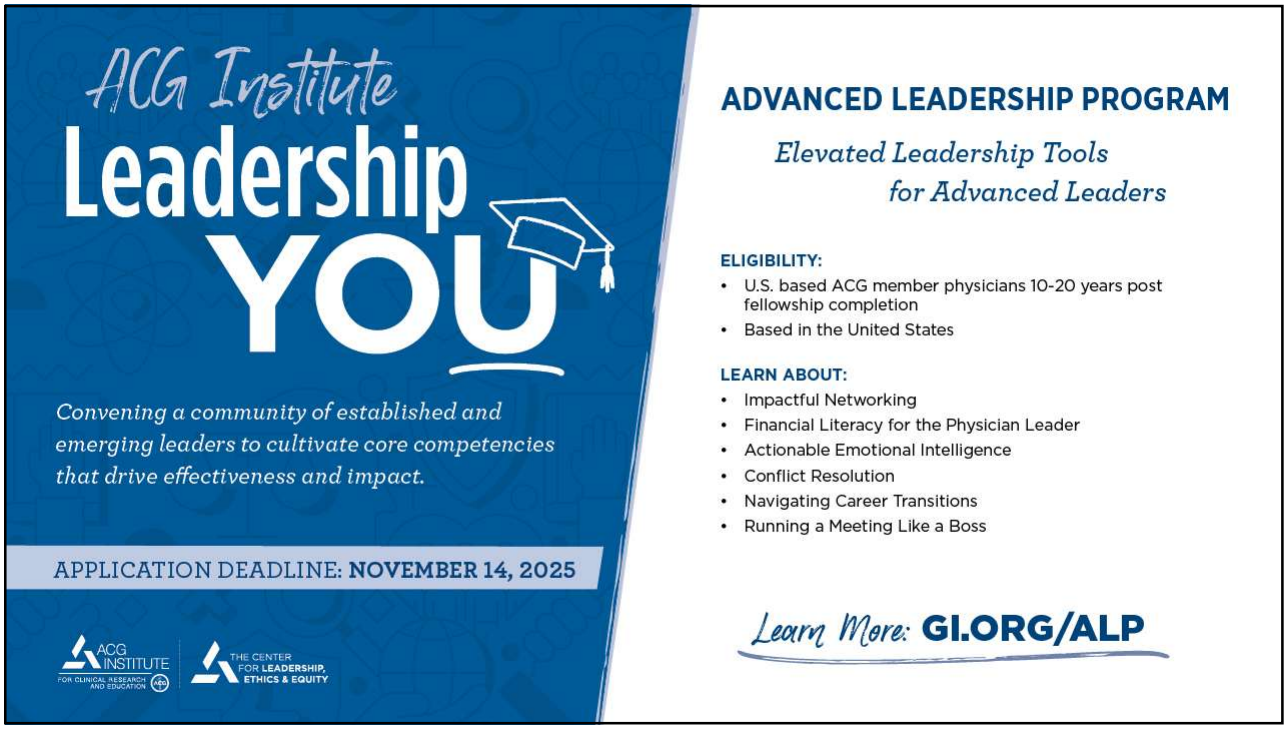
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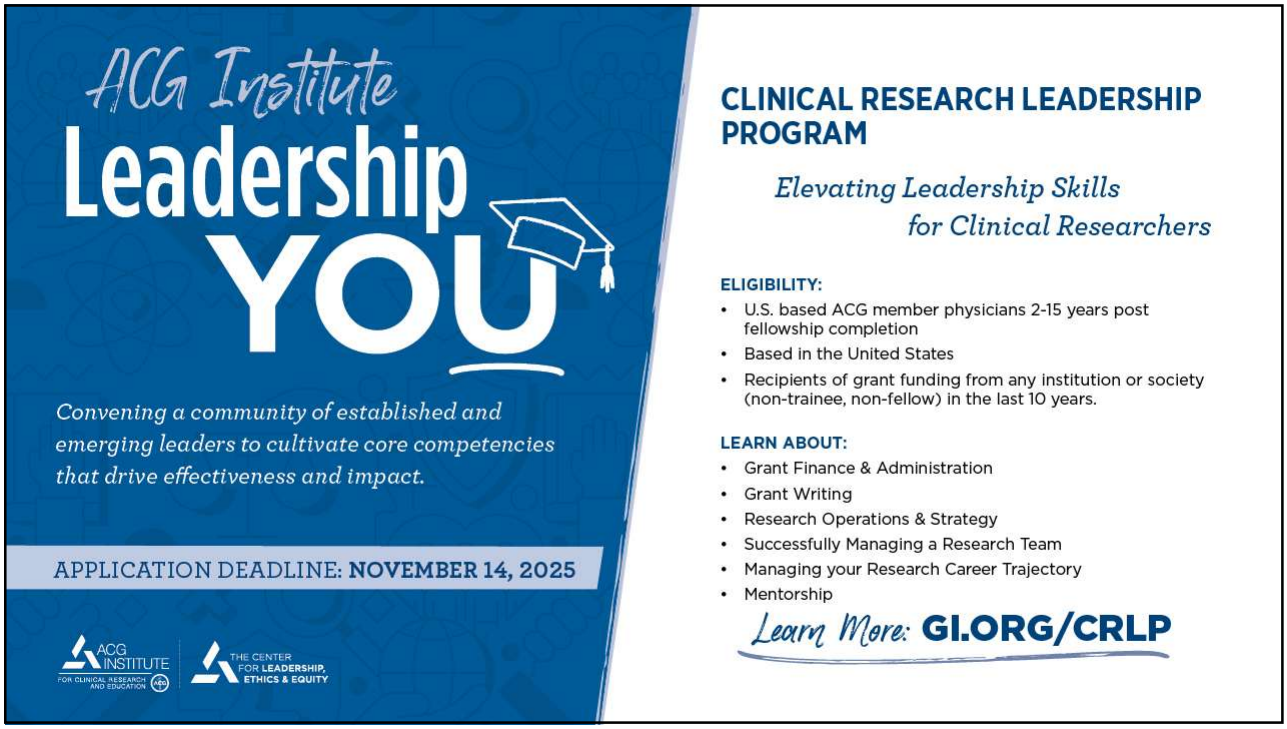
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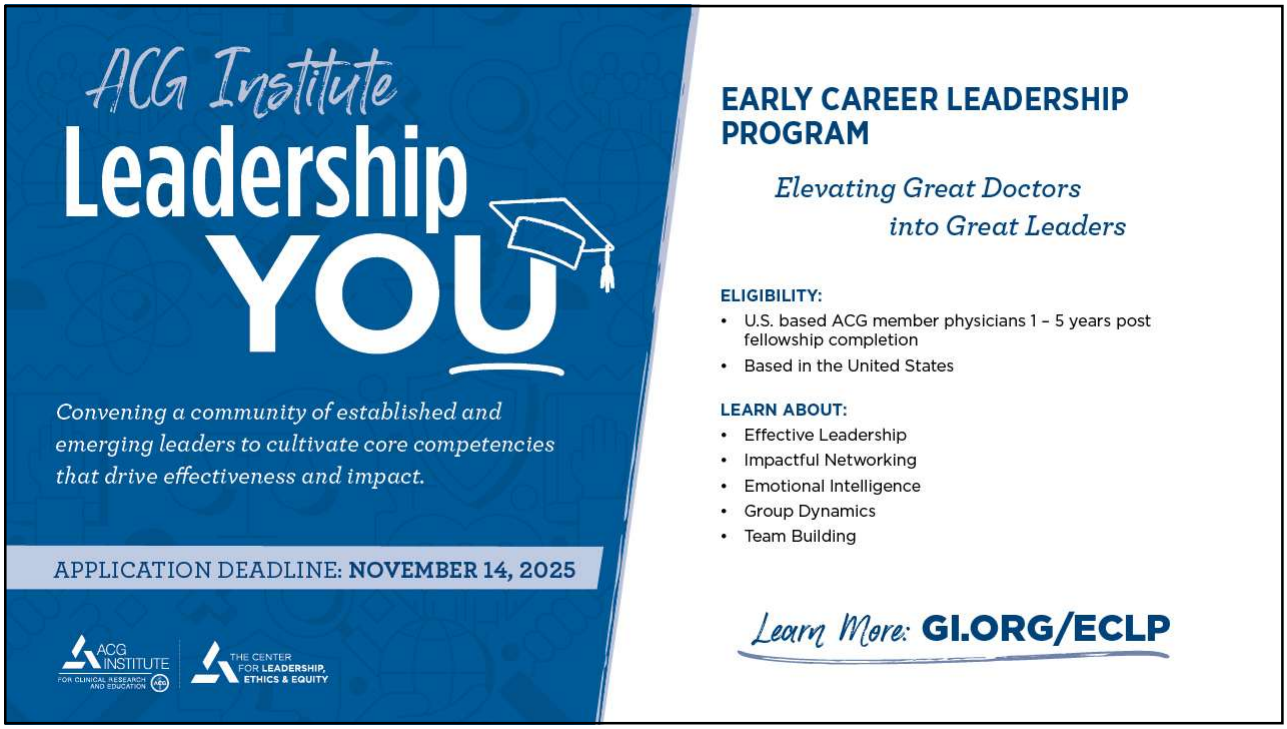
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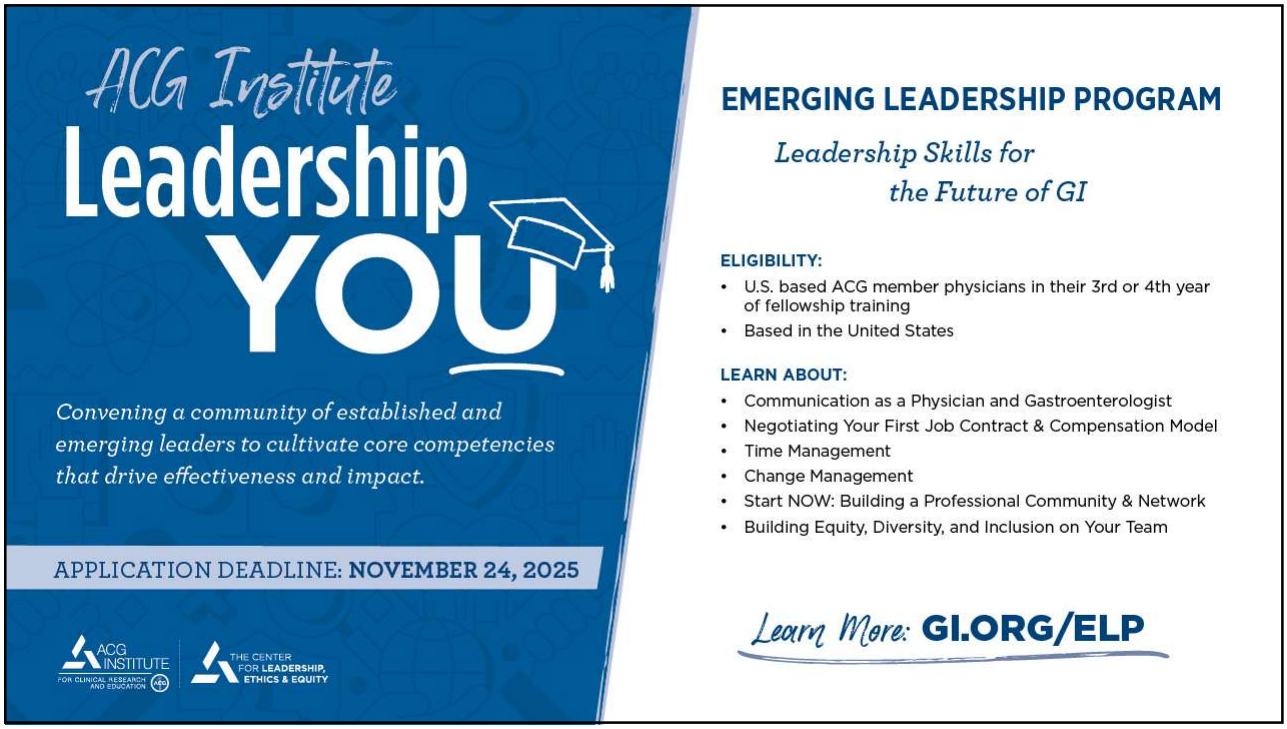
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NOTE: Must complete Prequalification Form (bit.ly/33guW6k) by November 3rd

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Participating in the Webinar

All attendees will be muted and will remain in "Listen Only Mode"

Type your questions here so that the moderator can see them.
Not all questions will be answered but we will get to as many as possible.

A handout with the slides and room to take notes can be downloaded from your control panel.


Moderator:
Gautam Naresh Mankaney, MD, and
Julie Yang, MD, FACG

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ACG Virtual Grand Rounds

Join us for upcoming Virtual Grand Rounds!


Week 40 – Thursday October 2, 2025
Short Bowel Syndrome: Maximizing Management to Convert Intestinal Failure to Intestinal Insufficiency
Faculty: Shirley C. Paski, MD
Moderator: John K. DiBaise
At Noon and 8pm Eastern


Week 41 – Thursday October 9, 2025
ACG Clinical Guideline: Management of Crohn's Disease in Adults
Faculty: Gary R. Lichtenstein, MD, FACG
Moderator: Edward V. Loftus, Jr., MD, FACG
At Noon and 8pm Eastern

Visit **gi.org/ACGVGR** to Register

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Disclosures

Katharine Germansky, MD:
Exact Sciences: Grant/Research Support;
Freenome:Grant/Research Support.

Gautam Naresh Mankaney, MD:
No relevant financial relationships with ineligible companies.

Pooja Dharwadkar, MD:
No relevant financial relationships with ineligible companies.

Julie Yang, MD, FACG:
Cook: Consultant; Interscope: Consultant; Olympus: Consultant; Steris: Consultant.

**All of the relevant financial relationships listed for these individuals have been mitigated*

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Updates in Chemoprevention: Lynch Syndrome

ACG-CGA Joint Webinar
Katharine Germansky, MD
September 25, 2025
Hereditary Cancer Week

Beth Israel Lahey Health
Beth Israel Deaconess Medical Center

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Objectives

1. Establish the importance of an ideal chemoprevention agent in Lynch syndrome (LS)
2. Review current data behind chemoprevention in Lynch syndrome
3. Highlight factors to consider when discussing chemoprevention for patients with Lynch syndrome

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Outline

- Importance of Chemoprevention in Lynch Syndrome
- Aspirin as Chemoprevention for CRC in Lynch Syndrome
- Promising Agents for CRC Chemoprevention
- Supplements
- Chemoprevention for Extracolonic Cancers
- GLP1s

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Chemoprevention

Noun…"the use of a synthetic or natural substance to decrease the risk of cancer developing, delay the time of cancer onset, or to reverse the carcinogenesis process"

Chemoprevention in LS is important:

--Elevated CRC risk

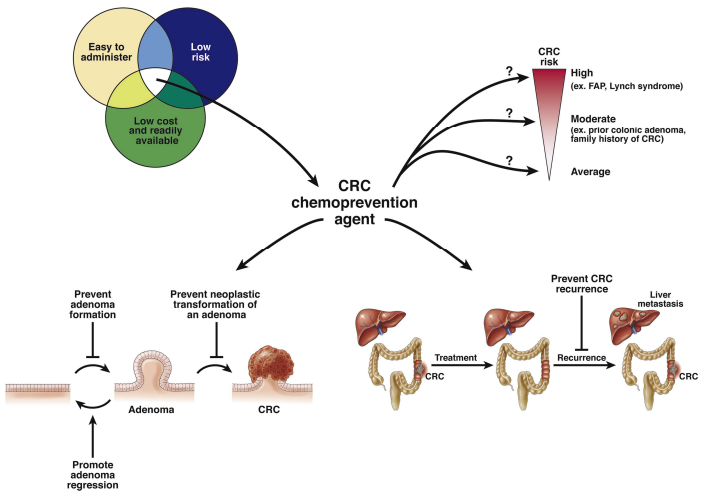
--Colonoscopies have limitations and require adherence

--Current long wait times

--CRC is 2nd most common cancer/significant global health burden

--1/6 sporadic cases share same molecular mechanism of MMR deficiency

--LS cancers can bypass the precursor adenoma phase/rapid interval tumors



Katona & Weiss, Gastro 2020

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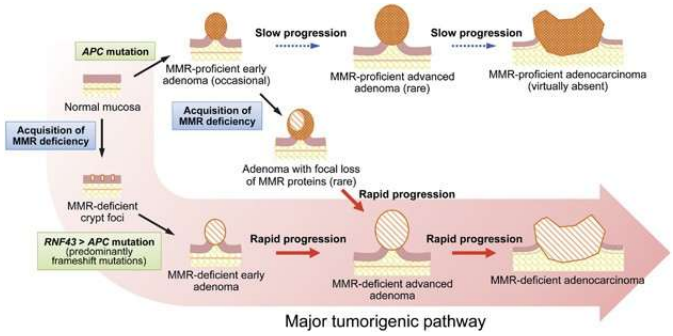
Challenges in chemoprevention

- Lengthy large trials required
- Significant financial cost
- Choice of endpoint
  - Adenoma
    - Easier, shorter trials
  - Abnormal crypt foci
    - Variable rates of detection
    - Unclear translation to CRC risk
  - CRC
    - Clinically most significant
    - Longer trials required
    - Subjects may modify their own risk



Katona & Weiss, Gastro 2020
Sekine et al, Mod Pathol 2017

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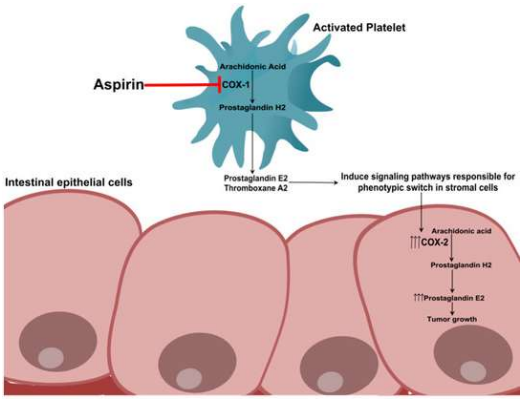
Aspirin as Colorectal Cancer Chemoprevention: Multimodal Mechanism

- Irreversible inhibition of COX-1 in platelets and COX2 in colorectal epithelial and stromal cells
  - Reduced prostaglandin synthesis (PGE2)
  - Decreases inflammation, cell proliferation, angiogenesis
  - Promotes apoptosis
- Inhibits platelet activation by suppressing thromboxane A2
- Reduces platelet derived growth factors key in colorectal tumorigenesis



https://doi.org/10.3390/ijms21239018

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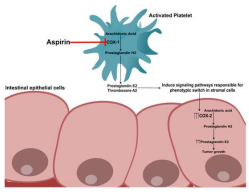
Aspirin as CRC Chemoprevention: Investigations

- 1988: first report of a case control study with fewer CRC cases in those taking ASA
- 2007: Cancer Prevention Study II Nutrition Cohort: ASA 325mg x5y with decreased CRC risk
- 2010: Long term follow up of CV trials note 21% reduction in CRC mortality in ASA arms >5y
- 2013: Women's Health Study: 18% reduction in CRC risk after 10 years of qod ASA 100mg

Cao et al, JAMA Onc 2016
Friis et al, Ann Intern Med 2015
Giovannucci et al, NEJM 1995
Jacobs et al, J Natl Cancer Inst 2007
Katona & Weiss, Gastro 2020
Kune et al, Cancer Res 1988
Rothwell et al, Lancet 2010



https://doi.org/10.3390/ijms21239018

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Aspirin as Colorectal Cancer Chemoprevention in Lynch Syndrome: Colorectal Adenoma/carcinoma Prevention Program: CAPP2

- **Design**
  - First large **genetically targeted trial in LS**
  - Only placebo-controlled RCT of ASA with CRC as the primary end point
  - 861 LS 600mg/d v placebo x2 years
  - Mean age 42
- **Results**
  - **2008**: no significant difference in incident CRC/adenomas after mean 25m
  - **2011**: significantly less CRC on PPA only w/HR 0.41 after mean of 55.7m when first enrolled reached 10y

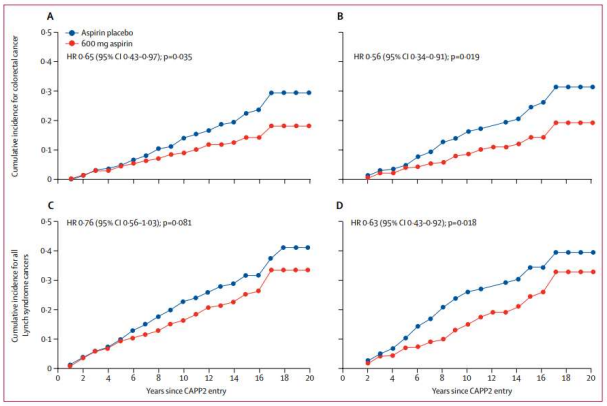

Figure 2: Time to first colorectal cancer and time to any Lynch syndrome cancer in all CAPP2 study participants followed up for 10 years and for 20 years in England, Finland, and Wales
Cox proportional hazards (HRs and 95% CIs) comparing those on aspirin *vs* those on placebo and depicted by Kaplan-Meier analysis (n=861). (A) Intention-to-treat analysis (n=427 aspirin, 434 placebo) by randomisation group. (B) Per-protocol analysis of all those achieving 2 years aspirin or placebo (n=259 aspirin; n=250 placebo). (C) Intention-to-treat analysis for any Lynch syndrome cancer. (D) Per-protocol analysis for any Lynch syndrome cancer. See appendix (p 16) for more details.

Burn et al, Lancet 2020

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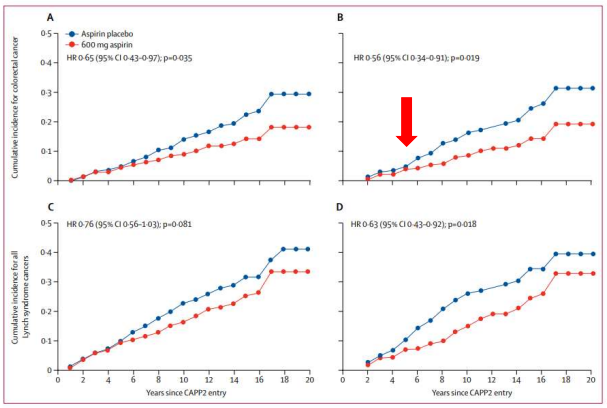

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Burn et al, Lancet 2020

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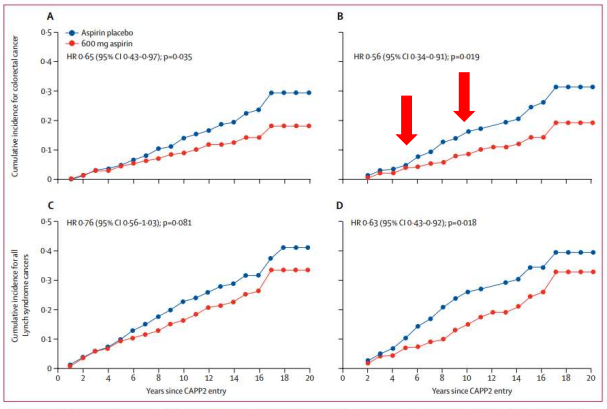

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Burn et al, Lancet 2020

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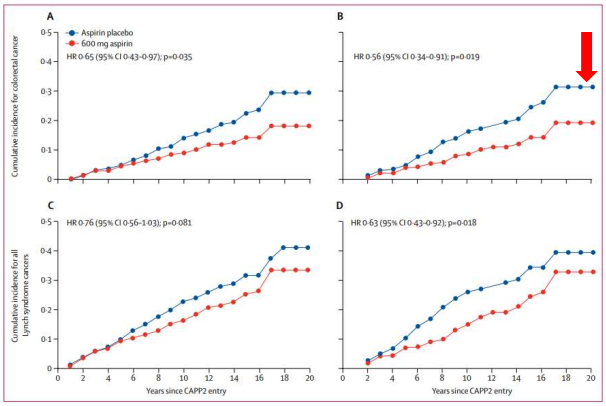
Aspirin as Colorectal Cancer Chemoprevention in Lynch Syndrome: Colorectal Adenoma/carcinoma Prevention Program: CAPP2

- 2020 preplanned secondary analysis after all pts reached 10y f/u
  - Robust reduction in CRC
    - HR 0.65 ITT
    - HR 0.56 PPA
    - NNT 24
  - Delayed effect: Benefit emerged after 5y
  - Legacy effect: sustained reduction in CRC incidence for >20y in those taking daily ASA (mean 25m)
  - Rare AE's, no sig increase in ASA group



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Burn et al, Lancet 2020

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Aspirin as Colorectal Cancer Chemoprevention in Lynch Syndrome: Cancer Prevention Program 3 Study: CaPP3

- **Design**
  - Dose noninferiority trial comparing 100 mg, 300mg, and 600 mg of daily aspirin for CRC prevention
  - 1866 LS pts randomized
  - Nick James 001
- **Results** not yet published
  - "The lowest dose works just as well as the larger doses" - Sir John Burn

Nick James, photo courtesy of BBC news 24 June 2025

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Aspirin as Colorectal Cancer Chemoprevention in Lynch Syndrome: AAS-Lynch

- **Design**
  - Prospective RCT
  - 3000 LS patients from 34 French specialist institutes
  - Placebo versus ASA 100mg or 300mg
  - Primary endpoint: colorectal adenoma occurrence and recurrence
  - Data collection: high quality colonoscopy details, ASA compliance, nutrition habits, microbial stool analysis
- Estimated date of primary completion: 12/2024

Table 2 Research timeline

	V0, inclusion	V1, M0	V2, M6	V3, M12	V4, M18	V5, M24	V6, M30	V7, M36	V8, M42	V9, M48
Protocol information	X									
Informed consent	X									
Antecedent	X									
Clinical exam	X		X	X	X	X	X	X	X	X
Blood analysis	X									
Chromo-colonoscopy	X (< 6 months)			If necessary		X	If necessary			X
Stool collection		X								X
Nutritional survey	X	X								
Physical activity survey	X	X								
Quality of life survey		X								X
Blood drops blotting paper		X								
Pregnancy test		X	X	X	X	X	X	X	X	X
Randomization		X								
Treatments dispensation		X	X	X						
Adverse effects			X	X	X	X	X	X	X	X
Compliance observation			X	X	X	X	X	X	X	X

Soualy et al, Trials 2020

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Aspirin as CRC Chemoprevention in LS: Current International Guidelines

Society	Recommendation
NCCN	Consider ASA use based on individual risk assessment
ACG	Insufficient evidence
ASCO	Consider ASA use in LS Insufficient evidence
BSG/ACPGBI/UKCGG	Advise that daily ASA reduces CRC risk and offer research opportunities for ASA dosing discovery
CCA	Start ASA at time of first colonoscopy
ESDO	Critical discussion of CAPP2 trial data
EHTG/ESCP	≤75-100mg ADA/d, increase with >BMI
FDA	No recommendation
NICE	Consider daily ASA for >2y
USMSTF	Consider ASA use based on individual risk assessment and discussion of treatment uncertainties

Adapted from Mraz et al, Front Oncol 2023

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Aspirin as CRC Chemoprevention in LS: Decision Considerations

Variable	Pros	Cons	Reference
Age	<65	>70, ASPREE trial	McNeil et al, NEJM 2018
Sex	M/F	Childbearing/desired pregnancy	
Genotype	MLH1, MSH2, MSH6	PMS2	
Family History	CRC		
Cancer history	Previous CRC	Proctocolectomy	
Helicobacter pylori	Negative	Positive	
Gastric ulcer/GI bleeding risk	Treat HP, use PPI	HP, Age 0.1% excess per year of use	Sir John Burn
Allergy	No	NSAID hypersensitivity	
CV risk	≥ 10%		
HTN history	Controlled	Uncontrolled	
Use of blood thinners	None	Yes	
Intracranial bleed risk	Reduced thrombotic events	0.01% excess per year of use	Hansson et al, Lancet 1998

Adapted and edited from Serrano et al, Genes (Basel) 2022

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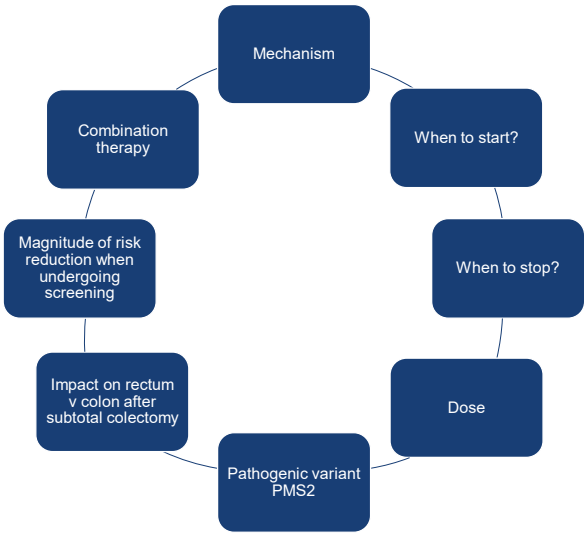
Aspirin as CRC Chemoprevention LS: Summary & Outstanding Questions

- **Low dose aspirin is safe and effective at reducing CRC risk in patients with Lynch syndrome**



Movahedi et al, J Clin Oncol 2015

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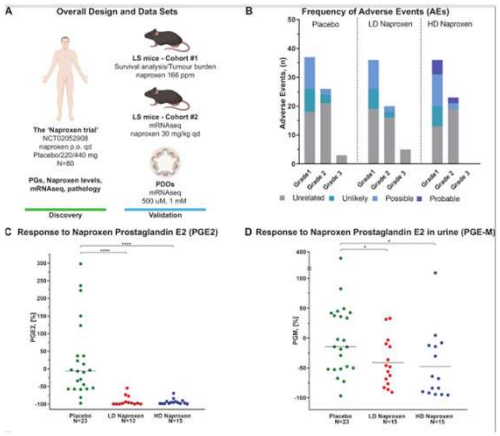
Naproxen as CRC Chemoprevention in LS: Competitive COX1/2 inhibition

- **Naproxen Study design:**
  - Phase 1B placebo controlled RCT in LS of high 440mg and low 220mg dose naproxen for 6m to 80 LS pts and genetically engineered mouse model of LS and patient-derived organoids
- **Results**:
  - Safe primary chemoprevention with no difference in AE's
  - Reduced PGE2 in colorectal tissue
  - Promotes colonic T cell proliferation and activation of resident cytotoxic lymphocytes
  - Modulated tumor growth while prolonging survival in mouse model
- **Next steps:**
  - Clarify mechanism, who responds and ideal dosing
  - Potential combination therapy ie neoantigen vaccines with naproxen as immune stimulant



Reyes-Uribe et al, Gut 2021
Bowen et al, Front Immunol 2023

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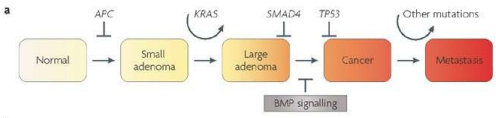
Statins as CRC Chemoprevention

- **Study Design**
  - Dutch population based study of pharmacy data and colorectal cancers
- **Results**
  - Reduced CRC incidence
  - Controlled for BB use to account for higher rates of CRC in CV disease pts
  - Unable to factor in tobacco, ASA/NSAID, BMI confounders
- **Less SMAD4 positive CRC**
  - High SMAD4 expression is found in in tumors with MSI and hypermethylated tumors (CIMP)
  - Effect in later stages of adenoma to carcinoma sequence



https://media.springernature.com/lw685/springer-static/image/art%3A10.1038%2Fnrc2467/MediaObjects/41568_2008_Article_BFnrc2467_Fig4_HTML.jpg

Ouahoud et al, Br J Cancer 2021

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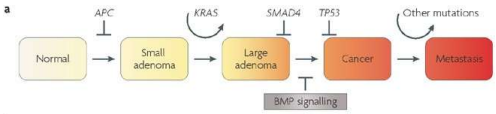

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Completed

Atorvastatin ± Aspirin in Lynch Syndrome Syndrome

ClinicalTrials.gov ID NCT04379999

Sponsor Fox Chase Cancer Center

Information provided by Fox Chase Cancer Center (Responsible Party)

Last Update Posted 2025-08-07

Ouahoud et al, Br J Cancer 2021

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Supplements as CRC Chemoprevention

- **Study Design**:
  - 1966 international **LS** pts from the Colon Cancer Family Registry from 1997-2012
- **Results**
  - Decreased CRC risk with MVI >3y HR 0.47 (95% CI 0.32-0.69) v never users
  - Decreased CRC risk with calcium >3y HR 0.42 (95% CI 0.23-0.74) v never users
  - More common in women and older ages
  - Adjusted for BMI, red meat, fruit and veggie intake
  - Not affected by country of recruitment, ascertainment method, mutated gene, sex or site of colorectal cancer
- **Study limitations**
  - Recall bias, dose and preparation variability, survival and selection bias, impact of vitamin D

Chau et al, Int J Epidemiol 2016

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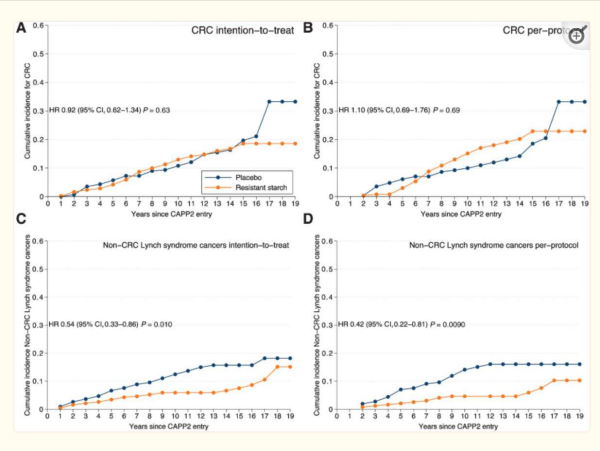
Chemoprevention in Upper GI Cancer

- **CAPP2: 30g resistant starch sachet daily v placebo x2y**
  - Dietary fiber which produces short chain fatty acids incl butyrate via colonic fermentation
  - Significant reduction in non CRC incidence, most in upper GI cancers
  - Protective legacy effect for up to 20y



Mathers et al, Cancer Prev Res (Phila). 2022
https://www.idealnutrition.com.au/podcast/ep51/

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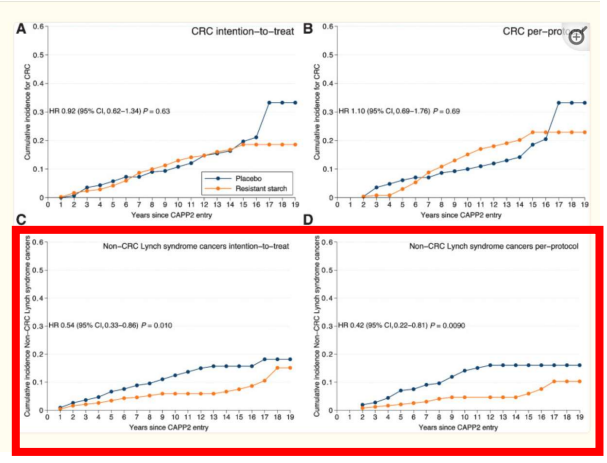

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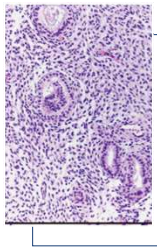
Chemoprevention in Uterine Cancer

Picture from medpagetoday.com

Aspirin

- Fewer endometrial cancers seen in the group taking ASA 600mg/d in CAPP2, although not statistically significant



Hormonal therapy

- Reduction in endometrial epithelial proliferation and histologic changes consistent with decreased cancer risk seen with progestin containing oral contraceptives, Depo-Provera, and levonorgestrel IUD in LS patients
- Prolonged use (>5y) of OCP's is associated with a significant reduction in endometrial cancer risk
- No RCT's with cancer incidence endpoints in LS

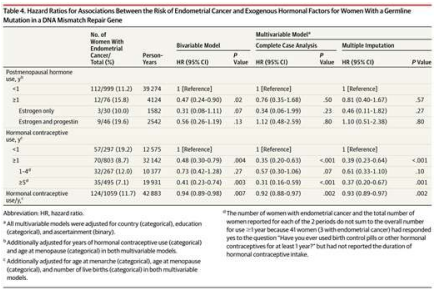


Table 4. Hazard Ratios for Associations Between the Risk of Endometrial Cancer and Exogenous Hormonal Factors for Women With a Germline Mutation in a DNA Mismatch Repair Gene

	No. of Women With Endometrial Cancer/ Total (%)	Person-Years	Bivariable Model HR (95% CI)	P Value	Multivariable Model[a] Complete Case Analysis HR (95% CI)	P Value	Multiple Imputation HR (95% CI)	P Value
Postmenopausal hormone use, y[b]								
<1	112/999 (11.2)	39 274	1 [Reference]		1 [Reference]		1 [Reference]	
≥1	12/76 (15.8)	4124	0.47 (0.24-0.90)	.02	0.76 (0.35-1.68)	.50	0.81 (0.40-1.67)	.57
Estrogen only	3/30 (10.0)	1582	0.31 (0.08-1.11)	.07	0.34 (0.06-1.99)	.23	0.46 (0.11-1.82)	.27
Estrogen and progestin	9/46 (19.6)	2542	0.56 (0.26-1.19)	.13	1.12 (0.48-2.59)	.80	1.10 (0.51-2.38)	.80
Hormonal contraceptive use, y[c]								
<1	57/297 (19.2)	12 575	1 [Reference]		1 [Reference]		1 [Reference]	
≥1	70/803 (8.7)	32 142	0.48 (0.30-0.79)	.004	0.35 (0.20-0.63)	<.001	0.39 (0.23-0.64)	<.001
1-4[d]	32/267 (12.0)	10 377	0.73 (0.42-1.28)	.27	0.57 (0.30-1.06)	.07	0.61 (0.33-1.10)	.10
≥5[d]	35/495 (7.1)	19 931	0.41 (0.23-0.74)	.003	0.31 (0.16-0.59)	<.001	0.37 (0.20-0.67)	.001
Hormonal contraceptive use(s),[e]	124/1059 (11.7)	42 883	0.94 (0.89-0.98)	.007	0.92 (0.88-0.97)	.002	0.93 (0.89-0.97)	.002

Abbreviation: HR, hazard ratio.

[a] All multivariable models were adjusted for country (categorical), education (categorical), and ascertainment (binary).

[b] Additionally adjusted for years of hormonal contraceptive use (categorical) and age at menopause (categorical) in both multivariable models.

[c] Additionally adjusted for age at menarche (categorical), age at menopause (categorical), and number of live births (categorical) in both multivariable models.

[d] The number of women with endometrial cancer and the total number of women reported for each of the 2 periods do not sum to the overall number for use ≥1 year because 41 women (3 with endometrial cancer) had responded yes to the question "Have you ever used birth control pills or other hormonal contraceptives for at least 1 year?" but had not reported the duration of hormonal contraceptive intake.

Dashti et al, JAMA 2015
Lu et al, Cancer Prev Res (Phila) 2013

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Chemoprevention in Ovarian Cancer

Photo credit: fertilityfamily.co.uk

OCP's

50% risk reduction in women at increased genetic risk, extrapolated from BRCA1/2 data

Protective effect increases with duration of use, and persists after termination

Balanced with individualized risk of breast cancer, clots

Photo credit:.Getty Images

Metformin

Lower risk of ovarian cancer incidence and mortality compared with non-use or use of other glucose control agents in DM

Risk reduction correlates with cumulative dose and duration

Risk reduction found in Asians

Investigational

Iodice et al, Eur J Cancer 2010
Havrilesky et al, Obstet Gynecol 2013
Wen et al, Eur J Obstet Gynecol Reprod Biol 2019

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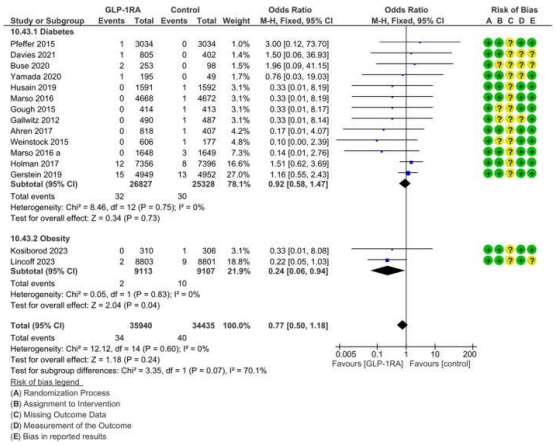
GLP-1RAs as Chemoprevention in Obesity and Diabetes

1. Retrospective cohort study from TriNetX US Research Network
   - Reduction in GI cancer risk in patients with DM2
   - Highest reduction with obesity and MASLD
2. Meta analysis of RCT's of GLP-1's to any comparator for DM and/or obesity lasting at least 52wks
   - Reduction in uterine cancer risk in patients with obesity, not DM
   - Increase in CRC in short term trials



Dai et al, JAMA Oncol 2025
Kuo et al, Diabetologia 2025
Maier et al, Diabetologia 2025
Silverii et al, Diabetes Obes Metab 2025

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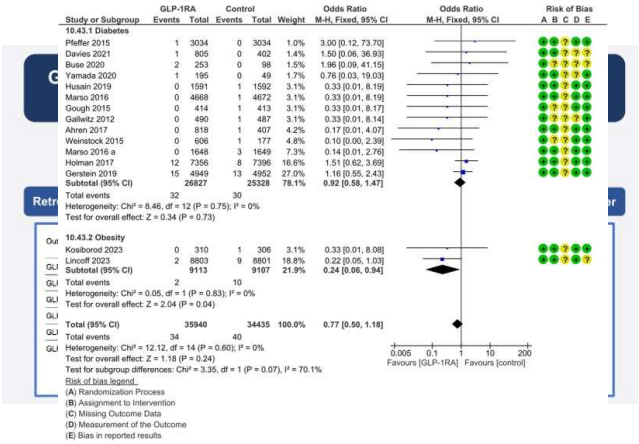

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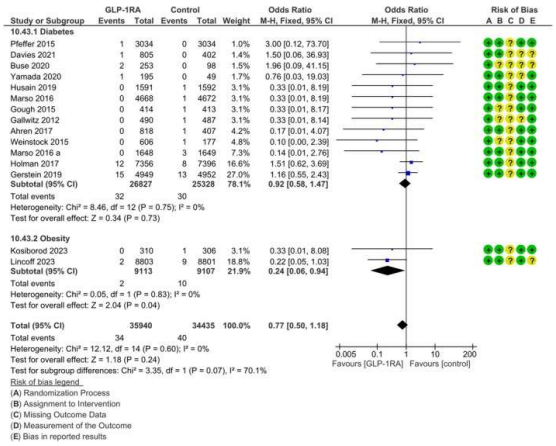

Dai et al, JAMA Oncol 2025
Kuo et al, Diabetologia 2025
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Silverii et al, Diabetes Obes Metab 2025

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Take Home Points

- Chemoprevention trials can be challenging to design and execute
- Lynch syndrome patients would dramatically benefit from genetically targeted chemoprevention agents given cancer mechanism and incidence
- Low dose aspirin is safe and very effective in reducing elevated CRC risk in LS after individualized risk assessment
- No downside to calcium, multivitamins and resistant starch
- Hope for naproxen and statins for both LS and CRC at large
- Hormonal therapy is used for gynecologic cancer risk reduction, but LS specific trials are lacking

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Chemoprevention Strategies in Familial Adenomatous Polyposis

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San Francisco

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Objectives

- Briefly review familial adenomatous polyposis epidemiology, clinical manifestations, and management and surveillance recommendations
- Discuss the goals of chemoprevention in FAP
- Evaluate currently available chemoprevention agents
- Analyze current trends in chemoprevention in FAP

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Familial adenomatous polyposis

- Most common adenomatous polyposis syndrome
  - 1% of all CRC diagnoses
  - Prevalence 3 in 10,000 people
- Germline variants of *APC* gene
  - Inherited in *autosomal dominant* pattern – diagnosis by identification of heterozygous pathogenic variant in *APC* gene
  - Up to 25% of pathogenic variants occur *de novo* without a known family history of FAP or FAP-related cancers
  - Inter- and intra-family variability in phenotype can be common

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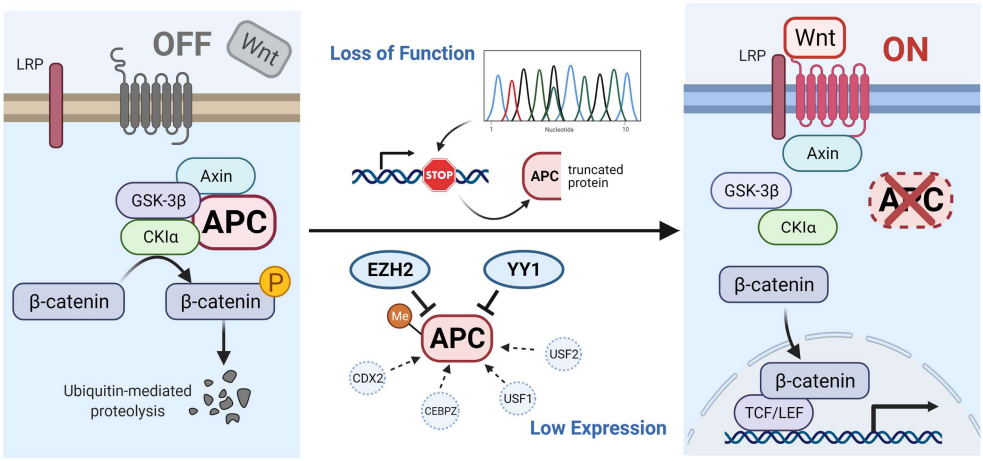
Familial adenomatous polyposis



Zhu et al. *APC* promoter methylation in gastrointestinal cancer. Front Oncol. 2021 Apr. PMID: 33968756

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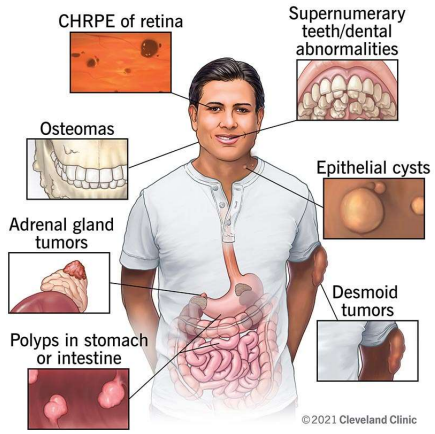
Classical FAP	Attenuated FAP
Hundreds to thousands of cumulative adenomas	Fewer than 100 cumulative polyps (average 30)
Mean age polyp onset 15 y	Mean age polyp onset 44 y
Lifetime risk CRC 95%	Lifetime risk CRC 70%
Mean age CRC in untreated individuals 39 years	Mean age CRC in untreated individuals 50-55 years
Distributed throughout colon, increased rectal polyp burden	Frequent right-sided distribution
Extraintestinal manifestations: congenital hypertrophy of the retinal pigment epithelium (CHRPE), desmoid tumors, osteomas, gastric fundic gland polyps	Fewer/variably present extraintestinal manifestations
Extracolonic malignancy risks: medulloblastoma, papillary thyroid cancer, hepatoblastoma, gastric cancer, duodenal/periampullary cancer	Extracolonic malignancy risks: duodenal/periampullary cancer, papillary thyroid cancer

Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS): *APC* promoter 1B pathogenic variant, >100 gastric polyps in body and fundus, predominantly fundic gland polyps and gastric adenoma. No colorectal or small intestinal polyposis.



Features of FAP/Gardner syndrome; https://my.clevelandclinic.org/health/diseases/22013-gardner-syndrome

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CRC Surveillance Recommendations

Society Guideline (year)	Classical FAP	Attenuated FAP
ACG (2015)	Sigmoidoscopy 10-12 y, repeat every 1-2 y Colonoscopy if older at first screening	Colonoscopy late teens to mid-20s, repeat every 1-2 y
ASGE (2020)	Sigmoidoscopy 10-12 y, repeat every 1-2 y Colonoscopy when polyps are found	Colonoscopy 18-20 y, repeat every 1-2 y
NCCN (2024)	Colonoscopy 10-15 y, repeat every 1 y	Colonoscopy 18-20 y, repeat every 1-2 years
ESGE (2019)	Colonoscopy 12-14 y, repeat every 1-3 y	Colonoscopy 12-14 y, repeat every 1-3 y
BSG/ACPGBI/ UKCGG (2019)	Colonoscopy 12-14 y, repeat every 1-3 y	Colonoscopy 12-14 y, repeat every 1-3 y
JSCCR (2021)	Colonoscopy 10 y, repeat every 1-2 y	Colonoscopy 18-20 y, repeat every 2-3 y

ACG: American College of Gastroenterology; ASGE: American Society of Gastrointestinal Endoscopy; NCCN: National Comprehensive Cancer Network; ESGE: European Society of Gastrointestinal Endoscopy; BSG: British Society of Gastroenterology; ACPGBI: Association of Coloproctology of Great Britain and Ireland; JSCCR: Japanese Society for Cancer of the Colon and Rectum

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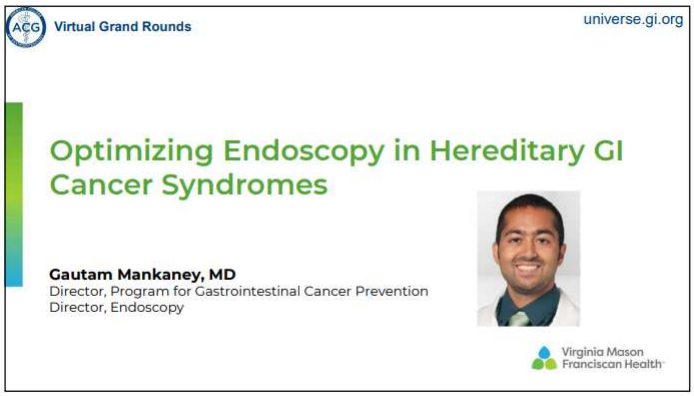
Endoscopic Surveillance and Management



ACG Virtual Grand Rounds September 26, 2024

55

Virtual Grand Rounds

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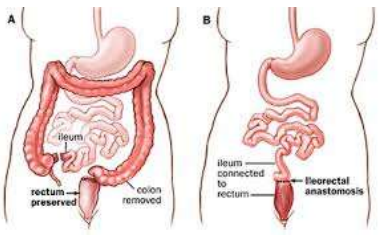
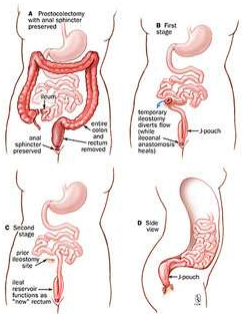
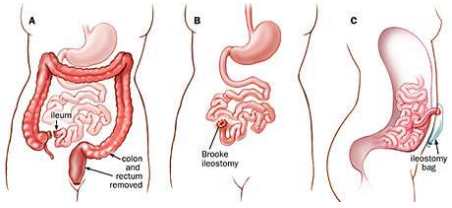
Surgical Management

- Goal is cancer prevention and maintenance of quality of life
  - Consider timing, type of surgery, fertility, risk of desmoid







Sinha et al. *Surgical management of the colorectum in FAP: tailored approaches for optimal outcomes*. Fam Cancer. 2025 Sep.

https://www.hopkinsmedicine.org/health/conditions-and-diseases/lynch-syndrome-treatment

56

Site	Avg age onset	Cumulative Risk	Cumulative Risk General Population (SEER)	Surveillance
Colorectal cancer (without colectomy)	39 y (median)	Approaches 100%	4%	Colonoscopy q1 y starting 10-15 y
Rectal/pouch cancer (post colectomy)	Rectal s/p IRA: 46-48 y Pouch s/p IPAA: ?	Rectal s/p IRA: 10-30% Pouch s/p IPAA: <1-3%	4%	6-12 months after surgery Rectal s/p IRA: endoscopy q6-12 m Pouch s/p IPAA: endoscopy q1 y
Duodenal or periampullary cancer	50-52 y	<1 – 10%	n/a	EGD w/ ampulla visualization starting 20-25 y *or before colectomy*, surveillance based on findings
Gastric cancer	52-57 y	0.1 – 7.1%	0.8%	As above
Small bowel cancer (distal to duodenum)	43 y	< 1%	0.3%	Consider if advanced duodenal polyposis
Intra-abdominal desmoid	31-33 y	10 – 24%	n/a	Imaging based on exam and symptoms
Thyroid cancer	26-44 y	1.2 – 12%	1.2%	US late teens, repeat q2-5 y (shorter interval if +FHx)
Hepatoblastoma	18-33 m	0.4 – 2.5%	n/a	Consider Abd US and AFP q3-6 m age 0-5 y
CNS	18 y	1%	0.6%	Imaging based on symptoms

NCCN Guidelines Version 1.2025 – Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric, Section: Familial Adenomatous Polyposis. June 13, 2025. Accessed 9/2025. https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

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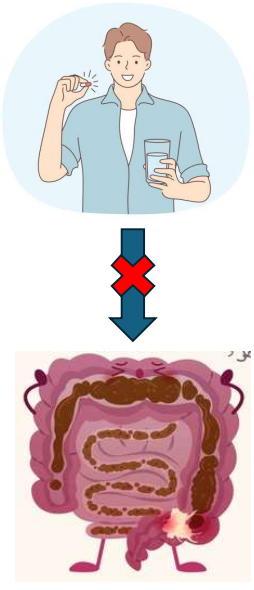
Chemoprevention?

- Goals:
  - Reduce CRC incidence and mortality
  - Prevent disease progression
  - Postpone surgical management
  - Extracolonic disease?
- Ideal agents:
  - Mechanism of action
  - Safe, tolerated for a long period of time
  - Durable and clinically meaningful effect
- Society recommendations



Bohan et al. *Chemoprevention in familial adenomatous polyposis: past, present, and future*. Fam Cancer. 2020 Jun.

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Chemoprevention in FAP

- 1981: Pollard and Luckert find that indomethacin decreases number of intestinal tumors in rats
- 1983: Waddell and Loughry publish case report of four members of a Gardner's syndrome family treated with indomethacin or sulindac after subtotal colectomy with residual rectal polyposis
  - Indomethacin therapy was ineffective in one patient
  - Sulindac therapy effective in almost complete disappearance of rectal polyps in 3 patients

Pollard and Luckert. *Science* 1981 Oct
Waddell WR and Loughry RW. *J Surg Oncol* 1983; 24:83-87

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TABLE I

Sulindac for Polyposis Involving the Rectal Segment After Subtotal Colectomy

Patient	Diagnosis	Sex & Age (yr)	Operation	Date of Operation	Sulindac Start	Sulindac mg/day	Follow-Up (mo)	Number of Polyps Before Treatment	Number of Polyps After Treatment
1	Gardner's syndrome	F, 31	SC, I	4/71	8/78	400	19	10	8
1a	Gardner's syndrome	F, 31	SC, I	4/71	7/80	400	84	8	0
2	Gardner's syndrome	M, 21	SC, I	5/80	7/81	400	62	3	0
3	Gardner's syndrome	M, 42	SC, I	6/66	10/82	300	53	>50	0
4	Gardner's syndrome	F, 16	SC, I	6/86	7/86	300	21	6	1
5	Gardner's syndrome	M, 36	SC, I	7/76	5/81	300	85	6	2
6	Familial polyposis coli	M, 23	SC, I	3/76	12/85	300	25	5 or 6	0
7	Familial polyposis coli	F, 35	SC, I	3/70	11/83	300	21	2	0

I = ileoproctostomy; SC = subtotal colectomy.

TABLE II

Sulindac for Diffuse Polyposis coli in Intact Colons

Patient	Diagnosis	Sex & Age (yr)	Operation	Sulindac Start	Sulindac mg/day	Follow-Up (mo)	Number of Polyps Before Treatment	Number of Polyps After Treatment
1	Gardner's syndrome	M, 19	None	1/84	400	12	>1,000	0
2	Familial polyposis coli	M, 12	None	12/85	150	24	Numerous throughout	3, each less than 7 mm
3	Familial polyposis coli	F, 24	None	5/86	300	21	50	Few, 2 mm
4	Gardner's syndrome	F, 16	None	6/81	300	14	>1,000	3

* Colonoscopies at 6-month intervals were carried out in all four patients.

Waddell et al. *Sulindac for Polyposis of the Colon*. Am J Surg 1989 Jan

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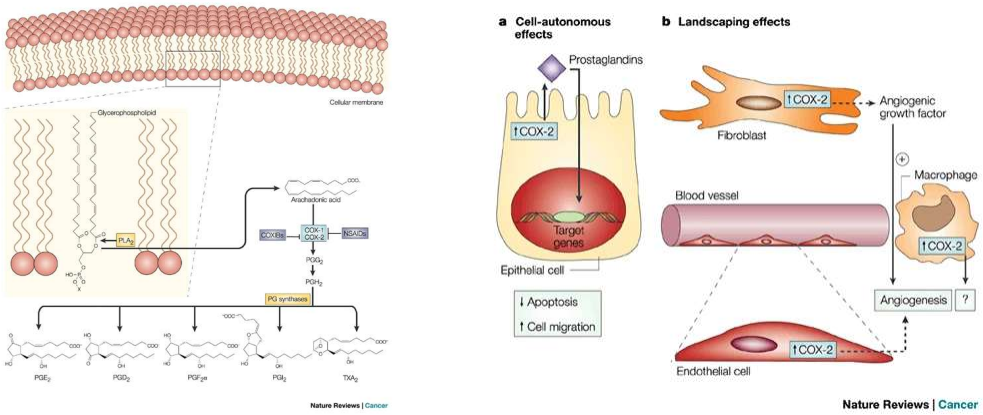
Chemoprevention in FAP – NSAIDs



Gupta RA and RN Dubois. *Colorectal cancer prevention and treatment by inhibition of cyclooxygenase-2*. Nat Rev Cancer 2001 Oct;1(1):11-21

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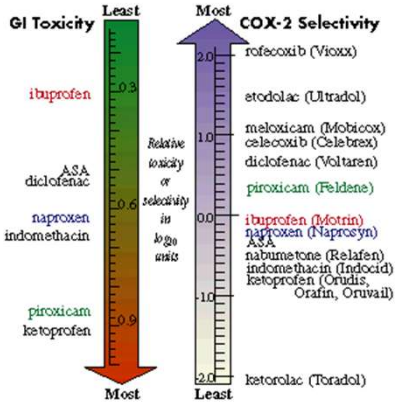
Chemoprevention in FAP – NSAIDs - Sulindac

- Inhibits COX1 and COX2
- 1980s-early 2000s: multiple case series showing regression of adenomas in patients with FAP
  - Heterogeneous cases: some patients post colectomy, others pre-colectomy with significant regression of adenomas
  - 2 case reports of rectal cancer while on sulindac; 1 report of rectal cancer in prospective cohort
- Dose generally 150 mg BID (75 mg BID in younger patients)



https://www.ti.ubc.ca/2001/02/28/selective-cox-2-inhibitors-are-they-safer/

Giardello F. *NSAID-induced polyp regression in familial adenomatous polyposis patients*. Gastroenterol Clin North Am. 1996 Jun;25(2):349-62

62

Study	Design	N	Mean age	Op History	Sulindac Dose	Follow-up time	Results/major adverse effects
Labayle et al (1991)	Randomized crossover	10	? (under 50)	s/p IRA	300 mg/day (maintenance 100-300 mg/d)	4 years	All rectal polyps regressed on 300 mg daily
Giardello et al (1993)	Randomized double blind placebo controlled	22	23.5	18 w/o colectomy	150 mg BID	9 months	44% decrease adenomas; 35% decrease size; no cases of complete regression
Nugent et al (1993)	Randomized double blind placebo controlled	24* With advanced duodenal polyposis	45	At least 5 yrs s/p colectomy	200 mg BID	6 months	Duodenum: 5/12 "improved" compared with 2/12 Rectum: 5/12 "improved" compared with 0/12
Keller et al (1999)	Randomized placebo controlled	21	24	12 w/o colectomy	150 mg BID	3 months	46% decrease rectal polyp number
Giardello et al (2002)	Randomized double blind placebo controlled	41	8-25	**Primary prevention**	75 or 150 mg BID (weight-based)	4 years	No significant difference in number of polyps or size

Labayle et al. *Gastroenterology*. 1991;101:635-9; Giardello et al. *N Engl J Med*. 1993;328:1313-6; Nugent et al. *Br J Surg*. 1993;80:1618-9; Keller et al. *Gut*. 1999;45(6):822-8; Giardello et al. *N Engl J Med*. 2002;346:1054-9.

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Study	Design	N	Mean age	Op History	Sulindac Dose	Follow-up time	Results/major adverse effects
Cruz-Correa et al (2002)	Prospective cohort	12	37.5	s/p IRA	158 mg daily	63.5 months	1 developed stage III rectal cancer at 3 yrs; Regression of polyp burden in all 6/12 with rectal erosions
Latchford et al (2015)	Retrospective On multiple different NSAIDs/doses (indomethacin, sulindac, celecoxib, mixed)	54	36	3 without colectomy		38.5 months	HGD present in 6/54 prior to NSAID initiation, of which 3 developed cancer Additional 1 developed cancer on rx All who developed cancer had decreased polyp burden Reduction in polyp burden 28/50; 22/50 showed no response
Neuhann et al (2022)	Retrospective On sulindac at least 2 yrs prior to study	39 with APC	45.2 (all patients)	25 without surgery (mean age 36)	200-400 mg daily (weight-dependent)	7.4 years (per patient, all patients)	0/25 without prior colectomy required surgery during observation period 30/39 had decrease in colorectal polyp burden 1/25 had increase in polyp burden 4/14 with hx surgery had stable disease 10/28 patients had increase in duodenal polyps; 5/8 patients had decrease in duodenal polyps

Cruz-Correa et al. *Gastroenterology*. 2002 Mar 122(3):641-5; Latchford et al. *Fam Cancer.* 2015 May 14:S47; Neuhann et al. *Fam Cancer*. 2022 Oct 21(4):463-72;

64

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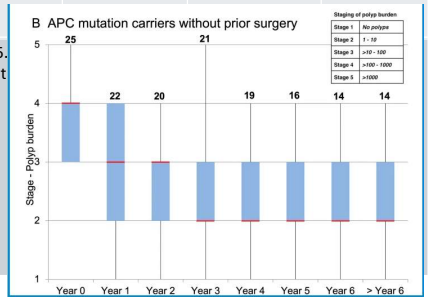

Cruz-Correa et al. *Gastroenterology*. 2002 Mar 122(3):641-5; Latchford et al. *Fam Cancer.* 2015 May 14:S47; Neuhann et al. *Fam Cancer*. 2022 Oct 21(4):463-72;

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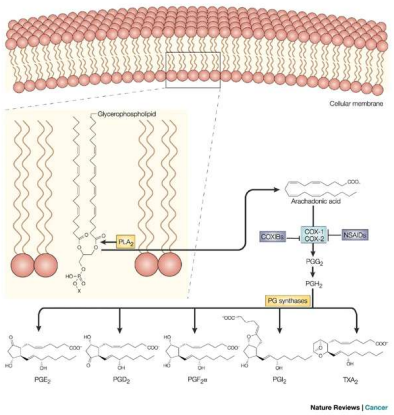
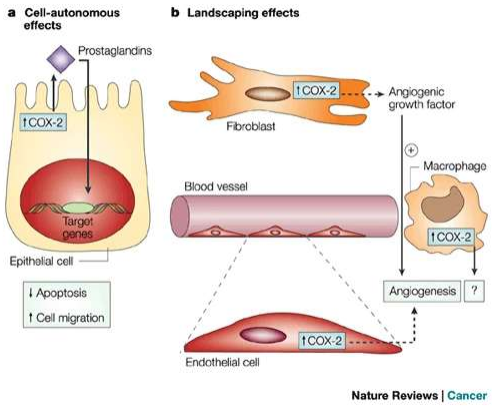
Chemoprevention in FAP – NSAIDs





Gupta RA and RN Dubois. *Colorectal cancer prevention and treatment by inhibition of cyclooxygenase-2*. Nat Rev Cancer 2001 Oct;1(1):11-21

66

Chemoprevention in FAP – Celecoxib

- Selective COX2 inhibitor
- RCT of 77 patients over 6 months: Dose of 400 mg BID had 28% reduction in mean number of polyps compared with placebo
  - 100 mg BID had 11.9% reduction compared with placebo
- Long-term observational study of celecoxib efficacy limited due to difficulty in recruitment and insufficient power
  - But did show relative safety of high-dose celecoxib over median 28.8 months; 6 adverse events (duodenal perforation, rash, abd pain, pancreatitis, upper abd pain)
  - No cardiovascular events
    - Similar studies with rofecoxib concerning for thrombotic events with prolonged use

Steinbach et al. *The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis*. N Engl J Med 2000 Jun;342(26):1946-52.
Huang et al. *Clinical characteristics and outcomes in familial adenomatous polyposis with a long-term treatment of celecoxib: a matched cohort study*. Fam Cancer 2011 Jun;10 (2):303-8.

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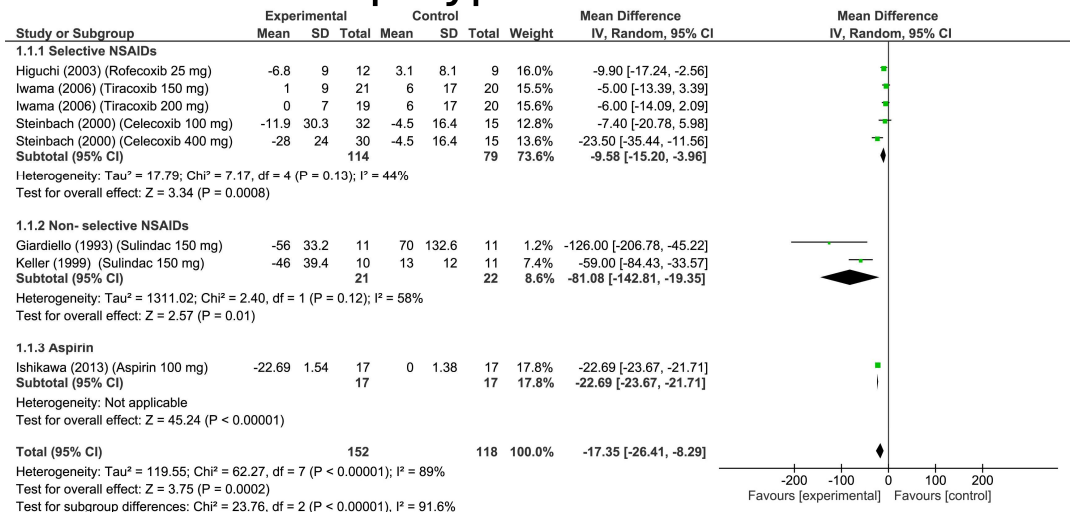
Chemoprevention in FAP – Celecoxib

- FDA approved Celebrex for FAP in 1999 under accelerated approval assuming that the surrogate endpoint of 30% reduction in colorectal polyps is "likely to predict clinical benefit"
  - With recommendation for labeling with strong warning precautions "emphasizing need for unaltered diagnostic procedures, monitoring, and surgical approaches."
  - EMEA approved celecoxib in FAP in 2003
- FDA approval withdrawn in 2012 due to lack of postmarketing study to verify clinical benefit
  - Does it reduce incidence of CRC in FAP patients?
  - Can endoscopic surveillance be less frequent?
  - What is the optimal duration of treatment?
  - What is the optimal timing of treatment?

https://www.accessdata.fda.gov/drugsatfda_docs/nda/99/21156-S007_Celebrex_medr.pdf
https://www.federalregister.gov/documents/2012/06/08/2012-13900/pfizer-inc-withdrawal-of-approval-of-familial-adenomatous-polyposis-indication-for-celebrex

68

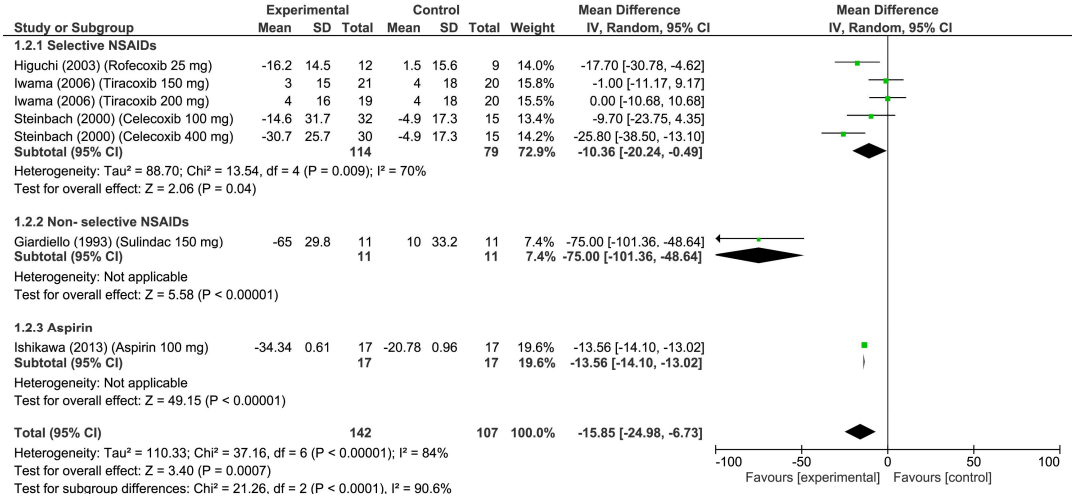
NSAIDs: effect on polyp number



Farooq et al. *NSAIDs for Chemoprevention in Patients with Familial Adenomatous Polyposis: A systematic review and meta-analysis*. Gastro Hep Adv 2023 Jun 10;2(7):1005-1013

69

NSAIDs: effect on polyp size



Farooq et al. *NSAIDs for Chemoprevention in Patients with Familial Adenomatous Polyposis: A systematic review and meta-analysis*. Gastro Hep Adv 2023 Jun 10;2(7):1005-1013

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Chemoprevention in FAP - Eflornithine

- Irreversible inhibitor of ornithine decarboxylase, which is overexpressed in tumor tissue and results in higher mucosal polyamine levels
- 2006 RCT in sporadic colorectal adenomas showed decreased adenoma recurrence in individuals taking difluoromethylorinthine (DFMO) 500 mg daily + sulindac 150 mg daily
- 2015 RCT 112 patients with familial adenomatous polyposis used combination therapy with celecoxib + DFMO compared to celecoxib alone with significant difference in global polyp change, although not adenoma count or adenoma burden

Meyskens FL et al. *Difluoromethylornithine plus sulindac for the prevention of sporadic colorectal adenoma: a randomized placebo-controlled double blind trial*. Cancer Prev Res (Phila). 2008 Jun;1 (1):32-8.
Lynch et al. *An international randomized trial of celecoxib versus celecoxib plus difluoromethylornithine in patients with familial adenomatous polyposis*. Gut 2016 Feb;(65(2):286-95.

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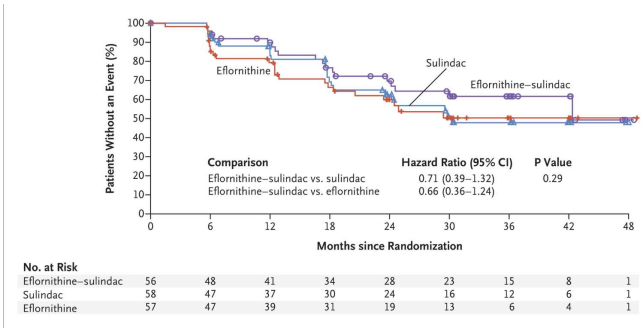
Chemoprevention in FAP - Eflornithine



- Primary end-point disease progression: composite of major surgery, excision of polyp at least 1 cm in retained rectum or pouch, HGD in rectum or pouch, or duodenal disease progression 1 stage in Spigelman classification
  - Major surgery: colectomy, proctocolectomy, duodenal polyp or ampullary excisions, duodenectomy, Whipple procedure, or pouch or retained rectum resection

Burke et al. *Eflornithine plus sulindac for prevention of progression in familial adenomatous polyposis.* N Engl J Med 2020;383:1028-39.

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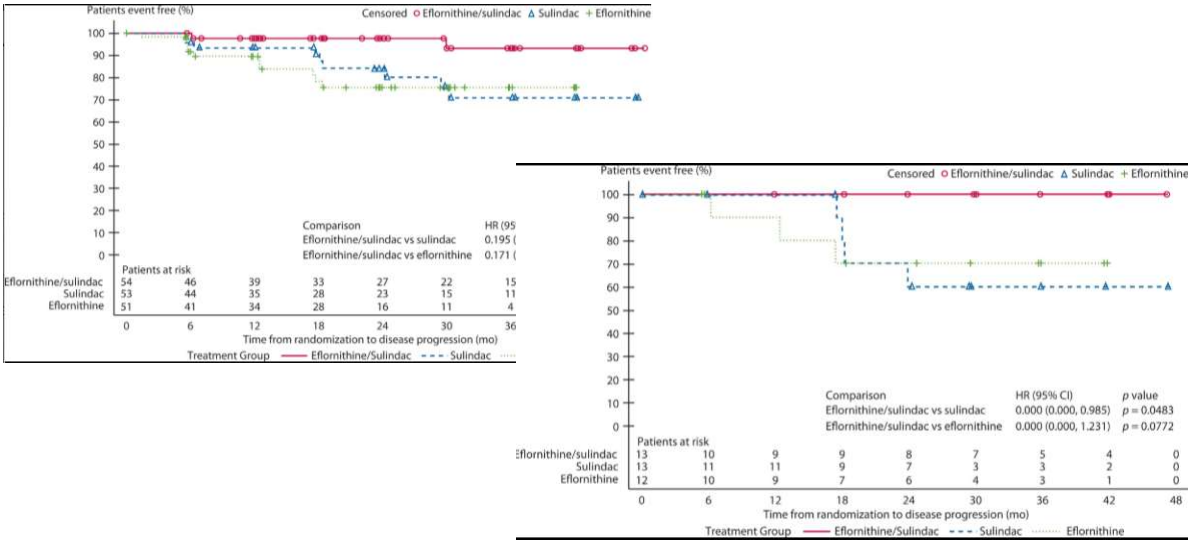
Chemoprevention in FAP - Eflornithine



Balaguer et al. *Combination of sulindac and eflornithine delays the need for lower gastrointestinal surgery in patients with familial adenomatous polyposis: post hoc analysis of a randomized clinical trial*. Dis Colon Rectum 2022 Apr 1;65(4):536-45.

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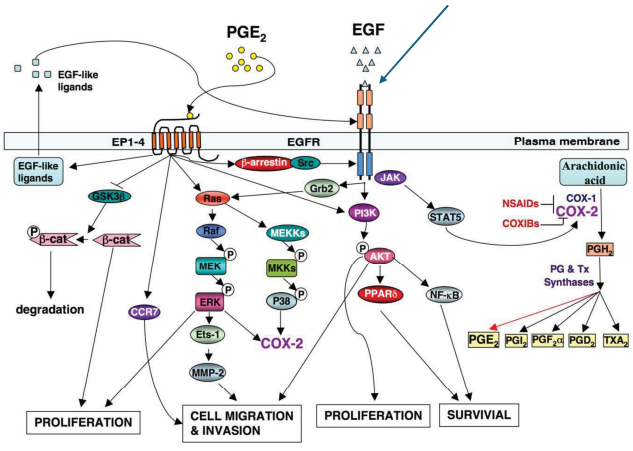
Chemoprevention in FAP - Erlotinib

- Tyrosine kinase inhibitor reversibly binding ATP-binding site of epidermal growth factor (EGFR)
  - EGFR signaling promotes COX2 expression and subsequent intestinal neoplasia
- FDA approved 2004 for NSCLC therapy, but promising results in many other cancers



Wang et al. *The crosstalk of PTGS2 and EGF signaling pathways in colorectal cancer*. 2011 Cancers 3(4):3894-3908

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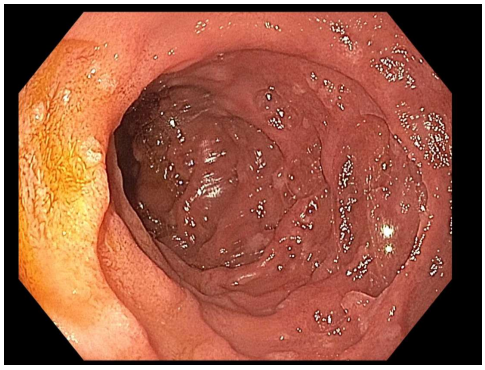
Chemoprevention in FAP - Erlotinib



- 2016 FAPEST RCT randomized 92 participants to sulindac 150 mg BID + erlotinib 75 mg daily vs placebo for 6 months to evaluate change in duodenal polyp burden
  - 37.9% decrease from baseline in duodenal polyp burden amongst treated participants; 30% increase from baseline in those on placebo (71% overall decrease)
  - Persistent benefit in individuals with classic FAP vs attenuated FAP

Sammader et al. *Effect of sulindac and erlotinib vs placebo on duodenal neoplasia in familial adenomatous polyposis*. JAMA 2016 Mar 22;315(12):1266-75

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Chemoprevention in FAP - Erlotinib

- 2018 secondary analysis of 82 evaluated lower GI polyp burden (22 with intact colon) – net percentage change 69.4%

Table. Change in Colorectal Polyp Number From Baseline for Intention-to-Treat Analysis

	Colorectal Polyp Number							
				Change (6-mo Follow-up-Baseline) Median (IQR)		Net Between-Group Differences (95% CI)		
Intention-to-Treat	Participants, No.	Baseline Median (IQR)	6-mo Follow-up, Median (IQR)	Median Change	Median Change, %		*P* Value	Net % Change (95% CI)
Intact colon (colorectal)								
Sulindac and erlotinib	11	39 (19 to 81)	2 (1 to 2)	−27 (−34 to −26)	−96.3 (−96.3 to −85)	−27.5 (−106.5 to −9.6)	.009	−69.4 (−109.2 to −28.8)
Placebo	11	16 (4 to 26)	14 (9 to 17)	−2 (−3 to −0.8)	−11.1 (−20.5 to −2.8)			
IPAA								
Sulindac and erlotinib	21	5 (2 to 17)	0 (0 to 1)	−4 (−5.1 to −3)	−83 (−100 to −71.8)	−14.5 (−28.1 to −3.5)	.003	−121.7 (−280 to −71.6)
Placebo	23	6 (0 to 22)	22 (8 to 28)	1 (0 to 3)	21.7 (0 to 120)			
Rectum (IRA)								
Sulindac and erlotinib	9	7 (4 to 15)	6 (2 to 15)	−1 (−5 to 5.9)	−60 (−71.4 to 93.9)	−13 (−30.5 to 3.9)	.24	−175.5 (−1087.3 to 52.5)
Placebo	7	3 (2 to 12)	18.3 (17 to 30)	11.4 (8 to 16)	119.3 (114.3 to 133.3)			

Abbreviations: IPAA, ileal pouch anal anastomosis; IQR, interquartile range; IRA, ileo-rectum.

Sammader et al. *Association Of Sulindac and Erlotinib vs Placebo with Colorectal Neoplasia in Familial Adenomatous Polyposis.* JAMA Oncol 2018 Feb 8;4(5):671-77

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Chemoprevention in FAP - Erlotinib

- Prior trial with many AEs, primarily acneiform rash in 80% of those who received sulindac + erlotinib
- 2023 Phase 2 trial of weekly erlotinib 350 mg x 6 months
  - 46 participants; co-primary endpoints of duodenal polyp burden and AE
    - 56% acneiform rash
  - Mean percent change -29.6% (compared to 37.9% with combination therapy); Spigelman stage also downstaged in 12% of participants
  - Secondary endpoint lower GI polyp burden (15 participants not examined) also modestly reduced -30.8%

Sammader et al. *Phase II trial of weekly erlotinib dosing to reduce duodenal polyp burden associated with familial adenomatous polyposis.* Gut 2022 May 30;72(2):256-263.

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Chemoprevention in FAP – mTOR inhibitors

- Rapamycin and sirolimus reduce polyp proliferation in *APC* mutant models
  - With sirolimus increasing survival and time to progression of dysplasia
- Sirolimus found to inhibit mTOR in intestinal adenomas and reduce polyp number in some patients but poorly tolerated
- Early 2025, FDA granted Fast Track Designation to eRapa for use in familial adenomatous polyposis based on results of phase II trial over 12 months

Hardiman K et al. *PLoS One*. 2014 Apr 24;9(4):e96023; Yuksekkaya et al. *Am J Gastroenterol* 2016 Jul;111(7):1040-41. Roos et al. *BMJ Open Gastroenterol*. 2020 Dec;7(1):e000497

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Chemoprevention in FAP – mTOR inhibitors

Adverse Event	Cohort 1, n=10	Cohort 2, n=10	Cohort 3, n=10	Total, n=30	p (χ^2)
Any AE, n (%)	7 (70.0)	9 (90.0)	9 (90.0)	25 (83.3)	0.38
Median time to first AE, in days (95% CI)	98.0 [15.0, NA]	35.5 [2.0, 57.0]	6.0 [1.0, 151.0]	29.0 [9.0, 85.0]	
DLTs, n (%)	0	0	1 (10.0)	1 (3.3)	0.36
Serious AEs, n (%)	2 (20.0)	1 (10.0)	2 (20.0)	5 (16.7)	0.79
Grade 3 or higher AEs, n (%)	2 (20.0)	1 (10.0)	4 (40.0)	7 (23.3)	0.27
Related AEs ≥ Grade 3, n (%)	0	1 (10.0)	1 (10.0)	2 (6.7)	0.59
All Related AEs, n (%)	2 (20.0)	4 (40.0)	8 (80.0)	14 (46.7)	0.02
Mean overall polyp burden (mm)					
Baseline	409.30	288.50	169.90	289.23	
6 months	280.00	272.00	111.40	221.13	
% reduction	32%	6%	34%	24%	
p (paired t-test)	0.1	0.62	0.33	0.04	

Table 1. Adverse Events (AEs) and Change in Overall Polyp Burden

- Phase 3 trial recruiting to evaluate 0.5 mg eRapa qd every other week vs placebo over 3 years:
  - Primary - progression free survival in high-risk patients with FAP
  - Safety/tolerability, effect on GI polyposis, Spigelman stage, QOL, T-cell phenotypes and function

Burke et al. *Phase IIA trial of encapsulated rapamycin (ERapa) in patients with familial adenomatous polyposis to reduce intestinal polyp burden: 6 month interim results*. Presented at DDW May 2024. Gastroenterology 166(5):S-266

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Chemoprevention in FAP – Other agents

- Eicosapentaeonic acid (fish oil): Downregulates mucosal arachidonic acid and can reduce COX2 expression
- Phytoestrogens: ER-β less expressed early in adenoma → carcinoma sequence; restoring ER-β may result in anti-proliferative signaling

Daca-Alvarez et al. *Familial adenomatous polyposis: non-surgical management of large bowel disease: endoscopic and chemoprevention strategies*. Fam Cancer 2025 Jun 1;24(2):53.

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Chemoprevention in FAP – Other agents

- Curcumin
- Black raspberries
- Imatinib
- Venetoclax
- Mesalazine
- Metformin
- Anti-inflammatory diet
- Vitamins B1, C, E
- Guselkumab
- Obetocholic acid
- Vaccines?





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Current Trends in Chemoprevention

- CGA-IGC collaboration amongst international hereditary cancer societies
  - LA-GETH (Latin America Hereditary Tumor Group)
  - InSiGHT (International Society for Gastrointestinal Hereditary Tumours)
  - EHTG (European Hereditary Tumor Group)
- Survey to report on current FAP and Lynch syndrome chemoprevention strategies on a global level
- Captures
  - Whether chemoprevention is offered
  - When chemoprevention is prescribed
  - Which type/dosage
  - Age groups for chemoprevention
  - Barriers to chemoprevention practice

InSiGHT
Grupo de Estudios de Tumores Hereditarios
European Hereditary Tumour Group

Mraz et al. *Current chemoprevention approaches in Lynch syndrome and Familial adenomatous polyposis: a global clinical practice survey*. Front Oncol. 2023 May.

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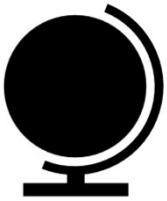
Current Trends in Chemoprevention

Practice Setting

Academic
Medical Center – 75%
Community
Hospital – 9.4%
Private practice – 8.3%

Specialty

Gastroenterology – 35.4%
Colorectal surgeon – 15.6%
Genetic counselor – 13.5%
Medical geneticist – 10.4%
Medical Oncologist – 9.4%



Geographic Location

North America – 52.1%
South America – 15.6%
Europe – 16.7%
UK – 7.3%
Asia – 4.2%

Time in Practice

< 5 years – 13.8%
5-10 years – 21.8%
10 + years – 64.4%

Mraz et al. *Current chemoprevention approaches in Lynch syndrome and Familial adenomatous polyposis: a global clinical practice survey*. Front Oncol. 2023 May.

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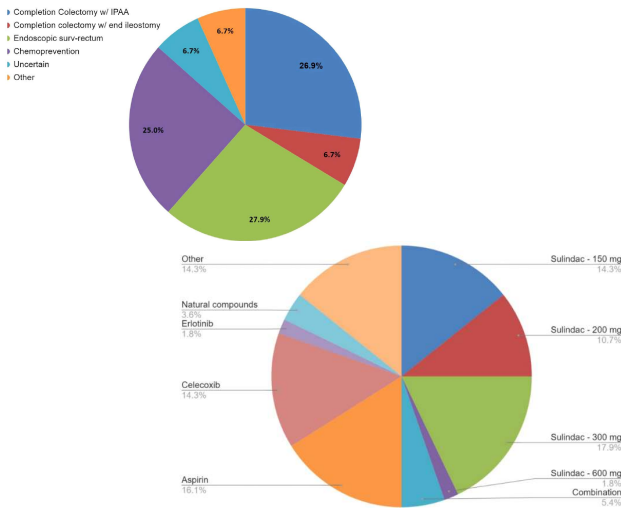
Current Trends in Chemoprevention



- Case vignette: 33-year-old M with FAP and subtotal colectomy with IRAA, with history of desmoid tumor, presenting with significant rectal and duodenal polyposis
  - Participants able to select multiple management options
  - Figure demonstrates cumulative number of selections, but not combinations

Mraz et al. *Current chemoprevention approaches in Lynch syndrome and Familial adenomatous polyposis: a global clinical practice survey*. Front Oncol. 2023 May.

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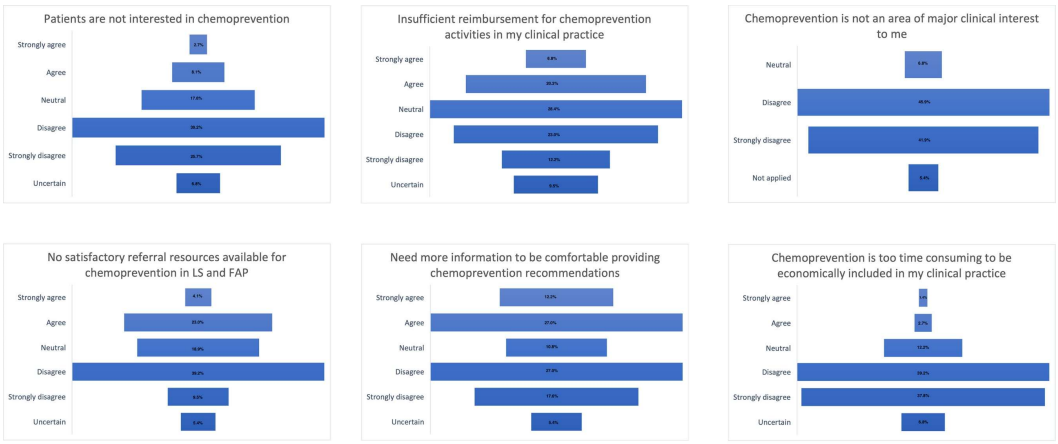
Current Trends in Chemoprevention



Mraz et al. *Current chemoprevention approaches in Lynch syndrome and Familial adenomatous polyposis: a global clinical practice survey*. Front Oncol. 2023 May.

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Current Trends in Chemoprevention

Mraz et al. *Current chemoprevention approaches in Lynch syndrome and Familial adenomatous polyposis: a global clinical practice survey*. Front Oncol. 2023 May.

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Current Trends in Chemoprevention

Mraz et al. *Current chemoprevention approaches in Lynch syndrome and Familial adenomatous polyposis: a global clinical practice survey*. Front Oncol. 2023 May.

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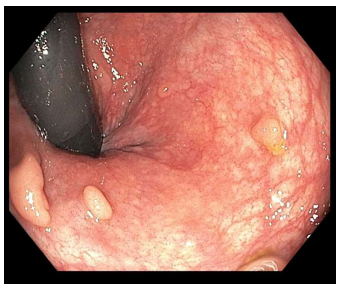
Current Trends in Chemoprevention

- Case vignette: 15-year-old M in family with known FAP. Grandmother had colectomy until age 60, and mother had colectomy in 20s. Started colonoscopy age 8 due to blood in stool with 5 adenomas on 1st colonoscopy. Polyp burden has consistently increased, now with carpeting of polyps, 14 rectal polyps, and one advanced polyp (1.2 cm tubular adenoma)



Mraz et al. *Current chemoprevention approaches in Lynch syndrome and Familial adenomatous polyposis: a global clinical practice survey*. Front Oncol. 2023 May.

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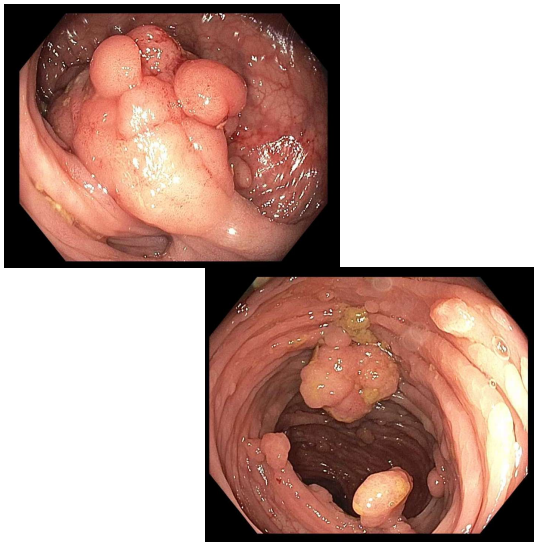
Familial adenomatous polyposis – Risk stratification

Stage#	Polyp Description
0	<20 polyps, all <5 mm
1*	20-200 polyps most <5 mm, none, >1 cm
2*	200-500 polyps, <10 that are >1 cm
3*	500-1000 polyps or any number if there are 10-50 that are >1 cm and amenable to complete polypectomy
4	>1000 polyps and/or any polyps grown to confluence and not amenable to simple polypectomy; any invasive cancer

Clinical Intervention		Comments
(A)	Repeat colonoscopy in 2 years	Biopsy at baseline to confirm histology; polyp removal discretionary (not clearly indicated)
(B)	Repeat colonoscopy in 1 year	Some would consider colectomy, especially when polyp count high
(C)	Repeat colonoscopy in 1 year polypectomy preferred	Removal of large polyps clearly necessary when done to postpone surgery alternative would be to consider surgery
(D)	Repeat colonoscopy in 6-12 months or consider colectomy	Removal of large number of larger polyps defensible, but only when clear reasons to delay surgery
(E)	Colectomy proctocolectomy clearly indicated within 3 months to a year	Any decision to delay surgery must be highly individualized and based on compelling circumstances

*Presence of High-Grade Dysplasia Warrants Upstaging of Patient to Stage 4.
Patients who cannot be allotted a particular stage (eg, patients with mix polyposis) call for an external discussion is a multidisciplinary specialty team.



Lynch et al. *A proposed staging system and stage-specific interventions for familial adenomatous polyposis*. Gastrointest Endosc. 2016 Jul;84(1):115-125

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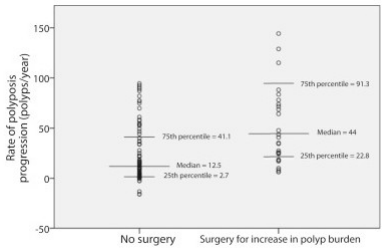
Familial adenomatous polyposis – Risk stratification

Table2. Differences in the rate of polyposis progression based on patient and polyp characteristics (in patients without exposure to chemoprevention)

Variable	No. of patients (%)	Rate of polyposis progression (polyps/year) [IQR]*	P value
Polyp characteristics			
Number of polyps at initial colonoscopy			
0-20	53 (42.4)	17 [4.3-34]	.004
21-99	46 (36.8)	38.5 [21.5-73.6]	
≥100	26 (20.8)	57.8 [0-231.4]	
Location of polyp predominance during surveillance			
Equal number of polyps on right and left colon	16 (12.8)	10.7 [0.5-54.3]	.237
>50% of polyps on right side	50 (40)	33 [9-69.8]	
>50% of polyps on left side	59 (47.2)	25.6 [14.6-76]	
Presence of advanced adenoma			
No	81 (64.8)	22.7 [9.0-68.4]	.444
Yes	44 (35.2)	34.0 [13.1-73.5]	

Table3. Multivariate linear regression of factors associated with the rate of polyposis progression (including patients on chemoprevention)

Variable	Rate of polyposis progression (95% confidence interval)	P value
Number of polyps at presentation (increment of 10 polyps)	1.2 (0.3-2.8)	.012
Chemoprevention	−36.5 (−83.6 to−10.6)	.013



Sarvepalli et al. *Natural history of colonic polyposis in young patients with familial adenomatous polyposis*. Gastrointest Endosc. 2018 Oct; 88(4):726-33.

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Guidelines - Chemoprevention

Society Guideline (year)	Chemoprevention Discussion
ACG (2015)	Sulindac: regression of colonic/rectal adenomas but cancer prevention uncertain; not substitute for colectomy but can use in rectal surveillance Celecoxib: previously approved for FAP; modest effect in colon and rectum, some effect for duodenal adenoma regression; CV side effects
ASGE (2020)	Recommend use of chemopreventive agents within confines of tertiary hereditary cancer center and/or as part of clinical trials Sulindac: reduces adenoma number/size; risk of interval cancer due to transformation of polyps; can use 150 mg BID for polyposis control in rectum after colectomy; possible utility to dual inhibition cyclooxygenase and epidermal growth factor signaling, including in duodenal polyposis (sulindac 150 mg BID + erlotinib 75 mg daily) Celecoxib: adenoma regression at 400 mg BID but no postmarketing study to verify clinical benefit
NCCN (2024)	May be considered for management of remnant polyp burden post-operatively Sulindac: unknown if decreased polyp burden decreases cancer risk Consider referral to expert center or enrollment in clinical trial
ESGE (2019)	No single chemoprevention drug has been approved for management of FAP
BSG/ACPGBI/ UKCGG (2019)	Insufficient evidence of benefit of chemoprophylaxis
JSCCR (2021)	It is strongly recommended that chemoprevention not be performed for colorectal adenomas in patients with FAP because evidence on agents in terms of efficacy and safety is still lacking

ACG: American College of Gastroenterology; ASGE: American Society of Gastrointestinal Endoscopy; NCCN: National Comprehensive Cancer Network; ESGE: European Society of Gastrointestinal Endoscopy; BSG: British Society of Gastroenterology; ACPGBI: Association of Coloproctology of Great Britain and Ireland; JSCCR: Japanese Society for Cancer of the Colon and Rectum

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Summary

- Currently no recommended chemoprevention strategies for individuals with FAP
- Who to consider for chemoprevention:
  - Young patients who have need to delay surgical intervention
  - Post-operative patients with high rectal/pouch adenoma burden
  - Significant duodenal polyposis
  - High risk of desmoid tumors
- Chemoprevention does *not* replace the need for surgical management and endoscopic surveillance
  - Need studies that evaluate clearer endpoints
- Need for improved personalization, risk stratification
- Consider referral to expert centers and/or clinical trials

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Questions

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