

Controversies of the Lower GI Tract

Post-Digestive Diseases Week 2009

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DDW 2009 Highlights To Be Covered

- CTC and intermediate-sized polyps (3 abstracts)
- Small polyps and colonoscopy (2 abstracts)
- Hyperplastic and serrated polyps (3 abstracts)
- Hypermethylation as a biomarker (3 abstracts)

CT COLONOGRAPHY AND INTERMEDIATE-SIZED POLYPS

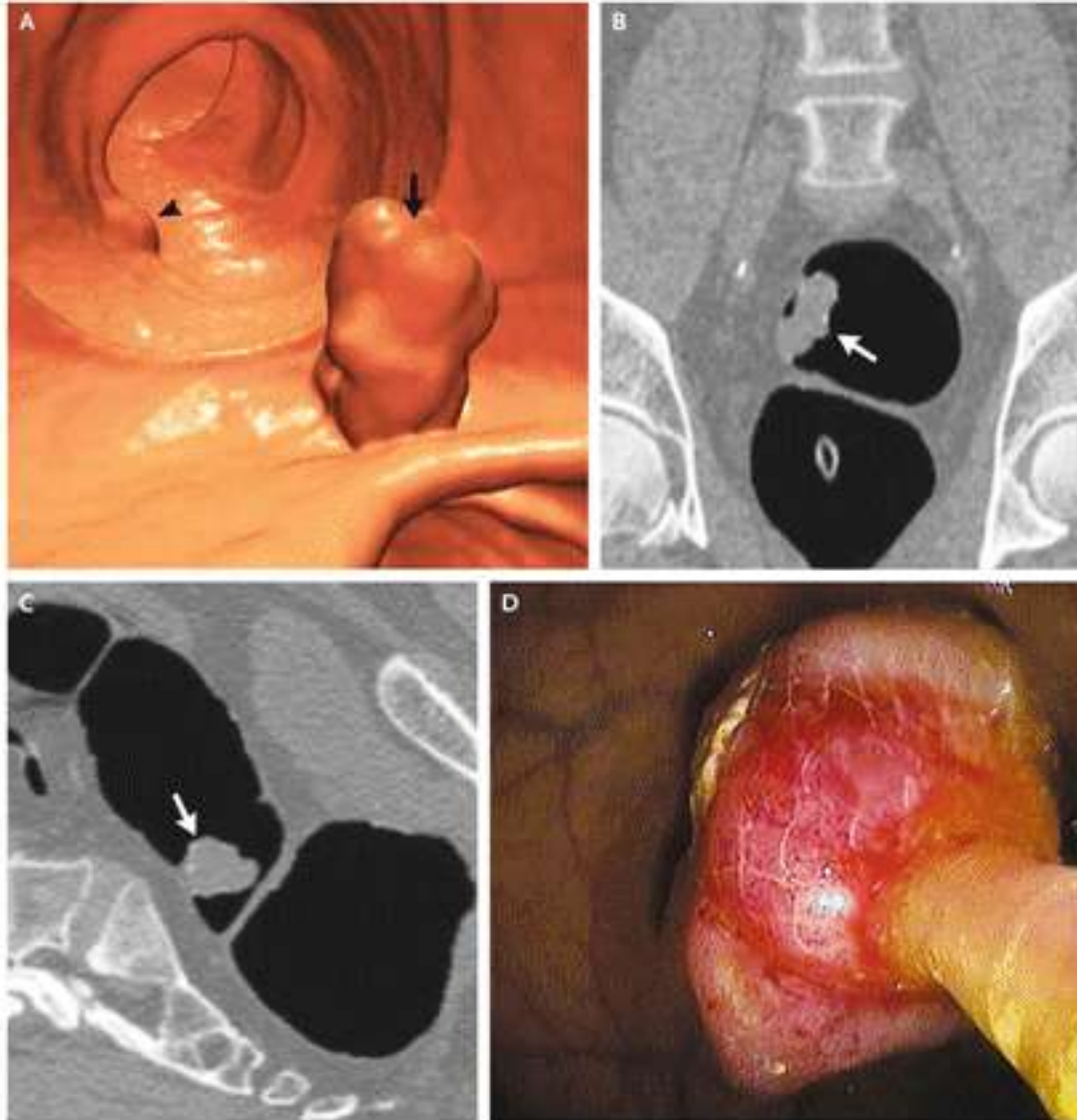
Screening for Cancers

CANCER	INCIDENCE (2008)*	DEATHS (2008)*	SCREENING TECHNIQUES
Breast	184,450	40,930	Mammography
Cervical	11,070	3,870	Pap Smear
Prostate	186,320	28,660	PSA Rectal Exam
Colorectal	148,810	49,960	FOBT FIT Stool DNA Tests Barium Enema Flexible Sigmoidoscopy Colonoscopy CT Colonography

*CA Cancer J Clin 58:71-96, 2008

Levin B et al. CA Cancer J Clin, Gastroenterology, and Radiology 2008

CT Colonography vs. Optical Colonoscopy



Guidelines for Screening

Tests that Detect Adenomatous Polyps and Cancer

Test	Interval	Key Issues for Informed Decisions
FSIG with insertion to 40 cm or to splenic flexure	Every 5 years	<ul style="list-style-type: none">• Complete or partial bowel prep is required• Sedation usually is not used, so there may be some discomfort during the procedure• The protective effect of sigmoidoscopy is primarily limited to the portion of the colon examined• Patients should understand that positive findings on sigmoidoscopy usually result in a referral for colonoscopy
Colonoscopy	Every 10 years	<ul style="list-style-type: none">• Complete bowel prep is required• Conscious sedation is used in most centers; patients will miss a day of work and will need a chaperone for transportation from the facility• Risks include perforation and bleeding, which are rare but potentially serious; most of the risk is associated with polypectomy
DCBE	Every 5 years	<ul style="list-style-type: none">• Complete bowel prep is required• If patients have one or more polyps ≥ 6 mm, colonoscopy will be recommended; follow-up colonoscopy will require complete bowel prep• Risks of DCBE are low; rare cases of perforation have been reported
CTC	Every 5 years	<ul style="list-style-type: none">• Complete bowel prep is required• If patients have one or more polyps ≥ 6 mm, colonoscopy will be recommended; if same day colonoscopy is not available, a second complete bowel prep will be required before colonoscopy• Risks of CTC are low; rare cases of perforation have been reported• Extracolonic abnormalities may be identified on CTC that could require further evaluation

FSIG, flexible sigmoidoscopy; DCBE, double contrast barium enema; CTC, computed tomographic colonoscopy; gFOBT, guaiac-based fecal occult blood test; FIT, fecal immunochemical test; sDNA, stool DNA test

CTC Recommendations

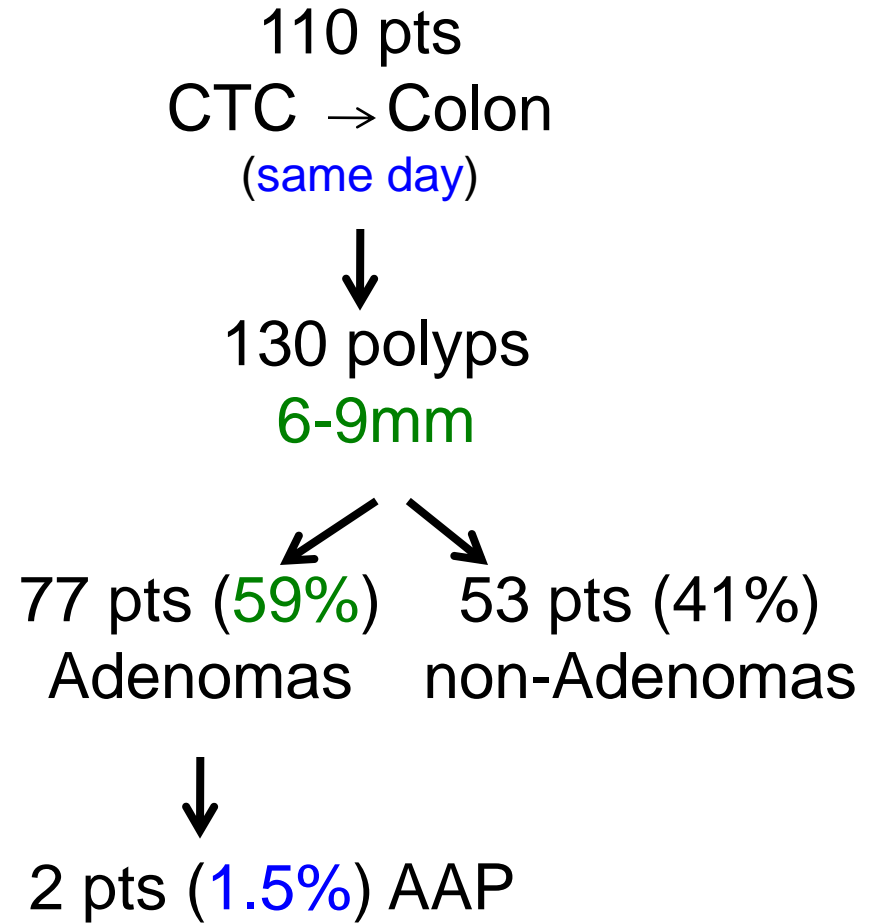
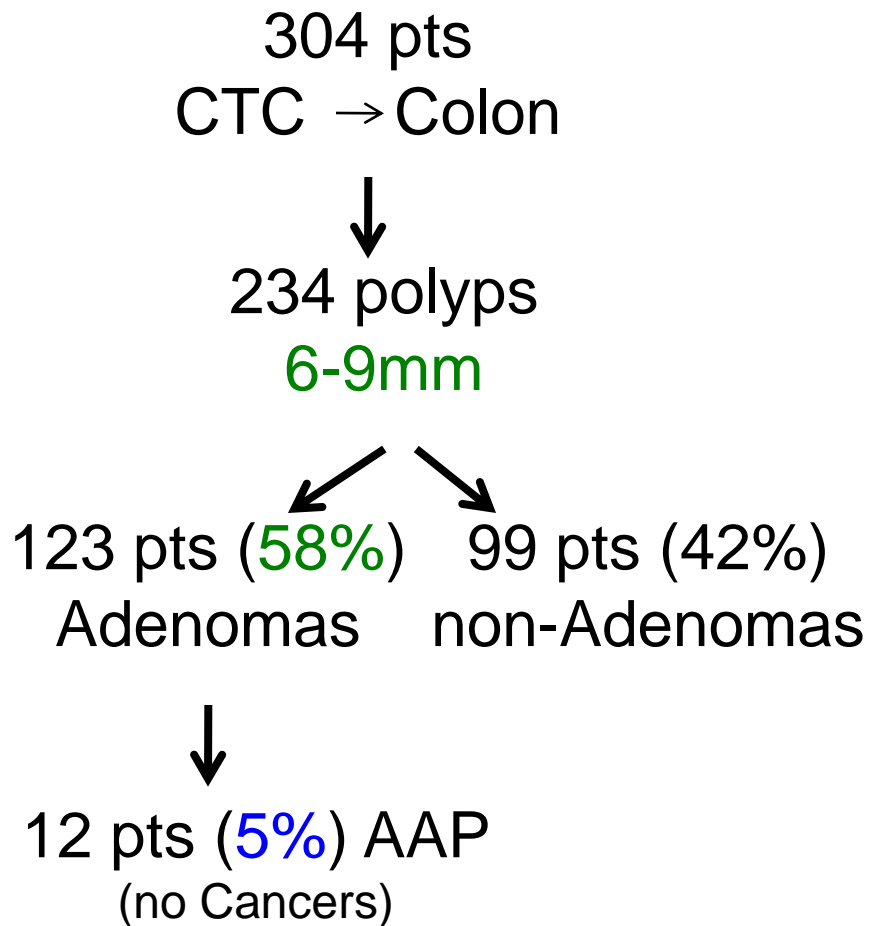
- ≥ 1 polyp that is $\geq 10\text{mm}$, or 3 or more polyps $\geq 6\text{mm}$
 - Referred for colonoscopy
- < 3 polyps in which largest polyp is 6-9mm
 - Controversial
 - Option to refer for colonoscopy
 - Option for surveillance with CTC
 - Prevalence of AAP: 3.4%-6.6%
 - AJR Am J Roentgenol 2007;188:940
 - Gastrointest Endosc 2007;65:822
 - Polyps $\leq 5\text{mm}$: not reported by CTC

#515

Pathology of the 6-9mm Polyp Found in a CT Colonography Screening Program: Implications for CT Polyp Surveillance vs. Resection

- Background: Little data exists on the pathology of polyps 6-9mm found on CTC to guide management
- Objectives:
 - Determine pathology of all 6-9mm polyps found on CTC and sent to colonoscopy
 - Determine polyp pathology in patients whose largest polyp was 6-9mm who had same day colonoscopy
- Methods:
 - All patients referred from CTC to colonoscopy
 - October 2004 to March 2008

#515 Results



AAP: adenoma of advanced pathology

#515 Conclusions

- Conclusions:
 - AAP found in 1.5% of patients with a 6-9mm polyp as largest lesion detected by CTC
 - ~40% of patients with 6-9mm polyps on CTC have only hyperplastic or non-adenomatous polyps
- Comments:
 - ~60% of CTC patients with polyps 6-9mm have adenomas
 - How does this compare to larger polyps?
 - 1.5% pts with AAP!
 - Polyps <5mm ignored

#271

Natural History of Intermediate-Sized Polyps on CTC: Growth Rates Predict Histology

- Background:

- CORI: In polyps 6-9mm, 5.3% are AAP (6.6% if includes serrated adenomas)
- GI Societies recommend removal of all polyps, unlike recommendations for CTC

- Objectives:

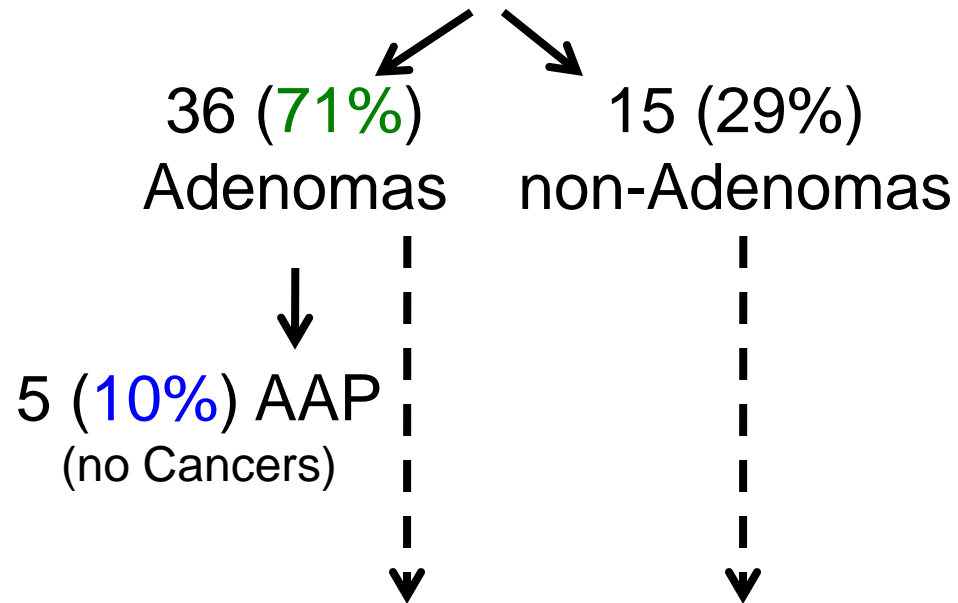
- Determine growth rates of polyps at one year during observation after initial CTC

- Methods:

- 3000 person, single center trial of CTC compared with colonoscopy
- Observed patients who had 1-2 6-9mm polyps on initial CTC exam
 - Electronic calipers on CTC determined size
- Polyp left *in vivo*
- Repeat CTC 1 year later, followed by same day colonoscopy
 - Matched polyps in adjacent colon segments

#271 Results

43 pts
51 matching 6-9mm polyps left *in vivo* for 1 year



Growth Rate: 1.3 mm/yr (P=0.0073) --

AAP: adenoma of advanced pathology

#271 Conclusions

- Conclusions:
 - 70% 6-9mm polyps are adenomas, with 10% AAP
 - Growth rates are 1.3mm/yr
 - Routine clinical practice: ~10% of avg. risk individuals would have at least 1 polyp 6-9mm
 - Supports colonoscopy with polypectomy
- Comments:
 - Small numbers
 - Matched polyps?

#T1358

Prevalence of Advanced Histology Based on Polyp Size at Screening Colonoscopy: Implications for Outcomes of CT Colonography

- Background:
 - Optimal management of polyps <10mm found on CTC uncertain
- Objectives:
 - Determine the prevalence of advanced histology based on size of polyp
- Methods:
 - 40-89 y.o.
 - Excluded prior h/o adenoma, CA, IBD, FAP, HNPCC, incomplete exams
 - Polyp size from pathology report
 - Jan 2005-December 2006

#T1358 Results

6905 consecutive patients for colonoscopy

4967 patients met inclusion criteria (41.4% male, 13% FH CRC)

↓
1361 (27.4%) polyps

↓
930 (18.7%)
Adenomas

↓
249 (5%) AAP
8 (0.16%) Cancers

Polyp Size	Total # Polyps	% Adenomas	% Advanced Adenomas
<5 mm	1025	64.0%	10.2%
6-9 mm	247	80.2%	27.1%
>10 mm	89	85.4%	50.6%

#T1358 Conclusions

- Conclusions:
 - Appreciable rate of adenomatous and AAP that may be left unreported based on CTC guidelines
- Comments:
 - Sized determined at pathology, may not mimic CTC sizing

SMALL POLYPS AND COLONOSCOPY

#274

Prevalence of Advanced Histology in Diminutive Colonic Polyps in An Average Risk Population: Implications for Colorectal Cancer Screening

- Background:

- Natural history of polyps 1-5mm is poorly defined
- Few data available on advanced histology is diminutive polyps

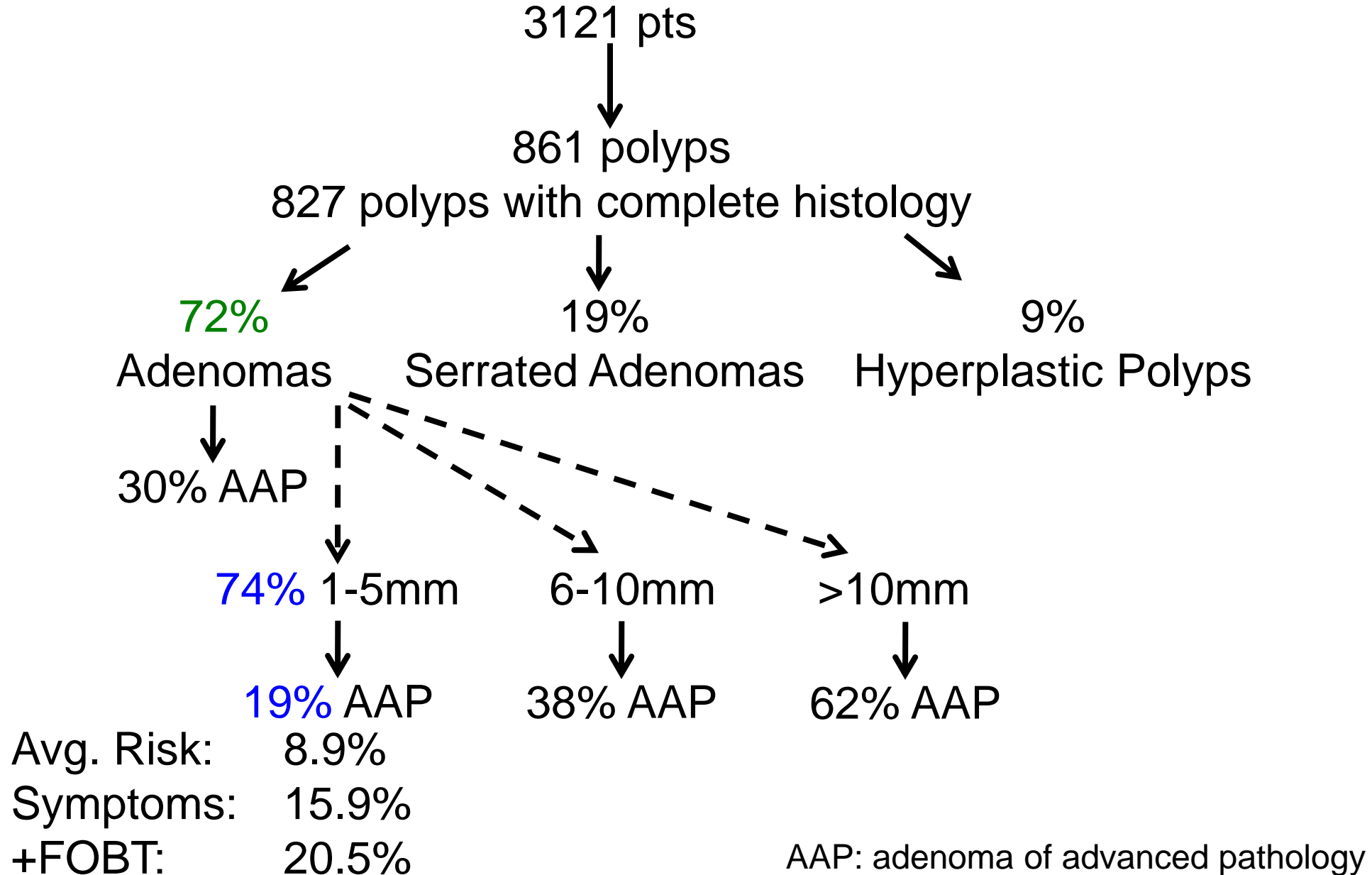
- Objectives:

- Determine prevalence of advanced histological features in polyps removed at colonoscopy

- Methods:

- 3121 consecutive patients (45% male, median age 60)
 - 915 average risk
 - 1760 lower GI symptoms
 - 446 asymptomatic patients with +FOBT
- Mean withdrawal time 10.3 min, Cecum intubated in 96% cases
- Pathology examine by 2 independent pathologists

#274 Results



#274 Conclusions

- Conclusions:
 - Higher prevalence of AAP in 1-5mm sized polyps
 - Diminutive polyps can harbor significant histology
- Comments:
 - Good study, large numbers
 - Higher prevalence than previous reports
 - Not all patients for screening

#M1298

Cold Snare Polypectomy for Diminutive Polyps: An Assessment of the Risk of Incomplete Removal of Small Adenomas

- Background:
 - Cold snare more common recently for small polyps
 - No assessment of adequate removal with cold snares
 - Hot biopsy associated with residual tissue in up to 17% of cases
- Objectives:
 - Assess completeness of cold snare on diminutive polyps
- Methods:
 - Data recorded prospectively from consecutive patients with diminutive polyps ($\leq 5\text{mm}$) on colonoscopy
 - Endoscopist choice for 10 or 13mm snare, or development of pseudostalk
 - Residuals determined by quadrantic forceps at edge of polypectomy site

#M1298 Results

52 pts (73% male, mean age 65 yrs)

64 consecutive cold snares (mean size 3mm)



1 sessile serrated
adenoma



43 tubular
adenomas



20 hyperplastic
polyps

Adenoma Location: Rt. Colon: 21/22 (95%)
 Lt. Colon: 21/28 (75%)
 Rectum: 2/14 (14%)

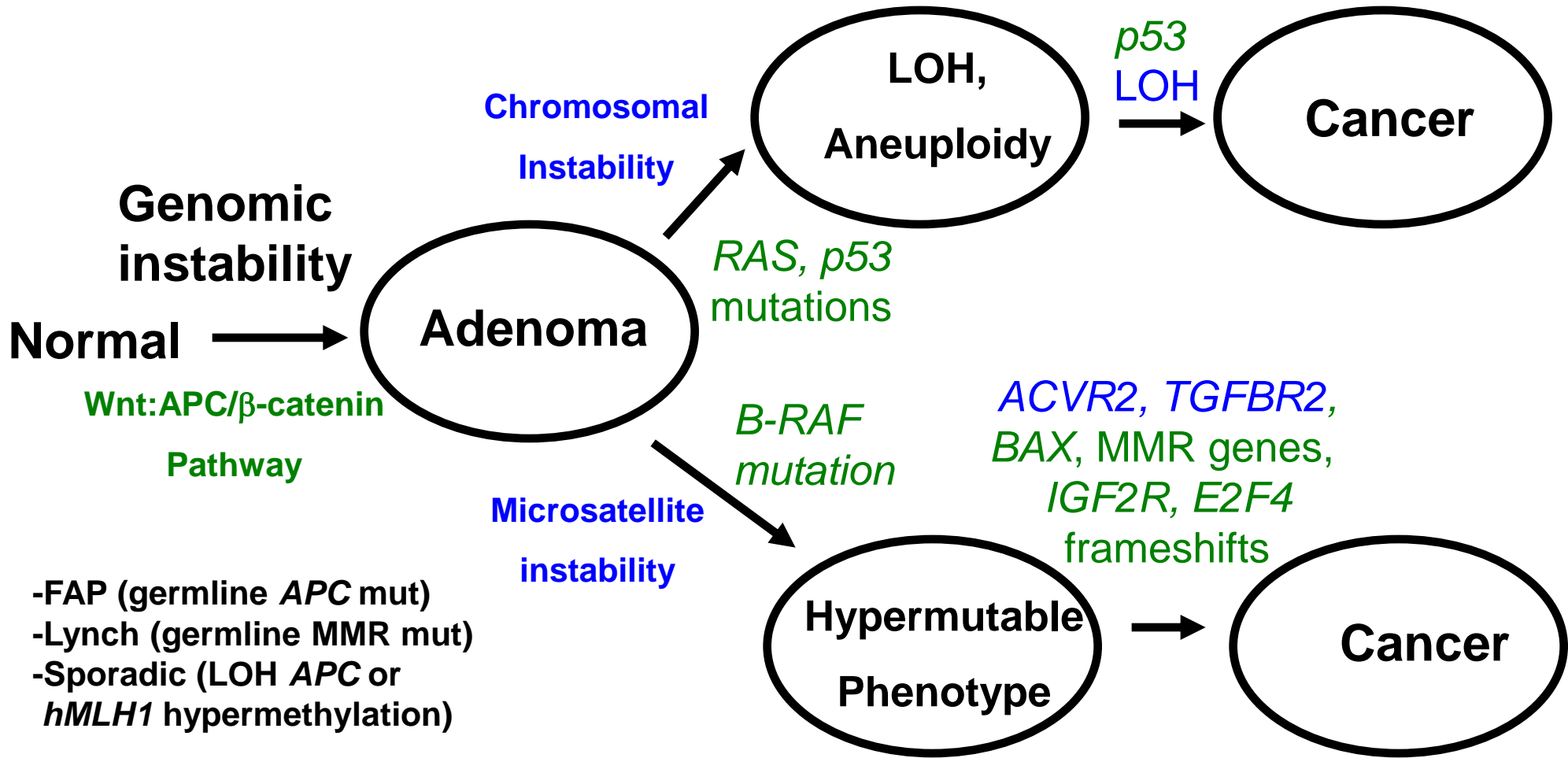
Residuals: 5/44 (**11.4%**); 2/19 (10%) with pseudostalk

#M1298 Conclusions

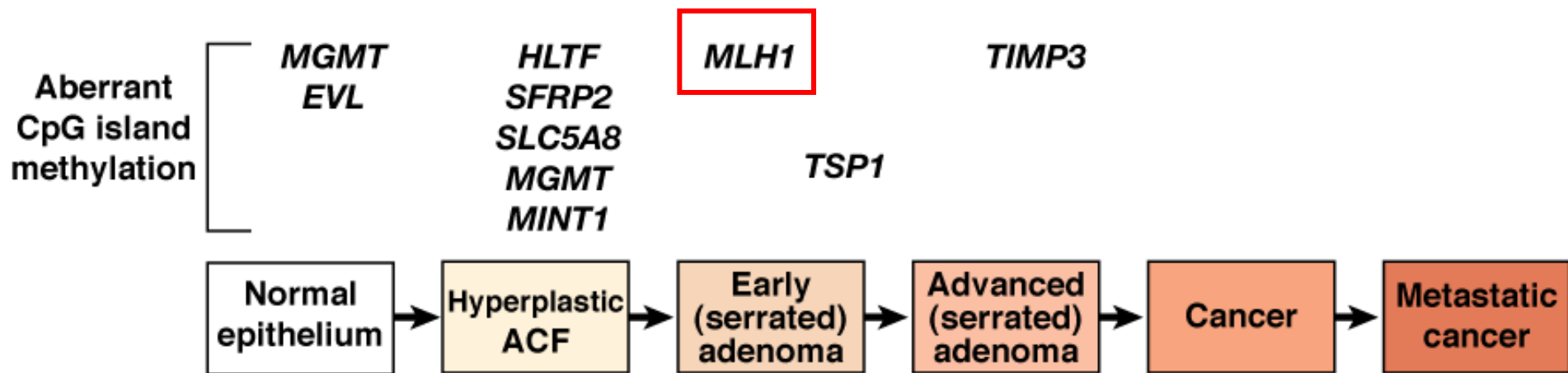
- Conclusions:
 - Significant residual polyp rate with cold snare (11.4%)
 - Similar rate to electrocautery (up to 17%)
 - Completeness of cold snare polypectomy cannot be assumed
- Comments:
 - Residual probably more common than we realize
 - Significance? Growth rate? Recurrent polyps at same site?

HYPERPLASTIC AND SERRATED POLYPS

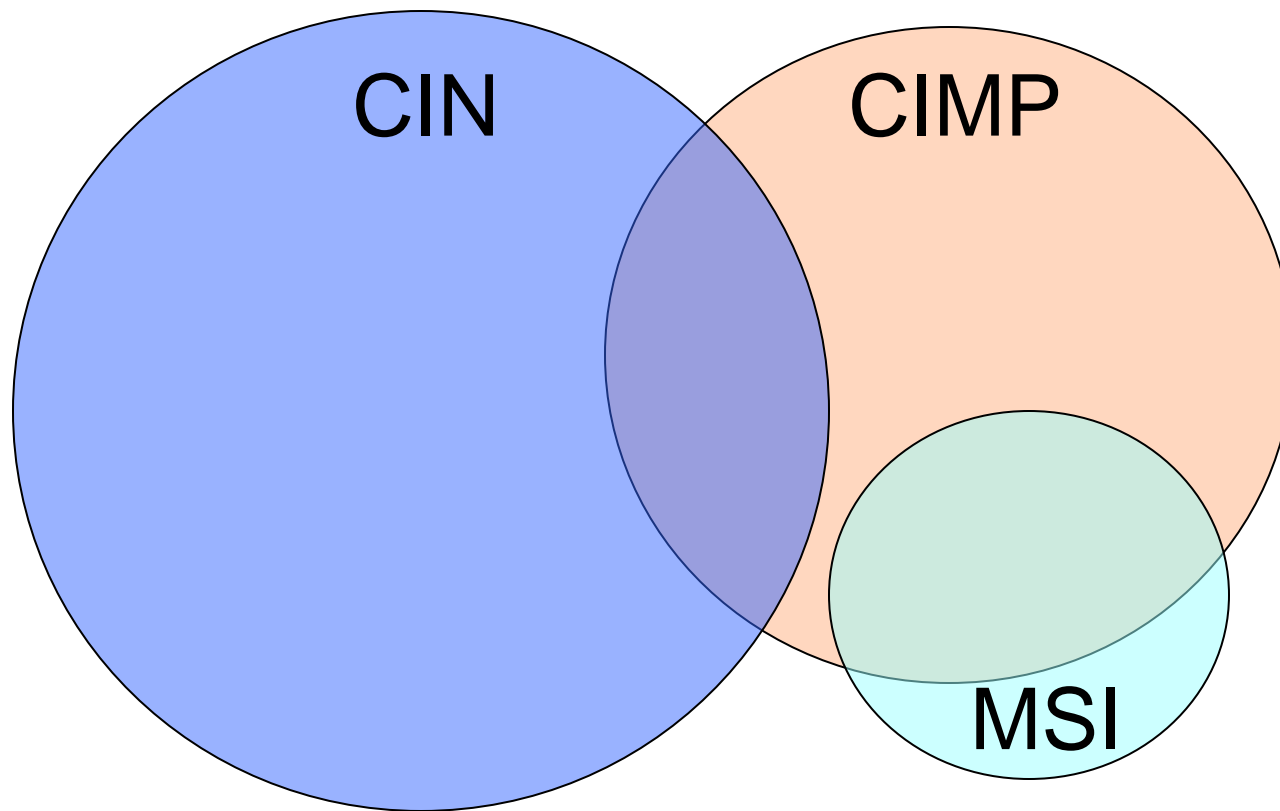
DUAL PATHWAYS FOR COLON CANCER DEVELOPMENT



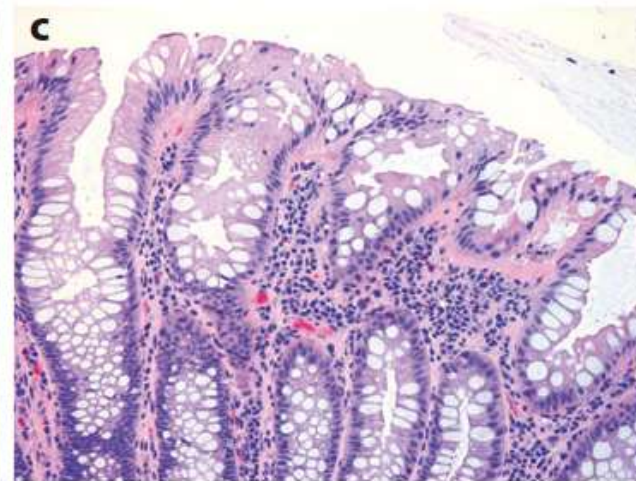
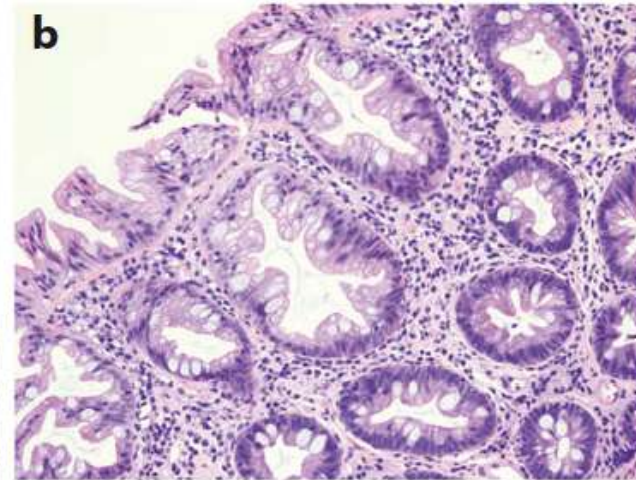
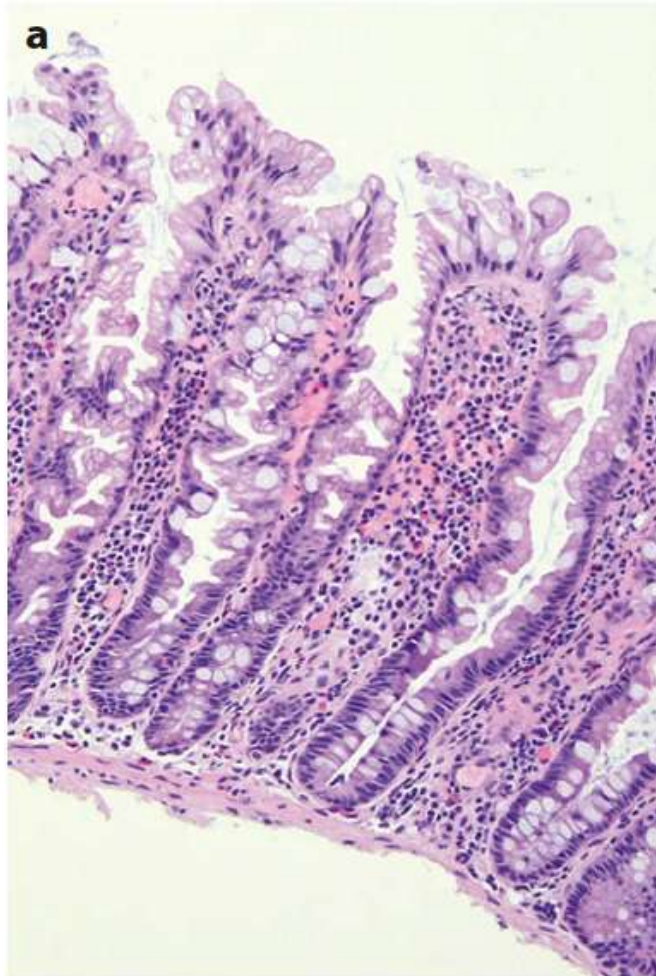
Pathogenesis of CIMP Colorectal Cancers



Three Pathways for CRC?



Hyperplastic Polyp



Traditional Serrated Adenoma

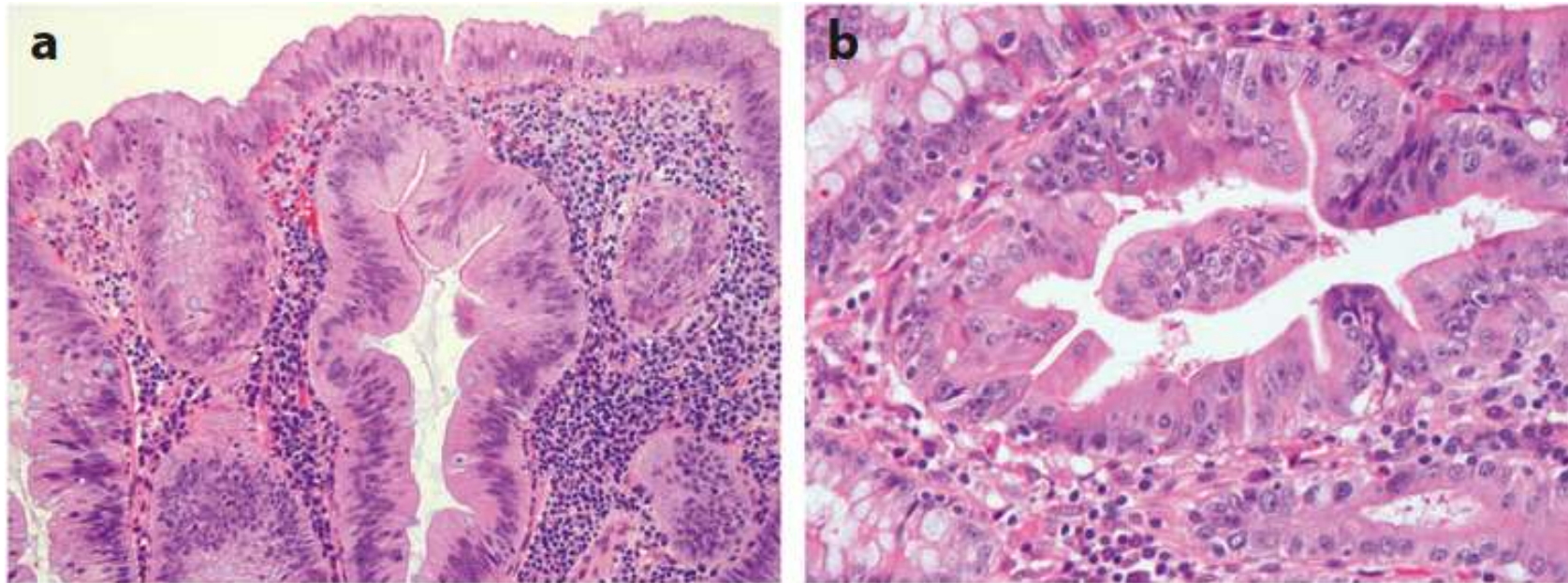


Figure 2

Traditional serrated adenoma. (a) The crypt lumens have a serrated appearance and are lined by tall columnar cells with enlarged, crowded, and somewhat hyperchromatic nuclei. Typically, the cytoplasm is brightly eosinophilic. (b) High-grade dysplasia, shown here, is sometimes present in these lesions.

Sessile Serrated Adenoma

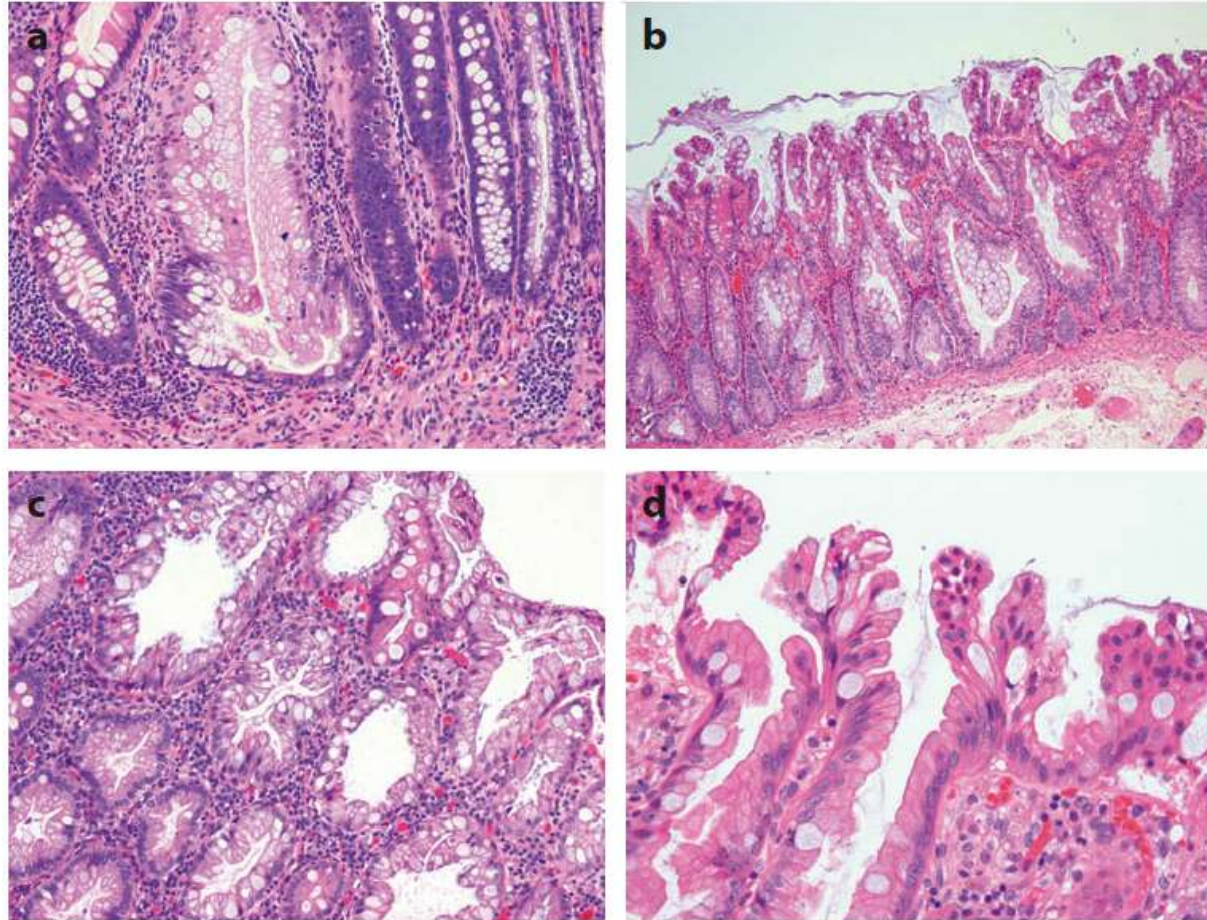
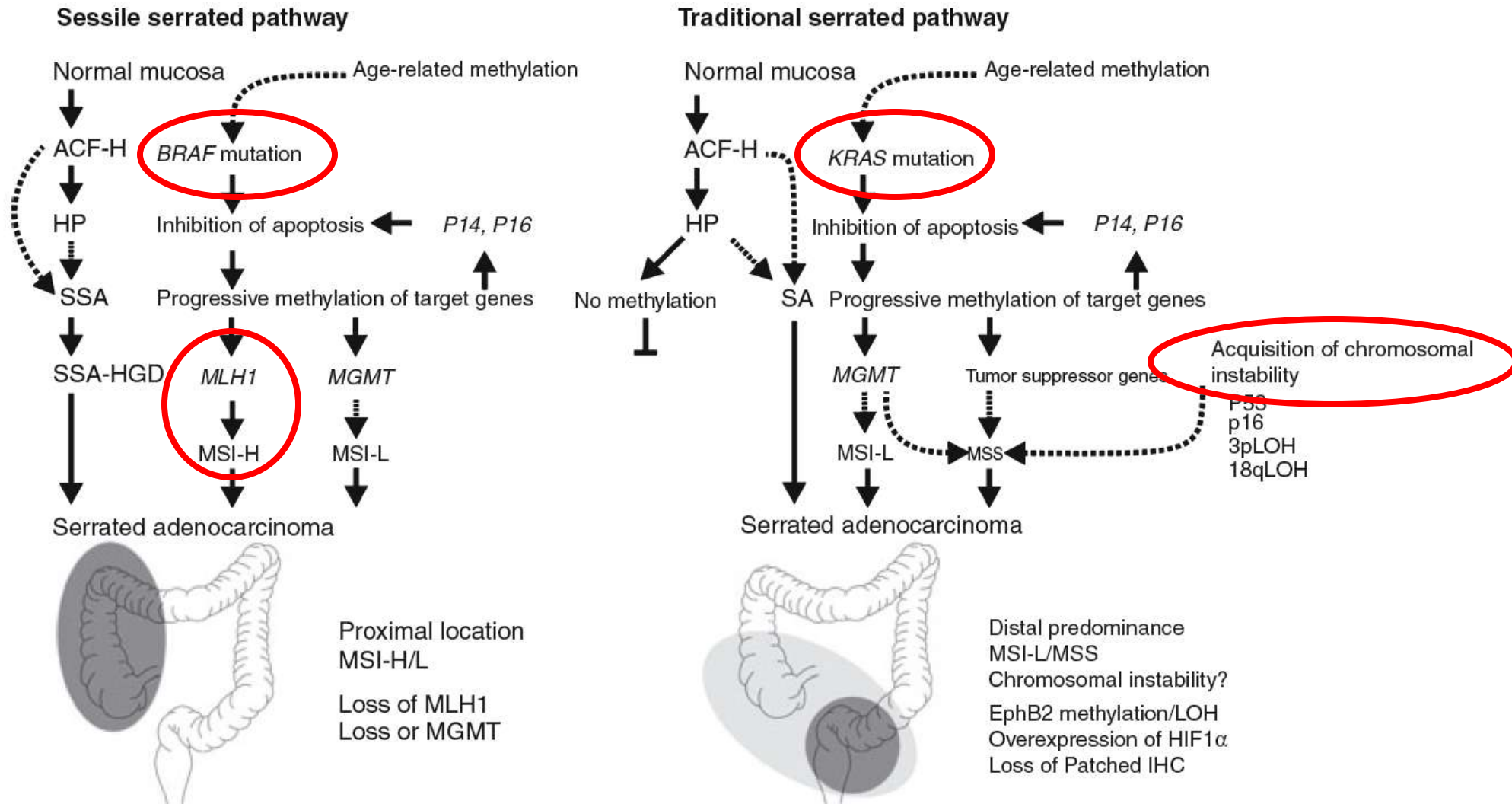


Figure 3

Sessile serrated adenoma. (a) Sessile serrated adenomas typically show abnormal architectural features such as L- or T-shaped crypts. (b) The crypts are often prominently dilated and show serrations that extend all the way to the crypt base. (c) Serration in sessile serrated adenomas is often exaggerated compared with that seen in true hyperplastic polyps. (d) The cells in the upper crypts and on the mucosal surface contain larger, more disorganized nuclei than those seen in hyperplastic polyps.

Serrated Adenoma Pathogenesis



CRC Pathway Classification

Table 4 Molecular classification of colorectal carcinoma

	Chromosomal instability pathway	Mismatch repair pathway	Serrated pathway		Hybrid pathway
Hereditary	Hereditary and sporadic	Hereditary	Hereditary and sporadic		Sporadic
CIMP status	Negative	Negative	High		Low
MSI status	MSS	MSI-H	MSI-H	MSI-L	MSI-L or MSS
Chromosomal instability	Present	Absent	Absent	Absent	Present
<i>KRAS</i> mutation	+++	+/-	---	---	+++
<i>BRAF</i> mutation	---	---	+++	+++	---
MLH1 status	Normal	Mutation	Methylated	Partial methylation	Normal
MGMT methylation	---	---	+/-	+++	+++

FAP
Sporadic CIN

Lynch

Hyperplastic Polyposis
Sporadic MSI

Sporadic MSS

#600

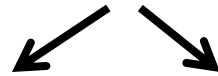
Are Hyperplastic Polyps Precursors of Colorectal Cancer? A Long-Term, Retrospective Study

- Background:
 - Hyperplastic polyps are considered innocuous lesions, with no malignant potential
 - Some may transform through serrated adenomas, increasing cancer risk
- Objectives:
 - Investigate relationship between hyperplastic polyps and CRC
 - Analyze predictors for CRC in pts. with hyperplastic polyps
- Methods:
 - Retrospective analysis through a Dutch national pathology database
 - 1991-1998
 - F/U 11 years
 - Endpoints were CRC, last colonoscopy, or death

#600 Results

568 pts (age 60 yrs, 57% male)

943 hyperplastic polyps



410 pts

Hyperplastic
polyps
only

158 pts

Hyperplastic
polyps and
adenomas

CRC Prevalence = 3.5% (2.5% Rt. Colon vs. 1.1% Lt. colon ($p=0.074$))

not different than prevalence seen in general population

Presence of **multiple** HPs: **HR 2.7** (CI 1.1-6.9, $p=0.043$)

Presence of **large (>5mm)** HPs: **HR 7.8**, CI 3.0-20.5, $p<0.0001$

Concomitant presence of adenomas: no additional risk

#600 Conclusions

- Conclusions:
 - Patients with large, Rt.-sided hyperplastic polyps have nearly 8-fold increased risk for CRC
 - Validates potential role for serrated adenoma pathway in pathogenesis
- Comments:
 - Overall small number of hyperplastic polyps
 - Stress issue of multiple, and Rt. Sided nature as potential means for increased surveillance

#T1351

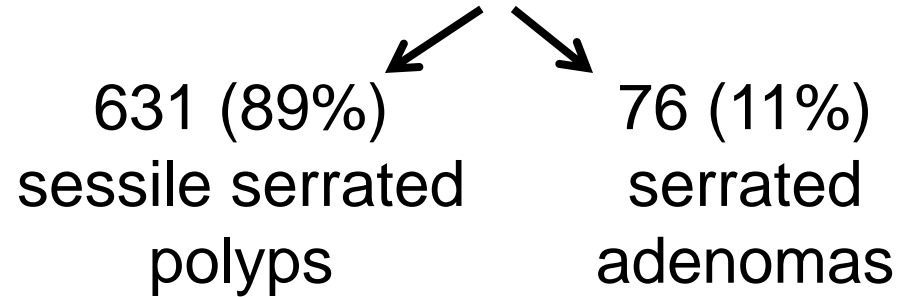
Demographic Factors and Endoscopic Findings in Individuals with Advanced Serrated Colorectal Polyps

- Background:
 - Sessile serrated polyps are precursors to CRC
- Objectives:
 - Define demographic and endoscopic findings of patients with serrated polyps
- Methods:
 - Identified sessile serrated polyps and serrated adenomas, TA, TVA, VA, HGD, HP as well
 - Hyperplastic polyps >10 mm classified as sessile serrated polyp
 - 17,750 path reports from April 2004 to November 2007
 - Excluded patients with colectomy, CRC, polyposis

#T1351 Results

496 pts (49% female, age 60.7 yrs, BMI 28.8, 66% smokers, FH CRC in 23%)

707 serrated polyps



- only 13 pts had co-existent SSP and SA
- SSP more often Rt. than SA ($p=0.013$)
- larger SSP in Rt. colon; not seen with SA
- synchronous polyps in 34%

46% (238) HP <10mm

47% (244) TA (3 HGD)

5% (26) TVA (3 HGD)

1 VA with HGD

11 CA (4 on Rt. with 2 arising from serrated lesion)

#T1351 Conclusions

- Conclusions:
 - M=F with serrated polyps
 - High percentage of smokers
 - Sessile serrated polyps more common than serrated adenomas
 - Sessile serrated polyps tend to be in Rt. colon, and larger than those in the Lt. colon
 - No association between size and serrated adenomas
- Comments:
 - Good study for associations

Hyperplastic Polyposis: Diagnostic Criteria

Table 3 Diagnostic criteria for hyperplastic polyposis

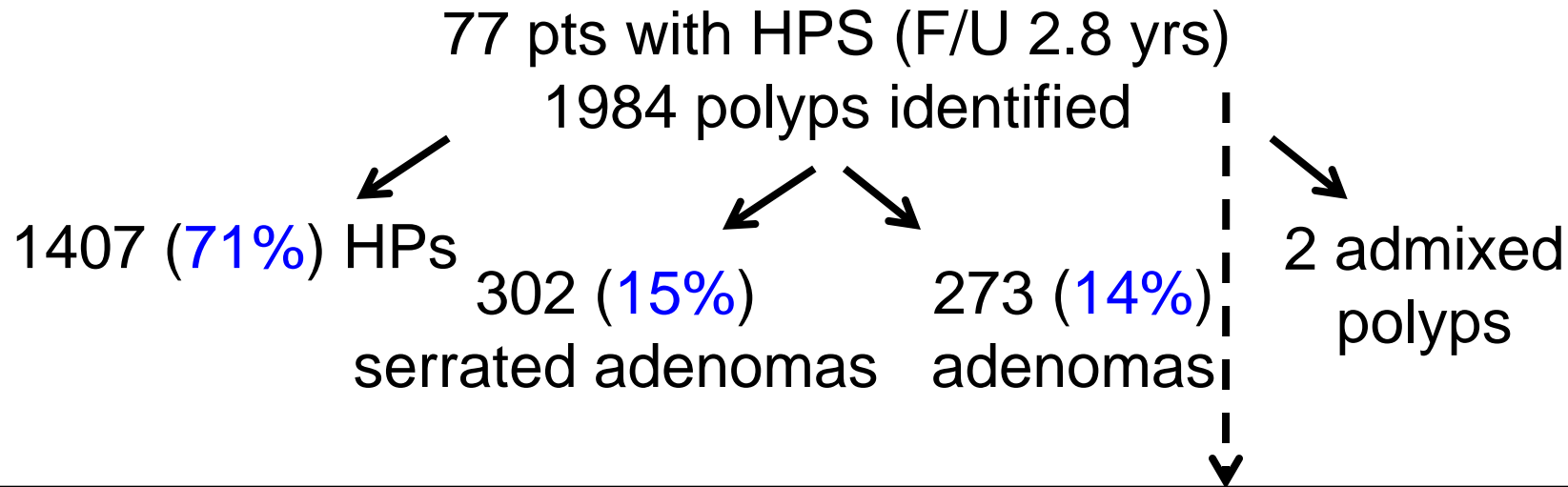
1. At least five histologically confirmed hyperplastic (serrated) polyps proximal to the sigmoid colon, of which two are greater than 1 cm in diameter
2. Any number of hyperplastic (serrated) polyps proximal to the sigmoid colon in a subject with a first-degree relative with hyperplastic polyposis
3. More than 30 hyperplastic (serrated) polyps of any size distributed evenly throughout the colon

#M1932

Increased Colorectal Cancer Risk During Follow-Up in Patients with Hyperplastic Polyposis Syndrome: A Multicenter Cohort Study

- Background:
 - Hyperplastic Polyposis Syndrome (HPS) is associated with increased risk for CRC, but long term follow-up for this risk has not been reported
- Objectives:
 - Assess cumulative risk of developing CRC during follow-up
 - Examine possible association with frequency and interval of surveillance endoscopies
- Methods:
 - 7 medical centers
 - Endoscopy reports, histopathology obtained

#M1932 Results



27 pts (35%) with CRC

22 at initial endoscopy

5 (6.5%) developed after 1.3 yrs and 3 surveillance colonoscopies

CRC detection 11 months after last surveillance

Cumulative Risk: **7% (at 5 yrs), 16% (at 10 yrs)**

4/5 pts: CRC detected within an HP or SA

4/5 pts had SAs and multiple (>30) polyps

#M1932 Conclusions

- Conclusions:
 - Hyperplastic polyps causally related to CRC development
 - Interval cancers develop in 6.5% of HPS patients despite surveillance endoscopy
 - SAs and multiple polyps associated with CRC development
- Comments:
 - Optimum surveillance not known (< 11 months?)

HYPERMETHYLATION AS A BIOMARKER

#196

A Sensitive Methylation Marker Panel That Discriminates Normal Mucosa from Colorectal Cancer Tissue with High Specificity

- Background:

- Colorectal cancer, overall, is hypomethylated
- Some genes become hypermethylated with age
- Promoters of tumor suppressor genes in cancer are often hypermethylated, abrogating their expression

- Objectives:

- Determine cancer specificity of methylation by semi-quantitative and qualitative methods

- Methods:

- Seven promoters: *FOXF1*, *CA4*, *NPY1R*, *GREM1*, *IFITM1*, *MLH1*, *MGMT*, comparing cancer/normal tissue, blood
- 105 CRC patients
- Quantitative methylation specific PCR (detects 1/3000 methylated alleles)

#196 Results

- 7 methylation marker panel
 - detected 87/105 (83%) of cancers
 - Covered 94% of all tumors in Rt. colon
- *FOXF1*: most sensitive marker
 - Hypermethylated in 96% Rt. vs. 55% Lt. (P=0.0003)
 - Age-dependent methylation increase in females (P=0.001)
 - Not seen in males

#196 Conclusions

- Conclusions:
 - 7 marker panel detected aberrantly methylated promoters specific to CRC, particularly in the Rt. colon
 - *FOXF1* demonstrates a gender and colon location pattern
- Comments:
 - Tools for stool DNA panels?

#S1964

Higher Prevalence of CpG Island Methylator Phenotype-Positive (CIMP+) Status in Advanced Adenomas Detected Using Colonoscopy for CRC Screening

- Background:

- Adenoma to carcinoma sequence is highlighted by (epi)genetic changes
- Promoter hypermethylation associated with transcriptional gene silencing of tumor suppressor genes

- Objectives:

- Study prevalence and correlation of CIMP+ and gene promoter hypermethylation with advanced features of *adenomas*

- Methods:

- 136 consecutive adenomas removed in a colonoscopy screening clinic
- Methylation of *CACNA1G*, *NEUROG1*, *IGF2*, *RUNX3*, *SOCS1*, *MGMT*, *HLTF*, *RASSF2A*, *P16* by MSP

#S1964 Results

126/136 adenomas with CIMP status determined



25% adenomas CIMP+
18/31 (58%) <6mm

AAP (18/45, 40%) CIMP+ vs. non-AAP (13/81, 16%), p=0.003

Villous (13/30, 43%) vs. non-villous (18/96, 19%), p=0.006

No difference with: HGD, location, size, gender

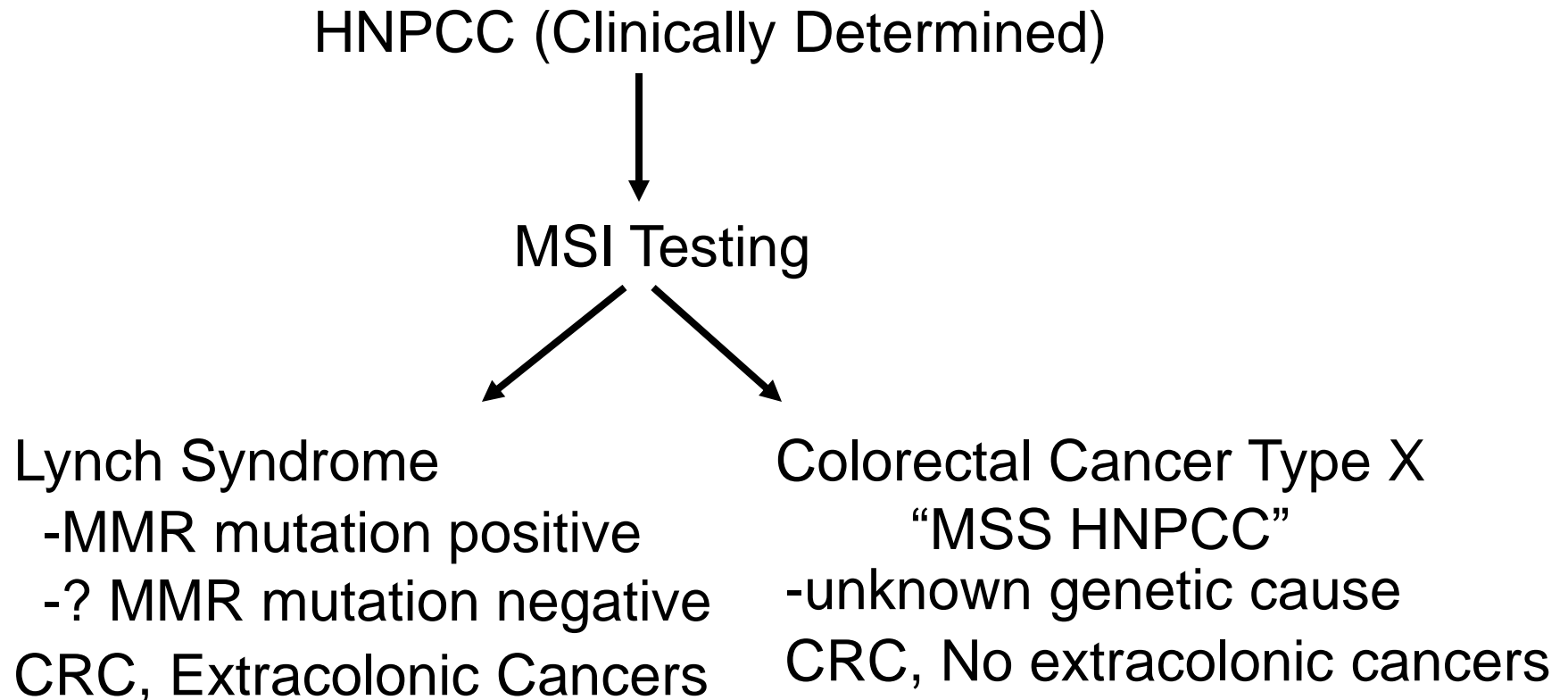
IGF2 methylation associated AAP, villous component, larger size

	IGF2	RUNX3	CACNA1G	NEUROG1G	SOCS1	HLTF	P16	RASSF2A	MGMT
methyl- ated(%)	35/124 (28.2%)	5/124 (4.03%)	12/126 (9.5%)	89/126 (70.6%)	76/130 (58.5%)	58/127 (45.7%)	54/126 (42.9%)	36/99 (36.4%)	82/126 (65.1%)

#S1964 Results

- Conclusions:
 - CIMP+ occurs more frequently in AAP
- Comments:
 - Implies detection of CIMP+ can detect pre-malignant lesions
 - No difference in colonic location

HNPPCC: More than 1 Disease



CRC Pathway Classification

Table 4 Molecular classification of colorectal carcinoma

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<i>BRAF</i> mutation	---	---	+++	+++	---
MLH1 status	Normal	Mutation	Methylated	Partial methylation	Normal
MGMT methylation	---	---	+/-	+++	+++

FAP
Sporadic CIN

Lynch

Hyperplastic Polyposis
Sporadic MSI

Sporadic MSS

#198

CpG-Island Methylator Phenotype (CIMP) and Alterations in *RAS-Raf* Signaling in Hereditary Non-Polyposis Colorectal Cancers Without Mismatch Repair Deficiency (MSS HNPCC)

- Background:
 - CIMP+ CRC associates with MSI-H, and *BRAF* mutations in older pts
 - HNPCC segregates into Lynch (MMR gene mutation) and MSS-HNPCC
 - Some Lynch pts also had aberrant methylation and *KRAS* mutations
- Objectives:
 - Determine contribution of CIMP+ to MSS HNPCC, and its relationship with RAS-Raf pathway
- Methods:
 - HNPCC, Lynch, sporadic MSS, sporadic MSI tumors
 - Pyrosequencing for methylation of CACNA1G, SOCS1, RUNX3, NEUROG1, MLH1
 - CIMP+ when >2/5 markers positive
 - *BRAF* (V600E) and *KRAS* (codon 12/13) assessed for mutation

#198 Results

	Sporadic MSI	Sporadic MSS	Lynch	MSS HNPCC
CIMP+	92.5%	52%	78%	64%
<i>BRAF</i> mut	+	2/84	0	0
<i>KRAS</i> mut	-	39%	9%	24%

No association between CIMP and *KRAS*

#198 Conclusions

- Conclusions:
 - CIMP may be involved in MSS HNPCC
 - CIMP and *KRAS* mutations may occur independently of each other
- Comments:
 - Pattern may be similar to sporadic MSS tumors
 - Etiology still unknown

THANK YOU