AACC

Better health through laboratory medicine.

PEARLS OF LABORATORY MEDICINE

SCREENING FOR EARLY DISEASE DETECTION: Not as Simple as it Seems

Julie E. Buring, ScD

CCTC Clinical Chemistry Trainee Council

PSA Screening for Prostate Cancer

- US Preventive Services Task Force final report (5/22/12) said most men of any age should not routinely get PSA (prostate-specific antigen) testing for early detection of prostate cancer.
- Based on review of 30 studies, does not save lives, leads to unnecessary anxiety, surgery and complications from overtreatment of slow-growing cancers that never would have become life threatening.
- Lifesaving benefit was "at best very small"…. and offset by overdiagnosis and overtreatment of nonlethal cancers.

Prostate Cancer Screening in the News

May 22, 2012 - after final recommendations:

- "Panel rejects PSA prostate screening: Report sparks controversy"
- "Men left to wonder as PSA test disputed"

PSA Screening for Prostate Cancer

- Would seem straightforward:
- PSA simple blood test; mechanism of measuring protein in blood produced by prostate tissue.
- Widely accepted and used: routinely given to 75+% men over 50.
- PSA testing is most common way diagnosis of prostate cancer triggered.
- Picks up prostate cancer long before symptoms. Significantly increases number of prostate cancers diagnosed at very early stages.
- Would think that treating prostate cancer earlier would lead to better prognosis – but does it? Can it hurt - risks?

The Conundrum

- **Conflicting emotions regarding screening for early disease detection (public, clinicians, insurers).**
- **Positive side: Intuitively holds such promise**
  - **How could early detection not be beneficial?**
  - **How could we not offer – and want to receive – screening tests?**
- **Negative side: Population data not clear screening itself has actually worked:**
  - **For some cancers, led to increase in diagnosis, but hasn't always led to decrease in mortality. Seen decreases in stomach and cervical cancer mortality which were definitely not due to screening.**

The Conundrum, con't

- **Why is effect of screening so difficult to evaluate….**
- **To understand, have to go back and understand the first principles of screening.**

Screening for Early Disease Detection

Application of a simple test to asymptomatic persons in order to classify them as likely or unlikely to have a disease.

Screening

- Not screening for safety of others; personal benefit on prognosis.
- Search for early asymptomatic disease.
- Assumption and purpose: early detection will lead to more favorable prognosis (e.g., treatment given before symptoms develop will be more beneficial).
- Not diagnostic test: screening classifies person as likely or unlikely to have a certain disease; then apply diagnostic test.

Screening

- For screening to be successful we need a:
  - Suitable disease
  - Suitable test
  - Suitable screening program

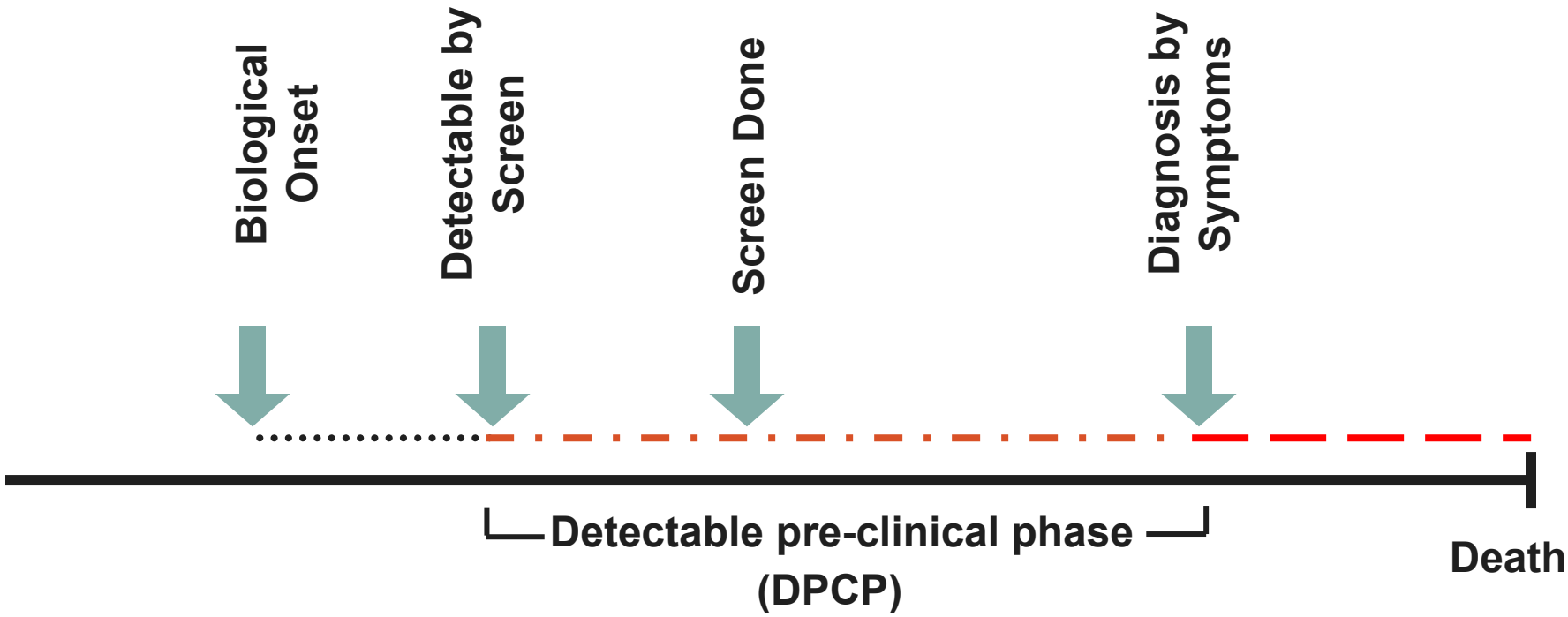
What are Appropriate Diseases for Screening?

- Diseases with serious outcomes – in actuality, or as perceived by community.
- Treatment given before symptoms develop is more beneficial than treatment given after symptoms develop (in terms of mortality, morbidity). So if disease treated asymptomatically, it is as highly fatal – or highly curable – as if diagnosed symptomatically, not good candidate for screening.

What are Appropriate Diseases for Screening?

- **Prevalence** of detectable preclinical disease (DPCP) is **high** in screened population.
- Don't need all three. Example: phenylketonuria (PKU) – not common, but very serious consequences that can be avoided if dietary modifications begun at birth.

Natural History of Disease



Screening

- For screening to be successful we need a:
  - Suitable disease
  - Suitable test
  - Suitable screening program

What is an Appropriate Screening Test?

- Simple, inexpensive, easy to administer, acceptable to large numbers of potential screenees.
- Valid – test does what supposed to do. If have the disease, want screen to test positive (high sensitivity); if you don't have the disease, want screen test negative (high specificity).

Validity of Screening Test

		Diagnostic Test: Yes	Diagnostic Test: No	
Screening Test	+	a	b	a+b
	-	c	d	c+d
		a+c	b+d	N

a = "true positives" b = "false positives"

c = "false negatives" d = "true negatives"

- Sensitivity = P (test + | disease +) = a / (a+c)
- Specificity = P (test - | disease -) = d / (b+d)

Validity of Screening Test: Health Insurance Plan of NY

		Breast Cancer: Yes	Breast Cancer: No	
Mammography + PE	+	132	983	1115
	-	45	63650	63695
		177	64633	64810

- Sensitivity = P (test + | disease +) = 132 / 177 = 0.75
- Specificity = P (test - | disease -) = 63650 / 64633 = 0.985
- Screening good at identifying women who did not have cancer (specificity), but missed 25% of women who did have cancer (sensitivity).

Suitable Test

- Can sensitivity and specificity be modified?
- Criterion of Positivity - test value at which the screening test outcome is considered positive

Test Result

Clearly Negative Grey Zone Clearly Positive

----------??????????????????----------

A B C

"Criterion of positivity" influences both sensitivity and specificity of the screening test:

↑ Criterion of positivity → ↑ sensitivity
↓ specificity

↓ Criterion of positivity → ↓ sensitivity
↑ specificity

Sensitivity and specificity are characteristics of the screening test, but can be modified and traded off against each other. Have to weigh cost of false positives (e.g., flooding health care system) against cost of false negatives (e.g., false sense of security).

Screening

- For screening to be successful we need a:
  - Suitable disease
  - Suitable test
  - Suitable screening program

Evaluation of Screening Program

- **Feasibility (can you do it?)**

- **Effectiveness (does it make a difference if you do it?)**

Evaluation of Screening Program: Feasibility

- Acceptability of screening test to potential screenees: proportion of target population who are screened.
- Proportion of those who test + who received diagnostic test and treatment as indicated (ie., success of follow-up).
- Cost and cost-effectiveness
  - total cost
  - cost per case detected
- Yield of screening program
  - assessment of how many who test positive actually have the disease (predictive value of a positive test); predictive value of a negative test.

Predictive Value of Screening Test

- Predictive value positive (PV+)
  - P (disease + | test +)
- Predictive value negative (PV-)
  - P (disease - | test -)
- PV+ and PV- do depend on sensitivity and specificity of the screening test, but more importantly on the prevalence of the detectable preclinical disease in the screened population.

Predictive Value of Screening Test

		Breast Cancer: Yes	Breast Cancer: No	
Mammography	+	132	983	1115
	-	45	63650	63695
		177	64633	64810

- PV + = P (disease + | test +) = 132 / 1115 = 0.12 or 12%
- PV - = P (disease - | test -) = 63650 / 63695 = 0.999 or 99.9%

- How change PV+? Hard to change sensitivity, specificity of test. But can change prevalence of DPCP: screen higher risk group; second screening test.

Evaluation of Screening Program: Effectiveness

- Early outcome measures
  - Pick up early disease: shift stage distribution of disease to the left (early stages, less severe).
  - Good, but relation with prognosis?
- Most definitive measure: mortality
  - Cause-specific mortality rates for screened and unscreened individuals.

Evaluation of Screening Program: Effectiveness

- Can evaluate through any epidemiologic design strategy (RCTs, observational studies).
- Special issues in evaluation of screening program
  - Volunteer bias in observational studies
  - Lead-time bias
  - Length bias

Sources of Bias in Evaluation of Screening Program

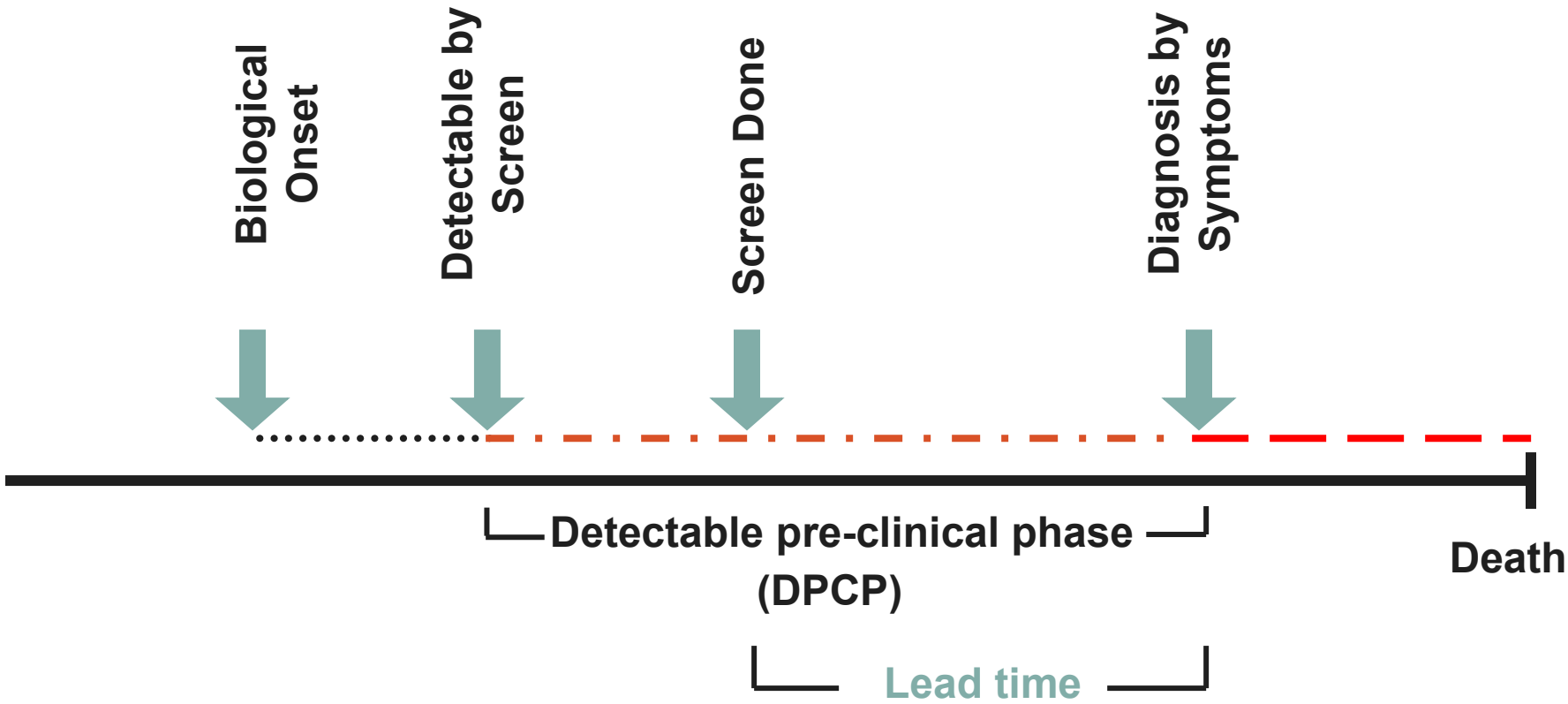
- **Volunteer Bias**

  In observational study, volunteers for screening (those who self-select to be screened) may be systematically different than non-volunteers, in ways related to outcome (confounding). Could be healthier, could be at higher risk than those who don't participate.

Sources of Bias in Evaluation of Screening Program

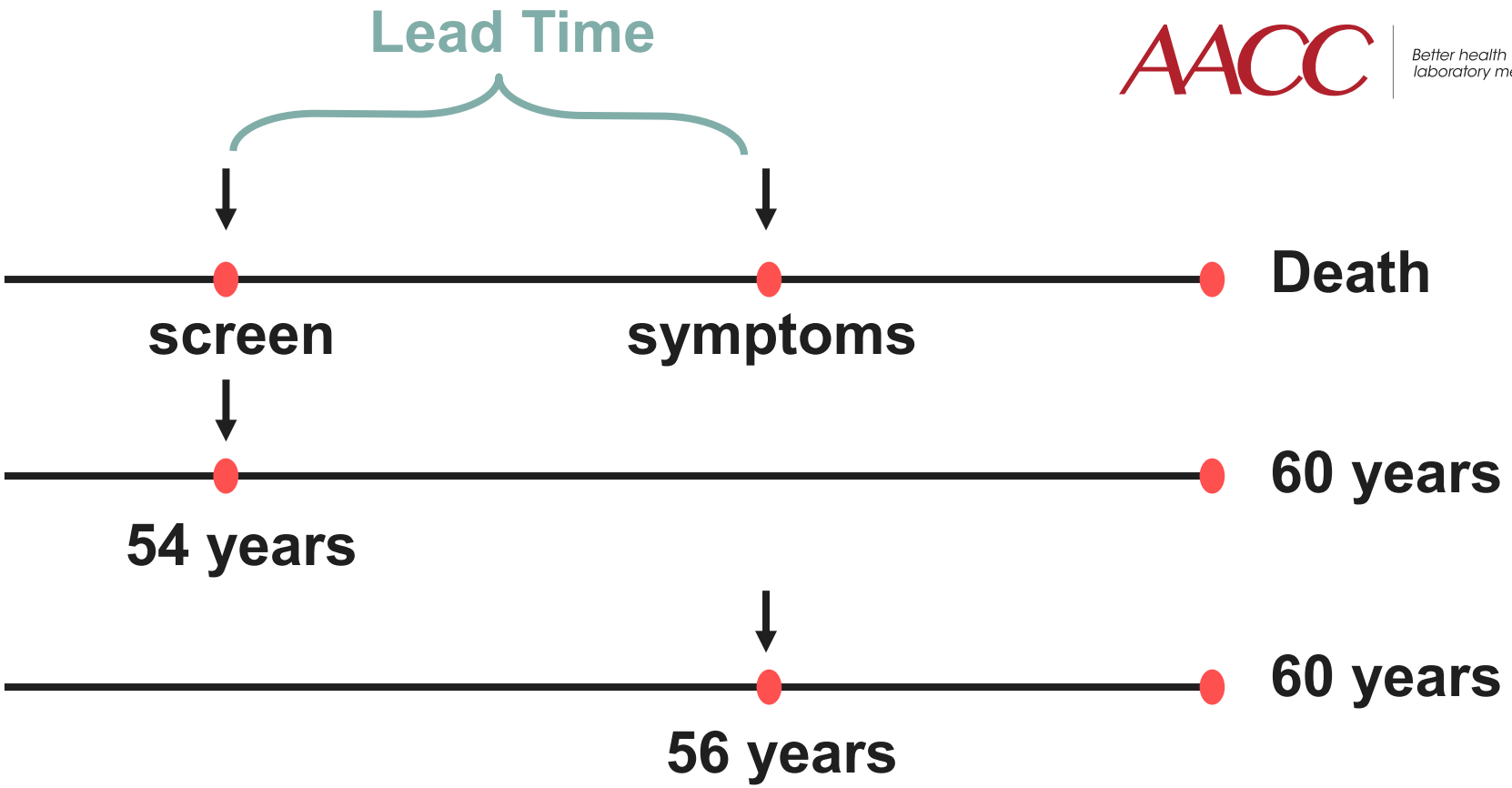
- Lead-Time Bias
  - **Lead time represents the time between when the disease was diagnosed because of the screening test and when diagnosis would have occurred by clinical symptoms (ie., time by which diagnosis was advanced by the screening test).**
  - **With lead-time bias, cases detected by screening may incorrectly appear to survive longer, only due to their earlier diagnosis.**

Natural History of Disease



Example

- A randomized trial was conducted to evaluate the effectiveness of a new screening program for colon cancer.
- Among those whose cancers were detected by the screening program, average age at diagnosis was 54 years and average age at death was 60 years: thus, average survival from diagnosis to death was 6 years.
- For those detected by clinical symptoms, average age at diagnosis was 56 years and average age at death was 60 years: thus, average survival from diagnosis to death was 4 years.
- The investigators reported a statistically significant 2 year increase in survival from colon cancer associated with screening. What is wrong with this picture?



Incorrect Conclusion: Two year increase in survival associated with screening

Problem: Lead time bias

Solution: Compare age-specific mortality rates

Sources of Bias in Evaluation of Screening Program

- Length Bias
  - **The initial screen will be over-represented by disease with longer duration in DPCP (prevalent cases), which are usually less aggressive and have a better prognosis compared to incident cases.**
  - **Less of a problem when comparing survival with groups on subsequent screens.**

Summary

- Appropriateness of screening for disease control is not always clear
- Need appropriate disease
- Need appropriate screening test
  - validity (sensitivity, specificity)
- Need to evaluate screening program
  - feasibility (predictive value)
  - effectiveness
    - controlling for special types of confounding, bias

Summary

Why diseases considered to be good or not good candidates for screening?

- **Breast cancer, colon cancer, hypertension, glaucoma – excellent candidates for screening program: serious disease, valid screening test, early treatment makes a difference.**
- **Ovarian, pancreatic cancers - not adequate screening test currently available to advance treatment enough to make difference in prognosis if picked up asymptomatically.**
- **Prostate?**

PSA (prostate-specific antigen) Screening

- Would seem straightforward:
- Major cancer in men.
- Simple blood test.
- Widely accepted and used.
- Picks up prostate cancer long before symptoms. Significantly increased number cancers diagnosed at very early stages.
- Better prognosis? Does this translate into reduction in death rates? Are there risks of the screening?

PSA Screening and Prostate Cancer

- Bottom line: RCTs have not found life-saving benefit of PSA 10 years after diagnosis. Postulated reason: many prostate cancers detected by screen slow-growing, might never have caused problems if not diagnosed because of screening (length bias)
- Diagnostic biopsy plus treatment (surgery, radiation) said by patients to be worse than disease.
- Since not sure what PSA level signals cancer, many have "false alarms.
- 13% of men who have regular PSA screening have at least one false PSA finding for every 4 screenings, and 6% have a biopsy for this false reading.

PSA Screening and Prostate Cancer

- Biopsies: painful and can cause serious complications (infections, bleeding, urinary).
- If diagnosed – what do you do?
- Option 1: Immediate surgery (radiation, hormones).
- Option 2: Active surveillance ("watchful waiting") with periodic biopsies.
- 20-30% of surgery/radiation have adverse effects (including urinary incontinence, erectile dysfunction, impotence, stroke, death).
- Watchful waiting: QOL issue -"get it out" – can't deal living with cancer that is not removed.

PSA Screening and Prostate Cancer

- Unfortunately don't have prostate screening test that distinguishes relatively harmless from bad cancer.
- How beneficial is it to treat prostate cancer early when majority not going to die of this disease, and we can't predict who will, and the diagnosis and treatment cause morbidity?

PSA Screening and Prostate Cancer

- Emotional reactions from individuals in terms of "denying" them potentially life-saving test.
- Some clinicians say whether saves lives or not irrelevant – it is picking up early disease – and bringing people into the health care system routinely for exams.
- All agree will have implications for what Medicare and private insurers will pay for. New federal health care law will base coverage requirements on these type of recommendations.
- Majority clinicians: Doesn't say an individual can't have the test: different men, different decision. But important change is to inform men of the pros and cons of testing for different risk factor profiles.

Message

- **Raise consciousness: trade-off of benefits and risks of screening are complex.**
- **Screening intuitively attractive, but can be double-edged sword.**
- **Need to avoid intuition, and conduct the necessary randomized trials to evaluate. Look at the data.**

Thank you for participating in this *Clinical Chemistry* Trainee Council Webcast

Find our upcoming Webcasts and other Trainee Council information at www.traineecouncil.org

Follow us