My Financial Disclosures:

- Bayer
- GI View
- Takeda
- Bio View
- Check-Cap
- Bio-Explorer
- Nawe-Pharma
- Nucleix
Can We Improve Screening Methods of CRC?

Nadir Arber MD, MBA, MSc
Health Promotion Center and Integrated Cancer Prevention Center
Tel Aviv Medical Center and Tel Aviv University
Yes we can!!!
Ideal CRC Screening Test

- Organized program
- High Uptake
- Test accuracy (\textit{NPV}, \textit{PPV}, \textit{Spec}, \textit{Sens})
- Quality (FIT, colonoscopy, polypectomy)
- Costs
- Adherence to surveillance
- Reduced incidence of CR neoplasia
- Reduced specific morbidity
- Reduced specific mortality
- Reduced overall mortality
Different Screening Modalities

- Blood tests *(Septin9, Medial, CD24)*
- Stool Tests *(FOBT, FIT, Cologuard, M2-PK)*
- Sigmoidoscopy
- Colonoscopy
- CT-colonography
- Capsule endoscopy *(Medtronics, Check-Cap)*
The best screening test is the one that gets done. Each one has different preferences.
No one likes stool testing

And you thought your job sucked
Blood test is highly desire but still does not exist
Low Public Compliance with CRC Screening

Colon Exam

No way...

Adapted from Jack Tippit, Saturday Evening Post
In 2017

Any Screening Modality is Better than Nothing

But colonoscopy is still the best option
Colonoscopy in Colorectal-Cancer Screening for Detection of Advanced Neoplasia

Jaroslaw Regula, M.D., Maciej Rupinski, M.D., Ewa Kraszewska, M.Sc., Marcin Polkowski, M.D., Jacek Pachlewski, M.D., Janina Orlowska, M.D., Marek P. Nowacki, M.D., and Eugeniusz Butruk, M.D.

ABSTRACT

BACKGROUND
Recommendations for colorectal-cancer screening are based solely on age and family history of cancer, not sex.

METHODS
We performed a cross-sectional analysis of the data from a large colonoscopy-based screening program that included 50,148 participants who were 40 to 66 years of age.
My wife is perfect......

I think I am ......

But colonoscopy is definitely not perfect...
Adenomas are missed...
High ADR Decreases the Risk of Interval Cancer:

Colonoscopy-based CRC screening
186 endoscopists
46,032 subjects
188,788 persons-years
42 interval cancers

Interval cancers according to ADR:

<table>
<thead>
<tr>
<th>Endoscopist ADR</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 20%</td>
<td>1</td>
</tr>
<tr>
<td>15-19.9%</td>
<td>12.50 (1.5-103.4)</td>
</tr>
<tr>
<td>11-14.9%</td>
<td>10.75 (1.3-85.0)</td>
</tr>
<tr>
<td>&lt; 11%</td>
<td>10.94 (1.3-87.0)</td>
</tr>
</tbody>
</table>

High ADR Decreases the Risk of CRC Death:

Each 1% ADR increase = 5% decrease in CRC death

Why Do We Miss Adenomas?

- Inadequate colon prep
- Flat/depressed lesions
- Colon anatomy (proximal folds and flexures)
- Suboptimal technique
  - Short withdrawal time
  - Missing cecal intubation

- Current technology limitations

Low ADR
Quality Indicators for Colonoscopy and the Risk of Interval Cancer

Michal F. Kaminski, M.D., Jaroslaw Regula, M.D., Ewa Kraszewska, M.Sc., Marcin Polkowski, M.D., Urszula Wojciechowska, M.D., Joanna Didkowska, M.D., Maria Zwierko, M.D., Maciej Rupinski, M.D., Marek P. Nowacki, M.D., and Eugeniusz Butruk, M.D.
Quality Colonoscopy

- Bowel Prep given in split doses
- Cecum should be intubated and documented by photography
- Colonoscopists should measure adenoma detection rate
  - 20% in women
  - 30% in men
- Withdrawal time in negative screening exams should average at least 6 minutes
Improving Polyps Detection

- **Extra Wide Angle View Endoscope (Olympus)**
- **Full Spectrum Endoscopy (EndoChoice)**
- **Third Eye Retroscope and Panoramic**
- **Aer-O-scope (GI-View)**
- **G-Eye (Pentax)**
- **EndoCuff (Medivator)**
- **EndoRings (Endoaid)**
- **Colonic Capsule (Medtronics)**
- **Prepless Colonic Capsule (Check-Cap)**
Mechanical Fold Flattening Approach

Cap assisted colonoscopy

Endocuff/Endoings
Endoscopic Over tube

G-EYE™ Colonoscope
Cap-Assisted Colonoscopy: A Meta-Analysis with Borderline Efficacy

Endpoint = Polyp Detection

16 RCTs, n = 8,991

Cap-Assisted Colonoscopy: A Meta-Analysis with Borderline Efficacy

Endpoint = Polyp Detection

RR (95% CI)
1.26 (1.02, 1.55)
1.20 (0.96, 1.51)
1.10 (1.01, 1.20)
1.02 (0.84, 1.23)
0.81 (0.68, 0.97)
0.95 (0.72, 1.25)
1.07 (0.59, 1.91)
1.05 (0.78, 1.40)
1.11 (0.94, 1.32)
1.28 (1.00, 1.63)
1.23 (1.06, 1.43)
1.00 (0.85, 1.19)
1.08 (1.00, 1.17)

NNT=13

16 RCTs, n= 8,991

Cap-Assisted Colonoscopy
NaviAid™ G-EYE™ Balloon-Colonoscope
SMART Medical Systems, Ra’anana, Israel

- Pentax colonoscope with permanently integrated, reusable balloon
- Balloon inflated by the endoscopist (foot pedal) through the colonoscope internally, no external mounted accessories
- Cecum with balloon deflated
  - Balloon inflated to engage the colon walls & withdrawn
  - Mechanical straightening of folds & flexures

Halpern Z. Endoscopy 2015
EndoCuff™ (Medivators)
EndoCuff™

- RCT, 2 centers, n=498
- Colonoscopy with and without endocuff,
- EC - 63% more polyps detected
- PDR = EC 56% vs no EC 42%, p=0.001
- EC – significantly more polyps (<1cm) detected in cecum (p=0.001) and sigmoid (p=0.002)
- ADR significantly increased by 86% (P=0.002)
- No adverse events

EndoRings™
EndoAid, Israel

The Beauty of Simplicity
EndoRings – CLEVER Study

- RCT, N=116  \textit{Dik, Siersema, Gralnek et al. (Endoscopy, 2015)}

- Tandem colonoscopy design,

- Study endpoint = adenoma miss rate

  - With endorings = 15%

  - Without endorings = 48%, p <0.01

- Time to cecum (9.6 min vs. 8.1 min, p=0.17)

- Withdrawal times (7.2 vs. 6.8 min, p=0.14)

- No adverse events
Improving Polyps Detection “Inspection Behind Folds”

Optical Approach

The third eye
FUSE full spectrum endoscopy
Omnivision
Extra Wide Angle View Endoscope (Ewave)
330° Field of View
The Fuse Story
◆ Kitchen trial: home made colon model
◆ Animal Lab: 3 screens
<table>
<thead>
<tr>
<th></th>
<th>SFV followed by Fuse (n=88)</th>
<th>Fuse followed by SFV (n=97)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years (mean ± SD)</strong></td>
<td>55.9 ± 9.5</td>
<td>55.7 ± 9.7</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Gender, female (%)</strong></td>
<td>46 (52.3%)</td>
<td>55 (56.7%)</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>Ottawa Bowel Preparation Score (mean ± SD)</strong></td>
<td>3.4 ± 2.6</td>
<td>3.4 ± 2.8</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>Indication for Colonoscopy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening n, (%)</td>
<td>53 (60.2%)</td>
<td>50 (51.5%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Surveillance n, (%)</td>
<td>16 (18.2%)</td>
<td>20 (20.6%)</td>
<td>0.68</td>
</tr>
<tr>
<td>Diagnostic Evaluation n, (%)</td>
<td>19 (21.6%)</td>
<td>27 (27.9%)</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>Additional Adenomas Detected</strong></td>
<td>69%</td>
<td>8%</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td><strong>Adenoma Miss Rate</strong></td>
<td>20/49 (40.8%)</td>
<td>5/67 (7.5%)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>ADR</td>
<td>30/88 (34.1%)</td>
<td>34/97 (35.1%)</td>
<td>0.89</td>
</tr>
</tbody>
</table>
FUSE Study in Italy – Not that Promising

Arnaldo Amato², Andrea Anderloni³, Franco Armelao⁵, Arrigo Arrigoni¹, Maurizio Cavina⁶, Giovanni DePretis⁵, Gianpiero Manes⁴, Gianni Miori⁵, Alessandra Mondardini¹, Franco Radaelli², Alessandro Repici³, Romano Sassatelli⁶, Nereo Segnan⁸, Cesare Hassan⁷

Endoscopy Unit, AOU Città della Salute e della Scienza – Ospedale San Giovanni Antica Sede, Turin¹; Endoscopy Unit, Ospedale Valduce, Como²; Endoscopy Unit, Istituto Clinico Humanitas, Rozzano (Milan)³; Endoscopy Unit, Ospedale di Circolo, Rho (Milan)⁴; Endoscopy Unit, Ospedale S Chiara, Trento⁵; Endoscopy Unit, IRCCS S Maria Nuova, Reggio Emilia⁶, Endoscopy Unit, Ospedale Nuovo Regina Margherita, Rome⁷; AOU Città della Salute e della Scienza, CPO Piemonte, Turin⁸.
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ARRIVING FALL 2016
WWW.SANESO.COM
Third Eye Retroscope

- **Device that passes through scope channel**
- **Automatically retroflexes 180°**
- **Provides forward and backward view simultaneously on side-by-side monitor**

*Courtesy of Prof. Jerry Way*
**TER: Leufkens et al. GIE 2011**

N=349

<table>
<thead>
<tr>
<th>SFV colonoscopy</th>
<th>Third-Eye Retroscope</th>
<th>Additional Adenomas Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SFV 22.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TER 45.8%</td>
</tr>
</tbody>
</table>

Adenoma Miss Rates

- SFV: 31.4%
- TER: 18.4%

**Limitations of Third Eye:**

1. **Not user friendly**
2. **Takes up working channel**
3. **Increases procedure time**
4. **Costs**
Third-Eye Panoramic (Avantis)

- Pilot and feasibility
- Single use device
- CMOS chips, LEDs
- N=17
- 100% cecal intubation

Rubin et al. WJG 2015
Aer-O-Scope™ Key Advantages

- OMNI-directional 360° vision
- Joystick controlled self propelled colonoscope
- Scanner induces lower pressure on the colonic wall
- Extremely safe system
- Disposable
- Single operator
- The only available FDA approved self propelled colonoscope
Aer-O-Scope® (Israel)

GI VIEW

AER-O-SCOPE™ Colonoscope System by GI View Ltd.
Motus GI

- Started in Boris house in Nazareth as a self-propelled single use colonoscope
- First funded an Arab - Jewish incubator
- *Changed direction* to an add-on device that cleans the colon during colonoscopy
PURE-VU (Israel)
Motus – Clinical Trial Real Movie ...

Still not FDA approved
Capsule Endoscopy
Overcome invasiveness
- Terminal Ileum
- Ileo-cecal Valve
Pillcam Colonoscopy: What did we learn?

- **ESGE 2012**
  - Average risk patients
  - Incomplete colonoscopy
  - Unwilling to undergo conventional colonoscopy
  - Colonoscopy contraindicated

- **FDA 2014**
  - Incomplete colonoscopy
  - Colonoscopy contraindicated

<table>
<thead>
<tr>
<th>For</th>
<th>Against</th>
</tr>
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<tbody>
<tr>
<td>Patient preference</td>
<td>Physician preference</td>
</tr>
<tr>
<td></td>
<td>Novelty</td>
</tr>
<tr>
<td></td>
<td>Training</td>
</tr>
<tr>
<td></td>
<td>Remuneration</td>
</tr>
<tr>
<td>Increased capacity</td>
<td>Increased work load</td>
</tr>
<tr>
<td>Pan-endoscopy</td>
<td>Histology</td>
</tr>
<tr>
<td>Non medical reading</td>
<td>Intervention</td>
</tr>
<tr>
<td>Increased access</td>
<td>Cost</td>
</tr>
<tr>
<td>Safety?</td>
<td>Time Lag</td>
</tr>
</tbody>
</table>
An expensive Selfi!!!!

Courtesy: Rami Eliakim
Prepless Capsule Colonoscopy: Ultra Low Dose X-ray-Based Imaging Technology (Check-Cap, Israel)

- Ultra-low dose (0.03 mSv)
- Low energy (56 – 70 Kev)

Moshkowitz, Gluk, Arber (Gut 2016)
Invendoscope (Germany)
ProtectiScope Israel

Power-assisted force at the tip to advance the scope

Stryker
Power-assisted force at the tip to advance the scope.
ClearPath (Israel)
Efficient Irrigation and Evacuation System

ISO 13485 Certified
FDA approved, 2009
CE Cleared, 2009

Moshkowitz...Arber, Endoscopy 2010
ClearPath (Israel)
Efficient Irrigation and Evacuation System

FDA Approved, 2009
CE Cleared, 2009

Moshkowitz...Arber, Endoscopy 2010

Withdrawn
Improve Imaging
Increase Magnification

- **Standard Endoscopy (SD)**: 0.4 megapixel
- **High definition (HD)**: 1.2 megapixel
- **Magnifying colonoscopy**: Zoom X300
- **Confocal Laser endomicroscopy**: X1000
Increase Magnification

Standard Endoscopy (SD) 0.4 megapixel
High definition (HD) 1.2 megapixel
Magnifying colonoscopy Zoom X300
Confocal Laser endomicroscopy X1000

No significant
Optic Imaging

• The behavior of visible ultraviolet and infrared light omitted from a source [i.e. laser, xenon] to a surface is variable

• Light may interact with tissue in various ways that can be measured and analyzed

• These interactions provide information about tissue type, Hb content, microstructure, and molecular characteristic
Image Enhanced Endoscopy

Chromo-endoscopy

NBI filter

FICE

i SCAN

Endoflag

Olympus

Fujinon

Pentax

Endopix

Courtesy of Prof. Halpern
Chromoendoscopy

• **Absorptive stains**
  - Lugol’s solution
  - Methylene blue
  - Crystal violet
  - Acetic acid

• **Contrast stains**
  - Indigocarmine
Chromoendoscopy is Most Useful in the Evaluation of Nonpolypoid Colorectal Neoplasms
(Kiesslich, Eur J Gastroenterol 2005)

In the real world....it is not

Prevalence of flat adenomas:
without Chromoendoscopy 1-5%
with Chromoendoscopy 20-35%
Electronic Chromoendoscopy?

A B

NBI

C D

i-Scan

Subramanian et al. Clin Gastroenterol Hepatol 2013
ASGE Technology Committee. GIE 2015
In real life.....probably no added value
NBI is equal to chromoendoscopy for distinguishing neoplastic from non-neoplastic lesions

Machida, Endoscopy 2004
The Future is Molecular Imaging

**Improved detection of tumor location**

**Malignant vs Benign**

**Tumor Margins**

**Pharmacologic therapy [response]**

**Minimize number of biopsy**

**Dysplasia in inflamed mucosa**
mAb to CD24 concentrating in CRC in nude mice (Arber’s lab)
…jumping into CONCLUSIONS

“A test is better than none, and the best test is the one that is done”

- Two stages approach
- Non invasive test as the initial step
  - Blood test
  - Stool test/virtual colonoscopy/ capsule/ prepless cap?
One Stage Colonoscopy

Advanced technologies are available, but are time and money consuming. Public demands and legal issues.
One Stage Colonoscopy

The big brother quality control

ADR/withdrawl time/cecal intubation rate

Advanced technologies are available, but are time and money consuming

- Public demands
- Legal issues
No Matter How Advanced the Technology and Equipment are.....
What Really Matter...
Is the Gastroenterologist!!!
THANK YOU FOR YOUR ATTENTION

PLEASE CLAP AND DO NOT MAKE TOUGH QUESTIONS