

# Colon Cancer and Polyps

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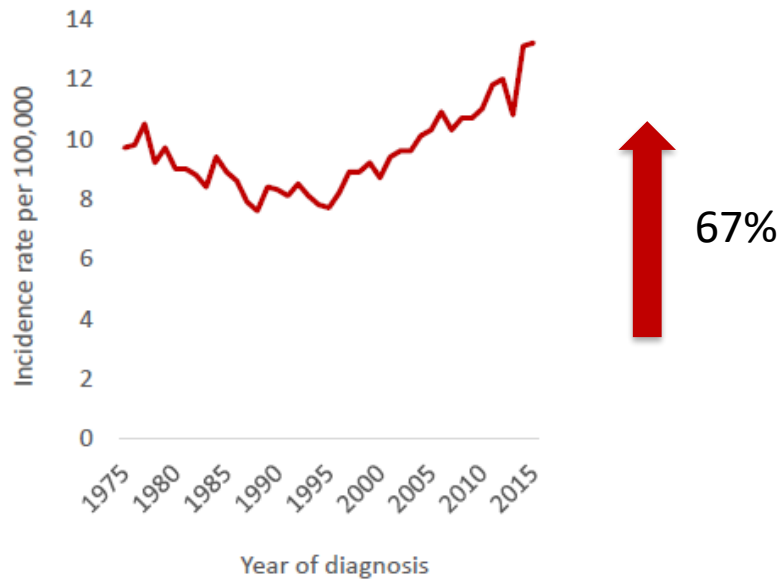
# Cost-Effectiveness and National Impact of Initiating Average-Risk Colorectal Cancer (CRC) Screening at Age 45 Instead of 50: The new American Cancer Society (ACS) recommendation

**Uri Ladabaum**, Ajitha Mannalithara, Reinier Meester, Samir Gupta, Robert Schoen

Stanford University, University of California San Diego, University of Pittsburgh

# Background

## Age 20-49



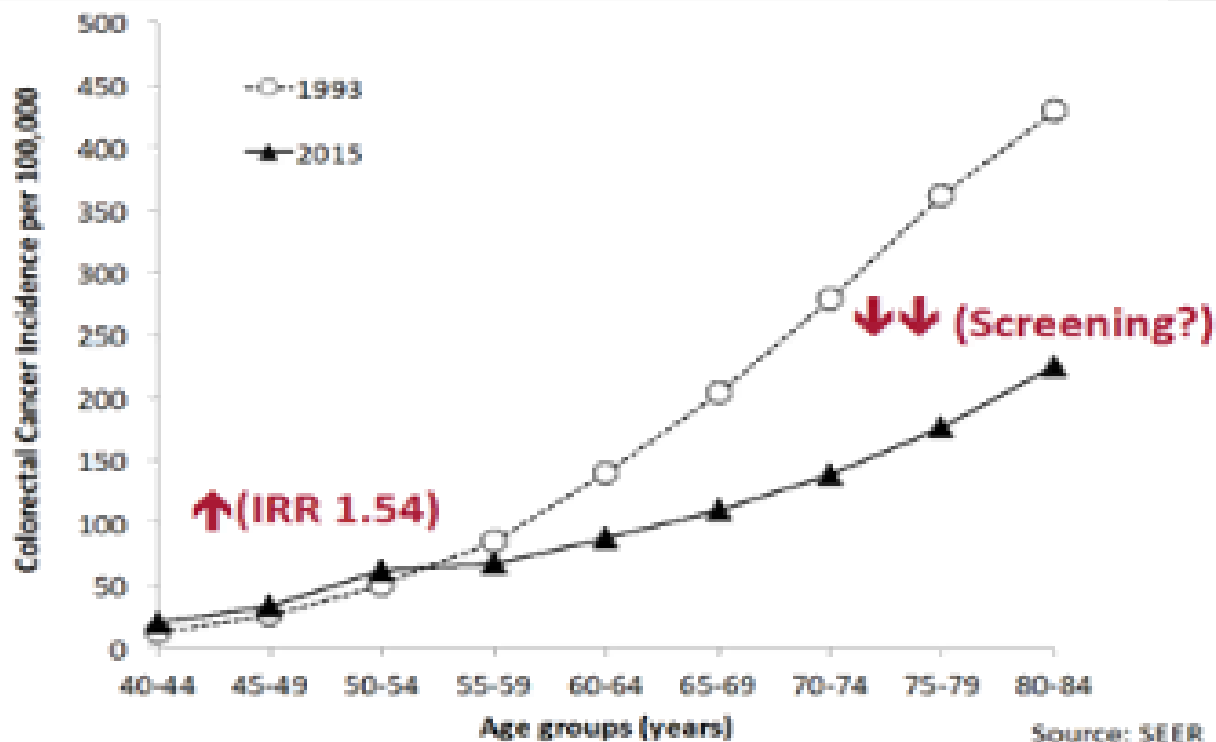
“ACS recommends that adults aged  $\geq 45$  with average risk of CRC undergo regular screening...”

- Disease burden
  - Modeling
  - Expect that screening performance  $< 50 \sim 50$
- \*Qualified recommendation

# Aim

- To estimate cost effectiveness
- Explore potential trade-offs (unscreened population, higher risk i.e. FIT +)
- Estimate national impact
  
- Of CRC screening 45+ vs. 50+

# Methods: CRC incidence as basis of modeling



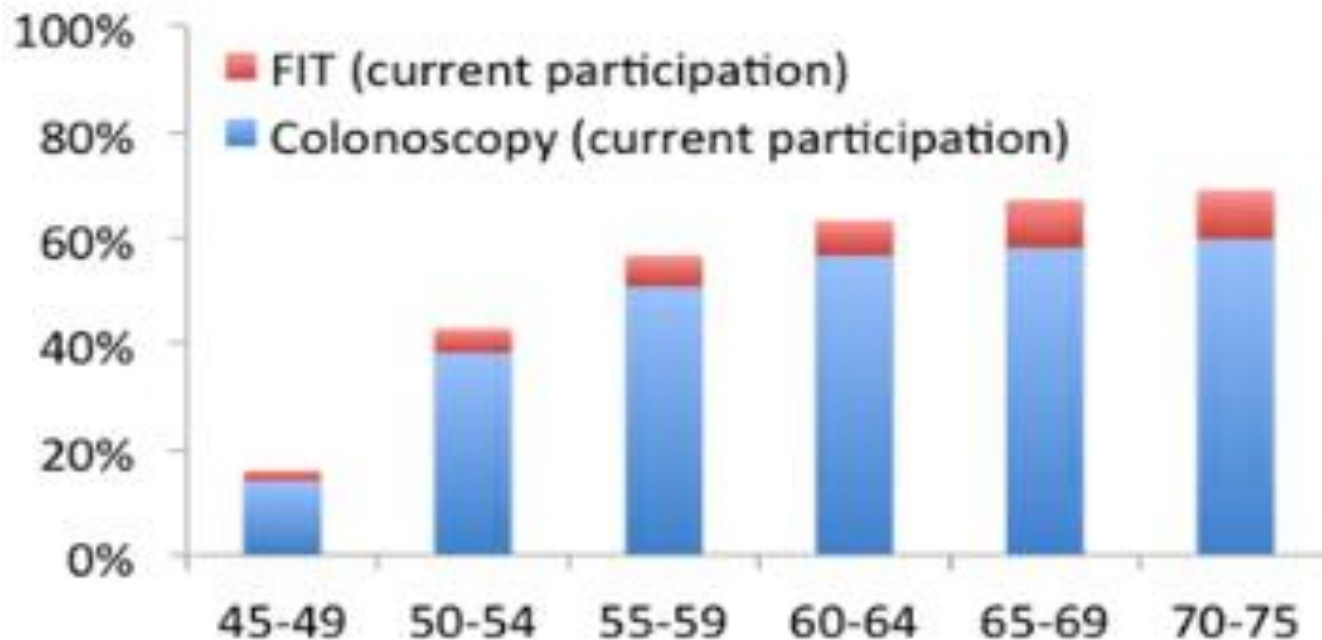
# Results: Cost-effectiveness

	Colo 45-75 vs 50-75	FIT 45-75 vs. 50-75
People (n)	1000	1000
↑ # colonoscopy	758	267
CRCs averted	4	4
CRC deaths averted	2	1
QALYs gained	14.4	14.0
↑ cost	\$486,500	\$107,800
Cost/QALY	\$33,900	\$7,700

# Results: Potential Trade-Offs

	Colo 45+ vs 50+	Unscrn 55+	Unscrn 65+	FIT + → colo (↑60 → 90%)
People (n)	1000	231	342	3,935
↑ # colonoscopy	758	758	758	758
CRCs averted	4	13	14	22
CRC deaths averted	3	6	7	10
QALYs gained	14	28	27	36
↑ cost	\$486,500	<b>\$163,700</b>	<b>\$445,800</b>	<b>\$843,900</b>
Cost/QALY	\$33,900	<b>SAVINGS</b>	<b>SAVINGS</b>	<b>SAVINGS</b>

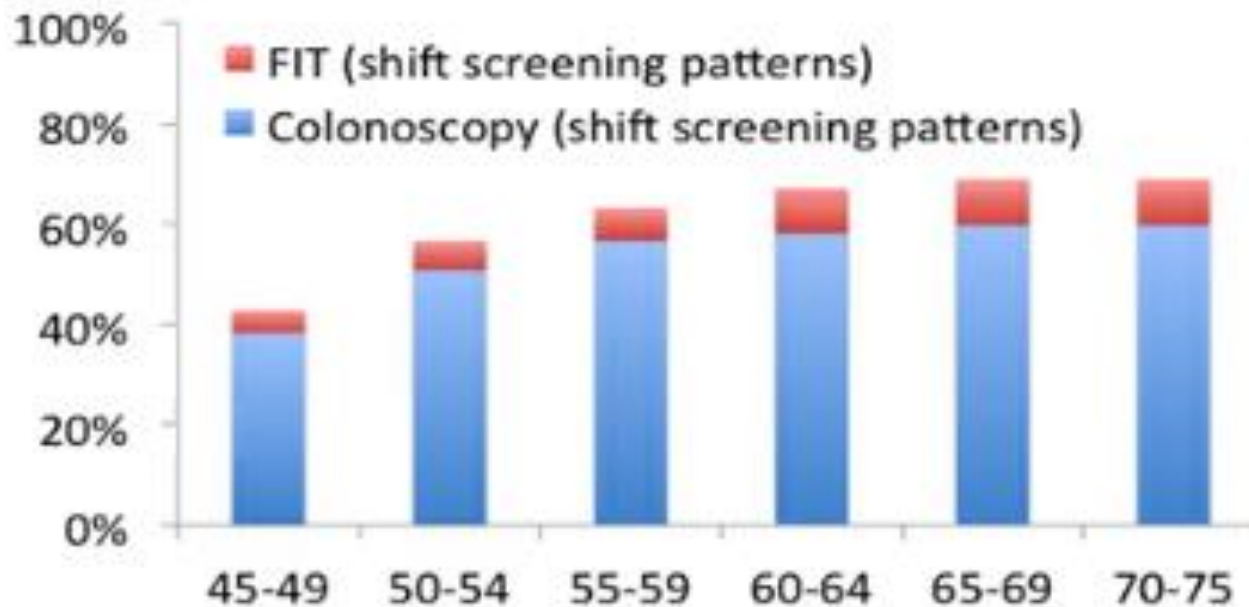
# Results: National Adherence



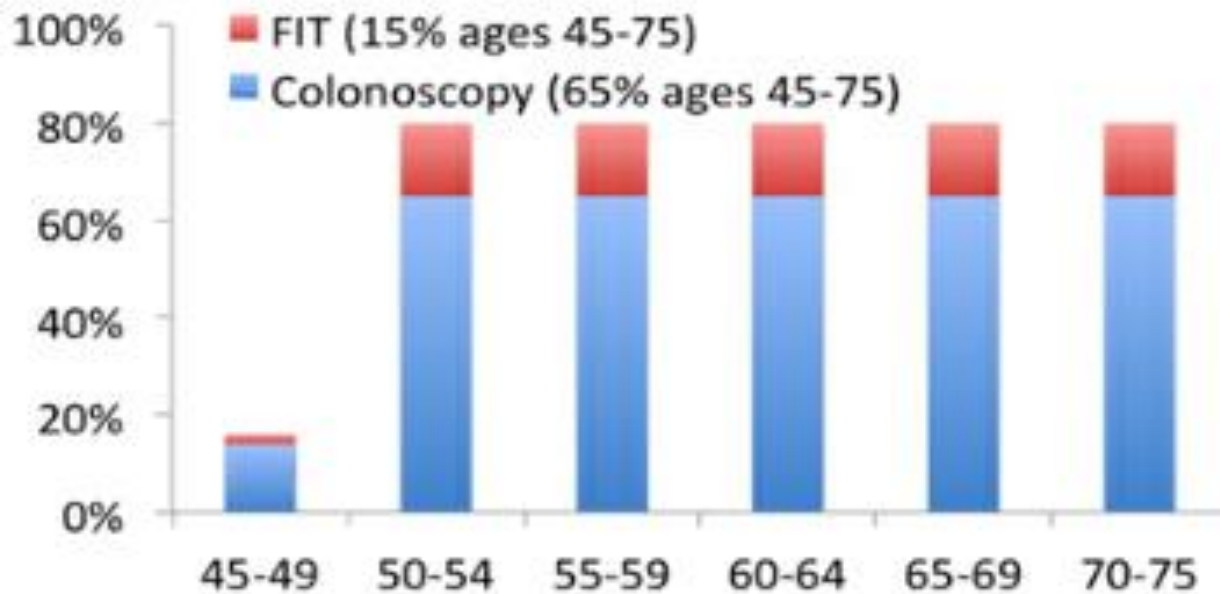
Sauer et al. Prev Med 2018



# If shifted to starting at 45

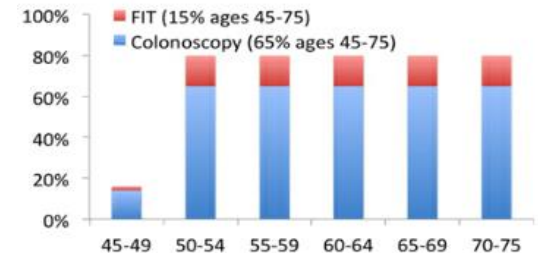
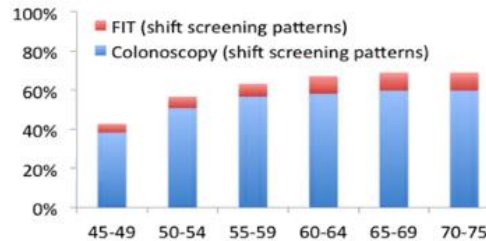


# If had 80% adherence rate



# Results: National Projections over next 5 years

	Starting at 45	80% Adherence in 50+
CRCs averted	29,400	77,500
CRC deaths averted	11,100	31,900
Incremental # colo	10.7 million	12.1 million
Incremental cost	\$10.4 billion	\$3.3 billion



# Conclusions

- Initiating average-risk CRC screening at age 45 *is likely to be cost-effective*
- **BUT, if resource restraints... improving screening rates in older people and FIT + f/u would be preferred**
- **But will they?? The debate continues.....**

# A Prospective Randomized Tandem Colonoscopy Study of Linked Color Imaging (LCI) or Narrow Band Imaging (NBI) for Detection of Colorectal Polyps

**Wai K Leung**, CG Guo, Michael KL KO, Elvis To, Ly Mak, Teresa Tong, LJ Chen, David But, Sy Wong, Kevin Sh Liu, Vivian Tsui, Frank YF Lam, Thomas KL Lui, Ka Shing Cheung, Ivan FN Hung, Sh Lo

University of Hong Kong

# Linked Color Imaging (LCI)

- A new image enhanced endoscopy & emphasizes direct mucosal color changes
- Improves contrast of hemoglobin
- Selectively obtains the info on a mucosal surface blood vessels/pattern
- Signal processing increases color contrast by expanding the color nearby mucosal redness

# LCI for colon polyps



The  
Spring Course

BEST OF DDW

2019

June 1, 2019



# Prior Studies: LCI

- LCI superior to white light (WL) for polyp & adenoma detection<sup>1</sup>
- LCI superior to WL for SSA detection<sup>2</sup>

<sup>1</sup> Min et al. Gastro Endosc 2017 <sup>2</sup> Fujimoto et al. Endosc Int Open 2018



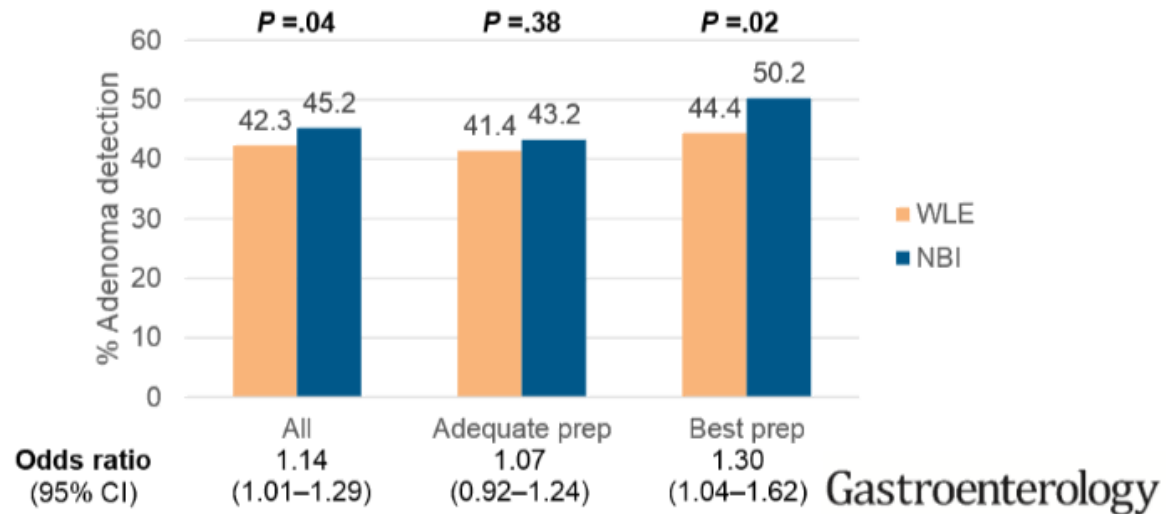
# Prior Studies: NBI

Individual patient level data meta-analysis for high definition White Light Endoscopy (WLE) vs Narrow Band Imaging (NBI) stratified by bowel preparation

11 international centers



4491 individual patient datasets



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Atkinson et al. Gastroenterology 2019

June 1, 2019



# Aim

- No head to head comparisons between LCI and existing imaged enhanced endoscopy technologies, particularly NBI...
- **To compare the polyp detection rate of LCI with NBI**

# Methods

- Prospective, randomized tandem colonoscopy study
- Single center study (Queen Mary Hospital in Hong Kong)
- Randomized **1:1 ratio** to receive **tandem colonoscopy** with both scope withdrawals using either LCI or NBI

# Inclusion & Exclusion Criteria

## Inclusion

- Consecutive adult patients
- Ages 40-80
- Colonoscopy for symptoms, screening or surveillance

## Exclusion

- Prior colorectal resection
- Hx of CRC, IBD, FAP, Lynch, or other polyposis syndrome
- Unsafe for polypectomy (comorbidities/bleeding)
- Unable/refused informed consent

# Randomization

## LCI (Fujifilm)

- 1<sup>st</sup> pass to cecum: WL
- Withdrawal: LCI (> 6min)
  - All polyps removed
- 2<sup>nd</sup> pass to cecum: WL
- 2<sup>nd</sup> withdrawal: LCI
  - Additional polyps removed

## NBI (Olympus)

- 1<sup>st</sup> pass to cecum: WL
- Withdrawal: NBI (> 6min)
  - All polyps removed
- 2<sup>nd</sup> pass to cecum: WL
- 2<sup>nd</sup> withdrawal: NBI
  - Additional polyps removed

# Outcomes

- Primary:
  - **Polyp detection rate** during 1<sup>st</sup> exam
    - Proportion of pts with at least one polyp on 1<sup>st</sup> exam
- Secondary:
  - **Adenoma detection rate** (proportion of pts with adenoma detected during 1<sup>st</sup> exam)
  - **Polyp miss rate** (based on per lesion analysis: # of polyps detected on 2<sup>nd</sup> exam/total # on both)
  - **Adenoma miss rate**

# Results

547 patients screened

275 excluded

272 patients randomized

LCI Group  
n=136

NBI Group  
n=136

1<sup>st</sup> colonoscopy:  
2 incomplete (obstructing tumors)

1<sup>st</sup> colonoscopy:  
0 incomplete

2<sup>nd</sup> colonoscopy:  
6 incomplete (3 tumors on 1<sup>st</sup> colon  
2 poor patient tolerance  
1 poor bowel prep)

2<sup>nd</sup> colonoscopy:  
7 incomplete (2 tumors on 1<sup>st</sup> colon  
4 severe looping  
1 poor bowel prep)

# Baseline Characteristics

	LCI (n=136)	NBI (n =136)	p
Age (yr)	62 +/- 10	62 +/- 9.3	0.96
Sex, f (%)	72 (52.9)	69 (50.7)	0.81
Indications:			
Screening	14 (10.3)	17 (12.5)	0.71
Surveillance	15 (11)	28 (20.6)	0.05
Bowel sx	107 (78.7)	91 (66.9)	0.04
BBPS			
<6 (%)	29 (21.3)	31 (22.8)	0.62
≥6 (%)	107 (78.7)	105 (77.2)	-





White light



LCI



NBI

# Findings on 1<sup>st</sup> Colonoscopy

	LCI	NBI	P
Pts w/polyps (%)	76 (55.9)	97 (71.3) ←	0.008
Pts w/adenomas	54 (39.7)	70 (51.5)	0.05
Pts w/advanced adenomas	9 (6.6)	9 (6.6)	1
Pts w/serrated polyps	30 (22.1)	47 (34.6) ←	0.02
Pts w/proximal polyps	56 (41.2)	56 (41.2)	1
Pts w/proximal adenomas	43 (31.6)	48 (35.3)	0.52
Mean # polyps/pt (SD)	1.35 (1.8)	2.04 (2.01) ←	0.019
Mean # adenomas/pt (SD)	0.9 (1.48)	1.26 (2.25)	0.11

# Findings on 2<sup>nd</sup> Colonoscopy

	LCI	NBI	P
Pts w/polyps (%)	38 (27.9)	48 (35.3)	0.19
Pts w/adenomas	21 (15.4)	28 (20.6)	0.27
Pts w/advanced adenomas	4 (2.9)	2 (1.5)	0.68
Pts w/serrated polyps	13 (19.6)	20 (14.7)	0.19
Pts w/proximal polyps	13 (9.6)	27 (19.9) ←	0.017
Pts w/proximal adenomas	8 (5.9)	18 (13.2) ←	0.04
Mean # polyps/pt (SD)	0.38 (0.7)	0.5 (0.82)	0.17
Mean # adenomas/pt (SD)	0.23 (0.61)	0.25 (0.54)	0.33

# Insertion and Withdrawal Times

	LCI	NBI	p
Intubation, 1 <sup>st</sup>	9.1 (5.1)	8.8 (6.2)	0.62
Withdrawal, 1 <sup>st</sup>	8.6 (3.1)	10.0 (4.1) ←	0.003
Intubation, 2 <sup>nd</sup>	5.3 (3.5)	5.3 (4.8)	0.91
Withdrawal, 2 <sup>nd</sup>	5.1 (1.4)	5.7 (1.7) ←	0.003

All in minutes, mean +/- SD

# Miss Rates

## Polyps

	LCI	NBI	p
All	21.8%	19.7%	0.53
≥ 5mm	12.9%	14.7%	1
< 5mm	23.2%	20.9%	0.55
Proximal	15%	19.4%	0.35
Distal	28.1%	19.9%	0.13
Serrated	28.6%	24.8%	0.62

## Adenomas

	LCI	NBI	p
All	20.1%	16.6%	0.39
≥ 5mm	15.4%	6.3%	0.23
< 5mm	21.7%	19.7%	0.78
Proximal	13.8%	16.7%	0.57
Distal	28.4%	16.5%	0.11
Advanced adenoma	43.8%	11.1%	0.05

# ↑ in detection rate by tandem colonoscopy

- % ↑ Polyp detection rate: 10.4%
  - LCI 15.7%, NBI 6.2%
- % ↑ Adenoma detection rate: 10.5%
  - LCI 14.9%, NBI 7.0%

# Conclusions

- NBI significantly better than LCI for polyp/adenoma detection
- Longer withdrawal time (> 8 min) associated w/higher polyp/adenoma detection
- BOTH missed about 20% of polyps
- 2<sup>nd</sup> colonoscopy could ↑ detection rate by 10%

# Efficacy and Safety of Combined CPP-1x/Sulindac vs. CPP-1x or Sulindac alone in patients with Familial Adenomatous Polyposis (FAP): Results from a Double-Blind, International Randomized Phase III Trial

**Carol A. Burke**, N Jewel Samadder, Evellen Dekker, Patrick Lynch, Ramona Lim, Francesc Balaguer, Steven Gallinger, Robert Huneburg, Christian Strassburg, Alfred M. Cohen, Samir Gupta, Elena Stoffel; **on behalf of the FAP-310 Investigators**



# Background

- Unmet clinical need in FAP: development of effective and safe drugs to ↓ neoplasia, ↓ endoscopic/surgical intervention with hopes of preventing cancer
- FAP patients: ↑ Polyamine (PA) levels and ornithine decarboxylate (ODC) activity<sup>1,2</sup>

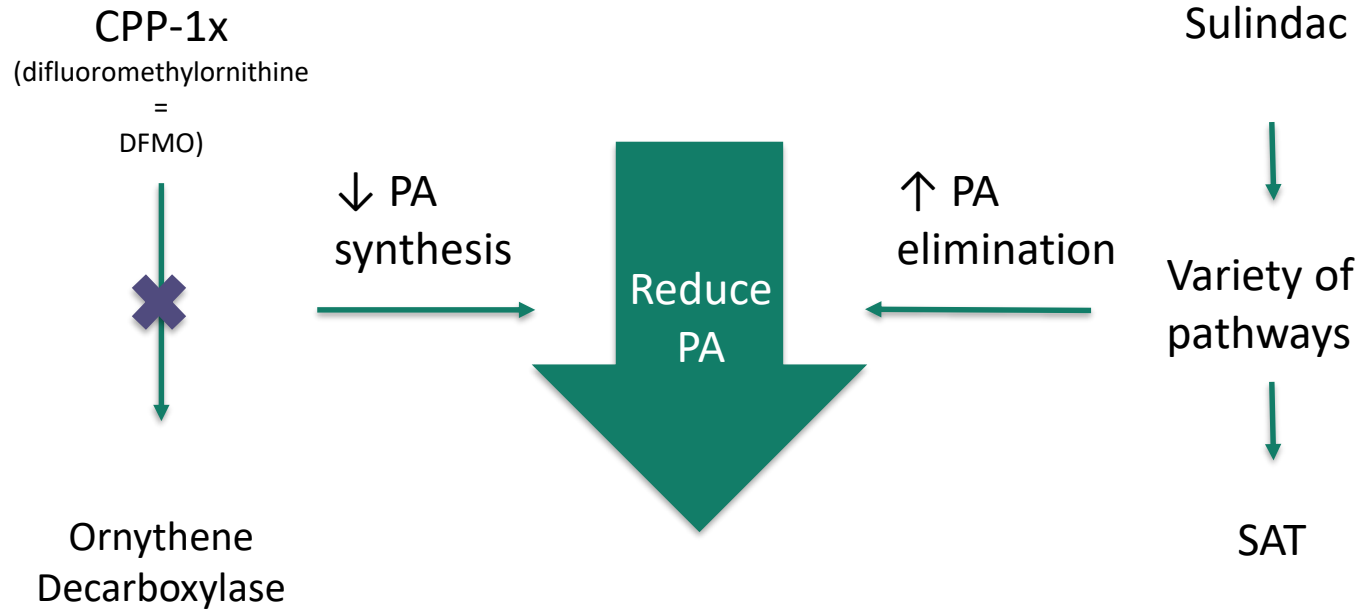
<sup>1</sup> Luk & Baylin NEJM 1984 <sup>2</sup> Giardiello et al. Cancer Res 1997

# Prior Studies

- Celecoxib + CPP-1x (DFMO) ↓ total polyp burden vs. celecoxib alone in FAP<sup>1</sup>
- CPP-1x + sulindac ↓ metachronous high risk sporadic adenomas by > 90% in 3 year trial<sup>2</sup>

<sup>1</sup> Lynch et al. Gut 2016 <sup>2</sup> Meyskens et al. Cancer Prev Res 2008

# MOA of CPP-1x/Sulindac: ↓ PA



# Aim of this Study

- To compare the time of 1<sup>st</sup> FAP-related event
  - disease progression in intact colon indicating need for colectomy,
  - Endoscopic snare/trans-anal excision to remove any polyp  $\geq 10\text{mm}$  or HGD in rectum/pouch,
  - Progression of duodenal polyposis
- and safety
- in FAP patients treated with
  - Combined CPP-1x/sulindac vs.
  - CPP-1x alone
  - Sulindac alone

# Study Design

- FAP patients undergoing screening randomized to:
  - CPP1x 750mg QD + sulindac 150mg QD
  - CPP1x 750mg QD + placebo
  - Sulindac 150mg QD + placebo
- For 24 months
- Outcomes:
  - Time to any 1<sup>st</sup> FAP related event
  - Safety

# Inclusion/Exclusion Criteria

## Inclusion

- Adults with FAP + APC mutation +  $\geq 1$ :
  - Intact colon with moderate adenoma burden or
  - $\geq 3$  year s/p IRA or IPAA with  $> 10$  polyps
  - Spigelman Stage 3 or 4 duodenal polyposis or downstaged to Stage 1 or 2 within the last 6 months

## Exclusion

- CV risk factors (CVA, MI, moderate/severe CHF)
- Hearing loss requiring hearing aid

# Methods

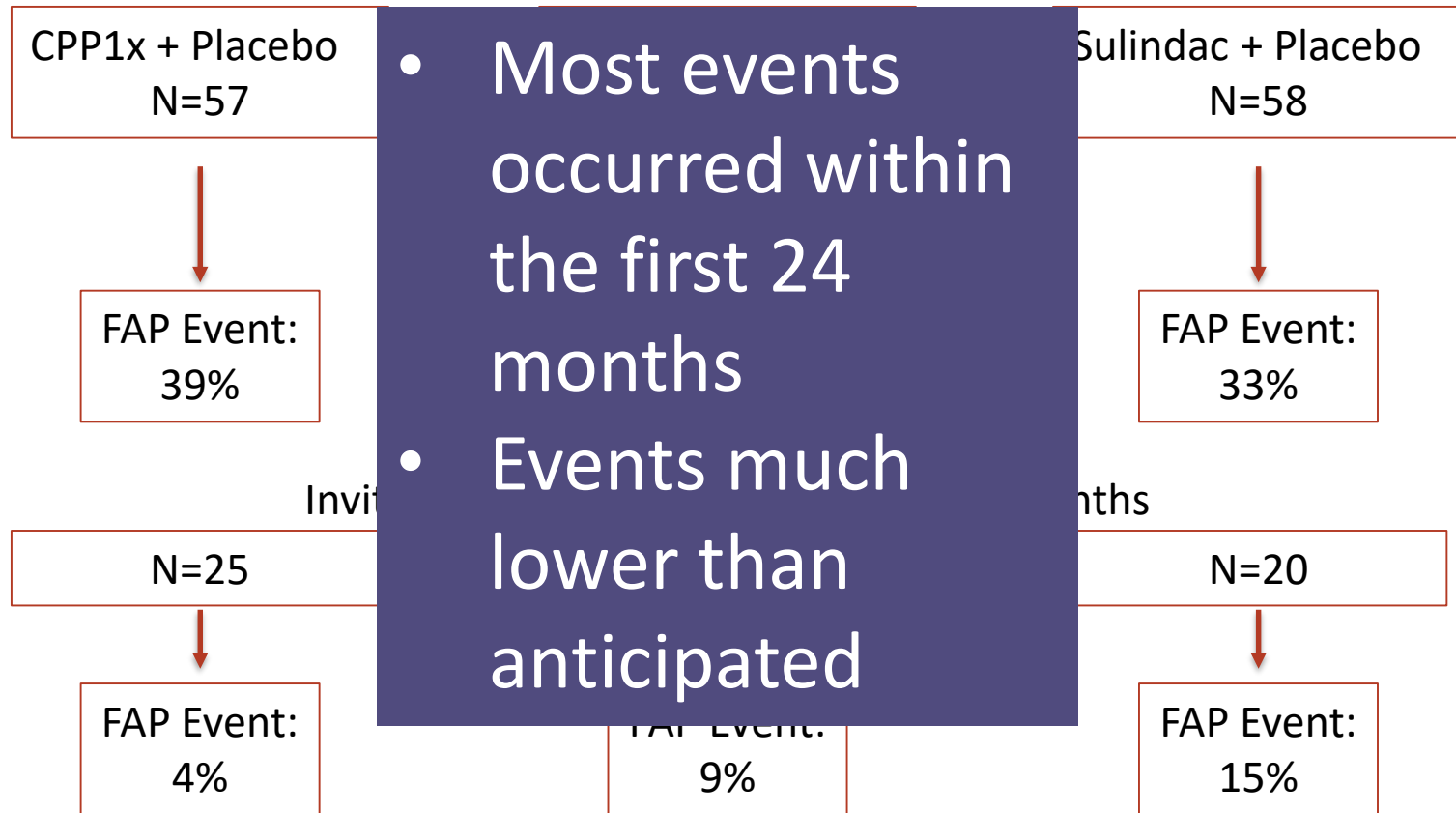
- Lower endoscopy + EGD @ baseline & q 6 mos
- Video recording and qualitative assessment of polyp burden
- Stratified log-rank analysis to compare time to 1<sup>st</sup> FAP event btwn groups

# FAP-related events powered to assume

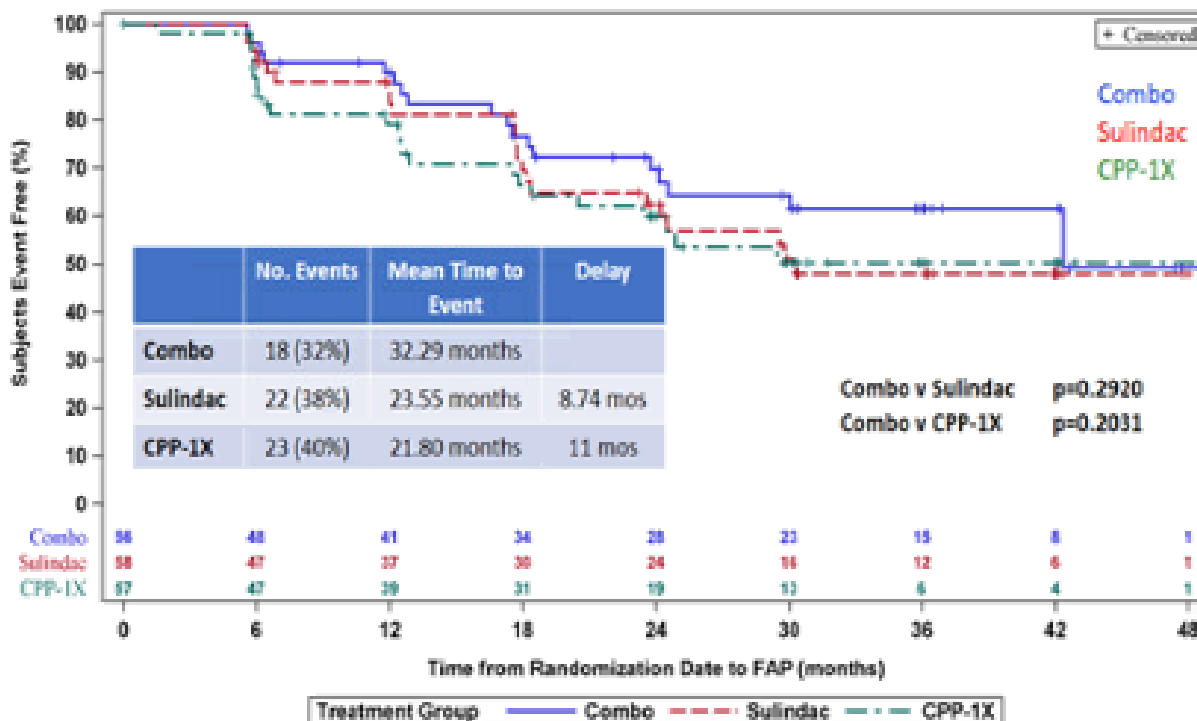
- Expected two year event rate proportion of 40% for the combination and 70% in each single agent



# Results: FAP events



# Primary Outcome: Time to First FAP-related Event



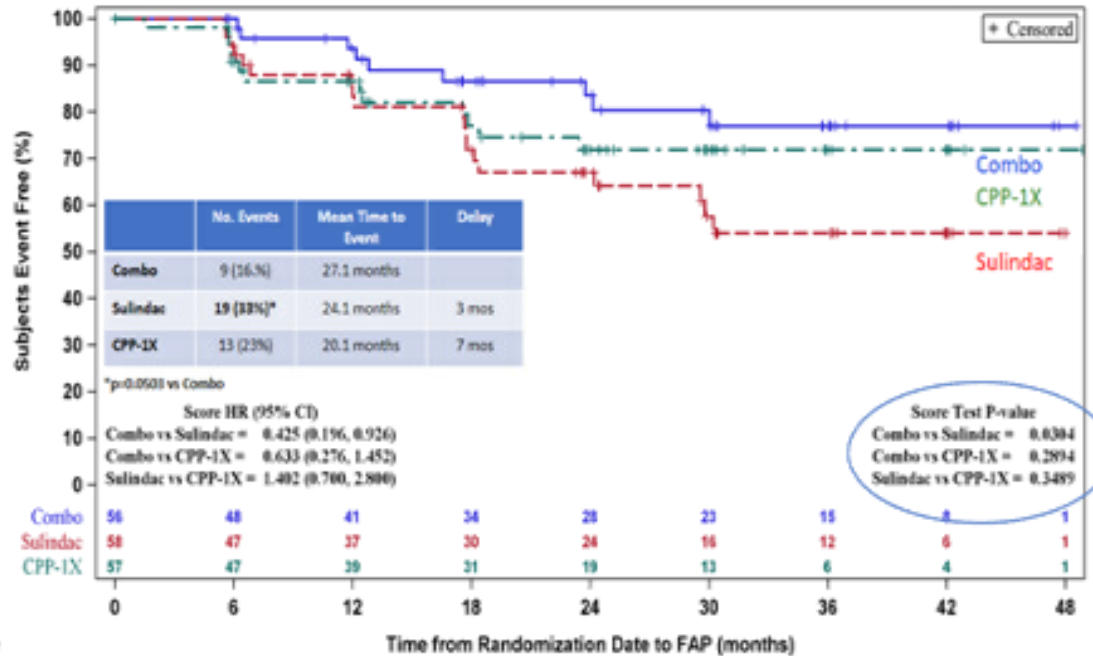
**NO difference** in time to 1<sup>st</sup> event btwn groups  
**BUT time to delay** was improved in combo arm

# FAP related events by disease site

Type		Combo	CPP-1X	Sulindac
Patients with Intact Colon		(N=12)	(N=13)	(N=13)
Disease progression indicating need for colectomy		0	3	4
Event-proportion		0%	23%	31%
Patients with Rectum and Pouch		(N=41)	(N=39)	(N=40)
Excision of $\geq 10$ mm adenoma		2	2	3*
Disease progression indicating the need for proctectomy or pouch resection		0	5	2
Event-proportion		5%	18%	12%
Patients with Duodenum		(N=54)	(N=55)	(N=57)
Disease progression indicating need for endoscopic/surgical intervention (Endo / Surg)		6 (2/4)	3 (2/1)	10 (4/6)
Spigelman stage progression		11	12	7
Event-proportion		31%	27%	30%

# Post-Hoc Analysis: Time to First FAP-related Event

22 patients censored for Spigelman stage progression and no excisional intervention



5/20  
9

14

Majority of events occurred within 1<sup>st</sup> 6 months  
 Difference btwn combo vs. sulindac alone

# Results: Safety

# pts reporting (n/%)	Total (n =171)	Dual (n = 56)	CPP-1x (n=57)	Sulindac (n=58)
Treatment Related AEs	111 (66)	38 (68)	31 (55)	42 (74)
Serious AEs	36 (21)	11(20)	14 (25)	11(19)
Treatment Related Serious AEs	8 (5)	3(5)	1(2)	4(7)
AEs leading to discontinuation	20(12)	9(16)	5(9)	6(11)

# Treatment Related Serious AE\*

CPP-1x/Sulindac	CPP-1x	Sulindac
Acute pancreatitis	Stroke	Severe nausea
Nephritis		DVT
Psychosis & Paranoia		Worsening depression
		Spontaneous abortion

\*All possibly related

## Treatment Related Hearing AE

	CPP-1x/Sulindac	CPP-1x	Sulindac
Hearing loss (n)	3	1	2
Tinnitus (n)	1	1	5

# Conclusions

- Time to FAP event NOT SIGNIFANTLY different btwn combo and each agent alone
- Similar AEs btwn groups
- Fewer than anticipated events occurred
- BUT, combo group
  - NO lower GI surgeries
  - Superior when looking at Spigelman stage progression