FORTE: Five or Ten Year Colonoscopy for 1-2 Non-Advanced Adenomas
CRC Screening is Increasing

• Up to date with recommended screening in U.S.:
  54% in 2002 → 65% in 2010

• 80% goal for 2018

• More people are getting screened
• Colonoscopy is primary modality
☑ More people with adenomas will be identified

MMWR 2012;62:881
Increased Emphasis on Adenoma Detection

ADR (Adenoma Detection Rate):

• Marker of colonoscopy quality because higher ADR associated with fewer interval CA’s
• Endoscopists encouraged to detect as many adenomas as possible
Anticipate Significant Increase in Future Demand For Surveillance Colonoscopy

- Increased Screening
- Increasing Adenoma Detection

→ Increased Surveillance
Surveillance Colonoscopy

- Performed to detect metachronous lesions, particularly advanced adenomas, to prevent subsequent cancers
- 20 - 25% of all colonoscopy is for surveillance
- The contribution of surveillance to protection against cancer is unknown and uncertain
Cost of Surveillance

- 14 million CS/yr estimated in 2002
- 25% surveillance or 3.5 million/yr
- Estimate $500/CS: 1.75B/yr on surveillance
- 70% of surveillance is 1-2 non-advanced adenomas
- Surveillance CS often mis-applied: over utilization in low risk, underutilization in high risk
Natural History of Non-advanced Adenoma
Natural History of Adenomas

N = 1618 persons with adenomas on rigid sigmoidoscopy which were removed: Individuals followed for 14 years

Overall risk colon CA = 2.1

Adenoma Characteristics:

Low Risk: Tubular, < 1 cm, even if multiple

High Risk: ≥ 1 cm, villous histology

Very High Risk: High Risk & multiple

RR

0.5

3.6

6.6

Atkin, NEJM 1992; 326:658
N=751, Rochester, MN

• < 1 cm polyps on sigmoidoscopy – fulgurated
• > 10,000 PYO
• 18 CRC cases vs. 15.3 expected (RR=1.2, NS)

Conclusion:
Small polyps not associated with ↑ CRC risk

Spencer RJ, Mayo Clinic Proceed 1984; 59:305
CRC Mortality after Adenoma Removal

- N= 41,000; Median f/u 7.7 yr
- Followed in Norwegian Cancer Registry
- 50% had low risk adenomas
- N=1273 Incident CA, N=383 deaths to CRC

Løberg M. NEJM 2014;371:799-807
Norway: Risk of CRC Mortality by Baseline Finding

Cumulative Risk of Death from Colorectal Cancer

P<0.001 with the use of Gray’s test

No. at Risk
Low-risk adenoma 19,934 17,701 13,372 8230 4095 1615
High-risk adenoma 20,892 17,947 13,270 8080 4334 1916

Natural History of 6-9 mm polyps by CT Colonography

N = 93 with 1-2 6-9 mm polyps
N = 70 repeat CTC 3.3 y
N = 57 CS

Defined progression: 30% increase by volume

35% (33/95) progressed
38% (36/95) stable
27% (26/95) regressed*

*14% disappeared

% Advanced
47
21
0

Nolthenius, AJG 2015;110:1682
Conclusion

• 65% of 6-9 mm polyps do not progress
• 14% disappear altogether
• Lesions that increase in volume, more likely to be AA’s at removal
Small Adenomas - Conclusions

- Is connection between small adenomas and cancer but not strong
- Many small adenomas were undoubtedly missed in past, yet we still observe effectiveness of screening
- Of course, large adenomas began as small – yet only a small minority advance
<table>
<thead>
<tr>
<th>Current Surveillance Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No polyps, or hyperplastic polyps in rectum/sigmoid</strong></td>
</tr>
<tr>
<td>Repeat in 10 years</td>
</tr>
<tr>
<td><strong>Neoplasia found</strong></td>
</tr>
<tr>
<td><strong>Serrated polyps/lesions</strong></td>
</tr>
<tr>
<td>Serrated polyposis</td>
</tr>
<tr>
<td>≥ 10 mm or With dysplasia or traditional serrated adenoma</td>
</tr>
<tr>
<td>&lt; 10 mm in Proximal colon and without dysplasia</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

These recommended intervals assume a complete exam to cecum, adequate bowel prep, and complete removal of polyps at the baseline exam.
EPoS trials
European Polyp Surveillance

Baseline colonoscopy (all polyps removed)

EPoS I
Low risk adenomas
13,746 patients

EPoS II
High risk adenomas
13,704 patients

EPoS III
Serrated polyps

1:1 randomization

End point acquisition: Colorectal cancer incidence

End point acquisition: Advanced neoplasia
FORTE Aim

To evaluate 5 and 10 vs. 10 yr surveillance on CRC incidence in subjects with 1-2 non-advanced adenomas

Non-inferiority Design
FORTE Proposed Schema

1-2 Low Risk Adenomas

Endpoint: CRC Incidence N = 15K
Screening Colonoscopy at Year 0:
1-2 Non-advanced Adenomas Removed - Guidelines Advise Surveillance at 5 - 10 Years

- Cancers detected between years 0 – 5 are interval cancers and are not preventable by surveillance colonoscopy at year 5
- Cancers between years 5-10 are potentially preventable by surveillance colonoscopy at year 5
- Cancers after year 10 are potentially preventable by surveillance colonoscopy at year 10
FORTE Proposed Schema

1-2 Low Risk Adenomas

Randomize

Endpoint: CRC Incidence
N = 15K
Eligibility (abbreviated)

1. ≥ 50 <70, with first time diagnosis of 1-2 non-advanced tubular adenomas
2. Complete to cecum/adequate preparation
3. Complete excision of polyps
4. Exclude high risk genetic syndromes, IBD, life expectancy <10y
N=218 Institutions
N=30 Lead Academic Performance Sites
N=32 NCORP Sites – 10 minority Underserved
Design Parameters for Study Power and Sample Size: Non-inferiority Trial

- $I[A]$: 10 Year cumulative CRC incidence in arm A (5/10-yr)
- $I[B]$: 10 Year cumulative CRC incidence in arm B (10-yr)
- Delta: Limit of difference between two groups that would be acceptable as non-inferior
- Arm B non-inferior to Arm A if upper 90% CI of $I[B] - I[A] \leq \Delta$

- **EPOS assumptions**
  - $I[A] = I[B] = 1.0\%$, Delta=$0.5\%$

- **FORTE assumptions**
  - $I[A] = I[B] = 0.387\%$, Delta=$0.307\%$
### Margin of Inferiority

<table>
<thead>
<tr>
<th>Number of CRCs observed in Arm B (5 &amp; 10 yr)</th>
<th>21</th>
<th>22</th>
<th>23</th>
<th>24</th>
<th>25</th>
<th>26</th>
<th>27￥</th>
<th>28</th>
<th>29</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>0.000%</td>
<td>-0.014%</td>
<td>-0.028%</td>
<td>-0.043%</td>
<td>-0.057%</td>
<td>-0.071%</td>
<td>-0.085%</td>
<td>-0.099%</td>
<td>-0.114%</td>
<td>-0.128%</td>
</tr>
<tr>
<td>22</td>
<td>0.014%</td>
<td>0.000%</td>
<td>-0.014%</td>
<td>-0.028%</td>
<td>-0.043%</td>
<td>-0.057%</td>
<td>-0.071%</td>
<td>-0.085%</td>
<td>-0.099%</td>
<td>-0.114%</td>
</tr>
<tr>
<td>23</td>
<td>0.028%</td>
<td>0.014%</td>
<td>0.000%</td>
<td>-0.014%</td>
<td>-0.028%</td>
<td>-0.043%</td>
<td>-0.057%</td>
<td>-0.071%</td>
<td>-0.085%</td>
<td>-0.099%</td>
</tr>
<tr>
<td>24</td>
<td>0.043%</td>
<td>0.028%</td>
<td>0.014%</td>
<td>0.000%</td>
<td>-0.014%</td>
<td>-0.028%</td>
<td>-0.043%</td>
<td>-0.057%</td>
<td>-0.071%</td>
<td>-0.085%</td>
</tr>
<tr>
<td>25</td>
<td>0.057%</td>
<td>0.043%</td>
<td>0.028%</td>
<td>0.014%</td>
<td>0.000%</td>
<td>-0.014%</td>
<td>-0.028%</td>
<td>-0.043%</td>
<td>-0.057%</td>
<td>-0.071%</td>
</tr>
<tr>
<td>26</td>
<td>0.071%</td>
<td>0.057%</td>
<td>0.043%</td>
<td>0.028%</td>
<td>0.014%</td>
<td>0.000%</td>
<td>-0.014%</td>
<td>-0.028%</td>
<td>-0.043%</td>
<td>-0.057%</td>
</tr>
<tr>
<td>27￥</td>
<td>0.085%</td>
<td>0.071%</td>
<td>0.057%</td>
<td>0.043%</td>
<td>0.028%</td>
<td>0.014%</td>
<td>0.000%</td>
<td>-0.014%</td>
<td>-0.028%</td>
<td>-0.043%</td>
</tr>
<tr>
<td>28</td>
<td>0.099%</td>
<td>0.085%</td>
<td>0.071%</td>
<td>0.057%</td>
<td>0.043%</td>
<td>0.028%</td>
<td>0.014%</td>
<td>0.000%</td>
<td>-0.014%</td>
<td>-0.028%</td>
</tr>
<tr>
<td>29</td>
<td>0.114%</td>
<td>0.099%</td>
<td>0.085%</td>
<td>0.071%</td>
<td>0.057%</td>
<td>0.043%</td>
<td>0.028%</td>
<td>0.014%</td>
<td>0.000%</td>
<td>-0.014%</td>
</tr>
<tr>
<td>30</td>
<td>0.128%</td>
<td>0.114%</td>
<td>0.099%</td>
<td>0.085%</td>
<td>0.071%</td>
<td>0.057%</td>
<td>0.043%</td>
<td>0.028%</td>
<td>0.014%</td>
<td>0.000%</td>
</tr>
<tr>
<td>31</td>
<td>0.142%</td>
<td>0.128%</td>
<td>0.114%</td>
<td>0.099%</td>
<td>0.085%</td>
<td>0.071%</td>
<td>0.057%</td>
<td>0.043%</td>
<td>0.028%</td>
<td>0.014%</td>
</tr>
<tr>
<td>32</td>
<td>0.156%</td>
<td>0.142%</td>
<td>0.128%</td>
<td>0.114%</td>
<td>0.099%</td>
<td>0.085%</td>
<td>0.071%</td>
<td>0.057%</td>
<td>0.043%</td>
<td>0.028%</td>
</tr>
<tr>
<td>33</td>
<td>0.170%</td>
<td>0.156%</td>
<td>0.142%</td>
<td>0.128%</td>
<td>0.114%</td>
<td>0.099%</td>
<td>0.085%</td>
<td>0.071%</td>
<td>0.057%</td>
<td>0.043%</td>
</tr>
<tr>
<td>34</td>
<td>0.185%</td>
<td>0.170%</td>
<td>0.156%</td>
<td>0.142%</td>
<td>0.128%</td>
<td>0.114%</td>
<td>0.099%</td>
<td>0.085%</td>
<td>0.071%</td>
<td>0.057%</td>
</tr>
<tr>
<td>35</td>
<td>0.199%</td>
<td>0.185%</td>
<td>0.170%</td>
<td>0.156%</td>
<td>0.142%</td>
<td>0.128%</td>
<td>0.114%</td>
<td>0.099%</td>
<td>0.085%</td>
<td>0.071%</td>
</tr>
<tr>
<td>36</td>
<td>0.213%</td>
<td>0.199%</td>
<td>0.185%</td>
<td>0.170%</td>
<td>0.156%</td>
<td>0.142%</td>
<td>0.128%</td>
<td>0.114%</td>
<td>0.099%</td>
<td>0.085%</td>
</tr>
<tr>
<td>37</td>
<td>0.227%</td>
<td>0.213%</td>
<td>0.199%</td>
<td>0.185%</td>
<td>0.170%</td>
<td>0.156%</td>
<td>0.142%</td>
<td>0.128%</td>
<td>0.114%</td>
<td>0.099%</td>
</tr>
<tr>
<td>38</td>
<td>0.241%</td>
<td>0.227%</td>
<td>0.213%</td>
<td>0.199%</td>
<td>0.185%</td>
<td>0.170%</td>
<td>0.156%</td>
<td>0.142%</td>
<td>0.128%</td>
<td>0.114%</td>
</tr>
<tr>
<td>39</td>
<td>0.256%</td>
<td>0.241%</td>
<td>0.227%</td>
<td>0.213%</td>
<td>0.199%</td>
<td>0.185%</td>
<td>0.170%</td>
<td>0.156%</td>
<td>0.142%</td>
<td>0.128%</td>
</tr>
</tbody>
</table>

- **Cells in black** represent a trial outcome of non-inferiority for Arm A relative to B.
- **Cells in red** represent a trial outcome of inferiority.

￥The expected number of CRCs on the control arm (Arm B, 5 and 10 years) is 27.
Feasibility

• Physician endorsement (hopefully) supports likelihood that patients will enroll

• While many subjects want comfort of repeated exams, many subjects do NOT want to undergo testing that is not needed

• Colonoscopy is not risk free

• Observational data (PLCO, Norway, UK) – suggestive that low risk adenomas not significantly different risk than no adenomas – but we need trial to provide definitive evidence
Why Randomized Trial?

• Endpoint of cancer incidence is rare: in observational cohorts, lost to follow up will impair confidence/reliability of conclusions

• Current use makes analysis of the benefit of surveillance difficult to assess

• For example: PLCO analysis – cancer incidence similar between NA to NAA – but NAA had more surveillance – maybe excess surveillance lowered risk in NAA?

• Only randomized design can insure surveillance frequency and underlying patient risk equally distributed
Summary

• General and widespread recognition that surveillance colonoscopy requires further study

• Surveillance is costly and of uncertain benefit

• A randomized design will provide the strongest, most definitive answers