



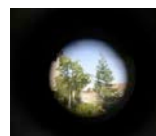
## What's New in Colon Cancer Screening and Surveillance, and How to do High Quality Colonoscopy?

Uri Ladabaum, MD, MS  
Professor of Medicine  
Stanford University

## Colon Cancer Screening and Surveillance: Who, When and How?

### With our colonoscopist tunnel vision

- Who?
  - EVERYONE
- When?
  - OFTEN AND INDEFINITELY  
(We must prevent all CRC!)
- How?
  - SERIOUSLY???



### With our colonoscopist tunnel vision

- Who?
  - EVERYONE
- When?
  - OFTEN AND INDEFINITELY  
(We must prevent all CRC!)
- How?
  - SERIOUSLY??? **COLONOSCOPY, OF COURSE!**



### But we know that's not right...

- Who?
  - EVERYONE WHO MIGHT BENEFIT
- When?
  - BASED ON RISK / BENEFIT BALANCE
- How?
  - THERE ARE ALTERNATIVES, AND PREFERENCES



## Outline

- Guidelines (briefly)
- Rationale / evidence
- What's new
- As a colonoscopist:
  - What should I be doing?
- Thoughts on the future

## Guidelines: (Average-Risk) Screening

	USPSTF	US MSTF, ACS, ACR	ACG
Age to begin	50 yrs	50 yrs	50 yrs 45 yrs in AA
Modality	gFOBT, FIT FIT-DNA (MT-sDNA) Colo CTC Flex Sig Flex Sig/FIT	gFOBT, FIT MT-sDNA Colo CTC Flex Sig DCBE	Colo Flex Sig CTC FIT FOBT Fecal DNA

USPSTF, JAMA. 2016;315(23):2564-2575.  
Levin et al., Gastroenterology 2008;134:1570

Rex et al., Am J Gastroenterol. 2009;104(3):739

## Guidelines: Higher-Risk Screening

	Average Risk	CRC or adenoma in FDR<60 yrs	Lynch syndrome
Age to begin	50 yrs	40 yrs, or 10 yrs before youngest case	20-25 yrs
Modality	FOBT/FIT MT-sDNA Flex Sig Colo DCBE CTC	Colo	Colo
Colo interval	10 yrs	5 yrs	1-2 yrs

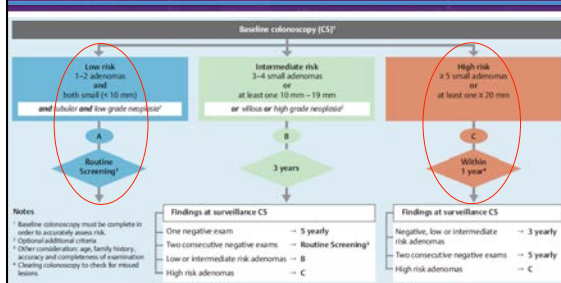
Levin et al., Gastroenterology 2008;134:1570

## Guidelines: Surveillance (US MSTF)

Baseline colonoscopy: most advanced finding(s)	Recommended surveillance interval (y)
No polyps	10
Small (<10 mm) hyperplastic polyps in rectum or sigmoid	10
1-2 small (<10 mm) tubular adenomas	5-10
3-10 tubular adenomas	3
>10 adenomas	<3
One or more tubular adenomas ≥10 mm	3
One or more villous adenomas	3
Adenoma with HGD	3
Serrated lesions	
Sessile serrated polyp(s) <10 mm with no dysplasia	5
Sessile serrated polyp(s) ≥10 mm	3
OR	
Sessile serrated polyp with dysplasia	
OR	
Traditional serrated adenoma	
Serrated polyposis syndrome <sup>a</sup>	1

Lieberman et al., Gastroenterology. 2012;143:844

## ...compare to European guidelines



Atkin et al., Endoscopy 2012; 44: SE151  
Ladabaum and Schoen, Gastroenterology 2016; 150:791

## Guidelines: Surveillance (US MSTF)

**Table 10.** Recommendations for Polyp Surveillance After First Surveillance Colonoscopy

Baseline colonoscopy	First surveillance	Interval for second surveillance (y)
LRA	HRA	3
	LRA	5
	No adenoma	10
HRA	HRA	3
	LRA	5
	No adenoma	5 <sup>a</sup>

Lieberman et al., Gastroenterology 2012;143:844

## Evidence: Screening

### RCTs demonstrate reductions in CRC incidence and mortality after screening with:

- A. sigmoidoscopy
- B. gFOBT, sigmoidoscopy
- C. gFOBT, FIT, sigmoidoscopy, colonoscopy
- D. gFOBT, FIT, sigmoidoscopy
- E. gFOBT, FIT, sigmoidoscopy, colonoscopy, MT-sDNA
- F. None of the above

### Screening: The evidence and what we do

- RCTs: ↓ in CRC incidence and mortality
  - gFOBT
  - Sigmoidoscopy
- Our leading modalities in practice
  - Colonoscopy
  - FIT
- Other / Emerging
  - CTC
  - MT-sDNA
  - Blood, urine biomarkers

### gFOBT decreases CRC mortality

Study	Patients (n)	Years of follow-up	Reduction with annual FOBT	Reduction with biennial FOBT
Mandel (US)	46,551	13	33%	(21%)
Kronborg (Denmark)	61,933	10		18%
Hardcastle (UK)	150,251	8		15%

Mandel et al, N Engl J Med 1993;329:672  
Kronborg et al, Lancet 1996;348:1467

Hardcastle et al, Lancet 1996;348:1472

### gFOBT decreases CRC incidence

Study	Patients (n)	Years of follow-up	Reduction with annual FOBT	Reduction with biennial FOBT
Mandel (US)	46,445	18	20%	(17%)

Mandel et al, N Engl J Med 2000;343:1603

### Flexible sigmoidoscopy

Study	Patients (n)	Years of follow-up (median)	CRC Incidence reduction	CRC Mortality reduction
UK Flex Sig Trial (UK)	170,432	11.2	23%	31%
SCORE Trial (Italy)	34,292	10.5	18%	22% (NS)
PLCO Trial (US)	154,910	11.9	21%	26%
NORCAPP (Norway)	98,792	10.9	20%	27%

Atkin et al, Lancet 2010;375:1624  
Segnan et al, JNCI 2011;103:1310

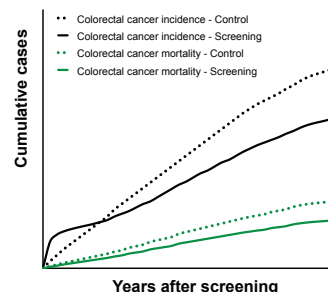
Schoen et al, NEJM 2012;366:2345  
Holme et al, JAMA 2014;312:606

### Flexible sigmoidoscopy: Per protocol

Study	CRC incidence reduction	CRC mortality reduction
UK Flex Sig Trial (UK)	33%	43%
SCORE Trial (Italy)	31%	38%

Atkin et al, Lancet 2010;375:1624  
Segnan et al, JNCI 2011;103:1310

### Flexible sigmoidoscopy



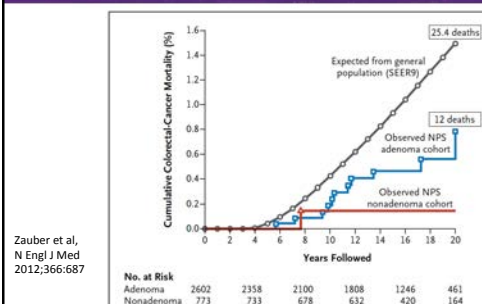
Ladabaum, Colorectal Cancer Screening, Yamada's Textbook, 6<sup>th</sup> Ed, 2015

### Colonoscopy: observational data

Colonoscopy Status	Proximal Cancer		Distal Cancer	
	OR	95% CI	OR	95% CI
No colonoscopy	1.00		1.00	
Any colonoscopy	0.58	0.53 to 0.64	0.24	0.21 to 0.27

Baxter et al, J Clin Oncol 2012;30

### Colonoscopy/polypectomy and CRC mortality



Zauber et al, N Engl J Med 2012;366:687

### Colonoscopy: observational data

Variable	No Lower Endoscopy	Polypectomy
<b>All participants</b>		
No. of person-yr	980,154	72,375
No. of cases of colorectal cancer	1164	82
Age-adjusted incidence rate <sup>†</sup>	45.7	31.4
Age-adjusted hazard ratio (95% CI)	1.00	0.60 (0.47–0.76)
Multivariate hazard ratio (95% CI) <sup>‡</sup>	1.00	0.57 (0.45–0.72)

Nishihara et al, NEJM 2013;369:1095

### Relative risks: Family history of adenoma

Person at risk	CRC, if relative had advanced adenoma <60	CRC, if relative had advanced adenoma 60+	Advanced adenoma, if relative had advanced adenoma
First degree relative	1.5	2.0	1.7
Second degree relative	(NS)	(NS)	(NS)
Third degree relative	0.6	(NS)	2.0

Tuohy et al, Cancer 2014;120:35-42

### CRC screening has been shown to decrease all-cause mortality

- A. True
- B. False

### Screening: What's new?

#### Clinical Review & Education

US Preventive Services Task Force | **RECOMMENDATION STATEMENT**

### Screening for Colorectal Cancer US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

**JAMA** June 21, 2016 Volume 315, Number 23

### USPSTF 2016

Screening Method	Frequency <sup>a</sup>	Evidence of Efficacy
<b>Stool-Based Tests</b>		
gFOBT	Every year	RCTs with mortality end points: High-sensitivity versions (eg, Hemoccult SENS-A) have superior test performance characteristics than older tests (eg, Hemoccult II)
FIT <sup>c</sup>	Every year	Test characteristic studies: Improved accuracy compared with gFOBT. Can be done with a single specimen
FIT-DNA	Every 1 or 3 y <sup>d</sup>	Test characteristic studies: Specificity is lower than for FIT, resulting in more false-positive results, more diagnostic colonoscopies, and more associated adverse events per screening test. Improved sensitivity compared with FIT per single screening test

JAMA. 2016;315(23):2564-2575.

### USPSTF 2016

Screening Method	Frequency <sup>a</sup>	Evidence of Efficacy
<b>Direct Visualization Tests</b>		
Colonoscopy <sup>c</sup>	Every 10 y	Prospective cohort study with mortality end point
CT colonography <sup>b</sup>	Every 5 y	Test characteristic studies
Flexible sigmoidoscopy	Every 5 y	RCTs with mortality end points: Modeling suggests it provides less benefit than when combined with FIT or compared with other strategies
Flexible sigmoidoscopy with FIT <sup>c</sup>	Flexible sigmoidoscopy every 10 y plus FIT every year	RCT with mortality end point (subgroup analysis)

JAMA. 2016;315(23):2564-2575.

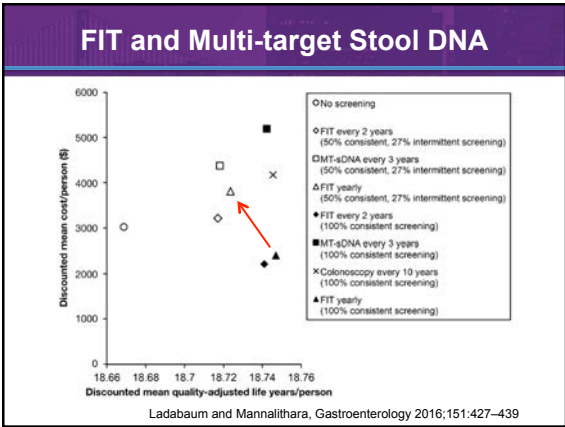
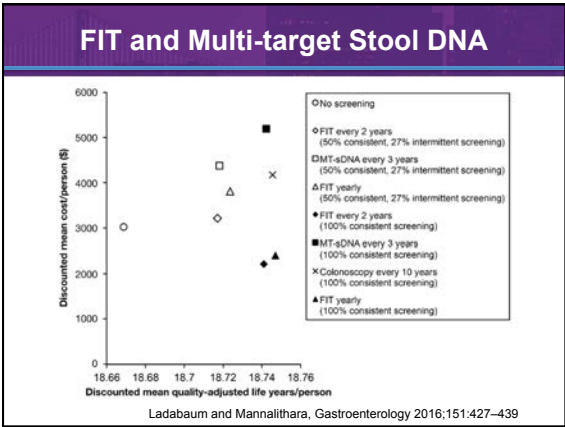
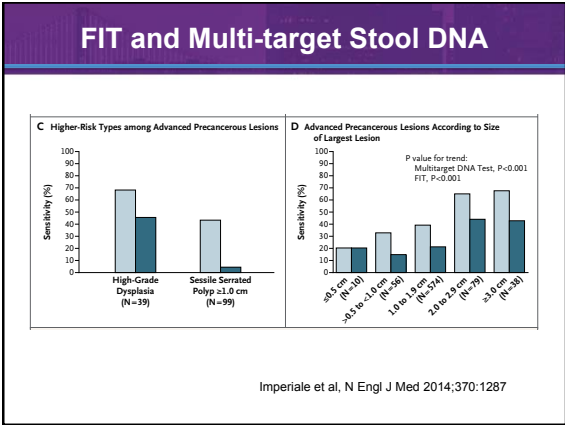
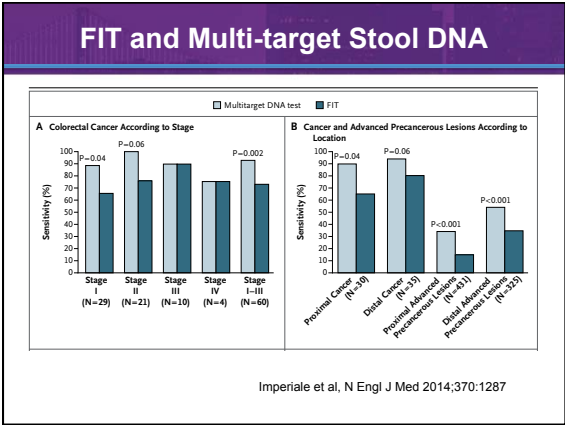
#### Clinical Review & Education

**JAMA | Review**

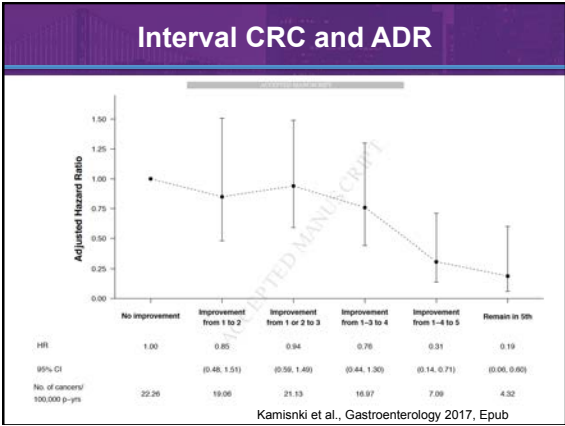
### Screening for Colorectal Cancer and Evolving Issues for Physicians and Patients A Review

David Lieberman, MD; Uri Ladabaum, MD, MS; Marcia Cruz-Correa, MD; Carla Ginsburg, MD, MPH; John M. Inadomi, MD; Lawrence S. Kim, MD; Francis M. Giardiello, MD; Richard C. Wender, MD

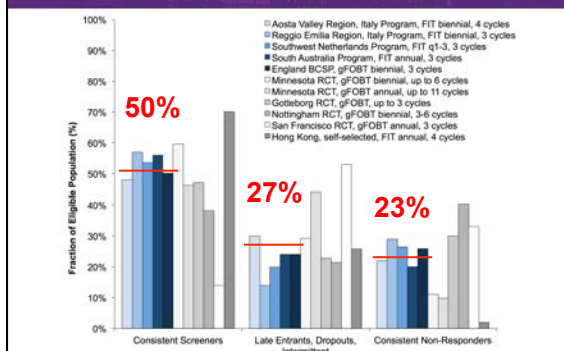
Lieberman D, Ladabaum U, et al. JAMA. 2016;316(20):2135-2145.



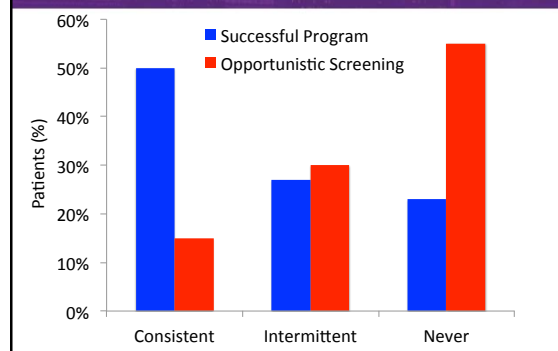
**Effectiveness = Efficacy x Participation**



### "Successful" Organized FIT Programs



### Contrast: Opportunistic FIT Screening



THE NEW ENGLAND JOURNAL of MEDICINE

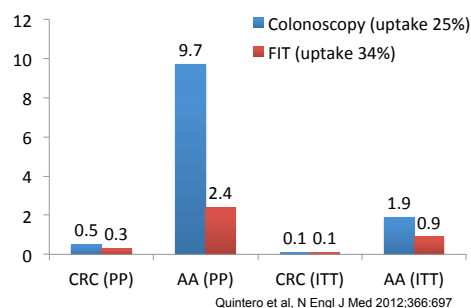
#### ORIGINAL ARTICLE

### Colonoscopy versus Fecal Immunochemical Testing in Colorectal-Cancer Screening

Enrique Quintero, M.D., Ph.D., Antoni Castells, M.D., Ph.D., Luis Bujanda, M.D., Ph.D., Joaquín Cubiella, M.D., Ph.D., Dolores Salas, M.D., Ángel Lanás, M.D., Ph.D., Montserrat Andreu, M.D., Ph.D., Fernando Carballo, M.D., Ph.D., Juan Diego Morillas, M.D., Ph.D., Cristina Hernández, B.Sc., Rodrigo Jover, M.D., Ph.D., Isabel Montalvo, M.D., Ph.D., Juan Arenas, M.D., Ph.D., Eva Laredo, R.N., Vicent Hernández, M.D., Ph.D., Felipe Iglesias, R.N., Estela Cid, R.N., Raquel Zubizarreta, M.D., Teresa Sala, M.D., Marta Ponce, M.D., Mercedes Andrés, M.D., Gloria Teruel, M.D., Antonio Peris, M.D., María-Pilar Roncales, R.N., Mónica Polo-Tomás, M.D., Ph.D., Xavier Bessa, M.D., Ph.D., Olga Ferrer-Armengou, R.N., Jaume Grau, M.D., Anna Serradesanferm, R.N., Akihiro Ono, M.D., José Cruzado, M.D., Francisco Pérez-Riquelme, M.D., Inmaculada Alonso-Abreu, M.D., Mariola de la Vega-Prieto, M.D., Juana María Reyes-Melian, M.D., Guillermo Cacho, M.D., José Díaz-Tasende, M.D., Alberto Herreros-de-Tejada, M.D., Carmen Poves, M.D., Cecilio Santander, M.D., and Andrés González-Navarro, M.D., for the COLONPREV Study Investigators\*

Quintero *et al*, N Engl J Med 2012;366:697

### FIT vs. colonoscopy



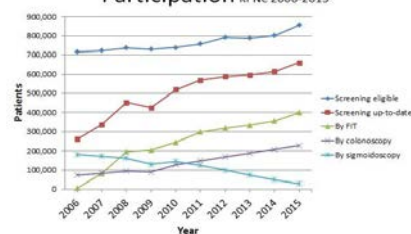
### 80% by 2018?

- Up to date with FIT, sigmoidoscopy, or colonoscopy, 2006-2015: 36.3% → 77.1%
- 60.7% of up-to-date attributable to FIT
- KPNC CRC mortality 42 → 29 / 100,000 (31% decrease)
- US population CRC mortality decrease is half of above (16.2%)

Corley *et al.*, KPNC, DDW 2017

### 80% by 2018?

Figure 1: CRC Screening Eligibility and Participation KPNC 2006-2015

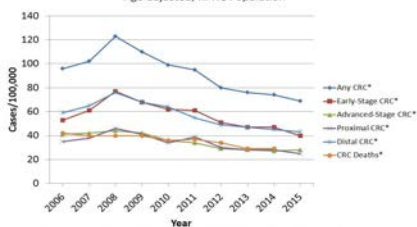


Corley *et al.*, KPNC, DDW 2017



## 80% by 2018?

Figure 2: CRC Incidence and Mortality  
Age-adjusted, KPNC Population



\*Among screening-eligible KPNC patients 50-75 years of age (2006-2015)

\*\*Among KPNC patients ≥50 years of age (2006-2014)

Corley et al., KPNC, DDW 2017

## Evidence: Surveillance

### Surveillance: The evidence

- Much less robust than for screening...
- Risk of metachronous advanced neoplasia after removal of 1-2 low risk adenomas:
  - Range 2.9% – 12.2% depending on specific risk factors

### Rationale and design of the European Polyp Surveillance (EPOS) trials

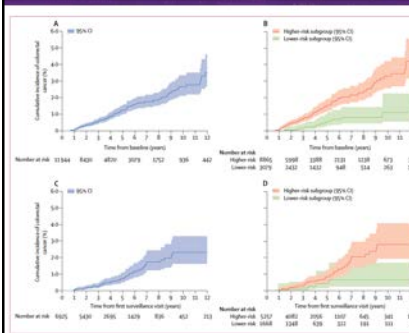
#### Authors

Rodrigo Jover<sup>1,\*</sup>, Michael Bretthauer<sup>2,3,4</sup>, Evellen Dekker<sup>5</sup>, Øyvind Høimer<sup>6</sup>, Michal F. Kaminski<sup>7,8</sup>, Magnus Laberg<sup>9</sup>, Ann C. Zach<sup>10</sup>, Miguel A. Herraiz<sup>11</sup>, Wm Lamsburg-Vogelaar<sup>12</sup>, Annika Sund<sup>13</sup>, Elzavir Møller<sup>14</sup>, Antonio Castells<sup>15</sup>, Jaroslav Regula<sup>16</sup>, Enrique Quintens<sup>17</sup>, Maria Pelluc<sup>18</sup>, Carlo Senore<sup>19</sup>, Mette Kulager<sup>20</sup>, Mario Dinis-Albreito<sup>21</sup>, Louise Emilsson<sup>22</sup>, David F. Ransohoff<sup>23</sup>, Gert Hoff<sup>24,25</sup>, Hans-Oliv Adel<sup>26</sup>

Jover et al., Endoscopy 2016;48:571

## Surveillance: What's new?

### Surveillance associated with ↓CRC



Adjusted hazard ratio after moderate risk adenomas:

0.57  
[0.40–0.80]  
for one visit

0.51  
[0.31–0.84]  
for two visits

Atkin et al, DDW 2017 and Lancet Oncology 2017; online, PMID: 28457708



## Our responsibility as colonoscopists

### Higher adenoma detection rate is associated with:

- A. Decreased interval CRC incidence
- B. Increased risk of bleeding and perforation
- C. Decreased interval CRC mortality
- D. Over-utilization of colonoscopy
- E. All of the above
- F. A and C
- G. A, C and D

### As a colonoscopist: What should I be doing?

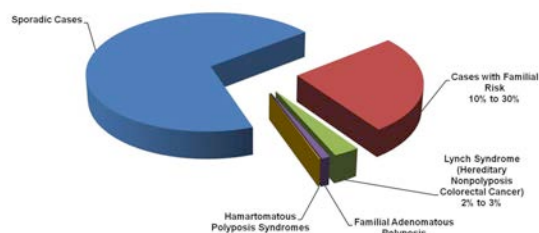
- High quality colonoscopy
  - Primary screening
  - Follow-up of FIT+, etc.
- Detection
- Complete resection
- Family history? Genetic syndromes?
- Appropriate utilization:
  - Surveillance is over-utilized AND under-utilized

### Colonoscopy: operator dependence

Variable	Proximal Cancer	
	OR	95% CI
No colonoscopy	1.00	
Any colonoscopy performed by:		
Gastroenterologist	0.52	0.46 to 0.59
Surgeon	0.74	0.59 to 0.91
Primary care physician	0.63	0.45 to 0.90
Other/unknown	0.72	0.56 to 0.92

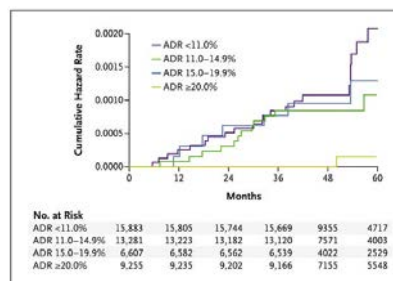
Baxter et al, J Clin Oncol 2012;30

Colon Cancer Cases Arising in Various Family Risk Settings

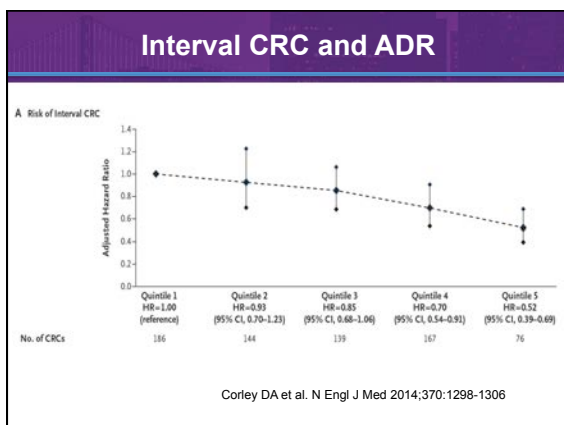


<http://www.cancer.gov/types/colorectal/hp/colorectal-genetics-pdq>

### Interval CRC and ADR



Kaminski et al., NEJM 2010, 362:1795



### Lesion detection rates by endoscopist

Endoscopist	Number of colonoscopies	Patient age*	Male	≥1 Adenoma	≥1 Proximal serrated polyp
1	3189	59.8 ± 8.0	52%	47%	18%
2	154	57.8 ± 8.0	45%	31%	10%
3	532	57.4 ± 7.3	45%	33%	6%
4	109	58.2 ± 7.0	46%	39%	11%
5	331	57.4 ± 6.9	48%	40%	13%
6	124	58.4 ± 6.9	44%	33%	8%
7	528	58.9 ± 7.7	41%	31%	11%
8	56	59.2 ± 7.6	50%	46%	13%
9	348	57.7 ± 7.5	37%	36%	12%
10	359	57.7 ± 7.3	53%	25%	3%
11	90	57.7 ± 6.7	52%	17%	1%
12	83	59.1 ± 8.3	52%	27%	2%
13	327	58.1 ± 7.8	60%	29%	11%
14	297	59.5 ± 8.2	50%	21%	4%
15	154	57.8 ± 8.0	45%	31%	10%
Combined	6681	58.9 ± 7.8	49%	38%	13%

\*Mean ± SD.

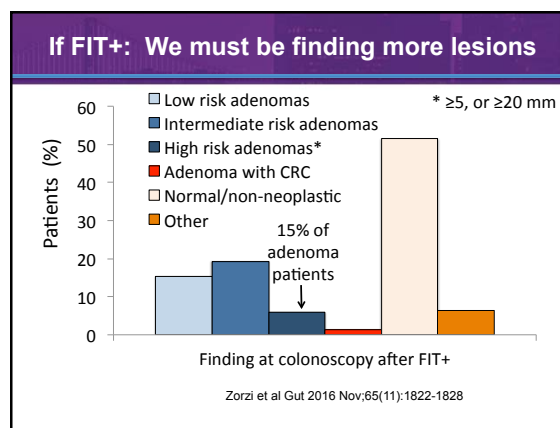
Kahi et al., Clin Gastro Hep 2011;9:42-46

### If FIT+: We must be finding more lesions

Study	CRC detection	Advanced neoplasia detection
Screening Colonoscopy	0.5 – 1 %	5 – 10 %
In FIT+ patients	2.9 – 7.8 %	34 – 54%

- Recommend ADR >45% in men, >35% in women if FIT+ with threshold of 20 mcg/g

Robertson et al., Gastrointestinal Endoscopy 2017;85:2



## High Quality Colonoscopy

- ### High quality colonoscopy: Process, Technique
- Appropriate patient selection and screening
  - Good preparation – split-dose preparation
  - Cecal intubation
  - Insertion with water – minimal air / gas
  - Water immersion / exchange
  - Carbon dioxide if available
  - Retroflexion in cecum or second look
  - Inspection and lesion removal on insertion

### High quality colonoscopy: Performance

- Adenoma detection rate (ADR)
- Serrated lesion detection rate
- Adenomas per colonoscopy
- Complete resection
- Optical diagnosis of high risk lesions
- Know when NOT to biopsy or resect only partially – refer if needed for complete resection
- Technologies to increase lesion detection?

### The future: Further personalization?

### "Average Risk" CRC Screening

#### One Size Fits All

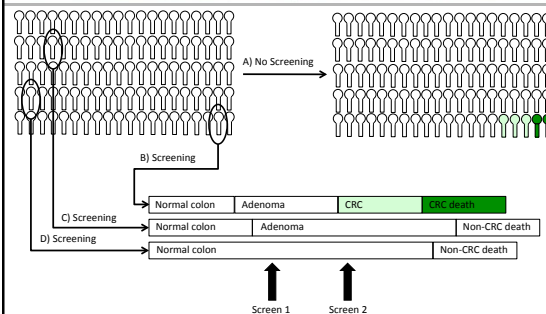


or



#### Personalized Tailoring?

### Average Risk Screening: Most people do not benefit



Ladabaum, Colorectal Cancer Screening, Yamada's Textbook, 6<sup>th</sup> Ed, 2015

### Inertia vs. sound policy vs. politics?

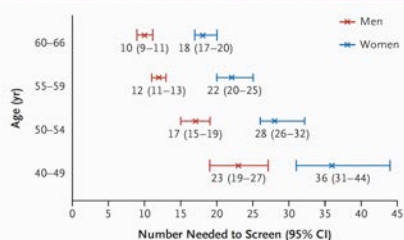


Figure 1. Numbers Needed to Screen in Order to Detect Advanced Neoplasia in the Large Bowel, According to Age Group and Sex.

Regula et al., NEJM 2006; 355(18):1863

### Inertia vs. sound policy vs. politics?

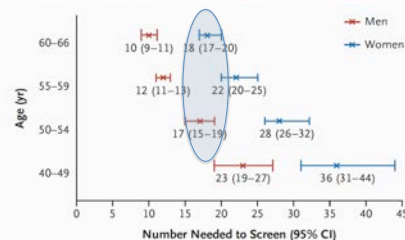


Figure 1. Numbers Needed to Screen in Order to Detect Advanced Neoplasia in the Large Bowel, According to Age Group and Sex.

Regula et al., NEJM 2006; 355(18):1863

## Inertia vs. sound policy vs. politics?

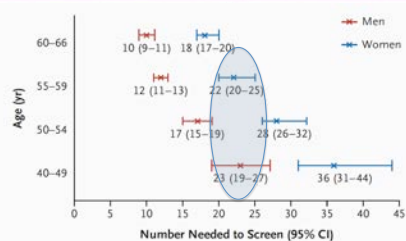
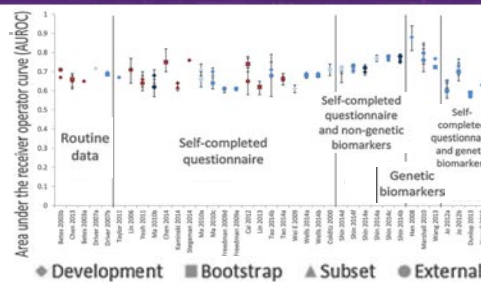


Figure 1. Numbers Needed to Screen in Order to Detect Advanced Neoplasia in the Large Bowel, According to Age Group and Sex.

Regula et al., NEJM 2006; 355(18):1863

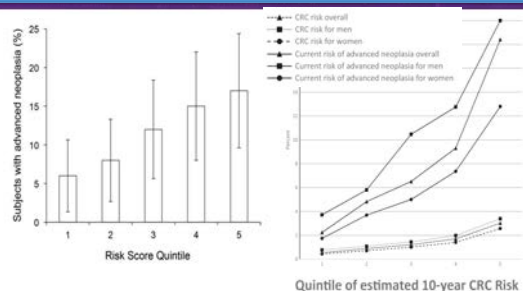
## Risk Prediction = Personalization?



Usher-Smith et al., Cancer Prev Res 2016;9:13

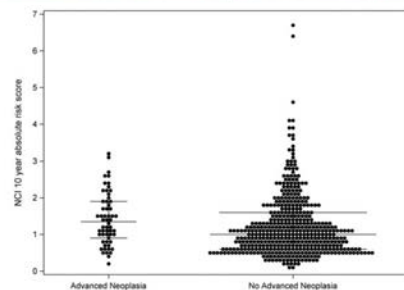
Ladabaum et al., Cancer 2016;122:2663  
Imperiale et al., JNCI 2017;109(1)

## NCI Risk Score Prospective Validations



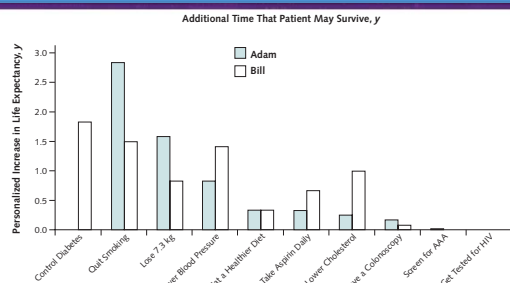
Ladabaum et al., Cancer 2016;122:2663  
Imperiale et al., JNCI 2017;109(1)

## Discriminatory ability is only modest...



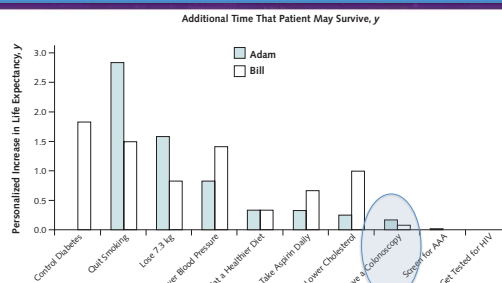
Ladabaum et al., Cancer 2016;122:2663

## Keeping it in perspective...



Taksler et al., Ann Int Med 2013;159:161

## Keeping it in perspective...



Taksler et al., Ann Int Med 2013;159:161

### But we know that's not right...

- Who?
  - EVERYONE WHO MIGHT BENEFIT
- When?
  - BASED ON RISK / BENEFIT BALANCE
- How?
  - THERE ARE ALTERNATIVES, AND PREFERENCES

