The FORTE trial: How Do I Handle Research as Guidelines Change?

Robert E. Schoen MD, MPH
Professor of Medicine & Epidemiology
Chief, Division of Gastroenterology, Hepatology and Nutrition
University of Pittsburgh | UPMC
Disclosures

Research Support:

- Freenome
- Immunovia
- Exact
What is the FORTE trial?

FORTE: Five OR Ten year colonoscopy for 1 or 2 non-advanced adenomatous polyps.
Surveillance Colonoscopy

25% of Colonoscopy is for Surveillance

15M Colonoscopy exams per year in U.S.

25% of Colonoscopy is for Surveillance
FORTE Trial Schema

First colonoscopy identifying adenomas

Non-inferiority endpoint comparison
Changing Guidelines Affecting Research: The Polyp Prevention Trial (PPT)
Objective: ….to determine whether a low-fat, high-fiber, high-vegetable and high-fruit eating plan, as compared with usual diet, reduces the recurrence of adenomatous polyps.
The polyp prevention trial I: rationale, design, recruitment, and baseline participant characteristics.

A Schatzkin, E Lanza, L S Freedman, J Tangrea, M R Cooper, J R Marshall, P A Murphy, J V Selby, M Shike, R R Schade, R W Burt, J W Kikendall, and J Cahill

DOI: Published May 1996
Lack of Effect of a Low-Fat, High-Fiber Diet on the Recurrence of Colorectal Adenomas

Arthur Schatzkin, M.D., Dr.P.H., Elaine Lanza, Ph.D., Donald Corle, M.S., Peter Lance, M.D., Frank Iber, M.D., Bette Caan, Dr.P.H., Moshe Shike, M.D., Joel Weissfeld, M.D., M.P.H., Randall Burt, M.D., M. Robert Cooper, M.D., J. Walter Kikendall, M.D., Jack Cahill, M.A., Laurence Freedman, James Marshall, Robert E. Schoen, Martha Slattery, and the Polyp Prevention Trial Study Group*

<table>
<thead>
<tr>
<th>Article</th>
<th>Figures/Media</th>
</tr>
</thead>
</table>

April 20, 2000

**Table 4. Risk of Recurrence of Adenomas Among the Subjects Who Completed the Study.**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>INTERVENTION GROUP (N=958)</th>
<th>CONTROL GROUP (N=947)</th>
<th>RISK RATIO (95% CI)*</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of subjects (%)</td>
<td>no. of subjects (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of adenomas</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≮1†</td>
<td>380 (39.7)</td>
<td>374 (39.5)</td>
<td>1.00 (0.90–1.12)</td>
<td>0.98</td>
</tr>
<tr>
<td>1</td>
<td>219 (22.9)</td>
<td>217 (22.9)</td>
<td>1.00 (0.85–1.18)</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>88 (9.2)</td>
<td>82 (8.7)</td>
<td>1.06 (0.80–1.41)</td>
<td>0.75</td>
</tr>
<tr>
<td>≮3</td>
<td>73 (7.6)</td>
<td>75 (7.9)</td>
<td>0.96 (0.71–1.31)</td>
<td>0.87</td>
</tr>
</tbody>
</table>
The Polyp Prevention Trial

N=2,079, low fat (20 gm/total Kcal), high fiber (18gm/1000 Kcal), high fruit/veg (3.5 serv/1000 Kcal)

Schatzkin, NEJM 2000;342:1149
Integration of Standard Clinical Practice into Study Design:

…the standard post-polypectomy surveillance involved repeat colonoscopies at 1 and 4 years after initial adenoma diagnosis and removal. This affords PPT investigators the opportunity to examine the study participants for recurrent adenomas as part of standard clinical practice.

The participants underwent colonoscopy 1 year after randomization (T1) to ensure the removal of any possible missed lesions from the qualifying (T0) examination.
Analytic Period:

The primary analytic period, on which sample size calculations were based, is 3 years (T1 to T4), which permits a 1-year lag time for the intervention to work and allows a more definitive clearing of lesions at T1, given that at least 10-15% of polyps may be missed at baseline. The final (T4) colonoscopies are expected to be completed in early 1998.

Schatzkin A. Ca Epi Bio Prev 1996;5:375
What caused a change in guidelines?
Objective:
We sought to determine whether follow-up colonoscopy at three years would detect important colonic lesions as well as follow-up colonoscopy at both one and three years.

Methods:
Patients were eligible if they had one or more adenomas, no previous polypectomy, and a complete colonoscopy and if all their polyps had been removed. They were randomly assigned to have follow-up colonoscopy at one and three years or at three years only. The two study end points were the detection of any adenoma, and the detection of adenomas with advanced pathological features (defined as those >1 cm in diameter and those with high-grade dysplasia or invasive cancer).
## Results

<table>
<thead>
<tr>
<th>FINDING</th>
<th>2 EXAMINATIONS (N = 338)</th>
<th>1 EXAMINATION* (N = 428)</th>
<th>RELATIVE RISK (95% CI)†</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adenoma detected</td>
<td>141 (41.7)</td>
<td>137 (32.0)</td>
<td>1.3 (1.1–1.6)</td>
<td>0.006</td>
</tr>
<tr>
<td>Adenoma with advanced pathological features‡</td>
<td>11 (3.3)§</td>
<td>14 (3.3)§</td>
<td>1.0 (0.5–2.2)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

*Referent category.
†CI denotes confidence interval.
‡Any adenoma that was large (>1.0 cm) or had high-grade dysplasia or invasive cancer.
§These values are based only on patients who returned for both examinations.
Conclusions:

Colonoscopy performed three years after colonoscopic removal of adenomatous polyps detects important colonic lesions as effectively as follow-up colonoscopy after both one and three years. An interval of at least three years is recommended before follow-up examination after colonoscopic removal of newly diagnosed adenomatous polyps. Adoption of this recommendation nationally should reduce the cost of post-polypectomy surveillance and screening.

Winawer SJ. NEJM 1993;328:901
Repeated colonoscopy to check for missed synchronous and for metachronous adenomas should be performed in 3 years for most patients with a single or only a few adenomas, provided they have had a high quality initial clearing examination.
A number of clinicians, health care providers, and researchers are now recommending that some individuals, especially those found to have only a small solitary tubular adenoma, have follow-up colonoscopy only after 3 years.

The elimination of the T1 colonoscopy is potentially troublesome for our end-point assessment.

**BUT:** Because a) most PPT participants have already had their T1 colonoscopies, and b) our participating endoscopists have been willing to adhere to the T0-T1-T4 colonoscopy protocol at least for study participants, it appears that the PPT will not be especially affected by this transition in post-polypectomy surveillance practice.

Schatzkin A. Ca Epi Bio Prev 1996;5:375
What did the PPT do?

Encouraged compliance with 1 year exam – at minimum, try and get it done before end of year 2
The one-year colonoscopy had to be performed at least 180 days after randomization but less than 2 years afterward.

We defined an adenoma as recurrent if it was found during any endoscopic procedure after the one-year colonoscopy or, for subjects who missed the one-year colonoscopy, during any endoscopic procedure performed at least two years after randomization. Adenomas found during the one-year colonoscopy were not considered recurrent.

Schatzkin A. NEJM 2000;342:1149
# 2012 Multi-Society Task Force Surveillance Recommendations

## No polyps, or hyperplastic polyps in rectum/sigmoid

<table>
<thead>
<tr>
<th>Neoplasia found</th>
<th>Serrated polyps/lesions</th>
<th>High risk adenomas</th>
<th>Low risk adenomas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Serrated polyposis</strong></td>
<td>&gt; 10 Adenomas</td>
<td>1–2 Tubular adenomas</td>
</tr>
<tr>
<td></td>
<td>Repeat in 1 year</td>
<td>Repeat in less than 3 years</td>
<td>&lt; 10 mm Repeat in 5–10 years</td>
</tr>
<tr>
<td>≥ 10 mm or With dysplasia or traditional serrated adenoma</td>
<td></td>
<td>3–10 Adenomas</td>
<td>Repeat in 3 years</td>
</tr>
<tr>
<td></td>
<td>Repeat in 3 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10 mm in Proximal colon and without dysplasia</td>
<td></td>
<td>Villous adenoma(s) or tubular adenoma(s) ≥ 10 mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Repeat in 5 years</td>
<td>Repeat in 3 years</td>
<td>Repeat in 3 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adenoma(s) with high grade dysplasia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Repeat in 3 years</td>
<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.
PLCO: Long-term CRC Incidence

No cancer difference in NAA vs NA

RR=1.2 (0.8-1.7)

Click. JAMA 2018:319:2021
CRC Risk after Adenoma: Kaiser

Lee. Gastro 2020; 158:884
If the cancer risk is similar at 10 years, why bring people back for surveillance colonoscopy at 5 years?
MSTF: New Recommendations: March 2020

High quality colonoscopy
- Complete to cecum
- Adequate bowel prep to detect polyps > 5mm
- Adequate colonoscopist adenoma detection rate
- Complete polyp resection

Risk-stratified repeat colonoscopy interval

<table>
<thead>
<tr>
<th>Interval</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 years</td>
<td>Normal colonoscopy&lt;br&gt;• ≤ 20 HP &lt; 10mm&lt;br&gt;7–10 years&lt;br&gt;• 1–2 adenomas &lt; 10mm</td>
</tr>
<tr>
<td>5–10 years</td>
<td>1–2 SSPs &lt; 10mm&lt;br&gt;3–5 years&lt;br&gt;• 3–4 adenomas &lt; 10mm&lt;br&gt;• 3–4 SSPs &lt; 10mm&lt;br&gt;• HP ≥ 10mm</td>
</tr>
<tr>
<td>3 years</td>
<td>5–10 adenomas&lt;br&gt;• 5–10 SSPs&lt;br&gt;• Adenoma or SSP ≥ 10mm&lt;br&gt;• Adenoma with villous or tubulovillous histology and/or high grade dysplasia&lt;br&gt;• SSP with dysplasia&lt;br&gt;• Traditional serrated adenoma</td>
</tr>
<tr>
<td>1 year</td>
<td>• &gt; 10 adenomas</td>
</tr>
</tbody>
</table>
Problem: Fly in the Ointment

Ignoring surveillance colonoscopy that already occurred!
For example: Surveillance at Kaiser

<table>
<thead>
<tr>
<th>Colonoscopy Surveillance Utilization</th>
<th>NA</th>
<th>NAA</th>
<th>AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>YEAR 6</td>
<td>9.2</td>
<td>40.5</td>
<td>60.0</td>
</tr>
<tr>
<td>YEAR 10</td>
<td>19.8</td>
<td>58.8</td>
<td>72.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Advanced Adenoma FOUND/REMOVED</th>
<th>NA</th>
<th>NAA</th>
<th>AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>YEAR 6</td>
<td>1.7</td>
<td>4.0</td>
<td>10.5</td>
</tr>
<tr>
<td>YEAR 10</td>
<td>3.9</td>
<td>6.4</td>
<td>13.3</td>
</tr>
</tbody>
</table>
Is surveillance colonoscopy at 5 years necessary and beneficial?
Recruitment Approach

Prospective:
People Currently Undergoing Colonoscopy

Retrospective:
Diagnosed in Previous 4 years
Fears for FORTE Enrollment

• Fear of participant decline of 10 yr option
• Fear of docs not participating due to 10 yr option
• Fear in pursuit of retrospective enrollment: Participant decline of an altered prescription for follow up
• Fear of insurance not covering 5 yr option
Multi-Society Task Force

Letter dated 6/18/2021 to FORTE investigators:

“The ACG, AGA, ASGE support the conduct of the FORTE Trial”
3.75 Million Surveillance CS exams/yr in U.S.:
Forte is randomizing 9,500 people (0.2%)
Conclusions

• No formula for handling changes in guidelines
• FORTE is open and looking for investigators - GI Working Group: establish affiliation with NRG/NCORP
• Trial innovations: use of natural language processing to recruit, incentive funding, etc.
Patient Recruitment

Qualifying colonoscopy up to 4 years ago

“Retrospective”

Now

“Prospective”

Reach Endpoint Sooner

Prospective

5y

10y

Retrospective

5y

10y

5y

10y

10y
It is likely that future polyp trials will have to adopt a T0-T3 design, which, because missed baseline lesions are not removed at T1, will inflate sample size requirements considerably.