CancerCare Manitoba
COMMUNITY ONCOLOGY PROGRAM
Community Cancer Programs | Uniting Primary Care and Oncology

PSA

To screen or not to screen?

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Disclosures

- **Faculty / Speaker's name: Darrel Drachenberg**

- **Relationships with commercial interests:**
  - **Grants/Research Support: None**
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  - **Consulting Fees: None**
  - **Other: None**

Mitigating Potential Bias

- Not Applicable

Learning Objectives

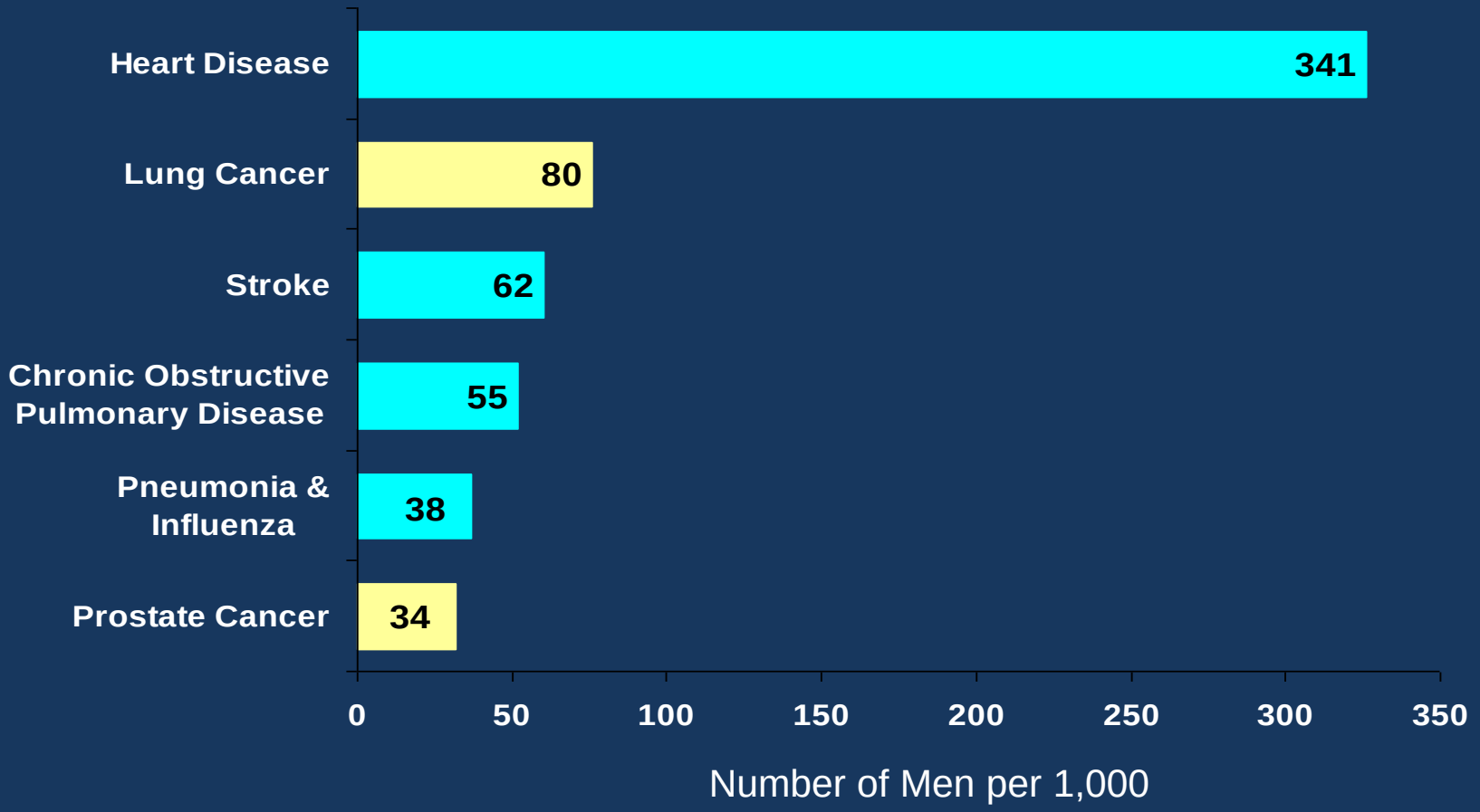
At the end of the presentation the learner will be able to:

1. Discuss what is known about the risk of prostate cancer and its natural history
2. Discuss how to screen for prostate cancer including addressing controversies and review of updated guidelines

Scope of the Problem

- Most common noncutaneous cancer in men
- 2017: estimated 189,000 new cases
  - 30,000 deaths in US
- A man in NA has a 3% chance of dying from CaP
  - (10x greater risk of Dx)

Risk of Death for 40 year old U.S. Men, to End of Life, by Leading Causes



Risk for Prostate Cancer

- Age: 80% of CaP cases are diagnosed in men over 65 years
- Race: Higher incidence and mortality rates for Black males
- Family history of prostate cancer- hereditary BRCA1/2
- Implicated (but not proven) risk factors
  - **Dietary (e.g., high fat diet)**
  - **Exogenous Androgen exposure**
  - **History of STDs?vasectomy?smoking?**

Natural History of Prostate Cancer

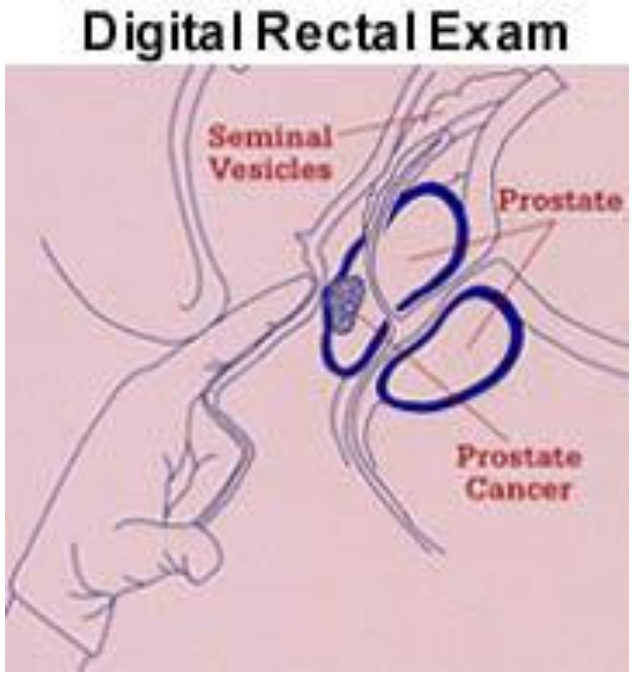
- Prostate cancer is biologically heterogeneous.
- Some prostate cancers grow slowly and never cause symptoms.
- Other prostate cancers are fast growing and metastasize quickly.
- Other types grow at a modest pace.

Screening for Prostate Cancer

- Screening methods
  - Digital rectal exam (DRE)
  - Prostate specific antigen (PSA) test

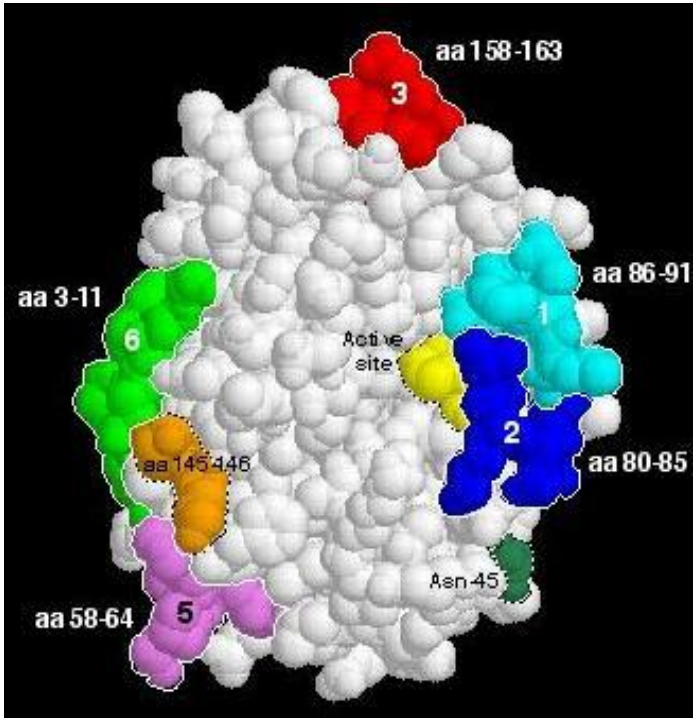
The Digital Rectal Exam (DRE)

- Only 1/3 of gland is examined
- nodularity/induration/ asymmetry suspect
- 60% of cancers detected by DRE have spread outside the prostate gland
- Useful for detecting 20%-35% of tumors with N PSA
- Should be continued in men >70

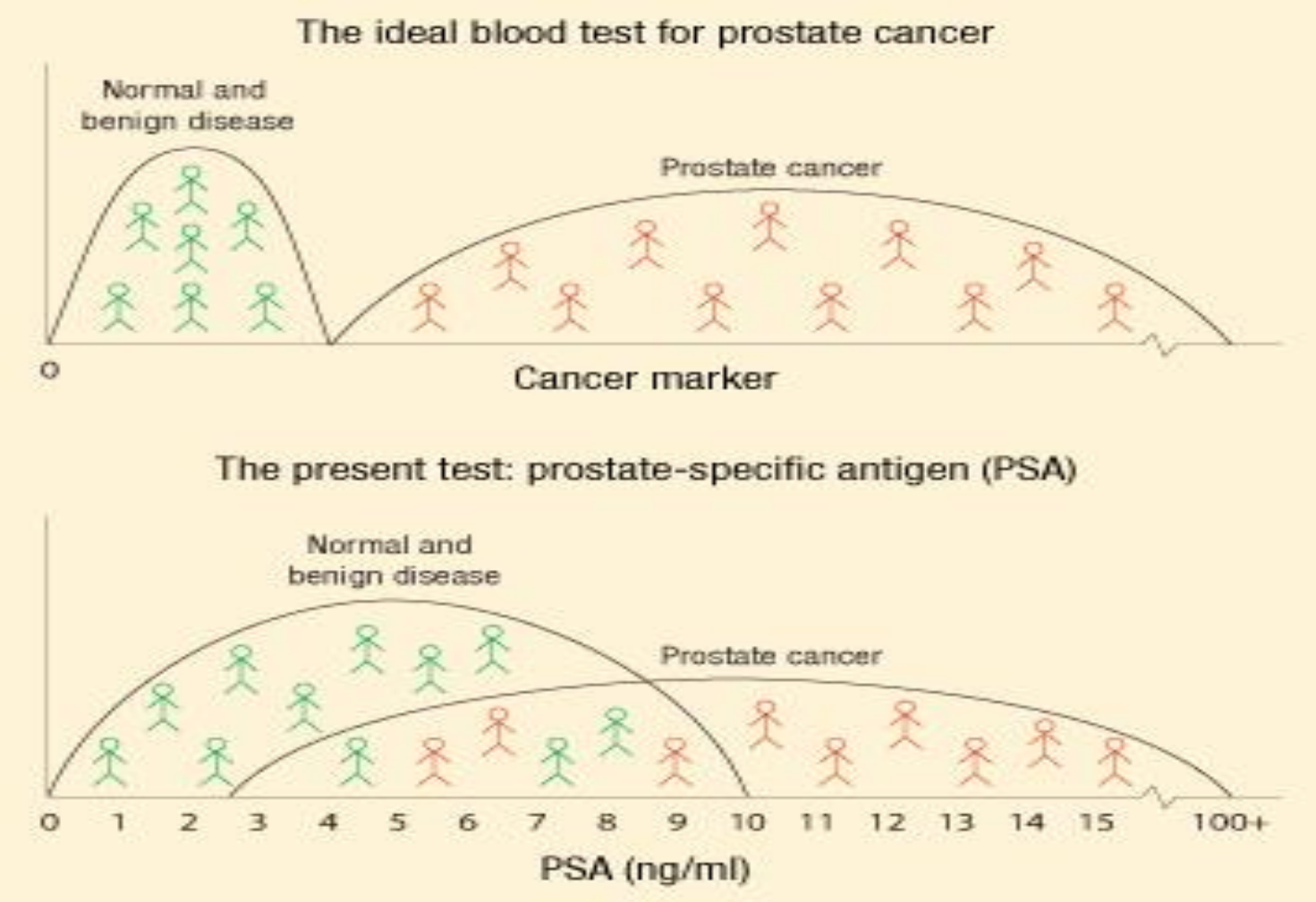


Prostate Specific Antigen (PSA)

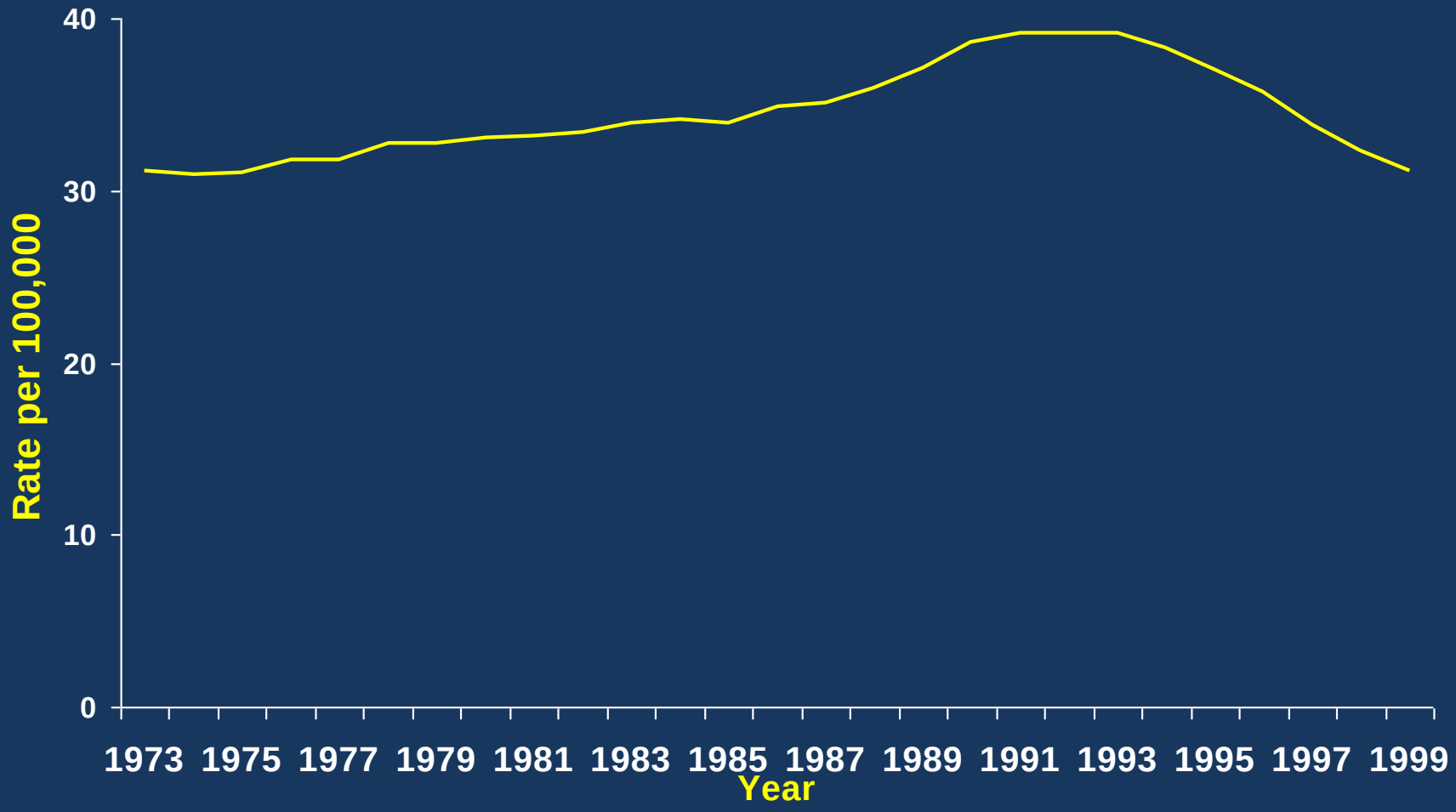
- PSA- serine protease glycoprotein
- Free and complexed species
- Malignant and benign tissue
  - PSA levels increase with age, BPH, Prostatitis, UTI, indwelling foley



PSA Test Efficacy



What Happened to Canadian Prostate Cancer Mortality Rates as Screening Rates Increased?

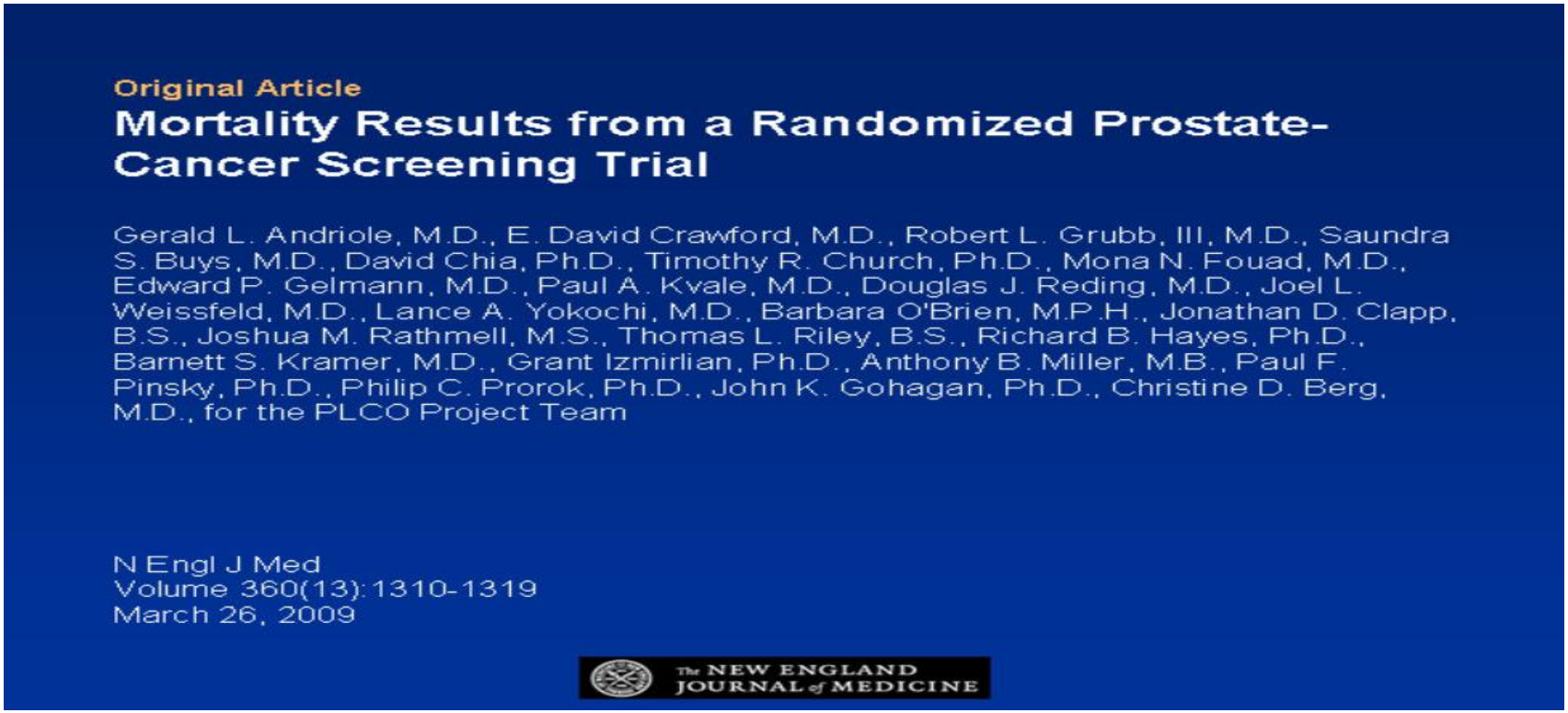


Recommendations

- ACS: physicians should *offer* annual DRE and PSA to men 50-70 yo, who have life expectancy at least 10 years. African-American, men with FHx of prostate ca should start screening at age 40
- AUA/CUA: recommends screening in men >50 or >40 if positive FHx or African-Am.
- Referral to Urology if PSA elevated over "normal" range or DRE abnormality for TRUS-guided Bx
- →BUT "THE TIMES THEY ARE A CHANGIN'"

Recent RCT Screening Studies

- PLCO- prostate, lung, colorectal, ovarian screening study



PLCO

- 1993-2001
- 76693 men at 10 US centers randomized to screening (38343 subjects) or usual care as control (38350 subjects) ages 55-74
- Screening with annual PSA and DRE
- After 10 yrs follow-up death rate from CAP very low (92 screening and 82 control grp)
- Conclusion: no difference in mortality at 10 yrs
- balance of benefits and harms unfavorable and does not support routine screening
- Screening may cause significant harm to many men

US PLCO Trial – update 2012

- 76693 men
- After 13 years of follow-up, the rate of death from prostate cancer was very low and did not differ significantly between the two study groups.
- 3.7 and 3.4 deaths per 10 000 person-years

European RCT- ERSPC

- Early 90's initiated f/u to Dec 31/07
- 182000 men ages 50-74
- Randomized to PSA screening once every 4 years vs control grp without screening PSA
- 8.2% incidence CAP in screening vs 4.8% in control arm
- 20% reduced rate of death from CAP (if adjust for non compliance 27% fewer deaths in men screened)
- absolute risk difference 7 death/10000men
- NNS 1410 men NNT 48 CAP to prevent one CAP death

European Screening Trial - 2012 update

- 182000 men, 11 year follow up
- 1055 men would need to be screened and 37 cases of prostate cancer would need to be treated to prevent one death from prostate cancer
- Overall survival the same in both groups

European Trial Criticisms

- Men screened every 4 years (2 in Sweden)
- PSA of 3
- Treatment at academic centres for screen detected patients
- Swedish site biasing whole trial

Mortality Results from the Goteburg Randomized Population Based Prostate Cancer Screening Trial. Hugosson J et al. Lancet Oncol 2010

- 20000 men, 14 years follow up
- 44% reduction in prostate cancer deaths in screened arm
- 293 men would have to be screened and 12 treated to prevent one prostate cancer death
- 3% contamination
- Younger men (50 to 64 years)

PLCO results differ from ERSPC –Why?

- Shorter average f/up
- Low rates of compliance with randomization
- PSA Testing in 44% of men prior to randomization decreased numbers of events
- Low rates of PC deaths in both arms (2.0 and 1.7 in S vs C, 3.3 vs 4.3 in ERSPC
- The window for effective screening is only 33% (85% screened in S arm vs 52% in C arm had PSA screening)

AUA response to screening studies

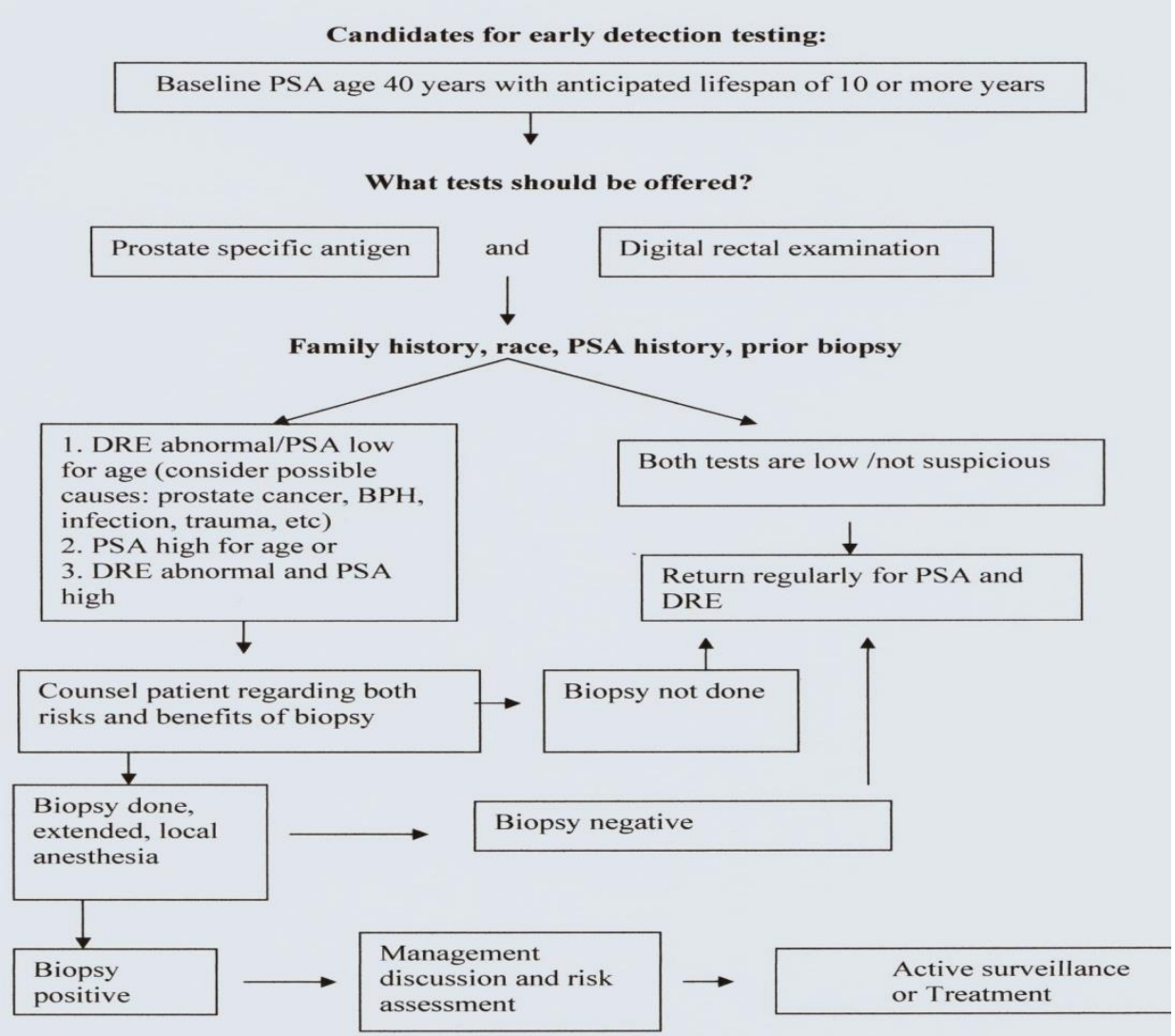


Figure 1: Early Detection

From AUA 2009 best practice statement*

Annals of Internal Medicine

U.S. Preventive Services
TASK FORCE
www.USPreventiveServicesTaskForce.org

SCREENING FOR PROSTATE CANCER

CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

Population	Adult Males
Recommendation	Do not use prostate-specific antigen (PSA)–based screening for prostate cancer.
	Grade: D

Do not use prostate-specific antigen (PSA)–based screening for prostate cancer.

Moyer et al. Ann Intern Med 157:120, 2012.

USPTF opposition to screening

- US Preventative Services Task Force 2009
  - Insufficient evidence to assess risks and benefits in men < 75 years
  - Felt that harms outweighed benefit in men > 75 years
- In 2012
  - Recommend against PSA screening

Canadian Task Force

Box 2: Summary of recommendations for clinicians and policy-makers

The recommendations apply to all men without a previous diagnosis of prostate cancer.

- For men aged less than 55 years, we recommend not screening for prostate cancer with the prostate-specific antigen (PSA) test. (*Strong recommendation; low-quality evidence.*)
- For men aged 55–69 years, we recommend not screening for prostate cancer with the PSA test. (*Weak recommendation; moderate-quality evidence.*)
- For men 70 years of age and older, we recommend not screening for prostate cancer with the PSA test. (*Strong recommendation; low-quality evidence.*)

CTFPHC. CMAJ 2014; 186:1225

CUA criticisms to Canadian Task Force 2014

Lack of Canadian perspective!!

- Level 1 evidence of a reduction in prostate cancer deaths seen in randomized Phase III trials,
- 45% reduction in deaths due to prostate cancer in Canada since 1995
- the widespread adoption of active surveillance for low risk disease (a Canadian invention)

AUA guidelines update 2013

- Recent release May 2013
- Rapid response to criticisms of past recommendations that were based on “expert opinion”
- Appearance of conflict of interest?
- Trying to repair image?
- Utilization of evidence-based medicine

AUA guidelines for PCa detection 2013

- Differs from Best Practice Statement 2009
  - Expert opinion and clinical experience
  - No systematic review of literature
- Current guideline is:
  - Evidence based evaluation of PC detection to reduce PC mortality
- based on evidence rather than values, opinions, or clinical experience
  - Intended to assist physicians in advising an “average” risk man without Sx’s
  - Multidisciplinary panel NOT just urology!!

Guidelines 2013-methodology

- Systematic review of literature 1995-Feb 2013
- 324 eligible studies reviewed
- RCT's
- Modeled data
- Population data

Rating of evidence strength and quality

- A- well conducted RCT's or exceptional observational studies
- B- RCT's and/or observational studies with some weaknesses
- C- observational studies inconsistent and/or difficult to interpret

Linking evidence to statement type

- Standard (evidence level A/B)
  - Benefits are > or < than the harms
- Recommendation (evidence level C)
  - Benefits are > or< than the harms
- Option (evidence level A-C)
  - Benefits = harms or balance is unclear

Interpretation of evidence

- Panel did not go beyond the evidence in formulating STATEMENTS (ie assumption of benefits in absence of evidence)
- Quality of evidence
  - Benefits of screening – moderate (B)
  - Harms of screening- high (A)

Guideline statement organization

- Panel evaluated early detection of PCa in average risk men by age, recognizing that the harm-benefit ratio is highly age dependent
- Index pt groups
  - <40 yrs
  - 40-54 yrs
  - 55-69 yrs
  - 70+ yrs

Guideline statement 1: age < 40yrs

- Recommend against PSA-based screening of men under 40 yrs (Recommendation; evidence strength: Grade C)
- In this age grp there is a low prevalence of clinically detectable PCa, no evidence of benefit of screening and considerable harms of screening (over-diagnosis and over-treatment)

Guideline Statement 2: Age 40-54yrs

- Screening not recommended in men at avereage risk (Recommendation; Evidence strength: Grade C)
- Evidence is marginal when compared to screening beginning at age 55 yrs, and quality of evidence for harm is high
- These men are often screened presuming they have the most to gain from early Dx and Rx
- Low prevalence of fatal PCa, long lead times, and extended time at risk for harm from Rx all may lead to greater harm than benefit

Guideline Statement 2: age 40-54yrs

- For certain men younger than 55yrs at higher than average risk
  - Decision individualized based on shared decision making and informed discussion about uncertainty of benefits vs harms

Guideline Statement 3: age 55-69 yrs

- Panel recommends *shared decision making* when considering PSA testing, proceeding based on pts values and preferences (Standard; Evidence Grade: B)
- Decision to undergo screening must weigh benefit of preventing 1 PCa death per 1000 screened over a decade vs the harms of screening and treatment

Guideline Statement 3: age 55-69 yrs

- Shared decision making should consider:
  - Life expectancy
  - Prostate cancer risk (race, Fam Hx)
- PSA-based screening should not be performed in the absence of shared-decision making (health fairs, health system promotions, community organizations)

Guideline Statement 4: Reducing Harms of Screening

- Increase screening interval to 2 or more yrs preferred over annual screening in men who have participated in shared-decision making and chosen screening
- Intervals >2 yrs preserves the majority of the benefits and reduces over-diagnosis and false positives (Option; Evidence Grade: C)
- Intervals for rescreening can be individualized by baseline PSA and/or prior PSA history
- Based on modeling studies

Guideline Statement 5: age 70yrs and above

- Recommend against *routine* PSA screening in men age 70+ or in any patient with < 10-15 yrs life expectancy (Recommendation; Evidence Grade C)
- some men in excellent health may benefit
- An absolute reduction in mortality while possible is likely small with a potential for harm high

Guideline statement: Age 70+

- If men 70+ have chosen screening panel suggests ways to reduce harm
  - Use higher PSA threshold for investigation and biopsy (>10 ng/ml)
  - Discontinue screening if PSA low (<3 ng/ml)

Guidelines require periodic review and updating

- Benefits beyond 15 yrs have yet to be assessed in large RCT's
- Absence of direct evidence for benefit outside of age range 55-69 yrs, non- Caucasians, positive Fam Hx
- Absence of direct evidence for benefit of tests other than PSA for primary screening

USPSTF April 2017

- Revision to original recommendations
- Based on further evidence that came to light with ERSPC study longer follow up (decrease CaP death and mets in screened pop) and other data like increasing adoption of active surveillance in US to prevent harms of overdiagnosis and treatment
- individualized approach to screening for age 55-69, based on clinician-patient discussions about the potential harms and benefits of screening (grade C recommendation).
- USPSTF submitted the recommendation for public comment, which ends May 8, 2017

A PIECE OF MY MIND

Underestimating the Value of Reassurance

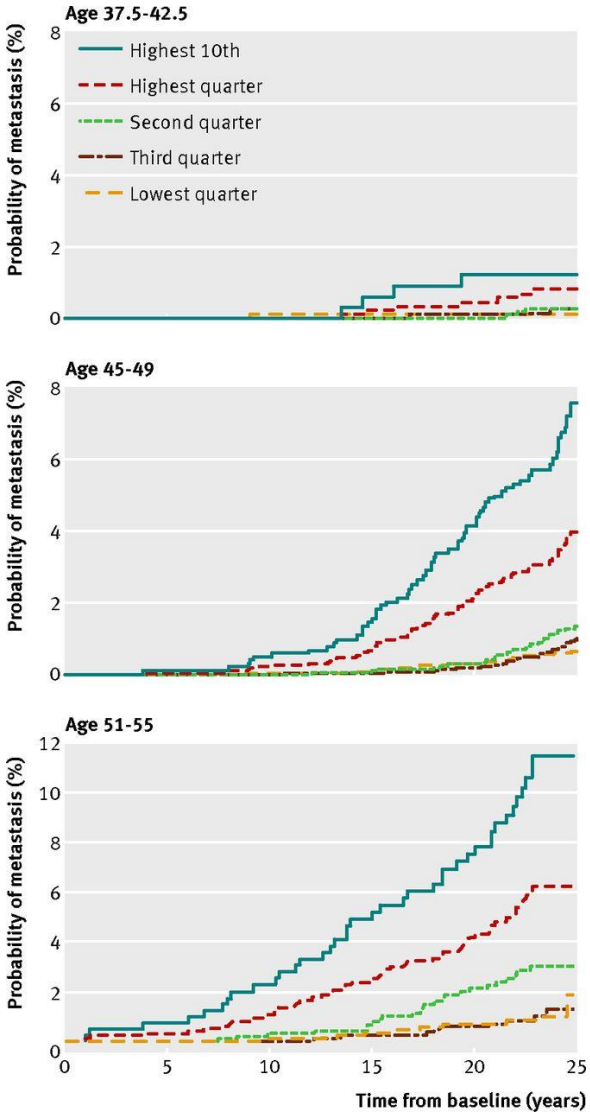
BIRTHDAYS THAT END IN ZERO PROVOKE REFLECTION ON past achievements and future plans. And as the decades advance, one's health and mortality come into focus. When I turned 50, I wrote about my personal experience with screening colonoscopy.[1] This year, as I turned 60, the Canadian news was dominated by the death of a high-

overall survival.[12] An accompanying editorial pointed out that this result maybe generalizable to low-risk early-stage prostate cancers identified by physical examination but not through routine PSA screening.[13] Of the prostate cancers, 88% were palpable tumors, and only 5.2% had been diagnosed by PSA screening tests.[13]

"What seems to be missing from most of the PSA discussion is that the majority of men will have a normal PSA value and they will be reassured… A normal PSA level offers peace of mind, a valued commodity in a world that is frequently full of troubling news."

Detsky et al. JAMA 307:1035, 2012

Value of establishing an early baseline



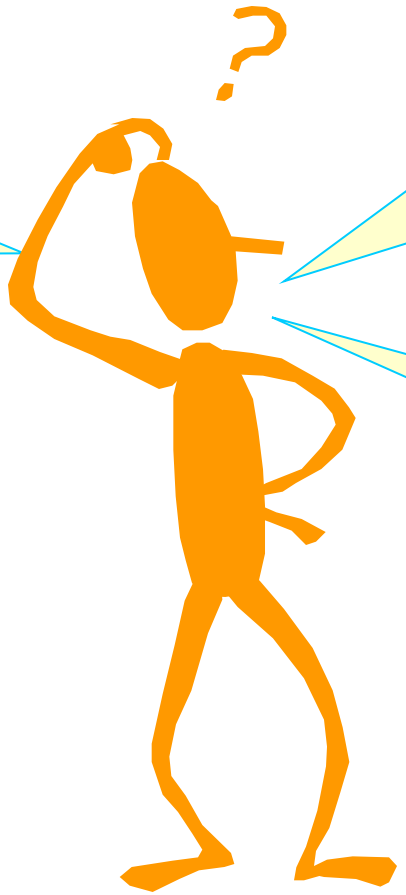
- If PSA <1.0 at 60 likelihood of prostate cancer death <0.3%
- 90% of all prostate cancer deaths occurred in men with psa > 2.0 (top quartile)

Vickers et al., *BMJ 2013; 346*

What advice can be given to men who wish to be screened?

- The message has changed dramatically
- Yes if you develop CAP early detection decreases the chance of dying from it by at least 27%
- Negatives
  - Overdiagnosis and overtreatment of indolent cancer
- One must “de-link” paradigm of diagnosis and treatment and offer active surveillance for those who do not need treatment (low risk, low volume, low grade CAP)
- Need new marker of disease and progression
- Shared decision making

Informing Patients



Do I know the potential benefits?

Do I know the likelihood of various outcomes?

Do I know the potential harms?

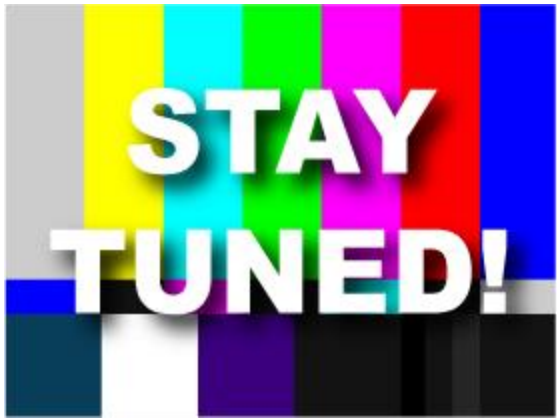
Do I know the potential consequences of my decisions?

Benefits of Shared Decision Making

- How the patient benefits:
  - Takes an active role in his health care.
  - Becomes better informed.
  - Chooses the option most consistent with his personal preferences.
- How the clinician benefits:
  - Solves a clinical dilemma.
  - Informs and involves a patient in his care.

Future of prostate cancer screening

- Assess for High Risk population through mutation analysis
    - BRCA1, BRCA2, HOXB13, etc
- Assess for High Risk Disease via T3 Diffusion weighted MRI to determine need for biopsy
- Liquid biopsy- CTC's, cell free DNA



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QUESTIONS?