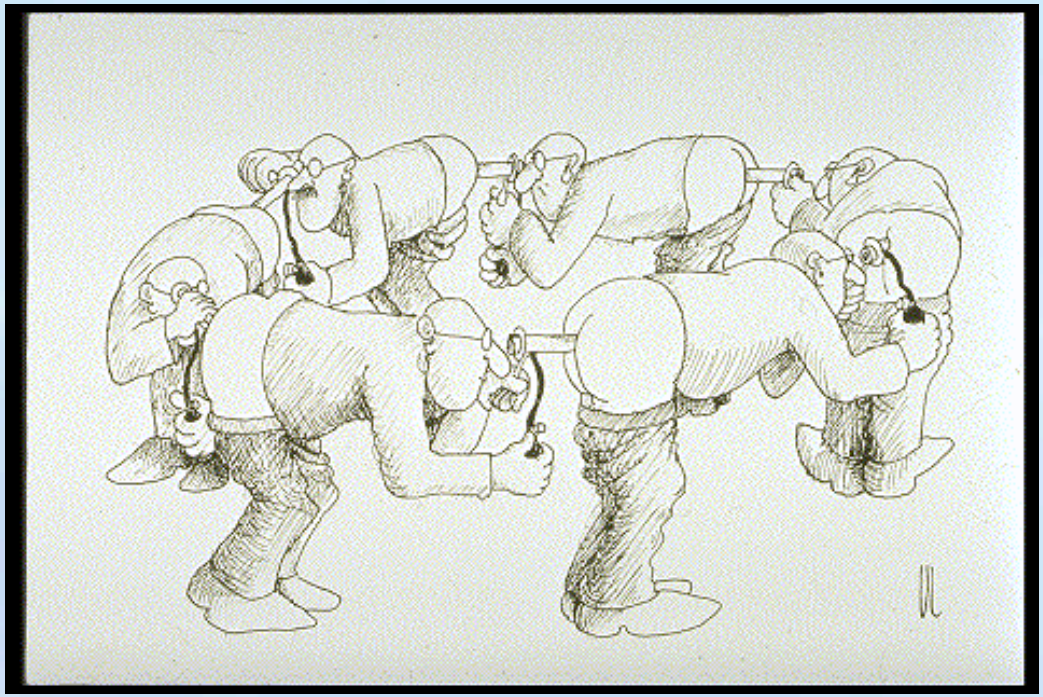
Future Screening Modalities for CRC

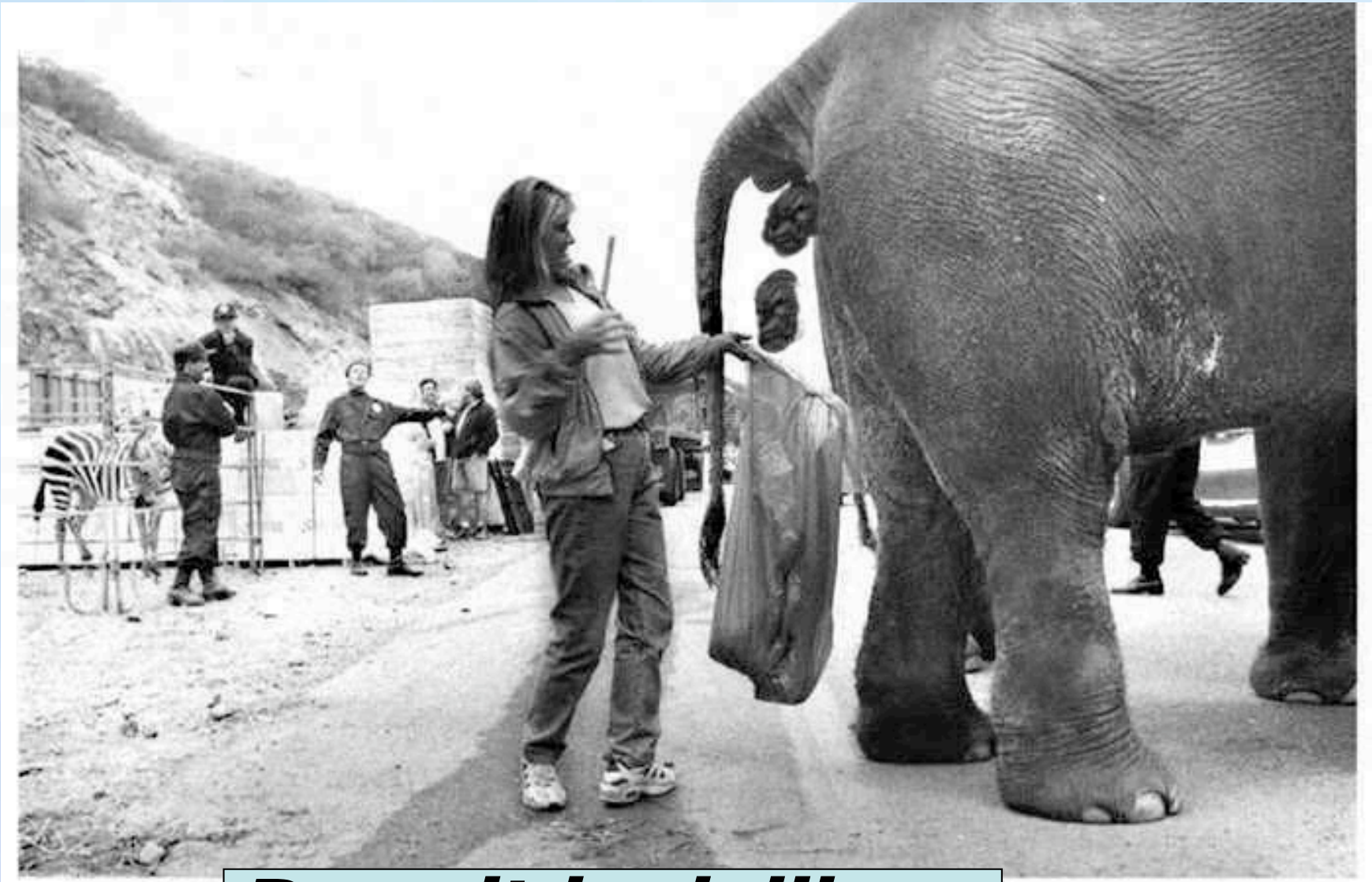
Perspectives dans le Pistage du Cancer Colorectal



Nadir Arber

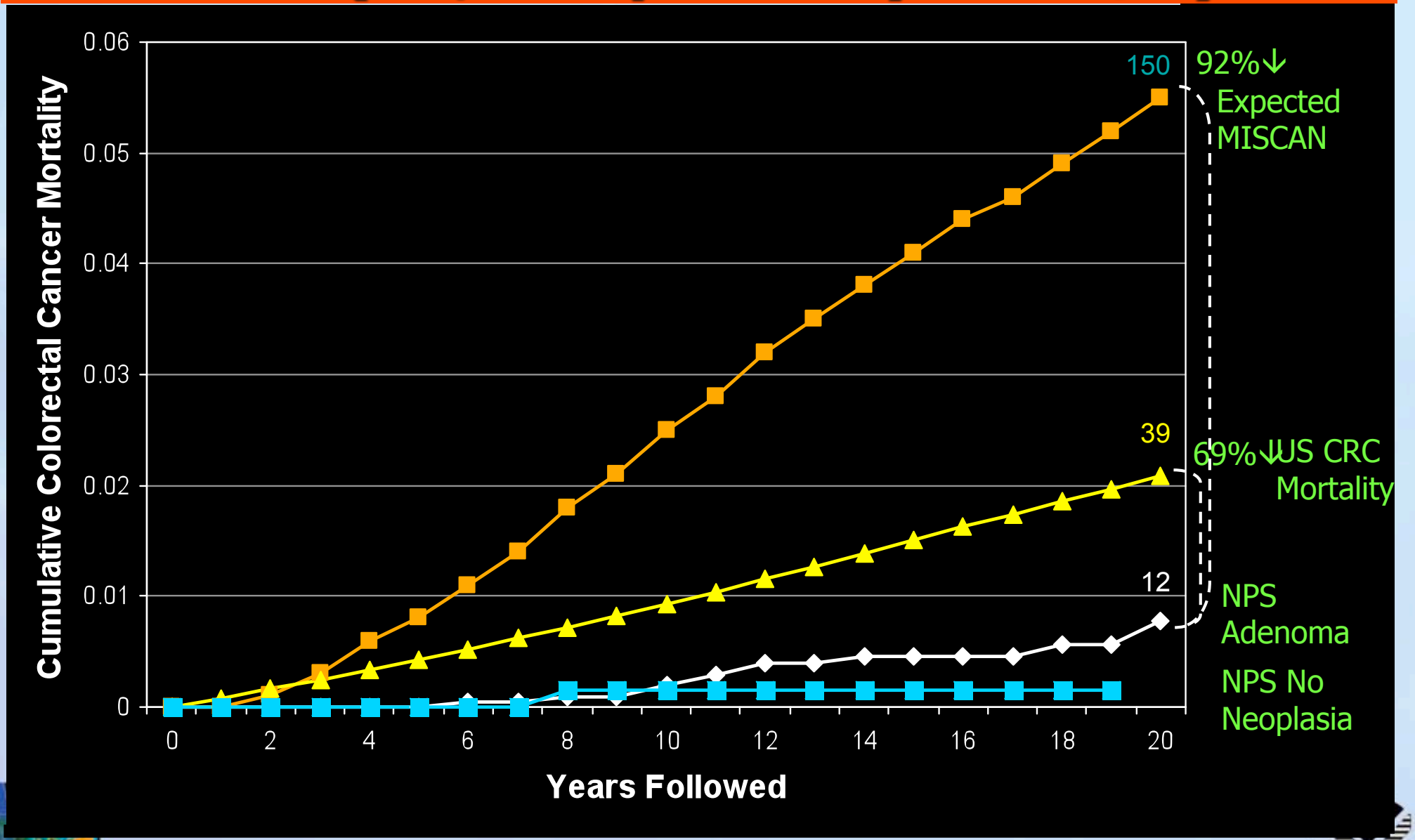
Integrated Cancer Prevention Center

Tel Aviv Medical Centre and Tel Aviv University



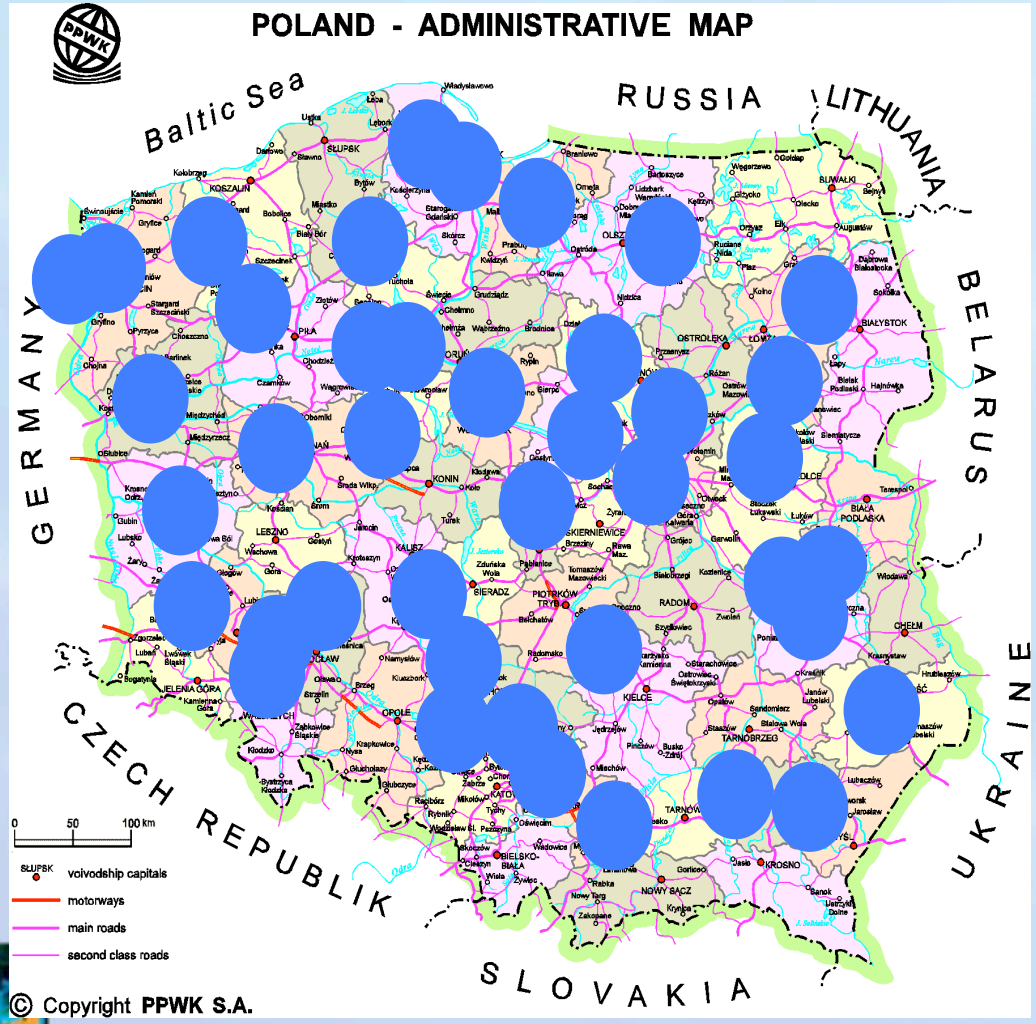
Does it look like a futuristic test?

CRC Mortality After Polypectomy
NPS (36,696 person years f/u)



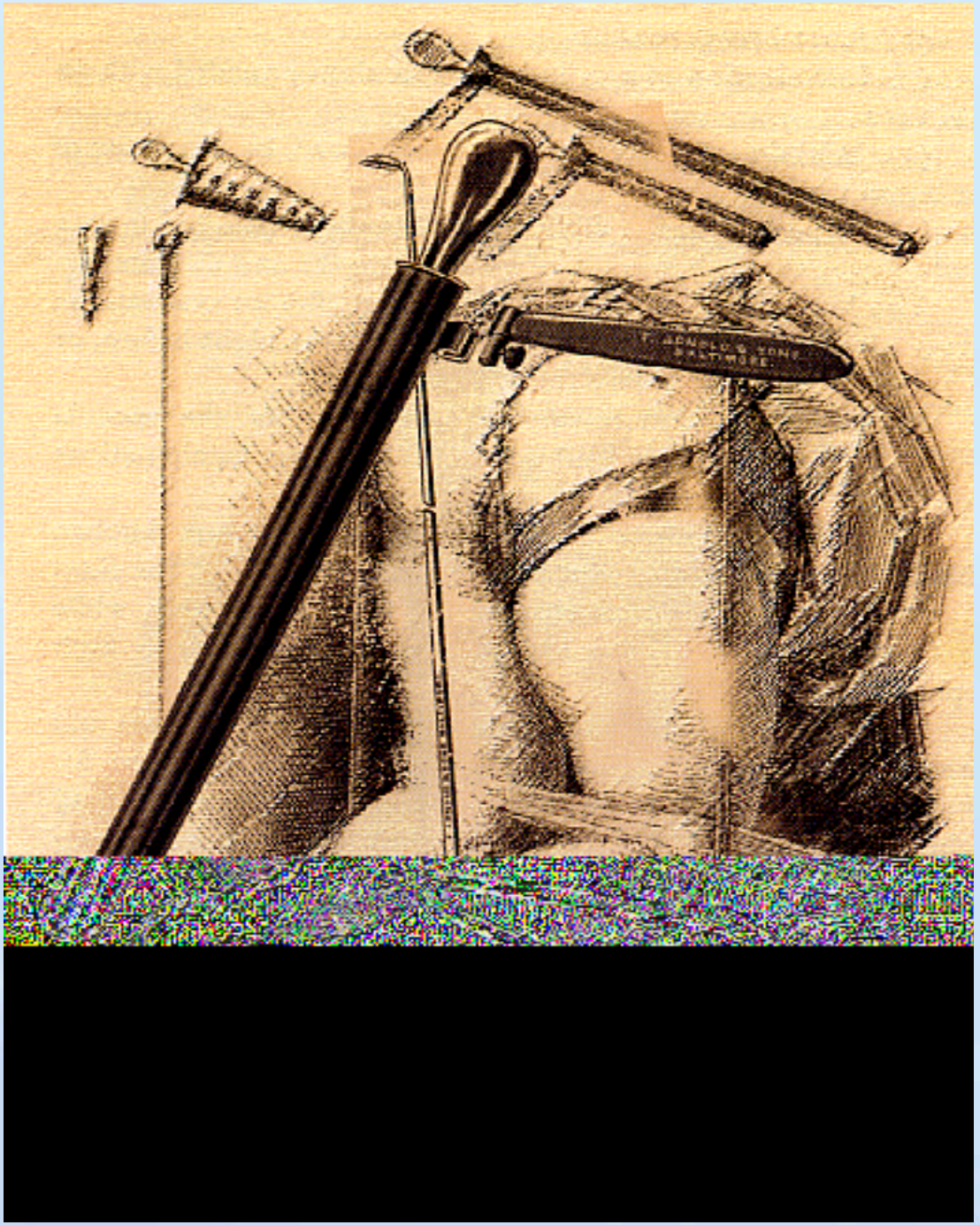
Zauber, Winawer, O'Brien, DDW2007

Screening Colonoscopy in Poland
200 000 Colonoscopies since 2000



> 80 centers in 2008

We have new colonoscopies modalities

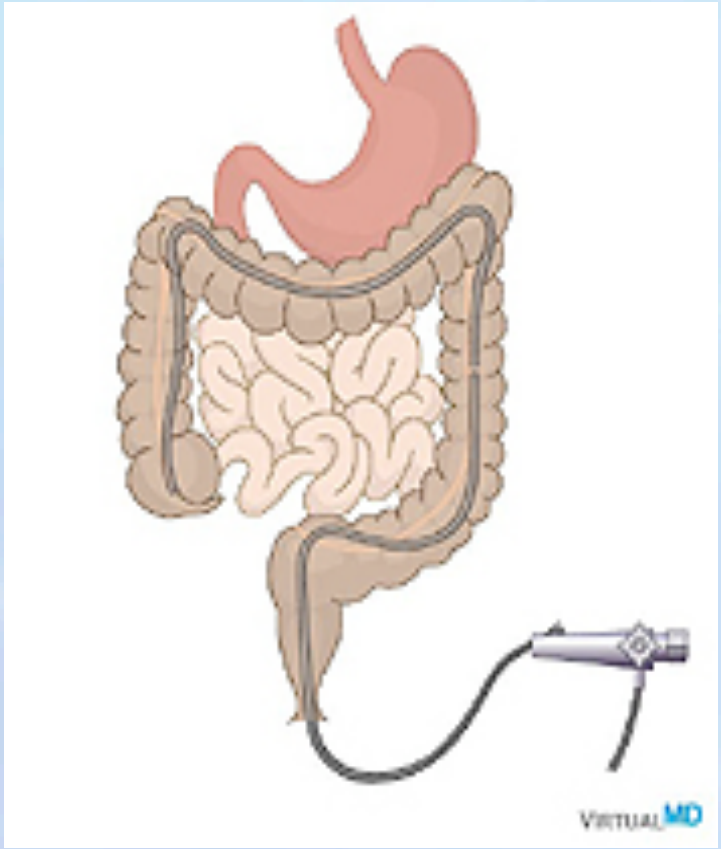


Low Public Compliance with CRC Screening

→ **Colon Exam**

Adapted from Jack Tippit, Saturday Evening Post

Physician Choice for CRC Screening



American Guidelines for CRC screening and surveillance

Levin, Gastroenterology 2008;134:1570

Tests that detect adenomatous polyps and cancer:

- FSIG every 5 years, or
- CSPY every 10 years, or
- DCBE every 5 years, or
- CTC every 5 years

Tests that primarily detect cancer:

- Annual gFOBT with high test sensitivity for cancer, or Annual FIT with high test sensitivity for cancer, or sDNA, with high sensitivity for cancer, interval uncertain

The CRC Screening Cascade

- ***Resource Level 1*** **(High Colonoscopy resources + high incidence of CRC)**
  - **Colonoscopy starting at the age of 50, *every 10 years***
- ***Resource Level 2*** **(Colonoscopy resources are more limited)**
  - **Colonoscopy at age of 50, *once in a lifetime***
- ***Resource Level 3*** **(Colonoscopy resources are limited, FS are available)**
  - **Flexible Sigmoidoscopy, *every 5 years***
- ***Resource Level 4-5*** **(Colonoscopy and FS resources are more limited)**
  - **Flexible Sigmoidoscopy at the age of 50, *once in a lifetime***
- ***Resource Level 6*** **(Colonoscopy and FS are severely limited)**
  - **FOBT at the age of 50, *every year***

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Winawer et al. WGO Practice Guideline 2007; 12: 17-22.

Reducing the Need for Colonoscopy

Appropriate Sensitivity

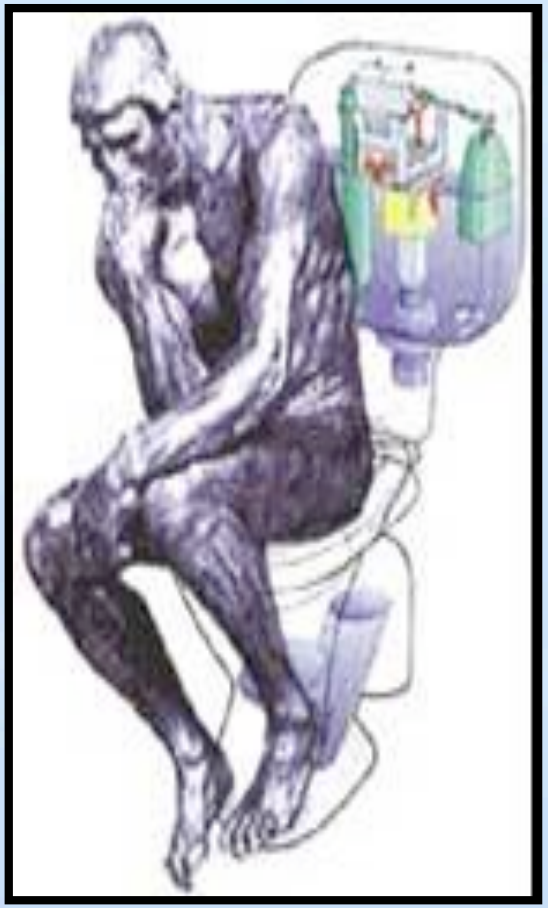
Appropriate Specificity

Affordable Cost

What's on the Horizon?

- **Imaging**
  - Virtual Colonoscopy
  - Enhanced performance
  - Prepless
- **Stool-based Techniques**
  - More sensitive gene-based tests
  - More sensitive fecal immunochemical tests
  - Proteomics
  - Adenoma markers
- **Blood tests**
- **Endoscopy**
  - Stiffener for colonoscopy
  - Optical biopsy; spectroscopy
  - Facilitated introduction of scope
  - Self propelling scopes

Stool DNA Gene-Based Testing



Stool DNA Testing for Colorectal Neoplasia (PreGen-Plus*)

- 31 point-specific mutations
  - APC (20)
  - K-ras (3)
  - p53 (8)
- MSI marker: BAT 26
- Apoptosis marker: long DNA

*From: M. Ross, 2003 *Exact Sciences Corp.*

Stool DNA Based Screening Test (PreGen – Plus)

	Cancer	Advanced Adenomas
* Sensitivity	52% (CI 51 - 71%)	
**Sensitivity	62% (CI 54 - 69%)	20% (CI 16 - 24%)
**Specificity	94.7% (CI 93.5-95.8%)	

* MCS Study: Imperiale *et al*, ACG 2003

** All prospective studies: general population and average risk (B. Berger, EXACT Sciences 2003)

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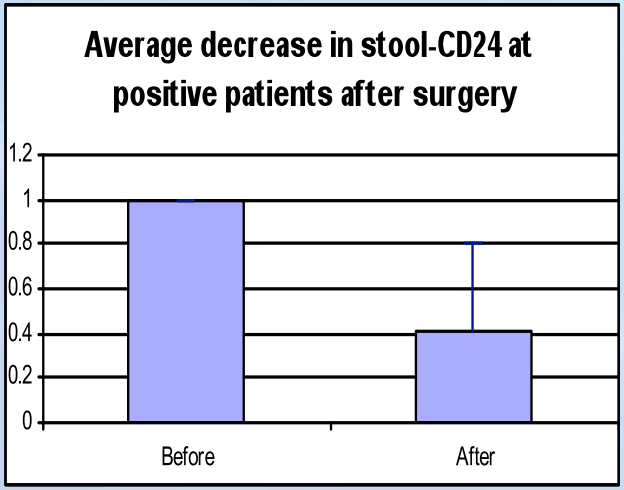
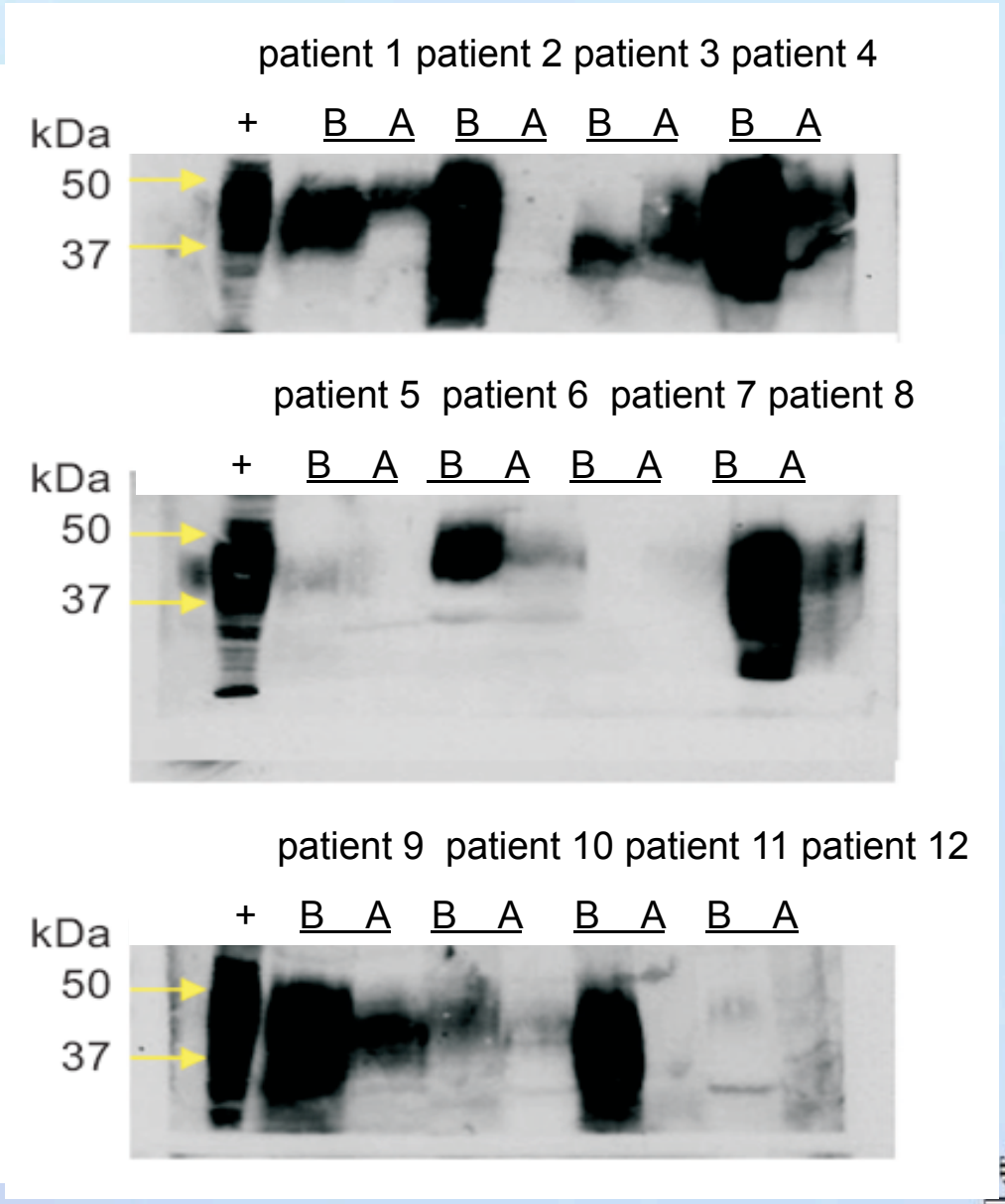
Fecal Analysis of CD24

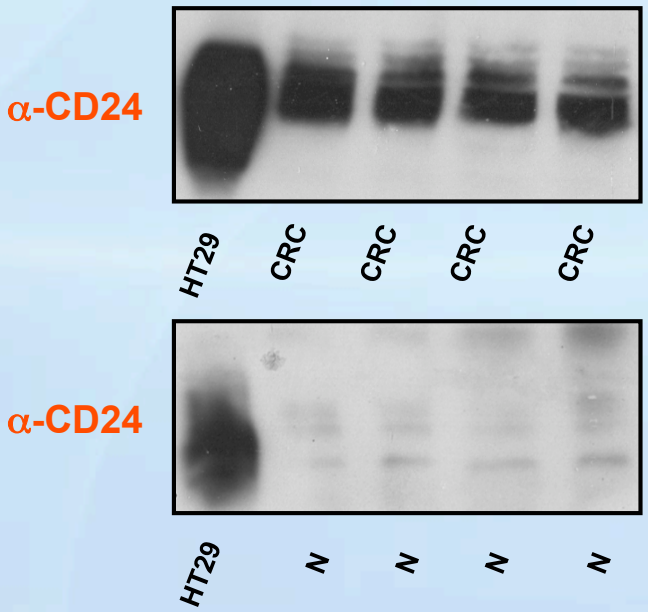
CD24 levels in stools were significantly decreased in 10/12 CRC patients following surgical removal of the tumors

B - before the surgical removal,
A - after the surgical removal



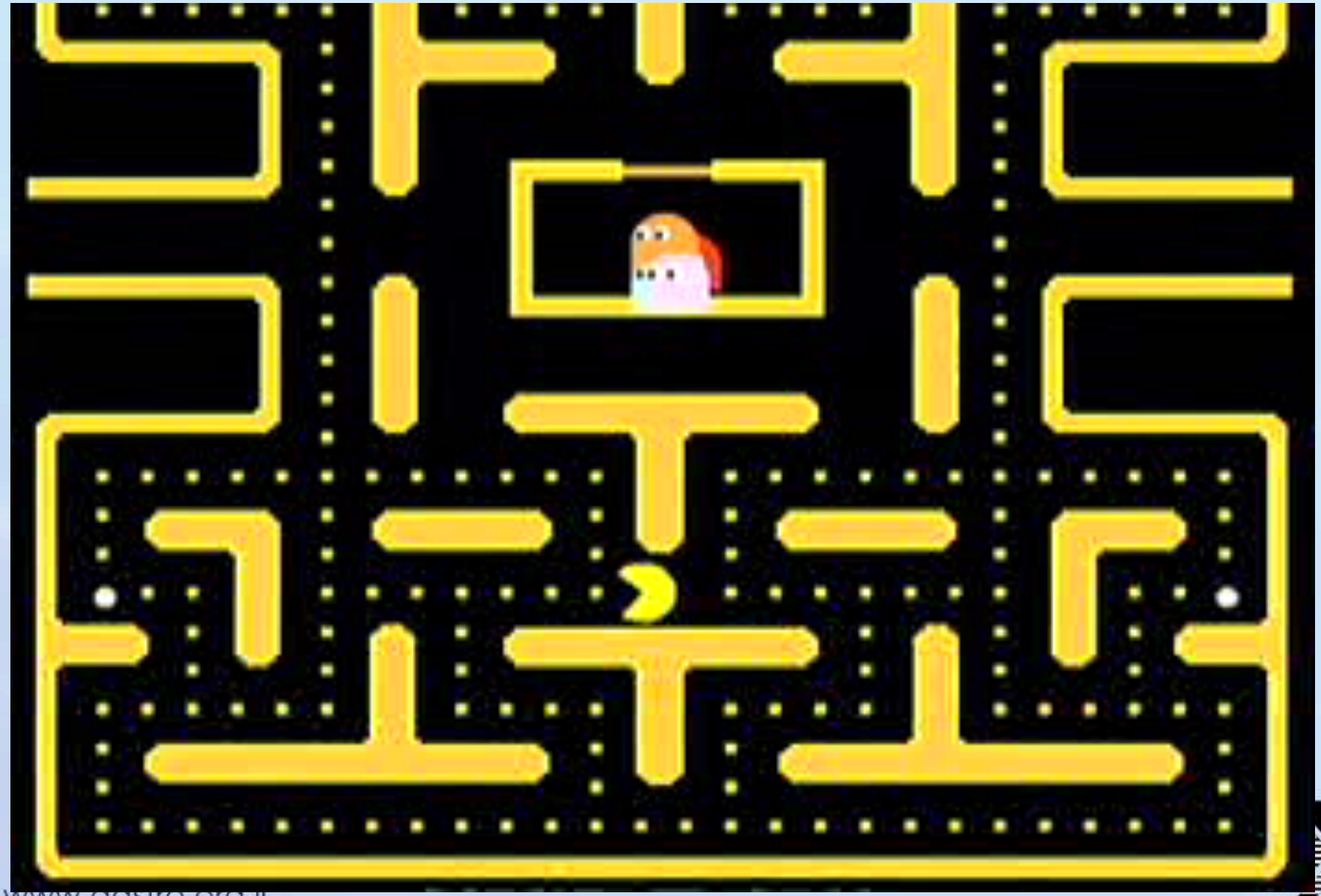


CD24 is over-expressed in peripheral blood mononuclear cells from CRC patients



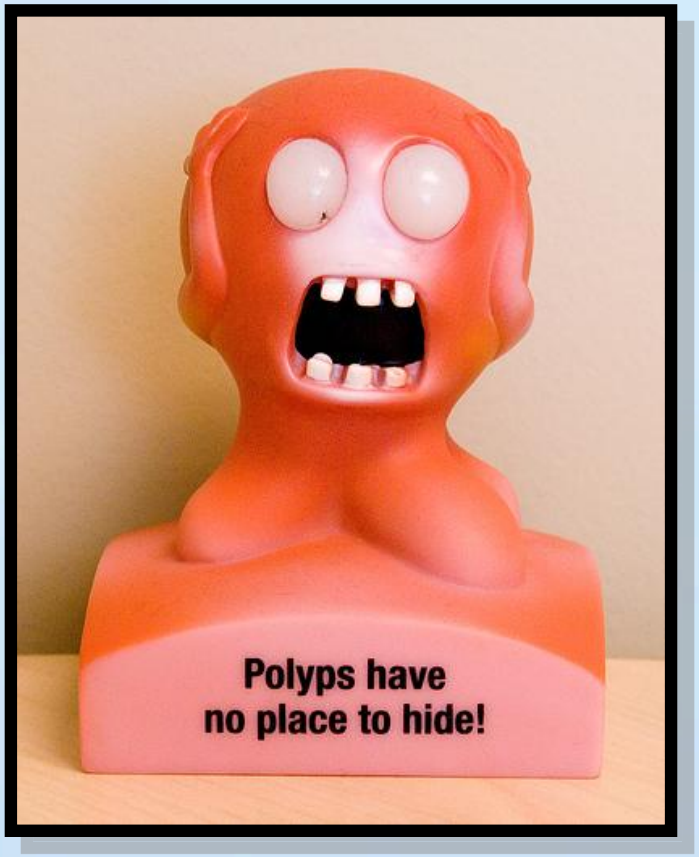
Western blot analysis showed that CD24 protein expression levels are elevated in the majority of CRC cases, and can distinguish cancer patients from healthy subjects.

Polypectomy in the next decade



The Ideal Colonoscopy

- Miniature device
- Disposable
- Harmless
- Self-propelling
- Self-navigating
- Sedation free
- Superior optics
- Low cost of disposable device
- Low capital equipment expense



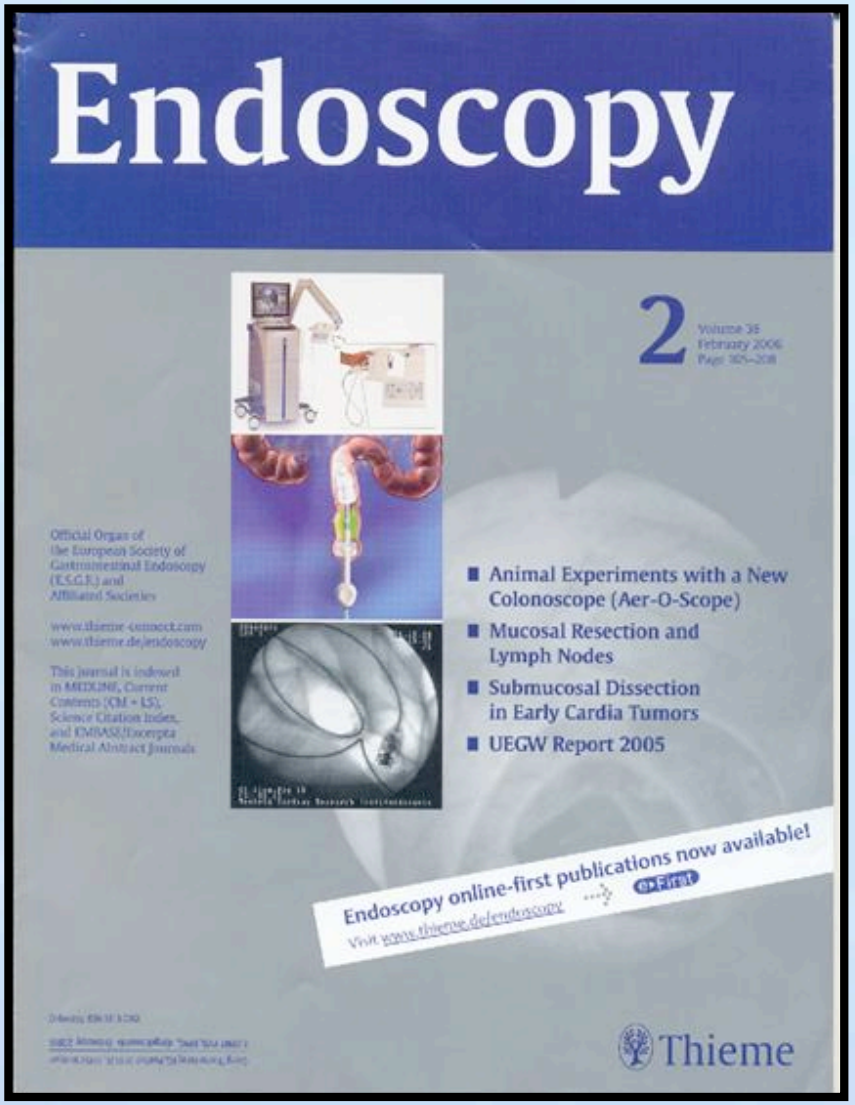
Novel Endoscopic Modalities

- Aer-O-scope
- Neoguide
- Given imaging
- ProtectiScope (Stryker)
- Invendo

The Aer-O-Scope

Animal experiments

More than 500 runs



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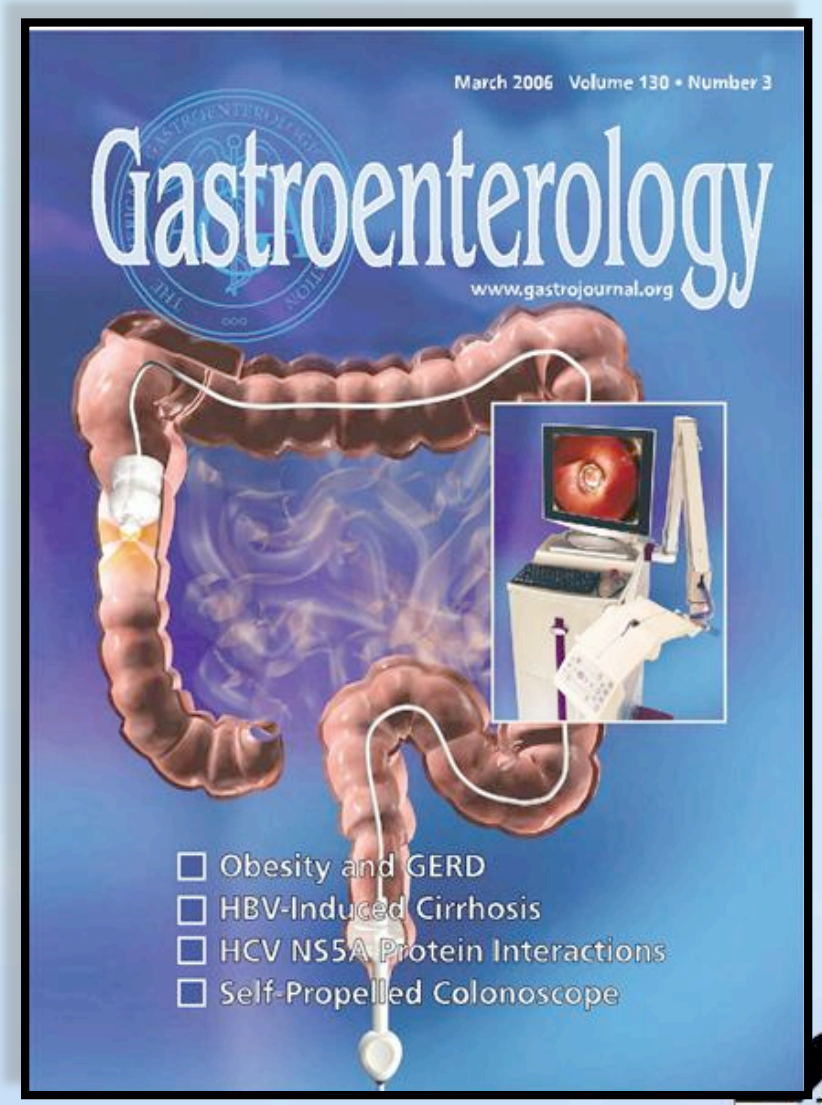
Human Studies

- 12 non-sedated volunteers
- Aer-O-Scopy followed by standard colonoscopy
- Cecal intubation:10 pts
- (83%) Time:14±7 min
  - Hepatic flexure:2 pts

  Both: failed regular colonoscopy
- 2 requested analgesia
- Driving pressure 34mBar



Clinical Experience

- 4 human studies in 71 healthy volunteers

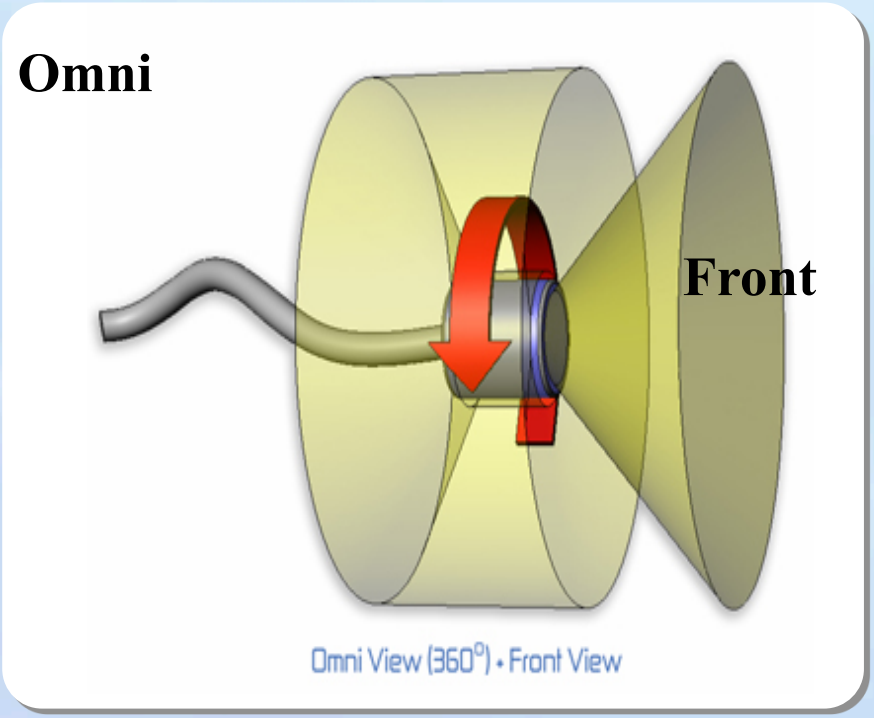
  Aer-O-Scopy followed by standard colonoscopy

  - **Study I: feasibility;**
  - **Study II: motion;**
  - **Study III: visualization;**
  - **Study IV: motion & visualization**
- Sedation was needed in only 6 out of 71 subjects
- No clinically significant complications

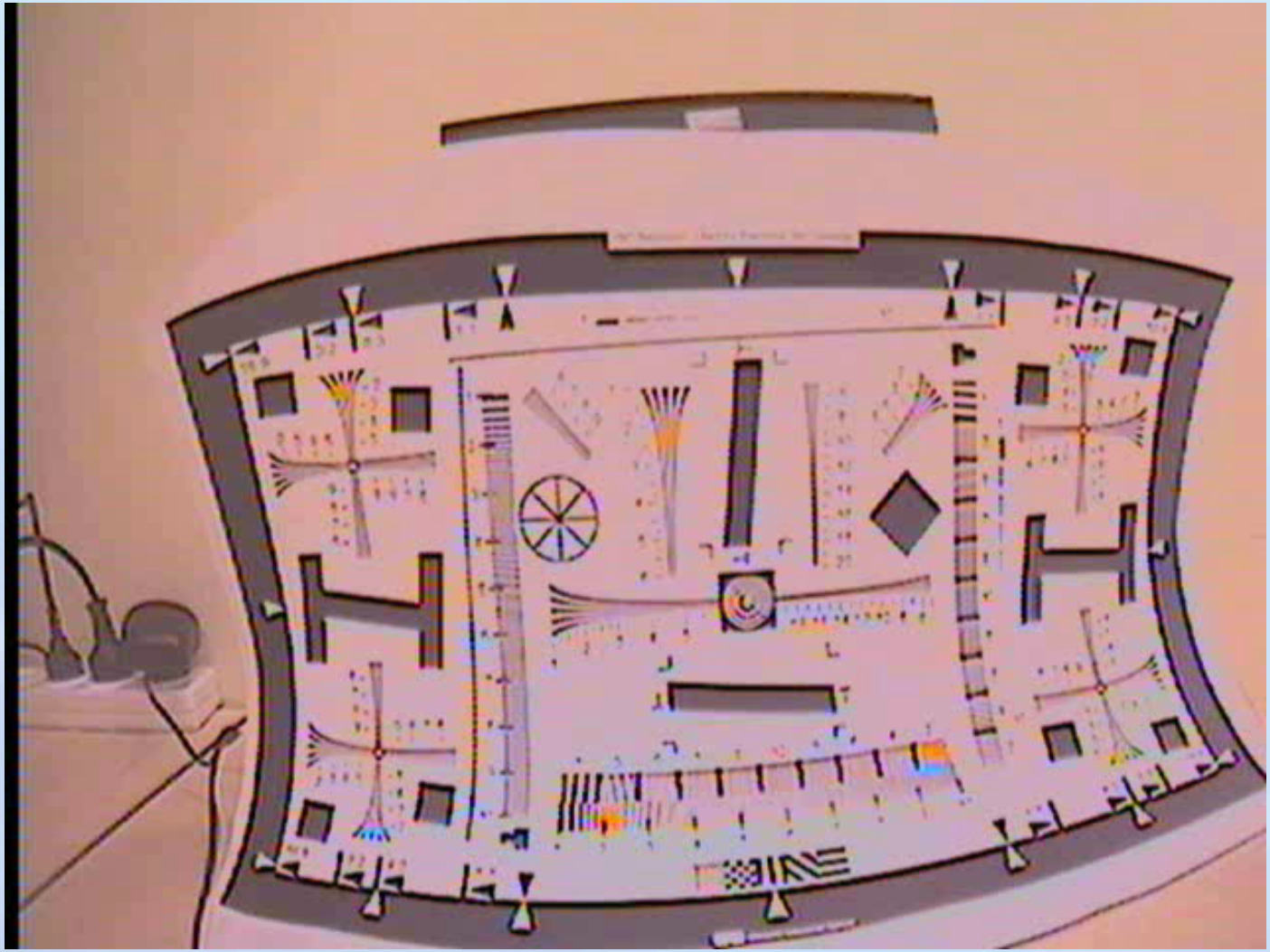
Unique vision system comprised of 2 components:

1. Omni-directional View –360^0 simultaneous view of the entire mucosal surface of the colon -ahead, behind and to all sides of the optical capsule, without the need for tip manipulation

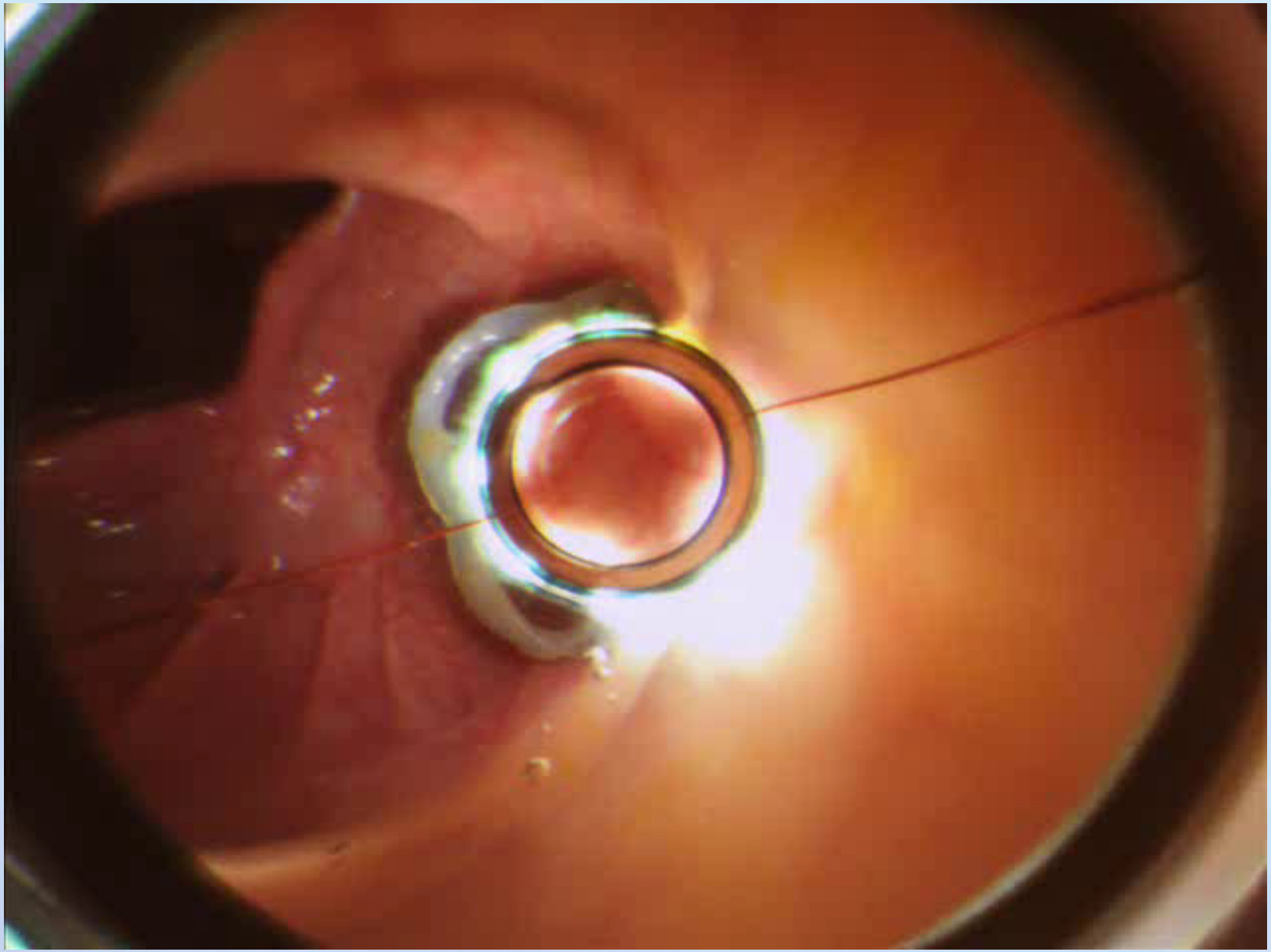
2. Front view of 90^0



Frontal vs Omni Views



Omni in a Human Colon



NeoGuide Endoscopy System

- The shape of the insertion tube, not just the tip, is controlled
- No force to the colonic wall is required to advance

Courtesy of Prof. Bar Meir

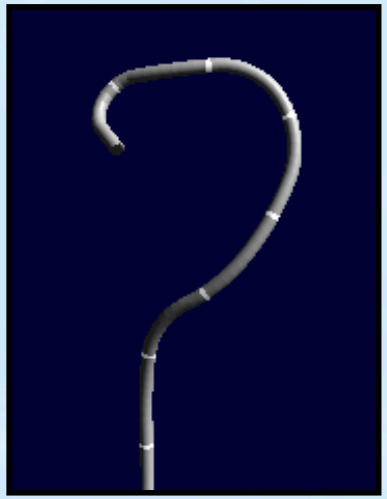
Neoguide

- Scope:15 segments behind steerable tip
- Segments are similar to the segment at the tip
- Segments are computer controlled
- Segments are directed to take the same angle as the tip at a given depth
- “Follow the leader” principle
- A real-time, three dimensional map of the path the scope's tip through the colon

Courtesy of Prof. Bar Meir

NeoGuide Endoscopy System: How does it work?

Tip Position Sensor
Constantly measures tip position



3D Colon Map
Generated as scope advances

External Position Sensor
Constantly measures tip depth

Console
Uses map to control segments
Motors drive segments

Colonoscope
Multiple articulating segments controlled by system

NeoGuide Endoscopy System: Fundamentally Different Operation

Conventional Scope (Olympus variable stiffness)

Requires force against colon wall to advance

NeoGuide

Provides physician with greater control

Courtesy of Prof. Bar Meir

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Feasibility Study

- Location
  - **Klinikum der Stadt, Ludwigshafen, Germany, September 2005**
- Investigators
  - **Prof. Dr. Riemann, Dr. Eichhoff, Dr. Hartmann, Dr. Elger, Prof. Van Dam**
- 10 Patients
  - **Mix of screening and diagnostic colonoscopies**
  - **2 patients with severe diverticulosis**
  - **3 patients had biopsy/polypectomy**
- 100% success rate reaching the cecum
- 9 patients- entering into ileum
- Cecum reached in 5 min in 3 pts

Neoguide – the end

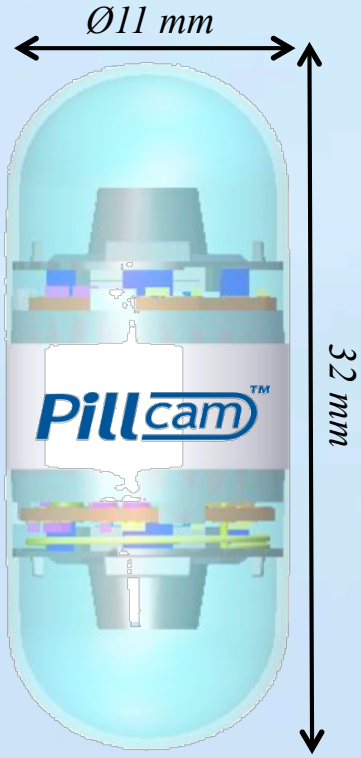
R & D was halted

The company moved into the field of NOTES

PillCam™ COLON

New design PillCam™ capsule

- No sedation
- Naturally ingested (no intubation)
- Improve compliance for screening



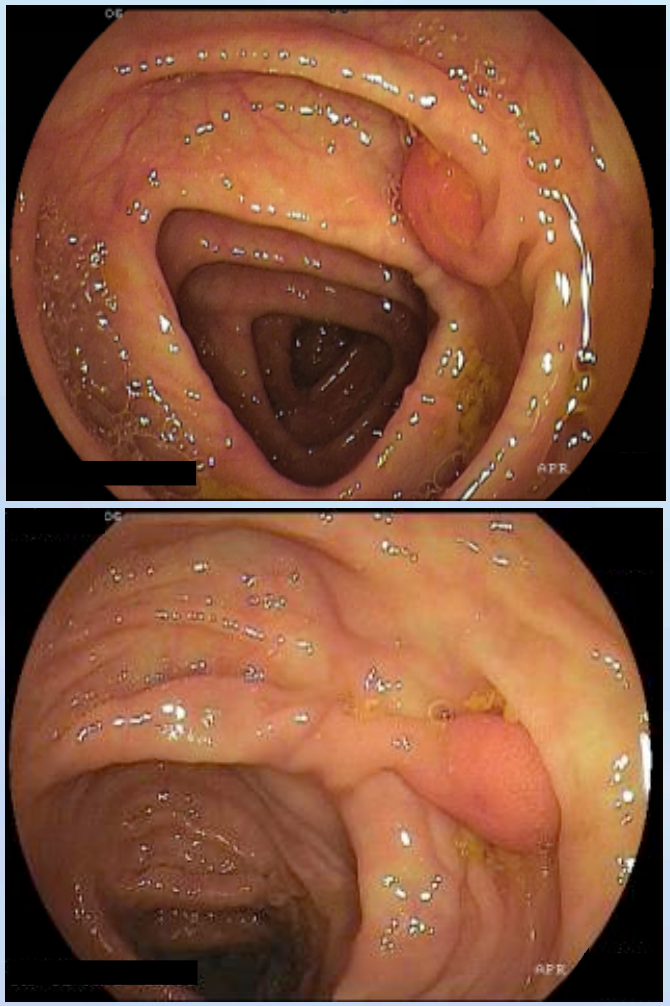
Colonic Capsule

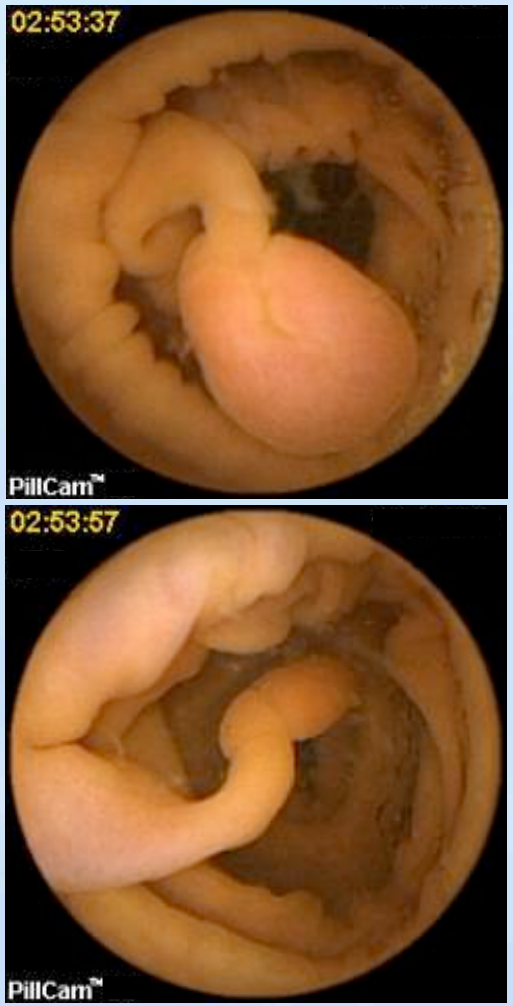
- On while passing the EG junction
- Sleeping for 1-2 hours while passing SI
- On in the terminal ileum
- Entire colon examined in 74%
- Recto-sigmoid reached in another 16%
- Significant lesions: caps- 70% colon- 80%

Eliakim R. Endoscopy 2006

Colonoscope vs. PillCam COLON

Polyp (~10 mm) at Transverse





European Trial

- 320 patients in 8 European centers
- Capsule first and then colonoscopy
- 93% capsule was expelled within 10 hours

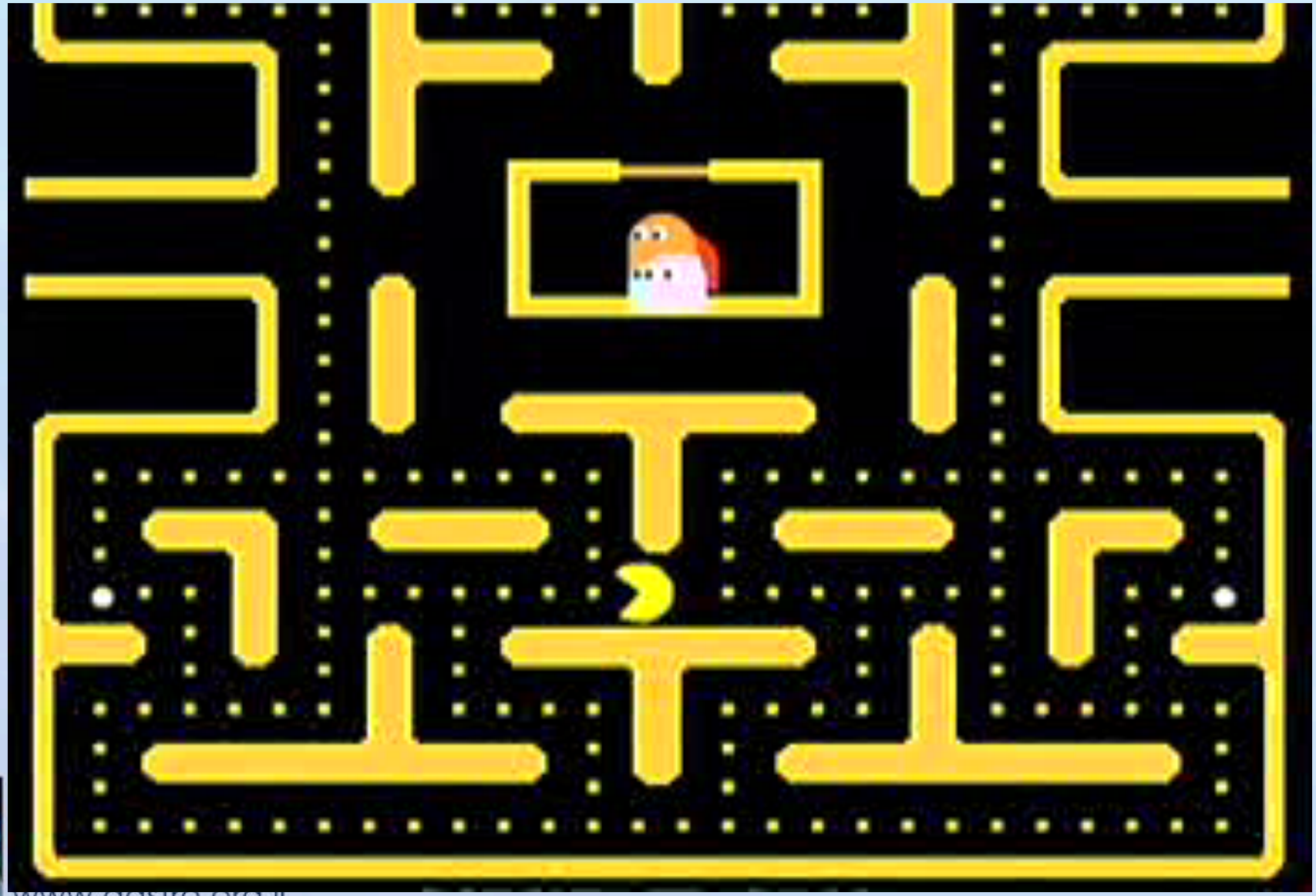
Deviere J et al DDW 2008

European Trial (polyps > 6mm)

Test	Significant polyp
Sensitivity	64%
Specificity	84%
PPV	60%
NPV	86%

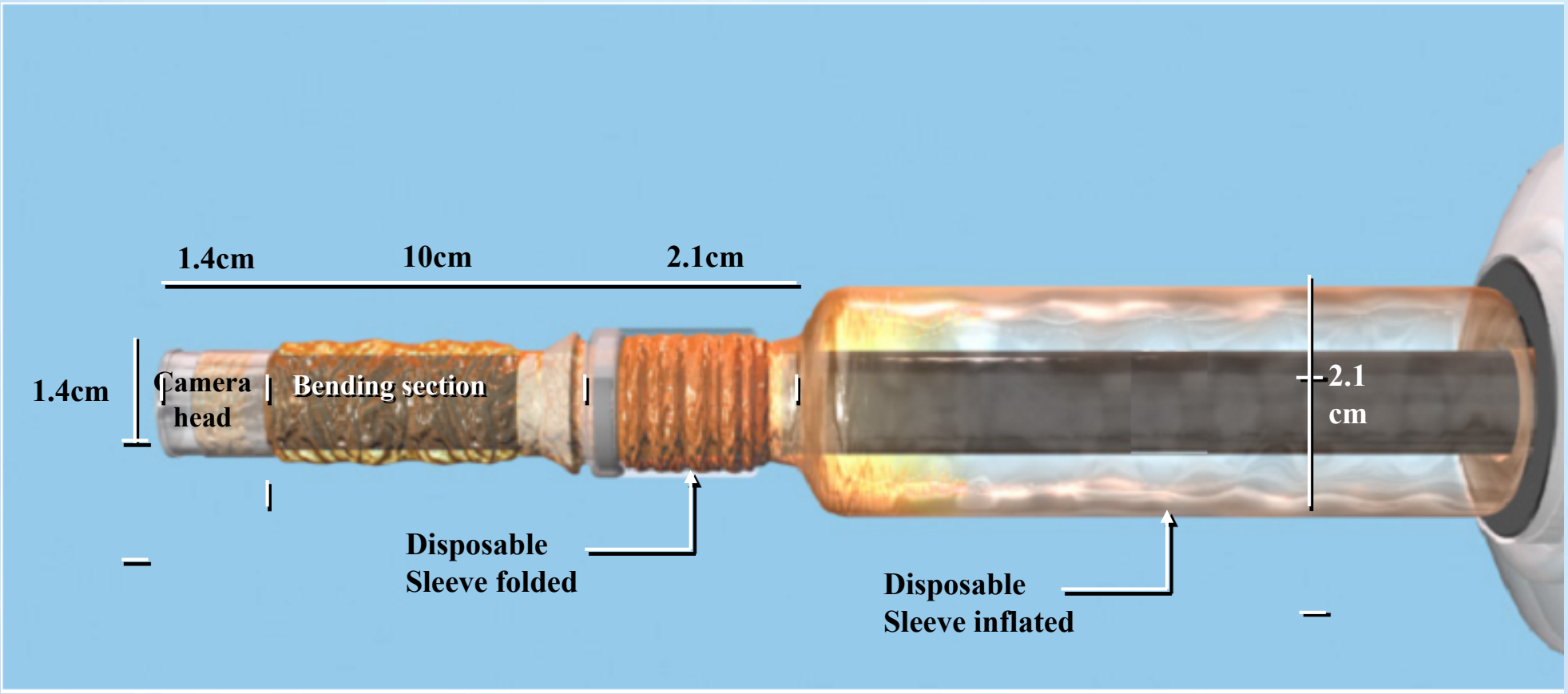
Deviere J et al DDW 2008

The Ultimate Screening Modality



ProtectiScope

The scope is inserted into a cassette that houses the protective sleeve. The portion of the scope that intubates is always covered



power-assisted force at the tip to advance the scope

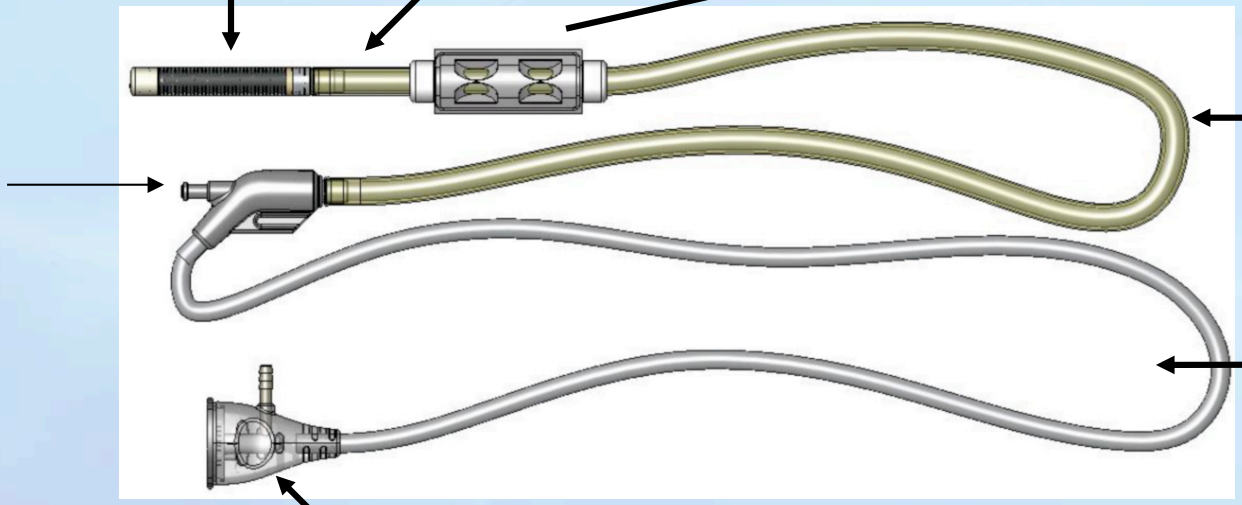
Human studies with ProtectiScope

- 178 pts
- Cecal intubation: 90%
- No major complications
- Biopsies and polypectomies possible
- Sheath barrier against infection is effective
- Usage in a community setting

  was disappointing

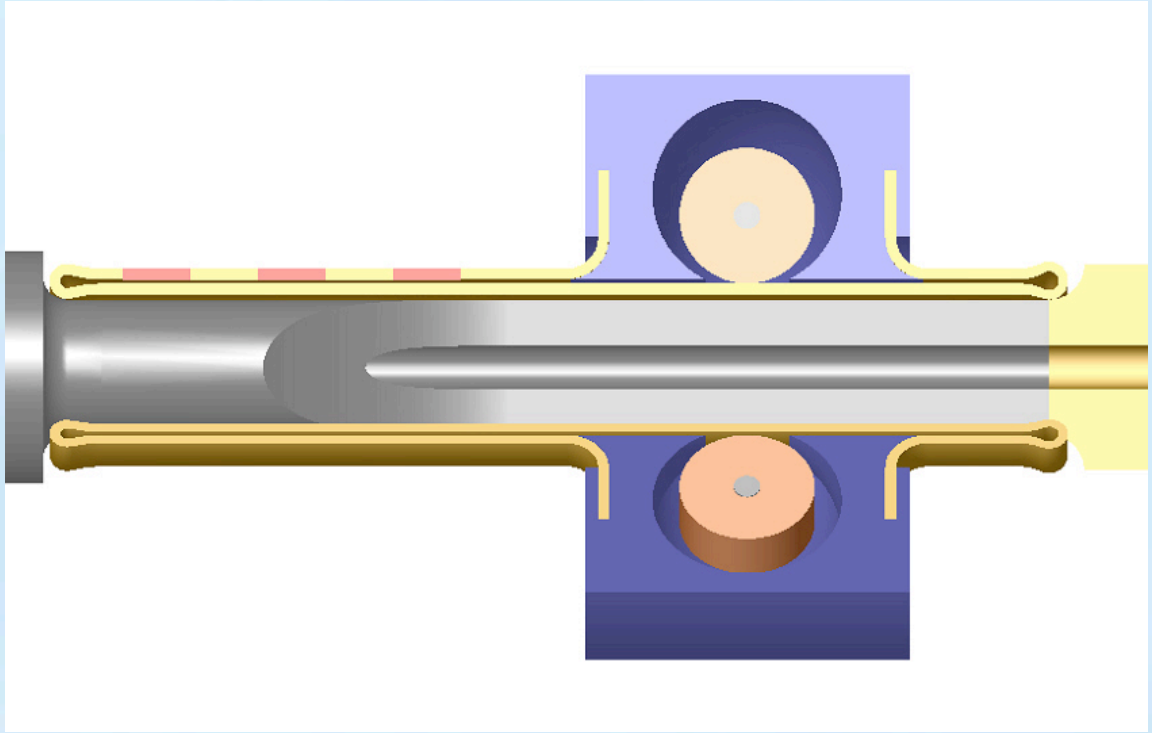
Shike M et al DDW 2004
&
Company information

Invendo single use colonoscope (Germany)



Courtesy of Prof. Roach

Inverted sleeve technology



- Wheels rolled on inner side of an inverted sleeve
- Inner sleeve is rolled out from inside to outside
- Outer side of the inverted sleeve stays in position
- Inner side is pulled forward below the distal tip, “Growing” the colonoscope into the colon by 10 cm each time
- No relative movement to the colon wall
- Minimizing the forces on the colon wall

Invendo- human studies

- 80 volunteers
- All examined unsedated
- If painful- discontinued
- < 80% cecal intubation
- Time to cecum > reg. colonoscopy

Roch et al GI Endoscopy 2008

Invendo – Current status

- Difficulties in reaching the cecum
- Working on elongation of the scope
- Increase friction and again difficulties in reaching the cecum
- Intend to launch the device in 2009

Prepless Virtual Colonoscopy (CT/MRI)

Multi society task force recommendations for screening 2008

In 2009

Any Screening Modality is Better than Nothing

But colonoscopy is the best option

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