

Classification & Detection of Colorectal Polyps

A Changing Landscape

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Disclosures

Relationship with Exact Sciences

- *Mayo Clinic*
 - Equity investor
 - Licensed technologies
- *Dr. Ahlquist*
 - Scientific Advisor
 - Inventor of licensed technology
 - Research collaborator

Polyp Detection by Colonoscopy

Questions

Is there a problem?

What are we looking for?

How can we improve detection?

Which methods benefit most?

The Problem

- **Despite screening in US, CRC remains the #2 cancer killer**
- **Shift to the right ($\geq 50\%$ prox)**

1980 → 2000 (rate/100,000)

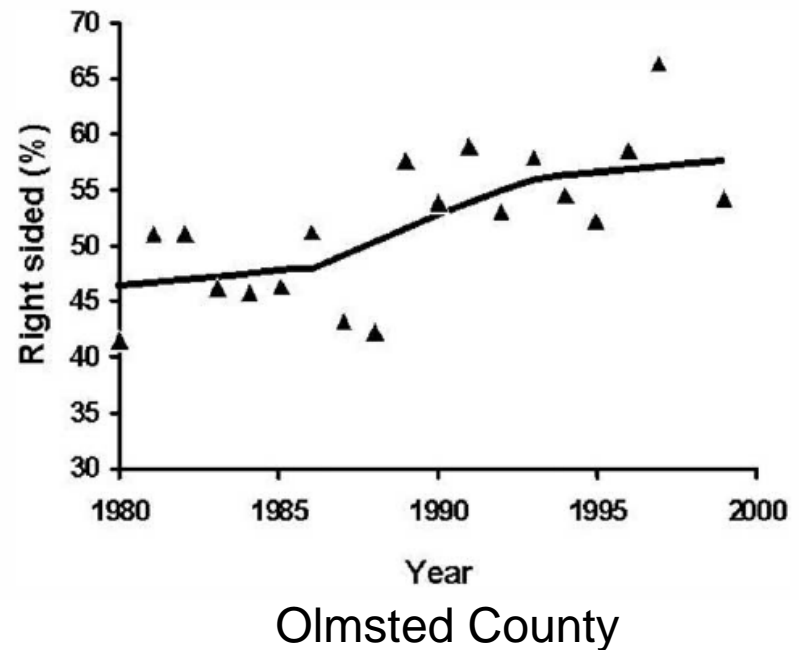
Polypectomies: 86 → 320

CRC incidence: 60 → 46

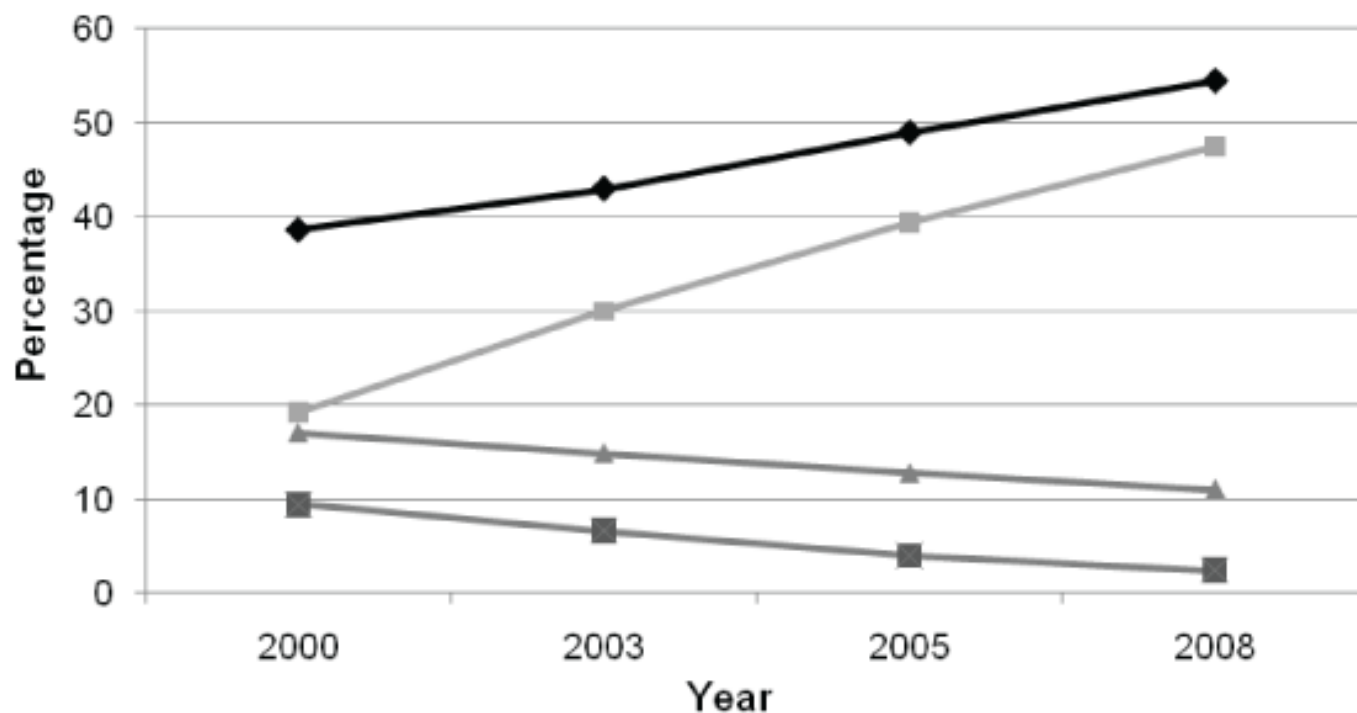
Left 32 → 19

Right 27 → 27

Gupta et al. CGH 2005;3:150



Colorectal Cancer Screening Modalities in US



No Screening
~50%

- ◆ Any exam (FOBT in past year, sigmoidoscopy in past 5 years, or colonoscopy in past 10 years)
- Colonoscopy in past 10 years
- ▲ Home FOBT in past year
- Sigmoidoscopy in past 5 years

National Health Interview Survey
National Ctr for Health Stat

Effectiveness of Colonoscopy?

Recent Wake-up Calls

Large case-control studies

- **CRC mortality** (Baxter et al. Ann Intern Med 2009;150:1)

- L sided ~ 70%
- R sided 0%



- **CRC incidence** (Brenner et al. JNCI 2010;102:89)

- L sided ~ 70%
- R sided 0%



Screening Outcomes by Specialty

	Colonoscopy by GI doctors	Colonoscopy by non-GI doctors
Rex Indiana 1997	CRC miss rate 3%	CRC miss rate 13%
Rabeneck Ontario 2010	Reference rate 1.0	HR for interval CRC Surgeons 1.39 Others 1.28
Baxter Ontario 2010	Reference rate 1.0	HR for interval CRC Surgeons 1.23 Others 1.87

Adapted from Dr Doug Rex

Long Term CRC Risk Reduction after Colonoscopy & Polypectomy

Nishihara et al (DDW 2012)

- **Prospective cohort study (Harvard System)**

N ~ 100,000

F/U ~ 2.5 million person-yrs

- **Relative CRC risk, HR**

Never screened 1.0 (ref)

Neg colonoscopy 0.45

Left 0.26

Right 0.66

After polypectomy 0.64

Adenoma Detection Rates

Variation among Gastroenterologists

	Number doctors	Lowest ADR	Highest ADR	Absolute Difference
Barclay Illinois 2006	12	9.4%	32.7%	23%
Chen Indiana 2007	9	15.5%	41.1%	26%
Imperiale Indiana 2009	25	7%	44%	37%
Shaukat Minnesota 2009	51	10%	39%	29%

Adapted from Dr Doug Rex

Serrated Polyp Detection Rates

Variation among Gastroenterologists

	Number doctors	Lowest proximal detection rate	Highest proximal detection rate	Absolute Difference
Hetzel Boston	13	1.1%	7.6%	6%
Kahi Indiana	15	1%	18%	17%

Adapted from Dr Doug Rex

Quality Indicators and Risk of Interval CRC

Kaminski et al. NEJM 2010

- Poland, n=45,026 patients
- Colonoscopists 186
- Stratified results

<u>ADR</u>	<u>Interval CRC (per 100,000)</u>
<11%	34
11-19.9%	24
<u>≥20%</u>	~2

Polyp Targets

Size Considerations

- **Most do not progress**
 - 50-70% get polyps
 - 6% get CRC
- **Small (5-9mm) & diminutive (<5mm)**
 - Controversial targets
 - Hard to predict natural hx
 - Relevant because of lengthy (10 yr) colonoscopy screening interval
- **Large ($\geq 1\text{cm}$)—consensus targets**
 - Risk of HGD & CRC increases exponentially with size above 1cm

Premalignant Polyp Types

- **Adenoma**

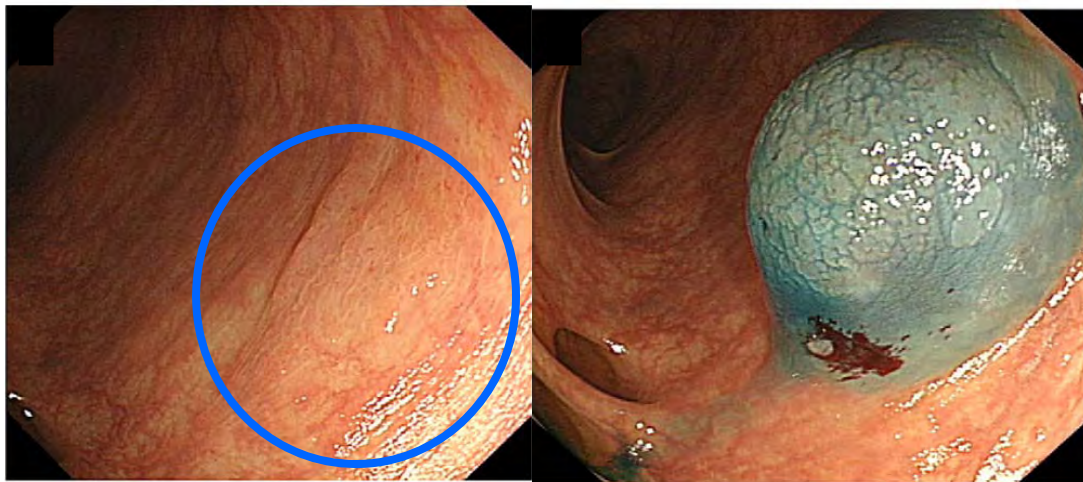
- Tubular (T), villous (V), tubulovillous (TV)
- **“Advanced” if $\geq 1\text{cm}$, V, or TV**

- **Serrated**

- Hyperplastic
- Sessile serrated polyp (*BRAF* + meth)
- Traditional serrated polyp (*KRAS* + meth)
- **“Advanced”? (if $\geq 1\text{cm}$)**

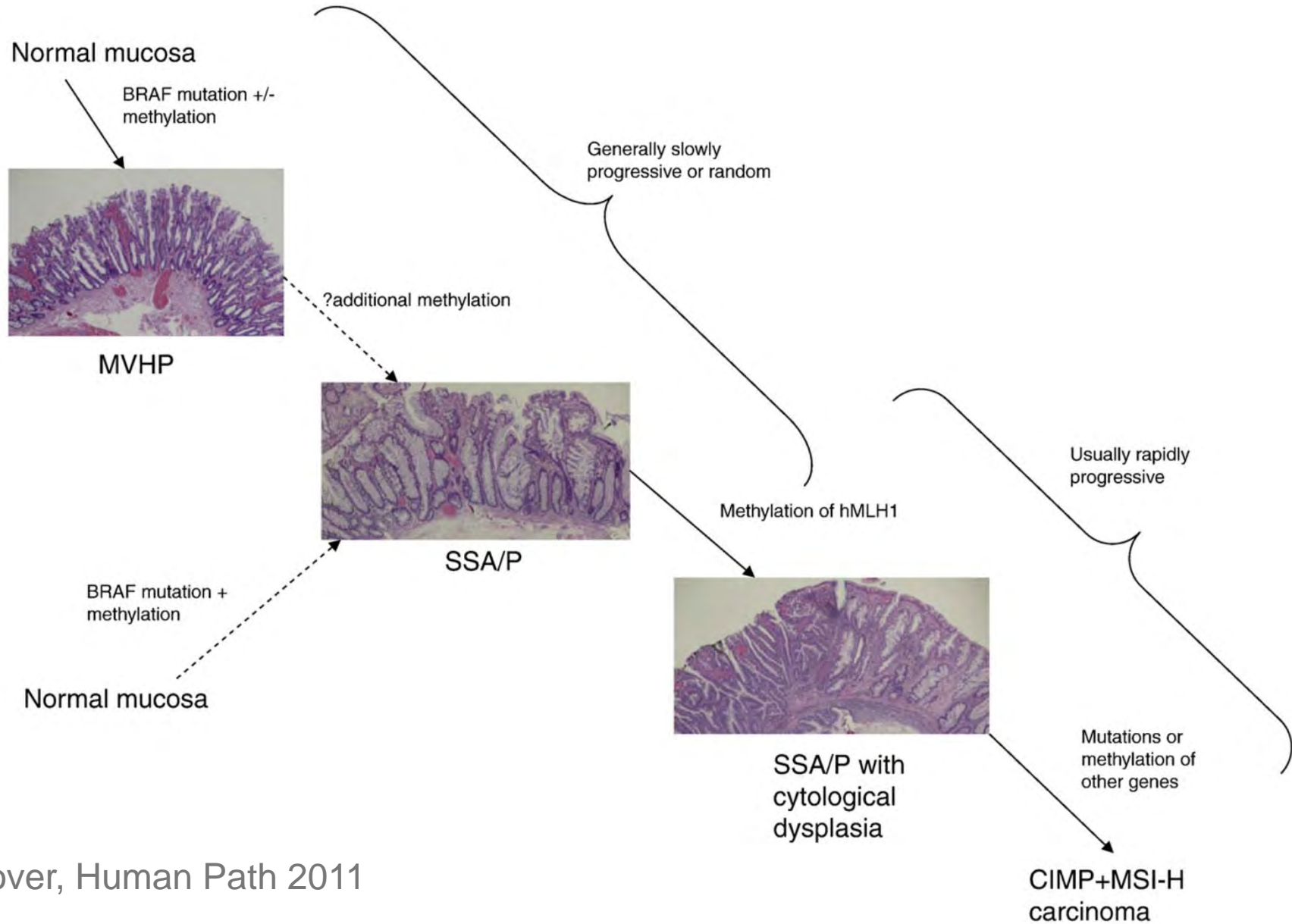
Sessile Serrated Polyps

- Precursors for ~1/3 of CRC
- Now account for ~1/3 of advanced polyps
- R>>L
- Detection requires mindfulness & a trained eye

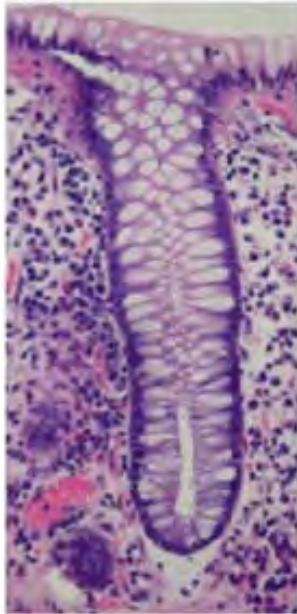


Images courtesy of
Drs Rex & Won Kee Song

Serrated Polyp Pathway to CRC

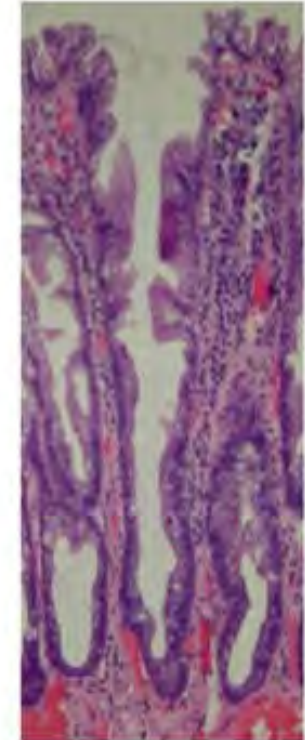


Hyperplastic Polyp



Normal Crypt

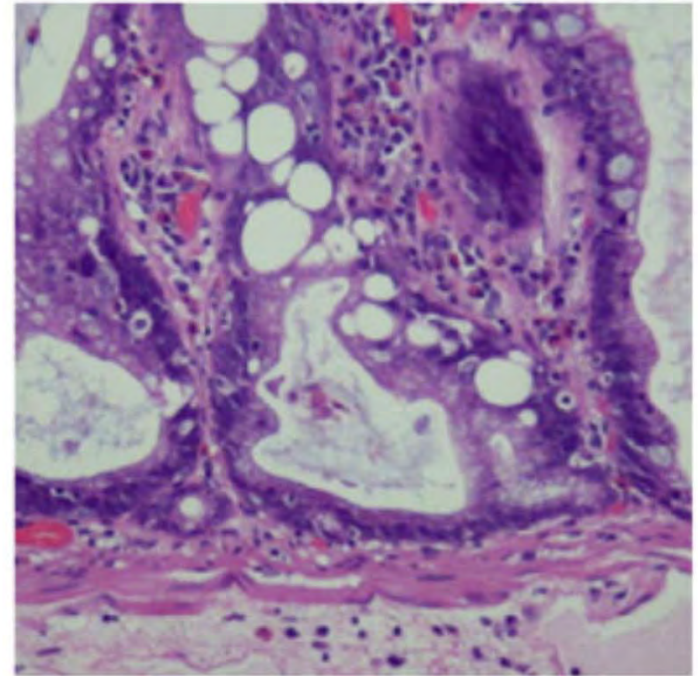
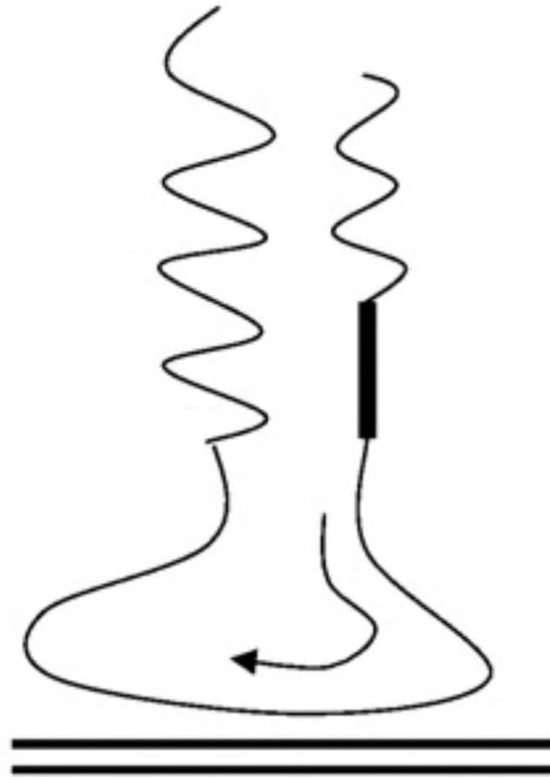
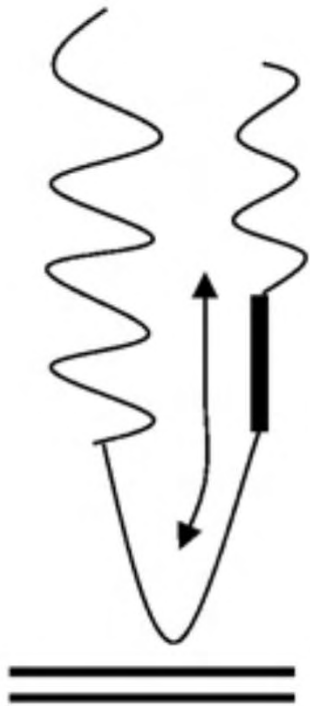
- Prolif at base
- Cells mature toward lumen



Hyperplastic Polyp

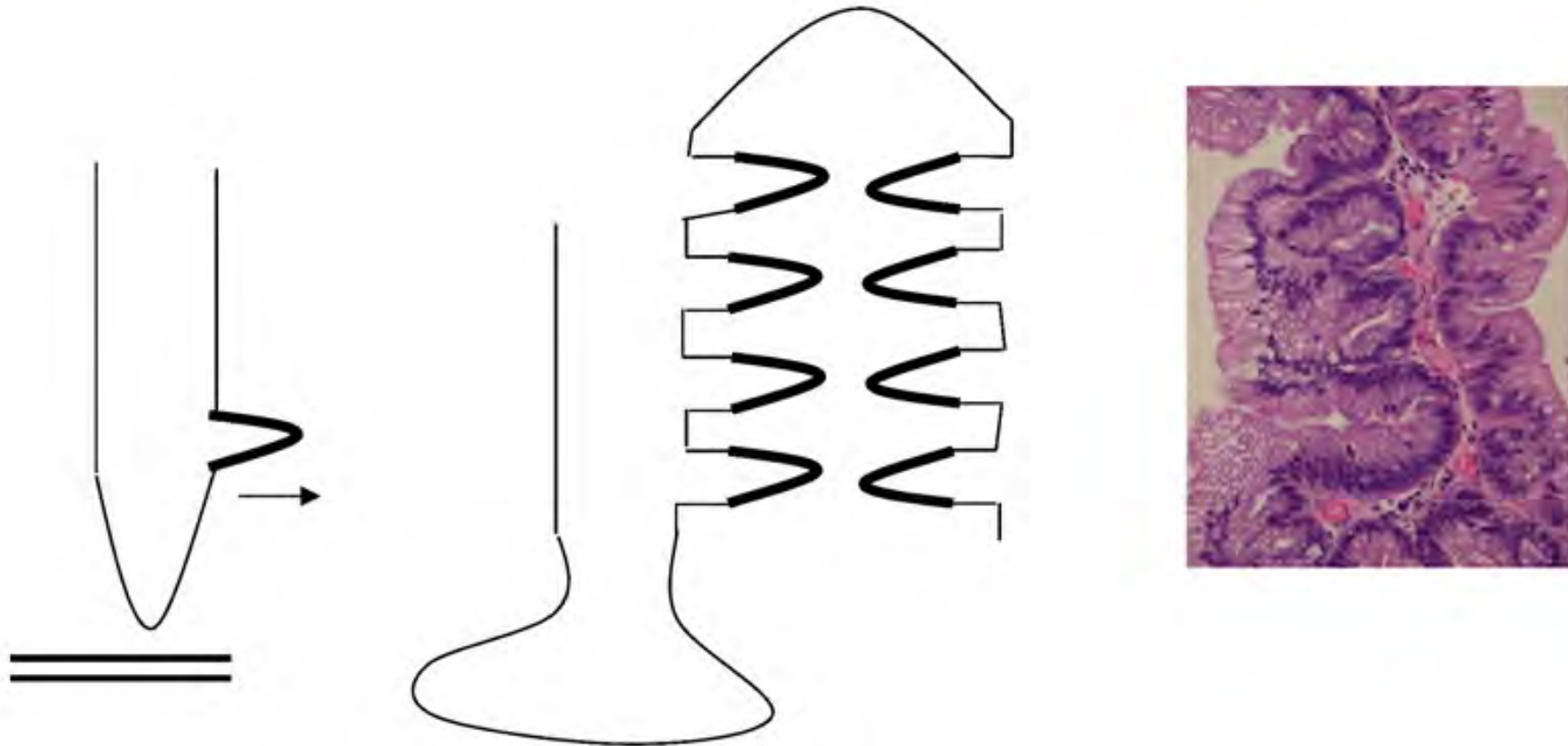
- Expanded basal prolifer
- Cells mature toward lumen
- ↓ apoptosis = serrations

Sessile Serrated Polyp



- Proliferative zone moves up side of crypt
- Movement of mature cells all directions

Traditional Serrated Polyp



- Emergence of proliferative zones on side of crypt
- Multiple ectopic crypts form

Polyp Targets

	Type*	Site	Detection Barrier
Pedunculated	AD	L>R	Surface exposure
Sessile	AD,S	Both	
Flat	AD,S	R>L	Surface exposure + Lesion discrimination
Depressed**	AD	R>L	

*AD = adenoma, S = serrated polyp

**Rare, disproportionate HGD

The “Mozart Effect”

3x increase
in polyp
detection

O’Shea, ACG Meeting 2011



Methods Intended to Enhance *Surface Exposure*

- Insertion to cecum
- Bowel prep & cleansing
- ~~Wide angle endoscopy~~
- Cap-assisted colonoscopy
- Through-the-scope
retroscopes
- Retroflexion



**Better views of
flexures & prox
sides of folds?**

Bowel Preparation

Lebwohl et al. GIE 2011

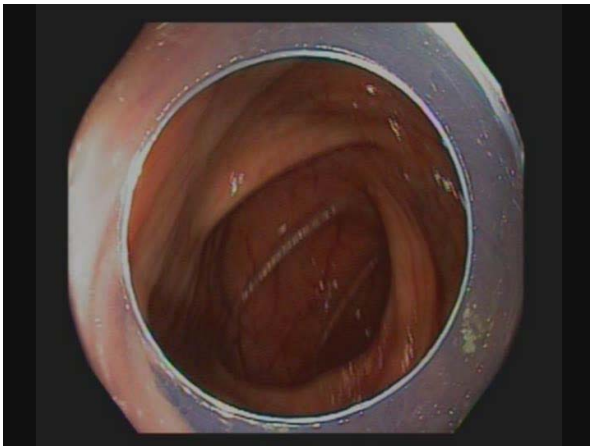
From 12,787 colonoscopies,
24% had suboptimal prep (poor/fair)



Among those who had repeat colonoscopy
with optimal prep <3yrs*

Adenomas	42%
Adv adenomas	27%

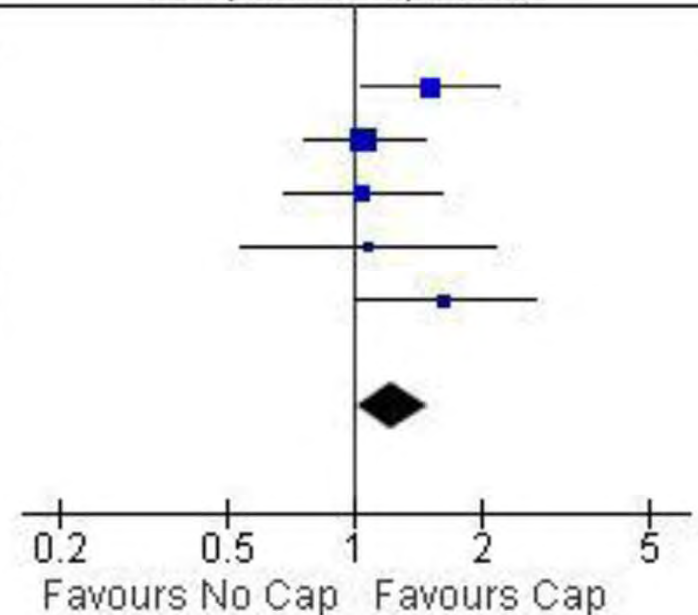
* not seen on index colonoscopy with poor prep



Polyp Detection with Cap-assisted Colonoscopy (CAC): Meta-analysis

Wani et al (DDW 2012)

Study	Weight	Odds Ratio		Year	Odds Ratio	
		M-H, Random, 95% CI	Year		M-H, Random, 95% CI	
Matsushita 1998		Not estimable		1998		
Kondo 2007	25.5%	1.51 [1.04, 2.19]		2007		
Harada 2009	32.5%	1.05 [0.76, 1.46]		2009		
Tee 2010	19.7%	1.05 [0.69, 1.60]		2010		
Dai 2010	7.5%	1.08 [0.54, 2.15]		2010		
Lee 2011	14.8%	1.64 [1.01, 2.68]		2011		
Total (95% CI)	100.0%	1.23 [1.02, 1.49]				



	CAC	Std Colo
All polyps	40%	36%
Adenomas	32%	34%

Endoscopic image from Dr Doug Rex₂₃

Through-the-Scope Retrosopes

Gains in polyp detection rates

- Uncontrolled studies ~10%
- RCT (Leufkens GIE 2011)
 - All adenomas 7%
 - Adv adenomas 2%



Issues

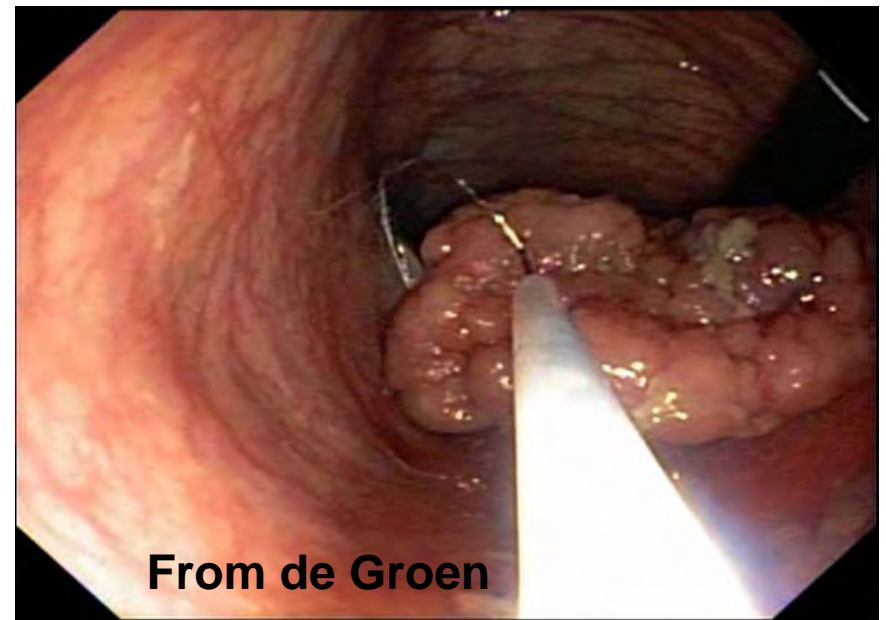
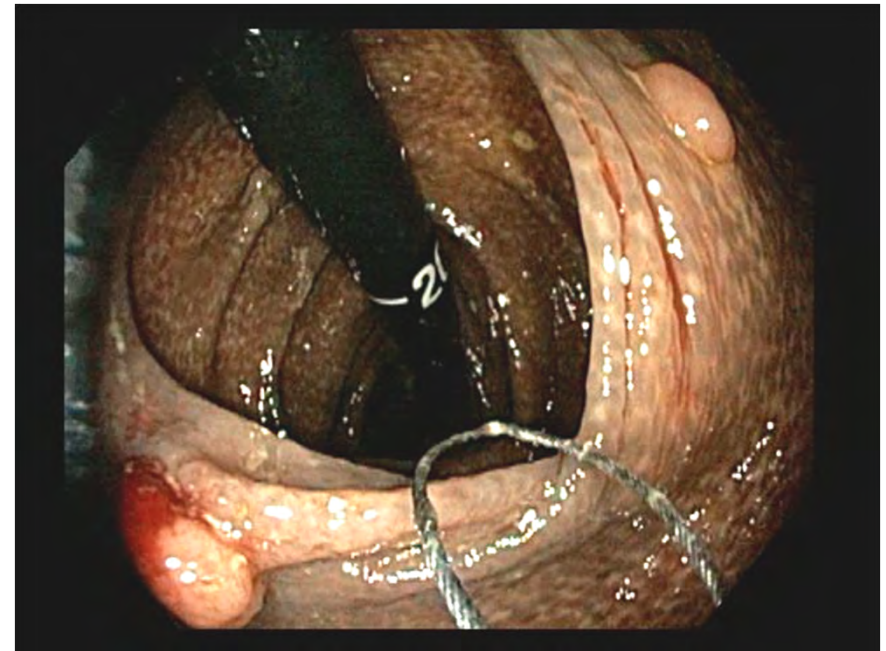
- Distraction from 2 simultaneous images
- Creation of blind spots
- Lens cleaning
- Suctioning impaired
- Procedure time ↑
- Cost & reimbursement

Adapted from Dr Doug Rex

Proximal Colon Retroflexion



From de Groen



From de Groen

Additional Polyp Yield with Retroflexion

Hewett & Rex, GIE 2011

Study

- 1000 consecutive patients
- 2 experienced colonoscopists
- Forward-viewing colonoscopy with removal of all polyps → then retroflex exam

Results

- Successful retroflexion 95%, safe
- Additional adenoma yield

Any	9.8%
Advanced	4.4%

Methods Intended to Enhance *Lesion Discrimination*

Tools

- Chromoendoscopy
- Narrow band imaging (NBI)
- High definition (HD)

Opportunity/need for optical innovations that better highlight flat/depressed lesions

Individual Performance/Skill

- Mindfulness, recognition clues, education
- Optimal metrics

Chromoendoscopy

- **Modest (~10%) increase in detection of small polyps** (Randomised studies: Kahi 2010 (US), Pohl 2011 (Germany))
- **But, tedious, nonspecific, and ↑ time + cost**
- **Thoughts**
 - Impractical for general CRC screening
 - Helpful to define flat lesions
 - Important role in IBD surveillance



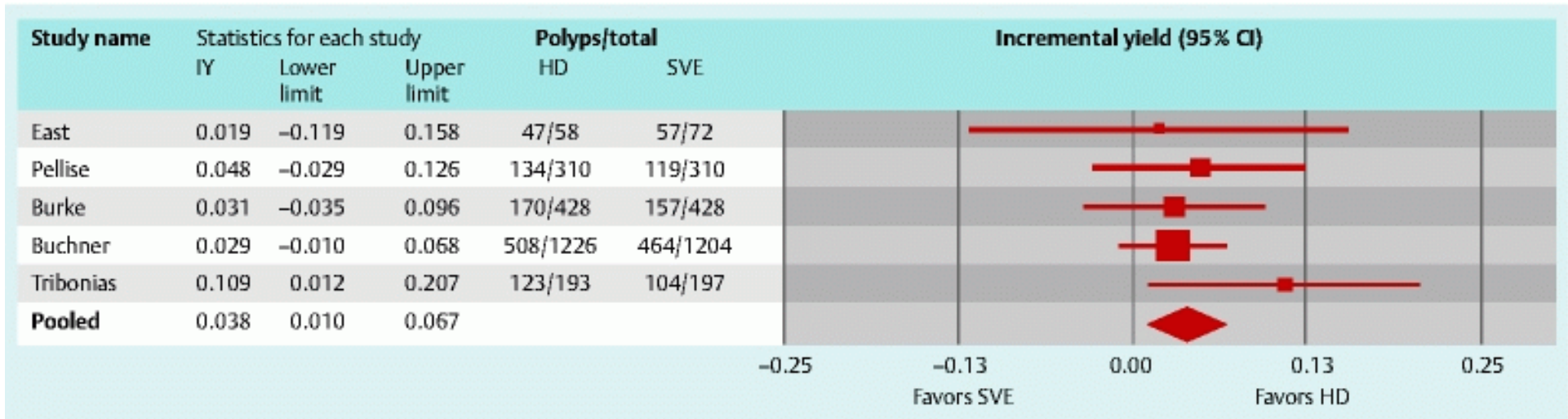
NBI vs White Light

Meta-analysis of Randomized Studies

Study	Pts with adenoma NBI	Pts with adenoma WLE	adenoma/pt NBI	adenoma/pt WLE	O.R. NBI vs WLE
Rex 2007 N=217	65%	67%	1.86	1.82	0.90 (0.61-1.34)
Adler 2007 N= 198	23%	17%	0.33	0.26	1.27 (0.88-1.84)
Inoue 2008 N=122	42%	34%	0.84	0.55	1.55 (1.14-2.11)
Pooled	44%	41%	1.06	0.96	1.23 (0.93-1.61)

Van den Broek et al. GIE 2009;69:124 (Adapted from Dr. Mike Wallace)

HD vs Standard Colonoscopy Meta-analysis



Increase adenoma detection by HD

Any 3.5%

Advanced (no increase)

Subramanian et al Endoscopy 2011;43:499 (Adapted from Dr. Mike Wallace)

Metachronous & Interval CRC

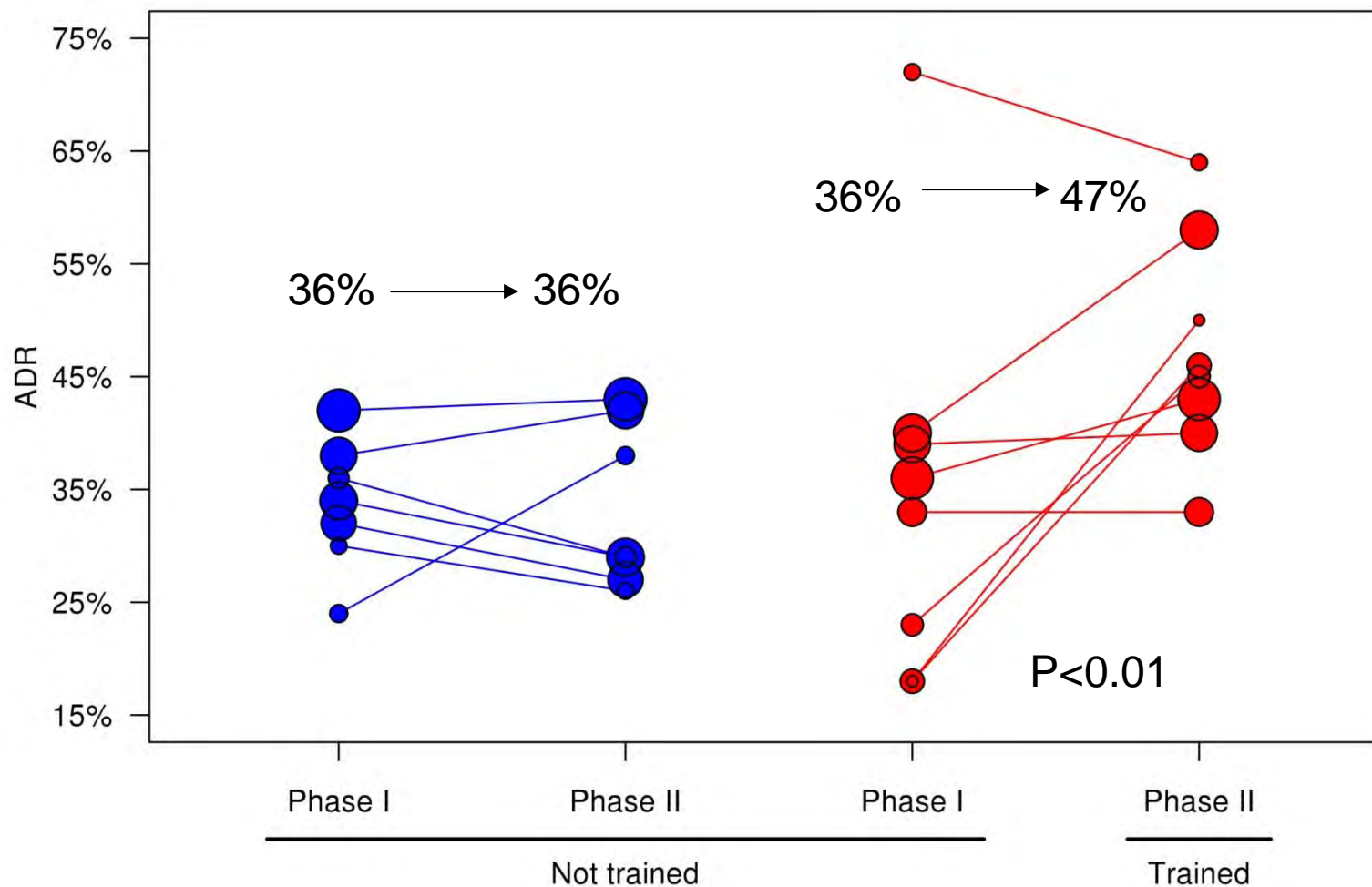
Program Failures

- Metachronous CRC incidence (%)

	<i>Years post-resection</i>				
	<u>3</u>	<u>5</u>	<u>6</u>	<u>10</u>	<u>20</u>
Bonvier 2008	--	1.8	--	3.4	7.2
Mulder 2012	1.1	--	2	3.1	--

- Interval CRC
 - 30-50% of CRC in screen/surveillance programs not detected soon enough or at all
 - R>L
- Potential causes and solutions
 - Non-compliance
 - Missed lesions
 - New lesions

Effect of Didactic Sessions on ADR



Quality Metrics

- **Ultimate metric: Interval CRC**

- **Surrogate measures**

Precursor targets

- Adenoma detection rate (ADR)
- Polyps per patient rate

Technical elements

- Cecal intubation rate, withdrawal time, etc

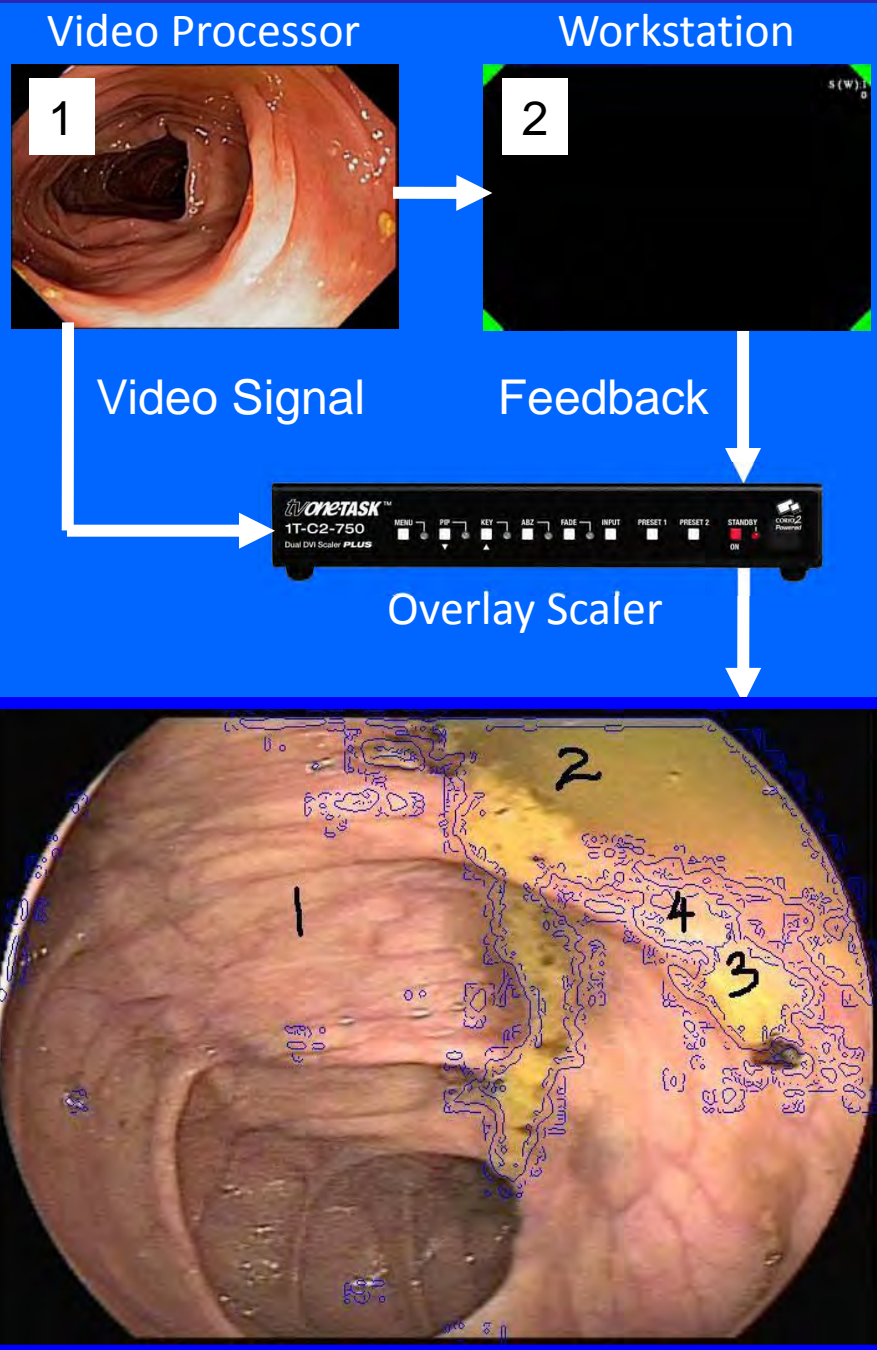
Aggregate quality score

- **Real-time computer systems**

Real-time Quality Analysis and Feedback

- Clear frame
- Retroflexion
- Circumferential inspection
- Withdrawal time
- Stool/fluid (score & map)

From Dr Piet de Groen, Mayo Clinic



EndoMetric Report

Prototype for Colonoscopy

Overall Quality Score

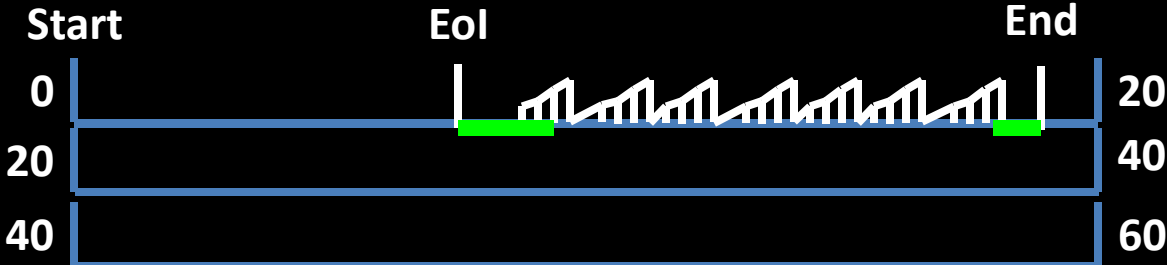


Preparation Score 8 (Min-Max)

Cleaning Score 8 (Min-Max)

Spiral Score 7 (0-∞)

Image Eol



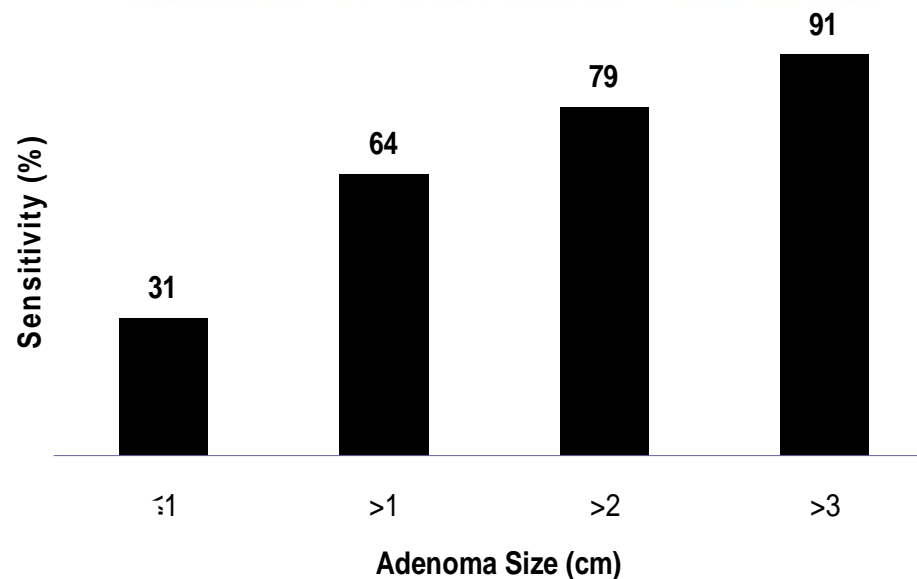
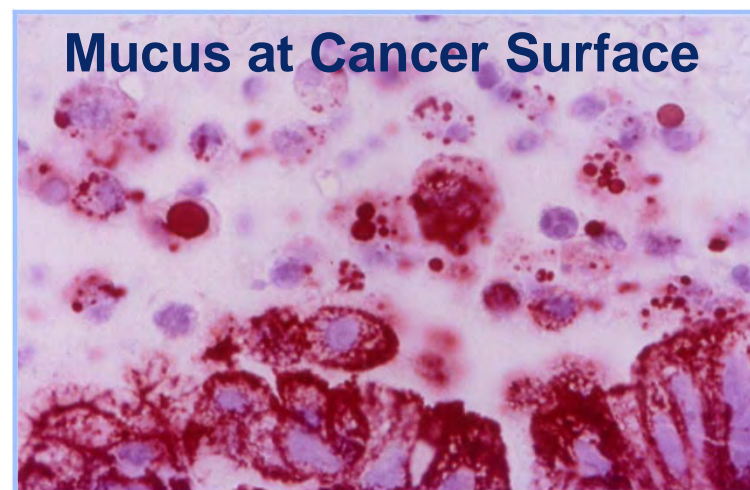
Retroflexion: 

Insertion Time (min): Total 8 Clear 6

Withdrawal Time (min): Total 10 Clear 7

Stool DNA Testing

- Biologically rational
- Noninvasive
- No cathartic prep
- No diet or med restriction
- Can be mailed
- Not affected by site*
- High sensitivity for both CRC (85-98%) & precancer*
- Primary screen + interval test



*Ahlquist et al. Gastroenterology 2012,
Lidgard et al, DDW 2012

Interventions for Polyp Detection Potential to Increase Yield?

Capture the unscreened **40-50%**

Reduce operator variation **15-20%**
e.g. training & metrics

Optimize longitudinal program **10%**

Retroflex routinely **5-10%**

Perfect preparation **5-10%**

Use ancillary tools **0-10%**

e.g. NBI, CAC, TTS retroscope

Summary

- **Colonoscopy is operator-dependent, and quality varies widely**
- **Polyp miss rates highest on right**
- **Impact: population screen capture > quality/skill > ancillary tools**

Clear opportunities to improve polyp detection