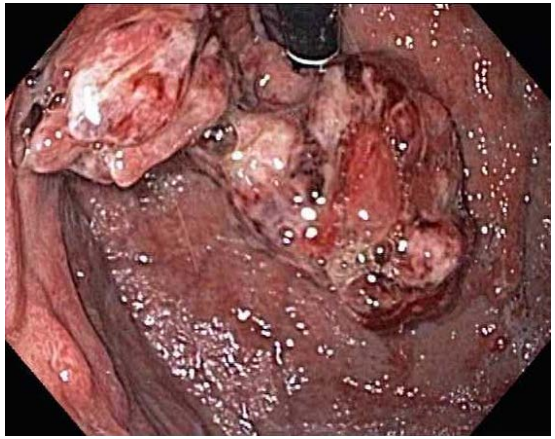
colon





stomach





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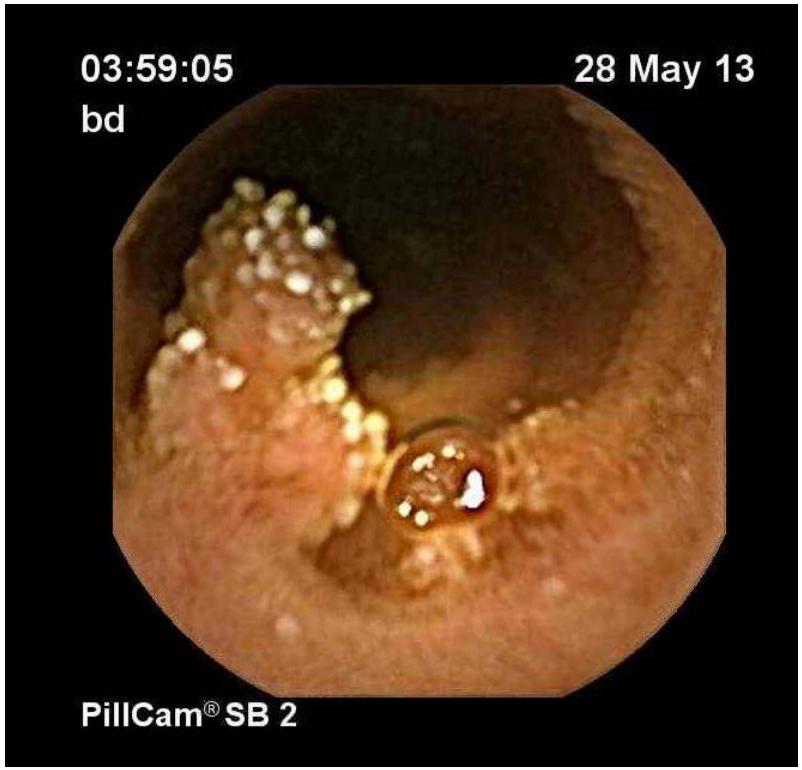
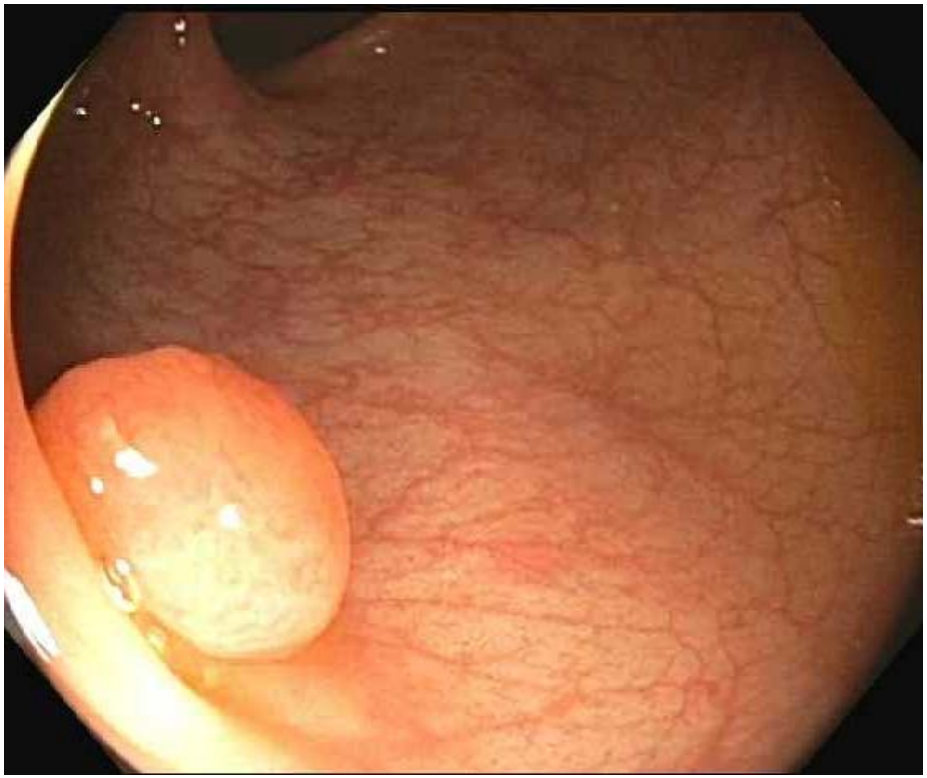
PJS polyps



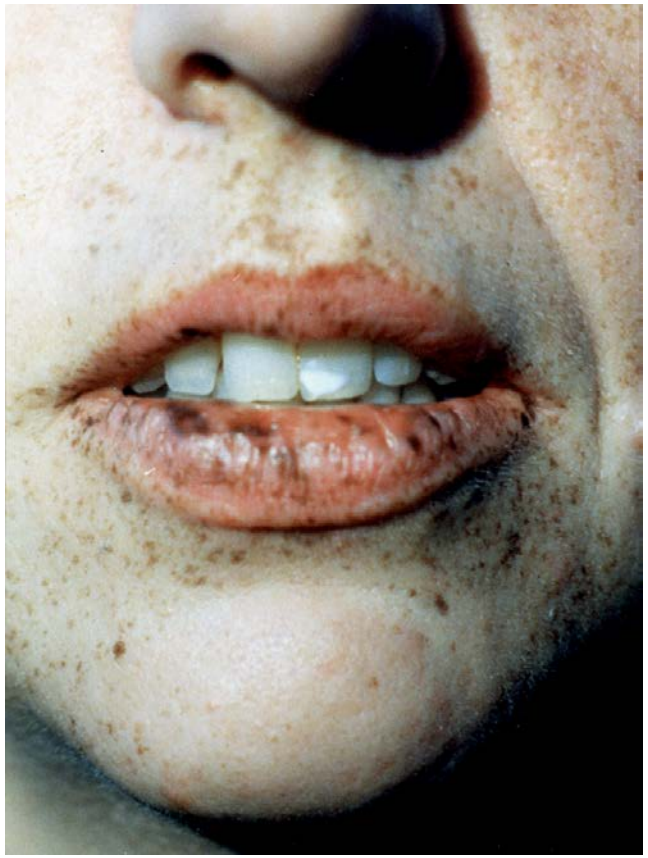
Small bowel polyp



Colon hamartoma

Peutz-Jeghers Syndrome (PJS)

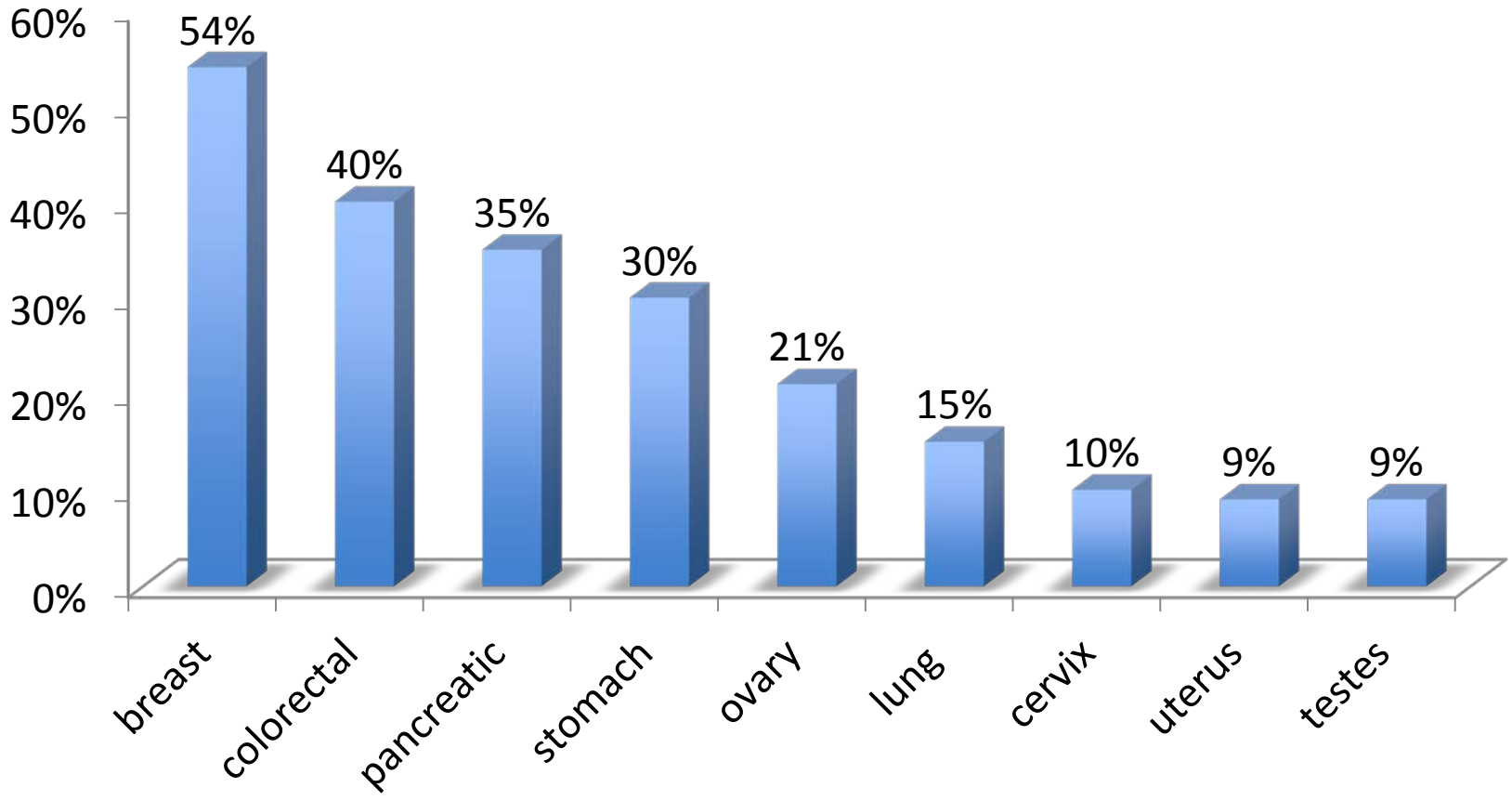
- Autosomal dominant
- 1 in 200,000 live births
- Peri-oral melanin pigment >95% of cases
- Characteristic polyps throughout GI tract
- Gene: *STK11* (19p13.3)
- Overall cancer risk 93% by age 65



PJS, GI Cancer Screening

- Colon cancer screening
  - Colonoscopy with symptoms or in late teens
  - Repeat every three years
- Pancreas:
  - endoscopic ultrasound q2 yrs, start 30 yrs alternate with MRI/MRCP?
- Stomach:
  - EGD q2 yrs, start 10 yrs
- Small intestine:
  - X-ray q2 yrs, start 10 yrs or Capsule endoscopy
- Esophagus:
  - same as stomach

PJS lifetime cancer risks



Hamartomatous Syndromes

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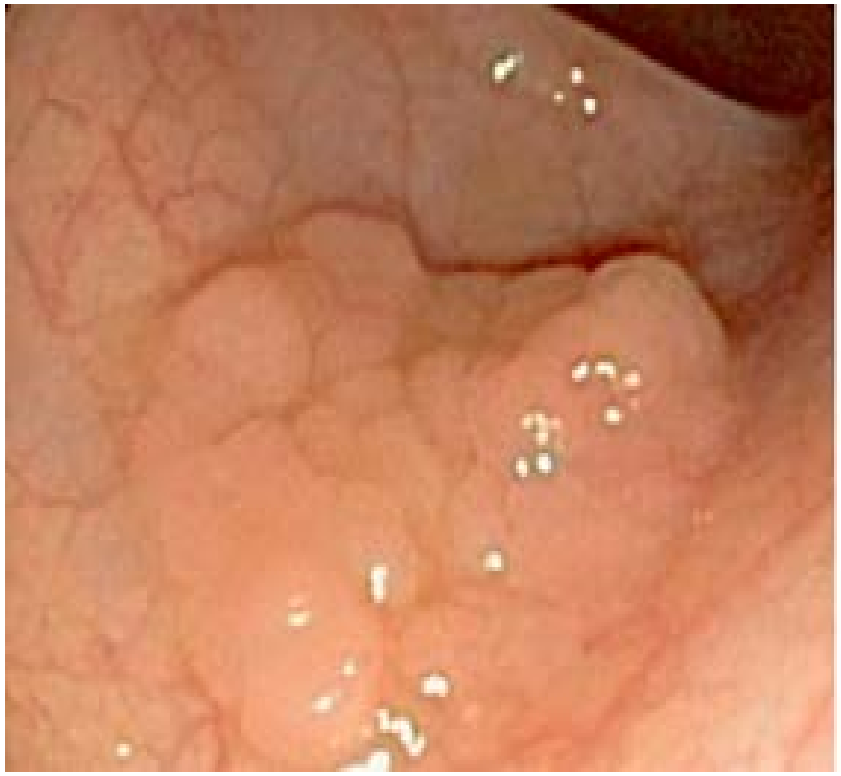
Cowden Syndrome

- Autosomal dominant, 1 in 200,000
- Mainly hamartomatous polyps throughout GI tract
- Characteristic Skin Findings: tricholemomas
- Large head circumference
- Colon cancer ? risk
- Extra-GI cancers:
  - Thyroid, 3% to 10%
  - Breast 25% to 50%
  - Uterine increased ? Risk

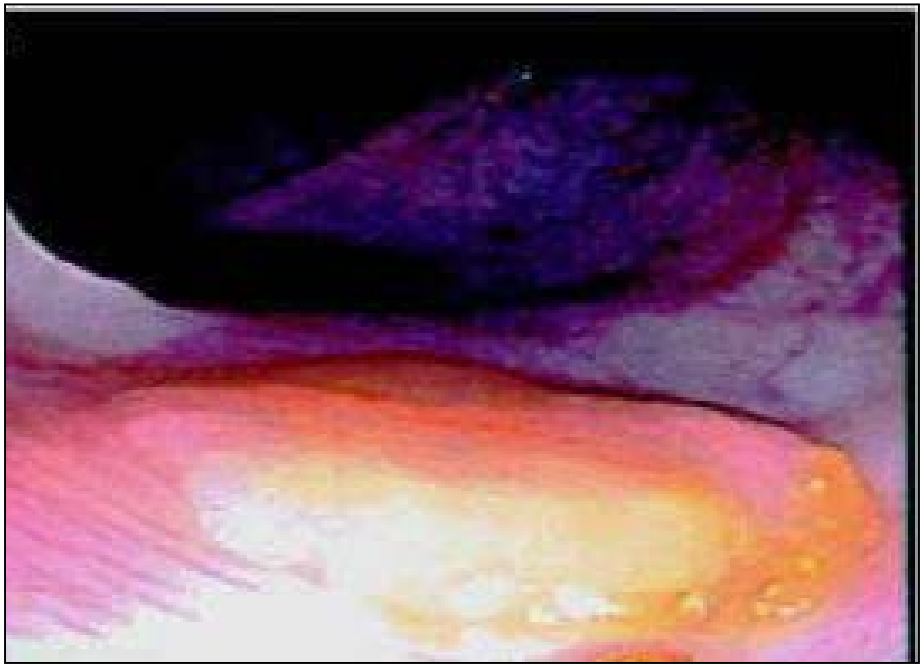
Serrated polyposis syndrome (SPS)

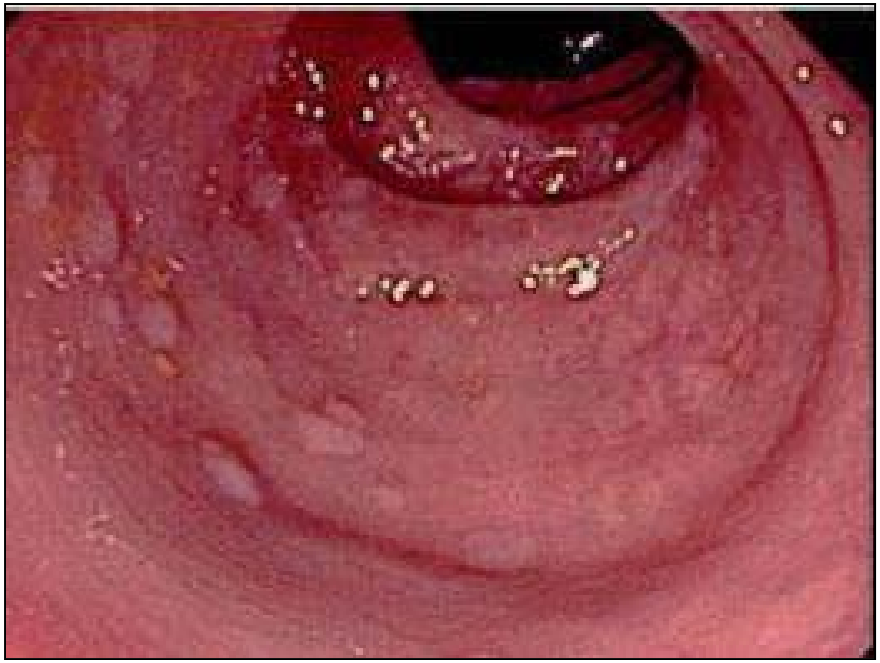
- Formerly called hyperplastic polyposis
- WHO criteria
  - 5 or more serrated polyps proximal to sigmoid colon with 2 > 1cm
  - 1 proximal serrated polyp in patient with family history
  - 20 or more cumulative serrated polyps
- Genetic basis yet to be identified
- CRC incidence 37-69%
- No screening or management guidelines exist



Boparai KS et al *Gut* 2010; Snover D et al *WHO classification of tumors* 2010; Kalady MF et al *Dis Colon Rectum* 2011

SPS Phenotypes





<u>>5 SP, 2 or more > 1cm</u>
SSA
BRAF
Right and Left sided CRCs

<u>>20 SP throughout</u>
HP
KRAS
Left sided CRCs

CRC Risk 25-70%, Family History of CRC 10-50%

Kalady MF et al. Dis Colon Rectum 2011;54:164-70

Gene Panels

- Next generation sequencing allows multiplex testing of multiple genes at once
- APC, Lynch, MUTYH, hamartomatous and many other genes
- Leads to variants and unexpected findings
- Often cheaper than specific tests
- Management can be complex

Vasen HFA et al *Gut* 2008

Gene Panels- Caveats

- Cannot counsel for all possible outcomes
- Variants of uncertain significance
  - More common than known deleterious mutations
  - Can lead to confusion
- Minor frequency mutations
  - Does genetic testing change screening above FH?
- Unexpected mutations
  - BRCA mutation when looking for hereditary CRC
  - CDH mutation (gastric cancer) when looking for hereditary CRC

Vasen HFA et al *Gut* 2008

Take Home Points

- ***Ask about family history and low threshold to refer for genetic evaluation***
- Failure to find a genetic mutation does not rule out a syndrome completely.
- Tumor MSI negative makes Lynch syndrome very unlikely
- Specific mutation testing should follow finding a pathogenic mutation in families
- When mutation not found in high risk family, screening is based on family history
- Ask for help in interpreting results of genetic panels

Acknowledgements

- My patients
- CCCC collaborators, UIC team
- Dr. John Carethers, University of Michigan
- Dr. Rick Boland, Baylor College of Medicine
- Dr. Sonia Kupfer, University of Chicago
- Dr. Dennis Ahnen, University of Colorado

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