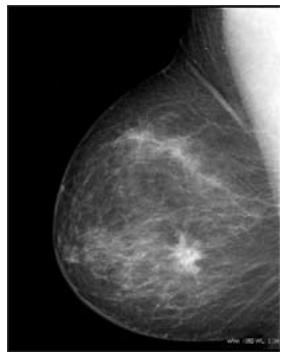
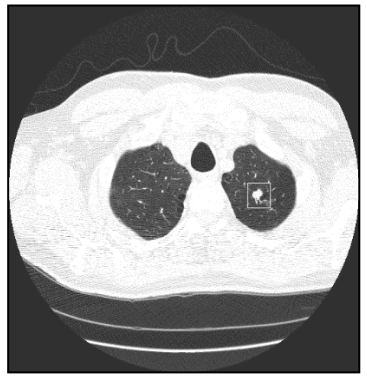
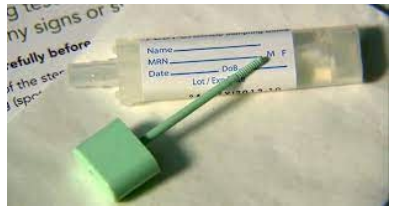
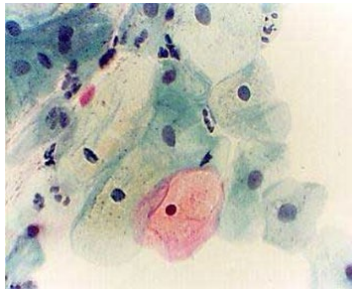
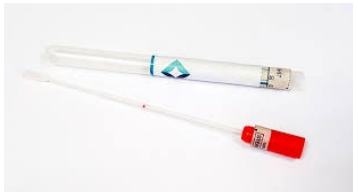
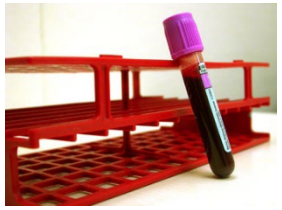






History of Cancer Early Detection Studies

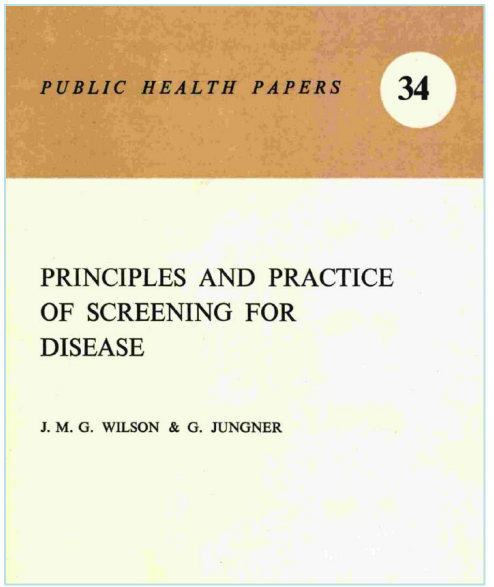
Robert A. Smith, PhD
Senior Vice President and Director,
Center for Early Cancer Detection Science
American Cancer Society
Atlanta, GA USA

NATIONAL ACADEMIES Sciences Engineering Medicine

Opportunities and Challenges for the Development and Adoption of Multicancer Detection Tests

The importance of early cancer detection

- In the last 100 years, our understanding of natural history of single organ cancers as localized at inception and systemic following progression led to an emphasis on early detection as a cornerstone of cancer control.
- Observations that outcomes were better with earlier detection of symptomatic disease led to an interest in detecting early, occult disease in asymptomatic individuals.
- In the 60s and 70s, the emergence of evidence-based criteria (Wilson & Jungner) and evidence-based medicine led to the prioritization of experimental methodology (randomized trials) as essential for establishing cancer screening policy, and evidence-based approaches to establishing screening guidelines.



The Evolution of Cervical Cancer Screening

1928

New Cancer Diagnosis

George N. Papanicolaou, M.D.

I will only give a report of some work of mine which may have some bearing on the diagnosis of certain malignant tumors, especially those of the female genital tract.

This work was started about two and one-half years ago in the spring of 1925, first in the clinic of Cornell Medical College, then in the Women's Hospital in New York City. First we selected a number of normal women, and we took vaginal smears every day. The technique was very simple. We used a small pipette and took a little fluid from the vagina every day. Our intention was to find out if there was any definite morphological change in the vagina and the vaginal smear that would reveal some of the more important changes that occur in the ovaries and in the uterus.

As you probably know, this method has been applied very successfully in other mammals, especially in the rodents, with really surprising results. It has been possible to diagnose or to recognize certain changes in the ovaries and in the uterus. For instance, the time of ovalescence in the ovary may be

This paper was originally presented at the Third Race Betterment Conference, Battle Creek, Michigan, January 2-6, 1928, and published in the Proceedings of the Conference the same year.

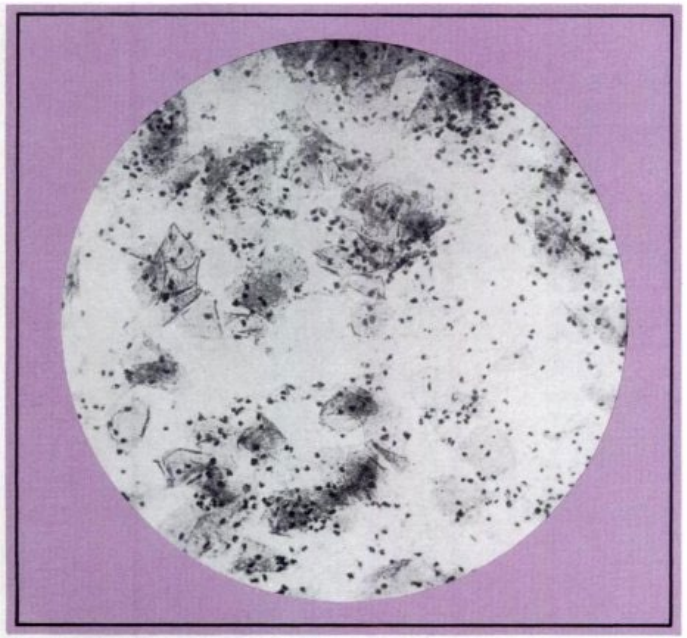


Fig. 1. Photograph of a normal human vaginal smear, showing squamous vaginal cells and a number of leukocytes. Magnification about 120 times.

https://acsjournals.onlinelibrary.wiley.com/doi/epdf/10.3322/canjclin.23.3.174

1941

American Journal of Obstetrics and Gynecology

VOL. 42 AUGUST, 1941 No. 2

Original Communications

THE DIAGNOSTIC VALUE OF VAGINAL SMEARS IN CARCINOMA OF THE UTERUS*

GEORGE N. PAPANICOLAOU, M.D., PH.D., AND HERBERT F. TRAUT, M.D.,
NEW YORK, N. Y.

(From the Departments of Anatomy and of Gynecology and Obstetrics of the Cornell University Medical College and the New York Hospital)

THE death rate from carcinoma of the female genital tract is approximately 32,000 per year in the United States and of this figure, four-fifths, or 26,000 deaths per year, may be said to be due to cancer of the uterus. This rate has remained practically constant during the past twenty-five years.[1]

One of the factors probably responsible for this rather discouraging situation is the fact that, despite the progress in methods of treatment, no significant improvement has been achieved in the diagnosis of malignant growths of the female genital tract, more particularly in their early stages. Indeed, it seems very likely that until enough is known about the etiology of cancer to make it possible to place efficient prophylactic weapons in physicians' hands, no radical change in the picture can be expected unless the introduction of new methods makes possible an early diagnosis of the disease.

Early diagnosis and treatment yield a high percentage of cures in both carcinoma of the fundus and of the cervix. The present difficulty in accomplishing an early diagnosis lies in the fact that we must depend largely upon the subjective symptoms of the disease to bring the patient to the physician, and by the time the patient becomes sufficiently aware

*This study has been aided by the Commonwealth Fund.
Presented before the New York Obstetrical Society, March 11, 1941.

Am J Obstet Gynecol. 1941 42:193–206

Trends in Mortality from Cervical Cancer in the Nordic Countries, 1953-1982

THE LANCET, MAY 30, 1987

THE LANCET, MAY 30, 1987

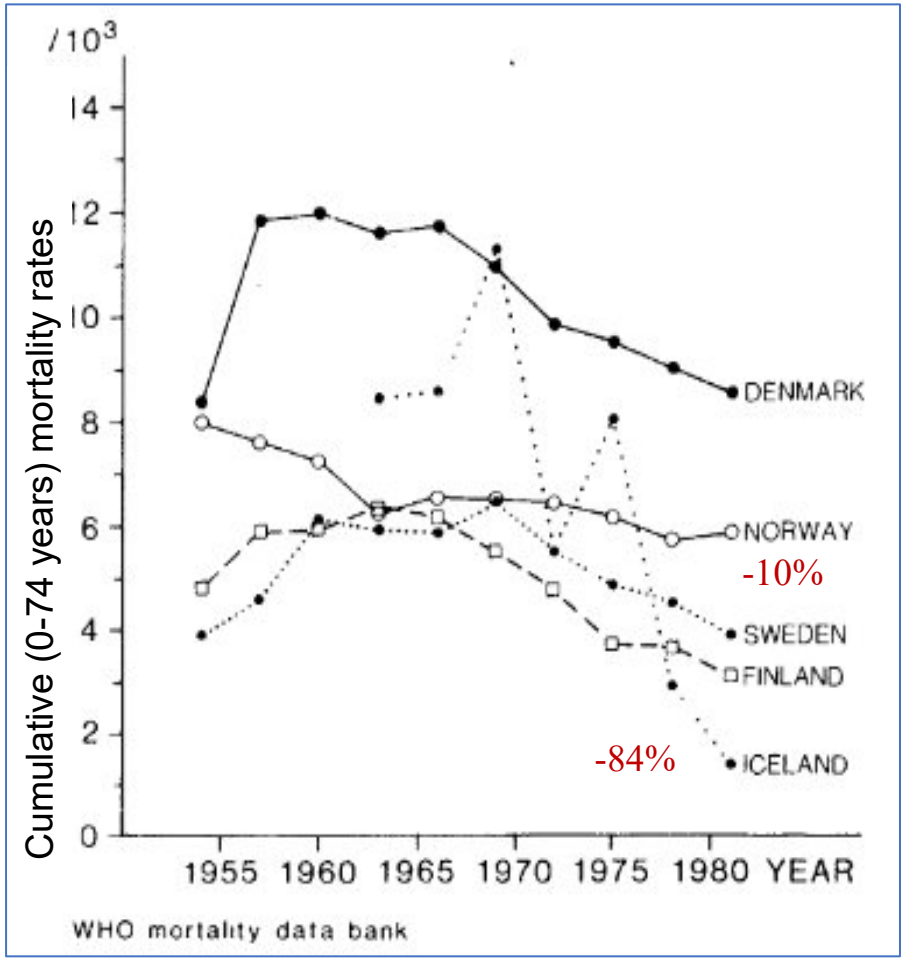
Public Health

TRENDS IN MORTALITY FROM CERVICAL CANCER IN THE NORDIC COUNTRIES: ASSOCIATION WITH ORGANISED SCREENING PROGRAMMES

ESA LÄÄRÄ[1,2]* NICHOLAS E. DAY[3]
MATTI HAKAMA[2,4]

Department of Community Health, University of Kuopio, Finland;[1] Finnish Cancer Registry, Helsinki, Finland;[2] Medical Research Council Biostatistics Unit, Cambridge;[3] and Department of Public Health, University of Tampere, Finland[4]

Summary Time trends in mortality from cervical cancer in Denmark, Finland, Iceland, Norway, and Sweden since the early 1950s were investigated in relation to the extent and intensity of organised screening programmes in these countries. In all five countries the cumulative mortality rates (0–74 years) fell between 1965 and 1982. In Iceland, where the nationwide programme has the widest target age range, the fall in mortality was greatest (80%). Finland and Sweden have nationwide programmes also; the mortality fell by 50% and 34%, respectively. In Denmark, where about 40% of the population are covered by organised programmes, the overall mortality fell by 25%, but in Norway, with only 5% of the population covered by organised screening, the mortality fell by only 10%. The results support the conclusion that organised screening programmes have had a major impact on the reduction in mortality from cervical cancer in the Nordic countries.



"No randomised trial to evaluate a screening programme for cervical cancer based on regular Pap smears in a defined population has ever been reported."

"The experience of the five Nordic countries provides an informative and reasonably reliable geographical evaluation."

The results support the conclusion that organised screening programmes have had a major impact on the reduction in mortality from cervical cancer in the Nordic countries.

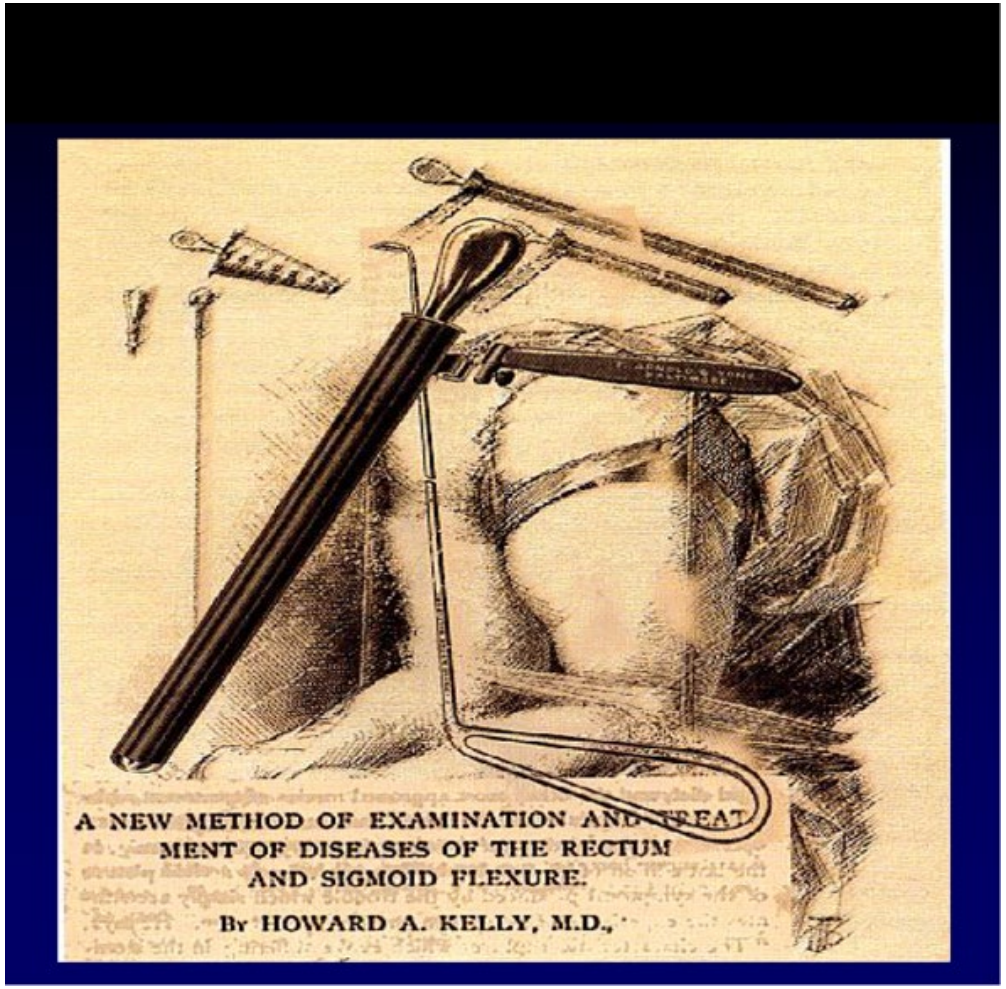
GUIDELINES FOR CERVICAL CANCER SCREENING HAVE EVOLVED WITH GREATER UNDERSTANDING OF THE ROLE OF HPV

YEAR	ACS Recommendation
1957	18 + Annual Pap tests
1980	< 20 if sexually active or 20 +, Annual Pap tests After 2 normal exams, every 3 years
1988	Onset of sexual activity, or age 18, Annual Pap tests. After 3 consecutive normal exams, less often based on Doctor's judgment
1991	No change
2002	3 years after onset of sexual activity or age 21. Annual/Biennial testing until age 30; Every 2-3 years after 30
2012	Age 21, every 3 years with Pap test 30-65, every 3 years with Pap test, or every 5 years with co-testing
2020	Age 25, every 5 years with primary HPV testing (preferred); every 5 years with cotesting, or every 3 years with Pap test (acceptable)

Dr. George Papanicolaou, Inventor of the Pap Test

The Era of Sigmoidoscopy and FOBT

- The understanding of the adenoma-carcinoma sequence, and that "earlier is better," led to the pursuit of strategies to diagnosis CRC at the first indication of symptoms, typically rectal bleeding, *and even before patients became symptomatic* **since it was presumed that occult bleeding must precede visible bleeding.**
- **However, early testing for occult blood in the laboratory was complex and unreliable.**
- The use of the rigid sigmoidoscope, developed at Johns Hopkins in 1895, began to be used in clinical centers for earlier diagnosis of CRC



Early Evidence for the Effectiveness of Sigmoidoscopy in the Reduction of Colorectal Cancer Mortality

SIGMOIDOSCOPY AND MORTALITY FROM COLORECTAL CANCER: THE KAISER PERMANENTE MULTIPHASIC EVALUATION STUDY

JOSEPH V. SELBY,* GARY D. FRIEDMAN and MORRIS F. COLLEN

Division of Research, Kaiser Permanente Medical Care Program, 3451 Piedmont Avenue, Oakland, CA 94611, U.S.A.

(*Received in revised form* 8 *October* 1987)

Sixteen years after randomization, 12 CRC deaths had occurred among the study group compared with 29 deaths among the control group (2.3 vs 5.2 deaths per 1000: $x2 = 5.85$, $p < 0.02$)

Selby, et al. concluded that the slight excess in exposure to sigmoidoscopy seen in the study group (30 vs 25% of subjects examined at least once) was unlikely to account for more than a small fraction of the study group's decrease in mortality—the results must be judged as inconclusive.

J Clin Epidemiol Vol. 41, No. 5, pp. 427–434, 1988

The New England Journal of Medicine

Volume 326 MARCH 5, 1992 Number 10

A CASE–CONTROL STUDY OF SCREENING SIGMOIDOSCOPY AND MORTALITY FROM COLORECTAL CANCER

JOE V. SELBY, M.D., M.P.H., GARY D. FRIEDMAN, M.D., M.S., CHARLES P. QUESENBERRY, JR., PH.D., AND NOEL S. WEISS, M.D., DR.P.H.

- "The efficacy of sigmoidoscopic screening in reducing mortality from colorectal cancer remains uncertain."
- "A randomized trial would be ideal for clarifying this issue but is very difficult to conduct."
- "Case-control studies provide an alternative method of estimating the efficacy of screening sigmoidoscopy. "

The New England
Journal of Medicine

Volume 326 MARCH 5, 1992 Number 10

A CASE–CONTROL STUDY OF SCREENING SIGMOIDOSCOPY AND MORTALITY FROM COLORECTAL CANCER

JOE V. SELBY, M.D., M.P.H., GARY D. FRIEDMAN, M.D., M.S., CHARLES P. QUESENBERRY, JR., PH.D., AND NOEL S. WEISS, M.D., DR.P.H.

Table 3. Odds of Having Had at Least One Screening Sigmoidoscopy during the 10-Year Period before the Diagnosis of Fatal Cancer in the Case Subjects.

ADJUSTMENT	CASE SUBJECTS (N = 261)	CONTROLS (N = 868)	ODDS RATIO (95% CI)*
	no. (%)		
Cancer within reach of sigmoidoscope			
Unadjusted	23 (8.8)	210 (24.2)	0.30 (0.19–0.48)
History of colorectal cancer or polyp, family history of colorectal cancer†	—	—	0.25 (0.16–0.42)
History of colorectal cancer or polyp, family history of colorectal cancer, no. of periodic health checkups‡	—	—	0.41 (0.25–0.69)
Cancer above reach of sigmoidoscope			
Unadjusted	56 (22.9)	67 (25.0)	0.80 (0.54–1.19)
History of colorectal cancer or polyp, family history of colorectal cancer†	—	—	0.80 (0.54–1.19)
History of colorectal cancer or polyp, family history of colorectal cancer, no. of periodic health checkups‡	—	—	0.96 (0.61–1.50)

*Odds ratios and 95 percent confidence intervals (CI) were obtained from matched conditional logistic-regression models.

†The odds ratio was adjusted by entering a history of colorectal cancer or polyp before the 10-year period and a family history of colorectal cancer noted before diagnosis in the case subject as dichotomous variables.

‡The odds ratio was further adjusted by entering the number of periodic health checkups during the 10-year period as a continuous variable.

Results:

- Data from 268 members of the Kaiser Permanente Medical Care Program who had died of cancer of the rectum or distal colon from 1971 to 1988
- Only 8.8% of case subjects had undergone screening sigmoidoscopy vs. 24% controls (OR=.30, 95% CI 0.19-0.48). Adjusting for confounding increased the OR to 0.41, 95% CI 0.25-0.69)
- OR for fatal CRC above the sigmoid was 0.96 (95% CI 0.61-1.50)
- Risk of fatal CRC was marked lower for 10 year after a single examination
- *"…our adjusted odds ratio of 0.41, implying a 59% reduction in mortality, suggests that a screening program using flexible sigmoidoscopy could lead to a reduction of at least 30 percent in total mortality from colorectal cancer."*

Minnesota Colon Cancer Control Study

The NEW ENGLAND JOURNAL of MEDICINE NEJM 1993; 328 (19)

REDUCING MORTALITY FROM COLORECTAL CANCER BY SCREENING FOR FECAL OCCULT BLOOD

Jack S. Mandel, Ph.D., M.P.H., John H. Bond, M.D., Timothy R. Church, Ph.D., Dale C. Snover, M.D., G. Mary Bradley, M.D., Leonard M. Schuman, M.D., and Fred Ederer, M.A., for the Minnesota Colon Cancer Control Study*

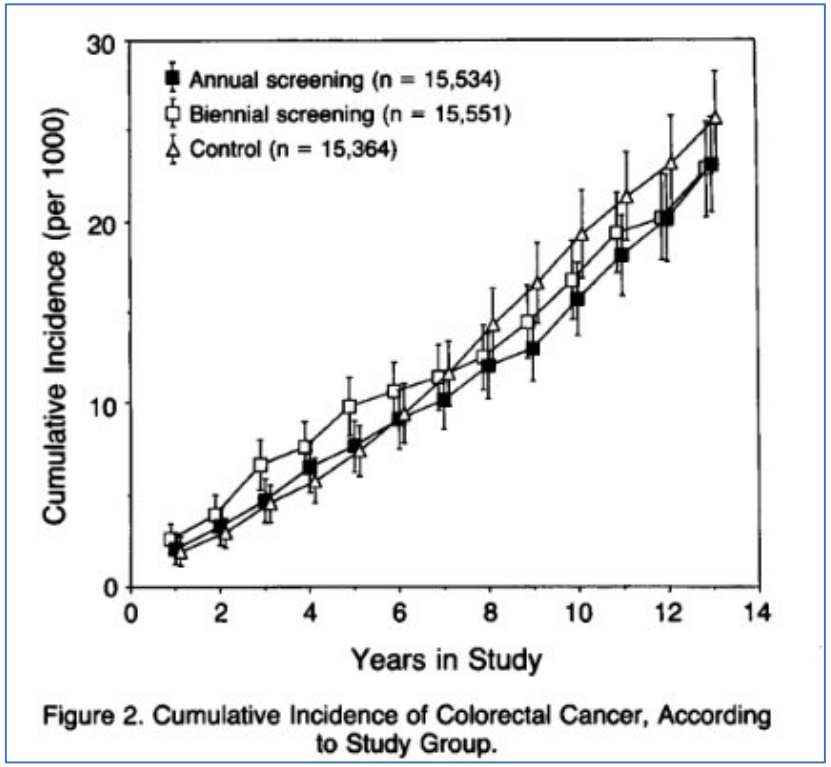


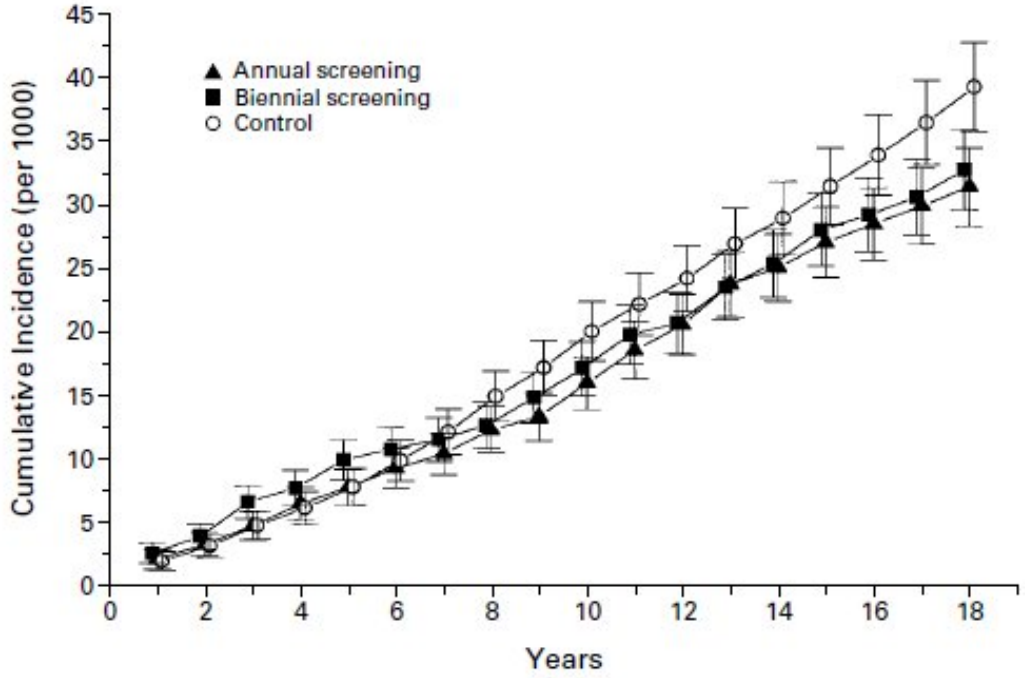
Figure 2. Cumulative Incidence of Colorectal Cancer, According to Study Group.

Conclusion: Annual FOBT with rehydration decreased the 13-year cumulative CRC mortality by 33%

The NEW ENGLAND JOURNAL of MEDICINE NEJM 2000; 343 (22)

THE EFFECT OF FECAL OCCULT-BLOOD SCREENING ON THE INCIDENCE OF COLORECTAL CANCER

Jack S. Mandel, Ph.D., M.P.H., Timothy R. Church, Ph.D., John H. Bond, M.D., Fred Ederer, M.A., Mindy S. Geisser, M.S., Steven J. Mongin, M.S., Dale C. Snover, M.D., and Leonard M. Schuman, M.D.



Conclusion: Annual FOBT with rehydration decreased the 18-year cumulative CRC incidence rate by 20%

In the 1990s……

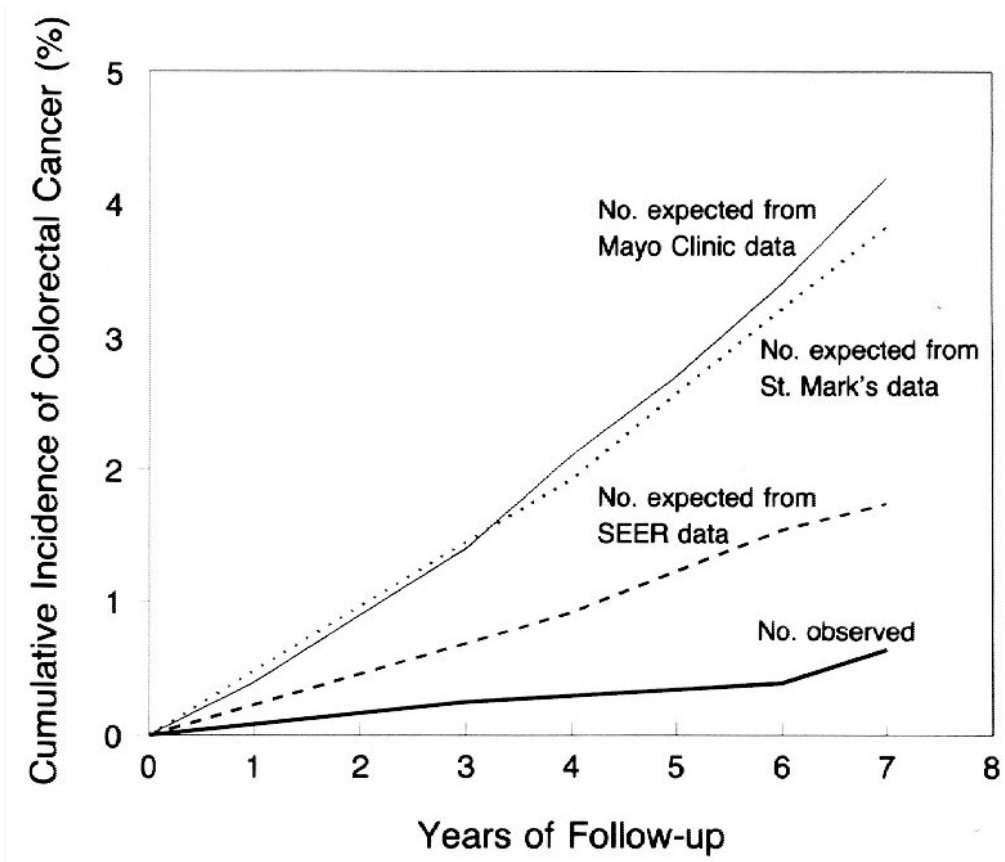
- Selby, et. al.'s case control study provided strong support for endoscopy by demonstrating reduced CRC mortality attributable to removal of lesions within the reach of the sigmoidoscope
- Additional support came from a report from the National Polyp Study in 1993, which demonstrated reduced CRC incidence associated with colonoscopic polypectomy

Winawer, et al. NEJM 1993;Vol 329 (27)

The NEW ENGLAND JOURNAL of MEDICINE

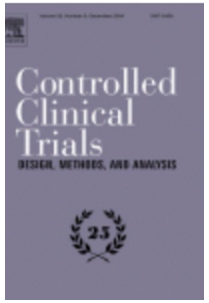
PREVENTION OF COLORECTAL CANCER BY COLONOSCOPIC POLYPECTOMY

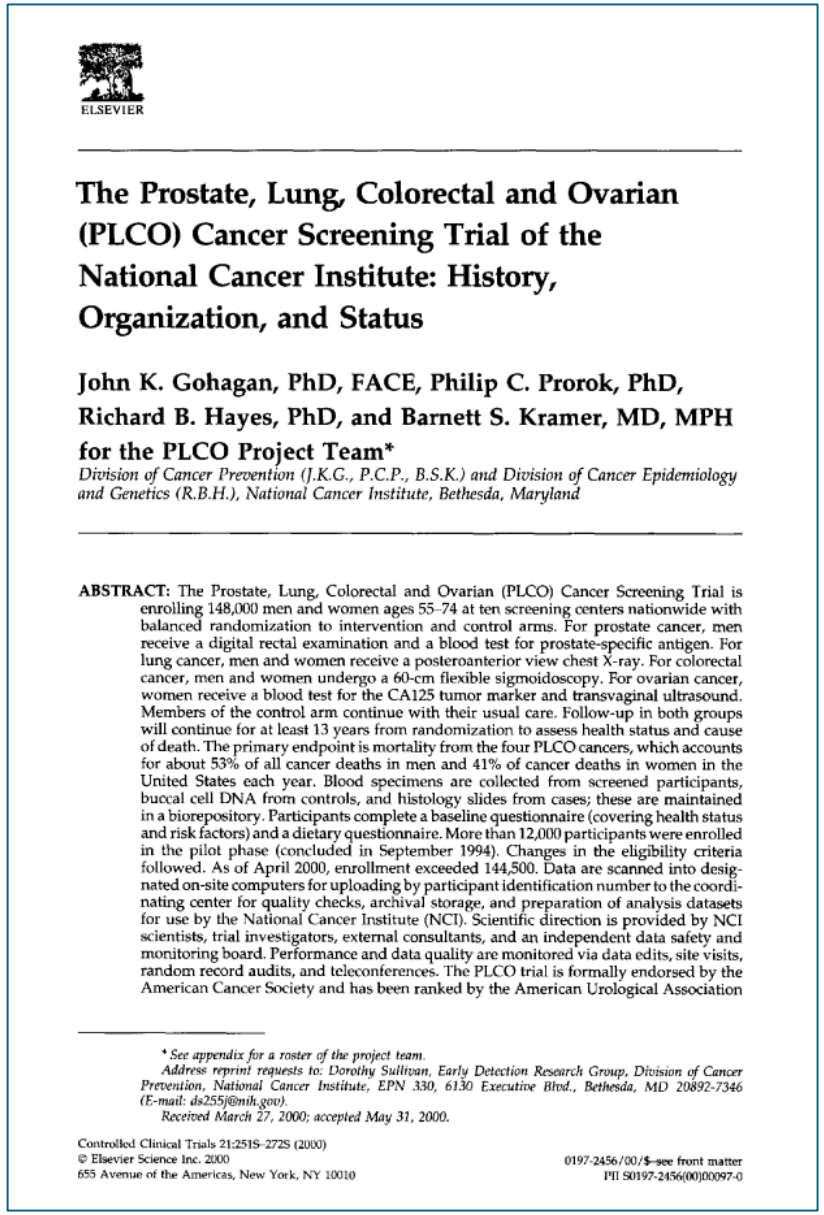
SIDNEY J. WINAWER, M.D., ANN G. ZAUBER, PH.D., MAY NAH HO, M.S., MICHAEL J. O'BRIEN, M.D., LEONARD S. GOTTLIEB, M.D., STEPHEN S. STERNBERG, M.D., JEROME D. WAYE, M.D., MELVIN SCHAPIRO, M.D., JOHN H. BOND, M.D., JOEL F. PANISH, M.D., FREDERICK ACKROYD, M.D., MOSHE SHIKE, M.D., ROBERT C. KURTZ, M.D., LYNN HORNSBY-LEWIS, M.D., HANS GERDES, M.D., EDWARD T. STEWART, M.D., AND THE NATIONAL POLYP STUDY WORKGROUP*



Reductions in the incidence of CRC compared with expected rates in the 3 reference groups were 90, 88, and 76 percent

The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial





ELSEVIER

The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial of the National Cancer Institute: History, Organization, and Status

John K. Gohagan, PhD, FACE, Philip C. Prorok, PhD, Richard B. Hayes, PhD, and Barnett S. Kramer, MD, MPH for the PLCO Project Team*

Division of Cancer Prevention (J.K.G., P.C.P., B.S.K.) and Division of Cancer Epidemiology and Genetics (R.B.H.), National Cancer Institute, Bethesda, Maryland

ABSTRACT: The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial is enrolling 148,000 men and women ages 55–74 at ten screening centers nationwide with balanced randomization to intervention and control arms. For prostate cancer, men receive a digital rectal examination and a blood test for prostate-specific antigen. For lung cancer, men and women receive a posteroanterior view chest X-ray. For colorectal cancer, men and women undergo a 60-cm flexible sigmoidoscopy. For ovarian cancer, women receive a blood test for the CA125 tumor marker and transvaginal ultrasound. Members of the control arm continue with their usual care. Follow-up in both groups will continue for at least 13 years from randomization to assess health status and cause of death. The primary endpoint is mortality from the four PLCO cancers, which accounts for about 53% of all cancer deaths in men and 41% of cancer deaths in women in the United States each year. Blood specimens are collected from screened participants, buccal cell DNA from controls, and histology slides from cases; these are maintained in a biorepository. Participants complete a baseline questionnaire (covering health status and risk factors) and a dietary questionnaire. More than 12,000 participants were enrolled in the pilot phase (concluded in September 1994). Changes in the eligibility criteria followed. As of April 2000, enrollment exceeded 144,500. Data are scanned into designated on-site computers for uploading by participant identification number to the coordinating center for quality checks, archival storage, and preparation of analysis datasets for use by the National Cancer Institute (NCI). Scientific direction is provided by NCI scientists, trial investigators, external consultants, and an independent data safety and monitoring board. Performance and data quality are monitored via data edits, site visits, random record audits, and teleconferences. The PLCO trial is formally endorsed by the American Cancer Society and has been ranked by the American Urological Association

* *See appendix for a roster of the project team.*
Address reprint requests to: Dorothy Sullivan, Early Detection Research Group, Division of Cancer Prevention, National Cancer Institute, EPN 330, 6130 Executive Blvd., Bethesda, MD 20892-7346 (E-mail: ds255j@nih.gov).
Received March 27, 2000; accepted May 31, 2000.

Controlled Clinical Trials 21:251S–272S (2000)

655 Avenue of the Americas, New York, NY 10010

0197-2456/00/$–see front matter
PII S0197-2456(00)00097-0

- The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial began enrolling ~ 148,000 men and women ages 55-74 at ten screening centers nationwide with balanced randomization to intervention and control arms.
- Protocol development phase began in 1992
- Target cancers included:
  - Prostate (PSA and DRE)
  - Lung (chest x-ray)
  - Colorectal (flexible sigmoidoscopy)
  - Ovarian (CA-125 and transvaginal ultrasound)

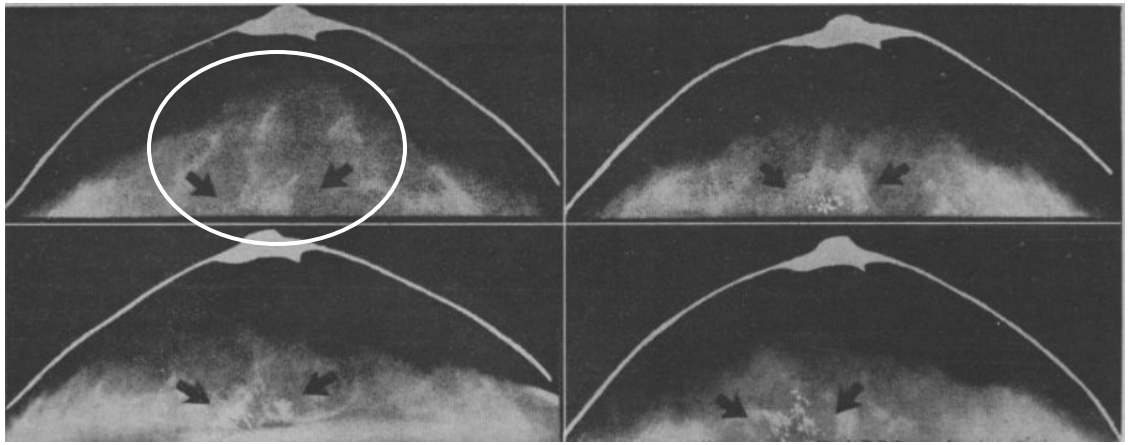
Early Research on Breast Imaging was initiated in 1913 by Solomon; Other pioneering work was conducted by Kleinschmidt (1927), Warren (1930), Vogel (1932), Gershon-Cohen (1937), Leborgne (1951), and Egan (1960)

JAMA 1961; 176 (13)

Detection of Breast Cancer by Periodic X-Ray Examinations

A Five-Year Survey

J. Gershon-Cohen, M.D., D.Sc. (Med.), M. B. Hermel, M.D., and S. M. Berger, M.D., Philadelphia



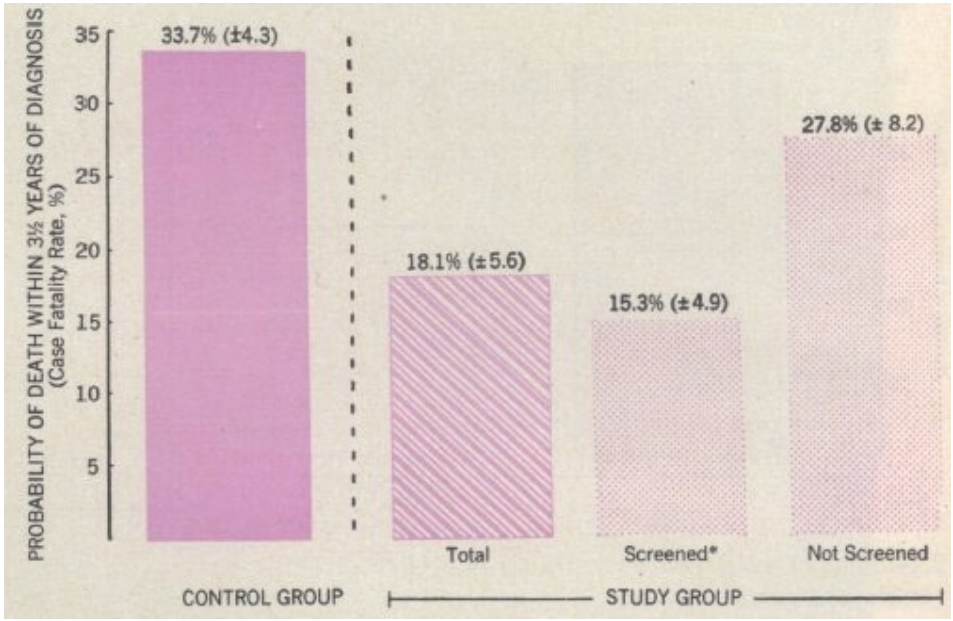
Periodic x-ray examination at 6-month intervals among 1,312 women for 5 years uncovered 23 cancers, at a case finding rate of 17.5 per 1,000. The lesions averaged 1.1 cm. in diameter and ranged in size from 0.5 to 3.0 cm. in diameter. Axillary metastasis was absent in 70%.

The Health Insurance Plan of Greater New York (HIP) RCT of Breast Cancer Screening

Periodic Breast Cancer Screening in Reducing Mortality From Breast Cancer

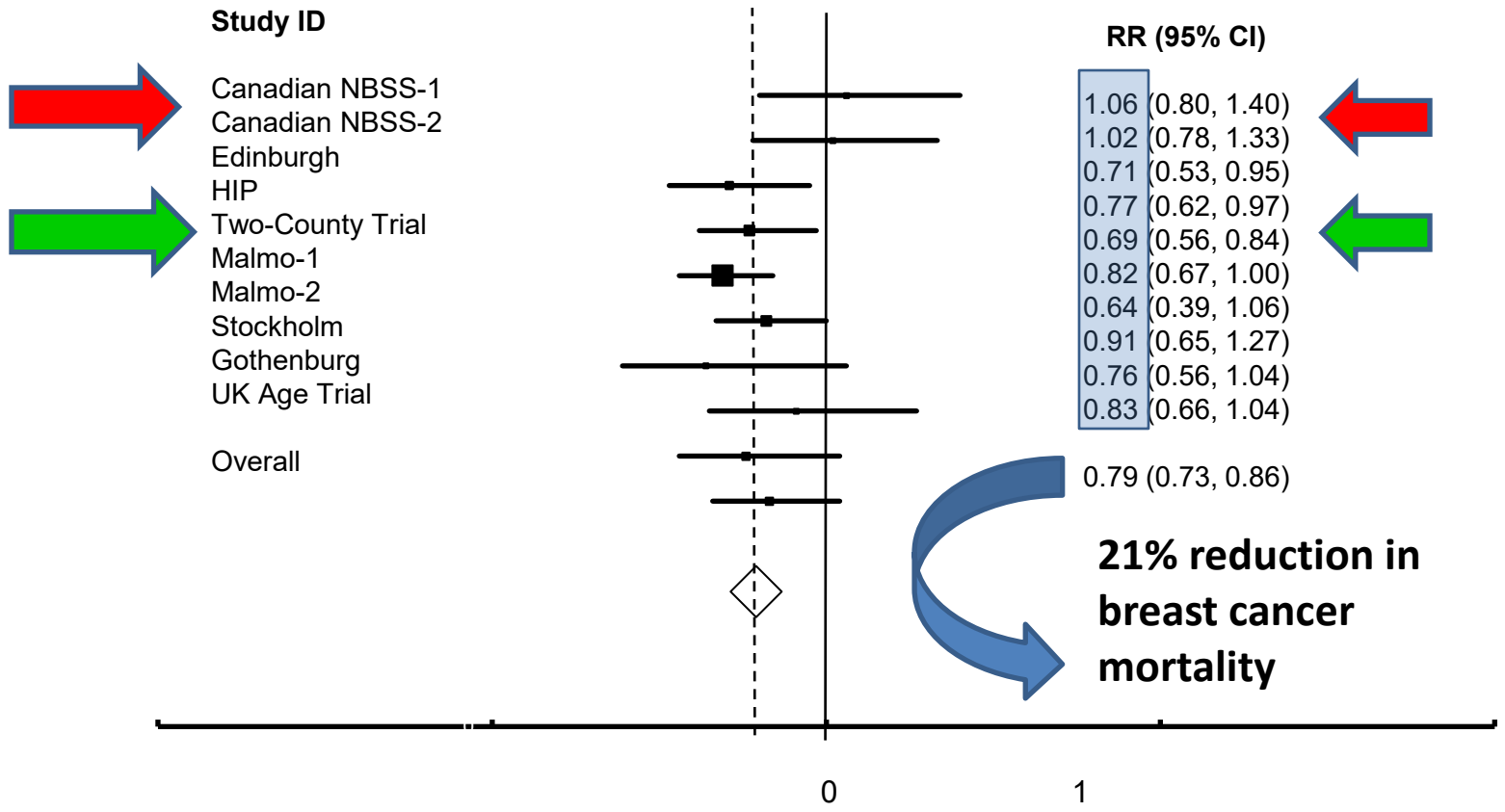
JAMA
THE JOURNAL of the American Medical Association
March 15, 1971 Vol 215, No 11

Sam Shapiro; Philip Strax, MD; and Louis Venet, MD



Intention-to treat-case fatality rates 3.5-years since diagnosis, adjusted for lead time. The rate for the control group is 33.7%; for the study group it is 18.1% ($P < 0.05$ level). Per protocol comparison in the study group also shown.

Nine RCTs of screening mammography: Overall results in terms of breast cancer mortality



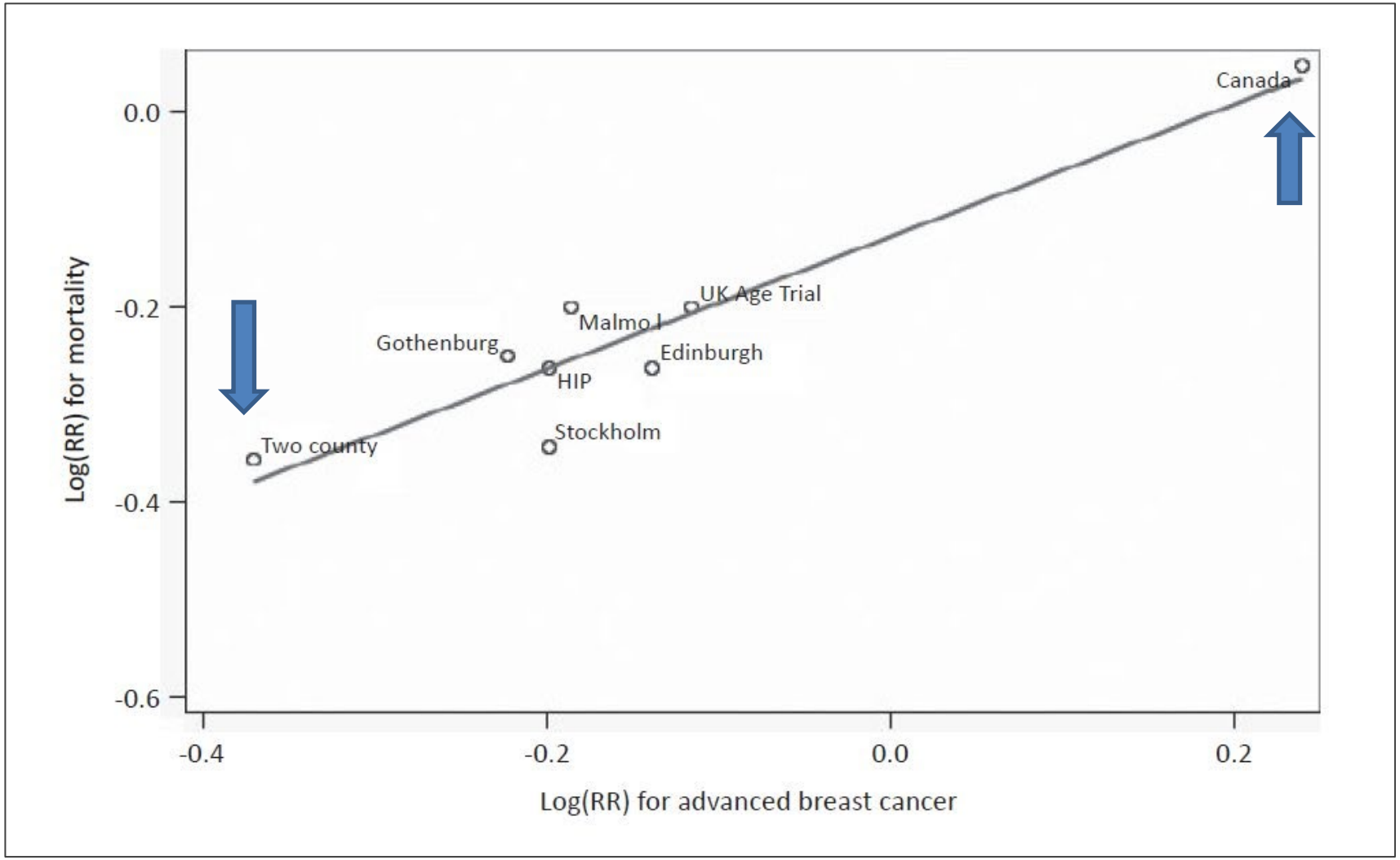
The RCTs varied in terms of:

- Randomization design
- Inclusion of physical exam
- Quality assurance
- X-ray technology
- Number of views
- Starting & stopping age
- Screening interval
- Duration of follow-up
- Generalizability

Overall RR = 0.79 (95% CI: 0.73, 0.86)

Tabar, et al. Breast J, 2014 https://doi.org/10.1111/tbj.12354 Heterogeneity p = 0.3

Plot of log (RR) for breast cancer mortality against log (RR) for diagnosis with advanced disease in the breast cancer RCTs, with meta-regression line



This graph shows that the greater the reduction in the risk of being diagnosed with an advanced breast cancer, the greater the breast cancer mortality reduction

Tabar, et al. Breast J, 2014 https://doi.org/10.1111/tbj.12354

Results from the PLCO and ERSPC Prostate Cancer Screening Trials were Published in the NEJM on March 26, 2009

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mortality Results from a Randomized Prostate-Cancer Screening Trial

Gerald L. Andriole, M.D., E. David Crawford, M.D., Robert L. Grubb III, M.D., Saundra S. Buys, M.D., David Chia, Ph.D., Timothy R. Church, Ph.D., Mona N. Fouad, M.D., Edward P. Gelmann, M.D., Paul A. Kvale, M.D., Douglas J. Reding, M.D., Joel L. Weissfeld, M.D., Lance A. Yokochi, M.D., Barbara O'Brien, M.P.H., Thomas L. Riley, B.S., Grant Izmirlian, Ph.D., Philip C. Prorok, Ph.D.,

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Screening and Prostate-Cancer Mortality in a Randomized European Study

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ABSTRACT

BACKGROUND

The European Randomized Study of Screening for Prostate Cancer was initiated in the early 1990s to evaluate the effect of screening with prostate-specific–antigen (PSA) testing on death rates from prostate cancer.

METHODS

We identified 182,000 men between the ages of 50 and 74 years through registries in seven European countries for inclusion in our study. The men were randomly assigned to a group that was offered PSA screening at an average of once every 4 years or to a control group that did not receive such screening. The predefined core age group for this study included 162,243 men between the ages of 55 and 69 years. The primary outcome was the rate of death from prostate cancer. Mortality follow-up was identical for the two study groups and ended on December 31, 2006.

RESULTS

In the screening group, 82% of men accepted at least one offer of screening. During a median follow-up of 9 years, the cumulative incidence of prostate cancer was 8.2% in the screening group and 4.8% in the control group. The rate ratio for death from prostate cancer in the screening group, as compared with the control group, was 0.80 (95% confidence interval [CI], 0.65 to 0.98; adjusted P= 0.04). The absolute risk difference was 0.71 death per 1000 men. This means that 1410 men would need to be screened and 48 additional cases of prostate cancer would need to be treated to prevent one death from prostate cancer. The analysis of men who were actually screened during the first round (excluding subjects with noncompliance) provided a rate ratio for death from prostate cancer of 0.73 (95% CI, 0.56 to 0.90).

CONCLUSIONS

PSA-based screening reduced the rate of death from prostate cancer by 20% but was associated with a high risk of overdiagnosis. (Current Controlled Trials number, ISRCTN49127736.)

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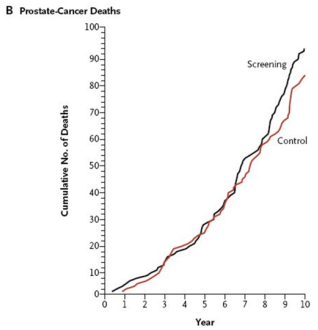
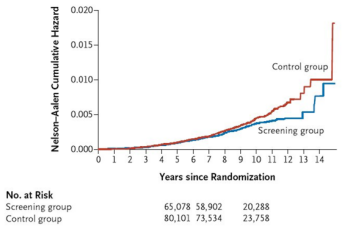
PLCO Trial



- At 7 years of follow-up
  - Screening: 50 deaths
  - Controls: 44 deaths
  - Rate ratio = 1.13
  - 95% CI, 0.75 – 1.70
- At 10 years of follow-up
  - Screening: 92 deaths
  - Controls: 82 deaths
  - Rate ratio = 1.11
  - 95% CI, 0.83 – 1.50

After 7 to 10 years of follow-up, the rate of death from prostate cancer was very low and did not differ significantly between the two study groups

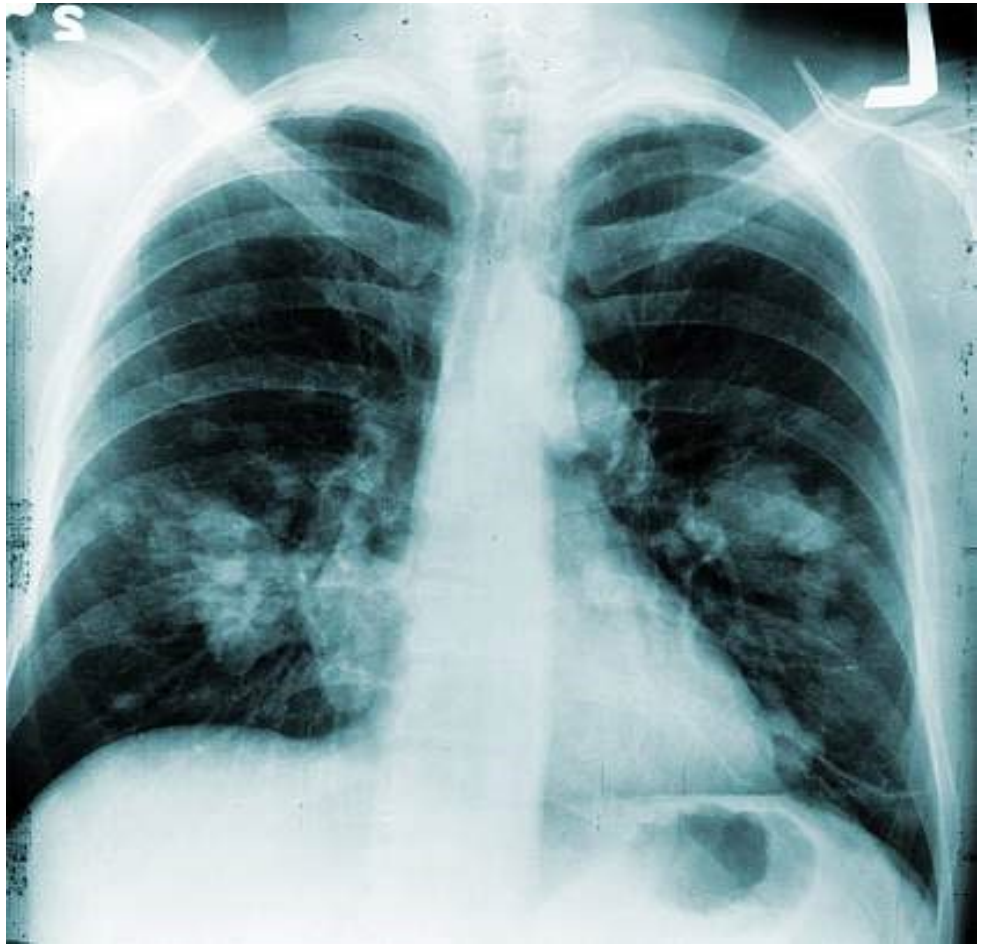
Cumulative risk from prostate cancer in the ERSPCS



- As of 12/2006
  - Average follow-up of 8.8 years
  - 214 deaths in the screening group vs. 326 in the control group
  - The adjusted rate ratio for prostate specific mortality was 0.80, (95% CI, 0.65 – 0.98, P = 0.04)
  - Adjusted for non-compliance, RR = 0.73, (95% CI, 0.56 – 0.90)

PSA-based screening reduced the rate of death from prostate cancer by 20% but was associated with a high risk of overdiagnosis

Until the late 1990s, lung cancer screening was a teaching case for the importance of randomized controlled trials for the evaluation of cancer screening tests.



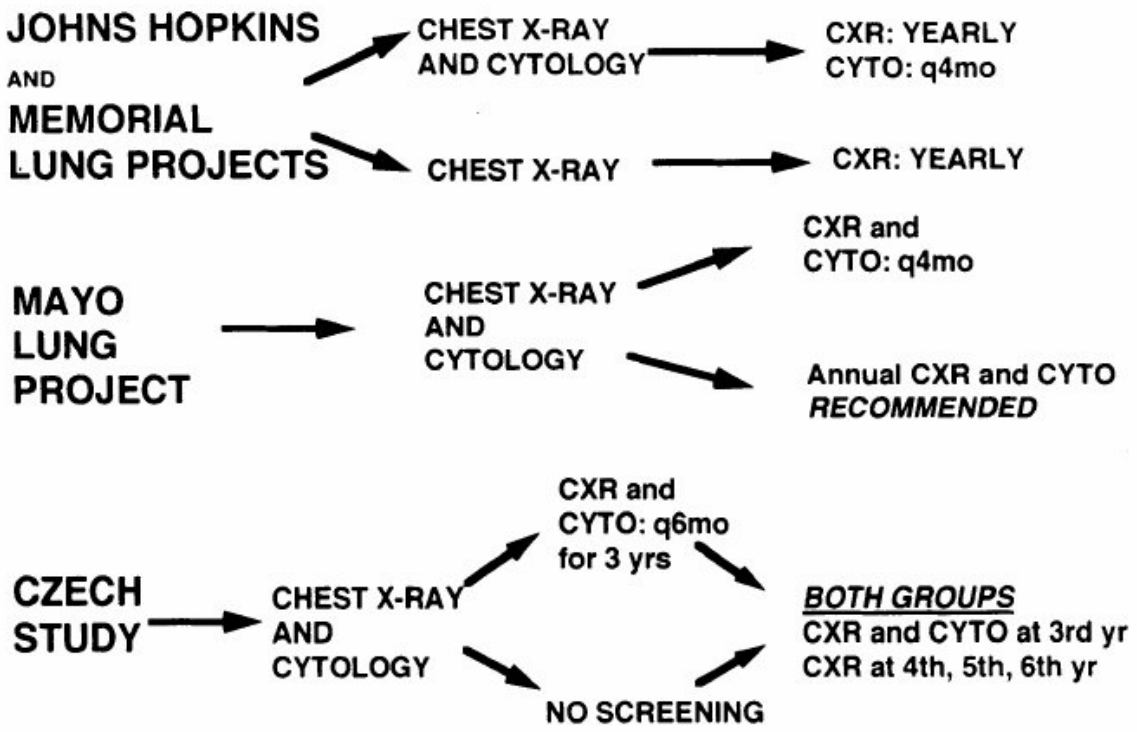
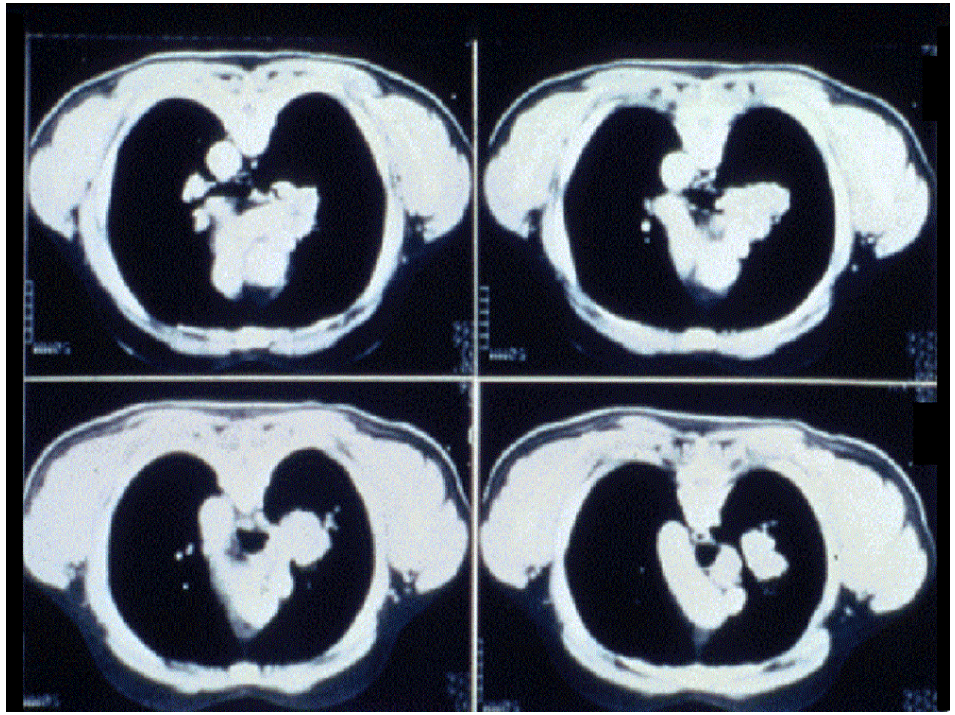


FIGURE 1. Schemata of four randomized studies on lung cancer screening. CXR=chest x-ray. CYTO=cytologic study.

Lung Cancer Screening with Low Dose Spiral CT, *Lancet* 1999

In the New York Early Lung Cancer Action Project, low-dose CT was associated with a **5-fold difference** compared with chest X-ray in the detection of early stage, resectable lung cancers



Henschke CI, McCauley DI, Yankelevitz DF, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening Lancet. 1999;354:99-105.

Results from the LDCT Randomized Trials Demonstrate the Efficacy of Screening

Trial (pub date)	Age Range	Smoking History	Mortality Reduction	Notes
NLST (US) (2011)	55-74	≥ 30 pack years; if Quit, < 15 years	**20% fewer deaths** in the LDCT arm compared with the x-ray arm	Baseline + 2 incidence rounds (12 months) compared with chest x-ray group, also 3 rounds annual screening. The trial was stopped on 10-28-2010
NELSON (NE) (2020)	50-75	≥ 15 pack years	**26% fewer deaths** in males	Baseline + 3 incidence rounds (12, 24, 30 mos.) compared with control group (usual care)
MILD (ITALY) (2019)	> 49	≥ 20 pack years	**39% at 10 years** **58% 5-10 years**	An annual screening and biennial screening arm vs. no intervention for 5+ screening rounds

Alternative/Supplemental Designs to Evaluate Cancer Screening

- Prospective, cross-sectional, multi-center study

The NEW ENGLAND JOURNAL of MEDICINE

Next-Generation Multitarget Stool DNA Test for Colorectal Cancer Screening

Authors: Thomas F. Imperiale, M.D., Kyle Porter, M.A.S., Julia Zella, Ph.D., Zubin D. Gagrat, B.S., Marilyn C. Olson, Ph.D., Sandi Statz, M.S., Jorge Garces, Ph.D., +6, for the BLUE-C Study Investigators* Author Info & Affiliations

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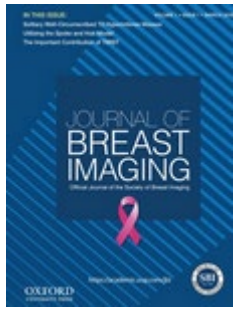
Multi-target stool tests, blood-based tests, etc. for cancer and advanced lesions

- Randomized Controlled Trials with Surrogate Endpoints



Tomosynthesis for Breast Cancer Screening: The Important Contribution the Tomosynthesis Mammographic Imaging Screening Trial Will Make to Our Knowledge of Breast Cancer Screening

Etta D Pisano, MD

Journal of Breast Imaging, Volume 1, Issue 1, March 2019, Pages 23–24, https://doi.org/10.1093/jbi/wby018

Comparisons of two imaging tests for cancer and advanced lesions

- Modeling Studies

Assessing the impact of increasing lung screening eligibility by relaxing the maximum years-since-quit threshold: A simulation modeling study

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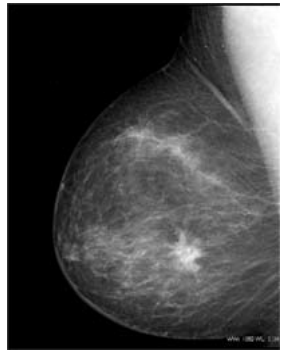
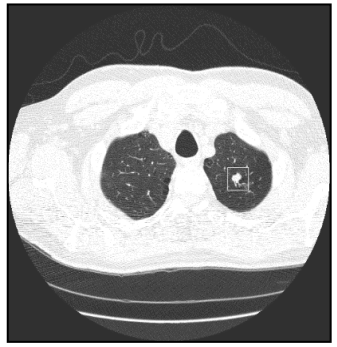
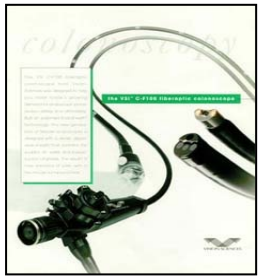
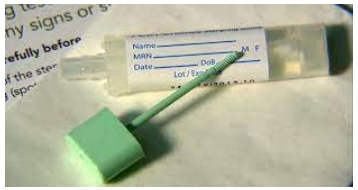
Simulation modeling in the absence of multiple, relevant large prospective studies

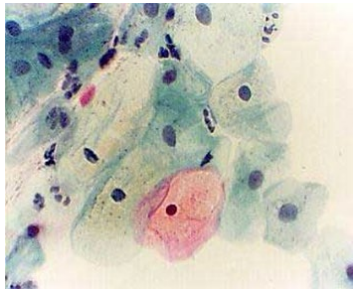
Conclusion

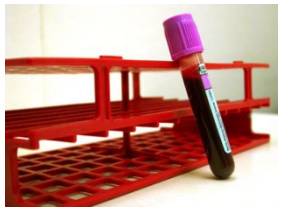
- Over the last 100 years, our understanding of natural history of single organ cancers as localized at inception and systemic following progression led to an emphasis on early detection as a cornerstone of cancer control.
- In the 60s and 70s, the emergence of *evidence-based criteria* (Wilson & Jungner) and *evidence-based medicine* led to an insistence on experimental methodology (randomized trials) as essential for establishing cancer screening policy.
- The history of cancer screening research reveals…
  - Over many years, observational studies commonly provided persuasive evidence supporting the effectiveness of screening.
  - For breast, colorectal, prostate, and lung, prospective randomized trials with mortality endpoints have provided reassuring evidence of the efficacy of screening to the range of groups who shape policy.

Conclusions

- *However,* against the background of promising evidence and the burden of disease, RCTs:
  - Have taken too long to initiate and launch, are too expensive, require long periods of enrollment, screening rounds, and follow-up, and are vulnerable to loss of statistical power, loss of relevance, and disagreement over the interpretation of findings
  - Some of these shortcomings can be remedied.
- The delays in time from confirming the efficacy of a screening test to: publication—guidelines—insurance coverage--and widespread adoption represent a glaring public health failure, one that we repeat over and over
- *We should reflect on the progress over the last 100 yrs, and resolve to (1) shorten the time to initiation of promising research, (2) evolve new experimental methodologies to shorten the duration of research studies, and (3) plan in advance for implementation if findings are favorable.*





Thank you

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Opportunities and Challenges for the Development and Adoption of Multicancer Detection Tests