

Screening and Prevention Update

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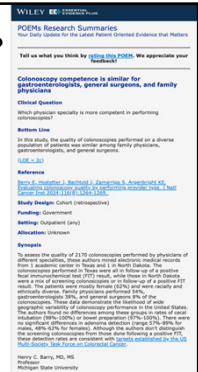
Questions we're going to answer:

1. What are pros and cons of different CRC screening tests, and starting at 45 vs 50 years?
2. What are the benefits and harms of starting screening mammography at age 40 instead of 45 years?
3. Is there a role for MRI and ultrasound in screening for breast cancer?
4. How beneficial is lung cancer screening?

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Where does this information come from?

- For 25 years, 6 of us have reviewed 110 journals/month
- We identify studies with the potential to change practice because they report patient-oriented evidence (not surrogate or disease-oriented endpoints)
- We summarize them in POEMs (Patient Oriented Evidence that Matters) and email them daily to subscribers
- Learn more at <http://www.essentialevidenceplus.com>
- Get 4 for free each month in *American Family Physician* journal
- Free podcasts: "Primary Care Update" and "Primary Care POEM of the Week" on Apple Podcasts, Spotify, etc.



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"All screening programs do harm...
some do good as well."

-- Sir Muir Gray,
Oxford University



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Guideline recommendations for colorectal CA screening

USPSTF recommendation statement

- Screen for colorectal cancer in adults aged 45-49 years (B recommendation).
- Screen for colorectal cancer in adults aged 50-75 years (A recommendation)
- Optionally screen in adults 76 to 85 if in good health (C recommendation)
- Use any of 7 tests (Colonoscopy, FIT, FOBT, Cologard, Flex sig + FIT, CT colo, etc)

American College of Physicians (POEM #1): Start 50, stop 75 or < 10 years left. If starting 45 do shared decision-making, not routine. Tests: **YES** to FIT, colonoscopy or flex sig + FIT. **NO** to Cologard, CT colonography, and blood tests.

Doing FIT right: single test, no diet prep needed, do not combine with DRE, and do not "confirm" positive FIT with a second one. Refer all positives FITs to colonoscopy within 3 months. But 50% don't get colo within 6 months!

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Summary of benefits and harms for 1000 persons screened over a lifetime

Remember: what matters is not performance at a single point in time, it is impact on mortality (and incidence) over a lifetime

	Colonoscopy q 10 years	FIT q year	Cologard q 3 years	Favors	Net Impact
CRC cases averted	61	50	47	Colonoscopy	11 fewer CRCs
CRC deaths averted	28	26	25	Colonoscopy	2 fewer CRC deaths
Lifetime colonoscopies	4.5	1.7	1.7	FIT	~3 fewer colonoscopies
GI and CV complications	16	10	10	FIT	6 fewer complications

If starting at age 45 instead of 50 (based on modeling) for 1000 persons over lifetime:
Benefit: 2-3 more cancers detected and 1 more death prevented
Harm: If colonoscopy every 10 years, 2 more serious complications and ~ 1 more colonoscopy

Source: Robertson, et al. *Gastroenterology* 2024;166:758-771 and USPSTF modeling for 2023 recommendation

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POEM #2: Invitation to a single colonoscopy has only modest impact on colorectal cancer incidence (NordICC)

- Went to places where CRC screening is not routine (Poland, Sweden, Norway) and randomized 84,585 participants aged 55 to 64 to colonoscopy or usual care.
- Only 42% invited to screening actually underwent colonoscopy.
- Median follow-up 10 years.
- Incidence of CRC significantly lower in the screened group (0.98% vs 1.20%, NNI = 455 over 10 years). No difference in CRC mortality (0.28% vs 0.31%) or all cause mortality (11.0 in both groups).
- Did analysis to estimate benefits if **everyone** invited to colonoscopy had been screened, adjusting for baseline differences between those accepting the invitation and those who ignored it.
- Larger decrease in incidence of CRC (0.84% vs 1.22, **NNS = 263**) and CRC mortality (0.15% vs 0.30%; **NNS = 667**)

	Modeling	NordICC
CRC incidence	NNS = 20	NNS = 263
CRC mortality	NNS = 39	NNS = 667

Contamination? Lower incidence? Not enough follow-up? Or modeling is wrong?

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POEM #3: FIT has similar yield as colonoscopy for colorectal cancer and advanced adenoma over 10 years

- Report of 5 rounds of biennial screening FIT persons aged 50 to 69 years in the Veneto region of northern Italy.
- Detection of CRC:
 - Round 1: 3.3/1000 persons
 - Rounds 2 to 5: ~ 1/1000 persons
- Detection of advanced adenomas
 - Round 1: 15.9 per 1000 persons
 - Rounds 2 to 5: ~10 per 1000 persons
- Over 10 years the cumulative rate of positive FIT was 25% for men and 18% for women.
- Cumulative rate for advanced adenoma was 60 per 1000 persons, and for CRC was 8.5 per 1000 persons.
- These rates are similar to those seen in studies of screening colonoscopy in both Italy and the United States (CRC < 1%)

Source: Zorzi, et al. Gut 2018; 67: 2124-30

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POEM #4. Colonoscopy vs FIT: initial report of an RCT (COLONPREV)

Recruited 57,404 Spanish adults aged 50 to 69 years between 2009 and 2021 and randomized them to invitation to:

- Single colonoscopy (32% uptake, with 21% colonoscopy) OR
- FIT every 2 years (40% uptake, with 53% doing ≥ 80% of tests)

As randomized results for all 57,404 patients

- CRC incidence: **1.13% colo vs 1.22% FIT**, RD 0.09%, 95% CI -.28 to +.10
- CRC mortality: **0.22% colo vs 0.24% FIT**, RD 0.02%, 95% CI -.10 to +.06



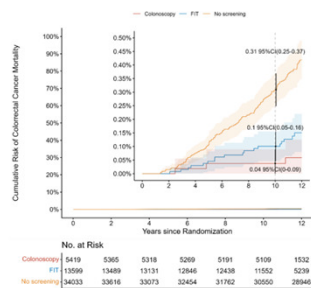
As Screened Results	Colo 10 yr risk %	FIT 10 yr risk %	Non-participant 10 yr risk %	Colo vs non-participants RR (95% CI)	FIT vs non-participants RR (95% CI)
CRC mortality	0.03%	0.09%	0.32%	0.10 (.02-.43)*	0.28 (.15-.51)*
CRC incidence	0.87%	1.16%	1.27%	0.68 (.48-.95)*	0.91 (.75-1.11)
All-cause mort	4.21%	5.21%	9.43%	0.47 (.39-.51)*	0.55 (.51-.60)*

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Figure S3. Cumulative risk of death from colorectal cancer at 10 years in as-screened analysis

Per protocol analysis: Colonoscopy reduced CRC mortality (RD -0.09%) and CRC incidence (RD -0.42%) more than FIT.

Bottom-Line: Both FIT and colonoscopy reduce CRC mortality, but colonoscopy may be a bit better. Both are reasonable options for your patients.



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POEM #5: Screening colonoscopies are overused

- Systematic review of 6 studies with 242,756 screening colonoscopies.
- About 1 in 4 to 1 in 6 (17% to 26%) colonoscopies to be out of compliance with national guidelines; amounts to about **1 million inappropriate colonoscopies/year** in US

POEM #6: Screening colonoscopy harms: 16 to 36 severe bleeds and 8 perforations/10,000 studies

- Systematic review of 6 studies that followed 467,139 average risk persons after screening colonoscopy for 30+ days.
- Severe bleeding:
 - 1 severe bleed per 276 to 610 colonoscopies**
- Perforation:
 - 1 perforation per 1250 colonoscopies**

Bottom-Line: Don't do colonoscopy more than every 10 years. Bleeds are more common than we thought.

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Guideline recommendations: breast cancer screening

USPSTF recommendation statement

- Screening mammography every other year in women aged **40-75** years (B)
- Clinical breast exam and self-exam by women no longer recommended
- No recommendation regarding MRI or USN for women with dense breasts

American Cancer Society: From 40 to 44 consider annual mammogram; from 45 to 54 annual mammogram; from 55 until 10 years left annual or biennial mammograms

Norway: Mammogram every other year from 50 to 69 years

Netherlands: Mammogram every other year from 50 to 75 years

Every other country in the world: Every 2 years.

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POEM #6: USPSTF recommends mammography every other year for all women 40 to 74 years old

- Had been optional ages 40 to 49. So there must be some really important new data, right? Well, no...
- Starting age 40 vs 50 per 1000 women:**
 - Benefit:** 1.5 breast cancer deaths averted and 44 life years gained
 - Harms:** 500 more false positives, 2 more overdiagnosed and treated without benefit

Table 2. Estimated Median Lifetime Benefits and Harms of Biennial Screening Mammography With Digital Breast Tomosynthesis for a Cohort of 1000 Women and a Cohort of 1000 Black Women by Starting Age of 40 vs 50 Years

Black women by starting age of 40-55-70 year					
Screening strategy (interval, start-stop ages in years)	Mammograms	BENEFITS		HARMS	
		Breast cancer deaths averted	Life-years gained	False-positive results	Overdiagnosis
All women (across 6 models)					
Biennial (40-74)	16 116	8.2	165.2	1376	14
Biennial (50-74)	11 208	6.7	120.8	873	12
Black women (across 4 models)					
Biennial (40-74)	15 801	10.7	228.9	1253	18
Biennial (50-74)	10 905	9.2	176.7	814	16

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POEM #7: Supplemental MRI screening in women with very dense breasts reduces interval cancers

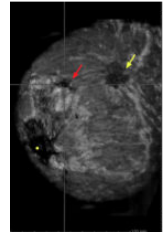
- Identified Dutch women with very dense breasts (4/4) and a normal digital mammogram. Randomized ~8k to supplemental MRI and ~32k to usual care
- 4783 of 8000 women underwent supplemental MRI
- 79 (1.65%) had breast cancer detected on MRI, 80% of which were invasive.
- Benefits:**
 - The rate of interval cancers was lower in MRI than in the usual care group (2.5 vs 5.0 per 1000 women).
 - At the second round of screening 2 years later, the rate of invasive cancers was lower in the MRI group (2.0 vs 7.0 per 1000) and they were more likely to be stage 0 or 1 cancers
- Harms:**
 - In MRI group, 9.5% were recalled and 6.3% of all women had a biopsy with an 8% false positive rate

Encouraging...needs longer follow-up and mortality data

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POEM #8: Adding ultrasound to mammography increases false-positive findings without an increase in cancer detection

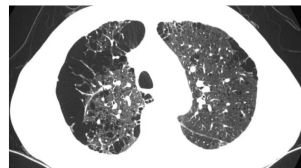
- Observational study compared:
 - 6,081 women got both mammography and ultrasound
 - 15,176 women got mammogram only
- 74% of the ultrasound screens were performed in women with dense breasts, and these women were more likely to be at increased risk of breast cancer.
- No benefit:** Cancer detection rate was similar across groups (5.4 vs 5.5 per 1000 screens), as was rate of interval cancers.
- Harms:** There were more than twice as many unnecessary biopsies with USN (52.0 vs 22.2 per 1000), and they got 3x as many calls for rescreening at shorter-than-normally-recommended intervals (RR= 3.10; 95% CI 2.6 - 3.7).



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Lung Cancer Screening: USPSTF recommendation

Who: Adults aged 50 to 80 years who have a 20 pack-year history and currently smoke or who quit in the last 15 years.



What: Low dose CT scan (radiation about 1/3 of annual background radiation or 15 chest x-rays)

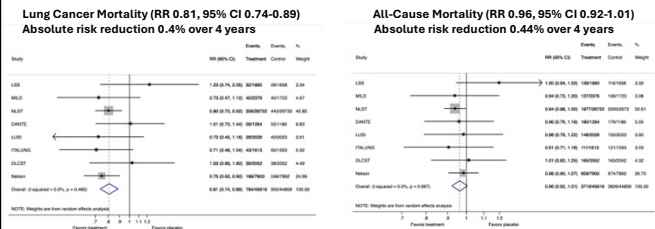
How often: Annually (?)

How long: ???

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POEM #9: Screening smokers for lung cancer with low-dose CT decreases lung cancer mortality

- We published a meta-analysis of 8 large RCTs of lung cancer screening with low dose CT in Annals of Family Medicine



NNS to prevent 1 lung cancer death = 250/5 years

NNS to prevent 1 death overall = 225

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POEM #10: Volume-based low-dose CT screening reduces lung cancer-specific mortality (NELSON)

- Dutch RCT of 13,195 men and 2594 women 50-74 with > 15 -20 pack years randomized to **low dose CT at 0, 1, 3 and 5.5 years** or no screening. Volume based protocol to reduce FP; only 2% needed biopsy due to FP
- Lung cancer mortality: RR 0.75, 95% CI 0.62-0.90, similar men & women.
- Absolute risk reduction 0.8%, number needed to screen = 127 (even better than US National Lung Screening Trial)
- They also saw a stage shift meaning less aggressive treatment:
 - 59% stage 1A or 1B if screen detected versus 14% stage 1A or B if symptomatic
 - 9.4% stage IV if screen detected versus 46% - 52% stage IV if symptomatic

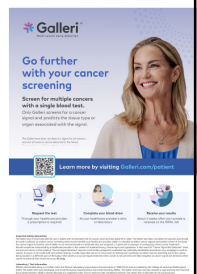
Key: We should learn from their success with longer intervals

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POEM #11: Multicancer early detection NNS: 1000 to detect one stage 1 or 2 cancer, 530 to detect any cancer (SPOT-MAS)

- Multicancer early detection test evaluated in 9057 Vietnamese asymptomatic adults 40+ with no history of cancer
 - Positive test → extensive diagnostic evaluation
 - Negative test → one year follow-up (enough?)

	SPOT-MAS (n = 9024)	Galleri (n = 6662)
Positive test results	43 (0.48%)	92 (1.38%)
New cancers	17 (0.19%)	29 (0.44%)
Stage 1 or 2	9 (0.1%)	14 (0.21%)
Stage 3	3 (0.03%)	9 (0.14%)
Stage 4	5 (0.05%)	6 (0.09%)
Sensitivity	70.8%	28.9%
Specificity	99.7%	99.1%
Positive predictive value	39.5%	38%
Negative predictive value	99.92%	98.6%



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POEM #12: Cell-free DNA blood test 83% sensitive for colorectal cancer, only 13% sensitive for advanced adenoma

- A new screening test for CRC that detects cell-free DNA in blood
- 22,877 participants 45 to 84 who were undergoing a screening colonoscopy, of whom 65 had colorectal cancer.
- Then took a random sample of 10,258 participants without cancer and added back the 65 with cancer to create an enriched final study population (inflates the predictive value by increasing the prevalence of CRC from 0.28% to 0.82%.
- The sensitivity overall for CRC was 83%, and for stage I, II or III CRC was 87%; specificity 90%
- But: the sensitivity for advanced adenomas was only 13% (FIT = 23%!)
- In an average-risk population of 100,000 persons
 - 11,000 will have an abnormal test result requiring colonoscopy
 - 3.2% will have cancer and 12.9% an advanced adenoma.

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POEM #13: Recommendations for care outpace the time available for a typical primary care practice

- Created 1000 hypothetical primary care panels of 1500 patients
- Took all 48 Grade A and B recommendations from USPSTF and ACIP; picked guidelines for the top 10 chronic illnesses; and added the average number and length of acute visits for adults.
- The complete basket of services was estimated to require 26.7 hours per day for a panel of 2500 patients
 - 3.2 hours for documentation and inbox management
 - 14.1 hours for preventive care
 - 7.2 hours for chronic disease care
 - 3.2 hours a day for acute care
- Estimates for practices using high-functioning teams are lower: 9.3 hours per day of clinician time, which includes 2.6 hours per day for and in inbox management.



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POEM #14: 0 cases of invasive cervical cancer with at least 1 dose of bivalent HPV vaccine at 12 or 13 years of age

- Used Scottish registry data to determine SES, # of HPV vaccine doses, the age of administration, and the rates of cervical carcinoma for women born between 1988 and 1996
- 447,845 women → 239 developed invasive cervical CA as of 2020
- No cases of invasive cervical CA in adults who received any doses of HPV vaccine when they were 12 to 13 years of age.

Group	Number of cancers	Cancers/100,000 (95% CI)	Vaccine effectiveness (95% CI)
Unvaccinated	210	8.4 (7.2 - 9.6)	—
Partial vaccination at 12-13 y	0	0.0 (0.0 - 199.6)	Too few to calculate
Complete vaccination at 12-13 y	0	0.0 (0.0 - 2.7)	100 (66.9 - 100)
Partial vaccination at 14+ y	8	6.5 (2.6 t - 13.6)	40.0 (-22.8 to 70.7)
Complete vaccination at 14+ y	21	2.7 (1.7 - 4.2)	73.8 (58.9 - 83.4)

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Bottom Lines

1. Screen for colorectal cancer. Use colonoscopy every 10 years or FIT every 1 year. They are pretty similar in benefits and harms.
2. Screening for colorectal cancer starting at age 45, or breast cancer starting at age 40, both have small benefits and harms compared to starting at 50.
3. Adding MRI may be beneficial for women with very dense breasts (grade 4/4), but ultrasound does not seem to add anything.
4. Lung cancer screening has the most favorable NNT of any major cancer screening test. Spreading out interval is safe and effective.
5. HPV vaccination clearly prevents cancer, with age 12 to 13 optimal

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